Comparison of the ESHRE–ESGE and ASRM classifications of Müllerian duct anomalies in everyday practice

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STUDY QUESTION: Does the European Society of Human Reproduction and Embryology–European Society for Gynaecological Endoscopy (ESHRE–ESGE) classification of female genital tract malformations significantly increase the frequency of septate uterus diagnosis relative to the American Society for Reproductive Medicine (ASRM) classification?

SUMMARY ANSWER: Use of the ESHRE–ESGE classification, compared with the ASRM classification, significantly increased the frequency of septate uterus recognition.

WHAT IS KNOWN ALREADY: The ESHRE–ESGE criteria were supposed to eliminate the subjective diagnoses of septate uterus by the ASRM criteria and replace the complementary absolute morphometric criteria. However, the clinical value of the ESHRE–ESGE classification in daily practice is difficult to appreciate. The application of the ESHRE–ESGE criteria has resulted in a significantly increased recognition of residual septum after hysteroscopic metroplasty, with a possible risk of overdiagnosis of septate uterus and problems for its management.

STUDY DESIGN, SIZE, AND DURATION: A prospective observational study was performed with 261 women consecutively enrolled between June and September 2013.

PARTICIPANTS/MATERIALS, SETTING, AND METHODS: Non-pregnant women of reproductive age presented for evaluation to a private medical center. A gynecological examination and 3D ultrasonography were performed to assess the anatomy of the uterus, cervix and vagina. Congenital anomalies were diagnosed using the ASRM classification with additional morphometric criteria as well as with the ESHRE–ESGE classification. We compared the frequency and concordance of diagnoses of septate uterus and all congenital malformations of the uterus according to both classifications. The morphological characteristics of septate uterus recognized by both criteria were compared.

MAIN RESULTS AND ROLE OF CHANCE: Of the 261 patients enrolled in this study, septate uterus was diagnosed in 44 (16.9%) and 16 (6.1%) patients using the ESHRE–ESGE and ASRM criteria, respectively (relative risk (RR)ESHRE–ESGE:ASRM 2.74; 95% confidence interval (CI), 1.6–4.72; P < 0.01). At least one congenital anomaly were diagnosed in 58 (22.2%) and 43 (16.5%) patients using the ESHRE–ESGE and ASRM classifications (RRESHRE–ESGE:ASRM, 1.35; 95% CI, 0.95–1.92, P = 0.1), respectively. The two criteria had moderate strength of agreement in the diagnosis of septate uterus (κ = 0.45, P < 0.01). There was good agreement in differentiation between anomaly and norm between the two assessment criteria (κ = 0.79, P < 0.01). The percentages of all congenital malformations and results of the differentiation between the anomaly and norm were obtained after excluding the confounding original ESHRE–ESGE criterion of dysmorphic uterus (internal indentation <50% uterine wall thickness). The morphology of septa identified by the ESHRE–ESGE [length of internal fundal indentation (mm): median, 10.7; lower–upper quartile, 8.1–20] significantly differed (P < 0.01) from that identified by the ASRM criteria [length of internal fundal indentation (mm): median, 21.1; lower–upper quartile, 18.8–33.1]. Internal fundal indentation in 16 out of 44 (36.4%) cases was <1 cm in the septate uterus by ESHRE–ESGE and met the criteria for normal uterus by ASRM.

LIMITATIONS AND REASONS FOR CAUTION: The study participants were women who visited a diagnostic and treatment center specialized in uterine congenital malformations for a medical assessment, not from the general public.

WIDER IMPLICATIONS OF THE FINDINGS: Septate uterus diagnosis by ESHRE–ESGE was quantitatively dominated by morphological states corresponding to arcuate uterus or cases that were not diagnosed as congenital malformations by ASRM. Relative overdiagnosis of septate uterus by ESHRE–ESGE in these cases may lead to unnecessary overtreatment without the expected benefits. The ESHRE–ESGE classification...
Introduction

Many attempts have been made to design the most appropriate classification method to manage Müllerian (Buttram and Gibbons, 1979), genital (the Vagina Cervix Uterus Adnex-associated Malformation system; Oppelt et al., 2005) and female genitourinary congenital malformations (the embryological–clinical system; Acien et al., 2004; Acien and Acien, 2011). The American Society for Reproductive Medicine (ASRM) classification is the most popular and has received the most acceptance over the last 25 years (Buttram et al., 1988).

Women with a history of miscarriages (Valle and Ekpo, 2013) and infertility (Pabuc¸cu and Gomel, 2004; Mollo et al., 2009), after diagnosis of septate uterus by ASRM classification criteria, commonly undergo hysteroscopic metroplasty to improve reproductive outcomes (Grimbizis et al., 2001; Brucker et al., 2011; Paradisi et al., 2014). Many non-controlled studies have confirmed the validity of such a procedure (Nouri et al., 2010; Valle and Ekpo, 2013), although we are waiting for confirmation in randomized controlled trials (Christiansen et al., 2005; Bosteels et al., 2010; Kowalik et al., 2011).

The European Society of Human Reproduction and Embryology–European Society for Gynaecological Endoscopy (ESHRE–ESGE) criteria (Grimbizis et al., 2012, 2013, 2014) were proposed to eliminate the subjective diagnosis of the original ASRM classification (Woelfer et al., 2001; Grimbizis and Campo, 2010) and enable differentiation between septate uterus and other similar conditions, independent of absolute morphometric criteria (Homer et al., 2000; Salim et al., 2003a; Troiano and McCarthy, 2004) complementing descriptive criteria (Buttram et al., 1988).

Our first experience (Ludwin et al., 2014b,c) using the ESHRE–ESGE classification prompted us to conduct a study to ascertain the influence of this classification on the frequency of septate uterus diagnoses, and the overall rate of congenital uterine anomalies compared with the ASRM criteria.

This study primarily aimed to determine whether the ESHRE–ESGE classification criteria significantly increases the diagnoses of septate uterus compared with the ASRM classification supplemented with absolute morphometric criteria. The study also aimed to evaluate the level of agreement between the two systems for classifying morphological forms of the uterus as a septate uterus or a congenital anomaly. In addition, we aimed to compare the morphological characteristics of septa (including the septal length) identified by both criteria, and assessed the potential clinical implications related to the use of ESHRE–ESGE.

Materials and Methods

Design and participants

This prospective observational study design was approved by the Bioethics Committee, Jagiellonian University (KBET/236/B/2013), and all the participants provided their written informed consents for participation.

The study was reported in accordance with the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (www.strobe-statement.org).

We recruited patients who visited the Ludwin & Ludwin Gynecology Private Medical Center (Krakow, Poland). Recruitment started in June 2013 and ended in September 2013. Data collection was completed in October 2013. Aggregated data were collected on Microsoft Excel for Mac 2011 version 14.1.0.

Non-pregnant women of reproductive age and <45 years of age, who consented to participate in the study, were enrolled. The following exclusion criteria were applied: (i) pregnancy confirmed by a positive beta-human chorionic gonadotrophin test; (ii) menopause (follicle-stimulating hormone >40 mIU/ml and 17β-estradiol <20 pg/ml); (iii) malignant neoplasms of the reproductive organs; (iv) presence of benign lesions in the myometrium of the uterine fundus or anterior or posterior wall, and lesions distorting the uterine cavity (myomas, adenomyosis, etc.) on ultrasonography (Hirai et al., 1995; Anderson, 1999); (v) surgeries that might affect the original shape of the uterine cavity, such as metroplasty, myomectomy and correction surgeries of congenital malformations of cervix and vagina, and prior removal of part of or the whole uterus; and (vi) Asherman’s syndrome.

Diagnostic tests

A gynecological examination with speculum and 3D ultrasonography were performed to assess the anatomy of the uterus, cervix and vagina. Ultrasonographic examinations were performed with an ultrasound system (Voluson E8 Expert BT12, GE Healthcare Ultrasound, Milwaukee, WI, USA) with volumetric intravaginal probes (GE RIC 5–9 MHz 3D/4D; GE Healthcare Ultrasound) between Days 17 and 25 of the menstrual cycle in a standardized manner (Ludwin et al., 2014a,c) by an experienced examiner (AL).

In patients with suspected congenital anomalies of the vagina or cervix or anatomical difficulties for speculoscopie (such as in the case of virgins), we used transrectal sonovaginocervicography (Supplementary data, Fig. S1) to evaluate the anatomic status of the vagina and cervix (Buttram et al., 1988; Grimbizis et al., 2013; Ludwin et al., 2013b).

Sonovaginocervicography

Transrectal 3D sonovaginography and sonocervicography was performed according to our own method. An 8-Fr Foley catheter (or two if the vagina was completely divided) was introduced into the vagina. The balloon was filled with 5–7 ml of saline to seal the vagina, and sterile saline solution was continuously applied to extend the vagina using a drip set and Foley catheter; manual pressure was applied on a 500-ml plastic bottle with saline. Manual pressure on the labia majora was applied to increase vaginal tightness and to prevent the catheter from falling out. The vagina and cervix were evaluated using 2D and 3D imaging. After obtaining a medial cervical sagittal section, volume acquisition was performed using a 3D static HD live surface render mode. Volume acquisition was repeated with the transverse orientation of the probes relative to the cervix. A detailed assessment was carried out offline immediately after the test in real-time using tomographic ultrasound imaging (for the evaluation of the vagina and endocervix) and the HD live surface render mode (for the evaluation of the ectocervix). The anatomical
### Table I Ultrasound criteria for the classification of congenital uterine anomalies by ASRM* and ESHRE–ESGE.

| Classification                   | Uterine cavity shape                                      | External contour                                      | Differentiation                                      |
|----------------------------------|----------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------|
| **ASRM**                         |                                                          |                                                        |                                                       |
| Norm                             | Straight, convex fundal contour<sub>a</sub> or internal indentation < 1 cm<sup>b,c</sup> | Straight, convex or external cleft < 1 cm<sup>b,c</sup> | Subjective impression and measurements                |
| Class I hypoplasia/agenesis      |                                                          |                                                        |                                                       |
| a. Vaginal, b. Cervical, c. Fundal, d. Tubal, e. Combined |                                                          |                                                        |                                                       |
| Class II uterus unicornuate      | Single well-formed uterine cavity with a single interstitial portion of Fallopian tube and concave fundal contour<sup>b</sup> | Asymmetric ellipsoidal shape (‘banana-shaped’)<sup>c</sup> with or without smaller horn | Subjective impression                                 |
| a. Communicating                | Connected with smaller contralateral uterine cavity with or without interstitial portion of Fallopian tube | External cleft > 1 cm dividing the two horns          | a. Measurements                                      |
| b. Non-communicating            | Unconnected with contralateral uterine cavity with or without interstitial portion of Fallopian tube | External cleft > 1 cm dividing the two horns<sup>b</sup>/variable if hemi hematometra is present in rudimentary horn | b. Measurements/subjective impression                |
| c. No cavity                    | Without uterine cavity in rudimentary horn              | External cleft > 1 cm dividing the two horns<sup>b</sup> | c. Measurements                                      |
| d. No horn                      | Rudimentary horn absent                                  |                                                        | d. Subjective impression                              |
| Class III uterus didelphys       | Two separate unicornuate uterine cavities              | Two corpus bodies with double cervix                  |                                                       |
| Class IV uterus bicornuate       | Internal indentation ≥ 1.5 cm<sup>b</sup>               | External cleft ≥ 1 cm<sup>b,c</sup>                   | a. Subjective impression                             |
| a. Complete                     |                                                          |                                                        |                                                       |
| b. Partial                      |                                                          |                                                        |                                                       |
| Class V septate uterus           | Internal indentation ≥ 1.5 cm<sup>b</sup>               | External cleft < 1 cm<sup>b,c</sup>                   | a. Subjective impression                             |
| a. Complete                     | Totally division of uterine cavity and cervical canal   |                                                        |                                                       |
| b. Partial                      | Partially or totally division of uterine cavity without or with partially septate cervix |                                                        |                                                       |
| Class VI arcuate uterus          | Internal indentation ≥ 1 cm; ≤ 1.5 cm<sup>b</sup>        | External cleft < 1 cm<sup>b,c</sup>                   | b. Subjective impression                             |
| Class VII T-shaped uterus        | T-shaped uterine cavity<sup>c</sup>                      | Hybrid form, non-characteristic conjunction of uterine, cervical and vaginal malformations | Subjective impression and measurements                |
| Anomaly without classification   |                                                          |                                                        |                                                       |
| **ESHRE–ESGE**                   |                                                          |                                                        |                                                       |
| Class U0: Normal uterus          | Straight, curved interstitial line or internal indentation < 50% myometrial thickness | Normal outline or external cleft < 50% of uterine wall thickness | Subjective impression and measurements                |
| Class U1: Dysmorphic uterus      | Abnormal                                                 |                                                        |                                                       |
| a. T-shaped                      | Narrow cavity; thickened lateral walls; correlation of two-third uterine corpus and one-third cervix |                                                        |                                                       |
| b. Infantilis                    | Narrow cavity without wall thickening; correlation of one-third uterine body and two-third cervix |                                                        |                                                       |
| c. Others (?)                    | Internal indentation < 50% myometrial thickness (?)      |                                                        |                                                       |
| Class U2: Septate uterus         | Internal indentation >50% myometrial thickness           | Normal outline or external cleft <50% of uterine wall thickness | Measurements                                          |
| a. Partial                      | a. Division above of the internal cervical os            |                                                        | a. Subjective impression                             |
| b. Complete                     | b. Division up to the internal cervical os               |                                                        | b. Subjective impression                             |
| Class U3: Bicorporeal uterus     | Division above of the internal cervical os               | External cleft >50% myometrial thickness              |                                                        |
| a. Partial                      |                                                        |                                                        |                                                        |
| b. Complete                     | Division above the cervix                                |                                                        |                                                        |
| c. Bicorporeal septate          | Division up to the cervix                                |                                                        |                                                        |

*Hybrid form, non-characteristic conjunction of uterine, cervical and vaginal malformations

**Continued**
### Classification of congenital malformations

Anatomical status was determined using the ASRM classification (Buttram et al., 1988) with additional morphometric criteria (Salim et al., 2003a; Bermejo et al., 2010; Ludwin et al., 2011, 2013a, 2014a,c) and the ESHRE–ESGE classification (Grimbizis et al., 2013; Table I). The results were categorized as follows: (i) congenital malformation of reproductive organ: absent/present, (ii) norm/class of congenital malformation/congenital malformation without classification and (iii) septate uterus: present/absent.

The ASRM diagnosis of septate uterus was confirmed if the depth of the external fundal indentation was < 1 cm and internal fundal indentation was > 1.5 cm (Table I). The indentations were measured after obtaining a coronal view with visible intramural parts of both the Fallopian tubes (Salim et al., 2003a,b; Ludwin et al., 2013a,b, 2014a,c).

Internal fundal indentations > 50% of the uterine wall were diagnosed as septate uterus by ESHRE–ESGE if the depth of the external intercornual cleft was < 50% (Table I). An average of the anterior and posterior wall thickness measurements (obtained in the sagittal plane at the thickest place) was used as a benchmark (Grimbizis et al., 2014; Ludwin et al., 2014b).

In the case of measurement-dependent anomalies (complete and long partial septum or bicorporeal uterus with deeper intercornual external cleft), where the endometrium was not visible in the sagittal section, the anterior and posterior walls were measured separately on the left and right sides, and the means of each set of values were calculated.

### Confounders and effect modifiers

We observed that one of the ESHRE–ESGE criteria for dysmorphic uterine recognition in the U1c subclass (with an inner indentation at the fundal midline level of < 50% of the uterine wall thickness; Grimbizis et al., 2013) is highly confusing because of similarities between criteria describing the identification of the normal uterus (internal indentation at the fundal midline not exceeding 50% of the uterine wall thickness; Grimbizis et al., 2013). Therefore, the U1c subclass was excluded from the results of the main report to avoid confusion, and the potential results of the application of this criterion have been analyzed in the Discussion section.

### Validation

Intrarater reliability of measurements of internal fundal indentation and uterine wall thickness was determined for a random selection of 30 patients.

### Sample size

The sample size was determined according to the alternative hypothesis that the frequency of septate uterus diagnoses significantly differs when ESHRE–ESGE criteria are applied in relation to diagnoses by the ASRM classification. Initial hypothesis and calculations [assuming a test power of 0.95 and \( \alpha = 0.05 \) (two-sided test)] was a priori based on the results of the first 190 patients [31 patients (16%) had septate uterus by ESHRE–ESGE and 11 (6%) had septate uterus according to the ASRM classification]. The required sample size was 252 patients (Chow et al., 2012). It was assumed that the number of patients enrolled should be higher by \( \sim 5\% \) due to the risk of exclusion from analysis in final stage (due to low quality of 3D volumes). We aimed to have \( \geq 190 \) patients in order to increase the power of the study, which was 0.88 for the preliminary results. The statistical power of a test calculated post hoc for the final results met the assumptions and was 0.97.

### Statistical analysis

All analyses were carried out using Statistica software (version 10.0, StatSoft, Inc., Tulsa, OK, USA). Categorical variables are presented as numbers of status of the cervix and vagina was subjectively evaluated (Supplementary data, Fig. S1).
Results

A total of 388 patients were eligible, and 262 were included (Fig. I). One patient was excluded from the analysis because the ultrasound scan quality was insufficient for diagnosis. Table II presents the demographic and clinical characteristics of the study population. Congenital genital tract anomalies were diagnosed in 43 (16.5%) and 58 (22.5%) of the 261 patients according to the ASRM and ESHRE–ESGE systems (Table II). Septate and arcuate uterus were the most common malformation (16 and 15 of 43 cases, respectively) diagnosed by the ASRM classification, and septate and bicornoral uterus were the most common malformations according to the ESHRE–ESGE classification.
ESHRE–ESGE classification (44 and 10 of 58 cases, respectively). The results of classification of congenital anomalies, including the anatomy of the uterus, cervix and vagina by the ESHRE–ESGE classification in relation to the ASRM classification are shown in Table III.

For congenital anomalies, 5/43 (11.6%) cases that had been diagnosed according to the ASRM criteria were considered as anomalies without classification because they possessed the characteristics of the two classes at the same time (didelphys uterus with septate cervix and bicor- nuate uterus with septate cervix; Tables II and III). No anomalies were present that could not be classified according to the ESHRE–ESGE criteria. The RR of unclassified anomalies using the ESHRE–ESGE against

Table III  Cross-tabulation of classification of female genital congenital tract anomalies using ASRM and morphometric criteria\textsuperscript{a} and ESHRE–ESGE system with anatomic status of cervix and vagina.\textsuperscript{b}

| ESHRE–ESGE | ASRM |
|------------|------|
| U0/C0/ V0  | U1A/C0/V0 | U2A/C0/V0 | U2B/C1/V1 | U3B/C2/V1 | U2B/C2/V2 | U3B/C2/V1 | U3C/C0/V0 | U3C/C1/V1 | U4B/C0/V0 | U5/C4/V4 | Total |
| No anomaly  | 202 | 1 | 15 | – | – | – | – | – | – | 1 | 1 | 218 |
| Class I     | – | – | – | – | – | – | – | – | – | 1 | 1 |
| Class II    | – | – | – | – | – | – | – | – | – | 2 | 2 |
| Class III   | – | – | – | – | – | – | – | – | 2 | 1 | – | – | – | 3 |
| Class IV    | – | – | – | – | – | – | – | – | – | 1 | – | 1 |
| Class VA    | – | – | – | – | – | – | – | – | – | – | – | 2 |
| Class VB    | – | – | 12 | 1 | – | – | – | – | – | 1 | – | – | 14 |
| Class VI    | 1 | – | 14 | – | – | – | – | – | – | – | – | 15 |
| Without Class | – | – | – | – | – | 2 | 1 | – | – | 2 | – | – | 5 |
| Total       | 203 | 1 | 41 | 1 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 261 |

ASRM, American Society of Reproductive Medicine; ESHRE–ESGE, European Society of Human Reproduction and Embryology–European Society for Gynaecological Endoscopy; U0, normal uterus; U1A, dysmorphic, T-shaped uterus; U2A, partial septate uterus; U2B, complete septate uterus; U3A, partial bicorporeal uterus; U3B, complete bicorporeal uterus; U3C, bicorporeal septate uterus; U4, hemi-uterus; U5, aplastic; U6, unclassified malformations; C0, normal cervix; C1, septate cervix; C2, double ‘normal’ cervix; C4, cervical aplasia; V0, normal vagina; V1, longitudinal non-obstructing vaginal septum; V2, longitudinal obstructing vaginal septum; V4, vaginal aplasia.

\textsuperscript{a}By Buttram et al. (1988) and Ludwin et al. (2013a, 2014b, c).

\textsuperscript{b}By Grimbizis et al. (2013).

Table IV  Criteria for the recognition of internal septation of the uterine cavity using the ESHRE–ESGE and ASRM classifications.\textsuperscript{a,b}

| Variable                  | ESHRE–ESGE |
|---------------------------|------------|
| Myometrial thickness (mm) | 12.9 [11.3–15.0] | 6.0–24.1 |
| Presence of internal fundal indentation (No/Yes) | 66 (25.7%)/191 (74.3%) |
| Length of internal fundal indentation (mm) | 2.8 [0–5.9] | 0–71.5 |
| Rate of internal fundal indentation/myometrial thickness | 0.22 [0–5.9] | 0–8.1 |

ASRM, American Society of Reproductive Medicine; ESHRE–ESGE, European Society of Human Reproduction and Embryology–European Society for Gynaecological Endoscopy.

\textsuperscript{a}N = 255 (after excluding one case of uterus agenesis, two cases of unicornuate uterus and three cases of uterus didelphys).

\textsuperscript{b}Data are reported as number (%), median [lower–upper quartile] and range.

Table V  A cross-tabulation of the results of evaluation of uterine morphology using the ESHRE–ESGE and ASRM\textsuperscript{a} criteria and estimates of concordance (\(\kappa\) statistic and \(P\)-value) in the diagnoses.

| ESHRE–ESGE | ASRM |
|------------|------|
| Uterus septate | Others | Total |
| P < 0.001 | 15 | 29 | 44 |
| Normal | 1 | 216 | 217 |
| Total | 16 | 245 | 261 |

\(\kappa = 0.45\)

| Anomaly | Normal | Total |
| P < 0.001 | 42 | 16 | 58 |
| Normal | 1 | 202 | 203 |
| Total | 42 | 218 | 261 |

\(\kappa = 0.79\)

| Septate and arcuate | Others | Total |
| P < 0.001 | 28 | 16 | 44 |
| Others | 3 | 214 | 217 |
| Total | 31 | 230 | 261 |

\(\kappa = 0.70\)

ASRM, American Society of Reproductive Medicine; ESHRE–ESGE, European Society of Human Reproduction and Embryology–European Society for Gynaecological Endoscopy.

\textsuperscript{a}Modified to include morphometric criteria for the recognition of bicornuate (Salim et al., 2003a; Ludwin et al., 2013a), septate (Salim et al., 2003a; Bermejo et al., 2010; Ludwin et al., 2013a), arcuate (Bermejo et al., 2010; Ludwin et al., 2013a) and normal uterus (Ludwin et al., 2013a, 2014b, c).
**Table VI** Characteristics of septate uterus recognized by the ASRM and ESHRE–ESGE criteria.

|                     | Septate uterus by ASRM (n = 16) | Septate uterus by ESHRE–ESGE (n = 44) | P       |
|---------------------|---------------------------------|--------------------------------------|---------|
| Myometrial thickness (mm) | 12.3 [9.8–13.7] (8.7–19.7)     | 12.5 [10.8–14.0] (8.7–19.7)          | 0.5b    |
| Internal fundal indentation (mm) | 21.1 [18.8–33.1] (16–72)     | 10.7 [8.1–20.0] (5–72)               | <0.01n  |
| Rate of internal fundal indentation/myometrial thickness | 1.9 [1.4–2.6] (0.9–8.1) | 0.8 [0.6–1.5] (0.5–8.1) | <0.01n  |
| Length of the uterine septum |                       |                                      |         |
| ≥ 1 cm               | 16 (100%)                     | 28 (63.6%)                           | <0.01a  |
| ≥ 1.5 cm             | 16 (100%)                     | 15 (34.1%)                           | <0.01f   |

ASRM, American Society of Reproductive Medicine; ESHRE–ESGE, European Society of Human Reproduction and Embryology–European Society for Gynaecological Endoscopy.

aData reported as number (%), mean ± SD (range), or median [lower–upper quartile] (range).

bTest Mann–Whitney U-test and cFisher’s exact test.

**Figure 2** Septate uterus by ESHRE–ESGE includes three morphological classes by ASRM; Top row, norm (internal indentation < 1 cm); middle row, arcuate; and bottom row, septate uterus.

ASRM criteria were lower but not of statistical significance (RR, 0.09, 95% CI, 0.01–1.6, P = 0.1).

Table IV presents the degree of internal indentation/septation of the uterine cavity by the ESHRE–ESGE and ASRM criteria in study population. Internal fundal indentation was present in 191 of 255 women (74.3%) in whom it could potentially occur.

Septate uterus was diagnosed with a significantly higher frequency in the ESHRE–ESGE classification (44 versus 16 of 261; RR, 2.74; 95% CI, 1.6–4.72; P < 0.01). The frequency of septate uterus diagnosis by ESHRE–ESGE was also higher than the total number of diagnoses of septate and arcuate uterus by the ASRM criteria, although this was only borderline statistically significant (44 versus 31 of 261; RR, 1.4; 95% CI, 0.92–2.2; P = 0.1; Tables II and V). Overall, congenital malformations were diagnosed at a higher frequency using the ESHRE–ESGE criteria, and this increased frequency also showed borderline statistical significance (RR, 1.35; 95% CI, 0.95–1.92, P = 0.1).
The diagnosis of septate uterus by both classifications showed moderate agreement ($\kappa = 0.45$, standard error, 0.08, 95% CI, 0.3–0.6, $P < 0.01$; Table V; Altman 1991; Fleiss et al., 2003). The diagnosis of septate uterus by ESHRE–ESGE showed good agreement with the diagnoses of arcuate and septate uterus by ASRM ($\kappa = 0.70$, standard error, 0.06, 95% interval, 0.6–0.8, $P < 0.01$). Strength of agreement in general classifications of uterine morphology in terms of congenital anomaly/normal was good ($\kappa = 0.79$, 0.05, 95% CI, 0.7–0.9, $P < 0.01$; Table V).

The morphology of septate uterus identified by ESHRE–ESGE significantly differed from that identified by ASRM (Table VI, Fig. 2). Internal fundal indentation and the ratio of the internal fundal indentation to thickness of the myometrium were significantly lower in the ESHRE–ESGE-diagnosed septate uterus compared with the ASRM-diagnosed septate uterus. Internal fundal indentation was $<1$ cm in 16/44 septate uterus cases diagnosed by ESHRE–ESGE, and met the criteria for normal uterus by ASRM. Thickness of the myometrium did not differ between both systems.

Excellent intrarater reliability was obtained for measurements of internal fundal indentation and uterine wall thickness (interclass correlation coefficient, 0.96; $P < 0.01$; Fleiss et al., 2003).

Discussion

This is the first study to compare the effects of the ESHRE–ESGE and ASRM classifications of the septate uterus and congenital malformations of the female reproductive organ in clinical practice. The ESHRE–ESGE classification was associated with an extraordinary (almost 3×) increase in the frequency of septate uterus recognition [44 (16.9%) versus 16 (6.1%) by the ASRM classification]. The diagnosis of septate uterus by both classifications showed moderate agreement. The morphology of septa differed between the ESHRE–ESGE and ASRM criteria (median length of the septum: $\sim1$ and 2 cm, respectively). Most diagnoses of septate uterus according to the ESHRE–ESGE system corresponded to arcuate or normal uterus diagnosed by ASRM (Fig. 2). Thus, the ESHRE–ESGE classification is associated with a serious risk of overdiagnosis and potential overtreatment of patients, which validates our initial suggestions (Ludwin et al., 2014b,c).

The overall distinction between congenital uterine malformation and norm by both systems showed good agreement, if the confounding criterion for dysmorphic uterus (UIc by ESHRE–ESGE, Fig. 3) diagnosis was excluded (Tables III and V). Despite this modification, the ESHRE–ESGE classification more often classified the morphological state as a malformation than the ASRM classification ($P < 0.1$). According to the original ESHRE–ESGE classification, congenital uterine malformation was present in as many as 195 of 261 (74%) patients compared with 43 (16.5%) by ASRM. The RR of uterine anomaly diagnosis by ESHRE–ESGE versus ASRM would reach very high values (RR, 4.5, 95% CI, 3.4–6, $P < 0.01$). It is irrational and would undermine using the entire classification system to distinguish congenital malformation from the norm. Therefore, we did not apply this criterion as an exponent of anomaly (Fig. 3).
The strengths of this study are its design that aims to verify the main hypothesis, the prospective nature of data collection, the use of one of the optimal diagnostic tests (3D ultrasonography) (Jurkovic et al., 1995; Chan et al., 2011; Grimbizis et al., 2012) of known high diagnostic accuracy (Salim et al., 2003a; Saravelos et al., 2008; Ludwin et al., 2013a; Berger et al., 2014) with high inter/intrarater agreement in the classification of congenital uterine anomalies (Salim et al., 2003a), standardization of diagnostic procedures, experience of the researchers in applied techniques and the object of study.

One study limitation may be that the study population was not sampled from the general public (Chan et al., 2011). Nevertheless, the clinical value and implications of using the ESHRE–ESGE classification are more important in daily practice (Grimbizis et al., 2013).

Our results with the ESHRE–ESGE classification suggest that by separating malformations of the corpus uteri, cervix and vagina, this classification system can be more useful than ASRM for cataloguing complex anomalies of the female reproductive system (Fig. 4; Supplementary data, Fig. S1) and transitional cases (Acién et al., 2009). However, more studies such as long-term, multicenter or retrospective studies of rare congenital anomalies (Acién et al., 2004; Fedele et al., 2013; Kisu et al., 2014) are required to verify this.

A major problem of the ESHRE–ESGE classification is its classification of the most common morphological forms and possible impact for their management. In our opinion, the thickness of the uterine wall is an inappropriate morphological indicator of disorders from a methodological point of view (Ludwin et al., 2014b,c; Fig. 5). The mean thickness of the anterior and posterior walls suggested as temporary reference values (Grimbizis et al., 2014) generate overdiagnosis of septate uterus, as we expected previously (Traiman et al., 1996; Youm et al., 2011; Ludwin et al., 2014c).

Absolute criteria (Salim et al., 2003a; Ludwin et al., 2013a,b) are not perfect as they delimit artificial boundaries (Detti, 2014; Grimbizis et al., 2014; Ludwin et al., 2014d) and can be considered as a simplification (Ludwin et al., 2013a,b; Grimbizis et al., 2014). However, we believe that within the population norm of uterus size in women of childbearing age, such criteria better reflect the degree of distortion in the structure of the uterine cavity (Salim et al., 2003b) and link it with the management of septate uterus (Fedele et al., 1996; Ludwin et al., 2014a,c).

The most important clinical implication here is to draw the attention of the medical community toward the risks of overdiagnosis and overtreatment of septate uterus associated with the ESHRE–ESGE criteria. Together with our previous results (Ludwin et al., 2014c), our study findings strongly warrant changing the ESHRE–ESGE criteria and discontinuing the use of uterine wall thickness as a reference value to detect internal and external structural distortions. The ESHRE–ESGE criteria should not be used to diagnose septate uterus and deem the patient eligible for hysteroscopic metroplasty if the uterus is classified as normal by ASRM (Fig. 6).

Finally, external validation of the study results in the general population would be of value. Future studies should focus on redefining the ESHRE–ESGE criteria using 3D ultrasonography, defining morphological cutoffs for commonly occurring similar morphological forms, and studying the clinical importance and proper management of the various morphologies.
**Figure 5** Differentiation of normal, septate and bicorporeal uterus by the ESHRE–ESGE classification system. (A–C) The use of uterine wall thickness to define uterine deformity is a serious shortcoming in the ESHRE–ESGE classification because, as an independent and variable parameter (B), it does not reflect the degree of deformation of the uterine cavity (A) and the degree of deformation of the outer structure (C).

**Figure 6** Normal uterus by ASRM with the same length of internal fundal indentation in coronal view (top row); may be recognized paradoxically by ESHRE–ESGE as a septate (case on left) or normal uterus (case on right) depending on the thickness of the uterine wall in the sagittal view (bottom row).
Conclusion
The ESHRE–ESGE classification leads to an extraordinary increase in the frequency of diagnosis of septate uterus. Septate uterus diagnosed by this classification system is quantitatively dominated by morphological states corresponding to arcuate uterus or cases where no congenital malformations are identified by the ASRM criteria. Surgical treatment in these cases may be unnecessary and may not provide the expected benefits.

Supplementary data
Supplementary data are available at http://humrep.oxfordjournals.org/.

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Conflict of interest
The authors declare that they have no conflict of interest.

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