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The Correlates of Postpartum Blood Loss: Examination of Means and Markers for Risk Reduction

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THE CORRELATES OF POSTPARTUM BLOOD LOSS:

EXAMINATION OF MEANS AND MARKERS FOR RISK REDUCTION

WENDY RUTH SHELDON

A DISSERTATION

PRESENTED TO THE FACULTY

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ABSTRACT

Using secondary data on more than 40,000 hospital-based births in five countries, this thesis examines the role of select clinical and demographic variables in postpartum blood loss. Each chapter builds on prior work in the field and addresses outstanding questions with important implications for clinical practice.

In chapter one I assess systematically the independent and combined effectiveness of three interventions that are recommended for prevention of postpartum hemorrhage: oxytocin prophylaxis, controlled traction of the umbilical cord, and uterine massage. I also examine for the first time the effect of route of oxytocin administration (intravenous versus intramuscular). Results affirm the importance of oxytocin and controlled cord traction, but suggest that their relative importance depends upon the combination of interventions used. Findings also indicate that route of administration is important only when oxytocin is given alone, and in such cases intravenous administration is superior to intramuscular administration.

In chapter two I examine the relationship between duration of the third stage of labor and postpartum blood loss among women with and without oxytocin prophylaxis. While delays in placental delivery are known to increase postpartum hemorrhage risk, the precise trajectory of risk over the duration of the third stage has not been established. In addition, the potential effect of oxytocin prophylaxis on this relationship is not known. Results indicate that hemorrhage odds increase with third stage duration, peaking at durations of 25 minutes or more. Findings also suggest that oxytocin prophylaxis has a large and consistent effect on absolute hemorrhage odds at all third stage durations, but does not obviate the incremental change in hemorrhage odds over time.

Chapter three examines the role of low and high maternal hemoglobin on postpartum blood loss. While anemia is widely considered a risk factor for postpartum hemorrhage, the role of elevated hemoglobin has not been previously explored. Results suggest that anemia is an important correlate of hemorrhage risk, irrespective of the receipt of oxytocin prophylaxis. However there was considerable country-level heterogeneity in the magnitude of effect, which raises questions about the underlying nature of this relationship. Findings also suggest that elevated hemoglobin may increase hemorrhage odds among those with no oxytocin prophylaxis.

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INTRODUCTION

Postpartum hemorrhage (PPH) is a major cause of maternal mortality, accounting for about one-third of all pregnancy-related deaths in Africa and Asia (Khan et al., 2006). It is also a substantial source of morbidity and can lead to blood transfusion, hysterectomy, renal or liver failure, anemia and fatigue. (McDonald, 2007; ACOG, 2006). Primary PPH is defined by the World Health Organization as the loss of 500 mL or more of blood from the genital tract within 24 hours following vaginal birth, and severe PPH as the loss of 1,000 mL or more during this same period (WHO, 2003).

In practice, average blood loss at birth has been found to be approximately 500 mL (Fahy, 2009; Pritchard, 1965), and a woman's ability to tolerate such blood loss depends upon individual factors such as overall health and nutritional status. In light of this, some studies use higher thresholds for identification and treatment of PPH, due to its greater clinical significance (AbouZahr, 2003). In low resource settings, however, where there is high prevalence of malnutrition, anemia and infectious diseases, women are believed to be less capable of tolerating blood loss ≥ 500 mL than are women from higher resource settings.

The incidence of PPH ranges from less than 5% to more than 10% of all pregnancies (Carroli et al., 2008; AbouZahr, 2003; Akins, 1994), and has been found to vary widely by geographic region (Calvert et al., 2012; Carroli et al., 2008). PPH incidence is also impacted by the use of uterotonics during the third stage of labor (see Chapter 1 for more details), which have been shown to reduce hemorrhage risk by up to 60% (Cotter et al., 2001). Other factors that are known to impact incidence estimates include the delivery setting and means used to quantify blood loss. PPH incidence has been found to be higher in rural than urban settings (Carroli et al., 2008); and

when blood loss is measured objectively as compared with visual estimation (Carroli et al., 2008; Patel et al., 2006; Prasertcharoensuk et al., 2000).

The etiology of PPH falls into four main categories: *tone* or contraction abnormalities; *tissue*, involving retention of placental fragments or blood clots, abnormal placental positioning, or connective tissue disorders; *trauma*, involving lower genital tract lacerations or uterine rupture; and *thrombosis* involving coagulation abnormalities (Kominiarek and Kilpatrick, 2007). The vast majority of cases (70-90%) are due to uterine atony, which is failure of the uterus to contract naturally after giving birth (ACOG, 2006). Uterine contractions in the postpartum period serve to aid placental separation from the uterine wall and arrest subsequent bleeding at the placental site. If contractions do not occur, the uterus is said to be atonic and the risk of hemorrhage is greatly increased.

PPH is a largely unpredictable event, as two-thirds of cases have no identifiable risk factors. For the remaining one-third of cases, risk factors cited in the literature include a history of prior PPH; nulliparity; grand multiparity; presence of fibroids; prior uterine surgery; overdistended uterus, often caused by multiple gestations or a large baby; placental abnormalities such as placenta previa or accreta; coagulation abnormalities; anemia; receipt of obstetric or anaesthetic interventions such as labor induction, augmentation or epidural; and prolonged labor lasting more than 15 hours (Fahy, 2009; RCOG, 2009; Brabin et al., 2001; Akins, 1994; Tsu, 1993; Combs et al., 1991).

Prevention of PPH

There are two primary clinical strategies for prevention of PPH. The first involves identification and management of antenatal risk factors, where possible; and the second involves provision of a

package of interventions to prevent PPH, which are known collectively as active management of the third stage of labor (see Chapter 1 for details). This dissertation examines the effectiveness of both strategies. Chapter one explores the effectiveness of three interventions recommended for active management of the third stage of labor: oxytocin prophylaxis, controlled traction of the umbilical cord, and uterine massage. Chapters two and three assess the roles of two variables that have been identified as risk factors for PPH—delays in progression of the third stage of labor and maternal anemia.

References

AbouZahr C. (2003). Global burden of maternal death and disability. *British Medical Bulletin,* 67:1-11.

The American College of Obstetricians and Gynecologists (ACOG). (2006). *ACOG Practice Bulletin: Postpartum hemorrhage.* 108(4):1039-1047.

Akins S. (1994). Postpartum hemorrhage. *Journal of Nurse-Midwifery,* 39:123S-134S.

Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V. (2012). Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. *PLoS ONE,*7(7):e41114.

Carroli G, Cuesta C, Abalos E, Gülmezoglu AM. (2008). Epidemiology of postpartum haemorrhage: a systematic review. *Best Practice & Research Clinical Obstetrics and Gynaecology,* 22:999-1012.

Combs CA, Murphy EL, Laros RK. (1991). Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol,* 77:69-76.

Cotter AM, Ness A, Tolosa JE. (2001). Prophylactic oxytocin for the third stage of labor. *Cochrane Database Syst Rev,* (4):CD000201.

Fahy KM. Third stage of labour care for women at low risk of postpartum haemorrhage. (2009). *American College of Nurse-Midwives,* 54:380-386.

Khan KS, Wojdyla D, Say L, Gülmezoglu MA, Van Look PFA. (2006). WHO analysis of causes of maternal death: a systematic review. *Lancet,* 367:1066-1074.

Kominiarek MA, Kilpatrick SJ. (2007). Postpartum hemorrhage: a recurring pregnancy complication. *Semin Perinatol,* 31:159-166.

Patel A, Goudar SS, Geller SE, Kodkany BS, Edlavitch SA, Wagh K, Patted SS, Naik VA, Moss N, Derman RJ. (2006). Drape estimation vs. visual assessment for estimating postpartum hemorrhage. *Int J Gynaecol Obstet,* 93(3):220-224.

Prasertcharoensuk W, Swadpanich U, Lumbiganon P. (2000). Accuracy of the blood loss estimation in the third stage of labor. *Int J Gynaecol Obstet,* 71:69-70.

Pritchard JA. (1965). Changes in blood volume during pregnancy and delivery. *Anaesthesiol,*26:395-398.

World Health Organization (WHO). (2003). *Managing complications of pregnancy and childbirth: a guide for midwives and doctors.* Geneva.

CHAPTER 1

How Effective are the Components of Active Management of the Third Stage of Labor?[1,2]

Abstract

Background: Active management of the third stage of labor is recommended for prevention of postpartum hemorrhage and commonly entails prophylactic administration of a uterotonic, controlled cord traction, and uterine massage. While oxytocin is the first-choice uterotonic, it is not known whether its effectiveness varies by route of administration. There is also insufficient evidence regarding the benefits of controlled cord traction or uterine massage. This analysis assessed the independent and combined effectiveness of all three interventions, and the effect of route of oxytocin administration on postpartum blood loss.

Methods: Secondary data were analyzed from 39,202 hospital births in four countries and two clinical regimens: one in which oxytocin was administered following delivery of the baby; the other in which it was not. We used logistic regression to examine associations between clinical and demographic variables and postpartum blood loss ≥ 700 mL.

[1] A version of this paper was published as: Sheldon WR, Durocher J, Winikoff B, Blum J, Trussell J. (2013). How effective are the components of active management of the third stage of labor? *BMC Pregnancy Childbirth,* 13:46.

[2] Parts of this paper were also presented at the XXII Asian and Oceanic Congress of Obstetrics and Gynecology in Taipei City, Taiwan (2011); and the XX FIGO World Congress of Gynecology and Obstetrics in Rome, Italy (2012).

Results: Among those with no oxytocin prophylaxis, provision of controlled cord traction reduced postpartum hemorrhage odds by nearly 50% as compared with expectant management ($P<0.001$). Among those with oxytocin prophylaxis, provision of controlled cord traction reduced hemorrhage odds by 66% when oxytocin was administered intramuscularly ($P<0.001$) but conferred no benefit when it was administered intravenously. Route of administration was important when oxytocin was the only intervention provided: intravenous administration reduced hemorrhage odds by 76% as compared with intramuscular administration ($P<0.001$); when combined with other interventions, route of administration had no effect. In both clinical regimens, uterine massage was associated with increased hemorrhage risk.

Conclusions: Recommendations for active management of the third stage of labor should account for setting-related differences such as the availability of oxytocin and its route of administration. The optimal combination of interventions will vary accordingly.

Background

Postpartum hemorrhage is a leading cause of maternal death in low resource settings (Khan et al., 2006). International guidelines for the prevention of postpartum hemorrhage currently recommend a package of interventions known collectively as Active Management of the Third Stage of Labor (AMTSL) (WHO et al., 2006; ICM/FIGO, 2004). These include prophylactic administration of a uterotonic agent, controlled traction of the umbilical cord, and uterine massage. AMTSL is intended to reduce postpartum blood loss through expediting placental delivery and preventing uterine atony (Begley et al., 2010).

Uterotonic agents are administered shortly following delivery of the baby to stimulate uterine contractions. Oxytocin is the first-choice agent due to its high efficacy and lower incidence of

adverse side effects (Gülmezoglu et al., 2007; McDonald et al., 2004; Cotter et al., 2001; Gülmezoglu et al., 2001). In a 2001 systematic review of seven randomized or quasi-randomized controlled trials involving more than 3,000 women, oxytocin prophylaxis was associated with a 50% reduction in the risk of postpartum bleeding ≥ 500 mL, as compared with no uterotonics (Cotter et al., 2001). Oxytocin can be administered intravenously or intramuscularly and it has been widely assumed that its effect on postpartum blood loss does not vary with route of administration (Gülmezoglu et al., 2001). This assumption is based largely on a 1972 pharmacokinetic study (N=26) that found little difference in the absorption rates of intramuscular and intravenous oxytocin (Gibbens et al., 1972). Since then, no published studies have further examined this question (Oladapo et al., 2012).

Controlled cord traction is intended to facilitate placental separation and delivery. It involves manual application of gentle downward tension on the umbilical cord while maintaining counter pressure on the uterus, and is administered in conjunction with uterine contractions (WHO et al., 2006; ICM/FIGO, 2004; Spencer, 1962). So far no studies have assessed the independent effect of controlled cord traction on postpartum blood loss, and few have assessed its effect in combination with other AMTSL components. Most recently, a large randomized controlled trial involving more than 24,000 participants found that provision of controlled cord traction had only a small, non-significant effect on the risk of severe hemorrhage among women who were already receiving oxytocin prophylaxis (intravenous or intramuscular) (Gülmezoglu et al., 2012). In contrast, a 1997 trial involving more than 1,600 women found that controlled cord traction combined with intramuscular oxytocin reduced the risk of postpartum bleeding ≥ 500 mL by 50%, as compared with expectant management (Khan et al., 1997). Lastly, a 2009 pilot study involving just over 200 participants found a non-significant decrease in median blood loss

among those who received all three AMTSL components, as compared with receipt of uterine massage plus oxytocin (intramuscular or intravenous) (Althabe et al., 2009).

Uterine massage is believed to stimulate uterine contractions through prompting the release of prostaglandins. As a result, in 2004 the International Confederation of Midwives and International Federation of Gynaecologists and Obstetricians (FIGO) added uterine massage to their updated joint AMTSL guidelines (ICM/FIGO, 2004). To date, two trials have assessed its effect on postpartum blood loss. The first was a pilot study (N=198) in which provision of all three AMTSL interventions was associated with a non-significant decrease in postpartum blood loss, as compared with oxytocin plus controlled cord traction (Abdel-Aleem et al., 2006). In the second trial uterine massage was associated with increased blood loss, although treatment was initiated before placental delivery rather than after, as per current AMTSL guidelines (Abdel-Aleem, 2010).

Numerous studies have also attempted to assess the cumulative effectiveness of the full AMTSL package. Findings from a 2010 systematic review of three randomized controlled trials, all comparing active with expectant management, indicated that provision of all three interventions reduced the average risk of severe postpartum hemorrhage (≥ 1,000 mL) by two-thirds (Begley et al., 2010). The studies in this review, however, used an early definition of AMTSL that did not include uterine massage, while also including early clamping of the umbilical cord, which is no longer recommended due to concerns about possible adverse neonatal effects.

There are a number of important, unanswered questions about the effect of the AMTSL components on postpartum blood loss. While this is partly due to a paucity of evidence, it also results from heterogeneity across studies in selection of treatment and control groups,

measurement of blood loss (e.g. visual assessment versus more objective means), and variation over time in the interventions included in the AMTSL package. The primary objectives of this analysis, therefore, were to assess systematically the independent and combined effectiveness of all three current AMTSL components, and to examine the effect of route of oxytocin administration on measured postpartum blood loss.

Methods

Data were collected as part of two randomized controlled trials that compared two uterotonics for the treatment of postpartum hemorrhage, the details of which have been reported elsewhere (Blum et al., 2010; Winikoff et al., 2010). The trials took place between August, 2005 and January, 2008 and involved nine secondary- and tertiary-level hospitals from five countries in two distinct clinical regimens. In the first regimen oxytocin was not routinely provided during the third stage of labor, while in the second oxytocin was routinely provided. Study sites included hospitals in Egypt (one), Ecuador (one) and Vietnam (two) in the no oxytocin prophylaxis regimen; and Burkina Faso (one), Egypt (one), Turkey (one) and Vietnam (two) in the oxytocin prophylaxis regimen. The original research was approved by the Western Institutional Review Board (Seattle, WA, USA) and relevant institutional review boards in participating countries.

All women were screened for eligibility and provided written informed consent upon admission to the hospital labor ward. Women were excluded if they delivered by caesarean section, delivery occurred outside the hospital facility, or they were enrolled in the no oxytocin prophylaxis regimen but received uterotonics for any reason during labor. The study protocols were identical across both clinical regimens, with exception of the provision of oxytocin prophylaxis. For

women in the oxytocin prophylaxis regimen, oxytocin (10 IU or 5 IU) was administered intramuscularly or intravenously in accordance with standard hospital procedures. For women in both clinical regimens, controlled cord traction and uterine massage were provided at the discretion of each site and in accordance with hospital procedures.

Information about basic demographic and obstetric characteristics, pre-partum hemoglobin concentrations, postpartum blood loss, provision of all AMTSL components, and route of oxytocin administration (if applicable) were recorded for each participant. Hemoglobin was measured using a Hemocue device (Hemocue®, Ängelholm, Sweden). Blood loss was measured using a polyurethane receptacle with calibrated funnel (Brasss-V Drapes®, Excellent Fixable Drapes, India) beginning immediately after birth and continuing for the first hour postpartum or, if hemorrhage was diagnosed, until the cessation of active bleeding. Treatment for hemorrhage was provided if bleeding reached 700 mL within the first hour postpartum or, prior to that, by clinical judgment.

Statistical analysis

For these analyses we used data from eight of the nine study sites. We excluded all 1,625 participants from Quito, Ecuador, the only high elevation site in the study, due to atypical blood loss patterns across the AMTSL groups studied (overall, rates of hemorrhage were 30% in Quito versus 2-12% at all other sites). We examined bivariate relationships between clinical and demographic variables and outcomes of mean and median postpartum blood loss, blood loss ≥ 500 mL, and blood loss ≥ 700 mL. For the multivariate analyses we used multivariable logistic regression with an outcome of blood loss ≥ 700 mL in order to capture the more serious cases, and because most women diagnosed with postpartum hemorrhage received treatment at this level

of blood loss. We also conducted analyses using an outcome of blood loss ≥ 500 mL and the results (not shown) were largely consistent with those obtained using the 700 mL cutpoint.

All analyses were stratified by receipt of oxytocin prophylaxis in order to adjust for heterogeneity that may have been due to clinical regimen. We were unable to include site controls directly in the regression models due to lack of within-site variation in the provision of AMTSL components.

Results

8,427 women were enrolled in the no oxytocin prophylaxis regimen, 8,221 of whom were included in these analyses. Among the 206 excluded from analysis, 45 had caesarean sections, 153 were missing information on postpartum blood loss, and eight were missing information on AMTSL components. 31,180 women were enrolled in the oxytocin prophylaxis regimen, 30981 of whom were included in these analyses. Among the 199 excluded from analysis, four delivered outside the hospital, 79 had caesarean sections, 45 were missing information on postpartum blood loss, 39 were missing information on AMTSL components, and nine did not receive oxytocin during the third stage of labor. 23 others received oxytocin plus uterine massage and were excluded due to the small number of participants for that AMTSL group.

The demographic and obstetric characteristics of study participants by AMTSL group are summarized in Table 1. There were important country-level differences in provision of AMTSL components that were largely site-driven. There were few other demographic differences across AMTSL groups with exception of educational attainment, which primarily reflected country-level disparities; and obstetric practices such as receipt of epidural and labor induction/augmentation, which reflected differences in standard hospital practices.

The distribution of postpartum blood loss across AMTSL groups is summarized in Table 2. The variation in median blood loss was greatest in the no oxytocin prophylaxis regimen and ranged from 300 mL among those receiving uterine massage only, to 135 mL among those receiving controlled cord traction only. Within the oxytocin prophylaxis regimen, median blood loss was highest (300 mL) among those who received intramuscular oxytocin only or intramuscular oxytocin plus controlled cord traction, and lowest (200 mL) among those who received all three AMTSL components, irrespective of route of oxytocin administration.

The incidence of postpartum hemorrhage across AMTSL groups is presented in Table 3. With no oxytocin prophylaxis, the rate of blood loss ≥ 700 mL was highest among those who received uterine massage plus controlled cord traction (13.8%) and lowest among those who received controlled cord traction only (4.9%). With oxytocin prophylaxis, the rate of blood loss ≥ 700 mL was highest among those who received oxytocin only by intramuscular administration (3.8%) and lowest among those who received oxytocin only by intravenous administration (1.0%).

Table 4 shows logistic regression results for both clinical regimens using an outcome of blood loss ≥ 700 mL. In the no oxytocin prophylaxis regimen, provision of controlled cord traction reduced postpartum hemorrhage odds by nearly 50% as compared with no AMTSL components (OR=0.53, 95% CI 0.42–0.66). Provision of uterine massage was associated with increased hemorrhage risk, although these differences were only statistically significant for those receiving controlled cord traction plus massage (OR=1.66, 95% CI 1.31–2.10). Other predictors of postpartum hemorrhage risk were nulliparity (OR=1.24, 95% CI 1.04–1.48) and anemia (OR=1.19, 95% CI 1.00–1.42).

In the oxytocin prophylaxis regimen, provision of controlled cord traction reduced postpartum hemorrhage odds by 66% when oxytocin was administered intramuscularly (OR=0.33, 95% CI 0.25–0.45) but conferred no benefit when oxytocin was administered intravenously (OR=1.13, 95% CI 0.43-2.96)[*]. Uterine massage, on the other hand, was consistently associated with increased postpartum hemorrhage risk. When comparing those who received all three AMTSL components with those who received oxytocin plus controlled cord traction, the odds of blood loss ≥ 700 were nearly twice as high among those with intramuscular oxytocin (OR 1.94, 95% CI 1.43–2.65)[*], and nearly three times as high among those with intravenous oxytocin (OR=2.86, 95% CI 1.46–5.59)[*].

Route of oxytocin administration was important when oxytocin was the only intervention provided: in such cases intravenous administration reduced postpartum hemorrhage odds by 76% as compared with intramuscular administration (OR=0.24, 95% CI 0.12–0.50). Route of administration had no effect, however, when oxytocin was combined with other active management interventions. There were no significant differences in the odds of blood loss ≥ 700 mL among those who received intravenous oxytocin plus controlled cord traction as compared with intramuscular oxytocin plus controlled cord traction (OR=1.21, 95% CI 0.60-2.46)[*]; or for receipt of intramuscular oxytocin plus controlled cord traction and uterine massage, as compared with intravenous oxytocin plus controlled cord traction and uterine massage (OR=0.83, 95% CI 1.00-1.44)[*].

Other factors associated with increased odds of postpartum blood loss ≥ 700 mL in the oxytocin prophylaxis regimen were nulliparity (OR=2.36, 95% CI 2.01–2.76), anemia (OR=1.28, 95% CI 1.11–1.49), prior postpartum hemorrhage (OR=5.17, 95% CI 3.21–8.31), age 35 or older

[*] Results for these tests are listed at the bottom of Table 4.

(OR=1.46, 95% CI 1.07–1.99), and completion of secondary school or higher (OR=1.20, 95% CI 1.00–1.44). In contrast with prior research, labor induction/ augmentation did not increase hemorrhage odds and, in both the oxytocin and no oxytocin regimens, neither did multiple pregnancy (Combs et al., 1991; Stones et al., 1993; Magann et al., 2005).

Table 5 shows the predicted probabilities of postpartum bleeding ≥ 700 mL for all AMTSL groups. In general, the probability of blood loss ≥ 700 mL was considerably higher among all groups in the no oxytocin prophylaxis regimen, as compared with those in the oxytocin prophylaxis regimen. There was also greater heterogeneity in predicted hemorrhage probabilities among those who did not receive oxytocin prophylaxis, with probabilities ranging from 4.8% for receipt of controlled cord traction to 13.7% for receipt of uterine massage plus controlled cord traction. In the oxytocin prophylaxis regimen, the predicted probability of blood loss ≥ 700 mL ranged from 1.0% for receipt of intravenous oxytocin only to 3.9% for receipt of intramuscular oxytocin only.

Discussion

This is the first systematic assessment of the relative effectiveness of almost every possible combination of AMTSL interventions. There were important findings related to the provision of controlled cord traction. Our results suggest this intervention plays a critical role in preventing postpartum hemorrhage under two circumstances: 1) when oxytocin prophylaxis is unavailable during the third stage of labor; and 2) when oxytocin prophylaxis is available but administered intramuscularly. On the other hand, it may be unnecessary if oxytocin prophylaxis is administered intravenously.

Our findings are especially relevant in light of recent evidence that suggests controlled cord traction has little effect on postpartum blood loss when combined with oxytocin (Gülmezoglu et al., 2013). In this study, however, oxytocin was provided intramuscularly or intravenously, and the analyses did not address the potential effect of route of oxytocin administration. Our findings are also important in light of recent concerns about whether controlled cord traction increases risks for uterine inversion or placental separation from the umbilical cord (Althabe et al., 2009). There were no reported complications related to AMTSL practices in either clinical regimen. However, the providers administering controlled cord traction were all highly skilled physicians and nurses working in hospital settings. On the other hand, this procedure may be most valuable in non-hospital settings where oxytocin is either unavailable or available by intramuscular injection only. Since providers in these settings often have less training than those in hospital settings, this could increase procedure-related complication risks.

We found no evidence to support provision of uterine massage for the prevention of postpartum hemorrhage. In fact, our findings uniformly suggest that uterine massage either increases postpartum blood loss or confers no added benefits. This was true in both clinical regimens and is consistent with findings from prior research (Abdel-Aleem et al., 2010). These findings likely reflect some selection bias, however, since uterine massage is often provided in response to heavy postpartum bleeding. We suspect this may have occurred to some degree in our study, particularly among those for whom uterine massage was initiated either before or during placental delivery, rather than after as per current AMTSL guidelines (ICM/FIGO, 2004). Furthermore application of abdominal pressure may facilitate expulsion of blood into the measurement receptacle at a more rapid pace than would otherwise occur. If so, this may also explain at least some of the positive association between uterine massage and time dependent

measures of postpartum blood loss, even if the intervention itself was not a direct cause of increased bleeding.

Our analysis also provided an opportunity to examine the effect of route of oxytocin administration on postpartum blood loss. The results indicate that the longstanding assumption of equivalent effect may be incorrect, and that intravenous administration is superior to intramuscular administration. The evidence for this can be found in the large differences in hemorrhage risk among those who received oxytocin only. The fact that route of administration had no discernible effect on hemorrhage risk when oxytocin was combined with other active management interventions suggests that any underlying differences due to route of administration are mediated by the presence of controlled cord traction and possibly also by uterine massage.

While one of the key strengths of this analysis was the large number of participants in each AMTSL group with measured blood loss postpartum, there were also several limitations. The studies were carried out in hospital facilities only, and thus may not be generalizable to other delivery settings. In addition, the provision of AMTSL components was not randomly assigned and there was little within-site variation in interventions given, thus preventing inclusion of site controls in the analyses. Finally, there was some variation in procedures for administering AMTSL , and these differences occurred both within- and between-sites. This variation is also a strength, however, since it reflects real differences in implementation of active management of the third stage of labor (Stanton et al., 2009; Winter et al., 2007; Festin et al, 2003; Farrar et al, 2010).

Conclusions

Our findings call into question current consensus regarding the provision of AMTSL components and suggest that practice guidelines should account for setting-related differences such as the availability of oxytocin and its route of administration. The optimal combination of interventions will vary accordingly.

Table 1. Demographic and obstetric characteristics of study participants by receipt of AMTSL components

	No oxytocin prophylaxis (N=8221)				Oxytocin prophylaxis (N=30981)		
	No AMTSL components (n=1832)	**UM only (n=959)**	**CCT only (n=4014)**	**CCT + UM (n=1416)**	**Oxytocin only (n=3638)**	**Oxytocin + CCT (n=6898)**	**Oxytocin + CCT + UM (n=20445)**
Country of residence							
Burkina Faso	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.1)	3684 (18.0)
Egypt	2 (0.1)	2 (0.2)	3979 (99.1)	1385 (97.8)	0 (0.0)	0 (0.0)	16305 (79.8)
Turkey	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2385 (65.6)	544 (7.9)	11 (0.1)
Vietnam	1830 (99.9)	957 (99.8)	35 (0.9)	31 (2.2)	1253 (34.4)	6345 (92.0)	445 (2.2)
Mean age in years ± SD	26.2 ± 4.9	26.2 ± 4.8	26.1 ± 5.1	26.9 ± 4.8	25.6 ± 5.2	25.6 ± 5.0	25.3 ± 5.2
Educational attainment							
No education	60 (3.3)	12 (1.3)	1122 (28.0)	357 (25.2)	102 (2.8)	161 (2.3)	8190 (40.1)
Primary	660 (36.1)	348 (36.4)	1178 (29.4)	439 (31.0)	1877 (51.7)	3384 (49.2)	2763 (13.5)
Secondary or higher	1111 (60.7)	597 (62.4)	1711 (42.7)	620 (43.8)	1655 (45.5)	3338 (48.5)	9477 (46.4)
Currently married	1812 (99.0)	952 (99.3)	4009 (99.9)	1415 (100.0)	3626 (99.7)	6830 (99.3)	20258 (99.1)
Parity							
0	930 (50.9)	489 (51.0)	1706 (42.5)	543 (38.4)	1759 (48.4)	3712 (53.8)	9175 (44.9)
1-3	895 (49.0)	468 (48.9)	2133 (53.1)	795 (56.2)	1860 (51.2)	3163 (45.9)	10084 (49.4)
4+	1 (0.1)	1 (0.1)	175 (4.4)	77 (5.4)	17 (0.5)	21 (0.3)	1159 (5.7)
Multiple pregnancy	26 (1.4)	9 (0.9)	31 (0.8)	26 (1.8)	39 (1.1)	61 (0.9)	351 (1.7)
Mean gestational age at delivery in weeks ± SD	38.7 ± 1.6	39.0 ± 1.2	39.5 ± 1.4	39.5 ± 1.3	39.0 ± 1.6	39.4 ± 1.3	39.1 ± 1.8
Prior known PPH	15 (0.8)	4 (0.4)	4 (0.1)	3 (0.2)	56 (1.5)	39 (0.6)	165 (0.8)

Mean pre-delivery hemoglobin in g/dL ± SD	11.9 ± 1.4	12.0 ± 1.1	11.1 ± 1.2	10.9 ± 1.4	12.1 ± 1.5	12.3 ± 1.3	11.0 ± 1.1
Epidural given	37 (2.0)	69 (7.2)	2 (0.1)	1 (0.1)	24 (0.7)	42 (0.6)	21 (0.1)
Labor induced/augmented	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1968 (54.3)	681 (9.9)	11898 (58.3)

Data are n (%) unless otherwise indicated. AMTSL denotes active management of the third stage of labor; CCT, controlled cord traction; UM, uterine massage; PPH, postpartum hemorrhage; and SD, standard deviation.

Table 2. Distribution of postpartum blood loss (mL) by receipt of AMTSL components

	n	Mean total blood loss (SD)	Median total blood loss (IQR)	Range
No oxytocin prophylaxis				
No AMTSL components	1832	325 (240)	250 (200)	50-1800
UM only	959	368 (268)	300 (250)	50-2000
CCT only	4014	181 (167)	135 (95)	10-1550
CCT + UM	1416	247 (255)	145 (125)	25-1350
Oxytocin prophylaxis				
Intramuscular administration				
Oxytocin only	2853	335 (234)	300 (200)	25-3000
Oxytocin + CCT	6103	279 (115)	300 (100)	100-2500
Oxytocin + CCT + UM	4085	240 (195)	200 (180)	0-2250
Intravenous administration				
Oxytocin only	785	277 (175)	250 (200)	50-2000
Oxytocin + CCT	794	272 (149)	250 (120)	50-1700
Oxytocin + CCT + UM	16343	235 (152)	200 (100)	30-2000

Note: Total blood loss was recorded upon cessation of active bleeding.
AMTSL denotes active management of the third stage of labor; CCT, controlled cord traction; UM, uterine massage; SD, standard deviation; and IQR, inter-quartile range.

Table 3. Incidence of postpartum hemorrhage by severity of blood loss and receipt of AMTSL components

	N	Blood loss ≥ 500 mL	Blood loss ≥ 700 mL
No oxytocin prophylaxis		**n=932**	**n=638**
No AMTSL components	1832	302 (16.5)	154 (8.4)
UM only	959	219 (22.8)	93 (9.7)
CCT only	4014	204 (5.1)	196 (4.9)
UM + CCT	1416	207 (14.6)	195 (13.8)
Oxytocin prophylaxis		**n=1740**	**n=807**
Intramuscular administration			
Oxytocin only	2853	560 (19.6)	109 (3.8)
Oxytocin + CCT	6103	147 (2.4)	90 (1.5)
Oxytocin + CCT + UM	4085	223 (5.5)	110 (2.7)
Intravenous administration			
Oxytocin only	785	99 (12.6)	8 (1.0)
Oxytocin + CCT	794	58 (7.3)	9 (1.1)
Oxytocin + CCT + UM	16343	653 (4.0)	481 (2.9)

Data are n (%). AMTSL denotes active management of the third stage of labor; CCT, controlled cord traction; UM, uterine massage; and PPH, postpartum hemorrhage.

Table 4. Factors associated with postpartum hemorrhage: Results from logistic regression analyses

	Blood loss ≥ 700 mL			
	No oxytocin prophylaxis (N=8154)		Oxytocin prophylaxis (N=30569)	
	OR (95% CI)	P-value	OR (95% CI)	p-value
Receipt of AMTSL components*				
None	ref	-	-	-
UM only	1.14 (0.87-1.50)	0.349	-	-
CCT only	0.53 (0.42-0.66)	0.000	-	-
CCT + UM	1.66 (1.31-2.10)	0.000	-	-
Oxytocin (IM) only	-	-	ref	-
Oxytocin (IM) + CCT	-	-	0.33 (0.25-0.45)	0.000
Oxytocin (IM) + CCT + UM	-	-	0.65 (0.48-0.88)	0.006
Oxytocin (IV) only	-	-	0.24 (0.12-0.50)	0.000
Oxytocin (IV) + CCT	-	-	0.28 (0.14-0.55)	0.000
Oxytocin (IV) + CCT + UM	-	-	0.79 (0.62-0.99)	0.044
Labor induced/augmented	-	-	0.91 (0.76-1.09)	0.284
Parity				
0	1.24 (1.04-1.48)	0.016	2.36 (2.01-2.76)	0.000
1-3	ref	-	ref	-
4+	0.61 (0.32-1.16)	0.130	0.51 (0.29-0.88)	0.017
Multiple pregnancy	1.33 (0.68-2.62)	0.401	1.62 (0.97-2.70)	0.065
Gestational age at delivery (weeks)				
<37	0.40 (0.22-0.73)	0.002	0.32 (0.20-0.51)	0.000
37-41	ref	-	ref	-
42+	0.82 (0.46-1.45)	0.495	1.48 (0.93-2.36)	0.102
Anemia**	1.19 (1.00-1.42)	0.049	1.28 (1.11-1.49)	0.001
Prior known PPH	2.18 (0.74-6.48)	0.159	5.17 (3.21-8.31)	0.000
Age (years)				
<20	1.24 (0.89-1.73)	0.195	0.78 (0.61-0.99)	0.041
20-34	ref	-	ref	-
35+	0.94 (0.66-1.32)	0.715	1.46 (1.07-1.99)	0.017
Educational attainment				
No education	ref	-	ref	-
Primary school	0.87 (0.67-1.13)	0.288	1.14 (0.91-1.43)	0.250
Secondary or higher	1.03 (0.81-1.32)	0.786	1.20 (1.00-1.44)	0.045

AMTSL denotes active management of the third stage of labor; CCT, controlled cord traction; and UM, uterine massage.
*Additional tests for differences between AMTSL groups yielded the following:

Oxy (IV)+CCT vs. oxy (IV) (ref): OR=1.13, 95% CI 0.43-2.96
Oxy (IM)+CCT+UM vs. oxy (IM)+CCT (ref): OR=1.94, 95% CI 1.43-2.65
Oxy (IV)+CCT+UM vs. oxy (IV)+CCT (ref): OR=2.86, 95% CI 1.46-5.59
Oxy (IV) + CCT vs. Oxy (IM) + CCT (ref): OR=1.21, 95% CI 0.60-2.46
Oxy (IM) + CCT + UM vs. Oxy (IV) + CCT + UM (ref): OR=0.83, 95% CI 0.64-1.07

**Anemia was defined as pre-delivery hemoglobin of < 11.0 g/dL.

Table 5. Predicted probability of postpartum blood loss ≥ 700 mL by AMTSL components and route of oxytocin administration

	Predicted probability
No oxytocin prophylaxis	
No AMTSL components	8.8%
UM only	9.9%
CCT only	4.8%
UM + CCT	13.7%
Oxytocin prophylaxis	
Intramuscular administration	
Oxytocin only	3.9%
Oxytocin + CCT	1.3%
Oxytocin + CCT + UM	2.6%
Intravenous administration	
Oxytocin only	1.0%
Oxytocin + CCT	1.1%
Oxytocin + CCT + UM	3.1%
Predictions were generated from regression models summarized in Table 4. They reflect the average probability of postpartum blood loss ≥700mL, assuming that all study participants in each clinical regime received each AMTSL treatment but otherwise retained their observed characteristics.	

References

Abdel-Aleem H, Singata M, Abdel-Aleem M, Mshweshwe N, Williams X, Hofmeyr GJ. Uterine massage to reduce postpartum hemorrhage after vaginal delivery. (2010). *Int J Gynecol Obstet*, 111:32-36.

Abdel-Aleem H, Hofmeyr GJ, Shokry M, El-Sonoosy E. (2006). Uterine massage and postpartum blood loss. *Int J Gynecol Obstet*, 93:238-239.

Blum J, Winikoff B, Raghavan S, et al. (2010). Treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet,* 375:217-223.

Althabe F, Alemán A, Tomasso G, et al. (2009). A pilot randomized controlled trial of controlled cord traction to reduce postpartum blood loss. *Int J Gynecol Obstet,* 107:4-7.

Begley CM, Gyte GML, Murphy DJ, Devane D, McDonald SJ, McGuire W. (2010). Active versus expectant management for women in the third stage of labour. *Cochrane Database of Systematic Reviews*, Issue 7. Art. No.: CD007412. DOI:10.1002/14651858.CD007412.pub2.

Combs CA, Murphy EL, Laros RK. (1991). Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol,* 77:69-76.

Cotter AM, Ness A, Tolosa JE. (2001). Prophylactic oxytocin for the third stage of labour. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001808. DOI: 10.1002/14651858.CD001808.

Farrar D, Tuffnell D, Airey R, Duley L. (2010). Care during the third stage of labour: a postal survey of UK midwives and obstetricians. *BMC Pregnancy Childbirth,* 10:23.

Festin MR, Lumbiganon P, Tolosa JE, et al. (2003). International survey on variations in practice of the management of the third stage of labour. *Bull World Health Organ,* 81:286-291.

Gibbens D, Boyd NRH, Crocker S, Baumber S, Chard T. (1972). The circulating levels of oxytocin following intravenous and intramuscular administration of syntometrine. *J Obstet Gynaecol Br Commonwealth,* 79:644-646.

Gülmezoglu AM, Villar J, Ngoc NTN, et al. (2001). WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet*, 358:689-695.

Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. (2007). Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database Systematic Rev*, Issue 3. Art. No.: CD000494. DOI: 10.1002/14651858.CD000494.pub3.

Gülmezoglu AM, Widmer M, Merialdi M, et al. (2012). Active management of the third stage of labor with and without controlled cord traction: a randomized non-inferiority controlled trial. *Lancet* 379:1721-1727.

International Confederation of Midwives (ICM) / International Federation of Gynaecologists and Obstetricians (FIGO). (2004). Joint statement: management of the third stage of labour to prevent postpartum haemorrhage. *J Obstet Gynaecol Can,* 26(12):1110-1112.

Khan GQ, John IS, Wani S, Doherty T, Sibai BM. (1997). Controlled cord traction versus minimal intervention techniques in delivery of the placenta: A randomized controlled trial. *Am J Obstet Gynecol,* 177:770-774.

Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. (2006). WHO analysis of causes of maternal death: a systematic review. *Lancet*, 367:1066-1074.

Magann EF, Evans S, Hutchinson M, Collins R, Howard BC, Morrison JC. (2005). Postpartum hemorrhage after vaginal birth: An analysis of the risk factors. *Southern Medical Journal*, 98:419-422.

McDonald S, Abbott JM, Higgins SP. (2004). Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. *Cochrane Database Systematic Rev*, Issue 1.

National Collaborating Centre for Women's and Children's Health. (2007). *Intrapartum care: care of health of women and their babies during childbirth.* London: RCOG Press.

Oladapo OT, Okusanya BO, Abalos E. (2012). Intramuscular versus intravenous prophylactic oxytocin for the third stage of labour. *Cochrane Database of Systematic Rev*, (2): CD009332. doi: 10.1002/14651858.CD009332.pub2.

Spencer PM. (1962). Controlled cord traction in management of the third stage of labour. *Br Med J,* 1(5294):1728-1732.

Stanton C, Armbruster D, Knight R, et al. (2009). Use of active management of the third stage of labour in seven developing countries. *Bull World Health Organ,* 87:207-215.

Stones RW, Paterson CM, Saunders NJ. (1993). Risk factors for major obstetric haemorrhage. *Eur J Obstet Gynecol Reprod Biol,* 48:15-18.

WHO, UNFPA, Unicef, World Bank Group. *Integrated Management of Pregnancy and Childbirth. Pregnancy, Childbirth, Postpartum and Newborn Care: A Guide for Essential Practice* [online] 2006. [http://www.who.int/making_pregnancy_safer/publications/PCPNC_2006_03b.pdf]. Last accessed 26 October 2011.

Winikoff B, Dabash R, Durocher J, et al. (2010). Treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet,* 375:210-216.

Winter C, Macfarlane A, Deneuz-Tharaux CD, et al. (2007). Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. *BJOG,* 114:845-854.

CHAPTER 2

Duration of the Third Stage of Labor, Postpartum Blood Loss and the Effect of Oxytocin Prophylaxis[3]

Abstract

Background: Delays in placental delivery are associated with increased postpartum hemorrhage risk, however the precise trajectory of this risk over the course of the third stage of labor remains unclear. This analysis examined the relationship between duration of the third stage of labor and postpartum blood loss among women with and without oxytocin prophylaxis.

Methods: Secondary analysis involving 39,110 hospital deliveries in four countries and two clinical regimens: one in which oxytocin prophylaxis was administered following birth of the baby; the other in which it was not. We used logistic regression with site-level random effects to examine the relationship between third stage duration (modeled in five-minute intervals) and postpartum blood loss ≥ 700 mL. We also assessed the effect of oxytocin prophylaxis on this relationship.

Results: For both clinical regimens, the odds of hemorrhage increased by about one-third for third stage durations of 5-9 minutes (OR=1.35, 95% CI 1.15-1.58) and 10-14 minutes (OR=1.33, 95% CI 1.06-1.66), as compared with 0-4 minutes. Hemorrhage odds rose more steeply from 15-

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19 minutes on, peaking at durations of 25 minutes or more (OR=3.26, 95% CI 2.15-4.94). Oxytocin prophylaxis reduced hemorrhage odds by nearly 80% throughout the third stage of labor (OR=0.22, 95% CI 0.14-0.36), but did not alter the trajectory of relative hemorrhage odds over time.

Conclusions: Postpartum hemorrhage odds increase with progression of the third stage of labor, irrespective of the receipt of oxytocin prophylaxis. While oxytocin prophylaxis has a large and consistent effect on absolute hemorrhage risk at all third stage durations, it does not obviate the incremental change in relative hemorrhage odds over the course of the third stage of labor.

Background

The third stage of labor is normally a rapid event, with an estimated 90% of women completing placental delivery within 15 minutes following birth of the baby (Dombrowski et al., 1995; Magann et al., 2006). Delays in placental delivery are known to be associated with increased risk of postpartum hemorrhage (Hibbard, 1964; Combs and Laros, 1991; Combs et al., 1991; Dombrowski et al., 1995; Magann et al., 2005; Magann et al., 2006), however the precise trajectory of this risk over the course of the third stage of labor remains unclear. The few studies that have investigated relationships between duration of the third stage and postpartum blood loss have produced inconsistent results. In one retrospective analysis of hospital records involving 12,979 women, the incidence of hemorrhage (≥ 500 mL) was constant for the first 30 minutes postpartum, but increased progressively thereafter until reaching a plateau at 75 minutes (Combs and Laros, 1991). In a prospective analysis of 45,852 hospital deliveries, the frequency of hemorrhage (≥ 500 mL) peaked at 40 minutes postpartum (Dombrowski et al., 1995). In yet another study involving 6,588 women, a third stage duration of 18 minutes was determined to be

the best predictor of severe hemorrhage (Magann et al., 2005). Most recently, a study involving 1,607 participants concluded that the risk of severe hemorrhage was indeed time related, and significant increases in risk were present by 10-15 minutes and >15 minutes postpartum, as compared with durations < 5 minutes (Magann et al., 2006).

The effect of oxytocin prophylaxis on the relationship between duration of the third stage of labor and postpartum blood loss is also unclear. Although administration of oxytocin immediately following birth of the baby is believed to expedite placental delivery and reduce postpartum blood loss (Brucker, 2001), this relationship has never been systematically examined among women with and without oxytocin prophylaxis. Of the four studies cited above, three did not record which interventions (if any) were used to manage the third stage of labor (Magann et al., 2006; Dombrowski et al., 1995; Combs and Laros, 1991), although one noted that prophylactic oxytocics were "rarely used" (Combs and Laros, 1991). In the fourth study, oxytocin prophylaxis was provided to all participants (Magann et al., 2005).

Better information about the relationship between duration of the third stage and postpartum blood loss, and the role of oxytocin prophylaxis, could improve clinical management of the third stage of labor. The primary objective of this analysis, therefore, was to examine this relationship among women with and without oxytocin prophylaxis.

Methods

Data were collected as part of two trials carried out simultaneously for the treatment of postpartum hemorrhage, the details of which have been reported elsewhere (Blum et al., 2010; Winikoff et al., 2010). Data collection took place between 2005 and 2008 and involved nine secondary or tertiary hospitals from five countries. The trials were differentiated by provision of

oxytocin prophylaxis: in one trial oxytocin was routinely provided immediately following birth of the baby; in the other it was not. Study sites in the no oxytocin prophylaxis trial included hospitals in Egypt (one), Ecuador (one) and Vietnam (two); sites in the oxytocin prophylaxis trial included hospitals in Burkina Faso (one), Egypt (one), Turkey (one), and Vietnam (two).

All participants were screened for eligibility and provided written informed consent upon admission to the hospital labor ward. Women were excluded if they delivered by caesarian section, delivery took place outside the hospital facility, or they were enrolled in the no oxytocin prophylaxis trial but received oxytocin or other uterotonics for any reason during labor. For all women, treatment for postpartum hemorrhage was provided if bleeding reached 700 mL within the first hour postpartum or, prior to that, by clinical judgment. Oxytocin was administered in accordance with standard hospital practices and controlled cord traction was provided at the discretion of each provider.

Information about basic demographic and clinical characteristics, postpartum blood loss, duration of the third stage, and provision of interventions to prevent hemorrhage were recorded for all participants. Blood loss was measured for the first hour postpartum using a polyurethane receptacle with calibrated funnel. If hemorrhage was diagnosed, blood measurement continued until the cessation of active bleeding. Duration of the third stage was measured in minutes using standard one-hour timers, beginning immediately after birth of the baby and continuing until the completion of placental delivery. For the 57 women for whom third stage duration exceeded one hour, the additional time was noted using clocks in the postpartum ward.

Statistical analysis

A total of 39,110 women were included in this analysis, 8212 with no oxytocin prophylaxis and 30898 with oxytocin prophylaxis. We excluded all 1,625 participants from one hospital site in Quito, Ecuador, the only high elevation site in the study, due to atypical blood loss patterns that disproportionately influenced the results of our analyses.

We examined bivariate relationships between duration of the third stage and outcomes of mean postpartum blood loss, median blood loss, and blood loss ≥ 700 mL. We conducted multivariate analyses using logistic regression with random effects in order to account for potential bias due to site-level clustering. We could not include site controls directly in the regression models due to overlap with the provision of oxytocin prophylaxis. The use of random effects made almost no difference in either the magnitude or significance of any of our estimates with exception of controlled cord traction, which became significant. We used a binary outcome of postpartum blood loss ≥ 700 mL to capture the more serious cases, and because all study participants who reached this level of blood loss received treatment for postpartum hemorrhage, thus censoring the natural progression of subsequent blood loss.

We assessed the independent effect of duration of the third stage of labor, demographic variables (age, education and marital status), and clinical variables (receipt of oxytocin and controlled cord traction, multiple pregnancy, gestational age at delivery, anemia, and history of prior postpartum hemorrhage). Duration of the third stage was modeled in five-minute intervals. We could not include labor augmentation/induction in the regression models due to overlap with oxytocin prophylaxis. We also tested interactions between oxytocin and all other independent variables in order to assess whether the effect of third stage duration or any other independent variables was dependent upon receipt of oxytocin prophylaxis. The final model presented includes only those variables that were significantly associated with blood loss ≥ 700 mL.

Results

Table 1 presents the demographic and clinical characteristics of study participants. Participants in both trials were demographically similar, with exception of educational attainment which was due mainly to country-level differences. In contrast there were some trial-level disparities in clinical practices. All five sites in the oxytocin prophylaxis trial routinely administered oxytocin for management of the third stage of labor, and were more likely than sites in the no oxytocin prophylaxis trial to provide controlled cord traction (88% vs. 66%). There were also differences in the use of oxytocics for labor induction/augmentation (47% vs. 0%), however trial enrollment criteria prevented the use of oxytocin for either indication among the no oxytocin prophylaxis sites.

The cumulative distribution of duration of the third stage is shown in Figure 1. There were notable differences by receipt of oxytocin for the first nine minutes postpartum (P<0.000). A greater share of those with no oxytocin prophylaxis completed placental delivery between 0-4 minutes (51.0% vs. 16.4%), while more of those with oxytocin prophylaxis completed placental delivery between 5-9 minutes (62.3% vs. 18.9%). By 10 minutes postpartum, however, 92% of women in both groups had completed placental delivery and from 13 minutes on, the distributions were statistically indistinguishable (P=0.187). By 15 minutes postpartum, approximately 97% of all participants from both groups had completed placental delivery.

Table 2 summarizes the distribution of postpartum blood loss by duration of the third stage. Among those with no oxytocin prophylaxis, mean and median blood loss increased steeply with progression of the third stage and, in both cases, peaked at durations of 20-24 minutes. Among those with oxytocin prophylaxis, mean blood loss also increased with progression of the third

stage, albeit less dramatically than among those with no oxytocin, peaking at durations of 25 minutes or more. However there was little change in median blood loss over time (range was 200-250 mL). Figure 2 shows trends in mean blood loss by duration of the third stage (in five-minute intervals). Mean blood loss was higher among those with oxytocin prophylaxis at the outset of the third stage, but this was reversed from 10-14 minutes postpartum and thereafter. The differences by receipt of oxytocin prophylaxis were greatest at durations of 20-24 minutes (433 mL vs. 299 mL).

Table 3 summarizes duration of the third stage by receipt of oxytocin prophylaxis and incidence of hemorrhage ≥ 700 mL. Overall the differences in mean and median third stage duration were 0.5 minutes and 1.0 minutes, respectively, with greater variation among those with no oxytocin prophylaxis. Although these differences were statistically significant (P<0.000), they are unlikely to be of clinical importance. Among those with blood loss ≥ 700 mL, there were no differences by receipt of oxytocin prophylaxis in mean third stage duration (7.2 versus 7.1 minutes, P=0.643). Within both groups, mean third stage duration was greatest among those with blood loss ≥ 700 mL, as compared with blood loss < 700 mL. Figure 3 shows the incidence of hemorrhage (≥ 700 mL) by duration of the third stage. Hemorrhage incidence was higher among those with no oxytocin prophylaxis at all third stage intervals, with the greatest disparity occurring at durations of 15-19 minutes or more.

Table 4 presents results from logistic regression with site-level random effects using an outcome of blood loss ≥ 700 mL. Oxytocin prophylaxis reduced absolute hemorrhage odds by nearly 80% (OR=0.22, 95% CI 0.14-0.36). None of the interaction terms for oxytocin by third stage duration were significant, indicating that receipt of oxytocin prophylaxis did not alter the trajectory of relative hemorrhage odds across any of the five-minute third stage intervals studied. For both

groups, hemorrhage odds increased by about one-third for durations of 5-9 minutes (OR=1.35, 95% CI 1.15-1.58) and 10-14 minutes (OR=1.33, 95% CI 1.06-1.66), as compared with durations of 0-4 minutes. Hemorrhage odds rose more steeply from 15-19 minutes on, peaking at durations of 25 minutes or more (OR=3.26, 95% CI 2.15-4.94).

Other factors associated with increased hemorrhage odds were nulliparity (OR=1.26, 95% CI 1.07-1.49), anemia (OR=1.32, 95% CI 1.18-1.48), and interactions between oxytocin and nulliparity (OR=1.69, 95% CI 1.35-2.11) as well as oxytocin and prior postpartum hemorrhage (OR=3.39, 95% CI 1.03-11.18). Factors associated with decreased odds of blood loss ≥ 700 mL were receipt of controlled cord traction (OR=0.60, 95% CI 0.44-0.83) and gestational age < 37 weeks (OR=0.33, P<0.000). Factors not significantly associated with blood loss ≥ 700 mL and thus dropped from the final model included age, educational attainment, marital status, and multiple pregnancy.

Discussion

This analysis is uniquely able to examine the relationship between duration of the third stage of labor and postpartum blood loss among women with and without oxytocin prophylaxis. Our results suggest that for both groups, postpartum hemorrhage risk increases with progression of the third stage. In both cases, mean and median postpartum blood loss increased with duration of the third stage and so did the incidence of blood loss ≥ 700 mL. Multivariate analysis showed that receipt of oxytocin prophylaxis did not obviate the incremental change in relative hemorrhage odds over the course of the third stage of labor. Furthermore relative hemorrhage odds were significantly greater at all intervals ≥ 5-9 minutes, as compared with 0-4 minutes. In contrast, Magann et al. (2005) found that hemorrhage risk (≥ 1000 mL) did not increase

significantly until third stage durations of 10-15 minutes or more. Additionally, our findings indicate that hemorrhage odds were greatest in the final third stage interval studied (25+ minutes), irrespective of the receipt of oxytocin prophylaxis. This suggests that oxytocin prophylaxis is least effective among those considered to be at highest risk of postpartum hemorrhage—women with delays in placental delivery.

On the other hand, our results show that oxytocin prophylaxis has a powerful and consistent protective effect on postpartum hemorrhage risk throughout the duration of the third stage. When compared with those who received no prophylaxis, the odds of bleeding ≥ 700 mL were approximately 80% lower among those with oxytocin at all third stage intervals studied. Although the role of oxytocin prophylaxis in controlling postpartum bleeding has been well-established (Cotter et al., 2001; Gülmezoglu et al., 2001; McDonald et al., 2004; Gülmezoglu et al., 2007), our results confirm prior evidence and further suggest that the magnitude of effect remains stable throughout the course of the third stage of labor.

Among those with oxytocin prophylaxis, we found that nulliparity and prior postpartum hemorrhage each increased hemorrhage odds. While both characteristics are considered risk factors for postpartum hemorrhage (Combs et al., 1991; Gilbert et al., 1987; Tsu, 1993; Magann et al., 2005), their association with additional risk in the presence of oxytocin prophylaxis has not been previously established. We suspect that the oxytocin by nulliparity interaction may be at least partly related to the use of oxytocics for labor induction/ augmentation. Prior research indicates that provision of oxytocin during early stages of labor may serve to desensitize oxytocin receptors, thereby diminishing the drug's subsequent effectiveness when administered postpartum (Phaneuf, 2000; Robinson et al., 2003). If such an effect exists, perhaps it is enhanced somehow among nulliparous women who are already less responsive to oxytocin than

their parous counterparts (Satin et al., 1992). In our sample, 50% of the 14,571 nulliparous women with oxytocin prophylaxis received labor induction/ augmentation and their rate of hemorrhage was 4.2%, as compared with 2.9% among the nulliparous women with oxytocin prophylaxis who did not receive labor induction/ augmentation. One possible mechanism for the interaction between oxytocin and prior postpartum hemorrhage might be the presence of occult bleeding disorders. Coagulation defects are known to elevate postpartum hemorrhage risk (Greer et al., 1991; Kadir et al., 1997; Kominiarek and Kilpatrick, 2007), and perhaps receipt of oxytocin serves somehow to further unmask this risk. We believe this possibility warrants further examination as there is currently very little literature on this topic.

Our results also highlight the importance of controlled cord traction, indicating it may reduce the odds of blood loss ≥ 700 mL by 40%. Although a large, recent trial by Gülmezoglu et al. (2012) found that controlled cord traction conferred little benefit among those with oxytocin prophylaxis, an earlier trial involving 1,600 women found that controlled cord traction plus oxytocin reduced hemorrhage risk by 50% (Khan et al., 1997). Our analysis is distinct from both of these studies in that it controls for duration of the third stage of labor as well as receipt of oxytocin prophylaxis.

The lack of differences by receipt of oxytocin prophylaxis in mean and median duration of the third stage of labor raise questions about the role of oxytocin in expediting placental delivery. In our analysis mean and median third stage duration were slightly lower among those with no oxytocin prophylaxis, appearing to support to a small body of evidence that suggests oxytocin has little effect on duration of the third stage (Jackson et al., 2001; Huh et al., 2004; Zamora, 1999). In one randomized controlled trial involving close to 1,500 participants, there were no differences in third stage duration between those who received oxytocin at the beginning versus

at the end of the third stage of labor (Jackson et al., 2001). Two smaller randomized controlled trials also found that the timing of oxytocin administration (at the beginning versus the end of the third stage) had little or no effect on third stage duration (Zamora, 1999; Huh et al., 2004). In order to examine this further, we performed univariate and multivariate linear regression analyses with site-level random effects, using a continuous outcome of third stage duration. In all of our analyses, receipt of oxytocin prophylaxis was not associated with third stage duration. On the other hand, the timing of oxytocin administration does appear to have an important effect on postpartum blood loss, even if it has little influence on the length of the third stage.

Finally, our data indicate that third stage duration might be a useful means for identifying need for clinical intervention related to postpartum hemorrhage. This is consistent with prior research, which has recommended manual removal of the placenta at 30 minutes postpartum (Combs and Laros, 1991), and 18 minutes postpartum (Magann et al., 2006). Our findings suggest that high-risk cases could be identified as early as 15 minutes postpartum, since 97% of women in both trials had completed placental delivery by this time, and since hemorrhage odds increased sharply beginning at 15-19 minutes postpartum. On the other hand, not all women with durations $\geq$ 15 minutes were diagnosed with hemorrhage, so universal treatment at 15 minutes postpartum would almost certainly result in over-intervention. Yet in many settings where there are no means for objectively identifying hemorrhage, the benefits of such a strategy might nevertheless outweigh the costs.

One of the main strengths of this analysis was the large number of women with objectively measured information about postpartum blood loss and duration of the third stage. One limitation was both trials were conducted in hospital facilities, thus the findings may not be generalizable to other delivery settings.

Table 1. Demographic and clinical characteristics of study participants

	No oxytocin prophylaxis (N=8212)	Oxytocin prophylaxis (N=30898)
Country of residence		
Burkina Faso	0 (0.0)	3627 (11.7)
Egypt	5363 (65.3)	16257 (52.6)
Turkey	0 (0.0)	2940 (9.5)
Vietnam	2849 (34.7)	8074 (26.1)
Mean age in years ± SD	26.3 ± 5.0	25.4 ± 5.2
Educational attainment		
No education	1549 (18.9)	8394 (27.2)
Primary	2618 (31.9)	8017 (26.0)
Secondary or higher	4039 (49.2)	14452 (46.8)
Currently married or cohabitating	8179 (99.7)	30633 (99.2)
Parity		
0	3661 (44.6)	14613 (47.3)
1-3	4289 (52.3)	15072 (48.8)
4+	254 (3.1)	1182 (3.8)
Multiple pregnancy	93 (1.1)	450 (1.5)
Mean gestational age at delivery in weeks ± SD	39.3 ± 1.5	39.2 ± 1.7
Mean pre-delivery hemoglobin in g/L ± SD	11.4 ± 1.3	11.4 ± 1.4
Prior known PPH	26 (0.3)	257 (0.8)
Receipt of controlled cord traction	5419 (66.1)	27212 (88.1)
Epidural given	109 (1.3)	90 (0.3)
Labor induced or augmented	0 (0.0)	14512 (47.1)

Data are n (%) unless otherwise indicated.
PPH denotes postpartum hemorrhage; SD, standard deviation.

Table 2. Postpartum blood loss by duration of the third stage of labor

Third stage duration (minutes)	n	Mean total postpartum blood loss (mL [SD])	Median postpartum blood loss (mL [IQR])	Range (mL)
No oxytocin prophylaxis	**8212**	**246 (226)**	**180 (180)**	**10-2000**
0-4	4166	190 (191)	125 (95)	10-1550
5-9	1555	246 (215)	185 (150)	30-1400
10-14	1896	327 (236)	250 (200)	50-2000
15-19	410	368 (288)	280 (250)	50-1700
20-24	108	433 (344)	300 (350)	50-1700
25+	77	383 (297)	200 (425)	30-1400
Oxytocin prophylaxis	**30898**	**256 (165)**	**200 (150)**	**0-3000**
0-4	5071	239 (159)	200 (150)	11-2100
5-9	19255	249 (155)	200 (150)	0-2100
10-14	4282	289 (178)	250 (100)	50-3000
15-19	1584	278 (205)	250 (150)	25-1800
20-24	438	299 (203)	250 (100)	80-2300
25+	268	336 (295)	250 (200)	80-2500

SD denotes standard deviation; IQR, inter-quartile range.

Table 3. Duration of the third stage of labor by receipt of oxytocin prophylaxis and postpartum blood loss ≥ 700 mL

	No oxytocin prophylaxis (N=8212)	Oxytocin prophylaxis (N=30898)	P-value*
Mean third stage duration in minutes (SD)	**6.0 (5.3)**	**6.5 (5.1)**	**0.000**
Blood loss < 700 mL	5.9 (5.2)	6.5 (5.0)	0.000
Blood loss ≥ 700 mL	7.2 (6.3)	7.1 (5.5)	0.643
Median third stage duration in minutes (IQR)	**4 (7)**	**5 (2)**	**0.000**
Blood loss < 700 mL	4 (7)	5 (2)	0.000
Blood loss ≥ 700 mL	5 (7)	5 (4)	0.000

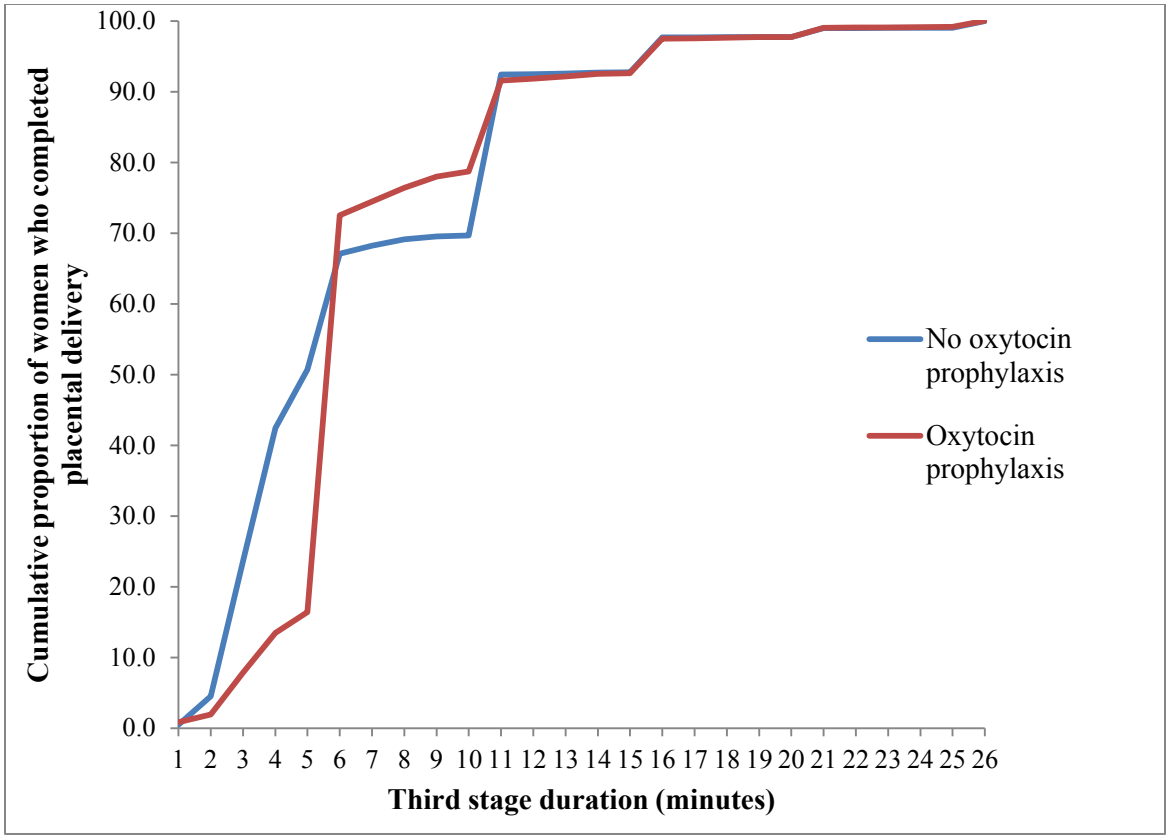
*P-values were obtained from two-sample t tests for unequal variance (for differences in means) and Wilcoxon rank-sum tests (for differences in medians).
SD denotes standard deviation; IQR, inter-quartile range.

Table 4. Relationship between duration of the third stage and postpartum blood loss ≥ 700 mL: Logistic regression with random effects

	Blood loss ≥ 700 mL (N=38853)	
	OR (95% CI)	P-value
Third stage duration (minutes)		
0-4	Ref	-
5-9	1.35 (1.15-1.58)	0.000
10-14	1.33 (1.06-1.66)	0.015
15-19	2.06 (1.55-2.73)	0.000
20-24	2.41 (1.60-3.63)	0.000
25+	3.26 (2.15-4.94)	0.000
Receipt of oxytocin prophylaxis	0.22 (0.14-0.36)	0.000
Receipt of controlled cord traction	0.60 (0.44-0.83)	0.002
Parity		
0	1.26 (1.07-1.49)	0.006
1-3	ref	-
4+	0.64 (0.35-1.19)	0.160
Parity X oxytocin prophylaxis		
0 X oxytocin prophylaxis	1.69 (1.35-2.11)	0.000
1-3 X oxytocin prophylaxis	ref	-
4+ X oxytocin prophylaxis	1.05 (0.47-2.38)	0.903
Gestational age at delivery (weeks)		
<37	0.34 (0.23-0.48)	0.000
37-41	ref	-
42+	1.06 (0.74-1.52)	0.754
Anemia*	1.32 (1.18-1.48)	0.000
Prior known PPH	1.86 (0.62-5.55)	0.268
Prior PPH X oxytocin prophylaxis	3.39 (1.03-11.18)	0.045

PPH denotes postpartum hemorrhage.
*Anemia was defined as pre-delivery hemoglobin of <11.0 g/dL.

Figure 1. Cumulative distribution of duration of the third stage of labor (N=39110)



*We conducted likelihood ratio chi-square tests for regimen-level differences in the distribution of duration of the third stage. Results were significant for third stage durations up to 12 minutes, while there were no significant differences for durations ≥ 13 minutes (P=0.187, 2 groups).

Figure 2. Postpartum blood loss by duration of the third stage of labor (N=39110)

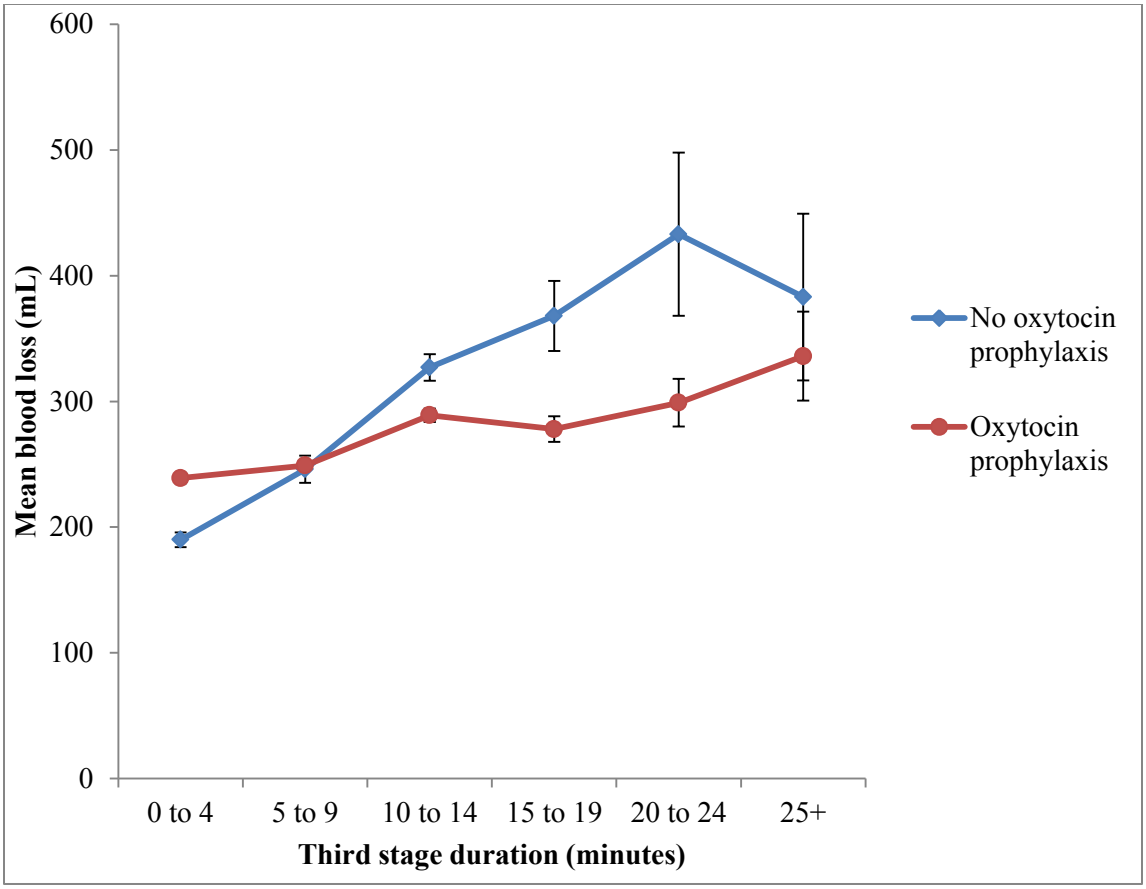
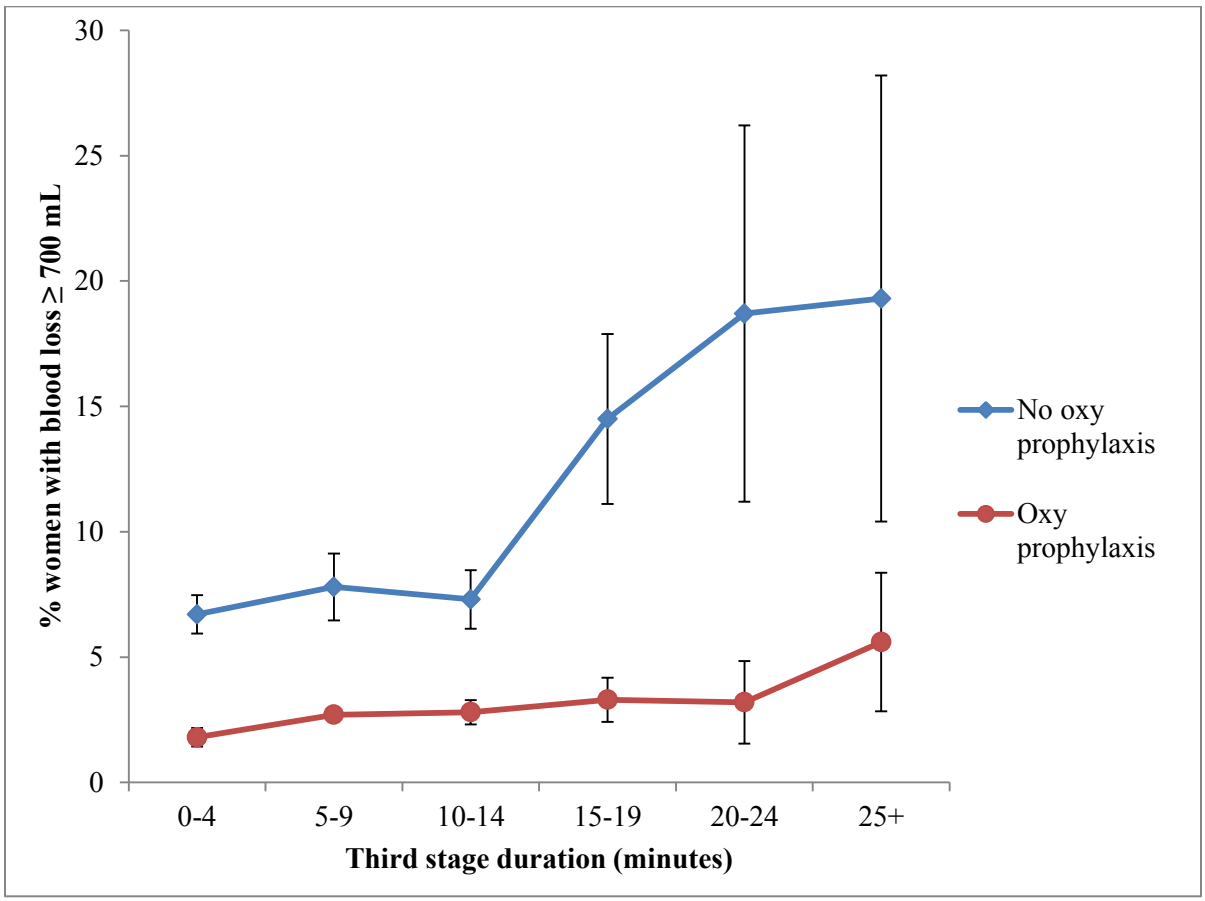


Figure 3. Incidence of postpartum hemorrhage by duration of the third stage of labor (N=39110)



References

Blum J, Winikoff B, Raghavan S, Dabash R, Ramadan MC, Dilbaz B, Dao B, Durocher J, Yalvac S, Diop A, et al. (2010). Treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet,* 375:217-223.

Brucker MC. (2001). Management of the third stage of labor: an evidence-based approach. *Journal of Midwifery and Women's Health,* 46(6):381-392.

Combs CA, Murphy EL, Laros RK. (1991). Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol*, 77(1):69-76.

Combs CA, Laros RK. (1991). Prolonged third stage of labor: Morbidity and risk factors. *Obstet Gynecol,* 77(6):863-867.

Cotter AM, Ness A, Tolosa JE. (2001). Prophylactic oxytocin for the third stage of labor. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001808. DOI: 10.1002/14651858.CD001808.

Dombrowski MP, Bottoms SF, Saleh AAA, Hurd WW, Romero R. (1995). Third stage of labor: analysis of duration and clinical practice. *Am J Obstet Gynecol*, 172:1279-1284.

Gilbert L, Porter W, Brown VA. (1987). Postpartum haemorrhage—a continuing problem. *Br J Obstet Gynaecol,* 94:67-71.

Greer IA, Lowe GDO, Walker JJ, Forbes CD. (1991). Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynaecol*, 98:909-918.

Gülmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, Hofmeyr G, Lumbiganon P, et al. (2001). WHO multicenter randomised trial of misoprostol in the management of the third stage of labour. *Lancet,* 358:689-695.

Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. (2007). Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD000494. DOI:10.1002/14651858.CD000494.pub3.

Gülmezoglu AM, Lumbiganon P, Landoulsi S, Widmer M, Abdel-Aleem H, Festin M, Carroli G, Qureshi Z, Souza JP, Bergel E. (2012). Active management of the third stage of labour with and without controlled cord traction: a randomised controlled, non-inferiority trial. *Lancet,* published online March 6 2012:DOI: DOI:10.1016/S0140-6736(12)60206-2.

Hibbard BM. (1964). Obstetrics in general practice: the third stage of labor. *BMJ,* 1:1485-1488.

Huh WK, Chelmow D, Malone FD. (2004). A double-blinded, randomized, controlled trial of oxytocin at the beginning versus the end of the third stage of labour for prevention of postpartum hemorrhage. *Gynecologic and Obstetric Investigation,* 58:72-76.

Jackson KW, Allbert JR, Schemmer GK, Elliot M, Humphrey A, Taylor J. (2001). A randomized controlled trial comparing oxytocin administration before and after placental delivery in the prevention of postpartum hemorrhage. *Am J Obstet Gynecol*, 185:873-877.

Kadir RA, Economides DL, Braithwaite J, Goldman E, Lee CA. (1997). The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol,* 104:803-810.

Khan GQ, John IS, Wani S, Doherty T, Sibai BM. (1997). Controlled cord traction versus minimal intervention techniques in delivery of the placenta: A randomized controlled trial. *Am J Obstet Gynecol*, 177:770-774.

Kominiarek MA, Kilpatrick SJ. (2007). Postpartum hemorrhage: a recurring pregnancy complication. *Semin Perinatol,* 31:159-166.

McDonald S, Abbott JM, Higgins SP. (2004). Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. *Cochrane Database of Systematic Reviews*, Issue 1.

Magann EF, Evans S, Chauhan SP, Lanneau G, Fisk AD, Morrison JC. (2005). The length of the third stage of labor and the risk of postpartum hemorrhage. *Obstet Gynecol*, 105:290-293.

Magann EF, Evans S, Hutchinson M, Collins R, Howard BC, Morrison JC. (2005). Postpartum hemorrhage after vaginal birth: an analysis of risk factors. *Southern Medical Journal,* 98(4):419-422.

Magann EF, Doherty DA, Briery CM, Niederhauser A, Morrison JC. (2006). Timing of placental delivery to prevent postpartum haemorrhage: Lessons learned from an abandoned randomized clinical trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 46:249-251.

Phaneuf S, Rodriguez Linares B, TambyRaja RL, MacKenzie IZ, López Bernal A. (2000). Loss of myometrial oxytocin receptors during oxytocin-induced and oxytocin-augmented labor. *J Reprod Fertil*, 120:91-97.

Robinson C, Schumann R, Zhang P, Young RC. (2003). Oxytocin-induced desensitization of the oxytocin receptor. *Am J Obstet Gynecol,* 188:497-502.

Satin AJ, Leveno KJ, Sherman ML, McIntire DD. (1992). Factors affecting the dose response to oxytocin for labor stimulation. *Am J Obstet Gynecol*, 166(4):1260-1261.

Soltani H, Hutchon DR, Poulouse TA. (2010). Timing of prophylactic uterotonics for the third stage of labour after vaginal birth. *Cochrane Database of Systematic Reviews*, Issue 8. Art. No.: CD006173. DOI: 10.1002/14651858.CD006173.pub2.

Tsu VD. (1993). Postpartum haemorrhage in Zimbabwe: a risk factor analysis. *Br J Obstet Gynaecol,* 100:327-333.

Winikoff B, Dabash R, Durocher J, Darwish E, Ngoc NTN, León W, Raghavan S, Medhat I, Chi HTK, Barrera G, et al. (2010). Treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet,* 375:210-216.

Zamora LA. (1999). A randomized controlled trial of oxytocin administered at the end of the second stage of labor versus oxytocin administered at the end of the third stage of labor in the prevention of postpartum hemorrhage. *Philippine Journal of Obstetrics and Gynecology*, 23:1251-1253.

CHAPTER 3

Does Maternal Hemoglobin Outside the Normal Range Increase the Risk of Postpartum Hemorrhage?[4]

Abstract

Background: Maternal anemia is believed to increase the risk of postpartum hemorrhage, yet the magnitude of effect and underlying biological mechanisms remain unclear. In addition, the potential role of elevated hemoglobin has not been previously explored. For all such relationships, the possible effect of oxytocin prophylaxis is also not known. This analysis examined the relationship between low and high pre-delivery hemoglobin and postpartum blood loss among women with and without oxytocin prophylaxis.

Methods: Retrospective analysis of 40,362 hospital births in Burkina Faso, Ecuador, Egypt, Turkey and Vietnam. To assess the predictors of low and high pre-delivery hemoglobin, we used multinomial logistic regression. To assess the relationship between pre-delivery hemoglobin and postpartum blood loss, we used logistic regression with a binary outcome of blood loss ≥ 700 mL. Hemoglobin was categorized as moderate-to-severe anemia (Hb <9.0 g/dL), mild anemia (Hb 9.0 to <11.0 g/dL), normal (11.0 to < 15.0 g/dL), and elevated (≥15.0 g/dL).

[4] Parts of this paper were presented at the annual meeting of the American College of Obstetricians and Gynecologists (2013).

Results: Pre-delivery anemia was associated with increased hemorrhage odds across countries and irrespective of the receipt of oxytocin prophylaxis, although there was considerable variation in the magnitude of effect. The relationship was strongest in Egypt and Vietnam, and among those with moderate-to-severe anemia. Among those with no oxytocin prophylaxis, elevated hemoglobin was also associated with a non-significant 60% increase in hemorrhage odds in Egypt and Vietnam.

Conclusions: Maternal anemia is an important risk factor for postpartum hemorrhage, however the variation in magnitude of effect across settings raises questions about the nature of this relationship. The role of elevated hemoglobin in postpartum blood loss also warrants further examination.

Background

While it has long been recognized that anemic women suffer disproportionately from the severe consequences of postpartum hemorrhage (WHO, 1990; Alauddin, 1986; Harrison & Rossiter, 1985; Harrison, 1975; Llewelyn-Jones, 1965), the question of whether maternal anemia increases the quantity of postpartum blood loss has yet to be resolved. One of the first papers to address this question was a case control study of risk factors for postpartum hemorrhage in Zimbabwe (Tsu, 1993). Results indicated that hemorrhage cases were 2.2 times as likely to have antenatal hemoglobin (Hb) <12.0 g/dL than were non-hemorrhage controls. These findings were limited, however, by missing hemoglobin measurements for two-thirds of study records and by very low incidence of Hb<11/0 g/dL, which is the conventional standard for anemia during pregnancy. (WHO, 2001)

Numerous studies have since explored relationships between maternal anemia and postpartum blood loss. Three recorded the incidence of hemorrhage among women with severe anemia. Two studies were conducted in India and both reported incidence of 26% among women with pre-delivery Hb <7.0 g/dL (Rohilla et al., 2010) or antenatal Hb <5.0 g/dL (Patra et al., 2005). The third study, conducted in Pakistan, reported incidence of 9.8% among women with pre-delivery Hb <7.0 g/dL, as compared with 0.8% among non-anemic controls (Jaleel et al., 2008). Other studies have tested associations between anemia and postpartum blood loss. In a review of 307,415 births in Norway, pre-delivery Hb < 9.0 g/dL was associated with 2.2 times the risk of bleeding >1500 mL (al-Zirqi et al., 2008). An analysis of 446,397 births in Peru found moderate and severe pre-delivery anemia were both associated with increased risk of blood loss > 500 mL. (Gonzales et al., 2012). A third study found that antenatal Hb < 9.0 g/dL increased total blood loss by an average of 91 mL as compared with Hb > 11.0 g/dL (Kavle et al., 2008). In contrast, a study of 447 births in India found no significant differences in hemorrhage incidence across four hemoglobin categories (Hb > 11.0, 9.0-10.0, 7.0-8.9, and <7.0 g/dL), however the authors concluded that this was likely due to the small number of study participants (Malhotra et al., 2002).

Despite accumulating evidence of a relationship between maternal anemia and postpartum blood loss, important outstanding questions remain. For instance the precise magnitude of effect by severity of hemoglobin deficit has not been clearly established. This is partly due to methodological variation across studies, including variance in definitions of anemia and hemorrhage, as well as in the means used to identify both conditions (e.g. measured versus visual blood loss). In addition, the underlying biological mechanisms responsible for such a relationship are not well understood. It has been suggested that anemia due to iron deficiency may contribute

to uterine atony, the primary cause of postpartum hemorrhage, through depletion of the myoglobin needed for uterine action (RCOG, 2009; Kavle et al., 2008; Jaleel et al., 2008; Rush, 2000), or through weakening resistance to infection (Rush, 2000; Koblinsky et al., 1995), with anecdotal evidence indicating that ascending lower genital tract infections might specifically serve to inhibit uterine contractility (Bergström, 2003).

The potential role of elevated hemoglobin in postpartum blood loss has also not been adequately explored. Most studies examining the relation between maternal hemoglobin and adverse maternal outcomes have treated all women with hemoglobin > 11.0 g/dL as one uniform group, assuming that higher concentrations yield consistently favorable outcomes. Yet there is much evidence that this is not always the case. Elevated hemoglobin has been associated with adverse perinatal outcomes (Steer et al., 1995; Murphy et al., 1986; Huisman et al., 1986; Garn et al., 1981; Garn et al., 1981) as well as pregnancy-induced hypertension and pre-eclampsia in prior research (Gonzales et al., 2012; Murphy et al., 1986; Huisman et al., 1986; Sagen et al., 1982; Heilman et al., 1981).

Finally, it is not known whether receipt of oxytocin prophylaxis might alter this relationship in any way. As a result, the main objective of this analysis was to examine the relationship between low and high pre-delivery hemoglobin and postpartum blood loss among women with and without oxytocin prophylaxis.

Methods

Study setting and participants

Data were collected between 2005 and 2008 as part of two randomized controlled trials that were carried out simultaneously for the treatment of postpartum hemorrhage, the details of which have

been reported elsewhere (Blum et al., Winikoff et al.). The trials were identical with exception of the provision of oxytocin or other uterotonics during labor. In the first trial, involving five hospitals from four countries (Burkina Faso, Egypt, Turkey and Vietnam), oxytocin prophylaxis was routinely administered following birth of the baby. In the second trial, involving four hospitals from three countries (Egypt, Ecuador and Vietnam), oxytocin prophylaxis was not routinely administered following birth of the baby.

For both trials, enrollment took place during admission to the hospital labor ward. Information about demographic and clinical characteristics, pre-delivery hemoglobin and postpartum blood loss were recorded for all participants. Hemoglobin was measured using a Hemocue device. Postpartum blood loss was measured using a polyurethane receptacle with calibrated funnel beginning immediately after birth of the baby and continuing for one hour postpartum or, if postpartum hemorrhage was diagnosed, until the cessation of active bleeding. Treatment for postpartum hemorrhage was provided to all women whose bleeding reached 700 mL within the first hour postpartum or prior to that, by clinical judgment.

Statistical analysis

For the statistical analyses we categorized hemoglobin as moderate-to-severe anemia (Hb <9.0 g/dL), mild anemia (Hb 9.0 to <11.0 g/dL), normal (11.0 to < 15.0 g/dL) and elevated (≥15.0 g/dL). The anemia categories were based on accepted standards for the third trimester of pregnancy (WHO, 2001). The cut point for elevated hemoglobin was selected based on a literature review and because hemorrhage incidence in our sample peaked at around 15.0 g/dL. We combined moderate with severe anemia due to the small number of participants (n=57) in the latter group.

To assess the predictors of low and high pre-delivery hemoglobin, we used multinomial logistic regression with a reference category of normal hemoglobin. To assess the relationship between pre-delivery hemoglobin and postpartum blood loss, we used logistic regression with a binary outcome of blood loss ≥ 700 mL. We also stratified the analyses by country of residence and receipt of oxytocin prophylaxis. For both sets of analyses, the final multivariate models include only those factors that were significantly associated with the outcome variables.

The protocol for this secondary analysis was approved by Princeton University's Institutional Review Board on 19 December 2009, protocol number 0000004672.

Results

A total of 40,362 women were included in this analysis, 9,339 with no oxytocin prophylaxis and 31,023 with oxytocin prophylaxis. A total of 870 women were excluded from analysis for the following reasons: 597 were missing information on postpartum blood loss, 23 were missing information on pre-delivery hemoglobin, 42 did not receive oxytocin as per the standard for their clinical trial, 203 delivered by caesarean section, and 5 delivered outside the study facility.

Table 1 presents the demographic and clinical characteristics of study participants by country of residence. The prevalence of any anemia was highest in Burkina Faso and Egypt, affecting about one-half of study participants in both settings, as compared with 15-25% of those in Turkey and Vietnam, and only 3% of those in Ecuador. Elevated hemoglobin was rare in all countries except Ecuador, the only high elevation site in the study, where there was a prevalence of 13%. The large, country-level disparities in educational attainment mirrored disparities in anemia prevalence: in Burkina Faso, where anemia prevalence was highest, so was the incidence of no education (60%); while in Ecuador, where anemia prevalence was lowest, only 1% of women

had no education. There were small differences in all other demographic and clinical variables with exception of the receipt of oxytocin prophylaxis, which reflected variation in hospital practices.

The distribution of pre-delivery hemoglobin by country of residence and receipt of oxytocin prophylaxis is presented in Table 2. Mean and median hemoglobin were lowest in Burkina Faso (10.9 g/dL) and highest in Ecuador (13.5 and 13.6 g/dL, respectively). In Egypt and Vietnam, there were small, site-driven differences by receipt of oxytocin prophylaxis that ranged from 0.2 g/dL to 0.4 g/dL.

Table 3 presents results from multinomial logistic regression analysis of the predictors of low and high pre-delivery hemoglobin. Results reflect the relative probability of each abnormal hemoglobin category (moderate-to-severe anemia, mild anemia or elevated hemoglobin), as compared with normal hemoglobin. Factors positively associated with the presence of low hemoglobin (moderate-to-severe anemia and/or mild anemia), included residence in Burkina Faso, Turkey or Egypt as compared with Vietnam; age under 20 years; multiple pregnancy; and gestational age < 37 weeks, as compared with 37-41 weeks. Factors negatively associated with low hemoglobin included residence in the high elevation setting of Quito Ecuador, completion of secondary school or higher as compared with completion of primary school, being married, and nulliparity. The only factors significantly associated with elevated hemoglobin were country of residence, for which there was a negative association for Burkina Faso and positive association for Ecuador; and completion of secondary school or higher.

Table 4 presents results from logistic regression analysis of the factors associated with postpartum blood loss ≥ 700 mL. Anemia was associated with increased hemorrhage odds in all

countries, although these differences were only significant in Egypt, Turkey and Vietnam. In most cases there was a greater magnitude among those with moderate-to-severe anemia than among those with mild anemia. In Egypt and Vietnam, elevated hemoglobin was also associated with a non-significant increase of about 60% in hemorrhage odds among those with no oxytocin prophylaxis, while the direction of effect was reversed among those with oxytocin prophylaxis. Other variables positively associated with hemorrhage odds in one or more countries included gestational age of 42 weeks or more as compared with 37-41 weeks, nulliparity, multiple pregnancy, and prior postpartum hemorrhage. Factors negatively associated with hemorrhage odds included gestational age < 37 weeks.

Discussion

This is the first multi-country assessment of the relationship between pre-delivery hemoglobin and measured postpartum blood loss. Our findings corroborate prior research and suggest that low hemoglobin is an important risk factor for postpartum hemorrhage. We obtained significant associations for both mild and moderate-to-severe anemia that persisted across countries and irrespective of receipt of oxytocin prophylaxis. In most cases, the magnitude of effect increased with severity of hemoglobin deficit, corroborating findings from prior research. At the same time, the considerable country-level variation in the magnitude of our estimates, particularly among those with moderate-to-severe anemia, raises questions about the relative contribution of biological mechanisms versus correlation with other underlying conditions.

The prior literature on this topic has largely assumed a causal relationship, yet biological plausibility has not been sufficiently established. Thus far speculation has focused on the contribution of iron deficiency anemia to uterine atony (RCOG, 2009; Kavle et al., 2008; Jaleel

et al., 2008; Rush, 2000; Bergström, 2003). We believe an alternate possibility also warrants exploration. For more than a half century, there has been a known association between hematocrit concentrations, bleeding time and platelet adhesiveness (Coller, 2012; Boneu et al., 1987; Turitto et al, 1980; Hellem et al., 1961). Anemia is thought to impair the normal interaction between platelets and blood vessels that typically serves to arrest bleeding and promote platelet aggregation. In light of this, anemia is considered the main source of prolonged bleeding time in patients with renal failure (Boccardo et al, 2004; Fernandez et al, 1985); while provision of erythropoietin/red blood cell transfusion to such patients has been shown to decrease bleeding time as well as hemorrhage frequency (Boccardo et al., 2004, Moia et al., 1987). In order to determine if maternal anemia has a similar effect on birth-related bleeding time and platelet adhesiveness in the postpartum period, there is a need for research along these lines.

At the same time, our anemia findings might have been at least partly due to correlation with other underlying conditions such as inherited coagulation disorders. Unfortunately we were unable to directly control for this possibility in our analyses. Coagulation disorders include von Willebrand's disease, which affects about 1% of the general population and is the most common disorder (Rodeghiero et al., 1987; Chi et al., 2012), followed by factor deficiencies, platelet disorders, and hemophilia A and B (SOGC Guidelines, 2005). Women with coagulation disorders frequently experience menorrhagia and excessive bleeding during surgeries and dental procedures. They are also at increased risk for primary and secondary postpartum hemorrhage (Chi et al., 2012; Kadir et al., 1998; Kadir et al., 1997; SOGC Guidelines, 2005; ACOG, 2009). As a result, these same women would be likely to have a higher prevalence of maternal anemia at the time of birth, although we were unable to find relevant published incidence information.

It is also possible that the relationship between anemia and postpartum blood loss is multifactorial and that the importance of any given factor varies across settings. This would help explain the country-level heterogeneity in our findings. Another source of variation might have been site-level error in the measurement of hemoglobin. While the Hemocue device that was used at all study sites to obtain hemoglobin measurements has been shown to be highly accurate (von Schenck et al., 1986), its precision relies upon regular maintenance/cleaning of the microcuvet devices. If the microcuvets were not cleaned properly at any of the study sites, this could have led to systematic inaccuracy in hemoglobin readings.

Finally, our results suggest that elevated hemoglobin may also be associated with increased odds of postpartum hemorrhage, albeit only among those with no oxytocin prophylaxis. Although our findings were not statistically significant, this may have been due to the small number of women with hemoglobin ≥ 15 g/dL in our dataset. To our knowledge, this is the first evidence of such a relationship. Elevated hemoglobin has been associated with adverse perinatal outcomes in prior research, but an association with increased postpartum bleeding has not been previously identified. Nevertheless, elevated hemoglobin is known to produce hyper-viscosity which increases the risk of thrombotic and hemorrhagic complications in a number of pathological conditions (Koller, 1982), so there is a potentially plausible pathway for such a relationship.

Alternatively, this finding could have been due to the presence of other underlying conditions. For instance, pre-eclampsia is known to be associated with elevated hemoglobin (Gonzales et al., 2012; Huisman et al., 1986; Sagen, 1982; Heilman et al., 1981) and is also thought to increase postpartum hemorrhage risk (Combs et al., 1991). We could not assess this possibility since we lacked information on the prevalence of pre-eclampsia among the women in our dataset. It's also unclear what might account for the divergent results by receipt of oxytocin prophylaxis.

Nevertheless given the consistency of our estimates in two of the three no oxytocin prophylaxis settings, the role of elevated hemoglobin in postpartum blood loss also warrants further examination.

Conclusions

Maternal anemia is an important risk factor for postpartum hemorrhage, however the variation in magnitude of effect across settings raises questions about the relative contribution of biological mechanisms versus correlation with other underlying conditions. The role of elevated hemoglobin in postpartum blood loss also warrants further examination.

Table 1. Demographic and clinical characteristics of study participants by country of residence

Participant characteristics	Country of residence				
	Burkina Faso (N=3702)	Ecuador (N=1112)	Egypt (N=21678)	Turkey (N=2940)	Vietnam (N=10930)
Pre-delivery hemoglobin in g/dL					
< 7.0	0.9 (34)	0.0 (0)	0.1 (14)	0.2 (5)	0.04 (4)
7.0 to < 9.0	5.9 (219)	0.2 (2)	1.8 (388)	3.0 (89)	0.6 (65)
9.0 to < 11.0	43.7 (1616)	3.2 (36)	42.2 (9138)	20.1 (592)	14.6 (1593)
11.0 to < 15.0	49.4 (1829)	83.2 (925)	55.4 (12015)	74.4 (2188)	82.9 (9056)
≥ 15.0	0.1 (4)	13.4 (149)	0.6 (123)	2.2 (66)	1.9 (212)
Mean age ± SD	25.6 ± 6.3	24.0 ± 6.3	25.5 ± 5.0	25.3 ± 5.1	25.8 ± 5.0
Education					
No education	59.8 (2204)	1.2 (13)	34.4 (7460)	2.1 (63)	2.6 (283)
Primary	18.5 (682)	36.9 (410)	15.8 (3422)	54.9 (1615)	45.3 (4941)
Secondary+	21.8 (803)	62.0 (689)	49.8 (10793)	42.9 (1262)	52.1 (5681)
Married	95.2 (3516)	84.4 (938)	100.0 (21669)	99.9 (2937)	99.3 (10825)
Gestational age at delivery in weeks					
<37	4.2 (153)	7.5 (83)	5.7 (1241)	7.2 (213)	4.9 (1224)
37-41	95.0 (3479)	88.3 (982)	92.4 (20039)	91.8 (2699)	92.3 (10036)
42+	0.9 (32)	4.2 (47)	1.8 (398)	1.0 (28)	3.2 (342)
Nulliparous	42.4 (1558)	36.3 (404)	44.4 (9624)	48.4 (1423)	52.5 (5736)
Multiple pregnancy	3.2 (118)	0.1 (1)	1.3 (275)	0.2 (6)	1.4 (149)
Prior known PPH	3.7 (135)	5.6 (62)	0.2 (33)	1.9 (57)	0.5 (59)
Receipt of oxytocin prophylaxis	100.0 (3702)	0.0 (0)	75.2 (16305)	100.0 (2940)	73.9 (8074)

Data are % (n) unless otherwise specified.
SD denotes standard deviation; PPH, postpartum hemorrhage.

Table 2. Distribution of pre-delivery hemoglobin by country of residence and receipt of oxytocin prophylaxis

		Pre-delivery hemoglobin (g/dL)	
	n	**Mean (SD)**	**Median (IQR)**
Oxytocin Prophylaxis			
Burkina Faso	3702	10.9 (1.4)	10.9 (1.6)
Egypt	16305	10.9 (1.0)	11.0 (1.5)
Turkey	2940	12.0 (1.5)	12.1 (2.0)
Vietnam	8076	12.3 (1.3)	12.3 (1.6)
No oxytocin prophylaxis			
Ecuador	1112	13.5 (1.3)	13.6 (1.9)
Egypt	5373	11.1 (1.3)	11.2 (1.8)
Vietnam	2854	11.9 (1.2)	12.0 (1.5)
SD denotes standard deviation; IQR, inter-quartile range.			

Table 3. Predictors of low and high pre-delivery hemoglobin: multinomial logistic regression results (N=40032)

	Moderate-to-severe anemia vs. normal hemoglobin		Mild anemia vs. normal hemoglobin		Elevated hemoglobin vs. normal hemoglobin	
	RRR (95% CI)	**P-value**	**RRR (95% CI)**	**P-value**	**RRR (95% CI)**	**P-value**
Country of residence						
Burkina Faso	16.26 (12.08-21.87)	0.000	4.64 (4.22-5.09)	0.000	0.09 (0.03-0.26)	0.000
Ecuador	0.25 (0.06-1.04)	0.057	0.21 (0.15-0.29)	0.000	7.02 (5.49-8.96)	0.000
Egypt	4.64 (3.54-6.08)	0.000	4.29 (4.02-4.57)	0.000	0.42 (0.32-0.53)	0.000
Turkey	5.32 (3.87-7.31)	0.000	1.51 (1.35-1.67)	0.000	1.31 (0.99-1.74)	0.059
Vietnam	ref	-	ref	-	ref	-
Age in years						
<20	1.09 (0.85-1.39)	0.489	1.11 (1.02-1.20)	0.011	0.86 (0.64-1.16)	0.327
20-34	ref	-	ref	-	ref	-
35+	1.06 (0.80-1.40)	0.672	1.08 (0.98-1.18)	0.115	1.24 (0.89-1.73)	0.193
Educational attainment						
No education	0.84 (0.69-1.02)	0.083	0.99 (0.93-1.06)	0.777	1.15 (0.81-1.65)	0.438
Primary	ref	-	ref	-	ref	-
Secondary plus	0.54 (0.45-0.65)	0.000	0.88 (0.83-0.93)	0.000	1.23 (1.01-1.49)	0.037
Currently married	0.55 (0.33-0.93)	0.027	0.77 (0.59-1.00)	0.049	1.21 (0.74-1.99)	0.402
Parity						
0	0.85 (0.72-0.99)	0.041	0.95 (0.90-1.00)	0.028	1.08 (0.90-1.31)	0.402
1-3	ref	-	ref	-	ref	-
4+	1.04 (0.75-1.44)	0.817	1.13 (1.00-1.27)	0.052	1.22 (0.73-2.04)	0.449
Multiple pregnancy	1.34 (0.82-2.20)	0.246	1.26 (1.05-1.51)	0.015	1.12 (0.46-2.74)	0.803
Gestational age at delivery						
<37	1.76 (1.35-2.29)	0.000	1.23 (1.12-1.35)	0.000	1.12 (0.78-1.61)	0.524
37-41	ref	-	ref	-	ref	-
42+	1.19 (0.71-2.00)	0.522	0.85 (0.72-1.01)	0.063	1.28 (0.81-2.05)	0.294

g/dL denotes grams per deciliter; OR, odds ratio; and CI, confidence interval.

Table 4. Factors associated with postpartum hemorrhage: logistic regression results

	Blood loss ≥ 700 mL [OR (95% CI)]						
	Oxytocin prophylaxis				No oxytocin prophylaxis		
	Burkina Faso (N=3578)	**Egypt (N=16303)**	**Turkey (N=2877)**	**Vietnam (N=7958)**	**Ecuador (N=1111)**	**Egypt (N=5361)**	**Vietnam (N=2808)**
Hb status in g/dL							
< 9.0	1.41 (0.58-3.43)	4.12 (2.36-7.19)‡	1.21 (0.29-5.11)	2.74 (0.84-8.92)+	2.55 (0.15-42.10)	0.96 (0.55-1.65)	3.13 (1.01-9.71)*
9.0 to < 11.0	0.87 (0.51-1.47)	1.35 (1.12-1.63)†	1.72 (0.99-2.98)+	1.58 (1.10-2.29)*	0.74 (0.34-1.62)	1.27 (1.03-1.58)*	1.17 (0.84-1.62)
11.0 to < 15.0	ref	ref	ref	ref	ref	ref	ref
≥ 15.0	-	0.32 (0.04-2.31)	0.73 (0.10-5.44)	0.42 (0.10-1.71)	1.02 (0.70-1.48)	1.60 (0.20-12.75)	1.56 (0.53-4.57)
Education							
No education	0.81 (0.42-1.57)	1.01 (0.73-1.38)	1.01 (0.13-7.67)	1.21 (0.52-2.81)	1.03 (0.28-3.86)	1.00 (0.76-1.31)	0.42 (0.10-1.76)
Primary	ref	ref	ref	ref	ref	ref	ref
Secondary plus	1.21 (0.59-2.49)	1.04 (0.77-1.41)	1.51 (0.91-2.52)	1.22 (0.92-1.63)	1.72 (1.30-2.27)‡	0.90 (0.70-1.16)	1.66 (1.24-2.22)†
Gestational age at delivery in weeks							
<37	0.34 (0.05-2.51)	0.19 (0.09-0.39)‡	0.61 (0.19-1.95)	0.69 (.030-1.59)	0.49 (0.28-0.88)	0.31 (0.11-0.83)*	0.46 (0.22-0.94)*
37-41	ref	ref	ref	ref	ref	ref	ref
42+	1.43 (0.19-10.96)	1.88 (1.03-3.42)*	1.92 (0.25-14.6)	0.80 (0.35-1.83)	2.30 (1.27-4.17)	0.50 (0.23-1.07)+	1.98 (0.81-4.80)
Nulliparity	1.72 (1.01-2.91)*	3.01 (2.46-3.69)‡	1.95 (1.15-3.32)*	1.07 (0.80-1.42)	1.15 (0.87-1.51)	1.25 (1.01-1.54)*	1.37 (1.05-1.79)*
Multiple pregnancy	1.63 (0.50-5.36)	2.73 (1.45-5.12)†	-	0.56 (0.13-2.32)	-	1.08 (0.38-3.03)	1.95 (0.79-4.78)
Prior known PPH	4.72 (2.11-10.56)‡	9.95 (3.33-29.74)‡	-	14.26 (6.58-30.93)‡	1.61 (0.93-2.77)+	-	3.14 (1.00-9.82)*

OR denotes odds ratio; CI, confidence interval; mL, milliliters; g/dL, grams per deciliter; and PPH, postpartum hemorrhage.
+ indicates P<0.10, * P<0.05; † P<0.01, and ‡ P<0.001.

References

Alauddin M. Maternal mortality in rural Bangladesh: The Tangail District. (1986). *Studies in Fam Plann,* 17:13-21.

al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. (2008). Prevalence and risk factors of severe obstetric haemorrhage. *BJOG,* 115:1265-1272.

Bergström S. (2003). Infection-related morbidities in the mother, fetus and neonate. *J Nutr,* 133:1656S-1660S.

Blum J, Winikoff B, Raghavan S, Dabash R, Ramadan MC, Dilbaz B, et al. (2010). Treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet,* 375:217-223.

Boccardo P, Remuzzi G, Galbusera M. (2004). Platelet dysfunction in renal failure. *Seminars in Thrombosis and Hemostasis,* 30:579-589.

Boneu B, Fernandez F. (1987). The role of hematocrit in bleeding. *Transfusion Medicine Reviews,* 1(3):182-185.

Chi C, Kadir RA. (2012). Inherited bleeding disorders in pregnancy. *Best Practice & Research Clinical Obstetrics and Gynaecology,* 26:103-117.

Coller BS. (2011). Historical perspective and future directions in platelet research. *J Thromb Haemost,* 9(Suppl 1):374-395.

Combs CA, Murphy EL, Laros RK. (1991). Factors associated with postpartum hemorrhage with vaginal birth. *Obstetrics & Gynecology,* 77:69-76.

Elliott MA, Tefferi A. (2004). Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. *British Journal of Haemotology,* 128:275-290.

Fernandez F, Goudable D, Sie P, et al. (1985). Low hematocrit and prolonged bleeding time in auremic patients: effect of red cell transfusions. *Br J Haematol,* 59:139-148.

Garn SM, Keating MT, Falkner F. (1981). Hematological status and pregnancy outcomes. *Amer J Clin Nutr,* 34:115-117.

Garn SM, Ridella SA, Petzold AS, Falkner F. (1981). Maternal hematologic levels and pregnancy outcomes. *Semin Perinatol,* 5:155-162.

Gonzales GF, Tapia V, Gasco M, Carrillo CE, Fort AL. (2012). Association of hemoglobin values at booking with adverse maternal outcomes among Peruvian populations living at different altitudes. *Int J Gynaecol Obstet,* 117:134-139.

Harrison KA, Rossiter CE. (1985). Maternal mortality. *Br J Obstet Gynaecol,* 92(suppl):100-115.

Harrison KA. (1975). Maternal mortality in anaemia in pregnancy. *W Afr Med J,* 23:27-31.

Heilman L, Siekmann U, Schmid-Schönbein H, Ludwig H. (1981). Hemoconcentration and pre-eclampsia. *Arch Gynecol,* 231:71.

Hellem AJ, Borchgrevink CF, Ames SB. (1961). The role of red cells in haemostasis: the relation between haematocrit, bleeding time and platelet adhesiveness. *Br J Haematol,* 7:42-50.

Huisman A, Aarnoudse JG. (1986). Increased 2nd trimester hemoglobin concentration in pregnancies later complicated by hypertension and growth retardation. *Acta Obstet Gynecol Scand,* 65:605-608.

Jaleel R, Khan A. (2008). Severe anemia and adverse pregnancy outcome. *Journal of Surgery Pakistan (International),* 13(4):147-150.

Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. (1998). Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol,* 105:314-321.

Kadir RA, Economides DL, Braithwaite J, Goldman E, Lee CA. (1997). The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol,* 104:803-810.

Kavle JA, Stolzfus RJ, Witter F, Tielsch JM, Khalfan SS, Caulfield LE. (2008). Association between anaemia during pregnancy and blood loss at and after delivery among women with vaginal births in Pemba Island, Zanzibar, Tanzania. *J Health Popul Nutr,* 26(2):232-240.

Koblinsky MA. (1995). Beyond maternal mortality – magnitude, interrelationship, and consequences of women's health, pregnancy-related complications and nutritional status on pregnancy outcomes. *Int J Gynaecol Obstet,* 48(suppl):S21-S32.

Koller O. (1982). The clinical significance of hemodilution during pregnancy. *Obstetrical and Gynecological Survey,* 37:649-652.

Llewellyn-Jones D. (1965). Severe anaemia in pregnancy (as seen in Kuala Lumpur, Malaysia). *Aust N Z J Obstet Gynec,* 5:191-197.

Malhotra M, Sharma JB, Batra S, Sharma S, Murthy NS, Arora R. (2002). Maternal and perinatal outcome in varying degrees of anemia. *Int J Gynaecol Obstet,* 79:93-100.

Moia M, Mannucci PM, Vizzotto L, et al. (1987). Improvement in the haemostatis defect of uraemia after treatment with recombinant human erythropoietin. *Lancet,* 2:1227-1229.

Murphy JF, O'Riordan JO, Newcombe RG, Coles EC, Pearson JF. (1986). Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet,* 1:992-994.

Patra S, Pasrija S, Trivedi SS, Puri M. (2005). Maternal and perinatal outcomes in patients with severe anemia in pregnancy. *Int J Gynaecol Obstet,* 91:164-165.

RCOG. (2009). Prevention and Management of Postpartum Haemorrhage. Green-top Guideline No. 52.

Rodeghiero F, Castaman G, Dini E. (1987). Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987;69:454-459.

Rohilla M, Raveendran A, Dhaliwal LK, Chopra S. (2010). Severe anemia in pregnancy: a tertiary hospital experience from northern India. *Journal of Obstetrics and Gynaecology,* 30(7):694-696.

Rush D. (2000). Nutrition and maternal mortality in the developing world. *Am J Clin Nutr,* 72(suppl):212S-240S.

Sagen N, Koller O, Haram K. (1982). Haemoconcentration in severe pre-eclampsia. *Br J Obstet Gynaecol,* 89:802-805.

SOGC. (2005). Gynaecological and obstetric management of women with inherited bleeding disorders. SOGC Clinical Practice Guidelines No. 163. *JOGC,* 707-718.

Steer P, Alam MA, Wadsworth J, Welch A. (1995). Relation between maternal haemoglobin concentration and birth weight in different ethnic groups. *BMJ,* 310:489-491.

Tsu VD. (1993). Postpartum haemorrhage in Zimbabwe: a risk factor analysis. *Br J Obstet Gynaecol,* 100:327-333.

Turritto VT, Weiss HJ. (1980). Red blood cells: their dual role in thrombus formation. *Science,* 207:541-543.

Vigano G, Benigni A, Mendogni D, et al. (1991). Recombinant human erythropoietin to correct uremic bleeding. *Am J Kidney Dis,* 18:44-49.

von Schenck H, Falkensson M, Lundberg B. (1986). Evaluation of "Hemocue," a new device for determining hemoglobin. *Clinical Chemistry* 32(3):526-529.

Winikoff B, Dabash R, Durocher J, Darwish E, Ngoc NTN, León W, et al. (2010). Treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet,* 375:210-216.

World Health Organization. (1989). *Preventing Maternal Deaths*. By E Royston and S. Armstrong (Eds.). Geneva, pp. 85-89.

World Health Organization (1990). The Prevention and Management of Postpartum Haemorrhage: Report of a Technical Working Group, WHO/MCH/90.7, Geneva.

World Health Organization. (2001). Iron deficiency anemia: assessment, prevention and control. A guide for programme managers, Geneva.

CONCLUSIONS

Each chapter of this thesis provides new or enhanced information about possible means for achieving further reductions in postpartum hemorrhage risk. In particular, it appears that controlled cord traction adds value when oxytocin prophylaxis is unavailable, as well as when it is available but given intramuscularly; and that manual removal of the placenta or other clinical intervention may be warranted when placental delivery is delayed for 15 minutes or more. It also appears that women with low pre-delivery hemoglobin should be considered at increased risk for postpartum hemorrhage, and especially those with moderate-to-severe anemia.

At the same time, there are some limits to the generalizability of the findings in this thesis. The analyses in all three chapters were based on secondary data and as a result, I was unable to account for potential bias due to omission of some important covariates, or due to collinearity issues. Furthermore the data were collected in secondary- and tertiary-level hospital facilities and as a result, the findings may not be relevant other delivery settings. Given these limitations, there is a need for additional, policy-relevant information prior to implementation of any broad changes in clinical practice. For instance, it would be important to determine whether controlled cord traction can be safely and effectively provided by non-physician clinicians outside of hospital facilities before altering clinical guidelines relevant to such settings. There is also a need to better understand the role of biological mechanisms that might be responsible for the relationship between anemia and postpartum blood loss; and to examine whether efforts to treat anemia (e.g. antenatal iron supplementation) have any effect on postpartum hemorrhage risk.