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Association of oxytocin augmentation and duration of labour with postpartum haemorrhage: A cohort study of nulliparous women

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ABSTRACT

Objective: Both duration of labour and use of oxytocin for augmentation are known risk factors for postpartum haemorrhage but distinguishing between the significance of these factors is complex. In this study, we aimed to investigate the association between both labour duration and oxytocin augmentation, for postpartum haemorrhage.

Design: A cohort study based on a secondary analysis of a cluster-randomised trial.

Participants and setting: Term nulliparous women with a single foetus in cephalic presentation, spontaneous onset of active labour and a vaginal birth. The participants were originally included in cluster-randomised trial conducted in Norway from December 1, 2014, to January 31, 2017, that aimed to compare the frequency of intrapartum caesarean sections when adhering to the WHO partograph versus Zhang's guideline.

Measurements: The data were analysed through four statistical models. Model 1 investigated the effect of oxytocin augmentation as a dichotomous variable (yes/no); Model 2 investigated the effect of the duration of oxytocin augmentation; Model 3 investigated the effect of the maximum dose of oxytocin; and Model 4 investigated the effect of both the duration of augmentation and the maximum dose of oxytocin. All four models included duration of labour divided into five time-intervals. We used binary logistic regression to estimate the odds ratios of postpartum haemorrhage, defined as blood loss of $\geq$ 1000 ml, including a random intercept for hospital and mutually adjusting for oxytocin augmentation and labour duration in addition to maternal age, maternal marital status, maternal higher education level, maternal smoking habits in the first trimester, maternal body mass index and birth weight.

Findings: Model 1 found a significant association between the use of oxytocin and postpartum haemorrhage. In Model 2, oxytocin augmentation of $\geq$ 4.5 h was associated with postpartum haemorrhage. In Model 3, we found an association between a maximum dose of oxytocin of $\geq$ 20 mU/min and postpartum haemorrhage. Model 4 showed that a maximum dose of oxytocin $\geq$ 20 mU/min was associated with postpartum haemorrhage both for those augmented $<$ 4.5 h and for those augmented $\geq$ 4.5 h. Duration of labour was associated with postpartum haemorrhage in all models if lasting $\geq$ 16 h.

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Key conclusions: We found both oxytocin augmentation and labour duration to be associated with postpartum haemorrhage. Oxytocin doses of ≥ 20 mU/min and a labour duration of ≥ 16 h showed an independent association.
Implication for practice: The potent drug oxytocin should be carefully administered, as doses of ≥ 20 mU/min were associated with an increased risk of PPH, regardless of the duration of oxytocin augmentation.

Introduction

As postpartum haemorrhage (PPH) is the leading cause of maternal mortality and morbidity worldwide (WHO 2012), knowledge about risk factors and prevention strategies require profound and close attention. Different definitions of PPH have been used worldwide (Borovac-Pinheiro et al., 2018). Previously PPH was defined as blood loss > 500 ml after a vaginal birth or > 1000 ml after a caesarean section. More recently, PPH has been redefined as blood loss ≥ 1000 ml within the first 24 h after birth regardless of mode of birth (Bienstock et al., 2021). The consequences of PPH are most critical in low-income countries, where 99% of all maternal deaths occur (Say et al., 2014; Hancock et al., 2015). In high-income countries, PPH is the main cause of severe maternal morbidity, and the incidence is increasing (Knight et al., 2009; Hancock et al., 2015; Committee on Practice 2017; Fukami et al., 2019). In Norway, PPH, which is registered as blood loss of ≥ 500 ml in the Medical Birth Registry of Norway, has increased from 5.2% in 1990 to 30.7% in 2020 (Medical Birth Registry of Norway, 2020). It is estimated that approximately 7.5% involve blood loss of ≥ 1000 ml (2020). Advanced maternal age, obesity, nulliparity, lacerations, ruptures, and caesarean section are examples of factors shown to be associated with PPH (van Stralen, von Schmidt Auf Altenstadt et al. 2016; Nyflot et al., 2017; Borovac-Pinheiro et al., 2018; Durmaz and Komurcu 2018; Fukami et al., 2019). PPH is most frequently attributed to uterine atony (Hancock et al., 2015; Committee on Practice 2017), which causes 70%–80% of PPH cases (Committee on Practice 2017). Uterine atony in turn is known to be caused by an exceeded labour duration and the use of oxytocin for augmentation (Miller et al., 2017).

Contemporary research suggests that labours nowadays are longer than in the past. When comparing labour patterns in modern obstetrics, Laughon et al. found an increased duration of 2.6 h in the first stage of labour, compared to patterns observed in the 1960s (Laughon et al., 2012). This is explained partly by changes in women's characteristics, as they are older and have a higher body mass index (BMI), and partly by changes in clinical practice, with an increased use of such interventions as oxytocin augmentation and epidurals (Laughon et al., 2012).

In case of slow labour progress, the synthetic oxytocin is used. The medication is much appreciated in labour when contractions are inefficient, but it is also feared as it holds the risk of hyperstimulation with potentially fatal consequences, including foetal hypoxia and uterine rupture (Nabhan and Boulvain 2020). The use of oxytocin to augment labour is increasing worldwide, and it has been suggested that its use may be triggered by organizational factors, including busy labour wards and efficiency requirements, in addition to reasonable indications, such as slow progress due to inefficient contractions (Nabhan and Boulvain 2020). In Norway, the use of oxytocin in labour for augmentation has increased from 26.0% in 2000 to 32.0% in 2020. In addition, the optimal dose of oxytocin and duration of augmentation remain unclear and require further research (Kenyon et al., 2013).

Despite the concerns of potential adverse birth outcomes, including PPH related to both long labours and oxytocin use, researchers have struggled to define the strongest predictor through multiple strategies (Le Ray et al., 2011; van Stralen, et al., 2016; Miller et al., 2017). Distinguishing between the significance of the effects of labour duration and oxytocin use for augmentation on PPH is complex. In real-life clinical settings, an exceeded duration of labour and the use of oxytocin are most often intertwined, and adjustment for one holds the risk of diminishing the effect of the other and vice versa. At the same time, prospective trials investigating them separately would be both practically and ethically challenging. In the current study, we aimed to explore how duration of labour and oxytocin use for augmentation may affect the risk of PPH in a cohort of nulliparous women giving birth vaginally in Norway.

Methods

This is a secondary analysis of the Labour Progression Study (LaPS) (Bernitz et al., 2019). The LaPS was a cluster randomised trial conducted in 14 birth-care units in all four health regions in Norway during the period between December 2014 and January 2017. The main aim of the LaPS was to investigate whether the intrapartum caesarean section rate differed when adhering to the WHO partograph (Health, 1994) or to Zhang's guideline for labour progression in active labour (Zhang et al., 2010). The LaPS trial recruited 7277 nulliparous women with a single foetus in cephalic presentation and spontaneous onset of active labour at term. The trial showed no differences in the caesarean section rates between the two groups (Bernitz et al., 2019). No difference was found in the proportion of women augmented with oxytocin during labour, even if the augmentation lasted for a longer period than when following Zhang's guideline (Dalbye et al., 2019). The median duration of active labour was longer in the Zhang group compared to the WHO group: 6.6 h versus 6.1 h, respectively. The duration of both the 1st and 2nd stages was also longer for women in the Zhang group compared to those in the WHO group (Dalbye et al., 2020).

The current study used data from women in the LaPS who had a vaginal birth and an onset of partograph registration at 4–5 cm. The study sample was divided in two groups, one with PPH, defined as haemorrhage ≥ 1000 ml and one group with estimated blood loss < 1000 ml. The blood loss was estimated visually within two hours postpartum which is when women are normally transferred to the post-natal ward in Norwegian hospitals.

In Norway, intrapartum care takes place in public hospitals and is free of charge. Midwives are the main caregivers for women during childbirth, and they are responsible for low-risk labours. Obstetricians are involved in care for high-risk women and called upon if medical assistance is needed during any labour. The routines for oxytocin for augmentation follow obstetric guidelines (Norwegian Society of Gynecology and Obstetrics 2020). A starting dose of 5 mU/min is recommended, with an increase of 2.5 mU/min every 15 min until a maximum dose of 30 mU/. When oxytocin augmentation is commenced, it is rarely discontinued before the baby is born (Dalbye et al., 2019). After birth, women are given an intramuscular injection of 5000 mU of oxytocin as a stan-

dard prophylactic action to prevent PPH (Norwegian Society of Gynecology and Obstetrics 2020).

Statistical analysis

We used binary logistic regression to estimate crude and adjusted odds ratios (ORs) of PPH, with associated 95% confidence intervals. We considered four different models with duration of labour and oxytocin augmentation as the main exposures. Duration of labour was calculated as the time from the first registration of cervical dilatation, which is routinely plotted in the partograph, until the baby was born. All four models included duration of labour as a five-level categorical variable (< 4 h, 4–7 h, 8–11 h, 12–15 h, or ≥ 16 h), whereas use of oxytocin was included using different variables.

Model 1. included use of oxytocin as a dichotomous variable (no or yes).

Model 2. included duration of oxytocin augmentation as a three-level categorical variable (no oxytocin augmentation, < 4.5 h or ≥ 4.5 h).

Model 3. included a three-level categorical variable for the maximum oxytocin dose reached (no oxytocin augmentation, < 20 mU/min or ≥ 20 mU/min).

Model 4. combined both the duration of oxytocin augmentation and the maximum oxytocin dose as a five-level categorical variable (no oxytocin augmentation, < 4.5 h and < 20 mU/min, < 4.5 h and ≥ 20 mU/min, ≥ 4.5 h and < 20 mU/min, or ≥ 4.5 h and ≥ 20 mU/min).

As the data in the current study were originated from a cluster-randomized controlled trial comparing two different treatment strategies for labour progression, each model included a random intercept for hospital (obstetric unit). All models involved mutual adjustment for duration of labour and the respective variables for use of oxytocin for augmentation. Further adjustments were made for maternal characteristics that significantly differed between the study groups; age (< 25 years, 25–34 years, or 35 ≥ years), BMI (underweight, normal weight, pre-obesity, obesity class I, or obesity classes II and III), and neonatal birthweight (< 3000 g, 3000–3499 g, 3500–3999 g, 4000–4499 g, or ≥ 4500 g).

All statistical analyses were performed in Stata 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

Results

Of the 7277 women participating in the LaPS, 4943 fulfilled the inclusion criteria for this cohort study and were included in the analyses (Fig. 1).

Table 1 displays maternal and foetal characteristics of the study sample by study group (PPH ≥ 1000 ml and EBL <1000 ml), and labour characteristics are displayed in Table 2. Of the included women, 4684 (94.8%) had an EBL after labour of < 1000 ml and 259 (5.2%) had a PPH of ≥ 1000 ml. Differences in characteristics between the groups were found. Compared with women who had an EBL < 1000 ml, women with PPH ≥ 1000 ml were older, had a higher BMI, and larger babies (Table 1).

Oxytocin for augmentation was given to 2153 (46.0%) women in the group without PPH and to 160 (61.8%) in the PPH group. A duration of oxytocin augmentation of ≥ 4.5 h occurred for 511 (10.9%) in the group without PPH and for 56 (21.6%) in the PPH group. A maximum dose of oxytocin of ≥ 20 mU/min was registered for 689 (14.7%) in the group without PPH and for 74 (28.6%) in the PPH group. A duration of oxytocin augmentation of < 4.5 h, combined with maximal dose of oxytocin of ≥ 20 mU/min occurred for 436 (9.3%) in the group without PPH and for 42 (16.2%) in the PPH group. A duration of oxytocin augmentation of ≥ 4.5 h combined with a maximal dose of oxytocin of ≥ 20 mU/min occurred for 252 (5.4%) in the group without PPH and for 32 (12.4%) in the PPH group. A duration of labour from the start of the partograph to birth of ≥ 16 h was registered for 172 (3.7%) in the group without PPH and 29 (11.2%) in the PPH group (Table 2). Results from the statistical analyses are displayed in Table 3. A duration of labour of ≥ 16 h was associated with an increased risk of PPH in all four models (ORs of 2.00 or greater).

In addition, Model 1 showed that oxytocin use in general was associated with an increased risk of PPH (adjusted OR of 1.43 [95% CI: 1.03–1.99]). In Model 2, we found that augmentation with oxytocin of ≥ 4.5 h was associated with an increased risk of PPH (adjusted OR of 1.73 [95% CI 1.09–2.75]). In Model 3, regarding the significance of the maximum oxytocin dose, we found a maximum dose of ≥ 20 mU/min to be associated with an increased risk of PPH (adjusted OR of 1.94 [95% CI: 1.30–2.90]). In Model 4, where the maximum dose of oxytocin and the duration of oxytocin augmentation were analysed combinedly, we found that a maximum dose of ≥ 20 mU/min was associated with an increased risk of PPH both for those augmented for < 4.5 h (adjusted OR of 2.00 [95% CI: 1.29–3.08] for < 4.5 h and ≥ 20 mU/min vs. 1.19 [95% CI: 0.82–1.72] for < 4.5 h and < 20 mU/min) and for those augmented for ≥ 4.5 h (adjusted OR of 1.99 [95% CI: 1.16–3.43] for ≥ 4.5 h and ≥ 20 mU/min vs. 1.61 [95% CI: 0.93–2.80] for ≥ 4.5 h and < 20 mU/min) (Table 3). Results from the adjusted regression analyses are also displayed in Fig. 2.

Discussion

Our results confirm that both the duration of labour and oxytocin use for augmentation were associated with PPH in nulliparous women with spontaneous onset of active labour. The maximum oxytocin dose reached is crucial, regardless of the duration of oxytocin augmentation, as we found that oxytocin given in doses of ≥ 20 mU/min increases the risk of PPH both for women augmented for ≥ 4.5 h, as well as for those augmented for < 4.5 h. In addition, an active labour duration of ≥ 16 h was found to be associated with an increased risk for PPH in all four models.

Nearly half of the included women in this study (46.8%) were augmented with oxytocin even though they all entered the active phase of labour spontaneously. Consistent with previous research, we found that augmentation with oxytocin was associated with PPH (Belghiti et al., 2011; Grotegut et al., 2011; Wormer et al., 2020), similarly, a long labour duration was also associated with severe PPH (Nyflot et al., 2017). The fact that oxytocin is used for augmenting contractions to accelerate and shorten labour results in a catch-22 situation, which is a frequent real-life clinical dilemma. To address this challenge, we wanted to investigate the joint contribution of the two variables, rather than to identify which has the highest predictive value.

In case of slow progress of labour because of inefficient uterine contractions, the administration of oxytocin can lead to efficient uterine action and normal labour progress. However, in recent decades, the use of oxytocin has changed from selective to almost a routine procedure in many settings, with consequences that are not yet fully understood. In 2018, WHO released recommendations that changed the paradigm for the duration of labour, recognising the variability in the rates of progression between women and suggesting that labours longer than previously thought can result in a vaginal birth and maintain good perinatal outcomes (WHO 2018). Reconciling the use of oxytocin when medically bene-

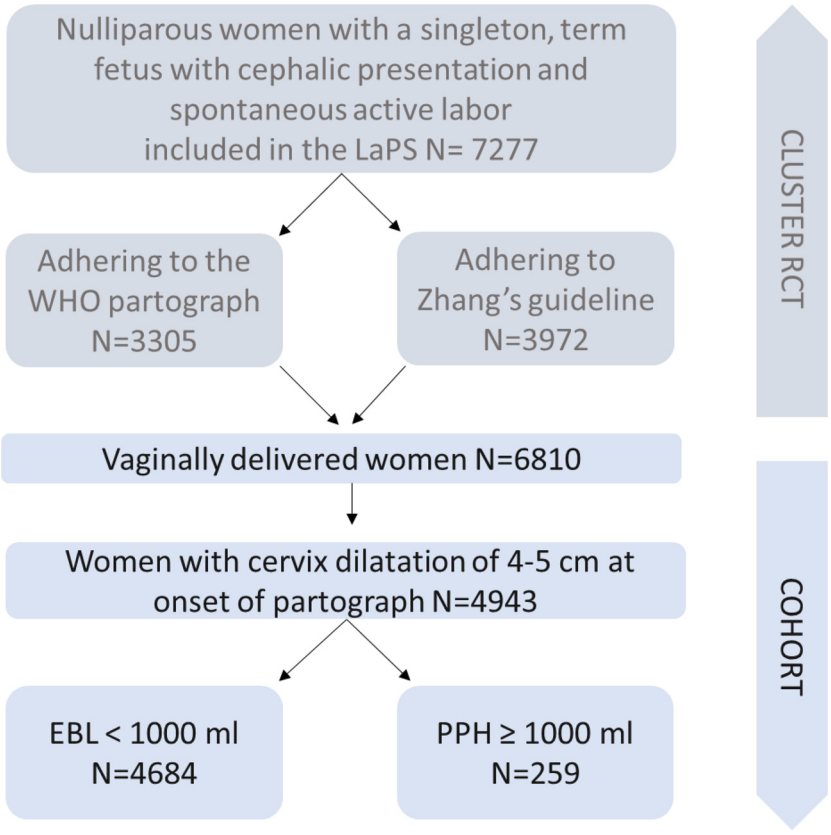

Fig. 1. Flowchart of inclusion process of the RCT and extraction to the cohort.

Table I
Maternal and foetal characteristics for the 4943 included participants[1].

Maternal characteristics	Postpartum haemorrhage ≥ 1000 ml				P value[2]
	No n = 4684 (94.8%)		Yes n = 259 (5.2%)		
Age at delivery					0.022
< 25 years	1209	(25.8)	49	(18.9)	
25–34 years	3146	(67.2)	185	(71.4)	
≥ 35 years	329	(7.0)	25	(9.7)	
Marital status					0.887
Married/cohabitant	4421	(94.4)	245	(94.6)	
Single or other	263	(5.6)	14	(5.4)	
Higher education (≥ 12 years)					0.088
No	1914	(40.9)	92	(35.5)	
Yes	2770	(59.1)	167	(64.5)	
Smoking during the first trimester					0.156
No	4346	(92.8)	248	(95.8)	
Yes	303	(6.5)	9	(3.5)	
Missing	35	(0.7)	2	(0.8)	
Body Mass Index (BMI)					0.035
< 18.5 (underweight)	197	(4.2)	8	(3.1)	
18.5–24.9 (normal weight)	3112	(66.4)	153	(59.1)	
25.0–29.9 (pre-obesity)	944	(20.2)	67	(25.9)	
30.0–34.9 (obesity class I)	303	(6.5)	18	(6.9)	
≥ 35.0 (obesity classes II and III)	110	(2.3)	12	(4.6)	
Missing	18	(0.4)	1	(0.4)	
Foetal characteristic					
Neonatal birthweight					< 0.001
< 3000 g	449	(9.6)	8	(3.1)	
3000–3499 g	1841	(39.3)	61	(23.6)	
3500–3999 g	1844	(39.4)	117	(45.2)	
4000–4499 g	492	(10.5)	61	(23.6)	
≥ 4500 g	58	(1.2)	12	(4.6)	

Data are presented as numbers and percentages.
[1] Nulliparous women with a singleton vertex foetus and spontaneous onset of active labour at term, restricted to women with cervical dilatation of 4–5 cm at start of the partogram and a vaginal birth.
[2] P value from Pearsonś chi-square test.

Table II
Labour characteristics of the study sample[1] related to interventions and maternal outcomes.

Labour characteristics	Postpartum haemorrhage ≥ 1000 ml				P value[2]
	No n = 4684 (94.8%)		Yes n = 259 (5.2%)		
Cervical dilation at start of partogram (in cm)					0.635
4	3043	(65.0)	172	(66.4)	
5	1641	(35.0)	87	(33.6)	
Oxytocin augmentation					< 0.001
No	2531	(54.0)	99	(38.2)	
Yes	2153	(46.0)	160	(61.8)	
Duration of oxytocin augmentation					< 0.001
No oxytocin augmentation	2531	(54.0)	99	(38.2)	
< 4.5 h	1641	(35.0)	104	(40.2)	
≥ 4.5 h	511	(10.9)	56	(21.6)	
Missing	1	(0.0)	0	(0.0)	
Maximum dose of oxytocin augmentation					< 0.001
No oxytocin augmentation	2531	(54.0)	99	(38.2)	
< 1200 mU/h	1463	(31.2)	86	(33.2)	
≥ 1200 mU/h	689	(14.7)	74	(28.6)	
Missing	1	(0.0)	0	(0.0)	
Duration and maximal dose of oxytocin augmentation					< 0.001
No oxytocin	2531	(54.0)	99	(38.2)	
< 4.5 h, < 1200 mU/h	1204	(25.7)	62	(23.9)	
< 4.5 h, ≥ 1200 mU/h	436	(9.3)	42	(16.2)	
≥ 4.5 h, < 1200 mU/h	259	(5.5)	24	(9.3)	
≥ 4.5 h, ≥ 1200 mU/h	252	(5.4)	32	(12.4)	
Missing	2	(0.0)	0	(0.0)	
Duration of labour from start of partogram to delivery					< 0.001
< 4 h	996	(21.3)	31	(12.0)	
4–7 h	1595	(34.1)	84	(32.4)	
8–11 h	1275	(27.2)	62	(23.9)	
12–15 h	646	(13.8)	53	(20.5)	
≥ 16 h	172	(3.7)	29	(11.2)	
Mode of delivery					< 0.001
Spontaneous vaginal delivery	3687	(78.7)	158	(61.0)	
Operative vaginal delivery (forceps and/or vacuum)	997	(21.3)	101	(39.0)	
Allocated guideline for assessing labour progression					0.002
WHO partogram	2161	(46.1)	94	(36.3)	
Zhang's guideline	2523	(53.9)	165	(63.7)	

Data are presented as numbers and percentages.
Abbreviations: cm — centimetres; g — grams; h — hours; mU; milliunits.
[1] Nulliparous women with a singleton vertex foetus and spontaneous onset of active labour at term, restricted to women with cervical dilatation of 4–5 cm at start of the partogram and a vaginal delivery.
[2] P value from Pearsonś chi-square test.

ficial and the physiologically normal duration of labour is essential to minimise PPH.

There is a lack of agreement on oxytocin administration for the initial dose, the increments and intervals for increasing the dose, and the maximum dose (Kenyon et al., 2013; NICE, 2014; WHO 2014; Rossen et al., 2016). The variations in administration complicate the interpretation of the effect. Our results indicate that oxytocin dose was an important risk factor for PPH, rather than just the duration of oxytocin augmentation itself.

Concerning the duration of augmentation, there is an even larger lack of consensus on when to terminate (Nabhan and Boulvain, 2020). The risk of uterine atony and PPH might increase with a long duration of oxytocin augmentation due to desensitisation of the oxytocin receptors in the myometrium (Phaneuf et al., 1998).

Prior research shows that long labours carry a risk of PPH (Nyflot et al., 2017). The WHO states that active labour (first and second stages) usually does not last longer than 15 h for nulliparous women (WHO 2018). The duration of active labour is highly individual and investigating the significance of labour duration is complex. To explore this challenge, we presented duration in five time intervals and found an increased risk of PPH when labour exceeded 16 h. The possibility of investigating the sole significance of labour duration, without the use of oxytocin, is both unfeasible and unethical.

Our findings indicate that the potent drug oxytocin should be carefully administered, as we found that doses of ≥ 20 mU/min were associated with an increased risk of PPH, regardless of the duration of oxytocin augmentation. When augmentation with oxytocin should be commenced to avoid long labours remains an unsolved question, and the answer may lie on an individual level rather than in predefined protocols. The wide range of uterine activity in normal labour progress and the potential harm of oxytocin augmentation should be considered when deciding to augment labour, to avoid a long duration of oxytocin augmentation and high doses of oxytocin to prevent PPH (Nabhan and Boulvain, 2020).

Further research is needed to better understand the independent effect of oxytocin on the uterus' contractibility over time and

Table III
Associations between oxytocin augmentation and duration of labour with postpartum haemorrhage ≥ 1000 ml based on the study sample[1].

Model 1	Crude analysis[2]		Adjusted analysis[2,3]	
	OR (95% CI)	P value	OR (95% CI)	P value
Oxytocin augmentation				
No	1		1	–
Yes	1.97 (1.52–2.57)	< 0.001	1.43 (1.03–1.98)	0.031
Duration of labour				
< 4 h	1	–	1	–
4–7 h	1.70 (1.12–2.59)	0.013	1.41 (0.91–2.19)	0.122
8–11 h	1.56 (1.00–2.42)	0.048	1.08 (0.66–1.77)	0.752
12–15 h	2.63 (1.67–4.14)	< 0.001	1.53 (0.90–2.60)	0.118
≥ 16 h	5.39 (3.15–9.22)	< 0.001	2.73 (1.46–5.10)	0.002
Model 2				
Duration of oxytocin augmentation				
No oxytocin augmentation	1	–	1	–
< 4.5 h	1.68 (1.26–2.24)	< 0.001	1.38 (0.99–1.93)	0.058
≥ 4.5 h	2.86 (2.03–4.03)	< 0.001	1.75 (1.10–2.78)	0.018
Duration of labour				
< 4 h	1	–	1	–
4–7 h	1.70 (1.12–2.59)	0.013	1.42 (0.92–2.20)	0.115
8–11 h	1.56 (1.00–2.42)	0.048	1.07 (0.65–1.75)	0.789
12–15 h	2.63 (1.67–4.14)	< 0.001	1.42 (0.82–2.46)	0.207
≥ 16 h	5.39 (3.15–9.22)	< 0.001	2.42 (1.26–4.68)	0.008
Model 3				
Maximum dose of oxytocin augmentation				
No oxytocin augmentation	1	–	1	–
< 1200 mU/h	1.56 (1.16–2.11)	0.003	1.26 (0.89–1.78)	0.199
≥ 1200 mU/h	2.95 (2.13–4.08)	< 0.001	1.94 (1.30–2.89)	0.001
Duration of labour				
< 4 h	1	–	1	–
4–7 h	1.70 (1.12–2.59)	0.013	1.42 (0.92–2.20)	0.116
8–11 h	1.56 (1.00–2.42)	0.048	1.06 (0.65–1.73)	0.816
12–15 h	2.63 (1.67–4.14)	< 0.001	1.45 (0.85–2.48)	0.172
≥ 16 h	5.39 (3.15–9.22)	< 0.001	2.46 (1.31–4.62)	0.005
Model 4				
Duration of oxytocin augmentation and maximum dose of oxytocin				
No oxytocin	1	–	1	–
< 4.5 h, < 1200 mU/h	1.38 (0.99–1.91)	0.057	1.19 (0.82–1.71)	0.359
< 4.5 h, ≥ 1200 mU/h	2.62 (1.78–3.85)	< 0.001	1.99 (1.29–3.07)	0.002
≥ 4.5 h, < 1200 mU/h	2.35 (1.47–3.74)	< 0.001	1.63 (0.94–2.84)	0.083
≥ 4.5 h, ≥ 1200 mU/h	3.46 (2.25–5.30)	< 0.001	2.00 (1.16–3.45)	0.012
Duration of labour				
< 4 h	1	–	1	–
4–7 h	1.70 (1.12–2.59)	0.013	1.43 (0.92–2.21)	0.112
8–11 h	1.56 (1.00–2.42)	0.048	1.05 (0.64–1.72)	0.850
12–15 h	2.63 (1.67–4.14)	< 0.001	1.39 (0.80–2.40)	0.244
≥ 16 h	5.39 (3.15–9.22)	< 0.001	2.28 (1.18–4.42)	0.014

Abbreviations: CI – confidence interval; OR – odds ratio.
[1] Nulliparous women with a singleton vertex foetus and spontaneous onset of active labour at term, restricted to women with cervical dilatation of 4–5 cm at start of the partogram and a vaginal delivery.
[2] Inclusion of a random intercept for hospital (obstetric unit).
[3] Mutual adjustment for oxytocin augmentation and duration of labour in addition to maternal age, maternal marital status, maternal higher educational level, maternal smoking habits in first trimester, maternal body mass index, and birthweight.

optimal regimens for augmentation. It would be particularly important under the recent changes recommended by the WHO for the progression and duration of labour (Hofmeyr et al., 2021).

Strengths and limitations

The data in this analysis are of a high quality, as they are derived from a randomised controlled trial and from a reliable source. All women included in this study entered active labour spontaneously, leaving out possible complications in connection with induction and early augmentation. Oxytocin was presented in detail to investigate the significance of both the duration of augmentation and the dose of oxytocin. Duration of labour was presented in five time-intervals to investigate the significance of labour duration in a mode gradual manner The mutual adjustment for oxytocin and the duration of labour in all four models strengthens our findings.

Our analysis has limitations. Measuring blood loss by visual estimation is inaccurate and represents a limitation in our study (Hancock et al., 2015; Committee on Practice 2017) yet it is still the most used assessment method in labour care all throughout Norway. Quantitative methods of measuring blood loss have been shown to be more accurate than visual estimation in determining the amount of blood loss and show a higher mean blood loss and more women identified as having PPH (Borovac-Pinheiro et al.,

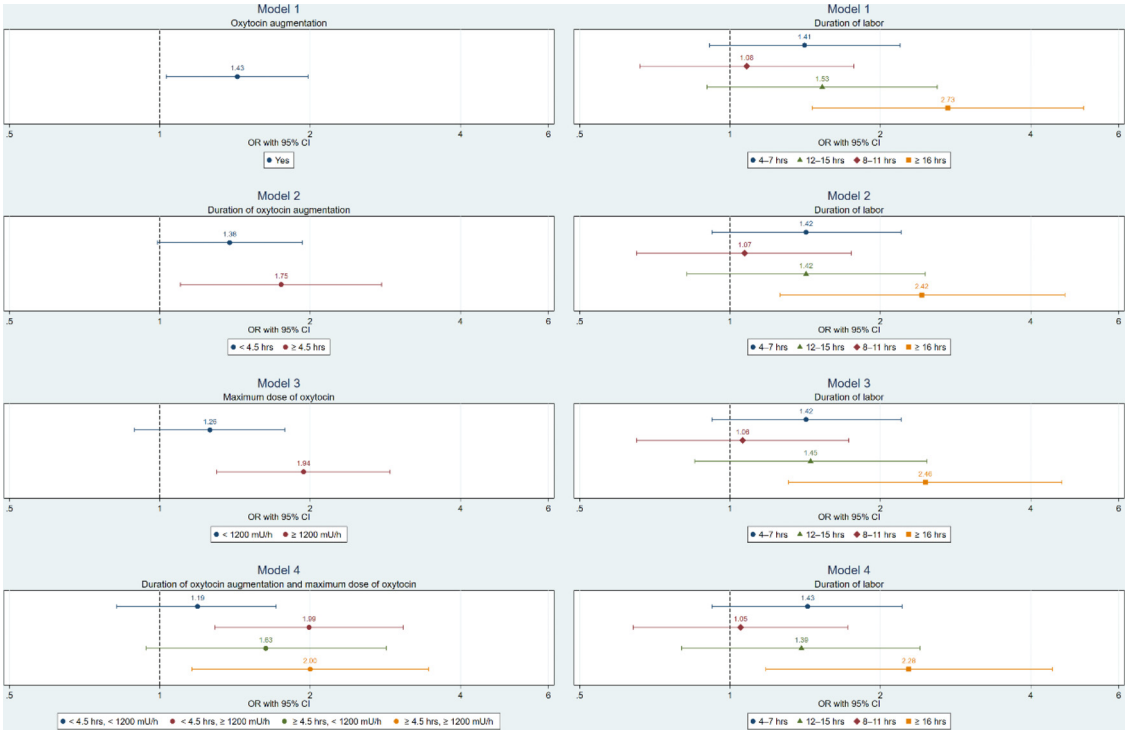

Fig. 2. Adjusted odds ratios (ORs) of postpartum haemorrhage ≥ 1000 ml, with associated 95% confidence intervals (CIs), for oxytocin augmentation and duration of labour plotted on a logarithmic scale based on four different regression models.

2018; Smith et al., 2022). However, no exact method for estimating blood loss exists. According to visual estimation of blood loss in our study, the number of women with PPH could therefore be underestimated. The choice of using a cut-off for PPH at 1000 ml in our study is explained by the clinical relevance and recently redefinitions of PPH (Bienstock et al., 2021). There is a statistical challenge of distinguishing the two groups based on visual estimation even if this is our clinical approach to estimation of blood loss. Still applying the average error to each visual estimation and using confidence intervals to distinguish between the two groups, implies that a good number of observations will have to be discarded since there certainly will be some values that lie on the borderline between the two categories. Hence either choice will represent a source of uncertainty.

The available information on oxytocin use includes starting point, maximum dosage and duration, but total amount is not reported. In our study, we aimed to investigate the significance of the duration of active labour and the use of oxytocin for women who spontaneously entered the active phase; hence, the duration of the second stage was not specified. Even if the length of the second stage was reported to be associated with PPH (Cheng et al., 2007; Le Ray, et al., 2011; Miller et al., 2017), it is likely believed that a prolonged total length of labour increases the risk of uterine atony and thereby increases the risk of PPH.

Our study is restricted to vaginally delivered nulliparous women, mainly Caucasian, and therefore precludes the risk of PPH related to multiparous women, caesarean sections, repeated PPH and the risk of PPH according to race (Kramer et al., 2013; Gyamfi-Bannerman et al., 2018).

Conclusions

The complexity of real-life clinical practice complicates the interpretation of oxytocin and labour duration as predictors for PPH. We found that for term nulliparous women with a singleton vertex foetus, spontaneous onset of active labour, and vaginal birth, the duration of labour was associated with PPH if it lasts 16 h or more. Caution should be paid to the use of oxytocin in high doses, as oxytocin doses of 20 mU/min or more were associated with PPH, regardless of the length of augmentation for vaginally delivered women.

Ethical approval

The Regional Committee for Medical and Health Research Ethics South-East Norway approved the LaPS on June 27, 2014 (2013/1862/REK). All participating women gave their written consent to use their data in the LaPS trial.

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Clinical trial registry and registration number

The study was registered at www.clinicaltrials.gov before enrolment of the first participant (NCT02221427).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Stine Bernitz: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ana Pilar Betran:**

Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Nina Gunnes:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **Jun Zhang:** Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Ellen Blix:** Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Pål Øian:** Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Torbjørn Moe Eggebø:** Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Rebecka Dalbye:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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