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Software toolbox for analysis of the endometrial myometrial junction - a pilot study

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Summary

Purpose: To develop and evaluate an algorithm for computerized evaluation and measurement of the endometrial-myometrial junction (EMJ). *Materials and Methods:* The advanced image processing toolbox of the Matlab software package was used for identification and quantitative analysis of the EMJ area on three-dimensional (3D) rendered coronal plane uterine images, with clear-cut borders of the EMJ. The algorithm was used to process the images and calculate the geometric parameters characterizing the identified EMJ. The manual measurements of the maximum thickness of the EMJ were compared to automated measurements performed by the algorithm on the same images. *Results:* For all three interfaces, the mean maximum manual measurement was less than the mean maximum computed measurement. The differences between the two measurements were not statistically significant (p = 0.275, 0.608 and 0.419 for the right wall, left wall, and fundus, respectively). The mean systematic and random errors ranged from 5.4% to19.3% and 20.4% to 48.6%, respectively. Pearson correlations for the right wall, left wall and fundus (r = 0.642, p = 0.001; r = 0.730, p < 0.001, and r = 0.694, p < 0.001, respectively) were good. *Conclusions:* Maximum EMJ thickness measurements performed by the innovative Matlab software algorithm are as accurate as manual measurements, and have the potential to reduce inter-observer variability.

Key words: Endometrial-myometrial junction; Software toolbox.

Introduction

The sonolucent endometrial-myometrial junction (EMJ) represents the inner layer of the myometrium [1] and is described as a subendometrial hypoecogenic halo. In the past 15 years, various ultrasound, magnetic resonance imaging (MRI) and histologic studies have been performed in order to determine the role of this anatomic area in menstrual cycle regulation and fertility [1-7]. Kunz *et al.* measured the thickness of the EMJ and estimated that in a gray scale mid-sagittal section image of endovaginal sonography, the halo may comprise up to one-quarter of the total myometrial thickness [2].

Histologically, this subendometrial area is different from other submucosal tissues and is characterized by tightly packed muscle cells with increased vascularity [3]. MRI studies demonstrate differences in the signals between the inner and the outer endometrium and emphasize the role of this junctional zone in contractions of the non-pregnant uterus. Disruption of the junctional zone seen in MRI has been proposed as a criterion for the diagnosis of adenomyosis [4-6]. The EMJ was also reported to be thick in diffuse adenomyosis [6]. The integrity of the EMJ may be affected by both benign and malignant uterine pathologies.

The EMJ can be measured using contemporary techniques by three-dimensional (3D) ultrasound, in mid- and paracoronal rendered images rather than in grayscale sagittal or axial sections [7-11]. Currently, evaluation of the EMJ is subjective and depends on the sonographer's experience and on simple, manual measurements performed on the lateral interfaces of a 3D rendered coronal image. Objective, automatic measurements of the EMJ can be achieved using a computerized image processing algorithm to evaluate and analyze the geometry of the EMJ in these 3D ultrasound images. The aim of the study is to propose and validate such an algorithm.

Materials and Methods

The innovative algorithm was developed by two of the authors (SOG and YZ) who received input digital files containing 3D rendered images of the coronal plane of the uterus and used Matlab-

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Figure 1. — A 3D image in the coronal plane selected for EMJ evaluation and measurements.

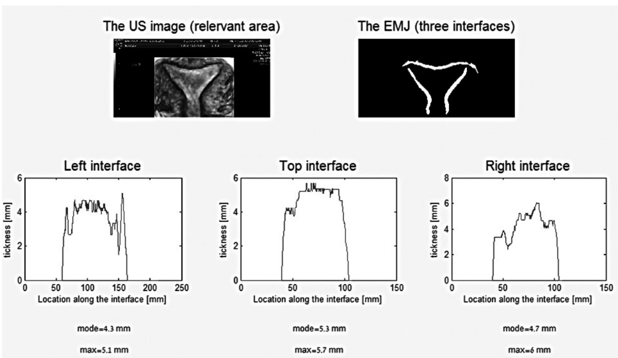

Figure 2. — The display and measurements of the EMJ in three interfaces after the user presses the 'start' button.

Figure 3. — A 3D image with manual measurements.

software, which is a commonly used tool for advanced applications in image processing. It can be run on a regular PC. The advanced image processing toolbox of the Matlab software package was used for the identification and quantitative analysis of the EMJ area on the images. The first step was to identify the EMJ in the 3D rendered image of the coronal plane of the uterus, with high resolution clear cut borders in all three interfaces of the coronal plane, right, left, and fundal uterine walls and to define quantitative measures to characterize the geometry of this interface region (Figure 1). The 3D coronal view reconstruction was achieved by using the 3D static rendering mode. After identifying the relevant area, the pre-defined numerical indices are calculated for the right, left, and fundal uterine walls. The original ultrasound image of 256 levels of brightness was reduced to only two, black and white, creating a binary image. The algorithm runs based on a 3D rendered coronal image with an initial point that the user marks subjectively at the border between the uterine body and cervix. After processing the image, the algorithm calculates the geometric parameters that characterize the identified EMJ. For the EMJ thickness calculation, the "bwdist" Matlab function was used. This function computes the Euclidean distance transformation of the binary image (Figure 2). The algorithm performs multiple thickness measurements in each of the three interfaces of the image. The maximum and mode thicknesses are calculated for each interface. These are also seen on the histogram attached to the figure. The mode thickness is the thickness that appears most often in the relevant interface. The continuity of the EMJ in the selected image is illustrated by the binary image displayed next to the gray scale image of the EMJ (Figure 2).

The authors performed a prospective, observational pilot study between December 2014 and March 2015. Eligibility was limited to non-pregnant pre-menopausal women in the luteal phase of the menstrual cycle in order to maximize the visualization of the EMJ. This study was approved by the local Institutional Review Board (IRB).

Patients who were referred to the Ultrasound Unit for consultation regarding uterine anomalies, infertility or poor reproductive outcomes were invited to participate in the study. Three-dimensional rendered coronal plane transvaginal ultrasound images were captured by an E8 ultrasound machine with a multi-frequency 3D volume endovaginal probe. To reduce interobserver error, all data rendering and manual measurements of the maximum thickness of the three EMJ interfaces were performed by a single user (RT)(Figure 3). The ultrasound default brightness (10%) and threshold settings were strictly kept using a pre-specified research protocol. These coronal plane images are routine in the work-up of patients with suspected uterine anomalies.

For the purpose of EMJ analysis, the authors captured a minimum of five images per patients. Out of those images, they selected images with undisturbed continuity of the EMJ, where the EMJ borders were best visualized in the right and left lateral and fundal interfaces, as close as possible to the interstitial part of the fallopian tubes, without evidence of a myometrial lesions like foci of adenomyosis or submucous fibroids close to the endometrium. Fifteen patients were excluded because the images failed to show intact continuity of the EMJ.The images were later uploaded to a regular PC and the algorithm was used to measure the EMJ by another author (RA) who was blinded to the manual measurements. Comparisons and accuracy calculations were performed by a third author (AA).

Comparisons and correlations were calculated using SPSS software, version 21.0. The Shapiro-Wilk test was used to test for normal distribution of the variables and the Wilcoxon test was used to attest differences. A p-value of < 0.05 was considered significant. Linear regression was calculated to determine the relationship between the manual sonographic and algorithm measurements and to calculate the R-square. The maximal-mode difference was calculated as the difference between the maximal and the mode of the al-

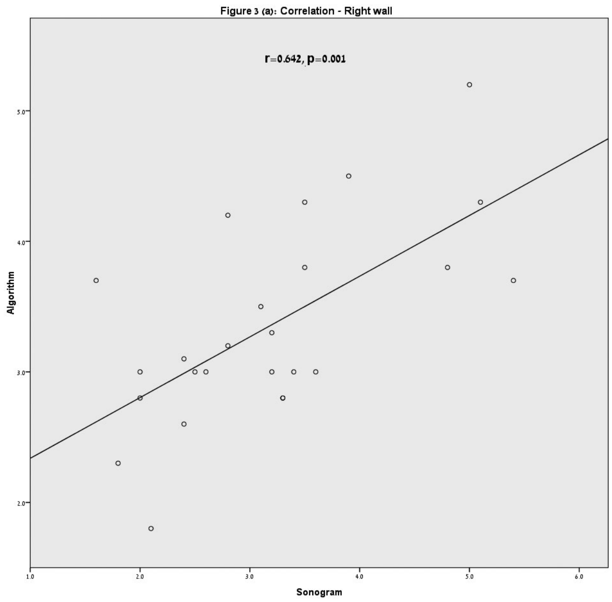

Figure 4a — Correlations between the sonogram and the algorithm measurements of the right wall.

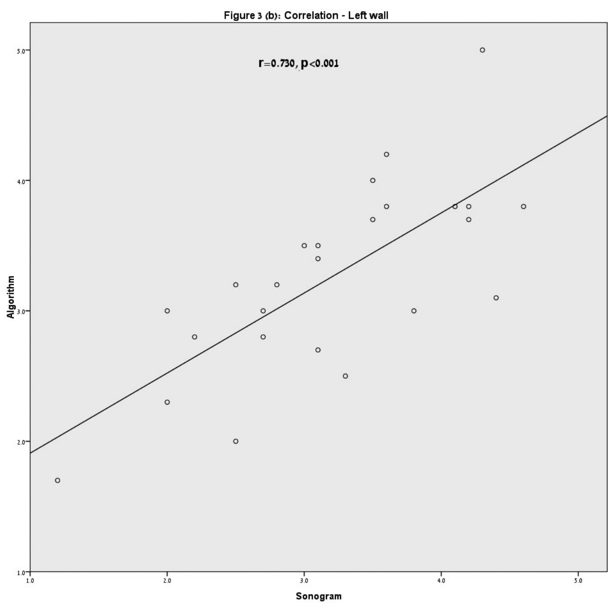

Figure 4b — Correlations between the sonogram and the algorithm measurements of the left wall.

gorithm measurements, divided by the maximal measurement and presented as percentage. Systematic error, as a measure of accuracy, was calculated as (algorithm measurement - sonographic measurement)/sonographic measurement. The random error was considered the standard deviation of the systematic errors.

Results

Twenty-five manual, maximum thickness measurements of the EMJ were compared with the respective algorithm

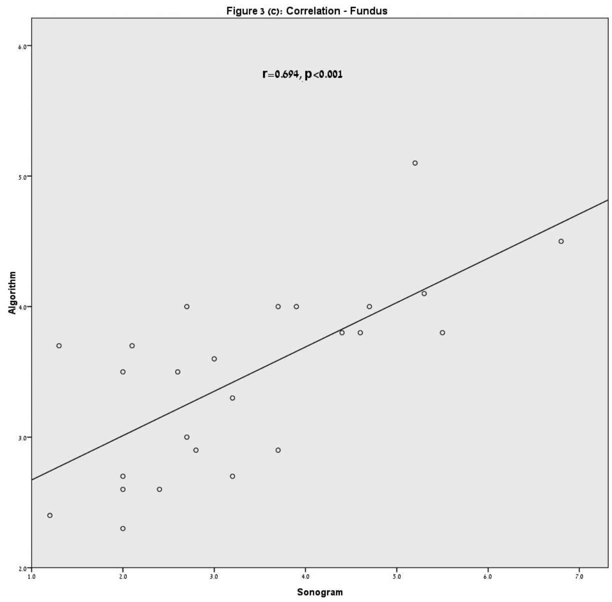

Figure 4c — Correlations between the sonogram and the algorithm measurements of the fundus.

measurements. A good correlation was found between the two techniques for all three interfaces ($r = 0.642$, $p = 0.001$; $r = 0.730$, $p < 0.001$, $r = 0.694$, and $p < 0.001$ for the right wall, left wall, and fundus, respectively) (Figures 3a–c). The mean maximal manual measurement was less than the mean maximal computed measurement in all three interfaces, and the difference between each pair of measurements was not statistically significant ($p = 0.275$, 0.608, and 0.419 for the right wall, left wall and fundus, respectively) (Table 1). The mean difference between the maximum computed measurement and the mode measurement was 22.9% for the right wall, 20.9% for the left wall, and 25.5% for the fundus. The mean systematic error was 12.2% for the right wall, 5.4% for the left wall, and 19.3% for the fundus, with random errors of 33.2%, 20.4%, and 48.6%, respectively.

Discussion

The functional role of the EMJ in regard to cycle regulation and fertility has not yet been determined. Functional imaging studies hypothesize that this zone has a role in uterine peristalsis [12]. The thickness and integrity of the EMJ has recently become the focus of studies in an effort to explain a correlation between its thickness and various pathologies such as endometriosis and recurrent miscarriage [8-11]. Currently, analysis and measurements of EMJ images are mainly visual and depend on the sonographer's experience, which might limit reproducibility.

The purpose of the current study was to develop a semiautomatic algorithm that could provide quantitative characteristics of the geometry of the EMJ, including thickness

Table 1. — *Comparison between manual and algorithm measurements.*

Measurement	Sonogram (mm)	Algorithm (mm)	*p*-value
Right wall	3.2 ± 1.0	3.3 ± 0.8	0.275
Left wall	3.2 ± 0.9	3.3 ± 0.7	0.608
Fundus	3.3 ± 1.4	3.5 ± 0.7	0.419

and continuity in normal uteri, and later in pathological situations using the Matlab software. The transition from manual, subjective to semi-automated, objective analysis based on consistent, objective, and quantitative criteria may enable better evaluation of the EMJ and more reliable detection of uterine pathologies.

The mathematical formulas of computerized image processing are well known. The advanced, image processing toolbox of the Matlab software package was first reported for medical use in ultrasound imaging of the common carotid artery [13]. The Matlab software used for evaluating the lumen and intima media thickness of the common carotid artery was validated on 100 ultrasound images and is similar to that used here. It is based on graphical user interface (GUI). The present authors are not aware of the use of this software package in gynecological ultrasound. The algorithm performs multiple thickness measurements in each of the three interfaces of the image and enables measurement of the maximum and mode thicknesses, allowing the continuity of the EMJ in the selected image to be confirmed or ruled out. Although the significance of interrupted EMJ has not been established yet, it may be related to fertility and to pathological conditions. The good correlation between the manual and algorithm maximum thickness EMJ measurements for all three interfaces of 0.64 and higher, is promising and further studies may strengthen the validity of this tool as replacement for manual measurements. The differences between the two techniques were not significant and that the systematic errors were relatively small. The significance of the EMJ mode thickness and whether it is superior to other EMJ measurements remains to be established in future studies that include known pathologies.

This study is not without limitations. The authors used a relatively small cohort for this research, and some technical issues prevented the inclusion of all patients. These limitations may have introduced a selection bias. Nonetheless, all images and scans were captured by on experienced sonographer using strict setting protocol, and were analyzed using the same strict algorithm, so interobserver variability and analysis errors were reduced to a minimum.

Combined with the relatively small systematic errors, the authors may very cautiously assume that the algorithm is accurate. Nonetheless, the random errors are still significant, indicating that additional cases with improved operator experience are needed to establish the accuracy and precision of this technology.

The authors also assume that the multiple measurements and objective analysis of the EMJ as proposed by the algorithm may be superior to the current manual measurements of the maximum and minimum thicknesses of the EMJ in one or two interfaces, and may better reflect the thickness of the EMJ and its continuity. Additional studies with more subjects are needed to fully validate the use of this technology, and to assess its usefulness in detecting pathologies. Future research evaluating the geometry of the EMJ may include surface area and volume.

References

[1] De Vries K., Lyons E.A., Ballard G., Levi C.S., Linsay D.J.: "Contractions of the inner third of the myometrium". Am. J. Obstet. Gynecol., 1989, *162*, 579.

[2] Kunz G., Beil D., Huppert P., Leyendecker G.: "Structural abnormalities of the uterine wall in women with endometriosis and infertility visualized by vaginal sonography and magnetic resonance imaging". *Hum. Reprod.*, 2000, *15*, 76.

[3] Tetlow R.L., Richmond I., Manton D.J., Greenman J., Turnbull L.W., Killick S.R.: "Histological analysis of the uterine junctional zone as seen by transvaginal ultrasound". Ultrasound Obstet. Gynecol., 1999, *14*, 188.

[4] Reinhold C., McCarthy S., Bret P.M., Mehio A., Atri M., Zakarian R, Glaude Y., Liang L., Seymour R.J.: "Diffuse adenomyosis: comparison of endovaginal US and MR imaging with histopathologic correlation". *Radiology*, 1996, *199*, 151.

[5] Brosens J.J., de Souza N.M., Barker F.G.: "Uterine junctional zone: function and disease". *Lancet*, 1995, *346*, 558.

[6] Exacoustos C., Brienza L., Di Giovanni A., Szabolcs B., Romanini M.E., Zupi E., Arduini D.: "Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology". *Ultrasound Obstet. Gynecol.*, 2011, *37*, 471.

[7] Naftalin J., Jurkovic D.: "The endometrial-myometrial junction: a fresh look at a busy crossing". *Ultrasound Obstet. Gynecol.*, 2009, *34*, 1.

[8] Naftalin J., Hoo W., Nunes N., Marvelos D., Nicks H., Jurkovic D.: "Inter- and intraobserver variability in three-dimensional ultrasound assessment of the endometrial–myometrial junction and factors affecting its visualization". *Ultrasound Obstet. Gynecol.*, 2012, *39*, 587.

[9] Lazzarin N., Exacoustos C., Vaquero E., De Felice G., Manfellotto D., Zupi E.: "Uterine junctional zone at three-dimensional transvaginal ultrasonography in patients with recurrent miscarriage: a new diagnostic tool?" *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2014, *174*, 128.

[10] Exacoustos C., Luciano D., Corbett B., De Felice G., Di Feliciantonio M., Luciano A., Zupi E.: "The uterine junctional zone: a 3-dimensional ultrasound study of patients with endometriosis". *Am. J. Obstet. Gynecol.*, 2013, *209*, 248.e1.

[11] Larsen S.B., Lundorf E., Forman A., Dueholm M.: "Adenomyosis and junctional zone changes in patients with endometriosis". Eur. J. Obstet. Gynecol. Reprod. Biol., 2011, *157*, 206.

[12] Meirzon D., Jaffa A.J., Gordon Z., Elad D.: "A new method for analysis of non-pregnant uterine peristalsis using transvaginal ultrasound". *Ultrasound Obstet. Gynecol.*, 2011, *38*, 217.

[13] Loizou C.P., Theofanous C., Pantziaris M., Kasparis T.: "Despeckle filtering software toolbox for ultrasound imaging of the common carotid artery". Comput. Methods Programs Biomed., 2014, *114*, 109.

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