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Oxytocin during labour and risk of severe postpartum haemorrhage: a population-based, cohort-nested case–control study

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ABSTRACT

Objectives: Postpartum haemorrhage (PPH) is a major cause of maternal mortality and morbidity worldwide. Experimental studies support the hypothesis that oxytocin administration during labour, a common although not evidence-based practice, may increase the risk of atonic PPH. The clinical studies, however, are inconclusive. The objectives of this study was to investigate the association between the level of oxytocin exposure during labour and the risk of severe PPH and to explore whether the prophylactic use of oxytocin after birth modifies this association.

Design: Population-based, cohort-nested case–control study.

Setting: 106 French hospitals from December 2004 through November 2006.

Participants: Women with term singleton vaginal deliveries, after an uncomplicated pregnancy. Cases were 1483 women with severe PPH, defined by peripartum change in haemoglobin of ≥4 g/dl or need for blood transfusion. Controls were 1758 women from a random sample of parturients without PPH.

Main outcome measures: The independent association between the level of oxytocin during labour and the risk of severe PPH was tested and quantified with ORs through two-level multivariable logistic regression modelling.

Results: Oxytocin was administered during labour to 73% of cases and 61% of controls (crude OR: 1.7, 95% CI 1.5 to 2.0). After adjustment for all potential confounders, oxytocin during labour was associated with a significantly higher risk of severe PPH (adjusted OR: 1.8, 95% CI 1.3 to 2.6) in women who did not receive prophylactic oxytocin after delivery; the OR for haemorrhage increased from 1 to 5 according to the level of oxytocin exposure. In women who had prophylactic oxytocin after delivery, this association was significant only for the highest exposure categories.

Conclusions: Oxytocin during labour appears to be an independent risk factor for severe PPH. The results emphasise the need for guidelines clarifying the evidence-based indications for this procedure and the minimal useful regimens.

ARTICLE SUMMARY

Article focus

- Postpartum haemorrhage is the main component of maternal morbidity, and increase in its incidence is reported.
- Experimental studies support the hypothesis that oxytocin administration during labour, a common although not evidence-based practice, may increase the risk of atonic postpartum haemorrhage.
- The clinical studies, however, are inconclusive.

Key messages

- In this study, oxytocin during labour appears to be an independent risk factor for severe Postpartum haemorrhage, with a dose-related association.
- Our results emphasise the need for guidelines clarifying the evidence-based indications for this procedure and the minimal useful regimens.

Strengths and limitations

- Source population: large population-based cohort; representativity of cases and controls.
- Detailed data on oxytocin administration during labour collected from medical files.
- Detailed data on potential confounders.
- Inherent limitation of observational studies: residual confounding cannot be excluded, although all potential confounders were taken into account.

INTRODUCTION

Obstetric haemorrhage remains one of the leading causes of maternal mortality in developed countries, accounting for 10%–30% of direct maternal deaths in countries with maternal death enquiries.[1 2] It is also a major component of severe maternal morbidity.[3 4] Recent increases in the prevalence of postpartum haemorrhage (PPH) have been reported in several developed

countries.[5–7] This rise is limited to immediate/atonic PPH in Australia, Canada and the USA and remains significant when temporal trends in known risk factors are taken into account.[5–7] This underlines the need for further investigation of possible PPH risk factors. We focused on components of care during labour because they might affect uterine tone, have changed over time and can be modified.

A good candidate is the administration of oxytocin, commonly used to induce or augment labour. Although data are sparse, oxytocin infusion during labour appears to have become a routine procedure in developed countries that may concern a significant portion of parturients, sometimes even a majority.[8–12] This evolution merits concern because it suggests that the use of oxytocin has been extended from specific to broader but poorly defined indications without either an evidentiary basis[13 14] or a rigorous evaluation of its safety, especially for the risk of PPH.

This endogenous hormone plays a physiological role in maintaining uterine contractility during labour and reinforcing it after delivery to stop postpartum bleeding. Its pharmacological use for inducing or augmenting labour can, however, desensitise receptors,[15 16] thereby impairing oxytocin's post-delivery effects on uterine contractility and increasing the risk of atonic PPH.[17] The effects of oxytocin administered during labour may differ in women who do or do not also receive exogenous oxytocin after delivery to prevent PPH, an intervention now recommended in routine practice.[18 19]

Clinical studies of the effect of oxytocin administration during labour on the risk of PPH have reported conflicting results,[20–24] and their conclusions are impaired by methodological limitations, mainly the failure to take into account the indication bias associated with prolonged labour, the amount of oxytocin infused or the possibility of a differential impact according to whether the woman received prophylactic oxytocin after birth or not. This flawed evidence likely contributes to the common belief that this treatment has no serious adverse effects.

Our objectives in this large population-based study were to investigate the independent association between the level of oxytocin exposure during labour and the risk of severe PPH and to examine whether the prophylactic use of oxytocin after birth modified this association.

METHODS

Study design

This was a population-based, cohort-nested case–control study.

Population

The study population included women selected from the Pithagore6 trial, a cluster randomised controlled trial conducted in 106 French maternity units operating as six perinatal networks. Its main objective was to evaluate a multifaceted educational intervention for reducing the rate of severe PPH, and it found no significant difference in this rate between the two groups of hospitals (details available elsewhere[25]). The 106 Pithagore6 maternity units represented 17% of all French maternity units and accounted for 20% of French deliveries. Data were collected for 1 year in each unit from December 2004 through November 2006.

PPH was clinically assessed by obstetricians or midwives or defined by a peripartum haemoglobin (Hb) delta of >2 g/dl (considered equivalent to the loss of >500 ml of blood). Prepartum Hb was measured during routine prenatal care near the end of pregnancy; postpartum Hb was the lowest measurement found 3 days after delivery. Birth attendants in each unit identified all deliveries with PPH and reported them to the research team. A research assistant reviewed each unit's delivery suite logbook monthly and any available computerised patient charts. For every delivery with a mention of PPH or examination of the uterine cavity or manual removal of the placenta, the patient's obstetrics file was further checked to verify the PPH diagnosis. During the 1-year data collection period, 9365 cases of PPH (defined either by estimated blood loss or by drop in Hb) occurred among 146 781 deliveries in the 106 Pithagore6 units, for a total PPH incidence of 6.4%.

A representative sample of women without PPH in the same units during the same period was assembled by randomly selecting 1/60 of all other deliveries.

We selected the study population from the Pithagore6 population by excluding subgroups of women likely to introduce bias due either to selection or major confounding by indication or other factors in the association between the augmentation of labour and the risk of severe PPH: women with pre-existing conditions, previous uterine surgery including caesarean delivery, multiple pregnancy, obstetric disease, fetal death, preterm delivery (before 37 weeks of gestation) and caesarean delivery. The study population finally included women with vaginal delivery of a term (at least 37 weeks) singleton after an uncomplicated pregnancy. For our case–control analysis, the 1487 cases were women with severe PPH defined by a peripartum Hb delta of 4 g/dl or more (considered equivalent to the loss of 1000 ml or more of blood) or by the need for blood transfusion; the delay between the prenatal Hb measurement and the delivery was (mean ± SE (25th, 75th percentile)) (in days) 11±0.7 (0, 14); a total of 1758 parturients without PPH served as controls. Figure 1 outlines the process that selected these two groups.

Study variables

Characteristics of the woman, pregnancy, labour and delivery were recorded shortly after delivery from the patient's chart.

The study variables included maternal age, body mass index (BMI) before pregnancy, previous PPH, previous

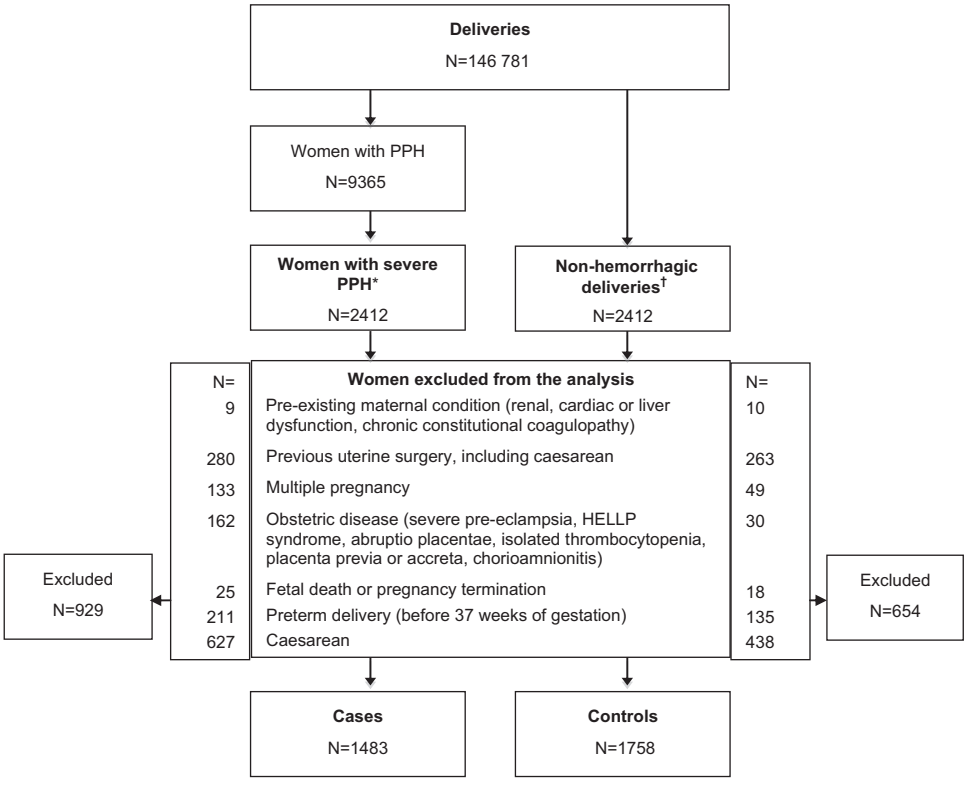

Figure 1 Selection of the study population. PPH, postpartum haemorrhage. *Severe PPH: peripartum haemoglobin delta of ≥4 g/dl or need for blood transfusion. †Randomly selected representative sample.

uterine curettage, primiparity, induction of labour, fever (>38°C) during labour, epidural analgesia, duration of active phase of labour (in minutes), oxytocin during labour, duration of expulsive efforts (in minutes, categorised according to the 50th, 75th and 90th percentiles of distribution in the control group), gestational age at delivery (in weeks, categorised as term (37–41) or post-term delivery (>41)), operative delivery, episiotomy, perineal tear, birth weight (in grams) and prophylactic oxytocin administration after delivery.

Oxytocin exposure during labour was studied as a binary variable and also with three quantitative variables: total dose (in international unit), maximal infusion rate (in milli international units per minute) and total duration of infusion (in minutes). These quantitative variables were categorised according to the 50th, 75th and 90th percentiles of their distribution in the control group, rounded to the nearest whole number.

Duration of labour, in particular its active phase, is a major confounding factor in the association studied and its assessment received special attention. The active phase of the first stage of labour starts when cervical dilation reaches 3 cm.[26] To prevent bias from the truncation of this record for women in labour before reaching the hospital, we applied several rules. The duration of the active phase for women admitted with cervical dilation of 3 cm or less was the time recorded between 3 cm and full dilation. In women admitted with cervical dilation >3 cm (12% of cases and 27% of controls), we hypothesised a constant speed of cervical dilation during this phase, and the total duration of the active phase of labour was estimated from each woman's mean cervical dilation rate (derived from the time of dilation measurement at admission to full dilation). Because mean cervical dilation speed could not be reliably estimated for women whose cervix was fully dilated at admission, the duration of their active labour was considered missing (0.7% (n=10) of cases and 1.3% (n=23) of controls).

Analysis

The case and control groups were compared with the χ^2 test for the characteristics of the women, pregnancies, labour and deliveries.

The independent effect of oxytocin treatment during labour on the risk of severe PPH was tested and quantified with a two-level multivariable logistic regression with a random intercept to take into account the hierarchical structure of the data, with women clustered in maternity units. We adjusted for covariables previously described as risk factors for severe PPH and for variables found to be potential confounders in bivariate analyses. Clinically relevant interactions were tested between oxytocin for augmentation of labour and other factors—parity, induction of labour and prophylactic oxytocin after delivery.

Less than 8% of cases and controls had missing values for any variables except BMI and duration of expulsive efforts, for which we created a specific missing value indicator variable for regression analyses. Sensitivity analyses tested the robustness of the results under best- and worst-case hypotheses of distribution of the missing values. Subjects with any missing values for other characteristics of women, labour and delivery were excluded

from the multivariable analyses: 63 (4.3%) cases and 55 (3.1%) controls.

A secondary analysis, using the same control group, limited the case definition to women whose severe PPH was due to uterine atony.

We estimated, based on a sample size of 1500 patients with severe PPH and 1500 controls, that the power of the study would exceed 80% for detecting an OR of 1.5 for exposures with a prevalence of 5% or more among controls and for detecting an OR of 1.3 for exposures with a prevalence of 15% or more among controls.

Statistical significance was defined as a p value of <0.05. Analyses were performed with Stata V.11 software (Stata Corporation).

RESULTS

Severe PPH was due to uterine atony in 545 (37%) women, partial or complete placenta retention in 255 (17%) women and cervical, vaginal or perineal wounds in 324 (22%) women. No cause was identified for 359 (24%) women. Overall, 315 (21%) women had blood transfusions, 68 (5%) had arterial embolisation, 25 (2%) had vascular ligation and 25 (2%) had a hysterectomy; 99 (7%) were transferred to intensive care. One woman died.

Women with severe PPH were older, more often primiparous and had a previous PPH more often than controls (table 1). Post-term delivery, induction of labour, epidural analgesia, longer labour, operative delivery, episiotomy or perineal tears and neonatal macrosomia were also more frequent in cases (table 2). Prophylactic oxytocin after delivery was more frequent in the control group.

Oxytocin was administered during labour significantly more often to women with severe PPH (73%) than to controls (61%) (OR: 1.7, 95% CI 1.5 to 2.0) (table 3). The crude OR for haemorrhage increased from 1 to 4 depending on the oxytocin infusion rate, duration of infusion and the total duration at a maximal rate (table 3).

There was a significant quantitative interaction between oxytocin during labour and its prophylactic use after birth for the risk of severe PPH (p=0.004 for Wald test of interaction). The crude OR for severe PPH associated with oxytocin during labour was 2.3 (95% CI 1.8 to 3.0) in women who did not receive prophylactic oxytocin after birth (N=593 cases and 518 controls) and 1.6 (95% CI 1.3 to 1.9) in women who did (N=890 cases and 1240 controls). We then stratified our multivariate analyses by the prophylactic use of oxytocin after delivery (tables 4 and 5) to examine its role in more detail.

When prophylactic oxytocin was not administered after delivery, oxytocin exposure during labour was associated with a higher risk of severe PPH, after controlling for all potential confounders (adjusted OR: 1.8, 95% CI 1.3 to 2.6) (table 4). The strength of the association increased with the amount of oxytocin infused. The risk of severe PPH, compared with that in women who did not receive oxytocin during labour, was about three times higher for a total dose from 2.0 to 4.0 IU (adjusted OR: 3.3, 95% CI 1.8 to 45.9) and six times higher for a total dose of >4.0 IU (adjusted OR: 5.7, 95% CI 2.5 to 12.9). Similarly, the association of severe PPH with the maximal infusion rate of oxytocin appeared dose related: the adjusted OR was 2.2 (95% CI 1.3 to 3.8) for a maximal rate between 10 and 15 mIU/min and 3.2 (95% CI 1.7 to 6.1) for a maximal rate of >15 mIU/min (table 4).

Among women who received prophylactic oxytocin after delivery, labour augmentation with oxytocin, considered globally, was not associated with a higher risk of severe PPH (adjusted OR: 1.1, 95% CI 0.8 to 1.5) (table 5). However, when the level of oxytocin exposure was considered, the risk of severe PPH appeared significantly higher for women in the most exposed categories: the adjusted OR was 2.1 (95% CI 1.3 to 3.3) for a total dose of >4 IU and 1.7 (95% CI 1.1 to 2.5) for a maximal infusion rate of >15 mIU/ml.

Sensitivity analyses showed that the various hypotheses about the distribution of missing values for BMI and duration of expulsive efforts did not change the results. The secondary analysis of cases limited to women with severe atonic PPH (n=545) and the same control group provided similar results (details provided in supplementary table).

Table 1 Maternal characteristics: distribution in cases and controls and bivariate analysis

	Women with severe PPH (N=1483), n (%)*	Controls (N=1758), n (%)*	p Value†
Maternal age (years)			
Mean (SD)	29.4 (5.0)	30.2 (5.0)	10^{-3}
Median	29.3	30.2	
(25th, 75th pc)	(26.0, 32.4)	(26.6, 33.8)	
<20	34 (2)	20 (1)	
20 to <30	789 (53)	831 (47)	
30 to <40	626 (42)	866 (49)	
≥40	34 (2)	41 (2)	
BMI (kg/m^2)			
Mean (SD)	22.5 (4.1)	22.4 (3.96)	0.3
Median	21.5	21.5	
(25th, 75th pc)	(19.7, 24.1)	(19.7, 24.2)	
<18	93 (7)	81 (5)	
18 to <25	960 (73)	1104 (74)	
25 to <30	187 (14)	223 (15)	
≥30	76 (6)	79 (5)	
MD	167 (11)‡	271 (15)‡	
Primiparous	1044 (70)	762 (43)	10^{-3}
Previous PPH	53 (4)	34 (2)	10^{-2}
Previous uterine curettage	153 (10)	179 (10)	0.9

BMI, body mass index; MD, missing data; pc, percentile; PPH, postpartum haemorrhage.
*Percentage of the total non-missing values.
†$\chi 2$ test.
‡Percentage of the total of cases and controls.

Table 2 Characteristics of labour and delivery: distribution in cases and controls and bivariate analysis

	Women with severe PPH (N=1483), n (%)*	Controls (N =1758), n (%)*	p Value†
Post-term delivery	292 (20)	230 (13)	10^{-3}
Induction of labour	356 (24)	316 (18)	10^{-3}
Epidural analgesia	1146 (77)	1282 (73)	0.05
Temperature >38°C during labour	42 (3)	19 (1)	10^{-3}
Duration of the active phase of the first stage of labour (min)‡			
Mean (SD)	333 (187)	263 (159)	10^{-3}
Median (25th, 75th pc)	310 (195, 445)	240 (143, 357)	
<240	474 (33)	843 (50)	
240−<357	353 (25)	434 (25)	
357−480	308 (22)	255 (15)	
≥480	285 (20)	171 (10)	
MD	63 (4)§	55 (3)§	
Duration of expulsive efforts (min)‡			
Mean (SD)	21 (14)	15 (11)	10^{-3}
Median (25th, 75th pc)	20 (10, 30)	11 (6, 20)	
<11	365 (28)	695 (50)	
11−<20	265 (21)	310 (22)	
20−<30	300 (23)	234 (17)	
≥30	351 (27)	159 (11)	
MD	202 (14)§	360 (20)§	
Operative delivery	490 (33)	220 (13)	10^{-3}
Episiotomy	913 (62)	591 (34)	10^{-3}
Perineal tear	399 (27)	542 (31)	0.01
Birth weight (g)			
Mean (SD)	3469 (446)	3337 (427)	10^{-3}
Median (25th, 75th pc)	3455 (3180, 3750)	3325 (3050, 3620)	
>4000	166 (11)	105 (6)	
Prophylactic oxytocin administration after delivery	890 (60)	1240 (71)	10^{-3}

MD, missing data; pc, percentile; PPH, postpartum haemorrhage.
*Percentage of the total non-missing values.
†$\chi 2$ test.
‡The thresholds correspond to the 50th, 75th and 90th percentiles of the distribution in the control group.
§Percentage of the total of cases and controls.

DISCUSSION

We found an independent dose-related association between oxytocin infusion during labour and severe PPH in women who did not receive prophylactic oxytocin after delivery. The association between oxytocin during labour and severe PPH in women who had prophylactic oxytocin after delivery was significant only for the highest category of exposure.

Despite particular attention to controlling for potential confounders, we cannot completely rule out the possibility that this association is due to residual confounding. Nonetheless, a residual confounder related to uterine tone that would both increase the need for oxytocin and the risk of PPH is unlikely, given our careful adjustment for duration of labour.

Our study design had several strengths. It was population based, and the resemblance of the Pithagore6 source population to the national population in terms of the characteristics of women and units[25 27] enhances the external validity of our results. The sample size provided adequate power to study the association of severe PPH with infrequent exposures, such as the highest oxytocin dose categories. The selection of cases and controls from the same population-based cohort ensures the comparability of these two groups. In view of the controversy over the definition of severe PPH,[28] we chose an objective criterion of severity (peripartum drop in Hb) because it is more likely to be determined consistently than estimated blood loss and especially because it is not dependent on medical practices. Data, collected directly from the medical files, included details on oxytocin administration (ie, quantities, timing and infusion rates) and other aspects of labour (eg, cervical dilation at admission, duration of labour). These detailed data allowed both precise characterisation of the exposure of interest and adequate control of confounders.

Finally, our analysis strategy was designed to minimise the biases that weaken the conclusions of previous studies exploring this association. Controlling for the duration of labour adequately is essential to avoid residual confounding. Our estimation of the actual total duration of the active phase, taking into account the degree of cervical dilation at arrival, likely reflects the dynamics of labour accurately. We also considered this estimated duration as a continuous variable, unlike

Table 3 Oxytocin treatment during labour in cases and controls and crude associations with severe PPH

	Women with severe PPH (N=1483), n (%)*	Controls (N=1758), n (%)*	Crude OR (95% CI)
Oxytocin during labour	1088 (73)	1077 (61)	1.7 (1.5 to 2.0)
Oxytocin total dose (IU)†			
Mean (SD)	2.4 (2.5)	1.6 (3.0)	
Median (25th, 75th pc)	1.6 (0.6, 3.4)	0.9 (0.3, 2.0)	
No oxytocin	395 (27)	681 (42)	Ref
<1.0	377 (26)	511 (31)	1.3 (1.1 to 1.5)
1.0–<2.0	229 (16)	207 (13)	1.9 (1.5 to 2.4)
2.0–<4.0	244 (17)	157 (10)	2.7 (2.1 to 3.4)
≥4.0	217 (15)	83 (5)	4.5 (3.4 to 6.0)
MD	21 (1)‡	119 (7)‡	
Maximal infusion rate (mIU/min)†			
Mean (SD)	9.8 (6.0)	8.2 (5.3)	
Median (25th, 75th pc)	8.3 (5, 12.5)	7.5 (5, 10)	
No oxytocin	395 (27)	681 (42)	Ref
<7.5	354 (24)	413 (25)	1.5 (1.2 to 1.8)
7.5–<10	184 (13)	187 (12)	1.7 (1.3 to 2.2)
10–<15	293 (20)	213 (13)	2.4 (1.9 to 2.9)
≥15	237 (16)	128 (8)	3.2 (2.5 to 4.1)
MD	20 (1)‡	136 (8)‡	
Total time of oxytocin infusion (min)†			
Mean (SD)	295 (187)	217 (158)	
Median (25th, 75th pc)	266 (150, 408)	182 (98, 294)	
No oxytocin	395 (27)	681 (39)	Ref
<180	342 (23)	517 (30)	1.1 (0.9 to 1.4)
180–<300	275 (19)	279 (16)	1.7 (1.4 to 2.1)
300–<420	215 (15)	158 (9)	2.3 (1.8 to 3.0)
≥420	255 (17)	100 (6)	4.4 (3.4 to 5.7)
MD	1 (0.1)‡	23 (1)‡	
Time at maximal infusion rate (min)†			
Mean (SD)	128 (109)	103 (91)	
Median (25th, 75th pc)	100 (45, 180)	78 (40, 140)	
No oxytocin	395 (28)	681 (44)	Ref
<90	471 (33)	472 (31)	1.7 (1.4 to 2.1)
90–150	216 (15)	198 (13)	1.9 (1.5 to 2.4)
150–210	136 (10)	109 (7)	2.2 (1.6 to 2.8)
≥210	201 (14)	87 (6)	4.0 (3.0 to 5.3)
MD	64 (4)‡	211 (12)‡	

MD, missing data; PPH, postpartum haemorrhage.
*Percentage of the total non-missing values.
†The thresholds correspond to the 50th, 75th and 90th percentiles of their distribution in the control group rounded to the nearest whole number.
‡Percentage of the total of cases and controls.

previous studies that studied length of labour as a binary variable (prolonged labour) and thereby increased their risk of residual confounding.[20 22]

This finding of an independent dose-related association between oxytocin infusion and PPH in women not receiving prophylactic oxytocin during the third stage of labour is consistent with previous studies showing desensitisation of the oxytocin receptor after prolonged or high-dose oxytocin exposure.[15 16] Similarly, a recent study of rat myometrial strips reported that oxytocin-induced contractile response decreased after pre-exposure to supraphysiologic oxytocin concentrations.[17] Our results suggest that these experimental findings are clinically relevant and have implications for the use of exogenous oxytocin during labour.

Previous clinical studies have reported an association between labour augmentation and PPH, but they had limitations. One small case–control study of 108 women found that women with PPH were exposed to higher amounts of oxytocin during labour.[21] In a population-based study including 153 000 women, Sheiner *et al*[22] reported a significant association between labour augmentation with oxytocin and PPH (adjusted OR: 1.4). Two other studies found similar ORs, with a risk of haemorrhage 1.6 times higher in women receiving oxytocin during labour.[20 24] The nature of the association reported in these studies was questionable, however, because they did not control for several confounding factors, including individual and obstetrical risk factors for PPH. Most critically, two of these studies did not

Table 4 Association between oxytocin during labour and the risk of severe PPH according to prophylactic administration of oxytocin after delivery: women with no prophylactic oxytocin administration after delivery

	Women with severe PPH (n=593), n (%)	Controls (n=518), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Oxytocin during labour	413 (70)	256 (49)	2.3 (1.8 to 3.0)	1.8 (1.3 to 2.6)
Oxytocin total dose (IU)†				
Mean (SD)	2.3 (2.3)	1.5 (4.5)		
No oxytocin	180 (31)	262 (53)	Ref	Ref
<1	155 (26)	124 (25)	1.8 (1.3 to 2.5)	2.0 (1.3 to 2.9)
1.0–<2.0	79 (13)	63 (13)	1.8 (1.2 to 2.7)	1.4 (0.8 to 2.4)
2.0–<4.0	101 (17)	30 (6)	4.9 (3.1 to 7.7)	3.3 (1.8 to 5.9)
≥4.0	74 (13)	12 (2)	9.0 (4.7 to 17.0)	5.7 (2.5 to 12.9)
Maximal infusion rate (mIU/min)†				
Mean (SD)	9.4 (5.8)	8.0 (5.2)		
No oxytocin	180 (31)	262 (54)	Ref	Ref
<7.5	138 (23)	101 (21)	2.0 (1.4 to 2.7)	1.9 (1.2 to 2.9)
7.5–<10	83 (14)	48 (10)	2.5 (1.7 to 3.8)	1.8 (1.1 to 3.1)
10–<15	99 (17)	52 (11)	2.8 (1.9 to 4.1)	2.2 (1.3 to 3.8)
≥15	88 (15)	25 (5)	5.1 (3.2 to 8.3)	3.2 (1.7 to 6.1)
Total time of oxytocin infusion (min)†				
Mean (SD)	288 (189)	191 (137)		
No oxytocin	180 (30)	262 (51)	Ref	Ref
<180	139 (23)	137 (27)	1.5 (1.1 to 2.0)	1.7 (1.1 to 2.5)
180–<300	102 (17)	71 (14)	2.1 (1.5 to 3.0)	1.7 (1.0 to 2.7)
300–<420	76 (13)	26 (5)	4.3 (2.6 to 6.7)	3.2 (1.6 to 6.1)
≥420	96 (16)	16 (3)	8.7 (5.0 to 15.3)	5.1 (2.4 to 10.6)
Time at maximal infusion rate (min)†				
Mean (SD)	128 (107)	96 (89)		
No oxytocin	180 (31)	262 (56)	Ref	Ref
<90	178 (31)	121 (26)	2.1 (1.6 to 2.9)	1.9 (1.2 to 2.8)
90–<150	87 (15)	48 (10)	2.6 (1.8 to 3.9)	2.0 (1.2 to 3.5)
150–<210	48 (8)	17 (4)	4.1 (2.3 to 7.4)	2.7 (1.3 to 5.7)
≥210	79 (14)	22 (5)	5.2 (3.1 to 8.7)	2.6 (1.3 to 5.1)

PPH, postpartum haemorrhage.
*Multilevel logistic regression models adjusted for body mass index, parity, induction of labour, epidural analgesia, duration of the active phase of the first stage of labour, duration of expulsive efforts, operative delivery, episiotomy, perineal tear and birth weight.
†The thresholds correspond to the 50th, 75th and 90th percentiles of their distribution in the control group rounded to the nearest whole number.

adjust for labour duration, a major confounding factor associated with both oxytocin use and PPH.[21 24]

Conversely, results from a multicentre hospital-based study in Latin America, including 11 323 women delivered vaginally, 211 of whom had severe PPH, recently led Sosa *et al*[23] to conclude that oxytocin during labour is not associated with severe PPH. However, this study was underpowered to detect an association of the magnitude we report here (RR: <2). Moreover, its incidence of severe PPH was higher, albeit not statistically significant, in women who received oxytocin during labour (2.4%) than in women who did not (1.9%); similarly, a higher, but not significant, risk of blood transfusion was associated with oxytocin use during labour (adjusted OR: 2.0, 95% CI 0.7 to 5.4). Thus, their failure to find a significant association cannot be considered strong evidence that oxytocin use during labour does not affect the risk of PPH, and their results do not contradict ours.

Randomised controlled trials have compared protocols of active management of labour with high doses of oxytocin to protocols with low doses[14] or delayed administration[13] of oxytocin, and some studied PPH as a secondary outcome, but they all lacked sufficient power to assess this outcome.

Among women who had prophylactic oxytocin after delivery, the association between oxytocin exposure and severe PPH was significant only for the highest category of total dose. We cannot rule out the possibility that this result was found by chance, considering the number of comparisons performed. However, one plausible explanation is that the pharmacologic amount of oxytocin provided at that phase attenuates the impact of oxytocin received during labour and restores uterine contractility by compensating the receptor desensitisation. Support for this hypothesis comes from an experimental study that found contractility restored in oxytocin-pre-exposed myocytes after a supraphysiologic stimulus.[17] Two other studies showed that the amount of oxytocin necessary to induce adequate uterine retraction after delivery was nine times higher in women who received oxytocin during labour for at least 2 h than in non-labouring women.[29 30]

Table 5 Association between oxytocin during labour and the risk of severe PPH according to prophylactic administration of oxytocin after delivery: women with prophylactic oxytocin administration after delivery

	Women with severe PPH (n=890), n (%)	Controls (n=1240), n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Oxytocin during labour	675 (76)	821 (66)	1.6 (1.3 to 1.9)	1.1 (0.8 to 1.4)
Oxytocin total dose (IU)†				
Mean (SD)	2.5 (2.6)	1.7 (2.3)		
No oxytocin	215 (25)	419 (37)	Ref	Ref
<1	222 (25)	387 (34)	1.1 (0.9 to 1.4)	1.0 (0.8 to 1.4)
1.0–<2.0	150 (17)	144 (13)	2.0 (1.5 to 2.7)	1.5 (1.1 to 2.2)
2.0–<4.0	143 (16)	127 (11)	2.2 (1.6 to 2.9)	1.4 (0.9 to 2.0)
≥4.0	143 (16)	71 (6)	3.9 (2.8 to 5.5)	2.1 (1.3 to 3.3)
Maximal infusion rate (mIU/min)†				
Mean (SD)	10.0 (6.1)	8.3 (5.3)		
No oxytocin	215 (25)	419 (37)	Ref	Ref
<7.5	216 (25)	312 (28)	1.3 (1.1 to 1.7)	1.1 (0.8 to 1.5)
7.5–<10	101 (12)	139 (12)	1.4 (1.0 to 1.9)	0.9 (0.6 to 1.3)
10–<15	194 (22)	161 (14)	2.3 (1.8 to 3.1)	1.7 (1.2 to 2.4)
≥15	149 (17)	103 (9)	2.8 (2.1 to 3.8)	1.7 (1.1 to 2.5)
Total time of oxytocin infusion (min)†				
Mean (SD)	300 (187)	225 (163)		
No oxytocin	215 (24)	419 (34)	Ref	Ref
<180	203 (23)	380 (31)	1.0 (0.8 to 1.3)	1.0 (0.7 to 1.3)
180–<300	173 (19)	208 (17)	1.6 (1.2 to 2.1)	1.2 (0.8 to 1.6)
300–<420	139 (16)	132 (11)	2.1 (1.5 to 2.7)	1.4 (1.0 to 2.0)
≥420	159 (18)	84 (7)	3.7 (2.7 to 5.0)	1.7 (1.1 to 2.6)
Time at maximal infusion rate (min)†				
Mean (SD)	127 (110)	105 (91)		
No oxytocin	215 (25)	419 (39)	Ref	Ref
<90	293 (35)	351 (33)	1.6 (1.3 to 2.0)	1.3 (1.0 to 1.8)
90–<150	129 (15)	150 (14)	1.7 (1.3 to 2.2)	1.1 (0.8 to 1.5)
150–<210	88 (10)	92 (9)	1.9 (1.3 to 2.6)	1.2 (0.8 to 1.8)
≥210	122 (14)	65 (6)	3.7 (2.6 to 5.2)	1.8 (1.2 to 2.8)

PPH, postpartum haemorrhage.
*Multilevel logistic regression models adjusted for body mass index, parity, induction of labour, epidural analgesia, duration of the active phase of the first stage of labour, duration of expulsive efforts, operative delivery, episiotomy, perineal tear and birth weight.
†The thresholds correspond to the 50th, 75th and 90th percentiles of their distribution in the control group rounded to the nearest whole number.

The dose-related relation we report here between oxytocin infusion during labour and the risk of severe PPH has implications for clinical practice. Oxytocin administered during labour, by enhancing uterine contractility, may prevent caesarean delivery for labour arrest. However, its current use during labour is unlikely to comply strictly with evidence-based indications and modalities of use. Indeed, its use in 60% of the women delivered vaginally in our study and the similar percentages reported in other developed countries[10] suggests that it is now a routine part of obstetric management and commonly administered in situations where no evidence suggests that it benefits clinically relevant outcomes. The gap between the widespread use of this drug and the paucity of scientific evidence on its safety is a matter of concern. Our results provide additional evidence documenting these risks and suggest that oxytocin during labour increases the risk of severe PPH. This effect appears to be dose related and significant even at moderate doses.

This excess risk of PPH was attenuated in women who had prophylactic oxytocin after birth. This finding raises the issue of the overmedicalization of labour and delivery, with one procedure (oxytocin during labour) leading to the need for another (prophylactic oxytocin after birth). It reinforces the need for new guidelines, as others have advocated,[9] that consider all available evidence about the benefits and risks associated with oxytocin use during labour. Conservative protocols for oxytocin administration, including restrictive indications and dose reduction or withdrawal once adequate uterine activity is obtained, should be evaluated and promoted.[31–33]

Oxytocin during labour appears to be an independent risk factor for severe PPH. Our findings provide new evidence emphasising the need for safeguards to minimise maternal complications when augmenting labour with oxytocin, including rigorous indications, use of the minimum useful dose and careful efficacy evaluation. Future large studies investigating these three key points should be undertaken to validate the use of this old drug in a modern and safe practice.

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Contributors JB participated in the design of the study, conducted the analysis, participated in the interpretation of the data and the drafting and revision of the paper and has seen and approved the final version. He has no conflicts of interest. GK participated in the design of the study, supervised the analysis and interpretation of the data and participated in the drafting and revision of the paper. He has seen and approved the final version. He has no conflicts of interest. CD participated in the design of the study, obtained funding for it, participated in the central monitoring of data collection, the cleaning of the data and the revision of the paper and has seen and approved the final version. She has no conflicts of interest. R-CR initiated the collaborative project, obtained funding for it, participated in the design of the study and the revision of the paper and has seen and approved the final version. He has no conflicts of interest. M-HB-C participated in the design of the study, obtained funding for it, participated in the revision of the paper and has seen and approved the final version. She has no conflicts of interest. CD-T participated in the design of the study, obtained funding for it, participated in the central monitoring of data collection, supervised the cleaning, analysis and interpretation of the data and the drafting and revision of the paper and has seen and approved the final version. She had full access to all the data in the study and had final responsibility for the decision to submit for publication. She has no conflicts of interest.

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