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Article · December 2018

DOI: 10.22159/ajpcr.2018.v11i12.27109

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**LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM IN ADENOMYOSIS; PREDICTORS FOR RESPONSE AND CLINICAL OUTCOME**FADIA J ALIZZI<sup>1</sup>, HIND ABDUL KHALIQ SHOWMAN<sup>1</sup>, HAYDER A FAWZI<sup>2</sup><sup>1</sup>Department of Obstetric Gynecology and Infertility, Al-Mustansiriyah College of Medicine, Baghdad, Iraq. <sup>2</sup>Department of Pharmacy, Baghdad Teaching Hospital, Baghdad, Iraq. E-mail: fadiaalizzi46@gmail.com

Received: 04 May 2018, Revised and Accepted: 30 July 2018

**ABSTRACT**

**Objectives:** The aim is to detect clinical and ultrasonographic characters that predict the response of adenomyosis to levonorgestrel-releasing intrauterine system (LNG-IUS) and to evaluate the clinical efficacy and the time needed to show a response.

**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. Women with symptomatic adenomyosis with age 39 years and above and who completed their families had been enrolled in this study. LNG-IUS was used as a treatment; the outcome measure was to evaluate its effect in improving the symptoms and the time needed to show a clinical response. Multivariate analysis was used to assess the contribution of the clinical and ultrasonographic parameters to the prediction of the response to LNG-IUS.

**Results:** Over the mean duration of follow-up period of the study (22.7±9.9 months), there was a significant improvement in menstrual blood loss, dysmenorrhea, and hemoglobin (Hb) with significant decrease in uterine volume ( $p < 0.001$ ). The time to show response was as early as 3 months and the first 6 months is the best time to predict failure. Initial menstrual blood loss and Hb were good predictors to show response while uterine volume an excellent one (positive predictive value 80% and negative predictive value 97.2%).

**Conclusion:** Levonorgestrel-releasing intrauterine device is an effective treatment of 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.

**Keywords:** Adenomyosis, Levonorgestrel-releasing intrauterine system, Uterine volume.

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**INTRODUCTION**

Adenomyosis of the uterus is a common condition among women in their 4<sup>th</sup> and 5<sup>th</sup> 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 diagnose 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 hydroxymethylbutyrate 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 participant 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, sever= 7-9, and sever 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 ellipsoidals;  $\text{Volume} = 0.5233 \times D1 \times D2 \times D3$  where, D1 = maximum length (longitudinal dimension), D2 = maximum AP dimension, and D3 = 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 utero was confirmed immediately by ultrasound and reconfirmed 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 1<sup>st</sup> year and 2<sup>nd</sup> 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 characters of the participants are shown in Table 1. The mean age of the women was  $44.5 \pm 2.5$  (39-49) years, and the mean number of parity was  $3.6 \pm 0.9$  (2-6). Before insertion of LNG-IUS, the mean menstrual blood loss using PMAC was  $144.1 \pm 25.9$  ml, mean pain  $3.65 \pm 1.04$  using VAS, and the mean uterine volume was  $139.8 \pm 33.2$ .

After insertion of LNG-IUS - there was a significant reduction in bleeding volume from baseline to 3 months ( $144.1 \pm 25.9$  to  $123.5 \pm 29.0$ ), there was significant reduction from 3 months to 6 months after using Marina ( $70.2 \pm 12.7$ ), there was again significant reduction from 6 months

to 12 months after using Marina ( $28.2 \pm 8.3$ ), and finally there was significant further reduction from 12 months to 24 months after using Marina ( $25.9 \pm 7.1$ ), as illustrated in Fig. 1.

There was significant reduction in median dysmenorrhea from VAS (3-4) to (2-3), there was significant change in medina 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  $131.8 \pm 25.5$  mm<sup>3</sup> which reduced significantly to  $111.1 \pm 22.3$  mm<sup>3</sup> after 6 months, after 12 months of using Mirena it reduced significantly to  $93.4 \pm 14.2$  mm<sup>3</sup> and finally after another 12 months (2 years) it continue to reduced significantly to  $82.3 \pm 10.1$  mm<sup>3</sup>, as illustrated in Fig. 3.

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

Table 2 shows the final outcome at the end of the study with a mean duration of follow-up  $22.7 \pm 9.9$  months. The success rate was 80.4%,

**Table 1: Basic clinical characteristics**

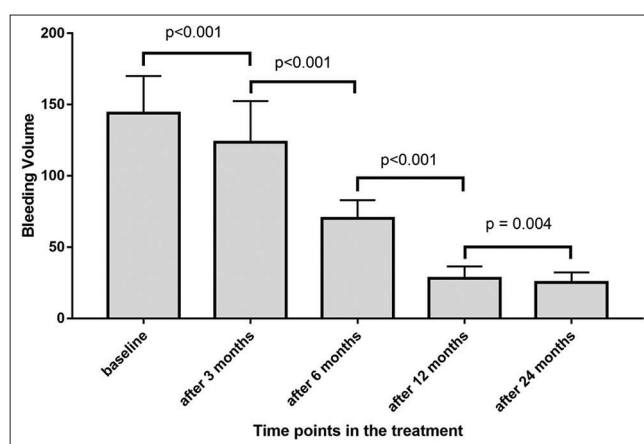
Variables	Value
Number	46
Age (years), mean±SD (range)	44.5±2.5 (39-49)
Parity, mean±SD (range)	3.6±0.9 (2-6)
BMI, mean±SD (range)	26.1±1.8 (22-29)
Bleeding volume, mean±SD (range)	144.1±25.9 (100-200)
Dysmenorrhea, mean±SD (range)	3.65±1.04 (2-6)
Mild dysmenorrhea, n (%)	19 (41.3)
Moderate dysmenorrhea, n (%)	27 (58.7%)
Uterine volume, mean±SD (range)	139.8±33.2 (90-240)
Past surgical history, n (%)	
Curettage, n (%)	8 (17.4)
CS, 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	
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)
Hysterectomy, n (%)	4 (8.7)

SD: Standard deviation, range (minimum - maximum)



**Fig. 1: Change in bleeding volume**

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.

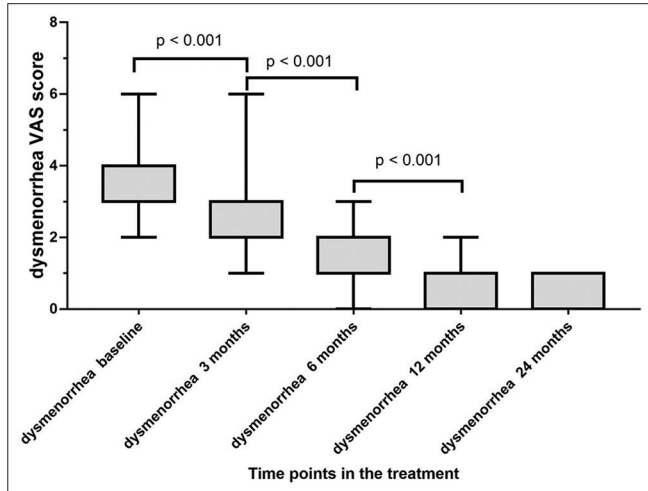


Fig. 2: Boxplot of the change in dysmenorrhea using visual analog pain scale score

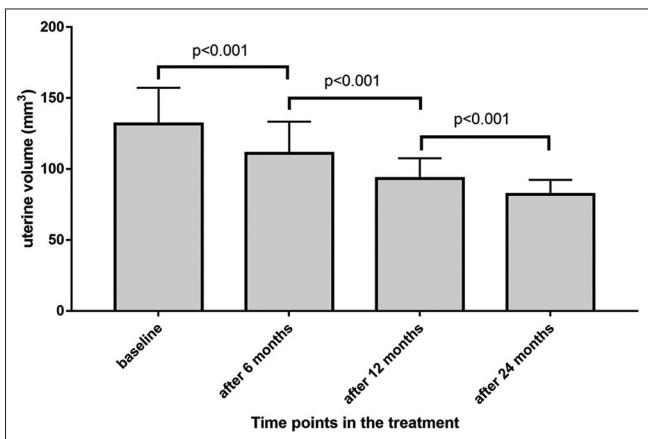


Fig. 3: Uterine volume change during the treatment periods

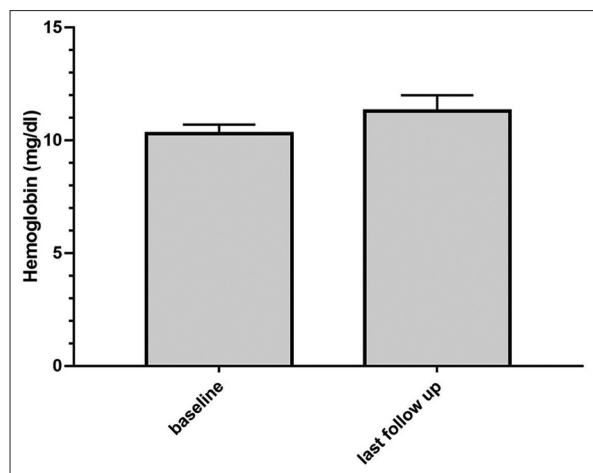


Fig. 4: Change in hemoglobin in the study

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 positive predictive value (PPV) which indicates it will more 45% increase in the post-test probability for predicting failure, uterine volume above 155 had also strong increase in predicting failure, and baseline Hb had slight increase in the post-test probability for predicting failure of implantation, as illustrated in Table 4 and Fig. 5. Duration of ≤6 months best predict failure of treatment, as illustrated in Table 4.

**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 1<sup>st</sup> and 2<sup>nd</sup> 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].

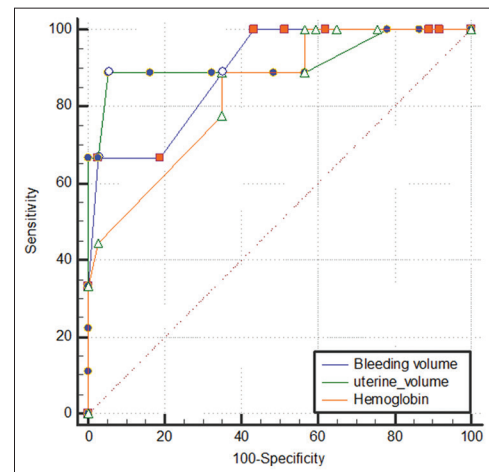


Fig. 5: ROC curve of the predictors of failure of implantation

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

Variables	Outcome		p
	Failure	Success	
Number	9	37	
Age, mean±SD	44.0±2.1	44.6±2.6	0.546
Parity, mean±SD	3.4±0.9	3.7±0.9	0.509
BMI, mean±SD	26.6±1.1	26.0±2.0	0.399
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

**Table 4: Utility of various predictors for failure in implantation of Marina at baseline**

Variables	AUC	Interpretation	Cut point	PPV (%)	NPV (%)	+LH	-LH
Bleeding volume	0.892	Good	>160	85.7	92.3	24.67	0.34
Uterine volume	0.916	Excellent	>155	80	97.2	16.44	0.12
Hb	0.833	Good	≤10.1	38.1	96.0	2.53	0.17
Duration (months)	1.0	Excellent	≤6	100	100	-	-

PPV: Positive predictive value, NPV: Negative predictive value, +LH: Positive likely hood ratio, -LH: Negative likely hood ratio. Hb: Hemoglobin

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 cm<sup>3</sup> had also strong increase in predicting failure. The cutoff value of more than 155 cm<sup>3</sup> was similar to that seen by Lee *et al.* study which showed that the optimum cutoff value of uterine volume of >150 cm<sup>3</sup> was significantly associated with LNG-IUD failure [22]. Zhang *et al.*, on the other hand, used the uterine volume of 180 cm<sup>3</sup> 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.

## ACKNOWLEDGMENTS

This study was supported by the Department of Obstetrics and Gynecology in Al-Mustansiriyah Medical College and the Infertility clinic in Al-Yarmouk Teaching Hospital/Baghdad/Iraq.

## 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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