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Duration of the second and third stages of labor and risk of postpartum hemorrhage: a cohort study stratified by parity

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Abstract

Background Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity and mortality worldwide. It is therefore important to improve our understanding of the risk factors for PPH according to parity, in particular, those linked to modifiable obstetric practices. The aim of this study was to assess the risk of PPH by the duration of the second and third stages of labor, stratified by parity.

Methods This study was based on secondary analysis of data from participants in a randomized controlled trial. A sample of women from three university hospitals in France aged at least 18 years, with a singleton pregnancy, in the first stage of labor, at 36–42 weeks of gestation, with epidural anesthesia and a vaginal delivery were included. The main outcome was PPH rates, defined by blood loss > 500 mL within 2 h after delivery. Characteristics of mothers, newborns, labor, and delivery, and their relation to PPH were explored with multivariable regression models.

Results Of 1598 women included, 864 were nulliparous and 680 parous; their respective PPH rates were 9.1% (79/864) and 7.4% (54/680) ($P = 0.2$), and the overall rate 8.3% (133/1598). The multivariable analysis found that PPH was associated with the durations of both oxytocin exposure (aOR 1.10, 95%CI 1.01–1.20) and the third stage of labour (aOR 1.80, 95%CI 1.37–2.38) among nulliparous women, and the PPH risk increased with both duration of the third stage (aOR 2.10, 95%CI 1.56–2.83) and history of PPH (aOR 3.02, 95%CI 1.38–6.59) among parous women.

Conclusions The duration of oxytocin exposure was found to be a risk factor for PPH among nulliparous women as was a history of PPH among parous women. Future studies should focus on duration of third stage of labor, especially when active management of the third stage of labor (AMTSL) is routinely used.

Trial registration The trial was registered at ClinicalTrials.gov NCT01113229.

Keywords Postpartum hemorrhage, Parity, Stage of labor, Risk factors

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Background

Postpartum hemorrhage (PPH) remains the leading cause of maternal morbidity and mortality in most countries around the world [1]. Although PPH has several identifiable risk factors, most cases occur unexpectedly [2–5]. Nonetheless, uterine atony can be anticipated and has known modifiable factors — elements of labor or management of delivery [6, 7]. Additionally, the risk of PPH can be reduced by active management of the third stage of labor (AMTSL) involving a prophylactic uterotonic administration, early cord clamping and controlled cord traction to deliver the placenta [8–10].

Many studies report that the risk of PPH is associated with prolonged second and [11–13] third stages of labor [14–18]. While international consensus exists for the definition of the start of this second stage, which begins at full dilation, definitions of "prolonged second stage" are very heterogeneous. For example, the American College of Obstetricians and Gynecologists (ACOG) proposes time limits beyond which the second stage is considered prolonged that vary by parity and use of an epidural [19]. Indeed, the presence of epidural analgesia has been shown to potential impact labor duration. For example, Shmueli et al. found that epidural analgesia extended the second stage by 82 min for both nulliparous and multiparous women at the 95th percentile and tripled the likelihood of prolonged labor in their cohort [20]. This study also indicated that other factors, such as the use of oxytocin, induction of labor, and maternal characteristics like nulliparity and maternal age, were significantly associated with prolonged second stage durations.

The relation between parity and pregnancy outcomes has been a concern for decades [21]. Most studies have found associations between nulliparity and PPH [22, 23]. Others have concluded that multiparity or grand multiparity (≥ 5 births) are risk factors for PPH [11, 24, 25]. Because parous women tend to be older have shorter lengths of labor, parity is an important confounding factor [18]. The literature has considered parity as either a continuous or dichotomous variable, to be adjusted for as a confounding factor [26, 27]. In addition, some risk factors, such as previous caesarean deliveries or a history of PPH are specific to parous women. It is therefore important to improve our understanding of the risk factors for PPH according to parity, in particular, those linked to modifiable obstetric practices. The duration of labor can be influenced or modified by certain obstetric practices. For example, the administration of drugs such as oxytocin can accelerate the onset of labor.

The aim of our study was to assess the risk for postpartum hemorrhage according to the durations of the second and third stages of labor, stratified by parity, in a cohort of women with epidural anesthesia.

Methods

This cohort study is a secondary analysis of data from women originally included in a randomized controlled trial (RCT). This double-blind, multicenter RCT took place in three French university hospitals around Paris from April 2010 to September 2013. Women in this RCT were randomly assigned during the first stage of labor at a one-to-one ratio to receive oral misoprostol (i.e., a total dose of 400 micrograms) or placebo immediately after delivery of the newborn.

Details and results of this trial were published in June 2016 [28]. The Ethics Committee of Poissy Saint-Germain Hospital (Comité de Protection des Personnes Ile de France XI) approved the study protocol for all centers. The trial was registered at ClinicalTrials.gov NCT01113229 on 2010-04-28 and was reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.

The objective of this trial was to evaluate the efficacy and safety of misoprostol administered concurrently with oxytocin in the active management of the third stage of labor. The clinical trial was stopped for futility. The primary outcome was the occurrence of PPH (500 ml or more within 2 h of delivery); Secondary outcomes included severe postpartum hemorrhage (1,000 mL or greater) and adverse maternal events such as fever, shivering, and nausea. It reported no difference between the study and control groups for the prevention of postpartum hemorrhage, duration of second or third stages of labor but increased the rate of adverse events in the study group.

Population

This study included women who were at least 18 years old, in the first stage of labor, at 36–42 weeks of gestation, had epidural anesthesia and provided written informed consent. Exclusion criteria of original RCT were multiple pregnancies, known hypersensitivity to prostaglandins, caesarean delivery, or participation in any other treatment trial.

All eligible women had active management of the third stage of labor (AMTSL), including a prophylactic intravenous injection of 10 IU oxytocin after delivery of the fetal anterior shoulder, early clamping of the umbilical cord, and controlled cord traction. The study group received an additional 400 micrograms of oral misoprostol.

Main outcome

The primary outcome was the rate of postpartum hemorrhage, defined as blood loss 500 mL or greater with in the 2 h after administration of the trial medication.

Monitoring of blood loss started as soon as the neonate was born and before delivery of the placenta. Blood loss was collected into a transparent graduated collector bag

maintained in place for at least 2 h after the neonate's birth. Blood from blood-soaked gauze swabs was also transferred into the plastic bag.

Study variables

We collected maternal, neonatal and labor characteristics (including obstetric procedures). The maternal and neonatal characteristics considered were maternal age (continuous variable, years), body mass index (BMI) (continuous variable, kg/m^2), mother's region of birth, previous caesarean delivery (Yes/No), history of PPH (Yes/No), and birth weight (continuous variable, kg). The characteristics of labor and delivery were labor induction (Yes/No), operative vaginal delivery (Yes/No), perineal tear (Yes/No), episiotomy (Yes/No), oxytocin during labor (Yes/No), and the durations of oxytocin exposure (continuous variable, min), total labor (continuous variable, h), active first stage of labor (continuous variable, min), second stage of labor (continuous variable, min), and third stage of labor (continuous variable, min).

Labor induction was conducted using oxytocin, dinoprostone, or misoprostol based on clinical indications. The use of oxytocin was left to the discretion of each physician.

All were continuous variables, with total labor expressed in hours and all the others as minutes.

Statistical analysis

The aim of this study was to assess the risk of PPH by analyzing the duration of the second and third stages of labor. To avoid the potential confounding effect of parity on outcomes, we stratified our cohort into nulliparous and parous women. The continuous variables of maternal age, BMI, and birth weight were dichotomized; BMI ≥ 25 kg/m2, birth weight ≥ 4 kg, maternal age ≥ 35 years, based on the literature. Categorical variables were described with numbers and percentages. Percentages were calculated for the available data. Numerical variables were described by their means and standard deviations (SD) and their medians and interquartile ranges [IQR]. In order to preserve the full variability of the data and facilitate comparisons, we treated the durations of both the second and third stages of labor as continuous variables and reported effect sizes per 60-minute increase for the second stage and per 10-minute increase for the third stage. The nulliparous groups were compared to parous group for baseline characteristics and outcomes, the continuous variables by the Wilcoxon rank sum test, and the categorical variables by the $\chi 2$ or Fisher's exact test, as appropriate.

A logistic regression analysis including all characteristics of women, labor, and delivery before the onset of PPH was performed to determine whether these characteristics were independently associated with PPH, separately for nulliparous and parous patients. The univariable logistic regression was then adjusted to include only those potential variables significant at $P \leq 0.10$. For each group, a multilevel model tested significant characteristics of women, labor, and delivery with a center effect. To avoid residual confounding we adjusted all models for the total duration of labor. Clinically relevant interactions were examined. Multicollinearity was assessed by computing the variance inflation factor (VIF). Results are expressed as odds ratios (ORs), with their 95% confidence intervals (CIs).

There were no missing data for the primary outcome. The multiple imputation using chained equations was performed with 5 iterations, and the results were consistent with the observed data, confirming the robustness of the imputation. A sensitivity analysis was performed with nonimputed data.

All *P*-values are two-sided and considered statistically significant if less than 0.05. Statistical analysis used R statistical software, version 3.1.

Results

Study population

This analysis covers 1598 women: 864 nulliparous (54.1%) and 734 (45.9%) parous. (Fig. 1)

The incidence of PPH among the 1598 singleton vaginal deliveries with epidural was 8.3% ($n = 133$). The PPH incidence in nulliparous women was 9.1% ($n = 79$) compared to 7.4% ($n = 54$) in parous women ($P = 0.20$). Table 1 describes the distribution of population characteristics by parity. Among parous women, 85.9% were in their second or third pregnancy. The statistical differences for most maternal and neonatal characteristics between nulliparous and parous women further justified an analysis stratified by parity. These two populations were comparable for the mothers' regions of birth, induction of labor, perineal tears (all type of tears were included), and durations of the third stage of labor. The two groups do not correspond to the two arms of the original RCT, however, the distribution of these two arms showed no statistical difference between nulliparous and parous women ($P = 0.80$).

Regarding the third stage of labor, 26.3% ($n = 343/1296$) patients had a duration ≥ 10 min, including 24.3% ($n = 168/692$) in nulliparous women and 28.7% (174/610) in parous women ($p = 0.07$).

For nulliparous women (Table 2), both the univariable and multivariable analyses found an association between the PPH risk and the durations both of oxytocin exposure per hour (OR 1.09, 95% CI 1.02–1.17; aOR 1.10, 95% CI 1.01–1.20) and of the third stage of labor per 10 min (OR 1.05 (1.02–1.08); aOR 1.73, 95% CI 1.31–2.27). The model was also adjusted for induction of labor and total duration of labor.

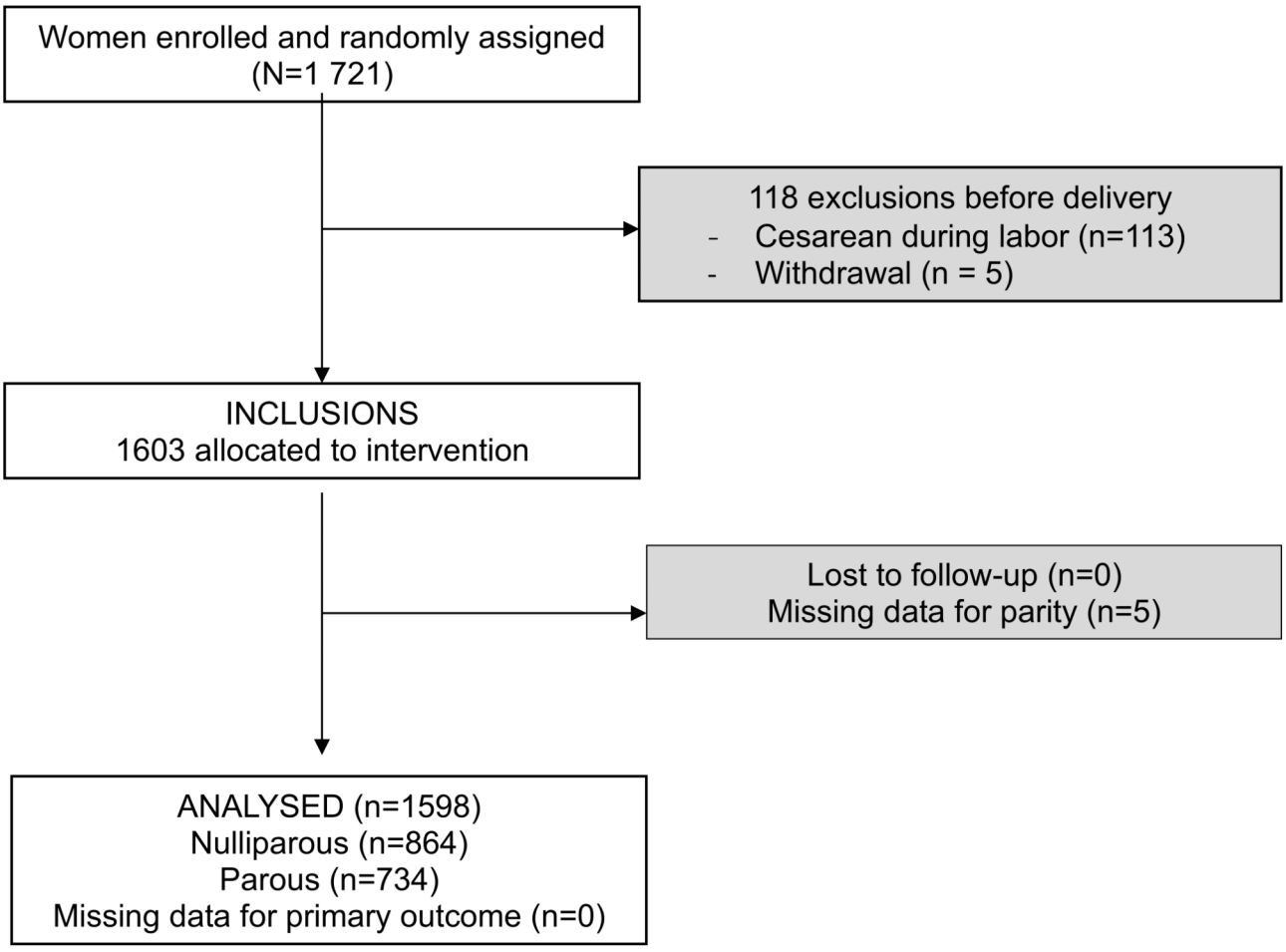

Fig. 1 Flowchart

For parous women (Table 3), univariable analysis found that risk of PPH was positively associated with a history of PPH (OR 3.29, 95% CI 1.53–6.60) as well as with the durations of oxytocin exposure per hour (OR 1.12, 95% CI 1.02–1.23) and of the third stage of labor (OR 1.05, 95% CI 1.02–1.08). The multivariable model found an increased risk of PPH was still associated with a history of PPH (aOR 3.07, 95% CI 1.41–6.68) and the duration of the third stage of labor (aOR 2.08, 95 M CI 1.55–2.81). The multivariable model was adjusted for episiotomy and the durations of oxytocin exposure, the second stage of labor and total labor. No adjustment was made for randomization groups in the trial as there was no difference between the two groups.

An association between the duration of the third stage of labor and the incidence of PPH was observed. However, only 26% of women—regardless of parity—experienced a third stage lasting ≥ 10 min, indicating that the majority had a shorter third stage.

Discussion

Main findings

The duration of exposure to oxytocin appears to be a risk factor for PPH in nulliparous but not in parous women. A history of PPH at previous delivery appears to be a major risk factor for PPH in parous women. Increased length of the third stage of labor was identified as risk factor in both groups, reinforcing the findings of the literature. A longer duration of the second stage was not associated with PPH.

Clinical meaning

The duration of exposure to oxytocin is a risk factor in nulliparous but not in parous women, most likely because of the latter's shorter labor and thus shorter exposure to oxytocin for women with vaginal delivery and epidural analgesia. Our findings are consistent with the literature [7, 17, 29]. A recent meta-analysis [30] found a significantly reduced risk of PPH in the group with oxytocin discontinued once active labor was induced (RR 0.78, 95% CI 0.65–0.93). Thus, stopping oxytocin infusion at that point, as suggested by Daniel-Spiegel et al. [31]

Table 1 Characteristics of women's and their neonates

Characteristics	Overall *N* = 1598	Nulliparous *N* = 864	Parous *N* = 734	*P*-value
Maternal and neonatal characteristics,				
Maternal age ≥ 35 years, n (%)	326 (20.4)	94 (10.9)	232 (31.6)	< 0.001
Mother's region of birth, n (%)				0.20
Europe	1246 (79.0)	691 (81.0)	555 (76.6)	
North Africa	163 (10.3)	80 (9.4)	83 (11.5)	
Sub-Saharan Africa	66 (4.2)	28 (3.3)	38 (5.2)	
Asia	37 (2.3)	20 (2.3)	17 (2.3)	
Other	66 (4.2)	34 (4.0)	32 (4.4)	
Missing data, n (%)	*20 (1.2)*			
BMI (kg/m2) ≥ 25, n (%)	353 (22.6)	167 (19.6)	186 (26.1)	0.002
Previous cesarean delivery, n (%)		--	76 (10.4)	
History of PPH, n (%)		--	60 (8.2)	
Birth weight ≥ 4 kg, n (%)	132 (8.3)	53 (6.2)	79 (10.8)	< 0.001
Labor characteristics				
Induction of labor, n (%)	314 (19.7)	172 (20.0)	142 (19.3)	0.80
Operative vaginal delivery, n (%)	358 (22.4)	282 (32.6)	76 (10.4)	< 0.001
Perineal tear, n (%)	919 (57.6)	498 (57.8)	421 (57.4)	0.90
Episiotomy, n (%)	503 (31.5)	396 (45.9)	107 (14.6)	< 0.001
Oxytocin during labor, n (%)	928 (58.3)	584 (67.8)	344 (47.0)	< 0.001
Duration of oxytocin exposure (min)				< 0.001
Mean (SD)	135 (177)	172 (194)	90 (145)	
Median [IQR]	60 [0, 227]	120 [0, 300]	0 [0, 142]	
Missing data, n (%)	*88 (5.5)*			
Active first stage (min)				< 0.001
Mean (SD)	184 (185)	209 (231)	153 (93)	
Median [IQR]	180 [120–240]	180 [120–240]	120 [60–180]	
Missing data, n (%)	*248 (15.5)*			
Second stage of labor (min)				< 0.001
Mean (SD)	112 (69)	132 (68)	88 (63)	
Median [IQR]	120 [60, 172]	145 [78, 180]	82 [30, 137]	
Missing data, n (%)	*51 (3.1)*			
Third stage of labor (min)				0.13
Mean (SD)	8 (7)	7 (7)	8 (7)	0.07
Median [IQR]	5 [3, 10]	5 [3, 9]	5 [3, 10]	
Third stage ≥ $\mathbf{10min}$, n(%)	343 (26.3)	168 (24.3)	174 (28.7)	
Missing data, n (%)	*296 (18.5)*			
Total labor duration (h)				< 0.001
Mean (SD)	7.01 (3.37)	8.00 (2.87)	5.84 (3.54)	
Median [IQR]	6 [5, 9]	8 [6, 10]	5 [4, 7]	
Missing data, n (%)	*5 (0.3)*			
Randomization groups in the trial, n (%)				0.80
Study group	803 (50.3)	431 (49.9)	372 (50.7)	
Control group	795 (49.7)	433 (50.1)	362 (49.3)	

BMI, body mass index; PPH, postpartum hemorrhage; SD, standard deviation; IQR, interquartile range

should be considered. It would be interesting to evaluate the discontinuous use of oxytocin during spontaneous labor [32]. As it is a modifiable risk factor, the indications for oxytocin must be carefully defined, especially during spontaneous labor [33]. Further investigation is needed to determine the cut-off points for the quantity or duration of oxytocin associated with an increased risk of atony.

Results about the duration of the second stage of labor are conflicting. The meta-analysis by Ende et al. did not find a prolonged second stage of labor to be a definite risk factor for atonic PPH (OR of 1.10, 95% CI 0.82–1.48) [4]. However, most studies have shown that the risk of PPH increases when the duration of the second stage is prolonged [12, 13, 15, 17, 34]. Notably, a large US multicenter cohort study (2002–2008) reported an increased risk of PPH in nulliparous women whose second stage

Table 2 Factors associated with PPH among nulliparous women: univariable and multivariable analysis

	Women with PPH (*n* = 79)	**Women with no PPH (*n* = 785)**	**Univariable**	**Multivariable**
Characteristics			**Crude OR (95% CI)**	**Adjusted OR(95% CI)***
Maternal age ≥ 35 years, n (%)	11 (13.9)	83 (10.6)	1.37 (0.66–2.59)	
BMI (kg/m2) ≥ 25, n (%)	16 (20.5)	151 (19.5)	1.06 (0.58–1.85)	
Induction of labor, n (%)	22 (28.2)	150 (19.1)	1.66 (0.97–2.77)	1.34 (0.77–2.33)
Operative vaginal delivery, n (%)	26 (32.9)	256 (32.6)	1.01 (0.61–1.64)	
Perineal tear, n (%)	43 (55.8)	455 (58.0)	0.92 (0.57–1.48)	
Episiotomy, n (%)	40 (50.6)	356 (45.4)	1.23 (0.78–1.96)	
Birth weight ≥ 4 kg, n (%)	8 (10.1)	45 (5.8)	1.85 (0.78–3.87)	
Duration of oxytocin exposure** (min), median [IQR]	206 [0, 360]	107 [0, 283]	**1.09 (1.02–1.17)**	**1.10 (1.01–1.20)**
Active first stage** (min), median [IQR]	180 [120, 350]	180 [120, 240]	1.02 (0.96–1.06)	
Second stage of labor** (min), median [IQR]	156 [96, 182]	140 [77, 180]	1.13 (0.92–1.39)	1.08 (0.86–1.34)
Third stage of labor***(min), median [IQR]	6 [4, 14]	5 [4, 8]	**1.05 (1.02–1.08)**	**1.73 (1.31–2.27)**
Total labor duration**(h), median [IQR]	8 [6, 10]	8 [6, 10]	1.06 (0.97–1.14)	0.95 (0.85–1.06)

OR, odds ratio, CI, confidence interval; BMI, body mass index. *OR adjusted for induction of labor, durations of oxytocin exposure, second stage, third stage, and total labor. **OR and aOR per 60-min increase. ***OR and aOR per 10-min increase

Table 3 Factors associated with postpartum hemorrhage among parous women: univariable and multivariable analysis

Characteristics	**Women with PPH (*n* = 54)**	**Women with no PPH (*n* = 680)**	**Univariable**	**Multivariable**
			Crude OR (95% CI)	**Adjusted OR* (95% CI)**
Maternal age ≥ 35 years, n (%)	19 (35.2)	213 (31.3)	1.19 (0.65–2.11)	
BMI (kg/m2) ≥ 25, n (%)	14 (27.5)	172 (26.0)	1.08 (0.55–2.00)	
Induction of labor, n (%)	13 (24.1)	129 (19.0)	1.35 (0.68–2.54)	
Operative vaginal delivery, n (%)	9 (16.7)	67 (9.9)	1.83 (0.81–3.75)	
Perineal tear, n (%)	26 (48.1)	395 (58.1)	0.67 (0.38–1.17)	
Episiotomy, n (%)	13 (24.1)	94 (13.8)	1.98 (0.99–3.73)	2.09 (1.00–4.36)
Birth weight ≥ 4 kg, n (%)	6 (11.1)	73 (10.8)	1.04 (0.39–2.33)	
Duration of oxytocin exposure** (min) median [IQR]	104 [0,217]	0 [0,135]	**1.12 (1.02–1.23)**	1.07 (0.95–1.21)
Active first stage** (min), median [IQR]	150 [60,240]	120 [60,180]	1.04 (0.86–1.24)	
Second stage of labor** (min), median [IQR]	91 [47, 150]	82 [30, 135]	1.20 (0.92–1.55)	1.10 (0.82–1.47)
Third stage of labor***(min), median [IQR]	8 [5,17]	5 [3,17]	**1.05 (1.02–1.08)**	**2.08 (1.55–2.81)**
Total labor duration** (h), median [IQR]	6 [5,8]	5 [4,7]	1.03 (0.96–1.09)	0.98 (0.98–1.11)
Previous caesarean, n (%)	9 (16.7)	67 (9.9)	1.83 (0.81–3.75)	
History of PPH, n (%)	11 (20.4)	49 (7.2)	**3.29 (1.53–6.60)**	**3.07 (1.41–6.68)**

PPH, postpartum hemorrhage; OR, odds ratio, CI, confidence interval; BMI, body mass index. *adjusted for adjusted for episiotomy, history of PPH, and durations of oxytocin exposure, second stage, third stage, and total labour. **OR and aOR per 60-min increase. ***OR and aOR per 10-min increase OR = Odds ratio, CI = Confidence Interval

of labor > 3 h (OR 1.50, 95% CI 1.27, 1.78) and in parous women whose second stage of labor > 2 h (OR 1.50, 95% CI 1.07, 2.10) — all with epidural analgesia [35]. We did not observe this result, probably because prolongation of the second stage of labor past 3 h was not a current practice in our study.

The longer the duration of the third stage of labor, the greater the risk of PPH in our study for both nulliparous and parous women, despite systematic AMTSL. Magann [16] found that a third stage of labor exceeding 18 min was associated with a significant risk of PPH in a prospective observational study. Frolova et al. [34] reported similar results after adjustment for induction of labor, prolongation of the first or second stage and parity (adjusted OR 1.82, 95% CI 1.43–2.31). Our study confirms that the reduction of the duration of the third stage of labor should be encouraged especially when AMTSL is used.

Strengths and limitation

The strengths of this study are the rigorous collection of data in the setting of an RCT and very few missing data. Inclusion in the first stage of labor, careful assessment of blood loss with a collector bag for all deliveries, precise criteria for the diagnosis of PPH, active management of all patients, and similar management techniques used for the second and third stages of labor — these strengths together allow a reliable description of the different durations. In addition, the selection of the population allowed us to control for confounding factors such as mode of delivery, epidural, gestational age and AMTSL. Moreover the risk of PPH observed in this population is similar to that reported in the literature for all vaginal deliveries when blood loss is measured with a collector bag [36, 37].

Most of women who present a PPH bleed within the two hours following the birth of the neonate and therefore are closely monitored in the delivery room. This is why we considered the risk of PPH within the first two hours and not within the first 24 h. Therefore, we did not identify the cases of PPH occurred after first two hours if there were any. This was a limitation of our methodology. Another limitation is that these results are not generalizable and can be applied only to populations that meet this trial's inclusion criteria.

To handle missing data, we applied multiple imputation, which strengthened the robustness of our results. However, the sample size reflects the potential impact of reduced statistical power due to stratification. Nonetheless, the association between the duration of the third stage of labor and PPH is well-documented in the medical literature. Finally, we did not collect the total dose of oxytocin in case of augmentation of labor with oxytocin infusion, data which could have improved our results.

Conclusion

The duration of oxytocin exposure was found to be a risk factor for PPH among nulliparous women as was a history of PPH among parous women. Additionally, we observed that an increased duration of the third stage of labor is associated with a higher risk of PPH, regardless of parity. Given these findings, future population-based studies should focus on the duration of the third stage of labor, particularly in the context of routine AMTSL.

Abbreviations

AMTSL	Active management of third stage of labor
BMI	Body mass index
IQR	Interval quartile range
PPH	Postpartum hemorrhage
RCT	Randomized controlled trial
SD	Standard deviation
WHO	World health organization

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Author contributions

SV undertook the analysis. SV compiled the tables and the figure. SV wrote the first draft of the manuscript, which was reviewed by AR, TQ, and PR.

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Data availability

All relevant data are within the paper and its Supporting Information files.

Declarations

Ethics approval and consent to participate

ClinicalTrials.gov, https://clinicaltrials.gov, NCT01113229. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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