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

Type

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Keywords

in vitro fertilization, polycystic ovary syndrome, propensity score matching, GnRH antagonist protocol, depot GnRH agonist protocol

Abstract

Introduction
Women with PCOS have been reported with low pregnancy rate and high OHSS risk in 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 the depot GnRH agonist (dGnRH-a) protocol are believed to improve endometrial receptivity and increase the pregnancy rate of fresh embryo transfer.

Material and methods
This study was a retrospective cohort study that included 2164 women with PCOS undergoing assisted reproductive technology (ART) treatment from January 2014 to April 2019. The two groups were matched by propensity scores with a ratio of 4:1 accounting for potential confounding factors.

Results
The live birth per treatment cycle was higher in the dGnRH-a group than in the GnRH-ant group (58.22% vs. 41.78%, P=0.0004), the same with live birth 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=0.333) 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 has a higher live birth rate than GnRH-ant protocol, and the difference is mainly due to fresh embryo transfer. For safety and economic cost, the incidence of moderate-to-severe OHSS and cost of COH is similar in two groups. Nevertheless, the incidence of moderate-to-severe OHSS in the dGnRH-a group is numerically higher than GnRH-ant protocol with no statistical difference. A subsequent prospective randomized controlled study is needed to confirm these results.

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

ABSTRACT

Introduction: Women with polycystic ovary syndrome (PCOS) have been reported with 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 preferred protocol. The depot GnRH agonist (dGnRH-a) protocol are believed to improve endometrial receptivity and increase the pregnancy rate of fresh embryo transfer. There have been no previous studies comparing the two protocol.

Material and methods: This study was a retrospective cohort study that included 2164 women with PCOS undergoing assisted reproductive technology (ART) treatment from January 2014 to 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 accounting 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). LBR was defined as live birth per treatment cycle after first fresh or frozen embryo transfer.

Results: The live birth per treatment cycle was higher in the dGnRH-a group than in the GnRH-ant group (58.22% vs. 41.78%, P=0.0004), the same with live birth per fresh transfer (64.42% vs. 44.64%, P=0.0045). However, the live birth per frozen transfer was similar in 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.

Conclusion: Our results indicated that the dGnRH-a protocol has a higher live birth rate than GnRH-ant protocol, and the difference is mainly due to fresh embryo transfer. For safety and economic cost, the incidence of moderate-to-severe OHSS and cost of COH is similar in two groups. Nevertheless, the incidence of moderate-to-severe OHSS in the dGnRH-a group is numerically higher than GnRH-ant protocol with no statistical difference. A subsequent prospective randomized controlled study is needed to confirm these results.

Keywords: 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% women of childbearing age. The primary pathophysiology of PCOS is insulin resistance, rebound hyperinsulinemia and hyperandrogenemia [1]. These actions result in several clinical features 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 1st line lifestyle interventions or ovulation induction treatment. However, recent studies find 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 rate and high OHSS rate 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 agonist is 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 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 reports that the depot GnRH agonist (dGnRH-a) protocol can increase the pregnancy rate, which could be explained by 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]. 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.

MATERIALS AND METHODS

Subjects and study design

In this retrospective cohort study, medical records were reviewed for patients who underwent IVF/ICSI-ET treatment from January 2014 to April 2019 in the Reproductive Medicine Center of ***. We analyzed clinical and economic outcomes of women with PCOS with GnRH-ant or

dGnRH-a protocol (Figure 1). PCOS is diagnosed according to the Rotterdam criteria [14]. This study was approved by the Institutional Review Board of ***.

The depot GnRH agonist protocol (dGnRH-a)

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 back 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 the 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 needed. 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 (Fig 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. 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, 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 has a deformed uterus or scar uterus (with history of cesarean section or hysteromyomectomy), and/or the BMI is less than 18.5 or greater than 28, only one embryo is allowed to be transferred.

Outcome assessment

Good-quality embryos on day 3 should consist of 7-10 blastomeres with a uniform size, no multiple nuclei and the fragment proportion should be less than 20%. Transferable embryos on 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 exceeds 5IU/L, a positive result is indicated. 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 long-acting GnRH agonist, GnRH antagonist medication, FSH medication, transvaginal ultrasonography and endocrine examination.

Propensity score matching

A PS was calculated by using multivariate logistic regression with age, body mass index, duration of infertility, AFC, proportion of pelvic or tubal factors, scar uterus, history of IVF/ICSI. The nearest neighbor match without replacement was used in 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 by SAS version 9.4. Categorical data were described by frequency and percentage, chi-square test was used to compare the differences between the study groups, with the use of Fisher's exact test for expected frequencies of less than 5. Kolmogorov-Smirnov and Shapiro-Wilk test were used to test the normality of the data. Continuous data that conform to a normal or approximate normal distribution were described as means (±SD) and compared by independent t test. Non-normal distributed data were described as median (IQR) and compared by Mann-Whitney U test. For a small number of missing values (such as hormone levels), the list deletion method is used. Statistical analysis was tested on two-sided settings, with $p < 0.05$ considered as statistically significant.

RESULTS

Baseline characteristics before and after PSM

Baseline characteristics in dGnRH-a group and GnRH-ant group before PSM were presented in Table 1. Before PSM, duration of infertility, history of IVF/ICSI, scar uterus, and AFC were significantly different between two groups ($P< 0.05$). After matching, all baseline characteristics became very similar between the two groups (Table 1). 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 embryos culture outcome

The results of COH and laboratory indicators were presented in Table 2. 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 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 HCG injection day in the dGnRH-a group were lower than those in the GnRH-ant group. Meanwhile, dGnRH-a group had a thicker endometrium on HCG injection day (10.84 vs. 9.62, P < 0.0001). For laboratory embryos culture outcome, the dGnRH-a group had more transferable day 3 embryos (7 vs. 5, P = 0.0219). More blastocyst and less number of 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 were presented in Table 3. 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. For 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<.0001) and exogenous Gn (4084.28 vs. 4355.08, P<.0001), and spent more on transvaginal ultrasonography (1010.62 vs. 717.67, P<.0001) and endocrine examination (1342.81 vs. 1101.64, P<.0001).

DISCUSSION

Controlled ovarian hyperstimulation (COH) is still a big 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 been recommended by WHO as a COH choice for PCOS patients [16]. At present, most of the studies on the comparison of COH protocol 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 was the first one to compare the dGnRH-a ptotocol (long-acting agonist with a high-dose (3.75 mg, depot) injection on day 2 of the menstrual cycle) and the GnRH-ant protocol from aspects 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. At last, our study showed that the dGnRH-a protocol could achieve a higher live birth rate after first embryo transfer, and there were no

significant differences in the incidence of OHSS or the cost of COH process when compared with GnRH-ant protocol.

Long-acting GnRH agonist is mainly utilized for the treatment of endometriosis by injecting 2-6 doses (3.75 mg) and has obtained relatively high pregnancy rates [9,18,19]. Later, the dGnRH-a protocol with only one injection has emerged in China and is gradually used in non-endometriotic infertile patients [20]. But the evidence of better clinical outcome from 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 normal ovarian response with the dGnRH-a protocol when compared with the standard long protocol. Similarly, compared with standard long protocol, this superiority was also found in patients with PCOS (60.13% vs. 48.95%, P=0.025) [10]. Moreover, Fei Gong et al. [12] reported a higher clinical pregnancy rate (77.94% vs. 61.29%, P=0.039) in patients suffering from PCOS using dGnRH-a protocol than those who used standard long protocol and our study further showed a higher live birth (58.22% vs. 41.78%, P=0.0004). However, mechanisms of the 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 in endometrium all showed significantly higher in the dGnRH-a protocol than in the GnRH-ant protocol and standard long protocol [21], suggesting a significant priority of dGnRH-a protocol on improving endometrial receptivity for patients with PCOS.

Baseline characteristics

We used the propensity score matching method to control the potential confounders between dGnRH-a group and GnRH-ant group. The PSM method was first described in the 1980s by Rosenbaum and Rubin [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 higher proportion of IVF treatment history and scar uterus. After matching, the difference in those characteristics between groups became very small.

Ovarian stimulation and embryos culture outcomes

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 GnRH-ant protocol. One of the possible explanations is that a long-acting GnRH-a injection could deeply suppress the pituitary-ovarian axis. In 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 dGnRH-a group. This might benefit from GnRH agonist, which reduced cancellation rate by preventing premature LH surge, and increased the number of oocytes and embryos transferred [24]. Animal studies showed that GnRH agonist increased the proportion of mouse embryos that reached the blastocyst stage in vitro [25]. Casan et al. [26] found the expression of GnRH and its receptor in human preimplantation embryos. Even so, direct evidence supporting the role of GnRH agonist in human embryo remains limited.

Previous studies [11,18] observed a thicker endometrium in prolonged GnRH agonist protocol than that in other protocols, which was consistent with our data. Endometrium thickness has been used as a marker of the 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].

Clinical outcome and economic indicators

Unlike other studies, our study defined the live birth rate as live birth per treatment cycle after first fresh or frozen embryo transfer. As we all know, the advantages of dGnRH-a protocol can only be reflected in the fresh transfer cycle. Therefore, it is not comprehensive to simply compare outcomes of fresh or frozen transfer cycle alone. Cumulative live birth rate (CLBR) was suggested as a suitable way to report success of an IVF treatment [30]. However, 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 the account 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 [31] showed PCOS patients with the GnRH-ant treatment had a lower severe OHSS rate (5.52% [35/634] vs. 12.42% [82/660]) than treated with standard long protocol. In 2016, Chen et al. [32] 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 freeze-all embryo 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 relatively higher than the GnRH-ant group (2.05% and 0%, respectively), but the difference was not significant.

For 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, the reason for which was 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 [33]. Previous studies have reported that the LH level during ovarian stimulation should neither be too high nor too low [34,35]. 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.

Limitations

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 enough to detect a statistical significance because of a large effect size. For economic outcomes, the power of independent t-test was acceptable for data following 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 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 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 GnRH antagonist protocol, but the total costs of COH is similar.

AUTHOR CONTRIBUTIONS

LZX and LFT contributed equally to this work. LZX: conception of the idea, study design, data analysis and drafting of the manuscript. LFT: study design, interpretation of data analysis results and revising of the manuscript. JT: revising of the manuscript. SSZ: revising of the manuscript. QFW: guidance on the research design, revising of the manuscript and final approval of the version to be published.

Conflict of interest

The authors declare no conflict of interest.

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Caption description of figure

Fig 1 Flow chart of the study.

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

Fig 3 The percentage distribution histogram of propensity scores before and after PSM.

Table 1 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[c]	809/2018(40.09%)	57/146(39.04%)	0.8029	252/584(43.15%)	57/146(39.04%)	0.3687
Concomitant infertility factors						
Pelvic or tubal factors[c]	1017/2018(50.4%)	65/146(44.52%)	0.1703	248/584(42.47%)	65/146(44.52%)	0.6536
Endometriosis[d]	38/2018(1.88%)	4/146(2.74%)	0.5255	10/584(1.71%)	4/146(2.74%)	0.4960
Advanced age (>=40)[d]	15/2018(0.74%)	2/146(1.37%)	0.3200	9/584(1.54%)	2/146(1.37%)	1.0000
History of IVF/ICSI[c]	110/2018(5.45%)	19/146(13.01%)	**0.0002**	62/584(10.62%)	19/146(13.01%)	0.4094
Intrauterine adhesions[c]	77/2018(3.82%)	5/146(3.42%)	0.8111	21/584(3.6%)	5/146(3.42%)	0.9205
Scar uterus[c]	118/2018(5.85%)	17/146(11.64%)	**0.0052**	79/584(13.53%)	17/146(11.64%)	0.5469
Male factors[c]	498/2018(24.68%)	41/146(28.08%)	0.3584	136/584(23.29%)	41/146(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]Chi-square 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.

Table 2 Results of COH and Laboratory indicators 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	**<.0001**
Dose of exogenous Gn(IU)[a]	2074.40±1077.66	1704.78±819.60	**<.0001**
rFSH(IU)[a]	1141.32±338.10	1382.17±577.44	**<.0001**
HMG(IU)[a]	933.09±1132.10	322.60±712.28	**<.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]	**<.0001**
P4 on HCG trigger day(pg/ml)[b]	0.69[0.46,0.95]	0.85[0.59,1.19]	**<.0001**
Endometrium thickness on HCG trigger day(mm)[a]	10.84±2.36	9.62±2.40	**<.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	475/558(85.13%)	125/131(95.42%)	
Blastocyst	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]			**<.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]Chi-square test

Gn: gonadotropin; FSH: follicle-stimulating hormone; HMG: human menopausal gonadotrophin; E2:estradiol; HCG: human choriogonadotropin; LH: luteinizing hormone; P4:

progesterone;

Table 3 The effectiveness, safety, and economic indicators between two groups

Items	dGnRH-a (n=584)	GnRH-ant (n=146)	P-value
Effectiveness index			
Biochemical pregnancy rate[b]	448/584(76.71%)	91/146(62.33%)	**0.0004**
Clinical pregnancy rate[b]	396/584(67.81%)	77/146(52.74%)	**0.0007**
Implantation rate[b]	547/976(56.05%)	106/244(43.44%)	**0.0004**
Live birth rate per treatment cycle[b]	340/584(58.22%)	61/146(41.78%)	**0.0004**
Cancel transfer[b]	26/584(4.45%)	15/146(10.27%)	**0.0063**
Live birth per fresh transfer[b]	239/371(64.42%)	25/56(44.64%)	**0.0045**
Live birth per frozen transfer[b]	101/187(54.01%)	36/75(48%)	0.3786
Live birth per cleavage embryos transfer[b]	287/475(60.42%)	58/125(46.4%)	**0.0048**
Live birth per blastocyst transfer[c]	53/83(63.86%)	3/6(50%)	0.6663
Safety index			
Incidence of OHSS[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[c]	25/584(4.28%)	3/146(2.05%)	0.3327
Multiple pregnancy rate[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	**<.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	**<.0001**
Transvaginal ultrasonography[a]	156.44±34.08	111.1±31.28	**<.0001**
Endocrine examination[a]	207.87±57.77	170.53±51.38	**<.0001**
Total cost[a]	1197.67±210.92	1245.6±348.15	0.1132

[a]Independent t test [b]Chi-square test [c]Fisher's exact test

OHSS: ovarian hyperstimulation syndrome; COH: controlled ovarian hyperstimulation; Gn: gonadotropin; FSH: follicle-stimulating hormone; HMG: human menopausal gonadotrophin.

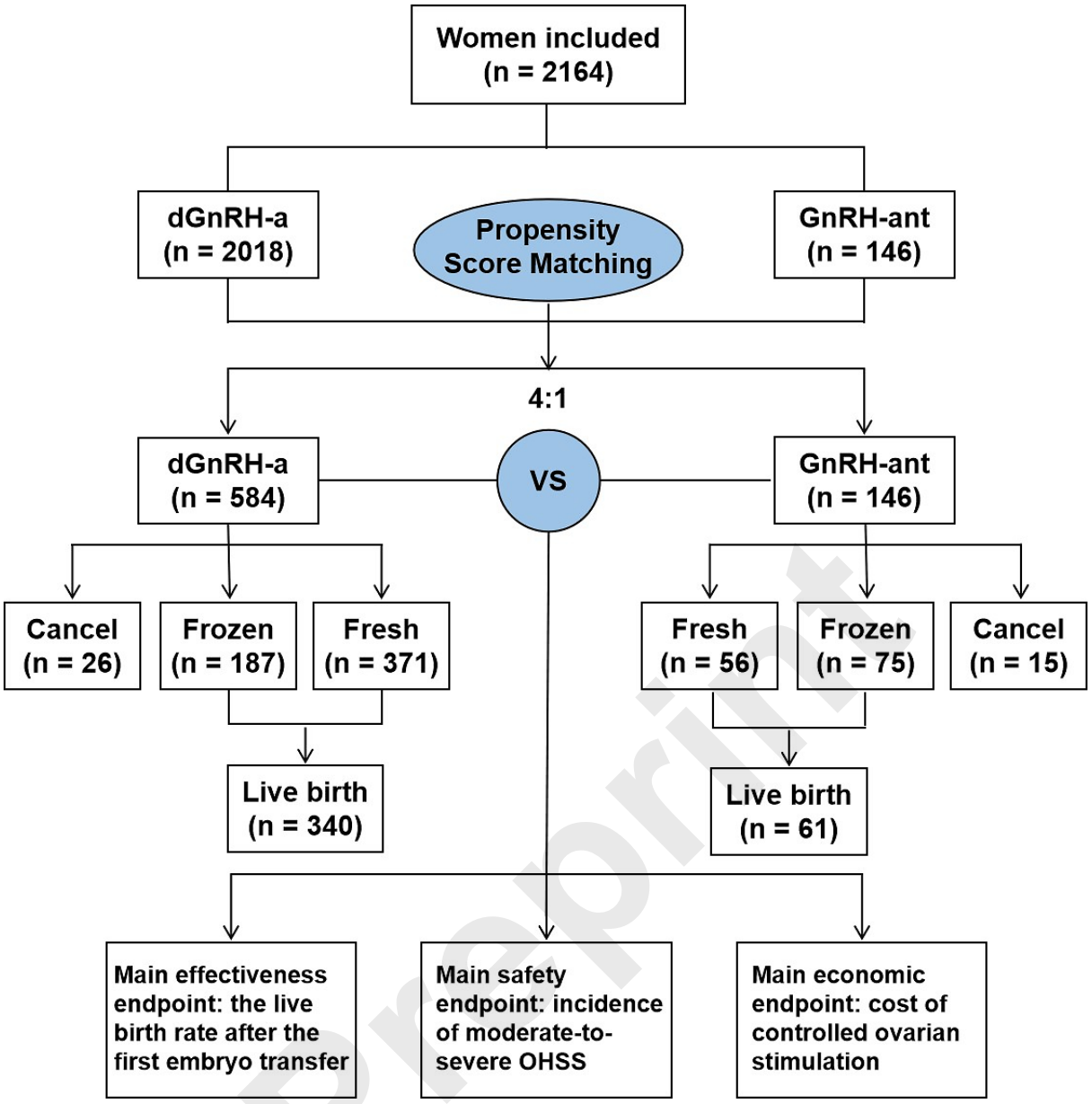

Fig 1 Flow chart of the study.

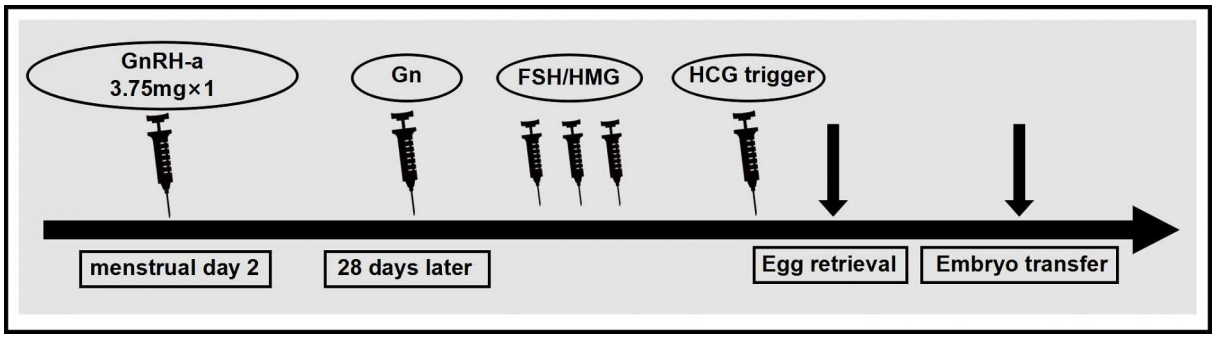

Fig 2 Brief explanation of the modified prolonged GnRH agonist protocol.

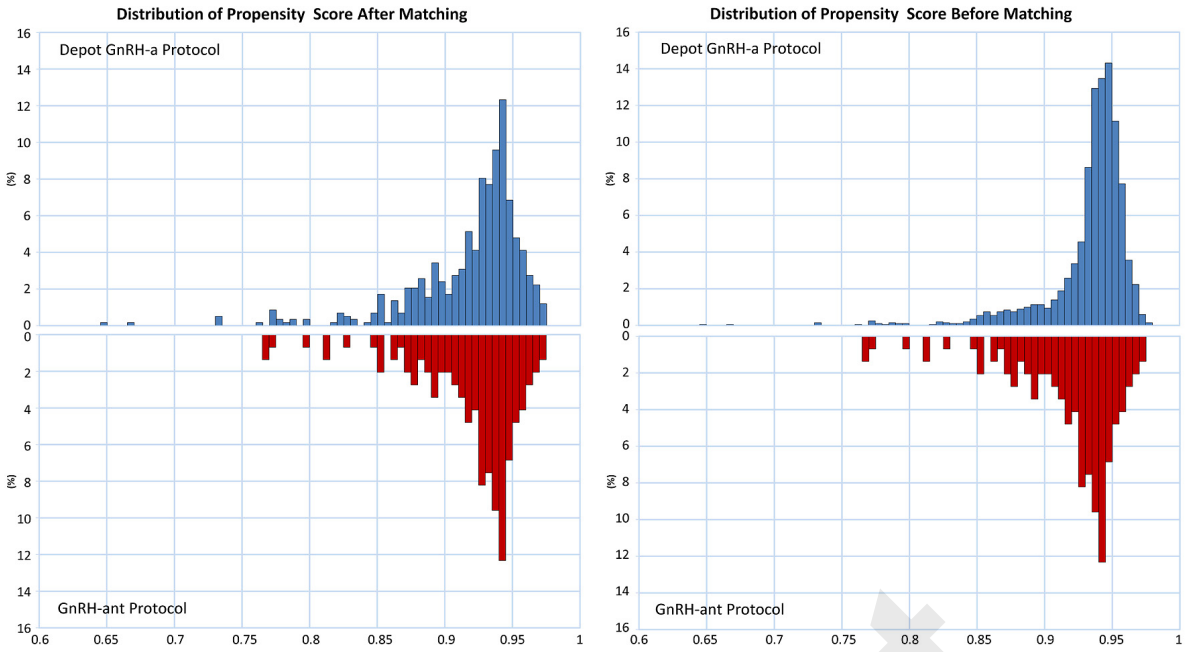

Fig 3 The percentage distribution histogram of propensity scores before and after PSM.