National Institute for Health and Care Excellence

Draft consultation document

# 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*

*June 2014*

*Draft for Consultation*

*Developed by the Centre for Clinical Practice at the National Institute for Health and Care Excellence*

**Disclaimer**
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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# Contents

# Clinical guidelines updates

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 Recommendations

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

2. **Tell 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. **Tell women that dysmenorrhoea may reduce during etonogestrel implant use.**

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

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

## 1.2 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://guidance.nice.org.uk/CG30/ReviewDecision/pdf/English

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').

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.

# 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. Patients 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 NICE clinical guideline 138 Patient experience in adult NHS services.

# 1.4 Methods

Please see the interim process and methods guide for the updates pilot programme 2013 and the guidelines manual 2012, both of which have been followed in the development of this update.

# 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, 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 flowchart 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]

#### *2.1.4.1.13 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

**Table 1: Linking evidence to recommendations (LETR) table**

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| 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.<br><br>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.<br><br>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 |

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| | 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 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 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.<br><br>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.<br><br>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.<br><br>The evidence on return to fertility following implant use was very low quality and |

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| | 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 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.<br><br>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. |

## 2.1.62 Recommendations

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

**2. Advise 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. Advise women that dysmenorrhoea may reduce during etonogestrel implant use.**

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

**5. Advise 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.

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# 4 Glossary & abbreviations

Please refer to the NICE glossary.

# Appendix A: Committee members and NICE teams

## A.1 Standing Committee members

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

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

Nicole Elliott, Associate Director

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Toni Tan, Technical Advisor

Susannah Moon, Project Manager

Kathryn Hopkins, Technical Analyst

Charlotte Purves, Administrator

Jemma Burchett-Vass, Information specialist

## A.4 NICE project team

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Mark Baker, Clinical Advisor

Steven Barnes, Technical Lead

Ben Doak, Guideline Commissioning Manager

Gareth Haman, Senior Medical Editor

Jennifer Wells, Guideline Co-ordinator

Laura Norburn, Public Involvement Advisor

# 1 Appendix B: Declaration of interests

2 **Table 2: Declaration of Committee members' interests**

| Member name | Interest declared | Date declared | Type of interest | Decision |
|---|---|---|---|---|
| **Standing Committee members** | | | | |
| Damien Longson | Chair, Internal Clinical Guidelines, NICE<br><br>Family member employee of NICE<br><br>Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust | 29/05/13 (on appointment) | Personal family non-specific<br><br>Personal non-specific pecuniary | Declare and participate |
| Catherine Briggs | GP Partner in Stockport.<br>Husband is a consultant anaesthetist at the University Hospital of South Manchester.<br><br>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<br><br>Personal family non-specific | 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.<br><br>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:<br>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.<br><br>Non-commercial:<br>NIHR, BHF, Royal College of Surgeons, Circulation foundation, European Venous Forum.<br><br>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 | 04/11/13 | Personal non-specific pecuniary | Declare and participate |

| Member name | Interest declared | Date declared | Type of interest | Decision |
|---|---|---|---|---|
| **Standing Committee members** | | | | |
| | exact source of funding is often not known.<br><br>Has received travel expenses to attend the Veith Meeting NY 2013 November to give lectures by Vascutek. | | | |
| 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.<br>Receives payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness to Practise Investigating Committee.<br>Lay reviewed with the Local Supervising Authority auditing supervision of midwives - receives payment and expenses for this work.<br>Lay reviewer for the NIHR; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews.<br>Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic girdle pain. This is a voluntary position.<br>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.<br><br>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<br>Member NICE – Intra-partum Care GDG<br>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 |

| Member name | Interest declared | Date declared | Type of interest | Decision |
|---|---|---|---|---|
| **Standing Committee members** | | | | |
| Tilly Pillay | None | 11/07/13 | | No action |
| Nick Screaton | Attending Thorax meeting – possible travel expenses paid. | 10/04/14 | | TBC |
| 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.<br>Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.<br>Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.<br>Speaker at conferences to talk about TS – invited by Novatis – travel expenses only.<br>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 | | 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 | | 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<br>○ Subgroups: Women using Nexplanon and Women using Implanon (evidence to be presented separately)<br>○ Subgroup: Women with a high body weight or BMI (as defined in study)<br>• Women below the age of 18 using etonogestrel sub-dermal implants for long-acting reversible contraception<br>• 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)<br>• No contraception<br>• No comparator |
| **Outcomes** | **Critical outcomes:**<br>• Nerve injury<br>• Pregnancy<br>• bleeding changes: frequency, infrequency, prolonged, dysmenorrhoea, amenorrhoea, irregularity<br>• removal: ease or difficulty with<br>**Important outcomes :**<br>• fractures of implant<br>• reaction at insertion site<br>• insertion: ease or difficulty with (including insertion errors)<br>• drug interactions<br>• return to fertility following removal |
| **Other criteria for inclusion / exclusion of studies** | **Inclusion**<br>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 |

| | Details |
|---|---|
| | level of evidence:<br><br>• Systematic reviews*<br>• Randomised controlled trials**<br>• Non-randomised controlled studies**<br>• Prospective comparative observational studies**<br>• Retrospective comparative observational studies**<br>• Prospective non-comparative studies (participants not selected on outcome)<br>• Retrospective non-comparative studies (participants not selected on outcome)<br>• Case series (cases selected on outcome)<br>• Case reports (cases selected on outcome)<br><br>*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.<br>**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.<br><br>**Exclusion**<br>• Narrative reviews<br>• Qualitative studies<br>• Studies comparing sub-dermal implants with other methods of contraception where data for implant arm cannot be separately extracted.<br>• 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<br>• Data on all included studies will be extracted into evidence tables<br>• Where statistically possible, a meta-analytical approach will be used to give an overall summary effect<br>• All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements |

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# 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 3: 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 4: 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 1 Search 2: 1995-2003

2 **Table 5: 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 |

3 **Table 6: 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 |

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# Appendix E: Review flow chart

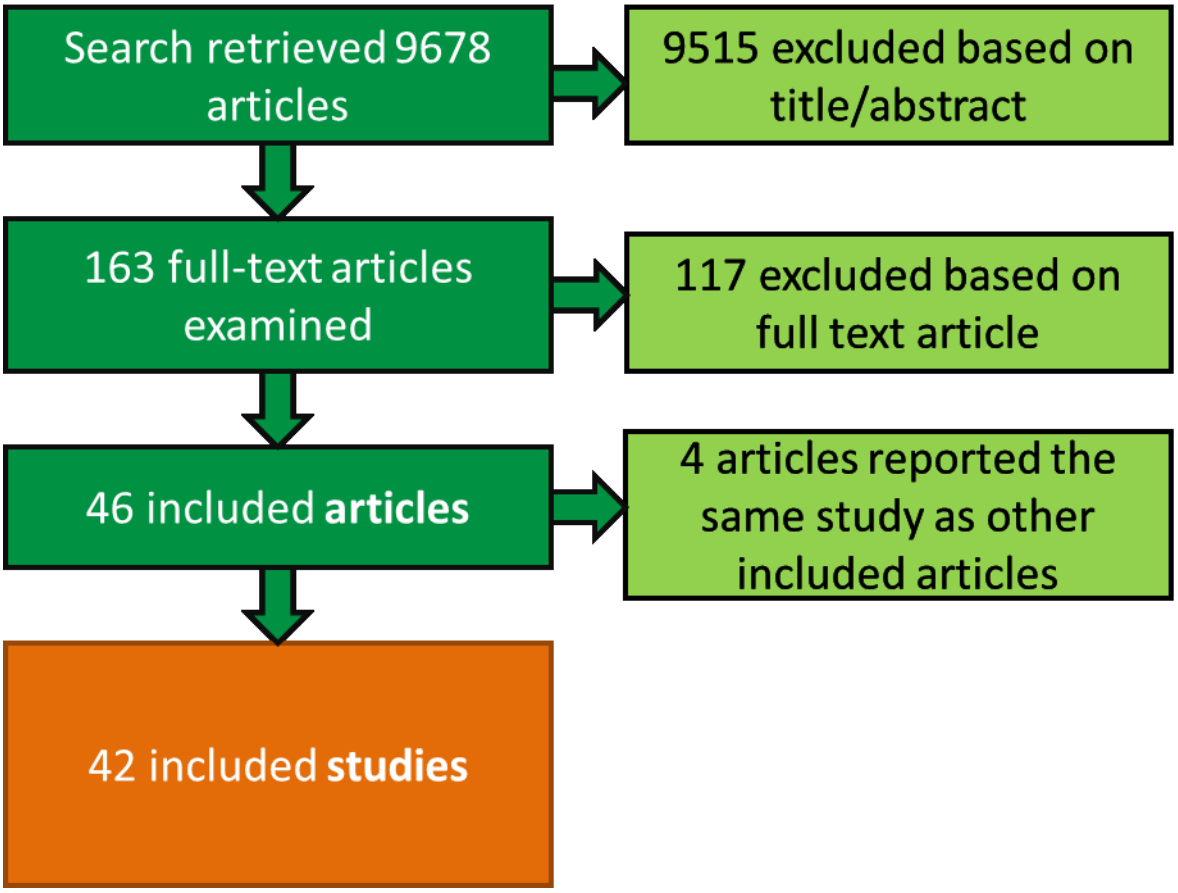


**Figure 1: Clinical review flowchart**

# 1 Appendix F: Excluded studies

2 **Table 7: Clinical search: 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 | Does not report outcomes |

| Reference | Reason for exclusion |
|---|---|
| subdermal contraceptive implants on serum lipids--a randomized comparative study. Contraception 68: 189-93. | specified in review protocol |
| 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 Health | Conference abstract, no full- |

| Reference | Reason for exclusion |
|---|---|
| S57. | text article |
| 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 mothers. Contraception 86 (3) 292. | Conference abstract, no full-text article |

| Reference | Reason for exclusion |
|---|---|
| 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 |

| Reference | Reason for exclusion |
|---|---|
| Mansour D (2007) Implanon failure or a natural event? Journal of Family Planning & Reproductive Health Care 33: 127. | Case report (higher quality 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 | Synthesis of data from clinical |

| Reference | Reason for exclusion |
|---|---|
| contraceptive implant. Journal of Drug Evaluation 1 (6). 181-218. | trials, some of which have now been retracted |
| 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 | Case report (higher quality |

| Reference | Reason for exclusion |
|---|---|
| of Family Planning & Reproductive Health Care 35: 265. | evidence available for all reported outcomes). |
| 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] |

| Reference | Reason for exclusion |
|---|---|
| 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, 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 for included studies

**Table 8: Agrawal and Robinson (2003)**

| 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<br>**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<br>The fracture of the implant was not associated with recalled trauma. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |

1

2 **Table 9: Aisien et al (2010)**

<table>
<tr><th>Bibliographic reference</th><td colspan="9">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>Study type</td><td colspan="9">Non-comparative (prospective)</td></tr>
<tr><td>Aim</td><td colspan="9">To evaluate the safety, efficacy and acceptability of an etonogestrel sub-dermal implant (Implanon)</td></tr>
<tr><td>Participant characteristics</td><td colspan="9">Inclusion criteria:<br>- Sexually active<br>- Healthy<br>- Regular normal menstrual cycle (not clear how defined)<br>Age: mean: 33.9 (range 24-45)<br>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 colspan="9">Etonogestrel implant (Implanon)</td></tr>
<tr><td>Comparator</td><td colspan="9">None</td></tr>
<tr><td>Number of Participants</td><td colspan="9">46 (32 data sets were complete and were analysed)</td></tr>
<tr><td>Length of follow up</td><td colspan="9">1 year</td></tr>
<tr><td>Location</td><td colspan="9">Nigeria</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="9">
<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>
</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** |
|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | 25 | 21.9 | 34.4 | 25 | 3.1 | 21.9 | 6.3 | 0 |
| 4 | 31.3 | 46.9 | 18.8 | 37.5 | 3.1 | 21.9 | 3.1 | 0 |
| **Mean (*Calculated from reported data by reviewer)** | **31.3** | **31.3** | **28.2** | **34.4** | **4.7** | **23.4** | **8.6** | **1.6** |

| **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<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |

1 **Table 10: Arribas-Mir et al (2009)**

<table>
<tr><th>Bibliographic reference</th><th>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</th></tr>
<tr><td>Study type</td><td>Non-comparative study (prospective)</td></tr>
<tr><td>Aim</td><td>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)</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:<br>- All women who had implant inserted at study centre during study period<br>Age: 27.17 (sd 6.41) BMI: Not specified<br>Weight: Not specified<br>Attrition: Discontinuation rates: 1 year, 9%, 2 years, 25.3%, 2 years 9 months, 34.9%</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>372</td></tr>
<tr><td>Length of follow up</td><td>3 years</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<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)
</td></tr>
<tr><td>Source of funding</td><td>Health district of Granada, Andalusian health service</td></tr>
</table>

| 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 |
|---|---|
| Comments | - No control group<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |
| | |

1 **Table 11: Bentley (2013)**

| 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 |
| 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<br>Participant 2: Fractured implant, (Nexplanon) replacement following by subsequent fracture of second implant and positive pregnancy test within 7 days of removal.<br>Participant 3: Fractured implant (Nexplanon), no other adverse effects<br>Participant 4: Fractured implant (Nexplanon), no other adverse effects<br>Participant 5: Fractured Implant (Nexplanon), no other adverse effects<br>Participant 6: Fractured implant (Nexplanon), no other adverse effects<br>Participant 7: Fractured implant (Implanon), no other adverse effects<br><br>The implant fracture was attributed to recalled trauma in one out of the seven cases. |
| Source of funding | None |
| Comments | - No control group |

| Bibliographic reference | Bentley J (2013) Experience and removal of damaged implants. Journal of Family Planning and Reproductive Health Care. 39: 233-4 |
|---|---|
| | - Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

1 **Table 12: Bhatia et al (2011)**

| 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:**<br>- At least one previous child<br>- Healthy<br>- Regular menstruation<br>**Age:** not specified **BMI:** Not specified<br>**Attrition:** Cumulative Discontinuation rates: 6 months: 8%, 12 months: 18.5%, 24 months: 29%, 30 months: 37%.<br>Only 74/200 implants were removed as part of the study – the reason for this is not reported. |
| Intervention | Etonogestrel implant (Implanon) |
| Comparator | None |
| Number of Participants | 200 |
| Length of follow up | 3 years (follow up at 7 days, 1,3,6,12,18,24,30 and 36 months) |
| Location | India |
| Outcomes measures and effect size | **Outcome** / **Etonogestrel implant (Implanon) n=200**<br>Difficulty with insertion / 0 (0%)<br>Pregnancy / 0 (0%) |
| | |

| 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** |
|---|---|

| **Outcome** | **Etonogestrel implant (Implanon) n=74** |
|---|---|
| Difficulty with removal | 0 (0%) |

| **Outcome** | **Etonogestrel implant (Implanon), followed by no contraception or contraception that was not oral contraception n=40** |
|---|---|
| Ovulation 1 month after removal | 16 (40%) |

| **Outcome** | | **Etonogestrel implant (Implanon), followed by no contraception n=24** |
|---|---|---|
| Return to fertility following removal | Pregnancy within 3 months | 7 (29.16%) |
| | Pregnancy within 6 months | 15 (62.50%) |
| | Pregnancy within 9 months | 16 (66.66%) |
| | Pregnancy within 12 months | 23 (95.80%) |

**Outcomes reported but not extracted here:** Reason for discontinuation, bleeding patterns (not reported as a change from baseline), weight gain

| | |
|---|---|
| Source of funding | Not specified |
| Comments | - No confirmation of absence of ovulation before implant removal (therefore ovulation following implant removal may be inaccurate measure of return to fertility)<br>- No control group<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |

1 **Table 13: Blumethal et al (2008), Darney et al (2009) and Graesslin and Korver (2008)**

| | |
|---|---|
| **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**<br><br>**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**<br><br>**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:**<br>- Aged 18-40<br>- Sexually active<br>- Healthy<br>- 80-130% of ideal body weight according to Metropolitan height and weight tables,<br>- Normal menstrual cycles (24-35 days, intra-individual variation <= 3days)<br>**Age:** mean: 27.7 (sd 5.4 ) **Weight:** mean: 59.7 (sd 9.7) Kg **BMI:** mean: 23 (sd 3.2) kg/$m^2$<br>**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) |
| 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** |
|---|---|

| | |
|---|---|
| **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**<br><br>**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**<br><br>**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** |

| | |
|---|---|
| Complications with insertion:<br>- implant retained in applicator<br>- bleeding<br>- hematoma<br>- difficulty with insertion | 9 (1%) |

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

| | |
|---|---|
| | Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary, and incidence of symptoms reported per 90-day reference period. |

| | |
|---|---|
| **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**<br><br>**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**<br><br>**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** |

| | 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<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |

1 **Table 14: Booranabunyat and Taneepanichskul (2004)**

| **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) |

<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>Participant characteristics</td><td>Inclusion criteria:<br>- Healthy (no chronic diseases, normal physical and pelvic examination)<br>- Aged over 35<br>- No use of oral contraceptives within 3 months or injectable contraceptives within 1 year,<br>Age: Mean: 39.7 (sd 3.1) BMI: Mean: 24.9 (sd 3.3)<br>Weight: Mean: 57.9 Kg (sd 8.3)<br>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<br>- Short follow-up period<br>- 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>

1 **Table 15: Brown and Britton (2012)**

| Bibliographic reference | Brown M, Britton J (2012) Neuropathy associated with etonogestrel implant insertion. Contraception 86: 591-3 |
|---|---|
| Study type | Case report |
| Aim | Not applicable |
| Participant characteristics | **Age:** 26 **BMI:** 23.8<br>**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.<br>. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

2

3 **Table 16: Chaudhry (2013)**

| Bibliographic reference | Chaudhry F (232) Adverse reaction to Nexplanon(R). Journal of Family Planning & Reproductive Health Care 39: 231-2 |
|---|---|
| Study type | Case report |

| Bibliographic reference | Chaudhry F (232) Adverse reaction to Nexplanon(R). Journal of Family Planning & Reproductive Health Care 39: 231-2 |
|---|---|
| Aim | Not applicable |
| Participant characteristics | **Age:** 24 **BMI:** Not specified<br>**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 3 weeks following insertion. Site red and swollen with purulent discharge. Recurred over 4 month period, culminating in partial extrusion, before implant was removed.<br><br>Author hypothesises adverse reaction to barium in implant.<br>. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

1

1 **Table 17: Croxatto et al (1999) and Croxatto (2000)**

| **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**<br><br>**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:**<br>- Healthy<br>- Sexually active<br>- Aged 18-40<br>- Regular menstrual cycles (24-35 days, +/- 3 days)<br>- Body weight within 80-130% of ideal (not specified how ideal defined)<br>**Age:** mean: 29 (sd 5.6) **BMI:** mean: 22.7 (sd 2.8)<br>**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) |
| Comparator | None |
| Number of Participants | 635 |
| Length of follow up | 2 or 3 years (initially planned to end after 2 years, some women given the option to continue for further year) |
| Location | Multicentre: Austria, Belgium, Chile, France, Germany, Hungary, Sweden, The Netherlands, UK |
| Outcomes measures and effect size | |

| **Outcome** | **Etonogestrel implant (Implanon) n=635 (2 years) n=147 (3 years)** |
|---|---|
| Pregnancy | 0 (0%) Pearl index =0.0 (95% CI: 0.0-0.2) |

| **Outcome** | | **Etonogestrel implant (Implanon) n=633** |
|---|---|---|
| Implant site reaction (at any time during treatment) | Swelling | 4 (0.6%) |
| | Redness | 3 (0.5%) |
| | Pain | 22 (3.5%) |

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

| | | |
|---|---|---|
| | Haematoma | 4 (0.6%) |
| **Any site reaction** | | 24 (3.8%) |

| | | 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 | N | Amenorrhoea (%) 90 days without bleeding or spotting | Infrequent (%) Less than 3 episodes | Frequent (%) 5+ episodes | Prolonged (%) 14+ days per episode |
| 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 |

<table>
<tr><th>Bibliographic reference</th><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<br><br>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></td><td>
<table>
<tr><td>10</td><td>129</td><td>14.0</td><td>34.1</td><td>5.4</td><td>20.2</td></tr>
<tr><td>11</td><td>129</td><td>11.6</td><td>35.7</td><td>2.3</td><td>19..4</td></tr>
<tr><td>12</td><td>122</td><td>10.7</td><td>29.5</td><td>3.3</td><td>22.1</td></tr>
<tr><td>Mean (*Calculated from reported data by reviewer)</td><td></td><td>14.6</td><td>34.0</td><td>6.6</td><td>21.1</td></tr>
</table>
<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</td></tr>
<tr><td>Source of funding</td><td>Organon (distributors of Implanon)</td></tr>
<tr><td>Comments</td><td>- No control group<br>- 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>

1

1 **Table 18: Edwards and Moore (1999)**

<table>
<tr><th></th><th>Edwards JE, Moore A (1999) Implanon. A review of clinical studies. [Review] [28 refs]. British Journal of Family Planning 24: Suppl-16</th></tr>
<tr><td>Study type</td><td>Synthesis of data from non-comparative studies and randomised comparative studies with Norplant (only Implanon arms extracted here)</td></tr>
<tr><td>Aim</td><td>To compare the ease of use, effect on bleeding patterns and adverse effects for Implanon and Norplant (only Implanon data extracted here)</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:<br>- Aged 18-40<br>- Good physical and mental health<br>- Regular menstrual cycles (not clear how defined)<br>Age: not stated BMI: mean: not stated<br>Attrition: Unclear</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>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)</td></tr>
<tr><td>Length of follow up</td><td>2-3 years (depending on study)</td></tr>
<tr><td>Location</td><td>Europe, Indonesia, South America</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=1458 (only women who used Implanon for 1 year included)</th></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=1716</th></tr>
<tr><td>Complication with insertion</td><td>10 (0.6%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=1616</th></tr>
<tr><td>Complication with removal</td><td>21 (1.3%)</td></tr>
</table>
<table>
<tr><th colspan="2">Outcome</th><th>Etonogestrel implant (Implanon) n=1728</th></tr>
<tr><td>Implant site reaction</td><td>Swelling</td><td>8 (0.5%)</td></tr>
</table>
</td></tr>
</table>

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

| | | |
|---|---|---|
| (at any time during treatment) | 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 |
| 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** | | **22.4** | **32.1** | **5.2** | **13.7** |

| | Edwards JE, Moore A (1999) Implanon. A review of clinical studies. [Review] [28 refs]. British Journal of Family Planning 24: Suppl-16 |
|---|---|
| | **reviewer)** |
| | **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<br>- Unclear discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).<br>- 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.<br>- Not clear how 'regular' menstrual cycles were defined – no clear that reported bleeding patterns represent change from baseline in all cases.<br>- 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). |

1 **Table 19: Funk et al (2005), Levine et al (2008)**

| **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**<br><br>**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:**<br>- Healthy (normal physical and gynaecological examination, normal routine blood and urine tests)<br>- Sexually active<br>- Aged 18-40 |

<table>
<tr><td>Bibliographic reference</td><td>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<br><br>Levine JP, Sinofsky FE, Christ MF et al. (2008) Assessment of Implanon insertion and removal. Contraception 78: 409-17</td></tr>
<tr><td></td><td>- Within 80-130% of ideal body weight (unclear how defined)<br>- ‘Apparently normal’ menstrual cycles (unclear how defined)<br>Age: Mean: not specified. 18-20: 13.0%, 21-25: 39.1%, 26-30: 25.8%, 31-35: 16.7%, 36-40: 5.5%<br>BMI: Mean: Not specified <= 20: 13.9%, 20-22: 25.5%, 22-24: 22.4%, 24-26: 13.9% >26: 24.2%<br>Weight: Not specified<br>Attrition: Discontinuation rates: 1 year: 32% 2 years: 49%</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>330</td></tr>
<tr><td>Length of follow up</td><td>2 years</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Pregnancy, insertion and removal complications reported in both Funk et al and Levine et al. Bleeding pattern changes reported in Funk et al only.<br><br>
<table>
<tr><td>Outcome</td><td>Etonogestrel implant (Implanon) n=330</td></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
<br>
<table>
<tr><td>Outcome</td><td>Etonogestrel implant (Implanon) n=330</td></tr>
<tr><td>Insertion complications</td><td>0 (0%)</td></tr>
</table>
<br>
<table>
<tr><td>Outcome</td><td>Etonogestrel implant (Implanon) n=330</td></tr>
<tr><td>Removal complications</td><td>2 (0.6%)</td></tr>
</table>
<br>
<table>
<tr><td></td><td>Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary,</td></tr>
</table>
</td></tr>
</table>

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

| | | 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 |
| 6 | 188 | 15 | 31 | 5 | 14 |
| 7 | 166 | 15 | 32 | 3 | 14 |
| 8 | 146 | 14 | 24 | 5 | 13 |
| **Mean (*Calculated from reported data by reviewer)** | | **14.0** | **33.1** | **7.3** | **19.5** |

**Outcomes reported but not extracted here:** Time for insertion/removal

| 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**<br><br>**Levine JP, Sinofsky FE, Christ MF et al. (2008) Assessment of Implanon insertion and removal. Contraception 78: 409-17** |
|---|---|
| Source of funding | Organon (distributors of Implanon) |
| Comments | - No control group<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |
| | |

1 **Table 20: Gillies et al (2011)**

| 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<br>**Weight:** Not specified |
| Intervention | Etonogestrel implant (Implanon) |
| 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.<br><br>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. |

| 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 |
|---|---|
| | |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |

1 **Table 21: Graesslin and Korver (2008)**

| 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:**<br>- Women using Implanon for contraception between 1998 and 2007<br>**Age:** not stated **BMI:** mean: not stated<br>**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 |
| Length of follow up | - |
| Location | Not stated |
| Outcomes measures and effect size | **Outcome** / **Etonogestrel implant (Implanon)**<br>Pregnancy (all categories) / 0.049 pregnancies per 100 implants sold<br>Of these: |

| 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** |
|---|---|

| | |
|---|---|
| | No active implant present: 50.3%<br>Conception took place => 10 days before insertion: 10.5%<br>Improper use: 0.6%<br>Conception took place => 10 days after removal: 0.4%<br>Method failure: 38.2% (of which 25% were attributed to drug interactions: CYP450 enzyme inducers, phenytoin, phenobarbital, rifampicin, primidone, nelfinavir, anti-retrovirals) |
| Ectopic pregnancy | 5% of all pregnancies reported |

| **Data estimated by reviewer from graph** | | |
|---|---|---|
| **Weight (Kg)** | **Pregnancy (method failure only) (%)** | **Total users (%)** |
| <40 | 0 | 0 |
| 40-50 | 4.7% | 3.1% |
| 50-60 | 21.9% | 26.6% |
| 60-70 | 37.5% | 34.4% |
| 70-80 | 15.6% | 16.4% |
| 80-90 | 7.8% | 6.3% |
| 90-100 | 3.1% | 3.1% |
| >100 | 0.8% | 3.1% |

**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.

| | |
|---|---|
| Source of funding | Organon (distributors of Implanon) |
| Comments | - Unclear how many users were included in post-marketing surveillance in total.<br>- 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)<br>- No control group. |

1 **Table 22: Guazzelli (2010)**

<table>
<tr><th>Bibliographic reference</th><th>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</th></tr>
<tr><td>Study type</td><td>Synthesis of data from non-comparative studies(prospective) and randomised comparative studies with Norplant (only Implanon arms extracted here)</td></tr>
<tr><td>Aim</td><td>To evaluate the bleeding pattern, efficacy and discontinuation rate for the etonogestrel implant (type not specified)</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:<br>- Aged less than 20<br>- Given birth in the last 6 months<br>- Regular menstrual cycles (not clear how defined)<br>Age: not stated BMI: mean: not stated<br>Attrition: 3 women were lost to follow up. Discontinuation rate: 6.4%</td></tr>
<tr><td>Intervention</td><td>Etonogestrel implant (type not specified)</td></tr>
<tr><td>Comparator</td><td>None</td></tr>
<tr><td>Number of Participants</td><td>47</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>Brazil</td></tr>
<tr><td>Outcomes measures and effect size</td><td><table><tr><th>Outcome</th><th>Etonogestrel implant n=44</th></tr><tr><td>Pregnancy</td><td>0 (0%)</td></tr></table><br>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.</td></tr>
<tr><td>Source of funding</td><td>Not stated</td></tr>
<tr><td>Comments</td><td>- No control group<br>- Mean age not given, so not clear whether the majority of women were aged under 18.<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).<br>- Not clear how ‘regular’ menstrual cycles were defined – no clear that reported bleeding patterns represent change from baseline in all cases.</td></tr>
<tr><td></td><td></td></tr>
</table>

| 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 |
|---|---|
| | |

1 **Table 23: Inal et al (2008)**

| 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:**<br>- Aged less than 20<br>- Given birth in the last 6 months<br>- Regular menstrual cycles (not clear how defined)<br>**Age:** mean: 28.5 (sd 3.4) **BMI:** mean:<br>**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**<br>Pregnancy / 0 (0%)<br><br>**Outcome** / **Etonogestrel implant (Implanon), reporting dysmenorrhoea at baseline n=21**<br>Improvement in dysmenorrhoea / 20 (95.2%)<br><br>**Outcomes reported but not extracted here:** Hormonal and biochemical parameters, acne |
| Source of funding | None |

| 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 |
|---|---|
| Comments | - No control group<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |

1 **Table 24: Kirwat et al (1998)**

| 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:**<br>- Aged 18-40<br>- Proven fertility<br>- Regular menstrual cycles (24-35 days variation no more than 3 days)<br>**Age:** not specified **BMI:** Not specified<br>**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**<br>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<br>15 \| 10 \| 55<br>16 \| 10 \| 50<br>**Mean (*Calculated from reported data by reviewer)** \| **22.3** \| **40.5**<br><br>**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<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |

1 **Table 25: Kreitchmann et al (2012)**

| 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:**<br>- HIV positive<br>- History of poor adherence to contraception<br>**Age:** Mean: 29 (range 20-39) **BMI:** Mean: not specified |

| 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** |
|---|---|
| | **Weight:** 59 kg (range 42-104 kg)<br>59.5% were receiving antiretroviral therapy at time of insertion and 11.4% began antiretroviral therapy during follow up period.<br>**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 | **Outcome** / **Etonogestrel implant (Implanon) n=79**<br>Pregnancy / 0 (0%)<br><br>**Outcomes reported but not extracted here:** Bleeding patterns (not reported as change from baseline) |
| Source of funding | Not specified |
| Comments | - No control group<br>- 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. |

1 **Table 26: Lakhi and Govind (2010)**

| 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 |

| 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 |
|---|---|
| Participant characteristics | **Age:** Participant 1: 33 Participant 2: 35 **BMI:** Not specified<br>**Weight:** Not specified |
| 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, emtricitabine and tenofovir disoproxil (antiretrovirals) for the treatment of HIV.<br><br>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<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample<br>- Surrogate outcome (pregnancy might have occurred in absence of drug interaction) |

1 **Table 27: Leticee et al (2012)**

| 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 |

| 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 characteristics | **Age:** Participant 1: 31 Participant 2: 35 **BMI:** Participant 1: 27 kg/m2 Participant 2: 24 kg/m2<br>**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.<br><br>Participant 2: Pregnancy during Implanon use. Participant was taking efavirenz, tenofovir and emtricitabine (antiretrovirals) for the treatment of HIV. Also regularly used condoms.<br><br>Both implants had been shown to be correctly inserted. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample<br>- Surrogate outcome (pregnancy might have occurred in absence of drug interaction) |
| | |

1 **Table 28: Makarainen et al (1998)**

<table>
<tr><th>Bibliographic reference</th><th>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</th></tr>
<tr><td>Study type</td><td>Randomised controlled trial (only Implanon arm extracted – treat as prospective non-comparative study)</td></tr>
<tr><td>Aim</td><td>To study the mechanism of action of the etonogestrel implant, Implanon.</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:<br>- Aged 18-40<br>- Confirmed ovulation at start of study<br>- Regular menstrual cycles (24-35 days)<br>- Body weight within 80-120% of ideal (not clear how ideal defined)<br>Age: mean: 29.8 (sd 5.9) BMI: not specified Weight: mean: *60 Kg (sd 6.7) *mean not given for Implanon arm separately<br>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%</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>16 (Implanon arm only)</td></tr>
<tr><td>Length of follow up</td><td>2-3 years depending on centre</td></tr>
<tr><td>Location</td><td>Finland and Sweden</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=16</th></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=16</th></tr>
<tr><td>Complication with insertion</td><td>0 (0%)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=?</th></tr>
<tr><td>Complication with removal</td><td>0 (0%)</td></tr>
</table>
</td></tr>
</table>

<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></td><td>
<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>
<br>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>
<tr><td>Source of funding</td><td>Organon (distributors of Implanon) assisted with statistical analysis</td></tr>
<tr><td>Comments</td><td>- No control group<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).<br>- Few details on bleeding pattern analysis</td></tr>
</table>

1 **Table 29: Mansour et al (2008)**

| **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). |

| 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** |
|---|---|
| Aim | To assess the effect of Implanon on menstrual bleeding patterns |
| Participant characteristics | **Inclusion criteria:**<br>- Regular menstrual cycles (unclear how defined)<br>- Age 18-40<br>- Sexually active and childbearing potential<br>- Good physical and mental health<br>**Age:** mean: 27.7 **BMI: mean:** 23.0 kg/m$^2$<br>**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 | |

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

| 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 |
|---|---|

| | | | | |
|---|---|---|---|---|
| 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)** |
|---|---|---|
| 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<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).<br>- Although 'regular cycles' was an inclusion criteria for the studies, there is no specification of what this means, so it is not clear |

| 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 |
|---|---|
| | 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.<br>- Some women were using other hormonal contraception before starting the trials, and this may have altered their 'baseline' pattern of bleeding.<br>- 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. |
| | |

1 **Table 30: Mansour et al 2010**

| 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<br><br>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:**<br>- Aged 18-40<br>- BMI 18-35 kg/m2<br>- Regular menstrual cycles (24-35 days)<br>**Age:** Mean: 28.2 (sd 6.7) **BMI:** Mean: 23.8 kg/$m^2$ (sd 3.7)<br>**Weight:** not specified<br>**Attrition:** Cumulative discontinuation rates: 1 year: 11%, 2 years: 38%, 3 years: 48% |
| Intervention | Radio-opaque etonogestrel implant (Nexplanon) |
| Comparator | - |
| Number of Participants | 302 |

<table>
<tr><th>Bibliographic reference</th><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<br><br>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>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>Outcome</th><th></th><th>Etonogestrel implant - Nexplanon (n=301)</th></tr>
<tr><td>Difficulty with insertion (judged by clinician)</td><td></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>Partial expulsion at time of insertion</td><td></td><td>2 (0.7%)</td></tr>
<tr><td>Any reaction</td><td></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>
<table>
<tr><th>Outcome</th><th>Etonogestrel implant (Implanon) n=296</th></tr>
<tr><td>Removal complications</td><td>16 (5.4%) 13 due to presence of fibrotic tissue</td></tr>
</table>
Outcomes reported but not extracted here: Clinician satisfaction with insertion, x-ray visibility, implant insertion time, Adverse events, implant removal time
</td></tr>
<tr><td>Source of funding</td><td>Editorial support was funded by Schering Corp., a division of Merck and Co. (manufacturers of Nexplanon)</td></tr>
<tr><td>Comments</td><td>- No control group<br>- 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 | **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**<br><br>**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** |
|---|---|
| | |

1 **Table 31: Matiluko et al (2007)**

| 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<br>**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 |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample<br>- Surrogate outcome (pregnancy might have occurred in absence of drug interaction) |

| 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 |
|---|---|
| | |

1 **Table 32: McCarty et al (2011)**

| 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<br>**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<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample<br>- Surrogate outcome (pregnancy might have occurred in absence of drug interaction) |
| | |

1 **Table 33: Meirik et al 2013**

<table>
<tr><th>Bibliographic reference</th><td colspan="3">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 colspan="3">Randomised controlled trial with additional non-randomised arm<br>**Only etonogestrel implant arm extracted, consider as Non comparative study (prospective)</td></tr>
<tr><td>Aim</td><td colspan="3">To compare the effectiveness of an etonogestrel implant (Implanon) with a levongestrel implant, and the copper interuterine device.<br>**Only etonogestrel implant arm extracted here.</td></tr>
<tr><td>Participant characteristics</td><td colspan="3">Inclusion criteria:<br>- Healthy<br>- Regular menstrual cycles<br>Age: 18-44<br>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 colspan="3">Etonogestrel implant (Implanon)</td></tr>
<tr><td>Comparator</td><td colspan="3">-</td></tr>
<tr><td>Number of Participants</td><td colspan="3">997</td></tr>
<tr><td>Length of follow up</td><td colspan="3">6 weeks</td></tr>
<tr><td>Location</td><td colspan="3">Multicentre: Brazil, Chile, Dominican Republic, Hungary, Thailand, Turkey, Zimbabwe</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">
<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>
</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** |
|---|---|
| Source of funding | World Health Organization, United Nations, World Bank |
| 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.<br>- No control group (in extracted data). |
| | |

1 **Table 34: Myrick et al (2012)**

| 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<br>**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<br>Participant 2: Fractured implant (Implanon), 2 incisions required for removal, no other adverse effects<br>Participant 3: Fractured implant (Implanon), no other adverse effects<br><br>The implant fracture was attributed to recalled trauma in one of the three cases. |
| Source of funding | None |

| Bibliographic reference | Myrick L, Howell C, Ramakrishnan K (2012) The broken (fractured) Implanon. Journal - Oklahoma State Medical Association 105: 394-5 |
|---|---|
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

1 **Table 35: Otero Flores et al (2005)**

| 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:**<br>- Regular menstrual cycles (unclear how defined)<br>- Age 15-49<br>**Age:** mean: 25.8 (sd 5.9 years)<br>**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) |
|---|---|

| 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** |
|---|---|

| | |
|---|---|
| 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% |

| | 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** | **20.6** | **4.2** | **2.2** | **22.6** |

| 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 |
|---|---|
| | **from reported data)** |
| | **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<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |

1 **Table 36: Partridge and Bush (2013)**

| 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<br>**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).<br>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. |

| Bibliographic reference | Partridge R, Bush J (2013) Infections post-Nexplanon(R) insertion. Journal of Family Planning & Reproductive Health Care 39: 309-10 |
|---|---|
| | Both participants experienced atopic eczema which the authors hypothesised was related. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

1 **Table 37: Pickard and Bacon (2002)**

| 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<br>**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: Fractured Implant (Implanon), associated with heavy bleeding, no other adverse effects<br>Implant fracture was associated with recalled trauma. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report |

| 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 |
|---|---|
| | - Participants selected based on outcome<br>- Very small sample |
| | |

1 **Table 38: Schindlbeck et al (2006)**

| 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<br>**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<br>- Retrospective report<br>- Participants selected based on outcome<br>- 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 |
|---|---|

1 **Table 39: Schnabel et al 2012**

| 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:**<br>- Good physical/mental health<br>- Regular menstrual cycles 24-35 days duration<br>- Body mass index 18-29 kg/$m^2$<br>- Aged 18-40<br>**Age:** mean: 27.1 (sd 6.7) **BMI:**22.4 (sd 2.4) kg/m2<br>**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)<br>** 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<br>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.<br>- High discontinuation rate in both groups (>40%) – incidence of adverse effects might have been higher if all women had completed the trial. |
| | |

1 **Table 40: Sullivan (2012)**

| 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<br>**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.<br>Author hypothesises adverse reaction to barium in implant.<br>. |
| Source of funding | None |

| Bibliographic reference | Sullivan MJ (2012) Allergy to nexplanon. Journal of Family Planning & Reproductive Health Care 38: 272 |
|---|---|
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |

1 **Table 41: Tocce et al (2012)**

| 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:**<br>- Aged 13-24<br>- In immediate post-partum period (4 weeks of delivery)<br>**Age:** mean at conception(implant fitted postpartum): 18.5 (sd 1.6) **BMI:** 24.1 (sd 5.1)<br>**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%)<br>*participant was taking carbamazepine (enzyme inducer) |

| 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** |
|---|---|
| | **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)<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial). |
| | |

1 **Table 42: Tomas-Tello and Hodgson (2010)**

| 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<br>**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<br>Participant 2: Fractured Implant (Implanon), associated with irregular bleeding, no other adverse effects<br>Implant fracture was not reported to be associated with recalled trauma in either case. |
| Source of funding | None |
| Comments | - No control group |

| Bibliographic reference | Tomas-Tello MD, Hodgson G (2010) Two cases of broken Implanon(). Journal of Family Planning & Reproductive Health Care 36: 255 |
|---|---|
| | - Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

1 **Table 43: Torres et al (2013)**

| 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<br>**Weight:** Not specified |
| Intervention | Etonogestrel implant, Implanon |
| Comparator | Not applicable |
| Number of Participants | 2 |
| 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<br>Participant 2: Fractured implant (Implanon), 2 incisions required for removal, no other adverse effects<br><br>The fracture of the implant was attributed to recalled trauma in one of the two cases. |
| Source of funding | None |
| Comments | - No control group<br>- Retrospective report<br>- Participants selected based on outcome<br>- 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 |
|---|---|
| | |

1 **Table 44: Vicente et al (2008)**

| 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:**<br>- Women with insulin-treated diabetes<br>- Sexually active<br>**Age:** mean:27.59 (sd 6.2) **BMI:** 25.51 (sd 3.58) **Weight:** 64.41 Kg (sd 9.83)<br>**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 effect size | **Outcome** / **Etonogestrel implant (Implanon) n=22**<br>Pregnancy (reported at 2 years) / 0 (0%)<br><br>**Outcome** / **Etonogestrel implant (Implanon) n=23**<br>Insertion complications / 0 (0%) |

| 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** |
|---|---|

| **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

| | |
|---|---|
| Source of funding | Organon (distributors of Implanon) |
| Comments | - No control group<br>- High discontinuation rates may have introduced bias (for example, higher levels of adverse events might have been reported if all women completed the trial).<br>- Unclear how insertion or removal complications were defined.<br>- Not clear whether diary method used to assess bleeding or whether relied on recall (relying on recall more susceptible to bias) |

| 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 |
|---|---|
| | |

1 **Table 45: Wechselberger et al (2006)**

| 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<br>**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<br>- Retrospective report<br>- Participants selected based on outcome<br>- Very small sample |
| | |

1 **Table 46: Xu et al (2012)**

<table>
<tr><th>Bibliographic reference</th><th>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</th></tr>
<tr><td>Study type</td><td>Sub-analysis of larger comparative study – only sub-dermal implant arm extracted – treat as non-comparative study (prospective)</td></tr>
<tr><td>Aim</td><td>To estimate contraceptive failure rates of etonogestrel implants (Implanon) for obese women compared with those of normal weight</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:<br>- Age 14-45<br><br>Age: mean age normal weight: 21.5, mean age overweight: 23.1 mean age obese: 24.2<br>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).</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>1168 (number of women in study who had contraceptive implant – total number was much larger, but these data not extracted here)</td></tr>
<tr><td>Length of follow up</td><td>3 years</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Outcome</th><th colspan="3">Etonogestrel implant (Implanon) n=1168</th><th></th></tr>
<tr><th></th><th>Normal weight (BMI 18.5-24.9, n=439)</th><th>Overweight (BMI 25-29.9, n=324)</th><th>Obese (BMI 30 or greater, n=405)</th><th>Overall (calculated by reviewer) n=1168</th></tr>
<tr><td>Pregnancy</td><td>0 (0%)</td><td>0 (0%)</td><td>1** (0.25%)</td><td>1 (0.09%)</td></tr>
</table>
**May have occurred before implant insertion<br>Outcomes reported but not extracted here: None</td></tr>
<tr><td>Source of funding</td><td>Not specified</td></tr>
<tr><td>Comments</td><td>- No control group<br>- No statistical comparison between groups of different weights</td></tr>
</table>

1 **Table 47: Yildizbas et al (2007)**

<table>
<tr><th>Bibliographic reference</th><th>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</th></tr>
<tr><td>Study type</td><td>Non-comparative study (prospective)</td></tr>
<tr><td>Aim</td><td>To assess side effects during the first 6 months of use of Implanon</td></tr>
<tr><td>Participant characteristics</td><td>Inclusion criteria:<br>- Regular menstrual cycles (unclear how defined)<br>- Age 18-40<br>- BMI 20-30 kg/m2<br>Age: mean: 29.3 (sd 4.8 years) BMI<br>Attrition: None (discontinuation rate: 0%)</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>41</td></tr>
<tr><td>Length of follow up</td><td>6 months</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Outcomes measures and effect size</td><td>The table below reports incidence of each outcome throughout the study at regular follow up visits.
<table>
<tr><th colspan="2">Outcome</th><th>Etonogestrel implant (n=41)</th></tr>
<tr><th colspan="2"></th><th>% with each pattern 3 months after fitting (1 reference period)</th></tr>
<tr><td rowspan="4">Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary and World Health Organisation 90-day reference period method.</td><td>Amenorrhoea (not bleeding in RP)</td><td>14 (34.1%)</td></tr>
<tr><td>Infrequent bleeding (<3 episodes)</td><td>2 (4.9%)</td></tr>
<tr><td>Frequent bleeding (5+ episodes)</td><td>3 (7.3%)</td></tr>
<tr><td>Irregular bleeding (3-5 episodes with more than 3 bleeding-free episodes of 14+ days)</td><td>7 (17.1%)</td></tr>
<tr><td></td><td>Prolonged bleeding (episode lasting 14+ days)</td><td>12 (29.3%)</td></tr>
</table>
<table>
<tr><th>Outcome (self-reported)</th><th>Before insertion</th><th>6 months after insertion</th><th>P value (unclear how derived)</th></tr>
</table></td></tr>
</table>

| 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 |
|---|---|
| | Dysmenorrhoea \| 17 (41.5%) \| 1 (2.4%) \| 0.00<br><br>**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<br>- 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. |

1 **Table 48: Zheng et al (1999)**

| 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:**<br>- Aged 20-35<br>- Regular menstrual cycles (24-35 days)<br>**Age:** mean:29.8 (sd 3) **BMI:** not specified **Weight:** 53.3 Kg (sd 7.2)<br>**Attrition:** Cumulative discontinuation rates: 2 years: 13% at 2 years, 3 years: 21%, 4 years: 24% |
| Intervention | Etonogestrel implant (Implanon) |
| Comparator | None |
| Number of Participants | 200 |
| Length of follow up | 2 years, with optional extension to 4 years |
| Location | China |
| Outcomes measures and effect size | |

| 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 |
|---|---|

| 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 |
| 1 | 0 | 5 | 3 | 68 |
| 2 | 8 | 8 | 2 | 44 |
| 3 | 16 | 9 | 1 | 42 |
| 4 | 12 | 8 | 2 | 43 |

| 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** |
|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 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** |

**Outcomes reported but not extracted here:** Removal time, Blood pressure, weight change

| | |
|---|---|
| Source of funding | Organon (distributors of Implanon) |
| Comments | - No control group<br>- 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 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 **Table 49: Zheng et al (1999)**

| 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:**<br>- Aged 20-35<br>- Regular menstrual cycles (24-35 days)<br>**Age:** mean:29.4 (sd 3.1) **BMI:** not specified **Weight:** 52.9 Kg (sd 6.6)<br>**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%) |

| | |
|---|---|
| | Bleeding pattern change (all had regular bleeding at baseline). Assessed using diary and World |

| 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** |
|---|---|

| | 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 |
| 14 | 5 | 6 | 0 | 41 |
| 15 | 4 | 4 | 4 | 33 |

| 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 |
|---|---|
| | 16 \| 2 \| 3 \| 1 \| 27<br>**Mean (*Calculated from reported data) \| 8.2 \| 9.6 \| 2.1 \| 42.3**<br><br>**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<br>- No control group<br>- 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 50: 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 51: 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 52: 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 (%)** | |

| Number of studies | Design | Length of follow up | Risk of bias | Indirectness | Imprecision | Number of participants | Effect | Quality |
|---|---|---|---|---|---|---|---|---|
| 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 53: 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 54: 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 55: 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 56: 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 57: 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 58: 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 59: 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%<br>Overweight: 0.0%<br>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 60: 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.41 Population 3: women aged over 40 using etonogestrel implants for contraception

2 **Table 61: 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 |

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

8

9

# Appendix I: Economic search strategy

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

**Table 62: 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 63: 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 |

| Line number | Search term | Number retrieved |
|---|---|---|
| 27 | cea.tw. | 22377 |
| 28 | cua.tw. | 900 |
| 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 |

| Line number | Search term | Number retrieved |
|---|---|---|
| 65 | willingness to pay.tw. | 3225 |
| 66 | standard gamble$.tw. | 774 |
| 67 | time trade off.tw. | 986 |
| 68 | time tradeoff.tw. | 225 |
| 69 | tto.tw. | 854 |
| 70 | or/39-69 | 519742 |
| 71 | 38 or 70 | 1550098 |
| 72 | 19 and 71 | 1130 |

# Appendix J: Economic review flowchart

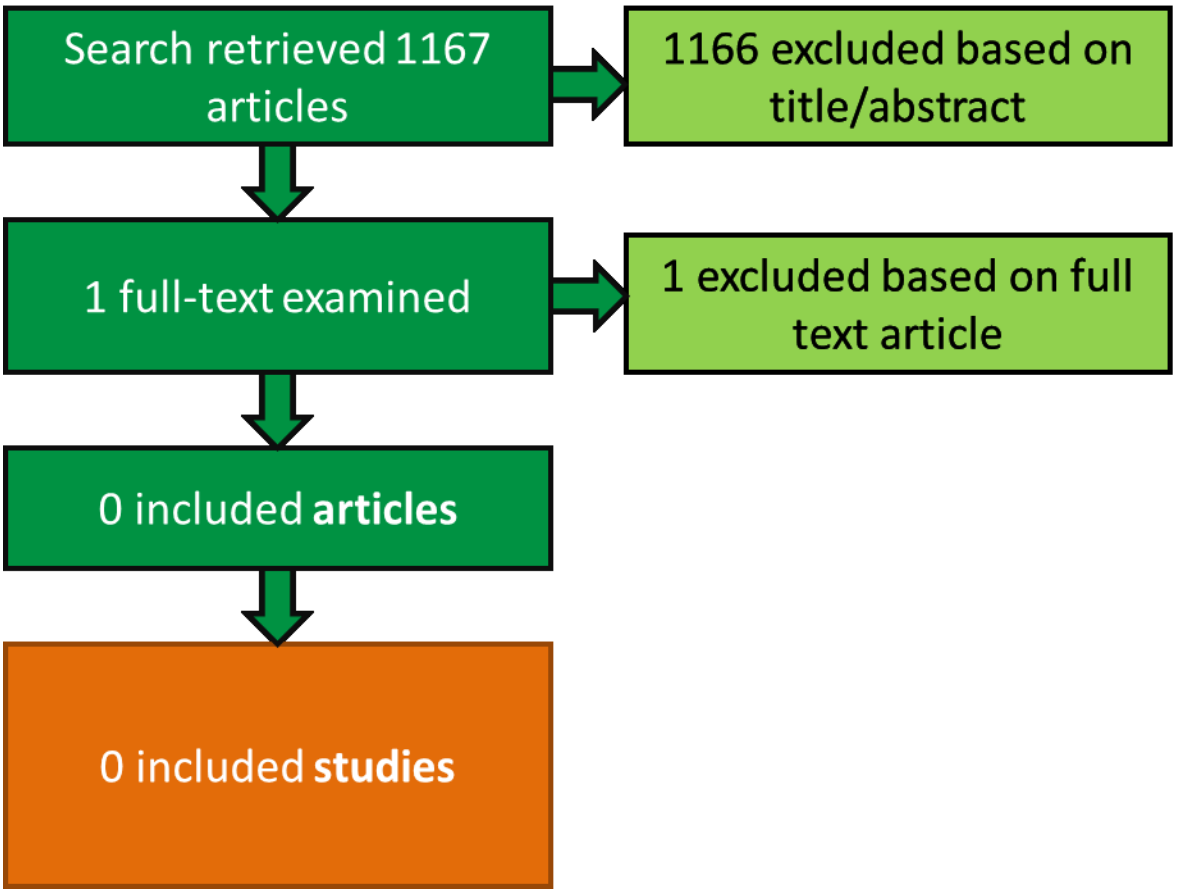


**Figure 2: Economic review flow chart**

# Appendix K: Economic excluded studies

**Table 64: Economic search: excluded studies**

| Reference | Reason for exclusion |
|---|---|

| 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 |

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