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Evaluation and treatment of the infertile women with Asherman syndrome: an updated review focusing on the role of hysteroscopy.

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Abstract

Asherman syndrome is a rare acquired clinical condition resulting in the obliteration of the uterine cavity due to the presence of partial or complete fibrous intrauterine adhesions involving at least two-thirds of the uterine cavity potentially obstructing the internal cervical os.

Common reported symptoms of the disease are alterations of the menstrual pattern with decreased menstrual bleeding leading up to amenorrhea and infertility. Hysteroscopy is currently considered the gold standard diagnostic and therapeutic approach of patients with intrauterine adhesions. However, an integrated approach including preoperative, intraoperative and postoperative therapeutic measures are warranted due to the complexity of the syndrome. This review aims to summarize the most recent evidence on the recommended preoperative, intraoperative and postoperative procedures to restore the uterine cavity and a functional endometrium, as well as on the concomitant use of adjuvant therapies to achieve optimal fertility outcomes.

Keywords: Asherman's syndrome; Hysteroscopy; Infertility; Intrauterine adhesions; Synechiae.

Introduction

Asherman syndrome is an acquired condition characterized by the development of obliteration of the uterine cavity due to partial or complete fusion of opposing uterine walls by fibrous adhesions, also referred as synechiae, leading to menstrual disorders such as amenorrhea or decreased menstrual flow, severe cramping pain, and/or subfertility and adverse pregnancy outcomes (Yu et al. 2008). Although intrauterine adhesions were first described by Fritsch in 1894 (Fritsch 1894), Joseph Asherman described the pathophysiology, clinical significance and the potential utilization of hysteroscopy for the treatment of intrauterine adhesions in 1950 and thus it is referred to as Asherman syndrome (Asherman 1950).

It is important to clarify that Asherman first described in 1948 a specific type of secondary amenorrhea following complicated labor or abortion due to a stenosis or blockage of the cervical internal os. Asherman stated that this 'amenorrhea traumatica' is not functional but organic; ovulation continues to occur but the uterus does not react and the endometrium remains in a state of inactivity. Hormonal therapy is neither reasonable nor effective, whereas simple removal of the blockage is sufficient to restore menstruation to normal (Asherman 1948). Therefore, the resulting secondary amenorrhea is a form of endometrial deactivation in the presence of cervical stenosis with a normal uterine cavity and is not Asherman syndrome due to intrauterine adhesions (IUAs).

Although the cause of IUAs is thought to be associated with vigorous curettage or uterine surgery involving the uterine cavity, pelvic infections such as pelvic inflammatory disease (PID) as a result of sexually transmitted infections may also lead to Asherman syndrome. Other causes of intrauterine infections like tuberculosis or schistosomiasis leading to IUAs are particularly important in developing countries.

Establishing prognostic criteria of this syndrome is challenging as it depends on multiple pathophysiologic factors as well as the need to use adequate diagnostic tools to determine the extent of the disease to then establish the appropriate therapy. Once the extent of the condition is determined, the next challenge is to plan the appropriate treatment not only to restore the intrauterine anatomy and potentially the physiology of the uterine cavity but also to prevent recurrence of IUAs to enhance/restore normal reproductive function.

Preoperative assessment of Asherman syndrome includes the use of transvaginal ultrasonography, hysterosalpingography (HSG), saline infusion sonohysterography (SIS) and, in particular, hysteroscopy (Schlaff and Hurst 1995, Salle et al. 1999, Reyes-Munoz et al. 2019). The use of a combination of preoperative, intraoperative and postoperative measures, as well as adjuvant therapy to prevent recurrence of IUAs, is generally accepted as the best approach to reduce the clinical symptoms, enhance fertility and obtain good reproductive outcomes. Such procedures include ultrasound-directed hysteroscopic adhesiolysis, mechanical lysis of adhesions to separate the fused uterine walls and the use of adjuvant therapy with systemic estrogen with or without progestin administration in conjunction with intrauterine barriers and adhesion preventing agents to induce endometrial proliferation (Farhi et al. 1993, Zikopoulos et al. 2004). This integrated approach allows to enhance the prognosis as well as to prepare the uterine cavity to conceive, especially with those interventions aimed to promote endometrial healing.

This review aims to summarize the most recent evidence on the recommended preoperative, intraoperative and postoperative procedures to restore the anatomy of the uterine cavity and a functional endometrium, as well as on the use of adjuvant therapies to achieve optimal fertility outcomes.

Material and Methods

The data research was conducted using MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library and querying for all the articles related to

Asherman syndrome from the inception of the database up to October 2019. The studies were identified with the use of a combination of the following text words: hysteroscopy, intrauterine synechiae, Asherman syndrome, infertility. The selection criteria of this narrative review included randomized clinical trials, non-randomized controlled studies (observational prospective, retrospective cohort studies, case-control studies, case series) and review articles of Asherman syndrome in infertile women and the diagnostic and therapeutic role of hysteroscopy. A review of articles also included the abstracts of all references retrieved from the search. Article not in English language, conference papers and reviews, and studies with information overlapping another publication were excluded. In the event of overlapping studies, we selected the most recent and/or most comprehensive manuscript.

Preoperative assessment

Advances in endoscopic technology allow the direct exploration of the uterine cavity and, consequently, a more accurate diagnosis and management options of intrauterine pathology. Asherman syndrome should be suspected in patients presenting with menstrual changes such as decreased menstrual flow, amenorrhea or dysmenorrhea in association with a history of infertility, especially in patients with previous curettage or intrauterine surgery. The diagnosis is commonly obtained by imaging the uterine cavity with contrast (Hysterosalpingogram). However, hysteroscopy is considered the gold standard technique for the evaluation of the uterine cavity for the diagnosis of Asherman syndrome (Vitale et al. 2017, Wamsteker K 1995, De Franciscis et al. 2019).

It allows direct access and a real-time view of the endometrial cavity, accurately confirming the presence, extent, and morphological characteristics of intrauterine adhesions and the quality of the endometrium. Besides, it enables an accurate description of the location, degree of the adhesions and classification allowing treatment at the same time "see and treat" (Reyes-Munoz et al. 2019).

Hysterosalpingography (HSG) is a cost-effective diagnostic method used to assess tubal patency in addition to the size, shape, and contents of the uterine cavity. Before the widespread use of hysteroscopy, HSG was the preferred diagnostic modality for Asherman syndrome showing contrast filling defects described as homogeneous opacity surrounded by sharp edges (Magos 2002). Severe Asherman's syndrome is characterized by a completely distorted and narrow uterine cavity occluding the uterine ostia. HSG has a diagnostic sensitivity of 75-81%, a specificity of 80% and for the diagnosis of IUAs but is a diagnostic tool with a high false-positive rate (Positive predictive value 50%) (Yu et al. 2008).

Transvaginal ultrasound (TVS) is frequently included in the initial evaluation of women with gynecologic complaints. Intrauterine adhesions are characterized by an echo-dense pattern resulting in difficult identification of the endometrial lining which contains one or more translucent "cyst-like" areas (Yu et al. 2008). Although ultrasound has been reported to have low diagnostic accuracy (Farhi et al. 1993, Magos 2002, Salle et al. 1999, Zikopoulos et al. 2004, Soares, Barbosa dos Reis, and Camargos 2000), it allows an adequate mapping of the uterine cavity when a complete obstruction of the cervix precludes performing an HSG or hysteroscopy.

The ultrasound scan can also be useful during hysteroscopic adhesiolysis to guide the procedure and prevent uterine perforation. Compared to laparoscopic guided adhesiolysis, ultrasound-guided adhesiolysis is certainly less invasive and has a lower cost, avoiding potential laparoscopic complications with a similar rate of uterine perforation risk (Schlaff and Hurst 1995). Moreover, the literature supports ultrasound as a better predictor of the surgical repair, because it allows the assessment of residual endometrium: if the residual endometrium after the initial treatment is thin or no endometrium is seen during the transvaginal ultrasound, the obstetric outcomes are greatly decreased (Kresowik et al. 2012).

The role of contrast (saline, gel) infusion sonography or sonohysterography, has also been widely investigated. It has a diagnostic sensitivity of 75% and a positive predictive value of 43%, similar to that reported for HSG. Salle et al. reported the same sensitivity and specificity when SHG is compared to the standard HSG (Salle et al. 1999). Recently, a retrospective study involving 149 women with intrauterine anomalies, demonstrated a significant difference in general accuracy at diagnosing intrauterine pathology favoring SHG. (50.3% in the HSG group and 81.8% in the SHG group) (Acholonu et al. 2011).

To the best of our knowledge, current data about the role of three-dimensional ultrasound imaging (3D US) in the diagnosis of intrauterine adhesions are limited (Knopman and Copperman 2007). However, 3D US is taking on a growing role in the evaluation of intrauterine synechiae, with a sensitivity of 87% and a specificity of 45%, which is higher than those obtained with TVS and SHG. Moreover, 3D US and intrauterine saline infusion, known as three-dimensional sonohysterography, (3D-SHG) both in combination with or without 3D power Doppler (3-DPD) have recently been proposed as a possible imaging modality for the diagnosis of intrauterine pathology. However, only low-quality data are reported to date on the efficacy of this technique in the diagnosis of intrauterine synechiae (Abou-Salem, Elmazny, and El-Sherbiny 2010) and until more robust evidence becomes available, the high cost of 3D ultrasound precludes its use in daily clinical practice.

Magnetic resonance imaging (MRI) represents a supplementary diagnostic tool, especially in the case of complete obliteration of the cervical canal. Intrauterine adhesions (IUA) are depicted as low signal intensity on T2 weighed-image inside the uterus (Bacelar et al. 1995). MRI is generally not necessary and is not used routinely for the diagnosis of Asherman syndrome as it is considered not cost-effective as a routine diagnostic tool.

Despite the availability of the multiple imaging techniques discussed above, hysteroscopy remains the gold standard for the diagnosis and management (assessment and treatment) of Asherman's syndrome.

Intraoperative assessment

Lysis of IUAs is considered the gold standard treatment of patients diagnosed with Asherman syndrome; nevertheless, there are no RCTs comparing outcomes of surgical intervention versus expectant management or between different methods of surgical intervention. Any surgical intervention aims to restore as much as possible the anatomy of the endometrial cavity and the cervical canal, restoring the normal volume and shape to facilitate the communication between the uterine cavity, the cervical canal and the fallopian tubes; subsequently, allowing both normal menstrual flow and adequate sperm transportation for fertilization and implantation.

To date, hysteroscopic adhesiolysis, using a variety of instruments with or without energy, has emerged as the gold standard technique for the treatment of intrauterine adhesions allowing the so-called, 'see and treat' approach. Hysteroscopy, reveals important features of intrauterine synechiae such as their number, location, extension, structure, and consistency. The location of the adhesions can be central or marginal and their extension can be described as mild, moderate or severe: in the latter case, only fibrous tissue is seen with small irregular endometrial bridges (Nappi and Di Spiezio Sardo 2014, Worldwide 2010). The structure and consistency of the adhesions depend on the predominant component that is present (mucosal, muscular or fibrous).

March and Israel introduced a classification based on the extension (mild, moderate and severe) of intrauterine synechiae (March, Israel, and March 1978). The American Fertility Society (1988) developed a new scoring system for classification of IUAs taking into account the menstrual history as well as hysteroscopic and hysterosalpingographic findings: a prognostic classification in 3 stages (stage I: mild; stage II: moderate; stage III: severe) resulted. The European Society of Hysteroscopy reported a more detailed classification of Asherman syndrome based on the nature and consistency of the adhesions but this classification is more cumbersome to use in clinical practice than the former (Wamsteker K 1995). The most recent classification takes into account the characteristics of intrauterine synechiae as well as the gynecologic and obstetric history of the patients: patients have an excellent prognosis if a numerical score ranges from 0 to 4 (level 1, mild), while the prognosis is considered favorable if the score ranges from 5 to 10 (level 2, moderate) or poor if scoring from 11 to 22 (level 3, severe). This classification, however, has been validated only on a small number of patients and requires further studies before it is adopted in clinical practice (Nasr et al. 2000) (Table 1).

In the case of mild filmy adhesions, office hysteroscopy without general anesthesia can be safely performed allowing the restoration of a normal uterine cavity by breaking the adhesions using only the uterine distension pressure and the tip of the hysteroscope (Sugimoto 1978). However, more vigorous approaches are required for severe and dense adhesions especially if they completely occlude the uterine cavity or if they do not allow the insertion of the hysteroscopic sheath inside the cervix. Intuitively, adhesiolysis should be initiated at the lowest part of the uterine cavity and advanced upwards as the uterine cavity is being restored (Yu et al. 2008).

The adhesions situated in the central part of the uterine cavity, if filmy and easy to break, should be separated first which will allow adequate distension of the uterine cavity. Finally, if more dense or lateral adhesions are present, their treatment should be performed at the end of the procedure to minimize the risk of bleeding and/or uterine perforation (Deans and Abbott 2010).

It has been reported that even the use of a sharp needle (Touhy needle) for hysteroscopic adhesiolysis has a good rate of success in normalizing the menstrual cycle. However, data on further fertility after the procedure are not consistent (Broome and Vancaillie 1999). Using cold-scissors to break the adhesions is thought to be a superior method because it does not cause thermal damage to the residual endometrium. On the other hand, the use of "hot" instruments (using energy, electric or laser) may be associated with potential thermal damage to the residual endometrial tissue promoting scar formation (Yu et al. 2008, Al-Inany 2001). In any case, in the presence of extensive or dense adhesions, the treatment should be performed by an expert hysteroscopist using the instruments that he/she is most familiar with.

Prevention of adhesion recurrence

Following hysteroscopic adhesiolysis, intrauterine devices (IUD), stents, or balloon catheters are frequently used to reduce the rate of postoperative adhesion formation, although there is limited data regarding the effect on preventing recurrence of IUAs and subsequent fertility outcomes when these barriers are used (Aagl Elevating Gynecologic Surgery 2017).

IUD and intrauterine adhesions

Following hysteroscopic adhesiolysis, the recurrence rate of IUA has been reported to range from 3.1% to 23.5% (Valle and Sciarra 1988, Pabuccu et al. 1997). Recurrent adhesions are usually thin and filmy (Shokeir, Fawzy, and Tatongy 2008). IUD has been used to prevent adhesion recurrence due to the mechanical effect of separating the anterior and posterior uterine walls (Conforti et al. 2013) which may help physiological endometrial regeneration. Although many authors have reported good results (Ventolini, Zhang, and Gruber 2004, Polishuk and Weinstein 1976), data regarding the preferred size and the type of IUD to prevent IUAs recurrence are still lacking. Moreover, IUD may induce the release of inflammatory agents which may aggravate endometrial injury delaying healing and endometrial regeneration (March 1995). Although it is reported that after the insertion of an IUD, a significant number of women regained regular menses (Vesce et al. 2000), the levonorgestrel-releasing IUD should be avoided because of its suppressing effect on estrogen receptors which are considered necessary for normal regeneration of the endometrium (Deans and Abbott 2010). It is important to note that the same rate in adhesion reformation has been found among women randomized to receive IUD device, estrogens treatment or no treatment after hysteroscopic septum resection (Tonguc et al. 2010).

Intrauterine balloons

An intrauterine balloon stent is another mechanical method frequently used to prevent the reformation of adhesions following intrauterine adhesiolysis (March 2011). It consists of a silicon triangular shape device fitting the uterine cavity (Cook Medical Inc, Bloomington, USA). Intrauterine balloon stent can be inserted immediately after the procedure with good results in terms of fertility outcome and prevention of adhesions recurrence (March 2011, Lin et al. 2013). A prophylactic broad-spectrum antibiotic is always recommended for the duration of the stent inside the uterine cavity.

Foley catheters

A standard pediatric Foley catheter is another commonly used method to prevent the recurrence of IUAs following hysteroscopic adhesiolysis (Asherman 1950, March, Israel, and March 1978, Ismajovich et al. 1985). In a study involving 25 women with moderate and severe adhesions, a fresh amnion graft draped over a Foley catheter balloon inserted into the uterus immediately after hysteroscopic lysis of intrauterine adhesions and left inside for two weeks showed a significant reduction of adhesion reformation (Amer and Abd-El-Maeboud

2006). When compared to IUD, Foley catheter showed a higher conception rate (33.9% versus 22.5%), reporting also restoration of normal menstrual pattern in 81% of women (Orhue, Aziken, and Igbefoh 2003). Although positive outcomes have been reported, randomized controlled trials (RCTs) on the efficacy of Foley catheters in the prevention of IUA, are not available. Limits of this approach are mainly the risk of potential uterine perforation, ascending infection from the vagina and patient discomfort.

Hyaluronic acid and other anti-adhesion barriers

During the last 10 years, hyaluronic acid-derived products have been developed, showing a possible role in gynecologic surgery to prevent intra-abdominal and intrauterine adhesions (Pellicano et al. 2003, Guida et al. 2004). Hyaluronic acid mechanically inhibits adhesions formation due to the temporary formation of a barrier (Reijnen et al. 2000). Autocross-linked hyaluronic acid (Hyalobarrier©) is frequently used after gynecological abdominal surgery and consists of a viscous gel formed by the autocross-linked condensation of hyaluronic acid, preventing intraperitoneal adhesions formation after laparoscopic myomectomy and intrauterine adhesions after hysteroscopic procedures (Mais et al. 2012).

Other anti-adhesion barrier products have been proposed to reduce IUAs recurrences such as the one made of chemically modified hyaluronic acid (sodium hyaluronate) and carboxymethylcellulose (Seprafilm©) and a newer hyaluronic acid derived (alginate carboxymethylcellulose hyaluronic acid). However scientific evidence is still inconsistent to allow the recommendation of one product over another.

Bone marrow-derived stem cell (BMDSC)

The potential to regenerate severely damaged endometrium with human stem cell treatment has also been explored with promising results in animal models and humans (Alawadhi et al.

2014, Kilic et al. 2014, Kuramoto et al. 2015). In a prospective series by Santamaria et al. (Santamaria et al. 2016), 16 women with IUAs confirmed by hysteroscopy were treated with uterine intravascular infusions of BMDSC. During the follow-up period, the menstrual function returned to normal within 6 months after BMDSC infusion with three spontaneous pregnancies and seven pregnancies following in vitro fertilization and embryo transfer (IVF-ET) reported (Santamaria et al. 2016).

Postoperative management

One out of three women with Asherman syndrome having mild to moderate IUAs (Preutthipan and Linasmita 2003) and two out of three with severe IUAs (Yang et al. 2016) have a recurrence of IUA after hysteroscopic adhesiolysis. Obtaining a restored normal uterine cavity and a functional endometrial layer are a clinical goal after hysteroscopic surgery, especially in women desiring future fertility. According to the AAGL (American Association of Gynecologic Laparoscopists) and ESGE (European Society of Gynaecological Endoscopy) guidelines, a repeated hysteroscopy is recommended for the follow-up assessment of the uterine cavity after treatment of IUAs (Aagl Elevating Gynecologic Surgery 2017).

Conventional wisdom dictates that good endometrial healing may be achieved in the presence of high estrogen levels. However, there is still not a clear consensus about when exogenous hormonal therapy should be initiated, or on the type of regimen, dose, and duration of therapy. The latest evidence on hormonal therapy aiming to restore the endometrial thickness is that both lower dosage (4 mg) and a higher dose (10 mg) of oestradiol valerate given daily in the postoperative period are effective in the reduction of adhesions formation, with better results associated with the higher dose. However, both doses allowed a normal restoration of menstrual patterns, but results for fertility outcomes have not yet been reported (Liu et al. 2019).

Prolonged preoperative and postoperative treatment with estrogens has been reported in a small study including 12 subjects with severe Asherman syndrome. All women resumed a normal menstrual pattern and six of them became pregnant (Myers and Hurst 2012). Oestradiol valerate 4 mg per day for 4 weeks and medroxyprogesterone acetate (MPA), 10 mg per day during the last two weeks of treatment have also been recommended as an ideal therapy after surgery for Asherman syndrome (Yu et al. 2008).

It has been reported that an estrogen-progestin combination administered after curettage for post-partum hemorrhage or incomplete abortion increases the endometrial thickness. Specifically, after 21 days of treatment, the transvaginal ultrasound showed a thicker endometrium with larger width and volume (Farhi et al. 1993). Also, Tsui et al. proposed estrogen treatment (8-10 weeks) after removal of the balloon and second look hysteroscopy. Transvaginal ultrasound may be used to asses the endometrial thickness and in-vitro fertilization and embryo transfer (IVF-ET) can be performed when the endometrial thickness exceeds 5 mm (Tsui et al. 2014).

Finally, after the failure of hormonal therapy in restoring the endometrium (Nagori, Panchal, and Patel 2011), several studies have been conducted during the last ten years exploring new horizons including the use of infusing bone marrow derivates or stimulating endometrial stromal stem cells. However, data are still inadequate about the effectiveness of stem cells in regenerating a physiologically normal endometrial lining and uterine cavity. In this context, solid scientific evidence is still needed.

Conclusions

Asherman syndrome is a rare pathology secondary to intrauterine adhesion formation that is associated with menstrual disorders and reproductive dysfunction. Hysteroscopy is currently considered the gold standard for the management because it allows simultaneous diagnosis and treatment ("see and treat"). Although there have been significant advances in the restoration of the endometrial cavity in the last decade, complete restoration of a normal functional endometrial lining has not been achieved. Preliminary evidence suggests a promising role of BMDSC in enhancing endometrial healing and reproduction. However, the evidence on the role of BMDSC in clinical practice is still limited and this treatment should not be offered outside of rigorous research protocols.

Finally, a consensus-based adjuvant therapy including the use of intrauterine stents and exogenous hormonal therapy aimed to achieve adequate endometrial growth and to prevent recurrence of IUAs has not yet been established. Restoration of a functional endometrial lining is one of the most important challenges for successful reproductive outcomes.

Although rare but with great clinical significance, Asherman syndrome requires further basic science research work to determine its etiology and potential preventing measures. Well designed clinical trials are needed to determine the most appropriate diagnostic and therapeutic modalities.

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Key Message

Asherman syndrome is a rare pathology secondary to intrauterine adhesion formation characterized by menstrual disorders and reproductive dysfunction. Hysteroscopy is currently considered the gold standard for the management because it allows simultaneous diagnosis and treatment. Asherman syndrome requires further basic science research to determine its etiology and potential preventing measures.

Table 1. Summary of the three main classification systems of intrauterine adhesions (IUA)

Authors (year of publication)	Classification
March et al. (1978)	IUA classified as mild, moderate, or severe based on hysteroscopic assessment of their extension.
American Fertility Society (1988)	Classification system including the extent of uterine cavity involved (<1/3, 1/3-2/3, >2/3) and the type of IUAs (filmy, filmy-dense, dense) as well as the menstrual pattern (normal, hypomenorrhea and amenorrhea) Stage I: mild (score 1-4) Stage II: moderate (score 5-8) Stage III: severe (score 9-12)
European Society for Hysteroscopy (1995)	Six types (I-VI) of IUA classified as following: Type I: subtle or velamentous IUA Type II: single fibrous synechiae Type IIa: obliterating isthmic synechiae in presence of normal uterine cavity Tipe III: multiple fibrous synechiae with frequent obliteration of one of the tubal ostium Type IIIa: wide involvement of uterine walls Type IIIb: combination of types III and IIIb Type IV: Fusion of the uterine cavity due to extensive fibrous synechiae, with frequent obliteration of both tubal ostium
Nasr et al. (2000)	Classification system including the characteristics of IUA as well as the gynecologic and obstetric history of the patient (isthmic synechia, viscous synechia, dense synechia, tubal ostia, menstrual pattern and reproductive anamnesis). Excellent prognosis: total score 0-4 (grade 1, mild) Favorable prognosis: total score 5-10 (grade 2, moderate) Severe prognosis: total score 11-20 (grade 3, severe)