



# Methotrexate infusion followed by uterine artery embolisation for the management of placental adhesive disorders: a case series

M.R. Babaei<sup>a</sup>, M. Oveysi Kian<sup>b</sup>, Z. Naderi<sup>b</sup>, S. Khodaverdi<sup>c</sup>, Z. Raoofi<sup>b</sup>,  
F. Javanmanesh<sup>b</sup>, I. Mohseni<sup>d</sup>, S. Nasiripour<sup>e</sup>, M. Farasatinasab<sup>f,\*</sup>

<sup>a</sup> Department of Interventional Radiology, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Department of Obstetrics and Gynecology, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran

<sup>c</sup> Department of Obstetrics and Gynecology, Endometriosis Research Center, Iran University of Medical Sciences (IUMS), Tehran, Iran

<sup>d</sup> Department of Radiology, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran

<sup>e</sup> Department of Clinical Pharmacy, Rasul-e Akram Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran

<sup>f</sup> Department of Clinical Pharmacy, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran

## ARTICLE INFORMATION

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**AIM:** To evaluate the efficacy and safety of the uterine artery embolisation (UAE) in combination with methotrexate (MTX) for conservative management of placental adhesive disorders.

**MATERIAL AND METHODS:** Patients with placental adhesive disorders (including accreta, increta, and percreta lesions) that were treated with UAE in combination with MTX were identified and were followed prospectively for outcomes including uterine preservation and complications.

**RESULTS:** Twenty-six patients were identified who had the diagnosis of abnormal placenta implantation during this study. Fourteen patients were excluded because they were treated by a caesarean hysterectomy. Among remaining 12 patients, the successful uterine preservation observed in seven (58%) cases. Menstruation cycles returned in all successfully treated patients, although they did not have desire to get pregnant. Five (42%) patients underwent primary or delayed hysterectomy due to severe post-partum haemorrhage in three cases, and intestinal adhesion/peritonitis and secondary post-partum haemorrhage/sepsis in two patients, respectively.

**CONCLUSION:** Although this interventional method is relatively successful in uterine preservation, the possibility of treatment failure cannot be ignored. Given that there are too few data regarding its efficacy and safety, this method should be reserved to patients who have a

\* Guarantor and correspondent: M. Farasatinasab, Department of Clinical Pharmacy, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, BehAfarin St - Karim Khan e Zand St, Tehran, Iran. Tel.: +982182141201.

E-mail address: [maryfarasati@gmail.com](mailto:maryfarasati@gmail.com) (M. Farasatinasab).

strong desire to maintain the uterus and their fertility, or if it is technically difficult to perform hysterectomy due to the extent of the invasion.

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## Introduction

Placental adhesive disorders, depending on the depth of invasion, include placenta accreta, increta, and percreta lesions.<sup>1</sup> These are associated with a high rate of severe maternal morbidities, such as massive maternal blood loss, uterine perforation, loss of fertility, disseminated intravascular coagulation (DIC), acute kidney injury (AKI), infection, and acute respiratory distress syndrome (ARDS).<sup>2</sup> The incidence of abnormal placentation in singleton pregnancies is estimated to be approximately 2%.<sup>3</sup> As a history of caesarean section is one of the main causes of placenta implantation disorder, the incidence rate of invasive placentation has increased in recent years.<sup>4</sup> Other risk factors of abnormal placentation include previous dilatation and curettage, placenta previa, multiparty (more than six pregnancies) as well as prior intrauterine infections and maternal age >35 years.<sup>4</sup>

A standard treatment for placental adhesive disorders is hysterectomy.<sup>5</sup> This treatment method may decrease maternal morbidity, but in contrast, the patient loses her fertility. Therefore, there has been a paradigm shift in the management of abnormal placenta implantation to more conservative methods. Some conservative treatments for uterus preservation comprise expectant management (wait and see), uterine artery embolisation (UAE), methotrexate (MTX) therapy, and uterus preserving surgeries (such as uterine internal/iliac artery ligation and balloon tamponade).<sup>6–9</sup>

UAE in combination with MTX has been assessed in the treatment of abnormal placenta implantation in some studies.<sup>10–22</sup> Although this method may result in accelerated involution or expulsion of placenta, and there are some beneficial effects on haemorrhagic events, there is little evidence regarding its efficacy and safety. The present study was undertaken to evaluate the efficacy and safety of UAE in combination with MTX in patients who underwent this method for invasive placentation.

## Materials and methods

### Patients and setting

This case series was performed at a major teaching hospital from January 2015 to the end of December 2017. The study protocol was approved by the local ethics committee. All patients provided written informed consent forms for the embolisation procedure before UAE.

Women with placental adhesive disorders who were treated with a combination of UAE and MTX were enrolled

in the study. This study was performed retrospectively and followed in a prospective fashion for the development of outcomes. Abnormal placenta implantation was diagnosed by colour Doppler ultrasound and magnetic resonance imaging (MRI). The decision to apply conservative management was made if the patient strongly insisted on preserving her uterus or in cases primary hysterectomy would be so difficult or more complicated due to the extent of the invasion.

### Study protocol

Uterus and placenta were left *in situ* after delivery (vaginal or caesarean delivery) in all patients. After surgery, the cases were transferred to the interventional radiology department adjacent to the operation room. In addition, occlusion balloons were on available to inflate if haemorrhage occurred. Embolisation procedures were performed by an interventional radiologist.

Pelvic angiography was performed with a common femoral arteries approach using a 5 F pigtail catheter via a 5 F vascular sheath (Super Torque®, Cordis, Miami Lakes, Florida, USA). A vascular road map for the uterine arteries was provided by pelvic angiography. In order to catheterise the uterine arteries, a Cobra catheter (Terumo, Tokyo, Japan) was used. Microcatheters (2.9 F, Embocath® Plus, Merit Medical, Paris, France) were applied whenever it was not possible to enter the distal uterine arteries using Cobra catheters.

First, MTX (70 mg/m<sup>2</sup>) was diluted in 50 ml normal saline and administered with an infusion pump in the uterine arteries during the 15 minutes before embolisation of the uterine arteries in all patients. Then UAE was undertaken using polyvinyl alcohol (PVA) particles (500–710 µm; Contour SE, Boston Scientific, Natick, MA, USA). Injection of the PVA particles mixed with iodinated contrast medium was continued to achieve full occlusion of the main uterine arteries.

In three patients it was followed by a regimen of intramuscular MTX (1 mg/kg) every week. The frequency of intramuscular MTX injection was two times in two of these three patients, and 10 times in one case.

All patients received folic acid 15 mg intramuscularly and then folic acid 1 mg BID for 15 days as MTX toxicity prevention. Ciprofloxacin and metronidazole was administered in all patients as prophylaxis for 7 days after embolisation.

### Assessment

Close observation including clinical and bimanual examination and periodic pelvic sonography was undertaken

for all patients during the follow-up period. Uterine preservation (not doing primary or delayed hysterectomy) was the main outcome of this study. In addition, the complications of this therapeutic method such as uterine necrosis, deep vein thrombophlebitis, pulmonary embolism, acute kidney, or liver injury, peritonitis, and sepsis were recorded as secondary outcomes.

## Results

The diagnosis of abnormal placenta implantation was made in 26 cases based on imaging findings, during this study period. As 14 patients were treated by caesarean hysterectomy, 12 patients were enrolled in the study after obtaining the written consent form.

The mean age of included patients was  $31.5 \pm 5.9$  years (range, 17–38 years). The mean gestational age at the time of delivery was  $29.9 \pm 5.5$  weeks (range, 22–37 weeks). Abnormal placentation diagnosis was suspected antepartum in all 12 cases. An abnormal Doppler ultrasonographic examination was reported in 11 patients. MRI was performed for one patient to confirm the diagnosis. Among these patients, two cases had placenta accrete and four and six patients had placenta percreta and increta, respectively. At least one risk factor for abnormal placentation was recognised in all patients except for two patients. Antepartum vaginal bleeding was reported in seven (58%) patients, but none required blood transfusion.

Treatment with UAE and MTX was successful in seven (~58%) patients with expulsion of the placenta. Among these seven patients, three (~42%) cases received intramuscular injection of MTX more than once. Resumption of menstruation cycles occurred in all successful treated patients, although they did not have the desire to get pregnant.

The procedure led to hysterectomy in five (42%) cases; severe post-partum haemorrhage was a cause for primary hysterectomy in three (60%) patients, and in two (40%) cases, intestinal adhesion/peritonitis and secondary post-partum haemorrhage/sepsis were the reason for delayed hysterectomy, 63 and 26 days after the procedure, respectively.

Table 1 summarises the patient demographic and obstetric characteristics, risk factors for abnormal placentation, placenta/uterine outcomes, complications, and subsequent menstruation.

## Discussion

To the authors' knowledge, this is the one of largest case series that evaluated the efficacy and safety of combination of UAE and MTX in placental adhesive disorders. In the present study, the successful uterine preservation rate was 58% and a maternal morbidity occurred in 42%.

The evaluation of efficacy and safety of combination of UAE and MTX, in the treatment of clinical–pathological or radiological abnormal placenta implantation was investigated in some case reports or case series.<sup>10–22</sup> Similar

results to the present study are starting to appear in these studies. The summarised data are shown in Table 2. Successful uterine preservation was obtained in 13 (65%) cases of 20 patients. Subsequent menstruation was reported in three patients. Generally, 35% (7/20) patients underwent hysterectomy<sup>10–13,15,18</sup>; however, in two of these seven cases, elective hysterectomy was performed to preserve bladder function, because when hysterectomy is performed at the time of delivery, there is a greater risk of massive haemorrhage and other surgical complications.<sup>15</sup> Significant complications led to delayed hysterectomy in five of these seven patients.<sup>10–13,18</sup> Dinkle *et al.* reported delayed emergency hysterectomy due to massive vaginal bleeding from the retained placenta; however, it possibly occurred because of anticoagulant therapy with heparin and phenprocoumon due to pulmonary embolism of unknown origin on day 6 after the procedure.<sup>10</sup> In one of the case reports, heavy vaginal bleeding developed 44 days after the procedure and total abdominal hysterectomy was performed because of the patient's unstable haemodynamic condition.<sup>12</sup> Genital infections were the reason for subtotal hysterectomy on day 25 in one case.<sup>13</sup> In another case, delayed hysterectomy was performed on day 23 because of uterine necrosis and sepsis.<sup>18</sup> One case of maternal death owing to injection of MTX through the umbilical cord and subsequent acute renal failure, peritonitis, and septic shock, was reported in the literature.<sup>18</sup>

Conflicting results has been described regarding the management of placental adhesive disorders with UAE in case reports or case series.<sup>15,23–25</sup> Su *et al.*<sup>23</sup> reported the results of UAE in eight pregnant females with abnormal placentation (including one accreta, three increta, and four percreta cases). Uterine preservation was successful in two (25%) of the cases, and severe maternal morbidity comprising coagulopathy, sepsis, early or delayed haemorrhage bladder damage, and fistula were reported in seven (87.5%) of patients; however, Matsuzaki *et al.*<sup>24</sup> performed a literature review on the effectiveness and safety of conservative strategies of placenta percreta between January 1990 and December 2016. Their study consisted of 72 patients; prophylactic UAE was carried out among 33 (46%) patients. Complete placental resorption was shorter in the prophylactic UAE group than in the non-UAE group (mean: 22.4 weeks versus 35.3 weeks;  $p=0.014$ ). The reported difference between the therapeutic UAE group and non-UAE group was similar ( $p=0.019$ ). Generally the total infection rate during the conservative management period was similar between groups: 32% in the non-UAE and 21% in prophylactic UAE groups ( $p=0.400$ ). In addition, resumption of menstruation in the study of Tong *et al.*<sup>15</sup> occurred in two patients with placenta accreta after 3 months of delivery who were treated by embolisation of uterine artery. Chan *et al.*<sup>25</sup> also reported effective conservative management of three cases of placenta accreta by using UAE after caesarean and leaving the placenta *in situ*. It should be mentioned that there is a special concern about the specific complications of this method including uterine necrosis, sepsis, ischaemic damage to other organs due to non-targeted embolisation, and iliac artery thrombosis.<sup>18,26</sup>

**Table 1**

Characteristics and outcomes of 12 patients with placental adhesive disorders treated with a combination of UAE and MTX.

Case	Age	Gravidity/ parity	Risk factors	Obstetric characteristics			Type of placenta	Complications	Outcomes		
				Gestational age (weeks) at Delivery	Mode of delivery	Placenta left in situ			Placenta/ uterine outcomes	Subsequent menstruation	Subsequent pregnancy
1	32	G3P2	Previous caesarean delivery, placenta previa	34	CS	Totally	Accreta	Severe vaginal bleeding	Hysterectomy	0	0
2	38	G2P2	Previous caesarean delivery, age >35 y	37	CS	Partially	Accreta	Intestinal adhesion, peritonitis	Hysterectomy	0	0
3	36	G1P1	age >35 y	35	Vaginal	Totally	Increta	Fever	Placenta expulsion	+1 year after management	No
4	32	G5P5	Previous caesarean delivery, placenta previa	33	CS	Totally	Increta	Severe vaginal bleeding/ Sepsis	Hysterectomy	0	0
5	17	G1P1	-	29	CS	Partially	Increta	Mild vaginal bleeding	Placenta expulsion	+2 months after management	No
6	28	G2P2	Previous caesarean delivery	22	CS	Partially	Increta	Severe vaginal bleeding	Hysterectomy	0	0
7	29	G3P2	Previous caesarean delivery, placenta previa	34	CS	Partially	Increta	-	Placenta expulsion	+1 months after management	No
8	26	G1P1	-	25	CS	Partially	Increta	-	Placenta expulsion	+3 months after management	No
9	32	G2P2	Previous caesarean delivery, placenta previa	22	CS	Totally	Percreta	Mild vaginal bleeding	Placenta expulsion	+one year after management	No
10	36	G1P1	age >35 y	30	Vaginal	Totally	Percreta	-	Placenta expulsion	+2 months after management	No
11	38	G2P1	Previous caesarean delivery, age >35 y	23	CS	Totally	Percreta	Severe vaginal bleeding	Hysterectomy	0	0
12	34	G4P4	Previous caesarean delivery	35	Vaginal	Partially	Percreta	-	Expulsion	+3 months after management	No

UAE, uterine arterial embolisation; MTX, methotrexate; CS, caesarean section.

The main mechanism of MTX against proliferating trophoblast is related to its action against rapidly dividing cells. For this reason, the use of MTX is one of the main treatment approaches for treating ectopic pregnancy and also in gestational trophoblastic disease. The advantages of MTX in a conservative approach to abnormal adhesive placenta have been challenged through various reports.<sup>27–32</sup> In a review of published data for the role of MTX in management of abnormal placenta implantation, Farasatinasab *et al.*<sup>9</sup> concluded, albeit MTX is used for acceleration of involution of placenta and in the literature some beneficial effects in haemorrhagic events are noted, evidence compatible with the safety and efficacy of using MTX for this purpose is not sufficient. Furthermore, alongside the side effects such as nephrotoxicity and pancytopenia, the immunosuppressive nature of MTX increases the risk of infection, which is already higher in patients with abnormal adhesive placentation.<sup>18,26</sup> Regarding the serious complications of MTX mentioned, it may be possible to reduce the final dose used and consequently reduce the related side effects with the use of another therapeutic approach such as UAE simultaneously with the administration of the drug.

As the best strategy for the management of placenta adhesive disorders is controversial, individualisation in any case remains the best treatment policy. Furthermore, a multidisciplinary approach including the gynaecologist, interventional radiologist, and general surgeon, is needed in order to manage these cases. In addition, the presence of an expert clinical pharmacist along with other specialists will be very helpful in minimising the side effects of the medications.

The limitations of this study are the retrospective collection of patients, single study arm, and intervention in an open-label fashion.

In conclusion, in this study, consisting of retrospective patient collection and prospective follow-up, the efficacy and safety of the conservative management of placental adhesive disorders with UAE and MTX were evaluated. This intervention may be effective in uterine preservation; however, the relative failure of this approach cannot be ignored. Therefore, as long as not sufficient data from well-designed clinical trial studies, this conservative management should be reserved for women with a strong desire to maintain fertility and/or in cases in which primary hysterectomy would be complicated due to the extent of invasion. This procedure should be restricted to centres that are well equipped with facilities for embolisation and have an expert

**Table 2**

Characteristics and outcomes of 20 reported cases with placental adhesive disorders treated with a combination of UAE and MTX.

Study	No	Age	Gravidity/ parity	Obstetric characteristics			Type of placenta	Complications	Outcome		
				Gestational age (weeks) at Delivery	Mode of delivery	Placenta left <i>in situ</i>			Placenta/ uterine outcomes	Subsequent menstruation	Subsequent pregnancy
Dinkel <sup>10</sup> case report (2003)	1	34	G3P2	32	CS	Totally	Percreta (Previa)	Pulmonary embolism, delayed vaginal bleeding	Hysterectomy	No	No
Wong <sup>11</sup> case report (2005)	1	30	G3P3	37	CS	Totally	Percreta (Previa)	Vaginal bleeding	Expulsion	+/Soon after passage of pieces of placenta	NR
Luo <sup>12</sup> case report (2005)	1	32	G2P1	32	CS	Totally	Percreta (Previa)	Delayed vaginal bleeding	Hysterectomy	No	No
Fiori <sup>13</sup> case report (2005)	1	35	G2P1	34	Vaginal	Totally	Accreta	Genital infections with multidrug- resistant <i>Pseudomonas aeruginosa</i> and Enterobacteriaceae	Subtotal Hysterectomy	No	No
Verma <sup>14</sup> case report (2007)	1	37	G6P3	15	-	Totally	Percreta	Vaginal bleeding	Involution	NR	+
Tong <sup>15</sup> case series (2008)	1 <sup>a</sup>	31	G5P1	35	CS	Totally	Accreta	Septicaemia and heavy vaginal bleeding	Involution	+/3 months after management	NR
Lee <sup>16</sup> case series (2008)	1	24	G5P2	31	CS	Totally	Percreta with bladder involvement	-	Hysterectomy (for bladder preservation)	0	0
	1	39	G3P2	34	CS	Totally	Percreta with bladder involvement	-	Hysterectomy (for bladder preservation)	0	0
Yee YH case report <sup>17</sup> (2008)	1	32	G2P1	34	CS	Totally	Percreta	-	Expulsion	2 months after normalisation of the uterus	NR
Sentilhes <sup>18</sup> retrospective cohort <sup>b</sup> (2010)	1	NR	NR	37	Vaginal	Partially	Accreta	Uterine necrosis and sepsis	Hysterectomy	0	0
	1	NR	NR	32	CS	Totally	Accreta	Aplasia, nephrotoxicity With acute renal failure, and then peritonitis with Septic shock	Hysterectomy & death due to MTX	0	0
Cho FN case report <sup>19</sup> (2011)	1	34	G1P0	22	Vaginal	Totally	Increta	Vaginal bleeding	Expulsion	NR	NR
Khan M case report <sup>20</sup> (2013)	1	28	G3P2	32	CS	Totally	Percreta	Genital infections with <i>Escherichia coli</i>	Involution	+/7 months after management	NR
Noufaily case report <sup>21</sup> (2017)	1	34	G3P1	29	CS	Totally	Percreta	Fever, nausea, occasional vomiting, and leucocytosis	Involution	NR	NR
Cui R case series (2018) <sup>22</sup>	6 <sup>c</sup>	NR	NR	NR	NR	NR	Placenta accreta spectrum (PAS) disorders	NR	Expulsion/ curettage under ultrasound guidance	NR	NR

UAE, uterine arterial embolisation; MTX, methotrexate; NR, not reported; CS, caesarean section.

<sup>a</sup> Two patients were excluded due to conservative management without MTX.<sup>b</sup> One hundred and sixty-seven patients underwent various type of conservative management, but only data for two patients who were managed with a combination of uterine arterial embolisation and MTX were available.<sup>c</sup> Among 29 patients with placenta accreta spectrum (PAS) disorder, the implanted placenta remained partly/totally *in situ* in 26 cases. These 26 patients underwent conservative management including UAE (12 cases) and medications (MTX *n*=19; traditional Chinese medicine *n*=13; mifepristone *n*=11). Six patients received bilateral uterine arteries injections of MTX before embolisation with sponge particles. There is no detailed information on these six patients; however, this intervention was successful.

surgical team to diagnose and treat the complications as needed.

## Conflict of interest

The authors declare no conflict of interest.

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