

COMMENTARY

Treating endometriosis with the levonorgestrel-releasing intrauterine system: real hope or gimmick?

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Background

Endometriosis is a condition that significantly affects the quality of life of approximately 10–15% of women in their reproductive years and yet treatment remains problematic.¹ Drug treatment, which is predominantly palliative, for symptoms of dysmenorrhoea, dyspareunia, non-cyclical pelvic pain and/or menorrhagia is hormonally based. Amongst the therapeutic options are anti-oestrogens (e.g. danazol) and regimens that induce either a medical menopause (e.g. GnRh agonists) or a pseudo-pregnant state (e.g. continuous combined oral contraceptives or high-dose progestogens).² Although these drugs are effective in the short term, due to expense and concerns about their long-term safety, some of them (e.g. GnRh agonists) should be withdrawn after a few months. Also, systemic side effects commonly affect compliance; the need for regular administration may further result in poor compliance, which undermines efficacy.

Another problem is the fact that even after successful treatment of endometriosis, symptom recurrence is common. It is reported that the cumulative recurrence rates for the fifth year following successful medical treatment are 37% for minimal disease and 74% for severe disease.³ Laparoscopic ablation or excision is usually effective, but even with this treatment modality, relapse is common.⁴

It is highly regrettable that there remains a paucity of established, simple and cost-effective drug regimens that can be used safely in the long term to control the symptoms of pelvic endometriosis. The development of drugs administered locally to the pelvic organs could limit the metabolic impact without detracting from efficacy and therein may lay the answer to the long-term therapeutic void.

Benefits of the LNG-IUS

The levonorgestrel-releasing intrauterine system (LNG-IUS) Mirena® provides an alternative means of administering progestogens. It was developed as a contraceptive device and releases levonorgestrel to the endometrium at a low rate of 20 µg/24 hours, and its effectiveness lasts 5 years. The progestogen induces endometrial atrophy with minimal systemic side effects due to limited diffusion of the hormone beyond the uterus. This results in a significant reduction in menstrual blood loss and associated dysmenorrhoea in menorrhagic women.⁵ The device is now licensed in the UK as a treatment for menorrhagia. Similar beneficial effects have been demonstrated in menorrhagic women with uterine pathology such as fibroids⁶ and adenomyosis.⁷

As far back as 10 years ago, Singer and Ikomi⁸ reported anecdotal cases of symptomatic relief in endometriosis patients using the LNG-IUS whilst awaiting laparoscopic surgery. It has taken some time but there are now a few published studies indicating a role for this device in treating endometriosis. In a small, prospective, non-comparative, pilot study, Vercellini *et al.*⁹ monitored the effect of the LNG-IUS on 20 parous women with recurrent moderate or severe dysmenorrhoea after conservative surgery for endometriosis in the previous 12 months. Subjects were eligible if they had at least moderate pain on visual analogue and verbal rating scales and a normal uterus and adnexae at clinical examination and transvaginal ultrasonography. At 12-month follow-up there was a highly significant reduction (>50%) in menstrual pain and this was associated with a high degree of patient satisfaction. The small sample size, the relatively short follow-up period and a failure to evaluate the effect on other symptoms such as dyspareunia and non-menstrual pain undoubtedly limited the strength of this pilot study, but provided a clear indication of the potential of the device in treating this condition.

A further study by Fedele *et al.*¹⁰ evaluated the effectiveness of the LNG-IUS as therapy in eleven symptomatic patients with rectovaginal endometriosis over 12 months. In this prospective, therapeutic, non-randomised study all the patients had been diagnosed with pelvic endometriosis and had been surgically treated by laparotomy or laparoscopy in the 12 months before enrolment. Deep endometriosis involving the rectovaginal septum had not been treated. The study demonstrated a great improvement in dysmenorrhoea, non-menstrual pelvic pain and dyspareunia, as well as a reduction in the ultrasonographic dimensions of the rectovaginal nodules. These findings reinforced those of the earlier study⁹ and provided the first indication of a potential cytoreductive effect on the endometriotic lesions.

This concept of a potential cytoreductive effect was explored in a recent prospective, non-comparative study of 34 women with clinically suspected and laparoscopically confirmed symptomatic minimal to moderate endometriosis.¹ In this study by Lockhat *et al.*¹¹ the severity of pelvic pain was scored using the visual analogue scale and the severity of pelvic pain (dysmenorrhoea and/or non-cyclical pelvic pain) was rated on a four-point verbal rating scale. All the subjects underwent a standard two-port diagnostic laparoscopy to confirm the diagnosis of endometriosis with video documentation prior to insertion of the IUS. After 6 months, 29 women remained in the study and five discontinued, for personal reasons (one), side effects of worsening acne (two) and lower abdominal/pelvic pain (three). Second-look laparoscopy was performed again on 26/29 of these women, with video documentation. There was a statistically significant improvement in the severity and frequency of pain as well as the staging of the disease. Peritoneal endometriotic lesions mainly appeared to respond, while the presence of adhesions was not altered. However, an improvement in symptoms was not necessarily associated with changes in the staging, a finding that is in keeping with the enigmatic nature of this condition.

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Long-term treatment options

Lockhat *et al.*¹¹ have recently published an update on the progress of women in the previous study that provides good evidence of longer-term therapeutic effect with the LNG-IUS. The women were followed up every 6 months for up to 3 years. The LNG-IUS continuation rates were 85%, 68%, 62% and 56% at 6, 12, 24 and 36 months, respectively. Overall, significant improvements in pain and menstrual loss scores were observed throughout the 36 months. The 56% continuation rate at 3 years was very reassuring and similar to that in previous studies of the LNG-IUS as a treatment for menorrhagia.¹² On the basis of this study, one should anticipate effective long-term symptom control in those patients who report an initial improvement in symptoms with the IUS *in situ*: an indication of its strong potential to fill the long-term therapeutic void to which we have previously alluded.

Ideally, the true worth of the LNG-IUS as a single primary treatment for endometriosis should be clarified by randomised controlled trials (RCTs), but unfortunately there are limiting factors. For example, it would be unethical to perform placebo comparison studies in symptomatic patients and double blinding would be most challenging in any direct comparisons with established primary treatment modalities. Nonetheless, the only published RCT to date¹³ provides highly encouraging evidence in support of a role for the LNG-IUS as an adjunct to primary treatment by conservative surgery. This open-label, parallel-group RCT compared immediate treatment with the LNG-IUS with expectant management after operative laparoscopy for symptomatic endometriosis. Forty women were recruited and randomised equally into both treatment groups. One year after surgery the median dysmenorrhoea scores were significantly lower in the IUS group compared to the expectant management group. Also, the incidence of significant dysmenorrhoea was lower in the LNG-IUS group (10% vs. 45%). The absolute risk reduction equates to prevention of recurrent dysmenorrhoea in one out of three patients, 1 year after surgery.

This demonstration of a reduction in medium-term risk of recurrent symptoms is highly important, considering previous reports of high relapse rates following initial successful treatment. Also, these data reinforce the potential of the IUS as a long-term treatment option and raise the possibility of a protective effect from the complications of endometriosis in long-term contraceptive users of the IUS. A protective effect from the complications of fibroids has already been reported.¹⁴

Mechanisms of action

What are the possible mechanisms of a beneficial effect of the LNG-IUS on endometriosis?¹ Its influence on menstrual pain can be explained either by reduced uterine spasm simply due to IUS-induced hypomenorrhoea or by a more complex effect on the now recognised paracrine activity of the endometrium. Prostaglandin $F_{2\alpha}$ is produced in secretory endometrium and is thought to be the main agent responsible for dysmenorrhoea by stimulating uterine contractions in the non-pregnant uterus.¹⁵ The IUS causes a decrease in endometrial proliferation and an increase in apoptosis in endometrial glands and stroma.¹⁶ The resultant atrophy leads to an altered expression of many locally acting mediators¹⁷ including vascular growth factors and prostaglandins, thus potentially affecting vascularity and uterine spasm/pain. An effect on non-menstrual pain, dyspareunia and cyto-reduction of the lesions is more difficult to explain. It has been suggested that this could be due to a receptor-mediated action of locally released levonorgestrel on deep endometriotic foci

adjacent to the isthmus and uterine cervix.¹³ This hypothesis is supported by an even more recent study by Lockhat *et al.*¹⁸ in which serum and peritoneal fluid levels of levonorgestrel were quantified in endometriosis sufferers 6 months after insertion of the IUS. In patients showing an improvement in symptoms they demonstrated a significant delivery of levonorgestrel to peritoneal fluid with levels approximating two-thirds of the serum levels, and showed that a linear relationship exists between levonorgestrel levels in these compartments. Other possibilities include theories about alterations in uterine blood flow or disruption of follicular activity.¹

Conclusions

Whilst the mechanisms remain open to question, it has become increasingly difficult to ignore the apparent and consistent effectiveness of the IUS in providing relief in a large proportion of patients with pain and menstrual disorder associated with endometriosis. Indeed, the current evidence has led many gynaecologists to include this device in their therapeutic armamentarium for endometriosis. Nevertheless, it is a fact that some questions remain unanswered and larger controlled trials are needed. Future research also needs to focus on the relative effectiveness of this device compared to other established medical options and to further clarify its effect on non-menstrual pain and dyspareunia.

On the basis of the available evidence, the LNG-IUS appears to be a very reasonable option for endometriosis patients with predominantly menstrual symptoms, especially if they also have contraceptive needs. With a monthly cost over 5 years of only £1.49, this is an option all practitioners must be prepared to consider for their patients. In our opinion, the resounding verdict is one of real hope. Treating endometriosis sufferers with the LNG-IUS is no gimmick.

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