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Updates in Surgery

ISSN 2038-131X

Updates Surg
DOI 10.1007/s13304-020-00828-0

Springer

Updates in Surgery
https://doi.org/10.1007/s13304-020-00828-0

ORIGINAL ARTICLE

Intrauterine infusion of platelet-rich plasma for severe Asherman syndrome: a cutting-edge approach

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Received: 28 March 2020 / Accepted: 31 May 2020

Abstract
Asherman syndrome (AS) consists of intrauterine adhesions development as a consequence of trauma, radiation, or infection in the endometrium. Clinical symptoms include menstrual alterations, infertility, and pregnancy complications, such as recurrent pregnancy loss or abnormal placentation. In this article, we performed a narrative review of the literature, searching electronic databases (i.e., Medline, Pubmed, and Google Scholar) to summarize the available pieces of evidence about epidemiology, pathophysiology, diagnosis, and treatment of AS. Hysteroscopy is essential for diagnosis and treatment, although adhesions may recur. Different postoperative therapies have been proposed to prevent recurrence and restore impaired endometrial function and promote endometrial regeneration, although these effects are usually temporary. We report a case of AS with adhesion recurrence and endometrial atrophy who was successfully treated with intrauterine autologous platelet–rich plasma (PRP) infusion. This therapy allowed endometrial tissue regeneration, leading to increased vascularity and endometrium thickness, and restoration of endometrial function that led to a successful pregnancy. Though there is limited experience supporting the use of PRP to improve endometrial function, it has been safely used in other fields of medicine; besides, it is easy to obtain, not expensive, and harmless being an autologous source. Future studies are encouraged to further assess this approach to treat AS.

Keywords Asherman syndrome · Intrauterine adhesions · Hysteroscopy · Platelet-rich plasma

Epidemiology

Post-traumatic intrauterine adhesions were first described by Heinrich Fritsch in 1894 [1]. Later, Asherman reported a case series of women with post-pregnancy adhesions producing partial or complete obliteration of the uterine cavity and/or cervical canal, as a consequence of trauma to the endometrium [2]. Such adhesions caused amenorrhea, hypomenorrhea, cyclical pain, reduced fertility, recurrent pregnancy loss, and abnormal placentation [2]. These symptoms, in particular menstrual irregularities, should be taken into account for differential diagnosis with other conditions such as endometriosis and uterine anomalies [3, 4]. To date, the term "Asherman syndrome" (AS) has also been used for women who present intrauterine adhesions with clinical symptoms and never had pregnancy [5]. Prevalence of this syndrome varies from 2.8 to 45.5% in infertile women, and from 1982 to 2008 more than 2500 cases have been reported [6, 7].

Pathophysiology

AS occurs after surgical interventions, most frequently dilatation and curettage for incomplete abortion (66.7%), postpartum curettage (21.5%), and elective abortion (17.5%) [8]. The incidence of intrauterine adhesions (IUA) is highest

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Published online: 08 June 2020

when curettage is performed between 2nd and 4th postpartum week, and lower when it is done in the first 48 h postpartum [9]. At the same time, the number of intrauterine procedures is proportionally related to the severity and recurrence of IUA [10]. Other causes can be abdominal/laparoscopic myomectomy (especially when the uterine cavity is opened during the procedure), uterine artery embolization, radiotherapy, as well as hysteroscopic surgery, with multiple submucosal fibroids removal associated with the highest risk [11]. Genital tuberculosis and schistosomiasis have also been associated with the development of IUA [12, 13]. In addition, chronic endometritis has been implicated in IUA pathogenesis [14, 15]. However, it seems there is an individual constitutional factor, since some patients develop severe IUA and others are not affected while undergoing the same surgical procedure [16].

The endometrium is a very complex tissue that undergoes cyclical phases of proliferation, shedding, and repair. Endometrium in women with IUA presents cellular, molecular, and structural differences compared with the endometrium of normal women [7]. There are very little data regarding abnormal repair mechanisms in women with IUA. Chen et al. [17] demonstrated a decreased ability for revascularization and angiogenesis in patients with IUAs, which may contribute to defective repair mechanisms. Levels of vascular endothelial growth factor and microvessel density, two factors associated with neo-angiogenesis and crucial for normal healing, were higher before and after surgery in patients who responded to surgical treatment. Patients with IUA also show increased expression of adhesion-related cytokines at the endometrial level: namely, transforming growth factor beta, platelet-derived growth factor, and b-fibroblast growth factor, all associated with adhesion formation [18]. High levels of ADAM (a disintegrin and metalloproteinase) protein family members were also associated with the presence and the severity of the IUA [19]. Besides these changes in repair function in the endometrium, surgical procedures can cause mechanical damage to the basalis of the endometrium, which can promote the loss of the local progenitor cells. This would lead to the regeneration failure of functional endometrium. Indeed, it has been hypothesized that a reduced number of progenitor cells in a setting of low circulating estrogen levels can impair endometrial regeneration [20]. When infection and inflammation also occur, inflammatory products may damage endometrial stem cells limiting their capacity of tissue regeneration [21].

Diagnosis

AS should be suspected in women presenting menstrual disorders (hypomenorrhea, amenorrhea), and/or infertility with a history of curettage or intrauterine surgery [5]. Different diagnostic modalities have been applied for the diagnosis of IUA: hysterosalpingography [22], ultrasonography [23, 24], sonohysterography [25], 3D ultrasonography [26, 27] and magnetic resonance [28, 29], although hysteroscopy [22, 30] is considered the gold standard for the diagnosis as well as for the evaluation of the severity of the disease. There are different classifications systems of AS, but there is no consensus on the optimum one as none of them offers a valuable prognostic tool. This lack of standardization also makes difficult to compare treatment outcomes between studies using different classification systems [6, 31–34].

Treatment

Hysteroscopy is the method of choice for symptomatic IUA, and allows also to rule out the possibility of concurrent malignancy with targeted biopsy [35]. Aim of surgery is to restore normal volume and shape of the uterine cavity covered with endometrial lining and free tubal ostia as well as prevent adhesion recurrence [7]. Adhesiolysis should begin inferiorly and advance cephalically until uterine architecture is normalized. Filmy and central adhesions should be divided first, while marginal and dense adhesions should be treated last [36], as the division of the latter is associated with a higher risk of uterine perforation. The use of mechanical instruments such as scissors or biopsy forceps for adhesiolysis has the advantage of avoiding complications related to energy sources, minimizing the damage of healthy endometrium [32, 37, 38]. If thermal energy is used, the minimum amount of energy must be applied to avoid damage to endometrial tissue [39–41]. Efficacy and safety of hysteroscopic surgery may be improved if the procedure is guided by different methods: for example, the instillation of blue dye may be used to stain the endometrium and guide the hysteroscopist to identify normal endometrium [32], especially for the treatment of mild and marginal adhesions. Fluoroscopic guidance [42, 43] or transabdominal ultrasound [5, 44, 45] may be used to monitor the procedure and decrease the risk for perforation even when the adhesions have completely or even completely obliterated the uterine cavity. Concomitant laparoscopy [32, 41, 45, 46] may be immediately performed to detect uterine perforation in case of suspicion, preventing any further trauma to adjacent organs. Other techniques have been described for the management of severe adhesions, including the use of laminaria tent [47], pressure lavage under guidance [48], and others [37, 45, 46]. When other treatments failed and symptoms are so severe to impair quality of life, we acknowledge the possibility of hysterectomy as definitive solution [49, 50].

Novel treatments

Preventing adhesion recurrence is essential for successful therapy, especially in cases with severe AS which

show a higher risk of recurrence [32, 37, 51, 52]. Second look hysteroscopy should be performed within 2 weeks to 2 months as the early second look can solve filmy adhesions [53, 54].

Different methods both hormonal and mechanical to prevent postoperative adhesions have been proposed. On the one hand, insertion of an intrauterine device (IUD) may be used to maintain dissected surfaces separated during the initial healing process, with loop IUD considered as the best choice [5, 8, 55]. On the other hand, copper-containing IUD should be avoided as it promotes inflammatory reaction [56], as well as T-shape IUD that is too small to be effective as a physical barrier [57], and progesterone loaded IUD that have a suppressive effect on the endometrium [58]. Intrauterine placement of Foley balloon catheter after the hysteroscopic adhesiolysis for 3–10 days has been reported to act as a physical barrier; in particular, in a non-randomized study comparing the use of Foley catheter for 10 days and IUD during 3 months after surgery, there were fewer infections and lower recurrence of IUA in the Foley group [59]. Besides, a retrospective cohort study comparing the use of Cook balloon, IUD and hyaluronic acid showed a greater reduction in the adhesion score for IUD and balloon group [60]. The efficacy of the balloon was greater than that of the use of IUD, probably because a Cook intrauterine balloon with a triangular shape has the advantage that it fits better the uterine cavity [60]. Hormonal therapy has shown a decrease recurrence of adhesions compared with no treatment, but optimum dose, duration, and route of administration have not been defined [61].

The aim of hysteroscopic treatment of AS is also to restore regular menstruation, fertility, and endometrial function. Success rates for restoration of menses varies from 67.7 [62] to 97.8% [52]. However, the most important factor confirming success of adhesiolysis is the live birth rate, which varies from 40.7 [62] to 79.4% [63]. Besides conception, women with AS still have a risk for pregnancy complications, such as spontaneous abortion, premature delivery, abnormal placentation, intrauterine growth restriction, and uterine rupture during pregnancy or delivery [32, 37, 45, 64, 65]. Thus, pregnancies in these women should be considered at high risk.

Regarding endometrial function, since cellular and molecular aspects of endometrial regeneration remain unknown, severe cases of AS with impaired endometrial function are treated nowadays with different endometrial cell therapies from different sources of stromal and hematopoietic cell populations [66, 67]: menstrual blood-derived stromal cells [68], umbilical cord-derived mesenchymal cells [69], bone marrow-derived mesenchymal stem cells [70, 71] or autologous peripheral blood $CD133^+$ cells [72]. The primary effect of cell therapy may act through the release of paracrine factors rather than cell engraftment [73, 74].

Platelet-rich plasma (PRP) is produced by centrifuging the patient's blood, to obtain a concentration of platelets 4–5 times above normal value [75]. Since it is prepared from autologous blood, risks for disease transmission, immunogenic reactions, or cancers are minimal. It has been extensively used to support tissue growth and repair in orthopedics, dermatology, dental and aesthetic surgery [76–78]. Alpha granules of platelets store cytokines and growth factors, such as vascular endothelial growth factor, transforming growth factor beta, fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, insulin growth factor type one, chemokine ligand five. These factors are concentrated through the centrifugation process and delivered to the affected area for regeneration and healing [79].

Aghajanova et al. [80] demonstrated in vitro that PRP promotes enhanced migration of endometrial epithelial cells and proliferation of endometrial stromal and mesenchymal cells, which are crucial for endometrial regeneration. These processes are probably mediated by growth factor receptors, as shown by the upregulation of some of them in cells treated with PRP.

For the first time, in 2015 Chang et al. [81] reported the use of intrauterine infusion of PRP that increased endometrium thickness in five patients with thin endometrium who were unresponsive to other therapies. Recent case series have also reported the successful use of PRP in the treatment of thin endometrium in frozen embryo transfer cycles in patients with a history of canceled cycles due to inadequate endometrial growth [82–84]. In the pilot study by Tandulwadkar et al. [82], in addition to increased endometrial growth, they also reported increased vascularity after PRP, which has been related to better outcomes in frozen embryo transfers, as reported by Sardana et al. [85].

Here, we reported a case of a patient who showed adhesion recurrence as well as impaired endometrial development, despite adhesiolysis and hormone therapy. Thus, we administered intrauterine autologous PRP to regenerate endometrium and its functions.

Case report

A 31-year-old woman, following in vitro fertilization (IVF) cycle at the Fertia Clinic (Fuengirola, Málaga, Spain) had a normal pregnancy and delivered through cesarean section. She underwent a postpartum curettage 48 h later because of retained placental remnants. She was discharged and then readmitted, since she developed endometritis that required intravenous antibiotics for 4 days. She returned to our clinic 2 years later with amenorrhea. Ultrasound evaluation showed anteverted uterus with homogeneous myometrium, endometrium lining of 3.5 mm with hyperechogenic tissue seen across fundus, branches of spiral vessels seen only on one-third of the myometrium at Power Doppler, both normal

size ovaries. The pattern of thin endometrium persisted through her cycle. To address suspected AS she underwent office hysteroscopy. The uterine cavity appeared as a fine narrow tunnel with severe adhesions, and tubal ostia were not visible (Fig. 1).

To restore normal uterine architecture, she followed surgical hysteroscopy with adhesiolysis using forceps and scissors. After the procedure, a Foley catheter was inserted and removed 1 week after. Second look hysteroscopy 4 weeks after showed very mild intrauterine adhesions that were solved by blunt dissection. She was treated first with cyclical estrogens and progesterone with oestradiol valerate 2 mg for 21 days and the last 10 days 0.5 mg norgestrel with a week interruption, during 3 months, to obtain a functional endometrium. She also underwent treatment with pentoxifylline 400 mg every 12 h and Vitamin E 500 UI every 12 h daily. She restored cyclical menses, and an ultrasound assessment of the endometrium in the following cycle showed endometrium thickness of 5.7 mm. Because of a poor endometrial growth, she was given oral oestradiol valerate in increasing doses as well as progesterone for another 3 months. However, the endometrium never reached thickness over 6 mm at a subsequent ultrasound scan. She followed the mock cycle with transdermal oestradiol 200 mg and vaginal micronized progesterone 600 mg for 5 full days. On day 6th, endometrial biopsy was performed, to perform endometrial receptivity array (ERA) test. The gene expression of the patient's endometrium was pre-receptive endometrium, so personalized embryo transfer was performed 1 day later. She then proceeded with an IVF cycle, and all her embryos were frozen at the blastocyst stage because of poor endometrium growth, less than 6 mm. She then followed endometrial preparation with transdermal oestradiol 200 mg and oral oestradiol valerate 4 mg. Day of embryo transfer endometrium thickness was 6.4 mm, and she had a grade-A blastocyst transferred following the ERA test recommendation, but she did not become pregnant. She then underwent an office hysteroscopy, where mild adhesions were seen at the fundus and right lateral uterine wall and were solved by laser (Velas II 15w Surgical diode laser, Gigaa Optronics Technology, Wuhan). The uterine cavity showed scanty areas of normal looking endometrium, with a very poor glandular development. After the procedure, a Cook balloon was inserted and removed 1 week after. Intrauterine infusion of platelet rich plasma (PRP) therapy was proposed to the patient: possibilities of failure and risks were discussed,

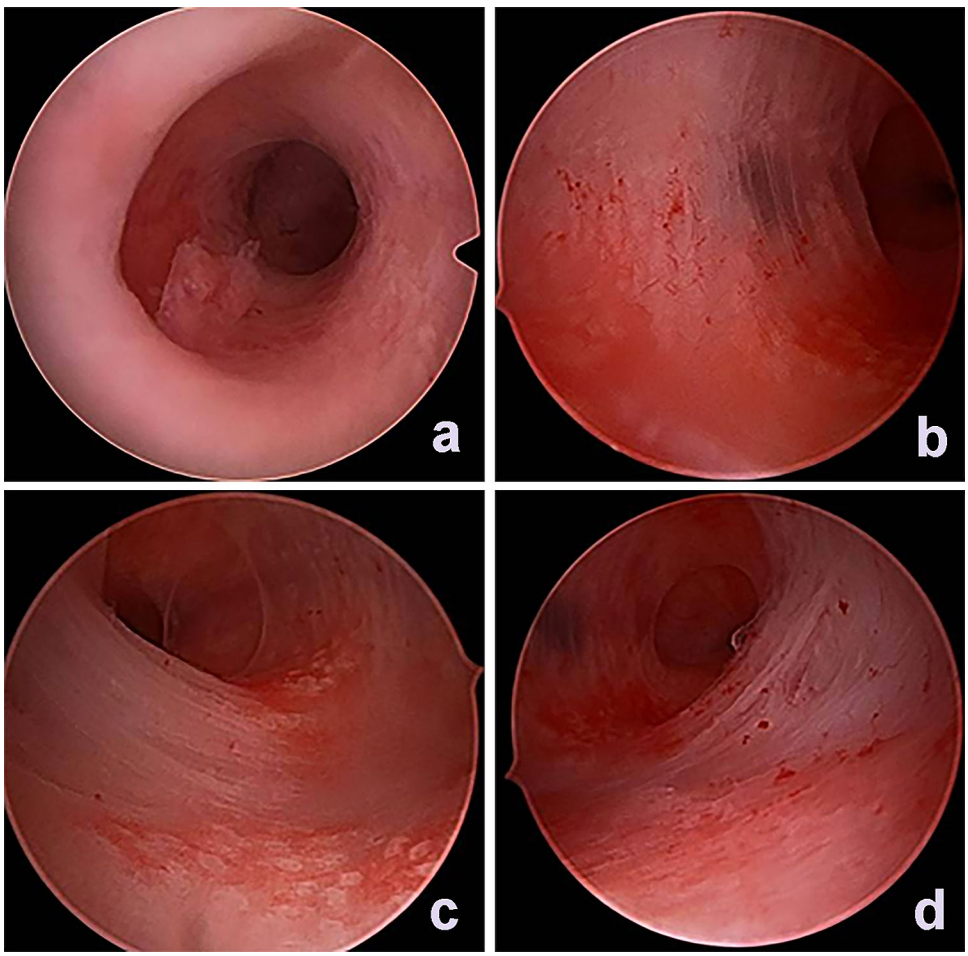

Fig. 1 Pre-operative assessment of Asherman syndrome: uterine cavity appeared as a fine narrow tunnel (**a**) with severe adhesions (**b**, **c**), and tubal ostia were not visible (**d**)

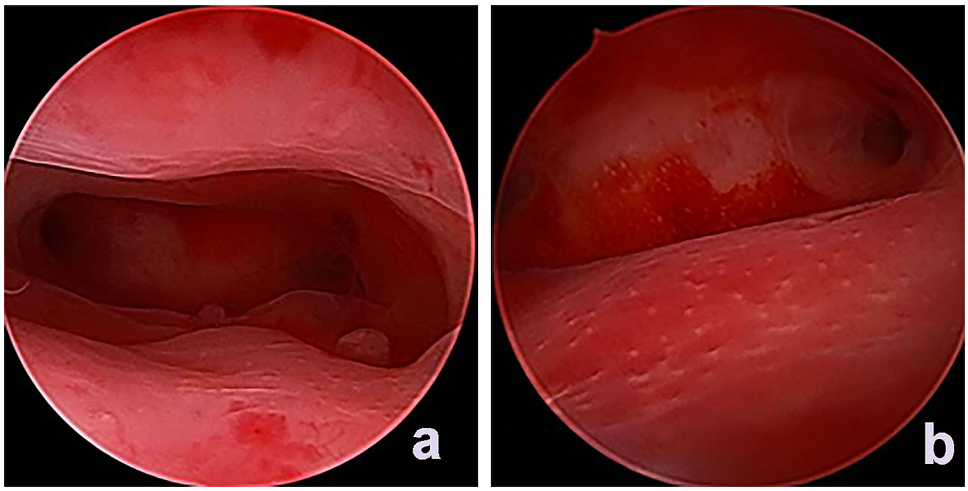

Fig. 2 Uterine cavity (**a**) and endometrial (**b**) appearance at second look hysteroscopy 2 days after intrauterine infusion of platelet-rich plasma

and she signed written informed consent. She then followed hormone replacement therapy for 2 months, and in the 3rd month, after 12 days of oestradiol therapy, she received 1 ml of autologous PRP. In particular, 15 ml of venous blood was collected in a syringe prefilled with a 5 ml anticoagulant solution (ACD-A). Blood was centrifuged at 600 rpm for 8 min. Three layers were formed after centrifugation, and the upper two layers were transferred into a sterile tube and centrifuged at 2000 rpm for 12 min. Three-quarters of the supernatant was discarded, and around 1 ml was then obtained from the bottom and activated with calcium chloride. Once PRP was prepared, the infusion was carried out 5–8 min after under transabdominal ultrasound guidance trough an intrauterine catheter (Gynetics Medical Products N.V., Lommel, Belgium) attached with 2 ml syringe, filled with 1 ml PRP suspension. PRP was infused very slowly into the uterine cavity and the catheter was very gently withdrawn out of the internal os, maintaining continuous pressure to avoid backflow. The procedure was repeated 3 days after, and a diagnostic hysteroscopy was performed 2 days after the last infusion. The endometrial lining was 6.3 mm before PRP and 7.7 mm after the second infusion. Colour Doppler assessment showed branches of spiral vessels seen across the myometrium reaching sub endometrial zone, while hysteroscopy showed improved glandular development in the whole cavity (Fig. 2).

Thus, a new cryotransfer was scheduled. She underwent therapy with transdermal oestradiol 150 mg and oestradiol valerate 4 mg, for 12 days, vaginal micronized progesterone 600 mg for 6 days, according to the ERA test recommendation [30]. A single grade A blastocyst was transferred. The patient became pregnant, had an uneventful healthy and underwent cesarean section at 37 gestational weeks due to the finding of a very thin cesarean section scar (2 mm) at the ultrasound, to avoid the risk of uterine rupture and according to the patient's decision. The neonatal weight was appropriate for gestational age (2730 gr), and postpartum was physiologic for all the maternal-neonatal parameters.

In conclusion, besides the improvement of endometrial thickness and vascularization on ultrasound, endometrial growth development and regeneration were improved after PRP, which led to a favourable endometrial environment for embryo implantation. This report suggests that autologous intrauterine PRP may hold the potential of being employed to promote endometrial regeneration in cases of moderate-severe endometrial atrophy and to create an adequate endometrial environment for embryo implantation. To the best of our knowledge, there is are not negative reports for intrauterine infusion of Platelet-Rich Plasma. Nevertheless, we acknowledge that follow up data concerning long-term complications, such as high risk of endometrial cancer, are currently not available so we cannot exclude these risks. In this scenario, further studies are encouraged to assess our findings and clarify the medium- and long-term outcomes.

Funding The work was not supported by any fund/Grant.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent is not required for this type of study.

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