Appendix H Evidence tables

Fertility (Updated guideline)

How accurate are tests of ovarian reserve in predicting pregnancy outcomes?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Lee,T.H., Liu,C.H., Huang,C.C., Hsieh,K.C., Lin,P.M., Lee,M.S., Impact of female age and male infertility on ovarian reserve markers to predict outcome of assisted reproduction technology cycles, Reproductive Biology and Endocrinology, 7, 100-, 2009 **Ref ID** 4526 **Country/ies where the study was carried out** Taiwan **Study type** Prospective cohort study **Aim of the study** To compare the predictive power of various markers of ovarian reserve for the outcome IVF/ICSI cycles using ROC analysis **Study dates** March 2007 and December 2007 **Source of funding** Not reported	**Sample size** n = 336 IVF/ICSI procedures **Characteristics** Women were initially divided into two groups by age for analysis (i.e., <35 and ≥35) **Inclusion Criteria** [1] Long protocol for the use of a GnRH agonist (leuprolide) [2] First stimulation cycle for IVF/ICSI [3] Presence of bilateral ovaries [4] Absence of endocrine disorders (PCOS or hyperprolactinemia) **Exclusion Criteria** NA	E2 (day 3) FSH (day 3) LH (day 3) AMH (day 3) AFC (days 3-5) - all follicles 2-10mm Age	Baseline hormonal (Day 3) and TVUS assessment (Days 3-5) of the pre-stimulation cycle. Women followed a long protocol for the use of GnRH agonist (leuprolide). Ovarian response was monitored with E2 and TVUS from day 7 of stimulation until day of hCG administration.	Live birth - FSH: AUC = 0.524 (0.468-0.579) N = 324 AMH: AUC = 0.577 (0.521-0.631) N = 324 Age: AUC = 0.549 (0.493-0.604) N = 324 E2: not reported AFC: not reported Low response - Not defined/not reported High response - Not defined/not reported Cancellation: Not defined/not reported Pregnancy - visible fetal heart beat within the uterus by TVUS FSH: not reported AMH: not reported Age: not reported E2: Not reported AFC: Not reported	**Limitations** CASP Checklist: No failed items **Other information** *12 patients were excluded from analysis (4 due to no oocytes retrieved and 8 due to no embryo transfer)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Bancsi,L.F., Broekmans,F.J., Looman,C.W., Habbema,J.D., te Velde,E.R., Impact of repeated antral follicle counts on the prediction of poor ovarian response in women undergoing in vitro fertilization, Fertility and Sterility, 81, 35-41, 2004 **Ref ID** 4860 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective cohort study **Aim of the study** To investigate the predictive accuracy of single and repeated antral follicle counts in the prediction of poor ovarian response and to assess the degree of agreement between antral follicle counts in subsequent cycles **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 120 **Characteristics** **Inclusion Criteria** 1] regular spontaneous menstrual cycle (25-35 days) 2] presence of both ovaries 3] no evidence of endocrine disorders 4] written informed consent **Exclusion Criteria** Not reported	Age (per year) Cycle 1 AFC	During ovarian stimulation for IVF, plasma concentration of E_2 were assayed with a monoclonal enzyme immuno assay. The IVF was conducted within 3 months from the AFCs. A long protocol of down-regulation with 1 mg of leuprolide acetate, from the midluteal phase onward was applied in all patients. After the development of at least three leading follicles hCG was administered and a transvaginal, ultrasound-guided oocyte retrieval was performed 36 hours later	AUC data reported in Bancsi 2002 <u>Threshold data:</u> AFC ≤ 4 to predict poor response True positive = 22 False positive = 10 False negative = 14 True negative = 74 AFC ≤ 6 to predict poor response True positive = 29 False positive = 19 False negative = 7 True negative =65	**Limitations** CASP checklist: No failed items **Other information** Poor response: Collection of <4 oocytes at retrieval or cycle cancellation due to an impaired follicular reaction (<£ follicles) in response to exogenous gonadotropins High response: Collection of >20 oocytes at retrieval. Patients whose cycles were cancelled because they were considered at risk of OHSS due to exagterated follicle growth were also defined as high responders. Normal and high responders were considered as one group

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation La,Marca A., Giulini,S., Tirelli,A., Bertucci,E., Marsella,T., Xella,S., Volpe,A., Anti-Mullerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology, Human Reproduction, 22, 766-771, 2007 **Ref ID** 74022 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort study **Aim of the study** To evaluate whether serum AMH measurement any day of the menstrual cycle could predict ovarian response in women undergoing ART **Study dates** March 2005 to January 2006 **Source of funding** NA	**Sample size** n = 48 28 women in the follicular phase and 20 in the luteal phase **Characteristics** Causes of infertility: male factor (26 couples) tubal factor (9 couples) idiopathic (13 couples) **Inclusion Criteria** [1] Age 18-43 years [2] First IVF or ICSI [3] Regular menstrual cycles **Exclusion Criteria** [1] Endocrinological disorders [2] PCO	AMH on day it was decided to introduce the couple to IVF/ICSI procedure	AMH assessment at enrolment (any time in the cycle). Long protocol GnRH-a down-regulation was used and COH with r-FSH (150-300 IU/day). When ≥3 follicles reached >18mm, 10 000 IU of hCG was administered	No ROC/AUC data Threshold data: AMH 0.5 to predict poor response - defined as < 4 oocytes retrieved or cancellation due to impaired or absent follicular growth in response to ovarian stimulation True positive = 10 False positive = 16 False negative = 2 True negative = 72 AMH 0.5 to predict poor response True positive = 9 False positive = 6 False negative = 3 True negative = 82	**Limitations** CASP checklist: No failed items **Other information** Poor ovarian response was defined as <4 oocytes or cancellation due to impaired or absent follicular growth in response to COH Normal ovarian response was defined as a collection of 4-8 oocytes Good ovarian response was defined as a collection of 9-16 oocytes High responders when >16 oocytes were collected or when cycle was cancelled due to exaggerated response According to Italian law regulating ART, only 3 oocytes were fertilized at one time On going pregnancy rate was calculated as the number of viable pregnancies detected at 6 weeks post-retrieval TVUS divided by the number of embryo transfers performed Absence of homogeneity in couples studied

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Bancsi,L.F., Broekmans,F.J., Looman,C.W., Habbema,J.D., te Velde,E.R., Predicting poor ovarian response in IVF: use of repeat basal FSH measurement, Journal of Reproductive Medicine, 49, 187-194, 2004 **Ref ID** 53462 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective cohort study **Aim of the study** To evaluate the additional value of a second basal follicle stimulating hormone (FSH) level, in a different cycle, in the prediction of poor response in in vitro fertilization by a single basal FSH measurement in a preceding cycle and by other possible predictors, such as chronologic age and infertility diagnosis **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 120 **Characteristics** <u>Patients with indicated infertility diagnosis (N = 120)</u> Tubal = 23 Male = 59 Unexplained = 38 **Inclusion Criteria** 1] regular, spontaneous menstrual cycle (25 -35 days) 2] presence of both ovaries 3] no evidence of endocrine disorders (normal levels of thyroid-stimulating hormone, testosterone, androstenedione and prolactin) **Exclusion Criteria** 1] patients over 40 years of age 2] basal FSH levels >15IU/L	Age Cycle 1 FSH	Basal FSH was measured in plasma specimens with the AxSYM immunoanalyzer and during ovarian stimulation for IVF, plasma concentrations of estradiol were assayed with a mono clonal enzyme immunoassay. IVF treatment followed within 3 months of basal FSH measurement. A long protocol of down-regulation with leuprolide acetate , from the midluteal phase onward, was applied in all patients. When at least 3 leading follicles developed, hCG was administered and transvaginal, ultrasound-guided oocyte retrieval was performed 36 hours later.	Poor response (AUC): Age (per year) = 0.61 Cycle 1 FSH (per IU/L) = 0.84 Clinical pregnancy (AUC): Age (per year) = 0.51 Cycle 1 FSH (per IU/L) = 0.45	**Limitations** CASP checklist: No failed items **Other information** Poor response: Collection of <4 oocytes at retrieval or cycle cancellation due to an impaired follicular reaction (<£ follicles) in response to exogenous gonadotropins High response: Collection of >20 oocytes at retrieval. Patients whose cycles were cancelled because they were considered at risk of OHSS due to exagterated follicle growth were also defined as high responders. Normal and high responders were considered as one group

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Khairy,M., Clough,A., El-Toukhy,T., Coomarasamy,A., Khalaf,Y., Antral follicle count at down-regulation and prediction of poor ovarian response, Reproductive Biomedicine Online, 17, 508-514, 2008 **Ref ID** 54623 **Country/ies where the study was carried out** London, UK **Study type** Prospective cohort study **Aim of the study** To assess the accuracy of AFC performed after pituitary down-regulation in predicting poor ovarian response and the influence of using different thresholds of follicle size and count on its accuracy **Study dates** September 2005 to June 2006 **Source of funding** NA	**Sample size** n = 148 (148 cycles) 137 participants completed treatment cycle: 9 were cancelled before oocyte retrieval and 2 had total fertilization failure **Characteristics** Down-regulated women prior to the start of ovarian stimulation **Inclusion Criteria** [1] Endometrial thickness <5mm and no ovarian follicles ≥10mm **Exclusion Criteria** [1] Ovarian endometriomas [2] Previous ovarian surgery [3] Single ovary	AFC (down-regulated cycle prior to the start of ovarian stimulation) Age BMI FSH (day 2-4 of a spontaneous cycle within 6 months of the start of treatment) LH (day 2-4 of a spontaneous cycle within 6 months of the start of treatment) E2 (day 2-4 of a spontaneous cycle within 6 months of the start of treatment)	AFC was assessed at the time of TVUS performed to confirm down-regulation prior to COH (dAFC)	Live birth - Not reported Low response – <4 oocytes retrieved or cycle cancellation due to poor follicular response High response - Not reported Cancellation: <3 follicles ≥12mm, after 10 days of COH Pregnancy - Not reported	**Limitations** CASP Checklist: No failed items **Other information** Participants with PCO/PCOS were not excluded as these represent about 15% of the authors' IVF population AUC data for AFC and biochemical tests not used in meta-analysis due to tests on stimulated women

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Kwee,J., Schats,R., McDonnell,J., Schoemaker,J., Lambalk,C.B., The clomiphene citrate challenge test versus the exogenous follicle-stimulating hormone ovarian reserve test as a single test for identification of low responders and hyperresponders to in vitro fertilization, Fertility and Sterility, 85, 1714-1722, 2006 **Ref ID** 54732 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised controlled study **Aim of the study** To find one simple test that could identify poor, normal and hyperresponders **Study dates** June 1997 and December 1999 **Source of funding** NA	**Sample size** n = 110 (n = 56 underwent CCCT; n = 54 underwent an EFFORT) **Characteristics** Women aged 18-39 years, who were eligible for ART. Their fertility was either idiopathic for >3 years and/or due to male factor and/or cervical hostility **Inclusion Criteria** [1] Regular menstrual cycles [2] Two ovaries [3] At least one patent fallopian tube **Exclusion Criteria** [1] PCOS [2] Severe male factor infertility [3] Untreated or insufficiently corrected endocrinopathies, clinically relevant systemic diseases [4] BMI >28	FSH Inhibin B E2 CCCT EFFORT	All women underwent TVUS on the 3rd day since the onset of menses to identify ovarian cysts. When there were ovarian cysts of >20 mm, the cycle was cancelled. Those who were eligible, were randomised into one of two groups, to receive CCCT or EFFORT. In all patients, the test was followed by an IVF treatment under a long protocol. Blood sample were drawn on Day 3, just before and after the administration of FSH	Live birth - Not defined Low response – <6 oocytes AUC data not used. High response - >20 oocytes Age: AUC = 0.71. n = 110 FSH: AUC = 0.80. N = 110 Inhibin B: AUC = 0.65. N = 110 CCCT: AUC = 0.82. N = 56 Cancellation - Not reported Pregnancy - Not defined <u>Threshold data:</u> FSH <4 IU/L to predict high response True positive = 3 False positive = 1 False negative = 14 True negative = 92 FSH <4 IU/L to predict high response True positive = 5 False positive = 6 False negative = 12 True negative = 87 FSH <5 IU/L to predict high response	**Limitations** CASP Checklist: No failed items. **Other information** None

				True positive = 11 False positive = 22 False negative = 6 True negative = 71 FSH <6 IU/L to predict high response True positive = 14 False positive = 36 False negative = 3 True negative = 57 FSH <7 IU/L to predict high response True positive = False positive = False negative = True negative = FSH <8 IU/L to predict high response True positive = 16 False positive = 55 False negative = 1 True negative = 38 CCCT <9 IU/L to predict high response True positive = 2 False positive = 1 False negative = 7 True negative = 46 CCCT <10 IU/L to predict high	

				response True positive = 4 False positive = 2 False negative = 5 True negative = 45 CCCT <11 IU/L to predict high response True positive = 4 False positive = 5 False negative = 5 True negative = 42 CCCT <12 IU/L to predict high response True positive = 6 False positive = 12 False negative = 3 True negative = 35 CCCT <13 IU/L to predict high response True positive = 7 False positive = 18 False negative = 2 True negative = 29	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Kwee,J., Elting,M.E., Schats,R., McDonnell,J., Lambalk,C.B., Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization, Reproductive Biology and Endocrinology, 5, 9-, 2007 **Ref ID** 74015 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised controlled study **Aim of the study** 'to compare the antral follicle count (AFC) and the basal ovarian volume (BOV), with the exogenous FSH ovarian reserve test (EFORT) and the clomiphene citrate challenge test (CCCT) with respect to their ability to predict poor and hyper response.' **Study dates** June 1997 - December 1999 **Source of funding** NA	**Sample size** n = 110 (n = 56 underwent CCCT; n = 54 underwent an EFFORT) **Characteristics** Women aged 18-39 years, who were eligible for ART. Cause of infertility: idiopathic for >3 years and/or male factor and/or cervical hostility **Inclusion Criteria** [1] Regular menstrual cycles [2] Two ovaries [3] At least one patent fallopian tube **Exclusion Criteria** [1] PCOS [2] Severe male factor infertility [3] Untreated or insufficiently corrected endocrinopathies, clinically relevant systemic diseases [4] BMI >28	FSH Inhibin B E2 CCCT EFFORT Age	All women underwent TVUS on the 3rd day since the onset of menses to identify ovarian cysts. When there were ovarian cysts of >20 mm, the cycle was cancelled. Those who were eligible, were randomised into one of two groups, to receive CCCT or EFFORT. In all patients, the test was followed by an IVF treatment under a long protocol. Blood sample were drawn on Day 3, just before and after the administration of FSH	Live birth - Not defined/Not reported Low response - defined as [1] collection of fewer than 6 oocytes at retrieval AUC data not used High response - defined as [1] defined as the collection of >20 oocytes at retrieval FSH: AUC = 0.80, N = 110 Ovarian Volume: AUC = 0.87. N = 110 AFC: AUC = 0.92. N = 110 Age: C = 0.71. N = 110 Cancellation: Not reported Pregnancy - Not defined/Not reported FSH: Not reported <u>Threshold data:</u> AFC > 10 to predict high response > 20 oocytes True positive: 15 False positive: 27 False negative: 1 True negative: 67 AFC > 12 to predict high response > 20 oocytes True positive: 14 False positive: 19 False negative: 2 True negative: 75 AFC > 14 to predict high response > 20 oocytes	**Limitations** CASP checklist: No failed itesms **Other information** Third report from a single RCT (two other reports included)

				True positive: 13 False positive: 10 False negative: 3 True negative: 84 AFC > 16 to predict high response > 20 oocytes True positive: 8 False positive: 4 False negative: 8 True negative: 90 AFC > 18 to predict high response > 20 oocytes True positive: 5 False positive: 2 False negative: 11 True negative: 92	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Bancsi,L.F.J.M., Broekmans,F.J.M., Eijkemans,M.J.C., de,JongF, Habbema,J.DikF, te,VeldeE, Predictors of poor ovarian response in in vitro fertilization: A prospective study comparing basal markers of ovarian reserve, Fertility and Sterility, 77, 328-336, 2002 **Ref ID** 72985 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective cohort study **Aim of the study** 'to determine which markers significantly contribute to the prediction of poor response to IVF, to identify the best single predictor, and to evaluate the additional predictive value of the remaining markers in bolstering the best single predictor' **Study dates** January 1997 - April 1998 **Source of funding** NA	**Sample size** n = 130 women were included, of whom 120 became eligible for analysis (102 conventional IVF and 18 ICSI). Six conceived spontaneously while on waiting list for IVF, two dropped out due to intercurrent disease and two withdrew consent. Of the 120 patients with data for ovarian response analysis, 107 were included in the pregnancy calculations **Characteristics** Cause of infertility: Male factor (49) Tubal factor (23) Unexplained (38) Mean Age: 34.9 ± 4.9 years Mean duration of infertility: 35 ± 25 months **Inclusion Criteria** First IVF cycle in women who had [1] regular menstrual cycles (25 to 35 days) [2] presence of both ovaries [3] no evidence of endocrine disorders (normal levels of TSH, testosterone, androstenedione and prolactin) **Exclusion Criteria** [1] Age > 45 years of age	Inhibin B; FSH; E2; AFC (all follicles > 5mm) Age	All women in IVF centre who met the inclusion criteria were assigned to one of three groups, based on main cause of infertility: tubal factor, male factor, or unexplained infertility. On day 3 of spontaneous menstrual cycle basal ovarian reserve screening tests were performed. IVF treatment protocol (pituitary desensitization by leuprolide acetate) followed within 3 months of the basal ovarian reserve screening	Live birth - Not reported Inhibin B: Not reported FSH: Not reported E2: Not reported AFC: Not reported Age: Not reported Low response - defined as [1] collection of fewer than 4 oocytes at retrieval or [2] cycle cancellation because of impaired follicular reaction (<3 follicles) in response to exogenous gonadotrophins. Inhibin B: AUC = 0.77. N = 120 FSH: AUC = 0.84. N = 120 E2: AUC = 0.53 n = 120 AFC: AUC = 0.84. N = 120 Age: AUC = 0.61. N = 120 High response - defined as [1] the collection of >20 oocytes at retrieval [2] cancellation because at risk of OHSS due to exaggerated follicle growth (>30 follicles and/or peak E2> 15000 pmol/L. Inhibin B: Not reported FSH: Not reported E2: Not reported AFC: Not reported Age: Not reported Cancellation: Included in high response Inhibin B: Not reported FSH: Not reported	**Limitations** CASP Checklist: No failed items **Other information** Normal and high responders were considered one group for the purpose of analysis Multiple pregnancy was regarded as one pregnancy. Data of patients whose cycles were cancelled because of poor response or risk of OHSS were included in ovarian response analysis but not in pregnancy rate calculations; however, patients with complete absence of follicle growth and levels of E2 < 200 pmol/L were considered to have zero chance of pregnancy, therefore were included in pregnancy rate calculations. 36 poor responders (20 with <4 oocytes retrieved and 16 cancelled with <2 oocytes). 10 high responders: 7 cycles were canceled due to risk of OHSS (not included in pregnancy rate analysis) and 3 patients had more than 20 oocytes retrieved (included in pregnancy rate analysis)

				E2: Not reported AFC: Not reported Age: Not reported Pregnancy - clinical and ongoing pregnancies defined as presence of fetal cardia activity beyond 6 and 12 weeks. Inhibin B: Not reported FSH: Not reported E2: Not reported AFC: Not reported Age: Not reported <u>Threshold data:</u> AFC ≤ 4 to predict poor response True positive = 22 False positive = 10 False negative = 14 True negative = 74 AFC ≤ 6 to predict poor response True positive = 29 False positive = 19 False negative = 7 True negative =65	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Hendriks,D.J., Broekmans,F.J., Bancsi,L.F., de Jong,F.H., Looman,C.W., te Velde,E.R., Repeated clomiphene citrate challenge testing in the prediction of outcome in IVF: a comparison with basal markers for ovarian reserve, Human Reproduction, 20, 163-169, 2004 **Ref ID** 73751 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective cohort study **Aim of the study** To investigate the predictive accuracy and clinical value of performing either a single or repeated CCCT in predicting poor response in IVF, compared to that of currently advocated basal ovarian reserve markers **Study dates** NA **Source of funding** NA	**Sample size** n = 63 IVF was planned in n = 53 ICSI was scheduled in n = 10 **Characteristics** First IVF treatment **Inclusion Criteria** [1] Regular menstrual cycles (25-35 days) [2] Presence of both ovaries [3] No evidence of endocrine disorders [4] Age <46 years **Exclusion Criteria** NA	AFC (number of antral follicles 2-5mm on day 3 of spontaneous cycle) FSH unstimulated (day 3) and stimulated (day 10) E2 unstimulated (day 3) Inhibin B unstimulated (day 3) and stimulated (day 10) CCCT with 100mg of CC (day 5-9)	On day 3 of spontaneous cycle patients underwent TVUS for AFC (2-5mm) and measurement of FSH, E2 and inhibin B. A CCCT was performed with 100mg of CC (day5-9). On day 10 measurement of FSH and inhibin B. After a wash-out cycle a second TVUS and CCCT was performed. The IVF treatment followed 3 months of the second CCCT.	Live birth - Not reported Low response – defined as <4 oocytes at retrieval or as cancellation (< 3follicles) Inhibin B: AUC = 0.72 (0.58-0.87) p = 0.008 FSH: AUC = 0.82 (0.69-0.95) p <0.001 E2: AUC = 0.54 (0.36-0.72) p = 0.09 AFC: AUC = 0.83 (0.73-0.94) p = 0.001 Age: AUC = 0.56 (0.39-0.73) p = 0.38 High response - exaggerated response (>30 follicles and/or E2 >15000) Inhibin B: Not reported FSH: Not reported E2: Not reported AFC: Not reported Age: Not reported Cancellation - due to impaired (<3 follicles) or total absence of follicular growth. In the group of 'normal' responders could also include patients with cancelled cycles due to exaggerated response (>30 follicles and/or E2 >15000) Inhibin B: Not reported FSH: Not reported	**Limitations** CASP Checklist: No failed items **Other information** Data from patients of whom the cycle was cancelled due to either risk of OHSS or poor response were not included in the pregnancy analysis. However, patients with complete absence of follicle growth and E2 <200 pmol/L were considered to have zero chance of pregnancy, and therefore data of their cycles were included in the analysis of pregnancy

				E2: Not reported AFC: Not reported Age: Not reported Pregnancy - viable pregnancy assessed by US, ≥11 weeks gestation Inhibin B: Not reported FSH: Not reported E2: Not reported AFC: Not reported Age: Not reported THRESHOLD DATA: not reported in this paper but extracted from Hendricks 2006: Poor response - <4 oocytes FSH: >10 ; Sens - 0.59; Spec - 0.96 > 15; Sens - 0.32; Spec - 0.98	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation McIlveen,M., Skull,J.D., Ledger,W.L., Evaluation of the utility of multiple endocrine and ultrasound measures of ovarian reserve in the prediction of cycle cancellation in a high-risk IVF population, Human Reproduction, 22, 778-785, 2007 **Ref ID** 74214 **Country/ies where the study was carried out** Australia **Study type** **Aim of the study** Not clear **Study dates** March 2004 - June 2005 **Source of funding** Not reported	**Sample size** N = 84 **Characteristics** Cause of infertility: unexplained infertility (30) male factor (32) tubal factor (13) endometriosis (9) Mean age: 37.3 ± 3.9 years Duration of infertility: 4.6 ± 3.7 years **Inclusion Criteria** [1] have a previously raised early follicular phase FSH concentration > 18 IU/L [2] > 39 YEARS OF AGE [4] have had a previous poor response to stimulation **Exclusion Criteria** [1] women with only 1 ovary	E2 (day 2) FSH (day 2) Inhibin B (day 2) AMH (day 2) AFC (day 2) Ovarian volume (day 2)	Blood collected on day 2 as were FC and ovarian violume data. Buserelin acetate 0.5 mg then given. second blood sample after 24 hours	Live birth: Not reported Low response: Not reported High response: Not reported Cancellation: defined as ≤ 2 subsidiary follicles of ≥ 14mm were seen when lead follicle reached 18mmE2 (day 2) FSH: AUC = 0.64. N = 84 Inhibin B: AUC = 0.78. N = 84 AMH: AUC = 0.78. N = 84 AFC: AUC 0.74. N = 84 Ovarian volume. AUC = 0.78. N = 84 Pregnancy: Not reported <u>Threshold data:</u> FSH ≥ 10IU/L to predict cancellation True positive = 6 False positive = 15 False negative = 7 True negative = 56 AMH ≤ 1.25 ng/ml to predict cancellation True positive =11 False positive = 28 False negative = 4 True negative = 45 AFC ≤ 5 to predict cancellation True positive =6 False positive = 16	**Limitations** CASP checklist: No failed items **Other information** None
				False negative = 7 True negative = 57	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation van Rooij,I, Broekmans,F.J., te Velde,E.R., Fauser,B.C., Bancsi,L.F., de Jong,F.H., Themmen,A.P., Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve, Human Reproduction, 17, 3065-3071, 2002 **Ref ID** 74914 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective cohort study **Aim of the study** To prospectively assess the significance of AMH as a marker of ovarian reserve in a large unselected IVF population. In addition, to assess the predictive value of AMH levels towards poor response in relation to other ovarian reserve tests. Finally to investigate wether serum AMH levels are affected by a rise in endogenous FSH and LH induced by a single, high dose GnRH agonist (GAST) **Study dates** NA **Source of funding** NA	**Sample size** n = 130 **Characteristics** n = 112 were planned for conventional IVF n = 18 were scheduled for ICSI **Inclusion Criteria** [1] First cycle IVF [2] Regular menstrual cycles (25-35 days) [3] Presence of both ovaries [4] Normal thyroid stimulating hormone, prolactin, testosterone and androstenedione [5] Age <46 years **Exclusion Criteria** NA	AFC (number of antral follicles 2-5mm on day 3 of spontaneous cycle) AMH (day 3 of spontaneous cycle) FSH (day 3 of spontaneous cycle) E2 (day 3 of spontaneous cycle) Inhibin B (day 3 of spontaneous cycle) GAST	On day 3 of spontaneous cycle within 3 months preceding IVF, patients underwent TVUS for measurement of AFC (2-5mm), AMH, FSH, E2, Inhibin B. In a subset of 23 patients a GnRH agonist stimulation test (GAST) was performed on cycle day 3 and returned exactly 24 hours later for a second measurement of AMH, FSH, E2 and Inhibin B	Pregnancy - viable pregnancy assessed by US of at least 11 weeks gestation Live birth - Not reported Low response – defined as <4 oocytes at retrieval or as cancellation AMH: AUC = 0.85 FSH: AUC = 0.83 Inhibin B: AUC = 0.76 AFC: AUC = 0.86 Age: AUC = 0.60 E2: AUC = 0.52 High response - >20 oocytes; Exaggerated response >30 oocytes and/or peak E2 >15000 Cancellation - <3 follicles or absent follicular growth in response to COH	**Limitations** CASP Checklist **Other information** High response was considered as secondary outcome and in the analysis of high response both the poor and normal responders are considered one group Data from patients whose cycles were cancelled were not included in the pregnancy rate analysis, however, patients with complete absence of follicle growth and E2 <200 were considered to have zero chance of pregnancy and data on their cycles was included in the analysis of pregnancy rates Group of 'normal responders' also included patients with cancelled cycles due to exaggerated response

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Younis,J.S., Jadaon,J., Izhaki,I., Haddad,S., Radin,O., Bar-Ami,S., Ben-Ami,M., A simple multivariate score could predict ovarian reserve, as well as pregnancy rate, in infertile women, Fertility and Sterility, 94, 655-661, 2010 **Ref ID** 75045 **Country/ies where the study was carried out** Israel **Study type** Prospective cohort study **Aim of the study** To find a simple multivariate score that uses both basal sonographic and endocrine parameters conjoined to predict ovarian reserve, as well as pregnancy rate in infertile women undergoing ART treatment **Study dates** NA **Source of funding** NA	**Sample size** n = 168 **Characteristics** Infertile women aged 19 to 44 years referred to the IVF centre for treatment. All women were menstruating spontaneously, had 2 intact ovaries and no evidence of thyroid disease, diabetes, significant hyperprolactinemia or hypogonadotropic hypogonadism. All women had hysterosalpingography and/or hysteroscopy to determine if they had normal uterine cavities. **Inclusion Criteria** [1] First cycle treatment **Exclusion Criteria** NA	FSH (day 2-4 of natural cycle before starting treatment) LH (day 2-4 of natural cycle before starting treatment) E2 (day 2-4 of natural cycle before starting treatment) P (day 2-4 of natural cycle before starting treatment) AFC (2-10mm) OV	Long protocol down-regulation with GnRH agonist (triptorelin) for IVF was used in each patient. COH with hMG (300 IU/day). hCG 10000IU when ≥2 follicles of 18-20mm and E2 ≥400 pg/mL. Luteal support with use of transvaginal micronized P treatment 800mg/day	Pregnancy - Not defined/not reported Live birth - Not reported Low response – defined as ≤3 oocytes achieved on day of retrieval Mean OV: AUC = 0.67 FSH: AUC = 0.78 AFC: AUC = 0.80 Age: AUC = 0.81 High response - Not reported Cancellation - Not reported	**Limitations** CASP Checklist **Other information** Heterogeneous causes of infertility and strict definition of low ovarian reserve The use of pregnancy as an outcome parameter for assessment of ovarian reserve may be insufficient if only one cycle is taken into account 11 of the patients had embryos cryopreserved because of risk of OHSS

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Al-Azemi,M., Killick,S.R., Duffy,S., Pye,C., Refaat,B., Hill,N., Ledger,W., Multi-marker assessment of ovarian reserve predicts oocyte yield after ovulation induction, Human Reproduction, 26, 414-422, 2011 **Ref ID** 111593 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** Ability of an ovarian reserve test to predict the outcome of ovulation stimulation both in terms of oocyte yield and chance of pregnancy. **Study dates** Women attending IVF clinic between January 2008 and August 2009 **Source of funding** N/A	**Sample size** 356 recruited. 291 underwent embryo transfer. **Characteristics** Group 1a (cancelled during stimulation due to poor response; n = 28)) Age = 35.8 (+/- 4.4) Cause of infertility • Unexplained = 9 • Male factor = 5 • Tubal = 4 • Ovulatory = 3 • Endometriosis = 1 • Combined = 6 FSH (IU/L) = 8.28 (+/- 2.91) Inhibin B (pg/ml) = 28.7 (+/- 31.4) AMH (ng/ml) = 2.19 (+/- 3.74) Group 1b (<=4 oocytes retireved after stimulation; n = 71) Age = 36.6 (+/- 3.8) Cause of infertility	Age FSH (day 2) - multianalysis system with chemoluminescence detection Inhibin B (day 2) - two-site enzyme-linked immunosorbent assay (ELISA) kit AMH (day 2) - AMH/MIS ELISA kit Blood collected on day 2 of menstrual cycle.	Women undergoing IVF/ICSI - Individualised programmes (69.9% antagonist, 15.5% GnRH agonist long protocol, 14.6% GnRH agonist 'flare' protocol) - Trigger 10,000 IU HCG Sample size base on 80% power and p-value of 5%. Assuming that the blood test score will be normally distributed, the odds of ongoing pregnancy at the mena blood test score is estimated to be one-third and the odds ratio following a 1 SD reduction in blood test score from the mean is estimated to be root 2 = 1.414. Sample size was 348. Mann-Whitney tets for continuous variables Kruskal-Wallis test to test more than two groups Fisher's exact test used for categorical variables Predictive value based on ROC and logistic regression	Poor response (<=4 oocytes) Age in years = AUC 0.676; cutoff = 36, sensitivity (%) = 63.6, specificity (%) = 60.5, LR+ = 1.61 FSH (IU/L) = AUC 0.721; cutoff = 7.0, sensitivity (%) = 69.7, specificity (%) = 67.9, LR+ = 2.17 Inhibin B (pg/ml) = AUC 0.686; cutoff = 49.4, sensitivity (%) = 64.0, specificity (%) = 63.6, LR+ = 1.76 AMH (ng/ml) = 0.827; cutoff = 1.36, sensitivity (%) = 75.5, specificity (%) = 74.8, LR+ = 2.99 Multivariate (all above) = 0.819; cutoff = 0.0, sensitivity (%) = 76.8, specificity (%) = 76.6, LR+ = 3.28 Negative pregnancy outcome Age in years = AUC 0.610; cutoff = 35, sensitivity (%) = 61.8, specificity (%) = 53.4, LR+ = 1.33 FSH (IU/L) = AUC 0.519; cutoff	**Limitations** QUADAS checklist: No failed items **Other information**

	• Unexplained = 27 • Male factor = 18 • Tubal = 11 • Ovulatory = 2 • Endometriosis = 4 • Combined = 9 FSH (IU/L) = 8.13 (+/- 2.71) Inhibin B (pg/ml) = 54.0 (+/- 67.5) AMH (ng/ml) = 1.07 (+/- 1.08) Group 2b (>4 oocytes retrieved; n = 244) Age = 33.5 (+/- 4.8) Cause of infertility • Unexplained = 52 • Male factor = 91 • Tubal = 39 • Ovulatory = 8 • Endometriosis = 8 • Combined = 46 FSH (IU/L) = 6.34 (+/- 1.89) Inhibin B (pg/ml) = 63.1 (+/- 36.9) AMH (ng/ml) = 2.64 (+/- 1.85)			= 6.8, sensitivity (%) = 53.4, specificity (%) = 52.4, LR+ = 1.12 Inhibin B (pg/ml) = AUC 0.541; cutoff = 53.2, sensitivity (%) = 50.0, specificity (%) = 49.6, LR+ = 0.99 AMH (ng/ml) = 0.575; cutoff = 1.76, sensitivity (%) = 56.8, specificity (%) = 56.3, LR+ = 1.30 Multivariate (all above) = 0.633; cutoff = 0.73, sensitivity (%) = 62.5, specificity (%) = 61.4, LR+ = 1.62	

	Group 2a (Excessive response so cycle cancelled; n = 9) Age = 30.2 (+/- 7.0) Cause of infertility • Unexplained = 4 • Male factor = 3 • Tubal = 2 • Ovulatory = 0 • Endometriosis = 0 • Combined = 0 FSH (IU/L) = 4.41 (+/- 0.99) Inhibin B (pg/ml) = 95.5 (+/- 36.2) AMH (ng/ml) = 7.44 (+/- 3.06) **Inclusion Criteria** None - all attending clinic **Exclusion Criteria** None - all attending clinic				

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Broer,S.L., Dolleman,M., Opmeer,B.C., Fauser,B.C., Mol,B.W., Broekmans,F.J., AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis, Human Reproduction Update, 17, 46-54, 2011 **Ref ID** 111618 **Country/ies where the study was carried out** Reviewing undertaken in Netherlands **Study type** Systematic review **Aim of the study** Assess the accuracy of AMH and AFC as predictors of an excessive response in IVF/ICSI treatment. **Study dates** All years covered on Medline until November 2009. **Source of funding** Not stated	**Sample size** 170 papers identified, 11 included in review **Characteristics** **Inclusion Criteria** Any paper examining AFC or AMH as a prognostic indicator of excessive ovarian response for COH in IVF or ICSI. No definition of excessive ovarian response was set. **Exclusion Criteria**	AMH AFC	Data extracted into 4X4 to allow sensitivity and specificity to be calculated Data meta-analysed using bivariate regression model ROC curve	AMH Two of these papers are included in the main review. Author, Cycles, Cutt-ff (ng/ml), Sensitivity, Specificity, LR+, LR- Van RooiJ et al (2002), 114, 3.50, 0.40, 0.95, 8.00, 0.63 Eldar-Geva et al (2005), 53, 3.50, 0.72, 0.89, 6.55, 0.31 Ebner et al (2006), 135, 1.66, 0.95, 0.31, 1.38, 0.16 Ebner et al (2006), 135, 4.52, 0.55, 0.81, 2.89, 0.56 La Marca et al (2007), 48, 2.60, 0.86, 0.56, 1.95, 0.25 La Marca et al (2007), 48, 7.00, 0.57, 0.83, 3.35, 0.52 Nelson et al (2007), 314, 2.10, 0.88, 0.79, 4.19, 0.15 Nelson et al (2007), 314, 3.50, 0.57, 0.96, 14.25, 0.45 Lee et al (2008), 262, 1.99, 0.90, 0.62, 2.37, 0.16 Lee et al (2008), 262, 3.36, 0.62, 0.87, 4.77, 0.44	**Limitations** Hetrogeniety of included studies caused by varying quality, study population and assay tests used. Included unpublished data requested from authors **Other information**

				Riggs et al (2008), 123, 1.59, 0.84, 0.67, 2.55, 0.24 Nardo et al (2009), 165, 3.50, 0.88, 0.70, 2.93, 0.17 Aflatoonian et al (2009), 159, 4.83, 0.93, 0.78, 4.23, 0.09 AFC Two of these papers are included in the main review. Author, Cycles, Cutt-ff (ng/ml), Sensitivity, Specificity, LR+, LR- Ng et al (2000), 128, 9, 0.60, 0.71, 2.07, 0.56 Ng et al (2000), 128, 14, 0.20, 0.94, 3.33, 0.85 Van RooiJ et al (2002), 114, 14, 0.92, 0.63, 2.49, 0.13 Eldar-Geva et al (2005), 56, 14, 0.94, 0.33, 1.40, 0.18 Kwee et al (2008), 110, 10, 0.94, 0.71, 3.24, 0.08 Kwee et al (2008), 110, 12, 0.88, 0.80, 4.40, 0.15	

				Kwee et al (2008), 110, 14, 0.81, 0.89, 7.36, 0.21 Kwee et al (2008), 110, 16, 0.50, 0.96, 12.50, 0.52 Kwee et al (2008), 110, 18, 0.31, 0.98, 15.50, 0.70 Aflatoonian et al (2009), 159, 16, 0.89, 0.92, 11.13, 0.12	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Aflatoonian,A., Oskouian,H., Ahmadi,S., Oskouian,L., Prediction of high ovarian response to controlled ovarian hyperstimulation: anti-Mullerian hormone versus small antral follicle count (2-6 mm), Journal of Assisted Reproduction and Genetics, 26, 319-325, 2009 **Ref ID** 111849 **Country/ies where the study was carried out** Iran **Study type** Prospective cohort study **Aim of the study** To compare the value of basal serum AMH and small AFC measurement in the prediction of high ovarian response to COH in ART cycles. **Study dates** January to December 2008 **Source of funding** N/A	**Sample size** 159 women recruited. 143 analysed. **Characteristics** Variable: Normal responders (n = 98), High responders (n=45) Age (years): 28.6 +/- 4, 27.5 +/- 3.6, p = 0.96 BMI: 25.1 +/- 2.3, 24.5 +/- 2.8, p=0.184 Basal FSH (mIU/mL): 5.36 +/- 1.4, 5.05 +/- 0.7, p = 0.163 Basal E2 (pg/mL): 46.8 +/- 1.1, 45.9 +/- 8.6, p = 0.624 Basal AMH (pmol/l): 25.1 +/- 9.7; 54.7 +/-24.8, p = 0.000 Small AFC (n): 13.1 +/- 2.9, 21.2 +/- 5.7, p =0.000 Oocyte retrieved (n): 8.1 +/- 2.9, 17.7 +/- 3.3, p = 0.000 E2 on day of hCG (pg/mL0: 1557.3 +/- 651.2, 3451.7 +/- 728.1, p = 0.000 Patients with top or good embryos (%): 60.2%, 73%, p=0.138 Type of infertility no outlined	AMH (pmol/l) Small AFC 2-6mm (n) FSH (mIU/mL E2 (pg/mL) Age (yrs) BMI (kg//$m^{2)}$	Ethics approval granted Ultrasound undertaken to single operator who was blinded to other outcomes. Number of 2 to 6mm antral follicles in both ovaries counted. Blood samples taken and assayed. FSH: Intra assay coeffiicents were 6% and inter-assay coefficients were 6.8% E2: Intra assay coeffiicents were 6.3% and inter-assay coefficients were 6.4% FSH: Intra assay coeffiicents were 12.3% and inter-assay coefficients were 14.2% Treatment All patients treated with a long protocol for ovarian stimulation. Pituitary suppression 0.5mg buserelin started during luteal phase. When ovaries quiescent on ultrasound, buserelin reduce to 0.25mb/d until hCG administration. COH with rFSH at 150IU/day on day 2 of cycle (if >35 years then 225 IU/day).	Predication of high response to COH defined as => 15 follicles with a mean diameter of =>12mm per ovary at the end of the follicular phase. Variable: AUC (95% CI), Cutoff, Sensitivity (%), Specificity (%), PPV, NPP Age: 0.409 (0.312 to 0.506) (equivalent to 0.591 when mirrored across 0.5) , 26.5, 58, 30, 0.39, 0.72 BMI: 0.468 (0.362 to 0.574) (equivalent to 0.532), 24.1, 67, 42, 0.25, 0.64 Bsasl FSH: 0.385 (0.294 to 0.475) (equivalent to 0.615), 5.05, 51, 36, 0.37, 0.72 Basal E2:0.474 (0.377 to 0572) (equivalent to 0.526), 43.5, 69, 33, 0.31, 0.68 AMH: 0.922 (0.876 to 0.968), 34.5, 93, 78, 0.65, 0.96 Small AFC: 0.961 (0.933 to 0.989), 16, 89, 92, 0.83, 0.94	**Limitations** QUADAS checklist: no items failed Intra-assay coefficient was greater than 10% for AMH test so considered high. Types of infertility not defined Day of testing not defined **Other information** Data on AMH also presented in Broer et al (2011) review`

	Inclusion Criteria - First cycle of IVF - <38 years of age - Both ovaries intact - Day 3 FSH < 10 - No history of ovarian surgery, chemotherapy, pelvic radiation and current hormonal therapy **Exclusion Criteria** - Ovarian cyst > 10mm - Poor response of COH excluded = < 3 follicles and or serum E2 <=500pg/ml, and/or 3 or fewer oocytes		Monitoring until hCG administration at 10,000 IU. Oocyte retrieval at 34 to 36 hrs after hCG. Outcomes High response = 15 follicles with a mean diameter of >= 12mm per ovary at the end of the follicular phase of COH or >15 oocytes retrieved or cycle cancellation on day o f hCG, and/or cryopreservation of all embryos because of risk of OHSS. (Ultrasound the comparartive standard) Embryo quality (results not reported here) Statistical analysis Student t-test and Chi-squared Logistic regression to determine independent effect of measures ROC curve analysis to determine maximum AUC cutoff		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Kunt,C., Ozaksit,G., Keskin,KurtR, Cakir,GungorA, Kanat-Pektas,M., Kilic,S., Dede,A., Anti-Mullerian hormone is a better marker than inhibin B, follicle stimulating hormone, estradiol or antral follicle count in predicting the outcome of in vitro fertilization, Archives of Gynecology and Obstetrics, 283, 1415-1421, 2011 **Ref ID** 147999 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Aim of the study** To compare AMH with other ovarian reserve markers and to find a cut-off value of the AMH for predicting ovarian reserve towards controlled ovarian hyperstimulation. **Study dates** September 2007 to September 2009 **Source of funding** n/a	**Sample size** 180 women **Characteristics** **Inclusion Criteria** Not specified, but women undergoing 1st IVF cycle **Exclusion Criteria** Not specified	Age AMH - MIS/AMH ELISA FSH - Imunoassay test AFC - 5-10mm antral follicles Inhibin B - - MIS/AMH ELISA Blood taken on day3 and ultrasound on same day	Treatment All patients under-going long down-regulation protocol. Pre-treatment - oral contraceptive from day 3-5 of cycle for 28 days Ovarian suppression - GnRH from day 18-20 of cycle (600ug of buserlin) Ovarian stimulation - recombinant FSH (dose varied by patient) Trigger - HCG (10,000 IU) Statistical analysis Sample size based on 90% power and 0.01 significant meant 700 needed to be recruited. Normal distribution assessed using Shapiro Wilk test Student's t-test or Mann-Whitney U test for continuous variables Chi-squared or fishers exact test for categorical data	Poor ovarian reserve (<5 follicles) AMH (<=2.97 ng/ml) = Sensitivity 100%, specificity 89.6%, PPP 76.8%, NPP 100% AMH + Age (>=40) = Sensitivity 95.7%, specificity 91.0%, PPP 78.5%, NPP 98.4% AMH + Age + BMI (=>30kg/m2) = Sensitivity 91.3%, specificity 95.5%, PPP 87.5%, NPP 97.0% AMH + Age + BMI + AFC (<=10) = Sensitivity 91.3%, specificity 95.5%, PPP 87.5%, NPP 97.0% AMH + Age + BMI + AFC + FSH (=> 10 IU/L) = Sensitivity 91.3%, specificity 95.5%, PPP 87.5%, NPP 97.0% AMH + Age + BMI + AFC + FSH + Inhibin B (<45 pg/ml) = Sensitivity 91.3%, specificity 95.5%, PPP 87.5%, NPP 97.0% Failure to achieve pregnancy AMH = Sensitivity 75.3%, specificity 70.6%, PPP 91.6%, NPP 40.0%	**Limitations** QANDAS checklist: three items were unclear or not reported for blinding during analysis, reporting of dropouts, and if all results were reported. **Other information**

				AMH + Age = Sensitivity 94.5%, specificity 41.2%, PPP 87.3%, NPP 63.6% AMH + Age + BMI = Sensitivity 94.5%, specificity 41.2%, PPP 87.3%, NPP 63.6% AMH + Age + BMI + AFC = Sensitivity 93.2%, specificity 41.2%, PPP 87.2%, NPP 58.5% AMH + Age + BMI + AFC + FSH = Sensitivity 91.3%, specificity 95.5%, PPP 87.5%, NPP 97.0% AMH + Age + BMI + AFC + FSH + Inhibin B = Sensitivity 94.5%, specificity 35.3%, PPP 86.1%, NPP 54.7%	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Li,H.W.R., Yeung,W.S.B., Lau,E.Y.L., Ho,P.C., Ng,E.H.Y., Evaluating the performance of serum antimullerian hormone concentration in predicting the live birth rate of controlled ovarian stimulation and intrauterine insemination, Fertility and Sterility, 94, 2177-2181, 2010 **Ref ID** 148147 **Country/ies where the study was carried out** Hong Kong **Study type** Retrospective cohort study **Aim of the study** Evaluate the role of serum AMH concentration in predicting live birth rates of controlled ovarian stimulation and IUI treatment. **Study dates** Women seen between March 2004 to March 2008 for controlled ovarian stimulation and IUI. **Source of funding** University of Hong Kong	**Sample size** n = 243 **Characteristics** Median age = 35 (range 23 to 43) Median BMI = 20.5 (range 16.0 to 34.0) Cause of infertility: • Male factor = 45.3% • Unexplained = 23.5% • Mild endoemtriosis = 15.2% • Anovulation = 9.5% • Mixed = 6.2% Median AMH = 17.1 (range <0.7 to 275.4) pmol/L or 2.48 (range <0.98 to 38.57) ng/mL Median FSH = 7.7 (0.1 to 30.0) IU/L Median AFC = 9 (range 0 to 34) **Inclusion Criteria** Inclusion criteria: age <43, duration of infertility >1 year, bilateral tubal patency documented, and no medical contraindications to pregnancy. **Exclusion Criteria** Exclusion criteria: subjects undergoing controlled ovarian stimulation or IUI, conversion to IUI from IVF because of	AMH (Day 2) FSH (Day 2) E_2 (Day 2) Progesterone (Day 2) AFC	Sample size base on 80% power and p-value of 5%. Assuming a cumulative live birth rate in patients with serum AMH concentration below and above a cut-off value to be 20% and 40%, respectively. Sample size was 164. Mann-Whitney U test used for continuous variables X^2 used for categorical variables Predictive value based on ROC and logistic regression	Live birth rate • AMH level = AUC 0.682 (95% CI 0.578 to 0.786) • AFC = AUC 0.622 (95% CI 0.518 to 0.726) • Serum FSH = AUC 0.623 (95% CI 0.524 to 0.722) Cumlative live birth rate (3 cycles) • AMH level = AUC 0.668 (95% CI 0.589 to 0.747) • AFC = AUC 0.560 (95% CI 0.468 to 0.653) • Serum FSH = AUC 0.610 (95% CI 0.528 to 0.692) Cumulative live birth rate after 3 cycles of IVF (yes vs. no) Age = 34 (32-36) vs 35 (32-37), p = 0.621 BMI = 20.9 (19.4-22.7) vs 20.4 (19.2-21.9), p = 0.229 Cause of infertility (male, unexplained, anovulation and	**Limitations** QUADAS Drop-outs not explained Blinding during analysis not explained In addition: Retropsective analysis Live birth reference standard not explained Drop-outs not explained **Other information**

	poor ovarian response.			other) p = 0.77 Serum AMH (pmol/L, ng/mL) = 24.6 (13.3 to 51.7) vs. 14.6 (7.7 to 24.9), p<0.001 Serum FSH (IU/L) = 7.5 (6.0 to 8.4) vs 7.8 (6.9 to 9.9), p = 0.010 AFC = 11 (6 to 18) vs. 9 (6 to 13), p =0.191	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Lee,R.K., Wu,F.S., Lin,M.H., Lin,S.Y., Hwu,Y.M., The predictability of serum anti-Mullerian level in IVF/ICSI outcomes for patients of advanced reproductive age, Reproductive Biology and Endocrinology, 9, 115-, 2011 **Ref ID** 148489 **Country/ies where the study was carried out** Taiwan **Study type** Retrospective cohort study **Aim of the study** Investigate the practicicability of combining serum AMH level with biological age as a sompple screening method for counselling IVF candiadtes of advanced reproductive age with potential poor outcomes prior to treatment initiation. **Study dates** December 1st 2006 to May 31st 2010. **Source of funding** Not stated	**Sample size** 116 women aged 40 or more; 1538 reference cases of all ages **Characteristics** Variable: total subjects,Serum AMH (ng/mL) low (<= 0.48), Middle (0.49 to 1.22), High (>= 1.23) Total cycles: 116, 21, 38, 57 Cancelled cycle (%): 17 (14.7), 10 (47.6), 6 (15.7), 1 (1.7) Mean age: 41.5 (+/- 1.4), 42.8 (+/- 2.3), 41.1 (+/- 1.3), 41.3 (+/- 1.4) Peak E2 level (pg/mL): 1542.1 (+/- 1146.5), 802.6 (+/- 748.9), 1050 (+/- 699), 2095.8 (+/- 1156.2) Number of oocytes retrieved: 6.1 (+/- 4.6), 2.4 (+/- 2.9), 4.7 (+/- 2.5), 8.1 (+/- 5.1) Embryos obtained: 3.8 (+/- 2.9), 1.8 (+/- 2.4), 3.1 (+/- 2.2), 4.8 (+/- 3.1) Clinical pregnancy per cycle (%): 26 (22.4), 0 (0) , 9 (23.7), 17 (29.8) Viable pregnancy per cycle (FHB+ and >7 weeks)(%): 19	AMH levels Age	IVF treatment Various agonist and antagonist protocols were used for stimulation. 10,000 IU hCG was used for triggering when at least 2 follicles reached 14mm in diameter. Oocyte retrieval was performed 34 to 36 hours later. Conventional IVF or ICSI were performed 4 to 6 ours after occyte retrieval. Embryo transfer was performed 72 hours after oocyte retrieval. The number of embryos transferred was not mentioned. Luteal phase support was given by intramuscular injection of 50mg of progesterone and vaginal supplementation of 300mg micronised progesterone. AMH measurment. AMH measured by enzyme-linked immuno-sorbent assay kit. Detection range of the assy was between 0.025 to 15 ng/mL with detection limit of 0.017 ng/mL. Values below of the deteciton limit were considered as zero. Intra and inter assay variation coefficients were 4.6% and	Non-pregnancy AMH cut-off 1.05, ROCAUC = 0.65, Sensitivity = 42.7, Specificity = 86.9, PPV = 91.14, NPV = 31.7, p = 0.022	**Limitations** Restricted population means results may not be applicable to all women. **Other information**

	(46.4), 0 (0), 9 (23.7), 10 (17.5) **Inclusion Criteria** Eligible for IVF - one year of unprotected sexual intercourse but not pregnant **Exclusion Criteria** Menopause or early ovarian failure (day 3 serum FSH level > 10IU/mL) History of ovarian or adnexal surgery Suspicious findings of ovarian maligancy Presence of endocrine disorders - diabetes Severe overweight or underweight (BMI < 20 or >27)		8.0%. Samples obtained via venipuncture and analysed at the same laboratory. Samples according to manufacturer instructions. Pregnancy measurement Clinical pregnancy defined by ultrasound visualisation of gestational sac. Viable pregnancy definedas gestational sac greater than 7th week and documented fetal cardaic activity by ultrasound. Statistical analysis - Chi square or Fisher exact test. 95% CI caluclated based on binomial distribution using Wald method. - ROC - Sensitivity, specificity, NPV, PPV caluclated based on optimal AMH cut-off		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Andersen,A.N., Witjes,H., Gordon,K., Mannaerts,B., Predictive factors of ovarian response and clinical outcome after IVF/ICSI following a rFSH/GnRH antagonist protocol with or without oral contraceptive pre-treatment, Human Reproduction, 26, 3413-3423, 2011 **Ref ID** 154865 **Country/ies where the study was carried out** Denmark and Netherlands **Study type** Randomised controlled study **Aim of the study** Determine predictive factors of ovarian response for patients undergoing COS with rFSH in a gonadotrophin-releasing hormone antagonist protocol and to determine the inter-cycle variability of these factors. **Study dates** October 2006 to July 2008 **Source of funding** Study funded by Merck, Sharp and Dohme & Co.	**Sample size** 442 women were randomised to either oral contraceptive or not. **Characteristics** **Inclusion Criteria** Women aged 18 to 39 years old BMI <+ 32 kg/m^2 Menstrual cycle length of 24 to 35 days Access to ejaculatory sperm An indication for COS and IVF or ICSI. Signed a consent form **Exclusion Criteria** Endocrine abnormalities Less than two ovaries or other ovarian abnormality Presence of unilateral or bilateral hydrosalpinx Any relevant pathology affecting the uterine cavity Fibroids => 5cm Recurrent miscarriage (3 or more)	Serum AMH levels determined at central laboratory using a validated enzyme-linked immunosorbent assay (DSL, Webster, Tx, USA) with a detection limit of 0.1 ng/ml. Other tests undertaken, but outcome data not reported on these.	Tests Tests were measured at randomisation (cycle 1 day 2 or 3) and at stimulation day 1 (cycle 2 [day 2 to 3 in non-OC group and 5 days after last OC pill in OC group) to assess inter-cyclle variation. IVF protocol Patients randomised to either 200 IU rFSH in GnRH antangonist protocol with ot without OC pretreatment. Stimulation continued for a maximum of 19 days. Starting from day 5 all patients given 0.25mg ganirelix daily. rFSH dose changed based on response to stimulation Triggering with hCG when 3 or more follicles of => 17mm IVF or ICSI performed 34 to 36 hours after trigger. Maximum of 2 embryos transferred 3 or 5 days after oocyte retrevial in those aged 36 or less (or a maximum of 3 embryos in those aged more	Low overian response (< 6 ooctyes) AUC: AMH only = 0.84 AMH, FSH, AFC and age at menatche = 0.85 High ovarian response (> 18 oocytes) AUC: AMH only = 0.77 AMH, FSH, AFC and age at menatche = 0.80 30% of AMH measurements not reported due sample being unsuitable for analysis	**Limitations** Study was not established to examine AMH 30% of AMH measurements not reported due sample being unsuitable for analysis **Other information** Data collected on: Age, BMI, cycle length, age at menarche, duration of infertility, smoking, alcohol use. Also on ovarian volume, AFC, basal FSH, LH, testerone, progesterone, E2, inhibin B. However, data only presented on AMH alone.

	FSH or LH level >12 IU/l in the early follicular phase		than 36 years). Luteal phase support using daily progesterone (600 mg/ml vaginally or 50mg/day) for at least 6 weeks, unless no pregnancy. Statistcial analysis Sample size based on 10 events per variable for 5 predicitive variables, a sample size of 50 was needed, but 200 was planned. Analysis based on ITT Stepwise linear regression applied to identify predicitive factors. Regression models built based on predicitive variables identified. ROC AUC calculated to determine discrimiative power of model		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Ben-Haroush,A., Farhi,J., Zahalka,Y., Sapir,O., Meizner,I., Fisch,B., Small antral follicle count (2-5 mm) and ovarian volume for prediction of pregnancy in in vitro fertilization cycles, Gynecological Endocrinology, 27, 748-752, 2011 **Ref ID** 154885 **Country/ies where the study was carried out** Israel **Study type** Prospective cohort study **Aim of the study** To assess the value of AFC and other parameters as predictors of pregnancy in IVF. **Study dates** January to June 2009 **Source of funding** Not stated	**Sample size** 115 women undergoing IVF treatment. 38 were pregnant after IVF treatment. **Characteristics** Variable, Non-pregnant (n = 77), pregnant (n = 38), p-value Age (years): 33.6 (+/- 6.0), 32.3 (+/- 5.0), 0.260 BMI: 25.4 (+/- 6.0), 24.6 (+/- 5.4), 0.536 Basal FSH (IU/L): 6.6 (+/- 3.2), 8.1 (+/- 12.8), 0.369 Basal sperm count ($X10^6$/ml): 34 (+/- 33), 23 (+/- 29), 0.093 Basal 1 hour sperm motility (%): 35 (+/- 21), 33 (+/- 20), 0.559 Treatment number: 4.1 (+/- 3.3), 4.1 (3.0), 0.981 Primary infertility, n (%): 25 (32.5), 16 (42.1), 0.310 **Inclusion Criteria** Unselected cohort of consecutive women undergoing fresh IVF cycles. Women underwent various IVF protocols. **Exclusion Criteria**	Basal FSH Age Total AFC by ultrasound Small AFC (2 to 5mm) by ultrasound Large AFC (5 to 10mm) by ultrasound BMI	Treatment Treatment undertaken at a single IVF centre. Various IVF agonist and antagonist protocols used. FSH dose varied depending on follicular growth. Luteal phase support using progesterone (Utrogestan 600 mg/day or Endometrin 200mg/day. Use of standard IVF or ICSI determined by previous IVF performance. Ovarian reverse monitoring Ovarian response was monitored by vaginal ultrasound of follicular growth every 1 to 3 days. Embryos graded by morphological appearance under light microscopy at 48 to 72 hours after oocyte collection using Staessen criteria. Statistical analysis Group divided depending on outcome of IVF. Analyse	Variable for predicting pregnancy: AUC, 95% CI, p-value BMI: 0.447, 0.332 to 0.562, 0.358 Small AFC: 0.622, 0.515 to 0.730, 0.034 Large AFC: 0.541, 0.432 to 0.650, 0.476 Total AFC: 0.613, 0.505 to 0.722, 0.048 Age: 0.586, 0.472 to 0.700, 0.134 Basal FSH: 0.435. 0.328 to 0.571, 0.26	**Limitations** QUANDAS score: failed on 2 item Women had varying IVF protocols Method of testing not described in detail **Other information**

	Not stated		undertaking usung t-test or $X^{2.}$ AUC caluclated for pretreatment and treatment variables. Stepwise multivariate logistic regression performed for predictive values of pregnancy. Difference at p-value 0.05 considered significant.		

Fertility (Updated guideline)

What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nicopoullos,J.D., Almeida,P., Vourliotis,M., Goulding,R., Gilling-Smith,C., A decade of the sperm-washing programme: where are we now?, Human Fertility, 13, 90-97, 2010 **Ref ID** 77096 **Country/ies where the study was carried out** UK **Study type** Retrospective comparative cohort study **Aim of the study** To outline 10 years of sperm washing within a fertility centre **Study dates** From 1999 to 2008 **Source of funding** None reported	**Sample size** N = 259 couples **Characteristics** Male age (years) = 38.1 (24 to 66) Female age (years): IUI group= 34.2 ± 4.6 IVF group=35.7±4.4 ICSI group=35.3±4.6 Median CD4 count= 409 (range 20 to 1207 cells/mm^3) Viral load= 64% undetectable, range from 57 to 570,000 copies/ml when detectable Co-infectious morbidities: Female HIV= 23/259 (9.5%) Female Hep B= 2/259 (0.8%) Female Hep C= 3/259 (1.2%) Male Hep B= 13/259 (5.3%) Male Hep C= 26/259 (10.7%) Tubal factor= 186/259 (17.3%) Coexisting fertility factors: None= 98/259 (41.7%) Male= 88/259 (37.4%) Tubal= 41/259 (17.5%) Ovarian= 23/259 (9.8%) Endometriosis/fibroids=	Washed sperm used in IUI, IVF and ICSI	The majority of treatments (56.2%) used a natural cycle with 78.7% of cycles having only one follicle at either natural ovulation or hCG trigger Positive post-wash pre-insemination testing in 10 sperm samples and there was one testing kit failure. Positive tests resulted in the cancellation of treatment or the use of frozen sperm. Seroconversion testing methods: not reported	**Results** The differences between the groups were not compared for significance Preterm birth rate not reported for singleton or twin births Fetal abnormalities were not reported Maternal seroconversions were not reported **Comparison of three methods** Outcome / IUI / IVF / ICSI / Total Cycles started: 439 / 114 / 117 / 670 Seroconversions in children: 0/439 (0%) / 0/114 (0%) / 0/117 (0%) / 0/97 (0%) Singleton delivery: 31/439 (7%) / 21/114 (18%) / 17/117 (15%) / 69/670 (10%) Twin delivery: 2/439 (1%) / 7/114 (6%) / 5/117 (4%) / 14/670 (2%) Adverse pregnancy outcomes: 20/439 (5%) / 14/114 (12%) / 7/117 (6%) / 39/670 (6%)	**Limitations** The cohort was not recruited in an acceptable way. It had a combination of couples with normal and abnormal (41.7%) fertility results as well as couples with and without co-morbidities. They have not taken account of the design and/or analysis because no subgroup analysis was done taking into account sub-groups of the population such as co-morbidities, fertility problems **Other information** Total number of included couples is 259, whereas the total number of treated couples is reported at 308. This implies some couples received more than one type of treatment Adverse pregnancy outcomes included 18 miscarriages in the IUI group, 13 in the IVF group and 7 in the ICSI group, one ectopic pregnancy in the IVF group and two intrauterine deaths in the IUI group.

	21/259 (8.9%) **Inclusion criteria** Couples with an HIV positive man who received fertility treatment including sperm washing from 1999 to 2008 **Exclusion criteria** None reported				Ten cycles were cancelled, nine as a consequence of positive post-wash virus and one due to a kit failure 66.9% of men were on HAART at referral, a further 6.1% started during the trial 293/439 (67%) cycles performed on men with undetectable viral load (283 on anti-retroviral therapy)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bujan,L., Hollander,L., Coudert,M., Gilling-Smith,C., Vucetich,A., Guibert,J., Vernazza,P., Ohl,J., Weigel,M., Englert,Y., Semprini,A.E., CREAThE,network, Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network, AIDS, 21, 1909-1914, 2007a **Ref ID** 4002 **Country/ies where the study was carried out** Italy, France, Switzerland, UK, Germany and Belgium **Study type** Retrospective comparative cohort study **Aim of the study** To examine the safety and effectiveness of assisted reproduction using sperm washing for HIV-1-serodiscordant couples wishing to procreate where the male partner is infected **Study dates** From 1989 to 2003 **Source of funding** CREAThE received an unconditioned grant for the project by Serono, Italy. Support for the collection of	**Sample size** N = 1036 couples **Characteristics** A fertility screen was performed for both partners, but the results of this were not reported Male mean age (years) = 35.4 (24 to 66) Female mean age (years) = 32.3 (19 to 49) CD4 count was not reported, viral load was not reported Comorbidities were not reported **Inclusion criteria** Serodiscordant couples with an HIV-1 positive male **Exclusion criteria** Not reported	Sperm washing used in IVF, ICSI and IUI	Post-wash pre-insemination testing was not reported Assisted reproduction procedure choice was based on results of couples' fertility screen and each centre's protocol. After each assisted reproduction cycle with washed sperm, HIV screening was performed on the female partners. A further HIV test was performed at least 6 months after the last assisted reproductive treatment Washed samples with detectable HIV-genomes were not used for assisted reproduction.	**Results** No female seroconversion occurred following treatment in the 3272 cycles for which the results were known, thus an estimation of probability of contamination risk to be zero (95% CI, 0 – 0.09%) There was a significant difference in the number of deliveries per cycle between the groups – IVF resulted in significantly more deliveries than ICSI and IUI, and ICSI resulted in significantly more deliveries than IUI. IUI resulted in significantly fewer deliveries than IVF or ICSI. Seroconversion tests in children were not reported. Fetal abnormalities were not reported. The number of pre-term births was not reported. The gestational age at delivery was not reported. **Comparison of three methods** Outcome / IUI / IVF / ICSI / Total Cycles / 2840 / 107 / 394 / 3341 Deliveries / 327/2840 (12%) / 24/107 (22%) / 62/394 (16%) / 410/3341 (12%)	**Limitations** Since the results of this study was collated from different studies, it is difficult to tell if the author has reported or taken into account the confounding factors for the individual studies. The follow-up was not complete enough because 74 (7.1%) couples were lost to follow-up **Other information** Deliveries in this study referred to only live births. The adverse pregnancy outcomes include 112 miscarriages, 8 extrauterine pregnancies and 1 intrauterine death. Women from eight centres in six European countries were included in this study: Italy= 588 couples (1 centre) (57%) France= 287 couples (3 centres) (28%) Switzerland= 65 couples (1 centre) (6%) UK= 57 couples (1 centre) (5%) Germany= 29 couples (1 centre) (3%) Belgium= 10 couples (1 centre)

the Italian data (CSA-01-288) was provided by Conrad, Eastern Virginia Medical School, under a Cooperative Agreement with the USAID (HRN-A-00-98-00020-00), which in turn received funds for AIDS research from an interagency agreement with the Division of Reproductive Health, Centres for Disease Control and Prevention (CDC)				<table><tr><td></td><td>Live singleton births</td><td>Not reported</td><td>not reported</td><td>not reported</td><td>368/3341 (11%)</td></tr><tr><td></td><td>Live twin births</td><td>Not reported</td><td>not reported</td><td>not reported</td><td>29/3341 (1%)</td></tr><tr><td></td><td>Live triplet births</td><td>Not reported</td><td>not reported</td><td>not reported</td><td>13/3341 (1%)</td></tr><tr><td></td><td>Adverse pregnancy outcomes</td><td>Not reported</td><td>not reported</td><td>not reported</td><td>121/3341 (4%)</td></tr><tr><td></td><td>Seroconversion tests</td><td>0/2940 (0%)</td><td>0/107 (0%)</td><td>0/394 (0%)</td><td>0/3341 (0%)</td></tr></table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
Savasi,V., Ferrazzi,E., Lanzani,C., Oneta,M., Parrilla,B., Persico,T., Safety of sperm washing and ART outcome in 741 HIV-1-serodiscordant couples, Human Reproduction, 22, 772-777, 2007

Ref ID
4321

Country/ies where the study was carried out
Italy

Study type
Prospective comparative cohort study

Aim of the study
To evaluate the safety of sperm washing and assisted reproduction technique (ART) outcome offered to serodiscordant couples with an HIV-1 positive male

Study dates
From January 2002 to January 2006

Source of funding
None reported

Sample size
N= 741

IUI group= 581
ICSI group= 160

Characteristics
Overall mean age:
Male = 41 years ± 4.4
Female= not reported

Mean age in IUI group:
Male= 38 years ± 4
Female= 33.9 years ± 4.1

Mean age in IVF/ICSI group:
Male= 40 years ± 4
Female= 36 years ± 4

638 (86%) of the men were receiving antiretroviral therapy on admission to the trial

Median CD4 count x 106/l (interquartile range) = 510 (341 to 675)

Viral load:
< 50 copies/ml= 267 (36%) men
> 50 copies/ml= 824 (64%) men
Interquartile range= <50 to 5958

Comorbidities in male partners:
Hepatitis C= 437 (59%)
Hepatitis B= 296 (40%)

Inclusion criteria

Exclusion criteria

Experimental

IUI with washed sperm

Comparator

ICSI with washed sperm

Seroconversion testing

Post-wash pre-insemination testing had a 4% positive test rate and 2% of testing kits failed. Only sperm that tested negative post-wash was used in insemination. In the case of a positive test, frozen sperm was used in the ICSI group. No frozen sperm was used in the IUI group

Mothers: The status of the female partner was confirmed by HIV antibody testing and viral load measurements in the 2 weeks before and 2 to 3 weeks after each ART attempt. These tests were repeated 3 and 6 months after treatment and again at delivery

Children: Tested once after birth

Results
The number of preterm births, live singleton births, and multiple births are not reported in either group. The number of fetal abnormalities is not reported in either group. The number of deliveries and the number of adverse pregnancy outcomes are not reported in the ICSI group

Comparison of two methods

		IUI	ICSI
	Cycles	2400	283
	Adverse pregnancy outcomes	59/2400 (2%)	Not reported
	Number of deliveries	325/2400 (14%)	Not reported
	Maternal seroconversion	0/2400 (0%)	0/283 (0%)
	Child seroconversion	0/2400 (0%)	0/283 (0%)

Limitations
The results from cycles that have used frozen sperm have not been analysed differently from those using fresh sperm

The follow-up of subjects was not complete enough as there were 72 ongoing pregnancies

The follow-up of subjects was not long enough as there was no reported HIV testing beyond the third month for 256 (44%) of women who did not deliver

Other information
Some of the women in this study may also be included in the Bujan (2007a) study. The Bujan study uses data from Italy from 1989 to 2003, although it is not clear if it uses women from the same centre or not

The study does not report the results of IVF and ICSI cycles separately

Of the adverse pregnancy outcomes in the IUI group, 54

	Sero discordant couples with HIV-infected male partner, seeking medical assistance Condom protected intercourse only CD4+ lymphocytes > 200/mm3 at least twice in the 4 months before treatment Stable viral load with no increase>0.5 log in two successive samples during the 4 months before treatment, Infection by a quantifiable amplifiable strain of HIV-1 Not reported				were miscarriages and 5 were tubal pregnancies The number of deliveries resulting from the multiple pregnancies was not reported, although there were a total of 337 newborn babies reported from 325 deliveries. It is not reported whether these came from twin, triplet or higher gestation pregnancies. The gestational age at which babies were delivered is not reported. Five IVF/ICSI cycles were cancelled – the reason for this is not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kashima,K., Takakuwa,K., Suzuki,M., Makino,M., Kaneko,S., Kato,S., Hanabusa,H., Tanaka,K., Studies of assisted reproduction techniques (ART) for HIV-1-discordant couples using washed sperm and the nested PCR method: A comparison of the pregnancy rates in HIV-1-discordant couples and control couples, Japanese Journal of Infectious Diseases, 62, 173-176, 2009 **Ref ID** 77085 **Country/ies where the study was carried out** Japan **Study type** Prospective comparative cohort study **Aim of the study** To evaluate the efficacy and safety of assisted reproduction techniques with sperm-washing method and nested PCR in HIV-1 discordant couples **Study dates** From January 2001 to July 2007 **Source of funding** Supported partly by grants from the Ministry of Health, Labour and Welfare in Japan	**Sample size** N= 444 Experimental group= 27 couples Control group= 417 couples **Characteristics** Mean female age: Washed sperm group= 32.3±5.0 years (range 21 to 41) Control group= 34.2 years ±3.5 and 35.6 years ±3.9 Median CD4 cell count = 377 cells/ml Viral load: <50 copies/ml= 15 men Mean viral load (excluding those <50 copies/ml)= 967 copies/ml (range 100 to 100,000) Comorbidities and existing fertility problems were not reported **Inclusion criteria** Serodiscordant couples with an HIV positive man willing to undergo fertility treatment with washed sperm **Exclusion criteria** None reported	IVF with washed sperm vs. IVF with unwashed sperm from HIV negative men ICSI with washed sperm vs. ICSI with unwashed sperm from HIV negative men	Control couples matched to the woman's age Only frozen sperm was used in this study IVF/ICSI: the standard long protocol was adopted for most ovulation stimulation cycles but short protocol used for poor responders. After testing and obtaining negative test for viron RNA and proviral DNA, the other portion of sperm was thawed and used for IVF or ICSI. The insemination method offered depended on the semen profile of each male. Embryos were tested for HIV and only those without HIV were transferred. It is not clear how many embryos tested positive and whether cycles were cancelled as a result Seroconversion tests:All female partners were tested for HIV antibodies, HIV-RNA and proviral DNA 1, 2 and 3 months after the embryo transfer. Babies born to mothers were also tested at birth or later	**Results** HIV-1 RNA and proviral DNA were negative in all of the females and infants throughout the study The gestational age at which the babies were born was not reported The number of fetal abnormalities and adverse pregnancy outcomes were not reported **Comparison of two methods** | Outcomes	IVF with washed sperm	IVF with unwashed sperm
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Cycles	13	465
Seroconversions in children	0/13 (0%)	0/465 (0%)
Seroconversions in mothers	0/13 (0%)	0/465 (0%)
Delivered pregnancy rate	8/13 (62%)	91/465 (20%)
Multiple pregnancy rate	3/13 (23%)	15/465 (3%)		**Limitations** There is a small sample size in the experimental group **Other information** Two cycles were cancelled due to a poor response and three due to a lack of fertilisation, although the study did not report which group/s these were in The study authors report 'delivered pregnancy rate' for singleton and multiple pregnancies and it is not clear whether this includes only live births or whether it also includes still births It is not clear whether the multiple pregnancy rate is included in the 'delivered pregnancy rate' or not The number of babies in each multiple pregnancy was not reported

Comparison of two methods
B

	Outcomes	ICSI with washed sperm	ICSI with washed sperm
	Cycles	23	209
	Seroconversions in children	0/23 (0%)	0/209 (0%)
	Seroconversions in mothers	0/23 (0%)	0/209 (0%)
	Delivered pregnancy rate	9/23 (39%)	47/209 (22%)
	Multiple pregnancy rate	2/23 (9%)	6/209 (3%)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Marina,S., Marina,F., Alcolea,R., Exposito,R., Huguet,J., Nadal,J., Verges,A., Human immunodeficiency virus type 1--serodiscordant couples can bear healthy children after undergoing intrauterine insemination, Fertility and Sterility, 70, 35-39, 1998 **Ref ID** 77090 **Country/ies where the study was carried out** Spain **Study type** Prospective non comparative cohort study **Aim of the study** To use semen from men who were seropositive for HIV-1 to inseminate their partners without infecting them. **Study dates** None reported **Source of funding** None reported	**Sample size** N= 63 couples **Characteristics** Women were tested for fertility problems – tests were normal apart from 'some' cases of ovulatory alterations Male mean age= 31.9 years Female mean age= 28.8 years **Inclusion criteria** HIV-1 seropositive men in one of the stages of AIDS, A_1, A_2, B_1, or B_2 according to the CDC classification Normal semen according to the WHO parameters or ≥4 X 10^6 motile spermatozoa after washing HIV-1-seronegative women aware of their partners HIV status **Exclusion criteria** None reported	IUI with sperm washing	Post-wash pre-insemination testing was positive for HIV in 6 samples. These samples were not used in the treatment. Maternal testing at 1, 3 and 6 months after the last IUI. Women with infants were tested again after delivery. Children were tested shortly after birth (exact time scale not reported)	**Results** The number of preterm births, fetal abnormalities and adverse pregnancy outcomes was not reported. **Observation of outcomes of one method** IUI Cycles: 101 Deliveries: 28/101 (28%) Delivered Babies: 37/101 (37%) Live singletons delivered: 20/101 (20%) Live sets of twins delivered: 7/101 (7%) Live sets of triplets delivered: 1/101 (1%) Perinatal death: 2/101 (2%) (1 twin and 1 triplet)	**Limitations** The authors have not identified the confounding factors. Some women in the study had ovulatory alterations and the analysis did not take this into account **Other information** 47/63 (74.6%) of the men were receiving antiretroviral treatment 6/101 (5.6%) semen samples tested positive for HIV-1 DNA after sperm washing. These samples were not used in IUI. The 6 women involved underwent other cycles with sperm negative for HIV-1. Frozen semen was not used in any of the women

				Viral transmission rate (maternal) 0/101 (0%) Viral transmission rate (neonatal) 0/101 (0%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mencaglia,L., Falcone,P., Lentini,G.M., Consigli,S., Pisoni,M., Lofiego,V., Guidetti,R., Piomboni,P., De,Leo,V, ICSI for treatment of human immunodeficiency virus and hepatitis C virus-serodiscordant couples with infected male partner, Human Reproduction, 20, 2242-2246, 2005 **Ref ID** 77092 **Country/ies where the study was carried out** Italy **Study type** Prospective non comparative cohort study **Aim of the study** To determine whether a particular protocol for ICSI in serodiscordant couples in which the male partner has HIV and/or hepatitis C is effective **Study dates** From January 2001 to December 2003 **Source of funding** None reported	**Sample size** N= 43 couples **Characteristics** Cormorbidities are not reported HIV seropositive males= 25/43 (58%) HIV and hepatitis C seropositive males= 10/43 (23%) Hepatitis C seropositive males= 8/43 (19%) Female mean age (years) = 34.95 years ±2.9 **Inclusion criteria** Male partner with plasma viral load of <50 copies of HIV and/or HCV RNA/ml Men had to be in good general health and stable CD4+ T-cell count for the past 6 months HIV- and HCV- seronegative females Condom protected sexual intercourse General reproductive screening was performed in all couples, but the results of this are not reported **Exclusion criteria** None reported	Washed sperm with ICSI	Post-wash pre-insemination testing of sperm for HIV was not reported Maternal testing at 1, 3 and 6 months after the last IUI. Women with infants were tested again after delivery. Children were tested shortly after birth (exact time scale not reported)	**Results** Number of deliveries, preterm births, and multiples births is not reported. The number of fetal abnormalities and the number of adverse pregnancy outcomes is not reported. **Observation of outcomes of one method** Outcome: ICSI Cycles: 78 Seroconversion tests (maternal): 0 Seroconversion tests (neonatal): 0	**Limitations** No serious limitations **Other information** Mean number of embryos transferred= 3.55 ± 1.11. Four or five embryos were transferred only if the women were aged > 36 years and failed the first ICSI cycle. Two men had received interferon therapy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Semprini,A.E., Levi-Setti,P., Bozzo,M., Ravizza,M., Taglioretti,A., Sulpizio,P., Albani,E., Oneta,M., Pardi,G., Insemination of HIV-negative women with processed semen of HIV-positive partners, Lancet, 340, 1317-1319, 1992 **Ref ID** 77866 **Country/ies where the study was carried out** Italy **Study type** Prospective non comparative cohort study **Aim of the study** To test the efficacy of sperm washing procedures to remove cell-free HIV **Study dates** None reported **Source of funding** None reported	**Sample size** 29 couples **Characteristics** Pre-exclusion: Male Mean (SD) years = 31 (3.8) years Female mean (SD) years = 30 (3.8) years Not reported after inclusion/exclusion CD4 count= not reported Viral load = not reported Comorbidites = not reported (couples were tested for syphilis, HBsAg, hepatitis C and cytomegalovirus, but the results of these tests were not reported) **Inclusion criteria** Couples who were serodiscordant for HIV Arbitrary spermatozoa ≥1.5 million with linear progressive motility Females with confirmed tubal patency, normal ovulatory function and no cervical pathogens **Exclusion criteria**	Washed sperm and IUI	Post-wash pre-insemination testing was conducted, but it was not reported whether the positive results led to cancelled cycles or whether frozen sperm were used instead A single IUI attempt per cycle was timed Seroconversion testing: Absence of HIV antibodies was checked before each insemination procedure and subsequently at 3 monthly follow-ups for a year	**Results** In 18 women, HIV negativity was confirmed 18 months from the earliest insemination attempt Fetal abnormalities were not reported **Observation of outcomes of one method** Outcomes: IUI Cycles: 59 Live singleton birth: 5/59 (8%) Live multiple birth: 3/59 (5%) (2 twin pregnancies and 1 triplet pregnancy) Adverse pregnancy outcome: 5/59 (8%) Pre-term births (=: 1/59 (2%) (1 twin birth) Seroconversion in mothers: 0/59 (0%)	**Limitations** The authors have not identified confounding factors - they only reported baseline characteristics of the couples prior to applying exclusion criteria and did not assess whether they differed significantly from the final group of couples Follow-up was incomplete because five pregnancies were still ongoing when the study was published (gestational ages of 35, 32, 21, 21 and 25) and so their data is also incomplete) Follow-up was also not long enough because women who did not conceive were not tested beyond 3 months **Other information** Adverse pregnancy outcomes in this study included preclinical miscarriages (n=3) and miscarriages at 7 weeks (n=2) The preterm birth was a twin pregnancy delivered at 35 weeks. Both babies survived. Some of the women in this study may also be included in the Bujan (2007a) study. The Bujan study uses data from

	None reported			Seroconversion in children: 0/59 (0%)	Italy from 1989 to 2003, although it is not clear if it uses women from the same centre or not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sauer,M.V., Wang,J.G., Douglas,N.C., Nakhuda,G.S., Vardhana,P., Jovanovic,V., Guarnaccia,M.M., Providing fertility care to men seropositive for human immunodeficiency virus: reviewing 10 years of experience and 420 consecutive cycles of in vitro fertilization and intracytoplasmic sperm injection, Fertility and Sterility, 91, 2455-2460, 2009 **Ref ID** 75574 **Country/ies where the study was carried out** USA **Study type** Retrospective non comparative cohort study **Aim of the study** A review of 10 years of experience providing fertility care to men seropositive for human immunodeficiency virus (HIV) using sperm washing and in vitro fertilization with intracytoplasmic sperm injection (ICSI) **Study dates** From January 1998 to December 2007 **Source of funding** None reported	**Sample size** N= 181 **Characteristics** Demographics HIV-serodiscordant couples, N = 181 Age of Male partner (years) = 37.5 ± 0.4 (Mean ± SEM), 22-51 (Range) Age of Female partner (years) = 33.8 ± 0.3 (mean ± SEM), 21 - 49 (Range) Baseline Characteristics All women were tested for HIV, gonorrhoea, Chlamydia, syphilis, hepatitis B and hepatitis C – the results of these tests were not reported <u>Male partner</u> Mean age= 37.5 years ±0.4 (range 22 to 51 years)	ICSI with washed sperm in serodiscordant couples	Post-wash pre-insemination testing of sperm for HIV was not reported Seroconversion testing: Pregnant patients were tested for HIV during each trimester of pregnancy in the immediate postpartum period, and again within 6 months of delivery. Infants were tested neonatally and at 3 to 6 months of age.	**Results** **Observation of outcomes of one method** Outcome: ICSI Cycles: 420 Deliveries: 116/420 (28%) Fetal abnormalities: 1/420 (Adverse pregnancy outcome: 26/420 (6%) Live infants: 170/420 (40%) Live deliveries at full term (> 37 weeks): 96/420 (23%) Pre-term deliveries (: 37/420 (9%) (6 singleton, 25 twin and 6 triplet pregnancies) Pre-term infants (: 74/420 (18%)	**Limitations** The authors have not identified confounding factors such as the fact that the cohort was made of 76 men with abnormal and normal semen analysis There was no subgroup analysis to adjust for the confounding factor The follow-up of the subjects was not complete enough as 18 pregnancies were still ongoing when the study was published **Other information** Adverse pregnancy outcomes were 21 spontaneous abortions and 5 ectopic pregnancies. All of the ectopic pregnancies were successfully treated One fetal abnormality was reported (trisomy 21), but this was in the context of the number of terminations of pregnancy and there may have been additional pregnancies with abnormalities that were not terminated. 157 (87%) of the men were on antiretroviral therapy. If the disease was not well controlled, they were prescribed HAART

	Comorbidities: Haemophillia= 21 (11%) Hepatitis B= 12 (7%) Hepatitis C= 27 (15%) Undetectable viral load= 107 (59%) Detectable viral load= 74 (41%) Mean detectable viral load= 3181.5 copies/ml ± 805.4 (range 87 to 29618) $CD4^+$ T-cell count= 608.3/mm^3 ± 24.2 (range 96 to 1810) <u>Female partner</u> Mean age= 33.8 years ±0.3 (range 21 to 49) Advanced maternal age= 85 (47%) (definition of advanced maternal age not given) **Inclusion criteria** Couples were required to attest to safe sex practices			<table><tr><td></td><td>Live singleton deliveries</td><td>68/420 (16%)</td></tr><tr><td></td><td>Live twin deliveries</td><td>42/420 (10%)</td></tr><tr><td></td><td>Live triplet deliveries</td><td>6/420 (1%)</td></tr><tr><td></td><td>Maternal seroconversion</td><td>0/420 (0%)</td></tr><tr><td></td><td>Child seroconversion</td><td>0/420 (0%)</td></tr></table>	Gestational age at delivery ranged from 26 to 41 weeks (mean of 38.9 weeks ±0.1 for term babies and 33.4 weeks ±0.5 for preterm babies) 355 (85%) of the cycles were performed using fresh embryos, the remaining 65 (15%)were performed with frozen embryo transfer

	Male partners were required to be under the care of an infectious disease specialist and have no evidence of acquired immunodeficiency syndrome or worsening infection Stable HIV viral loads (<50, 000 copies/mL) and CD4 counts (>250 cells/mm^3) over a 6-month period before enrolment Oligospermic men had to have at least 1 million total motile sperm **Exclusion criteria** Men with any evidence of acquired immunodeficiency syndrome (AIDS) or worsening infection Women with HIV				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bujan,L., Sergerie,M., Kiffer,N., Moinard,N., Seguela,G., Mercadier,B., Rhone,P., Pasquier,C., Daudin,M., Good efficiency of intrauterine insemination programme for serodiscordant couples with HIV-1 infected male partner: a retrospective comparative study, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 135, 76-82, 2007 **Ref ID** 4001 **Country/ies where the study was carried out** France **Study type** Retrospective comparative cohort study **Aim of the study** To investigate the efficiency of sperm washing and IUI in serodiscordant couples with HIV-1 infected male partner **Study dates** From June 2000 to October 2003 **Source of funding** Grant ANRS 096 from the Agence National de Recherche sur le SIDA, Paris, France	**Sample size** N = 365 Sperm washing group= 84 couples Control groups: IUI with semen donor= 90 couples ICI with semen donor= 191 couples **Characteristics** Female age: Sperm washing group=33.16 years ± 4.45 Control group = 32.59 years ± 4.08 Women's age did not differ significantly between groups Male Age: Sperm washing group= 32.3 years ± 5.5 Control group= not reported Fertility tests showed no significant differences between females in both groups Mean $CD4^+$ T-cell count = 610 ± 243 mm^3	IUI with washed sperm <u>Comparators:</u> IUI with donor semen ICI with donor semen	Post-wash pre-insemination testing was not reported HIV-1 screening was performed in the women at the beginning of each IUI cycle (10-15days before IUI), at 1, 3 and 6 months after IUI and at delivery in the case of pregnancy. Method of IUI chosen depended on results of an assessment of the woman's fertility	**Results** There was no significant difference in pregnancy rates per couple, multiple pregnancy rates, or baby take-home rates between the two groups There were no seroconversions in any of the women of serodiscordant couples Seroconversion in the children, the number of preterm births and the number of fetal abnormalities are not reported **Comparison of three methods** | Outcomes	IUI with washed sperm	IUI with semen donor	ICI with semen donor | |---|---|---|---| | Cycles	294	320	320 | | Seroconversions in mothers	0/294 (0%)	0	0 | | Deliveries	44/294 (15%)	37/320 (12%)	64/630 (10%) | | Live birth rate	52.4%	41.1%	33.5% | | Twin pregnancies	6/294 (2%)	6/320 (2%)	5/320 (2%)		**Limitations** Follow-up of the subjects was not complete enough as 4 women were lost to follow-up The sperm characteristics of the donor semen and washed sperm were not compared. **Other information** Only frozen sperm were used in this study, in both the control and washed sperm groups Reported adverse pregnancy outcomes consisted of 9 miscarriages in the experimental group, 10 in the IUI control group and 14 in the ICI control group The term 'deliveries' is used, and it is not clear whether this includes stillbirths as well as live births It is not reported whether the twin and triplet pregnancies delivered live babies, what gestational age they delivered at or whether they miscarried 81 (96.4%) of the men in the experimental group were receiving HAART

	Mean viral load: Blood= 633±3696 copies/ml Seminal= 581±1377 copies/ml **Inclusion criteria** Couples seen at a male sterility centre For the experimental group: HIV-1 seropositive men that were clinically asymptomatic, in good health, with a CD4 count >200mm^3 and stable viral load for at least 4 months who had seronegative female partners aware of their HIV status and who had only condom protected intercourse **Exclusion criteria** Couples where the man had azoospermia or severe oligospermia			<table><tr><td></td><td>Triplet pregnancies</td><td>1/294 (</td><td>1/320</td><td>0/320 (0%)</td></tr><tr><td></td><td>Adverse pregnancy outcomes</td><td>9/294 (3%)</td><td>10/320 (3%)</td><td>14/320 (4%)</td></tr></table>	The HIV group in this study are also included in the larger Bujan (2007) study (Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network). However, not all of the comparisons reported in this study are presented in the larger study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Garrido,N., Meseguer,M., Bellver,J., Remohi,J., Simon,C., Pellicer,A., Report of the results of a 2 year programme of sperm wash and ICSI treatment for human immunodeficiency virus and hepatitis C virus serodiscordant couples, Human Reproduction, 19, 2581-2586, 2004 **Ref ID** 77074 **Country/ies where the study was carried out** Spain **Study type** Retrospective non comparative cohort study **Aim of the study** To evaluate the results of ICSI treatment for HIV and HCV serodiscordant couples **Study dates** From August 2001 to October 2003 **Source of funding** None reported	**Sample size** N= 91 couples **Characteristics** HIV positive males= 18/91 (20%) Couples with hepatitis C/HIV positive males= 33/91 (36%) Infertile couples with a hepatitis C positive male= 40/91 (44%) Male mean age = 36.6 years (range 25 to 47) Mean viral load: HIV = 48,623 copies/ml (range 74 to 525,000 IU/ml) HCV= 125,000 copies (range 31,750 to 2,500,000) Undetectable viral load for HIV= 46/91 (51%) Undetectable viral load for HCV= 56/91 (62%) CD4 count = 502.7 cells/mm^3 (range 26 to 1664) HCV seropositive males, viral load = 31750 – 2500000 Male comorbidities were not reported Female fertility status: Normal= 59 (65%) >36 years old= 15 (16%)	ICSI with washed sperm	Depending on patient characteristics, women were treated with two assisted reproduction procedures: ICSI with their own oocyte or with oocytes obtained from young healthy donors. Two (8%) of the samples from men with HIV alone tested positive for HIV in post-wash pre-insemination testing. Six (12%) of the samples from men with HIV and HCV tested positive for HIV and 6 (11%) for HCV in post-wash testing. Four (7%) of the samples from men with HCV alone tested positive for HCV in post-wash testing. In cases where a positive post-wash pre-insemination result was obtained, the sample was destroyed and another sperm wash was programmed after 2 – 3 weeks. No positive results were obtained after a second wash. Seroconversion tests for the female partner were programmed 3 and 6 months after finishing each embryo transfer treatment.	**Results** The number of cycles and the number of live singleton births is not reported separately for the HIV, HIV with HCV and the HCV alone groups. The number of births from multiple pregnancies was not reported. The number of adverse pregnancy outcomes, fetal abnormalities and preterm births were not reported. Seroconversion in the babies was not reported **Observation of outcomes of one method** Outcome: Cycles — ICSI: 113 Outcome: Delivered live babies — ICSI: 23/113 (20%) Outcome: Viral transmission rate (maternal) — ICSI: 0/113 (0%)	**Limitations** No serious limitations **Other information** One pregnancy was terminated, although the reason for this was not reported Six (10.3%) of the men with HIV were not receiving antiretroviral treatment

	Low responders= 5 (6%) Endometriosis= 8 (9%) Not reported= 4 (4%) **Inclusion criteria** Females with absence of HIV and HCV antibodies Condom protected intercourse **Exclusion criteria** None reported				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wu,M.Y., Chang,L.J., Chen,M.J., Chao,K.H., Yang,Y.S., Ho,H.N., Outcomes of assisted reproductive techniques for HIV-1-discordant couples using thawed washed sperm in Taiwan: Comparison with control and testicular sperm extraction/microscopic epididymal sperm aspiration groups, Journal of the Formosan Medical Association, 110, 495-500, 2011 **Ref ID** 132034 **Country/ies where the study was carried out** Taiwan **Study type** Prospective observational study **Aim of the study** Not reported **Study dates** 2005 to 2009 **Source of funding** Not reported	**Sample size** n = 14 serodiscordant couples **Characteristics** Female mean age ± SD = 33.3 ± 4.9 years Male mean age ± SD = 36.1 ± 3.6 years $CD4^+$ >250/mm^3 = 6/6 Serum HIV-1 <40 copies/ml = 6/7 **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1. Washed sperm (fresh and frozen) with ICSI 2. Frozen sperm with ICSI 3. Testicular sperm extraction/microscopic epididymal sperm aspiration (TESE/MESA) with ICSI	Recruitment of serodiscordant couples:The subject couples were seeking reporductive services. HIV-1 infection status of the couples including $CD4^+$ cells and plasma viral load was assessed first. Gynecological examinations including pelvic ultrasound, and hormone profiles, and semen analysis were subsequently performed to decide which couples would receive IUI or IVF cycles. Indications for IVF in these HIV-1 discordant couples were the same as for other patients. Recruitment of control couples: To verify the pregnancy rates of HIV-1 discordant coupes, another two groups were enrolled within the study period. First group was the normal control group who were using frozen sperm for personal reasons because the husband was often abroad for business. The few cases where IVF was applied were excluded, so only ICSI cases were enrolled. The second group was the TESE/MESA group. The sperm specimens were always frozen because the operation by the urologists might not match the TVOR schedule.	**Results** **Comparison of three methods** Outcomes: ICSI with washed sperm; ICSI with frozen sperm; ICSI with TESE/MESA Clinical pregnancy: 30/68 (44.1%); 4/14 (28.6%); 20/36 (55.6%) **Observation of outcomes of one method** Outcome: ICSI with washed sperm Cycles: 22 Clinical pregnancy (fresh): 5/14 (35.7%) Clinical pregnancy (frozen): 3/14 (21.4%) Multiple pregnancy: 2/14 (14.3%) Adverse pregnancy: 1/14 (7.1%)	**Limitations** 1. Semen analysis and fertility results of couples were not reported and it is not clear whether there were pre-existing fertility problems that might have affected the results. 2. Incomplete reporting: Post-wash testing was performed but the results were not reported. It is not clear whether follow-up was complete in women that did not conceive **Other information** 1. Of the 14 couples that participated, there was one case in which an oocyte was fertilised but did not show cleavage and so did not undergo embryo transfer.

			Serodiscordant couples: Semen samples were processed using a density grdient and after centrifugation and swim-up a supernatant volume was recovered per testup and one of the aliquots was tested for detectable HIV-1 RNA. Results were tested for HIV-1 RNA using PCR and visualised on a computer. Sensitivity ranged from 40 copies/mL to 10,000,000 copies/mL. ICSI was performed in all 14 cases after a long gonadotropin-releasing hormone agonist protocol or by short protocols for some poor responders. rFSH was given on day 3 or day 5 depending on protocol type and oocyte retrieval performed 34 to 36 hours after hCG administration. Cleavage stage transfer of no more than 4 embryos was followed by luteal phase support. Patients were screened for HIV-1 negativity at the beginning of the trial and 6 months after insemination. There was follow-up of women and babies from 14 months to 52 months.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Schuffner,A., Lisboa,A.P., da,Rosa,V, da Silva,M.M., Use of assisted reproductive technology to separate sperm from human immunodeficiency virus infected men resulting in pregnancy among serodiscordant couples, Brazilian Journal of Infectious Diseases, 15, 397-398, 2011 **Ref ID** 155011 **Country/ies where the study was carried out** Not reported **Study type** Case series **Aim of the study** To report pregnancies following intrauterine insemination in HIV type 1 seronegative women after the use of processed semen from their seropositive husband. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 10 serodiscordant couples n = 10 intrauterine inseminations. **Characteristics** Female age = <35 years. **Inclusion criteria** Not reported **Exclusion criteria** Not reported	Sperm washing with IUI	Participants: All men were on anti-retroviral medication and presented undetectable plasma HIV-1 viral loads. Following a sexual abstinence period between 2 to 5 days, semen samples were collected by masturbation. Intervention: Sperm was processed by discontinuous gradient centrifugation and repeated washing, followed by a swim-up procedure. A fraction of the final volume was tested with an ultrasensitive method of HIV-1 RNA detection with a threshold of 50 copies. The remainder was cryropreserved till results of HIV testing were obtained. Treated sperm was only used if the results of the testing of the final product showed HIV levels below the detection limit of the test. Before treatment, couples were submitted to a complete infertility work up. All women undergone ovarian stimulation with gonadotrophins in order to obtain more than one follicle. Follow up was done one month and three months post insemination, as well as, twelve months after (on mother and babies).	**Results** **Observation of outcomes of one method** Outcome: IUI with washed sperm Cycles: 10 Pregnancy rate: 4/10 (40%) Seroconversion in mothers: 0/10 (0%) Seroconversion in babies: 0/10 (0%)	**Limitations** 1. Study design 2. Incomplete reporting on patient characteristics 3. Small sample size **Other information**

Fertility (Updated guideline)

Transmission with low viral load studies and PrEP studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Vernazza,P.L., Graf,I., Sonnenberg-Schwan,U., Geit,M., Meurer,A., Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child, AIDS, ePub Ahead of Print, -, 2011 **Ref ID** 137213 **Country/ies where the study was carried out** Switzerland **Study type** Case series **Aim of the study** Not reported **Study dates** February 2004 **Source of funding** Not reported	**Sample size** n = 46 couples **Characteristics** Female median age at time of conception = 33 years **Inclusion criteria** 1] Male partner was under fully suppressed HIV therapy (HIV-RNA <50 copies/ml) for at least 6 months. **Exclusion criteria** Not reported	1] timed intercourse with Preexposure prophylaxis 2] Insemination with processed semen.	Recruitment:The program was started in February 2004. Serodiscordant couples (male partner HIV-positive) who attended the counseling service for artificial insemination with processed semen received an update regarding current knowledge on HIV transmission under HAART. During the first 3 years of the program, couples were given information about two alternative ways to conceive a child: insemination with processed semen at the clinic or timed intercourse. After the counseling visit, couples received e-mail or telephone interviews. The counseling was guided by a structured guideline and the following guidelines were proposed to the couples: 1] Male partner has been successfully treated with undetectable HIV-RNA in plasma (<50 copies/ml) without the need of HIV-RNA testing in semen. 2] No report of current symptoms of genital infections	Seroconversion: PrEP = 0/46	**Limitations** Non-comparative study design Sample size **Other information** 1] 9/46 women just perfomred timed intercourse and were not seroconverted

			and no unprotected sex with other partners 3] LH-test in the uring is used to determine the optimal time of conception (36h after LH-peak) 4] Administration of PrEP with tenofovir, first dose at LH-peak and second 24h later. 5] After six unsuccessful attempts, a fertility evaluation was suggested <u>Intervention:</u> Timed intercourse with PrEP consisted of daily determination of LH-peak in urine to optimise the timing of sexual intercourse and two doses of tenofovir. The female partner took the first dose of tenofovir in the morning of the LH-peak and a second dose the next morning. Intercourse was timed at the evening after the second dose of tenofovir. Women whose male partners were treated with a coformulated tenofovir and emtricitabine did use the partner's Truvada instead of tenofovir with the same dosing interval as described.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Castilla,J., Del,Romero J., Hernando,V., Marincovich,B., Garcia,S., Rodriguez,C., Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV, Journal of Acquired Immune Deficiency Syndromes: JAIDS, 40, 96-101, 2005 **Ref ID** 132190 **Country/ies where the study was carried out** Spain **Study type** Prospective cohort study **Aim of the study** To evaluate the effectiveness of HAART in reduction of sexual transmission of HIV **Study dates** January 1991 to December 2003 **Source of funding** Supported by a grant from FIPSE and by the Spanish Networks for Research on AIDS (RIS) and Public Health (RCESP) which are funded by the Instituto de Salud Carlos III.	**Sample size** n = 393 couples **Characteristics** Not reported **Inclusion criteria** 1] Ongoing sexual relationship during the pas 6 months in which one of the partners had been diagnosed with HIV-1 with a well-identified probable route of infection and the nonindex partner had not had a previous diagnosis of HIV 2] Where the sexual relationship with the index case was the sole known risk exposure. **Exclusion criteria** Not reported	1] HAART 2] Non-HAART	The study was conducted in a clinic that launched a specific program for HIV-serodiscordant sexual couples in 1987. Stable heterosexual couples attending the program were prospectively included in an observational study to analyse HIV sexual transmission risk, determinant factors, and needs related to prevention and reporduction aspects. Couples were recruited when the non-index partner came to the clinic for first HIV test within the study period. Data collection: Both members of each couple were interviewed separately during a medical visit by means of a structured questionnaire before the serologic HIV result for the nonindex partner was known. The information collected for index cases included sociodemographic characteristics, probable route of infection, date of HIV infection diagnosis, AIDS-defining diseases, last CD4 lymphocyte count, and antiretroviral treatments. Plasma HIV RNA level was available since 1997. The history of sexually transmitted diseases and presence of	Seroconversion by female +male index cases: HAART = 0/66 Non-HAART = 7/113 Seroconversion by male index cases (n = 142): HAART = 0 Non-HAART = 5	**Limitations** The authors reported that with the results, it is difficult to rule out the effect of factors other than antiretroviral therapy on the reduction of HIV prevalence among the nonindex partners. **Other information** It is not clear how many male index cases were in the HAART and Non-HAART group.

			dysuria, genital discharge, ulcers, or warts were obtained through anamnesis and medical examination. HAART has been available free of charge in Spain to all patients since 1997. With this fact in mind, HIV prevalence among nonindex partners was compared for 3 calendar periods: pre-HAART (1991 - 1995); early HAART (1996 - 1998), the transition period; and late HAART (1999 - 2003).		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Melo,M.G., Santos,B.R., De Cassia,Lira R., Varella,I.S., Turella,M.L., Rocha,T.M., Nielsen-Saines,K., Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil, Sexually Transmitted Diseases, 35, 912-915, 2008 **Ref ID** 132085 **Country/ies where the study was carried out** Brazil **Study type** Retrospective cohort study **Aim of the study** Not reported **Study dates** February 2000 to January 2006 **Source of funding** Not reported	**Sample size** n = 93 heterosexual HIV serodiscordant couples n = 26 serodiscordant couples with male index case **Characteristics** Male index case = 26 CD4 <350 or opportunistic infection = 5/26 (19.2%) Intravenous drug use = 15/26 (57.7%) Unprotected sexual intercourse = 11/26 (42.3%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] HAART 2] Non-HAART	Recruitment: In preparation for a large multicentre randomised clinical trial of HIV-1 serodiscordant couples, the investigators researched the number of antiretrovial naive HIV-1 infected individuals receiving medical care at the instituion with a steady HIV-1 uninfected partner of the opposite sex. Among 4,500 patients, 56 fulfilled this criteria and were retrospectively enrolled. In adition, 37 couples were enrolled prospectively in the first year of observation. Such additional cases were identified during regular clinic appointments and from a network of basic health units within the vicinity of the the medical centre supported by the institution. Data collection: All new patients were interviewed and a questionnaire with sexual practices was presented. To the uninfected partner, pretest counseling was offered before a new anti-HIV ELISA test was performed. Anti-HIV testing was performed following local standards requiring two enzyme-based tests with confirmation through immunofluorescence and	Seroconversion: HAART = 0/5 (0%) Non-HAART = 4/21 (19%)	**Limitations** 1] Sample size. 2] Reporting bias: Despite all male index cases reporting consistent practice of safe sex, there were 4 events of seroconversion and 1 event of pregnancy. **Other information** Median viral load of male index cases was 18,031 copies/ml

			repitition of the enzyme-based tests in a second sample. Retrospectively identified cases were defined as serodiscordant if at least one negative anti-HIV test of a regular partner was available at the last appointment.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Peterson,L., Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial, PLoS Clinical Trials, 2, -, 2007 **Ref ID** 132582 **Country/ies where the study was carried out** Ghana, Cameroon, Nigeria **Study type** Multicentre RCT **Aim of the study** To investigate the safety and preliminary effectiveness of a daily dose of 300 mg of TDF versus placebo in a HIV-uninfected women. **Study dates** June 2004 to Sepetember 2005 **Source of funding** Support for the study was provided by the Bill and Melinda Gates Foundation to Family Health Internaltional.	**Sample size** n = 936 HIV-negative women **Characteristics** Female Mean age ± SD (range): TDF group = 23.6 ± 4.0 (18 to 34) years Placebo group = 23.5 ± 3.9 (18 to 34) years History of STI (past 6 months) TDF group = 170/427 (39.8%) Placebo group = 184/432 (42.6%) **Inclusion criteria** 1] HIV-antibody-negative women 18 to 35 years old who were at risk of HIV infection by virtue of having an average of three or more coital acts per week and four or more sexual partners per month. 2] Willingness to use the study drug as directed and participate for up to 12 months of follow-up. 3] Adequate renal function, liver function and serum phosphorus **Exclusion criteria** Pregnant, lactating mothers or women wishing to become pregnant during the 12 month of study participation.	1] Tenofovir Disoproxil Fumarate 2] Placebo	Recruitment: Recruitment was done from areas within each city considered high HIV transmission area. Participants were not asked whether they were sex workers but most of them exchanged sex for money. Method: During monthly follow-up visits, participants underwent OMT HIV and pregnancy testing, adverse even assessment, risk reduction counseling, and study drug and condom re-supply. At months 1,3, 6, 9, 12 and as needed, participants underwent physical examination and blood was drawn for laboratory assessment of hepatic and renal function. For the randomisation, a randomisation manager not involved in any other part of the study developed a random allocation sequence using a permuted block design stratifed by site, with random block sizes of 12, 18 and 32. The randomisation list was sent to the manufacturer who filled each drug bottle with a 30 day supply of TDF or placebo. Placebo tablets were identical to the TDF tablets and each drug bottle was	Seroconversion: TDF = 2/427 Placebo = 6/432 Rate ratio (95% CI) = 0.35 (0.03 to 1.93) p- value = 0.24	**Limitations** The study was not adequately powered **Other information**

			marked with a sequential randomisation number, but no product identifier. Participants, field study staff, monitors, statisticians and other family health internation staff involved in the trial were blinded to drug assignment. Study staff assigned each eligible participant the next sequential number, and gave her the first month's supply of study drug after she had fully qualified for the study and signed or marked the enrollment consent form. Sample size: The study was designed to have 90% power to conclude with 95% conficence that TDF reduced the rate of HIV infection by 50% if the true rate of reduction due to TDF was at least 83%. The planned sample size was 1,200 participants, with 12 month follow-up for each		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Quinn,T.C., Wawer,M.J., Sewankambo,N., Serwadda,D., Li,C., Wabwire-Mangen,F., Meehan,M.O., Lutalo,T., Gray,R.H., Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group, New England Journal of Medicine, 342, 921-929, 2000 **Ref ID** 132581 **Country/ies where the study was carried out** Uganda **Study type** **Aim of the study** Not reported **Study dates** November 1994 to October 1998 **Source of funding** Supported by grants from the National Institute of Allergy and Infectious Diseases; by a grant from National Institute of Child Health and Human Development and by the Rockefeller Foundation and the World Bank Uganda Sexually Transmitted Infections Project.	**Sample size** n = 415 serodiscordant couples. n = 228 couples with male index partners **Characteristics** Median age at enrollment: HIV-positive partners = 29.4 years HIV-negative partners = 30.3 years **Inclusion criteria** Not reported. **Exclusion criteria** Not reported	1] Non-HAART	The study is based on a cluster trial whereby 5 clusters were randomly assigned to receive intervention for sexually transmitted diseases and 5 clusters were randomly assigned to a control group. Five community-based surveys were conducted at intervals of 10 months. Methods: Subjects in both groups received identical, intensive instruction on the prevention of HIV-1 infection and condom use and were offered free condoms and voluntary, confidential serologic testing for HIV-1 and counseling by trained project counselors. Since this was a community-based trial that enrolled all consenting adults, the identification of couples within the general population was done only retrospectively. The limit detection was 400 copies of HIV-1 RNA per milliliter, and samples with values below this limit were assigned a value of 399 per milliliter for the purpose of analysis. Among couples in which the HIV-1-negative partner seroconverted, the HIV-1 RNA assay was performed on the serum sample obtained from the	Seroconversion: <400 copies (all couples) = 0 <1500 copies (male index cases) = 0 All male index cases: 50/228 (21.9%)	**Limitations** The measurement of the viral load in the index subject and documentation of seroconversion in the partner was 10 months, resulting in some imprecision as to the viral load at the time of transmission. **Other information** HIV-1 RNA levels were not influenced by the use of antiretroviral drugs because antiretrovial drugs were not available in rural Uganda at that time The study was designed to compare seroconversion in male index with female index partners

			HIV-1-positive index partner at the study visity before the 10-month interval in which there was a risk of seroconversion. Couples in which there was no serovonversion were matched with couples with seroconversion according to sex and age of the HIV-1-positive and HIV-1-negative partners and the timing of the follow-up visit.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cohen,Myron S., Chen,Ying Q., McCauley,Marybeth, Gamble,Theresa, Hosseinipour,Mina C., Kumarasamy,Nagalingeswaran, Hakim,James G., Kumwenda,Johnstone, Grinsztejn,Beatriz, Pilotto,Jose H.S., Godbole,Sheela V., Mehendale,Sanjay, Chariyalertsak,Suwat, Santos,Breno R., Mayer,Kenneth H., Hoffman,Irving F., Eshleman,Susan H., Piwowar-Manning,Estelle, Wang,Lei, Makhema,Joseph, Mills,Lisa A., de Bruyn,Guy, Sanne,Ian, Eron,Joseph, Gallant,Joel, Havlir,Diane, Swindells,Susan, Ribaudo,Heather, Elharrar,Vanessa, Burns,David, Taha,Taha E., Nielsen-Saines,Karin, Celentano,David, Essex,Max, Fleming,Thomas R., Prevention of HIV-1 Infection with Early Antiretroviral Therapy, New England Journal of Medicine,N Engl J Med, 365, 493-505, 2011 **Ref ID** 137214 **Country/ies where the study was carried out** **Study type**	**Sample size** n = 1763 HIV serodiscordant couples. **Characteristics** Female age 18 - 25 years = **Inclusion criteria** 1] Couples were required to have had a stable relationship for at least 3 months 2] To have reported three or more episods of vaginal or anal intercourse. 3] To have reported three or more episodes of vaginal or anal intercourse during this time 4] Willingness to discolose their HIV-1 status to their partner. 5] Patients with HIV-1 infection were eligible if their CD4 count was between 350 and 550 cells per cubic millimenter and they had received no previous antiretroviral therapy except for short-term prevention of mother -to child transmission of HIV-1. **Exclusion criteria** Provided in the Supplementary Appendix, available with the full text of this article at NEJM. org	1] Early anti-retroviral therapy (initiated at enrollment) 2] Delayed anti-retroviral therapy (initiated after two measurements showing CD4 count was ≤250 cells per cubic millimeter or after development of an illness AIDS related)	Recruitment: HIV-1 serodiscordant couples were enrolled at 13 sites in 9 countries. A pilot phase started in April 2005 and enrollment took place from june 2007 through May 2010. Method: HIV-1 serodiscordant couples were randomly assigned in a 1:1 ratio to either an early or delayed strategy for receipt of antiretroviral therapy. Permuted-block randomisation was used with stratification according to site. Samples from all seroconversion events were evaluated at ta central laboratory, and results were reviewed by an independent HIV end-point committee. Intervention: Antiretroviral drugs given to patients were a combination of lamivudine and zidovudine, efavirenz, atazanavir, nevirapine, tenofofir, lamivudine, zidovudine, didanosine, stavudine, a comination of lopinavir and ritonavir, ritonavir and a combination of emtricitabine and tenofovir. A prespecified combination of these drugs was provided to participants at monthly or quarterly visits. After enrollment, study participants		**Limitations** **Other information**

Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand and USA Multi-centre randomised controlled trial **Aim of the study** **Study dates** June 2007 to May 2010 **Source of funding** Supported by the HIV Prevention Trials Network and by grants from the National Institute of Allergy and Infectious Diseases. Grant support from Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, Merck, ViiV Healthcare, Gilead Sciences.			were asked to attend three onthly visits, which were followed by quarterly visits unless they became ill or needed additional antiretroviral medications. HIV-1-infected participants who were receiving antiretroviral therapy had one additional visit 2 weeks. after starting therapy. HIV-1-uninfected partners were tested for seroconversion on a quarterly basis. After the initiation of antiretroviral therapy, virologic failure for HIV-1-infected participants was defined as two consecutive plasma HIV-1 RNA measurements of more than 1000 copies per mililiter Statistical analysis		

Fertility (Updated guideline)

in women with WHO Group 2 ovulation disorders?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Atay,V., Cam,C., Muhcu,M., Cam,M., Karateke,A., Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation, Journal of International Medical Research, 34, 73-76, 2006 **Ref ID** 53392 **Country/ies where the study was carried out** Turkey **Study type** RCT **Aim of the study** To compare the effect on ovulation induction of letrozole with CC treatment in women with PCOS in order to investigate the role of letrozole as a first-line treatment **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 106 women [1] Letrozole = 51 [2] CC = 55 **Characteristics** Age in years ±SD: Letrozole: 27.1±0.9 CC: 26.2±1.1 BMI ±SD: Letrozole: 26.1±1.9 CC: 25.8±1.8 Duration of infertility in years ±SD: Letrozole: 2.2±0.7 CC: 2.4±0.9 **Inclusion criteria** - Primary infertility - PCOS with no other known cause of infertility **Exclusion criteria** Not reported	Letrozole + hCG + Timed intercourse Comparison Clomiphene citrate + hCG + Timed intercourse	Letrozole Patients were randomised to receive 2.5mg of Letrozole daily for 5 days, from day 3-9 of menstrual cycle. CC Patients were randomised to receive 100mg of CC daily for 5 days, from day 3-9 of menstrual cycle. Follicular development was monitored using transvaginal ultrasound from day 10 onwards. When at least one mature follicle (with mean diameter ≥18mm) was observed, 10.000IU of hCG were given to trigger ovulation.	Pregnancy Letrozole: 11/51 (22%) CC: 5/55 (9%) Multiple pregnancy Letrozole: 0 CC: 1/55 (2%)	**Limitations** - Randomisation and concealment of allocation not reported - Blinding and power analysis not reported **Other information** Diagnosis of PCOS based on a history of oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2-10mm in diameter and hyperechogenic stroma Pregnancy was diagnosed measuring β-hCG levels obtained 2 weeks after timed intercourse, and ultrasound was performed 4 weeks after a positive pregnancy test to confirm clinical pregnancy by the presence of cardiac activity.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Badawy,A.M., Allam,A., Abulatta,M., Extending clomiphene treatment in clomiphene-resistant women with PCOS: A randomized controlled trial, Reproductive Biomedicine Online, 16, 825-829, 2008 **Ref ID** 67986 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To test the effect of extended clomiphene citrate treatment compared with gonadotrophin therapy for the management of clomiphene-resistant women with polycystic ovary syndrome (PCOS) **Study dates** May 2004 - May 2007 **Source of funding** Not reported	**Sample size** N = 318 women [1] hMG = 158 [2] CC = 160 **Characteristics** Age in years ±SD: hMG: 26.3 ±3.0 CC: 24.1 ±3.1 BMI ±SD: hMG: 32.5 ±2.9 CC: 30.5 ±3.1 Duration of infertility in years ±SD: not reported **Inclusion criteria** - Clomiphene-resistant PCOS women - Patent fallopian tubes proven by HSG - Partners with normal semen parameters (WHO criteria) - Normal serum prolactin, TSH and 17-OH-progesterone **Exclusion criteria** Not reported	hMG + hCG + Timed intercourse Comparison Clomiphene citrate + hCG + Timed intercourse	hMG Patients in the gonadotrophin group were given hMG 75IU daily for 5 days starting on day 3 of menses. CC Patients in the CC group received 100mg of clomiphene citrate daily starting on day 2 of menses for 9 days. All patients were monitored by transvaginal ultrasound. The radiologist was blinded to the treatment allocation. hCG injection was given when at least one follicle measured at least 18mm. Patients were advised to have intercourse 24-36 hours after hCG injection.	Pregnancy hMG: 20/158 (13%) CC: 28/160 (17%) Miscarriage hMG: 4/23 (17%) CC: 5/28 (18%) Multiple pregnancy hMG: 4/158 (3%) CC: 1/160 (1%) OHSS hMG: 2/158 (1%) CC: 0	**Limitations** - Randomisation described - The radiologist monitoring ovulation by TVUS was blinded to the treatment groups - Power analysis not reported **Other information** Diagnosis of PCOS was based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS (Rotterdam ESHRE/ASRM, 2004) Clomiphene-resistance was defined as failure of ovulation after administration of 150mg of CC for 5 days. Pregnancy was considered when serum hCG concentration was 50mIU/ml or more (biochemical pregnancy only)

					Miscarriage was considered when spontaneous termination of pregnancy ocurred before 20 weeks of gestation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bayar,U., Basaran,M., Kiran,S., Coskun,A., Gezer,S., Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial, Fertility and Sterility, 86, 1447-1451, 2006 **Ref ID** 53501 **Country/ies where the study was carried out** Turkey **Study type** RCT **Aim of the study** To compare the use of aromatase inhibitor (Letrozole) with the use of clomiphene citrate (CC) as a first line ovulation induction agent in PCOS patients **Study dates** 2004 - 2005 **Source of funding** Not reported	**Sample size** N = 80 women [1] Letrozole: 40 [2] CC: 40 **Characteristics** Age in years ±SD: Letrozole:32.2±3.9 CC: 30.6±4.0 BMI ±SD: NA Duration of infertility (range) in years: Letrozole: 5 (1-10) CC: 3 (1-11) **Inclusion criteria** - Anovulatory PCOS patients diagnosed by using 2003 Rotterdam criteria - Tubal, peritoneal and uterine causes of infertility were excluded by HSG, laparoscopy or transvaginal ultrasonography **Exclusion criteria** - Specific endocrine abnormalities (Cushing's disease, hypothyroidism, hyperthyroidism, congenital adrenal hyperplasia and prolactinoma) - Male factor infertility - Women with BMI of >25 kg/m2	Letrozole + hCG + Timed intercourse Comparison Clomiphene citrate + hCG + Timed intercourse	Letrozole Women received 2.5mg/day of Letrozole. CC Women received 100mg/day of Clomiphene citrate. Both treatments were administered on days 3 to 7 of the menstrual cycle. Patients were monitored for follicular development and serial measurements of E2 and LH. In both groups 10 000IU of hCG was administered to trigger the ovulation when at least one mature follicle (≥ 18mm) developed, followed by timed intercourse.	Live birth: data reported per cycle Pregnancy: data reported per cycle Miscarriage: Letrozole: 1/38 (2.6%) CC: 0 Multiple pregnancy: Letrozole: 0 CC: 0	**Limitations** Randomisation and allocation concealment described Sample size calcullation powered to detect the difference in ovulation **Other information** Pregnancy diagnosis used β-hCG measured 5 days after the first missed menstrual period. A positive result on serum β-hCG >10mIu/l

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Begum,M.R., Ferdous,J., Begum,A., Quadir,E., Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome, Fertility and Sterility, 92, 853-857, 2009 **Ref ID** 53526 **Country/ies where the study was carried out** Bangladesh **Study type** RCT **Aim of the study** To compare the effectiveness of letrozole and clomiphene citrate (CC) in induction of ovulation in CC unresponsive patients with polycystic ovary syndrome (PCOS) **Study dates** August 2004 - December 2005 **Source of funding** Not reported	**Sample size** N = 64 women [1] Letrozole = 32 [2] CC = 32 **Characteristics** Age in years ±SD: Letrozole:25±4 CC: 26±4 BMI ±SD: Letrozole: 23±3 CC: 24±3 Duration of infertility in years ±SD: Letrozole: 3±1 CC: 3±1 **Inclusion criteria** - Anovulatory CC unresponsive patients with PCOS **Exclusion criteria** - Hyperprolactinemia - Thyroid disorder - Male factor infertility - Known or suspicious tubal factor infertility (endometriosis and pelvic inflamatory disease) - Unexplained infertility	Letrozole + hCG Comparison Clomiphene citrate + hCG	Letrozole Patients received 7.5mg of Letrozole daily for 5 days starting from day 3 of the cycle. CC Patients received 150mg of CC daily for 5 days starting from day 3 of the cycle. Follicular monitoring was done by sequential transvaginal ultrasonography (TVS) until a mature follicle was detected. A single injection of 10 000IU of hCG was given if at least one follicle attained 18mm. Six ovulatory cycles were observed for pregnancy rates	Pregnancy: Letrozole:13/32 (40.6%) CC: 6/32 (18.7%) Miscarriage: Letrozole: 2/13 (15.4%) CC: 0 Multiple pregnancy: Letrozole:0 CC: 0 Patient adverse effects: Letrozole:0 CC: 0	**Limitations** Method of randomisation inadequate Blinding and power analysis not reported **Other information** CC unresponsive patients with PCOS defined as patients with PCOS who did failed to ovulate by taking 100mg of CC/day for 5 days in two consecutive cycles PCOS was diagnosed by 2003 Rotterdam criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Legro,R.S., Barnhart,H.X., Schlaff,W.D., Carr,B.R., Diamond,M.P., Carson,S.A., Steinkampf,M.P., Coutifaris,C., McGovern,P.G., Cataldo,N.A., Gosman,G.G., Nestler,J.E., Giudice,L.C., Leppert,P.C., Myers,E.R., Cooperative Multicenter Reproductive Medicine Network., Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome, New England Journal of Medicine, 356, 551-566, 2007 **Ref ID** 54798 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To test the hypothesis that treatment of women with polycystic ovary syndrome with extended-release metformin is more likely to result in a live birth than is treatment with clomiphene citrate and that the combination of the two therapies will result in the highest birth rate **Study dates** November 2002 - February 2006 **Source of funding** National Institutes of Health Glucophage XR and matching placebo were provided by Bristol-Myers Squibb	**Sample size** N = 626 women Metformin + CC = 209 Metformin + Placebo = 208 CC + Placebo = 209 **Characteristics** Age in years ±SD: Metformin + CC: 28.3±4.0 Metformin + Placebo: 28.1±4.0 CC + Placebo: 27.9±4.0 BMI ±SD: Metformin + CC: 34.2±8.4 Metformin + Placebo: 35.6±8.5 CC + Placebo: 36.0±8.9 Duration of infertility in months ±SD: Metformin + CC: 40.7±36.0 Metformin + Placebo: 39.0±31.9 CC + Placebo: 41.4±39.4 **Inclusion criteria** - Diagnosis of PCOS - Normal uterine cavity and at least one patent fallopian tube - Normal semen analysis (WHO 1999 parameters) **Exclusion criteria** - Hyperprolactinemia - Congenital adrenal hyperplasia - Thyroid disease - Other causes of amenorrhea, including premature ovarian failure - Clinically suspected Cushing's syndrome	Metformin + CC Comparison 1 Metformin + Placebo Comparison 2 CC + Placebo	Metformin + CC Each subject received a monthly medication package consisting of 500mg tablets of Metformin and blister pack containing 50mg tablets of CC. The two drugs were begun concurrently. Subjects gradually increased the dose of Metformin until reaching the maximum dose of 4 tablets (2 tablets twice daily). Subjects took one tablet a day of CC for 5 days, beginning on day 3 of menses; this dose was maintained if adequate ovulation was documented. However, in subjects who had no response or poor response, the dose was increased by one tablet a day (either after 5 weeks of anovulation or after a menses until the maximum dose of 3 tablets/day was reached) Metformin + Placebo Similar to described above, however instead of CC, patients received matching placebo tablets CC + Placebo Similar to described above, however instead of Metformin, patients received matching placebo tablets Subjects were instructed to have regular intercourse every 2 to 3 days and to keep a diary recording intercourse, vaginal bleeding and symptoms. Repeated measures of serum progesterone level were	Live birth: Metformin + CC = 56/209 (26.8%) Metformin + Placebo = 15/208 (7.2%) CC + Placebo = 47/209 (22.5%) Pregnancy (clinical): Metformin + CC = 65/209 (31.1%) Metformin + Placebo = 18/208 (8.7%) CC + Placebo = 50/209 (23.9%) Multiple pregnancy: Metformin + CC = 2/209 (1%) Metformin + Placebo = 0 CC + Placebo = 3/209 (1.4%) Miscarriage (pregnancy loss in first trimestre): Metformin + CC = 20/80 (25%) Metformin + Placebo = 10/25 (40%) CC + Placebo = 14/62 (22.6%) Ectopic pregnancy: Metformin + CC = 2/80 (2.5%) Metformin + Placebo = 0 CC + Placebo = 2/62 (3.2%) Adverse pregnancy events (pregnancy loss in second or third trimester): Metformin + CC = 4/80 (5%) Metformin + Placebo = 0 CC + Placebo = 2/62 (3.2%)	**Limitations** Randomisation method not described Study powered to detect difference in birth rate **Other information** Diagnosis of PCOS was defined as oligomenorrhea (with a history of no more than 8 spontaneous menses per year) and hyperandrogenemia (with elevated testosterone level documented within the previous year in an outpatient setting on the basis of local laboratory results, with a predetermined cutoff level set by the principal investigator at each study site) Ultrasonography for follicular and endometrial response was not included in the protocol, and ovulation triggering with hCG was not permitted. Pregnancy was

	- Androgen secreting neoplasm - Other causes of infertility		collected in order to monitor ovulation. Subjects were treated for up to 6 cycles	Congenital anomaly: Metformin + CC = 2/56 (3.1%) Metformin + Placebo = 0 CC + Placebo = 0 Patient reported adverse events: <u>Hemorrhagic corpus luteum cyst needing hospitalization and surgery</u>: Metformin + CC = 0 Metformin + Placebo = 0 CC + Placebo = 1/209 (0.5%) <u>Hypersensitivity reaction</u>: Metformin + CC = 0 Metformin + Placebo = 1/208 (0.5%) CC + Placebo = 0 <u>Bronchitis or back pain needing hospitalization</u>: Metformin + CC = 1/209 (0.5%) Metformin + Placebo = 0 CC + Placebo = 1/209 (0.5%) <u>Death</u>: Metformin + CC = 0 Metformin + Placebo = 1/208 (0.5%) CC + Placebo = 0 <u>Abdominal distension</u>: Metformin + CC = 39/209 (18.7%)	diagnosed by ultrasonography which documented fetal viability

				Metformin + Placebo = 56/208 (26.9%) CC + Placebo = 45/209 (21.5%) <u>Abdominal pain or discomfort</u>: Metformin + CC = 137/209 (65.6%) Metformin + Placebo = 123/208 (59.1%) CC + Placebo = 110/209 (52.6%) <u>Constipation</u>: Metformin + CC = 22/209 (10.5%) Metformin + Placebo = 21/208 (10.1%) CC + Placebo = 32/209 (15.3%) <u>Diarrhea</u>: Metformin + CC = 126/209 (60.3%) Metformin + Placebo = 135/208 (64.9%) CC + Placebo = 48/209 (23.0%) <u>Dyspepsia</u>: Metformin + CC = 14/209 (6.7%) Metformin + Placebo = 24/208 (11.5%) CC + Placebo = 9/209 (4.3%) <u>Flatulence</u>: Metformin + CC = 39/209	

				(18.7%) Metformin + Placebo = 37/208 (17.8%) CC + Placebo = 38/209 (18.2%) <u>Nausea</u>: Metformin + CC = 138/209 (66.0%) Metformin + Placebo = 128/208 (61.5%) CC + Placebo = 82/209 (39.2%) <u>Stomach discomfort</u>: Metformin + CC = 16/209 (7.7%) Metformin + Placebo = 15/208 (7.2%) CC + Placebo = 8/209 (3.8%) <u>Vomiting</u>: Metformin + CC = 72/209 (34.4%) Metformin + Placebo = 62/208 (29.8%) CC + Placebo = 28/209 (13.4%) <u>Decreased appetite</u>: Metformin + CC = 33/209 (15.8%) Metformin + Placebo = 27/208 (13%) CC + Placebo = 17/209 (8.1%) <u>Back pain</u>:	

				Metformin + CC = 22/209 (10.5%) Metformin + Placebo = 22/208 (10.6%) CC + Placebo = 25/209 (12%) <u>Dizziness</u>: Metformin + CC = 34/209 (16.3%) Metformin + Placebo = 35/208 (16.8%) CC + Placebo = 26/209 (12.4%) <u>Impaired sense of taste</u>: Metformin + CC = 10/209 (4.8%) Metformin + Placebo = 11/208 (5.3%) CC + Placebo = 10/209 (4.8%) <u>Headache</u>: Metformin + CC = 87/209 (41.6%) Metformin + Placebo = 88/208 (42.3%) CC + Placebo = 92/209 (44%) <u>Altered mood or mood swings</u>: Metformin + CC = 27/209 (12.9%) Metformin + Placebo = 36/208 (17.3%) CC + Placebo = 32/209 (15.3%)	

				Hot flashes: Metformin + CC = 59/209 (28.2%) Metformin + Placebo = 32/208 (15.4%) CC + Placebo = 58/209 (27.8%) Adnexal pain: Metformin + CC = 12/209 (5.7%) Metformin + Placebo = 4/208 (1.9%) CC + Placebo = 10/209 (4.8%) Anovulatory bleeding: Metformin + CC = 7/209 (3.3%) Metformin + Placebo = 18/208 (8.7%) CC + Placebo = 6/209 (2.9%) Breast tenderness or pain: Metformin + CC = 47/209 (22.5%) Metformin + Placebo = 36/208 (17.3%) CC + Placebo = 41/209 (19.6%) Dysmenorrhea or cramps: Metformin + CC = 43/209 (20.6%) Metformin + Placebo =	

				26/208 (12.5%) CC + Placebo = 42/209 (20.1%) <u>Sore throat</u>: Metformin + CC = 8/209 (3.8%) Metformin + Placebo = 14/208 (6.7%) CC + Placebo = 13/209 (6.2%) <u>Respiratory tract infection</u>: Metformin + CC = 16/209 (7.7%) Metformin + Placebo = 24/208 (11.5%) CC + Placebo = 27/209 (12.9%) <u>Fatigue</u>: Metformin + CC = 45/209 (21.5%) Metformin + Placebo = 42/208 (20.2%) CC + Placebo = 38/209 (18.2%) Pregnancy related adverse events: <u>Cervical incompetence or preterm labour:</u> Metformin + CC = 1/65 (1.5%) Metformin + Placebo = 0 CC + Placebo = 1/50	

				(2%) Severe preeclampsia: Metformin + CC = 2/65 (3.1%) Metformin + Placebo = 0 CC + Placebo = 0 Mild preeclampsia: Metformin + CC = 7/65 (10.8%) Metformin + Placebo = 1/18 (5.6%) CC + Placebo = 6/50 (12%) HELLP syndrome: Metformin + CC = 1/65 (1.5%) Metformin + Placebo = 0 CC + Placebo = 1/50 (2%) Gestational diabetes: Metformin + CC = 5/65 (7.7%) Metformin + Placebo = 2/18 (11.1%) CC + Placebo = 9/50 (18%) Premature rupture of membranes: Metformin + CC = 3/65 (4.6%) Metformin + Placebo = 1/18 (5.6%)	

				CC + Placebo = 1/50 (2%) <u>Placental abruption:</u> Metformin + CC = 2/65 (3.1%) Metformin + Placebo = 0 CC + Placebo = 2/50 (4%) <u>Placenta previa:</u> Metformin + CC = 1/65 (1.5%) Metformin + Placebo = 0 CC + Placebo = 1/50 (2.0%) <u>Other placental abnormality:</u> Metformin + CC = 1/65 (1.5%) Metformin + Placebo = 1/18 (5.6%) CC + Placebo = 1/50 (2%) <u>Other pregnancy complication:</u> Metformin + CC = 4/65 (6.2%) Metformin + Placebo = 2/18 (11.1%) CC + Placebo = 6/50 (12%) <u>Postpartum</u>	

				depression requiring intervention: Metformin + CC = 2/65 (3.1%) Metformin + Placebo = 0 CC + Placebo = 1/50 (2%) Endometritis: Metformin + CC = 3/65 (3.1%) Metformin + Placebo = 0 CC + Placebo = 0 Postpartum haemorrhage: Metformin + CC = 0 Metformin + Placebo = 0 CC + Placebo = 2/50 (4%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lopez,E., Gunby,J., Daya,S., Parrilla,J.J., Abad,L., Balasch,J., Ovulation induction in women with polycystic ovary syndrome: randomized trial of clomiphene citrate versus low-dose recombinant FSH as first line therapy, Reproductive Biomedicine Online, 9, 382-390, 2004 **Ref ID** 54862 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** To compare the efficacy and safety of clomiphene citrate and low-dose recombinant FSH as the first-line pharmacological treatment for anovulatory infertility associated with PCOS **Study dates** April 2000 - December 2001 **Source of funding** Not reported	**Sample size** N = 76 women [1] rFSH = 38 [2] CC = 38 **Characteristics** Age (range) in years rFSH: 30 (22-39) CC: 29 (23-38) BMI ±SD: rFSH: 21.9±1.9 CC: 22.3±1.9 Duration of infertility (range) in years: rFSH: 3 (1-8) CC: 3 (1-8) **Inclusion criteria** - Age <40 years - Anovulatory infertility due to PCOS of at least 1 year duration - Ultrasonographic appearance of polycistic ovaries - Positive response to progestin challenge test - Normal serum prolactin, S-DHEA, fasting glucose concentrations - A normal HSG (and laparoscopy when appropriate) and no history of pelvic surgery or pelvic inflammatory disease - Male partner with normal semen analysis (WHO criteria) **Exclusion criteria**	rFSH + hCG + Timed intercourse Comparison Clomiphene citrate + hCG + Timed intercourse	rFSH Women were randomised to receive low-dose recombinant FSH (rFSH) for up to 3 cycles. Treatment with rFSH was commenced on day 3 following spontaneous or induced menses. The chronic low-dose, step-up regimen of a starting dose of 75IU daily, with dose increments of 37.5IU daily every 7 days if there was no evidence of ovarian response by ultrasonography (i.e. no follicle >10mm). This stepwise increase was continued until ovarian activity was seen. CC In the other group CC was given at a daily dose of 50mg for 5 days, from day 5-9. If ovulation was documented but no pregnancy ensued, the same dose was used in the next cycle. However, if no ovulatory response occurred, the daily dose was increased by 50mg for the subsequent cycle, up to a maximum daily dose of 150mg. In both groups ovarian response was monitored by transvaginal ultrasound (TVUS) and 5000IU of hCG was administered when lead follicle was >17mm in diameter in TVUS. Couples were advised to have sexual intercourse the evening of the hCG injection and the following day.	Live birth rFSH: 11/38 (29%) CC: 6/38 (16%) Pregnancy rFSH: 16/38 (42%) CC: 9/38 (24%) Miscarriage rFSH: 5/16 (31%) CC: 3/9 (33%) Multiple pregnancy rFSH: 3/38 (8%) CC: 1/38 (3%) OHSS rFSH: 2/38 (5%) CC:0	**Limitations** Randomisation procedure and concealment of treatment allocation described Sample size calculation performed and reasons for not attaining the calculated sample size described Women not conceiving after 3 cycles of treatment crossed over to alternative treatment for a firther 3 cycles, with an interval of at least 45 days between treatments (outcomes are reported before the crossover) **Other information** Criteria for diagnosis of PCOS that were used were as described in the 2003 ESHRE/ASRM Rotterdam consensus Pregnancy was diagnosed by increasing serum concentrations of

	- Women with previous pregnancy or previous treatment with ovarian stimulation drugs				β-hCG after missed menses and the subsequent demonstration of an intrauterine gestational sac by TVUS

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Palomba,S., Orio,F.,Jr., Falbo,A., Manguso,F., Russo,T., Cascella,T., Tolino,A., Carmina,E., Colao,A., Zullo,F., Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome, Journal of Clinical Endocrinology and Metabolism, 90, 4068-4074, 2005 **Ref ID** 55286 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To compare the efficacy of metformin to CC as the first-line treatment for the anovulatory infertility in nonobese women with PCOS in a randomised, double-blind, double-dummy, controlled fashion **Study dates** April 2003 - September 2003 **Source of funding** Not reported	**Sample size** N = 100 Metformin + Placebo = 50 CC + Placebo = 50 **Characteristics** Age in years ±SD: Metformin + Placebo: 26.4±2.9 CC + Placebo: 25.9±2.7 BMI ±SD: Metformin + Placebo: 27±2.9 CC + Placebo: 26.7±2.8 Duration of infertility in years ±SD: Metformin + Placebo: 19.2±4.6 CC + Placebo: 20.3±4.1 **Inclusion criteria** - nonobese primary infertile anovulatory women with PCOS **Exclusion criteria** - Age <20 years or > 34 years - BMI >30 kg/m2 - neoplastic, metabolic (including glucose intolerance), hepatic and cardiovascular disorders - other concurrent medical illnesses: hypothyroidism, hyperprolactinemia, Cushing's syndrome, nonclassical congenital adrenal hyperplasia - current or previous (within last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic and antiobesity drugs, or other	Metformin + Placebo + Timed intercourse Comparison CC + Placebo + Timed intercourse	Metformin + Placebo* Metformin was used at a dose of 850mg twice daily plus placebo tablets (3 tablets daily for 5 days starting from the third day of a progesterone induced withdrawl bleeding). CC + Placebo* Women received 2 placebo tablets daily plus CC at a dose of 150mg (3 tablets daily for 5 days starting from the third day of a progesterone induced withdrawl bleeding). Each patient underwent TV-USG monitoring of ovulation every 3 days beginning on the 7th day after treatment. When follicular dimensions achieved at least 18 mm, patient was asked to have intercourse four times every 2 days. No agent to induce ovulation, e.g. hCG, was administered * The placebo tablets consisted of polyvitamins in tablets similar in appearance to metformin and/or CC. The duration of the treatment was 6 months	Live birth Metformin + Placebo: 26/50 (52%) CC + Placebo: 9/50 (18%) Pregnancy Metformin + Placebo: 31/50 (62%) CC + Placebo: 16/50 (32%) Multiple pregnancy Metformin + Placebo: 0 CC + Placebo: 0 Miscarriage Metformin + Placebo: 3/31 (9.7%) CC + Placebo: 6/16 (37.5%) Intrauterine fetal death Metformin + Placebo: 1/50 (2%) CC + Placebo: 1/50 (2%) Pregnancy induced hypertension Metformin + Placebo: 1/50 (2%) CC + Placebo: 0 Glucose intolerance Metformin + Placebo: 0 CC + Placebo: 2/50 (4%) Adverse drug related effects Metformin + Placebo: 1/50 (diarrhea, flatulence and	**Limitations** Method of randomisation using an online software (www.randomization.it) to generate random allocation sequence in double block as method of restriction Random allocation sequence was concealed until the interventions were assigned Operators and patients were blind to the treatment allocation Power calculation reported **Other information** Diagnosis of PCOS was made according to the National Institutes of Health criteria After 6 months of treatment women who did not achieve ovulation were administered CC and metformin respectively, at the same doses and

	hormonal drugs - no uterine bleeding after progesterone challenge test (100mg of natural progesterone) - Organic pelvic diseases - previous pelvic surgery - suspected peritoneal factor infertility - tubal or male factor infertility - women who intended to start a diet or specific program of physical activity			nausea) CC + Placebo: 1/50 (headache, hot flushes and nervousness)	regimens as described above. PCOS women having ovulatory cycles who did not achieve pregnancy were treated with 3 cycles of controlled ovarian stimulation followed by IUI before assisted reproductive techniques A rising β-hCG and the sonographic evidence of intrauterine gestational sac were considered criteria to define pregnancy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Qublan,H.S., Yannakoula,E.K., Al-Qudah,M.A., El-Uri,F.I., Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study, Saudi Medical Journal, 28, 1694-1699, 2007 **Ref ID** 55422 **Country/ies where the study was carried out** Jordan **Study type** Randomised controlled trial **Aim of the study** To compare the clinical results and the reproductive outcome in obese women with PCOS following diet or metformin **Study dates** January 2003 to April 2005 **Source of funding** None reported	**Sample size** 46 women **Characteristics** Age: Weight reduction group= 31.5 (19 to 38) years Metformin group= 30.8 (20 to 37) years Not significantly different BMI: Weight reduction group= 32.2 (29 to 43) Metformin group= 31.9 (29 to 44) Not significantly different Duration of infertility: Weight reduction group= 5.4 years Metformin group= 5.2 years Not significantly different **Inclusion criteria** PCOS (Rotterdam ESHRE/ASRAM workshop group definition) <36 years Duration of infertility > 2 years BMI > 29 kg/m^2 Clomiphene resistant (definition: failure to ovulate after clomiphene citrate treatment up to a daily dose of 150mg from cycle day 5-9 for at least 3 consecutive cycles)	Dietary intervention (24 women) Metformin (22 women)	Patients were randomised into groups using a random numbers table Dietary group= 1200 to 1400 kcal diet (25% proteins, 25% fat, 50% carbohydrates plus 25-30 gm of fibre per week). Weight was assessed every 4 weeks Metformin group= 850mg Metformin twice a day continuously. Treatment in both groups continued until women resumed their first regular cycle (first cycle to occur 24 to 35 days after treatment). Pregnancy tests were carried out in women who did not menstruate. If there was no resumption of regular cycle and no evidence of ovulation, treatment was continued for 6 months. Women were followed up for 12 months.	Pregnancy rate: Dietary group= 8/24 (33.3%) Metformin group= 6/22 (27.3%) Not significantly different Multiple pregnancy rate (per pregnancy): Dietary group= 1/8 (12.5%) Metformin group= 1/6 (16.6%) Not significantly different Abortion rate (pre pregnancy): Dietary group= 1/8 (12.5%) Metformin group= 1/6 (16.7%) Not significantly different	**Limitations** A power calculation was not reported **Other information**

	Normal uterine cavity and tubal patency on hysterosalpingography Male partners with normal semen parameters (WHO criteria) **Exclusion criteria** Congenital adrenal hyperplasia Cushing's syndrome Hyperprolactinemia Thyroid disease				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sohrabvand,F., Ansari,Sh, Bagheri,M., Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease, Human Reproduction, 21, 1432-1435, 2006 **Ref ID** 55696 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To compare and determine the efficacy of combined metformin-letrozole administration to that of metformin-clomiphene citrate in clomiphene-resistant infertile women with PCOS **Study dates** 2003 - 2004 **Source of funding** Not reported	**Sample size** N = 60 women Metformin + Letrozole = 30 Metformin + CC = 30 **Characteristics** Age in years ±SD: Metformin + Letrozole: 28.2±3.1 Metformin + CC: 29.5±3.5 BMI ±SD: Metformin + Letrozole: 29.9±4.8 Metformin + CC: 30.2±3.9 Duration of infertility in years ±SD: Metformin + Letrozole: 3.8 Metformin + CC: 3.8 **Inclusion criteria** - Clomiphene-resistant patients with PCOS - Normal thyroid function - Normal prolactin level - Normal HSG - Normal semen analysis **Exclusion criteria** - History of liver and kidney failure - Cardiovascular disease - Diabetes or patients who consumed metformin or drugs effecting insulin secretion or clomiphene citrate in the previous 2 months	Metformin + Letrozole Comparison Metformin + CC	Metformin + Letrozole Patients reveived 1500mg of Metformin a day (500mg tablets three times a day) for 6-8 weeks. If pregnancy occured, the patient was excluded from the study. In case of failure of pregnancy after the end of this period, the patients received 2.5mg of Letrozole for 5 days from day 3 of their menstrual cycle Metformin + CC Patients reveived 1500mg of Metformin a day (500mg tablets three times a day) for 6-8 weeks. If pregnancy occured, the patient was excluded from the study. In case of failure of pregnancy after the end of this period, the patients received 100mg of clomiphene citrate for 5 days from day 3 of their menstrual cycle Follicular growth was assessed by TVS every other day from day 12 of the cycle. 10 000IU of hCG was administered to those in whom at least one ovarian follicle was ≥18mm in size. The patients were advised to have intercourse every other day for 1 week, starting 24-36 hours after receiving hCG	Live birth Metformin + Letrozole = 11/30 (36.6%) Metformin + CC = 3/30 (10%) Pregnancy Metformin + Letrozole = 11/30 (36.6%) Metformin + CC = 5/30 (16.6%) Miscarriage Metformin + Letrozole = 0 Metformin + CC = 2/5 (40%)	**Limitations** - Randomisation described: patients were invited to pull out an envelope in a series of blind numbered envelopes - Investigators were blinded whereas patients were not blinded because of the medication tablets known different shapes **Other information** Diagnosis of PCOS in accord with the revised 2003 Rotterdam criteria of PCOS Clomiphene-resistant PCOS defined as PCOS patients who had failed to become pregnant after 3 courses of 150mg of clomiphene citrate Pregnancy was confirmed in TVS with the observation of fetal heart rate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zain,M.M., Jamaluddin,R., Ibrahim,A., Norman,R.J., Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial, Fertility and Sterility, 91, 514-521, 2009 **Ref ID** 56103 **Country/ies where the study was carried out** Australia **Study type** RCT **Aim of the study** To determine the first-line medication to be used in anovulatory patients with polycystic ovary syndrome (PCOS) for ovulation induction and pregnancy achievement **Study dates** September 2005 - December 2006 **Source of funding** Not reported	**Sample size** N = 115 women Metformin = 38 CC = 39 Metformin + CC = 38 **Characteristics** Age in years ±SD: Metformin: 27.8±3.6 CC: 29.6±4.3 Metformin + CC: 29.3±5.0 BMI ±SD: Metformin: 33.9±3.6 CC: 32.9±4.2 Metformin + CC: 33.0±4.1 Duration of infertility in years ±SD: Metformin: 3.1±0.3 CC: 2.9±0.2 Metformin + CC: 3.3±0.1 **Inclusion criteria** - Patients newly diagnosed with PCOS - Age <40 years old **Exclusion criteria** - Diabetes - Underlying liver, renal or heart disease - Partner's sperm quality indicating male factor infertility on at least 2 occasions (WHO 1999 criteria)	Metformin Comparison 1 CC Comparison 2 Metformin + CC	Metformin Patients were given Metformin tablets at the initial dose of 500mg and increased in a stepwise fashion during the first 3 weeks to accommodate the side effects until patients were taking a total dose of 1.500mg/day. The patients were asked to telephone once they had a menstrual period and a transvaginal ultrasound (TVS) for assessing follicular growth and ovulation on days 2, 8, 12 and 16. A menstrual calendar chart recorded menstrual cycles monthly CC Patients received CC at a dose of 50mg on days 2-6. The TVS for follicular growth and ovulation on days 2, 8, 12 and 16. If there was absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis after a P withdrawl bleed to a maximum of 200mg/day of CC. If there was evidence of ovulation but the woman did not get pregnant, the same dosage was continued for a maximum of 6 cycles. Metformin + CC Patients received combination of medication in a similar manner to the metformin only and CC only group. In all groups a urine pregnancy test was done 3 weeks after documented ovulation and the patient remained	Live birth Metformin = 3/38 (8%) CC = 6/39 (15.4%) Metformin + CC = 7/38 (18.4%) Pregnancy (clinical) Metformin = 3/38 (8%) CC = 6/39 (15.4%) Metformin + CC = 8/38 (21.1%) Multiple pregnancy Metformin = 0 CC = 0 Metformin + CC = 0 Miscarriage Metformin = 0 CC = 0 Metformin + CC = 1/8 (12.5%)	**Limitations** Method of randomisation and allocation described Investigators and patients were not blinded to the treatment Power calculation described **Other information** Diagnosis of PCOS was based on Rotterdam 2003 criteria Tubal patency was not tested before induction of ovulation All patients were given advice on the importance of diet and exercise. Appropriate patients were referred for dietary advice Anovulatory patients had a withdrawl bleed induced with medroxyprogesterone acetate (MPA) before the initiation of the study medication

			amenorrheic. Pregnant patients had their medications discontinued and were then followed up until a ultrasound could document the viability of pregnancy		All patients continued to take the study medication until they had a positive pregnancy test, six ovulatory cycles, or developed CC resistance, whichever came first

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Badawy,A., Abdel,Aal,I, Abulatta,M., Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial, Fertility and Sterility, 92, 849-852, 2009 **Ref ID** 53426 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To compare the effects of Letrozole (5mg) and Clomiphene citrate (100mg) for ovulation induction in women with polycystic ovary syndrome (PCOS) **Study dates** January 2004 - September 2006 **Source of funding** Not reported	**Sample size** N = 438 women [1] Letrozole: 218 [2] CC: 220 **Characteristics** <u>Age in years (±SD):</u> Letrozole: 27.1±3.2 CC: 29.3±2.9 <u>BMI (±SD):</u> Letrozole: 28.1±3.2 CC: 27.1±3.1 <u>Duration of infertility in years (±SD):</u> NA **Inclusion criteria** - infertility - PCOS - patent fallopian tubes proven by HSG - partners with normal semen analysis (WHO criteria) - normal serum prolactin, TSH and 17-OH progesterone **Exclusion criteria** Not reported	Letrozole + hCG + Timed intercourse Comparison Clomiphene citrate + hCG + Timed intercourse	<u>Letrozole</u> Patients in the Letrozole group had 5mg of Letrozole daily for 5 days starting on day 3 of menses. <u>CC</u> Patients in the CC group had 100mg of Clomiphene citrate daily starting day 3 of menses for 5 days. All patients were monitored by transvaginal ultrasound on the days 10, 12 and 14 of the cycle. The hCG injection (5000-10000IU) was given when at least one follicle measured ≥18mm. Patients were advised to have intercourse 24 to 36hours after hCG.	Pregnancy Letrozole: 33/218 (15%) CC: 41/220 (19%) Miscarriage Letrozole: 4/33 (12%) CC: 4/41 (10%) Multiple pregnancy Letrozole: 0 CC: 3/220 (1%) OHSS Letrozole: 0 CC: 0	**Limitations** - Method of randomisation and allocation described - Blinding and power analysis not reported **Other information** The diagnosis of PCOS was based on the revised 2003 consensus diagnostic criteria for PCOS (ESHRE/ASRM, 2004) Pregnancy was determined by serum hCG concentration 2 weeks after hCG injection in the absence of menstruation.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dasari,P., Pranahita,G., The efficacy of metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS, Journal of Human Reproductive Sciences, 2, 18-22, 2009 **Ref ID** 68178 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** To find out the ovulatory and pregnancy rates in infertile PCOS subjects who receive CC alone and a combination of metformin and CC **Study dates** August 2003 to August 2005 **Source of funding** Not reported	**Sample size** N = 40 women Metformin + CC = 16 CC = 24 **Characteristics** Age in years: Metformin + CC: 20 to 38 (38% aged 20-25 years, 44% aged 26-30, 19% aged >31 years) CC: 20 to 38 (50% aged 20-25 years, 42% aged 26-30, 8% aged >31 years) BMI: Metformin + CC: BMI<25: 10 (63%) BMI>25: 6 (37%) CC: BMI<25: 15 (63%) BMI>25: 9 (37%) Duration of infertility in years ±SD: Not reported **Inclusion criteria** - PCOS - Tubal factor was excluded by performing hysterosalphingogram or laparoscopy chromotubation **Exclusion criteria** - Recent pelvic inflammatory disease - Male factor infertility	Metformin + CC + hCG + Timed intercourse Comparison CC + hCG + Timed intercourse	Metformin + CC The Metformin + CC group received 500 mg of metformin continuously (the same dose) three times a day, from the first cycle for 6 months or until pregnancy was confirmed. CC was started at a dose of 50 mg from day 2 of the menstrual cycle till day 6 for a total of 5 days. The dose of CC was increased to 100 mg in the second cycle and 150 mg during the third cycle and CC was given at a dose of 150 mg for the remaining three cycles. Follicular growth was monitored by transvaginal ultrasound from the 10^{th} day of the menstrual cycle till the follicle reaches 18–20 mm. At this time, the patient was given 10,000 IU of HCG intramuscularly and was advised to have coitus after 36h. CC The CC only group received only CC at the same incremental dosage as that of the intervention group and was monitored similarly. Monitoring was performed for a maximum of six cycles or till pregnancy occurred.	Pregnancy: Metformin + CC = 4/16 (25%) CC = 2/24 (8%) Adverse patient outcomes: Metformin + CC = 0 CC = 0	**Limitations** Method of randomisation not reported Blinding and power analysis not reported **Other information** The diagnosis of PCOS was based on the Rotterdam revised criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dehbashi,S., Kazerooni,T., Robati,M., Alborzi,S., Parsanezhad,M.E., Shadman,A., Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome, Iranian Journal of Medical Sciences, 34, 23-28, 2009 **Ref ID** 68196 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To compare the effects of Letrozole and Clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome. **Study dates** January 2004 - November 2006 **Source of funding** Not reported	**Sample size** N = 100 women [1] Letrozole = 50 [2] CC = 50 **Characteristics** Age in years ±SD: Letrozole: 24±3 CC: 24±3 BMI ±SD: Letrozole: 27±5 CC: 27±4 Duration of infertility ±SD: Letrozole: 2±1 CC: 2±2 **Inclusion criteria** - Diagnosis of PCOS - Infertility for at least 1 year - Have patent tubes on HSG - Normal semen analysis **Exclusion criteria** Not reported	Letrozole + hCG + Timed intercourse Comparison Clomiphene citrate + hCG + Timed intercourse	Letrozole Women received Letrozole 5mg daily. Women underwent ovulation induction only for one menstrual cycle and took Letrozole as the first line treatment. CC Women received Clomiphene citrate (CC) 100mg daily. Women underwent ovulation induction only for one menstrual cycle and took CC as the first line treatment. 10 000IU of hCG was administered to trigger ovulation when at least one mature follicle (≥18mm) was developed followed by timed intercourse	Live birth Letrozole: 10/50 (20%) CC: 6/50 (12%) Pregnancy Letrozole: 13/50 (26%) CC: 7/50 (14%) Miscarriage Letrozole: 3/13 (23%) CC: 1/7 (14%) Multiple pregnancy Letrozole: 1/50 (2%) CC: 1/50 (2%) Congenital abnormality Letrozole: 0 CC: 1/50 (2%)	**Limitations** Randomisation procedure and concealment of treatment allocation described Blinding described Power calculation not reported **Other information** Criteria for diagnosis of PCOS as described in the 2003 ESHRE/ASRM Rotterdam consensus Serum βhCG was measured 5 days after missed period and ultrasound performed 2 to 4 weeks after a positive pregnancy test to confirm clinical pregnancy by fetal cardiac activity and number of gestational sacs

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Farquhar,C.M., Williamson,K., Gudex,G., Johnson,N.P., Garland,J., Sadler,L., A randomized controlled trial of laparoscopic ovarian diathermy versus gonadotropin therapy for women with clomiphene citrate-resistant polycystic ovary syndrome, Fertility and Sterility, 78, 404-411, 2002 **Ref ID** 68278 **Country/ies where the study was carried out** New Zealand **Study type** RCT **Aim of the study** To compare the effectiveness of laparoscopic ovarian diathermy with gonadotrophin ovulation induction for women with clomiphene-resistant polycystic ovary syndrome **Study dates** Mid 1996 - Late 1999 **Source of funding** Supported in part by Auckland Medical Research Foundation	**Sample size** N = 50 women [1] Surgery: 29 [2] hMG or rFSH: 21 **Characteristics** Age in years ±SD: Surgery: 29.6±4.7 hMG or rFSH: 29.6±4.2 BMI ±SD: Surgery: 28.3±3.9 hMG or rFSH: 27.8±4.8 Duration of infertility in months (range): Surgery: 36 (18-60) hMG or rFSH: 24 (16-28) **Inclusion criteria** - Age 20 to 38 years - Clomiphene citrate resistance - Infertility >12 months duration - Polycystic ovaries on ultrasound scan - BMI <33 kg/m2 for women of European descent and <35 kg/m2 for women of Pacific Island or NZ Maori descent - Normal semen analysis (WHO criteria) **Exclusion criteria** - Other known causes of infertility, including male factor infertility or known tubal disease.	Laparoscopic ovarian diathermy Comparison hMG or rFSH + hCG	Surgery: Women who received laparoscopic ovarian diathermy were followed for 6 months. If no ovulation was detected over a 6 month follow-up, treatment with 3 cycles of gonadotrophins was offered. No further treatment was offered to women who received laparoscopic ovarian diathermy who ovulated on follow-up. hMG or rFSH: Initially this group received only urinary gonadotrophins, but these became unavailable after 1988 and recombinant gonadotrophins were then given. Initially 75IU/day was given and ultrasound scan performed every 2 to 3 days until a follicle ≥18mm was measured. 5000IU of hCG was used to trigger ovulation. All women in the gonadotrophin group who had not conceived at the end of 3 cycles were offered laparoscopic ovarian diathermy	Live birth: Surgery = 4/29 (14%) hMG or rFSH = 4/21(19%) Pregnancy: Surgery = 8/29 (28%) hMG or rFSH = 7/21 (33%) Miscarriage: Surgery = 3/8 (37%) hMG or rFSH = 3/7 (43%) Multiple pregnancy: Surgery = 0 hMG or rFSH = 0 OHSS: Surgery = 0 hMG or rFSH = 0	**Limitations** Randomisation and method of allocation described Power calculation described **Other information** Clomiphene citrate resistance defined as no ovulation after one or more cycles of 150mg of CC from day 2 to day 6 each month PCOS poorly defined Not all women who were randomised had had tubal status established Women were randomised to either laparoscopic ovarian diathermy or three cycles of gonadotrophins (Metrodin or Puregon).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kamel,M.A., Abdel,HamidA, bdel-Rahim,M., Mostafa,S.A., Laparoscopic ovarian re-electro cautery versus ovulation induction with FSH for persistant anovulation after laparoscopic PCOS treatment, Middle East Fertility Society Journal, 9, 70-78, 2004 **Ref ID** 68521 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To determine the effectiveness and safety of either another laparoscopic ovarian drilling or purified urinary FSH for induction of ovulation in PCOS patients who were treated previously by laparoscopic electrocautery but still anovulatory **Study dates** April 2000 - November 2001 **Source of funding** Not reported	**Sample size** N = 55 women [1] LOD redrilling + CC = 30 [2] FSH = 25 **Characteristics** Age in years ±SD: LOD redrilling + CC: 27.4±3.2 FSH: 26.5±4.4 BMI ±SD: Not reported Duration of infertility ±SD: LOD redrilling + CC: 5.6±2.1 FSH: 4.7±2.1 **Inclusion criteria** - Previous treatment by laparoscopic drilling for management of anovulatory infertility of PCOS - Age <35 years old - Infertility: primary or secondary of at least two years duration - Documented PCOS (clinically, US or laboratory) - Normal semen analysis according to WHO 1999 criteria - Patent fallopian tubes (confirmed by positive methylene blue test in the report of the first laparoscopy and at the time of second look laparoscopy) **Exclusion criteria** Not reported	LOD + Clomiphene citrate + hCG + Timed intercourse Comparison FSH + hCG + Timed intercourse	All patients had previously treated by laparoscopic ovarian drilling (LOD) for management of anovulatory infertility due to PCOS. All patients were subjected to induction of ovulation by CC (starting from 100mg daily from day 3-7 of the cycle for 2 cycles and if anovulation persisted in the third cycle, 250mg daily from day 3-7) with ovulation monitoring by serial TVUS. If anovulation was persistent after these 3 cycles, women were randomly allocated into 2 main groups before performing the second look laparoscopy (to evaluate the condition of the ovaries, to assesss the presence of adhesions, to localize their sites and to determine their degree). LOD + CC LOD was performed and they were given CC 100mg daily from day 3-7. FSH No electrocautery was performed in this group and women were given 75IU of FSH (Metrodin®) daily from the 3rd day of the cycle. In both groups follow up of ovulation was performed with serial TVUS and when one mature follicle was identified, 10000IU of hCG were given and timed intercourse recommended	Pregnancy LOD redrilling + CC: 2/30 (6.6%) FSH: 4/25 (16%)	**Limitations** Randomisation procedure described Power calculation not described **Other information** Diagnose of PCOS based on finding bilateral enlarged ovaries with finding at least 10 small follicles (2-8mm), in one plane, in each ovary encircling the ovarian cortex, together with an expanded, brightly echogenic stromal compartment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Karimzadeh,M.A., Javedani,M., An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome, Fertility and Sterility, 94, 216-220, 2010 **Ref ID** 68532 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To compare the effect of lifestyle modification with the medical treatment of PCOS using clomiphene, metformin, and clomiphene + metformin. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 343 women [1] Lifestyle modification = 75 [2] Clomiphene citrate (CC) = 90 [3] Metformin = 90 [4] Clomiphene citrate + Metformin = 88 **Characteristics** Age in years ±SD: Lifestyle modification: 27±3 CC: 27±2 Metformin: 27±2 CC + Metformin: 27±2 BMI ±SD: Lifestyle modification: 28±1 CC: 27±3 Metformin: 27±2 CC + Metformin: 28±1 Duration of infertility in years ±SD: Lifestyle modification: 4±1 CC: 4±1 Metformin: 4±1 CC + Metformin: 4±1 **Inclusion criteria** - Age between 19 and 35 years old - BMI 25-29.9 kg/m2 - Primary infertility with PCOS - Normal thyroid, liver and kidney function - Serum level of PRL within normal levels - Fewer than 6 menstruation cycles per year	Lifestyle modification Comparison 1 Clomiphene citrate Comparison 2 Metformin Comparison 3 Clomiphene citrate + Metformin	Lifestyle modification The patients randomised to the lifestyle modification group were referred to dietitians and received the following advice regarding their diets: low-calorie diet (500 calories less than daily requirements). They were prescribed with an average 30 minutes exercise everyday, such as climbing up steps or simply walking. All patients in the 4 groups were followed up in an 8 month period. Clomiphene citrate The patients randomised to CC were given only CC at a dose of 100mg/day on days 3-7. Transvaginal ultrasonography and follicular monitoring were performed. If there was evidence pf ovulation but the patient did not get pregnant, the same dosage was continued for a maximum of 3 to 6 cycles. Metformin The patients randomised for the Metformin group were given the initial dose of 500mg/day, which was increased in a stepwise manner during the first 3 weeks to accommodate the side effects until the patients were taking a total of 1500mg/day for 3-6 months. Metformin + CC In the combination treatment group, Metformin and CC were given in a	Pregnancy: Lifestyle modification: 15/75 (20%) CC: 11/90 (12.2%) Metformin: 13/90 (14.4%) CC + Metformin: 13/88 (14.4%) Multiple pregnancy: Lifestyle modification: 0 CC: 2/90 (2.2%) Metformin: 0 CC + Metformin: 1/88 (1.1%)	**Limitations** Method of randomisation and allocation to groups not clear Blinding and power calculation not reported **Other information** Diagnosis of PCOS according to 2003 Rotterdam criteria, as including at least 2 of the following 3 criteria: chronic anovulation; clinical or biochemical signs of hyperandrogenism; and polycystic ovary morphology shown on ultrasound scan Pregnancy was diagnosed with β-hCG after 7 days of delay in menstruation and abdominal ultrasound for detection of fetal heart beat

	- Not taking metformin in previous 8 weeks for ovulation induction - Partner with normal sperm count (WHO criteria) **Exclusion criteria** Not reported		similar manner as described above.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Vandermolen,D.T., Ratts,V.S., Evans,W.S., Stovall,D.W., Kauma,S.W., Nestler,J.E., Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone, Fertility and Sterility, 75, 310-315, 2001 **Ref ID** 69129 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine whether metformin treatment increases the ovulation and pregnancy rates in response to clomiphene citrate (CC) in women who are resistant to CC alone **Study dates** Not reported **Source of funding** National Institute of Child Health and Human Development, National Institutes of Health	**Sample size** N = 27 Metformin + CC = 12 Placebo + CC = 15 **Characteristics** Age in years ±SD: Metformin + CC: 29±1.2 Placebo + CC: 30±1.0 BMI ±SD: Metformin + CC: 37.6±4.3 Placebo + CC: 38.4±2.2 Duration of infertility in years ±SD: NA **Inclusion criteria** - Age 18-35 years - Desire to become pregnant - Anovulation/CC-resistant PCOS - Hyperandrogenism (androstenedione, free T or total T or clinical evidence of hirsutism) - normal levels of TSH, PRL and 17-hydroxyprogesterone - normal renal function - normal results on liver function tests - tubal patency on HSG - partner with normal semen analysis (WHO 1999 criteria) **Exclusion criteria** - Diabeted mellitus according to American Diabetic Association criteria for glucose tolerance testing	Metformin + CC Comparison Placebo + CC	Metformin + CC Women were randomly assigned to take 500mg of metformin 3 times daily (total daily dose, 1500mg) for 7 weeks. They returned on days 10, 20, 30 and 40 for serum P measurement to determine whether they had ovulated (P ≥ 4ng/mL). Participants who ovulated in response to metformin in 7 weeks were excluded from further study. Anovulatory participants continued to take metformin and received 50mg of CC daily for 5 days. With ovulation, the daily dose of CC was not changed, but with anovulation, it was increased by 50mg for the next cycle up till 150mg dose Placebo + CC Women were randomly assigned to take placebo 3 times daily for 7 weeks. Participants who ovulated in response to placebo alone in 7 weeks were excluded from further study. Anovulatory participants continued to take placebo and received 50mg of CC daily for 5 days. With ovulation, the daily dose of CC was not changed, but with anovulation, it was increased by 50mg for the next cycle up till 150mg dose	Live birth Metformin + CC = 4/12 (33.3%) Placebo + CC = 1/15 (6.6%) Pregnancy Metformin + CC = 6/12 (50%) Placebo + CC = 1/15 (6.6%) Multiple pregnancy Metformin + CC = 0 Placebo + CC = 0 Miscarriage Metformin + CC = 2/6 (33.3%) Placebo + CC = 0	**Limitations** Randomisation was done by computer generation in blocks of six Blinding and power calculation not described **Other information** CC-resistant PCOS defined as anovulatory response to a 5-day course of CC, 150mg/day Pregnancy defined as presence of gestational sac on ultrasonography

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abdel,Gadir A., Mowafi,R.S., Alnaser,H.M., Alrashid,A.H., Alonezi,O.M., Shaw,R.W., Ovarian electrocautery versus human menopausal gonadotrophins and pure follicle stimulating hormone therapy in the treatment of patients with polycystic ovarian disease, Clinical Endocrinology, 33, 585-592, 1990 **Ref ID** 72846 **Country/ies where the study was carried out** Kuwait/UK **Study type** RCT **Aim of the study** To test the hypothesis that laparoscopic ovarian eletrocautery can be offered as a primary method for treating PCO patients who are clomiphene citrate non-responders **Study dates** Not reported **Source of funding** Kuwait University	**Sample size** N = 88 women [1] Surgery = 29 [2] hMG = 30 [3] FSH = 29 **Characteristics** Age in years ±SD: Surgery:27.6±0.7 hMG:26.5±0.7 FSH:27.3±0.7 BMI ±SD: Surgery:28.9±0.7 hMG: 28.5±0.9 FSH:29.2±0.7 Duration of infertility in years ±SD: Surgery: 12.0±0.8 hMG:11.6±0.8 FSH:12.2±0.8 **Inclusion criteria** - Infertile women with oligomenorrhoea or amenorrhoea attributable to polycystic ovarian disease and had failed to respond to CC therapy in incremental doses - No other factor contributing to their infertility as verified by HSG, diagnostic laparoscopy and repeated semen analysis - Normal prolactin levels - Euthyroid - Normal serum DHEA-S **Exclusion criteria** Not reported	laparoscopic ovarian eletrocautery* Comparison 1 hMG + hCG Comparison 2 FSH + hCG * 10/29 patients were offered Clomiphene citrate in daily dose of 100mg for 5 days if they failed to menstruate for 2 months following laparoscopic ovarian eletrocautery or during the monitoring period thereafter. This treatment was repeated for 3 cycles.	Surgery Laparoscopic ovarian eletrocautery was performed in 29 patients. hMG The hMG (n = 30) therapy was decided individually for each patient according to serial serum oestradiol (E2), cervical mucus assessment and ultrasonic monitoring. Treatment was started using 75IU of Pergonal (hMG) per day respectively in the first cycle. In the following cycles, the last effective dose used in the previous cycle was given as a starting dose and the dose of gonadotrophins increased by one ampoule according to ultrasound scan and E2 monitoring. FSH The FSH (n = 29) therapy was decided individually for each patient according to serial serum oestradiol (E2), cervical mucus assessment and ultrasonic monitoring. Treatment was started using 75IU of Metrodin (FSH) per day respectively in the first cycle. In the following cycles, the last effective dose used in the previous cycle was given as a starting dose and the dose of gonadotrophins increased by one ampoule according to ultrasound scan and E2 monitoring. At midcycle, 5000IU of hCG were given at follicular diameter of 18mm or more in gonadotrophin groups. Treatment	Live birth: Surgery:11/29 (37%) hMG:7/30 (23%) FSH:6/29 (21%) Pregnancy: data not clearly reported Miscarriage: data not clearly reported Multiple pregnancy: Surgery: 0 hMG: 3/30* (10%) FSH: 2/29 (7%) * One set of quadruplets ended in a second trimester abortion in the hMG group	**Limitations** Randomisation and allocation not clear (Patients were divided into three groups at random allocation with serial entry) Power analysis not described Not clear the diagnosis of PCOS 10/29 patients in the Laparoscopic ovarian eletrocautery group were offered CC **Other information** All patients had failed previously to respond to CC therapy in incremental doses up to 150mg daily for 5 days for three cycles

			with gonadotrophins and monitoring after laparoscopic ovarian eletrocautery were offered for 6 cycles.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bayram,N., van,Wely M., Kaaijk,E.M., Bossuyt,P.M., van,der,V, Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial, BMJ, 328, 192-, 2004 **Ref ID** 73021 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To compare the effectiveness of an electrocautery strategy with ovulation induction using recombinant FSH in patients with PCOS **Study dates** February 1998 - October 2001 **Source of funding** Not reported	**Sample size** N = 168 [1] Surgery = 83 [2] rFSH = 85 **Characteristics** Age in years ±SD: Surgery: 28.5±3.7 rFSH: 28.7±4.1 BMI ±SD: Surgery: 27.9±6.3 rFSH: 27.3±8.8 Duration of infertility ±SD: Surgery: 2.8±2.2 rFSH: 2.8±2.1 **Inclusion criteria** - Chronic anovulation (WHO group II) and PCO diagnosed by TVUS - CC-resistant PCOS **Exclusion criteria** - Other causes of infertility, including severe male factor subfertility - Tubal obstruction, extensive adhesions of the ovaries or fallopian tubes and endometriosis stage III or IV - Age >40	Laparoscopic Ovarian Electrocautery* (if anovulation persisted for 8 weeks after surgery or the patient became anovulatory again, treatment with CC or rFSH was added) Comparison rFSH + hCG	Laparoscopic Ovarian Electrocautery In the first group if anovulation persisted for 8 weeks after LOD or the patient became anovulatory again, treatment with 50mg of CC was added. If ovulation occured, this dose was maintained for a maximum of 6 ovulatory cycles. If no ovulation occurred the dose was increased to a maximum of 150mg. If they remained anovulatory, treatment with rFSH was started. CC In the second group patients were allocated to receive 75IU of rFSH daily according to the low-dose step up regimen. If the diameter of the follicles remained <10mm, the dose was increased by half an ampoule (37.5IU) on each of cycle days 16 and 23. If no follicle development (diameter >10mm) was seen by cycle day 30, the cycle was terminaded because of poor response. If one follicle at least 18mm was present then ovulation was triggered with 10 000IU of hCG	Live birth Surgery: 28/83 (34%) rFSH: 51/85 (60%) Pregnancy Surgery: 31/83 (37%) rFSH: 64/85 (75%) Miscarriage Surgery: 3/31 (10%) rFSH: 7/64 (11%) Multiple pregnancy Surgery: 0 rFSH: 9/85 (11%) Premature birth Surgery: 0 rFSH: 6/85 (7%)	**Limitations** Randomisation procedure and concealment of treatment allocation described Power calculation described **Other information** CC-resistant PCOS defined as persistent anovulation after taking 150mg of CC daily for 5 days During diagnostic laparoscopy patients were randomised and allocated either to receive Surgery or ovulation induction with rFSH.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation George,S.S., George,K., Irwin,C., Job,V., Selvakumar,R., Jeyaseelan,V., Seshadri,M.S., Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: A randomized, controlled trial, Human Reproduction, 18, 299-304, 2003 **Ref ID** 73638 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** To determine whether sequential treatment with Metformin and Clomiphene citrate would be as effective as hMG in improving ovulation and pregnancy rates in Clomiphene-resistant PCOS women. **Study dates** 1999 - 2001 **Source of funding** USV Ltd	**Sample size** N = 60 [1] Metformin + CC = 30 [2] hMG = 30 **Characteristics** Age in years ±SD: Metformin + CC: 25.1±3 hMG: 26±2.9 BMI ±SD: Metformin + CC: 25.5±3.7 hMG: 24.6±2.6 Duration of infertility in years ±SD: NA **Inclusion criteria** - Infertile women with PCOS who were also resistant to clomiphene - Normal liver, renal and thyroid function - Normal glucose tolerance test - Normal prolactine levels **Exclusion criteria** - Women with associated tubal or male factor infertility - BMI >35kg/m2	Metformin + CC + hCG Comparison hMG + hCG	Metformin + CC + hCG: The first group received metformin 1500mg/day in three divided doses for 6 months. After the 6 months of metformin treatment, the clinical and biochemical parameters were rechecked. Clomiphene citrate (CC) 150mg/day was restarted along with Metformin after 6 months. Follicular monitoring with ultrasound scan was performed. The CC was increased to 200mg if the woman did not ovulate. When the leading follicle reached >20mm, 5000IU of hCG was given to induce ovulation. hMG + hCG: The second group women underwent ovulation induction with hMG 75IU on day 5 of cycle by use of low-dose, step-up regimen. The dose was increased by 75IU every 7-10 days if there was no evidence of an ovarian response on ultrasound, i.e. no follicle >10mm in diameter. When the leading follicle was >18mm, 5000IU of hCG was given to induce ovulation.	Live birth: Metformin + CC: 2/30 (6.7%) hMG: 6/30 (20%) Pregnancy: Metformin + CC: 5/30 (17%) hMG: 7/30 (23%) Intra-uterine death at 28weeks: Metformin + CC: 1/5 (20%) hMG: 0 Miscarriage: Metformin + CC: 1/5 (20%) hMG: 1/7 (14%) Ectopic pregnancy: Metformin + CC: 1/5 (20%) hMG: 0 Patient reported adverse events: Metformin + CC: Nausea and vomiting = 3/30 (10%) hMG: not reported	**Limitations** Method of randomisation not described Study was underpowered to detect a difference in effect between groups **Other information** A diagnosis of PCOS was based on clinical features of oligomenorrhoea and hyperandrogenism, along with either biochemical abnormalities of a raised LH/FSH ratio or LH or ultrasound features of polycystic ovary Clomiphene resistance was defined as failure to ovulate to dose schedule of 200mg/day for 5 days Diagnosis of pregnancy not defined

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abu,Hashim H., Shokeir,T., Badawy,A., Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial, Fertility and Sterility, 94, 1405-1409, 2010 **Ref ID** 92632 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To compare the effect of letrozole with combined metformin and clomiphene citrate (CC) for ovulation induction in CC resistant women with polycystic ovary syndrome (PCOS) **Study dates** June 2006 - January 2009 **Source of funding** Not reported	**Sample size** N = 250 women [1] Letrozole = 123 [2] Metformin + CC = 127 **Characteristics** Age in years ±SD: Letrozole: 28.3±2.7 Metformin + CC: 26.2±2.2 BMI ±SD: Letrozole: 29.1±3.2 Metformin + CC: 30.1±2.3 Duration of infertility in years ±SD: not reported **Inclusion criteria** - CC-resistant PCOS - Patent fallopian tubes proved by HSG - Normal semen analysis (WHO 1999 criteria) **Exclusion criteria** Not reported	Letrozole + hCG + Timed intercourse Comparison Metformin + CC + hCG + Timed intercourse	Letrozole Women received 2.5mg of Letrozole daily from day 3 of menses for 5 days Metformin + CC Women received 500mg of Metformin three times a day for 6-8 weeks, followed by 150mg of CC for 5 days starting on day 3 of menstruation. Patients continued treatment for 3 successive cycles using the same protocol. Alll patients were monitored by transvaginal ultrasound for the mean follicular diameter and endometrial thickness. Serum E2 was measured at the time of hCG injection. 10 000IU of hCG was given when one follicle >18mm was found. Patients were advised to have intercourse 24-36 hours after hCG injection Patients were randomly allocated using a computer-generated random table	Pregnancy: Data not reported per woman Multiple pregnancy: Letrozole = 0 Metformin + CC = 3/127 Miscarriage: Data not reported per woman OHSS: Letrozole = 0 Metformin + CC = 0 Patient reported adverse events: Letrozole = 0 Metformin + CC = 10/127	**Limitations** Study powered to detect increse in ovulation **Other information** Diagnosis of PCOS based on Rotterdam 2003 criteria CC-resistant PCOS was defined as women who previously treated with 150mg of CC daily for 5 days per cycle, for 3 cycles with persistent anovulation Pregnancy was diagnosed using serum hCG determined 2 weeks in the absence of menstruation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cheng,J., Lv,J., Li,C.Y., Xue,Y., Huang,Z., Zheng,W., Clinical outcomes of ovulation induction with metformin, clomiphene citrate and human menopausal gonadotrophin in polycystic ovary syndrome, Journal of International Medical Research, 38, 1250-1258, 2010 **Ref ID** 92708 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** To evaluate the effects of coadministration of metformin with clomiphene citrate (CC) and human menopausal gonadotrophin (hMG) in women with CC-resistant polycystic ovary syndrome (PCOS) **Study dates** March 2005 - June 2007 **Source of funding** Not reported	**Sample size** N = 60 women [1] Metformin = 30 [2] Placebo = 30 **Characteristics** Age in years ±SD: Metformin: 27.0±2.9 Placebo: 27.7±3.1 BMI ±SD: Metformin: 21.6±1.5 Placebo: 22.0±1.4 Duration of infertility in years ±SD: Metformin: 3.5±1.6 Placebo: 3.7±1.8 **Inclusion criteria** - <40 years old - PCOS - Primary infertility - CC resistance - Normal glucose tolence during 75g oral glucose challenge test - Patent tubes confirmed by HSG - Had received no other hormone drugs within the last 3 months **Exclusion criteria** - Endometrial pathology - Other common causes of hyperandrogenism (prolactinoma, congenital adrenal hyperplasia, Cushing syndrome and virilizing ovarian or adrenal tumours	Metformin + Clomiphene citrate + hMG + hCG + Timed intercourse Comparison Placebo + Clomiphene citrate + hMG + hCG + Timed intercourse	Metformin + CC + hMG Women received combined therapy with 500mg of metformin three times daily from the first day of the cycle for 3 months, CC and hMG. Placebo + CC + hMG Women received placebo tablets three times daily from the first day of the cycle for 3 months. The drug and the placebo were packaged identically. CC (50 mg/day) was administered on days 3-7 of each cycle and 75IU/day of hMG was administered from day 5 of each cycle in both groups. Once the dominant follicle was approaching maturity (one reaching 20mm in diameter, two dominant follicles reaching 18mm in diameter or three dominant follicles reached 17mm in diameter), 5000IU of hCG was administered. Sexual intercourse was advised 36h after hCG injection.	Pregnancy Metformin + CC = 13/30 (43%) CC + Placebo = 6/30 (20%) OHSS Metformin + CC = data reported per cycle CC + Placebo = data reported per cycle	**Limitations** Method of randomisation not reported Patients who dropped out of the study were included in the final analysis Biochemical diagnosis of pregnancy was recorded **Other information** The diagnosis of PCOS was based on the Rotterdam revised criteria CC resistance was defined as the failure to ovulate with a CC dose of 150mg/day for 5 days from day 3 of the period for 3 months consecutively Semen analysis not reported in inclusion criteria If there were more than 4 dominant follicles, hCG was not used to induce ovulation (cycle cancellation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hwu,Y.M., Lin,S.Y., Huang,W.Y., Lin,M.H., Lee,R.K.K., Ultra-short metformin pretreatment for clomiphene citrate-resistant polycystic ovary syndrome, International Journal of Gynecology and Obstetrics, 90, 39-43, 2005 **Ref ID** 92831 **Country/ies where the study was carried out** Taiwan **Study type** RCT **Aim of the study** To evaluate the effect of ultra-short (12 days) metformin pretreatment in CC resistant PCOS. **Study dates** 2000 - 2003 **Source of funding** Not reported.	**Sample size** N = 80 women. [1] Metformin + CC = 40 [2] CC = 40 **Characteristics** Age in years ± SD Metformin + CC: 29.1 ± 4.5 CC: 27.8 ± 3.8 BMI ± SD Metformin + CC: 25.3 ± 3.3 CC: 24.1 ± 3.6 Duration of infertility: Not reported **Inclusion criteria** - Women with CC-resistant PCOS. - PCOS was diagnosed on the basis of chronic oligomenorhea - Clinical symptoms of hyperandrogenism or biochemical hyperandrogenemia - Polycystic ovaries seen on ultrasound (12 or more follicles 2 - 9 mm in diameter in each ovary) - Failure tof follicular development after CC treatment up to 150 mg daily for 5 days for two cycles. **Exclusion criteria** Not reported	Intervention Metformin + Clomiphene + hCG Comparison Clomiphene + hCG	Metformin + CC For women in this group, on day 1 after induced menstruation, oral metformin was started at a dose of 500 mg three times a day for 12 days. On day 13, CC 150 mg a day for 5 days was added while the metformin was continued. Three days after the last dose of CC, transvaginal ultrasound scanning was performed. If there were follicles greater than 12 mm in diameter, metforming was continued until the dominant follicles reached 20 mm. hCG, 5000 IU, was then given i.m, and the patients were instructed to have intercourse during the next 2 days. Ovulation was confirmed by ultrasound scanning and serum progesterone levels higher than 5 ng/ml on day 7 after hCG administration. Clomiphene For women in this group no metformin was given. On day 13 of an induced menstruation cycle, the women underwent ultrasonography, and CC 150 mg daily was given for 5 days. Follicular monitoring and the hCG protocol were the same as in the metformin pretreatment group.	Live birth: Metformin + CC = 4/40 (10%) CC = 0/40 (0%) Pregnancy: Metformin + CC = 6/40 (15%) CC = 0 Miscarriage: Metformin + CC = 2/6 (33.3%) CC = 0	**Limitations** - Method of randomisation was not reported - Blinding not reported - Power calculation not reported **Other information** - Figures for 'Live full-term singleton birth' reflect numbers of term delivery. It is unclear if it includes multiples and still-births. - 'Clinical pregnancy' was defined as the presence of a gestational sac seen on ultrasound. - Adverse pregnancy outcome reported was miscarriage.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Johnson,N.P., Stewart,A.W., Falkiner,J., Farquhar,C.M., Milsom,S., Singh,V.P., Okonkwo,Q.L., Buckingham,K.L., REACT-NZ (REproduction And Collaborative Trials in New Zealand), PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene, Human Reproduction, 25, 1675-1683, 2010 **Ref ID** 92842 **Country/ies where the study was carried out** New Zealand **Study type** RCT (Multi-centre trial) **Aim of the study** To assess whether metformin provides benefit when added to standard treatment and to assess the best first line treatment for women with ovulation dysfunction related to PCOS. **Study dates** 21 August 2003 - 28 February 2007 **Source of funding** Supported by grants from Auckland Medical Research Foundation, Mercia Barnes Trust and University of Auckland Research Committee.	**Sample size** n = 171 women. [1] Metformin = 35 [2] Clomiphene citrate = 36 [3] Metformin + CC = 35 **Characteristics** Age in years ± SD Metformin = 28.9 ± 4.4 CC = 28.2 ± 4.0 Metformin + CC = 29.2 ± 4.7 BMI ± SD Metformin = 26.5 ± 3.5 CC = 26.2 ± 3.4 Metformin + CC = 26.9 ± 4.1 Median Duration of infertility in years (IQR) Metformin = 1.5 (1 - 4) CC = 2 (1 - 3) Metformin + CC = 2 (1.5 - 5) **Inclusion criteria** - Anovulatory or oligo-ovulatory women with PCOS defined by the Rotterdam consensus criteria **Exclusion criteria** - Previous fertility treatment involving more than 5 months treatment with CC or metformin. - Any other important infertility factor known to be present including known tubal factor where at least one fallopian tube was blocked. However, women known to have stage 1 or 2 endometriosis and men with very	Metformin + CC Comparison 1 Metformin Comparison 2 Clomiphene citrate (CC)	Metformin + CC Metformin 500 mg standard release tablets, CC 50 mg tablets with identical placebo tablets (to maintain blinding) for both metformin and CC were purchased from Pacific pharmaceuticals and packaged in the research pharmacy. Each patient received up to two 3-month treatment packages. Drugs were commenced concurrently and standard monitoring as for a CC cycle was undertaken in each case, with any required dose modifications initiated as previously described (Johnson, 2006). Briefly, metformin 500 mg three times daily in a gradual increasing dose over 2 weeks was given: for CC 50 mg was the initial dose and 150 mg the highest dose used. All study drugs were stopped once pregnancy was diagnosed.	Live birth: Metformin + CC = 15/35 (43%) Metformin = 10/35 (29%) CC = 13/36 (36%) Pregnancy (clinical): Metformin + CC = 19/35 (54%) Metformin = 14/35 (40%) CC = 14/36 (39%) Multiple pregnancy: Metformin + CC = 1/35 (2.9%) Metformin = 1/35 (2.9%) CC = 1/36 (2.8%) Miscarriage: Metformin + CC = 3/35 Metformin = 4/35 CC = 0 Adverse pregnancy outcome: Metformin + CC = 19/19 (100%) Metformin = 15/14 (28.6%) CC = 11/14 (78.6%)	**Limitations** Indirectness of population: The study population were of BMI ≤32 kg/m^2, the results may not be generalisable to a population of higher BMI. **Other information** - Figures for 'Live full term singleton birth' reflect 'Live birth' outcome and no definition was given for this. This may include preterm and multiple births. - Clinical pregnancy was defined as positive urine or serum pregnancy test plus visualisation of intrauterine gestation sac on ultrasound scan or histological evidence of trophoblastic tissue with spontaneous abortion or ectopic pregnancy. - Adverse pregnancy outcomes were grouped under serious, moderate and mild adverse events. It is unclear

	mild oligospermia were included. - Women with important medical disorders.			Fetal abnormalities: Metformin + CC = 0 Metformin = 0 CC = 1/14 (7.1%) Pregnancy related complications: <u>Ectopic pregnancy</u> Metformin + CC = 1/19 (5.3%) Metformin = 0 CC = 0 <u>Gestational hypertension</u> Metformin + CC = 1/19 (5.3%) Metformin = 0 CC = 2/14 (14.3%) <u>Gestational diabetes</u> Metformin + CC = 1/19 (5.3%) Metformin = 0 CC = 0 <u>Preterm labour or PPROM</u> Metformin + CC = 1/19 (5.3%) Metformin = 0 CC = 1/14 (7.1%)	what these adverse events were and some patients also had severity combinations. - Figures for 'Multiple births' reflects multiple pregnancy. It is unclear if all the pregnancies resulted in births. Others -Specific side effects mentioned were vasomotor and gastrointestinal side effects. -Pregnancy related complications were ectopic pregnancy, gestational hypertension, gestational diabetes, preterm labour or PPROM.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Malkawi,H.Y., Qublan,H.S., The effect of metform plus clomiphene citrate on ovulation and pregnancy rates in clomiphene-resistant women with polycystic ovary syndrome, Saudi Medical Journal, 23, 663-666, 2002 **Ref ID** 92893 **Country/ies where the study was carried out** Jordan **Study type** RCT **Aim of the study** To study the effect of metformin in combination with clomiphene citrate, as compared with placebo plus clomiphene citrate, on the ovulation and pregnancy rates in clomiphene resistant women with polycystic ovary syndrome **Study dates** January 2001 - July 2001 **Source of funding** Not reported	**Sample size** N = 28 [1] Metformin + CC = 16 [2] Placebo + CC = 12 **Characteristics** Age in years ±SD: Metformin + CC: 29±3.1 Placebo + CC: 29±7.3 BMI ±SD: Metformin + CC: 27.5±4.1 Placebo + CC: 27.8±3.3 Duration of infertility in years ±SD: Metformin + CC: 3.2±1.1 Placebo + CC: 3.0±1.3 **Inclusion criteria** - CC-resistant PCOS women - Normal uterine cavity and tubal patency on HSG - Normal semen parameters (WHO 1999 criteria) **Exclusion criteria** - Congenital adrenal hyperplasia - Cushing's syndrome - Hyperprolactinemia - Thyroid disease	Metformin + CC Comparison Placebo + CC	Metformin + CC Women were randomly assigned to receive 850mg of Metformin twice daily throught the cycle along with 50mg CC, starting on day 5-9 of the same cycle. Placebo + CC Women assigned to take Placebo with CC During cycles 2-6, CC was added with increments of 50mg (up to 200mg/day) for both groups. With ovulation daily dose of CC was unchanged, but with anovulation, it was increased by 50mg for the next cycle	Pregnancy: Metformin + CC: 9/16 (56.3%) Placebo + CC: 2/12 (16.6%) OHSS: Metformin + CC: 0 Placebo + CC: 2/12 (16.6%)	**Limitations** Method of randomisation not described Blinding and power calculation not described **Other information** Diagnosis of PCOS was based on the presence of polycystic ovaries on vaginal ultrasound examination combined with 3 or more of the following criteria: oligomenorrhea (<6 menstrual periods in the preceding year), hirsutism (when Ferriman-Gallwey score >7), hyperandrogenemia (elevated free testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), and elevated concentrations of LH/FSH ratio >2. CC-resistance was

					defined as failure to ovulate or to conceive after CC treatment up to daily dose of 150mg from cycle day 5-9 for at least 3 consecutive cycles Clinical pregnancy was considered when gestational sac was detected by ultrasonography

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sahin,Y., Yirmibeş, U, timur,F., Aygen,E., The effects of metformin on insulin resistance, clomiphene-induced ovulation and pregnancy rates in women with polycystic ovary syndrome, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 113, 214-220, 2004 **Ref ID** 92995 **Country/ies where the study was carried out** Turkey **Study type** RCT **Aim of the study** To evaluate the effects of metformin on insulin resistance, ovarian androgen production, and clomiphene-induced ovulation and pregnancy rates in infertile women with polycystic ovary syndrome (PCOS) **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 21 women [1] Metformin + CC = 11 [2] CC = 10 **Characteristics** Age in years (range): Metformin + CC: 27 (21-31) CC: 24.5 (19-28) BMI (range): Metformin + CC: 30.4 (24.6-33.9) CC: 25.7 (23.1-35.7) Duration of infertility in years (range): Metformin + CC: 5 (2-10) CC: 3.5 (1-8) **Inclusion criteria** - PCOS - Infertility - Normal renal and liver function tests **Exclusion criteria** - Male factor infertility - Tubal-uterine factor infertility - Androgen secreting tumors of ovarian or adrenal origin - Cushing's syndrome - Thyroid dysfunctions - Non-classic adrenal hyperplasia - Hyperprolactinemia - Diabetes mellitus	Metformin + CC + hCG Comparison CC + hCG	Metformin + CC Metformin only was administered at a dose of 850mg two times daily for 3 months. Spontaneous ovulation was checked by assessing serum progesterone levels on day 21 of the cycle. After 3 months of metformin use, clomiphene citrate (CC) was added at a dose of 100mg/day from day 5-9 of each cycle. Metformin administration continued during induction of ovulation and terminated the day of hCG administration. The same treatment regimen was repeated until either pregnancy occurred, or a maximum of 6 CC cycles were reached. Follicular development was monitored by serial ultrasound scanning. Ovulation was induced by 10 000IU of hCG. CC CC was administered at a dose of 100mg/day from day 5-9 of each cycle. The same treatment regimen was repeated until either pregnancy occurred, or a maximum of 6 CC cycles were reached. Follicular development was monitored by serial ultrasound scanning. Ovulation was induced by 10 000IU of hCG.	Live birth Metformin + CC = 3/11 (27.3%) CC = 3/10 (30%) Pregnancy Metformin + CC = 5/11 (45.5%) CC = 3/10 (30%) Preterm delivery Metformin + CC = 1/5 (20%) CC = 0 Miscarriage Metformin + CC = 1/5 (20%) CC = 0 Adverse drug effects Metformin + CC = 0 CC = 1/10 (10%)* * One patient had one cycle cancelled due to the development of a large follicle cyst	**Limitations** - Method of randomisation not reported - Blinding and power analysis not reported **Other information** The diagnosis of PCOS was made on the basis of 3 or more of the following criteria: polycystic ovaries on pelvic ultrasound examination, oligo/amenorrhoea, hirsutism, hyperandrogenaemia (total testosterone >80 ng/dl and/or free testosterone > 3.18 pg/ml) and elevated serum LH:FSH ratio Pregnancy was defined by ultrasound evidence of gestational sac and the presence of fetal heart motion

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zakherah,M.S., Nasr,A., El,SamanA, Shaaban,O.M., Shahin,A.Y., Clomiphene citrate plus tamoxifen versus laparoscopic ovarian drilling in women with clomiphene-resistant polycystic ovary syndrome, International Journal of Gynecology and Obstetrics, 108, 240-243, 2010 **Ref ID** 93069 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To compare the effects of CC plus tamoxifen with those of laparoscopic ovarian drilling (LOD) in women with CC-resistant PCOS **Study dates** January 2007 - February 2009 **Source of funding** Not reported	**Sample size** N = 150 women [1] Surgery = 75 [2] CC + TMX = 75 **Characteristics** Age in years ±SD: Surgery: 25.6±4.1 CC + TMX: 25.6±3.5 BMI ±SD: Surgery: 27.9±6.3 CC + TMX: 27.7±4.2 Duration of infertility ±SD: Surgery: 5.6±2.8 CC + TMX: 6.0±2.6 **Inclusion criteria** - CC-resistant women with PCOS - Age between 18 and 38 years old - At least 2 years of primary or secondary infertility due to anovulation - Patent fallopian tubes on HSG or diagnostic laparoscopy - No hormonal treatment in the last 3 months - Normal semen analysis (WHO 1999) **Exclusion criteria** - Other etiologies of anovulation other than PCOS	Laparoscopic ovarian drilling + hCG + Timed intercourse Comparison CC + TMX + hCG + Timed intercourse	Surgery LOD was performed and the procedure was followed by timed intercourse in each cycle. CC + TMX Ovarian stimulation was achieved using 150mg of CC and 40mg of TMX from day 3-7 of the cycle. Induction cycles were repeated for a maximum of 6 consecutive cycles in women who did not become pregnant. In both groups ovulation was monitored using TVUS and 10 000IU of hCG was administered when at least 1 leading follicle was ≥18mm. Participants were advised to have intercourse 24 to 36 hours after hCG.	Live birth Surgery: 33/75 (44%) CC + TMX: 37/75 (49.3%) Pregnancy Surgery: 38/75 (50.6%) CC + TMX: 40/75 (53.3%) Miscarriage Surgery: 5/38 (13.2%) CC + TMX: 3/40 (7.5%)	**Limitations** Randomisation procedure described Power and sample size calculation described **Other information** CC-resistant PCOS was defined as a lack of ovulation after 6 consecutive induction cycles with 50mg of CC. then with 150mg daily for 5 days Criteria for diagnosis of PCOS that was used were as described in the 2003 ESHRE/ASRM Rotterdam consensus Biochemical pregnancy was defined as a decrease in βhCG concentration following increase. Clinical pregnancy was defined as the presence of a gestational sac with beating fetal heart on transvaginal ultrasound when the serum βhCG

					concentration was greater than 1500IU/l Miscarriage was defined as a spontaneous loss of pregnancy before the end of the 28th week

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Moll,E., Bossuyt,P.M., Korevaar,J.C., Lambalk,C.B., van,der,V, Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial, BMJ, 332, 1485-, 2006 **Ref ID** 112975 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To compare the effectiveness of clomiphene citrate plus metformin and clomiphene citrate plus placebo in women with newly diagnosed polycystic ovary syndrome **Study dates** June 2001 - May 2004 **Source of funding** Merck Sante France	**Sample size** N = 228 women Metformin + CC = 111 Placebo + CC = 114 **Characteristics** Age in years ±SD: Metformin + CC: 27.9±3.7 Placebo + CC: 28.4±4.7 BMI ±SD: Metformin + CC: 28.5±7.1 Placebo + CC: 27.8±6.7 Duration of infertility in years ±SD: Metformin + CC: 1.6±1.2 Placebo + CC: 1.3±1.1 **Inclusion criteria** - Chronic anovulation (menstrual cycle ≥35 days, WHO type II, normogonadotrophic, normo-oestrogenic, oligoanovulation or anovulation) and polycystic ovaries diagnosed by transvaginal ultrasound - Women wanting to conceive **Exclusion criteria** - Other causes of anovulation - Age >40 - Liver, kidney or heart disease or failure - Partner's sperm quality indicating subfertility (total sperm count <10X10^6	Metformin + CC Comparison Placebo + CC	Metformin + CC Women took metformin for one month. If no spontaneous menstruation occurred and the pregnancy test was negative one month after the study medication was started, the menstruation was induced with dydrogesterone 10mg three times a day for 10 days. From day 5 of the spontaneous or induced menstruation, women took 50mg of clomiphene citrate (CC) a day. If ovulation did not occur with this dose, it was increased with steps of 50mg to a maximum of 150mg a day the next cycles. Ovulation was detected either with a biphasic basal temperature curve, a follicle with a diameter ≥16mm on TVUS, or progesterone ≥14 nmol/l in the second half of the menstrual cycle. If a woman ovulated she continued taking the same dose of CC. Placebo + CC Women took placebo in the same way as described above Women received up to six cycles of medication	Live birth: Metformin + CC = 21/111 (19%) Placebo + CC = 30/114 (26.3%) Pregnancy (Clinical): Metformin + CC = 44/111 (40%) Placebo + CC = 52/114 (46%) Multiple pregnancy: Metformin + CC = 1/111 (0.9%) Placebo + CC = 3/114 (2.6%) Miscarriage: Metformin + CC = 13/44 (29.5%) Placebo + CC = 12/52 (23%) Premature delivery: Metformin + CC = 4/44 (9.0%) Placebo + CC = 3/52 (5.7%) Pregnancy related adverse events: Gestational diabetes: Metformin + CC = 1/44 (2.3%) Placebo + CC = 2/52 (3.8%) Hypertension: Metformin + CC = 4/44 (9%) Placebo + CC = 2/52 (3.8%) Pre-eclampsia: Metformin + CC = 1/44 (2.3%) Placebo + CC = 3/52 (5.7%)	**Limitations** Randomisation and blinding described Study was powered to detect difference in ovulation rate **Other information** Diagnosis of PCOS according to the revised Rotterdam 2003 consensus Tubal patency was not tested before induction of ovulation

				<u>Congenital abnormality:</u> Metformin + CC = 2/44 (4.5%) Placebo + CC = 1/52 (1.9%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abu,HashimH, Wafa,A., El,RakhawyM, Combined metformin and clomiphene citrate versus highly purified FSH for ovulation induction in clomiphene-resistant PCOS women: A randomised controlled trial, Gynecological Endocrinology, 27, -196, 2011 **Ref ID** 118226 **Country/ies where the study was carried out** Egypt **Study type** Randomised controlled trial **Aim of the study** To compare the effect of combined metforming-clomiphene citrate with highly purified urinary FSH for ovulation induction in CC-resistant women with PCOS. **Study dates** September 2007 to July 2009 **Source of funding** Not reported	**Sample size** n = 153 women **Characteristics** Age = 27.1 ± 2.3 years BMI = 26.3 ± 3.4 kg/m^2 Duration of infertility = 4.7 ± 1.4 years **Inclusion criteria** Diagnosis of PCOS was based on the revised 2003 Rotterdam consensus diagnostic criteria and long-term health risks related to PCOS. 1] All women were previously treated with 150 mg of CC daily for 5 days per cycle, for at least three cycles and had persistent anovulation. 2] They had patent fallopian tubes proved by hysterosalpingography and their partners semen analysis was normal. 3] Normal serum prolactin, TSH and 17-OHP **Exclusion criteria** 1] Other causes of infertility 2] Age over 40 years 3] BMI > 35 and women who had received metformin, gonadotrophin, OC or other hormal drugs during the preceding 6 months 4] Women who intented to start a diet or a specific program of physical activity	1] Group A : Combined metformin-CC 2] Group B: HP-uFSH	Method: Women were randomised according to a computer-generated random numeric table prepared by an independent statistician with concealment of treatment allocation by use of opaque envelopes that were given to a third party (nurse) who assigned patients to study arms: group A or group B. One allocated the treatment was revealed to both the investigator and the patient. However, the radiologist who performed transvaginal US assessment was blinded to the treatment groups. Intervention: In group A, all patients received metformin HCl, 500 mg thrice daily for 6-8 weeks. At the end of this period, they received 100 mg CC for 5 days starting from day 3 of spontaneous or induced menstruation. hCG was given when one follicle measured at least 18 mm.Patients were advised to have intercourse 24 to 36 h after thCG injection. In group B, ovulation induction was carried out with HP-uFSH by using low-dose, step-up regimen for three cycles. HP-uFSH was commenced on day 3 following spontanous or induced menses with a starting dose of 75 IU daily i.m. Dose was increased by 37.5 IU daily every 7 days if there was no evidence of ovarian response by ultrasonography. When folliclular development had started, the dose was not altered. Patients were monitored by transvaginal US for the	<u>Pregnancy</u> Metformin-CC = 18/75 (24%) HP-uFSH = 32/78 (41%) <u>Multiple pregnancy</u> Metformin-CC = 2/75 (2.7%) HP-uFSH = 6/78 (7.7%) <u>Adverse pregnancy outcome</u> Metformin-CC = 4/75 (5.3%) HP-uFSH = 5/78 (6.4%)	**Limitations** 1] Power calculation not reported for pregnancy outcomes **Other information** 1] A rising serum Beter-hCG 2 weeks after hCG injection in the absence of menstruation and the sonographic evidence for intrauterine gestational sac at 6 weeks gestation were considered criteria to define a pregnancy. 2] Only twin pregnancies were reported. It is not clear whether there were other multiple pregnancies 3] Adverse pregnancy outcomes reported were miscarriages. 4] 6/75 patients in the metformin-CC group suffered gastrointestinal side effects mainly nausea and vomiting but they continued therapy.

			mean follicular diameter and endometrial thickness every other day. Statistical analysis: The primary outcome measures were principally the ovulation rate as well as the number of growing and mature follicles, serum E", endometrial thickness at the time of hCG administration and serum P in the luteal phase. Secondary outcome measures were pregnancy and miscarriage rates. Sample size was based upon the fact that with an expected rate of ovulation of 85% in the HP-uFSH group. 146 women were required to show an absolute difference of -20% in ovulation rate in the combined metformin-CC group, with a power of 80% at 95% CI		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abu,Hashim H., El,Lakany N., Sherief,L., Combined metformin and clomiphene citrate versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial, Journal of Obstetrics and Gynaecology Research, 37, 169-177, 2011 **Ref ID** 129427 **Country/ies where the study was carried out** Egypt **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of combined metformin-CC administration for six cycles to that of LOD for ovulation induction in CC-resistant infertile women with PCOS **Study dates** September 2005 to February 2009 **Source of funding** None reported	**Sample size** 282 women **Characteristics** Mean age: Metformin-CC= 27.2 years +/- 2.5 LOD= 26.5 years +/- 2/3 Duration of infertility: Metformin-CC= 4.4 years +/- 1.2 LOD= 4.6 years +/- 1.3 Mean BMI: Metformin-CC= 26.2 +/- 3.4 LOD= 26.1 +/- 3.5 No significant differences between the groups **Inclusion criteria** Previous treatment with 150mg CC daily for five days per cycle, for at least three cycles, with persistent anovulation Patent Fallopian tubes proved by hysterosalpingography Normal semen analysis Normal serum prolactin, thyroid-stimulating hormone and 17-hydroxyprogesterone **Exclusion criteria** Other causes of infertility > 40 years Contraindications to general	Combined metformin-clomiphene citrate (n= 138) Laproscopic ovarian drilling (LOD) (n= 144)	Sample size was based upon the fact that with an expected rate of ovulation of 70% in the LOD group, 244 women were needed to show an absolute increase of 15% in ovulation rate in the combined-CC group, with a power of 80% at confidence intervals of 95% using a two tailed X2 test with a 5% significance level (type a error). Women were instructed to maintain their usual lifestyle and eating habits during the study Ethics approval was given Women were randomised according to a computer-generated random numeric table. Opaque envelopes that were numbered and sealed containing the allocation information were given to a third party who assigned women to study arms. Metformin group received metformin HCl 500mg thrice daily for 6 to 8 weeks. They then received 100mg clomiphene citrate for 5 days starting from day 3 of spontaneous or induced menstruation. With anovulation, it was increased by 50mg for the next cycle. If patients ovulated in six subsequent cycles, became pregnant, or experience anovulation with 150mg CC, no further treatment was given. Metformin was stopped only when pregnancy was documented. Patients	Pregnancy: Metformin-CC= 89/138 (64%) women* LOD= 95/144 (66%) women* Pregnancy indicated by rising serum B-hCG two weeks after the hCG injection in the absence of menstruation and sonographic evidence of an intrauterine gestational sac at 6 weeks' gestation Miscarriage: Metformin-CC= 8/138 (6%) women, 8/89 (9%) pregnancies LOD= 9/144 (6%) women, 9/95 (9%) pregnancies Multiple pregnancies: Metformin-CC= 4 multiple pregnancies out of 138 women* (3%), 4 multiple pregnancies out of 89 pregnancies (4%) (all twins) LOD= 0 multiple pregnancies out of 144 women (0%), 0 multiple pregnancies out of 95 (0%) pregnancies No higher order pregnancies occured No incidences of OHSS occured in either group	**Limitations** No serious limitations **Other information** *this is not reported per woman in the study. As women received up to six cycles, it is possible that some women miscarried in an early cycle and then conceived again in a later cycle.

	anesthetic Use of metformin, gonadtrophin or oral contraceptives in preceeding six months		were advised to have intercourse 24-36 hours after hCG injection. All women showing ovulation were advised to undertake natural intercourse.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sheikh-El-Arab,ElsedeekM, Elmaghraby,H.A.H., Predictors and characteristics of letrozole induced ovulation in comparison with clomiphene induced ovulation in anovulatory PCOS women, Middle East Fertility Society Journal, 16, 125-130, 2011 **Ref ID** 149818 **Country/ies where the study was carried out** Egypt **Study type** Randomised controlled trial **Aim of the study** To explore the use of aromatase inhibitors for routine ovulation induction **Study dates** Not reported **Source of funding** Not reported	**Sample size** 122 women **Characteristics** Age: CC= 25 +/- 3.59 years Letrozole= 24/95 +/- 3.11 years Not a significant difference Weight: CC= 74 +/- 10.7 (unit not reported) Letrozole= 71.35 +/- 11.42 (unit not reported) Not a significant difference BMI: CC= 29.18 +/- 3.47 Letrozole= 27.7 +/- 3.48 Not a significant difference Groups were also comparable for duration of infertility **Inclusion criteria** PCOS Nulliparous **Exclusion criteria** BMI > 35 Presence of other causes of infertility > 5 years infertility duration Known poor response to either drugs in previous cycles Baseline ovarian cysts or	Clomifene citrate (62 women) Letrozole (62 women)	Women were randomised using computer generated tables to undergo one cycle of either CC or letrozole CC: 100 mg/day for 5 days Letrozole: 5 mg/day for 5 days Both patients and sonographers were blinded to the allocation.	Clinical pregnancy: (defined as sonographically visualised intra-uterine gestational sac with pulsating fetal pole) CC= 16/57 (28%) Letrozole= 20/59 Not a significant difference	**Limitations** A power calculation was not reported **Other information** 5 women in the CC group and 3 in the letrozole group were lost to follow up (no women discontinued the intervention).
	endometrial pathology				

Fertility (Updated guideline)

in women with unexplained infertility

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Badawy,A., Shokeir,T., Allam,A.F., Abdelhady,H., Pregnancy outcome after ovulation induction with aromatase inhibitors or clomiphene citrate in unexplained infertility, Acta Obstetricia et Gynecologica Scandinavica, 88, 187-191, 2009 **Ref ID** 53430 **Country/ies where the study was carried out** Egypt **Study type** Randomised controlled trial **Aim of the study** To present the pregnancy and neonatal outcomes following the use of aromatase inhibitors and CC for ovulation induction in comparison with the outcome after spontaneous (non-stimulated) pregnancy **Study dates** From October 2003 to March 2007 **Source of funding** Not reported	**Sample size** n= 996 **Characteristics** All women had at least one year of continuous marriage without conception. All women had patent Fallopian tubes and normal ovulating cycles. All men had normal semen analysis. Mean age: Letrozole group= 25.8 +- 3.2 years Anastrozole group= 24.3 +- 2.9 years Clomiphene citrate group= 23.5 +- 2.6 years No significant differences between the groups **Inclusion criteria**	Letrozole (aromatase inhibitor, 5mg days 3 to 5) + hCG (269 couples) Intervention 2 Anastrazole (aromatase inhibitor, 1mg days 3 to 5) + hCG (107 couples) Intervention 3 Clomiphene citrate (100mg days 3 to 5) + hCG (420 couples) Comparator Age matched control group (200 women)	Couples were randomly allocated to one of the three treatment groups using a computer generated random table. A control group of women who conceived naturally during the same period were also used in the study hCG injection given when at least one follicle =>18mm. Couples were advised to have intercourse 24-36 hours after hCG. In the absence of menstruation serum hCG was determined for diagnosis of pregnancy The control group were an age-matched group who 'conceived naturally during the same period'	Cycles Letrozole + hCG= 323 Anastrozole + hCG= 143 Clomiphene citrate + hCG= 634 Age matched control= 298 Couples Letrozole + hCG= 269 Anastrozole + hCG= 107 Clomiphene citrate + hCG= 420 Age matched control= 200 Deliveries Letrozole + hCG= 30/323 (9%) Anastrozole + hCG= 11/143 (8%) Clomiphene citrate + hCG= 65/634 (10%) Age matched control= 23/298 (8%) Clinical pregnancy Letrozole+hCG= 36/323 (11%) Anastrozole + hCG= 15/142 (11%) Clomiphene citrate + hCG= 77/634 (12%) Age matched control= 21/298 (7%) OHSS Letrozole + hCG= 0/323 (0%)	**Limitations** Blinding was not performed **Other information** The definition of clinical pregnancy was not reported The two cases of congenital abnormalities in the letrozole group were complete cleft palate and one case of major congenital heart problem, which ended in early neonatal death

	Women with unexplained fertility attending an Egyptian university's outpatient clinic and private practice settings **Exclusion criteria** None reported			Anastrozole + hCG= 0/143 (0%) Clomiphene citrate + hCG= 0/634 (0%) Congenital abnormalities Letrozole + hCG= 2/323 (1%) Anastrozole + hCCG= 0/143 (0%) Clomiphene citrate + hCG= 1/634 (<1%) Age matched control= 1/298 (<1%) Multiple pregnancies Letrozole + hCG= 3 Anastrozole + hCG= 1 Clomiphene citrate + hCG= 7 Miscarriage Letrozole + hCG= 6 Anastrozole + hCG= 3 Clomiphene citrate + hCG= 11 Ectopic pregnancy Letrozole + hCG= 0 Anastozole + hCG= 0 Clomiphene citrate + hCG= 1 Pre-term births Letrozole + hCG= 4 Anastrozole + hCG= 1 Clomiphene citrate + hCG= 2 No significant differences between the groups were reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008 **Ref ID** 68035 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of clomiphene citrate and IUI compared with expectant management in couples with unexplained infertility **Study dates** From September 2001 to September 2005 **Source of funding** Chief Scientist Office, Scotland	**Sample size** n= 580 couples **Characteristics** <u>Mean Age (SD):</u> Women: Clomiphene citrate group= 32 (3.5) years Expectant management group= 32 (3.4) years Unstimulated IUI group= 32 (3.7) years Men: Clomiphene citrate group= 34 (5.1) years Expectant management group= 34 (5.1) years Unstimulated IUI group= 34 (5.2) years Mild endometriosis: Clomiphene citrate group= 9/194 (5%) Expectant management group= 17/193 (9%) Unstimulated IUI group= 13/193 (7%) Mild factor male infertility: Clomiphene citrate group= 11/194 (6%) Expectant management group= 9/193 (5%) Unstimulated IUI group= 14/193 (7%)	Clomiphene citrate (n= 192) Intervention 2 'Expectant management' group that received only general advice (n= 193) Intervention 3 Unstimulated IUI (n= 191)	Randomisation was performed with an independent statistician generating a randomisation allocation sequence. Participants were assigned by nurses using a central telephone randomisation system. Duration of the intervention was 6 months and women were followed up for these six months Clomiphene citrate group: 50mg dose between day 2 and day 6 of each treatment cycle. Couples were advised to have intercourse on days 12 to 18 of the cycle. If three or more ovarian follicles were detected in the first cycle, the cycle was cancelled and couple advised to avoid intercourse. These women received a reduced dose of clomifene (25mg) on the second cycle, with a further reduction to alternate days of 25mg in the third cycle (if necessary). Expected management group: Six months of no clinic visits or medical interventions. General advice given regarding need for regular intercourse, no specific measures	Cycles Clomiphene citrate= 883 Advice only= 1158* Unstimulated IUI= 785 Couples Clomiphene citrate= 192 Advice only= 193 Unstimulated IUI= 191 Live birth Clomiphene citrate= 26/883 (3%) Advice only= 32/1158* (3%) Unstimulated IUI= 43/785 (5%) Clinical pregnancy Clomiphene citrate= 29/883 (3%) Advice only= 33/1158* (3%) Unstimulated IUI= 43/785 (5%) Miscarriage Clomiphene citrate= 10/883 (1%) Advice only= 14/1158* (1%) Unstimulated IUI= 9/785 (1%) Ectopic pregnancy Clomiphene citrate= 0/883 (0%) Advice only= 1/1158* (<1%) Unstimulated IUI= 2/785 (<1%) Preterm birth Clomiphene citrate= 3/883 (<1%)	**Limitations** No serious limitations **Other information** *estimated by the reviewer as 6 cycles per couple (1 cycle per month over 6 months) Clinical pregnancy was confirmed by the presence of an intrauterine gestatinal sac on ultrasonography, with a fetal heartbeat five weeks later Spontaneous pregnancies in the clomiphene citrate and unstimulated IUI arms were included in the final analysis. Three women (2%) in the clomiphene citrate group and 14 (7%) in the unstimulated IUI group became pregnant spontaneously and had a live birth. 2 couples in the clomiphene citrate group and 2 women in the unstimulated IUI group were lost to follow up Some women received alternative treatment to that for which they were randomly allocated. 6 women allocated to expectant management received clomiphene citrate (n= 3) or unstimulated IUI (n=

	Median female BMI (IQR): Clomiphene citrate group= 23 (22 to 26) Expectant management group= 23 (21 to 25) Unstimulated IUI group= 23 (21 to 26) Anxiety (HADS subscale ≥ 11): Clomiphene citrate group= 28/194 (14%) Expectant management group= 29/193 (15%) Unstimulated IUI group= 23/193 (12%) Depression (HADS subscale ≥ 11): Clomiphene citrate group= 1/194 (1%) Expectant management group= 3/193 (2%) Unstimulated IUI group= 2/193 (1%) **Inclusion criteria** • At least two years of infertility • Bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography) • Ovulation demonstrated by appropriately timed mid-luteal progesterone • Normal semen variables **Exclusion criteria** None reported		recommended. Unstimulated IUI group: Single insemination performed 20 to 30 hours after an endogenous surge detected by mid-morning urinary luteinising hormone concentration. Couples were advised to avoid intercourse from day 12 of the cycle until the day of insemination. A woman who missed a luteising hormone surge did not receive IUI in that cycle A pregnancy test was performed two weeks after IUI and by day 28 in the clomiphene citrate and expectant management groups Women who miscarried within six months of randomisation were allowed to have further treatment in their randomised groups for the rest of their allocated time	Advice only= 5/1158* (<1%) Unstimulated IUI= 6/785 (1%) Treatment related hospital admission Clomiphene citrate= 2/192 (1%) Advice only= 2/193 (1%) Unstimulated IUI= 0/191 (0%) Abdominal pain Clomiphene citrate= 40/192 (21%) Advice only= 5/193 (3%) Unstimulated IUI= 12/191 (6%) Vaginal bleeding Clomiphene citrate= 7/192 (4%) Advice only= 4/193 (2%) Unstimulated IUI= 10/191 (5%) Nausea Clomiphene citrate= 22/192 (11%) Advice only= 4/193 (2%) Unstimulated IUI= 3/191 (2%) Vomiting Clomiphene citrate= 1/192 (1%) Advice only= 0/193 (0%) Unstimulated IUI= 0/191 (0%) Headache Clomiphene citrate= 33/192 (17%)	3). 26 women allocated to clomiphene citrate received expectant management (n= 24) or IUI (n= 2). 33 women allocated to unstimulated IUI received expectant management (32) or clomiphene citrate (n= 1)

				Advice only= 6/193 (3%) Unstimulated IUI= 4/191 (2%) Hot flushes Clomiphene citrate= 30/192 (16%) Advice only= 4/193 (2%) Unstimulated IUI= 0/191 (0%) Bloating Clomiphene citrate= 33/192 (17%) Advice only= 0/193 (0%) Unstimulated IUI= 6/191 (3%) Process of treatment acceptable Clomiphene citrate= 159/192 (83%) Advice only= 123/193 (64%) Unstimulated IUI= 155/191 (81%) Outcome of treatment acceptable Clomiphene citrate= 100/192 (52%) Advice only= 82/193 (42%) Unstimulated IUI= 117/191 (61%) Anxiety (HADS subscale => 11) Clomiphene citrate= 34/192 (18%) Advice only= 31/193 (16%)	

				Unstimulated IUI= 22/191 (12%) Depression (HADS subscale => 11) Clomiphene citrate= 4/192 (2%) Advice only= 4/193 (2%) Unstimulated IUI= 2/191 (1%) Multiple pregnancy Clomiphene citrate= 2/192 (1%) Advice only= 2/193 (1%) Unstimulated IUI= 1/191 (1%) Adjustment for maternal age, parity, duration of infertility and recruitment centre gave similar results for live birth. Number needed to treat for harm with clomiphene citrate compared to expectant management was 33 (10 to 24). Number needed to treat for benefit with unstimulated IUI compared to expectant management was 17 (51 to 7). There was no significant differences in the time to pregnancy leading to live	

				birth with clomiphene citrate or unstimulated IUI compared with expectant management.	

Fertility (Updated guideline)

What is the effectiveness of intrauterine insemination (IUI) compared with expectant management for unexplained infertility?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008 **Ref ID** 68035 **Country/ies where the study was carried out** Scotland **Study type** RCT **Aim of the study** To compare the effectiveness of CC and unstimulated IUI with expectant management for the treatment of unexplained infertility **Study dates** September 2001 - September 2005 **Source of funding** Chief Scientist Office, Scotland	**Sample size** N = 580 couples IUI = 193 EM = 193 CC = 194 **Characteristics** Mean Age years (±SD): IUI = 32 (± 3.7) EM = 32 (3.4) Median duration of infertility in months (range): IUI = 30 (25-40) EM= 30 (25-38) Infertility diagnosis (%) Pure unexplained infertility: n = 332 (86%) IUI = 165/191 EM= 167/193 Mild male infertility factor infertility and/or mild endometriosis: n = 57 (14%) IUI = 28/191 EM = 29/193	**Interventions** IUI **Comparisons** Expectant management (EM)	IUI: Women were asked to monitor mid-morning urinary LH from day 12 of their cycle using Clearview (Unipath, Bedford). A single insemination was performed 20-30h after endogenous LH surge was detected. Couples were advised to avoid intercourse from day 12 of the cycle until the day of the IUI EM: This involved 6 months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse, but no specific measures such as basal temperature charts or LH kits were recommended	Live birth (all): IUI = 43/191 (23%) EM= 32/193 (17%) Live birth (unexplained infertility): IUI = 38/165 (23%) EM= 26/167 (16%) Pregnancy (all): IUI = 43/191 (23%) EM= 33/193 (17%) Multiple pregnancy (all): IUI = 1/191 (1%) EM= 2/193 (1%) Pregnancy related adverse events: Miscarriage/pregnancy (all): IUI = 9/55 (10%) EM= 14/46 (30%) Ectopic/pregnancy (all): IUI = 2/55 (4%) EM= 1/46 (2%) Preterm birth/pregnancy (all): IUI = 6/43 (14%) EM= 5/31 (16%) Patient related adverse events: Treatment related hospital admissions:	**Limitations** - Method of randomisation: An independent statistician generated the randomisation allocation sequence. Research nurses enrolled participants in each centre and assigned them to their groups using a central telephone randomisation system (the coordinating centre). The minimisation algorithm balanced allocation of treatment by age, parity and durantion of subfertility. Women were stratified by centre. - Because of the nature of the intervention blinding was not possible. - Sample size calculation was performed (95% power at the 5% level of significance to detect a difference in live birth rates of 20% (10% to 30%; odds ratio 4) between expectant management

	Inclusion criteria [1] at least 2 years of infertility [2] bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography) [3] ovulation demonstrated by appropriately timed mid-luteal progesterone [4] normal semen variables **Exclusion criteria** Not reported			IUI = 0/163 (0%) EM= 2/160 (1%) <u>Abdominal pain:</u> IUI = 12/164 (7%) EM= 5/159 (3%) <u>Vaginal bleeding:</u> IUI = 10/164 (6%) EM= 4/159 3%) <u>Nausea:</u> IUI = 3/164 (2%) EM = 4/159 (3%) <u>Vomiting:</u> IUI = 0/164 (0%) EM= 0/158 (0%) <u>Headache:</u> IUI = 4/164 (3%) EM= 6/159 (4%) <u>Hot flushes:</u> IUI = 0/164 (0%) EM= 4/159 (3%) <u>Bloating:</u> IUI = 6/164 (4%) EM = 0/158 (0%) <u>Process of treatment acceptable (patient satisfaction)</u> IUI = 155/162 (96%) EM= 123/153 (80%) <u>Outcome of treatment acceptable (patient satisfaction)</u> IUI = 117/159 (74%)	and unstimulated IUI - Couples with mild male factor infertility (minimum sperm motility of 20%) and or minimal endometriosis were also included in the study (14% of sample in the IUI versus EM group) - 17% of women allocated to IUI (n = 33) received alternative treatment (EM) and 3% of women in the EM group (n = 6) received alternative treatment (IUI) **Other information** Clinical pregnancy was defined as the presence of an intrauterine gestational sac on ultrasonography, with a fetal heartbeat five weeks

				EM = 82/148 (55%) <u>Anxiety:</u> IUI = 22/173 (13%) EM= 31/171 (18%) <u>Depression:</u> IUI = 2/172 (1%) EM= 4/170 (3%)	

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Full citation Tummon,I.S., Asher,L.J., Martin,J.S., Tulandi,T., Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Fertility and Sterility, 68, 8-12, 1997 **Ref ID** 74873 **Country/ies where the study was carried out** Canada **Study type** RCT **Aim of the study** Evaluate the efficacy of superovulation and IUI versus no treatment for infertility associated with minimal or mild endometriosis. **Study dates** Couples were recruited between December 1990 to September 1993 **Source of funding** Funding from Serono Canada	**Sample size** 117 couples agreed to join study. 58 in superovulation plus IUI arm and 59 in the no treatment arm. Results are reported for 53 (91%) from the superovulation and IUI arm and 50 (85%) from the no treatment arm. **Characteristics** <u>Superovulation plus IUI group</u> Previous surgical reduction performed (%): 47 Female age (years): 31.2 (SD 4.5) Duration of infertility (months): 43 (SD 26) <u>No treatment group</u> Previous surgical reduction performed (%): 68 Female age (years): 30.6 (SD 3.3) Duration of infertility (months): 42 (SD 22) **Inclusion criteria** Female age 20 to 39 years, regular menstruation and	**Interventions** Ovarian stimulation: menstrual day 3 a daily IM injection of FSH. Initial dose of => 75 IU adjusted for weight and age. Dose adjusted after monitoring until at least 1 follicle >1.8cm. Final trigger with IM injection of 5,000 IU of hCG. IUI: sample prepared and transferred approximately 20 hours after trigger. **Comparisons** No treatment: no information given.	Ethics approval gained. Sample size calculation based on cycles at 80% power and 5% significnace assuming 15% difference in birth rates. Gave a sample size of 142 cycles per group. Statistical analysis using Cox proportional hazard model and Odd ratios at 5% significance level.	<u>Live biths</u> Superovulation plus IUI group = 14 of 53 No treatment = 4 of 50 <u>Live singleton biths</u> Superovulation plus IUI group = 11 of 53 No treatment = 4 of 50 <u>Live multiple biths</u> Superovulation plus IUI group = 3 of 53 No treatment = 0 of 50 <u>OHSS</u> Superovulation plus IUI group = 0 of 53 No treatment = 0 of 50 No other outcomes reported	**Limitations** Study design and analysis was based on cycles rather than couples. This can introduce bias as failed couples are more likely to fail again. Couples with greater than 4 follicles at 1.8cm or greater were offered IVF-ET. Method of randomisation was not described. Blinding was not described. Relatively high dropout rate from no treatment arm. Nine couples either did no start or were ineligible. **Other information**

	evidence of ovulation, normal serum PRL, normal TSH, bilaterla tubal patency, minimal or mild endometriosis diagnosed visually via laparoscopy in 12 months before enrollment, total motile count >40*10^6 on semen screening. Informed consent from both partners. **Exclusion criteria** Hormonal endometriosis therapy in 6 months before enrollment, ovulation induction within 3 months, previous ovulation indiction with gonadotrophins, bidy weight <52kg or >88kg. Day-3 FSH level => 20 mIU/mL.				

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Full citation Bensdorp,Alexandra, Cohlen,Ben J., Heineman,Jan Maas, Vanderkerchove,Patrick, Intra-uterine insemination for male subfertility, Cochrane Database of Systematic Reviews, -, 2010 **Ref ID** 88268 **Country/ies where the study was carried out** **Study type** Cochrane systematic review **Aim of the study** The aim of this review was to determine whether for couples with male subfertility, IUI improves the live birth rates or ongoing pregnancy rates compared with timed intercourse (TI), with or without OH. Only data for natural cycle/expectant management comparisons was extracted. **Study dates** Cochrane Menstrual and Disorders Subfertility Group Trials Special Register, the Cochrane Central Register of Controlled Trials (the Cochrane Library, 2006, issue 3), MEDLINE (1966 to May 2006), EMBASE (1980 to May 2006), SCIsearch and the reference lists of articles. **Source of funding** Not stated	**Sample size** <u>Goverde</u> Number of cycles started: 248 whole group (incl IVF) <u>Guzick</u> Number of couples: 932 **Characteristics** <u>Goverde</u> Couples: male and unexplained subfertility Definition male subfertility: total motile sperm count of < 20 million progressively motile sperm. Number of semen samples: 3 out of 5 Mean age women whole group IUI + OH 31.7 ys, (SD± 3.92), IUI 31.6 ys (SD ± 3.73) Duration subfertility IUI + NC 3.9 (± 1.7); IUI + OH 4.2 (± 1.9)	**Interventions** 1) IUI versus TI or expectant management both in natural cycles 2) IUI versus TI both in cycles with OH 3) IUI in natural cycles versus TI + OH 4) IUI + OH versus TI in natural cycles 5) IUI in natural cycles versus IUI + OH **Comparisons**	Standard Cochrane review methodology. Binary data for each comparison and each study were summarised in a two-by-two table and expressed as odds ratios with 95%confidence intervals. Where appropriate, data were pooled and a metaanalysis was performed with RevMan software (using the Petomodified Mantel-Haenszel method) using a fixed-effect model.	<u>Live births</u> Number of studies 2 Number of women 20 of 53 Risk Ratio (M-H, Fixed, 95% CI) 0.92 [0.46, 1.83] <u>Pregnancies</u> Number of studies 2 Number of women 20 of 305 Risk Ratio (M-H, Fixed, 95% CI) 1.35 [0.94, 1.95]	**Limitations** Data is based on personal correspondence between authors of review and the RCTs. The reduced sample sizes means statistical usefullness of results are reduced. **Other information** Only data on sub-groups from the Guzick and Goverde RCTs included in the evidence table.

	Ovulatory Status: BBT, endometrial biopsy Tubal Patency: DLS + HSG PCT: done Previous treatment: not stated. Couples: male and unexplained subfertility Definition male subfertility: total motile sperm count of < 20 million progressively motile sperm. Number of semen samples: 3 out of 5 Mean age women whole group IUI + OH 31.7 ys, (SD± 3.92), IUI 31.6 ys (SD ± 3.73) Duration subfertility IUI + NC 3.9 (± 1.7); IUI + OH 4.2 (± 1.9) Ovulatory Status: BBT, endometrial biopsy Tubal Patency: DLS + HSG PCT: done				

	Previous treatment: not stated. <u>Guzick</u> Couples: male and unexplained subfertility Definition male subfertility (SF): <20* million sperm concentration, motility <50% . Number of semen samples: not stated. Age women whole group:32 ys, (SD± 4.0) Duration SF:> 1 yr IUI + NC 3.8 (± 2.6); IUI + OH 3.5.2 (± 2.2) Ovulatory Status: in phase endometrial biopsy Tubal Patency: DLS + HSG PCT: not stated Previous treatment: not stated.				

	Inclusion criteria Participants included were couples with male subfertility who had been trying to conceive for at least one year, with evidence of the following: (1) Ovulation confirmed by: (a) biphasic basal body temperature chart, or (b) mid luteal progesterone within the ovulatory range, or (c) in-phase endometrial biopsy, or (d) ultrasound evidence of ovulation. (2) Tubal patency of at least one tube confirmed by hysterosalpingographyand/or laparoscopy. (3) Male subfertility: All men with male factor infertility, including oligo, terato and or asthenospermia, preferably measured in two separate semen samples, were included.				

	Exclusion criteria Participants which were excluded; (1) Couples with female subfertility as the primary reason for the subfertility (e.g. tubal diseases, cervical hostility, anovulation). Authors were contacted to obtain the raw data. If data regarding male subfertility could not be extracted separately, the study was excluded. (2) Couples with unexplained subfertility. Studies in which only couples with unexplained subfertility were treated were excluded because this is the subject of a different review (Verhulst 2006). (3) Couples withmale factor subfertility with normal spermcount parameters but anti-sperm antibodies as the only abnormality. (4) Couples where donor sperm was used for insemination.				

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Full citation VeltmanVerhulst,Susanne M., Cohlen,Ben J., Hughes,Edward, Heineman,Jan Maas, Te Velde,Egbert, Intra-uterine insemination for unexplained subfertility, Cochrane Database of Systematic Reviews, -, 2010 **Ref ID** 90575 **Country/ies where the study was carried out** **Study type** Cochrane systematic reviw **Aim of the study** To determine whether for couples with unexplained subfertility IUI improves the live birth rate compared with timed intercourse (TI), both with and without ovarian hyperstimulation. **Study dates** Cochrane Menstrual Disorder and Subfertility Group Trials Register (searched March 2005), the Cochrane Central egister of Controlled Trials (The Cochrane Library 2005, Issue 4), MEDLINE (1966 to November 2005), EMBASE (1980 to November 2005), SCIsearch and reference lists of articles. **Source of funding** Not stated	**Sample size** 331 couple with unexplained infertility across 2 studies. **Characteristics** <u>Goverde</u> Couples with unexplained subfertility and couples with male factor subfertility Age: IUI+NC 31.6 years (±3.7); IUI+OH 31.7 years (±3.9) Duration of subfertility: IUI+NC 3.9 (±1.7); IUI+OH 4.2 (±1.9) Basic fertility work up normal, semen normal when >20 million progressive motile in ejaculate Previous treatment: not stated <u>Guzick</u> Couples with unexplained subfertility and couples with stage I or II treated endometriosis or male	**Interventions** - IUI versus TI, both in a natural cycle; - IUI versus TI, both in a stimulated cycle; - IUI in a natural cycle versus IUI in a stimulated cycle; - IUI with OH versus TI in natural cycle; - IUI in a natural cycle versus TI with OH. **Comparisons**	Standard Cochrane review methodology. Review based on RCT data only. <u>Goverde:</u> Trial design: parallel Single centre Randomisation: computer -generated randomisation schedule Allocation concealment: numbered, masked and sealed envelopes A power calculation was performed Nr of patients randomised: 120 Nr of withdrawals: unclear <u>Guzick</u> Trial design: Parallel Multicentre (10 clinical sites) Randomisation: computer generated permuted block	<u>Live births</u> Number of studies 2 Number of women 331 Risk Ratio (M-H, Fixed, 95% CI) 1.83 [1.18, 2.84] <u>Pregnancies</u> Number of studies 2 Number of women 331 Risk Ratio (M-H, Fixed, 95% CI) 1.83 [1.18, 2.84]	**Limitations** Results based on sub-group analysis and therefore liable to bias. Results based on personal communication between review authors and RCT authors **Other information** Only data on sub-groups from the Guzick and Goverde RCTs included in the evidence table.

	factor subfertility Age: IUI+NC 32 years (±4) IUI+OH 32 years (±4) Duration of subfertility: IUI+NC 3.8 (±2.6); IUI+OH 3.5 (±2.2) Basic fertility work up normal, semen normal (according to WHO 1992) Previous treatment: No previous treatment. (Pt excluded if previous ART) **Inclusion criteria** Participants included Couples with unexplained subfertility defined as follows. Normal ovulatory status (determined by either biphasic basal body temperature chart, normal luteal progesterone, in phase endometrial biopsy or ovulation detected with ultrasound). Tubal patency (determined by hysterosalpingography or laparoscopy, or both). A normal semen sample according toWHO		Allocation concealment: locked computer files Nr of Pt randomised: 932 (465 treated with IUI) Nr of Pt with unexplained subfertility: 211 Nr of withdrawals: 72 total (15%)		

	criteria current at the time of trial. - Sperm concentration of at least 20 x 106 per ml - total motility of at least 50% - normal morphology of at least 30% (WHO 1987, at least 50%) or Kruger criteria - no anti-sperm antibodies. **Exclusion criteria** Participants excluded Couples with a known cause of infertility including a moderate male factor, moderate to severe endometriosis (according to the ASRM classification), tubal disease and a cervical factor. Authors were contacted to obtain the raw data. If relevant data could not be extracted separately for included participants the study was excluded. Trials that included patients with mild to moderate endometriosis only were excluded.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cohlen,B.J., te Velde,E.R., van Kooij,R.J., Looman,C.W., Habbema,J.D., Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study, Human Reproduction, 13, 1553-1558, 1998 **Ref ID** 96328 **Country/ies where the study was carried out** **Study type** RCT cross-over design, but only data from pre-crossover outcomes presented. **Aim of the study** whether the use of controlled ovarian hyperstimulation with low-dose human menopausal gonadotrophin in couples with male subfertility leads to a higher probability of conception when intrauterine insemination (IUI) is applied **Study dates** **Source of funding**	**Sample size** **Characteristics** Couples; male subfertility Definition male subfertility (in at least 2 semen samples): concentration < 20 million/mL and/or motility < 40 % and /or normal morphology < 40%. Number of semen samples at least 2 Age of the women: 30.7 ys (range: 24-39). Duration of subfertility: 3.1 ys (range 2-9). Ovulatory status: BBT, NLP Tubal patency: HSG and/or DLS. PCT: done to exclude cervical factor. Previous treatment: not stated. No antibodies in semen. Couples; male subfertility Definition male subfertility (in at least 2 semen samples): concentration < 20 million/mL and/or motility < 40 % and /or normal morphology < 40%.	**Interventions** Comparison: IUI + OH versus IUI + NC Treatment duration: max 6 cycles Method OH: 75 IU hMG/day up to 150 IU/day max. (day 3- Ovulation induction: 5,000 IU hCG. Cancellation criteria: > 3 foll > 17 mm and E2 > 6,000 pmol/L, premature LH surge, no LH surge detected. Number of IUI per cycle: 1. Estimation of ovulation: LH in blood and ultrasound. Timing: OH cycle: 38-40 hrs after hCG. Natural / OH cycle with premature LH surge: 26 hrs after detecting LH-rise. Sperm preparation: Wash (Ham's F10) and Percoll. Comparison: IUI + OH versus IUI + NC Treatment duration: max 6 cycles	Design: Cross-over, alternating Method of Randomisation: Opaque sealed envelopes. Pre-cross-over data: available Power Calculation: stated Design: Cross-over, alternating Method of Randomisation: Opaque sealed envelopes. Pre-cross-over data: available Power Calculation: stated	<u>Pregnancy rates</u> IUI with stimulation = 3 of 36 IUI without stimulation = 4 of 38 <u>Miscarriages</u> IUI with stimulation = 3 of 36 IUI without stimulation = 3 of 38	**Limitations** Cross-over design so only data from pre-crossover reported. This impacts on statistical power of study. **Other information**

	Number of semen samples at least 2 Age of the women: 30.7 ys (range: 24-39). Duration of subfertility: 3.1 ys (range 2-9). Ovulatory status: BBT, NLP Tubal patency: HSG and/or DLS. PCT: done to exclude cervical factor. Previous treatment: not stated. No antibodies in semen. **Inclusion criteria** **Exclusion criteria**	Method OH: 75 IU hMG/day up to 150 IU/day max. (day 3- Ovulation induction: 5,000 IU hCG. Cancellation criteria: > 3 foll > 17 mm and E2 > 6,000 pmol/L, premature LH surge, no LH surge detected. Number of IUI per cycle: 1. Estimation of ovulation: LH in blood and ultrasound. Timing: OH cycle: 38-40 hrs after hCG. Natural / OH cycle with premature LH surge: 26 hrs after detecting LH-rise. Sperm preparation: Wash (Ham's F10) and Percoll. **Comparisons**			

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Full citation Goverde,A.J., McDonnell,J., Vermeiden,J.P.W., Schats,R., Rutten,F.F.H., Schoemaker,J., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: A randomised trial and cost-effectiveness analysis, Lancet, 355, 13-18, 2000 **Ref ID** 96385 **Country/ies where the study was carried out** Netherlands **Study type** RCT **Aim of the study** 'To investigate the efficacy of IUI, both in spontaneous and stimulated cycle, compared with that of IVF for both male subfertility and idiopathic subfertility' **Study dates** February 1992 - September 1995 **Source of funding** Health Insurance Executive Board, Amstelveen, Netherlands	**Sample size** N = 120 patients/486 cycles (idiopathic subfertility undergoing IUI) **Characteristics** <u>Mean (±SD) age of woman</u> IUI + ovarian stimulation = 31.73 (±3.92) years IUI alone = 31.61 (±3.73) years <u>Mean (±SD) years duration of infertility</u> IUI + ovarian stimulation = 4.2 (±1.87) IUI alone = 3.88 (±1.71) <u>Unexplained infertility</u> IUI + ovarian stimulation = 61 (71.8%) IUI alone = 59 (68.6%) <u>Male factor subfertility</u> IUI + ovarian stimulation = 24 (28.2%) IUI alone = 27 (31.4%) **Inclusion criteria** [1] diagnosis of unexplained infertility if no abnormality was found during the full infertility investigation [2] at least 3 years infertility **Exclusion criteria**	**Interventions** IUI + low dose FSH + hCG A low dose of FSH was given to achieve the growth of 2-3 dominant follicles before the administration of hCG and a single IUI was done 20-30h after the detection of the LH surge Comparison IUI in a spontaneous cycle timed to endogenous LH surge A single IUI was done 20-30h after the LH surge was detected **Comparisons**	Patients underwent a maximum of 6 IUI cycles. For IUI in mildly stimulated cycles, a low dose of daily FSH was given for ovarian stimulation before the administration of hCG. Patients tested urine twice daily for the occurence of the LH surge. In the event of such a surge, 10 000IU of hCG was given as soon as possible and a single IUI was done 20-30h after the LH surge. When no LH surge was detected in the presence of at least one follicle ≥18mm, 10 000IU of hCG was given and a single IUI was done 40-42h later. hCG was withheld and IUI was not done when transvaginal US showed >3 follicles with at least 18mm diameter or >6 follicles with a diameter of at least 14mm were present. The daily dose of FSH was increased in every subsequent cycle when the dose of the previous cycle had resulted in monofollicular growth.		**Limitations** Pregnancy rates included only the pregnancies that resulted in at least one livebirth Pregnancy rates were calculated per started cycle and cumulatively after termination of the treatment programme **Other information** Further considerations in Goverde et al., 2005

	[1] woman with cycle disorders [2] untreated endometriosis (American Fertility criteria grade 2-4) [3] bilateral occluded tubes [4] semen sample yielding <1 million progressively motile spermatozoa, >20% of spermatozoa carried antibodies, or >50% of spermatozoa had no acrosome				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P.W., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: Effects on pregnancy and multiple pregnancy rates, Human Reproduction, #20, 3141-3146, 2005 **Ref ID** 96386 **Country/ies where the study was carried out** **Study type** RCT **Aim of the study** To investigate data from an earlier prospective trial (Goverde et al., 2000) with regard to the specific question of whether the application of mild hyperstimulation in IUI cycles could be an alternative strategy for obtaining acceptable pregnancy rates while preventing a high multiple pregnancy rate, compared with natural cycles for IUI **Study dates** February 1992 - September 1995 **Source of funding** Financial support by the Health Insurance Executive Board, Amstelveen, Netherlands	**Sample size** N = 171 couples IUI + FSH = 85 IUI = 86 **Characteristics** <u>Age ±SD in years</u> IUI + FSH = 31.7 ± 3.9 IUI = 31.6 ± 3.7 <u>Duration of infertility ±SD in years</u> IUI + FSH = 4.2 ± 1.9 IUI = 3.9 ± 1.7 <u>Diagnosis of cause of infertility (%)</u> Unexplained infertility: n = 120/171 (70.2%) IUI + FSH = 61/85 (71.8%) IUI = 59/86 (68.6%) Male subfertility: n = 51/171 (29.8%) IUI + FSH = 24/85 (28.2%) IUI = 27/86 (31.4%) **Inclusion criteria** [1] Couples with unexplained infertility for at least 3 years [2] Mild to moderate male subfertility for at least 1 year **Exclusion criteria** [1] If the woman had cycle disorders [2] Untreated	**Interventions** IUI + FSH + hCG Comparison IUI <u>IUI + FSH</u> The stimulation protocol stipulated a low dose of FSH in order to limit the number of dominant follicles to ≤3, with the goal of optimizing the pregnancy rate while preventing a high multiple pregnancy rate. Baseline pelvic US was done at cycle day 3 and 75IU of FSH was injected daily until transvaginal US showed at least one follicle with a diameter of 18mm. Patients tested their urine twice daily (morning and evening void) for the occurence of an LH surge. In the event of such surge, 10000IU of hCG was given as soon as possible, and a single IUI was done 20-30h after the detection of the surge. When no LH		Live birth IUI + FSH = 31/85 (36.5%) IUI = 25/86 (29.1%) Ongoing pregnancy IUI + FSH = 33/85 (38.8%) IUI = 28/86 (32.6%) Singleton pregnancy IUI + FSH = 24/85 (28.2%) IUI = 27/86 (31.4%) Multiple pregnancy IUI + FSH = 9/85 (10.6%) IUI = 1*/86 (1.2%) * one monozygotic twin pregnancy but both twins were stillborn after premature rupture of membranes	**Limitations** - Method of randomisation: computer-generated randomisation schedule, administered by numbered masked and sealed envelopes - Power calculation for pregnancy rate per cycle **Other information** - Unexplained infertility was defined as couples with no abnormality found during extensive investigation of infertility, including basal body temperature chart, a late luteal phase endometrial biopsy, a post-coital test, a hysterosalpingogram, a diagnostic laparoscopy, and at least two semen analysis - Male subfertility was diagnosed if at least 3 out of 5 semen analysis showed a total motile sperm count of fewer than $20X10^6$ progressively motile spermatozoa in the ejaculate and if the remainder of the infertility investigation revealed no additional abnormalities

	endometriosis (American Fertility Society criteria grade 2-4) [3] Bilateral occluded tubes [4] Partner's semen sample yielded less than 1 million progressively motile spermatozoa after processing/centrifugation [5] >20% of spermatozoa carried antibodies [6] If more than 50% of spermatozoa had no acrosome	surge was detected in the presence of at least one follicle with a diameter of 18mm or more, 10000IU of hCG was given and a single IUI was done 40-42h later <u>IUI</u> Women underwent a basal transvaginal US assessment at the beginning of their menstrual period, and on the 10th day of the cycle. Patients tested their urine sample twice daily (second morning void and between 18:00 and 19:00) for the occurence of the endogenous LH surge. As soon as they had detected the LH surge, patients contacted the clinic and ultrasonography was performed to assess follicular development. A single IUI was done 20-30h after the detection of the LH peak **Comparisons**			- The administration of hCG was withheld and IUI was not performed when more than 3 follicles ≥18 mm or more than 6 follicles ≥14mm were present - Pregnancy was defined as ongoing pregnancy with at least one fetal heartbeat at 12 weeks of gestation - Multiple pregnancy was defined as more than one fetal heartbeat at 12 weeks gestation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network, New England Journal of Medicine, 340, 177-183, 1999 **Ref ID** 96394 **Country/ies where the study was carried out** US **Study type** RCT **Aim of the study** To report on the efficacy of superovulation and IUI **Study dates** Not reported **Source of funding** Cooperative Agreements with the National Institute of Child Health and Human Development and by Serono Laboratories	**Sample size** n = 465 couples/2301 cycles **Characteristics** <u>Women's Age ±SD years</u>: IUI + COH = 32 ±4 IUI alone = 32 ±4 <u>Duration of infertility (months):</u> IUI + COH = 42±26 IUI alone = 46±31 **Inclusion criteria** [1] Age ≤40 years for women and ≤55 years for men [2] Negative pregnancy test [3] Normal pelvis and uterine cavity [4] 'in phase' endometrial biopsy [5] negative serum antisperm antibody test [6] normal FSH and Thyrotropin on days 1-5 of cycle [7] regular cycles [8] history of infertility >1 year [9] Presence of any motile sperm on screening semen analysis **Exclusion criteria** [1] Previous use of IVF or other ART [2] Previous treatment with gonadotrophins	**Interventions** IUI + FSH Comparison: IUI timed to spontaneous ovulation **Comparisons**	Eligible couples were randomly assigned to one of 4 groups: intracervical insemination timed to the surge of LH, IUI timed to the surge of LH, superovulation + intracervical insemination or superovulation and IUI. Each couple received 4 treatment cycles Women assigned to the superovulation groups (Intracervical insemination or IUI) were treated according to a standard protocol where FSH was administered from day 3 to 7. Daily administration of FSH was continued, with the dose adjusted if necessary, until at least 2 follicles reached ≥18 mm and E2 concentration ranged from 500 to 3000pg/ml. Once these criteria were met, treatment with FSH was discontinued and 10 000IU of hCG was administered. A single insemination was performed 36 to 40 hours later	IUI + COH IUI alone couples 231 234 cycles 618 717 pregnancies 77 42 Term live birth 41 28 Preterm 9 2 Stillbirth 0 1	**Limitations** Mild endometriosis included in the sample Only biochemical pregnancies are reported **Other information** Definition of pregnancy: serum β-hCG was measured 15 days after IUI There were 17 of the 18 sets of twins were in the superovulation groups, however the authors do not report which group 6 women had OHSS requiring hospitalization During treatment 72 couples (IUI + COH = 50 and IUI alone = 22) withdrew for reasons related to treatment (i.e., absence of response to COH, OHSS and anovulatory cycles for two consecutive cycles) or for reasons not related to treatment (i.e. other medical problems, desire to adopt a child and the cost of treatment).

	[3] previous IUI with current partner [4] History of cronic disease [5] History of chemotherapy or radiation to the abdomen or pelvis [6] History of tubal surgery [7] Extensive tubal adhesions [8] Endometriosis of more than stage II [9] History of myomectomy, ovarian cystectomy or unilateral oophorectomy			Miscarriage 22 6 Induced abortion 0 1 Ectopic 4 2 Quadruplets 2 0 Triplets 3 0	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Steures,P., van der Steeg,J.W., Hompes,P.G., Habbema,J.D., Eijkemans,M.J., Broekmans,F.J., Verhoeve,H.R., Bossuyt,P.M., van,der,V, Mol,B.W., Collaborative Effort on the Clinical Evaluation in Reproductive Medicine, Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial, Lancet, 368, 216-221, 2006 **Ref ID** 96565 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To assess the effectiveness of intrauterine insemination with controlled ovarian stimulation compared to expectant management in couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy in the next 12 months **Study dates** June 1, 2002 - July 1, 2005 **Source of funding** ZonMW (The Netherlands Organization for Health Research and Development, The Hague, Netherlands)	**Sample size** n = 253 couples IUI + gonadotrophins = 127 Expectant management = 126 **Characteristics** Mean age years (±SD; range) IUI + gonadotrophins = 33 (±3.4; 23 - 40) Expectant management = 33 (±3.1; 24 - 38) Mean duration of subfertility years (±SD; range) IUI + gonadotrophins = 2.0 (±0.5; 1 - 3) Expectant management = 1.9 (±0.5; 1 - 3) **Inclusion criteria** [1] the couple had not conceived after at least a year of frequent unprotected intercourse [2] the woman <39 years [3] woman with regular cycles [4] the couple had an intermediate prognosis of spontaneous ongoing pregnancy within the next month (intermediate prognosis was defined as the chance of spontaneous ongoing	**Interventions** IUI + gonadotrophins **Comparisons** Expectant management	IUI + FSH or hMG Couples were randomly assigned to IUI + gonadotrophins or expectant management for 6 months. Couples assigned to IUI + gonadotrophins started treatment during the next menstrual cycle. Gonadotrophins, semen preparation and IUI regimens were done according to hospital specific protocols. Baseline transvaginal US was done on cycle day 3 to exclude ovarian cysts >20 mm. Thereafter women started daily injections of FSH or hMG until transvaginal US showed at least 1 follicle of at least 16mm in diameter. Ovulation was induced with hCG and women were inseminated 36-40h later. Cycles were cancelled if there were >3 follicles of diameter >16mm or >5 of diameter >12mm. Expectant management Couples assigned to expectant management were followed up until an ongoing pregnancy occured or for 6 months if no pregnancy occured.	Live birth: IUI + gonadotrophins = 28/127 (22.0%) Expectant management = 31/126 (24.6%) Pregnancy (Clinical/ongoing): IUI + gonadotrophins = 29/127 (22.8%) Expectant management = 30/126 (23.8%) Multiple pregnancy: IUI + gonadotrophins = 2/127 (1.6%) Expectant management = 1/126 (0.8%) Pregnancy related adverse events: Miscarriage: IUI + gonadotrophins = 13/42 (30.9%) Expectant management = 6/40 (15.0%)	**Limitations** Method of randomisation The randomisation sequence was computer generated in balanced block multiples of 2 or 4, stratified by centre. The sequence was concealed, and sealed opaque envelopes containing details of the treatment allocation were assembled by an independent person. No blinding reported - Sample size calculation was performed (80% power at 5% level of significance to detect a difference in ongoing pregnancy rates of 13% between expectant management and stimulated IUI - 25 (20%) women in the expectant management group started IUI before 6 months - 17 (7%) men had a sperm motility count of <10 million, 7 in the intervention group and 10 in the expectant management group (male

	pregnancy between 30% and 40% within the next 12 months) - computer model (http://www.freya.nl/probability.php) **Exclusion criteria** Not reported				factor infertility) - In 31 (24%) women assigned to the intervention group and in 32 (25%) assigned to expectant management group, tubal function had not been assessed by hysterosalpingography or laparoscopy before randomisation. In some couples participating in the study, cases of endometriosis and tubal pathology could not be ruled out since hysterosalpingography or laparoscopy were not done - The study protocol recommended use of gonadotrophins for ovarian stimulation, however in 11% of cycles clomifene citrate was used - In the IUI + gonadotrophins group there were 6 spontaneous pregnancies before IUI; one miscarried. 7 conceived spontaneously between IUI; one miscarried **Other information**

					Tubal pathology was judged to be absent if the chlamydia antibody test was negative or subsequent hysterosalpingography, laparoscopy, or both showed two normal patent tubes. Those for whom the tubal function had been assessed only by chlamydia antibody test at the time of randomisation sometimes would have a hysterosalpingography or laparoscopy before the first cycle of gonadotrophins or after 3 cycles of treatment. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography at a duration of gestation of at least 12 weeks

Fertility (Updated guideline)

What is the effectiveness of intrauterine insemination (IUI), with or without ovulation induction agents, for unexplained infertility? (Part 2)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: effects on pregnancy and multiple pregnancy rates, Human Reproduction, 20, 3141-3146, 2005 **Ref ID** 4127 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To investigate data from an earlier prospective trial (Goverde et al., 2000) with regard to the specific question of whether the application of mild hyperstimulation in IUI cycles could be an alternative strategy for obtaining acceptable pregnancy rates	**Sample size** N = 171 couples IUI + FSH = 85 IUI = 86 **Characteristics** <u>Age ±SD in years</u> IUI + FSH = 31.7 ± 3.9 IUI = 31.6 ± 3.7 <u>Duration of infertility ±SD in years</u> IUI + FSH = 4.2 ± 1.9 IUI = 3.9 ± 1.7 <u>Diagnosis of cause of infertility (%)</u> Unexplained infertility: n = 120/171 (70.2%) IUI + FSH = 61/85 (71.8%) IUI = 59/86 (68.6%) Male subfertility: n = 51/171 (29.8%) IUI + FSH = 24/85 (28.2%) IUI = 27/86 (31.4%) **Inclusion criteria**	IUI + FSH + hCG Comparison IUI	<u>IUI + FSH</u> The stimulation protocol stipulated a low dose of FSH in order to limit the number of dominant follicles to ≤3, with the goal of optimizing the pregnancy rate while preventing a high multiple pregnancy rate. Baseline pelvic US was done at cycle day 3 and 75IU of FSH was injected daily until transvaginal US showed at least one follicle with a diameter of 18mm. Patients tested their urine twice daily (morning and evening void) for the occurence of an LH surge. In the event of such surge, 10000IU of hCG was given as soon as possible, and a single IUI was done 20-30h after the detection of the surge. When no LH surge was detected in the presence of at least one follicle with a diameter of 18mm or more, 10000IU of hCG was given and a single IUI was done 40-42h later	Live birth IUI + FSH = 31/85 (36.5%) IUI = 25/86 (29.1%) Ongoing pregnancy IUI + FSH = 33/85 (38.8%) IUI = 28/86 (32.6%) Singleton pregnancy IUI + FSH = 24/85 (28.2%) IUI = 27/86 (31.4%) Multiple pregnancy IUI + FSH = 9/85 (10.6%) IUI = 1*/86 (1.2%) * one monozygotic twin pregnancy but both twins were stillborn after premature rupture of membranes	**Limitations** - Method of randomisation: computer-generated randomisation schedule, administered by numbered masked and sealed envelopes - Power calculation for pregnancy rate per cycle **Other information** - Unexplained infertility was defined as couples with no abnormality found during extensive investigation of infertility, including basal body temperature chart, a late luteal phase endometrial biopsy, a post-coital test, a hysterosalpingogram, a diagnostic laparoscopy, and at least two semen analysis - Male subfertility was diagnosed if at least 3 out of 5 semen analysis showed a total motile sperm count of fewer than $20X10^6$ progressively motile spermatozoa in the ejaculate and if the remainder

while preventing a high multiple pregnancy rate, compared with natural cycles for IUI **Study dates** February 1992 - September 1995 **Source of funding** Financial support by the Health Insurance Executive Board, Amstelveen, Netherlands	[1] Couples with unexplained infertility for at least 3 years [2] Mild to moderate male subfertility for at least 1 year **Exclusion criteria** [1] If the woman had cycle disorders [2] Untreated endometriosis (American Fertility Society criteria grade 2-4) [3] Bilateral occluded tubes [4] Partner's semen sample yielded less than 1 million progressively motile spermatozoa after processing/centrifugation [5] >20% of spermatozoa carried antibodies [6] If more than 50% of spermatozoa had no acrosome		<u>IUI</u> Women underwent a basal transvaginal US assessment at the beginning of their menstrual period, and on the 10th day of the cycle. Patients tested their urine sample twice daily (second morning void and between 18:00 and 19:00) for the occurence of the endogenous LH surge. As soon as they had detected the LH surge, patients contacted the clinic and ultrasonography was performed to assess follicular development. A single IUI was done 20-30h after the detection of the LH peak		of the infertility investigation revealed no additional abnormalities - The administration of hCG was withheld and IUI was not performed when more than 3 follicles ≥18 mm or more than 6 follicles ≥14mm were present - Pregnancy was defined as ongoing pregnancy with at least one fetal heartbeat at 12 weeks of gestation - Multiple pregnancy was defined as more than one fetal heartbeat at 12 weeks gestation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Goverde,A.J., McDonnell J.V., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis., Lancet, 355, 13-18, 2000 **Ref ID** 123972 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To investigate the efficacy of IUI, both in spontaneous and in the stimulated cycle, compared with that of IVF for both male subfertility and idiopathic subfertility **Study dates** February 1992 - September 1995 **Source of funding** Financial support by the Health Insurance Executive Board, Amstelveen, Netherlands	**Sample size** See Goverde et al., 2005 **Characteristics** See Goverde et al., 2005 **Inclusion criteria** See Goverde et al., 2005 **Exclusion criteria** See Goverde et al., 2005	See Goverde et al., 2005	See Goverde et al., 2005	See Goverde et al., 2005	**Limitations** See Goverde et al., 2005 **Other information** See Goverde et al., 2005

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility., New England Journal of Medicine,N.Engl.J.Med., 340, 177-183, 1999 **Ref ID** 123973 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To assess the efficacy of superovulation and intrauterine insemination **Study dates** Not reported **Source of funding** Supported in part by Cooperative Agreements with the National Institute of Child Health and Human Development and by Serono Laboratories	**Sample size** N = 465 couples IUI + FSH = 231 IUI alone = 234 **Characteristics** <u>Age ±SD in years</u> IUI + FSH: 32±4 IUI: 32±4 <u>Duration of infertility ±SD in months</u> IUI + FSH: 42±26 IUI: 46±31 **Inclusion criteria** [1] Age (women) ≤40 years; (men) ≤55 years [2] Negative pregnancy test [3] Normal pelvis and uterine cavity [4] "In phase" endometrial biopsy [5] Negative serum antisperm antibody test [6] Normal serum FSH and thyrotropin values on days 1-5 of cycle [7] Length of 2 of the 3 most recent menstrual cycles between 24 and 40 days [8] History of infertility for >1 year [9] Normal semen analysis	IUI + FSH + hCG Comparison IUI	Before enrollment, each couple underwent a standard evaluation for infertility, including male partner's semen analysis, endometrial biopsy, hysterosalpingography, and laparoscopy in the woman. Eligible couples were randomly assigned to one of four groups: [1] intracervical insemination timed to the surge in urinary excretion of LH; [2] IUI timed to the LH surge; [3] superovulation and intracervical insemination or; [4] intrauterine insemination. Each couple received 4 treatment cycles unless pregnancy occurred <u>IUI + FSH + hCG</u> Women were treated according to standard protocol. Baseline pelvic ultrasonography was performed on day 1, 2, or 3 of the menstrual cycle. Then 150IU of FSH was administered IM from day 3 through day 7. On day 8, ultrasonography was repeated and serum E2 was measured. Daily administration of FSH was continued with the dose adjusted if necessary, until at	Live birth at term IUI + FSH = 41/231 (17.7%) IUI = 28/234 (12.0%) Live birth preterm IUI + FSH = 9/231 (3.9%) IUI =2/234 (0.8%) Pregnancy (biochemical) IUI + FSH = 77/231 (33.3%) IUI = 42/234 (17.9%) Multiple pregnancy (triplets + quadruplets)* IUI + FSH = 5/231 (2.2%) IUI = 0 * Data for twin pregnancies not reported separately for each group Stillbirth IUI + FSH = 0 IUI = 1/234 (0.4%) Miscarriage IUI + FSH = 22/77 (28.6%) IUI = 6/42 (14.3%) Ectopic pregnancy IUI + FSH = 4/77 (5.2%) IUI = 2/42 (4.8%)	**Limitations** - Method of randomisation: randomisation was carried out with the use of a permuted-block procedure, stratified according to centre - No power analysis not reported **Other information** - Women who had received treatment for minimal or mild endometriosis (American Fertility Society stage I or II endometriosis) were enrolled only if 6 months had elapsed after either surgical therapy or the return of ovulatory cycles after medical therapy - In superovulation cycles, treatment was cancelled after Day 3 if the serum estradiol concentration exceeded 3000 pg/mL - In the IUI cycles, if no surge in urinary excretion of LH was detected - Rest cycles in the superovulation group were the result of the detection of ovarian cysts at the beginning of the cycle - Definition of pregnancy: Serum β-hCG was measured 15 days after insemination (luteal day 15). If the value

	(WHO, 1993) **Exclusion criteria** <u>Women</u> [1] Previous use of in vitro fertilization or other assisted reproductive technology [2] Previous treatment with gonadotrophins [3] Previous intrauterine insemination with current partner [4] History of chronic disease [5] History of chemotherapy or radiation to the abdomen or pelvis [6] History of tubal surgery [7] Extensive tubal adhesions [8] Endometriosis of more than stage II [9] History of myomectomy, ovarian cystectomy, or unilateral oophorectomy <u>Men</u> [1] Previous use of in vitro fertilization or other assisted reproductive technology [2] Previous intrauterine insemination [3] History of vasovasostomy [4] Varicocelectomy within 6 months before study [5] History of pelvic-node dissection		least 2 follicles reached ≥18mm and serum E2 ranged from 500 to 3000 pg/mL. Once these criteria were met, treatment with FSH was discontinued and 10 000IU of hCG was administered and a single IUI was performed 36 to 40 hours later <u>IUI</u> Women underwent IUI timed to spontaneous ovulation. Four days before the expected time of ovulation, women began daily testing of their second morning urine specimen for LH. IUI was performed on the day after the surge in urinary excretion of LH		exceeded 10 mIU/mL, the measurement was repeated on luteal day 17. Pregnancy was indicated by an increase in the β-hCG - The rate of withdrawl from the study was higher among the couples in the superovulation group (50/231)

Fertility (Updated guideline)

How accurate are clinical scoring systems in predicting the outcome of IVF treatment?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation La,Marca A., Nelson,S.M., Sighinolfi,G., Manno,M., Baraldi,E., Roli,L., Xella,S., Marsella,T., Tagliasacchi,D., D'Amico,R., Volpe,A., Anti-Mullerian hormone-based prediction model for a live birth in assisted reproduction, Reproductive Biomedicine Online, 22, 341-349, 2011 **Ref ID** 148488 **Country/ies where the study was carried out** Italy and Scotland **Study type** Retrospective cohort study **Aim of the study** The objective was to develop a simple multivariate score based on basal patients characteristics which was capable of predicting the outcome of the treatment cycle and to express this in a clean format which could be easily adopted into daily clinical practice. **Study dates** 2005 to 2008 **Source of funding** Not stated	**Sample size** 389 **Characteristics** Characteristic Study population (n = 381) Age (years) 34.8 ± 4.48 BMI (kg/m2) 24 ± 5.8 AMH (ng/ml) 1.3 (0.03–13.8) Duration of infertility (months) 34.1 ± 20.2 Type of infertility Primary 294 (77.2) Secondary 87 (22.8) Cause of infertility Anovulation 82 (21.5) Tubal factor 57 (15.0) Unexplained 140 (36.8) Male infertility 123 (32.4) Endometriosis 45 (11.8)	Serum AMH was measured by enzyme-linked immunosorbent assay (ELISA) using the Beckman Coulter AMH ELISA kit (Immunotech, Marseilles, France). The detection limit of the assay was 0.14 ng/ml; intra- and inter-assay coefficients of variation were 12.3% and 14.2%, respectively (conversion factor: 1 ng/ml = 7.14 pmol/l). The immunoassay is specific for AMH. No cross-reaction was observed with transforming growth factor b.	Treatments The long GnRH agonist protocol (Enantone; Takeda Italia, Rome, Italy) is based on the administration of leuprorelin on day 21 of the previous luteal phase of the stimulation cycle. Recombinant FSH at a dose ranging between 150 and 300 IU/day subcutaneously was commenced on cycle days 2–3 and then the dose was adjusted on days 7–8 according to the ovarian response. When at least two follicles reached >18 mm, 10,000 IU of human chorionic gonadotrophin was administrated intramuscularly and 34–36 h later follicles were aspirated under patient sedation. Insemination was performed by standard IVF or ICSI.. Clinical pregnancy was defined as ultrasound visualization of a gestational sac with evidence of a fetal heart	Univariate and multivariate analysis showed that AMH (0.00004) and age (p = 0.0002) were useful in predicting pregnancy and live birth, but that BMI or duration, type or cause of infertility were not associated with live birth. The discrimination ability of the model was assessed by determining the area under the curve and was 0.66 (95% CI 0.61 to 0.72). At the best cut-off, the model permitted the identification of live birth with a sensitivity of 79.2%, specificity of 44.2% and the patients correctly classified were 53.5%. Calibration testing - Expected chance of a live birth versus observed live birth, with the difference in predicted and observed <0.5% indicating a good calibration of the predictive model (Pearson chi-squared goodness-of-fit	**Limitations** Small sample size Limited number of variables available for modelling **Other information**

	Inclusion Criteria inclusion criteria were satisfied: • first IVF/ICSI attempt; • normal uterus and regular uterine cavity; • no previous ovarian surgery; • absence of severe male factor (defined as sperm count less than 106/ml or normal forms less than 5%; • female age <42; • absence of recurrent abortion; • absence of antiphospholipid syndrome and any other relevant systemic condition; • treatment with a long gonadotrophin-releasing hormone (GnRH) agonist protocol; • complete computer based patient records on anamnestic, clinical and IVF cycle characteristics and pregnancy follow-up • a stored serum sample taken within 3 months of commencing IVF suitable for measurement of AMH. All patients had been trying to conceive for at least 12 months and all had undergone a fertility workup. **Exclusion Criteria** Not stated		Live birth was defined by the birth of at least one live-born child. Written consent Statistical analysis Multivariate logistic regression used to determine component of model Decrimination assessed using ROC. Pearson's chi-squared goodness of fit test was used to assess the overall performance of the model Pearson's chi-squared goodness of fit test was used to assess the overall performance of the model	test). Covariate decile, probability, observed live birth, expected live birth, observed no live birth, expected no live birth, total 1 0.0531 1 1.4 26 25.6 27 2 0.0865 1 1.3 14 13.7 15 3 0.1336 1 0.3 1 1.7 2 4 0.1824 18 18.4 83 82.6 101 5 0.2734 36 35.0 92 93.0 128 6 0.2861 4 3.1 7 7.9 11 7 0.3800 15 15.6 26 25.4 41 8 0.4035 11 11.7 18 17.3 29 9 0.5242 14 14.2 13 12.8 27	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Nelson,S.M., Lawlor,D.A., Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles, PLoS medicine, 8, e1000386-, 2011 **Ref ID** 130546 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** Assess the extenet tp which baseline characteristics can be used to predict live birth after IVF. **Study dates** HFEA dataset from January 2003 to December 2007 **Source of funding** No specific funding for project.	**Sample size** Total dataset 242,733. Eligible cohort (fresh, non-donor, IVF treatment) = 163,245. Missing data = 19,407. Analysis dataset 144,018. **Characteristics** Summary characteristics of population were not provided. Dataset was provided by the HFEA and included all episodes of assisted reproduction undertaken in the UK. **Inclusion Criteria** IVF treatment only Fresh cycle transfers only (no GIFT or ZIFT) Non-donor material only Complete data available **Exclusion Criteria** N/A	Development of predcition model for live birth as a result of IVF treatment. Model included: - Source of eggs - Type of hormonal preparation - ICSI - Type of infertility - Duration of infertility - Woman's age - IVF cycle number - Previous pregnancies with or without IVF - Previous live births with or without IVF	Data collection Routine mandatory data collection by clinics and submitted to the HFEA on all episodes of assisted reproduction. Outcome Live birth defined as baby born alive after 24 weeks gestation. Further defined as at least one baby born alive and surviving for at least 1 month. Statistical methods Univariable and multivariable logistic regression to assess associations between predictive variables and live birth. Multiple regression used all variables included in model. Predicitive value of model assessed using discrimination via AUCROC and calibration by ranking participants into tenths based on their predicted risk for the Templeton prediction model, and then within each tenth comparing the predicted mean rate to the observed rate of live births.	Multiple regression analysis found the following factors were significantly associated with live birth ($p < 0.001$ for all) - Maternal age - decreases with age - Duration of infertility - decreases with duration - Cause of infertility - known causes have lower rates - Number of previous unsuccessful IVf cycles - decreases with number - Previous obstetric history - improves with previous pregnancies and live births - Hormonal preparation - changes with type - Cycle number - decreased with more cycles tried - Source of egg - improves with donor eggs - Treatment type - improves with ICSI (Adjusted ORs for individual variables not reported)	**Limitations** High level of missing data at 12% could impact on results. Episodes not linked to individual women and treated as independent. Both single and multiple pregnancy included Model has not been externally validated. **Other information**

			Missing data Assessment showed no systematic difference between episodes with and without missing data. Therefore, complete case analysis was undertaken.	Model performance Disrimination using AUCROC Templeton = 0.6184 (0.6152 to 0.6217) Nelson and Lawlor = 0.6335 (0.6202 to 0.6367), p < 0.001 Calibration using observed against predicted Decile of risk prediction by model, Templeton, Nelson ratio Lowest 10th: 0.43 vs 0.94 2nd: 0.47 vs 1.00 3rd: 0.45 vs 1.00 4th: 0.45 vs 1.03 5th: 0.50 vs 1.01 6th: 0.52 vs 1.03 7th: 0.46 vs 1.01 8th: 0.55 vs 0.97 9th: 0.54 vs 0.99	

				Highest 10th: 0.63 vs 1.00	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Leushuis,E., van,derSteegJ, Steures,P., Bossuyt,P.M.M., Eijkemans,M.J.C., van,derVeenF, Mol,B.W.J., Hompes,P.G.A., Prediction models in reproductive medicine: A critical appraisal, Human Reproduction Update, 15, 537-552, 2009 **Ref ID** 111697 **Country/ies where the study was carried out** Netherlands **Study type** Systematic review **Aim of the study** Evaluate pregnancy prediction models for reproductive medicine (natural, IUI or IVF) **Study dates** Medline, Embase and Cochrane libraries from inception to October 2008 **Source of funding** Not stated	**Sample size** 1082 articles identified. 66 papers retrieved for evaluation. 36 papers (29 models) included in review. 12 were treatment independent, 4 were for IUI and 20 were for IVF. **Characteristics** Jerrzejczak et al, 2008: n = 242, case-control study, Patients = infertile men. Hunault et al, 2002: n = 1061, prospective cohort, couples at first visit to subfertility clinic, Snick et al, 1997: n = 726, prospective cohort, patients = subfertile couples from secondary care; Collins et al, 1996: n = 2198, prospective cohort, patients = first visit to subfertility clinic; Bahamondes et al,1994: n = 559, retrospective cohort, patients = patients visiting subfertility clinic with 3 years followup or pregnancy Wichman et al, 1994: n = 907, prospective cohort, patients = subfertile men; Elmers et al, 1994: n = 966, prospective cohort, patients =	Prediction models of pregnancy and live birth used in reproductive medicine.	Databases Medline, Embase and Cochrane libraries from inception to October 2008 Search strategy Information specialist designed a search strategy to identify studies in relation pregnancy or live birth prediction models in reproductive medicine. No language, study design or date restrictions were placed on the search. Quality assessment Two reviewers independently screened the search results for inclusion. Papers meeting initial inclusion criteria were retrieved and the full-text versions assessed. Quality was graded on if: patient selection was consecutive, data collection was prospective, description of variables and outcomes was detailed and the statistical methods for creating models was described.	Variables used in models for predicting treatment independent pregnancy Jerrzejczak et al, 2008: Sperm Motility, Sperm morphology, Sperm concentration, HOS test, Hunault et al, 2002: Age, Duration of infertility, Primary or secondary, Sperm Motility, Referral status, Snick et al, 1997: Duration of infertility, Ovulation disorder, Tubal defect, Abnormal PCT, Collins et al, 1996: Age, Duration of infertility, Tubal defect, Endometriosis, WHO semen defect, Primary or secondary, Bahamondes et al,1994: Age, Duration of infertility, Primary or secondary, Sperm morphology, Pelvic surgery, Wichman et al, 1994: Age, Duration of infertility, Sperm Motility, Sperm morphology, Urethritis in history, Elmers et al, 1994: Age, Duration of infertility, Primary or secondary, Sperm Motility,	**Limitations** **Other information**

	subfertile couples using fertility centre Bostofte et al, 1993: n = 321, prospective cohort, patient = couples being investigated for subfertility Bostofte et al, 1987: n = 765, retrospective cohort, patients = male factor inferility van Weert et al, 2008: n = 275, retrospective cohort Lintsen et al, 2007: n = 4928, prospective cohort Verberg et al, 2007: n = 201, prospective cohort Carrera et al, 2007,: n = 110, prospective cohort Ottoson et al, 2007: n = 2193, retrospective cohort Ferkitsch, 2004: n = 170, retrospective cohort Hunault et al, 2002: n = 642, retrospective cohort Bancsi et al, 2000: n = 435, retrospective cohort Stolwijk et al, 2000: n = 757, prospective cohort		Development of prediction models based on published three stage process (McGinn et al, 2000) - model derivation phase (identifying variables); internal and external validation phase (does the model work); impact analysis (what effect will the use of the model have in the real world). Statistical analysis A model ability to discriminate between groups was based on ROC curve of sensitivity and specificity pairs, with an AUC <70 showing poor performance. A model level of calibration - agreement between predicted and observed outcomes - was examined. Based on 1) goodness-of-fit (Hosmer, 2000); 2) Linear regression line assessment between preidction and observed - intercept at 0 and diagonal line if perfect prediction. 3) visual assessment of plot of mean predicted probability with observed proportion.	Abnormal PCT, Fertility problems in male's family Bostofte et al, 1993: Duration of infertility, UA and ovulation or cervical disorders, Abnormal PCT, Bostofte et al, 1987: Sperm Motility, Sperm morphology, Sperm concentration, Male age Variables used in models for prediciting outcome of IVF van Weert et al, 2008: Age, Tubal defect, Hisotry of unsuccessful IVF, Cycle number, Primary or secondary, Sperm Motility, Sperm morphology, Antisperm antibodies, Lintsen et al, 2007: Duration of infertility, Endometriosis, Cervical factor infertility, Mild male factor, Severe male factor, Primary or secondary, Verberg et al, 2007: BMI, Total amount of rFSH used, Top quality embryos available, Number of oocytes retrieved, Carrera et al, 2007: Age,	

	Minaretzis et al, 1998: n = 544, prospective cohort Commenges-Duces et al, 1998: n = 923, retrospective cohort Stolwijk et al, 1996: n = 757, retrospective cohort Bouckaert et al, 1994: n = 581, retrospective cohort Haan et al, 1991: n = 3092, prospective cohort Hughes et al, 1989: n = 716, prospective cohort Nayudu et al, 1989: n = 222, retrospective cohort Templeton et al 1996: n = 36961, retrospective cohort **Inclusion Criteria** Study presented a pregnancy or live birth prediction with: - treatment independent, IUI or IVF - Multivariate regression model - a score chart, a prediction rule or as regression			Antral follicle count, E2 on day 4, Ottoson et al, 2007: Age, BMI, Basal FSH, Score best embryo, Score second best embryo, Ferkitsch, 2004: BMI, Basal FSH, Hunault et al, 2002: Age, Score best embryo, Developmental score, Morphology score, Number of oocytes retrieved, Bancsi et al, 2000: Age, Male factor subfertility (WHO), Basal FSH, Tuboperitoneal disease, Stolwijk et al, 2000: Age, Primary or secondary, Minaretzis et al, 1998: Age, Developmental score, Commenges-Duces et al, 1998: Age, Previous successful IVF, Donor sperm, Number of ampoules, Stolwijk et al, 1996: Age, <=1 previous pregnancy, Bouckaert et al, 1994: Age, Fertilisation ratio in the first cycle, Number of oocytes	

	coefficients **Exclusion Criteria** Not stated			retrieved, Haan et al, 1991: Age, Duration of infertility, Unexplained infertility, Tubal reasons for IVF, Male factor subfertility (WHO), Treatment episode Hughes et al, 1989: Age, Previous successful IVF, Nayudu et al, 1989: hCG usuage, E2 change, Pregnancy type follicle, Total protein, Nelson et al, 2009: Age, Duration of infertility, Number of previous unsuccessul IVF, Cycle number, Cause of infertility (Tubal cause of infertility; PCO; Endometriosis; Idiopathic; Male)), Previous IVF pregnancy no live birth; Previous pregnancy, no live birth, Previous IVF live birth, Previous live birth, Treatment type; Hormonal preparation; Source of egg. Templeton et al, 1996: Age, tubal defects, revious IVF pregnancy no live birth; Previous pregnancy, no live birth, Previous IVF live birth, Previous live birth.	

				(IUI models have not been summarised) Of 29 models assessed 8 (Hunault 2004, Snick 1997, Collins, 1995, Elmers, 1994, Steures 2004, Hunault 2002, Templeton 1996 and Stolwijk 1996) had been externally validated and were assessed in detailed for dicrimination and calibration. Of these 8 models 3 were found to have good performance in terms of calibration. For treatment independent prediction the Hunault et al 2004 model had the best performance (AUC= 0.59; calibration slope = 0.82, p-value = 0.08) For IUI the Steures performed best. AUC= 0.59, calibration = "good" For IVF the Templeton et al 1996 model performed best. AUC= 0.63	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Roberts,S.A., Hirst,W.M., Brison,D.R., Vail,A., towardSET,collaboration, Embryo and uterine influences on IVF outcomes: an analysis of a UK multi-centre cohort, Human Reproduction, 25, 2792-2802, 2010 **Ref ID** 90061 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** As specified in report • To collate high-quality cohort data from a series of individual treatment centres to be considered alongside data collated by the HFEA for regulatory purposes. • To develop predictive models from each of the data sources for successful live birth and twinning probabilities from fresh and frozen embryo transfers. • To understand, through qualitative work, patients' perspectives as they travel through the treatment process, including appropriate	**Sample size** Two datasets used for the quantitative analysis In HFEA original dataset: 172,189 embryo transfers from 104,610 patients in 84 treatment centres. After data cleaning and removing missing records: 139,848 transfers from 85,349 patients in 84 treatment centres. Towards eSET Original dataset from 5 fertility centres 23,582 cycles (17,857 fresh, 5725 frozen) from 11,767 patients were available for analysis. After cleaning the total number of cycles available for analysis was 16,096: 12,487 fresh and 3609 frozen, from 9040 couples **Characteristics** **Inclusion Criteria**	All types of IVF and ICSI, but focus on number of embryos transferred	Logistic regression modelling	The main report findings were on the impact of different policies to reduce twinnings. These were summarised in tables that are shown below. Numbers of patients needed to receive SET in order to achieve a range of twin target rates for selection using patientcharacteristics. The predictions for selection using random selection are also shown for comparison Numbers of patients needed to receive SET in order to achieve a range of twin target rates for selection using patient characteristics. The predictions for selection using random selection are also shown for comparison Twin rate (%), Cut-off, Policy, % SET, Live births (%) 25, -, All DET, 0, 24.3 20, -, Random, 25.9, 22.3	**Limitations** Limited data of SET - only 9.5% of the HFEA dataset and 15.4% in the Towards eSET dataset. **Other information**

outcome measures, attitudes towards twins, opinions on SET and potential policies for reducing the number of twin births. • To predict outcomes for treatment scenarios, based on proposals in the literature and developed with patients and clinicians. • To use the modelling results to investigate with patients the acceptability of twin reduction policies within the current regulatory, funding and clinical environment • To consider the need for future randomised controlled trials and surveys of patient attitudes. **Study dates** 2000 to 2005 **Source of funding** NIHR grant for health technology assessment Project number 05/43/0	HFEA dataset Parameter Categoriesa Fresh cycles (%) Frozen cycles (%) Numbers of transfers 119,930 (86%) 19,918 (14%) Number of embryos transferred 1: 10,139 (8%)3146 (16%) 2: 92,271 (77%)13,872 (70%) 3: 17,520 (15%)2900 (15%) Age Mean (SD) [range] 34.4 (4.4) [19–50] 34.5 (4.4) [19–54] Number of eggs collected Mean (SD) [range] 10.5 (5.9) [1–85] Number of eggs inseminated Mean (SD) [range] 9.4 (5.4) [1–65] Number of embryos created/recovered Mean (SD) [range] 6.5 (4.2) [1–45] 3.7 (2) [1–22] Treatment attempt 1st69,123 (58), 1073 (5 2nd27,354 (23%), 8835 (44%)			20, Age < 28.9, Age , 15.8, 23.0 20, Age < 29.2, Age + good , 14.1, 23.1 20, >9.0 embryos, Embryo number , 19.2, 22.5 20, >8.7 embryos, Embryo number + good, 17.6, 22.6 15, -, Random, 48.9, 20.5 15, Age < 31.1, Age , 32.1, 21.5 15, Age < 31.8, Age + good , 29.7, 21.6 15, >6.4 embryos, Embryo number, 38.2, 20.8 15, >6.0 embryos, Embryo number + good, 35.3, 20.9 10, -, Random, 68.3, 19.0 10, Age < 33.3, Age , 51.8, 19.8 10, Age < 34.3, Age + good , 48.2, 19.9 10, >4.7 embryos, Embryo number, 56.6, 19.2 10, >4.0 embryos, Embryo	

	3rd12,835 (11%), 4826 (24%) > 3rd10,618 (9%), 5184 (26%) IVF or ICSI IVF: 63,182 (53%)11,461 (58%) ICSI: 56,748 (47%)8457 (42%) Total previous pregnancies/births Never pregnant: 69,681 (58%),8835 (44%) Previously pregnant: 29,919 (25%), 5872 (29%) 1 previous live birth16,315 (14%), 4469 (22%) ≥2 previous live births: 4015 (3%), 742 (4%) Years infertile Mean (SD) [range] 5.1 (3.9) [0–25] 4.8 (4) [0–25] Tubal diagnosis Yes 29,108 (24%) 5446 (27%) Diagnosis of PCOS Yes 15,116 (13%) 2927 (15%)			number + good, 52.7, 19.4 0, -, All SET, 100, 16.5 Numbers of patients needed to receive SET in order to achieve a range of twin target rates for selection using age, conditional on having a good quality embryo and four or five embryos created. Random selection and the full model are shown for comparison Twin rate, Cut-off, Policy, % SET, Live births (%) 25, -, All DET, 0, 24.3 20, -, Random , 25.9, 22.3 20, Age < 30.0, Age + good + four embryos , 13.3, 23.1 20, Age < 30.5, Age + good + five embryos , 13.2, 23.0 20, -, Full model , 10.9, 23.1 15, -, Random , 48.9, 20.2	

	Endometriosis Yes 8567 (7%) 1105 (6%) Male factor diagnosis Yes 52,300 (44%) 8380 (58%) Idiopathic diagnosis Yes 25,305 (21%) 3877 (19%) Donor sperm Yes 2681 (2%) 495 (2%) Day of transfer < 2: 1386 (1%) 2: 82,299 (69%) 3: 31,560 (26%) > 3: 685 (4%) Year 2000: 17,338 (14%), 1478 (7%) 2001: 18,834 (16%,)2694 (14%) 2002: 19,195 (16%,)3235 (16%) 2003: 19,864 (17%,)4003 (20%) 2004: 22,031 (18%,)4066 (20%) 2005: 22,668 (19%,)4442 (22%)			15, Age < 33.4, Age + good + four embryos, 29.9, 21.4 15, Age < 34.8, Age + good + five embryos, 31.3, 21.2 15, -, Full model, 24.9, 21.6 10, -, Random , 68.3, 19.0 10, Age < 40.5, Age + good + four embryos , 52.0, 19.5 10, NA, Age + good + five embryos, NA, NA 10, -, Full model, 41.2, 20.0 0, -, All SET, 100, 16.5	

	Transfers per couple 1:55,020 (67%), 11,228 (75% 2: 19,083 (23%), 2709 (18%) > 2: 7862 (10%), 947 (7%) Towards eSET dataset Parameter Categories Fresh cycles Frozen cycles Number of embryo transfers 12,487 3609 Number of patients 8775 2088 Numbers of embryos transferred 1 1330 (11%) 1142 (32%) 2 10,418 (83%) 2226 (62%) 3 739 (6%) 241 (7%) Age Mean (SD) [range] 33.8 (4.2) [19–47] 33.8 (4.1) [19–47] Number of embryos created/recovered Mean				

	(SD) [range] 6 (3.7) [1–26] 2.9 (1.5) [1–21] Treatment attempt 1st 6797 (54%) 0 2nd 2904 (23%) 1399 (39%) 3rd 1426 (11%) 945 (26%) > 3rd 1360 (12%) 1265 (35%) IVF or ICSI IVF 6470 (52%) 2188 (61%) ICSI 6017 (48%) 1421 (39%) Total previous pregnancies/births No previous pregnancies 6788 (54%) 1556 (43%) Previously pregnant 3481 (28%) 1259 (35%) 1 previous live birth 1769 (14%) 675 (19%) ≥ 2 previous live births 449 (4%) 119 (3%) Years infertile Mean (SD) [range] 5.2 (3.5) [0–24] 5.1 (3.6) [0–21] Tubal diagnosis Yes 3133				

	(25%) 1203 (33%) Diagnosis of PCOS Yes 1298 (10%) 512 (14%) Endometriosis Yes 1144 (9%) 284 (8%) Male factor diagnosis Yes 4667 (37%) 1158 (32%) Idiopathic diagnosis Yes 3348 (27%) 849 (24%) Donor sperm Yes 354 (3%) 117 (3%) Day of transfer 2 11,671 (93%) NA 3 816 (7%) NA Year 2000 1494 (12%) 220 (6%) 2001 1682 (13%) 465 (13%) 2002 2307 (18%) 577 (16%) 2003 2208 (18%) 670 (19%) 2004 2472 (20%) 812 (22%) 2005 2324 (19%) 865				

	(24%) Embryo growth rate Mean (SD) [range] 1 (0.2) [0–2.5] NA Embryo grade Mean (SD) [range] 3.2 (0.5) [1–4] 3 (0.6) [1–4] Transfers per couple 1 6086 (69%) 1223 (59%) 2 1935 (22%) 497 (24%) > 2 754 (9%) 368 (17%) Cycles were included if they met the following inclusion criteria: • treatment type: ICSI or IVF • cycles with one, two, or three embryos transferred • age 19–54 • patient's own eggs • date started trying to conceive or last pregnant after start of 1980. **Exclusion Criteria** Cycles were excluded if they				

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Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation Roberts,S., McGowan,L., Hirst,W., Brison,D., Vail,A., Lieberman,B., Towards single embryo transfer? Modelling clinical outcomes of potential treatment choices using multiple data sources: predictive models and patient perspectives, Health Technology Assessment (Winchester, England), 14, 1-237, 2010 **Ref ID** 90060 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** As specified in report • To collate high-quality cohort data from a series of individual treatment centres to be considered alongside data collated by the HFEA for regulatory purposes. • To develop predictive models from each of the data sources for successful live birth and twinning probabilities from fresh and frozen embryo transfers.	**Sample size** Two datasets used for the quantitative analysis In HFEA original dataset: 172,189 embryo transfers from 104,610 patients in 84 treatment centres. After data cleaning and removing missing records: 139,848 transfers from 85,349 patients in 84 treatment centres. Towards eSET Original dataset from 5 fertility centres 23,582 cycles (17,857 fresh, 5725 frozen) from 11,767 patients were available for analysis. After cleaning the total number of cycles available for analysis was 16,096: 12,487 fresh and 3609 frozen, from 9040 couples **Characteristics** **Inclusion Criteria**	All types of IVF and ICSI, but focus on number of embryos transferred	Logistic regression modelling	The main report findings were on the impact of different policies to reduce twinnings. These were summarised in tables that are shown below. Numbers of patients needed to receive SET in order to achieve a range of twin target rates for selection using patientcharacteristics. The predictions for selection using random selection are also shown for comparison Numbers of patients needed to receive SET in order to achieve a range of twin target rates for selection using patient characteristics. The predictions for selection using random selection are also shown for comparison Twin rate (%), Cut-off, Policy, % SET, Live births (%) 25, -, All DET, 0, 24.3 20, -, Random, 25.9, 22.3	**Limitations** Limited data of SET - only 9.5% of the HFEA dataset and 15.4% in the Towards eSET dataset. **Other information**

• To understand, through qualitative work, patients' perspectives as they travel through the treatment process, including appropriate outcome measures, attitudes towards twins, opinions on SET and potential policies for reducing the number of twin births. • To predict outcomes for treatment scenarios, based on proposals in the literature and developed with patients and clinicians. • To use the modelling results to investigate with patients the acceptability of twin reduction policies within the current regulatory, funding and clinical environment • To consider the need for future randomised controlled trials and surveys of patient attitudes. **Study dates** 2000 to 2005 **Source of funding** NIHR grant for health technology assessment Project number 05/43/01	HFEA dataset Parameter Categoriesa Fresh cycles (%) Frozen cycles (%) Numbers of transfers 119,930 (86%) 19,918 (14%) Number of embryos transferred 1: 10,139 (8%)3146 (16%) 2: 92,271 (77%)13,872 (70%) 3: 17,520 (15%)2900 (15%) Age Mean (SD) [range] 34.4 (4.4) [19–50] 34.5 (4.4) [19–54] Number of eggs collected Mean (SD) [range] 10.5 (5.9) [1–85] Number of eggs inseminated Mean (SD) [range] 9.4 (5.4) [1–65] Number of embryos created/recovered Mean (SD) [range] 6.5 (4.2) [1–45] 3.7 (2) [1–22] Treatment attempt 1st69,123 (58), 1073 (5 2nd27,354 (23%), 8835 (44%) 3rd12,835 (11%), 4826 (24%)			20, Age < 28.9, Age , 15.8, 23.0 20, Age < 29.2, Age + good , 14.1, 23.1 20, >9.0 embryos, Embryo number , 19.2, 22.5 20, >8.7 embryos, Embryo number + good, 17.6, 22.6 15, -, Random, 48.9, 20.5 15, Age < 31.1, Age , 32.1, 21.5 15, Age < 31.8, Age + good , 29.7, 21.6 15, >6.4 embryos, Embryo number, 38.2, 20.8 15, >6.0 embryos, Embryo number + good, 35.3, 20.9 10, -, Random, 68.3, 19.0 10, Age < 33.3, Age , 51.8, 19.8 10, Age < 34.3, Age + good , 48.2, 19.9 10, >4.7 embryos, Embryo number, 56.6, 19.2 10, >4.0 embryos, Embryo	

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Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full Citation van Loendersloot LL, van Wely M, Limpens J, Bossuyt PM, Repping S, van der Veen F., Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis., Human Reproduction, 16, 577 - 589, 2010 **Ref ID** 155647 **Country/ies where the study was carried out** Netherlands **Study type** Systematic review **Aim of the study** Identify the most relevent predictors for success (pregnancy) of IVF. **Study dates** Literature search from 1978 to 2009 **Source of funding** Not stated	**Sample size** 1397 articles identified. 58 retireved for review. 14 studies met the inclusion criteria. **Characteristics** Review limited to nine pre-selcted data. **Inclusion Criteria** Studies that evaluated associations between one or more predictive factors and pregnancy after IVF, if the study group consisted of subfertile women undergoing a fresh autologous IVF/ICSI cycle, and if a stimulation protocol with down-regulation had been used. **Exclusion Criteria** Studies that reported on a specific patient group within the subfertile IVF/ICSI population or if odds ratios were not reported or could not be calculated.	Included variables The study identified all predictive variables, but focused meta-analysis on nine predicitive factors: - female age - parity - basal FSH - duration of subfertility - indication for subfertility - number of oocytes retrieved - method of fertilisation - number of embryos transferred - embryo quality	Search strategy Search strategy designed by a medical librarian to identify all relevant literature. Search undertaken on OVID Medline and OVID Embase. No language restriction applied. Statistical analysis Odds ratios calculated for individual studies Meta-analysis undertaken by calculating pooled ORs using random effects model and corresponding CIs	Summary of the predictive factors found in the 14 included studies Ebbesen et al, 2009: pregnancy or live birth, Age, BMI, Method of fertilization - ICSI or IVF, Smoking habits, Daily coffee, Stress measures, bFSH, Number of oocytes, Sabatini et al, 2008: pregnancy or live birth, Age, bFSH, Wang et al, 2008: pregnancy or live birth, Age, Ottosen et al, 2007: pregnancy or live birth, Age, Duration of infertility, Indication for IVF, BMI, Method of fertilization - ICSI or IVF, bFSH, Score of best-/second best embryo, Number of oocytes, Number of fertilized oocytes, Fertilization rate, Ferlitsch et al, 2004: pregnancy or live birth, Endometrium thickness, TSH level, BMI, LH, bFSH, E2, Prolactin, TSH, Protocol Hauzman et al, 2004: pregnancy or live birth, Age, Number of oocytes, Day 11	**Limitations** Varying definitions of pregnancy used in included studies (biochemical, ongoing, clinical) Figures were unadjusted for other variables **Other information**

				hCG level, Mean inhibin A level, Number of embryos transferred, Hunault et al, 2002: pregnancy or live birth, Age, Duration of infertility, Indication for IVF, Total number of sperm cells, Primary or secondary, Progressive motile sperm cells, Estrogen level, Number of pre-ovulatory follicles, Stage development best and second best embryo, Morphology score of the best and second best embryo, Day of embryo transfer, Number of oocytes retrieved, Proportion of ooctyes fertilized, Sharma et al, 2002: pregnancy or live birth, Age, Number of oocytes, Number of embryos transferred, Maugey-Laulom et al, 2002: pregnancy or live birth, Age, Endometrium morphology, Endometrium thickness, Protodiastole notch Sub- and intra endometrial vascular signals, Pulsatility index, Hart et al, 2001: pregnancy or live birth, Age Intramural	

				fibroid ≤5 cm in size, Number of ampoules, bFSH, FSH Number of oocytes, Number of available embryos, Bancsi et al, 2000: pregnancy or live birth, Age, Indication for IVF, Type of infertility, bFSH, Duration of infertility, Strandell et al, 2000: pregnancy or live birth, Age, Indication for IVF, Previous pregnancy, FSH total dose, Duration of ovarian stimulation, FSH initial daily dose, Previous childbirth, Number of good quality embryos transferred, Day of embryo transfer, Number of good quality embryos available, No of embryos suitable for freezing, Number of oocytes, Number of fertilized oocytes, Proportion of fertilized oocytes, Syrop et al, 1999: pregnancy or live birth, Age, Smoking (current/former) E2, bFSH, Smallest ovarian size Stolwijk et al, 1997: pregnancy or live birth, Age	

				Results for pre-specified predictors for predicting pregnancy Age 3 studies OR 0.95 (95%CI 0.94 to 0.96) - likelihood of pregnancy decreases with age. Duration of subfertility 2 studies (n = 1077) OR = 0.99 (95% CI 0.98 to 1.00) Type of subfertility 2 studies (n = 1077) OR = 1.04 (95% CI 0.65 to 1.43) Indication for IVF No summary statistic Basal FSH 5 studies OR = 0.94 (95%CI 0.88 to 1.00) - lower pregnancy rates with increasing bFSH Number of oocytes retrieved 4 studies OR = 1.04 (95%CI 1.02 to 1.07) - higher	

				pregnancy rate with increasing oocytes Method of fertilisation No summary statistic Number of embryos transferred No summary statistic Embryo quality No summary statistic	

Fertility (Updated guideline)

Pre-treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Smulders,B., van,OirschotS, Farquhar,C., Rombauts,L., Kremer,J.A., Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques, Cochrane database of systematic reviews (Online), #2010. Date of Publication, CD006109-, 2010 **Ref ID** 83120 **Country/ies where the study was carried out** **Study type** Cochrane review of randomised controlled trials **Aim of the study** To assess whether pre-treatment with combined OCPs, progestogens or estrogens in ovarian stimulation protocols affects outcomes in subfertile couples undergoing any form of ART. **Study dates** Searches were conducted in November 2008 **Source of funding**	**Sample size** 23 randomised controlled trials (covering 14 to 504 women per study) Four trials used a cross-over design **Characteristics** 8 studies reported no data or limited reporting on baseline characteristics **Inclusion criteria** Types of studies: Only RCTs were included (both published and unpublished). Cross-over trials that had pre-crossover data were included Participants: Women of any age with subfertility, regardless of any cause, undergoing assisted reproductive therapy. Further details of patient criteria: Sub fertility-Regular indication for IVF (18 studies), special indicatin for IVF (5 studies), women with limited ovarian reserve (1 study), women with PCOS (1 study), women with ovarian cyst of over 5 mm in diameter or endometrial	1] Combined OCP vs no pre-treatment (11 studies) Ag vs Ag (Biljan 1998a; Raoofi 2008) Ant vs Ant (Cederin-Durnerin 2007; Kolibianakis 2006; Rombauts 2006; Obruca 2001; Huirne 2006b; Kim 2005) Ant vs Ag (Huirne 2006a; Hwang 2004; Rombauts 2006; Kim 2005) Ag vs Ant (Wang 2008) 2] Progestogen vs no pre-treatment (8 studies) Ag vs Ag (Aston 1995; Engmann 1999; Cederin-Durnerin 1996; Shaker 1995; Hugues 1994; Ditkoff 1996) Ant vs Ant (Cederin-Durnerin 2007) No GnRH + FSH +hMG (Salat-Baroux 1988) 3] Estrogen vs no pre-treatment (3 studies) Ant vs Ant (Cederin-Durnerin 2007; Franco Jr 2003) Ant vs Ag (Franco Jr 2003) 4] Combined OCP vs	Method: All 23 included trials were claimed to be randomised. 10 studies were clasiffied as 'yes' with regard to allocation concealment. Three trials used blinding, 9 trials reported that the study was open labelled or not blind and the other eleven studies did not report whether the women, assessors or investigators were blind Statistical analysis: 10 studies performed and adhered a power calculation.	COCP VS NO PRE-TREATMENT Live births a] COCP + Ant vs Ant (1 study: Cedrom-Durnerin 2007) COCP + Ant = 3/21; Ant = 7/24 OR = 0.43 [0.11 to 1.74] b] COCP + Ant vs Ag (1 study: Huirne 2006a) COCP + Ant = 17/91; Ag = 17/91 OR = 1.00 [0.48 to 2.10] I^2 = 0% d] COCP + Ant vs Ant-low response (1 study: Kim 2005) COCP + Ant = 8/27; Ant = 5/27 OR = 1.82 [0.53 to 6.25] I^2 = NA e] COCP + Ant vs Ag-low response (1 study: Kim 2005) COCP + Ant = 8/27; Ag = 6/28 OR = 1.53 [0.46 to 5.09] I^2 = NA Clinical pregnancy a] COCP + Ag vs Ag (1 study: Biljan 1998a) COCP Ag = 19/51; Ag = 17/51 OR = 1.19 [0.53 to 2.66]	**Limitations** 1] 12/23 studies did not report the method of randomisation 2] Seven studies did not adhere a power calculation and this is unclear in 5 other studies **Other information** 1. Live births was defined as the delivery of a fetus with signs of life after twenty competed weeks of gestational age, counted as live birth event. When there were multiple births, these were counted as one live birth event. 2. Clinical/ongoing pregnancies was defined as evidence of a gestational sac with fetal heart motion at six weeks or later, confirmed with ultrasound. Multiple gestational sacs in one patient was counted as one clinical pregnancy 3. Multiple pregnancy: when there were multiple gestation sacs in one patient, these were counted as one multiple pregnancy. 4. Adverse outcomes: Number of pregnancy loss- was defined as the sum of the number of

Not reported	thickness of over 5 mm and serum E2 concentration > 100 pmol/L after fourteen days of GnRH agonist treatment. Age: only women <38 years (4 studies), <39 years (5 studies). Upper age limit- ≤41 (1 study), ≤42 (2 studies), ≤44 (1 study); Lower age limit- ≥18 years of age (4 studies), ≥28 years of age (1 study). 10 studies did not mention an age limit in their description of the women. BMI: <29 or 30 kg/m^2 **Exclusion criteria** Types of studies: Trials with quasi randomisation. Cross-over trials were excluded unless pre-crossover data were available. Studies that compared different doses of the same pre-treatment. Participants: Women with premature ovarian failure and women who participated in ovarian stimulation protocols as oocyte donors were excluded Other patient criteria: High baseline serum FSH level, the evidence of ovarian cycsts or endometrioma and PCOS	pre-treatment with progestogen (1 study) Ant vs Ant (Cederin-Durnerin 2007) 5] Combined OCP vs pre-treatment with oestrogen (2 studies) Ant vs Ant (Cedrin-Durnerin 2007) Ag vs Ant (Daly 2002) 6] Progestogen vs oestrogen Ant vs Ant (Cedrin-Durnerin 2007)		I2 = NA b] COCP + Ant vs Ant (4 studies: Cedrom-Durnerin 2007; Huirne 2006b; Kolibianakis 2006; Rombauts 2006) COCP + Ant = 80/420; Ant = 109/427 OR = 0.69 [0.50 to 0.96] I^2 = 30% c] COCP + Ant vs Ag (3 studies: Huirne 2006 a; Hwang 2004; Rombauts 2006) COCP + Ant = 49/235; Ag = 58/237 OR = 0.82 [0.53 to 1.26] I^2 = 0% d] COCP + Ant vs Ant-low response (1 study: Kim 2005) COCP + Ant = 9/27; Ant = 6/27 OR = 1.72 [0.53 to 5.60] I^2 = NA e] COCP + Ant vs Ag-low response (1 study: Kim 2005) COCP + Ant = 9/27; Ag = 7/28 OR = 1.49 [0.47 to 4.71] I^2 = NA f] COCP + Ag vs Ant-low response (1 study: Wang 2008) COCP + Ag = 22/63; Ant = 18/58	spontaneous abortions (pregnancy loss before twenty completed weeks of gestation) and the number of stillbirths (pregnancy loss after twenty completed weeks of gestation) 5. OHSS: defined as a condition that can occur from drugs used in ART, through stimulating a large number of follicles in the ovary to develope and ovulate. a] None of the studies used a placebo in the control group b] When Estrogen was compared with no pre-treatment, the denominator in the intervention group (Estrogen + Ant) was less by two women for the Multiple pregnancy outcome unlike the other outcomes

				OR = 1.19 [0.56 to 2.53] Pregnancy losses a] COCP + Ant vs Ant (4 studies: Cedrin-Durnerin 2007; Huirne 2006b; Kolibianakis 2006; Rombauts 2006) COCP Ant = 35/420; Ant = 29/427 OR = 1.26 [0.76 to 2.12] I^2 = 42% b] COCP + Ant vs Ag (3 studies: Hwang 2004; Huirne 2006a; Rombauts 2006) COCP Ant = 10/235; Ant = 19/237 OR = 0.52 [0.24 to 1.10] I^2 = 10% c] COCP + Ant vs Ant-low response (1 study: Kim 2005) COCP Ant = 1/27; Ant = 1/27 OR = 1.0 [0.06 to 16.42] I^2 = NA d] COCP + Ant vs Ag-low response (1 study: Kim 2005) COCP Ant = 1/27; Ant = 1/28 OR = 1.04 [0.06 to 17.04] I^2 = NA Multiple pregnancy a] COCP + Ant vs Ant (1 study: Cedrin-Durnerin 2007)	

				COCP Ant = 2/21; Ant = 1/24 OR = 2.32 [0.23 to 23.65] I^2 = NA b] COCP + Ant vs Ag (2 studies: Huirne 2006; Hwang 2004) COCP Ant = 2/21; Ant = 1/24 OR = 1.02 [0.37 to 2.82] I^2 = 0% c] COCP + Ant vs Ant-low response (1 study: Kim 2005) COCP Ant = 2/27; Ant = 1/27 OR = 2.00 [0.2 to 20.08] I^2 = NA d] COCP + Ant vs Ag-low response (1 study: Kim 2005) COCP Ant = 2/27; Ag = 1/28 OR = 2.08 [0.21 to 20.84] I^2 = NA OHSS a] COCP + Ant vs Ant (1 study: Rombauts 2006) COCP Ant = 3/117; Ant = 2/117 OR = 1.50 [0.26 to 8.80] I^2 = NA b] COCP + Ant vs Ag (2 studies: Hwang 2004; Rombauts 2006)	

				COCP Ant = 5/144; Ag = 8/146 OR = 0.63 [0.21 to 1.92] I^2 = 0% PROGESTOGEN VS NO PRE-TREATMENT Live births a] Prog + Ag vs Ag (2 studies: Ditkoff 1996; Engmann 1999) Prog + Ag = 24/110; Ag = 19/112 OR = 1.35 [0.69 to 2.62] I^2 = 22% b] Prog + Ant vs Ant (1 study: Cedrin-Durnerin 2007) Prog + Ant = 5/23; Ant = 7/24 OR = 0.68 [0.19 to 2.50] I^2 = NA Clinical pregnancy a] Prog + Ag vs Ag (3 studies: Aston 1995; Ditkoff 1996; Engmann 1999) Prog + Ag = 53/187; Ag = 31/187 OR = 1.95 [1.20 to 3.17] I^2 = 0% b] Prog + Ant vs Ant (1 study: Cedrin-Durnerin 2007)	

				Prog + Ant = 7/23; Ant = 11/24 OR = 0.53 [0.17 to 1.69] I^2 = NA c] Prog + Gon vs Gon (1 study: Salat-Baroux 1988) Prog + Gon = 3/21; Gon = 4/21 OR = 0.72 [0.14 to 3.56] I^2 = NA Pregnancy loses a] Prog + Ag vs Ag (2 studies: Ditkoff 1996; Engmann 1999) Prog + Ag = 9/110; Ag = 4/112 OR = 2.17 [0.71 to 6.69] I^2 = 0% b] Prog + Ant vs Ant (1 study: Cedrin-Durnerin 2007) Prog + Ant = 2/23; Ant = 5/24 OR = 0.39 [0.08 to 1.92] I^2 = NA c] Prog + Gon vs Gon (1 study: Salat-Baroux 1988) Prog + Gon = 1/21; Gon = 1/21 OR = 1.00 [0.06 to 16.55] I^2 = NA Multiple pregnancy	

				a] Prog + Ant vs Ant (1 study: Cedrin-Durnerin 2007) Prog + Ant = 1/23; Ant = 1/24 OR = 1.04 [0.06 to 17.23] I^2 = NA ESTROGEN VS NO PRE-TREATMENT Live Birth a] Estr + Ant vs Ant (1 study: Cdrin-Dumerin 2007) Estr + Ant = 3/25; Ant = 7/24 OR = 0.36 [0.09 to 1.41] b] Est + Ant vs Ag (1 study: Franco jr 2003) Est + Ant = 5/16; Ag = 2/6 OR = 0.91 [0.13 to 6.53] I^2 = 0.0% Clinical pregnancy a] Estr + Ant vs Ant (2 studies: Cdrin-Dumerin 2007; Fanchin 2003a) Estr + Ant = 20/72; Ant = 22/67 OR = 0.79 [0.38 to 1.62] I^2 = 81% b] Est + Ant vs Ag (1 study: Franco jr 2003) Est + Ant = 5/16; Ag =	

				2/6 OR = 0.91 [0.13 to 6.53] I^2 = 0.0% Pregnancy loss a] Estr + Ant vs Ant (1 study: Cdrin-Dumerin 2007) Estr + Ant = 1/25; Ant = 5/24 OR = 0.22 [0.04 to 1.17] b] Est + Ant vs Ag (1 study: Franco jr 2003) Est + Ant = 0/16; Ag = 0/6 OR = 0.00 [0.00 to 0.00] Multiple pregnancies a] Estr + Ant vs Ant (1 study: Cdrin-Dumerin 2007) Estr + Ant = 0/25; Ant = 1/24 OR = 0.13 [0.00 to 6.55] b] Est + Ant vs Ag (1 study: Franco jr 2003) Est + Ant = 2/14; Ag = 0/6 OR = 4.52 [0.20 to 101.00] I^2 = 48%	

				OHSS a] Est + Ant vs Ag (1 study: Franco jr 2003) Est + Ant = 0/16; Ag = 0/6 OR = 0.00 [0.00 to 0.00] COCP VS PROGESTERONE Live birth a] COCP + Ant vs Prog + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ant = 3/21; Prog + Ant = 5/23 OR = 0.61 [0.13 to 2.79] Clinical pregnancy a] COCP + Ant vs Prog + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ant = 5/21; Prog + Ant = 7/23 OR = 0.72 [0.19 to 2.68] Pregnancy loss a] COCP + Ant vs Prog + Ant (1 study: Cdrin-Dumerin 2007)	

				COCP + Ant = 2/21; Prog + Ant = 2/23 OR = 1.10 [0.14 to 8.43] Multiple pregnancies a] COCP + Ant vs Prog + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ant = 2/21; Prog + Ant = 1/23 OR = 2.22 [0.22 to 22.56] COCP VS ESTROGEN Live birth a] COCP + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ant = 3/21; Estr + Ant = 3/25 OR = 1.22 [0.22 to 6.69] Clinical pregnancy a] COCP + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ag = 5/21; Estr + Ant = 4/25 OR = 1.62 [0.38 to 6.90]	

				b] COCP + Ag vs Estr + Ant (1 study: Daly 2002) COCP + Ag = 2/12; Estr + Ant = 8/13 OR = 0.17 [0.03 to 0.80] I^2 = 77% Pregnancy loss a] COCP + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ant = 2/21; Estr + Ant = 1/25 OR = 2.43 [0.24 to 24.79] b] COCP + Ag vs Estr + Ant (1 study: Daly 2002) COCP + Ag = 1/12; Estr + Ant = 1/13 OR = 1.09 [0.06 to 18.49] I^2 = 0.0% Multiple pregnancies a] COCP + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) COCP + Ant =	

				2/21; Estr + Ant = 0/25 OR = 9.40 [0.56 to 156.66] PROGESTERONE + ESTROGEN Live Birth a] Prog + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) Prog + Ant = 5/23; Estr + Ant = 3/25 OR = 1.99 [0.44 to 8.94] Clinical pregnancy a] Prog + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) Prog + Ant = 7/23; Estr + Ant = 4/25 OR = 2.23 [0.59 to 8.44] Prenancy loss a] Prog + Ant vs Estr + Ant (1 study: Cdrin-Dumerin	

				2007) Prog + Ant = 2/23; Estr + Ant = 1/25 OR = 2.19 [0.22 to 22.19] Multiple pregnancies a] Prog + Ant vs Estr + Ant (1 study: Cdrin-Dumerin 2007) Prog + Ant = 1/23; Estr + Ant = 0/25 OR = 8.06 [0.16 to 407.60]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Andersen,A.N., Witjes,H., Gordon,K., Mannaerts,B., Predictive factors of ovarian response and clinical outcome after IVF/ICSI following a rFSH/GnRH antagonist protocol with or without oral contraceptive pre-treatment, Human Reproduction, 26, 3413-3423, 2011 **Ref ID** 154865 **Country/ies where the study was carried out** USA, Denmark, Germany, Spain and Turkey **Study type** Randomised controlled trial **Aim of the study** To identify factors capable of predicting ovarian response in patients undergoing their first treatment cycle with a daily dose of 200IU rFSH in a GnRH antagonist protocol. Women were randomised into two groups (with or without oral contraceptive pretreatment) to investigate the predictive vaue in both groups separately. **Study dates** October 2006 to July 2008 **Source of funding** Supported and funded by Merck, Sharp and Dohme & Co.	**Sample size** 442 women **Characteristics** Mean age: OC= 31.8 years (SD 3.7) Non-OC= 31.6 years (SD 4.1) Mean BMI: OC= 24.2 Non-OC= 23.6 Mean duration of infertility: OC= 3.9 years (SD 3.2) Non-OC= 3.7 years (SD 3.0) **Inclusion criteria** Women aged 18 to 39 years BMI =< 32 Menstrual cycle length of 24 to 35 days Women with access to ejaculatory sperm Women with an indiciation for COS and IVF and/or ICSI	Oral contraceptive pre-treatment (n=223) No oral contraceptive pre-treatment (n=219)	A total sample size of 200 randomised subjects per treatment group was planned, with an additional 20 subjects to compensate for discontinued subjects. Women were randomised to receive a fixed daily dose of 200 IU rFSH in a GnRH antagonist protocol either with OC pre-treatment or without any OC pre-treatment. Randomisation was done by central remote allocation using an interactive voice response telephone system and was stratified for centre and age (=< 32 years and > 32 years). The OC group received OC for 14 to 21 days. On day 5 after stopping OC, 200 IU rFSH was given, with 0.25 mg Ganirelix. hCG was given when 3 follicles => 17 mm. The non-OC group received stimulation with rFSH (200 IU) on day 2 or 3 of menses, with 0.25 mg Ganirelix. hCG was given when 3 follicles => 17 mm. If withdrawal bleeding did not occur in the OC group, the start of COS was delayed up to	Clinical pregnancy rate: OC= 62/223 (28%) women Non-OC= 86/219 (39%) women Clinical pregnancy was not defined	**Limitations** Allocation concealment was not clearly reported **Other information** 14 women in the OC group and 20 women in the non OC group did not receive rFSH 19 women in the OC group and 27 women in the non OC group did not receive hCG for final oocyte maturation 14 women in the OC group and 14 women in the non-OC group did not have embryo transfer

	Exclusion criteria History of endocrine abnormality Less than two ovaries Any ovarian abnormality (including endometrioma > 10mm visible on ultrasound) Unilateral or bilateral hydrosalpinx Any clinically relevant pathology affecting the uterine cavity (upon discretion of the investigator) Fibroids => 5cm History of recurrent miscarriage (three or more) FSH or LH levels > 12 IU/l in early follicular phase		the first day of bleeding. Maximum total duration of stimulation was 19 days. Oocyte pickup was performed 34 to 36 hours after induction of ovulation maturation, followed by IVF or ICSI. Embryo transfer occured 3 to 5 days after oocyte pickup, and a maximum of 2 embryos (=< 36 years) or 3 embryos (>36 years). All patients received daily progesterone (=> 600 mg/day vaginally or => 50 mg/day intramuscularly) for luteal phase support for => 6 weeks in case of pregnancy or until menses or up to a negative prenancy test performed => 14 days after embryo transfer.		

Fertility (Updated guideline)

Down-regulation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Polson,D.W., MacLachlan,V., Krapez,J.A., Wood,C., Healy,D.L., A controlled study of gonadotropin-releasing hormone agonist (buserelin acetate) for folliculogenesis in routine in vitro fertilization patients, Fertility and Sterility, 56, 509-514, 1991 **Ref ID** 68862 **Country/ies where the study was carried out** Australia **Study type** Randomised study **Aim of the study** [1] To compare folliculogenesis and pregnancy outcome in women with a previously normal response to CC-hMG after randomisation to receive either hMG, or GNRH agonist plus hMG (at two different GnRH doses) [2] To determine any differences in patient response to either of there two doses of GnRH **Study dates** **Source of funding**	**Sample size** N = 157 GnRH agonist (600ug/d): n =51 GnRH agonist (1200ug/d): n = 56 hMG: n = 50 **Characteristics** Patients with tubal infertility (n = 76) Patients with idiopathic infertility (n = 81) Womens mean age: GnRH agonist + hMG (600ug/d): 31.3 GnRH agonist + hMG (1200ug/d): 32.5 hMG: 32.7 **Inclusion criteria** Couples with idiopathic infertility had failed to conceive after at least 18 months regular unprotected intercourse despite ovulatory cycles, a normal semen analysis as (defined by WHO) and a normal pelvic appearance at laparoscopy All women were <37 years old.	1] GnRH agonist (600ug/d) + hMG + hCG + hCG 2] GnRH agonist (1200ug/d) + hMG + hCG + hCG 3] hMG + hCG + hCG	Randomisation: Patients were randomised by simple randomisation using a single sequence of random numbers. Power calculation: The sample size based on 80% power and a level of significance of 5% was 150 patients. Statistical analysis: Probability value < 0.05 was considered significant Intervention: Women assigned GnRH agonist (buserelin acetate) started on day 3(after measurements of E_2, P and LH), 150ug x 4 a day internasally (if in 1200ug group in both nostrils to double dose). When serum E_2 concentrations were <180pmol/L for two days hMG was started. In the group where hMG alone was considered, treatment was started at day 3. In all groups hMG is given in the following doses for the first 4 days of administration: 300IU, 300IU, 150IU and 150IU. Following	Clinical pregnancy defined as presence of gestational sac with or without fetal complex, or ectopic pregnancy Clinical pregnancy (events/cycle) in IVF and GIFT GnRH agonist (600ug/d): 9/56 GnRH agonist (1200ug/d): 11/64 hMG: 3/56 Clinical pregnancy (event/women) in IVF and GIFT* GnRH agonist (600ug/d): 9/51 GnRH agonist (1200ug/d): 11/56 hMG: 3/50 Based on calculated assumption (see limitations)	**Limitations** - The clinical pregnancy data is presented per cycle, in all groups there are more cycles than women - The was no allocation concealment - Outcomes only presented for IVF and GIFT combined, it is impossible to separate IVF specific outcomes - No explanation of why certain women would received IVF or not. **Other information**

September 1988 to February 1989 Not reported	All women had responded to authors standard CC and hMG regimen previously. **Exclusion criteria** None reported		that hMG was adjusted depending on E2, P and LH concentrations. Method: hCG was administered (5000IU) when there was at least 3 follicles with diameter >17mm and E2 concentration was >3600pmol/L. Depending on infertility indication IVF, pronuclear transfer or GIFT was undertaken. In IVF ET was done 48-72hours after aspiration. Luteal phase support was hCG every 3 days (1000IU, down regulated to 500IU after 2 cases of OHSS). The cycle was cancelled when there was an unsatisfactory response.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Neveu,S., Hedon,B., Bringer,J., Chinchole,J.M., Arnal,F., Humeau,C., Cristol,P., Viala,J.L., Ovarian stimulation by a combination of a gonadotropin-releasing hormone agonist and gonadotropins for in vitro fertilization, Fertility and Sterility, 47, 639-643, 1987 **Ref ID** 74339 **Country/ies where the study was carried out** France **Study type** Randomised study **Aim of the study** The study was designed to evaluate the effect of a GnRH agonist in combination with ovarian stimulation by gonadotrophins for IVF. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 20 (Group a) n =10 (Group b) n =10 **Characteristics** Women aged between 28 to 38 years **Inclusion criteria** - Tubal infertility - Normal ovulation - Normal plasma prolactin - Normal androgen levels Before the study patients had to have had at least 1 attempt at IVF with ET to judge ovarian stimulation response **Exclusion criteria** Women with unexplained infertility with or without endometriosis and male infertility were excluded Women who failed to respond to previous ovarian stimulation	[1] FSH + hCG + hCG [2] GnRH agonist + FSH + hCG + hCG	Randomisation: 20 patients were randomly divided into two groups. Intervention: In group A, 10 patient were stimulated with pFSH. 250IU FSH was given for 4 days, from day 2 to 5 of the cycle. 150IU was administered at day 6 or 7. From day 8 the dose of pFSH is determined by ovarian response. In group B, 10 patients were stimulated with pFSH after pituitary desensitization. Patients received 0.3ml GnRH agonist (busereline) subcutaneously twice a day for 14days, starting on day 1 or 2 of the cycle. On day 14 response was measured (E_2, E_1 and no follicle size >10mm), if these criteria weren't matched there would be a further 5 days treatment. FSH stimulation was started when the down regulation criteria were met. The protocol for FSH was the same as in group A. Method: All patients were monitored from 8th day, the criteria for hCG (5000IU) administration was estrogen >120ug/gm creatine and follicle diameter >17mm.	Clinical pregnancy (event/women) FSH: 1/10 (10%) GnRH + FSH: 6/10 (60%) (clinical pregnancy criteria not reported) Multiple pregnancy (event/pregnancy) FSH: 0/1 (0%) GnRH + FSH: 3/6 (50%)	**Limitations** - No randomisation method reported - No allocation concealment - No power calculation done - Unclear what is meant by clinical pregnancy - Unclear how many embryos were transfer (per women) **Other information** The paper also contained information details of a second study in women who had a previously had a poor response, this data was not included on the basis of no evidence of randomisation and no comparison group.

			Oocyte retrieval took place 35 hours after hCG injection. ET was done 48 hours after retrieval. Luteal phase support was 1500IU hCG on day of retrieval, then repeated on the day of ET and finally repeated 4 days after ET.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation van de-Helder,A.B., Helmerhorst,F.M., Blankhart,A., Brand,R., Waegemaekers,C., Naaktgeboren,N., Comparison of ovarian stimulation regimens for in vitro fertilization (IVE) with and without a gonadotropin-releasing hormone (GnRH) agonist: results of a randomized study, Journal of in Vitro Fertilization and Embryo Transfer, 7, 358-362, 1990 **Ref ID** 83243 **Country/ies where the study was carried out** Not reported **Study type** Randomised study **Aim of the study** The aim of the study was to diminish the cancellation rate in hMG/hCG stimulated cycles due to a premature endogeneous LH surge and/or due to a poor response in ordered to increase pregnancy rate per cycle. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 153 **Characteristics** Womens ages (mean): 32 years (23-40) Number of embryos per ET hMG/hCG: 2.5 GnRH (short): 2.9 GnRH (long): 2.6 **Inclusion criteria** All patients had blocked oviducts but apparently normal ovarian function and regular menstrual cycles No evidence or history of pituitary, thyroid, or adrenal disease All patients were <41 years old All male partners had normal spermiogram **Exclusion criteria** Not reported	1] hMG + hCG + P + hCG 2] GnRH agonist short protocol + hMG + hCG + P + hCG 3]GnRH agonist long protocol + hMG + hCG + P + hCG	Randomisation: Women were randomised into 3 groups Power calculation: Power calculation not done Intervention: Patients in group I were stimulated with hMG and hCG, buserelin was used as the GnRH agonist in groups II and III. GnRH agonist was given as 200ug 3 times a day. The patients in group II (short) started GnRH agonist on the first day after the ultrasound scan. The patients in group III (long) treatment was commenced in midluteal phase. In groups I and II hMG was administered on day 4. In group III hMG treatment was commenced when a sustained suppression of gonadotrophin secretion had been achieved as demonstrated by consistently low estrogen levels. Subsequent doses of hMG were adjusted depending on ovarian response. Method: hCG (10000IU) was injected when estrogens were rising continuously for at least 4 days and when the leading follicle had reached a diameter of <16mm, aspiration was done 36 hours later. Up a	Clinical pregnancy (event/women) hMG/hCG: 5/52 (9.6%) GnRH (short): 14/51 (27.5%) GnRH (long): 9/50 (18%) Pregnancy was defined as an intrauterine fetus was ultrasonically proven heart rate or a histological ectopic chorion villus. Ongoing pregnancy rate (event/women) hMG/hCG: 4/52 (7.7%) GnRH (short): 10/51 (19.6%) GnRH (long): 6/50 (12%) Multiple pregnancy rate (event/clincial pregnancy) hMG/hCG: 2/5 (40%) GnRH (short): 1/14 (7.1%) GnRH (long): 1/9 (11.%)	**Limitations** - No reported method of patient randomisation - No allocation concealment - No power calculation **Other information** Definition of poor response to superovulation is an absence of significant estrogen rise and absent or slow follicular growth.

			maximum of 4 embryos were transferred on day 2 or 3 after aspiration. Luteal phase support was done using daily progesterone pessaries and by hCG (1500IU) 4 days after transfer.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Antoine,J.M., Salat-Baroux,J., Alvarez,S., Cornet,D., Tibi,C., Mandelbaum,J., Plachot,M., Ovarian stimulation using human menopausal gonadotrophins with or without LHRH analogues in a long protocol for in-vitro fertilization: a prospective randomized comparison, Human Reproduction, 5, 565-569, 1990 **Ref ID** 81733 **Country/ies where the study was carried out** France **Study type** Randomised Controlled Trial **Aim of the study** Compare normo-ovulatory women between HMG alone and HMG associated with an LHRH agonist in a long protocol. **Study dates** No specified **Source of funding** No specified	**Sample size** 180 women were randomised into two groups. Group 1 (HMG and LHRH) = 90, and group 2 (HMG alone) = 90. **Characteristics** Group 1 (HMG and LHRH) <u>Age (years)</u> Group 1 (HMG and LHRH) = 32.7 (+/- 3.0) Group 2 (HMG alone) = 31.9 (+/- 3.6) <u>Duration of infertility</u> Group 1 (HMG and LHRH) = 6.3 (+/- 2.3) Group 2 (HMG alone) = 7.0 (+/- 4.2) <u>Number of embryos tranferred</u> Group 1 (HMG and LHRH) = 6.3 (+/- 2.3) Group 2 (HMG alone) = 7.0 (+/- 4.2) **Inclusion criteria** **Exclusion criteria**	Group 1 (HMG and LHRH) received a depot injection of 3.75 mg DTRP. Pituitary desensitisation was verified on day 26 and then depot DTRP 0.1 mg for 3 days. Starting on 28th day or when desensitisation was achieved, stimulation was commenced using HMG at fixed dose of 3 ampoules per day for 6 days. Agonist continued at dose of 0.1 mg until day of trigger with HCG. Group 2 (HMG alone) received individualised dose of HMG from 2nd to 7th day of cycle depending on plasma gonadotrophin measurement. If normal levels obtained then 2 ampoules given, if not reached then 3 ampoules given. In both groups from 7th day of stimulation the dose of HMG was adjusted depeneding on E_2, P and LH measures and cervical mucus assessment. Luteal support using progesterone (3 x 100mg tablets per day via vaginal route) was given from the day of replacement and 2500 IU of HCG on day 1, 3, and 5.	Ethical approval was not specified Randomisation was undertaken, but the method of randomisation was not specified Blinding was not specified Statistcial analysis was undertaken using Chi-squared or Stundent's t-test.	<u>Clinical pregnancies</u> Group 1 (HMG and LHRH) = 19/90 Group 2 (HMG alone) = 11/90 <u>Ongoing pregnancies</u> Group 1 (HMG and LHRH) = 15/90 Group 2 (HMG alone) = 9/90 <u>Multiple pregnancies</u> Group 1 (HMG and LHRH) = 5/90 Group 2 (HMG alone) = 0/90	**Limitations** **Other information**

	Normo-ovulatory, aged =< 38 years, being treated in an IVF programme for complete or incomplete tubal obstruction (duration of infertility > 3 years) and no associated male factor infertility. Not specified	The cycle was cancelled in cases of premature LH surge and a poor ovarian response.			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Weigert,M., Krischker,U., Pohl,M., Poschalko,G., Kindermann,C., Feichtinger,W., Comparison of stimulation with clomiphene citrate in combination with recombinant follicle-stimulating hormone and recombinant luteinizing hormone to stimulation with a gonadotropin-releasing hormone agonist protocol: a prospective, randomized study, Fertility and Sterility, 78, 34-39, 2002 **Ref ID** 69156 **Country/ies where the study was carried out** Austria **Study type** Randomised trial **Aim of the study** To compare IVF-ET outcome with a new stimulation protocol using CC with rFSH and LH to stimulation with the standard long GnRH-a protocol. **Study dates** Not reported **Source of funding** Supported by Serono Austria GmbH, Wienerbergstr	**Sample size** n = 294 women **Characteristics** Population: Ovulatory women undergoing their first IVF or ICSI attempt with the infertility diagnoses listed below. Study II Female mean age = 32.8 ± 4.1 years Duration of infertility = NR BMI/ Weight = NR Cause of infertility: Male factor = 167 (56.8%) Tubal factor = 71 (23.8%) Endometriosis = 4 (1.4%) Unexplained = 29 (9.9%) Mixed factor = 21 (7.1%) **Inclusion criteria** Unclear **Exclusion criteria** Unclear	[1] GnRH agonist + rFSH [2] CC + rFSH + rLH	Recruitement: Participants were recruited in an outpatient infertility clinic. Method: Randomisation was achieved with a computer-generated list. Intervention: Patients in group A were stimulated with CC + rFSH + rLH and Prednisolone was given daily for 1 month. All women in this group were pretreated with oral contraceptive for 18 - 28 days. The patients also received oral dydrogesterone for luteal support. Patients in group B were started on buserelin nasal spray in the luteal phase of the preceding cycle. GnRH-a was continued until the hCG injection. Once suppression was achieved, rFSH was started. Injections were given everyday On day 8 of stimulation patients returned for ultrasound evaluation. Thereafter, the cycle was managed and monitored according to routine IVF protcols. Ovulation was induced with hCG once the largest follicle was >18mm. Transvaginal oocyte retrieval	Clinical pregnancy GnRH agonist + rFSH: 41/140 (29.3%) CC + rFSH + rLH: 54/154 (35.1%) Adverse pregnancy outcome GnRH agonist + rFSH: 7/140 (5%) CC + rFSH + rLH: 10/154 (6.5%) OHSS GnRH agonist + rFSH: 12/140 (8.6%) CC + rFSH + rLH: 4/154 (2.6%) [1] Figures for clinical pregnancy reflect 'normal pregnancy' which was defined as a positive fetal heart beat at 8 weeks on the ultrasound. [2] Adverse pregnancy outcome reported were biochemical pregnancies and early pregnancy losses. [3] OHSS was moderate and definition was not reported	**Limitations** [1] No blinding of study participants, personnel and staff reported. [2] No power calculation reported. [3] Allocation concealment not reported **Other information** [1] Cycles were cancelled if there was a low response (no evidence of follicle development on ultrasound on day 8), if the hormone levels were elevated at baseline (LH >8 IU/L; FSH >15 IU/L; E2 >50 pg/mL), if there was no fertilisation or if other causes developed, such as ovarian cysts, endometrial polyps, or hydrosalpinx. [2] In total, 48 cycles were cancelled and 8 additional cycles did not progress to ET - in group A, 26 cycles were cancelled and 2 additional cycles (1.3%) did not progress to ET; in group B, 22 cycles were cancelled and 6 additional cycles (4.3%) did not progress to ET. However, there was no difference in cancellation rates between the two groups

			was performed 35h after the hCG injection. Oocytes were inseminated or injected, in the case of ICSI, on the afternoon of the retrieval and transvaginal embryo transfer was performed on day 2 or 3		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Grochowski,D., Wolczynski,S., Kuczynski,W., Domitrz,J., Szamatowicz,J., Szamatowicz,M., Good results of milder form of ovarian stimulation in an in vitro fertilization/intracytoplasmic sperm injection program, Gynecological Endocrinology, 13, 297-304, 1999 **Ref ID** 68380 **Country/ies where the study was carried out** Poland **Study type** Randomised trial **Aim of the study** To compare two protocols of ovulation stimulation, the clomiphene citrate/hMG versus D-triptorelin/hMG, in terms of pregnancy rates and cost-effectiveness of drugs used. **Study dates** January 1996 - June 1998 **Source of funding** Not reported	**Sample size** n = 324 patients **Characteristics** Population: Ovulatory women undergoing their first attempt who had the following infertility diagnoses listed below. Female mean age = 30.1 ± 3.7 years Duration of infertility = NR BMI / Weight = NR Cause of infertility: Male factor = 143 (44.1%) Tubal factor = 111 (34.3%) Unexplained = 19 (5.9%) Endometriosis = 18 (5.6%) Mixed factor = 33 (10.2%) **Inclusion criteria** [1] Age <36 years [2] Regular menstrual cycles (25 - 35 days) [3] Cause of infertility solvable by IVF/ICSI For ICSI: [1] Patient had to have very poor sperm parameters according to WHO criteria **Exclusion criteria** For ICSI: [1] Azoopermia	[1] GnRH agonist + hMG [2] CC + hMG	Recruitment: The study population consisted of 324 infertile patients, who within the study period entered their first trial in the IVF/ICSI program at the IVF unit. Method: The couples were allocated to the two different drug regimens by drawing serially numbered envelops. Intervention: Two stimulation protocols were used simultaneously: 164 cycles were stimulated using CC from day 2 of the cycle for 5 days and hMG on days 4, 6 and 8 of the cycle. Depending on the serum estradiol concentrations and ultrasound findings, the dose of hMG was then adjusted if necessary. In another 160 cycles, pituitary desensitisation was achieved with the use of D-triptorelin in a single injection in the midluteal phase. hMG was given from day 3 of the cycle for 5 days. For the following days, the dose of hMG was adapted according to the response to the treatment. When at least two growing follicles >18 mm in diameter in group 1 and >20mm in group 2 were present and serum	Clinical pregnancy (event/women) GnRH agonist + hMG: 38/160 (23.8%) CC + hMG: 41/164 (35%) OHSS (event/women) GnRH agonist + hMG: 5/160 (3.1%) CC + hMG: 0/164 (0%) [1] Clinical pregnancy was diagnosed when a gestational sac was detected by ultrasonography two weeks after embryo transfer. [2] OHSS reported was severe OHSS and was not defined Twin pregnancies: CC + hMG= 7/41 (17%) pregnancies (7/164 women [4%]) GnRH agonist + hMG= 3/38 (8%) pregnancies (3/160 women [2%]) The number of births from these pregnancies was not reported	**Limitations** [1] Inadequate randomisation method [2] Inadequate allocation concealment [3] Blinding not reported **Other information** [1] There were 8 cases of spontaneous ovulation in the CC + hMG group and 2 aspiration failures in the GnRH agonist/hMG group. [2] Fertilisation failure occurred in 18 patients (11/18 patients had only one oocyte collected) in the CC +hMG group compared with 8 in the GnRH agonist/hMG group. [3] There was about 5% spontaneous ovulations. [4] Results from subgroup analysis by ART did not differ from the general results (IVF and ICSI)

			estradiol concentrations of at least 500pg/ml were achieved, hCG was given to induce ovulation. Transvaginal ovum collection was performed 36h later. Four hours after collection, oocytes were inseminated and incubated. Fertilisation was then assessed 14 - 16h later and the two best quality embryos were transferred into the uterus on the following day. If an embryo selection was possible, the two best quality embryos were replaced and surplus embryos were further cultured into the blastocyst stage and then cryopreserved. Statistical analysis: An estimated 270 couples was required to detect a 15% difference in pregnancy rates with a power of 80% and 5% level of significance. The sample size in each drug regimen was balanced for the IVF and ICSI procedure. The population in the two groups was homogeneous.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dhont,M., Onghena,A., Coetsier,T., De,Sutter P., Prospective randomized study of clomiphene citrate and gonadotrophins versus goserelin and gonadotrophins for follicular stimulation in assisted reproduction, Human Reproduction, 10, 791-796, 1995 **Ref ID** 68205 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** To investigate whether the use of GnRH agonist in unselected patients would provide a clear advantage in terms of pregnancy rate/cycle. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 238 women **Characteristics** Population: Patients with mixed infertility diagnosis (not stated but mainly abnormal spermiogram) coming for their first IVF attempt. Female mean age = NR Duration of infertility = NR BMI/ Weight = NR Cause of infertility: Abnormal spermiogram = 167 (55.1%) Other factors = NR **Inclusion criteria** [1] Only patients who entered a first trial of assisted reproduction. **Exclusion criteria** Not reported	[1] GnRH agonist +hMG [2] CC + hMG	Recruitment: Patients who entered a first trial of assisted reproduction were included. From a retrospective analysis of IVF data, a pregnancy rate of of 20 - 25% per cycle with CC/hMG was anticipated. Method: In total, 303 patients were included. Because of a number of potential confounders, patients were allocated to one of the treatment groups using a computerised minimisation procedure in which three main prognostic factors: ART type, sperm characteristics and age. The two treatment groups were equally randomised along those three parameters. Intervention: In both groups, the cycle before starting stimulation was suppressed by means of an oral contraceptive which was given for at least 2 weeks and this period could be extended up to 6 weeks depending on circumstances. Stimulation with either CC or hMG was started 7 days after the cessation of the oral contraceptive. CC was given for 5 days. In group A, pituitary desensitisation by a	Pregnancy rate (event/women) GnRH agonist +hMG: 44/119 (37.6) CC + hMG: 28/119 (23.5%)	**Limitations** [1] Allocation concealment not reported [2] Blinding not reported **Other information** [1] Figures for 'Adverse pregnancy outcomes' reflect numbers of abortion and ectopic pregnancy and presented as a rate. The rates in the goserelin + hMG group and the CC + hMG group were 34% and 24.3% respectively; p = NS. [2] There was no definition for 'Live birth', however, the rates in both groups (CC + hMG and goserelin +hMG) were 18.5% and 25.7% respectively; p = 0.13.

			subcutaneous implant of goserelin was initiated 2 - 3 weeks before starting the stimulation, while the patient was still on the oral contraceptive. hMG was started 7 days after cessation of the oral centraceptive and between 14 and 21 days after the administration of goserelin. In group B, the stimulation with hMG started at the end of CC administration for 3 - 5 days. To prevent premature LH rise as far as possible, hCG was given when the diameter of the largest follicle was 18 mm in the CC/hMG group, whereas in the goserelin/hMG group, hCG was given when the largest follicle was ≥20 mm in diameter. Oocyte retrieval took place 35 - 37 h after hCG injection. In IVF cycles, up to three good quality embryos were transferred into the uterus. If fewer than three good quality embryos were available for transfer, additional intermediate embryos, up to 5 in total were transferred Statistical analysis: A sample size of 300 was required to detect a relative difference in pregnancy rate per cycle of		

			50% with a power of 90% and with α error = 0.05. In total, 303 patients were included.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation AlInany,Hesham G., Youssef,AFM Mohamed, Aboulghar,Mohamed, Broekmans,Frank, Sterrenburg,Monique, Smit,Janine, AbouSetta,Ahmed M., Gonadotrophin-releasing hormone antagonists for assisted reproductive technology, Cochrane Database of Systematic Reviews, -, 2011 **Ref ID** 125107 **Country/ies where the study was carried out** **Study type** Cochrane review: Systematic review and meta-analysis **Aim of the study** To evaluate the effectiveness and safety of gonadotrophin-releasing hormone (GnRH) antagonists with the standard long protocol of GnRH agonists for controlled ovarian hyperstimulation in assisted conception cycle. **Study dates** Search covered from 1987 to April 2010 **Source of funding** Not specified	**Sample size** 45 randomised controlled studies, involving 7511 randomised women, were included. Thirty-three studies were excluded **Characteristics** <u>Allocation</u> • Randomisation was done at the time of recruitment of participants. • All trials had a parallel design and proper randomisation was carried out by 31 studies by using: interactive voice response systems; stratified randomisation; computer-generated random number tables with or without sealed envelopes for allocation concealment; or random number table. • Allocation concealment was properly performed by a nurse or by an interactive telephone system. • The methods of sequence generation and allocation concealment were not clearly reported in the remaining trials	All included studies compared GnRH antagonist with long GnRH agonist protocols in women undergoing IVF or ICSI cycles. Three types of antagonist protocols were identified: • single, long-acting administration • fixed, daily administration ; and • flexible daily administration.	Data synthesis The data from primary studies were combined using the Petomodified Mantel-Haenszel method for dichotomous outcomes; and using the inverse variance method for continuous outcomes. All analyses were performed using Review Manager software (RevMan 5, The Cochrane Collaboration, Oxford, UK). Subgroup analysis and investigation of heterogeneity Subgroup analysis has been performed for the following categories. 1) GnRH antagonist regimen (fixed or flexible). 2) GnRH antagonist type (cetrorelix or ganirelix). 3) GnRH antagonist plus pre-treatment with oral contraceptive pill (OCP). 4) Patient characteristics (polycystic ovary syndrome (PCOS); poor responders). 5) Patients undergoing mild ovarian stimulation. Sensitivity analysis Sensitivity analysis was performed for the primary outcome, LBR or OPR, after	<u>Live birth</u> (number of RCTs, number of women, Odds Ratio) All women (9 RCTs) GnRH antagonist 222/824 vs. GnRH agonist 217/691, Odds Ratio (M-H, Fixed, 95% CI) 0.86 [0.69, 1.08] <u>Ongoing pregnancy</u> All women (28 RCTs), GnRH antagonist 751/2913 vs. GnRH agonist 637/2101 Odds Ratio (M-H, Fixed, 95% CI) 0.88 [0.77, 1.00] <u>Clinical pregnancy</u> All women (41 RCTs) GnRH antagonist 1018/3748 vs. GnRH agonist 890/2823, Odds Ratio (M-H, Fixed, 95% CI)0.84 [0.75, 0.94] <u>Miscarriage</u> All women (27 RCTs) Total (95% CI) GnRH antagonist, 98/873 vs. GnRH agonist 91/774 Odds Ratio (M-H, Fixed, 95% CI)0.96 [0.70, 1.31] <u>Ovarian hyperstimulation</u>	**Limitations** Some studies did not clearly report the method of randomisation Some studies did not blind, and other studies did not report blinding Some studies did not perform allocation concealment, and other studies did not report whether allocation concealment was performed or not **Other information** <u>Incomplete outcome data</u> Live-birth rate was reported in only nine trials. <u>Selective reporting</u> All studies reported their outcome measures in a pre-specified manner. <u>Commercial funding</u> Twelve studies received commercial funding.Thirteen studies reported no conflict of interest or commercial support. The other studies did not clearly report funding.

	Blinding • Blinding was examined with regards to who was blinded in the trials. All levels were sought and categorized as follows: (i) double blind (neither the investigator nor the participants knew of the allocation); (ii) single blind (the investigator only knew of the allocation); (iii) no blinding (both investigator and participants knew the allocated treatment); (iv) unclear. • Since it was impossible to administer the different medications (that is long agonist and antagonist) according to one standard protocol without the use of a double dummy, almost all the studies were open-label (that is no blinding). • None of the trials were reported as being double blinded, with 27 trials reporting no blinding. The remaining trials did not clearly report if blinding was performed. **Inclusion criteria** Types of studies		exclusion of studies with a higher risk of bias; that is studies in which the mode of randomisation was unclear or that used inadequate allocation concealment compared with the studies that used adequate methods (Moher 1999).	All women (29 RCTs) (GnRH antagonist 97/3542 vs. GnRH agonist 210/2658, Risk Difference (M-H, Fixed, 95% CI) -0.04 [-0.05, -0.03] Cancelled or coasting due to high risk of OHSS All women (16 RCTs) GnRH antagonist 40/2096 vs. GnRH agonist 56/1416, Odds Ratio (M-H, Fixed, 95% CI) 0.50 (0.33, 0.76) Cancellation due to poor ovarian response All women (17 RCTs) GnRH antagonist 102/1916 GnRH agonist 94/1284 Odds Ratio (M-H, Fixed, 95% CI) 0.76 (0.56, 1.03)	

	Only randomised controlled trials (RCTs) with a parallel design were eligible for inclusion. Quasi-randomised trials were not included. If cross-over studies with cross-over occurring between cycles were available only inclusion of the first cycle, before the crossover, would have been included. <u>Types of participants</u> Subfertile couples undergoing controlled ovarian hyperstimulation (COH) as part of an IVF or ICSI program using GnRH antagonists for the prevention of premature LH surges. **Exclusion criteria** Not specified				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Maheshwari, A., Gibreet, A., Siristatidia, C. S., Bhattacharya, S., Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction, 2011 **Ref ID** 128785 **Country/ies where the study was carried out** **Study type** Cochrane review: systematic review and meta-analysis of RCTs **Aim of the study** To evaluate the effectiveness of the different GnRHa protocols as adjuncts to ovarian stimulation in women undergoing ARTcycles. **Study dates** All the searches were updated to August 2010. **Source of funding** Not stated	**Sample size** **Characteristics** Results of the search After searching the electronic databases, we found a total of 1049 studies: 492 studies in the MDSG Specialised Register of controlled trials, 123 studies in CENTRAL, 350 studies in MEDLINE, 61 studies in EMBASE, 3 studies in CINAHL and 20 studies in PsycINFO. After removing the duplicates and searching other resources, there were approximately 900 studies left. Sixty-seven studies seemed eligible for inclusion, after reading full text articles, and we were able to include 29 studies in this review. Included studies Twenty-nine studies were included. • Long versus short protocol: Compared by 17 studies. • Long versus ultrashort protocol: Compared by two studies. • Short versus ultrashort protocol: No studies were found for this comparison. • Follicular versus luteal start	• All long protocols versus a short protocol. • Long versus ultrashort protocol. • Short versus ultrashort protocol. • Long follicular versus long luteal protocol. • Continuation of down-regulation versus discontinuing GnRHa at start of stimulation, in a long protocol. • Continuation of down-regulation with the same dose versus reducing the GnRHa dose at start of stimulation, in a long protocol	Standardised Cochrane methodology. <u>Data synthesis</u> Analysis was done using Rev Man 5.1 software. For binary (or dichotomous) outcomes, results for each study were expressed as Peto odds ratios (OR) with 95% confidence intervals (CI) and combined for meta-analysis, where appropriate. For continuous outcome data, results from each study were expressed as a difference in means with 95% CI and combined for meta-analysis using the mean difference (MD). <u>Subgroup analysis and investigation of heterogeneity</u> When substantial heterogeneity was found, the following steps were undertaken. We performed a random-effects model meta-analysis; and considered completing subgroup analysis of prognostic factors such as the number of embryos transferred, previous failed cycles, maternal age and duration of treatment.	<u>Long versus short protocol (17 RCTs)</u> Live birth rate (3 RCTs): n = 251 women, OR 1.80, 95% CI 0.92 to 3.50 Clinical pregnancy rate (17 RCTs): N = 1437 women, OR 1.50, 95% CI 1.16 to 1.93 Ongoing pregnancy rate (7 RCTs): N = 574 women, OR 1.41, 95% CI 0.91 to 2.17 Cycle cancellation rate (8 RCTs): N = 825 women, OR 1.01, 95% CI 0.42 to 2.44 <u>Long versus ultrashort protocol (2 RCTs)</u> Live births (1 RCT): N = 150 women, OR 1.78 95% CI 0.72, 4.36 Clinical pregnancy rate (2 RCTs): N =-230 women, OR 1.55, 95% CI 0.80 to 3.01 Cycle cancellation (1 RCT): N = 150 women, OR 1.11, 95% CI 0.40 to 3.05	**Limitations** Not all studies clearly reported allocation concealment Not all studies clearly reported the method of randomisation used Not all studies blinded participants or clearly reported blinding of participants **Other information**

	of GnRHa: Four studies were included in this comparison. • Continuation of GnRHa versus stopping GnRHa at start of stimulation:Three studies were included for this comparison. • Continuation of same dose GnRHa versus reduced dose GnRHa: Three studies were included in this comparison. • Short versus short stop protocol: Only one study was included in this comparison. **Inclusion criteria** <u>Types of studies</u> Only randomised controlled trials (RCTs) comparing various GnRHa protocols in ART. In vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment cycles were included. Trials were excluded if allocation was found to be non-random. Crossover trials were also excluded as the design was deemed not suitable for this review. Quasi-randomised trials were excluded as well, even if they had been included in the original review. <u>Types of participants</u> • Women undergoing ART using GnRHa for pituitary		<u>Sensitivity analysis</u> Sensitivity analysis was performed by excluding studies with unclear randomisation. There were not enough studies to support meta-regression or other formal considerations of prognostic factors.	<u>Short versus ultrashort protocol</u> No studies were found for this comparison. <u>Luteal versus follicular start of GnRHa (4 RCTs)</u> Live births (1 RCT): N = 124 women, OR 1.89 95% CI 0.87, 4.11 Pregnancy rate (4 RCTs): N = 569 women, OR 1.06, 95% CI 0.72 to 1.56 Cycle cancellation (1 RCT):N = 86 women, OR 1.64, 95% CI 0.28 to 9.45 <u>Long protocol (continue GnRHa versus stop GnRHa) (3 RCTs)</u> Live births: None of the three studies reported on live birth. Clinical pregnancies (3 RCTs): N = 264 women, OR 0.76, 95% CI 0.40 to 1.44 Ongoing pregnancies (2 RCTs): N = 194 women, OR	

	down-regulation • Women receiving donor oocytes were excluded. <u>Types of interventions</u> Studies comparing any two protocols using GnRHa for pituitary suppression in an ART programme. Ultrashort; short; and long (follicular or luteal with or without discontinuation during the stimulation phase) protocols were included. The definitions used in this review for the various protocols were as follows. • Long protocol: GnRHa commenced at least two weeks before starting stimulation and continued up until HCG is given. • Short protocol: GnRHa commenced at the same time as starting stimulation and continued up until the day of hCG administration. • Ultrashort protocol: stimulation is commenced one to two days after starting GnRHa (and given only for three days). **Exclusion criteria** Studies comparing: (1) agonist versus antagonist protocols and (2) different routes of			0.67, 95% CI 0.30 to 1.48 Cycle cancellation rate (3 RCTs): N = 264 women, OR 1.19, 95% CI 0.14 to 10.33 <u>Long protocol (continued same dose GnRHa versus reduced dose GnRHa) (3 RCTs)</u> Live births: No study reported on the live birth rate. Clinical pregnancy rate (3 RCTs): N = 311 women, OR 1.02, 95% CI 0.64 to1.62 Cycle cancellation rate (1 RCT): N = 132 women, OR 1.00, 95% CI 0.14 to 7.32 <u>Short versus stop short protocol (1 RCT)</u> Live births: This was not reported for the comparison. Clinical pregnancy rate (1 RCT): N = 230 women, OR 0.59, 95% CI 0.30 to 1.17 Cycle cancellation (1 RCT): N = 230 women, OR 0.73, 95% CI 0.34 to 1.59	

	administration of agonist were excluded as they are the topics of other Cochrane reviews. Studies assessing agonist versus placebo protocols were excluded as well as meta-analysis already exist on this topic.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Long,C.A., Sopelak,V.M., Lincoln,S.R., Cowan,B.D., Luteal phase consequences of low-dose gonadotropin-releasing hormone agonist therapy in nonluteal-supported in vitro fertilization cycles, Fertility and Sterility, 64, 573-576, 1995 **Ref ID** 68624 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare the clinical effects of low-dose leuprolide acetate (GnRH agonist) combined with hMG to CC and hMG during follicular stimulation for IVF. **Study dates** Not reported **Source of funding** None reported	**Sample size** 70 women **Characteristics** 25 to 45 years old First IVF-ET program **Inclusion criteria** None reported **Exclusion criteria** None reported	GnRH agonist + hMG + hCG CC + hMG + hCG	GnRH agonist group: 0.25 mg GnRH agonist (Lupron) with 150 IU hMG (Pergonal) daily starting on day 2 of cycle. CC group: 50mg CC on days 2 to 6 of menstrual cycle and 150 IU hMG (Pergonal) on a daily basis beginning on day 3 HCG (10,000 IU) administered when three or more follicles measured => 15 mm and circulating E2 was >200 pg/mL per follicle Aspiration performed 34 hours after hCG administration No luteal support was given to either group	Clinical pregnancy: GnRH agonist group= 5/36 (14%) CC group= 5/34 (15%) Clinical pregnancy was confirmed if rising hCG concentrations were observed and an intrauterine gestation or tubal pregnancy was confirmed Singleton live births: GnRH agonist group= 1/36 (3%) women CC group= 4/36 (11%) women Babies born from multiple pregnancies: GnRH agonist group= 2/3 (67%) babies CC group= 0/4 (0%) babies Miscarriages:	**Limitations** Power calculation not reported Blinding not reported Method of randomisation not reported Allocation concealment not reported **Other information** GnRH agonist group had four cancellations for poor response, one for enlarged ovarian cyst, one for hyperstimulation CC group had three cancellations for poor response, two for premature LH surge, and one for enlarged ovarian cyst

				GnRH agonist group= 2/36 (6%) women, 2/5 (40%) pregnancies CC group= 0/36 (0%) women, 0/5 (0%) pregnancies Ectopic pregnancies: GnRH agonist group= 0/36 (0%) women, 0/5 (0%) pregnancies CC group= 1/36 (3%) women, 1/5 (20%) pregnancies	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Harrison,R.F., Kondaveeti,U., Barry-Kinsella,C., Gordon,A., Drudy,L., Cottell,E., Hennelly,B., Frankish,A., Unwin,A., Should gonadotropin-releasing hormone down-regulation therapy be routine in in vitro fertilization?, Fertility and Sterility, 62, 568-573, 1994 **Ref ID** 68409 **Country/ies where the study was carried out** Ireland **Study type** Randomised clinical trial. **Aim of the study** To compare the efficacy of differing starter doses of rFSH for IVF and ICSI cycles when the treatment is administered both subcutaneously and intramuscularly. **Study dates** January 1 to December 31, 1997. **Source of funding** Organon UK	**Sample size** n = 345 women Group 1 = 297 women Group 2 = 48 women **Characteristics** <u>Group 1</u> Mean age = 33.6 ± 3.8 years Duration of infertility = 5.0 ± 3.3 years Cause of infertility: Tubal factor = 27 (9.1%) Male factor = 86 (29%) Endometriosis = 52 (17.5%) Unexplained = 108 (36.4%) Other = 24 (8.1%) <u>Group 2</u> Mean age = 35.6 ± 3.8 years Duration of infertility = 4.6 ± 2.5 years Cause of infertility: Tubal factor = 5 (10.4%) Male = 11 (22.9%) Endometriosis = 12 (25%) Unexplained = 20 (41.7%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	<u>Group 1 (n = 297)</u> 1] 150 IU FSH 2] 200 IU FSH <u>Group 2 (n = 48)</u> 1] 300 IU FSH 2] 400 IU FSH	Recruitment: All of the patients undergoing their first IVF or ICSI attempt in the unit during study period were eligible for inclusion in the study. ICSI was used only in the presence of male factor infertility. Method: The starter dosages of rFSH were randomised through the hospital pharmacy, and they were blinded to the clinicians with the use of a computer-generated list provided by Organon Ltd. Intervention: Two different groups were catered for. In the light of previous experience using day-3 FSH levels as a guide to starter dosage, the women with day-3 FSH levels of <8.5 IU/l were randomised to commence treatment with either 150 IU or 200 IU rFSH. Those with day-3 FSH levels of greater than 8.5 to 15 IU/l were selected to begin treatment with a starter dosage of rFSH at 300 IU or 400 IU. Down-regulation using a GnRH long-protcol was commenced on day 1 of the cycle. The maority of patients used a buserelin acetate nasal spray. Occasionally, patients who failed to down-regulate	Clinical pregnancy: 150 IU rFSH = 29/146 (19.9%) 200 IU rFSH = 31/151 (20.5%) 300 IU rFSH = 2/24 (8.3%) 400 IU rFSH = 2/24 (8.3%)	**Limitations** 1] Power calculation was not done for pregnancy outcome. 2] Allocation concealment not reported 3] It is not clear whether blinding was adequate **Other information**

			with buserelin or had endomentriosis used Decapeptyl SR. Pituitary down-regulation was confirmed on day 14 by quiescent ovaries, as revealed by an ultrasound scan, and E_2 levels measured at less than 100 pmol/L. Once pituitary down-regulation was achieved, the controlled ovarian stimulation. Once pituitary down-regulation was achieved, the controlled ovarian stimulation using rFSH was commenced. The starting dosage was determined by the group randomisation code. After appropriate laboratory procedures, up to a maximum of three zygotes were transferred optimally to the uterus approximately 48 hours after ooycte collection. Luteal support in the form of hCG or progesterone pessaries was given based on the number of oocytes retrieved and the E_2 levels measured on the day of hCG administration. Statistical analysis: Based on calculations, it was estimated that a total sample size of 210 subjects would have 95% power to detect a difference of between 10 to 11 oocytes retrieved with a standard		

			deviation of 2. With a standard deviation of 2.5, 328 subjects would be required; at a standard deviation of 2.75, 400 subjects would be needed. In Group 1, 297 patients were included in the analysis, of which 259 provided oocytes.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hojgaard,A., Ingerslev,H.J., Dinesen,J., Friendly IVF: Patient opinions, Human Reproduction, 16, 1391-1396, 2001 **Ref ID** 68437 **Country/ies where the study was carried out** Denmark **Study type** Questionnaire study **Aim of the study** To evaluate how the patients balance advantages and disadvantages of low stimulation regimens in terms of unstimulated cycles or clomiphene for IVF versus a long down-regulation protocol with GnRH analogue and FSH. **Study dates** Not reported **Source of funding** Funded by the Danish Institute for Health Technology Assessment	**Sample size** n = 283 women Low stimulation group = 167 women Standard IVF group = 116 women. **Characteristics** Previously reported by Ingerslev et al., 2001 **Inclusion criteria** Previously reported by Ingerslev et al., 2001 **Exclusion criteria** Previously reported by Ingerslev et al., 2001	1] Low stimulation group (LS-IVF) - CC or Unstimulated IVF 2] Standard IVF (S-IVF) - GnRH analogue and FSH or hMG	Recruitment: Two patient groups receiving either a low stimulation type regimen or a long down-regulation protocol were approached by a questionnaire. In addition to treatment-specific questions they were asked general questionson subjects related to overall satisfaction with the clinic to evaluate if the two patient grouups studied were comparable in this aspect. Method: A 23-item questionnaire was designed to answer questions about patient satisfaction and stress throughout IVF treatments. The questions in the final questionnaire related to the latest treatment cycle and to satisfaction with the amount of information and preferences of treatment. Finally, respondents were encouraged to comment on the treament. Scores were measured on a five-point Likert-type scale. Satisfaction concerning information was rated on a scale as follows: very satisfied, satisfied, neutral/do not kno, dissatisfied, very disatisfied. The respondents were asked to characterise the information given as: to	Patient satisfaction: LS-IVF = 139/141 (99%) S-IVF = 60/64 (94%) Side-effects of hormone treatment (unacceptable/severe): LS-IVF = 4/75 (5%) S-IVF = 38/63 (60%) Stress from hormone treatment (unacceptable/severe): LS-IVF = 2/73 (3%) S-IVF = 15/65 (23%) Painfrom oocyte retrieval (unacceptable/severe): LS-IVF = 45/130 (35%) S-IVF = 27/64 (42%) Preferences of future treatments LS-IVF treatment: LS-IVF = 50/135 (37%) S-IVF = 3/60 (5%) S-IVF treamtent: LS-IVF = 10/143 (7%) S-IVF = 30/63 (48%)	**Limitations** 1] Response rate was significantly higher in the LS-IVF group compared with the S-IVF group. 2] The information on side effects of the different treatment types may have resulted in a possible biase towards the LS-IVF protocol. **Other information** 1] The mean number of started cycles was comparable in both groups. 2] There was no significant difference between pregnant and non-pregnant responders.

			optimistic, realisitc or too pessimistic. Stress, physical pain and side-effects were rated in the following way: unacceptably severe, sever, acceptable, mild, none. The importance of a question was measured on a three-point scale: very important, important and unimportant. Since the patients in the two groups had no experience as to the alternative tratment protocol, a short neutral description of LS-IVF and S-IVF regimens was offered in the questionnaire. Intervention groups: For the present study, the 167 patients enrolled in the pilot study and the previously published series wee selected. During 1997 and 1998, the 167 patients received a total of 452 LS-IVF cycles of which 153 were unstimulated IVF cycles and 299 were stimulated with CC. For the S-IVF, among all couples having received their first and subsequent IVF cycles following the long down-regulatin protocol (GnRH analogue and FSH or hMG), 116 couples fulfilled the same criteria as in the LS-IVF group and had a total of 190 treatments during the period.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Devesa,M., Martinez,F., Coroleu,B., Tur,R., Gonzalez,C., Rodriguez,I., Barri,P.N., Poor prognosis for ovarian response to stimulation: results of a randomised trial comparing the flare-up GnRH agonist protocol vs. the antagonist protocol, Gynecological Endocrinology, 26, 509-515, 2010 **Ref ID** 106795 **Country/ies where the study was carried out** Spain **Study type** Randomised clinical trial **Aim of the study** To compare the efficacy of the flare-up and the GnRH antagonist protocols, in a group of patients with poor prognosis for ovarian response to stimulation. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 221 women **Characteristics** Flare-up group Age = 38.48 ± 3.93 years BMI = 22.52 ± 3.2 kg/m^2 Antagonist group Age = 38.85 ± 3.82 years BMI = 22.6 ± 2.95 kg/m^2 **Inclusion criteria** Age ≤45 years At least one of the following:prior cycle cancellation (folliclular development <4 follicles after 8 - 10 days of intensive gonadotropin stimulation), prior poor response to controlled ovarian hyperstimulation (<5 follicles larger than 12 mm of diameter on the day of hCG administration after intensive stimulation), a pathologic CCCT (FSH day 3 + FSH day 10 ≥25) and/or antral follicle count ≤7 follicles. **Exclusion criteria** Not reported	1] Flare-up protocol group 2] Antagonist group	Recruitment: A total of 221 women who were candidates for IVF and considered as having poor prognosis for ovarian response to stimulation, were included in the study. Method: Randomisation was performed by the statistics unit, using a computer generated randomisation list in a 1:1 ratio. After clinical evaluation for inclusion criteria, patients were randomised into the flare-up or the antagonist protocol, by the study nurse coordinator. Within each group, patients were allocated randomly to stimulation either with rFSH alone or in combination with hMG. Intervention: The flare-up group consisted of 80 patients in which GnRH agonist, 0.2 ml/day, was administered from cycle day 2 until the day of hCG administration. The antagonist group consisted of 92 patients in which GnRH antagonist was administered when at least one follicle ≥14 mm was detected on the ultrasound scan. In both groups, patients were pretreated with OC in the previous cycle. Ovarian	Pregnancy Flare up group = 12/110 (11%) Antagonist group = 13/111 (12%)	**Limitations** 1] Blinding not reported. 2] After randomisation, there was 22% drop-out. 3] Patient characteristics were compared only in participants that completed the study. It is not clear whether both groups had similar characteristics after randomisation. **Other information** 1] Patients that had been randomised initially were later excluded due the following reasons: Non adhesion to allocated treatment - n = 31 (Flare-up group = 21, Antagonist group = 10), spontaneous pregnancy - n = 2 (Flare-up group = 1, Antagonist group = 1) 'No start' of intervention - n = 8 (Flare-up group = 5, Antagonist = 3) Discontinuation due to personal reasons - n = 8 (Flare-up group = 3, Antagonist = 5) 2] The E_2 level, the day of hCG administration was significantly higher in the flare-up protocol. However all other treatment comparisons and patient characteristics showed no statistically

			suppression was confirmed by E_2 levels and absence of ovarian activity on the ultrasound examination. Stimulation was started 5 days after last contraceptive pill either with rFSH alon, 375 IU/day or with rFSH 300 IU/day plus hMG 75 IU/day, accourding to randomisation to prevent bias. When ≥2 follicles were observed on transvaginal sonography, rhCG was administered. Transvaginal oocyte retrieval was permed 36h after hCG administration. Embryo transfer was performed 2 or 3 days after oocyte retrieval. Luteal-phase support was initiated the day after oocyte retrieval and consisted of vaginally administered micronised progesterone. The distribution of Statistical analysis: The study was designed to have sufficient power to detect an absolute difference of 15% in the clinical pregnancy rate per initiated cycle, assuming a baseline pregnancy rate of 25% in the highest group and of 10% in the lowest one. It was calculated that 100 patients in each group would be an adequate number to achieve an 80% power of detection of differences at a		significant differences.
			significance level of 0.05.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation DiLuigi,A.J., Engmann,L., Schmidt,D.W., Benadiva,C.A., Nulsen,J.C., A randomized trial of microdose leuprolide acetate protocol versus luteal phase ganirelix protocol in predicted poor responders, Fertility and Sterility, 95, 2531-2533, 2011 **Ref ID** 129855 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To dtermine, in a randomised controlled fashion, whether a protocol using both transdermal E2 and a GnRH antagonist in the preceeding luteal phase was superior to a microdose LA protocol in treating poor responders undergoing IVF. **Study dates** July 2006 to July 2009 **Source of funding** 1 author is a member of Merck speraker's bureau and 1 author is a member of EMD Serono speaker's bureau.	**Sample size** 54 women **Characteristics** Mean age: Antagonist= 37.5 years +/- 3.6 Agonist= 37.2 years +/- 3.3 At least one prior IVF cycle: Antagonist= 80.8% Agonist= 78.6% Mean number of prior IVF cycles: Antagonist= 1.0 +/- 6 Agonist= 0.9 +/- 0.6 Described as 'similar' between the two groups **Inclusion criteria** 21 to 44 years Undergoing IVF Poor response to prior IVF (at least one of: =< 4 mature follicles, =< 4 oocytes retrieved, peak E2 =< 1,000 pg/ml, prior IVF cycle cancelled for poor response) OR predicted poor response (at least one of: >40 years, FSH => 10 mIU/mL, poor response in prior gonadotrophin stimulation cycles [E2 <500 pg/ml]) **Exclusion criteria** Previous IVF cycle with either luteal phase ganirelix (GnRH antagonist) or microdose leuprolide acetate (GnRH	GnRH antagonist (n= 26) GnRH agonist (n= 28)	A power analysis indicated that approximately 24 patients would be needed in each group to detect a difference of one in the number of oocytes retrieved with a power of 80% and alpha of 0.05. Randomisation was performed in a 1:1 ratio in blocks of four and stratified based on history of a prior IVF cycle. Sealed envelopes were used for protocol assignment. Women were randomised to either the antagonist or agonist group. Antagonist group (labelled LPG) started one E2 transdermal patch 10 days after LH surge of preceding menstrual cycle (0.1 mg/day, changing every other day) followed by ganirelix acetate (250 ug/day for 3 days) starting 11 days after the LH surge. On the second day of menses, patches were discontinued and ovarian stimulation with gonadotrophins was started. Ganirelix was started (250 ug/day) with a follicle >13mm or E2 > 300 pg/ml and was continued through the day of hCG administration.	Clinical pregnancy: Antagonist= 9/26 (35%) Agonist= 8/28 (29%) Clinical pregnancy was defined as the presence of fetal heart activity on transvaginal ultrasound. Deliveries: Antagonist= 6/26 (23%) Agonist= 7/28 (25%)	**Limitations** No serious limitations **Other information** Two women in the antagonist group did not return to the centre after randomisation and did not start ovarian stimulation protocols. They were included in the analysis.

	agonist)		Agonist group (labelled ML) received OCP for 21 days starting on the 3rd day of preceding menstrual cycle. On the second day of menses, microdose leuprolide acetate was started twice daily and continued until the day of hCG administration. Ovarian stimulation with gonadotrophins was started 2 days following microdose LA initiation. Both groups received 300 IU of rFSH and 150 IU/day hMG. hCG was administered when at least three follicles were 18mm or more in mean diameter. All women were started on 50 mg of IM progesterone the day after oocyte retrieval and if pregnant, continued until approximately 7 weeks gestation. Embryo transfer was performed on day 3 of embryo development.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Garcia-Velasco,J.A., Bermejo,A., Ruiz,F., Martinez-Salazar,J., Requena,A., Pellicer,A., Cycle scheduling with oral contraceptive pills in the GnRH antagonist protocol vs the long protocol: A randomized, controlled trial, Fertility and Sterility, 96, 590-593, 2011 **Ref ID** 151915 **Country/ies where the study was carried out** Spain **Study type** Prospective randomised controlled trial **Aim of the study** To compare cycle outcomes after scheduling with the standard long protocol versus the use of oral contraceptive pills (OCPs) in patients undergoing GnRH antagonist cycles. **Study dates** From June 2009 to May 2010 **Source of funding** No sources of funding were reported	**Sample size** 233 couples undergoing IVF-ICSI **Characteristics** Age: Antagonist group= 34.1 years (+/- 0.8) Agonist group= 33.7 years (+/- 0.9) BMI: Antagonist group= 22.1 (+/- 2.1) Agonist group= 22.9 (+/- 2.8) **Inclusion criteria** ≤ 38 years Regular normo-ovulatory menstrual cycles (26-35 days) BMI 18-30 Normal cycle day-3 basal serum hormones (FSH < 10 IU/L and E_2 < 60 pg/mL) **Exclusion criteria** Previous ovarian surgery Low ovarian response (fewer than five oocytes) in a previous IVF-ICSI cycle Polycystic ovaries (Rotterdam criteria)	OCP + GnRH antagonist + FSH + progesterone (n=115) GnRH agonist + FSH + progesterone (n=113)	A power calculation was performed based on the results of the largest most recent RCT, with an alpha of 0.05 and power of 80%. However, the results of the power calculation were not used by the study authors when determining their sample size. A study nurse randomised patients at the time of cycle scheduling the month before using a computer-generated random number list. Sequence was concealed in opaque, consecutively numbered envelopes until an intervention as assigned. The study nurse generated the allocation sequence, enrolled the participants and assigned participants to their group. Antagonist group: OCP started on day 1-2 of menses of previous cycle for 12-16 days. Five days after the last pill, FSH was started (200-225 IU) with 0.25 antagonist (Ganirelix) daily. Agonist group: Long protocol with GnRH agonist (triptorelin) beginning on cycle day 20	Live birth rate: Antagonist= 51/115 (44%) Agonist= 53/113 (47%) OR 0.9 (0.5 to 1.5) It is not clear if these were all singleton births. The gestational age at the time of birth was not reported Clinical pregnancy rate: Antagonist= 56/115 (49%) Agonist= 64/113 (57%) OR 0.7 (0.4 to 1.2) Clinical pregnancy rate: intrauterine sac with heart beat 4 weeks after embryo transfer Multiple pregnancy rate: Antagonist= 15/56 (27%) Agonist= 18/64 (28%) OR 0.9 (0.4 to 2.1) Miscarriage rate: Antagonist= 5/56 pregnancies (9%) Agonist= 11/64 pregnancies (17%) OR= 0.5 (0.1 to 1.4)	**Limitations** The authors conducted a power calculation but the number of cycles needed (377 per group) was deemed to be too high. They therefore aimed for a 'large set of patients' with the aim of their data being incorporated into a future meta-analysis. **Other information**

			In both groups, rhCG was given as soon as two leading follicles reached ≥17 mm mean diameter, and ovum pickup performed 36 hours later. Either IVF or IVF-ICSI was used depending on 'individual requirements'. Two embryos were transferred on day 2 or 3 depending on availability and emrbyologist decision. Luteal support was started with 200mg/12 hrs of micronised vaginal progesterone beginning the night after ovum pickup and maintained until the 10th week of pregnancy. Data were analysed according to an intention to treat analysis.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tehraninejad,E., Nezamabadi,A.G., Rashidi,B., Sohrabi,M., Bagheri,M., Haghollahi,F., Nekoo,E.A., Jafarabadi,M., Gnrh antagonist versus agonist in normoresponders undergoing ICSI: A randomized clinical trial in Iran, Iranian Journal of Reproductive Medicine, 9, 171-176, 2011 **Ref ID** 154812 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial **Aim of the study** To compare the outcomes of GnRH agonist and GnRH antagonist ICSI cycles **Study dates** January 2008 to January 2010 **Source of funding** None reported	**Sample size** 300 women **Characteristics** Mean age: Agonist= 30.4 years Antagonist= 31.1 years Mean BMI: Agonist= 26.7 Antagonist= 24.7 Mean duration of infertility: Agonist= 7.8 years Antagonist= 7.6 years Number of previous attempts: Agonist= 0.95 Antagonist= 0.85 Cause of infertility: Female factor: Agonist= 52/150 (34%) Antagonist= 54/150 (36%) Male factor: Agonist= 70/150 (46%) Antagonist= 68/150 (45%) Male and female: Agonist= 14/250 (9%) Antagonist= 16/150 (10%) Unexplained: Agonist= 14/150 (9%) Antagonist= 12/150 (8%)	GnRH agonist (n=150) GnRH antagonist (n=150)	Patients were allocated to two groups according to a sequence of computer generated random numbers (0 or 1). In the GnRH agonist group, on cycle day 21, Busereline acetate (0.5mg daily, SC) until menstruation and adequate suppression was achieved. At day 3 of next menstrual cycle, Buserelin was reduced to 0.2mg and rFSH was started (Gonal F). Starting dose for the first 5 days varied between 150 and 225 IU daily by SC injection depending on age (< or > 35 years) and history of patient. Ovulation was induced with 10,000 IU IM injection of hCG when at least two follicles 18 to 20 mm were observed and serum estradiol was between 1,000 and 3,000 pg/ml. In the GnRH antagonist group, rFSH treatment was begun on day 3 of menstrual cycle. The starting dose for the first 5 days varied between 150 and 225 IU SC depending on patients' age and history. When there was on follicle 14mm in diameter, antagonist 0.25mg SC was administered	Clinical pregnancy: Agonist= 53/150 (35%) women Antagonist= 51/150 (34%) women Clinical pregnancy was defined as the presence of a gestational sac with a visible heartbeat Abortion: Agonist= 9/150 (17%) women Antagonist= 18/150 (30%) women OHSS: Agonist= 26/150 (17%) Antagonist= 19/150 (13%) OHSS classification was that used by Golan et al. (1989)	**Limitations** Allocation concealment was not reported Blinding was not reported **Other information**

	There was no significant difference in baseline characteristics between the two groups **Inclusion criteria** < 38 years Normal basal serum FSH BMI between 20 and 30 Regular menstrual cycle **Exclusion criteria** PCOS Severe endometriosis History of poor response in previous cycles History of repeated IVF failure (more than 3 failed cycles)		until hCG administration. When at least 2 follicales 18 to 20mm in diameter were seen, rFSH and hCG was injected. Oocyte retrieval was performed 36 hours after hCG administration. Two or three embryos were transferred 72 hours after oocyte retrieval. In both groups, luteal phase was supported with vaginal suppository of cycleogest (400 mg/BD). Progesterone treatment was started on the day of oocyte retrieval and continued until the day of pregancy test (14 days after ET). In the case of a positive test, progesterone was continued during the first trimester of pregnancy.		

Fertility (Updated guideline)

Stimulation agents

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation van Wely,Madelon, Kwan,Irene, Burt,Anna L., Thomas,Jane, Vail,Andy, Van der Veen,Fulco, Allnany,Hesham G., Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles, Cochrane Database of Systematic Reviews, -, 2011 **Ref ID** 118399 **Country/ies where the study was carried out** **Study type** Cochrane review of 42 trials **Aim of the study** To compare the effectiveness of recombinant gonadotrophin (rFSH) with the three main types of urinary gonadotrophins (ie hMG, FSH-P and FSH-HP) for ovarian stimulation in women undergoing IVF or ICSI treatment cycles **Study dates** Searches performed up to May 2010 **Source of funding** Cochrane review: Academic Medical Centre, Netherlands Individual trials: 22 trials were industry sponsored (10 by Serono, 3 by Organon, 7 by Ferring, 2 by IBSA).	**Sample size** 42 trials including a total of 9606 couples and 9644 cycles **Characteristics** Participants were normogonadotrophic women undergoing fresh and/or frozen-thawed IVF or ICSI **Inclusion criteria** Randomised controlled trials Trials of ovarian stimulation with rFSH versus hMG, FSH-P or FSH-HP, with or without the use of down regulation **Exclusion criteria** Quasi-randomised, alternate allocation and cross-over trials	12 trials (3775 couples) compared rFSH with hMG or hp-hMG 7 trials (1560 couples) compared rFSH with FSH-p 22 trials (4147 couples) compared rFSH with FSH-hp 1 trial (124 women, 137 cycles) compared hMG, FSH-P, FSH-hp, and rFSH	20 trials only used IVF, 6 used only ICSI and 16 used both IVF and ICSI Additional data on randomisation, concealment of allocation, blinding, sponsoring, and/or data relevant for effect size calculation was received from the authors of 24 studies Additional data was not needed in 7 trials Contact with study authors failed for 11 trials <u>Allocation</u> Five studies had unclear method of randomisation Allocation was adequately concealed in 28 trials Allocation was inadequate in 6 trials and unclear in 8 trials	<u>Live birth or ongoing pregnancy (beyond 20 weeks)</u> rFSH vs hMG/hp-hMG (11 trials, 3197 women) rFSH= 359/1604 women (22%) hMG/hp-HMG= 406/1593 women (25%) OR 0.84 (0.72 to 0.99) I^2= 0% rFSH vs FSH-P (5 trials, 1430 women) rFSH= 171/825 women (21%) FSH-P= 103/605 women (17%) OR 1.26 (0.96 to 1.64) I^2= 0% rFSH vs FSH-HP (13 trials, 2712 women) rFSH= 364/1367 women (27%) FSH-HP= 359/1345 women (27%) OR 1.03 (0.86 to 1.22) I^2= 0% rFSH vs urinary gonadotrophins (antagonist protocols, 1 trial, 280 women) rFSH= 44/140 women (31%) Urinary gonadotrophins= 48/140 women (35%) OR 0.88 (0.53 to 1.45) I^2= not applicable rFSH vs urinary gonadotrophins	**Limitations** **Other information** It is not clear if six studies presented data according to intention to treat. A sensitivity analysis was done excluding these trials Four trials presented data per cycle and women may have received multiple cycles. A sensitivity analysis was done excluding these trials for live birth, OHSS and clinical pregnancy Live birth may include preterm and births from multiple pregnancies

Six were unclear regarding funding. Remaining 14 trials had no funding or government funding only			Blinding None of the studies were double blinded 13 studies were partially blinded	(long agonist protocol, 22 trials, 6437 women) rFSH= 760/3315 women (23%) Urinary gonadotrophins= 739/3122 women (24%) OR 0.98 (0.87 to 1.10) I^2= 0% rFSH vs urinary gonadotrophins (short agonist protocol, 3 trials, 402 women) rFSH= 60/217 women (28%) Urinary gonadotrophins= 60/185 women (32%) OR 0.84 (0.54 to 1.31) I^2= 0% rFSH vs urinary gonadotrophins (no down regulation, 2 trials, 220 women) rFSH= 30/124 women (24%) Urinary gonadotrophins= 21/96 women (22%) OR 1.17 (0.62 to 2.20) I^2= 0% rFSH vs urinary gonadotrophins (29 trials, 7339 women - all down regulation protocols and all urinary gonadotrophins) rFSH= 894/3796 women (24%) Urinary gonadotrophins= 868/3543 women (25%) OR 0.97 (0.87 to 1.08) I^2= 0% Clinical pregnancy rFSH vs hMG/hMG-HP (12 trials) rFSH = 504/1900 hMG/hMG-HP = 557/1875 OR = 0.85 (0.74 to 0.99); I^2 = 0%	

				rFSH vs FSH-P (7 trials) rFSH = 244/891 FSH-P = 150/669 OR = 1.27 (1.01 to 1.60); I^2 = 0% rFSH vs FSH-HP (23 trials) rFSH = 605/2073 FSH-P = 594/2074 OR = 1.05 (0.91 to 1.20); I^2 = 0% rFSH vs urinary gonadotrophins (1 trial: with antagonist protocol) rFSH = 55/140 urinary gonadotrophins = 59/140 OR = 0.89 (0.55 to 1.43); I^2 = NA rFSH vs urinary gonadotrophins (31 trials: with long agonist protocol) rFSH = 1096/3942 urinary gonadotrophins = 1059/3776 OR = 1.00 (0.90 to 1.11); I^2 = 0% rFSH vs urinary gonadotrophins (4 trials: with short down-regulation protocol) rFSH = 151/513 urinary gonadotrophins = 147/467 OR = 0.92 (0.70 to 1.21); I^2 = 0% rFSH vs urinary gonadotrophins (5 trials: with no down-regulation protocol) rFSH = 51/269 urinary gonadotrophins = 36/235 OR = 1.23 (0.77 to 1.97); I^2 = 48%	

				Total: rFSH vs urinary gonadotrophins (42 trials) rFSH = 1353/4864 urinary gonadotrophins = 1301/4618 OR = 0.99 (0.91 to 1.09); I^2 = 78.2% Fresh/frozen policy: rFSH vs urinary gonadotrophins (42 trials) rFSH = 1378/4864 urinary gonadotrophins = 1314/4618 OR = 1.00 (0.91 to 1.10); I^2 = 50.7% <u>OHSS</u> rFSH vs HMG/HMG-HP (11 trials, 3197 women) rFSH= 27/1604 women (2%) hMG/hMG-HP= 27/1593 women (2%) OR 1.00 (0.58 to 1.71) I^2= 0% rFSH vs FSH-P (6 trials, 1490 women) rFSH= 24/855 women (3%) FSH-P= 9/635 women (1%) OR 1.79 (0.89 to 3.62) I^2= 0% rFSH vs FSH-HP (16 trials, 3053 women) rFSH= 41/1535 women (3%) FSH-HP= 37/1518 women (2%) OR 1.11 (0.70 to 1.75) I^2= 17% rFSH vs urinary gonadotrophins	

				(antagonist protocol, 1 trial, 280 women) rFSH= 2/140 women (1%) Urinary gonadotrophins= 2/140 women (1%) OR 1.00 (0.47 to 7.17) I^2= not applicable rFSH vs urinary gonadotrophins (long agonist protocol, 27 trials, 7092 women) rFSH= 90/3644 women (2%) Urinary gonadotrophins= 71/3448 women (2%) OR 1.18 (0.86 to 1.62) rFSH vs urinary gonadotrophins (short agonist protocol, 2 trials, 148 women) rFSH= 0/86 women (0%) Urinary gonadotrophins= 0/62 women (0%) OR not estimable rFSH vs urinary gonadotrophins (no down regulation, 2 trials, 220 women) rFSH= 0/124 women (0%) Urinary gonadotrophins= 0/96 women (0%) OR not estimable rFSH vs urinary gonadotrophins (33 trials, 7740 women - all down regulation protocols and all urinary gonadotrophins)	

				rFSH= 92/3994 women (2%) FSH-HP= 73/3746 women (2%) OR 1.18 (0.86 to 1.61) I^2= 0% <u>Multiple pregnancy</u> Per woman rFSH vs urinary gonadotrophins (25 trials) rFSH = 243/3150 urinary gonadotrophins = 269/3179 OR = 0.91 (0.76 to 1.09); I^2 = 0% Per pregnancy rFSH vs urinary gonadotrophins (25 trials) rFSH = 232/906 urinary gonadotrophins = 260/989 OR = 0.96 (0.78 to 1.18); I^2 = 20% - <u>Miscarriage</u> rFSH vs urinary gonadotrophins (30 trials) rFSH = 192/3329 urinary gonadotrophins = 166/3334 OR = 1.16 (0.93 to 1.44); I^2 = 12%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Out,H.J., David,I., Ron-El,R., Friedler,S., Shalev,E., Geslevich,J., Dor,J., Shulman,A., Ben-Rafael,Z., Fisch,B., Dirnfeld,M., A randomized, double-blind clinical trial using fixed daily doses of 100 or 200 IU of recombinant FSH in ICSI cycles, Human Reproduction, 16, 1104-1109, 2001 **Ref ID** 74410 **Country/ies where the study was carried out** Israel **Study type** Randomised multicentre trial **Aim of the study** To assess the efficacy and efficiency of 100 IU and 200 IU dosing regimens in down-regulated women undergoing ovarian stimulation prior to ICSI. **Study dates** May 1997 to June 1999 **Source of funding** Not reported	**Sample size** n = 180 women **Characteristics** Age ± SD = 27.5 ± 4.0 years BMI ± SD = 22.9 ± 3.1 kg/m^2 Duration of infertilit = 4.4 ± 2.8 years Cause of infertility: Primary infertility = 125 (69.8%) Secondary infertility = 54 (30.2%) **Inclusion criteria** 1] At least 18 and at most 37 years of age at the time of screening 2] Male infertility (total motile count <5x10^6 spermatozoa) solvable by ICSI using ejaculatory spermatozoa 3] Normal regular cycles with a mean length of between 24 and 35 days; 4] Presence of two ovaries 5] Good physical and mental health 6] BMI between 18 and 29 kg/m^2 **Exclusion criteria** 1] Female cause of infertility, except mild endometriosis or a mechanical factor 2] Previous IVF or ICSI cycle after which less than three oocytes were retrieved 3] Previous IVF or ICSI cycles with hospitalisation due to OHSS. 4] More than four previous IVF or ICSI cycles 5] Total fertilisation failure in a previous IVF or ICSI cycle 6] LH/FSH ratio at screening ≥3 7] Chronic cardiovascular, hepatic, renal or pulmonary disease 8] History of (within 12 months) or	1] GnRH agonist long protocol + 100 IU rFSH 2] GnRH agonist long protocol + 200 IU rFSH	Intervention: Pre-treatment with intranasal buserelin for pituitary down-regulation was started in the midluteal phase. Recombinant FSH was supplied as lyophilised spheres in ampoules containing 50 or 100 IU FSH in-vivo bioactivity. For subcuaneious injection, two ampoules were reconstitued with 1 ml solvent. hCG in doses of 5000 IU per ampoule was supplied to trigger ovulation. For IM injection of hCG, one ampoule was reconstituted with 1ml solvent. When down-regulation was achieved, treatment with rFSH was started and continued until at least three follicles ≥17 mm had developed. Dose adaptations were not allowed. hCG (5000IU) was given to triger ovulation. After oocyte retrieval and ICSI, a maximum of 3 embryos were	Clinical pregnancy* (per woman) 100 IU = 17/91 (18.7%) 200 IU = 15/88 (17%) Adverse pregnancy outcome** (per woman) 100 IU = 1/91 (1.1%) 200 IU = 7/88 (8%) OHSS*** 100 IU = 0/91 (0%) 200 IU = 4/88 (4.5%)	**Limitations** 1] The study was not powered for outcomes relevant to the research question. **Other information** *Figures for Clinical pregnancy reflect 'Vital pregnancy'. Vital pregnancy was defined as an intrauterine pregnancy with positive heart action. Clinical pregnancy was reported and the figures varied from those of vital pregnancy however, no definition of clinical pregnancy was reported. **Adverse pregnancy outcome reflect 'Miscarriage rate'. ***Figures reflect the number of patients hospitalised for risk of hyperstimulation. -Reasons for drop-out before the stage of embryo transfer differed between the two treatment groups. In the low-dose group, insufficient ovarian response (n = 14), premature LH surge and or progesterone too high (n = 2), poor quality oocytes at retrieval (n = 1), adverse event (n = 1), no

	current abuse of alcohol or drugs 9] Administration of non-registered investigational drugs within 3 months prior to screening		replaced. Progesterone was given as luteal support according to the routine regimens of the centre. Method: Eligible subjects were randomised by receiving a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. The 50 and 100 IU ampoules were indistinguishable one from another. The randomisation was carried out in blocks of four and was computer-generated using random numbers. Statistical analysis: With 100 subjects included in each treatment group, and assuming a SD of 450 IU of rFSH for the total dose used and a SD of 6.4 oocytes for the number of oocytes retrieved, a difference of 180 IU		fertilisation (n = 2) and other causes (n = 4) were reported. In the high-dose group, the reasons for drop-out were risk of hyperstimulation (n = 1), insufficient ovarian response (n = 1), poor quality oocytes at retrieval (n = 1), adverse events (n = 2), no fertilisation (n = 4) and other causes (n = 1).

			rFSH and 2.5 oocytes could be detected between the two treatment groups with a power of 80% using a two-sided t-test and a significance threshold of 5% (not adjusted for two primary outcomes)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hoomans,E.H., Mulder,B.B., Asian Purgeon Study Group., A group-comparative, randomized, double-blind comparison of the efficacy and efficiency of two fixed daily dose regimens (100- and 200-IU) of recombinant follicle stimulating hormone (rFSH, Puregon) in Asian women undergoing ovarian stimulation for IVF/ICSI, Journal of Assisted Reproduction and Genetics, 19, 470-476, 2002 **Ref ID** 82394 **Country/ies where the study was carried out** Hong Kong, India, Singapore and Thailand **Study type** Randomised multi-centre trial **Aim of the study** To compare the efficacy, and safety of a fixed daily dose of rFSH of a 100 and 200 IU regimen in Asian women undergoing ovarian stimulation for IVF/ICSI. **Study dates** December 1997 to July 1999. **Source of funding** Not reported	**Sample size** n = 330 women. **Characteristics** Mean age ± SD = 31.9 ± 3.7 years Mean BMI ± SD = 22.3 ± 2.9 kg/m^2 Duration of infertility = 5.6 ± 3.2 years Cause of infertility: Tubal factor = 136 (41.2%) Male factor = 116 (35.2%) Endometriosis = 49 (14.8%) Unknown = 63 (19.1%) Mixed causes = 10 (3%) **Inclusion criteria** 1] Subjects had to be at least 18 and at most 39 yearss of age at the time of screening, having a cause of infertility suitable for IVF or ICSI. 2] All subjects had to have normal ovulatory cycles with a mean length of between 24 and 35 days, a good physical and mental health 3] A BMI between 18 and 29 kg/m^2 **Exclusion criteria** 1] Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS and absence of ovarian function 2] Previous assisted reproduction in which fewer than three oocytes were retrieved. 3] Previous hospitalisation due to severe OHSS 4] Chronic cardiovascular, hepatic, renal, or pulmonary disease 5] History of or currently indulged in abuse of alcohol or drugs, or had used	1] 100 IU rFSH 2] 200 IU rFSH	Recruitment: The study was involved nine study centres in Hong Kong (n=2), India (n=3), Singapore (n = 1) and Thailand (n = 3). The aim was to include, in each study sentre, 300 subjects, 150 in each treatment group. Method: The study was designed as a randomised, group-comparative, double-blind, multicentre investigation. Eligible sugjects were randomised to one of the two starting-dose groups by means of a computer-generated randomisation list using random numbers. Intervention: Pretreatment with GnRH agonist for pituitary downregulation was started either on the first day of the menstrual cycle or in the midluteal phase. rFSH was supplied as lyophilised spheres in	Clinical pregnancy 100 IU rFSH = 32/163 200 IU rFSH = 30/167 Multiple pregnancy 100 IU rFSH = 9/163 200 IU rFSH = 9/167 Miscarriage* 100 IU rFSH = 2/163 200 IU rFSH = 3/167 OHSS 100 IU rFSH = 4/163 200 IU rFSH = 3/167 1] There was no definition of clinical pregnancy. 2] Adverse events: Low-dose group - OHSS = 4; High-dose group - OHSS = 3; Abdominal pain = 1; Ectopic pregnancy = 1; Frequent micturition = 1. *The difference between Clinical pregnancy and Ongoing pregnancy in both groups was 5 vs 5 however, these figures differed from the reported figures for miscarriage rate. Therefore, 3 vs 2 pregnancy in both groups were not accounted for.	**Limitations** 1] No mention of allocation concealment 2] Blinding was not described 3] No power calculation reported. **Other information** 1] Some participants had more than one infertility diagnosis. 2] In the low-dose group there was no cycle cancellation due to the risk of hyperstimulation but in the high dose group, there were two cancellations due to the risk of hyperstimulation. 3] The difference between figures for 'Clinical pregnancy' and 'Ongoing pregnancy', n = 5 in the Low dose group and n = 5 in the high dose group. It is not clear whether this was due to pregnancy loss, loss to follow up or drop-out.

	investigational drugs within 3 months before screening.		ampoules containing 50 or 100 IU FSH in vivo bioactivity. When downregulation was achieved, treatment with rFSH was started and continued until at least three follicles of ≥17 mm in diameter had developed for a maximum period of 3 weeks. hCG was administered to induce ovulation, and after oocyte retrieval a maximum of three embryos was replaced. Luteal support was given according to the preference of the treatment centre. Statistical analysis: No power calculation reported		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Out,H.J., Braat,D.D., Lintsen,B.M., Gurgan,T., Bukulmez,O., Gokmen,O., Keles,G., Caballero,P., Gonzalez,J.M., Fabregues,F., Balasch,J., Roulier,R., Increasing the daily dose of recombinant follicle stimulating hormone (Puregon) does not compensate for the age-related decline in retrievable oocytes after ovarian stimulation, Human Reproduction, 15, 29-35, 2000 **Ref ID** 74409 **Country/ies where the study was carried out** France, Spain, The Netherlands and Turkey **Study type** Randomised multicentre trial **Aim of the study** To assess the impact of 150 and 250 IU of rFSH regimens in down-regulated women between 30 and 39 years of age undergoing ovarian stimulation prior to IVF or ICSI on the number of oocytes retrieved and total dose used. **Study dates** February 1997 to July 1998 **Source of funding** Not reported	**Sample size** n = 141 women **Characteristics** Mean age ± SD = 34.8 ± 2.9 years Mean BMI ± SD = 23.6 ± 3.1 years Duration of infertility ± SD = 7.4 ± 4.8 years Cause of infertility: Tubal factor = 40 (30%) Male factor = 63 (45.7%) Endometriosis = 6 (4.3%) Other/unknown = 21 (15.2%) Mixed causes = 8 (5.8%) **Inclusion criteria** 1] Aged at least 30 and at most 39 years of age at the time of screening 2] Cause of infertility potentially solvable by IVF or ICSI 3] Normal ovulatory cycles with a mean length of between 24 and 35 days 4] Good physical and mental health 5] BMI of between 18 and 29 kg/m^2 **Exclusion criteria** 1] Infertility caused by endocrine abnormalities such as hyperprolactinaemia, PCOS, and absence of ovarian function; one ovary and (or) a history of ovarian surgery; severe endometriosis; previous ovarian stimulation cycles in which fewer than three oocytes were retrieved; chronic carciovascular, hepatic, renal, or pulmonary disease; 2] A history of or current abuse of alcohol or drugs 3] Administration of non-registered	1] 150 IU rFSH 2] 250 IU rFSH	Recruitment: The study was performed in six specialised infertility centres and the aim was to include 200 patients with ~100 patients in each treatment group. Method: Eligible subjects were randomised by receiving a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. The 50, 100 and 150 IU ampoules were indistinguishable. The randomisation was done in blocks of four and was computer-generated using random numbers. The randomisation was stratified for age in order to end up with equal numbers of subjects in each treatment group for the age groups 30-36 and 37-39 years. Intervention: Pretreatment with a GnRH agonist for	Clinical pregnancy: 150 IU = 10/67 (14.9%) 250 IU = 9/73 (12.3%)	**Limitations** 1] Power calculation was not done for pregnancy outcomes. **Other information** 1] 57/67 women in the low-dose group had an embryo transfer while 64/71 women in the high-dose group had an embryo transfer. 2] Figures for 'Clinical pregnancy' were different from the figures for 'Vital pregnancy'. However, no definition of 'Clinical pregnancy' was reported. A suitable definition of 'Vital pregnancy' was reported and was chosen to reflect 'Clinical pregnancy'. 3] There were no reports of OHSS, however there were cancellations in both groups (n = 1 per group) due to the risk of hyperstimulation. 4] Three women were hospitalised during the treatment period: 2 in the 150 IU group (extrauterine pregnancy and

	investigational drugs within 3 months prior to screening.		pituitary down-regulation was started either on the first day of the menstrual cycle or in the mid-luteal phase, according to the centre's protocol. rFHS was supplied as lyophilised spheres in ampoules containing 50, 100 IU or 150 IU FSH in-vivo bioactivity. When oestradiol serum levels were <200 pmol/l, treatment with rFSH was started and continued until at least three follicles ≥17 mm diameter had developed. Dose adaptations were not allowed. The maximum treatment period was 3 weeks. hCG was given to trigger ovulation. After oocyte retrieval and IVF or ICSI, a maximum of three embryos was replaced. Luteal phase support was given according to the preference of the treatment center. Statistical analysis: With 100 subjects		miscarriage) and 1 in the 250 IU group (fever with UTI)

			included in each treatment group and under the assumption of common slopes for treatment by age and assuming an SD of 6.4 oocytes for the number of oocytes retrieved and an SD of 2.5 treatment days, a difference of ~2.5 oocytes and a difference of ~1 treatment day could be detected between the two treatment groups with a power of 80% using a two-sided t-test with a significant level of 5%.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wikland,M., Bergh,C., Borg,K., Hillensjö, T, Howles,C.M., Knutsson,A., Nilsson,L., Wood,M., A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI, Human Reproduction, 16, 1676-1681, 2001 **Ref ID** 83326 **Country/ies where the study was carried out** Sweden **Study type** Randomised dual-centre trial **Aim of the study** The objective of the study was to investigate whether 150 IU or 225 IU of rhFSH resulted in a similar number of oocytes in IVF/ICSI cycles using a multiple dose regimen of cetrorelix to avoid premature LH surges. **Study dates** September 15 to December 20, 1999. **Source of funding** ASTA Medica and Serono International	**Sample size** n = **Characteristics** Mean age ± SD = 32.7 ± 3.9 32.2 ±3.9 years BMI ± SD = 22.9 ± 2.6 22.9 ± 2.5 Duration of infertility = 3.6 ± 1.7 3.7 ± 2.1 years Causes of infertility: Tubal = 21 Endometriosis = 2 Unexplained = 23 Male factor = 58 Mixed = 95 **Inclusion criteria** 1] 20 to 39 years of age 2] Regular menstrual cycles of 25 to 32 days 3] Two normal ovaries and a normal uterine cavity as judged by ultrasonography and were being treated for infertility due to tubal, male or idiopathic factors or mild endomentriosis 4] Not more than 3 previous ART attempts or any ovarian stimulation in the 3 months prior to study entry **Exclusion criteria** 1] BMI >30 kg/m^2, previous history of severe OHSS, previous failure of IVF or ICSI treatment due to poor response to gonadotrophin therapy ()fewer than three mature follicles) or to ICSI failure	1] 150 IU rhFSH 2] 225 IU rhFSH	Intervention:Ovarian stimulation was by rhFSH an, and patients were randomised to receive a starting dose of either 150 IU or 225 IU rhFSH beginning on day 2 or 3 of the menstrual cycle. The dose was fixed for the first 5 days of stimulation. Suppression of LH was provided by daily injection of cetrorelix from day 6 of the stimulation cycle until the day of hCG administration. Ovarian response was monitored by ultrasound on day 6 and on days 9 and 10, with additional ultrasound scans when needed. From day 6 of stimulation, the dose of rhFSH could be altered by increasing or decreasing the dose by one or two ampoules of 75 IU, as judged by the clinician and based on the number and size of the developing follicles. When the three largest	1] Pregnancy: 150 IU rhFSH = 21/60 225 IU rhFSH = 24/60 2] Adverse pregnancy outcome: 150 IU rhFSH = 6/60 225 IU rhFSH = 9/60 3] Multiple pregnancies: 150 IU rhFSH = 3/60 225 IU rhFSH = 5/60 1] No definition of 'Pregnancy' was reported. This figure may be biochemical or clinical pregnancy. 2] Adverse pregnancy outcome reported were miscariages and extrauterine pregnancies. The figures also reflect the difference between 'pregnancy' and 'ongoing pregnancy' 3] Multiple pregnancies reflect 'Number of twins'. It is not clear whether there were other types of multiple pregnancies	**Limitations** 1] The method of randomisation was not reported 2] Allocation concealment not reported 3] Blinding not reported. 4] No power calculation for pregnancy outcome **Other information** 1] In the 'low dose' group, one patient became pregnant without treatment between randomisation and start of FSH. One patient in each group was excluded because of a protocol violation related to the randomised dose of rhFSH. After exclusion of these patients, there were 117 evaluable patients. 2] In the 'low dose group, 57 patients received hCG and had oocyte retrieval performed, but one patient did not receive hCG due to poor follicular development. In the high dose group, all 59 patients received hCG and had oocyte retrieval. In the low dose group four patients did not reach embryo transfer due to absence of fertilisation or poor

	2] History of abnormal gynaecological bleeding of undetermined origin, any contraindication to pregnancy, or the presence of a clinically significant systemic disease.		follicles measured ≥18 mm, final ovarian maturation was triggered with a single s.c injection of hCG 10,000 IU. Oocytes were retrieved 34 to 38 h after injection of hCG and were fertilised invitro acording to standard procedures. A maximum of 2 embryos were replaced 48 to 72 hours after oocyte retrieval. Luteal support consisted of micronised progesterone. Treatment was discontinued in any patient who had an excessive ovarian response which was considered to indicate a risk of OHSS or if there was any serious adverse reaction to treatment. Statistical analysis: The clinical equivalence of starting doses of rhFSH 150 and 225 IU was to be declared if the limits of the 90%		embryo quality. 3] Ongoing pregnancy was defined as >12 weeks gestation. 4] One case of moderate OHSS (in the high dose group) requiring hospitalisation occurred. 5] There was 3% drop out after randomisation.

			confidence interval for the difference in the mean number of oocytes retgrieved in the two groups included ±3 oocytes. To demonstrate this equivalence with a probability of 95%, using a two-sided 90% CI interval for difference in the mean number of oocytes retrieved, 54 evaluable patients per group were required (at least 120 patients in total to allow for any drop-outs). The analysis was performed on an intention-to-treat basis.		

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Full citation Out,H.J., Lindenberg,S., Mikkelsen,A.L., Eldar-Geva,T., Healy,D.L., Leader,A., Rodriguez-Escudero,F.J., Garcia-Velasco,J.A., Pellicer,A., A prospective, randomized, double-blind clinical trial to study the efficacy and efficiency of a fixed dose of recombinant follicle stimulating hormone (Puregon) in women undergoing ovarian stimulation, Human Reproduction, 14, 622-627, 1999 **Ref ID** 74407 **Country/ies where the study was carried out** Australia, Canada, Denmark, Spain **Study type** Randomised multicentre trial **Aim of the study** To assess the efficacy and efficiency of these dosing regimens in down-regulated women undergoing ovarian stimulation prior to IVF or ICSI. **Study dates** October 1996 to December 1997 **Source of funding** Not reported	**Sample size** n = 204 women **Characteristics** Mean age ± SD = 32.6 ± 3.3 years Mean BMI ± SD = 22.9 ± 2.8 Mean duration of infertility ± SD = Cause of infertility: Tubal factor = 54 (27.1%) Male factor = 61 (30.7%) Endometriosis = 6 (3.0%) Unknown causes = 34 (17.1%) Mixed causes = 44 (22.1%) **Inclusion criteria** 1] At least 18 and at most 39 years of age at the time of screening 2] Cause of infertility potentially solvable by IVF or ICSI 3] Normal ovulatory cycles with a mean length of between 24 and 35 days 4] Good physical and mental health 5] BMI between 18 and 29 kg/m^2 **Exclusion criteria** 1] Infertility caused by endocrine abnormalities such as hyperprolactinaemia, PCOS and asence of ovarian function. Previous ovarian stimulation cycles in which less than three oocytes were retrieved. 2] Chronic cardiovascular, hepatic, renal, or pulmonary disease	1] 100 IU rFSH 2] 200 IU rFSH	Recruitment: The study was performed in five specialised infertility centres. The aim was to include 200 patients with 100 patients in each group. Method: Eligible subjects were randomised by receiving a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. The 50 and 100 IU ampoules were indistinguishable. The randomisation was done in blocks of four and was computer-generated using random numbers. Intervention: Pretreatment with a gonadotrophin-releasing hormone agonist for pituitary down-regulation was started either on the first day of the menstrual cycle or in the midluteal phase. All available GnRHa	1] Clinical pregnancy: 100 IU = 16/101 (15.8%) 200 IU = 23/98 (23.5%) 2] Adverse pregnancy outcome: 100 IU = 10/101 (9.9%) 200 IU = 2/98 (2.0%) 1] Figures for 'Clinical pregnancy' reflect 'vital pregnancy'. A vital pregnancy was defined as an intrauterine pregnancy with positive heart action. 2] Adverse pregnancy outcome reported were ectopic pregnancy and miscarriage. 3] Abdominal pain and/or OHSS: 100 IU group = 3/101 200 IU group = 13/98 No strict definition of OHSS was given. In the analysis of the occurence of this syndrome, its incidence was based on the fact that it was reported as such by the investigator.	**Limitations** 1] Power calculation for pregnancy outcomes was not reported **Other information** 1] In the 100 IU group, 70/101 women had an embryo transfer. In the 200 IU group, 83/98 women had an embryo transfer. 2] Cycle cancellations: 100 IU group = 31 patients 200 IU group = 15 patients

	3] A history of (within 12 months) or current abuse of alcohol or drugs 4] Administration of non-registered investigational drugs within 3 months prior to screening.		were allowed except the IM depot preparations. rFSH was supplied as lyophilised spheres in ampoules containing 50 or 100 IU FSH in-vivo bioactivity. hCG in doses of 5000 IU per ampoule was supplied to trigger ovulation. When down-regulation was achieved, defined as oestradiol serum concentrations <200 pmol/l, treatent with rFSH was strted and continued until at least three follicles ≥17mm had developed. Dose adaptations were not allowed. The maximum treatment period was 3 weeks. hCG (10,000 IU) was given to trigger ovulation. After oocyte retrieval and IVF or ICSI, a maximum of three embryos was replaced. Luteal phase support was given according to the preference of the treamtent centre. Statistical analysis:		

			With 100 subjects included in each treatment group and assuming a SD of 450 IU of rFSH for the total dose used and a SD of 6.4 oocytes for the number of oocytes retrieved, a difference of 180 IU rFSH and 2.5 oocytes could be detected between the two treatment groups with a power of 80% using a two-sided t-test and a significance threshold of 5%.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tan,S.L., Child,T.J., Cheung,A.P., Fluker,M.R., Yuzpe,A., Casper,R., Leung,P., Cadesky,K., Davis,V.J., A randomized, double-blind, multicenter study comparing a starting dose of 100 IU or 200 IU of recombinant follicle stimulating hormone (Puregon) in women undergoing controlled ovarian hyperstimulation for IVF treatment, Journal of Assisted Reproduction and Genetics, 22, 81-88, 2005 **Ref ID** 74804 **Country/ies where the study was carried out** Canada **Study type** Randomised multicentre study **Aim of the study** To compare the efficiency and efficacy of a starting dose of 100 IU versus 200 IU of follitropin-β maintained during the first 4 days of ovarian timuylation in pituitary-suppressed women undergoing IVF treatment. **Study dates** Not reported **Source of funding** Medication, statistical analysis and support for the trial provided by Organon Canada.	**Sample size** n = 192 women **Characteristics** Mean age ± SD = 33.3 ± 3.2 years Mean weight ± SD = 61.3 ± 8.4 kg Mean duration of infertility ± SD = 4.7 ± 2.8 years Cause of infertility: Tubal factor = 87 (45.3%) Male factor = 65 (33.9%) Endometriosis = 18 (9.4%) Other = 12 (6.3%) Unknown = 1 (0.5%) **Inclusion criteria** 1] Age 18 to 39 years at the time of screening 2] Cause of infertility potentially treatable by IVF or ICSI 3] Normal ovulatory cycles with a mean cycle length of between 24 and 35 days 4] Good physical and mental health 5] BMI between 18 and 29 kg/m^2 6] Normal early follicular phase (day 2 - 4) serum FSH concentration **Exclusion criteria** 1] Infertility caused by endocrine abnormalities such as hyperprolactinaemia, PCOS, absence of ovarian function. 2] Previous ovarian stimulation cycles in which less than 3 oocytes were	1] 100 IU rFSH 2] 200 IU rFSH	Recruitment: The study was a multicentre study (six centres in Canada). The aim was to include 200 patients (100 in each treatment group). Method: Eligible subjects were randomised by receiving a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. The randomisation was carried out in blocks of four according to random numbers generated by the computer. The ampoules used in the study were individually numbered for each subject. After allocation of subject code number, each subject used medications with the same code number throughout the study.The investigator had no knowledge regarding the	1] Clinical pregnancy: 100 IU = 26/97 (26.8%) 200 IU = 23/95 (24.2%) 2] Adverse pregnancy outcome: 100 IU = 3/97 (3.1%) 200 IU = 3/95 (3.2%) 3] OHSS: 100 IU = 4/97 (4.1%) 200 IU = 2/95 (2.1%) 1] Figures for Clinical pregnancy reflect 'Ongoing pregnancy' (>12 weeks gestation). 2] Adverse pregnancy outcomes reported were miscarriages (n = 3) and ectopic pregnancies (n = 3). 3] No definition was reported for OHSS Other adverse events: 100 IU group : 3 events (n = 1/97 patients) - Severe OHSS, abdominal pain, and ovarian abscess. 200 IU group: 4 events (n = 4/95 patients) - Ruptured ectopic pregnancy, moderate OHSS, pelvic pain and ovarian torsion.	**Limitations** 1] Power calculation for pregnancy outcomes was not reported. **Other information** 1] For 9/192 recruited patients, the cause infertility was not reported. 2] Seven (4%) patients reported injection site inflammation. 3] 5 patients in the 100 IU group and 8 patients in the 200 IU group had cancelled cycles due to poor ovarian response, premature LH surge, increased risk of OHSS and development of endometrial polyps.

	retrieved. 3] Chronic cardiovascular, hepatic, renal or pulmonary disease. 4] Either current or previous (within 12 months) alcohol or drug abuse. 5] Administration of any investigational drugs within 3 months prior to screening.		treatment assigned therefore the study was performed as a double-blind trial. After day 4 of stimulation, the rFSH dose was adjusted if deemed necessary but the initial rFSH dose received was not revealed. The treatment cycle was no longer, from that point forward, assessor or patient blind. Intervention: Subjects were administered a long protocol of GnRH agonist in which GnRH agonist was administered daily, commencing either from the first day of the menstrual period or the midluteal phase of the preceding menstrual cycle. In both cases, GnRH agonist was continued until pituitary suppression was achieved as shown by a serum estradiol level <200 pmol/L. Once pituitary suppression was achieved, two		

			ampoules of either 50 IU or 100 IU of rFSH, were administered as a fixed, daily subcutaneous dose for a minimum of 4 days. Gonadotropin treatment was continued until at least three follicles with mean diameters ≥17 mm developed,when hCG was administered to achieve final oocyte maturation. Oocyte retrieval was performed and fertilisation achieved by IVF or ICSI. A masimum of three embryos were transferred and progesterone supplementation was given for luteal support. rFSH was supplied in 50 and 100 IU ampoules and the two different dosage ampoules appeared identical. Statistical analysis: Analysis was performed on an intention-to-treat basis. The two		

			primary efficacy parameters were the numbers of oocytes retrieved and the total dose of follitropin-β administered. Assuming a SD of 6.4 oocytes, and values of α = 0.05 and β = 0.08, a sample size of 100 subjects per treatment group (total = 200 patients) was requred to ddtect a statistically significant difference of 2.5 ooctyes between the two treatment groups. The total sample size of 200 subjects also allowed for detecting a statistically significan difference of 180 IU rFSH between the two treatment groups, assuming a SD of 450 IU for the total dose of rFSH administered.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cavagna,M., Comparison of 150 and 225 IU of follitropin (beta) in a fixed-dose regimen for ovarian stimulation using a depot formulation of GnRH agonist: a prospective randomised clinical trial, J Bras Reproducao Assistida, 10, 21-24, 2006 **Ref ID** 125846 **Country/ies where the study was carried out** Brazil **Study type** Randomised clinical trial **Aim of the study** To compare 150 IU and 200 IU of follitropin-β in a fixed dose regimen, employing the long protocol of pituitary down-regulation with a depot formulation of GnRH agonist, in normo-ovulatory women undergoing IVF or ICSI cycles. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 76 women **Characteristics** Mean age ± SD = 31.5 ± 2.8 years Mean weight/BMI = Not reported Mean duration of infertility ± SD = 6.4 ± 2.9 years Cause of infertility: Tubal factor = 40 (52.6%) Male factor = 20 (26.3%) Endometriosis = 5 (6.6%) Unexplained = 11 (14.5%) **Inclusion criteria** 1] Age <35 years old 2] Normal menstrual cycles (range of 24 - 35 days) 3] BMI between 19 and 29 kg/m^2 4] FSH <10 mIU/mL **Exclusion criteria** 1] Age <18 and >35 years old 2] Endocrine abnormalities. 3] Previous ART cycle with poor response to ovarian stimulation 4] Systemic chronic disease.	1] 150 IU rFSH 2] 200 IU rFSH	Recruitment: Seventy six normo-ovulatory women <35 years old undergoing ART cycles were studied. All patients had indications for treatment with IVF or ICSI cycles. Intervention: After pituitary suppression with a single IM administration of a GnRH agonist, patients were randomised into groups A and B. In group A (n = 40), ovarian stimulation was performed with a fixed daily dose of 150 IU of follitropin-β. In group B (n = 36), ovarian stimulation was performed with a fixed daily dose of 200 IU of follitropin-β. In both groups, the fixed dose was maintained until hCG administration. When at least 3 follicles ≥17 mm had developed, ovulation was triggered with 10,000 IU of hCG or 250 µg of rHCG. Cycle monitoring	1] Pregnancy: 150 IU rFSH = 9/40 200 IU rFSH = 10/36 2] OHSS: 150 IU rFSH = 0/40 200 IU rFSH = 0/36 1] No definition of 'Pregnancy' reported. It is not clear whether they were clinical or biochemical pregnancies. 2] No definition of 'OHSS' reported.	**Limitations** 1] No detailed description of method of randomisation. 2] Blinding not reported. 3] Allocation concealment not reported. 4] Power calculation was not reported for pregnancy outcomes. **Other information** 1] In group A, 1 cycle was cancelled beccause of risk for OHSS determined by US parameters. In group B, 3 cycles were cancelled, 2 because of risk of OHSS and 1 because of poor response to ovarian stimulation. 2] There was no case of OHSS in the 72 patients that completed their cycles. This may have been due to the cancellation of cycles that showed a risk of OHSS (n = 3 cycles). See [1] above.

			was carried out using only US findings. Follicular aspiration was scheduled 35-36hours after the hCG administration. The luteal phase was supported daily with 90mg of intravaginal progesterone gel.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Latin-American Puregon IVF Study Group., A double-blind clinical trial comparing a fixed daily dose of 150 and 250 IU of recombinant follicle-stimulating hormone in women undergoing in vitro fertilization, Fertility and Sterility, 76, 950-956, 2001 **Ref ID** 74045 **Country/ies where the study was carried out** Argentina, Brazil, Chile, Colombia, Mexico **Study type** Randomised multicentre trial **Aim of the study** To assess the impact of two dosing regimens in pituitary down-regulated women between 30 and 39 years of age undergoing COH before IVF or ICSI on the number of oocytes retrieved and total dose used. **Study dates** June 1998 to September 1999 **Source of funding** Supported by the Red Latinoamericana de Reproduccion Asistida and NV Organon, Oss, The Netherlands.	**Sample size** n = 404 women **Characteristics** Mean age ± SD = 35.2 ± 3.0 years Mean BMI ± SD = 23.0 ± 2.7 kg/m^2 Mean duration of infertility = 5.3 ± 3.4 years Cause of infertility: Male factor = 177 (43.8%) Tubal factor = 97 (24 %) Endometriosis = 17 (4.2%) Mixed causes = 66 (16.3%) Other or unknown = 47 (11.6%) **Inclusion criteria** 1] Age 30 - 39 years of age at the time of screening. 2] Cause of infertility potentially solvable by IVF or ICSI. 3] Normal regular cycles with a mean length of between 24 and 35 days. 4] Good physical and mental health. 5] A BMI between 18 and 29 kg/m^2. **Exclusion criteria** 1] Infertility caused by endocrine abnormalities such as hyperprolactinemia, PCOS, and absence of ovarian function 2] One ovary or a history of ovarian resection. 3] Severe endometriosis (grade III and IV). 4] Previous COH cycles in which less than three ooctes wee retrieved.	1] Fixed dose of 150 IU of rFSH 2] 250 IU dose of rFSH	Recruitment: The study was performed in 15 specialised intertility centres in Argentina (n = 5), Brazil (n = 3), Chile (n = 2), Colombia (n = 2), Mexico (n = 1), and Venezuela (n = 2). The aim was to include 450 patients with 225 patients in each treatment according to sample size considertions. Method: Eligible subjects were randomised by receiving a subject number from a randomisation corresponding with patient boxes in which the medication was kept. The 50-, 100-, and 150-IU ampoules were indistinguishable. The randomisation was done in blocks of four and was computer-generatred using random numbers. The randomistion was stratified for age to achieve equal number	Clinical pregnancy* 150 IU = 34/201 (16.9%) 250 IU = 33/203 (16.3%) Adverse pregnancy outcome** 150 IU = 1/201 (0.5%) 250 IU = 0/203 (not estimable) Multiple pregnancy 150 IU = 16/201 (8%) 250 IU = 9/203 (4.4%) OHSS**** 150 IU = 5/201 (2.5%) 250 IU = 8/203 (3.9%) *Figures for 'Clinical pregnancy' reflect 'Vital pregnancy'. Vital pregnancies were those pregnancies where a fetal heart beat was observed under ultrasound investigation. **Adverse pregnancy outcome reported was extrauterine pregnancy **** OHSS: No strict definition of the OHSS was given. In the analysis of the occurrence of this syndrome, its incidence and severity was based on the fact that the investigator reported it as such.	**Limitations** 1] Power calculation was done for pregnancy outcomes **Other information** 1] Figures for 'Clinical pregnancy' and 'Vital pregnancy' were reported but they were different from each other. There was no definition for 'Clinical pregnancy' but there was a definition for 'Vital pregnancy'. The figures for 'Vital pregnancy' was chosen to reflect 'clinical pregnancy' since the definition was suitable. 2] In both groups, from the multiple pregnancies, there were seventeen twins, five triplets, and four quadruplets. 3] Cycle cancellations: Of 201 women who started on the low-dose goup, 183 had an oocyte retrieval and 172 had embryo transfer. In the high-dose group, 185 of 203 women who started rFSH treatment had a retrieval and 171 had an embryo transfer. Reasons for cancellation in the

	5] Previous hospitalisation due to the OHSS. 6] Chronic cardiovascular, hepatic, renal or pulmonary disease. 7] A history (within 12 months) or current abuse of alcohol or drugs. 8] Administration of nonregistered investigational drugs within 3 months before screening		of subjects in each treatment group for the age groups 30 - 36 and 37 - 39 years. With 22 subjects included in each treatment goup and under assumption of common slopes for treatment by age and assuming a standard deviation of 6.4 oocytes for the number of oocytes retrieved and a standard deviation of 2.5 treatment das, a difference of approximately 1.7 oocytes and 0.6 treatment day could be detected between the two treatment groups with a power of 80% using a two-sided t-test with a significance level of 5%. Intervention: Pretreatment with leuprolide for pituitary down-regulation was started in the midluteal phase. Recombinant FSH was supplied as lyophilised spheres in ampoules containing		low-dose group were insufficient ovarian response, risk of hyperstimulation, no fertilisation or other.

			50, 100, or 150 IU FSH invivo bioactivity. For subcutaneous injection, two ampoules were reconstituted with 1 mL of solvent. hCG in doses of 5,000 IU per ampoule was supplied to trigger ovulation. When E_2 serum levels were <200 pmol/L, treatment with rFSH was started and continued until at least 2 follicles ≥20 mm had developed. Dose adaptations were not allowed. The maximum treatment period was 3 weeks. After oocyte pick-up and IVF or ICSI, a maximum of four embryos was replaced. Luteal phase support was given as P in a route of administration and dosage regimen as routinely done in each centre.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Out,H.J., Rutherford,A., Fleming,R., Tay,C.C.K., Trew,G., Ledger,W., Cahill,D., A randomized, double-blind, multicentre clinical trial comparing starting doses of 150 and 200 IU of recombinant FSH in women treated with the GnRH antagonist ganirelix for assisted reproduction, Human Reproduction, #19, 90-95, 2004 **Ref ID** 89843 **Country/ies where the study was carried out** United Kingdom **Study type** Randomised multicentre trial **Aim of the study** To investigate the effect of an increase in the starting dose of rFSH from 150 to 200 IU on the number of oocytes retrieved in GnRH antagonist protocols for assisted reproduction. **Study dates** June 2000 to December 2001 **Source of funding** Not reported	**Sample size** n = 264 women (randomised) n = 257 women (treated) **Characteristics** Mean age ± SD = 32.5 ± 3.6 years Mean BMI ± SD = 23.5 ± 2.8 kg/m^2 Mean duration of infertility ± SD = 4.6 ± 2.6 years Cause of infertility: Tubal factor = 68 (26.5%) Male factor = 92 (35.8%) Endometriosis = 22 (8.6%) Other/unknown = 55 (21.4%) Mixed causes = 20 (7.8%) **Inclusion criteria** 1] Females of infertile couples for whom COH and IVF with or without ICSI was indicated. 2] Age at least 18 years but not more than 39 years at the time of screening. 3] BMI between 18 and 29 kg/m^2. 4] Body weight between 50 and 90kg. **Exclusion criteria** 1] History of/or current endocrine abnormality such as PCOS or evidence of ovarian dysfunction 2] Elevated early follicular phase (menstural cycle day 2-7) circulating FSH and/or LH concentrations	1] 150 IU rFSH 2] 200 IU rFSH	Recruitment: The study was performed in 6 infertility centres in the UK. The aim was to include 260 patientw, with 130 patients in each treatment group. Method: Eligible subjects were randomised by receiving a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. The 150 and 200 IU rFSH vials were indistinguishable. The randomisation was done in blocks of four and was computer-generated using random numbers. Intervention: rFSH was supplied as solution for injection in vials containing 100, 150 or 200 IU in vivo bioactivity. hCG in doses of 5000 IU per ampoule was supplied to trigger ovulation. On day 2 or 3 of the	1] Clinical pregnancy: 150 IU rFSH = 41/132 200 IU rFSH = 32/132 2] Adverse pregnancy outcome: 150 IU rFSH = 8/132 200 IU rFSH = 9/132 3] OHSS: 150 IU rFSH = 8/132 200 IU rFSH = 10/132 1] Figures for 'Clinical pregnancy' reflect 'Vital pregnancy'. Vital pregnancies were those pregnancies where a fetal heartbeat was observed under US investigation. 2] Adverse pregnancy outcome reported were miscarriage and ectopic pregnancy 3] No strict definition of the OHSS was given. In the analysis of the occurrence of OHSS, its incidene and severity were based onthe fact that the investigator reported it as such.	**Limitations** 1] Power calculation was not reported for pregnancy outcomes 2] There was a 3% drop-out due to high FSH levels at screening. **Other information**

	according to cut-off levels used in the local laboratory. 3] Any clinically significant abnormal laboratory value 4] any ovarian and/or abdominal abnormality that would interfere with adequate US investigation of at least one ovary 5] Only one ovary 6] Contra-indications for the use of gonadotropons. 7] Use of hormonal preparations within 1month prior to the date of signing consent. 8] Alcohol or drug abuse or history thereof, within the 12 months preceding signing informed consent. 9] Administration of investigational drugs within 3 months prior to screening.		menstrual period, rFSH was started and remained fixed for the first five rFSH treatment days. On treatment day 6, ganirelix treatment was started by daily s.c administration in the morning up to and including the day of hCG administration. The last rFSH dose was administered on the day of hCG injection. During ganirelix treatment, the dose of rFSH could be adjusted downwards to100 IU daily based on the clinical judgment of the investigator. For this purpose Statistical analysis: With 130 subjects included in each treatment group and assuming a SD of 6.0 oocytes for the number of oocytes retrieved, a difference of 2.06 oocytes could be detected between the two treatment groups with a power of 80% and a		

			significance threshold of 5%		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dhont,M., Onghena,A., Coetsier,T., De,Sutter P., Prospective randomized study of clomiphene citrate and gonadotrophins versus goserelin and gonadotrophins for follicular stimulation in assisted reproduction, Human Reproduction, 10, 791-796, 1995 **Ref ID** 68205 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** To investigate whether the use of GnRH agonist in unselected patients would provide a clear advantage in terms of pregnancy rate/cycle. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 238 women **Characteristics** Population: Patients with mixed infertility diagnosis (not stated but mainly abnormal spermiogram) coming for their first IVF attempt. Female mean age = NR Duration of infertility = NR BMI/ Weight = NR Cause of infertility: Abnormal spermiogram = 167 (55.1%) Other factors = NR **Inclusion criteria** Only patients who entered a first trial of assisted reproduction. **Exclusion criteria** Not reported	GnRH agonist +hMG CC + hMG	Recruitment: Patients who entered a first trial of assisted reproduction were included. From a retrospective analysis of IVF data, a pregnancy rate of of 20 - 25% per cycle with CC/hMG was anticipated. Method: In total, 303 patients were included. Because of a number of potential confounders, patients were allocated to one of the treatment groups using a computerised minimisation procedure in which three main prognostic factors: ART type, sperm characteristics and age. The two treatment groups were equally randomised along those three parameters. Intervention: In both groups, the cycle before starting stimulation was suppressed by means of an oral contraceptive which	Clinical pregnancy GnRH agonist +hMG = 44/119 CC + hMG = 28/119 Definition of 'Clinical pregnancy' not reported.	**Limitations** Allocation concealment not reported Blinding not reported **Other information** Figures for 'Adverse pregnancy outcomes' reflect numbers of abortion and ectopic pregnancy and presented as a rate. The rates in the goserelin + hMG group and the CC + hMG group were 34% and 24.3% respectively; p = NS. There was no definition for 'Live birth', however, the rates in both groups (CC + hMG and goserelin +hMG) were 18.5% and 25.7% respectively; p = 0.13.

			was given for at least 2 weeks and this period could be extended up to 6 weeks depending on circumstances. Stimulation with either CC or hMG was started 7 days after the cessation of the oral contraceptive. CC was given for 5 days. In group A, pituitary desensitisation by a subcutaneous implant of goserelin was initiated 2 - 3 weeks before starting the stimulation, while the patient was still on the oral contraceptive. hMG was started 7 days after cessation of the oral centraceptive and between 14 and 21 days after the administration of goserelin. In group B, the stimulation with hMG started at the end of CC administration for 3 - 5 days. To prevent premature LH rise as far as possible, hCG was given when the diameter of the		

			largest follicle was 18 mm in the CC/hMG group, whereas in the goserelin/hMG group, hCG was given when the largest follicle was ≥20 mm in diameter. Oocyte retrieval took place 35 - 37 h after hCG injection. In IVF cycles, up to three good quality embryos were transferred into the uterus. If fewer than three good quality embryos were available for transfer, additional intermediate embryos, up to 5 in total were transferred Statistical analysis: A sample size of 300 was required to detect a relative difference in pregnancy rate per cycle of 50% with a power of 90% and with α error = 0.05. In total, 303 patients were included.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Duffy,MN James, Ahmad,Gaity, Mohiyiddeen,Lamiya, Nardo,Luciano G., Watson,Andrew, Growth hormone for in vitro fertilization, Cochrane Database of Systematic Reviews, -, 2010 **Ref ID** 73416 **Country/ies where the study was carried out** **Study type** Cochrane review of randomised controlled trials **Aim of the study** To assess the effectivness of adjuvant growth hormone in in-vitro fertilisation protocols **Study dates** Searches done up to June 2009 **Source of funding** Department of Obstetrics and Gynaecology, University of Auckland, New Zealand Department of Health, UK ($5000 initiative fund)	**Sample size** 10 randomised controlled trials representing 440 couples (range 14 to 61 couples in each study) **Characteristics** Women aged 30 to 40 years Two trials concerned the routine use of growth hormone as an adjuvant in IVF protocols (Tapanainen, 1992; Younis, 1992) Eight trials concerned the use of adjuvants growth hormone in IVF protocols for poor responders (Bergh, 1994; Dor, 1995; Kueuk, 2008; Owen, 1991; Suikkari, 1996; Hazout, 2003; Tesarik, 2005; Zhang, 1994) (only data from the trials using growth hormone in poor responders is reported here as this is relevant to the current review protocol) Hazout (2003) and Suikkari (1996) were multi arm trials comparing two different doses of growth hormone to a control arm. The separate arms were allocated different study IDs in the Cochrane review. **Inclusion criteria** **Exclusion criteria**	Dose ranged from 8IU to 24IU Bergh (1994) - growth hormone + buserelin acetate + hMG and/or FSH + hCG vs placebo + buserelin acetate + hMG and/or FSH + hCG Dor (1995) - growth hormone + GnRH agonist + FSH + hMG + hCG vs GnRH agonist + FSH + hMG + hCG Hazout (2003) - growth hormone + unclear protocol + hCG vs unclear protocol + hCG Kueuk (2008) - growth hormone + GnRH agonist + FSH + hMG + hCG vs GnRH agonist + FSH + hMG + hCG Owen (1991) - growth hormone + hMG + GnRH agonist + hCG vs placebo + hMG + GnRH agonist + hCG Suikkari (1996) - growth hormone (12 IU) + leuprolide acetate + Metrodin +	The Cochrane review reported results for two different definitions of poor responders. 1) As described in the individual study (Bergh, 1994; Dor, 1995; Kueuk, 2008; Owen, 1991; Suikkari, 1996; Hazout, 2003; Tesarik, 2005; Zhuang, 1994) 2) Previous sub-optimal response following controlled ovarian stimulation (Bergh, 1994; Dor, 1995; Kueukm 2008; Owen, 1991; Suikkari, 1996) The results consistent with the second definition are reported here	Live birth rate (2 studies: Owen, 1991; Suikkari 1996 4IU) Growth hormone= 6/23 (26%) No growth hormone= 0/15 (0%) OR 5.81 (0.67 to 50.39) I^2= 0% (The analysis in the Cochrane review shows the odds ratio was weighted 60/40 in favour of the Suikkari study, despite the Owen study including more women and being of better quality. It was not clear in the Cochrane review why this was done. When considered separately, neither study had a significant result) It is not clear whether the live birth rate only reports full term singleton births Pregnancy rate (4 studies: Bergh, 1994; Kueuk, 2008; Owen, 1991; Suikkari, 1996 4 IU) Growth hormone= 19/62 (31%) No growth hormone= 8/54 (15%) OR 2.58 (1.03 to 6.46) I^2= 0% Definition of 'pregnancy' is not reported Adverse events (2 studies: Owen, 1991; Suikkari 1996 4IU) [includes pregnancy and non-pregnancy related events]	**Limitations** **Other information**

		hCG vs growth hormone (4 IU) + leuprolide acetate + Metrodin + hCG Tesarik (2005) - growth hormone + long protocol + hCG vs long protocol + hCG Zhaung (2004) - growth hormone + Buserelin + hMG + hCG vs Buserelin + hMG + hCG		Growth hormone= 3/23 (13%) No growth hormone= 1/15 (7%) OR 1.63 (0.21 to 12.59) I^2= 0%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Grochowski,D., Wolczynski,S., Kuczynski,W., Domitrz,J., Szamatowicz,J., Szamatowicz,M., Good results of milder form of ovarian stimulation in an in vitro fertilization/intracytoplasmic sperm injection program, Gynecological Endocrinology, 13, 297-304, 1999 **Ref ID** 68380 **Country/ies where the study was carried out** Poland **Study type** Randomised trial **Aim of the study** To compare two protocols of ovulation stimulation, the clomiphene citrate/hMG versus D-triptorelin/hMG, in terms of pregnancy rates and cost-effectiveness of drugs used. **Study dates** January 1996 - June 1998 **Source of funding** Not reported	**Sample size** n = 324 patients **Characteristics** Population: Ovulatory women undergoing their first attempt who had the following infertility diagnoses listed below. Female mean age = 30.1 ± 3.7 years Duration of infertility = NR BMI / Weight = NR Cause of infertility: Male factor = 143 (44.1%) Tubal factor = 111 (34.3%) Unexplained = 19 (5.9%) Endometriosis = 18 (5.6%) Mixed factor = 33 (10.2%) **Inclusion criteria** Age <36 years Regular menstrual cycles (25 - 35 days) Cause of infertility solvable by IVF/ICSI For ICSI: Patient had to have very poor sperm parameters according to WHO criteria **Exclusion criteria** For ICSI: Azoopermia	GnRH agonist + hMG CC + hMG	Recruitment: The study population consisted of 324 infertile patients, who within the study period entered their first trial in the IVF/ICSI program at the IVF unit. Method: The couples were allocated to the two different drug regimens by drawing serially numbered envelops. Intervention: Two stimulation protocols were used simultaneously: 164 cycles were stimulated using CC from day 2 of the cycle for 5 days and hMG on days 4, 6 and 8 of the cycle. Depending on the serum estradiol concentrations and ultrasound findings, the dose of hMG was then adjusted if necessary. In another 160 cycles, pituitary desensitisation was achieved with the use of D-triptorelin in a single injection in the midluteal phase. hMG	Clinical pregnancy GnRH agonist + hMG = 38/160 CC + hMG = 41/164 OHSS GnRH agonist + hMG = 5/160 CC + hMG = 0/164 Clinical pregnancy was diagnosed when a gestational sac was detected by ultrasonography two weeks after embryo transfer. OHSS reported was severe OHSS and was not defined Twin pregnancies: CC + hMG= 7/41 (17%) pregnancies (7/164 women [4%]) GnRH agonist + hMG= 3/38 (8%) pregnancies (3/160 women [2%]) The number of births from these pregnancies was not reported	**Limitations** Inadequate allocation concealment Blinding not reported **Other information** There were 8 cases of spontaneous ovulation in the CC + hMG group and 2 aspiration failures in the GnRH agonist/hMG group. Fertilisation failure occurred in 18 patients (11/18 patients had only one oocyte collected) in the CC +hMG group compared with 8 in the GnRH agonist/hMG group. There was about 5% spontaneous ovulations. Results from subgroup analysis by ART did not differ from the general results (IVF and ICSI)

			was given from day 3 of the cycle for 5 days. For the following days, the dose of hMG was adapted according to the response to the treatment. When at least two growing follicles >18 mm in diameter in group 1 and >20mm in group 2 were present and serum estradiol concentrations of at least 500pg/ml were achieved, hCG was given to induce ovulation. Transvaginal ovum collection was performed 36h later. Four hours after collection, oocytes were inseminated and incubated. Fertilisation was then assessed 14 - 16h later and the two best quality embryos were transferred into the uterus on the following day. If an embryo selection was possible, the two best quality embryos were replaced and surplus embryos were further		

			cultured into the blastocyst stage and then cryopreserved. Statistical analysis: An estimated 270 couples was required to detect a 15% difference in pregnancy rates with a power of 80% and 5% level of significance. The sample size in each drug regimen was balanced for the IVF and ICSI procedure. The population in the two groups was homogeneous.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ingerslev,H.J., Hojgaard,A., Hindkjaer,J., Kesmodel,U., A randomized study comparing IVF in the unstimulated cycle with IVF following clomiphene citrate, Human Reproduction, 16, 696-702, 2001 **Ref ID** 68493 **Country/ies where the study was carried out** Denmark **Study type** Randomised controlled trial **Aim of the study** To evaluate the efficiency, in terms of pregnancy rates per cycle and embryo transfer, of low cost, low intervention IVF with minimal monitoring comparing IVF in the unstimulated cycle with IVF following stimulation with clomiphene citrate **Study dates** August 1 to December 31 1997 **Source of funding** Danish Institute for Health Technology Assessment funding (project no. 3126-88-1997) Astra Denmark supplied Clomivid	**Sample size** 132 women **Characteristics** Mean age: Clomiphene citrate= 30.19 years (SD 2.85) Unstimulated= 30.71 years (SD 2.50) No significant difference Duration of infertility: Clomiphene citrate= 4.19 (SD 2.03) Unstimulated= 4.54 (SD 1.88) No significant difference **Inclusion criteria** • <35 years • unexplained infertility, tubal infertility or severe male factor infertility with indication for ICSI • regular menstrual cycles (SD 3 days) • presence of two ovaries • no previous IVF treatment **Exclusion criteria** None reported	Clomiphene citrate + IVF + hCG (n= 68) Unstimulated IVF + hCG (n= 64)	Women were randomised using block randomisation by sealed envelope Clomiphene citrate was given in 100mg dose from cycle day 3 to day 7 hCG was given when dominant follicle was ≥17 mm (natural cycle) or ≥20mm (clomiphene citrate cycle) - if spontaneous ovulation occured in one cycle, these criteria were 1mm less in the next cycle. hCG was given and oocyte retrieval took place when morning urine sample tested positive for LH. Women did not cross over, but a wash out period of at least one cycle was interposed between cycles due to the relatively long half life of zuclomiphene Couples who had male factor infertility were treated with ICSI.	<u>Clinical pregnancy</u> Clomiphene citrate + IVF + hCG = 20/68 Unstimulated IVF + hCG = 4/64 Clinical pregnancy was defined as a live intrauterine pregnancy 132 women started their first cycle, 90 received two cycles and three started a third cycle Cancellation due to lack of follicular development or to spontaneous ovulation occured in 16/111 (14%) initiated clomiphene citrate cycles and 40/114 (35%) of unstimulated cycles Side effects were only reported per cycle: 51/111 clomiphene citrate cycles some type of side effect was registered 2/114 unstimulated cycles reported side effects (hot flushes in one and mammary tenderness in the other) p<0.0001 Of the clomiphene citrate cycles, 14 (12.6%) were associated with nausea, 35 (31.5%) hot flushes, 6 (5.4%) mammary tenderness, 4 (3.6%) with visual disturbance.	**Limitations** Randomisation of couples undergoing ICSI and women with unexplained infertility to stimulated and unstimulated cycles was not ideal (24/68 in the CC vs 13/64 in the unstimulated group for male factor/ICSI, chi squared= 3.67; 13/68 in the CC vs 21/64 in the unstimulated group for unexplained, chi square= 3.23) A power analysis was not undertaken **Other information**

			Women with tubal and unexplained infertility were treated with IVF.	Twin pregnancies: Clomiphene citrate= 2/20 (10%) pregnancies (2/68 [3%] women) Unstimulated= 0/4 (0%) pregnancies (0/64 [0%] women) Births from the twin pregnancies were not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Karimzadeh,M.A., Ahmadi,S., Oskouian,H., Rahmani,E., Comparison of mild stimulation and conventional stimulation in ART outcome, Archives of Gynecology and Obstetrics, 281, 741-746, 2010 **Ref ID** 68531 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial **Aim of the study** To provide a treatment for particular condition that is the most effective treatment with the least risk and cost for the patient by comparing the efficacy of using clomiphene 100mg + delayed low dose gonadotropin + flexible GnRH antagoist administration for ovarian stimulation protocol and GnRH agonist + gonadotropin for stimulation protocol in IVF outcome. **Study dates** 1 January 2008 - 30 December 2008 **Source of funding** Not reported	**Sample size** n = 243 patients **Characteristics** Population: Ovulatory women undergoing their first IVF or ICSI attempt who had the infertility diagnoses listed below. Female mean age = 29.7 ± 2.4 years Duration of infertility = 5.7 ± 1.0 years BMI = 25.6 ± 2.1 kg/m^2 Cause of infertility: Male factor = 119 (60%) Tubal factor = 28 (14%) Unexplained = 7 (3.5%) Endometriosis = 11 (5.5%) Mixed = 28 (14%) Others = 7 (3.5%) **Inclusion criteria** Female patient age 18 - 35 years Presence of a regular and proven ovulatory menstruation cycle with a length of 26 - 35 days. Basal FSH <10IU/L BMI of 18 - 30 kg/m^2 First IVF attempt **Exclusion criteria** Not reported	Group A: GnRH agonist + rFSH Group B: CC + rFSH + GnRH antagonist	Recruitment: The study included 243 patients who where candidate for ART Method: Patients were randomised in to one of two treatment groups using a computer-generated randomisation schedule assigned via numbered sealed envelops. Intervention: In group A, the patients were stimulated conventional. They desensitised with buserelin subcutaneously everyday for menstrual cycle 21, until the baseline evaluateion, which takes place in the first few days of menstruation. If baseline levelso f estradiol had been achieved, then the dose of buserelin would be reduced and ovarian stimulation would commence with rFSH subcutaneously. Patients in group B were stimulated with CC from cycle day 3	Clinical pregnancy GnRH agonist + rFSH = 31/100 CC + rFSH + GnRH antagonist = 37/100 OHSS GnRH agonist + rFSH = 6/100 CC + rFSH + GnRH antagonist = 0/100 Clinical pregnancy was considered as the presence of gestational sac with fetal heart activity by TVS that performed 3 weeks after positive ß-hCG OHSS was defined by ≥15 follicles with a mean diameter ≥14mm per each ovary at the end of the follicular phase of stimulation and/or E2 levels on the day of hCG administration >3,000 pg/mL and/or the prescence of ascites after hCG administration in ultrasonography.	**Limitations** No blinding of participants, staff and study personal reported. No power calculation reported. It is not clear whether the study was adequately powered. **Other information** A total of 43 patients dropped out of the study. In group A, 6 were excluded, 13 patients did not comeback and 3 patients were lost to follow-up (n = 22 patients); In group B, 2 patients were excluded, 12 patients did not come back and 7 were lost to follow-up (n = 21 patients). In group A, 2 embryo transfers were cancelled because of OHSS while in the CC+rFSH+GnRH antagonist group, 4 cycles were cancelled due to LH surge. There was no significant difference in number of patients using the different ART types (conventional IVF, ICSI, combined IVF-ICSI) between the two groups.

			through day 7 and continuous gonadotrophin stimulation with rFSH daily from cycle day 5. GnRH antagonist daily was started with dominant follicle ≥12 mm and in this day, hMG increased to the initial gonadotropin. LH assessment on the day of starting antagonist was performed and if premature LH surge occured, cycle was cancelled. hCG was given when one to three follicles reached 18mm. Oocyte pic-up was performed 34 - 36h after hCG injection by transvaginal ultrasound-guided puncture of follicles and IVF or ICSI was performed. Embryo transfer was done on the day 2 or 3.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lin,Y.H., Hwang,J.L., Seow,K.M., Huang,L.W., Hsieh,B.C., Tzeng,C.R., Comparison of outcome of clomiphene citrate/human menopausal gonadotropin/cetrorelix protocol and buserelin long protocol--a randomized study, Gynecological Endocrinology, 22, 297-302, 2006 **Ref ID** 54832 **Country/ies where the study was carried out** Taiwan **Study type** Randomised trial **Aim of the study** To evaluate the efficacy of a stimulation protocol with clomiphene citrate/human menopausal gonadotrophin/cetrorelix and its effect on oocyte quality and endometrium. **Study dates** July 2003 - December 2004 **Source of funding** Not reported	**Sample size** n = 120 women **Characteristics** Population: Ovulatory women having their first ICSI attempt whose partners had male factor infertility. Female mean age = 31 ± 4.4 years Weight = 54.4 ± 8.2 kg Cause of infertility: Male factor = 120 (100%) **Inclusion criteria** Women: coming for their first ICSI cycles. aged 20 - 38 years. with regular cycles. with normal basal hormonal profile - day-3 FSH <10mIU/ml, LH <10 mIU/ml and E2 <60 pg/ml. BMI between 18.5 and 24.9kg/m2. whose partners had male factor infertility. **Exclusion criteria** Patients with other indications for infertility including endometriosis, anovulation, PCOS and hydrosalpinx. Patients whose laparoscopic examination results showed abnormalities.	CC + hMG + GnRH antagonist hMG + GnRH agonist	Recruitment: Within the study period, infertile couples who were about to undergo their first ICSI cycles and fulfilled the inclusion criteria were evaluated after which, the patients came back within 3 days of the cycle for ovarian stimulation. Method: The couples were then randomised by block randomisation to receive either of two stimulation protocols. The allocated numbers were sealed in envelopes and the physicians were not aware of the allocation until the patients were about to start ovarian stimulation. Intervention: Sixty women in the first group were stimulated by the CC/hMG/cetrorelix protocol. Clomiphene citrate was given from cycle day 3 to 7; hMG was given on days 4, 6 and 8 at 4 ampoules, then every day from	Live full-term singleton birth CC + hMG + GnRH antagonist = 22/60 hMG + GnRH agonist = 21/60 Clinical pregnancy CC + hMG + GnRH antagonist = 25/60 hMG + GnRH agonist = 24/60 Adverse pregnancy outcome CC + hMG + GnRH antagonist = 3/60 hMG + GnRH agonist = 3/60 OHSS CC + hMG + GnRH antagonist = 1/60 hMG + GnRH agonist = 3/60 Live birth was not defined so figures reported may include both full-term and pre-terms. Clinical pregnancy was defined as a visible fetal heart beat on ultrasonography. Adverse pregnancy outcome reported were abortions (n = 5) and still-births (n = 1 from the intervention group). OHSS was severe	**Limitations** No blinding of participants, staff and study personnel reported. **Other information** No cycle was cancelled. All patients went through oocyte retrieval and embryo transfer

			day 9. Cetrorelix acetate was given when the leading follicle had reached 14 mm. If hCG was not given 4 days after cetrorelix injection, 0.25mg cetrorelix was given every day until the day of hCG injection. Sixty women assigned to the second group were stimulated by GnRH agonist long protocol. The women received 2 - 4 ampoules of hMG or FSH per day after pituitary suppression with buserelin. hCG, was administered when tat least two follicles reached18mm with adequate E_2 levels. For both groups, oocyte retrieval was performed 34 - 36 h later. Fertilisation was assessed 16 - 18 h after ICSI by the appearance of two pronuclei and two polar bodies. Embryo transfer was performed 2 or 3 days after ICSI. Statistical analysis:		

			Assuming that the CC/hMG/cetrorelix protocol would reduce the amount of gonadotropin used by 20% compared with the GnRHa long protocol, the sample size required would be 50 in each group to give a power of 0.9.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation MacDougall,M.J., Tan,S.L., Hall,V., Balen,A., Mason,B.A., Jacobs,H.S., Comparison of natural with clomiphene citrate-stimulated cycles in in vitro fertilization: a prospective, randomized trial, Fertility and Sterility, 61, 1052-1057, 1994 **Ref ID** 68638 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** To compare the outcome of natural with clomiphene citrate (CC)-stimulated cycles in IVF **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 30 women Natural cycle + IVF = 14 CC + IVF = 16 **Characteristics** Age = 32.5 ± 1.1 years BMI = NR Duration of infertility = Not reported Diagnosis of infertility: Tubal damage: 17/30 (57%) Unexplained infertility: 7/30 (23%) Failed donor insemination: 6/30 (20%) **Inclusion criteria** >1 year of infertility Spontaneous ovulatory cycles (26 to 34 day length with <4 days difference from cycle to cycle) Midluteal phase Progesterone > 10ng/ml Normal semen analysis **Exclusion criteria** Age >38 years Severe endometriosis	Clomiphene citrate (CC) + hCG + IVF Comparator Natural cycle + hCG + IVF	Women were randomised to receive either no treatment (n = 14) or stimulation with CC 100mg/day from days 2-6 (n = 16). All patients had US scan of the pelvis on day 2 and 7 of the cycle, followed by daily scans once the leading follicle reached 14mm in diameter 5000IU of hCG was administered. Oocyte collections were performed 35 hours later and embryos transferred 48 hours later. Intrauterine insemination was instead performed in those cases in which premature LH surge was detected and the patient had patent tubes. Intrauterine insemination was also performed if no oocytes were obtained at collection.	<u>Clinical pregnancy</u> Clomiphene citrate (CC) + hCG + IVF = 2/16 Natural cycle + hCG + IVF = 0/14 Definition of clinical pregnancy not reported <u>Live singleton birth</u> Clomiphene citrate (CC) + hCG + IVF = 2/16 Natural cycle + hCG + IVF = 0/14 It is not clear whether these births were at term	**Limitations** Blinding was not reported. Allocation concealment not reported Power calculation was not reported **Other information** N = 13 patients (Natural cycle IVF = 5; CC + IVF = 8) were identified as having PCO according to ultrasound criteria (i.e., if there were 10 or more cysts, 2 to 8 mm in diameter, arranged around a dense stroma or scattered throughout an increased amount of stroma) Diagnosis of pregnancy not described Randomisation using computer-selected random numbers

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Morgia,F., Sbracia,M., Schimberni,M., Giallonardo,A., Piscitelli,C., Giannini,P., Aragona,C., A controlled trial of natural cycle versus microdose gonadotropin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization, Fertility and Sterility, 81, 1542-1547, 2004 **Ref ID** 5446 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** To determine the efficacy of natural-cycle IVF compared with controlled ovarian hyperstimulation in poor responders. **Study dates** January 2000 - July 2002 **Source of funding** Not reported	**Sample size** n = 129 women **Characteristics** Population: Ovulatory women that had undergone ≥1 previous IVF cycle that resulted in a poor response. Poor response was defined as ≤3 follicles recruited or cycle cancelled because of no follicle activation. Female mean age (range) = 39.3 ± 3.6 (30 - 43) years Duration of infertility = NR BMI/ Weight = NR Cause of infertility: Male factor = 61 (47.3%) Tubal factor = 29 (22.5%) Unexplained = 24 (18.6%) Hormonal factor = 15 (11.6%) **Inclusion criteria** Age ≤43 years Patients who had undergone a previous IVF cycle at the IVF clinic that resulted in a poor response. **Exclusion criteria** Not reported	GnRH agonist (Buserelin) + purFSH Natural cycle IVF	Recruitment: The study was conducted on poor-responding patients undergoing IVF. These patients had regular menstrual cycles (26 - 39 days) with primary infertility and poor ovarian reserve, as shown by their previous IVF outcomes. Method: The patients were randomised according to a computer-generated number sequence at the time that their cycle was scheduled. Patients selected for one type of treatment were not allowed to change treatment if the first IVF cycle failed. Patients refusing to be treated again with the same protocol were dropped from the study for the successive cycles. Intervention: In the patients who underwent natural-cycle IVF, from the 7th day of the cycle a daily monitoring of follicle	Clinical pregnancy GnRH analogue + purFSH = 7/70 Natural cycle IVF = 7/59 All pregnancies were confirmed by a rising titre of serum ß-hCG from 12 days after embryo transfer and ultrasound demonstration of the gestation sac 4 weeks after embryo transfer.	**Limitations** Allocation concealment was not reported Blinding of participants, staff and study personnel not reported Power calculation not reported. **Other information** After a failed cycle, patients undergoing ovarian stimulation required a rest between stimulated cycles. Furthermore, they showed less compliance in following the protocols, owing to the expense of each ovarian stimulation, the amount of gonadotrophins used for the stimulation and the psychological stress related to cycle failure: only 20 patients in this group underwent two or more IVF cycles. Conversely, the patients in the natural cycle group showed better compliance.

			size was performed. The criterion used for triggering ovulation with hCG was a follicle ≥16mm diameter. Oocyte retrieval was performed 36 hours after injection of hCG. ICSI was performed in all the patients and oocytes were examined 18 hours after for pronuclei and 44 hours after insemination for embryo development. Embryos were transferred 48 - 72 hours after insemination.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Owen,E.J., Shoham,Z., Mason,B.A., Ostergaard,H., Jacobs,H.S., Cotreatment with growth hormone, after pituitary suppression, for ovarian stimulation in in vitro fertilization: a randomized, double-blind, placebo-control trial, Fertility and Sterility, 56, 1104-1110, 1991 **Ref ID** 82859 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To explore the effect of cotreatment with growth hormone for ovarian stimulation after pituitary suppression. **Study dates** January 1989 - December 1989. **Source of funding** Supplies of Norditropin (growth hormone) from Novo Nordisk A/S Denmark.	**Sample size** n = 25 women. **Characteristics** Population: Non-ovulatory poor responders that had undergone ≥1 previous attempt. Poor response was defined as <6 oocytes collected, <4 developed embryos in previous cycle. Female mean age = 32.9 ± 2.8 years Duration of infertility = 5.7 ± 2.9 years BMI = 22.3 ± 3.5 kg/m^2 Cause of infertility: Male factor = 7 (28%) Tubal factor = 11 (44%) Unexplained = 7 (28%) **Inclusion criteria** Age <38 years Having undergone one or more IVF embryo transfer cycle(s) in which ovarian stimulation had been carried out using the combined regimen of GnRH analogue and hMG in which the response had been considered suboptimal. **Exclusion criteria** Not reported.	GH (24 IU)+ GnRH agonist + hMG + hCG Placebo + GnRH agonist + hMG + hCG	Recruitment: Patients who underwent IVF-ET within the study period were candidates for the study. Twenty five patients were recruited into this study which was a phase II trial of cotreatment with biosynthetic natural sequence human GH compared with previous treatment and with cotreatment with placebo in addition to the patients' standard treatment for IVF. Method: Patients with ultrasound findings of normal ovaries and patients with US-diagnosed PCOS were randomised inot two groups, i.e, GH or placebo. Two randomisation lists were made with 20 patients on each list and block randomised in blocks of four. GH or placebo was given on alternate days to each patient depending on the group randomised to	Live full-term singleton birth GnRH agonist + hMG + GH = 2/13 GnRH agonist + hMG + placebo = 0/12 Clinical pregnancy GnRH agonist + hMG + GH = 4/13 GnRH agonist + hMG + placebo = 1/12 Adverse pregnancy outcome GnRH agonist + hMG + GH = 0/13 GnRH agonist + hMG + placeb = 1/12 Multiple births GnRH agonist + hMG + GH = 4/6 GnRH agonist + hMG + placebo = 0/1 Figures for 'clinical pregnancy' reflect number of 'pregnancy'. No definition was given for 'pregnancy' and it is not clear whether it represents biochemical or clinical pregnancy. 'Adverse pregnancy outcome' reported was ectopic pregnancy. Multiple births reported were 2 sets of twins. Twin pregnancies: GH group= 2/4 (50%) of	**Limitations** No allocation concealment. No blinding of participants, staff and study personnel No power calculation reported. **Other information** Patients in the group receiving GH had a significantly longer mean duration of infertility than the patients that received placebo; (p <0.03).

			for a maximum period of 2 weeks until the administration of hCG. At the completion of the cycle, the assignment code was broken. Those who received GH were considered to have completed the study; patients who had received placebo were then placed in an open study in which they received GH. The results of this open study are not reported in the analysis. In all cases, an interval of 2 months was allowed to elapse between cycles of treatment. Intervention: All patients had had at least one previous IVF-ET attempt using pituitary gonadotropin suppression. In all treatment cycles, the analog was administered daily from day 1 of the menstrual cycle for a minimum of 14 days. If ovarian suppresion	pregnancies (2/13 [15%] women) Placebo= 0/1 (0%) of pregnancies (0/12 [0%] women)	

			was confirmed, hMG was commenced and treatment with buserelin acetate continued until the day of hCG administration. If serum E2 concentrations indicated lack of pituitary suppression, the dose of buserelin acetate was increased for 7 days. If desensitisation had still not occured, treatment with buserelin acetate was continued weekly till hypoestrogenemia was observed. Once ovarian suppression was achieved, the dose of busereline acetate was reduced daily until the day of hCG administration. Ovarian stimulation was performed using hMG. HCG was administered when 3 follicles of >14 mm in diameter were detected on US scanning of the ovaries, with at least one ≥17 mm in		

			diameter, in the diameter, in the presence of serum e2 concentration >1,500 pmol/L. Oocyte retrieval was performed 35 h later. The technique of IVF, culture of oocytes and embryos, fertilisation and embryo transfer were described by Owen et al,1989.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Suikkari,A., MacLachlan,V., Koistinen,R., Seppä,lä, M, Healy,D., Double-blind placebo controlled study: human biosynthetic growth hormone for assisted reproductive technology, Fertility and Sterility, 65, 800-805, 1996 **Ref ID** 83155 **Country/ies where the study was carried out** Finland **Study type** Randomised controlled trial **Aim of the study** To investigate in a double-bline placebo-controlled study the dose-response effect of adjuvant biosynthetic human GH treatment with ovarian stimulation in known poor IVF responer patients. **Study dates** Not reported. **Source of funding** Kabi Pharmacia, Stockholm, Sweden, and grants from the Nordisk Forsknings Kimite and the Academy of Finland, Helsinki, Finland.	**Sample size** n = 22 women **Characteristics** Population: Ovulatory women that had had ≥2 previous cycles and were poor responders. Poor IVF responsiveness was determined as having ≤2 oocytes retrieved or ≥48 ampoules of hMG consumed in a stimulation cycle. Female mean age (range) = NR (25 - 40) years Duration of infertility = NR BM (range) = 19 - 27 kg/m^2 Cause of infertility: Male factor = 2 (9.1%) Tubal factor = 10 (45.5%) Endometriosis = 1 (4.5%) Unexplained = 9 (40.9%) **Inclusion criteria** Age 25 to 40 years BMI between 19 ad 27 kg/m^2 **Exclusion criteria** Medication for ≥2months before the treatment cycle.	GnRH agonist + metrodin + GH GnRH agonist + metrodin + placebo	Recruitment: A total of 22 women with previously determined need for IVF who had been poor IVF responders in at least two treatment cycles were recruited in randomised double-blind placebo-controlled fashion. All patients underwent clinical assessment before entering the study. None of the patients had hypertension, diabetes mellitus, thyroid disorder, hyperprolactinemia or history of acromegaly. Method: The patients were allocated randomly to the three groups. Intervention: A "boost" flare-up protocol was used for ovarian stimulation. The GnRH agonist leuprolide acetate administered sc. daily from day 2 of a spontaneous menstrual cycle. A venous blood sample was obtained after an overnight fast	Pregnancy Placebo (n = 6): 0/6 Human GH 4 IU (n = 10): 2/10 Human GH 12 IU (n = 6) : 0/6 Live birth full term singleton Placebo (n = 6): 0/6 Human GH 4 IU (n = 10): 1/10 Human GH 12 IU (n = 6) : 0/6 Multiple pregnancies Placebo: 0/6 women (0/0 pregnancies) Human GH 4 IU: 1/10 women (10%) (1/2 pregnancies, 50%, a triplet pregnancy) Human GH 12 IU: 0/6 women (0/0 pregnancies) Number of babies born from multiple pregnancies Placebo (n = 6): 0/0 babies Human GH 4 IU (n = 10): 1/2 (50%) babies Human GH 12 IU (n = 6) : 0/0 babies It is not clear whether the singleton birth was full-term or pre-term. The multiple birth was a triplet. The study does not report what happened to the two fetuses from the triplet pregnancy that were not born alive	**Limitations** Method of randomisation was not clearly stated No blinding reported. No power calculation reported and 12/22 patients (54.5%) did not reach embryo transfer, hence, a further reduction in sample size. Allocation concealment not reported. **Other information** No adverse effects to human GH were observed during the study

			immediately before daily morning injections for the measurements of E2, P, LH, GH, IGF-I, IGFBP-1, and IGFBP-3. The daily gonadotrophin and the human GH or placebo sc. were started on the morning of day 3. The gonadotrophin dose was maintained at 300 IU for at least 4 days, and was thereafter adjusted according to the serum E_2 measurements and follicular growth assessments. hCG was administered when the largest follicle or follicles reached a diameter of 18 to 20mm. Oocytes were retrieved by transvaginal aspiration of follicles 36 hours after the hCG injection. The oocytes were inseminated and embryo transfer was performed 2 days later.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Van,der Auwera,I, Meuleman,C., Koninckx,P.R., Human menopausal gonadotrophin increases pregnancy rate in comparison with clomiphene citrate during replacement cycles of frozen/thawed pronucleate ova, Human Reproduction, 9, 1556-1560, 1994 **Ref ID** 69107 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** To investigate the effect of both hMG and clomiphene/hMG ovulation induction protocols on the pregnancy rate in replacemanet cycles of frozen/thawed pronucleate ova. **Study dates** November 1991 - April 1993 **Source of funding** Not reported	**Sample size** n = 209 patients **Characteristics** Population: Ovulatory women having their first IVF attempt and had the infertility diagnoses listed below. Female mean age = 31.3 ± 0.4 years Duration of infertility = 5.2 ± 0.3 years BMI/ Weight = NR Cause of infertility: Male factor = 32 (15.3%) Tubal factor = 70 (33.5%) Unexplained = 37 (17.7%) Mixed = 26 (12.4%) Others = 44 (21%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	hMG and Clomiphene-hMG in replacement cycles of frozen/thawed pronucleate ova.	Recruitment: All patients who started an embryo replacement cycle within the study period were included. Method: The patients were randomised. Method of randomisation not reported Intervention: After randomisation, patients reveived either hMG daily from day 2 of the menstrual cycle or CC from day 2 - 6 and hMG from day 6 of the menstrual cycle. From day 7 onwards, ovulation induction was done on an individual basis with hCG. In case of a spontaneous LH surge with the presence of a mature follicle, an additional injection of hCG was given the same day. Pronucleate ova obtained in previous IVF cycles frozen by slow-freezing method were thawed at room temperature in synchrony with the age of the	Live full-term singleton birth hMG = 19/102 Clomiphene-hMG = 9/107 Clinical pregnancy hMG = 28/102 Clomiphene-hMG = 16/107 Adverse pregnancy outcome hMG = 5/102 Clomiphene-hMG = 4/107 Multiple births hMG = 8/102 Clomiphene-hMG = 6/107 Live birth was not defined. Figures reported may include pre-term and full term births 'Pregnancy' was not defined. Figures reported may reflect biochemical or clinical pregnancy. Adverse pregnancy outcome reported was miscarriage. The number of multiple pregnancies was not reported	**Limitations** Method of randomisation not reported. Allocation concealment not reported No blinding reported. There were 188 embryo transfers for 209 patients that were recruited, 21 patients were not accounted for at the end of the trial. It is not clear whether the study was adequately powered. **Other information** Routinely 3 embryos or less would be thawed and replaced but in 2 patients (over 38 years of age and very long duration of infertility), 4 embryos were transferred since they did not want further treatment after the transfer. This study used frozen embryos

			post-ovulatory endometrium i.e 64h after hCG and up to three embryos were replaced on the third day after hCG injection. On days 4, 7 and 10 after embryo transfer, all women received hCG together with daily vaginal suppositories containing 100mg/day progesterone as supplementation of luteal phase.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Weigert,M., Krischker,U., Pohl,M., Poschalko,G., Kindermann,C., Feichtinger,W., Comparison of stimulation with clomiphene citrate in combination with recombinant follicle-stimulating hormone and recombinant luteinizing hormone to stimulation with a gonadotropin-releasing hormone agonist protocol: a prospective, randomized study, Fertility and Sterility, 78, 34-39, 2002 **Ref ID** 69156 **Country/ies where the study was carried out** Austria **Study type** Randomised trial **Aim of the study** To compare IVF-ET outcome with a new stimulation protocol using CC with rFSH and LH to stimulation with the standard long GnRH-a protocol. **Study dates** Not reported **Source of funding** Supported by Serono Austria GmbH, Wienerbergstr	**Sample size** Study I 3 groups - n = 12 women (total n = 36) Study II n = 294 women **Characteristics** Population: Ovulatory women undergoing their first IVF or ICSI attempt with the infertility diagnoses listed below. Study I Women between 20 and 39 years Diagnosis of tubal infertility, male factor infertility, unexplained infertility - eligible Study II Female mean age = 32.8 ± 4.1 years Duration of infertility = NR BMI/ Weight = NR Cause of infertility: Male factor = 167 (56.8%) Tubal factor = 71 (23.8%) Endometriosis = 4 (1.4%) Unexplained = 29 (9.9%) Mixed factor = 21 (7.1%) **Inclusion criteria** Unclear **Exclusion criteria** Study I Chronic medical disease contraindication and/or allergy to study medicine BMI >30 or <20	Study I rFSH (300iU) rFSH (150iU) + LH(150iU) rFSH (225iU) + LH (75iU) Study II GnRH agonist + rFSH CC + rFSH + rLH	Study I Recruitment: Participants were recruited in an outpatient infertility clinic. Method: Randomisation of women in 3 study groups Intervention: Original protocol - two ampules hMG (approx 150 IU FSH amd 150 IU LH) on alternate days + CC 5 days Replaced with 3 study groups (below) - women pre-treated with OCP for 18-28 days. Prednisolone was given daily to supress DHEAS and T levels Group I - 4x 75IU rFSH Group II - 2x 75IU rFSH and 2x 75IU LH Group III - 3x 75IU rFSH and 1x 75IU LH Study II Recruitement: Participants were recruited in an outpatient infertility clinic.	Study I Clinical pregnancy rFSH (300iU) = 10% (1.2/12) rFSH (150iU) + LH(150iU) = 25% (3/12) rFSH (225iU) + LH (75iU) = 35% (4.2/12) Study II Clinical pregnancy GnRH agonist + rFSH = 41/140 CC + rFSH + rLH = 54/154 Adverse pregnancy outcome GnRH agonist + rFSH = 7/140 CC + rFSH + rLH = 10/154 OHSS GnRH agonist + rFSH = 12/140 CC + rFSH + rLH = 4/154 Figures for clinical pregnancy reflect 'normal pregnancy' which was defined as a positive fetal heart beat at 8 weeks on the ultrasound. Adverse pregnancy outcome reported were biochemical pregnancies and early pregnancy losses. OHSS was moderate and definition was not reported	**Limitations** No blinding of study participants, personnel and staff reported. No power calculation reported. Allocation concealment not reported **Other information** Cycles were cancelled if there was a low response (no evidence of follicle development on ultrasound on day 8), if the hormone levels were elevated at baseline (LH >8 IU/L; FSH >15 IU/L; E2 >50 pg/mL), if there was no fertilisation or if other causes developed, such as ovarian cysts, endometrial polyps, or hydrosalpinx. In total, 48 cycles were cancelled and 8 additional cycles did not progress to ET - in group A, 26 cycles were cancelled and 2 additional cycles (1.3%) did not progress to ET; in group B, 22 cycles were cancelled and 6 additional cycles (4.3%) did not progress to ET. However, there was no difference in cancellation rates between the two groups

	Baseline FSH level >15IU/L Study II Unclear		Method: Randomisation was achieved with a computer-generated list. Intervention: Patients in group A were stimulated with CC + rFSH + rLH and Prednisolone was given daily for 1 month. All women in this group were pretreated with oral contraceptive for 18 - 28 days. The patients also received oral dydrogesterone for luteal support. Patients in group B were started on buserelin nasal spray in the luteal phase of the preceding cycle. GnRH-a was continued until the hCG injection. Once suppression was achieved, rFSH was started. Injections were given everyday On day 8 of stimulation patients returned for ultrasound evaluation. Thereafter, the cycle was managed and monitored according		

			to routine IVF protcols. Ovulation was induced with hCG once the largest follicle was >18mm. Transvaginal oocyte retrieval was performed 35h after the hCG injection. Oocytes were inseminated or injected, in the case of ICSI, on the afternoon of the retrieval and transvaginal embryo transfer was performed on day 2 or 3		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ragni,G., De,LauretisYankowskiL, Piloni,S., Vegetti,W., Guermandi,E., Colombo,M., Crosignani,P.G., In vitro fertilization for patients with poor response and occult ovarian failure: A randomized trial, Reproductive Technologies, 10, 98-102, 2000 **Ref ID** 82951 **Country/ies where the study was carried out** Italy **Study type** Randomised clinical trial **Aim of the study** To compare the outcome in poor responders of IVF and ICSI and spontaneous cycles with IVF and ICSI in cycles stimulated by a daily GnRH agonist long protocol plus highly purified uFSH. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 14 women **Characteristics** Mean age (range) = 36.1 (32 - 40) years **Inclusion criteria** 1] Regular cycling patients with a previous poor response to an IVF or ICSI cycle **Exclusion criteria** Not reported	1] Natural cycle 2] GnRH agonist + uFSH	Method: Patients were randomly assigned to be treated using either spontaneous cycles or stimulated cycles. Intervention: Ovarian stimulation was achieved using a GnRH agonist administered daily and a daily dose of 450 IU of highly purified uFSH. GnRH agonist was started in the lmidluteal phase of the preceding cycle according to a long protocol schedule. After the menstrual cycle that followed GnRH agoniost administration and when pituitary desensitisation was achieved, administration of highly purified uFSH was initiarted. 10,000 IU of hCG were adminstered when at least one follicle had reached a diameter greater than 17 mm. Oocyte retrieval was performed 34 hours after hCG administration. Oocytes were	Clinical pregnancy: Natural cycle = 2/7 (28.6%) GnRH agonist +uFSH = 2/7 (28.6%) Pregnancy was assessed by ultrasound examination, and only viable pregnancies were considered (visualisation by ultrasound of gestational sac with cardiac embryo activity)	**Limitations** 1] Method of randomisation not reported 2] Allocation concealment not reported 3] Blinding not reported 4] Power calculation not reported **Other information**

			inseminated or microinjected 4 hours after pick-up. Viable embryos were transferred 48 hours after oocyte retrieval. Spontaneous cycles were monistored by daily ultrasound when the growing follicle reached a diameter of 17 mm, 500 IU of hCG were administered. The timing of oocyte retrieval in vitro inseminatiion, and embryo transfer time was identical to that used for stimulated cycles.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Battaglia,C., Regnani,G., Petraglia,F., Genazzani,A.R., Artini,P.G., Volpe,A., The use of a starting dose of recombinant follicle stimulating hormone for controlled ovarian hyperstimulation: a randomized pilot study2837, Gynecological Endocrinology, 14, 311-315, 2000 **Ref ID** 81814 **Country/ies where the study was carried out** Italy **Study type** Randomised clinical trial **Aim of the study** To analyse the costs and effects of two different COH treatments in normally ovulating patients undergoing ART: a starting dose of rFSH, following by highly purified uFSH (FSH-HP) or FSH-HP only. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 46 women **Characteristics** Mean age ± SD = 32.6 ± 3.8 years Duration of infertility = 6.2 ± 1.9 years **Inclusion criteria** 1] Women who had suffered from tubal infertility 2] Regular menstrual cycles (28 ±4 days) and their partners were fertile according to WHO standards. 3] <38 years of age with plasma FSH concentrations of <15 IU/l and estradiol levels <200 pmol/l on day 3 of the menstrual cycle and a normal uterine cavity. 4] The women had not received hormaonal treatment for at least 6 months before the IVF attempt **Exclusion criteria** 1] Patients with concurrent illness were excluded 2] BMI >30, endometriosis, ovarian functional cysts and PCOS 3] Patients who took regular exercise, heavy smokers (>10 cigarettes/day), and those with hypertension were excluded	1] rFSH +FSH-HP 2] FSH-HP	Randomisation was performed by opening sequentially sealed envelopes containing treatment allocation determined by a random number table. Intervention: After pituitary desensitisation obtained by an injection on day 20 of the cycle of i.m. GnRH agonist triptorelin, ovarian stimulation was achieved as follows: group 1 were given 225 IU i.m. of rFSH for the first 4 days of the trial, then FSH-HP in an individually assessed dosage; grou 2 were given 225 IU i.m of Metrodin 75 HP in an individually assessed dosage. The IVF cycles were cancelled when fewer than three follicles >12 mm in diameter were recruited by cycle day 8. When at least three follicles >17 mm in diameter were present, FSH was withdrawn and 10,000	Clinical pregnancy: rFSH +FSH-HP = 5/20 FSH-HP = 2/18 Multiple pregnancy/births: rFSH +FSH-HP = 0/20 FSH-HP = /18 OHSS: rFSH +FSH-HP = 0/20 FSH-HP = 0/18 1] All pregnancies were singleton and none of them aborted. A clinical pregnancy was diagnosed by ultrasonographic evidence of embryonic heart activity. 2] No cases of OHSS	**Limitations** 1] Blinding not reported 2] Power calculation not reported **Other information** 1] There were no ectopic pregnancies or miscarriages. Its not clear whether there were other adverse pregnancy outcomes. 2] In group 1, 3 cycles were cancelled because of inadequate follicular growth. In group 2 cancellations were due to inadequate follicular growth (n = 4) or risk of OHSS. 3] The cancellation rates were 13 and 22% respectively in the two groups.

			IU hCG were adminstered i.m. During the ovarian stimulation regimen the patients underwent transvaginal US evaluation of endometrial thickness and measurement of follicular number and size. US oocyte recovery was carried out transvaginally 35h after hCG injection.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tanbo,T., Dale,P.O., Abyholm,T., Recombinant follicle-stimulating hormone stimulates ovarian androgen synthesis in down-regulated ovulatory women, Gynecological Endocrinology, 15, 407-412, 2001 **Ref ID** 74808 **Country/ies where the study was carried out** Norway **Study type** Randomised clinical trial **Aim of the study** To examine to what extent the increased E_2 synthesis and secretion during rFSH stimulation in down-regulated patients for IVF is followed by a concomitant increase in ovarian androgen synthesis. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 50 women **Characteristics** Group 1 Mean age = 32.4 ± 3.6 years Weight = 62.9 ± 13.2 kg Group 2 Mean age = 31.8 ± 2.9 years Weight = 59.4 ± 13.3 kg **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] rFSH 2] uFSH	Randomisation was performed by drawing of sealed envelopes. All patients were down-regulated with busereling nasal spray from the mid luteal phase. After a minimum of 14 days, a withdrawal bleeding and an E_2 level of <0.2 nmol/l, FSH stimulatin was started, giving 150 - 225 IU daily initially and adjusting the dose according to response as evaluated by vaginal ultrasound examination and E_2 levels. Ovulation induction with 10,000 IU hCG s.c. was performed when at least three follicles >17 mm were observed. Oocyte retrieval was performed 34 hours later by vaginal ultrasound. In most cases 2 embryos were transferred on day two following oocyte retrieval.	Pregnancy: rFSH = 9/25 (36%) uFSH = 6/22 (27.3%) No definition of 'pregnancy' was reported	**Limitations** 1] 3/25 patients from the uFSH group withdrew from the study during the down-regulation period. The baseline characteristics measured after the withdrawal showed no difference between the two groups, however, the baseline characteristics before withdrawal was not reported. 2] No power calculation reported 3] No allocation concealment reported 4] No blinding reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Blockeel,C., De,Vos M., Verpoest,W., Stoop,D., Haentjens,P., Devroey,P., Can 200 IU of hCG replace recombinant FSH in the late follicular phase in a GnRH-antagonist cycle? A pilot study, Human Reproduction, 24, 2910-2916, 2009 **Ref ID** 73072 **Country/ies where the study was carried out** Belgium **Study type** Randomised clinical trial **Aim of the study** To compare a standard antagonist protocol (rFSH) with a modified treatment protocol with low dose hCG as a substitute for rFSH. **Study dates** September 2007 to October 2008 **Source of funding** Not reported	**Sample size** n = 70 women **Characteristics** Mean age = 29.8 ± 3.5 years Mean BMI = 22.7 ± 3.1 kg/m^2 **Inclusion criteria** Women below 36 years of age who underwent a first or second treatment cycle of IVF with ICSI. **Exclusion criteria** 1] Patients were excluded from the study if they requested PGD 2] Azoospermic partner or serum FSH level on Day 3 of the menstrual cycle of more than 12 IU/l.	1] rFSH stand treatment group 2] rFSH + low-dose hCG treatment group	Recruitment:The study was conducted in 70 normogonadotrophic women seeking infertility treatment within the study period to compare two protocols for COS with antagonists. Methods: Randomisation was performed at the outpatient clinic, when the results of the pretreatment hormonal analyses were discussed with the patient. A computer-generated list was used for randomisation, concealed to the physician but not to the study nurse. Intervention: The GnRH antagonist protocol with rFSH has been described elsewhere (Papanikolaou et al., 2005a, b). On day 2 of menstural cycle, daily injections of rFSH, were initiated at a dose of 200 IU/day and maintained for 6 consecutive days. On	Live birth: rFSH = 8/35 rFSH + hCG = 11/35 Miscarriage: rFSH = 3/35 rFSH + hCG = 3/35 Ectopic: rFSH = 1/35 rFSH + hCG = 0/35 Biochemical pregnancy: rFSH = 5/35 rFSH + hCG = 1/35	**Limitations** 1] Blinding was not reported 2] The study was not powered to detect a difference in pregnancy outcome between the two groups **Other information** Ongoing pregnancy was reported as rFSH group = 2/35 and hCG group = 2/35 but it is not clear how these figures were calculated since they are less than the number of live births.

			day 7 of the cycle, s.c administration of the GnRH antagonist ganirelis was started at a daily dose of 0.25 mg. In the hCG group, the administration of rFSH was discontinued when at least 6 follicles of ≥12 mm were observed and E_2 levels were higher than 600ng/l. rFSH was then substituted by 200 IU hCG daily, until final oocyte maturation. Final oocyte maturation was induced by the administration of 10,000 IU of hCG, when at least three follicles of 17 mm of diameter were visualised on ultrasonography. Cumulus-oocyte-complexes were collected 36h after pregnyle administration. Luteal phase support consisted of 600mg of vaginally administered micronised natural progesterone per day. A single embryo transfer policy was		

			applied in all cycles. Statistical analysis: Assuming an anticipated ongoing pregnancy rate for both treatment options of at least 30%, as observed in our current day-to-day clinical practice, and referring to sample size determination procedures as described by Simon et al. 1985 for pilot trials in cancer research, sample size of 35 patients can provide a 90% probability of selecting a promising treatment option that has a true response rate of 45% (By comparison, for a randomised equivalence trial, the sample size needed to demonstrate equivalence within 10% of the standard with 90% power at 5% significance level is 454 per arm)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Griesinger,G., Schultze-Mosgau,A., Dafopoulos,K., Schroeder,A., Schroer,A., von,Otte S., Hornung,D., Diedrich,K., Felberbaum,R., Recombinant luteinizing hormone supplementation to recombinant follicle-stimulating hormone induced ovarian hyperstimulation in the GnRH-antagonist multiple-dose protocol, Human Reproduction, 20, 1200-1206, 2005 **Ref ID** 54296 **Country/ies where the study was carried out** **Study type** Randomised controlled trial **Aim of the study** To assess a starting dose of 150 IU rFSH vs 150 IU rFSH plus 75 IU rLH for controlled ovarian hyperstimulatioin in the GnRH-antagonist multiple-dose protocol. **Study dates** June 2003 to May 2004 **Source of funding** Not reported	**Sample size** n = 127 women **Characteristics** Mean age = 30.4 ± 4.4 years Mean BMI = 24.1 ± 4.2 kg/m^2 Duration of infertility = 4.2 ± 2.8 years Cause of infertility: Tubal factor = 16 (13%) Male factor = 66 (52%) Mixed causes = 22 (17.3%) Other causes = 23 (18.1%) **Inclusion criteria** 1] Indication for treatment with IVF or ICSI. 2] Age between 20 and 39 years 3] BMI between 18 to 35 kg/m^2 4] Regular menstrual cycle ranging from 24 to 35 days 5] Intra-individual cycle variability of ≤3 days 6] Use of fresh as well as frozen-thawed sperm retrieved by testicular biopsy. **Exclusion criteria** 1] >3 previous unsuccessful assisted reproduction technique attempts 2] Previous poor response to gonadotrophin stimulation defined as <3 preovulatory follicles 3] History of OHSS grade II - III 4] PCOS, any other endocrine disorder 5] No natural luteal phase prior to treatment cycle 6] Abnormal uterine cavity as evaluated by ultrasonography 7] Presence of a clinically significant	1] rFSH 2] rFSH/rLH	Method: The randomisation process was conducted by drawing sealed envelopes and patients were free to start ovarian stimulation within the next three spontaneous menstrual cycles after randomisation. Intervention: Ovarian stimulation started on day 2 of the natural cycle with 150 IU rFSH in the control group (rFSH group), and 150 IU rFSH plus 75 IU rLH in the study group. All injections were given one daily s.c in the morning by the patient. After 5 days of gonadotropin treatment, GnRH antagonist cetrorelix 0.25 mg administration was started by one daily s.c injection in the morning. Gonadotropin and antagonist treatment was continued up to and including the day of hCG administration. rHCG 250 µg was administered s.c. as	Clinical pregnancy: rFSH = 12/65 (18.5%) rFSH/rLH = 8/62 (12.9%) Adverse pregnancy outcome: rFSH = 3/65 (4.6%) rFSH/rLH = 8/65 1] Clinical pregnancy was defined as an ongoing pregnancy at 12 weeks of gestation 2] Figures for 'Adverse pregnancy outcome' reflect miscarriages before 12 weeks of gestation. Miscarriages in the rFSH/rLH group includes 1/8 extrauterine gravidity (treated by laparoscopy)	**Limitations** 1] Method of randomisation was not reported 2] Blinding was not reported 3] The study was not powered to detect difference in pregnancy outcomes **Other information**

	systemic disease.		soon as three follicles were ≥18 mm in diameter, and 34 to 36 h thereafter oocyte retrieval was performed. After IVF or ICSI according to standard procedures, no more than three embryos were to be replaced on day 2 after oocyte retrieval. Luteal phase support started the morning after oocyte retrieval and was provided with daily 90mg micronised progesterone. Additionally, 5000 IU urinary hCG were administered once on the day of embryo transfer in case E_2 levels on the day of hCG were ≤2500 pg/ml. Statistical analysis: The study was powered to detect a difference of 1 day between the two treatment modalities. In a previous GnRH antagonist multiple-dose trial with a similar ovarian stimulation study protocol and similar		

			patient population, the number of days of gonadotropin stimulation was 12.04 ± 1.7 in the GnRH antagonist multiple-dose protocol study arm with rFSH for ovarian stimulation and a fixed start of the antagonist on day 6. Group sample sizes of 47 and 47 patients who reach hCG administration achieve 81% power to detect a difference of 1 day in the number of gonadotropin treatment days between the null hypothesis that both group means are 12.0 days and the alternative hypothesis that the mean of group 2 is 11.0 days with assumed group SD of 1.7 and 1.7 and with a significance level of 0.05 using a two-sided two-sample t-test.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Klinkert,E.R., Broekmans,F.J., Looman,C.W., Habbema,J.D., te Velde,E.R., Expected poor responders on the basis of an antral follicle count do not benefit from a higher starting dose of gonadotrophins in IVF treatment: a randomized controlled trial, Human Reproduction, 20, 611-615, 2005 **Ref ID** 73948 **Country/ies where the study was carried out** **Study type** Randomised clinical trial **Aim of the study** To evaluate the effect of doubling the starting dose of gonadotrophins on the ovarian response in IVF patients with a low AFC. **Study dates** May 2001 and November 2002 **Source of funding** Not reported	**Sample size** n = 52 women **Characteristics** Mean age (range) = 41.3 (33.7 - 44.6) years Mean BMI (range) = 21.5 (19.1 - 30.5) kg/m^2 Duration of infertility = 3.0 (1.0 - 5.5) years Cause of infertility: Tubal factor = 14 (27%) Male factor = 22 (42%) Unexplained = 16 (31%) **Inclusion criteria** 1] Patients who were normally excluded from IVF treatment at the centre because of age (41-46 years) or basal FSH (>15 IU/) 2] <5 follicles on ultrasound. 3] Regular spontaneous menstrual cycle of 25 to 35 days 4] Presence of both ovaries **Exclusion criteria** Patients with large ovarian cysts	1] 150 IU rFSH 2] 300 IU rFSH	Recruitment: All 520 women who started their first IVF treatment in the study centre within the study period underwent an AFC just prior to the start of the hyperstimulation with gonadotrophins. Method: Patients that met the inclusion criteria were randomised by opening a sealed envelope that contained information on the starting dose: 150 IU of rFSH (standard dose, group I) or 300 IU of rFSH (study dose, group II) Intervention: The stimulation protocol that has been used was a long suppression protocol. In the midluteal phase, pituitary desensitisation was started by leuprolide acetate injections. After menstruation, the ovarian stimulation was started with either the standard dose of 150 IU or the double	Clinical pregnancy: 150 IU rFSH = 3/26 300 IU rFSH = 1/26 Multiple pregnancy: 150 IU rFSH = 0/26 300 IU rFSH = 0/26 Adverse pregnancy: 150 IU rFSH = 1/26 300 IU rFSH = 0/26 OHSS: 150 IU rFSH = 0/26 300 IU rFSH = 0/26 1] No definition of clinical pregnancy was reported. 2] Figures for adverse pregnancy reflect the difference in figure between clinical and ongoing pregnancy.	**Limitations** 1] It is not clear whether the method of randomisation was adequate. 2] Allocation concealment not reported. 3] Blinding not reported 4] The study was not powered to detect difference in pregnancy outcome between both groups. **Other information** 1] In nine of the patients who started with 150 IU, the dose had to be increased to 300 IU due to an insufficient response. Despite this dose adjustment, all these patients remained poor responders according to the definition applied (<4 oocytes)

			dose of 300 IU of follitropin alpha. In patients who were stimulated with the standard dose of 150 IU of rFSH, the dose was doubled after 7 days of stimulation if the estradiol level was <200 pmol/l or after 10 days if the estradiol level was <500 pmol/l, based on our clinical practice. In group II, the dose remained fixed. hCG was administered 36h before the transvaginal oocyte collection. The maximum number of embryos repolaced was two in women aged <38 years and three in older women. The luteal phase was supported by hCG or micronised progesterone. Statistical analysis: The study was designed to detect a difference of two oocytes with a standard deviation of 3.5 oocytes. For this purpose a total number of 50 cases		

			was needed (power of 80% and a significance level of 5%)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation Drakakis,P., Loutradis,D., Beloukas,A., Sypsa,V., Anastasiadou,V., Kalofolias,G., Arabatzi,H., Kiapekou,E., Stefanidis,K., Paraskevis,D., Makrigiannakis,A., Hatzakis,A., Antsaklis,A., Early hCG addition to rFSH for ovarian stimulation in IVF provides better results and the cDNA copies of the hCG receptor may be an indicator of successful stimulation, Reproductive Biology and Endocrinology, 7, 110-, 2009 **Ref ID** 53967 **Country/ies where the study was carried out** **Study type** Randomised clinical trial **Aim of the study** To determine whether low dose hCG added to rFSH in gefimens of ovarian stimulation could produce better results compared to the addition of rLH in women entering IVF-ET, especially in those women who had previous IVF failures. An additional aim was to find an indicator that would allow follow-up of the ovarian stimulation and, possibly, predict a better IVF outcome in some women that may lead to the modification of the stimulation; and that indicator may be the cDNA copies of the LH/hCG receptor. **Study dates** January 2007 to December 2007 **Source of funding**	**Sample size** n = 120 women **Characteristics** Mean age = 36.8 ± 3.3 years Mean BMI = 23.2 ± 3.2 kg/m^2 Duration of infertility = 6.8 ± 2.5 years Cause of infertility: Tubal factor = 112 (93.3%) Male factor = 76 (63.3%) Other = 12 (10%) **Inclusion criteria** 1] Age between 36 and 42 years old 2] BMI of 32 or less 3] Menstrual cycle lasting between 21 and 35 days 4] normal serum levels of FSH, prolacting and TSH 5] Normal uterine cavity confirmed by hysteroscopy or hysterosalpingography 6] No treatment with clomiphene citrate or gonadotrophins for at least 3 months before screening. **Exclusion criteria** Not reported	1] hCG + rFSH 2] rLH + rFSH	Method: The randomisation scheme was prepared by a computer using Proc PLAN in SAS version 6.12. Patients were randomly assigned to rLH or hCG treatment according to balanced blocks of four subjects. Intervention: Commercially available GnRH antagonist was self-administered subcutaneously into the thigh at a dose of 200 µg/day, starting on the 2nd day of the menstrual cycle and continuing until 24 h before the administration of hCG. Treatment with rFSH was started on the third day of the menstrual cycle with 200 IU and continued until the administration of hCG for ovulation induction. rFSH was administered once daily as a s.c injection in the abdomen. In group A patients, 200 IU of hCG were also	Clinical pregnancy: hCG = 16/60 (26.7%) rLH = 6/60 (10%) 1] Clinical pregnancy: endometrial gestational sac with a transvaginal ultrasound scan.	**Limitations** 1] No blinding 2] No allocation concealment 3] Power calculation not reported **Other information** 1] 6/120 women failed to complete the study (two at risk of OHSS and four failed to develop a follicle with a mean diamter of at least 17 mm)

Not reported			administered sc for the first five days of ovarian stimulation. In group B patients, 200 IU of rLH were administered sc for the same number of days. Ovulation was induced with 10,000 IU of hCG within 24h after the last rFSH and GnRH antagonist administration. Oocytes were retrieved by regular follicle aspiration 34 to 38 h after hCG injection. From one to three embryos were replaced in the uterine cavity on day 2 or 3 after OPU. Micronised progesterone was administered by the vaginal route as luteal phase support starting after oocyte collection.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Balasch,J., Fabregues,F., Creus,M., Moreno,V., Puerto,B., Penarrubia,J., Carmona,F., Vanrell,J.A., Pure and highly purified follicle-stimulating hormone alone or in combination with human menopausal gonadotrophin for ovarian stimulation after pituitary suppression in in-vitro fertilization, Human Reproduction, 11, 2400-2404, 1996 **Ref ID** 72972 **Country/ies where the study was carried out** Spain **Study type** Randomised clinical trial **Aim of the study** To compare the efficacy of a combined therapy of uFSH and hMG with pFSH alone and FSH-HP alone for stimulating multiple ovarian follicular development in whomen undergoing IVF-embryo transfer. **Study dates** Not reported **Source of funding** Not reported	**Sample size** Study 1: n = 188 women Study 2: n = 252 women **Characteristics** <u>Study I</u> Mean age = 33.9 ± 3.2 years Mean BMI = 23.5 ± 2.3 kg/m^2 Duration of infertility = 6.8 ± 3.5 years Cause of infertility: Tubal factor = 92 (48.9%) Male factor = 20 (10.6%) Unexplained = 40 (21.3%) Endometriosis = 26 (14.2%) <u>Study II</u> Mean age = 33.5 ± 3.3 years Mean BMI = 23.2 ± 2.4 kg/m^2 Duration of infertility = 6.4 ± 2.9 Cause of infertility: Tubal factor = 104 (41%) Male factor = 41 (16%) Unexplained = 55 (22%) Endometriosis = 52 (21%) **Inclusion criteria** 1] Premenopausal women aged 23 - 39 years with no ovarian failure according to FSH concentrations <12 mIU/ml **Exclusion criteria** Not reported	Study I 1] pFSH 2] pFSH +hMG Study II 1] FSH-HP 2] FSH-HP + hMG	Recruitment: The report shows the results of two successive randomised prospective studies including IVF patients. The study populations consisted of two groups of 188 (study I) and 252 (study II) consecutive patients respectively, scheduled for IVF-ET Method: For the specific purpose of the present investigation patients were allocated to a gonadotrophin treatment group according to a computer-generated randomisation table. Intervention: The scheme of gonadotrophin administration was the same in the four groups studied. On days 1 and 2 of ovarian stimulation 3 ampoules per day of hMG were administered together with three ampoules of either pFSH or FSH-HP. Patients included in	<u>Study I</u> Clinical pregnancy: pFSH = 13/92 (14.1%) pFSH +hMG = 11/96 (11.5%) Clinical abortion: pFSH = 2/92 (2.2%) pFSH +hMG = 2/96 (2.1%) OHSS: pFSH = 1/92 pFSH +hMG = 2/96 <u>Study II</u> Clinical pregnancy: FSH-HP = 16/123 (13%) FSH-HP +hMG = 21/129 (16.3%) Clinical abortion: FSH-HP = 2/123 (1.6%) FSH-HP +hMG = 4/129 (3.1%) OHSS: FSH-HP = 2/123 (13%) FSH-HP +hMG = 3/129 (16.3%)	**Limitations** 1] Allocation concealment not reported 2] Blinding not reported 3] The study was not powered for pregnancy outcomes **Other information** 1] No definition of clinical pregnancy was reported

			groups pFSH and FSH-HP were given 6 ampoules daily of these respective gonadotrophin preparations on days 1 and 2 of ovulation induction therapy. On days 3 - 7 of ovarian stimulation, two ampoules per day of hMG, pFSH or FSH-HP were administered to each patient. From day 8 onward, each gonadotrophin preparation was administered on an individual basis according to the ovarian response. The criteria for hCG administration were the presence of two or more follicles .17 mm in diameter and oestradiol concentrations >800 pg/ml. Oocte aspiration was performed by vaginal ultrasonography 35 to 37 h after hCG administration under local anaesthesia. Up to four embryos were replaced and the remaining were cryopreserved.		

			Additional doses of 5000, 2500 and 2500 IU hCG were given on the day of follicle aspiration and 2 and 5 days later, respectively, to supplement the luteal phase in all patients. In patients with serum oestradiol concentrations >4000 pg/ml, hCG support was withheld to reduce the risk of OHSS. Statistical analysis: The sample size (<90 patients/group) was calculated assuming a power of 80% to detect a difference of 20% between groups in the number of oocytes retrieved, with a type I risk of 0.05.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Harrison,R.F., Kondaveeti,U., Barry-Kinsella,C., Gordon,A., Drudy,L., Cottell,E., Hennelly,B., Frankish,A., Unwin,A., Should gonadotropin-releasing hormone down-regulation therapy be routine in in vitro fertilization?, Fertility and Sterility, 62, 568-573, 1994 **Ref ID** 68409 **Country/ies where the study was carried out** Ireland **Study type** Randomised clinical trial **Aim of the study** To compare the classic CC and hMG regime for ovarian stimulation before IVF in women who received hMG post-long protocol down-regulation with either 3 mg triptorelin IM or 150 mg busereline acetate four times daily intranasally. Furthermore, if possible, to determine the preferred method of down-regulation **Study dates** January 4, 1992 to September 1, 1993 **Source of funding** Supported by Ipsen Biotech, Dublin, Ireland.	**Sample size** n = 150 women **Characteristics** Triptorelin vs CC (n = 100) Female mean age = 34.1 ± 3.8 years Duration of infertility = 4.9 ± 4.0 years Buserelin vs CC (n = 100) Female mean age = 34.3 ± 3.3 years Duration of infertility = 5.0 ± 4.0 years Cause of infertility: Tubal factor = 21 (14%) Male factor = 17 (11.3%) Endometriosis = 51 (34%) Unexplained = 60 (40.7%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] Triptorelin (n = 50) 2] Buserelin (n = 50) 3] CC (n = 50)	Methods:They were randomised into three groups of 50 patients each by the Hospital Pharmacist in accordance with a computer-gnerated randomisation code blind to the clinicians. Intervention: Group A received 3 mg triptorelin IM from day 1 of the cycle. hMG 225 IU IM was given daily from when down-regulatio was achieved. Group B was prescribed 100 mg CC daily for 5 days from day 2 of the cycle from hMG 150 IU IM daily from day 4. Group C took buserelin acetate to down-regulated at a dosage of 150 mg intranasally four times daily from day 1. hMG 225 IU IM was given daily from when down-regulation was achieved. hCG 10.000 IU IM was administered when the leading follicle reached 17 mm as measured by ultrasound. Luteal support was given in	<u>Triptorelin vs CC</u> Multiple pregnancy: Triptorelin = 5/50 (10%) CC = 3/50 (6%) Pregnancy loss: Triptorelin = 3/50 (6%) CC = 4/50 (8%) <u>Buserelin vs CC</u> Multiple pregnancy: Buserelin = 5/50 (10%) CC = 3/50 (6%) Pregnancy loss: Buserelin = 3/50 (6%) CC = 4/50 (8%)	**Limitations** 1] Power calculation not reported. **Other information** 1] 'Take-home baby rate' per ET was Group A = 31%, Group B = 34%, Group C = 34%. This may include both singletons and multiples. 2] Clinical pregnancy was reported in the paper as 'pregnancy rate' (ultrasonographically confirmed). Group A = 38.9%, Group B = 45.7%, Group C = 41.5% per ET 3] 14% of group B (CC) had minor complications associated with hMG therapy compared with 4% of group A (triptorelin) and 8% of group C (buserelin).

			each case where ET took place. When <10 oocytes were harvested, hCG 5.000 IU IM was administered on the day of ET and 2 days afterward. To diminish the possibility of OHSS , when over 10 oocytes were collected, 200 mg cyclogest pessaries daily were administered per vaginum for 14 days.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation de,Jong D., Macklon,N.S., Fauser,B.C., A pilot study involving minimal ovarian stimulation for in vitro fertilization: extending the "follicle-stimulating hormone window" combined with the gonadotropin-releasing hormone antagonist cetrorelix, Fertility and Sterility, 73, 1051-1054, 2000 **Ref ID** 73336 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised clinical trial **Aim of the study** To determine whether a minimal intervention during the middle to late folliclular phase, designed to extend the duration of the "FSH window", results in multiple dominant follicle development sufficient for IVF. **Study dates** Not reported. **Source of funding** Supported by the "Stichting Voortplantingsgeneeskunde Rotterdam," Rotterdam, the Netherlands.	**Sample size** n = 15 randomised patients n = 12 treated patients. **Characteristics** Median age (range) = 32 (25 - 37) years Mean BMI = Not reported Duration of infertility = Not reported Cause of infertility: Not reported **Inclusion criteria** Women <38 years of age. **Exclusion criteria** 1] Insufficient response to ovarian stimulation (defined as <3 follicles ≥15 mm)	1] 100 IU rFSH 2] 200 IU rFSH	Recruitment:A total of 15 normo-oulatory women <38 years of age who enrolled in the IVG program were included and studied during a single IVG treatment cycle. Method:Before ovarian stimulation, the subjects were randomly assigned (with sealed envelopes) to one of the two stimulation regimens. Intervention: Patients received either 100 IU or 150 IU of rFSH from cycle day 5 onward until the day hCG was administered. Participants in both groups were also trated with a GnRHa from cycle day 8 onward then ≥1 follicle of 13 mm was present. Otherwise, cetrorelix administration was postponed. When ≥1 follicle of ≥18 mm and three follicles of ≥15 mm were observed on transvaginal US 10,000 IU of hCG was administered to trigger	Viable pregnancy: 100 IU FSH= 2/8 (25%) 200 IU FSH= 1/7 (14%) Viable pregnancy was defined as positive fetal heart activity observed by transvaginal US 5 - 6 weeks after ET.	**Limitations** 1] Method of randomisation was not described 2] Blinding not reported 3] Power calculation was not done. **Other information** 4/8 women in the low dose group underwent ET while 5/7 women in the high-dose group underwent ET.

			the final stages of oocyte maturation. No luteal phase support was provided. Oocytes were collected 36 hours after hCG administration. A maximum of two embryos was transferred on days 3 - 5 after oocyte retrieval. Statistical analysis: No power calculation reported.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hojgaard,A., Ingerslev,H.J., Dinesen,J., Friendly IVF: Patient opinions, Human Reproduction, 16, 1391-1396, 2001 **Ref ID** 68437 **Country/ies where the study was carried out** Denmark **Study type** Questionnaire study **Aim of the study** To evaluate how the patients balance advantages and disadvantages of low stimulation regimens in terms of unstimulated cycles or clomiphene for IVF versus a long down-regulation protocol with GnRH analogue and FSH. **Study dates** Not reported **Source of funding** Funded by the Danish Institute for Health Technology Assessment	**Sample size** n = 283 women Low stimulation group = 167 women Standard IVF group = 116 women. **Characteristics** Previously reported by Ingerslev et al., 2001 **Inclusion criteria** Previously reported by Ingerslev et al., 2001 **Exclusion criteria** Previously reported by Ingerslev et al., 2001	1] Low stimulation group (LS-IVF) - CC or Unstimulated IVF 2] Standard IVF (S-IVF) - GnRH analogue and FSH or hMG	Recruitment: Two patient groups receiving either a low stimulation type regimen or a long down-regulation protocol were approached by a questionnaire. In addition to treatment-specific questions they were asked general questionson subjects related to overall satisfaction with the clinic to evaluate if the two patient grouups studied were comparable in this aspect. Method: A 23-item questionnaire was designed to answer questions about patient satisfaction and stress throughout IVF treatments. The questions in the final questionnaire related to the latest treatment cycle and to satisfaction with the amount of information and preferences of treatment. Finally, respondents were	Patient satisfaction: LS-IVF = 139/141 (99%) S-IVF = 60/64 (94%) Side-effects of hormone treatment (unacceptable/severe): LS-IVF = 4/75 (5%) S-IVF = 38/63 (60%) Stress from hormone treatment (unacceptable/severe): LS-IVF = 2/73 (3%) S-IVF = 15/65 (23%) Painfrom oocyte retrieval (unacceptable/severe): LS-IVF = 45/130 (35%) S-IVF = 27/64 (42%) Preferences of future treatments LS-IVF treatment: LS-IVF = 50/135 (37%) S-IVF = 3/60 (5%) S-IVF treamtent: LS-IVF = 10/143 (7%) S-IVF = 30/63 (48%)	**Limitations** 1] Response rate was significantly higher in the LS-IVF group compared with the S-IVF group. 2] The information on side effects of the different treatment types may have resulted in a possible biase towards the LS-IVF protocol. **Other information** 1] The mean number of started cycles was comparable in both groups. 2] There was no significant difference between pregnant and non-pregnant responders.

			encouraged to comment on the treament. Scores were measured on a five-point Likert-type scale. Satisfaction concerning information was rated on a scale as follows: very satisfied, satisfied, neutral/do not kno, dissatisfied, very disatisfied. The respondents were asked to characterise the information given as: to optimistic, realisitc or too pessimistic. Stress, physical pain and side-effects were rated in the following way: unacceptably severe, sever, acceptable, mild, none. The importance of a question was measured on a three-point scale: very important, important and unimportant. Since the patients in the two groups had no experience as to the alternative tratment protocol, a short neutral description of		

			LS-IVF and S-IVF regimens was offered in the questionnaire. Intervention groups: For the present study, the 167 patients enrolled in the pilot study and the previously published series wee selected. During 1997 and 1998, the 167 patients received a total of 452 LS-IVF cycles of which 153 were unstimulated IVF cycles and 299 were stimulated with CC. For the S-IVF, among all couples having received their first and subsequent IVF cycles following the long down-regulatin protocol (GnRH analogue and FSH or hMG), 116 couples fulfilled the same criteria as in the LS-IVF group and had a total of 190 treatments during the period.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Popovic-Todorovic,B., Loft,A., Bredkjaeer,H.E., Bangsboll,S., Nielsen,I.K., Andersen,A.N., A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment, Human Reproduction, 18, 2275-2282, 2003 **Ref ID** 74488 **Country/ies where the study was carried out** Denmark **Study type** Randomised dual-centre trial. **Aim of the study** To compare the use of a standard dose of rFSH of 150 IU/day with an individual dose between 100 and 250 IU/day, calculated on the basis of the rFSH dose normogram. **Study dates** January 2002 to January 2003. **Source of funding** Not reported.	**Sample size** n = 262 women **Characteristics** Mean age ± SD = 32.3 ± 3.8 years Mean BMI ± SD = 22.8 ± 3.2 kg/m^2 Mean duration of infertility = Not reported Cause of infertility: Tubal factor = 74 (28.2%) Male factor = 154 (58.8%) Unexplained = 36 (13.7%) Other causes = 5 (1.9%) **Inclusion criteria** 1] First IVF/ICSI treatment cycle. 2] Normal basal serum FSH level (with current assays, up to 12.3 IU/l) 3] Presence of both ovaries 4] Regular spontaneous menstrual cycle (21-35 days) 5] Maximum age 39 years at the onset of treatment 6] No evidence of endocrine disorders. **Exclusion criteria** Presence of ovarian cysts and inaccessible ovaries.	1] Individual dose - 100-250 IU/day rFSH 2] Standard dose - 150 IU/day rFSH	Method: On the first day of stimulation, patients were randomised via computer-gnerated lists using 'clusters of 10'. Randomisation was carried out after the US examination, whenthe patient was considered ready to start stimulation. The randomisation system was open, but handled independently of the clinicians treating the patients. Intervention: All patients were treated with the long protocol using nafarelin 200 µg administeed intranasally 3 times daily during down-regulation, beginning on day 21 of the cycle, and with 200 µg twice daily from day 1 of rFSH stimulation until the day of hCG treatment. The duration of down-regulation was at least 14 days. The study group received an individual starting dose of 100-250	Clinical pregnancy 100-250 IU dose: 48/131 (37%) 150 IU dose: 32/131 (24%) Figures for 'Clinical pregnancy' reflect 'Ongoing pregnancy' and no definition was provided. Adverse pregnancy outcome 100-250 IU dose: 11/131 (8%) 150 IU dose: 15/131 (11%) Adverse pregnancy outcomes were biochemical pregnancy, abortion and extrauterine pregnancy. Pain: (mean VAS scale value) 100-250 IU dose: 3.1 (n = 120 patients) 150 IU dose: 3.2 (n = 122 patients)	**Limitations** 1] Allocation concealment not reported 2] Blinding was not clear. 3] Power calculation was not reported for pregnancy outcomes. **Other information** 1] Some patients may have had more than one cause of infertility. 2] Patients in the standard dose group had significantly higher abortion rates than those in the individual dose group. 3] No case of OHSS reported however there were 3 cases of risk of OHSS in the standard dose group that led to cycle cancellation but none in the individual dose group.

			IU/day rFSH, while the control group were allocated to the standard starting dose of 150 IU/day rFSH. The dose was maintained during the first 8 days of stimulation. The ovarian respose was assessed on day 8 of stimulation. Dose adjustments were allowed after day 8 stimulation. The rFSH dose was reduced if a risk of developing an excessive number of follicles (>20) was acknolwedged. Aspiration was performed at 36h after hCG administration. The number of follicles aspirated and oocytes retrieved were recorded during aspiration. Standard IVG and ICSI procedures were used, and the embryos were transferred on day 2. Four-cell embryos with <20% fragmentation were considered to be good quality		

			embryos. All patients were treated ith vaginal progesteron 200mg three times daily from the day of embryo transfer until hCG evaluation 14 days later. No further progesteron suplementation was administered. Patients were asked to score any associated pain and discomfort at 1 week after aspiration by using a VAS. The VAS allowed patients to grade their perceived intensity of pain on a line between 0 and 100mm Statistical analysis:Having arbitrarily defined appropriate responses as the retrieval of 5 - 14 oocytes, the last 2442 cycles at the Fertility clinic were analysed. Sample size calculation showed that with 125 patients in each treatment group, a 15% increase in the		

			incidence of an appropriate response could be detected between the study and the control group with a power of 80% using a two-sided chi-square test and a significance threshold of 5%.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation De,Placido G., Mollo,A., Alviggi,C., Strina,I., Varricchio,M.T., Ranieri,A., Colacurci,N., Tolino,A., Wilding,M., Rescue of IVF cycles by HMG in pituitary down-regulated normogonadotrophic young women characterized by a poor initial response to recombinant FSH, Human Reproduction, 16, 1875-1879, 2001 **Ref ID** 73345 **Country/ies where the study was carried out** Italy **Study type** Randomised clinical trial **Aim of the study** To investigate the effects of adding hMG during controlled ovarian stimulation in normoovulatory normogonadotrophic patients showing an intital suboptimal response to a standardised long protocol therapy with rFSH. **Study dates** November 1999 to July 2000 **Source of funding** Not reported	**Sample size** n = 43 women **Characteristics** Mean age = 31.0 ± 3.8 years Mean BMI = 22.9 ± 2.7 kg/m^2 Duration of infertility = 6.4 ± 3.2 years Cause of infertility: Tubal factor = 14 (34%) Male factor = 15 (35%) Mixed factors = 7 (16%) Other = 7 (16%) **Inclusion criteria** 1] Menstrual cycles in the range of 24 - 35 days as well as hysteroscopic evidence of a normal uterine cavity **Exclusion criteria** 1] Elevated basal FSH concentrations 2] Age ≥37 years 3] BMI >29 4] Biochemical and/or ultrasound evidence of PCOS 5] Stage III-IV endometriosis 6] Auto-immune, thyroid, and chromosomal abnormalities 7] Presence of only one ovary	1] rFSH +hMG 2] rFSH	Recruitment: All patients undergoing their first ICSI attempt within the study period were enrolled. Method: On the eighth day of stimulation, patients with serum oestradiol concentrations ≤0.6 pmol/ml and ultrasound evidence of no follicles with a mean diameter >10 mm were randomised into two groups using random number tables. Intervention: Pituitary desensitisation was induced with triptorelin on the first day of the menstrual cycle. After 15 days, pituitary suppression was assessed by measuring serum oestradiol and LH concentrations; endometrial and ovarian status was also assessed by transvaginal ultrasound. A fixed dose of 150 IU of rFSH was administered s.c. twice daily as per the	Pregnancy: rFSH + hMG = 10/20 (50%) rFSH = 8/23 (34.8%) Abortions: rFSH + hMG = 1/20 (5%) rFSH = 2/23 (8.7%)	**Limitations** 1] Blinding not reported 2] Allocation concealment not reported 3] Power calculation not reported **Other information** No definition of pregnancy was reported.

			clinic routine. On the fifth day of stimulation, serum oestradiol was measured at 8.00 am and the evening rFSH dose was reduced to 75 IU in patients whose concentrations were >0.6 pmol/ml. In group A, the evening rFSH dose was substitued by 150 IU of hMG. The stimulation regime of Group B involved the increase of the evening rFSH dose to 225 IU. When 3 follicles measured at least 17 mm in diameter, hCG was administered. Oocytes were retrieved by trans-vaginal ultrasound guided aspiration 35h after the hCG injection. Patients began 50 mg/day i.m. progesterone supplementation on the day of oocyte retrieval.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Koundouros,S.N., A comparison study of a novel stimulation protocol and the conventional low dose step-up and step-down regimens in patients with polycystic ovary syndrome undergoing in vitro fertilization, Fertility and Sterility, 90, 569-575, 2008 **Ref ID** 54697 **Country/ies where the study was carried out** Cyprus **Study type** Randomised clinical trial **Aim of the study** To compare the efficacy of a sequential step-up/step-down protocol with the conventional low dose step-up and the step-down regimens in patients with PCOS undergoing IVF. **Study dates** Not reported **Source of funding** Supported by IBSA Cyprus.	**Sample size** n = 225 women **Characteristics** Mean age = 25.6 ± 2.7 years Mean BMI = 23.2 ± 1.7 kg/m^2 **Inclusion criteria** 1] Women with 30 years old or younger with infertility due to PCOS 2] All women had either failed to ovulate after receiving a maximum daily dosage of 100-150 mg of CC for 5 days or failed to conceive after at least three ovulatory cycles using CC or gonadotropin treatment. 3] Patent fallopian tubes 4] No previous IVF attempts, and partners with normal semen parameters. **Exclusion criteria** Not reported	1] Low dose step-up protocol 2] Step-down protocol	Method: The stimulation protocol was assigned under the basis of prospective randomisation using sealed and numbered envelopes Interventions: 75 patients (group A) received the low dose step-up regimen, whereas an equal number of patients followed the step-down protocol (group B). Group C was also comprised of 75 patients. These were treated using a sequential step-up/step-down regimen. The inital dosage in the low dose step-up regimen (group A) was 75 IU/d of FSH for the first 6 days followed by an increase of 37.5 IU thereafter. In the step-down regimen (group B) patients received a starting dose of 225 IU/d of FSH for the first 3 days followed by a decrease to 150 IU/d for the	Live birth: Low dose step-up = 17/75 (22.7%) Step-down protocol = 16/75 (21.3%) Singleton live birth: Low dose step-up = 13/75 (17%) Step-down protocol= 11/75 (15%) Clinical pregnancy: Low dose step-up = 18/75 (24%) Step-down protocol = 20/75 (26.7%) Multiple pregnancy: Low dose step-up = 4/75 (5.3%) Step-down protocol = 5/75 (6.7%) Multiple births: Low dose step-up = 8/21 (38%) babies born Step-down protocol = 10/21 (48%) babies born All of the babies born from multiple pregnancies were twins Miscarriages: Low dose step-up = 7/75 (9.3%) Step-down protocol = 9/75 (12%) OHSS: Low dose step-up = 3/75 (4%) Step-down protocol = 8/75 (10.7%)	**Limitations** 1] The method of randomisation was not clearly reported 2] Blinding was not reported 3] Power calculation was not clearly reported. **Other information** 1] Clinical pregnancy was defined as the presence of a fetal heart pulse on ultrasound 3 weeks after positive serum β-hCG analysis. 2] All the multiple pregnancies were carried to term 3] Miscarriages related to singleton pregnancies 4] Cancellation rates between the 2 groups was 22.7% and 17.3%

			next 3 days. This dosage was further decreased to 75 IU/d or sustained at I50 IU until the day of the hCG injection. In group C, patients received 150 IU on day 1 followed by a decrease to 75 IU on day 2. On day 3 the dosage was increased back to 150 IU. This alternation of injection dosage was followed until day 6. According to the initial ovarian response the dosage was sustained at 150 IU/d or 75 IU/d until the day of the hCG injection. Ultrasound-guided follicular aspiration was performed at 35 hours after the administration of the hCG injection. All patients had two embryos replaced 3 days after egg collection. The luteal phase was supported by progesterone started on the day of the egg collection. Statistical analysis: The power of the		

			study which incorporates a sufficient number of subjects is being described using a probability of <0.05 to indicate statistical significance.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Harrison,R.F., Jacob,S., Spillane,H., Mallon,E., Hennelly,B., A prospective randomized clinical trial of differing starter doses of recombinant follicle-stimulating hormone (follitropin-beta) for first time in vitro fertilization and intracytoplasmic sperm injection treatment cycles, Fertility and Sterility, 75, 23-31, 2001 **Ref ID** 73735 **Country/ies where the study was carried out** Ireland **Study type** Randomised clinical trial. **Aim of the study** To compare the efficacy of differing starter doses of rFSH for IVF and ICSI cycles when the treatment is administered both subcutaneously and intramuscularly. **Study dates** January 1 to December 31, 1997. **Source of funding** Organon UK	**Sample size** n = 345 women Group 1 = 297 women Group 2 = 48 women **Characteristics** <u>Group 1</u> Mean age = 33.6 ± 3.8 years Duration of infertility = 5.0 ± 3.3 years Cause of infertility: Tubal factor = 27 (9.1%) Male factor = 86 (29%) Endometriosis = 52 (17.5%) Unexplained = 108 (36.4%) Other = 24 (8.1%) <u>Group 2</u> Mean age = 35.6 ± 3.8 years Duration of infertility = 4.6 ± 2.5 years Cause of infertility: Tubal factor = 5 (10.4%) Male = 11 (22.9%) Endometriosis = 12 (25%) Unexplained = 20 (41.7%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	<u>Group 1 (n = 297)</u> 1] 150 IU FSH 2] 200 IU FSH <u>Group 2 (n = 48)</u> 1] 300 IU FSH 2] 400 IU FSH	Recruitment: All of the patients undergoing their first IVF or ICSI attempt in the unit during study period were eligible for inclusion in the study. ICSI was used only in the presence of male factor infertility. Method: The starter dosages of rFSH were randomised through the hospital pharmacy, and they were blinded to the clinicians with the use of a computer-generated list provided by Organon Ltd. Intervention: Two different groups were catered for. In the light of previous experience using day-3 FSH levels as a guide to starter dosage, the women with day-3 FSH levels of <8.5 IU/l were randomised to commence treatment with either 150 IU or 200 IU rFSH. Those with day-3 FSH levels of greater than 8.5 to 15 IU/l were selected to begin treatment	Clinical pregnancy: 150 IU rFSH = 29/146 (19.9%) 200 IU rFSH = 31/151 (20.5%) 300 IU rFSH = 2/24 (8.3%) 400 IU rFSH = 2/24 (8.3%)	**Limitations** 1] Power calculation was not done for pregnancy outcome. 2] Allocation concealment not reported 3] It is not clear whether blinding was adequate **Other information**

			with a starter dosage of rFSH at 300 IU or 400 IU. Down-regulation using a GnRH long-protcol was commenced on day 1 of the cycle. The maority of patients used a buserelin acetate nasal spray. Occasionally, patients who failed to down-regulate with buserelin or had endomentriosis used Decapeptyl SR. Pituitary down-regulation was confirmed on day 14 by quiescent ovaries, as revealed by an ultrasound scan, and E_2 levels measured at less than 100 pmol/L. Once pituitary down-regulation was achieved, the controlled ovarian stimulation. Once pituitary down-regulation was achieved, the controlled ovarian stimulation using rFSH was commenced. The starting dosage was determined by the		

			group randomisation code. After appropriate laboratory procedures, up to a maximum of three zygotes were transferred optimally to the uterus approximately 48 hours after ooycte collection. Luteal support in the form of hCG or progesterone pessaries was given based on the number of oocytes retrieved and the E_2 levels measured on the day of hCG administration. Statistical analysis: Based on calculations, it was estimated that a total sample size of 210 subjects would have 95% power to detect a difference of between 10 to 11 oocytes retrieved with a standard deviation of 2. With a standard deviation of 2.5, 328 subjects would be required; at a standard		

			deviation of 2.75, 400 subjects would be needed. In Group 1, 297 patients were included in the analysis, of which 259 provided oocytes.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Segal,S., Casper,R.F., Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in in vitro fertilization, Fertility and Sterility, 57, 1254-1258, 1992 **Ref ID** 83047 **Country/ies where the study was carried out** Canada **Study type** Randomised controlled trial **Aim of the study** "to determine if there is a difference in the pregnancy rates (PRs) between hCG and GnRH-a use to trigger follicle maturation" **Study dates** Not reported **Source of funding** Abbott Pharmaceutical Company	**Sample size** n = 214 couples **Characteristics** Population: Women undergoing controlled ovarian hyperstimulation. Female mean age (± SEM) GnRH-a 33.2 ± 0.4 years hCG = 33.7 ± 0.4 years Duration of infertility Not reported BMI/Weight Not reported Cause of infertility Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	hCG 5,000 IU intramuscularly GnRH-a 500 µg subcutaneously	Recruitment: Not reported Method: The selection of hCG or GnRH-a was determined before starting ovarian hyperstimulation by random numbers table. Intervention: Clomiphene citrate 100 mg/d from cycle days 5 to 9 and 150 IU/d og human menopausal gonadotropin for day 6 or, alternatively, with a comnbination of human FSH 150 IU and hMG 150 IU on days 5 and 6 of the cycle followed by hMG 150 IU/d IVF and ET were performed using standard techniques. Semen samples were washed, centrifuged and a swim-up was used to harvets motile sperm.At 18 to 22 hours after insemination, the oocytes were	Pregnancy: GnRH-a 17/96 (17.7%) hCG 18/118 (15.3%) Pregnancy not defined but term 'conceived' was used	**Limitations** Allocation concealment: Not reported Blinding of participants, staff and study personnel: Not reported Power calculation: Not reported **Other information** NA

			transferredto fresh medium, cumulus cell stripped mechanically and the oocytes examined for presence of pronucleu. At 43 to 45 hours post fertilization, yp to three two to six-cell embryos were transferred to the uterus.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Barrenetxea,G., Agirregoikoa,J.A., nez,M.R., de Larruzea,A.L., Ganzabal,T., Carbonero,K., Ovarian response and pregnancy outcome in poor-responder women: a randomized controlled trial on the effect of luteinizing hormone supplementation on in vitro fertilization cycles, Fertility and Sterility, 89, 546-553, 2008 **Ref ID** 81794 **Country/ies where the study was carried out** Spain **Study type** Randomized controlled trial **Aim of the study** "to prospectively assess the effect of using a combination of rFSH and rLH on ovarian stimulation parameters and treatment outcome among poor-responder patients" **Study dates** Patient recruitment between January and June 2005 **Source of funding** Not reported	**Sample size** n = 84 **Characteristics** Population: infertility ≥ 1 year who were poor responders defined as Age ≥ 40 years and elevated 3-day FSH level (≥ 10mIU/mL) **Inclusion criteria** Not reported **Exclusion criteria** Women with only one ovary Mean age ± sd GnRH + rFSH + rLH = 42.06 ± 0.12 years GnRH + rFSH = 41.83 ± 0.28 years Duration of infertility GnRH + rFSH + rLH = 29.11 ± 4.12 months GnRH + rFSH = 38.00 ± 8.42 months BMI GnRH + rFSH + rLH = 22.22 ± 0.21 kg/m^2 GnRH + rFSH = 23.73 ± 0.41 kg/m^2 Cause of infertility Not reported	GnRH + rFSH + rLH GnRH + rFSH	Recruitment: This study was conducted on poor-responder patients undergoing IVF defined as Age ≥ 40 years and elevated 3-day FSH level (≥ 10mIU/mL) Method: The patients were randomised according to a commputer-generated block randomisation using sealed envelopes. The sealed envelopes were opened on the day of stimulation start by a nurse who assigned participants to their groups and was responsible for coding protection. The doctor and the biological team performing the ART were blinded to group assignment. Intervention: A flare up protocol was used for ovarian stimulation. Obvarian stimulation started on day 2 of a natural cycle with GnRH-a 0.10 mL and rFSH 375 IU in b oth	Pregnancy rate GnRH + rFSH + rLH = 10/42 (23.8%) GnRH + rFSH = 9/42 (21.4%) Cancellation rate GnRH + rFSH + rLH = 4/42 (9.5%) GnRH + rFSH = 4/42 (9.5%)	**Limitations** Allocation concealment: Adequate Blinding of participants, staff and study personnel: Adequate Power calculation: Adequate - study was power to see a 10% difference **Other information** NA

			groups. ON day 7 of stimulation in both groups, monitoring of follicle size by ultrasound was performed, and plasma level of E_2 were measured every 2 days. When two follicles ≥ 18 mm in diameter were observed on transvaginal sonography rhCG 250 µg was administered. Follicle puncture was planned 36 hours after rhCG administration. In case of no follicle growth or unique follicular development, the cycle was cancelled. All patients underwent intracytoplasmic sperm injection according to published procedures to maximise chances of fertilisation and to avoid confounding factors resulting from differnt procedures of oocyte retrieval. The embryos of		

			highest morphological grade were transferred into the uterine cavity 72 hours after retrieval using ET catheter. A maximum of three embryos were transferred on day 3 after oocyte recovery according to Spanish law. Luteal0phase support starting the day after oocyte retrieval was the same in both treatment groups and consisted of micronised P 600 mg vaginally administered.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Balasch,J., Creus,M., Fabregues,F., Civico,S., Carmona,F., Puerto,B., Casamitjana,R., Vanrell,J.A., The effect of exogenous luteinizing hormone (LH) on oocyte viability: evidence from a comparative study using recombinant human follicle-stimulating hormone (FSH) alone or in combination with recombinant LH for ovarian stimulation in pituitary-suppressed women undergoing assisted reproduction, Journal of Assisted Reproduction and Genetics, 18, 250-256, 2001 **Ref ID** 72975 **Country/ies where the study was carried out** Spain **Study type** Randomised controlled trial **Aim of the study** "to compare the use of rhFSH alone or in combination with recombinant human LH (rhLH) for ovarian stimulation in down-regulated women undergoing ART" **Study dates** Not reported **Source of funding** Recombinant FSH and LH provided by Ares-Serono International	**Sample size** n = 30 **Characteristics** Population: Women undergoing IVF or ICSI. No women had undergone two previous ART attempts. Female mean age ± SD rhFSH = 33.6 ± 0.8 years rhFSH + rhLH = 34.8 ± 0.8 years Duration of infertility ± SD rhFSH = 4.7 ± 0.5 years rhFSH + rhLH = 5.7 ± 0.9 years BMI ± SD rhFSH = 22.4 ± 0.9 kg/m^2 rhFSH + rhLH = 23.1 ± 0.7 kg/m^2 Cause of infertility Male factor 17 (56.7%) Minimal/mild endometriosis 5 (16.7%) Tubal factor 4 (13.3%) Unexplained 2 (6.7%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	rhFSH rhFSH + rhLH	Recruitment: All women were premenopausal (age 29–40 years) and were menstruating regularly; all had both ovaries and showed no evidence of occult ovarian failure as judged by a basal FSH concentration below 11 IU/L [Standard International Reference Preparation (IRP) 78/549]. No patient had polycystic ovarian disease. Each patient underwent a complete infertility evaluation, including laparoscopy when necessary and ultrasound examination of the ovaries. No woman had undergone more than two previous ART attempts. All patients provided informed consent to be included in the study. Method: Patients were allocated to a gonadotropin treatment group according to a	Clinical pregnancy rhFSH = 2/14 (14.3%) rhFSH + rhLH = 0/16 (0%)	**Limitations** Allocation concealment: Adequate Blinding of participants, staff and study personnel: Adequate Power calculation: Not reported **Other information** NA

			computer-generated randomization table. Sealed envelopes for the randomization list were used. Patients in group F (n=14) received s.c. rhFSH alone and patients in group L (n = 16) were treated with the combination of s.c. rhFSH and s.c.rhLH. In both groups, rhFSH was administered according to a step-down regimen consisting of 450 IU (6 ampoules) on day 1, 300 IU (4 ampoules) on day 2, and 150 IU (2 ampoules) on days 3 to 5. From day 6 onward, rhFSH was administered in both treatment groups according to the ovarian response as objectively assessed by follicular development and E2 levels. In no case did the ultrasonographer or the hormonal laboratory know the treatment groups in which the patients were included.		

			Intervention: Ovarian stimulation is routinely accomplished by gonadotropin treatment after pituitary suppression with leuprolide acetate. Suppression is started in the midluteal phase of the previous cycle at a daily dose of 1 mg s.c. This dose is reduced to 0.5 mg/day once ovarian arrest has been achieved and treatment is continued until the day of administration of human chorionic gonadotropin (hCG). Gonadotropin stimulation of the ovaries was started when serum estradiol (E2) concentrations declined to less than 30 pg/ml and a vaginal ultrasound scan showed an absence of follicles above 10 mm in		

			diameter. In both groups, rhFSH was administered according to a step-down regimen consisting of 450 IU (6 ampoules) on day 1, 300 IU (4 ampoules) on day 2, and 150 IU (2 ampoules) on days 3 to 5. From day 6 onward, rhFSH was administered in both treatment groups according to the ovarian response as objectively assessed by follicular development and E2 levels. Patients in group L received a fixed daily dose of 75 IU of rhLH throughout the treatment period. Oocyte aspiration was performed by vaginal ultrasonography under local anesthesia 35–37 hr afterhCG administration.The maturational status of the oocytes and		

			embryo grading were recorded according to the criteria of Veeck (13); embryos of Veeck grade 1 or 2 were considered high quality. Up to four embryos per patient were replaced and those remaining were cryopreserved. Luteal-phase support was performed with hCG.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nyboeandersen,A., Humaidan,P., Fried,G., Hausken,J., Antila,L., Bangsboll,S., Rasmussen,P.E., Lindenberg,S., Bredkjaer,H.E., Meinertz,H., Nordic LH study group., Recombinant LH supplementation to recombinant FSH during the final days of controlled ovarian stimulation for in vitro fertilization. A multicentre, prospective, randomized, controlled trial, Human Reproduction, 23, 427-434, 2008 **Ref ID** 55182 **Country/ies where the study was carried out** Denmark (10 centres), Finland (2 centres), Norway (4 centres, and Sweden (6 centres) **Study type** Randomised Controlled Trial **Aim of the study** Whether addition of rLH to sFSH from day 6 of controlled ovarian stimulation increased the ongoing pregnancy rate after IVF or ICSI using the long agonist stimulation protocol. **Study dates** Women were enrolled from August 2003 to November 2004. **Source of funding** Serono Nordic provided the rLH and funded measurement of serum LH. The statistical unit of Serono International did the statistical analysis.	**Sample size** 526 women randomised. Group 1 = 261, Group 2 = 265. **Characteristics** <u>Group 1 (mean, SD)</u> Age 31.80 (3.98) Duration of infertility = 3.07 (1.88) 1st Cycle = 182 (70.3%) Male infertility = 127 (48.7%) Embryos transferred = 1.6 (0.5) <u>Group 2 (mean, SD)</u> Age 31.72 (3.87) Duration of infertility = 3.21 (1.92) 1st Cycle = 168 (64.4%) Male infertility = 131 (49.4%) Embryos transferred = 1.6 (0.5) **Inclusion criteria** Indication for IVF or ICSI. 1st to 3rd cycle of treatment. Regular menstrual cycle (21 to 35 days). Mean daily dose of rFSH of =<225 IU/day. Women aged <40 years. Basal serum FSH below 10IU/l at cycle days 2 to 5. **Exclusion criteria** Not specified	All women received a long agonist protocol. GnRH agonist (200 ug three times daily) started on day 21 of cycle and continued for at least 14 days, then dose decreased to 200 ug twice daily until 250 ug hCG trigger administered. Then a fixed dose of rFSH (150 IU/day in women aged =< 35 years and 225 IU/day in women aged > 35 years) until day 6 of stimulation. Group 1 after day 6 to continue with rFSH alone. Group 1 after day 6 to continue with rFSH plus rLH (75 IU/day in those aged =<35 years, and 150IU/day in those aged > 35 years). All women received luteal phase support with either progesterone vaginal tablets or gel.	Ethics approval gained. Randomisation undertaken on day 6 of ovarian stimulation. Randomisation using sequentially number, sealed envelopes. Blocks of 10 (blinded from centres) used at each centre to avoid unbalanced groups. Study nurse undertook randomisation and gave study medications. Sample size calculated based on published data showing 25% ongoing pregnancy rate in control arm and detect absolute 9% change in pregnancy ratein the rFSH + rLH arm. The study would need 400 women per arm (800 in total) to give alpha of 0.05 and beta of 77%. Statistical all two-sided 0.05 significance level. ITT analysis undertaken. Fisher's exact test used for	<u>Clinical pregnancy</u> Group 1 = 88/261 Group 2 = 83/265 <u>Ongoing pregnancy</u> Group 1 = 75/261 Group 2 = 72/265 <u>Multiple pregnancies</u> Group 1 = 16 Group 2 = 20	**Limitations** Power calculation reported - not enough women were recruited Blinding was not reported. **Other information**

			binary outcomes. CMH test used for categorical outcomes. ANOVA used for continuous outcomes.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Pacchiarotti,A., Aragona,C., Gaglione,R., Selman,H., Efficacy of a combined protocol of urinary and recombinant follicle-stimulating hormone used for ovarian stimulation of patients undergoing ICSI cycle, Journal of Assisted Reproduction and Genetics, 24, 400-405, 2007 **Ref ID** 6025 **Country/ies where the study was carried out** Italy **Study type** Randomised clinical trial **Aim of the study** To evaluate the efficacy of using both urinary and recombinant FSH in a combined protocol for ovarian stimulation in an IVF treatment program. **Study dates** June 2005 to March 2006. **Source of funding** Not reported	**Sample size** n = 119 women **Characteristics** Mean age = 34.6 ± 2.9 years Mean BMI = 23.1 ± 1.8 kg/m^2 Duration of infertility = 4.6 ± 1.4 years Cause of infertility: Tubal factor = 53 (44.5%) Male factor = 47 (39.5%) Unexplained = 16 (13.4%) Primary infertility = 85 (71.4%) **Inclusion criteria** 1] Women aged 27 to 38 years 2] Infertility attributable to tubal factor, male factor or idiopathic infertility 3] Serum hormonal profile within the normal range. 4] Regular ovulatory menstrual cycles 5] Presence of normal uterine cavity 6] BMI ≥20 to ≤26 kg/m^2 7] First IVF treatment **Exclusion criteria** 1] Previous poor response to gonadotropins 2] history of severe OHSS or PCOS 3] If the male partner had azoospermia or clinical signs of infection detected in semen analysis within 12 months before treatment.	1] uFSH/rFSH 2] rFSH	Recruitment: Only the first IVF patients that satisfied the inclusion criteria were enrolled in the study to reduce the hetrogeneity of the patients and minimisation confounding variables that may affect the results. Method: Randomisation was performed using a computer-generated random assignment schedule for each patient. Sealed and numbered envelopes were used to conceal the treatment allocation until randomisation. The randomisation took place after the confirmation of down-regulation and immediately before gonadotropin administration in order to minimise post-randomisation withdrawals. Intervention: All patients underwent a standard down-regulation	Clinical pregnancy: uFSH/rFSH = 25/58 (43.1%) rFSH = 13/61 (21.3%) Abortion: uFSH/rFSH = 3/58 (5.2%) rFSH = 2/61 (3.3%)	**Limitations** 1] No blinding reported. **Other information** No definition of clinical pregnancy was reported

			protocol with GnRH analogue hormone. The first group received 225 IU of uFSH for 6 days from the second day of the cycle and then rFSH from the 7th day of stimulation until hCG administration and the second group, patients received 225 IU rFSH alone from the second day of the cycle until hCG administration. Final oocyte maturation was triggered by the administration of 10,000 Iu of hCG when the leading follicle was 18 - 19 mm and there were at least tow follicles of 16 - 17 mm. Oocyte retrieval was performed 36 h after hCG administration and the harvested oocytes were denuded from their cumulus cell and were assesed for their maturity. Ultrasound guided embryo transfer took place 48h following insemination. The luteal phase was		

			supported with the administration of 50 mg/day of progesterone. Statistical analysis: Statistical power calculation was based on an alpha level of 0.05 with 80% power to detect a 20% difference with 50 evaluable patients per group. All analyses were adjusted for age stratum in line with the study design. Correction for multiple comparison analysis was performed using either Bonferroni's or Sidak's adjustment methods by lowering the alpha for each test to 0.0039 with t value for double sided testing: ≥3.0. The difference had greater significance of pregnancy and implantation rates when linear mixed model, which controls for intrasubject variation was used to compare the data (p≤0.001)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Durnerin,C.I., Erb,K., Fleming,R., Hillier,H., Hillier,S.G., Howles,C.M., Hugues,J.N., Lass,A., Lyall,H., Rasmussen,P., Thong,J., Traynor,I., Westergaard,L., Yates,R., Luveris Pretreatment Group., Effects of recombinant LH treatment on folliculogenesis and responsiveness to FSH stimulation, Human Reproduction, 23, 421-426, 2008 **Ref ID** 53981 **Country/ies where the study was carried out** United Kingdom, Denmark, France **Study type** Randomised multi-centre trial **Aim of the study** Not reported. **Study dates** Not reported **Source of funding** Serono Ltd, UK and MerckSerono	**Sample size** n = 146 women **Characteristics** Causes of infertility: Tubal = 91 (62.3%) Male factor = 22 (15.1%) Unexplained = 73 (50%) **Inclusion criteria** 1] Normal menstrual rhythm (25 - 34 days) 2] Presence of both ovaries 3] Aged between 19 and 39 years 4] BMI <28kg/m^2 **Exclusion criteria** 1] Ultrasound determination of PCOS 2] Previous poor response (<5 follicles) 3] Other compromising disease stages such as diabetes and kidney disease which may aftect ovarian responsiveness.	1] rhLH 2] No rhLH	Recruitment: The 146 patients enrolled in the study were randomised to receive rhLH pretreatment or no rhLH. The four centres contributed 43, 22, 32 and 49 patients to the total with no difference in age or BMI of patients between the centres. Method:They were block randomised by centre in blocks of 10, to receive pretreatment with rhLH. Different centres used different embryo assessment criteria, so the embryologist staff were blinded to the treatment group. Intervention: Patients were treated in a standard long agonist protocol with the following sequence. Down-regulation treatment was effected with the high dose GnRH agonist depo Trypotorelin which was administered starting in the luteal phase. 14 days after starting the	Ongoing pregnancy: rhLH + rhFSH = 24/75 (32%) rhFSH = 23/71 (32.4%)	**Limitations** 1] Allocation concealment not reported 2] It is not clear whether there was adequate blinding 3] The study was not powered for pregnancy outcomes 4] Luteal phase support may have varied across centres. **Other information** No definition of ongoing pregnancy was reported

			GnRH agonist, patients who were randomised to the rhLH pretreatment arm received 300 IU/day for 7 days, whereas those ranomised to no rhLH treatment received no treatment during that week. After the 7-day pretreatment period, stimulation with rhFSH was started at a fixed daily dose (150 IU) for 7 days, with subsequent dose adjustment according to ovarian response assessed on that day. FSH stimulation was continued until hCG administration criteria were attained. Final follicular maturation was achieved using 250 µg rhCG. Luteal phase support was according to local practice and a maximum of 2 embryos were replaced in the fresh cycle. Statistical analysis: Power calculation was done for		

			follicular development recorded both prior to and following FSH stimulation (the primary outcome)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Yong,P.Y., Brett,S., Baird,D.T., Thong,K.J., A prospective randomized clinical trial comparing 150 IU and 225 IU of recombinant follicle-stimulating hormone (Gonal-F*) in a fixed-dose regimen for controlled ovarian stimulation in in vitro fertilization treatment, Fertility and Sterility, 79, 308-315, 2003 **Ref ID** 83361 **Country/ies where the study was carried out** United Kingdom **Study type** Randomised clinical trial **Aim of the study** To compare fixed daily doses of recombinant FSH (rFSH) gonal-F (150 IU vs 225 IU) for ovarian stimulation in IVF-ET. **Study dates** September 1999 to December 2000 **Source of funding** Not reported	**Sample size** n = 123 women **Characteristics** Mean age = 33.9 ± 3.5 years Duration of infertility = 5.1 ± 2.9 years **Inclusion criteria** 1] Aged 23 to 41 years 2] BMI of <34 kg/m^2 3] Regular 25 to 35 day menstrual cycles **Exclusion criteria** 1] Serum FSH of >10IU/l 2] PCOS 3] One ovary or previous ovarian surgery 4] Previous poor response to COS (4 or less oocytes retrieved) 5] OHSS 6] Any chronic cardiovascular, renal, hepatic, or pulmonary disease and ooycte donation cycles 7] Indications for conventional IVF or ICSI	1] 150 IU rFSH 2] 225 IU rFSH	Method: Envelopes containing equal numbers of instructions for each treatment had been thoroughly mixed and then numbered consecutively before commencement of the study. The treatment arm allocated was determined by opening the next consecutively numbered envelope. The study was subsequently performed in a nonblinded fashion. No alteration of dose of Gonal-F was allowed during treatment Intervention: Pituitary down-regulation with intranasal nafarelin or with buserelin SC administered for 2 to 3 weeks was confirmed The subjects were then randomised to have either 150 or 225 IU of Gonal-F for a maximum of 23 days. When there were at least three follicles that were ≥17 mm in	Live singleton birth: 150 IU = 7/60 (11.7%) 225 IU = 9/63 (14.3%) Multiple pregnancies: 150 IU = 2/60 (3.3%) 225 IU = 3/63 (4.8%) Miscarriages: 150 IU = 1/60 (1.7%) 225 IU = 1/63 (1.6%) OHSS: 150 IU = 0/60 (0%) 225 IU = 4/63 (6.3%)	**Limitations** 1] There was no blinding 2] The study is not powered to detect differences in pregnancy outcomes **Other information** 1] It was not reported whether all the babies reached full term 2] Only twin births were reported. It is not clear whether there were other multiple births.

			dameter, hCG was administered, and transvaginal oocyte recover was performed about 36 hours later. All subjects received 10,000 IU of hCG, unless there was a risk of developing OHSS in which case 5,000 IU of hCG was administered. All embryo transfers were carried out 48 hours after oocyte retrieval. It is the usual practice to transfer only two embryos. Subjects who were >37 years of age and in whom additional embryos would not have otherwise been cryopreserved were offered three-embryo transfers. For luteal support, progesterone pessaries were given for 2 weeks. Statistical analysis: Power calculation was done to detect a difference in oocytes retrieved.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Drakakis,P., Loutradis,D., Kallianidis,K., Liapi,A., Milingos,S., Makrigiannakis,A., onyssiou-Asteriou,A., Michalas,S., Small doses of LH activity are needed early in ovarian stimulation for better quality oocytes in IVF-ET, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 121, 77-80, 2005 **Ref ID** 53965 **Country/ies where the study was carried out** Greece **Study type** Randomized controlled trial **Aim of the study** "to examine whether exogenous LH administration has a beneficial effect on the quality of oocytes, fertilization potential, as well as pregnancy rate in IVF-ET cycles" **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 46 **Characteristics** Population: Infertile couples Age Mean ± SD rFSH = 33.0 ± 3.7 years rFSH + HMG = 32.4 ± 3.1 years Duration of infertility Not reported BMI/Weight Not reported Cause of infertility Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	rFSH rFSH + HMG	Recruitment: This study was conducted in normogonadotropic women presenting for infertility treatment. Method: The women were randomised using closed envelopes. Intervention: On cycle day 21, a baseline ultrasound was performed, followed by pituitary down-regulationwith GnRH-a intranasal spray 100 µg five times daily. GnRH-a administration was continued until HCG administration. The extend of ovarian suppression was evaluatedby ultrasound scan and serum E2 (<40 pg/ml) before starting exogenous gonadotropin administration. In Group A ovarian stimulation started with rFSH 200 IU/day for the first four days. In Group B, the	Clinical pregnancy rFSH = 6/22 (27.8%) rFSH + HMG = 5/24 (20.8%) Clinical pregnancy not defined	**Limitations** Allocation concealment: Adequeate Blinding of participants, staff and study personnel: Not reported Power calculation: Not reported **Other information** We assumned that as women were randomised then the denominator for pregnancy rate was women as it is not explicit.

			stimulation protocol started with one amp hMG (75 IU FSH + 75 IU LH activity) daily for four days, with simultaneous administration of rFSH 200 IU/day. The latter was continued with HMG administration. In both the groups, the daily hormonal dose was individualized according to ovarian response and GnRH-a was continued until hCG (10,000 IU,IM) was administered.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Coelingh,BenninkH, Fauser,B.C.J.M., Out,H.J., Recombinant follicle-stimulating hormone (FSH; puregon) is more efficient than urinary FSH (Metrodin) in women with clomiphene citrate- resistant, normogonadotropic, chronic anovulation: A prospective, multicenter, assessor-blind, randomized, clinical trial, Fertility and Sterility, 69, -25, 1998 **Ref ID** 73244 **Country/ies where the study was carried out** Europe **Study type** Randomised multicentre study **Aim of the study** To compare the safety and efficacy of recombinant FSH and urinary FSH. **Study dates** June 1992 to March 1994 **Source of funding** Supported by NV Organon, Oss, the Netherlands	**Sample size** n = 178 women **Characteristics** Mean age = 29.1 ± 4.1 years Mean BMI = 24.4 ± 3.3 kg/m^2 Duration of infertility = 4.1 ± 2.5 years **Inclusion criteria** 1] Patients had to be 18 - 39 years of age at the time of screening and in good physical and mental health. 2] Chronic anovulation had to be present, with positive progestogen withdrawal bleeding or spontaneous menstrual bleeding. 3] Serum levels of FSH, prolactin, and TSH had to be normal in the early follicular phase. 4] Serim concentrations of testosterone, androstenedione, dehydroepiandrosterone, and 17-OH-progesterone had to be below 7, 20, 25, and 20 nmol/L respectively. 5] Patients who ovulated bu failed to conceive with CC had to have a normal uterine cavity and at least one patent fallopian tube. 6] Semen analysis of the partner had to reveal ≥10% normal morphology, ≥20% normal motility, and a total motile count of ≥10 X 10^6 sperm/mL. 7] The BMI had to fall between 19 and 32 kg/m^2 8] Finally the results of a urinary pregnancy test and a test for hepatitis B surface antigen had to be negative. **Exclusion criteria**	1] rFSH 2] uFSH	Recruitment: Women with CC-resistant anovulatory infertility were recruited at 12 different centre throughout Europe. The aim was to include 200 patients. Method: Eligible subjects were randomised by receiving a subject number from a randomisation list corresponding with patient boxes in which the medication was kept. The randomisation procedure included a ratio between rFSH and uFSH of 3:2. All centres followed an identical clinical protocol and used standardised case report forms. For technical reasons, rFSH was supplied in vials and uFSH in ampoules, a double blind design was not feasible. Instead, an assessor-blind design was chosen in which the preparation and administration of the	Clinical pregnancy: rFSH = 32/105 (30.5%) uFSH = 19/67 (28.4%) Abortion: rFSH = 10/105 (9.5%) uFSH = 6/67 (9.0%)	**Limitations** 1] No power calculation reported **Other information** 1] No definition of clinical pregnancy was reported. Figures included pregnancies that aborted before 12 weeks after hCG administration 2] Abortion rate reflects the number of clinical pregnancies that aborted before 12 weeks after hCG administration

	1] The presence of a persistent cyst. 2] endocrine or metabolic abnormalities 3] Current or past abuse of alcohol or drugs 4] Clinically relevant laboratory test abnormalities as well as the use of nonregistered investigational drugs within 3 months before screening.		medication was done by a study coordinator who took no part in any decision concerning the FSH dose during treatment. Intervention: FSH treatment was started within 5 days after a spontaneous or progestogen-induced withdrawal bleed. A stepwise, gradually increasing dosing scheme was used, starting with 75 IU of FSH daily im for up to 14 days in the first treatment cycle. After this period, weekly upward adjustments of half an ampoule were made when no follicles of ≥12 mm or a significant rise in serum E_2 levels were observed. The maximum daily dose was three ampoules of 75IU. Treatment was discontinued after 6 weeks. In the second and third treatment cycles, upward adjustments could be made after 1 week of treatment, if		

			needed. hCG was given as a single IM injection to trigger ovulation.Ovulation was confirmed by a mid-luteal serum progesterone concentration of 25 nmol/L or higher on at least one occasion. Statistical analysis: All analyses were done on an ITT basis, including all subjects who received at least 1 ampoule of FSH.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zhu,L., QUAN,S., XING,F., Zhang,W., Application of Ultra-low-dose Incremental Gn Protocol in Controlled Ovarian Hyperstimulation of the Patients with Ovary Hyperreaction, Journal of Reproduction and Contraception, #20, 145-152, 2009 **Ref ID** 108445 **Country/ies where the study was carried out** China **Study type** Randomised Controlled Trial **Aim of the study** Clinical outcome of iltra low dose incremental protocol in the ocntrolled ovarian hyperstimulation for the ovary hyperreaction patient. **Study dates** June 2006 to February 2008 **Source of funding** Not stated	**Sample size** 130 or 126 patients. Four refused to join, and 2 from control group withdraw. Experimental (low dose) group = 60, Control (standard dose) = 60. **Characteristics** <u>Experimental group</u> Age 29.3 +/- 3.2 <u>Control group</u> Age 30.2 +/- 3.0 **Inclusion criteria** Aged less than 35 years. BMI an sugar tolerance 'normal'. Female oviducal factor infertility only. First IVF cycle. Basal follicule count > 12 on day 2 or 3 of cycle. FSH, LH, $E_{2,}$ T and P values normal at day 2 of cycle. **Exclusion criteria** None stated	All women followed the same protocol. At the follocular phase of previous cycle women started taking an oral contraceptives tablet daily. After 17 to 20 days women received a subcutaneous injection of GhRH agonist (1.5 to 1.875 mg) and continued with contraceptives for a further 10 days (or onset of menstruation). Women then randomly assigned to one of two groups. Experimental group received 4 days of between 37.5 to 75.0 IU/d of FSH, doseage then varied depending on follicular growth.. Control group received 4 days of between 112.5 and 225.0 IU/d of FSH, doseage then varied depending on follicular growth. No luteal phase support described	Ethics approval not stated Randomisation by random number table (odd in experimental group and even in control group)	<u>Clinical pregnancy</u> Experimental group = 33/60 (56.9%) Control group = 31/60 (59.6%) <u>OHSS</u> Experimental group = 4/60 (6.9%) Control group = 12/60 (23.1%) <u>Quantities of FSH used (ampules)</u> Experimental group = 29.6 (+/- 13.0) Control group = 26.9 (+/- 10.0)	**Limitations** Power calculation not reported Blinding not reported Allocation concealment not reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Pacchiarotti,A., Sbracia,M., Frega,A., Selman,H., Rinaldi,L., Pacchiarotti,A., Urinary hMG (Meropur) versus recombinant FSH plus recombinant LH (Pergoveris) in IVF: a multicenter, prospective, randomized controlled trial, Fertility and Sterility, 94, 2467-2469, 2010 **Ref ID** 82870 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** To compare these two ovarian stimulation protocol in down-stimulated cycles and to confirm the paramount importance of LH in endometrial and follicular development, oocytes, and embryo quality, pregnancy and implantation rate, total number of oocytes retrieval, duration of stimulation, risk of OHSS. **Study dates** July 2008 to September 2009. **Source of funding** Not reported	**Sample size** n = 122 women **Characteristics** Not reported **Inclusion criteria** 1] Main causes of infertility attributable to tubal, idiopathic or male factors 2] Serum levels of FSH on day 3 of the ovarian cycle <12 IU/l 3] regular menstrual cycle 4] endogenous LH <1.2 IU/l 5] Normal uterine cavity **Exclusion criteria** Not reported	1] uhMG 2] rFSH + rLH	Method: Patients were assigned to the two study groups after computering randomisation. The physicians were blinded to the randomisation. The participants were reviewed at the same time intervals and received the same amount of attention from researchers and staff. Intervention: Group A patients treated with a down-regulation protocol consisting of triptorelin at day 21 of the cycle and an ovarian stimulation with hMG starting with 225 IU fromthe second day of the cycle until hCG day. Goup B patients were treated with a down-regulation protocol consisting of Triptorelin 0.1 mg from day 21 and with rFSH plus rLH starting with 225 IU daily from the second day of the cycle until hCG day. hCG 10,000 IU was given	Pregnancy: uHMG = 17/60 (28.3%) rFSH/rLH = 15/62 (24.2%)	**Limitations** 1] Allocation concealment not clearly reported 2] Blinding not clearly reported **Other information** 1] No definition of pregnancy was reported. 2] Cancellation rates due to the risk of OHSS in both groups were Group A: 1/60 (1.7%) and Group B: 7/63 (11.1%).

			i.m. Transvaginal US-guided oocyte retrieval was done 36h after hCG injection. Of note, in Italy, only three oocytes are permitted to be inseminated; therefore, we performed ICSI as an IVF technique of choice to select good quality oocytes for insemination. The luteal phase was supplemented with progesterone im. US-guided embryo transfer was performed at day 2. Statistical analysis: Statistical power calculatin was based on an alpha level of 0.05 with 80% power to detect a 20% difference with 50 evaluable patients per group. The difference between treatments was evaluated using a two-sided, 95% confidence interval.All analyses were adjusted for age stratum in line with the study design.		

			Correction for multiple comparison analysis was performed using either Bonferroni's or Sidak's adjustment methods by lowering the alpha for each test to 0.0039 with t value for double sided testing: ≥3.0. The difference had greater significance of pregnancy and implantation rates when linear mixed model, which controls for intrasubject variation was used to compare the data (p≤0.001).		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Levi-Setti,P.E., Cavagna,M., Bulletti,C., Recombinant gonadotrophins associated with GnRH antagonist (cetrorelix) in ovarian stimulation for ICSI: comparison of r-FSH alone and in combination with r-LH1268, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 126, 212-216, 2006 **Ref ID** 82576 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** "to compare the outcome of intracytoplasmic sperm injectio (ICSI) cycles in two different ovarian stimulation protocols: the first, using GnRH antagoniist (cetrorelix) and r-FSH alone, and the second using Cetrorelix with combined r-FSH and r-LH." **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 40 **Characteristics** Population: Women undergoing ovarian stimulation for ICSI Female mean age ± sd 32.3 ± 2.4 years Duration of infertility: Not reported BMI/Weight: Not reported Cause of infertility: Male factor = 40 (100%) **Inclusion criteria** Ejaculated spermatoza **Exclusion criteria** [1] Frozen or testicular sperm [2] previous pelvic surgery [3] endometriomas at transvaginal ultrasound	rFSH rFSH + rLH	Recruitment: The study was conducted on women undergoing ICSi. These women were normo-ovulatory, with regular menstrual cycles ranging from 25 ro 35 days, aged ≤ 37 years, BMI <25 kg/m^2, had basal FSH < 12 IU/ml, measured no more than three cycles before starting induction therapy. Method: The women were randomly allocated by computer-generated lists. Intervention: We performed a pre-treatment with an oral contraceptive and on day 2 of the cycle we bgan the administration of 225 IU rFSH. When follicales reached the mean diameter of 14 and 15 mm we initiated the administration of cetrorelix in a daily dose of .25 mg subcutaneously.	Clinical pregnancy rFSH = 6/20 rFSH + rLH = 7/20 Pregnancy defined as > 12 weeks gestation OHSS rFSH = 0/20 rFSH + rLH = 0/20	**Limitations** Allocation concealment: Not reported Blinding of participants, staff or study personnel: Not reported Power calculations: Adequate **Other information** NA

			In both groups 10,000 IU of hCG was administered when at least three follicles measuring > 17 mm were onserve, and oocyte retrieval was performed 35 and 36 hours later. Oocyte retrieval was followed by ICSI and two to three embryos were replaced 72 hours aftewards. Luteal phase support was performed with 50 mg of intramuscular progesterone.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Matorras,R., Prieto,B., Exposito,A., Mendoza,R., Crisol,L., Herranz,P., Burgué,s S., Mid-follicular LH supplementation in women aged 35-39 years undergoing ICSI cycles: a randomized controlled study184, Reproductive Biomedicine Online, 19, 879-887, 2009 **Ref ID** 82685 **Country/ies where the study was carried out** Spain **Study type** Randomised controlled trial **Aim of the study** To determine whether r-HLH supplementation in women aged 35-39 years undergoing ICSI is associated with an improvement in the number and maturity of oocytes retrieved when compared with patients receiving r-HFSH alone. **Study dates** January 2005 to November 2006 **Source of funding** Merck-Serono	**Sample size** N = 131 (Intervention r-HLH) n = 63 (r-HFSH comparison) n = 68 **Characteristics** Age r-HFSH - 36.7 (+/-1.5) r-HFSH + r-HLH - 36.6 (+/-1.6) BMI r-HFSH - 22.6 (+/-2.7) r-HFSH + r-HLH - 22.7 (+/-2.8) Infertility duration r-HFSH - 4.4 (+/-2.3) r-HFSH + r-HLH - 4.7 (+/-2.4) Aetiology (%) Tubal factor r-HFSH - 3 (4.4) r-HFSH + r-HLH - 2 (3.2) Male factor r-HFSH - 31 (45.6) r-HFSH + r-HLH - 31 (49.2) Endometriosis r-HFSH - 3 (4.4) r-HFSH + r-HLH - 1 (1.6) Mixed cause r-HFSH - 22 (32.4) r-HFSH + r-HLH - 11 (17.5) Unknown cause r-HFSH - 9 (13.2) r-HFSH + r-HLH - 18 (28.6)	Intervention: GnRH agonist long protocol + r-HFSH + r-HLH + hCG + P Comparison: GnRH agonist long protocol + r-HFSH + hCG + P	Randomisation: Computer generated list into sealed envelopes Method: Treatment for both group was initiated with GnRH agonist (triptorelin acetate) on day 20-22 of the proceeding cycle (0.1mg/day). Once pituitary desensitization was documented (oestradiol values < 30pg/ml and absence of follicles >10mm) the GnRH agonist dose was decreased by half and ovarian stimulation was started. Women were given r-HFSH at a fixed dose (300-450IU) until day 6 of stimulation at which point they were randomised and split into two groups Intervention: The control group continued with r-HFSH alone whereas the intervention group received r-HLH (150IU/day) until the end of stimulation supplemented to	Live birth rate (not singleton) Event/Women (%) r-HFSH:5/68 (7.4%) r-HFSH + LH: 12/63 (19%) Clinical pregnancy: r-hFSH: 10/68 (15%) r-hFSH + LH: 17/63 (27%) Definition of clinical pregnancy not reported	**Limitations** Randomisation of women was poorly executed (two women received incorrect treatment) Blinding not reported **Other information** The results discussion is poorly written and/or executed, the narrative does not explain the given results and the results moving from intention to treat to per protocol do not correlate if the exclusion and crossover of women is to be accepted as written.

	Inclusion criteria BMI between 18 and 30 Baseline FSH less than or equal to 10 IU/l Baseline LH and oestradiol within the normal range for institution Presence of both ovaries and uterine cavity capable of sustaining a pregnancy Clomiphene or gonadotrophin was out for more than or equal to 30 days prior to starting GnRH agonist Confirmed absence of pregnancy **Exclusion criteria** Human immunodeficiency virus or Hepatitis B/C positive Clinically significant condition preventing them from undergoing gonadotrophin treatment More than two previous assisted cycles Cancellation of two previous cycles Cryopreserved embryos available from previous assisted reproductive treatment Unexplained gynaecological bleeding PCOS or an ovarian cyst if unknown aetiology Pregnancy contraindication Active substance abuse Simultaneous participation in another trial or re-entry in the current trial Refusal or inability to comply with the procedures set forth in the protocol.		r-HFSH. In both groups r-HFSH was adjust if needed. In both groups triggering was done 36 hours before retrieval with rhCG, the diameter of (at least) 3 follicles had to have beem of greater or equal to 18.5mm Upto 3 embryos were transferred, followed by 12 days of micronized progesterone luteal phase support (200mg/12hours) Power calculation- a total of 124 patients are needed, 62 randomised to each group.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation Selman,H., Pacchiarotti,A., El-Danasouri,I., Ovarian stimulation protocols based on follicle-stimulating hormone glycosylation pattern: impact on oocyte quality and clinical outcome, Fertility and Sterility, 94, 1782-1786, 2010 **Ref ID** 83051 **Country/ies where the study was carried out** Italy **Study type** Randomised clinical trial **Aim of the study** To evaluate the impact of FSH with different glycosylation pattersn on oocyte quality and clinical outcomes in an in vitro fertilisation treatment program. **Study dates** Januar 2008 to February 2009. **Source of funding** Not reported	**Sample size** n = 188 women **Characteristics** hFSH/rFSH Mean age = 36.6 ± 3.2 years Mean BMI = 23.6 ± 1.6 kg/m^2 Duration of infertility = 4.1 ± 1.2 years rFSH Mean age = 34.9 ± 3.74 years Mean BMI = 23.6 ± 1.7 kg/m^2 Duration of infertility = 4.1 ± 1.4 years hFSH Mean age = 35 ± 4.01 years Mean BMI = 23.1 ± 1.8 kg/m^2 Duration of infertility = 4.5 ± 1.3 years Cause of infertility: Tubal factor = 81 (43.1%) Male factor = 69 (36.7%) Unexplained = 12 (6.4%) Other causes = 26 (13.8%) **Inclusion criteria** 1] Women aged 27 to 38 years 2] Infertility attributable to tubal factor, male factor, or idiopathic infertility 3] Serum hormonal profile within normal range 4] Regular ovulatory menstrual cycles 5] Presence of a normal uterine cavity 6] BMI of 20 to 26 kg/m^2 7] First IVF treatment **Exclusion criteria** Not reported	1] rFSH/hFSH 2] rFSH 3] hFSH	Method: Randomisation was performed using a computer-generated random assignment schedule for each patient. Sealed and numbered envelopes were used to conceal the treatment allocation until randomisation. The randomisation took place after the confirmation of down-regulation and immediately before gonadotropin administration to minimise postrandomisation withdrawals. Intervention: The participating patients underwent a standard down-regulation protocol with a GnRH analogue homone, triptorelin, at 0.1 mg/day on day 21 of their cycle. All patients were given a fixed dose of FSH from day 2 of their cycle until hCG administration. The patients were randomised into 3	Pregnancy: hFSH/rFSH = 27/63 (42.9%) rFSH = 21/65 (32.3%) hFSH = 23/60 (38.3%) Abortion: hFSH/rFSH = 4/63 (6.3%) rFSH = 3/65 (4.6%) hFSH = 3/60 (5%)	**Limitations** Blinding not reported **Other information** 1] Prengnacy was not clearly defined

			groups: group A received 225 IU of acidic hFSH for the first 6 days starting from day 2 of the cycle and followed by 225 IU of less acidic rFSH until hCG administration; group B received 225 IU of less acidic rFSH alone from day 2 of the cycle until hCG administration and group C received 225 IU of acidic hFSH. The FSH dose was adjusted until necessary according to the follicular size and estradiol level. Final oocyte maturation was triggered by the administration of 10,000 IU of hCG. In observance of the current law in Italy, only three oocytes were then inseminated by ICSI. Statistical analysis: For a desired statistical power of 90% based on an alpha level of 0.05, confidence intervals of 95%, and anticipated effective		

			size of 0.5, the minimum total sample size required according to two-tailed hypothesis was 174 patients-at least 58 evaluable patients per group.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Raga,F., Bonilla-Musoles,F., Casañ, EM, Bonilla,F., Recombinant follicle stimulating hormone stimulation in poor responders with normal basal concentrations of follicle stimulating hormone and oestradiol: improved reproductive outcome3140, Human Reproduction, 14, 1431-1434, 1999 **Ref ID** 82949 **Country/ies where the study was carried out** Spain **Study type** Randomised clinical trial **Aim of the study** To evaluate the reproductive performance of young patients, who normally have a low response to ovarian stimulation, despite normal basal FSH and oestradiol when treated with high doses of either rFSH or uFSH. **Study dates** January to June 1998 **Source of funding** Not reported	**Sample size** n = 30 women. **Characteristics** Mean age = 30.5 ± 3.6 years Mean BMI = 23.0 ± 6.6 kg/m^2 Duration of infertility = 4.7 ± 1.1 years Cause of infertility: Tubal factor = 13 (43.3%) Male factor = 2 (6.7%) Endometriosis = 5 (16.7%) Unexplained = 10 (33.3%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] rFSH 2] uFSH	Recruitment: A total of 30 infertile patients, being ≤35 years old, who exhibited a poor response to uFSH (<4 follicles) in two previous cycles, despite having normal basal oestradiol and FSH, were invited to participate. All patients had normal ovulatory cycles, and good physical and mental health. Method: The study was not blinded because it is very important in such studies to avoid 'therapeutic suspicion' bias when evaluating treatment results. Such bias may be introduced in both the application of the treatment and interpretation of results and is likely to occur when the investigators have a prior expectation of results. Therefore the clinicans were not blinded and applied a rigid protocol in all patients. The other	Pregnancy: rFSH = 5/15 (33.3%) uFSH = 1/15 (6.7%)	**Limitations** 1] Method of randomisation was not clearly reported 2] Lack of blinding 3] Allocation concealment not reported 4] No power calculation reported **Other information** No definition of pregnancy was reported

			authors were blinded to the patients' characteristics and treatment group, and performed the randomisation, data analysis and interpretation. Eligible subjects received a number from a randomised list. Intervention: Concentrations of FSH and oestradiol on cycle day 3 were determined in a spontaneous cycle preceding the cycle of ovarian stimulation in all patients. The ovarian stimulation protocol began with the administration of 300 IU/day of either rFSH (two vials of 150 IU rFSH) or uFSH HP (four ampoules of 75 IU uFSH HP) depending on the randomisation, along with two ampoules of hMG/day for the first 4 days. After day 4, the dose of hMG and FSH was adjusted on an individual basis according to follicular development as		

			assessed by transvaginal US scanning and serum oestradiol concentrations. FSH/hMG injections were discontinued on the day of hCG administration. Oocyte retrieval 36 - 38 h after hCG administration, fertilisation procedures, and embryo transfer were done according to the local standards, both proedures bieng performed by the same author. Micronised vaginal progesterone were prescribed for luteal support		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kovacs,P., Kovats,T., Kaali,S.G., Results with early follicular phase recombinant luteinizing hormone supplementation during stimulation for in vitro fertilization, Fertility and Sterility, 93, 475-479, 2010 **Ref ID** 5960 **Country/ies where the study was carried out** Hungary **Study type** Randomised controlled trial **Aim of the study** "to evaluate whether early follicular phase LH administration has a beneficial effect on ovarian stimulation during IVF" **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 50 **Characteristics** Population: Women undergoing IVF Female age (Mean ± SD) 32.7 ± 3.3 years Duration of infertility Not reported BMI/Weight Not reported Cause of infertility Not reported **Inclusion criteria** [1] ≤ 40 years [2] baseline FSH < 10 IU/L on cycle day 3 [3] on first or second IVF attempt [4] no need for donor gamete use **Exclusion criteria** [1] use of surgically retrieved sperm	Standard stimulation Standard stimulation + recombinant LH	Recruitment: The study was conducted on women undergoing IVF. Method: The women were randomised using block-randomisation in blocks of two. Intervention: All stimulations followed the standard luteal long GnRHa down-regulation protocol. In the midluteal phase 0.5 mg of buserelin was started and administered for 10 to 12 days until suppresson was achieved. At suppression patients in the experimental group received 75 IU of rLH daily for 4 days and rFSH at a fixed starting dose of 150IU for the first 5 days was started a day later, on day 2 of rLH. In the control group, patients started rFSH at a fixed dose of 150 IU for the first 5 days of	Pregnancy Standard stimulation = 14/25 (56%) Standard stimulation + recombinant LH = 13/25 (52%) Ptregnancy was not defined Ongoing pregnancy Standard stimulation = 7/25 (28%) Standard stimulation + recombinant LH = 11/25 (33%)	**Limitations** Allocation concealment: Not reported Blinding of participants, staff and study participants: Not reported Power calculation: Not reported **Other information** NA

			suppression. The rFSH could be adjusted for response after the first ultrasound on day 5. Stimulation continued until at least 2 follicles reached 17mm or more. Before oocyte collection 250 µg rhCG was given to induce final oocyte maturation. Transvaginal oocyte retrieval was scheduled 35 to 36 hours after the trigger injection. Transcervic al embryo transfer was performed on day 3 or 5. The luteal phase of the cycles was supported by transvaginal micronized progesterone.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Loutradis,D., Stefanidis,K., Drakakis,P., Kallianidis,K., Kallipolitis,G., El,SheihA, Milingos,S., Michalas,S., Does the addition of menopausal gonadotropin to recombinant FSH in pituitary suppressed women improve clinical pregnancy in an intracytoplasmic sperm injection program?12460, Middle East Fertility Society Journal, 8, 30-35, 2003 **Ref ID** 82623 **Country/ies where the study was carried out** Greece **Study type** RCT **Aim of the study** To determine in patients with many failed attempts [of IVF/ICSI] if it would be possible to improve pregnancy rates if stimulation was done with rFSH and hMG , and to detect which women will need additional LH administration. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 382 (Group 1) n = 308 (Group 2) n = 74 **Characteristics** Group 1 Age: 31.5 (+/-4.1) Days of ovarian stimulation: 10.59(+/-1.012) Starting dose (fixed dose at 5 first days): 150 Group 2 Age: 32.2 (+/-3.5) Days of ovarian stimulation: 10.33(+/-0.9) Starting dose (fixed dose at 5 first days): 175 **Inclusion criteria** One to six previous attempts of ICSI Aged between 21-43 FSH <12mIU/mL **Exclusion criteria** None reported	Comparison (Group 1): GnRH agonist long protocol + rFSH Intervention (Group 2): GnRH agonist long protocol + rFSH + hMG	Randomisation: Drawing sealed envelopes - split into two groups (4:1 ratio) Method: On day 21 of the previous cycle, a baseline ultrasound scan was performed and buserelin (GnRH agonist) intranasal spray (100ug 5 times a day). The extent of ovarina suppression was evaluated by ultrasound and E2 levels before gonadotrophin treatment. Intervention: Stimulation in group 1 was done with 3 ampoules rFSH (150IU) daily. Group 2 received one ampoule hMG (FSH 75IU + LH 75IU) and 2 ampoules of rFSH (100IU) daily. Both administered for 4 days, dosage was adjusted after ovarian response after day 5. GnRHa was administered up until hCG trigger 36 hours before retrieval (follicle >18mm diametre), luteal phase	Clinical pregnancy (event/women) Group one (rFSH): 107/308 (34.7%) Group two (rFSH + hMG): 22/74 (29.7) (Clinical pregnancy is defined a transvaginal 4 weeks after retrieval)	**Limitations** Unclear if research term were blinded No power calculation reported **Other information**

			support was two injections hCG (2500IU) on day of ET and fours days after ET. one to five embryos were transferred		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gomes,M.K.O., Vieira,C.S., Moura,M.D., Manetta,L.A., Leite,S.P., Reis,R.M., Ferriani,R.A., Controlled ovarian stimulation with exclusive FSH followed by stimulation with hCG alone, FSH alone or hMG, European Journal of Obstetrics Gynecology and Reproductive Biology, 130, 99-106, 2007 **Ref ID** 73672 **Country/ies where the study was carried out** Brazil **Study type** Randomised controlled trial **Aim of the study** to compare "the exclusive use of hCG in the late follicular phase to the sue of FSH alone or LH/FSH containing preparationS (hMG) in terms of optimization of teh cycle and better safety" **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 51 **Characteristics** Population: Infertile women aged 25-35 years in good general health were selected. Female age (mean ± sd) Duration of infertility (mean ± sd) BMI (mean ± sd) Cause of infertility Male factor = 39 (76.5%) Tubal factpr = 7 (13.7%) Association = 5 (9.8%) **Inclusion criteria** Not reported **Exclusion criteria** [1] presence of PCOS [2] reduced ovartian function (FSH of more than 10 IU/mL) during the early follicular phase [3] endometriosis or uterine myomas [4] use of an injectable hormonal contraceptive up to 6 months befoer stimulation [5] a history of poor ovarian response to controlled ovarian stimulation [6] concomitant uterine alterations or absecence of one ovary	hCG hMG rFSH	Recruitment: The study included women aged 25-35. The women had regular menstrual cycles, normal BMI of 20-25 kg/m2 and infertility due to tubal factors, infertility with no known cause and moderate/severe male factor infertility. Method: Participants were randomised using computerized randomisation. Intervention: All women were submitted to inhibition of the natural cycle with a low-dose oral contraceptive administered on the firts the previous cycle and discontinued 5 days before beginning of stimulation. aGnRH 0.5 mg/day was also used for inhibitiopn ten days before beginning of induction and continued until the day preceding the pre-ovulartory injection of HCG. In the	Clinical pregnancy hCG = 6/17 (35.3%) hMG = 6/17 (35.3%) rFSH = 3/17 (17.6%) Definition of clinical pregnancy not given Miscarriage hCG = 3/17 (17.6%) hMG = 0/17 (0%) rFSH = 1/17 (5.9%)	**Limitations** Allocation concealment: Not reported Blinding of participants, staff and study personnel: Not reported Power calculation: Adequate **Other information** NA

			first phase, all women were supplemented with 200 IU rFSH administered daily subcutaneously on the first days of induction until the dominant follicles reached 12-13 mm in diameter. In the second phase the women were divided into study groups hCg daily does of 200 IU intramuscularly until the presence of follicles 18-19 mm in diameter were detected. hMG received daily IM injections of 225 IU hMG rFSH received dailyy SC 200mIU rFSH When the desired follicle size was reached 10,000 IU hCG was administered IM to all women between 18.00 and 20.00 Oocyte retrieval was performed 36 hours after pre-ovulatory hCG injection.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ku,S.Y., Suh,C.S., Kim,S.H., Choi,Y.M., Kim,J.G., Moon,S.Y., A pilot study of the use of low dose human menopausal gonadotropin in ovulation induction, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 109, 55-59, 2003 **Ref ID** 74002 **Country/ies where the study was carried out** South Korea **Study type** Randomised Controlled Trial **Aim of the study** To evaluate the clinical efficacy of combined regimen of FSH and low dose human menopausal gonadrtrophin, used for LH supplementation, following the GnRH agonist ultralong protocol in COH for IVF-ET. **Study dates** Not specified. **Source of funding** Not specified	**Sample size** n = 45 women. GnRHa+HP-FSH+hMG group = 26, GnRHa+HP-FSHb group = 19 **Characteristics** <u>Age (years)</u> GnRHa+FSH+hMG group = 33.0 (+/- 4.3) GnRHa+FSHb group = 34.6 (+/- 4.5) <u>Number of previous IVF cycles</u> GnRHa+FSH+hMG group = 2.1 (+/- 1.3) GnRHa+FSHb group = 2.8 (+/- 2.4) <u>Number of embryos transferred</u> GnRHa+FSH+hMG group = 3.2 (+/- 1.2) GnRHa+FSHb group = 3.4 (+/- 0.9) <u>Cause of infertility</u> Endometriosis: 15 vs. 9	All women received had long-acting GnRH agonist down-regulation. Women then randomised to receive either: • GnRHa+FSH+hMG group: FSH individualised to patient plus hMG at 75 IU per day • GnRHa+FSHb group: SH individualised to patient When lead follicule reached 18mm or three or more reached 14mm and E_2 leverl of 200 pg/ml then hCG trigger used.	Ethics approval not specified. Statistical analysis using t-test and chi-squared.	<u>Pregnancies</u> GnRHa+FSH+hMG group = 6/26 GnRHa+FSHb group = 2/19	**Limitations** Method of randomisation not specified. Blinding not specified. Sample size calculation not specified. **Other information**

	Adenumyosis: 2 vs. 2 Myoma uteri: 7 vs. 6 Others: 2 vs. 2 Male factor combined: 3 vs. 3 **Inclusion criteria** Women with uterine or peritoneal factor or uterine myoma problems. **Exclusion criteria** Not specified				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Check,J.H., Davies,E., Brasile,D., Choe,J.K., Amui,J., A prospective comparison of in vitro fertilization (IVF) outcome following controlled ovarian hyperstimulation (COH) regimens using follitropin alpha exclusively or with the addition of low dose human chorionic gonadotropin (hCG) and ganirelix, Clinical and Experimental Obstetrics and Gynecology, 36, 217-218, 2009 **Ref ID** 73208 **Country/ies where the study was carried out** USA **Study type** Randomised Controlled Trial **Aim of the study** To compare FSH only to FSH with hCG used in a GnRH antagonist protocol **Study dates** Not specified **Source of funding** Not specified	**Sample size** 70 women enrolled. 35 in FSH only group and 35 in FSH with hCG group. Data analsed for 22 (37% loss to follow-up) in FSH group and 20 (40% loss to follow-up) in FSH with hCG group. **Characteristics** <u>Age</u> FSH group = 33.6 FSH with hCG group = 35.1 <u>Embryos transferred</u> FSH group = 3.0 FSH with hCG group = 3.0 **Inclusion criteria** No specified **Exclusion criteria** Women with hypogonadotropic amenorrhea or those with diminished egg reserve were excluded.	GnRH antagonist protocol with women ranomised to either: • FSH only group: 300 IU daily of follitropin alpha only • FSH plus hCG group: 300 IU daily of follitropin alpha with 25 IU hCG. Ganrelix added to both groups when lead follicule >14mm. Oocyte retrieval 35 hours after hCG trigger injection. Embryo transfer on day 3.	Ethics approval not specified. Statistical methods not specified.	<u>Deliveries</u> FSH only group = 6/22 FSH+hCG group = 6/20 <u>Pregnancies</u> FSH only group = 7/22 FSH+hCG group = 10/20 <u>Multiple pregnancies</u> FSH only group = 2/22 FSH+hCG group = 2/20	**Limitations** Pilot study and poor reporting of results Method of randomisation not specified. Blinding not specified. Sample size calculation not undertaken as a pilot study. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ferraretti,A.P., Gianaroli,L., Magli,M.C., D'Angelo,A., Farfalli,V., Montanaro,N., Exogenous luteinizing hormone in controlled ovarian hyperstimulation for assisted reproduction techniques1838, Fertility and Sterility, 82, 1521-1526, 2004 **Ref ID** 82205 **Country/ies where the study was carried out** Italy **Study type** Randomised Controlled Trial **Aim of the study** To investigate the role of exogenous LH in controlled ovarian hyperstimulation for assisted reproductive technologies. **Study dates** January 2002 to April 2003 **Source of funding** Not specified	**Sample size** 1009 women assessed for inclusion. Group A = 54, Group B = 54 and Group C = 26. Group D were a age-matched but not randomly assigned to treatment. Embryo transfer was undertaken on Group A = 45, Group B = 41 and Group C = 18. Frozen cycle transfers included in the figures. **Characteristics** <u>Age (mean, SD)</u> Group A = 31.66 (+/- 2.8) Group B = 31.49 (+/- 3.2) Group C = 32.02 (+/- 4.1) <u>Male factor infertility</u> Group A = 36 Group B = 31 Group C = 123 <u>Number of cancelled cycles</u> Group A = 2	All women received GnRH agonist down-regulation. Ovarian stimulation was started at a dose of 150 IU in women <30 years old, 225 IU in women aged 30 to 37, and 300 IU in women => 38 years. Women who after 7 to 10 days of stimulation showed a plateau in follicule growth (no increase in the E_2 level and follicular size were ranomised to receive: Group A = increased dose of rFSH (maximum of 450 IU/daily) Group B = increased dose of rFSH (maximum of 450 IU/daily) plus 75 to 150 IU of rLH. Group C = increased dose of rFSH (maximum of 450 IU/daily) and LH using hMG. Luteal phase support using 50mg/day of progesterone in oil starting 3 days after egg retireval.	Ethics approval received. Randomisation method not specified Blinding not specified Sample size calculationot specified Statistical analysis using chi-squared and fishers exact test.	Results include additional thawed embryo transfers. <u>Number of pregnancies</u> Group A = 11/45 Group B = 22/41 Group C = 2/18 <u>Frozen embryo transfers</u> Group A = 1 Group B = 2 Group C = 2 <u>Number of abortions</u> Group A = 1 Group B = 2 Group C = 0 <u>Number of abortions</u>	**Limitations** **Other information** Data may already have been in 2004 publication.

	Group B = 4 Group C = 2 <u>Number of embryos transferred</u> Group A = 1.93 Group B = 1.85 Group C = 1.63 **Inclusion criteria** Women showing hyporesponsiveness to FSH. Age =< 37 years, BMI =< 27, normo-ovulatory cycles, no ovarian stimulation within past 6 months, normal uterine cavity, presence of both ovaries and normal karyotupes in both women and man. **Exclusion criteria** Not specified			Group A = 1 Group B = 2 Group C = 0	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Long,C.A., Sopelak,V.M., Lincoln,S.R., Cowan,B.D., Luteal phase consequences of low-dose gonadotropin-releasing hormone agonist therapy in nonluteal-supported in vitro fertilization cycles, Fertility and Sterility, 64, 573-576, 1995 **Ref ID** 68624 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare the clinical effects of low-dose leuprolide acetate (GnRH agonist) combined with hMG to CC and hMG during follicular stimulation for IVF. **Study dates** Not reported **Source of funding** None reported	**Sample size** 70 women **Characteristics** 25 to 45 years old First IVF-ET program **Inclusion criteria** None reported **Exclusion criteria** None reported	GnRH agonist + hMG + hCG CC + hMG + hCG	GnRH agonist group: 0.25 mg GnRH agonist (Lupron) with 150 IU hMG (Pergonal) daily starting on day 2 of cycle. CC group: 50mg CC on days 2 to 6 of menstrual cycle and 150 IU hMG (Pergonal) on a daily basis beginning on day 3 HCG (10,000 IU) administered when three or more follicles measured => 15 mm and circulating E2 was >200 pg/mL per follicle Aspiration performed 34 hours after hCG administration No luteal support was given to either group	Clinical pregnancy: GnRH agonist group= 5/36 (14%) CC group= 5/34 (15%) Clinical pregnancy was confirmed if rising hCG concentrations were observed and an intrauterine gestation or tubal pregnancy was confirmed Singleton live births: GnRH agonist group= 1/36 (3%) women CC group= 4/36 (11%) women Babies born from multiple pregnancies: GnRH agonist group= 2/3 (67%) babies CC group= 0/4 (0%) babies Miscarriages: GnRH agonist group= 2/36 (6%) women, 2/5 (40%) pregnancies	**Limitations** Power calculation not reported Blinding not reported Method of randomisation not reported Allocation concealment not reported **Other information** GnRH agonist group had four cancellations for poor response, one for enlarged ovarian cyst, one for hyperstimulation CC group had three cancellations for poor response, two for premature LH surge, and one for enlarged ovarian cyst

				CC group= 0/36 (0%) women, 0/5 (0%) pregnancies Ectopic pregnancies: GnRH agonist group= 0/36 (0%) women, 0/5 (0%) pregnancies CC group= 1/36 (3%) women, 1/5 (20%) pregnancies	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gholami,H., Vicari,E., Molis,M., La,Vignera S., Papaleo,E., Cappiello,F., Pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women aged **Ref ID** 73647 **Country/ies where the study was carried out** Italy **Study type** Randomised Controlled Trial **Aim of the study** To compare the pregnancy outcome of IVF-ET cycles in which either hFSH or rFSH were used for controlled ovarian stimulation when GnRH agonist id used for pituitary desensitisation in 'good prognosis' patients aged <37 years. **Study dates** January 2008 to September 2008 **Source of funding** Not specified	**Sample size** 115 women enrolled. 62 in hFSH group and 53 in rFSH group **Characteristics** <u>Age (mean, SD)</u> hFSH group = 32 +/- 4.1 rFSH group = 32 +/- 4.8 <u>Duration of infertility (months)</u> hFSH group = 47 +/- 17.6 rFSH group = 41.9 +/- 10.3 <u>BMI</u> hFSH group = 23.6 +/- 6.5 rFSH group = 22.7 +/- 6.8 <u>Enbryos transferred</u> hFSH group = 2.1 +/- 0.6 rFSH group = 2.2 +/- 0.3 <u>Cause of infertility (hFSH vs rFSH)</u>	hFSH (n= 53) rFSH (n= 62)	Ethics approval obtained. All women underwent GnRH agonist downregulation started at mid-luteal phase until hCG (10,000 IU) administration. Women were then randomised to one of two groups: hFSH group: 150 IU per day but adjusted if needed. rFSH group: 150 IU per day but adjusted if needed. Women were monitored and hCG admiinistered when 3 follicules >18mm were seen. Cycle cancelled if estradiol level rose above >4000 pg/ml Chi-squared or t-test used in statistical analysis.	<u>Clinical pregnancy (cardiac activity at 7 weeks)</u> hFSH group = 24/62 rFSH group = 21/53 Non significant <u>Spontaneous abortion rate</u> hFSH group = 3/24 rFSH group = 2/21 Non significant	**Limitations** Sample size calculation not specified. Method of ransomisation not specified. Blinding not specified. **Other information**

	Ovulatory = 6 vs. 5 Endometriosis = 2 vs. 2 Male = 25 vs. 22 Tubal = 19 vs. 18 Unexplained = 10 vs. 6 **Inclusion criteria** <37 years of age Basal FSH <12 mIU/ml **Exclusion criteria** Not specified				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Marrs,R., Meldrum,D., Muasher,S., Schoolcraft,W., Werlin,L., Kelly,E., Randomized trial to compare the effect of recombinant human FSH (follitropin alfa) with or without recombinant human LH in women undergoing assisted reproduction treatment2049, Reproductive Biomedicine Online, 8, 175-182, 2004 **Ref ID** 82675 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To compare the effect the r-HFSH with or without r-HLH in ovulation stimulation in IVF. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 431 Group 1 (FSH + LH) n = 212 Group 2 (FSH) n = 219 **Characteristics** Group one (FSH + LH) Age: 32.4 (+/-3.8) BMI: 24.3 (+/-4.7) Smoker (%): 13 (6.1) Duration of infertility (years): 3.9 (+/-3.1) Previous assisted cycle(s) (%): 56 (26.4) Group two (FSH) Age: 31.9 (+/-3.7) BMI: 24.8 (+/-5.6) Smoker (%): 16 (7.3) Duration of infertility (years): 3.7 (+/-2.6) Previous assisted cycle(s) (%): 60 (27.4) **Inclusion criteria** Normal ovulation Women aged between 18 and 40 Serum/plasma FSH within the normal range (up to 11.2mIU/ml) Male partner with a male factor infertility **Exclusion criteria** Clinically significant disease Smoking more than 10 cigarrettes a day Any contraindication to pregnancy Serum/plasma levels LH:FSH ratio .2 More than two previous ICSI cycles in which gonadotrophin stimulation was used.	Intervention: GnRH agonist + r-HFSH + r-HLH + hCG Comparison: GnRH agonist + r-HFSH + hCG	Randomisation: A computer-generated randomization sequence was used Method: Pituitary down-regulation was carried out using leuprodile acetate (GnRH agonist) 0.5mg/day, starting 7-8 after estimated ovulation. Treatment with r-hFSH (225IU/day) was started when serum oestradiol was ,75pg/mk. After 5 days, the r-hFSH dose could be increased by 75-150IU/day every 2-3 days if necessary. Intervention: The intervention group began treatment with r-hLH (150IU/day) on stimulation day 6. The dose of r-hLH remained constant throughout the treatment period. Patients recieved a single intramuscular injection of hCG when: largest >18mm, 2 others /16mm, oestradiol	Clinical pregnancy (event/women) r-hFSH + r-hLSH Total: 90/212 (42.5%) <35 years old: 63/147 (42.9%) >35 years old: 27/65 (41.5%) r-hFSH Total: 91/219 (41.6%) <35 years old: 74/163 (45.4%) >35 years old: 17/56 (30.4) (Clinical pregnancy was defined as 35-42 day after hCG administration, number of fetal sacs and fetal heart activity was recorded)	**Limitations** None obvious **Other information** The FSH + LH group contained 60 women >35 years old, 56 were in the FSH group.

			concentration within the acceptable range. Upto 3 embryo's were transferred.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mikkelsen,A.L., Smith,S., Lindenberg,S., Possible factors affecting the development of oocytes in in-vitro maturation, Human Reproduction, 15 Suppl 5, 11-17, 2000 **Ref ID** 74252 **Country/ies where the study was carried out** Denmark **Study type** RCT **Aim of the study** To investigate the possible effects of FSH priming before aspiration, time interval for maturation, and the timing of aspiration by monitoring follicular size and the serum concentrations of oestradiol and inhibin A. **Study dates** Not reported **Source of funding** Supported in part by Medi-Cult AS	**Sample size** 20 women **Characteristics** Characteristics for all of the included women were: Age range: 18 to 37 years Normal ovulatory cycles: mean duration of 26 to 35 days BMI range: 18 to 29 kg/m2 The characteristics of the 20 women included only in the first part of the study were not reported separately. **Inclusion criteria** Women referred for IVF/ICSI because of male factor infertility and/or tubal disease **Exclusion criteria** Infertility caused by endocrine abnormalities (e.g. hyperprolactinaemia) Women with low ovarian reserve (day 3 antral follicle count of three or less at 2-5mm and/or and FSH concentration of >15 IU, and/or an inhibin B concentration of <45 pg/ml) Patients who had more than three failed IVF attempts Patients with possible poor quality oocytes (<20% cleavage rate at conventional IVF)	1) No stimulation with FSH (n=10) 2) rFSH (150IU) for three days (n=10)	Women were randomly allocated to two groups - no stimulation or simulation with rFSH (150 IU) for three days (started on day 3) [no further details of FSH administration were provided) Oocytes were aspirated after the leading follicle reached 10mm in diameter Endometrial priming with 17B-oestradiol started on the day of oocyte retrieval (2 mg orally, 3x day) Progesterone suppositories initiated two days after aspiration until pregnancy test If pregnancy test was positive, oestrogen and progesterone were continued until 50 days gestation All oocytes were	Pregnancies No FSH: 3/10 (30%) FSH: 2/10 (20%) There was no significant difference between the groups Pregnancy was not defined	**Limitations** Blinding was not reported Allocation concealment was not reported Method of randomisation was not reported Power analysis was not reported **Other information** This study was in three parts: the first part looked at FSH priming compared to no priming, the second part looked at the maturation period, and the third part looked at the timing of aspiration. Only the first part of the study is reported here.

	Women with PCOS (>10 follicles in one plane on ultrasound, elevated LH/FSH ratio or elevated androgens)		matured for 36hrs then inseminated by ICSI Maximum of two oocytes were transferred on day 2.5 or 3 (day 0=day of insemination) per woman		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sohrabvand,F., Golestan,B., Kashani,H., Saberi,M., Haghollahi,F, Maasomi,M., Bagheri,M., Comparison of ART Outcomes between two COH Protocols: Gonal-F versus Gonal-F Plus HMG, International Journal of Fertility and Sterility, 3, 161-164, 2010 **Ref ID** 125844 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial **Aim of the study** To investigate the effects of LH on women treated with human FSH in cycles down regulated with a RnGH agonist in the long protocol **Study dates** June 2006 to June 2007 **Source of funding** None reported	**Sample size** 64 women **Characteristics** Mean age: rFSH group= 27.6 years (+/- 4.3) rFSH + hMG group= 28.6 years (+/- 4.0) Mean BMI: rFSH group= 24.3 (+/-3) rFSH + hMG group= 23.3 (+/- 4.2) Mean length of infertility: rFSH group= 5.8 years (+/- 3.2) rFSH + hMG group= 6.4 years (+/- 3.4) There was no significant difference in any of the above, or basic LH, basic FSH, or basic estradiol between the two groups. Couples had normal karyotypes with primary cause of their infertility as either tubal or male factor	rFSH + hCG + progesterone (n=32) rFSH + hMG + hCG + progesterone (n=32)	All women underwent: OCP pretreatment Pituitary down regulation with GnRH agonist (once daily dose of 0.2cc Buserelin) from 21st day of cycle After at least 12 days of desensitisation, rFSH started (Gonal-F, 150 IU/day for first six days) Women were then randomised: Group A: continued with 150IU FSH if they had 2-3 follicles => 10 mm. When there were two follicles => 18 mm and two others >16 mm, 10,000 hCG given. If response was insufficient, on the seventh day they received additional rFSH (Gonal-F, 75 to 150 IU) Group B: same	Clinical pregnancy: FSH only group= 6/32 (19%) FSH + hMG group= 6/32 (19%) Clinical pregnancy was 'confirmed with ultrasound examination' six weeks after chemical pregnancy test (itself two weeks after embryo transfer) Live birth: FSH only group= 6/32 (19%) FSH + hMG group= 6/32 (19%)	**Limitations** No power analysis was reported Blinding was not reported Allocation concealement was not reported Method of randomisation was not reported **Other information** There were significant differences in the serum levels of progesterone ($p<0.001$) and estradiol ($p=0.037$) after stimulation, the number of follicles >15mm ($p=0.040$), and number of grade B embryos ($p=0.003$) between the two groups.

	Inclusion criteria Patients aged 20 to 35 years BMI 18 to 30 kg/m2 No underlying medical conditions No contraindications for pregnancy **Exclusion criteria** Women with PCOS FSH levels > 12 IU/L		treatment as group A until day seven when hMG (Merional) was administered alongside rFSH (Gonal-F, 75 IU). If response was insufficient, additional hMG was given (75-100 IU) until at least 2 follicales => 18 mm were observed) Women in both groups then received an intramuscular injection of hCG (10,000 IU) and oocyte pickup was performed 34 to 36 hours after ICSI was performed Embryo transfer was done on day 3 of ovum pickup with no more than 3 embryos being transferred per patient Luteal phase supported in both groups by progesterone (Cyclogest,		
			400mg/Bid) from the day of oocyte retrieval		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tarlatzis,B., Tavmergen,E., Szamatowicz,M., Barash,A., Amit,A., Levitas,E., Shoham,Z., The use of recombinant human LH (lutropin alfa) in the late stimulation phase of assisted reproduction cycles: a double-blind, randomized, prospective study, Human Reproduction, 21, 90-94, 2006 **Ref ID** 4605 **Country/ies where the study was carried out** Israel, Greece, Turkey, Poland **Study type** Double blind, randomized, prospective study **Aim of the study** To assess need for additional LH by comparing the yield of oocytes in infertile women undergoing assisted reproduction with and without supplementary r-hLH. **Study dates** None reported **Source of funding** None reported	**Sample size** N = 123 women, 114 were randomized. N = 57 (+2 excluded) in R-hFSH + placebo N = 55 r-hFSH + r-hLH **Characteristics** Women had normal ovulatory cycles of 24-35 days Maximum FSH and prolactin concentrations of 12IU/L and 1040mIU/l during follicular phase (days 2-6) No evidence of other gynaecological pathology (except tubal) <u>r-hFSH</u> age - 30.3 BMI - 22.9 <u>r-hFSH</u> age - 30.5 BMI - 23 **Inclusion criteria** Women's age was >18 and <37 Normal uterus and two ovaries Scheduled to undergo ovarian stimulation prior to IVF + ICSI **Exclusion criteria**	Intervention: GnRH long protocol + r-hFSH + r-hLH + hCG + Progesterone Comparison: GnRH long protocol + r-hFSH + placebo + hCG + Progesterone	<u>Randomisation:</u> Patients were randomised according to treatment number by a computer program. <u>Blinding:</u> Participants and clinicians were blinded to treatment allocation <u>Method:</u> Women given GnRH long protocol. Treatment with r-hFSH was started in women with E2 concentrations <200pmol/l. Dosage was 150 IU daily for 5 days after which it was increased to 450 IU/day according to ovarian response. Once the leading follicle is 14mm patients either 75IU/day r-hLH for a maximum 10days or placebo. HCG (10 000IU) was induced after 2 follicles >17mm. Progesterone was used at post implantation support 600mg/day for 3 weeks.	<u>Live birth rate (number of women giving birth)</u> r-hFSH + placebo - 10 (event)/57 (women) (17.5%) r-hFSH + r-hLH - 6/55 (10.9%) <u>Clincial pregnancy</u> r-hFSH + placebo - 14/57 (24.6) r-hFSH + r-hLH - 9/55 (16.4%) (Pregnancy was confirmed by presence of a fetal sac and heart beat on examination on day 35 after oocyte retrieval) <u>Miscarriages/pregnancy</u> r-hFSH + placebo - 4/14 (28.6%) r-hFSH + r-hLH - 3/9 (33.3%) <u>Pregnancy loss</u> r-hFSH + placebo - 4/57 (7%) r-hFSH + r-hLH - 3/55 (5.5%)	**Limitations** No power calculation was reported **Other information** Patients medication was provided in treatment box - placebo and intervention ampules were identical.

	Women in whom a previous IVF cycle had been unsuccessful due to poor response (<2 oocytes recovered)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Quigley,M.M., Collins,R.L., Blankstein,J., Pure follicle stimulating hormone does not enhance follicular recruitment in clomiphene citrate/gonadotropin combinations, Fertility and Sterility, 50, 562-566, 1988 **Ref ID** 68877 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine if FSH enhances follicular recruitment in CC/gonadotrophin combination stimulation **Study dates** February 1987 to November 1987 **Source of funding** Not reported	**Sample size** N = 98 Group A n = 48 Group B n = 50 **Characteristics** CC/hMG Age - 32.5 (+/-4.1) Infertility cause Tubal - 25 Oligospermia - 2 Unexplained - 13 Endometriosis - 12 Cervical - 1 Other male - 5 Other female - 11 CC/FSH Age - 32.7 (+/-4.4) Infertility cause Tubal - 25 Oligospermia - 3 Unexplained - 6 Endometriosis - 25 Cervical - 0 Other male - 7 Other female - 12 **Inclusion criteria** Women ovulate normally (either spontaneously or in response to ovulation inducing agents) Women have a receptive uterus **Exclusion criteria** Patients who had previously responded poorly to standard CC/hMG stimulation	Group one - CC + hMG + hCG + P Group two - CC + hFSH + hCG + P	Randomisation: Sequential drawing of numbered envelopes - allocation used random number table Method: Patients received 100mg CC and one ampule of either of drugs outlined below from day 4 to 8. Follicular development was monitored by daily serum estradiol from day 3 to 9. From day 9 until hCG administration the patient received 1, 2 or 3 ampoules of their allocated gondotrophin depending on follicular response. Embryo placement was scheduled for 48 hours after retrieval. If there are >5 embryos 3 are used, four or fewer then all were used. Luteal phase support was 25mg of progesterone-in-oil at time or transferred. 25mg suppositories administered twice daily for 14 days. Intervention: The first	Biological pregnancy (event/women) CC/hMG - 6/48 (12.5%) CC/FSH - 5/50 (10%) (Pregnancy diagnosed with a serum qualitive hCG determination on the 18th day after hCG administration with pregnancy documented by ultrasound examination) Pregnancies aborted CC/hMG - 2/48 (4.2%) CC/FSH - 3/50 (6%) Pregnancies delivered CC/hMG - 4/48 (8.3%) CC/FSH - 2/50 (4%)	**Limitations** none obvious **Other information** Timing of hCG and middle IVF protocol referenced (not described) in study. Power calculation done

			group received drug A and the other group received drug B. one of the drugs was a combination of 75IU LH and 75IU FSH (per ampule) the other 75IU FSH and <1IU LH (per ampule)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Keye,W.R.,Jr., Marrs,R.P., Check,J.H., Schnell,V., Surrey,M., Marshall,D.C., EMBRACE Study Group., Evaluation of mixed protocols with Bravelle (human-derived FSH) and Repronex (hMG) to assess clinical efficacy (EMBRACE) in women undergoing in vitro fertilization, Fertility and Sterility, 82, 348-357, 2004 **Ref ID** 5273 **Country/ies where the study was carried out** USA **Study type** 2 RCTs conducted in parallel **Aim of the study** This study was designed to explore the efficacy and safety of three different ratios of human-derived FSH:hMG, in an attempt to identify any substantial differences in these regimens for ovulation induction in IVF. **Study dates** Not reported **Source of funding** Not reported	**Sample size** Study one N = 108 Study two N = 120 **Characteristics** Study one (women <34 years old) Age (mean yr): 30.1 BMI (mean): 24,2 Primary infertility diagnosis (%) - Tubal factor: 52.9 - Endometriosis: 18.3 - Unexplained: 28.8 Study two (women 34-40 years old) Age (mean yr): 36.6 BMI (mean): 24.7 Primary infertility diagnosis (%) - Tubal factor: 48.4 - Endometriosis: 9.2 - Unexplained: 42.4 **Inclusion criteria** Women age <34 years old (study one) Women aged 34 to 40 (study two) Regular ovulatory menstrual cycles of 24-35 days Documents history of infertility attributed or associated with: - tubal factor - endometriosis - Unexplained causes Male partners had normal semen analysis (WHO) A minimum of one menstrual cycle , without any involvement with ART was required	GnRH long protocol + FSH + hMG + hCG + P The dose of hMG and therefore LH was varied - the three groups are outlined in the method and are defined below. Group 1: Ratio 1:1 (the proportion of FSH:LH remains constant throughout stimulation) Group 2: hMG add (hMG added to stimulation midway into gonadotrophin stimulation) Group 3: Low dose hMG	Method: Women received GnRH agonist long protocol (0.5 mg/day) from 7 before the anticipated next menses, continuing for a maximum of 20 until estradial levels of <45pg/mL were achieved and endometrial thickness of <6mm was observed. After this GnRHa was reduced to 0.25mg/day until hCG was administered. The women were allocated one of three protocols below. When 3 follicles were >16mm hCG was used and the oocytes were retrieved 36 hours later. Upto 4 embryos were transferred 3 to 5 days after oocyte retrieval. Luteal phase support used progesterone and continued up to clinical pregnancy or negative test. Intervention: There are 3 hMG:FSH ratio's being considered, the FSH remains constant in all arms. Ratio one	(Continuing clinical pregnancy confirmed using transvaginal around 4 weeks after ET then repeated 1 week later) Study one (women <34 years old) Continued clinical pregnancy (women/event) 1:1 hFSH:hMG - 16/35 (45.7%) hMG add on - 16/39 (41%) Low dose hMG - 15/34 (44.1%) Live births 1:1 hFSH:hMG - 16/35 (45.7%) hMG add on - 15/39 (38.5%) Low dose hMG - 14/34 (41.2%) OHSS 1:1 hFSH:hMG - 4/35 (11.4%) hMG add on - 2/39 (5.1%) Low dose hMG - 2/34 (5.9%) Study two (women 34-40 years old) Continued clinical pregnancy (women/event) 1:1 hFSH:hMG - 17/41 (41.5%) hMG add on - 15/40 (37.5%) Low dose hMG - 16/39 (41%) Live births	**Limitations** 1) Randomisation method not reported 2) No concealment method reported 3) No researcher blinding reported **Other information** Power calculation done.

	Exclusion criteria Women smoking Clinically relevant systemic disease/surgical or medical condition Positive pregnancy test in within the last 3 months BMI . 34 History of abnormal uterine bleeding History of chemotherapy Document intolerance or allergy to any gonadotropin Active history of substance allergy Currently breast feeding Taking OCP in cycle prior Any experimental drug study within the previous 60 days		1:1 (225 FSH:112.5 LH) increasing proportionally after day 6 (maximum 450FSH: 225LH) Ratio two (hMG add-on) 3:0 (225 FSH:0 LH) increasing to 1:1 ratio (as above) on day 6 (maximum 450FSH: 225LH) Ratio three (Low dose hMG) 2:1 (225 FSH:75 LH) FSH increasing after day 6 but not LH (maximum 450FSH :75 LH)	OHSS 1:1 hFSH:hMG - 0/41 (0%) hMG add on - 3/40 (7.5%) Low dose hMG - 2/39 (5.1%) 1:1 hFSH:hMG - 16/41 (39%) hMG add on - 11/40 (27.5%) Low dose hMG - 14/39 (35.9%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kahn,J.A., Sunde,A., von,DuringV, Out,H.J., A prospective randomized comparative cohort study of either recombinant FSH (Puregon) or urinary FSH (Metrodin) in in vitro fertilization treatment, Middle East Fertility Society Journal, 4, 206-214, 1999 **Ref ID** 82468 **Country/ies where the study was carried out** Holland **Study type** RCT **Aim of the study** To investigate the efficact and safety of the recombinant produced FSH in IVF treatment. **Study dates** April 1992 to April 1994 **Source of funding** Not reported	**Sample size** N = 150 (N = 146 given FSH stimulation) **Characteristics** Recombinant FSH Women's age - 32.7mean (+/-3.1sd) Years of infertility - 8.0 (+/-3.4) Prior pregnancy (%) - 75% Cause of infertility (%) - Tubal defects 84% - Endometriosis 11% - Unexplained 3% Urinary FSH Women's age - 31.8 (+/-3.1) Years of infertility - 7.4 (+/-4.1) Prior pregnancy (%) - 73% Cause of infertility (%) - Tubal defects 89% - Endometriosis 7% - Unexplained 2% **Inclusion criteria** Women aged between 18 and 40 A maximum of 3 previous IVF/ART attempts (at least 1 oocytes retrieved) Normal ovulatory cycle 24-35days (+/-3days) Good physical and mental health Body weight between 80 and 130% of ideal body weight **Exclusion criteria** Infertility caused by: -Endocrine abnormalities -PCOS -Hyperprolactinaemia Absence of ovary function	Intervention: GnRH agonist long protocol + rFSH + hCG + P Comparison: GnRH agonist long protocol + uFSH + hCG + P	Randomisation: Random numbers given to women that corresponded to a list a box of medication. Method: GnRH agonist long protocol, initial dose was 4x150ug daily for 14 days. If suppression was achieved (E2 <200pmol/l and no ovarian cysts >20mm diameter) stimulation of FSH was started. If E2 >200pmol, FSH stimulation doubled. GnRHa administered until afternoon of hCG trigger. For the first 5 days of cycle FSH remains constant, on day 6 dose was adjusted according to follicular response (assessed by E2 concentration). The second and third cycles FSH dose was determined by response to first. When at least 3 follicles reach 17mm diameter (vaginal ultrasound) hCG administered	Clinical Pregnancy (defined as ultrasound detection of gestational sac with a foetus with a heartbeat) uFSH (event/women) - Cycle one - 25/60 (41.6%) - Cycle two - 16/38 (42.1%) - Cycle three - 7/17 (41.2%) - Total - 48/115 (41.7%) rFSH - Cycle one - 41/86 (47.7%) - Cycle two - 13/38 (34.2%) - Cycle three - 5/23 (21.7%) - Total - 59/147 (40%)	**Limitations** 1) No power calculation 2) The blinding of the researcher was insufficient (impossible to blind delivery of FSH) **Other information** Unclear what was meant by "take home birth rate" results below: uFSH (event/women) - Cycle one - 19/60 (31.1%) - Cycle two - 12/38 (41.9%) - Cycle three - 7/17 (41.2%) - Total - 38/115 (33%) rFSH - Cycle one - 36/86 (41.9%) - Cycle two - 9/38 (23.7%) - Cycle three - 4/23 (11.4%) - Total - 49/147 (33.3%)

	Any ovarian/abdominal abnormality that could interfere with ultrasound Hypertension Pulmonary, hepatic or renal disease Alcohol or drug abuse Administration of any nonregistered investigational drugs Male infertility defined as sperms cells <10x10^6 per ml and <40% motility and <40% normal morphology		(10,000IU), oocytes retrieved 33-35hours later. A maximum of 2 embryos were transferred following examination after 54hours. Luteal phase support was done with 200mg progesterone twice daily for 15 days. Cryopreservation was done to spare embryo's, cycles using frozen embryos were considered additional and done in natural cycles (preferred). Cycles were cancelled if E2 ever reached above 15,000pmol/l Intervention: Women were either given urinary and recombinant FSH		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wiser,A., Gonen,O., Ghetler,Y., Shavit,T., Berkovitz,A., Shulman,A., Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study, Human Reproduction, 25, 2496-2500, 2010 **Ref ID** 83334 **Country/ies where the study was carried out** Israel **Study type** Randomised controlled trial **Aim of the study** To evaluate the effect of dehydroepiandrosterone (DHEA) supplementation on in vitro fertilization (IVF) data and outcomes among poor-responder patients **Study dates** January 2008 to July 2009 **Source of funding** None reported, although DHEA was provided by SuperPharm Ltd.	**Sample size** n= 33 women **Characteristics** Mean age: DHEA group= 36.9 years (+/- 4.7) Control group= 37.8 years (+/- 4.6) Mean BMI: DHEA group= 26/1 (+/- 5.5) Control group= 25.7 (+/- 4.6) Primary infertility: DHEA group= 7/17 (41%) women Control group= 10/16 (63%) women Cause of infertility not reported No significant differences between the groups **Inclusion criteria** Previous prior response to ovarian stimulation in IVF (defined as retrieval of < 5 oocytes, poor-quality embryos, or cycle cancellation due to poor response to ovarian stimulation, whenever the gonadotrophin starting dose for induction of ovulation was at least 300 IU/day) **Exclusion criteria** > 42 years Women who received DHEA at any time prior to enrollment	Study group= DHEA in addition to long protocol (n= 17) Control group= long protocol with no DHEA (n= 16)	Randomisation was performed using computer generated random numbers The study was designed for two consecutive cycles Study group: 75mg DHEA orally, once a day, at least 6 weeks before starting the first cycle of ovulation induction. Patients who did not conceive and continued to the second cycle took DHEA for at least 16 to 18 weeks Both groups: standard long-stimulation protocol of GnRH agonist (triptorelin acetate - 0.1mg Decapeptyl) started during luteal phase. When down regulation was achieved, 450IU rFSH and 150 IU rLH were given. When leading follicle = 18mm in diameter, 500ug of rhCG was given. Ovum pickup	<u>Live singleton births</u> DHEA group= 6/17 (35%) women Control group= 1/16 (6%) women p=0.05 <u>Clinical pregnancies</u> DHEA group= 7/17 (41%) women Control group= 3/16 (19%) women p=0.07 <u>Abortions</u> DHEA group= 1/17 (6%) women, 1/7 (14%) pregnancies Control group= 2/16 (13%) women, 2/3 (67%) pregnancies p value not reported	**Limitations** No power analysis was undertaken Blinding was not reported **Other information** DHEA taken for an average of 13.5 weeks in the study group One woman in the study group conceived spontaneously 45 days after DHEA exposure, before starting IVF treatment, and was included among among the study group pregnancies

			performed 36 hours after triggering with rhCG Vaginal progesterone was given from confirmation of fertilisation until the pregnancy test for luteal phase support. If a positive pregnancy test, progesterone was continued for another 4 weeks. All women also received an additional injection of 250 ug.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Pezzuto,A., Ferrari,B., Coppola,F., Nardelli,G.B., LH supplementation in down-regulated women undergoing assisted reproduction with baseline low serum LH levels, Gynecological Endocrinology, 26, 118-124, 2010 **Ref ID** 74473 **Country/ies where the study was carried out** Italy **Study type** Randomised clinical trial **Aim of the study** To evaluate the effect of rhLH supplementation on vascular endothelial growth factor concentrations in the follicular fluid (FF VEGF), ovarian response and pregnancy outcome, during ovarian stimulation, in down-regulated women with baseline low serum LH levels, undergoing assisted reproduction. **Study dates** March 2004 to October 2007 **Source of funding** Not reported	**Sample size** n = 80 women **Characteristics** Age = 34.5 ± 4.1 years BMI = 24.1 ± 0.8 kg/m^2 <u>Cause of infertility</u> Tubal factors = 31 (38.8%) Male factors = 28 (35%) Unexplained factors = 9 (11.3%) Endometriosis = 12 (15%) **Inclusion criteria** Healthy female partners of interile couples, regular menstrual cycles of 26 to 34 days; Age between 20 and 39 years at the time of screening BMI between 20 and 25 kg/m^2 Baseline serum FSH levels <10 IU/l Baseline serum E_2 levels ≤45 pg/ml on cycle Day 3 **Exclusion criteria** Not reported	1] Group A: GnRH agonist + Follicular stimulation using only rFSH 2] Group B: GnRH agonist + Follicular stimulation was FSH + rLH	<u>Intervention</u>: A long conventional protocol with a dose of 0.1 ml/day s.c. of GnRH agonist plus rFSH was used. The starting dose of FSH was 225 UI daily in women <30 years old and 300 UI daily in women >31 years old. Only the patients showing stimulation on Day 6 LH <0.5 mIU/ml were enrolled for the study.At that time the patients were assigned randomly (computer generated randomisation list;SPSS, Chicago IL) to two groups. In Group A (40 patients) follicular stimulation was continued using only rFSH (225 - 300 UI daily); in Group B (40 patients) follicular stimulation was continued using only r-FSH; in Group B follicular stimulation was continuously administered; FSH together with rLH 75 UI daily. The neeed for additional rFSH doses was determined by	<u>Clinical pregnancy</u> Group A = 2/40 (5%) Group B = 9/40 (22.5%) <u>Adverse pregnancy</u> Group A = 2/40 (5%) Group B = 3/40 (7.5%)	**Limitations** 1] Allocation concealment not reported 2] Blinding not reported 3] Power calculation not reported **Other information** 1] Clinical pregnancy was diagnosed by ultrasound at Day 35 after oocytes pick-up. 2] Adverse pregnancy outcome reported was biochemical pregnancy. 3] There was no embryo transfer in 30/40 patients in Group A and 10/40 in group B.

			monitoring. As soon as the oocytes maturation parameters were achieved, 10,000 IU of hCG were administered to trigger ovulation. The oocytes were retrieved 36h later by transvaginal US-guided aspiration. For each couple a maximum of three oocytes were to be subjected to ICSI. The luteal phase was supported with 200 mg micronised progesterone administered daily.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Aboulghar,M., Saber,W., Amin,Y., Aboulghar,M., Mansour,R., Serour,G., Prospective, randomized study comparing highly purified urinary follicle-stimulating hormone (FSH) and recombinant FSH for in vitro fertilization/intracytoplasmic sperm injection in patients with polycystic ovary syndrome, Fertility and Sterility, 94, 2332-2334, 2010 **Ref ID** 88005 **Country/ies where the study was carried out** Egypt **Study type** Randomised clinical trial **Aim of the study** To compare highly purified urinary FSH with recombinant FSH in IVF/ICSI cycles for patients with PCOS **Study dates** August 2008 to April 2009 **Source of funding** Sponsored in part by IBSA Institut Biochimique SA.	**Sample size** n = 84 women **Characteristics** Age = 27.8 ± 3.8 years BMI = 29.9 ± 4.7 kg/m^2 **Inclusion criteria** 1] Patients diagnosed as having PCOS according to Rotterdam criteria 2] Good physical health 3] Age <39 years and normal basal FSH and prolactin levels **Exclusion criteria** 1] Patients with fibroids, endometriosis, general or medical disorders 2] BMI >35 kg/m^2 3] Patients who had participated in previous IVF trials	1] rFSH 2] hp-uFSH	Method: Dark, sealed envelopes containing the intervention were created by a third party not involved in the allocation process. Randomisation was performed by picking one envelope for each patient from sequentially numbered envelopes on day of intervention initiation by a nurse not involved in the study, and the patient was informed about the allocated arm. Intervention: We used our routine long GnRHa protocol. Starting dose of FSH was 2 to 3 ampoules, depending on age and weight of the patient. All patients received 500 mg metformin twice daily. Ovulation was triggered when the lead follicle reached 18 mm. In case of risk of OHSS, coasting was performed and a routine IVF/ICSI procedure was applied.	<u>Clinical pregnancy</u> HP-uFSH = 21/42 (50%) rFSH = 22/42 (52.3%)	**Limitations** 1] No blinding 2] Study was not powered to detect difference in pregnancy outcomes **Other information** No definition of clinical pregnancy was reported

			Statistical analysis: The power of the study showed that a sample size of 42 women in each arm was sufficient to detect a difference of 10% in oocyte maturity to ensure a power of 80% based on the oocyte maturity in the study.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Devesa,M., Martinez,F., Coroleu,B., Tur,R., Gonzalez,C., Rodriguez,I., Barri,P.N., Poor prognosis for ovarian response to stimulation: results of a randomised trial comparing the flare-up GnRH agonist protocol vs. the antagonist protocol, Gynecological Endocrinology, 26, 509-515, 2010 **Ref ID** 106795 **Country/ies where the study was carried out** Spain **Study type** Randomised clinical trial **Aim of the study** To compare the efficacy of the flare-up and the GnRH antagonist protocols, in a group of patients with poor prognosis for ovarian response to stimulation. (Although it was not the main aim of the study, a subsequent comparison was performed between patients having stimulation with rFSH aone or with rFSH and hMG.) **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 221 women **Characteristics** <u>Flare-up group</u> Age = 38.48 ± 3.93 years BMI = 22.52 ± 3.2 kg/m^2 <u>Antagonist group</u> Age = 38.85 ± 3.82 years BMI = 22.6 ± 2.95 kg/m^2 Although it was not the main aim of the study, a subsequent comparison was performed between patients having stimulation with rFSH aone or with rFSH and hMG. **Inclusion criteria** Age ≤45 years At least one of the following:prior cycle cancellation (folliclular development <4 follicles after 8 - 10 days of intensive gonadotropin stimulation), prior poor response to controlled ovarian hyperstimulation (<5 follicles larger than 12 mm of diameter on the day of hCG administration after intensive stimulation), a pathologic CCCT (FSH day 3 + FSH day 10 ≥25) and/or antral follicle count ≤7 follicles. **Exclusion criteria** Not reported	rFSH (n= 89) rFSH + hMG (n= 83)	<u>Recruitment</u>: A total of 221 women who were candidates for IVF and considered as having poor prognosis for ovarian response to stimulation, were included in the study. <u>Method</u>: Randomisation was performed by the statistics unit, using a computer generated randomisation list in a 1:1 ratio. After clinical evaluation for inclusion criteria, patients were randomised into the flare-up or the antagonist protocol, by the study nurse coordinator. Within each group, patients were allocated randomly to stimulation either with rFSH alone or in combination with hMG. <u>Intervention</u>: The flare-up group consisted of 80 patients in which GnRH agonist, 0.2 ml/day, was administered from cycle day 2 until the	Pregnancy rFSH= 12/89 (13%) women rFSH + hMG= 13/83 (16%) women	**Limitations** 1] Blinding not reported. 2] After randomisation, there was 22% drop-out. 3] Patient characteristics were compared only in participants that completed the study. It is not clear whether both groups had similar characteristics after randomisation. **Other information** Although it was not the main aim of the study, a subsequent comparison was performed between patients having stimulation with rFSH aone or with rFSH and hMG. 1] Patients that had been randomised initially were later excluded due the following reasons: Non adhesion to allocated treatment - n = 31 (Flare-up group = 21, Antagonist group = 10), spontaneous pregnancy - n = 2 (Flare-up group = 1, Antagonist group = 1) 'No start' of intervention - n = 8 (Flare-up group = 5, Antagonist = 3) Discontinuation due to personal reasons - n = 8 (Flare-up group = 3,

			day of hCG administration. The antagonist group consisted of 92 patients in which GnRH antagonist was administered when at least one follicle ≥14 mm was detected on the ultrasound scan. In both groups, patients were pretreated with OC in the previous cycle. Ovarian suppression was confirmed by E_2 levels and absence of ovarian activity on the ultrasound examination. Stimulation was started 5 days after last contraceptive pill either with rFSH alon, 375 IU/day or with rFSH 300 IU/day plus hMG 75 IU/day, accourding to randomisation to prevent bias. When ≥2 follicles were observed on transvaginal sonography, rhCG was administered. Transvaginal oocyte retrieval was permed 36h after hCG administration.		Antagonist = 5) 2] The E_2 level, the day of hCG administration was significantly higher in the flare-up protocol. However all other treatment comparisons and patient characteristics showed no statistically significant differences.

			Embryo transfer was performed 2 or 3 days after oocyte retrieval. Luteal-phase support was initiated the day after oocyte retrieval and consisted of vaginally administered micronised progesterone. The distribution of Statistical analysis: The study was designed to have sufficient power to detect an absolute difference of 15% in the clinical pregnancy rate per initiated cycle, assuming a baseline pregnancy rate of 25% in the highest group and of 10% in the lowest one. It was calculated that 100 patients in each group would be an adequate number to achieve an 80% power of detection of differences at a significance level of 0.05.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Caserta,D., Lisi,F., Marci,R., Ciardo,F., Fazi,A., Lisi,R., Moscarini,M., Does supplementation with recombinant luteinizing hormone prevent ovarian hyperstimulation syndrome in down regulated patients undergoing recombinant follicle stimulating hormone multiple follicular stimulation for IVF/ET and reduces cancellation rate for high risk of hyperstimulation?, Gynecological Endocrinology, 27, 862-866, 2011 **Ref ID** 154959 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** To assess the efficacy of recombinant luteinizing hormone supplementation in the late follicular phase, during multiple follicular stimulation with recombinant follicle stiulating hormone in Triptoreline down-regulated patients undergoing IVF, for preventing clinical OHSS and cycles cancellation for OHSS risk. **Study dates** 2005 to April 2010 **Source of funding** None reported	**Sample size** 999 women **Characteristics** Mean age rFSH= 34.8 years +/- 3/6 rFSH + rLH= 34.3 years +/- 3.5 BMI rFSH= 24.1 +/- 4.2 rFSH + rLH= 24.2 +/- 4.1 Duration of infertility rFSH= 4.42 +/- 2.7 rFSH + rLH= 3.98 +/- 2.9 Cause of infertility Male factor rFSH= 23% rFSH + rLH= 21% Endometriosis rFSH= 14% rFSH + rLH= 12% One patent tube rFSH= 26% rFSH + rLH= 29% Anovulation rFSH= 3% rFSH + rLH= 3% Male and tubal factor rFSH= 14% rFSH + rLH= 15%	rFSH alone (n= 501) rFSH + rLH (n= 498)	Sealed envelopes were used for allocating to groups Study was blinded to investigators Both groups were down regulated with Triptorelin and then received rFSH (150 IU/day) from day 2. Women were randomly assigned to either received 75 IU of rLH on the 7th day of gonadotrophin stimulation, or to not receive any rLH. In both groups, the dose of rFSH was customised on the 7th day. rhCG was given (250 ug) to induce oocyte maturation. Retrieval took place 35-37 hours after hCG. Luteal phase support was given in the form of progesterone (800 mg/day). Patients were considered at wirsk of OHSS if there were more than 30 follicles and/or E2 was higher than 2500 pg/ml, and the cycle was cancelled.	Clinical pregnancies rFSH= 50/501 (10%) rFSH + rLH= 79/498 (16%) p < 0.05 OHSS rFSH= 6/501 (1%) rFSH + rLH= 1/498 (<1%) p < 0.05	**Limitations** Method of randomisation was unclear It is not clear whether participants were blinded **Other information** 80 women in the non-rLH group and 29 in the rLH group were withdrawn from the study before hCG was given (various reasons, including for high risk of OHSS, premature luteinisation, premature LH rise, follicular regression and because the couple wanted to withdraw from the study).

	Male factor and endometriosis rFSH= 11% rFSH + rLH= 10% Other rFSH= 9% rFSH + rLH= 10% No significant differences between the groups **Inclusion criteria** =< 40 years Basal FSH =< 12 mUI/ml Indication for IVF/ICSI **Exclusion criteria** >3 unsuccessful assisted reproduction attempts Previous poor response to gonadotrophin stimulation (<3 preovulatory follicles) History of OHSS PCOS Abnormal uterine cavity by ultrasonography Clinically significant system disease				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ashrafi,M., Kiani,K., Ghasemi,A., Rastegar,F., Nabavi,M., The effect of low dose human chorionic gonadotropin on follicular response and oocyte maturation in PCOS patients undergoing IVF cycles: a randomized clinical trial of efficacy and safety, Archives of Gynecology and Obstetrics, 284, 1431-1438, 2011 **Ref ID** 155036 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To compare the efficacy of two regimens of low dose human chorionic gonadotrophin on follicular response and oocyte maturation in women with polycystic ovary syndrome. **Study dates** January 2006 to December 2008 **Source of funding** None stated	**Sample size** n= 90 **Characteristics** <u>Age</u> rFSH alone: 29.5 years +/- 0.64 rFSH + 100 IU hCG: 28.5 years +/- 0.74 rFSH + 200 IU hCG: 29.4 yeras +/- 0.81 p= 0.549 <u>BMI</u> rFSH alone: 27.5 +/- 0.81 rFSH + 100 IU hCG: 27.8 +/- 0.99 rFSH + 200 IU hCG: 27.7 +/- 0.89 p= 0.974 <u>Duration of infertility</u> rFSH alone: 9.2 years +/- 0.78 rFSH + 100 IU hCG: 8.3 years +/- 0.88 rFSH + 200 IU hCG: 7 years +/- 0.76 p= 0.175 **Inclusion criteria** PCOS diagnosis by Rotterdam criteria Normal uterine cavity and patent tubes by hysterosalpinogram, laparoscopy or hysteroscopy Normal semen analysis according to WHO criteria **Exclusion criteria** Previous IVF or ICSI cycles Gonadotrophins in the three previous months	rFSH alone rFSH+100 IU hCG rFSH+200 IU hCG	Approved by the Ethics Committee at Royan Institute Research Centre. Based on 0.8 power to detect a significant difference (p=0.05, two-sided), 30 patients were needed in each group Block randomisation with a permuted block design used. Block lengths were six. A computerised random number sequence was used to select the next block. Allocation performed by the physician responsible for the patient. Outcome assessors, including data analysts, were blinded to group assignment. Standard long protocol was used. GnRH agonist was given, with rFSH started 14 days after (Gonal F, 150 IU daily). Dose and duration of FSH treatment were	<u>Clinical pregnancy</u> rFSH alone: 14/27 (52%) rFSH + 100 IU hCG: 13/27 (48%) rFSH + 200 IU hCG: 13/24 (54%) p= 0.910 <u>Multiple pregnancy</u> rFSH alone: 4/27 (15%) rFSH + 100 IU hCG: 2/27 (7%) rFSH + 200 IU hCG: 1/24 (4%) p= 0.389 <u>Severe OHSS</u> rFSH alone: 4/27 (15%) rFSH + 100 IU hCG: 0/27 (0%) rFSH + 200 IU hCG: 0.24 (0%) p= 0.019	**Limitations** Allocation concealment was not reported **Other information** Cancelled cycles occurred in 12 women (3 in rFSH alone group, 3 in rFSH + 100 hCG group, and 6 in rFSH + 200 hCG group).

			adjusted by monitoring follicular development with ultrasound and estradiol. Maximum dose was 225 IU/day. In the second group, rFSH was reduced to 75 IU once the lead follicle reached 14mm in mean diameter. Low dose hCG (100 IU/day) given until at least 2 to 3 follicles with a mean diameter of => 17mm was achieved. In the third group, rFSH was discontinued and low dose hCG (200 IU/day) was given when the lead follicle was 14mm and continued until at least 2 to 3 follicles with a mean diameter of => 17mm was achieved. In all groups, if the follicle mean diameter failed to grow sufficiently after 2 weeks of stimulation, monitoring was		

			stopped and the cycle cancelled. Treatment was also stopped in women who had no embryos for transfer. When 2 to 3 follicles of => 17mm were achieved, 10,000 IU of hCG was administered. Oocyte retrieval performed 34 to 36 hours after hCG administration. Luteal-phase support provided with vaginal progesterone (400mg twice a day) until day of B-hCG test. If B-hCG test was positive, then progesterone was continuted until 10 weeks' of gestation.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Fabregues,F., Iraola,A., Casals,G., Creus,M., Carmona,F., Balasch,J., Evaluation of two doses of recombinant human luteinizing hormone supplementation in down-regulated women of advanced reproductive age undergoing follicular stimulation for IVF: A randomized clinical study, European Journal of Obstetrics Gynecology and Reproductive Biology, 158, 56-61, 2011 **Ref ID** 148155 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** To evaluate the effects of mid-follicular recombinant human luteinizing hormone supplementation in down-regulated women of advanced reproductive age undergoing in vitro fertilisation. **Study dates** January 2007 to February 2008 **Source of funding** Supported in part by a grant from the Agencia de Gestio dAjuts Universitaris i de Recerca - Generalitat de Catalunya (2009SGR 1099)	**Sample size** 187 women **Characteristics** Mean age rFSH alone= 37.6 years +/- 0.4 rFSH + rhLH 37.5= 37.3 years +/- 0.3 rFSH + rhLH 75= 37.7 years +/- 1.8 Mean BMI rFSH alone= 23.0 +/- 3.7 rFSH + rhLH 37.5= 22.5 +/- 2.5 rFSH + rhLH 75= 21.9 +/- 3.6 Duration of infertility rFSH alone= 5.1 years +/- 1.9 rFSH + rhLH 37.5= 5.5 years +/- 1.2 rFSH + rhLH 75= 6 years +/- 2.9 Cause of infertility Male factor: rFSH alone= 27 (44%) rFSH + rhLH 37.5= 25 (40%) rFSH + rhLH 75= 27 (43%) Tubal factor: rFSH alone= 16 (26%) rFSH + rhLH 37.5= 15 (24%) rFSH + rhLH 75= 16 (25%) Unexplained: rFSH alone= 14 (23%) rFSH + rhLH 37.5= 16 (26%) rFSH + rhLH 75=15 (24%) Endometriosis: rFSH alone= 5 (8%) rFSH + rhLH 37.5= 6 (10%)	rhFSH (n= 62) rhFSH + rhLH (37.5 IU/day) (n= 62) rhFSH + rhLH (75 IU/day) (n=63)	Approved by an internal ethics committee. Sample size calculations based on Marrs et al. - sample size required to provide a power of 80% was calculated as 52 women per group using a two tailed analysis. Women were randomised into three treatment groups, allocated at the time of menses preceding their IVF cycle. Randomisation was done using a computer-generated simple randomisation table. Sealed opaque envelopes were used. Three groups: rhFSH alone rhFSH with rhLH (37.5 IU/day) rhFSH with rhLH (75 IU/day) Triptorelin acetate was used for pituitary desensitisation in all	Clinical pregnancy rhFSH alone= 22/62 (35%) rhFSH with rhLH 37.5= 14/62 (23%) rhFSH with rhLH 75= 17/63 (27%) No significant difference between the groups Twin pregnancies rhFSH alone= 6/62 (10%) rhFSH with rhLH 37.5= 4/62 (6%) rhFSH with rhLH 75= 2/63 (3%) No significant difference between the groups Miscarriage rhFSH alone= 4/62 (6%) rhFSH with rhLH 37.5= 2/62 (3%) rhFSH with rhLH 75= 4/63 (6%) No significant difference between the groups	**Limitations** Blinding was not clearly reported **Other information** Five women in the rhFSH alone group had their cycles cancelled due to low response and one woman had no embryos available One patient in the rhFSH + rhLH (37.5 IU/day) group conceived during pituitary desensitisation preceding IVF, one woman had no embryos available, and six women had their cycles cancelled due to low response One woman in the rhFSH + rhLH (75 IU/day) group was withdrawn as her husband was unable to produce a semen specimen at the time of oocyte retrieval and seven women had their cycles cancelled due to low response

	rFSH + rhLH 75= 5 (8%) There were no significant differences between the groups. No women had received any hormone therapy (inc. gonadotrophins) for at least 6 months preceding the study. **Inclusion criteria** First cycle of IVF or ICSI Menstrual cycle of 25 to 33 days Aged 35 to 41 BMI 19.8 to 27.6 Normal ovaries and no history of ovarian surgery Day 2 to 4 FSH concentration =< 12 IU/l in cycle preceeding IVF/ICSI **Exclusion criteria**		women (0.1 mg daily, reduced to 0.05mg) until day of hCG. Gonadotrophins were given when serum estradiol concentations declined to <50 pg/ml and absence of follicles > 10mm. rhFSH was given - 450 IU on day 1, 300 IU on day two, 150 IU on days 3 and 4. From day 5, dose was given according to ovarian response. rhLH in two of the groups was started on day 6 of FSH, at a fixed dose of either 37.5 or 75 IU/day. hCG was given (250 uG) if there were 2 follicles => 18mm and at least 4 follicles => 14mm in association with a consistent rise in serum E2 concentration. If there were less than three follicles => 14mm after 8 to 9 days of gonadotrophin therapy, or the criteria for hCG administration were		

			not attained or nearly attained after 4 to 5 treatment days, the cycle was cancelled. Up to three embryos were replaced (depending on age, indication for IVF/ICSI, and the number and quality of embryos available) 2-3 days after oocyte retrieval. The luteal phase support by progesterone (600 mg/day at 8 hr intervals) starting on the day of oocyte aspiration and continuing until menstruation, or if pregnancy occured, at least the first three weeks of pregnancy. Comparison of quantitative variables was performed using analysis of variance with Bonferroni's post hoc analysis. Comparison of qualitative variables was performed using Chi-squared test.		

Fertility (Updated guideline)

What is the effectiveness and safety of different embryo/blastocyst transfer strategies?

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>
Full citation
Lukassen,H.G., Braat,D.D., Wetzels,A.M., Zielhuis,G.A., Adang,E.M., Scheenjes,E., Kremer,J.A., Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial, Human Reproduction, 20, 702-708, 2005

Ref ID
4535

Country/ies where the study was carried out
The Netherlands

Study type
Randomised trial

Aim of the study
'To investigate the live birth rate of double embryo transfer after one treatment cycle, excluding freeze-thaw cycles'.

Study dates
January 2001 - February 2003

Source of funding
Not reported
</td>
<td>
Sample size
N = 107 patients

SET group = 54 patients
DET group = 53 patients

Characteristics
<u>Single embryo transfer group</u>

Age (mean±SD) = 30.2 ± 3.2 years

Duration of infertility (mean±SD) = 3.1 ± 1.4 years

<u>Double embryo transfer group</u>

Age (mean±SD) = 31.2 ± 2.9 years

Duration of infertility (mean±SD) = 3.5 ± 1.9 years

<u>Cause of infertility</u>

Male factor = 62 (57.9%)

Tubal factor = 14 (13.1%)
</td>
<td>
[1] Single cleavage-stage transfer

[2] Double cleavage-stage transfer
</td>
<td>
<u>Recruitment</u>: A total of 494 IVF patients underwent oocyte retrieval and embryo transfer. Of the 494 IVF patients, 217 did not agree to participate or were excluded.

<u>Power calculation</u>: Not reported.

<u>Randomisation:</u> A total of 107 patients were randomised to the single or double embryo transfer group was performed using a computer-generated random block number table, stratified for primary or secondary infertility, executed by an independent statistician.

<u>Allocation concealment:</u> Allocation was undertaken by an opaque, sealed envelop took place just before embryo transfer by the Laborory personnel.

<u>Blinding</u>: Patients and physicians were not blinded to treatment group.

<u>Interventions:</u> Insemination was carried out by adding motile spermatoa to the oocytes in IVF medium. If ICSI was performed, the oocytes were treated with
</td>
<td>
Results

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>1 Embryo</td><td>14</td><td>54</td></tr>
<tr><td>2 Embryos</td><td>19</td><td>53</td></tr>
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Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>1 Embryo</td><td>20</td><td>54</td></tr>
<tr><td>2 Embryos</td><td>25</td><td>53</td></tr>
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Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
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<tr><td>2 Embryos</td><td>7</td><td>53</td></tr>
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Pre-term delivery
<table>
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<tr><td>1 Embryo</td><td>2</td><td>54</td></tr>
<tr><td>2 Embryos</td><td>5</td><td>53</td></tr>
</table>
Adverse pregnancy outcome
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<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>1 Embryo</td><td>6</td><td>54</td></tr>
</table>
</td>
<td>
Limitations
No power calculation.

No blinding of patients and physicians.

Other information
'Clinical pregnancy' was confirmed by ultrasonic evidence of an intrauterine gestational sac and a positive heartbeat five weeks after embryo transfer.

'Live birth full term' reflects 'live birth' and includes full term, preterm, live births, singletons and multiples.

9/10 preterm births were from twin pregnancies.

Figures for 'Multiple pregnancy' reflect 6 twin births and 1 dizygotic triplet.

The 'Adverse pregnancy' outcomes reported in the study were miscarriage
</td>
</tr>
</table>

	Male/Female factor = Not reported Other = 31 (29%) The characteristics of the randomised patients were similar between the single and double embryo transfer group. There was no statistical significant difference in the number of ICSI cycles performed in both groups **Inclusion criteria** Patients undergoing their first IVF/ICSI cycle ever or the first cycle after a successful treatment. <35 years of age. Basal FSH level <10IU/l. ≥2 embryos had to be available for transfer on day 3 after oocyte retrieval during the first cycle. **Exclusion criteria** Patients with a medical reason for elective single embryo transfer.		hyaluronidase solution and denuded with a capillary pipette before injection was performed. On day 3 after oocyte retrieval, the embryos were scored and transferred. Excess embryos of good morphological quality were cryopreserved using the standard protocol with the cryoprotectant 1,2-propanediol. All patients completed their first treatment cycle while only 40/54 patients in the SET group completed a second cycle. <u>Statistical analysis</u>: Intention-to-treat analysis.	2 Embryos | 6 | 53	and ectopic pregnancy. In the SET group, 40/54 had a second cycle treatment but only results from the first cycle have been presented.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gardner,D.K., Surrey,E., Minjarez,D., Leitz,A., Stevens,J., Schoolcraft,W.B., Single blastocyst transfer: a prospective randomized trial, Fertility and Sterility, 81, 551-555, 2004 **Ref ID** 5128 **Country/ies where the study was carried out** USA **Study type** Randomized controlled trial **Aim of the study** 'To determine whether high blastocyst implantation rates could be translated into high pregnancy rates, while eliminating associated multiple pregnancies, when a single embryo was transferred' **Study dates** Not reported **Source of funding** Supported in part by Organon Inc and Vitrolite AB	**Sample size** N = 48 patients SET group = 23 patients DET group = 25 patients **Characteristics** SET group (N = 23) Age (mean±SD) = 33.5±0.9 years DET group (N = 25) Age (mean±SD) = 34.2 ± 0.7 years Mean duration of infertility: Not reported Cause of infertility: Not reported There was no differences in indications for IVF, patient age, or percentage of ICSI patients in both groups **Inclusion criteria** [1] Day 3 FSH ≤10 mIU/ml [2] E_2 < 80 pg/ml [3] hysterosxcopically normal endometrial	[1] Single blastocyst-stage transfer [2] Double blastocyst-stage transfer	Recruitment:Participation in the study was offered to all patients undergoing IVF-ET with their own oocytes during a 24-month period for blastocyst stage embryo transfer Power calculation: Not reported Randomisation: Patients were randomised at the time of transfer by a computer-generated table to either transfer of one or two blastocysts on day 5. Allocation concealment: Not reported Interventions: Patients received standard insemination or ICSI as clinically appropriate, and subsequent embryos were cultured. All blastocysts were evaluated using a previously described scoring system (Gardner and Schoolcraft, 1999). No embryos underwent assisted hatching before transfer. Cryopreservation of supernumerary blastocysts on days 5 or 6 was performed using controlled rate freezing Statistical analysis: ITT not reported	**Results** **Clinical pregnancy** | | Events | Total | |---|---|---| | 1 Embryo | 14 | 23 | | 2 Embryos | 19 | 25 | **Multiple pregnancy** | | Events | Total | |---|---|---| | 1 Embryo | 0 | 23 | | 2 Embryos | 9 | 25 |	**Limitations** No power calculation. No allocation concealment. **Other information** Ongoing pregnancy was determined by the presence of intrauterine gestational sacs with cardiac activity noted on ultrasound examination performed at least 4.5 weeks after transfer per cycle initiated. Figures for 'Clinical pregnancy' outcome reflect number of 'ongoing pregnancy'. Multiple pregnancy was reported as twin pregnancy. It is not clear if triplet pregnancies, quadruplets and other multiple pregnancies had occurred.

	cavity [4] at leats 10 follicles > 12 mm in diameter on day of hCG administration **Exclusion criteria** None				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kolibianakis,E.M., Zikopoulos,K., Verpoest,W., Camus,M., Joris,H., Van Steirteghem,A.C., Devroey,P., Should we advise patients undergoing IVF to start a cycle leading to a day 3 or a day 5 transfer?, Human Reproduction, 19, 2550-2554, 2004 **Ref ID** 5292 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** 'To compare ongoing pregnancy rates per started cycle between patients randomised, prior to initiation of stimulation, to have embryo transfer either on day 3 or on day 5 of in-vitro culture'. **Study dates** January 2001 to December 2003 **Source of funding** Grants from the Fund for Scientific Research, Flanders	**Sample size** N = 460 patients Cleavage-stage group = 234 patients Blastocyst-stage group = 226 patients **Characteristics** Cleavage-stage group (N = 234) Age (mean±SD) = 31.3 ± 0.3 years Duration of infertility = Not reported Blastocyst-stage group (N = 226) Age (mean±SD) = 31.5 ± 0.2 years Duration of infertility = Not reported Cause of infertility Male factor = 300 (65.2%) Tubal factor = 45 (9.8%) Male/Female factor = Not reported	[1] Cleavage-stage transfer (single or double) [2] Blastocyst-stage transfer (single or double)	Recruitment: 460 patients treated by IVF within the study period were included. Patients could entre the study only one. Power calculation:To detect a difference of 5% in ongoing pregnancy rates between the two groups compared assuming a baseline ongoing pregnancy of 30% at an α level of 0.05 and β of 0.2, 1416 patients were needed for inclusion in each group. Randomisation: Randomisation was performed by the attending physician according to a computer-generated list. Allocation concealment: The sequence of randomisation was not concealed. Interventions: Conventional IVF (120 couples), ICSI (312 couples) and both (28 couples) were carried out. The ICSI and IVF procedures have been described in detail previously (Devroey et al., 1995; Devroey and Van Steirteghem, 2004). As a matter of principle, 1 - 2 embryos were transferred on day 3 or day 5 after oocyte retrieval. Supernumerary embryos were frozen at the blastocyst stage in both groups. Statistical analysis: No	**Results** **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 20 | 234 | | Day 5 - 6 | 15 | 226 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 21 | 234 | | Day 5 - 6 | 19 | 226 |	**Limitations** The study was not adequately powered No allocation concealment The number of embryos transferred varied between single and double and no subgroup analysis was done. **Other information** Where embryo transfer was performed, similar numbers of embryos were replaced in both groups. Adverse pregnancy outcome reported include biochemical pregnancy (number of biochemical pregnancy that did not result in delivery), first trimester miscarriage and extrauterine pregnancy.

	Other = 115 (25%) **Inclusion criteria** <43 years and the presence of indication for IVF. **Exclusion criteria** Preimplatation genetic screening and azoospermia.		intention-to-treat analysis.		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Levitas,E., Lunenfeld,E., Har-Vardi,I., Albotiano,S., Sonin,Y., Hackmon-Ram,R., Potashnik,G., Blastocyst-stage embryo transfer in patients who failed to conceive in three or more day 2-3 embryo transfer cycles: a prospective, randomized study, Fertility and Sterility, 81, 567-571, 2004

Ref ID
5355

Country/ies where the study was carried out
Israel

Study type
Randomised trial

Aim of the study
To compare blastocyst-stage embryo transfers with day 2-3 embryo transfers in patients who failed to conceive in three or more day 2 - 3 IVF/ET cycles

Study dates
Not reported

Source of funding
Not reported</td>
<td>Sample size
N = 46 patients

Characteristics
<u>Day 2 - 3 embryo transfer (N = 29)</u>

Age (years) = 31.2±3.4

Duration of Infertility (years) = 7.0 ± 3.2

FSH level(day 3) (mIU/mL) = 6.0 ± 3.3

No of ET's per cycle: 3.4 (+/-0.7)

<u>Diagnosis</u>

Male infertility(%) = 62.5

Tubal factor (%) = 33

<u>Day 5 - 7 embryo transfer (N = 17)</u>

Age (years) = 29.1±3.1

Duration of Infertility (years) = 7.1 ± 3.6

FSH level(day 3) (mIU/mL) = 7.4 ± 3

No of ET's per cycle: 1.9 (+/-0.4)</td>
<td>≥ Double cleavage stage vs ≥ Double blastocyst stage transfer.</td>
<td><u>Recruitment</u>: The study was designed to include 100 patients who failed to conceive during at least three IVF embryo transfer cycles. HAll patients fulfilling the entry criteria were offered enrollment, and 54 couples with primary or secondary infertility agreed to enter the study.

<u>Randomisation</u>: Randomisation was performed according to a computer-generated random-number table

<u>Allocation concealment</u>: Blind randomisation with sealed and opaque envelopes was performed immediately after informed consent was signed.

<u>Interventions:</u> All women participating in the study were treated with GnRH agonist. Transvaginal ultrasound-guided ovum retrieval was performed under general anesthesia 36 - 38 hours after hCG administration. According to semen quality on the day of oocyte retrieval, the oocytes were inseminated or subjected to ICSI.
Embryo transfer for the day 2 - 3 group of patients was carried out using embryos with the highest number of blastomeres and having the highest embryo grading score. A</td>
<td>Results
(Clinical pregnancy confirmed by pregnancy sac and cardiac activity on ultrasound)

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>3</td><td>31</td></tr>
<tr><td>Day 5 - 6</td><td>3</td><td>23</td></tr>
</table>
Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>4</td><td>31</td></tr>
<tr><td>Day 5 - 6</td><td>5</td><td>23</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>3</td><td>31</td></tr>
<tr><td>Day 5 - 6</td><td>2</td><td>23</td></tr>
</table>
</td>
<td>Limitations
Small sample size and no sample size calculation

Fewer embryos per transfer in the blastocyst group compared to the day 2 - 3 group might have been the reason for reduced multiple-pregnancy rate in the blastocyst group

Other information
The unequal number of patients included in the groups was due to randomisation among 100 sealed envelopes.</td>
</tr>
</table>

	Diagnosis Male infertility(%) = 78.9 Tubal factor (%) = 21.1 No statistically significant differences were noted between the two groups for for any of the variables tested **Inclusion criteria** Female patients <37 years who were being treated mainly for tubal or male factor infertility Evidence of a normal uterine cavity and no contraindications to pregnancy **Exclusion criteria** Poor ovarian response on previous IVF cycles Patients with embryo transfers from donor oocytes or frozen-thawed embryos.		5-grade embryo scoring system was pplied according to the amount of embryonic fragmentations and the size and shape of blastomeres. Blastocyst transfer was performed using 5 - 7 day embryos cultured according to the sequential media system: the first 72 hours of culture in G1.2 medium followed by G2.2 medium to day 5 - 7		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Moustafa,M.K., Sheded,S.A., El Aziz Mousta,M.A., Elective single embryo transfer versus double embryo transfer in assisted reproduction, Reproductive Biomedicine Online, 17, 82-87, 2008 **Ref ID** 5447 **Country/ies where the study was carried out** Saudi Arabia **Study type** Randomised trial **Aim of the study** 'To determine the result of cryo-embryo transfer cycles in women undergoing elective single embryo transfer versus double embryo transfer'. **Study dates** September 2004 - September 2006 **Source of funding** Not reported	**Sample size** N = 81 patients SET group = 40 patients DET group = 41 patients **Characteristics** SET group (N = 40) Age (mean±SD) = 25.1 ± 3.0 years Duration of fertility (mean±SD) = 3.5 ± 3.1 years DET group (N = 41) Age (mean±SD) = 25.4 ± 3.2 years Duration of fertility (mean±SD) = 2.9 ± 2.6 years Cause of infertility = Not reported The two groups were similar with regard to patient age, cause of infertility, duration of infertility and cycle characteristics. **Inclusion criteria** **Exclusion criteria**	[1] Single cleavage-stage transfer. [2] Double cleavage-stage transfer.	Recruitment: 81 patients undergoing embryo transfer in the assisted reporduction unit within the study period were prospectively included. Randomisation: Randomisation was performed on the day of transfer by a third party (a nurse) who was not involved in any other aspect of the study Allocation concealment: Not reported Interventions: All aspects of the IVF procedure including medication and fertilisation protocol were similar between the two groups, with the exception of the number of embryos transferred. ICSI was performed for all cases as standard and injected oocytes were cultured using VitroLife culture media. Embryo quality was assessed by two embryologists and surplus embryos were frozen and thawed according to standard method. All embryo transfers were performed on day 2 - 3 by the same physician using a standardised technique. Patients were followed up for 1 year to determine the results of cryo-embryo transfers. The number of embryos transferred during this period was the same as the original randomisation	**Results** **Live birth - Full-term - Cumulative** | | Events | Total | |---|---|---| | 1 Embryo | 18 | 40 | | 2 Embryos | 19 | 41 | **Live birth - Full-term - Fresh cycle** | | Events | Total | |---|---|---| | 1 Embryo | 12 | 40 | | 2 Embryos | 13 | 41 | **Live birth - Full-term - Frozen cycle** | | Events | Total | |---|---|---| | 1 Embryo | 6 | 10 | | 2 Embryos | 6 | 16 | **Clinical pregnancy** | | Events | Total | |---|---|---| | 1 Embryo | 13 | 40 | | 2 Embryos | 16 | 41 | **Multiple pregnancy** | | Events | Total | |---|---|---| | 1 Embryo | 0 | 40 | | 2 Embryos | 5 | 41 |	**Limitations** No power calculation. No allocation concealment. The method of randomisation was not clearly reported. The results might not be widely applicable because the studied population was relatively young (20 - 30 years) in comparison to the majority of patients who undertake IVF treatment, and the results may be different in other age groups. **Other information** Live birth was defined as a living fetus born ≥28 weeks of gestation. The figures for 'Live birth' reported may have included preterm, full term, singletons and multiples. Clinical pregnancy was defined as increasing maternal serum β-HCG concentration combined with an intrauterine gestational sac and positive fetal heartbeat visualised on ultrasound examination. All multiple pregnancies were twins.

	Women undergoing embryo transfer in a fresh cycle ≥1 good quality embryo (Grade I - II) on the day of transfer Women's age ≥30 years at the time of embryo transfer No contraindication for pregnancy Women's age >30 years Only poor quality embryos available for transfer Refusal to consent or participate in the clinical trial		Statistical analysis: Intention-to-treat analysis not reported		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Papanikolaou,E.G., Camus,M., Kolibianakis,E.M., Van,Landuyt L., Van,Steirteghem A., Devroey,P., In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos, New England Journal of Medicine, 354, 1139-1146, 2006 **Ref ID** 5509 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** 'To determine whether there were any differences in the rates of pregnancy and delivery between women randomly assigned to undergo transfer of a single cleavage-stage embryo and those assigned to undergo transfer of a single blastocyst-stage embryo'. **Study dates** July 2003 - November 2004 **Source of funding** Research support from Organon	**Sample size** N = 351 patients Cleavage-stage group = 176 patients Blastocyst-stage group = 175 patients **Characteristics** Cleavage-stage group (N= 176) Age (mean±SD) = 30.5±3.2 years Duration of infertility (mean±SD) = 3.7 ± 2.2 years Blastocyst-stage group (N = 175) Age (mean±SD) = 30.4 ± 3.6 years Duration of infertility (mean±SD) = 3.5 ± 2.1 years Cause of infertility Male = 196 (55.8%) Female = 85 (24.2%) Other (idopathic) = 39	[1] Single cleavage-stage transfer [2] Single blastocyst-stage transfer	Recruitment: 351 women requesting infertility treatment within the study period were randomly assigned to undergo transfer of either a single cleavage-stage embryo or a single blastocyst-stage embryo. Power calculation: Using group sequential methods, calculations showed that the enrollement of 351 patients in each group would give the study a statistical power of 80% to detect an absolute difference of 10% in the rate of ongoing pregnancy between the groups (given rates of 20 and 30%) at α level of 0.05 with the use of a two-sided z-test. It was prespecified that the study would be stopped if the first interim analysis identified a significant difference (p = 0.03) in pregnancy rates between groups. At the first interim analysis, the pregnancy rate in the blastocyst-stage group was greater than that in the cleavage-stage group at an alpha level of 0.02, and therefore, the study was terminated. Randomisation: Randomisation was perfomed after the first consultation at the outpatient clinic. A computer-generated list was used for randomisation; this list was not concealed from the physicians, but it did not explicitly state the	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 38 | 176 | | Day 5 - 6 | 56 | 175 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 41 | 176 | | Day 5 - 6 | 58 | 175 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 2 | 176 | | Day 5 - 6 | 0 | 175 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 21 | 176 | | Day 5 - 6 | 17 | 175 |	**Limitations** No allocation concealment. **Other information** Clinical pregnancy was defined by the observation of fetal cardiac activity on ultrasonography after seven weeks of gestation. The 'Adverse pregnancy' outcome reported in the study include ectopic pregnancy, first trimester and second trimester pregnancy loss. Figures for 'Live birth full term' reflects number of births and may include full term, preterm, live, still-births, singletons and multiples. In the initial design there was no plan for the subsequent transfer of frozen embryos in patients who did not conceive. In the day 5 - 6 group, 13/169 (7.7%) patients did not undergo tranfer because of lack of embryos (11 patients) or OHSS (2 patients).

	(11.1%) Male/female = 31 (8.8%) There were no significant differences between the groups in age (p=0.84), duration of infertility (p = 0.75), cause of infertility (p = 0.68) or cycle characteristics (p = Not reported). **Inclusion criteria** Women <36 years of age who were undergoing a first or second trial of IVF or ICSI. Serum follicle stimulating hormone level on day 3 of the menstrual cycle of 12 IU/l or less. Undergoing transfer of one embryo. **Exclusion criteria** Use of preimplantation genetic diagnosis		treatment strategy, identifying the strategies only as "A" or "B". A patient could enter the study only once. Blinding: The embryo transfers were performed with ultrasound guidance by clinicians and embryologists who were blinded only with respect to the patient's participation in the study. Interventions: Sperm preparation, IVF abd ICSI procedures, and embryo culture were carried out as described by Van Landuyt et al., 2001. Embryo quality was assessed daily until the moment of transfer or freezing. On the morning of day 3, the embryos were removed from cleavage medium and placed in blastocyst medium. Supernumerary embryos were frozen on day 5 or 6. Embryos were scored 1 - 4 and embryos with a score of 4 were not transferred. Statistical analysis: Analysis was performed according to intention to treat.		In the day 3 group, embryo transfer was not performed in 9/171 (5.3%) patients because of lack of embryos on day 3 (8 patients) and OHSS (1 patient)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bungum,M., Bungum,L., Humaidan,P., Yding,Andersen C., Day 3 versus day 5 embryo transfer: a prospective randomized study, Reproductive Biomedicine Online, 7, 98-104, 2003 **Ref ID** 65163 **Country/ies where the study was carried out** Denmark **Study type** Randomised trial **Aim of the study** 'To investigate whether embryos from good prognosis patients hava a different implantation potential comparing day 3 to day 5 embryo transfer when equal numbers of embryos are transferred'. **Study dates** December 2001 - May 2002 **Source of funding** Not reported	**Sample size** N = 118 patients Cleavage-stage group = 57 patients Blastocyst-stage group = 61 patients **Characteristics** Cleavage-stage group (N = 57) Age (mean) = 31.3 years Blastocyst-stage group (N = 61) Age (mean) = 31.2 years Duration of infertility = Not reported Cause of infertility = Not reported No statistical differences in age. **Inclusion criteria** Three or more 8-cell embryos with <20% extracellular fragments on day 3. Female age <40 years and BMI <30. Baseline FSH <12 IU/l.	[1] Double cleavage-stage transfer [2] Double blastocyst-stage transfer	Recruitment: During the study period, a total of 118 patients undergoing standard IVF or ICSI were included in the study. Power calculation: The power of the statistical test comparing the clinical pregnancies is 0.32 and the total number of observations should be 726 to obtain a power of 0.90. Randomisation: Randomisation was performed by drawing lots. Allocation concealment: Sealed envelops. Interventions: On the morning of day 3, patients with three or more 8-cell embryos with <20% extracellular fragments were randomly selected to have their embryos cultured for either 3 or 5 days in the sequential media system used in the standard IVF/ICSI programme. A maximum of two embryos were transferred on day 3 or 5 after retrieval according to the randomisation in the morning of day 3. On day 3, embryos were scored using criteria set up by Ziebe et al.,1997. Strict criteria for cryopreservation were used. Only embryos containing at least seven blastomeres and <20% intracellular fragments were cryopreserved on day 3. On day 5, embryos were	**Results** **Clinical pregnancy** Events / Total Day 2 - 3: 35 / 57 Day 5 - 6: 32 / 61 **Multiple pregnancy** Events / Total Day 2 - 3: 15 / 57 Day 5 - 6: 13 / 61 **Adverse pregnancy outcome** Events / Total Day 2 - 3: 6 / 57 Day 5 - 6: 13 / 61	**Limitations** The study was not adequately powered. It is not clear whether the allocation concealment was adequate 2/61 patients in the day 5 group had only one embryo transferred due to lack of other viable embryos; 4/61 patients in the day 5 group did not have two blastocysts available for transfer, instead, two morulae or bombined blastocyst/morulae were transferred and it was not reported whether they were excluded from the analysis. **Other information** All randomised patients within the day 3 group had two embryos transferred. according to the protocol, whereas in the day 5 group two patients had only one embryo transferred, due to lack of other viable embryos for transfer. A clinical pregnancy was defined as an intrauterine gestational sac with a heartbeat 3 weeks after a

	Standard hormonal treatment as follows: pituitary down-regulation with gonadotrophin-releasing hormone agonist (GnRHa), 0.8mg s.c. daily from the mid-luteal phase for 14 days. **Exclusion criteria** Not reported.		assessed according to scoring criteria for blastocysts. Only expanded blastocysts were cyropreserved. Statistical analysis: Intention-to-treat analysis not reported		positive HCG test. An early pregnancy loss was defined as a preclinical or a clinical abortion before gestational week 12. 'Adverse pregnancy' outcome is reported as 'early pregnancy lost'.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Coskun,S., Hollanders,J., Al-Hassan,S., Al-Sufyan,H., Al-Mayman,H., Jaroudi,K., Day 5 versus day 3 embryo transfer: A controlled randomized trial, Human Reproduction, 15, -1952, 2000 **Ref ID** 81992 **Country/ies where the study was carried out** Saudi Arabia **Study type** RCT **Aim of the study** The objective of the study was to determine whether transferring blastocysts on day 5 could result in better pregnancy and implantation rates than transferring early embryos on day 3 in a wide patient population selected according to number of zygotes. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 201 (Day 3 n = 101) (Day 5 n = 100) **Characteristics** Day 3 group Age: 30.7 (+/- 5.4) Diagnosis: - Male: 62 - Male/tubal: 0 - Tubal: 18 - Unexplained: 15 - PCOS: 3 - Endometriosis: 2 - Others: 1 Number of embyos transferred: 2.3 (+/- 0.6) Day 5 group Age: 30.4 (+/- 4.9) Diagnosis: - Male: 64 - Male/tubal: 5 - Tubal: 21 - Unexplained: 6 - PCOS: 3 - Endometriosis: 0 - Others: 1 Number of embyos transferred: 2.2 (+/- 0.5) **Inclusion criteria** All IVF or ICSI cycles from consenting patients with four or more fertilized oocytes on the day of	Double cleavage-stage vs Double blastocyst transfer	Randomisation: An equal number of sealed envelopes containing day 3 or day 5 labels were drawn by embryologist when the paitent qualified for the study Power calculation: Not reported Statistical analysis: P < 0.05 Method: Ovarian suppresion was down with GnRH agonist long protocol, 26 days after stimulation was done with hMG . 10,000IU hCG was used to trigger when diametre of oocyte >18mm. Retrieval of oocytye was done with aspiration needle 36 hours after trigger. Zygotes for day 3 transfer were cultured IVF medium, day 5 zygotes transferred to G1.2 and G2.2 on day 1 and day 3 respectively. Embryo's graded as described in Coskun et al 1998b. Implementation support used 100mg/day progesterone. Intervention: The best two quality embryos from both groups were transferred into the uterus on day 3 or day 5. When no blastocyst was availible on day 5, the two most advanced embryo's were used or embryo's were cultured for one more day according to embryologist judgement. Women older than 36 years or couples who had 6 or more unsuccessful previous cycles had 3	**Results** Pregnancy rates were confirmed with hCG test at 13 days and ultrasound at 5 weeks Adverse pregnancy outcomes were abortions and biochemical pregnancies Pregancy rate (event/women): Day 3 transfer - 39/101 (39%) Day 5 transfer - 39/100 (39%) **Clinical pregnancy** Day 2 - 3: Events 39, Total 101 Day 5 - 6: Events 39, Total 100 **Multiple pregnancy** Day 2 - 3: Events 13, Total 101 Day 5 - 6: Events 15, Total 100 **Adverse pregnancy outcome** Day 2 - 3: Events 6, Total 101 Day 5 - 6: Events 4, Total 100	**Limitations** - No power calculation was carried out - No obvious researcher concealment **Other information** Pregnancy rate (as described in results) in >36 years (3 embryo transfer) Day 3 transfer - 5/20 (25%) Day 5 transfer - 3/14 (23%) Number of blastocysts for transfer (day 5) 0 availible - 2/23 (9%) More than or equal to one - 37/77 (48%)

	fertilization check (day1) were included. **Exclusion criteria** Not reported		embryos transferred.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gardner,D.K., Schoolcraft,W.B., Wagley,L., Schlenker,T., Stevens,J., Hesla,J., A prospective randomized trial of blastocyst culture and transfer in in-vitro fertilization, Human Reproduction, 13, 3434-3440, 1998 **Ref ID** 82261 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine the efficacy of sequential culture media for human blastocyst development and transfer on day 5 **Study dates** October 1997 to March 1998 **Source of funding** Not reported	**Sample size** N = 92 (Group day 3, n = 47) (Group day 5, n = 45) **Characteristics** Day 3 transfer Age (mean years): 34.5 (+/-0.6) Age range (years): 26-43 Cause of infertility - tubal: 12 - endometriosis: 8 - ovulatory disorders: 3 - unexplained: 15 - male factor: 9 Number of embryos transferred: 3.7 (+/-0.1) Day 5 transfer Age (mean years): 33.6 (+/-0.7) Age range (years): 26-43 Cause of infertility - tubal: 10 - endometriosis: 11 - ovulatory disorders: 3 - unexplained: 9 - male factor: 12 Number of embryos transferred: 2.2 (+/-0.1) **Inclusion criteria** Requirement for IVF: - Basal FSH,15mIU/ml - Women's age <45 years - Presence of normal uterine cavity	Double cleavage stage vs Double blastocyst transfer	Randomisation: Computer generated randomisation table Power calculation: Not reported Statistical analysis: Unpaired t-tests, Fishers exact test Method: Ovarian hyper stimulation was initiated with GnRH agonist long protocol for 10 days, hCG was begun after down regulation and continued until 10 follicles reached a mean diameter of 12mm. hCG was administered when at least two follicles had a mean diameter of 18mm. Oocyte retrieval was scheduled for 35 hours after hCG injection. Intervention: Patients having embryo transfer on day 3 had embryos with two pronuclei cultured in groups of 3-4. On day 3, the majority of embryos for transfer underwent assisted hatching. For those in day 5 group, embryos with two pronuclei were cultured in groups of 3 or 4. At day 3 all embryos transferred to G2.2 medium. No embryos underwent assisted hatching. Up to 3 blastocysts chosen for transfer	**Results** Clinical pregnancy is undefined **Clinical pregnancy** Day 2 - 3: Events 31, Total 47 Day 5 - 6: Events 32, Total 45	**Limitations** - No allocation concealment - No power calculation **Other information** Pregnancy vs. number of blastocysts transferred (event/number of women) 2 blastocysts transferred - 17/25 (68%) 3 blastocysts transferred - 13/15 (87%)

	- Adequate sperm parameters for IVF - absence of any contraindications In addition, at least 10 follicles > 12mm in diameter (visible by transvaginal ultrasound) were required on day of hCG administration **Exclusion criteria** Not reported				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Rienzi,L., Ubaldi,F., Iacobelli,M., Ferrero,S., Minasi,M.G., Martinez,F., Tesarik,J., Greco,E., Day 3 embryo transfer with combined evaluation at the pronuclear and cleavage stages compares favourably with day 5 blastocyst transfer, Human Reproduction, 17, 1852-1855, 2002 **Ref ID** 84479 **Country/ies where the study was carried out** Spain **Study type** Randomised trial **Aim of the study** 'To report pregnancy and implantation rates achieved with the use of combined pronuclear and cleavage-stage evaluateion criteria and day 3 embryo transfer as compared with those achieved with day 5 blastocyst transfer'. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 98 patients Cleavage-stage group = 48 patients Blastocyst-stage group = 50 patients **Characteristics** Cleavage-stage group (N = 48) Age (mean ± SD) = 31.6± 3.1 years Duration of infertility = not reported Blastocyst-stage group (N = 50) Age (mean ± SD) = 32.3 ± 2.5 years Duration of infertility = not reported Cause of infertility = not reported Basic characteristics of the patients were similar between the two groups. **Inclusion criteria** Couples with female age of <38 years who were treated with ICSI	[1] Double cleavage-stage transfer [2] Double blastocyst-stage transfer	Randomisation: All patients meeting inclusion criteria were randomized on the day following oocyte retrieval by a computer-generated randomization list. Intervention: Oocytes were freed from the cumulus oophorus, followed by the removal of the corona radiata and subjected to ICSI. Abnormally fertilised oocytes (1 or 3pronuclei) were excluded from further consideration. Normally fertilized oocytes were cultured in G.1.2 meduim up to day 3 after ICSI and in G.2.2 medium from day 3 to 5 where applicable. Two best-scoring embryos, selected were transferred to the patient's uterus on either day 3 or day 5 according to the study design. For day 5 transfers, blastocyst morphology was given priority to gronuclear score in case of discrepance. the remaining good quality embryos were cryopreserved if they did not show a developmental blockage. Cryopreservation was performed for those patients for whom supernumerary good quality embryos or blastocysts were available. Power calculation: Not reported Allocation concealment: Not	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 31 | 48 | | Day 5 - 6 | 36 | 50 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 27 | 48 | | Day 5 - 6 | 29 | 50 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 7 | 48 | | Day 5 - 6 | 9 | 50 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 3 | 48 | | Day 5 - 6 | 5 | 50 |	**Limitations** No allocation concealment No power calculation No blinding of clinician, patients or assessor. **Other information** Clinical pregnancy was defined as the detection of embryonic heartbeat on ultrasound at 8 weeks gestation. This inappropriate definition implies that the figures do not include clinical pregnancies that were lost before 8weeks. Figures for 'Adverse pregnancy' reflect the number of clinical pregnancies that did not result in any deliveries. Figures for 'Life full term birth' reflect number of births and may include live births, still-births, full term, preterm, singletons and multiples.

	≥8 two-pronucleated zygotes on the day following ICSI. **Exclusion criteria** Not reported		reported Statistical analysis: Not reported		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Emiliani,S., Delbaere,A., Vannin,A.S., Biramane,J., Verdoodt,M., Englert,Y., Devreker,F., Similar delivery rates in a selected group of patients, for day 2 and day 5 embryos both cultured in sequential medium: a randomized study, Human Reproduction, 18, 2145-2150, 2003 **Ref ID** 88770 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** "To compare, in a prospective randomised trial, the outcome of day 2 and day 5 transfer of human embryos cultured in an 'in-house' sequential medium". **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 171 **Characteristics** Day 2 embryo transfer group (N = 89) Age = 31 ± 3 Duration of infertility = Not reported Day 5 embryo transfer group (N = 89) Age = 32 ± 4 Duration of infertility = Not reported Cause of infertility = Not reported **Inclusion criteria** All IVF and ICSI cycles from consenting patients aged <39 years, having had not more than three previous IVF cycles and with at least 4 fertilised oocytes on day 1. **Exclusion criteria** Six patients in the day 2 transfer group and one patient in the day 5 transfer group were excluded for violation of the protocols.	Day 2 embryo transfer vs Day 5 embryo transfer with IVF and ICSI	Recruitment: All couples were informed about the study and if they agreed to participate, they were included. Sample size calculation: The miminum number of patients to be included was calculated by the Stat Calcul software for Windows 98 Randomisation: Patients were randomised on the basis of their inclusion in a randomisation list with permuted blocs for the two types of transfer. Allocation concealment: Not reported Blinding: Not reported Interventions: For day 2 transfer, a maximum of two embryos was transferred for all patients <35 years old and /or with less than four previous IVF attempts, excetp for women for whom the total score of the two best scoring embryos was <8, for whom a third embryo was transferred. if available. Patients aged ≥35 years or with more than 3 previous IVF failures had two embryos replaced if the toal score of the three best-scoring embryos was ≥15, while if the total score was <15 a third embryo was replaced, if available. For day 5 transfer, two	**Results** **Clinical pregnancy** Events / Total Day 2 - 3: 46 / 89 Day 5 - 6: 39 / 82 **Adverse pregnancy outcome** Events / Total Day 2 - 3: 4 / 89 Day 5 - 6: 6 / 82	**Limitations** Allocation concealment, blinding and intention to treat analysis not reported Sample size calculation was not clearly reported **Other information** 94 day 2 transfers (89 patients) included three cycles with a single embryo replaced, 79 cycles with two embryos replaced and in 11 cycles with three embryos replaced and one cycle with no replacement because of embryo quality. The 99 day 5 transfers (82 patients) included 10 cycles with a single embryo replaced, 79 cycles with thwo embryos replaced and 10 cycles in which there were no blastocysts available for fransfer. There was a significant difference in the number of replaced embryos between both groups with fewer blastocy For the two groups, ICSI accounted for 134/171 cycles

			blastocysts were replaced , if available. For the transfer of thawed embryos, only day 2 thawed embryos that cleaved or thawed blastocysts that re-expanded after a further 18h of culture were replaced Statistical analysis: No intention to treat analysis		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Frattarelli,J.L., Leondires,M.P., McKeeby,J.L., Miller,B.T., Segars,J.H., Blastocyst transfer decreases multiple pregnancy rates in in vitro fertilization cycles: a randomized controlled trial, Fertility and Sterility, 79, 228-230, 2003 **Ref ID** 88863 **Country/ies where the study was carried out** USA **Study type** Randomised trial **Aim of the study** To test the hiypothesis that a day 5 embryo transfer would be associated with a lower multiple gestational rate than would a day 3 embryo transfer **Study dates** From January 1999 to May 2000 **Source of funding** Not reported	**Sample size** N = 57 patients **Characteristics** <u>Day 3 transferred</u> Womens age: 31.0 (+/-2.8) Basal FSH (mIU/mL): 6.0 (+/-1.3) Number of embryos transferred: 2.96 (+/-0.5) <u>Day 5 transferred</u> Womens age: 30.2 (+/-3.2) Basal FSH (mIU/mL): 6.6 (+/-1.5) Number of embryos transferred: 2.04 (+/-0.2) **Inclusion criteria** Age <35 years, no previous IVF cycles day 3 FSH <12 mIU/ml ≥10 follicles that were ≥14 mm on the day of hCG administration, ≥6 high-grade embryos 72 hours after fertilisation **Exclusion criteria** Not reported	≥ Double cleavage-stage vs Double blastocyst-stage transfer	<u>Recruitment</u>: All patients who initiated IVF cycles from January 1999 to May 2000, meeting the inclusion criteria were offered participation in the study. <u>Sample size calculation:</u> Controlling for the probability of type 1 error at alpha = 0.05, a sample of 68 patients per group (for a total of 136 patients) would have an 80% chance of detecting a 25% difference in multiple pregnancy rates <u>Randomisation:</u> Randomisation was accomplished on the day of retrieval using a computer-generated randomisation table. The sequences of randomisation were concealed until intervention was assigned. <u>Allocation concealment</u>: Not reported <u>Blinding:</u> Not reported <u>Intervention:</u>Not reported <u>Statistical analysis:</u> No intention-to-treat analysis <u>Power calculation:</u> Power calculation completed.	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | |---|---|---| | Day 2 - 3 | 8 | 23 | | Day 5 - 6 | 15 | 26 |	**Limitations** Small sample size It is not clear which patients had single or double embryo transfer Randomisation and allocation concealment not reported **Other information** The methods used were not described at length Spontaneous pregnancy loss was defined as a pregnancy loss after sonographic visualisation of an intrauterine genstational sac Live birth rate was defined as those pregnancies proceeding to deliver a viable infant Initial multiple pregnancies were detected by evaluating the number of gestational sacs at 6 weeks gestation 8/57 patients withdrew from the study. Four patients were withdrawn for having <6 high-grade embryos after

					fertilisation, one patient developed severe ovarian hyperstimulation syndrome and elected to not have an embryo transfer, one patient withdrew for personal reasons and two patients had family emergencies necessitating an earlier transfer. In total 5/28 from the day 3 group weer removed and 3/29 patients from the day 5 group were removed.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gerris,J., De,Neubourg D., Mangelschots,K., Van,Royen E., Van de,Meerssche M., Valkenburg,M., Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial, Human Reproduction, 14, 2581-2587, 1999 **Ref ID** 88924 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** 'To obtain data on the implantation rate and the (multiple) pregnancy rate after single embryo transfer and double embryo transfer, when compared in a prospective manner'. **Study dates** November 1997 - May 1999. **Source of funding** Clinical research grant by the 'Fondation Marguerite-Marie Delacroix'	**Sample size** N = 53 patients SET group = 26 patients DET group = 27 patients **Characteristics** Age (mean) = 31.9 years Duration of infertility(mean) = 3.5 years Cause of infertility = Not reported **Inclusion criteria** Only patients in their first IVF/ICSI cycle and who were <34 years of age The patients had to agree to participate in the study ≥2 top quality embryos at the time of embryo transfer. **Exclusion criteria** Not reported	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	Recruitment: In total, 327 patients participated in the IVF/ICSI programme during the study period. Of those agreeing to participate in the study, 53 fulfilled the study inclusion criteria. Patients were told that super numerary embryos would be frozen and that the study was limited to the first treatment cycle. Power calculation: Not reported Allocation concealment: Not reported Randomisation: Randomisation took place at the time of embryo transfer using external concealment. Interventions: For standard IVF, 3 - 5h after retrieval every oocyte was inseminated and incubated overnight. The ICSI procedure was performed. On day 3 embryo quality was evaluated, selection for embryo replacement was made according to the top quality embryo selection criteria described by Van Royen et al. All transfers were performed as an outpatient procedure. Statistical analysis: Intention-to-treat analysis not reported.	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | 1 Embryo | 10 | 26 | | 2 Embryos | 20 | 27 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 14 | 26 | | 2 Embryos | 21 | 27 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 1 | 26 | | 2 Embryos | 6 | 27 |	**Limitations** No allocation concealment No power calculation No blinding of the clinician, patients or assessor No detailed description of method of randomisation. **Other information** Ongoing pregnancy was defined as a conception cycle with at least one fetal sac with a positive heart beat beyond 12 weeks of amenorrhoea. Clinical pregnancy was not defined The figures for 'Live birth full term' reflect numbers of 'ongoing pregnancies'. This may include multiples, preterm, still-births, live births, full term and some miscarriages. Multiples from the double embryo transfer were dizygotic twins.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hreinsson,J., Rosenlund,B., Fridströ,m M, Ek,I., Levkov,L., blom,P., Hovatta,O., Embryo transfer is equally effective at cleavage stage and blastocyst stage: a randomized prospective study, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 117, 194-200, 2004 **Ref ID** 89135 **Country/ies where the study was carried out** Sweden **Study type** Randomised trial **Aim of the study** 'To compare the implantation and pregnancy rates after cleavage stage embryo transfer with transfer of blastocyst-stage embryos'. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 144 patients Cleavage-stage group = 80 patients Blastocyst-stage group = 64 patients **Characteristics** Cleavage-stage group (N = 80) Age (mean) = 33.1 years Duration of infertility = not reported Blastocyst-stage group (N = 64) Age (mean) = 32.1 years Duration of infertility = not reported Cause of infertility: Male = 45 (31.3%) Tubal = 29 (20.1%) Other = 58 (40.3%) Male/Female factor = 16 (11.1%) Some couples seem to have had more than one type of infertility	[1] Double cleavage-stage transfer [2] Double blastocyst-stage transfer	Recruitment: Women undergoing either IVF or ICSI treatment cycles, who had at least six follicles as observed at the final ultrasound scan before hCG administration were included in the study, after they had given an informed consent Power calculation: Assuming a pregnancy rate of 35% in the Day 2 - 3 group and 45% in the Day 5 - 6 group, power analysis showed that 395 subjects would be needed in each group to achieve an 80% power to detect such a difference at a 95% conficence level. Initially it was not possible to find partners for a multi-centre study. Recruiting couples to a randomised study took a long time, and in when new guidelines for embryo transfers were issued in Sweden according to which embryo transfer with two embryos was only to be carried out in exceptional cases, the study was discontinued. Randomisation: Not clear Allocation concealment: Sealed envelopes were used for randomisation of the patients to each group Intervention: After aspiration, the oocytes were collected into IVF medium and incubated before	**Results** **Clinical pregnancy** | | Events | Total | | Day 2 - 3 | 25 | 80 | | Day 5 - 6 | 22 | 64 | **Multiple pregnancy** | | Events | Total | | Day 2 - 3 | 4 | 80 | | Day 5 - 6 | 2 | 64 | **Adverse pregnancy outcome** | | Events | Total | | Day 2 - 3 | 2 | 80 | | Day 5 - 6 | 4 | 64 |	**Limitations** No blinding of the clinican, patients, or assessors. It is not clear whether the allocation concealment was adequate The study was not adequately powered as only 18% of the estimated sample size was achieved. One pregnancy resulted from the transfer of two morulae and was not excluded from the analysis. Confidence interval and p-value were not reported whenever a comparison was made between the groups. **Other information** 19/137 embryo transfers were SET and the others were DET 'Clinical pregnancy' was not defined All patients had one stimulated cycle each. Some patients might have had more than one type of infertility.

	Both groups were not significantly different in terms of age **Inclusion criteria** Not reported **Exclusion criteria** Not reported		insemination by IVF or ICSI. Double embryo tranfer was the routine when the study started, but towards the end of the study period, single embryo transfer was performed. One or two embryos with the highest score was selected for transfer and if no good grade embryos were available, up to two of the available ones were transferred. Morulae was also transferred in two cases on Day 5-6, since fully developed blastocysts were not available. All patients had one stimulated cycle each <u>Statistical analysis</u>: Intention-to-treat analysis not reported.		In two cases, blastocysts were cryopreserved because of OHSS. The 'Adverse pregnancy' outcome reported in this study include 'miscarriage in first trimester and ectopic pregnancies'.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
Karaki,R.Z., Samarraie,S.S., Younis,N.A., Lahloub,T.M., Ibrahim,M.H., Blastocyst culture and transfer: a step toward improved in vitro fertilization outcome, Fertility and Sterility, 77, 114-118, 2002

Ref ID
89251

Country/ies where the study was carried out
Jordan

Study type
RCT

Aim of the study
The aim of this study is to evaluate the efficacy of blastocyst transfer in comparison with day 3 embryo tansfer,

Study dates
June 1999 to June 2000

Source of funding
Not reported

Sample size
N = 162
(3 day group n = 82)
(5 day group n = 80)

Characteristics
Day 3 transfer group
Women's (mean) age: 29.2 (+/-5)
Mean infertility duration: 6.7 (+/-4.3)
Cause of infertility:
- Male factor: 51%
- Tubal: 10%
- Endometriosis: 7%
- PCOS: 9%
- Combined factor: 18%
- Unexplained: 5%

No. embryos transferred: 3.5 (+/-0.63)

Day 5 (blastocyst) transfer group:
Women's (mean) age: 30.0 (+/- 4.5)
Mean infertility duration: 6.8 (+/- 4.6)
Cause of infertility:
- Male factor: 52%
- Tubal: 8%
- Endometriosis: 5%
- PCOS: 11%
- Combined factor: 17%
- Unexplained: 7%

No. embryos transferred: 2.0 (+/-0.1)

Inclusion criteria

Exclusion criteria

Double cleavage stage vs Double blastocyst transfer

Randomisation: A box containing two types of card within envelopes. The card was drawn on the day of zygote transfer.

Power calculation: Not reported

Statistical analysis: P < 0.05 was deemed significant and P < 0.01 was considered highly significant

Method: GnRH agonist used in either long or short protocols to down regulate ovary. rFSH and hpFSH was used to stimulate until at least follicles were >18mm diameter, at which hCG used to trigger - oocytes were retrieved 35 hours after hCG injection. Implementation support was a vaginal dose of progesterone of 400mg.

Intervention: For patients receiving 3 day ET, 2PN embryos were cultured in IVF medium until transfer. The day 5 (blastocyst) patients were transferred to G1.2 medium then to G2.2 medium on day 1 and 3 respectively. On day 5 the embryos were assessed and then transferred on either day 5 or 6 depending on blastocyst expansion. The number of blastocysts transferred depended oy the availability of embryos, the patients age and previous cycle

Results
(A viable pregnancy was determined by fetal cardiac activity detected by ultrasound at 7 weeks)

Clinical pregnancy

	Events	Total
Day 2 - 3	21	82
Day 5 - 6	23	80

Multiple pregnancy

	Events	Total
Day 2 - 3	10	82
Day 5 - 6	9	80

Limitations
- No double blinding

- No user concealment

- No power calculation

Other information

	A patients had a good prognosis as determined by post insemination parameters (at least fove two-pronuclei embryos were available) None reported		history. If the patient was >35 years or had failed to achieve pregnancy after 2 attempts then up three blastocysts were selected for transfer (normal was to transfer 1-2).		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kjellberg,A.T., Carlsson,P., Bergh,C., Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis, Human Reproduction, 21, 210-216, 2006 **Ref ID** 89308 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Limitations** **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Levron,J., Shulman,A., Bider,D., Seidman,D., Levin,T., Dor,J., A prospective randomized study comparing day 3 with blastocyst-stage embryo transfer, Fertility and Sterility, 77, 1300-1301, 2002

Ref ID
89452

Country/ies where the study was carried out
Israel

Study type
Randomized prospective study

Aim of the study
The study looks to compare the outcome of IVF after a day 3 and a day 5 embryo transfer in a randomized prospective study.

Study dates
Not reported

Source of funding
Not reported</td>
<td>Sample size
N = 90
(Day 3 transfer n = 44)
(Day 5 transfer n = 46)

Characteristics
Day 3 transfer
Womens age (mean): 31.5 (+/-7.4)
No. of embryos per ET: 3.1 (+/-0.6)

Day 5 transfer
Womens age (mean): 30.9 (+/-4.0)
No. of embryos per ET: 2.3 (+/-0.8)

(Difference in ET significant P = 0.0001)

Inclusion criteria
- Maternal age <38 years
- Fewer than five previous IVF attempts
- Presence of more than 5 zygotes on day 1

Exclusion criteria
Not reported</td>
<td>≥Double cleavage stage vs ≥Double blastocyst transfer</td>
<td>Ninety consenting couples were recruited after approval of the local internal review board was obtained. Gametes and embryo handling procedures were done by using a commercial sequential IVF medium. For most patients, up to three embros were replaced on day 3 or day 5. Sequential use of G-1/G-2 media was used in the day 5 group.</td>
<td>Results
(No definition of clinical pregnancy)

Clinical pregnancy
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Day 2 - 3</td><td>20</td><td>44</td></tr><tr><td>Day 5 - 6</td><td>8</td><td>46</td></tr></table>
Multiple pregnancy
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Day 2 - 3</td><td>8</td><td>20</td></tr><tr><td>Day 5 - 6</td><td>4</td><td>8</td></tr></table></td>
<td>Limitations
- Randomisation method of patients not reported

- Allocation concealment not reported

- Power calculation not reported

- Clinical pregnancy was not reported

- Limited method reported

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Martikainen,H., Tiitinen,A., Tomá,s C, Tapanainen,J., Orava,M., Tuomivaara,L., Vilska,S., Granskog,C., Hovatta,O., Finnish ET Study Group., One versus two embryo transfer after IVF and ICSI: a randomized study, Human Reproduction, 16, 1900-1903, 2001 **Ref ID** 89588 **Country/ies where the study was carried out** Finland **Study type** Randomised trial **Aim of the study** 'To compare the effectiveness of one and two embryo transfer in a good prognosis group of patients'. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 144 patients SET group = 74 patients DET group = 70 patients **Characteristics** SET group (N = 74) Age (mean±SD) = 30.8 ± 3.9 years Duration of infertility = Not reported DET group (N = 70) Age (mean ±SD) = 30.5 ± 4.1 years Duration of infertility = Not reported Cause of infertility Male factor = 50 (34.7%) Tubal factor = 18 (12.5%) Male/Female factor = 7 (4.9%) Other = 51 (35.4%) The two groups were similar in relation to age and aetiology of infertility.	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	Recruitment: A total of 1301 couples fulfilled the inclusion criteria, and 144 agreed to participate in the randomised study. In all, 187 chose elective on embryo transfer and 970 two embryo transfer. Power calculation: Not reported Randomisation: Patients were randomised into the two groups using a computer-gnerated random number table balanced in sets of 10. Randomisation was done just before embryo(s) transfer by the laboratory personnel. Allocation concealment: Not reported Blinding: Not reported Interventions: One or two embryos were transfered into tho the uterine cavity 46-50h after oocyte retrieval. Supernumerary good quality embryos were frozen using a slow freezing protocol. The frozen embryo transfers were carried out in natural or stimulated cycles and embryo transfer was carried out 3 - 4 days later. The replacement of frozen embryos was not subjected to any protocol policy related to the present study. Statistical analysis: ITT not reported	**Results** **Live birth - Full-term - Cumulative** | | Events | Total | | --- | --- | --- | | 1 Embryo | 29 | 74 | | 2 Embryos | 36 | 70 | **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | 1 Embryo | 22 | 74 | | 2 Embryos | 28 | 70 | **Live birth - Full-term - Frozen cycle** | | Events | Total | | --- | --- | --- | | 1 Embryo | 7 | 54 | | 2 Embryos | 8 | 38 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 24 | 74 | | 2 Embryos | 33 | 70 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 1 | 74 | | 2 Embryos | 11 | 70 | **Pre-term delivery** | | Events | Total |	**Limitations** No power calculation. No allocation concealment. No blinding of physician, patient or assessor. **Other information** Adverse pregancy outcome reported were miscarriage and extrauterine pregnancy Figures for 'Live birth full term' reflect number of 'Live birth' and this includes preterm, full term, singletons and multiples. The replacement of frozen embryos was not subjected to any protocol policy related to the present study. Preterm birth - <37 weeks 'Clinical pregnancy' was not defined

	Inclusion criteria Four good quality embryos In Oulu the age of the woman was not taken into account and the first two cycles were regarded as eligible In the two units in Helsinki, only women <36 years who were undergoing their first treatment cycle were included **Exclusion criteria** Not reported			<table><tr><td>1 Embryo</td><td>1</td><td>74</td></tr><tr><td>2 Embryos</td><td>6</td><td>70</td></tr></table> **Adverse pregnancy outcome** <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>1 Embryo</td><td>2</td><td>74</td></tr><tr><td>2 Embryos</td><td>5</td><td>70</td></tr></table>	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Papanikolaou,E.G., D'haeseleer,E., Verheyen,G., Van,DeVeldeH, Camus,M., Van,SteirteghemA, Devroey,P., Tournaye,H., Live birth rate is significantly higher after blastocyst transfer than after cleavage-stage embryo transfer when at least four embryos are available on day 3 of embryo culture. A randomized prospective study, Human Reproduction, #20, 3198-3203, 2005

Ref ID
89875

Country/ies where the study was carried out
Belgium

Study type
Randomised controlled trial

Aim of the study
"To determine, where at least four good-quality embyos have been developed by day 3, whether the extension of embryo culture to day 5, and eventually a blastocyst-stage transfer, is feneficial in terms of increasing ongoing pregnancy and live birth rates, compared with cleavage-stage embryo transfer".

Study dates
January 2001 - November 2003

Source of funding
Not reported</td>
<td>Sample size
N = 164

Characteristics
<u>Double day 3 group (N = 84)</u>
Age = 29.6 (±0.4)
Duration of infertility = 2.7 (±0.3)
Cause of infertility
- Male factor: 55.4%
- Female factor: 30.1%
- Combined: 9.6%
- Idiopathic: 4.8%
Number of embryos/patient: 2.0 (+/-0.02)

<u>Double day 5 group (N = 80)</u>
Age = 29.9±0.4
Duration of infertility = 2.9 ± 0.2
Cause of infertility
- Male factor: 53.8%
- Female factor: 26.3%
- Combined: 11.3%
- Idiopathic: 8.8%
Number of embryos/patient: 1.97 (+/-0.5)

Inclusion criteria
Female age ≤ 37 years;

rank trial ≤3;

FSH on day 3 of the cycle ≤12 IU/ml;</td>
<td>Double day 3 embryo transfer vs Double day 5 embryo transfer.</td>
<td><u>Recruitment</u>: Within the study period, 301 patients seeking infertility treatment were found to be eligible to partiipate with the study. Finally 274 patients initiated multifollicular ovarian stimulation, among whom 164 fulfilled the embryological inclusion criterion of having at least four good-quality embryos on day 3 of embryo culture.

<u>Sample size calculation:</u> In order to detect a difference of 15% in ongoing pregnancy rates between the groups in which embryo transfer was performed on day 3 or day 5, 157 patients would be required in each group assuming a baseline pregnancy rate of 25%.

<u>Randomisation</u>: Every patient entered the study only once. Randomisation was performed on day 3 of embryo culture by the mbryologist in the IVF laboratory using a computer-generated randomised list.

<u>Allocation concealment</u>: Not reported;

<u>Blinding</u>: Not reported

<u>Interventions:</u> Two ovarian stimulation protocols were used for 274 patients in this study. Sperm</td>
<td>Results
Day 5 transfer resulted in a significantly higher clinical pregnancy (p = 0.008; CI: 1.23 - 4.40) and live birth rate (p = 0.01; CI: 1.25 - 4.59) compared with day 3 embryo transfer.

Adverse pregnancy (pregnancy loss) between the two groups did not differ (p = >0.05 and CI = not reported).

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>23</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>38</td><td>80</td></tr>
</table>
Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>27</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>42</td><td>80</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>8</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>18</td><td>80</td></tr>
</table>
Adverse pregnancy outcome
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>12</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>15</td><td>80</td></tr>
</table>
</td>
<td>Limitations
No mention of allocation concealment and/or blinding

The participants in the two groups received varying numbers of embryo (1, 2, or 3) which might have introduced bias and no subgroup analysis was conducted.

Other information
Clinical pregnancy was defined by the ultrasound observation of fetal cardiac activity after 7 weeks of gestation.

Embryos of good quality were defined as having a minimum of 6 blastomeres of normal size on the morning of day 3, a maximum of 20% of anucleate fragments and no multinucleated blastomeres.

A high initial multiple pregnancy rate in the day 5 group resulted in more than one-third of the births after day 5 transfer being twins.

5/80 patients in the day 5</td>
</tr>
</table>

	Ejaculated sperm origin; IVF or ICSI cycles; equal numbers (n = 2) of embryos should be transferred in each group. **Exclusion criteria** Oocyte donation cycles; Non-ejaculated sperm; PGD.		preparation, IVF/ICSI procedures and embrto culture were carried out as described by Van Landuyt et al. 2005. On the morning of day 3, embryos were transferred from cleavage medium to blastocyst medium. Normal fertilisation was confirmed by the presence of two pronuclei with two distinct or fragmented polar bodies. Embryo quality was assessed daily until the moment of transfer and/or freezing of the supernumerary embryos. Embryo quality on day 3 was scored based on number of blastomeres, rate of fragmentation, multinucleation of the blastomeres, and early compaction. Selected for transfer with preference for embryos which showed the normal developmental pattern of early cleavage on day 1, four cells on day 2 and eight cells on day 3 with minimal fragmentation and no multinucleation. Embryo quality on day 5 ranged from arrested multicellular embryos to advanced blastocysts. For transfer on day 5, preferably full or advanced blastocysts with many cells in the inner cell mass and in the trophectoderm were selected. <u>Statistical analysis:</u> Analysis was by intention to treat		group received a single embryo; 3/80 patients in the day 5 group and2/84 patients in the day 3 group asked for and finally had 3 embryos replaced. Adverse pregnancy outcome (Pregnancy loss) in both groups consisted of: Pregnancy loss at First trimester (23/27), second trimester(3/27) and ectopic pregnancies (1/27)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Thurin,A., Hausken,J., Hillensjö, T, Jablonowska,B., Pinborg,A., Strandell,A., Bergh,C., Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization, New England Journal of Medicine, 351, 2392-2402, 2004 **Ref ID** 90437 **Country/ies where the study was carried out** Sweden **Study type** Randomised multicentre trial **Aim of the study** 'To test the hypothesis: among women less than 36 years of age, the rate of pregnancies resulting in at least one live birth in patients who undergo the transfer of a single fresh embryo and, if no live birth results, the subsequent transfer of a frozen-and-thawed embryo, would be equidvalent to the rate in patients who undergo the simultaneous transfer of two fresh embryos'. **Study dates** May 2000 - October 2003 **Source of funding** Grant from Serono Nordic, by Sahlgrenska Academy and Sahlgrenska University Hospital, by the Goteborg Medical Society, and by the Hjalmar Svensson Foundation.	**Sample size** N = 661 patients SET group = 330 patients DETgroup = 331 patients **Characteristics** SET group (N = 330) Age (mean±SD) = 30.9 ± 3.0 years Duration of infertility (mean±SD) = 3.6 ± 1.7 years DET group (N = 331) Age (mean±SD) = 30.8 ± 3.0 years Duration of infertility(mean±SD) = 3.8 ± 3.9 years Cause of infertility Male factor = 319 (48.3%) Tubal factor = 130 (19.7%) Male/Female factor = Not reported Others = 366 (55.4%)	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	Recruitment: Eleven clinics, both public and private, participated. A total of 661 patients underwent randomisation. Of those, 331 patients were randomly assigned to undergo double-embryo transfer and 330 to undergo elective single-embryo transfer. Power calculation: Before the start of the study, sample size was calculated on the basis of the live-birth rate, after applying the following assumptions: if the true rate of live births in the two treatment groups is 0.30, then the probability is 0.80 that the upper limit of the 95% confidence interval for the difference in the probability of live birth between the groups is lower than 0.10, if 330 patients who can be evaluated are included in each group. The number of patients lost to follow-up was assumed to be zero. Thus, 660 patients were needed Randomisation: Randomisation was performed locally by the embryologist with the use of a computerised randomisation program at a ratio of 1:1. Optimal allocation was applied according to Pocock's minimisation technique for sequential randomisation with consideration given to the woman's age, the presence or absence of	**Results** **Live birth - Full-term - Cumulative** | | Events | Total | | 1 Embryo | 128 | 330 | | 2 Embryos | 142 | 331 | **Live birth - Full-term - Fresh cycle** | | Events | Total | | 1 Embryo | 91 | 330 | | 2 Embryos | 142 | 331 | **Adverse pregnancy outcome** | | Events | Total | | 1 Embryo | 20 | 330 | | 2 Embryos | 32 | 331 |	**Limitations** Allocation concealment was not reported. **Other information** Figures for 'Live birth full term' include live births, full term, preterm, singletons and multiples. A pregnancy was defined as a positive test for hCG in urine (>20 IU per liter) or a serum level of hCG 2 IU per liter or more two weeks after embryo transfer. The figures for 'Clinical pregnancy' outcome reflect number of 'pregnancy' (as reported in the study). The original protocol stipulated that the patient had to be <35 years of age and have ≥3 good-quality embryos available, but these criteria were modified in an amendment after the first 215 patients were enrolled, owing to a change in usual clinical practice in Sweden. Adverse pregnancy outcomes reported in this

Speaker's fees from Organon	Some couples/patients may have had >1 type of infertility **Inclusion criteria** <36 years of age at the time of the transfer of the fresh embryo Undergoing first or second IVF cycle ≥2 embryos of good quality available for transfer or freezing **Exclusion criteria** Not reported		tubal infertility, the number of previous IVF cycles involving transfers, the number of previous IVF cycles resulting in birth, the day of embryo transfer, and the number of good-quality embryos available. Allocation concealment:Not reported Blinding: Double blinding (neither the patient nor the physician knew whether one embryo or two embryos had been transferred). Interventions: Oocyte retrieval and fertilisation were performed by conventional IVF or ICSI by means of standard techniques. Embryo transfer was performed two, three, or five days after oocyte retrieval. Patients in the SET group who did not conceive in the cycle in which the fresh embryo had been transferred, or who miscarried, subsequently underwent the transfer of a single frozen-and-thawed embryo in a natural or a hormone-stimulated cycle. If the first frozen-and-thawed embryo was not viable, other embryos were thawed, one by one, until a viable embryo could be transferred. Statistical analysis: Intention to treat analysis (included 661patients).		study include ectopic pregnancy, spontaneous abortions at ≤12 weeks and >12 weeks, stillborn infants ≥28 weeks of gestation Spontaneous abortions at >12 weeks of gestation includes 1/17 patient in the single-embryo transfer group that underwent termination of pregnancy owing to fetal acrania.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation van Montfoort,A.P., Fiddelers,A.A., Janssen,J.M., Derhaag,J.G., Dirksen,C.D., Dunselman,G.A., Land,J.A., Geraedts,J.P., Evers,J.L., Dumoulin,J.C., In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial, Human Reproduction, 21, 338-343, 2006 **Ref ID** 90527 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised controlled trial **Aim of the study** 'The primary aim was to compare the pregnancy rates in elective single embryo transfer and double embryo transfer study groups. A sendoary aim of the study was to evaluate pregnancy rates after elective single embryo transfer and double embryo transfer when the decision of whether to transfer one or two embryos was based on female age (<38 years) and the presence of at least one good quality embryo'. **Study dates** January 2002 - December 2004 **Source of funding**	**Sample size** N = 308 patients SET group = 154 patients DET group = 154 patients **Characteristics** <u>SET group (N = 154)</u> Age (mean±SD) = 32.7 ± 3.3 years Duration of subfertility (mean±SD) = 3.3 ± 1.8 years <u>DET group (N = 154)</u> Age (mean±SD) = 32.4 ± 3.3 years Duration of subfertility (mean±SD) = 3.3 ± 2.1 years <u>Cause of infertility</u> Male factor = 172 (55.8%) Tubal factor = 52 (16.9%) Male/Female factor = Not reported Other = 84 (27.3%) Patient and cycle characteristics were comparable between the two study groups of the study. **Inclusion criteria** **Exclusion criteria**	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	<u>Recruitment</u>: 807 patients who started their first IVF or IVF/ICSI cycle within the study period were assessed for eligibility to participate in the study. Of the 621 eligible patients, 348 agreed to participate and 308 were randomised, 40 could not be randomised because of fertilisation failure or because only one embryo was available. <u>Power calculation</u>: Assuming an ongoing pregnancy rate of 29% (reported in previous study) for the double embryo transfer group in the study and considering an ongoing pregnancy rate in the elective single embryo transfer group of <15% as clinically unacceptable, the required sample size was 150 cycles in both study groups with a power of 80% and an α of 0.05. <u>Randomisation</u>: Randomisation was performed immediately prior to embryo transfer. To ensure comparablility between the two groups with respect to female age (<38 or ≥38 years) and fertilisation technique (IVF or IVF/ICSI), the patient population was stratified with respect to these four characteristics. <u>Allocation concealment</u>: The groups were further subdivided to ensure	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | |---|---|---| | 1 Embryo | 32 | 154 | | 2 Embryos | 73 | 154 | **Clinical pregnancy** | | Events | Total | |---|---|---| | 1 Embryo | 33 | 154 | | 2 Embryos | 62 | 154 | **Multiple pregnancy** | | Events | Total | |---|---|---| | 1 Embryo | 0 | 154 | | 2 Embryos | 12 | 154 | **Adverse pregnancy outcome** | | Events | Total | |---|---|---| | 1 Embryo | 18 | 154 | | 2 Embryos | 11 | 154 |	**Limitations** No blinding of the physician, patients or assessors **Other information** Any subsequent IVF or IVF/ICSI cycle and all transfer cycles of cryopreserved embryos were not a part of the study. The multiple pregnancy reported in the study was twin pregnancy. Other types of multiples were not reported. An ongoing pregnancy was defined as the presence of at least one intrauterine gestational sac with fetal heart beat on ultrasound at 7 weeks gestation; The figures for 'Clinical pregnancy' outcome reflect the number of 'ongoing pregnancy' reported. Some of the clinical pregnancies may have become miscarried at the time of examination. Figures for 'Live birth full term' reflect 'Live biirth'

Research grant from the Dutch Organisation for Health Research and Development(ZonMW) and the Dutch Health Insurance Board (CvZ) in a joint research programme on health technology assessment of infertility	Consenting patients had to have normal fertilisation of ≥2 oocytes in order to be randomised between elective single embryo transfer and double embryo transfer group Patients [1] applying for pre-implantation genetic diagnosis [2] requiring the transfer of only one embryo (in most cases because of medical reasons) [3] who could not be informed adequately because of a language barrier		an equal distribution of single embryo transfer and double embryo transfer. By varying the size of these subgroups and by using a non-transparent box containing the sealed opaque envelopes, the randomisation procedure was blinded. Interventions: Embryos were transferred on day 2 after ovum pick-up or in a minortity of cases, for reasons of convenience, on day 3. In all cases, embryos with the highest embryo score were transferred. Cryopreservation of supernumerary embryos was performed on the morning of the third day after ovum pic-up if one or more embryos had reached the 8-cell stage, and if there were of good morphological quality. After transfer, patients were informed about the number of embryos transferred. Any subsequent IVF or IVF/ICSI cycle and all transfer cycles of cryopreserved embryos were not a part of the RCT. Statistical analysis: No ITT		and may include full term, preterm, singletons and multiples. Live birth – Full – term – Fresh cycle (reported in follow-up study, see Fiddelers 2006) The 'Adverse pregnancy' outcome reported in the study was Abortion <13 weeks.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Van,der Auwera,I, Debrock,S., Spiessens,C., Afschrift,H., Bakelants,E., Meuleman,C., Meeuwis,L., D'Hooghe,T.M., A prospective randomized study: day 2 versus day 5 embryo transfer, Human Reproduction, 17, 1507-1512, 2002

Ref ID
90539

Country/ies where the study was carried out
Belgium

Study type
Randomised trial

Aim of the study
'To test the hypothesis that blastocyst transfers resultin higher clinical pregnancy rates per oocyte retrieval when compared with day 2 transfers'.

Study dates
February 1999 - September 2000

Source of funding
Not reported</td>
<td>Sample size
N = 136 patients

N = 129 patients (included in the analysis)
Cleavage-stage group = 63
patients
Blastocyst-stage group = 66 patients

Characteristics
Cleavage-stage group (N = 63)

Age (mean±SD) = 31.7 ±3.3 years

Duration of infertility = Not reported

Blastocyst-stage group (N = 66)

Age (mean±SD) = 31.5 ± 3.5 years

Duration of infertility = Not reported

Type of Infertility

Male = 74 (54.4%)

Tubal = 20 (14.7%)</td>
<td>[1]
Double cleavage-stage transfer

[2] Double blastocyst-stage transfer</td>
<td>Recruitment: IVF and ICSI patients who started their cycle within the study period were randomised.

Randomisation/Allocation concealment: Blind randomisation using sealed envelopes was performed at the beginning of the hormonal stimulation before the hormal response was known.

Power calculation: Power calculation had shown that 175 patients were needed in each group to demonstrate a significant difference of 15% in pregnancy rate/oocyte retrieval between the groups.

Interventions: A maximum of two selected embryos were transferred on day 2, while the remaining embryos (maximum of three) were cultured for another 3 - 4 days and frozen at the blastocyst stage if available. In the day 5 group, all fertilitized ova were cultured in vitro to achieve blastocysts. A maximum of two blastocysts was transferred while those remaining were frozen on day 5 or 6. All frozen-thawed embryos from the study period were included in the evaluation of the cryo-augmented pregnancies per oocyte retrieval. Freezing was achieved using the slow</td>
<td>Results

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>26</td><td>66</td></tr>
<tr><td>Day 5 - 6</td><td>33</td><td>70</td></tr>
</table>
Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>20</td><td>66</td></tr>
<tr><td>Day 5 - 6</td><td>29</td><td>70</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>9</td><td>66</td></tr>
<tr><td>Day 5 - 6</td><td>9</td><td>70</td></tr>
</table>
Adverse pregnancy outcome
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>3</td><td>66</td></tr>
<tr><td>Day 5 - 6</td><td>5</td><td>70</td></tr>
</table>
</td>
<td>Limitations
The sample size did not meet power calculation. Its not clear whether the allocation concealment was adequate.

The person/people (patient, clinician or assessor) that were blinded were not mentioned.

The method of randomisation was not reported in details.

27% of the patients in the blastocyst group did not receive an embryo transfer due to a lack of blastocysts on day 6 and no intention to treat analysis was conducted.

When comparisons were made between the two groups, no confidence intervals were reported alongside p-value.

Other information
Three patients were excluded for analysis from the cleavage group because they wanted an</td>
</tr>
</table>

	Other = 26 (19.1%) Male/Female = 9 (6.6%) At randomisation, no differences were found for age, duration of infertility, type of infertility or IVF indication, nor ratio of ICSI:IVF cycles . **Inclusion criteria** Not reported **Exclusion criteria** Not reported		freezing protocol. <u>Statistical analysis</u>: Intention-to-treat analysis not reported		elective blastocyst culture. Four patients were excluded from the blastocyst group because they wanted an elective day 2 transfer. Clinical pregnancy was not defined Figures for 'Multiple pregnancy' reflect number of delivered twins. It does not include any lost multiple pregnancies and its not clear if there were other types of multiples. Figures for 'Live birth full term' reflect number of children born. This may include live births, still-births, preterm, full term, singletons and multiples 'Adverse pregnancy' is the number of clinical pregnancies that did not result in any deliveries.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Zech,N.H., Lejeune,B., Puissant,F., Vanderzwalmen,S., Zech,H., Vanderzwalmen,P., Prospective evaluation of the optimal time for selecting a single embryo for transfer: day 3 versus day 5, Fertility and Sterility, 88, 244-246, 2007

Ref ID
90739

Country/ies where the study was carried out
Belgium and Austria

Study type
Randomised clinical trial.

Aim of the study
To determine the best day for the selection and transfer of a single embryo.

Study dates
November 2003 to February 2005.

Source of funding
Not reported.</td>
<td>Sample size
n = 227 women

Characteristics
Not reported.

Inclusion criteria
1. ≤36 years of age.
2. First or second attempt at IVFF or ICSI.
3. Women who underwent treatment using ≥5 fertilised oocytes.

Exclusion criteria
Not reported.</td>
<td>Single cleavage stage vs Single blastocyst transfer</td>
<td>16 to 20 hours after insemination or ICSI, all oocytes were checked for the presence of two pronuclei, and the patients were randomised for embryo culture to either day 3 or day 5, according to even or odd year of birth</td>
<td>Results
Ongoing pregnancy was defined by the ultrasound observation of a positive heartbeat 6 weeks after oocyte retrival
Adverse pregnancy outcome reported was miscarriage.

Clinical pregnancy
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Day 2 - 3</td><td>23</td><td>99</td></tr><tr><td>Day 5 - 6</td><td>42</td><td>128</td></tr></table>
Adverse pregnancy outcome
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Day 2 - 3</td><td>8</td><td>99</td></tr><tr><td>Day 5 - 6</td><td>9</td><td>128</td></tr></table></td>
<td>Limitations
1. It is not clear whether the method of randomistion was adequate.
2. No blinding
3. No allocation concealment
4. No power calculation

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation McLernon,D.J., Harrild,K., Bergh,C., Davies,M.J., de,Neubourg D., Dumoulin,J.C., Gerris,J., Kremer,J.A., Martikainen,H., Mol,B.W., Norman,R.J., Thurin-Kjellberg,A., Tiitinen,A., van Montfoort,A.P., van Peperstraten,A.M., Van,Royen E., Bhattacharya,S., Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials, BMJ, 341, c6945-, 2010 **Ref ID** 96729 **Country/ies where the study was carried out** Various **Study type** Individual patient meta-analysis **Aim of the study** To compare the effectiveness of eSET versus DET **Study dates** Search conducted in 2008, but included RCTs were before this date. **Source of funding** Wellcome Trust	**Sample size** 1539 citations identified, 11 assessed for inclusion, 8 included. The 8 RCTs included 683 eSET and 684 DET patients. **Characteristics** Type of treatment: eSET vs DET IVF 365 (53%) vs 388 (57%) ICSI 318 (47%) vs 293 (43%) Both 0 vs 2 Missing 0 vs 1 Embryos transferred in first fresh cycle: 0: 2 vs 1 1: 677 vs 7 2: 4 vs 676 Day of fersh embryo	eSET IVF or ICSI using cleavage stage embryos DET IVF or ICSI using cleavage stage embryos	Literature review: Medline and Embase search upto 2008 Authors of identified trials contacted about individual data being made avaialble Included studies: Patient inclusion criteria varied between the RCTs IVF and ICSI protocols varied between the included RCTs Individual patient data: BMI, woman's age, duration, type and cause of infertility and type of treatment. Characteristics of cycle - eSET or DET, day of transfer, quality of embryo. Outcome of treatment - live birth, multiple live birth, cumulative blive birth, cumulative multiple live birth, miscarriage, preterm delivery, term singleton delivery and low birth weight. Statistical analysis:	**Results** Included studies: Gerris et al, 1999 Lukassen et al, 2005 Martikainen et al, 2001 Thurin et al, 2004 Van Montfoort et al, 2006 unpublished data Thurin, 2005 Davies, 2003 Bhattacharya, 2006 Term singleton births DET vs eSET OR = 4.93 (2.98 to 8.18) Miscarriage eSET = 60 of 245 (24%) vs DET = 63 of 355 (18%); OR = 1.52 (1.01 to 2.28)	**Limitations** Variation in entry criteria and clinical protocols used between RCTs could introduce hetrogeneity. RCTs only included women with 'good' prognosis. The outcomes after cumulative embryo transfers were not reported. **Other information**

	Day 2: 540 vs 539 Day 3: 130 vs 131 Day 5: 10 vs 9 No transfer: 2 vs 1 Missing: 1 vs 4 Grade of embryos transferred Grade A: 571 vs 597 Grade B: 79 vs 51 Missing: 31 vs 35 **Inclusion criteria** Only RCTs that compared cleavage stage eSET or DET transfers using either IVF or ICSI. **Exclusion criteria** N/A		Test of hetrogeneity using funnel plots, with a figure greater than 50% considered to show substantial heterogeneity. If none found then logistic regression model was fitted, adjusted for trial, duration of infertility, type of infertility (primary or secondary). type of treatment, cause of infertility, woman's age, BMU and quality of embryos	Preterm birth (<= 37 weeks) eSET vs DET OR = 0.33 (0.20 to 0.55) Predictors of live birth (live birth vs no live birth) (n = 466 vs 900) eSET vs DET OR = 0.50 (0.40 to 0.63) Mean age OR = 0.97 (0.94 to 1.01) BMI of woman OR = 0.96 (0.90 ro 1.02) Duration of infertility (years) OR = 0.96 (0.90 to 1.02) Type of infertility Female vs male OR = 0.86 (0.64 to 1.16); AOR = 0.8 (0.38 to 0.88) Unexplained vs male OR = 1.17 (0.85 to 1.61); AOR = 0.79 (0.51 to 1.22) Secondary vs primary OR = 1.03 (0.79 to 1.35) Day of transfer Day 3 vs day 2 OR = 1.10 (0.70 to 1.74)	

Day 5 vs day 2 OR = 0.51 (0.17 to 1.58)

Quality of embryo

Grade A vs Garde B OR = 1.93(1.23 to 3.04)

Live birth - Full-term - Fresh cycle

	Events	Total
1 Embryo	181	683
2 Embryos	285	683

Multiple pregnancy

	Events	Total
1 Embryo	3	181
2 Embryos	84	285

Fertility (Updated guideline)

What is the effectiveness and safety of different embryo/blastocyst transfer strategies?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lukassen,H.G., Braat,D.D., Wetzels,A.M., Zielhuis,G.A., Adang,E.M., Scheenjes,E., Kremer,J.A., Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial, Human Reproduction, 20, 702-708, 2005 **Ref ID** 4535 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised trial **Aim of the study** 'To investigate the live birth rate of double embryo transfer after one treatment cycle, excluding freeze-thaw cycles'. **Study dates** January 2001 - February 2003 **Source of funding** Not reported	**Sample size** N = 107 patients SET group = 54 patients DET group = 53 patients **Characteristics** Single embryo transfer group Age (mean±SD) = 30.2 ± 3.2 years Duration of infertility (mean±SD) = 3.1 ± 1.4 years Double embryo transfer group Age (mean±SD) = 31.2 ± 2.9 years Duration of infertility (mean±SD) = 3.5 ± 1.9 years Cause of infertility Male factor = 62 (57.9%) Tubal factor = 14 (13.1%) Male/Female factor = Not reported Other = 31 (29%) The characteristics of the	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	Recruitment: A total of 494 IVF patients underwent oocyte retrieval and embryo transfer. Of the 494 IVF patients, 217 did not agree to participate or were excluded. Power calculation: Not reported. Randomisation: A total of 107 patients were randomised to the single or double embryo transfer group was performed using a computer-generated random block number table, stratified for primary or secondary infertility, executed by an independent statistician. Allocation concealment: Allocation was undertaken by an opaque, sealed envelop took place just before embryo transfer by the Laborory personnel. Blinding: Patients and physicians were not blinded to treatment group. Interventions: Insemination was carried out by adding motile spermatoa to the oocytes in IVF medium. If ICSI was performed, the oocytes were treated with hyaluronidase solution and denuded	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | 1 Embryo | 14 | 54 | | 2 Embryos | 19 | 53 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 20 | 54 | | 2 Embryos | 25 | 53 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 0 | 54 | | 2 Embryos | 7 | 53 | **Pre-term delivery** | | Events | Total | | --- | --- | --- | | 1 Embryo | 2 | 54 | | 2 Embryos | 5 | 53 |	**Limitations** No power calculation. No blinding of patients and physicians. **Other information** 'Clinical pregnancy' was confirmed by ultrasonic evidence of an intrauterine gestational sac and a positive heartbeat five weeks after embryo transfer. 'Live birth full term' reflects 'live birth' and includes full term, preterm, live births, singletons and multiples. 9/10 preterm births were from twin pregnancies. Figures for 'Multiple pregnancy' reflect 6 twin births and 1 dizygotic triplet. The 'Adverse pregnancy' outcomes reported in the study were miscarriage and ectopic pregnancy. In the SET group, 40/54 had a

	randomised patients were similar between the single and double embryo transfer group. There was no statistical significant difference in the number of ICSI cycles performed in both groups **Inclusion criteria** Patients undergoing their first IVF/ICSI cycle ever or the first cycle after a successful treatment. <35 years of age. Basal FSH level <10IU/l. ≥2 embryos had to be available for transfer on day 3 after oocyte retrieval during the first cycle. **Exclusion criteria** Patients with a medical reason for elective single embryo transfer.		with a capillary pipette before injection was performed. On day 3 after oocyte retrieval, the embryos were scored and transferred. Excess embryos of good morphological quality were cryopreserved using the standard protocol with the cryoprotectant 1,2-propanediol. All patients completed their first treatment cycle while only 40/54 patients in the SET group completed a second cycle. <u>Statistical analysis</u>: Intention-to-treat analysis.	**Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | 1 Embryo | 6 | 54 | | 2 Embryos | 6 | 53 |	second cycle treatment but only results from the first cycle have been presented.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gardner,D.K., Surrey,E., Minjarez,D., Leitz,A., Stevens,J., Schoolcraft,W.B., Single blastocyst transfer: a prospective randomized trial, Fertility and Sterility, 81, 551-555, 2004 **Ref ID** 5128 **Country/ies where the study was carried out** USA **Study type** Randomized controlled trial **Aim of the study** 'To determine whether high blastocyst implantation rates could be translated into high pregnancy rates, while eliminating associated multiple pregnancies, when a single embryo was transferred' **Study dates** Not reported **Source of funding** Supported in part by Organon Inc and Vitrolite AB	**Sample size** N = 48 patients SET group = 23 patients DET group = 25 patients **Characteristics** SET group (N = 23) Age (mean±SD) = 33.5±0.9 years DET group (N = 25) Age (mean±SD) = 34.2 ± 0.7 years Mean duration of infertility: Not reported Cause of infertility: Not reported There was no differences in indications for IVF, patient age, or percentage of ICSI patients in both groups **Inclusion criteria** [1] Day 3 FSH ≤10 mIU/ml [2] E_2 < 80 pg/ml [3] hysterosxcopically normal endometrial cavity [4] at leats 10 follicles > 12 mm in diameter on day of hCG administration **Exclusion criteria** None	[1] Single blastocyst-stage transfer [2] Double blastocyst-stage transfer	Recruitment:Participation in the study was offered to all patients undergoing IVF-ET with their own oocytes during a 24-month period for blastocyst stage embryo transfer Power calculation: Not reported Randomisation: Patients were randomised at the time of transfer by a computer-generated table to either transfer of one or two blastocysts on day 5. Allocation concealment: Not reported Interventions: Patients received standard insemination or ICSI as clinically appropriate, and subsequent embryos were cultured. All blastocysts were evaluated using a previously described scoring system (Gardner and Schoolcraft, 1999). No embryos underwent assisted hatching before transfer. Cryopreservation of supernumerary blastocysts on days 5 or 6 was performed using controlled rate freezing Statistical analysis: ITT not reported	**Results** **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 14 | 23 | | 2 Embryos | 19 | 25 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | 1 Embryo | 0 | 23 | | 2 Embryos | 9 | 25 |	**Limitations** No power calculation. No allocation concealment. **Other information** Ongoing pregnancy was determined by the presence of intrauterine gestational sacs with cardiac activity noted on ultrasound examination performed at least 4.5 weeks after transfer per cycle initiated. Figures for 'Clinical pregnancy' outcome reflect number of 'ongoing pregnancy'. Multiple pregnancy was reported as twin pregnancy. It is not clear if triplet pregnancies, quadruplets and other multiple pregnancies had occurred.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kolibianakis,E.M., Zikopoulos,K., Verpoest,W., Camus,M., Joris,H., Van Steirteghem,A.C., Devroey,P., Should we advise patients undergoing IVF to start a cycle leading to a day 3 or a day 5 transfer?, Human Reproduction, 19, 2550-2554, 2004 **Ref ID** 5292 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** 'To compare ongoing pregnancy rates per started cycle between patients randomised, prior to initiation of stimulation, to have embryo transfer either on day 3 or on day 5 of in-vitro culture'. **Study dates** January 2001 to December 2003 **Source of funding** Grants from the Fund for Scientific Research, Flanders	**Sample size** N = 460 patients Cleavage-stage group = 234 patients Blastocyst-stage group = 226 patients **Characteristics** Cleavage-stage group (N = 234) Age (mean±SD) = 31.3 ± 0.3 years Duration of infertility = Not reported Blastocyst-stage group (N = 226) Age (mean±SD) = 31.5 ± 0.2 years Duration of infertility = Not reported Cause of infertility Male factor = 300 (65.2%) Tubal factor = 45 (9.8%) Male/Female factor = Not reported Other = 115 (25%) **Inclusion criteria** <43 years and the presence of indication for IVF. **Exclusion criteria** Preimplatation genetic screening and azoospermia.	[1] Cleavage-stage transfer (single or double) [2] Blastocyst-stage transfer (single or double)	Recruitment: 460 patients treated by IVF within the study period were included. Patients could entre the study only one. Power calculation:To detect a difference of 5% in ongoing pregnancy rates between the two groups compared assuming a baseline ongoing pregnancy of 30% at an α level of 0.05 and β of 0.2, 1416 patients were needed for inclusion in each group. Randomisation: Randomisation was performed by the attending physician according to a computer-generated list. Allocation concealment: The sequence of randomisation was not concealed. Interventions: Conventional IVF (120 couples), ICSI (312 couples) and both (28 couples) were carried out. The ICSI and IVF procedures have been described in detail previously (Devroey et al., 1995; Devroey and Van Steirteghem, 2004). As a matter of principle, 1 - 2 embryos were transferred on day 3 or day 5 after oocyte retrieval. Supernumerary embryos were frozen at the blastocyst stage in both groups. Statistical analysis: No intention-to-treat analysis.	**Results** **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 20 | 234 | | Day 5 - 6 | 15 | 226 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 21 | 234 | | Day 5 - 6 | 19 | 226 |	**Limitations** The study was not adequately powered No allocation concealment The number of embryos transferred varied between single and double and no subgroup analysis was done. **Other information** Where embryo transfer was performed, similar numbers of embryos were replaced in both groups. Adverse pregnancy outcome reported include biochemical pregnancy (number of biochemical pregnancy that did not result in delivery), first trimester miscarriage and extrauterine pregnancy.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>
Full citation
Papanikolaou,E.G., Camus,M., Kolibianakis,E.M., Van,Landuyt L., Van,Steirteghem A., Devroey,P., In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos, New England Journal of Medicine, 354, 1139-1146, 2006

Ref ID
5509

Country/ies where the study was carried out
Belgium

Study type
Randomised trial

Aim of the study
'To determine whether there were any differences in the rates of pregnancy and delivery between women randomly assigned to undergo transfer of a single cleavage-stage embryo and those assigned to undergo transfer of a single blastocyst-stage embryo'.

Study dates
July 2003 - November 2004

Source of funding
Research support from Organon
</td>
<td>
Sample size
N = 351 patients

Cleavage-stage group = 176 patients
Blastocyst-stage group = 175 patients

Characteristics
<u>Cleavage-stage group (N= 176)</u>

Age (mean±SD) = 30.5±3.2 years

Duration of infertility (mean±SD) = 3.7 ± 2.2 years

<u>Blastocyst-stage group (N = 175)</u>

Age (mean±SD) = 30.4 ± 3.6 years

Duration of infertility (mean±SD) = 3.5 ± 2.1 years

<u>Cause of infertility</u>

Male = 196 (55.8%)

Female = 85 (24.2%)

Other (idopathic) = 39 (11.1%)

Male/female = 31 (8.8%)

There were no significant differences between the groups in age (p=0.84), duration of infertility (p = 0.75), cause of
</td>
<td>
[1] Single cleavage-stage transfer

[2] Single blastocyst-stage transfer
</td>
<td>
<u>Recruitment</u>: 351 women requesting infertility treatment within the study period were randomly assigned to undergo transfer of either a single cleavage-stage embryo or a single blastocyst-stage embryo.

<u>Power calculation</u>: Using group sequential methods, calculations showed that the enrollement of 351 patients in each group would give the study a statistical power of 80% to detect an absolute difference of 10% in the rate of ongoing pregnancy between the groups (given rates of 20 and 30%) at α level of 0.05 with the use of a two-sided z-test. It was prespecified that the study would be stopped if the first interim analysis identified a significant difference (p = 0.03) in pregnancy rates between groups. At the first interim analysis, the pregnancy rate in the blastocyst-stage group was greater than that in the cleavage-stage group at an alpha level of 0.02, and therefore, the study was terminated.
<u>Randomisation:</u> Randomisation was perfomed after the first consultation at the outpatient clinic. A computer-generated list was used for randomisation; this list was not concealed from the physicians, but it did not explicitly state the treatment strategy, identifying the strategies only as "A" or "B". A patient could enter the study only once.
</td>
<td>
Results

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>38</td><td>176</td></tr>
<tr><td>Day 5 - 6</td><td>56</td><td>175</td></tr>
</table>
Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>41</td><td>176</td></tr>
<tr><td>Day 5 - 6</td><td>58</td><td>175</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>2</td><td>176</td></tr>
<tr><td>Day 5 - 6</td><td>0</td><td>175</td></tr>
</table>
Adverse pregnancy outcome
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>21</td><td>176</td></tr>
<tr><td>Day 5 - 6</td><td>17</td><td>175</td></tr>
</table>
</td>
<td>
Limitations
No allocation concealment.

Other information
Clinical pregnancy was defined by the observation of fetal cardiac activity on ultrasonography after seven weeks of gestation.

The 'Adverse pregnancy' outcome reported in the study include ectopic pregnancy, first trimester and second trimester pregnancy loss.

Figures for 'Live birth full term' reflects number of births and may include full term, preterm, live, still-births, singletons and multiples.

In the initial design there was no plan for the subsequent transfer of frozen embryos in patients who did not conceive.

In the day 5 - 6 group, 13/169 (7.7%) patients did not undergo tranfer because of lack of embryos (11 patients) or OHSS (2 patients).

In the day 3 group, embryo transfer was not performed
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</table>

	infertility (p = 0.68) or cycle characteristics (p = Not reported). **Inclusion criteria** Women <36 years of age who were undergoing a first or second trial of IVF or ICSI. Serum follicle stimulating hormone level on day 3 of the menstrual cycle of 12 IU/l or less. Undergoing transfer of one embryo. **Exclusion criteria** Use of preimplantation genetic diagnosis		Blinding: The embryo transfers were performed with ultrasound guidance by clinicians and embryologists who were blinded only with respect to the patient's participation in the study. Interventions: Sperm preparation, IVF abd ICSI procedures, and embryo culture were carried out as described by Van Landuyt et al., 2001. Embryo quality was assessed daily until the moment of transfer or freezing. On the morning of day 3, the embryos were removed from cleavage medium and placed in blastocyst medium. Supernumerary embryos were frozen on day 5 or 6. Embryos were scored 1 - 4 and embryos with a score of 4 were not transferred. Statistical analysis: Analysis was performed according to intention to treat.		in 9/171 (5.3%) patients because of lack of embryos on day 3 (8 patients) and OHSS (1 patient)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
Bungum,M., Bungum,L., Humaidan,P., Yding,Andersen C., Day 3 versus day 5 embryo transfer: a prospective randomized study, Reproductive Biomedicine Online, 7, 98-104, 2003

Ref ID
65163

Country/ies where the study was carried out
Denmark

Study type
Randomised trial

Aim of the study
'To investigate whether embryos from good prognosis patients hava a different implantation potential comparing day 3 to day 5 embryo transfer when equal numbers of embryos are transferred'.

Study dates
December 2001 - May 2002

Source of funding
Not reported

Sample size
N = 118 patients

Cleavage-stage group = 57 patients
Blastocyst-stage group = 61 patients

Characteristics
Cleavage-stage group (N = 57)

Age (mean) = 31.3 years

Blastocyst-stage group (N = 61)

Age (mean) = 31.2 years

Duration of infertility = Not reported

Cause of infertility = Not reported

No statistical differences in age.

Inclusion criteria
Three or more 8-cell embryos with <20% extracellular fragments on day 3.

Female age <40 years and BMI <30.

Baseline FSH <12 IU/l.

Standard hormonal treatment as follows: pituitary down-regulation with gonadotrophin-releasing hormone agonist (GnRHa), 0.8mg s.c. daily from the mid-luteal phase for 14 days.

[1] Double cleavage-stage transfer

[2] Double blastocyst-stage transfer

Recruitment: During the study period, a total of 118 patients undergoing standard IVF or ICSI were included in the study.

Power calculation: The power of the statistical test comparing the clinical pregnancies is 0.32 and the total number of observations should be 726 to obtain a power of 0.90.

Randomisation: Randomisation was performed by drawing lots.

Allocation concealment: Sealed envelops.

Interventions: On the morning of day 3, patients with three or more 8-cell embryos with <20% extracellular fragments were randomly selected to have their embryos cultured for either 3 or 5 days in the sequential media system used in the standard IVF/ICSI programme. A maximum of two embryos were transferred on day 3 or 5 after retrieval according to the randomisation in the morning of day 3. On day 3, embryos were scored using criteria set up by Ziebe et al.,1997. Strict criteria for cryopreservation were used. Only embryos containing at least seven blastomeres and <20% intracellular fragments were cryopreserved on day 3. On day 5, embryos were assessed according to scoring criteria

Results

Clinical pregnancy

	Events	Total
Day 2 - 3	35	57
Day 5 - 6	32	61

Multiple pregnancy

	Events	Total
Day 2 - 3	15	57
Day 5 - 6	13	61

Adverse pregnancy outcome

	Events	Total
Day 2 - 3	6	57
Day 5 - 6	13	61

Limitations
The study was not adequately powered.
It is not clear whether the allocation concealment was adequate

2/61 patients in the day 5 group had only one embryo transferred due to lack of other viable embryos; 4/61 patients in the day 5 group did not have two blastocysts available for transfer, instead, two morulae or bombined blastocyst/morulae were transferred and it was not reported whether they were excluded from the analysis.

Other information
All randomised patients within the day 3 group had two embryos transferred. according to the protocol, whereas in the day 5 group two patients had only one embryo transferred, due to lack of other viable embryos for transfer.

A clinical pregnancy was defined as an intrauterine gestational sac with a heartbeat 3 weeks after a positive HCG test.

An early pregnancy loss was

	Exclusion criteria Not reported.		for blastocysts. Only expanded blastocysts were cyropreserved. Statistical analysis: Intention-to-treat analysis not reported		defined as a preclinical or a clinical abortion before gestational week 12. 'Adverse pregnancy' outcome is reported as 'early pregnancy lost'.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Coskun,S., Hollanders,J., Al-Hassan,S., Al-Sufyan,H., Al-Mayman,H., Jaroudi,K., Day 5 versus day 3 embryo transfer: A controlled randomized trial, Human Reproduction, 15, -1952, 2000 **Ref ID** 81992 **Country/ies where the study was carried out** Saudi Arabia **Study type** RCT **Aim of the study** The objective of the study was to determine whether transferring blastocysts on day 5 could result in better pregnancy and implantation rates than transferring early embryos on day 3 in a wide patient population selected according to number of zygotes. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 201 (Day 3 n = 101) (Day 5 n = 100) **Characteristics** Day 3 group Age: 30.7 (+/- 5.4) Diagnosis: - Male: 62 - Male/tubal: 0 - Tubal: 18 - Unexplained: 15 - PCOS: 3 - Endometriosis: 2 - Others: 1 Number of embyos transferred: 2.3 (+/- 0.6) Day 5 group Age: 30.4 (+/- 4.9) Diagnosis: - Male: 64 - Male/tubal: 5 - Tubal: 21 - Unexplained: 6 - PCOS: 3 - Endometriosis: 0 - Others: 1 Number of embyos transferred: 2.2 (+/- 0.5) **Inclusion criteria** All IVF or ICSI cycles from consenting patients with four or more fertilized oocytes on the day of fertilization check (day1) were included.	Double cleavage-stage vs Double blastocyst transfer	Randomisation: An equal number of sealed envelopes containing day 3 or day 5 labels were drawn by embryologist when the paitent qualified for the study Power calculation: Not reported Statistical analysis: P < 0.05 Method: Ovarian suppresion was down with GnRH agonist long protocol, 26 days after stimulation was done with hMG . 10,000IU hCG was used to trigger when diametre of oocyte >18mm. Retrieval of oocytye was done with aspiration needle 36 hours after trigger. Zygotes for day 3 transfer were cultured IVF medium, day 5 zygotes transferred to G1.2 and G2.2 on day 1 and day 3 respectively. Embryo's graded as described in Coskun et al 1998b. Implementation support used 100mg/day progesterone. Intervention: The best two quality embryos from both groups were transferred into the uterus on day 3 or day 5. When no blastocyst was availible on day 5, the two most advanced embryo's were used or embryo's were cultured for one more day according to embryologist judgement. Women older than 36 years or couples who had 6 or more unsuccessful previous cycles had 3	**Results** Pregnancy rates were confirmed with hCG test at 13 days and ultrasound at 5 weeks Adverse pregnancy outcomes were abortions and biochemical pregnancies Pregancy rate (event/women): Day 3 transfer - 39/101 (39%) Day 5 transfer - 39/100 (39%) **Clinical pregnancy** Day 2 - 3: Events 39, Total 101 Day 5 - 6: Events 39, Total 100 **Multiple pregnancy** Day 2 - 3: Events 13, Total 101 Day 5 - 6: Events 15, Total 100 **Adverse pregnancy outcome** Day 2 - 3: Events 6, Total 101 Day 5 - 6: Events 4, Total 100	**Limitations** - No power calculation was carried out - No obvious researcher concealment **Other information** Pregnancy rate (as described in results) in >36 years (3 embryo transfer) Day 3 transfer - 5/20 (25%) Day 5 transfer - 3/14 (23%) Number of blastocysts for transfer (day 5) 0 availible - 2/23 (9%) More than or equal to one - 37/77 (48%)

	Exclusion criteria Not reported		embryos transferred.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gardner,D.K., Schoolcraft,W.B., Wagley,L., Schlenker,T., Stevens,J., Hesla,J., A prospective randomized trial of blastocyst culture and transfer in in-vitro fertilization, Human Reproduction, 13, 3434-3440, 1998 **Ref ID** 82261 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine the efficacy of sequential culture media for human blastocyst development and transfer on day 5 **Study dates** October 1997 to March 1998 **Source of funding** Not reported	**Sample size** N = 92 (Group day 3, n = 47) (Group day 5, n = 45) **Characteristics** Day 3 transfer Age (mean years): 34.5 (+/-0.6) Age range (years): 26-43 Cause of infertility - tubal: 12 - endometriosis: 8 - ovulatory disorders: 3 - unexplained: 15 - male factor: 9 Number of embryos transferred: 3.7 (+/-0.1) Day 5 transfer Age (mean years): 33.6 (+/-0.7) Age range (years): 26-43 Cause of infertility - tubal: 10 - endometriosis: 11 - ovulatory disorders: 3 - unexplained: 9 - male factor: 12 Number of embryos transferred: 2.2 (+/-0.1) **Inclusion criteria** Requirement for IVF: - Basal FSH,15mIU/ml - Women's age <45 years - Presence of normal uterine cavity - Adequate sperm parameters for IVF - absence of any contraindications In addition, at least 10 follicles >	Double cleavage stage vs Double blastocyst transfer	Randomisation: Computer generated randomisation table Power calculation: Not reported Statistical analysis: Unpaired t-tests, Fishers exact test Method: Ovarian hyper stimulation was initiated with GnRH agonist long protocol for 10 days, hCG was begun after down regulation and continued until 10 follicles reached a mean diameter of 12mm. hCG was administered when at least two follicles had a mean diameter of 18mm. Oocyte retrieval was scheduled for 35 hours after hCG injection. Intervention: Patients having embryo transfer on day 3 had embryos with two pronuclei cultured in groups of 3-4. On day 3, the majority of embryos for transfer underwent assisted hatching. For those in day 5 group, embryos with two pronuclei were cultured in groups of 3 or 4. At day 3 all embryos transferred to G2.2 medium. No embryos underwent assisted hatching. Up to 3 blastocysts chosen for transfer	**Results** Clinical pregnancy is undefined **Clinical pregnancy** Day 2 - 3: Events 31, Total 47 Day 5 - 6: Events 32, Total 45	**Limitations** - No allocation concealment - No power calculation **Other information** Pregnancy vs. number of blastocysts transferred (event/number of women) 2 blastocysts transferred - 17/25 (68%) 3 blastocysts transferred - 13/15 (87%)

	12mm in diameter (visible by transvaginal ultrasound) were required on day of hCG administration **Exclusion criteria** Not reported				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Rienzi,L., Ubaldi,F., Iacobelli,M., Ferrero,S., Minasi,M.G., Martinez,F., Tesarik,J., Greco,E., Day 3 embryo transfer with combined evaluation at the pronuclear and cleavage stages compares favourably with day 5 blastocyst transfer, Human Reproduction, 17, 1852-1855, 2002 **Ref ID** 84479 **Country/ies where the study was carried out** Spain **Study type** Randomised trial **Aim of the study** 'To report pregnancy and implantation rates achieved with the use of combined pronuclear and cleavage-stage evaluateion criteria and day 3 embryo transfer as compared with those achieved with day 5 blastocyst transfer'. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 98 patients Cleavage-stage group = 48 patients Blastocyst-stage group = 50 patients **Characteristics** Cleavage-stage group (N = 48) Age (mean ± SD) = 31.6± 3.1 years Duration of infertility = not reported Blastocyst-stage group (N = 50) Age (mean ± SD) = 32.3 ± 2.5 years Duration of infertility = not reported Cause of infertility = not reported Basic characteristics of the patients were similar between the two groups. **Inclusion criteria** Couples with female age of <38 years who were treated with ICSI ≥8 two-pronucleated zygotes on the day following ICSI. **Exclusion criteria** Not reported	[1] Double cleavage-stage transfer [2] Double blastocyst-stage transfer	Randomisation: All patients meeting inclusion criteria were randomized on the day following oocyte retrieval by a computer-generated randomization list. Intervention: Oocytes were freed from the cumulus oophorus, followed by the removal of the corona radiata and subjected to ICSI. Abnormally fertilised oocytes (1 or 3pronuclei) were excluded from further consideration. Normally fertilized oocytes were cultured in G.1.2 meduim up to day 3 after ICSI and in G.2.2 medium from day 3 to 5 where applicable. Two best-scoring embryos, selected were transferred to the patient's uterus on either day 3 or day 5 according to the study design. For day 5 transfers, blastocyst morphology was given priority to gronuclear score in case of discrepance. the remaining good quality embryos were cryopreserved if they did not show a developmental blockage. Cryopreservation was performed for those patients for whom supernumerary good quality embryos or blastocysts were available. Power calculation: Not reported Allocation concealment: Not reported Statistical analysis: Not reported	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 31 | 48 | | Day 5 - 6 | 36 | 50 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 27 | 48 | | Day 5 - 6 | 29 | 50 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 7 | 48 | | Day 5 - 6 | 9 | 50 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 3 | 48 | | Day 5 - 6 | 5 | 50 |	**Limitations** No allocation concealment No power calculation No blinding of clinician, patients or assessor. **Other information** Clinical pregnancy was defined as the detection of embryonic heartbeat on ultrasound at 8 weeks gestation. This inappropriate definition implies that the figures do not include clinical pregnancies that were lost before 8weeks. Figures for 'Adverse pregnancy' reflect the number of clinical pregnancies that did not result in any deliveries. Figures for 'Life full term birth' reflect number of births and may include live births, still-births, full term, preterm, singletons and multiples.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Emiliani,S., Delbaere,A., Vannin,A.S., Biramane,J., Verdoodt,M., Englert,Y., Devreker,F., Similar delivery rates in a selected group of patients, for day 2 and day 5 embryos both cultured in sequential medium: a randomized study, Human Reproduction, 18, 2145-2150, 2003 **Ref ID** 88770 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** "To compare, in a prospective randomised trial, the outcome of day 2 and day 5 transfer of human embryos cultured in an 'in-house' sequential medium". **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 171 **Characteristics** Day 2 embryo transfer group (N = 89) Age = 31 ± 3 Duration of infertility = Not reported Day 5 embryo transfer group (N = 89) Age = 32 ± 4 Duration of infertility = Not reported Cause of infertility = Not reported **Inclusion criteria** All IVF and ICSI cycles from consenting patients aged <39 years, having had not more than three previous IVF cycles and with at least 4 fertilised oocytes on day 1. **Exclusion criteria** Six patients in the day 2 transfer group and one patient in the day 5 transfer group were excluded for violation of the protocols.	Day 2 embryo transfer vs Day 5 embryo transfer with IVF and ICSI	Recruitment: All couples were informed about the study and if they agreed to participate, they were included. Sample size calculation: The miminum number of patients to be included was calculated by the Stat Calcul software for Windows 98 Randomisation: Patients were randomised on the basis of their inclusion in a randomisation list with permuted blocs for the two types of transfer. Allocation concealment: Not reported Blinding: Not reported Interventions: For day 2 transfer, a maximum of two embryos was transferred for all patients <35 years old and /or with less than four previous IVF attempts, excetp for women for whom the total score of the two best scoring embryos was <8, for whom a third embryo was transferred. if available. Patients aged ≥35 years or with more than 3 previous IVF failures had two embryos replaced if the toal score of the three best-scoring embryos was ≥15, while if the total score was <15 a third embryo was replaced, if available. For day 5 transfer, two	**Results** **Clinical pregnancy** Day 2 - 3: Events 46, Total 89 Day 5 - 6: Events 39, Total 82 **Adverse pregnancy outcome** Day 2 - 3: Events 4, Total 89 Day 5 - 6: Events 6, Total 82	**Limitations** Allocation concealment, blinding and intention to treat analysis not reported Sample size calculation was not clearly reported **Other information** 94 day 2 transfers (89 patients) included three cycles with a single embryo replaced, 79 cycles with two embryos replaced and in 11 cycles with three embryos replaced and one cycle with no replacement because of embryo quality. The 99 day 5 transfers (82 patients) included 10 cycles with a single embryo replaced, 79 cycles with thwo embryos replaced and 10 cycles in which there were no blastocysts available for fransfer. There was a significant difference in the number of replaced embryos between both groups with fewer blastocy For the two groups, ICSI accounted for 134/171 cycles

			blastocysts were replaced , if available. For the transfer of thawed embryos, only day 2 thawed embryos that cleaved or thawed blastocysts that re-expanded after a further 18h of culture were replaced Statistical analysis: No intention to treat analysis		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>
Full citation
Gerris,J., De,Neubourg D., Mangelschots,K., Van,Royen E., Van de,Meerssche M., Valkenburg,M., Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial, Human Reproduction, 14, 2581-2587, 1999

Ref ID
88924

Country/ies where the study was carried out
Belgium

Study type
Randomised trial

Aim of the study
'To obtain data on the implantation rate and the (multiple) pregnancy rate after single embryo transfer and double embryo transfer, when compared in a prospective manner'.

Study dates
November 1997 - May 1999.

Source of funding
Clinical research grant by the 'Fondation Marguerite-Marie Delacroix'
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Sample size
N = 53 patients

SET group = 26 patients

DET group = 27 patients

Characteristics
Age (mean) = 31.9 years

Duration of infertility(mean) = 3.5 years

Cause of infertility = Not reported

Inclusion criteria
Only patients in their first IVF/ICSI cycle and who were <34 years of age

The patients had to agree to participate in the study

≥2 top quality embryos at the time of embryo transfer.

Exclusion criteria
Not reported
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<td>
[1] Single cleavage-stage transfer

[2] Double cleavage-stage transfer
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Recruitment: In total, 327 patients participated in the IVF/ICSI programme during the study period. Of those agreeing to participate in the study, 53 fulfilled the study inclusion criteria. Patients were told that super numerary embryos would be frozen and that the study was limited to the first treatment cycle.

Power calculation: Not reported

Allocation concealment: Not reported

Randomisation: Randomisation took place at the time of embryo transfer using external concealment.

Interventions: For standard IVF, 3 - 5h after retrieval every oocyte was inseminated and incubated overnight. The ICSI procedure was performed. On day 3 embryo quality was evaluated, selection for embryo replacement was made according to the top quality embryo selection criteria described by Van Royen et al. All transfers were performed as an outpatient procedure.

Statistical analysis:
Intention-to-treat analysis not reported.
</td>
<td>
Results

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>1 Embryo</td><td>10</td><td>26</td></tr>
<tr><td>2 Embryos</td><td>20</td><td>27</td></tr>
</table>
Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>1 Embryo</td><td>14</td><td>26</td></tr>
<tr><td>2 Embryos</td><td>21</td><td>27</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>1 Embryo</td><td>1</td><td>26</td></tr>
<tr><td>2 Embryos</td><td>6</td><td>27</td></tr>
</table>
</td>
<td>
Limitations
No allocation concealment
No power calculation
No blinding of the clinician, patients or assessor
No detailed description of method of randomisation.

Other information
Ongoing pregnancy was defined as a conception cycle with at least one fetal sac with a positive heart beat beyond 12 weeks of amenorrhoea.

Clinical pregnancy was not defined

The figures for 'Live birth full term' reflect numbers of 'ongoing pregnancies'. This may include multiples, preterm, still-births, live births, full term and some miscarriages.

Multiples from the double embryo transfer were dizygotic twins.
</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
Hreinsson,J., Rosenlund,B., Fridströ,m M, Ek,I., Levkov,L., blom,P., Hovatta,O., Embryo transfer is equally effective at cleavage stage and blastocyst stage: a randomized prospective study, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 117, 194-200, 2004

Ref ID
89135

Country/ies where the study was carried out
Sweden

Study type
Randomised trial

Aim of the study
'To compare the implantation and pregnancy rates after cleavage stage embryo transfer with transfer of blastocyst-stage embryos'.

Study dates
Not reported

Source of funding
Not reported

Sample size
N = 144 patients

Cleavage-stage group = 80 patients
Blastocyst-stage group = 64 patients

Characteristics
Cleavage-stage group (N = 80)

Age (mean) = 33.1 years

Duration of infertility = not reported

Blastocyst-stage group (N = 64)

Age (mean) = 32.1 years

Duration of infertility = not reported

Cause of infertility:

Male = 45 (31.3%)

Tubal = 29 (20.1%)

Other = 58 (40.3%)

Male/Female factor = 16 (11.1%)
Some couples seem to have had more than one type of infertility

Both groups were not significantly different in terms of age

Inclusion criteria
Not reported

Exclusion criteria

[1] Double cleavage-stage transfer

[2] Double blastocyst-stage transfer

Recruitment: Women undergoing either IVF or ICSI treatment cycles, who had at least six follicles as observed at the final ultrasound scan before hCG administration were included in the study, after they had given an informed consent

Power calculation: Assuming a pregnancy rate of 35% in the Day 2 - 3 group and 45% in the Day 5 - 6 group, power analysis showed that 395 subjects would be needed in each group to achieve an 80% power to detect such a difference at a 95% conficence level. Initially it was not possible to find partners for a multi-centre study. Recruiting couples to a randomised study took a long time, and in when new guidelines for embryo transfers were issued in Sweden according to which embryo transfer with two embryos was only to be carried out in exceptional cases, the study was discontinued.

Randomisation: Not clear

Allocation concealment: Sealed envelopes were used for randomisation of the patients to each group

Intervention: After aspiration, the oocytes were collected into IVF medium and incubated before

Results

Clinical pregnancy

	Events	Total
Day 2 - 3	25	80
Day 5 - 6	22	64

Multiple pregnancy

	Events	Total
Day 2 - 3	4	80
Day 5 - 6	2	64

Adverse pregnancy outcome

	Events	Total
Day 2 - 3	2	80
Day 5 - 6	4	64

Limitations
No blinding of the clinican, patients, or assessors.
It is not clear whether the allocation concealment was adequate

The study was not adequately powered as only 18% of the estimated sample size was achieved.

One pregnancy resulted from the transfer of two morulae and was not excluded from the analysis.

Confidence interval and p-value were not reported whenever a comparison was made between the groups.

Other information
19/137 embryo transfers were SET and the others were DET

'Clinical pregnancy' was not defined

All patients had one stimulated cycle each.

Some patients might have had more than one type of infertility.

In two cases, blastocysts

	Not reported		insemination by IVF or ICSI. Double embryo tranfer was the routine when the study started, but towards the end of the study period, single embryo transfer was performed. One or two embryos with the highest score was selected for transfer and if no good grade embryos were available, up to two of the available ones were transferred. Morulae was also transferred in two cases on Day 5-6, since fully developed blastocysts were not available. All patients had one stimulated cycle each Statistical analysis: Intention-to-treat analysis not reported.		were cryopreserved because of OHSS. The 'Adverse pregnancy' outcome reported in this study include 'miscarriage in first trimester and ectopic pregnancies'.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>
Full citation
Karaki,R.Z., Samarraie,S.S., Younis,N.A., Lahloub,T.M., Ibrahim,M.H., Blastocyst culture and transfer: a step toward improved in vitro fertilization outcome, Fertility and Sterility, 77, 114-118, 2002

Ref ID
89251

Country/ies where the study was carried out
Jordan

Study type
RCT

Aim of the study
The aim of this study is to evaluate the efficacy of blastocyst transfer in comparison with day 3 embryo tansfer,

Study dates
June 1999 to June 2000

Source of funding
Not reported
</td>
<td>
Sample size
N = 162
(3 day group n = 82)
(5 day group n = 80)

Characteristics
<u>Day 3 transfer group</u>
Women’s (mean) age: 29.2 (+/-5)
Mean infertility duration: 6.7 (+/-4.3)
Cause of infertility:
- Male factor: 51%
- Tubal: 10%
- Endometriosis: 7%
- PCOS: 9%
- Combined factor: 18%
- Unexplained: 5%
No. embryos transferred: 3.5 (+/-0.63)

<u>Day 5 (blastocyst) transfer group:</u>
Women’s (mean) age: 30.0 (+/-4.5)
Mean infertility duration: 6.8 (+/-4.6)
Cause of infertility:
- Male factor: 52%
- Tubal: 8%
- Endometriosis: 5%
- PCOS: 11%
- Combined factor: 17%
- Unexplained: 7%
No. embryos transferred: 2.0 (+/-0.1)

Inclusion criteria
A patients had a good prognosis as determined by post insemination parameters (at least fove two-pronuclei embryos were
</td>
<td>Double cleavage stage vs Double blastocyst transfer</td>
<td>
<u>Randomisation:</u> A box containing two types of card within envelopes. The card was drawn on the day of zygote transfer.

<u>Power calculation:</u> Not reported

<u>Statistical analysis:</u> P < 0.05 was deemed significant and P < 0.01 was considered highly significant

<u>Method:</u> GnRH agonist used in either long or short protocols to down regulate ovary. rFSH and hpFSH was used to stimulate until at least follicles were >18mm diameter, at which hCG used to trigger - oocytes were retrieved 35 hours after hCG injection. Implementation support was a vaginal dose of progesterone of 400mg.

<u>Intervention:</u> For patients receiving 3 day ET, 2PN embryos were cultured in IVF medium until transfer. The day 5 (blastocyst) patients were transferred to G1.2 medium then to G2.2 medium on day 1 and 3 respectively. On day 5 the embryos were assessed and then transferred on either day 5 or 6 depending on blastocyst expansion. The number of blastocysts transferred depended oy the availability of embryos, the patients age and previous cycle history. If the patient was >35 years or had failed to achieve pregnancy
</td>
<td>
Results
(A viable pregnancy was determined by fetal cardiac activity detected by ultrasound at 7 weeks)

Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>21</td><td>82</td></tr>
<tr><td>Day 5 - 6</td><td>23</td><td>80</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>10</td><td>82</td></tr>
<tr><td>Day 5 - 6</td><td>9</td><td>80</td></tr>
</table>
</td>
<td>
Limitations
- No double blinding

- No user concealment

- No power calculation

Other information
</td>
</tr>
</table>

	available) **Exclusion criteria** None reported		after 2 attempts then up three blastocysts were selected for transfer (normal was to transfer 1-2).		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kjellberg,A.T., Carlsson,P., Bergh,C., Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis, Human Reproduction, 21, 210-216, 2006 **Ref ID** 89308 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Limitations** **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Levron,J., Shulman,A., Bider,D., Seidman,D., Levin,T., Dor,J., A prospective randomized study comparing day 3 with blastocyst-stage embryo transfer, Fertility and Sterility, 77, 1300-1301, 2002

Ref ID
89452

Country/ies where the study was carried out
Israel

Study type
Randomized prospective study

Aim of the study
The study looks to compare the outcome of IVF after a day 3 and a day 5 embryo transfer in a randomized prospective study.

Study dates
Not reported

Source of funding
Not reported</td>
<td>Sample size
N = 90
(Day 3 transfer n = 44)
(Day 5 transfer n = 46)

Characteristics
Day 3 transfer
Womens age (mean): 31.5 (+/-7.4)
No. of embryos per ET: 3.1 (+/-0.6)

Day 5 transfer
Womens age (mean): 30.9 (+/-4.0)
No. of embryos per ET: 2.3 (+/-0.8)

(Difference in ET significant P = 0.0001)

Inclusion criteria
- Maternal age <38 years
- Fewer than five previous IVF attempts
- Presence of more than 5 zygotes on day 1

Exclusion criteria
Not reported</td>
<td>≥Double cleavage stage vs ≥Double blastocyst transfer</td>
<td>Ninety consenting couples were recruited after approval of the local internal review board was obtained. Gametes and embryo handling procedures were done by using a commercial sequential IVF medium. For most patients, up to three embros were replaced on day 3 or day 5. Sequential use of G-1/G-2 media was used in the day 5 group.</td>
<td>Results
(No definition of clinical pregnancy)

Clinical pregnancy
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Day 2 - 3</td><td>20</td><td>44</td></tr><tr><td>Day 5 - 6</td><td>8</td><td>46</td></tr></table>
Multiple pregnancy
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Day 2 - 3</td><td>8</td><td>20</td></tr><tr><td>Day 5 - 6</td><td>4</td><td>8</td></tr></table></td>
<td>Limitations
- Randomisation method of patients not reported

- Allocation concealment not reported

- Power calculation not reported

- Clinical pregnancy was not reported

- Limited method reported

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Martikainen,H., Tiitinen,A., Tomá,s C, Tapanainen,J., Orava,M., Tuomivaara,L., Vilska,S., Granskog,C., Hovatta,O., Finnish ET Study Group., One versus two embryo transfer after IVF and ICSI: a randomized study, Human Reproduction, 16, 1900-1903, 2001 **Ref ID** 89588 **Country/ies where the study was carried out** Finland **Study type** Randomised trial **Aim of the study** 'To compare the effectiveness of one and two embryo transfer in a good prognosis group of patients'. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 144 patients SET group = 74 patients DET group = 70 patients **Characteristics** SET group (N = 74) Age (mean±SD) = 30.8 ± 3.9 years Duration of infertility = Not reported DET group (N = 70) Age (mean ±SD) = 30.5 ± 4.1 years Duration of infertility = Not reported Cause of infertility Male factor = 50 (34.7%) Tubal factor = 18 (12.5%) Male/Female factor = 7 (4.9%) Other = 51 (35.4%) The two groups were similar in relation to age and aetiology of infertility. **Inclusion criteria** Four good quality embryos In Oulu the age of the woman was not taken into account and the first	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	Recruitment: A total of 1301 couples fulfilled the inclusion criteria, and 144 agreed to participate in the randomised study. In all, 187 chose elective on embryo transfer and 970 two embryo transfer. Power calculation: Not reported Randomisation: Patients were randomised into the two groups using a computer-gnerated random number table balanced in sets of 10. Randomisation was done just before embryo(s) transfer by the laboratory personnel. Allocation concealment: Not reported Blinding: Not reported Interventions: One or two embryos were transfered into tho the uterine cavity 46-50h after oocyte retrieval. Supernumerary good quality embryos were frozen using a slow freezing protocol. The frozen embryo transfers were carried out in natural or stimulated cycles and embryo transfer was carried out 3 - 4 days later. The replacement of frozen embryos was not subjected to any protocol policy related to the present study. Statistical analysis: ITT not reported	**Results** **Live birth - Full-term - Cumulative** | | Events | Total | | 1 Embryo | 29 | 74 | | 2 Embryos | 36 | 70 | **Live birth - Full-term - Fresh cycle** | | Events | Total | | 1 Embryo | 22 | 74 | | 2 Embryos | 28 | 70 | **Live birth - Full-term - Frozen cycle** | | Events | Total | | 1 Embryo | 7 | 54 | | 2 Embryos | 8 | 38 | **Clinical pregnancy** | | Events | Total | | 1 Embryo | 24 | 74 | | 2 Embryos | 33 | 70 | **Multiple pregnancy** **Pre-term delivery** **Adverse pregnancy outcome**	**Limitations** No power calculation. No allocation concealment. No blinding of physician, patient or assessor. **Other information** Adverse pregancy outcome reported were miscarriage and extrauterine pregnancy Figures for 'Live birth full term' reflect number of 'Live birth' and this includes preterm, full term, singletons and multiples. The replacement of frozen embryos was not subjected to any protocol policy related to the present study. Preterm birth - <37 weeks 'Clinical pregnancy' was not defined

	two cycles were regarded as eligible In the two units in Helsinki, only women <36 years who were undergoing their first treatment cycle were included **Exclusion criteria** Not reported			<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>1 Embryo</td><td>1</td><td>74</td></tr><tr><td>2 Embryos</td><td>11</td><td>70</td></tr><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>1 Embryo</td><td>1</td><td>74</td></tr><tr><td>2 Embryos</td><td>6</td><td>70</td></tr><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>1 Embryo</td><td>2</td><td>74</td></tr><tr><td>2 Embryos</td><td>5</td><td>70</td></tr></table>	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Papanikolaou,E.G., D'haeseleer,E., Verheyen,G., Van,DeVeldeH, Camus,M., Van,SteirteghemA, Devroey,P., Tournaye,H., Live birth rate is significantly higher after blastocyst transfer than after cleavage-stage embryo transfer when at least four embryos are available on day 3 of embryo culture. A randomized prospective study, Human Reproduction, #20, 3198-3203, 2005

Ref ID
89875

Country/ies where the study was carried out
Belgium

Study type
Randomised controlled trial

Aim of the study
"To determine, where at least four good-quality embyos have been developed by day 3, whether the extension of embryo culture to day 5, and eventually a blastocyst-stage transfer, is feneficial in terms of increasing ongoing pregnancy and live birth rates, compared with cleavage-stage embryo transfer".

Study dates
January 2001 - November 2003

Source of funding
Not reported</td>
<td>Sample size
N = 164

Characteristics
<u>Double day 3 group (N = 84)</u>
Age = 29.6 (±0.4)
Duration of infertility = 2.7 (±0.3)
Cause of infertility
- Male factor: 55.4%
- Female factor: 30.1%
- Combined: 9.6%
- Idiopathic: 4.8%
Number of embryos/patient: 2.0 (+/-0.02)

<u>Double day 5 group (N = 80)</u>
Age = 29.9±0.4
Duration of infertility = 2.9 ± 0.2
Cause of infertility
- Male factor: 53.8%
- Female factor: 26.3%
- Combined: 11.3%
- Idiopathic: 8.8%
Number of embryos/patient: 1.97 (+/-0.5)

Inclusion criteria
Female age ≤ 37 years;

rank trial ≤3;

FSH on day 3 of the cycle ≤12 IU/ml;

Ejaculated sperm origin;

IVF or ICSI cycles;

equal numbers (n = 2) of embryos should be transferred in each group.</td>
<td>Double day 3 embryo transfer vs Double day 5 embryo transfer.</td>
<td><u>Recruitment</u>: Within the study period, 301 patients seeking infertility treatment were found to be eligible to partiipate with the study. Finally 274 patients initiated multifollicular ovarian stimulation, among whom 164 fulfilled the embryological inclusion criterion of having at least four good-quality embryos on day 3 of embryo culture.

<u>Sample size calculation:</u> In order to detect a difference of 15% in ongoing pregnancy rates between the groups in which embryo transfer was performed on day 3 or day 5, 157 patients would be required in each group assuming a baseline pregnancy rate of 25%.

<u>Randomisation</u>: Every patient entered the study only once. Randomisation was performed on day 3 of embryo culture by the mbryologist in the IVF laboratory using a computer-generated randomised list.

<u>Allocation concealment</u>: Not reported;

<u>Blinding</u>: Not reported

<u>Interventions:</u> Two ovarian stimulation protocols were used for 274 patients in this study. Sperm preparation, IVF/ICSI procedures and</td>
<td>Results
Day 5 transfer resulted in a significantly higher clinical pregnancy (p = 0.008; CI: 1.23 - 4.40) and live birth rate (p = 0.01; CI: 1.25 - 4.59) compared with day 3 embryo transfer.

Adverse pregnancy (pregnancy loss) between the two groups did not differ (p = >0.05 and CI = not reported).

Live birth - Full-term - Fresh cycle
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>23</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>38</td><td>80</td></tr>
</table>
Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>27</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>42</td><td>80</td></tr>
</table>
Multiple pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>8</td><td>84</td></tr>
<tr><td>Day 5 - 6</td><td>18</td><td>80</td></tr>
</table>
</td>
<td>Limitations
No mention of allocation concealment and/or blinding

The participants in the two groups received varying numbers of embryo (1, 2, or 3) which might have introduced bias and no subgroup analysis was conducted.

Other information
Clinical pregnancy was defined by the ultrasound observation of fetal cardiac activity after 7 weeks of gestation.

Embryos of good quality were defined as having a minimum of 6 blastomeres of normal size on the morning of day 3, a maximum of 20% of anucleate fragments and no multinucleated blastomeres.

A high initial multiple pregnancy rate in the day 5 group resulted in more than one-third of the births after day 5 transfer being twins.

5/80 patients in the day 5 group received a single embryo;</td>
</tr>
</table>

	Exclusion criteria Oocyte donation cycles; Non-ejaculated sperm; PGD.		embrto culture were carried out as described by Van Landuyt et al. 2005. On the morning of day 3, embryos were transferred from cleavage medium to blastocyst medium. Normal fertilisation was confirmed by the presence of two pronuclei with two distinct or fragmented polar bodies. Embryo quality was assessed daily until the moment of transfer and/or freezing of the supernumerary embryos. Embryo quality on day 3 was scored based on number of blastomeres, rate of fragmentation, multinucleation of the blastomeres, and early compaction. Selected for transfer with preference for embryos which showed the normal developmental pattern of early cleavage on day 1, four cells on day 2 and eight cells on day 3 with minimal fragmentation and no multinucleation. Embryo quality on day 5 ranged from arrested multicellular embryos to advanced blastocysts. For transfer on day 5, preferably full or advanced blastocysts with many cells in the inner cell mass and in the trophectoderm were selected. <u>Statistical analysis:</u> Analysis was by intention to treat	**Adverse pregnancy outcome** Events / Total Day 2 - 3: 12 / 84 Day 5 - 6: 15 / 80	3/80 patients in the day 5 group and2/84 patients in the day 3 group asked for and finally had 3 embryos replaced. Adverse pregnancy outcome (Pregnancy loss) in both groups consisted of: Pregnancy loss at First trimester (23/27), second trimester(3/27) and ectopic pregnancies (1/27)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Thurin,A., Hausken,J., Hillensjö, T, Jablonowska,B., Pinborg,A., Strandell,A., Bergh,C., Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization, New England Journal of Medicine, 351, 2392-2402, 2004 **Ref ID** 90437 **Country/ies where the study was carried out** Sweden **Study type** Randomised multicentre trial **Aim of the study** 'To test the hypothesis: among women less than 36 years of age, the rate of pregnancies resulting in at least one live birth in patients who undergo the transfer of a single fresh embryo and, if no live birth results, the subsequent transfer of a frozen-and-thawed embryo, would be equidvalent to the rate in patients who undergo the simultaneous transfer of two fresh embryos'. **Study dates** May 2000 - October 2003 **Source of funding** Grant from Serono Nordic, by Sahlgrenska Academy and Sahlgrenska University Hospital, by the Goteborg Medical Society, and by the Hjalmar Svensson Foundation.	**Sample size** N = 661 patients SET group = 330 patients DETgroup = 331 patients **Characteristics** SET group (N = 330) Age (mean±SD) = 30.9 ± 3.0 years Duration of infertility (mean±SD) = 3.6 ± 1.7 years DET group (N = 331) Age (mean±SD) = 30.8 ± 3.0 years Duration of infertility(mean±SD) = 3.8 ± 3.9 years Cause of infertility Male factor = 319 (48.3%) Tubal factor = 130 (19.7%) Male/Female factor = Not reported Others = 366 (55.4%) Some couples/patients may have had >1 type of infertility **Inclusion criteria** **Exclusion criteria**	[1] Single cleavage-stage transfer [2] Double cleavage-stage transfer	Recruitment: Eleven clinics, both public and private, participated. A total of 661 patients underwent randomisation. Of those, 331 patients were randomly assigned to undergo double-embryo transfer and 330 to undergo elective single-embryo transfer. Power calculation: Before the start of the study, sample size was calculated on the basis of the live-birth rate, after applying the following assumptions: if the true rate of live births in the two treatment groups is 0.30, then the probability is 0.80 that the upper limit of the 95% confidence interval for the difference in the probability of live birth between the groups is lower than 0.10, if 330 patients who can be evaluated are included in each group. The number of patients lost to follow-up was assumed to be zero. Thus, 660 patients were needed Randomisation: Randomisation was performed locally by the embryologist with the use of a computerised randomisation program at a ratio of 1:1. Optimal allocation was applied according to Pocock's minimisation technique for sequential randomisation with consideration given to the woman's age, the presence or absence of tubal infertility, the number of previous IVF	**Results** **Live birth - Full-term - Cumulative** | | Events | Total | | --- | --- | --- | | 1 Embryo | 128 | 330 | | 2 Embryos | 142 | 331 | **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | 1 Embryo | 91 | 330 | | 2 Embryos | 142 | 331 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | 1 Embryo | 20 | 330 | | 2 Embryos | 32 | 331 |	**Limitations** Allocation concealment was not reported. **Other information** Figures for 'Live birth full term' include live births, full term, preterm, singletons and multiples. A pregnancy was defined as a positive test for hCG in urine (>20 IU per liter) or a serum level of hCG 2 IU per liter or more two weeks after embryo transfer. The figures for 'Clinical pregnancy' outcome reflect number of 'pregnancy' (as reported in the study). The original protocol stipulated that the patient had to be <35 years of age and have ≥3 good-quality embryos available, but these criteria were modified in an amendment after the first 215 patients were enrolled, owing to a change in usual clinical practice in Sweden. Adverse pregnancy outcomes reported in this study include ectopic pregnancy, spontaneous abortions at ≤12 weeks and >12 weeks, stillborn infants ≥28 weeks of

Speaker's fees from Organon	<36 years of age at the time of the transfer of the fresh embryo Undergoing first or second IVF cycle ≥2 embryos of good quality available for transfer or freezing Not reported		cycles involving transfers, the number of previous IVF cycles resulting in birth, the day of embryo transfer, and the number of good-quality embryos available. Allocation concealment:Not reported Blinding: Double blinding (neither the patient nor the physician knew whether one embryo or two embryos had been transferred). Interventions: Oocyte retrieval and fertilisation were performed by conventional IVF or ICSI by means of standard techniques. Embryo transfer was performed two, three, or five days after oocyte retrieval. Patients in the SET group who did not conceive in the cycle in which the fresh embryo had been transferred, or who miscarried, subsequently underwent the transfer of a single frozen-and-thawed embryo in a natural or a hormone-stimulated cycle. If the first frozen-and-thawed embryo was not viable, other embryos were thawed, one by one, until a viable embryo could be transferred. Statistical analysis: Intention to treat analysis (included 661patients).		gestation Spontaneous abortions at >12 weeks of gestation includes 1/17 patient in the single-embryo transfer group that underwent termination of pregnancy owing to fetal acrania.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
van Montfoort,A.P., Fiddelers,A.A., Janssen,J.M., Derhaag,J.G., Dirksen,C.D., Dunselman,G.A., Land,J.A., Geraedts,J.P., Evers,J.L., Dumoulin,J.C., In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial, Human Reproduction, 21, 338-343, 2006

Ref ID
90527

Country/ies where the study was carried out
The Netherlands

Study type
Randomised controlled trial

Aim of the study
'The primary aim was to compare the pregnancy rates in elective single embryo transfer and double embryo transfer study groups. A sendoary aim of the study was to evaluate pregnancy rates after elective single embryo transfer and double embryo transfer when the decision of whether to transfer one or two embryos was based on female age (<38 years) and the presence of at least one good quality embryo'.

Study dates
January 2002 - December 2004

Source of funding

Sample size
N = 308 patients

SET group = 154 patients
DET group = 154 patients

Characteristics
SET group (N = 154)

Age (mean±SD) = 32.7 ± 3.3 years
Duration of subfertility (mean±SD) = 3.3 ± 1.8 years

DET group (N = 154)

Age (mean±SD) = 32.4 ± 3.3 years
Duration of subfertility (mean±SD) = 3.3 ± 2.1 years

Cause of infertility
Male factor = 172 (55.8%)
Tubal factor = 52 (16.9%)
Male/Female factor = Not reported
Other = 84 (27.3%)

Patient and cycle characteristics were comparable between the two study groups of the study.

Inclusion criteria
Consenting patients had to have normal fertilisation of ≥2 oocytes in order to be randomised between elective single embryo transfer and double embryo transfer group

Exclusion criteria

[1] Single cleavage-stage transfer

[2] Double cleavage-stage transfer

Recruitment: 807 patients who started their first IVF or IVF/ICSI cycle within the study period were assessed for eligibility to participate in the study. Of the 621 eligible patients, 348 agreed to participate and 308 were randomised, 40 could not be randomised because of fertilisation failure or because only one embryo was available.

Power calculation: Assuming an ongoing pregnancy rate of 29% (reported in previous study) for the double embryo transfer group in the study and considering an ongoing pregnancy rate in the elective single embryo transfer group of <15% as clinically unacceptable, the required sample size was 150 cycles in both study groups with a power of 80% and an α of 0.05.

Randomisation: Randomisation was performed immediately prior to embryo transfer. To ensure comparablility between the two groups with respect to female age (<38 or ≥38 years) and fertilisation technique (IVF or IVF/ICSI), the patient population was stratified with respect to these four characteristics.

Allocation concealment: The groups were further subdivided to ensure an equal distribution of single embryo

Results

Live birth - Full-term - Fresh cycle

	Events	Total
1 Embryo	32	154
2 Embryos	73	154

Clinical pregnancy

	Events	Total
1 Embryo	33	154
2 Embryos	62	154

Multiple pregnancy

	Events	Total
1 Embryo	0	154
2 Embryos	12	154

Adverse pregnancy outcome

	Events	Total
1 Embryo	18	154
2 Embryos	11	154

Limitations
No blinding of the physician, patients or assessors

Other information
Any subsequent IVF or IVF/ICSI cycle and all transfer cycles of cryopreserved embryos were not a part of the study.

The multiple pregnancy reported in the study was twin pregnancy. Other types of multiples were not reported.

An ongoing pregnancy was defined as the presence of at least one intrauterine gestational sac with fetal heart beat on ultrasound at 7 weeks gestation; The figures for 'Clinical pregnancy' outcome reflect the number of 'ongoing pregnancy' reported. Some of the clinical pregnancies may have become miscarried at the time of examination.

Figures for 'Live birth full term' reflect 'Live biirth' and may include full term, preterm, singletons and multiples.

Live birth – Full – term –

Research grant from the Dutch Organisation for Health Research and Development(ZonMW) and the Dutch Health Insurance Board (CvZ) in a joint research programme on health technology assessment of infertility	Patients [1] applying for pre-implantation genetic diagnosis [2] requiring the transfer of only one embryo (in most cases because of medical reasons) [3] who could not be informed adequately because of a language barrier		transfer and double embryo transfer. By varying the size of these subgroups and by using a non-transparent box containing the sealed opaque envelopes, the randomisation procedure was blinded. Interventions: Embryos were transferred on day 2 after ovum pick-up or in a minortity of cases, for reasons of convenience, on day 3. In all cases, embryos with the highest embryo score were transferred. Cryopreservation of supernumerary embryos was performed on the morning of the third day after ovum pic-up if one or more embryos had reached the 8-cell stage, and if there were of good morphological quality. After transfer, patients were informed about the number of embryos transferred. Any subsequent IVF or IVF/ICSI cycle and all transfer cycles of cryopreserved embryos were not a part of the RCT. Statistical analysis: No ITT		Fresh cycle (reported in follow-up study, see Fiddelers 2006) The 'Adverse pregnancy' outcome reported in the study was Abortion <13 weeks.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Van,der Auwera,I, Debrock,S., Spiessens,C., Afschrift,H., Bakelants,E., Meuleman,C., Meeuwis,L., D'Hooghe,T.M., A prospective randomized study: day 2 versus day 5 embryo transfer, Human Reproduction, 17, 1507-1512, 2002 **Ref ID** 90539 **Country/ies where the study was carried out** Belgium **Study type** Randomised trial **Aim of the study** 'To test the hypothesis that blastocyst transfers resultin higher clinical pregnancy rates per oocyte retrieval when compared with day 2 transfers'. **Study dates** February 1999 - September 2000 **Source of funding** Not reported	**Sample size** N = 136 patients N = 129 patients (included in the analysis) Cleavage-stage group = 63 patients Blastocyst-stage group = 66 patients **Characteristics** Cleavage-stage group (N = 63) Age (mean±SD) = 31.7 ±3.3 years Duration of infertility = Not reported Blastocyst-stage group (N = 66) Age (mean±SD) = 31.5 ± 3.5 years Duration of infertility = Not reported Type of Infertility Male = 74 (54.4%) Tubal = 20 (14.7%) Other = 26 (19.1%) Male/Female = 9 (6.6%) At randomisation, no differences were found for age, duration of	[1] Double cleavage-stage transfer [2] Double blastocyst-stage transfer	Recruitment: IVF and ICSI patients who started their cycle within the study period were randomised. Randomisation/Allocation concealment: Blind randomisation using sealed envelopes was performed at the beginning of the hormonal stimulation before the hormal response was known. Power calculation: Power calculation had shown that 175 patients were needed in each group to demonstrate a significant difference of 15% in pregnancy rate/oocyte retrieval between the groups. Interventions: A maximum of two selected embryos were transferred on day 2, while the remaining embryos (maximum of three) were cultured for another 3 - 4 days and frozen at the blastocyst stage if available. In the day 5 group, all fertilitized ova were cultured in vitro to achieve blastocysts. A maximum of two blastocysts was transferred while those remaining were frozen on day 5 or 6. All frozen-thawed embryos from the study period were included in the evaluation of the cryo-augmented pregnancies per oocyte retrieval. Freezing was achieved using the slow freezing protocol.	**Results** **Live birth - Full-term - Fresh cycle** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 26 | 66 | | Day 5 - 6 | 33 | 70 | **Clinical pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 20 | 66 | | Day 5 - 6 | 29 | 70 | **Multiple pregnancy** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 9 | 66 | | Day 5 - 6 | 9 | 70 | **Adverse pregnancy outcome** | | Events | Total | | --- | --- | --- | | Day 2 - 3 | 3 | 66 | | Day 5 - 6 | 5 | 70 |	**Limitations** The sample size did not meet power calculation. Its not clear whether the allocation concealment was adequate. The person/people (patient, clinician or assessor) that were blinded were not mentioned. The method of randomisation was not reported in details. 27% of the patients in the blastocyst group did not receive an embryo transfer due to a lack of blastocysts on day 6 and no intention to treat analysis was conducted. When comparisons were made between the two groups, no confidence intervals were reported alongside p-value. **Other information** Three patients were excluded for analysis from the cleavage group because they wanted an elective blastocyst culture. Four patients were excluded from the blastocyst group

	infertility, type of infertility or IVF indication, nor ratio of ICSI:IVF cycles . **Inclusion criteria** Not reported **Exclusion criteria** Not reported		Statistical analysis: Intention-to-treat analysis not reported		because they wanted an elective day 2 transfer. Clinical pregnancy was not defined Figures for 'Multiple pregnancy' reflect number of delivered twins. It does not include any lost multiple pregnancies and its not clear if there were other types of multiples. Figures for 'Live birth full term' reflect number of children born. This may include live births, still-births, preterm, full term, singletons and multiples 'Adverse pregnancy' is the number of clinical pregnancies that did not result in any deliveries.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Zech,N.H., Lejeune,B., Puissant,F., Vanderzwalmen,S., Zech,H., Vanderzwalmen,P., Prospective evaluation of the optimal time for selecting a single embryo for transfer: day 3 versus day 5, Fertility and Sterility, 88, 244-246, 2007

Ref ID
90739

Country/ies where the study was carried out
Belgium and Austria

Study type
Randomised clinical trial.

Aim of the study
To determine the best day for the selection and transfer of a single embryo.

Study dates
November 2003 to February 2005.

Source of funding
Not reported.</td>
<td>Sample size
n = 227 women

Characteristics
Not reported.

Inclusion criteria
1. ≤36 years of age.
2. First or second attempt at IVFF or ICSI.
3. Women who underwent treatment using ≥5 fertilised oocytes.

Exclusion criteria
Not reported.</td>
<td>Single cleavage stage vs Single blastocyst transfer</td>
<td>16 to 20 hours after insemination or ICSI, all oocytes were checked for the presence of two pronuclei, and the patients were randomised for embryo culture to either day 3 or day 5, according to even or odd year of birth</td>
<td>Results
Ongoing pregnancy was defined by the ultrasound observation of a positive heartbeat 6 weeks after oocyte retrival
Adverse pregnancy outcome reported was miscarriage.

Clinical pregnancy
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>23</td><td>99</td></tr>
<tr><td>Day 5 - 6</td><td>42</td><td>128</td></tr>
</table>
Adverse pregnancy outcome
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Day 2 - 3</td><td>8</td><td>99</td></tr>
<tr><td>Day 5 - 6</td><td>9</td><td>128</td></tr>
</table>
</td>
<td>Limitations
1. It is not clear whether the method of randomistion was adequate.
2. No blinding
3. No allocation concealment
4. No power calculation

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation McLernon,D.J., Harrild,K., Bergh,C., Davies,M.J., de,Neubourg D., Dumoulin,J.C., Gerris,J., Kremer,J.A., Martikainen,H., Mol,B.W., Norman,R.J., Thurin-Kjellberg,A., Tiitinen,A., van Montfoort,A.P., van Peperstraten,A.M., Van,Royen E., Bhattacharya,S., Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials, BMJ, 341, c6945-, 2010 **Ref ID** 96729 **Country/ies where the study was carried out** Various **Study type** Individual patient meta-analysis **Aim of the study** To compare the effectiveness of eSET versus DET **Study dates** Search conducted in 2008, but included RCTs were before this date. **Source of funding** Wellcome Trust	**Sample size** 1539 citations identified, 11 assessed for inclusion, 8 included. The 8 RCTs included 683 eSET and 684 DET patients. **Characteristics** Type of treatment: eSET vs DET IVF 365 (53%) vs 388 (57%) ICSI 318 (47%) vs 293 (43%) Both 0 vs 2 Missing 0 vs 1 Embryos transferred in first fresh cycle: 0: 2 vs 1 1: 677 vs 7 2: 4 vs 676 Day of fersh embryo Day 2: 540 vs 539 Day 3: 130 vs 131 Day 5: 10 vs 9	eSET IVF or ICSI using cleavage stage embryos DET IVF or ICSI using cleavage stage embryos	Literature review: Medline and Embase search upto 2008 Authors of identified trials contacted about individual data being made avaialble Included studies: Patient inclusion criteria varied between the RCTs IVF and ICSI protocols varied between the included RCTs Individual patient data: BMI, woman's age, duration, type and cause of infertility and type of treatment. Characteristics of cycle - eSET or DET, day of transfer, quality of embryo. Outcome of treatment - live birth, multiple live birth, cumulative blive birth, cumulative multiple live birth, miscarriage, preterm delivery, term singleton delivery and low birth weight. Statistical analysis:	**Results** Included studies: Gerris et al, 1999 Lukassen et al, 2005 Martikainen et al, 2001 Thurin et al, 2004 Van Montfoort et al, 2006 unpublished data Thurin, 2005 Davies, 2003 Bhattacharya, 2006 Term singleton births DET vs eSET OR = 4.93 (2.98 to 8.18) Miscarriage eSET = 60 of 245 (24%) vs DET = 63 of 355 (18%); OR = 1.52 (1.01 to 2.28)	**Limitations** Variation in entry criteria and clinical protocols used between RCTs could introduce hetrogeneity. RCTs only included women with 'good' prognosis. The outcomes after cumulative embryo transfers were not reported. **Other information**

	No transfer: 2 vs 1 Missing: 1 vs 4 Grade of embryos transferred Grade A: 571 vs 597 Grade B: 79 vs 51 Missing: 31 vs 35 **Inclusion criteria** Only RCTs that compared cleavage stage eSET or DET transfers using either IVF or ICSI. **Exclusion criteria** N/A		Test of hetrogeneity using funnel plots, with a figure greater than 50% considered to show substantial heterogeneity. If none found then logistic regression model was fitted, adjusted for trial, duration of infertility, type of infertility (primary or secondary). type of treatment, cause of infertility, woman's age, BMU and quality of embryos	Preterm birth (<= 37 weeks) eSET vs DET OR = 0.33 (0.20 to 0.55) Predictors of live birth (live birth vs no live birth) (n = 466 vs 900) eSET vs DET OR = 0.50 (0.40 to 0.63) Mean age OR = 0.97 (0.94 to 1.01) BMI of woman OR = 0.96 (0.90 ro 1.02) Duration of infertility (years) OR = 0.96 (0.90 to 1.02) Type of infertility Female vs male OR = 0.86 (0.64 to 1.16); AOR = 0.8 (0.38 to 0.88) Unexplained vs male OR = 1.17 (0.85 to 1.61); AOR = 0.79 (0.51 to 1.22) Secondary vs primary OR = 1.03 (0.79 to 1.35)	

Day of transfer

Day 3 vs day 2 OR = 1.10 (0.70 to 1.74)

Day 5 vs day 2 OR = 0.51 (0.17 to 1.58)

Quality of embryo

Grade A vs Garde B OR = 1.93(1.23 to 3.04)

Live birth - Full-term - Fresh cycle

	Events	Total
1 Embryo	181	683
2 Embryos	285	683

Multiple pregnancy

	Events	Total
1 Embryo	3	181
2 Embryos	84	285

Fertility (Updated guideline)

Ovulation triggers

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation Youssef,AFM Mohamed, AlInany,Hesham G., Aboulghar,Mohamed, Mansour,Ragaa, Proctor,Michelle, Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles, Cochrane Database of Systematic Reviews, -, 2011 **Ref ID** 102259 **Country/ies where the study was carried out** **Study type** Cochrane review **Aim of the study** To assess the efficacy and ssafety of subcutaneous recombinant hCG (rhCG) and high dose recombinant LH (rLH) compared with intramuscular uhCG for inducing final oocyte maturation triggering in IVF and ICSI cycles. **Study dates** Searches to 28 January 2010 **Source of funding** Source of internal support: University of Auckland, New Zealand.	**Sample size** n = 2306 women (30 to 310 patients per study) n = 14 studies (Abdelmassih 2005; Borges 2004; Driscoll 2000; ERHCG Group; Jie 2005; Schoolcraft 2002; Vidal 2005; Kovacs 2008; Chang 2001; Goswami 2007; Farrag 2008; ERLH Group 2001; Manau 2002; Study 21447) **Characteristics** Studies: Fourteen studies involving 2306 randomised women: 11 RCTs compared rhCG with uhCG (n = 1827) and three RCTs compared rLH with uhCG (n = 479). -9 trials were published as full papers. One study was unpublished and 4 studies were published as abstracts. -6 trials were multicentre trials and 8 trials were single centre -Limited data about methodology and clinical outcomes were obtained by contact with the authors -All trials were designed as non-inferiority trials	1] GnRH agonist + recombinant hCG vs GnRH agonist + urinary hCG (11 trials: Abdelmassih 2005; Borges 2004; Driscoll 2000; ERHCG Group; Jie 2005; Schoolcraft 2002; Vidal 2005; Kovacs 2008; Chang 2001; Goswami 2007; Farrag 2008) 2] GnRH agonist + recombinant LH (3 trials: ERLH Group 2001; Manau 2002; Study 21447)	The data for primary studies were combined using the fixed-effect model. Sensitivity analyses were conducted for the primar outcomes to determine whether the conclusions werer robust to arbbitrary decisions made regarding eligibility and analysis. These analyses included consideration of whether conclusions would have differed if: 1. studies at high risk of bias had been excluded. 2. A random-effects model had been adopted.	rhCG vs uhCG Live birth rate (6 studies): rhCG = 179/506; uhCG = 205/513 OR = 1.04; 95% CI = 0.79 to 1.37* I^2 = 0% Clinical pregnancy (7 studies): rhCG = 236/649; uhCG = 174/557 OR = 1.28; 95% CI = 1.00 to 1.65** I^2 = 0%*** Miscarriage (7 studies): rhCG = 26/599; uhCG 32/507 OR = 0.69; 95% CI = 0.41 to 1.18 I^2 = 0% Severe OHSS (3 studies): rhCG = 11/324; uhCG = 6/225 OR = 1.49 (0.54 to 4.10) I^2 = 0% rhLH vs uhCG Live birth rate (2 studies): rhLH = 27/144; uhCG = 27/136 OR = 0.94; 95% CI = 0.50 to 1.76 I^2 = 0% Clinical pregnancy (2 studies): rhLH = 36/144; uhCG = 36/136 OR = 0.93; 95% CI = 0.53 to	**Limitations** 3 studies did not reported a power calculation and in 8 other studies the power calculation was unclear 4 studies did not report the method of randomisation 7 studies had unclear allocation concealment 3 studies were not blinded, and blinding was unclear in 5 other studies **Other information** * reported in text as 1.39. ** Sensitivity analysis after the exclusion of studies with high risk of bias (OR = 1.21; 95% CI = 0.92 to 1.58). *** Reported in text as 8%. 1] Live birth rate: If live birth rates were not reported then ongoing pregnancy rate was used. Ongoing pregnancy was defined as the number of women who were pregnancy for more than 12 weeks divided by the number of women who received the intervention.

	-8 studies were supported by pharmaceutical companies. 4 studies were reported as being free of commercial funding. The other studies did not report funding sources clearly -3 studies performed an apriori power calculation to determine sample size. 3 studies stated no sample size calculation and no clear statement was made in the remaining studies. Participants: Subfertile couples undergoing final oocyte maturation triggering as part of IVF or ICSI cycles using either rhCG or rLH preparation vs uhCG. One study included donor female patients (Vidal 2005) **Inclusion criteria** Studies: Only RCTs comparing rhCG or a rLH preparation to uhCG for inducing finaly oocyte maturation and early luteinisation in patients undergoing IVF and ICSI Participants: 1] Age at least 18 years but not older than 45 years 2] Regular menstrual cycles ranging from 24 to 35 days 3] FSH <12 IU/L during the early follicular phase 4] No prior history of OHSS			1.63 I^2 = 0% Miscarriage (2 studies): rhLH = 9/144; uhCG = 9/136 OR = 0.94; 95% CI = 0.37 to 2.38 I^2 = 0% Severe OHSS (2 studies): rhLH = 15/144; uhCG = 17/136 OR = 0.82; 95% CI = 0.39 to 1.69 I^2 = 5%	2] Clinical pregnancy: Fetal heart activity on ultrasound assessment, trohoblastic tissue on ppathologic examination at time of miscarriage or surgery for ectopic pregnancy. 3] OHSS: Women who expereienced OHSS and cancelled cycles as a result of high perceived risk of OHSS. 4] One study included donor female patients (Vidal 2005)
	Exclusion criteria Thirty eight studies				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Youssef,AFM Mohamed, Van der Veen,Fulco, AlInany,Hesham G., Griesinger,Georg, Mochtar,Monique H., Aboulfoutouh,Ismail, Khattab,M., Sherif, van Wely,Madelon, Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles, Cochrane Database of Systematic Reviews, -, 2011 **Ref ID** 108420 **Country/ies where the study was carried out** **Study type** Cochrane review of randomised controlled trials **Aim of the study** To evaluate the effectiveness and safety of GnRH agonists in comparison to hCG for triggering final oocyte maturation in IVF and ICSI for women undergoing controlled ovarian hyperstimulation in a GnRH antagonist protocol **Study dates** Searches to October 2010 **Source of funding** University of Amsterdam, Netherlands	**Sample size** 11 randomised controlled trials in total (covering 23 to 302 women per study) 8 trials looked at fresh autologous cycles (Babayof, 2006; Beckers, 2003; Fauser, 2002; Humaidan, 2010; Humaidan, 2005; Humaidan, 2006; Kolibianakis, 2005; Pirard, 2006) 3 trials looked at donor recipient cycles (these were not reported in this review) **Characteristics** Baseline characteristics were reported to be comparable between groups **Inclusion criteria** Randomised controlled trials **Exclusion criteria** Quasi randomised trials Cross over trials	Babayof (2006): rFSH + cetrotide + decapeptyl vs rFSH + cetrotide + hCG Beckers (2003): rhFSH + triptorelin vs rhFSH + hCG vs rh FSH + rLH Fauser (2002): rFSH + ganirelix + triptorelin vs rFSH + ganirelix + leuprorelin vs rFSH + ganirelix + hCG Humaidan (2010): rFSH + ganirelix + buserelin + hCG vs rFSH + ganirelix + hCG Humaidan (2005): rFSH + ganirelix + buserelin vs rFSH + ganirelix + hCG Humaidan (2006): rhFSH + ganirelix + buserelin + hCG vs rhFSH + ganirelix + buserelin + hCG (35hrs after buserelin) Kolibianakis (2005): rFSH + orgalutran + triptorelin vs rFSH + orgalutran + hCG Pirard (2006): hMG/FSH + orgalutran + hCG + progesterone vs hMG/FSH + orgalutran + buserelin	Fixed effects model Unit of analysis was per woman randomised	Live birth rate (4 studies: Babayof, 2006; Humaidan, 2010; Humaidan, 2005; Humaidan, 2006) GnRH agonist= 47/252 (19%) hCG= 81/245 (33%) OR 0.44 (0.29 to 0.68) I^2= 64% (live birth rate varied from 5% to 24% in GnRH group and from 15% to 53% in hCG group) random effects OR 0.31 (0.11 to 0.86) It is not clear whether live birth rate includes multiple and/or pre-term births Clinical pregnancy (8 studies: Babayof, 2006; Beckers, 2003; Fauser, 2002; Humaidan, 2010; Humaidan, 2005; Humaidan, 2006; Kolibianakis, 2005; Pirard, 2006) GnRH agonist= 87/368 (24%) hCG= 116/345 (34%) OR 0.57 (0.41 to 0.80) I^2= 41% (random effects OR not reported) Definition of clinical pregnancy is not reported OHSS (5 studies: Babayof, 2006; Humaidan, 2010; Humaidan, 2006; Kolibianakis, 2005; Pirard, 2006)	**Limitations** 2 studies did not perform allocation concealement and allocation concealment was unclear in 1 study 8 studies were not blinded and blinding was unclear in 2 other studies There was no power calculation in 3 studies, and it is not clear if a power calculation was performed in one other study. 2 studies failed to achieve the target sample size **Other information**

				GnRH agonist= 0/266 (0%) hCG= 7/238 (3%) OR 0.10 (0.01 to 0.82) I^2= 0% Miscarriage rate (8 studies: Babayof, 2006; Beckers, 2003; Fauser, 2002; Humaidan, 2010; Humaidan, 2005; Humaidan, 2006; Kolibianakis, 2005; Pirard, 2006) GnRH agonist= 44/368 (12%) hCG= 22/345 (6%) OR= 1.89 (1.11 to 3.21) I^2= 23% (random effects OR not reported)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Papanikolaou,E.G., Verpoest,W., Fatemi,H., Tarlatzis,B., Devroey,P., Tournaye,H., A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study, Fertility and Sterility, 95, 1174-1177, 2011 **Ref ID** 118365 **Country/ies where the study was carried out** Belgium, Greece **Study type** RCT **Aim of the study** To assess the success of using a GnRH agonist trigger and a low does of LH in luteal phase support (with progesterone) against a standard hCG and progesterone protocol. **Study dates** Between Apr 2006 and Jan 2007 **Source of funding** Medication funded by Merck-Serono	**Sample size** N = 39 Four women dropped out the rest were randomised and split into two arms: hCG protocol n = 17 GnRH agonist + LH protocol n = 18 **Characteristics** hCG Age - 30.6 (+/- 0.8) GnRH agonist + LH Age - 30.1 (+/- 0.7) **Inclusion criteria** Women < 36 years old eSET on day 5 Basal FSH < 12mIU/mL **Exclusion criteria** PCOS Use of testicular sperm endometriosis stages III and IV	Intervention: GnRH agonist (rFSH + GnRH antagonist + GnRH agonist + LH + progesterone) Comparison: hCG (rFSH + GnRH antagonist + hCG + progesterone)	Randomization: Computer generated list Method: rFSH (187.4IU) from day 2 of cycle and GnRH antagonist (0.25mg cetrorelix) from day 7 of cycle, both given until trigger Intervention: one group given 250ug rhCG for standard ovulation triggering, followed by standard progesterone (600mg, vaginally administered from day after oocyte retrieval to 7 weeks gestation). The other group was given 0.2mg GnRH agonist (triptorelin) for ovulation triggering as well as the progesterone protocol outlined above. The women in this second group also received six doses every other day of 300 IU rLH from the day of oocyte retrieval	Clinical pregnancy GnRH agonist - 4(event)/18(women) (22.2%) hCG - 4/17 (23.5%) (Clinical pregnancy is defined as cardiac activity after 7 weeks) Live birth rate GnRH agonist - 4/18 (22.2%) hCG - 4/17 (23.5%) P = 0.9 Pregnancy loss GnRH agonist - 1/18 (5.6%) hCG - 2/17 (11.7%) One of the women in the hCG group had a multiple pregnancy but opted for a embryo reduction, it can be assume the live birth rate is singleton.	**Limitations** No power calculation reported **Other information** Allocation concealment was done by research nurse Clinicians were blind until the day of trigger

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Segal,S., Casper,R.F., Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in in vitro fertilization, Fertility and Sterility, 57, 1254-1258, 1992 **Ref ID** 83047 **Country/ies where the study was carried out** Canada **Study type** Randomised controlled trial **Aim of the study** "to determine if there is a difference in the pregnancy rates (PRs) between hCG and GnRH-a use to trigger follicle maturation" **Study dates** Not reported **Source of funding** Abbott Pharmaceutical Company	**Sample size** n=214 couples **Characteristics** Population: Women undergoing controlled ovarian hyperstimulation. Female mean age (± SEM) GnRH-a 33.2 ± 0.4 years hCG = 33.7 ± 0.4 years Duration of infertility Not reported BMI/Weight Not reported Cause of infertility Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	hCG 5,000 IU intramuscularly GnRH-a 500 µg subcutaneously	Recruitment: Not reported Method: The selection of hCG or GnRH-a was determined before starting ovarian hyperstimulation by random numbers table. Intervention: Clomiphene citrate 100 mg/d from cycle days 5 to 9 and 150 IU/d og human menopausal gonadotropin for day 6 or, alternatively, with a comnbination of human FSH 150 IU and hMG 150 IU on days 5 and 6 of the cycle followed by hMG 150 IU/d IVF and ET were performed using standard techniques. Semen samples were washed, centrifuged and a swim-up was used to harvets motile sperm.At 18 to 22 hours after insemination, the oocytes were transferredto fresh medium, cumulus cell stripped mechanically and the oocytes examined for presence of pronucleu. At 43 to 45 hours post fertilization, yp to three two to six-cell embryos were transferred to the uterus.	Pregnancy: GnRH-a 17/96 (17.7%) hCG 18/118 (15.3%) Pregnancy not defined but term 'conceived' was used	**Limitations** Allocation concealment: Not reported Blinding of participants, staff and study personnel: Not reported Power calculation: Not reported **Other information** NA

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Papanikolaou,E.G., Fatemi,H., Camus,M., Kyrou,D., Polyzos,N.P., Humaidan,P., Tarlatzis,B., Devroey,P., Tournaye,H., Higher birth rate after recombinant hCG triggering compared with urinary-derived hCG in single-blastocyst IVF antagonist cycles: a randomized controlled trial, Fertility and Sterility, 94, 2902-2904, 2010 **Ref ID** 89879 **Country/ies where the study was carried out** Belgium, Greece, Denmark **Study type** Randomised controlled trial **Aim of the study** To evaluate, in GnRH antagonist cycles, whether triggering of final oocyte maturation with either recombinant hCG or the gold standard of 10,000 unit of uhCG was any effect on the blastulation rate and the reproductive outcome **Study dates** October 2005 to January 2007 **Source of funding** None reported	**Sample size** 119 women **Characteristics** Mean age: rhCG= 29.5 years +/- 0.6 uhCG= 29.7 +/- 0.8 No significant differences between the groups **Inclusion criteria** <36 years Rank trial =<2 [EF - what does this mean?] FSH on day 3 of the cycle =< 12 IU/mL Male or tubal infertility One embryo at the blastocyst stage to be transferred **Exclusion criteria** None reported	rhCG (n= 59) uhCG (n= 60)	Ethics approval granted Group sample sizes of 56 and 56 achieve 80% power to detect a meaningful difference in blastulation rate Randomisation was performed by a research nurse after the final concsultation at the outpatient clinic. An unconcealed computer-generated list was used. Day of embryo transfer was fixed for day 5, regardless of patient prognosis or ovulation induction parameters. The consulting physician was blinded. Gonadotrophins given at an initial dose of 187.5 IU for all patients and remained fixed for five days. At day 5 onwards a GnRH antagonist was co-administered. Final oocyte maturation was induced with either 10,000 IU uhCG or 250 ug recombinant hCG when at least three follicles of 17mm were present. Luteal phase support was administered in the form of 600mg micronised progesterone vaginally.	Clinical pregnancy: rhCG= 27/59 (46%) women uhCG= 18/60 (30%) women Clinical pregnancy defined at presence of a heart beat at 7 weeks' gestation. First trimester abortion: rhCG= 0/59 (0%) women, 0/27 (0%) pregnancies uhCG= 2/60 (3%) women, 2/18 (11%) pregnancies Second trimester abortion: rhCG= 1/59 (2%) women, 1/27 (4%) pregnancies uhCG= 0/60 (0%) women, 0/18 (0%) pregnancies Deliveries: rhCG= 26/59 (44%) women uhCG= 16/60 (27%) women	**Limitations** Allocation was not concealed **Other information** Two patients in the rhCG group and four in the uhCG group did not undergo embryo transfer because none of their embryos reached the blastocyst stage

Fertility (Updated guideline)

Luteal phase support

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Goudge,C.S., Nagel,T.C., Damario,M.A., Duration of progesterone-in-oil support after in vitro fertilization and embryo transfer: A randomized, controlled trial, Fertility and Sterility, 94, 946-951, 2010 **Ref ID** 82317 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** Efficacy of short-term progesterone-in-oil (11days) vs. traditional long-term progesterone-in-oil (6-weeks) after IVF and embryo transfer. **Study dates** Patients recruited between January 2005 and August 2007 **Source of funding** Not specified	**Sample size** 101 women enrolled into study. Group 1 = 48, Group 2 = 53. Four women withdrew from the study, 2 from group 1 and 2 from group 2. 4 patient from group 2 continued P treatment **Characteristics** <u>Group 1 (n = 46)</u> Age = 31.8 (3.2) Male factor infertility = 20 Number of embryos transferred = 2.12 (0.32) <u>Group 2 (n = 51)</u> Age = 32.7 (3.1) Male factor infertility = 13 Number of embryos transferred = 2.13 (0.49) **Inclusion criteria** Women aged <=37 years First IVF-embryo transfer cycle **Exclusion criteria** None specified	Progesterone from day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) Progesterone from day of embryo transfer until pregnancy test (approximately 11 days)	Ethics approval gained. Randomisation using sequentially numbered, opaque, sealed envelopes at time of assessment for IVF. All women underwent either a long down-regulation protocol or GnRH antagonist protocol Group 1 : 50mg of P-in-oil IM daily, beginning on the day of oocyte retrieval and continuing until pregnancy confirmation with ultrasound (5 to 6 weeks). Group 2 : 50mg of P-in-oil IM daily, beginning on the day of ET and continuing until pregnancy test (approximately 11 days). Women evaluated by P levels to see if this could be safely done. If it was less than 15 ng/ML then told to continue treatment. Statistical analysis was undertaken using Student T-test, X^2, and Fisher's exact test. Significance level set at p <0.05	<u>Biochemical pregnancies</u> Group 1: 31 of 46 Group 2: 35 of 51 <u>Clinical pregnancies</u> Group 1: 29 of 46 Group 2: 32 of 51 Clinical pregnancy was not defined <u>Ongoing pregnancies</u> Group 1: 27 of 46 Group 2: 26 of 51 <u>Singleton live birth rate</u> Group 1: 20 of 29 Group 2: 13 of 32 <u>Multiple pregnancies</u> Group 1: 4 of 29 pregnancies were twin pregnancies Group 2: 12/32 pregnancies were twin pregnancies All multiple pregnancies were twin pregnancies <u>Births from multiple pregnancies</u> Group 1: 8/28 (29%) babies born were from multiple pregnancies Group 2: 24/37 (65%) babies born were from multiple pregnancies All multiple pregnancies were twins	**Limitations** Power calculation was not reported Blinding was not reported **Other information**

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Full citation Nyboe,Andersen A., Popovic-Todorovic,B., Schmidt,K.T., Loft,A., Lindhard,A., jgaard,A., Ziebe,S., Hald,F., Hauge,B., Toft,B., Progesterone supplementation during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial, Human Reproduction, 17, 357-361, 2002 **Ref ID** 82803 **Country/ies where the study was carried out** 2 centres in Denmark **Study type** Randomised Controlled Trial **Aim of the study** To determine whether prolongation of luteal support during pregnancy influences the delivery rate after IVF. **Study dates** March 1999 to April 2000 **Source of funding** Not stated	**Sample size** 303 women included in the study. 150 in progesterone group and 153 in control group. No drop-outs. **Characteristics** <u>Progesterone withdrawal group</u> Mean age = 32.1 years +/- 4.1 Type of infertility: Ovulatory defect = 13 Tubal factor = 52 Male factor = 50 Unexplained = 50 Number of embryos transferred = 1.9 (range 1 to 3) <u>Control group</u> Mean age = 32.2 years +/- 4.3 Type of infertility: Ovulatory defect = 16 Tubal factor = 58 Male factor = 56 Unexplained = 35 Number of embryos transferred = 2.0 (range 1 to 3) **Inclusion criteria** Women who became pregnant after an IVF or ICSI cycle Serum or urinary HCG >	Progesterone from day of embryo transfer until positive hCG test (13 to 15 days) Progesterone from day of embryo transfer until 3 weeks after positive hCG test	Ethics approval received Sample size calculation based on published data on delivery rate with HCG (66%). Sample size was set at 300, and using alpha of 0.05 and beta of 80% the a difference of 10.7% could be detected. Randomised undertaken using computer generated lists in blocks of 10 to avoid unbalanced numbers per centre. Statistical analysis t-test or chi-squared. All patients were treated with a long protocol. Down-regulation with GnRH agonist for at least 14 days. Ovarian stimulation with rFSH. IVF or ICSI undertaken and then embryos transferred. All women received vaginal progesterone 200 mg three times a day from ET until HCG measurement. Those with a positive HCG test were then randomised to either: Progesterone withdrawal group: progesterone withdrawn on day of positive HCG test. Control group: continue with progesterone for an additional three weeks.	All women had positive HCG test <u>Ongoing pregnancy at 7 weeks</u> Progesterone withdrawal group = 133/150 Control = 139/153 <u>Singleton deliveries</u> Progesterone withdrawal group = 86/150 Control = 94/153 <u>Biochemical pregnancy only</u> Progesterone withdrawal group = 10/150 Control = 7/153 <u>Miscarriage on or before 7 weeks</u> Progesterone withdrawal group = 7/150 Control = 5/153 <u>Miscarriage after 7 weeks</u> Progesterone withdrawal group = 15/150 Control = 13/153 <u>Ectopic pregnancies</u> Progesterone withdrawal group = 0/150 Control = 2/153 <u>Ongoing multiple pregnancies</u> Progesterone withdrawal group = 37/150 (all twin pregnancies) Control = 39/153 (38 twin pregnancies, 1 triplet pregnancy)	**Limitations** Blinding not reported **Other information** Women were randomised after positive pregnancy test

	25IU/l 14 days after transfer or absence of vaginal bleeding **Exclusion criteria** None stated			<u>Births from multiple pregnancies</u> Progesterone withdrawal group = 64/150 babies born were twins (no triplets) Control = 64/158 babies born were twins (no triplets)	

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Full citation Ata,B., Kucuk,M., Seyhan,A., Urman,B., Effect of high-dose estrogen in luteal phase support on live birth rates after assisted reproduction treatment cycles, Journal of Reproductive Medicine, 55, 485-490, 2010 **Ref ID** 111911 **Country/ies where the study was carried out** Turkey **Study type** Randomised controlled trial **Aim of the study** To evaluate the effect of high dose 17β-estradiol as an adjunct to progesterone for luteal phase support on the probability of live birth after ART. **Study dates** September 2006 and November 2007 **Source of funding** Not reported	**Sample size** n = 60 women **Characteristics** Age = 32.3 ± 4.3 years Cause of infertility: Tubal = 7 (8.3%) Endometriosis = 3 (5%) Male = 26 (43.3%) Unexplained = 18 (30%) Mixed factor = 1 (1.7%) Other = 5 (8.3%) **Inclusion criteria** 1] Couples undergoing assisted reproduction treatment with their own gametes 2] Female partner under 40 years of age 3] Women stimulated with a long GnRH agonist protocol 4] Couples having at least one embryo available for transfer **Exclusion criteria** 1] Participation in another clinical trial that was being conducted in our unit at the same time. 2] Preimplantation genetic screening cycles 3] Women undergoing frozen thawed embryo transfer	1] Progesterone 2] Estradiol valerate	Method: Women meeting the inclusion criteria were enrolled and allocated to treatment arms by one of the investigators, who had no role in assessment and/or treatment of the participating patients, and were randomised according to a computer-generated randomisation list prepared by another investigator. Patients were assigned to the study groups immediately after embryo transfer. Intervention: Pituitary suppression was achieved with daily subcutaneous injections of leuprolide acetate 0.1 mg/day starting on the 21st day of the preceding cycle.The daily rFSH dose ranged between 150 and 300 IU, depending on BMI and age of the woman and the anticipated ovarian response. hCG 10,000 IU was administered i.m. when the leading follicle reached 20 mm in the mean diameter accompanied by ≥2 follicles >16 mm. Oocyte retrieval was undertaken 36 hours after the administration of hCG. Embryo transfer was performed on day 3.A maximum of three embrys were transferred under ultrasound guidance using a soft embryo transfer catheter. All	<u>Live birth</u> Progesterone = 11/30 (36.7%) Estradiol Valerate =10/30 (33.3%) <u>Clinical pregnancy</u> Progesterone = 16/30 (53.3%) Estradiol Valerate = 14/30 (46.7%) <u>Miscarriage</u> Progesterone = 4/16 (25%) Estradiol Valerate = 2/14 (14.3%)	**Limitations** 1] Sample size did not meet the power calculation. 2] Blinding not reported. **Other information** <u>Incomplete reporting</u> Progesterone group: 1/16 reported clinical pregnancies resulted in an intrauterine fetal demise in the third trimester. This figure was not reported as a miscarriage or live birth. Estradiol valerate group: 2/14 reported clinical pregnancies were lost to follow-up before delivery.

			women were given 90mg vaginal progesterone gel starting from the day of oocyte collection. Women in the estradiol group received 6 mg/day 17β-estradiol orally in three divided doses, starting from the day of embryo transfer.Luteal phase support was continued until the pregnancy test performed 12 days after embryo transfer. Statistical analysis: Assuming a live birth rate of 30% in the control group approximating previous results achieved in our centre, it was calculated that approximately 1,400 participants per arm would be required to detect an absolute 5% increase, which could be considered the smallest clinically relebant difference, with an α error level of 0.05 and β error level of 0.2		

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Full citation Kyrou,D., Fatemi,H.M., Zepiridis,L., Riva,A., Papanikolaou,E.G., Tarlatzis,B.C., Devroey,P., Does cessation of progesterone supplementation during early pregnancy in patients treated with recFSH/GnRH antagonist affect ongoing pregnancy rates? A randomized controlled trial, Human Reproduction, 26, 1020-1024, 2011 **Ref ID** 130290 **Country/ies where the study was carried out** Belgium **Study type** Randomised controlled trial **Aim of the study** To assess whether the cessation of progesterone supplementation during early pregnancy after GnRH antagonist cycles is not inferior to its continuation in terms of pregnancy rates beyond 12 weeks of gestation. **Study dates** September 2008 to April 2010 **Source of funding** Not reported	**Sample size** n = 200 women **Characteristics** Age = 31.4 ± 4.3 years BMI = 23.7 ± 3.6 kg/m^2 Cause of infertility: Andrological = 102 (51%) Tubal = 17 (8.5%) Dysovulation = 11 (5.5%) Unexplained = 70 (35%) **Inclusion criteria** 1] ≤39 years of age 2] BMI between 18 and 29 kg/m^2 3] Presence of both ovaries, basal levels of E2 ≤80 pg/ml, 4] P (≤1.6ng/ml) and FSH (<12 IU/l) at initiation of stimulation 5] Fewer than 3 prior IVF cycles **Exclusion criteria** 1] Presence of PCOS (Rotterdam criteria) 2] Endometriosis classification stage >3, 3] Azoospermia 4] Testicular sperm extraction or PGD.	1] Control group: Progesterone till 7 weeks of gestation 2] Study group: Progesterone till 16days post ET	Recruitment: 200 patients with a positive β-hCG test 14 days post-embryo transfer and a doubling in β-hCG levels, following an antagonist protocol for IVF or ICSI and a fresh embryo transfer, were included in the study. Method: Fourteen days after the ET, 200 patients with a positive β-hCG test, absence of vaginal bleeding and a normal doubling of β-hCG levels 48h after the first measurement, were randomised. Allocations were concealed in opaque sealed envelops, opened once written informed consent was obtained. Randomisation was performed by the attending physician according a computer-generated concealed randomisation list (ratio 1:1) using randomly permutated blocks with a fixed block size of two. The control group continued to receive P until 7 weeks of gestation. The study group discontinued the P administration 16 days post-ET Intervention: All patients were treated with 150 - 200 IU of rFSH, started in the afternoon of Day 2 of the cycle. To inhibit a premature LH surge, daily GnRH antagonist was administered from the morning of Day 6 of	<u>Ongoing pregnancy at 7 weeks</u> 1] Control group = 83/100 (83%) 2] Study group = 90/100 (90%) <u>Multiple pregnancy</u> 1] Control group = 7/100 (7%) 2] Study group = 9/100 (9%) <u>Abortion ≤7 weeks + Abortion >7 weeks</u> 1] Control group = 22/100 (22%) 2] Study group = 17/100 (17%) <u>Biochemical pregnancy</u> 1] Control group = 1/100 (1%) 2] Study group = 0/100 (Not calculable) <u>Ectopic pregnancy</u> 1] Control group = 4/100 (4%) 2] Study group = 1/100 (1%)	**Limitations** 1] Study was not adequately powered 2] Blinding not reported **Other information** <u>Bleeding episodes</u> 1] Control group = 19/100 (19%) 2] Study group = 14/100 (14%)

			the stimulation. Final oocyte maturation was achieved by administration of 10,000 IU of hCG as soon as ≥3 follicles of ≥17 mm were present. Oocyte retrieval was carried out 36h after hCG administration. One day after oocyte retrieval, all patients initiated luteal phase supplementation with vaginal administration of 600 mg natural micronised in three separate doses until the first β-hCG measurement 14 days after the embryo transfer. According to Belgian IVF legislation, one to two embryos were transferred on Day 3 after fertilization. Statistical analysis: The study was not adequately powered to detect a difference in pregnancy outcome		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation van der,Linden M., Buckingham,K., Farquhar,C., Kremer,J.A., Metwally,M., Luteal phase support for assisted reproduction cycles, Cochrane Database of Systematic Reviews, CD009154-, 2011 **Ref ID** 154839 **Country/ies where the study was carried out** Various **Study type** Cochrane review **Aim of the study** To determine the relative effectiveness and safety of methods of luteal phase support in subfertile women undergoing assisted reproductive technology. **Study dates** Final search conducted in February 2011 **Source of funding** None reported	**Sample size** 69 studies of 16,327 women **Characteristics** hCG vs. placebo/no treatment= 5 studies (746 women) Progesterone vs. placebo/no treatment= 8 studies (875 women) Progesterone vs. hCG= 15 studies (2117 women) Progesterone vs. progesterone + hCG= 7 studies (1080 women) Progesterone vs. progesterone + estrogen= 9 studies (1571 women) **Inclusion criteria** Randomised controlled trials Use of progesterone, hCG or GnRH agonist for luteal phase support IVF or ICSI cycles **Exclusion criteria** Quasi-randomised trials Frozen transfers Donor cycles GIFT or ZIFT > 20% cycles or unclear number of cycles	hCG vs. placebo/no treatment Progesterone vs. placebo/no treatment Progesterone vs. hCG Progesterone vs. progesterone + estrogen	Search strategies in the Cochrane Menstrual Disorder and Subfertility Group Module Searched for all published and unpublished RCTs that described progesterone or hCG or both Indexed and free text terms were used Searches on Cochrane Central Register of Controlled Trials, Medline, EMBASE, PsychINFO, MDSG Specialised Register, CINAHL, and the Database of Abstracts of Reviews of Effects. Additional searches on ClinicalTrials.gov, WHO International Trials Registry Platform, ISI Web of Knowledge, OpenSigle, LILACS, Clinicalstudyresults.org. Titles and abstracts were screened independently by two reviewers. Data extraction was performed by two reviewers and disagreements resolved by a third reviewer. Original authors were contacted when a study was unclear or information was missing. Data was reported as Peto Odds ratios. Primary analysis was per woman randomised. Multiple live births were counted as one live birth. Crossover data from	hCG vs. placebo/no treatment Live birth rate (1 study) hCG= 3/13 (23%) Placebo= 3/25 (12%) Peto OR 2.25 (95% CI 0.37 to 13.80) Clinical pregnancy rate (5 studies) hCG= 75/361 (21%) Placebo= 65/385 (17%) Peto OR 1.30 (95% CI 0.90 to 1.88) Miscarriage rate (2 studies) hCG= 4/64 (6%) Placebo= 3/76 (4%) Peto OR 0.67 (95% CI 0.15 to 3.09) OHSS (1 study) hCG= 30/193 (16%) Placebo= 8/194 (4%) Peto OR 0.28 (95% CI 0.14 to 0.54) Progesterone vs. placebo/no treatment Live birth rate (1 study) Progesterone= 15/104 (14%) Placebo= 2/52 (4%) Peto OR 2.95 (95% CI 1.02 to 8.56) Clinical pregnancy rate (7 studies) Progesterone= 96/470 (20%) Placebo= 52/371 (14%) Peto OR 1.83 (95% CI 1.29 to 2.61) Miscarriage rate (3 studies) Progesterone= 10/207 (5%)	**Limitations** The quality of the studies was assessed in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. An in depth analysis of the quality of the included studies can be found in the Cochrane Review. **Other information**

			the first phase of the study was included. If data could not be obtained from study authors, imputation was undertaken for the primary outcome (live birth rate).	Placebo= 9/218 (4%) Peto OR 0.84 (95% CI 0.33 to 2.11) Multiple pregnancy (1 study) Progesterone= 1/12 (8%) Placebo= 0/22 (0%) Peto OR 0.06 (95% CI 0.00 to 3.55) Progsterone vs. hCG Live birth rate (2 studies) Progesterone= 4/96 (4%) hCG= 11/107 (10%) Peto OR (non-event) 2.43 (95% CI 0.84 to 6.97) Clinical pregnancy rate (10 studies) Progesterone= 182/772 (24%) hCG= 173/676 (26%) Peto OR 1.14 (95% CI 0.90 to 1.45) Miscarriage rate (5 studies) Progesterone= 21/381 (6%) hCG= 16/389 (4%) Peto OR 0.75 (95% CI 0.39 to 1.44) OHSS (4 studies) Progesterone= 30/372 (8%) hCG= 42/334 (13%) Peto OR 0.63 (95% CI 0.38 to 1.03) Multiple pregnancy (1 study) Progesterone= 1/70 (1%) hCG= 3/77 (4%) Peto OR 0.40 (95% CI 0.05 to 2.88) Progesterone vs. progesterone + hCG	

				Live birth rate (1 study) Progesterone= 3/70 (4%) Progesterone + hCG= 5/62 (8%) Peto OR (non-event) 1.93 (95% CI 0.46 to 8.05) Clinical pregnancy rate (7 studies) Progesterone= 169/540 (31%) Progesterone + hCG= 155/540 (29%) Peto OR 0.96 (0.74 to 1.25) Miscarriage rate (1 study) Progesterone= 4/70 (6%) Progesterone + hCG= 4/62 (6%) Peto OR 1.14 (0.27 to 4.74) OHSS (3 studies) Progesterone= 18/359 (5%) Progesterone + hCG= 37/354 (10%) Peto OR 0.45 (0.26 to 0.79) Multiple pregnancy (1 study) Progesterone= 1/70 (1%) Progesterone + hCG= 3/62 (5%) Peto OR 0.32 (0.04 to 2.30) Progesterone vs. progesterone + estrogen Live birth rate (1 study) Progesterone= 11/50 (22%) Progesterone + estrogen= 10/50 (20%) Peto OR 1.13 (95% CI 0.43 to 2.94) Clinical pregnancy rate (5 studies)	

				Progesterone= 326/709 (46%) Progesterone + estrogen= 270/636 (42%) Peto OR 1.25 (95% CI 0.99 to 1.59) <u>Miscarriage rate (6 studies)</u> Progesterone= 98/694 (14%) Progesterone + estrogen= 59/587 (105) Peto OR 0.99 (0.69 to 1.43) <u>OHSS (1 study)</u> Progesterone= 0/29 (0%) Progesterone + estrogen= 2/30 (7%) Peto OR 0.14 (0.01 to 2.21) Clinical pregnancy defined throughout as presence of a gestational sac with or without a fetal heartbeat	

Fertility (Updated guideline)

What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Agarwal,A., Ranganathan,P., Kattal,N., Pasqualotto,F., Hallak,J., Khayal,S., Mascha,E., Fertility after cancer: a prospective review of assisted reproductive outcome with banked semen specimens, Fertility and Sterility, 81, 342-348, 2004 **Ref ID** 3942 **Country/ies where the study was carried out** USA **Study type** Prospective observational study **Aim of the study** To present a comprhensive follow-up of all cancer patients who had cryopreserved their sperm since the founding of the sperm bank. [1] To examine the prefreeze and postthaw semen quality in patients with cancer before their treatment for cancer [2] report on the utilization rates and outcome of ART cycles using cryopreserved semen [3] correlate ART outcomes	**Sample size** n = 31 (29/31 of the patients who cryopreserved their semen used ART) **Characteristics** <u>Age</u> Median age (interquartile range) = 30 (25 to 32) years <u>Cancer type</u> Testicular Cancer = 11 (35%) Hodgkin's disease = 12 (39%) Other = 8 (26%) **Inclusion criteria** None reported **Exclusion criteria** None reported	Cryopreserved semen for IUI, IVF or ICSI	Patients who withdrew their samples from the sperm bank for ART were contacted for collecting information on their ART outcomes and the status of their offspring. The reproductive centers to which the semen specimens were transferred were contacted to request information on the method of ART used (IUI, IVF, ICSI), process and outcomes. Oncologists who treated these patients were contacted for obtaining information on status of cancer patients after therapy (whether in remission or with recurrence)	<u>Pregnancy (N = 15)</u> IUI (42 cycles) = 2 ICSI (19 cycles) = 7 IVF (26 cycles) = 6 <u>Live birth (N = 12)</u> IUI (42 cycles) = 3 ICSI (19 cycles) = 4 IVF (26 cycles) = 5	**Limitations** CASP Checklist: 5/31 patients had confounding female factor infertility but there was no subgroup analysis to adjust for it Variations to procedure across the 20 different reprodcutive centres were not taken into account **Other information** 2/31 patients achieved natural pregnancy and were excluded from the analyses

with the duration and nature of cancer treatment as well as the current status of the patients **Study dates** from 1982 - 2001 **Source of funding** None reported					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Crha,I., Ventruba,P., Zakova,J., Huser,M., Kubesova,B., Hudecek,R., Jarkovsky,J., Survival and infertility treatment in male cancer patients after sperm banking, Fertility and Sterility, 91, 2344-2348, 2009 **Ref ID** 4044 **Country/ies where the study was carried out** Czech Republic **Study type** Prospective observational study **Aim of the study** To analyze the sperm counts of cancer patients, examine possible correlation between sperm pathology and cancer diagnosis, determine mortality rate, provide an overview of the use of frozen sperm during the twelve years of sperm banking **Study dates** Between October 1995 and the end of December 2006 **Source of funding** Supported by the Internal Grant Agency (IGA) of the Ministry of Health of the Czech Republic	**Sample size** n = 619 (28 patients used cryopreserved samples) **Characteristics** <u>Age</u> Mean age = 26.2 ±6.8 years Median age = 26 years <u>Cancer type</u> Testicular Cancer = 270 (43.6%) Hodgkin's lymphoma = 103 (16.6%) Leukemia = 50 (8.1%) Non-Hodgkin lymphoma = 44 (7.1%) Malignant tumors of the bone and cartilage = 41 (6.6%) **Inclusion criteria** None reported **Exclusion criteria** Not reported	Semen analysis pre-treatment of malignant disease and Cryopreserved semen for IUI and ICSI	Male adolescents and adults aged 13 to 64 years referred to the ART centre for cryopreservation of sperm before treatment for malignant tumors.	<u>Pregnancy (N = 15)</u> IUI (9 cycles) = 2 ICSI (44 cycles) = 13 <u>Live birth (N = 11)</u> IUI (9 cycles) = 2 ICSI (44 cycles) = 9	**Limitations** CASP Checklist: No serious limitations **Other information** The reported number of pregnancies and live births resulting from 44 ICSI cycles includes 6/44 cycles that used fresh tissue The interval between cryopreservation and infertility treatment was in the range of 7-70 months (mean 22.2 ± 14.7 months, median 18 months)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation van Casteren,N.J., van Santbrink,E.J., van,Inzen W., Romijn,J.C., Dohle,G.R., Use rate and assisted reproduction technologies outcome of cryopreserved semen from 629 cancer patients, Fertility and Sterility, 90, 2245-2250, 2008 **Ref ID** 4372 **Country/ies where the study was carried out** The Netherlands **Study type** Retrospective observational study **Aim of the study** To assess the use of cryopreserved semen and sucess rates of ART of the cryopreserved semen of cancer patients with an average follow-up of 7 years **Study dates** Between 1983 and December 2004 **Source of funding** None reported	**Sample size** n = 629 males (749 semen samples) n = 17 (2.7%) patients were unable to produce a semen sample n = 55 (8.7%) patients the semen sample provided did not contain motile spermatozoa and therefore not suitable for cryopreservation n = 557 (88.6%) patients were able to preserve semen **Characteristics** Male cancer patients <u>Age</u> Mean age = 27 (14 - 57) years <u>Cancer type</u> Testicular germ cell tumors = 236 Hodgkin's lymphomas = 143 non-Hodgkin's lymphomas = 81 Sarcomas = 31 Carcinomas = 28 Acute myeloid leukemias = 26 Acute lymphoid leukemias = 30 Brain tumours = 18 Chronic lymphoid leukemia = 4 Chronic myeloid leukemia = 10 Other Haematological malignancies = 11 Extragonadal germ cell tumours = 8 Melanoma = 1	Cryopreservation of semen for IUI, IVF or ICSI	From a total of 907 cancer patients counseled for semen cryopreservation, 629 were referred for sperm banking before receiving a potential gonadotoxic therapy. Semen samples were cryopreserved if motile spermatozoa were found. After diluting the semen sample with cryoprotectant (Orange Medical, Tilburg, The Netherlands), the samples were cooled and stored in aliquots in liquid nitrogen vapor. Spermatogenesis recovery (if motile spermatozoa were seen in post-treatment sperm analysis) was assessed 6 months after treatment to evaluate sperm production. If patients were in remission for at least 2 years and proven to be infertile, the sperm could be used for ART. Depending on the amount and quality of the semen cryopreserved, IUI, IVF, or ICSI was considered.	<u>Pregnancy (N = 27)</u> IUI (7 cycles) = 1 IVF (32 cycles) = 8 ICSI (53 cycles) = 16 ET (9 cycles) = 2 <u>Live birth (N = 25)</u> IUI (7 cycles) = NR IVF (32 cycles) = NR ICSI (53 cycles) = NR ET (9 cycles) = NR	**Limitations** CASP Checklist: The follow up was not long enough as there were two ongoing pregnancies **Other information** The number of live births were reported as a total and not according to ART type There was no significant difference in age between females who did or did not achieve a pregnancy No correlation was found between the storage time and pregnancy rate

	Schwannomas = 2 <u>Female partners age</u> Mean age (range) = 32 (21 to 40) **Inclusion criteria** None reported **Exclusion criteria** None reported				

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Full citation Hourvitz,A., Goldschlag,D.E., Davis,O.K., Gosden,L.V., Palermo,G.D., Rosenwaks,Z., Intracytoplasmic sperm injection (ICSI) using cryopreserved sperm from men with malignant neoplasm yields high pregnancy rates, Fertility and Sterility, 90, 557-563, 2008 **Ref ID** 82400 **Country/ies where the study was carried out** USA **Study type** Retrospective observational study **Aim of the study** To investigate the efficacy of IVF-ICSI in patients who cryobankded semen before treatment for a variety of malignant diseaes and to compare the results in similar patients who underwent standard IVF **Study dates** January 1994 to April 2005 **Source of funding** None reported	**Sample size** N = 118 **Characteristics** <u>Age (at the time of IVF)</u> Male partner = 38.5 ± 9.5 years Female partner = 34.8 ± 3.9 <u>Cancer type</u> Testicular = 47 (39.8%) Lymphoma = 37 (31.4%) Prostate = 10 (8.5) Other = 24 (20.3%) <u>Semen analysis pre-treatment</u> Abnormal parameter = 43.3% Total motile sperm count <5million = 20.5% **Inclusion criteria** None reported **Exclusion criteria** None reported	Cryopreserved semen for ICSI	Charts were reviewed to obtain data regarding type of malignancy, duration of cryopreservation, pre- and post-thaw semen quality, the ovarian stimulation protocol used, number of mature oocytes retrieved, fertilization rate, the number of embryos transferred and pregnancy outcome.	Delivery rates were significantly higher in patients undergoing IVF than ICSI <u>Pregnancy (N = 103)</u> IVF (169 cycles) = 96 IVF (25 cycles) = 7 <u>Live birth (N = 85)</u> IVF (169 cycles) = NR IVF (25 cycles) = NR	**Limitations** CASP Checklist: 13.6% of the women had another cause of infertility and this was not adjusted for in the analysis **Other information**

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Full citation Menon,S., Rives,N., Mousset,Sim, Sibert,L., Vannier,J.P., Mazurier,S., Massé, L, Duchesne,V., Macé, B., Fertility preservation in adolescent males: experience over 22 years at Rouen University Hospital, Human Reproduction, 24, 37-44, 2009 **Ref ID** 84591 **Country/ies where the study was carried out** France **Study type** Retrospective observational study **Aim of the study** To evaluate the feasibility of sperm banking in adolescents, pre-freeze and post-thaw parameters according to disease type and stage, sperm quality after gonadotoxic treatment, the outcome of fertility and to establish recommendations concerning fertility preservation **Study dates** Between January 1984 and December 2006 **Source of funding** None reported	**Sample size** N = 131 n = 3 patients attempted ART with cryopreserved semen **Characteristics** <u>Age</u> Mean age (range) = 17.81 ± 0.14 (13 to 20 years) <u>Cancer typen (malignant disease accounted for 84% of the patients n = 131)</u> Hodgkin Lymphoma = 23% Testicular cancer = 21% Acute Leukemia = 20% Non-Hodkin lymphoma = 13% Malignant bone tumour = 13% Soft tissue sarcoma = 3% Malignant brain tumour = 3% Other cancer = 2% Carcinoma = 2% **Inclusion criteria** [1] age <20 years [2] A disease diagnosis was obtained for all the patients included in the study according to urological and oncological information **Exclusion criteria** None reported	Cryopreservation of semen	Review of cryopreservation database for patients who cryobanked sperm between January 1984 and December 2006. Clinical and biological data were recorded for each patient at the time of the first semen collection (pre-treatment). Information concerning follow-up is routinely sent by the urologists or oncologists. An accurate histological diagnosis determined cases of malignant disease. The type of treatment was recorded in the database and fertility status was assessed by a questionnaire sent to those patients who annually maintained sperm storage.	<u>Pregnancy (N = 0)</u> <u>Live birth (N = 0)</u> <u>ART type and cycle = NR</u>	**Limitations** CASP Checklist: The results cannot be applied to the local population because of the small sample size **Other information** It is not clear what type of ART was used and the number of cycles

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Revel,A., Haimov-Kochman,R., Porat,A., Lewin,A., Simon,A., Laufer,N., Gino,H., Meirow,D., In vitro fertilization-intracytoplasmic sperm injection success rates with cryopreserved sperm from patients with malignant disease, Fertility and Sterility, 84, 118-122, 2005 **Ref ID** 84658 **Country/ies where the study was carried out** Israel **Study type** Retrospective observational study **Aim of the study** To describe the success rate of ICSI using thawed cryopreserved sperm in male cancer patients **Study dates** January 1999 to December 2002 **Source of funding** Not reported	**Sample size** n = 21 **Characteristics** <u>Age</u> Mean male age = 33 ±7.1 years (range 24 - 49 years) Mean female age = 33 ±6 years (range 21 - 42 years) <u>Cancer type</u> Hodgkin's lymphoma = 5 non-Hodgkin's lymphoma = 4 Sarcoma = 4 Seminoma = 3 Testicular teratoma = 2 Inguinal hystiocytoma = 1 Prostate carcinoma = 1 Lymphocytic leukemia = 1 **Inclusion criteria** None reported **Exclusion criteria** None reported	Cryopreserved semen for ICSI	Couples treated by IVF with frozen-thawed sperm from oligoazoospermic patients being treated for cancer were enroled in the study. Azoospermia was diagnosed when 2 semen samples revealed no sperm after rapid centrifugation. ICSI was performed in all of these cases with a supply of frozen-thawed sperm	<u>Pregnancy (N = 26)</u> ICSI (62 cycles) = 26 <u>Live birth (N = 23)</u> ICSI (62 cycles) = 23	**Limitations** CASP Checklist: No serious limitations **Other information** ICSI was performed in azoospermic cases to achieve the highest possible fertilization rates with limited supply of frozen thawed sperm

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Fitoussi,O., Eghbali,H., Tchen,N., Berjon,J.P., Soubeyran,P., Hoerni,B., Semen analysis and cryoconservation before treatment in Hodgkin's disease, Annals of Oncology, 11, 679-684, 2000 **Ref ID** 84892 **Country/ies where the study was carried out** France **Study type** Retrospective observational study **Aim of the study** To study the population undergoing cryopreservation, determine sperm quality, to review requests to use cryopreserved semen and to study fertilization and pregnancy outcomes **Study dates** Between 1976 and 1996 **Source of funding** None reported	**Sample size** N = 94 N = 13 attempted ART with cryopreserved semen **Characteristics** <u>Age</u> Mean age = 27.5 (16 to 48) years <u>Cancer type</u> Hodgkin's disease staging: 40% stage I; 38% stage II; 15% stage III; and 4% stage IV Semen quality and spermatozoid count before cryopreservation showed overall 53% of normal cases Neither clinical nor biological or pathological characterisics were different from the whole population There was no relationship between semen quality and age **Inclusion criteria** [1] Age >16 and <50 [2] HD any stage **Exclusion criteria** None reported	Semen analysis and Cryopreserved semen before treatment of HD was used in ART: IUI (n = 80) or IVF (n = 8)	All ejaculates presenting a spermatozoa concentration >1.106/ml and a mobile spermatozoa rate >10% were subjected to cryopreservation. Within one hour following freezing, a 'thaw out' test was conducted. After positive test of >100,00 spermatozoa, patients were invited for another cryopreservation session. These are the criteria that determined the preservation and utilization techniques	<u>Pregnancy (N = NR)</u> IUI (80 cycles) = 9 IVF (8 cycles) = NR <u>Live births (N = 2)</u> IUI (80 cycles) = 2 IVF (8 cycles) = 0	**Limitations** CASP Checklist: No serious limitations **Other information** 18 patients had 29 spontaneous births (1 patient = 3 births; 9 patients = 2 births; 8 patients = 1 birth) After 15 failed attempts, 1/13 patients requested for donor sperm which succeeded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Audrins,P., Holden,C.A., McLachlan,R.I., Kovacs,G.T., Semen storage for special purposes at Monash IVF from 1977 to 1997, Fertility and Sterility, 72, 179-181, 1999 **Ref ID** 84898 **Country/ies where the study was carried out** Australia **Study type** Retrospective observational study **Aim of the study** To review 20 years of experience with sperm storage before vasectomy or before chemotherapy and/or radiation therapy, and to evaluate its usefulness **Study dates** from 1977 to 1997 **Source of funding** None reported	**Sample size** n = 256 (men who underwent vasectomy) n = 258 (men who underwent medical therapy for cancer) n = 18 men attempted ART with cryopreserved semen **Characteristics** Age Mean±SD age = 29.0±7.3 **Inclusion criteria** none reported **Exclusion criteria** none reported	Cryopreserved semen	Review of patient clinical notes The characteristics of men who cryopreserved their semen before they underwent chemotherapy and/or radiation therapy were investigated and compared to that of men who cryopreserved their semen before they underwent vasectomy	Pregnancy (N = 10) AIH (53 cycles) = 3 IVF (cycles NR) = 7 Live birth (N = 6) AIH (53 cycles) = 1 IVF (cycles NR) = 5	**Limitations** CASP Checklist: No serious limitations **Other information** 3/18 couple with coexisting female factors still achieved no pregnancy even after IVF

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Meseguer,M., Molina,N., Velasco,J.A., Remohí, J, Pellicer,A., Garrido,N., Sperm cryopreservation in oncological patients: a 14-year follow-up study, Fertility and Sterility, 85, 640-645, 2006 **Ref ID** 84910 **Country/ies where the study was carried out** Spain **Study type** Prospective observational study **Aim of the study** To describe males following cancer treatments who banked sperm samples for future use, the use rate, and the results obtained when using these stored samples to determine the usefulness of banking semen before antitumoral treatments **Study dates** January 1991 to October 2004 **Source of funding** None reported	**Sample size** n = 186 male (320 sperm samples were frozen) Among these, 184 were able to produce sperm cells (98.9%), and the remaining were diagnosed as azoospermic n = 16 attempted ART with cryopreserved semen **Characteristics** <u>Age</u> Mean age = 27.1 ±6.4 years (range 15 - 58) <u>Cancer type</u> Hodgkin's lymphoma = 29 (21%) Testicular cancer = 84 (61%) Leukemia = 5 (4%) Non-Hodgkin's lymphoma = 5 (4%) Brain tumour = 3 (2%) Colon cancer = 3 (2%) Ewing's sarcoma = 3 (2%) Lung cancer = 3 (2%) **Inclusion criteria** None reported **Exclusion criteria** [1] patients with sperm obtained by the intrusive method	Cryopreserved semen before surgery or chemo or radiotherapy treatments	All samples were obtained by masturbation. After liquefaction semen samples were examined for concentration and motility according to WHO guidelines. Semen samples were frozen by dropwise addition of glycerol-based cryoprotectant with continuous shaking (Sperm Freezing Medium; MediCult, Jyllinsge, Denmark)	<u>Pregnancy (N = 16)</u> ICSI (30 cycles) = 14 FET (5 cycles) = 1 Ai (5 cycles) = 1 <u>Live birth (N = 12)</u> ICSI (30 cycles) = NR FET (5 cycles) = NR Ai (5 cycles) = NR	**Limitations** CASP Checklist: 4% of patients had already received some chemotherapy sessions before sperm freezing and were not excluded from the analysis Follow up was not long enough as there were 3 ongoing pregnancies **Other information** The number of live births is not reported by ART type, rather as a total from all the ART's

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Magelssen,H., Haugen,T.B., von,D., Melve,K.K., Sandstad,B., Fosså, SD., Twenty years experience with semen cryopreservation in testicular cancer patients: who needs it?, European Urology, 48, 779-785, 2005 **Ref ID** 85016 **Country/ies where the study was carried out** Norway **Study type** Retrospective observational study **Aim of the study** To evaluate the role of semen cryopreservation in the fertility saving management of testicular cancer patients **Study dates** Between 1983 and 2002 **Source of funding** None reported	**Sample size** n = 422 men n = 29 attempted ART with cryopreserved semen **Characteristics** Testicular cancer patients Age: Median age at orchiectomy (years) = 26.6 (16.9 - 37.7) **Inclusion criteria** [1] unilateral orchiectomy <2 months before referral to sperm bank [2] palpable testicle on the contralateral side **Exclusion criteria** None reported	Semen cryopreservation	The medical records of newly diagnosed testicular cancer patients were reviewed for pre and post-treatment paternity, semen cryopreservation and performance of ART.	Pregnancy (N = 16) Live birth (N = 14) ART type and cycle = NR	**Limitations** CASP Checklist: No serious limitations **Other information** The type of ART used in the study was not stated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ragni,G., Somigliana,E., Restelli,L., Salvi,R., Arnoldi,M., Paffoni,A., Sperm banking and rate of assisted reproduction treatment, Cancer, 97, 1624-1629, 2003 **Ref ID** 96102 **Country/ies where the study was carried out** Italy **Study type** Retrospective observational study **Aim of the study** To analyze and present data from a 15-year cryopreservation program for male cancer patients **Study dates** Between January 1986 and July 2001 **Source of funding** None reported	**Sample size** N = 776 N = 686 were able to cryopreserve their semen N = 36 attempted ART with cryopreserved semen **Characteristics** <u>Age</u> Median (Range) years = 28 (15 to 53) <u>Cancer type</u> Testicular tumours = 367 (47.3%) Hodgkin lymphoma = 237 (30.5%) non-Hodgkin lymphoma = 76 (9.8%) Leukemia = 40 (5.2%) Tumours of different origin = 56 (7.2%) **Inclusion criteria** None reported **Exclusion criteria** Patients where already undergoing chemotherapy before referral for semen cryopreservation	Cryopreservation of semen with IUI, IVF + ET or ICSI	Male cancer patients were referred for semen cryopreservation before undergoing chemotherapy and/or radiotherapy. Ejaculate was obtained by masturbation and the prefreeze semen sample was analyzed accourding to WHO guidelines. A decision was taken to freeze any sample with viable sperm, even if it was below the required minimum standard for IVF. Sperm banking was not performed for azoospermic patients and they were excluded.	<u>Pregnancy (N = 14)</u> IUI (40 cycles) = 3 IVF + ET (6 cycles) = 0 ICSI (42 cycles) = 11 <u>Live birth (N = 12)</u> IUI (40 cycles) = NR IVF + ET (6 cycles) = NR ICSI (42 cycles) = NR	**Limitations** CASP checklist: Follow up was incomplete as two singleton pregancies were still ongoing at the time of last follow-up **Other information** The number of live births is reported as a total for all the ART's 1 set of twins from the ICSI group was anencephalic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Khalifa,E., Oehninger,S., Acosta,A.A., Morshedi,M., Veeck,L., Bryzyski,R.G., Muasher,S.J., Successful fertilization and pregnancy outcome in in-vitro fertilization using cryopreserved/thawed spermatozoa from patients with malignant diseases, Human Reproduction,Hum.Reprod., 7, 105-108, 1992 **Ref ID** 96103 **Country/ies where the study was carried out** USA **Study type** Retrospective observational studies **Aim of the study** To present data from an in-vitro fertilization and embryo transfer programme using cryopreserved/thawed spermatozoa from patients with testicular tumours, lymphopathies and some other malignant diseases **Study dates** From 1986 to 1990 **Source of funding** None reported	**Sample size** N = 10 **Characteristics** <u>Age</u> Mean (range) years = 33.4 ± 1.6 (28 to 46) <u>Age of Female Partners</u> Mean (range) years = 32.6 ± 0.9 (30 to 38) <u>Cancer type</u> Hodgkin's lymphoma = 3 Non-Hodgkin's lymphoma = 1 Testicular carcinoma = 3 Seminoma = 1 Leimyosarcoma of the prostate = 1 Wegener's granulomatosis of the lung = 1 **Inclusion criteria** None reported **Exclusion criteria** None reported	Cryopreserved semen for IVF	Patients with malignant diseases who had cryopreserved spermatozoa before initiation of cancer therapy were referred for IVF. In all cases, insemination was performed with multiple oocytes per dish. In those cases (two patients with three cycles) in which no motility was observed after thawing, oocyte micromanipulation was used in order to assist fertilization	<u>Pregnancy (N = 4)</u> <u>Live birth (N = 5)</u> <u>ART type and cycles = NR</u>	**Limitations** CASP checklist: The results cannot be applied to the local population because of the small sample size **Other information** Their infertility work-up revealed one of the patients' partners with stage I endometriosis The ART type used was not reported. The live births includes one set of triplets

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lass,A., Akagbosu,F., Abusheikha,N., Hassouneh,M., Blayney,M., Avery,S., Brinsden,P., A programme of semen cryopreservation for patients with malignant disease in a tertiary infertility centre: lessons from 8 years' experience, Human Reproduction,Hum.Reprod., 13, 3256-3261, 1998 **Ref ID** 96104 **Country/ies where the study was carried out** United Kingdom **Study type** Retrospective observational study **Aim of the study** To present 8 years experience of semen cryoprerservation for patients with malignant disease in a tertiary infertility centre **Study dates** Between August 1989 and December 1997 **Source of funding** None reported	**Sample size** N = 225 N = 6 attempted ART with cryopreserved semen **Characteristics** <u>Age</u> Mean (range) years = 28 (15 to 56) years <u>Cancer type</u> Testicular Cancer = 79 (34.2%) Haematological malignancy = 121 (52.4%) Solid tumours = 31 (13.4%) **Inclusion criteria** None reported **Exclusion criteria** None reported	Cryopreserved semen for IUI, IVF or ICSI	Men diagnosed with malignant disease were referred for semen cryopreservation before proceeding with chemotherapy. Ejaculate was obtained by masturbation and pre-freeze semen sample was analysed according to WHO guidelines. Post-thaw analysis was not done routinely because in many cases the sperm concentration was so low that perfroming this test would have jeopardized the amount available for freezing. All samples with motile sperm were frozen even if below the required minimum for standard IVF. Cryopreservation was not performed in cases of complete azoospermia.	<u>Pregnancy (N = 6)</u> IUI (cycles NR) = 2 IVF (cycles NR) = 2 ICSI (cycles NR) = 2 <u>Live birth (N = 4)</u> IUI (cycles NR) = 2 IVF (cycles NR) = 2 ICSI (cycles NR) = NR	**Limitations** CASP checklist: The follow-up of subjects was not long enough because there were 2 cases of ongoing prregnancy The results cannot be applied to the local population because of the small sample size **Other information** The number of cycles was not reported for any of the ART's There was one set of twin from the IVF group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kelleher,S., Wishart,S.M., Liu,P.Y., Turner,L., Di Pierro,I., Conway,A.J., Handelsman,D.J., Long-term outcomes of elective human sperm cryostorage, Human Reproduction,Hum.Reprod., 16, 2632-2639, 2001 **Ref ID** 96105 **Country/ies where the study was carried out** Australia **Study type** Retrospective observational study **Aim of the study** To review 22 years of experience in a single teaching hospital centre involving elective sperm cryopreservation for 930 men prior to undergoing treatment likely to cause infertility **Study dates** Between May 1978 and August 2000 **Source of funding** None reported	**Sample size** N = 833 N = 64 attempted ART using cryopreserved semen **Characteristics** <u>Age</u> Mean age (years) = 28 years <u>Cancer type</u> Testicular tumours = 348 Hodgkin's and non-Hodgkin's lymphoma = 230 Sarcoma, leukaemia or other metastatic disease = 281 Non-malignant diseases scheduled to undergo treatment = 71 **Inclusion criteria** None reported **Exclusion criteria** None reported	Cryoprerserved semen for AIH, IVF or ICSI	Men scheduled to undergo treatment likely to compromise their fertility were referred early during evaluation for cancer treatments. The standard protocol for elective sperm cryostorage involves three semen collections at 2 day intervals. Throughout the history of programme, three different methods of cryopreservation of semen had been used. Cryoprotectant medium 199/FS was used from 1980-1985, this was later reduced to a one-step preparation in late 1989, from 1992 the static vapour gradient freezing method was used and finally using a modified Ackerman's cryopreservation media of GEYC fomulation. Semen analysis was performed according tothe contemporaneous WHO laboratory standards. However, due to changes in WHO manual morphology criteria over the study period, sperm morphology was not analysed.	<u>Pregnancy (N = 29)</u> ICSI (28 cycles) = 12 AIH (35 cycles) = 11 IVF (28 cycles) = 6 <u>Live birth (N = 39)</u> ICSI (28 cycles) = NR AIH (35 cycles) = NR IVF (28 cycles) = NR	**Limitations** CASP checklist: The cohort was a combination of cancer patients and patients with non-malignant diseases. The semen parameters of these two groups were not compared. Follow up of subjects was not complete as 2/68 patients who stored and used their cryopreserved semen were lost to follow up **Other information** The number of live births was reported as a total for all the ART's . It is not clear how many live births resulted from each ART

Fertility (Updated guideline)

Cryopreservation versus vitrification for oocytes, embryos or ovarian tissue

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Huang,C.C., Lee,T.H., Chen,S.U., Chen,H.H., Cheng,T.C., Liu,C.H., Yang,Y.S., Lee,M.S., Successful pregnancy following blastocyst cryopreservation using super-cooling ultra-rapid vitrification, Human Reproduction, 20, 122-128, 2005 **Ref ID** 5213 **Country/ies where the study was carried out** Taiwan **Study type** RCT **Aim of the study** To evaluate the efficiency of super-cooling vitrification for blastocyst cryopreservation. **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 38 couples/153 blastocysts **Characteristics** Age of participants not reported Day 5/6 embryos **Inclusion criteria** [1] human blastocysts for cryopreservation with an intact inner cell mass and trophectoderm **Exclusion criteria** Not reported	[1] Vitrification [2] Slow freezing	Participating patients underwent a general medical work-up for infertility and were enrolled in the in-house IVF programme - down-regulation with GnRH agonist and ovarian stimulation with rFSH. When the leading follicles reached 18mm diameter and appropriate E2 level determined, hCG was administered and oocyte retrieval was performed 34-36 hours later. Two to three blastocysts of the best quality blastocysts were selected for embryo transfer. A fraction of the remaining blastocysts were randomly cryopreserved using a random number table. <u>Vitrification procedure</u> (n = 81, 23 patients) A two-step cryoprotectant loading process was used. The 100% vitrification solution was pre-warmed in 37^{o}C incubators for balance. The blastocysts were then exposed to 50 and 100% vitrification solution (VS) at 37^{o}C for 2 min	**Results** **Number surviving** | | Events | Total | | --- | --- | --- | | Vitrification | 68 | 81 | | Slow-freezing | 41 | 72 |	**Limitations** CASP Checklist: No serious limitation **Other information**

			and 30s respectively. Two or three blasocysts treated with 100% VS were transferred onto a thin layer formed by coading 100% VS (0.5 µl) onto the nylon loop of a cryoloop. After the cryoloops containing blastocysts were plunged directly into the super-cooled LN, they were mounted on a stainless steel tube fixed to the inside of the cryovials. <u>Slow freezing procedure</u> (n = 72, 15 patients) The supernumerary blastocysts were exposed to 5% glycerol and 9% clycerol with 0.2mol/l sucros for 10 min at room temperature. After treatment, the blastocysts were cooled using slow cooling, seeding at -7^{O}C and holding for 15 min. The temperature was then decreased followed by temperature reductin and the frozen blastocysts were then stored in liquid nitrogen After vitrification or slow cooling, human blastocysts were removed from cryovials for warming in a solution (37^{O}C) containing 0.5 mol/l sucrose for 10 mins and then observed		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Li,Y.B., Zhou,C.Q., Yang,G.F., Wang,Q., Dong,Y., Modified vitrification method for cryopreservation of human ovarian tissues, Chinese Medical Journal, 120, 110-114, 2007 **Ref ID** 84739 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** 'to investigate a modified vitrification protocol for cyropreservation of the human ovarian tissues and compare it with a routine slow freezing method' **Study dates** October 2004 - May 2005 **Source of funding** Not reported	**Sample size** N = 15 **Characteristics** Age Mean:33.1 ± 2.9 (Mean ± SEM) range: 22 - 37 years Diagnosis: Benign ovarian cysts Tissues collected: Laparocopy: 11 Laparotomy: 4 **Inclusion criteria** Not reported **Exclusion criteria** Not reported	[1] Fresh tissue [2] Vitrification [3] Slow freezing	Tissue was collected post ovarian cystectomy and was cut into strips (5mm X 1mm X 1 mm) using optical tweezers. Tissue was examined histologically before the study to exclude malignant cysts. <u>Vitrification</u> Tissue strips were dehydrated by using a two step regimen (i) 2.0mol/L dimethyl sulfoxide (DMSO) + 0.1 mol/L sucrose in teh base medium for 5 minutes (ii) 2.0 mol/L DMSO + 2.0 mol/L Propanediol (PROH) + 0.2 mol/Lsucrose in the base medium for 5 minutes. Tissue was then drawn into a Pasteur pipette and allowed to drop slowly intio liquid nitrogen. The solid drops were collected by precooled forceps, sealed in aseptic liquid nitrogen-filled cryovials, and stored in a liquid niotrogen tank for at least 2 months. Tissue was thawed by immersing in a 38^{O}C water bath, and then gently agitated until the ice melted nearly completely. The water bath solution was prepared in a phosphate-buffered saline (PBS) medium. The tissue was	**Results** Number surviving (from total N thawed) Not reported Number of clinical pregnancies (per transfer) Not reported Number of live births (per embryos implanted) Not reported Number with abnromal morphology Vitrification: 19.7% Slow-freezing: 27.4% **Number with abnormal morphology** |	Events	Total
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Vitrification	16	81
Slow-freezing	26	95		**Limitations** CASP checklist: No serious limitations **Other information** Study also reports in in-vitro culture of thawed ovarian tissue, levels of estradiol and progesterone production

			then put into a 0.5mol/L sucrose in the base medium for 5 minutes at room temperature and then taken through 0.25mol/L and 0.125mol/L sucrose medium each for 5 mins at ambient temperature. Finally the warmed tissue were rinsed 3 times in the base medium and put into a 37^{o}C, 5.5% CO_2 humidified incubator for 15 minutes, <u>Slow freezing</u> The base medium was supplemented with 1.5 mol/L DMSO as the first cryo-solution and 1.5 mol/L DMSO with 0.1 mol/L sucrose as the second cryo-solution. At ambient temperature, the tissues were transferrred into the first crup-solution for 5 minutes and then in 1.8 ml Nunc cryovials filled with 1 ml of the second cryo-solution fro 30 minutes at 4^{o}C to allow equillibrium of the cryoprotective agent. The vials were colled in a programmable freezer as follows: (1) cooled from 4^{o}C to -8oC at -2^{o}C/min (2)soaked for 10 mins at -8^{o}C, then seeded manually with prechilled forceps, continually held for 10 mins		

			(3)cooled to -40^{o}C at -0.3^{o}C/min (4)cooled to -150^{o}C at -30^{o}C/min (5) plunged immediately into liquid nitrogen and syored for 2 months The cryovials were thawed at room temperature for 1 minute and then immersed in a water bath at 37^{o}C for 2 minutes. After that the ovarian tissue were washed through sucrose mediums with gradually lowered concentrations (0.25mol/L, 0.125mol/L sucrose in base medium) and then rinsed and put into an incubator.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cao,Y.X., Xing,Q., Li,L., Cong,L., Zhang,Z.G., Wei,Z.L., Zhou,P., Comparison of survival and embryonic development in human oocytes cryopreserved by slow-freezing and vitrification, Fertility and Sterility, 92, 1306-1311, 2009 **Ref ID** 88409 **Country/ies where the study was carried out** China **Study type** Randomised controlled trial **Aim of the study** To compare the survival, fertilization, early embryonic development, and meiotic spindle assembly and chromosome alignment in frozen-thawed human oocytes after slow-freezing and vitrification **Study dates** Not reported **Source of funding** Not reported	**Sample size** N = 415 oocytes (from 111 women) **Characteristics** Age: Not reported Duration of infertility Not reported Cause of infertility: Not reported **Inclusion criteria** Not reported **Exclusion criteria** [1] severe male factor infertility	[1] Vitrification [2] Slow freezing	Mature oocytes were obtained from patients who were undergoing ICSI treatment at the infertility center. The patients were given standard ovarian stimulation using a long protocol. When more than 15 mature oocytes were collected from a patient undergoing ICSI treatment, additional surplus oocytes were used for the study. Based on preliminary results, the oocytes from each patient were randomly allocated to slow-freezing or vitrification with a ratio of 1 versus 2 for cryopreservation. Patients were offered oocyte cryopreservation by slow-freezing for vitrification for the patient's own use in the future; or oocytes donated to another couple if the patient became pregnant in the treatment cycle; or oocytes donated for research purposes without fertilitzation. Slow-freezing and thawing procedure Breifly, for 10 minutes the oocytes were placed in human tubal fluid (HTF) medium supplemented with 30% serum substitue suplement. Oocytes were then transferred to a	**Results** Number surviving (per number frozen) Vitrification = 91.8% Slow freezing = 61% Cleavage rate (per number frozen) Vitrification = 33.3% Slow freezing = 53% Number of eggs fertilised (per number frozen) Vitrification = 67.9% Slow freezing = 61.3% Number of blastocysts surviving (per number frozen) Vitrification = 17.5% Slow freezing = 42.9% Number with abnormal morphology (per number frozen) Not reported **Number surviving** Events / Total Vitrification: 268 / 292 Slow-freezing: 75 / 123 **Cleavage rate** Events / Total Vitrification: 142 / 292 Slow-freezing: 25 / 123 **Number of eggs fertilized**	**Limitations** CASP Checklist: No serious limitations **Other information**

freezing medium containing 1.5 M PROH and 0.3 M sucrose for 10 mins. Two to three oocytes were loaded into 0.25 mL French straws. The straws were heated and sealed at both ends and placed in a programmable freezer set at 25^{o}C. After cooling, seeding was performed and the straws were heald at -7^{o}C for 10 minutes and were cooled before being plunged into liquid nitrogen. Thawing was performed on the same day by exposing the straws to air at room-temperature for 40 seconds, then into a 31^{o}C water bath for an additional of 60 s. The oocytes were rinsed sequentially through six drops of medium including HTF. While still in the HTF medium, the oocytes were placed in an incubator at 37oC for 2 to 3 hours before ICSI.

<u>Vitrification and thawing procedure</u>

The oocytes were vitrified with a vitrification kit (MediCult Company, Jyllinge, Denmark). Briefly, the oocytes were suspended for 5 minutes at room temperature and then were transferred to vitrification

	Events	Total
Vitrification	182	292
Slow-freezing	46	123

Number of blastocysts surviving

	Events	Total
Vitrification	47	292
Slow-freezing	3	123

			medium at room temperature for 45 to 60 seconds. They were loaded on a specially designed vitrification device and were plunged immediately into LN for at least 1 month of storage. For the thawing, the McGill Cryoleaf was directly inserted into thawing medium containing 1 M sucrose for 1 minute at 37^{o}C. The thawed oocytes were transferred to diluents medium-I & II of sucrose for 3 minutes each. Oocytes were washed for 3 mins each and survival rate after thawing was evaluated microscopically. Thawing was performed the same day		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Smith,G.D., Serafini,P.C., Fioravanti,J., Yadid,I., Coslovsky,M., Hassun,P., Alegretti,J.R., Motta,E.L., Prospective randomized comparison of human oocyte cryopreservation with slow-rate freezing or vitrification, Fertility and Sterility, 94, 2088-2095, 2010 **Ref ID** 90278 **Country/ies where the study was carried out** Brazil **Study type** Randomized controlled trial **Aim of the study** 'to compare mature human oocytes with slow-rate freezing and vitrification in a prospective randomized manner with a focus on oocyte survival, embryo development and pregnancy outcome measures' **Study dates** From January 2005 to April 2009 **Source of funding** Irvine Scientific provided closed-pulled straws and vitrification/warming solutions.	**Sample size** N = 230 patients of whom 78 used thawed/warmed 587 oocytes **Characteristics** Age Mean 31.6 + 1.1 years Duration of infertility: Not reported Cause of infertility: Not reported **Inclusion criteria** [1] infertility attributable to tubal factor, severe male factor or unexplained factor [2] regular, spontaneous menstrual cycles of 25 to 35 days [3]acceptable follicular phase serum concentrations of follicle stimulating hormone (FSH; ≤10 IU/L), luteinizing hormone (LH ≤ 13.5 IU/L), and estradiol (E_2 ; ≤ 60 pg/mL) [4] BMI ≤ 30kg/m^2 [5] presence of both ovaries and normal uterine cavity [6] willingness to participate in the study and comply with procedures **Exclusion criteria** [1] previous histrory of OHSS [2] previous history of intolerance to any of the	[1] Vitrification [2] Slow-freezing	Oocyte cryopreservation was offered to those couples that conveyed concerns with embryo freezing and had supranumerary mature oocytes (>9 oocytes) retrieved in their ovarian stimulation ICSI/IVF cycle. Patients were randomly allocated by random number generator to oocyte cryopreservation by either slow-rate freezing or vitrification. All patients who failed to achieve pregnancy in the fresh cycle and had supranumerary oocytes cryopreserved were provided the option to transfer embryos derived from frozen/thawed or vitrified/warmed oocytes <u>Slow-freezing and thawing</u> Denuded mature oocytes were first placed ointo Dulbecco's phosphate-buffered solution with 12% synthetic serum substitute and 1.5M propanediol at 22^{O}C for 10 min. OOcytes were then transferred to PBS, 12% SSS, 1.5 M propanediol, and 0.3 M sucrose at 22^{O}C for 5 min. Within this solution one to four oocytes were loaded into a cryopreservation straw and placed into a programmable	**Results** Number of live births (per woman) Not reported Number of clinical pregnancies (per woman) Vitrification: 18/48 Slow-freezing: 4/30 **Number of clinical pregnancies** |	Events	Total
---	---	---
Vitrification	18	48
Slow-freezing	4	30		**Limitations** CASP checklist: No serious limitations **Other information** All patients (n = 230) in the 'fresh' IVF cycle and had supernumerary mature oocytes (more than 9 mature oocytes recovered after cumulus cell removal) were randomly allocated in oocyte slow-rate cryopreservation or vitrification. From those patients, 78 did not get pregnant within their fresh IVF cycle and returned to the clinic requesting an oocyte thaw (n = 30) or warming (n = 48) procedure to achieve pregnancy. Once an oocyte thaw or warming cycle was initiated, a semen sample was collected from partners and analysed before insemination by ICSI

	agents used in the study [3] clinically significant conditions/disease or active substance abuse [4] abnormal gynecologic bleeding of unknown orgin and [5] if their fertility treatment entailed preimplantation genetic screening		freezer at 20^{o}C. The program decreased temperature to allow manual seeding and subsequently dropped. Samples were plunging in liquid nigrogen and stored until thawing. At thawing, straws containing oocytes were removed from liquid nitrogen, heldat 22^{o}C for 30 seconds, and then immersed into water at 30^{o}C for 40 seconds. <u>Vitrification and warming</u> Denuded MII oocytes were initially placed into a drop of HEPES-buffered medium, SSS for 1 minute before merging with an adjacent drop of equilibration solution. Oocytes were subsequently pipetted into vitrifcation solution. All solution exposures were performed at 22^{o}C. During the final 90 seconds in vitrifiication solution, oocytes to be cryopreserved were loaded into pulled straws with this solution, heat sealed at the thin end , had protective metal jackets positioned over the thin portion of the straw, were heat sealed at the large end and submerged in liquid nitrogen. For warming, straws containing oocytes		

			were rapidly transferred from liquid nitrogen into a 37^{o}C water bath for 3 seconds.		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Isachenko,V., Lapidus,I., Isachenko,E., Krivokharchenko,A., Kreienberg,R., Woriedh,M., Bader,M., Weiss,J.M., Human ovarian tissue vitrification versus conventional freezing: Morphological, endocrinological, and molecular biological evaluation, Reproduction, 138, 319-327, 2009

Ref ID
96242

Country/ies where the study was carried out
Germany

Study type
RCT

Aim of the study
'to compare the safety and effectiveness of vitrification and conventional freezing of human ovarian tissue'

Study dates
Not reported

Source of funding
ESF</td>
<td>Sample size
N = 15

Characteristics
Age
Mean: 23.1 ± 4.9 years
Range: 28 and 33 years

Inclusion criteria
Not reported

Exclusion criteria
Not reported</td>
<td>[1] Vitrification
[2] Slow-freezing</td>
<td>A small sample of ovarian tissue of each patient was removed for routine histology

and follicle counts and immediately fixed with Bouin solution. Small pieces measuring ~1mm^3 of experimental ovarian tissue were randomly distributed as follows: non-treated fresh control group1 immediately after transport to the laboratory; n=45), “vitrification” group 2 (n=45) and “freezing” group 3 (n=45).

<u>Vitrification</u>
The vitrification solution, prepared on Dulbecco phosphate buffered solution with serum substitute supplement (SSS Irvine Sci., St. Ana, CA, USA) and antibiotic-antimycotic, contained 2.62 M DMSO, 2.60 M acetamide, 1.31 M prophylene glycol, and 0.0075 M polyethylene glycol. The ovarian tissue pieces (OPs) were dehydrated in vitrification solution of increased concentration: 12.5%, 25%, 50%, and 100%. The first two steps were performed at room</td>
<td>Results
Number surviving (from total N thawed)
Not reported

Number of clinical pregnancies (per transfer)
Not reported

Number of live births (per embryos implanted)
Not reported

Number with abnormal morphology
Vitrification: 20%
Slow-freezing: 17%

Number with abnormal morphology
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Vitrification</td><td>9</td><td>45</td></tr>
<tr><td>Slow-freezing</td><td>8</td><td>45</td></tr>
</table>
</td>
<td>Limitations
CASP checklist:

No serious limitations

Other information</td>
</tr>
</table>

			temperature, which lasted 5 min each, and the next two steps lasted 15 min each at 4°C. After this last step of saturation by cryprotectants, the OPs were dropped directly into liquid nitrogen, together with a small volume (~20µl).of 100% vitrification solution. For warming, the vitrified OPs were directly plunged into 10 ml of 40°C pre-warmed 50% vitrification solution under gentle shaking with vortex until the ice melted. The dilution of the cryoprotectants was performed in a decreasing concentration of vitrification solution (25%, 12.5%) at room temperature and OPs were finally washed three times in a culture medium at 37°C and 5% CO2. Each step of the dilution protocol lasted 5 min. <u>Slow-freezing</u> OPs were transferred to cryo-vials and these cryo-vials were introduced in ice water for 30min. After that, cryo-vials were placed in the freezer, the freezing chamber of which was previously stabilized to 2°C for 20 – 30 min. The freezing program		

			was as follows: (1) the starting temperature was at 2°C; (2) cooling from 2 °C to –6°C at a rate of -2°C/min; (3) autoseeding initiated at –6 °C; (4) after beginning of crystal formation the temperature increased to -5.7°C and remained at this temperature for 10 min; (5) cooling from –5.7°C to –40°C at a rate of -0.3°C/min; (6) cooling to –140°C at a rate of -10°C/min and plunging of cryo-vials into liquid nitrogen. The procedure of thawing was achieved by holding the vials for 30 s at room temperature followed by immersion in a 100°C (boiling) water bath for 60 s, and expelling the contents of the tubes into the solution for removal of cryoprotectants. The exposure time in the boiling water was visually controlled by the presence of ice in the medium; as soon as the ice was ~2 mm apex, the tube was expelled from the boiling water. The final temperature of medium after expelling from 10°C water bath ranged between 4 and 10°C. After thawing, OPs were		

			transferred within a few seconds (5 to 7) to a 100 ml specimens container (Sarstedt, Nuemrecht, Germany) with 10 ml of solution for removal of cryoprotectants (0.75 M sucrose+10% SSS+L-15 medium). The container was placed on the shaker and continuously agitated with 200 osc/min for 15 min at room temperature. For dropping rehydration, we used 50 ml of holding solution (L-15 medium+10%SSS) in a 50 ml tube (Greiner Bio-One GmbH, Frickenhausen, Germany). This method includes the slow adding (dropping) of holding medium to the solution of sucrose with OPs. The final sucrose oncentration was 0.125 M. Finally, the OPs were washed three times each in DPBS supplemented with 10% SSS and in culture medium for 10 min.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation **Ref ID** **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** **Characteristics** **Inclusion criteria** **Exclusion criteria**				**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Fasano,G., Vannin,A.S., Biramane,J., Delbaere,A., Englert,Y., Cryopreservation of human failed maturation oocytes shows that vitrification gives superior outcomes to slow cooling, Cryobiology, 61, 243-247, 2010 **Ref ID** 96246 **Country/ies where the study was carried out** Belgium **Study type** RCT **Aim of the study** The aim of this study was to randomly compare the viability of human failed maturation oocytes subjected to three different cryopreservation methods (classical slow-cooling NaCl based medium and two new protocols: slow-cooling ChCl based medium and vitrification) to give a new potential option and future clinical applications for fertility preservation in many pathological conditions and as an adjunct to IVF cycles **Study dates** May 2006 - August 2007 **Source of funding**	**Sample size** N = 169 patients/289 oocytes **Characteristics** Mean age (±SD) years: 33.84 (±5.0) **Inclusion criteria** [1] commonly discarted failed maturation oocytes from ICSI cycles (Germinal vesicle - GV stage oocytes and metaphase MI oocytes) **Exclusion criteria** Not reported	[1] Vitrification [2] Slow-cooling (NaCl based medium) [3] Slow-cooling (ChCl based medium)	Failed maturation oocytes obtained from patients who underwent an ICSI cycle were used in this study. All retrieved MII oocytes were used for patients treatments, while failed matured GV and MI oocytes were randomly allocated to one of three groups. In the slow-cooling NaCl group, all cryoprotectant solutions were prepared using modified hepes buffered NaCl based medium. In the slow-cooling ChCl group, all cryoprotectan solutions were prepared using choline chloride. For both groups of slow-cooling the cryoprotectants were removed at room temperature. In the vitrification group oocytes were vitrified and cryoprtotectants were removed at room temperature. Finally all the oocytes were cultured at 37°C in a humidified atmosphere, in the fertilization medium and checked after 1h for survival. All the intact oocytes were placed in in vitro maturation medium. The mature oocytes were inseminated by ICSI using sperm donors. A total of 95 additional failed	**Results** **Number surviving** | | Events | Total | | Vitrification | 108 | 131 | | Slow-freezing | 75 | 107 | **Number of eggs fertilized** | | Events | Total | | Vitrification | 12 | 131 | | Slow-freezing | 3 | 107 |	**Limitations** Because of the low survival rate of oocytes in the slow-cooling ChCl group, the study continued comparing only slow-cooling NaCl and vitrification groups. In this part of the study, 95 additional failed maturation oocytes, obtained from patients who underwent an ICSI cycle in the same period, were added to these groups to obtain a larger sample size. CASP checklist: No serious limitations **Other information** No significant difference was observed in survival rates between vitrification and slow cooling in NaCl based medium, regardless of maturation stage (GV + MI) at collection.

Belgium Fonds National de la Recherche Scientifique (FNRS) and a grant from Merck Pharmaceuticals			maturation oocytes, obtained from patients who underwent ICSI cycle in the same period, were added to these groups to obtain a larger sample size		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wilding,M.G., Capobianco,C., Montanaro,N., Kabili,G., Di,Matteo L., Fusco,E., Dale,B., Human cleavage-stage embryo vitrification is comparable to slow-rate cryopreservation in cycles of assisted reproduction, Journal of Assisted Reproduction and Genetics, 27, 549-554, 2010 **Ref ID** 96247 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** 'to compare embryo survival, pregnancy and implantation rates after slow-rate cryopreservation or vitrification using a modified blastocyst vitrification technique to enable its application to the cryopreservation of cleavage stage embryos (day 3)' **Study dates** July 2009 - December 2009 **Source of funding** No financial contributions were received or offered during the entire study.	**Sample size** N = 99 patients/320 thawed embryos **Characteristics** Mean Age ±SD (range years) Vitrification: 34.5 ±3.3 (29-40) Slow-freezing: 32.8 ±2.9 (28-39) Day 3 embryos **Inclusion criteria** [1] female menstrual cycle of 24 - 35 days (intra-individual variability ± 3 days) [2] karyotype of both parents was normal [3] biochemical assessments demonstrated the absence of metabolic, autoimmune abnd infectious disorders. **Exclusion criteria** [1] female basal FSH > 10 IU/l [2] BMI > 29 [3] biochemical and/or unltrasound suggested polycystic ovarian syndrome (PCOS) [4] female partner with stage III-IV endometrosis [5] presence of autoimmune, thyroid or chromosomal abnormalities [6] if one 1 ovary was present [7] if semen was derived from either a cryopreserved sample or a surgical retrieval	[1] Vitrification [2] Slow freezing	Patients were prepared for IVF/ICSI treatment using standard protocols for oocyte and sperm preparation. ICSI of retrieved oocytes was performed at a maximum of 42h after hCG administration. Fertilization was checked 16-20h after ICSI insemination. A morphological and development check was performed 40-41h and 64-65h post fertilization. After the fresh embryo transfer procedure, excess to cycles of assisted reproduction grade I, day 3 embryos, with a maximum of 5 blastomeres and <10% fragmentation, were cryopreserved by vitrification or slow freezing. Vitrification A standard blastocyst vitrification kit was used (Manufactored = COOK) . Embryos were vitrified in straws either singly or in pairs. Time in pre-vitrification (solution 2 + 8% Dimethlysulfoxide) for 3 mins. Vitrification then performed in 16% DMSO in solution 3 of the kit (contents not disclosed by manufacturer) Embryos were thawed as	**Results** Number surviving (from total N thawed) Vitrification = 93.1% Slow-freezing = 87.0% p = 0.89 Number of clinical pregnancies (inc Fetal heart beats detected) (per patient) Vitrification = 18/51 Slow-freezing = 17/48 Number of live births (per patient) Vitrification = 17/51 Slow-freezing = 1748 **Number of clinical pregnancies** Vitrification: Events 21, Total 147 Slow-freezing: Events 19, Total 141 **Number of live births** Vitrification: Events 19, Total 147 Slow-freezing: Events 17, Total 141	**Limitations** CASP checklist: No serious limitations **Other information** Patients that did not achieve pregnancy in the fresh cycle were prepared for frozen-thawed embryo transfer with standard protocols of down-regulation with GnRH agonist

			follows; [1] removed from straws under liquid nitrogen and placed in thaw solution 1 at 37^{O}C. [2] washed in a new drop of solution 1 for 5 minutes at 37^{O}C and incubated for 5 mins. [3] passed into solution 2 for 5 minutes at 37^{O}C. [4] washed in solution 2 for 5 minutes at 37^{O}C. [5] washed into equilibrated culture medium and incubated 2 hours at 37^{O}C prior to transfer. <u>Slow freezing</u> A standard programmable rate freezer (manufacurer - Cryologic). The colling procedure consisted of a step of -2oC/min between 25oC and -7oC followed by a pause of 10 mins and a step of -0.3oC/min between -7oC and -35oC. Straws were then plunged in liquid nitrogen and stored. Embryos were thawed as follows [1] The straws were exposed to air for 30 seconds follwed by immersion in water at 30oC for 30 seconds. [2] embroys were then expelled and put into thawing		

			solution 1 for 5 mins followed by solution 2 etc. [3] when solution 4 was reached the dish was placed at 37oC for 5 mins to achieve embryo rewarming [4] embryos were then washed into equilibrated culture medium and incubated 2 hours at 37^{o}C prior to transfer.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kim,S.H., Lee,S.W., Lee,J.H., Kang,S.M., Oh,H.J., Lee,S.M., Lee,S.G., Yoon,H.G., Yoon,S.H., Park,S.P., Song,H.B., Lim,J.H., Study on the vitrification of human blastocysts: II. Effect of vitrification on the implantation and the pregnancy of human blastocysts, Korean Journal of Fertility and Sterility, 27, 67-74, 2000 **Ref ID** 96613 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** 'to investigate the effect of vitrification on the implantation and the pregnancy of human blastocysts' **Study dates** January 1998 - July 1999 **Source of funding** Unclear	**Sample size** Unclear **Characteristics** Day 5 embryos **Inclusion criteria** Unclear **Exclusion criteria** Unclear	[1] Vitrification [2] Slow-freezing	The zygotes derives from IVF were cocultured with cumulus cells in YS medium containing 20% hFF for 5days. Two or three of the best blastocysts produced on day 5 were transferred into the uterus, and then supernumerary blastocysts were randomly divided into two groups. Vitrification The vitrification procedure was performed in three steps (10% glycerol for 5 min, 10% glycerol + 20% ethylene glycol for 5 min, 25% glycerol + 25% ethylene glycol and directly LN_2 within 1 min). The blastocysts frozen by vitrification were thawed at 20^{o}C water then removed cryoprotectant in 3 steps. Slow-freezing The slow freezing procedure was performed in two steps (5% glycerol and 9% glycerol + 0.2 M sucrose for 10 min, respectively) using programmed freezer (-2^{o}C/min to -7^{o}C$, manual seeding at -7^{o}C, -0.3^{o}C/min to -30^{o}C and plunged into LN_2 within 1 minute.	**Results** Number surviving (from total N thawed) Not reported Number of clinical pregnancies (per transfer) Not reported Number of live births (per embryos implanted) Not reported Number with abnromal morphology Vitrification: 19.7% Slow-freezing: 27.4% **Number surviving** Events / Total Vitrification: 105 / 141 Slow-freezing: 537 / 790	**Limitations** CASP checklist No serious limitations **Other information**

			The blastocysts frozen by slow freezing were thawed at 36^{o}C then removed glycerol in 7 steps. In each group, thawed blastocysts were cocultured with cumulus cells in YS medium containing 20% hFF for 18h and transferred into the uterus.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zheng,W.T., Zhuang,G.L., Zhou,C.Q., Fang,C., Ou,J.P., Li,T., Zhang,M.F., Liang,X.Y., Comparison of the survival of human biopsied embryos after cryopreservation with four different methods using non-transferable embryos, Hum Reprod, 20, 1615-1618, 2005 **Ref ID** 96615 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** To compare survival of human biopsied embryos after cryopreservation with four different methods including vitrification using non-transferable embryos obtained from clinical IVF/ICSI **Study dates** Not clear **Source of funding** Not reported	**Sample size** Not clear **Characteristics** Day 3 embryos **Inclusion criteria** Not reported **Exclusion criteria** Not reported	[1] Vitrification [2]Standard programmed slow cryopreservation		**Results** Number surviving (from total N thawed) Vitrification: 94% Slow-freezing: 85%. p > 0.05 Number of clinical pregnancies (per transfer) Not reported Number of live births Not reported Number with abnormal morphology - reported as intact embryos Vitrification: 20% Slow-freezing: 64%. p < 0.001 Number of blastocysts surviving - reported as blastomeres surviving Vitrification: 90% Slow-freezing: 71%. p < 0.001 Cleavage rate Not reported Number of eggs fertilized NA **Number surviving** |	Events	Total
---	---	---
Vitrification	46	49
Slow-freezing	45	53		**Limitations** **Other information**

Number with abnormal morphology

	Events	Total
Vitrification	10	49
Slow-freezing	35	53

Number of blastocysts surviving

	Events	Total
Vitrification	218	243
Slow-freezing	223	316

Fertility (Updated guideline)

Safety of ovulation stimulating agents in women and long term effects on children conceived via ART

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Althuis,M.D., Scoccia,B., Lamb,E.J., Moghissi,K.S., Westhoff,C.L., Mabie,J.E., Brinton,L.A., Melanoma, thyroid, cervical, and colon cancer risk after use of fertility drugs, American Journal of Obstetrics and Gynecology, 193, 668-674, 2005 **Ref ID** 53328 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To evaluate melanoma, thryoid, colon, and cervical cancer risks after clomiphene or gonadotrophins. **Study dates** 1965 - 1999 **Source of funding** Not reported	**Sample size** n = 8422 women; PY = 155527 Clomiphene = 3276 Gonadotrophins = 865 **Characteristics** Mean length of follow-up = 18.8 years Women included in the analyses and those excluded were not significantly different according to calendar year and age at first evaluation. **Inclusion criteria** Previously reported in Brinton et al 2004 **Exclusion criteria** [1] Previously reported in Brinton et al 2004 [2] Self-reported melanomas (n = 11) and colon cancer (n = 1) found on medical record review to be benign. [3] Patients lost to follow-up after their inital clinic visit, those who denied access to their records. [4] Those who had cancer diagnosed within 1 year of their registration clinic visit (n = n = 10)	[1] Clomiphene [2] Gonadotrophins	Previously described in Brinton et al 2004 Statistical analysis: Risk ratios adjusted for attained age, calender time, study sites, and gravidity at entry.	Clomiphene Melanoma: Treated (n = 21) - Risk ratio = 1.66; 95% CI = 0.9 to 3.1 Not treated (n = 21) - Risk ratio = 1.00 Thyroid: Treated (n = 8) - Risk ratio = 1.42; 95% CI = 0.5 to 3.7 Not treated (n = 10) - Risk ratio = 1.00 Cervical: Treated (n = 7) - Risk ratio = 1.61; 95% CI = 0.5 to 4.7 Not treated (n = 7) - Risk ratio = 1.00 Colon: Treated (n = 8) - Risk ratio = 0.83; 95% CI = 0.4 to 1.9 Not treated (n = 20) - Risk ratio = 1.00 Gonadotrophins Melanoma: Treated (n = 4) - Risk ratio = 0.90; 95% CI = 0.3 to 2.6 Not treated (n = 38) - Risk ratio = 1.00 Thyroid: Treated (n = 2) - Risk ratio = 1.10; 95% CI = 0.2 to 4.9 Not treated (n = 16) - Risk ratio	**Limitations** **Other information**

				= 1.00 Cervical: Treated (n = 2) - Risk ratio = 1.39; 95% CI = 0.3 to 6.4 Not treated (n = 12) - Risk ratio = 1.00 Colon: Treated (n = 0) - Risk ratio = NA; 95% CI = NA Not treated (n = 28) - RR = NR	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Althuis,M.D., Moghissi,K.S., Westhoff,C.L., Scoccia,B., Lamb,E.J., Lubin,J.H., Brinton,L.A., Uterine cancer after use of clomiphene citrate to induce ovulation, American Journal of Epidemiology, 161, 607-615, 2005 **Ref ID** 53329 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To report the risk of developing uterine cancer in a cohort of women evaluted for infertility. **Study dates** 1965 - 1988 **Source of funding** National Cancer Institute intramural funding was provided by the US Government.	**Sample size** n = 8,401 women; person years = 145,876 Clomiphene = 3,280 women Gonadotrophins = 867 women **Characteristics** Median age at first evaluation = 30 years Subjects included in the analyses and those excluded were not significantly different according to calendar year and age at first evaluation. **Inclusion criteria** Previously reported in Brinton et al, 2004 **Exclusion criteria** Previously reported in Brinton et al, 2004	[1] Clomiphene [2] Gonadotrophins	Previously described in Brinton et al, 2004 Statistical analysis: Rate ratio adjusted for calender year, age, study site, gravidity at study entry, BMI and hormone replacement therapy use.	Clomiphene Uterine cancer: Treated- n = 19; PY = 55,461 Rate ratio = 1.79; 95% CI = 0.9 to 3.4 Not treated - n = 20; PY = 90,415 Rate ratio = 1.0	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Brinton,L.A., Scoccia,B., Moghissi,K.S., Westhoff,C.L., Althuis,M.D., Mabie,J.E., Lamb,E.J., Breast cancer risk associated with ovulation-stimulating drugs, Human Reproduction, 19, 2005-2013, 2004 **Ref ID** 53611 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To evaluate the effects of infertility medications independent of other breast cancer predictors. **Study dates** 1965 - 1999 **Source of funding** Additional support for the study was provided by Giannela Derienzo and Usha Singh (Westat, Inc.).	**Sample size** n = 8431 women **Characteristics** Median age at first evaluation = 30 years Median length of follow-up = 18.8 years There were no significant differences according to calendar year or age at evaluation between the subjects included and excluded from the analyses. **Inclusion criteria** Patients were eligible if they: [1] Had a US address at the time of evaluation [2] Were seen more than once or had been referred by another physician who provided relevant medical information [3] Primary or secondary infertility **Exclusion criteria** [1] Patients evaluted for reversal of a tubal ligation [2] Self-reported cancers found to be benign based on medical record review (n = 2)	[1] Clomiphene [2] Gonadotrophins [3] Clomiphene + Gonadotrophins	Recruitment: Eligible study subjects comprised women who had sought advice for infertility between 1965 and 1988 at one of five large reproductive endocrinology practices. The practices were selected because they had retained all original records and had evaluated large numbers of infertile patients, many of whom received high doses of ovualtion-stimulating drugs. Data collection:Trained abstractors reviewed medical records of all patients evaluated for infertility at these practices to determine eligiblility. Location information for eligible study subjects was sought through a variety of sources, including clinic records, telephone directories, credit bureaus, postmasters and motor vehicle administration records. Additional information about vital status and development of cancers was obtained by administration of questionnaires to located, living subjects and through linkage of the cohort against selected cancer registries and the National Death Index. For patients traced as alive,	Breast cancer Clomiphene: n = 80, PY = 46245 Rate ratio = 0.97; 95% CI = 0.7 to 1.3 Gonadotrophins: n = 3, PY = 2585 Rate ratio = 0.59; 95% CI = 0.2 to 1.8 Clomiphene + Gonadotrophins: n = 28, PY = 12459 Rate ratio = 1.15; 95% CI = 0.8 to 1.7	**Limitations** **Other information**

			information on the development of cancers was obtained from clinic records, completed questionnaires and cancer registries. Questionnaires initially were mail mailed to patients begining in early 1998, with telephone follow-up attempted for non-respondents. Attempts were made to veryfy medically any cancers reported in the questionnaires by obtaining discharge summaries, operative reports and pathology reports from the institutions where the diseases had been diagnosed and/or treated. Additional information on cancers was obtained from the cancer registeries, from information on causes of death available from the NDI or copies of death certificates obtained from individual state vital statistics registeries. Death certificates which noted cancer as a cause of death were searched for information on the duration of the disease to define an approximate diagnositic date. Statistical analysis: Standardised incidence ratios (IR) and 95% confidence		

			intervals were calculated to compare breast cancer within the cohort of infertile women with rates for US women. Additional analyses were conducted within the cohort of infertile women, allowing exposures to be evaluated for multivariable adjustment for other potential risk factors. Rate ratios adjusted for calender year and age at follow-up, study site and mother or sister with breast cancer		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Brinton,L.A., Lamb,E.J., Moghissi,K.S., Scoccia,B., Althuis,M.D., Mabie,J.E., Westhoff,C.L., Ovarian cancer risk after the use of ovulation-stimulating drugs, Obstetrics and Gynecology, 103, 1194-1203, 2004 **Ref ID** 53612 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To asses the long-term effects of ovulation-stimulating drugs on the risk of ovarian cancer. **Study dates** 1965 - 1999 **Source of funding** Supported by National Institutes of Health intramural contract funds.	**Sample size** n = 8369 women; PY = 148318 **Characteristics** Median age of first evaluation = 30 years Median length of follow-up (range) = 18.8 (1 - 34) years **Inclusion criteria** Previously reported in Brinton et al 2004 **Exclusion criteria** [1] Previously reported in Brinton et al 2004. [2] Patients whose date of last contact was within 1 year of their initial clinical visit. [3] Those who denied access to their records. [4] Those who were diagnosed with ovarian cancer during the first year of follow-up (n = 3). [5] Those who had both ovaries removed within 1 year of their first clinic visit (n = 60).	[1] Clomiphene [2] Gonadotrophins [3] Clomiphene + Gonadotrophins	Previously described in Brinton et al 2004. Statistical analysis: Rate ratio adjusted for age at follow-up, calender time, study site, and gravidity at first clinic visit.	Ovarian cancer Clomiphene: n = 11, PY = 44003 Rate ratio = 0.78; 95% CI = 0.4 to 1.6 Gonadotrophins: n = 1, PY = 2559 Rate ratio = 1.16; 95% CI = 0.1 to 8.2 Clomiphene + Gonadotrophins: n = 4; PY = 12079 Rate ratio = 1.02; 95% CI = 0.3 to 2.8 No treatment: n = 29; Rate ratio = 1.00	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Brinton,L.A., Kruger,Kjaer S., Thomsen,B.L., Sharif,H.F., Graubard,B.I., Olsen,J.H., Bock,J.E., Childhood tumor risk after treatment with ovulation-stimulating drugs, Fertility and Sterility, 81, 1083-1091, 2004 **Ref ID** 53613 **Country/ies where the study was carried out** USA **Study type** Case-cohort study **Aim of the study** To assess childhood cancer risk among children conceived following the use of ovulation-stimulating drugs. **Study dates** 1968 - 1996 **Source of funding** Supported by the U.S. Government (intramural research funds) and the Danish Cancer Society	**Sample size** n = 34,277 children (born during follow-up period); person years = 259,988 cases = 47 children subcohort = 967 children **Characteristics** Age = 0 to 20 years Mean duration of follow-up = 10.1 years **Inclusion criteria** Not reported **Exclusion criteria** [1] Women (n = 17) without valid identification numbers in the Central Personal Register (CPR) [2]Those who entered the cohort after December 31, 1996 (n = 2,894) [3] Stillbirths (n = 384), foreign adoptions (n = 6,569), danish adoptions (n = 965) and births with uncertain (n = 141) [4] Exclusion criteria for women previously reported in Brinton et al, 2004.	[1] Clomiphene [2] hCG [3] hMG	Recruitment: The study population was based on children delivered to a cohort of women whose admission to a hospital or private fertility clinic in Denmark, beginning in the early 1960s, resulted in a diagnosis of infertility. These patients were identified from medical files, microfilms, and local computerised systems. Subcohort: The subcohort included all children of a stratified random sample of 1,360 women who were originally selected as a comparison subcohort in a case-cohort analysis of cancer risk oin the mothers. Data collection: The infertility cohort was linked to a central personal register (CPR) to obtain information on migrations and deaths of the women through the end of 1996. The identification of the children born to women in this cohort was achieved by linking the cohort with the Medical Birth Register, which contains information on all births in Denmark since 1973 and with the CPR. The cohort was also linked to the CPR to obtain information on liveborn children during the	Childhood tumours Clomiphene: Treated - 11/265; Rate ratio = 0.77 95% CI = 0.4 to 1.6 Not treated - 34/594; Rate ratio = 1.0 hCG: Treated - 10/260; Rate ratio = 0.69 95% CI = 0.3 to 1.5 Not treated - 35/600; Rate ratio = 1.0 hMG: Treated - 2/83; Rate ratio = 0.59 95% CI = 0.1 to 3.1 Not treated - 44/779; Rate ratio = 1.0	**Limitations** **Other information**

			time period not covered by the Medical Birth Register. Tumor cases were identified by linking the cohort to the Danish Cancer Registry, which has recorded tumor incidence nationwide in Denmark since 1943. Cases: The mothers' hospital files related to infertility were requested from the respective hospitals/clinics for the children who developed cancer subsequent to their mothers being evaluated for infertility. Statistical analysis: Rate ratio adjusted for mother's age at birth of study subject		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gauthier,E., Paoletti,X., Clavel-Chapelon,F., group,N., Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study, Human Reproduction, 19, 2216-2221, 2004 **Ref ID** 54205 **Country/ies where the study was carried out** France **Study type** Prospective cohort study **Aim of the study** To evaluate the impact of infertility treatment on breast cancer risk using data from the E3N prospective cohort of ~ 100,000 women. **Study dates** June 1990 - November 1991 **Source of funding** The French League against Cancer, the European Community, the 3M Company and the Mutuelle Generale de l'Education Nationale supported the original E3N study	**Sample size** n = 92,555 women n = 6602 women with infertility problems Clomiphene = 2390 Chorionic gonadotrophin = 1888 Menotrophin = 789 **Characteristics** Duration of follow-up (years) = 9.7 (±1.4) Treatment by fertility drugs = 71.4% Mean duration of use (months) = 13 (±19.6) Mean age at first use (years) = 30 (±4.8) **Inclusion criteria** Not reported **Exclusion criteria** [1]history of cancer other than basal cell carcinoma at baseline (n = 4567) [2]no available date of diagnosis (n = 239) [3]no history of sexual intercourse (n = 1636) [4] Women who had received other treatments	Information on fertility drugs, IVF, surgery or other complementary alternative medicine was collected. The brand names of six drugs were mentioned: Clomid (clomiphene citrate), Ondogyne (cyclofenil), Inductor and Neopergonal (both HMG), Humegon (menotrophin, a purified preparation of gonadotrophin) and GCE (chorionic gonadotrophin). Finally the investigation was carried out for the group of women who received any of the three major fertility drugs: [1] Clomiphene (clomid) [2] Chorionic gonadotrophin (GCE) [3] Menotrophin (Humegon)	Recruitment:The cohort consists of 98,997 women that were originally part of the E3N, a prospective cohort study on risk factors for serious diseases, conducted in France. Part of the E3N cohort is also included in the European Prospective Investigation into Cancer and Nutrition. Participants were aged 40 - 65 years at entry and enrolled in the study after replying to a baseline questionaire. Follow-up questionnaires were sent out at ~24 month intervals. Data collection: Information on infertility was recorded in three questionnaires. The first two questionnaires to ascertain if the women had been treated for infertility and the type of fertility drug. The third questionnaire was sent to women who had mentioned in any of the first two that they had been treated with fertility drugs. Start and end date of use were requested for each drug. Information on potential confounders were recorded at baseline. Deaths in the cohort were detedted from reports by family members or by the postal service and by searching	Breast cancer Clomiphene: No treatment = 2388/85953 (person years:831342) Relative risk: 1.00; Treatment = 66/2390 (person years: 23089) Relative risk: 0.96; 95% CI = 0.75 to 1.23 Chorionic gonadotrophin: No treatment = 2388/85953 (person years: 831342) Relative risk: 1.00 Treatment = 56/1888 (person years: 18203) Relative risk: 0.97; 95% CI = 0.74 to 1.27 Menotrophin: No treatment = 2388/85953 (person years: 831342) Relative risk: 1.00; Treatment = 23/789 (person years: 7628) Relative risk: 0.99; 95% CI = 0.65 to 1.49	**Limitations** 1] Observational study. 2]Loss to follow-up: Only 1815 women could not be traced and non respondents in this group were considered lost to follow-up. **Other information**

			the insurance company (MGEN) file. Cause of death information was obtained from the National service on causes of deaths. Information on the reimbursement of hospital fees of non-respondents to any questionnaires was obtained from the MGEN file. In this case, the subjecs physician was contacted for diagnostic information, making it possible to find additional breast cancer cases. Statistical analysis: Relative risk, RR, adjusted for educational level, active smoking, BMI, family history of breast cancer in first-degree relatives, personal history of benign breast disease, age at menarche, menopausal status, composite variable for parity and age at first full-term pregnancy		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hannibal,C.G., Jensen,A., Sharif,H., Kjaer,S.K., Malignant melanoma risk after exposure to fertility drugs: results from a large Danish cohort study, Cancer Causes and Control, 19, 759-765, 2008 **Ref ID** 54362 **Country/ies where the study was carried out** Denmark **Study type** Case-cohort study **Aim of the study** To examine the effects of fertility drugs on malignant melanoma risk using data from the largest cohort of infertile women to date. **Study dates** 1963 - 1998 **Source of funding** Not reported	**Sample size** n = 54,362 women; PY = 566,500 Cases = 112 women Subcohort = 1226 women **Characteristics** Median age at cohort entry = 30 years Median length of follow-up = 8.8 years **Inclusion criteria** Previously reported in Hannibal et al 2007. **Exclusion criteria** [1] Women (from the cases = 21; subcohort = 93) whose records could not be found. [2]Women (from the subcohort = 8) whose infertility diagnosis could not be confirmed [3] Women (from the subcohort = 33) with infertility diagnosis due to previous sterilisation	[1] Clomiphene [2] Gonadotrophins [3] hCG [4] GnRH	Previously descrived in Hannibal et al, 2007. Statistical analysis: Rate ratios, RR, stratified for age at cohort entry and calendar year of cohort entry, adjusted for parity status	Malignant melanoma Clomiphene: Treated - 42/406; Rate ratio = 1.12 95% CI = 0.74 to 1.70 Not treated - 70/820; Rate ratio = 1.0 Gonadotrophins: Treated - 25/165; Rate ratio = 1.65 95% CI = 0.93 to 2.94 Not treated - 87/1061; Rate ratio = 1.0 hCG: Treated - 40/396; Rate ratio = 1.10 95% CI = 0.74 to 1.65 Not treated - 72/830; Rate ratio = 1.0 GnRH: Treated - 14/98; Rate ratio = 1.55 95% CI = 0.77 to 3.10 Not treated - 98/1128; Rate ratio = 1.0	**Limitations** **Other information** Six women diagnosed with malignant melanoma during the follow-up period were included both as cases and subcohort members in the analyses

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hannibal,C.G., Jensen,A., Sharif,H., Kjaer,S.K., Risk of thyroid cancer after exposure to fertility drugs: results from a large Danish cohort study, Human Reproduction, 23, 451-456, 2008 **Ref ID** 54363 **Country/ies where the study was carried out** Denmark **Study type** Case-cohort study **Aim of the study** To evaluate the effects of different groups of fertility drugs on thyroid cancer risk after adjustment for reproductive factors. **Study dates** 1963 - 1998 **Source of funding** Supported by the Danish Cancer Society.	**Sample size** n = 54,362 women cases = 29 women subcohort = 1226 women **Characteristics** Median age ate cohort entry = 30 years Median length of follow-up = 8.8 years **Inclusion criteria** Previously reported in Hannibal et al 2007. **Exclusion criteria** [1] Women (from the cases = 4; subcohort = 93) whose records could not be found [2] Women (from the subcohort = 8) whose infertility diagnosis could not be confirmed [3] Women (from the subcohort = 33) with infertility diagnosis due to previous sterilisation	[1] Clomiphene [2] Gonadotrophins [3] hCG [4] GnRH [5] Progesterone	Previously described in Hannibal et al 2007. Statistical analysis: Rate ratios, RR, stratified for age at cohort entry and calendar year of cohort entry, adjusted for age at first live birth.	Thyroid cancer Clomiphene: Treated - 16/406; Rate ratio = 2.29 95% CI = 1.08 to 4.82 Not treated - 13/820; Rate ratio = 1.0 Gonadotrophins: Treated - 6/165; Rate ratio = 1.43 95% CI = 0.54 to 3.83 Not treated - 23/1061; Rate ratio = 1.0 hCG: Treated - 13/396; Rate ratio = 1.67 95% CI = 0.79 to 3.54 Not treated - 16/830; Rate ratio = 1.0 GnRH: Treated - 4/98; Rate ratio = 1.82 95% CI = 0.47 to 7.02 Not treated - 25/1213; Rate ratio = 1.0 Progesterone: Treated - 2/13; Rate ratio = 10.14 95% CI = 1.93 to 53.34 Not treated - 27/1213; Rate ratio = 1.0	**Limitations** **Other information** Three women diagnosed with thyroid cancer during the follow-up period were included both as cases and subcohort members in the analyses

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Jensen,A., Sharif,H., Svare,E.I., Frederiksen,K., Kjaer,S.K., Risk of breast cancer after exposure to fertility drugs: results from a large Danish cohort study, Cancer Epidemiology, Biomarkers and Prevention, 16, 1400-1407, 2007 **Ref ID** 54537 **Country/ies where the study was carried out** Denmark **Study type** Case-cohort study **Aim of the study** To evaluate the effects of different types of fertility drugs on the risk of breast cancer after adjustment for reproductive factors. **Study dates** 1965 - 1998 **Source of funding** Grant support from Danish National Cancer Institute.	**Sample size** n = 54,362 women; PY = 564,971 years cases = 331 women subcohort = 1,226 women **Characteristics** Median age at entry = 30 years Median length of follow-up (range) = 8.8 (0 - 35.2) years There were no marked differences in the distribution of the demographic variables (median year and age at cohort entry, median age at the end of the study, and median length of follow-up) between the subjects in the subcohort and the subjects of the toal infertility cohort. **Inclusion criteria** [1] All gynecological departments and all private fertility clinics in Denmark. [2] Women with primary and secondary infertility **Exclusion criteria** [2] Women (from the cases = 10; subcohort = 33) where the cause of infertility was sterilisation [3] Women (from the cases = 31; subcohort = 93) for whom the records could not be found [4] Women (from the subcohor = 8) with unconfirmed	[1] Clomiphene [2] Gonadotrophins [3] hCG [4] GnRH [5] Progesterone	Recruitment: A cohort of women with infertility problems referred to Danish hospitals or private fertility clinics in the period 1965 to 1998 was established. Patients were identified from medical files, microfilms, or index cards. In addition, the study included patients with an infertility diagnosis recorded in the National Patient Registry, a nationwide registry of virtually all somatic discharges in Danish Hospitals since 1977. Cases: To determine breast cancer status after enrollement in the study, the cohort was linked to the Danish Cancer Registry. The cancer registry is supplemented by linkages to The Causes of Death Registry and The National Patient Registry to ensure a complete registry. Subcohort: A subcohort was selected and compared with the identified cases. The subcohort of 1,360 women were randomly selected from the cohort in four strata for the age at entry to the infertility cohort and five strata for the year of entering the infertility cohort, equaling 20 strata.	Breast cancer Clomiphene: Treated - 102/405; Rate ratio = 1.08 95% CI = 0.85 to 1.39 Not treated - 229/82; Rate ratio = 1.0 Gonadotrophins: Treated - 36/165; Rate ratio = 1.20 95% CI = 0.82 to 1.78 Not treated - 295/1061; Rate ratio = 1.0 hCG: Treated - 94/395; Rate ratio = 0.94 95% CI = 0.73 to 1.21 Not treated - 237/831; Rate ratio = 1.0 GnRH: Treated - 18/98; Rate ratio = 1.28 95% CI = 0.75 to 2.19 Not treated - 313/1,128; Rate ratio = 1.0 Progesterone: Treated - 8/13; Rate ratio = 3.36 95% CI = 1.60 to 7.07 Not treated - 323/1,213; Rate ratio = 1.0	**Limitations** **Other information** Twenty four women were diagnosed with breast cancer in the follow-up period. These women were therefore included both as cases and as memebers of the subcohort in the analyses

	infertility diagnosis		Data collection: All data were edited and merged into a single database with a record for each woman with an infertility diagnosis. To veryfy the personal identification number and to determine eventual migration date or date of death, the cohort of infertile women was linked with the Civil Registration System using the personal identification number. The computerised Civil Registration system founded on 1 April, 1968 includes information about current and former addresses, migration dates, and date of death on all persons ever living in denmarch since it was established and is updated weekly. To obtain information about reproductive history, the cohort of infertile women was linked to the Civil Registration System and the Danish National Birth Registry using the Personal identification numbers as key identifiers. The population-based Danish National birth registry contains information about all births in Denmark since 1973. Cases: At the time of linkage, a total 372 women were		

			diagnosed with breast cancer in the follow-up period. Statistical analysis: Rate ratios adjusted for childbirth and number of addition births		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Jensen,A., Sharif,H., Kjaer,S.K., Use of fertility drugs and risk of uterine cancer: results from a large Danish population-based cohort study, American Journal of Epidemiology, 170, 1408-1414, 2009 **Ref ID** 54538 **Country/ies where the study was carried out** Denmark **Study type** Case-cohort study **Aim of the study** To clarify the association between risk of uterine cancer and fertility drugs. **Study dates** 1965 - 1998 **Source of funding** Supported by the Danish Cancer Society	**Sample size** n = 54,362; person years = 957,887 cases = 83 women subcohort = 1,241 women **Characteristics** Median age at cohort entry = 30 years Median length of follow-up (range) = 16 (0.0 - 42.6) years **Inclusion criteria** Not reported **Exclusion criteria** [1] Women (from the cases = 18; subcohort = 78) whose records or hospital files could not be found. [2] Women (from the subcohort = 8) for whom a diagnosis of infertility could not be confirmed. [3] Women (from the subcohort = 33) for whom the cause of infertility was previous sterilisation	[1] Clomiphene [2] Gonadotrophins [3] hCG [4] GnRH	Previously described in Hannibal et al, 2007. Statistical analysis: Rate ratio, RR, stratified according to calender year and age at start of follow-up, adjusted for parity and number of additional births.	<u>Uterine cancer</u> Clomiphene: Treated - N = 29/417; Rate ratio = 1.36; 95% CI = 0.83 to 2.23 Not treated - N = 54/826; Rate ratio = 1.00 Gonadotrophins: Treated- N = 17/184; Rate ratio = 2.21; 95% CI = 1.08 to 4.5 Not treated -N = 66/1,059; Rate ratio = 1.0 hCG: Treated - N = 31/413; Rate ratio = 1.36; 95%CI = 0.83 to 2.23 Not treated - N = 52/830; Rate ratio = 1.0. GnRHa: Treated - N = 7/110; Rate ratio = 1.09; 95% CI = 0.47 to 2.52 Not treated - N = 76/1,133; Rate ratio = 1.0	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Jensen,A., Sharif,H., Frederiksen,K., Kjaer,S.K., Use of fertility drugs and risk of ovarian cancer: Danish Population Based Cohort Study, BMJ, 338, b249-, 2009 **Ref ID** 54539 **Country/ies where the study was carried out** Denmark **Study type** Case-cohort study **Aim of the study** To examine the effects of fertility drugs on overall risk of ovarian cancer using data from a large cohort of infertile women. **Study dates** 1963 - 1998 **Source of funding** Supported by the Danish Cancer Society	**Sample size** n = 54,362 women; person years = 957,454 cases = 156 women subcohort = 1241 women **Characteristics** Median age at cohort entry = 30 years Median length of follow-up (range) = 16 (0.0 - 42.6) years **Inclusion criteria** Previously reported in Hannibal et al 2007. **Exclusion criteria** [1] Women (from the cases = 18; subcohort = 78) whose records could not be found. [2] Women (from the cases = 2;subcohort = 33) with cause of infertility due to sterilisation. [3] Women (from the subcohort = 8) whose infertility diagnosis could not be confirmed.	[1] Clomiphene [2] Gonadotrophin [3] hCG [4] GnRH	Previously described in Hannibal et al, 2007. Statistical analysis:Rate ratios, stratified according to calendar year and age at start of follow-up, adjusted for parity and number of additional births.	Ovarian cancer Clomiphene: Treated - 58/417; Rate ratio = 1.14 95% CI = 0.79 to 1.64 Not treated - 98/824; Rate ratio = 1.0 Gonadotrophins: Treated - 26/184; Rate ratio = 0.83 95% CI = 0.5 to 1.37 Not treated - 130/1057; Rate ratio = 1.0 hCG: Treated - 49/413; Rate ratio = 0.89 95% CI = 0.62 to 1.29 Not treated - 107/828; Rate ratio = 1.0 GnRH: Treated - 15/110; Rate ratio = 0.80 95% CI = 0.42 to 1.51 Not treated - 141/1131; Rate ratio = 1.0	**Limitations** **Other information** Eight women diagnosed with ovarian cancer during the follow-up period were included both as cases and as members of the subcohort in the analyses

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Klemetti,R., Sevon,T., Gissler,M., Hemminki,E., Health of children born as a result of in vitro fertilization, Pediatrics, 118, 1819-1827, 2006 **Ref ID** 54655 **Country/ies where the study was carried out** Finland **Study type** Retrospective cohort study **Aim of the study** To use nationwide registries to examine the health of children up to 4 years of age who were born as a result of IVF **Study dates** Not reported **Source of funding** Supported financially by the Academy of Finland, the SII, the Ministry of Education (School of Doctoral Programs in Public Health), and the National Research and Development Centre for Welfare and Health.	**Sample size** IVF Children = 4559 Control = 190,398 **Characteristics** Maternal age at delivery IVF = 33.9±4.5 years Control = 29.7±5.3 years *Maternal age at delivery was significantly higher in women that underwent IVF. **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] IVF births 2] Births other than IVF or ovulation induction	The study is based on children born to women who received IVF between 1996 and 1998 in Finland. The women were identified, with a predesigned alogrithm, from the reimbursement files of the SII. Data on children born as a result of IVF treatment and their perinatal health were obtained from the Finnish Medical Birth Register by using women's personal identification numbers and the children's dates of birth as the linkage keys. The identified children were linked to 4 other nationwide registries through the children's identification numbers, namely, cause-of-death statistics, the Hospital Discharge Register, the Care Register for Social Welfare, and health-related social benefits from the SII. As control groups, 2 groups of children were selected from the Medical birth register. The first control group consisted of all children other than IVF children or those born as a result of ovulation induction who had been conceived during the same period. The second control group was a random sample of the first control group, selected to	Proportions, cases per 1000; Odds ratios (95% CI) adjusted for mother's socioeconomic position 1] Any child disability allowance: IVF = 10.6 Control = 9.5; Odds ratio 1.1 (1.0 to 1.2) 2] Any long-term medication use: IVF = 3.3 Control = 2.8; Odds ratio 1.2 (1.0 to 1.4) 3] Cerebral Palsy: IVF = 3.8 Control = 1.4; Odds ratio 2.9 (1.6 to 5.3) 4] Epilepsy: IVF = 3.3 Control = 2.5; Odds ratio 1.3 (0.8 to 2.3) 5] Behavioural disorders IVF = 6.6 Control = 4.1; Odds ratio 1.68 (1.1 to 2.5) 6] Diabetes mellitus IVF = 0.9 Control = 0.5; Odds ratio 1.6 (0.5 to 4.8) 7] Asthma	**Limitations** Retrospecive study design **Other information** 1] When the outcomes were analysed for singletons and multiples, there was no significant difference between children born by IVF and non IVF children except Total number of hospital episodes outcome where IVF singletons had significantly higher numbers of Total number of hospital episodes than non-IVF singletons.

			reduce the workload caused by larg registry linkages in the SII. Data collection: The number of deaths of all children from 1996 to 2001 until the age of 2 years was obtained from cause-of-death statistics. The Health Discharge Register (HDR) collects information on inpatient care and visits to outpatient clinics involving surgical or other procedures. All hospitalisations until the children were 4 years of age were studied. The Care register collects information on care episodes in social institutions, such as institutions for people with intellectual disabilities. The rates of institutionalised children was compared with the national rates for children born in 1997 or 1998, excluding the numbers of children from IVF or ovulation induction.	IVF = 30.3 Control = 28.1; Odds ratio 1.1 (0.9 to 1.3) 8] Allergy IVF = 59.9 Control = 53.8; Odds ratio 1.07 (0.9 to 1.2) 9] Pneumonia IVF = 9.9 Control = 11.4; Odds ratio 0.9 (0.6 to 1.2) 10] Diarrhoea IVF = 44.2 Control = 38.6; Odds ratio 1.2 (1.0 to 1.4) 11] Total no. of hospital episods IVF = 40/4397 (9.1) Control = 33/136782 (0.2)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Pappo,I., Lerner-Geva,L., Halevy,A., Olmer,L., Friedler,S., Raziel,A., Schachter,M., Ron-El,R., The possible association between IVF and breast cancer incidence, Annals of Surgical Oncology, 15, 1048-1055, 2008 **Ref ID** 55322 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort study **Aim of the study** To evaluate the incidence of breast cancer in a cohort of women exposed to IVF **Study dates** 1986 to 2003 **Source of funding** Support from The Israel Cancer Association	**Sample size** n = 3,375 IVF patients **Characteristics** Mean female age at first treatment (range) = 32.1 ± 5.7 (18 to 45) years Mean length of follow-up (range) = 8.1 ± 4.3 (1.0 to 18.7) years **Inclusion criteria** 1] All patients who received at least one treatment cycle. **Exclusion criteria** Not reported	IVF	Recruitment: Women who underwent treatment for infertility at the IVF unit within the study period were identified from the computerised database of the unit. Data collection: The study cohort computerised file was linked to the National Cancer Registry to identify cancer cases. The registry contained data on cases of cancer noted on hospital discharge reports from all hospitals, and noted on cytological and histological reports from all Departments of Pathology and Oncology in the country. In cases where only needle biopsy reports were provided by the registry, the investigators reviewed the individual medical chart and the final histological report to validate the diagnosis of breast cancer. Data analysis: The observed cancer cases in the IVF population were compared to the general population and standardised incidence ratio's calculated taking into account person years, which were calculated from the date of first fertility treatment until the end of follow up, or until the date of breast cancer	Breast cancer: Observed = 35 cases Expected = 24.8 cases SIR = 1.4; 95% CI 0.98 to 1.95	**Limitations** 1] Retrospective study design. 2] Over 40% of the women in the cohort received more than one treatment protocol and individual analysis per protocol could not be performed. **Other information** 1] When results were analysed by age, type of infertility, diagnosis of infertility, number of IVF cycles, women who were 40 years or older at their first IVF treatments, those with secondary infertiltiy and those who underwent four or more IVF cycles were at higher risk of breast cancer than the general population.

			diagnosis, whichever came first. SIR values were also computed by categories of age, type of infertility, diagnosis of infertility, number of treatment cycles and outcome of the infertility treatment when available.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sanner,K., Conner,P., Bergfeldt,K., Dickman,P., Sundfeldt,K., Bergh,T., Hagenfeldt,K., Janson,P.O., Nilsson,S., Persson,I., Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden, Fertility and Sterility, 91, 1152-1158, 2009 **Ref ID** 55559 **Country/ies where the study was carried out** Sweden **Study type** Historical cohort study **Aim of the study** To study the association between hormonal infertility treatment and ovarian neoplasia. **Study dates** 1961 - 1975 **Source of funding** Funded in part by the Swedish Cancer Society	**Sample size** n = 2768 women **Characteristics** Mean age at inclusion (range) = 27 (16 - 45) years Mean follow-up period (range) = 33 (1 - 47) years **Inclusion criteria** Not reported. **Exclusion criteria** [1] Diagnosis of other cancer types not relevant to the study (n = 5). [2] Diagnosis of ovarian cancer before fertility treatment (n = 2).	[1] Clomiphene citrate [2] Gonadotrophins [3] Clomiphene citrate + Gonadotrophins	Recruitment: Women who were assessed for infertility and infertility-associated disorders at three departments of Obstetrics and gynecology. Some women counselled regarding infertility problems but did not receive hormonal treatment while the others received HIT. Data collection: All information concerning the women in the cohort was abstracted from individual medical records and entered into a standardised protocol. The study cohort was linked to the Swedish Inpatient Register, providing information on diagnoses and surgical procedures during inpatient care at all swedish hosptials. For women in the study and the control cohorts, linkages were made to the Swedish Cancer Register to ascertain all cases of epithelial ovarian neoplasia from 1958 throu December 31, 2004. Statistical analysis: Rate ratios adjusted for age and indication.	Clomiphene Invasive ovarian cancer: Rate ratio = 1.52; 95% CI = 0.31 - 7.39 Borderline ovarian tumors: Rate ratio = 3.06; 95% CI = 0.69 - 13.68 Gonadotrophins Invasive ovarian cancer: Rate ratio = 5.21; 95% CI = 1.67 - 16.20 Borderline ovarian tumors: Rate ratio = 1.11; 95% CI = 0.12 - 10.17 Clomiphene + Gonadotrophins Invasive ovarian cancer: Rate ratio = 0.72; 95% CI = 0.09 - 6.00 Borderline ovarian tumors: Rate ratio = 2.70; 95% CI = 0.58 - 12.65	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tulandi,T., Martin,J., Al-Fadhli,R., Kabli,N., Forman,R., Hitkari,J., Librach,C., Greenblatt,E., Casper,R.F., Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate, Fertility and Sterility, 85, 1761-1765, 2006 **Ref ID** 55867 **Country/ies where the study was carried out** Canada **Study type** Multicentre retrospective cohort study. **Aim of the study** To evaluate the incidence and type of congenital malformation among offspring of mothers who conceived with letrozole compared to a control group of infertile women conceiving with clomiphene citrate. **Study dates** January 2001 - December 2001 **Source of funding** Not reported	**Sample size** n = 911 babies **Characteristics** Mean birthweight = 3238.8 ± 609.1 grams **Inclusion criteria** Not reported **Exclusion criteria** [1] Babies born as a result of IVF treatment.	[1] Clomiphene [2] Letrozole [3] Clomiphene + FSH [4] Clomiphene + FSH + Progesterone [5] Letrozole + FSH [6] Letrozole + FSH + Progesterone [7]Letrozole + FSH + Metformin	Recruitment: Within the study period, 931 babies born from women who conceived following clomiphen or letrozole treatment at 5 fertility centres in Canada were identified. Intervention: Women undergoing ovulation induction or augmentation for timed intercourse or IUI received either letrozole or clomiphene administered orally for 5 days from day 3 to 7 of the cycle. Data collection: Pregnancy outcome and demographic data were retrieved from the medical files of both mother and baby and cross-checked with the patients by telephone calls.	Clomiphene (n = 293) Major malformation:10 (3.4%) Minor malformation: 6 (2.0%) Letrozole (n = 252) Major malformation: 1 (0.4%) Minor malformation: 4 (1.6%) Clomiphene + FSH (n = 104) Major malformation: 2 Minor malformation: 0 Clomiphene + FSH + Progesterone Major malformation: 0 Minor malformation: 1 Letrozole + FSH (262) Major malformation: 2 Minor malformation: 2 Letrozole + Progesterone Major malformation: 1 Minor malformation: 1 Letrozole + Metformin Major malformation: 2 Minor malformation: 0	**Limitations** Incomplete follow-up (20 babies were lost to follow-up) The fact that infertile women are more likely to adopt healthy lifestyles might have attenuated the risks of some congenital abnormalities (only 3 women smoked during pregnancy). **Other information** [1] 20 babies were lost to follow-up out of which 11 were conceived following letrozole treatment and another 9 following clomiphene. [2] 'Congenital malformation' was defined as deformations and chromosomal abnormalities as stated in Chapter XVII, WHO, International Statistical Classification of Diseases and Related Health Problems. [3] 'Major malformations reported are VSD, esophageal atresia, cleft palate, trisomy 18, down's syndrome, potters syndrome [4] 'Minor malformations reported are Preauricular skin tag, congenital ptosis, plagiocephaly, hydrocele, hypospadia, polydactyly, syndactyly, umbilical and inguinal hernias.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Calderon-Margalit,R., Friedlander,Y., Yanetz,R., Kleinhaus,K., Perrin,M.C., Manor,O., Harlap,S., Paltiel,O., Cancer risk after exposure to treatments for ovulation induction, American Journal of Epidemiology, 169, 365-375, 2009 **Ref ID** 68081 **Country/ies where the study was carried out** Israel **Study type** Non-comparative Cohort study **Aim of the study** To study the association between ovulation-inducing treatments and the incidence of cancer in a unique population-based cohort of parous women. **Study dates** 1964 - 1976 **Source of funding** Supported by National Institutes of Health grant	**Sample size** n = 15,047 women **Characteristics** No pooled data **Inclusion criteria** Only parous women **Exclusion criteria** [1] Mothers who were diagnosed with cancer prior to their first birth in the postpartum cohort (n = 17 mothers)	Ovulation induction treatments were categorised into any treatment versus none and include: [1] Clomiphene citrate [2] hMG [3] Others [4] Unknown [5] Combination of some or all of the above	Recruitment: The Jerusalem Perinatal Study is a population-based cohort study of all births to residents of West Jerusalem, Israel, and its surroundings in 1964 - 1976.The database includes demographic, obstetric, and neonatal information on 92408 births to 41206 mothers collected from birth notifications and maternity ward log books. Data collection:15,426 mothers were interviewed in the hospital on the first or second day after giving birth. The postpartum subcohort included 98% of births occurring in the 3 major obstetric units in West Jerusalem and covered 91% of all births in the area at the time. Linkage of the cohort with the Israeli Population Registry using mothers' identity numbers permitted tracing and ascertainment of vital status for 97.5% (n = 15047) of mothers. Information on cancer incidence as of December 31, 2004 was obtained by linking the ascertained cohort with the Israel Cancer Registry, which receives notification of	Clomiphene Breast cancer: Hazard ratio = 1.27; 95% CI = 0.79 - 2.04; p = 0.331 Uterine cancer: Hazard ratio = 4.56; 95% CI = 1.56 - 13.34; p = 0.006 Non-Hodgkin lymphoma: Hazard ratio = 2.46; 95% CI = 0.74 - 8.13; p = 0.140 Melanoma: Hazard ratio = 2.56; 95% CI = 1.10 - 5.97; p = 0.030	**Limitations** Observational study **Other information**

			all malignancies diagnosed throughout the country. Statistical analysis: Hazard ratio for incident cancer, adjusted for age, socioeconomic status, country of birth, BMI and family size.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Rossing,M.A., Daling,J.R., Weiss,N.S., Moore,D.E., Self,S.G., Ovarian tumors in a cohort of infertile women, New England Journal of Medicine, 331, 771-776, 1994 **Ref ID** 68916 **Country/ies where the study was carried out** U.S.A **Study type** Case-cohort study **Aim of the study** To determine whether infertile women have an increased risk of ovarian tumors and, if so, whether that risk is influenced by the apparent cause of the infertility or the treatment received for it. **Study dates** January 1, 1974 to December 31, 1985 **Source of funding** Supported in part by a grant from (R35 CA-39779) and a contract (NO1-CN-05230) with the National Cancer Institute.	**Sample size** n = 3837 women (43,438 person-years of observation) cases = 11 subcohort = 135 women **Characteristics** Age = 17 to 44 years **Inclusion criteria** [1] At the time of the evaluation, they resided in the 13-county area of western Washington covered by the Cancer Surveillance System, a population-based tumor registry operating as part of the Surveillance Epidemiology and End Results program of the National Coancer Institute [2] They had attempted conception for a period of at lease one year [3] They had made at lease two visits to an infertility clinic participating in the study **Exclusion criteria** Not reported	[1] Clomiphene citrate [2] hCG	Recruitment: The cohort was composed of women evalusted for infertility at participating clinics within the study period. Subcohort: A comparison group of women were randomly selected from the cohort in four strata for age at the time of enrollement. For each stratum, the number of women selected was three times as larg as the number of women with the most common type of cancer in that stratum. Data collection: Identifying information, including name, address, date of birth and social security number, was collected for each member of the cohort from the records of the infertility clinic where she was evaluated. These data were linked by computer to CSS records to identify women who received a diagnosis of cancer after enrollment in the study and before January 1, 1992. Ascertainment of exposure: Clinic records of the women with ovarian tumors and the members of the subcohort.	OVARIAN TUMORS Clomiphene citrate (Relative risk adjusted for age, year of and gravidity at enrollment) Relative risk = 2.3; 95% CI = 0.5 to 11.4 hCG (Relative risk adjusted for age, year of and gravidity at enrollment) Relative risk = 1.0; 95% CI = 0.2 to 4.3	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Salhab,M., Al,SarakbiW, Mokbel,K., In vitro fertilization and breast cancer risk: A review, International journal of fertility and women's medicine, 50, 259-266, 2005 **Ref ID** 68932 **Country/ies where the study was carried out** **Study type** Review **Aim of the study** To review the literature, beginning with a case report from 1977, and examine the potential effects of IVF treatment on breast cancer risk. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 15 studies n = 60,050 patients **Characteristics** Follow-up period = 0.5 to 34 years. 11 Cohort studies- Gauthier et al 2004 Brinton et al 2004 Lerner-Geva et al 2003 Doyle et al 2002 Dor et al 2002 Venn et al 1999 Potashnik et al 1999 Modan et al 1998 Rossing et al 1996 Venn et al 1995 Ron et al 1987 4 Case control studies- Bernstein et al 1995 Burkman et al 2003 Braga et al 1996 Ricci et al 1999 **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] Clomiphene citrate 2] hCG 3] hMG		BREAST CANCER <u>hCG</u> Bernstein et al 1995: Number of cases treated = 45/744 Number of control treated = 65/744 Odds ratio (95% CI) = 0.77 (0.5 to 1.19) Other studies were not reported for one of the following reasons: 1] Results reported as Standardised incidence ratio 2] Individual studies had previously been included	**Limitations** It is not clear whether the authors of the individual studies had adjusted for confounders. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Stromberg,B., Dahlquist,G., Ericson,A., Finnstrom,O., Koster,M., Stjernqvist,K., Neurological sequelae in children born after in-vitro fertilisation: A population-based study, Lancet, 359, 461-465, 2002 **Ref ID** 90346 **Country/ies where the study was carried out** Sweden **Study type** Retrospective cohort study **Aim of the study** To retrospectively assess development of severe neurological sequelae, mental retardation, and severe visual defects in children born after IVF and in population-based controls. **Study dates** 1982 to 1995 **Source of funding** Supported by the Swedish National Board of Health and Welfare, through a task force of members of the board and of Sweedish gynaecologists, obstericians and paediatricians.	**Sample size** n = 5680 infants **Characteristics** Not reported **Inclusion criteria** 1] Children born between 1982, when the first Swedish child born after IVF was delivered , and December 31, 1995. **Exclusion criteria** Not reported	1] IVF 2] Non-IVF	The investigators did a population-based retrospective cohort study to ascertain the long-term neurological sequelae of children born after IVF in Sweden between 1982 and 1995. The National Board of Health and Welfare records the details of women, reported to them prospectively by the 14 IVF clinics which do IVF treatment in Sweden. Personal identification numbers of the women in the register were used to cross-reference this information with that recorded in the Swedish Medical Birth Registry, to identify children born after IVF and who survived the neonatal period. To ensure an accurate neurological diagnosis, only children aged 18 months or older at time of follow-up (1997) were enroled. For every child born after IVF two population-based controls were identified, selected from the Swedish Medical Birth Register, which were stratified for sex, year of birth, and birth hospital. Twenty six childhood disability centres in Sweden participated in the study. Children who	Odds ratios (95% CI) adjusted for sex, year of birth, and birth hospital <u>Cerebral palsy</u> IVF = 31/5680; Controls = 17/11,360. Odds ratio 3.7 (2.0 to 6.6) <u>Suspected developmental delay</u> IVF = 22/5680; Controls = 11/11,360. Odds ratio 4.0 (1.9 to 8.3) <u>Mental retardation</u> IVF = 7/5680; Controls = 18/11,360. Odds ratio 0.8 (0.3 to 1.9) <u>Chromosomal aberration</u> IVF = 9/5680; Controls = 15/11,360. Odds ratio 1.2 (0.5 to 2.7) <u>Behavioural disorders</u> IVF = 3/5680; Controls = 10/11,360. Odds ratio 0.6 (0.2 to 2.2)	**Limitations** 1] Retrospective study design 2] Results were not adjusted for family history **Other information** There was no significant difference in any of the outcomes when the results were analysed for multiples (twins). However, when the results were analysed for singletons, there were significantly more cases of cerebral palsy in IVF singletons compared to controls while all the other relevant outcomes were not significant.

			attended a habilitation centre had between one and five different neurological diagnoses. 138 different diagnoses were reported and classified into one of 20 groups: mental retardation, infantile autism, behavioural disorders, speech disorders, suspected developmental delay, cerebral palsy, congenital malformations, chromosomal aberrations, neuromuscular disorders, torticollis, brachial plexus injury, disorder of the joints, disorders of the eye, hearing loss, hydrocephalus, habitual tip-toeing, accidents, seizures, other neurological disorders, and other disorders.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bowen,J.R., Gibson,F.L., Leslie,G.I., Saunders,D.M., Medical and developmental outcome at 1 year for children conceived by intracytoplasmic sperm injection, Lancet, 351, 1529-1534, 1998 **Ref ID** 106508 **Country/ies where the study was carried out** Australia **Study type** Prospective cohort study **Aim of the study** To assess the medical and developmental outcome at 1 year of a cohort of children conceived by ICSI and to compare the physical and developmental outcome of these children with children conceived by conventionaly IVF and children conceived naturally. **Study dates** May 1993 to June 1995. **Source of funding** Not reported	**Sample size** n = 89 ICSI children n = 84 IVF children n = 80 naturally conceived children **Characteristics** Mean age of children = 13.7 months **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] ICSI 2] IVF 3] Natural conception	Children conceived by routine IVF and naturally, were recruited between September 1992 and September 1995, as part of a separate study assessing cognitive development and psycho-social adjustment of parents and their IVF concerned children during the first year of life. Children conceived by IVF were enrolled by approching women who had conceived by conventional IVF in the North Shore assisted reproductive technology programme at 28-30 weeks of pregnancy. Children conceived naturally were recruited by approaching women who were 28-30 weeks pregnant and were attenting the Royal North Shore Hospital for obstetric care. To match the parental age, parity, and multiplicity of pregnancy of the babies conceived by natural conception with the babies conceived by ICSI and routine IVF, only older primiparous women were invited to participate in the study. At birth, all children were assessed by a paediatrician or hospital doctor and information regarding the child's birth and	Mental development index (Mean ± SD) ICSI (range) = 95.9 ± 10.7 (64 to 123) IVF (range) = 101.8 ± 8.5 (82 to 122) Control (range) = 102.5 ± 7.6 (82 to 118); p <0.0001 Psychomotor development index (Mean ± SD) ICSI = 89.8 ± 16.6 IVF = 89.2 ± 15.1 Control = 88.3 ± 15.7; p = 0.861	**Limitations** 1] Likelihood of investigator bias 2] It is not clear whether the results were adjusted for confounding factors **Other information** 1] The mean age at follow-up was similar for each group. 2] Children conceived by ICSI differed from both IVF and naturally conceived children in being more likely to have fathers with an unskilled ocupation, the infestigtors did a subset analysis on those chldren whose fathers had a managerial, professional, or skilled occupation and excluded all infants whose fathers had an unskilled occupation but the results were not any different from the inital results.

			neonatal status was recorded in a personal-health record book which is provided for all children born in New South Wales. The parents of ICSI, IVF, and naturally conceived children were contacted soon after birth, and information was collected on the babies' sex, gestational age, birthweight, length, head circumference, Apgar scores at 1 min and 5 min, need for admission to a special-care or intensive-care baby unit, and presence of any major malformation noted by the paediatrician or hospital doctor on initial assessment. The children were formally assessed at 1 year, with children who were born prematurely being assessed at 1 year corrected age.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation Forman,R., Gill,S., Moretti,M., Tulandi,T., Koren,G., Casper,R., Fetal safety of letrozole and clomiphene citrate for ovulation induction, Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 29, 668-671, 2007 **Ref ID** 106944 **Country/ies where the study was carried out** Canada **Study type** Retrospective multicenter study **Aim of the study** The primary objective was to compare the malformation rates in the offspring of women who conceived using letrozole, women who conceived spontaneously (age-matched controls, and women who conceived using clomiphene citrate (disease-matched controls). The secondary objective was to compare other pregnancy outcomes (birth weight and gestational age at birth) among the three groups. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 383 babies **Characteristics** There were no statistically significant differences in the median maternal age at time of delivery or gestational age at birth when the letrozole, clomiphene and motherrisk group. **Inclusion criteria** Not reported **Exclusion criteria** Not reported	[1] Clomiphene [2] Letrozole [3] Motherrisk (natural conception)	This study reviewed the records of women who had delivered after using either letrozole or clomiphene citrate for ovulation induction during treatment at two fertility centres. Each woman in the letrozole group was matched by age with a control from the Motherisk database. All Motherisk controls conceived spaontaneously. In each group, data were analysed with and with out exclusion of multiples, and centriles for birthweight adjusted for gestational age.	<u>Malformation</u> Clomiphene: 7/271 (2.6%) Letrozole: 0/94 Motherisk: 3/112 (3.2%) There was no statistically significant difference in rate of malformations when the three groups were compared	**Limitations** Observational study **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hansen,M., Kurinczuk,J.J., Bower,C., Webb,S., The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization, New England Journal of Medicine, 346, 725-730, 2002 **Ref ID** 107086 **Country/ies where the study was carried out** Australia **Study type** Retrospective cohort study **Aim of the study** Not reported **Study dates** 1993 to 1997 **Source of funding** Supported by a research grang (6-FY98-497) from the March of Dimes Birth Defects Foundation, New York, and a program grant (003209) from the National Health and Medical Research Council of Australia.	**Sample size** Infants conceived with ICSI = 301 Infants conceived with IVF = 837 Infants conceived naturally = 4000 **Characteristics** Maternal age at delivery: ICSI = 32.6±4.0 years IVF = 34.1±4.6 years Natural conception = 28.2±4.4 years *Maternal age at delivery for IVF and ICSI were significantly higher than that of women that conceived naturally. **Inclusion criteria** 1] Approximately 90 percent of cases in the registry involve at least one major defect (with or without minor defects); the remainder involve minor defects only. 2] Birth defects diagnosed prenatally and in children up to six years of age are included **Exclusion criteria** 1] Most minor defects (listed article at http://www.nejm.org) are excluded from the registry; however, defects on the exclusion list that require treatment or are disfiguring are included.	1] ICSI 2] IVF 3] Natural conception	Data from the Reproductive Technology Register were used to identify all pregnancies of at least 20 weeks' gestation resulting from ICSI or standard IVF tretament undertaken between 1993 and 1997 and all terminations of such pregnancies because of fetal abnormalities. A random sample of 4000 infants born in Western Austrialia between 1993 and 1997 was selected after the exclusion of the infants conceived with assisted reproductive technology. The Midwives' Notification System collects information on all infants delivered in Western Australia at 20 weeks' gestation or later. The western Australian Birth Defects Registry collects information on birth defects occurring in liveborn and stillborn infants delivered in Western Australia, and on pregnancies terminated because of fetal malformations. Data collection: Automatch (probabilistic matching software) was used to link the records of the three registers. When linkage was complete, birth records were available for all infants in the study; records of birth defects were	Major birth defects; Odds ratio (95% CI) adjusted for maternal age and parity, the sex of the infant and correlation between siblings. Natural conception = 168/4000 (4.2%) ICSI = 26/301 (8.6%); Odds ratio 2.0 (1.3 to 3.2) IVF = 75/837 (9.0%); Odds ratio 2.0 (1.5 to 2.9)	**Limitations** Retrospective study. **Other information** 1] Results were reported differently for all singletons, term singletons and all infants but the was no difference in the results. 2] Major birth defects according to the organ system affected include cardiovascular, urogenital, musculoskeletal, gastrointestinal, central nervous system, chromosomal, metabolic and others. Others include Klippel-Trenaunay-Weber syndrome, Holt-Oram syndrome, infantile Marfan's syndrome, and nonimmune hydrops fetalis.

			available for those for whom a link was found within the Birth Defects Registry. To assess the potential effects of differential surveillance according to mode of conception, a list of all birth defects reported for each child was prepared without identification of whether conception was assisted or natural.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kallen,B., Finnstrom,O., Nygren,K.G., Olausson,P.O., In vitro fertilization in Sweden: child morbidity including cancer risk, Fertility and Sterility, 84, 605-610, 2005 **Ref ID** 107246 **Country/ies where the study was carried out** Sweden **Study type** Retrospective cohort study **Aim of the study** To study long-term morbidity among children conceived by IVF. **Study dates** 1982 to 2001 **Source of funding** Supported by a grant from the K. and A. Wallenberg Foundation	**Sample size** n = 16,280 infants **Characteristics** Median follow up time = 5.5 years **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] IVF 2] Non-IVF	The material consists of 16,280 infants born in Sweden during the period 1982 to 2001 who had been conceived after various types of IVF. Among them, 11,283 were born after standard IVF, 4,949 after ICSI, and 48 after other or unspecified methods. The mothers were identified from the Swedish IVF clinics, and the delivery outcome was obtained from the nationwide Medical Birth Register. Further links were established with the Hospital Discharge Register to identify hospitalisations of the children (1987 to 2002) and with the Swedish Cancer Register to study cancer occurrence (1982 to 2002). The study refers to the number of children hospitalised at any time and at various ages: first week of life, 1 week to 1 month, each month up to 6 months age, secong half of the first year of life, and subsequently each year of life, with an open upper class (11+ years). It also refers specifically to certain diagnoses, identified from the International Classification of Diseases diagnoses in the Hospital Dischar Register. Only admissions after the age of 7	Odds ratio (95% CI) adjusted for year of birth, maternal age, parity, and smoking Rate of Hospitalisations IVF = Not reported; population = not reported Odds ratio = 2.09 (2.0 to 2.2) Mental retardation IVF = 17 cases; population = 2,023 cases Odds ratio = 1.0 (0.5 to 2.0) Cerebral palsy IVF = 37 cases; population = 2,754 cases Odds ratio = 1.1 (0.7 to 1.8) Epilepsy IVF = 70 cases; Population = 5,767 cases Odds ratio = 1.5 (1.3 to 1.9) Behavioural problems IVF = 37 cases; Population = 3,657 cases Odds ratio = 1.6 (1.1 to 2.2) Convulsions IVF = 272 cases; Population = 12,459 cases Odds ratio = 1.5 (1.2 to 1.8) Sepsis IVF = 43 cases; Population = 3,388 Odds ratio = 1.1 (0.7 to 1.8)	**Limitations** Retrospective study design **Other information**

			days were studied for these diagnoses. Comparisons were made with corresponding data for all children in the Medical Birth Register. Children who developed cancer were identified by linkage with the nationwide Swedish Cancer Register, and the observed number of cases was compared with the expected number, estimated fro the cancer rate for all infants born in Sweden during these years.	Pneumonia IVF = 449 cases; Population = 42,293 cases Odds ratio = 1.1 (0.9 to 1.3) Appendicitis IVF = 64 cases; Population = 12,458 cases Odds ratio = 1.3 (0.9 to 1.9) Upper respiratory tract infection IVF = 891 cases; Population = 95,112 cases Odds ratio = 1.2 (1.1 to 1.3) Asthma/bronchitis IVF = 816 cases; Population = 61,572 cases Odds ratio = 1.4 (1.3 to 1.6) Any accident IVF = 2,234 cases; Population = 220,166 cases Odds ratio = 1.6 (1.5 to 1.7) Fracture IVF = 228 cases; Population = 32,969 cases Odds ratio = 1.1 (0.9 to 1.4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Klip,H., Burger,C.W., Kenemans,P., van Leeuwen,F.E., Cancer risk associated with subfertility and ovulation induction: a review. [196 refs], Cancer Causes and Control, 11, 319-344, 2000 **Ref ID** 107312 **Country/ies where the study was carried out** **Study type** Review **Aim of the study** To give a complete outline of the available literature available on cancer risk associated with subfertility and ovulation induction. **Study dates** Searches from 1 January 1966 to 1 November 1999 **Source of funding** The review was conducted within the framework of a larg Dutch cohort suty which is supported by grants from the Dutch prevention Fund, the Ministry of Health and the Netherlands Cancer Institute.	**Sample size** Unclear **Characteristics** NA **Inclusion criteria** 1. Only papers on subfertility and cancer risk that specifically examined the cause of subfertility were included 2. Additional papers were added by examining references of overview articles in the relevant fields. 3. No selection was made on the basis of inclusion/exclusion criteria and the quality of individual reports. **Exclusion criteria** No selection was made on the basis of inclusion/exclusion criteria and the quality of individual reports. Included studies of the review that are not reported here were excluded for the following reasons: 1] No specific drugs were reported 2] Results were reported as standard incidence ratio 3] Results had been reported in a more recent review or the individual studies have already been included in this question	1] CC 2] hMG 3] hMG + CC 4] hCG 5] CC + hCG 6] hMG + hCG 7] hMG + GnRH-agonist	Adjustment variables 1. Shushan et al was adjusted for Family history, age, parity, BMI, region of birth, education and interviewer 2. Mosgaard et al was adjusted for Family history, age, parity, area of residence, use of OC's, interuterine device, menopausal status, previous cancer, HRT, BMI 3. Ron et al: No information available so it is not clear whether the results are adjusted for confounders.	OVARIAN CANCER <u>Clomiphene citrate</u> Shushan et al = Odds ratio: 0.9; 95% CI: 0.3 to 2.3 Mosgaard et al = Odds ratio: 0.7; 95% CI: 0.2 to 2.0 <u>hMG</u> Shushan et al = Odds ratio: 3.2; 95% CI: 0.9 to 11.8 <u>CC/hMG</u> Shushan et al = Odds ratio: 1.4; 95% CI: 0.7 to 3.1 <u>CC/hCG</u> Mosgaard et al = Odds ratio: 1.2; 95% CI: 0.3 to 4.0 <u>hMG/hCG</u> Mosgaard et al = Odds ratio: 0.8; 95% CI: 0.2 to 3.7 BORDERLINE TUMOR Shushan et al CC = Odds ratio: 1.3; 95% CI: 0.3 to 6.9 hMG = Odds ratio: 9.4; 95% CI: 1.7 to 52.1 CC/hMG = Odds ratio: 3.1; 95% CI: 0.98 to 9.7	**Limitations** 1] No detailed description of the individual studies. 2] No information available on whether the result on breast cancer from Ron et al 1987 on breast cancer was adjusted for confounders. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Klip,H., Burger,C.W., de,Kraker J., van Leeuwen,F.E., OMEGA-project group., Risk of cancer in the offspring of women who underwent ovarian stimulation for IVF, Human Reproduction, 16, 2451-2458, 2001 **Ref ID** 107313 **Country/ies where the study was carried out** The Netherlands **Study type** Cross-sectional study **Aim of the study** To examine the late effects of hormon stimulation for IVF in treated women. **Study dates** January 1, 1980 and January 1, 1995 **Source of funding** Supported by grants from the Health Research and Development Counsel and the Ministry of Health.	**Sample size** n = 26,428 women n = 17,000 children **Characteristics** Maternal age ART and/or Fertility drugs = 33.6 ± 3.8 years Natural conception = 30.2 ± 6.1 years Age of child at end of follow-up ART and/or Fertility drugs = 4.6 ± 2.7 years Natural conception = 8.6 ± 5.2 years Duration of follow up ART and/or Fertility drugs = 4.6 ± 2.7 years Natural conception = 7.8 ± 4.7 years **Inclusion criteria** 1] Women had to be unable to achieve conception after ≥1 year of frequent unprotected intercourse and they had to be >18 years old at the time of their first visit to the fertility clinic. 2] Offspring were considered eligible for analysis if the duration of gestation was at least 26 weeks. 3] In case the mother had not indicated whether or not the	1] IVF 2] Non-IVF	The OMEGA-study is a nationwide cohort study of 26,428 women diagnosed with subfertility problems in 12 IVF clinics in the Netherlands. Women alive on January 1, 1997 were mailed a questionnaire to obtain information on gynaecological disorders before and after subfertility treatment, reporductive risk factors for hormon-related cancers and a number of other variables. Cohort members were traced through the Dutch Telephone Service Company and searches at municipal resident registries to assess vital status. The study population consisted of all offspring of women who returned questionnaires. Data collection: In each participating clinic, research assistants specifically trained for data collection in the study abstracted detailed information from the medical records on the type of subfertility of the parents. For each mother, subfertility was determined from the IVF clinic record and linked to the children's cohort. For each reported child, the questionnaire completed by the study participants	Relative risk (95% CI) adjusted for gender <u>Childhood cancer</u> Natural = 9 cases; Person years - 58,764; RR = 1.0 IVF = 5 cases; Person years - 34,302; RR = 0.8 95% CI = 0.2 to 2.4	**Limitations** 1] Selection and/or reporting bias since information was collected retrospectively **Other information** Maternal age of women in the study group was significantly higher than that of those in the control group. Children in the IVF group were younger and followed up for a significantly shorter time than children in the control group.

	child was born alive, the child had to weigh at least 1000 g to be included in the cohort **Exclusion criteria** 1] Death (n = 97) 2] Unknown, incomplete or foreign addresses (n = 495) 3] Specific reasons related to privacy (n = 66) 4] All reported miscarriages 5] All infants who were born dead 6] All children yet to be born at the time of the interview. 7] 78 pregnancies where it was unclear whether the child was born alive, missing information on duration of gestation and birthweight 8] Unknown gender, birth date, or exposure status 9] Children with a 15th birthday before January 1, 1980 and children who died before January 1, 1980		provided detailed information on the method of conception, the duration of gestation in weeks, date of birth, gender, birthweight and months of breast feeding. Information on cancer in the offspring was gathered in two separate sections of the questionnaire. The paediatrician was asked to provide information the date of diagnosis, morphology, clinical stage and pathological stage.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kristiansson,P., Bjor,O., Wramsby,H., Tumour incidence in Swedish women who gave birth following IVF treatment, Human Reproduction, 22, 421-426, 2007 **Ref ID** 107354 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** To compare the incidences of invasive and non-invasive tumours in women following pregnancy and live birth as a result of IVF treatment, with pregnancy and live birth without such treatment. **Study dates** 1 January 1981 to 31 December 2001 **Source of funding** Grants from the Emil Andersson fund for medical research	**Sample size** n = 647,704 women **Characteristics** Average age at first conception leading to delivery IVF women = 32.8 (3.7) years Non-IVF women = 26.7 (4.3) years **Inclusion criteria** 1] Women with live birth following pregnancy achieved by IVF treatment in a stimulated cycle, without or with ICSI, were allocated to the IVF group. 2] Women with live birth without such treatment were allocated to the non-IVF group. **Exclusion criteria** 1. Women with IVF treatment with ovum transfer in a natural cycle or frozen-thawed embryo transfer. 2. Women diagnosed with an invasive tumour before the first conception leading to birth.	1] IVF 2] Non-IVF	The investigators did not take into account women with repated pregnancies following IVF because the number of cases among women with multiple pregnancies were too few. Tumour cases were ascertained by record linkage. Groups of all invasive and all non-invasive tumours were formed, and women with multiple tumours registered were only counted once. Average time between date of conception and date of invasive tumour was 4.9 for IVF-group and 6.0 years for non-IVF group. For non-invasive tumour the average time was 2.7 for IVF and 3.1 for non-IVF group. Follow-up began at the time of first conception leading to a delivery and continued until date of tumour diagnosis, death, or the end of the observation period, whichever came first. Date of conception was estimated from ultrasonographic measurement in gestational week 18 or, when not available, from the date of last menstrual period. IVF treatment was handled as a time dependent variable, that is person-years were allocated to the non-IVF group until an IVF pregnancy occurred.	IVF/Non-IVF; Rate ratios (95% CI) standardised by age at follow-up, age at first conception, calendar year at follow-up, number of parities and multiple births Non-invasive tumour = 48/2,890; 0.9 (0.6 to 1.2) Invasive tumour = 41/1,565; 1.0 (0.7 to 1.4) CIS of the cervix = 35/2328; 0.9 (0.6 to 1.2) Breast = 13/617; 0.7 (0.4 to 1.3)	**Limitations** Average follow-up time of 7 years may be too short to reveal any possible carcinogenic effects of IVF treatment **Other information** Results reported reflect tumour incidence recorded at Date of conception plus 3 years. Results reported at Date of conception plus 1 year also showed no significant difference between IVF and non-IVF in all the tumours reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Leslie,G.I., Gibson,F.L., McMahon,C., Cohen,J., Saunders,D.M., Tennant,C., Children conceived using ICSI do not have an increased risk of delayed mental development at 5 years of age, Human Reproduction, 18, 2067-2072, 2003 **Ref ID** 107430 **Country/ies where the study was carried out** Australia **Study type** Cross-sectional study **Aim of the study** To determine the developmental outcomes for children conceived using ICSI, compared with groups conceived naturally or using IVF, at 5 years of age. **Study dates** Not reported **Source of funding** Supported by grants from The (Australian) Financial Markets Foundation for Children, Serono Australia Pty Ltd and North Shore ART (now IVF Australia)	**Sample size** n = 287 (ICSI = 97;IVF = 80;NC = 110) **Characteristics** Mean age = 60.8 months No difference in family history of developmental problems No difference in preterm births between the three groups There was a significantly lower number of naturally conceived twins compared to IVF or ICSI **Inclusion criteria** Singletons and twins **Exclusion criteria** 1] Refusal to participate 2] Children that were uncontactable at their last known address	1] ICSI 2] IVF 3] Natural conception	Details of the enrolment of ICSI, IVF and naturally conceived control children had previously been reported in the Bowen et el., 1998 study on 1-year outcomes for the cohort. Some of the children from the original cohort were not included in the study for reasons in the exclusion criteria section. Therefore Additional ICSI and naturally conceived children were enrolled to ensure adequate power for the study to confirm the 1-year findings. The additional ICSI children enrolled at 5 years of age were the next singleton or twin children conceived in the same ART programme after those enrolled in the original study. Also, the aditional naturally conceived children were enrolled from preschools in comunities that matched the demographics of the ICSI cohort. Method: Assessment of development at 1 year of age was performed using Bayley Scales of Infant Development. The test consists of two major scales: mental and psychomotor. The mental scale assesses memory, problem-solving and language	Performance IQ: ICSI (n = 97) = 112 ± 16 (79 to 155) IVF (n = 80) = 112 ± 13 (81 to 141) NC (n = 110) = 114 ± 13 (79 - 146) p = 0.66 Verbal IQ: ICSI (n = 97) = 107 ± 15 (78 to 148) IVF (n = 80) = 107 ± 12 (67 to 148) NC (n = 110) = 111 ± 14 (77 - 148) p = 0.10 Full-scale IQ: ICSI (n = 97) = 110 ± 18 (43 to 156) IVF (n = 80) = 111 ± 13 (77 to 149) NC (n = 110) = 114 ± 13 (77 - 147) p = 0.21	**Limitations** No limitations **Other information** 1] There was no difference in MDI between children lost to follow up at 1 year compared to those reassessed at 5 years. 2] There was one child in the ICSI group who was profoundly delayed and who could not be tested using the WPPSI-R; hence, the perfomrance of verbal IQ scores for this individual could not be reported. However, a full-cale IQ was determined using an alternative measure and this valuse is included in the analysis

			skills, and the psychomotor scale assesses conctrol of the fine and gross muscle groups. The child's perfomrance on these scales is used to determine mental development index and psychomotor development index. Assessment of mental development at 5 years was performed using the Wechsler Preschool and Primary Scales of Intelligence-Revised. The test consists of two majore scales: verbal, and performance. The verbal scales includes vocabulary, comprehension and arithmetic sckills. The performance scale includes visuo-spatial skills, copying designs and block patters, and attention to visual detail. The childs performance on these scales is used to determine a verbal intelligence quotient and a performance IQ. Blinding: The investigators testing the children were blinded to the 1-year results of those who were being re-assessed, and also to the study group. Statistical analysis: The study numbers provided 99% power to detect the same difference in six points in the mean full-scale IQ value at 5		

			years that was found for mean MDI values in the cohort at 1 year of age. The study numbers also provided 83% power to detect the actual difference of four points that was found at 5 years of age.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Marees,T., Dommering,C.J., Imhof,S.M., Kors,W.A., Ringens,P.J., van Leeuwen,F.E., Moll,A.C., Incidence of retinoblastoma in Dutch children conceived by IVF: an expanded study, Human Reproduction, 24, 3220-3224, 2009 **Ref ID** 107536 **Country/ies where the study was carried out** The Netherlands **Study type** Retrospective cohort study **Aim of the study** Not reported **Study dates** 1995 to 2001 **Source of funding** Supported by award VU 2004-3046 from the Dutch Cancer Society.	**Sample size** n = 165 patients **Characteristics** Not reported **Inclusion criteria** Patients with retinoblastoma who were diagnosed between 1 January 1995 and 31 December 2007. **Exclusion criteria** One patient that had retinoma and two patients that were lost to follow-up.	1] IVF conception 2] Non-IVF	From nationwide estimates of numbers of live births conceived by IVF from 1996 to 2007, the investigators estimated the expected numbers of patients with retinoblastoma conceived by IVF in the period 1995 to 2007. The actual(observed) number of children coneived by IVF among Dutch patients with retinoblastoma was obtained by questionnaires sent to the parents and from data in medical files. In total data was available for 1068 Dutch cases diagnosed from 1862. The registry is estimated to have had nationwide coverage since 1945. For each cohort member data were collected concerning demography, family history of retinoblastoma, tumour laterality, treatment for retinoblastoma, second and subsequent cancers and date and cause of death. Data collection: Questionnaires sent to the parents of patients with retinoblastoma diagnosed between 1995 and 2005 also included questions about number of pregnancies, infertility treatments, gestational age, pregnancy	Retinoblastoma IVF = 7/2.76 RR = 2.54 (1.0 to 5.2)	**Limitations** 1] The IVF registry is based on retrospective data obtained from the centres. Relevant data, such as numbers of embryos per transfer, complications, number of live births, congenital abnormalities and health of the child, are not registered. 2] Some assumptions were made to estimate the risk of retinoblastoma and the overall percentage of live births among children conceived by IVF, therefore, it is possible that the risk might have been overestimated or under-estimated. **Other information**

			outcome and birthweight. When the child with retinoblastoma was conceived by IVF, further information on number of IVF cycles, cause of infertility and other fertility treatments was collected and cross-checked at the fertility centres concerned. Since the early 2000s, parents of all newly diagnosed patients with retinoblastoma were asked whether the child was conceived by IVF or other fertility treatments, which was recorded into the medical file. For patients diagnosed after 2005 and the non-responders of the questionnaire, information on whether the child was conceived by IVF was obtained from these medical files. Information about the conception status recorded in the medical files and given in the questionnaires did not differ. The expected number of retinoblastoma cases in children conceived by IVF were calculated using the number of births and the 1-year age, sex and calendar year-specific mortality rates from the statistics Netherlands, and the age-and sex-specific retinoblastoma		

			incidence rates from the Netherlands Cancer Registry. The Rate ratio was calculated as the ratio of the observed to expected number of retinoblastoma diagnoses.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Montgomery,T.R., Aiello,F., Adelman,R.D., Wasylyshyn,N., Andrews,M.C., Brazelton,T.B., Jones,G.S., Jones,H.W.,Jr., The psychological status at school age of children conceived by in-vitro fertilization, Human Reproduction, 14, 2162-2165, 1999 **Ref ID** 107614 **Country/ies where the study was carried out** U.S.A **Study type** Cross-sectional study **Aim of the study** To assess the behavioural and psychological profiles of children conceived by IVF who are now at school age. **Study dates** 1981 to 1990 **Source of funding** not reported	**Sample size** n = 743 IVF children **Characteristics** Age = > 4 years **Inclusion criteria** Not reported **Exclusion criteria** 1] 39 children raised overseas	1] IVF 2] Control	A total of 787 IVF children were born at the institute and were all over 4 years old at the time of the study. Three questionnaire forms devised by T.M. Achenbach were used: The Achenbach Child Behaviour Checklist 4 to 18 years, The Teacher Report Form and the Youth Self Report form. A national sample of children was used as a control group in the Achenback questionaires. The youth self report form was sent to families with a child 11 years or older. The questionnaires were completed independently by parents, teachers and children (11 years or older). Achenbach defines scores that are less than the 95th percentile as 'normal'. However, for the purposes of the study, it was elected to narrow the definition of normal by using scores of less than the 85th percentile, that is one standard deviation above the mean, as the definition of normal. The control group for this study was the normative sample that was used for establishing the Achenbach behavioural questionnaires.	Percentage with normal scores (less than 85th percentile) Thought problems Control = 85; Male = 94.7; P-value = 1.0 Control = 85; Female = 92.8; P-value = 1.0 internalizing problems Control = 85; Male = 87.3; P-value = 0.8 Control = 85; Female = 86.6; P-value = 0.8 Externalizing problems Control = 85; Male = 94.3; P-value = 1.0 Control = 85; Female = 90.1; P-value = 1.0 Attention problems Control = 85; Male = 94; P-value = 1.0 Control = 85; Female = 92.7; P-value = 1.0 Social problems Control = 85; Male = 93.8; P-value = 1.0 Control = 85; Female = 97.4; P-value = 1.0	**Limitations** 1]It is not clear whether the results were precise as confidence intervals were not reported. 2] It is not clear whether the results were adjusted for confounding factors **Other information** 1] There was no difference between responders and non-responders. 2] When the outcomes were analysed by 'percentage with abnormal scores (greater than 95th percentile)' there was no significant difference in any of the outcomes between males or females born after IVF compared to control.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Morin,N.C., Wirth,F.H., Johnson,D.H., Frank,L.M., Presburg,H.J., Van,de Water,V, Chee,E.M., Mills,J.L., Congenital malformations and psychosocial development in children conceived by in vitro fertilization, Journal of Pediatrics, 115, 222-227, 1989 **Ref ID** 107624 **Country/ies where the study was carried out** U.S.A **Study type** Cross-sectional study **Aim of the study** To determine whether IVF as a method of conception is associated with an increased risk of congenital malformationsor developmental dysfunction. **Study dates** October 1983 to September 1984 **Source of funding** Not reported	**Sample size** n = 83 IVF subjects n = 93 non-IVF subjects **Characteristics** Age = 12 to 30 months **Inclusion criteria** Children ≥12 **Exclusion criteria** Not reported	1] IVF 2] Non-IVF	Data for the study were gathered by Eastern Virginia Medical School in Norfold, Virginia, under contract to the National Institute of Child Health and Human Development. non IVF subjects were randomly selected from the entire civilian obstetric population within a 100-mile radius of Norfold. To make the populations as comparable as possible in regard to known risk factors for congenital malformations, the case subjects and control subjects were matched by age of the infant (±3 months), multiple conceptions, sex, race and maternal age (±3 years). Parental education and income were matched when possible. A random number method was used to identify the most closely matched non-IVF infant, on the basis of labor, delivery and nursing records. The attending physician for each patient was asked whether there were any reasons not to ask the patient's family to take part. Each non-IVF subject was sent a letter explaining the nature of the study and an invitation to participate. Evaluations were performed by a	<u>Mental development index score</u> IVF = 115 ± 13 Non-IVF = 111 ± 13; p = 0.12 <u>Psychomotor development index score</u> IVF = 114 ± 14 Non-IVF = 108 ± 15; p = 0.04	**Limitations** 1] It is not clear whether the study was adequately powered and how precise the results are. **Other information** There were no significant differences between the two groups in matching factors

			multidisciplinary team of physicians who did not know whether the subject was an IVF or a non-IVF infant. Examinations were performed with a standard checklist protocol to ensure that the same defects would be sought in all subjects. With the exception of the cardiovascular portion, a single examiner performed each examination to reduce the problem of interobserver variability.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Pinborg,A., Loft,A., Schmidt,L., Greisen,G., Rasmussen,S., Andersen,A.N., Neurological sequelae in twins born after assisted conception: controlled national cohort study, BMJ, 329, 311-, 2004 **Ref ID** 107801 **Country/ies where the study was carried out** Denmark **Study type** Cross-sectional study **Aim of the study** To compare neurological sequelae in twins born after assisted conception with singletons after assisted conception and naturally conceived twins and to assess neurological sequelae in children conceived after IVF compared with ICSI. **Study dates** 1 January 1995 to 31 December 2000 **Source of funding** Danish Medical Research Council; Danish Hospital Foundation for Medical Research; Region of Copenhagen, the Faroe Islands and Greenland; and the Research Foundation of Queen Louise's Paediatric Hospital.	**Sample size** IVF-ICSI twins = 3393 Naturally conceived twins = 10,239 IVF-ICSI singletons = 5,130 **Characteristics** Mean children's age at follow up IVF-ICSI twins = 4.2 (1.7) years Control twins = 4.4 (1.7) years IVF-ICSI singletons = 4.1 (1.7) years *IVF-ICSI twins were significantly younger than the control twins **Inclusion criteria** 1] Children dying from delivery until 31 December 2000 in the cohorts **Exclusion criteria** Stillborn children	1] IVF-ICSI 2] Control	The Danish medical birth registry used in recording all births in Denmark to identify all women giving birth to twins and singletons within the study period. All citizens in Denmark have a unique identification number in the civil registration system. Identification of women in the birth registry was based on this number. Subsequently, a cross reference with the Danish registry for IVF enabled the investigators to dichotomise into women who coneived naturally or after IVF. A unique existing linkage between the identification number of a mother in the civil registration system and her children in the medical birth registry was used to establish the identification number of every individual child in the three cohorts. Records on fertilisation method and obstetric outcome were drawn from the compulsory IVF registry and the medical birth registry. Outcome measures: The investigators cross referenced the Danish patiens' registry to identify all children diagnosed or treated in a hospital setting from birth until 31 December	Odds ratio (95% CI) adjusted for (Child's sex and year of birth) <u>Cerebral palsy</u> IVF-ICSI twins = 11/3393 (0.3%) Control twins = 41/10,239 (0.4%); Odds ratio 1.2 (0.6 to 2.3) <u>Mental retardation diagnoses</u> IVF-ICSI twins = 19/3393 (0.6%) Control twins = 57/10,239 (0.6%); Odds ratio 1.0 (0.6 to 1.7) <u>Neurological sequelae (CP + mental retardation)</u> IVF-ICSI twins = 30/3393 (0.9%) Control twins = 98/10,239 (1.0%); Odds ratio 1.1 (0.7 to 1.6)	**Limitations** 1] Lack of data on the extent to which women in the group of naturally conceived twins had received ovarian stimulation with or without IUI **Other information**

			2002. They also established a database with files from the different registries with each individual child in the three cohorts as the key variable and entered the neurological and psychiatric diagnoses as outcomes.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Place,I., Englert,Y., A prospective longitudinal study of the physical, psychomotor, and intellectual development of singleton children up to 5 years who were conceived by intracytoplasmic sperm injection compared with children conceived spontaneously and by in vitro fertilization, Fertility and Sterility, 80, 1388-1397, 2003 **Ref ID** 107812 **Country/ies where the study was carried out** Belgium **Study type** Prospective cohort study **Aim of the study** To assess the somatic, psychomotor, and intellectual development of children conceived through ICSI over the whole preschool period. **Study dates** Not reported **Source of funding** Supported by a grant from the Belgian Natioal Fund for Scientific Research.	**Sample size** n = 66 ICSI Children n = 52 IVF Children n = 59 Spontaneously conceived (SC) Children **Characteristics** Maternal age (SD) = 31.9 (3.8) years Paternal age (SD) = 34.9 (6.3) years **Inclusion criteria** 1] Full term singletons **Exclusion criteria** 1] Pregnancies obtained after frozen and thawed ETs (either IVF or ICSI) as well as children with a birth weight of <2,500g	1] ICSI 2] IVF 3] Spontaneous conception	The population samples were families who rsorted to IVF or ICSI treatments at the fertility clinic of the Erasme hospital. For the spontaneously conceived children, families who gave birth in the matrnity ward of the Erasme Hospital were contacted. For the ICSI and IVF groups, the head of the fertility clinic wrote to these families well after the birth of the child and asked for their concent to participate in the prospective study that included a clinical follow-up of their child. All full-term singleton children conceived by ICSI that fell into the inclusion criteria over 24 months from April 1998 to March 2000 were contacted. The control groups were matched as closely as possible with the ICSI group with respect to date of birth, age and sex of the child, age of the mother, social class, ethnic background, family size and birth order of the child. Data collection: Information was gathered on the family background, the history of the couple's infertility, the pregnancy, the birth and the child's physical development, his or her medical history, as	Mean (SD) Intellectual assessments at 3 years of age adjusted for the levels of education of the parents Performance skills ICSI = 92.4 (12.6) IVF = 90.5 (14.7) SC = 100.6 (12.2) P value (Confidence interval) = 0.2 (91.7 to 97.9) Verbal skills ICSI = 97.2 (13.1) IVF = 94.1 (14.7) SC = 106.3 (14.7) P value (Confidence interval) = 0.1 (96.2 to 103) Intelligence quotient ICSI = 94.1 (12.7) IVF = 91.7 (15.4) SC = 103.9 (14.1) P value (Confidence interval) = 0.1 (93.7 to 100.3)	**Limitations** 1] At 3 years, there was at least 50% loss to follow up from each group. 2] It is not clear whether the study was powered enough to detect any differences at this stage **Other information** At 3 years, ICSI = 31 children, IVF = 19 children and SC = 27 children.

			well as demographic information on the family. The mothers also completed a questionnaire covering diseases and functional disorders.To avoid overreliance on self-report questionnairesin which parents might try to present their child in the best possible way, a multimethod design was used to gather information from several sources (parent, doctors, medical records) and by means of a variety of techniques		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Silver,R.I., Rodriguez,R., Chang,T.S., Gearhart,J.P., In vitro fertilization is associated with an increased risk of hypospadias, Journal of Urology, 161, 1954-1957, 1999 **Ref ID** 108064 **Country/ies where the study was carried out** U.S.A **Study type** Retrospective cohort study **Aim of the study** To determine if there is an increased incidence of hypospadias in male offspring conceived by IVF. **Study dates** 1988 to 1992 **Source of funding** Not reported	**Sample size** Conceived by IVF with hypospadias = 14 Non-IVF conception with hypospadias = 14 **Characteristics** Mean age of participants IVF group = 4.3±2.2 years Control = 3.4±2.0 years *No difference between both groups in terms of age, hamily history of hypospadias, family history of infertility, family history cryptorchidism or number of male twin but the IVF group had significantly higher gestational progestins. **Inclusion criteria** Not reported **Exclusion criteria** Six patients excluded from the control group due to an abnormal karyotype (n = 3), adoption and unavailable family history (n = 1), and unavailability for an interview (n = 1)	1] IVF 2] Non-IVF	The clinical data for the study were acquired in a retrospective chart review. The study design included all live male births conceived by IVF at the greater Baltimore Medical Centre (GBMC) from 1988 to 1992 as well as all patients with hypospadias after IVF referred to John Hopkins Hospital between 1988 and 1995. Control data were taken from contemporaneous patients with hypospadias seen at the pediatric urology clinic at Johns Hopkins Hospital without a history of IVF and statistics from the Maryland Birth Defects Registry from 1988 to 1994. Demographic and physical data were compared.	<u>Incidence of hypospadias (1988 to 1992)</u> IVF = 7/481 (1.5%) Non-IVF = 461/173,055 (0.3%) p-value = <0.001	**Limitations** 1] Retrospective study design 2] Sample size **Other information** There was a significant difference in the exposure of fetus to exogenous maternal progestin in the IVF group and exposure to progestins has been reported to be a risk factor for hypospadias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Venn,A., Hemminki,E., Watson,L., Bruinsma,F., Healy,D., Mortality in a cohort of IVF patients, Human Reproduction, 16, 2691-2696, 2001 **Ref ID** 108288 **Country/ies where the study was carried out** Australia **Study type** Prospective cohort study **Aim of the study** To compare the mortality rates of women who received IVF treatment, as well as those who were referred but were not treated, with the mortality rate in the general female population, to determine the maternal mortality rate following IVF conception and to establish whether any deaths had occurred as a result of treatment complications. **Study dates** Not reported **Source of funding** Supported by grants from the Kathleen Cuningham Foundation, the Fertility Society of Australia, the Anti-Cancer Council of Victoria and IVF Friends.	**Sample size** n = 29,700 women **Characteristics** Median age at entry (range) = 32 (18 - 54) years **Inclusion criteria** Not reported **Exclusion criteria** Not reported	1] IVF 2] Non-IVF	The cohort consisted of 29,700 women who registered with at least one of 10 Australian IVF clinics before January 1, 1994. Details of the cohort study methodology have been described elsewhere. Clinics provided electronic data including patient's name, date of birth, address, date of registration with the clinic and dates and types of treatment. Date on IVF conceptions and pregnancy outcomes were not included in the electronic dataset. Women who commenced at least one treatment cycle, including natural cycles without ovarian stimulation, were classified as treated (n = 21,086). Women classified as untreated were those who were registered for IVF but did not commence treatment (n = 8614). The reasons why women did not start IVF treatment were not routinely recorded, but included the occurrence of pregnancy while on the waiting list, pursuit of other treatment options, relationship or financial difficulties and change of mind for other personal reasons. Ascertainment of deaths: Ascertainment of deaths from	Standard mortality ratios (95% CI) All Causes of death: IVF treated = 0.6 (0.48 to 0.69) Not treated = 0.6 (0.5 to 0.8) Diseases of the cirulatory system IVF treated = 0.4 (0.3 to 0.7) Not treated = 0.7 (0.3 to 1.2) Injury and poisoning IVF treated = 0.52 (0.4 to 0.8) Not treated = 0.5 (0.3 to 0.7) Suicide IVF treated = 0.3 (0.2 to 0.6) Not treated = 0.6 (0.3 to 1.2) All neoplasms IVF treated = 0.7 (0.6 to 0.9) Not treated = 0.7 (0.5 to 1.0) Breast cancer IVF treated = 1.1 (0.8 to 1.7) Not treated = 0.7 (0.4 to 1.2)	**Limitations** It is not clear whether the results were adjusted for confounding factors or not **Other information**

			all causes was by record-linkage with the NDI for women residing in all Australian States and Territories except South Australia. The NDI contains records on deaths that have occurred in Australia since 1980. Where a death occurred within 12 months of IVF treatment in a woman who had not conceived with treatment, and of causes that could be related to IVF treatment, further information was sought from the death certificate and from the IVF clinic records to investigate whether there appeared to be a causal relationship.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zreik,T.G., Mazloom,A., Chen,Y., Vannucci,M., Pinnix,C.C., Fulton,S., Hadziahmetovic,M., Asmar,N., Munkarah,A.R., Ayoub,C.M., Shihadeh,F., Berjawi,G., Hannoun,A., Zalloua,P., Wogan,C., Dabaja,B., Fertility drugs and the risk of breast cancer: a meta-analysis and review, Breast Cancer Research and Treatment, 124, 13-26, 2010 **Ref ID** 108451 **Country/ies where the study was carried out** Lebanon, USA **Study type** Meta-analysis **Aim of the study** To determine the relationship between fertility drugs used in assisted reproductive procedures and the risk of breast cancer. **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 22 studies n = 61 to 29,700 women in total Bernstein et al Braga et al Burkman R et al Brinton LA et al Calderon-Margalit et al Dor et al Doyle et al Gauthier E et al Jensen A et al Kotospoulos et al Kristiansson et al Lerner-Geva L et al Lerner-Geva L et al Modan B et al Orgeas et al Pappo et al Potashnik et al Ricci et al Ron et al Rossing MA et al Terry et al Ven A et al **Characteristics** **Inclusion criteria** **Exclusion criteria**	[1] CC (11 studies) [2] CC + hMG (4 studies) [3] Other specific drugs - hCG, hMG, hMG + GnRH, GnRH, Gonadotrophins (11 studies)	Because the number of fertility treatment cycles was reported as ranges in the original articles, the mid point of each range was used as the number of treatment cycles for each cohort. Also, because the duration of follow up was reported in various ways, the meadian follow-up duration was used and the mid point of follow-up intervals were used to represent the duration of follow up.	<u>Breast cancer</u> [1] CC (11 studies): Risk Ratio (95% CI) = 1.08 (0.98 to 1.19); Overall (I^2 = 3.3%, p = 0.41) [2] CC + hMG (4 studies): Risk Ratio (95% CI) = 1.19 (0.96 to 1.48) Overall (I^2 = 0%, p = 0.75) [3] Other specific drugs - hCG, hMG, hMG + GnRH, GnRH, Gonadotrophins (11 studies): Risk Ratio (95% CI) = 0.99 (0.89 to 1.11) Overall (I^2 = 0.7%, p = 0.45)	**Limitations** [1] The inability of the studies to adjust for the essential factors in the etiology of breast cancer [2] The heterogeneity of the studies [3] The nature of some of the included studies with the inherent weaknesses in their design. **Other information** 1] The studies that reported on the use of GnRH analogues, it is not clear what type of GnRH analogue was used.

	[1] CC (duration of follow up) Jensen A et al (2007) - 8.8 years follow up Lerner-Geva L et al (2003) - 6.5 years follow up Burkman R et al (2003) - Missing Kotospoulos (2008) - Missing Ven A et al (1995) - 5.2 years follow up Gauthier E et al (2004) = 9.7 years follow up Modan B et al (1998) - 21.4 years follow up Brinton LA et al (2004) - 18.5 years follow up Lerner-Geva L et al (2006) - 20.9 years follow up Calderon-Margalit et al (2009) - 29 years follow up Orgeas et al (2009) - >30 years follow up Rossing MA et al (1996) - 11.3 years follow up [2] CC + hMG Venn A et al (1999) - 10 years follow up Lerner-Geva L et al (2003) - 6.5 years follow up Modan B et al (1998) - 21.4 years follow up Orgeas et al (2009) - >30 years follow up Lerner-Geva L et al (2006) - 20.9 years follow up Study type				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation Hvidtjorn,D., Grove,J., Schendel,D., Schieve,L.A., Svaerke,C., Ernst,E., Thorsen,P., Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study, Journal of Epidemiology and Community Health, 65, 497-502, 2011 **Ref ID** 123233 **Country/ies where the study was carried out** Denmark **Study type** Retrospective cohort **Aim of the study** To assess the risk of autism spectrum disorders in children born after assisted conception compared with children born after natural conception. **Study dates** 1 January 1995 to 31 December 2003 **Source of funding** The study was funded as a co-financed PhD project by the Danish Agency for Science, Technology and Innovation, University of Aarhus and the Elsass Foundation. Further funding was supplied by Sofiefonden, The Health Insurance Foundation, The	**Sample size** n = 588,967 children n = 18,148 children from OI **Characteristics** Median follow-up time (range) = 9 (4 to 13) years **Inclusion criteria** Not reported **Exclusion criteria** 1] 10,137 children born to mothers aged <20 years	1] Downregulation 2] FSH 3] CC 4] Clomiphene citrate	Recruitment: The study was based on data from Danish National Registers and linkage between the registers was achieved by use of the unique registration number given to all citizens in Denmark. It comprised all children born alive in Denmard from 1 January 1995 to 31 December 2003, identified through the Danish Medical Birth Register (MBR) which contains information on all births in Denmark. Data collection: Children exposed to IVF were identified through the IVF register which holds data from all private and public fertility clinics including underlying causes of infertility. Children exposed to ovulation induction were identified through the Danish Drug Prescription Register (DDPR) which holds information on all prescription drugs sold at pharmacies in Denmark. The medications used during ovulation induction are prescription drugs bought at the pharmacy, enabling identification of the women who went through OI in the DDPR. Drugs used in assisted conception were identified by the authors by cross-checking	Autism spectrum disorder Downregulation: Hazard rate ratio = 1.09; 95% CI = 0.48 to 2.51 FSH: Hazard rate ratio = 1.29; 95% CI = 0.89 to 1.89 hCG: Hazard rate ratio = 1.17; 95% CI = 0.79 to 1.71 CC: Hazard rate ratio = 0.82; 95% CI = 0.53 to 1.28	**Limitations** **Other information**

Augustinus Foundation, Julie von Mullens Foundation, Director Jacob Madsen and Hustru Olga Madsens Fond and Aase and Ejnar Danielsen Foundation			with the official Danish Pharmaceutical Classified Catalogue, www.medicin.dk, the US website www.drugs.com, books of instruction of Danish fertility clinics from the time period in question and by means of clinical experience. To identify women who had hormonal treatment in relation to the index pregnancy, we set up a time window for the date of dispatch of 12 weeks before and 4 weeks after the last menstrual period. As the drugs used in OI are also used in IVF, women from OI group who were included in the IVF Register with the same LMP date were excluded. Children with a diagnosis of ASD or specifically, infantile autism up to 8 May 2008 were identified via the Danish Psychiatric Central Register (DPCR). The DPCR contains information on all Danish psychiatric inpatient and outpatient admissions since 1995, and in Denmark all autism diagnoses are made at publich child mental health services, reporting all inpatient and outpatient discharge diagnoses to the DPCR Statistical analysis: The		

			hazard rate ratios were adjusted for maternal age, education, parity, smoking, body weight and multiplicity.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lerner-Geva,L., Geva,E., Lessing,J.B., Chetrit,A., Modan,B., Amit,A., The possible association between in vitro fertilization treatments and cancer development, International Journal of Gynecological Cancer, 13, 23-27, 2003 **Ref ID** 123351 **Country/ies where the study was carried out** Israel **Study type** Cross-sectional study **Aim of the study** To evaluate the cancer incidence in a cohort of infertile women treated with IVF, with special attention to women who were diagnosed with cancer within the first year of the IVF treatment. **Study dates** 1984 to 1992 **Source of funding** Not reported	**Sample size** n = 1082 women **Characteristics** Female age at the first IVF treatment = 32.7 ± 4.8 years Mean years of follow-up = 6.5 ± 2.2 years **Inclusion criteria** 1] Patients attending the IVF unit who received at least one treatment cycle **Exclusion criteria** 1] Cancer cases that were diagnosed within one year of the initiation of IVF treatment were excluded from the analyses	IVF	Recruitment: The study cohort included women who were treated for infertility within the study period at an IVF unit in Tel Aviv. The patients were identified from the medical records of the unit and obtained data on demographic characteristics as well as information regarding the type of infertility, diagnosis of infertility, number of treatment cycles and treatment outcome, using a preconstructed questionnaire. Data collection: The study cohort computerised file was linked to the national cancer registry oto identifie cancer cases. The records were linked by computer matching in patients' identification numbers, names, and demographic variables with the cancer registry data file. Expected numbers of cancer were computed based on age, sex, continent of birth, and year-specific national cancer incidence rates	All sites: Observed = 16 Expected = 11 SIR (95% CI) = 1.5 (0.8 to 2.4) Breast: Observed = 4 Expected = 4.9 SIR (95% CI) = 0.8 (0.2 to 2.1) Ovary: Observed = 1 Expected = 0.6 SIR (95% CI) = 1.7 (0 to 9.3) Cervix: Observed = 3 Expected = 0.7 SIR (95% CI) = 4.6 (0.9 to 13.5) Other (melanoma, hodgkin's lymphoma, multiple myeloma, angiosarcoma, brain, sarcoma): Observed = 8 Expected = 4.9 SIR (95% CI) = 1.6 (0.7 to 3.2)	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Brandes,J.M., Scher,A.I, Itzkovits,J., Thaler,I., Sarid,M., Gershoni-Baruch,R., Growth and development of children conceived by in vitro fertilization, Pediatrics, 90, 424-429, 1992 **Ref ID** 147858 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort study **Aim of the study** To assess the physical and mental development of infants born after IVF. **Study dates** February 1985 to March 1989 **Source of funding** Not reported	**Sample size** n = 116 children 66 singletons 19 pairs of twins, and 4 sets of triplets **Characteristics** Age: IVF = 22.4±10.3 months Control = 24±11.8 months **Inclusion criteria** Only Hebrew speaking children **Exclusion criteria** 11 Arab speaking children were excluded because of language barriers. 6 children who lived abroad	IVF	Recruitment: The study population included IVF children that were born within the study period that were over the age of one year. To each IVF child a control, non-IVF child, was matched for birth weight, gestational age, birth orger, order in multiple delivery, mode of delivery, sex, age and maternal age and education. Data collection: Data on age, education, parity, and medical and obstetrical history of mothers were obtained by interview and by review of the obstetrical and medical records. Data on gestational age, mode of delivery, Apgar scores, and measurements of weight, length, and head circumference of newborns at birth were retrieved from delivery records. Data concerning the physical and psychomotor development of the children were obtained from child welfaire clinic records. Weight, recumbent croun-to-heel length until 2 years of age, and standing height after 2 years of age were computed for each child using the table sof Tanner et al. Head circumference was computed for each child with	Weight (p = NS) IVF (n:116) = 32.6±28.7 Control (n:116) = 36.1±38.5 Head circumference (p = NS) IVF (n:116) = 45.5±22.5 Control (n:116) = 45.9±23.1 Body length (p = NS) IVF (n:116) = 39.3±29.0 Control (n:116) = 40.9±28.3 Mental developmental index score (p = NS) IVF (n: 84) = 106±19.6 Control (n: 84) = 110.6±19.3 Composite index score (p = NS) IVF (n: 31) = 106.2±8.0 Control (n: 31) = 104.4±10.2	**Limitations** Retrospective study design **Other information** The outcomes were compared in IVF singletons and non-IVF singletons and the results were not significant. The same results were obtained when multiples were compared.

			the charts of Nelhaus. Measurements of length at birth were not evaluated because the investigators did not regard them to be sufficiently accurate. Methodology: All the children were examined in a double-blind manner by the same clinical psychologist and paediatrician. The parents' interview was recorded on a pre-prepared protocol. Eighty-five children 12 to 30 months of age were assess on the Bayley scale. Thirty one children, 30 to 45 months of age were assessed by the Stanford-Binet Intelligence Scale.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Moll,A.C., Imhof,S.M., Cruysberg,J.R., Schouten-van Meeteren,A.Y., Boers,M., van Leeuwen,F.E., Incidence of retinoblastoma in children born after in-vitro fertilisation., Lancet, 361, 309-310, 2003 **Ref ID** 147860 **Country/ies where the study was carried out** Netherlands **Study type** Cross-sectional study **Aim of the study** Not reported **Study dates** November 2000 to February 2002 **Source of funding** Not reported	**Sample size** Not reported **Characteristics** Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	IVF	In this study, the ratio of observed to expected numbers of retinoblastoma cases was calculated using data from the Dutch retinoblastoma registry and the Netherlands cancer registry. Incidence of the disease was 2.6 per 100,000 children in the first year of life, 0.9 per 100,000 in those aged between 1 and 4 years, and 0.1 per 100,000 in 5 to 9 year olds. In the Netherlands, an estimated 1 to 1.5% of children are conceived after IVF. The investigators calculated tha 0.69 retinoblastoma cases would be expected in children conceived after IVF between 1995 and 2001 using numbers of births since 1995 and the 1-year age-specific mortality rates in the Netherlands, the estimate that 1% of all births are conceived by IVF, and the sex-specific and age-specific retinoblastoma incidence rates.	Retinoblastoma (observed/expected cases: standardised incidence ratio (95% CI) IVF = 5/0.69: 7.2 (2.4 to 17.0)	**Limitations** Results are based on assumptions therefore, may either be underestimated or overestimated. **Other information** None of the patients had a history of retinoblastoma

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Raoul-Duval,A., Bertrand-Servais,M., Letur-Konirsch,H., Frydman,R., Psychological follow-up of children born after in-vitro fertilization, Human Reproduction,Hum.Reprod., 9, 1097-1101, 1994 **Ref ID** 147861 **Country/ies where the study was carried out** France **Study type** Prospective cohort study **Aim of the study** To compare a group of IVF infants and mothers individually paired with two control groups. **Study dates** 1987 to 1989 **Source of funding** Not reported	**Sample size** At 9 months, n = 93 parent-infant At 18 months, n = 83 parent-infant At 3 years, n = 49 parent-infant **Characteristics** Groups were pared according to: parity, socio-economic status, mother's age and number of children. Throughout the study period, there was no significant difference in number of working mothers, maternal depression or additional pregnancies between the three groups **Inclusion criteria** All children included in the study were singleton and delivered at term. **Exclusion criteria** Twins	IVF = 25 mothers Sterility = 11 mothers Natural conception = 13 mothers	33 IVF couples and thier children born within the study period were investigated. Each IVF parent-infant group was paired with two control groups. The first control group comprised one parent-invant group of 33 patients with a history of sterility (ovarian stimulation without IVF) and the second was a one parent-infant group of 33 patients in which conception occurred naturally without any special difficulties. Data collection: The study was based on four interviews of each couple conducted over a period of 3 years. These groups were seen in the hospital after delivery, then at home after 9 months, 18 months and 3 years. Each assessement involved a semi-directive interview and a questionnaire. The interview noticed: the past of the mother and the relationship with her family; the story of the sterility and the medical course; the somatic and psychological development during pregnancy; the eventual delivery problems; the relation with the newborn. Questionnaires and interviews were accompanied at 9	Results at 3 years Infant illness (p = NS) IVF = 23/25 (92%) Sterility = 10/11 (91%) Control = 13/13 (100%) Infant accidents (p = NS) IVF = 5/25 (20%) Sterility = 1/11 (9%) Control = 4/13 (31%) Infant insomnia (p = NS) IVF = 4/25 (16%) Sterility = 0/11 (0%) Control = 3/13 (23%) Feeding difficulties (p = NS) IVF = 6/25 (24%) Sterility = 3/11 (27%) Control = 2/13 (15%) Mother-child relationship (p = NS) IVF = 2/25 (8%) Sterility = 0/11 (0%) Control = 1/13 (7%)	**Limitations** 1. Risk of attrition bias: no comparison was made between patients that were lost and those that continued 2. Small sample size **Other information** The results remained non-significant when children were examined at 9 months, 18 months and 36 months.

			months, 18 months and 3 years by the Brunet-Lezine test. Subjects were lost after at least three unanswered letters and/or regularly missed appointments		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation van Leeuwen FE, Klip H, Mooij TM, van de Swaluw AM, Lambalk CB, Kortman M, Laven JS, Jansen CA, Helmerhorst FM, Cohlen BJ, Willemsen WN, Smeenk JM, Simons AH, van der Veen F,Evers JL, van Dop PA, Macklon NS, Burger CW., Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort., Human Reproduction, 2011 **Ref ID** 151913 **Country/ies where the study was carried out** Netherlands **Study type** Prospective cohort **Aim of the study** The risk of ovarian malignancies in the IVF group was compared with risks in the general population and the subfertile comparison group The risk of ovarian malignancies in the IVF group was compared with risks in the general population and the subfertile comparison group	**Sample size** 19861 women who underwent IVF; 6604 women with subfertility who did not undergo IVF. **Characteristics** IVF group (n =19 146), Non-IVF group (n = 6006), Total (n = 25152) Age at first IVF treatment or visit (years) ≤26 yrs: 1425 (7.4) 1159 (19.3) 2584 (10.3) 27–29 yrs: 3015 (15.7) 1233 (20.5) 4248 (16.9) 30–32 yrs: 4929 (25.7) 1339 (22.3) 6268 (24.9) 33–35 yrs: 4711 (24.6) 1152 (19.2) 5863 (23.3) ≥36 yrs: 5066 (26.5) 1123 (18.7) 6189 (24.6) Subfertility diagnosis - n (%) Tubal: 6025 (31.5) 1938 (32.3) 7963 (31.7) Endometriosis: 1970 (10.3) 349 (5.8) 2319 (9.2)	IVF protocols were not outlined in detail.	Ethics approval granted. Patient questionnaire to identify history and risk-factors Medical record abstraction to identify IVF protocol used Linkage of patient records with Netherlands Cancer Registry for ovarian cancer and Dutch nationwide network and registry of histo- and cytopathology for borderline cases. Standardized incidence ratio and Cox proportional hazard ratios produced. Case-mix adjustment based on forward stepwise confounder selection.	61 and 55 16 and 13 77 and 68 IVF group Person years All ovarian malignancies Invasive ovarian cancer Borderline ovarian tumours Obs Exp SIR 95% CI Total number of IVF cycles 1–2 cycle(s) 82 599 1.50 0.93–2.29 1.35 0.68–2.42 1.70 0.97–3.74 3–4 cycles 84 025 1.52 0.95–2.30 1.19 0.57–2.18 1.99 1.22–4.14 ≥5 cycles 47 661 1.42 0.74–2.49 1.41 0.57–2.90 1.45 0.47–3.38 Subfertility diagnosis Tubal 84822 2.34 1.63–3.25 1.69 0.94–2.78 3.30 2.02–5.10	**Limitations** 1. Analysis based in IVF protocols from 1983 to 1995. Protocols have changed substantially since this preiod, so generalisibility of findings is limited. 2. Severity of subfertility could differ between groups. 3. Poor response to patient questionnaires 4. Low absolute event rates means small changes can have significant effect on relative rates. **Other information**

Study dates Women who received IVF between 1983 and 1995, and comparison group of subfertile women who did not receive IVF between 1980 and 1995. Follow-up until June 2007. **Source of funding** This study was supported by grants from the Health Research and Development Counsel (28–2540) and the Dutch Ministry of Health. Funding to pay the Open Access publication charges for this article was provided by the Netherlands Cancer Institute.	Male factor: 5492 (28.7) 809 (13.5) 6301 (25.1) Hormonal factor: 1287 (6.7) 409 (6.8) 1696 (6.7) Unexplained: 3412 (17.8) 537 (8.9) 3949 (15.7) Other factors: 912 (4.8) 360 (6.0) 1272 (5.1) Missing: 3309 (17.3) 2388 (39.8) 5697 (22.7) Number of IVF treatments 1–2 cycles: 6304 (32.9) 3–4 cycles: 6271 (32.8) 5 or more cycles: 3352 (17.5) Missing: 3219 (16.8) **Inclusion criteria** <u>IVF group</u> Women who underwent IVF in Netherlands between 1985 and 1995. Were able to link records to national cancer registry. <u>Subfertility group</u>			Endometriosis 26853 3.05 1.67–5.12 3.73 1.79–6.86 2.10 0.57–5.38 Male factor 70793 1.39 0.79–2.25 1.67 0.83–2.99 1.01 0.33–2.36 Hormonal factor 16 873 1.14 0.23–3.32 1.34 0.16–4.84 0.87 0.02–4.86 Unexplained 45 846 0.63 0.20–1.46 0.64 0.13–1.88 0.61 0.07–2.19 Other factors 12 005 1.98 0.54–5.07 1.71 0.21–6.19 2.35 0.28–8.48 Previous FD use No 95782 1.84 1.20–2.69 1.08 0.49–2.05 2.93 1.71–4.69 Yes 109149 1.30 0.79–2.01 1.69 0.95–2.79 0.77 0.25–1.79 Missing 49297 1.23 0.56–2.33 0.93 0.25–2.38 1.65 0.53–3.85	

	Women who did not undergo IVF in four clinics during 1980 and 1995. Were able to link records to national cancer registry. **Exclusion criteria** N/A			Parity Nulliparous 86058 1.87 1.20–2.79 1.19 0.54–2.25 2.86 1.60–4.72 Parous 123242 1.21 0.75–1.85 1.40 0.76–2.34 0.95 0.38–1.96 Missing 44928 1.50 0.72–2.75 1.28 0.41–2.98 1.81 0.59–4.22 Total no. of ampoules hMG/FSH No association found Total no. of oocytesg No association found Mean no. of oocytes 0–3 oocytes 21 468 1.57 0.58–3.43 1.25 0.26–3.65 2.12 0.44–6.20 4–6 oocytes 46 899 1.91 1.05–3.21 1.60 0.64–3.29 2.39 0.96–4.93	

				≥7 oocytes 100 747 1.12 0.63–1.85 0.80 0.29–1.74 1.54 0.70–2.92 Missing 85 113 1.61 0.98–2.49 1.66 0.86–2.90 1.55 0.67–3.05 Maximum no. of oocytesg No association found Adjusted HRs for cancer risk in IVF group versus non-IVF group Hazard ratio (95% CI): Overall; ≥1 year ; ≥10 years All ovarian malignancies: 2.05 (1.10–3.82) 2.14 (1.07–4.25) 2.08 (0.86–5.00) Invasive ovarian cancer: 1.14 (0.54–2.4)1 1.51 (0.65–3.54) 2.26 (0.78–6.55) Borderline ovarian tumours: 6.38 (2.05–19.84) 4.23 (1.25–14.33) 2.26 (0.46–11.05)	