Atonic Postpartum Hemorrhage: Blood Loss, Risk Factors, and Third Stage Management

Sarka Lisonkova, MD, PhD,[1,2] Azar Mehrabadi, PhD,[1] Victoria M. Allen, MD, MSc,[3] Emmanuel Bujold, MD, MSc,[4] Joan M. G. Crane, MD, MSc,[5] Laura Gaudet, MD, MSc,[6] Robert J. Gratton, MD,[7] Noor Niyar N. Ladhani, MD, MPH,[8] Olufemi A. Olatunbosun, MD,[9] K. S. Joseph, MD, PhD[1,2]

[1]Department of Obstetrics and Gynaecology, University of British Columbia and the Children's and Women's Hospital and Health Centre of British Columbia, Vancouver BC

[2]School of Population and Public Health, University of British Columbia, Vancouver BC

[3]Department of Obstetrics and Gynaecology, Dalhousie University, Halifax NS

[4]Centre de recherché en biologie de la reproduction et Centre de recherché du CHU de Québec, Université Laval, Québec QC

[5]Department of Obstetrics and Gynecology, Memorial University, St. John's NL

[6]Department of Obstetrics and Gynecology, University of Ottawa, Ottawa ON

[7]London Health Sciences Centre, Department of Obstetrics and Gynaecology, London Western University, London ON

[8]Sunnybrook Health Sciences Centre, Toronto ON

[9]Department of Obstetrics and Gynecology and Reproductive Sciences, University of Saskatchewan, Saskatoon SK

Abstract

Objective: Atonic postpartum hemorrhage rates have increased in many industrialized countries in recent years. We examined the blood loss, risk factors, and management of the third stage of labour associated with atonic postpartum hemorrhage.

Methods: We carried out a case-control study of patients in eight tertiary care hospitals in Canada between January 2011 and December 2013. Cases were defined as women with a diagnosis of atonic postpartum hemorrhage, and controls (without postpartum hemorrhage) were matched with cases by hospital and date of delivery. Estimated blood loss, risk factors, and management of the third stage labour were compared between cases and controls. Conditional logistic regression was used to adjust for confounding.

Results: The study included 383 cases and 383 controls. Cases had significantly higher mean estimated blood loss than controls. However, 16.7% of cases who delivered vaginally and 34.1% of cases who delivered by Caesarean section (CS) had a blood loss of < 500 mL and < 1000 mL, respectively; 8.2% of controls who delivered vaginally and 6.7% of controls who delivered by CS had blood loss consistent with a diagnosis of postpartum hemorrhage. Factors associated with atonic postpartum hemorrhage included known protective factors (e.g., delivery by CS) and risk factors (e.g., nulliparity, vaginal birth after CS). Uterotonic use was more common in cases than in controls (97.6% vs. 92.9%, $P < 0.001$). Delayed cord clamping was only used among those who delivered vaginally (7.7% cases vs. 14.6% controls, $P = 0.06$).

Conclusion: There is substantial misclassification in the diagnosis of atonic postpartum hemorrhage, and this could potentially explain the observed temporal increase in postpartum hemorrhage rates.

Key Words: Postpartum hemorrhage, blood loss, risk factors, third stage

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Résumé

Objectif : Au cours des dernières années, le taux d'hémorragies de la délivrance par atonie utérine a augmenté dans de nombreux pays industrialisés. Nous avons examiné les pertes sanguines, les facteurs de risque et la prise en charge du troisième stade du travail associés à ce type d'hémorragies.

Méthodologie : Nous avons mené une étude cas-témoins auprès de patientes de huit hôpitaux de soins tertiaires canadiens, entre janvier 2011 et décembre 2013. Nous avons étudié des femmes ayant reçu un diagnostic d'hémorragie de la délivrance par atonie utérine (cas); nous avons apparié les témoins (sans hémorragie) aux cas selon l'hôpital visité et la date d'accouchement. Nous avons comparé les pertes sanguines estimées, les facteurs de risque et la prise en charge du troisième stade du travail des deux groupes. Enfin, nous avons utilisé la régression logistique conditionnelle pour tenir compte des variables parasites.

Résultats : L'échantillon à l'étude comprenait 383 cas et 383 témoins. Les pertes sanguines moyennes estimées du premier groupe étaient significativement supérieures à celles du deuxième. Cependant, 16,7 % des cas qui ont accouché par voie vaginale et 34,1 % des cas qui ont accouché par césarienne ont perdu moins de 500 et 1000 ml de sang, respectivement, tandis que 8,2 % des témoins qui ont accouché par voie vaginale et 6,7 % des témoins qui ont accouché par césarienne ont perdu une quantité de sang correspondant à un diagnostic d'hémorragie de la délivrance. Les

facteurs associés à l'hémorragie de la délivrance par atonie utérine comportaient des facteurs de protection connus (p. ex. accouchement par césarienne) et des facteurs de risque (p. ex. nulliparité, accouchement vaginal après une césarienne). L'administration d'utérotoniques était plus fréquente chez les cas que chez les témoins (97,6 % contre 92,9 %; $P < 0,001$), et le clampage tardif du cordon a seulement été réalisé chez des femmes qui ont accouché par voie vaginale (7,7 % pour les cas contre 14,6 % pour les témoins; $P = 0,06$).

Conclusion : La classification du diagnostic de l'hémorragie de la délivrance par atonie utérine est souvent erronée, ce qui pourrait expliquer la hausse observée du taux d'hémorragies de la délivrance.

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INTRODUCTION

Postpartum hemorrhage, a major cause of maternal morbidity and mortality worldwide, is reported to have increased in frequency and severity in several industrialized countries.[1–12] Rising rates of postpartum hemorrhage were first reported from Australia (where rates increased from 4.7 per 100 deliveries in 1994 to 6.0 in 2002)[1,2] and Canada (where rates increased from 4.1 per 100 deliveries in 1991 to 5.1 in 2004[3] and 6.2 in 2010).[11] Other industrialized countries have also shown similar temporal increases[4–12]; in the United States, postpartum hemorrhage rates increased from 2.1 per 100 deliveries in 1994 to 2.9 per 100 deliveries in 2006,[6] and rates of severe postpartum hemorrhage rose from 1.9 per 1000 deliveries in 1999 to 4.2 per 1000 deliveries in 2008.[4]

Although studies have identified the aforementioned increase in postpartum hemorrhage as having occurred mainly because of an increase in atonic postpartum hemorrhage,[3,5,11,12] the reasons behind this rising trend have not been adequately explained. Temporal changes in risk factors such as advanced maternal age, obesity, multi-fetal pregnancy, induction of labour, and delivery by CS do not explain the temporal rise in postpartum hemorrhage.[2–12] Similarly, studies examining medication use in pregnancy have not implicated drug use as contributing significantly to the rising rates of postpartum hemorrhage.[13–15] Although antidepressants, including selective serotonin reuptake inhibitors, appear to modestly increase rates of postpartum hemorrhage,[14–16] the relatively low population-attributable fraction for selective serotonin reuptake inhibitor use among pregnant women means that such drug use does not explain the temporal trends in postpartum hemorrhage.[14]

One hypothesis regarding the increase in atonic postpartum hemorrhage that has not been investigated relates to the management of the third stage of labour. Active management of the third stage of labour includes a package of interventions, including the following: administration of a uterotonic agent (oxytocin and/or ergometrine), umbilical cord clamping and cutting, and controlled cord traction, with uterine massage sometimes included as an additional component.[17–24] However, a lack of consensus on the efficacy of each component of such active management means that these interventions are used variably in clinical practice.[25]

Most of the epidemiologic studies that have investigated the temporal increase in postpartum hemorrhage have used data from large perinatal databases.[2–16] Such data lack detailed clinical information on the active management of labour, and previous studies have also not adequately examined issues related to estimated blood loss, obstetric history, and related factors. We therefore carried out a multicentre medical chart abstraction study to determine the estimated blood loss associated with atonic postpartum hemorrhage and to quantify the association between risk factors (including obstetric history, medication use, and management of the third stage of labour) and atonic postpartum hemorrhage.

METHODS

We conducted a case-control study of women who delivered between January 2011 and December 2013 in eight tertiary hospitals in Canada, with cases of atonic postpartum hemorrhage selected from each hospital and controls sampled from the catchment population of the same hospitals (secondary base[26]). We defined cases as women with a diagnosis of atonic postpartum hemorrhage (ICD-10 code 0721) selected from hospital discharge records. Controls were matched to cases for hospital and date of delivery (± 3 days) and included women without any diagnosis of postpartum hemorrhage (i.e., women without a diagnosis of atonic or other postpartum hemorrhage).

Information about maternal characteristics, obstetric history, pregnancy, labour, and delivery was abstracted from the medical charts of cases and controls. Trained medical record abstractors used standard forms to enter data into customized software (RedCap; Research Electronic Data Capture[27]). The data collection software was programmed to restrict entry of implausible values to enhance accuracy of collected data, and interim analyses were performed to detect discrepant values that were then corrected by reference to the original medical charts.

The timing and amount of estimated blood loss for cases and controls were obtained from the charts. The diagnosis of atonic postpartum hemorrhage was predominantly based on the estimated amount of blood loss, including blood clots and additional characteristics of bleeding. The definition of postpartum hemorrhage (as used across Canada) was $\geq$ 500 mL of blood loss following a vaginal delivery and $\geq$ 1000 mL blood loss following a CS. Because the blood loss criteria for postpartum hemorrhage differ following vaginal delivery and CS, analyses were stratified by mode of delivery, and we identified characteristics of women who appeared to have "false positive" and "false negative" diagnoses of atonic postpartum hemorrhage based on blood loss criteria alone.

Crude and adjusted ORs (aORs) and 95% CIs expressing the effects of risk and protective factors on atonic postpartum hemorrhage were estimated using conditional logistic regression. We used ICD-10 code-identified cases of atonic postpartum hemorrhage and not the estimated blood loss criteria because the physician's judgement was the final criterion for a diagnosis of postpartum hemorrhage. Three stages of sequential conditional logistic regression modelling were used to identify independent risk factors for atonic postpartum hemorrhage. In the first stage, maternal characteristics and obstetric history were included in the model. In second stage modelling, pregnancy characteristics, complications, and interventions (including medications) were introduced in the model together with pre-pregnancy risk factors independently associated with postpartum hemorrhage (identified in first stage modelling). The last stage of the modelling involved the addition of interventions during labour and delivery (including medications). Stepwise backward selection of statistically significant variables ($P < 0.05$) was used at each stage, and the final model included all significant variables and interaction terms. Medication use during pregnancy, during hospitalization for delivery, and during labour was categorised into the following broad groups: analgesics, anti-asthma agents, anti-hypertensive drugs, antibiotics, antidepressants, thyroid medication, vitamins, and herbal supplements. Lastly, the effect of each component of management of the third stage of labour was assessed, including timing and dose of oxytocin, use of other uterotonic medications and other means to control bleeding, controlled cord traction, and timing of cord clamping.

Sensitivity analyses were performed after excluding cases and controls among whom the diagnosis of atonic postpartum hemorrhage (or its lack thereof) was contradicted by the estimated blood loss recorded in the medical chart (i.e., cases with estimated blood loss $<$ 500 mL and $<$ 1000 mL among women with vaginal delivery and delivery by CS, respectively), and controls with estimated blood loss exceeding these cut-offs were excluded. Conditional logistic regression analysis was carried out after these exclusions to re-identify risk factors for atonic postpartum hemorrhage. Analyses were carried out using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Ethics approval was obtained from the Research Ethics Board of the University of British Columbia and from each participating site.

RESULTS

Eight participating centres collected data on 393 cases of atonic postpartum hemorrhage and 393 controls without postpartum hemorrhage. After excluding pairs with incomplete data, 383 matched pairs (766 women) were included in the study. Of these, 296 cases and 272 controls delivered vaginally, whereas 87 cases and 111 controls delivered by CS.

Estimated Blood Loss

Blood loss was significantly greater in cases with atonic postpartum hemorrhage than in controls without postpartum hemorrhage (Table 1). Blood loss $\geq$ 2000 mL was reported in 2.1% of cases with a vaginal delivery and 3.5% of cases with delivery by CS. A sizeable proportion of women had a borderline level of estimated blood loss for a diagnosis of postpartum hemorrhage; that is, 14.6% of cases who delivered vaginally had an estimated blood loss of exactly 500 mL, and 23.0% of cases who delivered by CS had a blood loss of exactly 1000 mL.

Among women who delivered vaginally, 16.7% of cases had a blood loss of $<$ 500 mL, and 8.2% of controls had an estimated blood loss $\geq$ 500 mL. Similarly, among women who delivered by CS, 34.1% of cases had an estimated blood loss $<$ 1000 mL, and 6.7% of controls had an estimated blood loss of $\geq$ 1000 mL (Table 1).

Cases of postpartum hemorrhage with vaginal delivery and $<$ 500 mL of blood loss noted in the chart (n = 47) differed from cases with $\geq$ 500 mL blood loss. Such women were significantly less likely to be primigravid and nulliparous, to receive augmentation with oxytocin, to have a prolonged second stage of labour ($>$ 2 hours), and to sustain a third- or fourth-degree perineal tear ($P < 0.05$ for each). They were also more likely to be positive for group B Streptococcus and more likely to have experienced artificial rupture of membranes ($P < 0.05$ for both). Three of these women received transfusions of packed red cells because of a low hemoglobin concentration or low

Table 1. Total estimated blood loss among cases with a diagnosis of atonic postpartum hemorrhage and controls without a diagnosis of postpartum hemorrhage during delivery hospitalization

	Vaginal delivery					Caesarean section				
	Cases		Controls			Cases		Controls		
Estimated blood loss	n (n = 296)	%	n (n = 272)	%	P^a	n (n = 87)	%	n (n = 111)	%	P^a
Blood loss (mL)										
< 500	47	16.8	223	91.8	< 0.001	0	0.00	13	12.4	< 0.001
500	41	14.6	18	7.41		4	4.60	14	13.3	
501 to 999	124	44.3	2	0.82		26	29.9	71	67.6	
1000	36	12.9	0	0.00		20	23.0	6	5.71	
1001 to 1999	26	9.29	0	0.00		34	39.1	1	0.95	
2000 to 2999	4	1.43	0	0.00		1	1.15	0	0.00	
≥ 3000	2	0.71	0	0.00		2	2.30	0	0.00	
Missing (blood loss)	16	5.41	29	10.7	0.07	0	0.00	6	5.41	-
Blood clots	26	8.75	3	1.10	0.002	6	6.82	0	0.00	-
Excessive bleeding noted	31	10.4	3	1.10	< 0.001	11	12.5	0	0.00	-

Postpartum hemorrhage was defined as blood loss of ≥ 500 mL among women with vaginal delivery and ≥ 1000 mL among women delivered by CS.

[a]*P* values obtained from conditional logistic regression models. Blood loss was modelled as a continuous variable.

hematocrit. All except one woman received uterotonics, one woman had balloon tamponade of the uterus, and one had vaginal packing. Excessive bleeding was explicitly mentioned in the medical charts of 12 such cases, and passage of blood clots was recorded for 10 women. Two women with missing values for blood loss received packed red cell transfusions for low hemoglobin concentration or low hematocrit. Among controls who delivered vaginally and experienced a blood loss of ≥ 500 mL (n = 20), 18 had an estimated blood loss of exactly 500 mL, and two had an estimated blood loss of 600 mL. No procedures to control bleeding were used in these women, although they received significantly higher doses of oxytocin.

Cases who delivered by CS and lost < 1000 mL of blood during delivery (n = 30) were not significantly different from cases who lost ≥ 1000 mL following CS ($P > 0.05$). Six of the former received packed red cells for a low hemoglobin concentration or low hematocrit. Excessive bleeding was mentioned in the charts of eight of these women (26.7%) and passage of blood clots in five (16.7%).

Risk Factors for Postpartum Hemorrhage

The unadjusted associations between maternal characteristics, obstetric history, pregnancy complications, and atonic postpartum hemorrhage are shown in Table 2, and associations between labour and delivery characteristics and atonic postpartum hemorrhage are shown in Table 3. Details of medication use are provided in Appendix Table A1.

Conditional logistic regression showed that multiparity, one or two previous abortions, and smoking were associated with lower odds of atonic postpartum hemorrhage (Table 4, model stage 1). Previous CS was associated with an increased rate of atonic postpartum hemorrhage in women who subsequently delivered vaginally (aOR 3.88; 95% CI 1.24 to 12.20) compared with women without previous CS who delivered vaginally.

Additional adjustment for pregnancy factors (Table 4, model stage 2) showed that use of vitamins and analgesics during pregnancy, preeclampsia, and use of magnesium sulfate were associated with atonic postpartum hemorrhage. Adjustment for labour and delivery factors (Table 4, model stage 3) showed that induction of labour with oxytocin, artificial rupture of membranes, intrapartum fever, forceps delivery, and antibiotic use during delivery increased the odds of atonic postpartum hemorrhage. Vaginal birth after CS increased the odds of postpartum hemorrhage (aOR = 3.70; 95% CI 1.08 to 12.71), whereas primary and repeat CS lowered the odds (aOR = 0.53; 95% CI 0.32 to 0.88, and aOR = 0.47; 95% CI 0.24 to 0.95, respectively) compared with vaginal delivery among women without a prior CS. Rare risk factors for atonic postpartum hemorrhage, including placenta accreta, chronic hypertension, and some medication use, could not be included in modelling due to their small numbers or strong correlation with other variables (collinearity).

Sensitivity analysis using conditional logistic regression was performed after exclusion of cases and controls with a diagnosis of postpartum hemorrhage that was contradicted by the estimated blood loss recorded in the medical chart. Most results did not change appreciably, but the aOR for delivery by CS in women without prior CS compared with

Table 2. Unadjusted associations between maternal characteristics, obstetric history, pregnancy characteristics, and atonic postpartum hemorrhage

Demographic characteristics and obstetric history	Case n = 383	Case %	Control n = 383	Control %	P[a]
Maternal age (years)					0.07
< 20	18	4.70	7	1.84	
20 to 24	44	11.49	36	9.45	
25 to 29	100	26.11	96	25.20	
30 to 34	122	31.85	138	36.22	
35 to 39	73	19.06	82	21.52	
≥ 40	26	6.79	22	5.77	
Gravida					
1 (primigravida)	190	49.74	104	27.37	ref.
2 to 3	135	35.34	212	55.79	< 0.001
≥ 4	57	14.92	64	16.84	0.002
Parity					
0	238	62.80	160	42.44	ref.
1 to 2	125	32.98	191	50.66	< 0.001
≥ 3	16	4.22	26	6.90	0.01
Prior abortion(s)	106	27.97	138	36.60	0.01
Iatrogenic	37	9.76	47	12.47	0.24
Spontaneous	65	17.15	82	21.75	0.11
Current smoker	32	8.63	56	15.14	0.007
Drug use	1	0.27	2	0.54	0.57
Previous CS	36	9.50	52	13.98	0.08
Uterine fibroids	8	2.09	5	1.31	0.41
Prior uterine surgery	29	7.57	33	8.62	0.57
Chronic hypertension	6	1.57	0	0.00	-
Diabetes mellitus	5	1.31	3	0.78	0.48
Hypertension during pregnancy	19	4.96	12	3.13	0.20
Preeclampsia	27	7.05	4	1.04	< 0.001
Gestational diabetes mellitus	26	7.05	23	6.17	0.65
Polyhydramnios	6	1.57	3	0.79	0.33
Chorioamnionitis	16	4.28	6	1.58	0.03
PROM	55	14.44	49	12.86	0.52
PROM for ≥ 24 hours	18	4.76	11	2.87	0.17
Suspected large fetus	13	3.4	7	1.83	0.16
Multiple pregnancy	15	3.92	8	2.09	0.13
Maternal infection	60	15.79	51	13.46	0.33
GBS positive	26	6.79	23	6.01	0.66
Male fetus	194	50.79	184	48.04	0.45
Magnesium sulfate (any)	14	3.66	1	0.26	0.01
Multiple doses	9	2.35	1	0.26	0.04
Preeclampsia indication	7	1.83	1	0.26	0.07
Neuroprotection[b]	7	1.83	0	0.00	-
Tocolytic	6	1.57	0	0.00	-

PROM: premature rupture of membranes; GBS: group B Streptococcus.

NOTE: Missing values < 4% not shown; 24 (3.1%) women had missing values for gestational diabetes mellitus; no CSs among women with multiple pregnancies and vaginal delivery.

[a]*P* values obtained from conditional logistic regression models. Maternal age was modelled as a continuous variable.

[b]One indication was for low magnesium blood level (case).

vaginal delivery in women without prior CS decreased (aOR = 0.16; 95% CI 0.06 to 0.46), and the aOR for artificial rupture of membranes also decreased (aOR = 2.23; 95% CI 0.93 to 5.37).

Procedures to Control Bleeding

Uterotonics were used extensively during the third stage of labour and to control postpartum hemorrhage (Appendix Table A2). Uterotonic use was significantly more common in cases with atonic postpartum hemorrhage than in controls without postpartum hemorrhage (97.6% vs. 92.9%, $P = 0.003$). Oxytocin was the most common uterotonic used, followed by prostaglandins and ergometrine. Blood transfusions were administered in 12.5% of cases (8.8% of cases who delivered vaginally and 25.3% of cases who delivered by CS). Atonic postpartum hemorrhage was associated with higher doses of oxytocin ($P < 0.001$; Appendix Table A3).

Management of the Third Stage of Labour

Information about management of the third stage of labour was incomplete in charts from most study sites. Data from three hospitals with < 10% missing values for controlled cord traction (n = 271) revealed no significant differences between cases with atonic postpartum hemorrhage and controls (30.1% of cases had controlled cord traction compared with 25.4% of controls, $P = 0.40$), irrespective of mode of delivery. Assessment of cord clamping (in four hospitals with a low proportion of missing values) showed that none of the women who delivered by CS (n = 102) had delayed cord clamping, and delayed cord clamping was non-significantly protective against atonic postpartum hemorrhage among women who delivered vaginally (7.7% vs. 14.6%, $P = 0.06$).

DISCUSSION

Our study showed a significant disagreement between the diagnosis of atonic postpartum hemorrhage and the volume of postpartum blood loss as documented in the medical

Table 3. Unadjusted associations between labour and delivery characteristics and atonic postpartum hemorrhage

Labour and delivery characteristics	Case		Control		P[a]
	n = 383	%	n = 383	%	
CS	87	22.72	111	28.98	0.065
No labour	33	8.62	60	16.67	0.003
Spontaneous onset of labour	178	46.6	213	55.61	0.01
Labour induction[b]	170	44.5	109	28.46	< 0.001
Oxytocin	122	31.94	73	19.16	< 0.001
Prostaglandin	64	16.84	42	10.99	0.02
Manual—Foley catheter	10	2.61	8	2.09	0.64
Manual—sweep of membranes	4	1.04	3	0.78	0.71
Manual—ARM	46	12.01	18	4.70	0.02
Failed induction	26	6.82	17	4.47	0.19
Labour augmentation	130	33.94	101	26.44	0.02
Oxytocin augmentation	126	33.07	93	24.80	0.01
Epidural analgesia	277	73.87	224	60.70	< 0.001
Spinal analgesia	34	9.14	67	18.21	< 0.001
General anaesthesia	14	3.73	8	2.17	0.26
Analgesia medication during labour[c]	180	47	152	39.90	0.03
Antiemetic use	124	33.33	109	28.61	0.14
Thromboprophylaxis (any)	20	5.26	23	6.04	0.68
Thromboprophylaxis with heparin	16	4.21	20	5.25	0.54
Placenta previa	8	2.09	1	0.26	0.05
Placental abruption	3	0.79	2	0.52	0.66
Placenta accreta	2	0.52	0	0.00	-
Presentation					0.74
Cephalic	358	96.5	351	95.38	
Breech	8	2.16	16	4.08	
Transverse	4	1.08	1	0.27	
Compound	0	0	1	0.27	
Oblique	1	0.27	0	0.00	
Prolonged second stage (> 2 hours)	82	22.84	39	10.96	< 0.001
Intrapartum fever	29	7.61	6	1.59	< 0.001
Emergency CS	66	17.23	57	14.88	0.40
Assisted vaginal delivery	74	25.87	37	14.29	< 0.001
Low forceps	23	6.01	9	2.35	0.01
Mid-pelvic forceps	13	3.39	3	0.78	0.02
Vacuum assisted	31	8.09	24	6.27	0.33
Gestational age (weeks)					0.40
< 28	5	1.31	1	0.26	
28 to 31	4	1.04	2	0.52	
32 to 36	26	6.79	26	6.79	
37 to 41	346	90.34	354	92.43	
≥ 42	2	0.52	0	0.00	
Lacerations	29	7.92	13	3.48	0.01
Perineal tear (third or fourth grade)	24	6.52	12	3.20	0.05
Cervical laceration	5	1.31	2	0.52	0.22
Uterine rupture	0	0	0	0.00	-
Macrosomic baby (> 4500 g)	16	4.21	6	1.60	0.04

ARM: artificial rupture of membranes.

NOTE: Male fetus, presentation, and macrosomia relate to twin A in multiple pregnancies; multiple pregnancy includes one set of triplets (delivery by CS); all multiples were delivered by one mode of delivery (either vaginal or CS); missing values < 2% not shown: 28 (3.6%) women had a missing value for presentation, 3.1% women had a missing value for perineal tear, and 3.0% of women had a missing value for the type of assisted vaginal delivery.

[a]*P* values obtained from conditional logistic regression models; presentation cephalic compared with other, preterm gestational age compared with term.

[b]Types of induction can overlap.

[c]Includes morphine, fentanyl, meperidine, butorphanol, nalbuphine, nitrous oxide.

chart. This discrepancy reflects the difficulty of estimating blood loss during childbirth and highlights the uncertain nature of a diagnosis of postpartum hemorrhage as documented routinely in hospital records. Our analysis of risk factors for atonic postpartum hemorrhage yielded results essentially consistent with the literature. Vaginal delivery after CS increased the odds, whereas repeat delivery by CS decreased the odds of atonic postpartum hemorrhage compared with vaginal delivery without prior CS. Finally, our examination of components of the third stage of labour was hampered by poor documentation (with the exception of uterotonic use, which was well-documented and uniformly high), although findings from study sites that had good documentation were consistent with expectations.

The definition of postpartum hemorrhage varies between countries.[5] In the United States and Canada, postpartum hemorrhage is defined as a blood loss of ≥ 500 mL following vaginal delivery and ≥ 1000 mL following CS.[3,17] The definition of postpartum hemorrhage in the United Kingdom specifies a blood loss of ≥ 500 mL,[28] whereas in Australia postpartum hemorrhage is diagnosed if blood loss is ≥ 500 mL following vaginal delivery and ≥ 750 mL following CS.[5] Our study showed that the diagnosis of postpartum hemorrhage was not consistent with stipulated blood loss criteria in a significant proportion of instances. In addition, a large proportion of diagnoses of postpartum hemorrhage had blood loss amounts that corresponded to

Table 4. Results of conditional logistic regression with sequential modelling of risk factors for atonic postpartum hemorrhage

	Unadjusted		Stage 1[a]		Stage 2[b]		Stage 3[c]	
Risk factor	OR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Demographics/obstetric history								
Parity 0	ref.		ref.		ref.		ref.	
≥ 1	0.44	(0.33 to 0.60)	0.41	(0.29 to 0.58)	0.50	(0.35 to 0.70)	0.47	(0.24 to 0.95)
Previous abortions 0	ref.		ref.					
1 to 2	0.62	(0.44 to 0.88)	0.66	(0.45 to 0.97)	0.58	(0.39 to 0.85)	0.62	(0.40 to 0.94)
≥ 3	1.04	(0.46 to 2.34)	1.50	(0.61 to 3.67)	1.55	(0.62 to 3.87)	1.21	(0.47 to 3.15)
Smoking during pregnancy	0.53	(0.33 to 0.84)	0.58	(0.35 to 0.95)				
Vaginal delivery without prior CS	ref.		ref.		ref.		ref.	
Vaginal delivery with prior CS	3.07	(1.00 to 9.43)	3.88	(1.24 to 12.2)	3.42	(1.07 to 11.0)	3.70	(1.08 to 12.7)
CS without prior CS	0.98	(0.68 to 1.43)	0.81	(0.53 to 1.24)	0.73	(0.48 to 1.12)	0.53	(0.32 to 0.88)
CS with prior CS	0.43	(0.24 to 0.74)	0.66	(0.36 to 1.22)	0.56	(0.30 to 1.03)	0.47	(0.24 to 0.95)
Pregnancy characteristics								
Magnesium sulfate	14.0	(1.8 to 106.4)			10.8	(1.24 to 94.6)	10.8	(1.19 to 98.8)
Preeclampsia	6.75	(2.36 to 19.3)			7.21	(2.23 to 23.3)	6.25	(1.77 to 22.1)
Analgesic medication (during pregnancy)	0.58	(0.30 to 1.13)			0.45	(0.20 to 0.98)		
Vitamin use (during pregnancy)	1.66	(1.10 to 2.50)			1.70	(1.06 to 2.71)	1.84	(1.12 to 3.02)
Labour and delivery characteristics								
Labour induction with oxytocin	2.09	(1.46 to 2.98)					1.62	(1.05 to 2.51)
Artificial rupture of membranes	3.18	(1.72 to 5.87)					2.50	(1.22 to 5.14)
Forceps delivery	3.56	(1.76 to 7.23)					2.38	(1.04 to 5.45)
Intrapartum fever	5.75	(2.22 to 14.9)					5.26	(1.75 to 15.7)
Antibiotic use (during delivery)	1.31	(0.98 to 1.75)					1.56	(1.04 to 2.35)

NOTE: Factors not significantly associated with postpartum hemorrhage in the logistic regression included the following:

[a]Maternal age (< 25, 25 to 34, ≥ 35 years); drug use; uterine fibroids; uterine surgery; chronic hypertension; and diabetes mellitus.

[b]Hypertension during pregnancy; gestational diabetes; polyhydramnios; chorioamnionitis; preterm premature rupture of membranes (none, < 24 hours, ≥ 24 hours); suspected large fetus; multiple pregnancy; maternal infection; Streptococcus B positive culture; antidepressants; thyroid drugs; acute asthma drug; chronic asthma drugs; antibiotics; herbal medicine use during pregnancy.

[c]Absence of labour; spontaneous onset of labour; labour induction by sweep of membranes; labour induction by Foley catheter; failed induction; epidural; spinal analgesia; general anesthesia; analgesics; antiemetic; thromboprohylaxis; placenta previa; placental abruption; cephalic position (compared with other); prolonged second stage (> 2 hours); emergency CS; forceps delivery; vacuum delivery; gestational age (< 34, 34 to 36, ≥ 37 weeks); laceration (third- to fourth-degree tear or high cervical laceration compared with none of these); macrosomic baby (> 4500 g); antidepressants; antibiotics; thyroid drugs; acute asthma drug; vitamin use during pregnancy hospitalization; antidepressants; thyroid drugs; vitamins; and herbal medicine during delivery. Placenta accreta and thyroid drugs during delivery were not included due to collinearity.

the threshold blood loss values (500 mL and 1000 mL) for postpartum hemorrhage, suggesting that there were challenges in estimating blood loss and rounding of blood loss estimates. Also noteworthy was the finding that 67.8% of controls with delivery by CS had an estimated blood loss of 501 mL to 999 mL, which would have led to a diagnosis of postpartum hemorrhage if these controls had delivered vaginally (or if these deliveries had occurred in the United Kingdom).

Our findings contrast with a report from Australia in which chart-recorded diagnoses underestimated the frequency of postpartum hemorrhage according to the amount of blood loss.[25,29] Our study also highlighted some discrepancies between estimated blood loss and the documentation of blood clots and excessive bleeding. These findings point to subjective diagnoses and/or incomplete documentation in medical charts. Routine visual estimates of blood loss are known to be inaccurate,[29,30] and temporal trends in postpartum hemorrhage may have been influenced by caregiver changes in awareness or heightened concern about excessive bleeding. Such misclassification of atonic postpartum hemorrhage may potentially explain the temporal increase in postpartum hemorrhage rates reported from several countries.[1–12] However, such a diagnostic change cannot explain the temporal increase in severe postpartum hemorrhage (i.e., postpartum hemorrhage associated with transfusion and operative procedures to control bleeding) also observed in several countries.[1–12] On the other hand, both the increase in postpartum hemorrhage and in severe

postpartum hemorrhage could be explained as a consequence of the gradual shift towards a culture of safety that has characterized obstetrics in recent years. The subjectivity involved in making a diagnosis of postpartum hemorrhage may have been affected by heterogeneity in maternal responses to blood loss; clinical signs of postpartum hemorrhage may be more pronounced among women with mild anemia.

Our study findings are in general agreement with the literature on risk factors for atonic postpartum hemorrhage. However, the associations between one and two previous abortions, vitamin and analgesic use, and atonic postpartum hemorrhage were unexpected and should be treated as preliminary and requiring confirmation in other studies. It is possible that previous pregnancies, ending in either childbirth or abortion, induce hormonal and other uterine changes that reduce the risk of postpartum hemorrhage.[31] The lower risk of postpartum hemorrhage following a CS has been observed previously,[2,12] although some studies have reported the opposite effect.[4,9–11] The conflicting findings are likely due to the different definitions of postpartum hemorrhage following vaginal delivery and CS used in different studies. Another significant consideration is the effect of previous CS. Our study showed that delivery by CS modifies the effect of previous CS; women with a previous CS who subsequently delivered vaginally had a higher rate of postpartum hemorrhage than women who did not have a previous CS, whereas women with a previous CS who delivered again by CS had significantly lower rates of atonic postpartum hemorrhage.

Our study showed a strong association between preeclampsia and postpartum hemorrhage, a finding consistent with the literature.[2,4,9,12] We also observed a strong association between use of magnesium sulfate and postpartum hemorrhage. Magnesium sulfate treatment is indicated for severe preeclampsia/eclampsia, which may in part explain the association with postpartum hemorrhage. However, approximately one half of the women in our study received magnesium sulfate for fetal neuroprotection. We could not examine these two indications separately due to small numbers, and magnesium sulfate was not included in the final regression model because of collinearity. Nevertheless, the independent effect of magnesium sulfate on postpartum hemorrhage deserves further scrutiny because the drug is known to have tocolytic effects[32] that may contribute to uterine atony regardless of indication.

Oxytocin use during the third stage of labour was almost ubiquitous, with cases receiving higher oxytocin doses. However, cases of atonic postpartum hemorrhage were significantly more likely to receive other uterotonics, including prostaglandins and ergometrine. Transfusions were more common in cases with delivery by CS than in those with vaginal delivery because the amount of blood loss was larger following CS. Besides use of uterotonics, recent recommendations for active management of the third stage of labour include delayed cord clamping and controlled cord traction.[20] Even though delayed cord clamping has been shown to confer significant benefits for the infant (increased birth weight and better hemodynamic indices), maternal benefits remain unclear.[33,34] Controlled cord traction has been shown to reduce the risk of manual removal of the placenta and to reduce blood loss of 500 mL or more.[20] In our study, approximately 30% of deliveries were reported to have controlled cord traction, although information on controlled cord traction and cord clamping was poorly documented. In comparison, reports from Australia show that controlled cord traction was applied in 30% of deliveries by CS and in 80% of vaginal deliveries.[25]

Our study has several strengths, including detailed information on cases of atonic postpartum hemorrhage and controls without postpartum hemorrhage collected through a standardized protocol from several hospitals in Canada. In particular, this level of detail describing the amount of estimated blood loss, type of induction of labour, and timing of medication has not been reported previously.

Limitations of our study include incomplete data on cord clamping, controlled cord traction, and uterine massage from several hospitals due to poor documentation in medical charts. Secondly, our study had limited statistical power to detect associations between relatively rare conditions (e.g., placenta previa, polyhydramnios, multifetal pregnancy, chorioamnionitis) and postpartum hemorrhage. Thirdly, our inferences regarding underdiagnoses and overdiagnoses of atonic postpartum hemorrhage and use or non-use of interventions were hampered by an inability to distinguish between poor documentation and incorrect diagnosis/management. Some inconsistencies between the diagnosis of atonic postpartum hemorrhage and estimated blood loss may have been due to the timing of diagnosis (e.g., made soon after delivery by physician) and difficulty in estimated blood loss due to hemorrhage occurring subsequently (e.g., small but persistent blood loss following delivery noted by nurse). Finally, while we quantified the effects of prior CS on women delivering vaginally and by CS, we did not include all the indications for CS in the regression model to avoid complexity.

CONCLUSION

Our study shows that the diagnosis of atonic postpartum hemorrhage is prone to significant misclassification because there are significant inconsistencies between blood loss and the diagnosis as documented in the medical chart. Population trends in postpartum hemorrhage may have been potentially influenced by secular changes in health care provider concerns about blood loss. Although our study shows low adherence to specific components of active management of the third stage of labour (such as controlled cord traction), we were unable to determine whether this was a consequence of poor documentation or due to the lack of use of such interventions. Careful adherence to proven strategies for managing the third stage of labour and improved documentation will help address concerns associated with the recent temporal increases in postpartum hemorrhage that have been reported in several industrialized countries.

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Appendix Table A1. Medication use during pregnancy and in the delivery hospitalization among cases with atonic postpartum hemorrhage and controls without postpartum hemorrhage

Medication	Case		Control		*P*	Examples
	n = 383	%	n = 383	%		
Analgesic medication	77	20.26	59	15.53	0.07	
During pregnancy	16	4.21	26	6.84	0.11	ibuprofen, acetylsalicylic acid, acetaminophen, lorazepam, acetaminophen+codeine+caffeine
During delivery hospitalization	31	8.68	17	4.47	0.03	
During delivery	33	8.68	17	4.47	0.02	
Acute antiasthmatics	9	2.36	7	1.83	0.62	albuterol, terbutaline, epinephrine, hydrocortisone, isoetharine
During pregnancy	8	2.1	7	1.83	0.79	
Chronic antiasthmatics	9	2.36	7	1.85	0.62	albuterol, beclomethasone, budesonide
Antihypertensives	19	5	12	3.15	0.19	furosemide, hydralazine, hydrochlorothiazide, labetalol, methyldopa, nifedipine, verapamil
During pregnancy	8	2.11	8	2.11	1.00	
During delivery hospitalization	6	1.58	2	0.52	0.18	
During delivery	8	2.11	7	1.84	0.79	
Antibiotics	180	47.24	161	42.37	0.18	amoxicillin, ampicillin, cefazolin, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, gentamicin, penicillin G, streptomycin, vancomycin, trimethoprim
During pregnancy	13	3.41	16	4.21	0.58	
During delivery hospitalization	30	7.87	22	5.79	0.23	
During delivery	157	41.21	131	34.47	0.07	
Antidepressants	11	2.89	5	1.31	0.16	amytriptyline, bupropion, citalopram, doxepin, duloxetine, fluoxetine, haloperidol, imipramine, nefazodone, paroxetine, sertraline, trimimpramine
During pregnancy	11	2.87	8	2.08	0.53	
During delivery hospitalization	1	0.26	0	0.00	-	
During delivery	1	0.26	1	0.26	-	
Thyroid medication	17	4.5	11	2.87	0.22	thyroxine
During pregnancy	17	4.5	11	2.87	0.22	
During delivery hospitalization	2	0.53	1	0.26	0.57	
During delivery	2	0.53	1	0.26	0.57	
Vitamins	220	57.89	199	52.51	0.03	Materna (prenatal multivitamin)
During pregnancy	214	56.32	190	50.13	0.02	
During delivery hospitalization	6	1.58	2	0.53	0.18	
During delivery	5	1.32	4	1.06	0.48	
Herbal supplements	5	1.31	4	1.05	0.74	herbal teas, homeopathic medication

NOTE: *P* values obtained from conditional logistic regression models.

Appendix Table A2. Procedures to control bleeding among cases with atonic postpartum hemorrhage and controls without postpartum hemorrhage

	Case		Control		
Procedures to control bleeding	n = 383	%	n = 383	%	P[a]
Uterotonics (any)	374	97.65	356	92.95	0.003
Oxytocin use	364	95.04	344	89.82	0.008
Prostaglandin use	179	46.74	11	2.87	< 0.001
Carboprost	85	22.19	1	0.26	< 0.001
Other (misoprostol)	145	37.86	10	2.61	< 0.001
Ergometrine use	23	6.01	0	0.00	-
Other medications[b]	17	4.44	12	3.13	0.34
Vaginal packing	10	2.61	0	0.00	-
Uterine packing	1	0.26	0	0.00	-
B-Lynch suture	6	1.57	0	0.00	-
Balloon catheter	22	5.74	0	0.00	-
Embolization of uterine arteries	2	0.52	0	0.00	-
Hysterectomy to control bleeding	4	1.04	0	0.00	-
Transfusion (blood products)	48	12.53	0	0.00	-

NOTE: Percentages may not add up to 100 due to missing values; missing values < 2% not shown.

[a] P values obtained from conditional logistic regression models.

[b] Includes carbetocin and tranexamic acid.

Appendix Table A3. Oxytocin doses during the third stage of labour among postpartum hemorrhage cases and controls

	Vaginal delivery				CS			
	Cases		Controls		Cases		Controls	
Oxytocin doses (units)	n = 296	%	n = 272	%	n = 87	%	n = 111	%
None	6	2.04	25	9.33	13	15.5	14	12.8
1 to 10	46	15.6	110	41.0	13	15.5	7	6.42
11 to 20	44	15.0	58	21.6	14	16.7	46	42.2
21 to 30	61	20.7	55	20.5	8	9.52	16	14.7
31 to 40	58	19.7	10	3.73	10	11.9	5	4.59
41 to 50	47	16.0	4	1.49	6	7.14	16	14.7
51 to 60	9	3.06	2	0.75	5	5.95	2	1.83
61 to 70	11	3.74	2	0.75	4	4.76	2	1.83
71 to 80	8	2.72	2	0.75	3	3.57	0	0.00
81 to 90	1	0.34	0	0.00	1	1.19	0	0.00
91 to 100	1	0.34	0	0.00	2	2.38	1	0.92
100 to 200	2	0.68	0	0.00	5	5.95	0	0.00

NOTE: Conditional logistic regression based P value < 0.001 for differences in oxytocin dose for cases and controls following vaginal delivery, and P value 0.054 following delivery by CS. Oxytocin dose modelled as a continuous variable.

Missing values: n = 11.