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Effect of GNRH Agonist and LNG-IUS for Treatment of Adenomyosis

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ABSTRACT
Background: Uterine adenomyosis is a chronic condition that is dependent on estrogen and affects approximately 20% of gynaecology patients. Dysmenorrhea, menorrhagia, and an enlarged uterus are commonly observed adenomyosis clinical symptoms. **Objective:** This study aimed to assess levonorgestrel-releasing intrauterine system (LNG-IUS) and gonadotropin-releasing hormone agonist (GnRH-a) effectiveness for adenomyosis symptoms improvement.
Methods: This case-control study was carried out on 60 women with adenomyosis who had regular follow-up examinations. The patients were categorized into 2 equal groups: Case group (group 1 receiving GnRH-a as well as LNG-IUS) and control group (group 2 receiving GnRH-a only). The indices observed included: Serum CA125 level during, before and after the treatment, hemoglobin value before and 3 months after treatment, verbal rating scale (VRS), visual analogue scale (VAS), and uterine volume.
Results: After treatment, the Hb level was significantly elevated in the case group compared to the control group (P=0.035), whereas CA125 was significantly lower in the case group compared to the control group (P=0.009). Regarding the clinical assessment, after treatment, the dysmenorrhea VRS score, and the dysmenorrhea VAS score were significantly reduced in the case group compared to the control group (P<0.05).
Conclusions: Both LNG-IUS and GnRH-a combination treatment is efficient and safe in adenomyosis and caused a significant reduction in serum CA125 and dysmenorrhea.
Keywords: GnRH agonist, LNG- IUS, Adenomyosis.

INTRODUCTION

Uterine adenomyosis is a chronic condition that is dependent on estrogen and affects approximately 20% of gynaecology patients. The most prevalent symptoms of this condition are infertility, intense pelvic pain, and heavy menstrual bleeding. The pathogenesis of the disease is not yet fully comprehended, despite its severe symptoms and high prevalence [1]. The absence of a universal classification system and a critical information lack on the disease origin have resulted in a therapeutic anarchy form. Approximately 82% of adenomyosis cases ultimately underwent hysterectomy, which is a somewhat extreme approach to treatment [2]. Transvaginal ultrasound (US) and magnetic resonance imaging are employed to diagnose adenomyosis, while the lesions presence is typically verified histologically when a surgical specimen is available [3]. Menorrhagia, dysmenorrhea, and an enlarged uterus are commonly observed adenomyosis clinical symptoms. In the past, adenomyosis was frequently observed in women who had delivered their babies [4].

This disorder prevalence among infertile patients has elevated as a result of the fact that a significant number of women elect to delay their initial delivery. However, the traditional hysterectomy is no longer accepted due to the growing number of participants who opt to preserve their uterus and fertility [5].

This disease is managed through a variety of approaches, including medical treatments and surgery. The efficacy of gonadotropin-releasing hormone agonist (GnRH-a), laparotomy or laparoscopy, and levonorgestrel-releasing intrauterine system (LNG-IUS) has been documented in numerous studies [6].

GnRH-a causes restricted ovarian function, which is referred to as drug oophorectomy, and improves dysmenorrhea and causes amenorrhea by controlling gonadotropin secretion. Bone loss, premenopausal symptoms, and elevated relapse rate following medication withdrawal are among the most significant side effects. The LNS-IUS improves hypermenorrhea and dysmenorrhea by distributing progestin derivatives, which leads to endometrial decidualization [7].

Nevertheless, the LNS-IUS is not appropriate for women with an enlarged uterus, particularly if the uterus is the size of a three-month gestation, as this is associated with a high risk of prolapse or expulsion [8].

Therefore, the efficacy of this strategy for adenomyosis is still a debate topic, and it is inevitable that a combination of multiple methods be employed to treat adenomyosis. Only researches handful have detected the optimal strategy. We aimed to determine the GnRH-a efficacy in addition to LNG-IUS for adenomyosis symptoms improvement.

PATIENTS AND METHODS

This case control study was carried out on 60 women with adenomyosis attending regular follow-up examinations at the General Military Hospital in Alexandria, Egypt.

Diagnosis of adenomyosis: Ultrasonography is a frequently employed diagnostic tool for adenomyosis. As follows are the typical symptoms of adenomyosis: The myometrium increased echotexture, heterogeneous

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echotexture of the myometrium, myometrial cyst, asymmetrically thickened uterine wall, and a globular enlarged uterus [9, 10]. Adenomyosis was identified when at least two of the aforementioned signs were observed.

Inclusion criteria: patients' age group between 20 to 45 years (reproductive age), had regular menstrual cycles, had a visual analogue scale (VAS) score of more than three points, had available trans-vaginal US examination data through the follow-up period and were diagnosed with focal or diffuse adenomyosis.

Exclusion criteria: Patients who had any contraindication or previously received hormonal therapy (LNG-IUS, GnRH-a, or combined oral contraceptives) and who had a history of malignant tumor or congenital valvular heart disease or coagulopathy. Those with a cervical, vaginal, or uterine congenital anomaly, uterus larger than 12-week gestation or acute pelvic inflammatory disease were also excluded from the study.

Grouping: Case group (group 1) (n=30): had LNG-IUS and GnRH-a and control group (group 2) (n=30): received GnRH-a only.

History taking: All patients were asked about the following: age, gravidity, average time with clinical symptoms, VAS scores of dysmenorrhea, time of symptom recurrence and pregnancy outcomes.

Clinical evaluation: All patients were subjected to a trans-vaginal US by an experienced ultra-sonographer and the uterine volume was measured utilizing the following formula [11]: The uterus 0.52 × width × length × thickness detected with trans-vaginal US. The uterine volume was estimated before the intervention and six months after the intervention [12].

GnRHa application: All patients were subjected to a subcutaneous injection of Goserelin (AstraZeneca, Cambridge, UK), Triptorelin (Ipsen S.A., Paris, France), or Leuprorelin (Livzon, Zhuhai, China) on one of the menstrual cycle first three days for six consecutive cycles [8].

LNG-IUS implantation: If uterine length was less than 10 cm by US, a Mirena (Bayer, Germany) was established by a specialist (P.Z.) in strict accordance with the operative directions. Positioning was then verified by a trans-vaginal and trans-abdominal US examination one week after the implantation.

Laboratory evaluation: From all patients involved in the research 3 to 5 mL of blood were withdrawn in the morning before the GnRH-a injection, one, three, and six months after treatment. The blood was gathered in a vacutainer tube with separation gel and haemoglobin value as well as CA125 levels were measured. CA125 levels were detected utilizing Elecsys CA125 kits from Roche, Switzerland, Basel, and electrochemiluminescence immunoassays were done automatically in strict accordance with the instrument and kit guidelines.

VAS and VRS: All patients involved in this study underwent both the VAS and the VRS before and six months after the intervention. Both scores were utilized to determine the dysmenorrhea grade. In the VAS score, the patient was asked to draw a vertical line on the horizontal scale representing the intensity of dysmenorrhea. The horizontal line is labelled "No pain" at the left end and "worst pain imaginable" at the right end. Between the two ends it is divided into 0–10 categories indicating the exact level of pain felt by the patient [13]. Levels between 0 and 3 were defined as slight pain that cases could endure; 4 to 6 were definite as moderate pain where the participants demanded medicine for relief; 7 to 10 were known as severe pain that could not be endured even with medicine for relief [12]. Additionally, a 4-grade VRS was chosen to assess the patient`s pain intensity. All patients were asked about the severity of the pain they endured and categorized as follows: severe pain = 3, moderate pain = 2, mild pain = 1, and no pain = 0 [14].

Ethical consideration: Before participating in the study, all patients provided written informed consent. The Ethics Committee of the Hospital approved this study, which is in accordance with the Helsinki Declaration to be conducted over a five-year period (2019-2023) (Approval code: Ms 3.3.2019).

Statistical analysis

SPSS version 28 (IBM Inc., Armonk, NY, USA) was employed to conduct the statistical analysis. The quantitative variables mean ± SD were presented and contrast between both groups utilizing an unpaired Student's t-test. The Fisher's exact or Chi-square test was employed to analyse qualitative variables, which were expressed as frequency and percentage (%) when appropriate. The paired sample t-test was employed to compare the means of two populations that were correlated. Statistical significance was detected as a two-tailed P value ≤ 0.05.

RESULTS

Baseline data (age, weight, height and BMI) did not exhibit any substantial disparities among the investigated populations (Table 1).

Table (1): Baseline characteristics of the studied participants (n=60)

	Case group (n=30)	Control group (n=30)	Test of sig.	P value
Age (Years)	28.3 ± 6.46	29.7 ± 6.57	t= 0.8325	0.409
Weight (Kg)	73.3 ± 8.49	70.9 ± 8.77	t = 1.077	0.286
Height (m)	1.66 ± 0.05	1.67 ± 0.05	t = 0.5401	0.591
BMI (Kg/m^2)	26.5 ± 3.35	25.4 ± 3.84	t = 1.117	0.268

Data is presented as mean ± SD. BMI: Body mass index.

The reproductive history including parity and average time with clinical symptoms was similar in both groups (Table 2).

Table (2): Reproductive history of the studied participants (n=60)

		Case group (n=30)	Control group (n=30)	Test of sig.	P value
Parity	**Nullipara**	13 (43.33%)	15 (50%)	X^2=0.710	0.701
	Multipara	17 (56.67%)	15 (50%)		
Average time with clinical symptoms (Years)		2.5 ± 1.11	2.7 ± 1.15	t = 0.5708	0.570

Data is presented as frequency (percentage), mean ± SD

Haemoglobin levels before the GnRH-a injection were similar in both groups, but after the GnRH-a injection treatment, the Hb levels were significantly increased in both groups. The Hb level in the case group was significantly increased compared to the control group (P=0.035) (Table 3).

Table (3): Haemoglobin level of the studied participants (n=60)

		Case group (n=30)	Control group (n=30)	Test of sig.	P value
Hb (g/dL)	**Before treatment**	9.8 ± 0.73	9.6 ± 0.72	t = 1.072	0.288
	After treatment	11.5 ± 1.16	10.9 ± 1	t = 2.162	**0.035***
	P value within group	**<0.001***	**<0.001***	---	---
	Test of sig.	t = 6.822	t = 6.335	---	---

Data is presented as mean ± SD. Hb: Hemoglobin, *: statistically significant as p value <0.05.

The CA125 levels before the GnRH-a injection were the same in both groups, but after the GnRH-a injection treatment, the CA125 levels were significantly lowered in both groups. The CA125 levels in the case group were significantly reduced compared to the control group (P=0.009) (Table 4).

Table 4: CA125 of the studied participants (n=60)

		Case group (n=30)	Control group (n=30)	Test of sig.	P value
CA125 (U/mL)	**Before treatment**	152.9 ± 7.12	134.4 ± 7.9	t = 1.030	0.307
	After treatment	23.7 ± 1.84	33 ± 4.79	t = 2.683	**0.009***
	P value within group	**<0.001***	**<0.001***	---	---
	Test of sig.	t = 10.014	t = 7.355	---	---

Data is presented as mean ± SD. CA125: Cancer antigen 125, *: statistically significant as p value <0.05.

Dysmenorrhea VRS and VAS scores before treatment were similar in both groups. Afterward treatment both groups showed a significantly decrease in dysmenorrhea VRS and VAS scores (P<0.05). The dysmenorrhea VRS and VAS scores were significantly reduced in the case group contrast to the control group afterward treatment (P<0.05) (Table 5).

Table (5): Dysmenorrhea score of the studied participants (n=60)

		Case group (n=30)	Control group (n=30)	Test of sig.	P value
Dysmenorrhea VRS score	**Before treatment**	2.9 ± 0.84	3.03 ± 0.81	t = 0.624	0.535
	After treatment	0.4 ± 0.43	1.03 ± 1.03	t = 3.449	**0.001***
	P value within group	**<0.001***	**<0.001***	---	---
	Test of sig.	t = 12.970	t = 9.832	---	---
Dysmenorrhea VAS score	**Before treatment**	7.6 ± 1.13	7.8 ± 1.19	t = 0.667	0.507
	After treatment	2.3 ± 0.74	2.7 ± 0.78	t = 2.370	**0.021***
	P value within group	**<0.001***	**<0.001***	---	---
	Test of sig.	t = 22.550	t = 19.646	---	---

Data is presented as mean ± SD. VRS: Verbal rating scale, VAS: Visual analog scale, *: statistically significant as p value <0.05.

Uterine volume before treatment was comparable in both groups and subsequent treatment the uterine volume significantly reduced in both groups (P<0.05). After treatment, the uterine volume was significantly lower in the case group compared to the control group (P<0.001). (Table 6).

Table (6): Uterine assessment of the studied participants (n=60)

		Case group (n=30)	Control group (n=30)	Test of sig.	P value
Uterine volume (cm^3)	**Before treatment**	184.8 ± 6.26	185.4 ± 6.7	t = 0.358	0.721
	After treatment	49.2 ± 49.2	88.7 ± 88.73	---	**<0.001***
	P value within group	**<0.001***	**<0.001***	---	---
	Test of sig.	t = 81.531	t = 55.130	---	---

Data is presented as mean ± SD. *: statistically significant as p value <0.05.

DISCUSSION

Infertility and a substandard quality of life are the primary consequences of adenomyosis, which primarily affects women of reproductive age. At present, there is a dearth of precise treatment guidelines, particularly for severe adenomyosis. Hysterectomy is the most effective management tool. However, patients with fertility aspirations must undergo uterine removal. The uterine rupture risk through pregnancy is exacerbated by the challenges associated with adequately isolating the adenomyotic lesions, which is why uterine-sparing surgery remains a contentious topic [15].

Despite the fact that neither hormonal nor non-hormonal drugs are cytoreductive, healthcare guidelines are designed to alleviate clinical symptoms and restore fertility. Consequently, the high recurrence risk following the cessation of medication remains a perplexing issue. Additionally, there are a variety of side effects that can affect the long-term use of all medications [16].

Hormone therapy is universally accepted as a supplement for the adenomyosis treatment, which is an estrogen-dependent benign disorder. Other treatments for this condition include hormone therapy (LNG-IUS and GnRH-a). Nevertheless, GnRH-a and LNG-IUS exhibited certain drawbacks that restricted their application [17]. We aimed to detect the GnRH-a and LNG-IUS efficacy for adenomyosis symptoms improvement compared to GnRH-a alone.

In the current study, the CA125 serum level was significantly reduced in the case group in contrast to the control group (P=0.009). Within both groups, Hb level and CA125 after treatment were significantly reduced compared to before treatment (P<0.001).

In a prospective cohort study, the recurrence rate of adenomyosis cases treated with GnRH-a was 28.1%, which was reduced in contrast with the rate of patients treated with surgery (49%). This was due to the direct release of progesterone into the uterine cavity by LNG-IUS [18]. Numerous investigations have verified that the LNG-IUS can alleviate symptoms for example; menorrhagia and dysmenorrhea in adenomyosis patients and to a certain extent lower CA125 level [19]. Nevertheless, certain studies have discovered that the slippage rate among adenomyotic patients with a larger uterus is as high as 37.5% following the LNG-IUS implantation [20]. According to **Lang *et al.*** [21], the downward movement and expulsion rate can be reduced in obvious uterine enlargement cases by administering GnRH-a for 3–6 months to lower the uterine volume prior to LNG-IUS insertion. The expulsion rate was 4.3% in our investigation. During the application of GnRH-a, a substantial decrease in uterine volume was detected; however, the GnRH-a efficacy was lost after three months.

In our study, after treatment, the Hb level was significantly elevated in case group compared to control group (P=0.035). Within both groups, Hb level after treatment was significantly reduced contrast to their levels before treatment (P<0.001). **Qin *et al.*** [12] in their case series, they enhanced this method by incorporating the "double-flap method" and the LNG-IUS and GnRH-a sequential treatment to ascertain the clinical efficacy and feasibility of this scheme in the severe adenomyosis treatment. They discovered that 64 cases successfully underwent the intervention. After the sequential treatment was completed, the CA125 level was lowered significantly one month following the operation, the average uterine volume was decreased significantly, the hemoglobin value was elevated to a certain extent three months later, and dysmenorrhea during the first menstruation was significantly lower than it was prior to the intervention.

Regarding clinical assessment, we found that after treatment, dysmenorrhea VRS score and dysmenorrhea VAS score were significantly reduced in case group compared to control group (P<0.05). Within both groups, dysmenorrhea VRS score, and dysmenorrhea VAS score were significantly reduced compared to their levels before treatment (P<0.05). After treatment, the uterine volume was significantly reduced in case group compared to control group (P<0.001). Within both groups, uterine volume was significantly reduced compared to before treatment (P<0.05).

Yang *et al.* [22] enrolled 47 patients with adenomyosis who had LNG-IUS and GnRH-a, instituted the control group. They reported that the VRS score and uterine volume in the control groups 1 year after placement and before treatment were significantly lowered after 1 year compared to pretreatment. While, HB level was significantly increased after treatment compared to before treatment.

Zhang *et al.* [8] reported that LNG-IUS and GnRHa (Mirena) combination protocol was proven to be an effective treatment option for an adenomyosis cases with an enlarged uterus in his recent study. GnRHa effectively decreased uterine volume. The uterine volume was lowered in comparison with the pre-GnRHa treatment values during the follow-up at 3, 6, and 12 months following Mirena implantation. Nevertheless, the uterus' volume was greater at 6- and 12-months post-implantation than it was at the time of implantation. These results indicate that Mirena was capable of maintaining the uterus inhibitory state following GnRHa treatment and effectively managing adenomyosis. In a previous study, the administration of Mirena was found to reduce blood loss, uterine volume and endometrial thickness [23, 24]. Nevertheless, a separate investigation demonstrated that the uterine volume had reverted to its pre-treatment level four months after the withdrawal of single GnRHa. Therefore, the combined GnRHa-Mirena protocol was more effective in controlling uterine volume than a single GnRHa application [24].

Additionally, the cost of Mirena and GnRHa combination protocol is less than that of surgery in China. For instance, the cost of Mirena administration following three GnRHa cycles is equivalent to USD

6,000. Conversely, the cost of a hysterectomy is doubled due to the hospital stay [8].

Yang *et al.* [11] have demonstrated that clinical symptoms are significantly enhanced by the GnRH-a, HIFU, and the LNG-IUS combination. The VRS and VAS scores were both significantly reduced following the combined treatment and were kept at a very low level according to our follow-up evaluation. Menstrual flow is significantly correlated with hemoglobin. Our investigation assessed the hemoglobin level and determined that the majority of participants experienced anemia to varying degrees prior to HIFU ablation. After the combined therapy, the hemoglobin level was evidently higher, suggesting that the treatment was effective in treating hypermenorrhea caused by adenomyosis. After the LNG-IUD implantation, the CA-125 value was maintained at normal levels, despite a significant decrease in value following HIFU ablation and subsequent GnRH-a treatment.

Wang *et al.* [25] selected 120 patients who were treated for AM. A study and control group were established for the patients. The control group was administered GnRH-a alone, while the study group was administered GnRH-a in conjunction with dienogest. The effective rate of the study group was 91.67%, while the control group's effective rate was 73.33%. This was determined by comparing the efficacy of the two groups. The study group efficacy was significantly greater than control group when comparing the two groups ($p < 0.05$). The study group dysmenorrhea scores were significantly less than those of the control group at 1-, 3-, and 6-months following treatment ($p < 0.05$). The researchers reported that GnRH-a alone only affects hormone levels and maintains low estrogen levels in cases by altering hormone secretion in the hypothalamic-pituitary-ovarian gonadal axis. GnRH-a reduced the blood supply to the uterine adenomyoma lesions, which led to a slower shrinkage of these lesions.

LIMITATIONS

The small sample size due to the few cases number that were enrolled in the study and lost follow up over the period of study (5 years). To add more, the long-term impacts of the intervention need to be further followed up and demonstrated further. Due to these constraints, a randomized controlled trial with a long-term follow-up has been developed to verify the intervention's efficacy.

CONCLUSION

GnRH-a + LNG-IUS combination treatment is harmless and efficacious in the reduction of signs and symptoms of adenomyosis through significantly reducing dysmenorrhea and serum CA125 levels and significantly increasing Hb levels.

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- **Conflict of Interest:** Nil.

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