National Institute for Health and Care Excellence

NICE clinical guideline CG30.1

Addendum to Clinical Guideline 30, Long-acting reversible contraception

This replaces Chapter 7: Progestogen-only subdermal implants (POSDIs) in clinical guideline 30

Clinical Guideline Addendum 30.1

Methods, evidence and recommendations

September 2014

Commissioned by the National Institute for Health and Care Excellence

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic-specific members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic-specific members.

Where 'standing Committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic-specific members' is referred to this means the recruited group of members with topic-specific expertise.

All of the standing members and the topic-specific members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE surveillance programme reviewed the guideline on Long-acting reversible contraception (NICE clinical guideline 30) in 2011, and found changes to product licensing that affected the section of the guideline on progestogen-only subdermal implants. The full report can be found here: http://www.nice.org.uk/CG30/

New recommendations relating to progestogen-only subdermal implants have been made in this addendum. You are invited to comment on these new recommendations.

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this addendum denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1. **Inform women that etonogestrel implants[a] have a very low failure rate (less than 1 pregnancy per 1000 implants fitted over 3 years).**

2. **Inform women that vaginal bleeding patterns are likely to change while using an etonogestrel implant. Vaginal bleeding may stop, become more or less frequent,**

a At the time of publication (date to be confirmed), Nexplanon was the only subdermal implant licensed in the UK and did not have UK marketing authorisation for use outside of the age range 18-40 years. Outside of this age range, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the Nursing and Midwifery Council's Standards of proficiency for nurse and midwife prescribers for further information.

or be prolonged during implant use.

3. **Inform women that dysmenorrhoea may reduce during etonogestrel implant use.**

4. **Inform women that there is no evidence showing a delay in return to fertility after an etonogestrel implant is removed.**

5. **Inform women that complications with etonogestrel implant insertion and removal are uncommon. (Possible complications are listed in the summary of product characteristics.)**

1.3 Patient-centred care

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. People should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

Please see the interim process and methods guide for updates pilot programme 2013 and the guidelines manual 2012.

2 Evidence review and recommendations

Introduction

The NICE surveillance programme undertakes regular reviews of published guidelines. Surveillance of the NICE guideline on long-acting reversible contraception concluded that there were changes to product licensing that meant that the chapter of the guideline on progestogen-only subdermal implants was out of date, because the guideline refers specifically to the subdermal implant Implanon, which is no longer available. Implanon has been replaced by the implant Nexplanon, which contains the same drug (etonogestrel) and dose, but also contains barium to make it radio-opaque, and has a different insertion device. Consequently, the clinical guidelines update programme was commissioned to review the evidence on progestogen-only subdermal implants and update the recommendations so that they were applicable to current clinical practice.

2.1 Progestogen-only subdermal implants

2.1.1 Review question

What is the effectiveness of subdermal implants for long-acting reversible contraception?

2.1.2 Evidence review

The aim of the review was to assess the effectiveness of etonogestrel subdermal implants for contraception in women by comparing etonogestrel subdermal implants to other etonogestrel subdermal implants (for example, Implanon with Nexplanon), no contraception or no comparator. It was not the aim to compare etonogestrel implants with other forms of contraception. We searched for studies investigating the effectiveness of etonogestrel subdermal implants.

A systematic search was conducted (see appendix D) which identified 9678 articles. The titles and abstracts were screened and 163 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 117 were excluded as they did not meet the criteria and 46 met the criteria and were included. A list of excluded studies together with their reason for their exclusion is provided in appendix G. Four articles reported the same studies as other included articles, and so there are 42 included studies in total.

Details of the included studies are given in evidence tables in appendix G. The quality of evidence for each critical and important outcome was appraised using a modification of the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (see appendix H). All studies except one small randomised controlled trial were observational, and did not include a control group. Consequently, conventional GRADE profiles would contain much missing information which has been removed for clarity. It was not possible to assess inconsistency between studies because only absolute (rather than relative) effects were reported (due to the non-comparative nature of the studies), and so this column has been omitted from the profile. Likewise, methods are not available to assess publication bias for non-comparative studies, and so this criterion has not been included. GRADE methodology allows observational studies (which are initially given a quality rating of 'LOW') to be 'upgraded' if they meet any of the following criteria:

- there is demonstration of a dose response relationship
- there is a large effect

- all possible sources of bias would act to reduce and effect if one is shown, or show an effect if no effect is shown

Again, due to the non-comparative nature of the studies presented, these criteria could not possibly be met, and so this column has been omitted.

Non-comparative studies also present a challenge for rating imprecision, as the usual guidelines given by GRADE to assess the extent of imprecision do not apply. For a sample size of 200, 95% confidence intervals are <15% for mean percentages in the range of 10-90%, and less than 2% for mean percentages close to zero (calculated according to the 'Wald' method described by Agresti and Coull (1998). We judged this level of precision sufficient to guide the formulation of recommendations. Hence, evidence for each outcome was downgraded one level for imprecision if the sample size was less than 200, and two levels if the sample size was less than 100. In cases where studies were grouped into a single line in the GRADE profile, the grouped studies were downgraded when the majority of the grouped studies met these criteria. Note that the effect estimate ranges are point estimates; the associated 95% confidence intervals are likely to incorporate much larger ranges, but were in general not reported. When 95% confidence intervals were reported, they have been included in the evidence tables.

2.1.3 Health economic evidence

An additional search was done using the same search terms with an economic evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of etonogestrel implants (see Appendix I). The same criteria were used as for the clinical review with the additional criteria that, to be included, studies must have been published since the original Long-acting reversible contraception guideline was published (2005), and must assess cost-utility or cost-effectiveness in the UK NHS. The search retrieved 1167 articles. The titles and abstracts were screened for possible inclusion, and 1 article was selected for further examination of the full-text version. This article was excluded because the economic model that was used was not reported in sufficient detail to allow a thorough quality assessment. A review flow chart is provided in appendix J, and the excluded study (with reason for exclusion) is shown in appendix K.

2.1.4 Evidence statements

2.1.4.1 Population: women aged 18-40

Outcome: nerve injury

Three case reports (reporting a total of 4 cases) identified nerve injury associated with etonogestrel implant use in a total of 4 cases. It was not possible to estimate the rate of nerve injury associated with implant use. [Very low quality]

Outcome: pregnancy

Pregnancy during etonogestrel implant treatment was assessed by 1 small randomised controlled trial, 17 non-comparative studies and 1 study reporting post-marketing surveillance. The majority of studies estimated pregnancy rates to be less than 1 case per 1000 implants fitted. [Low – very-low quality].

Outcome: bleeding pattern changes

Thirteen non-comparative studies assessed the effect of etonogestrel implant use on menstrual bleeding pattern changes. The definition of bleeding pattern types varied among studies.

- All studies found that the majority of women experienced bleeding changes during implant use.
- All studies reported that both increases and reductions in bleeding frequency and duration were commonly associated with implant use.

Three studies found that implant use was associated with a reduction in the severity of dysmenorrhoea. [Very low quality]

Outcome: removal difficulties

Nine non-comparative studies assessed removal complications for etonogestrel implants. The rate of removal complications was less than 6% in all studies. [Very low quality]

Outcome: fracture of implant

Six case reports identified implant fractures during use in a total of 16 cases. It was not possible to estimate the rate of implant fracture from these studies. [Very low quality]

Outcome: implant site reaction

Five non-comparative studies assessed the rate of implant site reaction for etonogestrel implants. The rate of reaction varied considerably among studies from 0.5-27.2%. A variety of criteria were used to define an implant site reaction. [Very low quality]

Outcome: insertion difficulty

Ten non-comparative studies assessed etonogestrel implant insertion difficulty. The rate of insertion difficulty was below 2 % for all studies. [Very low quality]

Outcome: drug interactions

One study of post-marketing surveillance and five case reports reported pregnancy during etonogestrel implant use that were attributed to drug interactions. Estimates from post marketing surveillance suggest that drug interactions accounted for around 25% of etonogestrel implant method failures. [Very low quality]

Outcome: return to fertility

Two non-comparative studies assessed return to fertility following implant removal. One study found that ovulation occurred in 40% of women the month following implant removal. Both studies assessed pregnancy following implant removal among women not using contraception. Pregnancy rates within 3 months of removal ranged from 13.8-29.2%. [Very low quality]

2.1.4.1.1 Subgroup: women with high body weight or body mass index (BMI)

Outcome: pregnancy

One large non-comparative study assessed pregnancy during implant use for women who had normal body weight, were overweight, or were obese. No pregnancies were reported in the normal and overweight groups, and one pregnancy was reported in the obese group (although it was suspected that fertilisation may have occurred before implant insertion). [Very low quality]

2.1.4.2 Population: women aged under 18

Outcome: pregnancy

Two small non-comparative studies that assessed pregnancy during implant use in young people were identified as indirect evidence (the study populations were under 20 and under 24 and the number of participants under the age of 18 were not reported). No pregnancies were reported in one study, and one pregnancy was reported in the second (which was attributed to an interaction between etonogestrel and carbamazepine). [Very low quality]

2.1.4.3 Population: women aged over 40

Outcomes: pregnancy and insertion difficulty

One very small non-comparative study which assessed insertion difficulty and pregnancy during implant use in women over the age of 35 was identified as indirect evidence. No pregnancies or insertion complications were reported during the study. [Very low quality]

2.1.5 Evidence to recommendations

	Committee discussion
Relative value of different outcomes	Important and critical outcomes were chosen and ranked by the topic-specific members of the Committee and then agreed by the other Committee members before the review was carried out. The relative value of different outcomes was discussed, and the final rankings were completed by each member independently and then collated. The following outcomes (listed in order of importance) were considered critical to decision making: nerve injury, pregnancy, vaginal bleeding pattern changes, and difficulty with device removal. The following outcomes (also listed in order of importance) were considered important for decision making: fracture of the implant, implant site reaction, insertion difficulty, drug interactions and return to fertility. The Committee noted that nerve injury was a serious adverse outcome as it can lead to loss of sensation and movement in the affected arm, and may be long lasting. Pregnancy was considered critically important as avoidance of pregnancy is the reason that most women use subdermal implants, and an unwanted pregnancy can have serious long-lasting consequences. Bleeding changes was included as a critical outcome because, in the experience of the topic-specific Committee members, this is the most common reason for women to discontinue implant use prematurely. Removal difficulty was included as a critical outcome because it can have potentially serious consequences such as nerve damage and may require referral to a specialist centre.
Trade-off between benefits and harms	Benefits of etonogestrel implants identified in the evidence review were avoidance of pregnancy, the apparent absence of a delay in return to fertility following implant removal, and an apparent reduction in dysmenorrhoea for the duration of implant use. The topic-specific members noted that some bleeding pattern changes could be considered as a benefit or harm by different women, and that this may be influenced by cultural factors. Other harms identified in the evidence review included nerve injury, complications with insertion or removal and implant site reactions. Nerve injury was considered a serious harm, but there was little evidence on which to estimate the likelihood of this outcome. The Committee noted that the evidence suggested that although insertion and removal complications and site reactions could occur, they were uncommon, and so the Committee concluded that the benefits of etonogestrel implants were likely to outweigh the harms for most women. However, the Committee believed that the trade-off between benefits and harms is likely to depend on individual values and preferences. Consequently, the Committee

	Committee discussion
	believed that information about the likely benefits and harms should be given to women to allow them to make an informed choice about etonogestrel implants.
Trade-off between net health benefits and resource use	NICE clinical guideline 30 included an economic model of the cost effectiveness of different types of long-acting reversible contraception and concluded that all forms of long-acting reversible contraception were cost-effective (including the subdermal implant, Implanon). Given that Nexplanon (the only currently available subdermal contraceptive implant in the UK) is bioequivalent to Implanon, and has a similar cost, the Committee agreed that it was reasonable to assume that etonogestrel implants are very likely to remain a cost effective option.
Quality of evidence	There was 1 small randomised controlled trial that reported pregnancy in groups randomised to receive either Nexplanon or Implanon, which provided low quality evidence for this outcome, although the trial was underpowered to detect a difference in pregnancy rate between arms, and reported zero pregnancy events. The rest of the evidence was from 24 non-comparative studies (1 of Nexplanon and 23 of Implanon) and 17 case reports and provided very low quality evidence. An important possible source of bias for many studies was that the dropout rate was often very high (typically 30-40% over 3 years). Most studies reported that the majority of women who left the study did so because they wished to have their implant removed. The Committee noted that women with adverse side effects such as unacceptable bleeding pattern changes might be more likely to wish to have their implant removed, so estimates of adverse outcomes might be underestimated due to the high dropout rate. The Committee noted that some of the studies reporting bleeding pattern changes extended beyond 3 years, which is the recommended time after which an implant should be replaced. Etonogestrel levels decrease over time following implant fitting, and so bleeding patterns measured more than 3 years following fitting might not reflect bleeding patterns experienced by women during typical etonogestrel implant use. The definitions of implant site reaction and insertion or removal difficulties were often poorly specified and varied across studies. The Committee noted that this made it difficult to assess the seriousness of these outcomes. The topic-specific Committee members were particularly interested to know whether barium, which is included in the device Nexplanon but not Implanon, was associated with an increase in implant site reactions, but the data to determine this was not available. The topic-specific Committee members strongly felt that complications with insertion and removal of implants were likely to be associated with inadequate method-specific training of the fitter or remover rather than an intrinsic problem relating to the implant. The topic-specific Committee members noted that training on the fitting and removal of subdermal implants is provided by the Faculty of Sexual and Reproductive Health. The evidence on return to fertility following implant use was very low quality and based on 2 small studies. One study reported ovulation rate in the month following removal. The Committee noted that the ovulation rate reported in the study was not different from what would be expected in a population not taking hormonal contraception, but that ovulation was a very indirect measure of fertility. Two studies reported pregnancy rates following implant removal, and the topic-specific Committee members noted that the pregnancy rates were not substantially different to those expected from a general population trying to conceive. However, the Committee noted that these studies were very small and there was no attempt to assess the fertility of the male partner. Overall the Committee agreed that there was no evidence for a delay in return to fertility following implant removal and some limited very low quality evidence to

	Committee discussion
	suggest that there was no delay in return to fertility.
Other considerations	Nexplanon was the only subdermal implant licensed for use in the UK at the time of publication (date to be confirmed). The product is licensed for women aged 18-40 years. However, the topic-specific members of the Committee indicated that Nexplanon is in common clinical use in the UK outside of this age range. The evidence for the efficacy of etonogestrel implants in women under 18 and over 40 from this review was indirect and limited to very small studies. However, the Committee felt that given that implants are in widespread use outside of the licensed age range, the evidence from the 18-40 population could be extrapolated to older or younger women. Consequently, recommendations were not restricted to the age 18-40 population specified in the product licence. The Committee noted that the summary of product characteristics for Nexplanon contains important information on contraindications, adverse effects and instructions for fitting and removal that should be consulted by clinicians advising women on contraception. The Committee felt that it was important that women received information about likely changes to bleeding patterns during implant use. They noted that changes were likely to occur for the whole time that the implant was fitted. However, the topic-specific members noted that it was important that women were not discouraged from seeking advice about changes in bleeding patterns while using etonogestrel implants, and that once a bleeding pattern with the implant has been established, further changes in bleeding patterns should be investigated in the normal way.

2.1.6 Recommendations

1. **Inform women that etonogestrel implants[b] have a very low failure rate (less than 1 pregnancy per 1000 implants fitted over 3 years).**

2. **Inform women that vaginal bleeding patterns are likely to change while using an etonogestrel implant. Vaginal bleeding may stop, become more or less frequent, or be prolonged during implant use.**

3. **Inform women that dysmenorrhoea may reduce during etonogestrel implant use.**

4. **Inform women that there is no evidence showing a delay in return to fertility after an etonogestrel implant is removed.**

5. **Inform women that complications with etonogestrel implant insertion and removal are uncommon. (Possible complications are listed in the summary of product characteristics.)**

b At the time of publication (date to be confirmed), Nexplanon was the only subdermal implant licensed in the UK and did not have UK marketing authorisation for use outside of the age range 18-40 years. Outside of this age range, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the Nursing and Midwifery Council's Standards of proficiency for nurse and midwife prescribers for further information.

3 References

Agraw al A, Robinson C (2003) Spontaneous snapping of an Implanon in tw o halves in situ. Journal of Family Planning & Reproductive Health Care 29: 238

Agresti A, Coull BA (1998) Approximate is better than “exact” for interval estimation of binomial proportions. The American Statistician 52(2): 119-126

Aisien AO, Enosolease ME (2010) Safety, efficacy and acceptability of implanon a single rod implantable contraceptive (etonogestrel) in University of Benin Teaching Hospital. Nigerian Journal of Clinical Practice 13: 331-5

Arribas-Mir L, Rueda-Lozano D, Agrela-Cardona M et al. (2009) Insertion and 3-year follow-up experience of 372 etonogestrel subdermal contraceptive implants by family physicians in Granada, Spain. Contraception 80: 457-62

Bentley J (2013) Experience and removal of damaged implants. Journal of Family Planning and Reproductive Health Care.39 (3) 233-4

Bhatia P, Nangia S, Aggarw al S et al. (2011) Implanon: subdermal single rod contraceptive implant. Journal of Obstetrics & Gynaecology of India 61: 422-5

Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M (2008) Tolerability and clinical safety of Implanon. [Review] [25 refs]. European Journal of Contraception & Reproductive Health Care 13: Suppl-36

Booranabunyat S, Taneepanichskul S (2004) Implanon use in Thai w omen above the age of 35 years. Contraception 69: 489-91

Brow n M, Britton J (2012) Neuropathy associated w ith etonogestrel implant insertion. Contraception 86: 591-3

Chaudhry F (232) Adverse reaction to Nexplanon(R). Journal of Family Planning & Reproductive Health Care 39: 231-2

Croxatto HB, Urbancsek J, Massai R et al. (1999) A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. Human Reproduction 14: 976-81

Croxatto HB (2000) Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. European Journal of Contraception & Reproductive Health Care 5: Suppl-8

Darney P, Patel A, Rosen K et al. (2009) Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertility & Sterility 91: 1646-53

Edw ards JE, Moore A (1999) Implanon. A review of clinical studies. British Journal of Family Planning 24: Suppl-16

Funk S, Miller MM, Mishell DR, Jr. et al. (2005) Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 71: 319-26

Gillies R, Scougall P, Nicklin S (2011) Etonogestrel implants - case studies of median nerve injury follow ing removal. Australian Family Physician 40: 799-800

Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. [Review] [11 refs]. European Journal of Contraception & Reproductive Health Care 13: Suppl-12

Guazzelli CA, de Queiroz FT, Barbieri M et al. (2010) Etonogestrel implant in postpartum adolescents: bleeding pattern, efficacy and discontinuation rate. Contraception 82: 256-9

Inal MM, Yildirim Y, Ertopcu K et al. (2008) Effect of the subdermal contraceptive etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow-up). European Journal of Contraception & Reproductive Health Care 13: 238-42

Kiriwat O, Patanayindee A, Koetsawang S et al. (1998) A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. European Journal of Contraception & Reproductive Health Care 3: 85-91

Kreitchmann R, Innocente AP, Preussler GM (2012) Safety and efficacy of contraceptive implants for HIV-infected women in Porto Alegre, Brazil. International Journal of Gynaecology & Obstetrics 117: 81-2

Lakhi N, Govind A (2010) Implanon failure in patients on antiretroviral medication: the importance of disclosure. Journal of Family Planning & Reproductive Health Care 36: 181-2

Leticee N, Viard JP, Yamgnane A et al. (2012) Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. Contraception 85: 425-7

Levine JP, Sinofsky FE, Christ MF et al. (2008) Assessment of Implanon insertion and removal. Contraception 78: 409-17

Makarainen L, van BA, Tuomivaara L et al. (1998) Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. Fertility & Sterility 69: 714-21

Mansour D, Mommers E, Teede H et al. (2010) Clinician satisfaction and insertion characteristics of a new applicator to insert radiopaque Implanon: an open-label, noncontrolled, multicenter trial. Contraception 82: 243-9

Mansour D, Korver T, Marintcheva-Petrova M et al. (2008) The effects of Implanon on menstrual bleeding patterns. [Review] [33 refs]. European Journal of Contraception & Reproductive Health Care 13: Suppl-28

Matiluko AA, Soundararjan L, Hogston P (2007) Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. Journal of Family Planning & Reproductive Health Care 33: 277-8

McCarty EJ, Keane H, Quinn K et al. (2011) Implanon failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies. International Journal of STD & AIDS 22: 413-4

Meirik O, Brache V, Orawan K et al. (2013) A multicenter randomized clinical trial of one-rod etonogestrel and two-rod levonorgestrel contraceptive implants with nonrandomized copper-IUD controls: methodology and insertion data. Contraception 87: 113-20

Mommers E, Blum GF, Gent TG et al. (2012) Nexplanon, a radiopaque etonogestrel implant in combination with a next-generation applicator: 3-year results of a noncomparative multicenter trial. American Journal of Obstetrics & Gynecology 207: 388-6

Myrick L, Howell C, Ramakrishnan K (2012) The broken (fractured) Implanon. Journal - Oklahoma State Medical Association 105: 394-5

Otero Flores JB, Lozano BM, Cortes BM et al. (2005) Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. International Journal of Gynecology and Obstetrics.90 (3) 228-33

Partridge R, Bush J (2013) Infections post-Nexplanon(R) insertion. Journal of Family Planning & Reproductive Health Care 39: 309-10

Pickard S, Bacon L (2002) Persistent vaginal bleeding in a patient with a broken Implanon. Journal of Family Planning & Reproductive Health Care 28: 207-8

Schindlbeck C, Janni W, Friese K (2006) Failure of Implanon contraception in a patient taking carbamazepin for epilepsia. Archives of Gynecology & Obstetrics 273: 255-6

Schnabel P, Merki-Feld GS, Malvy A et al. (2012) Bioequivalence and x-ray visibility of a radiopaque etonogestrel implant versus a non-radiopaque implant: a 3-year, randomized, double-blind study. Clinical Drug Investigation 32: 413-22

Sullivan MJ (2012) Allergy to nexplanon. Journal of Family Planning & Reproductive Health Care 38: 272

Tocce KM, Sheeder JL, Teal SB (2012) Rapid repeat pregnancy in adolescents: do immediate postpartum contraceptive implants make a difference? American Journal of Obstetrics & Gynecology 206: 481-7

Tomas-Tello MD, Hodgson G (2010) Two cases of broken Implanon(). Journal of Family Planning & Reproductive Health Care 36: 255

Torres R, Mendes N, Machado AI et al. (2013) In situ breakage of Implanon--two cases of a rare occurrence. Contraception 88: 189-91

Vicente L, Mendonca D, Dingle M et al. (2008) Etonogestrel implant in women with diabetes mellitus. European Journal of Contraception & Reproductive Health Care 13: 387-95

Wechselberger G, Wolfram D, Pulzl P et al. (2006) Nerve injury caused by removal of an implantable hormonal contraceptive. American Journal of Obstetrics & Gynecology 195: 323-6

Xu H, Wade JA, Peipert JF et al. (2012) Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstetrics & Gynecology 120: 21-6

Yildizbas B, Sahin HG, Kolusari A et al. (2007) Side effects and acceptability of Implanon: a pilot study conducted in eastern Turkey. European Journal of Contraception & Reproductive Health Care 12: 248-52

Zheng SR, Zheng HM, Qian SZ et al. (1999) A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. European Journal of Contraception & Reproductive Health Care 4: 85-93

Zheng SR, Zheng HM, Qian SZ et al. (1999) A randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon) and a six-capsule (Norplant) hormonal contraceptive implant. Contraception 60: 1-8

4 Glossary and abbreviations

Please refer to the NICE glossary.

Appendices

Appendix A: Committee members and NICE teams

A.1 Standing Committee members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Senior Research Fellow, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Nuala Lucas	Consultant Anaesthetist, Northwick Park Hospital, Middlesex
Kath Nuttall	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset PCT
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 Topic-specific Committee members

Name	Role
Nicola Davies	GP Principal, Honeypot Medical Centre, Harrow CCG
Alyson Elliman	Consultant in Sexual and Reproductive Healthcare, Croydon Health Service NHS Trust
Sonja Jutte	Lay member
Shelley Mehigan Raine	Nurse Specialist, Ringwood, Hampshire
Jan Wake	GP - special interest in sexual health, DeMontfort Surgery

A.3 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Jemma Burchett-Vass	Information specialist
Nicole Elliott	Associate Director
Kathryn Hopkins	Technical Analyst
Susannah Moon	Project Manager
Charlotte Purves	Administrator

Name	Role
Toni Tan	Technical Advisor

A.4 NICE project team

Name	Role
Christine Carson	Guideline Lead
Mark Baker	Clinical Advisor
Steven Barnes	Technical Lead
Ben Doak	Guideline Commissioning Manager
Gareth Haman	Senior Medical Editor
Laura Norburn	Public Involvement Advisor
Jennifer Wells	Guideline Co-ordinator

Appendix B: Declaration of interests

Member name	Interest declared	Date declared	Type of interest	Decision
Standing Committee members				
Damien Longson	Family member employee of NICE	29/05/13 (on appointment)	Personal family non-specific	Declare and participate
Damien Longson	Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust	29/05/13 (on appointment)	Personal non-specific pecuniary	Declare and participate
Catherine Briggs	Husband is a consultant anaesthetist at the University Hospital of South Manchester.	08/07/13	Personal family non-specific	Declare and participate
Catherine Briggs	Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA.	08/07/13	Personal non-specific pecuniary	Declare and participate
John Cape	Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the department of health and the national institute for health research.	10/07/13	Personal non-specific non-pecuniary	Declare and participate
John Cape	Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies.	10/07/13	Personal non-specific non-pecuniary	Declare and participate
Alun Davies	Research grant funding: Commercial: Vascular Insights; Acergy Ltd; Firstkind; URGO laboritoire; Sapheon Inc (terminated 2013). All administered by Imperial College London as Sponsor and Prof Davies as CI.	04/11/13	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: NIHR, BHF, Royal College of Surgeons, Circulation foundation, European Venous Forum.	04/11/13	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: Attendance at numerous national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known.	04/11/13	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: Has received travel expenses to attend the Veith Meeting NY 2013 November to give lectures by Vascutek.	04/11/13	Personal non-specific pecuniary	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Alison Eastwood	Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through NIHR to undertake technology assessment reviews.	10/07/13	Non-personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Receives payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness to Practise Investigating Committee.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Lay reviewed with the Local Supervising Authority auditing supervision of midwives - receives payment and expenses for this work.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Lay reviewer for the NIHR; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic girdle pain. This is a voluntary position.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy.	11/11/13	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Recently appointed by Mott MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work.	11/11/13	Personal non-specific pecuniary	Declare and participate
Jim Gray	None	10/07/13		No action
Nuala Lucas	Member Obstetric Anaesthetists' Association Executive Committee	08/01/14	Personal non-specific non-pecuniary	Declare and participate
Nuala Lucas	Member NICE – Intra-partum Care GDG	08/01/14	Personal non-specific non-pecuniary	Declare and participate
Nuala Lucas	Member, Editorial Board, International Journal of Obstetric Anesthesia	08/01/14	Personal non-specific non-pecuniary	Declare and participate
Kath Nuttall	None	02/07/13		No action
Tilly Pillay	None	11/07/13		No action
Nick	Attended Thorax meeting – travel	10/04/14	None specific	No action

Member name	Interest declared	Date declared	Type of interest	Decision
Screaton	expenses paid.		personal pecuniary	
Lindsay Smith	None	09/10/13		No action
Philippa Williams	None	27/06/13		No action
Sophie Wilne	Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Speaker at conferences to talk about TS – invited by Novatis – travel expenses only.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Presented at educational meetings sponsored by drug companies – not paid for educational events.	08/06/13	Personal non-specific non-pecuniary	Declare and participate
Topic-specific Committee members				
Nicola Davies	None	13/01/14		No action
Alyson Elliman	Support from pharmaceutical companies and suppliers of equipment (model arms and dummy inserters) – Durbin Sales, Merck, SD Bayer - to enable training and updating in all aspects of implant theory and procedures. No payments made - refreshment provided.	11/11/13	Specific non-personal pecuniary	Declare and participate
Sonja Jutte	None	08/01/14		No action
Shelley Mehigan Raine	Consultancy work for, and lecturing sponsored by, Bayer, MSD and Pfizer. Giving advice about training requirements and on advisory board related to release of new formulation of injectable.	13/11/13	Specific personal pecuniary	Declare and participate
Jan Wake	None	20/01/14		No action

Appendix C: Review protocol

	Details
Review Question	What is the effectiveness of sub-dermal implants for long-acting reversible contraception?
Objectives	The effectiveness of the etonogestrel sub-dermal implant, Implanon was reviewed in the existing guidelines on long-acting reversible contraception (CG30). At the time, Implanon was the only sub-dermal contraceptive implant licensed for use in the UK. Implanon is no longer available. It has been replaced by Nexplanon, which contains the same drug and dose, with the addition of barium to make it radio-opaque and a change to the inserter device to make sub-dermal positioning easier. The objective is to update the recommendations made in CG30 on sub-dermal contraceptive implants so that they apply to current clinical practice in the UK.
Type of Review	Intervention
Language	English
Study Design	Randomised controlled trials, non-randomised controlled studies, systematic reviews, observational studies, case series, case reports (see: other criteria for inclusion/exclusion of studies below)
Status	Published papers (full text only)

Population	• Women aged between 18 and 40 using etonogestrel sub-dermal implants for long-acting reversible contraception
	  ○ Subgroups: Women using Nexplanon and Women using Implanon (evidence to be presented separately)
	  ○ Subgroup: Women with a high body weight or BMI (as defined in study)
	• Women below the age of 18 using etonogestrel sub-dermal implants for long-acting reversible contraception
	• Women above the age of 40 using etonogestrel sub-dermal implants for long-acting reversible contraception

Intervention	Etonogestrel sub-dermal implants (Nexplanon or Implanon)
Comparator	• Other etonogestrel sub-dermal implant (Implanon if intervention is Nexplanon) • No contraception • No comparator
Outcomes	**Critical outcomes:** • Nerve injury • Pregnancy • bleeding changes: frequency, infrequency, prolonged, dysmenorrhoea, amenorrhoea, irregularity • removal: ease or difficulty with **Important outcomes :** • fractures of implant • reaction at insertion site • insertion: ease or difficulty with (including insertion errors) • drug interactions • return to fertility following removal
Other criteria for inclusion / exclusion of studies	**Inclusion** For each outcome, we will search for evidence using a step-wise approach based on the following hierarchy of evidence. If no evidence or evidence that is insufficient to support a recommendation is found following each step, we will proceed to the next level of evidence:

	Details
	• Systematic reviews* • Randomised controlled trials** • Non-randomised controlled studies** • Prospective comparative observational studies** • Retrospective comparative observational studies** • Prospective non-comparative studies (participants not selected on outcome) • Retrospective non-comparative studies (participants not selected on outcome) • Case series (cases selected on outcome) • Case reports (cases selected on outcome) *Systematic reviews must have the same inclusion and exclusion criteria as defined in this protocol, and meet the quality standards defined in the NICE clinical guidelines methods handbook. **If the comparator is another form of contraception, data will be extracted from the etonogestrel implant arm only and will be considered as a non-comparative study. **Exclusion** • Narrative reviews • Qualitative studies • Studies comparing sub-dermal implants with other methods of contraception where data for implant arm cannot be separately extracted. • Studies published before 1995.
Search strategies	Due to the wide range of study design types included, no search filters will be incorporated into the search strategy.
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements

Appendix D: Search strategy

Databases were initially searched with a date restriction of 2003-2013 (search 1 below). Later, an additional search was carried out with the same terms, but a date restriction of 1995-2003 (search 2 below). The results of the two searches were combined for the evidence review. For both searches, the EMBASE search strategy is shown. The same strategy was translated for the other databases listed.

D.1 Search 1: 2003-2013

Table 1: Clinical search 1 summary

Database	Date searched	Number retrieved
CDSR (Wiley)	12/12/13	13
Database of Abstracts of Reviews of Effects – DARE (Wiley)	12/12/13	0
HTA database (Wiley)	12/12/13	0
CENTRAL (Wiley)	12/12/13	0
MEDLINE (Ovid)	12/12/13	2717
MEDLINE In-Process (Ovid)	12/12/13	272
EMBASE (Ovid)	12/12/13	6721
Pubmed	13/12/13	114
PsycINFO (Ovid)	12/12/13	127

Table 2: Clinical search 1 terms (EMBASE)

Line number	Search term	Number retrieved
1	implanon.tw.	768
2	nexplanon.tw.	50
3	etonogestrel/	1298
4	etonogestrel.tw.	394
5	norplant*.tw.	1537
6	levonorgestrel/	9057
7	levonorgestrel.tw.	4100
8	desogestrel/	2775
9	desogestrel.tw.	1125
10	progestin implant/	4
11	((progestogen* or progestagen* or progestin* or gestagen* or contracept*) adj4 (implant* or subderm* or subcut*)).tw.	1308
12	(POSDI* or LARC).tw.	606
13	(long adj4 acting adj4 contracept*).tw.	780
14	(contracept* adj4 (implant* or subderm* or subcut*)).tw.	1094
15	or/1-14	13528
16	Nonhuman/ not Human/	3349671
17	15 not 16	13113
18	limit 17 to english language	11165

Line number	Search term	Number retrieved
19	limit 18 to em=200300-201349	6721

D.2 Search 2: 1995-2003

Table 3: Clinical search 2 summary

Database	Date searched	Number retrieved
CDSR (Wiley)	14/2/14	32
Database of Abstracts of Reviews of Effects – DARE (Wiley)	14/2/14	0
HTA database (Wiley)	14/2/14	0
CENTRAL (Wiley)	14/2/14	0
NHS EED (Wiley)	14/2/14	1
MEDLINE (Ovid)	14/2/14	1563
MEDLINE In-Process (Ovid)	14/2/14	1
EMBASE (Ovid)	14/2/14	1902
PsycINFO (Ovid)	14/2/14	39

Table 4: Clinical search 2 terms (EMBASE)

Line number	Search term	Number retrieved
1	implanon.tw.	770
2	nexplanon.tw.	52
3	etonogestrel/	1315
4	etonogestrel.tw.	405
5	norplant*.tw.	1540
6	levonorgestrel/	9175
7	levonorgestrel.tw.	4171
8	desogestrel/	2793
9	desogestrel.tw.	1135
10	progestin implant/	5
11	((progestogen* or progestagen* or progestin* or gestagen* or contracept*) adj4 (implant* or subderm* or subcut*)).tw.	1323
12	(POSDI* or LARC).tw.	623
13	(long adj4 acting adj4 contracept*).tw.	795
14	(contracept* adj4 (implant* or subderm* or subcut*)).tw.	1107
15	or/1-14	13706
16	Nonhuman/ not Human/	3381252
17	15 not 16	13288
18	limit 17 to english language	11333
19	limit 18 to em=200300-201349	2807
20	limit 19 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or letter or note)	493
21	19 not 20	2314
22	limit 21 to embase	1902

Appendix E: Review flowchart

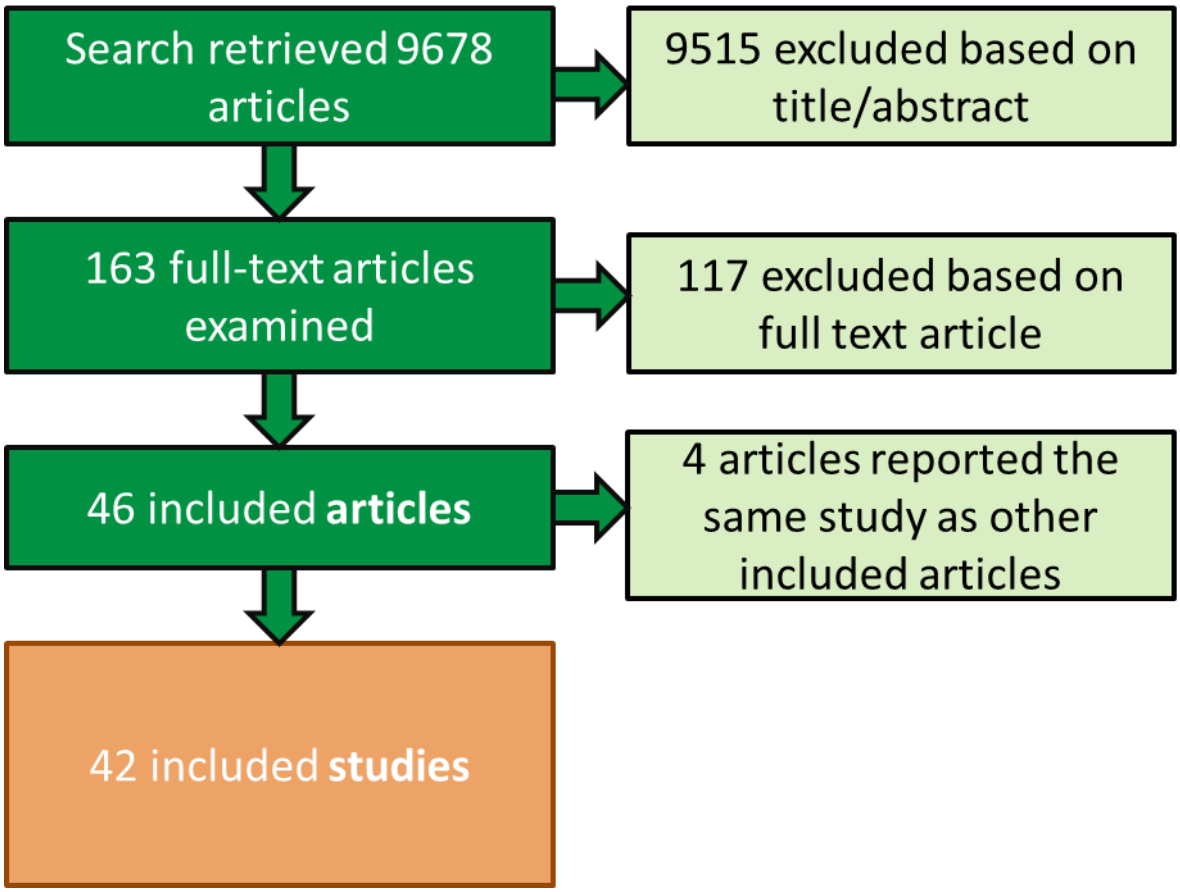

Figure 1: Clinical review flowchart

Appendix F:Excluded studies

Reference	Reason for exclusion
Anon (2008) Etonogestrel contraceptive implant: ulnar nerve damage. Prescrire International 17: 63.	Not primary research (describes previous case reports)
Anon (2008) Etonogestrel implants: drug interactions and unintended pregnancies. Keep in mind enzyme inducers. Prescrire International 17: 67.	Not primary research (Advice/opinion)
Anon (2001) Etonogestrel subcutaneous implant: Contraception lasting 2-3 years. Prescrire International.10 (55) (pp 159).	Not primary research (Clinical advice/narrative review)
Anon (2010) Unintended pregnancy due to interaction between etonogestrel implant (Implanon) and carbamazepine. Australian Prescriber.33 (6) (pp 185)	Exclude: Not primary research (Clinical advice)
Affandi B, Korver T, Geurts TBP et al. (1999) A pilot efficacy study with a single-rod contraceptive implant (Implanon) in 200 Indonesian women treated for <=4 years (Retraction in: Contraception (2004) 70:5 (433)). Contraception.59 (3) (pp 167-174),	Retracted
Affandi B (1998) An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon (Retraction in: Contraception (2004) 70:5 (433)). Contraception.58 (6 SUPPL.) (pp 99S-107S),	Retracted
Agrawal A, Robinson C (2005) An assessment of the first 3 years' use of Implanon in Luton. Journal of Family Planning & Reproductive Health Care 31: 310-2.	Retrospective non-comparative study (higher quality evidence available for all reported outcomes)[a]
Bahamonde M, Siqueira L (2011) Hispanic adolescents' satisfaction and continuation rates with Implanon. Journal of Adolescent Health.Conference 48 (2 SUPPL.1) (pp S117- : S117-S118.	Conference abstract, no full-text article
Bahamondes L, Monteiro-Dantas C, Espejo-Arce X et al. (2006) A prospective study of the forearm bone density of users of etonorgestrel- and levonorgestrel-releasing contraceptive implants. Human Reproduction 21: 466-70.	Does not report outcomes specified in review protocol
Beerthuizen R, van BA, Massai R et al. (2000) Bone mineral density during long-term use of the progestagen contraceptive implant Implanon compared to a non-hormonal method of contraception. Human Reproduction 15: 118-22.	Does not report outcomes specified in review protocol
Beligotti F, Mommers E, Marintcheva-Petrova M (2012) Women's expectations and satisfaction on bleeding pattern when using implanon nxt. International Journal of Gynecology and Obstetrics.Conference 119 (pp S571-S572)	Conference abstract, no full-text article
Benavides C, Munoz X, Contreras B et al. (2009) Effects of the etonorgestrel-releasing contraceptive implant Implanon on menstrual bleeding pattern and acceptability. International Journal of Gynecology and Obstetrics.Conference 107 (pp S125)	Conference abstract, no full-text article
Bennink HJ (2000) The pharmacokinetics and pharmacodynamics of Implanon, a single-rod etonogestrel contraceptive implant. [Review] [20 refs]. European Journal of Contraception & Reproductive Health Care 5: Suppl-20.	Not primary research (Narrative review)
Bennink HJTC (1998) Presentation of clinical data on Implanon. Contraception 58: 75S.	Not primary research (Introductory commentary for Implanon journal supplement)
Biswas A, Viegas OA, Roy AC (2003) Effect of Implanon and Norplant subdermal contraceptive implants on serum lipids--a	Does not report outcomes specified in review protocol

Reference	Reason for exclusion
randomized comparative study. Contraception 68: 189-93.	
Biswas A, Viegas OA, Bennink HJ et al. (2000) Effect of Implanon use on selected parameters of thyroid and adrenal function. Contraception 62: 247-51.	Does not report outcomes specified in review protocol
Biswas A, Viegas OA, Coeling Bennink HJ et al. (2001) Implanon contraceptive implants: effects on carbohydrate metabolism. Contraception 63: 137-41.	Does not report outcomes specified in review protocol
Bitzer J, Tschudin S, Alder J et al. (2004) Acceptability and side-effects of Implanon in Switzerland: a retrospective study by the Implanon Swiss Study Group. European Journal of Contraception & Reproductive Health Care 9: 278-84.	Retrospective non-comparative study (higher quality evidence available for reported outcomes)[a]
Bouquier J, Fulda V, Bats AS et al. (2012) A life-threatening ectopic pregnancy with etonogestrel implant. Contraception 85: 215-7.	Case report (higher quality evidence available for reported outcome)
Buitron R, Rodriguez A, Gonzalez J et al. (2009) Complex location of subdermic single-rod contraceptive implant: A case report. International Journal of Gynecology and Obstetrics 107 S616	Conference abstract, no full text article
Casey PM, Long ME, Marnach ML et al. (2013) Association of body mass index with removal of etonogestrel subdermal implant. Contraception 87: 370-4.	Retrospective non-comparative study (higher quality evidence available for all reported outcomes)[a]
Casey PM, Long ME, Marnach ML et al. (2011) Bleeding related to etonogestrel subdermal implant in a US population. Contraception 83: 426-30.	Retrospective non-comparative study (higher quality evidence available for all reported outcomes)[a]
Chakhtoura Z, Canonico M, Gompel A et al. (2011) Progestogen-only contraceptives and the risk of acute myocardial infarction: A meta-analysis. Journal of Clinical Endocrinology and Metabolism 96 (4):1169-74.	Systematic review - does not match review protocol (includes oral contraceptives)
Chakhtoura Z, Canonico M, Gompel A et al. (2009) Progestogen-only contraceptives and the risk of stroke: A meta-analysis. Stroke 40 (4): 1059-62.	Systematic review - does not match review protocol (includes oral contraceptives)
Chandy C (2008) Implant removal by modifying access. Journal of Family Planning and Reproductive Health Care 34 (4) 273.	Case report (higher quality evidence available for reported outcome)[a]
Chaouki M, Najeh H, Abdelaziz AB et al. (2013) Ectopic pregnancy under Implanon contraception: A case of encysted haematocele Tunisie Medicale 91 (8-9) 561-2.	Case report (higher quality evidence available for reported outcome)[a]
Chaovisitsaree S, Piyamongkol W, Pongsatha S et al. (2005) One year study of Implanon on the adverse events and discontinuation. Journal of the Medical Association of Thailand 88: 314-7.	Does not report outcomes specified in review protocol
Cooling H, Pauli H (2006) Full-term pregnancy with Implanon in situ. Journal of Family Planning & Reproductive Health Care 32: 204.	Does not report outcomes specified in review protocol (case report of pregnancy before Implanon insertion)
Croxatto HB, Makarainen L (1998) The pharmacodynamics and efficacy of Implanon: An overview of the data (Retraction in: Contraception (2004) 70:5 (433)). Contraception 58 (6 SUPPL.) 91S-7S.	Retracted
Curtis KM (2002) Safety of implantable contraceptives for women: data from observational studies. [Review] [64 refs]. Contraception 65: 85-96.	Systematic review. Use for cross check.
Dawson R, Hansen S, Stafford E (2010) Etonogestrel implant related experiences in an adolescent medicine clinic. Journal of Adolescent	Conference abstract, no full-text article

Reference	Reason for exclusion
Health S57.	
Deokar AM, Jackson W, Omar HA (2011) Menstrual bleeding patterns in adolescents using etonogestrel (ENG) implant. International Journal of Adolescent Medicine & Health 23: 75-7.	Not primary research (Advice/Best practice guidance)
Dhesi S, Davis M (2008) Implanon insertion in Zimbabwe. Journal of Family Planning & Reproductive Health Care 34: 136.	Does not report outcomes specified in review protocol.
Di CC, Sansone A, De RN et al. (2013) Impact of an implantable steroid contraceptive (etonogestrel-releasing implant) on quality of life and sexual function: a preliminary study. Gynecol.Endocrinol.	Does not report outcomes specified in review protocol
Dilbaz B, Ozdegirmenci O, Caliskan E et al. (2010) Effect of etonogestrel implant on serum lipids, liver function tests and hemoglobin levels. Contraception 81: 510-4.	Does not report outcome specified in review protocol
Egberg N, van BA, Gunnervik C et al. (1998) Effects on the hemostatic system and liver function in relation to Implanon and Norplant. A prospective randomized clinical trial. Contraception 58: 93-8.	Does not report outcomes specified in review protocol
Evans R, Holman R, Lindsay E (2005) Migration of implanon: two case reports. Journal of Family Planning & Reproductive Health Care 31: 71-2.	Does not report outcomes specified in review protocol
Finnegan S, Conlon O, Kirk S (2007) Non-continuing twin pregnancy on Implanon. Journal of Family Planning & Reproductive Health Care 33: 279.	Case report (higher quality evidence available for reported outcome)[a]
French RS, Cowan FM, Mansour DJA et al. (2000) Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: Two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness. Health Technology Assessment 4: i-98.	Systematic review. Not updated since 2000. Use for cross check.
Garrido JF, Deulofeu P, Avecilla A et al. (2010) Complications in the removal of subdermal contraceptive implants for seven years. Migration of the implants. European Journal of Contraception and Reproductive Health Care. 51-2.	Conference abstract, no full-text article
Gbolade BA (2012) Ectopic pregnancy with Implanon in a patient on anticonvulsant therapy. European Journal of Contraception and Reproductive Health Care. S67.	Conference abstract, no full text article
Gilliam M, Mornar S, Chan LN et al. (2011) Pharmacokinetics of the etonogestrel contraceptive implant in obese women. Contraception 84 (3) 305-6.	Conference abstract, no full-text article
Guazzelli CA, de Queiroz FT, Barbieri M et al. (2011) Etonogestrel implant in adolescents: evaluation of clinical aspects. Contraception 83: 336-9.	Does not report outcomes specified in review protocol (reports bleeding patterns, but not as change from baseline)
Gurel K, Gideroglu K, Topcuoglu A et al. (2012) Detection and Localization of a Nonpalpable Subdermal Contraceptive Implant Using Ultrasonography: A Case Report. Journal of Medical Ultrasound 20 (1) 47-9.	Case report (higher quality evidence available for reported outcome)[a]
Gwinnell E (2007) Expulsion of Implanon. Journal of Family Planning & Reproductive Health Care 33: 211.	Case report (higher quality evidence available for reported outcome)[a]
Hamontri S, Weerakul W (2007) Implanon failure. Journal of the Medical Association of Thailand 90: 381-3.	Case report (higher quality evidence available for reported outcome)[a]
Han L, Sheeder J, Teal S et al. (2012) Cost-effectiveness of immediate postpartum etonogestrel implant insertion for adolescent	Conference abstract, no full-text article

Reference	Reason for exclusion
mothers. Contraception 86 (3) 292.	
Han L, Sheeder J, Thurman B et al. (2013) Cost comparison of immediate postpartum etonogestrel implants to immediate post-placental IUDS in adolescent mothers. Contraception 88 (3) 453.	Conference abstract, no full-text article
Han L, Fan H, Gong Q et al. (1999) Effects of three types of long-acting contraceptive implants on menstrual blood loss in 89 women. Journal of reproduction & contraception 10: 91-7.	Does not report outcomes specified in review protocol.
Harrison-Woolrych M, Hill R (2005) Unintended pregnancies with the etonogestrel implant (Implanon): a case series from postmarketing experience in Australia. Contraception 71: 306-8.	Case series (higher quality evidence available for reported outcome)[a]
Henderson PM, Gillespie MD (2007) Ectopic pregnancy with Implanon. Journal of Family Planning & Reproductive Health Care 33: 125-6.	Case report (higher quality evidence available for reported outcome)[a]
Hlavackova O, Apetauer I (2009) Clinical experience with Implanon in Czech Republic. International Journal of Gynecology and Obstetrics. 107 S619-S620.	Conference abstract, no full text article
Hoggart L, Newton VL (2013) Young women's experiences of side-effects from contraceptive implants: a challenge to bodily control. Reproductive Health Matters 21: 196-204.	Qualitative study
Hohmann H (2009) Examining the efficacy, safety, and patient acceptability of the etonogestrel implantable contraceptive. Patient preference & adherence 3: 205-11.	Not primary research (Narrative review)
Huber J, Wenzl R (1998) Pharmacokinetics of Implanon. An integrated analysis.[Erratum appears in Contraception 1999 Feb;59(2):145], [Retraction in Rekers H, Affandi B. Contraception. 2004 Nov;70(5):433; PMID: 15504385]. Contraception 58: Suppl-90S.	Retracted
Iltemir DC, Onaran Y, Aktepe KE et al. (2013) Does etonogestrel contraceptive implant (IMPLANON) effect bone metabolism during lactation period? Fertility and Sterility. S314.	Conference abstract, no full-text article
Ismail H, Mansour D, Singh M (2006) Migration of Implanon. Journal of Family Planning & Reproductive Health Care 32: 157-9.	Does not report outcomes specified in review protocol.
Jaffer K, Whalen S (2005) Self removal of Implanon: a case report. Journal of Family Planning & Reproductive Health Care 31: 248.	Does not report outcomes specified in review protocol.
James P, Trenery J (2006) Ultrasound localisation and removal of non-palpable Implanon implants. Australian & New Zealand Journal of Obstetrics & Gynaecology 46: 225-8.	Case series (higher quality evidence available for reported outcome)[a]
Le J, Tsourounis C (2001) Implanon: a critical review. Annals of Pharmacotherapy 35: 329-36.	Not primary research (Non-systematic review - inclusion criteria and search strategy unclear)
Lewis LN, Doherty DA, Hickey M et al. (2010) Implanon as a contraceptive choice for teenage mothers: a comparison of contraceptive choices, acceptability and repeat pregnancy. Contraception 81: 421-6.	Does not report outcomes specified in review protocol (bleeding patterns reported, but not reported as change in bleeding patterns from baseline)
Lyons J, Armitage C, Mitchell C et al. (2012) High early continuation rates of etonogestrel contraceptive implant (Nexplanon) in a university general practice. European Journal of Contraception and Reproductive Health Care. S112-S113.	Conference abstract, no full-text article.
Mahmoud H, Webb A (2010) Follow-up and review of 946 sub-dermal Implanon inserted in the first half of 2008. European Journal of Contraception and Reproductive Health Care. 38.	Conference abstract, no full text article
Mansour D (2007) Implanon failure or a natural event? Journal of	Case report (higher quality

Reference	Reason for exclusion
Family Planning & Reproductive Health Care 33: 127.	evidence available for reported outcome)[a]
Mansour D, Walling M, Glenn D et al. (2008) Removal of non-palpable etonogestrel implants. Journal of Family Planning & Reproductive Health Care 34: 89-91.	Not primary research (Narrative review/good practice guidance)
Mascarenhas L (1998) Insertion and removal of Implanon (Retraction in: Contraception (2004) 70:5 (433)). Contraception.58 (6 SUPPL) 79S-83S.	Retracted
Mascarenhas L (2000) Insertion and removal of Implanon: practical considerations. European Journal of Contraception & Reproductive Health Care 5: Suppl-34.	Not primary research (Narrative review/commentary)
Mbarki C, Hsayaoui N, Ben AA et al. (2013) Ectopic pregnancy under Implanon contraception: a case of encysted haematocele. Tunisie Medicale 91: 561-2.	Article not in English
Meirik O (2002) Implantable contraceptives for women. Contraception 65: 1-2.	Not primary research (Narrative review/commentary)
Merki-Feld GS, Imthurn B, Seifert B (2008) Effects of the progestagen-only contraceptive implant Implanon on cardiovascular risk factors. Clinical Endocrinology 68: 355-60.	Does not report outcomes specified in review protocol.
Merki-Feld GS, Imthurn B, Seifert B (2008) Effects of the progestagen-only contraceptive implant Implanon on transforming growth factor beta1 and endothelin-1. Hormone & Metabolic Research 40: 692-6.	Does not report outcomes specified in review protocol.
Merki-Feld GS, Imthurn B, Rosselli M et al. (2011) Implanon use lowers plasma concentrations of high-molecular-weight adiponectin. Fertility & Sterility 95: 23-7.	Does not report outcomes specified in review protocol.
Merki-Feld GS, Rosselli M, Imthurn B et al. (2011) No effect of Implanon on inflammatory cardiovascular parameters. Gynecological Endocrinology 27: 951-5.	Does not report outcomes specified in review protocol.
Monteiro-Dantas C, Espejo-Arce X, Lui-Filho JF et al. (2007) A three-year longitudinal evaluation of the forearm bone density of users of etonogestrel- and levonorgestrel-releasing contraceptive implants. Reproductive Health 4: 11.	Does not report outcomes specified in review protocol.
Mornar S, Chan LN, Mistretta S et al. (2012) Pharmacokinetics of the etonogestrel contraceptive implant in obese women. American Journal of Obstetrics & Gynecology 207: 110-6.	Does not report outcomes specified in review protocol.
Mulayim B, Yigit CN, Aytekin F (2012) Ultrasound localization and removal of impalpable 'lost implanon': Case report. Turkiye Klinikleri Jinekoloji Obstetrik.22 (2) 137-40.	Article not in English
Mutihir JT, Daru PH (2008) Implanon sub-dermal implants: a 10-month review of acceptability in Jos, North-Central Nigeria. Nigerian Journal of Clinical Practice 11: 320-3.	Retrospective non-comparative study (higher-quality evidence available for all reported outcomes)[a]
Namratha S (2013) Review of bleeding problems with progestogen-only implant. European Journal of Contraception and Reproductive Health Care S113-S114.	Conference abstract, no full-text article
Navani M, Robinson C (2005) Clinical challenge with Implanon removal: a case report. Journal of Family Planning & Reproductive Health Care 31: 161-2.	Case report (higher quality evidence available for this outcome).[a]
Newton J, Newton P (2003) Implanon - The single-rod subdermal contraceptive implant. Journal of Drug Evaluation 1 (6). 181-218.	Synthesis of data from clinical trials, some of which have now been retracted

Reference	Reason for exclusion
Nodler JL, Smith HJ, Arbuckle JL et al. (2013) Immediate postpartum placement of an etonogestrel implant (impla-non) improves contraceptive continuation and reduces unplanned pregnancy. Fertility and Sterility 99 (3 SUPPL.1) S19.	Conference abstract, no full-text article
Noraziana AW (2012) Subdermal contraceptive implant in post partum women: A prospective study in a single tertiary centre in pahang, malaysia: A preliminary study. International Journal of Gynecology and Obstetrics.119 S570-S571.	Conference abstract, no full text article
Nouri K, Pinker-Domenig K, Ott J et al. (2013) Removal of non-palpable Implanon with the aid of a hook-wire marker. Contraception 88: 577-80.	Does not report outcomes specified in review protocol.
Oloto E, Mascarenhas L (2000) Subdermal contraceptive implants. British Journal of Family Planning 26: 171-4.	Not primary research (Narrative review)
Olowu O, Karunaratne J, Odejinmi F (2011) Ectopic pregnancy with Implanon as a method of contraception in a woman with a previous ectopic pregnancy - case report. European Journal of Contraception & Reproductive Health Care 16: 229-31.	Case report (higher quality evidence available for reported outcome).[a]
Patni S, Ebden P, Kevelighan E et al. (2006) Ectopic pregnancy with Implanon. Journal of Family Planning & Reproductive Health Care 32: 115.	Case report (higher quality evidence available for reported outcome).[a]
Peters KP, Blum GF, Gent TG et al. (2012) Radiopaque etonogestrel implant with the new applicator: 3-year study. Contraception 86 (2) 182.	Conference abstract, no full-text article
Piessens SG, Palmer DC, Sampson AJ (2005) Ultrasound localisation of non-palpable Implanon. Australian & New Zealand Journal of Obstetrics & Gynaecology 45: 112-6.	Does not report outcomes specified in review protocol.
Pongsatha S, Ekmahachai M, Suntornlimsiri N et al. (2010) Bone mineral density in women using the subdermal contraceptive implant Implanon for at least 2 years. International Journal of Gynaecology & Obstetrics 109: 223-5.	Does not report outcomes specified in review protocol.
Postlethwaite D, Mason I, Merchant M et al. (2012) Subdermal contraceptive implant: "Typical use" in a California managed care setting. Contraception. 85 (3) 327.	Conference abstract, no full text article
Power J, French R, Cowan F (2007) Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Cochrane Database of Systematic Reviews : CD001326.	Systematic review, does not match review protocol, use for cross check
Queiroz F, Tapis T, Barbieri M et al. (2013) Use of etonogestrel implants in postpartum adolescents: A safe and effective contraceptive method. European Journal of Contraception and Reproductive Health Care. S108.	Conference abstract, no full-text paper
Queiroz F, Guazzelli C, Guazzelli T et al. (2010) Use of hormonal contraception in adolescents: Etonogestrel implant European Journal of Contraception and Reproductive Health Care. 77.	Conference abstract, no full-text paper
Rai K, Gupta S, Cotter S (2004) Experience with Implanon in a northeast London family planning clinic. European Journal of Contraception & Reproductive Health Care 9: 39-46.	Retrospective non-comparative study (higher quality evidence available for all outcomes reported)[a]
Rai K, Gupta S, Cotter S (2004) Experience with Implanon in a northeast London family planning clinic. European Journal of Contraception & Reproductive Health Care 9: 39-46.	Retrospective non-comparative study (higher quality evidence available for all outcomes reported)[a]
Reader CA (2009) Pregnancy at time of change of Implanon implant. Journal of Family Planning & Reproductive Health Care 35: 265.	Case report (higher quality evidence available for all reported outcomes).

Reference	Reason for exclusion
Reinprayoon D, Taneepanichskul S, Bunyavejchevin S et al. (2000) Effects of the etonogestrel-releasing contraceptive implant (Implanon on parameters of breastfeeding compared to those of an intrauterine device. Contraception 62: 239-46.	Does not report outcomes specified in review protocol
Reuter S, Smith A (2003) Implanon: user views in the first year across three family planning services in the Trent Region, UK. European Journal of Contraception & Reproductive Health Care 8: 27-36.	Retrospective non-comparative study (higher quality evidence available for all reported outcomes)[a]
Riney S, O'Shea B, Forde A (2009) Etonogestrel implant as a contraceptive choice; patient acceptability and adverse effect profile in a general practice setting. Irish Medical Journal 102: 24-5.	Retrospective non-comparative study (higher quality evidence available for reported outcomes)[a]
Rowlands S, Sujan MA, Cooke M (2010) A risk management approach to the design of contraceptive implants. Journal of Family Planning & Reproductive Health Care 36: 191-5.	Not primary research (Comment/good practice guidance)
Shepherd DJ (2012) Self-removal of a contraceptive implant. Journal of Family Planning & Reproductive Health Care 38: 208.	Does not report outcomes specified in review protocol.
Singh M, Mansour D, Richardson D (2006) Location and removal of non-palpable Implanon implants with the aid of ultrasound guidance. Journal of Family Planning & Reproductive Health Care 32: 153-6.	Case series (higher quality evidence available for reported outcome)
Smith A, Reuter S (2002) An assessment of the use of Implanon in three community services. Journal of Family Planning & Reproductive Health Care 28: 193-6.	Retrospective non-comparative study (higher quality evidence available for all reported outcomes)[a]
Stillwell S, Sheppard P, Searle S (2003) The impalpable Implanon: a case report. Journal of Family Planning & Reproductive Health Care 29: 156-7.	Case report (higher quality evidence available for reported outcome)[a]
Suherman SK, Affandi B, Korver T (1999) The effects of Implanon on lipid metabolism in comparison with Norplant.[Retraction in Rekers H, Affandi B. Contraception. 2004 Nov;70(5):433; PMID: 15504385]. Contraception 60: 281-7.	Retracted
Taiwo AC, Segilola VA, Delano GE et al. (2012) Implant contraception in an ngo-managed primary health facility in Ibadan, Nigeria. Contraception. 86 (2) 185.	Conference abstract, no full-text article
Tennant C, Schreiber C (2012) Long-term continuation rates after immediate postpartum insertion of etonogestrel implant in a high-risk urban population. Contraception. 86 (3) 294.	Conference abstract, no full-text article
Thamkhantho M, Jivasak-Apimas S, Angsuwathana S et al. (2008) One-year assessment of women receiving sub-dermal contraceptive implant at Siriraj Family Planning Clinic. Journal of the Medical Association of Thailand 91: 775-80.	Retrospective non comparative study (higher quality evidence available for all reported outcomes)[a]
Tocce K, Sheeder J, Teal S (2012) Offering adolescents immediate postpartum etonogestrel implant: 2-year continuation and repeat pregnancy rates. Contraception. 86 (3) 295.	Conference abstract, no full-text article
Urbancsek J (1998) An integrated analysis of nonmenstrual adverse events with Implanon (Retraction in: Contraception (2004) 70:5 (433)). Contraception.58 (6 SUPPL.) 109S-15S.	Retracted
Vidin E, Garbin O, Rodriguez B et al. (2007) Removal of etonogestrel contraceptive implants in the operating theater: report on 28 cases. Contraception 76: 35-9.	Case series (higher quality evidence available for reported outcome)[a]
Walling M (2005) How to remove impalpable Implanon implants. Journal of Family Planning & Reproductive Health Care 31: 320-1.	Not primary research (Opinion/clinical advice)
Weisberg E, Fraser I (2005) Australian women's experience with Implanon. Australian Family Physician 34: 694-6.	Does not report outcomes specified in review protocol (reports bleeding patterns,

Reference	Reason for exclusion
	but not as change from baseline)
Weisberg E, Bateson D, McGeechan K et al. (2013) A three-year comparative study of continuation rates, bleeding patterns and satisfaction in Australian women using a subdermal contraceptive implant or progestogen releasing-intrauterine system. European Journal of Contraception and Reproductive.Health Care (epub)	Does not report outcomes specified in review protocol (reports bleeding patterns, but not as change from baseline)
Wilson JM (2013) Early implant removal. Journal of Family Planning and Reproductive Health Care.39 (3) 233.	Not primary research (Letter/comment)
Winkler CE, Levancini M, Fernandez C et al. (2012) Implanon users experience in a primary care facility in Santiago Chile. International Journal of Gynecology and Obstetrics. 119 S581.	Conference abstract, no full-text article
Winner B, Peipert JF, Zhao Q et al. (2012) Effectiveness of long-acting reversible contraception. New England Journal of Medicine 366: 1998-2007.	Comparative study, implant outcomes not reported separately to other forms of long-acting reversible contraception
Wong RC, Bell RJ, Thunuguntla K et al. (2009) Implanon users are less likely to be satisfied with their contraception after 6 months than IUD users. Contraception 80: 452-6.	Does not report outcomes specified in review protocol

(a) For each outcome, a step-wise approach based on the hierarchy of evidence specified in the review protocol (appendix C). If no evidence or evidence that was insufficient to support a recommendation was found following each step, we proceeded to the next level of evidence. The following levels of evidence were reached for each outcome:
Nerve damage: Case reports
Pregnancy: Prospective non-comparative studies
Bleeding pattern changes: Prospective non-comparative studies
Removal difficulty: Prospective non-comparative studies
Fracture of implant: Case reports
Implant site reaction: Prospective non-comparative studies
Insertion difficulty: Prospective non-comparative studies
Drug interactions: Case reports
Return to fertility: Case reports

Appendix G: Evidence tables

Bibliographic reference	Agrawal A, Robinson C (2003) Spontaneous snapping of an Implanon in two halves in situ. Journal of Family Planning & Reproductive Health Care 29: 238
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 30 **BMI:** Not specified **Weight:** 148 Kg
Intervention	Etonogestrel implant, Implanon
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Fractured Implant (Implanon), 2 incisions required for removal, no other adverse effects The fracture of the implant was not associated with recalled trauma.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	Aisien AO, Enosolease ME (2010) Safety, efficacy and acceptability of implanon a single rod implantable contraceptive (etonogestrel) in University of Benin Teaching Hospital. Nigerian Journal of Clinical Practice 13: 331-5
Study type	Non-comparative (prospective)
Aim	To evaluate the safety, efficacy and acceptability of an etonogestrel sub-dermal implant (Implanon)
Participant characteristics	**Inclusion criteria:** - Sexually active - Healthy - Regular normal menstrual cycle (not clear how defined) **Age:** mean: 33.9 (range 24-45)

<table>
<tr><td>Bibliographic reference</td><td>Aisien AO, Enosolease ME (2010) Safety, efficacy and acceptability of implanon a single rod implantable contraceptive (etonogestrel) in University of Benin Teaching Hospital. Nigerian Journal of Clinical Practice 13: 331-5</td></tr>
<tr><td></td><td>Attrition: 14 women did not have complete data at the end of the study, so were excluded from the analysis, but only 2 women were reported to have discontinued implant use (not clear why the data were incomplete for the other women). Discontinuation rate: 30.4%</td></tr>
<tr><td>Intervention</td><td>Etonogestrel implant (Implanon)</td></tr>
<tr><td>Comparator</td><td>None</td></tr>
<tr><td>Number of Participants</td><td>46 (32 data sets were complete and were analysed)</td></tr>
<tr><td>Length of follow up</td><td>1 year</td></tr>
<tr><td>Location</td><td>Nigeria</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td></td><td colspan="8">Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period.</td></tr>
<tr><td>90 day Reference period</td><td>Amenorrhoea (%) 90 days without bleeding or spotting</td><td>Amenorrhoea (%) 60 days without bleeding or spotting</td><td>Infrequent (%) Fewer than 2 episodes</td><td>Few bleeding (%) days (<5)</td><td>Frequent (%) 5+ episodes</td><td>Prolonged (%) 8+ days per episode</td><td>Numerous (%) 21+ bleeding or spotting days</td><td>Numerous (%) 31+ bleeding or spotting days</td></tr>
<tr><td>1</td><td>18.8</td><td>34.4</td><td>34.4</td><td>37.5</td><td>6.3</td><td>31.3</td><td>12.5</td><td>3.1</td></tr>
<tr><td>2</td><td>50</td><td>21.9</td><td>25</td><td>37.5</td><td>6.3</td><td>18.3</td><td>12.5</td><td>3.1</td></tr>
<tr><td>3</td><td>25</td><td>21.9</td><td>34.4</td><td>25</td><td>3.1</td><td>21.9</td><td>6.3</td><td>0</td></tr>
<tr><td>4</td><td>31.3</td><td>46.9</td><td>18.8</td><td>37.5</td><td>3.1</td><td>21.9</td><td>3.1</td><td>0</td></tr>
<tr><td>Mean (*Calculated from reported data by reviewer)</td><td>31.3</td><td>31.3</td><td>28.2</td><td>34.4</td><td>4.7</td><td>23.4</td><td>8.6</td><td>1.6</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Aisien AO, Enosolease ME (2010) Safety, efficacy and acceptability of implanon a single rod implantable contraceptive (etonogestrel) in University of Benin Teaching Hospital. Nigerian Journal of Clinical Practice 13: 331-5**

Outcome		Etonogestrel implant (Implanon) n=32
Pregnancy		0 (0%)
Self-reported bleeding pattern changes	Reduced bleeding	18 (56.3%)
	Increased bleeding	1 (3.1%)
	Combinations of reduced and increased	13 (40.6%)

Outcomes reported but not extracted here: Weight, Blood pressure, User satisfaction, Haematological parameters, Headache, Libido

Source of funding	Not specified
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Arribas-Mir L, Rueda-Lozano D, Agrela-Cardona M et al. (2009) Insertion and 3-year follow-up experience of 372 etonogestrel subdermal contraceptive implants by family physicians in Granada, Spain. Contraception 80: 457-62**
Study type	Non-comparative study (prospective)
Aim	To assess user profile, continuation rate, reasons for discontinuation, problems with insertion and removal and effectiveness for the subdermal implant, Implanon (user profile and reason for discontinuation not extracted here)
Participant characteristics	**Inclusion criteria:** - All women who had implant inserted at study centre during study period **Age:** 27.17 (sd 6.41) **BMI:** Not specified **Weight:** Not specified **Attrition:** Discontinuation rates: 1 year, 9%, 2 years, 25.3%, 2 years 9 months, 34.9%
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	372
Length of follow up	3 years

Bibliographic reference	**Arribas-Mir L, Rueda-Lozano D, Agrela-Cardona M et al. (2009) Insertion and 3-year follow-up experience of 372 etonogestrel subdermal contraceptive implants by family physicians in Granada, Spain. Contraception 80: 457-62**
Location	Spain
Outcomes measures and effect size	<table><tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=372</th></tr><tr><td>Pregnancy</td><td>0 (0%)</td></tr></table> <table><tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=372</th></tr><tr><td>Insertion complications</td><td>3 (0.81%) 2 vagal episodes, 1 cutaneous perforation</td></tr></table> <table><tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=312</th></tr><tr><td>Removal complications</td><td>7 (2.2%) 2 difficulty due to deep insertion, 3 transient paraesthesia of the hand, 2 local reaction</td></tr></table> **Outcomes reported but not extracted here:** Reasons for discontinuation, bleeding patterns (not reported as change from base line, and not stated whether women had regular menstrual cycles at start of study)
Source of funding	Health district of Granada, Andalusian health service
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Bentley J (2013) Experience and removal of damaged implants. Journal of Family Planning and Reproductive Health Care. 39: 233-4**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Not specified **BMI:** Not specified
Intervention	Etonogestrel implant, Nexplanon or Implanon
Comparator	Not applicable
Number of Participants	7

Bibliographic reference	**Bentley J (2013) Experience and removal of damaged implants. Journal of Family Planning and Reproductive Health Care. 39: 233-4**
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Fractured implant (Nexplanon) associated with heavy bleeding following previous amenorrhoea Participant 2: Fractured implant, (Nexplanon) replacement following by subsequent fracture of second implant and positive pregnancy test within 7 days of removal. Participant 3: Fractured implant (Nexplanon), no other adverse effects Participant 4: Fractured implant (Nexplanon), no other adverse effects Participant 5: Fractured Implant (Nexplanon), no other adverse effects Participant 6: Fractured implant (Nexplanon), no other adverse effects Participant 7: Fractured implant (Implanon), no other adverse effects The implant fracture was attributed to recalled trauma in one out of the seven cases.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	**Bhatia P, Nangia S, Aggarwal S et al. (2011) Implanon: subdermal single rod contraceptive implant. Journal of Obstetrics & Gynaecology of India 61: 422-5**
Study type	Non-comparative (prospective)
Aim	To determine the acceptability, efficacy, safety and return to fertility for Implanon.
Participant characteristics	**Inclusion criteria:** - At least one previous child - Healthy - Regular menstruation **Age:** not specified **BMI:** Not specified **Attrition:** Cumulative Discontinuation rates: 6 months: 8%, 12 months: 18.5%, 24 months: 29%, 30 months: 37%. Only 74/200 implants were removed as part of the study – the reason for this is not reported.
Intervention	Etonogestrel implant (Implanon)

<table>
<tr><td>Bibliographic reference</td><td>Bhatia P, Nangia S, Aggarwal S et al. (2011) Implanon: subdermal single rod contraceptive implant. Journal of Obstetrics & Gynaecology of India 61: 422-5</td></tr>
<tr><td>Comparator</td><td>None</td></tr>
<tr><td>Number of Participants</td><td>200</td></tr>
<tr><td>Length of follow up</td><td>3 years (follow up at 7 days, 1,3,6,12,18,24,30 and 36 months)</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=200</th></tr>
<tr><td>Difficulty with insertion</td><td>0 (0%)</td></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=74</th></tr>
<tr><td>Difficulty with removal</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon), followed by no contraception or contraception that was not oral contraception n=40</th></tr>
<tr><td>Ovulation 1 month after removal</td><td>16 (40%)</td></tr>
</table>
<table>
<tr><th colspan="2">Outcome</th><th>Etonogestrel implant (Implanon), followed by no contraception n=24</th></tr>
<tr><td rowspan="4">Return to fertility following removal</td><td>Pregnancy within 3 months</td><td>7 (29.16%)</td></tr>
<tr><td>Pregnancy within 6 months</td><td>15 (62.50%)</td></tr>
<tr><td>Pregnancy within 9 months</td><td>16 (66.66%)</td></tr>
<tr><td>Pregnancy within 12 months</td><td>23 (95.80%)</td></tr>
</table>
Outcomes reported but not extracted here: Reason for discontinuation, bleeding patterns (not reported as a change from baseline), weight gain
</td></tr>
<tr><td>Source of funding</td><td>Not specified</td></tr>
<tr><td>Comments</td><td>- No confirmation of absence of ovulation before implant removal (therefore ovulation following implant removal may</td></tr>
</table>

Bibliographic reference	**Bhatia P, Nangia S, Aggarwal S et al. (2011) Implanon: subdermal single rod contraceptive implant. Journal of Obstetrics & Gynaecology of India 61: 422-5**
	be inaccurate measure of return to fertility) - No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M (2008) Tolerability and clinical safety of Implanon. European Journal of Contraception & Reproductive Health Care 13: Suppl-36** **Darney P, Patel A, Rosen K et al. (2009) Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertility & Sterility 91: 1646-53** **Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. European Journal of Contraception & Reproductive Health Care 13: Suppl-12**
Study type	Non-comparative (prospective) *Graesslin and Korver (2008) also reports post-marketing surveillance data which is reported separately in Table 15.
Aim	To present safety, efficacy and bleeding profile results for an integrated analysis of 11 trials of the etonogetrel implant, Implanon.
Participant characteristics	**Inclusion criteria:** - Aged 18-40 - Sexually active - Healthy - 80-130% of ideal body weight according to Metropolitan height and weight tables, - Normal menstrual cycles (24-35 days, intra-individual variation <= 3days) **Age:** mean: 27.7 (sd 5.4) **Weight:** mean: 59.7 (sd 9.7) Kg **BMI:** mean: 23 (sd 3.2) kg/m^2 **Attrition:** 4 women had no implant inserted.16 women were excluded from efficacy analysis because they were breastfeeding. 3 subjects had no post-baseline assessments and so were excluded. 35% of women exited study before end of the trial in which they were enrolled. Discontinuation rate: 35%.
Intervention	Etonogestrel implant (Implanon)
Comparator	None
Number of Participants	946
Length of follow up	2 - 4 years (depending on trial)

Bibliographic reference	**Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M (2008) Tolerability and clinical safety of Implanon. European Journal of Contraception & Reproductive Health Care 13: Suppl-36** **Darney P, Patel A, Rosen K et al. (2009) Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertility & Sterility 91: 1646-53** **Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. European Journal of Contraception & Reproductive Health Care 13: Suppl-12**
Location	Integrated analysis of trials from US, Chile, Asia, and Europe
Outcomes measures and effect size	

Outcome	**Etonogestrel implant (Implanon) n=923**
Pregnancy	0 (0%) *6 pregnancies within 14 days of removal

Outcome	**Etonogestrel implant (Implanon) n=941**
Complications with insertion: - implant retained in applicator - bleeding - hematoma - difficulty with insertion	9 (1%)

Outcome	**Etonogestrel implant (Implanon) n=900**
Complications with removal: - implant breakage - impalpable implant - removal difficulty due to deep insertion - fibrous tissue - difficulty locating implant - adhered to underlying tissue - implant too flexible for easy removal	15 (1.7%)

Bibliographic reference	**Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M (2008) Tolerability and clinical safety of Implanon. European Journal of Contraception & Reproductive Health Care 13: Suppl-36** **Darney P, Patel A, Rosen K et al. (2009) Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertility & Sterility 91: 1646-53** **Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. European Journal of Contraception & Reproductive Health Care 13: Suppl-12**

	Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period.			
	Amenorrhoea (%) 90 days without bleeding or spotting	Infrequent (%) Less than 3 episodes	Frequent (%) More than 5 episodes	Prolonged (%) More than 14 days episode beginning in reference period
Mean for 90 day Reference periods 2-8	**29.5**	**34.6**	**3.9**	**11.3**

Outcomes reported but not extracted here: adverse events (most frequent: female reproductive disorders), serious adverse events, discontinuation rates, reasons for discontinuation

Source of funding	Organon (distributors of Implanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Booranabunyat S, Taneepanichskul S (2004) Implanon use in Thai women above the age of 35 years. Contraception 69: 489-91**
Study type	Non-comparative study (prospective)
Aim	To evaluate the menstrual pattern and side effects of Implanon in women over the age of 35 (bleeding pattern data not extracted here)
Participant	**Inclusion criteria:**

<table>
<tr><th>Bibliographic reference</th><th>Booranabunyat S, Taneepanichskul S (2004) Implanon use in Thai women above the age of 35 years. Contraception 69: 489-91</th></tr>
<tr><td>characteristics</td><td>- Healthy (no chronic diseases, normal physical and pelvic examination)
- Aged over 35
- No use of oral contraceptives within 3 months or injectable contraceptives within 1 year,
Age: Mean: 39.7 (sd 3.1) BMI: Mean: 24.9 (sd 3.3)
Weight: Mean: 57.9 Kg (sd 8.3)
Attrition: 2 women withdrew (cumulative discontinuation rate 4%)</td></tr>
<tr><td>Intervention</td><td>Etonogestrel implant (Implanon)</td></tr>
<tr><td>Comparator</td><td>Not applicable</td></tr>
<tr><td>Number of Participants</td><td>53</td></tr>
<tr><td>Length of follow up</td><td>6 months</td></tr>
<tr><td>Location</td><td>Thailand</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=51</th></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=53</th></tr>
<tr><td>Insertion complications</td><td>0 (0%)</td></tr>
</table>
Outcomes reported but not extracted here: Bleeding patterns (not reported as change from baseline), blood pressure, adverse effects
</td></tr>
<tr><td>Source of funding</td><td>Organon (distributors of Implanon)</td></tr>
<tr><td>Comments</td><td>- No control group
- Short follow-up period
- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).</td></tr>
</table>

Bibliographic reference	Brown M, Britton J (2012) Neuropathy associated with etonogestrel implant insertion. Contraception 86: 591-3
Study type	Case report

Bibliographic reference	Brown M, Britton J (2012) Neuropathy associated with etonogestrel implant insertion. Contraception 86: 591-3
Aim	Not applicable
Participant characteristics	**Age:** 26 **BMI:** 23.8 **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Participant presented with impalpable implant and 2 year history of pain, numbness and paresthesiain right forearm at a time corresponding to Implanon insertion. Removed surgically and found to be lying next to the medial nerve. Symptoms completely resolved following removal. .
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	Chaudhry F (232) Adverse reaction to Nexplanon(R). Journal of Family Planning & Reproductive Health Care 39: 231-2
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 24 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Nexplanon)
Comparator	Not applicable
Number of Participants	1

Bibliographic reference	**Chaudhry F (232) Adverse reaction to Nexplanon(R). Journal of Family Planning & Reproductive Health Care 39: 231-2**
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Implant site reaction 3 weeks following insertion. Site red and swollen with purulent discharge. Recurred over 4 month period, culminating in partial extrusion, before implant was removed. Author hypothesises adverse reaction to barium in implant. .
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	**Croxatto HB, Urbancsek J, Massai R et al. (1999) A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. Human Reproduction 14: 976-81** **Croxatto HB (2000) Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. European Journal of Contraception & Reproductive Health Care 5: Suppl-8**
Study type	Non-comparative study (prospective)
Aim	To investigate the clinical profile of Implanon
Participant characteristics	**Inclusion criteria:** - Healthy - Sexually active - Aged 18-40 - Regular menstrual cycles (24-35 days, +/- 3 days) - Body weight within 80-130% of ideal (not specified how ideal defined) **Age:** mean: 29 (sd 5.6) **BMI:** mean: 22.7 (sd 2.8) **Attrition:** Cumulative discontinuation rates: 6 months: 10%, 12 months: 20%, 24 months: 31%. 9% of the subset of women who continued into a third year discontinued before the end of the year.
Intervention	Etonogestrel implant (Implanon)

<table>
<tr><td>Bibliographic reference</td><td>Croxatto HB, Urbancsek J, Massai R et al. (1999) A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. Human Reproduction 14: 976-81

Croxatto HB (2000) Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. European Journal of Contraception & Reproductive Health Care 5: Suppl-8</td></tr>
<tr><td>Comparator</td><td>None</td></tr>
<tr><td>Number of Participants</td><td>635</td></tr>
<tr><td>Length of follow up</td><td>2 or 3 years (initially planned to end after 2 years, some women given the option to continue for further year)</td></tr>
<tr><td>Location</td><td>Multicentre: Austria, Belgium, Chile, France, Germany, Hungary, Sweden, The Netherlands, UK</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=635 (2 years) n=147 (3 years)</th></tr>
<tr><td>Pregnancy</td><td>0 (0%) Pearl index =0.0 (95% CI: 0.0-0.2)</td></tr>
</table>
<table>
<tr><th colspan="2">Outcome</th><th>Etonogestrel implant (Implanon) n=633</th></tr>
<tr><td rowspan="4">Implant site reaction (at any time during treatment)</td><td>Swelling</td><td>4 (0.6%)</td></tr>
<tr><td>Redness</td><td>3 (0.5%)</td></tr>
<tr><td>Pain</td><td>22 (3.5%)</td></tr>
<tr><td>Haematoma</td><td>4 (0.6%)</td></tr>
<tr><td colspan="2">Any site reaction</td><td>24 (3.8%)</td></tr>
</table>
<table>
<tr><td colspan="2"></td><td colspan="4">Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period.</td></tr>
<tr><td>90 day Reference period</td><td>N</td><td>Amenorrhoea (%) 90 days without bleeding or spotting</td><td>Infrequent (%) Less than 3 episodes</td><td>Frequent (%) 5+ episodes</td><td>Prolonged (%) 14+ days per episode</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Croxatto HB, Urbancsek J, Massai R et al. (1999) A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. Human Reproduction 14: 976-81 Croxatto HB (2000) Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. European Journal of Contraception & Reproductive Health Care 5: Suppl-8

1	555	0.9	51.0	11.5	40.2
2	508	16.5	34.8	8.7	22.0
3	487	19.3	34.1	8.0	19.9
4	460	19.8	30.2	8.3	18.3
5	430	19.1	29.5	7.0	16.5
6	407	16.5	34.2	6.4	17.4
7	395	16.7	31.1	7.3	17.0
8	354	11.9	33.9	4.2	17.8
9	140	17.9	29.3	7.1	20.7
10	129	14.0	34.1	5.4	20.2
11	129	11.6	35.7	2.3	19..4
12	122	10.7	29.5	3.3	22.1
Mean (*Calculated from reported data by reviewer)		**14.6**	**34.0**	**6.6**	**21.1**

Bibliographic reference	**Croxatto HB, Urbancsek J, Massai R et al. (1999) A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. Human Reproduction 14: 976-81** **Croxatto HB (2000) Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. European Journal of Contraception & Reproductive Health Care 5: Suppl-8**
	<table><tr><th>Outcome (reported only in Croxatto (2000)</th><th>Etonogestrel implant (Implanon) users using no contraception following removal n=174</th></tr><tr><td>Return to fertility (pregnancy within 90 days of removal)</td><td>24 (13.8%)</td></tr></table> **Outcomes reported but not extracted here:** Reasons for discontinuation, frequently reported adverse events
Source of funding	Organon (distributors of Implanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

	Edwards JE, Moore A (1999) Implanon. A review of clinical studies. [Review] [28 refs]. British Journal of Family Planning 24: Suppl-16
Study type	Synthesis of data from non-comparative studies and randomised comparative studies with Norplant (only Implanon arms extracted here)
Aim	To compare the ease of use, effect on bleeding patterns and adverse effects for Implanon and Norplant (only Implanon data extracted here)
Participant characteristics	**Inclusion criteria:** - Aged 18-40 - Good physical and mental health - Regular menstrual cycles (not clear how defined) **Age:** not stated **BMI:** mean: not stated **Attrition**: Unclear
Intervention	Etonogestrel implant (Implanon)
Comparator	None
Number of Participants	1655 (**calculated by reviewer from table of included studies – unclear, as appears to contradict total number of women with device inserted or removed in studies – see reported outcomes below)**
Length of follow up	2-3 years (depending on study)

	Edwards JE, Moore A (1999) Implanon. A review of clinical studies. [Review] [28 refs]. British Journal of Family Planning 24: Suppl-16
Location	Europe, Indonesia, South America
Outcomes measures and effect size	

Outcome	**Etonogestrel implant (Implanon) n=1458 (only women who used Implanon for 1 year included)**
Pregnancy	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=1716**
Complication with insertion	10 (0.6%)

Outcome	**Etonogestrel implant (Implanon) n=1616**
Complication with removal	21 (1.3%)

Outcome		**Etonogestrel implant (Implanon) n=1728**
Implant site reaction (at any time during treatment)	Swelling	8 (0.5%)
	Redness	6 (0.3%)
	Pain	32 (1.9%)
	Haematoma	4 (0.2%)
	Expulsion	0
Any site reaction		50 (2.9%)

		Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 3 month reference period.			
3 month Reference period	N	Amenorrhoea (%) No bleeding or spotting in reference period	Infrequent (%) Fewer than 3 episodes	Frequent (%) 5 or more episodes	Prolonged (%) More than 14 days in one episode

	Edwards JE, Moore A (1999) Implanon. A review of clinical studies. [Review] [28 refs]. British Journal of Family Planning 24: Suppl-16

1	1463	1.8	50.8	9.4	27.8
2	1415	19.8	34.0	6.5	15.1
3	1377	26.2	29.8	5.7	13.5
4	1321	27.4	29.3	5.0	12.1
5	1263	26.4	29.7	4.8	10.8
6	1253	27.1	28.1	3.6	10.5
7	1227	26.2	26.7	4.2	9.5
8	1148	24.0	28.3	2.7	10.2
Mean (*Calculated from reported data by reviewer)		**22.4**	**32.1**	**5.2**	**13.7**

Outcomes reported but not extracted here: Insertion and removal times, dysmenorrhoea (not reported as change from baseline), weight change, BMI change, Acne, adverse effects, discontinuation rates, reasons for discontinuation, blood pressure, haemoglobin, return of menses following implant removal

Source of funding	Biotechnology and biological sciences research council, SmithKline Beecham Consumer Health care, Organon (distributors of Implanon)
Comments	- No control group - Unclear discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). - In some studies, use of condoms or other non-hormonal contraception was allowed in addition to implant, so this could have contributed to contraceptive efficacy. - Not clear how 'regular' menstrual cycles were defined – no clear that reported bleeding patterns represent change

	Edwards JE, Moore A (1999) Implanon. A review of clinical studies. [Review] [28 refs]. British Journal of Family Planning 24: Suppl-16
	from baseline in all cases. - Some of the studies used Implanon with a different dose than the device that was eventually marketed (40 or 60 mg rather than 68mg etonogestrel).

Bibliographic reference	Funk S, Miller MM, Mishell DR, Jr. et al. (2005) Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 71: 319-26 Levine JP, Sinofsky FE, Christ MF et al. (2008) Assessment of Implanon insertion and removal. Contraception 78: 409-17
Study type	Non-comparative study (prospective)
Aim	To investigate the safety and efficacy of a etonogestrel contraceptive implant (Implanon)
Participant characteristics	**Inclusion criteria:** - Healthy (normal physical and gynaecological examination, normal routine blood and urine tests) - Sexually active - Aged 18-40 - Within 80-130% of ideal body weight (unclear how defined) - 'Apparently normal' menstrual cycles (unclear how defined) **Age:** Mean: not specified. 18-20: 13.0%, 21-25: 39.1%, 26-30: 25.8%, 31-35: 16.7%, 36-40: 5.5% **BMI:** Mean: Not specified <= 20: 13.9%, 20-22: 25.5%, 22-24: 22.4%, 24-26: 13.9% >26: 24.2% **Weight:** Not specified **Attrition:** Discontinuation rates: 1 year: 32% 2 years: 49%
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	330
Length of follow up	2 years
Location	USA
Outcomes measures and effect size	Pregnancy, insertion and removal complications reported in both Funk et al and Levine et al. Bleeding pattern changes reported in Funk et al only.

Bibliographic reference	**Funk S, Miller MM, Mishell DR, Jr. et al. (2005) Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 71: 319-26** **Levine JP, Sinofsky FE, Christ MF et al. (2008) Assessment of Implanon insertion and removal. Contraception 78: 409-17**

Outcome	**Etonogestrel implant (Implanon) n=330**
Pregnancy	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=330**
Insertion complications	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=330**
Removal complications	2 (0.6%)

		Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period. ***All data estimated by reviewer from graph**			
90 day Reference period	N	Amenorrhoea (%) 90 days without bleeding or spotting	Infrequent (%) Less than 3 episodes	Frequent (%) 5+ episodes	Prolonged (%) 14+ days per episode
1	295	2	43	15	37
2	253	14	30	8	25
3	220	19	38	7	22
4	212	15	35	7	17
5	194	18	32	8	14

Bibliographic reference	**Funk S, Miller MM, Mishell DR, Jr. et al. (2005) Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 71: 319-26** **Levine JP, Sinofsky FE, Christ MF et al. (2008) Assessment of Implanon insertion and removal. Contraception 78: 409-17**
	<table><tr><td>6</td><td>188</td><td>15</td><td>31</td><td>5</td><td>14</td></tr><tr><td>7</td><td>166</td><td>15</td><td>32</td><td>3</td><td>14</td></tr><tr><td>8</td><td>146</td><td>14</td><td>24</td><td>5</td><td>13</td></tr><tr><td>**Mean (*Calculated from reported data by reviewer)**</td><td></td><td>**14.0**</td><td>**33.1**</td><td>**7.3**</td><td>**19.5**</td></tr></table> **Outcomes reported but not extracted here:** Time for insertion/removal
Source of funding	Organon (distributors of Implanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Gillies R, Scougall P, Nicklin S (2011) Etonogestrel implants - case studies of median nerve injury following removal. Australian Family Physician 40: 799-800**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 44 Participant 2: 26 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)

Bibliographic reference	**Gillies R, Scougall P, Nicklin S (2011) Etonogestrel implants - case studies of median nerve injury following removal. Australian Family Physician 40: 799-800**
Comparator	Not applicable
Number of Participants	2
Length of follow up	Not applicable
Location	Australia
Outcomes measures and effect size	Participant 1: Partial high median nerve lesion 7 days following attempted removal of impalpable etonogestrel implant requiring repair under general anaesthetic. Muscle weakness, dysaethesis and paraesthesia persisting at 4 months following injury. Participant 2: Presented 7 months after removal of impalpable implant with wasting of the thenar eminence, muscle weakness of muscle innervated by median nerve and decreased sensation in the hand. Nerve conduction studies confirmed significant median nerve injury. Symptoms began to resolve at 2 years following injury.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	**Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. European Journal of Contraception & Reproductive Health Care 13: Suppl-12**
Study type	Post-marketing surveillance (also includes report of non-comparative (prospective) synthesis of data from 11 studies, reported in table 14).
Aim	Post-marketing surveillance of Implanon efficacy.
Participant characteristics	**Inclusion criteria:** - Women using Implanon for contraception between 1998 and 2007 **Age:** not stated **BMI:** mean: not stated **Attrition:** Data based on reports of pregnancy during clinical use. Not clear what proportion of pregnancies were reported.
Intervention	Etonogestrel implant (Implanon)
Comparator	None
Number of Participants	Not stated

<table>
<tr><th>Bibliographic reference</th><td>Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. European Journal of Contraception & Reproductive Health Care 13: Suppl-12</td></tr>
<tr><td>Length of follow up</td><td>-</td></tr>
<tr><td>Location</td><td>Not stated</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon)</th></tr>
<tr><td>Pregnancy (all categories)</td><td>0.049 pregnancies per 100 implants sold
Of these:
No active implant present: 50.3%
Conception took place => 10 days before insertion: 10.5%
Improper use: 0.6%
Conception took place => 10 days after removal: 0.4%
Method failure: 38.2% (of which 25% were attributed to drug interactions: CYP450 enzyme inducers, phenytoin, phenobarbital, rifampicin, primidone, nelfinavir, anti-retrovirals)</td></tr>
<tr><td>Ectopic pregnancy</td><td>5% of all pregnancies reported</td></tr>
</table>
<table>
<tr><th colspan="3">Data estimated by reviewer from graph</th></tr>
<tr><th>Weight (Kg)</th><th>Pregnancy (method failure only) (%)</th><th>Total users (%)</th></tr>
<tr><td><40</td><td>0</td><td>0</td></tr>
<tr><td>40-50</td><td>4.7%</td><td>3.1%</td></tr>
<tr><td>50-60</td><td>21.9%</td><td>26.6%</td></tr>
<tr><td>60-70</td><td>37.5%</td><td>34.4%</td></tr>
<tr><td>70-80</td><td>15.6%</td><td>16.4%</td></tr>
<tr><td>80-90</td><td>7.8%</td><td>6.3%</td></tr>
<tr><td>90-100</td><td>3.1%</td><td>3.1%</td></tr>
<tr><td>>100</td><td>0.8%</td><td>3.1%</td></tr>
</table>
Outcomes reported but not extracted here: Also includes report of non-comparative (prospective) synthesis of data from 11 studies, reported in table 14. Method failure by year of use.
</td></tr>
<tr><td>Source of funding</td><td>Organon (distributors of Implanon)</td></tr>
</table>

Bibliographic reference	Graesslin O, Korver T (2008) The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. European Journal of Contraception & Reproductive Health Care 13: Suppl-12
Comments	- Unclear how many users were included in post-marketing surveillance in total. - Not clear how weight data was collected, or what proportion of people this data was available for (only women with weight data available were included in the analysis) - No control group.

Bibliographic reference	Guazzelli CA, de Queiroz FT, Barbieri M et al. (2010) Etonogestrel implant in postpartum adolescents: bleeding pattern, efficacy and discontinuation rate. Contraception 82: 256-9
Study type	Synthesis of data from non-comparative studies(prospective) and randomised comparative studies with Norplant (only Implanon arms extracted here)
Aim	To evaluate the bleeding pattern, efficacy and discontinuation rate for the etonogestrel implant (type not specified)
Participant characteristics	**Inclusion criteria:** - Aged less than 20 - Given birth in the last 6 months - Regular menstrual cycles (not clear how defined) **Age:** not stated **BMI:** mean: not stated **Attrition:** 3 women were lost to follow up. Discontinuation rate: 6.4%
Intervention	Etonogestrel implant (type not specified)
Comparator	None
Number of Participants	47
Length of follow up	12 months
Location	Brazil
Outcomes measures and effect size	**Outcome** / **Etonogestrel implant n=44** Pregnancy / 0 (0%) **Outcomes reported but not extracted here:** Discontinuation rate, bleeding pattern (not reported as change from baseline, and regular cycles before insertion not an inclusion criteria, haemoglobin, cholesterol, triglycerides, liver enzymes, glycemia.
Source of funding	Not stated
Comments	- No control group - Mean age not given, so not clear whether the majority of women were aged under 18.

Bibliographic reference	**Guazzelli CA, de Queiroz FT, Barbieri M et al. (2010) Etonogestrel implant in postpartum adolescents: bleeding pattern, efficacy and discontinuation rate. Contraception 82: 256-9**
	- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). - Not clear how 'regular' menstrual cycles were defined – no clear that reported bleeding patterns represent change from baseline in all cases.

Bibliographic reference	**Inal MM, Yildirim Y, Ertopcu K et al. (2008) Effect of the subdermal contraceptive etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow-up). European Journal of Contraception & Reproductive Health Care 13: 238-42**
Study type	Non-comparative study (prospective)
Aim	To determine whether the etonogestrel subdermal implant 'Implanon' affects serum hormonal and biochemical indices (only incidentally reported efficacy data extracted here)
Participant characteristics	**Inclusion criteria:** - Aged less than 20 - Given birth in the last 6 months - Regular menstrual cycles (not clear how defined) **Age:** mean: 28.5 (sd 3.4) **BMI:** mean: **Attrition:** 32 women did not complete the study (unspecified reasons). Discontinuation rate: 31.4%
Intervention	Etonogestrel implant (type not specified)
Comparator	None
Number of Participants	102
Length of follow up	3 years
Location	Brazil
Outcomes measures and effect size	

Outcome	**Etonogestrel implant (Implanon) n=70**
Pregnancy	0 (0%)

Outcome	**Etonogestrel implant (Implanon), reporting dysmenorrhoea at baseline n=21**
Improvement in dysmenorrhoea	20 (95.2%)

Bibliographic reference	**Inal MM, Yildirim Y, Ertopcu K et al. (2008) Effect of the subdermal contraceptive etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow-up). European Journal of Contraception & Reproductive Health Care 13: 238-42**
	Outcomes reported but not extracted here: Hormonal and biochemical parameters, acne
Source of funding	None
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Kiriwat O, Patanayindee A, Koetsawang S et al. (1998) A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. European Journal of Contraception & Reproductive Health Care 3: 85-91**
Study type	Non-comparative study (prospective)
Aim	To investigate the contraceptive efficacy, safety and acceptability of the etonogestrel implant, Implanon
Participant characteristics	**Inclusion criteria:** - Aged 18-40 - Proven fertility - Regular menstrual cycles (24-35 days variation no more than 3 days) **Age:** not specified **BMI:** Not specified **Attrition:** 14 women discontinued before 2 years, 6 were lost to follow up in this period. 68 entered the optional extension to 4 years, 60 completed 3 years, and 47 completed 4 years. Discontinuation rates: 2 years: 20%, 3 years: 40%, 4 years:53%
Intervention	Etonogestrel implant (Implanon)
Comparator	None
Number of Participants	100
Length of follow up	2 years with optional extension to 4 years
Location	Thailand
Outcomes measures and effect size	**Outcome** | **Etonogestrel implant (Implanon) n=100** Pregnancy | 0 (0%)

Bibliographic reference	Kiriwat O, Patanayindee A, Koetsawang S et al. (1998) A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. European Journal of Contraception & Reproductive Health Care 3: 85-91				
		Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period.			
	90 day Reference period	Amenorrhoea (%) No bleeding/spotting in reference period. **Estimated by reviewer from graph.**	Infrequent (%) <3 episodes. **Estimated by reviewer from graph.**	Frequent (%) 5+ episodes	Prolonged (%) Episode lasting 14+ days
	1	4	45	<=6% throughout all reference periods	
	2	29	33		7-15% for reference period 2 onwards
	3	34	23		
	4	39	28		
	5	29	38		
	6	34	33		
	7	36	27		
	8	23	35		
	9	17	47		
	10	22	38		
	11	18	52		
	12	15	44		
	13	18	50		

Bibliographic reference	**Kiriwat O, Patanayindee A, Koetsawang S et al. (1998) A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. European Journal of Contraception & Reproductive Health Care 3: 85-91**

	14	18	50		
	15	10	55		
	16	10	50		
	Mean (*Calculated from reported data by reviewer)	**22.3**	**40.5**		

Outcomes reported but not extracted here: Time for insertion/removal, adverse events, blood pressure, reasons for discontinuation, pregnancy following implant removal (did not specify number of women not using contraception following implant removal)

Source of funding	None
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Kreitchmann R, Innocente AP, Preussler GM (2012) Safety and efficacy of contraceptive implants for HIV-infected women in Porto Alegre, Brazil. International Journal of Gynaecology & Obstetrics 117: 81-2**
Study type	Non-comparative study (prospective)
Aim	To evaluate the safety and efficacy of Implanon among HIV-infected women
Participant characteristics	**Inclusion criteria:** - HIV positive - History of poor adherence to contraception **Age:** Mean: 29 (range 20-39) **BMI:** Mean: not specified **Weight:** 59 kg (range 42-104 kg) 59.5% were receiving antiretroviral therapy at time of insertion and 11.4% began antiretroviral therapy during follow up

Bibliographic reference	**Kreitchmann R, Innocente AP, Preussler GM (2012) Safety and efficacy of contraceptive implants for HIV-infected women in Porto Alegre, Brazil. International Journal of Gynaecology & Obstetrics 117: 81-2**
	period. **Attrition:** 3 women had implant removed before end of study (3 years). Discontinuation rate: 4%
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	79
Length of follow up	3 years (6 monthly follow up)
Location	Brazil
Outcomes measures and effect size	<table><tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=79</th></tr><tr><td>Pregnancy</td><td>0 (0%)</td></tr></table> **Outcomes reported but not extracted here:** Bleeding patterns (not reported as change from baseline)
Source of funding	Not specified
Comments	- No control group - Around half of the participants were taking antiretrovirals for HIV treatment, which is not recommended according to the summary of product characteristics due to possible drug interactions.

Bibliographic reference	**Lakhi N, Govind A (2010) Implanon failure in patients on antiretroviral medication: the importance of disclosure. Journal of Family Planning & Reproductive Health Care 36: 181-2**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 33 Participant 2: 35 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	2

Bibliographic reference	**Lakhi N, Govind A (2010) Implanon failure in patients on antiretroviral medication: the importance of disclosure. Journal of Family Planning & Reproductive Health Care 36: 181-2**
Length of follow up	Not applicable
Location	US/UK
Outcomes measures and effect size	Participant 1: Pregnancy during Implanon use. Participant was taking efavirenz, emtricitabine and tenofovir disoproxil (antiretrovirals) for the treatment of HIV. Participant 2: Pregnancy during Implanon use. Participant was taking efavirenz and lopinavir (antiretrovirals) for the treatment of HIV.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample - Surrogate outcome (pregnancy might have occurred in absence of drug interaction)

Bibliographic reference	**Leticee N, Viard JP, Yamgnane A et al. (2012) Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. Contraception 85: 425-7**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 31 Participant 2: 35 **BMI:** Participant 1: 27 kg/m2 Participant 2: 24 kg/m2 **Weight:** Participant 1: 69 kg Participant 2: 63 kg
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	2
Length of follow up	Not applicable
Location	US/UK
Outcomes measures and effect size	Participant 1: Pregnancy during Implanon use. Participant was taking efavirenz, zidovudine, and lamivudine (antiretrovirals) for the treatment of HIV.

Bibliographic reference	Leticee N, Viard JP, Yamgnane A et al. (2012) Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. Contraception 85: 425-7
	Participant 2: Pregnancy during Implanon use. Participant was taking efavirenz, tenofovir and emtricitabine (antiretrovirals) for the treatment of HIV. Also regularly used condoms. Both implants had been shown to be correctly inserted.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample - Surrogate outcome (pregnancy might have occurred in absence of drug interaction)

Bibliographic reference	Makarainen L, van BA, Tuomivaara L et al. (1998) Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. Fertility & Sterility 69: 714-21
Study type	Randomised controlled trial (only Implanon arm extracted – treat as prospective non-comparative study)
Aim	To study the mechanism of action of the etonogestrel implant, Implanon.
Participant characteristics	**Inclusion criteria:** - Aged 18-40 - Confirmed ovulation at start of study - Regular menstrual cycles (24-35 days) - Body weight within 80-120% of ideal (not clear how ideal defined) **Age:** mean: 29.8 (sd 5.9) **BMI:** not specified **Weight:** mean: *60 Kg (sd 6.7) *mean not given for Implanon arm separately **Attrition:** 9/16 women completed 2 years. 7 consented to a further year, and all 7 completed this year. Discontinuation rates: 2 years: 44% 3 years: 56%
Intervention	Etonogestrel implant (Implanon)
Comparator	None
Number of Participants	16 (Implanon arm only)
Length of follow up	2-3 years depending on centre

<table>
<tr><td>Bibliographic reference</td><td>Makarainen L, van BA, Tuomivaara L et al. (1998) Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. Fertility & Sterility 69: 714-21</td></tr>
<tr><td>Location</td><td>Finland and Sweden</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Outcome</td><td>Etonogestrel implant (Implanon) n=16</td></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><td>Outcome</td><td>Etonogestrel implant (Implanon) n=16</td></tr>
<tr><td>Complication with insertion</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><td>Outcome</td><td>Etonogestrel implant (Implanon) n=?</td></tr>
<tr><td>Complication with removal</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><td></td><td colspan="4">Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period.</td></tr>
<tr><td></td><td>Amenorrhoea (%)</td><td>Infrequent (%) Fewer than 3 episodes</td><td>Frequent (%) Not clear how defined</td><td>Prolonged (%) Not clear how defined</td></tr>
<tr><td>Range for 90 day Reference periods 1-12</td><td>Percentage not calculable from data given. Experienced by 1 person in 6 RPs and 2 people in 1 RP.</td><td>14.3-53.3</td><td colspan="2">Mentioned in methods section but results not reported</td></tr>
</table>
Outcomes reported but not extracted here: Hormonal and biochemical parameters, follicular assessment, endometrial thickness, return to ovulation following removal (specifies ‘most’ women returned to ovulation – but does not give number)
</td></tr>
</table>

Bibliographic reference	**Makarainen L, van BA, Tuomivaara L et al. (1998) Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. Fertility & Sterility 69: 714-21**
Source of funding	Organon (distributors of Implanon) assisted with statistical analysis
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). - Few details on bleeding pattern analysis

Bibliographic reference	**Mansour D, Korver T, Marintcheva-Petrova M et al. (2008) The effects of Implanon on menstrual bleeding patterns. European Journal of Contraception & Reproductive Health Care 13: Suppl-28**
Study type	Amalgamation of Non-comparative studies (prospective) and studies comparative with Norplant or intrauterine device (for which only Implanon arm data used).
Aim	To assess the effect of Implanon on menstrual bleeding patterns
Participant characteristics	**Inclusion criteria:** - Regular menstrual cycles (unclear how defined) - Age 18-40 - Sexually active and childbearing potential - Good physical and mental health **Age:** mean: 27.7 **BMI: mean:** 23.0 kg/m^2 **Attrition:** Discontinuation rate: 39.2% (trials were 1-5 years)
Intervention	Etonogestrel implant (Implanon)
Comparator	Some of the trials included a Norplant or intra-uterine device comparator (data not used in amalgamated analysis reported)
Number of Participants	923
Length of follow up	1-5 years
Location	Data amalgamated from 11 trials: United States, Thailand, Chile, Singapore, Austria, Germany, Finland, Hungary, The Netherlands, Russia, Malaysia
Outcomes measures and effect size	<table><tr><td></td><td>Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary and World Health Organisation 90-day reference period method.</td></tr></table>

Bibliographic reference	Mansour D, Korver T, Marintcheva-Petrova M et al. (2008) The effects of Implanon on menstrual bleeding patterns. European Journal of Contraception & Reproductive Health Care 13: Suppl-28

90 day Reference period (RP)	Amenorrhoea (%) No bleeding/spotting in RP.	Infrequent (%) Fewer than 3 episodes in RP	Frequent (%) 5+ episodes in RP	Prolonged (%) Any episode lasting 14+ days
1	10	39	12	31
2	19	34	8	21
3	25	36	6	19
4	23	32	6	17
5	21	34	7	16
6	21	33	6	15
7	21	32	5	14
8	17	33	4	15
9	18	36	5	17
10	17	35	4	17
11	15	39	3	18
12	12	34	2	17
Mean (*Calculated from reported data)	**18.3**	**34.8**	**5.7**	**18.1**

Outcome	Women reporting dysmenorrhoea at baseline (n=315)

Bibliographic reference	**Mansour D, Korver T, Marintcheva-Petrova M et al. (2008) The effects of Implanon on menstrual bleeding patterns. European Journal of Contraception & Reproductive Health Care 13: Suppl-28**
	Dysmenorrhoea at implant removal (only assessed in 5 of 11 trials): Symptoms resolved 77%; Symptoms less severe 6%; Symptoms more severe 5.5% **Outcomes reported but not extracted here:** Reasons for discontinuation, Haemoglobin
Source of funding	Oragnon (distributors of Implanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). - Although 'regular cycles' was an inclusion criteria for the studies, there is no specification of what this means, so it is not clear whether the data on bleeding patterns can really be considered as a true reflection of bleeding pattern changes, or whether some women would have fallen into these categories before received the implant. - Some women were using other hormonal contraception before starting the trials, and this may have altered their 'baseline' pattern of bleeding. - Dysmenorrhoea was assessed at the time of Implanon removal; this varied among trials, and could have been earlier than the specified end of the trial if a woman requested early removal. It is possible that the effect of Implanon on dysmenorrhoea may differ depending on how long the device has been inserted for, but this was not assessed.

Bibliographic reference	**Mansour D, Mommers E, Teede H et al. (2010) Clinician satisfaction and insertion characteristics of a new applicator to insert radiopaque Implanon: an open-label, noncontrolled, multicenter trial. Contraception 82: 243-9** **Mommers E, Blum GF, Gent TG et al. (2012) Nexplanon, a radiopaque etonogestrel implant in combination with a next-generation applicator: 3-year results of a noncomparative multicenter trial. American Journal of Obstetrics & Gynecology 207: 388-6**
Study type	Non-comparative study (prospective)
Aim	To evaluate clinician satisfaction and insertion complications for implants inserted using the 'Nexplanon' insertion device (Mansour et al 2010). To investigate the efficacy, safety, removal characteristics and x-ray visibility of Nexplanon (Mommers et al 2012)
Participant characteristics	**Inclusion criteria:**

<table>
<tr><td>Bibliographic reference</td><td>Mansour D, Mommers E, Teede H et al. (2010) Clinician satisfaction and insertion characteristics of a new applicator to insert radiopaque Implanon: an open-label, noncontrolled, multicenter trial. Contraception 82: 243-9

Mommers E, Blum GF, Gent TG et al. (2012) Nexplanon, a radiopaque etonogestrel implant in combination with a next-generation applicator: 3-year results of a noncomparative multicenter trial. American Journal of Obstetrics & Gynecology 207: 388-6</td></tr>
<tr><td></td><td>- Aged 18-40
- BMI 18-35 kg/m2
- Regular menstrual cycles (24-35 days)
Age: Mean: 28.2 (sd 6.7) BMI: Mean: 23.8 kg/m^2 (sd 3.7)
Weight: not specified
Attrition: Cumulative discontinuation rates: 1 year: 11%, 2 years: 38%, 3 years: 48%</td></tr>
<tr><td>Intervention</td><td>Radio-opaque etonogestrel implant (Nexplanon)</td></tr>
<tr><td>Comparator</td><td>-</td></tr>
<tr><td>Number of Participants</td><td>302</td></tr>
<tr><td>Length of follow up</td><td>Unclear (Mansour et al) 3 years (Mommers et al)</td></tr>
<tr><td>Location</td><td>Multicentre: Australia, UK, France, Norway, Sweden, Germany</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th colspan="2">Outcome</th><th>Etonogestrel implant - Nexplanon (n=301)</th></tr>
<tr><td colspan="2">Difficulty with insertion (judged by clinician)</td><td>6 (2%)</td></tr>
<tr><td rowspan="4">Implant site reaction</td><td>Redness</td><td>12 (4.0%)</td></tr>
<tr><td>Haematoma</td><td>10 (3.3%)</td></tr>
<tr><td>Swelling</td><td>2 (0.7%)</td></tr>
<tr><td>Pain</td><td>3 (1.0%)</td></tr>
<tr><td colspan="2">Partial expulsion at time of insertion</td><td>2 (0.7%)</td></tr>
<tr><td colspan="2">Any reaction</td><td>26 (8.6%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=302</th></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Mansour D, Mommers E, Teede H et al. (2010) Clinician satisfaction and insertion characteristics of a new applicator to insert radiopaque Implanon: an open-label, noncontrolled, multicenter trial. Contraception 82: 243-9** **Mommers E, Blum GF, Gent TG et al. (2012) Nexplanon, a radiopaque etonogestrel implant in combination with a next-generation applicator: 3-year results of a noncomparative multicenter trial. American Journal of Obstetrics & Gynecology 207: 388-6**
	Outcome / **Etonogestrel implant (Implanon) n=296** Removal complications / 16 (5.4%) 13 due to presence of fibrotic tissue **Outcomes reported but not extracted here:** Clinician satisfaction with insertion, x-ray visibility, implant insertion time, Adverse events, implant removal time
Source of funding	Editorial support was funded by Schering Corp., a division of Merck and Co. (manufacturers of Nexplanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Matiluko AA, Soundararjan L, Hogston P (2007) Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. Journal of Family Planning & Reproductive Health Care 33: 277-8**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 23 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Ectopic pregnancy during Implanon use. Participant was taking efavirenz, zidovudine and lamivudine (antiretrovirals) for the treatment of HIV.
Source of funding	None

Bibliographic reference	**Matiluko AA, Soundararjan L, Hogston P (2007) Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. Journal of Family Planning & Reproductive Health Care 33: 277-8**
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample - Surrogate outcome (pregnancy might have occurred in absence of drug interaction)

Bibliographic reference	**McCarty EJ, Keane H, Quinn K et al. (2011) Implanon failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies. International Journal of STD & AIDS 22: 413-4**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 34 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Ectopic Pregnancy during Implanon use. Participant was taking tenfovir, emtricitabine and efavirenz (antiretrovirals) for the treatment of HIV.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample - Surrogate outcome (pregnancy might have occurred in absence of drug interaction)

<table>
<tr><th>Bibliographic reference</th><td>Meirik O, Brache V, Orawan K et al. (2013) A multicenter randomized clinical trial of one-rod etonogestrel and two-rod levonorgestrel contraceptive implants with nonrandomized copper-IUD controls: methodology and insertion data. Contraception 87: 113-20</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial with additional non-randomised arm
**Only etonogestrel implant arm extracted, consider as Non comparative study (prospective)</td></tr>
<tr><td>Aim</td><td>To compare the effectiveness of an etonogestrel implant (Implanon) with a levongestrel implant, and the copper interuterine device.
**Only etonogestrel implant arm extracted here.</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:
- Healthy
- Regular menstrual cycles
Age: 18-44
Attrition: 6 women were randomised to etonogestrel group, but did not receive implant, 11 women were lost to follow up (Discontinuation rate: 1.1%)</td></tr>
<tr><td>Intervention</td><td>Etonogestrel implant (Implanon)</td></tr>
<tr><td>Comparator</td><td>-</td></tr>
<tr><td>Number of Participants</td><td>997</td></tr>
<tr><td>Length of follow up</td><td>6 weeks</td></tr>
<tr><td>Location</td><td>Multicentre: Brazil, Chile, Dominican Republic, Hungary, Thailand, Turkey, Zimbabwe</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th colspan="2">Outcome</th><th>Etonogestrel implant (n=997)</th></tr>
<tr><td colspan="2">Insertion difficulty (judged by clinician)</td><td>20 (2%)</td></tr>
<tr><td rowspan="6">Implant site reaction (assessed at 6 weeks post-insertion)</td><td>Pain</td><td>96 (9.7%)</td></tr>
<tr><td>Itching</td><td>104 (10.6%)</td></tr>
<tr><td>Sensibility problems</td><td>51 (5.2%)</td></tr>
<tr><td>Induration</td><td>18 (1.8%)</td></tr>
<tr><td>Bruising</td><td>6.9 (6.9%)</td></tr>
<tr><td>Redness</td><td>15 (1.5%)</td></tr>
<tr><td></td><td>Any implant site reaction</td><td>269 (27.2%)</td></tr>
</table>
Outcomes reported but not extracted here: Implant insertion time, pain at insertion
</td></tr>
<tr><td>Source of funding</td><td>World Health Organization, United Nations, World Bank</td></tr>
</table>

Bibliographic reference	**Meirik O, Brache V, Orawan K et al. (2013) A multicenter randomized clinical trial of one-rod etonogestrel and two-rod levonorgestrel contraceptive implants with nonrandomized copper-IUD controls: methodology and insertion data. Contraception 87: 113-20**
Comments	- The 6 week follow-up period means that the study is likely to record most adverse events associated with insertion, and the loss to follow up was small in comparison with the sample size. - No control group (in extracted data).

Bibliographic reference	**Myrick L, Howell C, Ramakrishnan K (2012) The broken (fractured) Implanon. Journal - Oklahoma State Medical Association 105: 394-5**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 35, Participant 2:23, Participant 3: 20 **BMI:** Not specified **Weight:** Participant 1:237 lb, Participant 2:175 lb, Participant 3: Not specified
Intervention	Etonogestrel implant, Implanon
Comparator	Not applicable
Number of Participants	3
Length of follow up	Not applicable
Location	USA
Outcomes measures and effect size	Participant 1: Fractured Implant (Implanon), 2 incisions required for removal, no other adverse effects Participant 2: Fractured implant (Implanon), 2 incisions required for removal, no other adverse effects Participant 3: Fractured implant (Implanon), no other adverse effects The implant fracture was attributed to recalled trauma in one of the three cases.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	**Otero Flores JB, Lozano BM, Cortes BM et al. (2005) Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. International Journal of Gynecology and Obstetrics.90 (3) (pp 228-233), 2005.Date of Publication: September 2005. 228-33**
Study type	Non-comparative study (prospective)
Aim	To evaluate the efficacy, adverse effects and user continuation of an etonogestrel subdermal implant (Implanon). Only efficacy and adverse effects extracted here.
Participant characteristics	**Inclusion criteria:** - Regular menstrual cycles (unclear how defined) - Age 15-49 **Age:** mean: 25.8 (sd 5.9 years) **Attrition:** 161 women discontinued implant use before the end of the study (cumulative discontinuation rates: 1 year 21.8%, 2 years 33.3%, 3 years 38.6%.
Intervention	Etonogestrel implant (Implanon)
Comparator	-
Number of Participants	417
Length of follow up	3 years
Location	Mexico (multicentre)
Outcomes measures and effect size	The table below reports incidence of each outcome throughout the study at regular follow up visits.

Outcome	Etonogestrel implant (n=417)
Pregnancy (confirmed by test)	0.0%
Acne attributed to implant	6.3%
Mood changes attributed to implant	9.6%
Decreased libido attributed to implant	5.9%
Weight gain attributed to implant (self-reported)	2.8%

Bibliographic reference	**Otero Flores JB, Lozano BM, Cortes BM et al. (2005) Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. International Journal of Gynecology and Obstetrics.90 (3) (pp 228-233), 2005.Date of Publication: September 2005. 228-33**

	Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary and World Health Organisation 90-day reference period (RP) method. ***All data estimated by reviewer from graph**			
90 day Reference period (RP)	Amenorrhoea (%) No bleeding/spotting in RP.	Infrequent (%) Fewer than 2 episodes in RP	Frequent (%) 5+ episodes in RP	Prolonged (%) Any episode lasting 10+ days
1	23	4	2	40
2	27	3	3	25
3	22.5	5	3	19.5
4	15.5	4	3.5	18
5	20	5	1	18
6	22.5	4.5	2	21.5
7	14	4	1	16
Mean (*Calculated from reported data)	**20.6**	**4.2**	**2.2**	**22.6**

Outcomes reported but not extracted here: Headache, Abdominal pain, Nausea, Local discomfort, dyspareunia, vaginal dryness, matalgia, weight gain

Source of funding	Oragnon (distributors of Implanon) provided the implants for the study. Funding not specified.
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Partridge R, Bush J (2013) Infections post-Nexplanon(R) insertion. Journal of Family Planning & Reproductive Health Care 39: 309-10**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 15 Participant 2: 33 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Nexplanon)
Comparator	Not applicable
Number of Participants	2
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Extrusion of implant and infected implant site which failed to heal with antibiotics (10 days following insertion). Participant 2: Infection at implant site 1 week post-fitting. Initially responded to antibiotics, but failed to heal, implant verged on self-extrusion and was removed. Both participants experienced atopic eczema which the authors hypothesised was related.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	**Pickard S, Bacon L (2002) Persistent vaginal bleeding in a patient with a broken Implanon. Journal of Family Planning & Reproductive Health Care 28: 207-8**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 29 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant, Implanon

Bibliographic reference	Pickard S, Bacon L (2002) Persistent vaginal bleeding in a patient with a broken Implanon. Journal of Family Planning & Reproductive Health Care 28: 207-8
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Fractured Implant (Implanon), associated with heavy bleeding, no other adverse effects Implant fracture was associated with recalled trauma.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	Schindlbeck C, Janni W, Friese K (2006) Failure of Implanon contraception in a patient taking carbamazepin for epilepsia. Archives of Gynecology & Obstetrics 273: 255-6
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 24 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	Germany
Outcomes measures and effect size	Participant 1: Pregnancy during Implanon use. Participant was taking carbamazepine for the treatment of epilepsy.
Source of funding	None
Comments	- No control group - Retrospective report

Bibliographic reference	Schindlbeck C, Janni W, Friese K (2006) Failure of Implanon contraception in a patient taking carbamazepin for epilepsia. Archives of Gynecology & Obstetrics 273: 255-6
	- Participants selected based on outcome - Very small sample

Bibliographic reference	Schnabel P, Merki-Feld GS, Malvy A et al. (2012) Bioequivalence and x-ray visibility of a radiopaque etonogestrel implant versus a non-radiopaque implant: a 3-year, randomized, double-blind study. Clinical Drug Investigation 32: 413-22
Study type	Randomised controlled trial
Aim	To determine whether radio-opaque and non-radio opaque versions of the contraceptive implant Implanon are bioequivalent. To compare the x-ray visibility of the implants. To report implant-related adverse events.
Participant characteristics	**Inclusion criteria:** - Good physical/mental health - Regular menstrual cycles 24-35 days duration - Body mass index 18-29 kg/m^2 - Aged 18-40 **Age:** mean: 27.1 (sd 6.7) **BMI:**22.4 (sd 2.4) kg/m2 **Attrition:** 6 women were not randomised because they did not meet the inclusion criteria. 24 (42.9%) from non-radio opaque group and 20 (38.5%) from radiopaque group did not complete the trial.
Intervention	Radio-opaque implant (Nexplanon) ** The implant was inserted with the original inserter designed for use with Implanon to maintain double binding.
Comparator	Non-radio-opaque implant (Implanon)
Number of Participants	Radio-opaque etonogestrel implant: 52 Non radio-opaque etonogestrel implant: 56
Length of follow up	3 years
Location	Multisite: France, the Netherlands, Switzerland
Outcomes measures and effect size	The table shows the number of women experiencing each outcome throughout the trial (includes women who exited the trial early). Outcomes are defined as in the Medical Dictionary of regulatory activities.

Outcome	Radio-opaque implant (n=52)	Non radio-opaque implant (n=56)
Pregnancy	0 (0%)	0 (0%)

Bibliographic reference	**Schnabel P, Merki-Feld GS, Malvy A et al. (2012) Bioequivalence and x-ray visibility of a radiopaque etonogestrel implant versus a non-radiopaque implant: a 3-year, randomized, double-blind study. Clinical Drug Investigation 32: 413-22**
	Outcomes reported but not extracted here: Serum Etonogestrel, X-ray visibility, Adverse events
Source of funding	Merck Sharp and Dohme Corp. (manufacturers of Nexplanon)
Comments	- The study was powered for the question of bioequivalence; it is not sufficiently powered for questions of effectiveness due to the low expected rates of pregnancy. - High discontinuation rate in both groups (>40%) – incidence of adverse effects might have been higher if all women had completed the trial.

Bibliographic reference	**Sullivan MJ (2012) Allergy to nexplanon. Journal of Family Planning & Reproductive Health Care 38: 272**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 32 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Nexplanon)
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Implant site reaction within 24 hrs of insertion (redness and swelling). No resolution in response to antibiotics or antihistamines. Persisted for 1 week, after which the implant was removed and the symptoms resolved. Another implant was inserted in the other arm, followed by the same reaction. No signs of infection on removal. Author hypothesises adverse reaction to barium in implant. .
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	Sullivan MJ (2012) Allergy to nexplanon. Journal of Family Planning & Reproductive Health Care 38: 272

Bibliographic reference	Tocce KM, Sheeder JL, Teal SB (2012) Rapid repeat pregnancy in adolescents: do immediate postpartum contraceptive implants make a difference? American Journal of Obstetrics & Gynecology 206: 481-7
Study type	Prospective observational comparative study (only implant arm extracted here, so treat as non-comparative (prospective))
Aim	To determine contraceptive continuation and repeat pregnancy rates in adolescents who are offered immediate postpartum etonogestrel implant (Implanon) insertion.
Participant characteristics	**Inclusion criteria:** - Aged 13-24 - In immediate post-partum period (4 weeks of delivery) **Age:** mean at conception(implant fitted postpartum): 18.5 (sd 1.6) **BMI:** 24.1 (sd 5.1) **Attrition:** Loss to follow up 5.8% at 6 months, 10.5% at 12 months
Intervention	Etonogestrel implant, Implanon
Comparator	Other method of contraception (not extracted here)
Number of Participants	171 (Implanon arm only)
Length of follow up	12 months
Location	USA
Outcomes measures and effect size	**Outcome** / **Etonogestrel implant (Implanon) n=171** Pregnancy (any time during treatment) / 1 (0.6%) *participant was taking carbamazepine (enzyme inducer) **also report pregnancies after implant removal, but not relevant here **Outcomes reported but not extracted here:** Reasons for discontinuation
Source of funding	Organon (distributors of Implanon)
Comments	- No control group (for extracted data) - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Tomas-Tello MD, Hodgson G (2010) Two cases of broken Implanon(). Journal of Family Planning & Reproductive Health Care 36: 255**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 18 Participant 2: 22 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant, Implanon
Comparator	Not applicable
Number of Participants	2
Length of follow up	Not applicable
Location	UK
Outcomes measures and effect size	Participant 1: Fractured Implant (Implanon), associated with heavy bleeding, no other adverse effects Participant 2: Fractured Implant (Implanon), associated with irregular bleeding, no other adverse effects Implant fracture was not reported to be associated with recalled trauma in either case.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	**Torres R, Mendes N, Machado AI et al. (2013) In situ breakage of Implanon--two cases of a rare occurrence. Contraception 88: 189-91**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** Participant 1: 37, Participant 2:29 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant, Implanon
Comparator	Not applicable
Number of Participants	2

Bibliographic reference	Torres R, Mendes N, Machado AI et al. (2013) In situ breakage of Implanon--two cases of a rare occurrence. Contraception 88: 189-91
Length of follow up	Not applicable
Location	Portugal
Outcomes measures and effect size	Participant 1: Fractured Implant (Implanon), 2 incisions required for removal, no other adverse effects Participant 2: Fractured implant (Implanon), 2 incisions required for removal, no other adverse effects The fracture of the implant was attributed to recalled trauma in one of the two cases.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	Vicente L, Mendonca D, Dingle M et al. (2008) Etonogestrel implant in women with diabetes mellitus. European Journal of Contraception & Reproductive Health Care 13: 387-95
Study type	Non-comparative study (prospective)
Aim	To evaluate the effect of the etonogestrel implant (Implanon) on the control of carbohydrate and lipid metabolism and vascular complications in diabetic women treated with insulin, and to assess the acceptability of contraceptive implants for these participants (only incidental data on efficacy and adverse effects extracted here).
Participant characteristics	**Inclusion criteria:** - Women with insulin-treated diabetes - Sexually active **Age:** mean:27.59 (sd 6.2) **BMI:** 25.51 (sd 3.58) **Weight:** 64.41 Kg (sd 9.83) **Attrition:** 1 woman discontinued before 12 months, one at 15 months, and one at 24 months. Cumulative discontinuation rates: 1 year: 4.3% 2 years: 12.5%
Intervention	Etonogestrel implant, Implanon
Comparator	None
Number of Participants	23
Length of follow up	2 years
Location	Portugal
Outcomes measures and	

Bibliographic reference	**Vicente L, Mendonca D, Dingle M et al. (2008) Etonogestrel implant in women with diabetes mellitus. European Journal of Contraception & Reproductive Health Care 13: 387-95**

effect size

Outcome	**Etonogestrel implant (Implanon) n=22**
Pregnancy (reported at 2 years)	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=23**
Insertion complications	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=22**
Removal complications	0 (0%)

	Bleeding pattern change (all had regular bleeding at baseline). Assessed using World Health Organisation 90-day reference period (RP) method. Not specified if diary method used, or relied on recall. ***Percentages calculated by reviewer**		
Assessment time	Amenorrhoea (no bleeding/spotting in reference period) n (%)	Infrequent (<3 episodes) n (%)	Frequent or Prolonged (5+ episodes or episode lasting 14+ days) (%)
3 months	13 (59%)	7 (32%)	2 (9%)
6 months	14 (64%)	8 (36%)	0 (0%)
12 months	9 (41%)	10 (45%)	3 (14%)
24 months	4 (22%)	10 (56%)	4 (22%)
Mean %excluding 3 months (*Calculated from reported data)	**46.5%**	**42.3%**	**11.3%**

Outcomes reported but not extracted here: hormonal and biochemical serum levels, weight change, adverse effects

Bibliographic reference	**Vicente L, Mendonca D, Dingle M et al. (2008) Etonogestrel implant in women with diabetes mellitus. European Journal of Contraception & Reproductive Health Care 13: 387-95**
Source of funding	Organon (distributors of Implanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). - Unclear how insertion or removal complications were defined. - Not clear whether diary method used to assess bleeding or whether relied on recall (relying on recall more susceptible to bias)

Bibliographic reference	**Wechselberger G, Wolfram D, Pulzl P et al. (2006) Nerve injury caused by removal of an implantable hormonal contraceptive. American Journal of Obstetrics & Gynecology 195: 323-6**
Study type	Case report
Aim	Not applicable
Participant characteristics	**Age:** 24 **BMI:** Not specified **Weight:** Not specified
Intervention	Etonogestrel implant (Implanon)
Comparator	Not applicable
Number of Participants	1
Length of follow up	Not applicable
Location	Austria
Outcomes measures and effect size	Participant 1: Paresthesia of the proximal ulnar forearm following unsuccessful Implanon removal. Surgery showed partially divided antebrachial cutaneous nerve and implant in direct contact with ulnar nerve. Sensation was normal 12 months after surgery.
Source of funding	None
Comments	- No control group - Retrospective report - Participants selected based on outcome - Very small sample

Bibliographic reference	Wechselberger G, Wolfram D, Pulzl P et al. (2006) Nerve injury caused by removal of an implantable hormonal contraceptive. American Journal of Obstetrics & Gynecology 195: 323-6

Bibliographic reference	Xu H, Wade JA, Peipert JF et al. (2012) Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstetrics & Gynecology 120: 21-6
Study type	Sub-analysis of larger comparative study – only sub-dermal implant arm extracted – treat as non-comparative study (prospective)
Aim	To estimate contraceptive failure rates of etonogestrel implants (Implanon) for obese women compared with those of normal weight
Participant characteristics	**Inclusion criteria:** - Age 14-45 **Age:** mean age normal weight: 21.5, mean age overweight: 23.1 mean age obese: 24.2 **Attrition:** Cumulative discontinuation rates 12, 24 and 36 months 6.9%, 12.8% and 22.5% respectively (percentages for whole cohort, not just implant users considered here, but states that loss to follow up did not vary by contraceptive method).
Intervention	Etonogestrel implant (Implanon)
Comparator	None
Number of Participants	1168 (number of women in study who had contraceptive implant – total number was much larger, but these data not extracted here)
Length of follow up	3 years
Location	USA
Outcomes measures and effect size	

Outcome	Etonogestrel implant (Implanon) n=1168			
	Normal weight (BMI 18.5-24.9, n=439)	Overweight (BMI 25-29.9, n=324)	Obese (BMI 30 or greater, n=405)	Overall (calculated by reviewer) n=1168

Bibliographic reference	**Xu H, Wade JA, Peipert JF et al. (2012) Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstetrics & Gynecology 120: 21-6**

Pregnancy	0 (0%)	0 (0%)	1** (0.25%)	1 (0.09%)

**May have occurred before implant insertion
Outcomes reported but not extracted here: None

Source of funding	Not specified
Comments	- No control group - No statistical comparison between groups of different weights

Bibliographic reference	**Yildizbas B, Sahin HG, Kolusari A et al. (2007) Side effects and acceptability of Implanon: a pilot study conducted in eastern Turkey. European Journal of Contraception & Reproductive Health Care 12: 248-52**
Study type	Non-comparative study (prospective)
Aim	To assess side effects during the first 6 months of use of Implanon
Participant characteristics	**Inclusion criteria:** - Regular menstrual cycles (unclear how defined) - Age 18-40 - BMI 20-30 kg/m2 **Age:** mean: 29.3 (sd 4.8 years) **BMI** **Attrition:** None (discontinuation rate: 0%)
Intervention	Etonogestrel implant (Implanon)
Comparator	-
Number of Participants	41
Length of follow up	6 months
Location	Turkey
Outcomes measures and effect size	The table below reports incidence of each outcome throughout the study at regular follow up visits.

Outcome		**Etonogestrel implant (n=41)**
		% with each pattern 3 months after fitting (1 reference period)
Bleeding pattern change	Amenorrhoea (not bleeding in RP)	14 (34.1%)

Bibliographic reference	**Yildizbas B, Sahin HG, Kolusari A et al. (2007) Side effects and acceptability of Implanon: a pilot study conducted in eastern Turkey. European Journal of Contraception & Reproductive Health Care 12: 248-52**

(all had regular bleeding at baseline). Assessed using diary and World Health Organisation 90-day reference period method.

Infrequent bleeding (<3 episodes)	2 (4.9%)
Frequent bleeding (5+ episodes)	3 (7.3%)
Irregular bleeding (3-5 episodes with more than 3 bleeding-free episodes of 14+ days)	7 (17.1%)
Prolonged bleeding (episode lasting 14+ days)	12 (29.3%)

Outcome (self-reported)	Before insertion	6 months after insertion	P value (unclear how derived)
Dysmenorrhoea	17 (41.5%)	1 (2.4%)	0.00

Outcomes reported but not extracted here: Depression, Acne, Headache, Abdominal pain, Nausea, Local discomfort, dyspareunia, vaginal dryness, matalgia

Source of funding	Oragnon (distributors of Implanon) provided the implants for the study. Funding not specified.
Comments	- No control group - The statistics used to derive the p values in the comparison of outcomes before and after insertation are not specified, and so should be treated with caution.

Bibliographic reference	**Zheng SR, Zheng HM, Qian SZ et al. (1999) A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. European Journal of Contraception & Reproductive Health Care 4: 85-93**
Study type	Non-comparative study (prospective)
Aim	To investigate the contraceptive efficacy, cycle control and acceptability of the etonogestrel implant, Implanon.
Participant characteristics	**Inclusion criteria:** - Aged 20-35 - Regular menstrual cycles (24-35 days) **Age:** mean:29.8 (sd 3) **BMI:** not specified **Weight:** 53.3 Kg (sd 7.2) **Attrition:** Cumulative discontinuation rates: 2 years: 13% at 2 years, 3 years: 21%, 4 years: 24%
Intervention	Etonogestrel implant (Implanon)
Comparator	None

Bibliographic reference	**Zheng SR, Zheng HM, Qian SZ et al. (1999) A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. European Journal of Contraception & Reproductive Health Care 4: 85-93**
Number of Participants	200
Length of follow up	2 years, with optional extension to 4 years
Location	China
Outcomes measures and effect size	

Outcome	**Etonogestrel implant (Implanon) n=200**
Pregnancy	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=200**
Insertion complications	0 (0%)

Outcome	**Etonogestrel implant (Implanon) n=198**
Removal complications	1 (0.5%) (impalpable implant)

Outcome	**Etonogestrel implant (Implanon) n=200**
Implant site reaction (any time during study)	1 (0.5%) (pain)

	Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary and World Health Organisation 90-day reference period (RP) method. ***All data estimated by reviewer from graph**			
90 day Reference period	Amenorrhoea (%) No bleeding/spotting in RP	Infrequent (%) Fewer than 2 episodes	Frequent (%) 5+ episodes	Prolonged (%) Episode lasting 10+ days

Bibliographic reference	Zheng SR, Zheng HM, Qian SZ et al. (1999) A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. European Journal of Contraception & Reproductive Health Care 4: 85-93				
	1	0	5	3	68
	2	8	8	2	44
	3	16	9	1	42
	4	12	8	2	43
	5	12	8	1	41
	6	11	5	2	38
	7	10	12	1	38
	8	10	13	2	32
	9	3	8	1	35
	10	3	8	1	36
	11	4	6	1	35
	12	6	3	1	30
	13	5	7	3	39
	14	1	6	1	25
	15	3	6	2	22
	16	5	7	3	23
	Mean (*Calculated from reported data)	**6.8**	**7.4**	**1.7**	**36.9**

Bibliographic reference	**Zheng SR, Zheng HM, Qian SZ et al. (1999) A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. European Journal of Contraception & Reproductive Health Care 4: 85-93**
	Outcomes reported but not extracted here: Removal time, Blood pressure, weight change
Source of funding	Organon (distributors of Implanon)
Comments	- No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Bibliographic reference	**Zheng SR, Zheng HM, Qian SZ et al. (1999) A randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon) and a six-capsule (Norplant) hormonal contraceptive implant. Contraception 60: 1-8**
Study type	Randomised controlled trial (only Implanon arm extracted here, so treat as non-comparative (prospective)
Aim	To compare the efficacy, tolerability, and bleeding patterns with Implanon and Norplant
Participant characteristics	**Inclusion criteria:** - Aged 20-35 - Regular menstrual cycles (24-35 days) **Age:** mean:29.4 (sd 3.1) **BMI:** not specified **Weight:** 52.9 Kg (sd 6.6) **Attrition:** Cumulative discontinuation rates: 1 year: 4.0%, 2 years: 10.0%, 3 years: 17.3%, 4 years:14.4% at 4 years
Intervention	Etonogestrel implant, Implanon
Comparator	Levongestrel implant, Norplant (only Implanon arm extracted)
Number of Participants	100
Length of follow up	2 years, with optional extension to 4 years
Location	China
Outcomes measures and effect size	

Outcome	Etonogestrel implant (Implanon) n=100
Pregnancy	0 (0%)

Outcome	Etonogestrel implant (Implanon) n=100
Insertion complications	0 (0%)

Bibliographic reference	**Zheng SR, Zheng HM, Qian SZ et al. (1999) A randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon) and a six-capsule (Norplant) hormonal contraceptive implant. Contraception 60: 1-8**

	Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary and World Health Organisation 90-day reference period (RP) method. ***All data estimated by reviewer from graph**			
90 day Reference period	Amenorrhoea (%) No bleeding/spotting in RP	Infrequent (%) Fewer than 2 episodes	Frequent (%) 5+ episodes	Prolonged (%) Episode lasting 10+ days
1	1	14	2	67
2	19	6	4	46
3	10	16	3	45
4	14	10	2	43
5	10	11	3	40
6	12	12	2	45
7	10	15	1	41
8	9	10	1	40
9	6	10	4	46
10	7	14	1	46
11	6	7	0	40
12	8	8	2	41
13	8	8	3	35

Bibliographic reference	**Zheng SR, Zheng HM, Qian SZ et al. (1999) A randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon) and a six-capsule (Norplant) hormonal contraceptive implant. Contraception 60: 1-8**

14	5	6	0	41
15	4	4	4	33
16	2	3	1	27
Mean (*Calculated from reported data)	**8.2**	**9.6**	**2.1**	**42.3**

Outcomes reported but not extracted here: Insertion and removal time, weight change, blood pressure, haemoglobin, adverse events, discontinuation reasons

Source of funding	Organon (distributors of Implanon)
Comments	- Unclear how 'insertion complications' were defined - No control group - High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).

Appendix H: Modified GRADE profiles

H.1 Population 1: women aged 18-40 using etonogestrel implants for contraception

Table 5: Critical outcome: nerve damage

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Implanon, Nerve damage							**Nerve damage**	
3[a]	Case report	-	very serious[b]	no serious	n/a	1-2	Reported in 4 cases	VERY LOW

(a) Gillies 2011, Wechselberger 2006, Brown 2012
(b) Downgraded 2 levels: no control group, retrospective report, cases selected by outcome so does not provide information on the rate of nerve damage

Table 6: Critical outcome: pregnancy

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants		Pregnancy (%)		Quality
Nexplanon vs Implanon, Pregnancy (any time in treatment)						**Nexplanon**	**Implanon**	**Nexplanon**	**Implanon**	
1[a]	RCT	3 years	no serious	no serious	very serious[b]	52	53	0%	0%	LOW
Nexplanon, Pregnancy (any time in treatment)								**Pregnancy (%)**		
1[c]	Non-comparative	3 years	very serious[d]	no serious	no serious	302		0%		VERY LOW
Implanon, Pregnancy (any time in treatment)								**Pregnancy (%)**		
16[e]	Non-comparative	1-4 years	very serious[f]	no serious	no serious	16-1458		0-0.09%		VERY LOW
1[g]	Post-marketing surveillance	-	very serious[h]	no serious	no serious	-		0.049 per 100 implants sold		VERY LOW

(a) Schnabel 2012
(b) Downgraded 2 levels: sample size < 100
(c) Mansour 2010, Mommers 2012

(d) Downgraded 2 levels: no control group
(e) Otero-Flores 2005, Xu 2012, Bhatia 2011, Blumenthal 2008, Darney 2009, Graesslin 2008, Croxatto 1999, Croxatto 2000, Edwards 1999, Zheng 1999a, Arribas-Mir 2009, Funk 2005, Levine 2008, Zheng 1999b, Kiriwat 1998, Aisien 2010, Inal 2008, Makarainen 1998, Vicente 2008, Kreitchmann 2012
(f) Downgraded 2 levels: no control group
(g) Graesslin 2008
(h) Downgraded 2 levels: no control group, relies on reporting of in-treatment pregnancy by clinicians to manufacturer

Table 7: Critical outcome: bleeding pattern changes

Number of studies	Design	Length of follow up	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Implanon, Amenorrhoea (no bleeding in reference period)							**Amenorrhoea (%)**	
12[a]	Non-comparative	0.5-5 years	very serious[b]	no serious	no serious	22-1463	6.8-46.5 %	VERY LOW
Implanon, Infrequent bleeding (<3 episodes in reference period)							**Infrequent bleeding (%)**	
7[c]	Non-comparative	1-5 years	very serious[b]	no serious	no serious	22-1463	32.1-42.3 %	VERY LOW
Implanon, Infrequent bleeding (<2 episodes in reference period)							**Infrequent bleeding (%)**	
5[d]	Non-comparative	0.5-4 years	very serious[b]	no serious	no serious	32-417	4.2-28.2%	VERY LOW
Implanon, Frequent bleeding (>4 episodes in reference period)							**Frequent bleeding (%)**	
11[e]	Non-comparative	0.5-4 years	very serious[b]	no serious	no serious	32-1463	1.7-7.3%	VERY LOW
Implanon, Prolonged bleeding (episode >7 days starting in reference period)							**Frequent bleeding (%)**	
1[f]	Non-comparative	0.5-4 years	very serious[b]	no serious	very serious[g]	32	23.4%	VERY LOW
Implanon, Prolonged bleeding (episode >9 days starting in reference period)							**Prolonged bleeding (%)**	
4[h]	Non-comparative	0.5-4 years	very serious[b]	no serious	no serious	41-417	22.6-42.3%	VERY LOW

Implanon, Prolonged bleeding (episode >13 days starting in reference period)							**Prolonged bleeding (%)**	
6[i]	Non-comparative	0.5-4 years	very serious[b]	no serious	no serious	22-1463	7.0-23.4%	VERY LOW
Implanon, Dysmenorrhoea – % reporting improvement if symptom reported at baseline							**Dysmenorrhoea improved (%)**	
2[j]	Non-comparative	1-5 years	very serious[b]	no serious	no serious	21-923	83-95.2%	VERY LOW
Implanon, Dysmenorrhoea – decrease in rate at removal compared with baseline							**Dysmenorrhoea (decrease,%)**	
1[k]	Non-comparative	6 months	very serious[b]	no serious	very serious[g]	41	39.1%	VERY LOW

(a) Otero-Flores 2005, Yildizbas 2007, Mansour 2008, Aisien 2010, Blumenthal 2008, Darney 2009, Graesslin 2008, Croxatto 1999, Croxatto 2000, Edwards 1999, Kiriwat 1998, Zheng 1999a, Zheng 1999b, Vicente 2008, Funk 2005
(b) Downgraded 2 levels: no control groups, large discontinuation rates
(c) Mansour 2008, Blumenthal 2008, Darney 2009, Graesslin 2008, Croxatto 1999, Croxatto 2000, Edwards 1999, Kiriwat 1998, Vicente 2008, Funk 2005
(d) Otero-Flores 2005, Yildizbas 2007, Aisien 2010, Zheng 1999a, Zheng 1999b
(e) Otero-Flores 2005, Yildizbas 2007, Mansour 2008, Aisien 2010, Blumenthal 2008, Darney 2009, Graesslin 2008, Croxatto 1999, Croxatto 2000, Edwards 1999, Kiriwat 1998, Zheng 1999a, Zheng 1999b, Funk 2005
(f) Aisien 2010
(g) Downgrade 2 levels: sample size < 100
(h) Otero-Flores 2005, Yildizbas 2007, Zheng 1999a, Zheng 1999b
(i) Mansour 2008, Blumenthal 2008, Darney 2009, Graesslin 2008, Croxatto 1999, Croxatto 2000, Edwards 1999, Kiriwat 1998, Funk 2005
(j) Mansour 2008 ,Inal 2008
(k) Yidizbas 2007

Table 8: Critical outcome: removal difficulty

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Nexplanon, removal difficulty							**Removal difficulty (%)**	
1[a]	Non-comparative	3 years	very serious[b]	no serious	no serious	296	5.4%	VERY LOW

Implanon, removal difficulty								
8[c]	Non-comparative	2-4 years	very serious[b]	no serious	no serious	22-1616	0 - 2.2%	VERY LOW

(a) Mansour 2010, Mommers 2012
(b) Downgraded two levels: no control group
(c) Blumenthal 2008, Darney 2009, Graesslin 2008,Edwards 1999, Arribas-Mir 2009, Funk 2005, Levine 2008, Bhatia 2011, Makarainen 1998, Zheng 1999, Vicente 2008

Table 9: Important outcome: fracture of implant

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Nexplanon, Fracture of implant							**Fracture**	
1[a]	Case report	-	very serious[b]	no serious	n/a	6	Six cases reported	VERY LOW
Implanon, Fracture of implant								
6[c]	Case report	-	very serious[b]	no serious	n/a	1-2	Ten cases reported	VERY LOW

(a) Bentley 2012
(b) Downgraded 2 levels: No control group, retrospective, cases selected on outcome
(c) Bentley 2012, Myrick 2012, Torres 2013, Agawal 2003, Tomas-Tello 2010, Pickard 2002

Table 10: Important outcome: implant site reaction

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Nexplanon, Implant site reaction (any time in study)							**Site reaction (%)**	
1[a]	Non-comparative	3 years	very serious[b]	no serious	no serious	301	8.6%	VERY LOW
Implanon, Implant site reaction (any time in study)								
4[c]	Non-comparative	6 weeks – 4 years	very serious[b]	no serious	no serious	200-1728	0.5-27.2%	VERY LOW

(a) Mansour 2010, Mommers 2012

(b) Downgraded 2 levels: No control group, large discontinuation rate
(c) Meirik 2013, Croxatto 1999, Croxatto 2000, Edwards 1999, Zheng 1999

Table 11: Important outcome: insertion difficulty

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Nexplanon, Insertion difficulty							**Insertion difficulty (%)**	
1[a]	Non-comparative	3 years	very serious[b]	no serious	no serious	301	2%	VERY LOW
Implanon, Insertion difficulty								
9[c]	Non-comparative	6 weeks – 4 years	very serious[b]	no serious	no serious	16-1716	0-2%	VERY LOW

(a) Mansour 2010, Mommers 2012
(b) Downgraded two levels: no control group
(c) Meirik 2013, Blumenthal 2008,Darney 2009, Graesslin 2008, Edwards 1999, Makarainen 1998, Zheng 1999a, Zheng 1999b. Vicente 2008, Arribas-Mir 2009, Funk 2005, Levine 2008

Table 12: Important outcome: drug interactions

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Implanon, Pregnancy attributed to interacting drug							**Pregnancy**	
1[a]	Post-marketing surveillance		very serious[b]	serious[c]	no serious	-	25% of method failures attributed to drug interactions	VERY LOW
5[d]	Case-report	-	very serious[e]	serious[c]	n/a	1--2	Seven cases reported	VERY LOW

(a) Graesslin 2010
(b) Downgraded two levels: no comparison to control group, relied on reported of pregnancy and suspicion of drug interaction by clinicians to manufacturer
(c) Use of surrogate outcome (pregnancy)
(d) Schindlbeck 2006, Lakhi 2010, Matiluko 2007, McCarty 2011, Leticee 2012

(e) Downgraded two levels: no control group, retrospective report, cases selected on outcome

Table 13: Important outcome: return to fertility

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Implanon, Ovulation 1 month following removal							**Ovulation (%)**	
1[a]	Non-comparative	3 years	very serious[b]	serious[c]	very serious[d]	40	40%	VERY LOW
Implanon, Pregnancy within 1 year of removal							**Pregnancy (%)**	
1[e]	Non-comparative	3 years	very serious[f]	no serious	very serious[d]	23	95.8%	VERY LOW
Implanon, Pregnancy within 90 days of removal							**Pregnancy (%)**	
2[g]	Non-comparative	2 – 3 years	very serious[f]	no serious	serious[h]	24-174	13.8-29.2%	VERY LOW

(a) Bhatia 2010
(b) Downgraded two levels: no control group, no confirmation of ovulation absence before implant removal
(c) Use of surrogate outcome (ovulation)
(d) Downgraded two levels: Sample size <100
(e) Bhatia 2010
(f) Downgraded two levels: no control group
(g) Croxatto 1999, Croxatto 2000, Bhatia 2010
(h) Sample size < 200

H.2 Subgroup analysis for population 1: women with high weight or BMI vs with women with normal weight

Table 14: Critical outcome: pregnancy

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality

Implanon, Pregnancy							Pregnancy (%)	
1[a]	Non-comparative	3 years	serious[b]	no serious	no serious	1168	Normal weight: 0.0% Overweight: 0.0% Obese: 0.25%	VERY LOW

(a) Xu 2012
(b) No statistical comparison between weight group, high discontinuation rates which are not specified separately across groups

H.3 Population 2: Women aged under 18 using etonogestrel implants for contraception

Table 15: Critical outcome: pregnancy

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Implanon, Pregnancy							Pregnancy (%)	
2[a]	Non-comparative	12 months	very serious[b]	serious[c]	serious[d]	44-171	0-0.6%	VERY LOW

(a) Guazzelli 2010, Tocce 2012
(b) No control group. Participant who became pregnant was taking carbamazepine which is contraindicated on the summary of product characteristics
(c) One study population was women < 20 years, and the other was women <24 years rather than <18 years as specified
(d) Sample size < 200

H.4 Population 3: women aged over 40 using etonogestrel implants for contraception

Table 16: Critical outcome: pregnancy, important outcome: insertion difficulty

Number of studies	Design	Study Length	Risk of bias	Indirectness	Imprecision	Number of participants	Effect	Quality
Implanon, Pregnancy							Pregnancy (%)	
1[a]	Non-comparative	6 months	very serious[b]	serious[c]	very serious[d]	51	0%	VERY LOW

Implanon, Insertion difficulty							Insertion complications (%)	
1[e]	Non-comparative	6 months	very serious[b]	serious[c]	very serious[d]	53	0%	VERY LOW

(a) Booranabunyat 2004
(b) Downgraded 2 levels: No control group
(c) Population was women aged 35+ rather than 40+ as specified
(d) Downgraded two levels: Sample size < 100
(e) Booranabunyat 2004

Appendix I: Economic search strategy

The EMBASE search strategy is shown. The same strategy was translated for the other databases listed.

Table 17: Economic search summary

Database	Date searched	Number retrieved
MEDLINE (Ovid)	13/2/14	261
MEDLINE In-Process (Ovid)	13/2/14	29
EMBASE (Ovid)	13/2/14	1130
HEED	13/2/14	68
NHS EED (Wiley)	13/2/14	4

Table 18: Economic search strategy (EMBASE)

Line number	Search term	Number retrieved
1	implanon.tw.	768
2	nexplanon.tw.	50
3	etonogestrel/	1299
4	etonogestrel.tw.	396
5	norplant*.tw.	1537
6	levonorgestrel/	9078
7	levonorgestrel.tw.	4119
8	desogestrel/	2778
9	desogestrel.tw.	1128
10	progestin implant/	4
11	((progestogen* or progestagen* or progestin* or gestagen* or contracept*) adj4 (implant* or subderm* or subcut*)).tw.	1311
12	(POSDI* or LARC).tw.	609
13	(long adj4 acting adj4 contracept*).tw.	783
14	(contracept* adj4 (implant* or subderm* or subcut*)).tw.	1096
15	or/1-14	13556
16	Nonhuman/ not Human/	3352573
17	15 not 16	13141
18	limit 17 to english language	11191
19	limit 18 to em=200300-201349	6721
20	exp Health Economics/	611412
21	exp "Health Care Cost"/	199940
22	exp Pharmacoeconomics/	170962
23	Monte Carlo Method/	21066
24	Decision Tree/	5841
25	econom$.tw.	212898
26	cba.tw.	10725
27	cea.tw.	22377
28	cua.tw.	900

Line number	Search term	Number retrieved
29	markov$.tw.	15587
30	(monte adj carlo).tw.	27007
31	(decision adj3 (tree$ or analys$)).tw.	11377
32	(cost or costs or costing$ or costly or costed).tw.	423531
33	(price$ or pricing$).tw.	33012
34	budget$.tw.	24003
35	expenditure$.tw.	45599
36	(value adj3 (money or monetary)).tw.	1909
37	(pharmacoeconomic$ or (pharmaco adj economic$)).tw.	6127
38	or/20-37	1114020
39	"Quality of Life"/	240705
40	Quality Adjusted Life Year/	11755
41	Quality of Life Index/	1489
42	Short Form 36/	10854
43	Health Status/	83479
44	quality of life.tw.	207250
45	quality adjusted life.tw.	8487
46	(qaly$ or qald$ or qale$ or qtime$).tw.	8406
47	disability adjusted life.tw.	1489
48	daly$.tw.	1603
49	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.	22241
50	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	1526
51	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	3939
52	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.	35
53	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.	329
54	(euroqol or euro qol or eq5d or eq 5d).tw.	6389
55	(qol or hql or hqol or hrqol).tw.	40498
56	(hye or hyes).tw.	85
57	health$ year$ equivalent$.tw.	43
58	utilit$.tw.	151071
59	(hui or hui1 or hui2 or hui3).tw.	1215
60	disutili$.tw.	355
61	rosser.tw.	90
62	quality of wellbeing.tw.	19
63	quality of well-being.tw.	372
64	qwb.tw.	192
65	willingnessto pay.tw.	3225
66	standard gamble$.tw.	774
67	time trade off.tw.	986
68	time tradeoff.tw.	225

Line number	Search term	Number retrieved
69	tto.tw.	854
70	or/39-69	519742
71	38 or 70	1550098
72	19 and 71	1130

Appendix J: Economic review flowchart

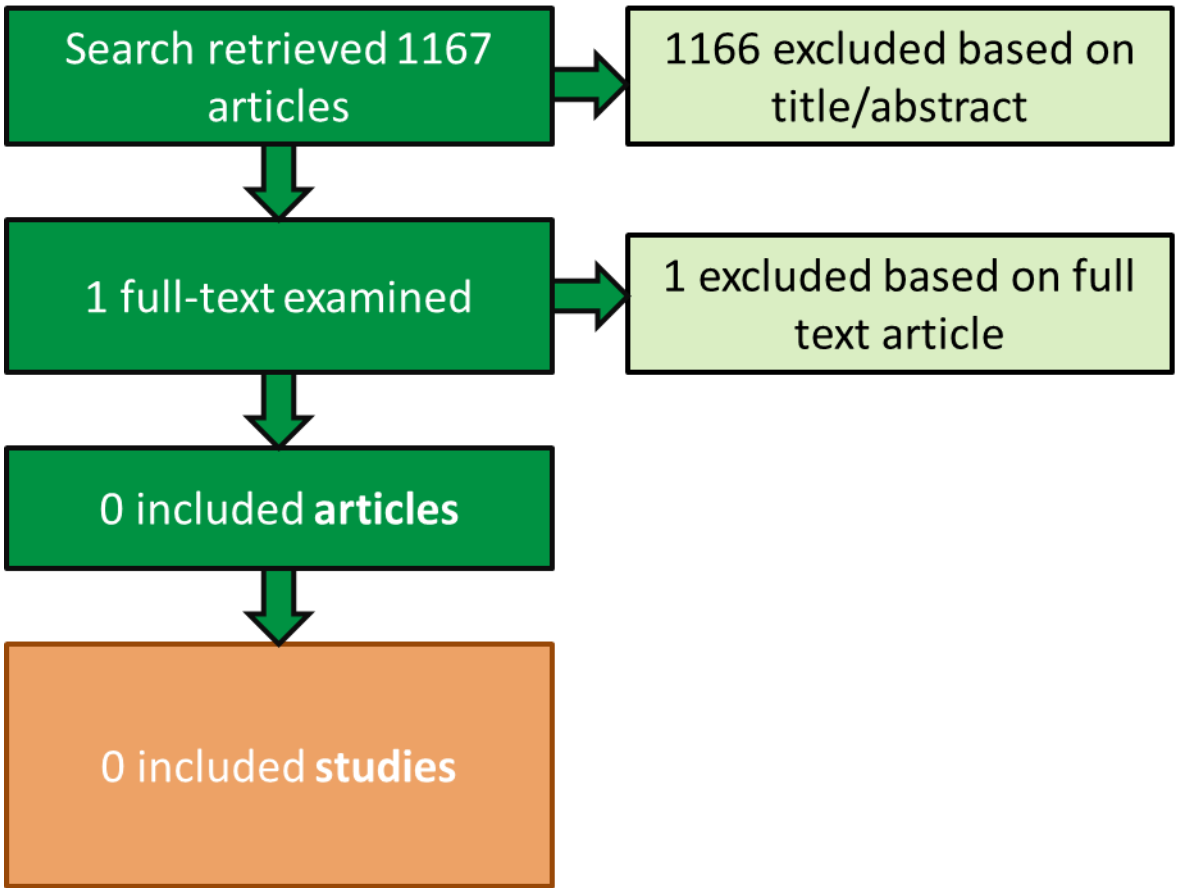

Figure 2: Economic review flow chart

Appendix K: Economic excluded studies

Reference	Reason for exclusion
Lipetz C, Phillips C, Fleming C (2009) Actual cost of providing long-acting reversible contraception: a study of Implanon cost. Journal of Family Planning & Reproductive Health Care 35: 75-9	Insufficient details available to judge study quality