Interventional procedure overview of removal, preservation and reimplantation of ovarian tissue to restore fertility after gonadotoxic treatment

Contents

Table 1 Abbreviations

Abbreviation	Definition
CI	Confidence interval
FSH	Follicle-stimulating hormone
IVF	In-vitro fertilisation
MD	Mean difference
OTC	Ovarian tissue cryopreservation
OTT	Ovarian tissue transplantation

Indications and current treatment

Some treatments for cancer or other medical conditions can damage the ovaries (gonadotoxic treatment). This can lead to early menopause and infertility.

There are a number of pharmacologic and surgical strategies that aim to reduce the risk of infertility after gonadotoxic treatment, including ovarian transposition, ovarian suppression, and fertility-sparing surgery.

Cryopreservation of oocytes or embryos before starting treatment are options for women who wish to preserve their fertility. These both involve ovarian stimulation, which may lead to a delay in treatment. For embryo cryopreservation there is also a need for sperm from either a partner or sperm donor.

What the procedure involves

Before starting gonadotoxic treatments, ovarian tissue is removed surgically through laparoscopy, mini-laparotomy, or laparotomy. Usually, at least half of one ovary is removed and the other ovary is left in place to act as a site for future orthotopic autotransplantation. After histological examination of a portion to exclude malignancy, most of the excised ovarian tissue is frozen for future autotransplantation.

When indicated, the frozen cortical ovarian tissue is thawed and transplanted back to the same person. It can be placed into pelvic sites such as the remaining ovary, ovarian fossa, or broad ligament (orthotopic autotransplantation) through laparoscopy or mini-laparotomy. Alternatively, it can be placed into extrapelvic sites such as the subcutaneous space of the abdominal wall or forearm (heterotopic autotransplantation). In this case, the follicle and oocyte develop

outside the usual environment, so subsequent ovarian stimulation, egg collection, and in vitro fertilisation are needed to achieve pregnancy. Another technique involves the vascular grafting and anastomosis of a frozen-thawed whole ovary through mini-laparotomy or laparotomy.

Future pregnancies may require assisted reproduction technologies, although the procedure can offer the possibility of natural conception.

Ovarian stimulation is not needed before removal of ovarian tissue for autotransplantation and gonadotoxic treatment can start immediately afterwards. It may be the only fertility preservation option suitable before puberty or for people with oestrogen-sensitive malignancies.

Outcome measures

The main outcomes included pregnancy rate, live birth rate, miscarriage rate, endocrine function, resumption of menstruation, method of conception and duration of graft function.

Evidence summary

Population and studies description

This interventional procedures overview is based on about 550 transplantation procedures from 3 systematic reviews, 1 retrospective cohort study, 1 multicentre case series and 1 registry analysis. Some patients had more than 1 OTT and there is patient overlap between the studies. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 6 studies as the key evidence in table 2 and table 3, and lists 78 other relevant studies in table 5.

The systematic review by Ni Dhonnabhain et al. (2022) included 39 studies on patients with cancer, 24 of which reported outcomes for ovarian tissue cryopreservation. Studies on embryo cryopreservation and oocyte cryopreservation were also included. According to the Newcastle-Ottawa scale, 21 studies were of good quality, 10 were fair and 8 were poor (6 of which were on ovarian tissue cryopreservation). Of the 24 studies on ovarian tissue cryopreservation, only 6 were described as prospective.

The systematic review by Gellert et al. (2018) reported outcomes from 360 procedures in 318 women published in peer-reviewed papers in combination with data from a Danish cohort. Evidence came from 21 countries, including Europe, North America, South America, Asia and Australasia. The mean age at

OTC was 28.9 years and the mean age at first transplant was 33.5 years. Among the diagnosis, breast cancer and haematological malignancies, were the main reasons for fertility preservation but non-malignant conditions were also included.

The systematic review by Khattak et al. (2022) included 87 studies with 735 women, 568 of whom were included in the meta-analysis. All studies that reported fertility or endocrine outcomes from either fresh or frozen–thawed ovarian transplants were included. Evidence came from many countries including Europe, North America, South America, Asia and Australasia. Of the 319 women for whom age at OTC was reported, 283 (89%) were 35 years or younger. Most of the included studies were small and there was clinical heterogeneity in the studies used for the meta-analysis. Authors of the included papers were contacted for individual patient data if relevant outcomes were not reported in the published manuscripts.

A retrospective cohort study of 1,302 women who had OTC, 58 of whom had OTT was reported by Beckmann et al. (2018). The data came from the FertiPROTEKT network, which covers Germany, Austria and Switzerland. The aim of the study was to evaluate complications associated with the removal and transplantation of ovarian tissue. Questionnaires were analysed from 13 centres that had done at least 5 removals of ovarian tissue or at least 3 ovarian tissue transplantations. The review by Dolmans et al. (2021) of 285 women who had OTT also included data from the FertiPROTEKT group, together with data from Denmark, Spain, Belgium and France. Case series with more than 20 women having OTT were included. The mean age at OTC was 29.3 years and the mean age at first OTT was 34.6 years. More recent results from the FertiPROTEKT network were reported by Lotz et al. (2022). This retrospective registry analysis included 196 women who had OTT with at least 12 month follow up. The mean age at OTC was 31.3 years and the mean age at OTT was 35.9 years.

Table 2 presents study details.

Figure 1 Flow chart of study selection

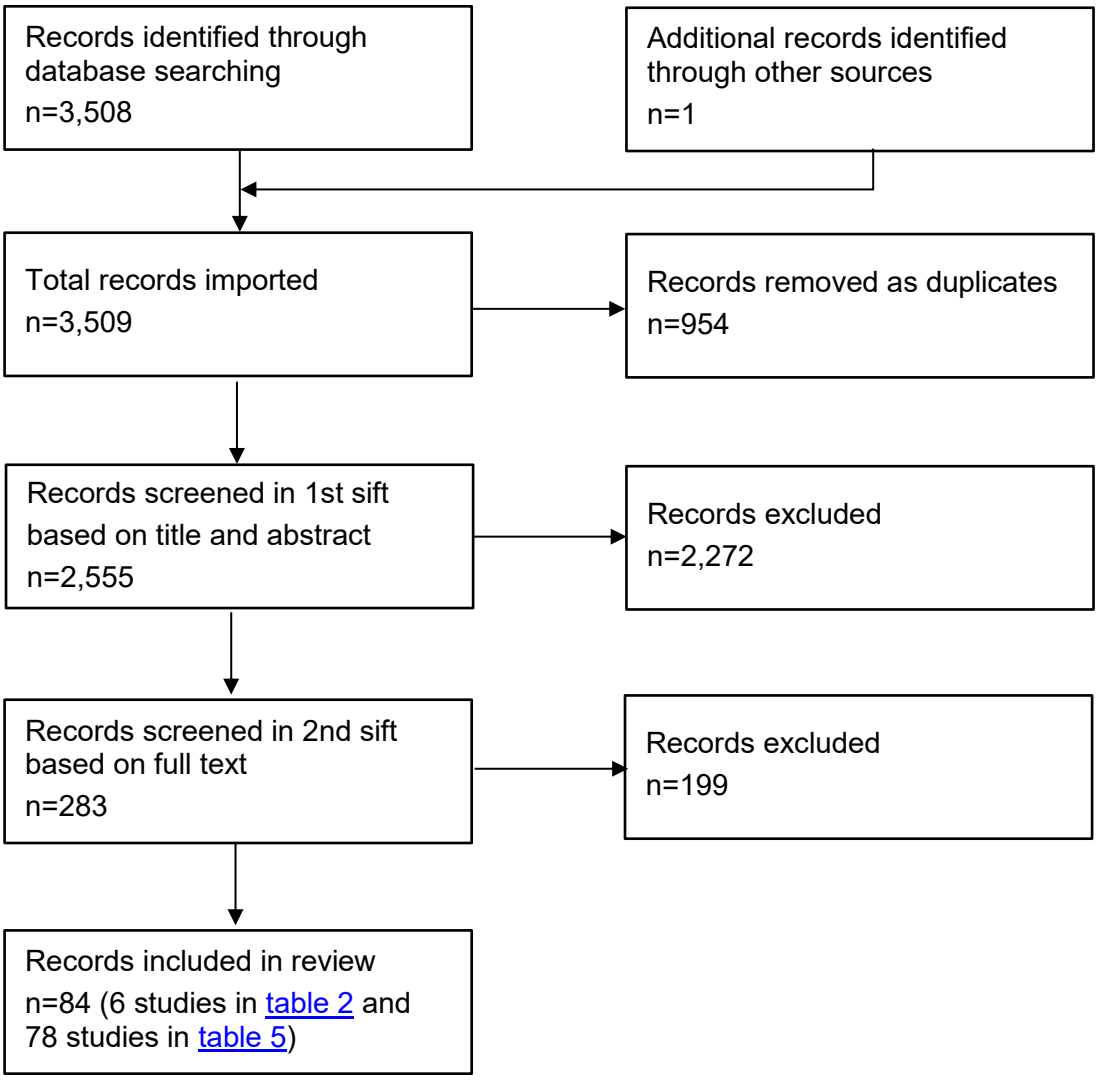

Table 2 Study details

Study no.	First author, date country	Patients	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Ni Dhonnabhain B, 2022 Country not reported for individual studies	Patients attempting pregnancy using cryopreserved cells or tissues frozen before cancer therapy. 550 ovarian tissue transplants (number of patients not reported), 102 embryo transfers (n=75), and 178 oocyte transfers (n=170)	Not reported	Systematic review and meta-analysis (39 studies)	Women at risk for infertility because of gonadotoxic medical treatment; completion of oocyte, embryo, or ovarian tissue cryopreservation procedures; documented follow-up, including reproductive or obstetric outcome; and articles with original data. Ovarian tissue transplants done exclusively for endocrine purposes, where there was no desire to conceive, were excluded. Cases using in vitro matured oocytes and fertility	Oocyte, embryo, or ovarian tissue cryopreservation. Some women had more than 1 ovarian tissue transplantation, when there was no return of menses or when menses ceased after some time.	Not reported

Study no.	First author, date country	Patients	Age	Study design	Inclusion criteria	Intervention	Follow up
					preservation because of gender reassignment therapy or surgery were also excluded. Case reports, conference abstracts, and review papers were excluded.		
2	Gellert S, 2018 Authors of review were based in Denmark. Procedures were done in 21 countries, including Europe, North America, South America, Asia and Australasia.	n=318 women who had OTT (360 procedures)	Mean age at OTC was 28.9 years (range 9 to 47 years). Mean age at first transplant was 33.5 years (range 13 to 47 years).	Systematic review and Danish cohort study (n=89 women, 115 procedures)	All peer-reviewed publications mentioning OTC and OTT in humans were included. Cases involving fresh OTC were excluded. In addition, data from pregnancies and live births from oocyte donations, patients in whom the date of conception was estimated to coincide with the	Transplantation of frozen thawed ovarian tissue. Ovarian tissue was grafted orthotopically (n=233), heterotopically (n=23), or both (n=17). The transplantation site was unknown for 87 procedures. Of the 306 procedures, 318	Not reported

Study no.	First author, date country	Patients	Age	Study design	Inclusion criteria	Intervention	Follow up
					date of transplantation, and patients in whom premature ovarian insufficiency had been diagnosed at the time of OTC were excluded. Data from patients who had had OTT before December 2017 in the Danish cohort were also included.	were first transplantations, 39 were second and 3 were third transplantations.	
3	Khattak H, 2022 Procedures were done in many countries, including Europe, North America, South America, Asia and Australasia.	n=735 (87 studies); 568 women were included in the meta-analysis. Women who received ovarian transplants, including frozen–thawed transplant, fresh or donor graft.	Age was reported for 319 women. Of these, 283 had their ovarian tissue retrieved at age 35 years or younger.	Systematic review	All studies that reported fertility or endocrine outcomes from either fresh or frozen–thawed ovarian transplants for at least 1 patient were included. These comprised cohort studies, observational studies, case	Frozen-thawed, fresh or donor graft ovarian transplants. There were 45 fresh transplants, 11 of which used a graft from a donor (twin sister). In 237 women for whom it was reported, 225	Not reported.

Study no.	First author, date country	Patients	Age	Study design	Inclusion criteria	Intervention	Follow up
					reports, case series, conference abstracts and grey literature (irrespective of country of origin, affiliations of authors, language or year of publication). Studies that reported 5 or more cases of ovarian transplants were included in the statistical analysis.	(95%) had laparoscopy and 12 (5%) had laparotomy for ovarian tissue collection. For transplantation, surgical approach was reported for 323 women; 205 (64%) had laparoscopy and 95 (29%) had laparotomy. The site of transplant varied and included orthotopic (a remaining ovary) and heterotopic sites (such as pelvic side wall or peritoneal pocket).	
4	Beckmann M, 2018 Germany, Austria, Switzerland	n=1,302 women who had OTC.	Not reported	Retrospective cohort study	All the centres that carry out transplantations were contacted by letter in November	Ovarian tissue was removed by laparoscopy in 1,292 (99%) women.	Not reported

Study no.	First author, date country	Patients	Age	Study design	Inclusion criteria	Intervention	Follow up
	(FertiPROTEKT network group)	58 women had a total of 71 transplantations			2015. For the data analysis, the centres that had returned the questionnaire by 30 June 2016 and had done at least 5 removals of ovarian tissue or at least 3 ovarian tissue transplantations were selected. Of the 15 FertiProtekt centres, 13 returned the questionnaire by the deadline.	A drainage tube was placed after ovarian tissue removal in 34% of women (440 of 1,302). In most cases, one-third or less of the removed ovary was transplanted.	
5	Dolmans M, 2021 Denmark, Spain, Belgium, France and the FertiPROTEKT network group from Germany, Switzerland, and Austria.	n=285 women who had OTT	Mean age was 29.3 years (range 9 to 44) at OTC and 34.6 years at first OTT.	Review (multicentre case series)	Case series with more than 20 women having transplantation reported by European clinical centres or groups were included.	277 (97.5%) women had orthotopic OTT, 3 had both orthotopic and heterotopic transplantation, and 5 had only heterotopic (subcutaneous abdominal wall or	Not reported.

Study no.	First author, date country	Patients	Age	Study design	Inclusion criteria	Intervention	Follow up
						forearm) transplantation. 59 patients had a second OTT and 7 patients a third.	
6	Lotz L, 2022 Germany, Austria and Switzerland (FertiPROTEKT network)	n=196 women who had OTT	Mean 31.3 years (range 17 to 44) at OTC and 35.9 years (range 23 to 47) at OTT.	Registry analysis (retrospective)	Women who had OTC and OTT after malignant (n=191) or non-malignant diseases (n=5). Transplantations were done between 2007 to 2019, with follow up till December 2020.	Orthotopic OTT. 43 patients had repeated transplantations; 39 had a second transplantation and 4 had a third transplantation. Collection, transportation and freezing of tissue were done according to the recommendations provided and published by the network FertiPROTEKT.	At least 12 months after OTT.

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Ni Dhonnabhain, 2022	**Clinical pregnancy rate** (cumulative number of clinical pregnancies per transfer for oocytes and embryos and per transplant for ovarian tissue) • Ovarian tissue cryopreservation=43.8% (22 studies, I^2=66.5%, p<0.001) • Oocyte cryopreservation=34.9% (7 studies, I^2=23.8%, p=0.25) • Embryo cryopreservation=49.0% (9 studies, I^2=0%, p=0.46) A random effects analysis found no statistically significant differences among subgroups (p=0.09). **Live birth rate** (cumulative number of live births per transfer for oocytes and embryos and per transplant for ovarian tissue) • Ovarian tissue cryopreservation=32.3% (20 studies, I^2=82.4%, p<0.001) • Oocyte cryopreservation=25.8% (8 studies, I^2=7.8%, p=0.37) • Embryo cryopreservation=35.3% (9 studies, I^2=16.7%, p=0.29) A random effects analysis found no statistically significant difference among the 3 subgroups (p=0.11).	No safety outcomes were reported.

First author, date	Efficacy outcomes	Safety outcomes
	Miscarriage rate (cumulative number of miscarriages per transfer for oocytes and embryos and per transplant for ovarian tissue) • Ovarian tissue cryopreservation=7.5% (13 studies, I^2=28.9%, p=0.15) • Oocyte cryopreservation=9.2% (5 studies, I^2=26.6%, p=0.24) • Embryo cryopreservation=16.9% (6 studies, I^2=0%, p=0.84) A fixed effects analysis found a statistically significant difference (p=0.02) among subgroups. Further fixed analyses showed no difference in miscarriage rates between the oocyte and embryo subgroups and significantly fewer miscarriages with ovarian tissue cryopreservation compared with embryo cryopreservation (p=0.01). No analysis was done comparing ovarian tissue with oocytes, as the effect size was the same.	
Gellert, 2018	The mean time from cryopreservation to first transplantation was 4.4 years (range 0.3 to 13.9 years) **Endocrine function** At the first OTT, endocrine function was restored for 95% (225 of 237) of cases (45 had unknown status). Mean period from OTT to follicular function=4 months (range 1 to 8, n=83) Of the 39 patients who had a second OTT and 3 who had a third transplantation, endocrine function was reported in 29 and	**Recurrence of malignancy** Of the 264 patients for whom the diagnosis was known, 230 (87%) had malignant disease and 34 (13%) had benign disease. From the cohort of 230 patients with malignancy, 9 had a recurrence after OTT, 4 of whom died.

First author, date	Efficacy outcomes	Safety outcomes
	the status was unknown for the remaining 10. The mean period from the second OTT and third OTT to follicular function was 3.9 months (range 2 to 6, n=13) and 4.5 months (range 3 to 6, n=2), respectively. **Pregnancies and live births** Of the 318 patients, 170 wished to restore fertility (data was unavailable for 123). In total, there were 131 pregnancies in 95 patients, counting both biochemical and clinical pregnancies. This resulted in 87 live births in 69 women, and a total of 93 children born. There were 81 singleton pregnancies, 6 twin pregnancies and 10 pregnancies ongoing. The age of patients who succeeded in having a live birth or ongoing pregnancy were significantly younger at OTC (mean 26.4 years, range 9 to 38 years) than patients who failed to conceive but had a pregnancy wish (mean 29.6 years, range 14 to 39 years); p=0.0019 **Method of conception** 46% of pregnancies and 51% of live births were conceived spontaneously. **Perinatal outcomes**	None of the recurrences were considered to be directly caused by the OTT. **Perinatal outcomes** From the total 93 children born, 1 was reported with a chromosome anomaly. A patient with a family history of limb malformations had a child with fetal arthrogryposis.

First author, date	Efficacy outcomes	Safety outcomes
	From the 40 children in whom data were available, birth weight and gestational age were similar to children born from normal pregnancies.	
Khattak, 2022	**Pregnancy rate (18 studies, n=547)** • Frozen transplant=37% (95% CI 32 to 43%) • Fresh transplant=52% (95% CI 28 to 96%) 184 women had at least 1 pregnancy and the overall total number of pregnancies reported in the literature was 290. Pregnancy rates were higher when ovarian tissue was cryopreserved at age 35 or younger (OR 0.35, 95% CI 0.13 to 0.92; p=0.03, I^2=0%). Of the pregnancies for which mode of conception was known, 199 (69%) were conceived naturally. **Live birth rate (17 studies, n=539)** • Frozen transplant=28% (95% CI 24 to 34%) • Fresh transplant=45% (95% CI 23 to 86%) 134 women had at least 1 live birth and the total number of live births of women included in the meta-analysis was 166. In addition to the 17 studies included in the meta-analysis, there were 34 live births described in case reports. Overall, 189 live births have been reported in the literature. **Miscarriage rate (15 studies)** • Frozen transplant=37% (95% CI 30 to 46%) • Fresh transplant=33% (95% CI 13 to 89%)	**Risks of surgery** The included studies did not report any specific complications related to ovarian transplantation other than those of gynaecological laparotomy and laparoscopic surgery. Complications included skin infection and injury to surrounding organs. **Risk of subsequent cancers in the ovarian graft** There were 2 case reports of cancer in the transplanted ovarian graft. One report diagnosed the recurrence of granulosa cell tumour in a patient at caesarean section delivery. The patient had not received any adjuvant chemotherapy before oophorectomy for ovarian tissue cryopreservation. In another case, a patient who was treated for Ewing's sarcoma and had ovarian tissue cryopreserved before receiving chemotherapy, presented

First author, date	Efficacy outcomes	Safety outcomes
	The mean age at cryopreservation in women who had miscarriages was 27.8 years. **Endocrine function** **Oestrogen (8 studies), pooled means (pmol/litre)** • Before transplant=101.6 (95% CI 47.9 to 155.3) • After transplant=522.4 (95% CI 315.4 to 729) • MD=228.2 (95% CI 180.5 to 276) An increase in oestrogen of >200 pmol/litre was noted in 117 women (75%) after transplant. The median time to return of oestrogen to a value >200 pmol/litre was 19.5 weeks (IQR 14 to 24 weeks, range 5 to 208 weeks). **FSH (11 studies, I^2=79%), pooled means (IU/litre)** • Before transplant=68.4 (95% CI 52.8 to 84) • After transplant= 14.1 (95% CI 10.9 to 17.3) • MD=61.8 (95% CI 57 to 66.6) A decrease in FSH below 25 IU/litre was achieved in 72% (135/187 women). The median time to return of FSH to a value <25 IU/litre was 19 weeks (IQR 15–26 weeks, range 0.4 to 208 weeks). **Luteinizing Hormone (6 studies, I^2=0%), pooled means (IU/litre)** • Before transplant=41.5 (95% CI 32.5 to 50.5) • After transplant=19 (95% CI 5.8 to 32.2) • MD=23.4 (95% CI 15.6 to 31.1)	with an ovarian mucinous cystadenoma in the transplant.

First author, date	Efficacy outcomes	Safety outcomes
	A decrease below 15 IU/litre was achieved in 67% (46/69) of women. The median time to return to a value <15 IU/litre was 19.5 weeks (IQR 14 to 27 weeks, range 8 to 156 weeks). **Return of menstruation** • 72% (196/273) women were reported to have resumed menstruation. The median time to return of menstrual activity was 18 weeks (IQR 14 to 22 weeks, range 3 to 48 weeks). **Duration of graft function (19 studies, n=181)** • In 15 studies, the median duration of function was 2.5 years (IQR 1.4 to 3.4 years), range 0.7 to 5 years. The mean age at cryopreservation for this group of women was 27.1 years. • In 3 further studies, including 26 women with a mean age at cryopreservation of 30.3 years, pooled duration of function ranged from 1.2 to 7.7 years.	
Beckmann, 2018	**Return of menstruation** 81% (47/58) of women wanting to have children after cytostatic therapy developed regular menstrual cycles after the ovarian transplantation. In 5 women, the follow up period was too short for any conclusions about the menstrual cycle to be drawn. **Oestradiol level**	**Complications** Postoperative complications after removal of ovarian tissue=0.2% (2/1,302): • 1 abdominal wall haematoma needing revision • 1 urinary tract infection

First author, date	Efficacy outcomes	Safety outcomes
	An increase in the oestradiol level to over 100 pmol/litre was seen after 63.2% (36/57) transplantations after at least 6 months. No data were available for 15 transplantations as the follow up period was still too short (less than 6 months). **Pregnancy and birth rate** At the time of data assessment, 16 pregnancies and 9 births in 14 different women had taken place among the patients who had transplantation (22.5%); birth rate was 12.7% per transplantation. There were 3 miscarriages and 4 ongoing pregnancies. **Method of conception** Spontaneous conceptions occurred in 13 cases. In the other cases, IVF with intracytoplasmic sperm injection was used to achieve pregnancy.	Complications associated with ovarian tissue transplantation procedure=1.4% (1/71) • 1 conversion from laparoscopy to laparotomy because of extensive adhesions **Transference of malignant cells** No cases of recurrent disease resulting from tumour cell transference during transplantation were identified.
Dolmans, 2021	**Pregnancy rate** Of the 276 women wishing to conceive, pregnancy rate was 38.4% (106/276). Women who became pregnant were statistically significantly younger at OTC than those who did not become pregnant (mean age 26.9 versus 29.8 years, p=0.005). Reimplanted tissue is still functioning in many women in the current study, and more pregnancies are likely to follow.	**Recurrence of malignancy** • Relapse=4.2% (12/285); 7 women had breast cancer and the remaining 5 had Ewing sarcoma, cervical cancer, non-Hodgkin's lymphoma, anal carcinoma, and a central nervous system tumour. The time from transplantation to relapse ranged from 2 months to 10 years.

First author, date	Efficacy outcomes	Safety outcomes
	Live birth rate • Overall=26% (75/285) • Women who conceived naturally=30% (52/176) • Women who had IVF=21% (23/109) **Miscarriage rates** • Overall=13% (38/285) • Women who conceived naturally=10% (18/176) • Women who had IVF=18% (20/109) **Number of children** • Overall=95 • Women who conceived naturally=67 • Women who had IVF=28 **IVF outcomes** Of the 109 women who had IVF, only 54 (50%) had an embryo transfer; 39 (36%) women conceived and 23 (21%) gave birth. The empty follicle rate was available for 53 women, yielding a 31% rate of follicles without an oocyte. **Resumption of menstruation**	All relapses were dependent on the primary disease and not related to OTT. All were distant from the grafting site, and most were very close to the location of the primary cancer. The cohort included 2 patients with acute myeloid leukaemia, neither of whom had a relapse after OTT. In both cases, the ovarian tissue was frozen after chemotherapy.

First author, date	Efficacy outcomes	Safety outcomes
	Of 258 patients who had OTT and had available follow up data, 204 had a diagnosis of premature ovarian insufficiency, of whom 181 (88.7%, ranging from 77.6% to 97.2 % according to centre) had resumption of endocrine function, as shown by resumption of menstruation. The mean interval between transplantation and first menstruation was 4.5 months. **Graft survival** In a subgroup of 45 women with more than 5 year follow up, the 5-year graft survival rate was 55% with a correlation between the duration of ovarian function and age at the time of OTC, regardless of whether chemotherapy was previously administered. **OTT after pelvic irradiation** Of the 285 women, 36 (12.6%) had some kind of pelvic irradiation before OTT. In this group, there were 9 pregnancies and 7 live births (19%), with differences depending on the disease. There were no live births in the 15 women with anal or cervical cancer who needed a high radiation dose. **Effect of chemotherapy before OTC** Data on chemotherapy was available for 95% (271/285) of women, 50 (18.5%) of whom were exposed to chemotherapy before OTC. The rate of resumption of ovarian function was not significantly different in those who had chemotherapy	

First author, date	Efficacy outcomes	Safety outcomes
	before OTC compared to those who had not (90% versus 85.3%, p=0.49). The rates of pregnancy in women who were previously exposed to chemotherapy were 50.0% compared with 28.1% in those who had not had chemotherapy before OTC (p=0.004). Univariate and multivariate analyses of pregnancy outcomes suggested that exposure to chemotherapy before OTC does not alter the results of OTT.	
Lotz, 2022	**Pregnancy rate per patient=32.7% (95% CI 26.1 to 39.7%)** There were a total of 80 pregnancies from 244 transplantations. Patients who became pregnant after the first transplantation were younger at the date of cryopreservation (mean 29.9 years) compared to those without a pregnancy (mean 31.9 years, p=0.01). Both patient groups also differed regarding age at the time of transplantation (with pregnancy: mean 34.8 years versus without pregnancy mean 36.4 years; p=0.02). In women younger than 35 years at the time of OTC, pregnancy rate after first transplantation was 34.5% (95% CI 26.7 to 42.9%) versus 20.4% (95% CI 10.6 to 33.5%) in women who were 35 years or older. **Live birth rate per patient=26.5% (95% CI 20.5 to 33.3%)** In women younger than 35 years at the time of OTC, live birth rate after first transplantation was 28.2% (95% CI 20.9 to	No safety outcomes were reported.

First author, date	Efficacy outcomes	Safety outcomes
	36.3%) versus 16.7% (95% CI 7.9 to 29.3%) in women 35 years or older. **Method of conception** • Spontaneous=61.7% • IVF=38.3% **Repeated transplantations** • Pregnancy rate per first transplantation=30.6% (60/196); 95% CI 24.2 to 37.6%. • Overall live birth rate per first transplantation=25.0% (49/196); 95% CI 19.1 to 31.7% • Of 9 women who had already become pregnant after the first OTT, 5 became pregnant again after repeated transplantation and 4 gave birth. • Of 34 women did not become pregnant after the first transplantation, 4 (11.8%, 95% CI, 3.3 to 27.5%) became pregnant and 3 (8.8%, 95% CI 1.9 to 23.7%) gave birth. These 3 women were younger than 35 at the time of cryopreservation. **Outcomes by centre** In centres with 10 or more transplantations (n=5 centres), the pregnancy rate was 34.1% (46/135) after first transplantation.	

First author, date	Efficacy outcomes	Safety outcomes
	In centres with fewer than 10 transplantations (n=21 centres), the pregnancy rate was 22.9% (14/61) after first transplantation (p=0.12). No difference in pregnancy rates was observed after pelvic irradiation. However, only 17 (8.7%) women had a history of pelvic irradiation and pregnancy occurred in only 3 of them.	

Procedure technique

Most of the transplantations were orthotopic but a small proportion were heterotopic, and some were both. Most of the studies only included transplantation of frozen–thawed ovarian tissue but the systematic review by Khattak et al. (2022) also included a small number of fresh or donor grafts. In this review, laparoscopy was the most common approach for both collection (95%) and transplantation (64%) of ovarian tissue. Some women had a second or third OTT.

Efficacy

Pregnancy rate

All 6 studies reported the pregnancy rate. In the systematic review by Ni Dhonnabhain et al. (2022), the clinical pregnancy rate (defined as the cumulative number of clinical pregnancies per transfer for oocytes and embryos and per transplant for ovarian tissue) was 44% for ovarian tissue cryopreservation (22 studies, I^2=67%), 35% for oocyte cryopreservation (7 studies, I^2=24%) and 49% for embryo cryopreservation (9 studies, I^2=0%). In the systematic review by Gellert et al. (2018), 170 of the 318 women were known to have a desire to restore fertility. There were 131 pregnancies (biochemical and clinical) in 95 women. In the systematic review by Khattak et al. (2022), the pregnancy rate was 37% (95% CI 32 to 43%) for frozen transplants and 52% (95% CI 28 to 96%) for fresh transplants. Of the 547 women included in 18 studies, 184 had at least 1 pregnancy and the total number of pregnancies reported was 290. Pregnancy rates were higher when ovarian tissue was cryopreserved at age 35 or younger (OR 0.35, 95% CI 0.13 to 0.92; p=0.03, I^2=0%).

In the cohort study of 1,302 women who had OTC, 58 women had a total of 71 transplantations and there were 16 pregnancies (23%) in 14 women

(Beckmann 2018). In the case series of 285 women who had OTT, pregnancy rate was 38% (106/276) in those wishing to conceive. Women who became pregnant were statistically significantly younger at OTC than those who did not become pregnant (mean age 26.9 versus 29.8 years, p=0.005; Dolmans 2021). In the registry study of 196 women who had OTT, pregnancy rate per patient was 33% (95% CI 26 to 40%). There were a total of 80 pregnancies from 244 transplantations. Patients who became pregnant after the first transplantation were younger at the date of cryopreservation (mean 29.9 years) compared to those without a pregnancy (mean 31.9 years, p=0.01). Both patient groups also differed regarding age at the time of transplantation (with pregnancy: mean 34.8 years versus without pregnancy mean 36.4 years; p=0.02; Lotz 2022).

Live birth rate

All 6 studies reported the live birth rate. In the systematic review by Ni Dhonnabhain et al. (2022), the live birth rate (defined as the cumulative number of live births per transfer for oocytes and embryos and per transplant for ovarian tissue) was 32% for ovarian tissue cryopreservation (20 studies, I^2=82%), 26% for oocyte cryopreservation (8 studies, I^2=8%) and 35% for embryo cryopreservation (9 studies, I^2=17%). In the systematic review by Gellert et al. (2018), 170 of the 318 women were known to have a desire to restore fertility. There were 87 live births in 69 women. The age of patients who succeeded in having a live birth or ongoing pregnancy were significantly younger at OTC (mean 26.4 years, range 9 to 38 years) than patients who failed to conceive but had a pregnancy wish (mean 29.6 years, range 14 to 39 years; p=0.0019).

In the systematic review by Khattak et al. (2022), the live birth rate was 28% (95% CI 24 to 34%) for frozen transplants and 45% (95% CI 23 to 86%) for fresh transplants. Of the 539 women included in 17 studies, 134 had at least 1 live birth

and the total number of live births reported was 166. In addition to the 17 studies included in the meta-analysis, there were 34 live births described in case reports.

In the cohort study of 1,302 women who had OTC, 58 women had a total of 71 transplantations and the birth rate was 13% per transplantation (Beckmann 2018). In the case series of 285 women who had OTT, the live birth rate was 26% (75/285); Dolmans 2021). In the registry study of 196 women who had OTT, the live birth rate per patient was 27% (95% CI 21 to 33%). In women younger than 35 years at the time of OTC, live birth rate after first transplantation was 28% (95% CI 21 to 36%) versus 17% (95% CI 8 to 29%) in women 35 years or older (Lotz 2022).

Miscarriage rate

Miscarriage rate was reported in 4 of the 6 studies. In the systematic review by Ni Dhonnabhain et al. (2022), the miscarriage rate (defined as the cumulative number of miscarriages per transfer for oocytes and embryos and per transplant for ovarian tissue) was 8% for ovarian tissue cryopreservation (13 studies, I^2=29%), 9% for oocyte cryopreservation (5 studies, I^2=27%) and 17% for embryo cryopreservation (6 studies, I^2=0%).

In the systematic review by Khattak et al. (2022), the miscarriage rate from 15 studies was 37% (95% CI 30 to 46%) for frozen transplants and 33% (95% CI 13 to 89%) for fresh transplants. The mean age at cryopreservation in women who had miscarriages was 27.8 years.

In the cohort study of 1,302 women who had OTC, 58 women had a total of 71 transplantations and there were 3 miscarriages (Beckmann 2018). In the case series of 285 women who had OTT, the miscarriage rate was 13% (38/285); Dolmans 2021).

Endocrine function

Endocrine function or return of menstruation was reported in 4 studies. In the systematic review by Gellert et al. (2018), endocrine function was restored for 95% (225/327) of women (45 had unknown status). The mean period from OTT to follicular function was 4 months (range 1 to 8, n=83).

In the systematic review by Khattak et al. (2022), an increase in oestrogen of more than 200 pmol/litre was reported in 117 women (75%) after transplant (8 studies). A decrease in FSH below 25 IU/litre was reported in 72% (135/187) women and a decrease in luteinizing hormone below 15 IU/litre was reported in 67% (46/69) of women. Return of menstruation was reported in 72% (196/273) of women after a median follow up of 18 weeks (range 3 to 48 weeks).

In the cohort study of 1,302 women who had OTC, return of menstruation was reported for 81% (47/58) of women after OTT. An increase in the oestradiol level to over 100 pmol/litre was reported after 63% (36/57) of transplantations that had at least 6 months follow up (Beckmann 2018). In the case series of 285 women who had OTT, 89% (181/204) of women who had premature ovarian insufficiency and had available follow up data resumed menstruation. The mean interval between transplantation and first menstruation was 4.5 months (Lotz 2022).

Method of conception

The method of conception was reported in 4 studies. In the systematic review by Gellert et al. (2018), 46% of pregnancies and 51% of live births were conceived spontaneously. In the systematic review by Khattak et al. (2022), 69% of pregnancies for which the mode of conception was known (n=199) were conceived naturally. In the cohort study by Beckmann et al. (2018), 81% (13/16) of pregnancies were conceived spontaneously. In the registry study of 196 women who had OTT, 62% of conceptions were spontaneous (Lotz 2022).

Duration of graft function

Duration of graft function was reported in 2 studies. In the systematic review by Khattak et al. (2022), the median duration of function was 2.5 years (range 0.7 to 5 years) reported in 15 studies. In 3 further studies, the pooled duration of function ranged from 1.2 to 7.7 years. In the case series of 285 women who had OTT, 5-year survival of the graft was 55% in a subgroup of 45 women (Dolmans 2021).

Perinatal outcomes

From the 40 children in whom data were available, birth weight and gestational age were similar to the general population (Gellert 2018).

Safety

Few safety outcomes were reported and 2 of the 6 studies did not report any safety outcomes.

Perioperative complications

The systematic review by Khattak et al. (2022) stated that there were no specific complications related to OTT other than those of gynaecological laparotomy and laparoscopy surgery. Complications included skin infection and injury to surrounding organs (not further described).

Postoperative complications after removal of ovarian tissue were reported in less than 1% (2/1,302) of women in the cohort study of 1,302 women who had OTC. There was 1 abdominal wall haematoma needing revision and 1 urinary tract infection. For the transplantation procedure, there was 1 conversion from laparoscopy to laparotomy because of extensive adhesions (Beckmann 2018).

Malignant cells in ovarian graft

In the systematic review of 87 studies by Khattak et al. (2022), there were 2 case reports of cancer in the transplanted ovarian graft. Chemotherapy had not been offered before OTC in both cases.

Recurrence of malignancy

In the systematic review by Gellert et al. (2018), 4% (9/230) of women who had malignant disease had a recurrence after OTT. None of the recurrences were considered to be directly caused by the OTT. In the case series of 285 women who had OTT, recurrence of malignancy was reported in 4% (12/285). The time from transplantation to relapse ranged from 2 months to 10 years. All relapses were dependent on the primary disease and not related to OTT. All were distant from the grafting site, and most were very close to the location of the primary cancer (Dolmans 2021).

Perinatal outcomes

From the total 93 children born, 1 was reported with a chromosome anomaly; a patient with a family history of limb malformations had a child with fetal arthrogryposis (Gellert 2018).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following theoretical or anecdotal adverse events:

- Operative risks associated with laparoscopy, including bleeding, organ damage, pain, infection and port site hernia
- Theoretical risk of reimplanting malignant cells within the ovarian tissue
- Earlier menopause
- The intervention may be unnecessary if the treatment is not gonadotoxic
- Delay to start of treatment (but this is much less of a problem with tissue storage than with embryo or oocyte storage)

Nine professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- There are data from Europe, North America, South America, Asia and Australasia. The systematic review by Gellert et al. (2018) includes 2 case reports from the UK.
- Only a small proportion of women who have had ovarian tissue removed and cryopreserved have had the tissue reimplanted. It is possible that, because the procedure can be offered before puberty, many patients are not yet at a family-planning stage of their life.
- The systematic review by Ni Dhonnabhain et al. (2022) excluded procedures that were done only for endocrine purposes, with no desire to conceive.
- Most of the women had been diagnosed with cancer but some women with benign conditions have also been reported.
- Outcomes of the procedure may differ according to the type of cancer and treatments such as pelvic radiation may also impact pregnancy outcomes.
- Surgical techniques differ across centres, regarding the removal of ovarian tissue, the site for reimplantation and the amount of tissue that is reimplanted.

Most of the transplantations were orthotopic but a small proportion were heterotopic.

- In the systematic review by Khattak et al. (2022), it was noted that most centres used slow freezing as a method of ovarian tissue cryopreservation with only 13 cases reported using vitrification.
- Some women had chemotherapy before the ovarian tissue was removed and others had it removed after chemotherapy. There is some limited evidence to suggest this may not affect the outcomes.
- Some women may have residual hormonal function from a remaining ovary.
- Duration of graft function was only reported in 2 studies.
- One author of the systematic review by Ni Dhonnabhain et al. (2022) was Co-Founder and Chief Operations Officer of Hertility Health Ltd. Three of the authors of the systematic review by Khattak et al. (2022) were shareholders in Profam, a private company that offers ovarian tissue cryopreservation and transplantation services. All other authors in the 6 studies declared no conflict of interest.
- Ongoing trials
    - Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function (DATOR) (NCT02846064); single group assignment; n=50; France; study completion date October 2022
    - Cryopreservation of Ovarian Tissue for Potential In Vitro Maturation or Autologous Transplantation (NCT01558544); single group assignment; n=100; US; study completion date December 2023
    - Preservation of Ovarian Cortex Tissue in Girls With Turner Syndrome (NCT03381300); single group assignment; n=106; the Netherlands; study completion date November 2071

- Gonadal Tissue Freezing for Fertility Preservation in Individuals at Risk for Ovarian Dysfunction and Premature Ovarian Insufficiency (NCT04948658); prospective cohort study; n=100; US; study completion date July 2030
- Biorepository in Participants Who Undergo OTC for Gonadotoxic Therapy (NCT05440617); prospective case series; n=100; US; study completion date September 2041

Existing assessments of this procedure

The European Society of Human Reproduction and Embryology published a guideline on female fertility preservation in 2020 (Anderson 2020). It includes 78 recommendations on organisation of care, information provision and support, pre-fertility preservation assessment, fertility preservation interventions and after treatment care. The following recommendations relevant to OTC were described as 'strong':

- 'To estimate the individual risk of gonadotoxicity, the characteristics of the proposed treatment, the patient and the disease should be considered.' (strength of supporting evidence=low)
- 'It is recommended to offer OTC in patients undergoing moderate/high-risk gonadotoxic treatment where oocyte/embryo cryopreservation is not feasible, or at patient preference.' (strength of supporting evidence=low)
- 'The slow-freezing protocol should be used for OTC as it is well established and considered as standard.' (strength of supporting evidence=very low)

- ‘For OTT, a one-step laparoscopy procedure should be performed as it is considered safe without causing additional surgical risk.’ (strength of supporting evidence=low)
- ‘OTT at the orthotopic site is recommended to restore fertility.’ (strength of supporting evidence=low)
- ‘OTT is not recommended in cases where the ovary is involved in the malignancy.’ (strength of supporting evidence=very low)
- ‘OTT and pregnancy can be considered in hormone-sensitive tumours such as endometrial cancer treated by fertility-sparing strategy or breast cancer, after complete remission of the disease.’ (strength of supporting evidence=low)

The American Society of Clinical Oncology published a guideline update on fertility preservation in patients with cancer in 2018 (Oktay 2018). It includes the following recommendation:

‘Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and hence may be the only method available in children. Finally, this method may also restore global ovarian function. However, it should be noted further investigation is needed to confirm whether it is safe in patients with leukemias.’

Selection criteria for OTC have been published (Wallace 2014). These are known as the Edinburgh selection criteria:

- Age younger than 35 years

- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years
- A realistic chance of surviving for 5 years
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (from parents and, where possible, patient)
- Negative serology results for HIV, syphilis, and hepatitis B
- Not pregnant and no existing children

Related NICE guidance

Interventional procedures

- NICE's interventional procedures guidance on Removal, preservation and subsequent reimplantation of ovarian tissue to prevent symptoms from the menopause (Recommendation: research).

NICE guidelines

- NICE guideline on Fertility problems: assessment and treatment
- Cancer service guideline on Improving outcomes in children and young people with cancer

Professional societies

- British Fertility Society
- Royal College of Obstetricians and Gynaecologists
- Faculty of Sexual and Reproductive Healthcare
- Association of Reproductive and Clinical Scientists
- Human Fertilisation and Embryology Authority.

References

1. Ni Dhonnabhain B, Elfaki N, Fraser K et al. (2022) A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis. Fertility and Sterility 117: 1266–76
2. Gellert SE, Pors SE, Kristensen SG (2018) Transplantation of frozen-thawed ovarian tissue: an update on worldwide activity published in peer-reviewed papers and on the Danish cohort. Journal of Assisted Reproduction and Genetics 35: 561–70
3. Khattak H, Malhas R, Craciunas L et al. (2022) Fresh and cryopreserved ovarian tissue transplantation for preserving reproductive and endocrine function: a systematic review and individual patient data meta-analysis. Human Reproduction Update 28: 400–16
4. Beckmann MW, Dittrich R, Lotz L et al. (2018) Fertility protection: complications of surgery and results of removal and transplantation of ovarian tissue. Reproductive Biomedicine Online 36: 188–96
5. Dolmans MM, von Wolff M, Poirot C et al. (2021) Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertility and Sterility 115: 1102–15
6. Lotz L, Bender-Liebenthron J, Dittrich R et al. (2022) Determinants of transplantation success with cryopreserved ovarian tissue: data from 196 women of the FertiPROTEKT network. Human Reproduction (Oxford, England) doi: 10.1093/humrep/deac225
7. Anderson RA, Amant F, Braat D et al. (2020) ESHRE guideline: Female fertility preservation. Human Reproduction Open doi:10.1093/hropen/hoaa052
8. Oktay K, Harvey BE, Partridge AH et al. (2018) Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology 36: 1994–2001
9. Wallace WHB, Smith AG, Kelsey TW et al. (2014) Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation. The Lancet. Oncology 15: 1129–36

Methods

NICE identified studies and reviews relevant to removal, preservation and reimplantation of ovarian tissue to restore fertility from the medical literature. The following databases were searched between the date they started to 8 November 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients who had OTC for fertility preservation.
- Intervention or test: OTT to restore fertility.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	08/11/2022	1946 to November 07, 2022
MEDLINE In-Process (Ovid)	08/11/2022	1946 to November 07, 2022
MEDLINE Epubs ahead of print (Ovid)	08/11/2022	1946 to November 07, 2022
EMBASE (Ovid)	08/11/2022	1974 to 2022 November 07
EMBASE Conference (Ovid)	08/11/2022	1974 to 2022 November 07
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	08/11/2022	Issue 11 of 12, November 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	08/11/2022	Issue 10 of 12, October 2022
International HTA database (INAHTA)	08/11/2022	-

Trial sources searched April 2022

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Cryopreservation/
2 Tissue Preservation/
3 Tissue Transplantation/ or Transplants/
4 or/1-3
5 Ovary/
6 Ovary/tr [Transplantation]

7 Ovary.tw.
8 or/5-7
9 4 and 8
10 (ovar* adj4 tissue* adj4 (transplant* or graft* or preserv* or reimplant* or re-implant* or freez* or frozen or cryopreserv* or cryofixat* or "cryonic suspen*")).tw.
11 (OTC or OTT or OTCT).tw.
12 9 or 10 or 11
13 infertility/ or infertility, female/
14 infertilit*.tw.
15 Ovary/de, re [Drug Effects, Radiation Effects]
16 (subfertili* or sub-fertil*).tw.
17 (Ovar* adj4 (damage* or fail* or fertil* or infert* or subfert* or sub-fert*)).tw.
18 or/13-17
19 12 and 18
20 animals/ not humans/
21 19 not 20
22 limit 21 to english language
23 Fertility Preservation/
24 (Fertil* adj4 (preservat* or keep* or gaurd* or stor*)).tw.
25 18 or 23 or 24
26 12 and 25
27 animals/ not humans/
28 26 not 27
29 limit 28 to english language
30 29 not 22

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Case reports and case series with 5 or fewer patients have been excluded unless they describe safety outcomes.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Abir R, Ben-Aharon I, Garor R et al. (2016) Cryopreservation of in vitro matured oocytes in addition to ovarian tissue freezing for fertility preservation in paediatric female cancer patients before and after cancer therapy. Human Reproduction 31: 750–62	Case series n=42	Ovarian tissue was successfully collected from 79% of patients. Although more oocytes were collected and matured from chemotherapy-naive paediatric patients, ovarian tissue and immature oocytes were also retrieved from young girls in whom cancer therapy has already been initiated.	Small case series, including immature oocyte collection as well as ovarian tissue collection.
Abir R, Aviram A, Feinmesser M et al. (2014) Ovarian minimal residual disease in chronic myeloid leukaemia. Reproductive Biomedicine Online 28: 255–60	Case report n=1	Despite the lack of positive pathological and immunohistochemical evidence, PCR and 2-step nested PCR revealed that the ovary was contaminated by malignant minimal residual chronic myeloid leukaemia.	Case report of cryopreserved-thawed ovarian tissue contaminated with residual malignancy.
Amorim CA, Leonel ECR, Afifi Y et al. (2019) Cryostorage and	Review	OTC has been successfully applied worldwide to preserve	Other systematic

retransplantation of ovarian tissue as an infertility treatment. Best Practice & Research. Clinical Endocrinology & Metabolism 33: 89–102		fertility in cancer patients and women with different types of benign conditions that have a negative impact on their fertility. Proper assessment of the risk of ovarian failure, existing ovarian reserve and patient choice have to be taken into account for the amount of the ovarian tissue needs to be retrieved.	reviews have been included.
Andersen CY, Rosendahl M, Byskov AG et al. (2008) Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Human Reproduction 23: 2266–72	Case series n=6	In all cases, the tissue restored menstrual cyclicity 14 to 20 weeks following transplantation. Four of the 6 women conceived following assisted reproduction: 2 women each, based on the orthotopic transplanted tissue, delivered 1 healthy child, 1 woman miscarried in gestational week 7; and the other had a positive hCG test but no clinical pregnancy. The remaining 2 women did not become pregnant.	Small case series.
Anderson RA, Wallace WHB, Baird DT (2008) Ovarian cryopreservation for fertility preservation: indications and outcomes. Reproduction 136: 681–9	Case series n=36	Of the 36 women, 11 have died and 5 have had spontaneous pregnancies. So far, none have requested reimplantation of their stored ovarian tissue.	Small case series, with no reimplantation procedures.
Anderson RA, Wallace WHB, Telfer EE (2017) Ovarian tissue cryopreservation for fertility preservation: Clinical and research perspectives.	Review	Ovarian tissue cryopreservation is becoming established as a valuable approach to the preservation of fertility in women. Its application in prepubertal girls may be of particular value, as it offers the only approach in	Other systematic reviews have been included.

Human Reproduction Open 2017: 1–9		this patient group. More accurate data are needed on the likelihood of successful childbirth after this procedure and the factors that underpin successful application of this approach.	
Bach AS, Macklon KT, Kristensen SG (2020) Futures and fears in the freezer: Danish women's experiences with ovarian tissue cryopreservation and transplantation. Reproductive Biomedicine Online 41: 555–65	Case series n=42	OTC was associated with positive experiences linked to the production of future-oriented hope and reproductive possibilities. It also generated a range of worries, particularly regarding hormone-sensitive cancers and the risk of re-transplanting malignant cells.	Small case series, exploring patient experiences and reflections on the procedure.
Bahroudi Z, Zarnaghi MR, Izadpanah M et al. (2022) Review of ovarian tissue cryopreservation techniques for fertility preservation. Journal of Gynecology Obstetrics and Human Reproduction 51: 102290	Review	This review of articles related to cryopreservation of ovarian tissue showed that recovery of endocrine function and the live birth rate following re-implantation had been steadily increasing.	Other systematic reviews have been included.
Beckmann MW, Dittrich R, Lotz L et al. (2017) Operative techniques and complications of extraction and transplantation of ovarian tissue: the Erlangen experience. Archives of Gynecology and Obstetrics 295: 1033–39	Case series n=38 (399 women had ovarian tissue extracted)	There were no surgical complications within 28 days of tissue extraction. There were 10 pregnancies and 9 live births after transplantation in 7 different women; 26 of the 38 women developed hormonal activity, confirmed by a menstrual cycle or raised serum oestradiol level.	Small case series.
Bedaiwy MA, El-Nashar SA, El Saman AM et al. (2008) Reproductive outcome after transplantation of ovarian tissue: a systematic	Systematic review n=46 (25 reports)	Transplantation of ovarian tissue can re-establish ovarian function after premature ovarian failure; however, the efficacy of OTT using cryopreserved	More recent systematic reviews are included.

review. Human Reproduction 23: 2709–17		tissues is not yet equivalent to that of fresh grafts. A controlled multicentre trial with sufficient follow-up would provide valid evidence of the potential benefit of this procedure.	
Biasin E, Salvagno F, Berger M et al. (2015) Ovarian tissue cryopreservation in girls undergoing haematopoietic stem cell transplant: experience of a single centre. Bone Marrow Transplantation 50: 1206–11	Case series n=47	93% (26/28) of evaluable patients developed hypergonadotropic hypogonadism at a median 23 months after haematopoietic stem cell transplant. One patient had autologous orthotopic transplantation that resulted in 1 live birth. Results show a very high rate of iatrogenic hypergonadotropic hypogonadism, highlighting the need for fertility preservation in these patients.	Small case series, included in the systematic review by Ni Dhonnabhain et al. (2022).
Bystrova O, Lapina E, Kalugina A et al. (2019) Heterotopic transplantation of cryopreserved ovarian tissue in cancer patients: a case series. Gynecological Endocrinology 35: 1043-1049	Case series n=10 Follow up: 36 months	Frozen-thawed grafts were implanted subcutaneously in the forearm (n=2), the abdominal wall (n=11) and the peritoneal lining (n=3). Although the peritoneal site gave better results, graft longevity averaged the same at around 3 years.	Small case series, assessing serum hormones and follicle growth in heterotopic sites.
Calagna G, Della Corte L, Giampaolino P et al. (2020) Endometriosis and strategies of fertility preservation: a systematic review of the literature. European Journal of Obstetrics, Gynecology, and Reproductive Biology 254: 218–25	Systematic review 3 articles on OTC	After ovarian tissue transplantation, 1 pregnancy with IVF and 1 case of endocrine function or ovulation recovery were described.	Review focuses on fertility preservation strategies for people with endometriosis.

Choi YJ, Hong YH, Kim S et al. (2022) The experience of fertility preservation in a single tertiary center in Korea. Frontiers in Endocrinology 13: 845051	Case series n=26 (OTC)	One woman had the cryopreserved ovarian tissue retransplanted and successfully generated embryos.	Small case series.
Christianson MS, Lukish DA, McCarter R Jr et al. (2021) Ovarian tissue cryopreservation in young females with cancer and its impact on ovarian follicle density. Journal of Pediatric Surgery 56: 2354–59	Case series n=6	Following cryopreservation, on average the ovarian tissue retained 89% of the follicle density of paired fresh samples (95% CI 83% to 95%). Follicle density in young females with cancer is significantly reduced after OTC. However, the degree of reduction may be less than that reported in adult women.	Small case series, assessing follicle density in cryopreserved ovarian tissue.
Cioffi R, Cervini L, Taccagni G et al. (2022) A prospective, observational study of chemotherapy-induced ovarian damage on follicular reserve and maturation. Archives of Gynecology and Obstetrics 306: 1723–29	Case series n=79	OTC appears to be feasible even after the start of chemotherapeutic treatment, since in treated patients, the main ovarian reserve indicators were not significantly reduced compared to untreated patients.	Study focuses on feasibility of OTC after chemotherapy has started.
Cordeiro Mitchell CN, Whiting-Collings LJ et al. (2020) Understanding patients' knowledge and feelings regarding their cryopreserved ovarian tissue: a qualitative interviewing study. Journal of Adolescent and Young Adult Oncology 9: 502–7	Case series n=8	Most patients desired future fertility. Although half of the interviewees understood the OTC procedure, only 2 knew that the tissue can be used for future fertility and only 1 was aware of the benefits for vasomotor symptoms. Five patients expressed positive emotions regarding OTC; 1 felt angry that the decision was made by her parents and 2 were	Small case series, focusing on patients' knowledge and feelings about the procedure.

		concerned that OTC might not have been a good choice. However, most expressed a desire to better understand OTC and most wished for more education about it.	
Corkum KS, Rhee DS, Wafford QE et al. (2019) Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: A systematic review. Journal of Pediatric Surgery 54: 2200–9	Systematic review 91 studies n=1,019 (OTC)	Eighteen patients had auto-transplantation of thawed ovarian cortical tissue that was harvested before the age of 21 years resulting in 10 live births.	A more recent systematic review is included.
Delattre S, Segers I, Van Moer E et al. (2020) Combining fertility preservation procedures to spread the eggs across different baskets: a feasibility study. Human Reproduction 35: 2524–36	Cohort study n=207	19 patients requested warming of their cryopreserved material because of ovarian insufficiency. Of those, eight (42%) patients had a livebirth, of whom 3 were after OTC combined with in vitro maturation of oocytes retrieved from ovarian tissue 'ex vivo'. Combining different fertility preservation procedures is likely to enhance the reproductive fitness of patients having gonadotoxic treatment	A range of different procedures were used in the study.
Diaz AA, Kubo H, Handa N et al. (2022) A systematic review of ovarian tissue transplantation outcomes by ovarian tissue processing size for cryopreservation. Frontiers in Endocrinology 13: 918899	Systematic review 103 studies	OTT was done in 92 patients that had ovarian tissue cryopreserved into strips (n=51), squares (n=37), and fragments (n=4). The pregnancy rate was 81%, 46%, 67% in the strips, squares, fragment groups, respectively. The live birth rate was 56%,18%, 67% in the	Review focuses on outcomes according to size of processed ovarian tissue.

		strips, squares, fragment groups, respectively. The mean time from OTT to ovarian hormone restoration was 3.9 months, 3.6 months, and 3 months in the strips, squares, and fragments groups, respectively.	
Diaz-Garcia C, Domingo J, Garcia-Velasco JA et al. (2018) Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study. Fertility and Sterility 109: 478-485e2	Cohort study n=1,824 (44 OTT)	Although we observed a trend toward higher live birth rate after oocyte vitrification, OTT is a very effective method to preserve fertility, allows for natural pregnancy, and restores ovarian function. In clinical scenarios where oocyte vitrification is not feasible, OTT remains the fertility preservation technique of choice and should no longer be considered experimental.	Study is included in the systematic review by Ni Dhonnabhain et al. (2022).
Dittrich R, Hackl J, Lotz L et al. (2015) Pregnancies and live births after 20 transplantations of cryopreserved ovarian tissue in a single center. Fertility and Sterility 103: 462–8	Case series n=20	Ovarian activity resumed in all patients except 1. Seven patients conceived, with 1 miscarriage and 4 ongoing pregnancies. Four patients delivered healthy babies.	Small case series, included in the systematic review by Ni Dhonnabhain et al. (2022).
Dolmans MM, Iwahara Y, Donnez J et al. (2016) Evaluation of minimal disseminated disease in cryopreserved ovarian tissue from bone and soft tissue sarcoma patients. Human Reproduction 31: 2292–302	Case series n=48	Minimal disseminated disease was not detected in frozen-thawed ovarian tissue from 26 patients by any of the sensitive methods applied.	Small study, assessing the presence of malignant cells in cryopreserved ovarian tissue.
Dolmans MM, Jadoul P, Gilliaux S et al. (2013) A review of 15 years of ovarian tissue bank activities. Journal of	Case series n=11 OTT (476 OTC)	At histology, malignant cells were found in ovarian tissue from leukaemia patients (n=3) and non-Hodgkin's lymphoma	Small case series, included in the systematic review by Ni

Assisted Reproduction and Genetics 30: 305–14		patients (n=2). Eleven patients had autotransplantation, resulting in 5 live births and 1 ongoing pregnancy.	Dhonnabhain et al. (2022).
Donnez J, Dolmans MM (2015) Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice. Journal of Assisted Reproduction and Genetics 32: 1167-70	Review n=60	The mean duration of ovarian function after transplantation is about 5 years in case of high follicular density which is age dependent. So far, 60 live births have been reported either in peer reviewed journals or in abstracts of congress. All of them but 2 were obtained when the slow freezing technique was applied.	More recent studies are included.
Donnez J, Dolmans MM, Pellicer A et al. (2013) Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertility and Sterility 99: 1503–13	Case series n=60	Among the 60 patients, 11 conceived and 6 of those had already delivered 12 healthy babies.	Small case series, included in the systematic review by Ni Dhonnabhain et al. (2022).
Dueholm Hjorth IM, Kristensen SG et al. (2020) Reproductive outcomes after in vitro fertilization treatment in a cohort of Danish women transplanted with cryopreserved ovarian tissue. Fertility and Sterility 114: 379–87	Cohort study n=28	Eleven women achieved 15 pregnancies, of which 60% were lost during the first or second trimester, resulting in 5 of 28 women having 1 or more live births, and 7 healthy children being born.	Small case series, included in the systematic review by Ni Dhonnabhain et al. (2022).
Fabbri R, Vicenti R, Magnani V et al. (2022) Ovarian tissue cryopreservation and transplantation: 20 years experience in Bologna University. Frontiers in	Cohort study n=24 (30 transplants)	To date, out of 1,026 total women, 812 (79%) had their tissue stored. Sixty-eight (7%) patients died from their primary disease. Twenty four (2%) women had 33 OTTs. Restoration	Larger studies are included.

Endocrinology 13: 1035109		of menstruation was observed in 15 out of 17 menopausal women. Six pregnancies were achieved, 2 ended in abortion and 4 in the birth of healthy babies.	
Fajau-Prevot C, Le Gac YT, Chevreau C et al. (2017) Ovarian mucinous cystadenoma after ovarian graft. Obstetrics and Gynecology 129: 1035–6	Case report n=1	During a caesarean delivery in a woman who had OTT, a cyst was removed from the ovarian graft. On pathologic evaluation, it was determined to be a mucinous cystadenoma.	Case report of cancer recurrence after OTT, also described in the systematic review by Khattak et al. (2022).
Findeklee S, Radosa JC, Takacs Z et al. (2019) Fertility preservation in female cancer patients: current knowledge and future perspectives. Minerva Ginecologica 71: 298–305	Review 11 studies on OTC	OTC has been developed as standard in fertility preserving treatment in recent years. Approximately 100 children have been born, with some pregnancies still in progress.	More recent systematic reviews are included.
Fleury A, Pirrello O, Maugard C et al. (2018) Breast cancer and ovarian tissue cryopreservation: Review of the literature. Journal of Gynecology Obstetrics and Human Reproduction 47: 351–7	Review 8 articles	Sixteen cases of ovarian transplants among patients treated for breast cancer were published with 14 pregnancies, 11 births and 3 failures. Two cases of breast recurrences were published after ovarian grafting. However, the evidence on this technique is limited, with a first transplant published in 2004 and only a low number of cases.	Review focuses on patients with breast cancer.
Fortin A, Azais H, Uzan C et al. (2019) Laparoscopic ovarian tissue harvesting and orthotopic ovarian cortex grafting for fertility preservation: less is	Case series n=34	Laparoscopic ovarian tissue harvesting and orthotopic ovarian cortex grafting restored ovarian endocrine activity in 88% of cases. Ten patients had become pregnant (29%),	Small case series.

more. Fertility and Sterility 111: 408–10		and the same number gave birth to at least 1 child.	
Gook D, Hale L, Polyakov A et al. (2021) Experience with transplantation of human cryopreserved ovarian tissue to a sub-peritoneal abdominal site. Human Reproduction 36: 2473–83	Cohort study n=17	Live births have resulted from oocytes aspirated from follicles within cryopreserved ovarian tissue transplanted in a sub-peritoneal abdominal site with similar outcomes observed in terms of number of mature oocytes recovered and embryo development from tissue transplanted to sub-peritoneal abdominal, ovarian, and pelvic sites.	Small study, focusing on grafting of ovarian tissue to sub-peritoneal abdominal sites.
Hoekman EJ, Louwe LA, Rooijers M et al. (2020) Ovarian tissue cryopreservation: Low usage rates and high live-birth rate after transplantation. Acta obstetricia et gynecologica Scandinavica 99: 213–21	Cohort study n=69	The usage rate of autotransplantation was 9% (7/69). Six babies were born to 4 women, giving a live-birth rate of 57% (4/7).	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Hornshoj VG, Dueholm M, Mamsen LS et al. (2021) Hormonal response in patients transplanted with cryopreserved ovarian tissue is independent of whether freezing was performed in childhood or adulthood. Journal of Assisted Reproduction and Genetics 38: 3039–45	Cohort study n=29	Ovarian tissue that was excised from girls at a time close to puberty, after which it was frozen and transplanted in adulthood, interacts with pituitary tissue in a similar manner to ovarian tissue that is frozen from adult women. Follicles located in the ovarian tissue from young girls are equally sensitive to gonadotropin stimulation as follicles from adult women when exposed to postmenopausal levels of gonadotropins.	Small study, assessing hormone response in transplanted ovarian tissue.

Hulsbosch S, Koskas M, Tomassetti C et al. (2018) A real-life analysis of reproductive outcome after fertility preservation in female cancer patients. Gynecologic and Obstetric Investigation 83: 156–63	Case series n=66 (OTC)	Of the 66 patients who had OTC, 18 attempted pregnancy. One patient who had a transplantation of her cryopreserved ovarian tissue tried to conceive without success.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Imbert R, Moffa F, Tsepelidis S et al. (2014) Safety and usefulness of cryopreservation of ovarian tissue to preserve fertility: a 12-year retrospective analysis. Human Reproduction 29: 1931–40	Cohort study n=8 OTT (225 OTC)	Of the 8 patients who had OTT, 3 have become pregnant.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Jadoul P, Guilmain A, Squifflet J et al. (2017) Efficacy of ovarian tissue cryopreservation for fertility preservation: lessons learned from 545 cases. Human Reproduction 32: 1046–54	Cohort study n=21 OTT (545 OTC)	Of the 21 patients who had autotransplantation (4%), 7 delivered a healthy baby, yielding a post-transplantation live birth rate of 33%. Of 451 patients who were sent a questionnaire, 143 agreed to respond (32%). Of 92 evaluable patients, 32% were menopausal and 69% showed persistent ovarian function. Of 52 women who attempted to conceive naturally, 37 were successful (71%). Among 140 patients who answered the questionnaire, 96% were satisfied with the procedure and only 1 major complication (intra-abdominal haemorrhage) was reported.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).

Janse F, Donnez J, Anckaert E et al. (2011) Limited value of ovarian function markers following orthotopic transplantation of ovarian tissue after gonadotoxic treatment. The Journal of Clinical Endocrinology and Metabolism 96: 1136–44	Cohort study n=10	On average, first menses took place after 4.7 months. Duration of graft functioning varied from 2 to more than 60 months. There were 2 spontaneous pregnancies.	Larger and more recent studies are included.
Jensen AK, Kristensen SG, Macklon KT et al. (2015) Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. Human Reproduction 30: 2838–45	Cohort study n=41	Among 32 women with a pregnancy-wish, 10 (31%) had a child (14 children in total); this included 1 woman with a third trimester ongoing pregnancy. In addition, 2 legal abortions and 1 second trimester miscarriage occurred. A total of 24 clinical pregnancies were established in the 32 women with a pregnancy-wish. The tissue remained functional for close to 10 years in some cases and lasted only a short period in others. Three relapses occurred but were unlikely to be due to the transplanted tissue.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Jensen AK, Macklon KT, Fedder J et al. (2017) 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. Journal of Assisted Reproduction and Genetics 34: 325–36	Review and case series (n=7)	Worldwide, approximately 95 children have been born or will be born in the near future from OTC. Information on the perinatal outcome was found on 40 children. The mean gestational age was 39 weeks and the mean birth weight was 3,168 g of the singleton pregnancies, which is within internationally recognised	Included in systematic review by Gellert et al. (2018)

		normal standards. Furthermore, half the singletons resulted from natural conception and all twins resulted from in vitro fertilisation treatment.	
Jensen AK, Rechnitzer C, Macklon KT et al. (2017) Cryopreservation of ovarian tissue for fertility preservation in a large cohort of young girls: focus on pubertal development. Human Reproduction 32: 154–64	Cohort study n=176 OTC	OTC should be recommended to all young girls, who present a high risk of developing ovarian insufficiency and/or infertility following high dose chemotherapy and/or irradiation.	None of the patients had OTT.
Karavani G, Schachter-Safrai N, Chill HH et al. (2018) Single-incision laparoscopic surgery for ovarian tissue cryopreservation. Journal of Minimally Invasive Gynecology 25: 474–79	Case series n=231 (OTC)	Procedure duration and overall complication rates were similar between single-incision and standard multiport laparoscopic surgery. Number of ampules extracted from the preserved tissue was somewhat higher in the single-incision group (14.7 compared with 10.6 in the multiport group, p<0.01).	Study focuses on single-incision laparoscopic technique for removing ovarian tissue.
Kristensen SG, Wakimoto Y, Colmorn LB et al. (2021) Use of cryopreserved ovarian tissue in the Danish fertility preservation cohort. Fertility and Sterility 116: 1098–1106	Cohort study n=117 OTT (1,186 OTC)	Stratified age analysis indicated that women aged 30 or above at OTC were more likely to return for OTT than women aged 18 to 29 years at OTC; mean storage times were 3.7 and 3.6 years, respectively. Only 4% of the girls aged less than 18 years at OTC had undergone OTT.	Study focuses on the use of cryopreserved tissue rather than outcomes of the procedure.
Leflon M, Rives-Feraille A, Letailleur M et al. (2022) Experience, and gynaecological and reproductive health follow-up of young adult	Cohort study n=9 OTT (87 OTC)	More than 70% of women who planned a pregnancy after the end of treatment succeeded, with a natural pregnancy rate close to 53%. Of the 9 patients	Larger studies are included.

women who have undergone ovarian tissue cryopreservation. Reproductive BioMedicine Online 45: 913–22		(8%) who had OTT for fertility restoration, 6 became pregnant and delivered at least once.	
Liebenthron J, Montag M, Reinsberg J et al. (2019) Overnight ovarian tissue transportation for centralized cryobanking: a feasible option. Reproductive Biomedicine Online 38: 740–49	Cohort study n=30	A subgroup of 30 women who had a single orthotopic transplantation with a complete follow-up after transplantation until the end of study, a premature ovarian insufficiency after gonadotoxic therapy as well as the absence of pelvic radiation, was analysed. In this group, transplantations into a peritoneal pocket accounted for 90%. Transplants were still active at 1 year and above after transplantation in 93%. Pregnancy and delivery rates were 47% and 43%, respectively, with 1 ongoing pregnancy at the end of the study.	Larger studies are included.
Lotz L, Dietl A, Hoffmann I et al. (2022) Endometriosis in women undergoing ovarian tissue transplantation due to premature menopause after gonadotoxic treatment or spontaneous premature ovarian failure. Acta obstetricia et gynecologica Scandinavica 101: 771–78	Case series n=17	The mean age of the patients was 29.5 years (range 14 to 39) at the time of ovarian tissue harvest and 34.6 years (range 28 to 40) at transplantation. The pregnancy rate in the study population was 41%, with a live birth rate of 35%. Of the 7 pregnancies, 3 occurred after spontaneous conception.	Small study, focusing on people with endometriosis.
Lotz L, Maktabi A, Hoffmann I et al. (2016) Ovarian tissue	Cohort study	Sixty-two women had tried to conceive; 33 reported pregnancies. Twenty-five	Larger studies are included.

cryopreservation and retransplantation--what do patients think about it? Reproductive Biomedicine Online 32: 394–400	n=5 OTT (147 OTC)	had delivered healthy children after conceiving naturally; 8 had conceived with assisted reproduction. Five patients had had their ovarian tissue retransplanted. Although many patients continued to have ovarian function, none of them regretted choosing cryopreservation of ovarian tissue.	
Lotz L, Barbosa PR, Knorr C et al. (2020) The safety and satisfaction of ovarian tissue cryopreservation in prepubertal and adolescent girls. Reproductive Biomedicine Online 40: 547–54	Cohort study n=1 OTT (53 OTC)	Ovarian tissue retrieval was without complications in 52 patients. In 23 (54%) of the 43 women who were post-menarchal at OTC, transient amenorrhoea occurred. At survey, 15 women reported a regular menstrual cycle, 25 used oral contraceptives, 9 women reported hormone replacement therapy due to primary ovary insufficiency and 4 had amenorrhoea. Two patients reported the birth of a healthy child after IVF, while 51 patients are still childless, mostly due to their young age (mean 21 years). To date, 1 patient has had transplantation of the ovarian tissue. Forty-nine of the interviewees would again decide on OTC, while 3 argued against it based on cost; 1 woman was unsure.	Larger studies are included.
Marin L, Bedoschi G, Kawahara T et al. (2020) History, evolution and current state of ovarian	Review	Ovarian transplantation with cryopreserved tissue has gone through remarkable evolution in	Other systematic reviews are included.

tissue auto-transplantation with cryopreserved tissue: a successful translational research journey from 1999 to 2020. Reproductive Sciences 27: 955–62		the last 20 years. The first live birth is likely to be the 1 reported by Meirow et al. in 2005. The technique has evolved to reach a level where most recent live birth rates are exceeding 35% and the procedure is no longer considered experimental by many.	
Meirow D, Ra'anani H, Shapira M et al. (2016) Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertility and Sterility 106: 467–74	Cohort study n=20	After transplantation, the endocrine recovery rate was 93%. Fourteen patients had IVF treatments with a fertilisation rate of 58%. Sixteen pregnancies were achieved (10 after IVF, 6 spontaneous), resulting in 10 live births, 2 (twins) after harvesting from the mother at the age of 37. Two pregnancies are currently ongoing. After transplantation, 53% of patients conceived, and 32% delivered at least once. One patient conceived 4 times. Chemotherapy exposure before harvesting was not associated with inferior outcomes. All patients, including 2 leukaemia survivors, remained cancer free.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Meng L, Kawamura K, Yoshioka N et al. (2022) Learning curve of surgeons performing laparoscopic ovarian tissue transplantation in women with premature ovarian insufficiency: a statistical process control	Case series n=100	The laparoscopic ovarian tissue transplantation surgery was generally safe given that the postoperative complications were infrequent (2%). Although the performance of all 3 surgeons was acceptable,	Case series, assessing the learning curve of the procedure.

analysis. Journal of Minimally Invasive Gynecology 29: 559–66		only surgeon A attained the level of competency after 66 cases. The transplantation method may not be the key factor for reducing surgery time in this surgery. An efficient ovarian tissue transplantation team is more important in reducing the surgery time than the surgeon's surgical technique alone.	
Oktay K, Marin L, Bedoschi G et al. (2022) Ovarian transplantation with robotic surgery and a neovascularizing human extracellular matrix scaffold: a case series in comparison to meta-analytic data. Fertility and Sterility 117: 181–92	Case series n=7	Robot-assisted autologous cryopreserved ovarian tissue transplantation was done using a neovascularising extracellular matrix scaffold. Ovarian function returned after 14 weeks. One recipient did not attempt to conceive, 2 needed a surrogate, and 4 delivered 6 healthy children.	Small case series, focusing on a new technique.
Oktay K, Oktem O (2010) Ovarian cryopreservation and transplantation for fertility preservation for medical indications: report of an ongoing experience. Fertility and Sterility 93: 762–8	cohort study n=3 OTT (59 OTC)	No complications occurred and no histologic evidence of cancer was found in the harvested tissue. One woman with a heterotopic transplant conceived spontaneously and delivered. Of the 3 transplants, 1 ceased function after 9 months and 2 are still functioning at up to 7 years follow up.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Pacheco F, Oktay K (2017) Current success and efficiency of autologous ovarian transplantation: a meta-analysis. Reproductive Sciences 24: 1111–20	Systematic review 19 reports	The cumulative clinical and live birth and ongoing pregnancy rates were 58% and 38%, respectively, and the endocrine restoration rate was 64%. Given these recent data, ovarian tissue	More recent systematic reviews are included.

		cryopreservation should be considered as a viable option for fertility preservation.	
Poirot C, Fortin A Lacorte JM et al. (2019) Impact of cancer chemotherapy before ovarian cortex cryopreservation on ovarian tissue transplantation. Human Reproduction 34: 1083–94	Cohort study n=31	At 1 year after OTT, the cumulative incidence of ovarian function recovery was 83% (93% in patients exposed to chemotherapy and 67% in others, p=0.14). Graft survival at 2 years after OTT was 77%. The cumulative incidence of pregnancy (Kaplan-Meier) at 3 years after OTT was 36% overall and 49% in case of previous chemotherapy, with no difference related to previous chemotherapy exposure. In total there were 13 pregnancies and 8 births in 7 patients.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Poirot C, Brugieres L, Yakouben K et al. (2019) Ovarian tissue cryopreservation for fertility preservation in 418 girls and adolescents up to 15 years of age facing highly gonadotoxic treatment. Twenty years of experience at a single center. Acta obstetricia et gynecologica Scandinavica 98: 630–37	Cohort study n=3 OTT (418 OTC)	Of the 418 patients who had OTC, 3 had OTT, 1 for puberty induction and the 2 others for restoring fertility. So far, no pregnancies have been achieved. Eighty-four patients who had OTC died.	Larger or more recent studies are included.
Poirot C, Fortin A, Dhedin N et al. (2019) Post-transplant outcome of ovarian tissue cryopreserved after chemotherapy in hematologic malignancies.	Cohort study n=25 Follow up: median 32 months	The cumulative incidence of ovarian function recovery at one year was 92% (95% CI 77% to 99%) with a median time to recovery of 4.6 months (range 2.2 to 7.6). The cumulative incidence of pregnancy was 52% (95%	Larger or more recent studies are included.

Haematologica 104: e360-e363		CI 31 to 77%) at 3 years and 60% (95% CI 37 to 83%) at 5 years, with no significant difference between post and per-chemotherapy groups. In the whole cohort, 11 patients became pregnant at least once (41% of all patients and 46% of patients who recovered ovarian function) and gave birth to at least 1 healthy child (n=8) or had an ongoing pregnancy (n=3).	
Pretalli JB, Frontczak Franck S, et al. (2019) Development of ovarian tissue autograft to restore ovarian function: protocol for a French multicenter cohort study. JMIR Research Protocols 30: e12944	Cohort study n=25	11 women succeeded in becoming pregnant (pregnancy rate=44%, delivery rate=40%). Among these, 6 women conceived twice, and 1 pregnancy led to a miscarriage.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Rodriguez-Wallberg KA, Marklund A, Lundberg F et al. (2019) A prospective study of women and girls undergoing fertility preservation due to oncologic and non-oncologic indications in Sweden-Trends in patients' choices and benefit of the chosen methods after long-term follow up. Acta obstetricia et gynecologica Scandinavica 98: 604–15	Cohort study n=335 (OTC)	Utilisation rate was 5%. Pregnancy rate was 25% and live birth rate was 7%.	Only a small proportion of patients had OTT.
Rodriguez-Wallberg KA, Tanbo T et al. (2016) Ovarian tissue cryopreservation and transplantation among	Case series n=46	17 healthy children have been born and several additional pregnancies are currently ongoing. Overall, ovarian tissue	More recent or larger studies are included.

alternatives for fertility preservation in the Nordic countries - compilation of 20 years of multicenter experience. Acta obstetricia et gynecologica Scandinavica 95: 1015–26		cryopreservation was reported to be safe.	
Rosendahl M, Andersen MT, Ralfkiaer E et al. (2010) Evidence of residual disease in cryopreserved ovarian cortex from female patients with leukemia. Fertility and Sterility 94: 2186–90	Case series n=26 (OTC)	Histology and immunohistochemistry did not reveal malignant cell infiltration in the ovarian cortex of any of the patients. In 6 of the 8 patients (75%) with chromosomal abnormalities in the malignant cells, PCR showed evidence of leukemic cells in the ovarian tissue.	Small case series, assessing the presence of malignant cells in harvested ovarian tissue.
Rosendahl M, Greve T, Andersen CY (2013) The safety of transplanting cryopreserved ovarian tissue in cancer patients: a review of the literature. Journal of Assisted Reproduction and Genetics 30: 11–24	Systematic review 42 studies	Ovarian tissue from 422 patients has been subject to testing for malignant cells by imaging, histology, immunohistochemistry, molecular biology, animal- or clinical transplantation. In 31 (7%) the applied test raised suspicion of malignant cell infiltration. Transplantation of frozen and thawed ovarian tissue may potentially re-introduce the malignancy. For most conditions, however, the risk is very low and is presumably related to the stage of disease at the time of OTC.	More recent systematic reviews are included.
Rosendahl M, Schmidt KT et al. (2011) Cryopreservation of	Case series	All women resumed ovarian function and 3	Larger or more recent studies are included.

ovarian tissue for a decade in Denmark: a view of the technique. Reproductive Biomedicine Online 22: 162–71	n=12 (18 transplants)	healthy babies were born to 2 women.	
Ruan X, Cheng J, Korell M et al. (2020) Ovarian tissue cryopreservation and transplantation prevents iatrogenic premature ovarian insufficiency: first 10 cases in China. Climacteric: the journal of the International Menopause Society 23: 574-580	Case series n=10	The average age at OTC was 33.7 years; the time from OTC to OTT was 15 months. The average time from OTT to restoration of ovarian function was 3.4 months. One year after OTT, all ovaries were still functioning normally. In the first case, the function now remains preserved for more than 3 years. So far, the woman who wishes to conceive has no pregnancy.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Ruan X, Cheng J, Du J et al. (2022) Analysis of fertility preservation by ovarian tissue cryopreservation in pediatric children in China. Frontiers in Endocrinology 13: 930786	Cohort study n=49 children	OTC is the only method to preserve the fertility of prepubertal girls, and it is safe and effective. Chemotherapy before OTC is not a contraindication to OTC.	Small study assessing the effect of chemotherapy before OTC.
Sanchez M, Novella-Maestre E, Teruel J et al. (2008) The Valencia Programme for Fertility Preservation. Clinical & Translational Oncology 10: 433–8	Cohort study n=4 OTT (200 OTC)	Of the 4 patients who had OTT, 2 had ovarian function resumption, in 1 case a month after the implant and in the other 5.5 months after.	More recent or larger studies are included.
Schifflers S, Delbecque K, Galant C et al. (2018) Microscopic infiltration of cryopreserved ovarian tissue in 2 patients with Ewing sarcoma. Journal of Pediatric Hematology/Oncology 40: e167-e170	case reports n=2	Reports of 2 female patients with Ewing sarcoma and microscopic ovarian infiltration. In both cases, the initial workup found no metastasis. However, the examination of cryopreserved ovarian tissues revealed the	Malignant cells in the ovarian graft is reported in the systematic review by Khattak et al. (2022)

		presence of tumour cells. These reports underline that, in patients with Ewing sarcoma, retransplantation of cryopreserved ovarian tissue is not harmless and could lead to cancer relapse.	
Schmidt KT, Rosendahl M, Ernst E et al. (2011) Autotransplantation of cryopreserved ovarian tissue in 12 women with chemotherapy-induced premature ovarian failure: the Danish experience. Fertility and Sterility 95: 695–701	Cohort study n=12	All 12 women regained ovarian function between 8 and 26 weeks (mean 19 weeks) after transplantation. There were 6 pregnancies: 2 biochemical, 1 clinical that miscarried in week 7, and 2 resulting in the delivery of 2 healthy infants born at term to 2 women. One of these women subsequently conceived spontaneously and delivered another healthy infant. The life span of the transplanted tissue has been between 6 months and still functioning after 54 months.	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).
Shapira M, Dolmans MM, Silber S et al. (2020) Evaluation of ovarian tissue transplantation: results from three clinical centers. Fertility and Sterility 114: 388–97	Cohort study n=60 (70 transplants)	Menses returned in 94% of patients. Fifty pregnancies and 44 deliveries were attained, with 50% of women achieving at least 1 pregnancy and 42% at least 1 delivery. Twelve patients had more than 1 transplant and had their endocrine activity restored. Repeated transplantations yielded 5 live births in 3 patients, 2 of whom had already given birth after the first transplantation. Preharvesting	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).

		chemotherapy was not associated with inferior outcomes. Of 7 patients whose pelvis was exposed to radiation before OTT, 4 conceived and delivered.	
Sheshpari S, Shahnazi M, Mobarak H et al. (2019) Ovarian function and reproductive outcome after ovarian tissue transplantation: a systematic review. Journal of Translational Medicine 17: 396	Systematic review n=210 OTT (693 OTC) 25 articles	In general, 70% of patients who OTT had ovarian and endocrine function restoration as well as follicular growth. Pregnancy was reported with 52% of the patients. The available evidence suggests that ovarian tissue transplantation is a useful and an applied approach to restore hormonal function, endocrine balance and eventually fertility outcomes in patients that are predisposed to lose their fertility, diagnosed with premature ovarian failure, as well as women undergoing cancer treatments.	More recent systematic reviews are included.
Silber SJ, Goldsmith S, Castleman L et al. (2022) In-vitro maturation and transplantation of cryopreserved ovary tissue: understanding ovarian longevity. Reproductive Biomedicine Online 44: 504–14	Cohort study n=17 OTT (119 OTC)	Every woman had a return of ovarian function 5 months after transplant, similar to previous observations. As observed before, anti-Mullerian hormone concentration rose as follicle-stimulating hormone fell 4 months later. The grafts continued to work up to 8 years. Of the 17, 13 (76%) became pregnant with intercourse at least once, resulting in 19 healthy live births, including 6 live births from 3 women who had had leukaemia.	Larger studies are included. An earlier publication from this author is included in the systematic review by Ni Dhonnabhain et al. (2022).

Stern CJ, Gook D, Hale LG et al. (2014) Delivery of twins following heterotopic grafting of frozen-thawed ovarian tissue. Human Reproduction 29: 1828	Case report n=1	At caesarean, there was macroscopic evidence of tumour involving the diaphragm and a peritoneal deposit at the left pelvic brim, in a patient who had OTT. There was no evidence of tumour in the graft sites. All macroscopic tumour was resected and histology confirmed granulosa cell tumour. The possibility that tumour recurrence resulted from the grafted tissue cannot be excluded.	Case report of cancer recurrence after OTT, also described in the systematic review by Khattak et al. (2022).
Takae S, Furuta S, Iwahataa H et al. (2022) Cryopreservation of paediatric ovarian tissue with an updated version of the Edinburgh criteria for appropriate patient selection. Reproductive Biomedicine Online 44: 667–76	Cohort study n=31 OTC	Two out of 31 had complications after surgery (infection and drug allergy) and 1 patient with leukaemia (3%) had minimum residual disease on the extracted ovarian tissue. Of the 14 patients who completed treatment, 12 (86%) had primary ovarian insufficiency more than a year after treatment. Two out of 31 (6.5%) died because of recurrence of their underlying disease (median 28 months, range 0 to 60 months).	None of the patients had OTT.
Tanbo T, Greggains G, Storeng R et al. (2015) Autotransplantation of cryopreserved ovarian tissue after treatment for malignant disease - the first Norwegian results. Acta obstetricia et gynecologica Scandinavica 94: 937–41	Cohort study n=2 OTT (164 OTC)	Of the 164 patients who had OTC between 2004 and 2014, 15 patients died during the observation period. Six patients requested OTT, which was done in 2 women. Both patients conceived, 1 spontaneously and 1 after assisted reproduction because of a concomitant male factor. The	Small study, included in the systematic review by Ni Dhonnabhain et al. (2022).

		pregnancies were uneventful and they each gave birth to a healthy child.	
Van der Ven H, Liebenthron J, Beckmann M et al. (2016) Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. Human Reproduction 31: 2031–41	Cohort study n=74 (95 transplants)	The average age of all transplanted 74 women was 31 years at the time of cryopreservation and 35 at the time of transplantation. Twenty-one pregnancies and 17 deliveries were recorded. Persistent tissue activity 12 months after transplantation suggests that the pregnancy and delivery rates may increase further in the future. As transplantation into the peritoneum results in a high success rate, this approach may be an alternative to transplantation into the ovary. However, in order to establish the best transplantation site, a randomised study is needed.	Study is included in the systematic review by Ni Dhonnabhain et al. (2022).
Vatel M, Torre A, Paillusson B et al. (2021) Efficacy of assisted reproductive technology after ovarian tissue transplantation in a cohort of 11 patients with or without associated infertility factors. Journal of Assisted Reproduction and Genetics 38: 503–11	Cohort study n=11	Nine pregnancies and 4 live births occurred after spontaneous conception in 5 patients without an infertility factor, none in the infertility group. This study confirms that IVF treatment in women with grafted frozen-thawed ovarian tissue is associated with poor outcomes. However, the chances of natural conception are high in women without an infertility factor. Patients with an infertility factor,	Larger studies are included.

		without the possibility of spontaneous pregnancy, should be informed of poor reproductive outcomes after OTT followed by assisted reproductive techniques.	