Reproductive Implications and Management of Congenital Uterine Anomalies

1. Background

Interest in congenital uterine anomalies (CUAs) has been increasing with the advent of three-dimensional (3D) ultrasound, which provides visible evidence of the internal and external contours of the uterus and makes diagnosis of uterine anomalies more accurate, and less invasive than other commonly employed radiological and surgical diagnostic modalities. CUAs are not uncommon. A recent meta-analysis estimated the overall prevalence of CUAs to be 5.5% in an unselected population, 8.0% in infertile women, 13.3% in those with a history of miscarriage and 24.5% in those with miscarriage and infertility. It is therefore evident that clinicians will be regularly required to counsel women with a CUA. However, these anomalies will present very differently – ranging from asymptomatic/incidental to very complex reproductive pathology and/or symptomatology. The task of counselling and managing women diagnosed with a CUA is proving to be difficult because of four main reasons:

1. There have been several different classifications in the literature in the past few decades.
2. Several different diagnostic modalities are being used.
3. Ascertaining the reproductive impact of each CUA – even through recent meta-analyses – has been challenging given the significant heterogeneity of existing studies.
4. There is no single randomised controlled trial (RCT) to address the question of surgical management of CUAs – specifically, the resection of the uterine septum, which is the most amenable.

The aim of this Scientific Impact Paper is to address these four issues and make recommendations.

2. Classification

Although the first classifications for CUAs originate from descriptions by Cruveilher, Foerster and von Rokitansky in the mid-19th century, the first classification/description to be widely recognised was that of Buttram and Gibbons in 1979, which was later revised and modified by the American Fertility Society (AFS), now known as the American Society of Reproductive Medicine (ASRM). This has been the most commonly-used classification over the past three decades. However, new classifications have emerged, since the original classification did not provide clear diagnostic criteria to distinguish between different embryologically neighbouring anomalies and a number of publications have subsequently described unclassifiable CUAs. These include the vagina cervix uterus adnexa-associated malformation (VCUAM) classification, which individually describes the anatomical anomalies of the vagina, cervix, uterus and associated malformations in order to categorise genital anomalies systematically and the embryological-clinical classification system proposed by Acién et al. originally in 1992 and subsequently in 2011. One of the most recent classifications was developed jointly by the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) in 2013, through a structured Delphi procedure.

The ESHRE/ESGE classification includes descriptions for all female genital tract malformations – not solely uterine – similar to the VCUAM classification (uterine U0–U6, cervical C0–C4 and vaginal V0–V4). It also provides a pictorial guide – similar to the AFS classification – to aid diagnosis based on imaging results and quantitative definitions to guide the diagnosis and distinguish anomalies. For example, an internal indentation at the fundal midline exceeding 50% of the uterine wall thickness
has been used to diagnose a septate uterus, while an external indentation at the fundal midline exceeding 50% of the uterine wall thickness has been used for a bicornoreal uterus.

Uterine anomalies based on the recent ESHRE/ESGE working group are classified into the following main classes which express uterine anatomical deviations from the same embryological origin (Appendix I):

- **U0**, normal uterus.
- **U1**, dysmorphic uterus (infantile and T-shaped mainly).
- **U2**, septate uterus – uterine cavity is partitioned by a fibromuscular septum, but has normal external contour/shape.
- **U3**, bicornoreal uterus (partial and complete – bicornuate and uterus didelphys based on AFS) – uterus is present as two separate uterine horns, double uterus with or without two separate cervixes, and rarely a double ovary. Each uteri horn is linked to one fallopian tube and ovary.
- **U4**, hemi-uterus (unicornuate) - only one horn of the uterus is present which is linked to one fallopian tube and ovary with the the other horn of uterus is absent or rudimentary.
- **U5**, aplastic uterus (absent uterus)
- **U6**, for still unclassified cases.

An arcuate uterus is considered a normal variant and is not included in this classification.

The 2016 ARSM publication, ‘Uterine septum- a guideline,’ also reported arcuate uterus as a normal variant, with proposing criteria for diagnosing septate and bicornuate uteri, different to that proposed by ESHRE/ESGE. Although the ESHRE/ESGE classification attempted to address all the previous shortcomings, with more objective definitions of CUAs, particularly for septate uterus, it has not been received without criticism, as some authors have observed an increase in the diagnosis of septate uterus compared with former classifications. The Congenital Uterine Malformation Experts (CUME) group (2018), based on a reproducibility and diagnostic accuracy study using 3D ultrasound, has recently criticised ESHRE/ESGE criteria as overestimating and ASRM criteria as underestimating the prevalence of septate uterus. CUME has proposed a simple and reproducible definition of internal indentation of more than 10 mm for diagnosing septate uterus. While there are various classification systems and nomenclature reported, the CUA terms used in this paper are those in the AFS classification, since most published evidence on CUAs are based on this.

Albeit the lack of a perfect classification system, the ESHRE/ESGE criteria seem to be an attempt to define CUAs objectively based on 3D ultrasound measurements, for example to define what is and what is not a septum, and when surgery should be considered to remove the septum. Careful 3D ultrasound measurements of external and internal fundal indentation should be made and recorded in every case to build up a sufficiently large database from which the ESHRE/ESGE criteria could be refined, according to observed reproductive outcome. Similarly, in any clinical trial relating to the septum, the subjective assessment or criteria should be replaced by objective 3D measurements.

### 3. Diagnosis

Accurate evaluation of the internal and external contours of the uterus is crucial in making a diagnosis and classifying CUAs correctly. Previously, the gold standard has been a combination of laparoscopy and hysteroscopy. However, imaging techniques such as ultrasonography, hysterosalpingography (HSG), sonohysterography and magnetic resonance imaging (MRI) are less invasive modes of screening, diagnosing and classifying CUAs. While conventional two-dimensional (2D) transvaginal scanning (TVS) and HSG are good for screening for uterine anomalies, 3D TVS and MRI can accurately classify CUAs.
Conventional 2D TVS is minimally invasive and a less expensive modality to assess CUA.\textsuperscript{15} Scanning in the second half of the menstrual cycle (the secretory phase) provides more accurate visualisation of the endometrium and is therefore appropriate for evaluating the uterus for CUA. Visualisation of a double endometrial complex on a transverse plane is indicative of a CUA. However, 3D TVS, through its unique feature of providing the coronal plane of the uterus, facilitates simultaneous visualisation of both external (serosal surface) and internal (uterine cavity) contours of the uterine fundus and helps classify bicornuate (partial bicorporeal), septate or partial septate uteri correctly.\textsuperscript{16} Uterus didelphys (complete bicorporeal), although very rare, also shows two endometrial complexes in the transverse plane of conventional 2D ultrasound, but 3D ultrasound, with a clinical demonstration of two cervices or two vaginas on speculum examinations, can confirm the diagnosis. In cases of unicornuate uterus (hemi-uterus), a normal long axis of the uterus is seen on one side of the pelvis alongside the absence of, or a rudimentary, uterine shadow on the other. A banana-shaped uterine cavity and single interstitial portion of fallopian tube in the coronal plane is seen using 3D ultrasound. Saline infusion sonography has been suggested as a method for diagnosing rudimentary horns, as saline can clearly be seen in the unicornuate uterus, with no passage into the rudimentary horn.

Three-dimensional TVS is now considered the gold standard for the assessment of CUAs as it is less invasive and can classify the varying types of uterine anomalies correctly. Criteria for the classification of uterine anomalies based on 3D ultrasound have been described in the Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies.\textsuperscript{9,17} MRI of the pelvis is sensitive and specific for diagnosing CUAs and is helpful in delineating the endometrium and detecting uterine horns, as well as defining aberrant gonadal location or renal anatomy. It is also less invasive than combined laparoscopy and hysteroscopy. While MRI is not routinely recommended in all women with a suspected CUA, it is useful for those women with unconfirmed diagnosis on 3D ultrasound and those with suspected complex anomalies.\textsuperscript{14}

CUAs may be associated with congenital renal anomalies because of their closely-related embryonic origin; consequently, a urinary tract ultrasound scan is recommended in all women diagnosed with a CUA.

4. Reproductive implications

CUAs are mostly diagnosed incidentally during investigations for subfertility, recurrent miscarriage or menstrual disorders.\textsuperscript{\textsuperscript{13}} CUAs associated with obstruction, such as unicornuate uterus with a rudimentary horn, uterine didelphys with obstructed hemivagina or vaginal/cervical agenesis or anomalies often present with pelvic pain secondary to haematometra, haematocolpos or endometriosis. Women with agenesis, such as Mayer-Rokitansky-Küster-Hauser syndrome or segmental hypoplasia, often present with primary amenorrhoea. CUA associated with longitudinal vaginal septa, may present with dyspareunia or menstrual abnormalities.\textsuperscript{18,19}

CUAs have been implicated as potential causes of infertility, recurrent miscarriages, preterm delivery and fetal malpresentation. The types of CUA are individually associated with varying degrees of adverse outcomes. A systematic review\textsuperscript{20} of 3805 women with CUAs reported that those with canalisation defects, such as septate and partial septate uteri, appear to have the poorest reproductive performance, with a reduced conception rate (OR 0.86; 95% CI 0.77–0.96) and increased risk of first-trimester miscarriage (OR 2.89; 95% CI 2.02–4.14), preterm birth (OR 2.14; 95% CI 1.48–3.11), and fetal malpresentation at delivery (OR 6.24; 95% CI 4.05–9.62). Compared with those with a partial septate uterus, women with a septate uterus have poorer outcomes throughout their pregnancies.\textsuperscript{20}
While there seems to be an association between canalisation defects and suboptimal reproductive performance, the definite aetiology and pathophysiological processes underlying infertility and miscarriage remain uncertain. Various hypotheses have been put forward, such as endometrium overlying the septum being abnormal thus providing a suboptimal site for implantation, disorderly and decreased blood supply insufficient to support placentation and embryo growth, and uncoordinated uterine contractions or reduced uterine capacity.

Unification defects, such as bicornuate, unicornuate and didelphic uteri, do not appear to reduce fertility but are associated with increased risks of adverse outcomes during pregnancy. The risks are dependent on the type of unification defect. Women with bicornuate and unicornuate uteri have an increased risk of first trimester miscarriage (OR 3.4; 95% CI 1.18–9.76 and OR 2.15; 95% CI 1.03–4.47 respectively), preterm birth (OR 2.55; 95% CI 1.57–4.17 and OR 3.47; 95% CI 1.94–6.22 respectively) and fetal malpresentation (OR 5.38; 95% CI 3.15–9.19 and OR 2.74; 95% CI 1.3–5.77 respectively), while women with uterus didelphys seem to have an increased risk of preterm labour (OR 3.58; 95% CI 2.0–6.4) and fetal malpresentation (OR 3.7; 95% CI 2.04–6.7).

Dysmorphic uterus is a CUA in which the uterine cavity is of abnormal morphology (T-shaped or a tubal shape called infantile uterus). This is a rare malformation, the exception being those exposed to diethylstilboestrol (DES) in utero. Women with this malformation have been reported to have poor reproductive outcomes; however, these studies are old. Dysmorphic uteri were not seen once DES usage was halted but with the advent of 3D pelvic ultrasound for fertility or recurrent miscarriage investigations, this CUA has re-emerged more recently.

5. Management options

While there is an association between CUAs and adverse reproductive outcomes, the effectiveness of surgical treatment of non-obstructive uterine anomalies to improve reproductive outcomes, especially if they are incidentally diagnosed, is debatable. Younger women diagnosed with a complex CUA may require psychosocial support and counselling to address functional and emotional effects. Future fertility options should be discussed with adolescents and their parents/guardians. The presence of associated renal tract anomalies needs to be ruled out prior to any surgical intervention.

The aims of CUA management are to treat anatomical distortions associated with obstructive anomalies to relieve symptoms such as pain, thereby improving quality of life and to avoid long-term health and reproductive adverse consequences; and for non-obstructive anomalies, to improve reproductive outcomes in infertile women or women who have experienced recurrent miscarriages. The ultimate goal is to increase live births.

5.1 Obstructive CUAs

While a unicornuate uterus does not warrant surgical intervention, functioning rudimentary uterine horns, frequently associated with unicornuate uterus, need surgical removal to prevent the risk of haematometra or pregnancy occurring in the horn.

5.2 Non-obstructive CUAs

Unification defects (bicornuate and didelphic uteri)

Traditionally, abdominal metroplasty was performed to unify or restore the shape of the uterus and remains the only surgical treatment available for women with unification defects such as bicornuate or didelphic uteri, but it is associated with higher risks of complications, including prolonged hospital
stay, longer recovery time, postoperative intraperitoneal adhesions and uterine rupture during subsequent pregnancy. This intervention is not generally considered or advised in the absence of significant adverse reproductive history. Evidence on improving reproductive outcomes following abdominal metroplasty for unification defects in women with past histories of repeated pregnancy loss or preterm deliveries is very limited. Only one controlled study\textsuperscript{23} of 21 patients, with 13 managed conservatively and eight managed with abdominal metroplasty, records no improvement in obstetric outcomes.

**Resorption defects (septate uterus)**

Hysteroscopic metroplasty or hysteroscopic transcervical division of the uterine septum has become the established treatment of choice for septate uterus.\textsuperscript{19} A variety of hysteroscopic instruments can be used for the division of a uterine septum including microscissors, bipolar electrosurgical needle or resectoscope with an operating loop. The procedure can be performed under transabdominal ultrasound or laparoscopic guidance to reduce the risk of uterine perforation and to ensure adequacy of the procedure. It is good practice to measure the septal length preoperatively using three-dimensional ultrasound or MRI to ensure surgical safety and efficacy. Preoperative endometrial suppression is not used routinely but may improve visualisation and operative precision. However, there is insufficient evidence for the use of gonadotrophin-releasing hormone (GnRH) agonists, danazol or any other medications to thin endometrium prior to hysteroscopic division of septum.\textsuperscript{24,25} The procedure is preferably performed in the early follicular phase of the menstrual cycle. The length of the uterine septum may vary from a small septum of 1 cm to a large septum extending from the fundus to the internal cervical os. The presence of a residual septum 0.5–1.0 cm in length does not adversely influence outcome.\textsuperscript{19} Moving the hysteroscope from side to side and visualisation of both ostia on a panoramic view from the level of internal os verifies completion of resection. Endometrial re-epithelialisation of the cut surface can occur centripetally by the proliferation of endometrial tissue and centrifugally from the base of the remaining glands to the margin of the incision. There is risk of intrauterine adhesions after the procedure. Various methods (copper intrauterine device [IUD], hormonal treatment with estrogen, combination therapy with IUD and hormonal treatment or intrauterine auto-crosslinked hyaluronic acid gel) have been used to prevent intrauterine adhesions after operative hysteroscopy.\textsuperscript{36} Intrauterine postoperative hormone treatment, especially if preoperative GnRH agonist has been given, is frequently used to enhance endometrial proliferation and to reduce adhesion formation but the evidence of its efficacy is lacking.\textsuperscript{26} While there is no evidence of benefit of using intrauterine devices or an intrauterine balloon to reduce the risk of adhesions after hysteroscopic septum resection, there is some evidence that intrauterine auto-crosslinked hyaluronic acid gel can reduce the risk of intrauterine adhesions after septum division.\textsuperscript{27} Re-evaluation by second-look hysteroscopy at 2 months postoperatively can be offered to evaluate adhesion formation and any residual septum. There is insufficient evidence to advocate a specific length of time before a woman should conceive after the procedure. However, observational studies\textsuperscript{28,29} suggest that uterine cavity is healed 2 months after septal division.

There are no published RCTs assessing effectiveness and complications of hysteroscopic metroplasty. Observational studies\textsuperscript{30,31} in women with no history of surgery have reported significant improvements in pregnancy outcomes, with reduction in miscarriage rates leading to increased live birth rates. A systematic review and meta-analysis of controlled studies\textsuperscript{4} published in 2014 reported a decreased probability of spontaneous miscarriages (both first and second trimester) in women treated with hysteroscopic resection of septum compared with women who were not treated (RR 0.37, 95% CI 0.25–0.55; heterogeneity I\textsuperscript{2} = 0%; six studies). However, there was no difference in conception rates (RR 1.14, 95% CI 0.79–1.65; heterogeneity I\textsuperscript{2} = 80%; four studies) and preterm delivery rates (RR 0.66, 95% CI 0.29–1.49; heterogeneity I\textsuperscript{2} = 0%; six studies) among the hysteroscopic resection and control groups. Although observational studies have found a benefit in removing the septum in women with a history of infertility and miscarriage, a Cochrane review\textsuperscript{32} published in 2011 reported no evidence...
for hysteroscopic metroplasty in women with recurrent miscarriage and a septate uterus and advised against offering this intervention as routine practice. A Cochrane review\textsuperscript{13} published in 2017 did not identify any published randomised controlled studies assessing the efficacy in pregnancy outcomes after hysteroscopy metroplasty. The Randomized Uterine Septum Transsection Trial (TRUST)\textsuperscript{34} to assess whether hysteroscopic septum resection improves reproductive outcome in women with a septate uterus and a history of (recurrent) miscarriage, subfertility or preterm birth is currently underway in the Netherlands.

NICE has produced guidance on hysteroscopic metroplasty of a uterine septum for recurrent miscarriage and for primary infertility\textsuperscript{35,36} which supports offering hysteroscopic metroplasty of a uterine septum to women with recurrent miscarriage as long as appropriate clinical governance arrangements are put in place. A multidisciplinary team including specialists in reproductive medicine, uterine imaging and hysteroscopic surgery should undertake patient selection and treatment. In women with infertility, NICE recommends that current evidence on efficacy to improve pregnancy rates is inadequate in quantity and quality. Hysteroscopic metroplasty should, therefore, only be offered with special arrangements for clinical governance, consent and audit or research.

Small observational studies\textsuperscript{17,37} report a beneficial effect of hysteroscopic metroplasty in women with a dysmorphic uterus, but the evidence is not robust enough to support routine surgical intervention for these women.

6. Opinion

- There is no uniformly accepted and perfect classification system of CUAs available currently. The ESHRE/ESGE criteria are an attempt to define CUAs objectively based on 3D ultrasound measurements. Careful 3D ultrasound measurements of external and internal fundal indentation should be made and recorded in every case to build up a sufficiently large database from which the ESHRE/ESGE criteria could be refined, according to observed reproductive outcomes.

- While 2D pelvic transvaginal ultrasound and HSG are good screening tests in low risk women, 3D pelvic ultrasound is recommended to diagnose and classify CUAs accurately for those with suspected screening tests or women who have had recurrent miscarriages. MRI or combined laparoscopy and hysteroscopy should be reserved for diagnosing complex CUAs.

- Most women with a CUA experience a normal reproductive outcome. However, controlled observational studies suggest that CUAs, including septate uteri, are associated with increased risks of first or second trimester miscarriages, preterm labour and malpresentation at birth, with the degree of risks varying depending on the type and severity of CUA.

- While high-quality evidence on the efficacy and safety of surgical treatment to improve reproductive outcomes is lacking, controlled studies have indicated that hysteroscopic septal division reduces miscarriage rates resulting in improvement in live birth rates and this evidence supports the use of hysteroscopic division of a uterine septum for women with recurrent miscarriage by experienced specialists. Treatment for incidentally diagnosed septum in infertile women is debatable. If surgery is planned, women should be fully informed of the limited evidence on its efficacy and of intra- and post-operative risks associated with surgery. The unit offering management of CUAs should ensure that appropriate arrangements for clinical governance and audit are in place.

- Abdominal metroplasty for unification defects is currently not advisable owing to its increased association with significant intra- and post-operative complications and lack of evidence to support improved reproductive outcomes.
References


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