Surgical management of early pregnancy loss

Women with repeat miscarriage require specialized management to optimize future reproductive outcomes

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IN THIS ARTICLE

CASE Concern for surgical management after repeat miscarriage

A 34-year-old woman (G3P0030) with a history of recurrent pregnancy loss was recently diagnosed with a 7-week missed abortion. After her second miscarriage, she had an evaluation for recurrent pregnancy loss which was unremarkable. Both prior miscarriages were managed with dilation & curettage (D&C), but cytogenetic testing of the tissue did not yield a result in either case. The karyotype from the first pregnancy resulted as 46, XX but was confirmed to be due to maternal cell contamination, and the karyotype from the second pregnancy resulted in cell culture failure. The patient is interested in surgical management for her current missed abortion to help with tissue collection for cytogenetic testing, she but is concerned about her risk of intrauterine adhesions with repeated uterine instrumentation given 2 prior D&Cs, one of which was complicated by retained products of conception.

How do you approach the surgical management of this patient with recurrent pregnancy loss?

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Approximately 1 in every 8 recognized pregnancies results in miscarriage. The risk of loss is lowest in women with no history of miscarriage (11%), and increases by about 10% for each additional miscarriage, reaching 42% in women with 3 or more previous losses. The population prevalence of women who have had 1 miscarriage is 11%, 2 miscarriages is 2%, and 3 or more is <1%.[1] While 90% of miscarriages occur in the first trimester, their etiology can be quite varied.[2] A woman's age is the most strongly associated risk factor, with both very young (<20 years) and older age (>35 years) groups at highest risk. This association is largely attributed to an age-related increase in embryonic chromosomal aneuploidies, of which trisomies, particularly trisomy 16, are the most common.[3] Maternal anatomic anomalies such as leiomyomas, intrauterine adhesions, Müllerian anomalies, and adenomyosis have been linked to an increased risk of miscarriage in addition to several lifestyle and environmental factor exposures.[1]

Regardless of the etiology, women with recurrent miscarriage are exposed to the potential for iatrogenic harm from the management of their pregnancy loss, including

intrauterine adhesions and retained products, which may negatively impact future reproductive attempts. The management of patients with recurrent miscarriages demands special attention to reduce the risk of iatrogenic harm, maximize diagnostic evaluation of the products of conception, and improve future reproductive outcomes.

Management strategies

First trimester pregnancy loss may be managed expectantly, medically, or surgically. Approximately 76% of women who opt for expectant management will successfully pass pregnancy tissue, but for 1 out of every 6 women it may take longer than 14 days.[4] For patients who prefer to expedite this process, medication abortion is a highly effective and safe option. According to Schreiber and colleagues, a combination of mifepristone and misoprostol together resulted in expulsion in approximately 91% of 148 patients, although 9% still required surgical intervention for incomplete passage of tissue.[5] Both expectant management and medical management strategies are associated with the potential for retained products of conception requiring subsequent instrumentation as well as tissue that is often unsuitable or contaminated for cytogenetic analysis.

The most definitive treatment option is surgical management via manual or electric vacuum aspiration or curettage, with efficacy approaching 99.6% in some series.[6] While highly effective, even ultrasound-guided evacuation carries with it procedure-related risks that are of particular consequence for patients of reproductive age, including adhesion formation and retained products of conception.

In 1997, Goldenberg and colleagues reported on the use of hysteroscopy for the management of retained products of conception as a strategy to minimize trauma to the uterus and maximize excision of retained tissue, both of which reduce potential for adhesion formation.[7] Based on these data, several groups have extended the use of hysteroscopic resection for retained tissue to upfront evacuation following pregnancy loss, in lieu of D&C.[8,9] This approach allows for the direct visualization of the focal removal of the implanted pregnancy tissue, which can:

- decrease the risk of intrauterine adhesion formation
- decrease the risk of retained products of conception
- allow for directed tissue sampling to improve the accuracy of cytogenetic testing
- allow for detection of embryo anatomic anomalies that often go undetected on traditional cytogenetic analysis.

For the remainder of this article, we will discuss the advantages of hysteroscopic management of a missed abortion in greater detail.

Hysteroscopic management

Like aspiration or curettage, hysteroscopic management may be offered once the diagnosis of fetal demise is confirmed on ultrasonography. The procedure may be accomplished in the office setting or in the operative room with either morcellation or resectoscopic instruments. Morcellation allows for improved visibility during the procedure given the ability of continuous suction to manage tissue fragments in the surgical field, while resectoscopic instruments offer the added benefit of electrosurgery should bleeding that is unresponsive to increased distention pressure be encountered. Use of the cold loop of the resectoscope to accomplish evacuation is advocated to avoid the thermal damage to the endometrium with electrosurgery. Regardless of the chosen instrument, there are several potential benefits for a hysteroscopic approach over the traditional ultrasound-guided or blind D&C.

Reducing risk of iatrogenic harm

Intrauterine adhesions form secondary to trauma to the endometrial basalis layer, where a population of adult progenitor stem cells continuously work to regenerate the overlying functionalis layer. Once damaged, adhesions may form and range from thin,

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Hysteroscopy allows for direct visualization during removal of implanted pregnancy tissue, offering several advantages over dilation and curettage, including decreasing the risk of retained products of conception

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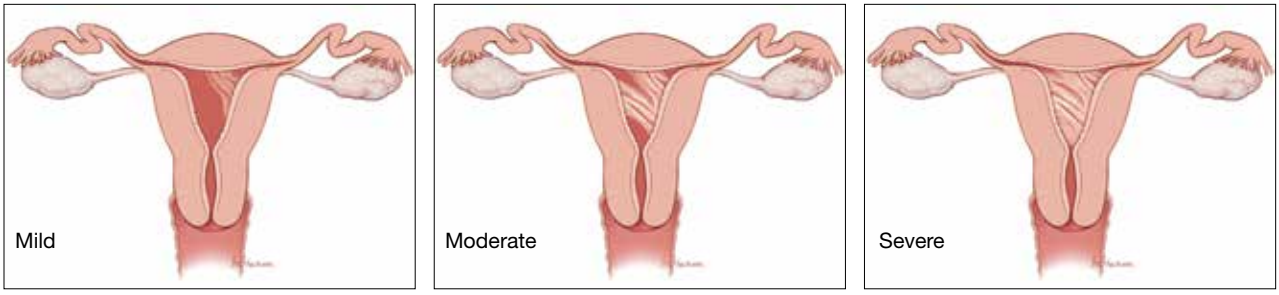
FIGURE Severity of intrauterine adhesions



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One meta-analysis found a 19.1% prevalence for intrauterine adhesions following D&C

filmy adhesions to dense, cavity obliterating bands of scar tissue (**FIGURE**). The degree of severity and location of the adhesions account for the variable presentation that range from menstrual abnormalities to infertility and recurrent pregnancy loss. While several classification systems exist for scoring severity of adhesions, the American Fertility Society (now American Society for Reproductive Medicine) Classification system from 1988 is still commonly utilized (**TABLE 1**).

Intrauterine adhesions from D&C after pregnancy loss are not uncommon. A 2014 meta-analysis of 10 prospective studies including 912 women reported a pooled prevalence for intrauterine adhesions of 19.1% (95% confidence interval [CI], 12.8–27.5) on hysteroscopic evaluation within 12 months following curettage.[10] Once formed, these adhesions are associated with long-term impairment in reproductive outcomes, regardless of if they were treated or not. In a long-term follow-up study of women with and without adhesions after recurrent D&C for miscarriage, women with treated adhesions reported lower live birth rates, longer time to pregnancy, higher rates of preterm birth and higher rates of peripartum complications compared with those without adhesions.[11]

Compared with curettage, hysteroscopy affords the surgeon complete visualization of the uterine cavity and tissue to be resected. This, in turn, minimizes trauma to the surrounding uterine cavity, minimizes the potential for post-procedural adhesion formation and their associated sequelae, and maximizes complete resection of tissue. Those treated with D&C appear to be significantly more likely to have adhesions than those treated via a hysteroscopic approach (30% vs 13%).[12]

Retained products of conception. Classically, a "gritty" sensation of the endometrium following evacuation of the uterus with a sharp curette has been used to indicate complete removal of tissue. The evolution from a nonvisualized procedure to ultrasound-guided vacuum aspiration of 1st trimester pregnancy tissue has been associated with a decreased risk of procedural complications and retained products of conception.[13] However, even with intraoperative

TABLE 1 American Fertility Society classification of intrauterine adhesions

Extent of cavity involved	< 1/3	1/3 to 2/3	> 2/3
	1	2	3
Type of adhesions	Filmy	Filmy & dense	Dense
	1	2	4
Menstrual pattern	Normal	Hypomenorrhea	Amenorrhea
	0	2	4

Stage 1 (Mild): 1-4 points, Stage 2 (Moderate): 5-8 points, Stage 3 (Severe): 9-12 points

Illustrations: Marcia Hartsock for OBG MANAGEMENT

imaging, the risk of retained products of conception remains because it can be difficult to distinguish a small blood clot from retained pregnancy tissue on ultrasonography.

Retained pregnancy tissue can result in abnormal or heavy bleeding, require additional medical or surgical intervention, and is associated with endometrial inflammation and infection. Approximately 1 in every 4 women undergoing hysteroscopic resection of retained products are found to have evidence of endometritis in the resected tissue.[14] This number is even higher in women with a diagnosis of recurrent pregnancy loss (62%).[15]

These complications from retained products of conception can be avoided with the hysteroscopic approach due to the direct visualization of the tissue removal. This benefit may be particularly beneficial in patients with known abnormal uterine cavities, such as those with Müllerian anomalies, uterine leiomyomas, preexisting adhesions, and history of placenta accreta spectrum disorder.

Maximizing diagnostic yield

Many patients prefer surgical management of a missed abortion not for the procedural advantages, but to assist with tissue collection for cytogenetic testing of the pregnancy tissue. Given that embryonic chromosomal aneuploidy is implicated in 70% of miscarriages prior to 20 weeks' gestation, genetic evaluation of the products of conception is commonly performed to identify a potential cause for the miscarriage.[16] G-band karyotype is the most commonly performed genetic evaluation. Karyotype requires culturing of pregnancy tissue for 7-14 days to produce metaphase cells that are then chemically treated to arrest them at their maximally contracted stage. Cytogenetic evaluation is often curtailed when nonviable cells from products of conception fail to culture due to either time elapsed from diagnosis to demise or damage from tissue handling. Careful, directly observed tissue handling via a hysteroscopic approach may alleviate culture failure secondary to tissue damage.

Another concern with cultures of products of conception is the potential for maternal cell contamination. Early studies from the 1970s noted a significant skew toward 46, XX karyotype results in miscarried tissue as compared with 46, XY results. It was not until microsatellite analysis technology was available that it was determined that the result was due to analysis of maternal cells instead of products of conception.[17] A 2014 study by Levy and colleagues and another by Lathi and colleagues that utilized single-nucleotide polymorphism (SNP) microarray found that maternal cell contamination affected 22% of all miscarriage samples analyzed and over half of karyotypes with a 46, XX result.[18,19]

Traditional "blind" suction and curettage may inadvertently collect maternal endometrial tissue and contaminate the culture of fetal cells, limiting the validity of karyotype for products of conception.[20] The hysteroscopic approach may provide a higher diagnostic yield for karyotype analysis of fetal tissue by the nature of targeted tissue sampling under direct visualization, minimizing maternal cell contamination. One retrospective study by Cholkeri-Singh and colleagues evaluated rates of fetal chromosome detection without maternal contamination in a total of 264 patients undergoing either suction curettage or hysteroscopic resection. They found that fetal chromosomal detection without contamination was significantly higher in the hysteroscopy group compared with the suction curettage group (88.5 vs 64.8%, $P<.001$).[21] Additionally, biopsies of tissue under direct visualization may enable the diagnosis of a true placental mosaicism and the study of the individual karyotype of each embryo in dizygotic twin missed abortions.

Finally, a hysteroscopic approach may afford the opportunity to also perform morphologic evaluation of the intact early fetus furthering the diagnostic utility of the procedure. With hysteroscopy, the gestational sac is identified and carefully entered, allowing for complete visualization of the early fetus and assessment of anatomic malformations that may provide insight into the pregnancy loss (ie, embryoscopy). In one series of

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TABLE 2 Patients who may benefit most from hysteroscopic management

- Recurrent pregnancy loss
- Suspected intrauterine pathology
- Müllerian anomalies
- History of multiple prior curettage
- History of intrauterine adhesions
- Thin endometrial lining at time of conception
- History of failed cell culture for cytogenetics
- History of retained products of conception
- History of maternal cell contamination of gestational tissue
- Euploid pregnancy loss
- History of placenta accreta spectrum disorder

272 patients with missed abortions, while nearly 75% of conceptuses had abnormal karyotypes, 18% were found to have gross morphologic defects with a normal karyotype.[22]

management. There are certain patients with pre-existing risk factors that may stand to benefit the most (**TABLE 2**). Much like the opening case, those at risk for intrauterine adhesions, retained products of conception, or in whom a successful and accurate cytogenetic analysis is essential are the most likely to benefit from a hysteroscopic approach. The hysteroscopic approach also affords concurrent diagnosis and treatment of intrauterine pathology, such as leiomyomas and uterine septum, which are encountered approximately 12.5% of the time after one miscarriage and 29.4% of the time in patients with a history of more than one miscarriage.[10] In the appropriately counseled patient and clinical setting, clinicians could also perform definitive surgical management during the same hysteroscopy. Finally, evaluation of the morphology of the demised fetus may provide additional information for patient counseling in those with euploid pregnancy losses.

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Many patients will benefit from hysteroscopy for early pregnancy loss, including those at risk for intrauterine adhesions, retained products of conception, or in whom a successful and accurate cytogenetic analysis is essential

Bottom line

When faced with a patient with an early pregnancy loss, physicians should consider the decreased iatrogenic risks and improved diagnostic yield when deciding between D&C versus hysteroscopy for surgical

CASE Resolved

Ultimately, our patient underwent complete hysteroscopic resection of the pregnancy tissue, which confirmed both a morphologically abnormal fetus and a 45, X karyotype of the products of conception. ●

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