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Automation of follicular measurements during ovarian stimulation using a convolutional neural network

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ABSTRACT

Background: The study aims to investigate the clinical use and measurement accuracy of the Cycle Clarity convolutional neural network follicle identification platform in ovarian simulations compared to SonoAVC and manual measurements by ultrasonographers.

Methods: This was a prospective cohort study conducted in a private reproductive endocrinology and infertility clinic. The study involved 157 ovarian ultrasound examinations from 66 women undergoing ovarian stimulations for infertility treatment. Follicular ultrasound measurements were performed manually by ultrasonographers, SonoAVC, and the Cycle Clarity convolutional neural network. The primary endpoint was the median size (mm) of ovarian follicles in Cycle Clarity compared to SonoAVC and ultrasonographer measurements. A key secondary endpoint was the number of ovarian follicles greater than or equal to 10mm in size in Cycle Clarity compared to SonoAVC and ultrasonographer.

Results: Sixty-six participants were enrolled, and 152 ovarian ultrasound examinations were performed on 114 unique ovaries as some patients were ultrasound on more than one visit. The ultrasonographer detected 815 follicles greater than or equal to 10mm in size with an average diameter of 14.55mm. Cycle Clarity without post-image proceeding detected 740 follicles with an average diameter of 14.87mm, a difference of 2.2%. 71 ovaries were imaged by both SonoAVCTM and Cycle Clarity. The median size (mm) of ovaries compared to the gold standard human read reduces the bias of Cycle Clarity by 2.69mm (95% CI: 1.97, 3.41), which indicates superiority and not just non-inferiority compared to SonoAVCTM. Ultrasound examinations were significantly faster with Cycle Clarity, including post-image analysis of 81.96 seconds compared to the ultrasonographer 706.79 seconds with an overall savings of 608 seconds per patient.

Conclusion: Cycle Clarity image analysis produced measurements equivalent to human measurements and superior to SonoAVC with significant time savings for the patient and clinical team.

KEYWORDS

Ovarian stimulation; Convolutional neural network; Follicular measurements; Ultrasonography; Infertility treatment; Reproductive endocrinology

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Introduction

Infertility affects approximately 19% of American couples and 25% of couples from developing countries [1]. This represents a total of over 200 million couples per year affected by infertility. For couples with infertility, two primary treatment options are available. The first option is typically a combination of ovulation induction and intrauterine insemination using oral agents or injectable gonadotropins with the hopes of developing 1-3 follicles during the ovarian stimulation. The second option is the use of assisted reproductive technologies (ART), typically in vitro fertilization (IVF), which uses the infertile couples' eggs or egg donation. Both forms of ART require controlled ovarian hyperstimulation (COH), which typically uses exogenous gonadotropins to recruit multiple oocytes, which ultimately are retrieved, fertilized, and the resulting embryos are later transferred into the uterus to enhance the pregnancy rates.

In ART, there are multiple different regimens for COH. However, a central tenant is to understand the number and size of the developing follicles to forecast the optimal time of oocyte retrieval. For safety and efficacy, COH is closely monitored with transvaginal ultrasound and hormonal assessment to adjust medication doses and the duration of the stimulation. Ultrasound monitoring allows the visualization of hypoechoic structures within the ovary, referred to as follicles, that contain the developing oocyte. The number and size of the follicles grows until peak maturity, which is typically between 18 and 21mm of average follicular diameter.

Ultrasound monitoring of the follicles is primarily performed with two dimension (2D) ultrasound, which can be challenging as the ovary and follicle are both 3 dimensional (3D) structures. The clinical goal is to measure the maximal average diameter averaged from two measurements performed perpendicularly [2]. To understand the complete follicular cohort, each follicle in the ovary greater than 10mm in size is typically measured. This ultrasound monitoring process is time-consuming for both the clinical team and the patient as frequently there are more than 10 developing

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follicles on each ovary. Identifying the maximal follicular diameter has significant inter and intra-observer variability. Foreman et al., 1991 compared four ultrasonographers measuring the same ovarian follicles of patients undergoing ovarian stimulation, demonstrating an intraobserver variability of 2mm (13%) range of measurement for a 15mm follicle and an interobserver variability of 3mm (20%) for a 15mm follicle [3,4].

3D measurements of anatomic structures, including the ovary have been available for years. Software applications are available from most ultrasound manufacturers' including Phillips InnoSight™, Samsung's 5D Follicle™ and Mindray Smart FLC™ and General Electric SonoAVC™. These technologies typically utilize edge detection algorithms and are semi-automatic technology that still requires significant assessment by the investigator, with over 20% of the images needing to be manually analyzed. The most studied is SonoAVCTM. Raine-Fenning studied 89 women undergoing IVF treatment and found a correlation between SonoAVC™ and conventional 2-dimension (2D) ultrasound of 0.84 with a SonoAVC™ time saving of less than one minute per patient [5]. Approximately 5% of patients cannot be monitored with the automatic technology, and another 15% require intensive postprocessing time by the clinical team. SonoAVC™ appeared to provide underestimated measurements compared with manual 2D measurements, and Sutter et al., therefore, concluded that SonoAVC™ is an automatic technology that still requires significant assessment by the investigator with over 20% of the images needed to be manually analyzed [5]. This assessment is further reinforced by Rodriguez-Fuentes et al., who in 2010 demonstrated in a prospective study of 58 women undergoing IVF that due to image quality issues, SonoAVC™ was only able to accurately correlate 62% of the ultrasound images [6].

Understanding the challenges associated with ultrasound monitoring of follicles in an ovarian stimulation cycle and the challenges associated with the current 2D and 3D technologies, Cycle Clarity has developed an artificial intelligence-based, FDA-cleared software platform (software as a medical device, SAMD) that can identify and measure developing follicles with the use of machine learning (ML) based on a Mask Region-based Convolutional Neural Network (R-CNN) which is new to the state of art architecture for instance segmentation of non-medical images. Cycle Clarity is an ultrasound manufacturer agnostic software application that can identify and measure developing follicles using machine learning. 3D images are acquired from the ultrasound machine, and the machine learning algorithms process and analyze the images, providing an assessment of the number and sizes of follicles. Moreover, machine learning can improve its accuracy, precision, and recall rate over time as additional annotated files are used for training over time.

This study aims to evaluate the validity of Cycle Clarity's Artificial Intelligence software (CCAI) for real-life measurements and counting of detected follicles compared to conventional 2D ultrasound measurements performed by an ultrasonographer. The solution will be evaluated for its accuracy, precision, and level of agreement with respect to manual 2D measurements and SonoAVC™ (Sono).

Materials and Methods

This cross-sectional study of infertile women undergoing ovarian stimulation was performed at Coastal Fertility Specialists, a single fertility clinic in Mount Pleasant, South Carolina, USA. This study was approved by the Western Institutional Review Board (Western IRB Pr. No.: 20203077, October 9, 2020). The first enrollment is February 17, 2021. Written consent was obtained from all participants.

Patient population

Patients with infertility between the ages of 21 and 45 years of age seen at Coastal Fertility Specialists undergoing ovarian hyperstimulation meeting the inclusion criteria were enrolled. Inclusion criteria included a patient having at least one ovary visible with transvaginal ultrasound with a follicle greater than or equal to 10mm in average size. Sixty-six participants were enrolled, and 157 ovarian ultrasound examinations were performed on 114 unique ovaries. Due to the frequency of ultrasound examinations during a treatment cycle, some patients were ultrasound more than one time.

Study protocol

This study is a prospective study to determine primary and secondary outcomes. This study is designed to evaluate the accuracy, precision, and level of agreement of the Cycle Clarity Mask R-CNN follicle segmentation and quantitation method in analyzing ultrasound images of patients undergoing ovarian stimulation for infertility treatment as a result of an infertility diagnosis. The results generated by the Mask R-CNN were not used in patient care. Enrollment comprised informing potential participants of the study objectives, design, duration, participant requirements, risks of participation, and potential benefits. Subjects, the females of any race, 21-24 years of age, undergoing ovarian hyperstimulation as part of the treatment care, with a follicle of at least 10mm in average diameter, screened, and if meeting inclusion criteria, will be enrolled in the study. Transvaginal ultrasound monitoring was performed by the team of 3 ultrasonographers using a 3D ultrasound probe on a GE Voluson E6 BT 13.5 ultrasound machine, a Siemens S2000, and a Philips EPIQ 5. Transvaginal ultrasound was performed on each ovary first with 2D ultrasound with the maximum diameter of each follicle measured in 2 dimensions perpendicular to each other and averaged. When ultrasound was performed on a GE ultrasound machine, GE SonoAVC™ on the GE Voluson E6 BT 13.5 ultrasound machines were used to semi-automatically measure the number and size of the developing follicles with 3D ultrasound sweeps of the ovaries.

After the ultrasound examination, 3D video images obtained from a 10-second volume sweep were transmitted through a Virtual Private Network (VPN) and analyzed by the Cycle Clarity Mask R-CNN method. The processing of images was performed by the software application residing on a secured Microsoft Azure cloud server with two-factor authentication. Using the FDA-cleared Softneta DICOM viewer, an ultrasonographer other than the original ultrasonographer performing the study performed an assessment of the number of follicles in each ovary greater than 10mm in size [3]. Ultrasound acquisition time was measured in seconds as the time from ultrasound probe placement to the completion and transmission of the ultrasound results. The ultrasonographer time required for Cycle Clarity post-image analysis was measured by the platform as the time from image download until the ultrasonographers marked the analysis as complete.

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Post-image analysis results were not performed for images from the Siemens machines due to the larger file size.

Statistical analysis

Study enrollment and imagining were performed per the protocol. Protocol deviations occurred, affecting 5 image acquisitions. The protocol deviations occurred due to improper saving of the Cycle Clarity image on the ultrasound machine by the ultrasonographers, resulting in no Cycle Clarity images being saved and sent for analysis on these five participants.

Sample size and assumptions

For both the primary and key secondary endpoints, two one-sided hypothesis tests (TOST) were tested. Each one-sided alpha was tested at α=0.025. For the primary endpoint, assuming a bias of 0mm and a standard deviation of 3, 13 ovaries are required to achieve a power of 0.90. For the key secondary endpoint, assuming a bias of 1 follicle and a standard deviation of 7.5, 120 ovaries are required to achieve a power of 0.90. The study was therefore, powered to accommodate the key secondary endpoint.

For each ovary, the number of follicles and the median size of the follicles were considered of clinical importance. The median follicle size was the primary endpoint. All measurements analyzed were without post-image processing. All endpoints were assessed by each of the three different ultrasound brands utilized in the study. Based on the gold standard of an ultrasonographer read on 2-D images for follicle size and both 2-D and 3-D (if available) ultrasonographer reads for the number of follicles, if the results differed, the 3-D result would be used in analyses, Schuirmann's two one-sided tests (TOST) method (Schuirmann, 1987) was utilized [7].

Primary endpoint of ovarian median follicle size

Based on the ultrasonographer read (Gold Standard (GStd)), all follicles < 10mm will not be included in the analysis. After excluding CCAI and Sono follicles measuring <10mm, the median follicle size per ovary was assessed for CCAI and Sono. The difference between the CCAI and Sono medians minus the GStd was then calculated. The primary endpoint is the difference between the bias of CCAI and Sono with the GStd. The primary endpoint states that the mean of the difference in median follicle size compared to GStd per ovary for CCAI is no more than +/- 3mm compared to Sono.

The primary hypotheses for the study are:

H_0: $\mu_{CCAI(med)} - \mu_{Sono(med)} < -3$ or $\mu_{CCAI(med)} - \mu_{Sono(med)} > 3$

H_1: $-3 \leq \mu_{CCAI(med)} - \mu_{Sono(med)} \leq 3$

Key secondary endpoint of ovarian number of follicles

For each ovary, the number of follicles ≥ 10mm will be assessed. The average difference between CCAI and GStd will be assessed by testing the following hypotheses:

H_0: $\mu_{CCAI(N)} - \mu_{Sono(N)} < -3$ or $\mu_{CCAI(N)} - \mu_{Sono(N)} > 3$

H_1: $-3 \leq \mu_{CCAI(N)} - \mu_{Sono(N)} \leq 3$

Accuracy of CCAI and Sono across the follicle count (<5, 5 to <10, 10 or more) and median, mean, minimum, and maximum follicle size (mm) dynamic range (<12, 13 to 15, 16 to 18, 19 to 21, 21 to 23, and >23mm). The study enrolled 66 participants. A minimum of 120 ovarian ultrasounds were required to achieve a power of 0.90. 157 ovarian ultrasounds were performed on 114 ovaries during 80 patient visits, 1,2,3. All 66 participants completed the study.

All statistical procedures were completed using SAS® version 9.4 or higher. Continuous variables were summarized using descriptive statistics, including the number of patients with non-missing value (n), mean, median, SD, minimum, and maximum. "n" are presented without a decimal point, minimum and maximum values are presented in the same precision as in the database, mean and median are presented in one more decimal place than the minimum and maximum, and SD are presented in one more decimal place than the mean and median. For categorical variables, summaries include counts of patients (frequencies) and percentages. Percentages are rounded to one decimal place. All patient data, including those derived, will be presented in individual patient data listings.

Results

Sixty-six participants were enrolled, during which 157 ovarian ultrasound examinations were performed on 114 unique ovaries, as some patients were ultrasound on more than one visit. The 157 ultrasound examinations yielded 152 evaluable ovarian assessments, as 5 images were not saved properly by the ultrasonographers. Patient demographics can be seen in Tables 1 and 2. Per protocol, the majority of ultrasounds were performed on GE ultrasound machines.

Table 1. Patient demographics.

	GE SonoAVC n=38*	Phillips n=19	Siemens n=17	All Subjects N=66
Age (years)				
Mean (SD)	35.2 (5.12)	33.7 (4.63)	32.8 (3.88)	34.5 (4.85)
Median	35.2	34.2	33.6	34.5
Min, Max	22.9 - 43.1	22.4 - 45.4	23.4 - 38.1	22.4 - 45.4
Race [n]				
Asian	0	1	0	1
Black	2	0	0	2
White	36	18	17	63
Ethnicity [n (%)]				
Hispanic or Latino	2	0	2	3
Non-Hispanic, Non-Latino	36	19	15	63

*8 subjects had one ultrasound performed with the GE SonoAVC and one with the Siemens ultrasound.

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Table 2. Evaluable ultrasounds by ovary, number of mean follicle measurements evaluated.

Variable	All Subjects, N (Subjects with at least 1 follicle > 10 mm per ultrasound)
Number of subjects (total ovaries)	66 (114)
Both ovaries	48 (96 ovaries)
Left ovary, only	4
Right ovary, only	14
Number of visits by subject	n=80
Visit 1	66
Visit 2	12
Visit 3	2
Manufacturer	n=152
GE Healthcare	71
Philips Medical Systems	38
Siemens	43

Of the 152 ovarian ultrasounds performed by both the ultrasonographer and CCAI, the ultrasonographer detected 815 follicles greater than or equal to 10mm in size with an average diameter of 14.55mm. CCAI without post-image proceeding detected 740 follicles with an average diameter of 14.87mm, a difference of 2.2% (Table 3).

The primary endpoint for this study was to compare the performance of the CCAI software and Sono software in measuring follicles. This was accomplished by calculating 1- the difference between the ultrasonographer measurement and the CCAI measurement and 2- the difference between the ultrasonographer measurement and the Sono measurement and then comparing 1 and 2. The authors did not directly compare the difference between CCAI and SONO as SONO does not provide specific follicle location within the ovary or video playback to compare individual follicles.

A total of 71 ovaries were imaged by both Sono and CCAI and only follicles 10mm and greater in size as measured by the ultrasonographer were analyzed. Study endpoint evaluations for the 71 imaged ovaries utilizing both Sono and CCAI are summarized in Table 4. Based on 71 matched ovaries, the median size (mm) of ovaries compared to the gold standard human read reduces the bias of CCAI by 2.69mm (95% CI: 1.97, 3.41), which indicates superiority and not just non-inferiority compared to Sono. Both Sono and CCAI overestimated the median ovary size; however, the bias for CCAI was only -3.12mm (SD= 3.20) versus Sono's -5.81mm (SD= 3.54).

Table 3. Mean of all follicle measurements >+ 10mm.

Technique	Ultrasounds	Follicles	Mean	Median	Std Dev	Min	Max
CCAI	152	740	14.87	14.53	3.91	10	34.7
Human	152	815	14.55	14.45	3.63	10	30

Table 4. Primary endpoint analysis.

Variable	N	Median (mm)	Std Dev
Median Follicle Measurement made by CCAI	71	14.53	2.255
Median Follicle Measurement made by Ultrasonographer	71	14.45	2.445
Median Follicle Measurement made by Sono	71	14.93	3.175
Median Difference between CCCAI and Ultrasonographer	71	0.08	1.866
Median Difference between Sono and Ultrasonographer	71	0.48	2.662
Diff: -0.4035, 95% CI: -1.1061 to 0.299, p-value 0.2559			

*A paired t-test was used for statistical analysis

The number of follicles detected was considered a secondary endpoint for the trial. To enhance accuracy, all images were reviewed by a second ultrasonographer using a DICOM viewer, counting all follicles greater than or equal to 10mm in size (Tables 5 and 6). The initial ultrasonographer read detected 5.86 follicles per ovary compared with the second ultrasonographer's DICOM viewer read of 6.22 follicles. CCAI detected 5.76 prior to post-image processing.

Comparison of the mean diameter (mm) of the ovarian follicles 10mm or greater in size analyzed with CCAI versus

Table 5. Number of follicles 10mm or greater identified by ultrasonographer (initial read), second read by ultrasonographer, and CCAI.

Simple Statistics						
Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
Initial Ultrasonographer Read	152	5.82	4.8	891	1	27
Second Read by Ultrasonographer	152	6.22	4.72	945	1	29
CCAI	152	5.76	4.51	876	0	26

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the ultrasonographer measurements made from ultrasounds taken from the Philips EPIQ 5 and Siemens S2000 ultrasound machines were also made (Table 7). In all cases, CCAI measurements were substantially equivalent to the human read measurements.

The average time for acquisition of follicular measurements varied significantly between ultrasonographer measurements and CCAI measurements, with CCAI having decreased ultrasound acquisition times in all categories. Overall, the acquisition time was 706.79 seconds for ultrasonographer measurement of all follicles in two dimensions compared to 16.72 seconds for CCAI with an average ultrasonographer CCAI post-image analysis time of 81.96 seconds (Table 8).

Table 6. Number of follicles 10mm or greater identified by ultrasonographer (initial read), second read by ultrasonographer and CCAI. Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations.

	Initial Ultrasonographer Read	Second Read by Ultrasonographer	Follicle Clarity
	1.00000	0.76331	0.89669
		<.0001	<.0001
Initial Ultrasonographer Read	152	152	152
	0.76331	1.00000	0.80813
	<.0001		<.0001
Second Read by Ultrasonographer	152	152	152
	0.89669	0.80813	1.00000
	<.0001	<.0001	
Follicle Clarity	152	152	152

Table 7. Comparison of the mean size of the median follicle measurement by ultrasound manufacturer compared to CCAI.

Philips (n=38)	Mean: 0.3158 (95% CI: 0.0188, 0.6128)	p-value: 0.0378
Siemens (n=43)	Mean: 0.1395 (95% CI: -0.1169, 0.3196)	p-value: 0.2784
GE (n=71)	Mean: -0.4648 (95% CI: -1.1645, 0.2349)	p-value: 0.1895

* Paired t-test used for statistical analysis

Table 8. Comparison of the ultrasound measurement acquisition time between.

	Median Follicle Measurement Time (sec) made by Ultrasonographer	Median Follicle Measurement Time (sec) made by CCAI	Post Image Analysis Time (sec)	Difference (sec)	P value
Patients One Ovary	424.52	10	57.5	357.02	<0.0001
Patients Two Ovaries	840	20	97.1	722.9	<0.0001
Patients ≤ 5 Follicles	490.29	12.57	49.9	427.82	<0.0001
Patients ≥ 10 Follicles	940.47	19.86	58.6	862.01	<0.0001

Discussion

Studies have demonstrated the ability of artificial intelligence to meet or exceed the performance of human experts on several tasks of medical image analysis, including systems of detection of breast cancer, lung cancer, eye disease, and kidney injury [8-12]. This is the first study to assess the feasibility and real-time clinical use of automating follicular identification and measurements with an artificial intelligence software network. Artificial intelligence may be uniquely positioned to help with medical image analysis challenges due to enhanced computational speeds and the ability to improve over time with additional training.

In this study, we present an FDA-cleared medical device (K212012, January 2021) developed by Cycle Clarity to identify and measure follicles within the ovary. The results of this prospective clinical trial demonstrate the accuracy of ovarian follicular measurement equal to the human and superior to GE SonoAVC™. The study design used human measurements as the gold standard and therefore, superiority between Cycle Clarity measurements and human measurements would not have been possible. The Cycle Clarity recurrent convolutional neural network used in this study is the product of an annotation project that included first the anonymizing of all images followed by the annotation of 91,782 follicles in 19,776 images of women undergoing ovarian stimulations for treatment of infertility. The AI-driven solution is based on a Mask Region-based Convolutional Neural Network (Mask R-CNN), which is new to the state-of-the-art architecture for instance, segmentation of non-medical images shows the generalizability and device-agnostic approach as this trial utilized ultrasound machines manufactured by General Electric, Siemens and Philips with measurement accuracy similar between the different systems. Image acquisition time measuring each of the follicles ≥ 10mm in two dimensions was significantly decreased between the ultrasonographer performing manual measurements and Cycle Clarity's automated measurements, including post-image processing, saving approximately 10 minutes per patient. The difference

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between Cycle Clarity manual measurements was 0.32mm or 2.2%, with a difference in follicular count of 0.21 follicles, which are both clinically insignificant.

Limitations of this study include the relatively small sample size of 152 ovarian ultrasounds. An additional limitation is the Cycle Clarity data was not used for clinical decision making and therefore, its impact could not be assessed with embryology outcomes. Additional studies will be necessary to determine the impact of Cycle Clarity's complete follicular analysis on oocyte number, maturity, fertilization, and blastocyst development. We live in a time when there are increased time pressures on clinical teams performing fertility treatment due to healthcare staff shortages and declining insurance reimbursement relative to inflation. Compounding the problems include a shortage of board-certified reproductive endocrinologists and a significant demand for ultrasonographers in hospitals and other medical specialties. As a result of these time pressures, clinics frequently measure the largest three to four follicles in one or two dimensions and don't monitor each and every developing follicle. Cycle Clarity has the unique ability to not only measure all of the follicles in the ovary 42 times faster but also provide a complete assessment of the follicular cohort to help physicians better understand the optimal time of oocyte retrieval.

Conclusions

The study showcased the ability of the software platform to provide accurate and efficient measurements, with performance comparable to human assessments and an advantage over existing ultrasound technology, particularly GE SonoAVC™. It significantly reduced the time required for follicle measurements, which is crucial given the time constraints and workforce shortages in fertility treatment. The minor discrepancies in follicle size and count compared to human assessments were deemed clinically insignificant, highlighting the software's reliability. However, it's essential to acknowledge the study's limitations, such as the relatively small sample size and the need for further exploration of the software's impact on clinical decision-making and embryology outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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