

## Conservative Management of Placenta Accreta by Systemic Metho-trexate: Report of Two Cases and Review of the Literature

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### Abstract

**Objective:** Owing to the growing number of cesarean deliveries, the abnormally invasive placenta-tion so called placenta accreta rate is increasing. Placenta accreta is difficult to manage and traditionally resolved by cesarean hysterectomy after the birth due to the following massive hemorrhage. In recent years different conservative treatments leaving partially or totally the placenta in the uterine cavity have been reported in patients willing to preserve their fertility.

**Methods:** We reviewed literature data about conservative management of placenta accreta in the PubMed, Researchgate and Medline from 2007 to date. We included in the review the studies about the use of methotrexate (MTX) for conservative treatment of placenta accreta.

**Results:** We reported 2 literature reviews and 4 studies about the use of MTX in the management of placenta accreta and 2 unpublished cases treated in our Department. MTX is administered when it is not possible to remove totally or partly the placenta accreta in order to promote the cytolysis of the residual trophoblast. The schedule and outcome of the methotrexate use have not been established yet due to the paucity of literature data.

**Conclusions:** The role of MTX to improve both, the feasibility and success rate of conservative management and placental resorption needs further studies. Hemodynamic stability of patients and informed consent are prerequisites before starting MTX treatment. Vaginal bleeding and infections may complicate the conservative treatment and close surveillance is recommended by imaging techniques and laboratory parameters.

**Keywords:** Placenta accreta; Conservative treatment; Fertility preservation; Methotrexate

### Introduction

Placenta accreta is an abnormal implantation of the chorionic plate in the myometrium due to the absence of basal decidua and incomplete development of the fibrinoid layer. The incidence has increased from 1/7000 delivery to 1/2500 delivery due to the increasing rate of caesarean sections [1]. The pathogenesis is not clear but the most accepted theory is a defective decidualization following an abnormal vascularization after myometrium surgery [2]. The vast majority of women with placenta accreta have identifiable risk factors: non-Caucasian race, myometrium scar from previous uterine surgery, curettage, irradiation or endometrial ablation [3], placenta praevia [4], Asherman syndrome, uterine leiomyomas, uterine anomalies, advanced maternal age, multiparity, hypertensive disorders in pregnancy and smoking [4]; recently, cryopreserved embryo transfer has been proposed to be an additional risk factor for placenta accrete [5]. The morbidity can be dramatic including disorders associated with massive bleeding such as disseminated intravascular coagulation, multi-organ failure and even death [6]. A small proportion of women require hysterectomy to control the bleeding [7]. Massive hemorrhage may depend on the attempts of placental manual removal that opens up spiral vessels and sinuses [8]. In the past due to a frequent diagnosis at the time of delivery, the management of placenta accreta was total or subtotal abdominal hysterectomy in an emergency setting with an increased risk of blood loss and damage of surrounding tissues [9]. In recent year's different conservative treatment strategies leaving partially or totally the placenta in the uterine cavity have been reported if patient wants to preserve her fertility [10].

We report two cases of placenta accreta successfully managed by leaving placenta in situ followed by intramuscular MTX an anti-folate drug that affects the rapidly dividing cells such as trophoblastic [11].

### Materials and Methods

We reviewed literature data about conservative management of

placenta accrete in the PubMed, Research Gate and Medline database using the following terms: "placenta accreta", "conservative management of placenta accreta", "methotrexate and placenta accreta" and "fertility preservation and placenta accreta". The search was restricted to English language. Abstracts were excluded.

### Our Cases

We performed a retrospective study on patients with placenta accreta treated with conservative management from January 2013 to June 2015 in our Department. Demographic information's, clinical and obstetric history of patients were collected. We performed ultrasound (US) scan in both patients and Magnetic Resonance Imaging (MRI) in one for suspected placenta accreta in antenatal era. Plasmatic  $\beta$ -HCG levels were monitored to assess the success of conservative treatment. We considered successfully managed the patients when  $\beta$ -HCG was undetectable and US confirmed the empty uterine cavity.

### Results

A small number of patients treated by MTX are reported in literature. We identified 2 literature reviews about conservative management of placenta accreta: Gupta and Sinha reported four out

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of six cases of placenta accreta successfully managed with MTX from 1986 to 1994 [12]; Timmerman et al., reported 7 patients out of 22 with placenta accrete successfully treated with MTX from 1994 to 2007 [13]. We found only 4 studies from 2007 to date including 28 patients managed with MTX at different schedules of administration. Conservative treatment was successful in 26 of them and hysterectomy was performed only in 2 patients due to a sepsis (Table 1). Our two cases as well showed that MTX management is a conservative option for the hemodynamically stable patients with placenta accreta. In our department from January 2013 to June 2015 we treated 15 patients with placenta previa; in 4 of them the placenta was accreta and in 2 patients we performed a conservative approach after evaluation of specific risks.

### Case 1

A 34 years old, Caucasian women, G2/P0 at 36 weeks of gestation was recovered for preeclampsia in January 2014 in our Department of Obstetrics and Gynecology. The patient underwent dilatation and curettage (D&C) two years before due to a miscarriage at 8 weeks of pregnancy. At 32 weeks of pregnancy US scan revealed a posterior inserted placenta without signs of adherence. Due to an abnormal fetal heart rate monitoring we performed an emergency cesarean section at 37 weeks. Manual removal of all placental tissue was impossible and we diagnosed a presumed abnormally adherent placenta. Due to the absence of active uterine bleeding we left 50% of the placenta in the uterine cavity after cutting the cord at the placental insertion. Intra-operatively prophylactic antibiotic treatment with ampicillin was made. After closing the hysterotomy, the uterus was contracted and the patient hemodynamically stable. The patient had a strong desire for future fertility and we informed her and her relatives about the possible risks involved in this conservative approach. In order to promote the placental tissue involution, we carried out an additional treatment by a single dose of intramuscular MTX injection (50 mg/mq) two days after cesarean section. On the 5th postoperative day we observed a slight liver toxicity.  $\beta$ -HCG plasmatic levels decreased from 490 IU/ml on the day 1st post delivery to 49 IU/ml on day 5th. Five days after MTX administration, US scan showed a progressive reduction of placental surface taking shape of not vascularized at the color Doppler inhomogeneous area. Patient was discharged in good health on the 10th postoperative day. Outpatient management consisted in weekly monitoring of C-reactive protein, red blood cell count,  $\beta$ -HCG plasmatic levels and US scan. Three weeks later US showed a two-centimeter inhomogeneous area in the uterine cavity; plasmatic  $\beta$ -HCG levels were undetectable and liver

toxicity was completely resolved. On the 30th post-operative day, due to a vaginal bleeding patient underwent D&C under US guidance: the residual placental tissue was completely pulled out.

Six months later the patient became pregnant again and she vaginally delivered at 38 weeks of gestation.

### Case 2

A 38 years old, Caucasian women, G2/P1 at 33 weeks of gestation was recovered for vaginal bleeding in May 2014 in our Department. US scan suggested placenta accreta on the anterior uterine wall and three-dimensional power Doppler US detected irregular shaped lacunae within the placenta, thinning of myometrium overlying the placenta, loss of retroplacental “non-lucent line” and turbulent blood flow through the lacunae (Figure 1). We made the magnetic resonance imaging (MRI) to confirm the diagnosis of anterior placenta accreta (Figure 2). We started tocolysis to achieve the fetal lung maturity by steroids (betamethasone). At the same time we counseled the patient and her husband about the advantages and disadvantages of cesarean hysterectomy or conservative management. The patient chooses conservative treatment and agreed to carry on the follow-up monitoring in our center. Preoperatively the patient received a transfusion of 2 units of red blood cells because her plasmatic level of hemoglobin was 8.5 g/dl. Due to persistent vaginal bleeding cesarean section was planned and performed at 35 weeks. Prophylactic antibiotic treatment was started intra-operatively. Complete manual placental removal was impossible, confirming the diagnosis of placenta accreta and we were able to remove only the small “non-accreta” portion of the placenta so as to reduce the placental volume left in the uterus to about 70%. One dose of intramuscular MTX injection (50 mg/mq) as adjunctive treatment was given starting from the first day after cesarean section. The  $\beta$ -HCG plasmatic levels decreased from 2000 IU/ml on day 1st post delivery to 1200 IU/ml on day 7th. The US scan was performed to monitor involution and placental vascularity, which decreased over time. The patient was discharged on the 12th postoperative day. Outpatient management consisted in weekly monitoring of C-reactive protein, red blood cell count,  $\beta$ -HCG and human placental lactogen (hPL) plasmatic levels and US scan. The patient complained intermittent vaginal bleeding during 20 days and on day 23 she discharged whole placental tissue.  $\beta$ -HCG was undetectable on day 16th while hPL on day 20th. US confirmed the empty uterine cavity and no further complications were observed.

Author	Pts	Mode of delivery	Weeks	Mtx regimens	Doses	Complications	Placenta expulsion (days)	Fertility
Sentilhes et al. [31,40]	2	V CS	37 32	i.m. i.u.	1 1	Hysterectomy for sepsis and uterine necrosis maternal death for multi organ failure after c intraumbilical injection	23 126	---
Hunt et al, 2010	1	V	34	i.m.(75 mg)	1(4 <sup>th</sup> day)	Hysterectomy for endomyometritis, peritonitis and intestinal ileus	29	--
Khan et al. [24]	1	CS	36	i.m. (50 mg/week)	3	None	150	---
Lin et al. [30]	24	NS	28.1 (13-39)	i.m. (50 mg/m <sup>2</sup> )	Different schedules	Vaginal bleeding (25%), fever (25%)	15-62 (33.3% spontaneously, 45.8% curette) 30 (curette)	42.1%
Our data	2	CS CS	37 35	i.m. (50 mg/m <sup>2</sup> )	1(2 <sup>th</sup> day) 1 (1 <sup>st</sup> day)	Vaginal bleeding Vaginal bleeding	23	1

V: vaginal delivery; CS: cesarean section; i.m.: intramuscular; i.u.: intraumbilical cord; NS: not specified

Table 1: Conservative management of placenta accrete: review of literature.

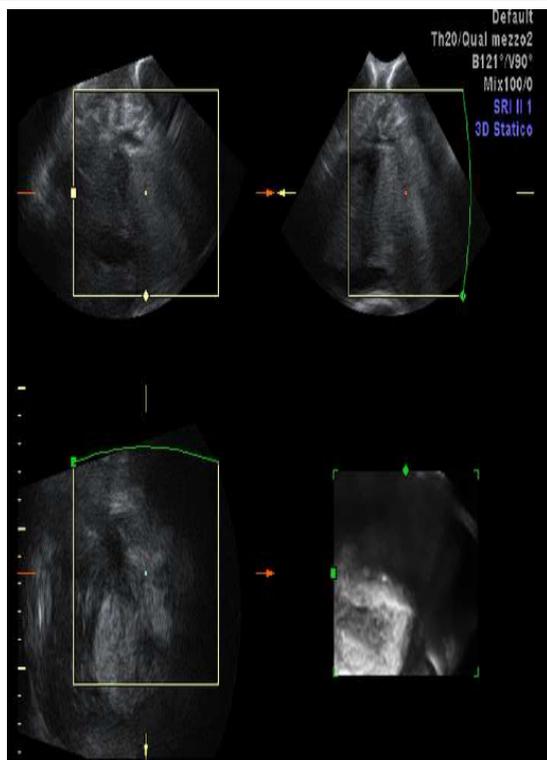


Figure 1: 3D US imaging of placenta accreta infiltrating into the anterior wall of the uterus.



Figure 2: Sagittal T2-weighted MRI of placenta accreta infiltrating into the anterior wall of the uterus: note the absence of the myometrium at the site of placental implantation, the nodular interface between the placenta and the uterus, and the dark intraplacental bands.

## Discussion

### Diagnosis

Antenatal imaging techniques can help to raise the suspicion

even if the definitive diagnosis can be made only at surgery [10]. In the setting of invasive trophoblastic processes US and MRI could be effective tools to evaluate placental invasion of the myometrium before delivery [14]. Warshak et al 2006 [15] reported that 3D power Doppler US have an high accuracy for diagnosis of placenta accreta with a sensivity of 77% and specificity of 96% while MRI has 88% and 100%. MRI has a further diagnostic value to assess posterior placenta accreta [16,17] if US findings are inconclusive [18]. MRI can identify bladder, lateral uterine wall and parametrial invasion by placenta accreta with a sensitivity of over 80% [6]. When US or MRI are used concomitantly on the same patients, the findings of the most aggressive diagnosis should be interpreted as correct and used in guiding management [19]. Pre-delivery diagnosis of placenta accreta is crucial because reduces maternal morbidity [20,21] and enables the multidisciplinary care team to plan the delivery in order to reduce the risks of intraoperative or postoperative complications [22]. Some studies have found an abnormal expression of some placental mRNA species in maternal blood from patients with placenta accreta. It has been suggested that the search of cell-free placental mRNA in maternal plasma could increase the accuracy of US and MRI in the detection of placental invasion [23].

### Counseling

The uterine preservation is a fertility-sparing option but feasible only in selected cases and patients should be informed about all treatment options and their possible consequences. Immediate hysterectomy can cause severe injuries to the pelvic organs [24]. Leaving placenta in the uterus causes risk of infections as endomyometritis or fever for tissue necrosis; persistent vaginal bleeding requires prolonged follow-up [13]. About 6% of women with persistent bleeding receive a hysterectomy [25].

### Different conservative approaches

Different strategies for conservative management of placenta accreta have been described in literature with different success rates [26]: mini invasive surgical treatments including uterine artery embolization [27], pelvic devascularisation [28], haemostatic sutures and balloon tamponed [29] and medical treatments by MTX administration [30]. All conservative managements have a favorable outcome in more than 90% of reported cases with a rate of maternal morbidity of 6% [31] but there are no randomized controlled trials comparing effectiveness of these different approaches.

### Methotrexate management

Arul Kumaran et al. first described medical treatment in 1986 by administering systemic MTX; the placental mass was expelled 11 days postnatally [32]. It has been hypothesized that MTX induce more rapid involution and placental necrosis. Otherwise lower rate of placental cell turnover at term and no further cell divisions after delivery has been reported and therefore MTX may be not helpful. However, vital placental tissue may be present even several weeks after a cesarean section [33]. Moreover some studies report little MTX effect on  $\beta$ -HCG levels and uterine vascular flow after at term delivery [34]. It should be noted that hemodynamic stability with minimal-to-moderate blood loss and informed consent are prerequisites before starting MTX treatment. Prior to and throughout MTX treatment, complete blood count, flogosis index, liver and renal function tests, should be monitored for early detection of toxicity such as myelosuppression and liver dysfunction. Several studies have reported expulsion of placenta tissue from 1 to 150 days following MTX treatment without major complications as hysterectomy [12,13,30]. There are no studies comparing MTX versus no MTX in the expectant treatment of placenta

accreta so that the role of MTX to improve the feasibility and success rate of conservative management and placental resorption needs further studies [30].

### Doses of MTX

There are no agreed-upon regimens of administration of MTX in the setting of placenta accreta and the better schedule has not been established yet. We obtained the resorption of placental tissue by low-dose of MTX administration without significant adverse effects like liver toxicity, myelosuppression, gastrointestinal complications and renal failure.

### Follow-up

Some Authors suggest that before, during and after MTX administration,  $\beta$ -HCG and hPL plasma levels should be serially measured together with clinical and US controls, in order to monitor response to therapy [35].  $\beta$ -HCG levels weekly are a surrogate marker for placental involution [36]; however, some studies have suggested that decreasing  $\beta$ -HCG levels do not correlate with placental involution [30]. Zepiridis et al., [35] found that hPL levels better than  $\beta$ -HCG correlate with placental perfusion on color Doppler. In their study hPL remained detectable until 7-10 days before expulsion of the placenta, while  $\beta$ -HCG levels fell to zero much earlier [35]. The RCOG guidelines specify US as the preferred imaging modality for follow-up in order to monitor the extent and vascularity of the residual placental tissue [37].

Utero-placental vascularization is a predictive factor for success of medical treatment with MTX. Measurement of the pulsatility index of the uterine arteries is a non-invasive method that has been proposed in the follow-up of conservative management as predictor of prognosis: an increased pulsatility index in the uterine arteries indicates a persisting utero-placental circulation [38,39]. Treatment failure due to vaginal bleeding is the most important complication of conservative management of placenta accreta requiring prolonged follow-up [13]. During hospitalization i.v. oxytocin administration should be given in order to control mild-to-moderate uterine bleeding; empirical antibiotic prophylaxis has been recommended although there is no consensus in the literature for its use [10].

### Fertility

Preservation of fertility with conservative approach of placenta accreta is fundamental end point. The first patient we reported had subsequent pregnancy after the conservative treatment of placenta accreta and she delivered at 38 weeks of pregnancy a healthy baby. Timmermans et al., identified 60 women treated with conservative management after diagnosis of abnormally invasive placentation. Conservative management was successful in 48 of them and subsequent pregnancies were reported in 8 women [13]. In a series of 96 patients who underwent conservative management for placenta accreta Senthiles et al reported 34 pregnancies and 21 infants born after 34 weeks of gestation. The mean time to conception was 17.3 months after treatment; however there was a 28.6% recurrence rate of placenta accreta [40]. In a retrospective study of twelve patients treated with hysteroscopic resection of retained placenta, 4 pregnancies occurred resulting in 1 ectopic pregnancy, 1 miscarriage and 2 deliveries [41].

### Conclusion

The major advantage of conservative management in patients with placenta accreta is the preservation of fertility while the disadvantage is the long length of follow-up required after delivery, as the risk of

bleeding remains until the placenta is completely involuted. Women willing to undertake this strategy should therefore be closely monitored and extensively counseled regarding the risks of vaginal bleeding and infections [29]. The paucity of literature data based on case reports and case series does not enable to set the optimal management and to define the success rate of methotrexate treatment in the conservative management of placenta accreta. The Steins Bishop et al systematic review reported in 17 patients receiving methotrexate therapy as conservative treatment of invasive placentation an hysterectomy rate of 6% whereas it was 18% after embolization of the uterine arteries and 19% in expectant management [42]. However, no conclusion about the effectiveness of methotrexate can be drawn comparing different conservative treatment modalities due to the lack of significant data. A prospective randomized study should be performed to investigate safety, efficacy and side effects of the several techniques. We recommend the use of all imaging techniques including the power color Doppler US and RMI to confirm diagnosis in order to plan both radical and conservative management.

The successful management of placenta accreta needs a multidisciplinary skilled care team including pelvic surgeons, maternal-fetal medicine specialists, blood bank team, anesthesia team and interventional radiologists in both mini invasive and radical surgical treatment. Regarding MTX use in the conservative management of placenta accreta we should remember that neither its effectiveness on placental vascularity after delivery nor superiority on the conservative management resulting from its additional use have been demonstrated so far.

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