PROGNOSTIC USE OF MEAN OVARIAN VOLUME IN IN-VITRO FERTILIZATION CYCLE: A PROSPECTIVE ASSESSMENT

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ABSTRACT

Successful outcomes of IVF are mainly dependent on the response to controlled ovarian hyperstimulation via the number of quality oocytes obtained. Ovarian volume measurements can predict the response to stimulation in IVF treatment. The study was designed to determine the predictive value of mean ovarian volume and define prognostic threshold measurement. The prospective cohort study was done at the University of Benin Teaching Hospital Assisted Conception Unit involving 106 women undergoing IVF treatment. All patients had basal ovarian volume and FSH measurement. In all the patients, the test was followed by a standard IVF treatment. The mean number of follicles, and mean of oocytes retrieved significantly increased with increasing mean ovarian volume ($P < 0.0001$), while the mean dose of HMG used for stimulation significantly decreased with increasing MOV ($P < 0.0001$). Multiple linear regression analysis showed that basal ovarian volume ($r = 0.488$), ($P < 0.001$) had a positive correlation with the number of oocytes retrieved, hence predicted good response. Age [($r= -0.433$) ($P < 0.001$) and basal FSH [($r = -0.389$) ($P < 0.001$) showed a negative correlation with the number of oocytes retrieved. Threshold analysis revealed a trend toward higher cancelation rate associated with MOV < 3cm³ (38.2% vs 21.1%) and lower number of oocyte retrieved with MOV < 3cm³ (0.6% vs 26%). The study suggests that mean ovarian volume provides better prognostic information on the occurrence of poor response during hormone stimulation for IVF than does the patient's chronological age and basal FSH.

KEYWORDS: infertility, in-vitro fertilisation, ovarian volume, ovarian stimulation, prediction

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INTRODUCTION

In-vitro fertilisation (IVF) has emerged as widely accepted management for many cases of infertility which defy conventional modes of treatment.[1] However, the prohibitive cost, especially in our environment, has engendered advances in IVF aimed at improving its success rate.[1,2]

Successful outcomes following assisted reproductive technique (ART) amongst other factors are largely dependent on the response to controlled ovarian hyperstimulation (COH), vis-à-vis the number of quality oocytes obtained, and ultimately the number of embryos available for transfer.[3] Given the marked variability in ovarian response among in-vitro fertilisation patients, the choice of stimulation protocol must be individualised, both for women with a history of prior cycles and for patients in their first cycle of IVF treatment.[2,3,4]

The concept of the diminished ovarian reserve has gained general acceptance in reproductive medicine.[2] In IVF, the association of poor ovarian response due to diminished ovarian reserve with a significant decline in success rates is well documented.[2,3] It is generally acknowledged that reproductive ageing is related to both a quantitative and a qualitative reduction of the primordial follicle pool.[3,4] As women age, there is a corresponding reduction in the responsive primordial pool, and consequently, the ovarian reserve diminishes leading to declining rates of both spontaneous and treatment-induced pregnancies.[4,5]

Ovarian reserve(OR) is currently defined as the number and quality of the follicles left in the ovary at any given time.[3,4] It is an estimate of the primordial follicle pool in the ovaries and therefore an indication of reproductive age rather than chronological age;[5] hence it is a parameter for calculating predictive potential and the remaining reproductive lifespan of a woman.[4,5] An accurate measure of the quantitative OR involves the counting of all follicles present in both ovaries, as is done in post-mortem studies.[3,4,5] This is not the case in real time evaluation, where instead some factors paramterers such as the pool size are used to determine the accuracy; like an ovarian response to hyperstimulation with exogenous follicle stimulating hormone (FSH)in IVF and the occurrence of menopause or menopausal transition, as these events are quantitatively determined .[4-6]

Similarly, the quality of the oocyte from the dominant follicles at ovulation represents the other aspect of ovarian reserve.[7] While the Proxy variables for oocyte quality currently used are the pregnancy probability in infertility treatment like Intrauterine Insemination (IUI) and IVF or in the follow-up of couples during and after the initial infertility workup. Ovarian response to adequate stimulation may be considered the most accurate, though still an indirect assessment of the state of the primordial follicle pool.[6,7] However, the occurrence of pregnancy in such an individual may be influenced by not just the oocyte, but other factors such as the embryo quality.[7] Also, the predictive value of the series of hormone markers has been demonstrated in the literature.[7,8] These hormones include Cycle day 3 serum levels of Follicular Stimulating Hormone (FSH), Luteinizing hormone (LH) and Estradiol (E_2), as well as Clomiphene Citrate Challenge Test (CCCT),[7] Despite their full acceptance in clinical practice, they are laden with a variety of shortcomings.[8] Principal among these is the low specificity of the tests.[7,8] The challenge is to what extent do other, endocrine or ultrasound-based ORTs could add to the

prognostic parameters already obtained from the infertility workup or the first IVF cycle? To date, studies specifically addressing this question are scarce or do not include the full range of prognostic factors available.[8,9] The poor performance of these tests has led investigators to continue to search for other markers that will identify these patients whose ovarian reserve is insufficient to allow conception.

Considering the financial and emotional laden state of IVF treatment, it's imperative that patients are told the prognosis in the course of a series of IVF treatment cycles. However, equally important in the prediction of the outcome are the characteristics of the couple seeking treatment.[7,8,9] SO much effort has been put into the build-up of prediction models that estimate the probabilities for success prior and during subsequent IVF cycles. Intuitively, many IVF centers will use factors like female age, parity, infertility duration, the ovarian response in the first IVF attempt and embryo quality for individual counselling, albeit not through a formal prediction model.[9,10] Within this practice, ORTs also may play a certain role, and female age will be the one ORT applied almost without exception.[9] The correlation between primordial follicle population and ovarian volume has been established in the literature.[10,11] Wallace and Kelsey have proposed that transvaginal estimation of ovarian volume may be used to determine ovarian reserve for an individual woman and hence a prediction of the responsiveness to controlled ovarian hyperstimulation for quality oocytes in IVF cycles.[10] It is also documented that a decrease in ovarian volume is an early sign of depletion of the follicles and its measurement is likely to be clinically useful.[11]

Accurate methods of predicting IVF success allow for appropriate stimulation protocol selection.[11,12] There are, however, few non-invasive predictors of IVF success.[11] Such predictors are helpful to counsel patients regarding the potential success expected when undergoing these

financially and emotionally tasking treatments. Measurements of ovarian volume by transvaginal ultrasonography are reproducible among examiners, accurate and easily performed in most women.[12,13] Interobserver and intraobserver variations among transvaginal ultrasound volume measurements have been shown to be very low.[12] The rationale for using ease of application of ovarian volume is based on the fact that it reflects the number of growing antral follicles and ovarian activity,[13] and with the development of 3-dimensional (3D) ultrasound, it has become possible to overcome the problem of varied shapes of human ovaries.[12,13] However, studies comparing ovarian volume determined by 2D and 3D ultrasound have been unable to show a significant difference in precision between these two biophysical techniques.[13]

Ovarian volume measurements can predict the response to stimulation in IVF treatments.[13,14] It remains debatable if this relationship of ovarian volume and subsequent follicular development is useful in determining the final oocyte yield. The predictive benefit of this measurement has been shown by some workers[10,14] while others have failed to demonstrate any usefulness.[15] Current literature does not support a consensus threshold for cut-off values of MOV,[15,16] hence the variability in different study reports. In the present study, we intend to measure MOV in all patients billed for IVF treatment over the study period and determine the mean for our population of patient vis-à-vis the relationship to oocyte yield.

OBJECTIVES

1. To determine the predictive value of the mean ovarian volume
2. To define prognostic threshold measurements of mean ovarian volume.

WORKING HYPOTHESIS

1. Small ovaries measured on transvaginal sonography (TVS) are associated with a poor response to ovarian stimulation.
2. Mean ovarian volume measurement prediction correlates with IVF cycle outcomes in respect of Quality oocyte yield.

METHODOLOGY

SETTING AND SELECTION OF SUBJECTS

A prospective cohort study in which consecutive women attending the infertility clinic in the Department of Obstetrics and Gynaecology, University of Benin Teaching Hospital between March 2012 and June 2012 for their first IVF treatment were recruited. Women of all ages who are still cycling at the time of treatment were included, according to the recruitment guideline issued by the Human reproductive and Research Program (HRRP) of the University of Benin Teaching Hospital. The indications of conventional IVF treatment included tubal, male factor, endometriosis, unexplained and mixed factors. ICSI was performed or couples with severe semen abnormalities.

EXCLUSION CRITERIA

Poor visualisation of ovaries because of abnormal positions, the presence of ovarian pathology or presence of ovarian cyst of >10mm in diameter on scanning were excluded.

SAMPLE SIZE

The sample size was calculated from the formula.[16]

$Ns = (Z/E)^2P(1 – P)$

Where Ns = the required sample size

Z = standard score corresponding to given confidence level (A constant = 1.96)

E = the proportion of sample error in a given situation

P = the estimated proportion of incidence of cases in the population

Also, a confidence level of 95% is desired hence a tolerable error of not greater than ± 0.01 is taken.

Hence our sample size calculated as:

$Z/E^2P(1 – P)$

$(1.96/0.10)^2(0.5)(1 – 0.6)$

$19.6^2 \times 0.20$

$Ns = 76.83 \approx 77.$

However, to broaden the base of the study, the total number of women who had IVF during the study period was included hence a sample size of 106 was used.

SPECIMEN COLLECTION AND LABORATORY PROCEDURES

Before the treatment cycle, a blood test for basal follicle stimulating hormone (FSH) concentration in the early follicular phase (day 3-4) of the cycle was done. Transvaginal 2D ultrasound (Mindray Digi Prince DP6600 made in Germany) was performed using a 6.5mHz vaginal probe. For volume calculations, the three planes measured were the longitudinal, anteroposterior and transverse diameter. Ovarian volume calculated with the prolate ellipsoid formula ($V = D^1 \times D^2 \times D^3 \times 0.523$. The mean ovarian volume (MOV) is defined as the average volume of the two ovaries ($[V^1 + V^2]/2$). The recruited women were down-regulated using the long protocol with Buserelin, 0.5mg subcutaneously daily from the mid-luteal phase in the

preceding cycle of the treatment cycle and then reduced to 0.25mg at the commencement of stimulation. On the 3rd day of the cycle, a repeat transvaginal scanning was performed to reassess the ovarian volume before stimulation and blood were taken for basal serum Estrogen concentration.

When the ultrasound scanning showed no ovarian cysts and serum estrogen concentration <200pmol/L, menopour (human menopausal gonadotrophin) injection was started at between 150iu – 450iu depending on the age of the patient; daily and dose adjusted according to the ovarian response afterwards. The ovarian response was monitored by serial transvaginal scanning and the menopour dosage modified as appropriate. Human chorionic gonadotrophin (hCG) was given intramuscularly when the leading follicles(at least 2 or more) reached 18mm in diameter. Cycles were cancelled when the follicles remained less than 10mm after 10 days of stimulations. Oocyte retrieval was performed even when there was only one dominant follicle and was scheduled 33-36 hours after the hCG injection, and any visible follicle was aspirated during the procedure. The oocyte is considered to be of good quality if it shows signs of maturity and is round and even in shape and an extended corona radiate and cumulus mass with no granular cytoplasm, the absence of aggregations of organelles and vacuoles.

Serum FSH and Estrogen concentration were measured using commercially available kits. The FSH assay was standardised against the W.H.O 2nd international standard reference material.

ETHICAL CONSIDERATION

Every woman who gave a verbal consent was allowed to participate in the study. Approval sought from the Ethics Committee, Faculty of Medicine University of Benin. The

women received no monetary compensation for participating in the study; however, they paid for their treatment according to the institutional policy.

The primary outcome measure was the sum total of oocytes retrieved. The secondary outcome measures included the number of follicles prior to oocyte retrieved, the dosage of gonadotrophin, and the cancellation rate. Poor response was defined as fewer than five oocytes retrieved at follicle puncture[17].

DATA ANALYSIS

Data were analysed with SPSS version 16 (SPSS Inc., Chicago IL, USA). Categorical data expressed as percentages and compared with Chi-square test, while numerical data were expressed as mean ± SD and compared using Student's t-test. Multiple Regressions were applied to evaluate the predictive value of the different parameter on the ovarian response. The correlation was assessed by the Pearson correlation method. $P<0.05$ was considered significant.

RESULTS

The study population comprised 106 couples in 120 *in vitro* fertilisation treatment cycles. Fourteen (14) patients were ultimately excluded, of these six patients had ovarian cysts > 10mm and eight patients had a poor visualisation of one or both ovaries preventing accurate ovarian

measurements. The mean age, as well as the duration of infertility in the study population, were 35± 5.0 (range of 24 – 43) years and 5.0± 2.5 (range 2 – 18) years respectively.

Of the 106 women who were eligible for the study 32 (30.2%) of the study population had primary infertility, 54 (50.9%) had secondary infertility, and 20 (18.9%) was unclassified. Furthermore, the cause of infertility was 41(38.7%) male factor, 49 (46.2%) was a female factor, and 16 (15.1%) was combined male and female factors. The mean basal ovarian volume was 5.1± 2.2 cm^3(range 2.1 – 8.4 cm^3) and mean basal FSH was 9.1± 2.6 i.u. But in isolated cases ranging up to 53.1, i.u (Table I).

Table I: Summary of Demographic Data and Ovarian Response

Parameter	N	Mean	SD	Range
Age (years)	106	35.58	5.00	24 – 43
Duration of Infertility (years)	106	5.02	2.49	2 – 18
Ampoules of GnRH used (SI unit/Ampoule)	106	5133.96	1007.94	2325 – 7050
Days of stimulation	106	11.47	0.693	10 – 14
Basal FSH (u/L)	106	9.05	2.55	1.6 – 13.4
Mean Ovarian	106	5.06	2.15	2.1 – 8.4

Volume (MOV)				
Basal LH (u/L)	106	8.31	3.12	0.8 – 12.9
Basal E_2 (Pg/ml)	106	41.66	15.92	8.0 – 86.9
No. of Follicles	106	7.13	6.36	1 – 24
No. of matured oocytes retrieved	106	3.17	4.35	0 – 20
Body mass index	106	28.19	3.70	22.0 – 35.6

FSH = Follicle stimulating hormone
LH = Luteinizing hormone
E_2 = Estradiol

The overall mature oocyte retrieved rate and cancellation rates were 64.2% and 35.9% respectively.

The relationship of the study outcome measures and mean ovarian volume is shown in Table II.

Table IIa: Relationship between basal Mean Ovarian Volume and the study outcome measures

Ovarian Volume	<3	3 – 6	7 – 10	P – value
Ampoules of GnRH used (SI unit/Ampoule)	5289.00±538.71	5101.67±984.33	4691.67±1149.02	0.004
No. of matured oocytes retrieved	0.52 ± 0.87	2.49 ± 2.74	5.86 ± 5.81	<0.0001

No of follicles	2.44 ± 1.85	6.33 ± 4.08	11.39 ± 7.92	<0.0001
Total	**39**	**73**	**54**	

As the mean ovarian volume increased the mean dose of HMG used progressively reduced. This relationship was statistically significant. Also, the mean follicle count and the mean number of retrieved oocytes increased progressively as mean ovarian volume increased ($p<0.0001$).

The mean number of follicle, mean oocyte retrieved, had a positive correlation with the MOV and negatively correlated with the mean HMG used. Similarly, the number of follicles significantly increased as the ovarian volume increased and the mean dose of HMG used for stimulation significantly decreased as ovarian volume increased ($p<0.0001$). While the mean dose of HMG used for ovarian stimulation significantly increased with advancing age of the women in this study ($p<0.0001$), there was a significant reduction in the mean number of retrieved oocytes ($p<0.0001$).

There was no significant difference in a number of the follicle with advancing age of the women (Table IIb).

Table IIb: Relationship between age and the study outcome measures

Age (years)	≤ 25	26 – 30	31 – 35	36 – 40	>40	P -value
Ampoules of GnRH used (SI unit/Ampoules)	4584.38 ± 986.42	4112.50 ± 1046.15	4692.86 ± 1059.14	5227.94 ± 593.30	6123.91 ± 535.420	<0.0001
No. of matured oocytes retrieved	7.38 ± 6.55	0.50 ± 1.23	520 ± 5.37	2.41 ± 2.16	0.43 ± 1.12	<0.0001

No. of follicles	12.38 ± 9.61	2.17 ± 1.33	8.83 ± 7.76	5.26 ± 4.25	6.78 ± 4.01	<0.0001
Total	**8**	**6**	**35**	**34**	**23**	**106**

The relationship between mean basal FSH and the outcome variables is presented in Table IIc.

Table IIc: Relationship between basal FSH and the study outcome measures

DAY 3 FSH(IU/L)	≤10	>10	P – value
Ampoules of GnRH used (SI unit/Ampoules)	5032.03±1005.23	5289.29±1004.08	0.200
No of matured oocytes retrieved	3.97 ± 5.12	1.95±2.40	0.019
No. of follicles	8.70 ± 7.14	4.74 ± 3.94	0.001
Total	**64**	**42**	**106**

Women with mean basal FSH >10 IU/L used higher doses of HMG compared to women with mean basal FSH levels ≤10 IU/L. Furthermore, a mean number of follicles and mean a number of oocytes retrieved were significantly higher among women with mean basal FSH ≤ 10 IU/L (p = 0.019).

Table III: Determinants of response to stimulation

Variables	Total	Good respond	Poor respond	P-value	OR	95% CI
Age						
≤25	8	7(10.3%)	1(2.6%)	0.004	25.200	2.481 – 256.00
26 – 30	6	1(1.5%)	5(13.2%)	0.785	0.720	0.068 – 7.665

31 – 35	35	29(42.6%)	6(15.8%)	<0.0001	17.400	4.626 – 65.454
36 – 40	34	26(38.2%0	8(21.1%)	<0.0001	11.700	3.289 – 41.622
>40[a]	23	5(7.4%)	18(47.4%)	0.0001	0.0855	0.024 – 0.304
Total	**106**	**68(64.2%)**	**38(35.8%)**			
Ovarian volume						
<3[b]	25	9 (13.2%)	16 (42.1%)	0.026	0.281	0.101 – 0.784
3 – 6	45	30 (44.1%)	15 (39.5%)	0.026	3.56	1.275 – 9.914
7 – 10	36	29 (42.6%)	7 (18.4%)	0.252	2.071	0.738 – 5.816
Total	**106**	**68 (64.2%)**	**38 (35.8%)**			
Basal FSH						
≤10	64	46 (67.6%)	18 (47.4%)	0.066	2.323	1.029 – 5.248
>10[c]	42	22 (32.4%)	20 (52.6%)	0.066	0.430	0.191 – 0.972
Total	**106**	**68 (64.2%)**	**38 (35.8%)**			

[a]Ref Category for Age
[b]Ref Category for Ovarian volume
[c]Ref Category for Basal FSH

Women with mean ovarian volume 3 – 6cm³ were 4 times likely to respond better than those with MOV < 3cm³ (odds ratio 3.61; CI: 1.281 – 9.91). With regards to maternal age, the odds of having good response decreased with increasing maternal age; ≤25 years (Odds ratio: 25.2; CI: 2.48 – 256.00), >40 years (Odds ratio: 0.086; CI: 0.024 – 0.304). Other predictive factors for good response to ovarian stimulation was Basal FSH of ≤ 10iu (Odds ratio: 2.323; CI: 1.02 – 5.248) and >10i.u. (Odds ratio: 0.43; CI: 0.191 – 0.972)

Association between a number of oocytes retrieved and age, basal ovarian volume and basal FSH were tested using the multiple linear regression analysis, the result showed that basal ovarian volume [(r= 0.488), (p<0.001)] were positively correlated with the number of oocytes retrieved

the hence predicted good response. Age [(r = –0.433) (p<0.001)] and basal FSH [(r= –0.389) (p<0.001) on the other hand showed a negative correlation with the no of oocytes retrieved and were independently associated with and therefore influenced the number of oocytes retrieved.

To determine whether the MOV correlated with ovarian reserve in assisted reproductive technology (ART). The stimulation parameters were evaluated with linear regression analysis. While the results of the univariate analysis are demonstrated in Table IV.

Table IV: Correlation of NROCYT with Ovvol, BFC, Basal FSH and age

	NROCYT	***Ovvol***	***Basal FSH***	***Age***
NROCYT	1			
Ovvol	0.488382*	1		
Basal FSH	–0.38924*	–0.1374	1	
Age	–0.43368*	–0.17088	0.157135	1

NROCYT – the number of retrieved oocytes.

Ovvol - basal ovarian volume; **FSH** – follicle stimulating hormone; ***Correlation** is significant at the 0.01 level (2 tailed)

There was a direct linear correlation between MOV and number of follicle and number of mature oocytes. The MOV showed a negative linear correlation with patient's age, basal FSH level and ampoules of gonadotrophins used. The MOV did not correlate with parity, basal luteinizing hormone (LH), Basal estradiol (E_2) or days of stimulation. Using multiple linear regression analysis, a number of ampoules of gonadotrophin used ($P < 0.05$) and a number of follicles ($P < 0.001$) was most significantly associated with MOV.

The threshold values for the prestimulation MOV that might help predict ovarian responsiveness was determined. Efficiency curves demonstrated an increased risk for cancellation in patients with a MOV <3cm³. Contingency table analysis confirmed that a mean

MOV of 3cm³ was associated with a clinically significant increased risk in cycle cancellation (38.2% for <3cm³ vs 21.1% for >3cm³) (P = 0.017, odds ratio = 2.035, 95% confidence interval 1.165 – 3.555). Efficiency curves demonstrated poorer overall number of mature oocyte retrieved in all patients with MOV < 3cm³. Contingency table analysis for number of mature oocyte retrieved confirmed that a MOV < 3cm³ was associated with a clinically significant lower number of mature oocyte retrieved 90.6% for <3cm³ vs 26.0% for > 3cm³) (P < 0.0001, odd = 0.015, 95% CI: 0.002 – 0.109). (Table V and Fig 1)

Table V: Correlation of mean ovarian volume with ovarian reserve and ART stimulation parameters

Variable	Linear Regression	Multiple Regression
Age (years)	r = –0.18, *P* = 0.1	*P* = 0.55
Parity	r = 0.07, *P* = 0.5	*P* = 0.10
Basal FSH level (mIU/mL	r = –0.14, *P* = 0.15	*P* = 0.48
Basal LH level (mIU/mL)	r = –0.12, *P* = 0.23	*P* = 0.24
Basal E_2 level (pg/mL)	r = 0.33, *P* = 0.0007	*P* = 0.003
Ampoules of gonadotropins used	r = –0.36, *P* = 0.0002	*P* = 0.04
Days of stimulation	r = –0.25, *P* = 0.0089	*P* = 0.39
No. of follicles	r = 0.59, *P* < 0.0001	*P* = 0.001
No. of mature oocytes retrieved	r = –0.49, *P* < 0.0001	*P* = 0.880

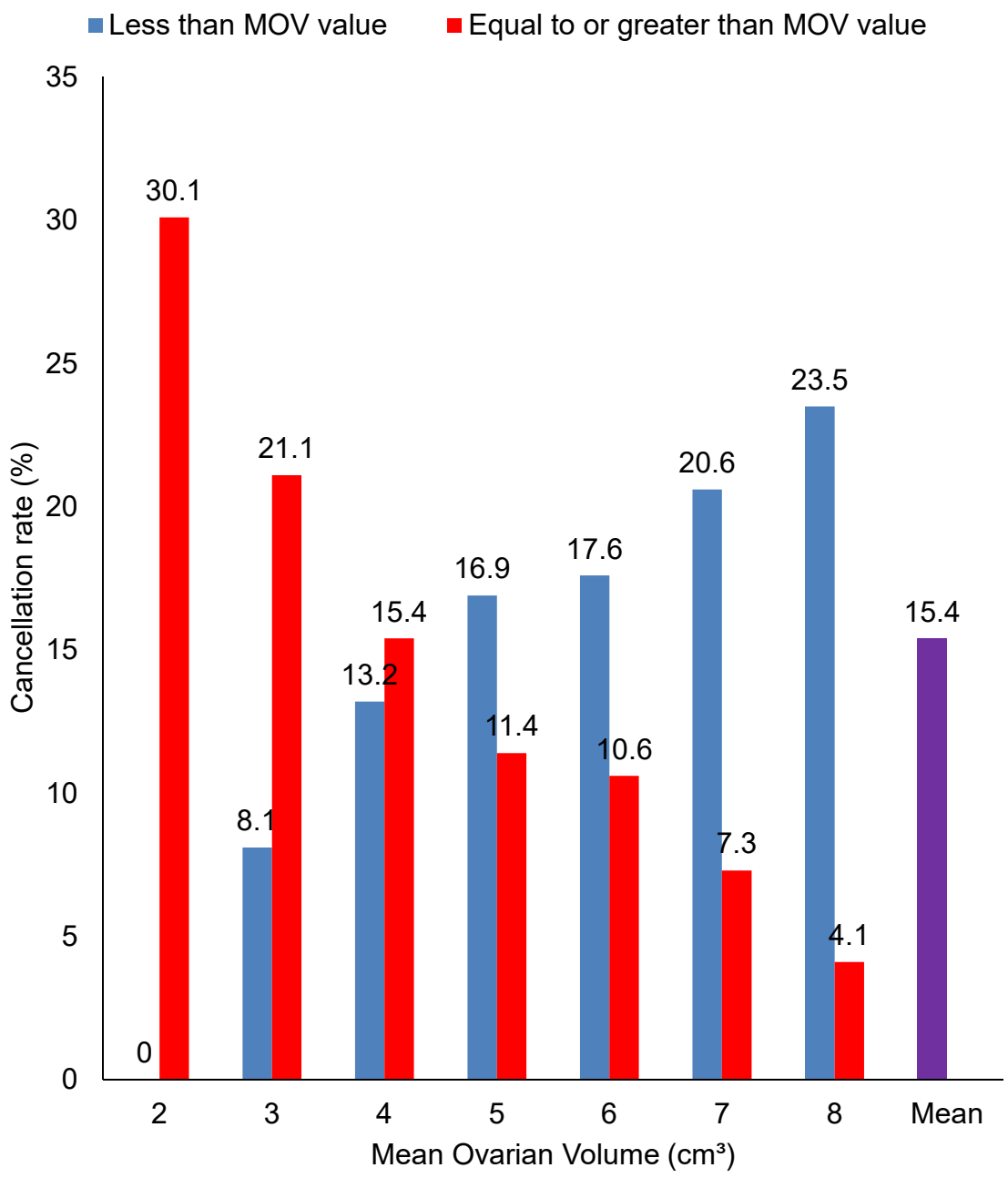

Fig. 1a: Graph demonstrating cancellation rates of incremental mean ovarian volumes (MOV). *Blue bars* demonstrate the cancellation rate for patients with a MOV less than that listed under the graph. *Red bars* demonstrate the cancellation rate equal to or greater than the MOV listed under the graph. The mean cancellation rate for the population studied is demonstrated with the purple bar. Contingency table analysis revealed that a MOV <3cm³ was associated with an increase in cycle cancellation (38.2%) for <3cm³ vs 21.1% ≥3cm³, (P = 0.017, odds ratio = 2.035, 95% confidence interval 1.165 – 3.555).

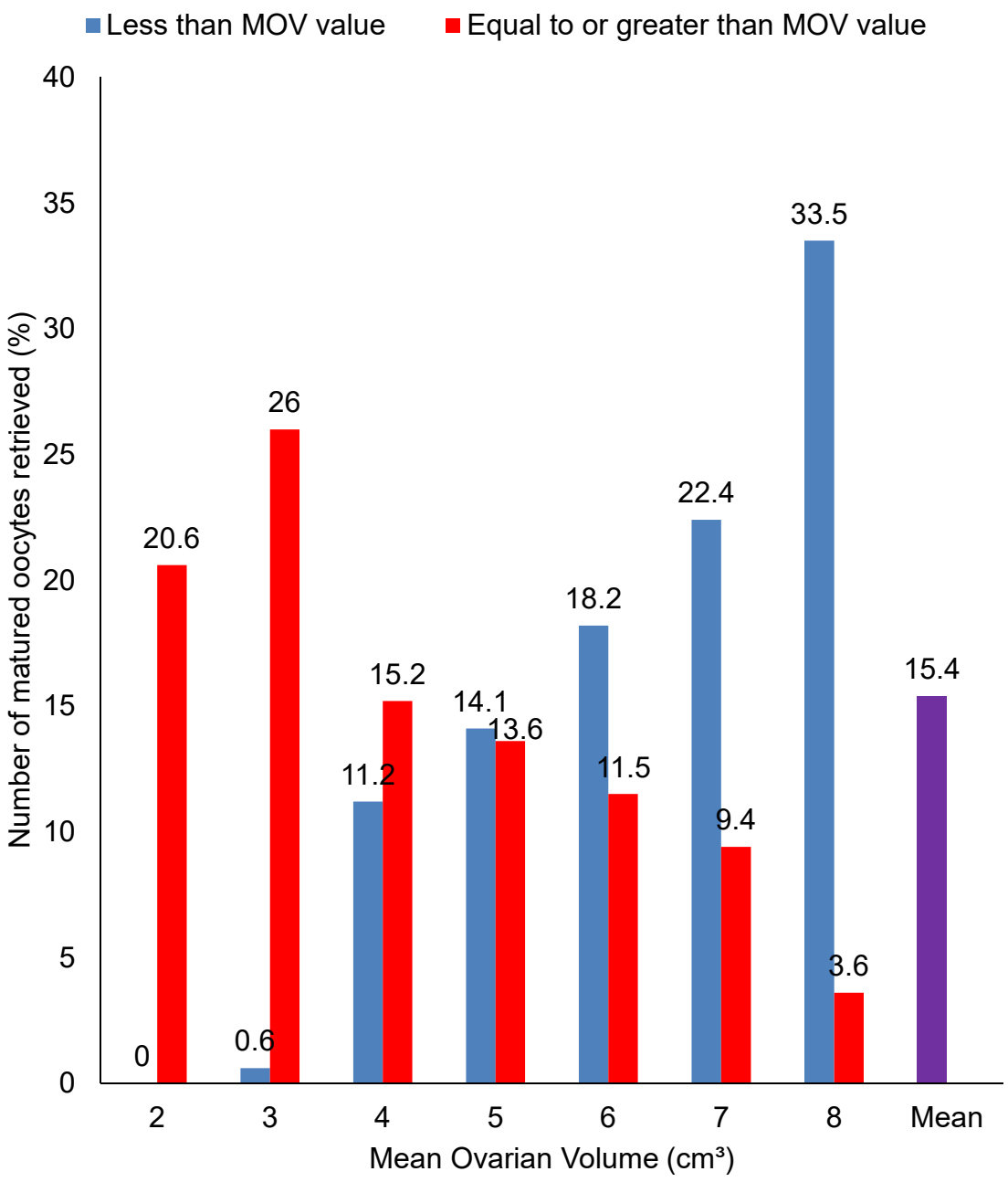

Fig. 1b: Graph is demonstrating a number of matured oocytes retrieved rate at incremental mean ovarian volumes (MOV). *Blue bars* demonstrate the number of matured oocytes retrieved rate for patients with a MOV less than that listed under the graph. *Red bars* demonstrate the number of matured oocytes retrieved rate equal to or greater than the MOV listed under the graph. The mean number of matured oocytes retrieved rate for the population studied is demonstrated with the purple bar. Contingency table analysis revealed that a MOV <3cm³ was associated with a decrease in the number of matured oocytes retrieved (0.6%) for <3cm³ vs 26.0% ≥3cm³, (P = 0.0001, odds ratio = 0.015, 95% confidence interval 0.002 – 0.109).

DISCUSSION

This study showed that ovarian volume, age and basal FSH could be used to predict ovarian reserve during controlled ovarian hyperstimulation (COH). The ovarian volume appeared superior to the other ovarian reserve tests. While some studies have demonstrated poorer outcome in patients with MOV < 3cm³,[9,12,14] other studies have revealed that ovarian volumes are less predictive[6,7,18]. Evidence suggests that an ideal IVF response following COH should produce approximately 5–15 mature eggs.[13,14,15] The production of fewer than five oocytes has been shown to significantly reduce a woman's chances of success in IVF program[12,15]. In particular, previous studies have also established the association between poor ovarian response due to diminished ovarian reserve with cycle cancellation and a significant decline in success rates[9,11,13]. Since response to exogenous stimulation is dependent on the ovarian reserve, it is therefore plausible that the mean ovarian volume at the onset of stimulation reflects the size of the pool of resting follicles and thus ovarian reserve.[14,15] Gougeon *et al*[19]demonstrated a clear association between MOV and the number of resting follicles in the follicle pool. This evidence correlated well with findings in this study which showed that the MOV > 3cm³ were significantly associated with good ovarian response during controlled ovarian hyperstimulation (COH) for IVF. Also, there was a definite correlation between MOV with the number of retrieved oocytes. Some authors have found that increasing the gonadotrophin dose, decreasing the duration of gonadotrophin-releasing hormone (GnRH) agonist and using GnRH antagonist may increase the number of oocytes.[18,20,21] The clinical implication of this finding is that IVF service providers in our locale can anticipate that patients who have a MOV >3cm³ will have a good response to COH; thus using it as a prognostic tool for optimal planning of care for these patients. Therefore, the basal MOV is an important tool to predict ovarian response in IVF

program and shows this method may also be useful when choosing the correct gonadotrophin dose in women who are likely to respond poorly to stimulation.

Women with MOV < 3cm³ required significantly higher doses of gonadotrophins (HMG) compared to the women with MOV > 3cm³.[19,20,23,24] Therefore, a MOV < 3cm³ may be an indicator of poor ovarian reserve in this cohort of women. Hence, the need for higher doses of gonadotrophin (HMG) for COH.[6,22,24] Available evidence in the literature has documented that increasing the dose of HMG used during COH for women with poor ovarian reserve did not necessarily translate into an increase in the number of retrieved oocytes.[23] Importantly, high doses of HMG for COH may be associated with complications such as ovarian hyperstimulation syndrome (ohss), miscarriage and others.[24] In contrast, other studies have shown that patients with good ovarian reserve do benefit from an upward adjustment of their starting dose of gonadotrophin from 100 IU/day to 150 IU/day to 200–300 IU/day, generating an extra one to four oocytes per cycle.[25-27] Therefore, poor ovarian reserve may predict cycle cancellation due to poor response during stimulation for IVF, with longer duration of stimulation (and hence more cost) and associated complications of excessive drug administration; thus these patients may be better served in a donor program.

Multivariate analysis using logistic regression of the determinants of good ovarian response following COH for IVF in this study showed that increasing ovarian volume greater than 3cm³ were significantly associated with good ovarian response to COH. Also, increasing maternal age and Basal FSH levels greater than 10 IU/L were associated with poor ovarian response to COH. These findings are consistent with published data available in the literature.[26,28] Although Tomars *et al*[29] demonstrated a positive correlation between ovarian volume when compared to basal FSH and age, with the number of recovered oocytes, they

concluded that the MOV before ovarian stimulation was a better predictor of the outcome than basal FSH and age. Furthermore, another study reported that ovarian volume less than 3cm³ was associated clinically with a higher cycle cancellation rate when compared with ovarian volume 3cm³ and above[30,] and the number of oocytes retrieved increased with increasing ovarian volume.[29,30]

The poor response to COH among women with increasing maternal age in this study is attributable to progressively fewer numbers of oocytes available in the ovary as the age increased. Indeed, from our findings, the oocyte yield was comparatively more in women <35 years old than those with advanced maternal age (> 35 years). This declining ovarian reserve associated with advancing maternal age is observed in the pattern of basal FSH among women with poor ovarian response to COH in this study as basal FSH >10i.u was commoner in this group of women. Elevated basal FSH levels are indicative of diminished quantitative ovarian reserve, as women with increased basal FSH levels frequently have been documented to have decreased oocyte yield in IVF programs.[21] Therefore, women ≥35 years old with elevated basal FSH (>10 mIU/mL) have a reduced follicle pool with diminished quality. Thus, basal FSH with advanced maternal age is good predictors of the size of the remaining follicle pool (i.e., the quantity of ovarian reserve). This observation corroborated by previous reports which showed that age and basal FSH are useful in the prediction of success in IVF.[31,32]

The probability of an oocyte yield per treatment cycle has been reported to decrease sharply as a function of patient age and increasing FSH concentrations in the infertile patient undergoing IVF.[32] In IVF programs, older women produce fewer oocytes and have lower implantation rates.[30-32] In this study, we found that women aged 40 years or more with elevated basal FSH (>10 mIU/mL) had comparatively poor IVF outcome compared to younger women.

Suggested reasons for the low success rate in these women may be due to an ageing population of oocytes with poor quality, gradual depletion of the follicle pool and endometrial factors influencing receptivity and implantation.[25-27,29] The age-related decrease in fertility is predominantly due to oocyte senescence rather than to poor endometrial receptivity, as suggested by the observation of high pregnancy outcome in oocyte donation programs in women with advanced maternal age. However, these findings may be constrained by the fact that additional determinants of pregnancy outcome during IVF treatment such as the quality of the embryo transferred, the transfer technique and endometrial receptivity were not assessed in this study. Future studies may address these factors including the role of Anti-Müllerian Hormone (AMH) assay in the evaluation of ovarian reserve.

The total number of gonadotrophins (HMG/FSH) used were significantly higher with advancing age. This is because they had a longer duration of stimulation and therefore consume more ampoules of gonadotrophins than the younger age group. This agrees with previous reports.[31] Thus, this group of patients should be carefully counselled on their low chances of conception with their own gametes, even when undergoing IVF treatments. An oocyte donation program will be a more reasonable alternative, if applicable and acceptable. With increasing age, ovarian reserve diminishes and spontaneous fecundity rate as well as success rates in IVF programs decline.

In this study, we have shown that MOV is an important tool to predict ovarian response in IVF programs. It is suggested that this may be useful when choosing the correct gonadotrophins dose in women who may respond poorly to COH. However, it was observed that MOV <3cm³ had mature oocyte retrieved rate of 0.6% and a cancellation rate of 38.2% while MOV >3cm³ had matured oocyte retrieved rate of 26% and a cancellation rate of 21.1%.

An attempt at defining this threshold levels, for the MOV in predicting IVF outcome was made. Although this could not be discerned, the value associated with a decrease ovarian response as demonstrated by an increase in cycle cancellation and reduction in the mature oocyte retrieved was determined.

In conclusion, ovarian volume, maternal age and basal FSH are important factors that may predict successful ovarian response during COH for IVF. Ovarian volume measurement is quick and cost-effective. When compared to the other parameters, it seems to be a more sensitive tool. However, no threshold value for MOV in predicting cycle cancellation rate or IVF success could be determined. There was no MOV that predicted absolute success or failure. A MOV less than $3cm^3$ was associated with higher cancellation rate and decreased in mature oocyte retrieved rate. This information will be relevant when counselling patients for IVF on the possibility of successful response to COH and need for donor oocytes, in addition to reducing complications of exposure to high doses of drugs for stimulation and duration of treatment. Also, the cost of IVF treatment usually influenced by the total amount of gonadotrophins used in COH may be reduced by better patient selection and fewer cycle cancellations due to poor response especially in our environment with scarce resources.

LIMITATION OF THE STUDY

Ultrasound scanning is operator dependent and as such intra-observer variations may occur in identification and measurement of the ovarian volume. This was eliminated or minimised by taking all measurements three times and an average of the three measurements for each of the dimensions taken.

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