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Averting maternal death and disability

Preventing postpartum hemorrhage in low-resource settings

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Abstract

Objectives: To review the literature to determine the most effective methods for preventing postpartum hemorrhage (PPH), the single most important cause of maternal death worldwide. **Methods:** Systematic review of published randomized controlled trials and relevant reviews. **Results:** Review of the literature confirms that active management of the third stage of labor, especially the administration of uterotonic drugs, reduces the risk of PPH due to uterine atony without increasing the incidence of retained placenta or other serious complications. Oxytocin is the preferred uterotonic drug compared with syntometrine, but misoprostol also can be used to prevent hemorrhage in situations where parenteral medications are not available (e.g. at home births in developing countries). **Conclusions:** The use of active management of the third stage of labor to prevent PPH due to uterine atony should be expanded, especially in developing country settings. © 2002 International Federation of Gynecology and Obstetrics. Published by Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Postpartum hemorrhage; Active management; Oxytocin; Misoprostol; Maternal death

1. Introduction

The World Health Organization (WHO) estimates that nearly 515 000 women die from com-

plications of pregnancy and childbirth every year [1]. It comes as no surprise that almost 99% of maternal deaths occur in developing countries [2] in areas having inadequate transport systems and limited access to skilled caregivers and emergency obstetric care services. Immediate postpartum hemorrhage (PPH), defined as excessive blood loss within 24 h after childbirth, is the single most

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important cause of maternal death worldwide, accounting for almost half of all postpartum maternal deaths in developing countries [3].

Hemorrhage, if uncontrolled or untreated, can quickly lead to shock and death. Most deaths due to PPH occur within the first 7 days after childbirth [3]; one study in Egypt found that 88% of these deaths occur within the first 4 h postpartum [4]. Many factors influence whether or not PPH is fatal. The high incidence of severe anemia among women in developing countries contributes to the high death toll; a woman who is already anemic is unable to tolerate blood loss that a healthy woman can [5]. Another important factor is that many births in developing countries occur in the home because of cultural preferences, economic reasons, poor quality services, or services that are difficult to access. A woman may give birth alone or in the presence of an untrained birth attendant or family members. If a woman begins to hemorrhage, the attendant is often unprepared to handle the emergency. In many cases, long delays occur in making the decision to seek help and in transporting the woman to a hospital or center equipped to treat PPH.

In some cases of PPH, uterine artery ligation or hysterectomy may become necessary to control the hemorrhage when simpler measures (e.g. use of drugs to stop the bleeding, bimanual compression of the uterus) are not taken or they fail. These surgical procedures are often only available in tertiary care or referral hospitals, and many women must be transported long distances to receive these life-saving services. In addition, these surgical procedures are costly and require comprehensive emergency surgical services, including general anesthesia. Blood transfusions are often required and expose women to the risk of serious transfusion reactions and infection with HIV or hepatitis B or C. Those women who survive PPH usually suffer from severe anemia, and the entire experience may be emotionally devastating to the women and their families.

Thus, in countries with high maternal mortality and limited resources, introducing low cost, evidence-based practices that prevent PPH is an important way to improve women's health. The purpose of this paper is to review the physiologic

process that leads to PPH and highlight the latest evidence-based practices that have been shown to prevent immediate PPH.

1.1. Postpartum hemorrhage and the third stage of labor

Although blood loss greater than 500 ml is the most commonly accepted definition of PPH (and the definition most commonly used in the randomized controlled trials (RCTs) reviewed in this paper), it is possible for blood loss to exceed this amount during a normal birth or cesarean section [6]. This definition is also not clinically useful because it is often difficult to accurately assess the amount of blood that a woman has lost. The blood may be mixed with amniotic fluid or urine, and may be dispersed on sponges or linens, in buckets, or on the floor. In addition, slow bleeding from an episiotomy or tear may go unnoticed by an attendant. A more accurate definition of PPH is any blood loss that causes a physiological change (e.g. low blood pressure) that threatens the woman's life. This definition also more accurately reflects the fact that anemic women in developing countries are more susceptible to blood loss after giving birth.

Immediate PPH is most commonly caused by uterine atony, the failure of the uterus to contract properly after childbirth. Other causes include trauma to the genital tract or a retained placenta or placental fragments. Understanding the processes that occur during the third stage of labor (the period of time from the birth of the newborn to when the placenta is delivered) and the anatomy and physiology of the uterus is important in understanding how to prevent PPH due to uterine atony.

The myometrium is the muscular component of the uterus and is composed of oblique muscle fibers arranged in a 'criss-cross' pattern surrounding blood vessels. During the third stage of labor, these muscle fibers contract and retract; the myometrium progressively becomes thicker and the intrauterine volume decreases. The placenta is unable to contract and thus begins to separate as

the surface area of the uterus becomes smaller. Upon separation of the placenta, the uterus becomes firm and globular, rising in the abdomen and possibly moving away from the abdominal midline. The umbilical cord may appear to lengthen. This process typically takes 10–30 min; if the placenta fails to separate within 30 min after childbirth the third stage is considered to be prolonged.

At the end of a term pregnancy, 500–800 ml of blood flow through the blood vessels at the placental site every minute [7]. As the placenta separates from the uterus, these vessels break and bleeding occurs. Continuous, coordinated contractions of the myometrium compress the local blood vessels to control bleeding at the placental site and allow formation of a retroplacental clot. When the uterus fails to have coordinated muscular contractions it is said to be atonic; blood vessels at the placental site are not constricted and hemorrhage occurs.

Numerous studies have examined factors that may lead to an increased incidence of PPH. Factors such as pre-eclampsia, multiple gestation, episiotomy, operative vaginal delivery, and prolonged labor have all been associated with PPH [6]. Although the presence of one or more of these factors may increase the woman's chances of PPH, two-thirds of PPH cases occur in women with no known risk factors [8]. Therefore, every woman must be closely monitored after childbirth for signs of PPH. In addition, steps should be taken to eliminate unnecessary procedures that contribute to the incidence of PPH, such as the use of episiotomy or operative vaginal delivery without clear indication. Because the presence of risk factors cannot be used to predict PPH, several groups have sought to determine if the third stage of labor should be actively managed in all women giving birth to decrease the incidence of uterine atony, the leading cause of PPH.

1.2. Active management of the third stage of labor

Active management of the third stage of labor is a three-part process intended to augment uterine contractions and prevent PPH due to uterine

atony. Active management of the third stage of labor is commonly used in the United Kingdom and Australia, but is not widely used in European or developing countries [9]. The recommended protocol comprises the following steps: (1) give a uterotonic drug within 1 min of the birth of the baby; (2) clamp and cut the umbilical cord soon after birth; and (3) deliver the placenta by applying controlled downward tension on the umbilical cord during a strong uterine contraction, while at the same time applying counter pressure (toward the woman's head) on the uterus through the abdomen.

2. Methods

We conducted a review of the literature to identify RCTs that evaluated the use of active management of the third stage of labor or the use of uterotonic drugs. We searched the electronic databases PubMed (National Library of Medicine, Bethesda, MD) and The Cochrane Library for all articles and reviews published through September 2001. Search terms included all variations of the words 'active management,' 'third stage of labor,' 'misoprostol,' 'oxytocin,' 'ergometrine,' and 'postpartum hemorrhage.' In addition, we searched the references of relevant articles, reviews, and textbooks.

3. Results

3.1. RCTs of active management of the third stage of labor

Three large RCTs, the Bristol, Hinchings-brooke, and Abu Dhabi trials, were selected because they examined the ability of active management of the third stage of labor to prevent PPH compared with physiologic management [10–12]. These trials were also included in the systematic review found in the Cochrane Library [9]. The methods used in the trials are summarized in Table 1. In all three trials, active management consisted of giving a prophylactic uterotonic drug

Table 1
Methods of managing the third stage of labor used in three trials comparing physiologic and active management

Methods	Physiologic management	Active management	Reference
Uterotonic drug	None	Syntometrine given after delivery of anterior shoulder (oxytocin given if high blood pressure)	[10]
	None	Syntometrine or oxytocin given after delivery of anterior shoulder	[11]
	Oxytocin given after delivery of placenta	Oxytocin given during delivery of anterior shoulder	[12]
Umbilical cord	Unclamped until placenta delivered	Immediately clamped	[10]
	Clamped after the cord stopped pulsating	Immediately clamped and cut	[11]
	Clamped and cut after delivery of baby	Immediately clamped and cut	[12]
Placenta	Delivered by maternal effort	Delivered by controlled tension on cord	[10]
	Delivered by maternal effort	Delivered by controlled tension on cord or by maternal effort	[11]
	Delivered by maternal effort	Delivered by controlled tension on cord	[12]

(i.e. before delivery of the placenta), clamping the umbilical cord, and delivering the placenta by controlled tension on the umbilical cord (one study also allowed delivery of the placenta by maternal effort). The physiologic management groups of the three trials differed from each other in that no prophylactic uterotonic drug was given in two of the trials, whereas one trial gave the drug routinely, but only after delivery of the placenta. The placenta was delivered by maternal effort in the physiologic groups in all three trials.

The results of these studies are summarized in Table 2. Compared with physiologic management, active management of the third stage of labor reduced the risk of PPH, the need for blood transfusion, the incidence of prolonged third stage (longer than 30 min), and the need for additional therapeutic uterotonic drugs in all three trials. The incidence of headache, increased blood pressure, or manual removal of retained placenta did not differ between the two groups in any of the

trials. Rogers et al. [11] also found that maternal position (supine vs. upright) had no effect on incidence of PPH in either group. Neonatal outcomes (Apgar score less than 6 at 5 min, admission to neonatal intensive care unit, and incidence of jaundice) did not differ between the active and physiologic management groups [10,11].

Although there are theoretical complications of active management of the third stage of labor (e.g. retained placenta, uterine inversion, cord avulsion), the use of active management did not increase the incidence of retained placenta and there were no reported cases of uterine inversion or cord avulsion in the studies reviewed here. To avoid these complications, however, tension should not be maintained on the cord if the placenta does not descend during 30–40 s of controlled tension during a contraction; the procedure should be attempted again with the next contraction of the uterus [12]. In addition, counter pressure on the lower segment of the

Table 2
Maternal outcomes in three trials comparing physiologic and active management of the third stage of labor

Outcome	Physiologic management	Active management	Significance	Reference
Blood loss > 500 ml	17.9%	5.9%	OR 3.13 (2.34–4.2)	[10]
	16.5%	6.8%	RR 2.42 (1.78–3)	[11]
	11%	5.8%	OR 0.50 (0.34–0.73)	[12]
Blood loss > 1000 ml	3.1%	0.8%	OR 3.22 (1.62–6.42)	[10]
	2.6%	1.7%	NS	[11]
	3.16%	0.72%	OR 0.22 (0.08–0.57)	[12]
Transfusion	5.7%	2.1%	OR 2.56 (1.57–4.19)	[10]
	2.6%	0.5%	RR 4.9 (1.68–14.25)	[11]
	0.49%	0.12%	OR 0.25 (0.01–2.33)	[12]
Low hemoglobin	6%	3.2%	OR 1.89 (1.2–2.99)	[10]
	28.4%	15.2%	RR 1.86 (1.51–2.3)	[11]
Change in hematocrit (mean ± S.D.)	8 ± 1.7	2 ± 1.2	$P < 0.001$	[12]
Retained placenta	2.6%	1.9%	NS	[10]
	1.7%	2%	NS	[11]
	4.5%	1.58%	OR 0.31 (0.15–0.63)	[12]
Third stage > 30 min	26%	3%	OR 6.42 (4.9–8.41)	[10]
	16.4%	3.3%	RR 4.9 (3.22–7.43)	[11]
Duration of third stage (min, mean ± S.D.)	14 ± 2.5	4 ± 2.5	$P < 0.001$	[12]
Therapeutic uterotonic drugs	29.7%	6.4%	OR 4.83 (3.77–6.18)	[10]
	21.1%	3.2%	RR 6.25 (4.33–9.96)	[11]
	5.17%	2.3%	OR 0.44 (0.24–0.78)	[12]
Increased diastolic blood pressure	0.9%	0.9%	NS	[10]
	0.1%	0.8%	NS	[11]
Headache	0.9%	1.5%	NS	[10]
	0.4%	0.7%	NS	[11]
Nausea	5.9%	11.5%	RR 0.51 (0.36–0.72)	[11]
Vomiting	6.5%	12.1%	OR 0.52 (0.37–0.72)	[10]
	2.2%	6.3%	RR 0.35 (0.21–0.61)	[11]

uterus (toward the woman's head) should always be applied to the uterus when tension is placed on the umbilical cord [12].

3.2. Uterotonic drugs

Although active management of the third stage of labor is typically a three-part process, giving a uterotonic drug soon after the birth of the baby is

the part of the process that has the greatest impact on the prevention of PPH. Two RCTs that assessed the effectiveness of oxytocin vs. placebo (saline) in preventing PPH when the placenta was delivered by maternal effort showed that the use of oxytocin significantly reduced the incidence of PPH and decreased the length of the third stage (Table 3) [13,14]. These studies support Prendiville et al. [15], who found that giving a uterotonic drug reduced the risk of hemorrhage by

Table 3
Use of oxytocin in preventing PPH

	Oxytocin	Placebo	Significance	Reference
Blood loss > 500 ml	25%	42%	$P = 0.02$	[14]
	20.3%	35.9%	$P < 0.001$	[13]
Duration of third stage (min, mean \pm S.D.)	9.9 \pm 7.4	11.7 \pm 6.4	$P = 0.01$	[14]
Retained placenta	3.5%	2.3%	NS	[14]
Mean hemoglobin 48 h postpartum (g/dl)	11.7	11.4	$P < 0.001$	[14]

NS, not significant.

approximately 40%. Administration of oxytocin also resulted in significantly higher hemoglobin levels 48 h postpartum and did not increase the risk of retained placenta compared with placebo [13,14]. Khan et al. [12] found that uterotonic drugs were more effective in preventing PPH if they were administered before, rather than after, the placenta was delivered.

Several RCTs have compared oxytocin to syntometrine (oxytocin plus ergometrine) to determine which drug is most effective for use in active management [16–18]. The results of these trials, which were also included in the systematic review found in the Cochrane Library [19], are summarized in Table 4. Although syntometrine resulted in a significant but small reduction in PPH compared with oxytocin in one study, it was consistently associated with an increased incidence of side effects such as nausea, vomiting,

headache, and increased blood pressure. These results, combined with the fact that ergometrine cannot be given to women with hypertension (a common problem during pregnancy), make oxytocin the preferred drug for use in active management.

Oxytocin and syntometrine, although effective in preventing PPH, do have disadvantages. In addition to the side effects mentioned above, these drugs must be handled and stored properly because they are unstable when exposed to light and high ambient temperatures. Furthermore, these drugs must be injected. Not only does this require that the attendant be trained and qualified to administer these drugs, but it also requires a readily available supply of sterile syringes and needles that must be handled and disposed of properly.

An alternative uterotonic drug is misoprostol

Table 4
Comparison of oxytocin vs. syntometrine for active management of the third stage of labor

Outcome	Results	Reference
Blood loss > 500 ml	No difference in ability to prevent PPH	[16,17]
	Syntometrine prevented PPH better than oxytocin	[18]
Retained placenta	No difference in incidence of retained placenta	[16,17]
	Syntometrine increased incidence of retained placenta	[18]
Duration of third stage	No difference in length of third stage	[16–18]
Therapeutic uterotonic drugs	Syntometrine decreased need for additional uterotonic drugs	[16–18]
Side effects	Syntometrine increased the incidence of nausea and vomiting, and increased blood pressure	[16–18]
	Syntometrine increased the incidence of headache	[16–18]

Table 5
Comparison of misoprostol vs. syntometrine and oxytocin for active management of the third stage of labor

Outcome	Results	Reference
Blood loss (ml)	No difference in ability to reduce blood loss	[20,21]
	Oxytocin prevented PPH better than misoprostol	[22]
Retained placenta	Syntometrine increased incidence of retained placenta	[20]
	No difference between oxytocin and misoprostol	[22]
Duration of third stage	No difference in incidence of prolonged third stage	[20,21]
Therapeutic uterotonic drugs	Misoprostol increased need for additional uterotonic drugs	[20,22]
	No difference in need for additional uterotonic drugs	[21]
Side effects	Misoprostol increased incidence of shivering and temperature greater than 38 °C	[20–22]

(Cytotec, Searle, Skokie, IL), a prostaglandin E₁ analogue. Misoprostol is inexpensive, stable at room temperature, and can be given orally or rectally; these are tremendous advantages over the uterotonic drugs that are currently available. Two RCTs found that misoprostol (administered either orally or rectally) was comparable to syntometrine for preventing PPH [20,21], although a large WHO multicenter RCT found that, in hospital settings, oxytocin is preferable to oral misoprostol [22] (Table 5). However, when skilled providers and/or the necessary supplies are not available to give an injection of oxytocin (e.g. at home birth), misoprostol is clearly useful, even if it is less effective than injectable uterotonic drugs [23]. For these situations, the use of 400–600 µg misoprostol as a part of active management of the third stage of labor has received a category A recommendation (good and consistent scientific evidence to support the recommendation) [24]. In addition, the United States Pharmacopeia has recently recommended that prevention of PPH is an acceptable indication for misoprostol, especially in settings where parenteral uterotonic drugs are not available [25].

4. Conclusions

Active management of the third stage of labor comprises one of the most important sets of practices available to prevent uterine atony, the most common cause of PPH. Active management decreases the incidence of PPH and the duration of the third stage of labor, reduces the need for

blood transfusion, and minimizes the severity of postpartum anemia.

Numerous studies have collectively and individually examined the components of active management of the third stage of labor. Data from RCTs provide strong and consistent support for the use of active management, especially in circumstances, such as home birth, where prevention of PPH is essential to reducing morbidity and mortality from PPH. Although oxytocin and syntometrine have both been shown to effectively prevent PPH, these drugs are not without side effects, they must be handled and stored properly, and they must be injected. Misoprostol appears to be an acceptable alternative in settings where parenteral uterotonic drugs are not available.

Although there are no published estimates of the extent to which active management of the third stage of labor is used, the data support the need to expand its use, especially in developing country settings.

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Editor's Comment

While it is often said that obstetric complications can be neither predicted nor prevented, there are, of course, some exceptions. Some proportion of all the major complications can be prevented by appropriate care during delivery as the table below shows. Antenatal care is effective in the prevention of eclampsia alone. Having said that, it is important to note that *death* from the

complication can almost always be prevented if appropriate care is available.

The five leading causes of maternal death in developing countries

Complication	Preventability
Unsafe abortion	Many, but not all, unwanted pregnancies can be prevented with comprehensive family planning programs
Sepsis	Many can be prevented using clean delivery techniques; some bacteria are endogenous
Hypertensive disorders eclampsia of pregnancy	Some eclampsias can be prevented if hypertension is well managed. Some happens without preceding symptoms
Obstructed labor	Cannot be prevented once pregnancy occurs. Some can be prevented by better nutrition in girlhood and adolescence. Use of partograph allows early identification, preventing prolonged labor and ruptured uterus
Postpartum hemorrhage	Many, but not all, can be prevented with active management of the third stage

The paper in this issue of the AMDD special section describes one of the very few effective means of preventing a complication that kills many thousands of women each year in develop-

ing countries. Active management of the third stage of labor is widely practiced in some, but not all, developed countries. It is practiced in few developing countries, and only rarely in home deliveries. McCormick and colleagues of the Maternal and Neonatal Health program of the Johns Hopkins University (at JHPIEGO) review the evidence for active management of labor of the third stage, including the evidence for an alternative uterotonic drug that can be safely and effectively used in home deliveries.

Critics will no doubt counter that the misuse of any uterotonic drug (i.e. giving it to accelerate labor, rather than after delivery of the newborn) can have disastrous consequences. This is true. But as countries move away from the use of traditional (and often untrained) birth attendants, and towards trained midwives either for home deliveries or in small maternities at the periphery, active management of the third stage with misoprostol becomes a realistic choice.

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