

Methotrexate for the Placenta in Situ in Advanced Abdominal Pregnancy: A Case of Remaining Intra-Abdominal Infection and Myelosuppression after Methotrexate Treatment

Running title: MTX for abdominal pregnancy placenta

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Abstract: *Advanced abdominal pregnancy is a kind of rare but life-threatening ectopic pregnancy, in addition to maternal and fetal safety till the birth, the placenta management after the fetus is out, is another challenge to obstetricians. Here we presented a 33-week primary advanced abdominal pregnancy case, the patient in this case experienced a laparotomy which showed placenta adhesion to abdominal viscera, so the placenta was left in situ. Methotrexate was used to accelerate the degradation of the placenta, however, severe intra-abdominal infection and myelosuppression emerged soon, which had never been reported in similar published cases. It is still controversial whether methotrexate should be used for placenta management in advanced abdominal pregnancy, and the dose and frequency of this drug as well as patients' condition should be comprehensively evaluated when methotrexate therapy is considered.*

Keywords: Intra-abdominal infection, methotrexate therapy, myelosuppression, placenta management, primary advanced abdominal pregnancy

Established Facts

- For the management of the placenta in situ in advanced abdominal pregnancy (AAP), Methotrexate (MTX) is often accompanied by intra-abdominal infection and/or hemorrhage;
- However, few recent studies achieved the safety of MTX in the management of AAP placentae in situ.

Novel Insights

- We present the first case of MTX caused myelosuppression during the therapy for the AAP placenta in situ.
- The administration frequency of MTX and patients' condition need special attention for avoiding related complications.

1. Introduction

Abdominal pregnancy, as one kind of ectopic pregnancy, is characterized with high mortality, though it accounts for only 1% of ectopic pregnancy, with 1% as the incidence in general population [1]. Since the implanting site of zygote is not the uterine wall, massive hemorrhage or the rupture of abdominal organ often emerges just in early pregnancy, so the diagnosis and intervention is rare to be put off till mid-pregnancy, let alone advanced pregnancy [2, 3]. Advanced abdominal pregnancy (AAP), is generally defined as abdominal pregnancy with the gestational age more than

20 weeks, even with lower incidence [4]. However, the mortality of AAP for mothers is as high as 18%, and AAP mothers faced other threats, especially from the placenta-related complications [4]. Herein, we presented an AAP case with 33-week gestation, the treatment for this case was a caesarean section followed by a methotrexate (MTX) therapy for the placenta not removed. However, a severe intra-abdominal infection and myelosuppression emerged after the MTX therapy, making the patient to stay in hospital for more than one month, which was never reported in similar published cases.

2. Case Report

A 24-year-old woman (gravida 2, para 1) at 33-week gestation was admitted (Women's Hospital Affiliated to Medicine School of Zhejiang University on April 13th, 2017) due to vaginal bleeding for 2 months and abdominal pain for 2 days. After collecting the patient's history, we came to know that the patient had never gone to any prenatal visit since menolipsis. Her past history was mainly a caesarean section at a 36-week gestation age for breech presentation and fetal hypoxia 5 years ago, without any more details. The physical examination showed the patient was underweight (body mass index (BMI): 15.6 kg/m²), with hypertension (172/92mmHg). The B ultrasonography and magnetic resonance imaging (MRI) both indicated that the fetus and fetal appurtenances were in the peritoneal

cavity, instead of the uterine cavity (Fig. 1a, Fig. 1b). In addition, we found that the fetus grew restrictedly, and the umbilical artery flow was not even detected in diastolic phase.

Given other auxiliary examinations results (urine protein: ++, hemoglobin: 82g/L), the diagnosis of abdominal pregnancy, severe preeclampsia, fetal growth restriction and moderate anemia was considered. Unfortunately, the bedside B-scan found no fetal heart beat right after the MRI examination, so fetal death was considered and an emergency exploratory laparotomy was performed immediately.

In the operation, 300 ml of blood was observed in the peritoneal cavity, and the fetus was in front of the omentum majus, without amniotic fluid around (Fig. 2). The obstetrician pulled out the fetus, and the evaluation to the neonate showed a 615-gram weight and Apgar score as zero at the first minute and the fifth minute. After the fetus was out, the placenta was seen adhered to abdominal viscera, especially to the omentum majus, hard to separate (Fig. 3). Therefore, the placenta was left in situ.

After the operation, symptomatic treatments were implemented until the patient got in a stable condition on the sixth day. On the seventh day, a methotrexate (MTX) therapy (20mg/day for total 4 days) was used to accelerate the degeneration speed of the placenta. However, abdominal pain with a recurrent fever as high as 39.4 °C emerged since the third treatment day, even though antibiotics were used all the time. Worse still, severe myelosuppression was observed on the third day after the MTX treatment (leukocyte: $0.8 \times 10^9/L$, hemoglobin: 74g/L, thrombocyte: $63 \times 10^9/L$). Therefore, antibiotics and leukocyte increasing drugs as well as blood transfusion were used for treatment, which lasted ten days till the body temperature and leukocyte got stable in a normal range. One month after the operation, the serum concentration of hCG declined to 4.17 IU/ml, and then the patient was discharged from hospital.

3. Discussion

Our case was a primary abdominal pregnancy, according to Studdiford's criteria [5], given the gestational age of 33 weeks, the complete diagnosis was primary advanced abdominal pregnancy (PAAP). Jamie et al. found that there were only 31 PAAP cases after reviewing the abdominal pregnancy articles from 1965-2012, nevertheless, many of mothers and fetus died in these cases. Therefore, it is so important to prevent PAAP in an early stage.

AAP is easy to diagnose with B ultrasonography in regular prenatal visits, however, the women in our case living in a poor rural area, with lower level of education, paid no attention to prenatal visits, which resulted in first prenatal visit at 33-week gestation with abdominal pain and vaginal bleeding, missing the chance of early intervention. As a matter of fact, PAAP resulted mainly from the neglect of prenatal visits as well as the misdiagnosis from ultrasound

doctors [6], hence, strengthening prenatal examinations, especially ultrasonic examinations, is the most effective way to avoid PAAP.

In our case, the patient's placenta was hard to remove so that we chose to leave it in situ, which is universally accepted by obstetricians now [7]. After the operation, we used MTX to accelerate the degradation of the placenta, however, severe intra-abdominal infection and myelosuppression emerged soon, which was a question worth thinking deeply. So far, there has been no consistent conclusion about how to manage the placenta in situ in AAP cases. In 1980s, Rahman et al [8] reported that five AAP patients received a MTX therapy (10mg/day for 5 days, lasting 2-3 courses), but they all got MTX-related intra-abdominal infection and two of them died. The authors speculated that MTX caused the destruction of the placenta too rapidly, and the enormous amount of necrosis tissue in the peritoneal cavity provided bacteria good medium to grow, resulting in complications like intra-abdominal infection and hemorrhage. To avoid intra-abdominal infection caused by rapid destruction of the placenta in situ, many obstetricians tried an expecting therapy with no intervention to the degradation speed, and most of them reported the natural absorption was accompanied by a good prognosis [9-11]. Nevertheless, the natural degradation and absorption might take a long time (months for hCG turning negative and years for the placenta), what's worse, patients still faced the risk of intra-abdominal infection, abscess and hemorrhage in the long period [9-12]. Hence, obstetricians are often troubled in a dilemma when managing the placenta in situ.

In recent years, some reported that AAP patients were not observed with MTX-related complications like intra-abdominal infection, after the use of MTX [13-15], which suggests to us that there may be a balanced method for the management of the placenta. Compared with the dosage schedule used by Rahman et al [8] the MTX regimen in these cases presented as a higher single dose and lower frequency: 20mg/m², twice a week for total 5 times [13] vs 50mg/m², once in three weeks for total 4 times [14] vs a single dose of 75mg [15] vs 10mg/day for 5 days as a course, lasting 2-3 courses in 6 weeks [8]. On the other hand, the time for hCG to turn negative in the four cases was not significantly different from each other (all about one month) [8, 13-15], which indicates that the risk of MTX-related complications might also be correlated with the frequency of MTX administration. In addition, Rahman et al reported their research results in 1980s, when the medical level of related complications prevention, monitoring and intervention was much lower than that in the era of the other three studies (2000s), and that might be one of the reasons for no severe complications emerged even with larger single doses of MTX in the three cases [8, 13-15].

In our case, the patient received a MTX therapy of 20mg/day for total 4 days, although the total dose was less than most of the MTX cases above, the frequency was as high as the study of Rahman et al [8], and the total dose in a

short period (like one week) was almost twice the dose they used, so the risk of intra-abdominal infection for this patient was not low enough. In addition to intra-abdominal infection, the patient got severe myelosuppression after the MTX therapy, which had never been reported among similar studies before (with or without MTX treatment). We speculated that the reasons were the weak body and relatively high dose of MTX. First, the patient was with malnutrition (BMI = 15.6 kg/m²) and anemia, and even weaker in the 6th day post operation, so the patient probably cannot tolerate the MTX therapy. Second, the patient's weight was less than 45 kilograms while both the dose and frequency were relatively high, which might also cause myelosuppression.

In summary, we presented a 33-week AAP case with severe malnutrition, a MTX therapy of 20mg/day for 4 days was used to deal with the placenta in situ post operation, which led to severe intra-abdominal infection and myelosuppression. This case makes us realize the importance of prenatal visits to the diagnosis of abdominal pregnancy, especially to the early intervention of AAP. Besides, when the placenta in AAP cases was left in situ, the methods of placenta management should be considered carefully. Whether MTX should be used is still in controversy, and further researches should focus on the influence of the dose and frequency on related complications. What's most important, the patient's condition should be comprehensively evaluated before a MTX therapy is implemented.

4. Disclosure of Interest

The authors declare no interest.

5. Funding

None

6. Ethical Approval

The signed informed consent from the patient and the approval from the Ethics Committee of Women's Hospital Affiliated to Medicine School of Zhejiang University were both obtained before this study started.

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Figure legends

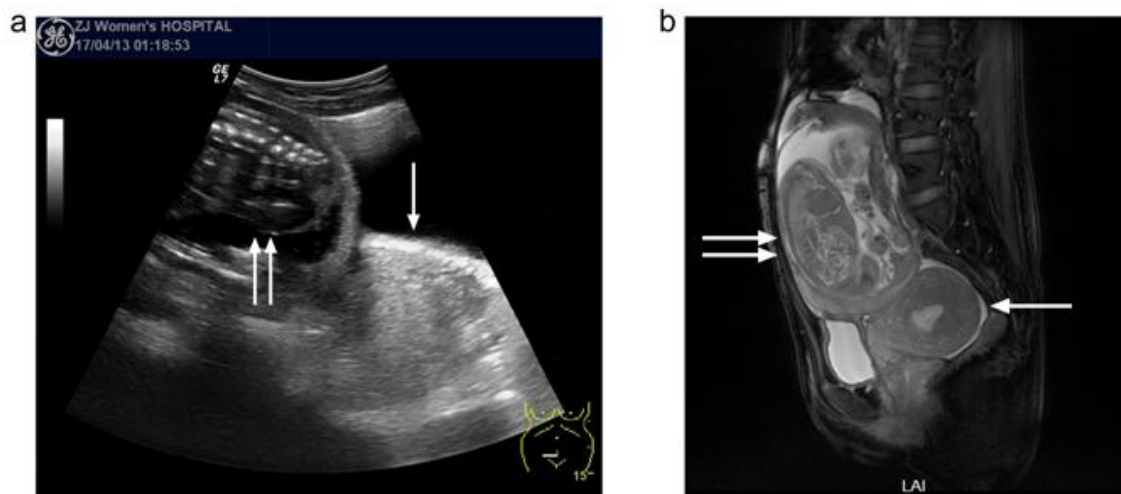


Figure 1: The B ultrasonography (a) and magnetic resonance imaging (b) both showed that the fetus and fetal appurtenances were in the peritoneal cavity, instead of the uterine cavity. ↑: the fetus and fetal appurtenances; ↑↑: the uterine cavity.

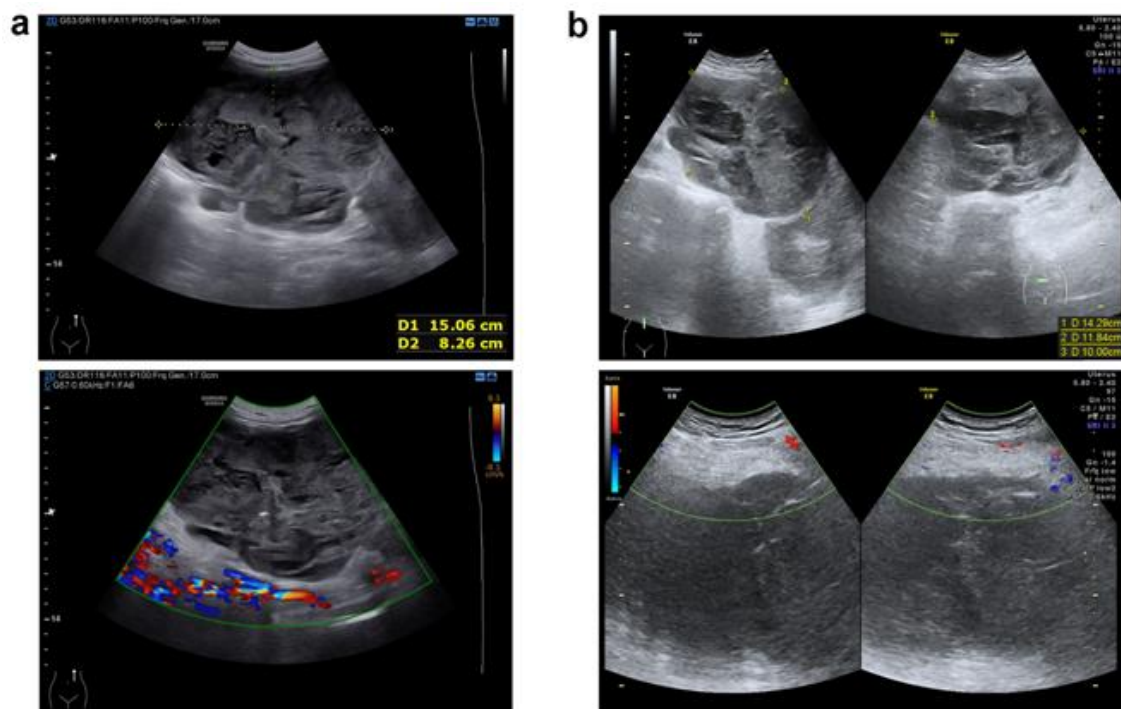


Figure 2: The fetus being pulled out.

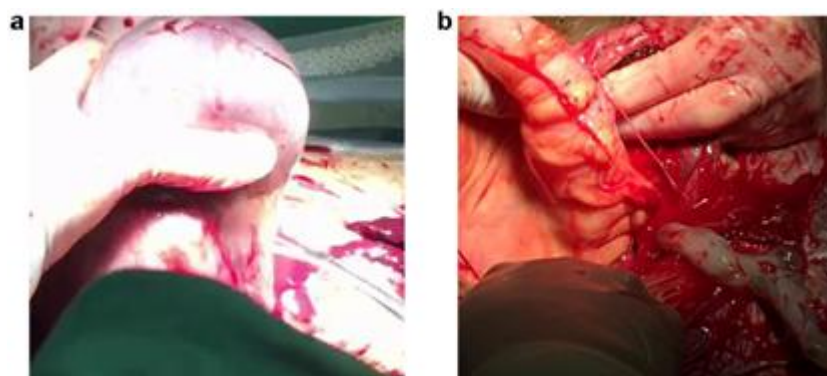


Figure 3: The placenta was adhered to abdominal viscera, especially to the omentum majus.