Clinical Radiology 74 (2019) 647–648

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Correspondence

In Reply to Letter to the Editor: methotrexate and uterine artery embolization for placenta accreta spectrum disorders: some clarifications

Sir—We are grateful to Drs Matsubara and Takahashi for their interest in our article and their knowledgeable insights. In their letter,[1] Drs Matsubara and Takahashi mentioned potential concerns regarding the indications for the interventional radiological procedure in our study consisting of patients' desire for uterus preservation or very difficult caesarean hysterectomy.[2]

Placental adhesive disorders or placenta accreta spectrum (PAS) disorders as per Drs Matsubara and Takahashi correct classification (based on the latest recommendation by the International Federation of Gynecology and Obstetrics (FIGO))[3] are challenging obstetrical problems worldwide. Severe maternal morbidities secondary to massive haemorrhage, infection, and injury to adjacent organs are the major concerns regarding these disorders.[4–6] Conservative management is a good choice in some cases of difficult caesarean hysterectomy depending on the depth of the invasion.[7,8] In addition, given that the preservation of the reproductive system is very important to the patient, which may be more evident in developing countries, conservative management is attempted to preserve uterine function.[7] In our study, uterine preservation (not performing primary or delayed hysterectomy) was considered the main outcome. Among the 12 patients, difficult hysterectomy was suspected in two patients (case 9 and case 11). The patients' desire for uterus preservation was the main reason for choosing preservative treatment in the remaining 10 cases. Based on our definition, the rate of successful uterine preservation was 58%.

Secondly, Drs Matsubara and Takahashi would like to know the intra-operative findings at delayed hysterectomy cases due to concerns about marked collateral circulation at the time of delayed hysterectomy in these patients.[2] We agree that there are conflicting results regarding the management of PAS with uterine artery embolization (UAE) in the literature, as was mentioned in the discussion section of our article, and there is special concern about the specific complications of this strategy.[3,7,9] In our study among 12 patients, five cases underwent hysterectomy, of which the reason for delayed hysterectomy in two cases was intestinal adhesion/peritonitis and secondary postpartum haemorrhage/sepsis, 63 and 26 days after procedure, respectively. Of these two cases, Case 2 was a 38-year-old woman (G2P2) with suspected placenta accreta who underwent UAE and methotrexate (MTX) therapy due to the patient's desire for uterus preservation. On postpartum day 60, she presented with a history of nausea, vomiting, loss of appetite, abdominal pain with eating, and constipation. On examination, she had noteworthy abdominal distension and tenderness on palpation. She was febrile with a heart rate of 85 beats/min and blood pressure of 100/60 mmHg. The patient was admitted. Her Complete Blood Count (CBC) revealed leucocytosis (white blood cells 16.2×10^9/l). Blood, urine, and endocervical swab cultures were obtained. Blood culture was positive for *Escherichia coli* and intravenous antibiotics were started. Computed tomography (CT) of the abdomen showed small bowel obstruction with a potential adhesion between the uterine fundus and small bowel. Placental tissue was still observed in the fundus. The consensus was endomyometritis due to *in situ* placenta accreta that had progressed to bacteraemia, and probably intestinal obstruction caused by adhesion formation. The patient consented to elective hysterectomy. On postpartum day 63, the patient underwent surgery. There was a necrotic defect associated with the infected remnants of the placenta at the uterine fundus. Moreover, the small bowel was folded and adherent to the defect area at the fundus of the uterus. Total hysterectomy and small bowel resection were performed. The estimated blood loss during surgery was 1,200 ml. The patient was discharged in stable condition on the fifth postoperative day. The pathology report confirmed placenta accreta.

The second of the two delayed hysterectomy cases, Case 4, was a 32-year-old woman (G5P5) with suspected placenta increta who also underwent conservative management due to the patient's emphasis on uterus preservation. The patient developed heavy vaginal bleeding and a high-grade fever with chills on postpartum day 26. The patient was admitted due to unstable haemodynamic condition. Consequently, hysterectomy was performed after

https://doi.org/10.1016/j.crad.2019.05.006

fluid resuscitation, starting antibiotic therapy, and obtaining consent for hysterectomy from the patient. The uterus was large (about 18 weeks) and soft. There were several pieces of the placenta that were adherent to the wall of the uterus. The estimated blood loss during surgery was 2,700 ml, which was managed by administration of appropriate blood products. The patient was discharged from the hospital on the seventh postoperative day in good condition. Pathology examination revealed focal invasion of the placental tissue throughout the myometrium. In both cases above, especially in the second, bleeding during surgery was more than expected in a routine hysterectomy. We think, as Drs Matsubara and Takahashi pointed out, this could have been due to collateral vessel development following UAE.

Thirdly, Drs Matsubara and Takahashi would like to know serum beta human chorionic gonadotropin (βhCG) levels during the treatment course. In addition, they explained that MTX targets rapidly dividing cells (first-trimester trophoblasts) and it does not target those dividing more slowly (third-trimester trophoblasts), so why did we use it?[2] MTX is a dihydrofolate reductase inhibitor that interferes with the synthesis of DNA. In ectopic pregnancy and gestational trophoblastic disease, there is active placental tissue with rapid cell division. MTX is one of the main treatment strategies for these disorders. Studies show that cell division stops approximately 1 month before term, in normal human placenta cells.[10,11] The mean gestational age at the time of delivery in our study, was 29.9±5.5 weeks ranging from 22–37 weeks; however, successful management of PAS at term using MTX without surgery has been reported.[11–13] MTX arrests cell division and likely leads to changes in non-dividing trophoblastic cells.[11] Based on these findings, injection of MTX through the uterine artery (causes higher concentrations of medication in the abnormal tissue and better efficacy, and also reduction in the required dosage and side effects of the MTX) with simultaneous use of another therapeutic approach such as UAE, seems reasonable. ß-hCG is made in the mitosing cytotrophoblasts. As cytotrophoblastic mitosis stops approximately 1 month before term, the level of ß-hCG could be low or even absent in these cases.[11] As a result, there is doubt about the usefulness of ß-hCG as a reliable marker, and Doppler ultrasound or magnetic resonance imaging are the preferred methods for follow-up of patients with PAS.[11–14] In our study, ß-hCG returned to normal levels in all patients; however, the drop in ß-hCG was not related to placenta expulsion in two cases. In one of the cases, Case 9, although ß-hCG reverted to normal levels after 10 weeks (from 3,404 mIU/ml to 8 mIU/ml), an inactive placenta bulk was still existent after 7 months on Doppler ultrasound examination. In another case, Case 3, the ß-hCG level dropped to normal after 6 weeks (from 1,079 mIU/ml to 11 mIU/ml), but there was an inactive placenta mass after 4 months on Doppler ultrasound examination.

Finally, until there is better evidence from well-designed studies, it is better to restrict this conservative approach just for two indications: (1) patient request for fertility preservation, and (2) whenever difficult hysterectomy is anticipated. In addition, this method should be restricted to centres that have adequate resources (equipment and expert surgical team) and a strict follow-up system to detect and treat any complications in a timely manner.

Conflicts of interest

The authors declare no conflict of interest.

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