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Original Research Article

Average gonadotropin dosage per follicle as a predictor of ovarian response

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ABSTRACT

Background: In ovarian stimulation, oocytes retrieved are commonly used to assess response to gonadotropins. Markers like FORT, FOI, and OSI have been proposed but show poor prediction of IVF outcomes. Each is limited by various clinical and technical factors. A novel index, average gonadotropin dosage per preovulatory follicle offers better prediction of ovarian response and clinical pregnancy rate, aiding in personalized stimulation and helping anticipate OHSS risk and cycle cancellations

Methods: This retrospective cohort study included 238 sub fertile women who underwent IVF at the Institute of Reproductive Medicine, Madras Medical Mission Hospital, from January 2019 to December 2023. It aimed to evaluate a new marker, average gonadotropin dosage per preovulatory follicle as a predictor of ovarian response and pregnancy outcomes. The index was calculated by dividing the total gonadotropin dose by the number of 16–22 mm follicles on trigger day. Patients were grouped by the 50th percentile, and stimulation parameters, MII oocyte ratio, clinical pregnancy rate, and live birth rate were compared between groups.

Results: Group A showed significantly higher oocyte yield, MII oocyte ratio, and fertilization rate ($p<0.001$). Clinical pregnancy and live birth rates were higher in Group A with statistical significance compared to Group B

Conclusion: Average gonadotropin dose per follicle proved to an ovarian response predictor in our study.

Keywords: Ovarian stimulation, Preovulatory follicle, Gonadotropin dose per follicle, Ovarian response.

INTRODUCTION

Ovarian stimulation is designed in assisted reproduction technology, to obtain a specific number of high-quality eggs for in vitro fertilization. This process enables the selection of the best quality embryos for transfer. Previous research has shown a strong correlation between the number of oocytes retrieved and the live birth rate (LBR) in ART.[1] While the goal of ovarian stimulation is to obtain an optimal number of oocytes, this may not be feasible for all patients. Based on the number of oocytes collected, patients are typically categorized as hyper responders, normal responders, or poor responders.[2] Accurate classification primarily depends on an ovarian reserve assessment before starting the treatment cycle.[3] Common indicators of ovarian reserve include age, basal hormone levels such as follicle-stimulating hormone (FSH), estradiol (E2), Anti-Müllerian Hormone (AMH) and antral follicle count (AFC).

With advancements in ART, several indicators have been introduced such as the follicle output rate (FORT), follicle-to-oocyte index (FOI), and ovarian sensitivity index (OSI), to assess ovarian response and sensitivity, as well as to predict pregnancy outcomes.[4-8] While these indexes appear useful for evaluating ovarian response, certain limitations should not be overlooked. Some patients have slow response to FSH, and require larger doses of

Gonadotropins which is not consistent with age, BMI, ovarian reserve and other indicators.[9-11] In women of advanced age with unexplained infertility, FOI, FORT, and OSI do not demonstrate a stronger or more informative correlation with live birth rates than the individual factors used in their calculation, such as the number of oocytes retrieved, antral follicle count (AFC), the number of pre-ovulatory follicles (PFC), and the total FSH dose.[12]

There is a need to further investigate indicators that reflect ovarian response or to use a combination of multiple indicators for a more accurate evaluation of ovarian sensitivity to Gonadotropin stimulation. Studies have shown that both total Gonadotropin dosage and the number of pre-ovulatory follicles (PFC) are key measures of ovarian response. Their ratio, referred to as the "average Gonadotropin dosage per follicle," may better represent ovarian response than either parameter alone. This retrospective study was conducted to assess the usefulness of average Gonadotropin dosage per follicle as a marker of ovarian response during stimulation and its potential in predicting pregnancy outcomes.

METHODS

The present study was retrospective observational study carried out in the Institute of reproductive medicine, Madras Medical Mission hospital between 2019 and 2023. The study was carried out among all women who underwent IVF treatment for Subfertility during the study period. Ethical clearance for the study was obtained from the institutional ethics committee. Total women who were enrolled were 258.

Inclusion criteria

The inclusion criteria were Age <40 years, Body mass index (BMI) ≤30 kg/m^2, baseline FSH≤10 mIU/ml, treated with gonadotropin releasing hormone (GnRH) antagonist protocol, Basal AFC >3, AMH> 1.5 ng/ml, Normozoospermia.

Exclusion criteria

It includes congenital uterine anomalies, endometrium diseases including endometrial atypical or complex hyperplasia, endometrial polyp and intrauterine adhesion, adenomyosis, history of ovarian or uterine surgery, spontaneous abortion 3 times or more (including biochemical pregnancy loss).

Data collection

Data were collected were from case sheets at the medical records department of the institution using a structured proforma. The data recorded include age, BMI, menstrual history, type of infertility and years of infertility. Baseline values of LH, E2, AMH and AFC were recorded. The other factors recorded included the gonadotrophin dose used and duration of stimulation were also recorded. The type of trigger provided and pre ovulatory follicles were noted down. Average gonadotropin dosage per follicle was calculated as ratio of total administered Gonadotropin dosage and pre ovulatory follicle (>16 mm).

The patients were categorized into two subgroups based on percentiles: Group A included those below the 50th percentile, Group B comprised those above 50th percentile. Each group contained 129 patients. The 50th percentile of average gonadotropin dosage per follicle was 301 IU.

Number of oocytes retrieved with number of MII oocytes collected as a measure of ovarian response was calculated as the primary outcome, clinical pregnancy and live birth were calculated as secondary outcome.

All patients underwent ovarian stimulation using a standard flexible GnRH antagonist protocol with the administration of recombinant FSH at a daily dose of 150–225 IU. The initial Gn dosage was determined based on factors such as age, BMI, basal FSH, and antral follicle count (AFC). Ovarian response was monitored through transvaginal ultrasound and hormone measurements, allowing for adjustments in Gonadotropin administration if necessary. GnRH antagonist at 0.25 mg per day was introduced when the leading follicle reached a diameter of over 14 mm or serum estradiol (E2) levels exceeded 300 pg/mL. This co-treatment continued until the trigger day.

The preovulatory follicle count (PFC) was defined as the number of follicles measuring 16-22 mm in diameter in both ovaries on the day of the trigger. The average gonadotropin (Gn) dosage per follicle was calculated by dividing the total administered FSH dose by the PFC. The follicular output rate (FORT) was derived by dividing PFC by AFC. The follicle-to-oocyte index (FOI) was calculated as the total number of retrieved oocytes divided by AFC.

For final oocyte maturation, patients received dual trigger of 0.2 mg of triptorelin and recombinant human chorionic gonadotropin when at least three follicles reached 17 mm in diameter. Ovum pick-up (OPU) was performed 36 hours later, followed by fertilization by intracytoplasmic sperm injection (ICSI). The patients underwent HRT cycle of FER in the subsequent cycle. The patients underwent HRT cycle of FER in the subsequent cycle.

In artificial endometrial preparation, patients received oral estradiol valerate from the second day of the menstrual cycle for 10-14 days. When endometrial thickness reached ≥8 mm, progesterone supplementation was initiated.

Embryo transfer was done on the 4th or 6th day of progesterone administration, depending on the embryo's developmental stage. Upto two high quality embryos or a single blastocyst was transferred. Luteal phase support was given with 10 mg dydrogesterone twice daily and 100 mg of injection of micronized Progesterone Upon pregnancy confirmation, luteal phase support continued until 8-10

weeks and stopped. A positive β-hCG result was defined as a plasma β-hCG level exceeding 10 IU/l, measured 10–14 days after embryo transfer. Clinical pregnancy was confirmed by the presence of a gestational sac on ultrasonography.

Ongoing pregnancy was defined as the detection of fetal heart activity on ultrasound from 12 weeks of gestation onward. Patients were subsequently monitored until live birth.

Blood samples and hormone assays

Serum levels of progesterone (P), estradiol (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured using a competitive chemiluminescence immunoassay. Blood samples were collected at a consistent time between 8:00 A.M and 8:30 A.M to minimize potential fluctuations due to circadian rhythm variations. All assays were conducted following the manufacturer's guidelines.

Statistical analysis

Data in each group was compared with pregnancy outcomes and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) v 23. Comparisons were analysed employing student's t test and Analysis of variance (ANOVA), whichever is relevant. The data was considered to be statistically significant when $p<0.05$.

RESULTS

Baseline characteristics were compared between the two groups, mean age, BMI, Basal LH, Basal Estrogen levels did not significantly differ between the two groups, while Basal FSH was significantly lower in Group A and mean AFC was higher in Group A with statistical significance (Table 1).

Stimulation characteristics significantly differed in both groups. The 50th percentile of average gonadotropin dosage per follicle was 301 IU. Group A had lower gonadotrophin dose requirement and higher levels of Estradiol on the trigger day compared to Group B with statistical significance. There was no difference on the total duration of stimulation (Table 2).

FORT, FOI, OSI were higher for patients of Group A implying higher ovarian response. Thus, gonadotrophin dosage per follicle, consistent with other ovarian response indicators predicts the ovarian response concisely (Table 3).

Embryological outcome was better in Group A, with higher number of retrieved oocytes and M2 oocytes, with statistical significance. However, there was no difference in good quality embryos in both groups (Table 4).

Group A had higher clinical pregnancy rate and live birth rate than Group B with statistical significance. Group A had higher first trimester pregnancy losses (Table 5).

Table 1: Baseline characteristics.

Patient characteristics	Group A (n=129)	Group B (n=129)	P value
Mean age (in years)	30.59±3.614	31.77±3.928	0.016
Basal FSH(IU/l)	5.03±1.082	6.98±1.101	<0.001
Basal LH(IU/l)	4.56±2.107	3.86±3.338	0.064
Basal E2(pg/ml)	34.76±9.391	34.43±8.234	0.774
Mean BMI	27.5±3.626	27.9±3.060	0.457
Mean AFC	22.06±8.341	14.11±5.246	<0.001

Table 2: Stimulation characteristics.

Stimulation characteristic	Group A (<50th Centile) n=129	Group B (>50th Centile) n=129	P value
Initial Gn dose (IU)	284.5±4.5504	359.4±61.8059	<0.001
Total Gn dose (IU)	3012.6±733.09	3894.8±648.48	<0.001
Gn duration (days)	10.41±0.969	10.43±0.988	0.447
E2 on day of trigger (pg/ml)	6056±2532	3543 ±1690	<0.001

Table 3: Ovarian response predictors.

Ovarian response predictor	Group A (< 50th Centile)	Group B (>50th Centile)	P value
Mean FORT	77.4±41.1	61.6±25	<0.001
Mean FOI	92±46.1	86±39.4	<0.001
Mean OSI	6.46±3.1	3.2±1.2	<0.001

Table 4: Embryological outcome.

Embryological outcome	Group A	Group B	P value
No of oocytes retrieved	18.11±6.213	12.17±4.009	<0.001
No of M II oocytes retrieved	13.23±4.884	8.61±3.258	<0.001
No of grade an embryo (percentage)	47.8±25.77	47.59±25.69	0.946

Table 5: Pregnancy outcome.

Pregnancy outcome	Group A	Group B	P value
Clinical pregnancy rate	51.3	45.4	0.002
Live birth rate	44.5	39.5	0.004
I TM loss	7.6	5.9	0.605
II TM loss	0.8	1.7	0.561

DISCUSSION

Accurately predicting ovarian response is essential for achieving the most effective and personalized ovarian stimulation. This allows clinicians to offer better guidance to patients and assess the risk of complications following ovarian stimulation, such as prolonged gonadotropin usage with increasing gonadotropin requirement, poor ovarian response, cycle cancellation, or ovarian hyperstimulation syndrome (OHSS). Biological and biochemical markers like antral follicle count (AFC) and anti-Müllerian hormone (AMH) have been shown to predict both poor and excessive ovarian response with relatively high accuracy.[2] However, previous research indicates that these biomarkers provide only a "static" snapshot of ovarian reserve, failing to capture the "dynamic" nature of follicular development in response to external ovarian stimulation4.

Follicular output rate (FORT) was first introduced by Genro et al in 2011 to assess ovarian response during stimulation. It is determined by calculating the ratio between the number of pre-ovulatory follicles developed in response to follicle-stimulating hormone (FSH) administration and the initial pool of small antral follicles. Subsequent studies suggested that a FORT value below 0.30 indicates low ovarian sensitivity6.[6,7] As one of the key indices for evaluating ovarian response, FORT has been examined across various populations and ovarian stimulation protocols.

Research by Hassan et al concluded that FORT is an independent factor influencing clinical pregnancy rates in IVF/ICSI cycles. Higher FORT values were associated with improved oocyte yield and increased clinical pregnancy rates in women with unexplained infertility undergoing IVF/ICSI who likely had a normal ovarian response.[13] In patients with polycystic ovary syndrome (PCOS) undergoing IVF-ET, FORT was also a valuable tool for assessing ovarian reactivity. A high FORT was linked to better embryo quality and successful frozen embryo transfer (FET), leading to favourable pregnancy outcomes.[14] For managing hypo-responders in assisted reproductive technology (ART), FORT has proven to be a crucial quantitative and qualitative measure. Reduced FSH sensitivity, as indicated by FORT, should be factored into decisions regarding treatment protocols, gonadotropin selection, and stimulation dosages for hypo-responders.[15] However, this index has some limitations that must be acknowledged. Notably, FORT does not account for the actual number of oocytes retrieved, which has a strong correlation with live birth rates.[1]

In 2018, the FOI was proposed to address the ovarian sensitivity. It was calculated as the ratio between the total number of oocytes collected at the end of ovarian stimulation, and the number of antral follicles available at the start of stimulation. FOI ≤0.50 indicated low ovarian sensitivity and FOI >0.50 for normal ovarian sensitivity. Hypo-responsiveness and suboptimal/poor response were not synonymous. FOI might be used alone or combined with FORT to most optimally reflect the ovarian response to Gn. However, FOI could be influenced by the initial Gn dosage, genetic or environmental factors, asynchronous follicular development, and technical issues during triggering and OPU.[4] Another indicator of ovarian capacity to produce oocytes in response to hormonal stimulation is the ovarian sensitivity index (OSI). It is calculated by dividing the total administered FSH dose by the number of retrieved oocytes. Initially developed by Biasoni et al, its definition was later refined.[8,16,17] OSI serves as a valuable tool for evaluating ovarian sensitivity to exogenous gonadotropins and can help adjust stimulation protocols in future IVF cycles.

A retrospective comparative cohort study involving 2,150 women undergoing their first IVF cycle with a long-agonist protocol confirmed OSI as a highly reliable measure of ovarian responsiveness to recombinant FSH, making it useful for estimating the required FSH dose.[18] Another retrospective cohort study focusing on women aged 39 and older undergoing their first ART cycle with an antagonist protocol suggested that OSI was the most accurate predictor of cumulative implantation rate and

cumulative live birth rate (CLBR). While both OSI and the follicular output index (FOI) were effective in predicting successful embryo culture, OSI demonstrated greater accuracy.[19] However, OSI has some limitations, as it does not account for the type of gonadotropin used (e.g., whether LH or an LH analog was included) or the antral follicle count (AFC).

The number of follicles on the trigger day in relation to the level of hormonal stimulation reflects how many units of exogenous gonadotropins (Gn) are required to develop each follicle. This measurement helps doctors minimize the impact of factors such as oocyte retrieval (OPU) techniques, improper trigger timing, and other variables. As a result, average gonadotropin level per follicle can be used alone or in combination with other indices to more accurately evaluate ovarian response.

In this retrospective study, patients with the lowest values for this index (Group A) were the youngest and had the best "static" ovarian reserve markers, such as baseline FSH and AFC. Additionally, despite receiving the lowest total Gn dose and undergoing the shortest stimulation duration, they produced the highest number of oocytes and good-quality embryos. Other ovarian response indicators, including FORT, FOI, and OSI, were also most favourable in this group. Regarding ART outcomes, patients with low (Group A). Gonadotropin dosage per follicle had a higher likelihood of achieving pregnancy or live birth compared to those with higher values for this index (Group B).

This study highlights that average gonadotropin dose per follicle; a new marker helps in predicting ovarian response accurately. The limitations of the study were that it was a single centre study. A multicentre study would have yielded more generalisable results. The patients of this study underwent antagonist protocol and whether this could be extrapolated to other protocol of ovarian stimulation needs further study. The sample size in the study was limited by the duration of the study.

CONCLUSION

Average gonadotropin dosage per follicle, along with other ovarian response predictors predicts the ovarian response precisely and could be used to predict pregnancy rate. This novel index could be used to counsel patients about the ART outcome and could be beneficial to prevent economic burden to the patient in case of early cancellation of cycles with poor response.

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