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Mifepristone and Misoprostol for the Management of Placenta Accreta: an Alternative Approach

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INTRODUCTION

The incidence of morbidly adherent placentas has increased ten-fold in the past 50 years, currently occurring at a frequency of 1 per 1000–2500 deliveries[1,2]. It is contributing to a large proportion of postpartum hemorrhages (PPH) and has led to some maternal mortalities and several surgical interventions.

Current management of morbidly adherent placentas – accreta, increta and especially percreta – reportedly result in a maternal mortality rate of up to 7%, and extensive morbidity due to massive hemorrhage, blood transfusions, infection, ureteral damage and fistula formation[3–5]. In developing countries, adherent placenta contributed to 13% of maternal deaths[6].

Traditionally there was a tendency to ensure complete removal of the placental tissue after the delivery to avoid the risk of PPH. This led to a high risk of intervention that sometimes was associated with higher morbidity. In reality, management of adherent placenta should be altered according to the cause of failed delivery of placenta and whether it is associated with PPH.

Several options have been developed over recent years for the management of placenta accreta with limited success rates[7–16]. Recently, the combination of mifepristone/misoprostol was introduced for the treatment of placenta accreta. Both drugs were used over several years for the management of termination of pregnancy with a high success rate to reach complete expulsion of products of conception.

MIFEPRISTONE

Mifepristone is a synthetic steroid compound that is a progesterone antagonist. It also has an anti-implantation effect in early gestation. It causes decidual necrosis which leads to placental detachment. It also increases uterine contractility, softens the cervix and encourages cervical dilatation as well as sensitizes the myometrium to respond to natural or externally administered prostaglandin. It was used successfully in the termination of pregnancy in the first and second trimester, and has been gradually introduced for the induction of labor in the third trimester. Its side-effects are minimal including nausea, vomiting, diarrhea, dizziness, fatigue and fever. Pelvic inflammatory disease (PID) is a very rare but serious complication[17]. Mifepristone's success rate in achieving a complete miscarriage varies around 88% and is sometimes associated with excessive bleeding and incomplete termination of pregnancy requiring further intervention.

MISOPROSTOL

Prostaglandin E1 analogue 'misoprostol' was developed to promote healing of gastric and duodenal ulcers. It soon became apparent that it stimulates uterine contractions[18]. Misoprostol, binds to myometrial cells to cause strong myometrial contractions leading to expulsion of tissue. It also causes cervical ripening with softening and dilatation of the cervix. It has been used successfully to treat uterine atony and hemorrhage in the third stage of labor. As it does not need to be stored refrigerated, it replaced oxytocin for the management of third stage of labor in developing countries and remote areas (see Chapter 15), it was then introduced for the management of PPH in developed countries[19,20] (see Chapter 32). When given in the postpartum period, it is known to cause only minimal side-effects, such as mild shivering and pyrexia. It has been used for induction of labor and induction of abortion[18,20–22].

Misoprostol can be administered orally, sublingually, vaginally or rectally[21]. Oral and sublingual misoprostol are faster and more practical than rectal administration[23,24]. Vaginal and oral misoprostol are of similar efficacy; however, vaginal application has been found to have lower gastrointestinal side-effects, while the oral route was preferred by women[25,26].

Misoprostol alone has been used for the management of adherent placenta with a limited success rate, although it is effective with the added benefit of decreased blood loss.

THE USE OF MIFEPRISTONE/MISOPROSTOL IN THE MANAGEMENT OF PLACENTA ACCRETA AND COMPARISON WITH OTHER TREATMENTS

It was expected that the combination of both drugs would significantly potentiate the success rate for the treatment of placenta accreta in parallel to the increase in the success rate of complete miscarriage from 88% to 96% when mifepristone was used as a pre-treatment to misoprostol[27–31]. Maximum effect of this regimen is achieved when misoprostol is administered 36–48 h after mifepristone. The choice of doses and best regimen has been debated as has the route of administration. The manufacturer recommends a dose of 600 mg of mifepristone prior to prostaglandin administration[32]. However, evidence from a randomized trial indicates that a dose of 200 mg has similar efficacy when compared with 400 mg or 600 mg[33].

When the above regimen is followed 36–48 h later, by a maximum of five doses of misoprostol 400 μg administered at 3 hourly intervals, vaginally or orally, completed abortions were achieved in 94.6% of pregnancies between 9 and 13 weeks and in nearly 91% of mid-trimester medical abortion[34,35].

The insight to use mifepristone and misoprostol in the management of placenta accreta followed on from the high success rate of this regimen to induce a complete abortion. The dose of the medications in such a specific indication has not been established due to the small number of cases treated. However, the safety of this combination has been established in several studies examining termination of pregnancy[36]. Due to the minimally reported possible side-effects, the choice of such a regimen will establish its place rapidly as a safer alternative for the management of placenta accreta[37]. The use of the mifepristone and misoprostol regimen in the management of placenta accreta has been reported in the literature in only two cases both of which resulted in expulsion of the placenta. In both instances manual removal of placenta was attempted and failed to remove any part of the placenta and a postpartum magnetic resonance imaging (MRI) and ultrasound scan established the diagnosis of placenta accreta. However, the timing and dosage of the medication varied between the two.

An attempt to avoid the complications of expectant management and close monitoring led to the first use of mifepristone/misoprostol combination for expulsion of the placenta 15 weeks after delivery. This combination was chosen instead of methotrexate due to the limited success rate and high risk of complications in the latter.

When compared with methotrexate, the mifepristone/misoprostol combination was preferred, as methotrexate has limited success in the treatment of placenta accreta with spontaneous loss of placental tissues occurring in 26% of cases. Furthermore, case reports have shown that intramuscular methotrexate may not have shortened the duration of management treatment from delivery till resorption of placenta. In all 13% of women had complications such as delayed hemorrhage, infection as well as added possible side-effects of vomiting, alopecia and bone marrow suppression, renal or hepatic impairment; and fatality has been reported[38,39]. Furthermore, in one case the human chorionic gonadotropin levels returned to normal, but the placenta was still attached; this raised more doubt about the success of methotrexate.

In the second case report, the expectant management also had to be abandoned within a few days of the delivery. The patient was developing severe infection and a rapid delivery of the placenta was needed. A dose of mifepristone 600 mg was given and 40 hours later, the placenta was expelled with minimal bleeding prior to the start of the misoprostol regimen[37].

As the mother showed severe signs of infection, surgical options – mainly hysterectomy or more recently myometrial resection – were the only other alternatives[40]. Again medical treatment with the combination of mifepristone/misoprostol compares favorably as a result of the high risk of complications with surgical options and the desire of the mother to preserve her fertility. Only 68 patients with anterior placenta accreta were included in a trial of myometrial resection and uterine repair, and in 18 patients hysterectomies had to be performed[40]. Furthermore, there were a large number of serious reported complications including pelvic hemorrhage, coagulopathies, uterine infection, low ureteral ligations, iatrogenic foreign bodies and collection[40]. Future fertility has only been recorded in 20% of those who had their uterus conserved.

The incidence of peripartum hysterectomy is approximately 1 in 2000 deliveries[41]. Emergency hysterectomy should be reserved only for the treatment of placenta accreta if associated with uncontrollable bleeding due to the associated high maternal morbidity and mortality from hemorrhage, blood transfusion, disseminated intravascular coagulopathy, infection and potential injury to the adjacent lower urinary tract[42–44].

THE POSSIBLE ROLE OF THE MIFEPRISTONE/ MISOPROSTOL REGIMEN IN THE MANAGEMENT OF PLACENTA ACCRETA

Following these successful experiences in our unit, further patients of different gestations were treated with the combination of mifepristone/ misoprostol within a few hours of delivery after failed attempts at manual removal of placenta. In our practice, we offer ultrasound evaluation after delivery which is usually beneficial in assessing placental separation, possibly avoiding intervention especially if the mother has not had any regional analgesia. An attempt at manual removal of the placenta is made if the placenta is adherent; however, the obstetrician should be aware of the other management options available and try to avoid aggressive piece meal removal of the placenta especially if no separation plane can be identified. The regimen of mifepristone 600 mg followed by 200 μg

of misoprostol orally at 3 hourly intervals to a maximum of five doses has been used to expel placenta accreta after confirmation of the diagnosis by MRI.

The treatment has been successful in all conditions; however, in one patient vaginal bleeding followed 1 week after completion of treatment and expulsion of the placenta. The bleeding led to hospital admission but did not necessitate any medical intervention. Such a treatment regimen has to be weighed against alternative treatment options.

Advantages of mifepristone/misoprostol regimen

Nearly all maternity units are familiar with the mifepristone/misoprostol combination. The patients do not need any special monitoring as the side-effects of the drugs are minimal and uncommon; however, most units will administer the mifepristone under medical supervision and ask the patient to remain in the unit for 1 hour. Mifepristone should be avoided if the patient suffers from severe asthma, chronic adrenal failure renal or hepatic impairment or acute porphyria, and caution should be used if she suffers from mild asthma, hemorrhagic disorders or is on anticoagulant therapy, or has risk factors for cardiovascular disease or adrenal suppression.

The cost of such a regimen is minimal compared with any alternative. The completed course will be less than £100 and the cost of 1 day of hospital admission if the misoprostol is administered as an inpatient – though this is not essential.

Mifepristone/misoprostol combination has been used successfully to shorten the duration of the conservative management of placenta accreta; therefore, it can be introduced at any time after the delivery, although administration soon after delivery is encouraged. More importantly, mifepristone/misoprostol combination has been shown not to affect future fertility and hence to be superior to surgical options.

The success rate of mifepristone/misoprostol management protocol compares favorably with all surgical interventions which should be avoided and only offered to the patient if there is severe bleeding or when other methods have been exhausted[45].

CONCLUSION

Placenta accreta is difficult to diagnose antenatally by imaging techniques and the diagnosis is usually established after delivery at the time of the manual removal of the retained placenta[46–51]. In hospitals lacking emergency access to an intervention radiologist or vascular surgeon, forcible traumatic removal of placenta accreta could initiate severe hemorrhage and should be avoided. Placenta accreta does not usually cause severe bleeding unless disturbed and partly removed manually. It is essential for the obstetrician to be aware of all management options for such a potential dangerous condition. With the established safety of the new mifepristone/misoprostol combination regimen and growing evidence of its potential efficacy in managing placenta accreta, this combination should have a role in sparing invasive procedures for the management of placenta accreta associated with severe PPH. This new regimen could be used soon after delivery or in association with conservative management. Furthermore, the treatment is cost-effective, easy to use and may be life-saving in many low-resource settings. A large study is needed to establish the overall success rate as well as possible future fertility rate. Meanwhile, obstetricians should be encouraged to report their experience with the use of the combination.

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