National Essential Medicine List Medication Review Process
Primary Healthcare
Component: Family planning

Date of review: 11 April 2013

Medication name: Levonorgestrel-releasing intrauterine system (LNG-IUS)

Indication: Long-acting reversible contraception

Introduction: [1 2 3]

The levonorgestrel intrauterine system (LNG-IUS) consists of a 32mm plastic T-shaped frame with a reservoir of 52mg of levonorgestrel around the vertical stem. Levonorgestrel is released into the uterine cavity through a rate-limiting membrane at a rate of 20mcg/day, declining to about 10mcg per day after 5 years. The LNG-IUS is registered for up to 5 years of use. The contraceptive effects of levonorgestrel include thickening of the cervical mucus, inhibition of sperm motility and function and suppression of endometrial growth. Ovulation is suppressed in some women.

The aim of this review is to evaluate the effectiveness and safety of the LNG-IUS for consideration for inclusion on the National Essential Medicines List as an additional long-acting reversible contraceptive method to the copper intrauterine contraceptive device (IUCD). The primary effectiveness outcome measure is defined as the rate of pregnancy. There is evidence supporting higher effectiveness with IUCDs having larger copper surface areas. This review will therefore be limited to comparative studies of copper IUCDs with a surface area $\geq$ 375 mm^2.

Search strategy and selection of studies:

An electronic literature survey using the following terminology was performed (database: PUBMED):

("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND ("copper"[MeSH Terms] OR "copper"[All Fields]) AND intrauterine[All Fields] AND ("contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang])

This returned 40 studies; 31 studies were excluded for one or more of the following reasons:

- If not randomized controlled studies;
- If the LNG-IUS was compared with a copper IUCD with a surface area < 375mm^2;
- If the reported clinical outcomes were not relevant to aim of the review;
- If the LNG-IUS was compared with a copper IUCD with a surface area < 375mm^2 but outcomes for both groups were not reported;
- If the LNG-IUS release rate was greater than 20mcg/day and;
- If the LNG-IUS was compared with subdermal implants.

A POPLINE search was conducted using various filter key words including: IUD, IUD hormone releasing, levonorgestrel, contraception, contraceptive effectiveness, contraceptive safety, IUD copper releasing and comparative studies and English. The search identified did not identify any additional randomized controlled trials eligible for inclusion in the review.

A search of The Cochrane Database of Systematic Reviews identified 1 relevant review (updated 2009). The Cochrane review compared the efficacy, tolerability and acceptability of intrauterine systems *versus* other reversible contraceptive methods which included a comparison of LNG-IUS with the copper IUCD with a surface area > 250mm^2.

A National Institute for Health and Clinical Excellence (NICE) guideline (2005) on long-acting reversible contraception and an earlier Health Technology Assessment (HTA) review of subdermal implants and intrauterine systems *versus* other reversible contraceptive methods (conducted in 2000) were identified.

The systematic reviews and NICE guideline identified 1 additional randomized controlled trial not identified from the literature survey but considered to be eligible for inclusion in the review.

Evidence synthesis and quality:

Effectiveness

Pregnancy rate

The Cochrane review found no significant difference in pregnancy rates (no. of events/total number of women months) at 1, 2, 3 (RR 0.11; 95% CI 0.01 - 2.12) and 5 years (RR 0.66; 95% CI 0.25 - 1.75) when comparing levonorgestrel intrauterine system

releasing 20mcg/day (LNG-20 IUS) with the copper IUCD with a surface area > 250mm^2. [4] The reviewers acknowledged the paucity of evidence supporting this finding *i.e.* data could only be extracted from 2 randomized controlled trials (these studies are presented in table 1; references 6 and 8). The earlier Health Technology Assessment (HTA) reported the same result.[5]

Table 1: Summary of pregnancy rates for randomized studies comparing LNG-20 IUS *vs*. copper IUCD with a surface area > 250mm^2

Study reference	Intervention/s (no. of patients)	Study follow-up (in years)	Description of participants	Number of pregnancies per treatment group/relative risk of pregnancy	Comments
6	LNG-20 IUS (475) Cu T380 Ag (434) Cu T200B (500) Cu T200C (496)	3	18-40 years Proven fertility History of regular menstrual pattern	0/475 4/434 RR = 0 NNT = 109	Method of randomization and allocation concealment explained, no blinding, analysis not intention to treat (ITT).
7	LNG-20 IUS (70) Cu T380 (70)	1	20-40 years Parous No contraindications to copper, contraceptive steroids or IUCD use	0/66 1/62 RR = 0 NNT = 62	Method of randomization unknown, single blinded, method of allocation concealment not known, analysis not ITT.
8	LNG-20 IUS (34 944) Cu T380 Ag (38 268)	5	18-38 years Parous No contraindications to copper, contraceptive steroids or IUCD use	6/34 944 10/36 268 RR 0.62; 95% CI 0.23 - 1.71, not significant ARR = 0.01% NNT = 9613	Method of randomization and allocation concealment explained, singled blinded, analysis not ITT.

The gross cumulative pregnancy rate at 5 years is reported to be 0.5 – 1.1%.[9]

Other outcomes

Expulsion rate

The HTA and Cochrane reviews reported a significant expulsion rate once follow-up had reached 5 years; rate ratio 1.53; 95% CI, 1.13 to 2.07 on the basis of a single study (refer table 1; reference 8). The study by Kapur and colleagues did not find a significant difference in the expulsion rate for LNG-20 IUS (1.5% or 1/66) and CuT 380 users (3.2% or 2/62), RR 0.48; 95% CI 0.044 - 5.140 (p = 0.67).

Continuation rate and reasons for discontinuation

The HTA and Cochrane reviews found no significant difference in the continuation rate at 1 (RR 0.97; 95% CI 0.90 - 1.06), 2 (RR 0.94; 95% CI 0.86 - 1.04), 3 (RR 0.89; 95% CI 0.71 - 1.11) and 5 years (RR 0.9; 95% CI 0.78 - 1.06) on the basis of 2 studies (refer to table 1, references 6 and 8). Similarly Kapur and colleagues did not find a significant difference in the continuation rate for the LNG-IUS (1.5% or 57/66) and CuT 380 group (3.2% or 49/62), RR 1.05; 95% CI 0.791 - 1.393.

Reasons for discontinuation

1. Hormonal adverse effects:

On the basis of 1 study (refer to table 1; reference 8), both the HTA and Cochrane reviews concluded that the LNG-20 IUS group were significantly more likely to discontinue the method because of hormonal side-effects when compared with women using the copper IUCD with a surface area > 250mm^2 once follow-up had reached 5 years; rate ratio 4.24; 95% CI, 1.99 - 9.05.

2. Menstrual disturbance:

Using data extracted from 2 studies (refer to table 1; references 6 and 8), both the Cochrane and HTA reviews reported that women using the LNG-20 IUS were significantly more likely to discontinue the method because of menstrual disturbance than women using the copper IUCD with a surface area > 250 mm^2 after year 1 (rate ratio 1.48; 95% CI, 1.02 - 2.14) and year 5 of follow-up (1.48; 95% CI, 1.23 - 1.79). Women were found to be significantly more likely to discontinue the LNG-20 IUS due to no menstrual bleeding after 1 year (rate ratio, 65.1; 95% CI, 4.01 - 109.84) and year 5 (48.92; 95% CI, 16.93 - 141.36) of follow-up. The rate of discontinuation as a result of bleeding and pain, was found to be significant at year 5; 0.71; 95% CI, 0.56 - 0.89.

Kapur *et al*. found that amenorrhoea was the main reason for termination in the LNG-20 IUS group (5% or 3 of 66) with no reports of amenorrhoea in the comparative copper IUCD group.

No significant differences were noted between the LNG-20 IUS and copper IUCD > 250 mm^2 comparative groups for other reasons for discontinuation.

Embedded device

The HTA and Cochrane reviews identified 1 study (refer to table 1; reference 8) that reported data on embedded device. The reviews concluded that there was no significance in the occurrence of embedded device between users of the LNG-20 IUS and CuT 380Ag IUCD after 5 years of follow-up, 7.00; 95% CI, 0.36 - 135.52).

Rate of planned pregnancy after removal

The HTA and Cochrane reported no significant difference in the relative risk for planned pregnancy after removal of the LNG-20 IUS compared to those who used the copper IUCD > 250 mm^2 on the basis of one study (refer to table 1; reference 8); RR 1.05; 95% CI, 0.83 - 1.33).

Safety considerations

Menstrual disturbances: no menstrual bleeding and prolonged bleeding

Using the data extracted from one study (refer to table 1; reference 8), the Cochrane review reported a significant difference in the risk of no menstrual bleeding between women using the LNG-20 IUS and CuT 380Ag IUCD at 3 months (RR 2.35; 95% CI 1.37 - 4.04) and 3 years follow-up (RR 11.08; 95% CI 6.61 - 18.57). The study by Kapur and colleagues found a statistically significant difference in the decrease in menstrual flow between the LNG-20 IUS (45/66) and CuT 380 (1/62) groups (RR 25.54; 95% CI 3.607-180.848). It was reported that 14 of the 45 women that experienced a decrease in menstrual flow had amenorrhoea at the end of year one.

In terms of prolonged bleeding, there was no significant difference noted between the treatment groups at both 3 months (RR 0.88; 95% CI 0.55 -1.39) and 3 years follow-up (RR 0.15; 95% CI 0.02 - 1.10).

Other adverse effects: ectopic pregnancy, pelvic inflammatory disease

The HTA and Cochrane reviews found no significant difference in the occurrence of ectopic pregnancy and pelvic inflammatory disease in women using the LNG-20 IUS compared with those using the copper IUCD > 250mm^2.

Alternative agents:

- 380 mm^2 copper intrauterine contraceptive device.

Summary:

The evidence presented suggests that LNG-20 IUS is an effective and safe long-term reversible contraceptive method. The effectiveness and safety profile is comparable to the copper IUCD > 375mm^2. Amenorrhoea was identified as the most common reason for discontinuation of LNG-20 IUS. It is important to note that the basis of key findings is 2 randomized controlled trials, both of which have methodological shortcomings.

Recommendation:

Given the comparable effectiveness and safety profile of LNG-20 IUS and the copper IUCD > 375mm^2, the committee did not support the inclusion of LNG-IUS on the Primary Health Care Standard Treatment Guidelines and Essential Medicines List on the basis of the greater cost of LNG-20 IUS.

References:

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