TO DETERMINE THE USE OF AN LNG-IUS FOR CONSERVATIVE MANAGEMENT IN WOMEN WITH SYMPTOMATIC MILD TO MODERATE ENDOMETRIOSIS

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BACKGROUND: Medical treatment of endometriosis, a condition which significantly affects the quality of life in only 10–15% of women in the reproductive years, rest have no improvement. Although oral progestogens are effective and cheap, their efficacy is significantly influenced by poor compliance and systemic side effects. A progestogen (levonorgestrel) administered via an intrauterine system (Lng-IUS) has been demonstrated to improve symptoms of endometriosis; however, its effect on the staging of the disease has not been evaluated. **OBJECTIVE:** The aims of this study were therefore to investigate the effectiveness of Lng-IUS in the symptomatic relief of minimal to moderate endometriosis and in the staging of the disease. **METHODS:** This was a prospective non-comparative observational study in which 33 women with clinically suspected and also confirmed by laparoscopically symptomatic minimal to moderate endometriosis had Lng-IUS inserted for 6 months. The symptom profile and stage of the disease before, during and after 6 months of treatment and patients' satisfaction with treatment and willingness to retain the device at the end of the study period were used to assess response to treatment. **RESULTS:** Out of the 33 women recruited, 29 (87%) completed the study; four discontinued. Rest 29 patients had significant improvements in severity and frequency of pain and menstrual symptoms as well as staging were achieved, and elected to continue with the device after 6 months of therapy. **CONCLUSION:** The levonorgestrel intrauterine system is an effective hormonal option for treating symptomatic endometriosis (minimal to moderate). It has the potential for providing long-term therapy in a substantial number of sufferers, although this would require further study and verification.

INTRODUCTION: Endometriosis is a gynecological medical condition in which cells from the lining of the uterus (endometrium) appear and flourish outside the uterine cavity, most commonly on the membrane which lines the abdominal cavity. The uterine cavity is lined with endometrial cells, which are under the influence of female hormones. Endometrial-like cells in areas outside the uterus (endometriosis) are influenced by hormonal changes and respond in a way that is similar to the cells found inside the uterus. Symptoms often worsen with the menstrual cycle.

- Endometriosis affects 6–20% of women of reproductive age ^{21,22,27}.
- Despite many theories, the exact aetio-pathogenesis is unknown; however, the disease is known to be estrogen dependent ⁸
- Dysmenorrhoea and menorrhagia is main symptoms of endometriosis.
- Amongst the therapeutic options are anti-estrogens (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 contraceptive or progestogens) ^{14,18}. Although these drugs are effective,

systemic side effects commonly affect compliance or preclude long-term use, and the need for regular administration may further result in poor compliance, which undermines efficacy. This is more so with oral progestogens which, although cheap and efficacious, are associated with poorly tolerated side effects of irregular bleeding, weight gain/fluid retention, seborrhoea and breast tenderness. More recently, concerns have also been raised over the possible effects of long-term use of systemic progestogens on bone metabolism²³.

The levonorgestrel intrauterine system (LNG-IUS) Mirena™ provides an alternative means of administering progestogens. It delivers levonorgestrel (a 19-C progestogen) into the uterine cavity at a steady rate of 20µg/day over its 5-year lifespan. The systemic levels following such administration are less than those achieved with therapeutic oral or parenteral doses of progestogens^{6,14,18,19}, hence side effects should theoretically be less severe. Its effects are predominantly localized to the endometrium where the high concentrations of levonorgestrel induce atrophy and pseudo-decidualization^{16,19,24}. It is this action on the endometrium that enables the LNG-IUS to be used as a highly effective intrauterine contraceptive device and has popularized its use in the management of menorrhagia^{2,10}. More recently, its role in protecting the endometrium has been advocated in women on estrogen-only hormone replacement therapy or tamoxifen⁷. Its role in extrauterine pathology such as endometriosis is uncertain, as the levels of levonorgestrel reaching the peritoneal fluid to potentially affect these lesions are unknown.

AIM AND OBJECTIVE: To determine the use of an LNG-IUS for conservative management in women with symptomatic mild to moderate endometriosis.

CRITERIA

INCLUSION CRITERIA:

- Women diagnosed endometriosis stage I-IV according to the revised American Society of Reproductive Medicine classification
- Moderate or severe pelvic pain
- Undergoing conservative laparoscopic surgery

EXCLUSION CRITERIA:

- Patients who have uterine or adnexal anomalies other than endometriosis (chronic pelvic inflammatory disease, leiomyomas, endometrial polyps, genital malformations, pelvic varices)
- Using treatments for endometriosis other than paracetamol, nonsteroidal anti-inflammatory drugs or narcotic derivative in the 3 months before study.
- Patients who have contraindications to LNG- IUS as defined by the World Health Organization (2004).
- Patients who are unwilling to tolerate menstrual changes.
- Plan to have children within 1 year
- Unwilling to participate this project

ORIGINAL ARTICLE

MATERIAL & METHOD: After obtaining approval from the ethical committee and full informed consent from patient with explanation about device in present study we evaluated prospectively the effectiveness of continuous intrauterine release of levonorgestrel for improving dysmenorrhea, chronic pelvic pain and dyspareunia associated with minimal to moderate endometriosis in a period of 20 months. (June 2011 to January 2013).

We included 33 women with a diagnosis of endometriosis clinically by examination, trans-vaginal sonography and confirmed by laparoscopic biopsy of endometrial implants.

All patients advised to stop any medical treatment one month before enrolment into the study. All patients enrolled had a score of more than 8 on 10- point visual analog pain scale.

After detailed counselling LNG IUS was inserted into the uterine cavity within 7 days of the menstrual cycle, using short G.A. No additional medical treatment was given.

After 6 months of continued LNG IUS dysmenorrhea, dyspareunia and chronic pelvic pain intensity was assessed, using a 10-point visual analog pain scale. Following visual analog pain scale was given to all patients..

RESULTS: Of the 33 women recruited, 29(87%) have completed 1 year of the provided. Four patients had discontinued even before completion of 6 months as patients were not satisfied by the side effects like dyspareunia, lower abdominal pain.

29 patients completed 6 months, and had significant improvement in severity and frequency of pain and menstrual symptoms (score < 6 on 10 point visual pain scale). These patients therefore elected to continue with LNG IUS.

COMPARISON BETWEEN PAIN SYMPTOMS AS ASSESSED BY VISUAL ANALOG SCALE

In the study 29 women with surgically staged minimal to moderate endometriosis that were treated with the LNG-IUS for up to 18 months showed a decrease in the visual scale (VAS) from an initial score of 7.7/10 to 2.7/10.

DISCUSSION: Endometriosis is a significant problem affecting 5%–10% of reproductive age of women. It is associated with chronic pelvic pain, dyspareunia and infertility, and is often a significant detriment to a patient's quality of life. Treatment has historically consisted of some combination of nonsteroidal anti-inflammatory medications (NSAIDs), progestational medications such as depot medroxyprogesterone acetate (DMPA) that function as anti-estrogens, ovulation suppression with oral contraceptive pills, androgenic medications such as danazol, gonadotropin-releasing hormone (GnRH) analogues to induce temporary pseudo-menopause^{8,9}, and surgical ablation.

The hormonal IUD is a small "T"-shaped piece of plastic, which contains levonorgestrel, a type of progestogen. The cylinder of the device contains the hormone and is coated with a membrane that regulates the release of levonorgestrel^{4,15,20}. Mirena releases the hormone at an initial rate of 20 micrograms per day⁵.

Although our series is small, it is larger than those previously studied^{6,26} and the results confirm that the LNG-IUS is beneficial in some women with endometriosis experiencing pain and menorrhagia. In assessing response to treatment, account has to be taken of the difficulties and limitations in objectively measuring pain¹².

This modality of treatment confers several advantages over other conventional systemic forms of therapy (avoidance of the need for repeated administration, delivery of a steady amount of levonorgestrel, effective contraception and fewer systemic side effects). Side effects were often transient and generally well tolerated; the side effects profile was similar to that previously described for the device³.

The exact mechanism by which this device is effective is uncertain, but we believe that this may be achieved via both local and systemic routes. The hypomenorrhoea which many of these patients experienced is likely to be a combination of atrophy of the endometrium (local activity) and ovarian suppression (systemic activity). It is recognized that in the first 3 months on the device, up to 85% of women have anovulatory cycles and by 12 months this figure falls to <35%¹³.

However, both noted a persistent symptom improvement at 12 months^{6,26}. In our series (data not presented), >80% of those who elected to continue with the Lng-IUS had no significant exacerbation of symptoms after 12 months therapy, suggesting that another mechanism contributes to the efficacy of the IUS in symptom relief. This second mechanism is likely to be local. Although it may be suggested that the Lng-IUS may alter uterine perfusion and decrease pelvic congestion that may contribute to symptom relief¹¹

Symptom improvement may therefore be due to a combination of menstrual interruption, disruption of follicular activity and a direct effect on the endometriotic lesions. Local levels of levonorgestrel in the peritoneal fluid may facilitate this direct mechanism. If the concentration of the levonorgestrel in the peritoneal fluid is high, then it may alter the steroid receptor expression on lesions (endometriotic receptor-mediated response) in a manner similar to endometrium²⁴. Alternatively, the progestogen may affect the peritoneal fluid macrophage activity, thus altering the production of various cytokines and factors that are responsible for the maintenance of lesions and symptoms (cytokine-mediated macrophage response); this may also be receptor mediated¹⁷. Finally, it may be possible that both systemic and local levonorgestrel down regulate or alter the local gene expressions associated with proliferation of lesions and progression of the disease.

CONCLUSION: It is a convenient alternative to systemic progestogens, and if the side effects, particularly of bleeding dysfunction, which are most common within the first 3 months, can be tolerated, then it could be retained for as long as 5 years. However, further studies are now required not only to verify if this device is equally as effective as other medical options, in the form of larger, well designed, controlled trials, but also to verify whether the device retains its therapeutic effects for its full 5-year lifespan and whether it could be beneficial to women with severe/extensive disease presenting with similar symptoms to those we investigated.

Further trials are needed, however, to verify whether the good results observed are maintained during an entire 5-year period, to confirm the efficacy on dysmenorrhoea, dyspareunia and dyschezia, chronic pelvic pain and to compare the effects of the levonorgestrel intrauterine device with those of other treatment options.

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