Original Article

Treatment Of Infertile Adenomyosis Patients Using Levonorgestrel-Releasing Intrauterine System Or Gonadotropin-Releasing Hormone Gonist Before Frozen Blastocyst Transfer Improves Manifestations And Increases The Chances Of Pregnancy

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ABSTRACT

Objectives: To examine the effects of Levonorgestrel-releasing Intrauterine System (LNG-IUS) and Gonadotropin-releasing Hormone agonist (GnRHa) therapy on adenomyosis symptoms and the outcomes of frozen blastocyst transfer (FBT).

Patients & Methods: In this study, 184 women with adenomyosis who underwent ICSI and achieved good quality FB were randomly divided into two groups (n= 92). They received either LNG-IUS or GnRHa (3.75mg monthly for three months) before FBT. Patients were monitored for changes in menstrual patterns, PEG scale (pain intensity, enjoyment of life, general activity), and FBT outcomes.

Results: At 3-m after treatment 62 women of LNG-IUS group and 10 of GnRHa group resumed normal menstrual pattern (P<0.001) and 30 women of LNG-IUS group and 25 of GnRHa group had oligomenorrhea (P= 0.421), while 57 women of GnRHa group developed amenorrhea. Pain frequency and severity significantly decreased in both groups at the end of treatment. Positive chemical pregnancy rate was 67.4%, while clinical pregnancy rate was 54.3% with insignificantly higher chemical, but significantly (P= 0.038) higher clinical pregnancy rates among women of GnRH group. The ectopic pregnancy rates were 4.7% and 1.8% and the early pregnancy loss rates were 23.3% and 31.6% among women of LNG-IUS and GnRHa groups, respectively with insignificant differences between both therapies.

Conclusion: Medical management using LNG-IUS or GnRHa significantly controlled adenomyosis manifestation in terms of pain; bleeding and menstrual pattern in infertile adenomyosis women planned to have FBT, but LNG-IUS provided superior outcomes. Also, LNG-IUS preparation optimized outcomes of FBT with results comparable to the GnRHa treatment.

Key Words: Adenomyosis; frozen blastocyst transfer; gonadotropin-releasing hormone agonist; levonorgestrel-releasing intrauterine System

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INTRODUCTION

Adenomyosis is benign uterine disorder, which is characterized by the infiltration of endometrial glands and stroma into the myometrium[1] resulting in ectopic intramyometrial endometrial tissue that leads to the generalized uterine enlargement[2]. Adenomyosis predisposes to female infertility and/or reduced clinical pregnancy rate, high risk of miscarriage and early pregnancy loss[3]. In a murine model of adenomyosis, progesterone resistance, reduced expression of the progesterone receptor and altered endometrial receptivity with decreased expression of implantation-related markers were detected [4].

Unfortunately, no particular therapy and algorithms was settled as the effective lines for adenomyosis management mostly due to the lack of precise diagnostics criteria[5].

Adenomyosis was associated with infertility and lower clinical pregnancy and live birth rates among infertile women undergoing assisted reproductive technologies[6]. Treatment of adenomyosis patients using gonadotropin-releasing hormone agonist (GnRHa) long downregulation prior to frozen embryo transfer may increase the clinical pregnancy and live birth rates[7], but not to the baseline expected success where there is no adenomyosis[8].

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The levonorgestrel-releasing intrauterine system (LNG-IUS), which was developed for contraception, releases LNG into the uterine cavity in a daily dose of 20 μg[9]. LNG-IUS was found to control symptoms of endometriosis and adenomyosis[10]. The endometrial LNG concentration on LNG-IUS insertion differs from that in myometrium, fallopian tubes and fat tissue, and was many-fold higher than that in the plasma[11].

OBJECTIVES

This study aimed to investigate the effects of LNG-IUS versus GnRH therapy on adenomyosis-associated manifestations and the outcomes of frozen blastocyst transfer (FBT) for these patients.

Design:

Prospective, comparative interventional study.

Setting:

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PATIENTS AND METHODS

During the study duration since June 2022, all women who presented with adenomyosis-associated manifestations, underwent successful ICSI and got good quality frozen embryos (FE) were eligible for evaluation of enrolment criteria. Clinically, patients' demographic data, marital and fertility statuses, menstrual regularity, and heaviness were determined. Pain severity and its impacts were assessed using the PEG scale that evaluated pain intensity, enjoyment of life, and general activity, each on a 0-10 scale with 0 indicating no and 10 indicating the worst effect. The sum of the scores for the three items was divided by three and a higher PEG score indicated more severity [12]. The assessed pain types included dysmenorrhea, dyspareunia, and chronic pelvic pain sensation. Transvaginal ultrasonography (TVU; DC 70 expert, 7.5 MHz, Mindray) was used to assess for the presence of thickened myometrium and determination of uterine volume.

Diagnosis of adenomyosis:

In addition to the clinical manifestations, diagnosis of adenomyosis depended on the standard ultrasound (US) criteria that included the presence of enlarged globular uterine configuration, asymmetrical thickening of uterine walls, poor identification of the junctional zone, heterogeneous myometrial texture, and sub-endometrial myometrial striations and cysts[13]. Adenomyosis was classified as focal on detection of solitary foci with adenomyosis-diagnostic US findings otherwise the disease was considered as diffuse adenomyosis[14].

Exclusion criteria:

Adenomyosis patients who underwent ICSI and got bad-quality zygotes were not enrolled.

Inclusion criteria:

Women who had adenomyosis diagnostic characteristics and underwent ICSI that resulted in good-quality FE were enrolled in the study.

Sample size:

The null hypothesis is obtaining a significant difference between pre-treatment and post-treatment incidence and severity of adenomyosis-associated symptoms with both therapeutic lines. A previous study included 243 adenomyosis patients detected improved effectiveness of high-intensity focused ultrasound if combined with LNG-IUS more than if high-intensity focused ultrasound alone or with GnRHa as adjuvant[15]. Another study including 173 adenomyosis women who underwent uterus-sparing surgery were divided into two groups to receive perioperative adjuvant therapy with GnRHa or the LNG-IUS showed a significant reduction of recurrence or progression of adenomyosis with both lines[16]. Accordingly, the calculated sample size was defined by the F test model to be 92 patients per group to provide the study a power of 80% with a 5% α-error and an effect size of 0.20[17] and to ensure the certainty of the null hypothesis using the G*Power (Version 3.1.9.2).

Randomization and grouping:

Patients were randomly divided into two groups (LNG-IUS group and GnRHa group) using the random block sizes of 2 and 4 by 1:1 allocation computer randomization method (Excel 2007, Microsoft, Redmond, WA, USA) to generate the sequence of patients between both groups. These sequences were printed on cards that were enveloped, and patients were asked to choose a card and propose it to the author in charge.

ETHICAL CONSIDERATION

The study hypothesis and protocol were discussed with and approved by the departmental committee before case collection and then approved by the Local Ethical Committee, Faculty of Medicine, Zagazig University (Approval No:506/11-Aug-2024). Also, the study was registered in clinicaltrial.gov by No: NCT06581679.

Therapeutic lines:

A. The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena IUD, Bayer, Leverkusen, Germany) releasing 20 levonorgestrel daily

B. GnHRa was given as a subcutaneous injection of triptoreline (Decapeptyl, Ferring Pharmaceuticals Ltd., Wittland, Germany) in a dose of 3.75mg monthly for three months.

Preparation for FET:

At the end of 3-m therapy, women of both groups were allowed to have a cycle of withdrawal bleeding before preparation for FET, and on the 2nd menstrual day estradiol valerate (Progynova, 2mg, Bayer Schering Pharma, UK) was given 6-mg daily for 4 days and then dose was adjusted according to the endometrial thickness. Endometrial thickness was judged by TVU in the midsagittal plane as the distance between the outer edges of the endometrial/myometrial interface on days 10 to 12. When the endometrial thickness was 8 mm, progesterone therapy 400 mg twice daily as progesterone vaginal supp (Cyclogest; Actavis Co., USA) for 5 days and BT was commenced after rapid thawing on day-6 of progesterone therapy. Progesterone therapy was continued after BT for 14 days at the time of chemical diagnosis of pregnancy that was assured clinically depending on the detection of a viable embryo with a pulsating heart by US examination.

Evaluation of outcomes:

*A. **Outcomes of adenomyosis treatment:***

- The change in menstrual patterns.
- The frequency and severity of pain and its impacts as judged by PEG scores.

B. Outcomes of FBT included the chemical and clinical pregnancy rates and the incidence of ectopic pregnancy and early pregnancy loss.

Statistical analysis:

Statistical analyses were performed using IBM® SPSS® Statistics software (Version 22, 2015; Armonk, USA). The significance of the intragroup differences was assessed using the One-way ANOVA test, and Chi-square test for the differences in percentage of data. The optimum cut-off point for significance was $P<0.05$.

RESULTS

Throughout the duration of the study, 214 women were diagnosed by the US as adenomyosis patients, 30 women were excluded because of having bad-quality zygotes, while 184 women had good-quality zygotes and were randomly divided into the study groups (Figure 1). All the enrolled women completed the treatment course without dropout cases and their enrolment data are shown in (Table 1).

Table 1: Patients' enrolment data:

Data	Group	LNG-IUS	GnRH	*P*-value
Age (years)		31.5±3.2	30.6±3.3	0.060
Body mass index (kg/m2)		30.7±2	30.5±2.1	0.545
Fertility	Primary	60(65.2%)	66(71.7%)	0.341
	Secondary	32(34.8%)	26(28.3%)	
Number of living offspring	Zero	64(69.6%)	71(77.2%)	
	One	21(22.8%)	18(19.6%)	0.333
	Two	7(7.6%)	3(3.2%)	
US type of adenomyosis	Focal lesion	14(15.2%)	10(10.9%)	0.381
	Diffuse lesion	78(84.8%)	82(89.1%)	

Pretreatment menstrual pattern was changed after treatment in both groups. Pretreatment patterns were polymenorrhagia in 113 (61.4%) and menorrhagia in 71 (38.6%) patients with insignificant differences between both groups as regards the frequency of women who had polymenorrhagia (P= 0.289) and/or menorrhagia (P= 0.458). (38.6%) patients with insignificant differences between both groups as regards the frequency of women who had polymenorrhagia (P= 0.289) and/or menorrhagia (P= 0.458).

Post-treatment patterns were variants; 55 patients (29.9%) developed oligomenorrhea; 30 patients (32.6%) in LNG-IUS group and 25 patients (27.2%) in GnRHa group with insignificant (P= 0.421) difference between both groups. GnRHa therapy resulted in amenorrhea in 57 women (62%) with significantly higher (P<0.001) frequency versus LNG-IUS (n= 0). As regards normal menstrual pattern, 72 (39.1%) women had resumed their normal pattern; 62 patients (67.4%) in the LNG-IUS group and only 10 patients (10.9%) in GnRHa group with significantly (P<0.001) higher frequency of women had regained their normal menstrual pattern among women received LNG-IUS than women of GnRHa (Table 2).

Pretreatment frequency and severity of pain types showed insignificant differences between both groups. Pain frequency and severity significantly (P<0.001) decreased at the end of treatment in comparison to pretreatment frequency and severity in both groups. The frequency of women who were still complaining of dysmenorrhea at the end of therapy showed an insignificant (P= 0.363) difference between both groups, while pain scores were significantly (P= 0.041) lower in patients who received LNG-IUS than those received GnRHa therapy.

On the contrary, the frequencies of patients who were still complaining of dyspareunia and deep pelvic pain were significantly (P= 0.045 & 0.026, respectively) lower in the LNG-IUS group. Similarly, patients who received LNG-

IUS showed significantly lower pain scores for dyspareunia (P=0.018) and deep pelvic pain (P=0.012) in comparison to patients of the GnRHa group (Table 3, Figure 2).

Among the 184 women who received FBT, 124 women gave positive pregnancy test for a positive chemical pregnancy rate of 67.4% with an insignificantly (P=0.345) higher chemical pregnancy rate among women of the GnRH group than women of LNG-IUS group (70.7% vs. 64.1%). One hundred women had clinically approved pregnancies for a clinical pregnancy rate of 54.3% among total studied patients and 80.6% among women had positive pregnancy tests with significant (P=0.038 and 0.037, respectively) differences in favor of women of the GnRHa group.

Three of the women who had clinically assured pregnancy had ectopic pregnancy for a rate of 3%; 4.7% and 1.8% among women of groups LNG-IUS and GnRH, respectively. The rate of early pregnancy loss among total patients was 15.2% and this accounted for 22.6% and 28% among women who had positive chemical and clinical pregnancy. The frequencies of women who had early pregnancy loss in group LNG-IUS were 10.9%, 16.9%, and 23.3%, respectively, and among women of group GnRHa were 19.6%, 27.7%, and 31.6%, respectively. The differences in the frequencies of early pregnancy loss were insignificantly (P=0.101, 0.153 & 0.359) higher among women who received GnRHa than women who received LNG-IUS (Table 4, Figure 3).

Table 2: Effect of treatment on menstrual pattern:

Time	Pre-treatment			Post-treatment		
Menstrual pattern	**LNG-IUS**	**GnRH**	***P* value**	**LNG-IUS**	**GnRH**	***P* value**
Polymenorrhagia	53(57.6%)	60(65.2%)	0.289	0	0	-
Menorrhagia	49(53.3%)	54(58.7%)	0.458	0	0	-
Oligomenorrhea	0	0	-	30(32.6%)	25(27.2%)	0.421
Amenorrhea	0	0	-	0	57(62%)	<0.001
Normal	0	0	-	62(67.4%)	10(10.9%)	<0.001

Table 3: Effect of treatment on frequency and severity of pain:

Time		Pre-treatment			Post-treatment		
Type	**Group**	**LNG-IUS**	**GnRH**	***P***	**LNG-IUS**	**GnRH**	***P***
Dysmenorrhea	Frequency	73(79.3%)	75(81.5%)	0.710	9(9.8%)	13 (14.1%)	0.363
	*P*2				<0.001	<0.001	
	Total PEG score	5.9±0.8	6±0.5	0.560	2.09±0.6	2.24±0.5	0.041
	*P*2				<0.001	<0.001	
Dyspareunia	Frequency	82(89.1%)	85(92.4%)	0.445	7(7.6%)	16 (17.4%)	0.045
	*P*2				<0.001	<0.001	
	Total PEG score	5.74±0.64	5.85±0.58	0.571	1.8±0.56	2.03±0.53	0.018
	*P*2				<0.001	<0.001	
Deep pelvic pain	Frequency	21(22.8%)	32(34.8%)	0.073	3(3.3%)	11 (12%)	0.026
	*P*2				<0.001	<0.001	
	Total PEG score	5±0.92	5.43±0.83	0.078	1.4±0.75	2±0.77	0.012
	*P*2				<0.001	<0.001	

P indicated the significance of the intergroup differences, *P*2 indicated the significance of the difference between pre-and post-treatment data.

Table 4: The outcomes of FBT for women of both groups:

Outcomes	Group		Total	LNG-IUS	GnRH	*P*
Chemical pregnancy rate	Positive		124 (67.4%)	59 (64.1%)	65 (70.7%)	0.345
	Negative		60(32.6%)	33 (35.9%)	27 (29.3%)	
Clinical pregnancy rate among patients	Total	Positive	100(54.3%)	43 (46.7%)	57 (62%)	0.038
		Negative	84(45.7%)	49 (53.3%)	35 (38%)	
	Had chemical pregnancy	Positive	100(80.6%)	43 (72.9%)	57 (87.7%)	0.037
		Negative	24 (19.4%)	16 (27.1%)	8 (12.3%)	
Ectopic pregnancy among patients who had clinical pregnancy			3 (3%)	2 (4.7%)	1 (1.8%)	0.561
Early pregnancy loss among patients	Total		28 (15.2%)	10 (10.9%)	18 (19.6%)	0.101
	Had chemical pregnancy		28 (22.6%)	10 (16.9%)	18 (27.7%)	0.153
	Had clinical pregnancy		28 (28%)	10 (23.3%)	18 (31.6%)	0.359

P indicates the significance of the intergroup difference.

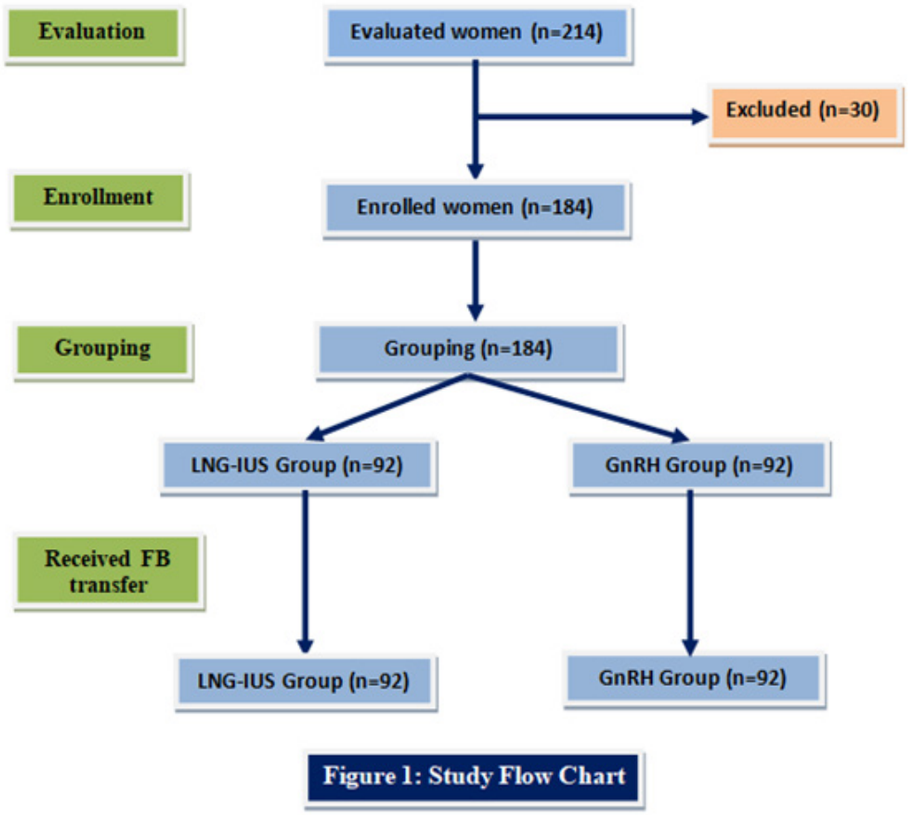

Fig.1: Study of flow chart.

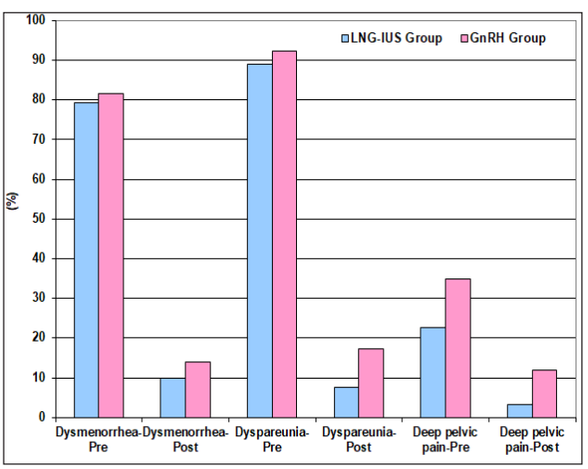

Fig. 2: Distribution of women of both groups according to the frequency of pain type before and after treatment.

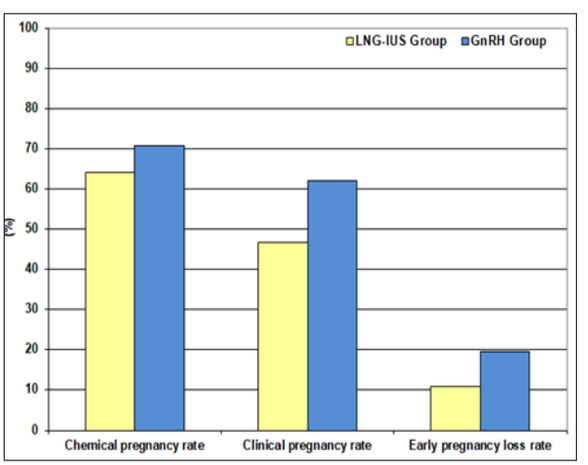

Fig. 3: The outcoomes of frozen blastocyst transfer after adenomyosis treatment in both groups.

DISCUSSION

The results of the current study assured the null hypothesis that both LNG-IUS and GnRHa therapy might effectively control adenomyosis-induced manifestations with significant differences in comparison to pre-treatment incidence and severity. Regrettably, scarce studies compared the effects of LNG-IUS versus GnRHa therapy on adenomyosis-induced manifestations where Wang *et al.*[18] reported significantly lower long-term relapse rate in women undergoing conservative surgery for focal adenomyosis with the use of GnRHa or LNG-IUS postoperatively in comparison to surgery alone.

Regarding the use of GnRHa therapy for control of adenomyosis manifestations, the results of the current study

coincided with Chen *et al.*[19] who found 3-m treatment with GnRHa before total hysterectomy for adenomyosis patients with uterine volume ≥12 gestational weeks and moderate or severe anemia improved dysmenorrhea, signs of anemia, reduced uterine volume with reduction of surgical complications and hospital costs. Also, Chan *et al.*[20] documented the safety and effectiveness of the combination of GnRHa as adjuvant treatment and dienogest as maintenance therapy after uterus-sparing surgery for adenomyosis. In a comparative study, Chu *et al.*[21] prospectively reported a significant reduction of uterine volume in all adenomyosis patients who received laparoscopic surgery alone or combined with GnRHa and ultrasound-guided percutaneous radiofrequency ablation alone or with GnRHa but found the total effective rates were higher with the use of GnRHa as an adjuvant to laparoscopic surgery (80% vs. 71.43%) or to radiofrequency ablation (100% vs. 82.86%) than each procedure alone.

The obtained results concerning the success rate of LNG-IUS for control of adenomyosis-manifestations go in hand with Atak *et al.*[22] who investigated the effectiveness of LNG-IUD in reducing bleeding in patients with abnormal uterine bleeding stratified by the underlying pathology and reported an overall effectiveness rate of 82%, and differential effectiveness rates of 95.5%, 88.7% and 55.6% in patients with endometrial hyperplasia, adenomyosis and leiomyoma, respectively and 92.3% in patients had unclassified bleeding. Also, Lv *et al.*[23] reported a low expulsion rate with composite effectiveness based on pain and bleeding at 1, 3, 6, and 12 months after hysteroscopic suture fixation of LNG-IUS of 92.4%, 97.4%, 96.2%, and 97.4% respectively.

However, the obtained results indicated superior control on adenomyosis manifestations with LNG-IUS than GnRHa therapy and this finding goes in hand with the recent studies compared LNG-IUS versus other lines used for adenomyosis-induced manifestations, where Whitaker *et al.*[24] in a comparative study of ulipristal acetate versus LNG-IUS assured the efficacy of both lines as medical treatments for adenomyosis-manifestations but with significantly higher amenorrhea rates (64% vs. 25%) at 12 months and higher cessation rate with ulipristal. Also, Shi *et al.*[25] retrospectively compared the insertion of LNG-IUS versus expectant treatment after laparoscopic excision of pelvic endometriosis in women with coexistent endometrioma and diffuse adenomyosis and reported significant reduction of uterine volume and higher percentage of complete pain remission with prevention of recurrence with LNG-IUS. Additionally, Cai *et al.*[26] retrospectively reported a significant decrease in the volume of the uterine lesion and reduction of the adenomyosis blood flow signals with effective rates of 72.1% and 71.3%, and at 6-m follow-up, the menstrual cycle was significantly decreased with significant shortening of the menstrual period, reduction of menstrual volume and significantly higher hemoglobin concentration using high-intensity focused ultrasound with than without LNG-IUS.

Thereafter, Wei *et al.*[27] reported that after 3 months of adenomyosis treatment using LNG-IUD or etonogestrel subcutaneous implant significant improvement in patients' evaluations, blood loss and uterine volume in comparison to pre-treatment data with significantly decreased uterine volume and blood loss with LNG-IUD and concluded that LNG-IUD had a more significant effect on adenomyosis-related dysmenorrhea, excessive menstrual flow, anemia, and uterine enlargement, with relatively fewer side effects. Also, Jiang *et al.*[28] found conservative surgery with intraoperative placement of LNG-IUS is more effective and provides well-accepted long-term outcomes with lower recurrence rates than conservative surgery alone.

The detected insignificant differences in outcomes of FBT for infertile adenomyosis patients who received either GnRH therapy or LNG-IUS indicated the appropriateness of both lines as preparatory therapy before FBT for these patients and support the previously obtained results in multiple comparative studies where Campo *et al.*[29] found insignificant differences regarding clinical pregnancy rate, miscarriage rate and cumulative live birth rate following ART for endometrial hyperplasia patients received either LNG-IUS or oral medroxyprogesterone acetate and concluded that the use of LNG-IUS does not jeopardize the chances of pregnancy in infertile women seeking treatment. Also, Sudhakar *et al.*[30] retrospectively detected the detrimental effect of adenomyosis on ICSI clinical outcome but reported significant improvement in clinical pregnancy rate with pretreatment with GnRH agonist, conservative surgery, or both. Moreover, Rao *et al.*[31] compared the outcomes of ART in women who had adenomyosis and prepared by GnRH therapy versus women free of adenomyosis and reported equivocal implantation rate and biochemical pregnancy and cumulative live birth rates between both groups.

Contrary to the obtained results and aforementioned data, a meta-analysis of studies that tried medical treatments of adenomyosis documented that adenomyosis decreased IVF clinical outcomes and pretreatment with long-term GnRHa could not be beneficial[32]. Further, Wang *et al.*[33] detected higher miscarriage rates and lower live birth rates among patients who had adenomyosis with/without endometriosis even after GnRHa treatment before FET cycles, especially in patients older than 38 years.

The concept of the current study is to transfer frozen blastocyst, not fresh embryo transfer. In line with this concept, Wu *et al.*[34] reported significantly higher implantation and live birth rates in adenomyosis women pre-treated with long-term GnRHa and received FET than women who received fresh embryo transfer and pre-treated by long or ultra-long GnRHa protocols. Also, Zhang *et al.*[35] documented that for adenomyosis women who

received either GnRH antagonist protocol with freeze-all or long-acting GnRHa protocol with fresh embryo transfer the clinical pregnancy, live birth, and cumulative live birth rates were comparable.

CONCLUSION

Medical management in women with adenomyosis using LNG-IUS or GnRHa significantly controlled adenomyosis manifestation in terms of pain, bleeding, and menstrual pattern in infertile adenomyosis women planned to have FBT, but LNG-IUS provided superior outcomes. Also, LNG-IUS preparation of infertile adenomyosis women before FBT optimized its outcomes with results at par with the GnRHa treatment.

LIMITATIONS

No follow-up was provided to assess the relapse rate of manifestations after the stoppage of the provided lines.

RECOMMENDATIONS

Wide-scale multicenter studies with long follow-up duration are mandatory to establish the obtained results. Trials for natural conception during follow-up especially for young women who received medical treatment for adenomyosis must be planned before restoring to ICSI.

LIMITATIONS

There are no conflict of interests.

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