Scientific Impact Paper No. 62
2nd edition; partial update

Reproductive Implications and Management of Congenital Uterine Anomalies

Scientific Impact Paper

Plain language summary

Congenital uterine anomalies (CUAs) are malformations of the uterus (womb) that develop during fetal life. When a baby girl is in her mother's uterus, her uterus develops as two separate halves from two tubular structures called 'Müllerian ducts', which fuse together before she is born. Abnormalities that occur during the baby's development can be variable, from complete absence of uterus through to more subtle anomalies, which are classified into specific categories. While conventional ultrasound is good in screening for CUAs, 3D ultrasound is used to confirm a diagnosis. If a complex uterine abnormality is suspected, MRI scanning may also be used, with a combination of laparoscopy in which a camera is inserted into the cavity of the abdomen, and hysteroscopy, when the camera is placed in the uterine cavity. As there can be a link between CUAs and abnormalities of the kidney and bladder, scans of these organs are also usually requested.

Although CUAs are present at birth, adult women typically do not have any symptoms, although some may experience painful periods. Most cases of CUA do not cause a woman to have difficulty in becoming pregnant and the outcome of pregnancy is good. However, these uterine anomalies are often discovered during investigations for infertility or miscarriage. Moreover, depending upon the type and severity of CUA, there may be increased risk of first and second trimester miscarriages, preterm birth, fetal growth restriction (smaller and lighter babies for the stage of pregnancy), pre-eclampsia (development of high blood pressure and protein in urine after 20th week of pregnancy) and fetal malpresentation (baby not facing head-first down the birth canal) at birth. Surgical treatment may be considered in women, who have had recurrent miscarriages and have a septate uterus, i.e. the uterine cavity is divided by a partition. In this case, surgery may reduce the chances of miscarriage. However, women must be informed that there is inconclusive and conflicting evidence regarding the improved live births in this context. Further evidence from large randomised controlled trials are required to provide conclusive evidence-based recommendations for surgical treatment for septate uterus. Surgical treatment for other types of CUAs is not usually recommended as the risks outweigh potential benefits, and evidence for any benefits is lacking. Women with CUAs may be at an increased risk of preterm birth even after surgical treatment for a septate uterus. These people, if suspected to be at an increased risk of preterm birth based on the severity of CUA, should be followed up using an appropriate protocol for preterm birth as outlined in UK Preterm Birth Clinical Network Guidance.

This guidance is for healthcare professionals who care for women, non-binary and trans people with congenital uterine anomalies.

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing.Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

1. Background

Congenital uterine anomalies (CUAs) are deviations from normal anatomy resulting from embryological maldevelopment of the Müllerian ducts. While most CUAs are asymptomatic and are associated with normal reproductive outcomes, some may be associated with adverse reproductive outcomes. Detection of 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 the assessment of uterine morphology more reproducible, as well as being less invasive than other commonly used radiological and surgical diagnostic modalities. CUAs are not uncommon. A comprehensive meta-analysis[1] 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 and often in the context of subfertility and miscarriage. The task of counselling and caring for women and people diagnosed with a CUA is proving to be difficult for four main reasons:

1. There have been several different classifications in the literature in the past few decades[2] (see 'classification', section 2).
2. Several different diagnostic modalities are still being used[3] (see 'diagnosis', section 3).
3. Ascertaining the reproductive impact of each CUA – even through recent meta-analyses – has been challenging given the significant heterogeneity of existing studies[4] (see 'reproductive implications', section 4).
4. Lack of good quality evidence on surgical management of CUAs – specifically, the resection of the uterine septum, which is the most amenable[5] (see management options, section 5).

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

2. Classification

Most classifications of CUAs are based on the extent of failure of Müllerian duct development. Knowledge of embryology helps to understand the classifications and types of CUAs better.

The female reproductive tract differentiates from two Müllerian ducts that develop within the first 6 weeks of fetal life. In females, the absence of anti-Müllerian hormone (AMH) allows the Müllerian ducts to fuse caudally to become the uterus and upper third of the vagina, and the unfused upper segments become the fallopian tubes. The intervening septum of the uterus (developed from the fusion of the upper portion of two Müllerian ducts) subsequently undergoes resorption or canalisation to become a single uterine cavity. The lower tip of the fused Müllerian ducts makes contact with the urogenital sinus to form the vaginal plate, which then canalises to form the vagina, with the upper portion derived from Müllerian duct and lower portion from the urogenital sinus. There are three phases of Müllerian duct development, and fault at any of these phases results in development of CUAs (Table 1).

1. Organogenesis (formation of both Müllerian ducts) – defects in the development of Müllerian ducts leads to agenesis or hypoplasia (e.g. absent uterus and unicornuate uterus).
2. Fusion of both Müllerian ducts leads to formation of a uterus and upper vagina.
    a. Horizontal fusion or unification (lower segments of paired Müllerian duct fuse to form uterus, cervix and upper vagina) – defects, depending on the degree, lead to partial fusion or unification defect (e.g. bicornuate uterus) or complete fusion or unification defect (uterine didelphys).

b. Vertical fusion (between the descending Müllerian duct and ascending urogenital sinus to form vaginal canal) – defects cause an imperforate hymen or a transverse vaginal septum.

3. Septal resorption or canalisation involves the resorption of the horizontally fused Müllerian ducts leading to development of the uterine cavity – failure of resorption or canalisation, depending on the degree of defect, leads to CUAs such as complete septate uterus, partial septate uterus or arcuate uterus.

Table 1: Phases of Müllerian duct development and defects

Phases of Müllerian duct development	**Defect**	**Anomaly**
Organogenesis: Development of Müllerian Duct	Failure to develop bilaterally	Aplasia/ agenesis (MRKH syndrome)
	Failure to develop unilaterally	Unicornuate uterus
Fusion or unification: between paired Müllerian ducts between fused Müllerian duct and urogenital sinus (sinovaginal bulbs)	Horizontal fusion defect	Bicornuate uterus Uterus didelphys
	Vertical fusion defect	Transverse vaginal septum Imperforate hymen
Septal resorption or canalisation	Defect in resorption or canalisation	Septate uterus Arcuate (?)

Although the first classifications for CUAs originate from descriptions by Cruveilher, Foerster and von Rokitansky in the mid-19th century,[6] 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).[7] This has been the most commonly-used classification over the past four decades. In 1988, the AFS published their classification scheme for mechanical problems associated with poor reproductive outcomes (Table 2). One component of this was Müllerian anomalies, which were classified as follows:

- Hypoplasia/agenesis
- Unicornuate
- Didelphus
- Bicornuate
- Septate
- Arcuate
- Diethylstilboestrol (DES) drug-related

The aim of this classification was to provide an easy-to-use, reliable reporting system to allow clinicians to group cases so that forward conclusions could be made about the different groups, and future patients could be counselled accurately and effectively.[7] 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, new classifications have emerged.[2] 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,[8] and the embryological-clinical classification system proposed by Acién et al. originally in 1992 and subsequently in 2011.[6] 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,[9] through a structured Delphi procedure.

Table 2: Summary of Müllerian anomalies classification based on three major published guidelines

Classification	Characteristics and classes
AFS (1988)	Classified based on failure of normal Müllerian development: seven classes. Hypoplasia/ Agenesis, Unicornuate, Bicornuate, Didelphys, Septate, Arcuate, DES drug related.
ESHRE/ESGE (2013)	Classified based primarily on uterine anatomy with cervical vaginal anomalies as supplementary subclasses. **Uterine:** U0-U6 (U0, normal uterus; U1, dysmorphic uterus (infantile and T-shaped mainly); U2, septate uterus; U3, bicorporeal uterus (bicornuate and uterus didelphys); U4, hemi-uterus (unicornuate); U5, aplastic uterus (absent uterus); U6, unclassified cases) **Cervical:** C0-C4 (C0, normal cervix; C1, septate cervix; C2, double cervix; C3, unilateral cervical aplasia; C4, cervical aplasia) **Vaginal:** V0-V4 (V0, normal vagina; V1, Longitudinal non-obstructive vaginal septum; V2, Longitudinal obstructive vaginal septum; V3, Transverse vaginal septum and/ or imperforate hymen; V4, vaginal aplasia
ASRM (2022)	Updated and expanded AFS (1988) classification incorporating cervical, vaginal and all complex anomalies. Nine classes: Müllerian agenesis, Cervical agenesis, Unicornuate, Uterus didelphys, Bicornuate, Septate, Longitudinal Vaginal septum, Transverse Vaginal septum, Complex anomalies

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 (Table 2). 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 bicorporeal 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:

- 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, bicorporeal 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 cervices, and rarely a double vagina. 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 other horn of uterus is absent or rudimentary.
- U5, aplastic uterus (absent uterus).

- U6, for still unclassified cases.

An arcuate uterus, although the mildest form of resorption failure, is not considered as clinically relevant and is not included in this classification.

The 2016 ARSM publication, 'Uterine septum: a guideline',[5] also reported arcuate uterus as not clinically relevant, with the following criteria for diagnosing septate and bicornuate uteri (different to that proposed by ESHRE/ESGE):[9]

- Normal/arcuate – depth from interstitial to apex of indentation more than 1 cm and angle of indentation more than 90°.
- Septate – depth of interstitial line to apex more than 1.5 cm and angle of indentation less than 90°.
- Bicornuate – external fundal indentation more than 1cm.[5]

This leaves a grey zone between normal/arcuate and septate where some women will not meet the criteria for either diagnoses.

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.[10] The Congenital Uterine Malformation Experts (CUME) group[11] has criticised ESHRE/ESGE criteria as overestimating and ASRM criteria as underestimating the prevalence of septate uterus, based on a reproducibility and diagnostic accuracy study using 3D ultrasound. The proportion of septate uteri using the ESHRE/ESHE classification was demonstrated to be much higher than using the ASRM criteria (RR 13.9; 95% CI 5.9–32.7, $P \leq 0.01$).[11] Concerns about overdiagnosis relate to the lack of evidence available to support improved reproductive outcomes for those originally diagnosed with a normal uterus, where the diagnosis remained, compared to those originally diagnosed with a normal uterus but reclassified as a septate uterus as a result of ESHRE/ESGE guidance.[12] The CUME group proposed a simple and reproducible definition of internal indentation of more than 10 mm for diagnosing septate uterus. CUME group has also proposed diagnostic criteria for T-shaped uterus in 2020 based on 3D ultrasound assessment including lateral indentation angle ≤130°, lateral indentation depth ≥7 mm and T-angle ≤40° with good diagnostic accuracy and moderate reproducibility[44] .

Notwithstanding 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. However, it should be remembered that, at present, these cut-offs have not been prospectively compared to reproductive outcomes. Furthermore, using uterine wall thickness, which is amenable to change in the presence of fibroids or adenomyosis, as a reference point to define uterine anomaly is criticised to be a serious shortcoming of the ESHRE/ESGE classification. 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. Until further refinement is done, the ESHRE/ESGE classification should be used with caution especially for diagnosis and management of uterine septum. In any clinical trial relating to the septum, the subjective assessment or criteria should be replaced by objective 3D measurements.

In 2021, ASRM updated and expanded the simple and historic AFS classification incorporating cervical, vaginal and all complex anomalies into nine distinct groups – Müllerian agenesis, cervical agenesis,

unicornuate uterus, didelphys, bicornuate uterus, septate uterus, longitudinal vaginal septum, transverse vaginal septum and complex anomalies[45] (Table 2). Müllerian anomalies have been recognised as continuum of variation in the embryological development and therefore variations can be unlimited with some anomalies mixed type and some complex anomalies. ASRM has defined diagnostic criteria for septate, arcuate and bicornuate uterus. While septate uterus is defined as septal length of >1 cm and septal angle of <90°, arcuate uterus is diagnosed when septal indentation is ≤1 cm and angle of ≥90°. Bicornuate uterus is diagnosed when the external indentation is >1 cm.

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, but imaging techniques such as ultrasonography, hysterosalpingography (HSG), sonohysterography and magnetic resonance imaging (MRI) to screen, diagnose and classify CUAs are less invasive.[1] 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.[3,13–15]

Conventional 2D TVS is minimally invasive and a less expensive modality to assess CUAs.[16] 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 two endometrial cavities on a transverse plane is indicative of a CUA. 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, which helps to classify bicornuate (partial bicorporeal), septate or partial septate uteri correctly.[17] Uterus didelphys (complete bicorporeal), although very rare, also shows two endometrial cavities 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 (if it is non-communicating).[15]

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 by various groups including the Thessaloniki ESHRE/ESGE consensus[9,18], CUME and ASRM.

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.[15]

CUAs may be associated with congenital renal anomalies (of which unilateral renal agenesis is most common) because of their closely-related embryonic origin. The risk of renal abnormalities was 18.8% with unilateral renal agenesis being the most common defect in a study of 378 women with CUA.[19] When different subtypes based on the ESHRE/ESGE criteria were assessed, the prevalence of renal anomalies in normal (U0), dysmorphic (U1), septate (U2), bicorporeal (U3), hemi uterus (U4) and aplastic (U5) were 5%, 0%, 15.6%, 24.7%, 29.5% and 11.7%, respectively. A urinary tract ultrasound

scan, MRI or intravenous pyelogram should be recommended in all women and people diagnosed with a CUA, choosing the most appropriate depending upon the clinical picture.[19]

4. Reproductive implications

CUAs are mostly diagnosed incidentally during investigations for subfertility, recurrent miscarriage or menstrual disorders.[14] 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, present with primary amenorrhoea. CUA associated with longitudinal vaginal septa may present most commonly with dyspareunia or occasionally menstrual abnormalities.[20,21]

CUAs have been implicated as potential causes of infertility, recurrent miscarriages, preterm delivery, fetal malpresentation, caesarean section and fetal growth restriction. These women are also reported to have increased rates of placental abruption, pre-eclampsia and stillbirth.[22,46]The types of CUA are individually associated with varying degrees of adverse outcomes. A systematic review[23] 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). A 2021 systematic review evaluating obstetric and neonatal outcome reported increased risk of intrauterine growth restriction or small for gestational age (OR 2.14; 95% CI 1.26–3.65), placental abruption (OR 9.22; 95% CI 3.42–24.82), caesarean section (OR 5.02; 95% CI 2.77–9.10) and perinatal mortality (OR 2.55; 95% CI 1.29–5.04) for septate and subseptate uteri.[46] Compared with those with a partial septate uterus, women with a septate uterus have poorer outcomes throughout their pregnancies.[22]

While there seems to be an association between canalisation defects and suboptimal reproductive performance, the definite aetiology and pathophysiological processes underlying infertility, miscarriage and other adverse reproductive outcomes including fetal growth restriction remain uncertain. Various hypotheses have been put forward,[23] 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).[23]

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, linked to those exposed to DES in utero.[7,9] Women with this malformation have been reported to have poor reproductive outcomes; although these studies are old.[24,25] In the past the presence of dysmorphic uteri was believed to be related to DES exposure only, but recent clinical experience has demonstrated that, despite the fact that use of DES in pregnancy was prohibited about 40 years ago, these anomalies are encountered in young

infertile patients with no history of DES exposure. The advent of 3D pelvic ultrasound has helped to identify these anomalies. T-shaped uteri may also be associated with marginal intrauterine adhesions (IUAs) and tuberculosis infection.

Women with canalisation defects (Septate or sub-septate uterus; RR 2.14; 95% CI 1.48–3.11) and unification defects (Bicornuate and didelphic uterus; RR 2.97; 95% CI 2.08–4.23) are at an increased risk of spontaneous preterm birth.[22] At present, there is a lack of conclusive evidence about the prediction and prevention of preterm birth in the general obstetric population and resources offered throughout the UK vary considerably. Several biomarkers are currently in use in clinical practice, in addition to transvaginal cervical length scanning to aid in prediction. A prospective study of 64 pregnant women with CUAs evaluated transvaginal cervical length scanning performed between 14 and 23 weeks of gestation and chances of preterm birth (less than 35 weeks of gestation) depending on cervical length.[26] Of the pregnancies studied, 16% (10/64) had a short cervical length of less than 2.5 cm. While the overall incidence of spontaneous preterm birth was 11%, the chance of spontaneous preterm birth was significantly higher in women with a short cervical length (RR 13.5; 95% CI 3.49–54.74 [50% (5/10]) when compared to those without a short cervix (4% [2/54]). Owing to the lack of robust data, it is currently not possible to draw firm conclusions regarding the screening and prevention of preterm labour in women with CUAs. Literature reports varying success of progesterone pessaries and cervical cerclage in prevention of preterm birth. At present, there is a paucity of evidence to suggest the use of these preventative measures in women diagnosed with CUAs.[54] In view of this, it may be beneficial for clinicians caring for a pregnant woman with a CUA to seek the advice of a clinician with expertise in preterm birth. This would also allow collection of further data to support better recommendations in the future.

5. Management options

While there is an unclear but probable 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 unproven and debatable. Women diagnosed with a complex CUA may require psychosocial support and counselling to address functional and emotional effects.[21] Future fertility options should be discussed with adolescents and their parents/guardians. The presence of associated renal tract anomalies must 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 at term, with an associated reduction in long term neonatal morbidity and mortality.

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 (if the horn is communicating with the cavity of the other horn).

5.2 Non-obstructive CUAs

Bicornuate and didelphic uteri (unification or fusion defects)

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. However, 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 on the uteri of women with past histories of repeated pregnancy loss or preterm deliveries is very limited. Only one controlled study[27] of 21 women with bicornuate uteri, 13 of whom did not undergo surgery and eight who underwent abdominal metroplasty, records no improvement in obstetric outcomes.

Septate uterus (resorption or canalisation defects)

Hysteroscopic metroplasty or hysteroscopic trans-cervical division of the uterine septum has been considered by many as the treatment of choice for septate uterus.[21] 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 3D 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 the endometrium prior to hysteroscopic division of the septum.[28,29] 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.[21] Moving the hysteroscope from side to side and visualisation of both ostia on a panoramic view from the level of internal os (subjective criteria), or using a graduated intrauterine palpator to objectively check the portion of septum resected, verifies completion of resection.[30] 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 IUAs 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 IUAs after operative hysteroscopy.[31] 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.[31] While there is no evidence of benefit of using IUDs 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 IUAs after septum division.[32] Re-evaluation by second-look hysteroscopy at 1–3 months postoperatively can be offered to evaluate adhesion formation and any residual septum. While observational studies[33,34] suggest that the uterine cavity is healed 2 months after septal division, there is insufficient evidence to advocate a specific length of time before a woman should conceive after the procedure.

The only randomised controlled study[47], albeit small sample size (n=80), having broad inclusion criteria and taking a long time (2010-2018) to recruit, questioned rationale behind the septal division due to lack of benefit observed. However, systematic reviews of published controlled studies[4, 48,49] have shown reduced miscarriage rates, but conflicting data on live birth rates. A systematic review and meta-analysis of six untreated controlled studies[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; I^2 = 0%,

six studies, n=191). There was no difference in conception rates (RR 1.14, 95% CI 0.79–1.65; I^2 = 80%, four studies, n=408) and preterm delivery rates (RR 0.66, 95% CI 0.29–1.49; I^2 = 0%, six studies, n=325) 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[37] published in 2011 reported insufficient evidence for hysteroscopic metroplasty in women with recurrent miscarriage and a septate uterus and advised against offering this intervention as routine practice. A more updated Cochrane review[38] published in 2017 did not identify any published randomised controlled studies assessing the efficacy in pregnancy outcomes after hysteroscopic metroplasty. The Randomised Uterine Septum Transsection Trial (TRUST)[39] to assess whether hysteroscopic septum resection improves reproductive outcomes in women with a septate uterus and a history of (recurrent) miscarriage, subfertility or preterm birth conducted at seven centres across Netherlands, UK, USA and Iran reported similar rates of live births of conceptions achieved within 12 months follow-up after randomisation in the treated group compared with untreated controls (12/39, 31% vs 14/40, 35%; RR 0.88, 95% CI 0.47-1.65). Miscarriage rates (28% vs 13%, RR 2.3, 95% CI 0.86-5.9) and preterm births were also similar (13% vs 10%, RR 1.3, 95% CI 0.37-4.4) [47] . A pilot single-centred randomised controlled trial of hysteroscopic septal resection in women with septate uteri, history of miscarriage or preterm birth, or infertility had been proposed in the UK, but has not been feasible because of difficulty in recruiting women and clinicians to participate – a problem experienced by the authors of the TRUST trial also.[40]

An updated systematic review (2022) of comparative studies evaluating effectiveness of septal division included 22 studies with 14 of them comparing with untreated controls and 8 studies comparing with women having normal uterine cavity [48]. Over all, the live birth rates were similar between the treated and untreated group (OR 1.14, 95% CI 0.67-1.96; I^2 = 67%; eight studies, n= 1304). On subgroup analysis, the live birth rates were similar between the treated and untreated controls for recurrent miscarriage population (OR 1.33, 95% CI 0.34-5.16; I^2 = 62%; two studies, n= 180), primary subfertility (OR 1.05, 95% CI 0.16-6.63; I^2 = 77%; two studies, n= 205) and mixed population (OR 1.05, 95% CI 0.45-2.46; I^2 = 76%; four studies, n= 740). The spontaneous miscarriage rate was lower in treated group compared to untreated group (OR 0.5, 95% CI 0.27-0.93; I^2 = 71%; 13 studies, n= 1145). Similar trend was seen for recurrent miscarriage (OR 0.28, 95% CI 0.08-0.98; I^2 = 66%; three studies, n= 171) and primary subfertility (OR 0.21, 95% CI 0.06-0.77; I^2 = 55%; four studies, n= 401) population. Miscarriage rate was similar in the treated group and normal uterus group (OR 1.25, 95% CI 0.89-1.76; I^2 = 26%; four studies, n= 2079) showing an improved outcome in the treated group. However, hysteroscopic septal division has not shown to reduce preterm delivery rates when compared to treated control group (OR 1.06, 95% CI 0.74-1.52; I^2 = 1%; 15 studies, n= 1690) and intact uterus group (OR 2.47, 95% CI 1.80-3.38; I^2 = 52%; five studies, n= 6341). While malpresentation rate was lower in the treated group, caesarean section rates and post-partum haemorrhage were higher in the treated groups compared to controls. While this review showed a reduced miscarriage rates and malpresentations with septal division, the live birth rates and pre-term births were similar. The studies included were heterogeneous in population and varying in definition of uterine septum.

A systematic review in 2023 of 5 cohort studies and 22 case series analysed reproductive outcome of natural pregnancies following septal surgery in patients with recurrent miscarriage, primary subfertility or secondary subfertility [49]. In recurrent miscarriage population, it reported septal surgery was associated with an increased live birth rate (RR, 1.77; 95% CI, 1.26-2.49, I^2 = 0%; three studies, n= 245), reduced miscarriage rate (RR, 0.36; 95% CI, 0.20-0.66, I^2 = 0%; two studies, n= 91) and reduced preterm birth rate (RR, 0.15; 95% CI, 0.04-0.53, I^2 = 0%; two studies, n= 61). In primary subfertility, septal surgery was associated with an increased live birth rate (RR, 4.12; 95% CI, 1.19-14.29, I^2 = 0%; two studies, n= 143), reduced miscarriage rate (RR, 0.19; 95% CI, 0.06-0.56, I^2 = not reported; two studies, n= 51) and similar preterm birth rate (RR, 0.44; 95% CI, 0.10-2.02, I^2 = not reported; two

studies, n= 39). The authors could not draw data for secondary subfertility population due to lack of any specific comparative studies.

While systematic reviews of controlled studies have reported conflicting results on live births, preterm births or caesarean sections, the miscarriage rates were reduced on meta-analysis of controlled studies in recurrent miscarriage and primary subfertility population. However, high-quality evidence on the efficacy and safety of surgical treatment is still lacking and majority of published studies consider all septate uteri as a single group, albeit different subtypes of uterine septum depending on its length, width, histological and cellular types may have varying effect on fertility and reproductive outcome.

While hysteroscopic septal division is a relatively safe procedure in experienced hands, it is not without risks. TRUST trial reported one uterine perforation in the treated group (1/39, 2.6%) [47]. The complication rate was 4.6% (7/151; three uterine perforations, three excessive blood loss and one fluid overload) in the large cohort study published by Rikken et.al. (2020) [50]. Heinonen (1997) [51] and Valli et. al (2004) [52] reported 3.1% (1/32) and 3.6% (1/28) of perforation during hysteroscopic septal division. Preoperative 3D ultrasound scanning with accurate measurement of septal length and concurrent live scanning during the procedure may improve the safety of septal division[53].

NICE has produced guidance on hysteroscopic metroplasty of a uterine septum for recurrent miscarriage and for primary infertility,[41,42] which states that women with recurrent miscarriage should be offered hysteroscopic metroplasty of a uterine septum 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 states 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[18,43] 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 (2013), ASRM (2016), CUME (2018) and ASRM (2021) criteria are attempts to define CUAs objectively based on 3D ultrasound measurements. Accurate 3D ultrasound measurements of external and internal fundal indentation should be made and recorded in every case to build up a sufficiently large database. It is recommended to record data of septal measurements, details of septal resection and associated reproductive outcomes. The reported classifications could then be evaluated and refined, according to observed reproductive outcomes.
- While 2D pelvic TVS 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, it is important to advise women with a CUA, depending on the type and severity, of the increased risks, not only of first or second trimester miscarriages, preterm labour, fetal malpresentation, but also fetal growth problems and pre-eclampsia. Women with a major fusion or unification defect essentially have unilateral placental implantation, which could lead to functional exclusion of one uterine artery from the uteroplacental circulation. This is linked to placental insufficiency, fetal growth problems and stillbirth.

- For women with recurrent miscarriage, hysteroscopic resection of a uterine septum may be considered on an individualised basis by experienced specialists because of probable benefit in these women. Treatment for incidentally diagnosed septum in infertile women is debatable and needs further study. If surgery is planned, women should be fully informed of the limited evidence on its efficacy and of intraoperative and postoperative risks associated with surgery. The unit offering management of CUAs should ensure that appropriate arrangements for clinical governance and audit are in place.
- Adequately powered multicentre randomised control studies assessing reproductive outcomes after hysteroscopic resection of uterine septum in women with recurrent miscarriages and/or recurrent implantation failure after assisted reproduction are warranted to generate evidence-based recommendations.
- Currently, abdominal or laparoscopic metroplasty for fusion or unification defects is generally not advisable owing to its potential association with significant intraoperative and postoperative complications and lack of evidence to support improved reproductive outcomes.
- Owing to the association between CUAs and renal tract abnormalities, clinicians should consider imaging the renal tract of women with CUAs.
- All women with CUAs (e.g. unicornuate, bicornuate, didelphys or septate uterus, depending on its severity) and those treated with hysteroscopic resection of uterine septum should be followed up by 12 weeks using an appropriate preterm birth care pathway as outlined in UK Preterm Birth Clinical Network Guidance. The guidance states all acute maternity units should offer basic measures to identify and manage women at high risk of preterm birth (Level 1), and more specialised care can be provided by more specialised centres within or adjacent to each Local Maternity System which can provide additional services such as high vaginal or transabdominal cerclage (Level 2).

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688 7;51(1):125-134.
689

This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
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The chair of the Scientific Advisory Committee was: Professor Katie Morris, MRCOG

All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this Scientific Impact Paper is available from: https://www.rcog.org.uk/en/guidelinesresearch-services/guidelines/sipXX/.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The paper will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

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