

THE CLINICAL EFFICACY OF SEQUENTIAL USE OF GONADOTROPIN-RELEASING HORMONE ANALOG - LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM IN MEDICALLY ILL WOMEN WITH SYMPTOMATIC AND RELATIVELY LARGE ADENOMYOSIS

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ABSTRACT

Objectives: To evaluate the clinical outcome of sequential therapy of gonadotropin-releasing hormone (GnRH) analog, followed by the levonorgestrel-releasing intrauterine system in medically ill women with relatively large and symptomatic adenomyosis.

Methods: A prospective cohorts study conducted in the Obstetrics and Gynaecology Department, Al-Yarmouk teaching hospital in Baghdad/Iraq from June 2016 to January 2018. 32 women, 40 years and above who complete their family and had significant medical disease along with symptomatic and relatively large adenomyosis ($\geq 150 \text{ cm}^3$) were included in the study. The primary outcome measure was to evaluate the clinical outcome of this sequential therapy in the form of improving menstrual blood loss and pelvic pain and the secondary outcome was decreasing uterine volume.

Results: There were significant improvements in both menstrual blood loss volume and dysmenorrhea at the end of the 1st year with $p < 0.001$, mainly in the first 6 months. There were also significant reductions in the uterine volume ($197.2 \pm 30.7 - 91.5 \pm 6.0 \text{ mm}^3$). The expulsion rate was 15.6%.

Conclusion: Sequential treatment protocol of GnRH agonist - LNG-IUS in symptomatic and relatively large adenomyosis ($> 150 \text{ cm}^3$) is effective in relieving symptoms and decreasing uterine volume with less possible expulsion rate, making the protocol good substitutions to surgery, especially in medically ill women were surgery carry more risk.

Keywords: Adenomyosis, Gonadotropin-releasing hormone analog, Levonorgestrel-releasing intrauterine system.

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INTRODUCTION

Adenomyosis is a frequent cause of abnormal uterine bleeding (AUB), dysmenorrhea, and uterine enlargement in women in their reproductive years [1].

Histologically, it is defined as the benign invasion of the endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands, and stroma surrounded by the hypertrophic and hyperplastic myometrium [2].

The average age of presentation is usually above 40 years, although it can be seen in young women [3] and its prevalence ranges from 5% to 70%, and the rate of diagnosis during hysterectomy is approximately 20–30% [4].

Gonadotropin-releasing hormone (GnRH) agonists were the first drugs used in the treatment of adenomyosis. They act by binding to GnRH receptors in the pituitary gland causing downregulation of GnRH activity and creating a reversible state of medically induced menopause. There is a reduction in uterine volume, amenorrhea, and relief of severe dysmenorrhea. However, discontinuation of treatments prompts regrowth of the uterus and results in recurrence of symptoms [5]. It is preferable to be used for limited periods of time (3–6 months) due to its side effects [6].

Levonorgestrel-releasing intrauterine system (LNG-IUS) is a highly effective treatment of heavy menstrual bleeding (HMB) in perimenopausal women. It is a safe, effective, and quality of life (QoL) after treatment makes it a good alternative to hysterectomy for HMB [7]. LNG-IUS is currently the best evaluated and the most efficacious treatment of adenomyosis-related symptoms with also a high rate of

symptom improvement, few side-effects, and improvement of the QoL that is at least comparable to that of hysterectomy [8].

Multiple mechanisms may explain the role of the LNG-IUS in adenomyosis including decidualization of the endometrium followed by atrophic changes, through direct action on the adenomyotic foci; in addition downregulation of ER, in both glandular and stromal endometrial layers, occurs rapidly after placement of the device and persists for at least the 1st year of use. Treatment with the LNG-IUS also resulted in reduced lymphangiogenesis and lymphovascular density in the endometrial and myometrial tissues of patients with adenomyosis [9-12].

LNG-IU devices (LNG-IUDs) are spontaneously expelled or removed from some women because of its failure to improve or worsening dysmenorrhea and/or menorrhagia. Heavier and larger uterine volume in women with adenomyosis could be a factor associated with discontinuation of the device [12,13].

The disadvantages of long-term administration of GnRHa in the form of cost, side effect, and possible rebound tendency of adenomyosis to recurs after discontinuation and using Mirena then after is suitable for long-term treatment for adenomyosis overcoming the possible cause of its initial expulsion, the combination of these two therapies could reduce the drawback-effect of GnRHa from one hand and reduce the expulsion rate of LNG-IUD from another hand.

In this study, we use GnRHa first to reduce uterine volume and blood loss and save time to correct anemia then followed by the placement of LNG-IUD. The primary outcome measure was to evaluate the clinical efficacy of this sequential therapy in medically ill women with relatively large and symptomatic adenomyosis.

METHODS

A prospective cohorts study conducted in the Obstetrics and Gynecology Department, Al-Yarmouk teaching hospital in Baghdad, Iraq, from June 2016 to January 2018 after approval of the ethical and scientific committee of the Obstetrics and Gynecology Department.

Women with adenomyosis diagnosed clinically and by ultrasound had been enrolled in the study after taking informed written consent from all participants; the inclusion criteria were age ≥ 40 years, who complete their family, with significant medical condition (hypertension, diabetes mellitus, heart, and renal disease), the participants' have menorrhagia and pelvic pain with uterine volume ≥ 150 cm³. Patients were excluded from this study if they have leiomyomas and when the fertility is an issue.

Complete history and examination with baseline hemoglobin (Hb) were performed for all participant followed by a transvaginal ultrasound to confirm the diagnosis.

The ultrasound features used to diagnose adenomyosis was the presence of myometrial cysts, linear myometrial striations, and poor delineation of the endomyometrial junction, heterogeneous myometrium, and a globular and/or asymmetric uterus [14]. Uterine volume based on the sonographic parameters was calculated using the formula for a prolate ellipsoid; Volume = $0.5233 \times D1 \times D2 \times D3$ where D1 = maximum length (longitudinal dimension) D2 = maximum AP dimension D3 = maximum width (transverse dimension) [12].

Menstrual blood loss was estimated using a pictorial blood loss assessment chart and menorrhagia was defined when chart score = 100 which was, in turn, equivalent to blood loss (80 mL) [15]. The presence and severity of dysmenorrhea were graded with 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].

After the settlements of the diagnosis, all the participants are subjected to an outpatient endometrial biopsy to rule out other possible endometrial pathology [17].

Assessment of the risk of surgery (hysterectomy) with medical consultation had been done for all the participants, patient who was considered to have high risk for major surgery or low-to-intermediate risk, but refuses surgery as a first line were included in this study; all women showed no contraindications for the use of steroid hormones and intrauterine devices.

All the participants were asked to come in the first 2-3 days of the menstrual cycle were a subcutaneous injection of Goserelin (Zoladex 3.6 mg, AstraZeneca) were administered and repeated every 28 days until the uterine volume decreased to a volume <150 cm³. Total doses of goserelin used were 2-6 injection with no estrogen add-back therapy given.

When the uterine volume was determined to be <150 cm³ by transvaginal ultrasound, levonorgestrel-releasing intrauterine device - Mirena (Bayer, Germany) was implanted. Its position was confirmed to be *in situ* 10-14 days after insertion using transvaginal ultrasound and repeated 3 months later to exclude partial or complete dislodgment.

Medical management using non-steroidal anti-inflammatory drugs, antifibrinolytics-tranexamic acid if not contraindicated for the first 2-3 months with cycle was given, and anemia was assessed and was corrected with folic acid supplements, iron sucrose [18].

The complete reassessment was done 6 months and 12 months after Mirena insertion by assessing menstrual blood loss and pain score with transvaginal ultrasound to assess uterine volume at each visit. Other outcome measures include encountered side effect of Mirena, failure and expulsion rate over 20-month follow-up period were recorded.

Statistical analysis

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

During the period of the study, 77 women had been diagnosed as adenomyosis, 32 of them met the inclusion criteria, the mean age of them was 46.6 ± 2.69 , and mean body mass index (BMI) 27.9 ± 1.1 . The mean menstrual blood loss using PMAC was 180 ± 16.2 ml and mean pain 4.75 ± 0.8 using VAS. All of them had associated chronic medical diseases (hypertension, diabetes, heart disease, one case chronic renal disease, and one chronic obstructive airway disease) as shown in Table 1.

There was significant reduction in menstrual blood loss volume from pre-goserelin to end-of-using goserelin ($180.0 \pm 16.2 - 57.8 \pm 3.8$) $p < 0.001$, also there was significant change from after using goserelin to 6 months after using Marina ($57.8 \pm 3.8 - 28.5 \pm 5.9$) with $p < 0.001$; however, from 6 months post-Marina to 12 month post-Marina, there was no significant change ($28.5 \pm 5.9 - 32.5 \pm 4.2$), as illustrated in Fig. 1.

There was significant reduction in VAS score from pre-goserelin to end-of-using goserelin ($4.75 \pm 0.8 - 2.5 \pm 0.5$), also there was significant change from after-using goserelin to 6 months after -using Marina (3.0 ± 0.8); however, from 6-month post -Marina to 12-month post-Marina, there was no significant change (3.5 ± 0.5), as illustrated in Fig. 2.

At baseline, uterine volume was 197.2 ± 30.7 mm³ which reduced significantly to 142.3 ± 8.6 mm³ after using GnRH agonists (goserelin), after 6 months of using LNG-IUS (Mirena) is reduced significantly to 109.8 ± 9.4 mm³ and finally after another 6 months (1 year) it continues to reduced significantly to 91.5 ± 6.0 mm³, as illustrated in Fig. 3.

There was a significant increase in Hb value from baseline to the end of follow-up ($9.8 \pm 0.4 - 11.0 \pm 0.4$, $p < 0.001$), as illustrated in Fig. 4.

Table 2 shows the mean period of follow-up was 17.1 ± 5.7 , during which

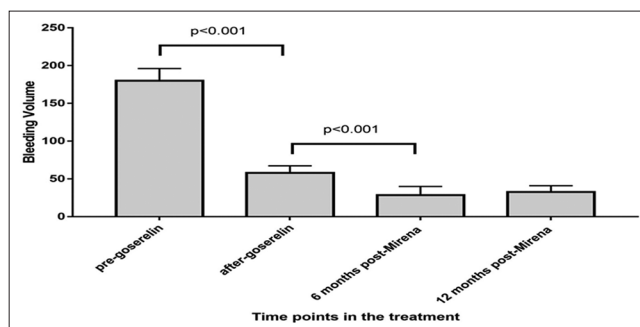


Fig. 1: Percentage change in blood volume

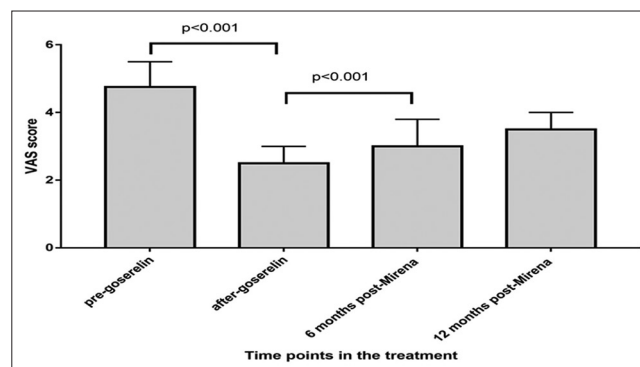


Fig. 2: Change in dysmenorrhea visual analog pain scale score

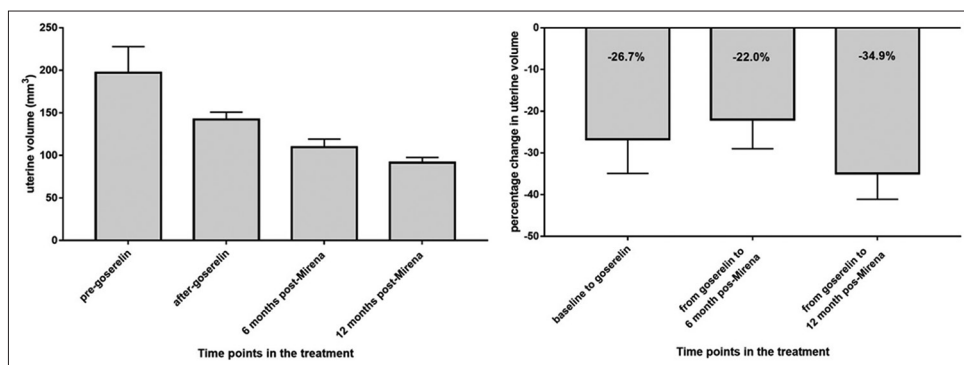


Fig. 3: Uterine volume change during the treatment periods

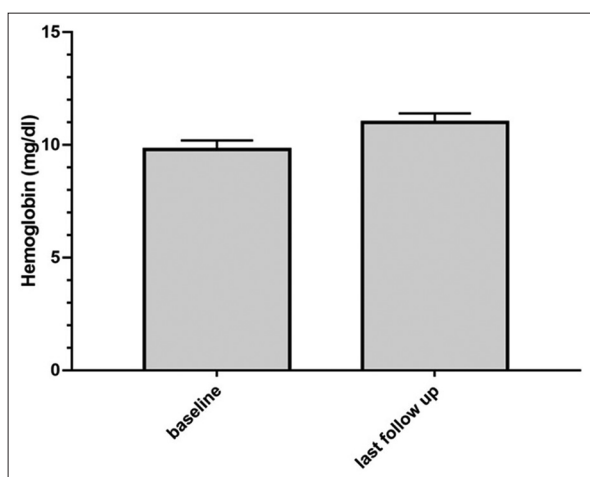


Fig. 4: Change in hemoglobin in the study

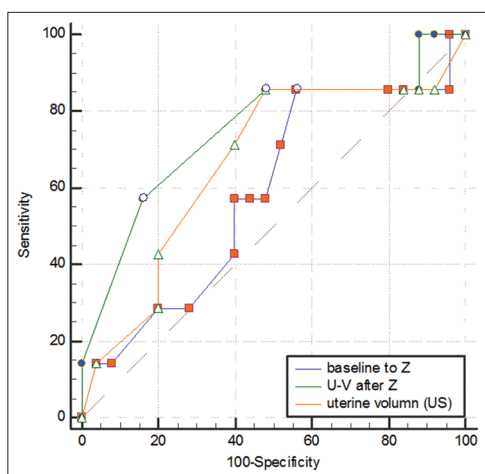


Fig. 5: Receiver operating characteristic curve of the predictors of failure of implantation

25 of women had successful treatment, 6 women (18.8%) have side effect which was mainly spotting, and 6 women had failure (5 expulsed and one woman ask to remove because of the spotting and fail to show response), the failure occurred within the first 6 months of using LNG-IUS, three of the patient enrolled in the study failed to show response and end up with hysterectomy. The histopathology of the products of surgery confirmed the diagnosis of diffuse adenomyosis.

Table 3 shows no significant difference in the age, parity, BMI, bleeding volume, and pain score according to the outcome of implantation. Although the baseline uterine volume and uterine volume after using

GnRH agonists was higher in the failure implantation group, this difference did not reach statistical significance and this, in turn, may be attributed to the small sample size of our study.

Both volume of uterine at baseline and percentage of change from baseline to the stopping of goserelin had poor ability to predict failure of implantation, while the final uterine volume after using goserelin had fair ability to predict failure of implantation with uterine volume >145 mm³ predicting best failure, the positive likelihood ratio for this cut point is 1.53 which indicate it increases the conformation by 0–15%, while the negative likely hood ratio is 0.32 which indicate it had the ability to add 15–30% exclusion to the prediction of failure. This indicates that the final uterine volume after using goserelin is better for predicting success that failure as illustrated in Table 4 and Fig. 5.

DISCUSSION

GnRH agonist was previously the first drug of choice used in the treatment of adenomyosis. It causes reduction in uterine volume, menstrual blood loss, and relief of dysmenorrhea. However, due to its adverse side effects and the possible rebound effect after discontinuation of treatment, their use is limited to a short period of time (3–6 months) and to certain conditions [5,6].

On the other hand, evidence supports that LNG-IUS is used as an effective treatment reducing adenomyosis-associated menorrhagia with a significant increase in Hb, hematocrit, and serum ferritin [9,19]. The efficacy of the LNG-IUS treatment has been widely assessed in decreased AUB and uterine volume at 12 months and has been extremely effective in resolving pain associated with adenomyosis [20]. Fedele *et al.* [19] and Kelekci *et al.* studies also showed that the LNG-IUS results in significant improvements in adenomyosis-associated HMB and dysmenorrhea [21]. However, its efficacy in treating larger uterine adenomyosis is not clear, and its ability to decrease uterine volume has not yet been determined. In clinical practice, an enlarged uterus (uterine volume >12-week gestation) is the main causes of LNG-IUS expulsion [22].

Rapid review of literature that studies the clinical efficacy of combing GnRHa-LNG-IUS in the treatment of symptomatic adenomyosis were few.

Our study design was to gain the advantages of using GnRHa for short period of time to control symptoms rapidly and treat anemia and to reduce the uterine volume by which it can decrease the risk of expulsion if we use LNG-IUS initially. The carry on effect of GnRHa supported by the advantages of use LNG-IUS then after can probably be a good option for medically ill women when surgery carry more risk for them.

Our study showed that there were significant improvements in dysmenorrhea and pelvic pain, as well as significant decrease in the menstrual blood loss, especially after the end-of-using GnRHa in which most of the women became amenorrhea or with minimum menstrual blood loss and this improvement, was maintained through after insertion of LNG-IUS till the end of the follow-up period.

The baseline uterine volume was $197.2 \pm 30.7 \text{ mm}^3$ which reduced significantly to $142.3 \pm 8.6 \text{ mm}^3$ after using GnRH α with 26.7% reduction from its initial size. Further reduction encountered after 6 months of using Mirena where the uterine volume reduced significantly to $109.8 \pm 9.4 \text{ mm}^3$ with 22% reduction from the uterine volume after discontinuation of GnRH α and finally it continues to reduced significantly to $91.5 \pm 6.0 \text{ mm}^3$ 1 year after LNG-IUS insertion with

34.9% reduction in the uterine volume after discontinuation of GnRH α (12.9% from uterine volume 6 m after LNG-IUS insertion).

Zhang *et al.* at 2013 studies the efficacy of LNG-IUS with LNG-IUS for the treatment of adenomyosis, and they end up in a conclusion that this regime was efficacious in patients with enlarged adenomyosis with significant improvement of pain and bleeding and low IUD expulsion rate which in turn allowed patients to avoid surgical treatment. In their study, they use uterine volume of 180 cm^3 as a cutoff level to stop GnRH α and insert LNG-IUS and that the reduction in uterine volume was mainly attributed to the use of GnRH α only and the role of LNG-IUS was to maintain the inhibitory state of the uterus after GnRH α treatment and in turn effectively controlled adenomyosis [22].

Lee *et al.* in their study showed that the optimum cutoff value of the uterine volume of $>150 \text{ mL}$ was significantly associated with LNG-IUD failure. Their study also showed that the mean uterine volume decreased significantly (10%) after 6 months of insertion of LNG-IUS [23].

Sheng *et al.* study also showed a significant reduction in uterine volume after using LNG-IUS and this reduction was mainly seen in the first 1 year of use. The study also showed that LNG-IUS appears to be an effective method in relieving dysmenorrhea associated with adenomyosis during 3 years making it a good long-term alternative for the treatment of adenomyosis [24].

In regard to the rate of expulsion of LNG-IUD, it is around 9-10% when it used as contraceptive purposes [25,26] increase up to 25% when LNG-IUD used in adenomyosis [27] and reach 37.5% when used in large adenomyosis (gestational age 12 weeks during the pelvic examination) [28]. The expulsion rate decrease significantly to 9.5% when LNG-IUD insertion was preceded by the use of GnRH agonists [22].

In our study, the expulsion rate was 15.6% which usually occurred within the first 6 months of insertion of LNG-IUD.

Recommendation of our study is to use case-control study with larger sample size and longer follow-up period.

CONCLUSION

Sequential treatment protocol of GnRH agonist (GnRH α) - LNG-IUS in symptomatic and relatively large adenomyosis ($>150 \text{ cm}^3$) is effective in relieving symptoms significantly by improving pain and heavy menstrual loss as well as its effectiveness in decreasing uterine volume with less possible expulsion rate. This protocol can be good substitutions to surgery, especially in medically ill women were surgery carry more risk.

AUTHOR CONTRIBUTIONS

Concept and collection of data, writing the article and critical review of the article, and final approval of the article - Fadia J Alizzi.

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Table 1: Basic clinical characteristics

Variables	Value
Number	32
Age (years), mean \pm SD (range)	46.6 \pm 2.69 (39-52)
Parity, mean \pm SD (range)	3.5 \pm 0.9 (2-5)
BMI, mean \pm SD (range)	27.9 \pm 1.1 (26-30)
Bleeding volume, mean \pm SD (range)	180.0 \pm 16.2 (150-220)
Dysmenorrhea (VAS), mean \pm SD (range)	4.75 \pm 0.80 (3-6)
Mild dysmenorrhea, no. (%)	2 (6.3%)
Moderate dysmenorrhea, no. (%)	30 (93.8%)
Associated chronic diseases	
Hypertension, no. (%)	20 (62.5%)
DM, no. (%)	25 (78.1%)
Heart, no. (%)	6 (18.8%)
Others, no. (%)	2 (6.3%)
Past surgical history, no. (%)	25 (78.1%)
Curettage, no. (%)	16 (50%)
CS, no. (%)	15 (46.9%)

SD: Standard deviation, range (minimum-maximum)

Table 2: Final outcome at the end of the study

Variables	Value
Expulsion, no. (%)	5 (15.6%)
Side effect, no. (%)	6 (18.8%)
Final outcome	
Success, no. (%)	25 (78.1%)
Failure, no. (%) - [expulsion+ask to remove]	6 (18.8%)
Duration of follow-up (months), mean \pm SD (range)	17.1 \pm 5.7 (5-24)
Hysterectomy, no. (%)	3 (9.4%)

SD: Standard deviation, range (minimum - maximum)

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

Variables	Outcome		p
	Success	Failure	
Number	25	7	-
Age, mean \pm SD	46.7 \pm 2.8	46.4 \pm 2.4	0.831
Parity, mean \pm SD	3.5 \pm 0.9	3.4 \pm 1.0	0.894
BMI, mean \pm SD	27.8 \pm 1.1	28.4 \pm 1.4	0.177
Bleeding volume, mean \pm SD	179.6 \pm 18.4	181.4 \pm 23.4	0.828
Dysmenorrhea score, mean \pm SD	4.8 \pm 0.7	4.7 \pm 1.1	0.897
Uterine volume baseline, mean \pm SD	194.0 \pm 29.2	208.6 \pm 35.8	0.274
Uterine volume after goserelin, mean \pm SD	141.0 \pm 8.2	147.1 \pm 9.0	0.096
Baseline Hb, mean \pm SD	9.8 \pm 0.3	9.6 \pm 0.4	0.141

SD: Standard deviation, Hb: Hemoglobin, BMI: Body mass index

Table 4: Utility of uterine volume as predictor of failure in implantation of Marina

Variables	AUC	Interpretation	Cut point	PPV (%)	NPV (%)	+LH	-LH
At baseline	0.666	Poor	>180	33.3	92.9	1.79	0.27
After using goserelin	0.749	Fair	>145	50.0	87.5	3.57	0.51
Change from baseline to stopping goserelin	0.586	Poor	≤ 23.7	30.0	91.7	1.53	0.32

PPV: Positive predictive value, NPV: Negative predictive value, +LH: Positive likelihood ratio, -LH: Negative likelihood ratio

College for helping us in the completion of this study.

CONFLICT OF INTEREST

Fadia J Alizzi declares that she has no conflict of interest.

HUMAN RIGHTS AND APPROVAL

The protocol for the research project including human subject has been approved by the ethical and scientific committee of the Obstetrics and Gynaecology Department in Al-Yarmouk Teaching Hospital and with the Helsinki Declaration of 1964 and its later amendment. Informed consent was obtained from all participants for being included in the study.

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