



# Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit

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## FFPRHC Guidance (April 2004)

### The levonorgestrel-releasing intrauterine system (LNG-IUS) in contraception and reproductive health

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This Guidance provides information for clinicians and women considering the use of a levonorgestrel-releasing intrauterine system for contraception or other reproductive health benefits. A key to the grades of recommendations, based on levels of evidence, is given at the end of this document. Details of the methods used by the Clinical Effectiveness Unit (CEU) in developing this Guidance and evidence tables summarising the research basis of the recommendations are available on the Faculty website ([www.ffprhc.org.uk](http://www.ffprhc.org.uk)). Abbreviations (in alphabetical order) used include: CEU, Clinical Effectiveness Unit; CI, confidence interval; IUD, copper-bearing intrauterine contraceptive device; HRT, hormone replacement therapy; LNG, levonorgestrel; LNG-IUS, levonorgestrel-releasing intrauterine system; MBL, menstrual blood loss; HTA, Health Technology Assessment; OR, odds ratio; PID, pelvic inflammatory disease; RR, relative risk; RCOG, Royal College of Obstetricians and Gynaecologists; STI, sexually transmitted infection; TCRE, transcervical endometrial resection; TOP, termination of pregnancy; WHO, World Health Organization; WHOMEC, WHO *Medical Eligibility Criteria for Contraceptive Use*; WHOSPR, WHO *Selected Practice Recommendations for Contraceptive Use*.

#### What is the levonorgestrel-releasing intrauterine system?

This Guidance provides recommendations and good practice points regarding the use of a levonorgestrel-releasing intrauterine system, the accepted abbreviation for which is LNG-IUS. The use of a copper-bearing intrauterine device (IUD) has been covered in previous Faculty Guidance.<sup>1</sup> The LNG-IUS has been licensed as a contraceptive in the UK since May 1995. Recent National Statistics suggest the LNG-IUS is used by only 1% of women aged 16–49 years who are currently using a method of contraception.<sup>2</sup> The LNG-IUS now also has a licence for the management of idiopathic menorrhagia<sup>3</sup> and may therefore be used by women who do not require contraception.

The LNG-IUS has a T-shaped, plastic frame with a reservoir on the vertical stem containing 52 mg (milligrams) levonorgestrel (LNG) mixed with polydimethylsiloxane. A rate-limiting membrane allows LNG to be released into the uterine cavity at a constant dose of 20 µg (micrograms) per day. Devices releasing lower doses of LNG are not currently licensed in the UK. This Guidance summarises evidence for the use of the LNG-IUS in all aspects of contraceptive and reproductive health.

#### What should a clinician assess before considering LNG-IUS use?

*Who is medically eligible to use the LNG-IUS?*

- 1 After counselling, the LNG-IUS is a suitable option for most women who need contraception and/or treatment for menorrhagia (Grade C).

Women who need contraception and/or medical treatment of menorrhagia may choose the LNG-IUS. The World Health Organization *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC) provides evidence-based recommendations to guide clinicians and women on the safe use of contraception.<sup>4</sup> WHOMEC is also relevant for

women considering the LNG-IUS for a non-contraceptive use. The LNG-IUS represents an intrauterine, and a long-term progestogen-only, method of contraception. There are few conditions where LNG-IUS use is associated with unacceptable health risks (WHO Category 4) or where the risks usually outweigh the benefits (WHO Category 3). There are conditions where the risks of LNG-IUS use outweigh the benefits because of its progestogen content, rather than its intrauterine site: current deep vein thrombosis or pulmonary embolus, ischaemic heart disease, active viral hepatitis, severe decompensated cirrhosis, benign liver tumours or malignant hepatoma (Table 1). This Guidance endorses WHOMEC unless otherwise stated. Outlined below are conditions where this Guidance suggests a less restrictive approach compared to WHOMEC.

*Women at risk of sexually transmitted infections and human immunodeficiency virus*

- ✓ After counselling about other contraceptive methods, women who are assessed as at a higher risk of STI may still choose to use the LNG-IUS.

WHOMEC recommends that the risks of using the LNG-IUS generally outweigh the benefits for women who are at increased risk of sexually transmitted infection (STI) (WHO 3). Most women with risk factors for STI will not have infection. The CEU recommends, as for IUD use,<sup>1</sup> that after counselling regarding other methods, women who are at a higher risk of STI may still choose the LNG-IUS. Safer sex and condom use in addition should be promoted.

As for copper IUDs, WHOMEC recommends that the risks of using the LNG-IUS generally outweigh the benefits for women who are at high risk of human immunodeficiency virus (HIV), who are HIV-positive or who have acquired immune deficiency syndrome (AIDS) (WHO 3). Much of the evidence is based on African cohort studies of IUD use.<sup>5,6</sup> The CEU considers that, as for IUD

**Table 1** Conditions where the risks of LNG-IUS use outweigh the benefits (WHO 3) or are an unacceptable health risk (WHO 4). WHO categories for IUD and other progestogen-only methods are also shown. Adapted from WHO Medical Eligibility Criteria for Contraceptive Use<sup>4</sup>

Condition	WHO Category				
	LNG-IUS	IUD	POP	DMPA	Implant
Thromboembolic disease: current deep vein thrombosis or pulmonary embolus	3	1	3	3	3
History of stroke	2	1	2 Initiation 3 Continuation	3	2 Initiation 3 Continuation
Migraine with focal symptoms at any age	2 Initiation 3 Continuation	1	2 Initiation 3 Continuation	2 Initiation 3 Continuation	2 Initiation 3 Continuation
Current trophoblast disease: benign	3	3	1	1	1
Current trophoblast disease: malignant	4	4	1	1	1
Breast cancer: current	4	1	4	4	4
Breast cancer: in the past and no current disease for 5 years	2	1	3	3	3
Endometrial cancer	4 Initiation 2 Continuation	4 Initiation 2 Continuation	1	1	1
Cervical cancer	4 Initiation 2 Continuation	4 Initiation 2 Continuation	1	2	2
Liver disease: active viral hepatitis	3	1	3	3	3
Cirrhosis: severe decompensated	3	1	3	3	3
Benign and malignant liver tumours	3	1	3	3	3

WHO categories: WHO 1, unrestricted use; WHO 2, benefits usually outweigh risks; WHO 3, risks usually outweigh benefits; WHO 4, unacceptable health risk. DMPA, depot medroxyprogesterone acetate injectable method; implant, progestogen-only implant (specifically Norplant®); IUD, intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; WHO, World Health Organization.

use,<sup>1</sup> women in the UK who are HIV-positive may use the LNG-IUS. Risk assessment and testing for bacterial STIs prior to insertion are recommended.

Data from a randomised trial<sup>7</sup> suggest that women using the LNG-IUS are less likely to have pelvic inflammatory disease (PID) diagnosed than women using an IUD. An earlier randomised trial suggested that LNG-IUS users were significantly less likely to discontinue their method due to clinically diagnosed PID than IUD users.<sup>8</sup> However, protection against PID with the LNG-IUS was not supported in a systematic review.<sup>9</sup> No differences were found in the incidence of PID between LNG-IUS and IUD users. Thus there are insufficient data to support a reduction in PID with LNG-IUS use.

Current or recent PID or STI

✓ **After considering other contraceptive methods, a woman may use the LNG-IUS within 3 months of treated pelvic infection, provided she has no signs or symptoms.**

WHOMEC recommends that the LNG-IUS should not be inserted when a woman has PID, or a STI, currently or within the last 3 months (WHO 4).<sup>4</sup> The CEU recommends, as for IUD insertion,<sup>1</sup> that after considering other contraceptive methods, a woman may use the LNG-IUS within 3 months of treated pelvic infection, provided she has no signs or symptoms.

Migraine with focal symptoms

✓ **Women with a history of migraine with focal symptoms may use the LNG-IUS. If, however, migraine with focal symptoms develops in a LNG-IUS user, these new symptoms should be investigated and other contraceptive options discussed.**

WHOMEC recommends that all progestogen-only methods, including the LNG-IUS, can be started when women have migraine with focal symptoms (WHO Category 2: benefits usually outweigh the risks). WHOMEC recommends that, for women using the LNG-IUS, the risk of continuing its use when migraine with focal

neurological symptoms occurs outweighs any benefits (WHO 3).<sup>4</sup> This is due to concerns that headaches may increase with LNG-IUS use. Focal symptoms indicate ischaemia and include homonymous hemianopia, unilateral paraesthesia and/or numbness, scotoma, fortification spectra or aphasia.<sup>10</sup> The risk of ischaemic stroke in women with migraine with focal symptoms is, however, very low (17–19 per 100 000 woman-years).<sup>11</sup> No evidence was identified of an association between the LNG-IUS, migraine and stroke. A systematic review, comparing the LNG-IUS with IUDs, identified no significant difference in reported headache with LNG-IUS use [relative risk (RR) 1.71; 95% confidence interval (CI) 0.49–6.02].<sup>9</sup> The CEU recommends that women with a history of migraine with focal symptoms may use the LNG-IUS. If migraine with focal symptoms develops as a new condition in LNG-IUS users, however, it should be investigated and all other contraceptive options discussed.

Breast cancer

✓ **Non-hormonal contraception is most appropriate for a woman with a history of breast cancer. However, the LNG-IUS may be considered individually, and in consultation with the woman's breast surgeon.**

WHOMEC recommends that use of a LNG-IUS by a woman with current breast cancer presents an unacceptable health risk (WHO 4).<sup>4</sup> Women with a past history of breast cancer (no disease for 5 years) are advised that the risks of LNG-IUS use usually outweigh the benefits (WHO 3). Plasma concentrations of LNG with LNG-IUS use are significantly lower than following oral progestogen administration.<sup>12</sup> A small, randomised trial suggested endogenous progesterone levels may also be reduced with LNG-IUS use.<sup>13</sup> Tamoxifen is used in the management of breast cancer<sup>14</sup> and is known to stimulate the endometrium, increasing the risk of endometrial hyperplasia and malignancy.<sup>15</sup> A randomised, controlled trial of women with previous breast cancer, using tamoxifen for over a year, suggested the LNG-IUS prevented tamoxifen-induced endometrial changes.<sup>16</sup> Bleeding problems associated with LNG-IUS use were common. Further randomised trials are needed. The CEU recommends that

non-hormonal methods of contraception are most appropriate for women with previous breast cancer. However, the benefits of LNG-IUS use may be considered on an individual basis and in consultation with the woman's breast surgeon.

*Women who are breastfeeding*

**2 Levels of LNG in breast milk are low with the LNG-IUS. Therefore, women who are breastfeeding and are 4 or more weeks postpartum may choose this method (Grade B).**

For women who are breastfeeding, WHOMEc recommends that the risks of LNG-IUS use up to 6 weeks postpartum outweigh any benefits (WHO 3).<sup>4</sup> Prospective observational studies have shown low concentrations of LNG in breast milk following insertion of a LNG-IUS releasing 10 or 30 µg LNG per day.<sup>17</sup> The total amount of LNG excreted into 600 ml breast milk each day was only 1% of the total daily dose. The use of the LNG-IUS by women who are breastfeeding does not appear to have any detrimental effect on infant development.<sup>18</sup> The CEU suggests that women who are breastfeeding and 4 or more weeks postpartum may choose the LNG-IUS.

*Are there any drugs that interact with LNG-IUS?*

**3 Women using the LNG-IUS may be reassured that there is no evidence of reduced efficacy with liver enzyme-inducers or other drugs (Grade B).**

WHOMEc recommends that the benefits of LNG-IUS use by women using liver enzyme-inducers generally outweigh the risks (WHO 2). Data from an ongoing survey have not identified any reduction in the efficacy of LNG-IUS with liver enzyme-inducers.<sup>19</sup> No other drugs are known to interact with the LNG-IUS.

**What do women need to know before considering the LNG-IUS?**

*Mode of action*

**4 Women should be informed that the LNG-IUS works primarily by its effect on the endometrium, thus preventing implantation. In addition, effects on cervical mucus prevent sperm penetration. Most women will continue to ovulate (Grade B).**

Most of the contraceptive effect of the LNG-IUS is mediated via its progestogenic effect on the endometrium.<sup>20</sup> Intrauterine concentrations of LNG are 1000 times higher than with subdermal progestogen implants.<sup>12</sup> High intrauterine levels of LNG lead to functional and histological changes within the endometrium which are evident within 1 month of insertion.<sup>21</sup> Endometrial oestrogen and progesterone receptors are down-regulated.<sup>22</sup> There is endometrial atrophy,<sup>23</sup> which is initially patchy,<sup>24</sup> but which becomes more uniform with increasing duration of use.<sup>25</sup> Changes in endometrial stroma occur<sup>26</sup> and there is a marked increase in inflammatory cell number.<sup>21,27</sup> These complex endometrial effects contribute to the contraceptive efficacy of the LNG-IUS, preventing implantation.<sup>26</sup>

In one small study, women were randomly assigned to use the LNG-IUS, an inert IUD or a copper IUD.<sup>13</sup> Cervical mucus from women using the LNG-IUS had reduced net weight (less water content) compared to other IUD users. Sperm penetration was decreased when cervical mucus quality was affected by LNG-IUS use.<sup>28</sup>

This may contribute to the contraceptive effect for some women.

The LNG-IUS has minimal effect on the hypothalamo-pituitary-ovarian axis.<sup>29</sup> Serum oestradiol levels are >100 pg/ml in most women, indicating follicular development.<sup>29</sup> Most women (>75%) will continue to ovulate.<sup>30,31</sup>

*Contraceptive efficacy*

**5 Women should be advised that the LNG-IUS is an effective, reversible method of contraception with a failure rate of less than 1 per 100 woman-years (Grade A).**

**6 Women should be informed that the failure rate of the LNG-IUS is similar to that of modern IUDs (Grade A).**

The LNG-IUS is an effective, reversible method of contraception (Pearl index 0.18 per 100 woman-years).<sup>32</sup> A multicentre, Phase III clinical trial<sup>33</sup> gave a gross cumulative pregnancy rate of 1 per 100 parous women at 5 years' use (95% CI 0.3–2.4).<sup>33</sup> A Cochrane systematic review<sup>34</sup> and a National Health Service Research and Development Health Technology Assessment (HTA) Programme report<sup>9</sup> compared the efficacy of the LNG-IUS with other reversible methods of contraception. The HTA report suggested that pregnancy rates were similar for the LNG-IUS and modern IUDs (>250 mm<sup>2</sup> copper).<sup>9</sup> Previous Guidance<sup>1</sup> recommended the use of an IUD with >300 mm<sup>2</sup> copper.

*Duration of use*

**7 Women should be informed that the LNG-IUS is licensed for 5 years' use (Grade C).**

**✓ All women using the LNG-IUS should be advised to return for review after 5 years' use to discuss the need for removal and replacement.**

There are data from randomised trials of contraceptive efficacy for up to 7 years' continuous LNG-IUS use.<sup>32,35</sup> However, the LNG-IUS has a license for 5 years' use.<sup>3</sup> There are studies that have shown that the LNG-IUS is safe for up to 12 years' use, with device replacement every 5 years.<sup>36</sup> After 5 years' use, women should be advised to return for review to discuss the need for removal and replacement. Women using the LNG-IUS for contraception should be advised to have the LNG-IUS replaced after 5 years. In the absence of evidence to suggest otherwise, this also applies to women aged over 40 years at the time of insertion. Women using the LNG-IUS for menorrhagia only, and whose symptoms are well controlled, may continue with the LNG-IUS beyond its licensed duration.

*Pelvic infection*

**✓ Women should be advised that a small increase in the risk of pelvic infection occurs following LNG-IUS insertion but thereafter the risk of infection is low.**

The CEU recommends that, as for IUD insertion,<sup>1</sup> women should be advised that a small increase in the risk of pelvic infection occurs in the 20 days following insertion. Thereafter, the risk is the same as for the non-IUD-using population. Women should be informed of the symptoms of



pelvic infection and advised how and where to seek medical help if these occur, particularly in the first 3–4 weeks after insertion.

Ectopic pregnancy

**8 Women can be reassured that the risk of ectopic pregnancy with the LNG-IUS is low (Grade A).**

WHOMEc recommends that women with a previous ectopic pregnancy may use the LNG-IUS (WHO Category 1: unrestricted use).<sup>4</sup> A systematic review suggested an increased risk of ectopic pregnancy with LNG-IUS use (21 of 100 pregnancies were ectopic compared to 4 of 100 in IUD users).<sup>37</sup> More recent data from randomised trials,<sup>32,38</sup> however, reported no ectopic pregnancies in a total of 34 944 woman-months of LNG-IUS use.<sup>38</sup> Two ectopic pregnancies were reported in 38 268 woman-months of use of the Cu T380Ag.<sup>38</sup> The HTA report was also reassuring, the risk of ectopic pregnancy being similar for the LNG-IUS and modern IUDs (>250 mm<sup>2</sup> copper).<sup>9</sup> Women can therefore be reassured that the risk of ectopic pregnancy with the LNG-IUS is low.

Return of fertility

**9 Women can be reassured that there is rapid return of fertility following LNG-IUS removal (Grade B).**

Follow-up studies of women recruited to randomised trials, who requested removal of the LNG-IUS to allow pregnancy, provide evidence of rapid return of fertility.<sup>39,40</sup> Life table analyses show a pregnancy rate of 90 per 100 women in the first year after LNG-IUS removal.<sup>39</sup> The mean time to pregnancy was 4 months following LNG-IUS removal and 3 months following IUD removal.<sup>39</sup>

Expulsion

**10 Women should be informed that the most likely cause of LNG-IUS failure is expulsion. The risk of this happening is around 1 in 20 (Grade A).**

Most contraceptive failures with the LNG-IUS are due to expulsion. The gross rate of expulsion increased from 4.5 per 100 users at 12 months and 5.2 per 100 users at 24 months up to 5.9 per 100 users at 60 months.<sup>33</sup> Rates of expulsion appear comparable to expulsion rates of IUDs.<sup>1</sup> A systematic review, however, showed that LNG-IUS users were more likely to experience expulsion than users of modern IUDs (>250 mm<sup>2</sup> copper).<sup>9</sup> This difference was only significant once follow-up had reached 5 years, when an increase of over 50% in the expulsion rate of the LNG-IUS (rate ratio 1.54; 95% CI 1.13–2.07) was shown.<sup>9</sup> No data were identified that permitted us to relate expulsion rates to reasons for insertion.

Perforation

**11 Women may be informed that uterine perforation occurs in fewer than 1 in 1000 LNG-IUS insertions (Grade B).**

The rate of perforation reported with the LNG-IUS in a large observational cohort study was 0.9 per 1000 insertions.<sup>41</sup>

Checking for LNG-IUS threads

Women should be offered instruction on how to check for the LNG-IUS and its threads and advised that if

they are unable to feel them it may be that the device has been expelled. Alternative contraception should then be used, if required, until medical advice has been sought.

Menstrual bleeding

**12 Women should be informed that the LNG-IUS can reduce menstrual blood loss by over 90% (Grade A).**

**13 Women should be informed that altered patterns of menstrual bleeding (prolonged bleeding and amenorrhoea) are common with the LNG-IUS (Grade A).**

Studies have shown that the LNG-IUS is effective in reducing menstrual blood loss (MBL).<sup>42,43</sup> A reduction in MBL of 94% was identified at 3 months in a randomised trial<sup>42</sup> and of up to 97% at 12 months in a non-comparative study.<sup>43</sup>

A systematic review concluded that LNG-IUS users were more likely to experience amenorrhoea than IUD users.<sup>9</sup> One study compared the LNG-IUS with an IUD (CuT 380Ag).<sup>38</sup> At 3 months, LNG-IUS users were twice as likely to be amenorrhoeic as IUD users (RR 2.15; 95% CI 1.31–3.56). This difference increased to seven-fold at 3 years' use (RR 7.24; 95% CI 4.14–12.65). Amenorrhoea or hypomenorrhoea were reported in 65% of women using an LNG-IUS at 1 year.<sup>44</sup>

No significant differences were identified between the LNG-IUS and an IUD (CuT 380Ag) in the incidence of prolonged bleeding when studied at 3 months' and 3 years' use.<sup>38</sup>

The mechanisms underlying bleeding patterns with the LNG-IUS are unclear. The LNG-IUS suppresses spiral arteriole formation<sup>23</sup> and has a localised effect on some vessels within the endometrium.<sup>45</sup> Matrix metalloproteinases, a family of enzymes within the endometrium, are involved in endometrial breakdown during normal menstruation. Expression of metalloproteinase-9 is increased in the endometrium from LNG-IUS users, which may contribute to abnormal bleeding.<sup>46</sup> Many other factors may also be involved.

Hormonal symptoms

**14 Women may be informed that although hormonal symptoms are reported by LNG-IUS users, these are not significantly different from IUD users (Grade A).**

A systematic review identified no significant differences in overall side effects (acne, headaches, breast tenderness, nausea, prolonged bleeding, embedded device or PID) between women using a LNG-IUS or an IUD.<sup>9</sup> Only one randomised trial, which compared the LNG-IUS with the Nova-T® 200 IUD, was used to provide this information.<sup>7</sup> At 5 years, the incidence of symptoms, which might be related to the hormonal content of the LNG-IUS, was not significantly different from those reported by IUD users: headache RR 1.71 (95% CI 0.49–6.02), breast tenderness RR 1.5 (95% CI 0.31–7.17) and acne RR 5.56 (95% CI 0.73–42.35).<sup>9</sup> Serum LNG levels with an LNG-IUS are lower than with oral or subdermal administration but wide interindividual variation in serum LNG occurs.<sup>31</sup> This may explain why there are wide variations in experience of hormonal symptoms.

## Ovarian cysts

**15 Women may be reassured that although ovarian cysts occur in LNG-IUS users, there is no significant increased risk compared to IUD users (Grade A).**

A randomised trial investigated the occurrence of ovarian cysts following LNG-IUS insertion or hysterectomy.<sup>47</sup> The incidence of ovarian cysts was higher in the LNG-IUS group at 6 months (17.5% vs 3%) and at 12 months (21.5% vs 8%). However, no correlation was identified between the presence of ovarian cysts and age or bleeding pattern. The majority of cysts were asymptomatic and resolved spontaneously. A systematic review did not identify an increased risk of ovarian cysts in LNG-IUS users at 5 years compared to IUD users (RR 1.5; 95% CI 0.51–4.4).<sup>9</sup> Small cohort studies identified ovarian cysts in almost one-third of women 3 months after LNG-IUS insertion.<sup>48</sup> Case reports suggest that ovarian pathology should be considered in the differential diagnosis of LNG-IUS users who present with abdominal pain.<sup>49</sup>

## Bone mineral density

**16 Women may be reassured that there is no evidence to suggest the LNG-IUS has a detrimental effect on bone mineral density (Grade C).**

No evidence was identified to suggest the LNG-IUS affects bone mineral density.

## Continuation and discontinuation

**✓ All women considering the LNG-IUS should be informed of potential bleeding patterns and hormonal symptoms that may occur with this method of contraception.**

A Cochrane review showed similar continuation rates for the LNG-IUS, copper IUDs and a subdermal progestogen-only implant (Norplant 2®).<sup>34</sup> Large postmarketing surveys provided evidence on the continuation rates for over 16 231 LNG-IUS insertions.<sup>50</sup> Continuation rates were good: 93% at 1 year, 87% at 2 years, 81% at 3 years, 75% at 4 years and 65% at 5 years. Individual trials, however, have shown lower continuation rates at 1 year (68%<sup>51</sup> to 79.9%<sup>7</sup>) and at 5 years (46.9%).<sup>7</sup> Although hormonal symptoms are similar among LNG-IUS and IUD users, women were still four times more likely to discontinue the LNG-IUS because of hormonal side effects (RR 4.24; 95% CI 1.99–9.04).<sup>38</sup> Amenorrhoea was more likely to lead to discontinuation than other bleeding patterns or pain.<sup>9</sup>

A recent systematic review concluded that there was insufficient evidence to show that counselling before LNG-IUS insertion has any impact on continuation rates.<sup>9</sup> However, individual studies have highlighted that discontinuation is often due to hormonal side effects and menstrual bleeding abnormalities, particularly amenorrhoea.<sup>33</sup> A large epidemiological study of 17 914 LNG-IUS users (75% response rate) evaluated patient information.<sup>52</sup> User satisfaction increased with increasing amount of information received. Counselling should therefore include discussion of these common side effects.

## What are the potential non-contraceptive uses of the LNG-IUS?

*Is the LNG-IUS effective in the management of menorrhagia?*

**17 The LNG-IUS can be used as a first-line option to treat menorrhagia (Grade A).**

**18 The LNG-IUS is effective in the management of menorrhagia, even in the presence of fibroids (Grade C).**

**19 It is not generally recommended that the LNG-IUS be used if fibroids are distorting the uterine cavity (Grade C).**

**20 Surgery (hysterectomy, endometrial resection or ablation) is more effective than the LNG-IUS in treating menorrhagia at 1 year (Grade A).**

**21 The LNG-IUS is as effective as conservative surgery (resection and ablation) in the management of menorrhagia after the first year (Grade A).**

**22 Patient satisfaction and quality of life appear similar following LNG-IUS or surgical treatment of menorrhagia (Grade A).**

A systematic review that included controlled trials and case series, of variable quality, provided evidence to support the use of the LNG-IUS in the treatment of menorrhagia (defined as MBL in excess of 80 ml or heavy cyclical menstrual bleeding over several consecutive cycles).<sup>53,54</sup> Most studies had follow-up for only 1 year, and studies with longer follow-up are required to assess treatment success after the first year. Prospective non-comparative studies<sup>43,55,56</sup> provided evidence that the LNG-IUS is effective in reducing MBL, as assessed by pictorial charts<sup>56</sup> or alkaline haematin techniques.<sup>43,57</sup> Treatment success may also appropriately be measured by assessing patient satisfaction with treatment. In a controlled trial, women were randomised to a LNG-IUS (28 women) or to continue with their current medical treatment (28 women) while awaiting hysterectomy.<sup>58</sup> A total of 64% of women using the LNG-IUS cancelled their hysterectomy (95% CI 44.1–81.4) compared with only 14% (95% CI 4.0–32.7) using their current medical treatment.

*Medical treatments for menorrhagia.* The LNG-IUS is more effective than oral treatments in the management of menorrhagia.<sup>42,53,59,60</sup> The LNG-IUS increases haemoglobin and ferritin levels.<sup>7,43,44</sup> The Royal College of Obstetricians and Gynaecologists (RCOG) guideline on the management of menorrhagia in primary care does not identify the LNG-IUS as a treatment option.<sup>61</sup> However, the RCOG guideline on the management of menorrhagia in secondary care<sup>54</sup> suggests the LNG-IUS may be used to treat menorrhagia after an assessment of the uterine cavity and endometrial biopsy where appropriate. The CEU, however, recommends that the LNG-IUS can be offered to women as a first-line treatment option for menorrhagia. Indications for endometrial biopsy are discussed in Recommendations 31 and 33.

Two observational studies were identified that investigated the effect of LNG-IUS on uterine fibroids.<sup>62,63</sup> The most recent study<sup>62</sup> showed a reduction in MBL with LNG-IUS use. Fibroid volume also appeared to decrease after 6 months' use. There is insufficient evidence to

support the use of LNG-IUS for women with asymptomatic fibroids. However, the LNG-IUS appears to be effective in the treatment of menorrhagia even in the presence of fibroids. WHOMEC recommends that if the uterine cavity is distorted with fibroids, the risks of LNG-IUS use outweigh the benefits (WHO 4) because this may not be compatible with insertion.<sup>4</sup>

**Surgical treatments for menorrhagia.** A Cochrane review, which included five studies, concluded that surgery (hysterectomy, endometrial resection and ablation) was more effective than medical treatment (oral and LNG-IUS) at reducing MBL at 1 year follow-up.<sup>64</sup> Only one was a comparative study between transcervical endometrial resection (TCRE) and oral medication.<sup>65</sup> The other trials compared LNG-IUS with TCRE,<sup>44,66</sup> thermal balloon ablation<sup>67</sup> or hysterectomy.<sup>51</sup> Compared to the LNG-IUS, conservative surgery appeared to be significantly more effective in controlling bleeding at 12 months [odds ratio (OR) 3.99; 95% CI 1.53–10.38].<sup>64</sup>

There are few data, however, regarding bleeding after the first year. One study, which included 66 women, 66% of whom were followed up at 3 years, did not show a significant difference between LNG-IUS and TCRE at 3 years.<sup>66</sup>

Despite using the LNG-IUS or undergoing conservative surgery, many women still require hysterectomy.<sup>68</sup> However, when quality of life was investigated, hysterectomy did not appear to be better than LNG-IUS, and was associated with more complications.<sup>51</sup>

A Cochrane review did not identify significant differences in quality of life, as assessed by Short Form 36, between a LNG-IUS and conservative surgery.<sup>64</sup> This review concluded that the LNG-IUS was as beneficial in improving quality of life as conservative surgery, in the long term.<sup>64</sup> Women using the LNG-IUS and those having TCRE or thermal ablation reported similar satisfaction rates and improvement in quality of life scores. The RCOG guideline on management in secondary care<sup>54</sup> outlines the importance of involving patients in decision-making regarding management options: appropriate information should be provided and quality of life issues should be explored during the consultation.

*Is the LNG-IUS effective in the management of dysmenorrhoea?*

**23 There is insufficient evidence to support the use of the LNG-IUS routinely for women with pain in the absence of heavy bleeding (Grade C).**

A prospective, non-comparative study showed that 80% of women reported a reduction in primary dysmenorrhoea, in addition to MBL, with the LNG-IUS.<sup>56</sup> A randomised trial showed that there was a significant reduction in dysmenorrhoea with the LNG-IUS when compared to a copper IUD.<sup>69</sup> This reduction in dysmenorrhoea with the LNG-IUS may be due to a reduction in heavy bleeding and associated pain. Adenomyosis is a cause of secondary dysmenorrhoea. A small, prospective, non-comparative study investigated the use of LNG-IUS by women with an ultrasound scan diagnosis of adenomyosis.<sup>70</sup> At 1 year follow-up, MBL was improved but no assessment was made regarding pain. A non-randomised study suggested a decrease in pain associated with rectovaginal endometriosis with LNG-IUS insertion.<sup>71</sup> An open, randomised, controlled trial provided further evidence to support the use of the LNG-IUS in this manner.<sup>72</sup> The postoperative insertion of a LNG-IUS, after conservative surgery, prevented recurrence of dysmenorrhoea for up to 1

year for 1 in 3 women (95% CI 2.0–11.00). This application is likely to be the remit of the endometriosis specialist and is unlikely to be requested in primary care. At present, there is insufficient evidence to support the use of LNG-IUS routinely for women with pain in the absence of heavy bleeding.

*Can the LNG-IUS be used as the progestogenic component of hormone replacement therapy?*

**24 Women using oestrogen replacement may choose the LNG-IUS to provide protection against hyperplasia and malignancy, but this is outside the current licence (Grade A).**

**25 The LNG-IUS should not be used routinely as a treatment for endometrial hyperplasia or malignancy (Grade B).**

Oestrogens stimulate the growth of endometrial glands and stroma. Exposure to unopposed oestrogens, endogenous or exogenous, increases the risk of endometrial hyperplasia and malignancy.<sup>73–76</sup> Progestogens, for at least 10 days each month, will reduce this risk.<sup>77,78</sup> Randomised trials suggest that the LNG-IUS is effective in providing endometrial protection from the stimulatory effects of oestrogen, oral<sup>79–81</sup> or transdermal.<sup>82,83</sup> Cohort studies provide evidence of endometrial protection with the LNG-IUS and percutaneous oestradiol gel use.<sup>84,85</sup> Endometrial protection is provided for both postmenopausal<sup>79,83</sup> and perimenopausal women.<sup>80–82</sup> The majority of postmenopausal women (98.2%) using an LNG-IUS as the progestogenic component of HRT were amenorrhoeic after 12 months' use.<sup>79</sup> Perimenopausal women using LNG-IUS had reduction in blood loss, but only 38% were amenorrhoeic at 12 months and 62% were amenorrhoeic at 24 months.<sup>80</sup> However, a randomised trial showed that for perimenopausal women using oral oestradiol, bleeding with the LNG-IUS was less than with oral progestogen.<sup>81</sup>

Women using the LNG-IUS who develop vasomotor symptoms and who wish to use oestrogen replacement may be advised that they can rely on their LNG-IUS for endometrial protection. Currently, in the UK, however, the use of an LNG-IUS in this way is outside product licence.

Recent data suggest an increased risk of cardiovascular disease<sup>86</sup> and breast cancer<sup>87</sup> with hormone replacement therapy (HRT). Current advice is that HRT should be limited to women who require short-term treatment of vasomotor symptoms.<sup>88</sup> The LNG-IUS is unlikely to be the best method of providing endometrial protection for short-term HRT, unless a woman is already using it.

Case reports have suggested that the LNG-IUS may be effective in the treatment of endometrial hyperplasia.<sup>89–91</sup> The largest case report found that all 12 women with simple hyperplasia or atypical hyperplasia had normal endometrium 12 months after LNG-IUS insertion.<sup>89</sup>

*Is the LNG-IUS effective in the management of premenstrual syndrome?*

**26 Women may be advised that there is insufficient evidence that the LNG-IUS alone is effective in the treatment of premenstrual symptoms (Grade C).**

There are few published data on the use of the LNG-IUS in the management of premenstrual syndrome or the more severe premenstrual dysphoric disorder. A non-comparative study of LNG-IUS identified a reduction in subjective premenstrual symptoms in 56% of women.<sup>56</sup>



## When can the LNG-IUS be inserted?

**27 Ideally, the LNG-IUS should be inserted in the first 7 days after the onset of menstruation (Grade C).**

**28 The LNG-IUS is not effective as emergency contraception (Grade C).**

✓ **The LNG-IUS can be inserted at any time in a woman's cycle if it is certain she is not pregnant and has not been at risk of pregnancy in that cycle. Barrier contraception is advised for the next 7 days.**

The Summary of Product Characteristics (SPC) for the LNG-IUS recommends insertion within 7 days of the onset of menstruation.<sup>3</sup> The CEU recommends that a LNG-IUS can be inserted at other times in the cycle if there has been no risk of pregnancy. In this situation barrier contraception is required for 7 days.

WHOMEC recommends that the LNG-IUS may be inserted immediately after surgical termination of pregnancy (TOP): first-trimester (WHO 1) or second-trimester (WHO 2).<sup>4</sup> A randomised trial investigated bleeding patterns following insertion of the LNG-IUS at surgical termination of pregnancy.<sup>92</sup> There was a high rate of loss to follow-up in the first and the last 3 months of the study and the results must be interpreted with caution. Bleeding patterns were better when the LNG-IUS was inserted following TOP than for routine postmenstrual insertion. The removal of the superficial endometrium during TOP may result in these improved bleeding patterns. In line with previous CEU Guidance,<sup>1</sup> following medical TOP the LNG-IUS should be inserted within 48 hours, or delayed until 4 weeks post-termination.<sup>1</sup>

Advice regarding the postpartum insertion of the LNG-IUS follows that for the IUD.<sup>1</sup> The LNG-IUS may be inserted safely 4 or more weeks postpartum.

When switching from another method of contraception the LNG-IUS may be inserted at any time if other hormonal methods have been used consistently and correctly. Additional contraceptive protection is then required for the next 7 days.

## Which examinations and tests should be performed prior to LNG-IUS insertion?

**29 All women considering the LNG-IUS should have examinations and tests as for insertion of any intrauterine method of contraception (Grade C).**

**30 Endometrial assessment (biopsy or ultrasound scan) is not routinely required prior to LNG-IUS insertion for the management of menorrhagia (Grade C).**

All women considering the LNG-IUS should have examinations and tests as outlined for the IUD.<sup>1</sup> This previous Guidance covers:

- bimanual pelvic examination
- testing for STI
- measurement of pulse and blood pressure
- prophylaxis to prevent pelvic infection
- prophylaxis to prevent bacterial endocarditis.

In addition, women considering the LNG-IUS as a treatment for menorrhagia should be managed according to RCOG guidelines on the initial management of menorrhagia<sup>61</sup> and management in secondary care.<sup>54</sup> Abdominal and pelvic examination should be performed for all women with menorrhagia (Grade B). A full blood

count is also indicated for all women (Grade B). Thyroid function tests are rarely indicated (Grade C) and no other endocrine investigation is routinely required (Grade C). An endometrial biopsy is not required in the initial assessment of women with menorrhagia (Grade C).

## What procedures and documentation are required for LNG-IUS insertion?

Procedures and documentation should follow those outlined for the IUD.<sup>1</sup> This previous Guidance covers:

- chaperones
- assistants
- emergency equipment
- documentation
- cervical cleansing
- sterile gloves
- analgesia and anaesthesia
- use of forceps and assessing the length of the uterine cavity
- training.

## What follow-up is required following LNG-IUS insertion?

**31 Women who present with persistent menorrhagia, despite LNG-IUS use, should be advised to return for further assessment of the uterine cavity (biopsy or ultrasound scan) to exclude pathology (Grade B).**

✓ **A follow-up visit should be advised after the first menses, or 3–6 weeks after LNG-IUS insertion.**

If menorrhagia persists despite medical treatments, women should be re-examined (Grade C).<sup>54</sup> An assessment of the uterine cavity should be performed using ultrasound scan (Grade B). An endometrial biopsy should be considered in all women with persistent menorrhagia (Grade C). When indicated, a hysteroscopy allows the assessment of the uterine cavity and biopsy under local anaesthesia (Grade A).<sup>54</sup> The WHO *Selected Practice Recommendations for Contraceptive Use* (WHOSPR)<sup>93</sup> does not specifically refer to the LNG-IUS. Follow-up 3–6 weeks following IUD insertion is recommended and the CEU advises similar follow-up for women using the LNG-IUS.

## How are LNG-IUS problems managed?

**32 Suspected perforation, lost threads, pregnancy, presence of actinomyces-like organisms and pelvic infection should be managed as for IUD use (Grade C).**

**33 Women using the LNG-IUS who present with a change in pattern of bleeding should be advised to return for further investigation to exclude infection, pregnancy and gynaecological pathology (Grade B).**

Advice regarding the management of problems arising with the LNG-IUS use is similar to that for IUD use.<sup>1</sup> This previous Guidance covers:

- suspected perforation
- 'lost threads'
- abnormal bleeding
- pregnancy
- presence of actinomyces-like organisms
- pelvic infection
- postmenopausal removal.

Abnormal bleeding is a particular problem with the LNG-IUS. Studies have shown that 40% of the LNG load

is still present in the LNG-IUS after 5 years' use.<sup>94</sup> It is, therefore, unlikely that any change in bleeding pattern is a result of hormone 'running out'. STIs, device misplacement and pregnancy are among the differential diagnoses to bear in mind when a woman presents with a change in pattern of bleeding. Case reports have described endometrial polyps, endometrial hyperplasia<sup>95,96</sup> and endometrial cancer<sup>97</sup> in women who presented with irregular bleeding following amenorrhoea. This highlights the importance of further investigation for a woman with a new pattern of bleeding.

### When can the LNG-IUS be removed?

✓ **The LNG-IUS may be removed at any time if the woman wishes to conceive; otherwise unprotected sex should be avoided in the 7 days prior to removal.**

When the LNG-IUS is to be removed to achieve pregnancy this can be done at any time. If pregnancy is not wished the LNG-IUS may be removed with menstruation or, if there has been no unprotected intercourse in the preceding 7 days, at other times. When the LNG-IUS is to be exchanged advice should be given to avoid intercourse in the 7 days prior to this procedure in case reinsertion fails.

When women using the LNG-IUS are amenorrhoeic and wish to use alternative contraception, in order to maintain contraceptive protection the LNG-IUS can be removed after seven consecutive combined oral pills, or after two consecutive progestogen-only pills have been taken. The LNG-IUS can be removed 7 days after giving the depot medroxyprogesterone acetate injection or inserting a subdermal progestogen-only implant. An IUD can be inserted immediately following LNG-IUS removal without the need for any additional contraception.

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This Guidance was developed by the Clinical Effectiveness Unit (CEU) of the Faculty of Family Planning and Reproductive Health Care (FFPRHC): Dr Gillian Penney (Director), Dr Susan Brechin (Unit Co-ordinator), Ms Gillian Stephen and Ms Alison de Souza (Research Assistants) in consultation with the Clinical Effectiveness Committee (CEC), which includes service user representation and an Expert Group of health care professionals involved in family planning and reproductive health care. The Expert Group comprised: Miss Louise Cadman (Senior Research Nurse, Margaret Pyke Centre and Wolfson Institute of Preventive Medicine, London), Dr Ruth Howlett-Shipley (SpR Public Health Medicine, Taunton Deane Primary Care Trust, Somerset/Trainee Member of the CEU), Dr Sarah Hughes (Consultant in Contraception and Sexual Health, Victoria Health Centre, Nottingham), Ms Shelley Mehigan (Clinical Nurse Specialist, Family Planning Garden Clinic, Slough Primary Care Trust), Dr Joanne Protheroe (General Practitioner and Medical Research Council Research Fellow, University of Manchester/CEC Representative), Dr Victoria Marilyn Pickles (Lead Senior Clinical Medical Officer, Day Gynaecology Unit, Princess Anne Hospital, Southampton), Dr Felix Ram (Senior Research Fellow, Royal College of Obstetricians and Gynaecologists, London), Dr Alison Scott (Locum Consultant Gynaecologist, Well Woman and Family Planning, Edinburgh) and Dr Alison Vaughan (Director of Contraceptive Services, East Dorset/Education Committee Representative). Written feedback was obtained from Expert Group members: Ms Toni Belfield (Director of Information, fpa, London), Dr Meera Kishen (Consultant in Family Planning and Reproductive Health, Central Abacus, Liverpool/FFPRHC Council Representative) and Dr Nick Panay (Consultant Obstetrician and Gynaecologist, Queen Charlotte’s and Chelsea Hospital, London).

This Guidance is also available online at [www.ffprhc.org.uk](http://www.ffprhc.org.uk). Evidence tables are available on the FFPRHC website. These summarise relevant published evidence on the LNG-IUS, which was identified and appraised in the development of this Guidance. The clinical recommendations within this Guidance (i.e. the text appearing within the red and blue boxes) are based on evidence whenever possible.

Grades of Recommendations	
A	Evidence based on randomised-controlled trials (RCTs)
B	Evidence based on other robust experimental or observational studies
C	Evidence is limited but the advice relies on expert opinion and has the endorsement of respected authorities
✓	Good Practice Point where no evidence exists but where best practice is based on the clinical experience of the Expert Group

Electronic searches were performed for: MEDLINE (CD Ovid version) (1980–2003); EMBASE (1980–2003); PubMed (1980–2003); the Cochrane Library (to December 2003) and the US National Guideline Clearing House. The searches were performed using relevant medical subject headings (MeSH), terms and text words. The Cochrane Library was searched for systematic reviews, meta-analyses and controlled trials relevant to the LNG-IUS. Previously existing guidelines from the Faculty of Family Planning and Reproductive Health Care (FFPRHC), the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization (WHO) and reference lists of identified publications were also searched. Similar search strategies have been used in the development of other national guidelines. Selected key publications were appraised according to standard methodological checklists before conclusions were considered as evidence. Evidence was graded as above, using a scheme similar to that adopted by the RCOG and other guideline development organisations.

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