Levonorgestrel-releasing intrauterine system (LNG-IUS)

This presentation includes data on the LNG-IUS 52 mg with a daily release of 20µg LNG

Advanced slide kit complementing the WHO training tool www.fptraining.org

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Contents

To enable teachers to understand and explain:

- What is the hormone-releasing intrauterine system (IUS) and why was it developed
- General characteristics of the LNG-IUS 20
- Mechanism of action of the LNG-IUS 20
- Contraceptive efficacy and duration of use of the LNG-IUS 20
- Adverse and serious adverse events, treatment
- Reasons for discontinuation of the LNG-IUS 20
- Medical indications for LNG-IUS 20 use
- New types of LNG-IUS (LNG-IUS 8 and 12)

A literature review identified four studies regarding extended use of the LNG-IUS, which is approved for 5 years of use. Based on cumulative, international data, the LNG-IUS appears to be highly effective for pregnancy prevention for up to 7 years among parous women whose mean age is greater than 25 at the time of insertion; no pregnancies were reported between years 5 and 7 in all four studies.


Side-effects and risks of LNG-IUS 20

Adverse events
- Short-term cramping after correct insertion, spotting, prolonged bleeding
- Longer lasting adverse events include amenorrhoea, functional ovarian cysts, hormonal side effects, effect on sexual function

Serious adverse events
- perforation, ectopic pregnancy, PID, dislocation
Adverse events of LNG-IUS 20

- Light to severe pelvic pain is the most common temporary reported adverse event (more frequent in nulliparous women), and the most frequent (25-30%) reason for requesting LNG-IUS removal in the first 6 months
- Hormonal effects (1%-10%): headaches, nausea, hair loss, breast tenderness, depression, decreased libido, acne
- Transient unfavorable bleeding pattern – frequent or prolonged bleeding in up to 35% of LNG-IUS users in the first three months


Ref 3: Menstrual diaries collected during the first year of a multicentre study were analysed to compare a copper IUD (Nova-T) with an LNG-IUS releasing 20 μg LNG/24 h. The diaries of 193 LNG-IUS users were included in analysis. Patterns reflecting a reduction in bleeding were clearly more common among the LNG-IUS users. During the last trimester, more than half of the women in the LNG-IUS group had infrequent bleeding and 11–16% were amenorrhoeic. The substitution of spotting in place of bleeding accounts for about half of the reduction in the frequency of bleeding in this group. This was confirmed when the patterns were constructed counting spotting as bleeding. When the patterns were analysed this way, only 19–20% of LNG-IUS users had infrequent bleeding.
Diagnostic assessment and treatment of irregular bleeding with the LNG-IUS

- In the first months of LNG-IUS use: reassurance
- After 6 months - exclude gynaecological pathology, STIs/PID, pregnancy, etc.
- Not effective: tranexamic acid, mefenamic acid, ulipristal acetate
- Some benefits: nonsteroidal anti-inflammatory drugs (NSAIDs)
- Empirical treatment: short-course (3 months) COCs in conventional and continuous regimen


2. French RS et al. Levonorgestrel-releasing (20 μg/day) intrauterine systems (Mirena) compared with other methods of reversible contraceptives. BJOG 2000; 107: 1218–25

Reference 3: A total of 61,448 women with a newly inserted IUD were enrolled in six European countries between 2006 and 2012. The copper IUD cohort contained more than 30 different types. Validated 1-year follow-up information for 58,324 users between 18 and 50 years of age (70% using LNG IUS, 30% using copper IUDs) was collected. Seven women with LNG IUS and 14 women with copper IUDs had an ectopic pregnancy, resulting in incidence rates of 0.02 per 100 WY (95% CI: 0.01–0.03) and 0.08 per 100 WY (95% CI: 0.04–0.13), respectively. The proportion of ectopic pregnancies among all contraceptive failure pregnancies was higher in LNG IUS users compared to copper IUD users (27% vs. 15%, p = .16), but due to the substantially lower risk of contraceptive failure in LNG IUS users, the overall risk for ectopic pregnancies was significantly lower in LNG IUS users compared to copper IUD users [HR 0.20 (95% CI: 0.08–0.48)].
Early removal of the LNG-IUS 20 vary between studies

Overall 1 year discontinuation rate: 7.3% - 20%

<table>
<thead>
<tr>
<th>Reason for requesting removal</th>
<th>Termination rate per 100</th>
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<tbody>
<tr>
<td>Pain or cramping</td>
<td>2 - 13%</td>
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<tr>
<td>Bleeding problems</td>
<td>3 - 10%</td>
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<tr>
<td>Hormonal side effects</td>
<td>1 - 5%</td>
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Nulliparous women have higher removal rates for pain (19%) than women aged 25 - 35 (10%).

3. Rowe, P et al. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception 2016; 498-506
   (In the case-control study to evaluate the association between postmenopausal hormone therapy (HT) and the risk for breast cancer in recently postmenopausal Finnish women was found that LNG-IUS used alone was associated with an elevated risk for breast cancer (1.45; 1.97–1.77), or as a complement to estradiol (2.15; 1.72–2.68) was also associated with an increased risk.)


Medical indications for LNG-IUS 20 use

Effect of LNG on endometrium

Local daily release of LNG 20 μg/day

High LNG concentrations in endometrium = 200-800 times higher than after daily oral dose

Low LNG plasma levels < 200 pg/mL

Inhibition of endometrial proliferation:
- reduced menstrual blood loss
- positive impact on dysmenorrhea
- mild hormonal and metabolic side-effects

LOCAL hormonal action
### Treatment of heavy menstrual bleeding (HMB) with different types of hormonal contraceptives

<table>
<thead>
<tr>
<th>LNG-IUS compared to:</th>
<th>Effectiveness in reducing heavy menstrual bleeding</th>
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<tbody>
<tr>
<td>Combined oral contraceptives (COC)</td>
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<tr>
<td>Mefenamic acid</td>
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<tr>
<td>Tranexamic acid</td>
<td>LNG-IUS more effective</td>
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<tr>
<td>Medroxyprogesterone acetate (10 mg 10 days)</td>
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<tr>
<td>Norethisterone (5 mg long cycle)</td>
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<tr>
<td>Transcervical resection of the endometrium</td>
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<tr>
<td>Thermal or rollerball ablation</td>
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<tr>
<td>Hysterectomy</td>
<td>Less effective*</td>
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</table>

In order to provide comparative estimates of clinical outcomes after placement of levonorgestrel-releasing intrauterine system (LNG-IUS), ablation, or hysterectomy for AUB, full articles published in 2006–2016 available in English comparing at least two treatment modalities of interest among women of reproductive age with AUB were included. A decision tree was generated to compare clinical outcomes in a hypothetical cohort of 100,000 premenopausal women with nonmalignant AUB. Authors evaluated complications, mortality, and treatment outcomes over a 5-year period, calculated cumulative quality-adjusted life years (QALYs), and conducted probabilistic sensitivity analysis. Levonorgestrel-releasing intrauterine system had the highest number of QALYs (406,920), followed by hysterectomy (403,466), non-resectoscopic ablation (399,244), and resectoscopic ablation (385,823). Ablation had more treatment failures and complications than LNG-IUS and hysterectomy. Findings were robust in probabilistic sensitivity analysis.
The influence of LNG-IUS 20 use on fibroid-associated heavy menstrual bleeding

- LNG-IUS is effective in selected women with fibroid-associated HMB.
- The size of the fibroids does not decrease markedly during treatment.


The prevalence and severity of dysmenorrhea were compared in a longitudinal analysis of variance performed in the same women using either intrauterine contraception (copper IUD or LNG-IUS) or COCs with other methods of contraception or no contraception. Random samples of 19-year-old women born in 1962 (n=656), 1972 (n=780) and 1982 (n=666) were assessed at 5 year intervals between 1981 and 2001. The current severity of dysmenorrhea was assessed on each occasion using a VMS and a VAS. The VMS is a scoring system which grades pain as none, mild, moderate or severe using grades 0, 1, 2 and 3, respectively. This scoring system also takes into account the effect on daily activity, systemic symptoms and whether analgesics are required. VAS is a technique where a 100 mm line on a paper represents the continuum of the woman’s opinion of the degree of pain. Use of the LNG-IUS (p<0.01) and COC (p<0.0001) were associated with a reduced severity of dysmenorrhea compared with non-hormonal methods/no contraception.
<table>
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<tr>
<th>Topic: LNG-IUS</th>
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<td><strong>LNG-IUS 20 use in women with symptomatic endometriosis</strong></td>
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<tr>
<td>The LNG-IUS can:</td>
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<tr>
<td>• Reduce chronic pelvic pain associated with endometriosis</td>
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<tr>
<td>• Reduce dysmenorrhoea</td>
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<tr>
<td>• Decrease the postoperative recurrence of endometriosis</td>
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<td>• Reduce dyspareunia</td>
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Ref 1: This systematic review and meta-analysis of 24 studies compared endometrial hyperplasia regression rates between an oral progestin and the LNG-IUS in 1001 patients. The LNG-IUS was superior in the treatment of simple hyperplasia (nine studies), complex hyperplasia (nine studies) and atypical hyperplasia (14 studies).

Hormonal therapy is regarded as the standard management plan for endometrial hyperplasia without atypia or benign endometrial hyperplasia. However, hormonal therapy can be selected in patients with atypical endometrial hyperplasia who desire to preserve their fertility or in patients who are poor surgical candidates due to severe medical comorbidities.

Ref 5: Seven randomized controlled trials (n = 766 women) were included. Main outcome measures were the therapeutic effect rate (histological response) after 3, 6, 12, and 24 months of treatment; rate of irregular vaginal bleeding; and the hysterectomy rate per woman randomized. Meta-analysis was performed with fixed effects model. For treatment of non-atypical endometrial hyperplasia, LNG-IUS achieves higher therapeutic effect rates and lower hysterectomy rates than oral progestins and should be offered as an alternative to oral progestins in these cases.


Gemzell-Danielson et al. (2012) reported on a multicentre, open-label, randomised three-arm phase II study, which included a total of 738 women successfully fitted with 19.5 mg LNG-IUS (Kyleena) (n=245), 13.5 mg LNG-IUS (Jaydess) (n=239) or 52 mg LNG-IUS (Mirena) (n=254). The study period was 3 years. This study was not powered to determine whether there was a significant difference in contraceptive effectiveness between the devices.

A large multicentre, open-label, randomised two-arm phase III study which included a total of 2,884 women. Nelson et al. (2013) compared women fitted with 19.5 mg LNG-IUS (n=1,452) or 13.5 mg LNG-IUS (1,432) over a study period of 3 years. 870 women using 19.5 mg LNG-IUS and 819 using 13.5 mg LNG-IUS completed the 3 year study. 707 women in the trial who were using 19.5 mg LNG-IUS then entered an optional 2 year trial extension period and the resulting 5 years of data for 19.5 mg LNG-IUS were reported by Gemzell-Danielsson et al. (2017).

Over the 3-year study period, 0.33 pregnancies per 100 women years (95% confidence interval [CI] 0.16–0.60) were observed with the 13.5 mg intrauterine contraceptive system compared with 0.31 per 100 women-years (95% CI 0.15–0.57) with the 19.5 mg intrauterine contraceptive system. The phase III trial reported an unadjusted Pearl Index of 0.29 (95% confidence interval [CI] 0.16-0.50) for 19.5 mg LNG-IUS over the 5-year duration of use. Both the phase II and phase III studies report that the mean number of bleeding spotting days decrease over time with 19.5 mg LNG-IUS and 13.5 mg LNG-IUS as is observed with 52 mg LNG-IUS. The phase II and III study authors’ graphical representation of the data suggests that the mean number of bleeding days over the course of 3 years is lower with 52 mg LNG-IUS than with 19.5 mg LNG-IUS and lower with 19.5 mg LNG-IUS than with 13.5 mg LNG-IUS. However statistical significance is not reported. Thus, limited evidence suggests the possibility that higher doses of LNG in the LNG-IUS could be associated with fewer bleeding/spotting days.

Amenorrhoea - The phase II trial reported that, at 3 years amenorrhoeic were 12.7% of women using 13.5mg LNG-IUS, 18.9% of women using 19.5 mg LNG-IUS and 23.6% using 52mg LNG-IUS (difference not statistically significant). In the phase III trial the incidence of amenorrhoea with 19.5 mg LNG-IUS was 12.7% at 1 year and 22.6% at 5 years.
New types of LNG-IUS: benefits and adverse events

| Adverse events do not differ from the LNG-IUS 20 in spite of lower LNG-dose |
|-------------------------------|----------------|
| Acne                          | 22-26%         |
| Headaches                     | 11-13%         |
| Altered mood                  | 10-14%         |
| Weight increase               | 11%            |

- In contrast, incidence of ovarian cysts is decreased.

Expulsion (complete or partial expulsion over 3 years):
- LNG-IUS 8: 4.5%; LNG-IUS 12: 3.6%

Ectopic pregnancy:
Both LNG-IUS (8 and 12) are not licensed for the treatment of heavy uterine bleeding and endometrial protection.


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The effect of both 13.5 mg LNG-IUS and 19.5 mg LNG-IUS on the endometrium is weaker compared to 52 mg LNG-IUS, and therefore these new devices are not licenced for the treatment of heavy uterine bleeding and endometrial protection. Side-effects are similar as with 52 mg LNG-IUS. Commonly-reported side effects include acne, pelvic pain, breast discomfort and weight gain.

The cumulative risk of at least partial expulsion over 3 years was 4.56% for the 13.5 mg system group and 3.58% for the 19.5 mg system group.

The absolute rate of ectopic pregnancies is low - 0.10 per 100 W-Y (13.5 mg LNG-IUS); 0.18 over 5 years (19.5 mg LNG-IUS). However, should a pregnancy occur with an IUC in situ then the likelihood of it being ectopic is greater than if a pregnancy were to occur without an IUC in situ. Over the course of the 3-year study, three and seven ectopic pregnancies occurred in the 13.5 mg and 19.5 mg system groups. With the extension for 19.5 mg LNG-IUS for additional two years in total, five intrauterine pregnancies (two of which resulted in healthy term births, and three in spontaneous abortions), and eight ectopic pregnancies were reported.