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The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies[†]

Grigoris F. Grimbizis*, Attilio Di Spiezio Sardo, Sotirios H. Saravelos, Stephan Gordts, Caterina Exacoustos, Dominique Van Schoubroeck, Carmina Bermejo, Nazar N. Amso, Geeta Nargund, Dirk Timmerman, Apostolos Athanasiadis, Sara Brucker, Carlo De Angelis, Marco Gergolet, Tin Chiu Li, Vasilios Tanos, Basil Tarlatzis, Roy Farquharson, Luca Gianaroli, and Rudi Campo

Congenital Uterine Anomalies (CONUTA) common ESHRE/ESGE Working Group and invited Experts, ESGE Central Office, Diestsevest 43/0001, 3000 Leuven, Belgium

*Correspondence address. 1st Department of Obstetrics & Gynecology, Aristotle University of Thessaloniki, Tsimiski 51 Street, 54623 Thessaloniki, Greece. E-mail: grigoris.grimbizis@gmail.com, grimbi@med.auth.gr

STUDY QUESTION: What is the recommended diagnostic work-up of female genital anomalies according to the European Society of Human Reproduction and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) system?

SUMMARY ANSWER: The ESHRE/ESGE consensus for the diagnosis of female genital anomalies is presented.

WHAT IS KNOWN ALREADY: Accurate diagnosis of congenital anomalies still remains a clinical challenge because of the drawbacks of the previous classification systems and the non-systematic use of diagnostic methods with varying accuracy, some of them quite inaccurate. Currently, a wide range of non-invasive diagnostic procedures are available enriching the opportunity to accurately detect the anatomical status of the female genital tract, as well as a new objective and comprehensive classification system with well-described classes and sub-classes.

STUDY DESIGN, SIZE, DURATION: The ESHRE/ESGE CONgenital UTerine Anomalies (CONUTA) Working Group established an initiative with the goal of developing a consensus for the diagnosis of female genital anomalies. The CONUTA working group and imaging experts in the field have been appointed to run the project.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The consensus is developed based on: (i) evaluation of the currently available diagnostic methods and, more specifically, of their characteristics with the use of the experts panel consensus method and of their diagnostic accuracy by performing a systematic review of evidence and (ii) consensus for the definition of where and how to measure uterine wall thickness and the recommendations for the diagnostic work-up of female genital anomalies, based on the results of the previous evaluation procedure, with the use of the experts panel consensus method.

MAIN RESULTS AND THE ROLE OF CHANCE: Uterine wall thickness is defined as the distance between the interostial line and external uterine profile at the midcoronal plane of the uterus; alternatively, if a coronal plane is not available, the mean anterior and posterior uterine wall thickness at the longitudinal plane could be used. Gynecological examination and two-dimensional ultrasound (2D US) are recommended for the evaluation of asymptomatic women. Three-dimensional (3D) US is recommended for the diagnosis of female genital anomalies in 'symptomatic' patients belonging to high risk groups for the presence of a female genital anomaly and in any asymptomatic woman suspected to have an anomaly from routine evaluation. Magnetic resonance imaging (MRI) and endoscopic evaluation are recommended for the subgroup of patients with suspected complex anomalies or in diagnostic dilemmas. Adolescents with symptoms suggestive for the presence of a female genital anomaly should be thoroughly evaluated with 2D US, 3D US, MRI and endoscopically.

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LIMITATIONS, REASONS FOR CAUTION: The various diagnostic methods should always be used in the proper way and evaluated by experts to avoid mis-, over- and underdiagnosis.

WIDER IMPLICATIONS OF THE FINDINGS: The role of a combined US examination and outpatient hysteroscopy should be prospectively evaluated. It is a challenge for further research, based on diagnosis, to objectively evaluate the clinical consequences related to various degrees of uterine deformity.

STUDY FUNDING/COMPETING INTEREST(S): None.

Key words: consensus / European Society of Human Reproduction and Embryology / European Society for Gynaecological Endoscopy / female genital anomalies / congenital uterine malformations / hysteroscopy / laparoscopy / ultrasound / hysterosalpingo-contrast sonography / hysterosalpingogram

Introduction

Female genital malformations are deviations from normal anatomy that could impair the reproductive potential of the woman or, in complex cases (e.g. obstructing anomalies), the woman's health (Grimbizis et al., 2001, 2004; Joki-Erkkilä and Heinonen, 2003; Fedele et al., 2005; Strawbridge et al., 2007; Mollo et al., 2009; Rock et al., 2010; Brucker et al., 2011; Chan et al., 2011b; Gergolet et al., 2012; Venetis et al., 2014). The malformations arise embryologically from failure of Müllerian ducts formation, canalization, fusion or absorption either as a single defect or in combination with different expression in the various parts of the female genital tract resulting in so-called complex anomalies.

Accurate diagnosis of congenital anomalies still remains a clinical challenge with serious consequences in the management of those patients. This is the result of the following methodological bias: (i) absence of clear definitions and objective diagnostic criteria in the existing classification systems, mainly that of the American Fertility Society (AFS, 1988) for their diagnosis and differential diagnosis and (ii) use of diagnostic methods with different accuracy, some of them quite inaccurate, to make the correct diagnosis of the anomaly (Saravelos et al., 2008). Thus, over the years, different investigators adopted their own subjective criteria for the categorization of mainly uterine anomalies that varied widely from one study to another, having as a result a highly subjective categorization of the various studied groups and patients' populations (Saravelos et al., 2008; Grimbizis and Campo, 2010; Di Spiezio Sardo et al., 2015).

In view of these diagnostic methodological and clinical drawbacks, the estimation of the exact prevalence of female genital anomalies in the general and selected populations was very difficult and evaluation of the clinical consequences of each different type of anomaly was inaccurate (Saravelos et al., 2008; Bermejo et al., 2010; Chan et al., 2011a). Furthermore, comparisons between different studies and grouping of the anomalies are hampered not only by the differences in study populations, but also by differences in the diagnostic methods and criteria used to differentiate between various types of uterine anomalies (Venetis et al., 2014). Moreover, the exact value of surgery is not known for patients' counseling and treatment, underlying the urgent need to test available interventions in well-designed studies with properly defined groups (Venetis et al., 2014).

In the recently published European Society of Human Reproduction and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification of female genital anomalies a clear definition of all types of anomaly was provided and the anomalies were categorized in well-described classes and sub-classes (Grimbizis et al., 2013a,b). Thus, the previously mentioned diagnostic drawback of subjectivity in definitions is effectively answered, enhancing their objective categorization (Grimbizis et al., 2013a,b; Di Spiezio Sardo et al., 2015). It seems that with the use of the new system, all the existing cases, previously poorly described and unclassified by the AFS, could be effectively described and classified (with very rare exceptions) offering a common 'language' of communication between the clinicians working in this field (Di Spiezio Sardo et al., 2015).

Currently, a wide range of non-invasive diagnostic procedures is available enriching the opportunity to detect the anatomical status of the female genital tract in an accurate way. However, the various existing methods have different characteristics, availability, invasiveness and diagnostic accuracy (Saravelos et al., 2008; Chan et al., 2011a). Thus, it is important to clarify the current role of the methods used in the diagnostic work-up and objective documentation of female genital tract anomalies. Furthermore, a standardized and systematic evaluation of asymptomatic women and of selected 'high risk' populations for the presence of female genital anomalies is fundamental for their management.

The aim of the Thessaloniki ESHRE/ESGE consensus is to provide researchers with recommendations for the diagnostic work-up of female genital anomalies; the definitions of the ESHRE/ESGE classification were used as a basis for their development. This is an initiative of the CONUTA (CONgenital UTerine Anomalies) Working Group started during the ESHRE Campus Workshop on Female Genital Anomalies in Thessaloniki.

Strategy for the consensus development

The development of the Thessaloniki ESHRE/ESGE consensus for the diagnosis of female genital anomalies by the CONUTA Working group was designed as described below.

Evaluation of the currently available diagnostic methods including

the evaluation of the characteristics of each different currently available diagnostic technique by the group of invited imaging experts and the members of the CONUTA group with the use of the experts panel consensus method (Jones and Hunter, 1995)—a draft was circulated in two rounds for comments and a live meeting was arranged for the consensus;

the evaluation of the diagnostic accuracy of the different diagnostic methods by performing a systematic review of evidence (undertaken by S.H.S., A.D.S.S. and G.F.G.) and

Consensus development, based on the results of the evaluation procedure, including the definition of where and how to measure uterine wall thickness by the invited imaging experts and the members of the CONUTA group with the use of the experts panel consensus method—a draft was circulated in two rounds for comments and a live meeting was arranged for the consensus;

the recommendations for the diagnostic work-up of female genital anomalies with the use of the experts panel consensus method—an initial proposal was circulated and the final document was prepared based on the comments.

The final document, including all the parts, was circulated again for final comments and approval of the consensus from all the members.

Evaluation of the currently available diagnostic methods

Diagnostic methods and their characteristics (consensus between experts)

Background

The anatomy of the female genital tract is the basis of the ESHRE/ESGE classification system. More specifically uterine anatomy is the basis for the main classes and subclasses. Cervical and vaginal anomalies are classified independently in supplementary subcategories. Thus, diagnosis of uterine anomalies has to be based on diagnostic modalities that determine the anatomical status of the female genital tract in an objective way.

Each diagnostic method should ideally provide objective and measurable information on the anatomical status of: (i) the vagina, (ii) the cervix, (iii) the uterine cavity, (iv) the uterine wall, (v) the external contour of the uterus and (vi) the other intra-peritoneal structures.

Question

What is the diagnostic potential, the advantages, the disadvantages and the manner of proper use of the available imaging techniques in the diagnosis of female genital tract congenital anomalies?

Gynecological examination

Diagnostic potential inherent to the method. Some vaginal and some cervical malformations (aplasia, double cervices, longitudinal septa reaching to the external cervical os) can be diagnosed objectively by inspection. Palpation (through the vagina and/or the rectum in cases of vaginal aplasia) cannot provide information for the uterine cavity and uterine wall and it could provide only some useful, but highly subjective, information for the uterine body (e.g. complete bicorporeal uterus). Palpation could provide information in cases of dilatation secondary to obstruction of menstrual flow (hematocolpos/hematometra/hemato-cavity in cases of non-communicating uterine horns).

Advantages. Gynecological examination is always the starting point and an essential part of any woman's clinical evaluation. It is non-invasive, simple, easy and low cost. It offers unique information in cases of some vaginal and cervical anomalies; it is also crucial that vaginal examination could elicit tenderness, which can aid diagnosis. It is included in the

basic training of Obstetricians and Gynecologists needing no additional expertise.

Disadvantages. It should not be used for the diagnosis of uterine anomalies due to its inherent inability to provide reliable information for uterine anatomy. It is not a primary approach in women who have never been sexually active.

Recommendations for its proper use. In cases of primary amenorrhea, careful inspection of the external genitalia for the presence of distal vaginal aplasia. Careful inspection of the vagina, to avoid mis-diagnosis in cases of longitudinal vaginal septa, by entering only one of the two existing vaginal spaces. Careful inspection of the vaginal vault with a speculum to establish the presence of one or more cervical body(ies) or one cervical body with one or two external cervical opening(s). In cases of cyclic pelvic pain, with or without primary amenorrhea, careful palpation for palpable masses secondary to accumulation of menstrual blood (obstructed parts).

X-ray hysterosalpingography

Diagnostic potential inherent to the method. It provides some reliable information for the anatomy of the uterine cavity in the absence of cervical obstruction. It could provide, also, information for the anatomy of the cervical canal in the absence of cervical obstruction; the information on the anatomy of the cervical canal may be limited due to the instruments placed within and in the vicinity of the cervix. It does not provide any information for the vagina (exception: blind vagina with small opening), the uterine wall and the external contour of the uterus. It does not provide any information for rudimentary non-communicating horns or cavities.

Advantages. It is widely available and offers printable films that could be re-evaluated any-time. It offers additional useful information in cases of infertile women for potential intra-cavitary pathology (presence of defects/differential diagnosis between adhesions, polyps, myomas) and tubal morphology.

Disadvantages. Painful, risk of infection, irradiation of the patient. It is more invasive than ultrasound, not always easy, needing a radiological unit. It cannot be used for the differential diagnosis of uterine anomalies due to its inherent inability to provide reliable information for the uterine wall and the uterine outline anatomy; uterine anomalies represent the vast majority of malformations. Its diagnostic accuracy is restricted by false positive and false negative results; air bubbles might be mistaken for intracavity pathology, distension of the cavity following fluid injection might distort the shape of the cavity to a degree that is related to whether there is a tubal ostia obstruction or not and, hence, limiting the value of assessing the interior contour. It cannot be used for the diagnosis of obstructing anomalies.

Recommendations for its proper use. The examiner has to be very cautious in order to be precise: pulling the uterus is necessary for the best imaging of the uterine cavity (otherwise small indentations could be missed). Careful inspection of the vagina and the cervix to avoid mis-diagnosis in cases of double or septate cervix with or without longitudinal vaginal septa; catheterization of both cervical canals, if present, is necessary.

Two-dimensional ultrasound

Diagnostic potential inherent to the method. It could provide reliable, objective and, most importantly, measurable information for the anatomy of the cervix, the uterine cavity, the uterine wall, the external contour of the uterus. It could provide useful information of associated pelvic pathology, e.g. ovarian pathology (benign and malignant tumors, endometriosis), hydrosalpinges, renal anomalies. It could provide, also, measurable information even for obstructing parts of the female genital tract. Transperineal two-dimensional ultrasound (2D US) may provide information on the vaginal cavity, especially in the presence of imperforate hemivagina.

Advantages. It is non-invasive, simple, low cost, available in almost every setting. Gynecologists are familiar with the technique since training in ultrasound is included in the basic training in Obstetrics and Gynecology; nowadays, ultrasound examination is an essential part of women's routine evaluation. Electronic storage of the diagnostic procedure is now feasible, for re-evaluation. It could provide the required planes in a flexible way since the examiner could change the position of ultrasound probes according to the needs of imaging. It offers additional valuable information in cases of infertile women for potential intra-cavitary (major adhesions might be suspected, presented as 'bridges' between the walls, polyps, myomas) and intramural pathology (myomas, adenomyosis).

Disadvantages. The diagnostic accuracy of 2D US, being a dynamic examination, is highly dependent on the experience of the examiner and on the proper and systematic way of performing the procedure. It is not always feasible to have the required planes because of the patient's anatomical characteristics.

Recommendations for its proper use. The endometrial line should be well visible for precise imaging of the uterine cavity (late proliferative or secretory phase or intracavitary fluid enhancement/avoid early follicular phase). Serial sagittal planes from beyond the outer margin of one side of the uterus to the other including both cervix and uterine body if feasible and transverse planes from the cervix to beyond the uterine fundal level should be taken in a systematic way. In cases of vaginal obstruction or stenosis, if the woman consents, transrectal ultrasound with a vaginal probe or transperineal could be performed to evaluate the vaginal canal and uterus (not in children or in adolescents). Abdominal palpation should be applied to improve the image by pushing away the bowel and to assess mobility of the pelvic organs; gynecologists are better able to do this compared with sonographers.

Hysterosalpingo-contrast-sonography

Diagnostic potential inherent to the method. It can provide reliable, objective and, most importantly, measurable information for the anatomy of the cervix, the uterine cavity, the uterine wall, the external contour of the uterus and for other peritoneal structures (e.g. ovaries) with the exception of tubes. The imaging of the uterine cavity is better owing to the use of the contrast medium or saline, enhancing the accuracy in identifying uterine cavity defects. Hysterosalpingo-contrast-sonography (HyCoSy) could be used as a tubal patency test (infertile patients).

Advantages. It is minimally invasive, simple, low cost, potentially available in almost every setting (since only contrast medium is needed). Gynecologists could easily apply the technique since training in ultrasound is included in the basic training in Obstetrics and Gynecology and insertion of an intrauterine catheter could be carried out easily by them. Electronic storage of the diagnostic procedure is, nowadays, feasible for re-evaluation. It could provide the required planes in a flexible way since the examiner could change the position of ultrasound probes according to the needs of imaging. It offers additional, more reliable information than that of 2D US in cases of infertile women for potential intra-cavitary (adhesions presented as 'bridges' between the walls, polyps, myomas) and intramural pathology (myomas, adenomyosis) but not necessarily for uterine malformations.

Disadvantages. The diagnostic accuracy of HyCoSy, being a dynamic examination, is highly dependent on the experience of the examiner and on the proper and systematic way of performing. Distension of the uterine cavity could potentially modify the internal uterine contour resulting in false negative imaging of the uterine cavity, especially in marginal uterine anomalies. It is not always feasible to have the required planes because of the patient's anatomical characteristics. It is rarely painful when difficulties in the insertion of the catheter arise.

Recommendations for its proper use. Early follicular phase is recommended as appropriate, to avoid pregnancies and artifacts due to thick secretory endometrium. Serial sagittal planes from beyond the outer margin of one side of the uterus to the other including both cervix and uterine body if feasible and transverse planes from the cervix to beyond the uterine fundal level should be taken in a systematic way.

Three-dimensional ultrasound

Diagnostic potential inherent to the method. It can provide highly reliable, objective and, most importantly, measurable information for the anatomy of the cervix, the uterine cavity, the uterine wall, the external contour of the uterus and for associated pelvic pathology; the coronal plane of the uterus does provide a clear image of the cavity and the external profile of the uterine fundus. 3D volumes give reliable and objective representation of the examined organs more independent of the examiner overcoming the limitations of obtaining coronal images with 2D sonography. It can provide, also, measurable information even for obstructed parts of the female genital tract.

Advantages. It is non-invasive and easily applied to the patient (no difference from conventional ultrasound). Reliable imaging of the uterus since uterine anatomy is presented in the sagittal, transverse and coronal planes in an objective way independent of the examiner's ability. It provides precise and objective measurements of the uterine dimensions, which is the absolute advantage in differential diagnosis between different classes. Electronic storage of the volume is, nowadays, routinely done for re-evaluation giving the opportunity for off-line analysis enabling the assessment of the uterus/uterine wall in different slices and to choose the plane of maximum interest in the coronal/sagittal or transverse sections for measurements. It offers additional information, which is more reliable than that of 2D US, in cases of infertile women for potential intra-cavitary (adhesions presented as 'bridges' between the walls, polyps, myomas) and intramural pathology (myomas, adenomyosis). Transperineal three-dimensional ultrasound (3D US) may offer the opportunity to view pelvic structures including the vagina and cervix.

Disadvantages. Not so widely available as 2D US (up to now). Need for experienced sonographers with special and adequate training in 3D image acquisition and post-processing techniques. Beware of artifacts related to inappropriate volume acquisition and/or manipulation of the volume. It cannot provide very detailed and reliable data in very few cases of complex anomalies. 3D US without saline infusion or contrast medium cannot be used as a real-time tubal patency test in cases of infertile patients.

Recommendations for its proper use. Start with a 2D evaluation of the uterus. Use in midcycle or luteal phase is encouraged as this demonstrates the endometrial wall and the outline of the cavity at its best. Contrast medium could be used for the evaluation of the cavity and the tubes; in these cases the examination has to be performed in the early follicular phase. Save a 3D volume for off-line analysis. The reconstructed coronal plane of the uterus might show the cavity and the external uterine profile as well as the tubal angle and the junctional zone, if possible along all the endometrium and cavity. Acquisition of an isolated cervical volume, without including the uterus: from a mid-sagittal plane, an axial plane of the cervix can be obtained in 80%, and a coronal plane in 20%, of the cases; in cases of uterine malformations, the extent of the cervix and the limits of the cervical canal may be studied better. Diagnosis of associated vaginal anomalies can be achieved by transperineal acquisition of the pelvic floor volume after filling the vagina with gel or saline; an axial plane can be obtained from a mid-sagittal plane.

Magnetic resonance imaging
Diagnostic potential inherent to the method. It can provide highly reliable and objective information for the anatomical status of the vagina, cervix, the uterine cavity, the uterine wall, the external contour of the uterus and for other peritoneal structures with the exception of tubes. It provides, also, reliable information even for dilated (obstructed) parts of the female genital tract.

Advantages. It is non-invasive and it has no radiation. It gives a reliable and objective representation of the examined organs in the sagittal, transverse and coronal plane (three dimensions). It can be used for diagnosis in cases of complex and obstructing anomalies. Electronic storage of the diagnostic procedure is, nowadays, routinely done for re-evaluation.

Disadvantages. More expensive and less available than ultrasound. Not appropriate for patients with claustrophobia and morbid obesity. Need for experience and training in the assessment of the results. The required planes are provided in a non-flexible way since planes are pre-defined and independent of the examiner, a disadvantage that could potentially impair the diagnostic accuracy of the method in the absence of an experienced radiologist. It cannot be used as a tubal patency test in cases of infertile patients.

Recommendations for its proper use. Gynecologists should be trained in magnetic resonance imaging (MRI) reading and work closely with the radiologist to review the images as the clinical background knowledge of the former supplements the radiological interpretation of the images by the latter.

Hysteroscopy
Diagnostic potential inherent to the method. It provides highly reliable information for the anatomical status of the vagina (vaginoscopic approach), the cervical canal and, mainly, the uterine cavity and the tubal ostia.

Advantages. It is minimally invasive giving the additional opportunity of treating T-shaped, septate and bicorporeal septate uterus. Objective estimation of the cervical canal and endometrial cavity (differential diagnosis of T-shaped and infantile uterus). Minimally invasive evaluation of the vagina and/or cervix in case of virgo. Electronic storage of the procedure is, nowadays, routinely done for re-evaluation.

Disadvantages. It is more complex to organize. No information for uterine wall thickness and uterine outline; unable to offer differential diagnosis between septate and bicorporeal uterus. Need for experience and training. Evaluation of the cavity is not feasible in cases of obstructed anomalies. It could not be used as a tubal patency test in cases of infertile patients.

Recommendations for its proper use. It complements ultrasound in the initial investigation of female genital tract malformations.

Endoscopy; laparoscopy and hysteroscopy
Diagnostic potential inherent to the method. It provides highly reliable information for the anatomical status of the vagina (vaginoscopic approach), the cervical canal, the uterine cavity, the tubal ostia, the external contour of the uterus and the intraperitoneal structures.

Advantages. Direct visualization of the cervical canal, endometrial cavity and the external contour of the uterus representing, until now, the 'gold standard' in the diagnosis and differential diagnosis. Electronic storage of the procedure is, nowadays, routinely done for re-evaluation. The endoscopic approach represents the minimally invasive route of choice in the treatment of a wide variety of female genital anomalies.

Disadvantages. It is invasive. No objective estimation of the uterine wall thickness. The diagnosis is mainly based on the subjective impression of the clinician performing the procedures and this is thought to be a limitation in the objective estimation of the anomaly. Need for experience and training.

Recommendations for its proper use. The invasiveness of the laparoscopic approach makes it not acceptable as a first line screening procedure; it complements indirect imaging in the diagnosis of more complex anomalies in combination with possible surgical actions. It offers supplementary information about partial or total absence of Fallopian tubes and abnormal localization of ovaries.

Computerized tomography scanning
Computerized tomography scanning no longer has a place in the diagnosis of female genital anomalies due to radiation and poor depiction of the female genital structures and it was not included in the evaluation.

Diagnostic accuracy of the different methods (systematic review of evidence)

Question

What is the diagnostic accuracy of the available imaging techniques in the diagnosis of female genital tract congenital anomalies as compared with the combined hysteroscopic and laparoscopic investigation (reference standard) based on the current evidence?

Limitations

Prior to approaching this problem, the limitations have to be recognized and disclosed as follows. First, the studies to date will not have based the assessment of different diagnostic accuracies on the current ESHRE/ESGE classification. Therefore, evidence will inevitably have to be drawn from the period following the initial Buttram and Gibbons classification (Buttram and Gibbons, 1979), which was later revised into the American Fertility Society classification (AFS, 1988), the most widely accepted classification worldwide for the last 25 years.

Second, the gold standard method of comparison for diagnosis to date has been the combined hysteroscopy (HSC) and laparoscopy (LSC) investigation, which allows for the direct visualization of the internal and external contour of the uterus, but does not always allow accurate and objective uterine measurements. With the new ESHRE/ESGE classification and need to measure fundal, septal and lateral uterine wall thickness, it might be possible and necessary that the gold standard test may evolve to become another imaging modality in the future.

Methods

Articles assessing the diagnostic accuracy of the most widely used imaging techniques were obtained by a search through MEDLINE, EMBASE and the Cochrane Library from 1988 to 2014. A combination of text words and Medical Subject Headings (MeSH) were used to generate the list of citations (Table I); these were primarily designed for MEDLINE and were modified appropriately for EMBASE and the Cochrane Library. In addition to the electronic searches, relevant articles were hand searched for further citations. The selection process for the articles retrieved by the search is shown in Fig. 1.

The diagnostic accuracy was estimated by combining the values of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each imaging technique according to the formula of Altman (1991); as reference standard, the combined hysteroscopic and laparoscopic investigation was used. When studies did not report

Table I Search terms used in the systematic review of diagnosis of female genital anomalies (either as MeSH terms or free text terms).

Uterus/abnormalities [Mesh]	Ultrasonography [Mesh]
Mullerian ducts/abnormalities [Mesh]	Hysterosalpingography [Mesh]
Female genital abnormalit*	Magnetic resonance imaging [Mesh]
Female genital anomal*	Hysteroscopy [Mesh]
	Laparoscopy [Mesh]

*Any character.
MeSH, medical subject headings.

these values in-text, 2 × 2 tables were manually constructed where possible, and these variables were individually estimated. Data were analyzed using the IBM Statistical Package for the Social Sciences version 21 for Windows (SPSS Inc., IL, USA). Means and 95% confidence intervals (CI) for sensitivity, specificity, PPV and NPV and accuracy were calculated for each individual methodology.

The primary outcome of this systematic review was the accuracy of each diagnostic method in terms of identifying a congenital malformation.

Results

Thirty-eight studies of high quality were included in the primary analysis. Several studies were excluded because an inadequate gold standard methodology was used and data regarding the diagnostic accuracy were incomplete/absent. There were no studies reporting on the use of MRI as a screening tool (studies included patients with a previous diagnosis of congenital malformations undergoing further evaluation), and therefore the secondary outcome but not the primary outcome could be assessed for this methodology.

Pooled analysis of the included studies showed that the highest degrees of overall diagnostic accuracy were, in decreasing order: 3D US (97.6%), sono hystero graphy (SHG) (96.5%), 2D US (86.6) and hysterosalpingography (HSG) (86.9%). MRI was shown to be able to correctly subclassify 85.8% of anomalies, which implies that the accuracy of identifying the presence of a malformation is well above 90% (Tables II–VI). Overall it appears that 3D US may be more accurate than MRI in subclassifying malformations, although it should be noted that subclassification is hindered owing to the subjective nature of the previous classifications adopted.

Consensus development

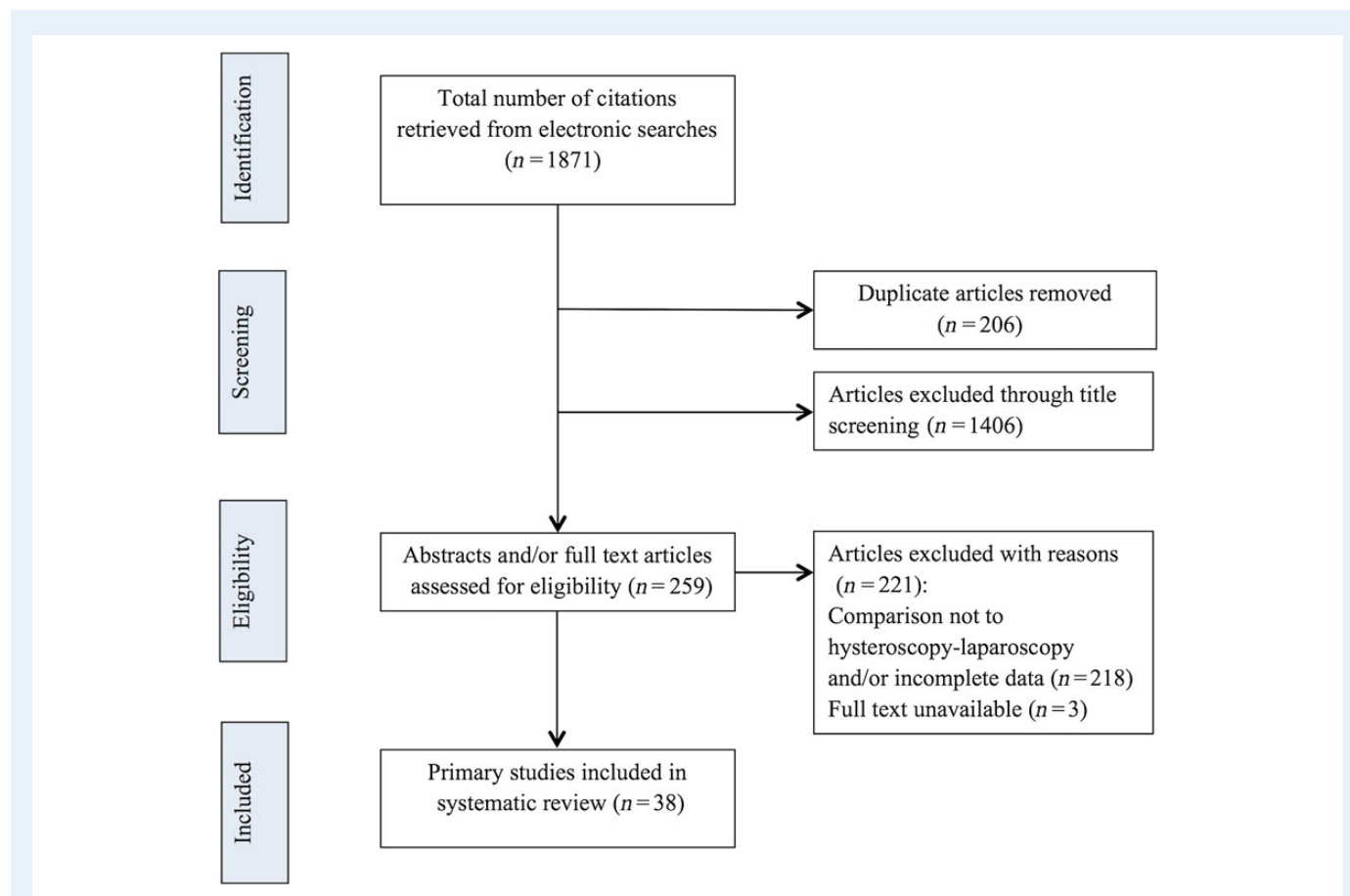## Measurement of the uterine wall thickness (consensus between experts)

Background

Uterine wall thickness is an important parameter and a reference point for the definitions of dysmorphic T-shaped, septate and bicorporeal uteri according to the new classification system. The adoption of an objective criterion for the definition of uterine deformity is one of the advantages of the new classification system since according to the AFS classification the detection of anomalies was based only on the subjective impression of the clinician performing the test. Although myometrial thickness at the various uterine regions cannot be easily assessed with endoscopic techniques, it can be measured with ultrasound or MRI.

However, the thickness of the uterine wall as the reference value for the estimation of the internal indentation at the midfundal level in cases of septate uterus, external indentation in cases of bicorporeal, and lateral wall thickness in cases of T-shaped uterus might, indeed, vary in different regions of the uterus. Thus, recommendations for the measurement of uterine dimensions and accurate description of uterine deformity are very important.

Question

Where and how to measure the reference value of the uterine wall thickness?

Figure 1 The study selection process for the systematic review on the diagnostic accuracy of the different methods used to assess female genital anomalies.

Table II Diagnostic accuracy of hysterosalpingography compared with hysteroscopy ± laparoscopy in diagnosing female genital tract congenital anomalies.

Study	Cases (*n*)	Sensitivity	Specificity	PPV	NPV	Accuracy
Bocca *et al.* (2012)	125	50	94	71	87	**76**
Ludwin *et al.* (2011)	83	77	100	100	35	**78**
De Felice *et al.* (2009)	208	100	100	100	100	**100**
Momtaz *et al.* (2007)	38	95	78	65	97	**84**
Guimaraes Filho *et al.* (2006)	54	63	98	83	94	**85**
Valenzano *et al.* (2006)	54	91	100	100	94	**96**
Traina *et al.* (2004)	80	100	97	85	100	**96**
Alborzi *et al.* (2003)	186	70	92	83	88	**83**
Preutthipan and Linasmita (2003)	336	100	97	69	100	**92**
Brown *et al.* (2000)	46	100	100	100	100	**100**
Soares *et al.* (2000)	65	44	96	67	92	**75**
Alatas *et al.* (1997)	62	100	100	100	100	**100**
Gaglione *et al.* (1996)	70	100	100	100	100	**100**
Goldberg *et al.* (1997)	32	100	100	100	100	100
Keltz *et al.* (1997)	18	90	20	53	67	**58**
Raziel *et al.* (1994)	60	74	59	62	72	**67**
Mean		**84.6**	**89.4**	**83.6**	**89.1**	86.9
(95% CI)		**(74.4–94.9)**	**(80.0–100)**	**(74.6–92.6)**	**(79.7–98.5)**	**(79.8–94.0)**

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

Table III Diagnostic accuracy of two-dimensional ultrasound compared with hysteroscopy ± laparoscopy in diagnosing female genital tract congenital anomalies.

Study	Cases (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Ludwin et al. (2013)	117	91	92	99	52	**84**
De Felice et al. (2009)	104	100	99	86	100	**96**
Momtaz et al. (2007)	38	55	95	84	83	**79**
Valenzano et al. (2006)	54	86	100	100	91	**94**
Ragni et al. (2005)	98	73	100	100	97	**93**
Traina et al. (2004)	80	64	99	88	94	**86**
Soares et al. (2000)	65	44	100	100	92	**84**
Alatas et al. (1997)	62	50	100	100	97	**87**
Nicolini et al. (1987)	89	43	98	94	68	**76**
Mean (95% CI)		67.3 (51.0–83.7)	98.1 (96.0–100)	94.6 (89.4–99.8)	86.0 (73.7–98.3)	86.6 (81.3–91.8)

Table IV Diagnostic accuracy of hysterosalpingo-contrast sonography compared with hysteroscopy ± laparoscopy in diagnosing female genital tract congenital anomalies.

Study	Cases (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Ludwin et al. (2013)	117	94	83	99	65	85
Ludwin et al. (2011)	83	96	89	99	73	89
De Felice et al. (2009)	104	100	100	100	100	100
Guimaraes Filho et al. (2006)	55	100	94	73	100	92
Valenzano et al. (2006)	54	100	100	100	100	100
Ragni et al. (2005)	98	91	100	100	99	98
Alborzi et al. (2003)	186	91	100	100	96	97
Dodero et al. (2001)	52	100	100	100	100	100
Brown et al. (2000)	46	100	100	100	100	100
Soares et al. (2000)	65	73	100	100	97	93
Alatas et al. (1997)	62	100	100	100	100	100
Goldberg et al. (1997)	32	100	100	100	100	100
Keltz et al. (1997)	18	100	100	100	100	100
Mean (95% CI)		95.8 (91.1–100)	97.4 (94.1–100)	97.8 (93.3–100)	94.6 (87.6–100)	96.5 (93.4–99.5)

Main option: distance between interostial line and external uterine profile at the midcoronal plane of the uterus (fitted to 3D US, MRI and, at times, 2D US).

Definition of the reference value of the uterine wall thickness: the distance between the line connecting the tubal ostia and the external uterine profile obtained with 3D US, MRI and, at times, with 2D US. *Comments*: in cases of an external indentation (fusion defects) the distance between the two lines, one connecting the tubal ostia and the other the external outline of the two uterine bodies.

Why use this as a reference parameter? Uterine anomalies are (fusion and/ or absorption) defects at the uterine fundal midline and, therefore, measurements should be oriented there. Until now, imaging at that level has always been used to diagnose congenital uterine anomalies.

How to measure (Figs. 2–4):

Step 1: imaging of the uterus in a midcoronal plane; a sectional plane or a rendered 3D US image of a coronal section of the uterus is now widely accepted as the most accurate plane for measurements.

Step 2: draw the line connecting the two tubal ostia; in cases of an external indentation draw a second line connecting the external profile of the two uterine bodies.

Step 3: in cases of patients with normal external uterine surface, the distance between the line connecting the tubal ostia and the external uterine outline is defined as the uterine wall thickness (reference value); in cases of patients with an existing external indentation, the distance between the two previously described lines is defined as the uterine wall thickness (reference value).

Step 4: estimate the length of any existing internal indentation by measuring the distance between the interostial line and the

Table V Diagnostic accuracy of three-dimensional ultrasound compared with hysteroscopy $\pm$ laparoscopy in diagnosing female genital tract congenital anomalies.

Study	Cases (*n*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Imboden *et al.* (2014)	10	100	100	100	100	**100**
Laganà *et al.* (2014)	224	100	100	100	100	**100**
Ludwin *et al.* (2013)	117	97	100	100	80	**94**
Moini *et al.* (2013)	214	87	97	99	54	**84**
Bocca *et al.* (2012)[a]	125	100	100	100	100	**100**
Faivre *et al.* (2012)	31	100	100	100	100	**100**
Ghi *et al.* (2009)	284	100	100	100	100	**100**
Makris *et al.* (2007)	248	100	100	100	100	**100**
Momtaz *et al.* (2007)	38	97	96	92	99	**96**
Radoncic and Funduk-Kurjak (2000)	267	100	100	100	100	**100**
Wu *et al.* (1997)	40	100	100	100	100	**100**
Mean (95% CI)		**98.3 (95.6–100)**	**99.4 (98.4–100)**	**99.2 (97.6–100)**	**93.9 (84.2–100)**	**97.6 (94.3–100)**

[a]Performed in conjunction with saline infusion.

Table VI Diagnostic accuracy of magnetic resonance imaging compared with hysteroscopy $\pm$ laparoscopy in diagnosing female genital tract congenital anomalies.

Study	Cases (*n*)	Correct sub-classification *n* (%)
Imboden *et al.* (2014)	13	7/13 (54%)
Faivre *et al.* (2012)	31	24/31 (77%)
Santos *et al.* (2012)	26	23/26 (89%)
Mueller *et al.* (2007)	105	83/105 (79%)
Deutch *et al.* (2006)	7	2/7 (29%)
Marten *et al.* (2003)	4	4/4 (100%)
Console *et al.* (2001)	22	21/22 (95%)
Minto *et al.* (2001)	9	7/9 (78%)
Letterie *et al.* (1995)	16	12/16 (75%)
Pellerito *et al.* (1992)	24	24/24 (100%)
Carrington *et al.* (1990)	29	29/29 (100%)
Fedele *et al.* (1989)	18	18/18 (100%)
Weighted mean		254/296 (85.8%)

Sensitivity, specificity, PPV and NPV cannot be assessed for magnetic resonance imaging as this was not used as a screening tool in the studies identified.

indentation's edge at the cavity; septum is considered any indentation >50% of the previously measured total fundal uterine wall thickness. Estimate the lateral wall thickness by measuring at an angle of 90° to the lining of the myometrial-endometrial border.

Comments: (i) The tubal ostia should be considered as the ultrasound border between the uterine cavity and the proximal intramural part of the tubes. (ii) The external uterine contour should be delineated clearly in ultrasound images to avoid under- or overestimation of the uterine wall thickness. A non-rendered image in the C plane may give a sharper outline compared with a (thin) sliced rendered image.

Drawbacks: (i) When an anomaly is present measurements in certain parts (fundus) could not be, sometimes, either feasible or representative, (ii) External profile of the uterus at the fundal level is not always clearly assessable leading to an inaccurate evaluation and (iii) In cases of bicorporeal uterus sometimes the two uterine bodies are not very close to each other and this could create some diagnostic bias.

Alternative option: mean thickness of the anterior and posterior uterine wall (fitted to 2D US)
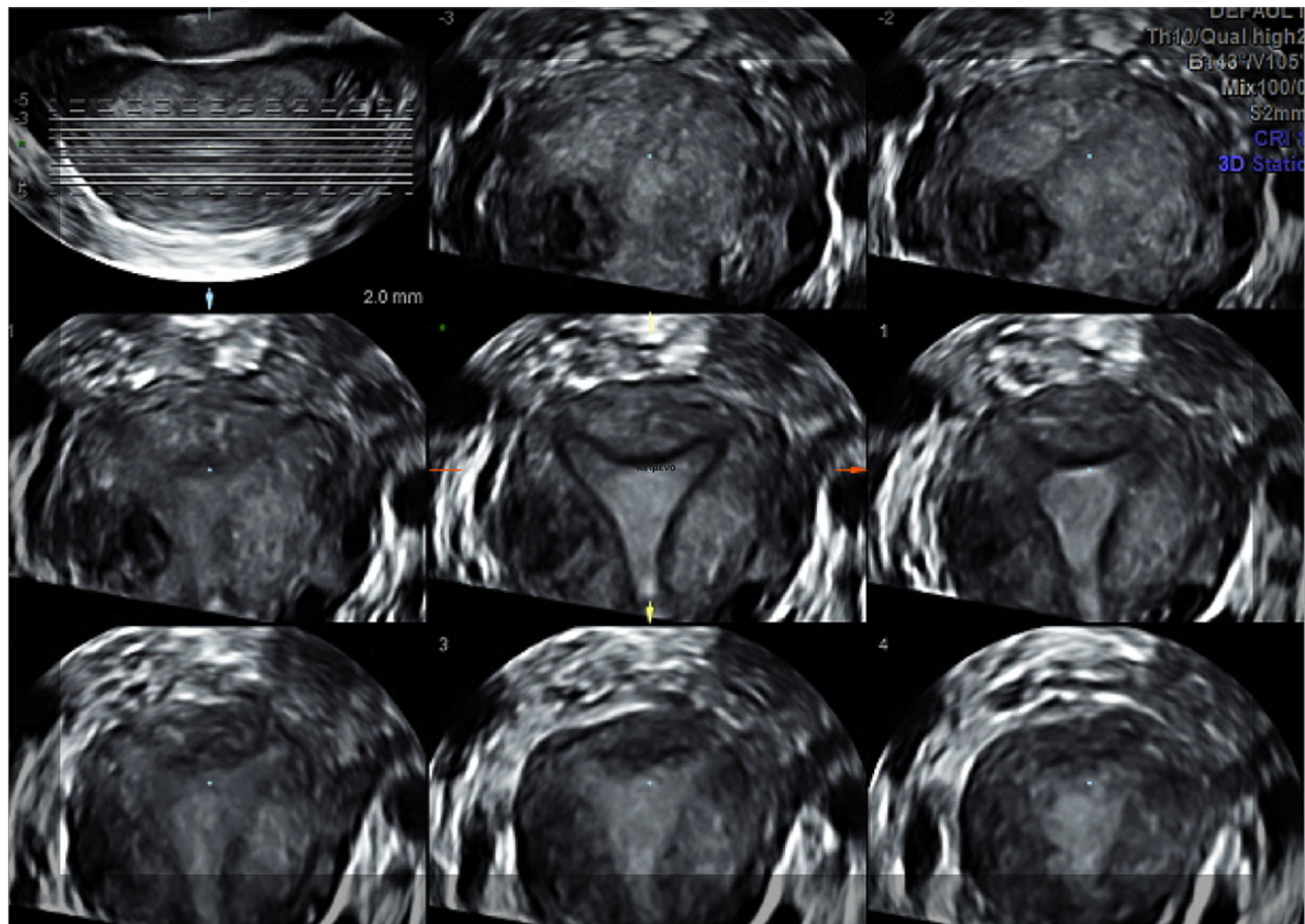
Definition of the reference value of the uterine wall thickness: Mean thickness of the anterior and posterior wall in 2D or 3D US longitudinal planes at the midpoint of the uterine corpus. *Comments*: in cases of septate or bicorporeal uteri with an internal indentation covering more than 50% of the uterine cavity, the longitudinal plane at the mid-cavity level is affected by the indentation and it could not be used as a reference plane for measurements. In that case, a longitudinal plane of the lateral cavities could be used as the reference for measurements in the same way.

Why use this as a reference parameter? This part of the uterine wall could be considered as representative for measurements since it is not affected in cases of uterine anomalies and, if it is affected, alternatives could be provided.

How to measure:

Step 1: imaging of the uterus in the longitudinal plane,
Step 2: estimation of midpoint between the fundal part of uterine cavity and the internal cervical os and,
Step 3: measurements of uterine wall thickness of the anterior and posterior wall at the midpoint level (estimated in step 2), taking the mean of those measurements as the reference point.

Drawbacks: (i) Uterine wall thickness at the posterior, anterior and lateral uterine wall level is, probably, different from that observed at the

Figure 2 How to obtain an optimal three-dimensional ultrasound (3D US) coronal plane. Tomographic ultrasound imaging is the representation by a series of parallel slices through the volume and the distance between the slices as well as their number can be configured; the plane is optimal only if the slices or cutting line is exactly on the coronal view of the endometrium and the junctional zone at the level of tubal ostia and isthmus (plane at the center).

fundal level even in the absence of any pathology, (ii) Uterine wall thickness at that level (mean of the anterior and posterior wall thickness on a longitudinal section) has never been used to define congenital uterine anomalies, (iii) Uterine wall thickness at the posterior and anterior level will be affected by a number of uterine conditions such as fibromas and adenomyosis. Furthermore, with the vascular network placed laterally, the wall thickness might well be different and (iv) Uterine anomalies are (fusion and/or absorption) defects at the uterine fundal midline and, therefore, measurements should be oriented there.

Recommendations (consensus between CONUTA group members and invited experts)

Background

Female genital anomalies are common benign entities with an estimated prevalence ranging from ∼6% in the general population up to ∼15% in selected populations with recurrent pregnancy losses. Thus, women of reproductive age during their routine examination should be examined for the presence of a potential congenital anomaly. Certainly in
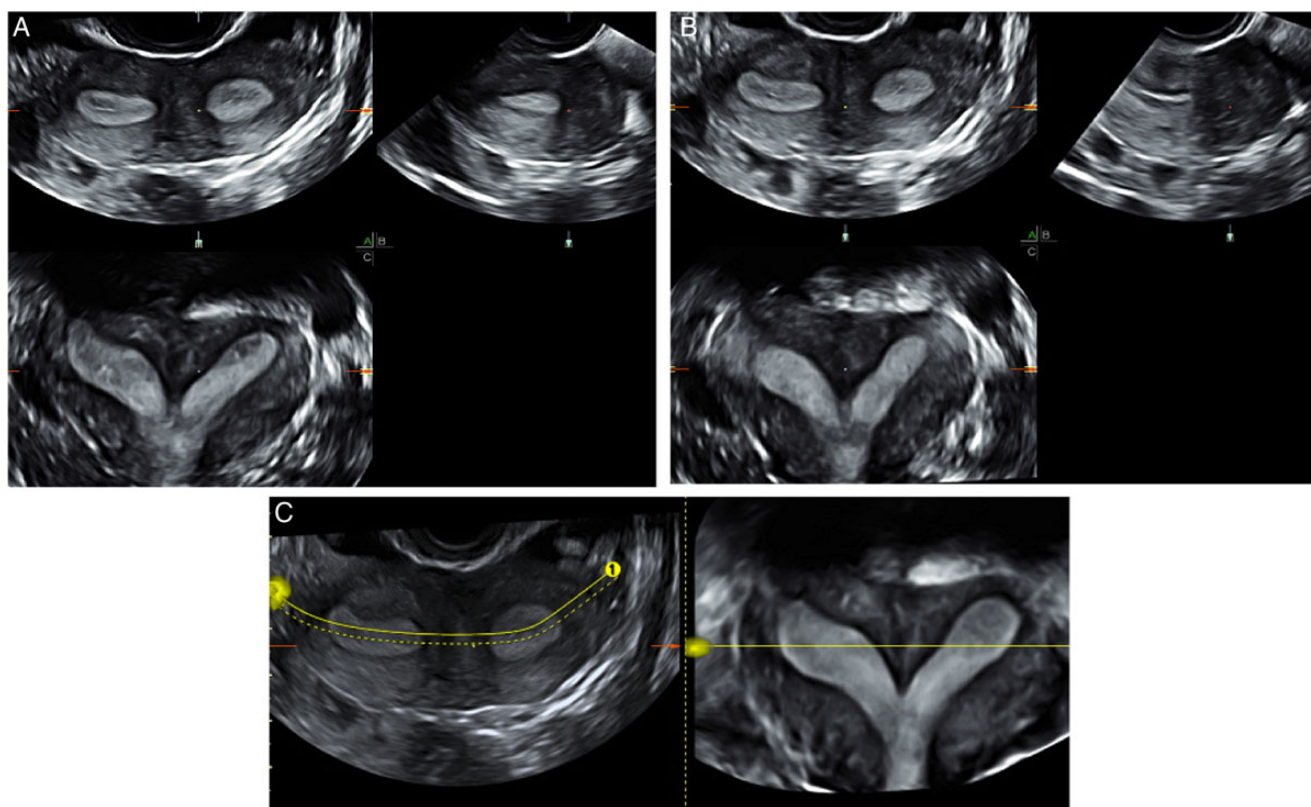
symptomatic patients or, otherwise, in patients with higher risk for the presence of an anomaly, special attention should be paid during their diagnostic work-up.

The recommendations for the diagnostic work-up were based on the diagnostic potential of the different methods and their diagnostic accuracy. Additional parameters (e.g. accessibility, need for training and expertise, cost) were also taken into account. The diagnostic methods should be used in a systematic way, taking into consideration the comments for their proper use. The anatomical characteristics should be recorded and documented as described previously based on the anatomical varieties of the ESHRE/ESGE Classification system.

Definitions

Asymptomatic patients: patients consulting for routine gynecological examination without complaints of chronic pelvic pain (i.e. dysmenorrhea, dyspareunia, cyclic low abdominal pain) and history of poor reproductive outcome having normal gynecological findings at clinical examination.

Symptomatic or high risk patients: defined as groups of patients presenting with clinical problems that could be associated with the presence of

Figure 3 (**A**–**C**) How to obtain an optimal 3D US coronal plane. Cutting line is not perfect on the endometrium in plane a and b; thus, if necessary, the dotted line can be curved to follow the endometrium and the tubal ostia, as shown in plane c.

female genital anomalies and expected to have higher prevalence than the general population. Thus, the following should be considered as symptomatic groups: (i) patients with primary amenorrhea, inability to have normal intercourse, chronic pelvic pain (dysmenorrhea, dyspareunia, cyclic abdominal pain) and (ii) patients with poor reproductive outcome including (a) patients with two or more IVF failures, (b) women with two or more first trimester pregnancy losses and/or one second trimester loss and (c) women with a history of preterm delivery and (iii) adolescents with symptoms suggestive for the presence of a female genital anomaly.

Recommended evaluation of asymptomatic women
Clinicians should, always, be attentive for the presence of a congenital anomaly in asymptomatic women of reproductive age during their routine examination, supplementing gynecological examination with a 2D US as follows:

Gynecological examination: the anatomy of the external genitalia, the vagina and the cervix should be carefully evaluated,
2D US: it should be carried out in a predefined and systematic manner to increase its diagnostic accuracy. The shape and the dimensions of the uterine cavity, the uterine wall (anterior, posterior, lateral and fundal width) and external uterine contour should be recorded in a systematic way in longitudinal and transverse planes.

The absence of findings suspicious for the presence of an anomaly should not be considered as definite and the presence of one could not be excluded.
Positive findings should be used for documentation only and counseling of the patients for further investigation given that they are asymptomatic women.
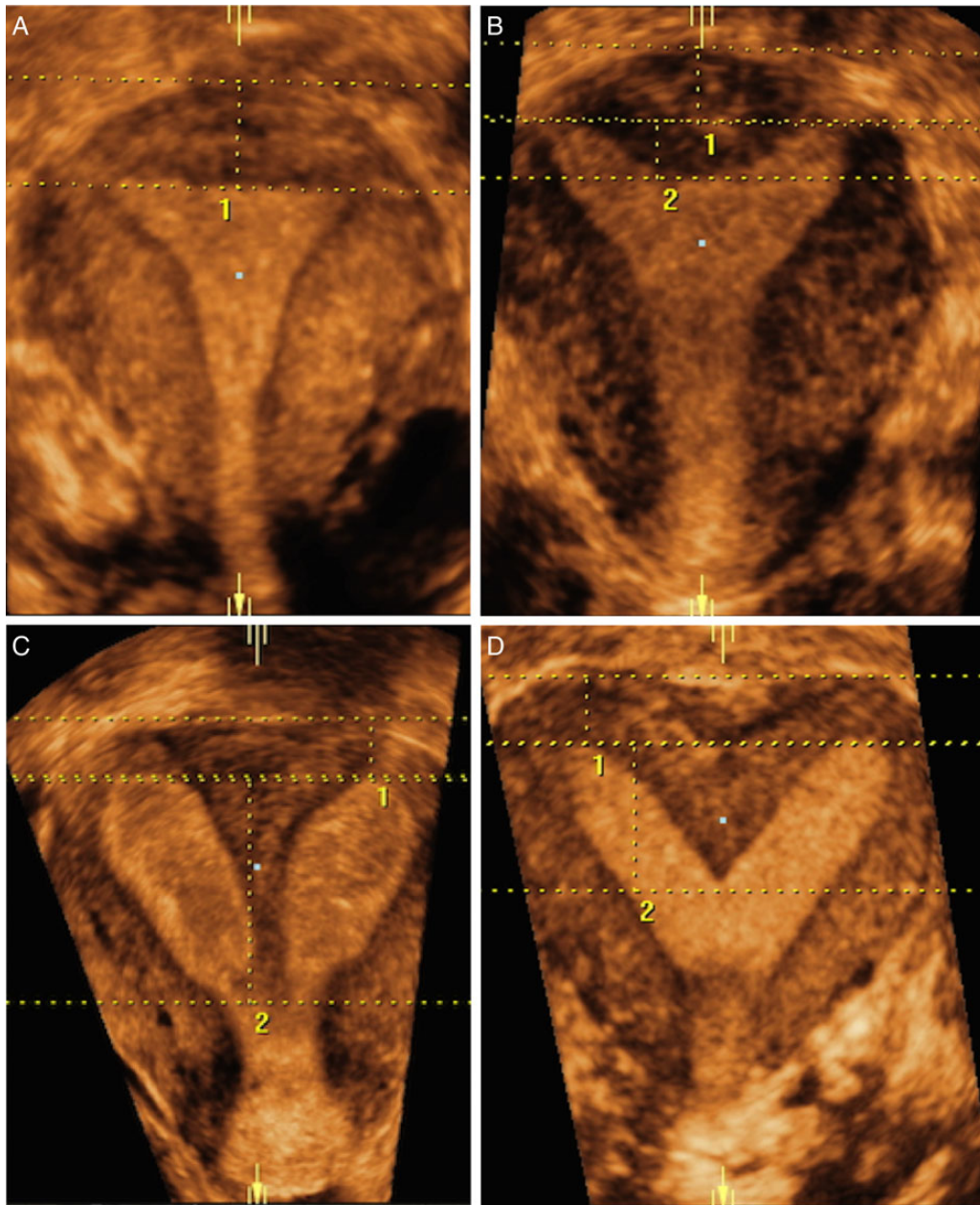
Recommended diagnostic work-up of selected population
The following thorough, preferably non-invasive, high accuracy diagnostic work-up is recommended for (i) all symptomatic patients of reproductive age, sexually active, belonging to 'high risk' groups for the presence of a female genital anomaly and (ii) any asymptomatic woman suspected to have an anomaly by routine evaluation and wishing to undergo a more thorough evaluation. Furthermore, although they could not be considered as symptomatic, careful inspection is recommended for infertile patients after a first trimester miscarriage where fetal heart beat was present at the beginning of pregnancy and for those entering IVF and/or older than 35 years.

Gynecological examination with careful evaluation and recording of the external genitalia, vaginal and cervical anatomy.
2D US (vaginal) in a predefined and systematic manner (to increase its diagnostic accuracy), where the shape and the dimensions of the uterine cavity, the uterine wall (anterior, posterior, lateral and fundal width) and external uterine contour should be recorded in a systematic way and predefined way in longitudinal and transverse

Figure 4 Coronal 3D US views of the uterus. (**A**) A normal uterus; uterine wall thickness: distance between the line joining tubal ostia (interostial line) and a parallel line on the top of the fundus. (**B**) A partial septate uterus; (1) uterine wall thickness: distance between the line joining tubal ostia (interostial line) and a parallel line on the top of uterine fundus and (2) internal midline indentation: distance between the interostial line and a parallel line on the top of midline indentation. (**C**) A complete septate uterus: (1) uterine wall thickness: distance between the line joining tubal ostia (interostial line) and a parallel line on the top of uterine fundus and (2) internal midline indentation: distance between the interostial line and a parallel line on the top of midline indentation (the line reaches the internal cervical os). (**D**) A bicorporeal septate uterus: uterine wall thickness: distance between the interostial line and a parallel line joining the external outline of the uterine horns.

planes. Measurements from 2D US examination could be used as a reference for the evaluation of uterine anatomy deviations in 3D ultrasound.

3D US (vaginal) in a predefined and systematic manner where the shape and the deviations from normal cervical and uterine anatomy should be recorded and documented.

In subgroups of patients with subfertility, recurrent IVF failures or recurrent pregnancy losses additional examinations can be performed:

HyCoSy or 2D or 3D SHG by an experienced sonographer when available.
HSC and, in cases of suspected adnexal pathology, hydrolaparoscopy or LSC. Those techniques should be offered by clinicians, endoscopic

reproductive surgeons, having also the ability to surgically treat any discovered pathology.

X-Ray HSG, nowadays, should no longer be considered as a 'first line' diagnostic procedure and should be reserved only for settings where the prementioned diagnostic methods are not available or for national health systems where indicated for other reasons. Congenital uterine anomaly may be suspected from HSG performed in women with infertility to verify tubal patency.

Recommended diagnostic work-up for complex anomalies

Subgroups of patients with suspected complex anomalies (defined as anomalies resulting from disturbances in more than one stage of normal embryological development and having as a result anatomical deviations in more than one organ of the female genital tract), and those where the application of the previously mentioned methods could not be applied (e.g. obstructing anomalies) should be evaluated as follows:

Abdominal and/or transrectal 3D US in a predefined and systematic manner where the shape and the deviations from normal cervical and uterine anatomy should be recorded and documented.

MRI. Evaluation of the results is recommended to be performed by an imaging expert in collaboration with an experienced gynecologist.

HSC and LSC. These techniques should be offered by clinicians (endoscopic reproductive) and surgeons with experience in the management of complex female genital anomalies in special centers after a thorough non-invasive evaluation and, mainly, in the context of concomitant surgical treatment of any discovered pathology.

Recommended diagnostic work-up for adolescents

Adolescents with symptoms suggestive for the presence of a female genital anomaly (primary amenorrhea and/or pelvic masses or pathology and/or cyclic pelvic pain) should be evaluated as follows:

Gynecological examination with careful evaluation and recording of the external genitalia.

Abdominal and/or transrectal 2D and 3D US where the shape and the deviations from normal cervical and uterine anatomy should be recorded and documented.

MRI as a first line diagnostic procedure. Evaluation of the results is recommended to be performed by an imaging expert in collaboration with an experienced gynecologist.

HSC and LSC. These techniques should be offered in the context of concomitant surgical treatment of any discovered pathology and only by endoscopic reproductive surgeons with experience in the management of complex female genital anomalies in special centers after a thorough non-invasive evaluation.

In patients with female genital anomalies, investigation of the urinary tract is also recommended as mandatory.

Conclusion

The combination of gynecological examination and 2D US could be recommended as the current standard for the evaluation of asymptomatic women; 3D US could be considered as the standard for diagnosis of female genital anomalies supplemented by MRI, HSC and LSC in complex ones or in diagnostic dilemmas.

Open issues for further research

The role of a combined ultrasound examination together with outpatient HSC as a one-stop diagnostic evaluation of symptomatic 'high risk' patients should be prospectively evaluated. The ESHRE/ESGE classification should be considered as a guide for diagnosis, offering a common terminology among the clinicians to convey the exact anatomical status of the female genital tract (Grimbizis *et al.*, 2014; Di Spiezio Sardo *et al.*, 2015); based on that, it is a challenge for further research to objectively estimate the clinical consequences related to various degrees of uterine deformity, e.g. the length of the septum and the potential co-factors that are associated with poor reproductive outcome. Large prospective studies with correct classifications and accurate measurements of the length of midline indentations are needed to establish optimal indications for reconstructive surgery in patients with congenital uterine anomalies.

Authors' roles

Scientific coordinators: G. F.G. and R. C.; Coordination of recommendations development: S. G.; Systematic evaluation of diagnostic accuracy: S. H.S., A. D. S. S. and G.F.G.; Conuta Scientific Committee and faculty members: S. B., R. C., C. D. A., A. D. S. S., R. F., M. G., L. G., S. G., G. F.G., T. C. L., V. T., B. T.; Invited experts: N. N.A., A. A., C. B., C. E., G. N., D. T., D. V. S.

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Conflict of interest

None.

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