National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Gynaecology

Date: 12 June 2015

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

Indication: Abnormal uterine bleeding/menorrhagia/heavy menstrual bleeding

Introduction: [1]

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 alternative to conventional medication treatment (CMT) (i.e. medroxyprogesterone, tranaxamic acid, combined oral contraceptives, and non-steroidal antiinflammatories), for heavy menstrual bleeding (HMB).

The primary effectiveness outcome measure is defined as menstrual blood loss, determined directly with the alkaline hematin method, or indirectly with the pictorial bleeding assessment chart (PBAC).

Secondary effectiveness outcomes are patient satisfaction, quality of life scores, reasons for discontinuation, and safety.

Search strategy:

An electronic literature search of the PubMed database was undertaken using:
((levonorgestrel-releasing[All Fields] AND intrauterine[All Fields] AND system[All Fields]) OR (("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND intrauterine[All Fields] AND system[All Fields]) OR levonorgestrel-IUS[All Fields] OR LNG-IUS[All Fields] OR (("progestins"[Pharmacological Action] OR "progestins"[MeSH Terms] OR "progestins"[All Fields] OR "progestogen"[All Fields]) AND releasing[All Fields] AND intrauterine[All Fields] AND systems[All Fields]) OR ("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields] OR "mirena"[All Fields])) AND (("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) OR ("ibuprofen"[MeSH Terms] OR "ibuprofen"[All Fields]) OR ("medroxyprogesterone"[MeSH Terms] OR "medroxyprogesterone"[All Fields]) OR ("contraceptives, oral"[Pharmacological Action] OR

"contraceptives, oral"[MeSH Terms] OR ("contraceptives"[All Fields] AND "oral"[All Fields]) OR "oral contraceptives"[All Fields] OR ("oral"[All Fields] AND "contraceptives"[All Fields])) OR ("progestins"[Pharmacological Action] OR "progestins"[MeSH Terms] OR "progestins"[All Fields] OR "progestin"[All Fields]) OR (medical[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR (medical[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]))) AND (("menorrhagia"[MeSH Terms] OR "menorrhagia"[All Fields]) OR menometrorrhagia[All Fields] OR ("metrorrhagia"[MeSH Terms] OR "metrorrhagia"[All Fields] OR ("dysfunctional"[All Fields] AND "uterine"[All Fields] AND "bleeding"[All Fields]) OR "dysfunctional uterine bleeding"[All Fields]) OR ("menorrhagia"[MeSH Terms] OR "menorrhagia"[All Fields] OR ("heavy"[All Fields] AND "menstrual"[All Fields] AND "bleeding"[All Fields]) OR "heavy menstrual bleeding"[All Fields]) OR (excessive[All Fields] AND ("uterine hemorrhage"[MeSH Terms] OR ("uterine"[All Fields] AND "hemorrhage"[All Fields]) OR "uterine hemorrhage"[All Fields] OR ("uterine"[All Fields] AND "bleeding"[All Fields]) OR "uterine bleeding"[All Fields])) OR (abnormal[All Fields] AND ("uterine hemorrhage"[MeSH Terms] OR ("uterine"[All Fields] AND "hemorrhage"[All Fields]) OR "uterine hemorrhage"[All Fields] OR ("uterine"[All Fields] AND "bleeding"[All Fields]) OR "uterine bleeding"[All Fields]))) NOT (ablation[All Fields] OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields]) OR ("copper"[MeSH Terms] OR "copper"[All Fields]) OR ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "costs"[All Fields]) OR ("economics"[Subheading] OR "economics"[All Fields] OR "economics"[MeSH Terms]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields]) OR ("hysterectomy"[MeSH Terms] OR "hysterectomy"[All Fields])) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp] OR Comparative Study[ptyp]) AND "humans"[MeSH Terms] AND English[lang]).

A second search was conducted in Google Scholar using the following terms: levonorgestrel, intrauterine, medroxyprogesterone, abnormal uterine bleeding". Filters for English were used.

A review of the Cochrane Database identified one review (updated 2015) on the use of progesterone or progesterone-releasing intrauterine systems for heavy menstrual bleeding.[3] However, as the login website appears to be down for the past week, only the abstract was available for review.

A review of the National Institute for Health and Care Excellence (NICE) revealed a clinical guideline for the treatment of HMB (2007).[6]

Selection of studies:

This resulted in 81 studies. Reasons for rejecting studies included:

- The study did not compare CMT to LNG-IUS
- Satisfaction surveys
- Review articles
- Economic analysis of LNG-IUS
- Studies using surrogate measures for LNG-IUS effectiveness.

Studies included were:

- Meta-analysis of 1170 patients (LNG-IUS: n=562; CMT: n=608). Studies included were of low to moderate quality of evidence.[2]
- Cochrane meta-analysis of 2082 patients comparing LNG-IUS to placebo, oral medical treatment, endometrial destruction techniques and hysterectomy.[3]
- Multicentre randomized control trial comparing LNG-IUS (n=285) to CMT (n=286). Moderate quality evidence.[4]
- Randomized controlled trial comparing LNG-IUS (n=82) to oral medroxyprogesterone (n=83). Moderate quality evidence.[5]
- NICE guideline on Heavy Menstrual Bleeding, using data from two systematic reviews.[6]

Evidence synthesis:

Effectiveness

Menstrual blood loss

The meta-analysis by Qiu *et al* showed greater reduction of menstrual blood loss with LNG-IUS compared to CMT (weighted mead difference 136; 95% confidence interval 74.43-197.57; P<0.001). It was noted that substantial heterogeneity was observed across studies (Q statistic =33.80; P<0.001, I^2=94%).[2]

The Cochrane analysis showed LNG-IUS was more effective at reducing HMB than CMT using the following methods[3]:

- Alkaline haematin method: Mean Difference 66.91mL, 95% CI 42.61 to 91.20, I^2=81%
- PBAC scores: MD 55.05, 95%CI 27.83 to 82.28, I^2=79%.

The RCT by Kauntz *et al* showed a significantly greater absolute reduction in menstrual blood loss (from baseline) with LNG-IUS than with medroxyprogesterone at the end of 6 months (-128.8mL compared with -17.8mL; P<0.001).[5]

The evidence statement from NICE showed a clinically relevant reduction in menstrual blood loss of between 71% to 96% in women with HMB. Benefit of treatment was not seen until after 6 months.[6]

Other outcome measures

Rate of satisfaction

The meta-analysis by Qui *et al* reported that satisfaction was higher in the LNG-IUS group compared to CMT (OR 5.19; 95% CI 2.73-9.86, P<0.01). Significant heterogeneity was observed (Q statistic=28.33; P<0.001; I^2=72%), which through sensitivity analysis was demonstrated to be the effect of all the outcomes of the study, not of any single study.[2]

The Cochrane study did not have sufficient evidence to reach conclusions on patient satisfaction.[3]

The RCT by Gupta *et al* showed significant improvement in the Menorrhagia Multi-Attribute Scale (MMAS) for both groups at 6 months and 1-year treatment, compared with baseline. Score

improvement was significantly greater in the LNG-UIS group than in the conventional medical treatment group (mean difference in score over 2 years, 13.4 points, 95% CI 9.9 – 16.9, P<0.001).[4]

The NICE guidelines did not mention rate of satisfaction with LNG-IUS.[6]

Discontinuing treatment

The meta-analysis by Qui *et al* showed fewer patients in the LNG-IUS discontinuing treatment than in the CMT (14.6% vs 28.9%; OR 0.39; 95% CI 0.20-0.74; P=0.004). This still held true after a study that contributed significant heterogeneity (26 out of 28 patients stopped mefenamic acid at 12 months) was removed (OR 0.45; 95% CI 0.31-0.66; P<0.01).[2] The reasons for discontinuation were not available for analysis.[2]

The Cochrane analysis showed a greater number of patients continuing LNG-IUS at 2 years compared with CMT.[3]

The RCT by Gupta *et al* showed women twice as likely to still be using LNG-IUS as compared to conventional medical treatment at 2 years (64% vs 38%; P<0.001). Reasons for discontinuing LNG-IUS were lack of effectiveness (37%), and irregular or prolonged bleeding (28%). Most common reason for discontinuation in CMT was lack of effectiveness (53%).[4]

The RCT by Kuantz *et al* showed similar discontinuation rates between the LNG-IUS and medroxyprogesterone groups. Reasons for discontinuation of the LNG-IUS included lower abdominal pain, intrauterine system dislocation, menorrhagia, and uterine cramp. Reasons for discontinuation in the medroxyprogesterone group included fluid retention and dizziness.[5]

Treatment failures

One study indicated treatment failures, which was lower for LNG-IUS than CMT (OR 0.25; 95% CI 0.16-0.39).[2]

Safety

The meta-analysis by Qiu *et al* defined serious adverse effects as those resulting in death, disability, or hospitalization. Pooled data from three of the studies showed no statistically significant difference in serious adverse events between LNG-IUS and CMT (OR 0.88; 95% CI 0.59-1.33; P=0.37; I^2=3%).[2]

The Cochrane analysis showed LNG-IUS was associated with more minor adverse effects (pelvic pain, breast tenderness, ovarian cysts) when compared to CMT.[3]

The RCT by Gupta *et al* showed no significant difference between LNG-IUS and CMT in the frequency of serious adverse events (LNG-IUS: n=49; CMT: n=58; P=0.59).[4]

Evidence quality:

The average evidence grade is low to moderate, due to methodological limitations such as low sample sizes and lack of concealment of treatment allocation.

Alternative agents:

- Surgical intervention: hysterectomy.

Summary:
LNG-IUS provides a clinically relevant reduction in menstrual blood loss due to HMB, with greater patient retention at 2 years than with CMT. The major reasons for discontinuing treatment were lower abdominal pain, menorrhagia, and uterine cramp. There is also mention of the greater cost-effectiveness of LNG-IUS as compared to surgical interventions up to 10 years.

Recommendation:
LNG-IUS not be added to the EML for management of heavy menstrual bleed (HMB) at secondary level of care.
Rationale: LNG-IUS was unaffordable and indication creep was a concern.

References

1. National Essential Medicine List Review Process Component: Levonorgestrel-releasing intrauterine system (LNG-IUS), 11 April 2013, for the indication of long-acting reversible contraception.
2. Qiu J, Cheng J, Wang Q, Hua J. Levonorgestrel-releasing intrauterine system versus medical therapy for menorrhagia: a systematic review and meta-analysis. Med Sci Monit, 2014;20:1700-1713
3. Lethaby A, Hussain M, Rishworth JR, Rees MC. Progesterone or progesterone-releasing intrauterine system for heavy menstrual bleeding. Cochrane Database of Systemic Reviews 2015. Issue 4. Art. No.: CD002126.
4. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J. Levonorgestrel Intrauterine System versus Medical Therapy for Menorrhagia. NEJM 2013. 368;2:128-37.
5. Kauntz AM, Bissonnete F, Monteiro I, Lukkari-Lax E, Muysers C, Jensen JT. Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding: A randomized controlled trial. Obstetrics and Gynecology 2010. 116(3):625-632.
6. Heavy menstrual bleeding. National Collaborating Centre for Women's and Children's Health, commissioned by the National Institute for Health and Clinical Excellence. 2007.