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The Predictive Value of the Follicular Output Rate on Pregnancy Outcome of Patients with Polycystic Ovary Syndrome Undergoing *In Vitro* Fertilization and Embryo Transfer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCEF **Haiyan Yang***
ABE **Jia Lin***
BCF **Congcong Jin**
CDF **Lvhe Meng**
CDE **Suichun Wu**
ABDEG **Ya Chen**

Reproductive Medicine Center of The First Affiliated Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, P.R. China

* Haiyan Yang and Jia Lin contributed equally to this study

Corresponding Author: Ya Chen, e-mail: dxh01228@sohu.com
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Background: This retrospective study aimed to evaluate the predictive value of the follicular output rate (FORT) on the pregnancy outcome of patients with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization and embryo transfer (IVF-ET).

Material/Methods: Between January 2012 and June 2016, a total of 1,541 patients with PCOS who underwent IVF-ET at our center were enrolled in the study. FORT was calculated as the pre-ovulatory follicle count (PFC)/antral follicle count (AFC)×100%.

Results: According to the FORT, patients were divided into low, medium, and high FORT groups. With an increase in the FORT, the PFC and serum estradiol at the day of human chorionic gonadotropin (hCG) injection, the number of retrieved oocytes, metaphase II (MII) oocytes, total number of embryos, and number of high-quality embryos significantly increased ($P<0.05$ and $P<0.001$) from the low to high FORT groups, while the AFC, gonadotropin (Gn) stimulation day, and total Gn decreased significantly ($P<0.001$). The live birth rate from frozen embryo transfer and the cumulative live birth rate was the lowest in middle FORT group but increased significantly in high FORT group ($P<0.05$). The correlation analysis between FORT and related factors showed that the FORT was negatively correlated with body mass index (BMI), Gn stimulation days, and total Gn ($P<0.05$).

Conclusions: FORT is a powerful tool for measuring ovarian reactivity. For patients with PCOS, a high FORT to obtain high-quality embryos and perform frozen embryo transplantation can achieve good pregnancy outcome.

MeSH Keywords: **Embryo Transfer • Pregnancy Complications • Reproductive Techniques, Assisted**

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Background

Controlled superovulation is essential in the implementation of assisted reproductive technology. Optimization of the ovulation program will ensure that the antral follicle will respond appropriately to follicle-stimulating hormone (FSH). Also, the use of high-quality oocytes is a prerequisite for a good pregnancy outcome [1]. Although the antral follicle count (AFC), basal follicle stimulating hormone (FSH), and anti-Müllerian hormone (AMH) have been used to predict ovarian reactivity [2–8], they have certain limitations.

Currently, no indicator can predict both the potential ovarian response to ovulation and oocyte development [2–8]. Genro et al. proposed the concept of the follicular output rate (FORT) [9]. In 2012, Gallot et al. studied the patients with regular menstrual cycles and found that the FORT could be a quantitative indicator to reflect the potential for follicular development [10], and showed that a higher FORT was associated with improved pregnancy outcome. Also, Hassan et al. investigated patients with unexplained infertility and showed that the number of high-quality embryos and the clinical pregnancy rate increased with increased FORT [11], and that FORT was an independent variable affecting the outcome of pregnancy.

In patients with polycystic ovary syndrome (PCOS), the number of follicles for *in vitro* fertilization and embryo transfer (IVF-ET) and the ovulation process are prone to ovarian hyperactivity. Although many oocytes could be retrieved, the quality of the oocytes and embryos is often poor [12]. Therefore, it is not clear whether FORT can predict follicular development potential and pregnancy outcomes for patients with PCOS. An early study showed that there was no difference in embryo implantation rate and clinical pregnancy rate among low, middle, and high FORT patients in 140 patients with PCOS, although the middle FORT group had the highest 2 pronuclei (2PN) fertilization rate and a good embryo rate, suggesting that middle FORT lead to better outcomes from IVF and intracytoplasmic sperm injection (ICSI) [13]. However, the number of cases in this previous study was small, and there have been no subsequent cumulative pregnancy data to support its conclusions [13].

Therefore, this retrospective study aimed to evaluate the predictive value of the follicular output rate (FORT) on the pregnancy outcome of patients with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization and embryo transfer (IVF-ET). It was hoped that the findings from this study might provide insights into the treatment of ovarian hyperstimulation for improved clinical outcome.

Material and Methods

Patients studied

A retrospective study included a total of 1,541 patients with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization and embryo transfer (IVF-ET). Study participants were enrolled from January 2012 to June 2016 at the Reproductive Medicine Center of the First Affiliated Hospital of Wenzhou Medical University.

Study participants were included based on the diagnostic criteria recommended by the 2004 European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) consensus [14]. Women were diagnosed with PCOS if they had two of the following three conditions, oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries. Patients with a history of ovarian surgery, or pelvic surgery within six months before the study, or having significant impairment of ovarian function due to radiotherapy or chemotherapy were excluded. Also, patients with contraindications for treatment with gonadotropin (Gn), endometriosis, adenomyosis, hydrosalpinx, uterine cavity abnormalities, thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome, or patients with androgen-secreting tumors were excluded. Patients included in the study were aged between 21–43 years, and the duration of infertility was 2–15 years. All patients underwent a standardized long agonist protocol. The Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (Approval No. 2017-209) approved the study and written informed consent was obtained from all study participants.

Treatment protocol of the superovulation program

All patients received a standardized pituitary down-regulation protocol with the gonadotropin-releasing hormone (GnRH) analog, decapeptyl (Ferring, Saint-Prex, Switzerland) at 5 days and 7 days after ovulation, or 14 days after the blended short-acting oral contraceptive pill was offered. At 13–14 days after pituitary down-regulation, serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2) and progesterone (P) were measured using a chemiluminescence microparticle immunoassay with a Unicel DXI800 chemiluminescence analyzer (Beckman Coulter, Brea, CA, USA) according to manufacturer's instructions. The antral follicle count (AFC) was assessed by transvaginal ultrasound using a color Doppler ultrasound scanner (Polytron Technologies, Shenzhen, China). If E_2 was <50 pg/ml, LH was <5 IU/L, FSH was <5 IU/L, and endometrial thickness was <5 mm, complete pituitary desensitization was achieved. The initial Gn was administered with a recombinant follicle stimulating hormone (rFSH), gonal F (Merck Serono,

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Geneva, Switzerland) or puregon (N.V. Organon, Molenstraat, the Netherlands) at doses between 75–150 IU/day according to the age, serum hormone levels and AFC, and body mass index (BMI) of patients. The Gn dose was adjusted according to the number and development of follicles, endometrial thickness, and serum hormone levels. 200–250 μg trigger of human chorionic gonadotropin (rhCG) ovidrel (Merck Serono, Geneva, Switzerland) was given when the diameter of dominant follicle was >18 mm, or the diameters of two dominant follicles were >17 mm, or the diameters of three dominant follicles were >16 mm.

Follicular output rate (FORT) calculation and patient grouping

The antral follicle count (AFC) with a diameter of 3–10 mm at baseline and the pre-ovulatory follicle count (PFC) with a diameter of 16–22 mm on the day of hCG injection were recorded. FORT was calculated as PFC/AFC×100%. All patients were divided into low, medium, and high groups according to FORT tertile values.

Oocyte retrieval, transfer, luteal support, and selection of high-quality embryos

Oocyte retrieval was performed 34–36 h after the administration of hCG and oocytes were fertilized either by conventional IVF or by intracytoplasmic sperm injection (ICSI) or by half ICSI based on the semen condition, the couple's history and the guidelines of our center. Conventional IVF was usually performed for patients with female factors of infertility (such as tubal factor or ovulation dysfunction). ICSI was usually performed for patients with a male factor of infertility, such as severe oligospermia, teratospermia, azoospermia, or cyclocephalospermia. Half the ICSI was usually performed for Patients with primary infertility with normal semen when the period of sterility exceeded five years. From the day of oocyte retrieval, intramuscular progesterone (40–60 mg/day) (Xianju Pharmaceuticals, Zhejiang, China) or crinone (90 mg/day) (Merck Serono, Geneva, Switzerland) and dydrogesterone (20 mg/day) (Abbott Labs, Abbott Park, Ill, USA) were administered as luteal support until 10 weeks after conception. Morphological observation and fresh-embryo transfer were performed 3 days after oocyte retrieval. Embryos were assessed according to the number of embryonic cells, embryo size, morphology, and the percentage of fragmentation. Embryos with two prokaryotic nuclei (2PN) sources, <0% debris, and 7–9 cells were judged to be high-quality. If possible, 1–2 embryos were transferred, and the remaining embryos were cryopreserved. If the patient was found to be at high risk for ovarian hyperstimulation syndrome (OHSS), the transfer was cancelled, and all high-quality embryos were cryopreserved for later transfer.

Outcomes of pregnancy

Serum β-hCG was measured 2 weeks after embryo transfer, and 28 days after embryo transfer, vaginal ultrasound examination was made using a Hi-Vision Preirus digital color ultrasonic scanner (Hitachi, Tokyo, Japan). Clinically, pregnancy was defined as the presence of a gestational sac in the uterine cavity 4 weeks after embryo transfer. Live birth rate was defined as the delivery of any viable infant after embryo transfer. The cumulative live birth rate was defined as the delivery of any viable infant after the first embryo transfer and subsequent frozen embryo transfer (FET).

Frozen embryo transfer (FET)

FET was performed if fresh embryo transfer failed. Serum FSH, LH, E_2, and P were assessed, and the endometrium was assessed by transvaginal ultrasound scan 2–5 days after the menstrual cycle. If these examinations were normal, oral estradiol valerate (4–8 mg/day) (Delpharm, Lille, France) was administered for endometrial preparation. Intramuscular progesterone (40 mg/day) or utrogestan (600 mg/day) and dydrogesterone (40 mg/day) (Laboratoires Besins International, Montrouge, France) were administered when the endometrial thickness reached 8 mm, and E_2 was ≥200 pg/ml. FET and pregnancy outcome were performed, as described above.

Calculation of cumulative live birth rate

The cumulative live birth rate was calculated as the number of live births after fresh embryo transfer and FET cycles/number of cycles.

Statistical analysis

Power analysis was performed before study initiation to determine sample size. Using an estimated cumulative live birth rate 5% change in subsequent trial analysis, We determined that a sample size of 1,500 patients (500 patients per group) was necessary to achieve a power of 80% at an αof 5%. Data were expressed using the mean ± standard deviation (SD) and compared using the Student's t-test, analysis of variance (ANOVA) and Tukey's post hoc test. The rate was compared using Pearson's chi-squared (χ^2) test. Correlation between FORT and other factors was analyzed using the Spearman correlation, and the importance of different variables in multiple linear regression was calculated. All statistical analysis was performed using SPSS version 19.0 (IBM, Chicago, IL, USA). A P-value of 0.05 was considered as statistically significant.

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Table 1. Baseline characteristics and ovarian stimulation data in pregnant and non-pregnant women in 1060 fresh-embryo transfers.

	Pregnant (n=669)	Non-pregnant (n=391)	*P* value
Age	29.64±3.78	29.38±3.44	0.255
Duration of infertility (year)	3.97±2.52	4.21±2.62	0.009
Body mass index (BMI) (kg/m^2)	23.17±3.78	23.37±3.51	0.756
Day 3 FSH (IU/L)	6.76±1.63	6.67±1.52	0.377
Day 3 oestradiol (pg/ml)	31.15±9.01	31.22±9.12	0.897
Antral follicle count	25.81±8.53	26.39±9.23	0.301
Pre-ovulatory follicle count	5.66±2.68	5.66±2.77	0.997
Follicular output rate	23.78±12.99	23.51±12.98	0.942
Stimulation days	12.28±3.41	11.92±3.19	0.129
Total follicle-stimulating hormone amount (IU)	1734.15±876.39	1641.07±823.99	0.088
Serum oestradiol on human chorionic gonadotrop day (pg/ml)	2833.60±1385.01	2797.06±1457.98	0.360
Retrieved oocyte	12.75±5.27	12.35±5.53	0.246
MII oocyte	11.43±4.89	10.87±5.23	0.076
Fertilized oocyte	8.38±4.03	7.51±4.14	0.001
Fertilization rate (%)	73.89±17.71	70.16±20.50	0.003
Total number of embryo	7.61±3.99	6.76±4.14	0.001
Number of high quality embryo	4.17±2.95	3.30±2.73	0.000
Number of transferred embryo	2.03±0.21	1.97±0.28	0.000

Results

Baseline status

The follicular output rate (FORT) on the pregnancy outcome of 1541 women with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization and embryo transfer (IVF-ET). There were 848 women who had primary infertility, and 693 women had secondary infertility. Routine IVF, intracytoplasmic sperm injection (ICSI), or combined IVF and ICSI treatments were performed on 902, 435, and 204 cycles, respectively. Fresh embryo transfer and frozen embryo transfer (FET) were conducted in 1060 and 481 cycles, respectively. A total of 610 patients underwent a total of 957 cycles of FET therapy. One patient was transferred for six cycles, two patients were transferred for five cycles, 14 patients were transferred for four cycles, and 55 patients were transferred for three cycles, 182 patients were transferred for two cycles, and the remaining 356 patients were transferred for one cycle.

Comparison of parameters between pregnancy and non-pregnancy, and live births and non-live births after fresh transfer cycles

Our results showed that the FORT was not significantly different between 669 clinical and 391 non-pregnancy cycles. However, the number of fertilized oocytes (8.38±4.03 *vs.* 7.51±4.14, P<0.05), the fertilization rate (73.89±17.71 *vs.* 70.16±20.50, P<0.05), the total number of embryos (7.61±3.99 *vs.* 6.67±4.14) (P<0.001), the number of transferred embryos (2.03±0.21 *vs.* 1.97±0.28, P<0.001) and the number of high-quality embryos (4.17±2.95 *vs.* 3.30±2.73, P<0.001) were significantly higher in clinical pregnancy group (Table 1). Similarly, no difference in FORT values was found between 545 live births and 515 non-live births.

However, the duration of infertility (3.86±2.44 *vs.* 4.27±2.67, P<0.05), the number of metaphase II (MII) oocytes (11.59±4.87 *vs.* 10.82±5.15, P<0.05), fertilized oocytes (8.43±3.96 *vs.* 7.66±0.67, P<0.05), the total number of embryos (7.64±3.94 *vs.* 6.92±4.16, P<0.05), the number of high-quality embryos (4.247±2.95 *vs.* 3.40±2.673, P<0.001) were significantly higher

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Table 2. Baseline characteristics and ovarian stimulation data in live birth and non-live birth women in 1060 fresh-embryo transfer.

	Live birth(n=545)	Non-live birth (n=515)	*P* value
Age	29.21±3.32	29.74±3.79	0.055
Duration of infertility (year)	3.86±2.44	4.27±2.67	0.009
Body mass index (BMI) (kg/m^2)	23.09±9.58	23.42±3.69	0.453
Day 3 FSH (IU/L)	6.81±1.62	6.65±1.56	0.106
Day 3 oestradiol (pg/ml)	31.24±8.24	31.30±8.84	0.897
Antral follicle count	26.17±8.59	26.24±8.75	0.882
Pre-ovulatory follicle count	5.74±2.67	5.62±2.68	0.475
Follicular output rate	23.93±13.20	23.29±12.67	0.423
Stimulation days	12.25±3.39	12.07±3.29	0.382
Total follicle-stimulating hormone amount (IU)	1707.33±857.11	1692.79±862.29	0.784
Serum oestradiol on human chorionic gonadotrop day (pg/ml)	2833.60±1385.01	2797.06±1457.98	0.550
Retrieved oocyte	12.89±5.22	12.28±5.51	0.064
MII oocyte	11.59±4.87	10.82±5.15	0.012
Fertilized oocyte	8.43±3.96	7.66±4.19	0.002
Fertilization rate (%)	73.42±17.83	71.58±19.89	0.113
Total number of embryo	7.64±3.94	6.92±4.16	0.004
Number of high quality embryo	4.28±2.95	3.40±2.67	0.000
Number of transferred embryo	2.02±0.21	1.99±0.27	0.057

in patients giving live births than in patients giving non-live births (Table 2).

Comparison of parameters among the FORT groups

The average FORT was 25.49. According to the FORT tertile values, the patients were divided into high, medium and low groups, with 516 low FORT cases with FORT values below the 33rd percentile, 529 medium FORT cases with FORT values between the 33rd and the 67th percentile, and 498 high FORT cases with FORT values above the 67th percentile.

Post hoc power analysis showed that the differences among the groups were significant for AFC (P=0.00), PFC (P=0.00), serum estradiol on the hCG day (P=0.00), MII oocytes (P=0.00), freeze-all rate (P=0.00, between low and high FORT groups for stimulation days (P=0.04), total FSH dose (P=0.00), between low and middle or middle and high FORT groups for fertilized oocytes (P=0.000, P=0.002), retrieved oocytes (P=0.00, P=0.01), total number of embryos (P=0.000, P=0.002), number of excellent quality embryos (P=0.000, P=0.01), live birth rate of frozen- embryos transfer (P=0.029, P=0.004), and between middle and high FORT groups in cumulative live birth rate (P=0.006).

We found that with the increase of FORT, PFC, serum E_2 at the day of hCG injection, the number of retrieved oocytes, MII oocytes, the total number of embryos, the number of high-quality embryos, embryo-frozen rate and the number of subsequent FET cycles increased significantly (P<0.001), while AFC, Gn stimulation days and total Gn amount decreased significantly (P<0.001) in the three groups (Table 3). However, the clinical pregnancy rate and the live birth rate of the new transplant cycles did not increase with the increase of these parameters, such as the number of high-quality embryos. The pregnancy loss rate was the highest, and the live birth rate was the lowest in the high FORT group, although the differences were not significant among the groups. The clinical pregnancy rate in high FORT group following subsequent FET was similar to those in the other groups, but the pregnancy loss rate was the lowest, leading to the higher live birth rates and the highest cumulative live birth rates as compared to the other two groups (P<0.001).

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Table 3. Baseline characteristics, ovarian stimulation data and IVF/ICSI outcomes in the low, medium and high FORT groups.

	Low FORT (n=516)	Medium FORT (n=529)	High FORT (n=496)	*P*-value
Age	29.33±3.57	29.38±3.45	29.39±3.67	0.799
Duration of infertility (year)	3.99±2.53	3.84±2.44	3.99±2.62	0.969
Body mass index (kg/m^2)	23.06±3.50	23.34±3.74	22.36±3.34	0.080
Day 3 follicle-stimulating hormone (IU/L)	6.66±1.57	6.59±1.56	6.64±1.61	0.837
Day 3 oestradiol (pg/ml)	31.08±8.19	31.10±8.14	30.96±8.09	0.689
Antral follicle count	31.63±10.05^{aa}	26.95±8.30^{bb}	22.70±6.86^{cc}	0.000
Pre-ovulatory follicle count	3.79±1.51^{aa}	6.12±1.96^{bb}	9.30±3.06^{cc}	0.000
Stimulation days	12.34±3.39	12.07±3.09	11.78±2.83^{c}	0.047
Total follicle-stimulating hormone amount (IU)	1660.98±811.07	1654.12±835.76	1562.72±684.88^{c}	0.000
Serum oestradiol on human chorionic gonadotrop day (pg/ml)	2981.59±1793.93^{aa}	3421.62±1841.81^{bb}	4036.08±1984.99^{cc}	0.000
Retrieved oocyte	14.31±7.41	14.98±7.60^{b}	16.58±7.37^{cc}	0.000
MII oocyte	12.53±6.67^{a}	13.46±7.09^{bb}	14.96±6.85^{cc}	0.000
Fertilized oocyte	9.01±5.28	9.66±5.55^{b}	10.71±5.55^{cc}	0.000
Fertilization rate (%)	72.05±19.17	71.97±19.01	72.01±18.98	0.921
Total number of embryos	8.31±5.35	8.91±5.46^{b}	9.97±5.56^{cc}	0.000
Number of high quality embryos	4.61±3.91	4.84±3.69^{b}	5.47±4.04^{cc}	0.000
Number of transferred embryos in fresh- embryo cycle	2.01±0.28	2.01±0.22	2.00±0.21	0.879
Clinical pregnancy rate of fresh-embryo transfer (%)	65.44 (267/408)	64.07 (230/359)	64.29 (189/294)	0.379
Pregnancy loss rate of fresh- embryo transfer (%)	19.10 (51/267)	16.52 (38/230)	21.16 (40/189)	0.229
Live birth rate of fresh- embryos transfer (%)	51.96 (212/408)	52.65 (189/359)	49.32 (145/294)	0.179
Freeze-all rate (%)	20.93 (108/516)^{aa}	32.14 (170/529)^{bb}	40.73 (202/496)^{cc}	0.000
Number of frozen embryo transfer cycle	276	311	370	–
Clinical pregnancy rate of frozen-embryo transfer (%)	56.88 (157/276)	52.09 (162/311)	58.11 (215/370)	0.149
Pregnancy loss rate of frozen-embryos transfer (%)	19.11 (30/157)	19.14 (31/162)	11.37 (24/211)	0.459
Live birth rate of frozen-embryo transfer (%)	43.48 (120/276)	40.84 (127/311)^{b}	51.35 (190/370)^{c}	0.016
Cumulative live birth rate (%)	64.34 (332/516)	59.74 (316/529)^{b}	67.68 (335/496)	0.032

^{a} and ^{aa} denotes $P<0.05$ or <0.001 between low and middle FORT groups; ^{b} and ^{bb} denotes $P<0.05$ or <0.001 between middle and high FORT groups; ^{c} and ^{cc} denotes $P<0.05$ or <0.001 between low and high FORT groups.

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Table 4. Univariate analysis of factors associated with FORT.

	Spearman correlation coefficient	*P* value
Age	–0.007	0.786
Duration of infertility (year)	0.008	0.757
D3 follicle-stimulating hormone (IU)	–0.005	0.856
Body mass index	–0.80	0.002
Day 3 oestradiol (pg/ml)	0.019	0.461
Stimulation days	–0.067	0.008
Total follicle-stimulating hormone amount	–0.50	0.049

Correlation between the FORT and related factors

Spearman correlation analysis showed that there was no correlation between FORT and age, basal FSH, or basal E_2. However, FORT was negatively correlated with BMI (r=–0.80, P<0.05), total Gn (r=–0.50, P<0.05) and Gn stimulation day (r=–0.067, P<0.05) (Table 4).

Discussion

The findings from this study showed that the numbers of retrieved oocytes, metaphase II (MII) oocytes, high-quality embryos, pre-ovulatory follicle count (PFC), and estradiol (E_2) on the day of human chorionic gonadotropin (hCG) injection increased significantly and progressively with the increase in the follicular output rate (FORT). This finding is consistent with the results previously reported in non-PCOS patients [10,11], but different from the results obtained with patients with PCOS [13]. It was found that in patients with PCOS, PFC and retrieved oocytes, but not fertilization rate and the number of high-quality embryos, increased correspondingly with the increase of FORT, which was the highest in medium FORT group [13]. Also, we did not find any difference in fertilization rate between the three groups. This finding is consistent with the earlier results in non-PCOS patients [10,13], but is different from other studies in patients with PCOS [11,13]. The difference between our results and other studies may be due to the difference in the study populations and the number of cases investigated. Despite these inconsistencies, these results showed that the FORT is a predictor for ovarian response to follicle-stimulating hormone (FSH), oocyte development potential, and embryo quality.

The results from the present study showed that in the lowest FORT group, antral follicle count (AFC), gonadotropin (Gn) stimulation days and total Gn were the highest, and were significantly higher than other two groups. Zhang et al. also found the highest AFC, Gn stimulation days but not total Gn in the low FORT group [15]. Gallon et al. and Hassan et al. showed that AFC was also the highest in the low FORT group, but there was no difference in Gn stimulation days and total Gn [10,11]. Even though more Gn and longer Gn duration were used to promote ovulation, the final PFC, E_2 on the day of hCG injection, the number of retrieved oocytes, MII oocytes, the total number of embryos and the number of high-quality embryos were far lower in the low FORT group than in the high FORT group. As for the difference between patients with PCOS and non-PCOS patients, we speculate that there may be several unknown differences except for the difference in the quantity of the follicles between PCOS and non-PCOS patients. For example, it has been shown that ovarian IGF system in patients with PCOS is abnormal [15], which may affect the production of follicles in superovulation therapy. Liu et al. found that in patients with PCOS, ANGPTL1, and ANGPTL2 mRNA were expressed abnormally in cumulus [16], leading to reduced oocyte quality and decreased development potential. Therefore, an increased number of antral follicles in patients with PCOS may result in more reduced response to FSH, leading to less PFC, lower fertilization rate, lower number of high-quality embryos and the total number of embryos despite more and more prolonged Gn treatment. It is also possible that due to a higher number of antral follicles in patients with PCOS, they are more likely to have ovarian hyperstimulation syndrome (OHSS) when ovulation is stimulated, and it is not suitable to use a high trigger dose of Gn. As a result, the optimal time for the recruitment and development of follicles might have missed, ultimately leading to reduced follicular reactivity, fewer retrieved oocytes, fewer mature oocytes, and fewer high-quality embryos.

In the present study, the number of subsequent frozen embryo transfer (FET) cycles were the highest in the high FORT group. The average FORT of patients with PCOS was much lower than that of non-PCOS patients, but because of large number of antral follicles, high FORT also increased the number of oocytes with an increased risk of ovarian hyperstimulation syndrome (OHSS), resulting in a higher rate of freeze-all and a more significant number of subsequent FET cycles. Although the number of high-quality embryos increased with FORT, the clinical

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pregnancy rate and live birth rate of new transplant cycle did not increase significantly with the increase of FORT, the abortion rate was the highest in high FORT group, resulting in the lowest live birth rate in the group. Our study also shows that there is no difference in FORT values between pregnant and non-pregnant patients and between patients giving live and non-live births during the new transfer cycles. This finding was different from the results obtained in non-PCOS patients but was similar to those obtained in patients with PCOS, where patients with medium FORT had the best pregnancy outcome [15].

The reason for the different results in patients with PCOS and non-PCOS patients may be because of differences in the endometrium. Huang et al. found that serum factor X (FX) of patients with PCOS significantly increased at the day of hCG injection and the embryo transfer day, serum factor VIII (FVIII) level significantly reduced at embryo transfer day, and hypercoagulability during the peri-implantation period resulted in poor microcirculation in the endometrium [17]. For the high FORT patients with PCOS, they had the highest levels of E_2 on the day of hCG injection, which had most significant impact on the endometrium. As a result, the pregnancy outcome is not as good as expected after fresh embryo transfer. The best cumulative live birth rate also confirms this, following subsequent FET treatment in high FORT patients, a result that is consistent with the earlier study [18]. Therefore, the adverse effects of high E_2 on the endometrium in the high FORT group are eliminated during FET, leading to the lowest abortion rate and highest live birth rate and consequently the best pregnancy outcome in the high FORT group.

The correlation analysis showed that the FORT does not correlate with age, basal FSH and E_2 negatively correlated with BMI, AFC, Gn stimulation days and total Gn, and positively correlated with PFC, suggesting that the FORT was a relatively independent indicator. FORT in combination with AFC could have a stable and independent assessment of ovarian functional reserve and the prediction of IVF-ET outcome. This finding also suggests that AFC does not lose its response to FSH sith increased age [19]. Unfortunately, this study did not analyze the correlation between FORT and anti-Müllerian hormone (AMH). Additionally, we showed that the FORT was negatively correlated with body mass index (BMI), which is consistent with earlier work [20]. They believed that leptin inhibits the synthesis and stimulation of granulocyte steroid hormone in obese patients, and obesity could be an independent factor that negatively affects IVF-ET [20].

This study had several limitations. As a retrospective study, there may have been some changes in the antral follicular count and follicular size on hCG day as assessed by different physicians. Superovulation was performed by different physicians, leading to different medications. Also, because PCOS is a high-responsive population, if it is unclear whether the Gn dosage and duration were controlled, this may have an impact on the outcome. Nevertheless, we calculated the cumulative pregnancy rate, which can reflect the utilization rate of eggs and embryos in each cycle. The findings from this study provide a relatively more objective evaluation of treatment outcome of IVF-ET.

Conclusions

This retrospective study aimed to evaluate the predictive value of the follicular output rate (FORT) on the pregnancy outcome of patients with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization and embryo transfer (IVF-ET). The findings showed that FORT is a powerful tool for measuring ovarian reactivity. For patients with PCOS, a high FORT to obtain high-quality embryos and perform frozen embryo transplantation can achieve good pregnancy outcome. However, for patients with PCOS, due to an increased number of antral follicles, FORT should not be too high, so that ovarian hyperstimulation syndrome (OHSS) can be avoided. However, the FORT should be as high as possible to obtain the best pregnancy outcome following IVF-ET.

Conflict of interest

None.

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