Uterine septum: a guideline

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The purpose of this guideline is to review the literature regarding septate uterus and determine optimal indications and methods of treatment for it. Septate uterus has been associated with an increase in the risk of miscarriage, premature delivery, and malpresentation; however, there is insufficient evidence that a uterine septum is associated with infertility. Several studies indicate that treating a uterine septum is associated with an improvement in live-birth rates in women with a history of prior pregnancy loss, recurrent pregnancy loss, or infertility. In a patient without infertility or prior pregnancy loss, it may be reasonable to consider septum incision following counseling regarding potential risks and benefits of the procedure. Many techniques are available to surgically treat a uterine septum, but there is insufficient evidence to recommend one specific method over another. (Fertil Steril® 2016;106:530–40. ©2016 by American Society for Reproductive Medicine.)

CLASSIFICATION

Uterine anomalies were described in the 1800s by Cruveilhier and Von Rokitansky (1). There are numerous classification systems to describe variations in uterine and cervical/vaginal anomalies, collectively referred to as müllerian anomalies (2–7). Adverse reproductive outcomes that have been attributed to septate uteri include infertility, pregnancy loss, and poor obstetrical outcomes, such as malpresentation and preterm delivery. However, many women with uterine septa do not experience any reproductive difficulties (8).

The purpose of this guideline is to review the literature regarding septate uterus and determine optimal indications and methods of treatment for it.

DESCRIPTION OF SEARCH

This clinical practice guideline was based on a systematic review of the literature. Systematic literature searches of relevant articles were performed in the electronic database MEDLINE through PubMed in March and April 2015, with a filter for human subject research. No limit or filter was used for time period covered or English language, but articles were subsequently culled for English language.

A combination of the following medical subject headings or text words/keywords were used: abortion, adhesion, adhesions, arcuate, bicornuate, birth control pill, congenital anomalies, congenital anomaly, congenital abnormalities, congenital abnormality, contraceptive, danazol, detection, diagnose, diagnosis, hysterosalpingogram, hysteroscopic, hysteroscopy, infertility, intrauterine, laparoscopic, laparoscopy, live birth, Lupron, metroplasty, miscarriage, MRI, outcome, perinatal outcome, perinatal outcomes, pregnancies, pregnancy, pregnancy loss, premature, preterm, progestin, repair, resection, resectoscope, septa, septal, septate, septum, sonohysterogram, surgery, treatment, ultrasonography, uteri, uterine, uterus.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed for inclusion/exclusion criteria. Protocols and results of the studies were examined according to specific inclusion criteria. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, implantation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Four members of an independent task force reviewed the full articles of all citations that possibly matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and solved by consensus or arbitration after consultation with an independent reviewer/epidemiologist. A summary of inclusion and exclusion criteria are provided in Table 1.

The quality of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

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TABLE 1

Summary of inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
Level 1, 2-1, 2-2, 2-3 studies; systematic reviews/meta-analyses	Level 3 studies: small series, case reports, reviews, opinions, off topic
Human studies	Animal studies
English	Non-English
Studies that report clinical (fertility and/or obstetrical) outcomes	Studies that focus on prevalence with no fertility and/or obstetrical outcome measures
Studies that focus on septate, arcuate, bicornuate uterine anomalies and/or adhesions	Studies that do not focus on septate uterus, but focus on unicornuate or didelphic uteri, or fibroids and polyps, or cervix and vagina, obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) or Herlyn-Werner-Wunderlich (HWW), Asherman, Fryns, or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome
	Studies with a focus on amenorrhea, blood flow, cancer, dysmenorrhea, endometriosis, hemodynamics, menorrhagia, ovarian maldescent, polycystic ovary syndrome, surgical technique only, uterine horn, uterine prolapse, vascular endothelial growth factor (VEGF)
	Studies with a focus on pediatric or postpartum population
	Studies with a focus on abdominal metroplasty

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Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

The strength of the evidence was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Number of studies identified in an electronic search and from examination of reference lists from primary and review articles = 1,034; number of studies included = 204.

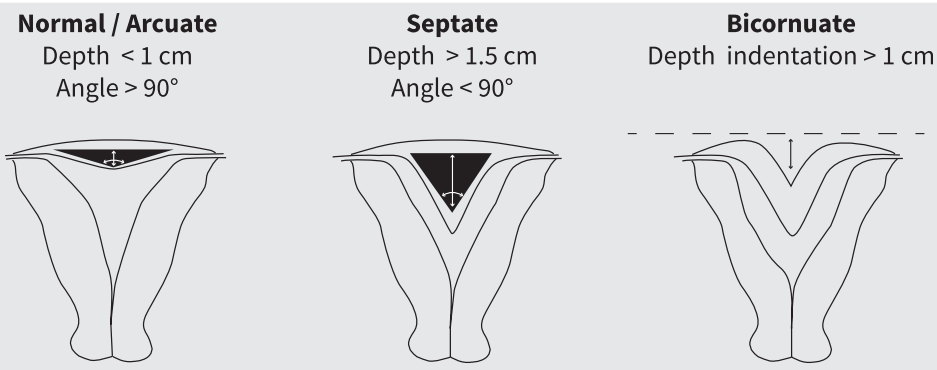
DEVELOPMENT

A uterine septum is believed to develop as a result of failure of resorption of the tissue connecting the two paramesonephric (müllerian) ducts prior to the 20th embryonic week. While the arcuate uterus represents the mildest form of resorption failure, unlike the septum, it is not considered clinically relevant. The true prevalence of the uterine septum is difficult to ascertain as many uterine septum defects are asymptomatic, but appear to range between 1 to 2 per 1,000 to as high as 15 per 1,000 (8). Initially, uterine septa were believed to be predominantly fibrous tissue. However, biopsy specimens and magnetic resonance imaging (MRI) suggest that septa are composed primarily of muscle fibers and less connective tissue (9, 10).

Müllerian anomalies in general may be associated with renal anomalies in approximately 11% to 30% of individuals (5). However, data do not exist to suggest an association between septate uterus and renal anomalies and, as such, it is not necessary to evaluate the renal system in all patients with a uterine septum.

Septate uteri have a spectrum of configurations including incomplete/partial septate to complete septate uterus. A partial septate uterus refers to a single fundus and cervix with a uterine septum extending from the top of the endometrial cavity toward the cervix. The size and shape of the septum can vary by width, length, and vascularity, although most have not been categorized systematically, and definitions are not standardized. For example, the definition of the septum by the European Society of Human Reproduction and Embryology and the European Society for Gynecological Endoscopy (ESHRE-ESGE) criteria is an internal indentation extending >50% of myometrial wall thickness (7), while the American Society for Reproductive Medicine (ASRM) criteria provide no strict parameters to define septate configurations (2, 3, 11). Some authors have proposed additional morphologic criteria for the American Fertility Society (AFS) criteria to better characterize and differentiate a septate from an arcuate uterus. These authors define a partial uterine septum as having the central point of the septum at an acute angle (to differentiate from an obtuse angle seen with an arcuate configuration) (12) and define the length of the septum to be greater than 1.5 cm, with arcuate defined as having a fundal invagination between 1 and 1.5 cm (13). As there is no universally accepted standard definition of septate uterus, differences among the available definitions may lead to variability in diagnostic classifications with correspondingly higher/lower incidence of surgery performed to correct these anomalies (11). Figure 1 represents the ASRM proposed definition of a septate uterus compared with arcuate and bicornuate uterus.

FIGURE 1



Diagrams of the ASRM definitions of normal/arcuate, septate, and bicornuate uterus based on assessment of available literature, understanding that these anomalies reflect points on a spectrum of development. Normal/arcuate: depth from the interstitial line to the apex of the indentation <1 cm and angle of the indentation >90 degrees. Septate: depth from the interstitial line to the apex of the indentation >1.5 cm and angle of the indentation <90 degrees. Bicornuate: external fundal indentation >1 cm. Internal endometrial cavity is similar to a partial septate uterus.

ASRM. Uterine septum. Fertil Steril 2016.

A complete septate uterus has a single uterine fundus, with a septum extending from the top of the endometrial cavity and continuing through the cervix or may extend into a duplicated cervix. Both may be seen in combination with a longitudinal vaginal septum. This configuration must be differentiated from the uterus didelphys in which the uterine horns are separated. Both of these anomalies have duplicated cervices and typically are associated with a longitudinal vaginal septum.

In addition, a combined bicornuate/septate configuration of the uterus has been described in which the external fundus has an indentation consistent with a bicornuate shape, but at hysteroscopy there is a septum dividing the endometrial cavities (14). Radiologic descriptions of this anomaly describe the fundus as not convex but rather with a fundal indentation that should be less than 1 cm, with greater than 1 cm more consistent with a pure bicornuate uterus (15, 16). In addition, the septum may be variable in length and width, and the cervix may be single, septate, or duplicated.

The arcuate uterus is difficult to classify. Although developmentally the arcuate uterus may be considered as part of the spectrum of failure of müllerian resorption, it is typically considered a normal variant and therefore functionally not part of the septate spectrum. The AFS classification system placed arcuate uterus in its own category as, in contrast to other uterine malformations, it does not cause adverse clinical outcomes (3). However, it is important to differentiate arcuate from septate uterus to better direct surgical intervention when appropriate for the septate uterus. Arcuate describes a uterus with an externally normal-appearing fundus and a small smooth indentation at the top of the endometrial cavity (3). There is no standard definition of the arcuate configuration, nor is there a widely accepted defining depth of the indentation into the endometrial cavity to differentiate it from septate. Descriptions of an arcuate shape in the literature are variable. Definitions include vague descriptions of a concave indentation into the endometrial cavity and vary from defining the angle making up the fundal portion of the myometrium protruding into the cavity as obtuse (to differentiate from the acute angle seen with a uterine septum), to defining the indentation to be less than 1.0–1.5 cm and include an obtuse angle (12, 13, 17, 18), and to defining the ratio of the depth of fundal indentation to the distance between the two uterine horns of less than 10% (19) (Fig. 1).

As a result of the numerous and varied definitions and terminology used to describe septate uteri, it is challenging to interpret the data regarding pre-treatment and post-treatment outcomes and ultimately determine optimal management.

DIAGNOSIS OF SEPTATE UTERUS

Historically, the gold standard method for diagnosing müllerian anomalies required direct visualization of the exterior and interior of the uterus using laparoscopy and hysteroscopy. Importantly, assessing both the outer and inner uterine contour makes it possible to distinguish a septate from a bicornuate uterus. As radiologic methods have improved over the past 20 years, the diagnosis of a septate uterus is typically made using radiographic rather than surgical techniques. While hysterosalpingography (HSG) is often the initial test that provides evidence for a müllerian anomaly in patients with infertility or recurrent pregnancy loss, the diagnostic accuracy of the HSG is low for distinguishing septate and bicornuate uteri. Indeed, compared with hysteroscopy/laparoscopy, several studies indicate that the diagnostic accuracy of HSG ranges from 5.6% to 88% (20–23). Some studies suggest that sonohysterography or saline infusion sonography (SIS) is superior to HSG since it is possible to assess the external as well as internal contour of the uterus. However, studies are limited since there has not been a consistent gold standard diagnostic method used for comparison nor a consistent definition of these anomalies

(13, 24). A study of 117 females found that the use of 3-dimensional (3-D) ultrasonography combined with saline infusion had 100% accuracy when compared with laparoscopy/hysteroscopy (25). Also, 3-D ultrasound without saline infusion has been found to be over 88% accurate for diagnosing uterine septa in two studies when compared with hysteroscopy/laparoscopy (25, 26). MRI is often used for the diagnosis of müllerian anomalies. There are few data comparing the diagnostic accuracy of MRI compared with laparoscopy/hysteroscopy. However, several studies have shown a high level of agreement between MRI and other radiologic techniques (10, 18). One study suggests that while MRI is an accurate method to diagnose müllerian abnormalities overall, it is only 70% accurate for the diagnosis of uterine septum (16).

It must be emphasized that studies to determine how to best diagnose a septum are limited by small sample sizes and are from select centers. Therefore, it is likely that interpretation of radiologic studies depends on the experience of the interpreter. It is important when confirming the diagnosis of septate uterus that the external uterine contour as well as the internal configuration of the endometrial cavity are assessed. Therefore, HSG or hysteroscopy alone is inadequate. When the diagnosis of a uterine septum is not clear, it may be helpful to seek consultation with a clinician with experience in the diagnosis and management of müllerian anomalies.

Summary statements:

- There is fair evidence that 3-D ultrasound, sonohysterography, and MRI are good diagnostic tests for distinguishing a septate and bicornuate uterus when compared with laparoscopy/hysteroscopy. (Grade B)
- It is recommended that imaging with hysteroscopy should be used to diagnose uterine septa rather than laparoscopy with hysteroscopy because this approach is less invasive (Grade B).

LIMITATIONS OF THE LITERATURE

The data regarding reproductive implications of a uterine septum are limited, making firm recommendations regarding treatment difficult. Only observational, principally descriptive studies without untreated control groups have been conducted to assess the reproductive consequences of a uterine septum. Importantly, there are no prospective randomized controlled trials (RCTs) that compare surgical treatment of a septum with no intervention. Many studies fail to adequately define the characteristics of uterine septa, and there are many different surgical techniques described. In addition, there are substantial differences among studies principally because the indication for septum incision varies widely. Studies include women with unexplained infertility, a single first-trimester loss, recurrent pregnancy loss, or no adverse reproductive history. Moreover, studies have inconsistent follow-up data and sometimes do not report live-birth outcomes. This guideline will review the uterine septum literature for the diagnosis of infertility, pregnancy loss, reproductive outcomes, surgical technique, and postoperative prevention of intrauterine adhesions.

"Uterine septum resection" is the term commonly used to describe all surgical procedures performed to treat a uterine septum. Initial procedures, such as the Jones metroplasty, described resection and removal of the uterine septum with subsequent uterine closure. However, most hysteroscopic techniques currently used involve incision rather than resection (or removal) of the septum. Therefore, for the purpose of this document, the term "uterine septum incision" will be used when referring to hysteroscopic procedures to treat a uterine septum as it more correctly reflects the predominant surgical technique utilized.

Summary statement:

- The data regarding reproductive implications of septate uteri and treatment effects are limited and comprised primarily of observational, principally descriptive studies without untreated control groups.

DOES A SEPTUM IMPACT FERTILITY?

Uterine septa are often diagnosed during an infertility evaluation. The incidence of uterine septa in this population has been noted to be higher than in the general population, suggesting a link with infertility (27–30). Given that infertility can be the result of multiple factors, it is often difficult to determine if the uterine septum is the sole reason for the infertility. Several small descriptive studies have evaluated the relationship between uterine septa and infertility. One of the larger studies compared 153 women with all types of uterine anomalies to a control group of 27 women with a normal uterus (30). In the 33 women diagnosed with a septate uterus there was a higher incidence of infertility compared with controls (21.9% vs 7.7%); however, this difference did not reach statistical significance (30). One study evaluated infertility in women with müllerian anomalies compared with those with external genital anomalies and a normal uterus. When all other causes had been excluded, infertility was not seen more frequently in the 17 women with a septate uterus (27). In another study, 33 women were followed prospectively for 24 months after hysteroscopic diagnosis of arcuate and septate/bicornuate uteri (31). There was no difference in cumulative pregnancy rates or monthly fecundity when compared with those with a normal-shaped cavity. In a more recent study, 92 women with a septate uterus were identified at laparoscopy and hysteroscopy performed for miscarriage or infertility (primary or secondary) and compared with 191 women found to have a normal uterus (32). Primary infertility was less common in those with a septate uterus compared with controls (43.5% vs 64.9%, $P=.001$) (32). However, in a meta-analysis evaluating the effect of congenital uterine anomalies on reproductive outcomes, septate uterus was the only anomaly that was associated with a significant decrease in the probability of natural conception when compared with controls (relative risk [RR] 0.86, 95% confidence interval [CI], 0.77–0.96) (33).

Summary statement:

- There is insufficient evidence to conclude that a uterine septum is associated with infertility. (Grade C)

DOES TREATING A SEPTUM IMPROVE FERTILITY IN INFERTILE WOMEN?

Although there is insufficient evidence supporting the association between septate uterus and infertility, there are many studies in which women with a uterine septum and the diagnosis of infertility underwent septum incision and the subsequent effect on pregnancy was assessed. There are no randomized controlled studies evaluating this intervention, and the majority of the studies are small observational studies with untreated controls.

One study evaluated 193 women with primary infertility of at least 2 years' duration. Following septum incision the cumulative pregnancy probability was 10% in the first 6 months, 18.1% in the first 6–12 months, and 23.3% after 18 months (34). A retrospective study involving 127 women diagnosed with unexplained infertility, normal semen analysis, and a uterine septum found that subsequent pregnancy rates in the 102 women who underwent septum incision were significantly higher than in the 25 women who chose not to undergo septum incision during a follow-up period of 14 months from time of diagnosis or treatment (43.1% vs 20%, $P=.03$), despite no significant difference in age, time to pregnancy, body mass index (BMI), or septum classification (35). In a prospective study, 44 women with a septate uterus and no other causes of infertility were compared with 132 women with unexplained infertility (36). Both groups were followed expectantly for 1 year without fertility treatment, but the septum group was initially treated with hysteroscopic septum incision. At 12 months, the group that underwent septum incision had a higher pregnancy rate of 38.6% compared with 20.4% in the unexplained infertility group ($P<.05$). In another prospective study 88 patients with a septate uterus and >2 years of unexplained infertility (all causes excluded) underwent septum incision. Following surgery, 41% of the patients conceived with a median time to conception of 7.5 ± 2.6 months (37). In women <35 years of age, 82.4% conceived while 17.6% did not ($P<.001$), while none of the women >40 years of age conceived. The pregnancy rate was higher in women with <3 years compared with ≥3 years of unexplained infertility (75% vs. 15%). A retrospective matched controlled study evaluated the outcome following embryo transfer in three groups of patients: patients with a uterine septum (n = 289), patients who underwent hysteroscopic septum incision (n = 538), and matched controls (n = 1,654) (28). Study and control populations were matched for age, BMI, stimulation protocol, quality of embryos, use of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), and infertility indication. Pregnancy and live-birth rates were significantly lower in those with a uterine septum compared with controls (12.4% vs. 29.2%, $P=.001$; 2.7% vs. 21.7%, $P=.001$, respectively). Pregnancy and live-birth rates following septum incision were not significantly different compared with controls (22.9% vs. 26.0%, not significant [NS]; 15.6% vs. 20.9%, NS, respectively). Pregnancy rates were higher in the group that had undergone septum incision compared with those who did not undergo incision of their uterine septum (odds ratio [OR] 2.507, 95% CI, 1.539–4.111, $P<.001$).

Summary statement:

- Several observational studies indicate that hysteroscopic septum incision is associated with improved clinical pregnancy rates in women with infertility. (Grade C)

DOES A SEPTUM CONTRIBUTE TO PREGNANCY LOSS OR ADVERSE PREGNANCY OUTCOME?

Although many women with a uterine septum have an uncomplicated reproductive history, septate uteri have been implicated in pregnancy loss and poor obstetrical outcomes. The studies evaluated for this guideline are relatively small descriptive studies, and there are no RCTs. All studies suggest that a septate uterus is associated with a higher rate of miscarriage as well as higher preterm delivery rates when compared with controls.

One of the larger studies evaluated 689 women found to have a septate uterus during diagnostic evaluation in an infertility clinic (38). Their reproductive outcomes were compared with obstetric outcomes in 15,060 women in the general pregnant population. The incidence of early miscarriage was 41.1% in patients with septate uterus compared with 12.1% in the control population. Late abortions and premature deliveries developed in 12.6% of patients with septate uterus compared with 6.9% in the general population. In another study uterine morphology was assessed in 1,089 women without a history of infertility or recurrent pregnancy loss, and findings were correlated with their reproductive history (12). In this group, 983 women were found to have a normal uterine cavity and 29 women were identified as having a partial uterine septum. The rate of first-trimester miscarriage was higher in women with a septate uterus compared with those with a normal uterine cavity (42% vs. 12%, $P<.01$). However, the rates of second-trimester miscarriage and preterm labor were no different in the septate group versus controls (second-trimester loss 3.6% vs. 3.5%; preterm labor 10.5% vs. 6.2%, respectively). Another study retrospectively evaluated pregnancy outcome in all women identified with a müllerian anomaly treated at a single institution over a 14-year period compared with a control group made up of pregnant women found to have a genital or urinary tract anomaly but with a normal uterus (30). Thirty-three women identified as having a septate uterus were noted to have a higher early abortion rate compared with controls (36.2% vs. 9.1%, $P<.001$) and a lower term-birth rate compared with controls (37.9% vs. 84.8%, $P<.001$). In a study of IVF patients, 289 embryo transfers were performed in women with a septate uterus before correction and compared with 1,654 consecutive embryo transfers in controls without uterine abnormalities matched for age, BMI, stimulation protocol, quality of embryos, use of IVF or ICSI, and infertility indication (28). The miscarriage rate in the septate uterus group was significantly higher compared with controls (77.1% vs. 16.7%, $P<.001$).

A meta-analysis evaluated the effect of congenital uterine anomalies on reproductive outcomes and found that septate

uterus was associated with a higher risk of adverse pregnancy outcomes (33). Women with a septate uterus were noted to have a higher rate of first-trimester miscarriage when compared with controls (RR 2.65, 95% CI, 1.39–5.06). When evaluating other pregnancy complications, the pooled relative risk of adverse outcomes for women with a septate uterus compared with controls was as follows: preterm delivery <37 weeks 2.11 (95% CI, 1.51–2.94), malpresentation at delivery 4.35 (95% CI, 2.52–7.50), intrauterine growth restriction 2.54 (95% CI, 1.04–6.23), placental abruption 4.37 (95% CI, 1.12–17.08), and perinatal mortality 2.43 (95% CI, 1.10–5.36).

Summary statements:

- There is fair evidence that a uterine septum contributes to miscarriage and preterm birth. (Grade B)
- Some evidence suggests that a uterine septum may increase the risk of other adverse pregnancy outcomes such as malpresentation, intrauterine growth restriction, placental abruption, and perinatal mortality. (Grade B)

DOES TREATING A SEPTUM IMPROVE OBSTETRICAL OUTCOMES?

There are many retrospective studies that evaluate obstetrical outcomes following hysteroscopic septum incision; however, there are no prospective randomized trials. In addition, there is significant heterogeneity within and between these studies, and indications for surgery are variable. However, the majority of studies suggest that a uterine septum leads to a higher pregnancy loss rate, and septum incision leads to improved miscarriage rates and obstetrical outcomes.

One of the largest studies to evaluate this question was a retrospective case series of 361 patients with septate uterus (including total, subtotal, and duplicated cervices) who had primary infertility of >2 years' duration, a history of 1–2 spontaneous miscarriages, or recurrent pregnancy loss (34). In women with a history of miscarriages, the miscarriage rate decreased from 91.8% to 10.4% following septum incision. In this group the live-birth rate prior to surgery was 4.3% while after septum incision the live-birth rate increased to 81.3%. In the recurrent pregnancy loss group, the miscarriage rate decreased from 94.3% to 16.1% following septum incision and the live-birth rate also improved from 2.4% to 75% after surgery. A large retrospective study evaluated reproductive outcomes following hysteroscopic incision of uterine septum in 90 women with recurrent pregnancy loss with a mean follow-up of 37 ± 18 months (39). In this group, 65.3% of patients achieved a pregnancy and the miscarriage rate was 34.1%. In another large observational study women with a uterine septum undergoing IVF were found to have a higher rate of abortion compared with controls (77.1% vs. 16.7%, $P<.001$), but after septum incision the abortion rate was not significantly different when compared with controls (29.2% vs. 18.4%) (28). In addition, live-birth rate following the transfer of two or three embryos prior to septum incision was lower in women with subseptate or septate uterus compared with controls (1.9% vs. 38.6%, OR 32.08, $P<.001$). After surgery the live-birth rate was comparable to that in women with a normal uterus.

A meta-analysis comprised of 29 studies evaluating the effect of septum incision in a mixed population of patients with infertility, miscarriage, and/or recurrent pregnancy loss found that the overall pregnancy rate after septum incision was 67.8% (95% CI, 62.5–72.8) and the live-birth rate was 53.5% (95% CI, 47.8–59.1) (8). A second analysis was then completed for 19 of the studies, eliminating those studies in which the reported pregnancy rate included more than one pregnancy per patient and/or had unreliable live-birth rates. The overall pregnancy rate in this "clean" subset was 63.5% (95% CI, 56.6–69.9) and the live-birth rate after septum incision was 50.2% (95% CI, 43.4–57.1) (8).

Another meta-analysis evaluated the effect of septum incision on pregnancy outcomes (33). Women who underwent septum incision had a significantly decreased probability of spontaneous abortion compared with women who did not undergo treatment (RR 0.37, 95% CI, 0.25–0.55). However, the probability of preterm labor in women <37 weeks was not significantly lower in women who had undergone septum incision compared with those who had not (RR 0.66, 95% CI, 0.29–1.49).

One study did not show an improvement in reproductive outcome following hysteroscopic uterine septum incision. This study evaluated the outcome in 22 patients following surgical treatment of a complete uterine septum and cervical septum (40). The spontaneous abortion and preterm delivery rates, and gestational age at delivery were not statistically different before and after surgery, although following cervical/uterine septum incision five women had a cervical cerclage placed during a subsequent pregnancy.

Summary statements:

- Some limited studies indicate that hysteroscopic septum incision is associated with a reduction in subsequent miscarriage rates and improvement in live-birth rates in patients with a history of recurrent pregnancy loss. (Grade C)
- Some limited studies indicate that hysteroscopic septum incision is associated with an improvement in live-birth rate in women with infertility or prior pregnancy loss. (Grade C)

ARE SEPTUM CHARACTERISTICS ASSOCIATED WITH WORSE REPRODUCTIVE OUTCOMES?

Uterine septa may be partial or complete, and the septum may be thick or thin. In considering prognosis and potential benefit of surgical excision, it would be helpful to know how the size or type of septum correlates with reproductive outcomes. However, few studies describe the type, length, or width of the uterine septum, and in addition there are no consistent definitions of large and small septa among the published studies.

When considering the outcomes with partial uterine septa of different lengths or widths there are a few small studies that address this issue. One study evaluated the length and width of uterine septa by saline ultrasound and 3-D ultrasound

and correlated this with the patient's prior obstetric outcomes (41). There were no differences in the incidence of abortions and late pregnancy complications in patients with uterine septum extending less than one third of the uterine cavity and those with a septal length of greater than two thirds of the uterine cavity. There were also no differences in the incidence of obstetrical complications when comparing a thick septum (defined as >1 cm) and thin septum (defined as <1 cm). One other study correlated septal size with incidence of preterm birth prior to and after hysteroscopic septum incision in 730 women (42). In this study, a small septum was defined as measuring 1.3–1.5 cm at the time of hysteroscopy, with a large septum defined as all other septa including complete septate uteri. The rates of preterm birth, neonatal death, stillbirth, and need for neonatal care in the small septate versus large septate groups were similar both before and after septum incision, although statistical analysis was not provided. Other studies have similarly found no correlation with size and shape of septum and reproductive outcome (12, 37, 43). These observational studies suggest that the length and thickness of the uterine septa do not correlate with reproductive outcomes.

Few studies have evaluated the reproductive outcomes in women with partial compared with complete uterine septa. One study recorded reproductive outcomes from the first pregnancy in 14 patients with a partial septate uterus and 17 patients with a complete septate uterus. Term-delivery rates prior to surgical correction were similar in the two groups (27). Another study evaluated 31 women with a partial septate and 60 women with a complete septate uterus and found that the incidence of first-trimester losses, second-trimester losses, and term-delivery rates were similar (44).

Summary statement:

- There is insufficient evidence to conclude that obstetric outcomes are different when comparing the size as defined by length or width of uterine septa. (Grade C)

SURGERY TO TREAT A UTERINE SEPTUM

The uterine septum may be repaired with a laparotomy (Jones or modified Tompkins procedures) or with hysteroscopic techniques. With the advent of the less invasive hysteroscopic techniques, these other procedures have largely been abandoned. Hysteroscopic management of a uterine septum can be performed in the operating room under anesthesia, or in an office setting. Commonly used techniques include incision of the septum utilizing cold scissors, unipolar or bipolar cautery, or laser, or resection of the septum. Use of distending media for the uterus is dependent on the incision technique or energy source and includes saline, glycine, sorbitol, or mannitol (45). Laparoscopy and, more recently, transabdominal ultrasound have been used concurrently with hysteroscopic incision to confirm uterine contour, decrease the risk of uterine perforation, and assess complete removal of the septum and the presence of other anomalies (46).

There are few RCTs evaluating the efficacy of or complications among hysteroscopic techniques compared to another. One prospective randomized trial in 160 women with recurrent pregnancy loss or infertility undergoing hysteroscopic septum incision compared two techniques: 26F resectoscope with unipolar knife (80 women) or a 5-mm diameter hysteroscope with VersaPoint (bipolar) device (Ethicon US) (80 women) (47). The women were then managed expectantly with follow-up of 1 year. There was no difference in reproductive parameters between the two techniques, including pregnancy and delivery rates, preterm delivery rate, or incidence of spontaneous abortions. Operative time, fluid absorption rates, and cervical trauma were significantly greater with the resectoscope compared with the VersaPoint. Another retrospective study evaluated 27F resectoscope compared with the 5-mm VersaPoint for hysteroscopic septum incision in 63 women (48). Reproductive outcomes such as pregnancies, abortions, term deliveries, and preterm deliveries were not significantly different between the two techniques. Another retrospective study in 70 women compared the results following hysteroscopic septum incision using cold scissors (17 women) compared with resectoscope with unipolar cautery (53 women) (49). Pregnancy rates and delivery rates were significantly greater in the scissors group, although the follow-up period was longer in the scissors group than the resectoscope group. Operative time was shorter with the resectoscope. A prospective study compared the use of ultrasound guidance with laparoscopic observation during hysteroscopic septum incision and found that ultrasound guidance was comparable to laparoscopic observation regarding efficacy and safety (50).

There have been 18 case reports in the literature of uterine rupture during pregnancy or delivery following septum incision (8). Risk of subsequent pregnancy-related uterine rupture is correlated with excessive septal excision, penetration of the myometrium, uterine wall perforation, and excessive use of cautery or laser energy during the initial septum incision procedure.

Summary statement:

- There is insufficient evidence to recommend a specific method for hysteroscopic septum incision. (Grade C)

HOW LONG AFTER SURGICAL TREATMENT OF A UTERINE SEPTUM SHOULD A WOMAN WAIT TO CONCEIVE?

The time from septum incision to attempting pregnancy has not been evaluated in randomized controlled studies. However, there are a few studies addressing this issue. One study assessed the postoperative appearance of the endometrium and correlated this with endometrial biopsy specimens in 19 women who were randomized to follow-up hysteroscopy at 1, 2, 4, or 8 weeks after hysteroscopic septum incision (51). At 2 weeks' postop the incised zone of the septum was depressed on both uterine walls and had wide areas lacking endometrial covering. By 8 weeks' postop the uterine cavity was morphologically normal and the covering endometrium was regular. Another prospective study evaluated 16 patients with office hysteroscopy for 2 weeks, then every 2 weeks following hysteroscopic incision of septum until wound healing was complete (52). Following septum incision, 19% of

patients at 1 month and 100% of patients by 2 months postoperatively demonstrated a healed uterine cavity. A retrospective cohort study evaluated pregnancy rates in 282 women following IVF/ICSI when the embryo transfer was performed at <9, 10–16, or >17 weeks after uterine septum incision (53). Pregnancy rates and miscarriage rates were no different among the three groups.

Summary statement:

- Although the available evidence suggests that the uterine cavity is healed by 2 months postoperatively, there is insufficient evidence to advocate a specific length of time before a woman should conceive. (Grade C)

SHOULD PREOPERATIVE MANAGEMENT TO THIN THE ENDOMETRIUM BE USED?

Hysteroscopic visualization is improved when the procedure is performed early in the menstrual cycle or with endometrial suppression using combined oral contraceptives or progestins. Therefore, it follows that utilizing agents to thin the endometrium prior to performing a hysteroscopy for septum incision may facilitate surgery and improve visibility. However, there are few studies that have evaluated this practice. In the available studies, agents used to thin the endometrium include danazol and gonadotropin-releasing hormone (GnRH) agonists. None of the studies have evaluated the use of combined oral contraceptives or progestins, and few compared the treatment with untreated controls. In a randomized prospective study of 30 patients, preoperative treatment with danazol (600 mg/day for 2–4 weeks) was compared with GnRH agonist (3.75 mg depot injection for 2 months) (54). Both groups were comparable with respect to bleeding, complications, adhesions, and residual septa, but the danazol group had less difficulty dilating the cervix, fewer endometrial fragments, and less difficulty maneuvering the resectoscope.

Agents used to thin the endometrium preoperatively usually create a hypoestrogenic environment which could potentially increase the risk for postoperative adhesion formation. A randomized placebo-controlled study was performed to address this concern in a group of 95 women undergoing operative hysteroscopy for a variety of indications (55). Of 15 women undergoing uterine septum incision, 8 were randomized to either danazol 400 mg/day or iron pills for 6 weeks prior to surgery. The other seven women were recruited prospectively for the surgery, but were not included in the randomization and were not pretreated. When the groups were compared, there were no significant differences in operative time or fluid deficit. The incidence of intrauterine adhesions at office hysteroscopy performed 14–30 days after the initial surgery revealed four of seven patients with adhesions in the danazol group and none in the other groups; however, this difference did not reach statistical significance.

Summary statement:

- There is insufficient evidence for or against recommending danazol or GnRH agonists to thin the endometrium prior to hysteroscopic septum incision. (Grade C)

IS ADHESION PREVENTION NEEDED?

Intrauterine adhesion formation following hysteroscopic uterine septum incision can have significant consequences. Although the risk is believed to be low, treatment options that have been proposed to decrease this risk include antibiotics, postoperative estrogen therapy, and placement of an intrauterine balloon or device to separate the endometrial walls in the postoperative period.

The largest study to evaluate adhesion prevention techniques was a randomized controlled study of 100 women undergoing hysteroscopic incision of uterine septum (56). Postoperative treatment was administered for 2 months and included 2 mg estradiol valerate and 0.5 mg norgestrel once daily (n = 25), copper intrauterine device (IUD) (n = 25), both hormone therapy and IUD (n = 25), or no treatment (n = 25). The uterine septum was resected using monopolar cautery, and follow-up hysteroscopy was performed 2 months after the initial surgery. The incidence of postoperative adhesions in the 79 patients eligible for final analysis was as follows: control group 5.3%, IUD-only group 10.5%, hormone + IUD 12%, and hormone-only group 0%. These differences were not statistically significant; however, the study was substantially underpowered. Another prospective randomized study in 20 patients evaluated postoperative intervention in 10 women (copper IUD plus conjugated estrogens 1.25 mg twice daily for 30 days with medroxyprogesterone acetate 10 mg/day for the last 5 days) and no therapeutic measures (control group) (57). The patients were evaluated postoperatively by HSG performed after hormone withdrawal bleed or first spontaneous menses. There were no intrauterine adhesions detected in either group, and there was no difference in incidence of a residual uterine septum ≥1 cm. Another prospective randomized controlled study in 28 patients undergoing septum incision evaluated postoperative Foley balloon placement (14 French pediatric Foley balloon with 5 mL normal saline for 5 days) compared with no treatment (58). None of the women were treated with antibiotics, preoperative endometrial thinning, or adjuvant postoperative hormonal therapy. There were no abnormalities noted by HSG at 3 months postoperatively in either group.

One prospective randomized study in 16 patients undergoing septum incision evaluated the use of intrauterine auto-crosslinked hyaluronic acid gel administered immediately following incision compared with no therapy (59). The incidence of postoperative adhesions assessed by hysteroscopy was lower in the gel group compared with controls (12.5% vs. 37.5% respectively, $P<.05$).

Summary statement:

- There is insufficient evidence to recommend for or against adhesion prevention treatment, or any specific method following hysteroscopic septum incision. (Grade C)

SUMMARY

- Septate uterus configurations include partial septum, and complete septum in association with cervical septum or duplicated cervix.

- There is no uniform definition of septate configurations.
- Most women with a septate uterus have efficient reproductive function.
- Arcuate uterus, although developmentally considered part of the spectrum of resorption failure, is considered a normal variant and should be differentiated from septate uterus for purposes of prognosis and surgical management.
- There is fair evidence that 3-D ultrasound, sonohysterography, and MRI are good diagnostic tests for distinguishing a septate and bicornuate uterus when compared with laparoscopy/hysteroscopy. (Grade B)
- The data regarding reproductive implications of septate uteri and treatment effects are limited and comprised primarily of observational, principally descriptive studies without untreated control groups.
- There is insufficient evidence to conclude that a uterine septum is associated with infertility. (Grade C)
- Several observational studies indicate that hysteroscopic septum incision is associated with improved clinical pregnancy rates in women with infertility. (Grade C)
- There is fair evidence that a uterine septum contributes to miscarriage and preterm birth. (Grade B)
- Some evidence suggests that a uterine septum may increase the risk of other adverse pregnancy outcomes such as malpresentation, intrauterine growth restriction, placental abruption, and perinatal mortality. (Grade B)
- Some limited studies indicate that hysteroscopic septum incision is associated with a reduction in subsequent miscarriage rates and improvement in live-birth rates in patients with a history of recurrent pregnancy loss. (Grade C)
- Some limited studies indicate that hysteroscopic septum incision is associated with an improvement in live-birth rate in women with infertility or prior pregnancy loss. (Grade C)
- There is insufficient evidence to conclude that obstetric outcomes are different when comparing the size as defined by length or width of uterine septa. (Grade C)
- Commonly used techniques to resect uterine septum include incision or removal of the septum utilizing cold scissors, unipolar or bipolar cautery, or laser.
- Use of distending media for the uterus is dependent on the incision technique or energy source and includes CO_2, saline, glycine, sorbitol, or mannitol.
- There is insufficient evidence to recommend a specific method for hysteroscopic septum incision. (Grade C)
- Although the available evidence suggests that the uterine cavity is healed by 2 months postoperatively, there is insufficient evidence to advocate a specific length.
- There is insufficient evidence for or against recommending danazol or GnRH agonists to thin the endometrium prior to hysteroscopic septum incision. (Grade C)
- There is insufficient evidence to recommend for or against adhesion prevention treatment, or any specific method following hysteroscopic septum incision. (Grade C)

RECOMMENDATIONS

- It is recommended that imaging or imaging with hysteroscopy should be used to diagnose uterine septa rather than laparoscopy with hysteroscopy because this approach is less invasive. (Grade B)
- In a patient with infertility, prior pregnancy loss, or poor obstetrical outcome it is reasonable to consider septum incision. (Grade C)
- In a patient without infertility or prior pregnancy loss, it may be reasonable to consider septum incision following counseling regarding potential risks and benefits of the procedure. (Grade C)

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