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Combination of Mifepristone and Methotrexate in Management of Placenta Increta: A Case Report and Literature Review

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Abstract

Background: The frequency of abnormal placentation was 1 in 731 deliveries in USA between 2008-2011. The rate of placenta increta was 14% of 138 abnormal placentation histologically confirmed which results from placental implantation caused by preexisting damage to endometrial-myometrial interface. Abnormal placentation confers a risk of severe postpartum bleeding, infection, hysterectomy. There is no robust evidence regarding the single best management strategy of abnormal placentation in the postpartum period.

Case Report: Here, we present a case of abnormal placentation diagnosed at the time of delivery when manual separation of the placenta yielded only a 60 × 20 × 20 mm fragment of placental tissue. A postpartum ultrasound confirmed the presence of placenta increta**.** The patient elected for conservative treatment with a combination of methotrexate and mifepristone, and the retained placental tissue was expelled five months later.

Conclusion: While the incidence of morbidly adherent placenta, including placenta percreta, is sure to increase in the years to come, there is no definitive evidence regarding the most optimal treatment. We present a case of a successfully managed placenta increta with methotrexate and mifepristone over a period of five months which resulted in placental regression and uterine preservation without significant complications.

Keyword: Placenta increta; Methotrexate; Mifepristone; Ultrasound

Key points

1. Abnormal placentation is not always visualized on prenatal ultrasounds and therefore may present unexpectedly at the time of delivery.
2. Combined administration of mifepristone and methotrexate may be used to treat placenta increta in stable patients.

Introduction

Abnormal placentation is a severe complication of pregnancy. The placenta accreta spectrum (PAS) is an umbrella term used to describe invasion of the placenta into the uterine wall secondary to defective decidualization. It is most commonly caused by preexisting injury to the endometrial-myometrial interface. In placenta accreta, the anchoring villi attach to the myometrium; in placenta increta, the villi invade into the myometrium; and in placenta percreta, the villi penetrate to or through the uterine serosa and may invade surrounding organs. Pooled data from two case series (comprising a total of 138 cases of abnormal placentation) indicate that the relative frequencies of each PAS subtype are 79% placenta accreta, 14% placenta increta, and 7% placenta percreta [1,2]. There are multiple management options for PAS, including placental resection, hysterectomy, and more conservative management modalities (such as expectant treatment, methotrexate), but evidence-based recommendations regarding the best treatment are lacking. Here, we report a case of placenta increta, successfully treated by a combination of methotrexate and mifepristone, which may represent a good alternative conservative management strategy for similar cases.

Case presentation

Consent for the reporting of this case was obtained from the patient. A 24-year-old woman, G9P0 (eight previous elective abortions for the unexpected pregnancy), presented to our hospital at 36 weeks and 2 days gestation with regular contractions (30"/5-6') and leakage of a small amount of vaginal fluid at 22: 40 on December 24th, 2017. She reported a sudden "gush" of clear to pale-yellow fluid from the vagina two hours prior to admission. The patient endorsed faint spotting but denied significant vaginal bleeding. On physical examination, amniotic fluid was observed draining from the cervical canal and pooling in the vaginal fornix. The patient had received routine prenatal care, including a screening ultrasound performed at seven weeks gestation, which identified an embryo measuring 30 × 16 × 12 mm, a 39 × 13 × 13 mm pool of fluid (suspected blood) in the uterus, heart beat invisible and suspected adherent uterine cavity. Prenatal history was also significant for elevated thyroid stimulating hormone (5.62 uIU/ml) detected at 14 weeks gestation, for which TSH was 5.62 uIU/ml at 14-week gestation and thyroxine therapy was administered initiated. At 25 weeks gestation, an oral glucose tolerance test detected impaired glucose metabolism, which the patient elected to control with dietary modification. Patient was diagnosed as gestational diabetes for OGTT was abnormal and offered diet control.

After two hours of labor, a 2.7 kg baby girl was delivered with Apgar scores of 10 and 10, at 1 and 5 minutes, respectively. Uterine contractions were strong and vaginal bleeding was not occult, however the placenta failed to spontaneously deliver within one hour. We attempted to manually extract the placenta but were only able to remove a 60 × 20 × 20 mm fragment of placenta tissue, with the majority of the organ morbidly adherent to the uterine wall. Estimated blood loss was 300 ml. A transabdominal ultrasound demonstrated retention of a 123 × 94 mm fragment of placenta with deep invasion of the uterine wall to within 2 mm of the serosa (Ultrasound 1). Potential postpartum complications (including severe hemorrhage necessitating blood transfusion) and possible interventions (both surgical and nonsurgical)

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were explained to the patient. Surgical options including hysterectomy and uterine artery embolism were suggested to prevent postpartum hemorrhage; however, the patient elected to pursue conservative, nonsurgical management.

The patient was treated with a single dose of intramuscular methotrexate (20 mg) and a 15-day course of oral mifepristone (50 mg daily), and the patient was closely monitored on an inpatient basis for the following week. Her serum β-human chorionic gonadotrophin (β-hCG) precipitously declined from 12,000 mIU/mL immediately after delivery to 3,848.59 mIU/mL at one week postpartum. Serial abdominal ultrasounds demonstrated no significant changes in the uterus (Ultrasound 2). Liver and renal function were assessed via blood test every three days (SGOT, SGPT, lactate dehydrogenase, total bilirubin, alkaline phosphatase, electrolytes, blood urea nitrogen, creatinine), and all values were within the normal range. Her complete blood count was also closely monitored, and a decline in her white blood cells from a baseline value of 12.49×10^9 cells/L to 1.87×10^9 cells/L was noted on the fifth day postpartum. She was treated with recombinant human granulocyte colony-stimulating factor, with successful recovery of her count. The patient was discharged and provided close surveillance, including weekly ultrasound examinations and serum β-hCG testing. The serum β-hCG decreased to normal levels by the second month postpartum.

Five months after delivery, the patient returned to the hospital with mild abdominal pain, vaginal bleeding, and discharge of soft tissue from the vagina. Microscopic examination of the expelled tissue confirmed it to be of placental origin and an ultrasound confirmed loss of the placenta from the uterus.

Discussion

During the prenatal examination, abdominal ultrasound has limitation of identify abnormal placentation. In a meta-analysis, sensitivity of lacunae which is multiple large, irregular intra-placental sonolucent spaces for identifying placenta accreta, increta, and percreta was about 75, 89, and 76 percent, respectively, and specificities were about 97, 98, and 99 percent, respectively [3]. Our case failed to be identified by ultrasound before delivery. We need pay attention to the patient with high risk of abnormal placenta, such as multiple C-sections and abortions. Despite decades of clinical experience and research, the appropriate management of abnormal placentation remains unclear. Although a range of management options are presented in the literature, insufficient data are available to identify the single best approach. In general, multidisciplinary team management and delivery in a tertiary care facility are associated with decreased rates of complications and improved outcomes [4,5]. Multidisciplinary teams may include maternal-fetal medicine specialists, neonatologists, anesthesiologists, interventional radiologists, blood bank directors, and nursing personnel. It is necessary to have a surgeon who is a gynecologist or general surgeon, or urologist, or vascular surgeon who have expertise in control of bleeding, bladder in the operating room resection, and/or isolation, partial resection of the ureters. A urologist, gynecologic oncologist, or urogynecologist may be consulted in cases of placenta percreta where there is expected invasion of the placenta into the bladder wall. Generally, a multidisciplinary team conference with all care participants is be scheduled at least two weeks before prior to the planed delivery the patient's anticipated delivery date to develop management plans for both the mother and infant make sure management plans implemented and all necessary preparations are completed. Some experts recommended elective delivery between 34 and 35 weeks of gestation in stable patients without vaginal bleeding or preterm labor [6-8]. However, most women with premature contractions (but without vaginal bleeding or rupture of membranes) remain stable through 36 weeks of gestation [9]. At our institution, the timing of delivery is individualized within this interval based on clinical symptoms, cervical length, obstetric history (particularly prior preterm birth), and the patient's distance from the medical center. This approach is supported by multiple studies [6-8] and is aligned with the Society for Maternal-Fetal Medicine's recommendation for delivery of stable patient with placenta accreta between 34 and 37 weeks of gestation. Amniocentesis to evaluate fetal pulmonary maturity is not recommended, as the results would not impact management. Antenatal corticosteroids are offered according to standard guidelines [10]. Although general anesthesia is most commonly performed, regional anesthesia (typically with continuous epidural) has been used successfully in scheduled deliveries [11]. However, the team should be prepared to convert to general anesthesia if necessary [12]. Postoperative care may be provided on either a general postpartum care unit or an intensive care unit, as medically necessary.

Management options can be broadly categorized into placental resection, hysterectomy, or conservative management with the placenta retained *in situ*. Multiple case reports recommend leaving the placenta *in situ* at the time of delivery with a planned interval hysterectomy later, with reported marked reduction in the rate of peri- and post-operative complications [13-16]. However, there is insufficient evidence to recommend a time interval after which hysterectomy should be performed. Local placental resection has also been presented as a conservative surgical alternative in cases of placenta percreta with bladder involvement; however, there have been significant postoperative complications of resection, including maternal death in up to 5% of cases [17]. Of note, the rates of urological complications in placenta percreta are decreased when urologists are involved preoperatively [18].

Studies regarding postsurgical complication rates following hysterectomy vary widely. A retrospective study by Shamshirsaz et al. (n = 66) found that 30% of cases treated with hysterectomy resulted in postsurgical complications, including hemorrhage (7.6%) and bladder injury (17%) [19]. Conversely, a prospective case series conducted by Camuzcuoglu et al. (n=58) reported bladder injury in only 6.9% of patients and hemorrhage requiring reoperation in only 1.7% of patients [16]. Yet almost one-third (29.3%) of patients required postsurgical transfusion with greater than four units of red blood cells [20]. Alternative surgical techniques to traditional Caesarean hysterectomy have been presented in several case studies, including iatrogenic cystotomy with resection of the affected bladder wall and subsequent bladder repair [21], subtotal hysterectomy with the invasive portion of placenta retained *in situ* [22], and retrograde Caesarean hysterectomy [23]. There is insufficient evidence to evaluate the comparative morbidities of these alternative surgical approaches, however, Caesarean hysterectomy in combination with arterial balloon tamponade has been shown to decrease intraoperative blood loss and transfusion requirements when compared to Caesarean hysterectomy alone [24]. A systematic review of greater than 60 studies examined the short-term outcomes of 434 patients with PAS managed without hysterectomy (i.e. expectant management, methotrexate therapy, uterine artery embolization, hemostatic sutures, arterial ligation, or arterial balloon tamponade) [25]. The review demonstrated that when the placenta was retained *in situ*, patients experienced a prolonged clinical course with significant risk of uterine loss. Data were not available for all outcomes in all studies, however, the rates of adverse outcomes were reported as follow: severe vaginal bleeding (53%), secondary hysterectomy (19%), sepsis (6%), and death (0.3%).

Conservative options include expectant management, methotrexate administration, uterine artery embolization, or a combination of these modalities. Conservative management offers the main advantages of controlling the risk of hemorrhage and other significant surgical morbidities at the time of delivery, along with preserving fertility. A review of over 400 cases of morbidly adherent placenta demonstrated that 85.7% of women were able to conceive following conservative management. The primary drawback to conservative management is the requirement for close surveillance, as severe complications such as secondary hemorrhage and severe infection (possibly requiring emergency hysterectomy) have been reported up to several months after delivery. A study by Clausen et. al found that among patients with conservatively treated placenta percreta, 61% of patients experienced at least one postoperative complication, compared to 12% of those treated with hysterectomy or placental resection (26). The most common complications were emergency hysterectomy (50%), hemorrhage (44%), sepsis (25%), and bladder damage (17%), occurring as late as nine months after delivery [26]. In a large study of long-term outcomes among 167 women with placenta accreta treated conservatively, 78% of women ultimately retained their uterus, but 11% required hysterectomy within 24 hours of delivery due to massive hemorrhage, and another 11% underwent delayed hysterectomy due to complications (median 39 days postpartum; range 9 to 105 days postpartum) [27]. Complications necessitating delayed hysterectomy included sepsis, vesicouterine fistula, and uterine necrosis. Among women who retained their uterus, placental resorption was monitored on follow-up at a median of 13.5 weeks. Although 75% either resorbed or expelled the placenta without physician intervention, 25% of the women underwent hysteroscopy, curettage, or both to remove retained placental tissue at a median of 20 weeks postpartum.

A potential conservative management strategy to minimize postpartum hemorrhage in patients with suspected PAS is the balloon catheter. Although many small case series and case reports utilizing balloon catheters have reported significantly reduced blood loss, decreased need for blood transfusion, and shorter duration of surgery [28-35], other small randomized trials have not demonstrated significant benefit [29-31]. The value of balloon catheters remains controversial, and it is not possible to predict which patients are most likely to benefit from this adjunct; additional data is needed for a definitive assessment. Uterine artery embolization is another common conservative strategy to treat postpartum hemorrhage of various etiologies, including PAS; however, 18–62% of patients may still require secondary hysterectomy [25,36-38]. So, further studies are needed to assess the advantage of balloon catheter and uterine artery embolization.

Conclusion

Management with methotrexate has been described in several small case series and case reports, with consequences ranging from successful placental resorption/expulsion without any complications [39-42] to severe complications including hemorrhage, coagulopathy, and need for secondary hysterectomy [43-49]. For cases treated successfully with expectant management alone, time to complete resorption or expulsion of the retained placental tissue ranges from eight months to three years postpartum [50,51]. Here, we report the first successful treatment of placenta increta with a combination of methotrexate and mifepristone. Methotrexate is a potent antimetabolite, with mechanisms of action that include inhibition of trophoblast cells, reduction of placental neovascularization, and attenuation of placental growth factors [52]. Mifepristone blockade of progesterone receptors directly causes endometrial decidual degeneration. We added mifepristone to strengthen the efficacy. Of note, the patient was compliant with our strict clinical surveillance and did not experience any of the aforementioned complications from her conservative therapy. Further cases are needed to evaluate the efficacy of this approach.

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