



Full length article

Management of patients with placenta accreta spectrum disorders who underwent pregnancy terminations in the second trimester: A retrospective study



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ABSTRACT

Purpose: To analyse the management of patients with placenta accreta spectrum (PAS) disorders who underwent 2nd trimester pregnancy terminations.

Method: The records of patients with PAS disorders who underwent 2nd trimester pregnancy terminations were collected and analysed.

Results: Twenty-eight patients were included; 8 (28.6%) patients received prenatal diagnoses and 20 (71.4%) patients received postnatal diagnoses. In the prenatal diagnosis group, scheduling hysterotomy and placenta removal were performed in 5 patients with complete placenta previa and previous caesarean delivery without hysterectomy or postpartum haemorrhage, and medical termination was performed in 3 patients, 2 of whom retained the placenta in situ. In the postnatal diagnosis group, the placenta remained in situ in 11 patients, and in 13 (46.4%) patients overall, adjuvant treatments were applied to the patients, and the abnormally implanted placenta was passed 43.5 (range: 7–102) days after termination. A complication associated with the placenta left in situ included intrauterine infection in one case. Uterus preservation was achieved in all the patients.

Conclusions: For patients with PAS disorders with complete placenta previa and previous caesarean delivery, hysterotomy is a safe choice for terminating a 2nd trimester pregnancy. When it is impossible to manually remove the placenta, leaving the placenta in situ with the administration of adjuvant treatment is a good choice for uterus preservation.

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Introduction

Placenta accretaspectrum (PAS) disorders can be defined as abnormal partial or complete adhesions of the placenta to the uterine wall, owing to the firm attachment of the placental villi to the uterine wall, accompanied by a partial or complete lack of normal intervening basal decidua and a Nitabuch fibrinoid layer. Most commonly, the placenta is directly attached to the myometrium (placenta accreta vera or placenta adherent); otherwise, the placental villi may invade the myometrium (placenta increta) or even penetrate it (placenta percreta) [1].

The prevalence of placenta accreta during dilation and evacuation (D&E) in the second trimester was 0.04% in 1995,

similar to that in the third trimester as reported by Rashbaum [2]; the incidence was much higher (2.3%) in the study by Morotti and colleagues in 2012 [3].

The main risk associated with any form of PAS disorder is massive obstetric haemorrhage, which can lead to secondary complications such as coagulopathy, multisystem organ failure, and even death [4]. However, there are insufficient data on 2nd trimester pregnancy terminations in patients with PAS disorders in the literature. Specific patient management strategies have rarely been reported, and their safety and efficacy remains unevaluated. Therefore, the present study analysed 28 patients with PAS disorders who underwent pregnancy termination in the second trimester, with the aim of discussing patient management strategies and our experiences with the cases, as well as a review of the related literature.

Materials and methods

The medical records of all patients with PAS disorders who underwent pregnancy termination in the second trimester (from

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13 to 27 + 6 weeks of gestation) at Peking Union Medical College Hospital between January 2012 and December 2017 were collected and analysed. Written informed consent was provided by the participants.

A pathological diagnosis of PAS disorders with documentation of abnormal trophoblast invasion of the myometrium in each case is not always feasible [1]. Prenatal suspicion of a PAS disorder was based on the presence of high-risk factors related to this disease and imaging evidence (ultrasound and/or magnetic resonance imaging [MRI] findings) [5]. The identified risk factors include maternal parity and age, personal history of uterine surgery, placenta previa, previous operative delivery, previous placenta accreta and uterine anomalies [6]. Ultrasound features included signs of myometrial thinning, lacunar spaces, retroplacental clear space loss and/or an irregular bladder wall with increased vascularity. MRI features, which have a supplemental role in the diagnosis, include dark intraplacental bands, placental heterogeneity, placental or uterine bulging, focal interruption of the myometrium and/or uterine extension of the placenta [7]. In cases without classic risk factors or pregnancies complicated by limited prenatal care [8], PAS disorders may be diagnosed at the time of vaginal or caesarean delivery. Findings in the third trimester that should raise suspicion of undiagnosed accreta include continued vaginal bleeding, the inability to remove the placenta, or endometritis [9]. We made the final diagnosis according to the patients' clinical, surgical, and pathological characteristics. We enrolled patients with PAS disorders based on the following criteria: 1. Manual removal of the placenta was partially or totally impossible and there was no cleavage plane between all or part of the placenta and the uterus. 2. The patient received prenatal diagnosis of placenta accreta, confirmed by the failure to remove the placenta during the third stage of labour. 3. There was evidence of invasive placental tissue at the time of surgery. 4. PAS disorders were histologically confirmed in a hysterectomy specimen.

The primary outcome was uterus preservation, and the secondary outcome was complications associated with conservative management. The method of pregnancy termination in the second trimester included surgical and medical methods [10]. Specifically, rivanol and mifepristone combined with misoprostol were used as medical methods. Hysterotomy conducted through lower abdomen transverse incision and a transverse incision in the lower segment of uterus or the position avoiding the placenta edge was performed in patients with any of the following situations: a prenatal diagnosis of PAS disorders with total placenta previa and a previous caesarean delivery and severe complications preventing a vaginal delivery or life-threatening heavy haemorrhaging during the induction of labour. Hysterectomy was performed to preserve life in situations involving heavy haemorrhaging, uterine rupture, uncontrollable intrauterine infection or other life-threatening. For patients with a prenatal suspicion of PAS disorders, prophylactic uterine artery embolization (UAE) was performed prior to pregnancy termination in cases of severe haemorrhaging. Intra-uterine gauze tamponades and balloon occlusion catheters were used during hysterotomy to decrease blood loss. For patients with a high risk of placenta in situ for whom the manual removal of placental tissue during vaginal delivery failed, the extirpative technique, consisting of forcibly removing the placenta manually in an attempt to empty the uterus at delivery, was avoided because of the possibility of serious haemorrhaging or uterine rupture [11]. The placenta was retained in situ instead, and this procedure was considered one of the conservative management strategies, specifically, expectant management [11]. Expectant management was performed with the patient's consent, that the patient was closely monitored. To promote the resolution of the in situ placenta and reduce the risk of heavy haemorrhaging and infection, certain adjuvant treatments, including UAE, methotrexate (MTX)

chemotherapy and mifepristone, were performed or administered, followed by hysteroscopic resection of the retained tissue guided by ultrasound or laparoscopy. UAE was used to prevent massive haemorrhaging but prompted a progressive decrease in blood circulation within the uterus, parametrium, and placenta, potentially resulting in secondary necrosis of the villous tissue. Theoretically, the placenta should progressively detach itself from the uterus and the percreta villi of the adjacent pelvic organs. MTX chemotherapy (50 mg/kg) was administered intramuscularly, and beta-human chorionic gonadotropin [β -HCG] values were tested 1, 4, and 7 days after the injection. If the decrease of each change was less than 15%, the patient's response to MTX was considered insufficient, and another cycle of MTX was recommended with a one-week interval.

Patients were closely monitored during expectant management, and prophylactic intravenous or oral antibiotics were administered to prevent infection-related complications. Serum β -HCG levels, blood measurements, biochemical tests and infection markers (e.g., C-reactive protein (CRP) and procalcitonin (PCT)) were assessed regularly, and blood and vaginal secretion cultures were assessed when necessary. Sonographic examinations were performed every 2 weeks to evaluate blood flow between the implanted placenta and myometrium as well as the volume of the residual placenta. If the serum β -HCG values decreased to normal or near normal (less than 5 IU/l) and a significant reduction in the placenta volume was not observed 4 months after delivery, hysteroscopic resection guided by ultrasound or laparoscopy was performed to shorten the treatment period, stop irregular vaginal bleeding, promote menstruation recovery, and relieve the psychological burden in patients.

Data were entered and analysed in SPSS (IBM Corp, Armonk, NY, USA). The results are presented as the mean and the standard deviation for the quantitative variables and the number (percentages) for the qualitative variables.

Results

In this study, 28 patients with PAS disorders underwent 2nd trimester pregnancy terminations in our hospital. Two (7.14%) patients suffered spontaneous delivery with the placenta retained in the uterus. The compelling reasons for pregnancy termination in the remaining 26 patients included the following: a prenatal diagnosis of foetal malformation (6 patients, 21.4%), stillbirth or intrauterine foetal death (5 patients, 17.8%), inevitable abortion or premature rupture of membranes (6 patients, 21.4%), obstetric complications (3 patients, 10.9%), and voluntary legitimate pregnancy termination according to our national law (6 patients, 21.4%). A prenatal diagnosis was suspected in 8 patients (35.7%), all of whom had a uterine surgical operation history (8 patients with caesarean section and one patient with a uterine septum section), and 5 of them had complete placenta previa. The remaining 20 patients (71.4%) with PAS disorders were diagnosed after delivery of the foetus (1 patient through caesarean delivery). The median duration of follow-up was 32 months (range: 6–90 months).

The mean age of the patients was 30.64 years (range: 17–37 years). The average gestational week at pregnancy termination was 20.76 weeks (range: 27 + 6–13 + 5 weeks). The median gravidity was 2.54, including 5 nulliparous patients (17.9%). The most common risk factor was a previous curettage operation (57.1%), followed by a previous caesarean delivery (42.9%) and placenta previa (35.7%). The clinical and obstetric characteristics of the 28 patients are listed in Table 1.

In the prenatal diagnosis group, 2 patients (25%) underwent medical termination after prophylactic UAE. The foetus was delivered through the vagina successfully, and both the patients' placentas remained in situ. One (12.5%) patient suffered

Table 1
Clinical characteristics of the patients.

Clinical Characteristics	Mean/Median or Number	Range or Percentage
Age (years) (mean/range)	30.64 ± 4.18	17–37
Gestational age (weeks) (mean/ range)	20.76 ± 4.37	13.5–27.6
Gravidity (mean/ range)	2.54 ± 1.17	1–6
Parity (mean/ range)	0.61 ± 0.79	0–2
Prenatal diagnosis (n/percent)	8	28.6
Postnatal diagnosis (n/percent)	20	71.4
Risk factors (n/percent)		
Previous D&C	16	57.1
Previous CDs	12	42.9
Once	4	14.3
Twice	8	28.6
Placenta previa	10	35.7
Low-lying placenta	1	3.6
Marginal placenta previa	6	21.4
Total placenta previa	3	10.7
Myomectomy	1	3.6
Uterine malformation	3	10.7
Uterus septum	3	10.7

Abbreviation: D&C: dilation and curettage; CD: caesarean delivery; SD: standard deviation.

spontaneous abortion after a prenatal diagnosis and prophylactic UAE; the partly implanted placenta was manually removed, and the patient experienced a blood loss of 100 ml. A scheduling hysterotomy was performed in the remaining 5 patients in the group (62.5%) who had complete placenta previa and previous caesarean deliveries. Preoperative UAE was performed in all patients, and examination and double-J tube implantation were performed under cystoscopy for 3 patients whose ultrasound or MRI images showed possible invasion of the placenta into the bladder. After the foetuses were delivered during surgery, the placenta was resected with sutures and ligation. During hysterotomy, intrauterine gauze tamponades (2 cases) and balloon occlusion catheters (1 case) were used to prevent severe haemorrhaging; the blood loss in these three patients was 400, 800, and 600 ml, respectively. The management and outcomes of the patients are shown in Fig. 1.

In the postnatal diagnosis group, the placenta could not be spontaneously passed after the foetus was delivered in all 20 patients. After manual removal of the placenta failed, the abnormally implanted placenta remained partly or completely in situ in 11 patients with informed consent. Thus, a total of 13 (13/28, 46.4%) patients overall partially or completely retained the implanted placenta in situ. Adjuvant treatments, including UAE and medication, as well as hysteroscopic resection of the retained tissue, were administered alone or in combination to the 13 patients with a placenta in situ. Adjuvant treatment details are listed in Table 2.

UAE was performed in 10 (76.9%) patients in the perioperative period. MTX chemotherapy was administered to 4 (30.8%) patients, one of whom received a repeated cycle of MTX chemotherapy; mifepristone was administered to 2 (15.4%) patients. The residual placenta was spontaneously passed through the vagina in 8 (61.5%) patients. For the remaining 5 (38.5%) patients, hysteroscopic resection visualized by ultrasound or laparoscopy was performed to remove the residual placenta.

In the study, the uterus was preserved in all 28 patients. Among the 13 patients who underwent expectant management, one patient in the prenatal diagnosis group who underwent vaginal delivery and with a placenta in situ developed an intrauterine infection, with lower abdominal pain and evidence of leucocytosis and a positive vaginal secretion culture of *Escherichia coli* a month after delivery. The patient was treated with intravenous cephalosporin antibiotics for a week; she recovered with negative culture results and the disappearance of symptoms, and menstruation regained regularity 50 days later.

The average interval between the date of foetal delivery and the complete passing of the placenta was 43.5 days (range: 7–102 days). The time required for serum β -HCG values to decrease to a normal level was 39.3 days (range: 21–98 days). Regular menstruation resumed 2.1 (range: 1–3) months after foetal delivery.

Discussion

It is very important but difficult to treat second trimester PAS disorders successfully because of the difficulties in prenatal diagnosis and the patients' strong desire for future fertility. In our study, 28.6% of the patients with one or several risk factors were diagnosed with PAS disorders before pregnancy termination in the second trimester through initial ultrasound and MRI screening; all of these patients presented placenta previa and/or had undergone a previous caesarean delivery. For high-risk patients, MRI was often required when PAS disorders were suspected based on the initial ultrasound examination [12]. MRI has an accuracy advantage if PAS disorders are suspected in the posterior placenta or in patients with obesity [13], as MRI is highly accurate in assessing the depth of the placental invasion [14]; this can help clinicians determine management strategies. In our hospital, for patients with a prenatal diagnosis of PAS disorders, especially those with complete placenta previa and a previous caesarean delivery, hysterotomy and placenta removal via surgery was the preferred method of termination. In a recent systematic review and meta-analysis of the outcomes of placenta previa and accreta diagnosed prenatally in patients with a previous caesarean delivery, 208 of 232 (89.7%) patients had an elective or emergent caesarean hysterectomy [15]. During hysterectomy, placental removal is attempted if spontaneous partial separation occurs, and the accreta portion of the placenta is limited in depth and laterality [16]. However, as a result of a lack of randomized clinical trials, the optimal management of PAS disorders with a prenatal diagnosis remains unclear, and management is determined by the capacity to preoperatively diagnose invasive placentation, local expertise, and the depth of villous invasion [17].

A postnatal diagnosis can be made during both vaginal delivery and caesarean delivery. If the abnormally implanted placenta cannot be separated from the uterine wall, approach of leaving the placenta in situ may be a wise decision in patients with stable haemodynamics and no life-threatening bleeding [11]. However, leaving the placenta in situ is accompanied by the risk of pelvic infection, delayed haemorrhaging, secondary hysterectomy, and potential complications from adjuvant treatments. Therefore, close

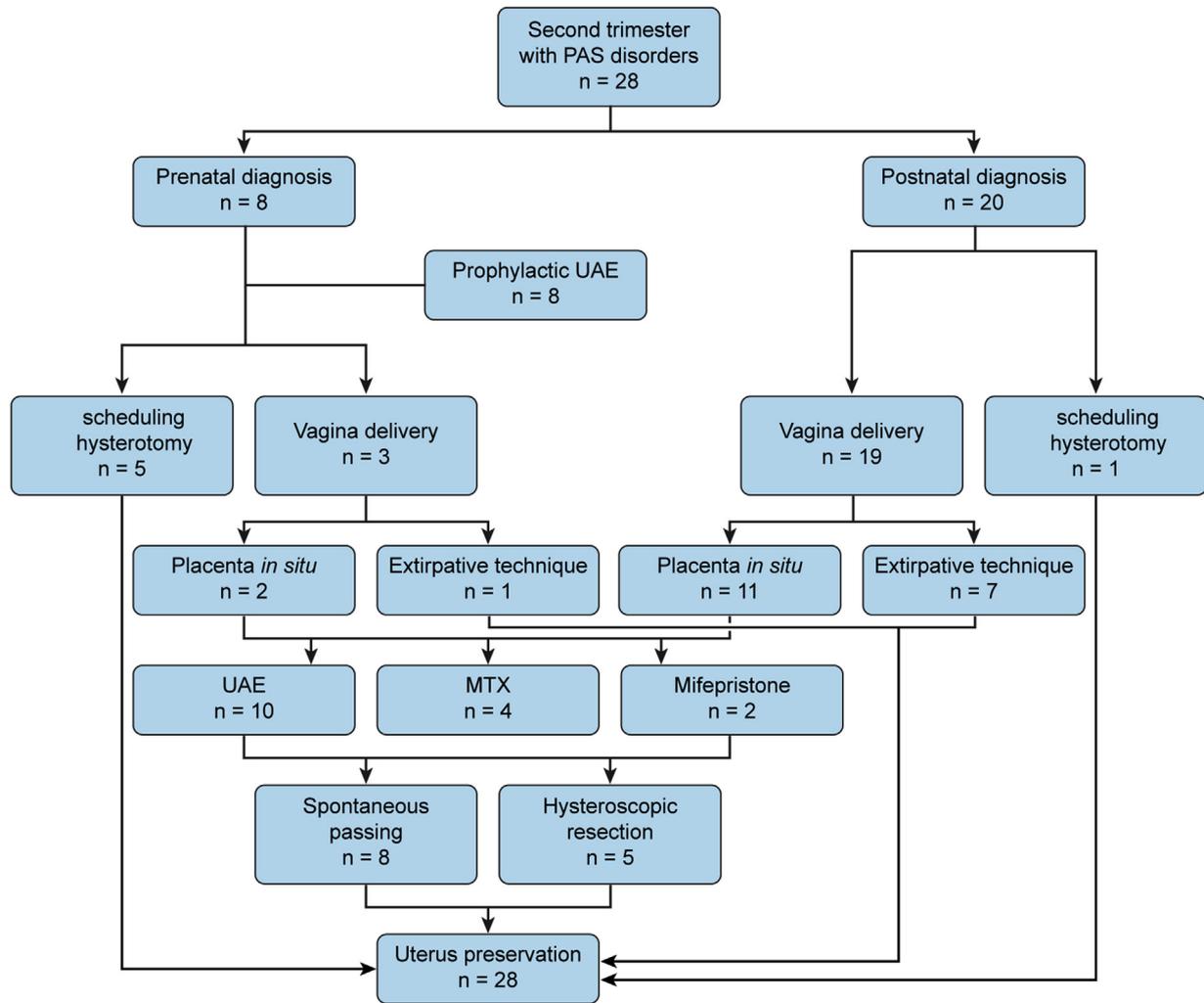


Fig. 1. Flow chart of the study.

Table 2
Details of the adjuvant treatments.

Adjuvant treatments	Number	Percentage
UAE	10	76.9
MTX chemotherapy	4	30.8
Mifepristone	2	15.4
Resection	5	38.5

UAE, uterine artery embolization; MTX, methotrexate.

surveillance, including various tests and imaging examinations, is necessary to detect complications. In our study, the placenta remained in situ in 13 patients, and only one patient developed an intrauterine infection.

UAE, MTX chemotherapy, mifepristone, and hysteroscopic resection of the retained placenta tissue under ultrasound or laparoscopic guidance were viable adjuvant treatments in the fertility-preserving approach in our study. A systematic review of uterine-preserving approaches indicated that UAE was a safe and effective treatment for preventing postpartum haemorrhaging caused by PAS disorders [18]. It was [19] reported that prophylactic UAE before placenta involution appeared to prevent postpartum haemorrhaging effectively during late gestation. In our study, prophylactic UAE was performed in 8 patients, and none of these patients suffered postpartum haemorrhaging. Based on our experience, prophylactic UAE before termination is a necessary

and effective procedure. In our study, MTX chemotherapy and mifepristone were used to promote the passing or degeneration of the retained placenta; some experts suggested that MTX therapy was effective against trophoblastic proliferation, which could be the case in our study too [20]. However, there is no unified recommended dosage and administration mode of MTX for PAS disorders, and dosages and administration modes varied widely in different studies [21]. Moreover, some studies and systematic reviews do not recommend the use of MTX chemotherapy for conservative management [22,23]. Because of its uncertain function and possible adverse effects, we could not form a definitive conclusion on its efficacy due to the small sample size; therefore, more evidence of its efficacy and safety is needed.

Serum β -HCG values that decreased to or close to the normal level and a reduced blood flow signal at the interface of the placenta and uterine wall in expectant management patients indicated the non-functioning of the placenta [24]. In these patients, it is recommended that hysteroscopic resection of the retained placenta tissue be performed under ultrasound or laparoscopic guidance [25]; resection was performed in 38.5% of patients in our study, and the operations went smoothly with minimal bleeding.

In conclusion, an accurate prenatal diagnosis, careful planning, and close communication are essential. Moreover, the creation of specialized surgical teams to execute a safe care plan for 2nd trimester pregnancy terminations in patients with PAS disorders is

essential. For patients with a high risk of PAS disorders, especially those with complete placenta previa and a previous caesarean delivery, hysterotomy is a safe choice to terminate the pregnancy in the second trimester. When it is impossible to manually remove the placenta partially or totally, leaving the placenta in situ is a good choice for uterus preservation, and multiple adjuvant treatments, either alone or in combination, may help to promote the passing or absorption of the abnormally implanted placenta under close monitoring.

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Compliance with ethical standards

i. Informed Consent: Written informed consent was provided by the participants.

ii. Ethical approval: The research protocol was approved by the Ethics Committee of Peking Union Medical College Hospital.

Author contribution

J Ou: Data collection, manuscript writing.

CY Li: Data analysis.

P Ping: Manuscript writing.

LR Teng: Planning and methodology development.

XY Liu: Protocol development, manuscript editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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