Comparison of stimulated cycles with low dose r-FSH versus hormone replacement cycles for endometrial preparation prior to frozen-thawed embryo transfer in young women with polycystic ovarian syndrome: A propensity scores matching analysis from 1434 patients

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Research

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Abstract

Objective

The principal purpose of this study was to compare reproductive outcomes for stimulated cycles (STC) and hormone replacement cycles (HRC) for endometrial preparation before frozen-thawed embryo transfer (FET) in young women with polycystic ovary syndrome (PCOS).

Methods

We conducted a retrospective study of 1434 FET cycles from January, 2017 to March, 2020 in our reproductive center, in which stimulated and hormone replacement cycles were used for endometrial preparation. Pregnancy outcomes of couples undergoing routine STC-FET or HRC-FET were analyzed before and after propensity score matching (PSM).

Results

Data on 1234 HRC protocols (86% of the total) and 200 STC protocols (14%) were collected. After PSM, 199 patients were included in both groups, respectively. There was no significant difference in positive pregnancy rate (52.7% vs. 54.8%, *p = 0.763*), clinical pregnancy rate (51.8% vs. 52.8%, *p = 0.841*), live birth rate (45.2% vs. 43.7%, *p = 0.762*), pregnancy loss rate (9.7% vs. 16.2%, *p = 0.164*) and ectopic pregnancy rate (1.5% vs. 0.5%, *p = 0.615*) between STC protocols and HRC protocols.

Conclusion

STC for endometrial preparation had similar pregnancy outcomes compared with HRC protocols by excluding heterogeneous factors after PSM. Evidence is available which shows that for young women with PCOS who were undergoing in-vitro fertilization, HRC could be a reasonable choice for patients who are unwilling to accept injections. Additionally, STC may offer more flexibility for young PCOS patients and reproductive centres.

Introduction

The first successful frozen-thawed embryo transfer (FET) was reported in 1983 and the first live birth in 1984[1,2]. Since then, elective embryo transfer and “freeze-all” strategy with segmentation of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment, aiming to cryopreserve all good quality embryos produced in a fresh cycle and to transfer these embryos in subsequent endometrial prepared cycles, has been widely used in in assisted reproductive technology (ART) in recent years [3]. FET can profoundly mitigate the risk of ovarian hyperstimulation syndrome (OHSS) and its use has now been extended to include those cycles of pre-implantation genetic diagnosis/screening, late-follicular progesterone elevation and embryo-endometrial asynchrony[4]. Compared with fresh embryo transfer, FET increase maternal safety, improve pregnancy rates,

decrease ectopic pregnancy rates[5]. In addition, FET, avoiding the negative impact of controlled ovarian stimulation (COS) on endometrial receptivity, can provide a more physiologic uterine environment for embryo implantation with a fresh start and regrowth under alternative less intensive endometrial preparation regimens[6].

PCOS is a heterogeneous endocrine disorder affecting reproductive aged women, with an estimated prevalence of between 8 and 13%[7]. Patients with PCOS usually had menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome. IVF had become an important therapeutic technique for infertility of PCOS[8]. As known, PCOS patients refer to high responder group, hence, elective freeze- all strategy is recommended worldwide to prevent OHSS, and to alleviate the harmful effects of supra-physiologic steroid hormones on the endometrium before embryo implantation[9]. Chen et al. reported that FET increases live birth rates (LBRs) in their RCT of women with PCOS[10].

Essentially, the outcomes for the FET could be affected by female age, embryo quality, endometrium and embryo synchronization, as well as endometrial receptivity, etc. If it is assumed that those factors do not differ between protocols, That Endometrial preparing cycles is critical for frozen-thawed embryo transfer[11,12]. There are different ways for endometrial preparation, ranging from natural cycle (NC-FET) to stimulated cycle (STC-FET), or hormone replacement cycle (HRC-FET)[13]. However, elucidating which is the best option remains to be determined[14]. The NC cycle is suitable for patients with regular menstrual periods. The endometrium is better developed and breakthrough bleeding is less likely when the NC regimen is used. However, it is reported that premature ovulation and follicular dysplasia lead to the cancelation of cycle, especially in women with PCOS[4,15]. In addition, In the light of menstrual dysfunction, the natural cycle used in the preparation of endometrium is not applicable[16]. The mild ovarian stimulation induces follicular development by generating endogenous hormones. That process of follicular development and ovulation is important to function of the corpus luteum. What calls for special attention is that the initial dosing of gonadotropins (Gn) should be low for preventing the risk of OHSS. Women also should be monitored closely[15]. The most commonly used FET protocol for women with PCOS is the HRC. This cycle is easy to plan, thus improving patient convenience[17]. The main reasons for canceling cycles in HRC group were related to an inadequate endometrial response[15,18].

Currently, there are few data comparing stimulated cycles with hormone replacement cycles for FET, especially in PCOS patients. A recent meta-analysis indicated that, compared with the hormone replacement cycles (HRC), the letrozole stimulation cycle may have a lower miscarriage rate (MR). No significant difference had been found between the mild ovarian stimulation(OS) cycle and AC protocols in live birth rate (LBR), ongoing pregnancy rate (OPR), clinical pregnancy rate (CPR) and embryo implantation rate (IR) [17]. some researches were opposed to this meta in artificial and stimulated cycle for FET in PCOS[18,19]. The main objective of this study was to compare reproductive outcomes for stimulated and hormone replacement endometrial preparation protocols in frozen embryo transfer (FET) cycles of PCOS. To minimize potential biases, we applied the PSM method to implement post-hoc randomization. A propensity score is a single score that represents the probability of receiving a treatment, conditional on a set of observed covariates[20].

Materials And Methods

Study design and participants

We performed a retrospective cohort study of 1434 FET cycles of PCOS from January 2017 to March 2020) in the fertility unit at a University Hospital. Patients in this present study had previously undergone treatment by IVF or intracytoplasmic sperm injection (ICSI) cycles. The study was approved by the Reproductive Ethics Committees of the Affiliated Hospital of Shandong University of TCM (ref approval no. SDTCM20201215). All participants provided written informed consent. Eligible patients included women with PCOS aged between 21 and 35 years, diagnosed by Rotterdam criteria[21]: oligo-or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovarian morphology on ultrasonography (defined as an ovary that either contains ≥ 12 antral follicles or that has a volume > 10 cm^3), with at least one embryo vitrified mainly at day 3, and for whom it was the first FET performed. The exclusion criteria were: (i) Body Mass Index (BMI) ≥ 30Kg/m^2 at the time of embryo vitrification; (ii) Endometriosis; (iii) Preimplantation genetic diagnosis/screening cycle; (iv) History of recurrent pregnancy loss or recurrent implantation failure; (v) Uterine pathology; (vi) Cycles cancelled due to failure of embryo thawing and survival.

Controlled ovarian stimulation protocol

All Participants had undergone the IVF/ICSI treatment as clinically indicated. Furthermore, a flexible GnRH antagonist (GnRH-ant) (Cetrorelix; Merck Serono, Darmstadt, Germany) protocol was employed with 150-225 IU/day of recombinant FSH (Gonal-F, Merck-Serono, Lyon, France). Additionally, the doses of gonadotropin were determined based on the characteristics of individual patients. Thereafter, oocyte retrieval was conducted under ultrasound transvaginal guidance, 34-36 hours after triggering with GnRH-a (Triptoreline, Decapeptyl, Ipsen, France) or recombinant hCG (Ovitrelle®, 250μg, Merck), after which conventional IVF/ICSI were performed as previously described [22]. The IVF/ICSI procedure had either been followed by a fresh embryo transfer and preservation of the redundant good embryos by vitrification or by a freeze-all strategy on clinical indication. Regular monitoring during controlled ovarian hyperstimulation (COS) treatment includes vaginal ultrasound (to assess endometrial thickness and follicle development) and blood hormone assays (including estradiol, progesterone and LH plasma levels).

The choice of embryos for vitrification was expected to focus on the inclusion of no less than six blastomeres with ≤ 20% fragmentation. Embryos that presented a fragmentation rate between 20% and 50% were vitrified only when they had reached the 8-cell stage on Day 3. The applied vitrification procedure has been described in detail before [22].

Endometrial preparation protocols

Women with PCOS were instructed to wait for spontaneous menses or prescribed with progestin to induce menses before endometrial preparation.[23] The two endometrial preparation protocols used before the FET were the following:

i. Hormone replacement cycles

In hormone replacement cycles, 4 mg of oral estradiol valerate was administered starting on the second or third day of the menstrual cycle and continuing for five days. This was followed by 6 mg of oral estradiol for 6-

8 days. When the endometrial thickness reached 7 mm and the serum progesterone level was below 1.5 ng/ml, we added vaginal supplementation with progesterone 90 mg daily (8% Crinone, Merck-Serono, Switzerland) prior to FET. The embryo was transferred according to its development stage at the time of freezing. The supplementation continued until a pregnancy test was performed. In case of a positive test, the patients were instructed to continue treatment until the 12thWG.[24]

ii. Stimulated cycles

In stimulated cycles, patients received a daily subcutaneous injection of Gonarfen (Merck Serono SA Aubonne Branch) (37.5–75 IU) from day 4 of the cycle onwards. The dose was adjusted according to the BMI, the ovarian reserve and any previous ovarian response to stimulation. A subcutaneous injection of hCG (5000 IU) or recombinant hCG (250 µg) was administered to induce oocyte ovulation, when the ovulation criteria were met (one dominant follicle ≥ 16 mm and peak plasma estradiol level > 200 pg/ml). These patients had no intercourse on ovulation day. The adequacy of the luteal phase was evaluated by measuring blood progesterone levels 3 days after ovulation had been triggered. If the progesterone level 3 days after ovulation triggering exceeded 3 ng/ml, FET was implemented (depending on the embryo's development stage at the time of freezing). STC protocols for endometrial preparation were not supplemented with progesterone. [25]

Study endpoints and definitions [26,27]

Positive pregnancy was defined as a serum β-hCG level greater than 10 U/L in the 14 days after cleavage embryo transfer. The Patient underwent ultrasonographic monitoring to determine the number of gestational sacs and fetal viability at the 6th-7th week of gestation, i.e., clinical pregnancy, if the β-hCG assay yielded a positive result. Pregnancy loss was defined as clinically recognized spontaneous loss of pregnancy before the completion of twenty gestational weeks. Ectopic pregnancy, defined as a pregnancy in which implantation takes place outside the uterine cavity, diagnosed by ultrasound, surgical visualization or histopathology. Live birth, defined as the birth of at least one child with breath and heartbeat, irrespective of the duration of gestation. A birth weight of 3500 g or more can be used if gestational age is unknown. Furthermore, this pathological state in which the death of a fetus prior to the complete expulsion from its mother after 20 completed weeks of gestational age was diagnosed as stillbirth. As opposed to live birth, the fetus does not breathe or show any other evidence of life.

Statistical analysis

All data are evaluated using version 26.0 of SPSS program (SPSS Inc., Chicago, USA). Quantitative variables are expressed as means ± standard deviations (SD) and were analyzed using Student's t-test, Independent-Samples Mann-Whitney U Test. Qualitative variables are expressed as frequencies and percentages and were analyzed using the $\chi 2$-test. $P< 0.05$ was considered statistically significant for the two groups of data tested. Furthermore, a propensity score matching (PSM) model was established to balance differences in baseline characteristics between the two groups.[20] The propensity scores were calculated using binary logistic regression analyses based on the following patients' characteristics: female age, infertility duration, body mass index (BMI), infertility type (primary or secondary), AMH, protocol of COS (Long GnRH-a protocol or GnRH-ant protocol), initial treatment (IVF or ICSI), Gn usage time, Gn dosage, oocytes retrieved, total number of

embryos, good quality embryos, transferred embryos. Patients undergoing STC were matched with the HRC group using the nearest-neighbor random matching algorithm in a ratio of 1:1.

Results

Demographic patient and ART characteristics

1434 cycles undergoing IVF or ICSI who had been performed the first freeze-thaw embryo transfer were studied. In detail, A total of 200 (14%) patients received STC, and 1234 (86%) underwent HRC before FET. Simultaneously, the 199 cycles were matched after PSM. Patient characteristics before and after PSM for STC and HRC are presented in Table 1. There were significantly different between two groups in initial treatment, good quality embryos, transferred embryos of D3 before PSM. Furthermore, no significant differences were found regarding patient characteristics between two groups after PSM.

Outcome measures

Pregnancy outcomes reflected by matched FET method are shown in Table 2. However, no statistical significance was detected between the two groups in terms of positive pregnancy rate (PPR), clinical pregnancy rate (CPR), live birth rate (LBR), pregnancy loss rate (PLR) and ectopic pregnancy rate (EPR). (all $P>0.05$)

Discussion

To our best knowledge, few studies have evaluated the different ways in which endometrium is prepared in young women with PCOS. In comparison to previous research, our practice can provide evidence-based guidance to select suitable endometrium preparation protocols for FET based on postdoc randomization and large sample. In the current retrospective cohort analysis, we compared two different endometrial preparation protocols for FET with STC and HRC. Our findings showed that there was no statistical significance in the pregnancy outcomes between two groups.

PCOS resulted in infertility could have been attributed to anovulation as well as endometrial dysfunction which affect endometrial receptivity[16]. In particular, hyperandrogenism and high level of LH during the follicular phase may decrease the rate of conception, the latter may lead to poor oocyte quality and embryo quality. In Tomas et al. noticed that the hormone replacement therapy (HRT) population has a higher pregnancy loss risk, which could be correlated with a higher prevalence of PCOS. [28]. Few studies have compared OS with HRT of PCOS patients in the reproductive outcomes. Most literature focuses on live birth rates and clinical pregnancy rates. In accordance with our outcomes, some literatures had the similar conclusion in HRT versus OS[17–19,29–31]. In Yu et al.'s retrospective study, the two protocols resulted in LPR (30.0 % vs. 31.7 %), CPR (41.0 % vs. 41.6 %), ongoing pregnancy rate (OPR) (36.6 % vs. 34.7 %), which were not statistically different. In addition, there is a relatively high cycle cancellation rate in stimulated cycle[18]. A systematic review and meta-analysis in 2016 similarly found STC and HRC endometrial preparation programs are equally effective, despite of the low quality of evidence, for women with PCOS[19]. A systematic review and meta-analysis including pooled results of only two studies of PCOS patients found letrozole produces similar CPR, LBR, and birth defect rates as NC

and HRC; there were similar CPR and lower LBR in letrozole-stimulated cycle compared to HMG stimulation[31]. Added to Chen et al.'s conclusions, A recent meta-analysis comparing OS using letrozole or HMG with HRT for FET in patients with PCOS found no difference found no difference between mild ovarian stimulation cycle and HRT groups for OPR and embryo implantation rate (IR); The letrozole-stimulated cycle may lower the miscarriage rate more than the HRT cycle[17]. Multiple retrospective cohort studied pointed out a different view, letrozole-stimulated cycle had significantly higher LBR and lower PLR compared with HRT after adjusting for possible confounding factors[32–34]. Therefore, whether letrozole has an advantage in preparing FET requires more high-quality researches for confirmation. In contrast with our findings, in a recent historical cohort analysis on women with PCOS, OS protocol achieves a better rate of pregnancy than the HRT protocol. In detail, that LBR with HRT accompanied by the poorest endometrial thickness, is lower than OS with low doses of human menopausal gonadotropin [15]. Peigne et al. verified the same perspective, despite a similar CPR(24.4% vs. 20.8%), LBR(17.1% vs. 9.8%) was significantly higher with mild OS than with HRT preparation, even after adjusting for potential bias, such as patient age at freezing, PCOS, and so on[24]. In Jouan et al.'s retrospective study, he demonstrated the superiority of clomiphene citrate cycles over HRC not only in OPR but also CPR[35]. Although Hatoum et al. concluded that HRC were associated with more PLR and lower LPR than stimulated cycles, the parameters effecting result statistics were not described and/or adjusted[25]. We can find that there is no comparative study on OSs with low dose r-FSH versus HRT in previous studies.

Previous studies have shown that HRC protocol can easily lead to the lack of corpus luteum increasing the incidence of hypertensive disorders of pregnancy and preeclampsia, which did not exist in natural or stimulated FET cycles [36,37]. This may cause changes in the structure and/or function of the extracellular matrix in the decidual layer and was associated with underdevelopment decidual layer after pregnancies[38]. Excessive estrogen may have adverse effects on the pregnancy outcome of anovulatory women, resulting in lower LBR [15,39]. Embryo implantation is not only related to the serum progesterone level but also the inner membrane[25]. When the P value exceeded 20 ng/dl which is associated, overall pregnancy rate and live birth rate would become lower, spontaneous abortion rate and biochemical pregnancy rate become higher[40]. Although thin endometrium is associated with lower success rate[41], implantation is related to the endometrial pattern, not to the thickness of the endometrium[42].

The retrospective study had a series of advantages. Firstly, our study aimed to explore the pregnancy outcomes ovaries stimulated cycles with low dose r-FSH versus hormone replacement cycles for endometrial preparation of FET. Secondly, in order to better avoid bias between groups and reduce other confounding factors, we use PSM to balance the variables that potentially affect the outcomes. In addition, there are some drawbacks to this study. Every retrospective nature may not avoid completely introduced selection or information bias. First of all, we cannot investigate other confounding factors, including exercise, nutritional supplements and diet, which can add information bias. Second, since this is not an RCT, according to professional experience, patients are assigned to multiple groups, which can add selection bias. However, we use PSM to control the confounding factors between the two groups.

Conclusion

In conclusion, STC for endometrial preparation had similar PPR, CPR, LBR, PLR, EPR compared with HRC by excluding heterogeneous factors after PSM. For young women with PCOS who were undergoing in-vitro fertilization, HRC could be a reasonable choice for patients who are unwilling to accept injections. Additionally, STC may reduce unnecessary anxiety and operational costs, and offer more flexibility for patients and IVF centres. To validate the obtained results, broader analyses, as well as an economic assessment of the costs involved, are required.

Declarations

Author contributions

Zhen-Gao Sun and Jing-Yan Song conceived and designed the study. Li Li and Yi Zhang contributed to the data collection. All the authors analyzed and interpreted the data. Jing-Yan Song performed the statistical analysis. Li Li wrote the manuscript. Jing-Yan Song revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

None of the authors have a conflict of interest to declare with regard to this study.

Data availability statement

The data generated and analyzed from the current study will be availed by the corresponding author upon request.

Consent for publication

Written informed consent for publication was obtained from all participants.

Ethics approval and consent to participate

The study was approved by the Reproductive Ethics Committees of the Affiliated Hospital of Shandong University of TCM (ref approval no. SDTCM20201215). All participants provided written informed consent.

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Tables

Table 1 PATIENT CHARACTERISTICS FOR Hormone Replacement Cycle (HRC) AND Stimulated cycle (STC) GROUPS

	Before Propensity Score Matching			After Propensity score Matching		
Variables	**STC (*N*=200)**	**HRC (*N*=1234)**	***P-value***	**STC (*N*=199)**	**HRC (*N*=199)**	***P-value***
Female age (years)	29.7±2.9	29.6±3.1	*0.725[a]*	29.7±2.9	29.9±3.1	*0.560[a]*
Infertility duration (years)	3.2±1.9	3.2±2.0	*0.800[b]*	3.2±1.9	3.2±2.1	*0.397[b]*
BMI (kg/m^2)	23.7±3.9	23.7±3.9	*0.786[a]*	23.8±3.9	23.8±3.5	*0.975[a]*
Infertility type (n, %)			*0.360[c]*			*0.367[c]*
Primary infertility	108/200(54.0%)	709/1234 (57.5%)		107/199 (53.8%)	98/199(49.2%)	
Secondary infertility	92/200(46.0%)	525/1234 (42.5%)		92/199 (46.2%)	101/199(50.8%)	
AMH (ng/ml)	6.3±2.0	6.5±2.1	*0.319[a]*	6.3±2.0	6.4±2.0	*0.837[a]*
Protocol of COS (n, %)			*0.632[c]*			*0.760[c]*
Long GnRH-a protocol	119/200 (59.5%)	712/1234 (57.7%)		119/199 (59.8%)	116/199 (58.3%)	
GnRH-ant protocol	81/200 (40.5%)	522/1234 (42.3%)		80/199 (40.2%)	83/199 (41.7%)	
Initial treatment (n, %)			***<0.001[c]***			*0.227[c]*
IVF	115/200 (57.5%)	427/1234 (34.6%)		114/199 (57.4%)	102/199 (51.3%)	
ICSI	85/200 (42.5%)	807/1234 (65.4%)		85/199 (42.7%)	97/199 (48.7%)	
Gn usage time (days)	11.2±1.7	11.0±1.6	*0.102[a]*	11.2±1.7	11.1±1.6	*0.319[a]*
Gn dosage (IU)	2326.6±547.6	2274.0±582.5	*0.232[a]*	2330.0±546.9	2239.7±558.2	*0.104[a]*
Oocytes retrieved (n)	19.1±8.7	18.6±9.1	*0.384[b]*	19.0±8.7	19.4±9.6	*0.897[b]*
Total	5.9±2.9	5.6±2.9	*0.190[b]*	5.9±2.9	6.1±3.0	*0.629[b]*

number of embryos (n)						
Good quality embryos (n)	2.2±2.1	1.9±2.2	***0.010***[b]	2.2±2.2	2.2±2.4	*0.310*[b]
Transferred embryos of D3 (n)	2.0±0.3	1.9±0.3	***0.002***[a]	2.0±0.3	2.0±0.2	*0.101*[a]

Data are presented as mean ± SD or n (%).

[a] t-test for Equality of Means.

[b] Independent-Samples Mann-Whitney U Test.

[c] χ^2-test.

Table 2 pregnancy outcomes FOR HRC AND STC GROUPS

	Before Propensity score Matching			**After Propensity score Matching**		
Outcomes	**STC (*N*=200)**	**HRC (*N*=1234)**	***P-value*** []	**STC (*N*=199)**	**HRC (*N*=199)**	***P-value*** [a]
Positive pregnancy rate, PPR (n, %)	106/200 (53.0%)	630/1234 (51.1%)	*0.609*	105/199 (52.7%)	109/199 (54.8%)	*0.763*
Clinical pregnancy rate, CPR (n, %)	104/200 (52.0%)	619/1234 (50.2%)	*0.630*	103/199 (51.8%)	105/199 (52.8%)	*0.841*
Live birth rate, LBR (n, %)	91/200 (45.5%)	505/1234 (40.9%)	*0.223*	90/199 (45.2%)	87/199 (43.7%)	*0.762*
Pregnancy loss rate, PLR (n, %)	10/104 (9.6%)	97/619 (15.7%)	*0.108*	10/103 (9.7%)	17/105 (16.2%)	*0.164*
Ectopic pregnancy rate, EPR (n, %)	3/200 (1.5%)	17/1234 (1.4%)	*1.000*	3/199 (1.5%)	1/199 (0.5%)	*0.615*

[] χ^2-test.