

Hormone Therapy with or without Platelet-Rich Plasma (PRP) for Treatment Asherman Syndrome; A Randomized Clinical Trial

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Abstract

Background: Asherman syndrome is a controversial issue in obstetrics and gynecology without any consensus on its management and treatment. It is characterized by variable lesions inside the uterine cavity and also causes menstrual irregularities, infertility, and placental abnormalities. The study aimed to assess the platelet-rich plasma (PRP) effect in women with intrauterine adhesions by evaluating the improvement of the menstrual cycle and intrauterine adhesion (IUA) stage.

Materials and Methods: This clinical trial study was performed on 60 women with Asherman syndrome in two groups of 30. For the first group, only hormone therapy was performed and for the second group, hormone therapy with platelet-rich plasma after hysteroscopy. Recovery of Asherman syndrome and IUA stage was assessed at 6 to 8 weeks after hysteroscopy and compared between the two groups.

Results: Our results demonstrated that there was no significant difference between demographic data in the two groups as well as the menstrual pattern of both groups before or after treatment ($P > 0.05$). Frequency distribution of IUA after the intervention in the PRP + hormone therapy group in grade I, II, and III were equal to 73.3%, 20%, and 6.7% and in the hormone therapy group were 53.3%, 26.7%, and 20%, respectively ($P = 0.22$). In addition, hypo menorrhea was observed in 33.3% of PRP + hormone therapy group and 40% of the hormone therapy group with no significant difference between the two groups ($P = 0.71$).

Conclusion: Hormone therapy with PRP compared to hormone therapy alone after routine surgical treatment had not a significant effect on the IUA stage, duration, and severity of menstruation.

Keywords: Adhesions, Asherman syndrome, hormone therapy, intrauterine, platelet rich plasma

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INTRODUCTION

Asherman syndrome is a type of intrauterine adhesion that results in menstrual cessation, menstrual irregularities, infertility, or recurrent miscarriage. Intrauterine adhesions were first described by Asherman in 1948.^[1,2] This problem usually occurs due to damage to the endometrial basal layer after pregnancy-related curettages, such as incomplete miscarriage (33.3%), postpartum hemorrhage (37.5%), and elective miscarriage (8.3%).^[3,4] Disease is often characterized by decreased flow and duration of menstrual bleeding

(no menstrual bleeding, reduced bleeding, or sudden menstrual bleeding) and infertility. Although menstrual irregularities are often commensurate with the severity of the bleeding, this relationship is not always true. The adhesion is limited to the cervix or lower part of the uterus and may stop menstrual bleeding. Pain during menstruation and ovulation is sometimes experienced and can be related to obstruction.^[5,6] The severity of intrauterine adhesions varies and usually involves small, local bands, extensive bandages, and some even leading to

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complete blockage of the uterine cavity. Uterine surgery and diagnostic curettage are common causes of adhesions, which usually result from pregnancy complications such as postpartum hemorrhage, complete or forgotten miscarriage, and placental retention. Multiple curettage, which is usually performed at the end of pregnancy, is considered an important risk factor for uterine adhesions so that in various studies, the risk of uterine adhesions after the third curettage has been mentioned up to 60%. Some infections, especially uterine tuberculosis, can cause severe adhesions.^[7] Postpartum chorioamnionitis or postpartum endometriosis and uterine compression scurvy to control postpartum hemorrhage increase the risk of Asherman syndrome.^[8]

Hysteroscopy has changed the treatment of intrauterine adhesions, both in diagnosis and treatment approaches and in helping the patients to be fertile. In fact, infertility due to uterine cavity abnormalities affects 10 to 15 percent of couples. Abnormal uterine findings have been found in 34% to 62% of infertile women. The role of hysteroscopy in the study of infertility is to identify possible intrauterine changes that can interfere with implantation, growth, or both, and to assess the benefits of different treatments in restoring the normal endometrial environment.^[9] Therefore, hysteroscopy is considered the gold standard in evaluating the uterine cavity. Enlargement and direct visibility of adhesions provide accurate and safe treatment of lesions. When the lesions are localized, these adhesions can be well removed using a hysteroscope tip or uterine infusion. However, this method is challenging in cases of dense and severe adhesions. Because severe uterine adhesions and thinning of the uterus reduce the possibility of effective treatment with hysteroscopy, and on the other hand, it is associated with a high probability of recurrence.^[10-12]

Platelet-rich plasma, or PRP, an autologous blood product obtained through blood centrifugation, is a rich source of growth factors. Growth factors have become a hot topic in the medical world since the early 1990s. It is clear that growth factors play a central role in healing all types of wounds. The first research on the use of PRP was reported in the early 1970s.^[13] PRP is safe and effective in accelerating natural wound healing processes, soft tissue regeneration and bone regeneration and strengthening.^[14] Recently, PRP has been used to aid endometrial growth and improve pregnancy outcomes during laboratory fertilization.^[15] Platelets provide a unique ability to heal wounds through growth factors. PRP accelerates endothelial, epithelial, and epidermal reproduction, stimulates angiogenesis, promotes soft tissue healing, and inhibits glucocorticoid-induced wound healing. High concentrations of PRP leukocytes have antimicrobial effects. Because PRP is an autologous blood product, there is no risk of transmitting infectious diseases. Up to 70% of the growth factor from active PRP can be released within 10 min.^[16] So, PRP probably has a positive effect on the damaged endometrium. In addition, based on long-term clinical experience, the use of PRP is considered safe and unlike bone marrow-derived stem cells (BMDSCs), it is much easier to obtain.^[17]

The aim of this study was to evaluate and compare the effectiveness of hormone therapy with and without platelet-rich plasma in the improvement of Asherman's syndrome and its effect on reducing recurrence and increasing patient recovery.

MATERIALS AND METHODS

This study is a randomized controlled clinical trial. The study population included all the women with Asherman syndrome referred to Al-Zahra and Shahid Beheshti hospitals in Isfahan from March 2019 to February 2020.

Due to the rarity of the cases, all patients who were eligible to enter the study were included using the census method.

Women younger than 18 and older than 43 years, unmarried, simultaneous active infection of the uterus and vagina, hemoglobin less than 11 g/dL, platelet less than 150,000 cell/mm³, with abnormal hormonal test, and history of anticoagulant use within at least 10 days were excluded.

After the approval of the ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.671) and obtaining the code of clinical trial (IRCT20200316046789N1), 60 women were selected. After filling out the written consent, they were diagnosed with Asherman syndrome by 3D sonography, sonohysterography, hysterosalpingography, or hysteroscopy. Then, demographic information, laboratory, and checkup results before treatment were evaluated and recorded.

The severity of intrauterine adhesions (IUA) was determined by hysteroscopic findings, including the extent of uterine cavity involvement and the type of adhesion, as well as clinical signs (menstrual status) according to the American Reproductive Medicine Association's (ASRM) scoring system.

Then, the patients were divided into two groups using random allocation software [Figure 1]. After hysteroscopy, patients in the first group received hormone therapy alone (control group) and the second group received hormone therapy with platelet-rich plasma (PRP) (case group). It should be noted that due to the different nature of the intervention in both groups the interfeerer was aware of the type of intervention in each group; but the data collector, patient, and statistician were not aware of it, so the study was single-blind.

PRP was prepared according to Arya Mabna Tashkhis, Iran (ARDM) as 8.5 mL of peripheral venous blood of the patient was taken through a syringe containing 1.5 mL of citrate acid. It was then centrifuged immediately at 1000 g for 10 min. The buffy coat layer and the plasma layer were collected and transferred to another tube to be centrifuged again at 3500 g for 5 min; finally, 1.5 mL of PRP with a good concentration was obtained.

To do the intervention in the case group, after removal of the adhesion by hysteroscopy, 1 mLPRP was injected into the uterine cavity wall and then the uterine cavity was filled with 5 mL of PRP gel. They then received hormone therapy; the

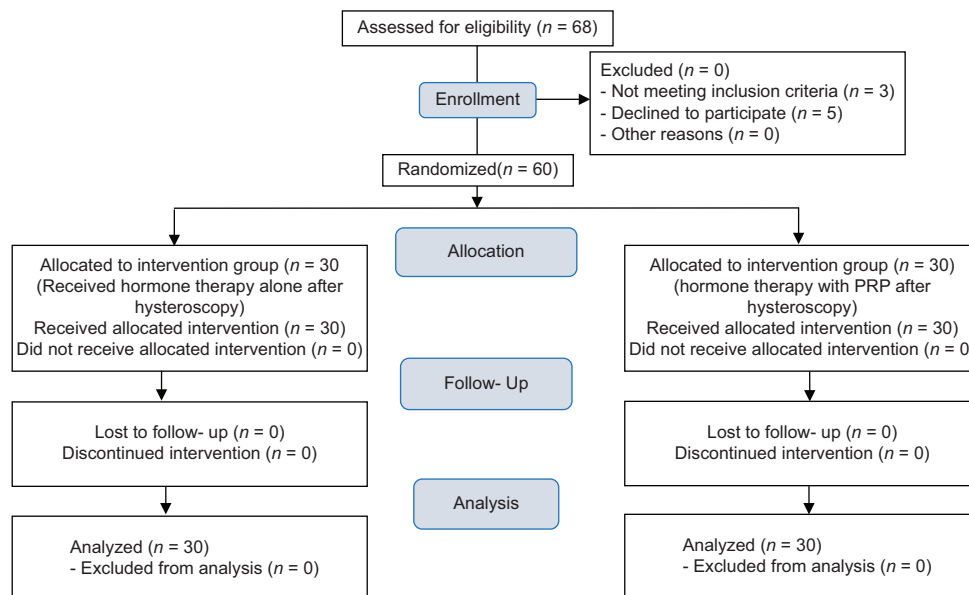


Figure 1: Consort flowchart of patients

usual regimen was 2.5 mg of conjugated estrogen once a day for 4 weeks. A progestin such as medroxyprogesterone acetate at a dose of 10 mg was added to treatment in the last week.

In the group of hormone therapy alone, after hysteroscopy and removal of adhesions, they were treated only with hormone therapy.

Finally, patients in both groups were examined using hysteroscopy. The IUA stage and menstruation pattern before and after the intervention were evaluated.

The collected information was entered into SPSS software (ver. 26). The data were shown as mean ± standard deviation (SD) or frequency (percentage). At the level of inferential statistics, according to the result of Kolmogorov–Smirnov test based on normal data distribution, Chi-Square test, and independent-sample t-test were used. In all analyses, a significance level of less than 0.05 was considered.

RESULTS

A total of 60 women were entered to study, 30 of them received PRP with hormone therapy and 30 of them, hormone therapy alone. According to the demographic data, there was no significant difference between two groups (age-gravidity-possible etiology) (P -value > 0.05) [Table 1].

In addition, there was no significant difference in the frequency distribution of IUA stage between the two groups of PRP + hormone and hormone alone before the intervention (P value > 0.05).

After the intervention compared to before, IUA in stage III was decreased in PRP + hormone therapy group (66.7% Vs. 6.7%) and hormone therapy group (60% Vs. 20%), but this reduction was not significantly different between the two groups (P -value = 0.22) [Table 2].

Table 1: Baseline characteristics

Characteristics	PRP + hormone therapy	Hormone therapy	<i>P</i>
Age; year	36.2±6.6	35.6±5.9	0.264**
BMI; kg/m ²	28.8±3.6	28.3±4.1	0.546**
Gravidity			
Null-gravida	8 (26.7)	6 (20)	1.00*
Multigravida	22 (73.3)	24 (80)	
Possible etiology			
Cesarean	8 (26.7)	6 (20)	1.00*
D & C	12 (40)	14 (46.7)	
Surgical hysteroscopy	2 (6.7)	4 (13.3)	
Myomectomy	8 (26.7)	6 (20)	

Data are presented as the Mean±Standard Deviation (SD) and number (%); PRP: Platelet-rich plasma; D & C: Dilation and Curettage. *Chi-square test was used. **Independent sample *t* test was used

Menstrual patterns did not differ significantly between the two groups before the intervention (P - value = 0.35). After the intervention, it was included normal and hypomenorrhea, which in the PRP+ hormone therapy group was 66.7% and 33.3%, respectively, and in the hormone therapy group was 60% and 40%, respectively (P -value = 0.71) [Table 3].

DISCUSSION

Numerous treatments have been performed for patients with Asherman’s syndrome including hysteroscopic adhesion removal, adhesion prevention by intrauterine device, Foley’s catheter, uterine balloon stent or amnion graft, different adhesion-barriers, such as bioresorbable membrane of chemically modified hyaluronic acid and carboxymethyl cellulose, renovation of normal endometrium by hormonal treatment or stem cells, but the definitive effect of these methods has not been proven.

Table 2: Comparing Adhesions stages between two groups

IUA stage	PRP + hormone therapy	Hormone therapy	P
Before			
Stage I	4 (13.3)	4 (13.3)	0.75
Stage II	6 (20)	8 (26.7)	
Stage III	20 (66.7)	18 (60)	
After			
Stage I	22 (73.3)	16 (53.3)	0.22
Stage II	6 (20)	8 (26.7)	
Stage III	2 (6.7)	6 (20)	

Data are presented as numbers (%); PRP: Platelet-rich plasma; Stage I: Mild; Stage II: Moderate; Stage III: Severe. *Chi-square test was used

Table 3: Comparing Menstrual pattern between two groups

Menstrual pattern	PRP + hormone therapy	Hormone therapy	P*
Before			
Amenorrhea	4 (13.3)	2 (6.7)	0.35
Hypo menorrhoea	20 (66.7)	18 (60)	
Normal	6 (20)	10 (33.3)	
After			
Amenorrhea	0 (0)	0 (0)	0.71
Hypo menorrhoea	10 (33.3)	12 (40)	
Normal	20 (66.7)	18 (60)	

Data are presented as numbers (%); PRP: Platelet-rich plasma. *Chi-square test was used

Also, various therapeutic effects for PRP have been mentioned in research studies.^[18-20]

This study demonstrated that the combination of hormone therapy and intrauterine injection of PRP was not significantly more effective compared to hormone therapy alone after surgical removal of IUAs. The combination therapy had a similar effect on the improvement of intrauterine adhesion stage according to hysteroscopy outcomes. Also, a comparison of the menstruation pattern between the two groups demonstrated that the outcome in the patient treated with hormone therapy and PRP was similar to the group of hormone therapy alone. In this study, according to the other studies, there were no short-term or long-term side effects in the group that used PRP.

PRP rich therapeutic agent is helpful for cell proliferation and injury renovation. According to *in vitro* study, PRP significantly promotes proliferation rate and improves the expression of studied genes in endometrial cells. Also, the studies have recently worked on animal models and identified the potential in improving the regeneration of damaged endometrium.^[21]

In another study by Kim *et al.*,^[22] intrauterine infusion of human PRP in a Murine Model of Asherman's Syndrome was evaluated and demonstrated that treatment with human PRP was associated with improved endometrial morphology, reduced degree of fibrosis, and down-regulated expression of fibrosis-related factors.

Another study by Jang *et al.* that administered autologous PRP in a murine model of damaged endometrium demonstrated using PRP can improve endometrial regeneration^[17] that was in accordance with the results of the current study.

A case report by L. Aghajanova for management of Asherman syndrome demonstrated that treatment by PRP was well tolerated as it showed no short-term or long-term complications and seemingly improved endometrial function as demonstrated by successful conception and ongoing clinical pregnancies. It was the first case of intrauterine PRP infusion.^[23] This was also approved by the results of our study that the two infertile women became pregnant after receiving the PRP + hormone treatment that may be due to the improvement of endometrial function.

Another randomized clinical trial study entitled the effect of autologous platelet rich plasma on expanding endometrial thickness and improving pregnancy rate during frozen-thawed embryo transfer cycle on 83 women showed that both groups received HRT in the PRP group on the thirteenth day of the HRT cycle, 0.5–1 cc of PRP was injected into the uterine cavity, resulting in a significant increase in endometrial thickness in the PRP group. In this group, the rate of implantation and the rate of clinical pregnancy increased significantly.^[24]

In a non-randomized clinical trial on 30 patients with Asherman's Syndrome by Javaheri *et al.*^[25] revealed that there was no significant difference in the menstrual pattern of either the control or test groups before or after treatment, and the IUA stage in both studied groups before and after treatment was similar. The duration of menstrual bleeding in both studied groups before and after treatment was also similar. The results of this study confirm our study and indicate there is no significant difference between the two groups before and after treatment.

In other study by Amer *et al.*^[26] on 60 patients with severe intrauterine adhesions, the effect of intrauterine PRP injection following hysteroscopy was evaluated. In this study, 30 patients (cases) were injected with PRP and 30 patients with IU balloons. Unlike our study, in which there was no significant difference between the two groups, this study showed that platelet-rich plasma after surgical hysteroscopy had high efficiency and safety in increasing the menses duration, amount, and adhesion score in cases of severe intrauterine adhesions and decreasing postoperative adhesions.

Although the number of recovery in the hormone therapy with PRP group was higher than in the hormone therapy alone group and two patients with stage I Asherman syndrome undergoing hormone therapy with PRP were able to regain their fertility in the short term, and it can be considered as the strength of our study, but this study revealed that there was no significant improvement in using the hormone therapy with PRP than the hormone therapy alone, and there was no complication recorded from using PRP. There were some limitations in this study such as not matching the samples regarding the factors that

can potentially be effective including body mass index (BMI), number of births, and also measuring the levels of luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) before and after the intervention. Further clinical trials are required to confirm its efficacy. As in this study, the same dose and method were used in the administration of PRP and the long-term results of this method, including its effect on improving the fertility rate of patients, were not determined, so it is recommended to other studies to evaluate this issue and compare this treatment with other available treatments.

CONCLUSION

Our study showed that hormone therapy with PRP compared to hormone therapy alone after routine surgical treatment does not have a significant effect on the intrauterine adhesion, duration, and severity of menstruation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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