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Pathophysiology of Postpartum Hemorrhage and Third Stage of Labor

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INTRODUCTION

The physiology of postpartum hemostasis depends primarily upon mechanical events, mediated by hormones, which induce strong uterine muscular contractions. Virtually all recent studies focus on the latter activity rather than the former, but the phenomenon cannot be understood without examining why uterine contraction stops bleeding. Broadly speaking, myometrium and decidua are arranged such that powerful muscular contractions after delivery favor hemostasis (Figure 1)[1–3]. Spiral arteries 'fan out' to create a low-resistance vascular bed in the intervillous space, which facilitates placental blood flow (see also Chapter 22). This flow decreases with muscular activity[4]. Third-stage contractions are powerful and prolonged: they act to stop placental blood flow and to separate the placenta and membranes.

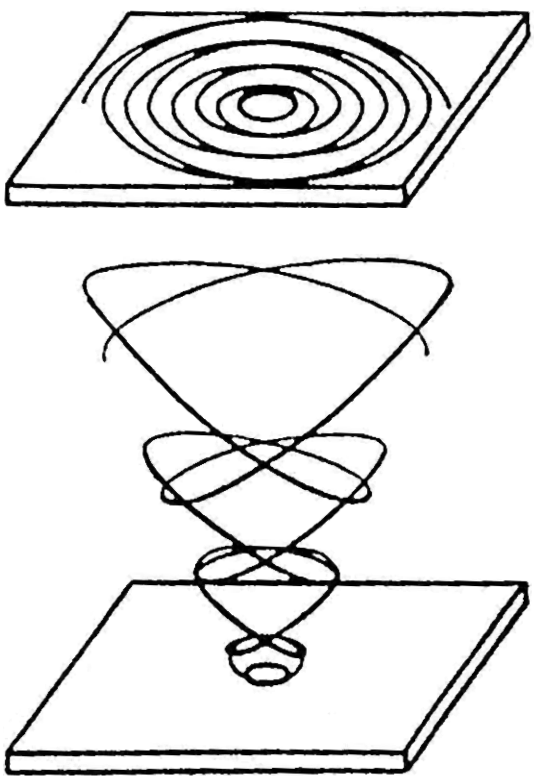

Figure 1 (a) Circular uterine muscle at rest: two sets of crossing spirals; (b) at term: stretching of the spirals[1]. The innermost part of the muscular layer has been described as superficially 'circular' musculature, which is in fact two sets of crossing spirals[2]. An alternative description of muscle fibers traveling in all directions has been described[3]. Both descriptions suggest that blood vessels are compressed during contraction of muscle cells

PLACENTAL SEPARATION AND UTERINE ACTIVITY

Mechanical events

The biomechanical events which lead to delivery of the placenta and its membranes begin even before the onset of the second stage of labor when membrane detachment starts during the first stage and slowly spreads upwards from the internal os[5].

As the trunk of the baby is delivered, the uterine muscle fibers undergo a very powerful contraction. Muscle fibers shorten, and the uterus is reduced in size and volume, a process characterized as retraction. These events are probably facilitated by the spiral arrangement of uterine muscle fibers, whereby the reduction in uterine volume leads to a reduction in placental site surface area. As the placenta is a relatively rigid and inelastic structure, the surface area of its attachment site decreases when it is tightly compressed.

According to Brandt, compression of the placenta forces placental blood back into the sinuses in the decidua basalis[6]. These sinuses become blocked by the action of the strong myometrial contraction, and thus the compressed placenta attempts to force blood back into a high-resistance system. Ultimately, the sinuses become so congested that they rupture. The blood from the ruptured sinuses tears the fine septae of the spongy layer of the decidua basalis, and ultimately the placenta is sheared off[7]. Dieckmann and colleagues implied that this 'retroplacental hematoma' has no functional value, and a subsequent investigation suggested that it is the contraction and retraction of the uterine wall itself that cause it to rend itself apart from the placenta[7,8]. *[Editor's note: the reader should be aware that both the Brandt and the Dieckmann references were published more than 50 years ago and reflect, to a certain extent, the relative lack interest among the obstetric community in updating older concepts on practical points that they dealt with on a daily basis. L.G.K.]*

Ultrasonographic investigations more recently corroborated that the Dieckmann theory is correct. Herman and colleagues conducted real-time ultrasonographic imaging of the third stage of labor and identified a 'detachment phase', wherein the placenta completes its separation[9]. This detachment is preceded by a 'contraction phase', in which the placental site uterine wall undergoes thickening. However, the 'latent phase' before this thickening occurs varies between patients and was thought to determine the overall length of the third stage. Of interest, neither the latent phase nor the contraction phase was associated with ultrasound evidence of retroplacental hematoma formation.

The two classical methods of placental delivery result in different bleeding patterns. In the Schultze method, separation begins in the center of the placenta (the fetal surface), and this part descends first, with the remainder following. The Matthew Duncan separation method involves detachment of the leading edge of the placenta, and the entire organ slips down and out of the uterus sideways. The latter method is much less common (20% of the total), but is supposed to result in more bleeding for two possible reasons. First, in the Schultze method, any extravasated blood is trapped within the membranes which follow the placenta and may form a retroplacental clot, whereas this blood escapes immediately in the Matthew Duncan method. Second, placental separation is slower in the Matthew Duncan method, allowing more time for bleeding[10]. As clinicians are able to neither predict nor alter the method of placental separation, the distinction between the Schultze and Matthew Duncan methods is most probably clinically irrelevant *[although it was noted in every delivery conducted by this editor in the 1960s. L.G.K.]*

Control of postpartum bleeding results from contraction and retraction of the interlacing myometrial fibers surrounding maternal spiral arteries of the placental bed. Myometrial contraction compresses the spiral arteries and veins, thereby obliterating their lumina. It is for this reason that these specific myometrial fibers are often referred to as 'living ligatures'[10]. In addition, it is thought that some hemostasis occurs by means of direct pressure as the uterine walls are forced firmly to oppose one another as a result of myometrial contraction (see Chapter 22).

It is worth noting the physiological effect of early cord clamping, a common intervention in the active management of the third stage of labor, is to retain blood in the placenta, which prevents it from being so tightly compressed by the uterus. This, in turn, reduces the amount of myometrial retraction and contraction, leading to more, not less, bleeding. However, this blood is thought to form a retroplacental clot, which speeds up the shearing off of the placenta. Ultimately, the consequent speedy delivery of the placenta should lead to quicker hemostasis, but the intervention of cord clamping is a paradox in that it involves causing increased initial bleeding to reduce ultimate total bleeding.

Unfortunately, apart from the recent ultrasound studies mentioned above, there is a decided paucity of information about the physical changes which lead to hemostasis and placental separation.

Endocrine mechanisms leading to mechanical events

Like all muscular activity, uterine contractility depends on both electrical and hormonal stimuli. 'Intrinsic' activity may be mediated by stretch receptors, although it is unclear whether such mechanisms are neural or neurohormonal. Two classes of hormones have been implicated in third-stage uterine contractility, namely oxytocin and prostaglandins.

Oxytocin

Interest in the role of oxytocin in the third stage has been partly motivated by the long-standing experience with the therapeutic use oxytocin to prevent postpartum hemorrhage (PPH). Broadly speaking, oxytocin causes increased uterine contractions by acting on myometrial oxytocin receptors. However, research has failed to show a clear and simple relationship between physiological oxytocin action and third-stage events for a number of reasons. Oxytocin assays are notoriously unreliable, because the decidua synthesizes its own oxytocin. As a result, plasma levels do not reflect oxytocin concentrations at the myometrial level. Moreover, plasma oxytocin levels take no account of the density of myometrial oxytocin receptors, which has been shown to participate in a complex control mechanism with oxytocin itself and other factors. Finally, oxytocinase, a plasma enzyme, denatures oxytocin before it reaches its site of action[11].

During labor, oxytocin is released in a pulsatile manner, and both the pulse frequency and duration increase[12]. Exactly what triggers the pulsatile oxytocin release is currently unclear. Ferguson speculated that uterine stretching of the rabbit cervix stimulates oxytocin release, leading to uterine contractions[13]. This phenomenon so far has not been demonstrated in humans, but there may be significant pressure changes on adjacent pelvic organs and the vagina which result in neurological stimulation.

A pulse of oxytocin does not necessarily correspond to a uterine contraction, and some women do not experience a rise in plasma oxytocin after the delivery of the baby[14]. Moreover, it is not necessary to have an oxytocin pulse in order to deliver the placenta and achieve hemostasis. Additional methods of control must be involved. Whereas it is known that myometrial oxytocin receptor density increases during pregnancy and labor, the precise controls of this up-regulation are unknown[15].

For many years, synthetic oxytocic agents have been successfully used in the third stage both to prevent and to treat PPH. At the same time, however, therapeutic oxytocic agents used to augment labor are sometimes associated with uterine atony in the third stage. In this latter circumstance, the non-pulsatile administration of these agents may lead to down-regulation of oxytocin receptors, as has been demonstrated in *in vitro* studies[15]. Despite the acknowledged therapeutic role of oxytocic agents in the third stage of labor, the true physiological role of oxytocin in the third stage remains unclear. It appears to have an inconsistent or paradoxical relationship with the third stage.

Prostaglandins

Prostaglandins are potent stimulators of myometrial contractility, acting via cyclic AMP-mediated calcium release. The therapeutic usefulness of prostaglandin agents in PPH lends credence to the possibility of a physiological role for prostaglandins in the third stage of labor. The prostaglandins involved in uterine contraction are produced in decidual tissue, placental tissue and fetal membranes[16]. The uterotonic action of prostaglandins does not depend on gestation. There are many classes of prostaglandin; the two classes implicated in uterine contraction are PGE2 and PGF2α.

Several observers have noted that large amounts of prostaglandin are released in the third stage of labor. In an elegant experiment, Noort and colleagues measured plasma levels of prostaglandin metabolites during and up to 48 h after labor[17]. PGF2α levels reached their maximum and started to decline within 10 min after placental separation (Figure 2). The subsequent rapid decline in these levels suggested that the prostaglandins arise from necrosis/cellular disruption either at the placental site or the fetal membranes. The latter are known to be a major source of prostaglandins. *In vitro* experiments have shown that intrapartum amniotic fluid triggers prostaglandin synthesis in fetal membranes. The 'active agent' in the amniotic fluid remains unknown[16]; however, these observations are thought to reflect the active role of prostaglandins in securing hemostasis by way of myometrial contraction in the third stage.

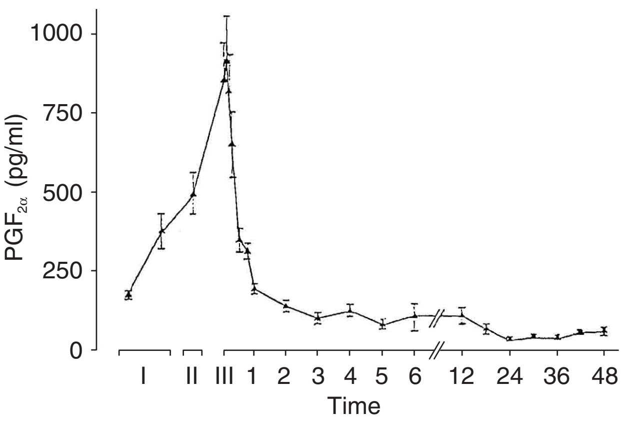

Figure 2 Plasma PGF2α levels (pg/ml; mean ± standard equivalent of the mean). (I) In early labor and at full dilatation; (II) at delivery of the fetal head; (III) at placental separation and up to 48 h after placental separation[17]

The interaction between prostaglandins and endogenous or therapeutic oxytocin in the third stage is not well understood. Numerous animal experiments have demonstrated interactions between prostaglandins and oxytocin at luteolysis, initiation and maintenance of pregnancy, and possibly at onset of labor[18]. However, therapeutic oxytocic agents used in the third stage do not appear to have a significant effect on prostaglandin metabolite concentrations[19]. Further studies are required better to understand from where these prostaglandins arise, and what controls their release.

In the past few years, misoprostol, a prostaglandin E1 analogue with uterotonic properties, has played an increasing role in the management of the third stage, as it is both cheaper and more thermostable than existing agents. Its uses are discussed in detail in several other chapters in this volume (see Chapters 32–35).

Coagulation

Many standard obstetric textbooks provide only the vaguest of suggestions that coagulation at the placental site represents an important hemostatic mechanism. Whilst this is certainly true, the exact pathway(s) involved are unclear (see Chapters 4 and 22). Before and after delivery, subtle changes take place in both coagulation factors and fibrinolysis agents. Plasma concentrations of clotting factors increase not only during pregnancy but also after delivery, which suggests a hypercoagulable state[20]. However, after placental separation, the fibrinolytic potential of the maternal blood also increases, and this tends to reduce the potential of blood to clot[21].

These conflicting changes are difficult to reconcile and are further complicated by changes in platelet activity before and after delivery. Perhaps of greater importance, they are poorly appreciated by many clinicians who are alone in a delivery room when what appears to be unusual bleeding commences. In addition to the changes in platelet activity, there are indications that an inflammatory response arises at the placental bed after placental delivery[22]. Such a response would promote local coagulation. This finding is important in terms of evolutionary advantage, because it allows prevention of hemorrhage at the placental site, while elsewhere (particularly in deep pelvic and leg veins) thrombi are less likely to persist, due to the increased fibrinolysis.

von Willebrand disease (factor VIII deficiency) is an important example of a coagulopathy which can result in increased risk of PPH. This is especially true in the disease variant featuring factor VIIIc deficiency. In many ways, von Willebrand disease mimics a platelet adhesion dysfunction, and indeed the only aspect of hematological hemostasis after placental delivery which can be emphasized with any certainty is the formation of platelet plugs at arterioles. PPH rates in von Willebrand's disease are in excess of 15%, and it has been suggested that this hemorrhage is largely preventable by minimizing maternal trauma at delivery and giving prophylactic treatment with desmopressin (DDAVP)[23].

In summary, the hemostatic mechanisms during and after placental separation probably involve the contraction of muscle sheaths around the spiral arteries, leading to platelet plug formation, retraction of the uterus causing mechanical occlusion of arterioles facilitating platelet plug formation, and the activation of both the clotting cascade and fibrinolysis. Many of these events are vague assumptions rather than demonstrated facts, as research into many aspects of third-stage physiology has been grossly neglected. Indeed, the fact that for decades effective treatments have been available for PPH in the developed world has acted as a true disincentive for novel work and ideas. It is tragic that the third stage of labor, the most dangerous moment of pregnancy, is so poorly understood.

PATHOPHYSIOLOGY OF POSTPARTUM HEMORRHAGE

Although most of the physiological processes in the third stage of labor remain unclear, they broadly help to explain the etiology of atonic PPH. In this section, the etiology and accompanying pathophysiology are discussed.

Uterine atony

The most common cause of PPH is uterine atony, i.e. failure of the uterus to contract. Primary PPH due to uterine atony occurs when the relaxed myometrium fails to constrict the blood vessels that traverse its fibers, thereby allowing hemorrhage. Since up to one-fifth of maternal cardiac output, or 1000 ml/min, enters the uteroplacental circulation at term, PPH can lead to exsanguination within a short time.

Whilst uterine atony is responsible for 75–90% of primary PPH, traumatic causes of primary PPH (including obstetric lacerations, uterine inversion and uterine rupture) comprise about 20% of all primary PPH. Significant but less common causes of PPH include congenital and acquired clotting abnormalities, which comprise around 3% of the total[24]. Uterine atony is responsible for the majority of primary PPH originating from the placental bed. Although the most important risk factor is a previous history of atonic PPH (relative risk 3.3)[25], many other important risk factors are often found in combination.

Failure of the uterus to contract may be associated with retained placenta or placental fragments, either as disrupted portions or, more rarely, as a succenturiate lobe. The retained material acts as a physical block against strong the uterine contraction which is needed to constrict placental bed vessels. In most cases, however, dysfunctional postpartum contraction is the primary reason for placental retention. It is more likely for the placenta to be retained in cases of atonic PPH, and so the contraction failure often becomes self-perpetuating. The reasons for this contractile dysfunction are unknown. The exception is uterine fibroids, where the source of distension cannot be removed by uterine contraction, and must therefore cause the atony. However, the uterus does not even have to be distended during the third stage for contractile dysfunction to occur. Distension prior to delivery, which occurs with multiple pregnancy and polyhydramnios, also affects the ability of the uterus to contract efficiently after delivery, and is thus another risk factor for atonic PPH.

When PPH occurs following an antepartum hemorrhage, the scenario is particularly difficult since there have been two episodes of blood loss. A rare but serious complication of abruption is extravasation of blood into the myometrium, known as a Couvelaire uterus, which impairs the physiological uterine contraction/retraction hemostatic process. However, the relationship between the extravasation process and uterine dysfunction is not fully understood. Chorioamnionitis has a similar effect for unknown reasons. Both antepartum hemorrhage and chorioamnionitis also impair uterine contraction during the first two stages of labor, and prolonged labor in general is a risk factor for PPH. Conventional wisdom suggests that delay in the first two stages leads to uterine atony, but it is more logical to suggest that uterine dysfunction before onset of labor results in delay in all three stages, and thus causes PPH. As far as we are aware, there is no ongoing research into this ‘universal uterine dysfunction’.

The lower segment as an implantation site

[Editor’s note: The three sections that follow can be supplemented by reading the chapters by Palacios-Jaraquemada and co-workers in Section 1 of this volume, which describe the differences in the blood supply to the upper and the lower segments. L.G.K.]

Classic teaching suggests that the lower segment arises from the cervical isthmus. The isthmus is the region joining the muscle fibers of the corpus uteri to the dense connective tissue of the cervix. Thus, the major part of the lower segment arises from the cervix, with an uncertain smaller portion coming from the corpus uteri.

In both placenta previa and placenta previa accreta, the placental bed (and thus the postpartum bleeding site) is in the lower segment. The presence of lower segment implantation makes hemorrhage and placental retention much more likely. Although existing evidence is scanty, there are indications that the etiology of pathological bleeding is inextricably linked with the anatomical and physiological limitations of the lower segment.

At term the lower segment is continuous with the upper segment. Goerttler’s original studies from the 1930s suggested that muscle fibers of the lower segment are more vertical than those of the upper segment, and run down like a spiral staircase[1]. The classical (and perhaps rather simplistic) interpretation of this arrangement suggests that, whereas upper segment fibers allow contraction and retraction in the third stage, lower segment fibers merely allow dilatation in parallel with the cervix.

There are large gaps of knowledge regarding the histology of the lower segment. Traditional teaching describes only gross differences in the amounts of muscle between upper and lower segments, and in the patterns of muscle fibers as already described[1,26]. More recently, some studies have investigated lower segment implantation, but the researchers have focused on parameters measuring placental invasion, usually with a view to explaining the etiology of pre-eclampsia[27].

A pregnancy sac implanted in a scarred myometrial area, with a deficient endometrium and blood supply, results in a cascade of poorly understood reactions with variable outcomes. These range from miscarriage to placenta accreta. The outcome probably depends on the nature and degree of the deficient endometrium, and where the blastocyst was implanted within it.

Placenta previa

In placenta previa, the placental site is located in an abnormally low position. Atonic PPH is a recognized complication and, even if cesarean section is performed, severe intraoperative bleeding is a significant risk[28]. The usual pharmacological methods used to stem hemorrhage are often less effective. Surgical methods, such as oversewing of bleeding sinuses and the B-Lynch suture (see Chapter 51), are sometimes also ineffective so that hysterectomy (see Chapter 55) proves necessary. Hemorrhage is often not stopped unless the entire lower segment is removed; a subtotal hysterectomy is often inadequate, and many surgeons perform total abdominal hysterectomy as the operation of choice. Thus, the involvement of the lower segment makes it more likely not only that hemorrhage will occur, but also that standard treatment modalities will fail (see Chapter 1).

Authors in conventional texts often suggest that, in lower segment implantation, the muscle surrounding the placental bed is inadequate to the task of postpartum contraction/retraction, and thus hemorrhage ensues[28]. As contraction and/or retraction are considered essential prerequisites for both placental detachment and postpartum hemostasis, the inference is that physiological hemostasis from a lower segment placental bed is difficult if not impossible. This is obviously not the case, however, as clearly not all cases of grade IV placenta previa necessitate hysterectomy. The only possible conclusion is that there are qualitative and quantitative differences in the musculature of the lower segment in different patients. A literature search on this topic confirms that neither the nature nor the origin of these differences have been investigated.

Biswas and colleagues have compared placental bed biopsy changes in placenta previa and normally implanted placenta, showing that previa is associated with significantly higher trophoblastic giant cell infiltration and physiological changes of the myometrial spiral arterioles[29]. This work is typical of modern obstetric research in that it concentrates on antenatal events while ignoring postpartum events. However, the findings are interesting because they suggest that the seeds of potential placenta accreta are sown in most cases of placenta previa. Nonetheless, no knowledge regarding the qualitative features of lower segment myometrium exists.

Placenta accreta

Placenta accreta is morbid adherence of placenta such that it invades the myometrium. It is rare; in 1990, the quoted incidence was around 1 in 2000 to 1 in 3500 pregnant women in North America[30]. This number may be increasing, however, not only in North America, but also worldwide for reasons discussed below. Placental adherence is also associated with a deficiency of decidua in the lower segment, the most common cause of which is endometrial scarring secondary to previous history of cesarean section or myomectomy, endometritis, evacuation of retained products of conception or uterine abnormalities (see also Chapter 28).

It is widely held in the recent literature that uterine surgery is a major risk factor for placenta previa and placenta accreta[31]. There is an increased tendency for placental implantation in the vicinity of the uterine scar with secondary trophoblast invasion of the myometrium. *[Editorial note: This is the most common reason to implicate prior cesarean sections, of which the numbers are rising worldwide, but it does not take into account the fact that this operation was performed regularly prior to the recent epidemic and accreta was an extraordinarily rare occurrence. L.G.K.]* Uterine scarring is also known to be associated with an increased risk of scar dehiscence, febrile morbidity and other factors[32]. Thus the scar is classically considered to be a 'weak area'. Scarring of muscle results in the normal tissue being replaced by fibrous tissue. Intrauterine retraction forces induced during labor tend to thin out the lower segment, and these forces stretch the scar to the point of rupture. Uterine rupture is not considered predictable[33], but is more likely with each cesarean section. Although poorly described in the literature, our personal clinical experience suggests that, with each ensuing cesarean section, the entire lower segment often seems to become thinner. Indeed, the lower segment may take on a translucent quality. This appearance is not limited to the scar itself. It is possible that the 'weak scar' in fact represents a generalized lower segment weakness induced by previous surgery.

Clinical experience also suggests that it is not enough to assume that PPH is more common with lower segment implantation purely because lower segment muscle is inadequate to the task. In cases of placenta previa and placenta accreta, the lower segment looks even thinner than normal. We hypothesize that the contractile nature of lower segment muscle, which is already less than that of the upper segment, is further lowered by the presence of the placenta. This would mean that implantation itself has an adverse effect on lower segment myometrium. Furthermore, there is a body of anecdotal evidence which implies that placental size and trophoblast invasion are greater in areas of limited decidual tissue, including implantation on scars and in ectopic pregnancies. We hypothesize that trophoblast would invade more readily into the poorly decidualized lower uterine segment, increasing the likelihood that placenta accreta will develop.

In terms of the previous discussion, it is unfortunate that a dramatic and remorseless rise in the cesarean section rate is being observed throughout the developed world. This phenomenon will inevitably give rise to an increase in the complications associated with placenta previa, placenta accreta and scar rupture. These complications are particularly important because they tend to be relatively less amenable to medical treatment and sometimes necessitate radical surgical intervention, such as hysterectomy; while such operations are readily available in many areas of the world with organized medical systems, they are not available in other parts of the world, a discrepancy which contributes heavily to the disparities seen in death rates.

Whereas knowledge of the ultrastructure of placental bed musculature is at best 'lacking' with regards to the upper segment, it is virtually non-existent for the lower segment. New research into this area is urgently needed, because all non-surgical therapeutic modalities for atonic PPH involve enhancement of uterotonicity and, in the absence of sufficient myometrium, they will simply not work. We hypothesize that lower segment placentation/surgery leads to structural and thus functional changes in the muscle histology. Thus, we envisage a new, clinically important class of PPH, 'lower segment PPH'. This new subclass will be best managed by new protocols which address the features specific to lower segment involvement (see Chapter 1).

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