LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM IN ADENOMYOSIS; PREDICTORS FOR RESPONSE AND CLINICAL OUTCOME

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INTRODUCTION

Adenomyosis of the uterus is a common condition among women in their 4th and 5th decades of life and is thought to affect 1% of women [1]. It occurs when there is a disruption in the normal interface between the endometrial basal layer and the myometrium, causing the invasion of ectopic endometrial glands into the myometrium. This invasion can be either diffuse (adenomyosis) or focal (adenomyoma) [2].

A reliable diagnosis of adenomyosis can be made by the combination of clinical history, gynecological examination, and transvaginal 2D and 3D ultrasound. In addition, Doppler sonography and magnetic resonance imaging might help to determine adenomyosis, especially in cases with combined uterine fibroids [3]. The diagnosis depends on triad of clinical manifestations composed of the abnormal uterine bleeding (50%), secondary dysmenorrhea (30%), and an enlarged, tender uterus [4].

Hysterectomy was previously recommended as a definitive treatment for adenomyosis; however, this may not be acceptable to some patients [5]. A reversible medical treatment alternative to hysterectomy does now exist the levonorgestrel-releasing intrauterine system (LNG-IUS). This device has been widely evaluated in terms of contraceptive efficacy and idiopathic menorrhagia, and it is highly effective in the treatment of hydrometra and in perimenopausal women and has been shown to be extremely effective in treating the symptoms associated with adenomyosis [6,7]. Moreover, LNG-IUS seems to demonstrate significant and comparable improvements in hemoglobin (Hb) levels to hysterectomy in treating symptomatic adenomyosis, and although both of them lead to improvements in health-related quality of life, LNG-IUS seems to have superior effects on psychosocial life [8].

LNG-IUS had been effectively used to treat adenomyosis through a reduction in thickness of the myometrial junctional zone and total uterine volume [9–11]. The reduction of menstrual blood loss is due to both direct effect of levonorgestrel on adenomyosis foci with decidualization and an increase in apoptosis in endometrial glands and stroma [12].

The LNG-IUS has fewer side effects in comparison to other oral treatment used, in contrast with relatively low serum levels, locally high concentrations of LNG in the endometrium and adjacent tissues [13].

Factors that can predict LNG-IUS treatment response or discontinuation due to expulsion or failure to show a response in women with adenomyosis were not well assessed [5,14].

The aim of this study was to detect clinical and ultrasonographic characters that predict the response of adenomyosis to LNG-IUS and to evaluate the clinical efficacy and the time needed to show response.

MATERIALS AND METHODS

A prospective single-arm study conducted in the Obstetrics and Gynaecology Department Al-Yarmouk Teaching Hospital in Baghdad/Iraq from August 2015 to March 2018 after ethical and scientific committee approval of the Obstetrics and Gynaecology Department.

Women with adenomyosis diagnosed clinically and by ultrasound had been recruited after taking informed written consent from all participants; patients with symptomatic adenomyosis, age 39 years and above and who completed their families had been enrolled in this study. Women with concomitant leiomyomas and other uterine pathology had been excluded as well as women who did not complete their family.
Detailed history, examination, and baseline Hb were performed for all participants followed by ultrasound (transabdominal and transvaginal) to confirm the diagnosis of adenomyosis and exclude other concomitant uterine pathology.

Pictorial blood loss assessment chart was used to assess menstrual blood loss/cycle and menorrhagia defined when the chart score was more than 100 which was, in turn, equivalent to blood loss of more than 80 mL [15].

The severity of dysmenorrhea and pelvic pain was graded by a 10 cm visual analog pain scale (VAS), where mild pain = 1–3, moderate = 4–6, severe = 7–9, and severe disabling pain = 10 [16].

The ultrasound features used to diagnose adenomyosis in this study were the presence of myometrial cysts, linear myometrial striations, poor delineation of the endomyometrial junction, heterogeneous myometrium, and a globular and/or asymmetric uterus [17]. Uterine volume based on the sonographic parameters was calculated using the formula for a prolate ellipsoid: Volume = \(0.5233 \times D_1 \times D_2 \times D_3\) where, \(D_1 = \) maximum length (longitudinal dimension), \(D_2 = \) maximum AP dimension, and \(D_3 = \) maximum width (transverse dimension) [14]. All the patients were subjected to an outpatient endometrial biopsy to rule out other associated possible endometrial pathology [18].

LNG-IUS (Mirena® Bayer, Germany) was inserted in the uterus at the end of the cycle by a specialist in strict accordance with the operating instructions and its place in the uterus was confirmed immediately by ultrasound and reaffirmed again 10–14 days after.

Medical management using nonsteroidal anti-inflammatory drugs, antifibrinolytics tranexamic acid if not contraindicated for the first 2–3 months with cycle was given, and anemia was assessed and corrected [19].

Each patient was asked to come for regular follow-up after Mirena insertion 3 m, 6 m and then at the end of 1st year and 2nd year was full history to see the clinical response regarding menstrual blood loss and pain score and to notify any possible encountered side effect. At each visit, transabdominal and transvaginal ultrasound was done to measure the uterine volume and to confirm that the Mirena is in place and not partially or completely displaced.

Failure was defined as expulsion or discontinuation of Mirena use due to failure to show a response or because of its side effects.

**Statistical analysis**

Anderson darling test was to assess normality of data, Chi-square test, or Fisher exact test used to analyze the discrete variables. Two independent samples t-test used to analyze the differences in means between two groups, for paired group paired t-test was used (normally distributed data), while Wilcoxon U test used for non-normally distributed data. Receiver operator curve used to assess the validity of different parameters. SPSS 20.0.0 (Chicago, IL), MedClac 14.8.1, and GraphPad Prism 7.0 software package used to make the statistical analysis, p value considered when appropriate to be significant if <0.05

**RESULTS**

A total of 46 women with symptomatic adenomyosis were evaluated. The basic clinical characteristics of the participants are shown in Table 1. The mean age of the women was 44.5±2.5 (39–49) years, and the mean number of parity was 3.6±0.9 (2–6). Before insertion of LNG-IUS, the mean menstrual blood loss using PMAC was 144.1±25.9 ml, mean pain score and to notify any possible encountered side effect. At each visit, transabdominal and transvaginal ultrasound was done to measure the uterine volume and to confirm that the Mirena is in place and not partially or completely displaced.

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There was significant reduction in median dysmenorrhea from VAS (3–4) to (2–3), there was significant change in median VAS score from 3 months to 6 months after using Marina 2 (1–2), there was significant change in median VAS score from 6 months to 12 months after using Marina 0 (0–1), and finally there was no significant change from 12 months to 24 months after using Marina 0 (0–1), as illustrated in Fig. 2.

At baseline uterine volume was 131.8±25.5 mm\(^3\) which reduced significantly to 111.1±22.3 mm\(^3\) after 6 months, after 12 months of using Mirena it reduced significantly to 93.4±14.2 mm\(^3\) and finally after another 12 months (2 years) it continued to reduced significantly to 82.3±10.1 mm\(^3\), as illustrated in Fig. 3.

There was a significant increase in Hb value from baseline to the end of follow-up (10.3±0.4–11.3±0.7, p<0.001), as illustrated in Fig. 4.

Table 2 shows the final outcome at the end of the study with a mean duration of follow-up 2.2±0.9 months. The success rate was 80.4%,

**Table 1: Basic clinical characteristics**

| Variables                        | Value               |
|----------------------------------|---------------------|
| Number                           | 46                  |
| Age (years), mean±SD (range)     | 44.5±2.5 (39–49)    |
| Parity, mean±SD (range)          | 3.6±0.9 (2–6)       |
| BMI, mean±SD (range)             | 26.1±1.8 (22–29)    |
| Bleeding volume, mean±SD (range) | 144.1±25.9 (100–200) |
| Dysmenorrhea, mean±SD (range)    | 3.65±1.04 (2–6)     |
| Mild dysmenorrhea, n (%)          | 19 (41.3)           |
| Moderate dysmenorrhea, n (%)      | 27 (58.7%)          |
| Uterine volume, mean±SD (range)  | 139.8±33.2 (90–240) |
| Past surgical history, n (%)      | 8 (17.4)            |
| Curettage, n (%)                  | 9 (19.6)            |
| Others, n (%)                     | 1 (2.2)             |

SD: Standard deviation, range (minimum – maximum)

**Table 2: Final outcome at the end of the study**

| Variables                        | Value               |
|----------------------------------|---------------------|
| Final outcome                    | 37 (80.4)           |
| Success implantation, n (%)      | 37 (80.4)           |
| Failure, n (%)                   | 9 (19.6)            |
| Duration of follow-up (months), mean±SD (range) | 22.7±9.9 (3–32)    |

SD: Standard deviation, range (minimum – maximum)
and the failure rate was 19.6% (expulsion + failure to show response), 4 of them end up with hysterectomy and histopathology then after confirm the diagnosis of adenomyosis.

Bleeding volume and uterine volume at baseline were significantly higher in patients with failure outcome; baseline Hb was significantly lower in patients with failure outcome; as illustrated in Table 3.

![Fig. 2: Boxplot of the change in dysmenorrhea using visual analog pain scale score](image)

![Fig. 3: Uterine volume change during the treatment periods](image)

![Fig. 4: Change in hemoglobin in the study](image)

![Fig. 5: ROC curve of the predictors of failure of implantation](image)

**DISCUSSION**

LNG-IUS is used as an effective treatment reducing adenomyosis-associated menorrhagia with a significant increase in Hb, hematocrit, and serum ferritin [11,20,21].

In our study, there was a significant reduction in bleeding volume/cycle 3 months, 6 months, 1 year, and continue to decrease 2 years after insertion of Mirena. Dysmenorrhea also showed significant improvement 3, 6 months, and 1 year after Mirena insertion. Clinical response was assessed objectively by significant improvement in Hb level throughout the follow-up period.

On the other hand, uterine volume decreased significantly in the first 6 months of using Mirena and continues to decrease significantly over the 1st and 2nd year - the period of the study. This result was in agreed with Lee et al who showed that mean uterine volume decreased in patients with adenomyosis 6 months after Mirena insertion as well as it shows significant improvement in the VAS and PABC scores [22]. However, Cho et al. study revealed that the efficacy of the LNG-IUS on uterine volume may begin to decrease in 2 years after its insertion [14].

**Table 3: Comparison between different variables in relation to the outcome of implantation**

| Variables                        | Outcome     | p    |
|----------------------------------|-------------|------|
|                                 | Failure     | Success |   |
| Number                           | 9           | 37    | 0.546 |
| Age, mean±SD                     | 44.0±2.1    | 44.6±2.6 | 0.509 |
| Parity, mean±SD                  | 3.4±0.9     | 3.7±0.9 | 0.399 |
| BMI, mean±SD                     | 26.6±1.1    | 26.0±2.0 | <0.001 |
| Bleeding volume, mean±SD         | 176.7±21.8  | 136.2±20.0 | <0.001 |
| Dysmenorrhea score, median (IQR) | 4 (3 – 4)   | 4 (3 – 4) | 0.839 |
| Uterine volume baseline, mean±SD | 182.2±35.3  | 129.5±23.3 | <0.001 |
| Baseline Hb, mean±SD             | 10.0±0.2    | 10.3±0.3 | <0.001 |

SD: Standard deviation
The current study shows a success rate of 80.4% and the failure rate of 19.6% (9 patients out of 46 patients - 8 of them had expulsion of the device, and one showed failure of response) and duration of ≥6 months best time to predict failure after LNG-IUD insertion. Lee et al. study showed a failure rate of about 21.6% and median time to failure was 6.7 months [22]. Merki-Feld et al. [23] and Socolov et al. [24] showed 15% and 10.7% failure rate, respectively, and that decreased within 1 year after LNG-IUD insertion.

Factors that can predict LNG-IUD treatment response or discontinuation due to expulsion or failure to show a response in women with adenomyosis were not well assessed [5,14].

In our study, we use multivariate analysis to detect possible factors that can predict response to Mirena before its use in adenomyosis.

This analysis showed that the bleeding volume and Hb had good ability to predict failure of implantation, while uterine volume had excellent ability to predict failure. Bleeding volume above 160 had high PPV - with more than 45% increase in the post-test probability for predicting failure.

Uterine volume above 155 cm³ had also strong increase in predicting failure. The cutoff value of more than 155 cm³ was similar to that seen by Lee et al. study which showed that the optimum cutoff value of uterine volume of >150 cm³ was significantly associated with LNG-IUD failure [22]. Zhang et al. on the other hand, used the uterine volume of 180 cm³ as a cutoff level to predict failure [25].

CONCLUSION
LNG-IUS is an effective option in treating symptomatic adenomyosis in term of time to response and duration of response. The presenting Hb, menstrual blood loss, and uterine volume are useful predictors of response.

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AUTHOR’S CONTRIBUTIONS
All authors certify that they have participated sufficiently in work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

CONFLICTS OF INTEREST
None of the authors have no conflicts of interest.

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