Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy (Unknown)

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Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy


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ABSTRACT

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.

Objectives
To assess the contraceptive efficacy, tolerability and acceptability of hormonally impregnated intrauterine systems (IUSs) in comparison to other reversible contraceptive methods.

Search strategy
Literature was identified through database searches, reference lists and individuals/organisations working in the field. Searches covered the period from 1972 to July 1998.

Selection criteria
All randomised controlled trials comparing IUSs with other forms of reversible contraceptives and reporting on pre-determined outcomes in women of reproductive years. The primary outcomes were pregnancy due to method/user failure and continuation rate.

Data collection and analysis
The quality assessment of studies and data extraction were completed independently by two blinded reviewers. A quality checklist was designed to identify general methodological and contraceptive specific factors which could bias results. Events per women months and single decrement life table rates were extracted where possible for pregnancy, continuation, adverse events and reasons for discontinuation. Events per total number of women at follow up were collected for hormonal side effects and menstrual disturbance.

When appropriate, data were pooled at the same points of follow up to calculate rate ratios in order to determine the relative effectiveness of one method compared to another. For the single decrement life table rates, the rate differences were pooled to determine the absolute difference in effectiveness of one method compared to another. Interventions were only combined if the contraceptive methods were similar. Non-hormonal IUDs were divided into three categories for the purpose of comparison with IUSs: IUDs >250mm² (i.e. CuT 380A IUD and CuT 380 Ag IUD), IUDs <=250mm² (i.e. Nova-T, Multiload, CuT 200 and CuT 220 IUDs) and non-medicated IUDs.
Main results

Nineteen RCTs comparing hormonally impregnated IUSs to a reversible contraceptive method met the inclusion criteria and it was possible to include eight of these in the meta-analyses, four comparing LNG-20 IUSs with non-hormonal IUDs, one comparing the LNG-20 IUS with Norplant-2 and three comparing Progestasert with non-hormonal IUDs.

No significant difference was observed between the pregnancy rates for the LNG-20 users and those for the IUD >250mm2 users. However, women using the LNG-20 IUS were significantly less likely to become pregnant than those using the IUD <=250mm2. Women using the LNG-20 IUS were more likely to experience amenorrhoea and device expulsion than women using IUDs >250mm2. LNG-20 users were significantly more likely than all the IUD users to discontinue because of hormonal side effects and menstrual disturbance, which on further breakdown of the data was due to amenorrhoea. When the LNG-20 IUS was compared to Norplant-2, the LNG-20 users were significantly more likely to experience amenorrhoea and oligomenorrhoea, but significantly less likely to experience prolonged bleeding and spotting. No other significant differences were observed.

Progestasert users were significantly less likely to become pregnant and less likely to continue on the method than non-medicated IUD users after one year, but no significant difference was noted for these two outcomes when Progestasert users were compared to IUD<=250mm2 users. The only other significant differences found in the meta-analyses were that Progestasert users were less likely to expel the device and more likely to discontinue the method because of menstrual bleeding and pain than users of IUDs <=-250mm2.

Reviewers’ conclusions

Current evidence suggests LNG-20 IUS users are no more or less likely to have unwanted pregnancies than IUD >250mm2 and Norplant-2 users. The LNG-20 IUS was more effective in preventing either intrauterine or extraterine pregnancies than IUDs <=250mm2. The contraceptive effectiveness of Progestasert was significantly better than non-medicated IUDs, but no difference was observed when compared to IUDs<=-250mm2. Continuation of LNG-20 IUS use was similar to continuation of the non-hormonal IUDs and Norplant-2. Amenorrhoea was the main reason for the discontinuation for the LNG-20 IUS and women should be informed of this prior to starting this method.

SYNOPSIS

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 change the environment inside the uterus to 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 amenorrhoea (no menstrual period) 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.

Progestasert

The first IUS to be marketed was 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 been not renewed by the company in some countries in light of its reported disadvantages. These included:-
- yearly reinterrations with the associated risk of pelvic inflammatory disease;
- increased ectopic pregnancy rate when compared to copper bearing devices;
- some women experiencing persistent menstrual spotting.

Levonorgestrel Intrauterine System
The levonorgestrel intrauterine system (LNG-IUS), Mirena, is licensed for contraceptive use in 25 countries (Schering 1999). 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 periods and may offer an alternative to hysterectomy (Barrington 1997; Irvine 1998).

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 referring to single or multiple decrement probabilities.

OBJECTIVES
To determine the 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?

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 intervention
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

Not enough evidence about hormonal contraceptive use during breastfeeding
Breastfeeding provides some protection against anogenital disease;

Secondary outcome measures
Comparisons of different contraceptive methods at 1 and 2 years

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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 changes:
- Dysmenorrhoea
- Spotting
- Oligomenorrhoea
- Amenorrhoea
- Menorrhagia
- 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 disturbance
- Adverse clinical event
- Local device problem

Planning pregnancy
Patient choice - other

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

The following search strategy was used:
- #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 PROGESTASERT
- #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

Computerised databases The Cochrane Controlled Trials Register, MEDLINE, EMBASE, POPLINE, the Science Citation Index and Psych. Lit. were searched (from 1972 to July, 1998) to identify publications describing randomised and controlled clinical trials of IUSs. The reference lists of all identified publications were searched for previously unidentified articles.

The relevant pharmaceutical companies were contacted and asked to release results of any relevant unpublished studies for inclusion in the review. Individuals and organisations with an interest in IUS research were contacted to identify unpublished and ongoing studies relevant to the review.

METHODS OF THE REVIEW

The selection of studies for inclusion and their methodological quality were independently assessed and reported by reviewers (RF and FC). Quality assessment forms were designed, and included general methodological factors, as well as some of contraceptive specific factors recommended by Trussell 1991. The following quality factors were included on the checklist:
- method of randomisation described,
- allocation concealment,
- blinded assessment of outcomes,
- groups treated identically other than named intervention,
- description of women who withdrew or were lost to follow up provided,
- description of hormonal contraceptive method or pregnancy immediately prior to study enrolment,
- statistical method (with reference) used to analyse pregnancy and continuation of methods,
- description of contraceptive failure provided (i.e. user or method failure or both),
- active follow up conducted (i.e. analysis of follow up delayed a few months to allow inclusion of undetected pregnancies)

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.

Menstrual disturbance outcomes were only collected if investigators had stipulated that they had been measured over 90 day intervals as recommended by Rodriguez 1976. Number of events and total number of women at each 90 day interval were collected to calculate risk ratios for menstrual disturbance 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, 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 case and control 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 synthesis life table probabilities, it was necessary to calculate the absolute measurement of 'treatment' effect. This was done by subtracting the control 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 control 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)
**DESCRIPTION OF STUDIES**

Nineteen RCTs, identified from 38 publications, comparing hormonally impregnated IUSs to a reversible contraceptive method met the inclusion criteria (See Table of Included Studies). Seven trials were conducted in developing or transitional countries (Afandi 1980; Andrade 1988; Baveja 1989; el Mahgoub 1982; Lavin 1983; Piazarro 1979; Wang 1992) six in developed countries (Andersson 1994; Fylling 1979; Heikkila 1982; Larsen 1981; Pakarinen 1996; Rybo 1983) and five were international multicentre studies conducted in both developed and developing countries (Luukkainen 1986; Sivin 1994; WHO 1983; WHO 1987; WHO 1997). In one publication it was not possible to determine the study setting (Newton 1979). The majority of trials (10) were set in community-based family planning clinics.

The age range of participants varied from 15 - 44 years. None of the studies confined entry to specific age requirements, other than ensuring the recruited women were of reproductive age. Thirteen of the 19 trials limited recruitment to women with proven fertility (Andersson 1994; Andrade 1988; Baveja 1989; Heikkila 1982; Lavin 1983; Luukkainen 1986; Piazarro 1979; Rybo 1983; Sivin 1994; WHO 1987; Wang 1992; el Mahgoub 1982). Three studies recruited women immediately post partum or post abortion (Heikkila 1982; Lavin 1983; el Mahgoub 1982). One study restricted recruitment to women who were breast feeding (Heikkila 1982). Three studies stated that they only included women with regular menstrual cycles (Baveja 1989; Pakarinen 1996; Piazarro 1979).

Nearly all of the interventions were either comparisons of IUSs with different hormonal release rates or of IUSs versus non-hormonal IUDs. The one exception was a comparison of LNG-20 IUS with Norplant-2 (Wang 1992).

It was documented in two of the 19 trials that contraceptive counselling had been provided (Andersson 1994; Wang 1992). None of the studies mentioned any specific training for those inserting the devices.

**METODOLOGICAL QUALITY**

Details of the methodological quality of each of the studies are provided in the Characteristics of Included Studies Table. It was documented that allocation of contraceptive method was concealed to the investigator in eight trials (Andersson 1994; Baveja 1989; Newton 1979; Pakarinen 1996; Sivin 1994; Wang 1992; WHO 1997; WHO 1983). It was reported that investigators were blind to contraceptive method when assessing outcomes in only three of the trials (Luukkainen 1986; Newton 1979; Piazarro 1979). Women were blind to allocated method in an additional two studies (Andersson 1994; Larsen 1981).

In 14 studies, the compared groups were treated identically in terms of measurement of outcomes (Andersson 1994; Baveja 1989; Fylling 1979; Larsen 1981; Lavin 1983; Luukkainen 1986; Newton 1979; Pakarinen 1996; Piazarro 1979; Rybo 1983; Sivin 1994; 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 1979; 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; Andrade 1988; el Mahgoub 1982; Heikkila 1982; Lavin 1983; Luukkainen 1986; Piazarro 1979; 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 1979; Sivin 1994; Wang 1992; WHO 1983; WHO 1987). Active follow up was conducted in three trials (Sivin 1994; WHO 1983; WHO 1987).

**RESULTS**

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; Pakarinen 1996; WHO 1983; WHO 1987). Three studies compared the LNG-20 IUS with the non-hormonal IUD >250mm2 (Baveja 1989; Sivin 1994; WHO 1997). It was possible to extract data from two of these studies (Baveja 1989; Sivin 1994). The other study was still in progress at the time of this review. Rate ratios and single decrement life table differences derived from the two studies are presented in Table 01 and Table 02, 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 380Ag IUD was 1.05 (95% CI 0.83 to 1.33) at one year (Sivin 1994). It was possible to extract data on menstrual disturbance outcomes from one study only (Sivin 1994). Data from this study indicated that women using LNG-20 pregnancy.
IUSs were more likely to experience amenorrhoea than women using CuT 380Ag IUDs and this risk increased over time, at three months the risk ratio was 2.25 [95% CI 1.36 to 3.56] which increased to 7.24 [95% CI 4.14 - 12.55] 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 0.90 [95% CI 0.62 to 1.30] at three months and 0.1 [95% CI 0.01 to 2.06] at three years. It was not possible to extract data for any other menstrual disturbance outcomes, but Sivin et al (1994) reported that LNG-20 IUS users were significantly less likely to experience dysmenorrhoea. No data were collected for hormonal side effects.

Three included studies compared the LNG-20 IUS with non-hormonal <=250mm2 IUDs (Andersson 1994; Baveja 1989; Luukkainen 1986). Data could be extracted from each of these studies. The calculated rate ratios and single decrement life table differences are shown in Table 03 and Table 04, 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 amenorrhoea 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-TIUD (Andersson 1994). The rate ratios at one and two years were 1.07 (95% CI 0.88 to 1.32) and 1.07 (95% CI 0.9 to 1.28), respectively. It was not possible to extract any data on menstrual disturbance 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, 1.71 [95% CI 0.49 to 6.02]; 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 04). 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 03). 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.

Seven trials comparing Progestasert with non-hormonal IUDs <=250mm2 were were identified (Affandi 1980; Andrade 1988; Fylling 1979; Larsen 1981; Lavin 1983; Piazarro 1979; Rybo 1983) and two of these provided data that could be included in the meta-analysis, one comparing Progestasert 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 Progestasert was compared to methods that are no longer or have never been licensed (Affandi 1980; Andrade 1988; Piazarro 1979) 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 05. No data for any of these outcomes were included in the meta-analysis. Lavin 1983 reported that Progestasert users were significantly more likely to experience intermenstrual spotting, but significantly less likely to experience dysmenorrhoea. One comparison of Progestasert 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 06. No data were included in the meta-analysis on menstrual disturbance or hormonal side effect outcomes.

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 07. There were significant differences found in the rates of reported menstrual disturbance. LNG-20 IUS users were significantly more likely to experience amenorrhoea 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 689.20] at two years’ follow up and 2.65 [95% CI 0.53 to 13.20] at three years’ follow up. They were also significantly more likely to experience oligomenorrhoea, 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.
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. Progestasert 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. Therefore, this review is unable to look at the relative advantages and disadvantages of contraceptive methods which rely on differing default states, such as comparing the LNG-20 IUS to oral contraceptives or to DMPA injections. 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. 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 disturbance. The one outcome that users of all types of IUSs were significantly more likely to experience was amenorrhoea. 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 dysmenorrhoea 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.

Progestasert’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 comparisons illustrate. Women using LNG-20 IUSs discontinued due to amenorrhoea, while IUD >250mm2 users discontinued because of bleeding and pain. The reporting of discontinuation due to amenorrhoea, 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 Anderson study (Leiras Ltd 1999). Women should be informed of these potential side effects prior to starting these methods. The amenorrhoea in users of the LNG-20 IUS is benign and is due to high concentrations of levonorgestrel in the endometrium, the end organ (Scholten 1989). Therefore, if women (and providers) are informed amenorrhoea 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.

 REVIEWERS’ 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 <=250mm2.
Women using the LNG-20 IUS were more likely to experience amenorrhoea 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 amenorrhoea.

For the most part IUS users will be parous women who require contraception for birth spacing purposes. Therefore, rather than the results being generalisable to all women seeking contraception, these findings may be applicable to this group of women.

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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• No sources of support supplied

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Andersson 1994 (published data only)

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Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

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Andrade 1988 [published data only]

Fylling 1979 [published data only]

Heikkila 1982 [published data only]

Larsen 1981 [published data only]

Lavin 1983 [published data only]

Luukkainen 1986 [published data only]


Newton 1979 [published data only]

Pakarinne 1996 [published data only]

Pizarro 1979 [published data only]


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Sivin 1994 [published data only]


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Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

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References to ongoing studies

WHO 1997
Ongoing study Starting date of trial not provided. Contact reviewer for more information.


Additional references

Barrington 1997

Dersimonian 1986

Farley 1986

Hassellblad 1995

Higgins 1985

Irvine 1998

Leiras Ltd 1999

Mcguire 1995

Pearl 1933

Petitti 1994

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Rodriguez 1976

Schering 1999

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Diaz 1993

Faundes 1993

Nilsson 1977

Nilsson 1986

Pedron Neueo 1992

Ulstein 1987

Yin 1993


WHO 1983 (published data only)


WHO 1987 (published data only)
Scholten 1989

Trussell 1991

References to other published versions of this review
French 2000

* Indicates the major publication for the study

TABLES

Characteristics of included studies

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<td>Methods</td>
<td>Setting: Indonesia&lt;br&gt;697 women randomised&lt;br&gt;Follow up: 2 years</td>
</tr>
<tr>
<td>Participants</td>
<td>Not stated</td>
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<tr>
<td>Interventions</td>
<td>Progestasert [n=72] vs. CuT 200, Cu 7 and Lippes loop IUDs [n=75, 75 and 75, respectively]</td>
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<tr>
<td>Outcomes</td>
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<tr>
<td>Notes</td>
<td>Abstract&lt;br&gt;Quality assessment not conducted</td>
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<table>
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<tr>
<th>Study</th>
<th>Andersson 1994</th>
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<tr>
<td>Methods</td>
<td>Setting: Multinational (Denmark, Finland, Hungary, Norway and Sweden), Family Planning Clinics (12) 2758 women randomised&lt;br&gt;Follow up: 5 years</td>
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<td>Participants</td>
<td>18-38 years&lt;br&gt;Parous&lt;br&gt;Not breast feeding</td>
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<tr>
<td>Interventions</td>
<td>LNG-20 IUS [n=1821] vs. Nova-T IUD [n=937]</td>
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<td>Outcomes</td>
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Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

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### Characteristics of included studies (Continued)

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<tr>
<th>Continuation</th>
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<th>Adverse events</th>
<th>Hormonal side effects</th>
<th>Pregnancy after discontinuation of method</th>
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#### Notes
- Quality assessment:
  - Randomisation technique: No mention
  - Allocation concealment technique: Centrally prepared envelopes
  - Description of prior contraceptive method / pregnancy provided
  - Measurement: Groups treated identically
  - Method of analysis: Life tables (multiple and single decrement rates)
  - User/method failure reported

### Allocation concealment
- B

---

#### Study Andrade 1988

- **Methods**
  - Setting: Chile and Brazil (see Notes), Hospital
  - 150 women randomised
  - Follow up: 2 years

- **Participants**
  - Parous

- **Interventions**
  - Progestasert \(n=49\) 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

- **Allocation concealment**
  - D

---

#### Study 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 Cu T 200B IUDs \(n=434, 496\) and 500, respectively

- **Outcomes**
  - Pregnancy
  - Continuation
  - Reasons for discontinuation
  - Menstrual disturbance

- **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

---

**Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy**

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### Characteristics of included studies (Continued)

**Study** | Fylling 1979  
---|---  
**Methods**  
Setting: Denmark  
326 women randomised  
Follow up: 1 year  
**Participants**  
Mixed parity  
**Interventions**  
Progestasert [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  
**Allocation concealment**  
D

**Study** | 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 disturbance  
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  
**Allocation concealment**  
D

**Study** | Larsen 1981  
---|---  
**Methods**  
Setting: Denmark  
382 women randomised  
Follow up: 1 year  
**Participants**  
15-44 years  
Variable parity
### Characteristics of included studies (Continued)

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#### Allocation concealment D

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<th>Study</th>
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<th>Study</th>
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<tr>
<td></td>
<td>Description of prior contraceptive method / pregnancy provided</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

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  

<table>
<thead>
<tr>
<th>Allocation concealment</th>
<th>Newton 1979</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Setting: Clinics (4)</td>
<td></td>
</tr>
<tr>
<td>676 women randomised</td>
<td></td>
</tr>
<tr>
<td>Follow up: 1 year</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Various parity</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Progestasert [n=359] vs. inert IUD [n=317]</td>
</tr>
</tbody>
</table>
| **Outcomes**           | Pregnancy  
Continuation  
Reasons for discontinuation  
Menstrual disturbance |
| **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 |
| Allocation concealment | D |

<table>
<thead>
<tr>
<th>Allocation concealment</th>
<th>Pakarinen 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Setting: Finland, Family Planning Clinics</td>
<td></td>
</tr>
<tr>
<td>298 women randomised</td>
<td></td>
</tr>
<tr>
<td>Follow up: 1 year</td>
<td></td>
</tr>
</tbody>
</table>
| **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 |
| Allocation concealment | B |

<table>
<thead>
<tr>
<th>Allocation concealment</th>
<th>Piazarro 1979</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Setting: Chile, Family Planning Clinics</td>
<td></td>
</tr>
<tr>
<td>295 women randomised</td>
<td></td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17-40 years</td>
<td>Progesterone T IUS [n=146] vs. Cu 7 IUD [n=149]</td>
<td>Pregnancy, Continuation, Reasons for discontinuation, Menstrual disturbance</td>
<td>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</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

| 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 |  

### Allocation concealment  
A

<table>
<thead>
<tr>
<th>Study</th>
<th>WHO 1983</th>
</tr>
</thead>
</table>
| 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 |
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 |
| Allocation concealment | A |

<table>
<thead>
<tr>
<th>Study</th>
<th>WHO 1987</th>
</tr>
</thead>
</table>
| Methods | Multinational (Thailand, China, India, Vietnam, Cuba, Russia, Yugoslavia 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  
Active follow up conducted |
| Allocation concealment | A |
### Study 1: Wang 1992

<table>
<thead>
<tr>
<th>Setting: China, Family Planning Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 women randomised</td>
</tr>
<tr>
<td>Follow up: 3 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40 years</td>
</tr>
<tr>
<td>Parous</td>
</tr>
<tr>
<td>Not breast feeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG-20 IUS [n=100] vs. Norplant-2 [n=100]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Continuation</td>
</tr>
<tr>
<td>Reasons for discontinuation</td>
</tr>
<tr>
<td>Menstrual disturbance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality assessment:</td>
</tr>
<tr>
<td>Randomisation technique: Sequential identification number</td>
</tr>
<tr>
<td>Allocation concealment technique:</td>
</tr>
<tr>
<td>Sealed envelopes</td>
</tr>
<tr>
<td>Description of prior contraceptive method / pregnancy provided</td>
</tr>
<tr>
<td>Measurement: Groups treated identically</td>
</tr>
<tr>
<td>Method of analysis: Life tables (single decrement rates)</td>
</tr>
<tr>
<td>User / method failure reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
</tbody>
</table>

### Study 2: El Mahgoub 1982

<table>
<thead>
<tr>
<th>Setting: Egypt, Family Planning Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 women randomised</td>
</tr>
<tr>
<td>Follow up: 3 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-40 years</td>
</tr>
<tr>
<td>Parous</td>
</tr>
<tr>
<td>Hormonal contraceptive users at enrollment and immediate post partum women excluded</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG-10 IUS and Norgestrel T (various doses) IUSs vs. CuT 200 IUD [n=100 in each group]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Continuation</td>
</tr>
<tr>
<td>Reasons for discontinuation</td>
</tr>
<tr>
<td>Menstrual disturbance and blood loss</td>
</tr>
<tr>
<td>Endometrial and cervical cell changes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality assessment:</td>
</tr>
<tr>
<td>Randomisation technique: No mention</td>
</tr>
<tr>
<td>Allocation concealment technique: No mention</td>
</tr>
<tr>
<td>Description of prior contraceptive method / pregnancy provided</td>
</tr>
<tr>
<td>Method of analysis: Life tables (method not stated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
</tr>
</tbody>
</table>

### Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaz 1993</td>
<td>Intervention: LNG-IUS vs. CuT 380Ag IUD</td>
</tr>
<tr>
<td></td>
<td>Primary outcomes: Pregnancy, continuation and reasons for discontinuation</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies (Continued)

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 1997
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)

Nilsson 1986
Intervention: d-norgestrel releasing IUS vs. Nova-T 200 IUD
Primary outcomes: Menstrual blood loss
Reported outcomes not relevant to review

Pedron Neuho 1992
Intervention: Various IUSs and IUDs (11)
Primary outcomes: Menstrual blood loss
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

Characteristics of ongoing studies

Study WHO 1997

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 1997</td>
<td>International multicentre (20)</td>
<td>LNG-20 IUS (n=1693) vs. CuT 380A (N=1691)</td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3384 women randomised</td>
<td></td>
<td>Continuation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reasons for discontinuation</td>
<td></td>
</tr>
</tbody>
</table>

Starting date
Contact information
Notes

GRAPHS

Comparison 01. LNG-20 IUS vs. IUDs >250mm2

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy due to method failure</td>
<td>Other data</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
</tr>
<tr>
<td>Continuation of method</td>
<td>Other data</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
</tr>
<tr>
<td>Planned pregnancy after</td>
<td>1</td>
<td>86</td>
<td>Peto Odds Ratio 95% CI</td>
<td>1.25 [0.45, 3.48]</td>
</tr>
<tr>
<td>discontinuation of method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>2</td>
<td>700</td>
<td>Peto Odds Ratio 95% CI</td>
<td>5.29 [3.64, 7.68]</td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>2</td>
<td>700</td>
<td>Peto Odds Ratio 95% CI</td>
<td>0.80 [0.51, 1.26]</td>
</tr>
<tr>
<td>Expulsion</td>
<td></td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
</tr>
</tbody>
</table>

Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Copyright © 2004 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
### Comparison 02. LNG-20 IUS vs. IUD<=250mm2

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy due to method failure</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Continuation of method</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Planned pregnancy after discontinuation of method</td>
<td>Other data</td>
<td></td>
<td>Peto Odds Ratio 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Headaches</td>
<td>1</td>
<td>1051</td>
<td>Peto Odds Ratio 95% CI</td>
<td>1.62 [0.53, 4.92]</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>1</td>
<td>1051</td>
<td>Peto Odds Ratio 95% CI</td>
<td>1.45 [0.35, 6.07]</td>
</tr>
<tr>
<td>Acne</td>
<td>1</td>
<td>1051</td>
<td>Peto Odds Ratio 95% CI</td>
<td>3.01 [0.95, 9.51]</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1051</td>
<td>Peto Odds Ratio 95% CI</td>
<td>4.18 [0.20, 86.14]</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Expulsion</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Hormonal reasons for discontinuation</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Menstrual reasons for discontinuation: all</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Menstrual reasons for discontinuation: bleeding &amp; pain</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Menstrual reasons for discontinuation: amenorrhoea</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Discontinuation because planning pregnancy</td>
<td>Other data</td>
<td></td>
<td></td>
<td>No numeric data</td>
</tr>
</tbody>
</table>
Comparison 03. LNG-20 IUS vs. Norplant-2

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation of method</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expulsion</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporting</td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligomenorrhoea</td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison 04. Progestasert vs. IUDs <=250mm2

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation of method</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expulsion</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual reasons for</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>discontinuation: bleeding &amp; pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison 05. Progestasert vs. non-medicated IUD

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation of method</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expulsion</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual reasons for</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>discontinuation: all</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation because planning pregnancy</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation for personal reasons</td>
<td>Other data</td>
<td>No numeric data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COVER SHEET**

**Title**
Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

**Authors**

**Contribution of author(s)**
Rebecca French: Reviewer
Frances Cowan: Reviewer and supervisor
Comparison 05. Pregnancy due to method failure

**GRAPHS AND OTHER TABLES**

**At 1 year**

**Study**
- Baveja 1989
- Sivin 1994

**Single decrement life table probabilities (SE) =**
- 0.0 (0.4) vs. 0.8 (0.4)
- 0.3 (0.2) vs. 0.3 (0.2)

**At 2 years**

**Study**
- Baveja 1989
- Sivin 1994

**Single decrement life table probabilities (SE) =**
- 0.0 (0.5) vs. 1.0 (0.5)

**At 3 years**

**Study**
- Baveja 1989

**Single decrement life table probabilities (SE) =**
- 0.0 (0.5) vs. 1.0 (0.5)

**At 5 years**

**Study**
- Sivin 1994

**Single decrement life table probabilities (SE) =**
- 1.1 (0.5) vs. 1.4 (0.4)

Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

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**Comparison 05. Continuation of method**

**At 1 year**

- **Study**
  - 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**

- **Study**
  - Baveja 1989: 257/8321 women months vs. 276/8333
  - 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**

- **Study**
  - Baveja 1989: 150/10589 women months vs. 170/10869 women months

**At 5 years**

- **Study**
  - Sivin 1994: 298/34944 women months vs. 335/38268 women months
  - Life table probabilities (SE) = 33 (1.5) vs. 40.6 (1.6)

**Comparison 05. Planned pregnancy after discontinuation of method**

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 01 LNG-20 IUS vs. IUDs >250mm2

Outcome: 03 Planned pregnancy after discontinuation of method

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 At 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivin 1994</td>
<td>39/49</td>
<td>28/37</td>
<td></td>
<td>100.0</td>
<td>1.25 [0.45, 3.48]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>37</td>
<td></td>
<td>100.0</td>
<td>1.25 [0.45, 3.48]</td>
</tr>
</tbody>
</table>

Total events: 39 (Treatment), 28 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=0.43 p=0.7
### Comparison 05. Amenorrhoea

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 01 LNG-20 IUS vs. IUDs >250mm2

Outcome: 04 Amenorrhoea

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI (%)</th>
<th>Weight Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 At 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivin 1994</td>
<td>41/215</td>
<td>20/226</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>215</td>
<td>226</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 41 (Treatment), 20 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=3.10 p=0.002

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI (%)</th>
<th>Weight Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 At 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivin 1994</td>
<td>75/120</td>
<td>12/139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>120</td>
<td>139</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 75 (Treatment), 12 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=9.13 p<0.00001

### Comparison 05. Prolonged bleeding

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 01 LNG-20 IUS vs. IUDs >250mm2

Outcome: 05 Prolonged bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI (%)</th>
<th>Weight Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 At 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivin 1994</td>
<td>42/215</td>
<td>49/226</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>215</td>
<td>226</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 42 (Treatment), 49 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.56 p=0.6

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI (%)</th>
<th>Weight Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 At 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivin 1994</td>
<td>0/120</td>
<td>4/139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>120</td>
<td>139</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (Treatment), 4 (Control)

(Continued ...)

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Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

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Comparison 05. Expulsion

At 1 year
Study
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
Study
Baveja 1989
Single decrement life table probabilities (SE) = 9.2 (1.4) vs. 7.1 (1.3)

At 3 years
Study
Baveja 1989
Single decrement life table probabilities (SE) = 10.6 (1.6) vs. 7.6 (1.4)

At 5 years
Study
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)

Comparison 05. Embedded

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

Comparison 05. Ectopic pregnancy

Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Copyright © 2004 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
At 1 year
Study
Sivin 1994 0/7680 women months vs. 0/7740 women months

At 2 years
Study
Sivin 1994 0/19644 women months vs. 0/20436 women months

At 5 years
Study
Sivin 1994 0/34944 women months vs. 2/38268 women months

**Comparison 05. Pelvic inflammatory disease**

At 1 year
Study
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)

**Comparison 05. Hormonal reasons for discontinuation**

At 1 year
Study
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
Study
Baveja 1989 10/10589 women months vs. 6/10869 women months

At 5 years
Study
Sivin 1994 31/34944 women months vs. 8/38268 women months

**Comparison 05. Menstrual reasons for discontinuation: all**

At 1 year
Study
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 decrement life table probabilities (SE) = 11.1 (7.5) vs. 1.6 (1.1)
At 2 years Study
Baveja 1989 Single decrement life table probabilities (SE) = 21.9 (2.1) vs. 10.8 (1.3)

At 3 years Study
Baveja 1989 Single decrement life table probabilities (SE) = 27.9 (2.3) vs. 13.4 (1.8)

At 5 years Study
Sivin 1994 252/34944 women months vs. 186/38268 women months

Comparison 05. Menstrual reasons for discontinuation: bleeding & pain

At 5 years Study
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)

Comparison 05. Menstrual reasons for discontinuation: pain

At 1 year Study
Sivin 1994 Single decrement life table probabilities (SE) = 2.5 (0.6) vs. 3.4 (0.8)

At 5 years Study
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)

Comparison 05. Menstrual reasons for discontinuation: amenorrhoea

At 1 year Study
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 Study
Sivin 1994 134/34944 women months vs. 3/38268 women months
Comparison 05. Discontinuation due to adverse event

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

Comparison 05. Discontinuation because planning pregnancy

At 1 year
Study
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
Study
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)

Comparison 05. Personal reasons for discontinuation

At 1 year
Study
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
Study
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)

Comparison 05. Pregnancy due to method failure

At 1 year
Study
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
Study
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
Study
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
Study
Andersson 1994 5/67380 women months vs. 35/33312 women months
Luukkainen 1986 1/5495 women months vs. 7/5176 women months

Comparison 05. Continuation of method

At 1 year
Study
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
Study
Baveja 1989 257/8321 women months vs. 617/18819 women months

At 3 years
Study
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
Study
Andersson 1994 67/5495 women months vs. 53/5176 women months
Luukkainen 1986 736/67380 women months vs. 315/33312 women months
**Comparison 05. Planned pregnancy after discontinuation of method**

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 02 LNG-20 IUS vs. IUD<=250mm2

Outcome: 03 Planned pregnancy after discontinuation of method

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 At 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 1994</td>
<td>96/138</td>
<td>46/71</td>
<td>1.24 [ 0.67, 2.29 ]</td>
<td></td>
</tr>
<tr>
<td>02 At 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 1994</td>
<td>104/138</td>
<td>50/71</td>
<td>1.29 [ 0.67, 2.46 ]</td>
<td></td>
</tr>
</tbody>
</table>

**Comparison 05. Headaches**

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 02 LNG-20 IUS vs. IUD<=250mm2

Outcome: 04 Headaches

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 At 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 1994</td>
<td>12/736</td>
<td>3/315</td>
<td>100.0</td>
<td>100.0</td>
<td>1.62 [ 0.53, 4.92 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>736</td>
<td>315</td>
<td></td>
<td>100.0</td>
<td>1.62 [ 0.53, 4.92 ]</td>
</tr>
<tr>
<td>Total events: 12 (Treatment), 3 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.85  p=0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Comparison 05. Breast tenderness

**Review:** Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

**Comparison:** 02 LNG-20 IUS vs. IUD<=250mm2

**Outcome:** 05 Breast tenderness

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 At 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 1994</td>
<td>7/736</td>
<td>2/315</td>
<td>100.0</td>
<td>1.45 [0.35, 6.07]</td>
<td>100.0</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>736</td>
<td>315</td>
<td>100.0</td>
<td>1.45 [0.35, 6.07]</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Total events: 7 (Treatment), 2 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=0.51 p=0.6

### Comparison 05. Acne

**Review:** Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

**Comparison:** 02 LNG-20 IUS vs. IUD<=250mm2

**Outcome:** 06 Acne

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 At 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 1994</td>
<td>13/736</td>
<td>1/315</td>
<td>100.0</td>
<td>3.01 [0.95, 9.51]</td>
<td>100.0</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>736</td>
<td>315</td>
<td>100.0</td>
<td>3.01 [0.95, 9.51]</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Total events: 13 (Treatment), 1 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=1.88 p=0.06
Comparison 05. Nausea

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 02 LNG-20 IUS vs. IUD<=250mm2

Outcome: 07 Nausea

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI (%)</th>
<th>Weight</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersson 1994</td>
<td>2/736</td>
<td>0/315</td>
<td>4.18 [0.20, 86.13]</td>
<td>100.0</td>
<td>4.18 [0.20, 86.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>736</td>
<td>315</td>
<td>100.0</td>
<td>4.18</td>
<td>4.18 [0.20, 86.13]</td>
</tr>
<tr>
<td>Total events: 2 (Treatment), 0 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.93 p=0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison 05. Ovarian cysts

At 1 year

Study

Andersson 1994 12/18664 women months vs. 4/9326 women months

Comparison 05. Expulsion

At 1 year

Study

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

Study

Baveja 1989 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 months

At 5 years

Study

Luukkainen 1986 2/5495 women months vs. 7/5176 women months

Comparison 05. Ectopic pregnancy
At 1 year
Study
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
Study
Andersson 1994 1/46200 women months vs. 5/23568 women months

At 5 years
Study
Andersson 1994 1/67380 women months vs. 7/33312 women months

Comparison 05. Pelvic inflammatory disease

At 1 year
Study
Luukkainen 1986 0/1654 women months vs. 0/1708 women months

At 2 years
Study
Luukkainen 1986 0/3083 women months vs. 3/2989 women months

Comparison 05. Hormonal reasons for discontinuation

At 1 year
Study
Andersson 1994 54/18664 women months vs. 5/9326 women months

At 3 years
Study
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
Study
Luukkainen 1986 11/5495 women months vs. 2/5176 women months
Comparison 05. Menstrual reasons for discontinuation: all

At 1 year
Study
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
Study
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
Study
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 years
Study
Luukkainen 1986  26/5495 women months vs. 21/5176 women months

Comparison 05. Menstrual reasons for discontinuation: bleeding & pain

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

Comparison 05. Menstrual reasons for discontinuation: amenorrhoea

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

Comparison 05. Discontinuation due to adverse event

At 1 year
Study
Andersson 1994  42/18664 women months vs. 21/9326 women months

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

Comparison 05. Discontinuation because planning pregnancy

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

Comparison 05. Discontinuation for personal reasons

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

Comparison 05. Pregnancy

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

At 2 years
Study
Wang 1992
1/2171 women months vs. 0/2218 women months

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

Comparison 05. Continuation of method

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

Comparison 05. Expulsion
Comparison 05. Breast cancer

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

Comparison 05. Ovarian cysts

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

Comparison 05. Spotting

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy
Comparison: 03 LNG-20 IUS vs. Norplant-2
Outcome: 06 Spotting

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
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<tbody>
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<td>Wang 1992</td>
<td>11/90 36/96</td>
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### Comparison 05. Oligomenorrhoea

**Review:** Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

**Comparison:** 03 LNG-20 IUS vs. Norplant-2

**Outcome:** 07 Oligomenorrhoea

<table>
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<td>95% CI</td>
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<td>Wang 1992</td>
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<td>21/96</td>
<td>1.77 [0.93, 3.37]</td>
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<tr>
<td>Wang 1992</td>
<td>8/65</td>
<td>8/69</td>
<td>1.07 [0.38, 3.03]</td>
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Comparison 05. Amenorrhoea

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 03 LNG-20 IUS vs. Norplant-2

Outcome: 08 Amenorrhoea

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<td>03 At 3 years</td>
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<td>Wang 1992</td>
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<td>2/69</td>
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<td>69</td>
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<td>Test for overall effect z=1.24 p=0.2</td>
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Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy
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Comparison 05. Prolonged bleeding

Review: Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy

Comparison: 03 LNG-20 IUS vs. Norplant-2

Outcome: 09 Prolonged bleeding

<table>
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<tr>
<th>Study</th>
<th>Treatment</th>
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<td>95% CI (%)</td>
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<td>02 At 2 years</td>
<td>Wang 1992</td>
<td>4/79</td>
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Comparison 05. Pregnancy

At 1 year

Study

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

Comparison 05. Continuation of method

At 1 year

Study

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

Comparison 05. Expulsion

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

Comparison 05. Ectopic pregnancy

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

Comparison 05. Menstrual reasons for discontinuation: bleeding & pain

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

Comparison 05. Pregnancy

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

Comparison 05. Continuation of method

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

Comparison 05. Expulsion

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

Comparison 05. Ectopic pregnancy
At 1 year  
Study  
Newton 1979 0/3389 women months vs. 1/2953 women months

**Comparison 05. Menstrual reasons for discontinuation: all**

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

**Comparison 05. Discontinuation because planning pregnancy**

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

**Comparison 05. Discontinuation for personal reasons**

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