Original Article

Three-Dimensional Automated Volume Calculation (Sonography-Based Automated Volume Count) versus Two-Dimensional Manual Ultrasonography for Follicular Tracking and Oocyte Retrieval in Women Undergoing *in vitro* Fertilization-Embryo Transfer: A Randomized Controlled Trial

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ABSTRACT

Aim: To compare the oocyte yield using three-dimensional (3D) automated and two-dimensional (2D) ultrasound-based follicle tracking in women undergoing *in vitro* fertilization-embryo transfer (IVF-ET). **Settings and Design:** A randomized controlled trial was conducted in the Reproductive Medicine Unit of a teaching medical institute from January 2017 to December 2018. **Materials and Methods:** A total of 130 patients undergoing IVF-ET were enrolled and randomized into two groups (65 patients in each group). In Group A, follicular tracking during controlled ovarian stimulation (COS) was done using 3D Sonography- based Automated Volume Count (SonoAVC), whereas in Group B, follicular tracking was done by manual ultrasonography (2D USG). The primary outcome measures were the number of oocytes retrieved (the total number and the number of mature oocytes). Secondary outcomes were fertilization rate, cleavage rate, total number of embryos and time taken to perform scans. Other outcome measures were clinical pregnancy rate, miscarriage rate and live birth rate (LBR). **Statistical Analysis Used:** Chi-square test, Student's *t*-test, Z-test, Wilcoxon rank-sum test, Bland–Altman's plot. **Results:** The two groups were comparable with regard to assisted reproductive technology (ART) outcomes. Group B required more time for performing the scan ($P < 0.01$). **Conclusion:** Automated SonoAVC ultrasound can be used interchangeably with manual 2D USG for follicle tracking during COS giving comparable ART outcomes with the added advantage of saving time. Our study implies the promising results of applying artificial intelligence in follicular tracking during COS.

KEYWORDS: *Artificial intelligence, follicular tracking, in vitro fertilization, sonography automated volume count, three-dimensional ultrasonography*

INTRODUCTION

*U*ltrasound-based follicular tracking is an indispensable part of any controlled ovarian stimulation (COS) cycle. Tracking is commenced on day 5 or 6 of ovarian stimulation with further scans scheduled according to the response of ovaries to gonadotropin stimulation. Follicular tracking is of utmost importance in deciding the most appropriate time for triggering ovulation.

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Conventionally, the size of a follicle is gauged by quantifying its diameter with a two-dimensional (2D) ultrasound. As of now, there is no definite agreement on how follicular measurements should be done and how many dimensions are to be measured.[1] COS is characterized by multi follicular growth which may result in crowding of follicles making accurate measurements difficult. The reliability of follicular measurements decreases as the number of follicles increases.[2,3] Considerable inter-observer and intra-observer variation in the measurements could also be encountered.[4] Moreover, the measurement of all the mature follicles is time-consuming. Three-dimensional (3D) ultrasound imaging may provide a way to circumvent some of these paradoxes encountered with traditional 2D imaging.[5,6] Sonography-based Automated Volume Count (SonoAVC: GE Medical Systems, Kretz, Austria) is a software that automatically delivers dimensions of follicles within a defined ovarian volume. Raine-Fenning *et al*.[7] established the validity of SonoAVC by comparing ovarian volume derived from this automated method for 24 women on the day of oocyte retrieval to the true volume of each follicle determined by manual measurement of the follicular aspirate. The software provided highly accurate automatic follicular volume measurements in all cases and was more reliable than 2D ultrasound measurements.[7] However, whether the accuracy of the software translates to improved *in vitro* fertilization (IVF) outcomes still needs to be established. The present study aims to compare the oocyte yield following SonoAVC and manual 2D USG-based follicular tracking during COS.

MATERIALS AND METHODS

The study was conducted in the Reproductive Medicine Unit of our hospital from January 2017 to December 2018 over a period of 2 years. Institutional Review Board approval (Ref. No. IESC/T-376/04.10.2013) was obtained and written informed consent was taken from all the participants before the study. Women aged between 22 and 38 years with average body mass index (BMI) (18–28 kg/m^2), having a normal ovarian reserve (basal follicle stimulating hormone [FSH] <10 miu/ml, antral follicle count >10 and anti-Mullerian hormone >1.8 ng/ml), and normal endometrial cavity were included in the study. Patients having endometriosis, prior failed IVF cycle, polycystic ovary syndrome (PCOS), poor ovarian reserve, severe male factor mandating Intracytoplasmic Sperm Injection (ICSI), and uterine factors affecting implantation were excluded from the study. Patients satisfying the eligibility criteria were randomized into two groups through computer-generated random numbers - Group

A included 65 patients who were allocated to undergo follicle tracking using automated SonoAVC method and Group B included 65 patients who were to undergo 2D manual method. Allocation concealment was done using sequentially numbered, opaque, sealed envelopes which were handed over to the patient at the time of registration and randomization. The patients handed over the envelopes to the observer performing ultrasound who would open the envelope and do follicle monitoring using 2D or 3D USG depending on the group allocated. A single observer knowing about the randomization did all the ultrasound monitoring, data collection, and data analysis. All images related data as well as details of allocation into the two groups were saved on a computer in password protected files accessible only to the single observer doing ultrasound. The patients, the clinician performing ovum pick up and the embryologist were blinded.

All patients underwent COS by long agonist protocol. Downregulation was done using gonadotropin-releasing hormone (GnRH) analog Leupride from day 21 of the previous cycle. On day 2 of subsequent cycle, serum estradiol <50 pg/ml and ultrasonography (USG) showing inactive ovaries and thin endometrium confirmed downregulation after which COS was initiated using daily injections of recombinant FSH. GnRH analog was continued until human chorionic gonadotropin (hCG) trigger.

Serial follicle tracking was started from day 6 of stimulation using Voluson S6 (GE Healthcare, Republic of Korea), with a 5–9 MHz transvaginal probe and further scans were done as per ovarian response till the day of hCG trigger. The observer performing the ultrasound also recorded the time taken to perform each scan in minutes from the time of first focus on one ovary to the time the total follicle count was obtained in both ovaries. For patients belonging to the SonoAVC group "time taken" also included the time required for postprocessing as described below.

In subjects allocated to Group A, following the application of a region of interest that defines the volume to be acquired over the ovary, a motorized sweep through 120° was carried out. The subsequent multiplanar display was inspected to confirm that the complete ovary had been captured. The image appeared in three orthogonal planes concurrently, and the handling of these planes allowed placing the ovary centrally. Applying 3D render mode to this image gave a cuboidal volume after which manual adjustments were made to remove extra-ovarian data. Following the correct positioning of the dataset, SonoAVC was applied. Each follicle within the multiplanar view and the rendered

image was displayed with a specific color [Figure 1a]. Apart from these images, a separate worksheet exhibited the dimensions and relative sizes of the follicles. This too was color-coded and matched against the individual follicles [Figure 1b]. Postprocessing helped to delineate missed follicles and exclude artefacts, using the "add" or "remove." options. The final number and size of the follicles were recorded and the data were saved onto the hard drive of the ultrasound machine with a unique identification code. The measurements included were the mean follicular diameter (MFD) which is the arithmetic mean of the three longest orthogonal diameters, the volume of the follicle (V), and the volume-based diameter (dV) of the follicle.

Subjects allocated to group B had each of the stimulated ovaries scanned and each follicle measured in two perpendicular diameters. All follicles ≥14 mm were measured. The number of follicles and their mean diameter was ascertained. MFD was the average of the longest diameter in two orthogonal planes.

The dV in Group A and MFD in Group B were used for hCG trigger. All patients were triggered with recombinant hCG when at least 1 follicle ≥18 mm were documented on ultrasound. Oocyte retrieval was done 36 h post trigger. Post retrieval insemination of oocytes, fertilization check, embryo grading, and embryo transfer were done as per the unit policy. Luteal support with intramuscular and vaginal progesterone was provided in all women. Serum β hCG was checked 16 days after embryo transfer and clinical pregnancy confirmed by sonography 4 weeks post embryo transfer. All pregnant patients were followed up in our antenatal clinic until delivery and all babies born alive after 24 weeks of gestation were included in live births.

The primary outcome measures were the number of oocytes retrieved (total number and the number of mature oocytes). Secondary outcomes were fertilization rate, cleavage rate, total number of embryos, and time taken to perform scans. Other outcome measures were clinical pregnancy rate, miscarriage rate, and live birth rate (LBR).

Sample size calculation

For calculating the sample size, considering the study by Murtinger *et al*., it was observed that the mean ± standard deviation (SD) number of metaphase II (MII) oocytes retrieved in the 2D procedure is 10 ± 5. In the present study, the mean ± SD for the 2D method is 9 ± 6 and it is assumed that an increase of about 30% MII oocytes with the 3D method is anticipated. Accordingly, the mean ± SD expected MII oocytes in 2D and 3D methods will be 9 ± 6 and 12 ± 6, respectively. Based on this information to achieve 80% power with a 95% confidence level the required sample size was calculated as 63 in each group. Hence, we enrolled 65 patients in each group.

Statistical analysis

Statistical analysis was carried out using Stata 11.0 (College Station, Texas, USA). The data were presented as number (percentage) or mean ± SD/ median (min-max) as appropriate. Categorical and continuous baseline variables were compared using the Chi-square test and Student's *t*-test for independent samples/Wilcoxon rank-sum test if the variables were not normally distributed. The difference in means of primary and secondary outcomes was compared using unpaired *t*-test and pregnancy rate was compared between the two groups using *Z*-test and the results were reported as difference in means or proportions (95% confidence interval). Bland–Altman's plot was drawn to show the agreement between the MFD and dV of the
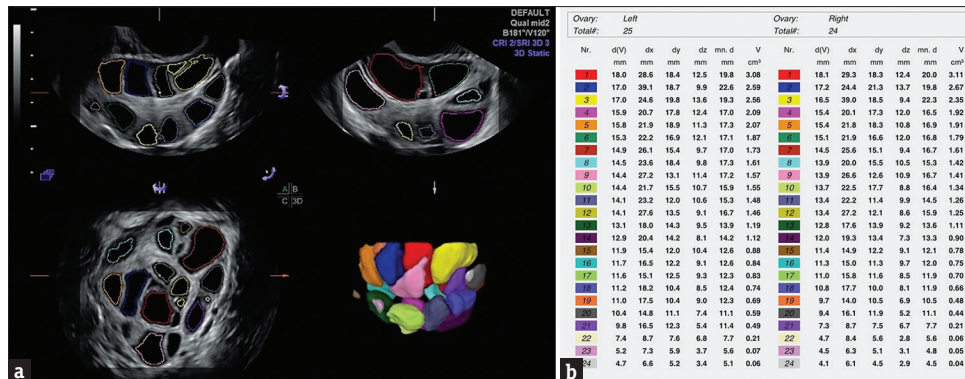

Figure 1: (a) The image of an ovary in three orthogonal planes (x, y and z) and the three-dimensional rendered image (bottom right side) having follicles color coded based on size. (b) Worksheet depicting the size-based color coding as in the three-dimensional rendered image in Figure 1a. d(V) is the volume-based diameter of follicle in millimeters (mm). dx is the maximal diameter of the follicle in x axis in millimeters (mm). dy is the maximal diameter of follicle in y axis in millimeters (mm). dz is the maximal diameter of follicle in z axis in millimeters (mm). mn.d is the mean follicular diameter in millimeters (mm) calculated by SonoAVC software, it is the average of maximal diameters in x, y and z axes. V is volume of follicle in cm3

leading follicle in Group A. *P* < 0.05 was considered statistically significant.

RESULTS

A total of 182 patients undergoing IVF were assessed for eligibility. Of them, 52 patients were omitted based on the exclusion criteria. The 130 subjects who met the eligibility criteria were prospectively randomized into two groups: 65 into 3 D USG automated follicular tracking and 65 into 2 D manual follicular tracking [Flow Chart 1].

The two groups were similar concerning baseline characteristics such as demographic variables, baseline ovarian reserve, and gonadotropin dose requirements. Endometrial thickness, serum estradiol, and progesterone on the day of trigger were also comparable [Table 1]. The mean of total number of follicles on the day of hCG trigger was 25.3 ± 9.2 in SonoAVC group and 8.4 ± 2.4 in 2D USG group. Hence, total follicle count on the day of trigger was significantly greater in the SonoAVC group (*P* < 0.01).

There was no significant difference between the two groups with respect to the total number of oocytes retrieved (*P* = 0.85), the number of MII oocytes (*P* = 0.51), fertilization rate (*P* = 0.23), cleavage rate (*P* = 0.92), and the total number of embryos (*P* = 0.18). The time taken to perform the scan was significantly higher in Group B (*P* < 0.01). The mean time taken in Group A was 6.2 ± 0.7 min and in Group B was 7.6 ± 0.8 min with an advantage of 1.4 min in Group A. The two groups were comparable with regard to the clinical pregnancy rate (*P* = 0.88), miscarriage rate (*P* = 0.66), and LBR (*P* = 1) [Table 2].

In 2D USG group, MFD of leading follicle was 19.9 ± 2.2 mm. In the SonoAVC group, the MFD of the largest follicle in each ovary was 19.9 ± 2.3 mm and the mean dV of the same follicle was 18.4 ± 1.8 mm. Hence, MFD was significantly greater than dV for the leading follicle per ovary, with a mean difference of 1.5 mm (*P* < 0.01) within SonoAVC group [Figure 2].

DISCUSSION

Our study revealed the number of follicles on the day of hCG trigger to be significantly greater in SonoAVC group compared to 2D USG group. This may be attributed to the fact that smaller follicles were picked up by automated ultrasound which were either missed or not measured during 2D ultrasound (follicles ≥14 mm were measured during manual measurements). Interestingly, this difference did not reflect in the number of oocytes retrieved and number of MII oocytes, both of which were comparable in the two groups. This study has also established noninferiority of 3D USG compared to manual follicular tracking with regard to the fertilization rate, cleavage rate, number of embryos obtained, clinical pregnancy rate, miscarriage
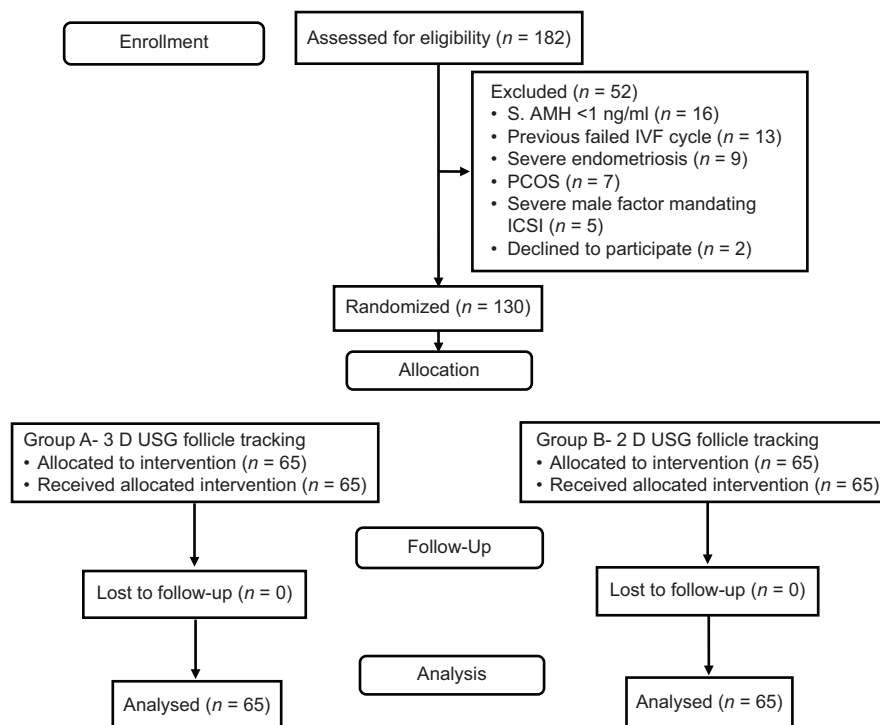
Flow Chart 1: CONSORT flow diagram

Table 1: Baseline characteristics

Population characteristics	Group A (SonoAVC) (*n*=65)	Group B (2D USG) (*n*=65)	*P*
Age (years)[a]	31.5±3.7	30.8±3.4	0.25
BMI (kg/m²)[a]	25±4.1	25.3±3.1	0.72
Type of infertility[b]			
Primary	53 (81.5)	50 (76.9)	0.52
Secondary	12 (18.5)	15 (23.1)	
Infertility factor[b]			
Tubal factor	43 (66.2)	33 (50.7)	0.15
"Male factor"	13 (20.0)	22 (34.0)	
Unexplained	9 (13.8)	10 (15.3)	
Day 2 Serum FSH (mIU/ml)[a]	5.6±1.6	5.5±2.0	0.66
Serum AMH (ng/ml)[c]	3 (1.8–8.1)	3 (1.8–5)	0.34
Antral follicle count[a]	12.5±3.7	11.7±3.5	0.24
Total dose of gonadotropin (IU)[a]	3570.4±1123.8	3301.5±1088.6	0.16
Total duration of stimulation (days)[a]	11.5±1.8	11.2±1.8	0.26
Endometrial Thickness on day of trigger (mm)[a]	9.6±1.6	9.1±1.6	0.08
Serum estradiol on day of trigger (pg/ml)[c]	3668 (865–10030)	3557 (1087–9481)	0.86
Serum progesterone on day of trigger (ng/ml)[c]	1.2 (0.3–5.8)	1.3 (0.4–11.3)	0.62
Total number of follicles on the day of hCG trigger (*n*)[a]	25.3±9.2	8.4±2.4	<0.01
Number of follicles in follicle size range (*n*)[c]	MFD	MFD	
<14 mm	6 (0–15)	0 (0–2)	<0.01
14–16.9 mm	4 (0–9)	2 (0–5)	<0.01
≥17 mm	3 (0–7)	3 (0–6)	0.95
Number of follicles in follicle size range (*n*)[c]	dV	MFD	
<14 mm	7.5 (0.5–19)	0 (0–2)	<0.01
14–16.9 mm	3.5 (0.5–8.5)	2 (0–5)	<0.01
≥17 mm	1.5 (0–4.5)	3 (0–6)	<0.01

Data were presented as [a]Mean±SD, [b]*n* (%), [c]Median (minimum–maximum). SD=Standard deviation, MFD=Mean follicular diameter, DV=Volume-based diameter, SonoAVC=Sonography-based Automated Volume Count, 2D USG=Two-dimensional ultrasonography, BMI=Body mass index, FSH=Follicle stimulating hormone, AMH=Anti-Mullerian hormone, hCG=Human chorionic gonadotropin

Table 2: Assisted reproductive technology outcomes

Outcome parameter	Group A (SonoAVC) (*n*=65)	Group B (2D USG) (*n*=65)	*P*	Difference in means or proportion	95% CI Lower limit	95% CI Upper limit
Primary outcomes						
Number of oocytes retrieved[a]	9.2±4.3	9.1±4.1	0.85	0.1	−1.3	1.6
Number of MII oocytes[a]	4.3±3.0	4.6±2.8	0.51	−0.3	−1.4	0.7
Secondary outcomes						
Fertilization rate (%)[a]	70.0±17.8	73.6±16.0	0.23	−3.6	−9.5	2.3
Embryo cleavage rate (%)[a]	92.0±10.8	92.2±11.3	0.92	−0.2	−3.7	4.0
Total number of embryos[b]	4 (1–18)	4 (0–14)	0.18	-	-	-
"Time taken to perform scans (min)"	6.2±0.7	7.6±0.8	<0.01	−1.4	−1.7	-1.2
Other outcomes						
Clinical pregnancy rate[c]	27.7 (18/65)	26.2 (17/65)	0.88	1.5%	−13.7	16.8
Miscarriage rate[c]	4.6 (3/65)	3.1 (2/65)	0.66	1.5%	−5.2	8.1
LBR[c]	23.1 (15/65)	23.1 (15/65)	1	0	−14.5	14.5

Data were presented as [a]Mean±SD, [b]Median (minimum–maximum) and [c]Percentage (*n*). SD=Standard deviation, SonoAVC=Sonography-based Automated Volume Count, 2D USG=Two-dimensional ultrasonography, CI=Confidence interval, MII=Metaphase II, ART=Assisted reproductive technology, LBR=Live birth rate

rate, and LBR. Moreover, it is observed that, in the SonoAVC group, only 36% of the follicle count yielded oocytes. In the 2D USG group, the oocytes retrieved were more than the follicle count on the day of hCG and nearly 8% of follicles containing oocytes were missed during ultrasound. However, this did not affect the IVF outcomes and may be of doubtful significance. Importantly, the time taken to perform the scan was significantly reduced in the SonoAVC group. Hence, our study has shown that automated follicular tracking
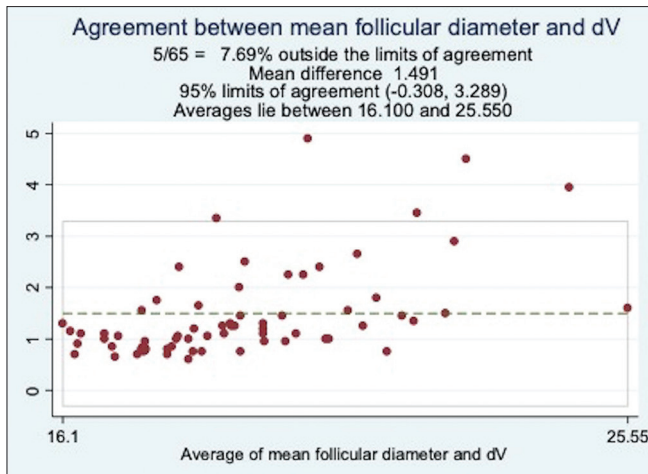
Figure 2: Graph shows the agreement between the mean follicular diameter (mn.d) and the volume-based diameter (dV) of the leading follicle in SonoAVC Group. A mean difference of 1.5 mm was found between the two parameters which was statistically significant

is as good as manual USG with respect to assisted reproductive technology (ART) outcomes in patients undergoing IVF-embryo transfer (IVF-ET).

SononAVC measures even smaller follicles which may be missed during manual measurements giving a large follicle count on the day of trigger. We need to be mindful of the fact that a follicle is more likely to contain a mature oocyte when it measures between 12 and 24 mm in diameter,[8] thereby, smaller follicles may not yield oocytes. Similar to our findings, the randomized controlled trial (RCT) conducted by Raine-Fenning *et al.*[9] also found oocyte yield to be comparable in the two groups. In contrast to our results, a significantly higher number of fertilized oocytes were found in the 3D group in the study conducted by Murtinger *et al.*[10] However, this did not translate into significantly higher pregnancy rates. In our study, no significant difference was obtained in IVF outcome which may be attributed to the fact that a single experienced clinician had carried out all the scans. However, in practice where there are several observers, 3D USG can be expected to reduce the inter- and intra-observer variation. That said, there is a paucity of literature comparing the pregnancy and LBRs in the two groups.

The time taken for performing the scan was significantly higher in the 2D USG group. This fact is agreed upon by several studies.[11,12] Raine-Fenning *et al.*[13] were the first to investigate time gained in stimulated cycles. In their study, 89 patients underwent an ultrasound scan on the 10th day of stimulation. The authors established that time required using the automatic 3D method was significantly shorter ($P < 0.01$) than using conventional 2D technology (180.50 ± 63.6 s vs. 236.1 ± 57.1 s,

respectively). In another study by Rodríguez-Fuentes *et al.*,[14] ultrasound lasted 9.6 min on average using conventional 2D technology compared with 5.6 min using automatic monitoring. Deutch *et al.*[12] found that SonoAVC saved 3.8 min per ovary and 7.6 min per patient. When time needed for postprocessing was deducted, the software required 5.8 s on average to determine the diameter of all follicles, compared with 56.8 s for the manual method ($P < 0.01$).[12] Hence, SonoAVC can make the workflow better by saving time needed for the ultrasound monitoring, along with better standardization and reproducibility of measurements.[11] The advantage of the time gained can be utilized in busy IVF units with high turnover rate. This may help in reducing the load on the clinic as well as reducing waiting time and associated anxiety in women undergoing IVF.

SonoAVC derived MFD was 1.5 mm larger than dV for the leading follicle in this group suggesting that dV tends to underestimate follicular size. Other authors have also reported a discrepancy between MFD measured by 2D USG and dV measured by the SonoAVC technique, with the mean difference ranging from 1.02 mm to 0.9 mm.[15,16] The mathematical principles of SonoAVC calculations may be able to explain these differences. Volume-based diameter dV is the relaxed sphere diameter of a perfect sphere with the same volume as the follicle. The mean of three maximal diameters of an irregular follicle will always be greater than the diameter of a perfect sphere with the same volume. This discrepancy tends to increase as follicle size increases.[16] Debatably, replacing 2D ultrasound-based follicle tracking with SonoAVC without adjusting for potential differences, may result in shifting the timing of hCG injection and oocyte collection in some cases. However, it is not known whether it will have an effect on the IVF outcomes and requires detailed study.

SonoAVC offers a spectrum of advantages over conventional 2D USG. It takes less time, reduces the discomfort of a prolonged ultrasound examination for the patient, has very good reproducibility, and is of particular advantage for busy IVF clinics.[2,9-11] Further with the advancement in technology and exploitation of artificial intelligence, automated scans may form the basis of developing models where-in images generated from such software can be digitalized to build in algorithms that obviate human error and need for human resources.[17]

SonoAVC software is not without limitations. A clear 2D image with well-defined follicular margins needs to be focused before the 3D sweep. The software may fallaciously consider neighboring blood vessels, cysts

or encysted collections as follicle and hence requires postprocessing. Poor resolution of ultrasound image, particularly in patients with high BMI, may result in more artefacts, increasing the post-processing time and making SonoAVC counter-productive. Another important disadvantage is that the machine is costly.[14,18]

The advantages of our study were the adequate sample size, well-formulated study design, homogeneity of subjects, and stimulation protocol and that all the scans were done by a single person obviating performance bias. However, our study population chiefly consists of normo-responders and therefore the results may not be extrapolated to some common factors such as PCOS and endometriosis. Another limitation of the study was that we did not take LBR as a primary outcome and sample size was calculated based on the "number of oocytes retrieved" which was the primary outcome measure of our study. More RCTs are warranted in this regard with LBR as the primary outcome and huge sample size to make the evidence more robust which can be accomplished only in a multicenter trial setting. We conclude that SonoAVC USG can be considered as an alternative to manual 2D follicular tracking in patients undergoing IVF-ET without compromising ART outcomes with the added advantage of saving time.

CONCLUSION

Automated SonoAVC ultrasound can be used interchangeably with manual 2D USG for follicle tracking during COS giving comparable ART outcomes with the added advantage of saving time. It also offers the promise of application of artificial intelligence in follicular tracking during COS.

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Conflicts of interest
There are no conflicts of interest.

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