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ORIGINAL ARTICLE

Automated measurement of follicle volume for the determination of trigger day in poor responder IVF patients

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ABSTRACT

Objective: To identify a cutoff value for volume using Sono-automatic volume calculation (Sono-AVC) that could be used to determine the appropriate time of human chorionic gonadotropin (hCG) during COH in antagonist cycles of low ovarian response in vitro fertilization (IVF) patients.

Material and Methods: Sixty-four IVF cases first underwent two-dimensional ultrasound. Subsequently, the follicles were analyzed via Sono-AVC. Using receiver operating characteristic (ROC) analysis, a cutoff value was identified for volume, to be used as the hCG criterion on the day of hCG measurement. A total of 544 follicles from 64 patients were screened by Sono-AVC and sorted descendingly. In all of the patients, the follicles in both ovaries had been visualized; only follicles identified manually as being larger than 10 mm and those measured by Sono-AVC to be over 0.4 cc in volume were screened and sorted.

Results: ROC analysis was done using the number of mature oocytes, and an hCG volume of 1.06 cc or greater on the day of measurement was identified as a cutoff value with a sensitivity of 91% for estimating maturation.

Conclusion: Using the Sono-AVC method to determine hCG timing in cases with a low ovarian reserve and/or those who are poor responders might enhance the efficacy and reliability of treatment.

Keywords: automated ultrasound, automated volume calculation, follicle monitoring, follicle tracking, Sono-AVC.

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INTRODUCTION

Accurate identification of the size and number of follicles during controlled ovarian stimulation (COS) is one of the key points for a successful assisted reproductive treatment process.[1] It allows optimal timing of trigger administration, which is strongly associated with the acquisition of mature oocytes.[2] Moreover, there is a linear correlation between the number of mature oocytes obtained and fertilization and pregnancy rates.[3] Thus, considerable care should be given to precisely determine follicle sizes.

No universally standard method exists for the measurement of follicle size. In general, two-dimensional (2D) transvaginal ultrasound (US) is the choice of modality for monitoring follicular growth in everyday practice.[4] However, 2D ultrasound (2D-US) may not be sufficient to measure actual follicular diameter as growing follicles may seem irregular by pressing each other. The reliability of 2D-US use is also limited due to its high interobserver variability.[5,6] Sono-automatic volume calculation (Sono-AVC) is an alternative method to 2D-US for follicle measurement. In this method, a data set is created by identifying and quantifying hypoechoic areas within an ovary by a three-dimensional ultrasound (3D-US) technology, followed by the calculation of follicle volume.[4,6]

Previous studies have demonstrated that Sono-AVC is an objective, reliable, and standard method for measuring follicle volume, with low interobserver variability.[7–14] Although studies have shown the utility of Sono-AVC to be advantageous in follicle measurement, a cutoff value for follicle volume that helps make decision on the trigger day has not yet been identified.[15,16] The aim of the present study was to determine the timing of trigger based on follicular volume calculated by Sono-AVC in women with a diminished ovarian reserve and/or poor response.

MATERIAL AND METHODS

In this retrospective cohort study, 64 women undergoing ovulation induction for in vitro fertilization (IVF) were monitored using a Voluson E8 ultrasound with a 5–9-MHz transvaginal "volume" transducer (General Electric Healthcare, Kretz, Austria) for a 12-month period. Patients who met all of the following criteria were included: age between 23 and 46 years, presence of both ovaries, diminished ovarian reserve (<5 antral follicles in each ovary on transvaginal US) and/or poor responders (<5 oocytes collected in previous attempts), and IVF cycles using gonadotropin-releasing hormone (GnRH) antagonist protocol. The exclusion criteria were as follows: presence of endometrioma, hydrosalpinx, and paraovarian or ovarian cyst, presence of any uterine morphologic abnormality and severe male factors (sperm count <1 million/mL or azoospermia).

All patients were monitored by US exams, with manual and automated follicle measurements performed using 2D-US and 3D-US, respectively. The 2D-US scans were done by different operators and the 3D-US scans by a single operator (M.K.). All operators had an experience of more than 5 years in follicle measurement. By 2D-US, the mean diameter of a follicle (millimeter) was calculated as the mean of the two longest perpendicular diameters of a follicle, which was measured by placing the calipers at the inner follicle borders. This was followed by a 3D volume acquisition using the Sono-AVC method. The entire ovary was captured with a single sweep. The user then adjusted the region of interest (ROI) box over the entire ovary, thereby ensuring to include only the region needed for analysis and calculation. Once this step was completed, the next step was to activate Sono-AVC mode to capture the chosen ROI. Sono-AVC mode automatically identified hypoechoic follicles within the captured ovarian volume and generated a set of measurements for each follicle. These were as follows: the three largest diameters of the follicle in orthogonal planes, mean follicle diameter, follicle volume, and volume-based diameter (dV) of the follicle. The volume calculation was based on the voxel count within the identified follicle, thus representing a true measure of follicular volume.

Upon completion of automated analysis but prior to generating the final report, the acquired sweeps were post-processed. In short, the images were manually rotated 360° to identify any possible errors that may have occurred during the automated volume acquisitions. These errors were scrutinized and corrected using the "add/remove," "cut," and "merge" functions of Sono-AVC mode. The follicles and their corresponding measurements were color coded for the easy interpretation of the worksheets. The volume of the follicles was calculated. The final number and size of the follicles identified after post-processing were recorded.

Data Recording

On the report sheets of the cases for whom hCG status had been decided and for whom data for all follicles had been recorded via 2D-US and Sono-AVC, the follicles were sorted according to size in the descending order. The follicles with diameters greater than 10 mm on manual measurement and volume greater than 0.4 cm3 on Sono-AVC were included in the recorded data. The total number of oocytes, number of mature oocytes, and number of fertilized oocytes obtained on ovum pick-up (OPU), along with pregnancy rates, were recorded. Receiver operating characteristic (ROC) analysis was done based on the follicle volumes obtained by Sono-AVC and recorded descendingly, as well as on the number of mature oocytes. On the basis of these values, a cutoff maturation value was identified for the hCG day.

Controlled Ovarian Stimulation

COS was initiated through the daily administration of recombinant follicle-stimulating hormone (rec-FSH) (Gonal-F; Merck Serono, Istanbul, Turkey) with/without human menopausal gonadotropin. The gonadotropin doses were decided according to age, ovarian reserve, body mass index (BMI), and previous responses. When the leading follicle reached a mean diameter of 12–13 mm, all patients began receiving daily injections of 0.25 mg cetrorelix (Cetrotide; Serono, Halle, Germany) until the trigger with recombinant human chorionic gonadotropin (rec-hCG) administration (Ovitrelle; Merck Serono, Istanbul, Turkey), when one or more follicle were ≥17 mm in diameter. Transvaginal US-guided oocyte retrieval was performed 36 h after the administration of rec-hCG. The collected oocytes were classified as mature and nonmature, and ICSI was used for fertilization. The embryos were cultured for 3–5 days. The day of embryo transfer and the number of embryos transferred were decided by the managing physician based on patient and cy-

Table 1: Demographic and clinical characteristics of the patients

Age (years)	37.00±5.29
BMI (kg/m^2)	25.60±4.09
Infertility duration	8.13±6.75
Total number of trials	3.47±2.15
E2 on hCG day	684.66±423.41
Total oocytes	3.23±2.31
MII	2.56±1.60
2PN	2.22±1.50
Number of transferred embryos	1.78±0.46
Day 3 FSH (IU)	14.81±6.63
β-hCG result	
Negative	42 (77.8)
Positive	11 (20.4)
Biochemical abortion	1 (1.9)
Rate of cancellation	10 (15.6)
Reason for cancellation	
Oocyte maturation defect	2 (3.1)
No oocyte at OPU	1 (1.6)
Fertilization failure	5 (7.8)
Cleavage arrest	2 (3.1)

Data are represented as mean±standard deviation or number (%), where appropriate. BMI: Body mass index; E2: Estradiol; hCG: Human chorionic gonadotropin; MII: Metaphase II; PN: Pronuclei; FSH: Follicle-stimulating hormone; ET: Embryo transfer; OPU: Ovum pick-up.

Table 2: Sensitivity, 1 – specificity, negative and positive predictive values for the cutoff value of a follicle volume of 1.06 cc for predicting oocyte maturation

	%	95% CI (Min–Max)
Sensitivity	91.0	86.5–95.5
1 – specificity	9.8	6.8–12.7
Negative predictive value	96.2	94.2–98.1
Positive predictive value	78.8	72.8–84.8

CI: Confidence interval; Min: Minimum; Max: Maximum.

Table 3: Coordinates of the curve

(Greater or equal)	Sensitivity	1 – specificity
0.98	0.916	0.108
0.99	0.916	0.105
1.00	0.916	0.103
1.01	0.916	0.100
1.03	0.910	0.100
1.06	**0.910**	**0.098**
1.07	0.897	0.098
1.08	0.890	0.090
1.10	0.884	0.090
1.11	0.884	0.087
1.12	0.884	0.082

Bold values: Optimal sensitivity and specificity.

cle characteristics. Luteal phases support consisted of administering 100 mg/day intramuscular (IM) progesterone (Progynex; Kocak Pharmacy, Turkey), starting on the day after the oocyte retrieval, which was continued until the pregnancy test. In pregnant women, IM progesterone was replaced with 90 mg/BID vaginal progesterone (Crinone gel, 8%; Serono, Bedford, United Kingdom), which was continued until 10 weeks of pregnancy.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows (version 15.0; Chicago, IL, USA) was used for the statistical analysis. The distribution of data was evaluated by the Kolmogorov–Smirnov test. Categorical variables were represented as number (percentage), whereas numeric variables were represented as mean±standard deviation or median (minimum–maximum). ROC curve analysis was performed to find a cutoff for predicting oocyte maturity based on the follicle volumes obtained by Sono-AVC. Pairwise comparison of the groups in which data were not distributed normally was performed using the Wilcoxon test, whereas the Friedman test was used for multigroup comparisons. A p value lower than 0.05 was considered to represent statistical significance.

It was estimated that the follicles with a diameter of 15 mm and over according to the classical method[1] and with a volume of 1.06 cm^3 and over according to Sono-AVC might be mature. These data were used to test the reliability of the measurement methods in predicting the number of oocytes using Cronbach's alpha test technique.

RESULTS

Sixty-four women with diminished ovarian reserve met the inclusion criteria of the study during the study period. The clinical pregnancy rate was 18.5% (n=10). The demographic and clinical characteristics of the patients are summarized in Table 1.

The follicles measured by 2D-US as a diameter of 10 mm or greater as well as by Sono-AVC as a volume of 0.4 cc or greater were recorded in all patients. In total, 544 follicles met these criteria. Of these, 155 (28.5%) were mature oocytes. ROC curve analysis showed that a follicle volume of 1.06 cc or over on the trigger day predicted oocyte maturation with a sensitivity of 91%, a specificity of 90%, a positive predictive value of 78.8%, and a negative predictive value of 96.2% in these women (Fig. 1, Table 2, 3).

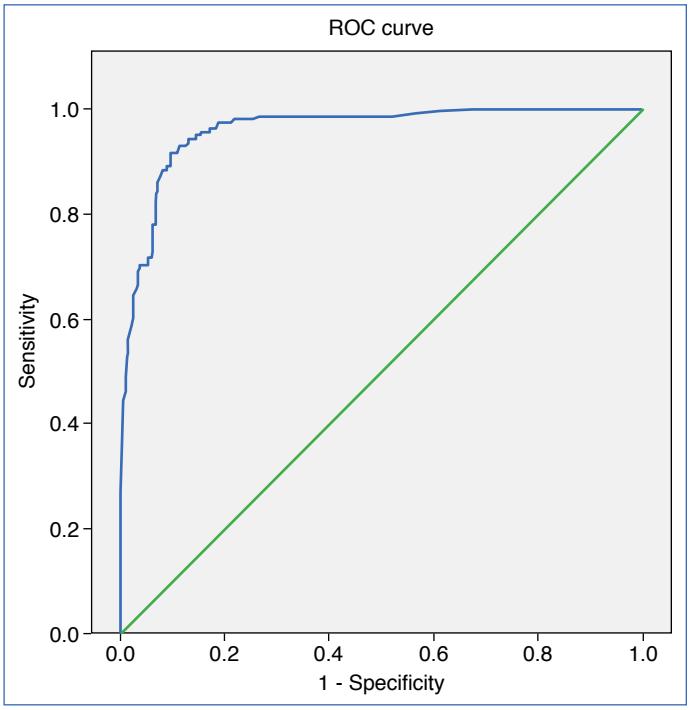

Figure 1: Receiving operating characteristic (ROC) curve; area under the curve (AOC)=0.960 (SE=0.008), p<0.001, 95% CI=0.944–0.976.

It was assumed that follicles with a diameter of 15 mm or larger as measured by 2D-US might be mature based on the literature data, while follicles with a volume over 1.06 cc measured by Sono-AVC might be mature. Figure 2 shows the estimated number of mature oocytes obtained when these cutoffs were used. The mean number of mature oocytes was 2.56±1.60 in the study population. Sono-AVC was a better predictor of estimating the number of mature oocytes compared with 2D-US (2.80±1.71 vs 2.08±1.44, p<0.001, respectively). The estimated number of mature oocytes was significantly lower when 2D-US was used compared with the actual number of oocytes collected (p=0.027). No statistically significant difference was found between the actual number of mature oocytes collected and the number of mature oocytes estimated by Sono-AVC (p=0.055) (Fig. 2).

The reliability of two different measurement techniques in estimating the number of mature oocytes was tested using Cronbach's alpha test. The reliability coefficient was higher for Sono-AVC (α=0.812) than for 2D-US (α=0.775).

DISCUSSION

To the best of our knowledge, it is the first study that proposes a cutoff for follicle volume calculated by Sono-AVC in determining the timing of trigger.[16] Our study shows that the cutoff of 1.06 cc for follicle volume predicts oocyte maturity with a sensitivity of 91%, a specificity of 90%, a positive predictive value of 78.8%, and a negative predictive value of 96.2% in poor responder women. Thus, the Sono-AVC method seems to be a good tool in the prediction of oocyte maturity. However, our study did not evaluate the clinical utility of the Sono-AVC method in determining the timing of trigger, which should be investigated by further studies.

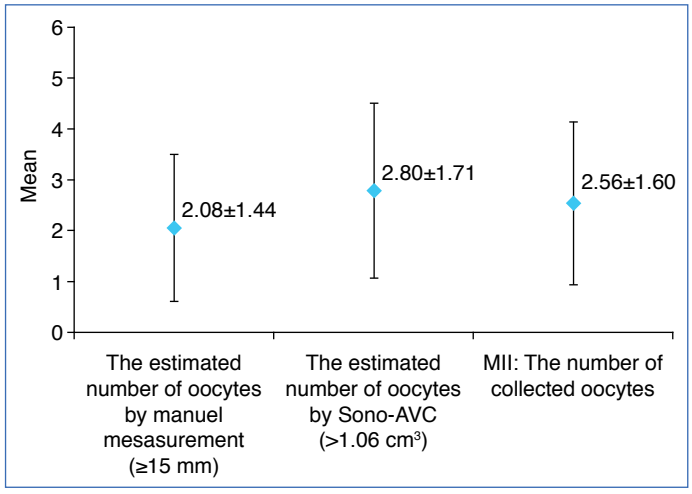

Figure 2: Estimation of the number of oocytes by manual measurement and by Sono-AVC and the number of collected oocytes (MII).

Studies have shown that 3D-US has a considerable advantage in follicle monitoring compared with 2D-US.[6] It has been shown that the follicular volumes calculated using the Sono-AVC are in accordance with the aspirated volumes.[7] Sono-AVC technique has been also found to be more accurate in the assessment of follicle volume.[8,14] As the utility of Sono-AVC decreases intra- and interobserver variabilities in follicle assessment, it allows for accurately calculating the diameter and volume of each follicle. Although studies have demonstrated several advantages of Sono-AVC in the follicle assessment, so far, no cutoff value has been identified for determining the timing of trigger. In the present study, the fact that we included poor responder women for this purpose provided feasibility to evaluating follicle volume. We found that a value ≥1.06 cc for follicle volume may be used to determine the timing of trigger in women with diminished ovarian reserve, as the maturation rate is high enough after this cutoff. The percentage of mature oocytes was 3.8% or 78.8% in case of follicle volume <1.06 cc or ≥1.06 cc, respectively.

In a study of 58 IVF cycles, Rodríguez-Fuentes et al.[17] reported a high rate of mature oocytes when using 0.06 cc as the cutoff value for follicle volume on the trigger day. However, their study evaluated each ovary separately and the proposed cutoff value was a predicted (estimated) value based on the maturation rate for each volume, rather than being a value obtained by ROC analysis. This value represented a volume close to the lower limit obtained for mature follicles. Also, they were able to obtain clear images only in 60% of the patients. Our study included only those with both ovaries satisfactorily visualized.

It has been shown that the intra- and interobserver reliabilities were lower with Sono-AVC than with conventional 2D-US in total antral follicle count.[18,19] The Sono-AVC method also allows a more rapid assessment of follicles compared with 2D-US.[19,20] Moreover, the Sono-AVC method provides a better image quality.[3,16] This shows that the use of Sono-AVC enables the collection of a higher number of oocytes, which is associated with a higher fertilization rate. The Sono-AVC method was more reliable than 2D-US in predicting the number of mature oocytes, with Cronbach's α values of 0.812 and 0.775, respectively.

Sono-AVC permits a rapid estimation of the number of obtainable mature oocytes. This aspect of the method is of importance in deciding on the timing of trigger in poor responders as premature ovulation, oocyte loss, and oocyte immaturity more commonly occur in those women. The timing of trigger should be more precisely adjusted in this group of patients, and thus follicle volume may be used as one of the trigger criteria.

In conclusion, the Sono-AVC method is a reliable technique that allows for the rapid and effective evaluation of follicles in determining the timing of trigger in poor responder women. The cutoff of 1.06 cc by Sono-AVC is a better predictor for oocyte maturity compared with the cutoff of 15 mm by 2D-US. The standardization of technique can be achieved over time as the inter- and intraobserver variabilities decrease. The technique may enhance the efficacy and reliability of the ART in poor responder women at high risk of having unexpected outcomes such as premature ovulation. Thus, the Sono-AVC method for follicle monitoring accurately determines the trigger timing in these women. Further studies are needed to reveal its role in clinical outcomes.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital University Clinical Research Ethics Committee granted approval for this study (date: 09.03.2022, number: 31).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MK, SK; Design – MK, SK, PK; Supervision – MK, SK; Resource – MK, SK; Materials – MK, SK; Data Collection and/or Processing – MK, SK, PK; Analysis and/or Interpretation – MK, PK; Literature Search – MK, PK; Writing – MK, SK; Critical Reviews – MK, SK, PK.

Conflict of Interest: The authors have no conflict of interest to declare.

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