# The levonorgestrel-releasing intrauterine system in modern gynaecology

***The levonorgestrel-releasing intrauterine system was initially developed for contraception but is now widely used for a variety of gynaecological conditions. Compliance can sometimes be hampered by troublesome side effects (principally breakthrough bleeding) but appropriate counselling can reduce unnecessary discontinuation.***

The levonorgestrel-releasing intrauterine system (LNG-IUS) has been licensed as a contraceptive in the UK since 1995 (Mirena, Schering Health Care Limited, West Sussex, UK). In that time gynaecologists have welcomed the introduction of a method of delivering a progestagen directly to the endometrial cavity – so much so that the LNG-IUS is currently used in the management of a wide range of gynaecological conditions.

The LNG-IUS is a T-shaped intrauterine device (IUD) composed of an inert polydimethylsiloxane core surrounded by a reservoir of LNG on its vertical arm. The device delivers LNG 20 μg into the endometrium every 24 hours in a sustained fashion lasting up to 5 years. During the first few weeks following insertion a stable plasma level of 150–200 pg/ml occurs. The plasma concentrations achieved by the LNG-IUS are lower and more constant (i.e. without peaks and troughs) than those seen with both LNG contraceptive implants and oral contraceptives.

## Clinical uses of the LNG-IUS

### Contraception

The LNG-IUS is licensed for intrauterine contraception for up to 5 years and, if continued contraception is desired, the system may be removed and replaced. The Pearl index (number of unwanted pregnancies per 100 users per year) was 0.18 over 5 years (Backman et al, 2000) which is as effective as female sterilization (Peterson et al, 1996). The major advantage is that the contraceptive effect is reversible. In contrast to inert or copper-bearing IUDs, the LNG-IUS also significantly reduces menstrual blood loss (MBL) with subsequent beneficial effects on haemoglobin concentrations and iron stores.

Pregnancy rates (including ectopic pregnancies) for LNG-IUS users are significantly lower than those of users of Nova-T, Copper T-220C and Copper 200 IUDs. However, LNG-IUS users are more likely to experience amenorrhoea and device expulsion than women using the other types of IUDs (French et al, 2000). Also, women using the LNG-IUS are more likely than IUD users to discontinue use because of hormonal side effects and amenorrhoea. Studies have found that continuation rates appear to improve with better pre-insertion counselling (Cameron, 2001; Backman et al, 2002; Cox et al, 2002).

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### Dysfunctional uterine bleeding

Dysfunctional uterine bleeding is the common clinical problem of excessive MBL in the absence of demonstrable pelvic pathology. Numerous medical and surgical treatments are available (Royal College of Obstetricians and Gynaecologists, 1998, 1999). Among women with objectively measured MBL greater than 80 ml, insertion of the LNG-IUS reduced MBL by 86%, 91% and 97% after 3, 6 and 12 months respectively; this correlated positively with increased levels of serum ferritin and haemoglobin (Andersson and Rybo, 1990).

The LNG-IUS is more effective than oral hormonal and non-hormonal medical treatments, e.g. oral progestagen, flurbiprofen (a non-steroidal anti-inflammatory drug) and cyclokapron (Milsom et al, 1991; Irvine et al, 1998). Most women reported vaginal spotting during the first 3 months but this reduced with the duration of use (Milsom et al, 1991).

The complaint of heavy periods is subjective and MBL is not routinely objectively measured in clinical practice; many women describing heavy periods have MBL within the normal range (Cameron et al, 1990). This has important implications for the overtreatment of a perceived illness especially with respect to surgical interventions. The last 20 years has seen the development of a range of endometrial ablation or resection techniques but hysterectomy remains a popular definitive therapeutic option. Such interventions, with their attendant morbidities, may be inappropriate in many younger women and unnecessary in women approaching the menopause. The LNG-IUS provides a therapeutic alternative since it is effective for 5 years, provides contraception and allows fertility to be retained.

Three randomized controlled trials (Crosignani et al, 1997; Istre and Trolle, 2001; Soyaal et al, 2002) and a further non-randomized comparison (Romer, 2000) have evaluated the LNG-IUS against hysteroscopic endometrial resection or thermal balloon ablation to treat menorrhagia. Twelve months following treatment, surgery appears more effective than the LNG-IUS but patient satisfaction and improvements in quality of life indices are similar. With more prolonged follow up, the effectiveness of the LNG-IUS is equivalent to that of surgical techniques (Faculty of Family Planning and Reproductive Health Care, 2004). This is not surprising since the incidence of amenorrhoea increases with the duration of use of the LNG-IUS, typically 20% at 12 months, reaching 60% after 7 years (Ronnerdag and Odlind, 1999).

Many hysterectomies are performed because of intolerable MBL; two randomized studies have reported the LNG-IUS as an alternative to hysterectomy. Women were assigned to either continued non-surgical treatments or the LNG-IUS while awaiting hysterectomy. The proportion of women who cancelled their planned hysterectomy because of satisfaction with LNG-IUS in the two trials was 80% (Hurskainen et al, 2001) and 64% (Lahteenmaki et al, 1998) compared to cancellation rates of 9% and 14% following conservative treatment. The threshold for offering (and accepting) hysterectomy varies between gynaecologists and patients and may partly account for such dramatic findings but the LNG-IUS offers an acceptable alternative to hysterectomy for some women with dysfunctional uterine bleeding.

### Hormone replacement therapy

In combined hormone replacement therapy, intrauterine administration of progestagen via the LNG-IUS opposes oestrogen-induced proliferation of the endometrium and, in many cases, induces amenorrhoea (Suvanto-Luukkonen and Kauppila, 1999). Use of the LNG-IUS through the climacteric therefore offers the potential for a continuing 'no bleed' preparation for women who choose to take hormone replacement therapy and need to take a progestagen for endometrial protection (i.e. have not had a hysterectomy). Several studies have reported the effectiveness of the LNG-IUS combined with various methods of oestrogen administration in protecting the endometrium from hyperplasia or neoplastic change (Andersson et al, 1992; Raudaskoski et al, 1995) and the LNG-IUS is now licensed for this.

### Endometrial protection

#### During tamoxifen therapy

Tamoxifen is widely used as adjuvant therapy to treat breast cancer but is associated with an increase in the incidence of endometrial hyperplasia and malignancy because tamoxifen acts as a partial oestrogen agonist, stimulating the endometrium. A randomized controlled trial suggested that the LNG-IUS attenuated the uterine response to tamoxifen (Gardner et al, 2000). Further large-scale studies will be needed to confirm these observations before the LNG-IUS can be routinely used for this indication.

#### During management of endometrial hyperplasia

Endometrial hyperplasia (in the absence of tamoxifen administration) is a precursor of endometrial carcinoma. In the absence of cytological atypia less than 2% of cases progress to carcinoma whereas if atypia is present it is estimated that 23% progress (Montgomery et al, 2004). Hysterectomy is recommended for women with atypical hyperplasia but oral progestagens have been used successfully in the management of endometrial hyperplasia for over 40 years, raising the possibility that the LNG-IUS might offer a further alternative.

Published experience is very limited although Wildemeersch and Dhont (2003) describe the successful treatment of 12 women (seven with simple hyperplasia, five with atypical hyperplasia) with a 'frameless' IUD releasing LNG 14 μg/day. The LNG-IUS is not licensed for the management of endometrial hyperplasia and it is not currently recommended for routine treatment of endometrial hyperplasia (Faculty of Family Planning and Reproductive Health Care, 2004); however, with close surveillance the LNG-IUS offers a logical and practical treatment alternative for the minority of women unable to tolerate oral therapy or who are not suitable for surgery.

### Endometriosis

Endometriosis is a common gynaecological condition associated with menstrual and non-menstrual pelvic pain, excessive bleeding and dyspareunia. It is characterized by the presence of endometrial tissue outwith the uterine cavity. Endometriosis has traditionally been treated with systemic synthetic progestagens so the use of the LNG-IUS in this condition appears logical.

Reported experience is limited to small-scale studies but the LNG-IUS is associated with a reduction in MBL and pain and also a reduction in the symptoms associated with and the size of recto-vaginal endometriosis deposits (Vercellini et al, 1999; Fedele et al, 2001). The only randomized controlled trial of the LNG-IUS in management of endometriosis compared the insertion of LNG-IUS *vs* no additional treatment among 40 women undergoing laparoscopic treatment for moderate to severe endometriosis; the LNG-IUS was associated with a significant reduction in the risk of the recurrence of dysmenorrhoea and a higher rate of patient satisfaction (Vercellini et al, 2003).

Adenomyosis, a variant of endometriosis, is characterized by the presence of endometrial tissue within the myometrium. Most patients present with painful, heavy periods. Clinical diagnosis is inexact but transvaginal ultrasound can identify adenomyotic deposits. Among 25 women with adenomyosis, Fedele et al (1997) reported marked relief from adenomyosis-associated menorrhagia. At 1-year follow-up 23 women were still using the device; two were amenorrhoeic, three were oligomenorrhoeic, two had spotting, and 16 women had regular flows. Significant increases in haemoglobin, haematocrit and serum ferritin were observed. In a randomized controlled trial, Maia et al (2003) showed a higher amenorrhoea rate among women receiving an LNG-IUS following endometrial resection in women with adenomyosis-associated menorrhagia compared to no post resection treatment.

### Uterine fibroids (leiomyomata)

Fibroids are common, benign tumours of the myometrium often associated with pelvic pain and menorrhagia. Forty per cent of women with an objective MBL >200 ml have fibroids (Rybo et al, 1985). The LNG-IUS may confer beneficial effects among women with fibroids by reducing MBL. The action of the LNG-IUS is primarily local, causing suppression of endometrial proliferation which may reduce the expression of locally produced growth factors, e.g. epidermal growth factor or platelet-derived growth factor, believed to be involved in the pathogenesis of uterine fibroids (Fayed et al, 1989).

The clinical effectiveness of the LNG-IUS in reduction of MBL in the presence of fibroids has been evaluated in two, uncontrolled, observational studies; among 19 women Mercorio et al (2003) showed a significant reduction in MBL but less marked than would be expected among women without fibroids, whereas Grigorieva et al (2003) described a more profound reduction in MBL and an increase in haemoglobin and ferritin levels among the 67 women studied.

Distortion of the uterine cavity by fibroids can affect the positioning of the LNG-IUS and hence its efficacy. Fibroids causing distortion of the uterine cavity are a relative contraindication to use of the LNG-IUS, mainly because of anticipated technical difficulties with safe insertion (Faculty of Family Planning and Reproductive Health Care, 2004); however, with experience and possibly the use of concomitant ultrasound or preliminary hysteroscopy, LNG-IUS insertion can be safely achieved in most cases.

### Premenstrual syndrome

Premenstrual syndrome is a common condition characterized by an exacerbation of physical and non-physical symptoms before the onset of menstruation. Fluctuations in the endogenous production of sex steroids are believed to be responsible. The LNG-IUS does not reliably suppress ovulation and is not recommended for treatment of premenstrual syndrome by itself but may form a component of treatment whereby it is used in conjunction with transdermal oestrogen (Brechin and Owen, 2003).

## Side effects of the LNG-IUS

The most common side effect of the LNG-IUS is the change in the pattern of vaginal bleeding. These changes can include intermittent or breakthrough bleeding, shorter or longer menstrual periods, or oligo-amenorrhoea. For many women with pre-existing menstrual disorders, such changes are not an issue and frequently represent a symptomatic improvement.

Breakthrough bleeding tends to occur within the first few months after insertion of the LNG-IUS. During this time the number of bleeding or spotting days is usually increased but the volume of blood lost is reduced when compared to the woman's normal menstruation.

The mechanism behind breakthrough bleeding is not completely understood. Work by McGavigan et al (2003) on hysterectomy specimens of women who had the device in situ showed that the histological response between patients varied considerably. However, all specimens showed areas of thinning of the endometrium and the presence of micropolyps. Polypoidal structures are known to develop after treatment with tamoxifen and often manifest with breakthrough bleeding (Hann et al, 2001), which suggests that endometrial surface irregularity or micro-polyps may contribute directly to bleeding patterns observed after exposure to the LNG-IUS.

Qualitative examination of the endometrial vasculature revealed that large vessels were apparent in the superficial part of the endometrium. These vessels lacked a muscularized wall and it is possible that these thin-walled vessels are more susceptible to breakdown leading to breakthrough bleeding (McGavigan et al, 2003).

With prolonged use MBL is dramatically reduced and many women develop oligo- or amenorrhoea. Most women comment favourably on the reduction of duration and quantity of MBL (Cox et al, 2002).

The LNG-IUS is expelled in approximately 5% of insertions and women must be made aware of this possibility and advised of the technique whereby the LNG-IUS threads can be located. Expulsion is most common in the first 12 months following insertion (Cox et al, 2002). Asymptomatic ovarian cysts are commonly encountered among LNG-IUS users but >90% will resolve spontaneously by 12 months post insertion (Inki et al, 2002).

Hormonal side effects most frequently appear at the beginning of treatment but their incidence is low probably because of the low level of systemic steroid. Women are most likely to report breast tenderness, mood changes, weight gain, headache and acne (Istre and Trolle, 2001; Cox et al, 2002). Device removals for such hormonal side effects were not more commonly observed when the LNG-IUS was compared with the Nova T380 IUD (Cox, 2001). Before insertion of the system counselling including an explanation of the anticipated short- and long-term effects of the LNG-IUS, supported with appropriate written material, is necessary in order to reduce unnecessary discontinuation.

## Conclusions

The LNG-IUS has been adopted by gynaecologists in the treatment of a wide range of conditions beyond provision of contraception. With careful patient selection and explanation of the likely results of treatment with the LNG-IUS, high levels of patient satisfaction can be obtained without subjecting women to unnecessary surgical intervention. As clinical experience of the LNG-IUS increases the threshold for offering it as first-line treatment for menorrhagia or as an adjunct to the treatment of endometriosis or fibroid-related bleeding is likely to fall, despite the limited published evidence base for some of these indications. **BJHM**

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## KEY POINTS

- The levonorgestrel intrauterine system was developed as a contraceptive device.
- The device is now widely used to treat a range of gynaecological conditions including menorrhagia, endometriosis and as a component of hormone replacement therapy.
- Minor troublesome side effects (most notably breakthrough bleeding) are often experienced during the first few months.
- Appropriate counselling before insertion of the device can reduce unnecessary discontinuation.