Partial placenta increta and methotrexate therapy: three case reports

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Summary

The term placenta accreta is used to describe any placental implantation in which there is abnormally firm adherence to the uterine wall. This condition complicates 1/2,500 deliveries and is rising in incidence. Abnormal placentation is associated with increased maternal morbidity and mortality from severe hemorrhage, uterine perforation, infection and loss of fertility. The reported experience of methotrexate treatment in the conservative management of placenta accreta is scant. Three cases of partial placenta increta managed with methotrexate are described. The patients were assessed with clinical surveillance, serum β human chorionic gonadotrophin (β-hCG) and imaging (ultrasonography and magnetic resonance in one case). In all cases conservative management with methotrexate resulted in undetectable serum β-hCG, a decrease in the size of partial placenta retained, and undetectable vascularization.

Key words: Placenta accreta; Conservative management; Methotrexate.

Introduction

The term placenta accreta is used to describe any placental implantation in which there is abnormally firm adherence to the uterine wall. There are three varieties of placenta accreta: placenta accreta vera if chorionic villi are attached to the myometrium; placenta increta in which the chorionic villi invade the myometrium; placenta percreta in which the whole thickness of the myometrium is invaded to the serosal surface with possibility of rupture into the peritoneal cavity. The abnormal adherence may involve all, a few or a single cotyledone (total, partial and focal). The condition complicates 1/2,500 deliveries and is rising in incidence. Associated risk factors include manual removal of placenta at a previous birth, vigorous and repeated curettage, presence of submucous fibroids, placenta previa, pregnancy in the uterine diverticulum and previous cesarean section scar. Abnormal placentation is associated with increased maternal morbidity and mortality from severe hemorrhage, uterine perforation, infection, and loss of fertility.

The reported experience of methotrexate treatment in the conservative management of placenta accreta is scant, based on few reported cases. Three cases of partial placenta increta managed with methotrexate are presented. The patients were followed-up with clinical surveillance, serum β-hCG and imaging (ultrasonography and magnetic resonance in one case). In all cases conservative management with methotrexate resulted in undetectable serum β-hCG, a decrease in the size of partial placenta retained, and undetectable vascularization.

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Case Reports

Case 1

A 27-year-old woman was admitted to the delivery ward in premature labor at 26 weeks and five days of gestation. She had had a previous termination of pregnancy at 14 weeks with curettage, and there was no significant previous medical history. Two antenatal ultrasound (US) examinations showed a healthy fetus and an anterior fundal placenta.

Cesarean section under epidural analgesia was performed because of breech presentation, and a male preterm infant, weighing 970 g was delivered. The placenta was retained and an examination in the operating room during surgery through the uterine incision confirmed that a portion of the placenta was firmly adherent to the right horn of the uterus, which was left there. During surgery there was heavy bleeding that was controlled with intravenous oxytocine, and a transfusion of two units of blood (hemoglobin 7.6 g/dl). The patient consented to be treated with 70 mg of methotrexate (50 mg/m^2) intramuscularly at first and eight days postpartum. On the 8th postpartum day Doppler US showed that the placental mass was in the right horn of the uterus, invading the myometrium, with increased vascularity and measuring 50 x 45 mm. The patient remained well and serum β-hCG was undetectable on postpartum day 17. The following Doppler US on postpartum day 24 showed no vascularity and a slight decrease in the placental mass (49 x 42 mm) (Figure 1). Five months postpartum, a further US showed that the mass measured 33 x 21 mm (Figure 2). Eight months following delivery, the patient had a normal pelvic ultrasound (Figure 3).

Case 2

A 33-year-old woman was admitted at 22 weeks of gestation because of ruptured membranes. She had a previous termination of pregnancy at seven weeks without curettage, and there was no significant previous medical history. She progressed quickly to full dilatation, and after fetal expulsion the placenta was retained and an attempt to remove all placental tissue manually was unsuccessful, so she was submitted to curettage under US control. Doppler US confirmed a portion of retained placenta in

the right horn, measuring 40 x 40 mm, up to 8 mm from the serosa. Because the uterus was well contracted, and there was no active bleeding, the procedure was finished and intravenous oxytocine, antibiotics and rectal misoprostol were administered. On postpartum day 4, 70 mg of methotrexate (50 mg/m^2) intramuscularly were given (after consent). On postpartum day 9, Doppler US showed that the placental mass was in the right horn of the uterus, invading the myometrium, with increased vascularity and measuring 33.3 x 32.8 mm (Figures 4 and 5). The patient remained well and serum β-hCG was undetectable on the 23rd postpartum day. A follow-up Doppler US one month after delivery still showed vascularity but a decrease in the placental mass (25.6 x 23.1 mm). Two months later, the mass measured 20 x 20 mm and vascularity was undetectable. Eleven months following delivery an US revealed a calcified mass of 15 x 9 mm (Figure 6). The patient feels well, menses are regular and with normal flow, and she plans future pregnancies.

Case 3

A 37-year-old woman was admitted at 32 weeks of gestation because of ruptured membranes. She had had two previous terminations of pregnancy with curettage, and a previous cesarean section because of face presentation. At 34 weeks, because of breech presentation, an elective cesarean section was performed under epidural analgesia with the delivery of a preterm male infant, weighing 2,280 g. The placenta was partially removed and an examination in the operating room during surgery, through the uterine incision, confirmed that a portion of the placenta was firmly adherent to the left horn of the uterus. Because there was not any substantial bleeding and the uterus was well contracted, the patient was treated with intravenous oxytocine, rectal misoprostol and antibiotics. Doppler ultrasound on postpartum day 4 confirmed a portion of retained placenta in the left horn, measuring 69 x 50 mm up to the serosa, with increased vascularity (Figure 7). She consented to two administrations of 82 mg of methotrexate (50 mg/m^2) intramuscularly on that same day and on the 11th postpartum day. MRI was performed on the 13th day after delivery to exclude placenta percreta. The images showed an enlarged uterus with a portion of placental tissue, but with no evidence of placenta percreta (Figure 8). The patient had no abnormal bleeding and serum β-hCG was undetectable 27 days after delivery. A follow-up Doppler US one month postpartum showed undetectable vascularity and a decrease in the placental mass (37 x 36 mm). Three months later the mass measured 24 x 22 mm (Figure 9). The patient is feeling well and does not plan any future pregnancies.

Discussion

Placenta accreta is a rare condition associated with considerable maternal morbidity and mortality. The classic review of Fox [1] in 1972 suggested a hysterectomy in women with placenta accreta to avoid serious complications. In an attempt to preserve childbearing function, a conservative mode of treatment with methotrexate has been described in a few cases. Arulkumaran *et al*. [2] in 1986 first reported the successful treatment of placenta accreta with methotrexate. They used 250 mg of intravenous methotrexate (5 doses on alternate days from postpartum day 1); expulsion of a necrotic placenta occurred on the 11th day of treatment. In 1990, Hwang JL *et al.* [3] described an unsuccessful case of conservative management of placenta increta. They used three doses of methotrexate (not mentioning the dose and route of administration) which required hysterectomy because of persistent vaginal bleeding. Raziel *et al.* [4] reported a case of placenta accreta treated with two doses of 20 mg of methotrexate IM, on the fourth and fifth postpartum day, which resulted in expulsion of a necrotic placenta on postpartum day 7. In the report by Legro *et al.* [5], in a case of placenta percreta they used ten doses (1 mg/kg per week) of intramuscular methotrexate, and the outcome was a slow involution of placenta over five to six months postpartum. In the same year Jaffe *et al*. [6] reported a case of correct antenatal diagnosis of placenta percreta invading the bladder wall. Their patient underwent cesarean section and the placenta was left in situ. She had 50 mg of methotrexate/week for six weeks (route of administration not specified). Because of vaginal bleeding a hysterectomy with partial cystectomy and ureteric reimplantantation was necessary. More recently four more articles with case reports have been published. Buckshee *et al.* [7] presented a case of placenta accreta treated with 50 mg of intravenous methotrexate (3 doses) with expulsion of placental tissue on the 18th postpartum day. In 2000 Mussali *et al.* [8] presented three cases of placenta accreta treated with methotrexate which resulted in uterine preservation in two of the cases. Panoskaltsis *et al*. [9] in the same year presented two cases of placenta increta, one treated expectantly and the other with methotrexate; neither required hysterectomy. Nijman *et al.* [10] reported a case of placenta percreta treated successfully with conservative management with methotrexate IM weekly (1 mg/kg) in a total dose of 240 mg.

Based on the few reported cases and our three recent cases it has been demonstrated that conservative treatment of placenta accreta can be successful. In our three cases, we did not leave the entire placenta *in situ;* a portion of the placenta was manually removed and we left *in situ* just a portion of placenta (partial increta placenta). We decided to start treatment with methotrexate because of persistent partially retained placenta with continuing active vascularity. The route of administration was intramuscular and the dose used was the same that we use for ectopic pregnancy (50 mg/m^2). It unknown whether a successful outcome has any relation to the amount of retained tissue, degree of placenta accreta, the dose used or other factors. The patients were followed-up with clinical surveillance, serum β-hCG and imaging.

As methotrexate is a potentially toxic drug, frequent blood counts, liver and renal function tests are required. In all cases conservative management with methotrexate resulted in undetectable serum β-hCG, a decrease in the size of partial placenta retained, and undetectable vascularization.

Conclusions

The three presented cases demonstrate that conservative treatment of persistent partial increta placenta can be successful. Although methotrexate causes a rapid involution of the placenta, there is not enough evidence to

Fig. 1

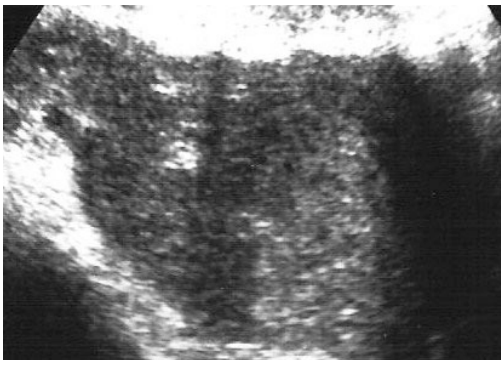


Fig. 2

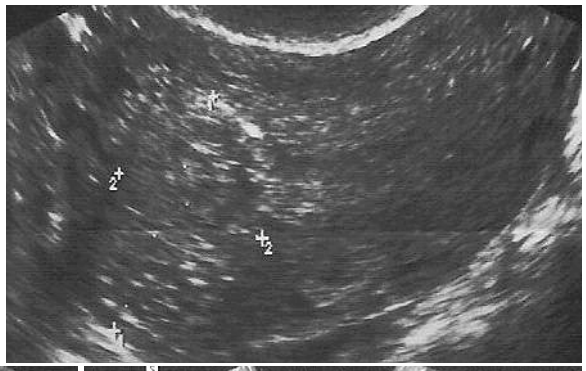


Fig. 3

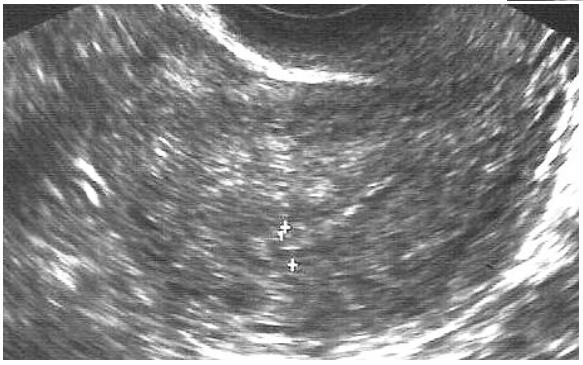
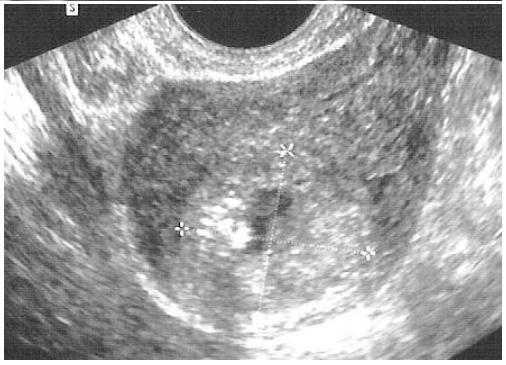


Fig. 4



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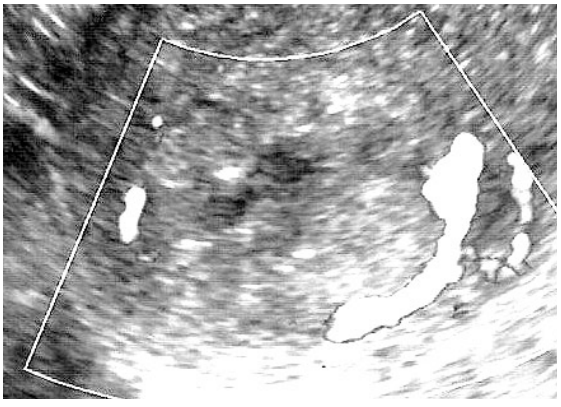


Fig. 6

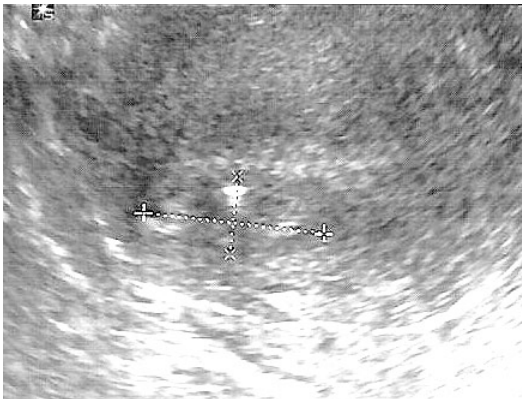
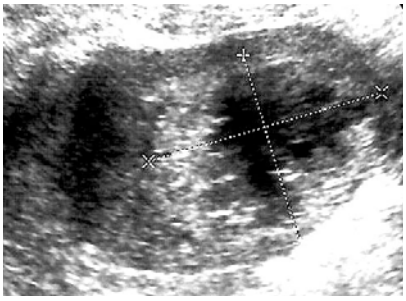


Fig. 7



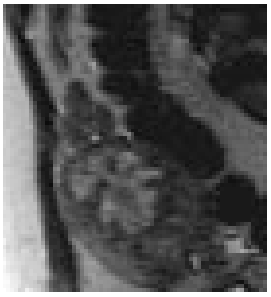


Fig. 9

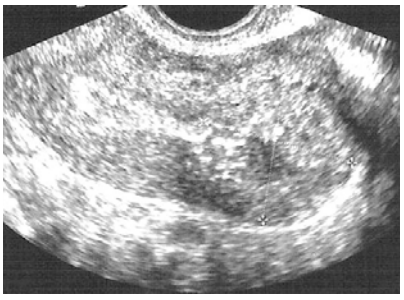


Fig. 8

Figure 1. — Doppler US on the 24th postpartum day showing no vascularity and a slight decrease in the placental mass (49 x 42 mm).
Figure 2. — Five months postpartum US showing that the mass measured 33 x 21 mm.
Figure 3. — Eight months following delivery a normal pelvic US can be seen.
Figure 4. — Doppler US on the 9th postpartum day showing that the placental mass was in the right horn of the uterus, invading the myometrium and measuring 33.3 x 32.8 mm.
Figure 5. — Doppler US on the 9th postpartum day showing increased vascularity.
Figure 6. — Eleven months following delivery US revealed a calcified mass of 15 x 9 mm.
Figure 7. — Doppler US on the 4th postpartum day confirmed a portion of retained placenta in the left horn, measuring 69 x 50 mm up to the serosa, with increased vascularity.
Figure 8. — MRI images showing an enlarged uterus with a portion of placental tissue, but excluding percreta placenta.
Figure 9. — Four months postpartum a US showing that the mass measured 24 x 22 mm.

suggest its routine administration in all cases of placenta accreta, especially considering its cytotoxicity. It should probably be reserved for cases of placenta percreta or when there is continuing active vascularity associated with persistent serum β-hCG levels.

Unless a life threatening hemorrhage occurs, a conservative approach is recommended even in women who do not want to preserve their fertility, considering the morbidity associated with cesarean hysterectomy. The utility of methotrexate treatment in the conservative management of placenta accreta requires further evaluation, and there is need for an agreement on a standardized protocol.

References

[1] Fox H.: "Placenta accreta 1946-1969". *Obstet. Gynecol. Surv.*, 1972, *27*, 475.

[2] Arulkumaran S., Ng C.S.A., Ingemarsson I., Ratnam S.S.: "Medical treatment of placenta accreta with methotrexate". Acta Obstet. Gynecol. Sand., 1986, *65*, 285.

[3] Hwang J.L., Huang S.C., Su I.J., Hsieh C.Y., Ouyang P.C.: "Placenta accreta in the second trimester of pregnancy: report of a case". *Taiwan I Hsuesh Huit Tsa chih.,* 1990, *89*, 1103.

[4] Raziel A., Golan A., Ariely S., Herman A.: "Repeated ultrasonography and intramuscular methotrexate in the conservative management of residual adherent placenta". *J. Clin. Ultrasound,* 1992, *20*, 288.

[5] Legro R.S., Price F.V., Hill L.M., Caritis S.N.: "Nonsurgical management of placenta percreta: a case report". *Obstet. Gynecol.,* 1994, *83*, 847.

[6] Jaffe R., DuBeshter B., Sherer D.M., Thompsom E.A., Woods J.R.: "Failure of methotrexate treatment for term placenta percreta". *Am. J. Obstet. Gynecol.,* 1994, *171*, 558.

[7] Buckshee K., Dadhwal V.: "Medical management of placenta accreta". *Int. J. Obstet. Gynaecol.,* 1997, *59*, 47.

[8] Mussalli G.M., Shah J., Berck D.J., Elimian A., Tejani N., Manning F.A.: "Placenta accreta and Methotrexate therapy: Three case reports". *J. Perinatol.,* 2000, *5*, 331.

[9] Panoskaltsis T., Ascarelli A., Souza N., Sims C., Edmonds K.: "Placenta increta: evaluation of radiological investigations and therapeutic options of conservative management". *Brit. J. Obstet. Gynecol.,* 2000, *107*, 802.

[10] Nijman G.W.R., Mantingh A., Aarnoudse J.: "Persistent retained placenta percreta: Methotrexate treatment and Doppler flow characteristics". *Int. J. Obstet. Gynaecol.,* 2002, *109*, 587.

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