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Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy (Review)

Power J, French R, Cowan FM

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	4
RESULTS	6
Figure 1.	8
Figure 2.	9
Figure 3.	10
Figure 4.	11
DISCUSSION	12
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	13
REFERENCES	14
CHARACTERISTICS OF STUDIES	16
DATA AND ANALYSES	21
Analysis 1.1. Comparison 1 Implanon vs Norplant, Outcome 1 Amenorrhoea at end of 1st shifted ref period.	22
Analysis 1.2. Comparison 1 Implanon vs Norplant, Outcome 2 Amenorrhoea at end of 4th ref period.	22
Analysis 1.3. Comparison 1 Implanon vs Norplant, Outcome 3 Amenorrhoea at end of ref period 8.	22
Analysis 1.4. Comparison 1 Implanon vs Norplant, Outcome 4 Infrequent bleeding at end 1st shifted ref period.	23
Analysis 1.5. Comparison 1 Implanon vs Norplant, Outcome 5 Infrequent bleeding at end of 4th ref period.	23
Analysis 1.6. Comparison 1 Implanon vs Norplant, Outcome 6 Infrequent bleeding at end of 8th ref period.	24
Analysis 1.7. Comparison 1 Implanon vs Norplant, Outcome 7 Frequent bleeding at end of 1st shifted ref period.	24
Analysis 1.8. Comparison 1 Implanon vs Norplant, Outcome 8 Frequent bleeding at end 4th ref period.	24
Analysis 1.9. Comparison 1 Implanon vs Norplant, Outcome 9 Frequent bleeding at end 8th ref period.	25
Analysis 1.10. Comparison 1 Implanon vs Norplant, Outcome 10 Prolonged bleeding at end 1st shifted ref period.	25
Analysis 1.11. Comparison 1 Implanon vs Norplant, Outcome 11 Prolonged bleeding at end 4th ref period.	26
Analysis 1.12. Comparison 1 Implanon vs Norplant, Outcome 12 Prolonged bleeding at end 8th ref period.	26
ADDITIONAL TABLES	26
WHAT'S NEW	29
HISTORY	29
CONTRIBUTIONS OF AUTHORS	29
DECLARATIONS OF INTEREST	29
INDEX TERMS	29

[Intervention Review]

Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy

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ABSTRACT

Background

Implantable methods of contraception offer long-acting reversible contraception. Their uptake rate in comparison to other contraceptive methods, particularly in developed countries, has historically been low.

Objectives

To assess the contraceptive effectiveness, tolerability and acceptability of subdermal implants in comparison to other reversible contraceptive methods.

Search methods

Literature were identified through database searches, reference lists and individuals/organisations working in the contraceptive field.

Selection criteria

All randomised and controlled trials comparing subdermal implants with other forms of reversible contraceptives and reporting on pre-determined outcomes in women of reproductive years. Primary outcomes were pregnancy and continuation.

Data collection and analysis

Quality assessment of studies and data extraction were completed independently by two reviewers. A quality checklist was designed to identify general methodological and contraceptive specific factors. Study authors and pharmaceutical companies were contacted to provide additional data.

Data were collected on pregnancy rates, continuation, side effects and adverse events.

Main results

All nine identified trials compared different types of contraceptive implant. Eight, involving 1578 women, compared Implanon with Norplant, and one, involving 1198 women, compared Jadelle with Norplant. There was no difference between Implanon and Norplant for contraceptive effectiveness rates or continuation over 4 years. Both were highly effective methods of contraception with no pregnancies occurring in any of the trials during 26,972 and 28,108 women months of follow up respectively. The most common side-effect with Implanon and Norplant was changes in bleeding pattern. The pattern with Implanon was initially more variable, bleeding with both

implants became less frequent with duration of use. After two years use the amenorrhoea rate was significantly higher with Implanon. The trials reported no significant difference in hormonal side-effects or adverse events. Implanon was significantly quicker to insert and remove than Norplant.

There was no difference in contraceptive effectiveness and in continuation rates between Jadelle and Norplant. Jadelle was significantly quicker to remove than Norplant.

Authors' conclusions

Implanon, Norplant and Jadelle are highly effective contraceptive methods. No significant differences were found in contraceptive effectiveness or continuation. The most common side-effect with all implants was unpredictable vaginal bleeding. Time taken for removal of Implanon and Jadelle was less than that for Norplant.

Although this systematic review was unable to provide a definitive answer on relative effectiveness, tolerability and acceptability of contraceptive implants in comparison to other contraceptive methods, it has raised issues around the conduct of contraceptive research.

PLAIN LANGUAGE SUMMARY

This review aimed to assess how effective contraceptive implants were at preventing pregnancy and how acceptable women found them compared to other methods of contraception.

All the trials identified compared different types of contraceptive implant. No trials were found that compared implants to other contraceptive methods. All the implants were highly effective methods of contraception in the selected women. The majority of women using contraceptive implants chose to continue with the method long term, over 80% of women were still using their implant at two years. Women in developed country studies were less likely to continue with these methods when compared to women in developing country studies. The most common reported side-effect was of irregular vaginal bleeding. Bleeding with all implants became less frequent with time. Removal was quicker for Implanon and Jadelle than for Norplant. Insertion problems were rare with any of the implants. Problems at removal were uncommon but were significantly more likely to occur in Norplant users than Implanon users.

BACKGROUND

All the currently available implantable contraceptive methods release progestogen hormones. They offer long acting reversible contraception. Many potential advantages have been cited for contraceptive implants including (IPPF 2000, WHO consultation):

- high contraceptive effectiveness;
- no need for user compliance, once inserted they are 'forgettable' methods of contraception;
- long life-span;
- minimal requirement for medical follow-up once inserted;
- low, stable serum hormone levels minimising metabolic effects;
- rapid reversibility upon discontinuation.

The uptake of implantable contraceptives in some countries has, however, been low. A number of reasons have been proposed to explain the low uptake of these contraceptive methods within contraceptive services:

- the initial cost of these methods is high. If women continue to use implants as a method of long-term contraception they may be cost-effective, but if the discontinuation rates are high soon after starting the method, implants may be a much more expensive option;
- insertion and removal of implants requires formal training;

media publicity surrounding problematic menstrual changes and a few high profile cases of difficult removal with Norplant have affected consumer demand (HMR Ltd 1999, IPPF 1999).

The first available contraceptive implant, Norplant, was registered for use in 1983, and since then several more implants have been developed. They are currently approved for use in more than 60 countries and are being used by over 11 million women worldwide (WHO 2003). This number is rising as the availability of devices that are easier to use increases their popularity. There are currently four implants that are registered for use, several additional systems are under development. This review will consider only those implants that are currently registered for use.

All implants are based on the same principle: the progestogen hormone is released from one or more biologically inert tubes which are placed in the subdermal layer of the upper inner aspect of the woman's non-dominant arm. An outline of the different implants is given below.

Norplant

Progestogen: Levonorgestrel

Licensed lifespan: 5 years

Reservoir: 6 silicone capsules

Registration: In over 60 countries worldwide

Norplant consists of six, sealed silicone capsules which are placed in a fan shaped pattern in the arm. Each Norplant capsule is 34 mm long and 2.4 mm in diameter and contains 36 mg of the progestogen, levonorgestrel. The original version of Norplant, available from 1983 until 1991, was manufactured with 'hard tubing'. Since 1991 Norplant has been manufactured using 'soft tubing' silicone capsules, this version has been shown to have a higher contraceptive effectiveness than the 'hard tubing' version

(Sivin 1988, Sivin 1998b). This review will consider only studies that used 'soft tubing' Norplant.

Jadelle

Progestogen: Levonorgestrel

Licensed lifespan: 5 years

Reservoir: 2 silicone rods

Registration: In USA, some EU countries

Jadelle consists of two individual sealed silicone rods, each is 2.5 mm in diameter and 4.3 cm in length, each rod contains 75 mg of levonorgestrel. Jadelle differs from a prototype two rod levonorgestrel implant, known as Norplant 2, which was manufactured pre 1990. This prototype was never registered because a supplier ceased manufacture of an elastomer used in the production process (Sivin 1997). Jadelle was developed after a suitable substitute component was identified. Jadelle and Norplant 2 have different contraceptive effectiveness (Sivin, personal communication). This review will consider only studies involving Jadelle.

Implanon

Progestogen: Etonogestrel

Licensed lifespan: 3 years

Reservoir: 1 polymer (ethylvinyl acetate) rod

Registration: In over 40 countries worldwide

Implanon is a single rod, 40 mm long, 2 mm in diameter, containing 68 mg of etonogestrel.

Elcometrine

Progestogen: Nestorone

Licensed lifespan: 6 months

Reservoir: 1 silicone capsule

Registration: In Brazil

This is the only implant releasing nestorone that is currently registered, others are under development. This implant is likely to be particularly suitable for breastfeeding mothers as this progestogen is inactive when ingested orally, therefore minimising the effect of any hormone transferred to infants via breast milk (WHO 2003).

OBJECTIVES

To determine the effectiveness, acceptability and tolerability of subdermal implantable contraceptives. In order to do this the following questions were asked:

1. What is the effectiveness of subdermal implants in comparison to other reversible contraceptive methods?
2. What is the acceptability and tolerability of subdermal implants in comparison to other reversible contraceptive methods (continuation of the method was used as a marker of acceptability and reported side-effects were used as a marker of tolerability)?
3. How do different types of subdermal implants compare in terms of effectiveness, acceptability and tolerability?

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trial and controlled clinical (i.e. quasi-randomised) trial comparisons of subdermal implantable contraceptives with other forms of reversible contraceptives.

Types of participants

Women of reproductive years seeking effective contraception. Pregnant women were excluded.

Types of interventions

Subdermal implants versus:

- non-hormonal intrauterine devices (IUDs)
- barrier contraceptives
- oral contraceptives
- injectable contraceptives
- progestogen-releasing intrauterine systems (IUSs)
- different subdermal implants (e.g. Norplant vs. Implanon)

Types of outcome measures

Primary outcome measures

- Pregnancy due to method failure at 1, 2, 3, 4, 5 years after starting contraceptive method
- Continuation of contraceptive method after 1, 2, 3, 4, 5 years of follow up

Secondary outcome measures

- Menstrual changes
- Hormonal side effects
- Adverse clinical events
- Study withdrawals/reason for discontinuation

Search methods for identification of studies

The following computerised databases were searched to identify publications, in any language, describing randomised or controlled clinical trials of subdermal implantable contraceptives versus other forms of reversible contraceptive methods.

- Cochrane Central Register of Controlled Trials (in The Cochrane Library) Issue 2, 2003
- MEDLINE (1966 to June 2003)
- EMBASE (1980 to June 2003)
- POPLINE (June 2003)
- Science Citation Index (1981 to June 2003)
- PsychLit (1972 to June 2003)

Strategies were devised as follows for the databases searched:

1. The Cochrane Library (searched 26th June 2003)

```
#1contracepti* near implant*
#2exp NORGESTREL/
#3LEVONORGESTREL/
```

```
#4norplant*
#5uniplant
#6keto near desogestrel
#7levonorgestrel
#8norgestrel
#9etonorgestrel
#10implanon
#11subdermal near implant*
#12subcutaneous near implant*
#13jadelle
#14nestorone
#15elcometrine
#16normegestrol
#17#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or
#12 or #13 or #14 or #15 or #16 or #17
```

2. MEDLINE (OvidWeb 1966-June Week 3 2003) (searched 26th June 2003)

```
1 (contracepti$ adj implant$.tw.
2 exp NORGESTREL/
3 LEVONORGESTREL/
4 norplant$.tw.
5 uniplant.tw.
6 (keto adj desogestrel).tw.
7 levonorgestrel.tw.
8 norgestrel.tw.
9 etonorgestrel.tw.
10 implanon.tw.
11 (subdermal adj implant$.tw.
12 (subcutaneous adj implant$.tw.
13 jadelle.tw.
14 nestorone.tw.
15 elcometrine.tw.
16 normegestrol.tw.
17 or/1-16
18 randomized controlled trial.pt.
19 controlled clinical trial.pt.
20 RANDOMIZED CONTROLLED TRIALS/
21 RANDOM ALLOCATION/
22 DOUBLE-BLIND METHOD/
23 SINGLE-BLIND METHOD/
24 clinical trial.pt.
25 exp CLINICAL TRIALS/
26 (clin$ adj25 trial$.tw.
27 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
28 PLACEBOS/
29 (placebo$ or random$.tw.
30 RESEARCH DESIGN/
31 CROSS-OVER STUDIES/
32 (crossover$ or cross-over$ or cross over$.tw.
33 INTERVENTION-STUDIES/
34 multicenter study.pt.
35 (latin-square$ or latin square$ or factorial$.tw.
36 COMPARATIVE STUDY/
37 exp EVALUATION STUDIES/
38 FOLLOW UP STUDIES/
39 PROSPECTIVE STUDIES/
40 (control$ or prospective$ or volunteer$.tw.
41 or/18-40
42 17 and 41
43 (ANIMAL not HUMAN).sh.
```

44 42 not 43

3. EMBASE (OvidWeb 1980-2003 week 25) (searched 26th June 2003)

1 (contracepti\$ adj implant\$).tw.
 2 LEVONORGESTREL/
 3 NORGESTREL/
 4 Norplant\$.tw.
 5 Uniplant.tw.
 6 (keto adj desogestrel).tw.
 7 levonorgestrel.tw.
 8 norgestrel.tw.
 9 etonorgestrel.tw.
 10 implanon.tw.
 11 jadelle.tw.
 12 nestorone.tw.
 13 elcometrine.tw.
 14 normegestrol.tw.
 15 (subdermal adj implant\$).tw.
 16 or/1-15
 17 random\$.tw.
 18 factorial\$.tw.
 19 (crossover\$ or cross-over\$ or cross over\$).tw.
 20 placebo\$.tw.
 21 (doubl\$ adj blind\$).tw.
 22 (singl\$ adj blind\$).tw.
 23 assign\$.tw.
 24 allocat\$.tw.
 25 volunteer\$.tw.
 26 CROSSOVER PROCEDURE/
 27 DOUBLE-BLIND PROCEDURE/
 28 RANDOMIZED CONTROLLED TRIAL/
 29 SINGLE-BLIND PROCEDURE/
 30 or/17-29
 31 16 AND 30
 32 exp ANIMAL/ or NONHUMAN/ or exp ANIMAL EXPERIMENT/
 33 exp HUMAN/
 34 32 not 33
 35 31 not 34

4. POPLINE (via <http://db.jhuccp.org/popinform/expert.html> updated June 16 2003) (searched 26th June 2003)

Contraceptive implant* / levonorgestrel / norgestrel / norplant* / uniplant / keto desogestrel / etonorgestrel / implanon / jadelle / nestorone / elcometrine / normegestrol / subdermal implant*

5. Science Citation Index (Web of Science 1981 - 27 June 2003) (searched 27th June 2003)

Contracepti* implant* or norgestrel or levonorgestrel or norplant* or uniplant or keto desogestrel or etonorgestrel or implanon or jadelle or nestorone or elcometrine or normegestrol or subdermal implant*

6. PsycINFO (OvidWeb 1972 - June week 1 2003) (searched 26th June 2003)

1 (contracepti\$ adj implant\$).tw.
 2 CONTRACEPTIVE DEVICES/
 3 Norplant\$.tw.
 4 Uniplant\$.tw.
 5 (keto adj desogestrel).tw.
 6 levonorgestrel.tw.

7 norgestrel.tw.
 8 etonorgestrel.tw.
 9 implanon.tw.
 10 jadelle.tw.
 11 nestorone.tw.
 12 elcometrine.tw.
 13 normegestrol.tw.
 14 (subdermal adj implant\$).tw.
 15 or/1-14

In addition:

- The reference lists of all identified publications were searched for previously unidentified articles.
- The relevant pharmaceutical companies were contacted and asked to release results of any relevant unpublished studies for inclusion.
- Individuals and organisations with an interest in contraceptive research were contacted to identify unpublished and ongoing studies relevant to the review.

Data collection and analysis

Study selection

The selection of studies for inclusion and their methodological quality were independently assessed and reported by reviewers (JP, RF and FC).

Non-English language publications were assessed by RF and a translator.

Quality assessment

The quality of each publication was assessed independently by two of the three reviewers (JP, RF and FC). Standard quality assessment forms were designed, and included general methodological factors, as well as some of contraceptive specific factors recommended by [Trussell 1991](#). The following quality factors were included on the checklist:

- method of randomisation described
- allocation concealment
- blinded assessment of outcomes
- groups treated identically other than named intervention
- description of women who withdrew or were lost to follow up provided
- description of hormonal contraceptive method or pregnancy immediately prior to study enrolment
- statistical method (with reference) used to analyse pregnancy and continuation of methods
- description of contraceptive failure provided (i.e. user or method failure or both)
- active follow up conducted (i.e. analysis of follow up delayed a few months to allow inclusion of undetected pregnancies)

All of the reviewer differences in initial assessment were resolved after discussion and it was not necessary to involve a third party.

Data collection and analysis

Contraceptive effectiveness and continuation

Although single-decrement life-table probabilities are the ideal method for the measurement of contraceptive effectiveness and continuation ([Trussell 1991](#)), they were not commonly employed in

the papers and therefore not used in this analysis. It was, however, usually possible to collect the number of reported pregnancies and the number of women months contributing to follow up. The number of pregnancies per women months of use, akin to the Pearl Index rate was collected at specific follow up points (at one, two, three, four and five years). The proportion of all women still using each implant at the specific time points was calculated. In order to obtain a relative measure of continuation taking account of the time the method was used, the number of women months contributing to follow up and the potential number of women months at the specified time points were collected. Potential women months were calculated by multiplying the number of women recruited onto each of the studies with the total number of months at each of the specified time points (e.g. at one year the number of women recruited into a study was multiplied by 12 months). This method has been described as a way of measuring completeness of follow-up (Clark 2002).

As it was not possible to calculate rate ratio and follow-up time ratios in RevMan, Microsoft Excel was used to calculate a summary effect size of pregnancies per women months. The rates of the experimental and control events were compared. This method gave a relative measure of 'treatment' effect, that is how much more or less likely implant users were to experience pregnancy in comparison to users of other contraceptive methods or different implants. In terms of continuation, this method provided a crude measure of how well the contraceptives were tolerated. The log rate ratios and the log follow-up ratios, and their variances were calculated for each study (Hasselblad 1995). It was then possible to combine studies using the inverse weighted average of the log rate or follow-up ratios. Events and follow-up were only combined if they were measured over the same time period (i.e. one year, two years and so on) because of their variability over time. For the purpose of data synthesis, in situations where there were no pregnancies in one arm of the trial a continuity correction was implemented by adding a half to each cell.

Menstrual changes, hormonal side-effects and adverse events

Menstrual change outcomes were only collected if investigators had stipulated that they had been measured over 90 day intervals as recommended by Rodriguez 1976 and Belsey 1986. Standard WHO definitions were used to describe vaginal bleeding patterns (Belsey 1986). Amenorrhoea was no bleeding or spotting (B-S) throughout the reference period (RP). Infrequent bleeding was less than three B-S episodes starting within a RP excluding amenorrhoea; frequent bleeding was more than five B-S episodes starting within a RP; and prolonged bleeding was at least one B-S episode lasting greater than 14 days starting within a RP. The number of women who experienced an event and total number of women at each 90 day interval were collected to calculate odds ratios for menstrual change outcomes.

Data on hormonal side effects and adverse events were to be collected at yearly time intervals for the calculation of odds ratios. RevMan was used to obtain a summary effect for the odds ratios. These were compared at specific time points e.g. after one year of use.

A description of the demographic characteristics of the study participants was collected so that a decision could be made whether it was appropriate to combine the data.

The degree of heterogeneity was investigated and reported. A fixed effects approach was used for the meta-analysis (DerSimonian 1986).

RESULTS

Description of studies

Nine subdermal implant trials met the inclusion criteria (See Table of Included Studies for further information including the total number of women and duration for each study). None of these trials compared implants to other reversible methods of contraception, they all compared different types of contraceptive implants.

Eight trials compared Implanon versus Norplant. The data from seven of these eight trials (Organon 34508, Organon 34509, Organon 34510, Organon 34511, Organon 34512, Organon 34514, Organon 34520) had already been combined and published as a series of five meta-analyses (Croxatto 1998, Mascarenhas 1998a, Huber 1998, Affandi 1998, Urbancsek 1998). The seven trials from these meta-analyses are referred to by the trial numbers allocated by Organon who supplied the individual trial data from these trials for this review.

One trial compared Jadelle versus Norplant (Sivin 1998).

Three of the nine trials were conducted in developing or transitional countries (Organon 34510, Organon 34520, Zheng 1999), four in developed countries (Organon 34508, Organon 34509, Organon 34511, Organon 34512); and the remaining two were multicentre trials conducted in both developing and developed countries (Organon 34514, Sivin 1998). However, when the number of women who were recruited is looked at, the gap between studies that were conducted in developing countries compared to those conducted in developed countries becomes even wider (1219 women recruited versus 278 women recruited, respectively). The international multicentre trials, undertaken in both developed and developing countries, recruited 1279 women. It was not possible to ascertain whether the women were from predominantly developing or developed countries.

The age of recruited women, across all studies, ranged from 18-40 years.

Information was collected from the papers on factors, other than the use of the contraceptive methods under investigation, that could potentially effect the fecundity of the study participants. It was only stated in one of the trials that all of the recruited women had had a previous birth or pregnancy, thus ensuring the proven fertility of the population under investigation (Zheng 1999). It was stated for one of the trials that the women were not breast feeding (Zheng 1999). One study stated that women were excluded if they had used hormonal injections in the six months prior to the study starting, or oral contraceptives in the month prior to commencement (Zheng 1999). Women were reported to have regular menses at recruitment in eight of the trials (Organon 34508, Organon 34509, Organon 34510, Organon 34511, Organon 34512, Organon 34514, Organon 34520, Zheng 1999).

Information was collected on additional factors that could potentially affect the study results. The extent of contraceptive counselling received prior to starting the method was not reported in any of the trials. None of the trials reported whether the health worker inserting the subdermal implants had received specialist training. Eight of the trials reported whether the timing of the

insertion in relation to the menstrual cycle was documented ([Organon 34508](#), [Organon 34509](#), [Organon 34510](#), [Organon 34511](#), [Organon 34512](#), [Organon 34514](#), [Organon 34520](#), [Zheng 1999](#)).

Risk of bias in included studies

In only one of the nine trials was both the method of randomisation and allocation concealment described by the authors ([Sivin 1998](#)). In this trial randomisation was done in blocks of 50 and women were allocated their method in sealed envelopes. In all other trials randomisation was computer generated but there was no mention of allocation concealment. The investigators were not blind at follow up assessments to allocated contraceptive methods in any of the trials.

The authors clearly stated the intervention groups were treated identically in all nine of the trials ([Organon 34508](#), [Organon 34509](#), [Organon 34510](#), [Organon 34511](#), [Organon 34512](#), [Organon 34514](#), [Organon 34520](#), [Sivin 1998](#), [Zheng 1999](#)). None of the included studies provided any information on women who withdrew or who were lost to follow-up, so it was not possible to determine whether or not this group was similar to the women who remained in the study.

In the Organon studies data Pearl Indices were used to provide summary effect sizes for pregnancy and discontinuation, the remaining study used life table analysis to report rates for these outcomes ([Sivin 1998](#)).

One of the nine included studies provided a description of the contraceptive methods women were using prior to enrolment ([Sivin 1998](#)).

Active follow-up analysis, to complete the assessment of pregnancy status at the time the trial concluded, was conducted in one study ([Sivin 1998](#)).

Details of the methodological quality for each trial are provided in the table 'Characteristics of Included Studies'.

Effects of interventions

Implanon versus Norplant

It was possible to combine eight studies in the meta-analysis comparing contraceptive effectiveness, continuation and bleeding patterns ([Organon 34508](#), [Organon 34509](#), [Organon 34510](#), [Organon 34511](#), [Organon 34512](#), [Organon 34514](#), [Organon 34520](#), [Zheng 1999](#)).

Contraceptive effectiveness

There was no difference in contraceptive effectiveness between the two implants. There were no pregnancies in either the Implanon or Norplant groups after 26,972 and 28,108 women months of follow up, respectively. We could not assess the effect of weight on contraceptive effectiveness as it was not possible to extract individual patient weight data. Women with a BMI above 29 were excluded from most of the Organon trials.

Continuation

There was no significant difference in the continuation of methods at 1 ([Table 1](#)), 2 ([Table 2](#)), 3 ([Table 3](#)) or 4 years ([Table 4](#)) (these were measured as the total number of women months contributed at each time interval compared with the total possible number of

women months if all women had continued using the implants). The proportion of women followed up and still using Implanon and Norplant, respectively, were 91.6% and 92.4% at Year 1, 82.5% and 81.4% at Year 2, 67.4% and 72.5% at Year 3, and 17.1% and 16.9% at Year 4. The summary follow-up time ratios for continuation of Implanon versus Norplant at 1, 2, 3 and 4 years were 0.98 (95% confidence intervals 0.96 to 1.01), 1.00 (95% CI 0.98 to 1.02), 0.99 (95% CI 0.97 to 1.01) and 1.04 (95% CI 1.00 to 1.09) respectively. There were however marked differences in the proportion of women continuing contraceptive methods depending on geographical area, the overall proportion being higher in the studies conducted in developing (90.6% of women continuing to use Implanon and 91.4% Norplant at two years) as compared to developed countries (55.4% for Implanon and 47.5% for Norplant at 2 years).

Menstrual changes

Menstrual changes were common with both Implanon and Norplant (see [Figure 1](#), [Figure 2](#), [Figure 3](#) and [Figure 4](#)). These figures show the percentage of women with a given bleeding pattern at each reference period. These were calculated as the number of women across all the studies with each bleeding pattern in a particular reference period as a percentage of the total number of women across all the studies in that reference period. Only one trial reported data beyond three years use ([Zheng 1999](#)), hence the bleeding data for reference periods 12 - 16 in the figures represents data from this single trial. Bleeding patterns were analysed at the end of the first shifted reference period and at the end of the 4th (equating to one years use) and 8th (equating to two years use) reference periods (see tables in comparisons and data section). In the first shifted reference interval infrequent and prolonged bleeding was more likely amongst Implanon users compared to Norplant users (odds ratios 1.30 [95% CI 1.04 to 1.63], and 1.49 [95% CI 1.09 to 2.03] respectively). No significant difference between the implants was observed for amenorrhoea (this was heterogeneous, $p=0.01$) and frequent bleeding. At the end of the 4th and 8th reference periods Implanon users were significantly more likely to report amenorrhoea (odds ratio 1.87 [95% CI 1.45 to 2.42] for reference period 4 and 2.14 [95% CI 1.63 to 2.81] for reference period 8). No significant differences between Implanon and Norplant users were observed for infrequent, frequent and prolonged (heterogeneous, $p=0.004$) bleeding. Amenorrhoea increased with duration of use with both implants ([Figure 1](#)) up to three years use, data beyond three years was limited.

It was not possible to extract individual trial data for discontinuation due to vaginal bleeding. [Affandi 1998](#) reports no significant differences between the two implants. There were, however, marked differences in the discontinuation of method because of menstrual disturbance depending on geographical area ([Affandi 1998](#)). Women in Europe were more likely to discontinue implants because of menstrual disturbance (30.2% discontinuing Implanon and 22.5% discontinuing Norplant at two years) compared to women in South Asia (0.9% discontinuing Implanon and 1.4% discontinuing Norplant at two years). Frequent irregular bleeding was the least acceptable bleeding pattern, constituting roughly 50% of the bleeding related discontinuations. Amenorrhoea, in contrast, was rarely a reason for discontinuation ([Affandi 1998](#)).

Figure 1. % of women, across all included trials, with amenorrhoea at each reference period

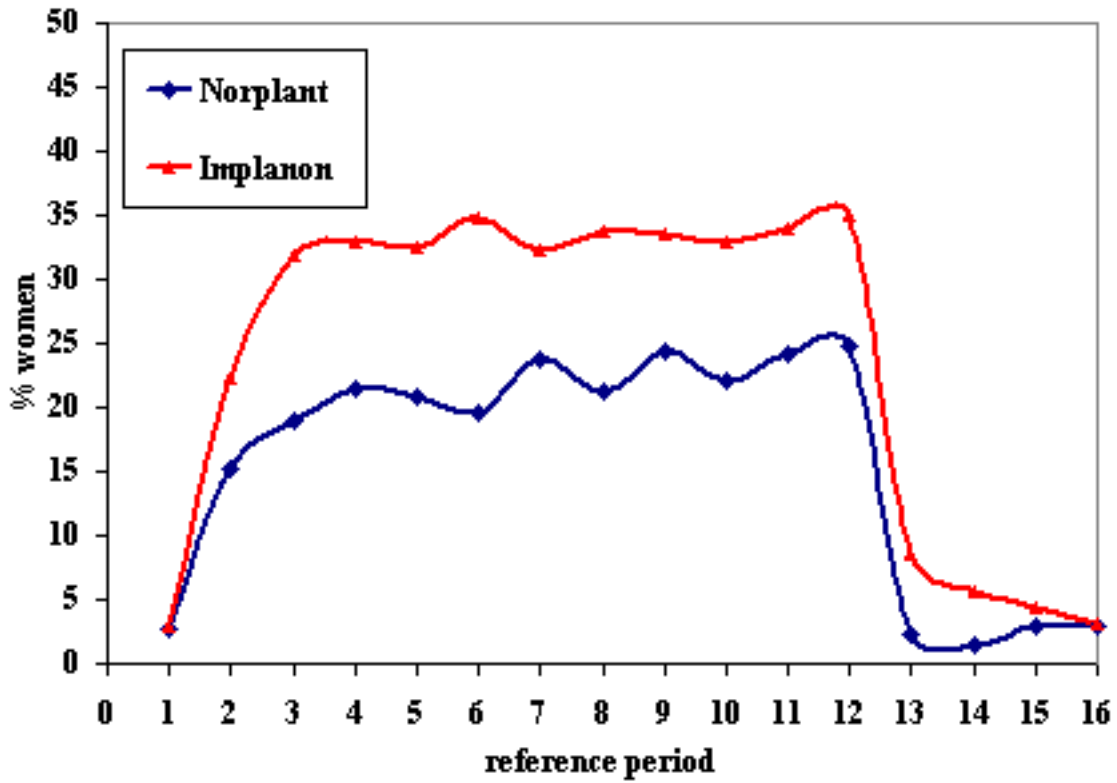


Figure 2. % of women, across all included trials, with infrequent bleeding at each reference period

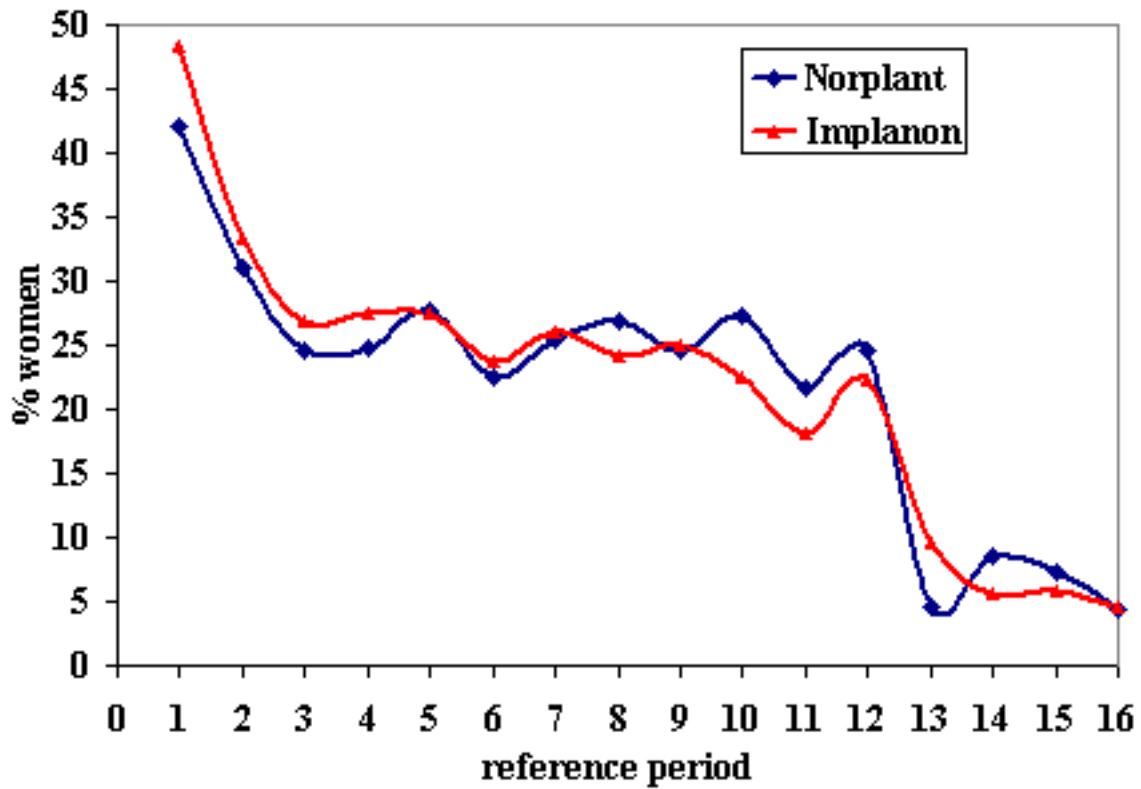


Figure 3. % of women, across all included trials, with frequent bleeding at each reference period

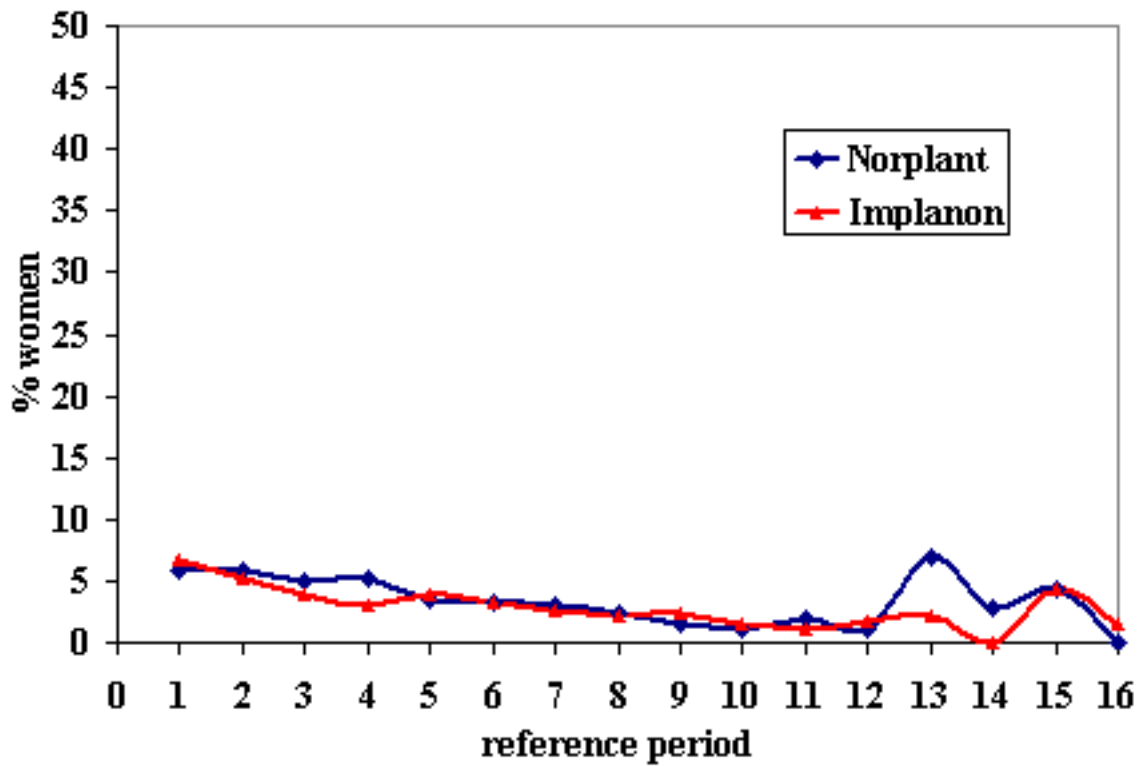
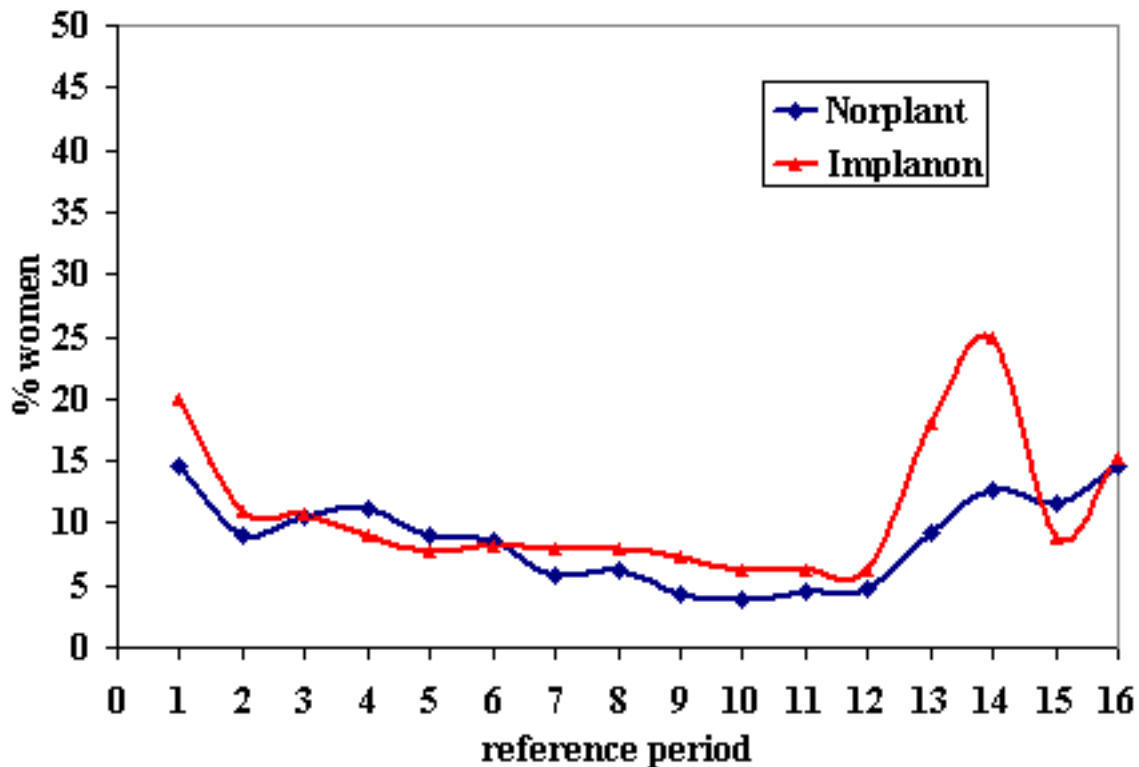


Figure 4. % of women, across all included trials, with prolonged bleeding at each reference period



Hormonal side effects

It was not possible to extract individual trial data for meta-analysis of side effects other than bleeding irregularities or for reasons for discontinuation. [Urbancsek 1998](#) had already combined data from seven trials ([Organon 34508](#), [Organon 34509](#), [Organon 34510](#), [Organon 34511](#), [Organon 34512](#), [Organon 34514](#), [Organon 34520](#)). He found no significant difference in the occurrence of drug related adverse events (61% versus 69% for Implanon and Norplant respectively, $p=0.17$). The most common hormonal side effects were acne (incidence 18.5% versus 21.2% for Implanon and Norplant respectively), headaches (16.8% versus 20.1%), breast pain (9.8% versus 11.4%) and increase in body weight (6.5% versus 7.1%). There was no significant difference in the percentage of women discontinuing Implanon or Norplant due to these adverse events (6.0% versus 7.6%).

Procedure times

It was not possible to extract individual trial data on procedure times for meta-analysis. Data from seven trials had already been combined by [Mascarenhas 1998a](#) ([Organon 34508](#), [Organon 34509](#), [Organon 34510](#), [Organon 34511](#), [Organon 34512](#), [Organon 34514](#), [Organon 34520](#)). Procedure times were available for 670 women having Implanon inserted and 665 women having Norplant inserted. It was not possible to extract these data from the other trial ([Zheng 1999](#)). The mean time for Implanon insertions was 1.1 minutes (SD 0.9, range 0.03 to 5 minutes) and for Norplant insertions was 4.3 minutes (SD 2.1, 0.83 to 18 minutes). Removal times were available for 633 Implanon users and 137 Norplant users. The mean time for Implanon was 2.6 minutes (SD 2.0, range

0.2 to 20 minutes) and for Norplant was 10.2 minutes (SD 8.2, range 1.3 to 50 minutes).

Problems at insertion were rare, being reported in two (0.3%) of the Implanon insertions (one case of bleeding and one case where the rod followed the cannula out of the skin) and none of the Norplant insertions. Norplant users were significantly more likely to experience problems at removal than Implanon users (0.2% vs. 4.8%; $p<0.001$), although the number of problematic removals was small (one complication out of 644 removals for Implanon and 7 out of 145 removals for Norplant). The most common problem with Norplant removals was broken capsules.

[Zheng 1999](#) also found the mean insertion and removal times to be significantly less for Implanon than Norplant: insertion 0.61 versus 3.90 mins $p<0.001$, removal 2.18 versus 11.25 mins $p<0.001$.

Jadelle versus Norplant

One study was identified that compared Jadelle with Norplant ([Sivin 1998](#)). There was no significant difference in pregnancy rate (0.13 and 0.09 per 100 women years for Jadelle and Norplant respectively), cumulative continuation rates (55.1 and 53.0 per hundred users of Jadelle and Norplant respectively at five years) or cumulative discontinuation rates for medical or menstrual problems (15 and 16.4 per 100 respectively for Jadelle versus 12 and 19.2 per hundred for Norplant). The mean time taken to remove Jadelle (4.84 minutes SE 0.22) was significantly less than that taken to remove Norplant (9.59 minutes SE 0.44) ($p<0.0001$).

Subdermal implants versus other reversible contraceptives

No RCTs were identified that compared subdermal implants with either IUDs, oral contraceptives, barrier methods or injectable contraceptives.

DISCUSSION

All of the studies included in the review were comparisons of different types of implants rather than studies comparing implants with other types of contraceptive method. Therefore, it was not possible to determine the relative effectiveness or acceptability of subdermal implants when compared to other forms of contraception. While the comparisons of different types of implants may provide useful information to policy makers and providers of family planning services, they are not necessarily informative to the contraceptive user who wishes to decide between different contraceptive methods.

The studies included demonstrated that subdermal implants were very effective methods for preventing unwanted pregnancy, with only two pregnancies in 4377 women years of follow up in Norplant users, three in 2307 women years of follow up with Jadelle and none in 2068 women years of follow up in those using Implanon. Giving pregnancy rates of 0.05, 0.13 and 0 per 100 women years of use for Norplant, Jadelle and Implanon respectively. These pregnancy rates were not significantly different.

There was no difference in continuation or rates of hormonal side effects for Implanon, Norplant or Jadelle. Continuation was much higher in developing countries than in developed. This might reflect access to alternative contraceptive methods as well as differences in culture and expectations. The most common side effect, with all the implants, was of irregular vaginal bleeding. Although the pattern of bleeding varied slightly between Implanon and Norplant, there was no significant difference in discontinuation rates due to vaginal bleeding between the two implants. However, the numbers involved, especially in the European studies where discontinuation appeared to be higher with Implanon, were small. Amenorrhoea increased with duration of use up to 3 years use, however, this may reflect the fact that women with unacceptable bleeding dropped out of the study. The apparent fall in amenorrhoea after the 12th reference period needs to be interpreted with caution as only one trial reported data beyond three years use, and in the 13th reference period data from only 6 women for Norplant and 2 for Implanon were included. Non-bleeding adverse effects were similar for all the implant types, the most common were acne, breast tenderness, headaches and weight gain.

Eight of the nine trials in this review were sponsored by the manufacturers of Implanon, Organon. In July 2004 a press release was issued explaining that incorrect data had been recorded in the some of study reports of the trials conducted in Indonesia (Rekers 2004). This may have affected trials [Organon 34510](#), [Organon 34514](#) and [Organon 34520](#) included in this review. In order to assess what impact this had on our findings we removed these trials from meta-analysis. Our sensitivity analysis found that this had no significant effect on the findings for the effectiveness or continuation. However, there were some changes noted for menstrual outcomes reported. Without knowing what the discrepancies were, in terms of the data recorded, it is difficult to reach conclusions on the findings and quality of these studies.

It is presumed that pre-treatment counselling, to ensure that women are informed about the potential side effects of a

contraceptive method, has a positive effect on continuation, but, we could find little unbiased published evidence to support this assumption.

There was very little information on failed insertion or failed removal of implants.

Women who agree to be part of a contraceptive RCT are not likely to be representative of the general population of female contraceptive users. They are more likely to be motivated and able to commit to continued follow up. Importantly, women who are prepared to be randomised are not likely to be representative; user choice of contraceptive method is related to effectiveness.

Only one of the trials described allocation concealment. Allocation concealment is always feasible, even if unblinding happens immediately afterwards. Schulz and colleagues (Schulz 2002) demonstrated that inadequate or unclear allocation concealment exaggerated treatment effect by up to 40%. Unfortunately, it was not possible to investigate what effect allocation concealment, as well as other quality factors, had on the findings because of the small number of eligible studies. The fact that in most studies the investigators were not blind to the methods of contraceptive at follow up visits for assessment of outcomes would not affect the number of pregnancies reported. However, reporting of hormonal side effects and menstrual disturbance, and even continuation, could be affected by either the investigator or the contraceptive user knowing the method.

It was interesting to note that none of the studies in the review provided any information on the characteristics of those women who withdrew or were lost to follow up. This may provide insight into the acceptability and tolerability of a contraceptive method as women who are dissatisfied with a method are more likely to drop out of a study and bias the results of a method's effectiveness.

Although this systematic review was unable to provide a definitive answer on the relative effectiveness, tolerability and acceptability of contraceptive implants in comparison to other contraceptive methods, it has raised issues around the conduct of contraceptive research; namely about study quality, the interpretation of results, the usefulness of the information to contraceptive users and the difficulties in trying to synthesize contraceptive data.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review found that subdermal implants were very effective methods of contraception, with few reported pregnancies over the course of the included studies in the selected women. No one subdermal implant was found to be any more or less effective in preventing unwanted pregnancy than another. Implanon and Jadelle were quicker to remove than Norplant.

Menstrual disturbances were common, these menstrual side effects should be explained to women so that they can make an informed choice as to whether or not implants are the most appropriate method of contraception for them.

Implications for research

1. Standardisation of methods and measurements employed in contraceptive research

This systematic review highlights the problems which arise because of inconsistent methods used to measure and report contraceptive effectiveness. We were not able to assess what impact these factors had on pooled data. Standardised methods need to be encouraged, from the recruitment to analysis stages. These problems do not just impact on individuals conducting systematic reviews. They affect how health care practitioners, policy makers, contraceptive users, researchers and the media interpret the contraceptive literature, whether it comes from articles in peer reviewed journals or from contraceptive information leaflets.

Guidance has been provided by [Trussell 1991](#) on the methodological issues which need to be considered when undertaking as well as interpreting contraceptive efficacy and effectiveness research. We would advocate that Trussell's recommendations are considered when contraceptive research is undertaken. We would also advocate that the CONSORT statement should be followed when reporting trials [Moher 2001](#).

2. Designing studies to measure relative effectiveness of contraceptive methods

While RCTs provide the best level of evidence and these comparisons of different types of subdermal implant may provide useful information to policy makers and providers of family planning services, they are not necessarily informative to the contraceptive user who wants to decide which of the various different contraceptive methods to use (e.g. implants versus the IUD). Non-randomised studies were not included in this review. This type of study design may be the most feasible way to compare subdermal implantable contraceptives with a broader spectrum of methods. However, they would need to be designed in such a way to minimise bias.

3. Consumer involvement in the development of contraceptive research

It is vital that contraceptive research is able to answer the queries and concerns of contraceptive users. Rates of pregnancy and

continuation may not accurately reflect the acceptability of a method. Not all women experiencing problematic side effects will discontinue the method. Their decision to discontinue may reflect many other factors as is illustrated by the marked differences in the discontinuation of implants in developing as compared to developed countries. If lay contraceptive users are involved in research development, attention can be directed to answering consumer related questions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Organon 34508

Methods	Setting: Finland and Sweden Randomised 3 years follow up
Participants	32 women randomised, 18-40 years Regular menses
Interventions	Implanon [n=16] vs. Norlant [n=16]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation User/method failure reported: Not applicable as no pregnancies No info on women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Organon 34509

Methods	Setting: Finland and Sweden Randomised
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Organon 34509 (Continued)

2 years follow up

Participants	86 women randomised, 18-40 years Regular menses
Interventions	Implanon [n=43] vs. Norlant [n=43]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation User/method failure reported: Not applicable as no pregnancies No info on women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Organon 34510

Methods	Setting: Indonesia and Thailand Randomised 3 year follow up
Participants	120 women randomised, 18-40 years Regular menses
Interventions	Implanon [n=60] vs. Norlant [n=60]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation User/method failure reported: Not applicable as no pregnancies No info on women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Organon 34511

Methods	Setting Singapore Randomised 2 year follow up
Participants	80 women randomised 18-40 years Regular menses
Interventions	Implanon [n=40] vs. Norlant [n=40]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation User/method failure reported: Not applicable as no pregnancies No info on women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Organon 34512

Methods	Setting: Finland Randomised 2 year follow up
Participants	80 women randomised, 18-40 years Regular menses
Interventions	Implanon [n=40] vs. Norlant [n=40]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation User/method failure reported: Not applicable as no pregnancies No info on women lost to follow up

Risk of bias

Organon 34512 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Organon 34514

Methods	Setting: Indonesia and UK Randomised 2 year follow up
Participants	81 women randomised 18-40 years Regular menses
Interventions	Implanon [n=41] vs. Norlant [n=40]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation User/method failure reported: Not applicable as no pregnancies

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Organon 34520

Methods	Setting: Indonesia Randomised 3 year follow up
Participants	899 women randomised 18-40 years Regular menses
Interventions	Implanon [n=449] vs. Norlant [n=450]
Outcomes	Pregnancy Continuation rates Menstrual disturbance Hormonal side effects Adverse events Insertions and removals
Notes	Quality assessment: Groups treated identically Computer generated randomisation

Organon 34520 (Continued)

User/method failure reported: Not applicable as no pregnancies
 No info on women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

Sivin 1998

Methods	Setting: International multicentre 1198 women randomised Follow up: 5 years
Participants	18-40 years Variable parity (<2 births on average)
Interventions	Jadelle [n=600] vs. Norplant [n=598]
Outcomes	Pregnancy Continuation Reasons for discontinuation LNG serum levels
Notes	Quality assesment: Groups treated identically Randomisation by blocks of 50 - sealed envelopes Description of prior contraceptive method / pregnancy provided Measurement: Groups treated identically Method of analysis: Life tables (single decrement rates) User / method failure reported: Not applicable Active follow up conducted No info on women lost to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Low risk	A - Adequate

Zheng 1999

Methods	Setting: China multicentre Randomised Follow up: 2 yrs with optional extension to 4 yrs
Participants	200 women randomised 20-35 yrs, regular menses, proven fertility, no recent hormonal contraception or pregnancy
Interventions	Implanon [n=100] vs. Norlant [n=100]
Outcomes	Pregnancy, continuation rates, bleeding patterns

Zheng 1999 (Continued)

Notes Quality assessment:
 Groups treated identically
 No info on women lost to follow up

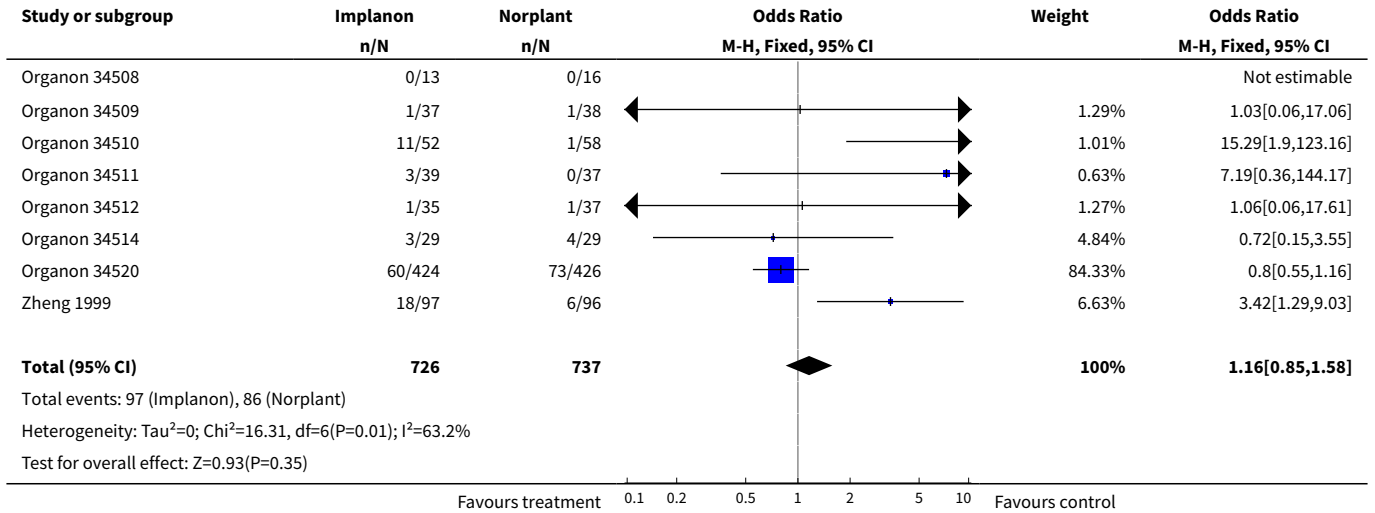
Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment	Unclear risk	B - Unclear

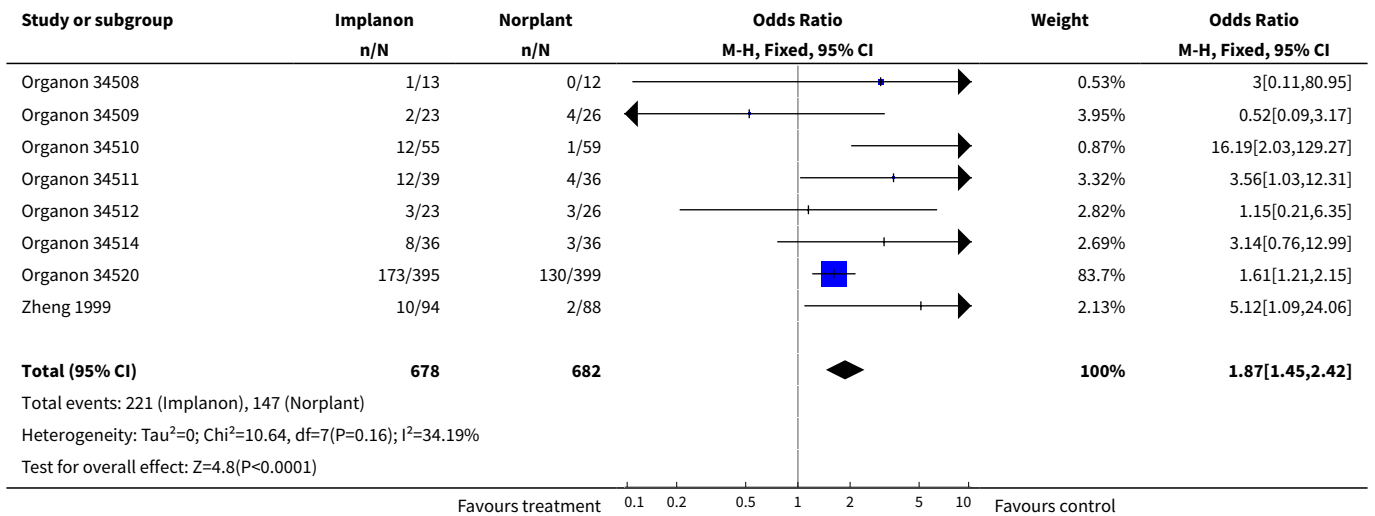
DATA AND ANALYSES
Comparison 1. Implanon vs Norplant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amenorrhoea at end of 1st shifted ref period	8	1463	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.85, 1.58]
2 Amenorrhoea at end of 4th ref period	8	1360	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [1.45, 2.42]
3 Amenorrhoea at end of ref period 8	8	1228	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [1.63, 2.81]
4 Infrequent bleeding at end 1st shifted ref period	8	1482	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [1.04, 1.63]
5 Infrequent bleeding at end of 4th ref period	8	1363	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.92, 1.49]
6 Infrequent bleeding at end of 8th ref period	8	1228	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.65, 1.09]
7 Frequent bleeding at end of 1st shifted ref period	8	1482	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.80, 1.79]
8 Frequent bleeding at end 4th ref period	8	1363	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
9 Frequent bleeding at end 8th ref period	8	1228	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.53, 2.15]
10 Prolonged bleeding at end 1st shifted ref period	8	1482	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [1.09, 2.03]
11 Prolonged bleeding at end 4th ref period	8	1363	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.52, 1.10]
12 Prolonged bleeding at end 8th ref period	8	1167	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.63, 1.70]

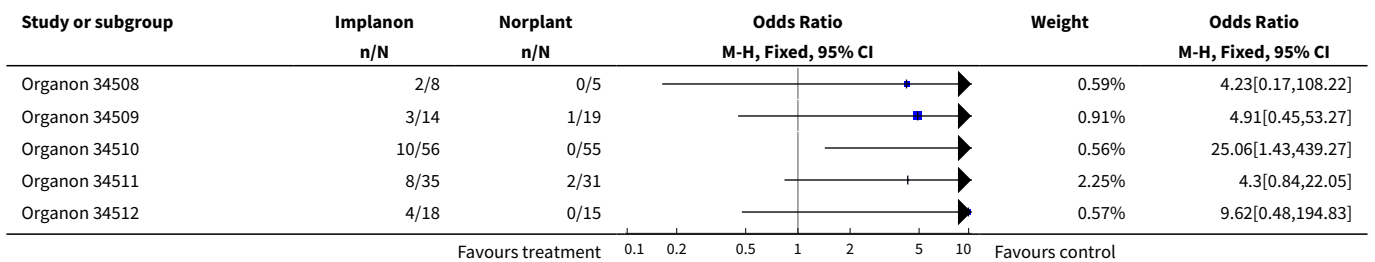
Analysis 1.1. Comparison 1 Implanon vs Norplant, Outcome 1 Amenorrhoea at end of 1st shifted ref period.

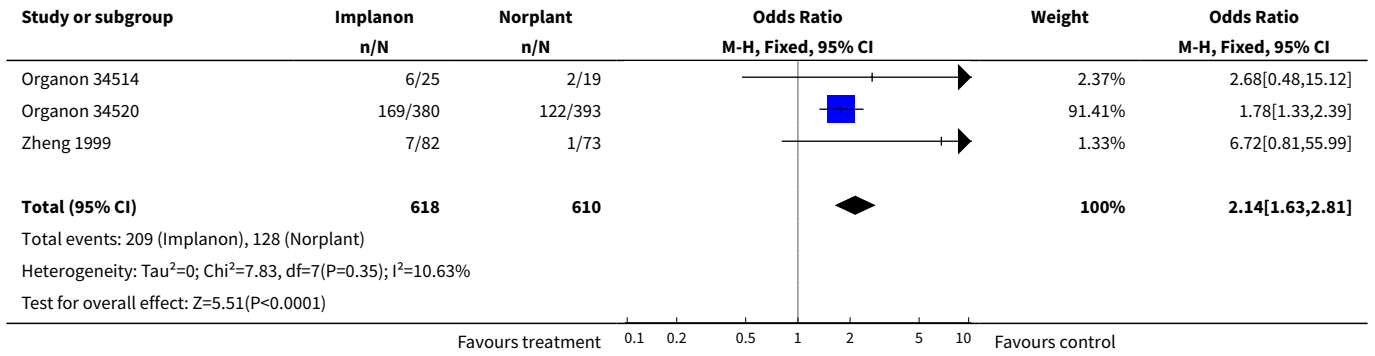


Analysis 1.2. Comparison 1 Implanon vs Norplant, Outcome 2 Amenorrhoea at end of 4th ref period.

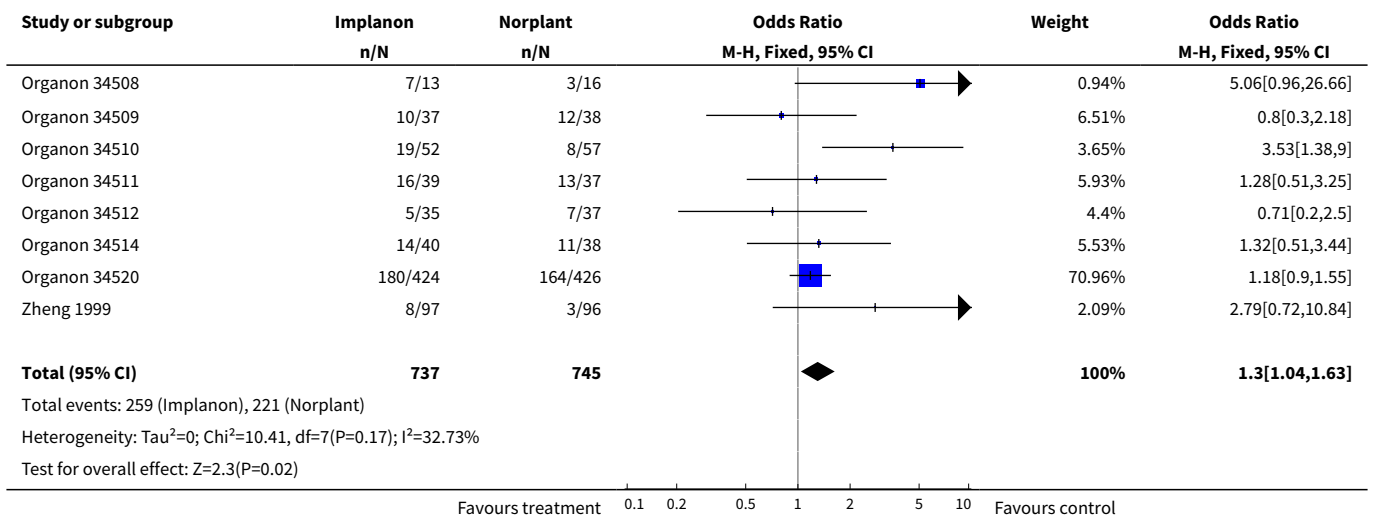


Analysis 1.3. Comparison 1 Implanon vs Norplant, Outcome 3 Amenorrhoea at end of ref period 8.

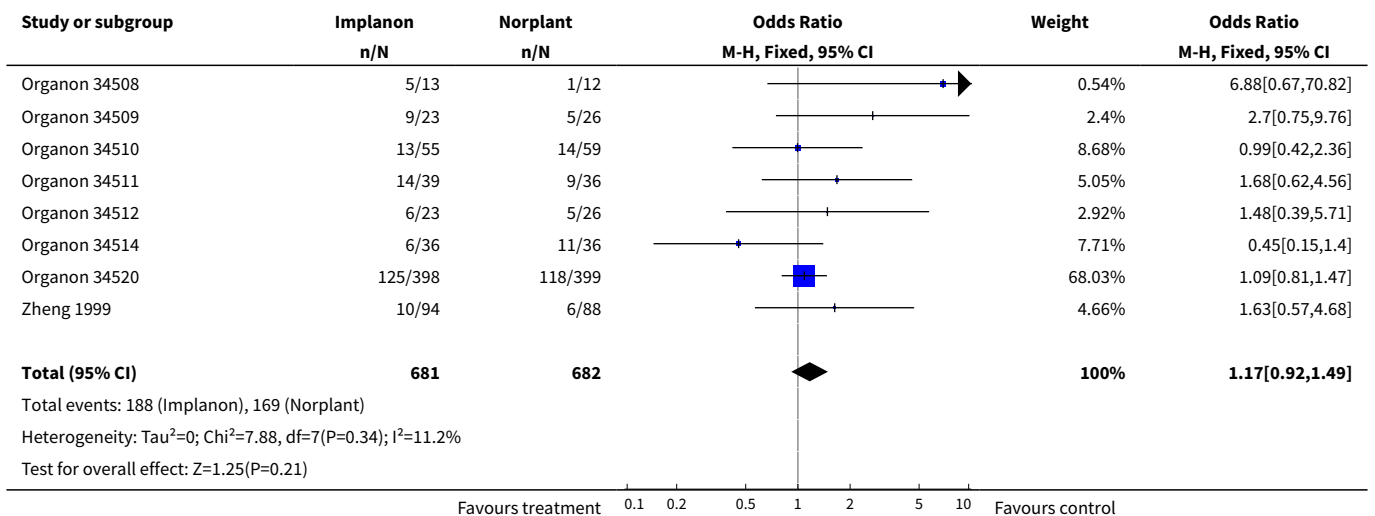




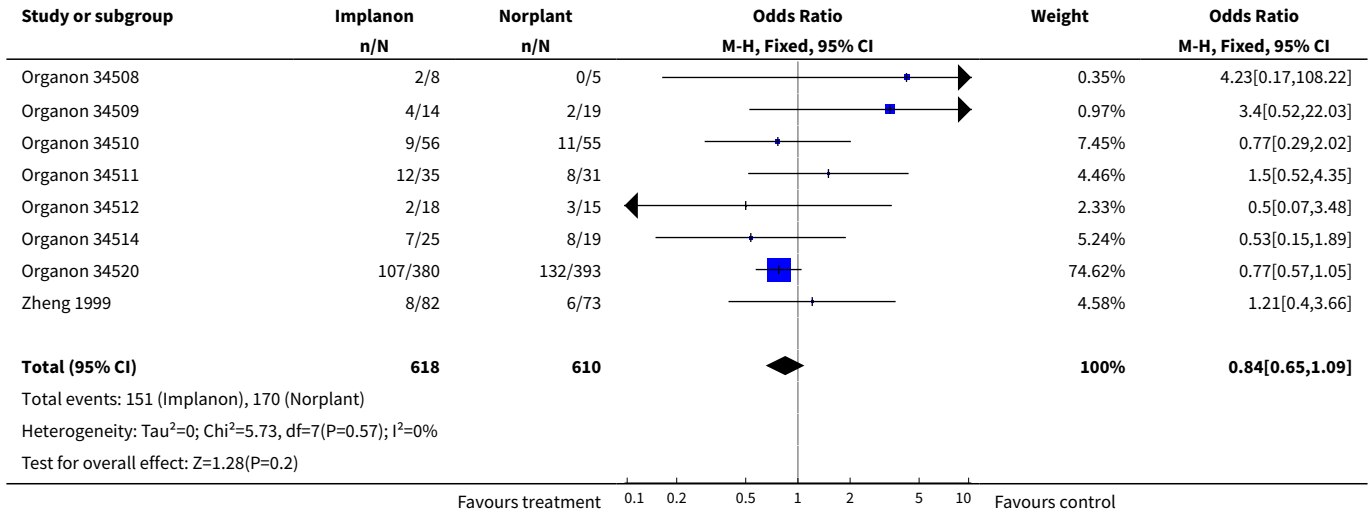
Analysis 1.4. Comparison 1 Implanon vs Norplant, Outcome 4 Infrequent bleeding at end 1st shifted ref period.



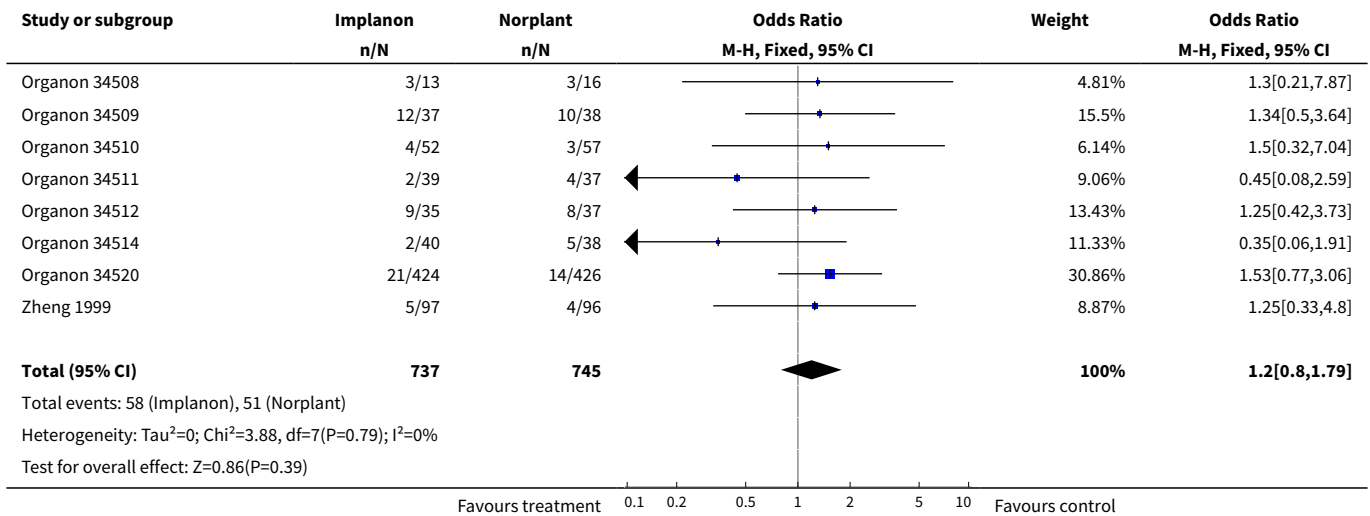
Analysis 1.5. Comparison 1 Implanon vs Norplant, Outcome 5 Infrequent bleeding at end of 4th ref period.



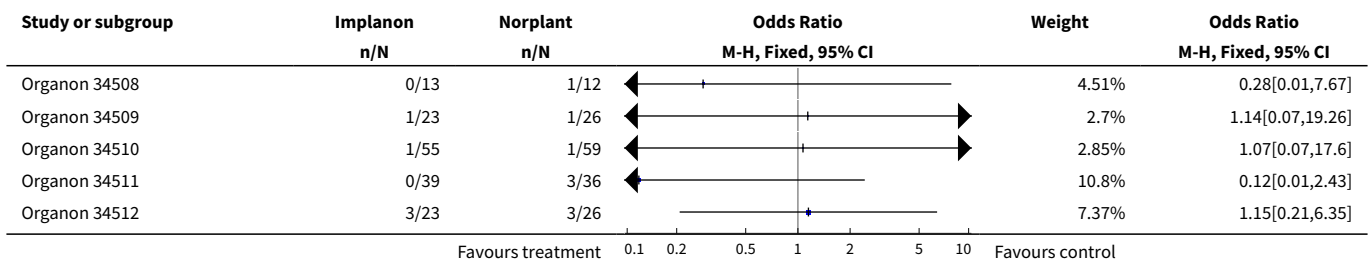
Analysis 1.6. Comparison 1 Implanon vs Norplant, Outcome 6 Infrequent bleeding at end of 8th ref period.

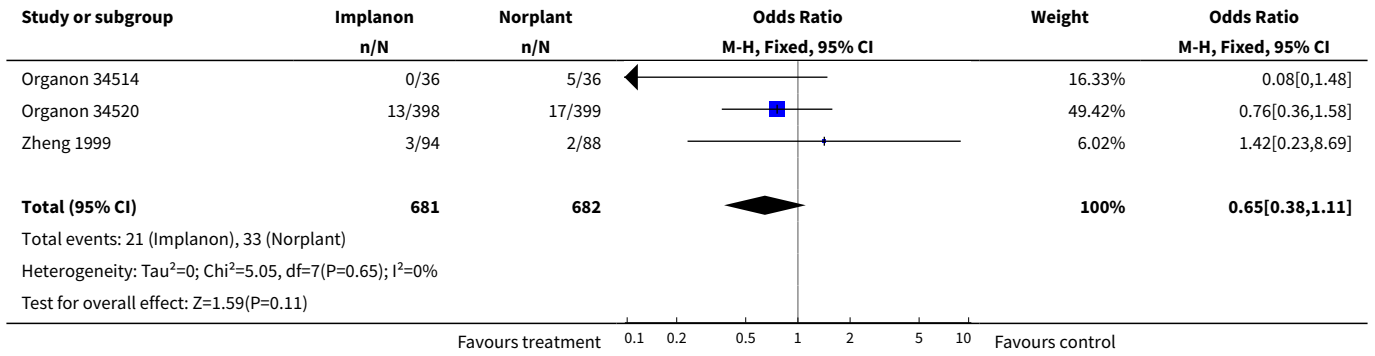


Analysis 1.7. Comparison 1 Implanon vs Norplant, Outcome 7 Frequent bleeding at end of 1st shifted ref period.

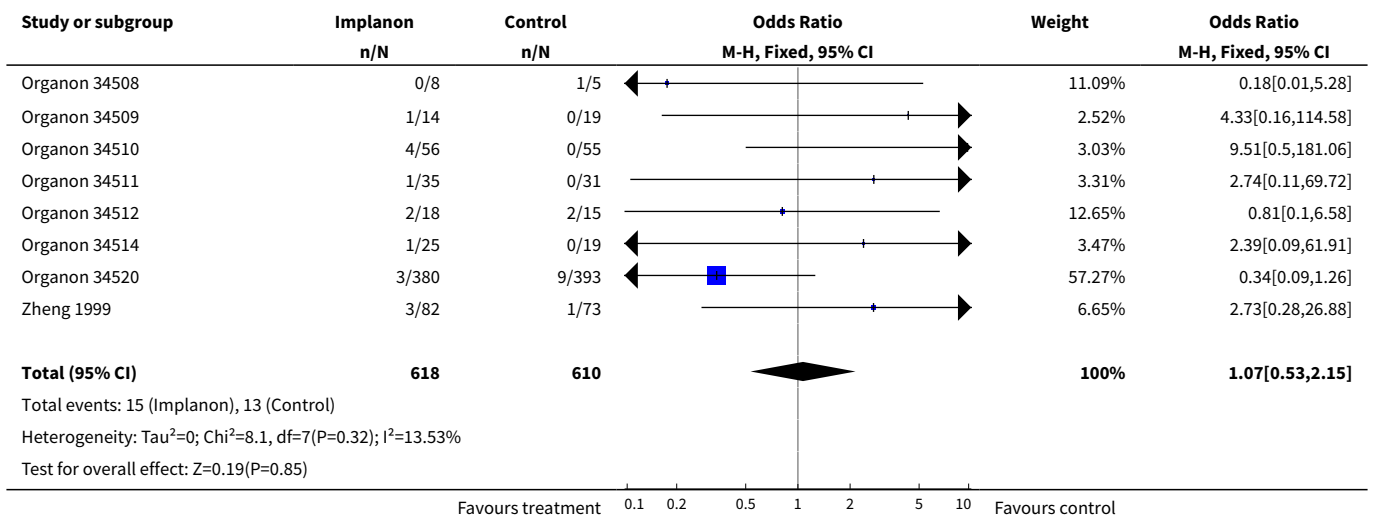


Analysis 1.8. Comparison 1 Implanon vs Norplant, Outcome 8 Frequent bleeding at end 4th ref period.

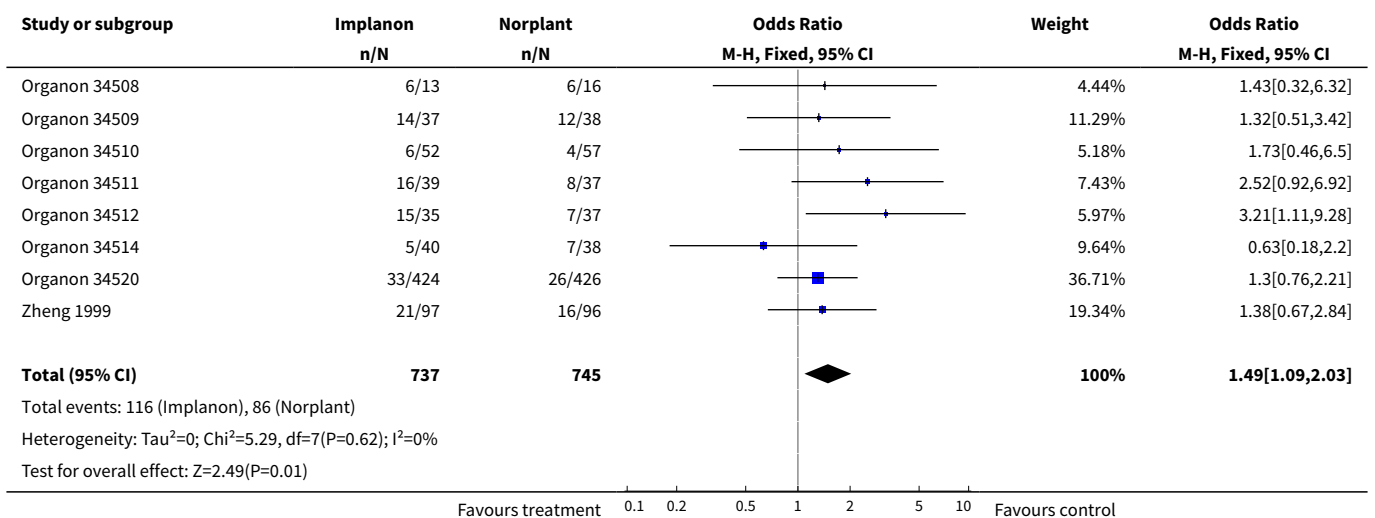




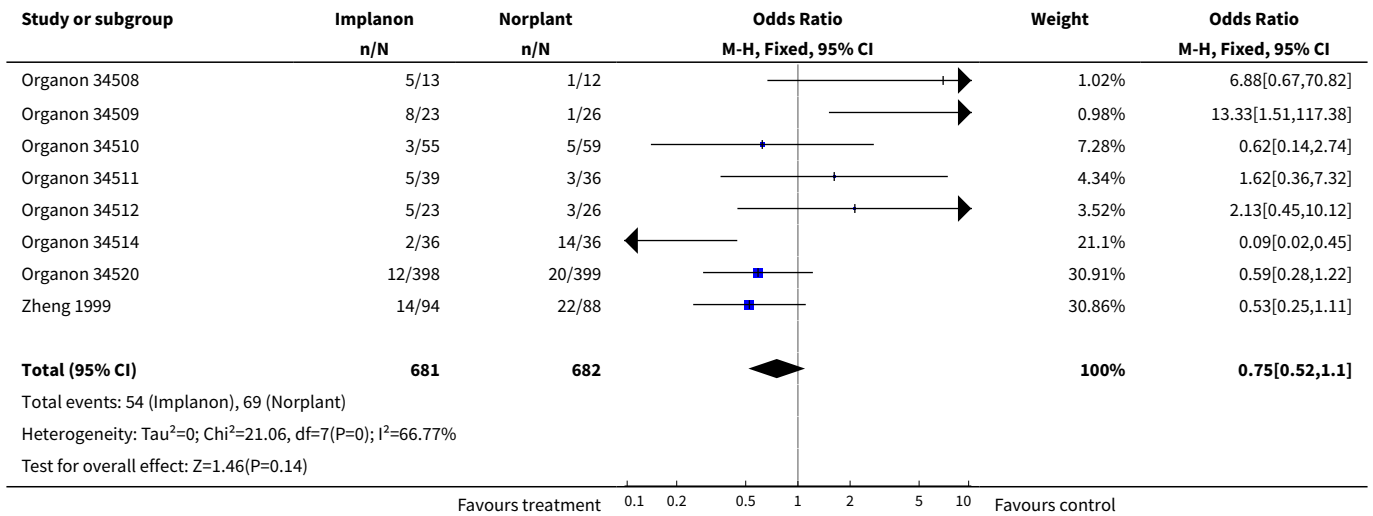
Analysis 1.9. Comparison 1 Implanon vs Norplant, Outcome 9 Frequent bleeding at end 8th ref period.



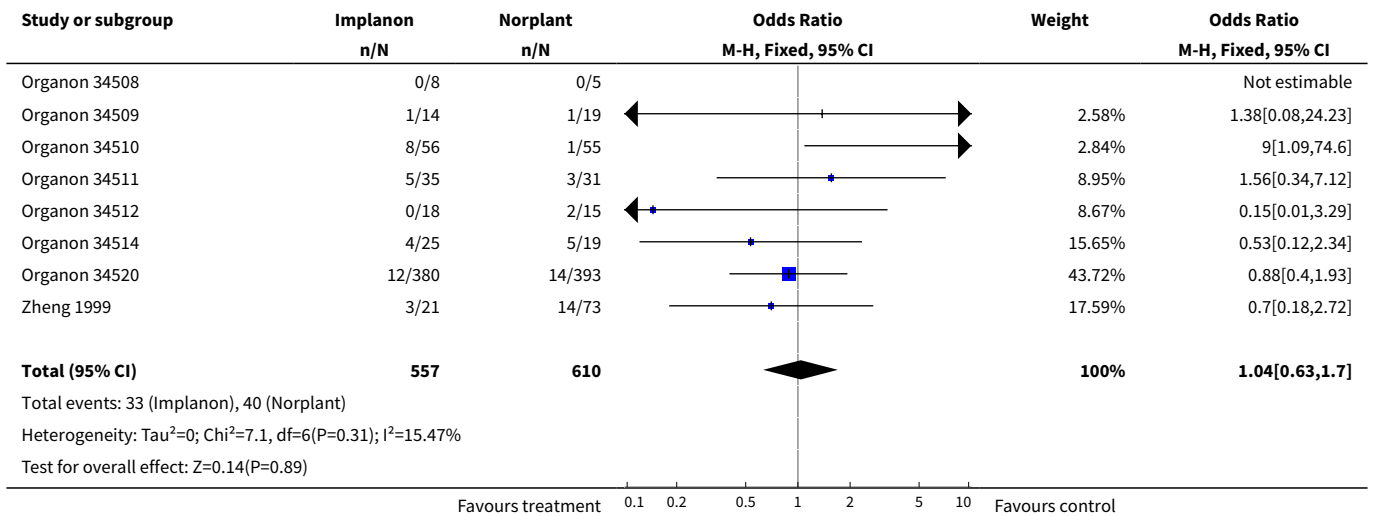
Analysis 1.10. Comparison 1 Implanon vs Norplant, Outcome 10 Prolonged bleeding at end 1st shifted ref period.



Analysis 1.11. Comparison 1 Implanon vs Norplant, Outcome 11 Prolonged bleeding at end 4th ref period.



Analysis 1.12. Comparison 1 Implanon vs Norplant, Outcome 12 Prolonged bleeding at end 8th ref period.



ADDITIONAL TABLES

Table 1. Year 1 Continuation Implanon v Norplant (women months [wm] / potential wm [pwm])

Study	Implanon wm	Implanon pwm	Norplant wm	Norplant pwm	Follow-up time ratio	95% CI
34508	179.8	192	166.7	192	1.08	4800 0.87-1.33
34509	434.5	516	457	516	0.95	0.83-1.08
34510	711.7	720	719.9	720	0.99	0.89-1.10
34511	473.9	480	451.3	480	1.05	0.92-1.19
34512	407.2	480	437.1	480	0.93	0.81-1.07
34514	341.7	492	345.2	480	0.97	0.83-1.12
34520	5302.2	5388	5348.7	5400	0.99	0.96-1.03
Zheng	1173.6	1200	1096.8	1200	0.93	0.86-1.01
Meta-analysis					0.98	0.96-1.01

Table 2. Year 2 Continuation Implanon v Norplant (women months [wm] / potential wm [pwm])

Study	Implanon wm	Implanon pwm	Norplant wm	Norplant pwm	Follow-up ratio	95% CI
34508	297.0	384	285.6	384	1.04	0.88-1.22
34509	712.3	1032	761.5	1032	0.94	0.84-1.04
34510	1309.2	1440	1432.3	1440	0.91	0.85-0.99
34511	924.2	960	842.4	960	1.10	1.0-1.20
34512	667.1	960	737.2	960	0.90	0.81-1.00
34514	643.3	984	633.2	960	0.99	0.89-1.11
34520	10461.9	10776	10555.7	10800	0.99	0.97-1.02
Zheng	2028	2400	1812	2400	1.12	1.05-1.19
Meta-analysis					1.0	0.98-1.02

Table 3. Year 3 Continuation Implanon v Norplant (women months [wm] / potential wm [pwm])

Study	Implanon wm	Implanon pwm	Norplant wm	Norplant pwm	Follow-up ratio	95% CI
34508	381.1	576	322.6	576	1.18	1.02-1.37
34510	1529.5	2160	1587.7	2160	0.96	0.90-1.03
34520	14839.4	16164	15095	16200	0.99	0.96-1.01
Zheng	2750.4	3600	2644.8	3600	1.04	0.99-1.10
Meta-analysis					0.99	0.97-1.01

Table 4. Year 4 Continuation Implanon v Norplant (women months [wm] / potential wm [pwm])

Study	Implanon wm	Implanon pwm	Norplant wm	Norplant pwm	Follow-up ratio	95% CI
Zheng	4099.2	21552	3949.2	21600	1.04	1.00-1.09

Table 4. Year 4 Continuation Implanon v Norplant (women months [wm] / potential wm [pwm]) *(Continued)*

Meta-analysis	1.04	1.00-1.09

WHAT'S NEW

Date	Event	Description
7 March 2012	Amended	Additional tables linked to the text

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 3, 2007

Date	Event	Description
15 April 2008	Amended	Converted to new review format.
22 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

RF had the idea to write the review and did the data extractions. Jo Power joined in later and together they finished the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Contraception [*methods]; Contraceptive Agents, Female [*administration & dosage]; Desogestrel [*administration & dosage]; Drug Implants; Levonorgestrel [*administration & dosage]; Menstruation [drug effects]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans