GnRH antagonist versus depot GnRH agonist protocol in polycystic ovary syndrome: analysis using propensity score matching

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Abstract

Introduction: Women with polycystic ovary syndrome (PCOS) have been reported to have a low pregnancy rate and high ovarian hyperstimulation syndrome (OHSS) risk in in vitro fertilization (IVF) programs due to the decreased endometrial receptivity and high ovarian reserve. The GnRH antagonist (GnRH-ant) protocol has been widely accepted as a prominent intervention to reduce the risk of OHSS, and been recommended as the preferred protocol. The depot GnRH agonist (dGnRH-a) protocol is believed to improve endometrial receptivity and increase the pregnancy rate of fresh embryo transfer. There have been no previous studies comparing the two protocols.
Material and methods: This was a retrospective cohort study that included 2164 women with PCOS undergoing assisted reproductive technology (ART) treatment between January 2014 and April 2019. Among them, 2018 women received dGnRH-a protocol treatment and 146 women received GnRH-ant protocol treatment. The two groups were matched by propensity scores with a ratio of 4 : 1 to account for potential confounding factors. The primary outcomes were the live birth rate (LBR), incidence of moderate-to-severe OHSS and the cost of controlled ovarian hyperstimulation (COH). Live birth rate was defined as live births per treatment cycle after the first fresh or frozen embryo transfer.
Results: The live birth rate per treatment cycle was higher in the dGnRH-a group than in the GnRH-ant group (58.22% vs. 41.78%, $p = 0.0004$), as was the live birth rate per fresh transfer (64.42% vs. 44.64%, $p = 0.0045$). However, the live birth rate per frozen transfer was similar in the two groups. There were no significant differences in the incidence of moderate-to-severe OHSS (4.28% vs. 2.05%, $p = 0.333$), the incidence of severe OHSS (0.17% vs. 0%, $p = 1$) and the cost of COH (RMB: 7736.9 vs. 8046.54, $p = 0.113$) between the two groups.
Conclusions: Our results indicated that the dGnRH-a protocol had a higher live birth rate than the GnRH-ant protocol, and the difference was mainly due to fresh embryo transfer. Regarding safety and economic cost, the incidence of moderate-to-severe OHSS and cost of COH were similar in the two groups. The incidence of moderate-to-severe OHSS in the dGnRH-a group was higher than in the GnRH-ant group, but without statistical difference. A subsequent prospective randomized controlled study is needed to confirm these results.

Key words: polycystic ovary syndrome, in vitro fertilization, GnRH antagonist protocol, depot GnRH agonist protocol, propensity score matching.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, affecting 8–13% of women of childbearing age. The primary pathophysiological features of PCOS are insulin resistance, rebound hyperinsulinemia and hyperandrogenemia [1]. These factors result in various clinical manifestations such as persistent anovulation, polycystic ovarian changes, hirsutism, acne and obesity [2].

For infertile women with PCOS, in vitro fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) technique offers an effective approach after a failure of first line lifestyle interventions or ovulation induction treatment. However, recent studies have revealed that women with PCOS suffering from endocrine and metabolic abnormalities often show decreased endometrial receptivity, which leads to a lower pregnancy rate [3, 4]. Moreover, the high antral follicular count (AFC) leads to abundant oocyte yield and high estradiol levels, which stimulate the occurrence of ovarian hyperstimulation syndrome (OHSS) [5]. Low success rates and high OHSS rates have always been problems faced by reproductive doctors.

The GnRH antagonist (GnRH-ant) protocol has been widely used as an effective strategy to reduce the risk of OHSS [6]. The main advantages of the antagonist protocol are that it does not need pituitary down-regulation, and requires a low dose of exogenous gonadotropin and fewer days of ovarian stimulation [7]. Additionally, the risk of OHSS can be further reduced by using the GnRH agonist trigger and freezing all strategies in the antagonist protocol [8]. Therefore, the GnRH-ant protocol has always been the mainstream protocol for PCOS.

GnRH agonists are commonly used to down-regulate the pituitary-gonadal system and prevent premature luteinization. There are two types of GnRH agonist administration methods: short-acting agonist with daily low-dose (0.1 mg) injections for 14 days in the luteal phase (standard long protocol) and long-acting agonist with a high-dose (3.75 mg, depot) injection on day 2 of the menstrual cycle (depot GnRH agonist protocol, also known as the early follicular phase long-acting regimen). Research has indicated that the depot GnRH agonist (dGnRH-a) protocol can increase the pregnancy rate, which could be explained by a positive effect on endometrial receptivity [9-12].

The balance between the desire for pregnancy and the patients' safety is a top priority. From the existing evidence, the GnRH antagonist protocol is beneficial in reducing the risk of OHSS [13].

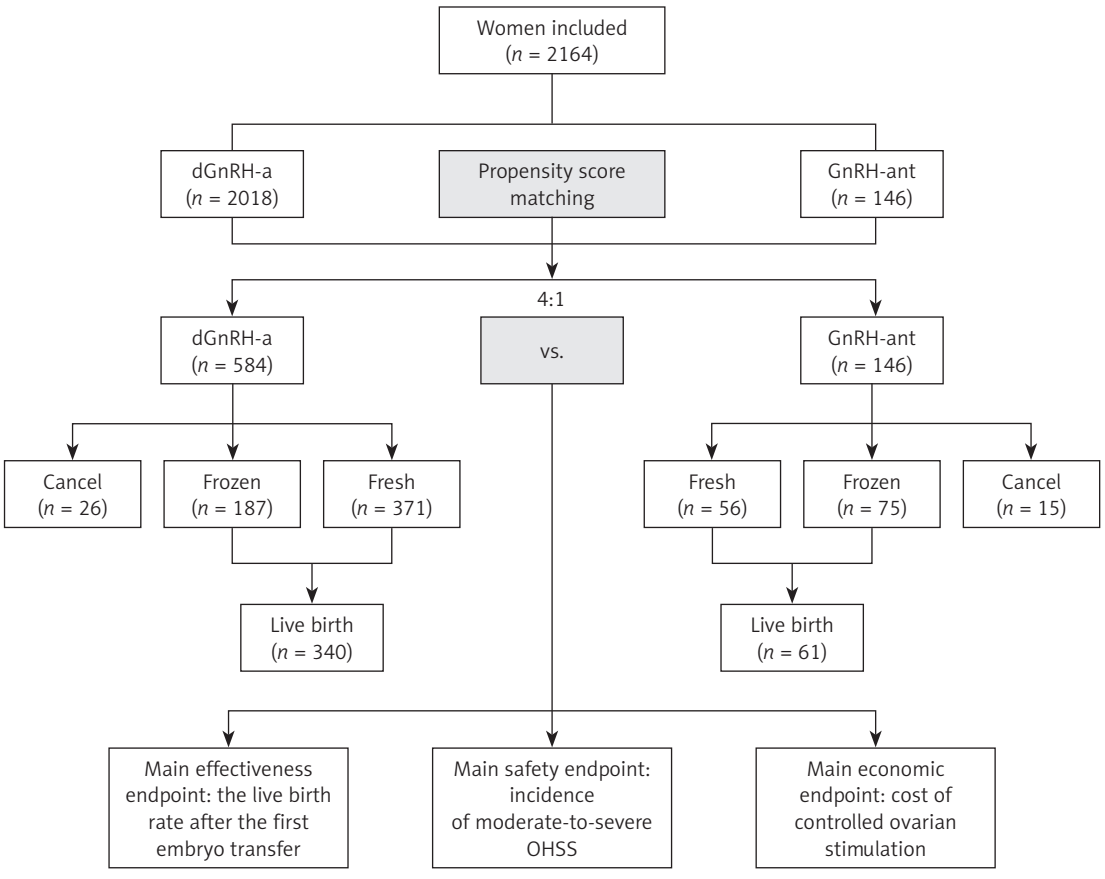

Figure 1. Flow chart of the study

However, no study has investigated the clinical outcome of the dGnRH-a protocol in women with PCOS. In this study, the two protocols were compared in detail in terms of safety, effectiveness and economic cost, hoping to find the best treatment for PCOS.

Material and methods

Subjects and study design

In this retrospective cohort study, medical records were reviewed for patients who underwent IVF/ICSI-ET treatment between January 2014 and April 2019 in the Reproductive Medicine Center of Jiangxi Maternal and Child Health Hospital Affiliated to Nanchang University. We analyzed clinical and economic outcomes of women with PCOS with the GnRH-ant or dGnRH-a protocol (Figure 1). PCOS was diagnosed according to the Rotterdam criteria [14]. This study was approved by the Institutional Review Board of Jiangxi Maternal and Child Health Hospital Affiliated to Nanchang University.

The depot GnRH agonist protocol

A long-acting GnRH agonist (Diphereline, Beaufour Ipsen, France) was injected with 3.75 mg on day 2 or 3 of the menstrual cycle. The patients returned to hospital 28 days later and underwent transvaginal ultrasonography and endocrine examination. If pituitary down-regulation (endometrial thickness ≤ 5 mm, serum follicle-stimulating hormone (FSH) < 5 mIU/ml, luteinizing hormone (LH) < 5 mIU/ml, estradiol (E2) < 50 pg/ml) was confirmed, administration of exogenous gonadotropin (Gn) was used to initiate controlled ovarian hyperstimulation (COH). Exogenous Gn included recombinant human FSH (Gonal-F, Merck Serono, Switzerland) and human menopausal gonadotrophin (HMG, Zhu Hai Livzon, China). During stimulation, the ovarian response was monitored by assessing serum E2, progesterone (P4) and LH, as well as serial transvaginal ultrasonographic examinations. Gn dosages were adjusted when necessary. 250 μg of recombinant human choriogonadotropin (HCG, Merck Serono, Switzerland) was administered until at least one follicle with a diameter ≥ 19 mm or 2 follicular diameters ≥ 18 mm were observed (Figure 2).

The GnRH antagonist protocol

Exogenous Gn was started on day 2 or 3 of the menstrual cycle. The starting dosage was determined based on age, body mass index (BMI), AFC, anti-Müllerian hormone (AMH) and previous ovarian response. These doses were adjusted according to the ovarian response, as monitored on ultrasonography and the measurement of serum sex hormone levels. The GnRH antagonist (Cetrorelix, Merck Serono, Switzerland) at a daily dose of 250 μg was started when the largest follicle exceeded 12 mm. The HCG trigger process is the same as described above.

Oocyte retrieval

Oocytes were retrieved 36 hours after HCG trigger by transvaginal ultrasound-guided puncture of follicles.

Embryo transfer strategy

The embryo transfer strategy was determined based on the number and quality of embryos, the risk of OHSS and the patient's constitution. The standards of embryo transfer strategy are as follows. If more than 15 oocytes were retrieved or the level of E2 exceeded 3000 pg/ml, the patient with ovarian diameter ≥ 7 cm and/or reported abdominal distension or bloating would be recommended to freeze all the embryos. If the number of good-quality embryos ≥ 2 and the number of transferable embryos ≥ 4 on day 3, blastocyst culture and single blastocyst transfer was selected. If the patient had a deformed uterus or scar uterus (with a history of cesarean section or hysteromyomectomy), and/or the BMI was less than 18.5 or greater than 28, only one embryo was allowed to be transferred.

Outcome assessment

Good-quality embryos on day 3 should consist of 7–10 blastomeres with a uniform size and no multiple nuclei, and the fragment proportion should be less than 20%. Transferable embryos on

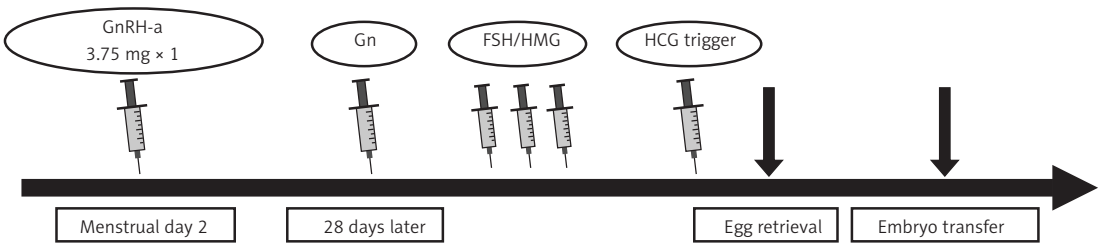

Figure 2. Brief explanation of the modified prolonged GnRH agonist protocol

day 3 should consist of more than 6 blastomeres, and the fragment proportion should be less than 40%. Serum β-HCG level was measured at 13 days after embryo transfer. When the serum β-HCG level exceeded 5 IU/l, a positive result was recorded. Clinical pregnancy was defined as the presence of a gestational sac in the uterine cavity at 30 days after embryo transfer, as detected on transvaginal ultrasonography. The primary outcome of effectiveness was the live birth rate per started treatment cycle, which was defined as delivery of any viable infant at 28 weeks or more of gestation during the first embryo transfer cycle. OHSS was defined according to the Golan criteria [15]. The cost of COH was mainly composed of the long-acting GnRH agonist, GnRH antagonist medication, FSH medication, transvaginal ultrasonography and endocrine examination.

Propensity score matching

A propensity score was calculated by using multivariate logistic regression with age, body mass index, duration of infertility, AFC, proportion of pelvic or tubal factors, scar uterus, and history of IVF/ICSI. The nearest neighbor match without replacement was used in propensity score matching (PSM) with a 4:1 ratio. An automated matching procedure was performed to match participants by using SAS software, version 9.4. To detect the power of matching, the percentage distribution of propensity scores and the comparison of demographic information before and after matching were implemented.

Statistical analysis

Statistical analysis was carried out using SAS version 9.4. Categorical data were presented as frequency and percentage; the χ^2 test was used to compare differences between the study groups, with Fisher's exact test used for expected frequencies of less than 5. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of the data. Continuous data conforming to a normal or approximate normal distribution were presented as mean (±SD) and compared using the independent *t* test. Non-normal distributed data

Table I. Baseline characteristics in dGnRH-a group and GnRH-ant group before and after propensity score matching

Characteristic	Before matching			After matching		
	dGnRH-a (*n* = 2018)	GnRH-ant (*n* = 146)	*p*-value	dGnRH-a (*n* = 584)	GnRH-ant (*n* = 146)	*p*-value
Age [years][a]	27.97 ±3.81	28.48 ±3.76	0.1159	28.73 ±4.03	28.48 ±3.76	0.4915
BMI [kg/m^2][a]	23.09 ±3.59	23.62 ±3.63	0.0871	23.86 ±3.86	23.62 ±3.63	0.4870
Duration of infertility [years][b]	4 (3–5)	4.58 (3–6)	0.0101	4 (3–6)	4.58 (3–6)	0.6673
Previous conception, *n* (%)[c]	809 (40.09)	57 (39.04)	0.8029	252 (43.15)	57 (39.04)	0.3687
Concomitant infertility factors						
Pelvic or tubal factors, *n* (%)[c]	1017 (50.4)	65 (44.52)	0.1703	248 (42.47)	65 (44.52)	0.6536
Endometriosis, *n* (%)[d]	38 (1.88)	4 (2.74)	0.5255	10 (1.71)	4 (2.74)	0.4960
Advanced age – ≥ 40, *n* (%)[d]	15 (0.74)	2 (1.37)	0.3200	9 (1.54)	2 (1.37)	1.0000
History of IVF/ICSI, *n* (%)[c]	110 (5.45)	19 (13.01)	0.0002	62 (10.62)	19 (13.01)	0.4094
Intrauterine adhesions, *n* (%)[c]	77 (3.82)	5 (3.42)	0.8111	21 (3.6)	5 (3.42)	0.9205
Scar uterus, *n* (%)[c]	118 (5.85)	17 (11.64)	0.0052	79 (13.53)	17 (11.64)	0.5469
Male factors, *n* (%)[c]	498 (24.68)	41 (28.08)	0.3584	136 (23.29)	41 (28.08)	0.2266
Basal AFC[a]	21.83 ±4.84	23.1 ±7.56	0.0471	22.85 ±5.41	23.1 ±7.56	0.7130
Basal T [ng/dl][b]	40.39 (29.77–54.1)	42.82 (34.5–57.18)	0.0821	41.96 (30.3–56.64)	42.82 (34.5–57.18)	0.4076
Basal LH [mIU/ml]/FSH [IU/l][b]	1.35 (0.88–2.04)	1.52 (0.89–2.02)	0.3668	1.42 (0.88–2.11)	1.52 (0.89–2.02)	0.6587
Basal E2 [pg/ml][b]	36.97 (27.49–48.9)	37.53 (27.6–49)	0.9574	36.43 (27.52–48)	37.53 (27.6–49)	0.8059

[a]Independent t test, [b]Mann-Whitney U test, [c]χ^2 test, [d]Fisher's exact test. BMI – body mass index, IVF/ICSI – in vitro fertilization/intracytoplasmic sperm injection, scar uterus – history of cesarean section or hysteromyomectomy, AFC – antral follicular count, T – testosterone, LH – luteinizing hormone, FSH – follicle-stimulating hormone, E2 – estradiol.

were presented as median (IQR) and compared by the Mann-Whitney *U* test. For a small number of missing values (such as hormone levels), the list deletion method was used. Statistical analyses were performed using two-sided tests, with $p < 0.05$ considered statistically significant.

Results

Baseline characteristics before and after PSM

Baseline characteristics in the dGnRH-a group and GnRH-ant group before PSM are presented in Table I. Before PSM, duration of infertility, history of IVF/ICSI, scar uterus, and AFC were significantly different between the two groups ($p < 0.05$). After matching, all baseline characteristics became very similar between the two groups (Table I). The percentage distribution histogram of propensity scores before and after PSM was plotted (Figure 3). The percentage distribution of propensity scores between groups became nearly identical after matching.

Ovarian stimulation and laboratory embryo culture outcome

The results of COH and laboratory indicators are presented in Table II. The dGnRH-a protocol had a longer duration of ovarian stimulation (12.89 vs. 10.58, $p < 0.0001$) and a higher dosage of Gn (2074.40 vs. 1704.78, $p < 0.0001$) with a higher dose of HMG (933.09 vs. 322.60, $p < 0.0001$) compared with the GnRH-ant protocol. The serum levels of E2 (2590.61 vs. 3224.80, $p = 0.0022$), LH (0.77 vs. 2.37, $p < 0.0001$) and P4 (0.69 vs. 0.85, $p < 0.0001$) on the HCG injection day in the dGnRH-a group were lower than those in the GnRH-ant group. Meanwhile, the dGnRH-a group had a thicker endometrium on the HCG injection day (10.84 vs. 9.62, $p < 0.0001$). For laboratory embryo culture outcome, the dGnRH-a group had more transferable day 3 embryos (7 vs. 5, $p = 0.0219$). More blastocysts and fewer embryos were transferred in the dGnRH-a group. Furthermore, compared with the GnRH-ant group, the rate of fresh embryo transfer was significantly higher in the dGnRH-a group (63.53% vs. 38.36%, $p < 0.0001$).

Clinical outcome and economic indicators

The effectiveness, safety and economic cost indicators are presented in Table III. The dGnRH-a protocol had an increased biochemical pregnancy rate (76.71% vs. 62.33%, $p = 0.0004$), clinical pregnancy rate (67.81% vs. 52.74%, $p = 0.0007$), implantation rate (56.05% vs. 43.44%, $p = 0.0068$) and live birth rate (58.22% vs. 41.78%, $p = 0.0004$) compared with the GnRH-ant protocol. The high live birth rate of dGnRH-a protocol was mainly due to the low cancellation rate (4.45% vs. 10.27%, $p = 0.0063$) and the high live birth rate per fresh transfer (64.42% vs. 44.64%, $p = 0.0045$). There were no significant differences in the incidence of moderate-to-severe OHSS (4.28% vs. 2.05%, $p = 0.3327$) and multiple pregnancy rate between the two groups. Regarding the cost of COH, the total cost was comparable between groups, whereas dGnRH-a spent less on GnRH agonist/antagonist (1299.2 vs. 1872.15, $p < 0.0001$) and exogenous Gn (4084.28 vs. 4355.08, $p < 0.0001$), and spent more on transvaginal ultrasonography (1010.62 vs. 717.67,

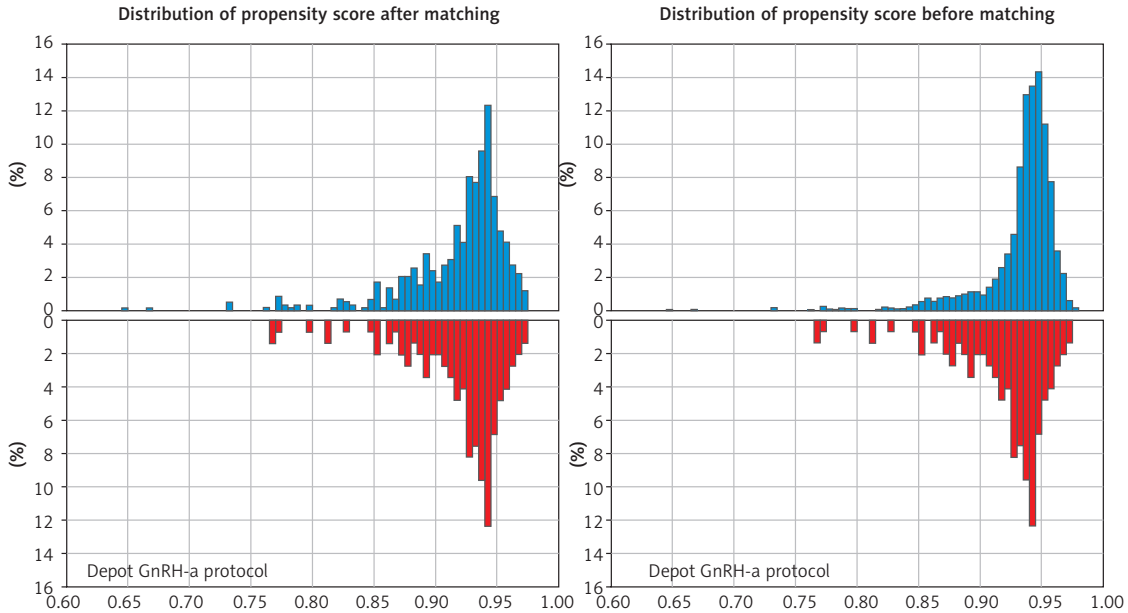

Figure 3. Percentage distribution histogram of propensity scores before and after propensity score matching (PSM)

Table II. Results of COH and laboratory indicators compared between two groups

Items	dGnRH-a (*n* = 584)	GnRH-ant (*n* = 146)	*P*-value
Days of stimulation[a]	12.89 ±3.34	10.58 ±2.63	< 0.0001
Dose of exogenous Gn [IU][a]	2074.40 ±1077.66	1704.78 ±819.60	< 0.0001
rFSH [IU][a]	1141.32 ±338.10	1382.17 ±577.44	< 0.0001
HMG [IU][a]	933.09 ±1132.10	322.60 ±712.28	< 0.0001
E2 on HCG trigger day [ng/ml][b]	2590.61 (1693–3943)	3224.8 (2037–4952.37)	0.0022
LH on HCG trigger day [mIU/ml][b]	0.77 (0.47–1.15)	2.37 (1.41–4.59)	< 0.0001
P4 on HCG trigger day [pg/ml][b]	0.69 (0.46–0.95)	0.85 (0.59–1.19)	< 0.0001
Endometrium thickness on HCG trigger day(mm)[a]	10.84 ±2.36	9.62 ±2.40	< 0.0001
No. of oocytes retrieved[b]	15 (11–21)	17 (9–22)	0.6908
Good-quality embryos on day 3[b]	2 (1–4)	2 (0–4)	0.6700
Transferable embryos on day 3[b]	7 (4–11)	5 (3–10)	0.0219
Phase of embryo transfer[c]			0.0016
Cleavage embryo, *n* (%)	475/558 (85.13)	125/131 (95.42)	
Blastocyst, *n* (%)	83/558 (14.87)	6/131 (4.58)	
No. of embryos transferred[c]			0.0054
1	140/558 (25.09)	18/131 (13.74)	
2	418/558 (74.91)	113/131 (86.26)	
Fresh/frozen embryo transfer[c]			< 0.0001
Cycles without transferable embryos[c]	26/584 (4.45%)	15/146 (10.27)	
Fresh transfer	371/584 (63.53%)	56/146 (38.36)	
Freezing-all	187/584 (32.02)	75/146 (51.37)	

[a]Independent t test, [b]Mann-Whitney U test; [c]χ^2 test. Gn – gonadotropin, FSH – follicle-stimulating hormone, HMG – human menopausal gonadotrophin, E2 – estradiol, HCG – human choriogonadotropin, LH – luteinizing hormone, P4 – progesterone.

$p < 0.0001$) and endocrine examination (1342.81 vs. 1101.64, $p < 0.0001$).

Discussion

Controlled ovarian hyperstimulation is still a major challenge in women with PCOS due to the abnormal endocrine and metabolic environment. The GnRH-ant protocol has been widely accepted as a prominent intervention to reduce the risk of OHSS [13], and has been recommended by the World Health Organization as a COH choice for PCOS patients [16]. To date, most studies comparing COH protocols in PCOS women have focused on the GnRH antagonist protocol and the standard long protocol (short-acting agonist with daily low-dose (0.1 mg) injections for 14 days in luteal phase) [17]. This study is the first to compare the dGnRH-a protocol (long-acting agonist with a high-dose (3.75 mg, depot) injection on day 2 of the menstrual cycle) and the GnRH-ant protocol in terms of effectiveness, safety, and economic cost. Although this was a retrospective study, the power was greatly improved by using PMS statistical methods to adjust for potential non-similarities between groups. Our study showed that the dGnRH-a protocol could achieve a higher live birth rate after the first embryo transfer, and there were no significant differences in the incidence of OHSS or the cost of the COH process compared with the GnRH-ant protocol.

Long-acting GnRH agonists are mainly used for the treatment of endometriosis by injecting 2–6 doses (3.75 mg) and have achieved relatively high pregnancy rates [9, 18, 19]. Later, the dGnRH-a protocol with only one injection emerged in China and is gradually being used in non-endometriotic infertile patients [20]. However, the evidence for better clinical outcomes from the dGnRH-a protocol is limited. In 2014, Ren *et al*. [11] observed a higher live birth rate (55.56% vs. 45.73%, $p = 0.006$) in women who had a normal ovarian response with the dGnRH-a protocol compared with the standard long protocol. Similarly, compared with the standard long protocol, this superiority was also found in patients with PCOS (60.13% vs. 48.95%, $p = 0.025$) [10]. Moreover, Gong *et al*. [12] reported a higher clinical pregnancy rate (77.94% vs. 61.29%, $p = 0.039$) in patients suffering from PCOS using the dGnRH-a protocol than those who used the standard long protocol, and our study further showed a higher live birth rate (58.22% vs. 41.78%, $p = 0.0004$). However, mechanisms of the

Table III. Effectiveness, safety, and economic indicators compared between two groups

Items	dGnRH-a (*n* = 584)	GnRH-ant (*n* = 146)	*P*-value
Effectiveness index			
Biochemical pregnancy rate, *n* (%)[b]	448/584 (76.71)	91/146 (62.33)	0.0004
Clinical pregnancy rate, *n* (%)[b]	396/584 (67.81)	77/146 (52.74)	0.0007
Implantation rate, *n* (%)[b]	547/976 (56.05)	106/244 (43.44)	0.0004
Live birth rate per treatment cycle, *n* (%)[b]	340/584 (58.22)	61/146 (41.78)	0.0004
Cancel transfer, *n* (%)[b]	26/584 (4.45)	15/146 (10.27)	0.0063
Live birth per fresh transfer, *n* (%)[b]	239/371 (64.42)	25/56 (44.64)	0.0045
Live birth per frozen transfer, *n* (%)[b]	101/187 (54.01)	36/75 (48)	0.3786
Live birth per cleavage embryos transfer, *n* (%)[b]	287/475 (60.42)	58/125 (46.4)	0.0048
Live birth per blastocyst transfer, *n* (%)[c]	53/83 (63.86)	3/6 (50)	0.6663
Safety index			
Incidence of OHSS, *n* (%)[b]			0.6361
Mild	21/584 (3.6)	6/146 (4.11)	
Moderate	24/584 (4.11)	3/146 (2.05)	
Severe	1/584 (0.17)	0/146 (0)	
Incidence of moderate-to-severe OHSS, *n* (%)[c]	25/584 (4.28)	3/146 (2.05)	0.3327
Multiple pregnancy rate, *n* (%)[b]	157/396 (39.65)	30/77 (38.96)	0.9104
Economic index			
The cost of COH ($)			
GnRH agonist/antagonist[a]	201.12 ±7.92	289.81 ±101.98	< 0.0001
Exogenous Gn [a]	632.25 ±165.48	674.17 ±240.87	0.0482
rFSH[a]	594.88 ±188.5	661.25 ±247.23	0.0026
HMG[a]	37.36 ±45.33	12.92 ±28.52	< 0.0001
Transvaginal ultrasonography[a]	156.44 ±34.08	111.1 ±31.28	< 0.0001
Endocrine examination[a]	207.87 ±57.77	170.53 ±51.38	< 0.0001
Total cost[a]	1197.67 ±210.92	1245.6 ±348.15	0.1132

[a]Independent t test, [b]χ^2 test, [c]Fisher's exact test. OHSS – ovarian hyperstimulation syndrome, COH – controlled ovarian hyperstimulation, Gn – gonadotropin, FSH – follicle-stimulating hormone, HMG – human menopausal gonadotrophin.

results are currently unclear. Some studies reported endometrial receptivity as the main limitation of gestation for women suffering from PCOS [12], and HOXA10, MEIS1, and LIF mRNA and protein expression levels in endometrium were all significantly higher in the dGnRH-a protocol than in the GnRH-ant protocol and standard long protocol [21], suggesting significant superiority of the dGnRH-a protocol in improving endometrial receptivity for patients with PCOS.

We used the PSM method to control the potential confounders between dGnRH-a and GnRH-ant groups. The PSM method was first described in the 1980s by Rosenbaum *et al*. [22], but it was not widely used by statisticians until the 2000s, especially in medicine. This method is useful for observational studies in which treatment allocation is non-random and can be viewed as an approach seeking to replicate random assignment in conventional randomized controlled trials [23]. The other advantage of the PSM method for this study is that it allows parallel comparisons among the three main outcomes instead of multiple logistic regression for each end point. Before matching, the GnRH-ant group had a longer duration of infertility, more AFC, and a higher proportion of IVF treatment history and scar uterus. After matching, the difference in those characteristics between groups became very small.

In our study, the dGnRH-a protocol had a longer follicular stimulation period, more Gn dosages and lower serum E2, LH, and P4 levels on the HCG trigger day than the GnRH-ant protocol. A possible explanation is that a long-acting GnRH-a injection could deeply suppress the pituitary-ovarian axis. In the GnRH-ant protocol, the ovarian stimulation period was short, which might be attributed to the rapid inhibition of the endogenous LH release without pituitary desensitization [7]. In addition, because of a higher E2 level on the HCG trigger day (3224.8 vs. 2590.6), the proportion of frozen embryo transfer in the GnRH-ant group should be higher than that in the dGnRH-a group to take precautions against the occurrence of OHSS.

An increasing number of transferable embryos and cycles with transferable embryos were observed in the dGnRH-a group. This might benefit from the GnRH agonist, which reduced the cancellation rate by preventing premature LH surge, and increased the number of oocytes and embryos transferred [24]. An animal study showed that a GnRH agonist increased the proportion of mouse embryos that reached the blastocyst stage in vitro [25]. Casan *et al*. [26] observed the expression of GnRH and its receptor in human preimplantation embryos. Even so, direct evidence supporting the role of GnRH agonists in human embryo remains limited.

Previous studies [11, 18] observed a thicker endometrium in the prolonged GnRH agonist protocol than that in other protocols, which was consistent with our data. Endometrium thickness has been used as a marker of uterine receptivity to embryos, and as a predictor of IVF-ET success [27, 28]. Although related mechanisms are still unclear, it could be associated with the hypothesis of endometrial recovery. A break of constant menstrual cycling by prolonged down-regulation may restore full function to the steroid-sensitive systems [29].

Unlike other studies, our study defined the live birth rate as live births per treatment cycle after the first fresh or frozen embryo transfer. As is well known, the advantages of the dGnRH-a protocol can only be reflected in the fresh transfer cycle. Therefore, it is not sufficient to simply compare outcomes of fresh or frozen transfer cycle alone. The cumulative live birth rate (CLBR) was suggested as a suitable way to report success of IVF treatment [30]. However, the follow-up time of two years is too long and difficult to achieve. The live birth rate after first fresh or frozen embryo transfer is an intermediate choice; it does not require all embryos to be transferred, and it can take into account the outcomes of both the fresh transfer and frozen transfer.

Women with PCOS who require IVF treatment are at particular risk of OHSS. A systematic review with 9 RCTs published before 2012 [17] showed that PCOS patients with the GnRH-ant treatment had a lower severe OHSS rate (5.52% (35/634) vs. 12.42% (82/660)) than those treated with the standard long protocol. In 2016, Chen *et al*. [31] reported a lower moderate or severe OHSS rate (1.3% (10/746) vs.7.1% (54/762)) in the frozen-embryo group than that in the fresh-embryo group. Therefore, the GnRH-ant protocol combined with the freeze-all embryo strategy can minimize the occurrence of OHSS. In our study, the dGnRH-a group had a moderate to severe OHSS rate of 4.28% (25/584) and a severe OHSS rate of 0.17% (1/584), which were higher than those of the GnRH-ant group (2.05% and 0%, respectively), but the differences were not significant.

As regards economic indicators, remarkably, our data significantly favored higher total dosages of exogenous Gn in the dGnRH-a group, but the costs were lower than expected, due to the fact that patients in the dGnRH-a group received more HMG injections. HMG contains the same dosage of LH and FSH, which may be one of the sources of exogenous LH. Too low serum LH level in COH may affect follicular development, which directly influenced the potentiality of oocyte and embryo [32]. Previous studies have reported that the LH level during ovarian stimulation should be neither too high nor too low [33, 34]. Thus, patients in the dGnRH-a group with low serum LH levels after prolonged pituitary depression usually used HMG instead of rFSH or added recombinant LH when serum LH levels were < 1 IU/l.

An apparent defect of this study was that there were only 146 patients in the GnRH-ant group. For the live birth rate outcome, this sample size is sufficient to detect a statistical significance because of a large effect size. For economic outcomes, the power of the independent *t*-test was acceptable for data following a continuous normal distribution with a relatively small standard deviation. However, there were only 3 patients with moderate-to-severe OHSS in the GnRH-ant group. The contingency of this probability suggests that more research with larger sample sizes should be conducted. It is estimated that the GnRH-ant protocol would achieve a lower OHSS rate by expanding the sample size.

In conclusion, this retrospective study shows that the depot GnRH agonist protocol produced significant improvement in the live birth rate compared with the GnRH antagonist protocol. There was no significant difference in the incidence of moderate to severe OHSS between the two groups in this study, but this conclusion still needs to be verified by large sample studies. The depot GnRH agonist protocol spent less on drug costs and more on transvaginal ultrasonography and endocrine tests compared with the GnRH antagonist protocol, but the total cost of COH is similar.

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Conflict of interest

The authors declare no conflict of interest.

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