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Research Article

Antral Follicle Responsiveness to Follicle Stimulating Hormone Administration Assessed by the Follicular Output Rate (FORT) May Predict In Vitro Fertilization-Embryo Transfer Outcome

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Abstract:

Objectives: In search of a qualitative indicator of ovarian function, we sought to determine if antral follicles' reproductive competence is correlated with their Follicular Output Rate (FORT), which indicates how sensitive they are to FSH administration.

Patients and Methods: After ethical committee approval and informed consent from the patients, this Prospective Cohort study was performed on 300 IVF-ET candidates, aged between 20 and 35, who had undergone controlled ovarian hyper-stimulation with comparable beginning levels of FSH and had primary infertility without apparent cause from January 2020 to June 2022 at Al-Azhar University Hospital and in a private IVF unit in Cairo, Egypt. Antral follicle (3–8 mm) count (AFC) and pre-ovulatory follicle (18–24 mm) count (PFC) were performed, respectively, at the achievement of pituitary suppression (before FSH treatment) and on the day of hCG administration. The FORT was calculated by PFC × 100/AFC. FORT groups were set according to tercile values: low (4.3%; n = 13), average (30.7%; n = 92) and high (65%; n = 195).

Results: The odds ratio for clinical pregnancy increases with increasing endometrial thickness, number of collected oocytes, and follicular output rate, with odds ratios of 1.123, 1.121, and 1.312, respectively.

Conclusion: The observed association between IVF-ET result and the proportion of antral follicles attaining pre-ovulatory maturity that successfully react to FSH injection shows that FORT may be a qualitative mirror of ovarian follicular competency. More research with broader inclusion criteria and more tailored techniques is required to verify these findings.

Keywords: follicular output rate; fort; fsh; controlled ovarian hyperstimulation / IVF-ET

Introduction

In vitro fertilization (IVF) effectiveness is dependent on regulated ovarian hyperstimulation, which results in a multi-follicular response. Granulosa cells in the follicles release the hormone estradiol (E2). Serum estradiol (E2) is essential for oocyte/follicular maturation and uterine preparation for implantation. It has been shown that 17 beta estradiol causes cytoplasmic maturation of GV oocytes by increasing intra-cytoplasmic calcium concentration; this has been linked to improved fertilization ***(1).***

Granulosa cells that respond appropriately to FSH are not only equipped with functioning FSH receptors, but are also capable of carrying out a series of specialized functions such as signal transduction, steroidogenesis, and cell proliferation and differentiation. This physiological context suggests that antral follicle FSH responsiveness may be a marker of their health and reproductive competence, leading us to hypothesize that patients with a high proportion of FSH-responsive antral follicles are more likely to become pregnant after assisted reproductive technologies ***(2).***

For the pretreatment evaluation of ovarian reserve for predicting response to COH, a variety of dynamic tests (clomiphene citrate challenge test, GnRH agonist stimulation test, exogenous FSH ovarian reserve test) and clinical indicators (age, previous response to COH), endocrine indicators (FSH, E2, inhibin-B, anti-mullerian hormone [AMH]), and ultrasonographic indicators

(antral follicle count [AFC], ovarian volume, ovarian vascularity indices) ***(3)*** have been recommended. In an effort to optimize a patient's prospective ovarian response and chances of a good treatment result, this enables adequate preoperative counseling and permits adjustment of a patient's treatment regimen ***(4).***

Unfortunately, because it is heavily impacted by the number of tiny antral follicles available before to treatment, the number of pre-ovulatory follicles acquired at the conclusion of COH is not a good indicator of antral follicle sensitivity to FSH. The inconsistent link between the absolute number of developing follicles achieved in COH and the result of IVF-ET may be explained by this unpredictability ***(5).***

The European Society of Human Reproduction and Embryology (ESHRE) recently released a report on clinical pregnancy rates in fresh cycles, which were 28.7% per ovum pick-up and 32% per embryo transfer, whereas thawed cycles had a clinical pregnancy rate of 20.9%. These results demonstrate the ongoing improvements in clinical and laboratory processes ***(4).***

We employed the Follicular Output Rate (FORT) to assess the antral follicles' reactivity to exogenous FSH in an objective manner**.** The ratio of pre-ovulatory follicles acquired in response to FSH injection to the pre-existing pool of tiny antral follicles is used to calculate this index ***(6).*** Thus, the goal of the current study was to examine any potential connections between the FORT and antral follicles' capacity for reproduction, as shown by the quality of oocytes and embryos produced during IVF-ET cycles.

Materials and Methods

This prospective study was performed in the period from January 2020 to June 2022 in a private IVF unit. It included 300 women with the following criteria:

1- Infertility that cannot be explained and has never been treated with assisted conception.

2- Age between 20 – 35 years.

3- Both ovaries are of average size and texture, free of any morphological abnormalities (such as cysts, endometriomas, etc.), and clearly visible on trans-vaginal ultrasound scans.

4- Regular menstrual cycles lasting between 21 and 35 days.

5- After pituitary desensitization (baseline), the total number of antral follicles measures 3–8 mm in diameter, and on days two to three, E2 > 50 pg/ml.

6- Body mass index (BMI) ranging from 18 to 25 kg/m2.

7- Normal hysteroscopic findings in the cycle preceding ICSI.

8- Normal Seminal profile of their husbands.

COH and IVF-ET protocol:

The COH and IVF-ET regimen employed in this study was the long protocol, which was as follows:

FSH, LH, and E2 levels were measured on cycle day two, then monophasic OCPs were started immediately after receiving the laboratory sample for the hormonal profile (day 2) for 21 days, then at day 18 we started subcutaneous injection of GnRH agonist (Decapeptyl 0.1 mg - FERRING) once daily until the day of hCG injection, and diagnostic hysteroscopy was performed on the same day we started GnRH agonist.

Complete pituitary desensitization was confirmed on day 2 of the next cycle by the discovery of low serum levels of progesterone (P4), E2, and LH (baseline), the presence of ovarian cysts was ruled out, and endometrial thickness of < 5 mm was confirmed.

The antral follicle count was noted, and FSH medication (Fostimon - IBSA) was started at 225 IU/day for at least 5 days, and continued until the day of hCG injection (Choriomon 10000 IU, i.m. - FERRING). Daily FSH dosages have been changed based on E2 levels and/or the number of developing follicles since the sixth day of FSH treatment.

Patients got daily visits after day 6 of COH for ultrasonographic and hormonal exams to determine the optimum timing for hCG injection. The administration of hCG (day of hCG administration; dhCG) began as soon as four pre-ovulatory follicles (18-24 mm in diameter) were seen, and E2 levels per pre-ovulatory follicle were 200 pg/ml, with a total of 3000 pg/ml.

Thirty-five hours after hCG was administered, oocytes were extracted using a stiff (Labotect) catheter and a metal (Wallace) transvaginal ultrasound-guided aspiration needle. Three days later, ETs were carried out.

On Day 2, the best quality embryos were those with four or five blastomeres, 20% anucleated fragments, and no multinucleated blastomeres. Micronized progesterone, 600 mg/day, was given daily by vaginal injection to pregnant women beginning on the evening of ovum pickup and continued until eight weeks of amenorrhea, in order to sustain the luteal phase.

When a gestational sac is seen during an ultrasound scan about seven weeks after the onset of amenorrhea, the pregnancy is considered clinical; if it is still there after twelve weeks, it is considered continuing.

Follicular output rate (FORT) calculation:

Calculation of FORT was as follows:

Ovarian ultrasound scans were done at baseline and on the day of hCG using a 5.0-9.0 MHz multi-frequency transvaginal probe (Sonoace R3, Medison) to assess the number and size of antral follicles. We will carefully count the number of all follicles measuring 3-8 mm in diameter to compute antral follicle count (AFC) and the number of all follicles measuring 18-24 mm in diameter to calculate pre-ovulatory follicle count (PFC) in both ovaries at baseline and on dhCG.

The FORT was determined as the ratio of PFC on dhCG100 to AFC at baseline.

FORT = PFC x 100 / AFC.

FORT and other supplementary study groups are defined. We decided to divide our cohort into three separate FORT groups to facilitate evaluation of the probable link between follicular responsiveness to COH and IVF-ET result. The three FORT groups will be chosen at random based on whether FORT values will be below the 33rd percentile (42%, low FORT group), between the 33rd and 67th percentiles (42-58%, average FORT group), or above the 67th percentile (>58%, high FORT group).

We constructed three more sets of three separate groups based on ages, AFC, and PFC levels to evaluate the prediction of FORT with that of other pre-IVF parameters that may impact result. We will employ a similar technique to FORT (terciles of data distribution) for them. Thus, with regard to women's age, there are three groups: younger (less than 25 years), middle (between 25 and 30 years), and older (more than 30 years); in terms of AFC, there are three groups: low (less than 14 antral follicles), average (between 14 and 17 antral follicles), and high (more than 17 antral follicles) in both ovaries; in terms of PFC, there are three groups: low (less than 6 pre-ovulatory follicles), average (6-7 pre-ovulatory follicles), and high (more than 8 pre-ovulatory follicles) in both ovaries.

Measurements of hormones Using a chemiluminescence approach, an automated multi-analysis system has assessed the levels of serum P4, E2, LH, and FSH.

The characteristics of P4 were as follows: linearity up to 60 ng/ml, a lower detection limit of 0.10 ng/ml, and intra- and inter-assay coefficients of variation (CVs) of 8 and 9%, respectively.

For E2, the intra- and inter-assay CVs will be 8 and 9%, respectively, and the lowest detection limit was 30 pg/ml. Linearity was observed up to 1000 pg/ml. The lowest

detection limit and intra- and inter-assay CVs for LH and FSH were 3 and 5%, respectively, and 0.1 mIU/ml.

Statistical methodology:

SPSS version 18 was used to collect, tabulate, and analyze the data. For parametrical data, the standard error was utilized as the measure of variability and the mean as the measure of central tendency. In situations when determining the normality of the data distribution was impossible, medians and minimum–maximum values were employed. When two continuous variables are independent of one another, their connection has been evaluated using correlation; when there is a dependence relationship, it has been evaluated using simple regression.

If the variables are parametric, Pearson's test is performed to find out if the coefficient of correlation is substantially different from zero; if the variables are non-parametric, Spearman's test is employed.

Analysis of variance was used to compare continuous variables from the low, average, and high FORT; AFC and PFC groups. The two-sided Pearson X2 test was utilized to compare the categorical variables among the three groups in each set.

Using dummy variables derived from terciles, a binary regression model was ran to account for potential confounders, ages, AFC, and PFC in the connection between pregnancy rate and FORT. P-values less than 0.05 were regarded as statistically significant.

Sample size justification:

Sample size was calculated using EpiInfo® version 7.0, setting the power (β) at 80% and the significance level (α) at 0.05. Data from a previous study by ***Gallot et al., (7),*** indicated that the average FORT was 50.6% (range, 16.7–100.0%). Clinical pregnancy rates per oocyte retrieval increased progressively from the low to the high FORT groups (33.3, 51.2 and 55.7%, respectively, $P < 0.003$). Calculation according to these values to produce an even narrower 95% confidence interval produced a minimal sample size of 298 women. Therefore, the total sample size will be approximately 300 cases.

Results

Table 1: Various types of follicular output rate (FORT) in the women who participated

FORT		Frequency	Percent
Category	High	195	65%
	Average	92	30.7%
	Low	13	4.3%
	Total	300	100%

Table 2: Clinical pregnancy rate among all women

Clinical pregnancy	Frequency	Percent
Yes	119	39.7%
No	181	60.3%
Total	300	100%

Table 3: Clinical pregnancy rates among different FORT categories

			Clinical pregnancy		Total
			Yes	No	
FORT category	Average	Count	13	79	92
		% within FORT category	14.1%	85.9%	100.0%
		% of Total	4.3%	26.3%	30.7%
	High	Count	105	90	195
		% within FORT category	53.8%	46.2%	100.0%
		% of Total	35.0%	30.0%	65.0%
	Low	Count	1	12	13
		% within FORT category	7.7%	92.3%	100.0%
		% of Total	.3%	4.0%	4.3%
Total		Count	119	181	300
		% within FORT category	39.7%	60.3%	100.0%
		% of Total	39.7%	60.3%	100.0%

Chi square test: P value = 0.000 (highly significant)

- With a P value less than 0.05, this table demonstrates that the high FORT group had the greatest clinical pregnancy rate (53.8%).

Table 4: Patient characteristics and laboratory data among low, average and high FORT groups

Variable	Low FORT (N = 13) Mean ± SD	Average FORT (N = 92) Mean ± SD	High FORT (N = 195) Mean ± SD	P value (significance) ANOVA
Age	31.2 ± 3	27.5 ± 4.7	28.4 ± 4.2	0.012 (NS)
BMI	20.8 ± 2.4	21.4 ± 2.3	21 ± 2.5	0.330 (NS)

FSH	5.1 ± 0.7	5.3 ± 1.6	5.4 ± 1.4	0.488 (NS)
LH	4.6 ± 1.4	4.3 ± 1.3	4.5 ± 1.4	0.638 (NS)
AMH	2.8 ± 1.1	2.3 ± 1.2	2.5 ± 1.3	0.244 (NS)

- NS = non-significant

- With a P value greater than 0.05, this table demonstrates that there is no significant difference in age, body mass index, FSH, LH, and AMH between the low, average, and high FORT groups.

Table 5: Patient characteristics and clinical data among low, average and high FORT groups

Variable	Low FORT (N = 13) Mean ± SD	Average FORT (N = 92) Mean ± SD	High FORT (N = 195) Mean ± SD	P value (significance) ANOVA
AFC	11 ± 3.6	8.6 ± 3.6	8.9 ± 3.3	0.056 (NS)
PFC	4.2 ± 1.4	4.1 ± 1.5	7.4 ± 3.2	0.000 (HS)
Number of ampoules	38 ± 2.4	35.2 ± 6.2	34 ± 5.4	0.017 (HS)
Days of stimulation	11.9 ± 2.2	11.8 ± 1.7	11.3 ± 1.3	0.041 (S)
Endometrial thickness (cm)	8.3 ± 0.4	8.1 ± 0.7	8.3 ± 0.8	0.170 (NS)
E2 at trigger	1044 ± 584.2	1150 ± 452.1	1757.3 ± 720.7	0.000 (HS)
Collected eggs	3.8 ± 1	3.6 ± 1.3	6.6 ± 2.9	0.000 (HS)
Fertilized eggs	3.2 ± 1.4	3.3 ± 1.4	5.4 ± 2.5	0.000 (HS)
Transferred embryos	2.5 ± 0.8	2.4 ± 0.8	2.8 ± 0.4	0.000 (HS)
FORT%	37.6 ± 3.1	49.1 ± 4.8	83.1 ± 12.36	0.000 (HS)

- NS = non significant
- S = significant
- HS = highly significant

- The preovulatory follicle count, number of ampoules, days of stimulation, E2 at trigger, collected ova, fertilized ova, and number of transferred embryos significantly differ between the low, average, and high FORT groups in this table, with a P value less than 0.05.

Table 6: Impact of several factors on the clinical pregnancy rate by binary logistic regression

Variable	Odds ratio	P value
Age	0.832	0.004
BMI	0.963	0.047
Endometrial thickness	1.123	0.032
E2 at triggering	2.225	0.212
Collected ova	1.121	0.033
Number of transferred embryos	1.322	0.321
FORT %	1.312	0.002

- The table indicates that the clinical pregnancy rate is significantly influenced by age, body mass index, endometrial thickness, number of harvested oocytes, and follicular output rate.
- The odds ratios for clinical pregnancy rate and age decrease, at 0.832 and 0.963, respectively, show a tendency for the latter to rise with the former.
- With odds ratios of 1.123, 1.121, and 1.312, respectively, the clinical pregnancy rate tends to rise with increasing endometrial thickness, number of collected oocytes, and follicular output rate.

Discussion:

Since ICSI is the final and most sophisticated step in the infertility therapy process, doctors find it to be a true challenge. While the success rate has improved significantly in recent years, neither the patient nor the doctor is ever satisfied with a success rate between 30% and 40%.

A woman's age, the quality of her sperm, the reason for her infertility, the quantity of injected oocytes, the quality of the transferred embryos, and the total number of embryos transferred are some of the factors that affect the success rate of ICSI. The effectiveness of ICSI is also greatly influenced by the practitioners' training and experience ***(8)***.

Before registering a couple for ICSI, it is advisable to discuss the expected success rate with them. Before beginning this treatment, the couple should be aware of their prospects of success given the expense and emotional strain involved ***(9)***.

ICSI technique, injection technique, sperm quality, egg quality, and the quantity and quality of transferred embryos are some of the factors that are thought to affect the success rate of ICSI ***(10)***.

The remarkable, covariate-independent association between FORT and IVF-ET result is the study's main discovery. Patients with a higher proportion of FSH-responsive antral follicles were more likely to get pregnant following IVF-ET, regardless of age or absolute pre-COH AFC and post-COH PFC.

This confirms the idea that antral follicles' lack of reactivity to exogenous FSH indicates some degree of follicle/oocyte dysfunction ***(9, 11)*** and establishes the FORT as a promising qualitative marker of antral follicles.

Accordingly, earlier researchers have noted that more than 40% of atretic follicles are present during the initial days of the follicular phase in the menstrual cycle ***(12)***. This percentage is corroborated by the mean FORT values of 70.7% found in our infertile population (Table 3).

Furthermore, the current findings encourage us to reevaluate the COH cancellation criteria based on the output of follicle response to exogenous FSH (FORT) rather than the absolute counting of follicles recruited by the treatment. This explanation helps to explain the reported weak predictability of absolute AFC ***(13)***.

Remarkably, standard indicators of ovarian aging, including women's age, AMH, and baseline FSH levels, had no discernible impact on FORT (Table 11).

This supports earlier indirect evidence by indicating that antral follicles do not significantly lose their ability to react to FSH as ovarian age progresses ***(14)***. It is noteworthy that the current series observations of decreased AFC in patients with enhanced FORT are consistent with this.

Therefore, rather than a per-follicle decrease of sensitivity to FSH, the poor ovarian response to COH often reported in older women is likely due to a pre-existing depletion of the follicular pool.

However, given the limitations of the FORT index that have been addressed elsewhere, the relevance of the current results should be considered ***(15)***. In summary, because their PFC could not be determined, individuals who had stopped their FSH therapy prior to hCG delivery were unable to have their FORT evaluated by design.

If the number of average-sized follicles in the mid-follicular phase of COH is utilized instead of the 18–24 mm follicles on dhCG, more research is required to confirm if FORT is still useful. A move like this can include patients who have promised to cancel back into the FORT computation. Furthermore, it is not always the case that the 3–8 mm follicles prior to COH respond in unison to FSH, as suggested by FORT ***(16).***

This restriction can only be addressed by measuring each follicle's growth individually in response to FSH, which is virtually impossible. Two other methodological approaches were used in its place. Firstly, a GnRH agonist was used to deeply inhibit endogenous FSH in order to minimize follicle size disparities and, to the greatest extent feasible, synchronize follicle development during COH. Secondly, rather large initial dosages of FSH were employed in order to attract as many follicles as feasible despite their pretreatment sizes.

Finally, tight follicle monitoring and ovulation triggering protocols were followed to avoid the potential impact of any improper prolongation of COH time on PFC and, therefore, the FORT calculation. Indeed, all subjects got hCG as soon as 4 follicles attained pre-ovulatory maturity (and E2 levels per pre-ovulatory follicle were 200 pg/ ml), and only those who clearly did not meet this condition were dropped.

In addition, FORT believed that only 18-24 mm follicles successfully responded to FSH on dhCG, despite the possibility that smaller follicles also showed some degree of FSH responsiveness.

However, because very small follicles, which were not countable by ultrasound at baseline, may have also begun their FSH-driven maturation after the start of COH and reached intermediate sizes on dhCG, including average-sized follicles on dhCG in the calculation of FORT may have complicated its interpretation.

Furthermore, further research focused on various follicle sizes will be beneficial in fine-tuning alternative appropriate cutoffs for the derivation of this new measures. These FORT properties, when combined, highlight its immense adaptability and motivate us to continue develop this novel approach.

Future research into various methods of calculating the FORT, namely utilizing different numerators and incorporating patients treated with lower, but potentially more discriminating, exogenous FSH signals, will likely contribute to its therapeutic use.

In conclusion, the current data show that antral follicle response to FSH, as measured by FORT, is favorably associated to IVF-ET outcome in normocycling women with polycystic ovaries. The FORT is therefore a promising qualitative index of ovarian function.

According to ***Gallot et al. (7),*** FORT is an objective technique to evaluate the real response of follicles to exogenous FSH that is unaffected by the size of the pre-existing cohort of antral follicles.

Zhang et al. (17) did another study to determine the real accuracy of follicular output rate (FORT) as a predictive biomarker of FSH response and reproductive competence following IVF/intracytoplasmic sperm injection. A total of 1643 cycles were analyzed, including 140 polycystic ovary syndrome (PCOS) patients who received ovarian stimulation. In line with our research, they came to the conclusion that among 1503 non-PCOS cycles, FORT gradually enhanced the number of retrieved oocytes and all embryos that could be transferred, as well as the rates of good-quality embryos, embryo implantations, and clinical pregnancies. Nevertheless, in contrast to non-PCOS individuals, FORT were considerably lower in patients with PCOS who achieved clinical pregnancy as opposed to those who did not (0.56±0.21 versus 0.66±0.29, P=0.031).

This novel indicator challenges us to reconsider the traditional COH cycle cancellation criterion based on the absolute number of developing follicles and sheds fresh light on the long-running dispute over the classification of 'poor responders' to COH ***(18, 19, 20, 21).***

Furthermore, the use of FORT in predicting IVF-ET outcome has to be verified in studies that employ more customized methods for COH and hCG delivery as well as larger inclusion criteria.

Furthermore, additional research focused on other characteristics thought to be involved in follicle response to FSH, such as FSH receptor polymorphisms (22) and granulosa cell activity (23), is needed to build on the current findings.

Declarations

Ethics approval and consent to participate

This study was approved by the Faculty of Medicine Al Azhar University, Research Ethics Committee. Each patient was provided a written informed consent for analysis of anonymized data.

Consent for publication

Not applicable.

Availability of data and materials

The data is available upon request of the editorial board.

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

ME conceived the study and designed it. All authors contributed equally to data collection and data analysis. Manuscript was written by AA and HA.

Statistical analysis done by ME. All authors have read and approved the manuscript.

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