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# **Delayed Hysterectomy after Methotrexate Treatment for Placenta Increta: A Case Report**

# Samera F AlBasri\*

Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

\*Corresponding author: Samera F AlBasri, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Citation: AlBasri SF (2022) Delayed Hysterectomy after Methotrexate Treatment for Placenta Increta: A Case Report. Ann Case Report 7: 837. DOI: 10.29011/2574-7754.100837

Received: 29 April 2022; Accepted: 03 May 2022; Published: 05 May 2022

#### Abstract

**Objective:** To describe a case of placenta increta and its management with methotrexate followed by delayed hysterectomy and review related literature. **Method:** A healthy 26-year-old woman P5+0 was referred to our institute on day 6 after cesarean section (CS) for a repeat sections. The placenta was found to be markedly adherent to the uterine wall; there was no bleeding. Therefore, the placenta was left in place and the patient was administered two doses of methotrexate and transferred to our institute for further management. **Results:** The patient was admitted for evaluation and monitored closely over 3 months. During this time, her beta-human chorionic gonadotropin (b-hCG) level dropped and there was no bleeding. In week 16 after CS, she presented to the emergency room with fever because of which hysterectomy was performed; the procedure was complicated by a bladder injury, which was repaired. This was the first case of delayed hysterectomy for placenta acrreta spectrum in our hospital. **Conclusion:** Delaying hysterectomy by using methotrexate may represent a strategy for minimizing the degree of hemorrhage and the need for blood transfusion in patients with placenta acrreta spectrum.

**Keywords:** Placenta acrreta spectrum; Morbidly adherent placenta; Conservative treatment for PAS; Delayed hysterectomy

## Introduction

King Abdulaziz University Hospital is the largest academic tertiary care center in the western region of Saudi Arabia. Over the last 20 years, the department of obstetrics and gynecology has managed more than 500 cases of abnormal placentation including placenta acrreta spectrum (PAS), which is one of the most serious obstetric conditions associated with morbidity and mortality due to bleeding and operative injuries. In 2016, a multidisciplinary team was constituted to manage such cases to achieve improved outcomes. PAS is the consequence of damage to the endometriummyometrium interface of the uterine wall [1]. It is believed to be due to uterine wall injury mainly by surgery, cesarean section (CS) in particular, because of failure of endometrial reepithelialization of the scar area where the trophoblast and villous tissue can invade deeply within the myometrium, including its circulation, and possibly the adjacent pelvic organs [2]. PAS is categorized into the following three types according to the tissue invasion chorionic villi: acrreta, increta, and percreta. Although prenatal

is no single sign for the depth of invasion. Therefore, operative findings and results of histopathological examination should be correlated to improve diagnostic accuracy. It is also not surprising that PAS might be first recognized at the time of CS delivery [3]. The most reasonable approach to the management of PAS with no other obstetric risk and no antenatal bleeding is to plan an elective cesarean hysterectomy by 36 weeks of gestation as a safe option for the mother and fetus. Although 90% of cases in which PAS is diagnosed antenatally are managed by cesarean hysterectomy, delayed hysterectomy in 4-12 weeks can be an option in select cases [4]. Cesarean hysterectomy in women with PAS carries a very high risk of complications, mainly due to hemorrhage and operative injuries. Urologic injuries account for about 30% of these complications, with bladder injury representing two-thirds of them [5]. A conservative management approach for PAS is employed, including the use of methotrexate therapy, in cases in which bleeding is not life-threatening for the mother, preservation of fertility is desired, or operative skills and facilities are limited. Overall, the management of PAS is challenging and may result in very serious complications. Herein, we describe a case of placenta

ultrasound imaging is a sensitive tool for diagnosing PAS, there

1

percreta with invasion into the myometrium.

# **Case Report**

Ahealthy-29-year-old woman, P5+0 with placenta increta due to prior repeated CS deliveries was diagnosed incidentally during an elective CS and was referred for conservative management with methotrexate and further care in a tertiary care center; the placenta increta was left in situ. She received two doses of methotrexate before admission to our hospital. She had no medical history and had undergone prior CS deliveries for all her births without any complications. Upon arrival, she was symptom-free and in a stable state of health. Her initial laboratory workup was unremarkable. The multidisciplinary team plan was to perform close follow-up with serial US and b-hCG level measurements with the aim of considering elective hysterectomy in 6-8 weeks unless indicated earlier (Table 1) (Figures 1 and 2). At week 16, she reported to the emergency department with complaints of high temperature of 2 days duration and no other associated symptoms or signs. Within 24 hours of starting antibiotic therapy, her temperature became normal. The abdominal examination revealed a soft and lax abdomen with a palpable uterus of 18 weeks' size. There were no bleeding or abnormal discharges per vagina. Septic workup was done and showed growth of Streptococcus agalactia. None of her other laboratory tests showed abnormal findings. Total abdominal hysterectomy was planned after a multidisciplinary team discussion.

| Time<br>Post CS | Ultrasound Scan at Maternal Fetal Medicine & Radiology Department   | b-hCG level (IU) |
|-----------------|---|------------------|
| Week 2          | Placenta acrreta with bridging vessels measuring $111 \times 95 \times 52.2$ mm   | 4534.00          |
| Week 3          | $118 \times 97.7 \times 59$ mm, looks the same compared to the previous scan  | 1376.38          |
| Week 5          | $107 \times 90.9 \times 59$ mm, no change in size from the previous scan  | 717.67           |
| Week 9          | 96.5 mm $\times$ 70 $\times$ 40 mm, no change in size from the previous scan  | 545              |
| Week 11         | 99.7 mm $\times$ 95.8 $\times$ 24.5 mm, no change in size from the previous scan  | 231              |
| Week 13         | $10.7 \times 95$ mm, no change in size from the previous scan   | 122.12           |
| Week 16         | The study demonstrates enlargement of the uterus and fundal location of the placenta with small amount of endometrial fluid, while the rest of the study is unremarkable. | 8                |

 Table 1: Summary of ultrasound reports and b-hCG level.



Figures 1 and 2: Some ultrasound images.

#### Results

The patient underwent laparotomy and total abdominal hysterectomy. Her surgery was completed in 175 min under general anesthesia. Laparotomy was done through the same lower transverse abdominal wall incision. Extensive adhesions were observed between the uterus and adjacent tissues and organs. The adhesions were released with meticulous sharp dissection. The uterus was found to be small and involuted with normal-looking tubes and ovaries, but the lower uterine segment was completed invaded by infarcted placenta, which had exteriorized out from some areas (Figures 3 and 4). No invasion by placenta to any adjacent organs was seen. With sharp dissection on anterior wall, the bladder showed an approximately 3-cm injury at the dome. The injury was recognized immediately and after complete total abdominal hysterectomy with bilateral salpingectomy, repair was performed successfully. The bladder was tested with methylene blue and revealed optimum repair. Surgery was concluded with a negative-pressure peritoneal drain inserted on the left lateral side. The estimated blood loss was 700 mL. The patient had an uneventful postoperative stay. On day 20, a postoperative cystogram was performed and showed no extravasation of contrast. Histopathology confirmed infarcted placenta increta and otherwise normal pathology (Figures 5 and 6).



Figures 3 and 4: Uterus, tubes, and placenta.



Figures 4 and 5: Gross pathology of the uterus and the placenta inside.

#### **Discussion and Review of Literature**

PAS is one of the most fatal adherent placental disorders in pregnancy [1,6]. It is thought to occur due to defects in the endometrialmyometrial interface mainly secondary to trauma and leads to different degrees of adherence and invasion. A combination of many factors such as a defective decidua, abnormal trophoblastic attachment, abnormal angiogenesis and vascular remodeling, and progressive uterine scar dehiscence are also thought to be responsible for the development of PAS [2,7] (Figure 7). Many risk factors contribute to this condition, including prior CS, placenta previa, and assisted reproductive technology [7]. Our patient had undergone CS deliveries for all her prior births, which as the main and only risk factor for PAS in this case. In fact, the incidence of PAS is increasing with increased rates of CS, and recent reports have described the incidence as one in 325-550 births [3]. Diagnosis is performed by ultrasound and magnetic resonance imaging is another tool to diagnose PAS [3]. However, nearly half of the cases with PAS remain undiagnosed until the time of delivery, especially in healthcare settings lacking maternal-fetal medicine services to look after high-risk cases, like our patient Histological examination [3].

4



Figure 7: Abnormal placentation\* (copy from article). PAS: Placenta Acrreta Spectrum; AIP: Abnormal Invasive Placenta.

Currently, cesarean hysterectomy immediately after childbirth is the gold standard treatment\* but not without a readily available team and services for possible operative complications and transfusion medicine. Conservative management includes leaving the placenta adherent to the uterus and can be an option in some cases. This avoids hysterectomy but requires careful and close monitoring for risk of bleeding and thrombotic complications as well as infections [8]. Another option is one-step conservative surgery, which involves resecting the invaded area, including the bladder, before resecting the placenta and reconstructing the myometrium [8]. One of the cornerstones of the management of PAS is to avoid any attempt to remove the placenta, either in the conservative or in the radical approach [8]. In the conservative approach, the umbilical cord is ligated close to its placental insertion after delivery, and without any attempt of removal, the placenta is left in situ adherent to the myometrium, similar to the approach employed by the other institute with our patient. Making no attempt to remove any of the placenta, either during conservative management or prior to cesarean hysterectomy, is associated with decreased levels of hemorrhage and a reduced need for blood transfusion [8]. The use of adjunctive measures to reduce blood loss and speed up the process of placental resorption has been reported, including MTX treatment, compression sutures, balloon tamponade, uterine artery embolization, and/or uterine artery ligation. The efficacy of these adjuvant treatment has not been proven, and in fact, they may be correlated with adverse outcomes. Several case reports of uterine necrosis in conservative management with uterine artery embolization have been reported [9,10]. However, we, at King Abdulaziz University Hospital, had never attempted the use of methotrexate for PAS.

Methotrexate acts by reducing the vascularity of the placenta, thereby causing necrosis and accelerating its involution [11]. However, its efficacy in PAS may be limited because the activity of MTX is more pronounced against dividing cells, as seen in the early placenta, rather than in non-dividing ones, as seen in the third trimester [12,13]. There is also no consensus about the

which may further cause a secondary infection in the remaining placenta [16]. Currently, the International Federation of Gynecology and Obstetrics, the American College of Obstetricians and Gynecologists, and the Royal College of Obstetricians and Gynecologists do not recommend its use in PAS [13,17]. The use of methotrexate was never attempted at our center with PAS, but we can see some benefits of its use by other centers and the resultant decreased blood loss during surgery. The use of methotrexate was linked to maternal death in the largest case series; therefore, the use of methotrexate is not recommended by any international consensus guideline and should be actively discouraged. Postoperative antibiotic therapy is usually prescribed to minimize the risk of infection. Placental expulsion or resorption usually takes from 4 weeks (expulsion) to 9-12 months (reabsorption), with a median of 13.5 weeks. The success rate is reported to be 78%. Severe maternal complications have been reported in as many as 6% of the women, including sepsis, uterine necrosis, postpartum uterine rupture, fistula, acute pulmonary edema, renal failure, venous-thromboembolism, and maternal death [18,19]. Our patient exceeded the time given in the literature for delayed hysterectomy and was not on antibiotics during the expectant time, therefore, she presented with early signs of sepsis. One of the benefits of delayed hysterectomy was the decreased blood loss and eventually the need for Transunion. The serum levels of b-hCG reflect the number of active trophoblasts present in the uterus. Therefore, in patients with retained placentas, the serum b-hCG levels tend to be higher than in those with a normal puerperium. In the assessment of b-hCG levels before removal of the placenta, they appeared to decrease in a time-dependent manner. The values dropped gradually over an average of 21-35 days postpartum, reaching <5 IU, after which the levels are not reflective of the uteroplacental circulation. However, several cases in the literature describe the persistence of placental tissue even in the absence

appropriate dosage or mode of administration [14,15]. Moreover,

MTX is contraindicated during breastfeeding and is linked to

serious side effects such as nephrotoxicity and pancytopenia,

5

of b-hCG. Currently, no clear protocols exist to guide the timing or the frequency of measurement of b-hCG levels postpartum in cases of PAS. In our case, the level remained at >5 IU until week 16; however, histopathological assessments confirmed infarcted placental and trophoblastic tissues. PAS is a condition occurring with pregnancy that has been recently on the rise and is associated with severe maternal morbidity [20]. Delayed hysterectomy with methotrexate may represent a strategy for minimizing the degree of hemorrhage and the need for blood transfusion in patients with an antenatal diagnosis of PAS by allowing time for uterine blood flow to decrease and for the placenta to regress from the surrounding structures. Our experience with PAS at KAUH was that it substantially facilitated patient management, supporting the demand for development of centers of excellence for PAS. The cost-effectiveness of delayed hysterectomy with the use of MTX and the serial US and b-hCG level monitoring should be assessed and correlated with its health benefits and the potential to avoid morbidities.

#### Conclusions

Delayed hysterectomy with methotrexate treatment may represent a strategic option for minimizing the degree of hemorrhage and the need for blood transfusion in patients with PAS.

**Ethical Approval:** Ethical approval was obtained from Research Ethics Committee

IRB (Ref. No. 239-22)

Ethics disclosures & Human subjects right: Written consent was obtained by author from the patient herself in this study.

**Acknowledgment:** I wish to thank Dr Estabraq G. AlHachim for the support and assistance.

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