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## Sonographic measurement of cervical volume in non-pregnant women with use of the geometric formula for a cylinder

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**Sonographic measurement of cervical volume in non-pregnant women with use of the geometric formula for a cylinder**

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For Peer Review

**ABSTRACT:**

**Purpose:** To sonographically evaluate the volume of uterine cervix in non-pregnant women with use of the geometric formula for a cylinder and to assess agreement with the reference VOCAL method.

**Methods:** Three-dimensional ultrasound volume datasets of the uterine cervix from 81 women were obtained prospectively within a 1-year period. Volume measurements were performed using Virtual Organ Computer aided AnaLysis (VOCAL™) and the geometric formula for a cylinder. Reliability was evaluated using *intraclass correlation coefficient* (ICC) and *Bland-Altman plots* were produced to examine intermethod agreement. Time needed to perform measurements was compared with *Student's t-test*.

**Results:** There was good agreement between VOCAL and the geometric formula for a cylinder (mean percentage difference, -0.78%; 95% limits of agreement, -17.59 to 16.03%). Measurements made by the formula for a cylinder were slightly greater than VOCAL by a mean ( $\pm$ SE) of 0.78% ( $\pm$ 0.95%). A high degree of reliability was observed between the two methods (ICC, 0.970; 95%CI, 0.954-0.981). Cervical volume estimation with the geometric formula for a cylinder was faster to obtain.

**Conclusion:** This method comparison study shows that the geometric formula for a cylinder has good agreement with VOCAL and can determine the volume of the cervix in a faster way.

**Key words:** Uterine cervix; ultrasound volume measurement; cylinder geometric formula

## **TEXT**

### **Introduction:**

Volume measurements of uterine cervix with use of three-dimensional (3D) ultrasound are increasingly being reported in literature. Though volume estimation of the cervix has not yet been introduced into clinical practice, there are certain fields of interest where importance of cervical volumetry is currently being investigated. In Obstetrics it is being investigated whether cervical volume may have a higher predictive value than cervical length in predicting preterm labor.<sup>1,2</sup> In Gynecology it is being explored whether complete or incomplete restoration of cervix after conization for cervical intraepithelial lesions may be a function of the initial volume of cervix.<sup>3</sup> In the above research fields, accurate cervical volumetry is essential to reach final conclusions.

In this study we aimed to calculate the volume of cervix with the use of the geometric formula for a cylinder, since the cervix has a cylindrical shape. There are only two reports in literature referring to use of this formula.<sup>4,5</sup> The first report compared the geometric formula with MRI cervical imaging and showed no statistically significant difference between the two methods.<sup>4</sup> In the second report, a small cohort of women (n=12) underwent two-dimensional ultrasound measurements prior to hysterectomy.<sup>5</sup> Size of uterine corpus and cervix were determined with the geometric formula of prolate ellipsoid and cylinder formula respectively and were compared to total size of the surgical specimen. Due to the small sample size and study design, the cylinder formula could not be fully validated as being accurate in cervical volume estimation. Considering the emerging interest of researchers in cervical

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volume measurements, we sought to validate these results by using 3D ultrasound measurements and more appropriate statistics.<sup>6,7</sup>

## **Patients and Methods**

This is an observational study of 81 non-pregnant women who were examined with 3D ultrasound within a 1-year period in the ultrasound department of our University teaching Hospital. Ethical approval was obtained from the Hospital's Ethics Committee. All patients gave written informed consent prior to participation in the study.

### **Volume acquisition-volume rendering**

Ultrasound examination was performed with a transvaginal probe of 7.5 MHz (RIC5-9H series) and a Voluson 730 Pro ultrasound machine (GE Healthcare, Austria). Women were examined in lithotomy position with an empty bladder. The vaginal probe was slowly introduced into the vagina until a satisfactory image was obtained without exerting undue pressure to the cervix. The sagittal view of cervix was centralised in the 3D sector and represented the initial plane of cervical volume acquisition. A volume dataset was acquired with a sweep angle of 90° and fast volume acquisition (low resolution) setting so as to minimize artifacts due to patient movement. Two 3D volume datasets containing cervix were acquired for each patient by the same investigator (D.P.) and stored for off-line analysis.

All volume datasets for each patient were reviewed by a single investigator (D.P.) and only that image with the best tissue contrast resolution was selected for further process. In this way, 81 selected volume datasets were used for final processing. 4D-View<sup>TM</sup> software (version 9.0, GE Healthcare) was used and the uterine cervix was visualised in the multiplanar

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3 display (**Figure 1a**). Plane A (upper left) shows the sagittal view of cervix,  
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6 Plane B (upper right) the transverse view and Plane C (lower left) the coronal  
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8 view. All identifying data were removed from images to limit bias in  
9  
10 measurement.

### **Identification of cervical os**

15 As the main problem in ultrasound cervical measurement is the  
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17 difficulty in identifying the upper cervical boundary at the level of internal os,  
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19 for this reason each Observer (P.D., G.D.) was allowed to freely manipulate  
20  
21 the volume dataset from initial orientation of the volume at acquisition.  
22  
23 Through this rotation and with use of plane C, the true mid-sagittal view of the  
24  
25 cervix was obtained. In mid-sagittal view, the hypoechogenic mucosa was  
26  
27 used as a guide to the true position of internal os.<sup>8,9</sup> The cervical os can be  
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29 seen by observing the cervical glands which have different echogenicity and  
30  
31 are quite distinct from the endometrium at lower uterine segment.<sup>10</sup> The  
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33 coronal view was used to discern the point where endocervical glands end  
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35 and where endometrium begins. Unfortunately, the two reports in  
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37 literature which used the cylinder formula in non-pregnant women did not  
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39 provide any information on how they identified the internal cervical os.<sup>4,5</sup>  
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41 Therefore, identification in our study was made according to instructions given  
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43 in reports that concerned pregnant patients.<sup>8-10</sup> Identification of the lower  
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45 cervical boundary at the level of external os was much easier as contrast to  
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47 the adjacent vaginal wall was much greater.  
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### **Volume measurements**

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56 To date, VOCAL technique is considered the gold-standard in 3D  
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58 ultrasound volume measurement and has been used in volumetry of other  
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Cervical volume with cylinder formula 6

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3 structures, such as the endometrium and ovaries.<sup>11-15</sup> This method concerns  
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5 rotation of the 3D volume dataset about a central axis through a number of  
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7 rotation steps and defining 2D contours on each plane. We employed manual  
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9 mode of VOCAL with a 30° rotational angle and after cervical contour was  
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11 manually traced in Plane A, the software generated cervical volume  
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13 automatically (in cm<sup>3</sup>) (**Figure 1a**).  
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17 Measurements were also made using the cylinder geometric formula:

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20 Volume=  $3.14 \times ([\text{anteroposterior} + \text{transverse diameter}]/4)^2 \times \text{cervical length}$   
21  
22 Cervical length was measured in plane A as the straight line from external to  
23  
24 internal cervical os. Anteroposterior diameter was also measured in plane A  
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26 and finally transverse diameter in plane B (**Figure 1b**). The three diameters  
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28 were measured as they would have been measured with use of standard 2D  
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30 ultrasound machines.  
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34 Observer 1 (D.P.) performed two sets of VOCAL and two sets of  
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36 cylinder formula measurements for each volume dataset (81 volume datasets).  
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38 The second set of measurements for Observer 1 was conducted after one  
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40 week time with random order of volume datasets. The investigator was  
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42 blinded to his own previous results and patient's data. Observer 2 (G.D.)  
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44 performed only one set of VOCAL and one set of cylinder formula  
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46 measurements. Overall, Observer 1 analysed 324 volume datasets and  
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48 Observer 2 analysed 162 volume datasets. Each Observer was blinded to each  
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50 other's results.  
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### 54 **Statistical analysis**

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57 In this method comparison study, statistics used were reliability  
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59 analysis and Bland-Altman method. In both cases, percentage difference (1<sup>st</sup>  
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3 measurement-2<sup>nd</sup> measurement/average X100) was used in a similar manner  
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5 proposed by other authors, as statistical results are more understandable in  
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7 clinical terms.<sup>13</sup> Reliability analysis concerned estimation of intraclass  
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9 correlation coefficient (ICC) for determination of intermethod, intraobserver  
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11 and interobserver reliability. Intermethod agreement was determined with  
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13 Bland-Altman method, where difference between two methods is plotted  
14  
15 against the mean.<sup>7</sup> After graphical presentation, 95% limits of agreement  
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17 were estimated, which represents the range we can expect 95% of  
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19 differences between two methods to lie. Time needed to perform  
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21 measurements was compared with Student's t-test and  $p$ -value=0.05 was  
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23 considered statistically significant. Statistical analysis was performed with  
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25 SPSS version 17.0 (SPSS Inc., USA).  
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## 31 32 Results

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34 Eighty one non-pregnant women with mean age of 38.1 years (18-62)  
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36 were examined with 3D ultrasound within a 1-year period. Mean volume of  
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38 cervix calculated with the geometric formula for a cylinder was  $25.13 \pm 8.82$   
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40  $\text{cm}^3$ , whereas mean volume of cervix estimated with VOCAL was  $24.81 \pm 8.46$   
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42  $\text{cm}^3$  (Table 1).  
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### 46 47 Time required for measurements

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49 As shown in Table 2, volume measurements with the geometric  
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51 formula were significantly faster compared to VOCAL ( $p < 0.001$ ).  
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### 53 54 Intermethod agreement

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56 For measurements between VOCAL and the geometric formula for a  
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58 cylinder, there was a high degree of reliability (ICC, 0.970; 95% CI, 0.954-  
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60 0.981) (Table 3). Bland-Altman plot is presented in Figure 2 for the

Cervical volume with cylinder formula 8

percentage of mean difference and the 95% limits of agreement (mean, -0.78%; 95% limits of agreement, -17.59% to 16.03%) are given in **Table 4**.

There was no systematic bias between the two methods since statistical analysis showed that zero lied within the interval of  $\text{mean} \pm 1.96\text{SE}$  (0.78%  $\pm$  1.86%). Also, differences were not increased with increasing of measurements and remained constant throughout the entire range of measurements.

### **Interobserver and intraobserver agreement**

Interobserver and intraobserver agreement for each technique was evaluated and there was a high degree of reliability demonstrated as shown in **Tables 3** and **4**. Bland-Altman plots for interobserver and intraobserver agreement between measurements performed by each technique are presented in **Figure 3** and **4** for the percentage of mean difference. Differences also remained constant throughout the entire range of measurements.

### **Discussion**

Though cervical volume measurement is still not implemented in daily clinical practice and is at this stage used for research purposes, there are reports in literature where cervical volumetry may be important and thus have significant clinical interest in the near future.<sup>1,2,3</sup> In our study, it is shown that the cylinder formula could be acceptable to use for cervical volume measurements, as the cervix is a quite regularly shaped organ. However, such a method would be unacceptable for irregularly shaped structures (i.e. the endometrium). The principal finding is that the cylinder formula is in good

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3 agreement with VOCAL method, the values obtained with the geometric  
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5 formula being slightly larger by a mean ( $\pm$ SE) of 0.78% ( $\pm$ 0.95%).  
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8 The Bland-Altman method is considered the proper statistical method  
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10 when comparing two different methods. The estimated 95% limits of  
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12 agreement represent the range which we can expect to find 95% of  
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14 differences between two methods. However, whether the 95% limits of  
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16 differences between two methods. However, whether the 95% limits of  
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18 agreement are acceptable is a clinical not a statistical decision. Mean volume  
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20 of cervix estimated with VOCAL was  $24.81 \pm 8.46 \text{ cm}^3$  and mean percentage of  
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22 difference with the geometric formula (95% limits of agreement) was 0.78% (-  
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24 17.59% to 16.03%). This means that if cervical volume estimated with VOCAL  
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26 is  $25 \text{ cm}^3$ , then mean cervical volume measured with cylinder formula would  
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28 be  $25.19 \text{ cm}^3$  and in 95% of measurements differences between the two  
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30 methods would lie between  $20.60 \text{ cm}^3$  and  $29.00 \text{ cm}^3$ . The limits of  
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32 agreement are in fact wide, indicating that small differences in cervical  
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34 volume may be difficult to discriminate with the geometric formula.  
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36 Nevertheless, in review of literature where VOCAL was used as the reference  
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38 technique in other method-comparison studies, similar and even wider limits  
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40 of agreement were reported by investigators when comparing newly  
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42 introduced ultrasound methods (i.e. inversion method, manual segmentation  
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44 method) to VOCAL.<sup>13</sup>  
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51 Limitations of our study are that validity of measurements could not be  
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53 tested, since true volume of cervix was not available. Nevertheless, VOCAL is  
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55 a well validated three-dimensional volumetric method and is considered the  
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57 reference standard for measurement against which the geometric formula  
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59 was compared. Additionally, a  $30^\circ$  rotational angle was used in VOCAL as it is  
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Cervical volume with cylinder formula 10

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3 shown to be both accurate and faster.<sup>15</sup> Perhaps, the use of lower angles (6°,  
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5 9°, 15°) would have led to different results. Moreover, identification of internal  
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7 cervical os was indeed difficult as women were of different age, varying parity  
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9 and ultrasound was performed at different time points in menstrual cycle  
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11 where cervical glands had a varying degree of echogenicity. Nevertheless, no  
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13 patients were excluded due to inadequate cervical images. However, in  
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15 everyday clinical practice, the borders of uterine cervix are not always clearly  
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17 contrasted against the surrounding tissue. This means that only when the  
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19 cervix is clearly imaged and well defined can the volume measurements be  
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21 accurate to the degree provided by our results. Finally, our study design  
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23 utilized 3D sonography where plane C represents the virtual reconstruction of  
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25 plane A and B. In clinical practice, sonographers will most likely use 2D  
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27 ultrasound machines, where plane C is not available, thus leading to more  
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29 difficulty in defining the internal cervical os and to less accurate  
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31 measurements.  
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39 The practical implications of this study are that if volume estimation of  
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41 cervix were to be implemented in clinical practice, the cylinder formula could  
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43 provide a simple, accurate, faster way of volumetry in comparison to  
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45 computerized and sophisticated methods such as VOCAL. It is easy and  
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47 faster to measure only three diameters of the cervix and use the geometric  
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49 formula for a cylinder even with conventional two-dimensional ultrasound  
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51 machines. In order to safely extrapolate these results to 2D sonography, a  
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53 more proper study design would be to compare the VOCAL method 3D  
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55 cervical measurements with the cylinder formula 2D cervical measurements.  
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Such a study design is currently being conducted in our department and results are soon expected.

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**LEGENDS**

<b>Figure 1.</b>	<p>a). Volume measurement (22.00 cm<sup>3</sup>) with VOCAL (manual mode, rotation step 30°).</p> <p>b). The volume is measured with the use of three diameters and the geometric formula for the cylinder (volume=20.69 cm<sup>3</sup>).</p>
<b>Figure 2.</b>	<p>Bland-Altman plot for the percentage of the mean difference and 95% limits of agreement between VOCAL method and the geometric formula for the cylinder.</p>
<b>Figure 3.</b>	<p>a) Bland-Altman plot for the percentage of the mean difference for VOCAL (Observer's 1-1<sup>st</sup> measurement — Observer's 2 measurement) and 95% limits of agreement for interobserver measurements.</p> <p>b) Bland-Altman plot for the percentage of the mean difference for geometric formula of cylinder (Observer's 1-1<sup>st</sup> measurement — Observer's 2 measurement) and 95% limits of agreement for interobserver measurements.</p>
<b>Figure 4.</b>	<p>a) Bland-Altman plot for the percentage of the mean difference for VOCAL (Observer's 1-1<sup>st</sup> measurement — 2<sup>nd</sup> measurement) and 95% limits of agreement for intraobserver measurements.</p> <p>b) Bland-Altman plot for the percentage of the mean difference for geometric formula of cylinder (Observer's 1-1<sup>st</sup> measurement — 2<sup>nd</sup> measurement) and 95% limits of agreement for intraobserver measurements.</p>

**Table 1.** Descriptive statistics of sample (n=81 patients/81 volume datasets).

	Mean±SD	Range
<b>Age</b> (in years)	38.1±10.4	18-62
<b>Dimensions of cervix</b> (in mm)		
Cervical length	35.3±5.2	23.0-46.3
Anteroposterior diameter	28.3±5.6	16.7-44.7
Transverse diameter	31.2±5.9	22.9-49.5
<b>Cervical volume</b> (in cm <sup>3</sup> )	<b>VOCAL</b>	<b>Cylinder formula</b>
1 <sup>st</sup> Observer		
1 <sup>st</sup> measurement	24.81±8.46 (10.72-47.74)	25.13±8.82 (10.09-47.59)
2 <sup>nd</sup> measurement	24.91±8.26 (10.94-46.28)	25.21±8.66 (10.29-45.33)
2 <sup>nd</sup> Observer	24.68±8.24 (11.28-45.98)	25.09±8.68 (10.09-47.60)

**Table 2.** Time (mean±SD) needed to perform cervical volume measurements with VOCAL method and the geometric formula of the cylinder.

		VOCAL (sec)	Cylinder formula (sec)	<i>p</i> -value
1 <sup>st</sup> Observer	1 <sup>st</sup> measurement	51.89±10.92	33.32±9.56	<0.001
	2 <sup>nd</sup> measurement	52.77±11.04	34.26±9.60	<0.001
2 <sup>nd</sup> Observer		50.70±11.26	31.96±9.15	<0.001

**Table 3.** Reliability analysis with the calculation of intraclass correlation coefficient (ICC) and 95% confidence intervals.

		ICC	95%CI
Intermethod agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement	0.970	0.954-0.981
	Observer's 2 Cylinder measurement		
Interobserver agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement	0.978	0.965-0.986
	Observer's 2 VOCAL measurement		
	Observer's 1- Cylinder 1 <sup>st</sup> measurement	0.954	0.930-0.970
	Observer's 2 Cylinder measurement		
Intraobserver agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement	0.992	0.988-0.995
	VOCAL 2 <sup>nd</sup> measurement		
	Observer's 1- Cylinder 1 <sup>st</sup> measurement	0.972	0.956-0.982
	Cylinder 2 <sup>nd</sup> measurement		

**Table 4.** Percentage of mean difference $\pm$ 95% limits of agreement.

		Percentage of mean difference	95% limits of agreement
Intermethod agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement — Observer's 2 Cylinder measurement	-0.78%	-17.59% to 16.03%
	Observer's 1- VOCAL 1 <sup>st</sup> measurement — Observer's 2 VOCAL measurement	-0.42%	-16.57% to 15.68%
Interobserver agreement	Observer's 1- Cylinder 1 <sup>st</sup> measurement — Observer's 2 Cylinder measurement	0.16%	-20.30% to 20.62%
	Observer's 1- VOCAL 1 <sup>st</sup> measurement — VOCAL 2 <sup>nd</sup> measurement	-0.66%	-9.14% to 7.82%
Intraobserver agreement	Observer's 1- Cylinder 1 <sup>st</sup> measurement — Cylinder 2 <sup>nd</sup> measurement	-0.51%	-18.38% to 17.36%

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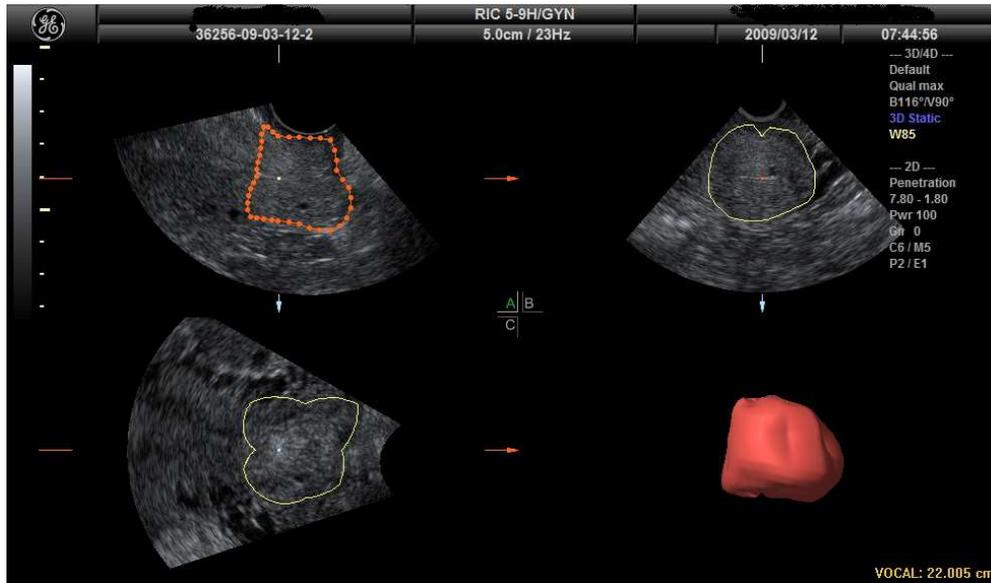


Figure 1a. Volume measurement (22.00 cm<sup>3</sup>) with VOCAL (manual mode, rotation step 30°).  
260x151mm (96 x 96 DPI)

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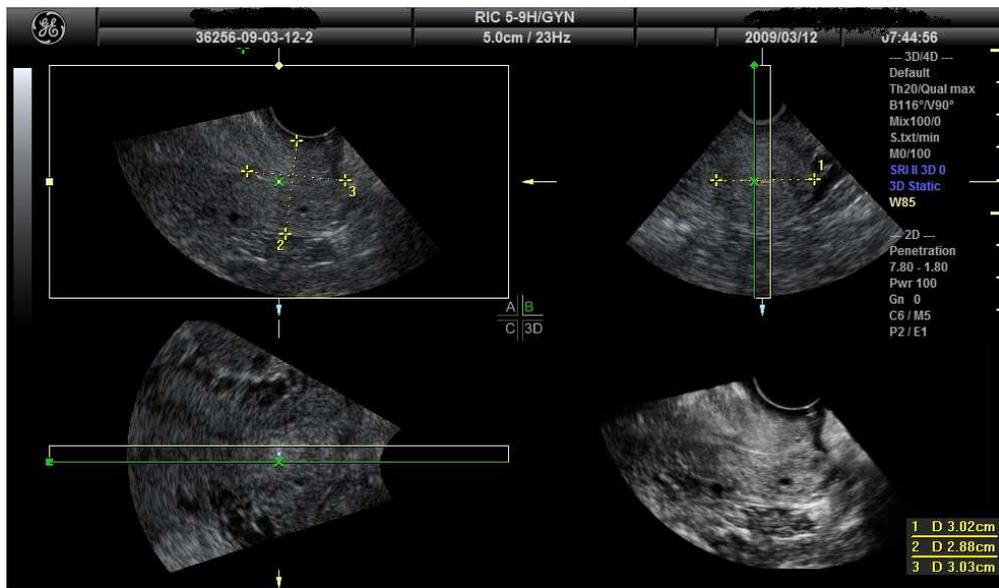


Figure 1b. The volume is measured with the use of three diameters and the geometric formula for the cylinder (volume=20.69 cm<sup>3</sup>).  
260x151mm (96 x 96 DPI)

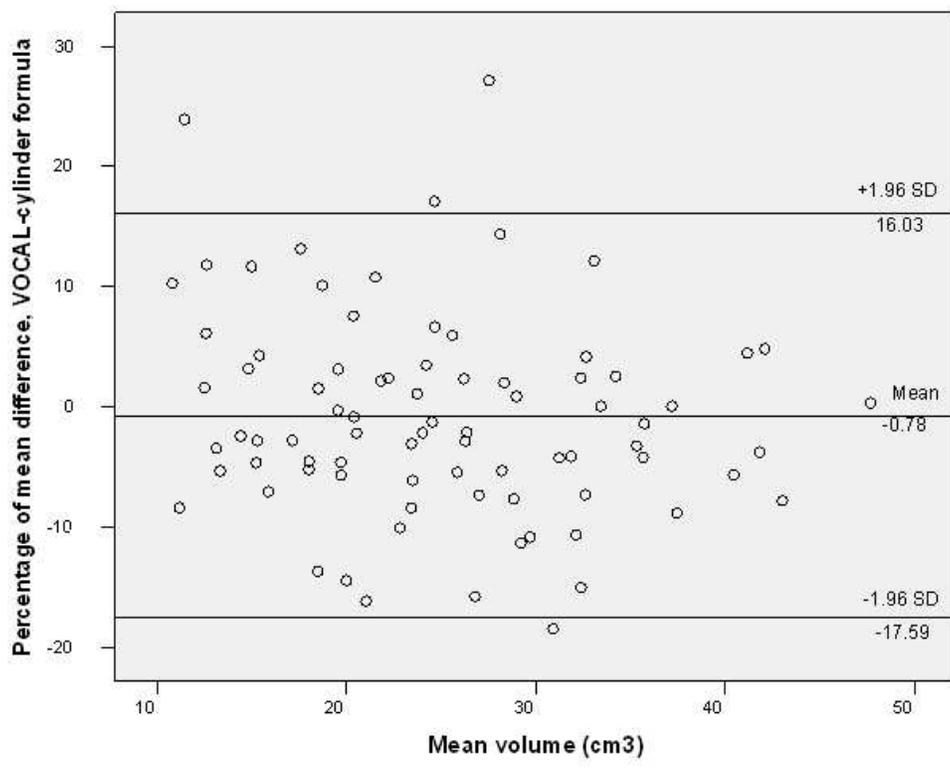


Figure 2. Bland-Altman plot for the percentage of the mean difference and 95% limits of agreement between VOCAL method and the geometric formula for the cylinder.  
166x132mm (96 x 96 DPI)

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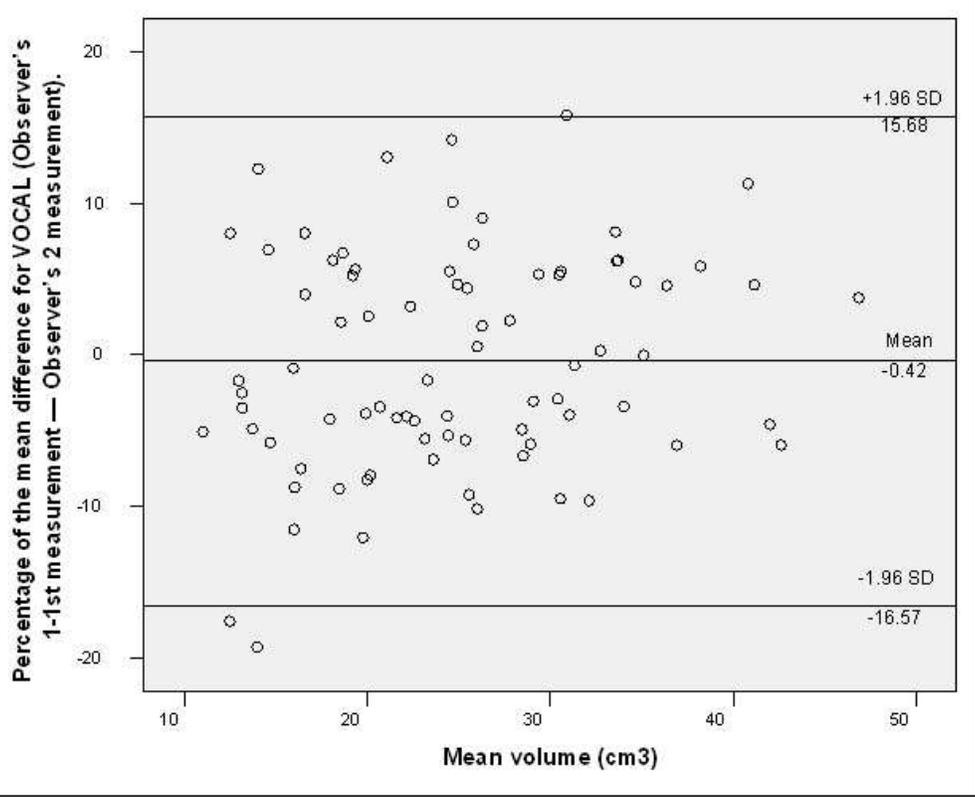


Figure 3a. Bland-Altman plot for the percentage of the mean difference for VOCAL (Observer's 1-1st measurement - Observer's 2 measurement) and 95% limits of agreement for interobserver measurements.  
165x133mm (96 x 96 DPI)

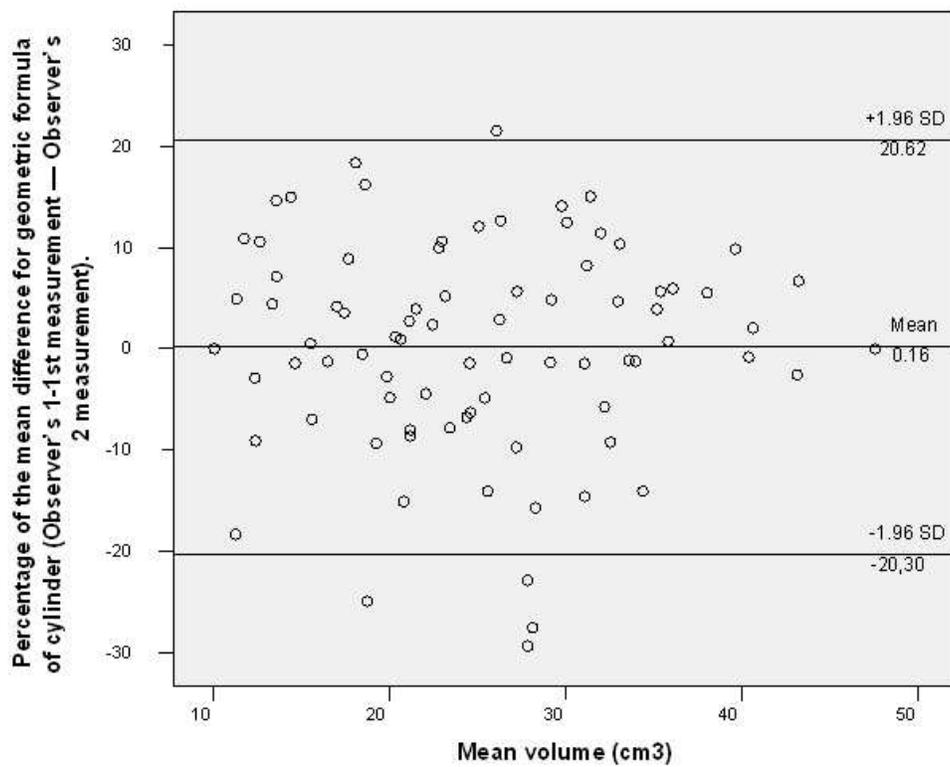


Figure 3b. Bland-Altman plot for the percentage of the mean difference for geometric formula of cylinder (Observer's 1-1st measurement - Observer's 2 measurement) and 95% limits of agreement for interobserver measurements.  
165x133mm (96 x 96 DPI)

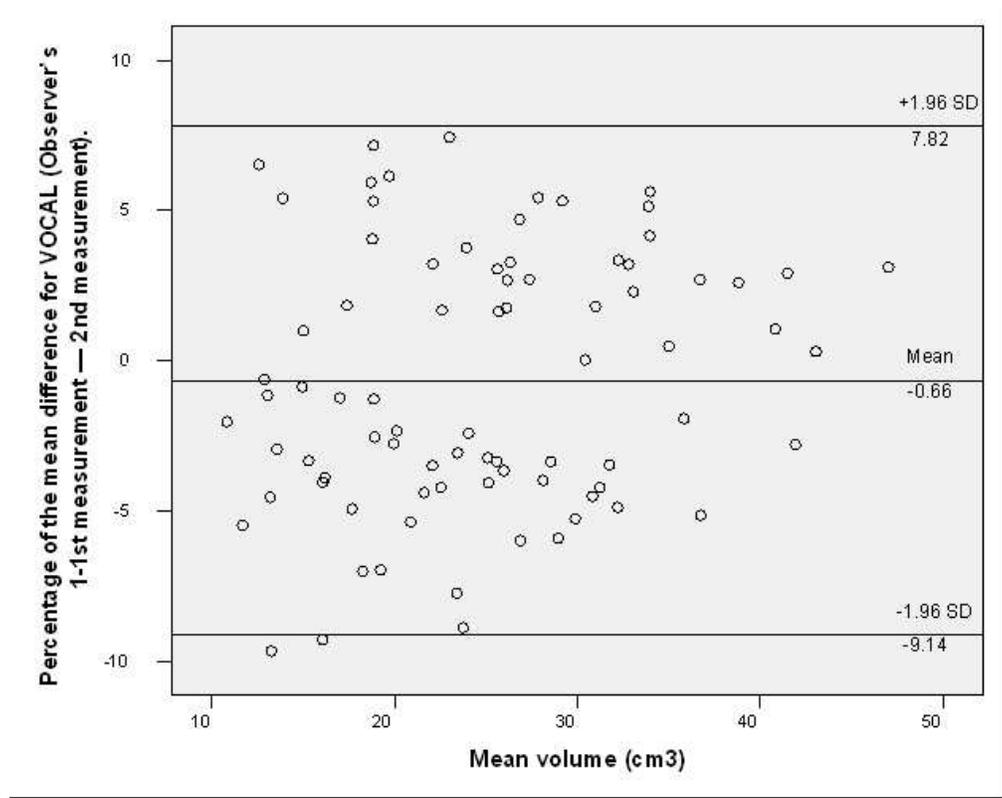


Figure 4a. Bland-Altman plot for the percentage of the mean difference for VOCAL (Observer's 1-1st measurement - 2nd measurement) and 95% limits of agreement for intraobserver measurements. 166x132mm (96 x 96 DPI)

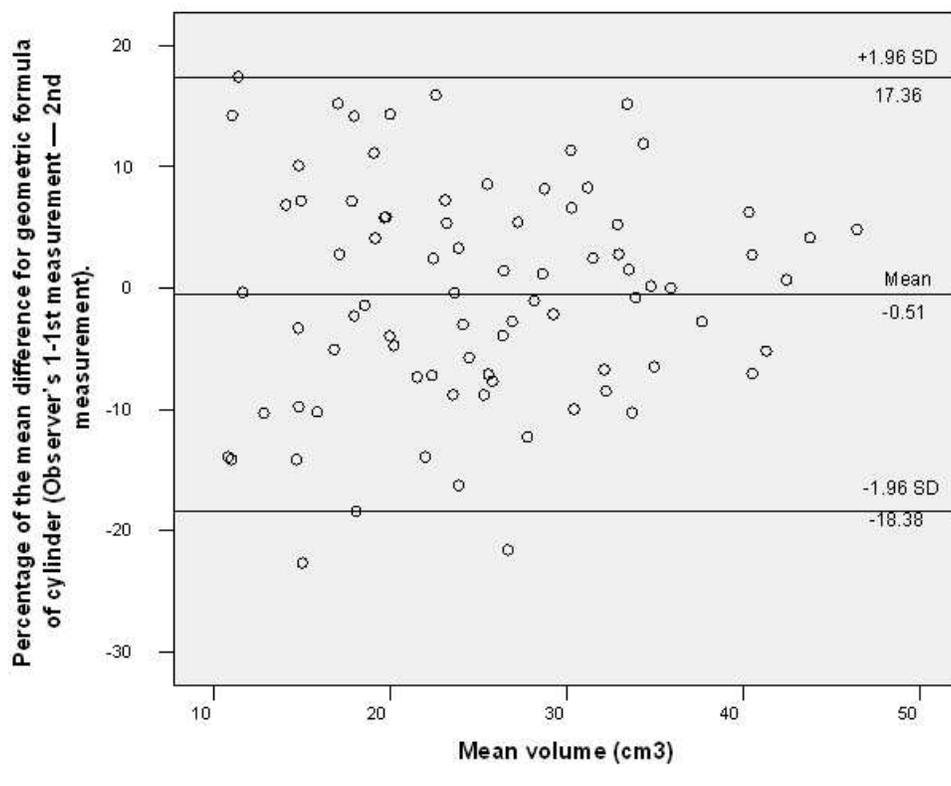


Figure 4b. Bland-Altman plot for the percentage of the mean difference for geometric formula of cylinder (Observer's 1-1st measurement - 2nd measurement) and 95% limits of agreement for intraobserver measurements.  
165x133mm (96 x 96 DPI)

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For Peer Review

**ABSTRACT:**

**Purpose:** To sonographically evaluate the volume of uterine cervix in non-pregnant women with use of the geometric formula for a cylinder and to assess agreement with the reference VOCAL method.

**Methods:** Three-dimensional ultrasound volume datasets of the uterine cervix from 81 women were obtained prospectively within a 1-year period. Volume measurements were performed using Virtual Organ Computer aided AnaLysis (VOCAL™) and the geometric formula for a cylinder. Reliability was evaluated using *intraclass correlation coefficient* (ICC) and *Bland-Altman plots* were produced to examine intermethod agreement. Time needed to perform measurements was compared with *Student's t-test*.

**Results:** There was good agreement between VOCAL and the geometric formula for a cylinder (mean percentage difference, -0.78%; 95% limits of agreement, -17.59 to 16.03%). Measurements made by the formula for a cylinder were slightly greater than VOCAL by a mean ( $\pm$ SE) of 0.78% ( $\pm$ 0.95%). A high degree of reliability was observed between the two methods (ICC, 0.970; 95%CI, 0.954-0.981). Cervical volume estimation with the geometric formula for a cylinder was faster to obtain.

**Conclusion:** This method comparison study shows that the geometric formula for a cylinder has good agreement with VOCAL and can determine the volume of the cervix in a faster way.

**Key words:** Uterine cervix; ultrasound volume measurement; cylinder geometric formula

## **TEXT**

### **Introduction:**

Volume measurements of uterine cervix with use of three-dimensional (3D) ultrasound are increasingly being reported in literature. Though volume estimation of the cervix has not yet been introduced into clinical practice, there are certain fields of interest where importance of cervical volumetry is currently being investigated. In Obstetrics it is being investigated whether cervical volume may have a higher predictive value than cervical length in predicting preterm labor.<sup>1,2</sup> In Gynecology it is being explored whether complete or incomplete restoration of cervix after conization for cervical intraepithelial lesions may be a function of the initial volume of cervix.<sup>3</sup> In the above research fields, accurate cervical volumetry is essential to reach final conclusions.

In this study we aimed to calculate the volume of cervix with the use of the geometric formula for a cylinder, since the cervix has a cylindrical shape. There are only two reports in literature referring to use of this formula.<sup>4,5</sup> The first report compared the geometric formula with MRI cervical imaging and showed no statistically significant difference between the two methods.<sup>4</sup> In the second report, a small cohort of women (n=12) underwent two-dimensional ultrasound measurements prior to hysterectomy.<sup>5</sup> Size of uterine corpus and cervix were determined with the geometric formula of prolate ellipsoid and cylinder formula respectively and were compared to total size of the surgical specimen. Due to the small sample size and study design, the cylinder formula could not be fully validated as being accurate in cervical volume estimation. Considering the emerging interest of researchers in cervical

Cervical volume with cylinder formula 4

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volume measurements, we sought to validate these results by using 3D ultrasound measurements and more appropriate statistics.<sup>6,7</sup>

## Patients and Methods

This is an observational study of 81 non-pregnant women who were examined with 3D ultrasound within a 1-year period in the ultrasound department of our University teaching Hospital. Ethical approval was obtained from the Hospital's Ethics Committee. All patients gave written informed consent prior to participation in the study.

### Volume acquisition-volume rendering

Ultrasound examination was performed with a transvaginal probe of 7.5 MHz (RIC5-9H series) and a Voluson 730 Pro ultrasound machine (GE Healthcare, Austria). Women were examined in lithotomy position with an empty bladder. The vaginal probe was slowly introduced into the vagina until a satisfactory image was obtained without exerting undue pressure to the cervix. The sagittal view of cervix was centralised in the 3D sector and represented the initial plane of cervical volume acquisition. A volume dataset was acquired with a sweep angle of 90° and fast volume acquisition (low resolution) setting so as to minimize artifacts due to patient movement. Two 3D volume datasets containing cervix were acquired for each patient by the same investigator (D.P.) and stored for off-line analysis.

All volume datasets for each patient were reviewed by a single investigator (D.P.) and only that image with the best tissue contrast resolution was selected for further process. In this way, 81 selected volume datasets were used for final processing. 4D-View<sup>TM</sup> software (version 9.0, GE Healthcare) was used and the uterine cervix was visualised in the multiplanar

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3 display (**Figure 1a**). Plane A (upper left) shows the sagittal view of cervix,  
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6 Plane B (upper right) the transverse view and Plane C (lower left) the coronal  
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8 view. All identifying data were removed from images to limit bias in  
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10 measurement.

### 11 12 **Identification of cervical os**

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15 As the main problem in ultrasound cervical measurement is the  
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17 difficulty in identifying the upper cervical boundary at the level of internal os,  
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19 for this reason each Observer (P.D., G.D.) was allowed to freely manipulate  
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21 the volume dataset from initial orientation of the volume at acquisition.  
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23 Through this rotation and with use of plane C, the true mid-sagittal view of the  
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25 cervix was obtained. In mid-sagittal view, the hypoechogenic mucosa was  
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27 used as a guide to the true position of internal os.<sup>8,9</sup> The cervical os can be  
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29 seen by observing the cervical glands which have different echogenicity and  
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31 are quite distinct from the endometrium at lower uterine segment.<sup>10</sup> The  
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33 coronal view was used to discern the point where endocervical glands end  
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35 and where endometrium begins. Unfortunately, the two reports in  
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37 literature which used the cylinder formula in non-pregnant women did not  
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39 provide any information on how they identified the internal cervical os.<sup>4,5</sup>  
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41 Therefore, identification in our study was made according to instructions given  
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43 in reports that concerned pregnant patients.<sup>8-10</sup> Identification of the lower  
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45 cervical boundary at the level of external os was much easier as contrast to  
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47 the adjacent vaginal wall was much greater.

### 48 49 **Volume measurements**

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51 To date, VOCAL technique is considered the gold-standard in 3D  
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53 ultrasound volume measurement and has been used in volumetry of other  
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Cervical volume with cylinder formula 6

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3 structures, such as the endometrium and ovaries.<sup>11-15</sup> This method concerns  
4 rotation of the 3D volume dataset about a central axis through a number of  
5 rotation steps and defining 2D contours on each plane. We employed manual  
6 mode of VOCAL with a 30° rotational angle and after cervical contour was  
7 manually traced in Plane A, the software generated cervical volume  
8 automatically (in cm<sup>3</sup>) (**Figure 1a**).

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17 Measurements were also made using the cylinder geometric formula:

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20 Volume=  $3.14 \times ([\text{anteroposterior} + \text{transverse diameter}]/4)^2 \times \text{cervical length}$   
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22 Cervical length was measured in plane A as the straight line from external to  
23 internal cervical os. Anteroposterior diameter was also measured in plane A  
24 and finally transverse diameter in plane B (**Figure 1b**). The three diameters  
25 were measured as they would have been measured with use of standard 2D  
26 ultrasound machines.

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34 Observer 1 (D.P.) performed two sets of VOCAL and two sets of  
35 cylinder formula measurements for each volume dataset (81 volume datasets).  
36 The second set of measurements for Observer 1 was conducted after one  
37 week time with random order of volume datasets. The investigator was  
38 blinded to his own previous results and patient's data. Observer 2 (G.D.)  
39 performed only one set of VOCAL and one set of cylinder formula  
40 measurements. Overall, Observer 1 analysed 324 volume datasets and  
41 Observer 2 analysed 162 volume datasets. Each Observer was blinded to each  
42 other's results.

### 43 44 45 46 47 48 49 50 51 52 53 54 55 **Statistical analysis**

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58 In this method comparison study, statistics used were reliability  
59 analysis and Bland-Altman method. In both cases, percentage difference (1<sup>st</sup>  
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3 measurement-2<sup>nd</sup> measurement/average X100) was used in a similar manner  
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5 proposed by other authors, as statistical results are more understandable in  
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7 clinical terms.<sup>13</sup> Reliability analysis concerned estimation of intraclass  
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9 correlation coefficient (ICC) for determination of intermethod, intraobserver  
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11 and interobserver reliability. Intermethod agreement was determined with  
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13 Bland-Altman method, where difference between two methods is plotted  
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15 against the mean.<sup>7</sup> After graphical presentation, 95% limits of agreement  
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17 were estimated, which represents the range we can expect 95% of  
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19 differences between two methods to lie. Time needed to perform  
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21 measurements was compared with Student's t-test and  $p$ -value=0.05 was  
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23 considered statistically significant. Statistical analysis was performed with  
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25 SPSS version 17.0 (SPSS Inc., USA).  
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## 31 32 **Results**

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34 Eighty one non-pregnant women with mean age of 38.1 years (18-62)  
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36 were examined with 3D ultrasound within a 1-year period. Mean volume of  
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38 cervix calculated with the geometric formula for a cylinder was  $25.13 \pm 8.82$   
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40  $\text{cm}^3$ , whereas mean volume of cervix estimated with VOCAL was  $24.81 \pm 8.46$   
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42  $\text{cm}^3$  (Table 1).  
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### 46 **Time required for measurements**

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48 As shown in Table 2, volume measurements with the geometric  
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50 formula were significantly faster compared to VOCAL ( $p < 0.001$ ).  
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### 53 **Intermethod agreement**

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55 For measurements between VOCAL and the geometric formula for a  
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57 cylinder, there was a high degree of reliability (ICC, 0.970; 95% CI, 0.954-  
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59 0.981) (Table 3). Bland-Altman plot is presented in Figure 2 for the  
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Cervical volume with cylinder formula 8

percentage of mean difference and the 95% limits of agreement (mean, -0.78%; 95% limits of agreement, -17.59% to 16.03%) are given in **Table 4**.

There was no systematic bias between the two methods since statistical analysis showed that zero lied within the interval of  $\text{mean} \pm 1.96\text{SE}$  ( $0.78\% \pm 1.86\%$ ). Also, differences were not increased with increasing of measurements and remained constant throughout the entire range of measurements.

### **Interobserver and intraobserver agreement**

Interobserver and intraobserver agreement for each technique was evaluated and there was a high degree of reliability demonstrated as shown in **Tables 3** and **4**. Bland-Altman plots for interobserver and intraobserver agreement between measurements performed by each technique are presented in **Figure 3** and **4** for the percentage of mean difference. Differences also remained constant throughout the entire range of measurements.

### **Discussion**

Though cervical volume measurement is still not implemented in daily clinical practice and is at this stage used for research purposes, there are reports in literature where cervical volumetry may be important and thus have significant clinical interest in the near future.<sup>1,2,3</sup> In our study, it is shown that the cylinder formula could be acceptable to use for cervical volume measurements, as the cervix is a quite regularly shaped organ. However, such a method would be unacceptable for irregularly shaped structures (i.e. the endometrium). The principal finding is that the cylinder formula is in good

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3 agreement with VOCAL method, the values obtained with the geometric  
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5 formula being slightly larger by a mean ( $\pm$ SE) of 0.78% ( $\pm$ 0.95%).  
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8 The Bland-Altman method is considered the proper statistical method  
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10 when comparing two different methods. The estimated 95% limits of  
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12 agreement represent the range which we can expect to find 95% of  
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14 differences between two methods. However, whether the 95% limits of  
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16 differences between two methods. However, whether the 95% limits of  
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18 agreement are acceptable is a clinical not a statistical decision. Mean volume  
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20 of cervix estimated with VOCAL was  $24.81 \pm 8.46 \text{ cm}^3$  and mean percentage of  
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22 difference with the geometric formula (95% limits of agreement) was 0.78% (-  
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24 17.59% to 16.03%). This means that if cervical volume estimated with VOCAL  
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26 is  $25 \text{ cm}^3$ , then mean cervical volume measured with cylinder formula would  
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28 be  $25.19 \text{ cm}^3$  and in 95% of measurements differences between the two  
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30 methods would lie between  $20.60 \text{ cm}^3$  and  $29.00 \text{ cm}^3$ . The limits of  
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32 agreement are in fact wide, indicating that small differences in cervical  
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34 volume may be difficult to discriminate with the geometric formula.  
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36 Nevertheless, in review of literature where VOCAL was used as the reference  
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38 technique in other method-comparison studies, similar and even wider limits  
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40 of agreement were reported by investigators when comparing newly  
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42 introduced ultrasound methods (i.e. inversion method, manual segmentation  
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44 method) to VOCAL.<sup>13</sup>  
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51 Limitations of our study are that validity of measurements could not be  
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53 tested, since true volume of cervix was not available. Nevertheless, VOCAL is  
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55 a well validated three-dimensional volumetric method and is considered the  
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57 reference standard for measurement against which the geometric formula  
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59 was compared. Additionally, a  $30^\circ$  rotational angle was used in VOCAL as it is  
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Cervical volume with cylinder formula 10

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3 shown to be both accurate and faster.<sup>15</sup> Perhaps, the use of lower angles (6°,  
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5 9°, 15°) would have led to different results. Moreover, identification of internal  
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7 cervical os was indeed difficult as women were of different age, varying parity  
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9 and ultrasound was performed at different time points in menstrual cycle  
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11 where cervical glands had a varying degree of echogenicity. Nevertheless, no  
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13 patients were excluded due to inadequate cervical images. However, in  
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15 everyday clinical practice, the borders of uterine cervix are not always clearly  
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17 contrasted against the surrounding tissue. This means that only when the  
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19 cervix is clearly imaged and well defined can the volume measurements be  
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21 accurate to the degree provided by our results. Finally, our study design  
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23 utilized 3D sonography where plane C represents the virtual reconstruction of  
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25 plane A and B. In clinical practice, sonographers will most likely use 2D  
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27 ultrasound machines, where plane C is not available, thus leading to more  
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29 difficulty in defining the internal cervical os and to less accurate  
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31 measurements.  
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39 The practical implications of this study are that if volume estimation of  
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41 cervix were to be implemented in clinical practice, the cylinder formula could  
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43 provide a simple, accurate, faster way of volumetry in comparison to  
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45 computerized and sophisticated methods such as VOCAL. It is easy and  
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47 faster to measure only three diameters of the cervix and use the geometric  
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49 formula for a cylinder even with conventional two-dimensional ultrasound  
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51 machines. In order to safely extrapolate these results to 2D sonography, a  
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53 more proper study design would be to compare the VOCAL method 3D  
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55 cervical measurements with the cylinder formula 2D cervical measurements.  
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Such a study design is currently being conducted in our department and results are soon expected.

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**LEGENDS**

<b>Figure 1.</b>	<p>a). Volume measurement (22.00 cm<sup>3</sup>) with VOCAL (manual mode, rotation step 30°).</p> <p>b). The volume is measured with the use of three diameters and the geometric formula for the cylinder (volume=20.69 cm<sup>3</sup>).</p>
<b>Figure 2.</b>	<p>Bland-Altman plot for the percentage of the mean difference and 95% limits of agreement between VOCAL method and the geometric formula for the cylinder.</p>
<b>Figure 3.</b>	<p>a) Bland-Altman plot for the percentage of the mean difference for VOCAL (Observer's 1-1<sup>st</sup> measurement — Observer's 2 measurement) and 95% limits of agreement for interobserver measurements.</p> <p>b) Bland-Altman plot for the percentage of the mean difference for geometric formula of cylinder (Observer's 1-1<sup>st</sup> measurement — Observer's 2 measurement) and 95% limits of agreement for interobserver measurements.</p>
<b>Figure 4.</b>	<p>a) Bland-Altman plot for the percentage of the mean difference for VOCAL (Observer's 1-1<sup>st</sup> measurement — 2<sup>nd</sup> measurement) and 95% limits of agreement for intraobserver measurements.</p> <p>b) Bland-Altman plot for the percentage of the mean difference for geometric formula of cylinder (Observer's 1-1<sup>st</sup> measurement — 2<sup>nd</sup> measurement) and 95% limits of agreement for intraobserver measurements.</p>

**Table 1.** Descriptive statistics of sample (n=81 patients/81 volume datasets).

	Mean±SD	Range
<b>Age</b> (in years)	38.1±10.4	18-62
<b>Dimensions of cervix</b> (in mm)		
Cervical length	35.3±5.2	23.0-46.3
Anteroposterior diameter	28.3±5.6	16.7-44.7
Transverse diameter	31.2±5.9	22.9-49.5
<b>Cervical volume</b> (in cm <sup>3</sup> )	<b>VOCAL</b>	<b>Cylinder formula</b>
1 <sup>st</sup> Observer		
1 <sup>st</sup> measurement	24.81±8.46 (10.72-47.74)	25.13±8.82 (10.09-47.59)
2 <sup>nd</sup> measurement	24.91±8.26 (10.94-46.28)	25.21±8.66 (10.29-45.33)
2 <sup>nd</sup> Observer	24.68±8.24 (11.28-45.98)	25.09±8.68 (10.09-47.60)

**Table 2.** Time (mean±SD) needed to perform cervical volume measurements with VOCAL method and the geometric formula of the cylinder.

		VOCAL (sec)	Cylinder formula (sec)	<i>p</i> -value
1 <sup>st</sup> Observer	1 <sup>st</sup> measurement	51.89±10.92	33.32±9.56	<0.001
	2 <sup>nd</sup> measurement	52.77±11.04	34.26±9.60	<0.001
2 <sup>nd</sup> Observer		50.70±11.26	31.96±9.15	<0.001

**Table 3.** Reliability analysis with the calculation of intraclass correlation coefficient (ICC) and 95% confidence intervals.

		ICC	95%CI
Intermethod agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement	0.970	0.954-0.981
	Observer's 2 Cylinder measurement		
Interobserver agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement	0.978	0.965-0.986
	Observer's 2 VOCAL measurement		
	Observer's 1- Cylinder 1 <sup>st</sup> measurement	0.954	0.930-0.970
	Observer's 2 Cylinder measurement		
Intraobserver agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement	0.992	0.988-0.995
	VOCAL 2 <sup>nd</sup> measurement		
	Observer's 1- Cylinder 1 <sup>st</sup> measurement	0.972	0.956-0.982
	Cylinder 2 <sup>nd</sup> measurement		

**Table 4.** Percentage of mean difference $\pm$ 95% limits of agreement.

		Percentage of mean difference	95% limits of agreement
Intermethod agreement	Observer's 1- VOCAL 1 <sup>st</sup> measurement — Observer's 2 Cylinder measurement	-0.78%	-17.59% to 16.03%
	Observer's 1- VOCAL 1 <sup>st</sup> measurement — Observer's 2 VOCAL measurement	-0.42%	-16.57% to 15.68%
Interobserver agreement	Observer's 1- Cylinder 1 <sup>st</sup> measurement — Observer's 2 Cylinder measurement	0.16%	-20.30% to 20.62%
	Observer's 1- VOCAL 1 <sup>st</sup> measurement — VOCAL 2 <sup>nd</sup> measurement	-0.66%	-9.14% to 7.82%
Intraobserver agreement	Observer's 1- Cylinder 1 <sup>st</sup> measurement — Cylinder 2 <sup>nd</sup> measurement	-0.51%	-18.38% to 17.36%