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

Medication: Levonorgestrel intrauterine system (LNG-IUS)

Date of Review: May 2015

Indication: Management of pain associated with endometriosis.

Introduction:
Endometriosis is the presence and proliferation of ectopic endometrial tissue (usually within the pelvis)[i] that evokes an estrogen-dependant chronic inflammatory process[ii] [iii] [iv]. This may present as pain (manifesting as dysmenorrhoea, dyspareunia or chronic pelvic pain), cyclical intestinal complaints, fatigue/weariness and infertility as well as atypical dyschezia and haematuria; as reported by observational studies[v] [vi] [vii] [viii] [ix] [x]. The predominant symptom is pain[xi] [xii]; however, endometriosis may be asymptomatic and an incidental finding during surgery[xiii]. Considered to be a progressive and often relapsing disorder and yet endometriosis has been reported to be static and self-limiting[xiv]. In young women, definitive diagnosis is often delayed and guidelines recommend early differential diagnosis of endometriosis[xiii]. The etiology and pathogenesis of endometriosis has not been clearly defined. However, theoretical mechanisms propose an inflammatory estrogen-dependant disorder. This approach guides medical and surgical management of endometriosis. The gold standard for diagnosis is laparoscopy with histological confirmation[xv]; although there is a paucity of evidence supporting a positive laparoscopy without histology confirms the disease[xvi].

Empirical therapy
Guidelines recommend empirical treatment without doing an invasive diagnostic laparoscopy, particularly where there is a high suspicion of endometriosis, in adolescents or in women who decide not to have a laparoscopy. This includes well-tolerated, low-cost, easily accessible, prescribing and administration of combined oral contraceptives (COCs) and progestins. Delaying medical management of pelvic pain to surgically confirm endometriosis is not pragmatic, despite RCT evidence having been mostly derived in surgically confirmed cases.

Combined oral contraceptives
COCs produce a pseudopregnancy, reducing symptoms associated with endometriosis. COCs is supported by limited data: a Cochrane review[xvii] found one underpowered study[xviii] (n=57) that showed that low-dose cyclic combined oral contraceptive (COC) was comparable to a gonadotropin-releasing hormone agonist (GnRHa) in reducing dysmenorrhea, non-menstrual pain or dyspareunia at 6 months follow-up (OR 4.87; 95% CI 0.96 to 24.65). It has been argued that COCs does not always confirm differential diagnosis of endometriosis[xix] [xx] and may delay diagnosis of severe endometriosis later in life, in young women[xxi]. However, this inexpensive well tolerated intervention is firmly entrenched in clinical practice and provides additional contraception.

Progestins
Progestins proposed mechanisms of action include the inhibition of endometriotic tissue growth[xxii], pituitary gonadotropin secretion and ovarian hormone production[xxiii].

Oral and depot progestins
A Cochrane review[xxiv] concluded that limited evidence suggests that progestins are more effective than placebo and comparable to low-dose COCs and GnRHas in reducing pain associated with endometriosis. However,

medroxyprogesterone (oral[xxv] [xxvi]and depot[xxvii] [xxviii] [xxix] preparations) were reported to be poorly tolerated with significantly more adverse effects (i.e. weight gain, irregular uterine bleeding/spotting, and mood changes) compared to low-dose COCs and GnRHas. Disconcertingly, long term uses of high dose oral and depot medroxyprogesterone (DMPA) are associated with bone loss, but are reversed when ovulatory and estrogen function is normalized. However, compared to danazol (an antigonadotrophin with proven efficacy for alleviating endometriotic symptoms) progestins do not adversely affect lipid levels or are associated with androgenic side-effects (i.e. acne, weight gain, hirsutism, oedema, muscle cramps, virility, etc.[xxx]).

Other progestin preparations
The levonorgestrel intrauterine system (LNG-IUS) or the etonogestrel subdermal implant has been reported not to significantly adversely affect bone mineral density or lipid levels. Etonogestrel subdermal implant has been shown to decrease endometriosis-related pain with comparable efficacy and side-effect profile to DMPA[xxxi] [xxxii]. A recent overview of Cochrane reviews suggests that low to moderate quality supports LNG-IUS[xxxiii].

Endometriosis is a common disorder, reported to affect approximately 176 million women of reproductive age worldwide[xxxiv].Thus, quality of life impact and economic burden of this disorder is high. Effective empirical treatment is dependent on available resources, patient preference and prescribers' skills. The objective of this review is to evaluate the role of LNG-IUS as an option for early management of endometriosis.

Objective
The aim of this review is to evaluate the effectiveness and safety of the LNG-IUS for consideration as an alternative to empirical therapy. There is evidence supporting combined oral contraceptives, oral and depot progestins as first line therapy in this clinical setting. This will assist in deciding whether this intervention should be recommended for use in South African public sector secondary level facilities.

Search strategy
Keyword searches were conducted on both titles and abstracts to identify relevant publications using combinations of the keywords "levonorgestrel", registered trade names of the LNG-IUS, "Mirena"®, " endometriosis", "pain" and other variants of pain nomenclature, "intrauterine", "device", "system" and abbreviations "LNG-IUS" or "LNG-IUD" and "IUD" or "IUS".

Selection of studies
Population: The primary population of interest is women with symptoms predictive of endometriosis who have not undergone diagnostic laparoscopy or surgery. Main focus is on relieving symptoms of pain associated with endometriosis and women prescribed LNG-IUS to resolve fertility, rectovaginal endometriosis, endometriomas or other cancers were excluded.
Intervention: The LNG-IUS consists of a 32mm plastic T-shaped frame with a reservoir of 52 mg of levonorgestrel around the vertical stem. Levonorgestrel is released into the uterine cavity through a rate-limiting membrane at a rate of 20 mcg per day, declining to about 10 mcg per day after 5 years.
Comparators: Other medical therapies and surgical intervention.
Outcomes: Primary outcome measure: self reported pain relief for dysmenorrhoea using validated pain scores. Secondary outcome measures: clinical improvement or resolution of endometriosis-related pain; pain recurrence, adverse events.
Timing: Only randomized controlled studies were considered. For studies with multiple follow-up periods, the longest follow-up times were preferentially considered.

Settings: Settings not pre-specified.

Electronic sources
Publications describing RCTs of LNG-IUS for endometriotic pain sourced using a systematic search strategy. The search strategy was performed in accordance with the Cochrane Handbook for Systematic Reviews[xxxv] with slight modification. Articles restricted to English with no set period of publication.

An electronic literature survey using the following terminology performed on the PUBMED database: ("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND (“intrauterine devices"[MeSH Terms] OR ("intrauterine devices"[All Fields]) AND ("pain"[MeSH Terms]) OR "pain"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]), both as exploded MESH headings and free text terms.

Other sources
Relevant Cochrane reviews sourced from the Cochrane database and Guidelines via google scholar reviewed to identify any additional RCTS not retrieved from the literature survey and appraised accordingly for inclusion in this review.

Eligibility criteria and appraisal of studies
Studies identified systematically by reviewing abstracts initially and proceeding to the full text article. RCTs included were of women with endometriosis (where the diagnosis was not confirmed by laparoscopy) that investigated the efficacy of LNG-IUS of symptoms of pain associated with endometriosis. Pain defined as dysmenorrhea, chronic pelvic pain or dyspareunia. Studies of insertion of LNG-IUS post-surgery were included, as the number of RCTs before surgery was very limited. Studies assessing the effect of LNG-IUS on fertility, rectovaginal endometriosis, endometriomas or other cancers were excluded. Assessment of the quality of the RCTs determined by study power, randomization, allocation concealment, inclusion and exclusion criteria, reported basic demographic and clinical data, loss to follow-up of study participants and follow-up duration. The risk of bias assessment of the included RCTs was evaluated, with adaptation, in accordance with the guidance of the Cochrane Handbook for Systematic Reviews[xxxv].

Outcome measures
Primary: study participant - self reported pain relief for dysmenorrhoea using validated pain scores.
Secondary: clinical improvement or resolution of endometriosis-related pain; pain recurrence, adverse events.

Results
PUBMED search returned 12 studies of which 10 studies were excluded for following reasons:

- Indication not relevant to the review: i.e. pain associated with rectovaginal endometriosis, adenomyosis.
- LNG-IUS not compared to a comparator.
- Reported clinical outcomes were not relevant to aim of the review.
- Published results of RCT not available, as yet.

The Cochrane Database of Systematic Reviews was searched and 1 relevant review was identified: Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery (updated 2012). The Cochrane review identified an additional RCT.
The Cochrane review compared postoperative LNG-IUD insertion in women with endometriosis to no postoperative treatment, postoperative insertion of a placebo, or postoperative therapy to improve pain and reduce recurrence of symptoms.

A search on google scholar identified the following guidelines and consensus statement:

- Guideline of the European Society of Human Reproduction and Embryology: Management of women with endometriosis[xxxvi]

- Society of obstetricians and gynaecologists of Canada guidelines for diagnosis and management of endometriosis[xxxvii].
- World Endometriosis Society consensus statements on the current management of endometriosis[xxxviii].

These guidelines were reviewed, and one additional RCT was identified.

Of the four RCTs that met the inclusion criteria, one study (Petta et al., 2005[xxxix]) was excluded because the follow up extended to only 6 months compared to the other three studies, which all included 1 year follow up where the LNG-IUS could be compared at one year follow up.

Evidence synthesis and efficacy information

Data from the 3 RCTs included in the review were extracted, using a standardised format. Efficacy and safety information including adverse drug reactions for two of the studies are summarized below (See Table 1).

Tanmahasamut *et al*.[xl] conducted a double blind RCT (n=55). Final analysis was conducted on 28 patients in the LNG-IUS treatment group (1 lost to follow up), but all 28 data analysed. In the control group 26 cases were analysed (1 protocol violation removed from intention to treat analysis). The primary outcome of interest was change of dysmenorrhea visual analog scale. The LNG-IUS group had greater reduction in dysmenorrhea visual analog scale (-81.0 vs. -50.0mm, p =0.06), and pelvic pain visual analog scale (-48.5 vs. -22.0mm, p=0.038) but comparable reduction in dyspareunia visual analog scale (-15.0 vs. -19.0mm, p=0.831). At 12 months both groups had significant improvement from baseline in dysmenorrhea score (p<0.001 for both groups), and noncyclic pelvic pain score (p<0.001 in treatment vs. p=0.031 in control group). NNT to prevent 1 case of recurrent moderate to severe dysmenorrhea was 3.7 (95% CI 2.1 to 15.6). Secondary outcome assessed was change of pelvic pain and dyspareunia visual analog scale (severity of chronic pelvic pain and dyspareunia), short form-36 score (changes in quality of life), overall satisfaction of the treatment, and adverse effects. The QoL scores improved in the treatment group but not in the control group; and were significantly better than control group for the total score (p=0.014), and physical subscale (p=0.035), but there was no significant difference between the two groups for the mental subscale (p=0.229). The proportion of patients who rated the treatment as very satisfied were lower in the control group vs. treatment group (RR 0.64, 95% CI 0.33 to 1.24; p=0.184). In terms of QoL, the SF 36 improved in the treatment group significantly from baseline for the total score (p=0.044), physical subscale (p=0.015), and mental subscale (p=0.022).

Adverse effects included bloating, acne, oily skin, weight gain, breast tenderness, headache, nauseas and leucorrhea in both groups. 20/27 patients in the treatment arm vs. 18 of 23 patients in the control group complained of 1 or more side effects. Adverse effects likely related to progestin. Bloating was more common in the control group (p=0.021). Melasma (6/27 patients) was noted only in the treatment group. No serious adverse event occurred. However, 4 patients in the treatment arm requested removal of the LNG-IUS after the one year treatment study period because of the bleeding side effect.

Tekin *et al.*[xli] conducted a prospective RCT (n=40); comparing LNG-IUS (n=20) to control, GnRH-a (n=20). The GnRh-a dose was repeated every 4 weeks for 24 weeks. Scores of chronic pelvic pain (CPP) measured using a visual analogue scale (VAS) and total endometriosis severity profile (TESP) used to measure the subtypes of CPP such as dysmenorrhea or dyspareunia. There was no statistically significant difference between the study and control groups. Mean pretreatment VAS pain scores were 42.5 ± 22.2 in the LNG-IUS group and 64.1 ± 25.8 in the GnRH-a group. There was no statistically significant difference between pretreatment levels of the VAS scores between the study and control groups. In the LNG-IUS group, the VAS score did not show a statistically significant difference at the 1-year follow-up, but in the GnRH-a group the VAS score was significantly reduced (p=0.048). The TESP score showed a significant decrease at the first, third, and sixth months of treatment (p<0.001) in both groups. However, at the final follow-up visit, 12 month visit, the score was elevated up to the pretreatment levels (p>0.05) in the LNG-IUS group. The lowest TESP levels were

detected at the 3 month visit. In the GnRH-a group the TESP score was significantly reduced at the 1-year follow-up (p<.001). Patient satisfaction was also higher in the GnRH-a group.
In the LNG-IUS group most common side effects were irregular menstrual bleeding and abdominal pain, weight gain, simple ovarian cysts. In the GnRH-a group vasomotor symptoms and amenorrhea were reported.

Vercellini *et al*.,[xlii] 2003 conducted an open label, RCT comparing LNG-IUD insertion in 20 patients vs. expectant management (n=20) after laparoscopic treatment of endometriotic lesions. Post-operative moderate or severe dysmenorrhea recurrence was reported to be less frequent in the LNG-IUS group (2/20 subjects or 10%) vs. the surgery group (9/20 subjects or 45%; p=0.03; RR=0.22; 95% CI,0.05 to 90). However, results should be interpreted with caution (see evidence quality section). At 12 months overall satisfaction was higher in the treatment group (75%, n=15 vs 50%, n=10).

Evidence Quality
There were concerns regarding bias in the 3 studies that were included in this review.
All 3 studies might have been limited by sample size.
Tanmahasamut *et al* adjusted for protocol violation in their analyses. However, although they allocated patients to treatment and control groups by simple randomization, as the study progressed randomisation might have been compromised as the study might not have truly been a double blind study as patients (92%, n=25/27) were able to guess on which treatment they received because of the side effect of uterine bleeding on LNG-IUS. Baseline comparison between the two groups showed the treatment and control groups were comparable in age, weight, body mass index, and obstetric history and baseline pain scores; but a significantly higher number of sexually active women in the treatment vs. control group (75% vs. 33%; p=0.010).
In the Tekin *et al* study, physicians other than the surgeons who operated took the VAS and TESP scores minimising bias when assessing surgical findings. No statistical difference existed between the treatment and control groups in terms of age, parity, gravity and revised American Fertility Society scores. No dropouts were reported, an intention-to-treat was used for analysis. Blinding of participants, researchers and assessors not reported. The researchers did not address any limitations.
Vercellini *et al* conducted an open label RCT because blinding included additional administrative requirements. This and the small samples size severely limited the study. Additionally, due to these limitations, the concluding statement that "***a medicated device inserted postoperatively will prevent the recurrence of moderate or severe dysmenorrhea in one out of three patients (5% CI,2-11) 1 year after surgery, relative risk reduction of 78%***" is very biased. The absolute risk reduction of 35% (95%CI, 9% to 61%) should be interpreted with caution. Adverse drug reactions were not addressed.

Safety Information
Adverse drug reactions were reported in 2 of 3 studies, but no serious adverse event was reported in any of the patients. Drop outs were reported in 2 of 3 studies, but there was no mention of drop outs being related to mortality.

Alternative Agents
Comparisons or alternatives to LNG-IUS included expectant management (usually surgery), and GnRH-a, empirical treatment without doing an invasive diagnostic laparoscopy, combined oral contraceptives, progestins, and oral and depot progestins and other progestin preparation.

Summary
Studies according to the inclusion criteria of this review were limited as in all the studies patient had undergone surgical procedure and the extent to which surgical procedure was conducted was unclear. Evidence shows results for up to one year follow up (but LNG-IUS can be used for up to 5 years). However, compared with expectant therapy LNG-IUS was shown to reduce CPP in the ***short term***, when patients reported higher overall satisfaction with the treatment.

Compared to GnRH-a, outcomes were similar after 1 year. It should be noted that total endometrosis severity improved with LNG-IUS but at 12 months returned to almost pretreatment levels. Also patients have been known to request removal of the device due to the side effect of intrauterine bleeding.

Summary

Consideration should be given to current treatment for chronic pelvic pain associated with endometriosis and the level of care at which the device should be recommended (secondary vs. tertiary). One should also consider that follow up for the RCTs was only for 1 year but the device remains in situ for up to 5 years. Additionally, patients have been known to request removal of the LNG-IUS. Evidence cannot completely confirm that CPP with endometriosis would be reduced post year 1 follow up. Device costs for improvement of symptoms for a period of 1 year; as well as additional costs when LNG-IUS requires surgical insertion must be considered before any final recommendations are made.

Recommendation

LNG-IUS not be included for on the Adult Hospital level EML for dysmenorrhoea caused by endometriosis, as the agent is expensive and indication creep is a concern.

Table 1: Evidence table of RCTs identified for this review

Study (year)	Study design	Participants (studies)	Study comparators	Summary of findings					Quality of study	Risk of bias
				Study event rates (%)		Absolute risk reduction (95% CI)	NNT/NNH:	Relative risk: (95% CI)		
				Intervention	Comparator					
1. Tanmahasamut et al .,2012	Double Blind RCT	n=55	LNG-IUS (n=28) vs. expectant management (n=27)	***Primary outcome:*** Change of dysmenorrhea visual analog scale (severity of dysmenorrhea)					Duration of follow up was only 1 year Although blinded, most patients in the treatment group were able to guess correctly as to which group they were assigned due to the side effect of abnormal bleeding experienced on LNG-IUS.	Randomisation might have been compromised due to occurrence of side effects. Baseline comparison comparable in age, weight, body mass index, obstetric history and baseline pain scores. Significantly higher no of sexually active women in the treatment vs. control group (75% *vs*. 33%. p=0.010)
							NNT to prevent 1 case of recurrent moderate –to severe dysmenorrhea was 3.7 (95% CI 2.1 to 15.6)			
				Secondary outcome(s): Changes of pelvic pain and dyspareunia visual analog scale (severity of chronic pelvic pain and dyspareunia), short form-36 score (changes in quality of life), overall satisfaction of the treatment and adverse effects.						Performance: 92.6% of patients (25 /27) were able to guess their allocation to the treatment group due to side effects experienced.
								RR 0.64, 95% CI 0.33 to 1.24; p=0.184		
				Adverse effects: Bloating, acne, oily skin, melasma, weight gain, breast tenderness, headache, nauseas and leukorrhea. No serious adverse event reported. 4 patients requested removal of the LNG-IUS after 1 year treatment study period because of associated bleeding side effect.						Attrition: 1 lost to follow up in treatment group, 3 in the control group (+ 1 protocol violation). Lost to follow up included in the analysis. However, protocol violation was excluded.
				20/27 patients complained of ≥ 1 side effect, probably related to progestin.	18/23 patients complained of ≥ 1 side effect, probably related to progestin. Bloating more common in control group 37.0% *vs*. 69.6 % (p=0.021)					
2.Tekin et al., 2011	Prospective RCT	n= 40	LNG-IUS (n=20) *vs.* GnRh-a (n=20). GnRh-a dose repeated every 4 weeks for 24 weeks	***Primary outcome:*** Scores of chronic pelvic pain measured using a visual analogue scale (VAS) and total endometriosis severity profile (TESP) used to measure the subtypes of CPP such as dysmenorrhea or dyspareunia. *LNG-IUS* : TESP score decreased in the LNG-IUS group at 1st, 3rd, and 6th month follow-up visits (p<0.001). TESP scores at the 12th month follow-up visit were increased to values similar to pretreatment values. VAS score had no significant alteration during the follow-up period of 1 year in the LNG-IUS group (p>0.05). The LNG-IUS treatment showed a lower patient satisfaction. *GnRH-a* group showed a significant decrease in the VAS score (p=0.048) and TESP score at the end of 1 year.					-Physicians other than the surgeons who operated took the VAS & TESP scores; to limit bias. -Limitations not addressed. -Underpowered (sample size of 40 subjects).	Randomisation. No statistical difference between the 2 groups in terms of age, parity, gravity and revised AFS scores. Details of allocation concealment unclear. Double-blinding methodology not reported.
				Adverse effects: LNG-IUS group reported irregular menstrual bleeding & abdominal pain, weight gain, simple						Attrition: No dropouts reported. Intention to treat

				ovarian cysts. GnRH-a group reported vasomotor symptoms and amenorrhea.						analysis.
3. Vercellini et al., 2003	Open label, parallel design RCT	n=40	LNG-IUS (n=20) vs. expectant management (n=20)	***Primary outcome:*** Recurrence of moderate or severe dysmenorrhea in the two study groups 1 year after surgery.						78 study participants identified but 32 were declined entry into study. Reasons not provided. No double blinding. Conclusion has a risk of bias as these limitations were not considered. Selection (allocation): Open label and small sample size .
						AR reduction of dysmenorrhea recurrence in LNG-IUS insertion vs. expectant management was 35% (95% CI 9 to 61%)		Dysmenorrhea recurred less in LNG-IUS group (RR=0.22; 95% CI 0.05 to 90).		
				Secondary outcome(s): Overall satisfaction of treatment was higher in the treatment group but researchers do not report significance						Attrition: 1 patient in each group was lost to follow up.

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