Chapter 10
Anatomic Abnormalities and Recurrent Implantation Failure

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Fibroids

Uterine myomas are the most common uterine abnormality with a lifetime incidence of up to 70% among white women and 80% in black women and an annual incidence that increases with age up to menopause [1]. They have been classified by International Federation of Gynecology and Obstetrics (FIGO) stage as submucosal, intramural, subserosal, and cervical [2–4] (Fig. 10.1).

Fibroids arise as benign monoclonal tumors of the smooth muscle cells of the myometrium, frequently due to a single event involving multiple chromosomal breaks with random reassembly [5]. Myoma origin has also been traced to point mutations in the mediator complex subunit MED12 [6]. In addition to causing anatomical distortions of the uterine cavity, leiomyomas are known to express higher levels of TGF-β mRNA [7]. Stro-1/CD44 has been proposed as a putative human fibroid (as well as myometrial) stem cell marker based on formation of fibroid-like lesions in xenotransplantation mouse models [8].

Infertility Associated with Fibroids

It is clear based on multiple prospective trials and systematic reviews that submucosal myomas adversely impact fertility, decreasing successful IVF outcomes by approximately 70%, whereas subserosal myomas appear to have minimal impact on fertility [9–11]. Although some early data on intramural myomas showed no adverse effect on fertility [9, 12, 13], several systematic reviews have since revealed a

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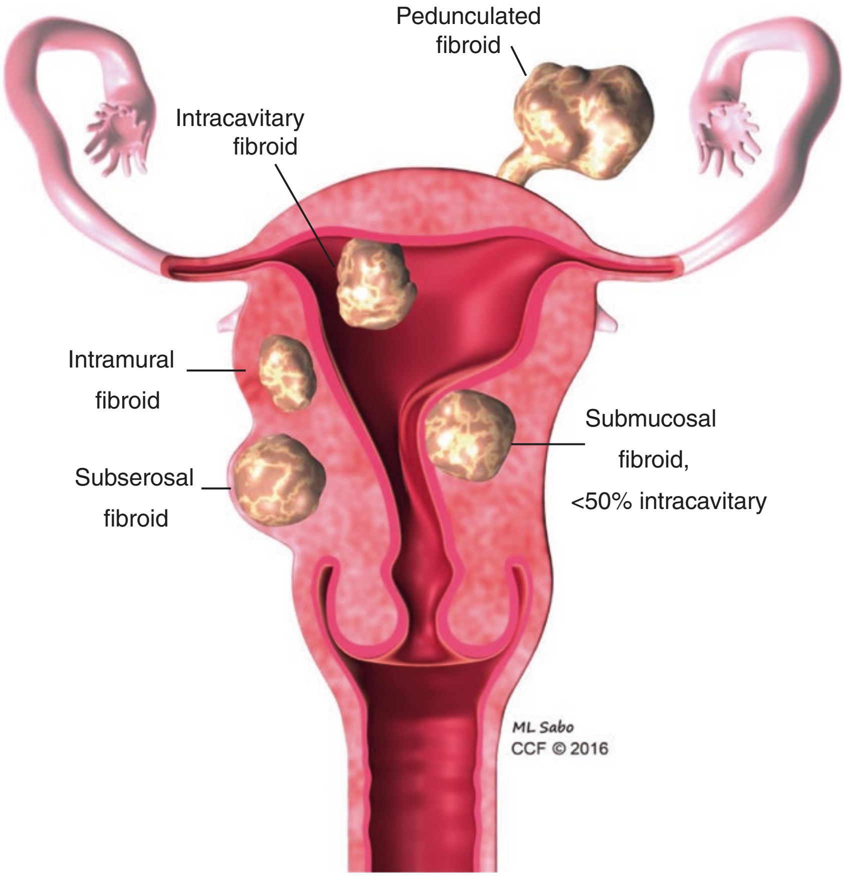

Fig. 10.1 Uterine fibroids. Fibroids may be present as submucosal, intramural, or subserosal lesions and may be located anywhere in the uterus, including the cervix. Myomectomy for fibroids distorting the endometrial cavity is recommended to improve fertility and reduce recurrent pregnancy loss. ©ML Sabo CCF 2016

reduction in IVF success rates of 20–30% associated with intramural fibroids [10, 11, 14]. A 2009 meta-analysis of 23 studies evaluated IVF outcomes among patients with and without uterine fibroids. Significantly decreased clinical pregnancy (RR, 0.363; 95% CI, 0.179–0.737) and live birth rates (RR, 0.283; 95% CI, 0.123–0.649) as well as an increased miscarriage rate (RR, 1.678; 95% CI, 1.373–2.051) were observed in patients with submucosal fibroids compared to controls [10]. There was no significant difference in clinical pregnancy, live birth, or miscarriage rates among patients with subserosal fibroids [10]. In patients with intramural myomas, the review reported decreased pregnancy (RR, 0.810; 95% CI, 0.696–0.941) and live birth (RR, 0.684; 95% CI, 0.587–0.796) rates, as well as an increased miscarriage rate (RR, 1.747; 95% CI, 1.226–2.489) [10]. Other systematic reviews reported similar findings [11, 14].

Pathophysiology

Infertility associated with fibroids has been attributed to a number of mechanisms, but the most significant effects of fibroids on fertility are thought to result from impaired implantation. Mechanical distortion of the uterine cavity may adversely affect implantation by obstructing fallopian tubes, increasing the presence of blood and clots in the uterine cavity, and disturbing normal uterine contractility [15–17]. Increased uterine contractility may prevent sperm migration, embryo transport, and ovum capture [18–21]. MRI studies show altered uterine contractility during the mid-luteal phase among infertile patients with intramural fibroids [17]. In a follow-up study, this increased contractility improved after myomectomy and was associated with improved pregnancy rates [22]. In addition to causing mechanical endometrial distortion, there is also evidence that fibroids may impair implantation at the histologic and molecular levels. Glandular atrophy, hypertrophy, adenomyosis, and the separation of glands from the basal layer of the endometrium have all been observed surrounding myomas in otherwise normal endometrium [23]. Studies have shown altered expression of the HOXA-10 and HOXA-11 genes, which are hypothesized to be involved in the molecular events leading to implantation, in fibroids [24]. These changes, together with focal endometrial inflammation [19, 21], may impair implantation. Finally, vascular disturbances such as venous congestion and diminished endometrial perfusion may compromise nidation [25–27].

Medical Interventions

Until the recent introduction of selective progesterone receptor modulators, gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate were considered the most effective medical option for management of symptomatic fibroids [28, 29]. In vitro studies show that GnRH agonists lead to increased expression of GnRHR1, COL1A1, fibronectin, and versican variant V0 in leiomyoma cells [30]. In addition, GnRH agonists inhibit the production of extracellular matrix proteins despite the presence of gonadal hormones [31]. A RCT comparing leuprolide plus iron with iron alone found a significant reduction in uterine and myoma volume with leuprolide treatment [29]. This finding is consistent across multiple similar studies [32–34] and confirmed by a Cochrane meta-analysis [35]. Unfortunately, menopausal side effects related to hypoestrogenism have been widely reported in the majority of leuprolide-treated patients in all studies and generally preclude long-term treatment [28, 29, 32–34]. Because this therapy is typically limited to short-term symptomatic treatment prior to surgery, it has not been explored as an alternative to surgery [36]. While the fertility outcomes of leuprolide therapy in management of myomas have never been tested, many have advocated for its use as an adjunct to surgical myomectomy in women who desire further fertility because of the decreased uterine trauma involved in excising smaller lesions [34, 37].

Selective progesterone receptor modulators, most notably ulipristal, have been evaluated as a nonsurgical option for fibroids [38]. A landmark double-blind non-inferiority study found that ulipristal was non-inferior to leuprolide in controlling bleeding from symptomatic fibroids, and significantly fewer (10 vs 40%) moderate to severe hot flashes were observed in the ulipristal group [28]. Although never studied as an intervention for infertility, multiple studies have demonstrated regression of fibroids after treatment with ulipristal with improvement of anemia and pelvic pain [28, 39, 40], suggesting that that medical management may reverse some of the endomyometrial changes that are hypothesized to diminish fertility. Ulipristal downregulates angiogenic factors and cell proliferation in leiomyoma cells but not normal myometrial cells by increasing the expression of caspase-3 and decreasing the expression of Bcl-2 [36, 41, 42]. Case series of pregnancies resulting from ulipristal treatment in infertile patients also have been reported, including two patients whose fibroid regression was significant enough to resolve previous cavitary distortion and permit a pregnancy without the need for surgery [43, 44].

Danazol is also frequently used to control bleeding from fibroids [36], but this therapy currently lacks reliable supporting evidence [45].

Surgical Intervention

The role of myomectomy for infertility varies based on the type, number, and size of fibroids, as well as other factors that affect a patient's fertility, including ovarian reserve and age [15]. Weak mechanistic evidence supporting the benefits of surgical intervention comes from a study of infertile patients with intramural leiomyomas (IM) not distorting the endometrial cavity that found that mRNA expression of HOXA-10 and HOXA-11 from mid-luteal endometrial biopsies had a trend toward decreased levels compared with fertile patients and that this expression significantly increased 3 months after myomectomy [46].

There is clear evidence that myomectomy for submucosal fibroids significantly improves fertility outcomes associated with both spontaneous conception and IVF. A meta-analysis reported that myomectomy doubled clinical IVF pregnancy rates compared with patients who did not undergo myomectomy (RR: 2.034, 95% CI: 1.081–3.826) [10]. Similarly, a prospective study evaluating 181 women with fibroids showed improved pregnancy rates in the year following myomectomy without additional fertility interventions [47]. Among patients with submucosal fibroids, 43.3% who underwent abdominal or hysteroscopic myomectomy achieved pregnancy, compared to 27.2% among patients who did not undergo surgery [47]. Overall, these data suggest an important role for myomectomy to improve fertility outcomes in patients planning to undergo IVF or pursue natural conception. The Society of Obstetricians and Gynecologists of Canada has issued clinical practice guidelines recommending the removal of submucosal fibroids to improve pregnancy rates in patients with otherwise unexplained infertility [48]. The benefits of myomectomy appear to be most pronounced in patients under the age of 35 with less than 3 years of infertility [49].

Although intramural fibroids appear to have a negative impact on fertility as well, there is no clear consensus on whether myomectomy for intramural myomas improves fertility outcomes. A prospective study evaluating spontaneous conception rates in 181 patients with fibroids showed improved pregnancy rates in patients with intramural fibroids in the year after myomectomy compared to patients who declined myomectomy (from 40.9 to 56.5%); however, this improvement did not reach statistical significance [47]. Another prospective cohort study evaluated IVF outcomes in patients with intramural or subserosal fibroids with at least one fibroid measuring >5 cm in diameter. These investigators showed significantly increased rates of clinical pregnancy and delivery across three IVF cycles among patients with fibroids who underwent myomectomy prior to IVF, as compared to those who did not [50]. Conversely, a 2012 Cochrane review including three randomized controlled trials found insufficient evidence to support an improvement in fertility outcomes after myomectomy for patients with intramural fibroids [51]. Given the lack of clear fertility benefit to myomectomy for intramural fibroids, decisions about when to pursue myomectomy can be challenging. The uncertain benefits of myomectomy must be balanced with the risks of surgery, including postoperative adnexal adhesions and uterine rupture during subsequent pregnancy [15]. The Society of Obstetricians and Gynecologists of Canada recommends against the removal of intramural fibroids in patients with unexplained infertility who have hysteroscopically confirmed normal endometrial cavity endometrium, regardless of the size of the fibroids [48]. However, large intramural myomas may increase the risk of pregnancy complications such as miscarriage, preterm delivery, malpresentation, outlet obstruction, postpartum hemorrhage, and pain from degeneration.

As there is no evidence for reduced fertility associated with subserosal fibroids, unless fibroids are large enough to obstruct the fallopian tubes or affect uterine growth, they should not be removed to optimize fertility outcomes [15, 48].

When myomectomy is indicated, there is little available data to suggest a benefit of one surgical approach over another. Resection of submucosal fibroids should be performed hysteroscopically when ≥50% of the myoma is intracavitary, as this is the least invasive mode of myomectomy. Expert opinion suggests that fibroids ≤5 cm in diameter can typically be resected hysteroscopically, though larger fibroids have successfully been removed using a hysteroscopic approach [48]. Two randomized trials compared reproductive outcomes after laparoscopic versus abdominal myomectomy. One study of 131 patients who underwent myomectomy showed no significant differences in the rates of pregnancy, miscarriage, cesarean delivery, or preterm delivery in the laparoscopic versus abdominal myomectomy groups [52]. Not surprisingly, the investigators reported a shorter hospital stay and a smaller postoperative hemoglobin drop in the laparoscopic compared with the abdominal group [52]. Another study of reproductive outcomes after minilaparotomy and laparoscopic myomectomy showed similar cumulative pregnancy, live birth, and miscarriage rates at 12 months [53]. Laparoscopic myomectomy is typically recommended for myomas <10–12 cm in size, less than 4 in number and for intramural myomas >3–5 cm in size with cavity distortion in cases of infertility [18, 38, 54]. Robotic-assisted laparoscopic myomectomy offers similar outcomes to laparoscopic myomectomy, but operative times and costs are increased [55].

Other Interventions

Uterine artery embolization (UAE) has been studied and effectively used to improve bulk symptoms and menorrhagia [56–59]. However, desire for future fertility is a contraindication to UAE given the poor reproductive and obstetric outcomes observed following the procedure. In an average follow-up of 33.4 months, only 1 in 31 women became pregnant after UAE [60]. A randomized controlled trial comparing UAE to myomectomy in 121 patients with intramural fibroids >4 cm revealed a significantly increased rate of miscarriage and a decreased rate of pregnancy in the UAE group compared to the myomectomy cohort [61]. Similarly, a cohort of 53 pregnancies after UAE and 139 pregnancies after laparoscopic myomectomy showed a higher rate of preterm delivery, fetal malpresentation, and cesarean section in the UAE group [62]. The most common complication reported in pregnancies after UAE is postpartum hemorrhage; however, cases of abnormal placentation have also been reported [63]. In addition, UAE may decrease ovarian reserve by compromising the ovarian blood supply through the utero-ovarian ligament, leading to a detectable increase in FSH and decrease in AMH compared with expected age-related changes [64]. Although pregnancy is possible following uterine artery embolization, the procedure should not be offered to patients seeking future fertility.

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) has also been explored as an intervention for fibroids [65]. MRgFUS permits thermal ablation of fibroids while minimizing damage to nearby structures using mapping from T2-weighted MRI. Preliminary experience of fertility outcomes from this technique has been most extensively described by Rabinovici, who reported 54 pregnancies in 51 women after MRgFUS [66].

Preliminary studies of a recently approved laparoscopic radiofrequency volumetric thermal ablation device [67] have observed a significantly shorter hospital stay, and less intraoperative blood loss with this treatment than with laparoscopic myomectomy, although fertility outcomes are still unknown [68].

Polyps

Endometrial polyps are focal overgrowths of endometrial glands and stroma within the uterine cavity supplied by a single blood vessel [69]. The functional layer of the polyp endometrium may be asynchronous with the surrounding endometrium,

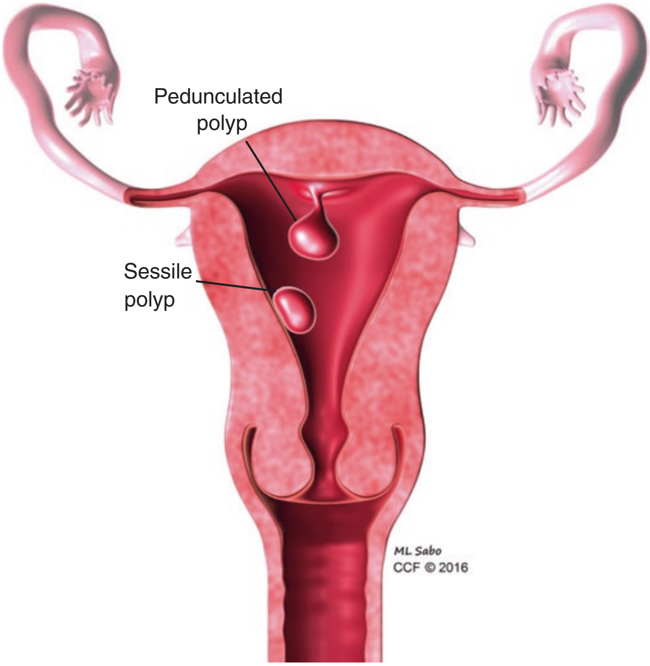

Fig. 10.2 Uterine polyps. Hysteroscopic resection of both pedunculated and sessile polyps is both technically straightforward and highly effective in improving IVF outcomes. ©ML Sabo CCF 2016

predisposing patients to symptoms of abnormal uterine bleeding [70]. Polyps are classified as sessile or pedunculated and can be found anywhere in the uterine cavity, but are particularly common near the fundus [71] (Fig. 10.2).

The overall prevalence of polyps in asymptomatic women undergoing treatment for infertility has ranged across studies from 6 to 32% [72, 73]. Polyps are more prevalent in women with unexplained infertility (15.6%) compared with those with a history of tubal ligation (3.2%) [70].

Pathophysiology

As with fibroids, mechanical distortion of the cavity impeding sperm or ovum transport is thought to play a role in reducing fertility [70]. Elevated nuclear factor kappa-B (NF-κB) expression and p65 immunoreactivity were observed in the endometrium of women with polyps compared with unexplained infertile and fertile controls [74]. In addition, elevated expression of progesterone receptor (PR) in the polyp stromal compartment and elevated Cox-2 and Bcl-2 in the glandular compartment were noted in obese females whose polyps were examined following resection [75]. Decreased LIF mRNA expression has been reported in women with abnormal uterine cavities (uterine submucosal myoma or an endometrial polyp) during the mid-secretory phase [76], and the presence of endometrial polyps is associated with decreased mid-secretory concentrations of IGFBP-1, TNF-α, and osteopontin [77]. These expression changes are reversed following surgical polypectomy [77]. These findings collectively suggest that inflammatory changes may contribute to polyp-associated infertility.

Surgical Intervention

In contrast to fibroids, there is consensus on the role of surgical intervention for endometrial polyps in the management of infertility. A systematic review reported that hysteroscopic polypectomy prior to IUI can increase clinical pregnancy rate compared with diagnostic hysteroscopy alone [78]. These findings are largely based on a single RCT of patients with polyps comparing hysteroscopic polypectomy with diagnostic hysteroscopy that found significantly higher pregnancy rates in the treatment group after up to four IUI cycles [79].

Expert opinion suggests that hysteroscopic polypectomy should be performed prior to IVF to optimize chances of successful implantation [80]. There remains some controversy about the true benefit of operative hysteroscopy in light of a meta-analysis of routine hysteroscopy prior to IVF that noted a benefit to hysteroscopy on pregnancy rates (RR, 1.44, 95% CI 1.08–1.92) that was not related to the degree of uterine pathology noted [81]. Nonetheless, evaluation of the uterine cavity and removal of any polyps remains the standard of care.

Intrauterine Adhesions

Intrauterine adhesions vary in extent from a single filmy adhesion to complete obliteration of the endometrial cavity [82, 83] (Fig. 10.3). They are most commonly the result of uterine instrumentation, particularly postpartum curettage [84]. Although the term Asherman syndrome is often used interchangeably with intrauterine adhesions, a distinction should be made between asymptomatic intrauterine adhesions and hysteroscopically confirmed adhesions associated with amenorrhea, hypomenorrhea, subfertility, recurrent pregnancy loss, or abnormal placentation including previa and accreta. The latter category is defined as Asherman syndrome [85].

Given a reported prevalence of adhesions of up to 38% in patients with early pregnancy loss [86] and 8% in infertile women [87], clinicians must be aware of the possibility of an adhesion among patients seeking infertility treatment even in the absence of secondary amenorrhea, a diagnosis associated with a 3% prevalence of adhesions [87].

Although hysteroscopy is the gold standard for diagnosis, hysterosalpingography and saline sonohysterography can also be used to evaluate for adhesions. However, hysteroscopy is required to determine the extent and location of adhesions [85].

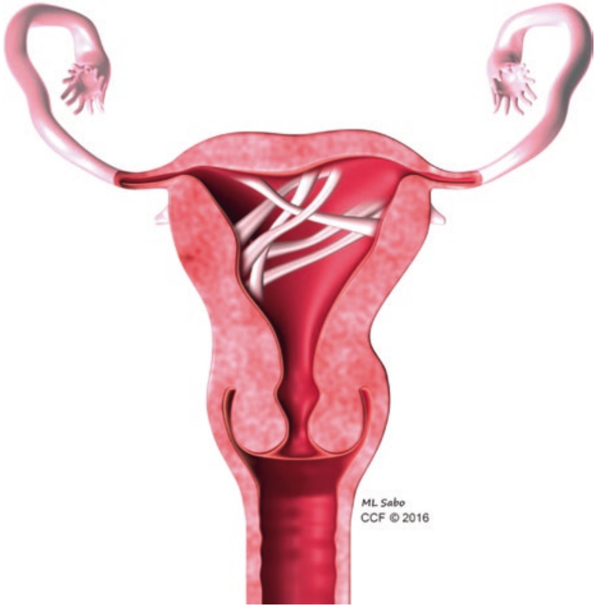

Fig. 10.3 Uterine adhesions may completely obliterate the uterine cavity and replace functional endometrium. Clinical success in terms of restoring normal menstrual and reproductive function is based on the degree of cavity scarring and the ability of the remaining endometrium to cover the raw surfaces following adhesiolysis. ©ML Sabo CCF 2016

Pathophysiology

In a review of 1856 cases of intrauterine adhesions, over 90% were associated with a previous pregnancy [84]. Of the patients with a pregnancy-related adhesion, two thirds had undergone a post-abortion/miscarriage curettage [84]. A possible explanation for the susceptibility of the gravid uterus to Asherman is the low estrogen status at the time of instrumentation, given that the endometrium requires estrogen for regeneration [85]. Other rare causes in a non-gravid uterus were traced to a diagnostic curettage, myomectomy, polypectomy, placement of an IUD, exposure to radiation, and genital tuberculosis [84, 88]. In addition, intrauterine adhesions are widely reported to form following endometrial ablation procedures [89, 90], contraindicating use of this treatment modality in women desiring fertility [91].

Intrauterine adhesions are characterized by multiple histologic changes, including replacement of endometrial stroma with fibrous tissue, replacement of the functionalis and basalis layers with cubo-columnar epithelium, and adherence of opposing endometrial surfaces, obliterating the cavity [85, 92]. The epithelial monolayer that replaces the functional endometrial layer is not responsive to hormonal stimulation, and synechiae form across the cavity. The tissue is typically avascular. Calcification or ossification may occur in the stroma, and glands may be either inactive or cystically dilated [88]. Alterations to the vascularity of the endometrium have been shown using angiography, with a significant reduction in myometrial blood flow and vascular occlusion in patients with hypomenorrhea [93]. These changes are likely to adversely affect implantation, as hypotrophic endometrium is unreceptive to an embryo [88, 93]. While inflammation is thought to play a role, a study of women who underwent cesarean sections found that endometritis alone does not play a significant role in adhesion formation [94].

An evaluation of 2151 cases of Asherman syndrome showed an infertility rate of 43% [84]. This infertility may be a result of obstruction of the fallopian tubes, uterine cavity, or cervical canal due to adhesions [85]. The synechiae may negatively affect sperm transport and implantation [85]. Elevated rates of pregnancy loss among patients with Asherman syndrome may be secondary to insufficient endometrial tissue to support implantation and placental development and abnormal vascularization of remaining endometrial tissue due to fibrosis [85].

Treatment

No high-quality RCTs exist to support surgical correction of intrauterine adhesions to treat infertility [78, 82]. Nonetheless cohort studies strongly support hysteroscopic adhesiolysis for patients found to have intrauterine adhesions. Hysteroscopic lysis of adhesions has become the standard of care for treating Asherman syndrome and pregnancy rates after intervention range from 33 to 80% [85]. In a study of 187 patients treated surgically, 80% subsequently achieved a term pregnancy [95], while another study of 90 patients with recurrent pregnancy loss found that intervention improved the newborn delivery rate of treated patients from 18.3 to 64% [96]. Patients with Asherman syndrome who become pregnant after treatment remain at increased risk of miscarriage, preterm delivery, abnormal placentation, intrauterine growth restriction, and uterine rupture [85].

A number of methods have been evaluated to prevent the recurrence of adhesions after surgery. Among these are unmedicated IUDs, balloon catheters, exogenous estrogens, and hyaluronic acid [82, 85]. With the exception of hyaluronic acid gel, which is not available in the US, the other adjuvant treatments were ineffective.

Female Genital Tract Malformations

Congenital uterine malformations represent a broad range of developmental disorders and syndromes. Isolated uterine malformations are typically the result of failure of the mullerian ducts to fuse in the midline, resulting in arcuate, didelphic, bicornuate, or unicornuate uteri, or failure of resorption of the fused medial walls, leading to a uterine septum (Fig. 10.4). There are numerous classification systems for this spectrum of disorders. The American Fertility Society classification system from 1988 is perhaps the most popular [97].

Uterine malformations have been estimated to be present in 6.7% of the general population and 7.3% of the infertile population, suggesting an overall limited role for these factors in contributing to infertility [98]. The arcuate uterus is the most common anomaly in the general population, while a septate uterus is the most

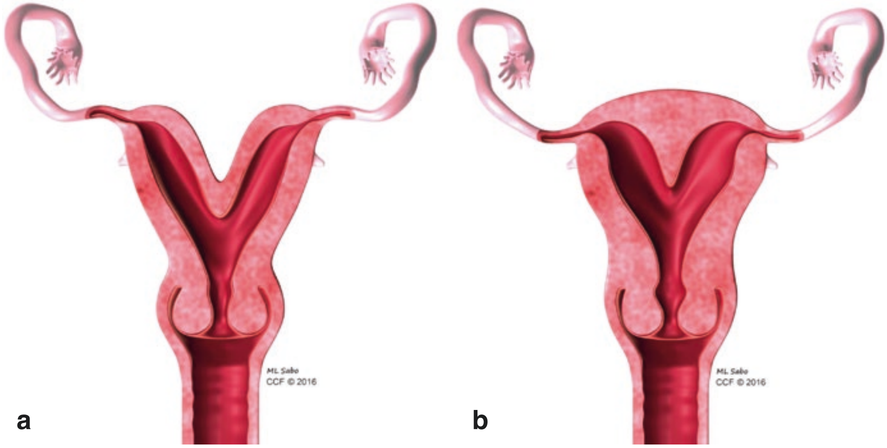

Fig. 10.4 Uterine anomalies including septate, arcuate, bicornuate, unicornuate, and didelphic uteri affect reproductive outcomes. (**a**) Bicornuate uterus. (**b**) Septate uterus. ©ML Sabo CCF 2016

Table 10.1 Effect of mullerian anomalies on reproduction

	Pregnancy	SAB	PTD	Malpresentation
Arcuate	1.0	1.4	1.5	2.5*
Septate	0.9*	2.9*	2.1*	6.2*
Bicornuate	0.9	3.4*	2.6*	5.4*
Unicornuate	0.7	2.2*	3.5*	2.7*
Didelphys	0.9	1.1	3.6*	3.7*

Meta-analysis of 9 controlled studies with 3805 patients
Relative risk compared to normal uterus, *$p < 0.05$
SAB spontaneous abortion, *PTD* preterm delivery
Modified from Chan et al. Ultrasound Obstet Gynecol 2011;38:31–82

common in the infertile population, suggesting that certain anomalies may introduce barriers to achieving fertility [98].

Congenital uterine anomalies have been most widely reported to occur in the recurrent miscarriage population, with an estimated prevalence of 13–17% [98–103]. Poor IVF and reproductive outcomes have been reported in patients with untreated uterine anomalies [104] (Table 10.1). An abnormal uterine cavity is thought to impair fertility by anatomical means, motivating surgery for restoration of normal anatomy [100]. Pregnancies resulting from anatomically distorted cavities are much more likely to result in breech presentation and necessitate Cesarean delivery than those in normal cavities [105]. A history of recurrent pregnancy losses is the primary indication for treatment of patients with uterine malformations [98, 106, 107]. Because no high-quality randomized controlled trials exist to support surgical correction of these anomalies in patients with recurrent pregnancy loss or infertility [78], there remains considerable debate in the field regarding appropriate management [108–110].

Uterine Septum

The septate uterus is the most common of the uterine anomalies and is the anomaly associated with the highest rates of pregnancy complications, including early abortion (44.3%), fetal malpresentation, intrauterine growth restriction, and preterm delivery (22.4%) [100]. A meta-analysis comparing women with septate uteri to normal controls noted reduced clinical pregnancy rates (RR 0.86), increased first-trimester miscarriage rates (RR 2.89), increased rates of preterm birth (RR 2.14), and an elevated risk of fetal malpresentation at delivery (RR 6.24) [111].

The association between the uterine septum and poor obstetric outcomes is not well understood. Several mechanisms are thought to underlie this association, including alterations in vascularity of the septum and changes in tissue composition and receptivity of the septum to steroids hormones [112–114]. A small study comparing the septal endometrium with endometrium from the lateral uterine wall showed altered differentiation and estrogenic maturation of septal endometrium, suggesting that the septum may be an unfit location for implantation [112]. A histopathologic study found increased muscular fibers in uterine septa compared to normal myometrium, leading the authors to theorize that irregular contractility from septum muscle fibers contributed to an increased spontaneous miscarriage rate [113]. mRNA expression of VEGF receptors was significantly lower in the endometrium lining the septum compared with the endometrium lining the walls of the normal uterus, suggesting that alterations in septum vascularity may contribute to poor obstetric outcomes [114].

Fortunately, the uterine septum is highly amenable to correction by hysteroscopic septoplasty. Abdominal metroplasty, i.e., Jones and Tomkins procedures, is of historic interest only [107]. Surgical intervention has been shown to improve reproductive outcomes in patients with uterine septa. A review of patients treated with hysteroscopic metroplasty found a significant decrease in abortion (16.4%) and preterm delivery rates (6.8%) compared with untreated controls [100]. Another study reported that the miscarriage rate decreased from 88% before metroplasty to 14% after, with an 80% live birth rate compared with a 4% preoperative rate [101]. Improved IVF implantation rates were reported following metroplasty [104], leading to the recommendation that it be performed prior to an embryo transfer [115]. A prospective trial comparing metroplasty in infertile patients with a septate uterus to expectant management in patients with unexplained infertility found a significantly higher pregnancy rate following surgical intervention (38.6 vs 20.4%), supporting the notion that a septum adversely impacts fertility [116]. These findings are supported by a meta-analysis noting that hysteroscopic resection of a uterine septum substantially reduced the probability of a spontaneous abortion (RR 0.37) compared with untreated patients [117]. A 2011 Cochrane review attempted to evaluate the impact of metroplasty in patients with recurrent pregnancy loss; however, no randomized controlled trials could be identified for inclusion [118]. A multicenter randomized trial known as the Randomized Uterine Septum Transection Trial (TRUST) is currently underway to evaluate reproductive outcomes after septoplasty in women with a history of recurrent miscarriage, infertility, or preterm birth.

Arcuate Uterus

Patients with an arcuate uterus have an 82.7% reported live birth rate [119], essentially comparable to unaffected patients. Early abortion (25.7%) and preterm delivery (7.5%) are relatively uncommon complications [100]. Existing literature has to date largely failed to demonstrate a significant association between an arcuate uterus and adverse fertility outcomes, and hysteroscopic intervention is not generally recommended [120]. However a recent meta-analysis finding increased rates of second-trimester miscarriage (RR 2.39) and fetal malpresentation at delivery (RR 2.53) in patients with arcuate uterus compared with normal controls may lead to a reevaluation of this question [111]. These latter findings may be due to inclusion of septate uteri as arcuate in the study classification.

Unicornuate Uterus

The live birth rate in patients with a unicornuate uterus has been reported to be approximately 54.2% [119]. Early abortion (36.5%) and preterm delivery (16.2%) are more common in this population compared with the arcuate uterus population [100]. Complications associated with a unicornuate uterus are more typically related to sustaining a pregnancy than to achieving one [121]. However, a 33% reduced implantation rate compared with normal anatomy controls has been observed in IVF transfers, suggesting that implantation may also be affected by unicornuate anatomy [104]. Because 13% of pregnancies in patients with a unicornuate uterus occur in a "noncommunicating" rudimentary horn due to sperm transmigration [103], surgical removal of a rudimentary horn has been recommended to prevent uterine rupture as well as address likely symptoms of dysmenorrhea [98, 115]. However, there is no evidence that such intervention improves reproductive outcomes [115].

Didelphic Uterus

A 40% live birth rate has been reported in patients with a didelphic uterus [119]. Early abortion (32.2%) and preterm delivery (28.3%) are also common [100]. In reproductive terms, the didelphic uterus is considered to have similar pregnancy outcomes to the unicornuate uterus because it can be viewed as a duplicated unicornuate uterus [100, 122]. However, a long-term follow-up of 49 cases of didelphic uterus did not find significant impairment in fertility (94% pregnancy rate, 75% fetal survival), although 84% ultimately delivered by cesarean section [123]. Highly unusual pregnancy outcomes have been reported in patients with didelphic uteri, including a multi-fetal gestation in separate uterine horns with a 72-day lapse between the delivery of one fetus and the other [124]. While surgical procedures to repair a didelphic uterus have been developed, none have been shown to improve reproductive outcome, and all carry risk of cervical incompetence [115].

Bicornuate Uterus

A 62.5% live birth rate has been reported in patients with a bicornuate uterus [119], and early abortion (36.0%) and preterm delivery (23%) rates are elevated compared with arcuate controls [100]. These adverse outcomes are related more to gestation than conception, leading many to reserve metroplasty (performed transabdominally) for patients who experience recurrent pregnancy loss or infertility [115]. However, in those treated with abdominal metroplasty for bicornuate uterus, fetal survival and term gestation rates approach 90% [125].

Hydrosalpinges

Hydrosalpinges are characterized by distal blockage of the fallopian tubes with fluid accumulation [126] (Fig. 10.5). The disease most commonly follows an ascending sexually transmitted infection [127]. Two large meta-analyses with approximately 6700 and 5600 patients undergoing fresh and frozen IVF cycles showed that the live birth rates were halved in women with uni- or bilateral hydrosalpinges [128, 129]. Implantation and pregnancy rates were also significantly reduced, and miscarriage rates significantly increased, in the presence of hydrosalpinges [128, 129].

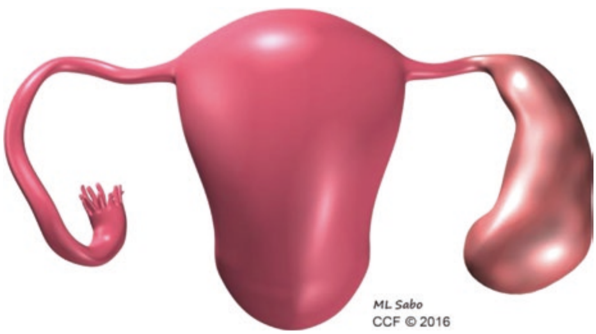

Fig. 10.5 Hydrosalpinx is characterized by distal blockage with fluid accumulation. It is treatable by salpingectomy, proximal tubal occlusion, or neosalpingostomy depending on the extent of the tubal damage. ©ML Sabo CCF 2016

Pathophysiology

Three potential mechanisms have been proposed to explain the detrimental effects of hydrosalpingeal fluid on embryo implantation. The mechanical factor suggests that reflux of the hydrosalpingeal fluid into the uterine cavity may flush out the embryo [130, 131] or create a fluid barrier to implantation [132]. Other mechanical effects are increased uterine peristalsis [133] and decreased endometrial perfusion [134].

The second mechanism is diminished endometrial receptivity through the alteration of various factors which may promote implantation. Leukemia inhibitory factor, integrin 3, and mucin 1 (MUC1) are significantly reduced in patients with hydrosalpinges [135]. Endometrial NF-κB is increased, and cystic fibrosis transmembrane conductance regulator and MUC1 are decreased with hydrosalpinges [136]. HOXA10 mRNA expression in endometrial cells is decreased when cultured with hydrosalpingeal fluid [137]. Some of these changes have been demonstrated to revert to normal following salpingectomy [138, 139].

The third mechanism is embryotoxicity which has been demonstrated in multiple studies in a mouse model but not in humans [133]. The adverse effects may be mediated by increased oxidative stress [140] or altered cytokine concentrations [141]. It is also possible that the embryotoxic effect is due to dilution of essential nutrients.

Treatment

A Cochrane review of prospective randomized studies concluded that salpingectomy for hydrosalpinges prior to IVF doubled the clinical pregnancy rate compared to untreated hydrosalpinges (OR 2.3, 95% CI 1.48–2.62), effectively negating the detrimental effects of hydrosalpinges on IVF success rates [142]. A randomized control trial comparing laparoscopic salpingectomy or tubal ligation with expectant management reported significant benefits with surgical intervention compared with the untreated control group [143]. There were no significant differences between the two treatment groups for ovarian response to stimulation, number of oocytes retrieved or embryos produced, clinical pregnancy rates, or live birth rates.

A retrospective study found that laparoscopic neosalpingostomy yielded comparable clinical pregnancy rates to salpingectomy for treating hydrosalpinges prior to IVF [144]. In patients who are poor candidates for laparoscopic treatment of hydrosalpinges, hysteroscopic placement of the Essure (Bayer, Whippany, NJ) device for proximal tubal occlusion may be considered. However, a randomized clinical trial comparing it to laparoscopic tubal ligation noted a significant reduction in implantation, clinical pregnancy, and live birth rates in the Essure group [145]. The spontaneous abortion rate was also doubled in the Essure group, though it did not reach statistical significance.

Ultrasound-guided aspiration of the hydrosalpinges fluid prior to IVF was also evaluated as a nonsurgical option. Unfortunately, the fluid rapidly reaccumulated, and no significant difference in clinical pregnancy rates compared with untreated controls was found in a randomized trial [146]. A subsequent study performed sclerotherapy by injecting 98% ethanol into the aspirated hydrosalpinges for 5–10 min, eliminating the problem of recurrence [134]. In this prospective nonrandomized trial comparing sclerotherapy to untreated hydrosalpinges, sclerotherapy significantly increased both the implantation and clinical pregnancy rates. In addition, the non-treated hydrosalpinges group had decreased endometrial perfusion based on Doppler ultrasound parameters. While it can be concluded from all of the above that hydrosalpinges impair implantation and that treating them by various means restores IVF success rates, it remains uncertain whether all hydrosalpinges behave the same. Specifically, it remains unknown if small hydrosalpinges that are not visible by transvaginal ultrasonography are a clinical concern and warrant treatment prior to initiating an IVF cycle.

Conclusions

Recurrent implantation failure with IVF may be due to anatomic disorders such as myomas, endometrial polyps, intrauterine adhesions, mullerian anomalies, and hydrosalpinges. In most cases, a detailed mechanistic understanding of how these conditions impair implantation remains elusive. Furthermore, evidence to support the effectiveness of surgical treatment on improving IVF outcomes is often limited by few studies with small sample sizes, inconsistent classification of the condition, lack of an appropriate control group, and variable follow-up intervals. Clearly, there is a need for research to address these knowledge deficiencies. In the meantime, the best available evidence favors myomectomy for myomas distorting the endometrial cavity. Hysteroscopic polypectomy, adhesiolysis, and septoplasty are also recommended prior to initiating an IVF cycle. In addition, salpingectomy, proximal tubal occlusion, or neosalpingostomy, in selected cases, should be performed for hydrosalpinges in order to restore optimal IVF success rates.

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