

Precision Follicular Self-Measurement Using a Pocket-Sized Transabdominal Ultrasound Device

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Abstract

Background: The purpose of this study was to determine the comparability of follicle diameters measured using a pocket-size transabdominal ultrasound (TAUS) device that produces images for self-assessment versus those measured using a conventional transvaginal ultrasound (TVUS) device. The pocket-sized device is fitted with a probe that can be connected to an electronic tablet for patient use and outputs follicle images for patient review.

Methods: A prospective study was performed in 25 women (50 follicles) who underwent in vitro fertilization (IVF)/intracytoplasmic sperm injection between November 2019 and March 2020 to treat infertility. Patients were first provided with guidance from a doctor; then, they used the probe attached to the pocket-sized TAUS device to acquire the follicle images. The doctor then measured the follicle diameter using a TVUS device and compared the measurements with those obtained by viewing the images taken by the patient. The transverse cross-sectional follicle diameter measured on transabdominal images was defined as the abdominal transverse (AT) diameter. The sagittal and coronal cross-sectional follicle diameters measured on transvaginal images were defined as the vaginal sagittal (VS) and vaginal coronal (VC) diameters, respectively. The mean values of each parameter and the variance ratio of the difference between the TAUS and TVUS measurements were evaluated.

Results: The results showed that the difference between AT-VS in the two imaging types was -0.382 mm (95% CI: -1.097-0.333 mm, P=0.288), whereas the difference between AT-VC was 0.342 mm (95% CI: -0.345-1.029 mm, P=0.322), and that between VS-VC was 0.724 mm (95% CI: 0.152-1.296 mm, P=0.014). The variance ratios for the differences between the TAUS and TVUS measurements and for the differences between the two TVUS cross-sectional measurements were $\sigma_{AT-VS}^2/\sigma_{VS-VC}^2=1.56$ and $\sigma_{AT-VC}^2/\sigma_{VS-VC}^2=1.44$, respectively.

Conclusion(s): Despite the presence of some differences in precision due to differences in the method of imaging when patients performed follicular self-measurement using pocket-sized devices, there was little scattering. Therefore, this method can be used to measure follicle diameter at a precision that presents no issues at the clinical level.

Trial Registration: Medical Park Shonan (2019001, 25 October 2019)

Plain English Summary

Follicular self-measurement using a pocket-size transabdominal ultrasound device offers the same degree of precision as conventional follicular measurements performed by a doctor using a transvaginal ultrasound device.

Background

The growth of ovarian follicles must be monitored during controlled ovarian stimulation (COS) as part of in vitro fertilization (IVF), and for this purpose, we perform transvaginal ultrasound (TVUS) examination and measure serum estradiol levels [1]. This allows appropriate timing of the administration of human chorionic gonadotropin (hCG) and gonadotropin releasing hormone agonist, which in turn facilitate the development of mature ova. In addition, careful monitoring of the ovaries during stimulation may reveal excessive follicular growth, which can function as a kind of alert system to adjust the dose of gonadotropin to avoid the onset of ovarian hyperstimulation syndrome [2].

Kratochwil et al. first reported on the use of TAUS computed tomography (CT) to perform follicle measurements, and since then, several reports have confirmed the usefulness of ultrasound-based follicle measurements to retrieve mature ova for in vitro fertilization (IVF) [3]. Reports from the 1980s suggested that TVUS was better for follicle measurement than TAUS at the time, and to date, TVUS is still the standard for monitoring follicle measurements when treating infertility [4, 5].

However, there are certain disadvantages to performing monitoring using TVUS. Since the follicle measurement must be monitored frequently for the purpose of IVF, women undergoing infertility treatment must make several visits to the hospital or clinic where they receive treatment. These monitoring visits place a great amount of strain on women, particularly working women, who are required to schedule hospital visits into their already busy lifestyle. There are some easy methods that patients may use at home, such as basal body temperature or urinary luteinizing hormone measurements to predict and detect ovulation, but these are not suitable for IVF.

Traditionally, medical devices were expensive, heavy, consumed large amounts of power and therefore could not be used outside of hospitals. However, in recent years, advances in technology have enabled the development of medical devices that are more cost-effective, smaller and consume less power. Recently, considering diagnostic ultrasound (US) devices, pocket-sized mobile devices have become popular within the fields of obstetrics and gynecology [6, 7], gastroenterology [8], cardiology [9], pulmonology [10], rheumatology [11] and emergency medicine [12]. Such devices are also expected to be critical equipment in rural areas and emerging economies [13]. If these pocket-sized US devices can be applied during IVF, it may reduce the burden placed on patients by lessening the frequency of hospital appointments.

Here, we compared the follicle diameter measurements obtained by a doctor using conventional TVUS to those obtained by patients from their own images acquired by using the pocket-sized TAUS, and verified their accuracy and precision.

Methods

Subjects

This study was conducted after approval by the institutional review board at Medical Park Shonan and Medical Park Yokohama between November 2019 and March 2020. Our patients, who were aged between

20 and 45 years old with BMI values of $\leq 30 \text{ kg/m}^2$, gave informed consent to participate in the study. We also measured the dominant follicle (follicle with a mean diameter $\geq 10 \text{ mm}$) in each ovary in patients undergoing controlled ovarian stimulation (COS). Data were obtained from follicle images suitable for evaluation that were either collected by the patient or by the doctor. Patients exhibiting development of ≥ 4 follicles in either ovary were excluded from the study as it would be difficult to identify the individual follicles.

COS techniques

The COS protocol is described as follows: (a) The CC-Gn method: the patient is administered clomiphene citrate at a dose of 50 mg/day from day 3 of the menstrual cycle and recombinant follicle-stimulating hormone (rec-FSH) or human menopausal gonadotrophin (HMG) at a dose of 225 IU on day 5 administered on alternate days; (b) The letrozole-FSH method: the patient is administered letrozole at a dose of 5 mg/day from day 3 to day 7 of the menstrual cycle and then receives rec-FSH injections at a dose of 150 IU on consecutive days from day 7 until the date of hCG administration; (c) The letrozole method: the patient is administered letrozole at a dose of 5 mg/day from day 3 of the menstrual cycle on consecutive days; (d) The short method: the patient is administered a GnRH agonist (buserelin acetate at a dose of 300 $\mu\text{g/day}$) from day 2 of the menstrual cycle and HMG at a dose of 300 IU/day on consecutive days from day 3, with hCG administered when the dominant follicle diameter reaches 18 mm. The selection of one of these stimulation methods is left to the discretion of the attending physician.

Follicle self-measurements by the patients using TAUS

The follicle diameter was measured on day 10 of the menstrual cycle or later. First, the patient ensured that their bladder was full, then they laid in the supine position and used a pocket-sized ultrasound device, known as the miruco (Japan Sigmax Co., Ltd., Osaka, Japan), that was fitted with an attached 3.5 MHz convex probe. The patient used the probe to perform a transabdominal scan to determine the transverse cross-section of the left and right ovaries. To do this, the patient scrolled down the left and right sides of the hypogastric region to capture both ovaries in their entirety, and then they stored the resulting videos (Fig. 1a). The entire procedure was performed under the guidance of a highly experienced gynecologist. Next, the acquired videos were stored on a tablet (ASUS) and sent to a computer (Lenovo Thinkpad X280, Lenovo, Tokyo, Japan). The individual ovarian follicle diameters were measured as follows. The maximum ovarian cross-sectional measurement was identified in the videos and saved as a still image. Next, the still images were uploaded to the image processing software ImageJ version 1.51n (National Institute of Health, Bethesda, MD, USA). These images were displayed at a resolution of 1920×1080 pixels on a 21.5-inch liquid crystal display sub-monitor (LCD-MF244ED, I-O DATA Co., Ltd., Kanazawa, Japan), and then the maximum follicle diameter and the diameter of the follicle on the line perpendicular to this diameter were calculated based on the scale used for US images. The mean value of these two values was taken as the abdominal transverse diameter (Fig. 1b).

Follicle measurements by the doctor using TVUS

After TAUS was completed, the doctor who provided guidance during TAUS performed TVUS. The patient was placed in the lithotomy position, and the measurements were taken using a SONOVISTA FX, premium edition (Konica Minolta, Inc., Tokyo, Japan). The dominant follicle in both ovaries was first identified, then the probe was aligned and rotated 90° to obtain the sagittal and coronal cross-sectional measurements. The maximum diameter of both follicles, and the length of the lines perpendicular to these diameters, were measured using the SONOVISTA FX premium edition display, and the mean values for each cross-sectional diameter were taken as the vaginal sagittal (VS) and vaginal coronal (VC) diameters.

Questionnaire

A questionnaire was conducted to enquire whether the patients who performed follicle self-measurement preferred TAUS to TVUS after the measurements were completed.

Statistical analysis

We evaluated the accuracy and precision of follicular size measurements from the pocket-sized US device to confirm whether the same follicular size was depicted in both the mobile US and TVUS images.

1. Evaluation of accuracy

(1) Detection bias

Detection bias was defined as ≥ 1 mm.

(2) Sample size

There were ≥ 48 target follicles in each group.

(3) Analysis method

We tested AT vs. VS and AT vs. VC using the paired t -test to determine the presence of statistically significant differences.

2. Evaluation of precision

The cross-sectional diameters measured using the two aforementioned measurement methods were different. For this reason, we were unable to exclude differences between the cross-sectional diameters measured during imaging when comparing the precision of the two measurement methods. The size of the individual ovarian follicles was also different. In consideration of the above, as shown in equations (I), (II) and (III) below, we calculated the amount of variance for the difference in follicle sizes obtained using TAUS and TVUS.

$$\sigma_{AT-VS}^2 \text{ (I)}$$

$$\sigma_{AT-VC}^2(II)$$

$$\sigma_{VS-VC}^2(III)$$

(III) clarifies the fact that with the TVUS cross-sectional diameter, it is the difference in the type of cross-section (sagittal or coronal) that is the dominant factor. Accordingly, during the comparison of image precision, we calculated the variance ratio to (III), i.e., (I)/(III) and (II)/(III), and performed a comparative evaluation.

Interclass correlation coefficient

The reliability of the measurements obtained using TVUS and TAUS were evaluated using the interclass correlation coefficient (ICC). The ICC ranged from 0 to 1, and the values were defined as follows: < 0.20 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 1.00 almost perfect [14].

Statistical analysis was performed using Minitab version 19, and a p value < 0.05 was considered statistically significant.

Results

It was possible to obtain clear US images from all 25 patients. The patients' characteristics are shown in Table 1. The mean patient age was 37.64 ± 4.07 years (30 to 44 years). The breakdown of ovarian stimulation methods was as follows: 44% (11/25) used the CC-Gn method, 28% (7/25) used the letrozole-FSH method, 24% (6/25) used the letrozole method, and 4% (1/25) used the short method.

The follicle diameters were as follows: AT (TAUS) 17.78 ± 2.87 mm, VS (TVUS) 18.16 ± 3.16 mm, and VC (TVUS) 17.44 ± 2.96 mm. The results for the paired *t*-test for AT vs. VS gave a p value of 0.288, and the mean difference between AT-VS was -0.382 mm, with a 95% CI of -1.097 to 0.333 mm. The p value for AT vs. VC was 0.322, and the mean difference between AT-VC was 0.342 mm, with a 95% CI of -0.345 to 1.029 mm. It was not possible to detect differences of ≥ 1 mm when we compared AT vs. VS and AT vs. VC. Furthermore, the p value for VS vs. VC was 0.014, whereas the mean difference between VS-VC was 0.724, with a 95% CI of 0.152 to 1.296 (Fig. 2).

The scattering for the difference in follicle size was 6.34 between AT and VS (I), 5.85 between AT and VC (II) and 4.05 between VS and VC (III). In addition, the variance ratios were 1.56 and 1.44 for (I)/(III) and (II)/(III), respectively.

The ICCs are shown below (Fig. 3).

$$AT \text{ vs. } VS \text{ vs. } VC \quad ICC(2,1) = 0.69$$

$$AT \text{ vs. } VS \quad ICC(2,1) = 0.65$$

AT vs. VC ICC (2,1) = 0.66

VS vs. VC ICC (2,1) = 0.77

The ICCs are substantial between TAUS and TVUS in accordance with the classification of Landis and Koch [14].

The questionnaire was conducted on all patients at the end of this study, including those who were unable to perform self-measurement, and we received responses from 29 patients. Regarding the two types of self-measurement, the results indicated that 26 patients (89.7%) preferred TAUS self-measurement over TVUS. The reasons for this were the fact that it would have been difficult to manipulate the transvaginal probe by themselves and because they thought that examination via the self-transvaginal procedure would be painful.

Discussion

It was possible to detect differences of ≥ 1 mm when comparing AT vs. VS and AT vs. VC. However, when we confirmed the 95% CI for the mean differences between the AT and VS follicle diameters and the AT and VC diameters (AT-VS, AT-VC), we found that the lower limit for AT-VS (-1.097 mm) and the upper limit for AT-VC (+1.029 mm) differed by only ± 1 mm (± 1.1 mm range). Meanwhile, a significant difference between VS and VC was detected. Based on the 95% CI for the mean VS-VC, there was a minimum difference of ≥ 0.152 mm, suggesting a maximum difference of 1.296 mm. Based on the above, the difference in accuracy between the follicle diameters measured using TVUS and TAUS was slightly greater than ± 1 mm. However, it was smaller than the difference (upper limit of VS-VC +1.296 mm) when only the cross-sectional direction was changed on the TVUS (i.e., when the sagittal cross-section was switched to the coronal cross-section). Based on the above, the images created using the pocket-sized US device are considered to offer accuracy that is clinically acceptable, and they are capable of depicting follicle size.

The following variance ratios were calculated: (I)/(III) = 1.56 and (II)/(III) = 1.44. These values made it clear that there were factors (differences in imaging methods) other than “differences in cross-sectional imaging” causing scattering between AT and VS, and between AT and VC. However, the variance ratios were both ≤ 2 -fold, so it is clear that cross-sectional imaging is a dominant factor causing scattering.

In addition, compared to the TVUS ICCs (ICC between VS and VC), the TAUS ICCs (ICC between AT and VS or AT and VC) were 0.1 units lower and fell into the “substantial” range, so we believe that the scattering caused by the imaging method is within the permissible range [14].

Based on the above, despite the presence of some differences in precision due to differences between the two measurement methods used to determine the follicle diameter, there was little scattering. Therefore, patient-operated mobile US devices can be used to measure follicle diameter at a precision that presents no issues at the clinical level.

In this study, we measured 50 follicles to verify the feasibility of follicular self-measurement using a pocket-sized mobile TAUS device. To date, there are few studies that verify the ability to measure follicle diameter using a patient-operated TAUS device. The TAUS AT and the mean difference and variance ratio of TVUS VS and VC in this study show that the follicle diameters obtained using the pocket-sized mobile TAUS device were identical to those obtained during conventional TVUS.

The cost of diagnostic US devices has dropped markedly in the past few years, and even mobile devices are now able to capture high-quality images. Pocket-sized TAUS devices are small, easy to handle, can be used by the patient to perform self-imaging of the ovary, and enable telemedicine as the images can be sent to a different location by connecting the US device to a mobile device. If patients and doctors are able to share ultrasound images over a global network, it may be possible to perform more accurate follicle monitoring and ovulation date prediction. We believe that the fact that pocket-sized TAUS devices facilitate follicle diameter measurement in IVF patients based on highly reliable images will decrease the number of appointments and commutes to the hospital and may be useful for monitoring COS. This in turn is expected to reduce the burden of hospital appointments and commutes placed on patients who need to undergo follicle measurements for the purpose of the timing method, artificial insemination, IVF or intracytoplasmic sperm injection, with no loss of follicle diameter measurement precision. It is also expected to be useful for patients who live far from hospitals or for patients who are busy and do not have time for appointments.

As a result, these devices are expected to contribute to increased fertility, particularly in developed countries, where infertility tends to occur in working women. Furthermore, in the future, it will become easier for patients to identify follicles using artificial intelligence, which may lead to more accurate measurements. Meanwhile, one of the disadvantages of this device is the fact that it is not capable of directly measuring the follicle on the video that is captured during imaging. For this reason, during the study, the patients sent the video from a tablet computer to a laptop, on which the still images were created and then used to measure the follicles. This entire process takes considerable time and effort.

Previous reports have documented the usefulness of home-based follicle measurements using TVUS [15-17]. However, the questionnaire conducted during this study revealed that there were many patients who were reluctant to use this method, as it involved performing TVUS alone, which was associated with pain and difficulty of manipulation. The questionnaire responses seemed to indicate that TAUS would be more readily accepted. However, compared to TVUS, it is sometimes more difficult to visualize the follicles on TAUS images, so we believe it would be useful to prescribe the US method on a case-by-case basis.

There were some limitations during this study. First, we only used patients from whom we were able to acquire good quality TAUS images during this study. Compared to the approach during TVUS, the ovary is located further away from the probe when performing TAUS, so it is difficult to avoid certain issues that arise due to the presence of abdominal wall fat, intestinal gas, intrapelvic adhesions or ovarian deviation. In addition, patients are not accustomed to performing US by themselves, so it is not easy to obtain a suitable image of the follicle. For this reason, follicle self-measurement by means of TAUS is reserved for

patients with follicles that can be examined easily. Second, patients performed self-measurement under the guidance of a doctor during this study. However, in practice, patients would be performing imaging alone at home, which may lead to an inadvertent decrease in quality. This point will require further verification.

Conclusions

The present study suggests that the ability to perform follicle self-measurement using a pocket-sized TAUS device offers the same degree of precision as conventional follicle measurements performed by a doctor using a TVUS device.

Abbreviations

AT: Abdominal transverse; COS: Controlled ovarian stimulation; hCG: Human chorionic gonadotropin; HMG: Human menopausal gonadotrophin; ICC: Interclass correlation coefficient; IVF: In vitro fertilization; rec-FSH: Recombinant follicle stimulating hormone; TAUS: Transabdominal ultrasound; TVUS: Transvaginal ultrasound; US: Ultrasound; VC: Vaginal coronal; VS: Vaginal sagittal

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of Medical Park Shonan on 25 October 2019 (2019001). All participants provided written informed consent. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

SE is an employee of Olympus and owns shares of Olympus. Olympus is applying for patents relating to the content of the manuscript. The authors other than SE declare that they have no competing interests.

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The patient questionnaire was supported by Olympus.

Authors' contributions

HF and IK participated in all steps of the study, including research planning, data collection, analysis and writing the manuscript. SE participated in the project planning and review of the manuscript. RN participated in enrolling patients and performing ultrasound exams. RK participated in the review of the manuscript. YT participated in the research planning and review of the manuscript. All authors gave suggestions, read the manuscript carefully, fully agreed on its content and approved its final version.

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Table

Table 01

Variable	n=25
Patient age, yr	37.64±4.07
Previous treatments, n	3.96±6.62
Measured day of menstrual cycle, day	12.12±1.73
Body mass index (kg/m ²)	21.38±2.62
Type of infertility, n	
Mechanical	14
Myoma	9
Polyp	5
Tubal	5
Endometriosis	3
PCOS	1
Male factor	2
Unexplained	8

Values are presented as mean ± SD where applicable

Figures

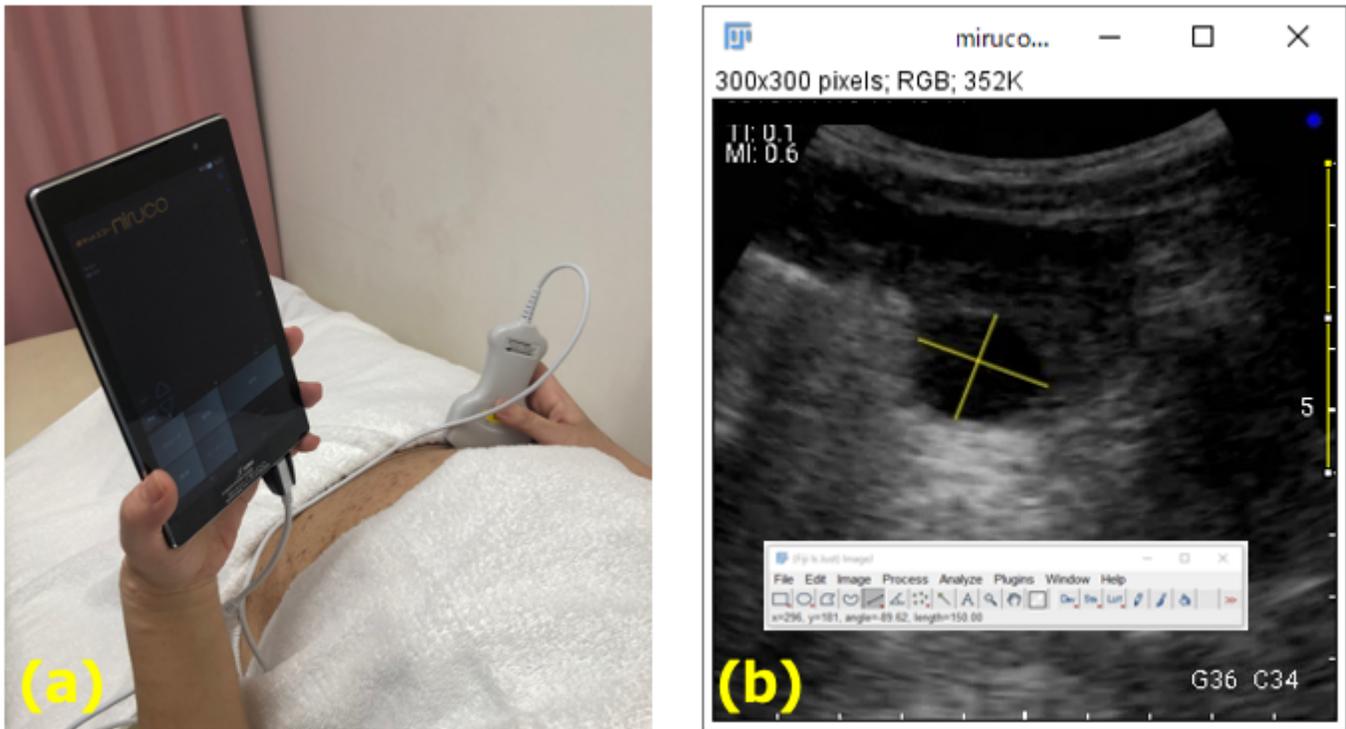


Figure 1

(a) Follicle self-imaging by the patient using the pocket-sized TAUS device. (b) Follicle measurements in the image processing software (ImageJ)

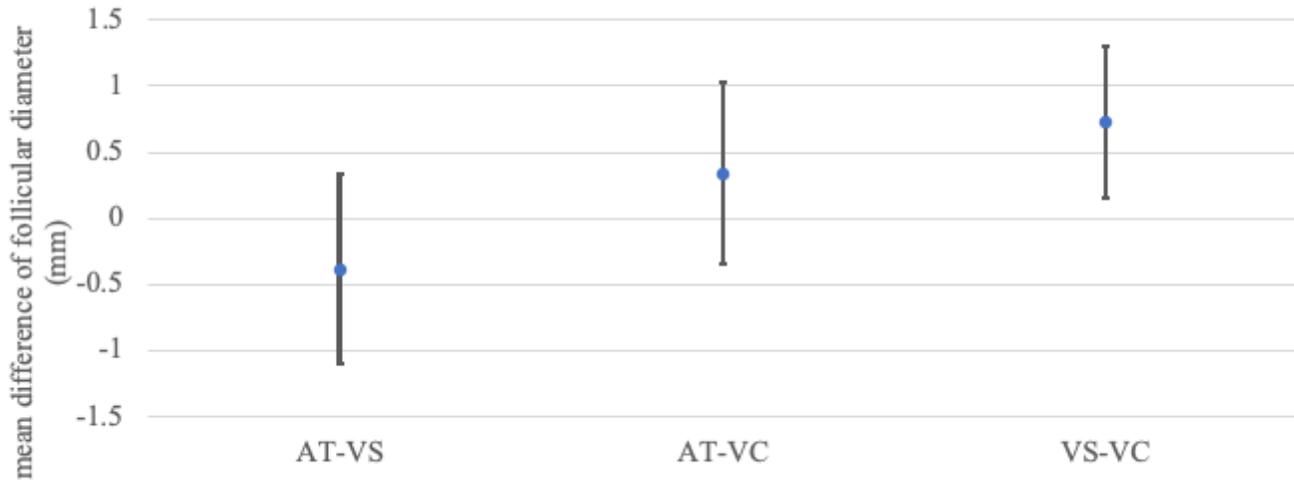


Figure 2

The 95% confidence intervals for the mean differences in follicle size

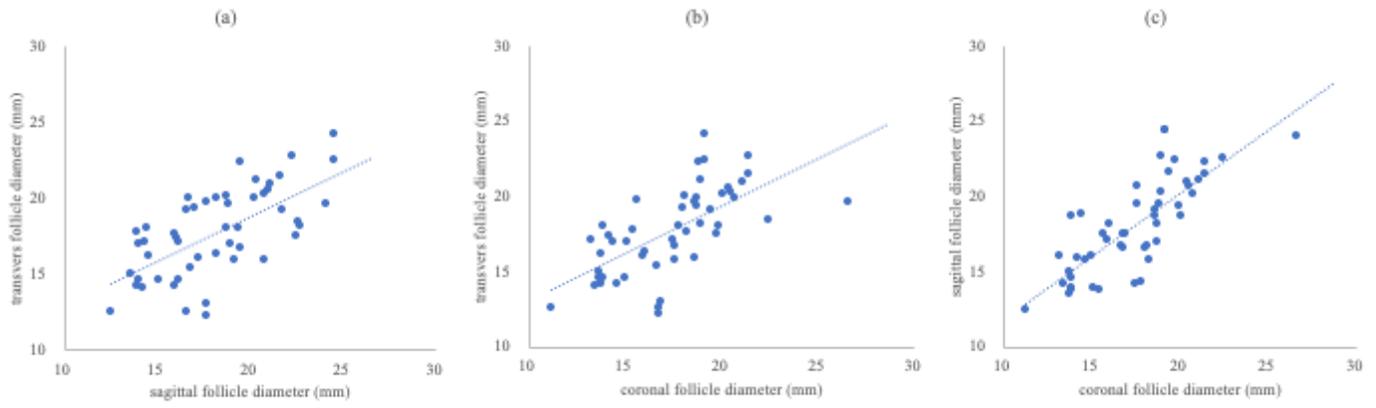


Figure 3

Scatter diagrams of (a) VS and AT, (b) VC and AT, and (c) VC and VS. AT: transabdominal transverse plane, VS: transvaginal sagittal plane, VC: transvaginal coronal plane