

Septate Uterus with Low Ovarian Reserve in Primigravida, can Adjuvant Treatment and Uterine Surgery Improve Outcome, Case Report

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Abstract

Despite persistent efforts to address fertility issues associated with diminished ovarian reserve, challenges persist. This case report highlights the management of a 32-year-old nulligravida woman with infertility due to a septate uterus and low ovarian reserve. The patient underwent laparoscopy and hysteroscopy for diagnostic and therapeutic purposes, along with intraovarian-uterine cavity platelet-rich plasma (PRP) injection. Remarkably, she achieved pregnancy within two months post-intervention.

We discuss the challenges faced in treating such complex cases and explore the efficacy of surgical correction and PRP therapy.

Our findings support personalized decision-making, emphasizing the need for comprehensive evaluation and tailored interventions. Despite the positive outcome in this case, further research is needed to strengthen evidence-based practices in managing similar scenarios.

Keywords: Septated Uterus; Low Ovarian Reserve; Laparoscopy; Intraovarian Platelet-Rich Plasma; Hysteroscopy

Introduction

In the 1800s, Cruveilhier and Von Rokitansky [1] first described uterine anomalies, which are known as Müllerian anomalies. These anomalies refer to deviations from normal anatomy resulting from maldevelopment of the Müllerian or paramesonephric ducts during embryonic development. Müllerian anomalies are relatively common and benign, with a prevalence ranging from 4% to 7% [2]. One specific anomaly is the uterine septum, which is believed to occur due to the failure of tissue resorption connecting the two paramesonephric ducts before the 20th week of embryonic development. While the arcuate uterus represents a milder form of this resorption failure, it is not typically considered clinically significant like the septum. Pinpointing the exact prevalence of uterine septum is challenging, as many cases are asymptomatic. However, estimates suggest it ranges from 1 to 2 per 1,000 to as high as 15 per 1,000 cases [3].

Septate Uterus Definitions: The latest ESHRE/ESGE classification system for female genital anomalies categorizes the septate uterus as Class U2, encompassing cases where the midline septum forms normally but fails to absorb properly. A septate uterus is characterized by a normal overall shape with an internal indentation at the midline of the fundus, exceeding 50% of the uterine wall thickness. This indentation, known as a septum, can partially or completely divide the uterine cavity, and in some instances, may extend into the cervix and/or vagina. Class U2 is further subdivided into two sub-classes based on the extent of deformity in the uterine corpus:

- Class U2a or partial septate uterus characterized by the existence of a septum dividing partly the uterine cavity above the level of the internal cervical Os.
- Class U2b or complete septate uterus characterized by the existence of a septum fully dividing the uterine cavity up to the level of the internal cervical Os. Patients with complete septate uterus (Class U2b) could have or not cervical (e.g. Bicervical septate uterus) and/or vaginal defects [4].

The Müllerian Anomalies Classification 2021 (MAC2021) by the American Society for Reproductive Medicine (ASRM) defines a septate uterus as one exhibiting an internal indentation depth greater than 10 mm, coupled with an internal indentation angle less than 90° [5].

Away from Mullerian anomalies, till now poor prognosis patients challenge reproductive clinicians every day. A recent classification of poor ovarian reserve patients in ART has been put forward by the POSEIDON (Patient Oriented Strategies Encompassing Individualized Oocyte Number) group [6].

In this classification, four subgroups have been suggested according to qualitative and quantitative parameters, like the Bologna criteria, namely:

- Age and the expected aneuploidy rate
- Ovarian biomarkers (AFC and AMH), and
- Ovarian response to COS in a previous ART/IVF cycle.

The four POSEIDON classification groups are:

1. POSEIDON group 1: Patients younger than 35 years old, with normal markers of ovarian reserve (AMH > 1.2 ng/mL, AFC > 5), and with an unexpected poor ovarian response (POR).
2. POSEIDON group 2: Patients older than 35 years old, with normal markers of ovarian reserve: AMH>1.2 ng/mL, AFC > 5, and with an unexpected poor ovarian response (POR).
3. POSEIDON group 3: Patients younger than 35 years old, with poor ovarian reserve: AMH < 1.2 ng/mL, AFC < 5,
4. POSEIDON group 4: Patients older than 35 years old, with poor ovarian reserve: AMH < 1.2 ng/mL, AFC < 5.

Case Presentation

A 32-year-old woman, who was nulligravida, accompanied by her 56-year-old husband, sought assistance for infertility at the British Syrian Center for Art and Fetal Medicine. The couple had been married for 1.5 years, and the husband had four children from a previous marriage. The woman underwent a comprehensive physical examination, which revealed normal findings, including a normal BMI and no abnormalities noted during the external genital exam (Valva-vagina). Her medical history showed no significant health issues, and she reported regular menstrual cycles since puberty, experiencing only mild dysmenorrhea.

In response to the infertility concern, the initial standard assessment protocol was implemented. A transvaginal ultrasound was conducted to evaluate the antral follicular count, indicating a total count of 6. Laboratory investigations yielded a thyroid-stimulating hormone (TSH) level of 2.7 iu/ml, a prolactin level of 8 ng/ml, an antimullerian hormone (AMH) level of 0.5, and a follicle-stimulating hormone (FSH) level of 17 mIU/mL. Both the AMH and FSH levels indicated poor ovarian response.

The husband's semen analysis yielded normal parameters (volume: 2.5 ml, count 30 million per ml, progressive motility: 39%, normal forms: 4%) and his medical history showed no notable issues. A hysterosalpingography (HSG) was performed, revealing a complete septum with a single cervix and normal patent tubes.

Following these findings, the decision was made to proceed with laparoscopy and hysteroscopy as a diagnostic and therapeutic tool if any surgically treatable anomaly was identified. Prior to the procedure, the patient provided informed consent, ensuring a comprehensive understanding of all potential benefits and risks associated with the intervention.

Furthermore, the patient was presented with the option of intraovarian-uterine cavity platelet-rich plasma (PRP) injection, aimed at revitalizing of her ovaries. After thoughtful deliberation of the alternatives, the patient elected to undergo this procedure.

During the laparoscopy, a meticulous examination unveiled a uterus of normal shape with a smooth contour and healthy tubes exhibiting satisfactory patency. The PRP injection was administered utilizing the [Doctors kits, USA] under a direct vision and with help of intravenous cannulation needle 1.5 ml of PRP was injected in both ovaries, while the (PRP) was prepared from fresh whole blood, which is collected from a peripheral vein, stored in acid citrate dextrose solution A (ACD-A) anticoagulant, and processed to increase platelets by separating various components of blood, hence the injected fluid prepared from autologous blood by centrifugation using Dr. PRP kits and equipment (USA). Concurrently, operative hysteroscopy was performed, revealing a complete septum with a fibrous consistency. The septum was successfully excised entirely using scissors within the same operative session, after ensuring good hemostasis a flush 5ml of PRP injected within the endometrium.

A strategy of expectant management was adopted for a duration of three months, with a focus on monitoring changes in the endometrium throughout the menstrual cycle. Our objective was to facilitate a natural conception. Following two months of this approach, the patient presented with amenorrhea upon return, and subsequent investigations confirmed pregnancy, indicating the effectiveness of the intervention.

Presently, the patient is in the early second trimester of an ongoing pregnancy with a healthy single fetus. Given her elevated risk of miscarriage and potential placental anomalies, we are providing thorough surveillance and close monitoring to ensure the best possible outcome.

Discussion

In this particular case, the patient faced two primary factors contributing to infertility. Firstly, she exhibited low AMH levels, mildly elevated FSH, and a reduced antral follicle count. Secondly, she had a complete uterine septum, adding complexity to the situation. Complicating matters further, the couple opted against assisted reproductive techniques (ART) or *in vitro* fertilization (IVF), and egg donation is not an option due to religious beliefs and local authority regulations.

Given these constraints, the plan involved rectifying the uterine abnormality to restore its shape and cavity as much as possible, alongside an attempt to rejuvenate ovarian function through PRP (platelet-rich plasma) injection.

Recent evidence has established that women with a septate uterus are at higher risk for subfertility, pregnancy loss, and preterm birth. To address this issue, Rikken, *et al.* conducted a study to determine whether septum resection improves reproductive outcomes in these women. In this randomized controlled trial, 80 women with a septate uterus and a history of subfertility, pregnancy loss, or preterm birth were randomly assigned to either undergo septum resection or receive expectant management. The primary outcome assessed was the occurrence of conception leading to live birth within 12 months after randomization. Surprisingly, the results showed that live births occurred in 31% (12 out of 39) of women who underwent septum resection and 35% (14 out of 40) of women under expectant management. These findings challenge the initial assumptions, suggesting that hysteroscopic septum resection does not improve live birth rates or other reproductive outcomes in women with a septate uterus. Consequently, the authors caution against routine septum resection in clinical practice [7].

In their critical analysis offering constructive feedback on the previously mentioned study, Adebayo A. Adewole, *et al.* raise several concerns. They argue that the study's sample size compromises the reliability of its findings. Furthermore, they question the inclusion of subfertile women regardless of underlying co-factors and express reservations about the adequacy of the 12-month follow-up period.

Adewole, *et al.* advocate for individualized management of each case through open dialogue with the patient, ensuring a thorough understanding of the potential benefits and drawbacks of intervention, as well as the limited availability of high-quality data to guide decision-making [8].

In another prospective study conducted by Li-Hong Pang, *et al.* the authors found that hysteroscopic septoplasty significantly improved pregnancy outcomes in women with a history of recurrent pregnancy loss. However, they observed no significant impact on reproductive outcomes in women with no history of adverse pregnancy outcomes [9].

In a separate retrospective cohort study and systematic literature review examining reproductive outcomes post-hysteroscopic septoplasty, the results suggest the procedure's safety and efficacy. The subsequent pregnancy rate was reported at 69%, with a live birth rate (LBR) of 49% [10].

Intraovarian platelet-rich plasma (PRP) therapy represents an innovative approach aimed at rejuvenating and restoring ovarian fertility, particularly beneficial for women with poor ovarian reserve or premature ovarian failure, especially when oocyte donation is not feasible as prohibited according to local authority. Several recent studies have explored the impact of PRP injections on ovarian reserve and stimulation.

In a retrospective observational study involving 469 women with a history of infertility, hormonal abnormalities, menstrual irregularities, and premature ovarian failure, hormonal levels were tracked for up to four months post-PRP treatment. The intervention demonstrated significant effects on FSH concentration, showing notable increases in FSH and E2 levels within the third and fourth months following PRP intervention [11].

In a comprehensive meta-analysis comprising fourteen studies involving 1632 participants, ten studies focused on women with Poor Ovarian Response (POR), one study included women with Premature Ovarian Insufficiency (POI), and three studies encompassed both POR and POI women. The aim was to evaluate the efficacy of intraovarian platelet-rich plasma (PRP) in women with diminished ovarian reserve.

The findings of this systematic review indicated a non-significant enhancement in ovarian hormones such as Anti-Müllerian Hormone (AMH), basal Follicle-Stimulating Hormone (FSH), or basal Estradiol (E2). However, there was a significant improvement observed in Antral Follicle Count (AFC), the number of retrieved oocytes, the number of cleavage embryos, and a reduction in the cancellation rate during IVF cycles [12].

In a retrospective study was done on 223 women to assess the effectiveness of intra-ovarian infusion of PRP in sub-fertile women in terms of improvement in ovarian reserve parameters and outcomes after assisted reproduction versus with no treatment, the authors found that autologous platelet-rich plasma (PRP) could improve the outcome of ovarian poor responder outcomes in the therapy of infertile women with moderate elevation of FSH level [13].

After thorough consideration of the aforementioned factors, we advocate for personalized decision-making when it comes to surgical correction of uterine anomalies. At our center, we prioritize septoplasty for cases of primary subfertility in alignment with our policy. Additionally, for women with poor ovarian reserve, particularly those ineligible for other IVF and egg donation procedures, we have

observed promising outcomes with Platelet-Rich Plasma (PRP) therapy. We see no hindrance in exploring ovarian rejuvenation through PRP, as it has shown numerous positive results in addressing subfertility thus far.

Conclusion

This case doesn't aim to defend or criticize any specific procedure; rather, it's a reflection on the outcomes of our patient's treatment. So far, we've observed encouraging results with PRP. As a teaching center in adjuvant fertility and fetal medicine, we're eager to document any pregnancies following various procedures, regardless of their complexity. In fact, we've witnessed numerous successful pregnancies post-intervention of PRP. However, to truly advance our understanding, we require more extensive and dependable research to inform our practices.

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