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MINIREVIEWS

Retained placenta: Do we have any option?

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Abstract

Retained placenta is a known cause of post-partum haemorrhage and maternal mortality. A recent systemic review has confirmed that the incidence of retained placenta had increased all over the world, which is more common in developed countries. Failure of retroplacental myometrium contraction is the main cause of retained placenta. Maternal age greater than 35 years, grandmultipara, preterm labor, history of previous retained placenta, and caesarean section were the risk factors for retained placenta. Manual removal of the placenta has been the treatment of choice. Attempts had been made by clinician and researchers to find a safe, effective and reliable method to avoid the need for surgical intervention. The efficacy and safety of prostaglandin, nitroglycerin or acupuncture in the management of retained placenta are yet to be further evaluated. Nonetheless, till date only intra-umbilical vein oxytocin has been studied extensively but with varied success. More randomized clinical trials are needed to address this issue. However, if immediate manual placenta removal service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU at a total volume of at least 40 mL while preparing for transfer to a tertiary center or theatre may result in spontaneous expulsion of the placenta.

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Key words: Retained placenta; Manual removal of the placenta; Intra-umbilical vein; Oxytocin; Prostaglandin; Misoprostol; Carboprost; Acupuncture

Core tip: Retained placenta is a known cause of post-partum haemorrhage and maternal mortality. The incidence of retained placenta had increased all over the world, which is more common in developed countries. Manual removal of the placenta has been the treatment of choice. However, it is a surgical intervention requiring anaesthesia with potential risk and complication. This manuscript reviews various methods that had been reported in the management of retained placenta.

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INCIDENCE OF RETAINED PLACENTA

Retained placenta (RP) is a known cause of post-partum haemorrhage (PPH) and maternal mortality. Although this is such an important event, it is often under-reported as the after-event consequences are much more focused and attract a more appealing report. In veterinary reports RP appears more in the dairy farms where cows are reported with this problem[1]. However, RP in women varies between regions of the world and also according to

how it is defined. The reported data may not truly give the exact number of events especially from those countries with lower resources and also as a result of its retrospective reporting. All types of previous uterine surgeries had been shown in early days to increase the incidence rate of RP. In fact it was three times higher with induced labour[2]. Although it was reported that RP was significantly higher in United Kingdom compared to Uganda[3], it is unclear whether or not this is a result of under-reporting. A recent systemic review[4] has confirmed that the incidence of RP had increased all over the world, which is more common in developed countries. In India, Chhabra[5] reported that RP occurred in 0.008% of childbearing women. Titiz *et al*[6] reported an incidence of 3.0% in Australia while Belachew *et al*[7] reported an incidence of 2.1% in Sweden. The median rate of RP at 30 min (2.67% *vs* 1.46%, $P < 0.02$) and median manual removal rate (2.24% *vs* 0.45%, $P < 0.001$) were found to be higher in developed countries. It was also found that the overall rate of manual removal in the United Kingdom has risen (mean of 0.66% in 1920s *vs* 2.34% in 1980s, $P < 0.0001$).

DEFINITION

To date, there is no consensus as to the duration of the third stage of labour, *i.e.*, when placenta should be delivered. Traditionally, interventions are advised if the placenta remains undelivered between 20 to 60 min at the third stage[8]. Studies[9,10] showed that the risk of PPH increased after 30 min elapsed of the third stage of labour, although any delay in active intervention would increase the chance of spontaneous placenta delivery. Hence, the placenta being labeled as "retained" largely depends on balance between the risk of PPH and likelihood of spontaneous placenta delivery. Availability of local facilities such as operating theater, blood bank, and trained medical personnel should be taken into consideration. Hence, National Institue for Health and Clinical Excellence guidelines suggested 30 min, while WHO recommended 60 min elapsed of the third stage to be defined as RP[11].

PATHOPHYSIOLOGY

Back in 1933, Brandt[12] had described the physiology of uterine contraction for placenta detachment from decidual bed in the third stage of labour. He divided the third stage into four phases: latent, contraction, detachment and expulsion phase. The latent phase is immediately after delivery of fetus, where all parts of the myometrium contract except the myometrium behind the placenta that remains relaxed. The retro-placental myometrium contracts during contraction phase, leading to placental detachment. Further contractions of the myometrium expel the placenta from the uterus.

Failure of retro-placental myometrium contraction is the main cause of RP. An observational study also revealed that retro-placental myometrium contraction in dysfunctional labour was lesser than in normal labour[13]. Hence, it is likely that retro-placental contractility fails to occur throughout the process of labour as RP and dysfunctional labour were found to be closely related[9]. A recent study using ultrasonography had confirmed this theory and further improved the understanding of normal and abnormal third stage of labour[14].

RISK FACTORS

Maternal age greater than 35 years and grandmultipara are associated with a seven-fold increase in risk of RP[15]. Fibrous tissue in the uterus of grandmultipara women results in a reduction of contractility power, which is more pronounced in women at an advanced maternal age. Increased abnormality of placenta implantation in grandmultipara also plays a major factor in the pathogenesis of RP.

A history of previous RP increases 2.4-fold the risk of recurrence in subsequent pregnancy[16]. This risk can be as high as 29-fold as demonstrated by another study conducted in Saudi Arabia[2], while a recent study also showed an OR of 12.6 to have recurrent RP[17]. Uterine surgeries such as Caesarean section (OR = 12) and dilatation curettage (OR = 4.4) are significantly associated with RP[18]. These procedures inadvertently cause injury to the endometrium, thus facilitating abnormal placenta implantation and further leading to morbidly adherent placenta.

RP is found strongly in association with preterm labour, particularly less than 27 wk of gestational age with a relative risk of 6 to 13[9,19]. It is believed that risk factors such as infarction or fibrinoid degeneration of decidual arterioles that frequently cause preterm labour lead to abnormal adherence of the placenta[20].

Uterine abnormalities are also associated with a certain degree of RP. Golan *et al*[21] found incomplete uterine septum at hysteroscopic examination in 15% of women who underwent manual removal of the placenta (MRP). Other documented risk factors include induction of labour (3-fold rise) and analgesia such as pethidine (3.5-fold rise)[2].

VARIOUS TREATMENT MODALITIES

Surgical intervention

Traditionally MRP is the treatment of choice for RP. MRP requires insertion of the operator's hand into the uterus through the vagina[22]. The operator's hand follows the umbilical cord to identify the interface between the uterus and maternal surface of the placenta. Dissection of the uterine-myometrium plane is achieved by using fingers in a side-to-side motion. The other hand should be placed at the uterine fundus over the abdomen to minimise risk of uterine perforation[23].

Regional anaesthesia such as spinal anaesthesia is recommended for MRP if epidural anaesthesia is not in place earlier during labour. Use of regional anaesthesia is preferred in obstetric cases to avoid the risk of general anaesthesia such as failed intubation and Mendelsons Syndrome from gastric content aspiration[24]. In the presence of rapid blood loss or haemodynamic instability, general

Table 1 Comparison of various trials[33].

Study	Number of patients	Oxytocin dose (IU)	Total volume infused (mL)	Manual removal of placenta rate (%)
Makkonen *et al*[31]	109	50	20	72.1
Frappell *et al*[40]	41	10	20	63.0
Weeks *et al*[23]	577	50	30	61.3
Selinger *et al*[36]	30	10	20	60.0
Caroli *et al*[37]	286	20	40	58.2
Gazvani *et al*[38]	81	20	20	53.8
Kristiansen *et al*[34]	51	10	10	52.6
Sivalingam *et al*[35]	35	30	30	47.0
Huber *et al*[39]	200	10	20	38.0
Wilken-Jensen *et al*[32]	37	100	30	27.8
Lim *et al*[33]	61	100	40	30.0

anaesthesia is required[25]. The availability of anaesthetist during the procedure would facilitate the performance of further interventions in the occurrence of complications associated with MRP such as haemorrhage, uterine perforation and occasionally morbidly adherent placenta.

An aseptic technique is essential to minimize the risk of haemorrhage and endometritis[23]. The time elapse "accepted" by many obstetricians to removal of the placenta varies between 30-60 min in the absence of haemorrhage[26]. As MRP is also associated with endometritis, the use of prophylactic broad-spectrum antibiotics is recommended[27]. Administration of glyceryl trinitrate (intravenous or sublingual) to relax the uterus in the presence of a tightly closed cervix and avoidance of using sharp curette reduce the risk of uterine perforation[28,29].

Pharmacological interventions

Intra-umbilical vein oxytocin injection: The use of oxytocin in the management of the third stage and RP had been reported in various studies. It is based on the finding of failure of retro-placental contraction, which resulted in RP. However, intra-umbilical vein oxytocin injection in the management of RP had been shown to have various degrees of success mainly due to different techniques, doses of oxytocin, volumes of fluid and timings of injection.

According to the injection method proposed by Pipingas *et al*[30], using size-10 infant feeding tube directly into the umbilical vein 5 cm before the insertion of cord into the placenta, delivery of oxytocin into the retro-placental myometrium has improved.

The dosage of oxytocin used ranges from 10 IU to 100 IU with a greater chance of success found at a higher dosage (Table 1). As reported by Makkonen *et al*[31], there was no significant change in the MRP rate when 50 IU oxytocin was used. This is consistent with a larger double-blind, randomized controlled trial (Release Study) using 50 IU oxytocin, which demonstrates no statistical difference in the MRP rate between oxytocin and placebo groups[3]. Nonetheless, two studies by Wilken-Jensen *et al*[32] and Lim *et al*[33] had achieved the lowest rate of MRP (< 30%) by advocating dosage 100 IU of oxytocin.

The total volume of fluid being injected into the umbilical vein also differs between trials[34-36]. Most of the studies used 10 to 30 mL except two studies by Caroli *et al*[37] and Lim *et al*[33] which used 40 mL. The reported MRP rate by Caroli *et al*[37] was higher than that by Lim *et al*[33] (58.2% *vs* 30.0%), but the disparity may be due to difference in the dosage of oxytocin used (20 IU *vs* 100 IU).

The interval from oxytocin administration to decision for MRP varies from 15 to 45 min or depending on clinical judgment of the obstetrician[31,34-40]. There is always a concern of the increasing risk of PPH with increment of this interval, especially more than 30 min, which had been shown in several studies[9,10].

A Cochrane review including 15 trials with 1704 women that compared the use of intra-umbilical vein oxytocin injection with saline solution had shown a reduction in MRP rate although there was no statistical difference (OR = 0.9). The authors concluded that the use of oxytocin *via* umbilical vein injection is simple and inexpensive but further research is required to ascertain the optimal timing for MRP[41].

Prostaglandin: Prostaglandin is an effective uterotonic agent and has a role in the management of PPH. It has a combination of pharmacodynamic properties with myometrial stimulation, vasoactive mechanism and reduction in platelet function. The use of prostaglandin in management of RP is based on the mechanism that retro-placental myometrium contracts during the contraction phase and leads to placental detachment[14].

The study to evaluate the efficacy of prostaglandin is limited. Prostaglandin resulted in a statistically significant reduction in MRP when compared with oxytocin (RR = 0.43; 95%CI: 0.25-0.75), with a shorter time interval from drug administration to delivery of the placenta (mean difference -6.00; 95%CI: -8.78--3.22)[39]. However, the meta-analysis only analysed two small trials[41], thus intra-umbilical vein injection of prostaglandin needs further evaluation.

Misoprostol: Van Stralen *et al*[42] review the usage of sublingual misoprostol 800 μg among 95 patients with RP in a low resource setting. The trial failed to show any benefit of using misoprostol in the management of RP. MRP was required in 40% of the treatment group patients compared to 33% in the placebo group.

Carboprost: Carboprost tromethamine, a methylated analogue of PGF2-α, is a uterotonic agent which is more potent and has a longer duration of action.

Lately, the use of carboprost has been extended for RP. According to Habek, intra-umbilical vein injection of 0.5 mg carboprost suspended in 20 mL of 0.9% saline yielded the highest therapeutic success rate of 85.7% as compared to two other groups of oxytocin (76.9%) and methylergometrine (64.2%)[43].

Nitroglycerine: Studies with regards to the use of nitroglycerine (NTG) in management of RP has been described and reported in several clinical trials using dif-

ferent dosages, routes of administration, alone or in combination with other agents. Various degrees of success were reported. However, most were observational studies with a small number of patients.

Chedraui and Insuasti[44] in 2003 reported successful deliveries of all RPs in 30 patients, which was in contrary to a 15% success rate in a study by Visalyaputra *et al*[45]. They were given intravenous NTG 50 μg, which was increased by 50 μg every 2 min until a maximum dose of 200 μg[44]. There were five patients who complained of short-duration headaches but no other significant clinical adverse events. The mean duration to achieve delivery of the placenta was 5.3 ± 1.1 min.

Bullarbo *et al*[46] in a small study of 24 patients demonstrated a success rate of 100% by administering subcutaneous NTG 1 mg after intravenous oxytocin compared to only 8.3% in the placebo group. Similarly, Ekerhovd *et al*[47] successfully delivered 21 out of total 24 RPs without significant side effects.

This is consistent with a Cochrane review[48], which then concluded that subcutaneous NTG appeared to be effective and safe but its routine use is not yet recommended due to small sample size.

Acupuncture

The use of acupuncture in the management of RP involves stimulation of certain acupoints to promote uterine contractions. Chauhan *et al*[49] in their retrospective review of 45 patients who required MRP found that 30 of them had acupuncture to expel the placenta. Twenty-five out of 30 patients who had acupuncture delivered the placenta within 20 min. Four of the remainder required MRP for placenta accreta. There were significantly fewer patients in the acupuncture group experiencing PPH (13% *vs* 47%).

UNDIAGNOSED MORBIDLY ADHERENT PLACENTA

Morbidly adherent placenta implies abnormal invasion of the placenta tissue into the inner or outer myometrium or through the serosa of the uterus (termed accrete, increta or percreta, respectively)[50]. It could be one of the reasons for RP, which is also associated with significant maternal morbidity and mortality. Over the last decades, there has been a steady rise in the incidence of morbidly adherent placenta as reflected by the rising number of caesarean deliveries. It is estimated the incidence of morbidly adherent placenta to be 1.7 per 10000 women[50]. In most cases, there were always established risk factors whereby at least one risk factor was identified in 94% of cases[51]. The risk of having morbidly adherent placenta increased in women with previous caesarean scar, previous uterine surgeries, *in vitro* fertilization pregnancy and placenta praevia[52]. Advanced maternal age, even without any previous caesarean delivery, has been found to be associated with morbidly adherent placenta[50].

A high index of clinical suspicion should be exercised in women who are at risk. The use of ultrasonography with Doppler studies and magnetic resonance imaging (MRI) may be of use in reaching the diagnosis antenatally, thus assisting in the delivery care[53]. Till date, there is difficulty in identifying cases of morbidly adherent placenta in those without any risk factor. In such cases, diagnosis is only made after unsuccessful removal of the placenta at delivery.

Traditionally, hysterectomy has been advocated for such cases. However, it is associated with various morbidities such as PPH, massive blood transfusion, intensive care unit admission, ureteric/bladder injury, infection and prolonged hospitalisation. Alternatively other conservative strategies have been implemented to minimise these complications and preserve fertility. Uterine devascularisation *via* embolisation, uterine compression sutures, uterine tamponade and administration of methotrexate during the post-partum period have all been used to manage morbidly adherent placenta conservatively[54]. However, these conservative approaches are very much dependent on the amount of bleeding, haemodynamic status, surgical expertise, facilities available and the desire for fertility preservation.

CONCLUSION

MRP remains the mainstay of treatment for RP. Clinicians and researchers had been trying hard to find a safe, effective, simple and reliable method to manage RP without the need for surgical intervention. The efficacy and safety of prostaglandin, NTG or acupuncture in the management of RP are yet to be further evaluated. Till date, only intra-umbilical vein oxytocin has been studied extensively but with varied success. More randomized clinical trials are needed to address this issue. However, if immediate MRP service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU at a total volume of at least 40 mL while preparing for transfer to a tertiary center or theatre may result in spontaneous expulsion of the placenta.

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