RESEARCH

Evaluation of correlation between antral follicle diameters with Follicular Output Rate (FORT) in women under controlled ovarian hyperstimulation for assisted reproductive techniques

Farahnaz Mardanian[1], Reihaneh Dehghani-Mohammadabadi[1], Hatav Ghasemi Tehrani[2], Elham Naghshineh[1] and Ferdous Mehrabian[2*]

Abstract

Background: This study aimed to determine the association of diametrical antral follicles with the ovarian response by Follicular Output Rate (FORT) ratio in 100 females undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). This study selected 100 women undergoing controlled ovarian hyperstimulation (COH). The number of antral follicles (diameter of 3–10 mm) was calculated with two-dimensional vaginal sonography on days 1–3 of the cycle. Then, on a triggering day with human chorionic gonadotropin (HCG), the number of follicles (with a diameter of 16–22 mm) and the ratio of FORT were determined. The correlation among FORT with age, antral follicle count (AFC), AFC ≤ 5, AFC > 5, number of preovulatory follicles (16–20 mm), number of metaphase II (MII) oocytes, body mass index (BMI), infertility period, and anti-Mullerian hormone (AMH) was assessed.

Results: There was a significant correlation between FORT and total AFC, AFC > 5, number of preovulatory follicles (16–20 mm), and number of MII oocytes retrieved. There is no significant relationship between FORT and examined two variables (AMH and AFC ≤ 5). Multiple linear regression analysis showed no significant relationship between FORT and examined two variables (AMH and AFC > 5). There was a significant correlation between MII oocytes retrieved and age, total AFC, AFC ≤ 5, AFC > 5, number of preovulatory follicles (16–20 mm), and AMH. A significant positive relationship existed between MII oocytes retrieved and examined two variables (AFC ≤ 5 and AFC > 5).

Conclusion: There was not much difference in the correlation between the AFC ≤ 5 and AFC > 5, and both positively correlated with the number of MII oocytes retrieved.

Keywords: Antral follicle count, Follicular Output Rate, Vaginal sonography, Anti-Mullerian hormone, Antral follicle diameter

1 Background

Follicular harvesting and optimization of the response to controlled ovarian hyperstimulation (COH) with gonadotropins are essential in treating infertility with assisted reproductive techniques [1]. Prediction of this response, assessed by ovarian reserve, is critical for prognosis and patient-specific treatment. Specifying treatment requires

*Correspondence: ferdous.mehrabian2020@gmail.com
[2] Department of Obstetrics & Gynecology, School of Medicine, Al-Zahra Hospital, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
Full list of author information is available at the end of the article

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the selection of the best gonadotropin-releasing hormone (GnRH) analog protocol and the best initial dose of gonadotropin to achieve the ideal ovarian response because it is known that both potentially low and excessive responses lead to cycle cancellation and increased costs [2]. While a low ovarian response may reduce the risk of pregnancy, an exaggerated response indicates the risk of ovarian hyperstimulation syndrome [3–5]. Ovarian storage has complex mechanisms of age, genetics, and environmental factors [6]. Several ovarian reserve markers have been studied in the last few decades, but no ideal marker remains. Prediction of response through ovarian reserve examination is superior only through calendar age. At present, the number of antral follicles (AFC) and anti-Mullerian hormone (AMH) have the best sensitivity and specificity for predicting ovarian response, despite the presence of a false positive rate of 10–20% [7]. Because ovarian response appears to be influenced by many factors, for determination of the individual starting dose of FSH in in vitro fertilization (IVF) cycles, nomograms are mainly based on age and AMH, AFC, and follicle-stimulating hormone (FSH) levels during the third menstrual period. This situation leads to a reduction in costs and an improvement in the possibility of pregnancy [8, 9].

The ovarian response is one of the most commonly studied parameters in clinical trials on IVF treatment [10]. Traditionally, the number of oocytes retrieved is the main result of the ovary responding to gonadotropin stimulation [5]. However, the number of obtained preovulatory follicles at the end of COH is not a reliable reflection of the sensitivity of the antral follicle to FSH. It correlates highly with the number of antral follicles before ovarian stimulation [11]. The diameter of antral follicles and the number of antral follicles may also be critical. The FORT evaluates the ratio of FSH-responsive follicles. These parameters can be calculated as below:

The number of preovulatory follicles $(16 - 20\text{ mm})$
$\times 100/$the number of antral follicles $(3 - 10\text{ mm})$.

This ratio is associated with IVF outcomes, including pregnancy rates [12]. Differentiation of different types of size may be related because several studies show that the endocrine function of a follicle is related to its diameter [13, 14]. A previous study reported that pregnant patients had the most significant number of antral follicles between 5 and 10 mm. Another study showed that the number of follicles with a diameter of 2–6 mm decreases with age, but the number of follicles with a diameter of 7–10 mm is constant. This situation suggests that follicles ≤ 6 mm may show ovarian function capacity. Bestow et al. showed a negative correlation between FORT and AFC. This group showed an inverse correlation between FORT and AFC at a significant level [15]. Bayu et al. showed that $AFC \geq 5$ had a higher significant effect on pregnancy rate than the $AFC < 5$ in IVF [16]. Due to the small number of available studies in this field and to confirm or reject the limited results obtained in studies such as Bessow et al. and Bayu et al. study, this study was designed to evaluate the correlation between antral follicle diameter and FORT in women under controlled ovarian hyperstimulation for assisted reproductive techniques.

2 Methods

In this prospective longitudinal cross-sectional study, 100 women (with an age range of 20–40) referred to the infertility center of Isfahan University of medical sciences (between September 2021 and April 2022) who underwent COH were selected. Sampling was done by census method, and all patients who met the study criteria were included in the study in the mentioned period. Inclusion criteria were: age under 40 years, presence of both ovaries, absence of cyst and endometrium, no history of ovarian surgery, and performance of 2-dimensional transvaginal ultrasound with sufficient visualization. The exclusion criteria were: clinical signs of hyperandrogenism, polycystic ovary syndrome, hyperprolactinemia and hypothyroidism, and patients with CAH. Patients are admitted for initiation of the GnRH antagonist protocol for COH. Demographic variables (age, AMH, and BMI) are determined before the start of the cycle. The number of antral follicles (with a diameter of 2–10 mm) is calculated by two-dimensional vaginal sonography (supersonic imagine-aixplorer ultimate) on days 1–3 of the cycle. In this study, AFC count was divided into follicles with a diameter of 5 mm or less and those with a diameter greater than 5 mm. The follicles with a diameter of 5 mm or less are represented by $AFC \leq 5$, and those with a diameter larger than 5 mm and up to 10 mm were represented by $AFC > 5$. For all patients, the GnRH antagonist protocol was used between days 1–3 of the menstrual cycle. The dose of Human Menopausal Gonadotropin (HMG) (Menotropin, Ferring) and recombinant FSH (Cinnal f, Follitropin alfa, Cinnagen, Tehran, Iran) was assessed based on patient weight, AMH, and previous response to ovarian stimulation. The dose range was between 150 and 300 IU. CETROTIDE 0.25 mg (GnRH antagonist, Serpero) was started when a follicle reached 14 mm. hCG 5000-10000 IU (human chorionic gonadotropin, Pregnyl, Organon, Netherlands) was injected after observation of three preovulatory follicles with a diameter of 16–22 mm. Oocytes were retrieved by transvaginal ultrasound-guided aspiration 36 h after

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Table 1 The demographic and reproductive data

Variable	Mean $\pm$ SD	Median	Range	Normal distribution
Age	32.56 $\pm$ 4.7			
FORT (Follicular Output Rate) (%)	71 $\pm$ 21.4			
Total AFC (antral follicle count)	9.42 $\pm$ 4.14			
AFC $\leq$ 5	4.28 $\pm$ 2.5			
AFC > 5	5.14 $\pm$ 3.29			
Number of metaphase II (MII) oocytes retrieved	6.99 $\pm$ 4.8			
Infertility period		6	1–24	
BMI (body mass index)		21	18–40	Yes
AMH (anti-Mullerian hormone)		1.8	0.1–11	Yes

hCG administration, and the embryologist determined the number of MII oocytes on the same day. On triggering day with HCG, the number of follicles 16–22 mm is determined, and the ratio of FORT was calculated. FORT calculation was done as the below formula:

Number of preovulatory follicles on hCG day administration

/number of antral follicles on day1−3cycles × 100.

It is noted that one specialist did vaginal sonography. After collecting the data, the information was entered into SPSS 25 (IBM, ARMONK NEW YORK, NY, USA). Mean and standard deviation were used to describe quantitative data, and frequency and percentage will be used for qualitative data. Pearson and Spearman's tests were used to analyze the data in terms of data distribution.

2.1 Ethical consideration

This study was approved by the Ethics committee of Isfahan University of Medical Sciences (registration number: IR.MUI.MED.REC.1400.413).

3 Results

This study was done on 100 women. The demographic and reproductive data are summarized in Table 1. Based on this table, the mean age of patients was 32.56 $\pm$ 4.7. The median for infertility period, BMI, and AMH was 6, 21, and 1.8, respectively. The mean of FORT (%), AFC $\leq$ 5, AFC > 5, and the number of MII oocytes was 71 $\pm$ 21.4, 4.28 $\pm$ 2.5, 5.14 $\pm$ 3.29, and 6.99 $\pm$ 4.8, respectively. The correlation between FORT and other related variables is shown in Table 2. Based on this table, there was a significant correlation between FORT and total AFC, AFC > 5, number of preovulatory follicles (16–20 mm), and number of MII oocytes retrieved ($P < 0.05$). There was no significant correlation between FORT with AFC > 5 and AFC $\leq$ 5 ($P > 0.05$). Other related variables (BMI, infertility period, AMH) also had no significant correlation

Table 2 Correlation among FORT (Follicular Output Rate) and other related variable

Variable	Correlation coefficient	*P* value
Age	0.060	0.551
Total AFC (antral follicle count)	0.244	0.014
AFC $\leq$ 5	0.114	0.258
AFC > 5	0.22	0.028
number of preovulatory follicles (16–20 mm)	0.578	0.000
Number of metaphase II (MII) oocytes retrieved	0.422	0.000
BMI (body mass index)	0.39	0.70
Infertility period	0.186	0.64
AMH (anti-Mullerian hormone)	0.19	0.058

Table 3 Multiple linear regression analysis among FORT (Follicular Output Rate) and related variables

Variables	95% Confidence interval		*P* value
AMH (anti-Mullerian hormone)	−239	−2.522	0.284
AFC (antral follicle count) > 5	−983	−3.316	0.104

with FORT ($P > 0.05$). For verification of the relationship between the AFC > 5 and FORT, multivariable linear regression was done. Acquired data are summarized in Table 3. This table indicated no significant relationship between FORT and examined two variables (AMH and AFC > 5). The correlation between the number of oocytes retrieved and other related variables is also shown in Table 4. Based on this table, there was a significant correlation between the number of MII oocytes retrieved and age, total AFC, AFC $\leq$ 5, AFC > 5, number of preovulatory follicles (16–20 mm), and AMH ($P < 0.05$). BMI and infertility period had no significant correlation with MII oocytes retrieved ($P > 0.05$). For verification of the relationship between the AFC and the number of MII

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Table 4 Correlation among number of metaphase II (MII) oocytes retrieved and other related variable

Variable	Correlation coefficient	*P* value
Age	−0.223	0.026
Total AFC (antral follicle count)	0.777	0.000
AFC ≤ 5	0.582	0.000
AFC > 5	0.518	0.000
number of preovulatory follicles (16–20 mm)	0.836	0.000
BMI (body mass index)	0.073	0.471
Infertility period	0.063	0.531
AMH (anti-Mullerian hormone)	0.543	0.000

Table 5 Multiple linear regression analysis among number of metaphase II (MII) oocytes retrieved and related variables

| Variables	95% Confidence interval		*P* value
AFC ≤ 5	0.651	1.189	0.000
AFC > 5	0.561	0.995	0.000

AFC antral follicle count

oocytes retrieved, multivariable linear regression was done. Acquired data are summarized in Table 5. This table indicated a significant positive relationship between the number of MII oocytes retrieved and examined two variables (AFC ≤ 5 and AFC > 5). There was not much difference in the correlation between the AFC ≤ 5 and AFC > 5, and both positively correlated with the number of MII oocytes retrieved. The scatter chart between FORT with AFC ≤ 5 and AFC > 5 is shown in Fig. 1. This figure showed a direct relationship of FORT with AFC ≤ 5 and AFC > 5.

4 Discussion

This study evaluated the correlation between antral follicular count and diameter with FORT in women under controlled ovarian hyperstimulation for assisted reproductive technology (ART). Some studies considered the antral follicle count as a predictive marker in this field [17, 18]. According to previous studies, there is a positive relationship between FORT and outcomes of IVF. Thus, FORT can be considered a suitable marker for follicular responsiveness [19–21]. There are few studies about the correlation between FORT and demographic and related factors, as well as antral follicle size in ovarian responsiveness. Our study showed that there was no significant correlation between FORT and age. Grynberg et al. showed a similar result. This group also indicated that FORT was not significantly associated with age [22]. Similar to our study, Bessow et al. showed no correlation

between FORT and age BMI [15]. There was a significant positive correlation between FORT and total AFC and AFC > 5 and the number of MII oocytes retrieved. However, no correlation was observed in regression analysis between AFC > 5 and FORT. According to Broer et al. [23] and Papathanasiou et al. study [24], AFC < 5, AFC > 5, and AMH are not sufficient for accurate prediction of ovarian response. We also showed that these variables had no significant correlation with ovarian response. Bestow et al. showed a negative correlation between the FORT and total AFC and the FORT and AFC < 6 and no correlation between FORT and AFC > 6 [15]. We considered number five as a cutoff for AFC. Unlike Bessow et al., we did not observe a negative correlation between FORT and AFC. In our study, a significant positive correlation was observed. Headsman et al. introduced follicular diameter as an effective parameter for the ovarian response. This group showed that AFC ≤ 6 correlated with ovarian responsiveness [14]. We used a better parameter, e.g., FORT. Grynberg et al. showed that FORT could be considered an efficient quantitative and qualitative marker of ovarian response during controlled ovarian stimulation (COS) [22]. These data are similar to our data. We also indicated that FORT positively correlates with AFC in women under controlled ovarian hyperstimulation for ART. Based on our acquired data, there is a significant correlation between the number of MII oocytes retrieved and age, total AFC, AFC ≤ 5, AFC > 5, number of preovulatory follicles (16–20 mm), and AMH. For verification of the relationship between the AFC and the number of MII oocytes retrieved, multivariable linear regression was done. The result showed a significant positive relationship between the number of MII oocytes retrieved and examined two variables (AFC ≤ 5 and AFC > 5). There was not much difference in the correlation between the AFC ≤ 5 and AFC > 5, and both had an almost equally positive correlation with the number of MII oocytes retrieved. An increase in age leads to a decrease in MII oocytes retrieved [25, 26]. Similarly, we showed a negative correlation between age and MII oocytes retrieved. Various studies indicated a positive correlation between MII oocytes retrieved and AFC, number of preovulatory follicles (16–20 mm), and AMH [27, 28]. In some studies, this correlation is significant. Some studies showed nonsignificant relationship [27–32]. Our study showed that all mentioned variables significantly positively correlated with MII oocytes retrieved. The ovarian response has an essential effect on the number of oocytes retrieved. This effect can be explained through Fort. AFC can be considered an independently associated factor in the oocyte retrieval cycle [20, 33, 34]. We showed a significant correlation between the number of MII oocytes retrieved and FORT. We also showed a significant correlation between

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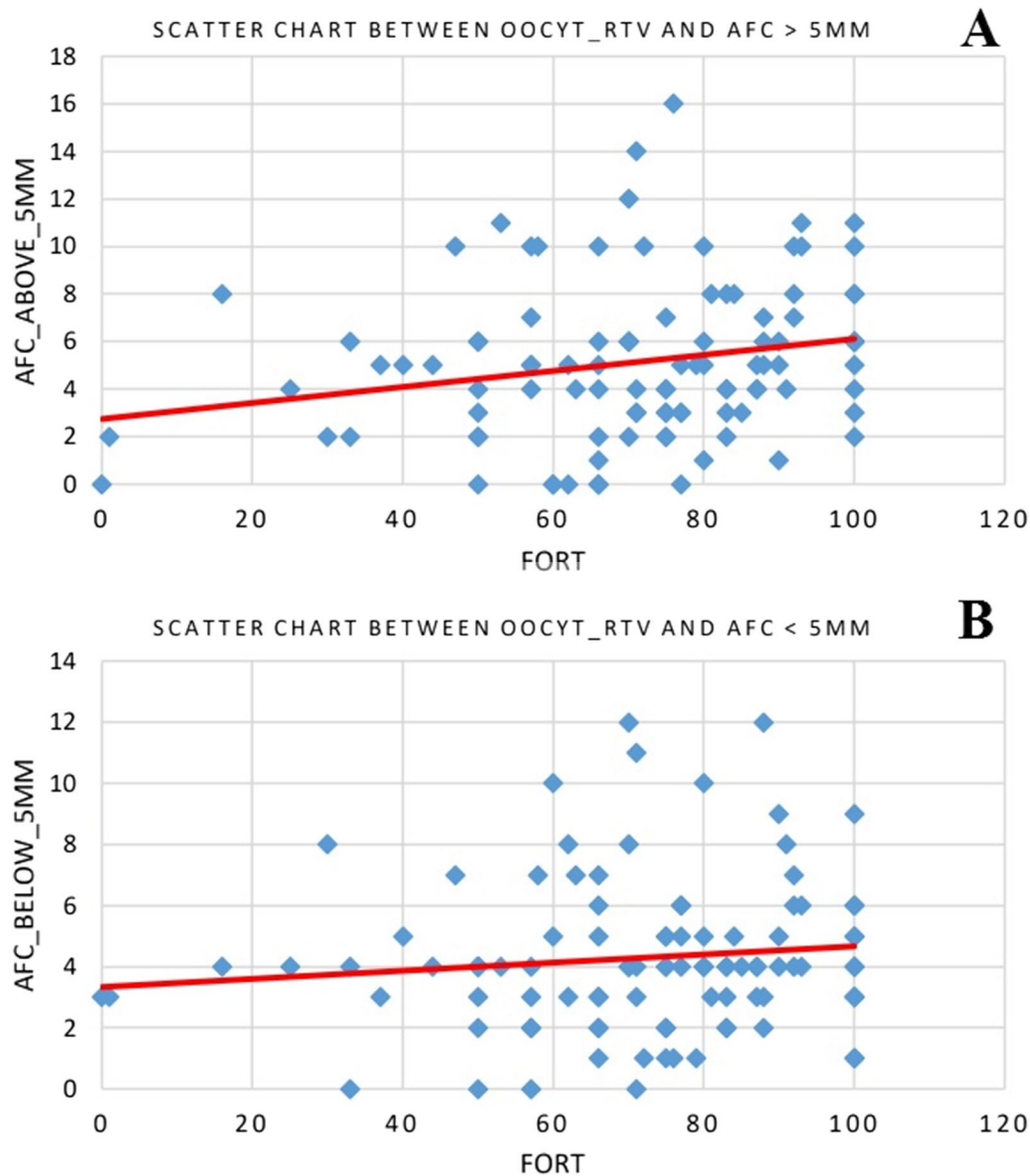
Fig. 1 Scatter chart between FORT (Follicular Output Rate) and AFC (antral follicle count) > 5 (**A**) and AFC (antral follicle count) ≤ 5 (**B**)

the number of MII oocytes retrieved with total AFC, AFC ≤ 5, AFC > 5, and AMH.

In our study, four specific goals were pursued:

- Determining the relationship between the number of antral follicles and the FORT ratio in women under COH showed a positive correlation (0.114) between FORT and AFC. Bestow et al. observed the negative correlation between FORT and AFC. This group showed an inverse correlation between FORT and AFC at a significant level [15].

- Determining the relationship between antral follicle diameter and FORT ratio in women undergoing COH for IVF. The follicular size is considered an essential parameter for follicles [13, 14]. Our study divided the AFC count into AFC ≤ 5 and AFC > 5. Data analysis showed that FORT and AFC > 5 and FORT and AFC ≤ 5 were directly correlated at significant and non-significant levels, respectively. However, after regression, data showed no significant correlation between AFC > 5 and FORT.

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– Determining the relationship between age and FORT ratio in women undergoing COH for IVF: Different parameters can change ovarian reserve. One of these parameters is age [35]. However, there is no ideal parameter for ovarian reserve [36]. Grynberg et al. and Bessow et al. showed that FORT had not significantly associated with age [15, 22]. We acquired a similar result.
– Determining the relationship between AMH levels and FORT ratios in women undergoing COH for IVF: AMH is a sensitive and specific variable for predicting ovarian response [37, 38].

In our study, the median AMH level was 1.8 ng/mL. We found a non-significant positive relationship between FORT and AMH. Based on Grynberg et al., FORT significantly decreased from the low, average, and high levels of AMH [22]. Genro et al. showed a negative association between AMH levels and FORT [13].

5 Conclusion
This study evaluated the correlation between FORT and total AFC and AFC diameter. Results showed a significant correlation between FORT and total AFC and AFC > 5. However, multiple linear regression analysis showed no significant relationship between FORT and AFC > 5. There is also a significant correlation between the number of MII oocytes retrieved and age, total AFC, AFC ≤ 5, AFC > 5, number of preovulatory follicles (16–20 mm), and AMH. Multiple linear regression analysis also showed that the AFC ≤ 5 and AFC > 5 had an almost equally positive correlation with the number of MII oocytes retrieved. Thus, based on the results, the effects of AFC ≤ 5 and AFC > 5 on follicular responsiveness are similar.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics committee of Isfahan University of Medical Sciences (registration number: IR.MUI.MED.REC.1400.413).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

Author details
[1] Department of Obstetrics & Gynecology, School of Medicine, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, Iran. [2] Department of Obstetrics & Gynecology, School of Medicine, Al-Zahra Hospital, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

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