

Levonorgestrel-releasing intrauterine system (LNG-IUS)

This presentation includes data on the LNG-IUS 52 mg (LNG 20 IUS), LNG-IUS 13.5 mg (LNG 12 IUS) and LNG-IUS 19.5 mg (LNG 16 IUS)

This advanced slide kit is complementing the WHO training tool which can be found at www.fptraining.org

Contents

To enable clinicians and trainers to understand and explain:

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

General LNG-IUS characteristics

Progestin-releasing IUDs were developed to reduce blood loss and cramping associated with the use of the copper-IUDs

- A long-acting, highly effective, and reversible form of contraception
- Releases LNG into the uterine cavity
- The progestin mainly acts at endometrial level
- The plasma level of LNG is low initially and lower after 6 months
- Free of estrogen-related serious adverse events



Differences between LNG-IUSs

LNG 20 IUS	Additional health benefit: profound reduction in menstrual blood loss. Contraceptive efficacy 5 years. (size of the vertical stem 32 mm and inserter 4.44 mm/4.75 mm)
LNG 12 IUS	Smaller frame and inserter diameter. Contraceptive efficacy 3 years. (size of the vertical stem 30 mm and inserter 3.75 mm)
LNG 16 IUS	Smaller frame and inserter diameter. Contraceptive efficacy 5 years. (size of the vertical stem 30 mm and inserter 3.75 mm)

Pharmacology and pharmacokinetics of different LNG-IUS

	LNG 20 IUS	LNG 16 IUS	LNG 12 IUS
LNG content of reservoir	52 mg	19.5 mg	13.5 mg
Initial LNG release rate ($\mu\text{g}/24\text{h}$)	20	16	12
Release rate at the end of approved lifetime ($\mu\text{g}/24\text{h}$)	10.7	7.6	5.5

The LNG release rate in users of all LNG-IUS types decreases with duration of use.

LNG serum levels in IUSs users are two to three times lower compared to LNG minipill users.

Mechanism of action of the LNG-IUSs

ENDOMETRIUM:

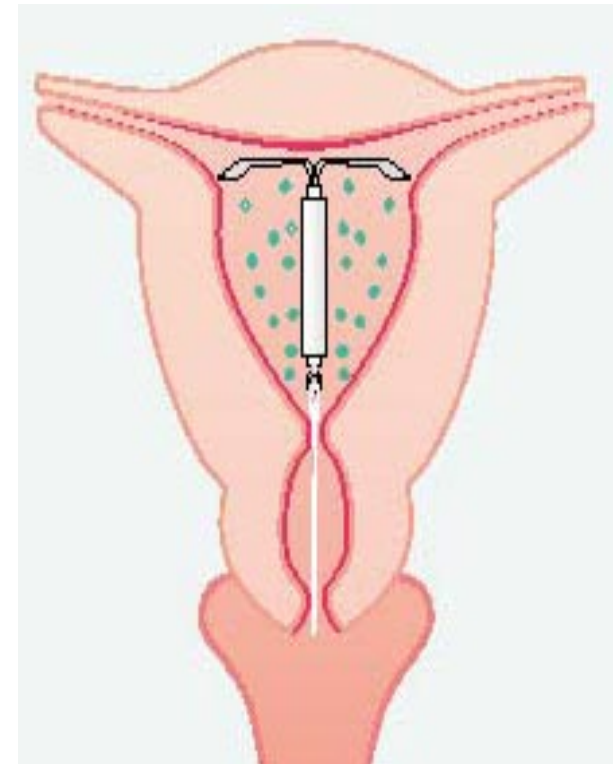
- alteration of endometrial receptivity
- suppression of endometrial proliferation
- local inflammatory reaction (foreign body reaction)

CERVICAL MUCUS:

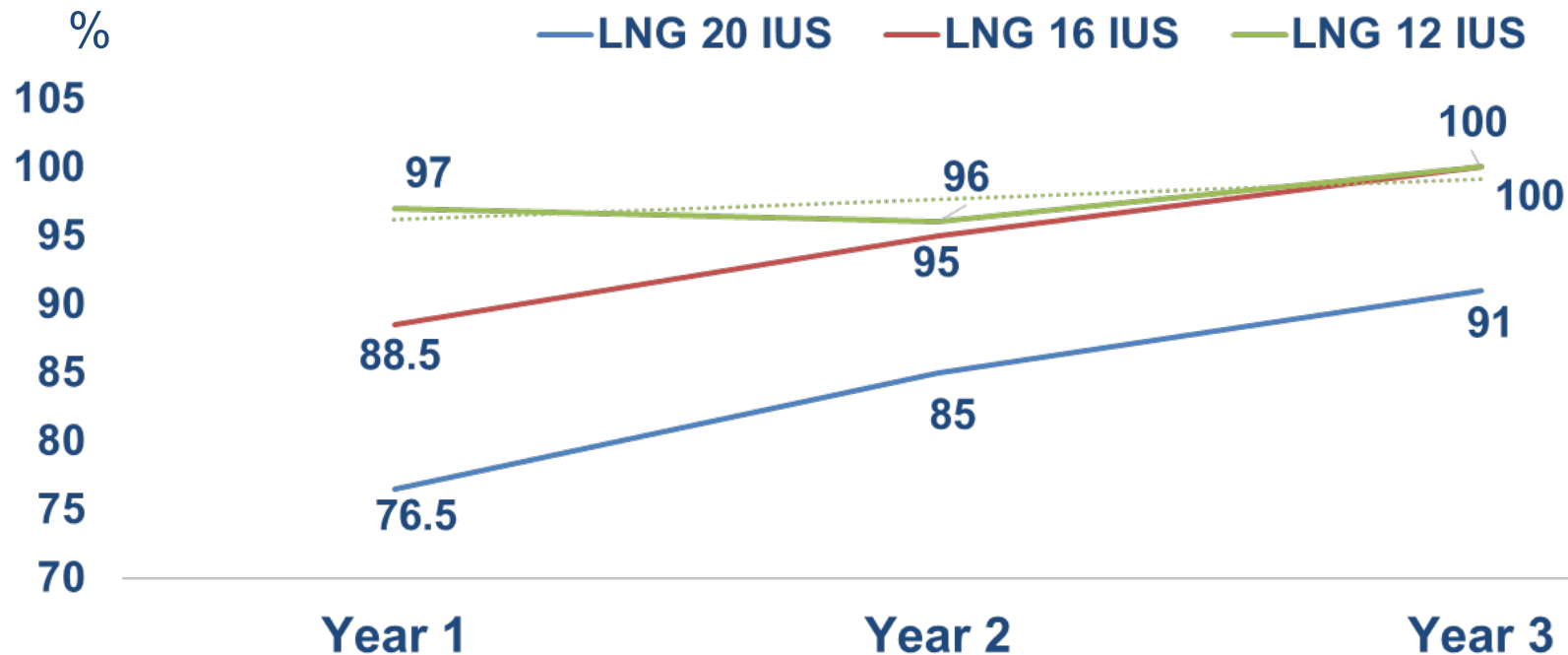
- inhibition of sperm migration
- thickening of cervical mucus

OVARY

- Some dose-dependent effect on follicular development and inhibition of ovulation



Ovulation rates in LNG-IUS users



- **LNG 20 IUS inhibits more ovulations than LNG 16 and LNG 12 IUS.**
- **Persistent follicles are the reason for the development of ovarian cysts in a subset of LNG 20 IUS users.**
- **Concurrent with the decreasing plasma levels over time the frequency of inhibited ovulation decreases.**

Contraceptive efficacy and ectopic pregnancy rates in LNG-IUS users

LNG IUS	Cumulative 3/5-years Pearl index (all pregnancies/100 woman-years)	Ectopic pregnancy rate for the first year of use (ectopic pregnancies/100 woman-years)
LNG 20 IUS	0.2	0.02
LNG 16 IUS	0.29	0.18
LNG 12 IUS	0.2 – 0.3	0.23

The risk for ectopic pregnancy is lower in users of all three types of LNG-IUS than in women without contraception.

Adverse events of LNG-IUSs

Three-years adverse events (%)	LNG 20 IUS	LNG 16 IUS	LNG 12 IUS
<i>Progestin related</i>			
Headache	17	13	12
Altered mood	10	10	14
Acne	28	22	26
Breast pain/discomfort	7/22	11/18	6/19
Increased weight	8	11	11
<i>Other adverse events</i>			
Pelvic pain	9.8	8.6	8.7
Ovarian cyst	22	9	6

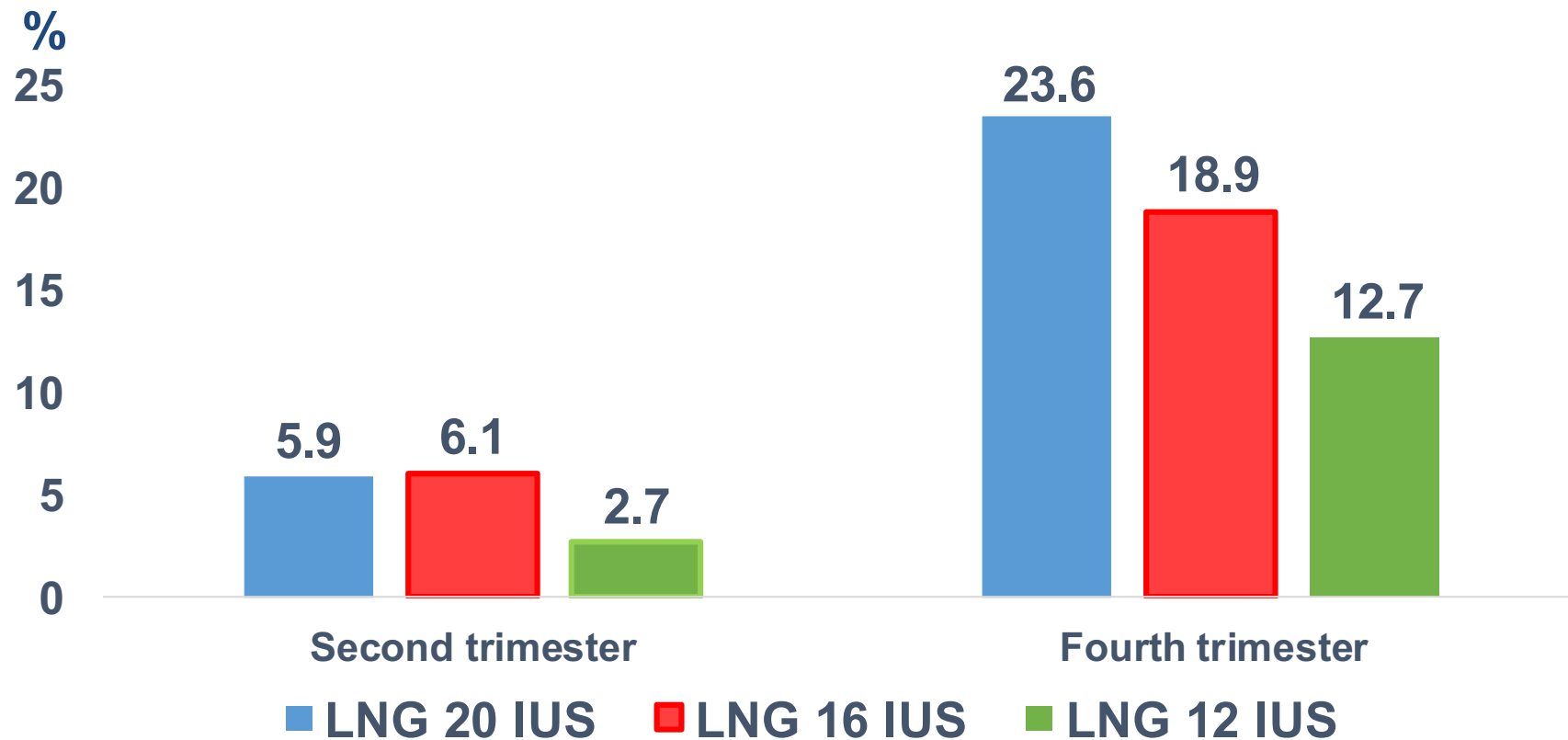
Early removal of the LNG-IUSs varies between studies

Overall 1 year discontinuation rate: 7.3% - 27%

Reason for requesting removal	Termination rate per 100
Pain or cramping	2 -13 %
Bleeding problems	2 - 26%
Hormonal side effects: headaches, nausea, hair loss, breast tenderness, depression, decreased libido, acne, increased weight	1 - 5%

Adolescents and nulliparous women tend to have higher removal rates for pain. This might be less with a smaller device.

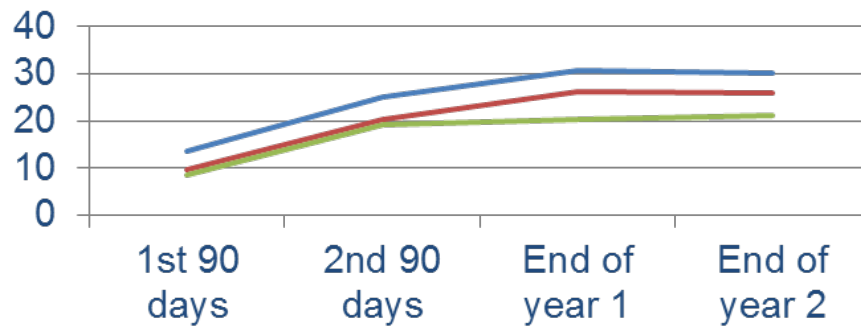
The rate of amenorrhea during first year of LNG-IUS use



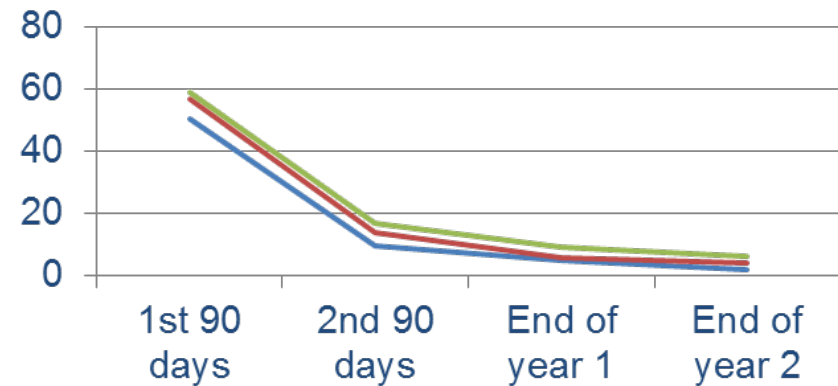
The proportion of LNG-IUS users with amenorrhea increases over time.

Bleeding pattern during LNG-IUS use

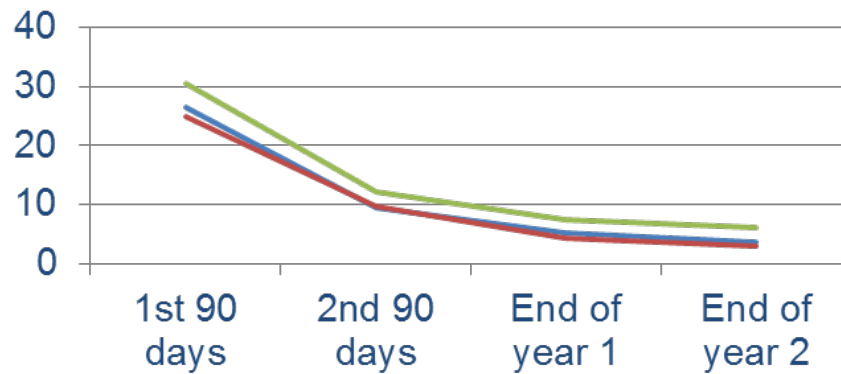
Infrequent bleeding rates



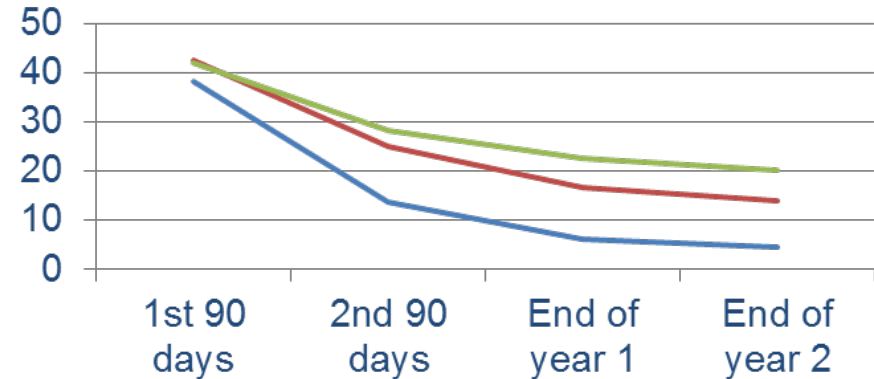
Prolonged bleeding rates



Frequent bleeding rates



Irregular bleeding rates



— LNG 20 IUS — LNG 16 IUS — LNG 12 IUS

Management of irregular bleeding with the LNG-IUS

In the first 3-6 months of LNG-IUS use: reassurance, if no other symptoms - exclude STIs or suspicion of a pregnancy

After 6 months - exclude gynaecological pathology, STIs/PID, pregnancy, etc.

Treatment options:

- **Not effective: tranexamic acid, mefenamic acid, ulipristal acetate**
- **Some benefits: nonsteroidal anti-inflammatory drugs (NSAIDs)**
- **Empirical treatment: transdermal estrogen 7 days or short-course (21 days) 30 µg EE COC (only in women without risk factors); doxycycline 2x100mg for 5 days; tamoxifen 2x10mg for 7-10 days (off label).**

Expulsion of the LNG-IUS

	LNG 20 IUS	LNG 16 IUS	LNG 12 IUS
Expulsion rate (complete and partial) over 3/5 years	1.6 – 6.3%	2 – 3.6%	0.4 - 4.6%

About half of all LNG-IUS expulsions occur during first six months.

The number of complete expulsions is approximately equal to the number of partial expulsions of the LNG-IUS.

Breast cancer risk in premenopausal LNG 20 IUS users

- Two newer high quality registry-based studies (including women aged 18-49 years observing > 500000 wy of use) found a minimal but significant risk increase for current users: RR 1.2 (*Ref 1,2*)*.
- Numbers (*Ref 1*)
 - Non-hormonal contraception 55 cases/100000 wy
 - LNG-IUS 70 cases/100000 wy
- The LNG-IUS should not be used in women with breast cancer and as contraceptive after breast cancer!

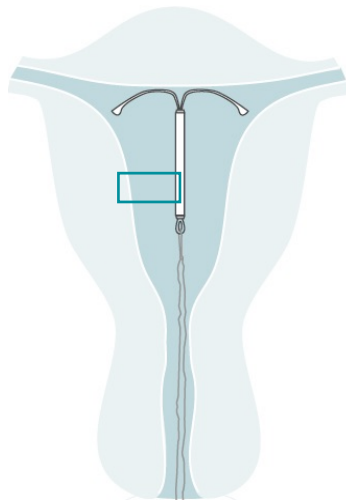
An increased risk for older peri- and postmenopausal women was not found (*Ref 3,5*)

Advantages of the LNG-IUS

- No negative impact on bone mineral density
- No increase in venous thromboembolism (VTE)
- No increase in arterial risks
- No significant impact on metabolic cardiovascular and inflammatory parameters

Therapeutic uses for LNG 20 IUS

Effect of LNG on endometrium



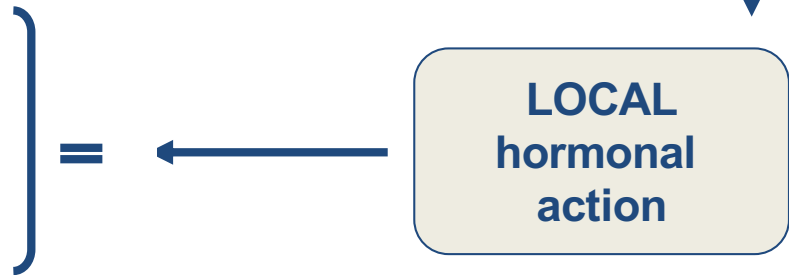
Local daily release of LNG 20 µg/day

High LNG concentrations in endometrium \approx 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 dysmenorrhoea
- mild hormonal and metabolic side-effects



Treatment of heavy menstrual bleeding (HMB) with LNG 20 IUS

LNG-IUS compared to:	Effectiveness in reducing heavy menstrual bleeding
Combined oral contraceptives (COC)	LNG 20 IUS more effective
Mefenamic acid 500mg/8h (3-5 days)	
Tranexamic acid 500mg/8h (3-5 days)	
Nonsteroidal antiinflammatory drugs	
Norethisterone 5 mg/12h (15-25 day of the cycle)	
Transcervical resection of the endometrium	LNG 20 IUS equally effective
Thermal or rollerball ablation	
Hysterectomy	LNG 20 IUS less effective

The influence of LNG 20 IUS use on fibroid-associated heavy menstrual bleeding*

Decrease in

- bleeding intensity
- number of bleeding days
- myoma-related surgery

- LNG-IUS is effective in selected women with fibroid-associated HMB (does not include submucous myoma)
- The size of the fibroids does not decrease markedly during treatment

** Not a licensed indication for LNG 20 IUS use*

LNG 20 IUS reduces dysmenorrhoea

In a longitudinal study including LNG-IUS users, COC users and copper-IUD users:

- LNG 20 IUS reduced severity of dysmenorrhoea ($p < 0.01$)
- COC reduced severity of dysmenorrhoea ($p < 0.0001$)
- Copper-IUD use did not improve dysmenorrhoea

Data were collected using a verbal multidimensional scoring system (VMS) and visual analogue scale (VAS)

LNG 20 IUS use in women with symptomatic endometriosis*

The LNG 20 IUS can:

- Reduce chronic pelvic pain associated with endometriosis
- Reduce dysmenorrhoea
- Decrease the postoperative recurrence of endometriosis

**** Not a licensed indication for LNG 20 IUS use***

LNG 20 IUS use in the treatment of adenomyosis*

Significant reduction up to 36 months in:

- pain score
- uterine bleeding and dysmenorrhoea
- uterine volume

Increase in

- Haemoglobin, haematocrit and serum ferritin levels
- Patient satisfaction evidenced by VAS scores

**** Not a licensed indication for LNG 20 IUS use***