

# Methotrexate Treatment for Retained Placental Tissue after Second Trimester Termination of Pregnancy

Andrey Kreinin MD<sup>1</sup>, Oshra Saphier PhD<sup>2</sup> and Tali Silberstein MD<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Soroka Medical Center, Ben-Gurion University of the Negev, Beer Sheva, Israel

<sup>2</sup>Department of Chemical Engineering, Sami Shamoon College of Engineering, Beer Sheva, Israel

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**P**lacenta accreta is one of the most common causes of emergency hysterectomy in the peripartum period, which is conducted to preclude massive hemorrhage and save the mother's life. Risk factors for placenta accreta include previous uterine surgery including cesarean section, multiparity, uterine cavity distorted by myomas, and increased maternal age [1]. If the patient desires future fertility, and in the absence of serious sequelae such as massive bleeding or a severe infection, conservative management of abnormally adherent placenta may be attempted, usually with methotrexate treatment [1]. However, the research about the treatment of placenta

accreta during second trimester abortion or termination of pregnancy is scant and much less established.

## PATIENT DESCRIPTION

A 34 year old married woman with three children was admitted to the gynecological emergency department at Soroka Medical Center, Beer Sheva, Israel, for gynecological evaluation due to uterus myomatosis and recurrent episodes of menometrorrhagia. On admission the patient's vital signs and general physical condition were normal.

Her medical history included thalassemia minor with mean hemoglobin values of approximately 10.0 mg/dl. Her gynecological history consisted of two vaginal deliveries, one cesarean section, and one lap myomectomy 4 years before the admission.

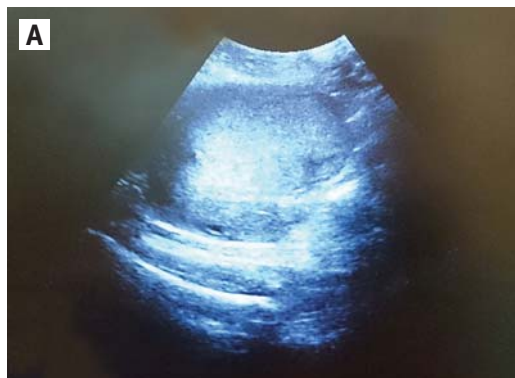
During a gynecological and sonographic evaluation, the patient was diagnosed with spontaneous viable pregnancy 10+6 weeks

based on her last menstrual period. A large 109 × 67 mm intrauterine myoma was diagnosed. The myoma was located on the anterior wall of the uterus close to the inner cervical os (Figure 1A). The woman decided to keep the pregnancy and postpone further evaluation and treatment for the myoma until after the birth.

Six weeks later, the woman was admitted to the hospital at 17+6 weeks of gestation with scant vaginal bleeding and a suspicion of preterm premature rupture of the membranes (PPROM) remote from term. During the evaluation, PPRM was ruled out, the vaginal bleeding ceased, the same intrauterine myoma was documented, and she was released from the hospital.

Two weeks later, the woman was admitted again to the hospital at the 20th week of gestation and was diagnosed with PPRM remote from term. While in the hospital, the patient decided to terminate the pregnancy, but emphasized that she had not

**Figure 1. [A]** A sonographic scan that shows a big submucosal, intramural leiomyoma located within the uterine cavity in the anterior wall of the uterus just behind internal cervical os



**[B]** A sonographic scan that shows adherent placenta located behind a big submucosal intramural leiomyoma



finished her family planning and would like to conceive again.

The woman was treated with repeated doses of misoprostol 400 µg for cervical ripening, and taken to the operating theater for a dilation and evacuation (D&E). Under sonographic guidance, the fetus was evacuated, but the placenta failed to separate. After several attempts of removal, and according to the sonographic scans, it was clear that the placenta had adhered to the uterine wall. Based on this information, we made a diagnosis of placenta accreta. The placenta was located in the anterior uterine wall behind the myoma (Figure 1B), which made the D&E of the placenta more difficult.

As the woman strongly wanted to preserve her fertility, a decision was made to stop the procedure and treat the retained placenta with repeated doses of methotrexate.

The patient received continuous treatment with methotrexate 50 mg intramuscular on days 1, 3, 5, 7, and folic acid 7.5 mg on days 2, 4, 6, 8, according to the local protocol, while continuous beta-human chorionic gonadotropin, quantitative (BHCG) measurements were made. The first dose of methotrexate BHCG was 9825 IU, after 4 days 7428 IU, and 2 days later 4739 IU.

While staying in ward, the patient felt well, the uterus underwent involution and only scant vaginal bleeding was observed, which ceased before the release of the patient. The uterine size with the myoma was approximately 18 weeks of gestation.

Hemoglobin levels were 10.0 mg/dl before the termination of pregnancy and 7.4 mg/dl after the attempted D&E. Due to severe anemia, the patient received a blood transfusion with two units of packed cells. Thereafter hemoglobin levels remained stable 8.7 mg/dl until the day of discharge.

After 14 days of observation, she was released home in a satisfactory condition. She continued weekly measurements of BHCG levels in an outpatient setting.

One month later, BHCG levels were 74 IU, and after 2 months 57 IU. No vaginal bleeding was reported by the woman and no vaginal bleeding was seen on gynecological examination. Two months later, the BHCG levels were undetectable. No

placental tissue was seen on repeated ultrasound examinations. The uterine size measured 18 weeks of gestation due to the large myoma inside the uterus.

Finally, the woman decided to undergo hysterectomy and was scheduled for the operation. The procedure and postoperative period were uneventful. The pathological analysis of the removed tissue confirmed the presence of residual necrotic placental tissue and the diagnosis of placenta accreta, as well as uterine leiomyoma with infarction type necrosis and unremarkable fallopian tubes.

### COMMENT

We report a case of successful treatment of retained placenta accreta after 2nd trimester termination of pregnancy with long protocol of methotrexate administration.

Little has been reported about conservative treatment of placenta accreta, increta, or percreta after late abortion or second trimester delivery [1]. Scant data exists about treatment of placenta accreta after second trimester termination of pregnancy. To the best of our knowledge, there have been no case reports in which the evacuation of the contents of the uterus during second trimester pregnancy termination was complicated by placenta accreta and large intrauterine myoma.

Abnormal placentation, including placenta accreta, increta, or percreta, is often associated with a history of cesarean section, myomectomy, D&E, or other intrauterine surgical procedures [1]. In this case, the patient had two risk factors for placenta accreta: a cesarean section and previous laparoscopic myomectomy. Each of these procedures could potentially lead to abnormal placentation and placenta accreta.

Traditionally, hysterectomy was the procedure of choice in a case of abnormally invasive placenta. In our case, however, the woman wanted to preserve her fertility. Thus, the conversion to hysterectomy was not an option during the time of attempted D&E of the uterine cavity. Furthermore, an emergent procedure has been associated with significant maternal morbidity and mortality [2]. In one systematic review,

emergent postpartum hysterectomy was associated with maternal morbidity in 56% of cases and with mortality of 3%. Complications include injury to the urinary tract or gastrointestinal tract, massive obstetrical hemorrhage, and infection [2]. Planned hysterectomy is associated with fewer perioperative complications compared to emergent procedures [3].

Based on existing information, our clinical experience, and the patient's desire to preserve fertility at the time of the attempted D&E of the uterus, a decision was made to treat the patient with a long protocol of methotrexate, as it has been considered an adjuvant treatment for the conservative management of placenta accreta, with surgery considered on an elective basis, on the woman's preferences [4].

Even though conservative management of retained placenta with methotrexate appears to be successful in many cases, there is still a potential for morbidity due to methotrexate side effects.

The most common side effects of methotrexate therapy include ulcerative stomatitis, leukopenia, nausea, abdominal distress, chills and fever, dizziness, and decreased resistance to infection [5]. Due to these potential side effects, strict monitoring of the patient is required. No treatment complications of methotrexate were observed in our patient.

Based on the available data, the patient was advised not to conceive for at least for 3 months after methotrexate treatment [5].

### CONCLUSIONS

Our case supports the published data, that shows that conservative management of various types of an abnormal placentation may be successful in carefully selected patients. Our case report adds information about an optional treatment regimen of retained placenta in a second trimester pregnancy when its surgical removal is impossible due to various circumstances such as large myoma.

### Correspondence

**Dr. T. Silberstein**  
 Dept. of Obstetrics and Gynecology, Soroka  
 University Medical Center, Beer Sheva 84101, Israel  
 email: talisil@bgu.ac.il

## References

1. Yarandi F, Eftekhari Z, Shojaei H, Rahimi-Sharbat F, Baradaran F. Conservative management of placenta increta: case report and literature review. *Acta Med Iran* 2011; 49 (6): 396-8.
2. Rossi AC, Lee RH, Chmait RH. Emergency postpartum hysterectomy for uncontrolled postpartum bleeding: a systematic review. *Obstet Gynecol* 2010; 115 (3): 637-44.
3. Briery CM, Rose CH, Hudson WT, et al. Planned vs. emergent cesarean hysterectomy. *Am J Obstet Gynecol* 2007; 197 (2): 154.e1-5.
4. Timmermans S, Van Hof AC, Duvekot JJ. Conservative management of abnormally invasive placentation. *Obstet Gynecol Surv* 2007; 62 (8): 529-39.
5. Hackmon R, Sakaguchi S, Koren G. Effect of methotrexate treatment of ectopic pregnancy on subsequent pregnancy. *Can Fam Physician* 2011; 57 (1): 37-9.

## Capsule

### Efficacy of epratuzumab, an anti-CD22 monoclonal IgG antibody, in systemic lupus erythematosus patients with associated Sjögren's syndrome

Using EMBODY 1 (ClinicalTrials.gov identifier: NCT01262365) and EMBODY 2 (ClinicalTrials.gov identifier: NCT01261793) **Gottenberg** and colleagues investigated the efficacy and safety of epratuzumab, a CD22-targeted humanized monoclonal immunoglobulin G (IgG) antibody, in patients with systemic lupus erythematosus (SLE). The studies showed no significant difference from placebo in primary or secondary clinical outcome measures but did demonstrate B cell-specific immunologic activity. The aim of this post hoc analysis was to determine whether epratuzumab had a different clinical efficacy profile in SLE patients with versus those without an associated diagnosis of Sjögren's syndrome (SS). A total of 1584 patients were randomized in the EMBODY 1 and EMBODY 2 trials; 113 patients were anti-SS-related antigen A-positive and had a diagnosis of associated SS, and 1375

patients (86.8%) had no diagnosis of associated SS (918 patients were randomized to receive epratuzumab and 457 to receive placebo). For patients with associated SS, but not those without associated SS, a higher proportion of patients receiving epratuzumab achieved a based composite lupus assessment response and a reduction from baseline in BILAG total score. B cell reduction was faster in patients with associated SS. The sensitivity of B cells to epratuzumab as measured by the mean concentration producing 50% of the maximum B cell count depletion was lower for patients with associated SS (9.5 µg/ml) vs. the total EMBODY population (87.1 µg/ml). No difference in the frequency of adverse events in those receiving placebo was reported.

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Eitan Israeli

## Capsule

### Identification of three rheumatoid arthritis disease subtypes by machine learning integration of synovial histologic features and RNA sequencing data

In this study, **Orange** and colleagues sought to refine histologic scoring of rheumatoid arthritis (RA) synovial tissue by training with gene expression data and machine learning. Twenty histologic features were assessed in 129 synovial tissue samples (n=123 RA patients; n=6 osteoarthritis [OA] patients). Consensus clustering was performed on gene expression data from a subset of 45 synovial samples. Support vector machine learning was used to predict gene expression subtypes using histologic data as the input. Corresponding clinical data were compared across subtypes. Consensus clustering of gene expression data revealed three distinct synovial subtypes, including a high inflammatory subtype characterized by extensive infiltration of leukocytes, a low inflammatory subtype characterized by enrichment in pathways including transforming growth factor β, glycoproteins, neuronal genes, and a mixed subtype. Machine learning applied to histologic features, with gene expression subtypes serving as labels,

generated an algorithm for the scoring of histologic features. Patients with the high inflammatory synovial subtype exhibited higher levels of markers of systemic inflammation and autoantibodies. C-reactive protein (CRP) levels were significantly correlated with the severity of pain in the high inflammatory subgroup but not in the others. Gene expression analysis of RA and OA synovial tissue revealed three distinct synovial subtypes. These labels were used to generate a histologic scoring algorithm in which the histologic scores were found to be associated with parameters of systemic inflammation, including the erythrocyte sedimentation rate, CRP level, and autoantibody levels. Comparison of gene expression patterns to clinical features revealed a potentially clinically important distinction: mechanisms of pain may differ in patients with different synovial subtypes.

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Eitan Israeli

**“Success is the ability to go from one failure to another with no loss of enthusiasm”**

Sir Winston Churchill, (1874–1965), British politician