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Comparison of ultra-long gonadotropin releasing hormone agonist versus standard downregulation in women with adenomyosis undergoing frozen-thawed embryo transfer: a randomized clinical trial

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Abstract

Background Adenomyosis can lead to infertility and failure of in vitro fertilization. Limited evidence suggests that the use of long-term treatment with gonadotropin-releasing hormone (GnRH) agonists followed by frozen-thawed embryo transfer (FET) may be the preferred approach for women with adenomyosis.

Objective The aim of this randomized controlled trial is to compare the efficacy of an ultra-long GnRH agonist with standard downregulation in women with adenomyosis undergoing FET.

Materials and methods This randomized controlled trial enrolled 72 women with adenomyosis diagnosed by sonographic criteria who underwent FET cycles at the Avicenna Infertility Center. These women were randomly assigned to two equal groups: one received GnRH agonist treatment for three months before the FET cycle and the other served as the standard downregulation group. Results were reported as chemical and clinical pregnancy rates.

Results The two groups were similar in age, body mass index, anti-Müllerian hormone levels, number of previous pregnancies and miscarriages, presence of uterine myomas, and endometriosis. However, the total dose of estradiol used until embryo transfer was significantly higher in the ultra-long GnRH agonist group than in the standard group (96.14 mg vs. 80.52 mg, p-value = 0.004). Nevertheless, chemical and clinical pregnancy rates did not differ significantly between the two groups.

Conclusions Ultra-long GnRH agonist downregulation did not improve the chemical and clinical pregnancy rate in the FET cycle in women with adenomyosis compared with standard GnRH agonist downregulation in the other words, ultra-long GnRH agonist downregulation is not superior to standard protocol. In women with adenomyosis (without history of endometriosis), downregulation of standard GnRH agonists prior to frozen-thawed embryo transfer may be the preferred embryo transfer protocol to gain higher clinical/chemical pregnancy rate.

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Trial registration Clinical trial registry: IRCT20160717028967N9, available at: https://irct.behdasht.gov.ir/trial/36103.
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Introduction

Adenomyosis is a disease in which the endometrial tissue invades the muscular wall of the uterus, causing symptoms such as dysmenorrhea, hypermenorrhea, bloating and abdominal pressure. Epidemiological studies of this condition are limited as it was previously diagnosed only after hysterectomy. The prevalence of adenomyosis is estimated at 5–70% and occurs in 20–30% of hysterectomies. While it was previously more commonly seen in women over 40 years of age, new diagnoses based on MRI and ultrasound show that it is more common in younger women of childbearing age [1]. Pelvic MRI is the standard method for diagnosing adenomyosis, no matter how high-resolution vaginal ultrasound has made adenomyosis diagnosis easier [2]. Adenomyosis can affect fertility by disrupting the normal function of the uterus and leading to failure of implantation and embryo development. The thickening of the uterus and changes in the uterine cavity can hinder sperm and embryo transfer. In addition, adenomyosis can lead to reduced fertility as well as an increase in ectopic pregnancies due to problems with uterine peristalsis, sperm transfer and embryo transfer in IVF procedures. Adenomyosis diagnosed by ultrasound has been shown to significantly reduce clinical and ongoing pregnancy rates and increase miscarriage rates in individuals undergoing IVF-ICSI, and screening for adenomyosis prior to beginning the IVF procedure is recommended [3–6], although Costello et al. did not conclude the same [7].

GnRH agonists are a suitable adenomyosis treatment option for individuals with infertility, repeated abortions and those who do not want surgery [8]. GnRH agonists, with amino acid substitutions in natural GnRH, have a longer half-life and are more resistant to degradation and temporarily shut down the ovaries. GnRH agonist reduces tissue inflammation, angiogenesis, and cell proliferation in adenomyosis and improves implantation. Adenomyosis inactivation with suppressive pituitary regimens also has been shown as an effective treatment in individuals with recurrent implantation failure [9]. According to limited findings, using long-term GnRH agonists before frozen-thawed embryo transfer (FET) is the preferred treatment in women with symptomatic adenomyosis.

Despite the importance of adenomyosis in infertility and IVF failure, different treatment protocols have not been adequately studied in prospective trials. This randomized clinical trial investigates the effect of ultra-long GnRH agonist versus standard downregulation on the results of FET in females with adenomyosis in the Avicenna Infertility Center.

Materials and methods

Study design and participants

This randomized clinical trial study was conducted on women with adenomyosis as confirmed by at least two sonographic criteria, including a large globular uterus in the absence of myomas, asymmetric thickening of the anterior or posterior wall of the myometrium, heterogeneous areas with unclear boundaries in the myometrium, anechoic cysts or cavities in the myometrium, striation radiating from the endometrium to the myometrium and the disruption of the border between the endometrium and myometrium [2], who were planned for frozen-thawed embryo transfer at the Avicenna infertility Centre. Diagnostic criteria of uterine adenomyosis include two of the five sonographic features on transvaginal ultrasonography [10]. All patients had informed consent to participate in the study. To be eligible for the study, participants also must be in the age range of 20 to 40 years and have good-quality embryos (A/AB or blastocyst) [11, 12].

Exclusion criteria include recurrent miscarriage, azoospermia in male partner, using alternative infertility treatment services (such as donation), uncontrolled underlying diseases such as diabetes, hypertension, kidney dysfunction, lupus, untreated thyroid dysfunction, abnormal karyotype, anatomical disorder of the uterus (such as congenital abnormalities, submucosal myoma with compression effect), thrombophilia, active and untreated infectious diseases, candidate of using any immunosuppressive or immunomodulatory drugs and interventions such as endometrial scratch or Platelet-Rich Plasma.

Randomization

72 participants were randomized into two equal groups: ultra-long GnRH agonist downregulation and standard downregulation, based on a randomized six-block table that is designed by Random allocation software.

Intervention

The study participants in the ultra-long GnRH agonist group received a dose of triptorelin 11.25 mg (Diphereline SR, IPSEN, France) intramuscularly on the third day of menstruation. After 8 weeks, they started a 21-day low-dose contraceptive pill (Desoceptive, Iran Hormone, Iran contains 20 microg estradiol) and from the third day of the upcoming menstrual period, Hormone

Replacement Therapy (HRT) with estradiol tab (estradiol valerate, Aburaihan, Iran) was started. Participants in the standard downregulation group received 21-day low-dose contraceptive pill starting from the third day of the menstrual period and on the 21st date of the menstrual cycle, triptorelin 1.875 mg (1/2 of 3.75 mg) (Diphereline SR, IPSEN, France) was injected intramuscularly, following by HRT with estradiol on the next menstrual cycle. Both groups were monitored with vaginal ultrasound and after the endometrial thickness reached 8 mm, progesterone injection (progesterone Amp, Iran Hormone, Iran) was added to the treatment and embryo transfer was done after 3 to 5 days according to the embryos' stage.

Outcome

14 and 16 days after embryo transfer serum beta HCG levels were measured by the ECLIA method to confirm the chemical pregnancy. In pregnant women we performed transvaginal ultrasound on the 6th week of gestation to confirm the clinical pregnancy and we followed the ongoing pregnancy till the 12th week with sonography. The blood test and ultrasound results were reviewed by one of our research co-workers in the clinic. Clinical pregnancy was confirmed by detecting the fetal heartbeat during the 6th-week transvaginal ultrasound. Abortion cases they were not included in the clinical pregnancy rates. Also, we had no ectopic cases in this study. A β-hCG level of more than 25 mIU/L was considered a chemical pregnancy. The primary outcomes were chemical and clinical pregnancy rates in both groups.

Statistical analysis

The statistical methods used in the study were descriptive statistics and inferential statistics. The descriptive statistics include mean and standard deviation to describe the data. The inferential statistics include the student's t-test for quantitative variables and the chi-square test for qualitative data. The statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, version 22.0, SPSS Inc., Chicago, Illinois, USA).

Results

Of 100 participants with adenomyosis who were candidates for FET, 10 people did not participate in the study due to lack of qualifying clinical criteria and 18 people refused to participate in the study. In this way, 28 out of 100 people were excluded from the study. So, 72 participants were randomly divided into two groups, the standard group ($n=36$) and the ultra-long downregulation group ($n=36$).In the ultra-long downregulation group, 6 women did not want to continue infertility treatment for personal reasons and 2 participants did not have embryo transfer due to thin endometrium. Finally, 64 women were analyzed. (Fig. 1)

Table 1 displays the demographic and clinical characteristics of the two groups, including their average age, body mass index, Anti-Mullerian hormone level, number of previous pregnancies and miscarriages, and the presence of uterine myoma and endometriosis history. The results showed that there were no significant differences between the two groups in these characteristics. The mean duration of the frozen-thawed embryo transfer cycle, from the last mensural period (LMP) to the transfer day, was similar in both groups (17 days in the ultra-long GnRH Agonist group and 17.13 days in the standard group). The endometrial thickness and quality of transferred embryos were the same in both groups (Table 2). However, the total dose of estradiol was higher in the ultra-long GnRH Agonist group compared to the standard group (96.14 mg vs. 80.52 mg, with a significant p-value of 0.004). The average number of embryos transferred in the standard group was slightly higher than in the ultra-long GnRH Agonist group (2.16 vs. 1.67, with a significant p-value of 0.006). The rate of chemical pregnancy was 47% in the standard group and 39% in the ultra-long GnRH Agonist group and this difference was not statistically significant. Clinical pregnancy rates in the two groups were 38% and 28% respectively, this was not a statistically significant difference. Three women in each group had first-trimester abortions. Among those with a history of endometriosis and adenomyosis, the rate of chemical pregnancy improved slightly with the use of ultra-long GnRH Agonist (46% compared to 36%). However, the clinical pregnancy rate in the ultra-long GnRH-a group and standard group was 26% versus 31%.

Discussion

The results of this study differ from some studies done on the one or two groups of our study [9, 13–15], which may be due to different study designs, as we also implemented GnRH-a in the control group at a lower dose. However, some retrospective studies also found no superiority for GnRH-a pretreatment [16–19]. In fact, despite a great deal of research, no clear consensus has been reached regarding the connection between adenomyosis and infertility. Overall, even after GnRH agonist treatment prior to FET cycles, patients with adenomyosis with or without endometriosis had lower cumulative live birth rates, lower live birth rates, and higher miscarriage rates, particularly in patients aged ≥ 38 years [20]. These findings were consistent with a study by Sharma et al. [21].

The results of our study, together with Costello and colleagues [7] and in contrast to other studies [3–6], showed that the average pregnancy rate in women with adenomyosis who underwent frozen-thawed embryo transfer was similar to the average pregnancy rate of the entire FET cycles, suggesting that mild to moderate adenomyosis alone may not have a significant impact on pregnancy

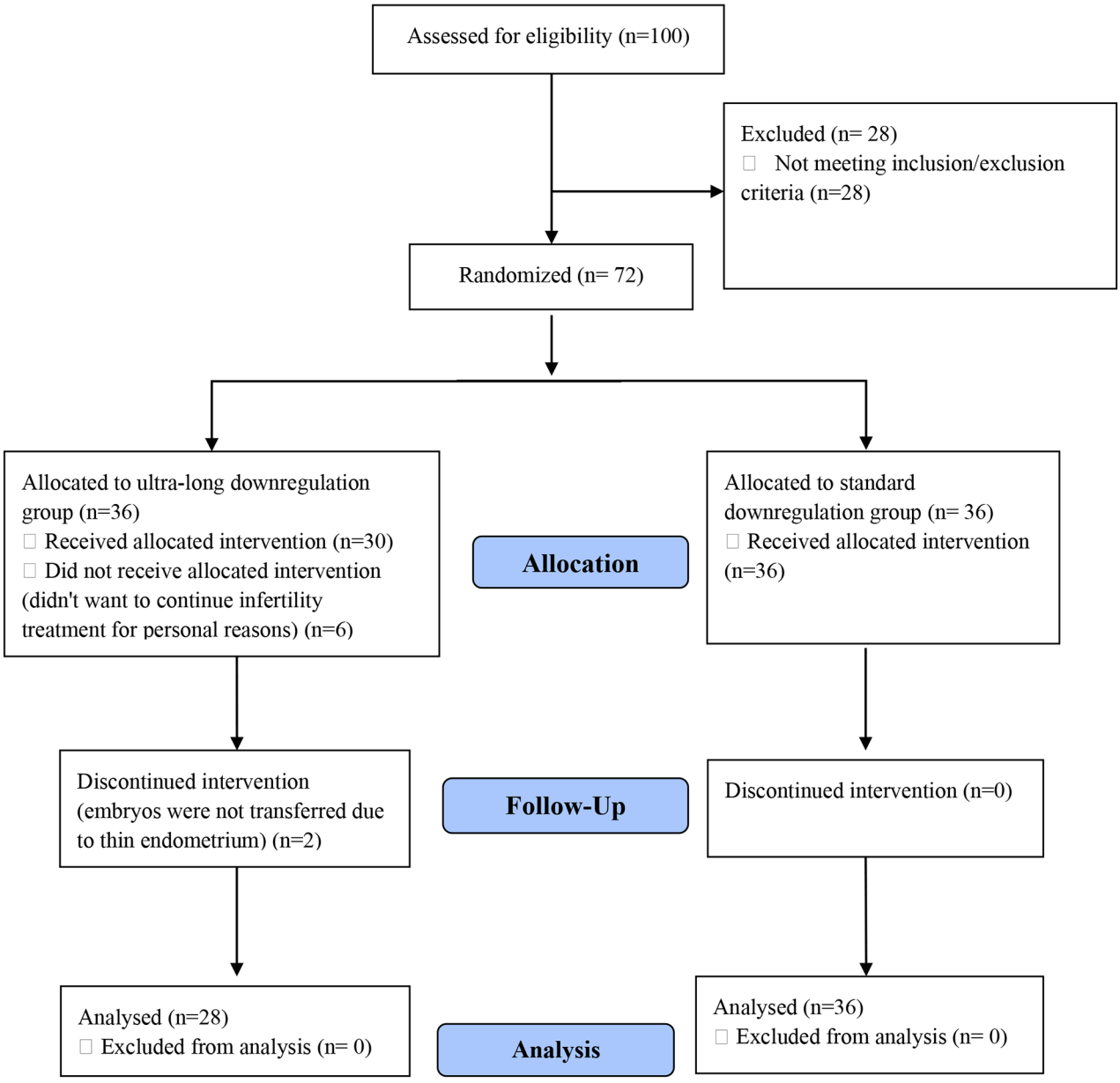

Fig. 1 CONSORT flow diagram

rates. The focus is on the need for adenomyosis categorization based on clear criteria. Further prospective studies with larger sample sizes are needed to confirm these results. The findings of our study revealed that the success rate of pregnancy was lower in individuals with adenomyosis who had an endometriosis history, likely due to the reduced quality of their eggs. In these participants the use of ultra-long GnRH agonist before the frozen-thawed embryo transfer did not improve the clinical pregnancy rate, despite a slight increase in the chemical pregnancy rate.

Furthermore, Lan et al. demonstrated that, when compared to the long GnRH-a protocol, the ultra-long GnRH-a protocol during IVF/ICSI improves pregnancy outcomes in women with adenomyosis, particularly in women with diffuse adenomyosis [22]. Moreover, Hou and colleagues. showed the same findings [23] and stated that, following a lengthy GnRH agonist regimen, adenomyosis may have a deleterious impact on IVF outcomes, regardless of ovarian reserve. Compared to patients with adenomyosis who follow the long GnRH agonist protocol, those who follow the ultra-long GnRH agonist protocol may have better pregnancy outcomes. But our results

Table 1 Characteristics of the participants with adenomyosis in the FET cycle, in the ultra-long GnRH agonist downregulation group and standard downregulation group

Variable	Ultra-long GnRH agonist downregulation, (*N* = 28)	Standard downregulation, (*N* = 36)	*P* value
	Mean ± SD	Mean ± SD	
Age, year	34.17 ± 3.87	32.62 ± 4.29	0.14
Body mass index, kg/m^2	24.67 ± 3.35	25.23 ± 4.22	0.57
Number of previous abortions	0.75 ± 1.17	0.47 ± 0.84	0.37
Number of previous pregnancies	1.17 ± 1.78	0.77 ± 1.14	0.28
Number of children	0.28 ± 0.80	0.30 ± 0.57	0.90
Anti-Mullerian hormone (ng/ml)	2.59 ± 1.84	3.63 ± 3.22	0.19
Uterine myoma without compression effect, yes/no	6/22(21%)	5/31(14%)	0.34
Endometriosis history*, yes/no	15/13(54%)	22/14(61%)	0.36

*Clinically diagnosed

Table 2 The results of frozen embryo transfer in women with adenomyosis, using ultra-long GnRH agonist vs. standard long protocol

Variable	Ultra-long GnRH agonist downregulation, (*N* = 28)	Standard downregulation, (*N* = 36)	*P* value
	Mean ± SD	Mean ± SD	
Duration of the FET cycle from the last mensural period, day	17.00 ± 2/05	17.13 ± 1.69	0.76
Endometrial thickness, mm	8.41 ± 1.16	8.7 ± 1.13	0.29
Oestradiol dose until transfer day, mg	96.14 ± 25.17	80.52 ± 11.51	0.004
Number of embryos transferred	1.67 ± 0.54	2.16 ± 0.77	0.006
Implantation rate	0.23 ± 0.35	0.22 ± 0.29	0.86
Quality of transferred embryos (A/AB/blastocyst)	6/8/14	16/9/11	0.16
Chemical pregnancy, yes/no	11/17(39%)	17/19(47%)	0.37
Clinical pregnancy, yes/no	8/20(28%)	14/22(38%)	0.28
Chemical pregnancy in women with endometriosis history, yes/no	7/8(46%)	8/14(36%)	0.52
Clinical pregnancy in women with endometriosis history, yes/no	4/11(26%)	7/15(31%)	0.37

did not show that ultra-long GnRH agonist downregulation is superior to standard downregulation for obtaining better pregnancy-related outcomes. According to our results, patients underwent standard downregulation had higher chemical (47% vs. 39%) and clinical (38% vs. 28%) pregnancy rates considering that this difference was not statistically significant. In patients who had history of endometriosis, ultra-long GnRH agonist downregulation resulted in higher percentage of chemical pregnancy (46% vs. 36%), however this difference was not statistically significant.

More prospective studies are needed to better understand this complex disease and develop more effective treatment approaches. Our results, together with the result of a recent study [24], suggest that downregulation of standard GnRH agonists before frozen-thawed embryo transfer may be the preferred embryo transfer protocol in women with adenomyosis.

Conclusion

In this study, ultra-long GnRH agonist downregulation did not improve the chemical and clinical pregnancy rate in the FET cycle in women with adenomyosis compared with standard GnRH agonist downregulation in the other words, ultra-long GnRH agonist downregulation is not superior to standard protocol. In women with adenomyosis (without history of endometriosis), downregulation of standard GnRH agonists prior to frozen-thawed embryo transfer may be the preferred embryo transfer protocol to gain higher clinical/chemical pregnancy rate.

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Author contributions

SA, KY and MA wrote the main manuscript text and MRS, NN, AK prepared revision. NM, FJ and FR interpreted the data. All authors reviewed the manuscript.

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Data availability

Data will be sent if formally requested by researchers.

Declarations

Human ethics and consent to participate

This clinical trial was carried out according to the ethical guidelines of the Helsinki Declaration and was funded by Avicenna Infertility Center. It was

registered with the IRCT in January 2019 and updated on 27 July 2023 (clinical trial registry: IRCT20160717028967N9, available at: https://irct.behdasht.gov.ir/trial/36103) after receiving ethical clearance (IR.ACECR.AVICENNA.REC.1397.015) from the Avicenna Research Institute's ethics committee. Informed consents were taken from all participants.

Competing interests
The authors declare no competing interests.

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