GnRH Antagonist Versus Modified Prolonged GnRH Agonist Protocol in Polycystic Ovary Syndrome (PCOS): Analysis Using Propensity Score Matching

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Research

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Abstract

Background: Women with polycystic ovary syndrome (PCOS) have been reported with low pregnancy rate and high OHSS risk in in vitro fertilization (IVF) programs due to the decreased endometrial receptivity and high ovarian reserve. The aim of the study was to compare the effectiveness, safety and economic cost of GnRH antagonist (GnRH-ant) and modified prolonged GnRH agonist (mGnRH-a) protocol in PCOS patients.

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 mGnRH-a treatment and 146 women received GnRH antagonist (GnRH-ant) treatment. The two groups were matched by propensity scores with a ratio of 1:4 (GnRH-ant versus mGnRH-a) 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 started treatment cycle after first fresh or frozen embryo transfer.

Results: Women with the mGnRH-a protocol had an increased endometrial thickness on HCG injection day, compared with GnRH-ant protocol (10.84 vs. 9.62, P<0.001), furthermore, the number of transferable embryos on day 3 (7 vs. 5, P=0.022), clinical pregnancy rate (67.81% vs. 52.74%, P=0.0007), implantation rate (56.05%, vs. 43.44%, P<0.001) and live birth rate (58.22% vs. 41.78%, P=0.0004) were also significantly higher in the mGnRH-a protocol group. However, 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).

Conclusion: The mGnRH-a protocol has a higher live birth rate than GnRH-ant protocol with the similar safety and economic cost among infertile women with PCOS.

Background

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. These actions result in several clinical features such as persistent anovulation, polycystic ovarian changes, hirsutism, acne and obesity [2].

For infertile women with PCOS, 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 patients 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 [5]. 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.

Recently, a modified prolonged GnRH agonist (mGnRH-a) protocol has emerged in China, also known as the early follicular phase long-acting regimen and depot GnRH agonist protocol. The mGnRH-a is improved from the conventional prolonged GnRH agonist protocol, which is widespread for women with endometriosis by injecting 2–6 doses (3.75 mg) of the long-acting GnRH agonist to improve endometrial receptivity [9]. However, waiting time of 2–6 months before IVF/ICSI-ET and severe perimenopausal symptoms are hardly accepted by patients. Therefore, one dose of the long-acting agonist is required in the modified protocol. Through clinical practice, we find that this treatment protocol is not restricted to endometriosis, but also includes PCOS, tubal factor and other factor infertility. Further studies have shown that the use of the long-acting GnRH-a in the early follicular phase can also improve the clinical outcomes of IVF [10–12].

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 mGnRH-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 Jiangxi Maternal and Child Health Hospital Affiliated to Nanchang University. We analyzed clinical and economic outcomes of women with PCOS with GnRH-ant or m-GnRHa protocol (Fig. 1). PCOS is diagnosed according to the Rotterdam criteria [14]. This study was approved by the Institutional Review Board of Jiangxi Maternal and Child Health Hospital (Nanchang, China).

The modified prolonged GnRH agonist protocol (m-GnRHa)

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 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, and the standards for embryo transfer strategy have changed slightly over time. The latest standards 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 5 IU/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 9.4 software. 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. 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 mGnRH-a group and GnRH-ant group before PSM were presented in Table 1. Duration of infertility, history of IVF/ICSI, scar uterus, and AFC were significantly different between two groups ($P < 0.05$). The variables for matching included duration of infertility, AFC, scar uterus, history of IVF/ICSI, age, BMI and proportion of pelvic or tubal factors, last three variables were chosen because the P-value of difference comparison was less than 0.2 and these variables were more closely related to clinical outcomes. 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 (Fig. 3). The percentage distribution of propensity scores between groups became nearly identical after matching.

Table 1
Baseline characteristics in mGnRH-a group and GnRH-ant group before and after propensity score matching

Characteristic	Before matching			After matching		
	mGnRH-a (n=2018)	GnRH-ant (n=146)	P-value	mGnRH-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 testosterone(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

Ovarian stimulation and laboratory embryos culture outcome

The results of COH and laboratory indicators were presented in Table 2. The mGnRH-a protocol had a longer duration of ovarian stimulation (12.89 vs. 10.58, P < 0.0001) and a higher dosage of Gn (2074.4 vs. 1704.78, P < 0.0001) with a higher dose of HMG (933.09 vs. 322.6, P < 0.0001) compared with GnRH-ant protocol. The serum levels of E2 (2590.61 vs. 3224.8, 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 mGnRH-a group were lower than those in the GnRH-ant group. Meanwhile, mGnRH-a group had a thicker endometrium on HCG injection day (10.84 vs. 9.62, P < 0.0001). For laboratory embryos culture outcome, the mGnRH-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 mGnRH-a group. Furthermore, compared with the GnRH-ant group, the rate of fresh embryo transfer was significantly higher in the mGnRH-a group (63.53% vs. 38.36%, P < 0.0001).

Table 2
Results of COH and Laboratory indicators

Items	mGnRH-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]	2074.4 ± 1077.66	1704.78 ± 819.6	**< .0001**
rFSH(IU)[a]	1141.32 ± 338.1	1382.17 ± 577.44	**< .0001**
HMG(IU)[a]	933.09 ± 1132.1	322.6 ± 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 ± 2.4	**< .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			

Clinical outcome and economic indicators

The effectiveness, safety and economic cost indicators were presented in Table 3. The mGnRH-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 agonist protocol. The high live birth rate of mGnRH-a protocol was mainly due to the low cancellation rate (4.45% vs. 10.27%, P = 0.0063) and the high live birth rate of 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, mGnRH-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).

Table 3
The effectiveness, safety, and economic indicators

Items	mGnRH-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 (RMB)			
GnRH agonist/antagonist[a]	1299.2 ± 51.19	1872.15 ± 658.81	**< .0001**
Exogenous Gn [a]	4084.28 ± 1068.97	4355.08 ± 1555.99	**0.0482**
rFSH[a]	3842.92 ± 1127.69	4271.63 ± 1597.08	**0.0026**
HMG[a]	241.36 ± 292.84	83.45 ± 184.24	**< .0001**
Transvaginal ultrasonography[a]	1010.62 ± 220.17	717.67 ± 202.1	**< .0001**
Endocrine examination[a]	1342.81 ± 373.21	1101.64 ± 331.93	**< .0001**
Total cost[a]	7736.9 ± 1362.54	8046.54 ± 2249.04	0.1132
[a]Independent t test [b]Chi-square test [c]Fisher's exact test			

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 [13]. This study was the first one to compare the mGnRH-a ptotocol and the mainstream GnRH-ant protocol from aspects of live birth rate, 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 mGnRH-a protocol could achieve a higher live birth rate and there were no significant differences in the incidence of OHSS or the cost of COH process when compared with GnRH-ant protocol.

Prolonged GnRH agonist protocol is mainly utilized for the treatment of endometriosis and has obtained relatively high pregnancy rates [9, 17, 18]. Later, the mGnRH-a protocol with only one injection has emerged in China and is gradually used among infertile patients including non-endometriosis. But the evidence of better clinical outcome from mGnRH-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 mGnRH-a protocol when compared with the GnRH agonist long protocol. Similarly, this superiority was also found in patients with PCOS who treated with mGnRH-a protocol (60.13% vs. 48.95%, P = 0.025) [10]. Moreover, Fei Gong et al. reported a higher clinical pregnancy rate (77.94% vs. 61.29%, P = 0.039) in patients suffering from PCOS using mGnRH-a protocol than those who used GnRH agonist 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 mGnRH-a protocol than in the GnRH-ant protocol and GnRH agonist long protocol [19], suggesting a significant priority of mGnRH-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 mGnRH-a group and GnRH-ant group. The PSM method was first described in the 1980s by Rosenbaum and Rubin [20], 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 [21]. 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 mGnRH-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 mGnRH-a group to take precautions against the occurrence of OHSS.

An increasing number of transferable embryos and cycles with transferable embryos were observed in mGnRH-a group compared with GnRH-ant 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 [22]. Animal studies showed that GnRH agonist increased the proportion of mouse embryos that reached the blastocyst stage in vitro. Casan et al. [24] 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. Moreover, with the increase of the number of transferable embryos, the proportion of blastocyst transfer in mGnRH-a group was higher than that in GnRH-ant group according to our standard of blastocyst culture.

Previous studies [11, 17] 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 [11, 17]. 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 [27].

Clinical outcome and economic indicators

Unlike other studies, we think it is more reasonable to define the live birth rate as live birth per started treatment cycle after first fresh or frozen embryo transfer, instead of live birth per fresh or frozen transfer in our study. Fresh or frozen embryo transfer was chosen according to the patient's conditions and laboratory tests results. For instance, it is more suitable to conduct frozen embryo transfer for GnRH-ant group with a high E2 level on the HCG trigger day. 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 [28]. However, follow-up time of two years is too long and difficult to achieve. The live birth per started treatment cycle 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 [29] 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 GnRH agonist long protocol. In 2016, Chen et al. [29] 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 mGnRH-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 statistically significant. However, this is a retrospective study and it spans 5 years. The protocol was constantly improved by increasing the intensity of single blastocyst transfer, reducing the initial Gn dose, and expanding the standard of freeze-all embryo. Further optimizations are still needed with the inherent defect of not being able to apply GnRH agonist trigger.

For economic indicators, remarkably, our data significantly favored higher total dosages of exogenous Gn in the mGnRH-a group, but the costs were lower than expected, the reason for which was that patients in the mGnRH-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. Previous studies have reported that the LH level during ovarian stimulation should neither be too high nor too low [31, 32]. Thus, patients in the mGnRH-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. In addition, the corresponding cost of transvaginal ultrasonography and endocrine hormone tests rose due to the longer period of ovarian stimulation in the mGnRH-a protocol.

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.

Conclusions

In conclusion, this retrospective study shows that a modified prolonged GnRH agonist protocol produced significant improvement in the live birth rate compared with the GnRH-ant 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 mGnRH-a protocol spent less on drug costs and more on transvaginal ultrasonography and endocrine tests, but they have similar total costs of COH with the GnRH-ant group.

Declarations

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Leizhen Xia and Lifeng Tian contributed equally to this work. The authors would like to thank the patients and all medical workers in the Reproductive Medicine Center of Jiangxi Maternal and Child Health Hospital. No external funding was used. There is no conflict of interest need to declare.

Authors' roles

L.Z.X.: conception of the idea, study design, data analysis and drafting of the manuscript. L.F.T.: study design, interpretation of data analysis results and revising of the manuscript. J.T.: revising of the manuscript. Q.F.W: guidance on the research design, revising of the manuscript and final approval of the version to be published.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Jiangxi Maternal and Child Health Hospital (Nanchang, China).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

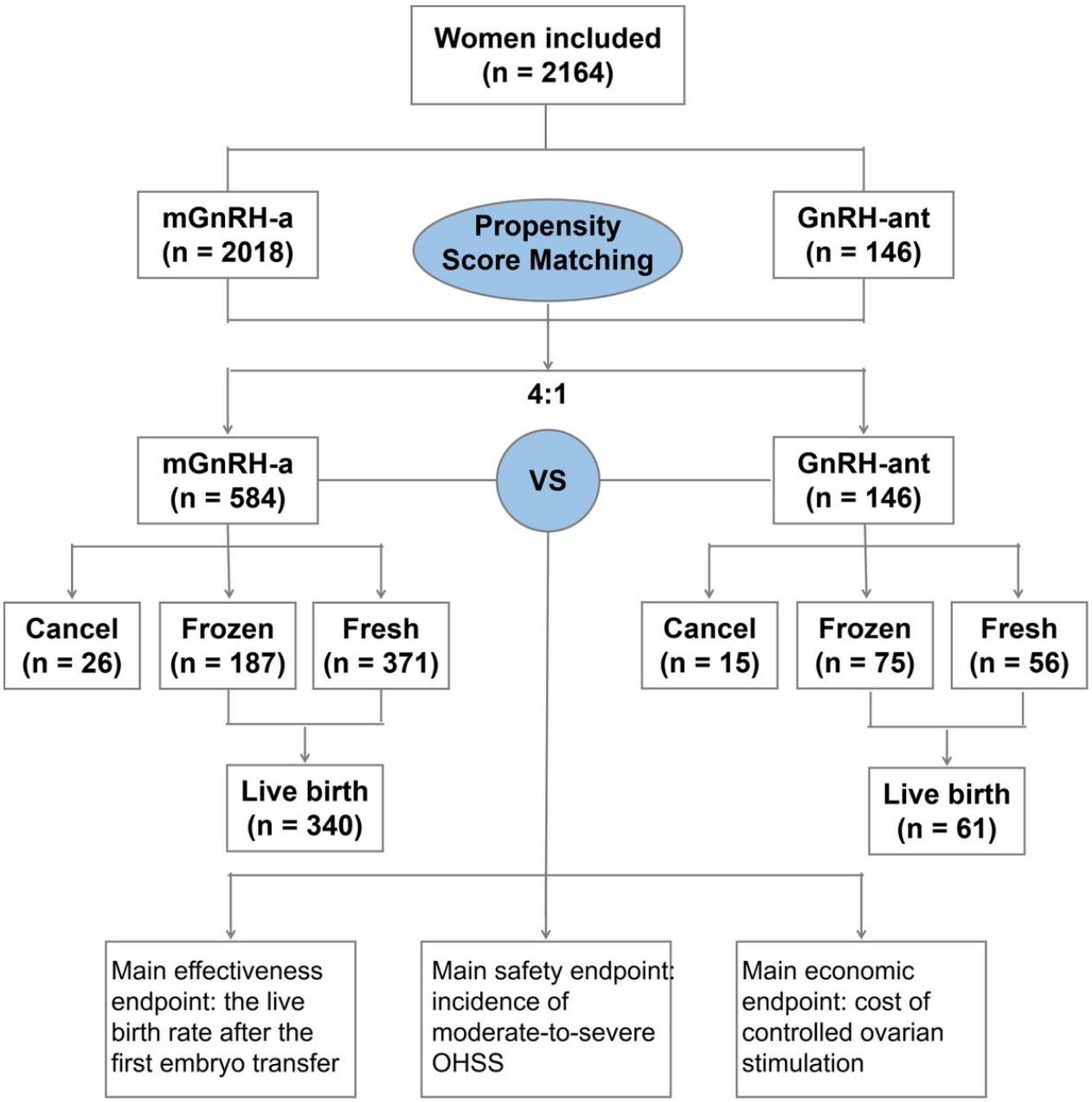

Figure 1

Flow chart of the study.

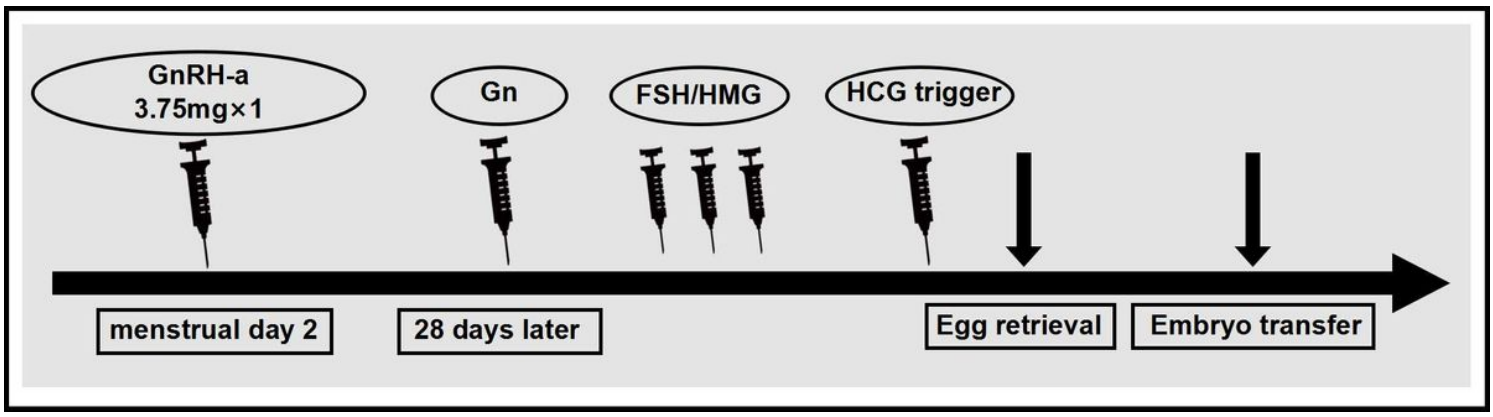

Figure 2

Brief explanation of the modified prolonged GnRH agonist protocol.

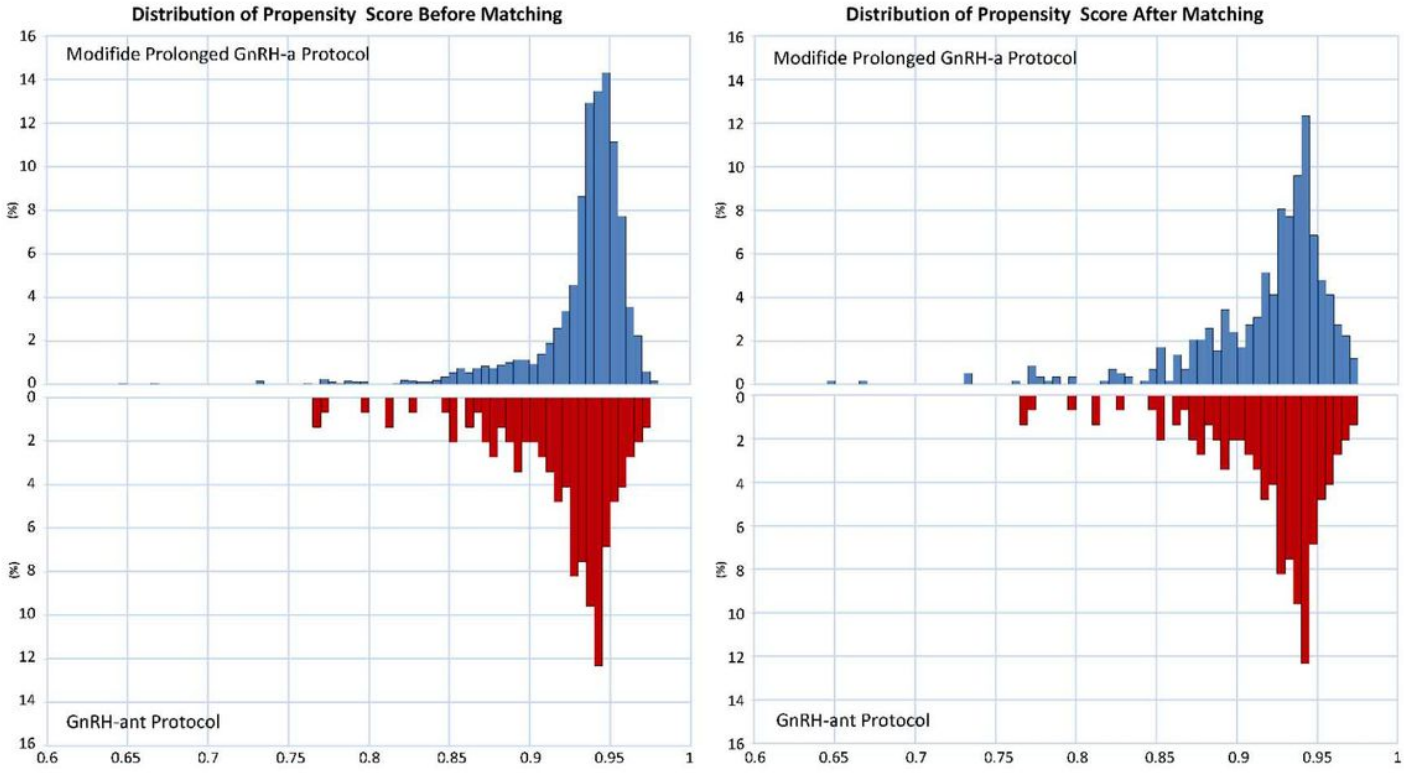

Figure 3

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