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(CASE REPORT)

IVF pregnancy in a case of Asherman's syndrome

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Abstract

Asherman's syndrome (AS), an increasingly diagnosed cause of infertility owing to improvement in diagnostic modalities, poses a challenge in achieving pregnancy. Intrauterine adhesions due to breach in the basalis layer of the endometrium interfere with implantation or obstruct tubal ostia. AS occurs subsequent to curettage performed for pregnancy related conditions more commonly than gynaecological conditions. Patients may present with infertility with or without menstrual complaints. Here we present a case of 29-year-old woman, P0L0A1 who presented to our clinic with secondary infertility for one year. The patient had undergone hystero-laparoscopic myomectomy with uterine artery ligation in view of multiple fibroids. A relook hysteroscopy on follow-up revealed a normal uterine cavity with synechiae formation at right cornua for which synechiolysis was done. Upon failure to conceive for the next six months, another hysteroscopy was performed which showed that the cavity was small with pale endometrium and right ostia could not be visualized. Subsequently a hysteroscopic reconstruction of the uterine cavity was done with bilateral lateral wall and fundal metroplasty followed by estrogen and progesterone therapy to avoid post-operative adhesion formation. The couple underwent an IVF cycle in the following month. Controlled ovarian stimulation was done and ovum pick up was performed on day 12 with intra-uterine PRP instillation. A fresh transfer was performed on day 5 after pick up. Luteal phase support was given with vaginal and subcutaneous progesterone support. A UPT 14 days later was positive and the patient is under follow-up for her antenatal care at present.

Keywords: Asherman's syndrome; Endometrial PRP; IVF in Asherman's syndrome; Uterine Factor Infertility; ART (Assisted Reproductive Techniques)

1. Introduction

Asherman's syndrome (AS), an increasingly diagnosed cause of infertility owing to improved diagnostic modalities, poses a challenge in achieving pregnancy. It involves intrauterine adhesions that interfere with various mechanisms of achieving pregnancy, mainly implantation.

The most common presenting complaints include decreased menstrual blood flow or secondary amenorrhea not responding to withdrawal therapy with progesterone, subfertility or infertility and recurrent pregnancy loss (RPL). These complaints, especially in the background of previous uterine instrumentation, should raise suspicion of AS.

The incidence is difficult to determine as these are assessed in a prospective fashion. However, adhesion formation tends to occur more commonly in a pregnant and postpartum uterus than non-pregnant uterus [1]. An incidence of 15% was reported by Gilman et. al. in those undergoing suction-evacuation (S&E) and curettage and spontaneous abortions [2]. The adhesion formation is seen less when instrumentation is done for a gynaecological causes like septum and fibroids which are managed with hysteroscopic resection or for polyps in which dilatation and curettage (D&C) may be done. Conversely, when enquired, majority of patients reported instrumentation in previous pregnancies, either for first trimester abortions or postpartum due to retained placenta [3].

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1.1. Risk factors

- Previous instrumentation in
  - Medically terminated pregnancy (MTP)
  - S&E, dilatation and evacuation (D&E) for spontaneous abortions
  - Retained products of conceptus (RPOC)
  - Retained placenta
- Hysteroscopic resection for
  - Fibroids
  - Polyps
  - Septum
- History of endometritis secondary to
  - Tuberculosis
  - Pelvic inflammatory disease

1.2. Pathogenesis

The endometrium is composed of a basalis and a functionalis layer. During a normal menstrual cycle, only the functionalis layer is shed off and the basalis layer regenerates in the next cycle. If there is any breach in the basalis layer of the endometrium, there will occur fibrosis. Hence, AS occurs subsequent to curettage performed for spontaneous abortions, MTPs, RPOCs and retained placenta. Similarly, the basalis layer also gets breached during myomectomy or polypectomy. However, just damage to the basalis is solely not responsible in these cases. In postpartum women, there is a low level of estrogen owing to withdrawal of placental estrogen and hyperprolactinemia leading to suppression of further production. Therefore, it may occur more commonly in postpartum women than those with early trimester interventions. Similarly, secondary to GnRH agonist administration prior to myomectomy can leads to low estrogen. In this hypoestrogenic environment, the basalis layer is unable to regenerate itself secondary to the trauma. This fibrosis further leads to formation of tissue bridges and obliteration of the endometrial cavity [4,5].

1.3. Clinical features

- Most present with menstrual complaints ranging from hypomenorrhea to secondary amenorrhea. Previous history in such may reveal underlying cause, such as previous uterine surgery or curettage, infections or hysteroscopic procedures. Secondary amenorrhea is more common than hypomenorrhea. It should be suspected in patients with no withdrawal bleeding with progesterone alone [3].
- Patients may also present with infertility with or without menstrual complaints. The fibrotic tissue and adhesions may obstruct tubal ostia or may decrease the endometrial surface favorable for implantation [3].
- Very rarely, due to outflow obstruction by adhesions, the patients may present with cyclical dysmenorrhea. Ultrasound in these patients may reveal a hematometra [6].
- Asymptomatic.

2. Case report

A 29-year-old woman, P0L0A1 with her 30-year-old male partner presented to our clinic with secondary infertility for one year. Upon history taking, the woman had regular, normal flow menstrual cycles and no history of any medical illnesses expect bronchial asthma. The patient has a spontaneous abortion two years prior for which no curettage was performed. Her husband had no addictions and no medical illnesses.

The couple had visited another hospital prior to visiting our clinic where the diagnosis of multiple fibroids was made on ultrasound. There were seven fibroids, one of which was submucosal (16mm), three were intramural (9mm fundal, 14mm on posterior wall and 17mm on anterior wall) and three were subserosal (25, 20 and 20mm). Following this, the patient underwent hystero-laparoscopic myomectomy with uterine artery ligation in June 2023.

In view of subfertility, a relook hysteroscopy was done in October 2023. Hysteroscopy revealed a normal uterine cavity with some synechiae formation at right cornua for which synechiolysis was done. Saline salpingography was done and bilateral tubal patency was confirmed.

The couple visited another hospital when they failed to conceive for 6 months in March 2024. Another hysteroscopy was performed. Findings were as follows – cavity was small with pale endometrium; right ostia could not be visualized. The couple was counseled about poor prognosis and possible chances of need of surrogacy.

In April 2024, the patient visited our clinic. In view of the hysteroscopic findings, a hysteroscopic reconstruction of the uterine cavity was done with bilateral lateral wall and fundal metroplasty. After the procedure, the patient was put on estrogen followed by progesterone to avoid post-operative adhesion formation.

Following this, the couple was planned for IVF cycle in the next month. Controlled ovarian stimulation was done and ovum pick up was performed on day 12 with intra-uterine PRP instillation. In the same cycle, a fresh transfer was performed on day 5 after pick up. The patient was put on luteal phase support with vaginal and injectable progesterone support. The patient had a positive UPT 14 days later and is at present under follow-up for her antenatal care.

3. Discussion

Asherman's syndrome is classified into mild, moderate and severe on the basis of the extent of adhesions as follows [7]:

- When less than 1/4th of the uterine cavity is obliterated with adhesions with minimal involvement of the ostia and fundus, it is classified as Mild.
- Moderate AS is when 1/4th to 3/4th of the cavity is obliterated with involvement of the ostia and fundus.
- Severe AS has more than 3/4th of the cavity obliterated with adhesions, with occlusion of ostia and fundus. The walls may be agglutinated or have thick bands.

In a case control study conducted by Fouks et.al., it was found that endometrial thickness was less than controls and the time to achieve pregnancy was longer in women with AS. It was also concluded that live birth rates were seen in those patients with AS who developed thicker endometrium [8].

3.1. Treatment strategies

Treatment for AS is done in the setting of menstrual complaints and subfertility.

3.1.1. Hysteroscopic adhesiolysis under ultrasound guidance

This procedure is performed with the aim of restoring the cavity to its normal shape, and to establish normal relationship between the endometrial cavity with tubal ostia and cervical os. It is done using either scissors or electrosurgery. Ultrasound guidance may be used to avoid uterine perforation.

Electrosurgery is less preferred as there may occur thermal damage to the surrounding viable endometrium and in the rare event of uterine perforation, to the surrounding tissue [9].

For minimal to moderate AS, office hysteroscopy with adhesiolysis can also be performed. Removing scar tissue does not cause any pain unless it has reached the myometrium. Therefore, in these procedures, patient's response can be used as a clue of entering the wrong plane [10].

Post-operatively, hormonal therapy with estrogen to cause endometrial proliferation, followed by progesterone to cause withdrawal bleeding is given to prevent adhesion formation.

Some also recommend the use of anti-adhesive gels. A lower post-operative recurrence of adhesions has been reported at follow-up after hysteroscopic adhesiolysis, however, no increase in live birth rates was observed [11].

A second-look hysteroscopy may be performed during follow-up to look for new adhesions and lyse them.

In our patient under study, hysteroscopy and relook hysteroscopy with uterine reconstruction was performed followed by estrogen and progesterone therapy. Only after this the patient was taken up for IVF cycle.

3.1.2. Platelet-rich plasma therapy

Tissue regeneration can be induced using PRP therapy due to multiple growth factors found in platelet granularities. This can be done as sub-endometrial PRP during hysteroscopy or a simple intrauterine PRP procedure from the 10^{th} day of the FET cycle and may be performed two or three times prior to FET until the thickness reaches 7mm. The instillation needs to be done within 1 hour of PRP preparation.

PRP administration has shown to improve the endometrial morphology. Kim et.al. in 2020 also demonstrated higher implantation and live birth rates in their study. The effect on endometrial thickness in their study was however not

significant. In this study, 0.7-1mL of PRP was put into the uterine cavity with the platelet concentration 717 x 10^3 to 1561 x 10^3/μL [12].

Other studies prior to this study were also done and demonstrated a positive effect of PRP on the endometrium in terms of thickness and pregnancy rates, however, there was limited information on the concentration used [13,14].

The patient in our case was given PRP therapy on the day of ovum pick-up and our experience with PRP instillation in our clinic patients has been positive.

3.1.3. Stem cell therapy

Stem cells more commonly used for endometrial regeneration are derived from bone marrow, however, can also be taken from umbilical cord, amnion and menstrual blood. Animal studies show promising results. Some studies in humans have also been performed which show increase in endometrial thickness and a decrease in the intrauterine adhesion formation [15,16].

- To increase endometrial receptivity, a variety of agents have been used like vitamin E, sildenafil and pentoxifylline. Here in our patient, we have administered vitamin E and vaginal sildenafil during the FET cycle.
- Bioengineering techniques [16]:
  These involves methods that integrate engineering and life science to develop biological substitutes for restoring natural functions of tissues.
  These include decellularized scaffolds, hydrogels, and microfluidics.

3.2. Prognosis after treatment

Treatment of AS is important in those women wanting conception since without adhesiolysis, the conception rates near 50%, however, 40% end in miscarriages [5].

A large retrospective study done by Chen L et.al. has reported an average time to conception of 9 months after adhesiolysis with 48% conception rates and birth rates over 80% [17].

However, these pregnancies still are at increased risk of complications. These include spontaneous abortions, preterm delivery, abnormal placentation, placenta accreta spectrum, still birth and post-partum hemorrhage.

4. Conclusion

Asherman's syndrome poses a challenge in achieving pregnancy mainly by affecting the endometrium and thus implantation. The major strategy still remains preventive measures to avoid adhesion formation. Once AS develops, these patients may require hysteroscopic reconstruction of the uterus. Hormonal therapy for endometrial regeneration and endometrial PRP show positive results in these patients. Luteal phase support is required with these patients. Stem-cell therapy needs further studies.

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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