Should we consider alternative therapies to operative hysteroscopy for the treatment of Asherman syndrome?

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PRO: Alternative therapies should be considered for the treatment of Asherman syndrome

Pro 1. Xavier Santamaria M.D., Ph.D.

The definition of refractory Asherman syndrome (AS) is not clear, so this question may have different interpretations. So far, the gold standard for diagnosis and treatment of AS is hysteroscopy since it confirms accurately the presence, extension and characteristics of intrauterine adhesions once the symptoms are present. Several classifications (1–7) have graded the severity of AS based on different hysteroscopic features such as extension, location, type of adhesion and in some classifications clinical symptoms such as menstrual characteristics or postoperative pregnancy rates are also included. However, based on the different nature of these classifications, the staging of AS only based on hysteroscopic findings seems quite heterogeneous.

CON: Operative hysteroscopy should be repeated as many times as necessary for the treatment of Asherman syndrome

Con 1. Keith Isaacson, M.D.

Peter Movilla, M.D.

The term refractory AS loosely refers to a subset of patients that have persistent intrauterine adhesions despite repeat hysteroscopic procedures or persistent clinical symptomatology following treatment such as amenorrhea or infertility (48). Although this terminology is often utilized in the

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A syndrome is a group of signs and symptoms that coincide with and characterize an abnormality or condition. In AS, infertility is probably the most serious and limiting condition. Therefore, in my opinion refractory AS should consist in patients with no clinical improvement (infertility) after the diagnosis and complete treatment with the gold standard procedure (hysteroscopy). In this sense, fertility restoration after hysteroscopic treatment achieve overall pregnancy rates of 40% to 63% (8, 9) ranging between 40.9% in severe cases (10) up to 66.1% in moderate and severe cases (11) . However, this prognosis significantly improve in minimal lesions with pregnancy rates above 87.5% (2, 12).

One of the complications of hysteroscopy is recurrence of adhesions, especially severe adhesions (20% to 62.5%) after adhesiolysis (13). Several methods have been proposed such as the placement of intrauterine devices: intrauterine stent or foley catheter, hyaluronic acid or hormonal replacement treatment (9). However, there is no consensus in the postoperative management of patients with AS nor in the number of hysteroscopies or attempts to do to remove adhesions and, therefore, this is a difficult question to answer. Salazar et al. (14) preformed second-look hysteroscopies within 2 weeks of the initial procedure to break any newly forming adhesions reaching effectiveness rates of 89% to 92% On the other hand, Fernandez et al. (10) reported that uterine cavities with complex or severe adhesions can be restored with more than two attempts Therefore, it seems reasonable to perform multiple procedures as long as the patient is well informed of the strategy and aware of the risks and benefits.

Recent studies have reported that bone marrow-derived stem cells contribute to the repair and regeneration of human endometrium (15–19) and have the capacity to differentiate into fully functional stromal and epithelial endometrial cells. Therefore, cell therapies represent an expanding field to treat several diseases involving chronic inflammation, fibrosis and wound repair. Hematopoietic stem cells such as CD133+ display different mechanisms of action seem to regenerate tissues, such as paracrine activity, tissue differentiation, resident stem cell recruitment/activation and endothelial differentiation (20).

In this sense , CD133+ cells secrete exosomes and cytokines that promote migration, growth, and differentiation and can potentially recruit resident stem cells through a paracrine effect, as shown in certain types of EPCs (21) as we observed an increased proliferation and cytokine expression of THBS1 and IGFR- 1 in the endometrium of mice with AS compared to non-treated mice (22). This rapid release of growth factors and cytokines and exosomes creates an immediate short-term effect (23) that contributes to endothelial regeneration as well as endometrial resident stem cell recruitment/activation (24) that finally leads to tissue remodeling.

Moreover, differentiated CD133+ cells can induce in vitro capillary tube formation in a 3D collagen gel culture system and contribute to vascular remodeling in vivo (25, 26).

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medical literature regarding AS, there is no consensus on the definition for this subset of patients in terms of either the percentage of intrauterine adhesion recurrence, number of attempted hysteroscopic procedures, or time period for recurrent clinical symptoms to be classified as having refractory AS. At our institution in the modern era of assisted reproductive technology, we use the term refractory Ashermans's to describe an intrauterine condition in which there is insufficient healthy endometrium to expect a reasonable chance of embryo implantation leading to a clinical pregnancy. While we have seen cases in which a pregnancy occurred with less than 25% of the cavity with normal endometrium, our typical cut off number is 50%. This estimation is based on biopsy proven healthy endometrium and not by an endometrial thickness measurement by ultrasound, which is often thin in patients with AS.

The reported recurrence rate of intrauterine adhesions following hysteroscopic lysis of adhesions varies based on the initial adhesion burden (i.e. March classification) and the utilization of adjuvant postoperative treatment methods aimed at preventing adhesion reformation. Such adjuvant postoperative methods include utilization of estrogen hormones for endometrial stimulation and regeneration, the use of mechanical barriers including either intrauterine balloons or intrauterine devices that act to separate the opposing endometrial walls during the postoperative healing phase, or second look adhesiolysis procedures (48–51). Published intrauterine recurrence rates following primary hysteroscopic lysis of adhesions with or without utilization of postoperative hormones or mechanical barriers ranges from 20% to 35%, with the eventual successful restoration of a normal uterine cavity ranging from 65% to 95% of treated patients following up to 3 hysteroscopic procedures, and with reported treatment periods ranging up to 5 to 6 months (38, 50, 52, 53). Adhesion recurrence rate have been shown to decrease to as low as 10 - 14% with the novel utilization hyaluronic acid placed within the uterine cavity following hysteroscopic lysis of adhesion (54–57). Therefore, using the presence of both persistently recurrent intrauterine adhesions and the inability to successfully restore the normal endometrial function as the definition for refractory AS, the range of patients with refractory AS following multiple hysteroscopic procedures in the published data ranges from 5% to 35% of patients.

Patients referred to our practice for management of AS undergo both a transvaginal 3-dimensional ultrasound and a diagnostic/therapeutic office hysteroscopy during their initial patient encounter. All intrauterine adhesions are completely lysed utilizing hysteroscopic scissors alone until normal uterine cavity anatomy is restored. All findings as well as a March classification of the disease is documented. Patients are then started on estradiol 2 milligrams po twice daily for 30 days, followed by medroxyprogesterone acetate 10 milligrams daily for the last five days of this regimen to

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Further, trans lineage commitment of CD133+ cells to cardiomyocytes and endothelial cells has also been demonstrated (25–27) supporting potential tissue regeneration properties.

Our group reported a pilot, prospective, experimental non-controlled open-labeled study including 18 patients aged 30-45 years with refractory AS or endometrial atrophy (28). A total of 16 patients completed the study, 11 were diagnosed from AS and 5 from endometrial atrophy with a prior mean of 2 hysteroscopies and two subsequent cycles of HRT with no improvement. In the study, after an initial hysteroscopy, bone marrow-derived stem cells were mobilized with granulocyte colony stimulating factor and CD133+ cells were isolated after obtaining peripheral blood mononuclear obtained through apheresis. These CD133+ were instilled through catheterization into the spiral arteries and finally endometrial characteristics as well as reproductive outcomes were analyzed.

All the patients experienced improvement in the scores in the second-look hysteroscopy based on the American Society for Reproductive Medicine classification (3) as well as significant improvement in the duration and intensity of menstrual periods, in the number of endometrial blood vessels and endometrial thickness. However, these effects seem to decrease progressively after 3-6 months of the treatment.

The functionality of the endometrium was assessed through reproductive outcomes of patients that underwent assisted reproductive technology after stem cell therapy. In this sense, three patients became pregnant spontaneously at 2, 4, and 19 months after cell therapy resulting in two healthy babies born and a miscarriage at the 17th week of pregnancy due to a premature rupture of membranes. Furthermore, seven positive pregnancies were reported after 14 embryo transfers, resulting in three biochemical pregnancies, one miscarriage at the 9th week due to a chromosomically abnormal embryo identified in the products of conception, one ectopic pregnancy and three healthy newborns out of two patients.

Other case studies have also been reported positive results with similar approaches (29, 30). Our study represented the first series of cases treating AS with CD133+ bone marrow derived stem cells. Based on all these clinical and preclinical results, I believe this approach may play an important role together with hysteroscopy in the treatment of incurable AS in the future. As a matter of fact, the European Medicines Agency (EMA) and the Food and Drug Administration have acknowledged CD133+ as an orphan drug based on prevalence, biological plausibility and significant benefit to support the research on this field.

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induce a withdrawal bleed. Patients are seen between 2 to 3 weeks postoperatively and again at 6 weeks postoperatively for repeat office hysteroscopy and further lysis of adhesions if warranted.

From a recent practice analysis, a total of 355 patients were seen for the treatment of AS from January 2016 to March 2019. A total of 813 hysteroscopic lysis of adhesions performed. Of these 355 patients, the distribution of disease severity via March classification demonstrated 43.3% of patients with mild disease, 52.0% with moderate disease, and 4.7% with severe disease. In our practice there is no maximum number of attempts at hysteroscopic lysis of adhesions, with subsequent procedures scheduled and performed until normal uterine cavity anatomy is restored. The mean number of hysteroscopic procedures performed for all patients in this time period was 2.3 procedures per patient, with a range of 1 to 7 procedures per patient. A total of 116 patients, or 32.7% of patients required more than 2 hysteroscopic procedures, which may be loosely be referred to as refractory AS. There was a trend towards increasing mean number of hysteroscopic lysis of adhesion procedures performed based on March classification with 1.5 procedures performed for patients with mild disease, 2.8 procedures performed for moderate disease, and 3.3 procedures performed for severe disease.

Pregnancy rates following hysteroscopic lysis of adhesions have been published ranging from 32.1% to 79.0% (10, 58–65). Live birth rates have been reported ranging from 27.2% to 85.6% amongst patients treated for AS, although there were various methods for defining the outcome live birth in available publications (10, 59, 61, 64, 66–68)

Based on a recent telephone survey of 127 patients treated for AS in our practice from January 2016 to March 2019 and actively trying to conceive, there was an overall pregnancy rate of 81.9%. The mean follow-up period measured as the time from initial patient encounter to date of telephone survey was 825.9 days or 2.3 years. When specifically defining live birth rate, as a newborn birth occurring after 24-weeks gestational age, then 65 or 51.2% of patients in this cohort had one or more live births during this follow up period. Additionally, there are 16 patients actively pregnant at time of telephone survey without a live birth yet, which may contribute to the total live birth rate if they continue with their current gestation and deliver past 24-weeks gestational age.

The progression of hysteroscopic technology has allowed for easier and quicker treatment for patients, most significantly by moving the operative hysteroscopy from the operating room to the office. Utilizing a 5 mm rigid hysteroscope with a 12-degree viewing angle, our practice performs the majority of hysteroscopic lysis of adhesions within the office setting with no analgesic or oral nonsteroidal anti-inflammatory drugs alone. Over time our practice has now adopted a vaginoscopic approach over the utilization of a speculum and tenaculum for hysteroscopic entry into the cervical canal. This anecdotally decreases patient discomfort

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Pro 2. James H Liu, M.D.

During the menstrual cycle, the uterine endometrium has enormous regenerative capacity and over a 12 to 14-day follicular phase can regenerate up to a 10-14 mm endometrial thickness. AS results from scar tissue formation between the endometrial surfaces in response to mechanical trauma from a dilation and curettage (D&C) procedure or in response to infectious/inflammatory damage most often in a low estrogenic environment. The dynamic regenerative capacity of normal endometrium is blocked by the prolonged hypoestrogenic environment following delivery of the placenta or abortion resulting in fibrotic healing rather than regeneration of endothelium. In contrast, AS is not often seen after D&C during the reproductive cycle when a normal estrogenic environment is already present. With this understanding, the routine use of estrogen sup-

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and allows for a higher percent of complete hysteroscopic lysis of adhesions in the office setting. Improved operative hysteroscopic skills does come with experience, and patients with significant intrauterine adhesive disease are managed by an experienced minimally invasive gynecologist with a firm handle on advance hysteroscopic techniques to decrease procedure related complications or prolonged procedures. In this setting the rate of infection and or perforation is less than 1%. For more advanced disease pathology, we utilize transabdominal ultrasonography to guide the hysteroscope and scissors to areas of normal appearing endometrium and reduce the risk of creating a false passage.

In summary, we believe that operative hysteroscopy without a specific limitation on the number of hysteroscopic lysis of adhesion procedures is the preferred treatment method for patients with AS, until there is restoration of the normal uterine cavity anatomy. The term refractory Asherman is loosely defined, and currently there is no consensus on the definition of the term. However, utilizing both recurrence of intrauterine adhesions and inability to restore normal uterine cavity anatomy as a surrogate for the term refractory AS, the rate of refractory AS ranges from 5 % to 35% in the reported literature. We believe that even in this subset of refractory Asherman cases, patients should be offered multiple hysteroscopic lysis of adhesions to optimize their chance of conception. This time proven methodology in our practice yields comparable pregnancy and live birth rates as available in the published literature.

Con 2. Hervé Fernandez, M.D.

Perrine Capmas, M.D.

There is no unanimous definition of refractory AS but it excludes women with a normal cavity after a first operative surgery. The main issue is recurrence of adhesions after the first procedure. If we consider all the women requiring more than one attempt of operative hysteroscopy to get a normal cavity and furthermore a pregnancy as refractory AS, percentage is between 12% and 30%

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plementation after any D&C procedure associated with pregnancy should be strongly considered (31).

The physiological principles in treatment of AS are resection of underlying scar tissue; prevention of scar tissue formation; and promotion of regeneration of the endometrial epithelium from nascent basalis stem cells remaining in the endometrium (usually located in the uterine cornual) with high dose estrogen therapy. Factors that can result in treatment failures of AS can be associated with insufficient scar tissue resection, failure of stem cells to repopulate the uterine cavity, and/or inflammation-adhesion reformation. Repeated attempts to treat AS with hysteroscopic approaches in the absence of applying these three key principles leads to lower overall rates of success. Current advances in treatment of AS focus on use of anti-adhesion barriers (32) alone or in combination with progenitor/stem cell regeneration strategies (33)

Although there is widespread clinical experience in the use of cryopresevered amniotic membrane (AmnioGraft [Biotissue, Miami, FL], Prokera [Biotissue, Miami, FL], Ambios [IOP Ophthalmics, South San Francisco, CA]) in the field of ophthalmology for prevention of corneal scar tissue formation from ocular inflammation, corneal epithelial trauma, and other corneal and limbal defects (34), there are almost no studies in its use for prevention of inflammation and scarring in gynecological applications such as treatment of AS. The amnion membrane contains keratocyte growth factor, epidermal growth factor, lamin and type VII collage as well as neurotropic substances. Based on the ophthalmology literature, amnion grafts have antimicrobial properties, releases anti-inflammatory cytokines, reduces expression of pro-inflammatory cytokines, and inhibits scar tissue formation. One advantage of the amnion graft over other anti-adhesion barriers is that the biomembrane seems to be absorbed or is "incorporated" into the underlying corneal tissue. Whether these desirable properties are present in AS treatment applications remains to be determined.

Only two published studies have utilized amnion grafts for the treatment of AS (35, 36). We have described the use of and the Food and Drug Administration-approved cryopreserved amnion membrane (Ambios-5 [IOP Ophthalmics South]) as an absorbable, anti-adhesion barrier applied over the Cook intrauterine balloon stent in the treatment of moderate to severe AS. Our initial case series demonstrated an encouraging improvement in endometrial stripe thickness postoperative and return of menses. In our cumulative series experience of 35 cases of moderate to severe AS, women aged under 41 years had a 55% (15/27) interval pregnancy rate and women >41 reported a 12.5% (1/8) interval pregnancy rate (37). These encouraging results will need to be replicated in larger, controlled trials to clearly determine the potential advantage(s) of this approach.

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depending on the grade of AS at initial diagnosis (10, 38, 69, 70). The grade of AS is defined using European Society for Gynaecological Endoscopy (ESGE) classification (70). In our recent data, 21 of 105 women required more than one procedure (20%). This result agrees with published results.

The question of the number of operative hysteroscopy that a woman should attempt is not an easy one. In a published study, a 40.9% pregnancy rate and a 27.2% live birth rate out of 23 women with more than two procedures in a 10.5 months mean time are reported (10). These results are very encouraging for women with severe AS (grade 3 or 4 in the ESGE classification) willing to conceive. Hanstede et al. (38) also concluded that surgeons should go to more than one procedure for section of intra-uterine adhesions. Surgeons must be aware that it is possible to do multiple procedures; however, women in these cases must be very well informed and implicated in the choice of an additional procedure. Another point is the office control hysteroscopy; when there is no improvement compared to the preoperative hysteroscopy, the question of the benefit of an additional surgery has to be raised even if there is no answer in published study.

Recent unpublished data from our center in 112 women with AS and a pregnancy desire concluded to a 52% pregnancy rate with no significant difference between women with one procedure compared to the ones with two or more. The only factor leading to a difference in fertility rates was the initial grade of adhesions with a lower pregnancy rate in severe intra-uterine adhesions (grade 3 or 4 of the ESGE classification) but without any difference regarding the number of procedures.

The first point is the technic of hysteroscopic adhesiolysis that seems to slightly increase with better pregnancy rates over years (58). In the Netherlands for example, as it is a small country, gestion of intra-uterine adhesions is centralized and led to higher success rate (38). The type of energy used can also be determinant but there is a lack of studies in this field. Bipolar energy might lead to less intra-uterine adhesions (71). A randomized study in hysteroscopic myomectomy is being performed in our center to evaluate the rate of adhesions after monopolar resection versus bipolar resection.

Another important point is the use of early office diagnostic hysteroscopy. Published results are in favor of its use (72). A non-significant improvement in pregnancy rate and live birth rate was observed after section of intra-uterine adhesions (73). It also seems to decrease rate of adhesions after resection of myoma (74).

Some skills may help section of intrauterine adhesions and decrease the risk of recurrences. The first one is the guidance that can be performed by sonography (75–78), by fluoroscopy (38, 79) or by laparoscopy (80) or laparoscopic ultrasound (81, 82). This guidance seems to reduce complications such as false ways and perforations (38). There is no evidence that one of these methods for guidance

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Pro 3. Aghajanova Lusine, M.D., Ph.D.

The American Society for Reproductive Medicine defines the severity of disease as mild, moderate and severe, based on the extent of uterine cavity involvement (3). Most patients seen in fertility clinics usually have mild or moderate AS and will respond to treatment. On the other hand, patients with severe AS with partial of complete obliteration of uterine cavity present significant clinical challenge. Commonly these patients, while significant minority, require multiple hysteroscopies and eventually proceed to using gestational carrier to fulfil their dreams of having a baby.

Studies showed that there is 30% to 66% recurrence rate of intrauterine adhesions (IUAs) after initial adhesiolysis (38). However, there is no data or guidelines regarding the number of hysteroscopies to be performed on patients with moderate to severe disease. Not uncommonly, initial adhesiolysis procedure in severe AS cases needs to be interrupted due to reaching fluid deficit limit, uterine perforation, anesthesia concerns or inability to see the anatomic landmarks (tubal ostia) after prolonged surgery. In such situations, second look hysteroscopy is planned. Typically, in moderate to severe cases, we place intrauterine Foley balloon for 1 week and initiate estrogen therapy for 3 weeks for adhesion prevention, and then perform lining check with transvaginal ultrasound. Thin or irregular lining with hyperechoic areas while on

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is better than another whereas laparoscopic guidance is much more invasive than fluoroscopy or sonography.

Another useful skill is the use of 7Fr instrument (Delmont Imaging, La Ciotat, France) instead of 5Fr in a 4 to 5 mm hysteroscope with operative channel. It allows the use of stronger instrument without the need of a cervical dilatation, which can lead to complications such as perforations. To our knowledge, there is no published data on the use of 7Fr instrument.

Finally, the last skill is the use of barrier methods to avoid recurrence after the first hysteroscopic surgery but also after recurrent surgeries if needed. There is not a lot of evidence about efficacy of barriers but the ones that seems to have the best efficacy is Foley catheter (72). The use of a postoperative intrauterine device is not recommended. The use of intra-uterine gel also give interesting results after dilatation curettage but there is no study after intrauterine adhesions' section (57).

To conclude, the main tool against AS is still hysteroscopic surgery even if many procedures are necessary. However, good quality studies need to be performed to define indications of barrier methods even if for the moment they always must be used as a complement of surgery.

Con 3. Jacques Donnez, M.D., Ph.D.

Since it was first described by Fritsch (83) in 1894 and then Asherman in 1950 (84), several classification systems have been proposed to characterize the severity of disease, but none have been validated in terms of reproductive performance (85). The ideal approach should consider location, extent, type of adhesions and pathology (86). However, as recently reported by Dreisler and Kjer (87), existing classification systems are all descriptive in different ways and are therefore incomparable. The former European Society for Hysteroscopy (70) applied four grades, the American Fertility Society three grades (3), while Donnez and Nisolle (86) uses six, based on hysterosalpingography and hysteroscopy, with postoperative pregnancy rates (Table 1) as the primary driver.

As reported by March (12), the acronym PRACTICE stands for prevention, anticipation, comprehensive therapy, timely surveillance of subsequent pregnancies, investigation, and continuing education. Let me focus on prevention and therapy. Prevention is essential, as the main cause of IUAs and AS is trauma, primarily curettage of the endometrial layer shortly after pregnancy. In women with retained products of conception after delivery or miscarriage, curettage was found to induce significantly more IUAs (95.9%) then hysteroscopic removal (4.2%) (88, 89) Other surgical origins, like

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estrogen therapy will prompt repeat hysteroscopic evaluation of uterine cavity.

No one would argue that in order to be successful, management of AS should include not only surgical removal of adhesions and prevention of their reformation, but also measures towards regeneration of endometrial lining in order to provide a healthy surface for establishment and support of pregnancy. Hence, the alternative therapies are being considered currently for endometrial regeneration.

One of the new biological methods suggested for use in patients with damaged endometrium is intrauterine infusion of platelet rich plasma (PRP). The biological plausibility of platelets is based on their ability to release alpha granules containing various growth factors and cytokines upon activation at a site of an injury during the healing process. They have been shown to accelerate healing in many other tissues and organs such as musculo-skeletal (bone, tendon, muscle), have been used in dental, plastic and cardiac surgery, ophthalmology, diabetic wound healing, dermatology, and in androgenic alopecia for tissue regeneration and repair (39, 40). Importantly, its safety and almost nonexistent side effect profile have been established before (41) and reported throughout the literature. Therefore, logically, PRP was applied to uterine cavity to enhance endometrial cells proliferation and function, with initial publication coming out in 2015 with just 5 patients (42). Use of PRP for endometrial repair was supported by preclinical in vitro studies, which showed significant acceleration of endometrial cell proliferation and migration potential upon PRP treatment (43), as well as successful regeneration of damaged endometrium in a rat model (44).

I would like to make an important point though: the success of PRP depends on the presence of endometrial differentiated (resident) and progenitor cells from which the cell layer will regenerate. The application of PRP on unhealthy scarred tissue with no viable endometrial cells is futile, thus very limited success is guaranteed, particularly in severe cases.

Our group was the first in the U.S. to perform studies on patients with AS (45), as well as thin (atrophic) endometrium in the absence of intrauterine scarring. The data on the use of PRP specifically in AS is almost nonexistent. However, there is growing number of reports of PRP use in the setting of thin (atrophic lining). Of note, it is unclear if studies are clearly separating subjects with surgically treated AS from subjects with thin (atrophic) endometrium with no scan tissue identified on hysteroscopy.

We are completing a pilot study on the effect of PRP intrauterine infusion in patients with AS after hysteroscopic adhesiolysis. Due to difficulties with recruiting patients into a randomized controlled trial, the study was converted to prospective case control study. It appears that performing proper RTC is challenging in our specific population of infertile women, thus probably explaining the number of publications

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myomectomy (by laparoscopy/laparotomy or hysteroscopy) have also been reported, as well as B-Lynch sutures and uterine embolization (12, 87). Genital tuberculosis may be responsisble for Asherman syndrome in countries where it is still endemic (86).

Cervical probing with dilatation and curettage used to be the primary mode of management of IUAs, but should no longer be performed, with the widespread use of hysteroscopic treatment for this pathology.

When adhesions partially occlude the uterine cavity (degree Ib), their section is simple: they are divided down the middle, the remaining stumps retract, and the uterine cavity distends, allowing a panoramic view. Marginal or lateral IUAs (degree IIa and b), particularly if they are extensive and fibromuscular or composed of connective tissue, may be difficult to divide and require experienced hands to avoid more damage.

For IUAs of degree III, hysteroscopic observation of the uterine cavity should begin at the internal cervical os: If adhesions extend to that area, their selective division begins there. As they are cut and the uterine cavity opens, the hysteroscope is advanced to the fundal area, and both uterotubal ostia are visualized. In some cases, increased pressure inside the uterine cavity, obtained by increasing the inflow, can facilitate dissection by distending the cavity. Although the plane of dissection is better exposed, this procedure may lead to excessive fluid intravasation if prolonged. In collective series, success rates of 50% to 70% have been achieved (12, 58, 66, 86), but it should be stressed that most were women with mild or moderate IUAs and pregnancy rate in women with severe adhesions is significantly lower than that in women with mild adhesion ($P=.02$) (58).

In women with type IIIa (pseudo-Asherman), if a residual cavity with normal endometrium is visible once stenosis of the internal os has been lysed, results in terms of recovery of menstruation and fertility are excellent (100% and 90%

TABLE 1

Classification according to the location and the aspect of the adhesions.

Degree	Location
I	Central adhesions (bridge-like adhesions) (a) thin or filmy adhesions (endometrial adhesions) (b) myofibrous or connective adhesions
II	Marginal adhesions (always myofibrous or connective) (a) ledge-like projections (b) obliteration of one horn
III	Uterine cavity absent on hysterosalpingography (a) occlusion of the internal os (upper cavity normal) (pseudo-Asherman's syndrome) (b) extensive coaptation of the uterine walls (absence of uterine cavity;true Asherman's syndrome)

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reporting prospective cohort studies with using patients' prior cycles as control (42, 46, 47)

Successful pregnancies have been described in the setting of treated AS or thin lining after PRP infusion even without increased endometrial thickness, suggesting that PRP might not only improve proliferation of endometrial cells, but could probably modulate endometrial functionality and receptivity on molecular level (45, 47).

The treatment is appealing to patients for multiple reasons (safe, easy, and relatively cheap) and often is the last option before giving up and moving to alternative option such as gestational carrier or adoption.

In conclusion, I believe that we should practice combined approach to such complex clinical situation such as AS, by initiating therapy with surgical methods for removal of adhesions, followed by means for prevention of adhesion reformation and endometrial tissue regeneration.

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respectively) (86). However, in case of type IIIb IUAs (absence of residual cavity, no endometrial lining), outcomes are very poor, even if some 'cavity' remains at the end of surgery. In these women, despite postoperative insertion of an intrauterine device and high doses of estrogen, 'reocclusion' will occur, with no recovery of menstruation or fertility. In the past, we tried to repeat the hysteroscopic procedure for this type of refractory AS, but outcomes were very poor in terms of fertility, even with early second-look hysteroscopy. Alternative therapies need to be investigated for this disease type.

In conclusion, in type I, IIa, IIb and IIIa IUAs, hysteroscopic surgery is the primary therapeutic approach, with early second-look hysteroscopy for IIa and b cases.

In type IIIb IUAs, the very poor results obtained with hysteroscopic surgery impel us to seek alternatives to regenerate the inadequate endometrium with the help of cell-based therapies using endometrial stem/progenitor cells (14, 90–92).

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