Amniotic Membrane Graft and Hysteroscopic Adhesiolysis as Treatment for Asherman Syndrome Case

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Abstract

Introduction: Secondary amenorrhea which caused by intrauterine adhesions is called Asherman's syndrome. This occurs when the uterine cavity becomes partially or completely blocked, which can damage the basal layer of the endometrium and cause the formation of adhesive cicatricial tissue. The prevalence or incidence of Asherman Syndrome ranges from 2.84-5.5% in women.

Case Report: A woman 33 years old had a history of amenorrhea for 2 years and three times curettage due to miscariage. Ultrasound findings showed 1.35 cm long cicatrix in the uterine cavity, and probe had only entered 3 cm. The patient underwent hysteroscopy adhesiolysis and grafting of intrauterine amniotic membrane. The intrauterine catheter was monitored for 1 month. Postoperatively the patient also received estradiol valerate therapy 3 x 2 mg for three months. Management of Asherman syndrome with hysteroscopy adhesiolysis with direct observation accompanied by grafting of amniotic membrane using intrauterine catheter tube is one of the techniques to overcome recurrent intrauterine adhesion.

Conclusion: Secondary amenorrhea in Asherman syndrome is better treated operatively with direct observation of the hysteroscopy and adhesiolysis. The using of amniotic membrane graft and supportive therapy are very helpful for the success of endometrial growth and preventing recurrent adhesions, increase the menstrual volume and chances of pregnancy.

Keyword: Amniotic Membrane Graft, Asherman Syndrome, Endometrial Reconstruction, Intrauterine Adhesion, Hysteroscopy.

Pencangkokan Selaput Ketuban dan Histeroskopi Adhesiolisis sebagai Penatalaksanaan untuk Kasus Sindrom Asherman

Abstrak

Pendahuluan: Amenorea sekunder yang disebabkan oleh perlengketan intrauterin disebut sindrom Asherman dengan prevalensi berkisar antara 2,84 - 5,5%.

Laporan Kasus: Seorang wanita berusia 33 tahun mempunyai riwayat amenore 2 tahun dan kuretase sebanyak 3 kali akibat abortus. Temuan USG menunjukkan cicatrix sepanjang 1,35 cm di rongga rahim, sondage hanya masuk 3cm. Pasien menjalani histeroskopi adhesiolisis dan pemasangan cangkok selaput ketuban intrauterin. Kateter intrauterin dipantau selama 1 bulan. Pascaoperasi pasien juga mendapat terapi estradiol valerat 3 x 2mg selama tiga bulan. Penatalaksanaan sindrom Asherman dengan histeroskopi adhesiolisis dengan observasi langsung disertai pemasangan cangkok selaput ketuban menggunakan selang kateter intrauterin merupakan salah satu teknik yang efekstif untuk mengatasi adhesiolisis intrauterin berulang.

Kesimpulan: Amenore sekunder pada sindrom Asherman lebih baik ditangani secara operatif dengan observasi langsung berupa histeroskopi dan adhesiolisis. Pemasangan cangkok selaput ketuban dan terapi suportif sangat membantu keberhasilan pertumbuhan endometrium dan mencegah perlengketan berulang, meningkatkan volume darah saat menstruasi dan peluang terjadinya pembuahan.

Kata kunci: Adhesi Intrauterin, Histeroskopi, Pencangkokan Selaput Ketuban, Rekonstruksi Endometrium, Sindrom Asherman.

Introduction

Secondary amenorrhea which is caused by intrauterine adhesions is called Asherman's syndrome. This occurs if the uterine cavity becomes partially or completely blocked, which can damage the basal layer of the endometrium and cause the appearance of adhesive cicatricial tissue. [1, 2] The prevalence or incidence of Asherman Syndrome ranges from 2.84-5.5% in women with abnormal menstruation and reproductive failure, and the potential causes of intrauterine adhesion (IUA) include curettage, especially in cases of pregnancy. [3,4] Clinical manifestations of intrauterine adhesions include hypomenorrhea, amenorrhea, infertility, recurrent spontaneous abortions, periodic abdominal pain, and placental adhesion.[1,2] Underlying causes vary widely but include operations on the uterine cavity (dilatation and curettage), endometrial resection, and uterine septal resection.[5] Adhesions to the uterine cavity can also be caused by scars from cesarean section, pelvic inflammatory disease, endometrial tuberculosis, and uterine artery embolism.[6,7] Treatment with hysteroscopic adhesiolysis and additional therapy such as hormonal, intrauterine device (IUD), use of intrauterine balloons has shown success rates in treating intrauterine adhesions.[4,8-10] However, no concrete evidence for improvement in clinical symptoms and pregnancy rates has been found in patients with moderate to severe intrauterine adhesions who have undergone therapy.[4,8-10] Amniotic membrane graft has been widely used for endometrial regeneration and preventing postoperative adhesions after hysteroscopic adhesiolysis since 2006. This approach has achieved therapeutic effects for increasing menstrual volume. However, the associated improvements in rates of adhesion recurrence and pregnancy remain unclear.[11]

In addition, estrogen is often used to promote endometrial proliferation and healing after surgery. [3,12] Amniotic membrane graft was found to be a promising treatment to inhibit infection, fibrosis, and adhesion reform. [3,11] In addition, a recent study reported a high success rate of hysteroscopic adhesiolysis in preventing spontaneous recurrence of IUA in patients with Asherman syndrome.[13] However, previous evidence shows that the recurrence rate of IUA after hysteroscopic adhesiolysis reaches 30 - 60%. [3,14] In this case report, we will present one case of a patient with secondary amenorrhea with Asherman's Syndrome who was treated with hysteroscopic adhesiolysis and endometrial reconstruction using an amniotic membrane graft.

Case report and management

A P1A3 woman with 1 living child aged 15 years, a 33-year-old patient came in to the gynecology clinic to treat complaints for she had not had menstruation for 2 years. The patient had been married for 1 year and 8 months and admitted that he had curettage 3 times for indications of miscarriage in 2015 at 11 weeks' gestation, in 2017 at 6 weeks' gestation, and in 2020 at 4 weeks' gestation. The patient experienced her last menstruation on August 10, 2020. Previously, the patient always had regular menstruation with cycles of 30 days, for 3-7 days, and changed pads 3 times a day. The patient admitted that he often experienced vaginal discharge that was itchy and smelly. The patient is in a high-risk group where the patient is a barmaid who works 12 hours a day, and consumes 4-8 glasses of alcohol and at least 1 pack of cigarettes per day, the patient said she never knew about her pregnancy until the patient had a miscarriage. The patient denied having a palpable lump in her stomach. After experiencing the condition of not menstruating for 3 months, the patient went to the obstetrician and only received oral hormonal therapy, namely estradiol valerate, and norethisterone, but the patient had not menstruated yet, then the patient

continued to seek treatment at an obstetrician consultant urology and was diagnosed with Asherman Syndrome. The patient then underwent curettage and insertion of an intrauterine catheter balloon and hormonal therapy with estradiol valerate at a dose of 3x2 mg for 1 week. The patient felt there had been no change and continued treatment with two other obstetricians and only received similar hormonal medication. The patient then went to Hasan Sadikin Hospital in Bandung and an ultrasound examination was carried out and obtained a homogeneous density anteflexion uterus, size 7.76 x 3.21 x 5.09 cm. Endometrial line: 4.8 mm. The impression is that there is a scar measuring 1.35 cm in the middle of the endometrial line, at a distance of 3 cm from the cervix. Right ovary measuring 2.87 x 1.94 x 2.68 cm and left ovary measuring 3.15 x 1.17 x 2.55 cm. Impression: Asherman Syndrome. From the inspection, it was also found that the depth of the probe was 4 cm. The patient then decided to undergo hysteroscopic adhesiolysis surgery and endometrial reconstruction using an amniotic membrane graft. Next, preparation of the amniotic membrane graft is carried out by the donor of an elective caesarean section patient who has given informed consent first. Informed consent is also given to the recipient. The requirements for being a donor are having clear amniotic fluid, no infection, and being willing to have a blood test for hepatitis B, hepatitis C, HIV, and preoperative syphilis. The amniotic membrane was separated from the placenta with a blunt under aseptic conditions, and washed repeatedly until free of blood and soaked in cefuroxime. Amnion should be used within 2-4 hours. The patient is first given premedication with vaginal misoprostol before surgery. During the operation, the patient is under general anesthesia, and placed in a lithotomy position, and disinfection is carried out. As well as installing the upper and lower speculum. The patient was then subjected to a sondation examination and found a depth of 4 cm, cervical dilatation was carried out with a Hegar cervical dilator to measure the depth, size, and direction of the uterine cavity, and the uterine ostium was widened mechanically in stages with a Hegar plug to size no. 7 cm. Followed by a hysteroscopy, the camera is inserted and the characteristics of the adhesions, location, extension, morphological characteristics of the adhesions, and the uterine cavity are examined in detail. Adhesiolysis is carried out using scissors and graspers to improve the shape and size of the uterine cavity. On exploration, an indentation appeared in the uterine fundus. The ostium of the right and left fallopian tubes were within normal limits. The hysteroscopy camera was removed. Curettage was carried out using manual vacuum aspiration systematically and carefully until the uterine cavity was clean with cannula no. 5, + 2 grams of endometrial tissue was removed and the tissue was sent to anatomical pathology. No active bleeding was found. The procedure was continued by the urogynecology division. An 18 silicone catheter coated with amniotic membrane (amniotic membrane graft) was inserted into the uterine cavity. The intrauterine catheter balloon was inflated to 10 cc. The patient was hospitalized for 2 days to monitor bleeding and fluid coming out of the uterine cavity. The antibiotic therapy was given doxycycline 2x100 mg and estradiol valerate 3x2 mg for 2 weeks, and the painkiller supplement ketoprofen 2x100 mg during treatment. Monitoring on the second day of treatment was obtained from an ultrasound of the intrauterine catheter tube inserted into the fundus, with vascularization (+), and the discharge was only serous. Patient was advised to control in 1 week, 2 weeks and 1 month later. The condition of the patient during 1 week was good, with the same ultrasound results, the discharge was still serous, and the second week there was no discharge. The patient brought the results of anatomic pathology with chronic, non-specific endometritis accompanied by fibrotic results. Therapy with estradiol valerate 3x2 mg was continued for up

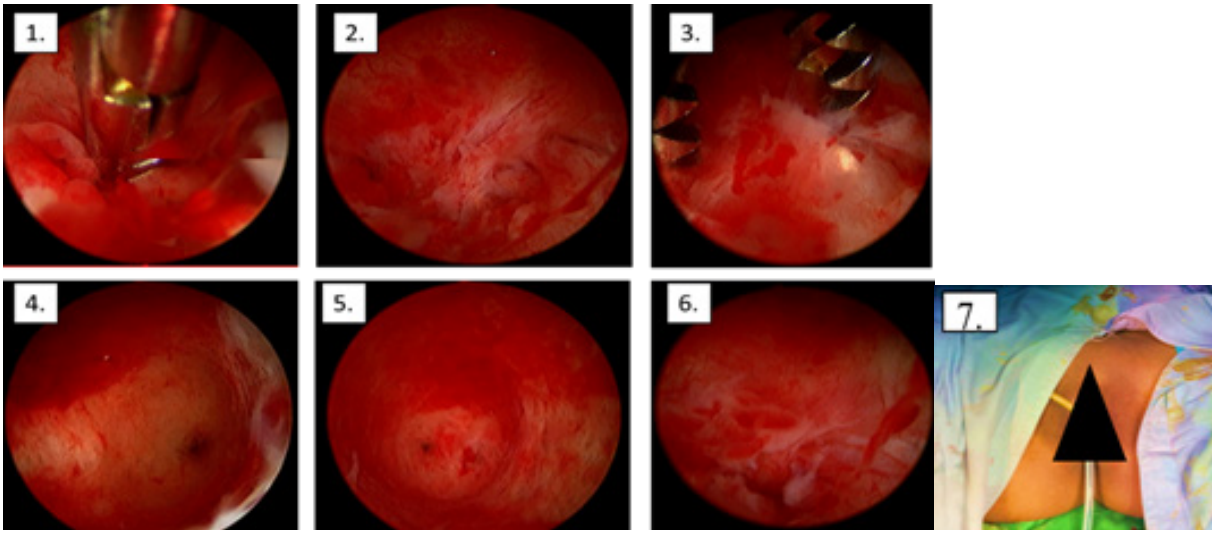

Figure 1 Hysteroscopy Adhesiolysis and Endometrial Reconstruction with Amniotic Graft Membrane (sequential pictures from number 1 to 7)

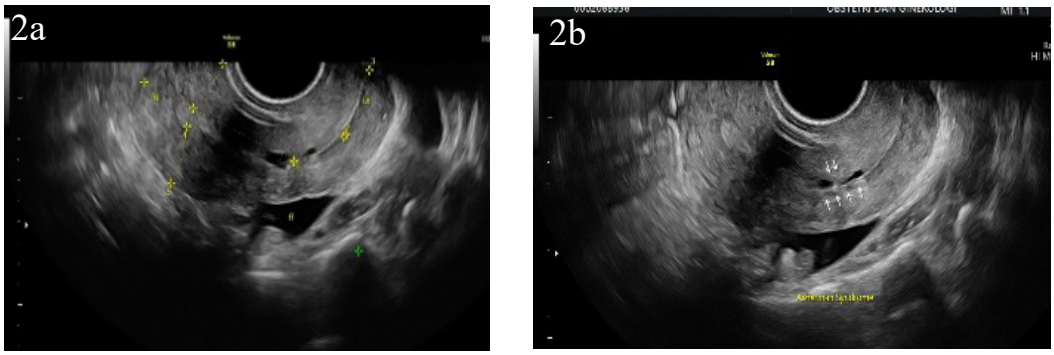

Figure 2a. and 2b. Ultrasound Asherman Syndrome preoperatively, visible intracavum uterine cicatricial length of 1.35 mm, 3 cm from the cervix

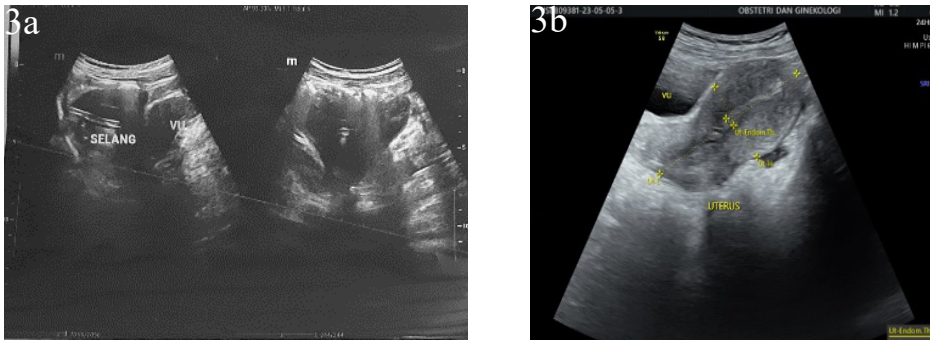

Figure 3a. Ultrasound 2 weeks after adhesiolysis hysteroscopy and endometrial reconstruction with amniotic membrane graft, visible intrauterine catheter balloon (+), visible vascularization. Figure 3b. Ultrasound 1 month after hysteroscopy adhesiolysis and endometrial reconstruction with amniotic membrane graft, the intrauterine catheter has been removed, the endometrial line has grown to a thickness of 4.66 mm and the scars are no longer there.

to 1 month postoperatively. During control 1 month after hysteroscopy, adhesiolysis and reconstruction of the amniotic membrane graft. The intrauterine tube was removed, and an ultrasound was performed depicted a uterus measuring 7.91 x 3.63 x 5.09 cm with an endometrial line of 4.66 cm, with no scars visible anymore. The patient received further therapy with estradiol valerate 3x2 mg for 1 month.

Discussion

Intrauterine adhesions (IUA) in Asherman Syndrome is a condition caused by various factors, such as trauma and infection which contribute greatly to fibrosis and scar tissue formation in the endometrium due to damage of the basal layer of the endometrium.[1,3,17,18] The clinical symptoms of IUA are hypomenorrhoea, amenorrhea, periodic hypogastralgia, infertility and obstetric complications which are very dangerous for women's reproductive health. [17,18]
Classification of IUA: https://doi.org/10.1080/13645706.2021.1893190

- Severe: >3/4 of the uterine cavity involved, agglutination of walls or thick bands, tubal ostium areas, and upper cavity occluded
- Moderate: 1/4-3/4 of the uterine cavity involved, no agglutination of walls-adhesions only, tubal ostium areas and upper fundus only partially occluded
- Mild: <1/4 of the uterine cavity involved, thin or filmy adhesions, tubal ostium areas, and upper fundus minimally involved or clear.

The hysteroscopic technique of adhesiolysis, also known as transcervical resection of adhesions (TCRA), is the first choice for patients diagnosed with moderate to severe intrauterine adhesions. However, how to reduce the recurrence of IUA is still a difficult problem for obstetricians. A study has shown that the incidence of IUA recurrence after TCRA is 3.1% − 23.5%, moreover, the regeneration rate of severe IUA has been reported as high as 62.5% of these cases.[17] With the improvement of comprehensive management including IUD, Foley catheter, estrogen therapy or adhesion barrier after TCRA, the recurrence of IUA has decreased to some extent, but the results remain unsatisfactory, especially for moderate to severe IUA. Currently, in the field of Gynecology, only a few studies have shown that amniotic membrane grafts can be helpful for cervical construction and vaginal reconstruction. [15] In recent years, several medical institutions have reported using amniotic membrane grafts to treat IUA. Amer (2006) used an amniotic membrane graft to prevent the recurrence of IUA after surgery in 25 women with moderate to severe IUA. These women were examined via hysteroscopy in the fourth month after surgery. Findings showed that no attachments occurred in 12 women with moderate IUA and 1 woman with severe IUA. The remaining 12 women with severe IUA showed recurrence. Although the recurrence was mild in 10 of 12 women (83.33%) and moderate in only 2 of 12 women (16.67%). These results suggest that more clinical trials are needed to confirm the effectiveness of the amnion. [11] In 2010, Amer conducted a homologous clinical study to determine the efficacy of fresh and dry amniotic membrane grafts after hysteroscopic adhesiolysis in severe IUA to reduce IUA recurrence and promote endometrial regeneration. The results showed that both methods were effective due to a decrease in the recurrence of IUA, but fresh amniotic membrane grafts performed better than dry-grafted amniotic membranes. Chang Li (2019) they used a fresh amniotic membrane graft after TCRA combined with a balloon catheter to prevent the formation of new adhesions and estrogen treatment to

stimulate endometrial growth to treat and prevent IUA. Only 8 of 52 (15.4%) showed recurrence 1 month after surgery. Among women who relapsed, there was one case of mild adhesion adhesions which was treated by blunt separation under hysteroscopy and followed for 3 months after surgery; 7 women had moderate adhesions that were treated with a second TCRA and a fresh amniotic membrane graft. Only 2 of these 8 women showed recurrence under hysteroscopy in the third month after surgery.[17] The results of that study demonstrated that the recurrence rate among women treated for moderate to severe IUA using fresh amniotic membrane grafts was much lower than reported by the literature. The reasons may be as follows: (1) The portion of the amniotic epithelium that should be on the outside covers the balloon catheter when a fresh amniotic graft is placed, whereas the literature reports that the amniotic epithelium on the inside covers the balloon catheter, and this is probably the most important aspect. (2) This study used continuous estrogen treatment in the first month after surgery, whereas the literature reverts to the use of artificial cycle therapy. Existing studies have reported that the first month after surgery is the peak time for adhesion recurrence; therefore, continuous estrogen treatment can increase the cure rate of IUA more and be more effective than artificial cycle therapy. (3) IUA formation starts with very few adhesions, but looks similar as scar healing progresses, adhesions become fibrotic and cannot be recovered. [16]
In this patient, treatment was also chosen with hysteroscopic adhesiolysis and endometrial reconstruction using a fresh amniotic membrane graft on a balloon catheter placed intrauterinely, as well as the choice of continuous estrogen hormonal support for 3 months at a dose of 3x2 mg.
The selection of a fresh amniotic membrane graft is of course based on existing research. Boning Li (2019), said that human amniotic epithelial cells (hAeC) have the characteristics of stem cells or stem cells. However, it is unclear whether hAEC has therapeutic potential to restore fertility after IUA. IUA uterine cavity shows adhesions and even atresia, accompanied by a thinner endometrium, fewer glands, increased areas of fibrosis, and fewer microvessels. However, hAEC significantly improved uterine structure after IUA. After hAEC treatment, the endometrium is thicker, the number of endometrial glands increases, fibrosis decreases, and more microvessels are generated. VEGF, PCNA, and ER expression levels increased in hAEC-treated endometrium, indicating increased angiogenesis and stromal cell proliferation.[18]
In Chiang Li's study (2019) using an amniotic membrane graft in hysteroscopy adhesiolysis, From the evaluation of the growth of the endometrial line it was found that the average growth was 7.08 mm in the first month, and repeated adhesions in the first month were only 15.4% and in the third month 3, 8% compared to giving chitosan injections only got an endometrial line that grew 6.5 mm in the first month, and repeated adhesions 47.9% in the first month and 37.5% in the third month. Thus in conclusion to TCRA, the use of amniotic membrane grafts is safer and more effective than intrauterine chitosan injections for recurrence of IUA, and may make a major contribution to preventing further regeneration of adhesions.[17]
The beneficial mechanisms of using the amnion in preventing IUA are as follows: (1) Acting as a biological barrier and promoting epithelial hyperplasia: the amnion attaches to the uterine wall to provide an ideal basement membrane for the proliferation, differentiation and regeneration of new epithelium. (2) Amnion inhibits the inflammatory response. The amnion is attached to the surface of the wound and can reduce the dead space between the wound and the amnion, thereby inhibiting the growth and spread of bacteria.

The amnion contains various protease inhibitors, and amniotic stroma can eliminate inflammation by promoting rapid apoptosis of inflammatory cells. (3) Amnion has anti-fibrosis effect. Studies have shown in women with IUA that the stroma is mostly replaced with fibrous tissue without blood vessels and glands invariably replaced by inactive cuboidal endometrial epithelium unresponsive to hormonal stimulation. In addition, transforming growth factor-ß1 (Transforming Growth Factor ß1/TGF-ß1) is highly expressed in the endometrium of the adhesion surface and is positively correlated with the level of adhesion. The amniotic stroma has a regulative effect on the levels of cytokines expressed by desmocytes; which can inhibit TGF-ß1 mRNA expression and reduce desmocyte differentiation and proliferation, thereby inhibiting the formation of fibrous scar tissue. (4) Contains stem cell-like cells: Numerous studies have shown that endometrial stem cells, which are present in the basal layer of the endometrium, play a key role in the regeneration of the functional layer in each menstrual cycle, and damage to the basal layer is the main reason for the formation of intrauterine adhesions. Amnion stem cells Humans have as many as 400 million mesenchymal stem cells, which have excellent differentiation potential. After hysteroscopy, the fresh amnion, which is rich in stem cells, is transplanted into the uterine cavity to regenerate the endometrium.[17]

A meta-analysis study on the use of amniotic membrane grafts after hysteroscopy adhesiolysis by Zheng Fei (2018), which evaluated the ability of the amniotic membranes to prevent recurrence of IUA, found that amniotic membrane grafts increased menstrual blood volume, but did not prove its prevention against recurrent IUA, nor did it increase its effect on pregnancy and the incidence of spontaneous abortion after surgery.[1]

Conclusion

Secondary amenorrhea in Asherman's syndrome which is treated through surgery with direct observation from a hysteroscopic camera and adhesiolysis as well as the installation of an amniotic membrane graft helps the success of endometrial growth and prevents recurrent adhesions, increasing menstrual blood volume and the fertility. Another important thing is post-operative monitoring and supportive therapy in the form of the hormone estradiol valerate in sufficient doses and long term to help the continuity of endometrial proliferation.

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