Section A-Review Paper
ISSN 2063-5346

FOLLICULAR OUTPUT RATE, FOLLICULAR-OOCYTE-INDEX, AND OOCYTE RETRIEVED PER FOLLICLE: A NARRATIVE REVIEW

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doi: 10.48047/ecb/2023.12.si6.6672023.17/07/2023

Section A-Review Paper
ISSN 2063-5346

ABSTRACT

Reproductive doctors struggle with low-prognosis ART patients. These patients have distinct biological profiles. Indeed, although women with reduced ovarian reserve have poor ovarian response, hypo-responders have unanticipated low or subpar response to controlled ovarian stimulation despite fulfilling ovarian criteria. These hypo-responders had slower estradiol and follicle growth responses to FSH stimulation, longer stimulations, and/or higher cumulative FSH dosages. Thus, ovarian sensitivity to gonadotropins seems to vary across patients and affects stimulation response. Genetic mutations or SNPs of gonadotropins and their receptors may affect ovarian sensitivity to FSH. Thus, ovarian sensitivity to FSH may increase IVF success rates in low-prognosis individuals and provide new therapeutic options.

Keywords: Follicular Output Rate, Follicular-Oocyte-Index, Oocyte Retrieved Per Follicle, Assisted Reproductive Technologies, Antral Follicular Count, *In Vitro* Fertilization

1. INTRODUCTION

One of the aspects of assisted reproductive technologies (ART) that has received the most research is the ovarian response to stimulation. One of the key variables impacting ART yield and, in turn, pregnancy rates is the size of the response to ovarian stimulation (OS), which directly affects the quantity of oocytes extracted. The primary indicator of ovarian response to ovarian stimulation is considered to be the quantity of oocytes recovered. The total amount of gonadotropins given, the length of stimulation, and the peak blood E2 levels are considered secondary outcome markers. Gonadotrophin dosages are modified in accordance with ovarian reserve markers such as antral follicle count (AFC), anti-Mullerian hormone (AMH), and basal FSH in order to customise and optimise OS result [1].

Although AMH and AFC give a reliable estimate of the quantity of oocytes collected, their ability to forecast the live birth rate is somewhat constrained. These indicators offer a static image of each person's ovarian reserve. The dynamic character of follicular development in response to exogenous COS (controlled ovarian stimulation) is not reflected by them. Individual responses to stimulation vary widely and are influenced by both extrinsic (gonadotropin dosage, etc.) and intrinsic factors (FSH receptor polymorphisms, etc.). Research into alternative ovarian response indicators has been prompted by the realisation that the total number of recovered

Section A-Review Paper
ISSN 2063-5346

oocytes does not always adequately indicate ovarian potential [2].

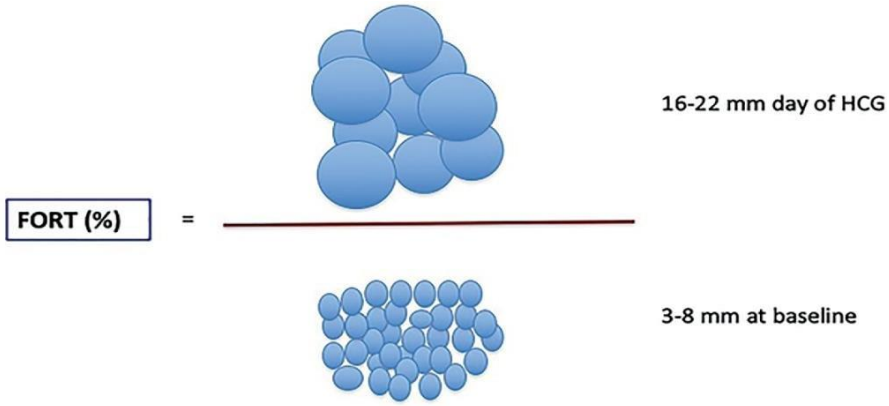

Figure 1. Follicular output rate.

Some of these metrics, such as the follicular output rate (FORT) **(Figure 1)** and the follicle-oocyte index (FOI) **(Figure 2)**, may better capture the dynamic character of follicular growth in response to exogenous gonadotropins. FORT was developed to measure the ovary's follicular competence. It is defined as the ratio of the number of pre-ovulatory follicles acquired after OS completion over the pool of AFC. Fort groupings were divided into low, medium, and high categories. The ratio of antral follicular count (AFC) to the number of oocytes recovered during pick-up is known as FOI. Since just a tiny portion of AFC was recruited during OS, there may be room to modify these women's fates in subsequent OS, according to low FOI interpretation [3].

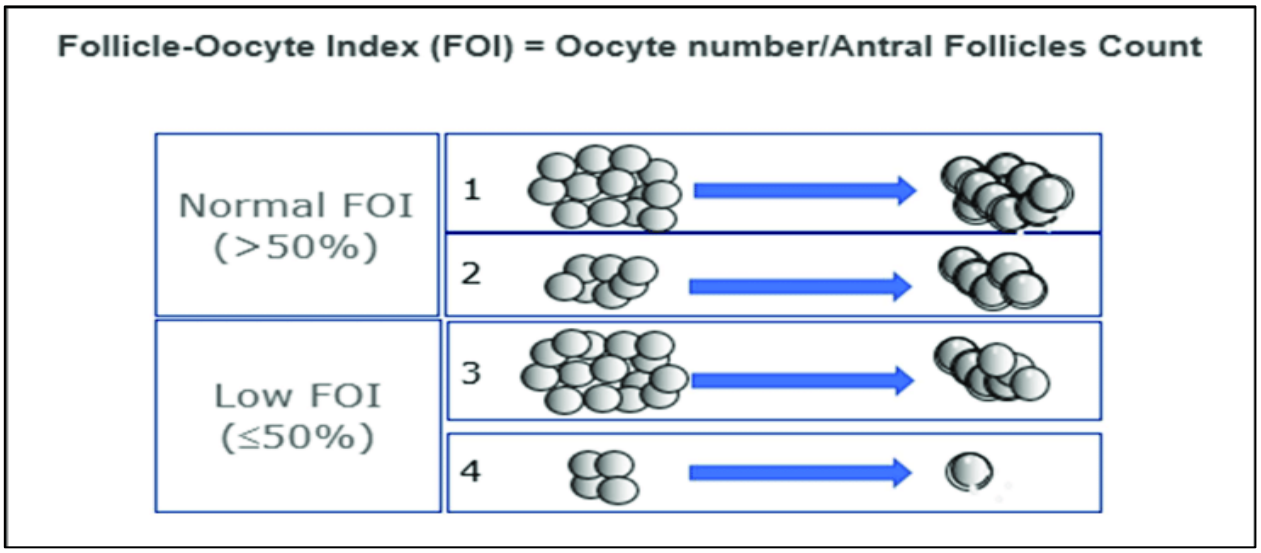

Figure 2. Follicle-oocyte index

Section A-Review Paper
ISSN 2063-5346

When using assisted reproductive technologies to treat infertility, follicular recruitment and development in response to controlled ovarian hyperstimulation (COH) using gonadotropins are crucial [4]. For both prognosis and therapy individualization, the prediction of this ovarian response, which is assessed by the ovarian reserve, is essential. Since both low and hyper-responses might result in cycle cancellation and higher expenses, treatment individualization comprises choosing the optimum GnRH analogue protocol and first gonadotropin dosage to produce the appropriate ovarian response. A poor ovarian response may reduce the likelihood of getting pregnant, whereas an excessive response raises the possibility of ovarian hyperstimulation syndrome [5].

Age, genetics, and environmental variables can all have an impact on the complicated systems that govern ovarian reserve [6]. Over the past few decades, a number of ovarian reserve indicators have been researched, however a perfect marker is still lacking. Tests of the ovarian reserve can predict responses more accurately than age alone does. Despite having 10–20% false-positive rates, the antral follicle count (AFC) and anti-Müllerian hormone (AMH) are now thought to have the greatest sensitivity and specificity for predicting the ovarian response [7]. Nomograms, which are primarily based on a woman's age, AMH, AFC, and day 3 FSH levels, have been developed in recent years to help determine the individual FSH starting dose in IVF cycles, which will lower costs and increase the likelihood of pregnancy [8].

One of the most often investigated variables in clinical studies on IVF therapy is ovarian response [9]. Traditionally, the primary indicator of ovarian response to gonadotropin treatment has been the number of oocytes recovered [10]. Although it is substantially connected with the number of antral follicles present prior to ovarian stimulation, the number of pre-ovulatory follicles discovered at the conclusion of COH is not a reliable indicator of the antral follicles' sensitivity to FSH [11]. However, it's possible that both the size and the number of antral follicles are significant. It is known that the Follicular Output RaTe (FORT), which is calculated by dividing the number of preovulatory follicles (16-20 mm) by 100 by the antral follicle count (3-8 mm), is correlated to the results of IVF, including pregnancy rates [12]. It assesses the proportion of follicles that were responsive to FSH.

Section A-Review Paper
ISSN 2063-5346

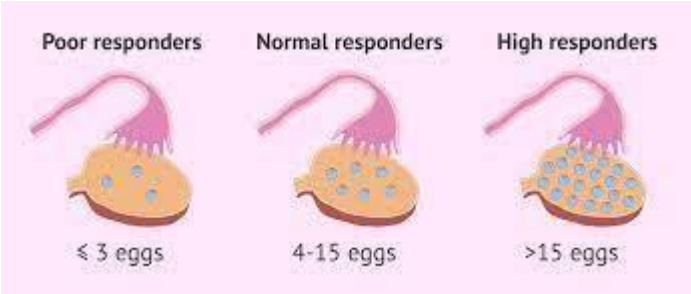

Figure 3. Oocyte retrieved per follicle.

Since several studies demonstrate a relationship between a follicle's diameter and its endocrine activity, the classification of different size groups may be pertinent. [13]. According to a previous study, women who became pregnant had the most antral follicles, which ranged in size from 5 to 10 mm. [14]. Another research found that while the number of follicles between 2 and 6 millimetres (mm) decreases with ageing, the number between 7 and 10 mm remains steady, indicating that follicles under 6 mm may be an indicator of the ovary's functional capability. It is still not entirely clear how antral follicles become sensitive to FSH. However, healthy and differentiated granulosa cells have a sufficient reactivity to FSH [15].

2. SPECIFIC STUDY

Le et al., 2023 was to determine the variables affecting the follicular output rate (FORT) and follicle-to-oocyte index (FOI) in infertile Vietnamese women, as defined by the Poseidon categorization of poor responders. Women who had IVF/ICSI therapy were included in this cross-sectional investigation. The GnRH antagonist was used to stimulate the ovaries under control in all of the patients. Groups 1 (n = 44), 2 (n = 33), 3 (n = 54), and 4 (n = 112) each had a total of 243 cases. Age, infertility type, menstrual cycle, waist-hip ratio (WHR), endocrine tests, total retrieved oocytes, and body mass index (BMI) were statistically different between the four groups (p 0.05). Each individual had an average of 7.27 oocytes, with group 1 having the most (10.77) and group 4 having the fewest (5.59). BMI (ß: 0.146), FSH beginning dosage (ß: 0.146), and AMH (ß: 0.166) all had a link with FORT. FOI and other factors showed no statistically significant association. AMH concentration and the first dosage of FSH for ovarian stimulation were shown to be favourably connected with FORT in patients with poor prognoses, but BMI was negatively correlated with FORT. No other characteristics were discovered to be correlated with FOI.

Section A-Review Paper
ISSN 2063-5346

Cesarano et al., 2022 429 patients were used for the retrospective analysis, and three major indices were examined in them: the ratio of recovered oocytes to the total dosage of gonadotropin delivered (FORT, FOI, and OSI). These indices were said to be able to predict the cumulative ART result in women older than 39 years. They discovered that both OSI and FOI successfully predict embryo culture, OSI is more precise. The quantity of M11 oocytes collected is substantially correlated with OSI, FOI, and FORT.

Boynukalin et al., 2022 conducted a prospective investigation with 86 individuals to assess the influences on FORT, FOI, and OPF that were induced by a GnRH agonist in hyper-responders. For the purpose of identifying women who have ovarian resistance to gonadotropin stimulation, FORT, FOI, and OPF can be employed as substitute measurements. It is important to emphasise the variables that impact these metrics. These findings may suggest ways to use more gonadotrophin or the addition of LH to regulate ovarian stimulations in the best possible way.

Chen et al., 2020 POSEIDON criteria for low prognosis patients were explored, including FORT and FOI. They came to the conclusion that ovarian sensitivity was highest in group 3 (young women with poor ovarian reserve), followed by group 4 (women at advanced age with poor ovarian reserve), group 1 (young women with good ovarian reserve), and group 2, (women at advanced age with good ovarian reserve), and it was lowest in group 2. altering the OS protocol is suggested for individuals with low ovarian sensitivity, whereas altering the gonadotropin beginning dosage is preferred for people with normal ovarian sensitivity.

Bessow et al., 2019 92 women with IVF indications, regular cycles, and no abnormalities in either ovary were included in a prospective cohort study to see if the diameter of the follicular cohort (AFC6: 6 mm or AFC > 6: > 6 mm) might be a predictor of ovarian response, as measured by FORT. The women's median FORT was 43.30%, and their mean age (SD) was 36.03 years. An association between the FORT and AFC6 was discovered ($r = 0.237$), but not between the FORT and AFC > 6 ($r = 0.055$). The inverse relationship between FORT and AFC6 shows that those follicles responded to exogenous FSH less well.

Hassan et al., 2017 sought to see if follicular output rate (FORT) may predict the clinical pregnancy rate in patients having IVF/ICSI for unexplained infertility. According on FORT tertile values, 303 women having IVF/ICSI for unexplained infertility were split into three

groups. Pre-ovulatory follicle count/antral follicle count divided by 100 is how FORT was determined. The clinical pregnancy rate (29.9%, 43.3%, and 57.8%), number of retrieved oocytes (5.4, against 6.8, and 7.4), and fertilisation rate (48.4, versus 55.3 and 57.4) all increased gradually and significantly from the low to the high FORT groups. A multivariate logistic regression study showed that there was no apparent confounding influence on the relationship between FORT and pregnancy. The study concluded that FORT is an independent variable affecting the clinical pregnancy rate in IVF/ICSI cycles. Higher FORT values had better oocyte yield and clinical pregnancy rates in women with unexplained infertility undergoing IVF/ICSI with potentially normal ovarian response.

Zhang et al., 2013 Follicular output rate (FORT) was evaluated for its real accuracy as a predictive indication of response to FSH and reproductive competence following IVF/intracytoplasmic sperm injection. The study involved 1643 cycles in all, including 140 PCOS patients who received ovarian stimulation. FORT was determined as the preovulatory follicle count on the stimulation day divided by 100 and the baseline number of small antral follicles (3–10 mm in diameter). Using tertile values, low, medium, and high FORT groups were established. For 1503 non-PCOS cycles, FORT gradually raised the number of retrieved oocytes, the total number of transferable embryos, the percentage of high-quality embryos, embryo implantations, and clinical pregnancies. Patients with PCOS who successfully achieved clinical pregnancy had substantially lower FORT than those who did not (0.56 0.21 versus 0.66 0.29, P = 0.031). With medium FORT compared to low and high FORT, the frequencies of fertilisation and good-quality embryos were considerably greater (P = 0.001 and P = 0.047, respectively). Better results from IVF/ICSI may be predicted by medium FORT in PCOS patients and high FORT in non-PCOS individuals.

Gallot et al., 2012 found a qualitative indicator of ovarian function and checked to see if the Follicular Output RaTe (FORT), which measures how sensitive antral follicles are to FSH injection, is associated with the ability of those follicles to become pregnant. 322 IVF-ET candidates between the ages of 25 and 43 who underwent controlled ovarian hyperstimulation with comparable starting FSH dosages were the subject of the study. Pre-ovulatory follicle (16-22 mm) count (PFC) and antral follicle (3-8 mm) count (AFC) were carried out on the day when hCG was administered and at the time that pituitary suppression was achieved (before FSH

therapy). By multiplying PFC by 100/AFC, the FORT was computed. Tercile values were used to divide FORT groups into low (42%; n=102), medium (42-58%; n=123), and high (>58%; n=97). 50.6% on average (range: 16.7 to 100.0%) was the FORT. Clinical pregnancy rates per oocyte retrieval went risen steadily from the low to the high FORT groups (33.3, 51.2, and 55.7%, respectively), and this association, as shown by logistic regression, was unaffected by the confounding factors, including the ages, AFC, and PFC of the women. The link between the success of IVF-ET and the proportion of antral follicles that mature before ovulation and successfully react to FSH injection implies that FORT may be a qualitative indicator of ovarian follicular competency. To verify these findings, more research is required with broader inclusion criteria and more individualised techniques.

Genro et al., 2012 evaluated if antral follicles respond less responsively to FSH treatment in carriers of common single-nucleotide polymorphisms (SNPs) of the FSH receptor (FSHR), as determined by the FORT. A prospective study was conducted by the study in a university hospital. There were 124 Caucasian IVF-ET candidates in the study population. The FSHR 307Ala and 680Ser variations were examined as distinct genes and in haplotypes. On cycle day 3, serum levels of FSH, estradiol (E2), and anti-Müllerian hormone (AMH) were assessed. Preovulatory follicle (16-22 mm) count and antral follicle (3-8 mm) count were carried out on the day of hCG injection and at the time pituitary suppression was achieved, respectively. The FORT (PFCx100/AFC) measures the antral follicle's response to the injection of FSH. Between SNPs carriers and controls, data on baseline and IVF-ET characteristics were comparable. Moreover, FORT was comparable for various haplotypes Thr307-Asn680 (45.9%) and Ala307-Ser680 (39.4%) and 307Thr/Ala-Ala/Ala (41.1%; 5.0-91.6%) vs 307Thr/Thr (44.4%; 17.3-83.3%) and in 680Asn/Ser-Ser/Ser (40.0%; 5.0-91.6%) versus 680Asn/Asn (42.2%; 8.3-90.0%) carriers. The presence of SNPs of FSHR 307Ala and 680Ser has no effect on the antral follicle response to FSH as determined by the FORT.

Genro et al., 2011 aimed at determining if blood AMH levels and the antral follicle's receptivity to exogenous FSH in normo-cycling women are related. On cycle day 3, patients receiving controlled ovarian hyperstimulation (COH) with a time-release GnRH agonist and standardised FSH dosages had their serum levels of AMH, estradiol (E2), and FSH analysed prospectively. Follicle counts were performed on 162 individuals at baseline (small antral

follicles, 3-8 mm), on the day of hCG (pre-ovulatory follicles, 16-22 mm), and after pituitary suppression and before FSH treatment. The ratio of pre-ovulatory follicle count on dhCG 100/small antral follicle count at baseline was used to calculate the Follicular Output RaTe (FORT), which estimates the antral follicle response to FSH. The number of small antral follicles at baseline and the number of pre-ovulatory follicles on dhCG were favourably linked with serum AMH levels (r = 0.59 and 0.17, respectively). Age, BMI, basal E2 and FSH levels, or the woman's overall FORT of 47.5 1.4%, had no effect. Contrarily, regardless of the length of COH and total FSH dosage, multiple regression analysis revealed a negative correlation between FORT and AMH levels (r = 0.30). The proportion of follicles that respond to FSH by maturing before to ovulation is adversely and independently correlated with serum AMH concentrations. This result is consistent with the theory that AMH reduces follicular sensitivity to FSH, even if the mechanisms behind it are yet unknown.

3. CONCLUSION

Ovarian resistance to gonadotropin stimulation is affected by many non-exclusive variables. Gonadotropin and receptor genotypes drive its pathogenesis. These patients are best identified by genetic phenotyping of relevant variants. The FORT and FOI may identify women with ovarian resistance (hypo-responsiveness) to gonadotropin stimulation until genotyping testing becomes generally accessible. FOI, which counts retrieved oocytes, may be a superior way to measure ovarian reserve use during stimulation. The best way to treat hypo-response to OS is to use higher FSH daily doses alone or in combination with recombinant LH supplementation.

CONFLICT OF INTEREST

No conflict of interest is declared.

ACKNOWLEDGEMENT

The authors highly acknowledge the help received from college management.

4. REFERENCES

1. Lai Q. The significance of antral follicle size prior to stimulation in predicting ovarian response in a multiple dose GnRH antagonist protocol. Int J Clin Exp Pathol. 2013;6:258–266.

2. La Marca, A. & Sunkara, S. K. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod. 20, 124–140 (2014).

3. van der Gaast, M. H. Optimum number of oocytes for a successful first IVF treatment cycle. Reprod Biomed. 13, 476–480 (2006).

4. Aboulghar, M. A. & Mansour, R. T. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. Hum Reprod. 9, 275–289 (2003).

5. Sunkara SK, et al. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod. 2011;26:1768–1774.

6. Tal R, Seifer DB, Tal R, Seifer DB. Potential mechanisms for racial and ethnic differences in antimüllerian hormone and ovarian reserve. Int J Endocrinol. 2013;2013:818912.

7. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod. 2006;12:685–718.

8. Lensen SF, et al. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI) Cochrane Database Syst Rev. 2018;2:CD012693.

9. Nyboe Andersen A, et al. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial. Fertil Steril. 2017;107:387–396.e4.

10. Li HWR, Lee VCY, Ho PC, Ng EHY. Ovarian sensitivity index is a better measure of ovarian responsiveness to gonadotrophin stimulation than the number of oocytes during in-vitro fertilization treatment. J Assist Reprod Genet. 2014;31:199–203.

11. Tomás C, Nuojua-Huttunen S, Martikainen H. Pretreatment transvaginal ultrasound examination predicts ovarian responsiveness to gonadotrophins in in-vitro fertilization. Hum Reprod. 1997;12:220–223.

12. Gallot V, et al. Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the follicular output RaTe (FORT) may predict in vitro fertilization-embryo transfer outcome. Hum Reprod. 2012;27:1066–1072.

13. Genro VK, et al. Serum anti-Müllerian hormone levels are negatively related to follicular output RaTe (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation. Hum Reprod. 2011;26:671–677.

14. Haadsma ML, et al. The number of small antral follicles (2-6 mm) determines the outcome of endocrine ovarian reserve tests in a subfertile population. Hum Reprod. 2007;22:1925–1931.

15. Pohl M, et al. Number and size of antral follicles as predictive factors in vitro fertilization and embryo transfer. J Assist Reprod Genet. 2000;17:315–318.

16. Le MT, Nguyen ND, Tran NQ, Le DD, Nguyen QH, Cao TN. Factors Influencing Follicular Output Rate and Follicle-to-Oocyte Index in POSEIDON-Defined Low-Prognosis Women in Vietnam: A Cross-Sectional Study. Int J Women's Health. 2023:523-32.

17. Cesarano S, Pirtea P, Benammar A, De Ziegler D, Poulain M, Revelli A, Benedetto C, Vallée A, Ayoubi JM. Are There Ovarian Responsive Indexes That Predict Cumulative Live Birth Rates in Women over 39 Years?. J Clin Med. 2022;11(8):2099.

18. Boynukalin K, Gultomruk M, Yarkiner Z. What effects the new markers of ovarian stimulation: follicular output rate (FORT), follicule-to-oocyte index (FOI) and oocytes retrieved per follicules (OPF)?. Fertil Steril. 2022;118(4):e317-8.

19. Chen L, Wang H, Zhou H, Bai H, Wang T, Shi W, Shi J. Follicular output rate and Follicle-to-Oocyte Index of low prognosis patients according to POSEIDON criteria: a retrospective cohort study of 32,128 treatment cycles. Frontiers Endocrinol. 2020;11:181.

20. Grynberg M, Labrosse J. Understanding follicular output rate (FORT) and its implications for POSEIDON criteria. Front Endocrinol. 2019;10:246.

21. Bessow C, Donato R, de Souza T, Chapon R, Genro V, Cunha-Filho JS. Antral follicle responsiveness assessed by follicular output RaTe (FORT) correlates with follicles diameter. J Ovarian Res. 2019;12(1):1-6.

22. Zhang N, Hao CF, Zhuang LL, Liu XY, Gu HF, Liu S, Chen ZJ. Prediction of IVF/ICSI outcome based on the follicular output rate. Reprod Biomed Online. 2013;27(2):147-53.

23. Gallot V, Berwanger da Silva AL, Genro V, Grynberg M, Frydman N, Fanchin R. Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the

Follicular Output RaTe (FORT) may predict in vitro fertilization-embryo transfer outcome. Human Reprod. 2012;27(4):1066-72.

24. Genro VK, Matte U, De Conto E, Cunha-Filho JS, Fanchin R. Frequent polymorphisms of FSH receptor do not influence antral follicle responsiveness to follicle-stimulating hormone administration as assessed by the Follicular Output RaTe (FORT). J Assist Reprod Genet. 2012;29:657-63.

25. Genro VK, Grynberg M, Scheffer JB, Roux I, Frydman R, Fanchin R. Serum anti-Müllerian hormone levels are negatively related to Follicular Output RaTe (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation. Human Reprod. 2011;26(3):671-7.