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Efficacy and Safety of *In Vitro* Fertilization (IVF)/Intracytoplasmic Sperm Injection (ICSI) Among Patients with Endometriosis After a Shortened Protocol of Long-Term Pituitary Downregulation

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Background: Patients with endometriosis (EMs) are routinely advised to take GnRH-a for 3–6 months to improve the internal reproductive environment, but this may not be necessary.

Material/Methods: This retrospective study examined the effects of *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) with shortened (n=311) or conventional (n=213) long-term pituitary downregulation in EMs patients between January 2013 and July 2017.

Results: The 2 groups showed no significant differences in gonadotropin (Gn) dose, number of oocytes retrieved, or miscarriage rate. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels on the initiation day and the LH level on human chorionic gonadotropin (hCG) day (1.22±1.39 *vs.* 0.74±0.55 P=0.0026) were higher in the study group than in the control group. The cumulative live birth rates in the second cycle were 69.13% in the study group (95% confidence interval (CI), 64–74.27%) *vs.* 68.54% in the control group (95% CI, 62.31–74.78%, P=0.88, respectively).

Conclusions: This study showed that the shortened regimen and the ultralong regimen did not produce different pregnancy outcomes after ART, and the single-application, long-term GnRH-a protocol may serve as a cost-effective and safe treatment protocol for EMs patients.

MeSH Keywords: Endometriosis • Fertilization *In Vitro* • Gonadotropin-Releasing Hormone • Pregnancy Rate

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Background

Endometriosis is a common disease known to be detrimental to fertility [1]. Evidence has demonstrated that EMs has deleterious effects on fecundity [2]. A Cochrane systematic review based on 3 small studies showed that GnRH-a for 3–6 months improved the internal reproductive environment of patients with EMs [3–5]. However, many relevant studies had small sample sizes and drastic differences in success rates, causing uncertainty regarding the ultimate effectiveness of the treatment [6,7]. Notably, GnRH-a causes women to be in a low-estrogen state and to have a poor ovary response, and long-term use is associated with osteoporosis.

However, a recent systematic review and meta-analysis examined 30 retrospective studies and 3 RCTs and found that, compared with patients without EMs, women with endometrioma had similar IVF/ICSI outcomes, fewer oocytes, and a higher cancelation rate [8]. Recent studies have compared GnRH antagonists or oral contraceptives [9] and short-acting GnRH agonists [10] and reported comparable outcome. Surrey demonstrated that a 2-month course of GnRH-a therapy is also effective [11]. Thus, whether a GnRH-a is administered for 3–6 months should be considered carefully. The optimum duration of long-term pituitary downregulation remains unknown [5,7]. Ren et al. reported that pregnancy rates were improved by long-term pituitary downregulation for women without endometriosis [12]. These findings may extend to patients with endometriosis.

Based on the above data, we hypothesized that one-time, long-term pituitary downregulation of D2 can produce outcomes comparable to those of the conventional prolonged course in terms of the IVF clinical pregnancy rate and the cumulative live birth rate in EMs patients.

Material and Methods

Patients

From January 2013 to July 2017, patients diagnosed with surgically confirmed endometriosis who were treated with IVF-embryo transfer (ET) consecutively assigned long-term GnRH-a regimen were included. A total of 311 patients who received a one-time regimen were assigned to the study group, and 213 patients who received the repeated ultralong regimen were assigned to the control group. Basic demographic and assisted reproductive technology (ART) data for this study were collected from the Clinical Reproductive Medicine Management System/Electronic Medical Record Cohort Database (CCRM/EMRCD) in the Reproductive Medical Center, the First Affiliated Hospital of Zhengzhou University.

Inclusion criteria were: (1) EMs diagnosed through laparoscopy/laparotomy; (2) age ≤42 years; (3) normal menstrual cycle; and (4) basal FSH (bFSH) ≤12 mIU/ml.

Exclusion criteria were: (1) endocrine-related diseases such as polycystic ovary syndrome or hyperprolactinemia; (2) uterine malformations; (3) previous history of recurrent miscarriages; (4) preimplantation genetic diagnosis/preimplantation genetic screening; (5) adenomyosis; (6) hydrosalpinx.

Ethics approval and consent to participate

The study received approval from the Zhengzhou University Research Ethics Board (Research-2017-LW-69).

Controlled ovarian stimulation protocols

The study group were treated with the standard full dose (3.75 mg) of triptorelin depot (Diphereline 3.75; Ipsen Pharma) on days 2–3 of the cycle, and 28 days later, transvaginal sonography as well as serum hormone levels of FSH, LH, E2, and progesterone (P) were monitored. The control group was treated with depot every 28 days for 56 days. Twenty days after the second administration, downregulation was confirmed. Ovary stimulation, oocyte retrieval, and embryo transfer were conducted as previously described [13]. Briefly, the dose of recombinant FSH (Gonal-F; Merck, Germany) was determined according to the subject's age, antral follicle count (AFC), body mass index (BMI), and levels of base FSH and anti-Mullerian hormone (AMH). The Gn dose was increased or decreased in a timely manner according to response. When the antral follicle size was 12–14 mm, human menopausal gonadotropin (hMG; Livzon, China) was added. When the dominant follicle size was ≥20 mm and at least 3 follicles were ≥18 mm, hCG (Ovidrel; Merck Sereno), either alone or combined with the hCG 2000IU, was injected as a trigger. In the case of frozen embryos, the endometrium was prepared through the natural cycle, an artificial cycle, or pituitary downregulation combined with an artificial cycle, according to ovulation.

Clinical follow-up

Pregnancy outcomes were determined according to the terms revised by the International Committee Monitoring Assisted Reproductive Technologies (ICMART) [14]. In calculating the CLB rate, 1 cycle was defined as the process from the start of ovarian stimulation to completion of transplantation of all fresh and frozen embryos [15].

End-points

The primary end-points of this study were clinical pregnancy rate and cumulative live birth rate. The secondary end-points

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Table 1. Demographic and cycle characteristics of the 2 groups.

Characteristics	Study group (n=311)	Control group (n=213)	*P*-value
Maternal age at cycle start (y)*	30.37±4.36	29.94±3.74	0.5159
infertility duration(y)	4.30±3.15	3.99±3.01	0.1392
BMI (Kg/m^2)*	22.14±2.89	22.05±2.81	0.8072
D2 FSH (mIU/ml)	7.24±3.51	7.52±3.25	0.0804
D2 E2 (pmol/l)	47.06±41.60	59.92±66.23	0.2156
D2 P (ng/ml)	0.77±1.01	0.84±0.75	0.8754
D2 LH(mIU/ml)	4.89±3.76	4.86±2.15	0.4350
Total Gn dose administered	2845.22±1082.62	3025.89±1002.08	0.0464
Days of Gn	13.77±2.32	13.86±2.48	0.8098
E2 on initiation day (pmol/l)	8.92±6.74	26.71±170.69	<0.0001
LH on initiation day (mIU/ml)	0.64±0.39	0.57±0.59	0.0007
FSH on initiation day (mIU/ml)	3.56±1.91	4.07±1.68	0.0021
P on initiation day (ng/ml)	0.47±0.23	0.45±0.25	0.5842
Endometrial thickness (mm)	12.60±2.66	13.08±2.82	0.0465
E2 on day hCG (pmol/l)	3338.14±2093.43	3803.20±2426.87	0.049
LH on day hCG (mIU/ml)	1.22±1.39	0.74±0.55	0.0026
P on day hCG (ng/ml)	1.05±0.67	1.03±0.68	0.3228
Dominant follicles ratio, %	79.79	82.88	0.0045

* *t*-test, the else Wilcoxon rank sum test; values are mean ±SD or n (%); NS – not statistically.

were hormone test results during ovarian stimulation, the total stimulating hormone dose, the mean number of oocytes retrieved, the fertilization rate, the miscarriage rate, and any adverse effects such as transplantation cancelation and associated complications during treatment.

Statistical analysis

All data were analyzed using SAS 9.3 statistical software. Measurement data are described as the means (standard deviation), and count data are described as frequencies (proportions). The means were compared using the *t* test or Wilcoxon rank sum test, and intergroup comparisons were performed using the chi-square test or Fisher's exact test. P<0.05 was considered statistically significant.

Results

A total of 245 patients underwent 1 ovarian stimulation cycle and 60 patients underwent 2 cycles in the study group, resulting in 461 ET cycles, including cryopreserved ETs. A total of 213 patients in the control group underwent 288 ET cycles (Table 1).

The overall demographic and cycle characteristics of the patients, including the average maternal age, infertility duration (years), basal hormonal test results, and BMI, were similar between the 2 groups. The total gonadotropin (Gn) dose used in the study group was 2845.22±1082.62 IU, while in the control group it was 3025.89±1002.08 IU (P=0.0464). The control group required more time (13.86±2.48 days *vs.* 13.77±2.32 days) for stimulation, although no significant differences were detected between the 2 groups (P>0.05). P and E2 levels and endometrial thickness on the hCG day were similar in both groups. The dominant follicles ratio was lower (79.79% *vs.* 82.88%, P=0.0045) and FSH, LH, and E2 levels on the initiation day and the LH level on the hCG day were significantly higher in the study group (1.22±1.39 *vs.* 0.74±0.55, P=0.0026) (Table 1). However, the biological parameters of the fresh cycles – the transplantation ratio (78.15% *vs.* 78.14%), the high response-induced cancelation ratio (10.28% *vs.* 10.93%), IVF/ICSI rank, the number of retrieved oocytes, the fertilization rate, and the numbers of transplantable embryos and high-quality embryos – were comparable between the 2 groups (Table 2).

The clinical outcomes of ET cycles are summarized in Table 3. No differences in the miscarriage rate, ectopic pregnancy rate,

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Table 2. Comparison of oocyte retrieval outcomes between the 2 groups.

Outcome	Study group (n=311)	Control group (n=213)	*P*-value#
Oocyte retrieval cycles			
1	245 (78.78)	190 (89.2)	
2	60 (19.29)	18 (8.45)	
3	3 (0.96)	1 (0.47)	
4	3 (0.96)	4 (1.88)	
Oocyte retrieval outcome			0.1536
No oocytes after oocyte retrieval	5 (1.60)	4 (1.88)	
Total unfertilization	3 (0.96)	1 (0.47)	
Abornamal fertilization	3 (0.96)	0 (0.00)	
Uncleavage	3 (0.96)	0 (0.00)	
Transplantation cancelleda	58 (18.64)	44 (20.66)	
High response	40 (12.86)	27 (12.68)	
No transplantable embryo	13 (4.18)	5 (2.34)	
Embryo transfer cycles	226 (72.67)	193 (78.14)	
Total oocytes, n (SD)*	10.46±6.47	10.31±6.77	0.6285
Fertilization, %	63.52	64.97	0.5982
Total embryos, n (SD)*	3.91±2.71	4.39±3.16	0.1744
High quality embryos, n (SD)*	3.45±2.51	4.08±3.13	0.053
Fertilization protocol			0.1805
ICSI	65 (16.71)	38 (15.38)	
IVF	308 (79.18)	205 (83)	
IVF+ICSI	16 (4.11)	4 (1.62)	

* Reasons: high response; personal reasons; presence of intra-cavity fluid due to a hydrosalpinx; high P on day of embryo transfer.
# Chi-square test, a Wilcoxon rank sum test, Values is mean ±SD, n (%) or median (range).

Table 3. Comparison of clinical outcomes of embryo transfer cycles* between the 2 groups.

	Study group (n=460)	control group (n=288)	*P*-value
Embryo transer			0.0884
Single-embryo transfer	69 (15.00)	57 (19.79)	
Double-embryo transfer	391 (85.00)	231 (80.21)	
Implantation rate, %	43.36	48.40	0.3664
Clinical pregnancy rate, n (%)#	262 (56.83)	175 (60.55)	0.3146
Ectopic pregnancy rate, n (%)#	10 (2.17)	3 (1.04)	0.3664
Miscarriage, n (%)#	35 (11.25)	22 (10.33)	0.7383

Chi-square test; values are mean ±SD, n (%) or median (range); NS – not statistically; * include thaw-ET.

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Table 4. Comparison of cumulative live birth rate outcomes between the 2 groups.

	Study group (n=330)		control group (n=261)		*P*-value*
Cumulative live birth rate (95% CI)					
First treatment	42.12	(36.63–47.61)	47.89	(41.18–54.6)	0.1921
First cycle#	59.81	(54.36–65.26)	65.73	(59.35–72.1)	0.1698
Second cycle	69.13	(64–74.27)	68.54	(62.31–74.78)	0.8866
≥3 cycles	69.45	(64.33–74.57)	69.01	(62.8–75.22)	0.9147

First treatment plus thaw embryo transfer; * Chi-square test; CI – confidence interval.

or clinical pregnancy rate were found between the groups (Table 3). The live birth rates of the 2 groups after the first treatment were similar (40.00% *vs.* 41.00%, P=0.81); no significant difference was found. The cumulative live birth rates of both groups showed an upward trend, with significant changes in the first cycle (59.81% (95% CI, 54.36–65.26%)) in the study group *vs.* 65.73% (95% CI, 59.35–72.1%) in the control group, P=0.17) and second cycle (69.13% (95% CI, 64–74.27%) in the study group *vs.* 68.54% (95% CI, 62.31–74.78%) in the control group, P=0.88), but no significant differences between the groups were observed (Table 4).

Discussion

To the best of our knowledge, this is the first study investigating the ultralong downregulation protocol in EMs patients. Although this retrospective study has limited power to draw strong conclusions regarding the proper dose for long-term pituitary downregulation before IVF, our findings may provide a new perspective. Our study supports the hypothesis that a single-application, long-term downregulation regimen can achieve comparable clinical outcomes to those of the conventional ultralong regimen. More importantly, shortening the downregulation duration minimizes patient costs and excessive pituitary suppression.

The proportions of poor cycle outcomes, such as failed oocyte retrieval and fertilization, abnormal fertilization, and no transplantable embryos, were similar in the 2 groups. The proportions of patients undergoing different fertilization methods did not differ between the groups, indicating that the baseline data of the 2 groups were not different.

Long-term pituitary downregulation is beneficial to endometrial receptivity. EMs alters endometrial receptivity by increasing estrogen exposure through CYP enzymes19 [16] and inflammation-dependent resistance to the effects of progesterone [17]. Many researchers have attempted to overcome this obstacle using either oral contraceptive pills [18] or levonorgestrel-releasing IUDs [19], but these methods cannot directly facilitate IVF. Two retrospective studies reported that GnRH antagonist (GnRH-ant) protocols can achieve comparable results to those of long-term GnRH-a protocols in EMs patients [20,21]. However, a Cochrane meta-analysis by Al-Inany and Aboulghar suggested that GnRH-ant protocols negatively affected pregnancy rates [22]. Khan et al. showed that long-term pituitary downregulation decreased the microvessel density of endometriotic lesions, reducing blood flow into the lesions [23]. With long-term amenorrhea, pinopodes can be restored [24]. Thus, long-term pituitary downregulation is useful for EMs. However, no data suggest that improved endometrial receptivity with long-term pituitary downregulation occurred in a dose-dependent manner. All CLB rates showed an upward trend and were higher than 66% after 2 cycles in the 2 groups, indicating that the effectiveness of the dose-reduced long-term regimen is not inferior to that of the conventional regimen.

Conflicting results have been reported regarding oocyte quality between patients with EMs and controls [25]. A randomized controlled trial showed that 3-month GnRH agonist treatment for peritoneal EMs prior to IVF did not produce a better outcome, such as a greater number of MII oocytes, compared with a longer protocol [26]. Van der Houwen found that ultralong pituitary downregulation can achieve a limited favorable effect in ongoing pregnancy in women who had experienced severe EMs during fresh cycles [27]. These results are generally consistent with ours, indicating the ultralong protocol may be unnecessary.

Moreover, long-term GnRH-a has been reported to result in a longer time to recovery of the pituitary gland [11]. The results obtained here are consistent with the above findings, with a higher LH level on hCG day in the study group than in the control group. When pituitary-ovarian function is excessively suppressed, egg and embryo quality are affected [28]. Our study showed no clear negative effect of the lower LH level in the control group. However, ultralong pituitary downregulation may suppress the ovarian response to Gn [26], and our results are consistent with this finding. The control group required a higher Gn dose and longer time for stimulation. More importantly, the live birth rate decreased with increasing FSH

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doses [29]. All these data suggest an inherent negative effect of ultralong pituitary downregulation.

This study had some limitations. The main limitation is the retrospective study design, which limits the robustness of the findings. The results of this study support the necessity of further prospective studies [13]. The sample sizes of the study are small. IVF-ET has become the first choice for the treatment of EMs patients with infertility. However, all therapies were administered in a single large IVF center that passed standard operation tests, thus ensuring the uniformity of the treatment paradigms. The study is limited by the lack of information on some patients' detailed surgical records. Thus, r-FS scoring was not performed, and the severity of the EMs of the patients was not analyzed in subgroups. However, the causal link between endometriosis and subfertility remains elusive except for bilateral tubal blockage [30]. Many patients with Ems of ASRM stage III and IV after surgery had poor ovarian reservation and limited number of oocytes [31], which might be exaggerated by longer downregulation.

Conclusions

A modified long-term downregulation regimen may serve as a cost-effective and safe treatment protocol for patients with EMs to improve the quality of care in assisted reproduction.

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Conflict of interest

None.

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