Human Reproduction Update, Vol.14, No.5 pp. 415–429, 2008 doi:10.1093/humupd/dmn018
Advance Access publication June 6, 2008

Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal

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BACKGROUND: The prevalence of congenital uterine anomalies in women with reproductive failure remains unclear, largely due to methodological bias. The aim of this review is to assess the diagnostic accuracy of different methodologies and estimate the prevalence of congenital uterine anomalies in women with infertility and recurrent miscarriage (RM). METHODS: Studies from 1950 to 2007 were identified through a MEDLINE search; all relevant references were further reviewed. RESULTS: The most accurate diagnostic procedures are combined hysteroscopy and laparoscopy, sonohysterography (SHG) and possibly three-dimensional ultrasound (3D US). Two-dimensional ultrasound (2D US) and hysterosalpingography (HSG) are less accurate and are thus inadequate for diagnostic purposes. Preliminary studies ($n = 24$) suggest magnetic resonance imaging (MRI) is a relatively sensitive tool. A critical analysis of studies suggests that the prevalence of congenital uterine anomalies is ~6.7% [95% confidence interval (CI), 6.0–7.4] in the general population, ~7.3% (95% CI, 6.7–7.9) in the infertile population and ~16.7% (95% CI, 14.8–18.6) in the RM population. The arcuate uterus is the commonest anomaly in the general and RM population. In contrast, the septate uterus is the commonest anomaly in the infertile population, suggesting a possible association. CONCLUSIONS: Women with RM have a high prevalence of congenital uterine anomalies and should be thoroughly investigated. HSG and/or 2D US can be used as an initial screening tool. Combined hysteroscopy and laparoscopy, SHG and 3D US can be used for a definitive diagnosis. The accuracy and practicality of MRI remains unclear.

Keywords: congenital uterine anomalies; infertility; prevalence; recurrent miscarriage

Introduction

Congenital uterine anomalies have been clearly implicated in women suffering with recurrent miscarriage (RM) (Acien, 1993; Raga *et al*., 1997; Grimbizis *et al*., 2001; Kupesic, 2001). In women with infertility, however, the role of these anomalies, and particularly that of the septate uterus, remains unclear (Homer *et al*., 2000; Taylor and Gomel, 2008). Correct assessment of the prevalence of these anomalies in the RM and infertile populations, and comparison to the general population, will help make any association more apparent. For any population group, the exact prevalence of congenital uterine anomalies is difficult to elucidate mainly due to three reasons:

(i) Different diagnostic procedures used;
(ii) Subjectivity of the diagnostic criteria used (Grimbizis *et al*., 2001; Woelfer *et al*., 2001) and
(iii) Inconsistent interpretation of the classification of congenital uterine anomalies (Salim *et al*., 2003b)

There are a number of studies which have investigated the prevalence of congenital uterine anomalies in the RM, infertile and general population. However, they lack consistency in the characteristics of each population examined and homogeneity in the diagnostic methods used. Previous reviews (Acien, 1997; Nahum, 1998; Propst and Hill, 2000; Grimbizis *et al*., 2001; Kupesic, 2001; Troiano and McCarthy, 2004) have not taken these two factors into account when assessing the prevalence of these anomalies. This critical review attempts to determine the true prevalence of congenital uterine anomalies in three populations. This is achieved by assessing and taking into account the accuracy of different diagnostic procedures, and considering the characteristics of different patient groups.

Materials and Methods

Literature search

Articles were identified through a MEDLINE search (1950–2007). References of all relevant articles were hand-searched for additional citations. There were no language restrictions.

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Accuracy of diagnostic procedures

Identification of the presence of congenital uterine anomalies

Studies comparing the diagnostic accuracy of different procedures used for assessing congenital uterine anomalies were identified. From these, the studies comparing hysterosalpingography (HSG), sonohysterography (SHG), 2D ultrasound (2D US), 3D ultrasound (3D US) and magnetic resonance imaging (MRI) to hysteroscopy were selected for analysis. This is because hysteroscopy allows for the direct visualization of the internal uterine contour, and was considered the most valid method of identifying the presence of an anomaly (but not the different subtypes). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each diagnostic procedure were individually calculated for each study. The value of total correct predictions (accuracy), which is dependent on the prevalence and is of more clinical significance (Altman, 1991), was also estimated using the formula:

$$\text{Accuracy} = \frac{\begin{array}{l}\text{Number of true positives}\\ +\text{Number of true negatives}\end{array}}{\begin{array}{l}\text{Numbers of true positives} + \text{false positives}\\ +\text{false negatives} + \text{true negatives}\end{array}}$$

Finally, the weighted mean values of sensitivity, specificity, PPV, NPV and accuracy were estimated for each procedure from all the studies.

Identification of congenital uterine anomaly subtypes

Studies assessing the accuracy of different procedures in diagnosing specific subtypes of congenital uterine anomalies were similarly reviewed. These reports compared the findings of each methodology to a definitive diagnosis made by means of visualization of both the internal and external uterine contour (e.g. hysteroscopy and laparoscopy).

Classification of diagnostic procedures

Following analysis, the diagnostic procedures were ranked into three classes (I–III) according to their diagnostic accuracy.

Class I.

Ia: Investigations capable of accurately identifying congenital uterine anomalies and classifying them into appropriate subtypes (accuracy $>90\%$).

Ib: Investigations capable of correctly identifying congenital uterine anomalies (accuracy $>90\%$) without being able to classify them into appropriate subtypes.

Class II.

Investigations capable of identifying congenital uterine anomalies with accuracy $<90\%$.

Class III.

Investigations of which the accuracy in identifying congenital uterine anomalies is uncertain.

Assessing the prevalence of congenital uterine anomalies

Studies assessing the prevalence of congenital uterine anomalies in three different populations: general/fertile, infertile and RM, were identified. Studies were excluded when the population examined or the diagnostic methods used, were not accurately defined. Studies were then grouped into three classes (I–III), as described above, according to the diagnostic procedures they used. The mean overall and subtype prevalence of congenital uterine anomalies (for each population group) were then estimated from each class of study.

Uterine development

Embryology

The uterus is formed at around 8–16 weeks of fetal life from the development of the two paired paramesonephric ducts, called Müllerian ducts. The process involves three main stages (Letterie, 1998; Braun *et al*., 2005):

(i) Organogenesis: the development of both Müllerian ducts.
(ii) Fusion: the lower Müllerian ducts fuse to form the upper vagina, cervix and uterus; this is termed lateral fusion. The upper cranial part of the Müllerian ducts will remain unfused and form the Fallopian tubes.
(iii) Septal absorption: after the lower Müllerian ducts fuse, a central septum is left which starts to resorb at ~9 weeks eventually leaving a single uterine cavity and cervix.

It is also important to note the role of the mesonephric (or Wolffian) ducts. These are a precursor and inducer of female reproductive tract development, and play a crucial role in renal development (Hannema and Hughes, 2007). In addition, they act with the Müllerian tubercle to form part of the vagina. As a result, abnormalities originating from mesonephric maldevelopment may also have an effect on genital tract and uterine formation (Acien *et al*., 2004).

This is reflected in the fact that up to 60% of women with unilateral renal agenesis have been shown to have genital anomalies (Barakat, 2002), most commonly a unicornuate uterus (Troiano and McCarthy, 2004). Interestingly, ~40% of all patients with a unicornuate uterus suffer from renal abnormalities (Fedele *et al*., 1996), while one study showed that >80% of patients with a uterus didelphys suffered from renal agenesis (Li *et al*., 2000). Consequently, the detection of a congenital renal abnormality should alert the physician to look for associated genital anomalies and vice versa (Oppelt *et al*., 2007).

Genetics

The role of genetic factors in the development of uterine anomalies remains unclear (Kobayashi and Behringer, 2003). A study of 1397 cases by Hammoud *et al*. (2008) showed that there is strong evidence for familiality contributing to congenital uterine anomalies, with first-degree relatives having a 12-fold risk of developing an abnormality. However, a specific genetic aetiology for each type of anomaly was considered unlikely, as members of the same family had different phenotypic expressions of uterine anomalies. The authors concluded that in addition to genetic predisposition, socioeconomic and geographic factors may also play a role, as the pattern of familial clustering was shown to be consistent with polygenetic/multifactorial disorders.

Interestingly, Rabinson *et al*. (2006) in a study of 24 women with uterine anomalies, found that 22.7% had an undiagnosed sensorineural hearing loss (200-fold higher rate than expected). Similar findings have been previously reported in the literature

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(Letterie and Vauss, 1991). Although the authors of this study were unable to identify a possible mutation contributing to this association, they suggested routine referral of all patients with congenital uterine anomalies for audiometric testing (Rabinson *et al*., 2006).

Nevertheless, there has been recent progress in understanding certain genetic processes that underlie genital tract development (Kobayashi and Behringer, 2003; Hannema and Hughes, 2007). Several genes, such as *Pax2* (paired box gene 2), *Pax8* (paired box gene 8), *Lim1* (LIM homeobox 1) and *Emx2* (empty spiracles homeobox 2), have been implicated in the development of the Wolffian and Müllerian ducts, although most data has been derived from mouse knockout studies (Hannema and Hughes, 2007). In addition, genes responsible for certain human syndromes that also affect the reproductive tract have been identified. Examples include maturity-onset diabetes of the young type V (*TCF2* mutation), McKusick–Kaufman syndrome (*MKKS* mutation), persistent Mullerian duct syndrome type I and II (*MIS* and *MISR2* mutations) and hand–foot–genital syndrome (*HOXA13* mutation) (Kobayashi and Behringer, 2003).

Classification of congenital uterine anomalies

Congenital uterine anomalies may arise from malformations at any step of the Müllerian developmental process (Devi Wold *et al*., 2006). Buttram and Gibbons (1979) first proposed a classification of the congenital uterine anomalies based on the degree of failure of the Müllerian ducts to develop normally, and divided them into groups with similar clinical manifestations, treatments and prognosis. This was revised and modified first in 1983 and then in 1988 by the American Society of Reproductive Medicine (formerly known as the American Fertility Society) to provide a classification which is now the most widely accepted and used worldwide (Fig. 1) (Letterie, 1998). This consists of seven groups, some with further subdivisions (Devi Wold *et al*., 2006):

(i) Müllerian agenesis or hypoplasia
   a) Vaginal
   b) Cervical
   c) Fundal
   d) Tubal
   e) Combined

(ii) Unicornuate uterus (agenesis or hypoplasia of one of the two Müllerian ducts)
   a) With a communicating rudimentary horn
   b) With a non-communicating rudimentary horn
   c) With a rudimentary horn with no cavity
   d) With an absent rudimentary horn

(iii) Didelphys uterus (failure of lateral fusion of the vagina and uterus Müllerian ducts)

(iv) Bicornuate uterus (incomplete fusion of the uterine horns at the level of the fundus)
   a) Complete
   b) Partial

(v) Septate uterus (absent or incomplete resorption of the uterovaginal septum)
   a) Complete
   b) Partial

(vi) Arcuate uterus (a mild indentation at the level of the fundus from a near-complete resorption of the uterovaginal septum)

(vii) Diethylstilbestrol (DES) exposed uterus (T-shaped uterus resulting from DES exposure of the patient *in utero*)

One limitation of this classification is that it does not specify the diagnostic methods or criteria that should be used in order diagnose the anomalies and as a result this is solely based on the subjective impression of the clinician performing the test (Woelfer *et al*., 2001).

In addition, this classification is by no means comprehensive. A number of rarer anomalies, such as a hypoplastic non-cavitated uterus with two rudimentary horns (Sadik *et al*., 2002), a uterus with a vaginal anastomosis and cervical atresia (Deffarges *et al*., 2001), a septate uterus with cervical duplication and a longitudinal vaginal septum (Wai *et al*., 2001; Pavone *et al*., 2006) and a normal uterus with a double cervix and vagina, and a blind cervical pouch (Dunn and Hantes, 2004) are not included. For this reason, the American Fertility Society classification system should function as a framework for the description of anomalies, rather than an exhaustive list of all possible anomaly types. Consequently, clinicians faced with complex or combined uterine anomalies, should try to describe them according to their component parts

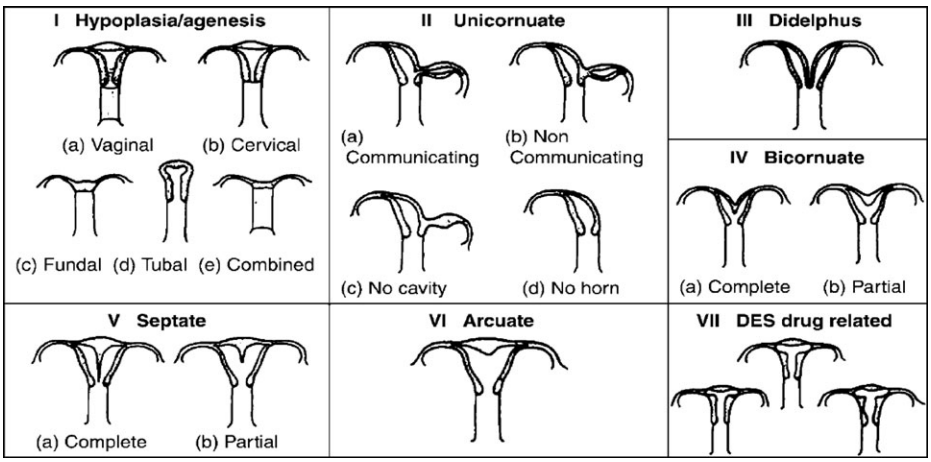

Figure 1: Classification of congenital uterine anomalies as described by the American Fertility society (1988).

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rather than categorize them into the class that most approximates the dominant feature (Troiano and McCarthy, 2004).

The above concept has been incorporated in another more recent classification proposed by Oppelt *et al.* (2005): the VCUAM classification. This intends to make the description of complex genital anomalies easier by subdividing external and internal female genital organs into the following subgroups: vagina (V), cervix (C), uterus (U), adnexa (A) and associated malformations (M). An anomaly is therefore graded individually for each anatomical structure. For example, a particular case of uterus didelphys could be described as: V2b (complete septate vagina), C1 (duplex cervix), U2 (bicornate uterus), A0 (normal adnexa) and M0 (no associated malformations) (Oppelt *et al.*, 2005).

Finally, Acien *et al.* (2004) have stressed the importance of considering the embryological origin of the different elements of the genitourinary tract in order to understand and effectively treat complex genital tract anomalies. For this reason, they proposed the revised 'Clinical and embryological classification of the malformations of the female genital tract', which classifies anomalies according to their embryological origin, and includes changes in the vagina, adnexa and renal system in addition to those of the uterus (Acien *et al.*, 2004).

Diagnostic procedures: characteristics and accuracy

Hysterosalpingography

HSG, first performed by Rindfleisch in 1910 (Golan *et al.*, 1989), is a widely acceptable and available diagnostic tool. It provides valuable information regarding the interior cavity of the uterus. When it shows a unicornuate uterus, however, a second cervical opening must be considered; if it is found, further injection of contrast into the cervix may lead to the diagnosis of a uterine didelphys or a complete septate uterus (Letterie, 1998). In assessing a unicornuate uterus with HSG, blocked or non-communicating rudimentary horns will not appear on film (Propst and Hill, 2000). This is of significance as studies have reported that in patients with such anomaly, 13% of pregnancies occur in the non-communicating rudimentary horn, secondary to transmigration of sperm (Letterie, 1998). As this would warrant removal of the rudimentary horn due to possible rupture, it is of great importance that non-communicating rudimentary horns are correctly identified and differentiated. By removing rudimentary horns, dysmenorrhoea and endometriosis (caused by retrograde menstrual effluent) may also be reduced or prevented (Taylor and Gomel, 2008). Transabdominal US has demonstrated 85% sensitivity and 100% specificity in diagnosing the presence of a rudimentary horn, and 80% sensitivity and 100% specificity in assessing the presence of a cavity in that horn. This was shown to be more accurate than a laparoscopic investigation (Letterie, 1998). In cases where clear US imaging is not achieved, MRI could be of use.

HSG does not evaluate the external contour of the uterus and therefore it cannot reliably differentiate between a septate and a bicornuate uterus (Kupesic, 2001; Troiano and McCarthy, 2004; Braun *et al.*, 2005). Some authors suggest that an angle of $<75^{\circ}$ between the uterine horns is suggestive of a septate uterus and an angle of $>105^{\circ}$ indicates a bicornuate uterus (Letterie, 1998; Troiano and McCarthy, 2004). Interestingly, an angle of $<60^{\circ}$ has been used for identifying septate uteri in MRI and US imaging (Letterie, 1998). However, a diagnostic accuracy of 55% in differentiating between the two has been reported in the past (Reuter *et al.*, 1989), although the criteria used in this study are not known. Small septal defects can also be missed with HSG (Homer *et al.*, 2000). In contrast, it has been considered accurate in diagnosing most DES-linked uterine anomalies (Nguyen *et al.*, 1997).

HSG has been reported to produce pain in more than half the patients, although often not severe enough to require analgesia (Homer *et al.*, 2000). Guimaraes Filho *et al.* (2006a) reported that 93.3% ($n = 56$) of women experienced moderate to severe pain during HSG, although they did not mention whether analgesia was required. In contrast, Tur-Kaspa *et al.* (1998) in a prospective randomized blinded study of 61 patients, found that from a pain scale of 0–10 (10 being very severe pain) women scored HSG as being 5.6 ± 2 when a metal cannula was used and 3.8 ± 2 when a balloon catheter was used. The difference reached statistical significance, and the authors concluded that balloon catheter HSG is superior to the traditional metal cannula technique, as it also requires significantly less fluoroscopic time, a smaller amount of contrast agent, is easier for the physician to perform and allows for concurrent transcervical tubal catheterization (Tur-Kaspa *et al.*, 1998).

Complications of HSG include pelvic inflammatory disease, particularly if the patient has previous tubal disease or is *Chlamydia trachomatis* positive (Homer *et al.*, 2000). Bleeding, and rarely reaction to the contrast media or uterine perforation may also occur (Simpson *et al.*, 2006). In addition, there is exposure to radiation and iodinated contrast media, although this has been shown to be within the safety limits (Letterie, 1998; Homer *et al.*, 2000).

There have been a number of reports assessing the diagnostic accuracy of HSG versus hysteroscopy. A summary of the reports is shown in Table I.

Although the weighted mean of sensitivity and specificity of HSG according to our review is ~78 and 90% respectively, this investigation seems to be poor in differentiating between classes of congenital anomalies. Alborzi *et al.* (2003) reported only 25% sensitivity in diagnosing bicornuate uteri. Furthermore, Pellerito *et al.* (1992), in an attempt to categorize congenital abnormalities into different types, found HSG to be incorrect in all 20 cases.

In conclusion, HSG remains a useful screening tool for the diagnosis of a normal or abnormal uterine cavity (Letterie, 1998). It has a good sensitivity for diagnosing uterine malformations with a more aggressive morphological expression (Soares *et al.*, 2000); however, it cannot reliably differentiate between different types of congenital uterine anomalies.

Two-dimensional ultrasound

Transabdominal or transvaginal US is a readily available diagnostic tool which is widely accepted and used. In assessing the presence of congenital uterine anomalies it may play a useful role. The advantage of US is that it allows measurements and quantification of observations to be made. However, there are no universally accepted criteria for the US diagnosis of congenital uterine anomalies. Different authors appeared to implement their own criteria. In a double cavity appearance of a uterus on US, Fedele *et al.*

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Table I. Sensitivity, specificity, PPV and NPV of HSG compared with hysteroscopy in diagnosing congenital uterine anomalies (Total cases $n = 625$).

Study	Cases, *n*	Sensitivity	Specificity	PPV	NPV	Accuracy
Alatas *et al*. (1997)	62	100	100	100	100	100
Brown *et al*. (2000)	46	100	100	100	100	100
Traina *et al*. (2004)	80	100	97	85	100	96
Valenzano *et al*. (2006)	54	91	100	100	94	96
Keltz *et al*. (1997)	18	90	20	53	67	58
Raziel *et al*. (1994)	60	74	59	62	72	67
Alborzi *et al*. (2003)	186	70	92	83	88	83
Guimaraes Filho *et al*. (2006a)	54	63	98	83	94	85
Soares *et al*. (2000)	65	44	96	67	92	75
Weighted mean		78	90	83	91	86

PPV, positive predictive value; NPV, negative predictive value.

(1989) and Troiano and McCarthy (2004) consider a uterus to be septate rather than double (i.e. bicornuate or didelphys) when there is a fundal distal border indentation of 5 mm above the line joining the two ostia (interostial line) or less. In contrast, Wu *et al*. (1997), Letterie (1998) and Woelfer *et al*. (2001) consider the uterus to be septate when the fundal indentation is <10 mm below the interostial line. There have also been quotes of a threshold of 10 mm of fundal indentation used in laparoscopy (Troiano and McCarthy, 2004). The use of an angle of $<60^{\circ}$ between the two indenting medial margins of the fundus can similarly be used to distinguish between the septate and bicornuate uterus. Nicolini *et al*. (1987) reported that using these criteria, 92% sensitivity and 100% specificity in diagnosing bicornuate uteri can be achieved. However, the value of these criteria remains unclear. The measurement of the serosal-endometrial thickness of the uterus along its fundal border in longitudinal sections could also be used as a criterion to aid diagnosis; in the septate uterus the thickness should increase reaching the midline as the septate becomes apparent (Letterie, 1998). However, there is no evidence in the literature of such criteria which describe the septate uterus and differentiate it from the arcuate deformity.

Pooled data from reports comparing 2D US and hysteroscopy suggest low sensitivities of under 60% but high specificities of nearly 100%. Results from these studies are summarized in Table II.

Although some authors in the past have quoted an accuracy of 90–92% in diagnosing congenital uterine anomalies (Byrne *et al*., 2000; Troiano and McCarthy, 2004), we failed to find valid reports (comparing 2D US to hysteroscopy) showing sensitivities of $>90\%$. There seems to be a pattern of low sensitivities coupled with high specificities with 2D US imaging. This suggests that although 2D US can only identify about half of the congenital uterine anomalies present, its diagnosis is very likely to be correct (due to its very low false positive rate). Therefore, it could prove to be a very effective screening tool in conjunction with HSG since they are both widely available.

Sonohysterography

SHG is also known as hysterosonography or saline-infused sonography (Devi Wold *et al*., 2006). It uses the introduction of fluid into the uterine cavity to enhance US imaging studies. It therefore improves the internal delineation of the uterine contour. It is a safe procedure (Hamilton *et al*., 1998) and not particularly painful for the patient (Alborzi *et al*., 2003). Guimaraes Filho *et al*. (2006a) reported that 21.7% ($n = 13$) women undergoing SHG experienced some degree of pain, which was however significantly reduced compared to HSG or hysteroscopy. Kelekci *et al*. (2005) also reported significantly lower pain scores for SHG compared to hysteroscopy (4.3/10 versus 7.2/10; $P = 0.042$).

Reports comparing SHG with hysteroscopy have suggested that SHG is highly accurate in both diagnosing and categorizing congenital uterine anomalies. The weighted mean sensitivity and specificity was 93 and 99%, respectively. A summary of the reports reviewed are shown in Table III.

It appears that SHG is a safe procedure which provides more information about uterine abnormalities than HSG or US alone (Devi Wold *et al*., 2006). It seems to be accurate not only in diagnosing congenital uterine anomalies, but also in classifying them into

Table II. Sensitivity, specificity, PPV and NPV of 2D US compared with hysteroscopy in diagnosing congenital uterine anomalies (Total cases, $n = 350$).

Study[a]	Cases, *n*	Sensitivity	Specificity	PPV	NPV	Accuracy
Valenzano *et al*. (2006)	54	86	100	100	91	94
Alatas *et al*. (1997)	62	50	100	100	97	87
Nicolini *et al*. (1987)	89	43	98	94	68	76
Traina *et al*. (2004)	80	64	99	88	94	86
Soares *et al*. (2000)	65	44	100	100	92	84
Weighted mean		56	99	96	87	84

[a]Studies by Raga *et al*. (1996) and Jurkovic *et al*. (1995) are not included due to inadequate diagnostic method of comparison used.

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Table III. Sensitivity, specificity, PPV and NPV of SHG compared with hysteroscopy in diagnosing congenital uterine anomalies (Total cases, $n = 486$).

Study	Cases, *n*	Sensitivity	Specificity	PPV	NPV	Accuracy
Alatas *et al*. (1997)	62	100	100	100	100	100
Brown *et al*. (2000)	46	100	100	100	100	100
Keltz *et al*. (1997)	18	100	100	100	100	100
Valenzano *et al*. (2006)	54	100	100	100	100	100
Guimaraes Filho *et al*. (2006a)	55	100	94	73	100	92
Alborzi *et al*. (2003)	186	91	100	100	96	97
Soares *et al*. (2000)	65	73	100	100	97	93
Weighted mean		93	99	97	98	97

appropriate groups (Alborzi *et al*., 2002; Ventolini *et al*., 2004; Valenzano *et al*., 2006).

Three-dimensional ultrasound

As in the case of 2D US, 3D US is a non-invasive method of investigation. 3D US works by attaining an initial 2D US image of the uterus and storing it onto a computer. A vaginal transducer then performs a sweep of transversal sections which are also subsequently stored. The computer then integrates the images and allows the investigator to view images of three planes simultaneously (Raga *et al*., 1996). This 3D image, along with the complete volume scan, can be stored for later viewing and appraisal (Devi Wold *et al*., 2006). As discussed above, both 2D and 3D US allow for the uterine dimensions to be measured, which could help in quantifying the morphological defects (Salim and Jurkovic, 2004). The introduction of appropriate criteria could improve the homogeneity of diagnoses in the future. A study by Salim *et al*. (2003b) evaluated the inter-observer variability of 83 US volumes using two different observers, who were blind to each other's findings. The results showed a 99% agreement between the two observers, suggesting that this investigation is highly reproducible.

Unfortunately, there have not been many reports comparing the accuracy of 3D US to hysteroscopy and or laparoscopy. Four reports identified in the literature, containing an overall of 679 subjects, all reported 100% sensitivity, specificity, PPV, NPV and accuracy of 3D US in diagnosing congenital uterine anomalies, when compared with hysteroscopy (Wu *et al*., 1997; Radoncic *et al*., 2000; Makris *et al*., 2007a, b). However, in the studies by Makris *et al*. (2007a, b), only a small number of congenital uterine anomalies were identified ($n = 6$) in the groups of women screened. Two other studies were excluded as their method of comparison were investigations other than hysteroscopy (Jurkovic *et al*., 1995; Raga *et al*., 1996).

In conclusion, reports suggest that 3D US has a very high accuracy rate in diagnosing congenital uterine anomalies. Wu *et al*. (1997) further showed that it is accurate in classifying the anomalies, although further studies are required to confirm this. With the prospect of an introduction of a classification based on 3D US criteria, this method seems promising.

Hysteroscopy

Hysteroscopy allows direct visualization of the intrauterine cavity and ostia. It is therefore very accurate in identifying congenital uterine anomalies and is often used to establish a definitive diagnosis after an abnormal HSG finding (Letterie, 1998; Soares *et al*., 2000; Homer *et al*., 2000). However, it does not allow for the evaluation of the external contour of the uterus and is therefore often inadequate in differentiating between different anomaly types. Consequently, for the correct differentiation between bicornuate and septate uteri, further investigation is required, most commonly a diagnostic laparoscopy. Some authors consider this

Table IV. Classification of investigations according to diagnostic accuracy.

Class Ia
- Investigations capable of accurately identifying congenital uterine anomalies and classifying them into appropriate subtypes (accuracy >90%):
  - Hysteroscopy and laparoscopy
  - SHG
  - 3D US

Class Ib
- Investigations capable of accurately identifying congenital uterine anomalies (accuracy >90%) without being able to classify them into appropriate subtypes:
  - Hysteroscopy alone

Class II
- Investigations capable of identifying congenital uterine anomalies with an accuracy <90%:
  - HSG
  - 2D US

Class III
- Investigations of which the accuracy in diagnosing congenital uterine anomalies is uncertain:
  - MRI
  - Physical examination during pregnancy or delivery

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Table V. Prevalence of congenital uterine anomalies in the general/fertile population.

Class	Study	Country	Cases, *n*	Reason for investigation	Initial investigation	Definitive investigation	Total, *n* (%)	Hypoplastic, *n* (%)	Unicornuate, *n* (%)	Didelphys, *n* (%)	Bicornuate, *n* (%)	Septate, *n* (%)	Arcuate, *n* (%)	T-shaped, *n* (%)
Ia	Salim *et al.* (2003a)[a]	UK	1976	Not stated	2D TVS	3D US	105 (5.3)	–	1 (0.05)	–	4 (0.2)	28 (1.4)	72 (3.6)	–
	Woelfer *et al.* (2001)[a]	UK	1089	Non-obstetric	–	3D TVS	106 (9.7)	–	–	–	5 (0.5)	29 (2.7)	72 (6.6)	–
	Jurkovic *et al.* (1997)	UK	1047	Various	–	3D US	55 (5.3)							
	Tur-Kaspa *et al.* (2006)	Canada/ USA	409	Abnormal uterine bleeding	–	SHG	39 (9.5)	–	–	1 (0.2)	1 (0.2)	11 (2.7)	26 (6.4)	
Ib	Cooper *et al.* (1983)	–	323	Hysteroscopic sterilization	–	HSc	20 (6.2)							
II	Byrne *et al.* (2000)	USA	2065	Non-obstetric	–	TAS/TVS	8 (0.4)	–	–	3 (0.1)	3 (0.1)	2 (0.1)	–	–
	Raga *et al.* (1997)	Spain	1289	Tubal sterilization	–	HSG/Lap	49 (3.8)	–	2 (0.2)	1 (0.1)	5 (0.4)	20 (1.5)	21 (1.6)	–
	Simon *et al.* (1991)[b]	Spain	679	Tubal sterilization	–	HSG/Lap	22 (3.2)	–	–	1(0.1)	1 (0.1)	20 (2.9)	–	–
	Ashton *et al.* (1988)[c]	–	840	Transcervical sterilization	–	HSG	19 (2.3)		1 (0.1)	–		15 (1.8)	–	3 (0.4)
	Nasri *et al.*, 1990	UK	300	Multiple	–	2D TVS	8 (2.7)	–	–	2 (0.7)	–	6 (2.0)	–	–
	Acien (1997)[d]	Spain	241	Contraception	2D TVS	HSG/Lap	26 (10.8)	5 (2.1)	1 (0.4)	–	3 (1.2)	4 (1.7)	13 (5.4)	–
	Sorensen (1988)[e]	Denmark	111	Laparoscopic sterilization	–	HSG/Lap	6 (5.4)	–	1 (0.9)	1 (0.9)	–	4 (3.6)	–	–
III	Nahum (1998) [Review: 1947–1990][f]	–	571619	Pregnancy/ delivery	–	Various	927 (0.16)							

[a]May have similar cases; [b]Included in the study by Raga *et al.* (1997) and thus not included in Table VI; [c]Bicornuate/septate diagnosis not included in Table VI; [d]HSG and laparoscopy/laparotomy was not performed in all cases detected by TVS; [e]Author does not consider 'mild to moderate fundal excavations' a uterine structural abnormality; [f]Not included in Table VI. US, ultrasound; TVS, transvaginal ultrasound; TAS, transabdominal ultrasound; HSG, hysterosalpingography; SHG, sonohysterography; HSc, hysteroscopy; Lap, laparoscopy/Laparotomy.

combination (hysteroscopy/laparoscopy) to be the gold standard in evaluating congenital uterine anomalies (Hamilton *et al*., 1998; Letterie, 1998; Homer *et al*., 2000; Grimbizis *et al*., 2001; Taylor and Gomel, 2008). However, it can still be criticized for relying solely on the subjective impression of the clinician and not on strict diagnostic criteria (Woelfer *et al*., 2001). Hysteroscopy with laparoscopy offers the added advantage of concurrent treatment, as in the case of a uterine septum resection.

Bettocchi *et al*. (2007) recently proposed a new method for differentiating between a septate and bicornuate uterus with the use of office hysteroscopy alone, in a procedure that may also be performed without the use of anaesthesia or analgesia. Three criteria were used while assessing 260 patients with a double uterine cavity: the presence of vascularized tissue, sensitivity of the tissue based on its innervation, and its appearance at incision (if suspected to be a septum). In this series, 93.1% of the patients went on to successfully undergo an office hysteroscopic metroplasty during this procedure. In 15 of 18 (83%) patients who underwent laparoscopy, the diagnosis of a suspected bicornuate uterus was confirmed.

Ultimately, the main disadvantage of hysteroscopy is the invasiveness of the procedure which in the past was usually performed under general anaesthetic. Nowadays, hysteroscopy is often performed under local anaesthetic. Complications are similar to HSG although rarely air emboli or uterine perforation may also occur (Kupesic, 2001).

Magnetic resonance imaging

MRI offers a non-invasive approach of assessing the internal and external contour of the uterus. Criteria used to distinguished bicornuate from septate uteri are often similar to those used in US: a 10 mm threshold of fundal indentation, an intracornual distance of >4 cm or an angle between the two indenting medial margins of the fundus of $>60^\circ$ (Letterie, 1998). Pellerito *et al*. (1992) reported 100% accuracy ($n=24$) in assessing women with a surgically proven uterine anomaly; results were compared with hysteroscopy and laparoscopy. Fedele *et al*. (1989) reported 100% sensitivity ($n=4$) and 79% specificity (11/14) in diagnosing congenital uterine anomalies; however their results were compared to HSG and laparoscopy.

MRI seems a relatively sensitive tool and some authors suggest that it could supplant invasive procedures such as laparoscopy for the diagnosis of a double uterus (Nguyen *et al*., 1997). However, due to the lack of evidence more studies are required to confirm its diagnostic accuracy.

Which method to use

Overall, hysteroscopy and laparoscopy, SHG and 3D US are the most accurate investigations and can be used as diagnostic tools. Three-dimensional US offers the advantage of being non-invasive. SHG requires the introduction of fluid into the uterine cavity and this can often be uncomfortable. Hysteroscopy and laparoscopy are both invasive procedures; however they offer the advantage of concurrent diagnosis and treatment. Hysteroscopy alone can identify the presence of an anomaly but cannot accurately differentiate between the different subtypes.

Two-dimensional US is the least accurate method of investigation; however it is the most widely available and easiest to perform. If used in conjunction with HSG, it can increase accuracy and serve as a valuable screening tool, particularly in the absence of 3D US, or where SHG is not practiced. MRI seems to be more accurate than 2D US or HSG alone, and could potentially be used for screening. However, its diagnostic accuracy remains unclear. Disadvantages are that it is more expensive than US and HSG, and is not available in the office setting.

A summary and classification of the procedures reviewed according to their diagnostic accuracy is presented in Table IV.

Prevalence

In assessing the prevalence of congenital uterine anomalies, investigators have used different diagnostic methods, some of which may be more accurate than others. In this aggregate analysis we grouped the studies into three classes (as shown in Table IV) according to the diagnostic accuracy of the methods they used: i.e. class Ia studies used hysteroscopy/laparoscopy, SHG or 3D US; class Ib studies used hysteroscopy alone; class II studies used HSG or 2D US and class III studies used a methodology of uncertain accuracy. The prevalence was then estimated for each class of studies.

General population

Assessing the prevalence of congenital uterine anomalies in the general population poses added difficulties. Many congenital uterine anomalies remain asymptomatic and investigations such as HSG, hysteroscopy and laparoscopy would not be warranted in women without a particular indication. The studies reviewed in this paper include patients either undergoing sterilization or being investigated for non-obstetric reasons such as pelvic pain, ovarian cancer screening, abnormal bleeding and suspected fibroids (Woelfer *et al*., 2001). Consequently, the results are

Table VI. Prevalence of congenital uterine anomalies in the general/fertile population from selected series.

Class	Studies[a], *n*	Cases, *n*	Total, *n* (%)	Hypoplastic, *n* (%)	Unicornuate, *n* (%)	Didelphys, *n* (%)	Bicornuate, *n* (%)	Septate, *n* (%)	Arcuate, *n* (%)	T-shaped, *n* (%)
Ia	4	4521	305 (6.7)[b]	–	1 (0.03)	1 (0.03)	10 (0.3)	68 (2.0)	170 (4.9)	–
Ib	1	323	20 (6.2)							
II	6	4846	116 (2.4)	5 (0.1)	5 (0.1)	7 (0.1)	11 (0.3)[c]	36 (0.9)[c]	34 (0.7)	3 (0.1)
Total	11	9690	441 (4.6)	5 (0.1)	6 (0.1)	8 (0.1)	21 (0.3)	104 (1.3)	204 (2.4)	3 (0.03)

[a]Summary of studies shown in Table V; [b]Jurkovic *et al*. (1997) (n of anomalies=55) do not provide a breakdown of the congenital uterine anomalies they diagnosed, however their data has been used to estimate the Total prevalence according to Class Ia studies; [c]Ashton *et al*. (1988) (n of bicornuate/septate uteri=15) do not distinguish between bicornuate and septate uteri; therefore their data has not been used for the prevalence estimates of these two subtypes.

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Table VII. Prevalence of congenital uterine anomalies in the infertile population.

Class	Study	Country	Cases *n*	Infertility description	Initial investigation	Definitive investigation	Total *n* (%)	Hypoplastic *n* (%)	Unicornuate *n* (%)	Didelphys *n* (%)	Bicornuate *n* (%)	Septate *n* (%)	Arcuate *n* (%)	T-shaped *n* (%)
Ia	Ugur *et al.* (1995)[a]	Turkey	3332	Majority of patients	–	PE/US/HSG/HSc/ Lap/	167 (5.0)	47 (1.4)	13 (0.4)	11 (0.3)	26 (0.3)	61 (1.8)	9 (0.3)	–
	Tulandi *et al.* (1980)	Canada	2240	–	HSG	HSc or Lap	23 (1.0)	–	2 (0.1)	1 (0.05)	13 (0.6)	–	7 (0.3)	–
	Tur-Kaspa *et al.* (2006)	Canada/ USA	600	–	–	TVS/SHG	120 (20)	1 (0.2)	1 (0.2)	–	–	28 (4.7)	90 (15.0)	–
	Hamilton *et al.* (1998)[b]	UK	500	–	–	US/SHG	24 (4.8)	–	1 (0.2)	–	2 (0.4)	21 (4.2)		–
	Radoncic *et al.* (2000)	Croatia	267	–	–	3D US/HSc	96 (36.0)	–	–	–	–	95 (35.6)	1 (0.4)	
	Arbozi *et al.*, 2003[c]	Iran	186	Infertile/RM		Hsc/Lap	58 (31.2)	–	7 (3.8)	–	7 (3.8)	35 (18.8)	9 (4.8)	–
	Soares *et al.* (2000)	Brazil	65	–	–	SHG/HSG/TVS/HSc	9 (13.8)	–	3 (4.6)	–	1 (1.5)	–	5 (7.7)	–
	Alatas *et al.* (1997)	Turkey	62	–	–	TVS/HSG/SHG/HSc	4 (6.5)							
	Raga *et al.* (1996)	Spain	42	–	–	HSG/Lap/3D US	12 (28.6)	–	1 (2.4)	1 (2.4)	5 (12.0)	5 (12.0)	–	–
	Wu *et al.* (1997)		38	–	–	2D US/ HSG/3D US/ HSc/Lap	25 (65.8)		4 (10.5)	2 (5.3)	3 (7.9)	11 (28.9)	5 (13.2)	–
Ib	Siegler *et al.*, 1976	USA	104	–	–	HSG/HSc	10 (9.6)	–	–	–	–	10 (9.6)	–	–
	Taylor *et al.*, 1979	Canada	68	–	–	HSG/HSc	1 (1.3)	–	–	–	–	1 (1.3)	–	–
II	Raga *et al.* (1997)	Spain	1024	>2 years	–	HSG/Lap	25 (2.4)	–	1 (0.1)	1 (0.1)	5 (0.5[d])	6 (0.6)	12 (1.1)	–
	Braun *et al.* (2005)	Spain	705	–	–	HSG	66 (9.4)	–	3 (0.4)	–	9 (1.3)	16 (2.3)	38 (5.4)	–
	Acien (1997)[d]	Spain	200	–	2D TVS	HSG/Lap	32 (16)	12 (6)	2 (1)	1 (0.5)	1 (0.5)	2 (1)	14 (7)	–
	Nickerson *et al.* (1977)[e]	USA	190	Primary	–	HSG	93 (48.9)	–	3 (1.6)	–	3 (1.6)	87 (45.8)	–	–
	Sorensen (1981)	Denmark	134	–	–	HSG	32 (23.9)	–	2 (1.5)	–	7 (5.2)	23 (17.2)		–
	Vasiljevic *et al.* (1996)	Serbia	102	–	–	HSG/Lap	6 (5.9)							

[a]The number of patients investigated by either of these investigations is not mentioned; [b]Septate/arcuate diagnosis has not been included in Table VIII; [c]3.8% of the cases were RM patients; [d]HSG and laparoscopy/laparotomy was not performed in all cases detected by TVS; [e]Author includes subdivision into subseptate ($n = 31$; 16.3%), mildly subseptate ($n = 31$; 16.3%), very mildly subseptate ($n = 25$; 13.2%).

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indicative of the fertile and general population combined. However, it has to be noted that the varying presentation of the patients and their different background/origin may have an effect on the homogeneity of the results. A summary of the studies reviewed is shown in Table V. The pooled prevalence estimated using these studies is summarized in Table VI.

According to our evaluation of the literature, the prevalence of congenital uterine anomalies in the fertile/general population based on class Ia and Ib studies is ~6.7% (95% CI, 6.0–7.4). This is higher than what is most commonly quoted in the literature (Grimbizis *et al*., 2001; Troiano and McCarthy, 2004; Nahum, 2006). Class II investigations seem to indicate a pooled prevalence of 2.4%, suggesting under-diagnosis. The 60–80% sensitivity of these class II investigations could have contributed to the finding of this lower prevalence.

The commonest congenital uterine anomaly diagnosed in both class I and class II investigations seems to be that of the arcuate uterus. This is different to the finding of other reviews which considered the septate uterus to be the commonest (Grimbizis *et al*., 2001; Troiano and McCarthy, 2004; Tayor and Gomel, 2008). According to the findings of this review the commonest anomalies follow the order of arcuate, septate and bicornuate at a ratio of approximately 17:7:1 (based on class Ia studies). It is interesting to note that this seems to follow the inverse sequence of the embryological events that occur during uterine formation. A unicornuate uterus was noted in only one of the three class Ia studies (Salim *et al*., 2003a) thus indicating a prevalence of approximately 1 in 4000 women. In contrast, class II studies suggested a prevalence of 1 in 1000 women. Keeping in mind that three of the five class II studies (Sorensen, 1988; Acien, 1997; Raga *et al*., 1997) used HSG with laparoscopy (an accurate way of diagnosing unicornuate uteri), the rate of 1 in 1000 may be closer to the true prevalence. This may suggest that 3D US (which comprised three of four class Ia studies reviewed) is not so sensitive in identifying unicornuate uteri. It could be that the single cavity of the unicornuate uterus is misleading when seen on US and is confused with a normal single uterine cavity. Similarly the transvaginal 2D US used as an initial screening method by Salim *et al*. (2003a) could have the same limitation. In addition, the use of 2D US as a screening tool could have led to an overall under-diagnosis of all congenital uterine anomalies in that study (as this investigation has shown to be ~60% sensitive). HSG should not have the limitation of under-diagnosing unicornuate uteri as the Fallopian tubes would be depicted on X-ray, unless a blocked tube is present. Similarly the tubal ostia should be visualized by hysteroscopy.

Infertile population

The role of congenital uterine anomalies in infertility remains unclear (Heinonen and Pystynen, 1983; Grimbizis *et al*., 2001; Kupesic, 2001; Sanders, 2006; Taylor and Gomel, 2008). However, it has been suggested that uterine anomalies may contribute to infertility, possibly by interfering with normal implantation and placentation (Taylor and Gomel, 2008). A review by Grimbizis *et al*. (2001) found that the overall prevalence was similar to the general population, which would suggest that there is no causal relation. Another review by Nahum (1998) found the prevalence in the infertile population to be 21 times higher than in the general population. However, in both these reviews the reliability of the diagnostic methods used by the reported studies was not considered. A summary of the studies reviewed in this paper is shown in Table VII. The pooled prevalence estimated using these studies is shown in Table VIII.

According to our evaluation of the literature, the prevalence of congenital uterine anomalies in the infertile population based on class Ia and Ib studies is ~7.3% (95% CI 6.7–7.9). This is comparable to that found for the general/fertile population. However, class II studies show a pooled prevalence of 10.8%, which is surprisingly higher.

In terms of different anomalies, in both class I and class II studies the septate uterus is the commonest observed followed by the arcuate and bicornuate uteri. The ratios based on class Ia studies are approximately 4:2:1. This is different to what was observed in the general/fertile population where the arcuate was more than twice as common as the septate uterus. Furthermore, there seems to be an increase in the prevalence of septate uteri in the infertile population compared with the general/fertile population, from 1.1 to 3.9%. This suggests a link between the septate uterus and infertility. This result is consistent with the findings of relatively small studies that have shown that women with a septate uterus and otherwise unexplained infertility may benefit from metroplasty. However, to date there has been no published trial to randomize and compare women with treatment versus no treatment. For this reason controversy exists as to whether infertile women should undergo metroplasty (Taylor and Gomel, 2008). On the other hand, as removal of the septum will potentially decrease the risk of miscarriage and preterm birth if these

Table VIII. Prevalence of congenital uterine anomalies in the infertile population from selected series.

Class	Studies[a], *n*	Cases, *n*	Total, *n* (%)	Hypoplastic, *n* (%)	Unicornuate, *n* (%)	Didelphys, *n* (%)	Bicornuate, *n* (%)	Septate, *n* (%)	Arcuate, *n* (%)	T-shaped, *n* (%)
Ia	10	7332	538 (7.3)[b]	48 (0.7)	32 (0.4)	15 (0.2)	57 (0.8)	235 (3.5)[c]	126 (1.9)[c]	–
Ib	2	172	11 (6.4)	–	–	–	–	11 (6.4)	–	–
II	6	2355	254 (10.8)[d]	12 (0.1)	11 (0.5)	2 (0.1)	25 (1.1)	111 (5.2)[e]	64 (3.0)[e]	–
Total	18	9859	803 (8.1)	60 (0.6)	43 (0.4)	17 (0.2)	82 (0.8)	357 (3.9)	190 (2.1)	–

[a]Summary of studies shown in Table VII; [b]Alatas *et al*. (1997) [0] (*n* of anomalies = 4) do not provide a breakdown of the congenital uterine anomalies they diagnosed, however their data has been used to estimate the Total prevalence according to Class Ia studies; [c]Hamilton *et al*. (1998) [0] (*n* of septate/arcuate = 21) do not distinguish between septate and arcuate uteri; therefore their data has not been used for the prevalence estimates of these two subtypes; [d]Vasiljevic *et al*. (1996) [0] (*n* of anomalies = 6) do not provide a breakdown of the congenital uterine anomalies they diagnosed, however their data has been used to estimate the Total prevalence according to Class II studies; [e]Sorensen (1998) (*n* of septate/arcuate uteri = 23) do not distinguish between septate and arcuate uteri; therefore their data has not been used for the prevalence estimates of these two subtypes.

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Table IX. Prevalence of congenital uterine anomalies in the recurrent miscarriage population.

Class	Study	Country	Cases, *n*	Miscarriage details	Initial investigation	Definitive investigation	Total, *n* (%)	Hypoplastic, *n*(%)	Unicornuate, *n* (%)	Didelphys, *n* (%)	Bicornuate, *n* (%)	Septate, *n* (%)	Arcuate, *n* (%)	T-shaped, *n* (%)
Ia	Salim *et al*. (2003a)	UK	509	≥3 consecutive unexplained first trimester	2D TVS	3D US	121 (23.8)	–	2 (0.4)	–	6 (1.2)	27 (5.3)	86 (16.9)	–
	Li *et al*. (2002)	UK	453	≥3 consecutive	2D US/HSG	HSc/Lap	49 (10.8)							
	Stephenson *et al*. (1996)	Canada	197	≥3 consecutive	HSG or HSc	SHG or Lap	15 (7.6)	–	1 (0.5)	1 (0.5)	1 (0.5)	8 (4.1)	–	4 (2.0)
	Weiss *et al*. (2005)[a]	Israel	165	≥2 consecutive[b]		HSc/Lap	32 (19.4)		1 (0.6)	–	3 (1.8)	13 (7.9)	13 (7.9)	
			98	≥3 consecutive	–	HSc/Lap	17 (17.3)							
Ib	Valli *et al*. (2001)	Italy	344	≥2 consecutive[b]	–	HSc	112 (32.6)	–	3 (0.9)	–		30 (8.7)	79 (23.0)	–
			141	≥3 consecutive	–	HSc	39 (27.7)	–	–	–	–	15 (10.6)	24 (17.0)	–
	Raziel *et al*. (1994)[b]	Israel	106	≥3	–	HSG/HSc	23 (21.7)	–	–	–	–	23 (21.7)	–	–
	Guimaraes Filho *et al*. (2006b)	Brazil	60	≥3 consecutive	–	HSc	8 (13.3)							
	Tulppala *et al*. (1993)[c]	Finland	55	RM clinic	–	HSc	4 (7.3)	–	–	–	–	4 (7.3)	–	–
	Ventolini *et al*. (2004)[b]	USA	23	≥3	–	US/HSc	3 (13.0)	–	–	–	–	3 (13.0)	–	Excluded
II	Makino *et al*. (1992)[b]	Japan	1200	≥2	–	HSG	188 (15.7)	–	5 (0.4)	–	–	50 (4.1)	133 (11.1)	–
	Clifford *et al*. (1994)[b]	UK	500	≥3	–	US	9 (1.8)	–	–	–	3 (0.6)	6 (1.2)	–	–
	Coulam (1991)[b]	USA	214	≥2	HSG	HSc	1 (0.5)	–	–	–	–	1 (0.5)	–	–
	Stray-Pedersen and Stray Pedersen (1984)	Norway	195	≥3 consecutive	–	HSG	19 (9.7)							
	Acien *et al*. (1996)[c]	Spain	189	RM clinic	–	HSG	71 (37.6)							
	Harger *et al*. (1983)[b]	USA	155	≥2 consecutive	HSG	HSc	17 (11.0)	–	1 (0.6)	–	5 (3.2)	3 (1.9)	4 (2.9)	4 (2.9)
	Coulam (1986)[b]	USA	110	≥3	–	HSG	11 (9.1)	–	1 (0.9)	2 (1.8)	6 (5.5)	2 (1.8)	–	–
	Tho *et al*. (1979)[b]	Georgia	100	≥2 or ≥1 abnormal conceptus	HSG	Gynae-cography	10 (10)	–	–	–	–	10 (10)	–	–
	Traina *et al*. (2004)[b]	Brazil	80	≥2 consecutive	–	HSG/TVS/HSc	11 (13.6)							
	Portuondo *et al*. (1986)	Spain	40	≥3 consecutive	–	HSG	9 (22.5)	–	–	–	–	6 (15)	3 (7.5)	–
	Keltz *et al*. (1997)[b]	USA	34	≥2 consecutive	–	SHG	5 (14.7)	–	–	–	1 (2.9)	2 (5.9)	–	2 (5.9)

[a]Contains also two undetermined bicornuate/septate uteri; [b]Data not included in Table X as subjects do not fulfil the criteria for RM; [c]Number or pattern of miscarriages not specified by author (assumed to be ≥3 consecutive as patients were attending a RM clinic).

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Table X. Prevalence of congenital uterine anomalies in the recurrent miscarriage population (≥3 consecutive miscarriages) from selected series.

Class	Studies[a], *n*	Cases, *n*	Total, *n* (%)	Hypoplastic, *n* (%)	Unicornuate, *n* (%)	Didelphys, *n* (%)	Bicornuate, *n* (%)	Septate, *n* (%)	Arcuate, *n* (%)	T-shaped, *n* (%)
Class Ia[a]	4	1257	202 (16.1) [b]	–	3 (0.4)	1 (0.1)	7 (1.0)	35 (5.0)	86 (12.2)	4 (0.6)
Class Ib	3	256	51 (19.9)[c]	–	–	–	–	19 (9.7)	24 (12.2)	–
Class II	3	424	99 (23.3)[d]	–	–	–	–	6 (15.0)	3 (7.5)	–
Total	20	1937	352 (18.2)	–	3 (0.3)	1 (0.1)	7 (0.7)	60 (6.4)	113 (12.0)	4 (0.4)

[a]Summary of studies shown in Table IX; [b]Weiss *et al*. (2005) and [0] Li *et al*. (2002) (total *n* of anomalies=66) do not provide a breakdown of the congenital uterine anomalies they diagnosed, however their data has been used to estimate the Total prevalence according to Class Ia studies; [c]Guimaraes Filho *et al*. (2006b) (*n* of anomalies=8) do not provide a breakdown of the congenital uterine anomalies they diagnosed, however their data has been used to estimate the Total prevalence according to Class Ib studies; [d]Acien *et al*. (1996) and Stray-Pedersen and Stray-Pedersen (1984) (total *n* of anomalies=90) do not provide a breakdown of the congenital uterine anomalies they diagnosed, however their data has been used to estimate the Total prevalence according to Class II studies.

Table XI. Approximate ratios of uterine anomaly types in different populations[a].

Population	Arcuate	Septate	Bicornuate
General/fertile	17	7	1
Infertile	2	4	1
RM	12	5	1

[a]Data based on class Ia studies.

women are to conceive, it could be argued that metroplasty should be considered in these cases (Homer *et al*., 2000).

In addition to the septate uterus, the prevalence of the unicornuate and hypoplastic uteri are also relatively higher in the infertile population compared with both the general/fertile and RM population, indicating an association. On the other hand, this does not seem to be the case for the arcuate uterus, which is of lower prevalence compared with the general/fertile and RM group. Interestingly, if pooled data from all studies (class I and II) is considered, the prevalence of arcuate uteri is almost identical to that of the general/fertile population (2.1 versus 2.4%). This would suggest that the arcuate uterus does not have a causal role in infertility. Ultimately, the results of this review highlight the necessity for further assessment of the role of the septate uterus in infertility.

RM population

Although the association between congenital uterine anomalies and RM has been well documented (Patton, 1994; Grimbizis *et al*., 2001; Homer *et al*., 2000; Kupesic, 2001; Taylor and Gomel, 2008), the exact prevalence in this population has not been clearly defined. A summary of the studies reviewed in this paper is shown in Table IX. The pooled prevalence estimated using a selection of these studies is shown in Table X.

According to our evaluation of the literature, the prevalence of congenital uterine anomalies in the RM population based on class Ia and Ib studies is ∼16.7% (95% CI 14.8–18.6). Studies with ≥3 consecutive miscarriages were included in the analysis. However, the study by Salim *et al*. (2003a), which provides ∼34% of the cases of class I studies, examined patients with unexplained recurrent pregnancy loss. By excluding all patients with concurrent diagnoses their findings could be exaggerated. By not including the study of Salim *et al*. (2003a) the pooled prevalence according to class I studies is reduced to ∼13.1%. Therefore it can be assumed that the true prevalence lies approximately somewhere between 13 and 17%. Surprisingly, class II studies show a pooled prevalence of 23.3%, suggesting an over-diagnosis, rather than an under-diagnosis, which would be expected from investigations of a low sensitivity (under 60% for 2D US). This could be partly due to the investigators having a lower threshold for diagnosing congenital uterine anomalies in patients suffering with RM.

Class I studies evaluating women with ≥3 non-consecutive miscarriages, show a pooled prevalence of 15.8%; this is similar to women with ≥3 consecutive miscarriages (16.7%). Corresponding class II studies show a prevalence of 23.3% for women with ≥3 consecutive miscarriages, and only 3.3% for those with ≥3 non-consecutive miscarriages; this decrease may be partly due to the different miscarriage pattern (consecutive versus non-consecutive), but may also be a chance finding. Class I studies of women with ≥2 consecutive miscarriages, show a pooled prevalence of 28.3%. Corresponding class II studies show a prevalence of 13%. Both findings suggest that women presenting with only two miscarriages may also warrant investigations for the presence of a congenital uterine anomaly. This has been suggested by the report of Weiss *et al*. (2005) who found no significant differences between the prevalence of congenital uterine anomalies in women with ≥2 versus ≥3 miscarriages. Unfortunately, the heterogeneity of the reports does not allow for further analysis to be conducted.

Table XII. Congenital uterine anomalies: percentage of subtypes in different population groups[a].

Population	Hypoplastic, %	Unicornuate, %	Didelphys, %	Bicornuate, %	Septate, %	Arcuate, %
General/fertile ($n = 250$)	–	0.4	0.4	4.0	27.2	68.0
Infertile ($n = 510$)	9.4	6.1	2.9	10.8	46.1	24.7
RM ($n = 132$)	–	2.3	0.8	5.3	26.5	65.2

[a]Data based only on class Ia studies using an appropriate classification of the congenital uterine anomaly types.

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Regarding the different anomaly types, class Ia studies suggest that the arcuate uterus is the commonest followed by the septate and bicornuate uterus with a ratio of approximately 12:5:1. This does not vary greatly from the findings for the general population; however it is different to what is observed in the infertile population. A summary of the ratios and prevalence of different anomaly types within the three population groups is shown in Tables XI and XII, respectively.

The prevalence of the arcuate uterus in the RM population is 12.2%, >3-fold the prevalence for the general/fertile population (3.8%). This suggests a causal relation between this type of deformity and RM, something which has been suggested by authors in the past (Grimbizis *et al*., 2001; Woelfer *et al*., 2001). Interestingly, although the arcuate uterus could be considered a mild form of partial septate uterus (Grimbizis *et al*., 2001), the study by Woelfer *et al*. (2001) suggests a different pattern of pregnancy loss in patients with arcuate versus septate uteri. Notably, their data supports the suggestion that women with arcuate uteri tend to miscarry more in the second trimester, whereas patients with septate uteri are more likely to miscarry in the first trimester. This finding could suggest a different mechanism of miscarriage for these two uterine anomaly types. Ultimately, the impact of the arcuate uterus on the reproductive outcome should not be underestimated.

Interestingly, in the current review, there are a number of class II studies that failed to identify any arcuate uteri. This could reflect the lower sensitivities of the investigations used (i.e. 2D US and HSG), which may have failed to identify the less prominent arcuate deformity. Overall, more studies are required to further clarify the prevalence of different congenital uterine anomalies within the RM population, and delineate their causal relation to RM.

Conclusion

Based on the data derived from class Ia and Ib studies, the prevalence of congenital uterine anomalies is ~6.7% (95% CI, 6.0–7.4) in the general/fertile population, 7.3% (95% CI, 6.7–7.9) in the infertile population and 16.7% (95% CI, 14.8–18.6) in the RM population. The prevalence in the infertile population is similar to that of the general/fertile population. However, there seems to be a higher prevalence of septate uteri in the infertile population, suggesting an association. In addition, the high prevalence of arcuate uteri in the RM population (12.2%) highlights the potentially important role of this deformity in RM, something which should not be underestimated. The relation between most congenital uterine anomalies and RM has been well documented in the literature; furthermore, it has been suggested that treatment of certain anomalies may result in an improved pregnancy outcome (Homer *et al*., 2000; Grimbizis *et al*., 2001; Kupesic, 2001; Taylor and Gomel, 2008). Therefore, any woman suffering from RM should be thoroughly investigated, to identify whether a congenital uterine anomaly is present. A number of different investigations can be used. Two-dimensional US and HSG have the lowest accuracy rates, which would not warrant use for diagnosis. However, they can be used alone or in combination as an effective screening tool. In contrast, SHG has been shown to be highly accurate in diagnosing and classifying uterine anomalies; however, it is more invasive and is not commonly practiced. Studies to date suggest that 3D US is also very accurate and can be used as a diagnostic tool; limitations include a possible under-diagnosis of unicornuate uteri and lack of availability in some centres. The accuracy and practicality of MRI has not yet been determined, however, its role in screening or diagnosing congenital uterine anomalies may become more important in the future. Combined hysteroscopy and laparoscopy allows for a direct visualization of the internal and external contour of the uterus, and is therefore considered by many to be the gold standard. The main advantage is that it allows concurrent diagnosis and treatment, whereas the disadvantage is the invasiveness of the procedures.

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Submitted on December 19, 2007; resubmitted on April 13, 2008; accepted on May 1, 2008

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