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Uterine Disorders and Infertility

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ABSTRACT

Uterine factors contribute significantly to female infertility, constituting 5% of all cases. This article explores key uterine disorders affecting fertility, including adenomyosis, fibroids, Müllerian anomalies, chronic endometritis, thin endometrium, and endometrial polyps. Adenomyosis, characterized by increased intrauterine pressure and abnormal inflammatory responses, poses challenges to spontaneous conception and assisted reproductive techniques (ART). Medical management, including Gonadotropin-Hormone-Releasing-Hormone Agonists and Letrozole, along with innovative approaches like High-Intensity Focused Ultrasound (HIFU), aim to improve pregnancy outcomes. Fibroids, responsible for <10% infertility cases, disrupt uterine architecture and vascularity. Diagnosis through MRI and hysteroscopy informs treatment decisions, with hysteroscopic myomectomy recommended for submucosal fibroids. Magnetic Resonance Guided Focused Ultrasound (MRgFUS) shows promise but requires further validation. Müllerian anomalies, observed in 8.13% of infertility cases, present varied outcomes. Diagnosis involves hysteroscopy, hysterosalpingography, and advanced imaging. The association of recurrent pregnancy loss with Müllerian anomaly remains debated. Chronic endometritis (CE), linked to decreased endometrial receptivity, affects 15% of infertile women undergoing IVF. Accurate diagnosis through hysteroscopy and biopsy informs antibiotic treatment. Thin endometrium and Asherman syndrome contribute to implantation failure. Early recognition and investigation are crucial for appropriate intervention. Endometrial polyps, common in subfertile women, are often removed before assisted reproductive procedures. The article emphasizes the importance of a comprehensive diagnostic approach, considering factors such as age, fibroid size, and endometrial involvement. Surgical interventions, including adenomyoma resection and myomectomy, aim to improve fertility outcomes, but risks like uterine rupture must be considered. The role of novel techniques like HIFU and MRgFUS offers alternatives but requires further research.
In conclusion, uterine factors significantly impact fertility, necessitating a thorough understanding and tailored interventions to enhance reproductive outcomes.

Keywords: Uterine factors, infertility, adenomyosis, fibroids, Müllerian anomalies, chronic endometritis, thin endometrium, endometrial polyps, assisted reproductive techniques, medical management, surgical treatment.

BACKGROUND

Uterine factors contribute to 5% of all cases of female infertility. Müllerian anomalies, adenomyoma, adenomyosis, leiomyoma, chronic endometritis, endometrial polyps, thin endometrium and Asherman's syndrome are some notable causes of uterine infertility. Following are some major uterine factors that lead to female infertility.

Adenomyosis

Most patients with adenomyosis have symptoms of dysmenorrhea, heavy menstrual bleeding, and dyspareunia. The incidence of adenomyosis has increased dramatically as increasing numbers of women are trying to conceive at an advanced age, with 22% of adenomyosis cases occurring in women under the age of 40. It is known that the junctional zone in an adenomyotic uterus is hyperplastic; It is this

myometrium adjacent to the endometrium that results in endometrial hyper-peristalsis and increased intrauterine pressure. This in turn impairs the normal utero tubal transport and endometrial function and receptivity. There is increasing evidence of an abnormal inflammatory response mediated by increased production of interleukin-6 (IL-6) and tumour necrosis factor- alpha (TNFalpha) by the endometrial stromal macrophages in an adenomyotic uterus. As levels of IL-6 and TNFalpha increase, expression of the HOX-A 10 gene (in the secretory endometrium) and Leukemia Inhibitor Factor (LIF) is reduced. LIF plays an important role in the implantation of the blastocyst.

Diagnosis

Diagnosis of adenomyosis is easily made on TVS ultrasound when three or more of the features below are seen: 1. Globular appearance of the uterus. 2. Cystic anechoic spaces in the myometrium. 3. The posterior wall of the uterus is disproportionately thicker than the anterior wall. 4. Sub-endometrial echogenic linear striations or venetian bands- Rain shower appearance 5. Heterogeneous echo-texture of the myometrium. 6. Indistinct endometrial myometrial junction (JZ). While a JZ of 8 to 12 mm thickness on MRI is suggestive of adenomyosis, a thickness of >12 mm is very predictive. 7. Diffused vascularity of the myometrium. 8. Folding of uterus towards the back of pelvisQuestion mark sign.

A localized spherical well-defined heterogeneous myometrial lesion with cystic spaces and diffuse blood supply on Doppler indicates an adenomyoma. 3D ultrasound and MRI are particularly useful for diagnosing an adenomyoma and planning surgery.

Pregnancy Outcome

The pregnancy outcome in women with adenomyosis varies with the grade of the disease and women usually fail to conceive spontaneously. Intrauterine insemination (IUI) is just as ineffective. Numerous authors have reported negative pregnancy-related outcomes in women with adenomyosis. Chiang et al. reported that women with diffuse adenomyosis were at high risk of spontaneous abortion[1]. Vercellini et al reported poor in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) outcomes with adenomyotic uterus in a meta-analysis[2]. Adenomyosis is associated with recurrent implantation failure in nearly 38% of women[3.] In addition, women with adenomyosis have an increased risk of preterm birth, preeclampsia, and second-trimester abortions.

Medical management

Infertility with adenomyosis can be difficult to treat.

- Gonadotropin-Hormone-Releasing-Hormone Agonist (GnRHa) use is associated with spontaneous conception in women with adenomyosis.
- Principles of assisted reproductive techniques (ART) in patients with adenomyosis: a.Pretreatment with GnRH analogues prior to IVF is associated with improved pregnancy outcomes. It has been seen that the mean uterine volume reduces significantly from 180 cm^3 to 86 cm^3 in women pre-treated with GnRH analogues. This leads to an improvement in embryo implantation and clinical pregnancy rates. b. GnRH analogues have also shown promising results in the two-stage IVF programs. In the first phase, ovarian stimulation precedes oocyte retrieval, fertilization and embryo freezing. This is followed by GnRH suppression for 3 months. In the second phase, frozen embryo transfer (FET) is performed in the first cycle induced by hormone replacement therapy (HRT) with the aim of transferring an embryo before regrowth of adenomyotic lesions.[4] c. Mock embryo transfer is particularly useful for assessing the length of the uterus before the actual transfer. A distorted uterine cavity can alert the treating specialist of difficult transfer. d. It is important to transfer only single embryo to

avoid the risks associated with multiple pregnancies. e. The role of Atosiban in relaxing the uterus at the time of embryo transfer has not been established.

• Letrozole 2.5 mg/day, through its aromatase inhibitory activity reduces estrogen synthesis and helps reduce uterine volume and improves symptoms.

• High intensity focussed ultrasound (HIFU): Zhou et al reported conception in 54 of 64 patients after HIFU with only 21 live births.[4] Abortion rates after HIFU were high, but there were no reports of uterine rupture. HIFU reduces uterine distensibility and predisposes to uterine rupture. Also, it is unsuitable for diffuse endometriosis.

Surgical treatment

• Adenomyomas larger than 5 cm should be removed. Resection of an adenomyoma is difficult but improves infertility outcomes.

• Adenomyosis causes recurrent implantation failure after IVF. For diffuse lesions warranting surgical excision of a significant amount of myometrium, a new technique involving H shaped incision and excision of the adenomyoma has shown better results. It should be considered in patients with IVF and early pregnancy failures. However, with this technique there is an increased risk of uterine rupture in the subsequent pregnancy. This risk can be significantly reduced if a uterine thickness of 9-15 mm is left after the surgery.[5]

• For hysteroscopic removal of the adenomyoma, it is important that it is less than 5 cm in size and protrudes into the uterine cavity. A three month pre-treatment with a GnRH analogue significantly reduces uterine vascularity in these women. Additionally, intrauterine vasopressin infiltration with an OPU needle contracts the uterus and aids in removal of the adenomyoma after incision of the overlying endometrium and myometrium. The adenomyoma can be removed with a cutting loop or with grasping forceps. This may require repeated attempts. Also, each case of adenomyoma requires individual treatment.

Fibroids

Uterine leiomyomas alone are responsible for infertility in less than 10% of cases[6]. Infertility due to fibroids is attributed to disrupted uterine architecture, abnormal uterine contractility that impedes sperm transport through an elongated uterine cavity, and distortion of uterine vascularity. Submucosal fibroids affect blastocyst implantation through altered expression of the endometrial HOXA-10 and HOXA-11 genes which play an important role in implantation. Intramyometrial fibroids larger than 5 cm, although not distorting the endometrial cavity, are associated with impaired embryo implantation and reduced pregnancy rates.

Diagnosis

Optimal modalities for diagnosing submucosal fibroids are MRI and hysteroscopy. 3D ultrasound can map the exact location of a fibroid in relation to the junction zone. Saline infusion sonography modality that has a sensitivity of 92% and a specificity of 89% for the diagnosis of intrauterine submucosal fibroids.

Treatment

1. A fibroid be considered as a cause of infertility only after all other causes of infertility have been ruled out . It is therefore important to examine a patient comprehensively and give her sufficient time, depending on her age. It is also important to determine the total number of fibroids, their size and location in the uterus. Good ultrasound mapping will determine the exact number, size and most importantly the degree of endometrial involvement of the fibroid, as this has a clear impact on planning an optimal treatment approach.

2. All FIGO types 0,1,2 fibroids (submucosal fibroids) should be treated by hysteroscopic myomectomy. For intramural fibroids larger than four centimetres or multiple fibroids, laparoscopic/open myomectomy should be considered in the presence of infertility when all other causes have been ruled out. Myomectomy itself is

associated with its share of complications such as excessive bleeding, blood component transfusion, intrauterine adhesion formation, incomplete myomectomy (all fibroids not removed), recurrence, and an uncertainty of conception after surgery. In older women with low ovarian reserve, time is of the essence. In these women, retrieval of the oocytes, followed by fertilization and cryopreservation of the embryo should be followed by FET three months later, after the uterus has adequately healed. Subserous fibroids do not alter fertility outcomes, so their removal is not recommended.

3. Magnetic Resonance Guided Focused Ultrasound (MRg FUS): Magnetic resonance-guided focused ultrasound involves the destruction of uterine fibroids by coagulative necrosis when the leiomyomatous tissue is heated above 70°C. This is achieved by focusing high-frequency ultrasound beams on the target tissue. It's a promising but expensive technique and more randomized controlled trials are needed to validate it.

Müllerian anomalies

Müllerian anomaly is observed in 8.13% of infertility patients, although its prevalence ranges from 0.06% to 38%. This large variation in prevalence rate is due to previous non-standard classification systems. Congenital uterine anomalies have been classified under the ESHRE-ESGE (2016) and ASRM/AFS classification systems; the latter is universally accepted. Müllerian anomalies are known to be associated with poor maternal and fetal outcomes. Rates of preterm birth, fetal presentations, placental abruption, and caesarean sections increases with all forms of congenital uterine malformations. It has been reported that the septate uterus is associated with low pregnancy rates while the bicornuate uterus is associated with high miscarriage rates. However, this does not apply to Uterus didelphys. In addition, women with an arcuate uterus, a minor Müllerian anomaly, have normal reproductive outcomes. The association of recurrent pregnancy loss with Müllerian anomaly is also well documented, but its association with infertility is controversial. Some studies report that resection of the uterine septum reduces the likelihood of spontaneous abortion, while others refute this. The surgical treatment of an incidental finding of uterine septa/fusion or unification defect is debatable and unproven[7-8.]

Diagnosis

Diagnosis of Müllerian anomaly can be made by hysteroscopy, hysterosalpingography, and trans vaginal ultrasound (TVS). 3D ultrasound and MRI are confirmatory. Diagnostic laparohysteroscopy is considered the gold standard method for diagnosing Müllerian anomalies.

Chronic endometritis (CE)

Chronic endometritis is associated with decreased endometrial receptivity due to insufficient endometrial cytokine secretion. 15% of infertile women undergoing IVF cycles have CE, and the prevalence rate of CE is up to 42% in patients with recurrent implantation failure. Diagnostic hysteroscopy, endometrial biopsy and their careful evaluation by an experienced histopathologist are key to an accurate diagnosis of CE. Treatment of CE requires 14 days of treatment with appropriate antibiotics

Thin endometrium

Asherman syndrome is an important cause of thin endometrium and is associated with a high rate of implantation failure. Thin endometrium should be recognized early and its aetiology thoroughly investigated so that it can be treated appropriately.

Endometrial polyp

Endometrial polyps are frequently observed in sub fertile women. Most clinicians are convinced that they should be hysteroscopically removed prior to an IUI, IVF or FET cycle

Summary

Uterine causes of infertility deserve as much attention as any other cause. Without an optimally functioning uterus, it is impossible to achieve positive reproductive outcomes. An experienced ART specialist diagnoses uterine pathology from the very first transvaginal ultrasound and directs a series of investigations for its optimal management.

Declaration by Authors

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