The Retained Placenta

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Abstract
The retained placenta is a significant cause of maternal mortality and morbidity throughout the developing world. It complicates 2% of all deliveries and has a case mortality rate of nearly 10% in rural areas.

Ultrasound studies have provided fresh insights into the mechanism of the third stage of labour and the aetiology of the retained placenta. Following delivery of the baby, the retro-placental myometrium is initially relaxed. It is only when it contracts that the placenta shears away from the placental bed and is detached. This leads to its spontaneous expulsion. Retained placenta occurs when the retro-placental myometrium fails to contract. There is evidence that this may also occur during labour leading to dysfunctional labour. It is likely that this is caused by the persistence of one of the placental inhibitory factors that are normally reduced prior to the onset of labour, possibly progesterone or nitric oxide.

Presently, the only effective treatment is manual removal of placenta (MROP) under anaesthetic. This needs to be carried out within a few hours of delivery to avoid haemorrhage. For women in rural Africa, facilities for MROP are scarce, leading to high mortality rates. Injection of oxytocin into the umbilical vein has been suggested as an alternative. This method relies on the injected oxytocin passing through the placenta to contract the retro-placental myometrium and cause its detachment. Despite several placebo controlled trials of this technique, no firm conclusion have been reached regarding its efficacy. This may be due to inadequate delivery of the oxytocin to the placenta. Further trials are in progress to assess the optimal dose of oxytocin as well as the efficacy of a new technique designed to improve delivery of the oxytocin to the placental bed.
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INTRODUCTION

Post-partum haemorrhage (PPH) is a significant cause of maternal mortality in the developing world. Many cases of PPH are associated with retained placenta, a condition that affects between 0.6 and 3.3% of normal deliveries.[1,2,3] Where there is easy access to hospital care and transfusion, mortality from this condition is very low. In the last triennial review from the UK there were no deaths from retained placenta in over 2 million deliveries[4]. In many parts of the developing world, however, the case fatality rate is high. In an observational study from rural India in which the majority of women were delivered at home by traditional birth attendants, there were 2 deaths (9%) from the 22 women who had placental retention of over 60 minutes[2]. In a large northern Nigerian hospital the mortality was 3% amongst 894 women treated for retained placenta over a 3 ½ year period.[5] The cause of death is usually haemorrhage. This is more frequent when manual removal is not immediately available or when travelling times to hospital are long. Clearly, an effective medical treatment could have major implications for the reduction of maternal mortality.

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The importance of the retro-placental myometrium

As long ago as 1933, Brandt described the necessity of a uterine contraction to cause detachment of the placenta from the decidual bed.[6] This has recently been confirmed using ultrasound where examination of the immediate post-partum uterus has clarified the process of both the normal and abnormal third stage of labour. Herman[7] first demonstrated ultrasonographically that a retro-placental myometrial contraction is mandatory in order to produce shearing forces upon the interface between the placenta and myometrium and lead to its detachment. He divided the third stage into 4 phases according to the ultrasound appearances.

In the **latent phase**, which immediately follows delivery of the fetus, all the myometrium contracts except for that behind the placenta which remains relaxed. In the **contraction phase** the retro-placental myometrium contracts leading to the **detachment phase** where the placenta is sheared away from the decidua. In the **expulsion phase** the placenta is expelled from the uterus by uterine contraction. Contractions occurring prior to delivery are insufficient to cause placental detachment as in the presence of the fetus, the myometrium is unable to achieve the necessary strain for detachment[8] Some later authors have suggested that there is no distinction between the contraction and detachment phases and have dropped the contraction phase from the classification.[9] The same group have further elaborated the process using Doppler. They demonstrated that the blood flow through the arcuate and radial arteries is reduced during the latent phase and then ceases completely at the onset of the contraction phase[9]. This occlusion occurs as a result of the myometrial 'physiological ligature'. The timing of this neat mechanism ensures that maternal blood flow to the placenta ceases prior to placental detachment. In this way, the only maternal blood lost is that from the intervillous spaces.

These ultrasound studies also shed light on the aetiology of the retained placenta. They demonstrate that the duration of the third stage of labour is dependant on the length of the latent phase and a prolonged third stage is due to contractile failure in the retro-placental area[7]. In the 5 cases of retained placenta in which they conducted serial ultrasonographic myometrial thickness measurements, they found a universal failure of retro-placental contraction. Doppler studies confirm that in these women blood flow continues through the myometrium to the placenta irrespective of whether the cause is placenta accreta or prolongation of the latent phase[9]. This provides a scientific explanation for the increased rates of haemorrhage during manual removal of placenta when compared with spontaneous delivery[10]. It also explains why partial or forced detachment of the placenta prior to onset of the contraction phase is associated with high rates of haemorrhage.

The finding that the basic abnormality in women with non-accreta retained placenta (or placenta adherans) is a failure of the contraction phase raises a number of issues. It is unlikely that this retro-placental contractile failure is limited to the post partum period. It is likely to have occurred throughout labour. This may explain the fact that retained placenta and dysfunctional labour have been shown to be closely associated,[1] even though all women with severe dysfunctional labour are delivered by caesarean section. Indeed, in a small study from the UK, the need for manual removal of placenta at the time of caesarean section was found to be higher in women having caesareans section for 'failure to progress' than for other reasons[11]. An attempt has also been made to compare the 'retro-placental' and 'extra-placental' myometrial contractility during labour using the increase in myometrial thickness during contractions (measured using ultrasound) as a measure of contractility. In 10 women in whom labour was progressing normally there was no difference in contractility between the two sites. In the 10 women with slowly progressing labour, however, whilst the extra-placental myometrium showed normal thickening, the retro-placental myometrium thinned during contractions. This suggests a localised failure of contractility.[11] The thinning is thought to occur as a result of stretching of the uncontracted myometrium by the raised intrauterine pressure.

The relative lack of contractile strength in the retro-placental myometrium may make evolutionary sense for both the mother and fetus. During strong contractions it not only prevents inadvertent placental detachment, but also allows good blood flow to the placenta to be maintained.

The second issue raised is the nature of the biochemical abnormality that produces the failure of retro-placental contractility. The localised nature of the contractile failure suggests that it is the placenta which is responsible, rather than an underlying myometrial abnormality. The placenta has been known for many years to be an important determinant of the onset of labour and it is likely that this occurs as a result of the loss of an inhibitory factor of placental origin. The association of retained placenta with both preterm delivery and the need for induction[1,12] suggests that it may be the same factor which is responsible for both. The role of the feto-placental unit in the regulation of uterine contractility is complex with a finely controlled balance between stimulatory and inhibitory factors.[13] This balance can be likened to a set of scales with inhibitory and stimulatory factors on either side. Loss of inhibition may result in the onset of labour (as with the administration of anti-progesterones) as may an increase in the stimulatory factors (as with the administration of exogenous oxytocin or prostaglandins). It could be hypothesised that if the pro-contractile stimuli were strong enough, then successful labour could occur even in the presence of persisting, localised placental inhibition. In this situation there would be a high risk of retained placenta due to the strong persistent placental inhibition of retro-placental myometrial contractility.

There are a number of candidates for the identity of this localised inhibitor. The placenta has a role in inhibiting myometrial contractions through the production of progesterone and possibly nitric oxide (NO). Progesterone is an important inhibitor of myometrial contractility in many animals, but the situation in humans is yet to be fully clarified. The anti-progesterone mifepristone is a powerful sensitisor of the myometrium to exogenous prostaglandins, and it is effective for induction of human labour in all trimesters of pregnancy.[14,15,16] Attempts to identify the mechanism for this, however, have so far been unsuccessful as, unlike in animal models, a reduction in serum progesterone is not seen prior to labour.[17] Recent evidence, however, suggests that its effect may occur through a reduction in progesterone metabolites.[18]

Nitric oxide is also a powerful smooth muscle relaxant which is produced in large quantities by nitric oxide synthase (NOS) in the placenta.[19] As it is rapidly oxidised following its production, its effect is very localised. Ramsay et al[20] showed decreases in villous trophoblast NOS activity through pregnancy, but Thompson et al[21] showed no change in placental NOS activity before and after labour. However, all the placentas studied came from women who had caesarean sections. The indication for most of these operations in the labouring group was 'failure to progress' and this is the very group who may have excessive NOS activity. This study therefore does not disprove the hypothesis that a reduction in placental NO is necessary for the onset of normal labour. Indeed, a change in the production of placental NO could explain the fact that exogenous NO appears to relax myometrium, but that infusion of NOS inhibitors (which may not reach the placenta) have no effect of myometrial quiescence in animal models.[22] The detail of how these various factors combine to initiate and sustain labour, as well as the pathological mechanisms that cause dysfunctional contractions and post-partum myometrial contractile dysfunction are not known. The study of this group of women with retained placenta in which there is a clear inhibitory effect of the placenta on myometrium may allow some of the mechanisms underlying dysfunctional labour as well as retained placenta to be elucidated.

The final implication of the discovery that the persistent latent phase is a cause of retained placenta is that contraction of this area would resolve the problem of dysfunctional labour and retained placenta. This could be either achieved through removing the inhibitor (e.g. by treatment with an anti-progesterone) or by stimulation with oxytocics. Umbilical vein oxytocin has been

suggested as a way of delivering a localised stimulus to the retro-placental myometrium.

Management of Retained Placenta

1. Manual removal

Presently, the most common treatment for a retained placenta is its manual removal under anaesthetic. During this procedure the woman is exposed to anaesthetic risks as well as the infective risk that comes from inserting a hand into the uterus. Both risks are higher in developing countries where the prevalence of infections is high and personnel skilled in obstetrics anaesthesia are in short supply. The time that is allowed to lapse before manual removal varies, but many authorities suggest a delay of 30-60 minutes in the absence of haemorrhage. This is because there is no increase in haemorrhage until at least 30 minutes post-partum,[1] and because of the finding that between 30 and 60 minutes a further 40% of placentas will spontaneously deliver with the loss of an average of only 300ml of blood.[23]

If the placenta is found to be accreta when manual removal is attempted then there are a number of management options. Often a partial removal is achieved manually and curettage is used to remove as much as possible of the remaining tissue. So long as haemorrhage is controlled with this method and the uterus remains well contracted, then this is usually adequate to prevent continued haemorrhage. The remaining trophoblast is usually reabsorbed spontaneously, although levels of ß-HCG take longer to return to normal.[24] A further curettage may be needed if haemorrhage continues. In the case of placenta percreta, blood will continue to flow through the area of invasion when the bulk of the placenta is removed due to the absence of the myometrial physiological ligature which would normally stem the flow.[9] If discovered at caesarean section then haemostasis may be achieved through the use of sutures placed deep into the myometrial bed, or through ligation of the uterine or internal iliac arteries.[25] However, a hysterectomy is usually required. If the diagnosis of placenta percreta can be made before any of the placental tissue is removed (as may be achieved antenatally using ultrasound[9]) then the patient may be treated conservatively. This involves delivering the baby as normal but leaving the placenta *in situ*. The levels of ß-HCG are followed and manual removal and curettage performed when they become undetectable.[26] Methotrexate may be beneficial in this situation.[27]

2. Systemic oxytocics

The role of systemic oxytocics in the management of retained placentas is controversial. Oxytocics given *prophylactically* at the time of delivery increase the number of placental deliveries at 20 and 40 minutes, but have no effect on the number of placentas that eventually need manual removal.[28] The only randomised trial to assess the use of intravenous ergometrine showed an increase in the rate of retained placenta.[29] This may have occurred as a result of myometrial spasm distal to a fundally-placed placenta leading to its forced retention.

The finding that prophylactic oxytocin injections (which last in the circulation for only 10 min) increase the number of placentas delivered in the first half hour following delivery, provides the theoretical basis for the use of oxytocics to try and deliver the remainder. Midwives have recommended nipple stimulation for many years to stimulate the production of endogenous oxytocin, but this has never been formally evaluated for this indication. The use of an intravenous infusion of oxytocin has never been subjected to a randomised trial, but it has been suggested that it (or intra-muscular ergometrine) may prevent haemorrhage during transfer or preparation for theatre.[30,31] Its use is widespread throughout the world in this situation. Oxytocin is given in the form of a continuous infusion of 5 i.u./hr as this increases the overall tone of the myometrium as well as stimulating strong phasic contractions. Ergometrine, which produces a long continuous contraction for up to 90 minutes, is less frequently used. However, because it is widely available and does not require an intravenous infusion, it is often used in rural areas whilst transfer is arranged. Misoprostol, an orally active prostaglandin E1 analogue, has an effect similar to that of an oxytocin infusion, producing increases in both background tone and contraction strength for around 90 minutes.[32] Results of trials in which it was being tested as a prophylactic agent to prevent post-partum haemorrhage found that there were significantly fewer retained placentas after its use than when syntometrine had been given.[33] Its cost, tolerance to heat and oral availability make it an excellent drug for rural African use where electricity and trained health workers may be scarce. It is therefore a promising drug for use for preventing complications of retained placenta and the results of further trials are awaited.

Umbilical vein oxytocin injection

Much interest has been aroused by the notion that oxytocin may be delivered directly to the retro-placental myometrium by injecting it into the placental bed via the umbilical vein. This allows the treatment to be directed specifically at the area with the contractile failure, whilst sparing the remainder. Results from trials of this treatment have been mixed. A recent Cochrane review[34] concludes that the use of umbilical oxytocin is effective in the management of retained placenta, despite the fact that their meta-analysis showed the reduction in retained placenta rates not to be significantly different to that obtained with *expectant* management (Peto odds ratio 0.70, 95% confidence intervals 0.48 to 1.02). The basis for this conclusion was additional data from *placebo-controlled* randomised trials of umbilical oxytocin which showed a significant reduction in need for manual removal of placenta with umbilical oxytocin injection (OR 0.59, 95% C.I. 0.43 to 0.82).

The inconclusive results from randomised trials may be due to inadequate delivery of the oxytocin to the retro-placental myometrium. Pipingas et al[35] compared various methods of intra-umbilical injection, using injections of radio-opaque dye into the delivered placenta to enable radiological comparisons. They found that the method of injection used in most trials (injection of oxytocin diluted in 20-30 mls saline and injected directly into the umbilical vein) only resulted in capillary filling in 60% of cases. As a result of their studies they proposed that the oxytocin should be diluted in 30mls of saline and injected down an infant naso-gastric feeding tube which has been passed along the umbilical

vein. They suggest that after re-cutting the cord (in order to achieve a clean end for insertion of the tube) a size 10 naso-gastic tube is passed along the vein until resistance is felt. The tube is then withdrawn by 5 cm to allow for any divisions of the vein prior to its insertion into the placenta. This method resulted in complete filling of the placental bed capillaries in all patients studied.

Another problem with the previous trials has been an inconsistency regarding the dose of oxytocin. There are no comparative studies that assess different doses of oxytocin and the choice of dosage has therefore largely been empirical. Trials to date have mainly used a dose of 10-20 i.u. oxytocin, although doses of up to 100 i.u. have been reported.[36] The published trials that have used higher dosages of oxytocin have, on the whole, found higher success rates. Clinicians are wary of using high doses, however, as a dose of as little as 5 i.u. when given to the mother intravenously can produce significant changes in maternal blood pressure.[37] Although oxytocin can clearly pass through the placenta, the data is unclear as to how quickly this occurs or whether it is complete.[38] Sub-group meta-analysis of the randomised trials from the Cochrane review[34] suggests that doses of over 20 i.u. may reduce the need for manual removal of placenta by over 75%. This is shown in Table 1, where the trials are listed and analysed according to the dosage of oxytocin.

Further evidence for the efficacy of higher doses comes from a recent observational study of 30 women with retained placenta for over 1 hour who were injected with 100 i.u of oxytocin diluted in 30mls of saline via an infant feeding tube as suggested by Pipingas. In this group, a 93% delivery rate of retained placentas was achieved within 5 minutes of injection.[48] Clearly there is a need for further randomised trials. In addition, a dose-finding study is needed in order to find the lowest dose that results in retro-placental contraction without significant hypotension. It is likely that different doses will be required depending on the gestational age of the pregnancy. A full randomised trial of the appropriate dosages is then required to assess the efficacy of the technique. The 'Release Study' is such a trial and is presently being conducted by Makerere University in Kampala, Uganda.

CONCLUSION

Recent ultrasound studies have demonstrated the crucial role that the retro-placental myometrium has to play in placental detachment in the third stage of labour. The finding that retained placentas are associated with a localised retro-placental contractile failure has promoted speculation into the significance of this contractile failure for the progress of labour. Initial studies suggest that this area fails to contract throughout labour in many women with dysfunctional labours.

The use of umbilical vein injections of oxytocin to overcome this contractile failure may allow retained placentas to be treated medically. If an improvement in the delivery of the oxytocin to the placenta can be achieved, then medical management of the retained placenta will become the treatment of choice, even where theatre facilities are available. This could have important public health implications in rural Africa where facilities for manual removal are scarce.

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Table 1.
Success rates of umbilical vein injection when injected with various doses of oxytocin compared with control. As the injection of saline solution alone appears to have no effect on manual removal rates, the data shown combines the trials in which either expectant management or saline solution were used as controls. Where published trials included both, the data from expectant management is quoted. An asterix indicates that the control group was injected with saline alone.

	Number requiring manual removal of placenta in oxytocin group	**Number requiring manual removal of placenta in control group**	**Odds ration (95% CI)**
Huber 1991[39]	27/72	25/69	
Kristiansen 1987[40]	10/19	9/16	
Thiery 2000[41]	9/19	10/13	
Calderdale 1994[42]	1/22	9/20*	
Frappell 1988[43]	14/22	15/19*	
Hansen 1987[44]	14/32	20/28*	
Selinger 1986[45]	9/15	8/15*	
Total	**84/201**	**96/180**	**0.63 (0.42-0.94)**
Oxytocin 20 i.u.			
Carroli 1998[23]	57/98	59/93	
Gazvani 1998[46]	14/26	26/29	
Total	**71/124**	**85/122**	**0.58 (0.34-0.99)**
Oxytocin > 20 i.u.			
Bider 1996[47] (30 i.u.)	5/11	7/7*	
Wilken-Jensen 1989[36] (100 i.u.)	5/18	11/19*	
Total	**10/29**	**18/26**	**0.2 (0.08-0.73)**