Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception (Review)

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[Intervention Review]

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ABSTRACT

Background

Hormonally impregnated intrauterine systems (IUSs) add a progestogen to a non-medicated contraceptive device to improve contraceptive action.

Objectives

To assess the contraceptive efficacy, tolerability and acceptability of IUSs versus other reversible contraceptive methods.

Search methods

Searched databases, reference lists and relevant individuals/organisations covering the period from 1972 to July 2009.

Selection criteria

Randomised controlled trials (RCTs) comparing IUSs with other reversible contraceptives and reporting on pre-determined outcomes, including pregnancy and continuation rates, in women of reproductive years.

Data collection and analysis

Two blinded reviewers independently assessed quality and extracted data on events per women months and single decrement life table rates for pregnancy, continuation, adverse events and reasons for discontinuation. Events per total potential number of women at follow-up were collected for hormonal side effects and menstrual change.

Data were pooled at the same points of follow-up to calculate rate ratios and single decrement life table rate differences. Similar interventions were combined and non-hormonal intrauterine devices (IUDs) were divided into three categories: copper IUDs >250mm^2, copper IUDs $\leq$250mm^2, and non-medicated IUDs.

Main results

Twenty-five RCTs met the inclusion criteria and nine were included in meta-analyses: four comparing LNG-20 IUSs (Mirena®) with non-hormonal IUDs, one with Norplant-2, one with combined oral contraceptives (COCs) and three comparing P4-IUS (Progestasert®) with non-hormonal IUDs.

No significant difference was observed between LNG-20 and IUD >250mm^2 or COC user pregnancy rates. LNG-20 IUS users were significantly less likely to become pregnant than IUD $\leq$250mm^2 users. LNG-20 IUS users were more likely to experience a lack of menstrual bleeding and device expulsion than IUDs >250mm^2 users. LNG-20 users were significantly more likely than all IUD users to discontinue because of the lack of menstrual bleeding. They were significantly more likely to experience lack of and infrequent mentrual bleeding, but significantly less likely to experience prolonged bleeding and spotting than Norplant-2 users.

P4-IUS users were significantly less likely to become pregnant and more likely to discontinue than non-medicated IUD users, but no significant difference was observed for P4-IUS versus IUD $\leq$250mm^2 for these two outcomes. P4-IUS users were less likely to expel the device and more likely to discontinue because of menstrual bleeding and pain than IUDs $\leq$250mm^2 users.

Authors' conclusions

Evidence suggests there is no difference in pregnancy rates among LNG-20 IUS, IUD >250mm^2 and Norplant-2 users. The LNG-20 IUS more effectively prevented intrauterine and extrauterine pregnancies than IUDs $\leq$250mm^2. P4-IUS was significantly more effective than non-medicated IUDs, but no difference was observed when compared to IUDs $\leq$250mm^2. Continuation rates for LNG-20 IUS, non-hormonal IUDs and Norplant-2 were similar. Lack of menstrual bleeding was the main reason for discontinuation of LNG-20 IUS.

Recent evidence, from studies meeting the review inclusion criteria for the update conducted in July 2009, suggests that the LNG-20 IUS does not impact upon breastfeeding performance or the growth and development of breastfed infants in lactating women nor did the device have an adverse effect on glucose metabolism among insulin-dependent diabetic women.

PLAIN LANGUAGE SUMMARY

No difference found in pregnancy rates for women using either the LNG-20 intrauterine system (IUS) or intra-uterine device (IUD) for contraception

Reversible methods of contraception include the use of a system or device placed inside the uterus. The IUD is a copper device inserted into the uterus to prevent pregnancy. The intrauterine system (IUS) contains hormones that will be gradually released and provide effective contraception until removed.

The review of trials compared IUDs to IUSs and found there was no difference in the rate of unplanned pregnancies. The review found that a lack of menstrual bleeding is more likely with IUS use and that IUD use is more likely to cause heavy menstrual bleeding and pain.

BACKGROUND

In the 1970s a new approach to the delivery of hormonal contraception was researched and developed. It was suggested that the addition of a progestogen to a non-medicated contraceptive device improved its contraceptive action. An advantage of these hormonally impregnated intrauterine systems (IUS) is that they are relatively maintenance free, with users having to consciously discontinue using them to become pregnant rather than taking a

proactive daily decision to avoid conception.

Levonorgestrel Intrauterine System

The levonorgestrel intrauterine system (LNG-IUS), Mirena®, is licensed for contraceptive use in over 100 countries and is used by over 12 million women worldwide (Bayer; FDA 2000). It has a T shaped plastic frame 32 mm long with a reservoir on the vertical stem of the IUS containing 52 mg of levonorgestrel mixed with polydimethylsiloxane. This allows a steady, local release of 20µg levonorgestrel per day. Insertion of the LNG-20 IUS may require local anaesthesia and dilatation of the cervical canal in nulliparous or peri-menopausal woman. The net ingredient cost of the LNG-20 IUS is more expensive than copper bearing IUDs, however it offers non-contraceptive benefits particularly in women with heavy menstrual bleeding and may offer an alternative to hysterectomy (Bayer 2009; Hurskainen 2004; Lahteenmaki 1998).

Progesterone intrauterine system

The first IUS to be marketed was progesterone intrauterine system (P4-IUS), Progestasert®. It has a plastic T shaped frame with a 32 mm horizontal cross bar and a 36 mm vertical stem. The vertical stem holds 38 mg of progesterone within a silicone base and when it is placed within the uterus will release 65 mcg of progesterone per day. Its contraceptive action lasts for 12-18 months (Barnhart 1985) and is achieved by the endometrial suppression preventing implantation. A second mechanism involves the thickening of the cervical mucus preventing sperm penetration. Ovulation, however, is not affected with normal hormonal cyclical patterns demonstrated in users.

The license has not been renewed by the company in some countries in light of its reported disadvantages. These included:

- yearly reinsertions with the associated risk of pelvic inflammatory disease;

- increased ectopic pregnancy rate when compared to copper bearing devices;

- some women experiencing persistent menstrual spotting.

Measuring contraceptive effectiveness

Extensive reviews have helped to provide greater clarity in the understanding of the various methods and terminologies employed to measure contraceptive effectiveness and have examined their relative advantages and disadvantages (Trussell 1991; Farley 1986). In brief, there are generally two methods which have been adopted, the Pearl Index (PI) and life-tables. The PI, the older method (Pearl 1933), provides a rate per women years and is calculated by dividing the number of events (such as the number of women who discontinue using a contraceptive method) by the total number of women months and multiplying by 1200 (or 1300 if measurement is calculated by menstrual cycle). This method has been criticised because it does not account for the variation in risk of outcomes over time, nor does it account for the variation in loss to follow up (Potter 1966; Higgins 1985). Life tables do account for these factors and are therefore the most appropriate way to report contraceptive data. Confusion arises because inconsistent methods are used to define and calculate these probabilities. In brief, multiple-decrement life table probabilities (also known as net, competing or crude rates) are calculated by working out the monthly probability of reasons for discontinuation, such as pregnancy or hormonal side effects, and multiplying these to establish the probability of discontinuation over a fixed period of time, i.e. at six months follow up, a year follow up, etc. However, single decrement life table probabilities (also known as gross, noncompeting or net rates) are recommended. They are calculated the same way but only for a single reason i.e. they censor women who discontinue a method for reasons other than the one being measured. Unfortunately, it is often impossible to distinguish which method has been used if it is not clearly stated by the authors as 'net' can be refering to single or multiple decrement probabilities.

OBJECTIVES

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

1. What is the relative effectiveness of IUSs in comparison to other reversible contraceptive methods?

2. What is the relative acceptability of IUSs in comparison to other reversible contraceptive methods?

3. What is the relative tolerability of IUSs in comparison to other reversible contraceptive methods?

4. What is the relative effectiveness of different types of IUS?

5. What is the relative acceptability of different types of IUS?

6. What is the relative tolerability of different types of IUS?

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 hormonally impregnated IUSs with other forms of reversible contraceptives.

Types of participants

Women of reproductive years

Types of interventions

Hormonally impregnated IUSs versus:
non-hormonal IUDs
barrier contraceptives
oral contraceptives
injectable contraceptives
subdermal implants
Comparisons of different IUSs

Types of outcome measures

Primary outcome measures
Pregnancy due to method/user failure at 1, 2, 3, 4 and 5 years after starting contraceptive method
Continuation of contraceptive method after 1, 2, 3, 4 and 5 years
Secondary outcome measures
Planned pregnancy after discontinuation of contraceptive method at 1 and 2 years
Failed removal
Hormonal side effects:
Headaches
Pelvic pain
Breast tenderness
Acne
Weight gain
Nausea/vomiting
Dizziness/vertigo
Hair growth
Hair loss
Ovarian cysts
Uterine cramps
Mood changes
Loss of libido
Menstrual bleeding changes (using termionology recommended by Fraser 2007):
Painful menstruation
Spotting
Infrequent menstrual bleeding
Lack of menstrual bleeding
Heavy menstrual bleeding
Prolonged bleeding
Irregular bleeding
Local device problems:
Malposition
Translocation
Expulsion
Adverse clinical events:
Ectopic pregnancy
Pelvic inflammatory disease
Sexually transmitted infections
Anaemia
Breast cancer
Fibroids
Vaginitis
Urinary tract infection
Cervical intraepithelial neoplasia I
Cervical intraepithelial neoplasia II
Cervical intraepithelial neoplasia III
Invasive cervical cancer
Myocardial infarction
Stroke
Pulmonary embolism/thrombophlebitis
Gall bladder disease
Death
Reason for discontinuation:
Hormonal side effects
Menstrual change
Adverse clinical event
Local device problem
Planning pregnancy
Patient choice - other

Search methods for identification of studies

We obtained relevant randomized and controlled clinical trials from a search of publications describing IUSs. We conducted computerized searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, POPLINE, LILACS and Web of Science using the following search strategy:
CENTRAL
intrauterine devices medicated
MEDLINE
intrauterine devices, medicated
AND
(clinical trial*)
EMBASE
1: intrauterine devices, medicated
2: intrauterine contraceptive device
3: IUS
4: 1 or 2 or 3
5: norgestrel
6: levonorgestrel
7: keto(w)desogestrel
8: etonorgestrel
9: P4-IUS or P4-IUS intrauterine progesterone contrac*
10: Mirena or Mirena coil or Mirena IUS
11: levonova
12: 5 or 6 or 7 or 8 or 9 or 10 or 11
13: 4 and 12
POPLINE

(kw) iud hormone releasing
AND
(subject or textword) clinical trial*
LILACS
intrauterine devices, medicated
In a previous version of this review the Science Citation Index and Psych. Lit. databases were searched from 1972 to 1998 July using the strategy:
#1 "INTRAUTERINE-DEVICES,-MEDICATED" / all subheadings
#2 INTRAUTERINE SYSTEM* or IUS*
#3 explode "NORGESTREL" / all subheadings
#4 "LEVONORGESTREL"/all subheadings
#5 NORGESTREL
#6 LEVONORGESTREL
#7 KETO near DESOGESTREL
#8 ETONORGESTREL
#9 P4-IUS
#10 MIRENA
#11 LEVONOVA
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
WEB OF SCIENCE (November 2003 - July 2009)
#1 "INTRAUTERINE-DEVICES,-MEDICATED" / all subheadings
#2 INTRAUTERINE SYSTEM* or IUS*
#3 explode "NORGESTREL" / all subheadings
#4 "LEVONORGESTREL"/all subheadings
#5 NORGESTREL
#6 LEVONORGESTREL
#7 KETO near DESOGESTREL
#8 ETONORGESTREL
#9 P4-IUS
#10 MIRENA
#11 LEVONOVA
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
The reference lists of all identified publications were searched for previously unidentified articles.
We contacted the relevant pharmaceutical companies and asked to release results of any relevant unpublished studies for inclusion in the review. Individuals and organisations with an interest in IUS research and databases housing information on clinical trials were solicited to identify unpublished and ongoing studies relevant to the review.

Data collection and analysis

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

Contraceptive effectiveness and continuation

Single-decrement life table probabilities with their standard errors (SEs), and events per women months, akin to the Pearl Index rate, were collected for each outcome at specific follow up points (at one, two, three, four and five years). It was decided to collect both ways of reporting event rates as, although single-decrement rates are the ideal, they are not commonly employed and there was usually sufficient information in the papers to collect events per women months. Of those papers which had reported single decrement probabilities, only a few had given SEs, a necessity for meta-analysis. Authors who had used single decrement probabilities but had not given their SEs were contacted and asked to provide them where possible. Unless otherwise stated, in the rest of the text life table probabilities refers to single decrement life tables for any discontinuation outcomes.
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 number of potential 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 to follow-up (Clark 2002).

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. Lack of menstrual bleeding 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 no menstrual bleeding; 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 events and total number of women at each 90 day interval were collected to calculate risk ratios for menstrual change outcomes.

Data on hormonal side effects and planned pregnancy (after discontinuation of contraceptive method) were collected at yearly time intervals. Data on these outcomes were only collected if the investigators provided number of events and total number of women at follow up, so that risk ratios for each of the side effects identified in the protocol could be determined. Data on weight change were collected by extracting the mean weight difference, with its standard deviation, between the contraceptive methods under investigation.

Data systhesis

A description of the demographic characteristics of the study participants, the interventions, environmental and geographical factors which may influence findings, quality and the measured outcomes were collected, so that a decision could be made about the results of individual studies and whether it was feasible to combine the data.

Studies were only combined when the comparative interventions were similar, such as IUSs versus subdermal implants or IUSs versus non-hormonal IUDs contraceptives. Non-hormonal IUDs were divided into three categories for the purpose of data synthesis. The first, defined as IUDs >250mm2, included CuT 380A and CuT 380Ag IUDs; the second, defined as IUDs <=250mm2, included the Nova-T, Multiload, CuT 200 and CuT 220 IUDs; and the third were non-medicated IUDs. The first two categories were based on the surface area of the copper wire. In situations where it was not possible or appropriate to synthesise data, a narrative description is provided.

In order to obtain a summary effect size of an event per women months the rate ratios of the treatment and comparison events were combined. This method gave a relative measure of 'treatment' effect, that is how much more or less likely IUS users experienced an event in comparison to users of other contraceptive methods. The log rate ratios and their variances for events were calculated for each study (Hasselblad 1995). It was then possible to calculate the inverse weighted average of the log rate ratios. Events 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 events in one arm of the trial a continuity correction was implemented by adding a half to each cell.

In order to synthesise life table probabilities, it was necessary to calculate the absolute measurement of 'treatment' effect. This was done by subtracting the comparison group probability from the intervention group probability. The SE for the measurement of true effect was then calculated by obtaining the square root of sum of the squared SE of the intervention group probability and the squared SE of the comparison group probability. If there was a probability of zero in one of the groups, its SE was assumed to be the same as the SE of the probability in the comparison group. The inverse weighted average of the rate differences was then calculated. It was thus possible to obtain an absolute difference in percentage terms of 'treatment' effect, that is the attributable risk, between IUS users and users of other contraceptive methods.

To order to obtain pooled estimates for risk ratios and mean differences, the inverse variance weighted average was used with the sample log risk ratio and the sample mean difference, respectively, calculated from each study (Petitti 1994). A continuity correction was performed when necessary as described above for the calculated rate ratios.

Microsoft Excel was used to calculate the pooled effect sizes as it was not possible to calculate rate ratios or life table differences in RevMan.

The degree of heterogeneity was investigated and reported. A random effects approach was used for the meta-analysis (Dersimonian 1986). In the absence of heterogeneity this coincides with a fixed effect analysis. No statistical heterogeneity was identified in the analyses unless explicitly stated in the results below.

An economic evaluation was conducted using the results of the systematic review and meta-analysis, and this has been published elsewhere (French 2000)

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Twenty-five RCTs comparing hormonally impregnated IUSs to a reversible contraceptive method met the inclusion criteria (See Included studies). Eleven trials were conducted in developing or transitional countries (Affandi 1980; WHO 1988; Baveja 1989; El Mahgoub 1982; Kapur 2008; Lavin 1983; Piazarro 1977; Rogovskaya 2005; Shaamash 2005; Wang 1992; Zhu 1991) eight in developed countries (Andersson 1994; Fylling 1979; Heikkila 1982; Janssen 2000; Larsen 1981; Pakarinen 1996; Rybo 1983; Suhonen 2004) and five were international multicentre studies conducted in both developed and developing countries (Luukkainen 1986; Sivin 1994;WHO 1983; WHO 1987; WHO 1988). In one publication it was not possible to determine the study setting (Newton 1979). The majority of trials (12) were set in community-based family planning clinics.

The age range of participants varied from 15 - 45 years. None of the studies confined entry to specific age requirements, other than

ensuring the recruited women were of reproductive age. Seventeen of the 25 trials limited recruitment to women with proven fertility (Andersson 1994; WHO 1988; Baveja 1989; Heikkila 1982; Kapur 2008; Lavin 1983; Luukkainen 1986; Piazarro 1977;Rogovskaya 2005; Rybo 1983; Shaamash 2005; Sivin 1994; WHO 1987; Wang 1992; El Mahgoub 1982; Zhu 1991). Four studies recruited women post partum or post abortion (Heikkila 1982; Lavin 1983; El Mahgoub 1982; Shaamash 2005). Two studies restricted recruitment to women who were breast feeding (Heikkila 1982; Shaamash 2005). Five studies stated that they only included women with regular menstrual cycles (Baveja 1989; Janssen 2000; Pakarinen 1996; Piazarro 1977; Zhu 1991).

Nearly all of the interventions were either comparisons of IUSs with different hormonal release rates or of IUSs versus non-hormonal IUDs. There were two exceptions: a comparison of LNG-20 IUS with Norplant-2 (Wang 1992) and a comparison with combined oral contraceptives (Suhonen 2004).

It was documented in two of the 21 trials that contraceptive counselling had been provided (Andersson 1994; Wang 1992). None of the studies mentioned any specific training for those inserting the devices.

Risk of bias in included studies

Details of the methodological quality of each of the studies are provided in the Characteristics of included studies. It was documented that allocation of contraceptive method was concealed to the investigator in eleven trials (Andersson 1994; Baveja 1989; Kapur 2008; Newton 1979; Pakarinen 1996; Rogovskaya 2005; Shaamash 2005; Sivin 1994; Wang 1992; WHO 1983). It was reported that investigators were blind to contraceptive method when assessing outcomes in only four of the trials (Janssen 2000; Luukkainen 1986; Newton 1979; Piazarro 1977). Women were blind to allocated method in an additional four studies (Andersson 1994; Janssen 2000; Larsen 1981; Rogovskaya 2005).

In 18 studies, the compared groups were treated identically in terms of measurement of outcomes (Andersson 1994; Baveja 1989; Fylling 1979;Kapur 2008 Janssen 2000; Larsen 1981; Lavin 1983; Luukkainen 1986; Newton 1979; Pakarinen 1996; Piazarro 1977; Rybo 1983; Shaamash 2005; Sivin 1994; Suhonen 2004; Wang 1992; WHO 1983; WHO 1987). A description of the characteristics of women lost to follow up or who withdrew from the study was not provided in any of the publications.

Twelve studies used life table analysis to determine pregnancy and continuation rates (Andersson 1994; Baveja 1989; El Mahgoub 1982; Larsen 1981; Luukkainen 1986; Newton 1979; Pakarinen 1996; Piazarro 1977; Sivin 1994; Wang 1992; WHO 1983; WHO 1987). It was possible to determine whether single or multiple decrement probabilities had been reported in nine of these studies (Andersson 1994; Baveja 1989; Larsen 1981; Luukkainen 1986; Pakarinen 1996; Sivin 1994; Wang 1992; WHO 1983; WHO 1987) and all but one provided single decrement probabilities (Larsen 1981).

Less than half of all studies provided information of contraceptive methods used or pregnancy immediately prior to enrolment (Andersson 1994; WHO 1988; El Mahgoub 1982; Heikkila 1982; Lavin 1983; Luukkainen 1986; Piazarro 1977; Wang 1992). In the 15 studies where pregnancy occurred, nine distinguished between user or method failure (or both) (Andersson 1994; Baveja 1989; Luukkainen 1986; Pakarinen 1996; Piazarro 1977; Sivin 1994; Wang 1992; WHO 1983; WHO 1987). Active follow up was conducted in three trials (Sivin 1994; WHO 1983; WHO 1987).

Effects of interventions

Some studies which would have met the inclusion criteria but examined prototype contraceptive methods or methods that are not (longer) available were excluded from the meta-analyses (El Mahgoub 1982; Heikkila 1982; Janssen 2000; Pakarinen 1996; WHO 1983; WHO 1987).

LNG-20 versus non-hormonal IUD >250mm2

Five studies compared the LNG-20 IUS with the non-hormonal IUD >250mm2 (Baveja 1989; Kapur 2008; Rogovskaya 2005; Shaamash 2005; Sivin 1994). It was possible to extract data from two of these studies for the meta analysis (Baveja 1989; Sivin 1994). Rate ratios and single decrement life table differences derived from the two studies are presented in Table 1 and Table 2, respectively (for the following outcomes: pregnancy, continuation, expulsion, embedded device, ectopic pregnancy, PID, and discontinuation due to hormonal side effects, menstrual side effects, adverse events, planning a pregnancy and/or personal choice). The relative risk for planned pregnancy after removal of the LNG-20 IUS compared to CuT 380 Ag IUD was 1.25 (95% CI 0.45 to 3.48) at one year (Sivin 1994) Figure 1. It was possible to extract data on menstrual change outcomes from one study only (Sivin 1994). Data from this study indicated that women using LNG-20 IUSs were more likely to experience no menstrual bleeding than women using CuT 380Ag IUDs and this risk increased over time, at three months the risk ratio was 2.35 (95% CI 1.37 to 4.04) Figure 2 which increased to 11.08 (95% CI 6.61 to 18.57) at three years follow up. No significant differences were noticed between LNG-20 IUS and CuT 380Ag IUDs in terms of prolonged bleeding, with risk ratios of 0.88 (95% CI 0.55 to1.39) at three months and 0.15 (95% CI 0.02 to1.10) at three years Figure 3. It was not possible to extract data for any other menstrual change outcomes, but Sivin et al (1994) reported that LNG-20 IUS users were significantly less likely to experience painful menstruation.

Figure 1. Forest plot of comparison: 1 LNG-20 IUS vs. IUDs >250mm2, outcome: 1.3 Planned pregnancy after discontinuation of method.

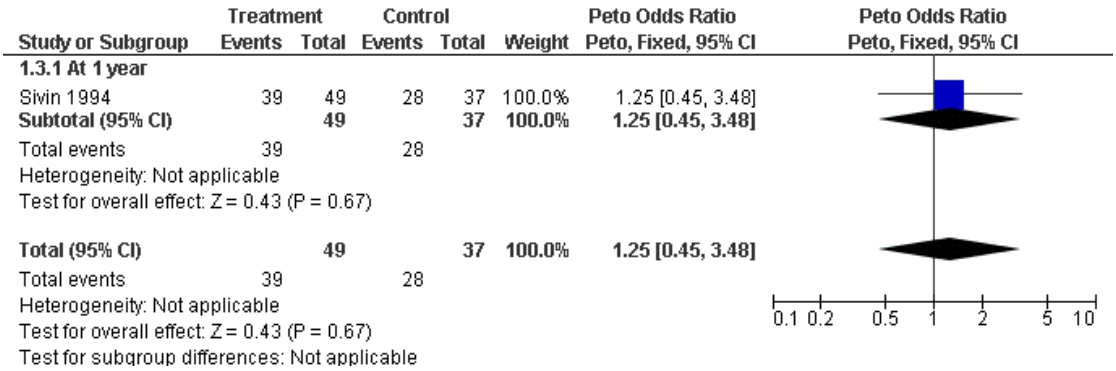


Figure 2. Forest plot of comparison: 1 LNG-20 IUS vs. IUDs >250mm2, outcome: 1.4 Absence of menstrual bleeding.

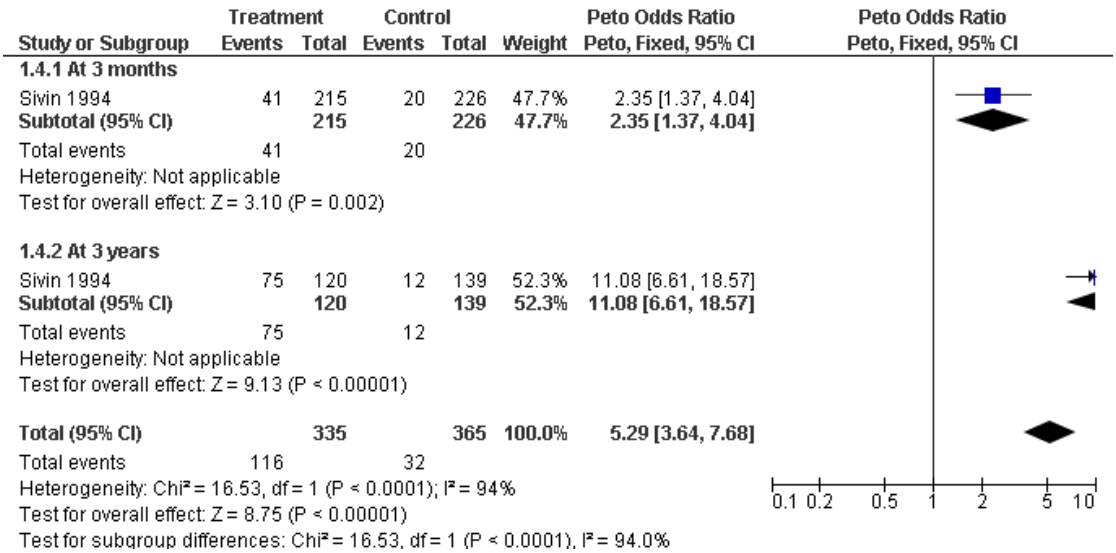
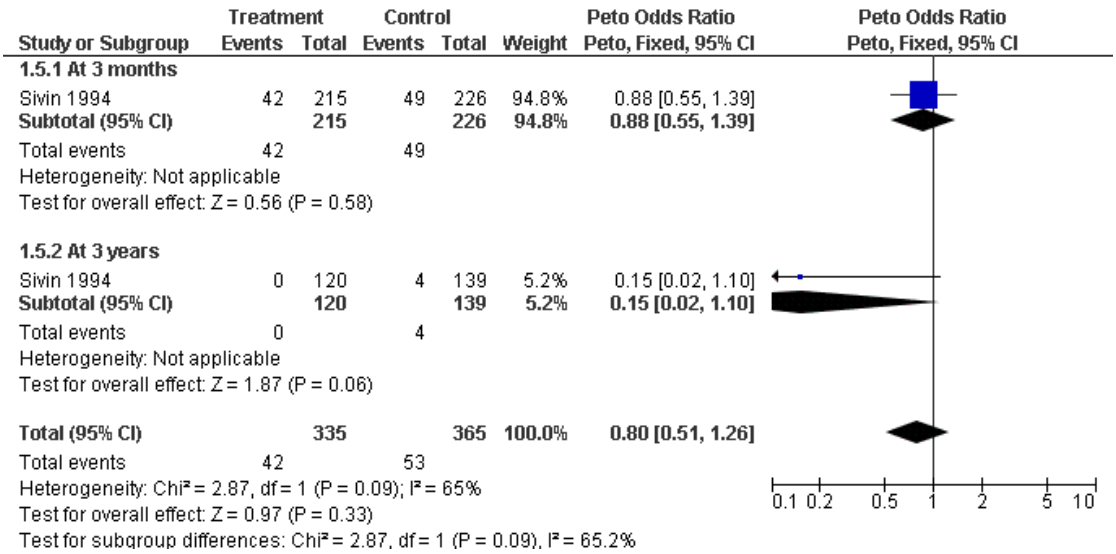


Figure 3. Forest plot of comparison: 1 LNG-20 IUS vs. IUDs >250mm2, outcome: 1.5 Prolonged bleeding.



In addition to the primary outcomes for this review, two trials, Rogovskaya 2005 and Shaamash 2005 also reported clinically important findings for LNG-20 IUS users with insulin-dependent diabetes and lactating users. The LNG-20 IUS demonstated no adverse effects to glucose metabolism at 6 weeks, 6 months and 12 months in diabetic women (Rogovskaya 2005). Among lactating women in the Shaamash et al sudy, there was no significant difference between the two groups with regard to breastfeeding performance and infant growth (Shaamash 2005).
No data were collected for hormonal side effects.

LNG-20 versus non-hormonal ≤250mm2 IUDs

Four included studies compared the LNG-20 IUS with non-hormonal ≤250mm2 IUDs (Andersson 1994; Baveja 1989; Luukkainen 1986; Zhu 1991). Data could be extracted from three of these studies (Andersson 1994; Baveja 1989; Luukkainen 1986). The calculated rate ratios and single decrement life table differences are shown in Table 3 and Table 4, respectively, for the following outcomes: unplanned pregnancy, continuation of method, adverse event outcomes and reasons for discontinuation. Unpublished data on discontinuation of the LNG-20 IUS compared to the Nova-T because of a lack of menstrual bleeding from Andersson 1994 (provided by Leiras Ltd 1999) demonstrated a huge variation between the participating centres, ranging from a multiple decrement probability of 2.7% in Finland to 19.6% in Hungary. No significant differences were observed in the rate ratios for planned pregnancy after discontinuation of the LNG-20 IUS and the Nova-T IUD (Andersson 1994). The rate ratios at one and two years were 1.24 (95 CI 0.67 to 2.29) and 1.29 (95% CI 0.67 to 2.46) Figure 4, respectively. It was not possible to extract any data on menstrual change outcomes that did not result in discontinuation. The Andersson 1994 study was the only one where it was possible to extract any data on hormonal side effects. No significant differences were observed between the risk of hormonal side effects for women using the LNG-20 IUS compared to women using the Nova-T IUD. These data were collected at five year follow up. The reported side effects and their risk ratios were as follows: acne, 5.56 [95% CI 0.73 to 42.35]; headaches, 1.62 (95% CI 0.53 to 4.92) Figure 5; breast tenderness, 1.50 (95% CI 0.31 to 7.17); ovarian cysts 1.50 (95% CI 0.51 to 4.40) and nausea, 4.99 (95% CI 0.24 to 103.86). Luukkainen 1986 observed that women using the LNG-20 IUS were more likely to report an increase in headaches and acne than women using the Nova-T IUD, but it was not possible to extract these data for the meta-analysis. The life table differences indicate there were no significant differences between the expulsion rates of these two methods (Table 4). However, the rate ratios suggest that women using the LNG-20 IUS are significantly less likely to have an expulsion after two years of follow up (Table 3). As it is data from one study used to calculate the life table differences (Baveja 1989) and data from two other studies used to calculate the summary rate ratios (Andersson 1994, Luukkainen 1986), it is impossible to ascertain what effect the different methods of analysis have had on the results or whether it is in fact caused by differences in the shape of the different IUDs. Andersson 1994 found that LNG-20 IUS users were significantly less likely to experience PID, in particular younger women, but we were unable to use the data in the meta-analysis. No other data on adverse outcomes were collected.

Figure 4. Forest plot of comparison: 2 LNG-20 IUS vs. IUD<=250mm2, outcome: 2.3 Planned pregnancy after discontinuation of method.

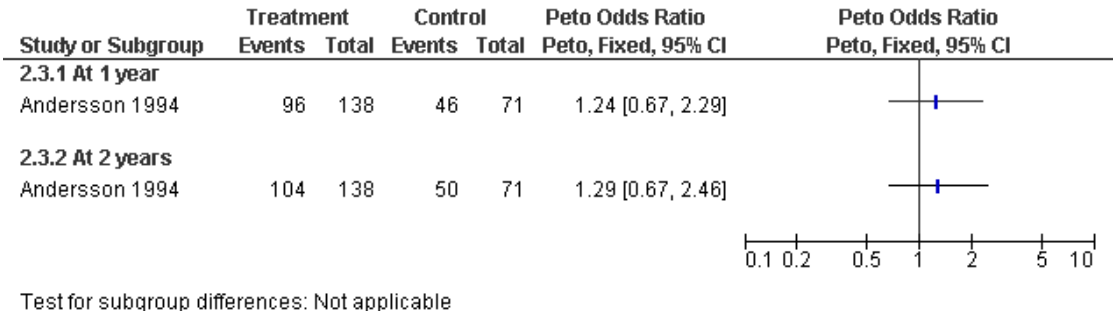
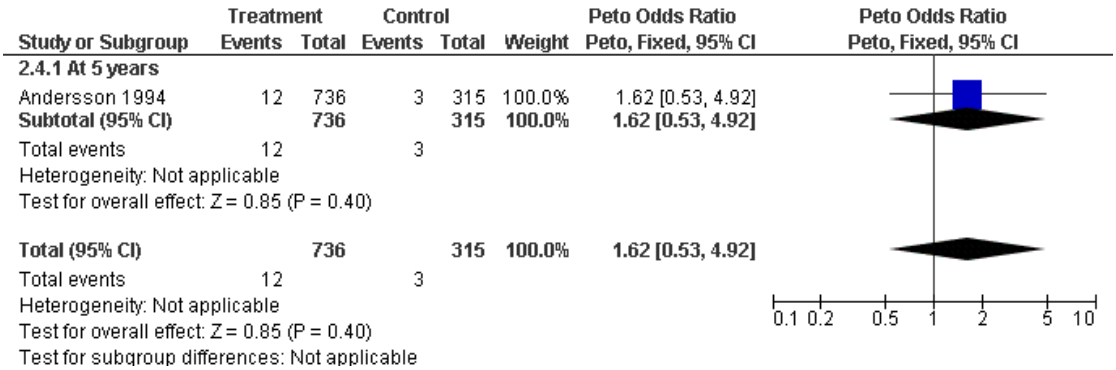


Figure 5. Forest plot of comparison: 2 LNG-20 IUS vs. IUD<=250mm2, outcome: 2.4 Headaches.



LNG-20 versus stainless steel ring IUD

One study comparing the LNG-20 IUS with a stainless steel ring IUD was included [Zhu 1989]. However, data on bleeding could not be extracted from the report.

LNG-20 versus subdermal implants

One study which compared users of the LNG-20 IUS with users of subdermal implants, Norplant-2, was identified (Wang 1992). The rate ratios calculated for pregnancy, continuation, expulsion, ovarian cysts, breast cancer, and discontinuation due to hormonal side effects, menstrual side effects, device problems and/or adverse events are presented in Table 5. There were significant differences found in the rates of reported menstrual change. LNG-20 IUS users were significantly more likely to experience no menstruation compared to Norplant-2 users. The risk ratios were 2.27 (95% CI 1.03 to 4.99) at one year follow up, 42.46 (95% CI 2.62 to 689) at two years' follow up and 2.65 (95% CI 0.53 to 13) at three years' follow up. They were also significantly more likely to experience infrequent mentrual bleeding, risk ratio 6.17 (95% CI 2.76 to 13.78) at two year follow up, although significant differences were not found at years' one and three follow up. LNG-20 IUS users were significantly less likely to experience spotting than Norplant-2 users, risk ratios 0.33 (95% CI 0.18 to 0.60) at one year, 0.18 (95% CI 0.07 to 0.5) at two years and 0.17 (95% CI 0.05 to 0.57) at three years, and significantly less likely to have prolonged bleeding, risk ratios 0.13 (95% CI 0.05 to 0.35) at one year, 0.17 (95% CI 0.06 to 0.46) at two years and 0.15 (95% CI 0.04 to 0.64) at three years.

LNG-20 versus combined oral contraceptive

One RCT compared LNG-20 IUS with combined oral contraceptives (Suhonen 2004). The rate ratios were calculated for pregnancy, continuation, hormonal side effects (headache, pelvic pain,

acne, weight gain, and mood changes), menstrual changes (painful menstruation and absence of menstrual bleeding), expulsion, and discontinuation due to hormonal side effects and pregnancy are presented in Table 6. No pregnancies were observed in either group. LNG-IUS users when compared to combined oral contraceptive users were signficantly more likely to report an absence of menstrual bleeding, risk ratio 8.00 (95% CI 3.24-19.75); breast tenderness, risk ratio 2.28 (95% CI 1.32-4.68); and acne, risk ratio 1.75 (95% CI 1.00-3.08) at one year.

P4-IUS versus non-hormonal IUDs <=250mm2

Seven trials comparing P4-IUS with non-hormonal IUDs ≤250mm2 were were identified (Affandi 1980; WHO 1988; Fylling 1979; Larsen 1981; Lavin 1983; Piazarro 1977; Rybo 1983) and two of these provided data that could be included in the meta-analysis, one comparing P4-IUS with the Nova-T IUD (Fylling 1979) and other with the CuT 200 IUD (Larsen 1981). The reasons for exclusion of data from the meta-analyses was either because P4-IUS was compared to methods that are no longer or have never been licensed (Affandi 1980; WHO 1988; Piazarro 1977) or it was not possible to extract data (Lavin 1983; Rybo 1983) Both included trials ran for one year. The rate ratios for pregnancy, continuation of method, expulsion and ectopic pregnancy calculated for these studies are presented in Table 7. No data for any of these outcomes were included in the meta-analysis. Lavin 1983 reported that P4-IUS users were significantly more likely to experience intermenstrual spotting, but significantly less likely to experience painful menstruation.

One comparison of P4-IUS and non-medicated IUDs was included (Newton 1979) and women were followed up for one year. Rate ratios for pregnancy, expulsion, ectopic pregnancy, and discontinuation for a planned pregnancy or personal reasons calculated from this study are presented in Table 8. No data were included in the meta-analysis on menstrual change or hormonal side effect outcomes. No pregnancies were reported in either group at one year.

DISCUSSION

There was insufficient evidence to suggest a difference in the pregnancy rates between LNG-20 IUS users and IUD >250mm2 users. The rate of pregnancy in LNG-20 IUS users was significantly lower than the rate in the IUD ≤250mm2 users. No pregnancies occured in the small study comparing LNG-20 IUS users with combined oral contraceptive users. P4-IUS was significantly better at preventing pregnancy than the non-medicated IUD after one year, but not when compared to copper IUDs ≤250mm2.

When interpreting these findings on contraceptive effectiveness consideration must be paid to the limitations of the data. First, in the main, comparisons were of contraceptive methods with similar default states rather than comparisons of IUSs with methods where user adherence is likely to be a factor in effectiveness. Second, very large numbers of women would need to be recruited into these trials where in general the contraceptive methods being compared are highly effective in preventing unwanted pregnancy. Failure to detect a significant difference in contraceptive effectiveness between methods may be due to the small number of women enrolled and followed up in the included studies. Third, although life tables have been recommended as the most appropriate way to analyse contraceptive effectiveness data, and many of the included studies employed this method, confusion arose because of the inconsistent way these methods were defined and calculated. This resulted in some studies being excluded from the meta-analysis. It was much easier to extract data on number of events and women months or years from papers to provide an estimate akin to the Pearl Index.

Although it is useful to know how many unwanted pregnancies a method prevents, this information is of little value without collecting data on outcomes which reflect the acceptability of a method. A method may be efficacious in terms of preventing unwanted pregnancy, but if the method is discontinued within a short period of time its value as a method of contraception is greatly reduced. The meta-analyses conducted for continuation at yearly follow ups showed variable results between the different comparisons.

Few data could be extracted on hormonal side effects and menstrual change. The one outcome that users of all types of IUSs were significantly more likely to experience was lack of menstrual bleeding. The fact that so little data were available was not necessarily because authors had not reported these outcomes, but was due to the ways these outcomes had been measured. For instance, some investigators reported a percentage of women experiencing an 'increase', 'decrease' and 'the same' as measurements for events, such as painful menstruation or headaches. This does not allow baseline patterns on risk factors, such as age and parity, to be taken account of in the analysis.

The evidence on LNG-20 IUS suggested that women using this method were significantly more likely to expel the device than IUD >250mm2 users. It has been recommended that only health care workers who have received specialist training should insert and remove these methods in order to prevent local device problems. None of the studies reported whether or not health care workers had received specialist training, therefore we were not able to investigate the effect this had device expulsions.

Breastfeeding provides some protection against another pregnancy, but the return of fertility is unpredictable. Which contraceptive method to use while breastfeeding, and when to start using it, are complicated decisions. Choices of contraception may be limited due to concerns about the effects of hormonal contraceptives on the quality and quantity of breastmilk, and the effects on the baby.

One study included in this review found that LNG-20 IUS does not impact upon breastfeeding or the growth and development of breastfed infants (Shaamash 2005). Findings from another review showed no adverse effect of combined oral contraceptives on infant growth (Truitt 2003)

P4-IUS's license was not renewed in some countries because of concerns about increased risk of ectopic pregnancy when compared to copper bearing devices. Too few studies were eligible for inclusion in the meta-analysis for this risk to be accurately determined.

Discontinuation due menstrual changes per se is not an informative outcome as the LNG-20 and IUD >250mm2 comparison illustrates. Women using LNG-20 IUSs discontinued due to an absence of menstrual bleeding, while IUD >250mm2 users discontinued because of bleeding and pain. The reporting of discontinuation due to absence of menstrual bleeding, bleeding and pain must be collected separately to provide a true picture.

An additional issue when interpreting data on discontinuation of methods due to menstrual changes is consideration of the 'cultural' setting in which the trials were conducted. For example, women from different backgrounds, as well as providers, may view menstrual change differently, as illustrated by the unpublished data from the Andersson study (Leiras Ltd 1999). Women should be informed of these potential side effects prior to starting these methods. The absence of menstrual bleeding in users of the LNG-20 IUS is benign and is due to high concentrations of levonorgestrel in the endometrium, the end organ (Silverberg 1986). Therefore, if women (and providers) are informed it has no ill effect on their health (and for some with heavy menstrual bleeding it may have a positive effect), the acceptability of these methods may be improved.

AUTHORS' CONCLUSIONS

Implications for practice

We found no significant difference in the risk of unwanted pregnancy between the LNG-20 IUS and IUDs >250mm2 or Norplant-2 although, given the very large numbers needed to provide adequate power to detect differences in uncommon events, this may reflect a lack of power in the included studies. We did find a lower risk of pregnancy when the LNG-20 IUS was compared to IUDs $\leq$250mm2.

Women using the LNG-20 IUS were more likely to experience an absence of menstrual bleeding and this event was a notable reason for discontinuation. The much higher net ingredient cost (i.e. the device cost) of the LNG-20 IUS when compared to IUDs, with no discernible benefit in terms of contraceptive effectiveness when compared to IUDs >250mm2, may suggest that its use should be targeted at those women who are concerned about menstrual bleeding and pain with IUD use. All women who are considering a LNG-20 IUS should be informed of the possibility of an absence of menstrual bleeding. Women who are diabetic or early postpartum and lactating should not be restricted from using the IUS.

Two other Cochrane reviews have shown that the LNG-IUS is also an effective treatment for heavy menstrual bleeding (Marjoribanks 2006; Lethaby 2005).

Implications for research

This systematic review highlighted the problems which arise because of inconsistent methods used to measure and report contraceptive effectiveness. Although we were not able to assess what impact these factors had on pooled data, standardised methods need to be encouraged.

It is vital that contraceptive effectiveness research is able to answer the queries and concerns of contraceptive users. Unfortunately, this has not been the case to date. Although rates of unplanned pregnancy, continuation and reasons for discontinuation of methods do provide information on acceptability and tolerability as well as effectiveness, many studies fail to report hormonal side effects and menstrual changes. Women's choice and acceptance of different methods is likely to be affected by acceptability, tolerability and availability of alternatives and the desire not to conceive. If lay contraceptive users are involved in research development, attention can be directed to answering questions of importance to consumers.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Affandi 1980

Methods	Setting: Indonesia 697 women randomised Follow up: 2 years
Participants	Not stated
Interventions	P4-IUS [n=72] vs. CuT 200, Cu 7 and Lippes loop IUDs [n=75, 75 and 75, respectively]
Outcomes	Pregnancy Reasons for discontinuation
Notes	Abstract Quality assessment not conducted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Andersson 1994

Methods	Setting: Multinational (Denmark, Finland, Hungary, Norway and Sweden), Family Planning Clinics (12) 2758 women randomised Follow up: 5 years
Participants	18-38 years Parous Not breast feeding
Interventions	LNG-20 IUS [n=1821] vs. Nova-T IUD [n=937]
Outcomes	Pregnancy Continuation Reasons for discontinuation Adverse events Hormonal side effects Pregnancy after discontinuation of method
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: Centrally prepared envelopes Description of prior contraceptive method / pregnancy provided

Andersson 1994 (*Continued*)

	Mesurement: Groups treated identically Method of analysis: Life tables (multiple and single decrement rates) User/method failure reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Baveja 1989

Methods	Setting: India, Family Planning Clinics 2118 women randomised Follow up: 3 years
Participants	18-40 years Proven fertility Regular menses
Interventions	LNG-20 IUS [n=475] vs. CuT 380Ag, CuT 220C and CuT 200B IUDs [n=434, 496 and 500, respectively]
Outcomes	Pregancy Continuation Reasons for discontinuation Menstrual change
Notes	Quality assessment: Randomisation technique: Computed random numbers Allocation concealment technique: Sealed envelopes Measurement: Groups treated identically Method of analysis: Life tables (single decrement rates) User / method failure reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

El Mahgoub 1982

Methods	Setting: Egypt, Family Planning Clinics 300 women randomised Follow up: 3 years
Participants	15-40 years Parous Hormonal contraceptive users at enrolment and immediate post partum women excluded
Interventions	LNG-10 IUS and Norgestrel T (various doses) IUSs vs. CuT 200 IUD [n=100 in each group]
Outcomes	Pregnancy Continuation Reasons for discontinuation Menstrual change and blood loss Endometrial and cervical cell changes
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy provided Method of analysis: Life tables (method not stated)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Fylling 1979

Methods	Setting: Denmark 326 women randomised Follow up: 1 year
Participants	Mixed parity
Interventions	P4-IUS [n=162] vs. Nova-T IUD [n=164]
Outcomes	Pregnancy Continuation Reasons for discontinuation Serum immunoglobin levels
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Measurement: Groups treated identically Method of analysis: Other

Fylling 1979 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Heikkila 1982

Methods	Setting: Finland, Maternity Unit 80 women randomised Follow up: 1 year
Participants	Postpartum Amenorrhoeic Breast feeding
Interventions	LNG-30 IUS[n=40] vs. Nova-T IUD [n=40]
Outcomes	Pregnancy Continuation Reasons for discontinuation Hormonal side effects Menstrual change LNG plasma concentration
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy provided Method of analysis: Other User / method failure reported: Not applicable

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Janssen 2000

Methods	Setting: The Netherlands, University Medical Centre 203 women randomised Follow up: 2 years
Participants	18-45 years Variable parity Regular menses

Janssen 2000 (*Continued*)

Interventions	Multiload Cu250 releasing different doses of 3-keto- desogestrel [n= 151] vs. Multiload Cu250 [n=51]
Outcomes	Menstrual blood loss Hemoglobin, ferritin and 3-keto-desogestrel concentration Bleeding pattern Subjective complaints
Notes	Quality assessment: Randomisation technique: Computer generated randomization list. Allocation concealment technique: No mention. Double-blinded assessment of outcomes. Description of prior contraceptive method / pregnancy not provided Measurement: Groups treated identically Method of analysis: Other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kapur 2008

Methods	Setting: India 170 women randomised Follow-up: 1 year
Participants	26-35 years Parous, desiring contraception
Interventions	LNG IUS [n=70] vs. Cu T 380 [n=70]
Outcomes	Pregnancy Menstrual change Reasons for discontinuation
Notes	Quality assessment: Randomisation technique: no mention Allocation concealment technique: no mention Women blinded to method Measurement: Groups treated identically Method of analysis: Other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Larsen 1981

Methods	Setting: Denmark 382 women randomised Follow up: 1 year
Participants	15-44 years Variable parity
Interventions	P4-IUS [n=196] vs. CuT 200 IUD [n=186]
Outcomes	Pregnancy Continuation Reasons for discontinuation
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Women blinded to method Measurement: Groups treated identically Method of analysis: Life tables (multiple decrement rates)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Lavin 1983

Methods	Setting: Chile, Maternity Unit 400 women randomised Follow up: 1 year
Participants	Postpartum
Interventions	P4-IUS [n=200] vs. CuT 200 IUD [n=200] - 100 inserted by hand and 100 inserted an inserter in each group
Outcomes	Pregnancy Continuation Menstrual change
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy provided Measurement: Groups treated identically Method of analysis: Other

Lavin 1983 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Luukkainen 1986

Methods	Setting: Finland and Brazil, Family Planning Clinics 484 women randomised Follow up: 2 years (Brazil and Finland) and 5 years (Finland only)
Participants	18-40 years Proven fertility Not breast feeding
Interventions	LNG-20 and LNG-30 IUSs [n=164 and 163, respectively] vs. Nova-T IUD [n=157]
Outcomes	Pregnancy Continuation Resaons for discontinuation Hormonal side effects Menstrual change
Notes	Quality assessment: Randomisation technique: Random tables (permutations of nine numbers) Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy provided Double-blinded assessment of outcomes Measurement: Groups treated identically Method of analysis: Pearl indices and life tables (multiple and single decrement rates) User / method failure reported

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Newton 1979

Methods	Setting: Clinics (4) 676 women randomised Follow up: 1 year
Participants	Various parity

Newton 1979 (*Continued*)

Interventions	P4-IUS [n=359] vs. inert IUD [n=317]
Outcomes	Pregnancy Continuation Reasons for discontinuation Menstrual change
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment: 'both types of device were externally identical' Double-blinded assessment of outcomes Measurement: Groups treated identically Method of analysis: Life tables

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pakarinen 1996

Methods	Setting: Finland, Family Planning Clinics 298 women randomised Follow up: 1 year
Participants	18-43 years Variable parity Regular menses
Interventions	LNG-20 IUS [n=147] vs. LNG-20 ICD [n=151]
Outcomes	Pregnancy Continuation Reasons for discontinuation Hormonal side effects
Notes	Quality assessment: Randomisation technique: Random number table with group allocation predetermined Allocation concealment technique: Consecutively numbered opaque sealed envelopes opened just before IUS insertion Measurement: Groups treated identically Method of analysis: Life tables (single decrement rates) User / method failure reported

Risk of bias

Pakarinen 1996 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Pakarinen 2003

Methods	Setting: Demark, Finland, Hungary, Norway, Sweden, family planning clinic 438 women randomised 2:1 as a segment of a larger trial of 3000 Follow-up: 1, 3 and 5 years
Participants	post elective termination
Interventions	Mirena [n=305] vs. Nova T [n=133]
Outcomes	Pregnancy Continuation Reasons for discontinuation
Notes	Quality assessment: Randomisation technique: not mentioned Allocation concealment: Sealed envelopes Measurement: Groups treated identically Method of analysis: Other data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Piazarro 1977

Methods	Setting: Chile, Family Planning Clinics 295 women randomised Follow up: 1 year
Participants	17-40 years Parous Regular menses
Interventions	Progesterone T IUS [n=146] vs. Cu 7 IUD [n=149]
Outcomes	Pregnancy Continuation Reasons for discontinuation Menstrual change

Piazarro 1977 (*Continued*)

Notes	Quality assessment: Randomisation technique: Computed tables Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy reported Blinded assessment of outcomes Measurement: Groups treated identically Method of analysis: Life tables (method not stated) User / method failure reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Rogovskaya 2005

Methods	Setting: Moscow Russia, Ob/Gyn outpatient department 60 women randomised Follow-up: 1 year
Participants	18-45, with controlled insulin-dependent diabetes mellitus Parous
Interventions	Levonorgestrel intrauterine system [n=26] vs. copper T 380A [n=28]
Outcomes	Continuation
Notes	Quality assessment: Randomisation technique: Computer generated random numbers Allocation concealment technique: Sealed opaque envelopes opened in numerical order Description of prior contraceptive method / pregnancy reported Women blind to method Measurement: Groups treated identically Method of analysis: Other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rybo 1983

Methods	Setting: France Follow up: < 1 year 30 women randomised
Participants	24-42 years Multiparous
Interventions	P4-IUS [n=13] vs. CuT 200 IUD [n=17]
Outcomes	Pregnancy Menstrual change and blood loss
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Measurement: Groups treated identically Method of analysis: Other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Shaamash 2005

Methods	Setting: Egypt, Department of Obstetrics and Gynecology 320 women randomised Follow-up: 1 year
Participants	Parous Exclusively breastfeeding for at least 1 year
Interventions	LNG-IUS [n=163] vs. Cu T380A IUD [n=157]
Outcomes	Continuation
Notes	Quality assessment: Randomisation technique: Computer generated sequential numbers Allocation concealment: Sealed opaque envelopes opened in sequential orderMeasurement: Groups treated identically Method of analysis:Other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sivin 1994

Methods	Setting: Multinational (Singapore, Brazil, Egypt and USA), Family Planning Clinics 2226 women randomised Follow up: 7 years
Participants	18-38 years Parous
Interventions	LNG-20 IUS [n=1125] vs. CuT 380Ag IUD [n=1121]
Outcomes	Pregnancy Continuation Reasons for discontinuation Insertion problems Hormonal side effects Menstrual change Adverse events Pregnancy after discontinuation of method
Notes	Quality assessment: Randomisation technique: Random numbers - blocks of 50 Allocation concealment: Sealed opaque envelopes opened in ascending numerical order Women blinded to method Measurement: Groups treated identically Method of analysis: Life tables (multiple and single decrement rates) User / method failure reported Active follow up conducted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Suhonen 2004

Methods	Setting: Helsinki Finland, Family-planning clinics 200 women randomised Follow-up: 1 year
Participants	18-25 years Nulliparous
Interventions	LNG-IUS [n=94] vs. oral contraceptives [n=99]
Outcomes	Continuation
Notes	Quality assessment: Randomisation technique: No mention

Suhonen 2004 (*Continued*)

	Measurement: Groups treated identically Method of analysis: Other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wang 1992

Methods	Setting: China, Family Planning Clinics 200 women randomised Follow up: 3 years
Participants	20-40 years Parous Not breast feeding
Interventions	LNG-20 IUS [n=100] vs. Norplant-2 [n=100]
Outcomes	Pregnancy Continuation Reasons for discontinuation Menstrual change
Notes	Quality assessment: Randomisation technique: Sequential identication number Allocation concealment technique: Sealed envelopes Description of prior contraceptive method / pregnancy provided Meseasurement: Groups treated identically Method of analysis: Life tables (single decrement rates) User / method failure reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

WHO 1983

Methods	Multinational (13 countries), Family Planning Clinics 5542 women randomised (2514 birth spacing insertion and 3028 post abortion insertion) Follow up: 2 years
Participants	16-40 years
Interventions	1. Alza T IPCS 52 [n=1254] vs. CuT 220C IUD [n=1260] - interval insertion 2. Alza T IPCS 52 [n=985] vs. CuT 220C and Multiload IUDs [n=1032 and 1011, respectively] - post abortion insertion
Outcomes	Pregnancy Continuation Reasons for discontinuation
Notes	Quality assessment: Randomisation technique: Computed random tables Allocation concealment technique: Sealed envelopes Measurement: Groups treated identically Method of analysis: Life tables (single decrement rates) User / method failure reported Active follow up conducted

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

WHO 1987

Methods	Multinational (Thailand, China, India, Vietnam, Cuba, Russia, Yugloslavia and Zambia) 4182 women randomised Follow up: 2 years
Participants	16-40 years Parous
Interventions	LNG-2 IUS [n=1377] vs. CuT 220C and Nova-T IUDS [n=1412 and 1393, respectively]
Outcomes	Pregnancy Continuation Reasons for discontinuation
Notes	Quality assessment: Randomisation technique: Computed tables Allocation concealment technique: Sealed envelopes Measurement: Groups treated identically Method of analysis: Life tables (single decrement rates) User / method failure reported

WHO 1987 (*Continued*)

	Active follow up conducted	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

WHO 1988

Methods	Setting: Chile and Brazil (see Notes), Hospital 150 women randomised Follow up: 2 years
Participants	Parous
Interventions	P4-IUS [n=49] vs. Lippes lopp and Cu 7 IUDs [n=51 and 50, respectively]
Outcomes	Menstrual blood loss Iron status
Notes	Brazil group excluded because not randomised Quality assessment: Randomisation technique: Random number table Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy provided Method of analysis: Not applicable

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Zhu 1989

Methods	Setting: China, University Medical Center 96 women randomised Folllow up: CuT220 and stainless steel ring: 2 years and LNG-IUS: 3-10 months
Participants	25 -35 years Proven fertility Regular menses
Interventions	LNG-IUS [n=19] vs. CuT 220 [n=43] vs. stainless steel ring [n=34]

Zhu 1989 (*Continued*)

Outcomes	Morphological structure of the endometrium Number of bleeding days Bleeding rate
Notes	Quality assessment: Randomisation technique: No mention Allocation concealment technique: No mention Description of prior contraceptive method / pregnancy not provided Method of analysis: other

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andrade 1998	Intervention: LNG-IUS vs. CuT 380A IUD We could not reach the authors for additional information on generation of allocation sequence
Chan 2007	Intervention: LNG-IUS vs. no method Primary outcomes: *De novo* endometrial pathology at 1 year tamoxifen Reported outcomes not relevant to review
Diaz 1992	Intervention: LNG-IUS vs. CuT 380Ag IUD We could not reach the authors for additional information
Diaz 1993	Intervention: LNG-IUS vs. CuT 380Ag IUD Primary outcomes: Pregnancy, continuation and reasons for discontinuation Only report outcomes for LNG-IUS users. Comparative results reported elsewhere (see Sivin 1994)
Faundes 1993	Intervention: LNG-IUS vs. CuT 380Ag IUD Primary outcomes: Pregnancy, continuation, reasons for discontinuation, ovarian function and LNG serum levels Only report outcomes for LNG-users. Comparative results reported elsewhere (see Sivin 1994)
Nilsson 1977	Intervention: d-norgestrel releasing IUS vs. Nova-T 200 IUD Primary outcomes: Menstrual blood loss Reported outcomes not relevant to review

(*Continued*)

Nilsson 1986	Intervention: LNg-20 IUS vs. LNG-30 IUS Primary outcomes: Plasma concentration of LNG Reported outcomes not relevant to review (other publications of study included - see Luukkainen 1986)
Pakarinen 1999	Intervention: LNG-IUS, NovaT380 and 30 mcg LNG oral contraceptive Primary outcomes: glucose, insulin, SHBG, IGFBP-1, testosterone and LNG concentration Reported outcomes not relevant to review
Pedron Neueo 1992	Intervention: Various IUSs and IUDs (11) Primary outcomes: Menstrual blood loss Reported outcomes not relevant to review
Skrzypulec 2008	Intervention: LNG-IUS, other IUD and no contraception Primary outcome: Quality of life Reported outcomes not relevant to review
Trinh 2008	Intervention: LNG-IUS vs. no history of LNG-IUS use in breast cancer patients Primary outcome: Breast cancer recurrence rate Reported outcomes not relevant to review
Ulstein 1987	Intervention: LNG-IUS vs. copper IUD Primary outcomes: Changes in cervical and vaginal microflora Reported outcomes not relevant to review
Yin 1993	Intervention: LNG-IUS, stainless steel ring and CuT 220 IUD Primary outcomes: Endometrial mast cell density Reported outcomes not relevant to review
Zhu 1991	Intervention: LNG-IUS, stainless steel ring and CuT 220 IUD Primary outcome: factor VIII actvity in endometrium Reported outcomes: not relevant to review

DATA AND ANALYSES

Comparison 1. LNG-20 IUS vs. IUDs >250mm2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy due to method failure			Other data	No numeric data
1.1 At 1 year			Other data	No numeric data
1.2 At 2 years			Other data	No numeric data
1.3 At 3 years			Other data	No numeric data
1.4 At 5 years			Other data	No numeric data
2 Continuation of method			Other data	No numeric data
2.1 At 1 year			Other data	No numeric data
2.2 At 2 years			Other data	No numeric data
2.3 At 3 years			Other data	No numeric data
2.4 At 5 years			Other data	No numeric data
3 Planned pregnancy after discontinuation of method	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.45, 3.48]
3.1 At 1 year	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.45, 3.48]
4 Amenorrhoea	1	700	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.29 [3.64, 7.68]
4.1 At 3 months	1	441	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [1.37, 4.04]
4.2 At 3 years	1	259	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.08 [6.61, 18.57]
5 Prolonged bleeding	1	700	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.51, 1.26]
5.1 At 3 months	1	441	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.55, 1.39]
5.2 At 3 years	1	259	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.02, 1.10]
6 Expulsion			Other data	No numeric data
6.1 At 1 year			Other data	No numeric data
6.2 At 2 years			Other data	No numeric data
6.3 At 3 years			Other data	No numeric data
6.4 At 5 years			Other data	No numeric data
7 Embedded			Other data	No numeric data
7.1 At 5 years			Other data	No numeric data
8 Ectopic pregnancy			Other data	No numeric data
8.1 At 1 year			Other data	No numeric data
8.2 At 2 years			Other data	No numeric data
8.3 At 5 years			Other data	No numeric data
9 Pelvic inflammatory disease			Other data	No numeric data
9.1 At 1 year			Other data	No numeric data
10 Hormonal reasons for discontinuation			Other data	No numeric data
10.1 At 1 year			Other data	No numeric data
10.2 At 3 years			Other data	No numeric data
10.3 At 5 years			Other data	No numeric data
11 Menstrual reasons for discontinuation: all			Other data	No numeric data
11.1 At 1 year			Other data	No numeric data
11.2 At 2 years			Other data	No numeric data
11.3 At 3 years			Other data	No numeric data
11.4 At 5 years			Other data	No numeric data

12 Menstrual reasons for discontinuation: bleeding & pain		Other data	No numeric data
12.1 At 5 years		Other data	No numeric data
13 Menstrual reasons for discontinuation: pain		Other data	No numeric data
13.1 At 1 year		Other data	No numeric data
13.2 At 5 years		Other data	No numeric data
14 Menstrual reasons for discontinuation: absence of menstrual bleeding		Other data	No numeric data
14.1 At 1 year		Other data	No numeric data
14.2 At 5 years		Other data	No numeric data
15 Discontinuation due to adverse event		Other data	No numeric data
15.1 At 3 years		Other data	No numeric data
16 Discontinuation because planning pregnancy		Other data	No numeric data
16.1 At 1 year		Other data	No numeric data
16.2 At 5 years		Other data	No numeric data
17 Personal reasons for discontinuation		Other data	No numeric data
17.1 At 1 year		Other data	No numeric data
17.2 At 5 years		Other data	No numeric data

Comparison 2. LNG-20 IUS vs. IUD<=250mm2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy due to method failure			Other data	No numeric data
1.1 At 1 year			Other data	No numeric data
1.2 At 2 years			Other data	No numeric data
1.3 At 3 years			Other data	No numeric data
1.4 At 5 years			Other data	No numeric data
2 Continuation of method			Other data	No numeric data
2.1 At 1 year			Other data	No numeric data
2.2 At 2 years			Other data	No numeric data
2.3 At 3 years			Other data	No numeric data
2.4 At 5 years			Other data	No numeric data
3 Planned pregnancy after discontinuation of method	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3.1 At 1 year	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 At 2 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4 Headaches	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.53, 4.92]
4.1 At 5 years	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.53, 4.92]
5 Breast tenderness	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.35, 6.07]
5.1 At 5 years	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.35, 6.07]
6 Acne	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [0.95, 9.51]
6.1 At 5 years	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [0.95, 9.51]

7 Nausea	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.18 [0.20, 86.13]
7.1 At 5 years	1	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.18 [0.20, 86.13]
8 Ovarian cysts			Other data	No numeric data
8.1 At 1 year			Other data	No numeric data
9 Expulsion			Other data	No numeric data
9.1 At 1 year			Other data	No numeric data
9.2 At 2 years			Other data	No numeric data
9.4 At 5 years			Other data	No numeric data
10 Ectopic pregnancy			Other data	No numeric data
10.1 At 1 year			Other data	No numeric data
10.2 At 3 years			Other data	No numeric data
10.3 At 5 years			Other data	No numeric data
11 Pelvic inflammatory disease			Other data	No numeric data
11.1 At 1 year			Other data	No numeric data
11.2 At 2 years			Other data	No numeric data
12 Hormonal reasons for discontinuation			Other data	No numeric data
12.1 At 1 year			Other data	No numeric data
12.2 At 3 years			Other data	No numeric data
12.3 At 5 years			Other data	No numeric data
13 Menstrual reasons for discontinuation: all			Other data	No numeric data
13.1 At 1 year			Other data	No numeric data
13.2 At 2 years			Other data	No numeric data
13.3 At 3 years			Other data	No numeric data
13.4 At 5 year			Other data	No numeric data
14 Menstrual reasons for discontinuation: bleeding & pain			Other data	No numeric data
14.1 At 5 years			Other data	No numeric data
15 Menstrual reasons for discontinuation: absence of menstrual bleeding			Other data	No numeric data
15.1 At 5 years			Other data	No numeric data
16 Discontinuation due to adverse event			Other data	No numeric data
16.1 At 1 year			Other data	No numeric data
16.2 At 3 years			Other data	No numeric data
16.3 At 5 years			Other data	No numeric data
17 Discontinuation because planning pregnancy			Other data	No numeric data
17.1 At 5 years			Other data	No numeric data
18 Discontinuation for personal reasons			Other data	No numeric data
18.1 At 5 years			Other data	No numeric data

Comparison 3. LNG-20 IUS vs. Norplant-2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy			Other data	No numeric data
1.1 At 1 year			Other data	No numeric data
1.2 At 2 years			Other data	No numeric data
1.3 At 3 years			Other data	No numeric data
2 Continuation of method			Other data	No numeric data
2.1 At 1 year			Other data	No numeric data
3 Expulsion			Other data	No numeric data
3.1 At 1 year			Other data	No numeric data
4 Breast cancer			Other data	No numeric data
4.1 At 1 year			Other data	No numeric data
5 Ovarian cysts			Other data	No numeric data
5.1 At 1 year			Other data	No numeric data
6 Spotting	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 At 1 year	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.14, 0.51]
6.2 At 2 years	1	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.08, 0.45]
6.3 At 3 years	1	134	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.08, 0.50]
7 Infrequent menstrual bleeding	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 At 1 year	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.93, 3.37]
7.2 At 2 years	1	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.16 [3.56, 14.40]
7.3 At 3 years	1	134	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.38, 3.03]
8 Absence of menstrual bleeding	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 At 1 year	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [1.06, 5.72]
8.2 At 2 years	1	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.89 [3.96, 24.72]
8.3 At 3 years	1	134	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.61 [0.57, 11.92]
9 Prolonged bleeding	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 At 1 year	1	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.08, 0.32]
9.2 At 2 years	1	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.08, 0.40]
9.3 At 3 years	1	134	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.07, 0.56]

Comparison 4. LNG-IUS vs. combined oral contraceptives

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy			Other data	No numeric data
1.1 At 1 year			Other data	No numeric data
2 Headaches	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.56, 1.77]
2.1 At 1 year	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.56, 1.77]
3 Breast tenderness	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [1.32, 4.68]
3.1 At 1 year	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [1.32, 4.68]
4 Acne	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [1.00, 3.08]
4.1 At 1 year	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [1.00, 3.08]
5 Absence of menstrual bleeding	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.00 [3.24, 19.75]
5.1 At 1 year	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.00 [3.24, 19.75]

6 Prolonged bleeding	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.42, 1.30]
6.1 At 1 year	1	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.42, 1.30]
7 Hormonal reasons for discontinuation			Other data	No numeric data
7.1 At 1 year			Other data	No numeric data
8 Discontinuation because planning pregnancy			Other data	No numeric data
8.1 At 1 year			Other data	No numeric data
9 Discontinuation for personal reasons			Other data	No numeric data
9.1 At 1 year			Other data	No numeric data

Comparison 5. P4-IUS vs. non-medicated IUD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy			Other data	No numeric data
1.1 At 1 year			Other data	No numeric data
2 Continuation of method			Other data	No numeric data
2.1 At 1 year			Other data	No numeric data
3 Expulsion			Other data	No numeric data
3.1 At 1 year			Other data	No numeric data
4 Ectopic pregnancy			Other data	No numeric data
4.1 At 1 year			Other data	No numeric data
5 Menstrual reasons for discontinuation: all			Other data	No numeric data
5.1 At 1 year			Other data	No numeric data
6 Discontinuation because planning pregnancy			Other data	No numeric data
6.1 At 1 year			Other data	No numeric data
7 Discontinuation for personal reasons			Other data	No numeric data
7.1 At 1 year			Other data	No numeric data

Comparison 6. P4-IUS vs. IUDs <=250mm2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy			Other data	No numeric data
1.1 At 1 year			Other data	No numeric data
2 Continuation of method			Other data	No numeric data
2.1 At 1 year			Other data	No numeric data
3 Expulsion			Other data	No numeric data
3.1 At 1 year			Other data	No numeric data
4 Ectopic pregnancy			Other data	No numeric data

4.1 At 1 year	Other data	No numeric data
5 Menstrual reasons for discontinuation: bleeding & pain	Other data	No numeric data
5.1 At 1 year	Other data	No numeric data

Analysis 1.1. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 1 Pregnancy due to method failure.

Pregnancy due to method failure

Study	
At 1 year	
Baveja 1989	Single decrement life table probabilities (SE) = 0.0 (0.4) vs. 0.8 (0.4)
Sivin 1994	2/7680 women months vs. 2/7740 women months Single decrement life table probabilities (SE) = 0.3 (0.2) vs. 0.3 (0.2)
At 2 years	
Baveja 1989	Single decrement life table probabilities (SE) = 0.0 (0.5) vs. 1.0 (0.5)
Sivin 1994	2/19644 women months vs. 7/20436 women months
At 3 years	
Baveja 1989	0/10589 women months vs. 4/10869 women months Single decrement life table probabilities (SE) = 0.0 (0.5) vs. 1.0 (0.5)
At 5 years	
Sivin 1994	6/34944 women months vs. 10/38268 women months Single decrement life table probabilities (SE) = 1.1 (0.5) vs. 1.4 (0.4)

Analysis 1.2. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 2 Continuation of method.

Continuation of method

Study	
At 1 year	
Baveja 1989	339/4809 women months vs. 350/4599 women months
Sivin 1994	743/11892 women months vs. 791/12084 women months Life table probabilities (SE) = 73.5 (1.4) vs. 79.8 (1.3)
At 2 years	
Baveja 1989	257/8321 women months vs. 276/8333

Continuation of method (*Continued*)

Sivin 1994	548/19644 women months vs. 605/20436 women months Life table probabilities (SE) = 59.4 (1.6) vs. 67.5 (1.5)
At 3 years	
Baveja 1989	150/10589 women months vs. 170/10869 women months
At 5 years	
Sivin 1994	298/34944 women months vs. 335/38268 women months Life table probabilities (SE) = 33 (1.5) vs. 40.6 (1.6)

Analysis 1.3. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 3 Planned pregnancy after discontinuation of method.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 1 LNG-20 IUS vs. IUDs >250mm2

Outcome: 3 Planned pregnancy after discontinuation of method

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 1 year					
Sivin 1994	39/49	28/37		100.0 %	1.25 [0.45, 3.48]
Total (95% CI)	**49**	**37**		**100.0 %**	**1.25 [0.45, 3.48]**
Total events: 39 (Treatment), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Not applicable					

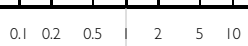
Analysis 1.4. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 4 Amenorrhoea.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 1 LNG-20 IUS vs. IUDs >250mm2

Outcome: 4 Amenorrhoea

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 3 months					
Sivin 1994	41/215	20/226		47.7 %	2.35 [1.37, 4.04]
Subtotal (95% CI)	**215**	**226**		**47.7 %**	**2.35 [1.37, 4.04]**
Total events: 41 (Treatment), 20 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.10 (P = 0.0019)					
2 At 3 years					
Sivin 1994	75/120	12/139		52.3 %	11.08 [6.61, 18.57]
Subtotal (95% CI)	**120**	**139**		**52.3 %**	**11.08 [6.61, 18.57]**
Total events: 75 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.13 (P < 0.00001)					
Total (95% CI)	**335**	**365**		**100.0 %**	**5.29 [3.64, 7.68]**
Total events: 116 (Treatment), 32 (Control)					
Heterogeneity: Chi^2 = 16.53, df = 1 (P = 0.00005); I^2 =94%					
Test for overall effect: Z = 8.75 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 16.53, df = 1 (P = 0.00), I^2 =94%					

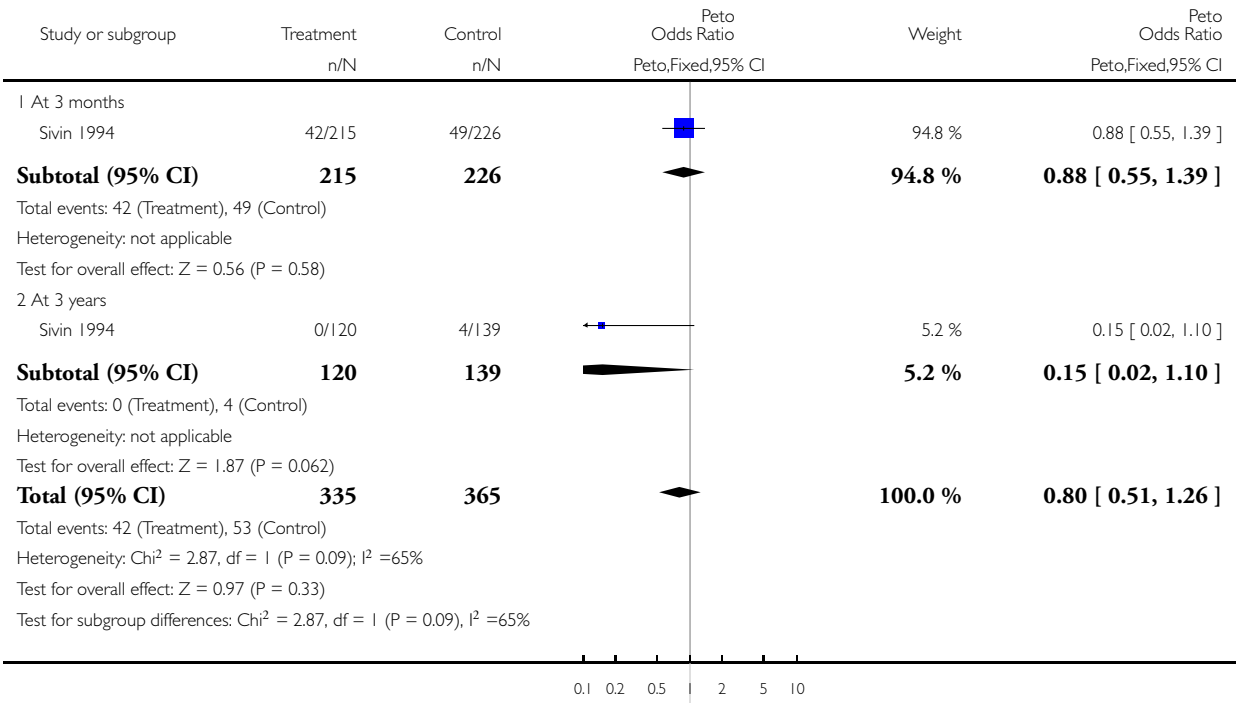


Analysis 1.5. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 5 Prolonged bleeding.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 1 LNG-20 IUS vs. IUDs >250mm2

Outcome: 5 Prolonged bleeding



Analysis 1.6. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 6 Expulsion.

Expulsion

Study	
At 1 year	
Baveja 1989	Single decrement life table probabilities (SE) = 6.5 (1.2) vs. 5.3 (1.1)
Sivin 1994	43/7680 women months vs. 39/7740 women months Single decrement life table probabilities (SE) = 6.4 (1.0) vs. 5.8 (1.9)
At 2 years	
Baveja 1989	Single decrement life table probabilities (SE) = 9.2 (1.4) vs. 7.1 (1.3)
At 3 years	

Expulsion (*Continued*)

Baveja 1989	Single decrement life table probabilities (SE) = 10.6 (1.6) vs. 7.6 (1.4)
At 5 years	
Sivin 1994	99/34944 women months vs. 71/38268 women months Single decrement life table probabilities (SE) = 11.8 (1.2) vs. 7.4 (0.9)

Analysis 1.7. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 7 Embedded.

Embedded

Study	
At 5 years	
Sivin 1994	3/34944 women months vs. 0/38268 women months

Analysis 1.8. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 8 Ectopic pregnancy.

Ectopic pregnancy

Study	
At 1 year	
Sivin 1994	0/7680 women months vs. 0/7740 women months
At 2 years	
Sivin 1994	0/19644 women months vs. 0/20436 women months
At 5 years	
Sivin 1994	0/34944 women months vs. 2/38268 women months

Analysis 1.9. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 9 Pelvic inflammatory disease.

Pelvic inflammatory disease

Study	
At 1 year	
Sivin 1994	10/7680 women months vs. 8/7740 women months Single decrement life table probabilities (SE) = 1.6 (0.5) vs. 1.3 (0.4)

Analysis 1.10. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 10 Hormonal reasons for discontinuation.

Hormonal reasons for discontinuation

Study	
At 1 year	
Sivin 1994	4/7680 women months vs. 5/7740 women months Single decrement life table probabilities (SE) = 0.7 (0.4) vs. 0.8 (0.4)
At 3 years	
Baveja 1989	10/10589 women months vs. 6/10869 women months
At 5 years	
Sivin 1994	31/34994 women months vs. 8/38268 women months

Analysis 1.11. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 11 Menstrual reasons for discontinuation: all.

Menstrual reasons for discontinuation: all

Study	
At 1 year	
Baveja 1989	Single decrement life table probabilities (SE) = 13.8 (1.7) vs. 7.1 (1.3)
Sivin 1994	69/7680 women months vs. 47/7740 women months Single decremt life table probabilities (SE) = 11.1 (7.5) vs. 1.6 (1.1)
At 2 years	
Baveja 1989	Single decrement life table probabilities (SE) = 21.9 (2.1) vs. 10.8 (1.3)
At 3 years	
Baveja 1989	Single decrement life table probabilities (SE) = 27.9 (2.3) vs. 13.4 (1.8)
At 5 years	
Sivin 1994	252/34944 women months vs. 186/38268 women months

Analysis 1.12. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 12 Menstrual reasons for discontinuation: bleeding & pain.

Menstrual reasons for discontinuation: bleeding & pain

Study	
At 5 years	
Sivin 1994	118/34944 women months vs. 183/38268 women months Single decrement life table probabilities (SE) = 15.4 (1.4) vs. 23.3 (0.6)

Analysis 1.13. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 13 Menstrual reasons for discontinuation: pain.

Menstrual reasons for discontinuation: pain

Study	
At 1 year	
Sivin 1994	Single decrement life table probabilities (SE) = 2.5 (0.6) vs. 3.4 (0.8)
At 5 years	
Sivin 1994	15/7680 women months vs. 47/7740 women months Single decrement life table probabilities (SE) = 19.7 (1.6) vs. 0.4 (0.2)

Analysis 1.14. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 14 Menstrual reasons for discontinuation: absence of menstrual bleeding.

Menstrual reasons for discontinuation: absence of menstrual bleeding

Study	
At 1 year	
Sivin 1994	32/7680 women months vs. 0/7740 women months Single decrement life table probabilities (SE) = 5.6 (1.0) vs. 0.0
At 5 years	
Sivin 1994	134/34944 women months vs. 3/38268 women months

Analysis 1.15. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 15 Discontinuation due to adverse event.

Discontinuation due to adverse event

Study	
At 3 years	
Baveja 1989	2/10589 women months vs. 2/10869 women months

Analysis 1.16. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 16 Discontinuation because planning pregnancy.

Discontinuation because planning pregnancy

Study	
At 1 year	
Sivin 1994	15/7680 women months vs. 16/7740 women months Single decrement life table probabilities (SE) = 2.8 (0.7) vs. 2.9 (0.7)
At 5 years	
Sivin 1994	155/34944 women months vs. 153/38268 women months Single decrement life table probabilities (SE) = 25.0 (1.9) vs. 23.5 (1.7)

Analysis 1.17. Comparison 1 LNG-20 IUS vs. IUDs >250mm2, Outcome 17 Personal reasons for discontinuation.

Personal reasons for discontinuation

Study	
At 1 year	
Sivin 1994	18/7680 women months vs. 13/7740 women months Single decrement life table probabilities (SE) = 3.0 (0.7) vs. 2.2 (0.6)
At 5 years	
Sivin 1994	56/34944 women months vs. 55/38268 women months Single decrement life table probabilities (SE) = 9.5 (1.3) vs. 9.4 (1.3)

Analysis 2.1. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 1 Pregnancy due to method failure.

Pregnancy due to method failure

Study	
At 1 year	
Andersson 1994	1/18664 women months vs. 8/9326 women months
Baveja 1989	Single decrement life table probabilities (SE) = 0.0 vs. CuT 220C 0.0 and vs. CuT 200B 0.9 (0.4)
Luukkainen 1986	1/1654 women months vs. 4/1708 women months
At 2 years	
Baveja 1989	Single decrement life table probabilities (SE) = 0.0 vs. CuT 220C 0.0 and vs. CuT 200B 0.9 (0.4)
At 3 years	
Andersson 1994	3/46200 women months vs. 24/23568 women months
Baveja 1989	0/10589 women months vs. 7/24225 women months (vs. CuT 220C 1/12076 women months and vs. CuT 220B 6/12149 women months) Single decrement life table probabilities (SE) = 0.0 vs. CuT 220C 0.3 (0.3) and vs. CuT 200B 1.6 (0.6)
At 5 years	
Andersson 1994	5/67380 women months vs. 35/33312 women months
Luukkainen 1986	1/5495 women months vs. 7/5176 women months

Analysis 2.2. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 2 Continuation of method.

Continuation of method

Study	
At 1 year	
Andersson 1994	1362/18664 women months vs. 680/9326 women months
Baveja 1989	339/4809 women months vs. 791/9814 women months
At 2 years	
Baveja 1989	257/8321 women months vs. 617/18819 women months
At 3 years	

Continuation of method (*Continued*)

Andersson 1994	902/46200 women months vs. 435/23568 women months
Baveja 1989	150/10589 women months vs. 344/24255 women months
At 5 years	
Andersson 1994	67/5495 women months vs. 53/5176 women months
Luukkainen 1986	736/67380 women months vs. 315/33312 women months

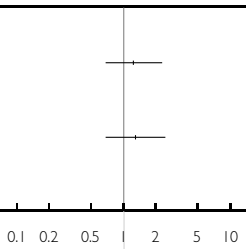
Analysis 2.3. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 3 Planned pregnancy after discontinuation of method.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 2 LNG-20 IUS vs. IUD<=250mm2

Outcome: 3 Planned pregnancy after discontinuation of method

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 At 1 year				
Andersson 1994	96/138	46/71		1.24 [0.67, 2.29]
2 At 2 years				
Andersson 1994	104/138	50/71		1.29 [0.67, 2.46]



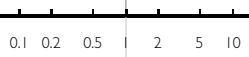
Analysis 2.4. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 4 Headaches.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 2 LNG-20 IUS vs. IUD<=250mm2

Outcome: 4 Headaches

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 5 years					
Andersson 1994	12/736	3/315		100.0 %	1.62 [0.53, 4.92]
Total (95% CI)	**736**	**315**		**100.0 %**	**1.62 [0.53, 4.92]**
Total events: 12 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.40)					
Test for subgroup differences: Not applicable					



Analysis 2.5. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 5 Breast tenderness.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 2 LNG-20 IUS vs. IUD<=250mm2

Outcome: 5 Breast tenderness

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 5 years					
Andersson 1994	7/736	2/315		100.0 %	1.45 [0.35, 6.07]
Total (95% CI)	**736**	**315**		**100.0 %**	**1.45 [0.35, 6.07]**
Total events: 7 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
Test for subgroup differences: Not applicable					

Analysis 2.6. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 6 Acne.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 2 LNG-20 IUS vs. IUD<=250mm2

Outcome: 6 Acne

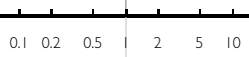
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 5 years					
Andersson 1994	13/736	1/315		100.0 %	3.01 [0.95, 9.51]
Total (95% CI)	**736**	**315**		**100.0 %**	**3.01 [0.95, 9.51]**

Total events: 13 (Treatment), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.88 (P = 0.061)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 7 Nausea.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 2 LNG-20 IUS vs. IUD<=250mm2

Outcome: 7 Nausea

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 5 years					
Andersson 1994	2/736	0/315		100.0 %	4.18 [0.20, 86.13]
Total (95% CI)	**736**	**315**		**100.0 %**	**4.18 [0.20, 86.13]**

Total events: 2 (Treatment), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 8 Ovarian cysts.

Ovarian cysts

Study	
At 1 year	
Andersson 1994	12/18664 women months vs. 4/9326 women months

Analysis 2.9. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 9 Expulsion.

Expulsion

Study	
At 1 year	
Andersson 1994	62/18664 women months vs. 32/9326 women months
Baveja 1989	Single decrement life table probabilities (SE) = 6.5 (1.2) vs. CuT 220C 4.8 (1.0) and vs. CuT 200B 4.9 (1.0)
At 2 years	
Baveja 1989	Single decrement life table probabilities (SE) = 9.2 (1.4) vs. CuT 220C 7.1 (1.2) and vs. CuT 200B 7.7 (1.3)
Luukkainen 1986	1/3083 women months vs. 9/2989 women montths
At 5 years	
Luukkainen 1986	2/5495 women months vs. 7/5176 women months

Analysis 2.10. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 10 Ectopic pregnancy.

Ectopic pregnancy

Study	
At 1 year	
Andersson 1994	0/18664 women months vs. 1/9326 women months
Luukkainen 1986	1/1654 women months vs. 0/1708 women months
At 3 years	
Andersson 1994	1/46200 women months vs. 5/23568 women months
At 5 years	

Ectopic pregnancy (*Continued*)

Andersson 1994	1/67380 women months vs. 7/33312 women months

Analysis 2.11. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 11 Pelvic inflammatory disease.

Pelvic inflammatory disease

Study	
At 1 year	
Luukkainen 1986	0/1654 women months vs. 0/1708 women months
At 2 years	
Luukkainen 1986	0/3083 women months vs. 3/2989 women months

Analysis 2.12. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 12 Hormonal reasons for discontinuation.

Hormonal reasons for discontinuation

Study	
At 1 year	
Andersson 1994	54/18664 women months vs. 5/9326 women months
At 3 years	
Andersson 1994	110/46200 women months vs. 5/23568 women months
Baveja 1989	Total: 10/10589 women months vs. 27/24225 women months (vs. CuT220C 13/12076 women months and vs. CuT200B 14/12149 women months)
At 5 years	
Luukkainen 1986	11/5495 women months vs. 2/5176 women months

Analysis 2.13. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 13 Menstrual reasons for discontinuation: all.

Menstrual reasons for discontinuation: all

Study	
At 1 year	

Menstrual reasons for discontinuation: all (*Continued*)

Andersson 1994	153/18664 women months vs. 65/9326 women months
Baveja 1989	Single decrement life table probabilities (SE) = 13.8 (1.7) vs. CuT 220C 6.0 (1.1) and vs. CuT 200B 5.7 (1.1)
At 2 years	
Baveja 1989	Single decrement life table probabilities (SE) = 21.9 (2.1) vs. CuT 220C 9.9 (1.4) and vs. CuT 200B 8.8 (1.4)
At 3 years	
Baveja 1989	Single decrement life table probabilities (SE) = 27.9 (2.3) vs. CuT 220C 15.4 (1.9) and vs. CuT 200B 14.6 (1.9)
At 5 year	
Luukkainen 1986	26/5495 women months vs. 21/5176 women months

Analysis 2.14. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 14 Menstrual reasons for discontinuation: bleeding & pain.

Menstrual reasons for discontinuation: bleeding & pain

Study	
At 5 years	
Luukkainen 1986	11/5495 women months vs. 21/5176 women months

Analysis 2.15. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 15 Menstrual reasons for discontinuation: absence of menstrual bleeding.

Menstrual reasons for discontinuation: absence of menstrual bleeding

Study	
At 5 years	
Luukkainen 1986	15/5495 women months vs. 0/5176 women months

Analysis 2.16. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 16 Discontinuation due to adverse event.

Discontinuation due to adverse event

Study	

Discontinuation due to adverse event (*Continued*)

At 1 year	
Andersson 1994	42/18664 women months vs. 21/9326 women months
At 3 years	
Baveja 1989	Total: 2/10589 women months vs. 4/24225 women months (vs. CuT220C 0/12076 women months and vs. CuT200B 4/12149 women months)
At 5 years	
Luukkainen 1986	5/5495 women months vs. 6/5176 women months

Analysis 2.17. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 17 Discontinuation because planning pregnancy.

Discontinuation because planning pregnancy

Study	
At 5 years	
Luukkainen 1986	10/5495 women months vs. 16/5176 women months

Analysis 2.18. Comparison 2 LNG-20 IUS vs. IUD<=250mm2, Outcome 18 Discontinuation for personal reasons.

Discontinuation for personal reasons

Study	
At 5 years	
Luukkainen 1986	6/5495 women months vs. 3/5176 women months

Analysis 3.1. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 1 Pregnancy.

Pregnancy

Study	
At 1 year	
Wang 1992	1/1157 women months vs. 0/1187 women months
At 2 years	

Pregnancy (*Continued*)

Wang 1992	1/2171 women months vs. 0/2218 women months
At 3 years	
Wang 1992	1/3098 women months vs. 0/3093 women months

Analysis 3.2. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 2 Continuation of method.

Continuation of method

Study	
At 1 year	
Wang 1992	81/1157 women months vs. 93/1187 women months

Analysis 3.3. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 3 Expulsion.

Expulsion

Study	
At 1 year	
Wang 1992	3/1157 women months vs. 0/1187 women months

Analysis 3.4. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 4 Breast cancer.

Breast cancer

Study	
At 1 year	
Wang 1992	0/1157 women months vs. 0/1187 women months

Analysis 3.5. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 5 Ovarian cysts.

Ovarian cysts

Study	
At 1 year	
Wang 1992	4/1157 women months vs. 1/1187 women months

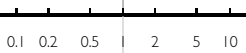
Analysis 3.6. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 6 Spotting.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 3 LNG-20 IUS vs. Norplant-2

Outcome: 6 Spotting

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 1 year					
Wang 1992	11/90	36/96		100.0 %	0.26 [0.14, 0.51]
Subtotal (95% CI)	**90**	**96**		**100.0 %**	**0.26 [0.14, 0.51]**
Total events: 11 (Treatment), 36 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.95 (P = 0.000077)					
2 At 2 years					
Wang 1992	4/79	22/79		100.0 %	0.19 [0.08, 0.45]
Subtotal (95% CI)	**79**	**79**		**100.0 %**	**0.19 [0.08, 0.45]**
Total events: 4 (Treatment), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.85 (P = 0.00012)					
3 At 3 years					
Wang 1992	3/65	18/69		100.0 %	0.20 [0.08, 0.50]
Subtotal (95% CI)	**65**	**69**		**100.0 %**	**0.20 [0.08, 0.50]**
Total events: 3 (Treatment), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.40 (P = 0.00066)					
Test for subgroup differences: Chi^2 = 0.42, df = 2 (P = 0.81), I^2 =0.0%					

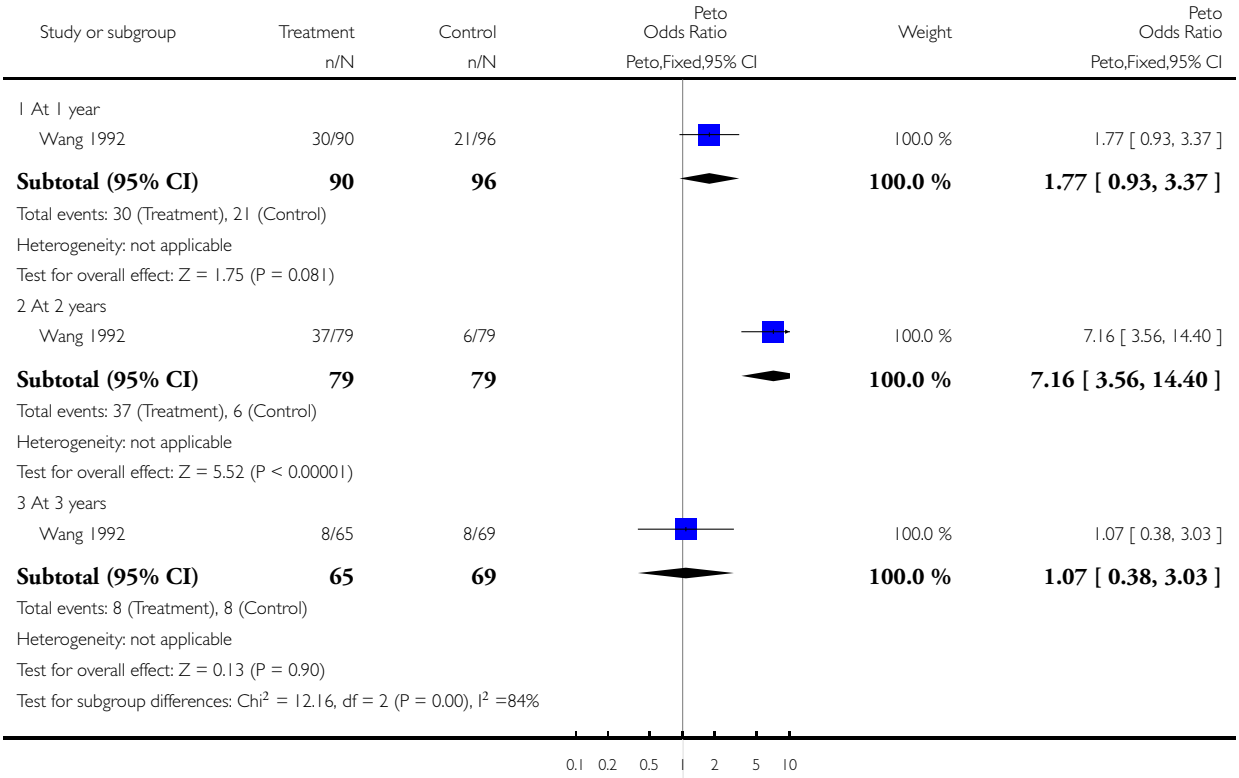


Analysis 3.7. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 7 Infrequent menstrual bleeding.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 3 LNG-20 IUS vs. Norplant-2

Outcome: 7 Infrequent menstrual bleeding

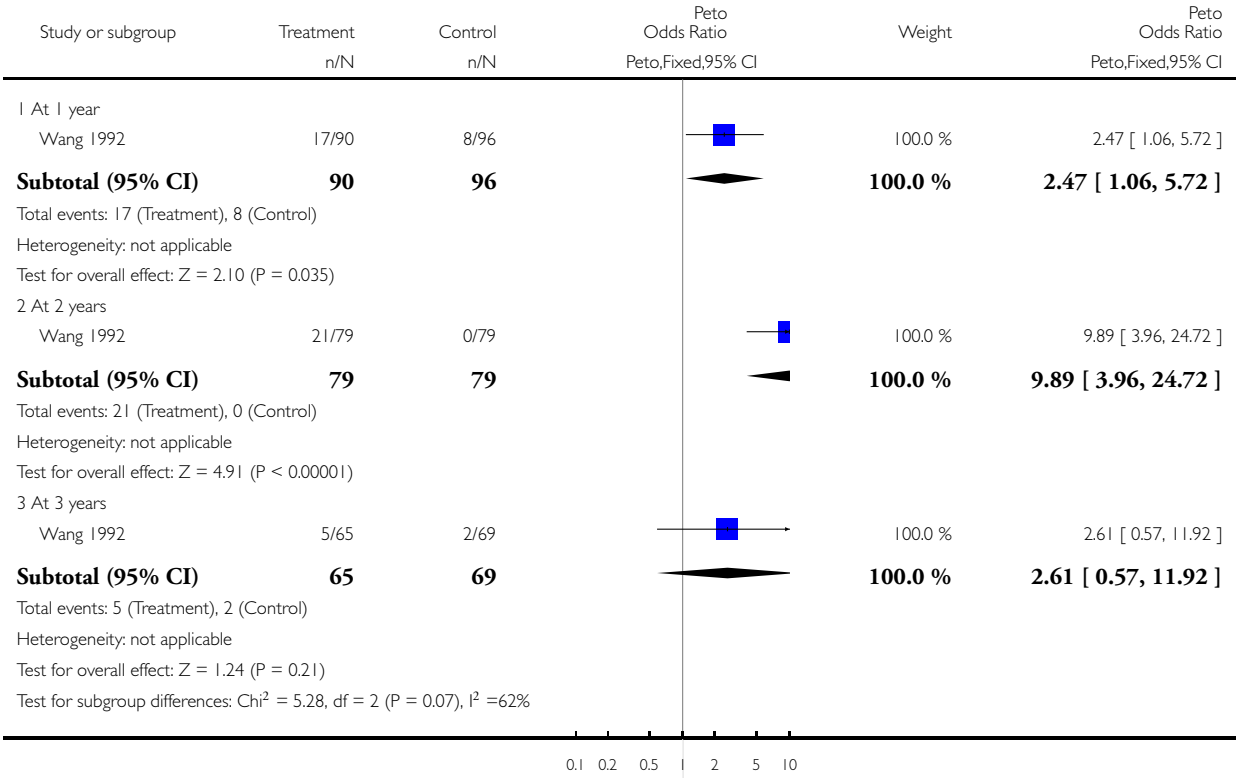


Analysis 3.8. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 8 Absence of menstrual bleeding.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 3 LNG-20 IUS vs. Norplant-2

Outcome: 8 Absence of menstrual bleeding



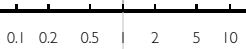
Analysis 3.9. Comparison 3 LNG-20 IUS vs. Norplant-2, Outcome 9 Prolonged bleeding.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 3 LNG-20 IUS vs. Norplant-2

Outcome: 9 Prolonged bleeding

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 At 1 year					
Wang 1992	4/90	33/96		100.0 %	0.15 [0.08, 0.32]
Subtotal (95% CI)	**90**	**96**		**100.0 %**	**0.15 [0.08, 0.32]**
Total events: 4 (Treatment), 33 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.10 (P < 0.00001)					
2 At 2 years					
Wang 1992	4/79	24/79		100.0 %	0.18 [0.08, 0.40]
Subtotal (95% CI)	**79**	**79**		**100.0 %**	**0.18 [0.08, 0.40]**
Total events: 4 (Treatment), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.15 (P = 0.000033)					
3 At 3 years					
Wang 1992	2/65	14/69		100.0 %	0.20 [0.07, 0.56]
Subtotal (95% CI)	**65**	**69**		**100.0 %**	**0.20 [0.07, 0.56]**
Total events: 2 (Treatment), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.06 (P = 0.0022)					
Test for subgroup differences: Chi^2 = 0.16, df = 2 (P = 0.92), I^2 =0.0%					



Analysis 4.1. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 1 Pregnancy.

Pregnancy

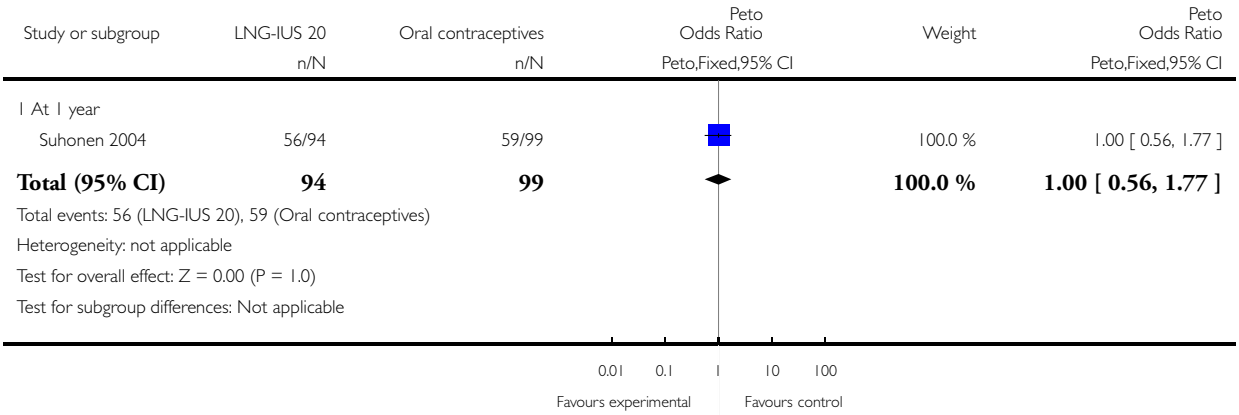
Study	
At 1 year	
Suhonen 2004	0/1128 women months vs. 0/1188 women months

Analysis 4.2. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 2 Headaches.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 4 LNG-IUS vs. combined oral contraceptives

Outcome: 2 Headaches

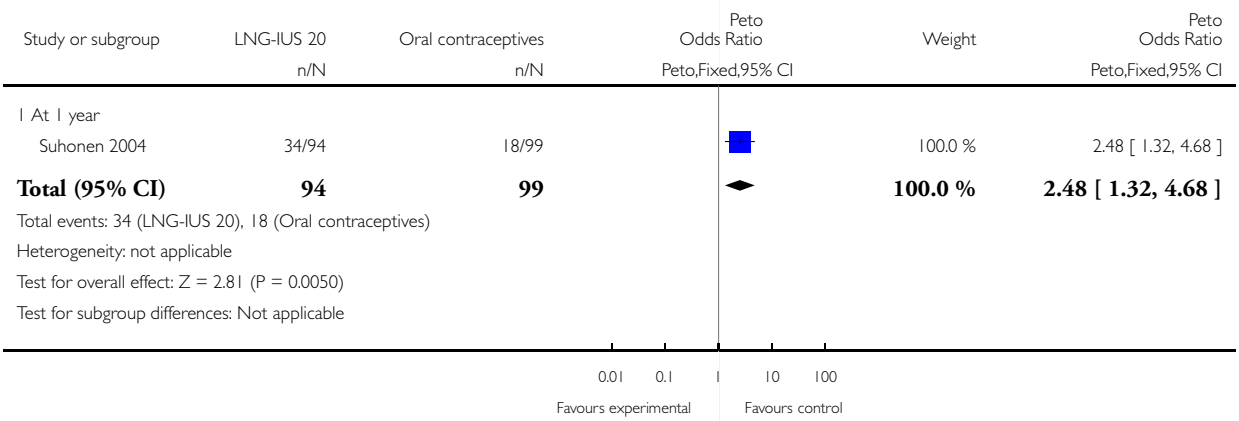


Analysis 4.3. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 3 Breast tenderness.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 4 LNG-IUS vs. combined oral contraceptives

Outcome: 3 Breast tenderness

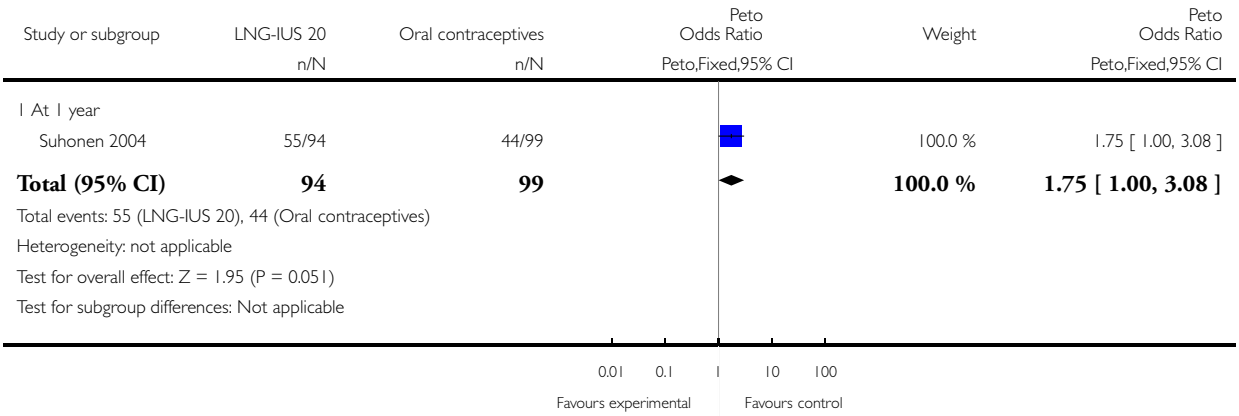


Analysis 4.4. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 4 Acne.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 4 LNG-IUS vs. combined oral contraceptives

Outcome: 4 Acne

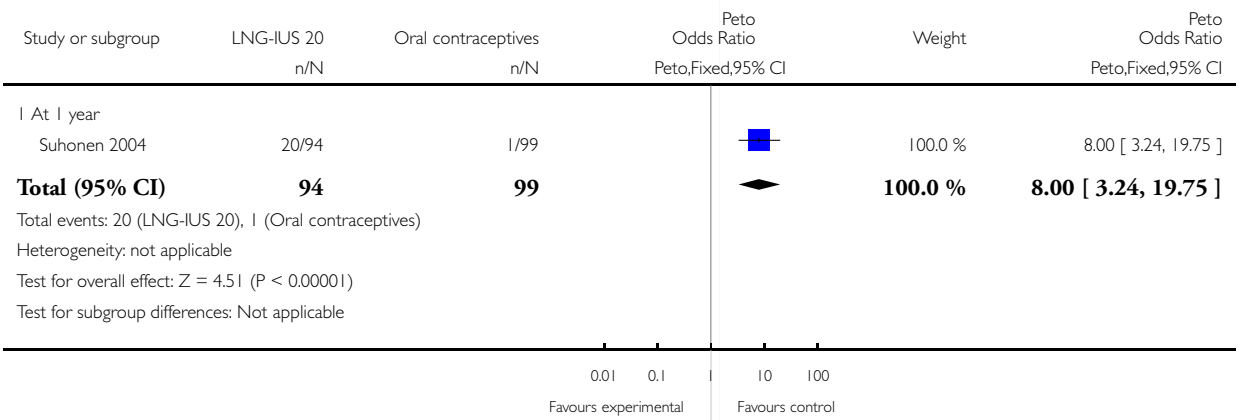


Analysis 4.5. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 5 Absence of menstrual bleeding.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 4 LNG-IUS vs. combined oral contraceptives

Outcome: 5 Absence of menstrual bleeding

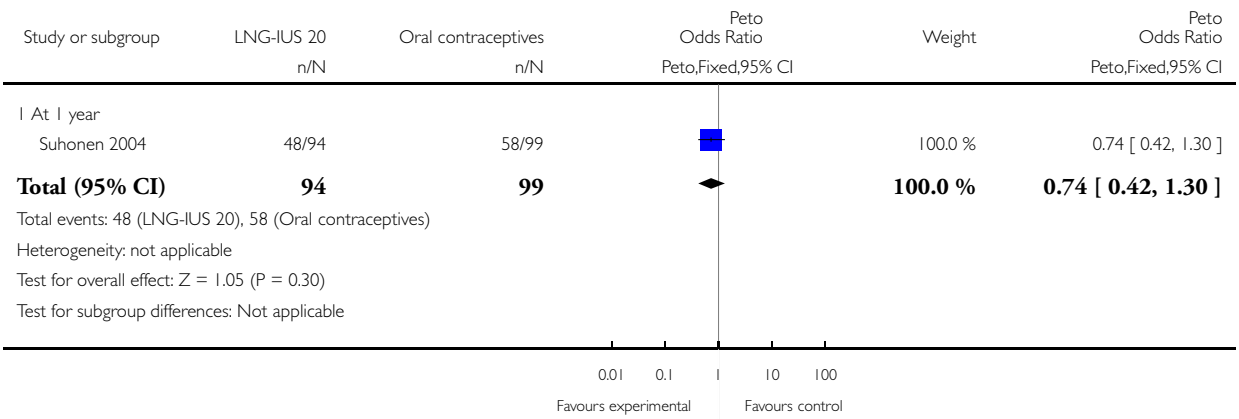


Analysis 4.6. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 6 Prolonged bleeding.

Review: Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception

Comparison: 4 LNG-IUS vs. combined oral contraceptives

Outcome: 6 Prolonged bleeding



Analysis 4.7. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 7 Hormonal reasons for discontinuation.

Hormonal reasons for discontinuation

Study	
At 1 year	
Suhonen 2004	4/1128 women months vs. 9/1188 women months

Analysis 4.8. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 8 Discontinuation because planning pregnancy.

Discontinuation because planning pregnancy

Study	
At 1 year	
Suhonen 2004	0/1128 women months vs. 2/1188 women months

Analysis 4.9. Comparison 4 LNG-IUS vs. combined oral contraceptives, Outcome 9 Discontinuation for personal reasons.

Discontinuation for personal reasons

Study	
At 1 year	
Suhonen 2004	4/1128 women months vs. 14/1188 women months

Analysis 5.1. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 1 Pregnancy.

Pregnancy

Study	
At 1 year	
Newton 1979	3/3389 women months vs. 28/2953 women months

Analysis 5.2. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 2 Continuation of method.

Continuation of method

Study	
At 1 year	
Newton 1979	Life table probabilities (SE) = 74.4 (2.4) vs. 65.8 (2.8)

Analysis 5.3. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 3 Expulsion.

Expulsion

Study	
At 1 year	
Newton 1979	25/3389 women months vs. 23/2953 women months

Analysis 5.4. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 4 Ectopic pregnancy.

Ectopic pregnancy

Study	
At 1 year	

Ectopic pregnancy (*Continued*)

Newton 1979	0/3389 women months vs. 1/2953 women months

Analysis 5.5. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 5 Menstrual reasons for discontinuation: all.

Menstrual reasons for discontinuation: all

Study	
At 1 year	
Newton 1979	29/3389 women months vs. 22/2953 women months

Analysis 5.6. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 6 Discontinuation because planning pregnancy.

Discontinuation because planning pregnancy

Study	
At 1 year	
Newton 1979	10/3389 women months vs. 6/2953 women months

Analysis 5.7. Comparison 5 P4-IUS vs. non-medicated IUD, Outcome 7 Discontinuation for personal reasons.

Discontinuation for personal reasons

Study	
At 1 year	
Newton 1979	8/3389 women months vs. 15/2953 women months

Analysis 6.1. Comparison 6 P4-IUS vs. IUDs <=250mm2, Outcome 1 Pregnancy.

Pregnancy

Study	
At 1 year	
Fylling 1979	7/1729 women months vs. 3/1483 women months
Larsen 1981	4/1996 women months vs. 4/1943 women months

Analysis 6.2. Comparison 6 P4-IUS vs. IUDs <=250mm2, Outcome 2 Continuation of method.

Continuation of method

Study	
At 1 year	
Larsen 1981	150/1996 women months vs. 142/1943 women months Life table probabilities (SE) = 76.2 (3.1) vs. 76 (3.2)

Analysis 6.3. Comparison 6 P4-IUS vs. IUDs <=250mm2, Outcome 3 Expulsion.

Expulsion

Study	
At 1 year	
Fylling 1979	2/1729 women months vs. 15/1483 women months

Analysis 6.4. Comparison 6 P4-IUS vs. IUDs <=250mm2, Outcome 4 Ectopic pregnancy.

Ectopic pregnancy

Study	
At 1 year	
Fylling 1979	2/1729 women moths vs. 0/1483 women months
Larsen 1981	1/1996 women months vs. 0/1934 women months

Analysis 6.5. Comparison 6 P4-IUS vs. IUDs <=250mm2, Outcome 5 Menstrual reasons for discontinuation: bleeding & pain.

Menstrual reasons for discontinuation: bleeding & pain

Study	
At 1 year	
Fylling 1979	35/1729 women months vs. 10/1483 women months

ADDITIONAL TABLES

Table 1. LNG-20 versus IUD >250mm2: Rate ratios with 95% CI

Outcome	One year	Two years	Three years	Four years	Five years
Pregnancy	1.01 (0.71 - 5.82) [Sivin 1994]	0.30 (0.07 - 1.24) [Sivin 1994]	0.11 (0.01 - 2.12) [Baveja 1989]	Not available	0.66 (0.25 - 1.75) [Sivin 1994]
Continuation	0.97 (0.90 - 1.06) [Sivin 1994, Baveja 1989]	0.94 (0.86 - 1.04) [Sivin 1994, Baveja 1989]	0.89 (0.71 - 1.11) [Baveja 1989]	Not available	0.91 (0.78 - 1.06) [Sivin 1994]
Expulsion	1.11 (0.72 - 1.71) [Sivin 1994]	Not available	Not available	Not available	1.53 (1.13 - 2.07) [Sivin 1994]
Embedded	Not available	Not available	Not available	Not available	7.0 (0.36 - 135.52) [Sivin 1994]
Ectopic Pregnancy	None	None	Not available	Not available	0.22 (0.01 - 4.56) [Sivin 1994]
PID	1.23 (0.50 - 3.03) [Sivin 1994]	Not available	Not available	Not available	Not available
Discontinuation: Hormonal	0.81 (0.23 - 2.80) [Sivin 1994]	Not available	1.71 (0.64 - 4.55) [Baveja 1989]	Not available	4.24 (1.99 to 9.05) [Sivin 1994]
Discontinuation: All Menstrual	1.48 (1.02 - 2.14) [Sivin 1994]	Not available	Not available	Not available	1.48 (1.23 - 1.79) [Sivin 1994]
Discontinuation: Menstrual - Bleeding & pain	Not available	Not available	Not available	Not available	0.71 (0.56 - 0.89) [Sivin 1990]
Discontinuation: Menstrual - Pain only	0.80 (0.41 - 1.56) [Sivin 1994]	Not available	Not available	Not available	Not available
Discontinuation: Menstrual: Absence of menstrual bleeding	65.51 (4.01 - 1069.85) [Sivin 1994]	Not available	Not available	Not available	48.92 (16.93 - 141.36) [Sivin 1994]
Discontinuation: Adverse event	Not available	Not available	1.03 (0.18 - 5.92) [Baveja 1989]	Not available	Not available
Discontinuation: Planning pregnancy	0.94 (0.47 - 1.89) [Sivin 1994]	Not available	Not available	Not available	1.11 (0.89 - 1.39) [Sivin 1994]

Table 2. LNG-20 IUS versus IUD >250mm2: Life table differences with 95%CI

Outcomes	One year	Two years	Three years	Four years	Five years
Pregnancy	-0.16 (-0.65 to 0.34) [Sivin 1994, Baveja 1989]	-1 (-2.39 to 0.39) [Baveja 1989]	-1 (-2.39 to 0.39) [Baveja 1989]	Not available	-0.3 (-1.56 to 0.96) [Sivin 1994]
Continuation	-6.3 (-10.00 to -2.56) [Sivin 1994]	-8.1 (-12.40 to -3.80) [Sivin 1994]	Not available	Not available	-7.6 (-11.90 to -3.30) [Sivin 1994]
Expulsion	0.84 (-1.19 to 2.88) [Sivin 1994, Baveja 1989]	2.1 (-1.64 to 5.84) [Baveja 1989]	3 (-1.17 to 7.17) [Baveja 1989]	Not available	4.4 (1.46 to 7.34) [Sivin 1994]
PID	0.3 (-0.96 to 1.56) [Sivin 1994]	Not available	Not available	Not available	Not available
Discontinuation: Hormonal	-0.1 (-1.21 to 1.01) [Sivin 1994]	Not available	Not available	Not available	Not available
Discontinuation: All menstrual	6.91 (2.87 to 10.94) [Sivin 1994, Baveja 1989]	11.1 (6.26 to 15.94) [Baveja 1989]	14.5 (8.78 to 20.22) [Baveja 1989]	Not available	Not available
Discontinuation: Menstrual - Bleeding & pain	Not available	Not available	Not available	Not available	-7.9 (-10.89 to -4.91) [Sivin 1994]
Discontinuation: Mentrual - Pain only	-0.9 (-2.86 to 1.06)	Not available	Not available	Not available	Not available
Discontinuation: Menstrual - Absence of menstrual bleeding	5.04 (3.19 to 6.90) [Sivin 1994, Baveja 1989]	9.5 (6.27 to 12.73) [Baveja 1989]	13.3 (9.30 to 17.30) [Baveja 1989]	Not available	19.3 (16.14 to 22.46) [Sivin 1994]
Discontinuation: Planning pregnancy	-0.1 (-2.04 to 1.84) [Sivin 1994]	Not available	Not available	Not available	1.5 (-3.50 to 6.50) [Sivin 1994]
Discontinuation: Personal choice	0.8 (-1.01 to 2.61) [Sivin 1994]	Not available	Not available	Not available	0.1 (-3.50 to 3.70) [Sivin 1994]

Table 3. LNG-20 IUS versus IUD <=250mm2: Rate ratios with 95% CI

Outcome	One year	Two years	Three years	Four years	Five years
Pregnancy	0.12 (0.03 - 0.49) [Andersson 1994; Luukkainen 1986] Evidence of heterogeneity	Not available	0.07 (0.02 - 0.19) [Andersson 1994; Baveja 1989]	Not available	0.08 (0.04 - 0.18) [Andersson 1994; Luukkainen 1986]
Continuation	1.03 (0.96 - 1.11) [Andersson 1994; Baveja 1989] Evidence of heterogeneity	0.93 (0.80 - 1.07) [Baveja 1989]	0.98 (0.80 - 1.07) [Andersson 1994; Baveja 1989]	Not available	1.04 (0.92 - 1.18) [Andersson 1994; Luukkainen 1986] Evidence of heterogeneity
Expulsion	0.71 (0.02 - 1.13) [Andersson 1994]	0.11 (0.02 - 0.6) [Luukkainen 1986]	Not available	Not available	0.27 (0.06 - 1.13) [Luukkainen 1986]
Ectopic pregnancy	0.72 (0.07 - 6.91) [Andersson 1994; Luukkainen 1986]	Not available	0.1 (0.02 - 0.62) [Andersson 1994]	Not available	0.07 (0.01 - 0.41) [Andersson 1994]
PID	None [Luukkaainen 1986]	0.4 (0.01 - 2.68) [Luukkainen 1986]	Not available	Not available	Not available
Discontinuation: Hormonal	5.40 (2.25 - 12.97) [Andersson 1994]	Not available	3.05 (0.24 - 38.34) [Andersson 1994; Baveja 1989] Evidence of heterogeneity	Not available	5.18 (1.32 - 20.34) [Luukkainen 1986]
Discontinuation: All Menstrual	1.18 (0.88 - 1.57) [Andersson 1994]	Not available	Not available	Not available	1.17 (0.66 - 2.06) [Luukkainen 1986]
Discontiuation: Mentrual - Bleeding & pain	Not available	Not available	Not available	Not available	0.49 (0.24 - 1.01) [Luukkainen 1986]
Discontinuation: Menstrual - Absence of menstrual bleeding	Not available	Not available	Not available	Not available	29.2 (1.75 - 488.04) [Luukkainen 1986]
Discontinuation: Adverse event	1.0 (0.59 - 1.68) [Andersson 1994]	Not available	1.14 (0.24 - 5.38) [Baveja 1989]	Not available	0.78 (0.25 - 2.44) [Luukkainen 1986]

Table 3. LNG-20 IUS versus IUD <=250mm2: Rate ratios with 95% CI (*Continued*)

Discontinuation: Planning pregnancy	Not available	Not available	Not available	Not available	0.59 (0.27 - 1.28) [Luukkainen 1986]
Discontinuation: Personal choice	Not available	Not available	Not available	Not available	2.70 (0.78 - 9.38) [Luukkainen 1986]

Table 4. LNG-20 IUS versus IUD<=250mm2: Life table differences with 95%CI

Outcomes	One year	Two years	Three years
Pregnancy	-0.90 (-2.01 to 0.21) [Baveja 1989]	-0.90 (-2.01 to -0.21) [Baveja 1989]	-0.56 (-1.30 to 0.18) [Baveja 1989]
Expulsion	1.65 (-0.51 to 3.81) [Baveja 1989]	1.81 (-0.80 to 4.41) [Baveja 1989]	2.2 (-0.75 to 5.14) [Baveja 1989]
Discontinuation: All Menstrual	7.95 (5.14 to 10.76) [Baveja 1989]	12.55 (9.05 to 16.05) [Baveja 1989]	12.9 (8.77 to 17.03) [Baveja 1989]
Discontinuation: Menstrual - Absence of menstrual bleeding	5.07 (3.36 to 6.77) [Baveja 1989]	9.80 (10.80 to 16.41) [Baveja 1989]	13.60 (10.80 to 16.41) [Baveja 1989]

Table 5. LNG-20 IUS versus subdermal implants: Rate ratios with 95% CI

Outcome	One year	Two years	Three years
Pregnancy	3.01 (0.13 - 75.56) [Wang 1992]	3.06 (0.12 - 75.56) [Wang 1992]	3.00 (0.12 - 73.53) [Wang 1992]
Continuation	0.97 (0.72 - 1.31) [Wang 1992]	Not available	Not available
Expulsion	7.18 (0.37 - 139.04) [Wang 1992]	Not available	Not available
Ovarian cysts	4.10 (0.65 - 26.04) [Wang 1992]	Not available	Not available
Breast cancer	None [Wang 1992]	None [Wang 1992]	None [Wang 1992]
Discontinuation: Menstrual	1.03 (.023 - 4.51) [Wang 1992]	Not available	Not available

Table 5. LNG-20 IUS versus subdermal implants: Rate ratios with 95% CI (*Continued*)

Discontinuation: Device problem	9.23 (0.5 - 171.51) [Wang 1992]	Not available	Not available
Discontinuation: Adverse events	1.03 (0.11 - 9.86) [Wang 1992]	Not available	Not available

Table 6. LNG-20 IUS versus oral contraceptives: Rate ratios with 95% CI

Outcome	One year
Discontinuation: Hormonal	1.00 (0.32 - 3.07) [Suhonen 2004]
Discontinuation: Planning pregnancy	0.21 (0.01 - 4.39) [Suhonen 2004]
Discontinuation: Patient choice	1.40 (0.48 - 4.02) [Suhonen 2004]

Table 7. Progestasert versus IUD <=250mm2: Rate ratios with 95% CI

Outcome	One year
Pregnancy	1.41 (0.57 - 3.51) [Larsen 1981; Fylling 1979]
Continuation	0.97 (0.78 - 1.23) [Larsen 1981]
Expulsion	0.11 (0.03 - 0.43) [Fylling 1979]
Ectopic pregnancy	3.57 (0.39 - 32.36) [Larsen 1981;Fylling 1979]

Table 8. Progestasert versus non-medicated IUD: Rate ratios with 95% CI

Outcome	One year
Pregnancy	0.09 (0.03 - 0.28) [Newton 1979]
Expulsion	0.95 (0.54 - 1.66) [Newton 1979]

Table 8. Progestasert versus non-medicated IUD: Rate ratios with 95% CI (*Continued*)

Ectopic pregnancy	0.29 - 7.13) [Newton 1979]
Discontinuation: Planning pregnancy	1.29 (0.88 - 1.90) [Newton 1979]
Discontinuation: Personal reasons	0.46 (0.20 - 1.07) [Newton 1979]

WHAT'S NEW

Last assessed as up-to-date: 14 July 2009.

Date	Event	Description
15 July 2009	New search has been performed	In 2009, three changes to the review methods were made from the original protocol. First, LILACS was added to the list of databases searched to identify studies. Second, the method for analysing contraception continuation rates was changed. The number of women months of continuation on each contraceptive method over the number of potential women months for each method was calculated at follow-up points (e.g. at one year) to provide a rate ratio. This method of analysis did not significantly change any findings from previous versions of this review. Finally, the terminology used to describe menstrual bleeding outcomes were changed to fit recommendations made by Fraser 2007, for example "heavy menstrual bleeding" replaces "menorrhagia" Four additional studies were identified, three compared the LNG IUS with intrauterine devices (Kapur 2008, Rogovskaya 2005, Shaamash 2005) and one compared the LNG IUS with combined oral contraceptives (Suhonen 2004). It was only possible to extract data from the Suhonen 2004 study. No pregnancies were reported in this study, but LNG IUS users were significantly more likely to report an absence of menstrual bleeding, breast tenderness and acne after one year compared to combined oral contraceptive users The primary outcomes for this review are pregnancy and continutation rates. However, the new studies also offer important findings for breastfeeding women and diabetic women. The LNG-20 IUS did not impact upon breastfeeding performance or the development of breastfed infants in lactating women (Shaamash 2005) and LNG-20 IUS use had no adverse effect on glucose metabolism among insulin-dependent diabetics (Rogovskaya 2005). Since the introduction of the LNG IUS and the inital publication of this review, few studies have been published employing rigourous methodologies, in line with CONSORT guidelines

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 2, 2001

Date	Event	Description
15 April 2008	Amended	Converted to new review format.
24 May 2004	New citation required and conclusions have changed	Substantive amendment

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DECLARATIONS OF INTEREST

None

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INDEX TERMS

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*Intrauterine Devices, Medicated [adverse effects]; Contraceptive Agents, Female [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy