**Name of journal: World Journal of Obstetrics and Gynecology**

**ESPS Manuscript NO: 9824**

**Columns: Minireviews**

Retained placenta: Do we have any option?

Lim PS *et al*. Management of retained placenta

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**Received:** February 28, 2014 **Revised:** June 6, 2014

**Accepted:** July 12, 2014

**Published online:**

**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, and more common in developed countries. Failure of retro-placental 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 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 prostaglandins, nitroglycerin or acupuncture in the management of retained placenta is yet to be further evaluated. Nonetheless, till date only intra-umbilical vein oxytocin have been studied extensively but with varied success rate. More randomized clinical trials are needed to address this issue. However, if immediate manual removal of placenta service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU with total volume of at least 40 mL while preparing for transfer to tertiary center or theatre may result in spontaneous expulsion of placenta.

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

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

Lim PS, Mohamed Ismail NA, Abd Ghani NA, Chandralega Kampan N, Sulaiman AS, Ng BK, Chew KT, Abdul Karim AK, Mohd Yassin MAJ. Retained placenta: Do we have any option? *World J Obstet Gynecol* 2014; In press

**INCIDENCE OF RETAINED PLACENTA**

Retained placenta is a known cause of post partum haemorrhage 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 report retained placenta (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 to its retrospective reporting. All type of previous uterine surgery had been shown in early days to increase the incidence and 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], whether or not this is as a result of under reporting. A recent systemic review[4] has confirmed that the incidence of RP had increased all over the world, and more common in developed countries. In India, Chhabra[5] reported that retained placenta occurred in 0.008%. 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 retained placenta 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**

Up to date, there is no consensus as to the duration of third stage of labour by when placenta should be delivered. Traditionally, interventions are advised if placenta remain undelivered between 20 to 60 min at third stage[8]. Studies[9,10] showed that the risk of post-partum haemorrhage 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 duration of placenta being labeled as “retained” largely depends on balance between the risk of post-partum haemorrhage and likelihood of spontaneous placenta delivery. Availability of local facilities such as operating theater, blood bank, trained medical personnel should be taken into consideration. Hence, NICE (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 retained placenta[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 third stage into four phases: latent, contraction, detachment and expulsion phase. Latent phase is immediately after delivery of fetus, where all myometrium contracts except myometrium behind the placenta that remains relaxed. The retro-placental myometrium contracts during contraction phase leading to placental detachment. Further contractions of myometrium expel the placenta from 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 progress labour[13]. Hence, it is likely that retro-placental contractility fail to occur throughout the process of labour as RP and dysfunctional labour were found to be closely related[9]. 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 seven folds of RP[15]. Fibrous tissue in uterus of grandmultipara women results in reduction of contractility power, more so in advanced maternal age. Increased abnormality of placenta implantation in grandmultipara also plays a major factor leading to RP.

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 odd ratio of 12.6 to have recurrent retained placenta[14]. 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 further leading to morbidly adherent placenta.

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

Uterine abnormalities are also associated with certain degree of retained placenta. Golan *et al*[21] found incomplete uterine septum at hysteroscopic examination in 15% of women who underwent manual removal of the placenta. 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 manual removal of placenta (MRP) is the treatment of choice for RP. MRP requires insertion of the operator’s hand into the uterus through vagina[22]. The operator’s hand follows the umbilical cord to identify the interface between uterus and maternal surface of placenta. Dissection of the uterine-myometrium plane is achieved by using fingers in side-to-side motion. The other hand should be placed at the uterine fundus over abdomen to minimise risk of uterine perforation [23].

Regional anaesthesia such as spinal anaesthesia is recommended for MRP if epidural 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 anaesthesia is required[25]. The availability of anaesthetist during the procedure would facilitate the performance of further interventions in 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 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 GTN (intravenous or sublingual) to relax the uterus in the presence of a tightly closed cervix and avoidance of using sharp curette reduces the risk of uterine perforation[28,29].

***Pharmacological***

**Intra-umbilical vein oxytocin injection:** The use of oxytocin in the management of third stage and retained placenta 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 degree of success mainly due to different techniques, doses of oxytocin, volume of fluid and timings of injection.

With introduction of 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 is ranged from 10 IU to 100 IU with a greater success found at higher dosage (Table 1). As reported by Makkonen *et al*[31], there was no significant difference in the MRP rate when concentration of 50IU 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, both studies by Wilken *et al*[32] and PS 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 study used 10 to 30 mL except two studies by Caroli *et al*[33] and PS Lim *et al*[37] used 40 mL. The reported MRP rate by Caroli *et al*[33] was higher than PS Lim *et al*[37] (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 between 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 post partum haemorrhage with increment of this interval, especially more than 30 minutes, which had been shown in several studies[9,10].

The Cochrane review included 15 trials involving 1704 women in comparing the use of intra-umbilical vein oxytocin injection with saline solution had shown a reduction in MRP rate although statistically was not significant (Risk ratio 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 post partum haemorrhage. It has a combination of pharmacodynamic properties with myometrial stimulation, vasoactive mechanism and reduction in platelet function. The use of PG in management of RP is based on the mechanism where retro-placental myometrial contraction which produces shearing forces between the placenta and myometrium thus tearing the decidual septae and resulted in detachment of placenta [14].

The study to evaluate the efficacy of PG is limited. Prostaglandin showed a statistically significant reduction in MRP when compared with oxytocin (RR 0.43; 95%CI: 0.25-0.75) with shorter time interval from drug administration to delivery of placenta (mean difference -6.00; 95%CI: -8.78 to -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*[43] review the usage of sublingual misoprostol 800 ug among 95 patients with retained placenta 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 placebo.

**Carboprost:** Carboprost tromethamine, a methylated analogue of PGF2-alpha is a uterotonic agent which is more potent with longer duration of action.

Lately, the use of carboprost has been extended for retained placenta. According to Habek, intra-umbilical vein injection of 0.5 mg carboprost suspended in 20 mL of a 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%)[42].

***Nitroglycerine***

Studies with regards to the use of Nitroglycerine (NTG) in management of RP has been described and reported in several clinical trials using different dosages, route of administration, alone or in combination with other agents. Various degrees of success were reported. However, most were observational studies with small number of patients.

Chedraui and Insuasti[44] in 2003 reported successful deliveries of all retained placentas in 30 patients, which was in contrary to 15% success rate in the study by Visalyaputra *et al*[45]. They were given intravenous NTG 50 ug, which was increased by 50 ug every 2 min until maximum dose of 200 ug [44]. There were five patients who complained of short duration headaches but no other significant clinical adverse event. The mean duration to achieve delivery of 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 placebo group. Similarly, Ekerhovd *et al*[47] successfully delivered 21 out of total 24 RP without significant side effects.

This is consistent with the 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 retained placenta involves stimulation of certain acupoints to promote uterine contractions. Chauhan *et al*[49] in his retrospective review of 45 patients who required manual removal of placenta (MRP), 30 of them had acupuncture to expel the placenta. About 25 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 experienced 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 retained placenta, 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].

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) maybe 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 placenta at delivery.

Traditionally, hysterectomy has been advocated for such cases. However, it is associated with various morbidities such as post partum haemorrhage, 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 post-partum 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 as the mainstay of treatment for RP. Clinician 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 prostaglandins, NTG or acupuncture in the management of RP is yet to be further evaluated. Till date, only intra-umbilical vein oxytocin have been studied extensively but with varied success rate. 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 with total volume of at least 40 mL while preparing for transfer to tertiary center or theatre may result in spontaneous expulsion of placenta.

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**P-Reviewer:** Geok CT **S-Editor:** Song XX **L-Editor: E-Editor:**

**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 *et al*[32] | 37 | 100 | 30 | 27.8 |
| Lim *et al*[33] | 61 | 100 | 40 | 30.0 |