TITLE: ESHRE/ESGE female genital tract anomalies classification system – The potential impact of discarding arcuate uterus on clinical practice

RUNNING TITLE: ESHRE/ESGE classification and arcuate uterus

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ABSTRACT:

Study question: What would be a potential impact of implementing the new ESHRE/European Society of Gynaecological Endoscopy (ESGE) female genital anomalies classification system on the management of women with previous diagnosis of arcuate uteri based on the modified American Society for Reproductive Medicine (ASRM) criteria?

Summary answer: A significant number of women with previous diagnosis of arcuate uteri are re-classified as having partial septate uteri according to the new ESHRE/ESGE classification system which may increase the number of remedial surgical procedures.

What is known already: The ESHRE/ESGE classification system has defined measurement techniques, reference points and specific cut-offs to facilitate the differentiation between normal and septate uteri. These criteria have been arbitrarily defined and they rely on the measurement of uterine wall thickness and depth of distortion of uterine fundus.

Study design, size, duration: This was a retrospective cohort study. We searched our ultrasound clinic database from January 2011 to December 2014 to identify all women diagnosed with arcuate uterus on three-dimensional ultrasound according to the modified ASRM criteria.

Participants/materials, setting, methods: For each woman, the ultrasound images were stored in our clinical database and they were re-examined according to ESHRE/ESGE specifications. The presence and location of all acquired uterine anomalies, such as fibroids or adenomyosis was noted. We applied the two diagnostic approaches as specified by the ESHRE/ESGE classification: the main option (MO) and the alternative option (AO). We used the Kappa statistic to quantify the agreement between the two approaches. We also compared the number of previous miscarriages in women with normal and partial septate uteri according to the ESHRE/ESGE classification. Non-parametric Mann-Whitney and Kruskal-Wallis tests were used for the analyses and receiver-operating characteristic (ROC) curves were constructed to assess the predictive values of the calculated uterine distortion indices for the detection of women at risk of suffering multiple pregnancy losses.

Main results and the role of chance: We included 270 women diagnosed with arcuate uterus in the study. 77 women (28.5%, 95% CI 23.1-33.9) had evidence of fibroids or adenomyosis. These abnormalities precluded the application of either proposed ESHRE/ESGE techniques to assess uterine morphology in 25 women (9.3%, 95% CI 5.8-12.7). When using the MO, 138/237 (58.2%, 95% CI 51.9-64.3) women were diagnosed with partial septate uterus compared to 61/230 (26.5%, 95% CI 21.2-32.6) women when using the AO. In 222 women in whom we were able to apply both MO and AO, there was agreement in the diagnosis of septate uterus between the two techniques in 146/222 cases (65.8%, 95% CI 59.3-71.7; Kappa 0.42, 95%CI 0.35-0.5). There was no statistical difference in the proportion of women with history of previous multiple miscarriages between those diagnosed with normal or partial septate uteri using either MO (6.2%, 95% CI 2.9-12.9 vs. 9.5%, 95% CI 5.6-15.6; p=0.47) or AO (7.2%, 95% CI 4.2-12.1 vs. 11.7%, 95% CI 5.8-22.2; p=0.29).

Limitations, reasons for caution: This study was retrospective in nature and the definition of arcuate uterus used in the study is not universally accepted. The reproductive history data were collected retrospectively and therefore may be prone to bias.

Wider implications of the findings: There are methodological weaknesses in the new ESHRE/ESGE classification system which would need to be addressed in future revisions. There was no significant difference in the past reproductive outcomes between women diagnosed with normal and anomalous uteri and the clinicians should exercise caution when offering surgical correction to women diagnosed with partial septate uteri using the new ESHRE/ESGE classification.

Study funding/competing interest(s): No study funding was received and no competing interests are present.

Trial registration number: N/A

KEY WORDS: ESHRE/ESGE female genital anomalies classification system, arcuate uterus, septate uterus, ultrasound, female infertility, female reproductive tract, uterine abnormalities

Introduction

Congenital uterine anomalies are relatively common with the reported prevalence ranging between 5.5% and 8% (Chan et al., 2011a). In the last decades, the diagnosis has largely relied on the American Society for Reproductive Medicine (ASRM) classification system (Gibbons et al., 1988). One of the main weaknesses of this system is that it provides no objective definition of the normal uterus and the diagnosis of an anomaly is based on the subjective impression of the clinician. Uterine anomalies were traditionally diagnosed in women presenting with poor reproductive outcomes, but the development of three-dimensional ultrasound has enabled non-invasive detection in low risk population as well (Woelfer et al., 2001). This has also enabled development of more reproducible diagnostic criteria and studies comparing the severity of uterine distortion with reproductive outcomes (Salim et al., 2003a, Salim et al., 2003b; Prior et al., 2017). However, the criteria to diagnose uterine anomalies were not evidence-based and they were defined arbitrarily. The same limitation applies to all classifications of uterine anomalies published so far.

In order to facilitate development of more consistent and reproducible criteria to diagnose uterine anomalies, the European Society of Human Reproduction and Embryology / European Society for Gynaecological Endoscopy (ESHRE/ESGE) female genital tract anomalies classification was developed (Grimbizis et al., 2013). This classification follows a similar approach to the description of uterine morphology as the ASRM classification, but in addition to defining several morphological types of anomalies, it also provides measurable cut-off limits which facilitate differential diagnosis between different groups of anomalies. The two key measurements are the uterine wall thickness and the depth of distortion of uterine fundus. The initial ESHRE/ESGE report did not recommend any specific technique for the measurement and this triggered a debate on how to appropriately apply the measurements in clinical practice (Ludwin et al., 2014; Grimbizis et al., 2014). The final clarification was provided in a more recent publication ("Thessaloniki ESHRE/ESGE consensus") in which instructions for measuring the uterine dimensions are described (Grimbizis et al., 2016).

Although similar in approach to the ASRM classification, one of the most controversial recommendations in the new classification is decision to abandon the term arcuate uterus. This common minor anomaly of the uterus according to the ASRM classification is now either described as normal or as a partial septate uterus, depending on the size of fundal indentation in relation to the uterine wall thickness. A study using these criteria has shown that this can consequently lead to increased frequency of diagnosing septate uterus. Since these women may often be offered surgical correction, this could lead to unnecessary overtreatment (Ludwin et al., 2015).

The primary aim of our study was to determine what proportion of women previously diagnosed with arcuate uteri on 3-D ultrasound would be re-classified as having septate uterus using the new ESHRE/ESGE classification with different measurement techniques suggested by Thessaloniki consensus (Grimbizis et al., 2016). We also compared the degree of uterine distortion with past reproductive outcomes to determine whether the proposed classification facilitates better identification of women who are likely to suffer pregnancy losses.

Materials and methods

Study design

We searched our database to identify all women diagnosed with arcuate uteri on 3-D ultrasound scan in our gynaecological outpatient clinic over a period of four years (from January 2011 to December 2014), regardless of indications for the visit. All women attending our clinic are seen and assessed by gynaecologists who are fully trained in gynaecological ultrasound. A full history is taken and entered into a clinical database (Viewpoint Bildverarbeitung GmbH, Munich, Germany). This includes a detailed gynaecological history, past obstetric history and medical history. All women in whom ultrasound is indicated are routinely offered a two-dimensional (2-D) transvaginal ultrasound scan in an attempt to identify possible causes of their symptoms. All women are routinely screened for the presence of any uterine abnormalities, including congenital uterine anomalies. Congenital uterine anomalies are suspected in all women with duplication of endometrial echo on transverse section through the uterus

and in those in whom it is not possible to visualize both interstitial tubes. In these women, 3-D ultrasound scan is used to reach a definitive diagnosis (Jurkovic et al., 1995). The technique of the examination has been previously described (Salim et al., 2003a). The analysis of uterine morphology was performed in a standardized reformatted plane, with the uterus visualised in the coronal plane using the interstitial portions of the Fallopian tubes as reference points. All images were stored electronically into the database containing women's clinical data and ultrasound measurements.

Arcuate uteri were diagnosed in accordance with the ASRM classification adopted for the use with 3-D ultrasound (Salim et al., 2003a). The uterus was categorised as arcuate if the central point of indentation was at obtuse angle (>90°). In cases where the indentation was at an acute angle (<90°), the diagnosis of a subseptate uterus was made. After confirming the diagnosis, the examiner routinely enters it into the database. All women with term "arcuate" in the diagnoses were included in the automated search process for the purpose of our study.

A single experienced Level 3 (EFSUMB, 2006) ultrasound examiner (JK) re-examined all stored images of women diagnosed with arcuate uteri using ESHRE/ESGE criteria. Only good quality images were selected and in all cases the diagnosis of arcuate uterus was confirmed prior to inclusion into the study. The authors of Thessaloniki "ESHRE/ESGE consensus" recommend two options to assess the uterine cavity, the "main" option (MO) and the "alternative" option (AO) (Grimbizis et al., 2016). The AO is utilised if the MO is not feasible or representative because of the abnormalities of the uterine fundus. Whenever possible, we used both approaches to analyse the uterine morphology in order to assess the level of diagnostic agreement between the two techniques. We applied the ESHRE/ESGE criteria first to the 3-D coronal views of the uteri. This involved first measuring the distance from the midpoint of the line joining the internal tubal ostia and the bottom of indentation of the cavity (I), this representing the fundal indentation. The distance from the external contour of the uterine fundus to the level of the line joining the internal tubal ostia in the coronal aspect was then measured, this representing the uterine wall thickness (W) (Figure 1). The I/W ratio was then calculated as per the

ESHRE/ESGE criteria. The internal indentation was defined as I/W x100 (%). We also used the AO, which involved the measurement of the thickness of the anterior and the posterior uterine walls at the midpoint of the uterine corpus in the sagittal section of 2-D image of the uterus. We then calculated the mean of these two values to obtain the average uterine wall thickness. Then, the I/W ratio/internal indentation were calculated as in the MO (Figure 2). Arcuate uteri with normal outer outline and internal indentation at the fundal midline exceeding 50% of the uterine wall thickness were re-classified as septate uteri. The remaining arcuate uteri with internal indentation ≤50% we re-classified as normal.

Confounders

ESHRE/ESGE introduces a new class of dysmorphic uterus, a diagnosis, which overlaps with normal uterus. This was excluded in our study to avoid confusion (Ludwin et al., 2015). Occasionally the interostial line may not be clearly visible on images or is placed below the intercornual line and this may present a limitation at measuring the internal indentation (Ludwin et al., 2017).

Statistical analyses

We investigated the association between ESHRE/ESGE calculated ratio (I/W) and the number of previous miscarriages. We calculated percentage of agreement and used Cohen's Kappa statistic to quantify the agreement between both ESHRE/ESGE approaches to assess the uterine cavities. Our sample size (n=270) allowed us to calculate Kappa statistics with a 95% confidence interval of width 0.2 assuming that Kappa is 0.8 and the proportion of disagreement between the methods is 0.16.

To compare differences between the investigated indices (as a continuous variable) and the number of previous miscarriages we used either the non-parametric Mann-Whitney *U* test or Kruskal-Wallis test. Fisher's exact test was used for categorical data. In an attempt to establish the predictive value of calculated indices of uterine distortion for the detection of women at risk of suffering multiple pregnancy losses, we have constructed receiver-operating characteristic (ROC) curves and evaluated

areas under the curve. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Ethical approval:

We sought advice from the Joint Research Office of University College London and University College London Hospital regarding ethical approval and were advised that formal ethics approval was not needed for this study as long as patient identifiable data was not seen by anyone outside the clinical care team.

Results

We identified a total of 285 women with an arcuate uterus according to the modified ASRM criteria and 270 with available good quality images were included in the analysis (Table I). Of these 270 women, 77 (28.5%, 95% CI 23.1-33.9) had evidence of uterine fibroids or adenomyosis affecting the thickness of the uterine wall. This subgroup consisted of 24 (8.9%, 95% CI 6.1-12.9) women with adenomyosis, 41 (15.2%, 95% CI 11.4-20.0) women with fibroids and 12 (4.4%, 95% CI 2.6-7.6) women with both fibroids and adenomyosis. In order to apply the ESHRE/ESGE classification properly, we studied the location of fibroids or adenomyosis and their effect on the uterine wall morphology. In 9 (3.3%, 95% CI 1.8-6.2) women they did not significantly alter the suggested reference points specified by the Thessaloniki consensus, and we were still able to use the ESHRE/ESGE criteria. In 18 women, there were fibroids in the fundal area of the uterus and in 15 women there was evidence of adenomyosis affecting the uterine fundus. In these 33 women (12.2%, 95% CI 8.8-16.7) we could not reliably apply the MO ESHRE/ESGE technique to assess the uterine cavity. 40 women (14.8%, 95% CI 11.1-19.5) had abnormalities of the anterior and/or posterior uterine wall: 18 women had fibroids and 13 had extensive adenomyosis and 9 women had both fibroids and adenomyosis. In these women, it was not possible to apply the AO ESHRE/ESGE technique. In a total of 25 women (9.3%, 95% CI 5.8-12.7) (Table II), neither of the proposed ESHRE/ESGE options to assess the uterine morphology could be applied (Figure 3).

We successfully assessed the uterine morphology using the MO in 237 women without evidence of acquired abnormalities of the uterine fundus. Out of these, 99 (41.8%, 95% CI 35.7-48.1) were re-classified as having normal uteri and 138 (58.2%, 95% CI 51.9-64.3) were diagnosed with partial septate uteri. When using the AO on 230 women, 169 (73.5%, 95% CI 67.4-78.8) were re-classified as having normal and 61 (26.5%, 95% CI 21.2-32.6) as partial septate uteri. We then analysed the findings in 222 women in whom we were able to use both options to assess uterine morphology. We achieved the same diagnosis using both options in 146/222 cases (65.8%, 95% CI 59.3-71.7) (Kappa 0.42, 95%CI 0.35-0.5) (Table II). Demographic characteristics of women classified as having arcuate uteri with morphometric classification, and their re-categorization using the ESHRE/ESGE criteria are shown in Table III.

We then compared the incidence of multiple miscarriages in women classified as having normal or partial septate uteri. For the purpose of this, we included only 264 women who attempted a pregnancy and had at least one pregnancy in their history. There was no significant difference in the number of women who suffered multiple miscarriages in the past between the two uterine types with either the MO or AO ESHRE/ESGE classification criteria (both $p>0.05$). 13/137 (9.5%, 95% CI 5.6-15.6) of women diagnosed with partial septate uteri by using the MO experienced more than one miscarriage in the past which was comparable to 6/97 (6.2%, 95% CI 2.9-12.9) of women with normal uteri ($p=0.47$). When using the AO, there were 7 out of 60 (11.7%, 95% CI 5.8-22.2) women with partial septate uterus experiencing more than one miscarriage, compared to 12/167 (7.2%, 95% CI 4.2-12.1) women with normal uteri ($p=0.29$).

We then compared the median indentation index calculated using the MO in women with and without history of multiple miscarriages. We found a significantly higher median indentation index in women who had multiple miscarriages in the past (69.2% (range 20-250) vs. 53.5% (range, 18-249), $p=0.04$). There was no statistically significant difference when the ESHRE/ESGE index was calculated using the AO ($p>0.05$).

We also evaluated whether the degree of the ESHRE/ESGE calculated index of indentation was related to the number of previously experienced spontaneous early miscarriages. Again, there was a significant association between the degree of fundal distortion calculated using the MO technique, but not when the AO was used (Table IV). We then constructed a ROC curve to assess the predictive ability of the ESHRE/ESGE MO to identify women who suffered multiple miscarriages in the past. The area under the curve (AUC) was 0.64 (95% CI 57.9-69.8), which indicates poor predictive ability for this outcome. The best cut-off for identifying women with a high risk of suffering multiple miscarriages was I/W of 54.8% (sensitivity of 63.2% (95% CI 36.4-80.0) and specificity of 51.9% (95% CI 45.7-57.9). This translates to positive predictive value (PPV) of 10.3% (95% CI 4.6-14.6) and negative predictive value (NPV) of 94.2% (95% CI 89.2-97.5).

Discussion

Our results showed the ESHRE/ESGE female genital anomalies classification system has important limitations which would need to be addressed in the near future. We found that the proposed techniques to assess the uterine morphology could not be applied in a significant number of women with a previous diagnosis of arcuate uteri on three-dimensional ultrasound using subjective modified ASRM classification. The assessment of uterine morphology in the ESHRE/ESGE classification is mainly based on the measurement of the uterine muscle distortion rather than the examination of the uterine cavity itself.

Acquired uterine abnormalities of the myometrium are very common which precludes the use of this classification in women with significant fibroids or adenomyosis. In our study 28% of women with arcuate uteri had concomitant fibroids or adenomyosis which is similar to the previous studies on the prevalence of uterine abnormalities in women attending general gynaecology clinic (Naftalin et al., 2012) The authors of ESHRE classification acknowledged that problem in the Thessaloniki consensus and they defined two different approaches to uterine assessment in women with myometrial abnormalities. In our study population, however, neither the MO nor AO technique could be applied

to nearly 10% of women. In view of that, clinicians would need to be provided with additional advice on the alternative options to assess these women.

We also found that in more than a third of cases the MO and AO techniques gave discordant results in classifying the uterus as being normal and partial septate. This is a major methodological issue and prospective studies are needed to examine further the level of agreement between the two assessment techniques. If our findings were confirmed, the two proposed options to assess the uterus would need to be substantially revised.

A very small number of studies have attempted to compare the severity of uterine cavity distortion with reproductive outcomes (Salim et al., 2003b, Prior et al., 2017). In the ESHRE classification the authors have decided that uterine septum should be diagnosed when the size of the cavity indentation exceeds half of the total fundal uterine wall thickness. There is no evidence to support the use of this particular cut-off which we presume was selected arbitrarily. In our population, we could not distinguish women with history of adverse reproductive outcome using this specific threshold. When indentation index (MO) was modelled as a continuous variable, women with history of multiple miscarriages had higher values compared to controls, but ROC analysis has shown only modest predictive ability with very low positive predictive value of 10.3%.

A systematic review and meta-analysis concluded that arcuate uterus is often considered as a variation of normal (Chan et al., 2011b). A total of four studies were included in the meta-analysis and only one of them showed increased risk of second trimester miscarriage (Woelfer et al., 2011). A recent study has shown that contrary to other uterine anomalies, arcuate uterus has no significant influence on pregnancy or live birth rates in women treated for subfertility (Prior et al., 2017). The diagnosis of arcuate uterus is often a subjective diagnosis and there is a lack of good quality data with regard to its clinical implications. Hence, different morphometric criteria to differentiate arcuate from septate uterus have been proposed (Salim et al, 2003a; Troiano and McCarthy, 2004). ASRM has also adopted approach to assessing uterine cavity shape that is consistent with morphometric criteria used in our

study and now recognises indentation at obtuse angle as a characteristic of arcuate uterus (ASRM, 2016).

We found that between 27% and 58% of women with previous diagnosis of arcuate uteri would be re-classified as having a partial septate uterus using the new ESHRE/ESGE classification. The ESHRE/ESGE classification system does not provide guidelines on the management of different types of uterine anomalies, but many reproductive medicine specialists feel compelled to treat partial septate uteri, especially in women with history of infertility or recurrent pregnancy loss. In view of that, there is a significant risk that non-critical adoption of the new classification could lead to an increased number of surgical corrections of uterine anomalies without any supporting evidence showing that such practice would be beneficial to women. This problem is compounded by the absence of any randomised clinical trials showing that surgical correction of congenital uterine anomalies, let alone arcuate uterus, results in improved pregnancy outcomes (NICE, 2015, ASRM 2016).

The strength of our study is that it includes a large number of women diagnosed with arcuate uteri using 3-D ultrasound which is considered the optimal technique for the diagnosis of the uterine anomalies (ASRM, 2016; Chan et al., 2011a). Although our study was retrospective in nature, we carried out all the required measurements prospectively using our electronically stored 3-D images and volumes. A single operator examined the images and results may differ between different operators. Another limitation is that all reproductive outcomes were collected retrospectively, but this is in common with most studies published so far looking at the effect of uterine anomalies on women's reproductive health.

In conclusion, the results of our study show that many women with arcuate uteri would be diagnosed with partial septate uterus according to the ESHRE/ESGE classification. There are methodological weaknesses that make the diagnostics unreliable and would need to be addressed in the future revisions. In addition, our findings support the recommendation of authors of the ESHRE/ESGE classification that further large, prospective, long-term multi-centre studies are required to examine

possible associations between the severity of uterine cavity distortion in different types of uterine anomalies and women's life-long reproductive outcomes.

Author's roles

D.J. made substantial contribution to the concept and design of the study. J.K. contributed to design of the study, collected and examined the data. J.K. and D.J. analysed the data and wrote the article. E.S., T.V.D.B., D.M. and G.A assisted in the analysis and interpretation of data. All authors contributed to revising the article for important intellectual content and approved the final version of the manuscript to be published.

Funding

No specific funding was sought for this study.

Conflict of interest

None declared.

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Figure legends:

Figure 1: Main option (MO) ESHRE/ESGE criteria applied to the 3-D rendered coronal view of the uterus. The uterine wall thickness is measured as a distance between the line joining tubal ostia and a parallel line on the top of uterine fundus (W). Internal midline indentation is a distance between the interostial line and a parallel line on the bottom of midline indentation (I). An example of partial septate uterus according to the ESHRE/ESGE classification is shown in 1a and an example of normal uterus is shown in 1b.

Figure 2: Representation of the alternative measurement option (AO) according to the ESHRE/ESGE criteria. The thickness of the anterior (A) and posterior (P) wall at the midpoint of the uterine corpus in the longitudinal plane is measured using 2-D ultrasound and then the mean value is calculated. The measurement of endometrial thickness (1) is also presented on the longitudinal view of the uterus. The midline fundal indentation (I) is measured as in the main option (MO) on 3-D coronal view of the uterus.

Figure 3: A uterus with multiple fibroids (F) in the fundus and posterior wall that preclude the application of both main option (MO) and alternative option (AO) ESHRE/ESGE criteria to assess the uterine cavity. Line (1) represents the measurement of endometrial thickness.