Uterine Factors

Carolyn R. Jaslow, PhD

KEYWORDS

• Recurrent miscarriage • Uterus • Septum • Fibroids • Uterine anomalies
• Pregnancy loss • Congenital • Acquired

KEY POINTS

- Uterine anomalies are one of the most common factors associated with recurrent pregnancy loss (RPL).
- Congenital anomalies, such as bicornuate, unicornuate, didelphic, and septate uteri, most likely result from HOX mutations in the developing Müllerian ducts.
- Of the acquired uterine anomalies, adhesions are typically formed after endometrial trauma, such as curettage, whereas fibroids and polyps are benign growths of the myometrium and endometrium, respectively.
- Many studies have explored the effects of uterine anomalies with respect to reproductive outcomes, but there are few randomized controlled trials, particularly for patients with RPL, and treatment methods lack strong supporting evidence.
- Nonetheless, metroplasty to correct a septate uterus and surgical removal of severe adhesions are recommended, and myomectomy of submucosal fibroids should be considered if no other causes have been identified.

INTRODUCTION

Recurrent pregnancy loss (RPL) is a frustrating disease that can cause considerable emotional distress in couples, often leading to a variety of other illnesses, both mental and physical.[1,2] Most often, RPL is caused by genetic abnormalities in the embryo[3]; nonetheless, chromosomal translocations, endocrine or metabolic disorders, autoimmune disorders, and anatomic anomalies of the uterus are considered the most likely parental causes associated with RPL.[4] Among the most prevalent of these parental factors are uterine anomalies, which are reported to occur in 19% of women with at least 2 consecutive miscarriages.[5] These anomalies include intrauterine adhesions, fibroids, and endometrial polyps that are acquired after birth, as well as congenital defects that arise from alterations in embryonic development, such as arcuate, bicornuate, didelphic, septate, T-shaped and unicornuate anomalies.

Disclosure: Nothing to disclose.
Department of Biology, Rhodes College, 2000 North Parkway, Memphis, TN 38112, USA
E-mail address: cjaslow@rhodes.edu

Obstet Gynecol Clin N Am 41 (2014) 57–86
http://dx.doi.org/10.1016/j.ogc.2013.10.002 **obgyn.theclinics.com**
0889-8545/14/$ – see front matter

IMAGING TO DIAGNOSE UTERINE ANOMALIES

Diagnostic testing for RPL causes can be costly and time consuming, but testing for anatomic abnormalities can bear the additional burden of subjecting a patient to an invasive procedure. Methods to identify uterine anomalies have included pelvic examination and dilation and curettage (D&C), hysterosalpingography (HSG), laparoscopy, laparotomy or other abdominal surgeries, two-dimensional or three-dimensional (3D) transabdominal or transvaginal ultrasonography alone or with saline infusion (sonohysterography [SHG]), magnetic resonance imagining (MRI), and hysteroscopy. Differences in sensitivity and specificity among these procedures have undoubtedly contributed to discrepancies in the literature regarding the prevalence and the reproductive consequences of uterine anomalies. Recent reviews identified 3D ultrasonography, SHG, hysteroscopy, and MRI as the most accurate procedures for diagnosis of uterine anomalies.[6–10] For detecting the separation of the uterine horns that distinguishes a bicornuate or didelphic uterus from a uterus with a partial or a complete septum, respectively, an external assessment of the uterus is needed. Thus, laparoscopy or laparotomy must accompany hysteroscopy for accurate diagnosis of these congenital anomalies.[6,7] Although hysteroscopy has the advantage of providing a direct view of the uterine cavity, and it can permit surgical correction of anomalies at the time of the procedure,[11] it is riskier and more invasive than the other imaging methods with high accuracy. Techniques such as MRI and 3D SHG are useful because they provide a recorded image of the anomaly, which can be saved and can allow subsequent measurements of the size and location of the anomaly.

NORMAL EMBRYOLOGY OF THE UTERUS

By the eighth week of gestation, the embryo has formed the paired Müllerian (paramesonephric) ducts that give rise to the oviducts, uterus, cervix, and the upper vagina.[12] Development of a single uterus starts with fusion of the Müllerian ducts near their caudal ends.[12] A septum initially separates the 2 ductal lumina, but it is gradually resorbed to produce a single uterine cavity.[12] This process may be controlled by uterine expression of Bcl-2, a protein that regulates apoptosis.[13] Case studies of women with a septate uterus and duplication of the cervix and vagina indicate that fusion begins at the developing uterine isthmus and progresses cranially and caudally simultaneously, followed by bidirectional resorption of the septum.[14] The unfused cranial portions of the 2 Müllerian ducts form the paired oviducts.

Based on studies of mice and other vertebrates, the Müllerian ducts originate from invagination of the coelomic epithelium lining the cranial end of the embryonic mesonephros.[15] These invaginating cells give rise to both the epithelium and the surrounding mesenchyme of the ducts, which canalize as they elongate caudally to contact the urogenital sinus.[14–16] The sites of invagination become the ostia of the oviducts, and the urogenital sinus becomes the lower vagina.[17] In the absence of testicular hormones (eg, anti–Müllerian hormone, testosterone), differentiation of the Müllerian ducts into the organs of the female reproductive tract involves reciprocal signaling between the duct epithelium and mesenchyme. Initially, the mesenchyme induces region-specific differentiation of the epithelium.[18] The epithelium then releases Wnt-7a signaling factors, which stimulate positional expression of a cluster of *Hoxa* genes located along the cranial-caudal axis of the mesenchyme, leading to proper morphogenesis of the oviducts, uterus, cervix, and upper vagina (**Box 1**).[19–21] In the uterus, the Müllerian duct epithelium forms the simple columnar epithelial lining and glands of the endometrium, and the mesenchyme forms the endometrial stroma and the myometrium.[18,22]