Platelet-rich plasma in the management of Asherman syndrome: case report

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Introduction

Fertility clinics worldwide are helping couples to achieve their goal of building a family. Infertility universally affects about 13% couples [1], and the etiology of the disease varies by region [2].

Asherman syndrome (AS) is defined as intrauterine synechiae developed in response to injury to the pars basalis of the endometrium most commonly after uterine instrumentation associated with pregnancy, such as curettage after miscarriage, postpartum bleeding, or retained placenta, as well as intrauterine surgery [3–7]. Tuberculosis is the most common infectious cause of intrauterine scarring worldwide, with poor response to treatment [8, 9]. AS is responsible for 7% cases of secondary amenorrhea in the USA [10].

The intrauterine adhesions can range from complete obliteration of the cavity to filmy, fluffy, or dense adhesions between uterine walls [7]. The main complications of the Asherman syndrome are infertility (43%) and impairment of menstrual flow, from oligomenorrhea to amenorrhea (62%) [11]. It was shown that 76% of patients after intrauterine adhesiolysis had new adhesion formation 1 month postoperatively, compared to 88% post-septum resection, 40% post-myomectomy, 0% post-polypectomy [12].

Current management approaches are directed towards the treatment and prevention of the subsequent intrauterine adhesion formation. The standard treatment is surgical, which involves lysis of intrauterine adhesions under direct

hysteroscopic visualization, with the goal of restoration of the uterine cavity, as well as endometrial function and fertility [13, 14]. Prevention of re-scarring is achieved with mechanical measures such as intrauterine balloon or intrauterine device (with outcomes reportedly better with the balloon) and/or postoperative estrogen treatment [15–17]. After such combination treatment, some report almost 100% restoration of menses [18, 19]; however, achieving pregnancy is much more complicated and challenging, with post-treatment intrauterine pregnancy rate ranging from about 23 to 45% and live births from 28.7 to 32.1%, depending on severity of adhesions and female age [18, 20]. In those who get pregnant, there is an increased risk of serious complication such as placenta accreta or intrauterine growth restriction [3, 7, 11].

Hence, it is very clear that the current management of AS should ideally be directed not only towards removal of adhesions and prevention of their re-formation, but also towards the regeneration/revival of endometrial lining in order to provide a healthy layer of cells to support the pregnancy. Herein, we describe, to the best of our knowledge, the first reports on clinical use of platelet-rich-plasma (PRP) in the setting of Asherman syndrome. The goal of this publication is to report a potentially successful clinical application, which we are following up with a pilot randomized control study in our center.

Patients signed informed consents after detailed discussions about the PRP treatment, with institutional IRB approval from University of California San Francisco in place.

Case report #1

IO presented to us at age 34 with secondary amenorrhea. Her past gynecological history included prior long-term use of oral birth control pills (OCP) for contraception, with short period (3 months) of amenorrhea upon discontinuation, followed by a spontaneous pregnancy, which ended in an early pregnancy loss. Her pregnancy loss was managed by dilation and curettage (D and C), followed by two more D and C (sharp and suction curetting) for retained products of conception (POCs).

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Following the procedures, she had a few episodes of light-cyclic menstrual bleedings, but eventually developed amenorrhea. She reported that since her second D and C she had cyclic right lower quadrant pain and pressure, usually resolved with ibuprofen. Her past medical and family history was otherwise unremarkable.

On our evaluation, she had normal hormonal profile (TSH, prolactin) and normal complete blood count. Transvaginal ultrasound demonstrated thin endometrial lining of 4.7 mm, with hyperechogenic tissue seen across the fundus, with very thin lining in lower uterine segment. Bilateral ovaries were of normal size, with total antral follicle count (AFC) of 8. Saline sonogram showed minimal uterine cavity distention, suggestive of intrauterine scarring. Repeat lining measurement after 2 weeks of exogenous estrogen demonstrated a thin endometrial stripe of 3.8 mm, with minimal interruptions. To address suspected AS, she had two hysteroscopies under general anesthesia with extensive lysis of adhesions, with postoperative intrauterine balloon placement and prolonged estrogen treatment both times. Resumed menses were light, and endometrial thickness increased to 5.4 mm in late proliferative phase, with luteal phase endometrial biopsy demonstrating good glandular development. She subsequently attempted spontaneous conception for 4 months and was unsuccessful. This was followed by four cycles of superovulation with aromatase inhibitors with intrauterine insemination without success, in which she was able to reach endometrial thickness of 6.3 mm. Repeat saline sonogram demonstrated very poor distention of uterine cavity, but no distinct intracavitary lesion.

She subsequently underwent two additional office hysteroscopies with lysis of adhesions. At the last hysteroscopy, 1 ml of autologous platelet-rich plasma (PRP) was slowly infused into the uterine cavity through a Wallace IUI catheter at the very end of the procedure, after all hysteroscopic fluid was allowed to drain. PRP was prepared from patient's peripheral blood by separation of platelets by centrifugation using Magellan Autologous Platelet Separator System (Isto Biologics, St Louis, MO). The catheter was slowly removed, and no leakage was noted. The patient tolerated the procedure well. Intrauterine balloon was placed to be removed after 7 days, while on antibiotic for 7 days and 4 mg of daily oral estradiol for 1 month (standard of care in our clinic). She remained in the dorsal position for 10 min prior to transitioning to recovery area. No postoperative pain or cramping was noted on the day of surgery or in the following days.

Endometrial lining 2 weeks post-PRP infusion and on oral estrogen was still thin at 4.8 mm, and she underwent second PRP infusion, which was again uncomplicated. Her lining, however, was still thin at 5.0 mm 1 week after.

The plan made with primary MD was to undergo an IVF cycle for embryo banking, with embryo transfer after improved endometrial lining, while option of using gestational

carrier was discussed as well. However, while preparing for IVF cycle, the patient became spontaneously pregnant, now at age 37, with pregnancy in the third trimester at the time of this report.

Case report #2

MA is a 40-year-old who was referred to us with Asherman syndrome. Her past gynecological history was significant for hysteroscopic polypectomy at age 36, followed by spontaneous pregnancy, resulting in D and C for missed abortion. She subsequently underwent one unsuccessful round of IUI. During preparation for IVF, she was diagnosed with intrauterine adhesions and underwent two hysteroscopic adhesiolysis procedures. She conceived after the second IVF cycle; however, pregnancy resulted in spontaneous miscarriage treated with misoprostol (prostaglandin E1). She then underwent two more IVF cycles, with no resulting pregnancy. Her past medical history was significant for irritable bowel syndrome and pelvic pain, and past surgical history was significant for two diagnostic laparoscopies with no pertinent findings, two hysteroscopies, and one D and C as above.

She was then referred to our center for care. Her recurrent pregnancy loss work-up (endocrine tests, parental karyotype, antiphospholipid antibodies, and inherited thrombophilia testing) was normal. Transvaginal ultrasound on cycle day 20 showed a 3.3-mm isoechoic endometrium, with small fluid collections at both cornuae. Bilateral ovaries were of normal size, with total AFC of 6. During office hysteroscopy, moderate adhesions noted at the fundus were removed, and 1 ml of autologous PRP was slowly infused into the uterine cavity through an IUI catheter at the very end of the procedure, as described in Case #1. The patient tolerated the procedure well and recovery was unremarkable. Intrauterine balloon was placed and remained in situ for 7 days, with antibiotic coverage. Patient was placed on 4 mg daily oral estradiol, as in Case #1.

Endometrial lining 2 weeks post-PRP infusion and on oral estrogen improved to 6.4 mm. Menses normalized, per patient. She then proceeded to an IVF cycle. PRP infusion was performed on cycle day 10 of the "lead-in" cycle, prior to starting estrogen priming, due to endometrial lining being < 7 mm (6.3 mm). Maximal endometrial thickness of stimulated endometrium in IVF cycle was 6.7 mm. Three day 2 embryos (all four cells, grade 2) were transferred. The patient became pregnant, with dichorionic-diamniotic twin intrauterine pregnancy, which spontaneously reduced to viable singleton pregnancy. Pregnancy is in the early third trimester at the time of this report.

Discussion

This is the first report on the clinical application of PRP in the management of Asherman syndrome (AS), which remains one of the most challenging pathologies fertility specialists encounter in daily practice. This report suggests that PRP potentially may not only affect endometrial growth as measured by improved endometrial thickness on ultrasound, but also improve its functional properties as suggested by successful pregnancy despite persistent thin lining after the treatment. These initial clinical data are supported by novel preclinical in vitro studies, which showed significant acceleration of endometrial cell proliferation and migration potential when treated with PRP [21]. These encouraging in vitro studies provided a solid base for transitioning towards the clinical application of PRP in our practice.

It is important to acknowledge that several other experimental approaches have been tried in the management of AS previously, including using different adhesion-barriers, such as bioresorbable membrane of chemically modified hyaluronic acid and carboxymethylcellulose—Seprafilm or a crosslinked gel derived from hyaluronic acid—hyaluronic acid gel, and even human amnion graft [22–24]. These approaches, however, have not gained wide acceptance.

Santamaria et al. [25] performed a pilot study in which autologous peripheral blood CD133+ bone marrow-derived mesenchymal stem cells (BM-MSC) were isolated and delivered into the uterine spiral arterioles by catheterization, with subsequent restoration of endometrium and pregnancies [25]. While this study is very promising and provides an evidence for possibility of endometrial regeneration using autologous stem cells, the treatment is medically complicated and requires substantial resources. A single-case report on intrauterine infusion of autologous BM-MSC with improved endometrial thickness and successful pregnancy after subsequent embryo transfer has been reported [26].

Reports on the usage of platelet rich plasma (PRP) in clinical settings have significantly increased over the past few years. PRP is an autologous concentration of platelets in plasma that is commonly used in orthopedics, dental and plastic surgery, diabetic wound healing, and dermatology for tissue regeneration and repair [27–32]. In the field of obstetrics and gynecology, use of PRP has only recently been reported. PRP was shown to accelerate the wound healing after cesarean delivery in high-risk patients in a case control study [33] and helped to close vaginal gap in three cases of vaginal mesh exposure, when applied after the mesh resection [34]. Platelets contain alpha-granules that store large numbers of growth factors and cytokines involved in cell proliferation, migration, differentiation, and angiogenesis and are released upon platelet activation at the site of injury or inflammation [35–37]. These features

of platelets/PRP are very attractive in situations when endometrial growth is compromised such as AS or thin (atrophic) endometrial lining.

Recent case series suggest that PRP can be successfully used in the management of thin endometrial lining in medicated frozen embryo transfer (FET) cycles and history of prior cancelations due to the thin lining [38, 39]. The researchers used intrauterine infusion of autologous PRP in medicated FET cycles in women with endometrium < 7 mm on cycle day 10–12, with 1–2 infusions 48–72 h apart, depending on the change in endometrial thickness. They reported that all patients had increased endometrial thickness at 48–72 h after PRP infusion to > 7 mm and had undergone embryo transfer, with subsequent pregnancies in all five patients in Chang [38] and 5/10 patients in the Zadehmodarres [39] articles.

The recent study on the in-vitro effects of PRP on different human endometrial cell types that demonstrated the increased proliferation and migration of endometrial adult and progenitor cells suggests these as mechanisms behind the endometrial regeneration in the setting of uterine scarring or atrophic (thin) endometrium (Aghajanova et al., in press). We believe that in the setting of AS, the removal of scar tissue and exposure of the normal endometrial cells to the growth factors and cytokines in PRP help boost the existing cellular functions involved in tissue regeneration.

In summary, we present the first cases of intrauterine PRP infusion for treatment of Asherman syndrome. Treatment was well tolerated, with no short-term or long-term side effects, and appeared to improve endometrial function as demonstrated by successful conception and ongoing clinical pregnancies. In conjunction with solid in vitro data on human endometrial cells, these pilot clinical outcomes were very reassuring. As a result, the first randomized controlled study is currently underway.

Compliance with ethical standards

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

References

1. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med.* 2012;9(12):e1001356. <https://doi.org/10.1371/journal.pmed.1001356>.
2. Leke RJ, Oduma JA, Bassol-Mayagoitia S, Bacha AM, Grigor KM. Regional and geographical variations in infertility: effects of environmental, cultural, and socioeconomic factors. *Environ Health Perspect.* 1993;101(Suppl 2):73–80.
3. March CM. Intrauterine adhesions. *Obstet Gynecol Clin N Am.* 1995;22(3):491–505.

4. Adoni A, Palti Z, Milwidsky A, Dolberg M. The incidence of intrauterine adhesions following spontaneous abortion. *Int J Fertil*. 1982;27(2):117–8.
5. Touboul C, Fernandez H, Deffieux X, Berry R, Frydman R, Gervaise A. Uterine synechiae after bipolar hysteroscopic resection of submucosal myomas in patients with infertility. *Fertil Steril*. 2009;92(5):1690–3. <https://doi.org/10.1016/j.fertnstert.2008.08.108>.
6. Taskin O, Sadik S, Onoglu A, Gokdeniz R, Erturan E, Burak F, et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. *J Am Assoc Gynecol Laparosc*. 2000;7(3):351–4.
7. Berman JM. Intrauterine adhesions. *Semin Reprod Med*. 2008;26(4):349–55. <https://doi.org/10.1055/s-0028-1082393>.
8. Bukulmez O, Yarali H, Gurgan T. Total corporal synechiae due to tuberculosis carry a very poor prognosis following hysteroscopic synechialysis. *Hum Reprod*. 1999;14(8):1960–1.
9. Sharma JB, Roy KK, Pushparaj M, Gupta N, Jain SK, Malhotra N, et al. Genital tuberculosis: an important cause of Asherman's syndrome in India. *Arch Gynecol Obstet*. 2008;277(1):37–41. <https://doi.org/10.1007/s00404-007-0419-0>.
10. Practice Committee of American Society for Reproductive M. Current evaluation of amenorrhea. *Fertil Steril*. 2008;90(5 Suppl):S219–25. <https://doi.org/10.1016/j.fertnstert.2008.08.038>.
11. Schenker JG. Etiology of and therapeutic approach to synechia uteri. *Eur J Obstet Gynecol Reprod Biol*. 1996;65(1):109–13.
12. Yang JH, Chen MJ, Chen CD, Chen SU, Ho HN, Yang YS. Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries. *Fertil Steril*. 2013;99(7):2092–6 e3. <https://doi.org/10.1016/j.fertnstert.2013.01.137>.
13. Yu D, Li TC, Xia E, Huang X, Liu Y, Peng X. Factors affecting reproductive outcome of hysteroscopic adhesiolysis for Asherman's syndrome. *Fertil Steril*. 2008;89(3):715–22. <https://doi.org/10.1016/j.fertnstert.2007.03.070>.
14. Myers EM, Hurst BS. Comprehensive management of severe Asherman syndrome and amenorrhea. *Fertil Steril*. 2012;97(1):160–4. <https://doi.org/10.1016/j.fertnstert.2011.10.036>.
15. Lin X, Wei M, Li TC, Huang Q, Huang D, Zhou F, et al. A comparison of intrauterine balloon, intrauterine contraceptive device and hyaluronic acid gel in the prevention of adhesion reformation following hysteroscopic surgery for Asherman syndrome: a cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(2):512–6. <https://doi.org/10.1016/j.ejogrb.2013.07.018>.
16. Orhue AA, Aziken ME, Igbehof JO. A comparison of two adjunctive treatments for intrauterine adhesions following lysis. *Int J Gynaecol Obstet*. 2003;82(1):49–56.
17. Johary J, Xue M, Zhu X, Xu D, Velu PP. Efficacy of estrogen therapy in patients with intrauterine adhesions: systematic review. *J Minim Invasive Gynecol*. 2014;21(1):44–54. <https://doi.org/10.1016/j.jmig.2013.07.018>.
18. Fernandez H, Al-Najjar F, Chauveaud-Lambling A, Frydman R, Gervaise A. Fertility after treatment of Asherman's syndrome stage 3 and 4. *J Minim Invasive Gynecol*. 2006;13(5):398–402. <https://doi.org/10.1016/j.jmig.2006.04.013>.
19. Pabuccu R, Atay V, Orhon E, Urman B, Ergun A. Hysteroscopic treatment of intrauterine adhesions is safe and effective in the restoration of normal menstruation and fertility. *Fertil Steril*. 1997;68(6):1141–3.
20. Fedele L, Bianchi S, Frontino G. Septums and synechiae: approaches to surgical correction. *Clin Obstet Gynecol*. 2006;49(4):767–88. <https://doi.org/10.1097/01.grf.0000211948.36465.a6>.
21. Aghajanova L, Houshdaran S, Balayan S, Manvelyan E, Irwin JC, Huddleston HG, Giudice LC. In vitro evidence that platelet-rich plasma stimulates cellular processes involved in endometrial regeneration. *J Assist Reprod Genet*. 2018. <https://doi.org/10.1007/s10815-018-1130-8>.
22. Tsapanos VS, Stathopoulou LP, Papathanassopoulou VS, Tzingounis VA. The role of Seprafilm bioresorbable membrane in the prevention and therapy of endometrial synechiae. *J Biomed Mater Res*. 2002;63(1):10–4.
23. Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G, et al. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. *Hum Reprod*. 2003;18(9):1918–21.
24. Amer MI, Abd-El-Maeboud KH, Abdelfatah I, Salama FA, Abdallah AS. Human amnion as a temporary biologic barrier after hysteroscopic lysis of severe intrauterine adhesions: pilot study. *J Minim Invasive Gynecol*. 2010;17(5):605–11. <https://doi.org/10.1016/j.jmig.2010.03.019>.
25. Santamaria X, Cabanillas S, Cervello I, Arbona C, Raga F, Ferro J, et al. Autologous cell therapy with CD133+ bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: a pilot cohort study. *Hum Reprod*. 2016;31(5):1087–96. <https://doi.org/10.1093/humrep/dew042>.
26. Nagori CB, Panchal SY, Patel H. Endometrial regeneration using autologous adult stem cells followed by conception by in vitro fertilization in a patient of severe Asherman's syndrome. *J Hum Reprod Sci*. 2011;4(1):43–8. <https://doi.org/10.4103/0974-1208.82360>.
27. Lacci KM, Dardik A. Platelet-rich plasma: support for its use in wound healing. *Yale J Biol Med*. 2010;83(1):1–9.
28. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. *Am J Sports Med*. 2014;42(3):610–8. <https://doi.org/10.1177/0363546513518416>.
29. Jo CH, Shin JS, Lee YG, Shin WH, Kim H, Lee SY, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: a randomized, single-blind, parallel-group trial. *Am J Sports Med*. 2013;41(10):2240–8. <https://doi.org/10.1177/0363546513497925>.
30. Cervelli V, Gentile P, Scioli MG, Grimaldi M, Casciani CU, Spagnoli LG, et al. Application of platelet-rich plasma in plastic surgery: clinical and in vitro evaluation. *Tissue Eng Part C Methods*. 2009;15(4):625–34. <https://doi.org/10.1089/ten.TEC.2008.0518>.
31. Oh DS, Cheon YW, Jeon YR, Lew DH. Activated platelet-rich plasma improves fat graft survival in nude mice: a pilot study. *Dermatol Surg*. 2011;37(5):619–25. <https://doi.org/10.1111/j.1524-4725.2011.01953.x>.
32. Picard F, Hersant B, Bosc R, Meningaud JP. The growing evidence for the use of platelet-rich plasma on diabetic chronic wounds: a review and a proposal for a new standard care. *Wound Repair Regen*. 2015;23(5):638–43. <https://doi.org/10.1111/wrr.12317>.
33. Tehranian A, Esfehiani-Mehr B, Pirjani R, Rezaei N, Sadat Heidary S, Sepidarkish M. Application of autologous platelet-rich plasma (PRP) on wound healing after caesarean section in high-risk patients. *Iran Red Crescent Med J*. 2016;18(7):e34449. <https://doi.org/10.5812/ircmj.34449>.
34. Castellani D, Valloni A, Piccirilli A, Paradiso Galatioto G, Vicentini C. An innovative approach to treating vaginal mesh exposure after abdominal sacral colpopexy: endoscopic resection of mesh and platelet-rich plasma; initial experience in three women. *Int Urogynecol J*. 2017;28(2):325–7. <https://doi.org/10.1007/s00192-016-3154-x>.
35. Langer HF, Stellos K, Steingen C, Frohofer A, Schonberger T, Kramer B, et al. Platelet derived bFGF mediates vascular integrative mechanisms of mesenchymal stem cells in vitro. *J Mol Cell Cardiol*. 2009;47(2):315–25. <https://doi.org/10.1016/j.jmcc.2009.03.011>.
36. Stellos K, Seizer P, Bigalke B, Daub K, Geisler T, Gawaz M. Platelet aggregates-induced human CD34+ progenitor cell proliferation and differentiation to macrophages and foam cells is mediated by stromal cell derived factor 1 in vitro. *Semin Thromb Hemost*. 2010;36(2):139–45. <https://doi.org/10.1055/s-0030-1251497>.

37. Gawaz M, Vogel S. Platelets in tissue repair: control of apoptosis and interactions with regenerative cells. *Blood*. 2013;122(15):2550–4. <https://doi.org/10.1182/blood-2013-05-468694>.
38. Chang Y, Li J, Chen Y, Wei L, Yang X, Shi Y, et al. Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. *Int J Clin Exp Med*. 2015;8(1):1286–90.
39. Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: a pilot study. *JBRA Assist Reprod*. 2017;21(1):54–6. <https://doi.org/10.5935/1518-0557.20170013>.