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Patterns of Recurrence of Postpartum Hemorrhage in a Large, Population-Based Cohort

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Abstract

Objectives—While a history of postpartum hemorrhage (PPH) is a recognized risk factor for PPH in subsequent pregnancies, little is known about how the risk accumulates over multiple pregnancies, how recurrence varies by PPH subtype, and whether recurrence can be explained by chronic maternal conditions.

Study design—Risks of PPH were assessed according to prior history of PPH, severity and subtype (atony, retained placenta, or lacerations) in 538 332 primiparous women included in the Swedish Medical Birth Register between 1997–2009. The role of stable maternal risk factors was evaluated in regression models predicting probability of recurrent PPH in 2nd and 3rd pregnancy.

Results—Women with a previous history of PPH had a 3-fold increased risk of PPH in their second pregnancy compared to unaffected women (15.0% vs. 5.0% respectively). Adjustment for stable maternal risk factors did not significantly attenuate this risk (adjusted relative risk: 3.0, 95% confidence interval 2.9–3.1). In third pregnancy, the risk of PPH was 26.6% after two previously affected pregnancies, compared to 4.4% in women with no previous PPH. A history of a specific type of PPH predicted recurrence of PPH in the second pregnancy, not only of the same type but other etiologies as well.

Conclusions—PPH risk is highest among women with >1 previously affected delivery and in those with a previous severe PPH. Chronic conditions known to be risk factors for PPH do not

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explain the recurrence risks. The recurrence patterns across PPH subtypes may point to shared pathological mechanisms underlying the varying PPH etiologies.

Keywords

Postpartum hemorrhage; Recurrence; Uterine atony; Retained placenta; Epidemiology

INTRODUCTION

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality in both the developing [1] and developed world. [2, 3] The incidence of PPH has increased substantially in developed countries over the past decade, even after adjustment for temporal trends in risk factors such as advanced maternal age, obesity and obstetric practice.[4–9] Common etiologies for PPH include uterine atony, retained or adherent placenta, and lacerations. Major risk factors for PPH include conditions that overdistend the uterus, labor induction and augmentation, prior cesarean delivery, hypertensive disorders of pregnancy, fibroids, placenta previa, coagulopathy, and obesity. [10, 11]

While a history of PPH is a recognized risk factor for PPH in subsequent pregnancies,[12–16] much remains unknown about the causes and patterns of recurrence. In particular, there are few data available regarding the accumulation of risk after several affected pregnancies and how risk of recurrence varies by the severity of prior PPHs. The role of PPH subtype for risks of recurrence is also poorly understood, and of importance since each etiology may have different underlying pathophysiology and risk factors. [10]

Identifying the patients with a history of PPH that are at the highest risk for recurrence may have crucial implications in guiding clinical management. Referral of patients to high-risk medical centers has been suggested as a means of improving outcomes for certain high-risk obstetric conditions [17, 18] and may be appropriate for some patients with a history of PPH. Recurrence risk data may also inform counseling regarding the risks of delivering outside of a hospitalized setting. Finally, it may affect the decision by clinicians about whether to place intravenous lines or order blood products in anticipation of possible PPH.

To further understand the epidemiology of recurrent PPH, we studied recurrence of PPH in women of the Swedish Medical Birth Register. In addition to describing overall PPH recurrence patterns in this nationwide sample, we specifically sought to (1) determine if PPH recurrence could be explained by known PPH risk factors expected to be present in all pregnancies and (2) to evaluate the impact of PPH subtype (atony, retained placenta, lacerations) and severity on recurrence risk.

MATERIAL AND METHODS

The Medical Birth Register contains information on 96–99% of all live births in Sweden since 1973, as well as stillbirths occurring after week 28 (and from week 22 since June 2008). [19] Information is retrieved from prenatal and delivery records, and includes baseline characteristics of the mother. Onset of delivery is routinely recorded according to standardized categories of either spontaneous, induced vaginal, or cesarean delivery. At the time of discharge, the obstetrician records potential pregnancy or delivery-related complications according to the International Classification of Diseases (ICD). Since 1997, procedures may further be recorded using the Swedish version of the NCSP (Nordic Medico-Statistical Committee Classification of Surgical Procedures). [20, 21]

PPH was identified through the ICD-10 code O72, and further specified as occurring before, or immediately after the delivery of the placenta (O72.0 and O72.1 respectively) or more

than 2 hours after the delivery of the placenta (O72.2). The diagnosis is applied by clinicians when blood loss is estimated to be in excess of 1,000ml. In the Swedish version of the ICD-10, PPH occurring after the delivery of the placenta can be further classified as either due to atony (A), lacerations (B), or unknown reasons (Z). In the present study we considered subgroups of PPH due to retained placenta (O72.0), atony (O72.1A), or lacerations (O72.1B). If more than one specific diagnosis was given for one delivery, the hemorrhage was classified as not otherwise specified (together with hemorrhages of unknown reason). For Cesarean delivery, hemorrhage is generally coded as a diagnosis of excessive (>1000ml) peri-operative bleeding, without further information on etiology (atony, retained placenta, etc.). We therefore included these as PPH in the setting of Cesarean in the overall analyses, but then also performed analyses restricted to vaginal deliveries (for which the etiology of PPH is generally coded). The distributions of diagnoses set in the study population are illustrated in Table 1. We defined severe PPH as hemorrhage leading to coagulopathy (O72.3) and/or with a concurrent coding of blood transfusion during the delivery hospitalization. Due to changes of the clinical definition of PPH following the transition from ICD-9 (>600ml bleeding) to ICD-10 (>1000ml), the evaluation of PPH recurrence was restricted to births occurring after the implementation of ICD-10 in Sweden (from 1997, except in the county of Skåne where it was implemented from 1998).

To study recurrence of PPH we first identified all deliveries to primiparous women in the Medical Birth Register between 1997 and 2009. These 583 332 women were followed with respect to subsequent deliveries, resulting in a total of 914 939 deliveries in the study period, 1.5% (N=13 626) of which were multiples. Frequency of PPH was assessed after first, second and third delivery, representing population risks of PPH. Among those with and without a diagnosis in their first pregnancy we estimated the proportion who undertook a second pregnancy and the risk of PPH in that pregnancy, and then repeated the procedure for a third pregnancy. Probabilities of subsequent delivery given PPH experience were compared with the chi-square test and p-values<0.05 considered statistically significant. Next we obtained relative risks (RR) of PPH given previous PPH history from log-linear regression models estimating the probability of PPH in the second and third pregnancy respectively. Analyses were performed in all deliveries and then restricted to vaginal deliveries, and in the latter also stratified according to specific subtype of PPH. To further assess the influence of known chronic risk factors for PPH (i.e., factors expected to be present across a woman's reproductive life), we adjusted for fixed demographic factors (measured during the first pregnancy) such as year of birth, maternal age, civil status, country of origin and diagnosis of chronic hypertension (I10–15; O10–11, which can predispose to superimposed preeclampsia), diabetes (E10–14; O24.0–24.3, which can predispose to macrosomia and polyhydramniosis), coagulopathy (D66–69), or fibroids (D25). We also evaluated the presence of one or more of these risk factors in the second pregnancy of women with PPH in the first pregnancy.

Lastly we assessed whether type of hemorrhage (any, specific type, severe) experienced in the first pregnancy influenced risk and type of hemorrhage recurrence in the second pregnancy. Permission for the study was obtained from the Regional Ethical Review board at Karolinska Institutet, Stockholm, Sweden.

RESULTS

Table 1 shows the distribution of PPH diagnoses in the first three pregnancies to all women giving birth between 1997–2009, stratified by birth order and mode of delivery. In this sample of 906 607 deliveries, there were 58 082 cases of PPH (6.4%). The risk of PPH was higher in the first delivery (7.0%) than in subsequent deliveries (5.5%). This pattern of

highest risk in first delivery was observed for all subtypes except for PPH associated with uterine atony, where risk remained largely unchanged across pregnancies.

In the same population, risk of PPH was assessed in relation to maternal characteristics obtained in the corresponding pregnancy (table 2). Risk of PPH was positively associated with maternal age and maternal chronic conditions including diabetes mellitus, hypertension, coagulopathy and uterine fibroids. In contrast, women who were single, or born outside of Scandinavia were at less risk of PPH than women living with the father or born in Scandinavia, respectively. There was also a trend of increasing occurrence of PPH in the 13-year study period.

Table 3 shows the risk of PPH in subsequent deliveries according to PPH history at 1st and 2nd delivery respectively. For both deliveries overall and when restricted to vaginal deliveries, the risk in a given pregnancy was greatly increased in women with previous history of PPH. In the second pregnancy this was reflected by a 3-fold higher risk in women with a history of PPH compared to those with no history (RR_{all} = 3.0, 95% CI: 2.9, 3.1). In the third pregnancy, women with PPH in each of their two previous pregnancies had a 6-fold higher risk of PPH than women with no previous history (RR_{all} = 6.1, 95% CI: 5.1, 7.2). Restricting to vaginal deliveries further strengthened the risks of recurrence. Adjusting for stable risk factors that could potentially explain the recurrence had little effect on the estimates. When each PPH subtype was considered separately (among vaginal deliveries only) similar patterns of recurrence were seen for PPH due to retained placenta and atony respectively, with the most pronounced recurrence seen for hemorrhage due to retained placenta (results not shown).

Table 4 shows relative risks of PPH in the second pregnancy, comparing women with and without PPH in the first pregnancy and restricted to vaginal deliveries to allow evaluation of how recurrence risk varies by PPH subtype. The columns show the risk of PPH overall and from retained placenta, atony, and lacerations, as well as for severe PPH. The rows represent the history of PPH in the first pregnancy. For all the PPH subtypes the highest RR was seen after a previous event of the same subtype. While risks of recurrence were greatest for PPH of the same subtype, they were also substantially increased for PPH from other causes (e.g. PPH from retained placenta in the first pregnancy increased risk of hemorrhage in second pregnancy not only from retained placenta, but from atony and lacerations as well).

COMMENT

In this large prospective cohort study, the risk of PPH in women with one prior affected pregnancy increased approximately 3-fold, and about 6-fold after two previously affected pregnancies compared with women without a history of PPH. At their second and third delivery respectively, 1 in 7 women with a prior PPH and 1 in 4 with two prior PPH will experience PPH with greater than 1000ml blood loss. Importantly, this study reports for the first time that irrespective of type, a previous PPH can predict subsequent risk of hemorrhage from any etiology (atony, retained placenta, lacerations), and that recurrence risk cannot be explained by known PPH risk factors.

These findings are consistent with and extend those from prior reports.[13–15] Studies examining risk factors for PPH have shown women with prior PPH to be at 2 to 3 times higher risk of PPH compared to those without such a history.[14, 15] A recent population-based study from New South Wales of 125 295 women reported a PPH recurrence risk of 15% in women with one previously affected pregnancy and 27% in those with two prior affected pregnancies,[13] estimates that are remarkably similar to those observed in our cohort. We extended the findings of previous studies by examining how recurrence risk varies according to the underlying etiology and severity of the PPH in the first pregnancy

and by exploring the role of chronic medical conditions and pregnancy characteristics for risk of recurrence.

Etiology of PPH following vaginal delivery was evaluated on the basis of the categories defined through the Swedish version of the ICD-10 -uterine atony, retained placenta, and lacerations. Remarkably, we found that PPH from one etiology conferred increased risk in subsequent pregnancies not only from that etiology, but from other causes as well. The pathophysiology underlying the various causes of PPH is generally not well understood, but finding that a history of each PPH subtype confers risk of others could suggest that there are shared underlying pathological factors across the different etiologies.

Chronic co-morbidities that are known to be risk factors for PPH (e.g. chronic hypertension, diabetes, inherited coagulopathy and fibroids) could potentially explain some of the recurrence of PPH. However, adjusting for known and chronic PPH risk factors did not substantially change the estimates of recurrence risk either for deliveries overall or when we restricted to vaginal deliveries. This suggests that risk of PPH recurrence depends on other risk factors, genetic or environmental, that affect the risk of women throughout their pregnancies.

All women who experience PPH in a prior pregnancy should be considered at risk of PPH in subsequent pregnancy. If the women in our cohort who had a PPH in the first pregnancy had been evaluated for risk of PPH in the subsequent pregnancy based on known chronic conditions (hypertensive disorders, diabetes, coagulopathy and fibroids) only 2% would have been classified at risk, and including age (>30 years) would identify a total of 15%. Considering also the history of PPH a risk factor would thus reclassify more than 80% of the women with a prior PPH as at-risk. Likewise, among all PPHs in second pregnancy, 24% occurred in women with at least one known risk factor (chronic condition or age at first birth > 30 years), and including prior history as a risk factor increased this proportion to 37%

Although the results did not change materially when diagnosis of coagulopathy was taken into account, a potential mechanism to explain these findings may be the presence of undiagnosed maternal coagulation disorders (particularly given the observation that risk of PPH from one etiology predisposed to risk of PPH from other etiologies in subsequent pregnancies). Such a mechanism would provide a biologically plausible explanation for the seemingly surprising finding that there was a shared predisposition to such mechanistically distinct forms of PPH as laceration, retained placenta, and uterine atony. Von Willebrand disease is the most common bleeding disorder in the general population with a prevalence of about 1%.[12] It is further a well-known risk factor for PPH.[12, 22–24] Other congenital coagulation disorders, including Factor II, VII, X, XI deficiencies and carriage of hemophilia A and B are rare, but have also been associated with excess bleeding with delivery.[12, 24–26] While based on small studies, the prevalence of undiagnosed coagulation disorders in the general population of patients with PPH is low,[27, 28] and further study is needed to ascertain whether this may not pertain to the population of women that experience recurrent PPH.

There may be other shared pathological mechanisms that underlie the recurrence risk of PPH across etiologies. Recently, in separate studies, the amount of oxytocin use during labor was shown to correlate with PPH from both atony[29] and retained placenta.[30] As oxytocin receptor desensitization and myometrial fatigue appear to be implicated in both PPH subtypes, a predisposition to such uterine dysfunction (whether due to genetic or other stable maternal characteristics) could be another plausible mechanism to explain our findings. Since we were unable to examine the use of oxytocin in this study, this should be an important avenue for future research in this area.

Irrespective of the underlying cause, the patterns of recurrence that we observed have important clinical implications. Because women with prior PPH are at markedly elevated risk in subsequent pregnancies, particularly if the initial PPH was severe or due to retained placenta, they should be delivered in settings that have the requisite obstetric, anesthetic, and blood bank expertise and personnel to rapidly respond to a PPH. These women should be counseled to avoid home delivery or other settings, such as freestanding birthing centers, that lack these resources. Placement of intravenous lines and performing a type and screen at the time of admission to the labor suite may also be indicated.

The data should be interpreted in the context of the study design. We had the ability to follow the delivery outcomes of all primiparous women in Sweden during the follow-up period, and the risks presented are thus population-risks. Studies suggest that there is substantial regional variability in the prevalence of PPH.[31] Because the blood loss threshold used to define PPH varies by country, the absolute risk of recurrence of the diagnosis will not be generalizable. However, we anticipate that the patterns of recurrence will apply to other populations. Further, the threshold for defining PPH in our study; greater than 1,000ml of blood loss, reflects clinically significant blood loss, and risk of recurrence for this amount of blood loss should be of great interest to all clinicians irrespective of their country of origin. The richness of the data (both in size and information available) allowed examination of recurrence patterns across multiple pregnancies and according to both etiology and severity. Detailed information on co-morbidity and pregnancy characteristics further allowed for evaluation of the underlying reasons for recurrence. A possible limitation of using register-based information in this setting concerns the accuracy of the PPH diagnosis and its etiology. While studies suggest that PPH is coded in claims data with high positive predictive value,[32, 33] it is also known that healthcare workers routinely underestimate blood loss in the setting of delivery.[34, 35] Our findings should be interpreted as risks of recurrence based on a clinician estimate of >1000ml blood loss; which may be an underestimate of the true occurrence of such blood loss. Assuming non-differential misclassification, this would if anything lead to an underestimation of recurrence risks in the present study. Potential surveillance bias from evaluating patients with a history of PPH more closely, on the other hand, could if present lead to an overestimation of recurrence risk. However, given that all patients are routinely evaluated for extent of blood loss after delivery, we estimate the potential for surveillance bias to be very small and certainly not adequate to explain the strong patterns of recurrence observed. Likewise, we cannot exclude some misclassification of subtype, which would contribute to the finding that one etiology confers increased risk across all PPH etiologies in subsequent pregnancies. However, previous investigations in the Medical Birth Register have identified obesity as a risk factor for PPH due to atony, but not other causes,[11] suggesting that the classification of subtype is applied with specificity by Swedish physicians. Further, given the strength of associations observed in our study, we consider it unlikely that potential subtype misclassification can account for the findings.

In conclusion, the prominent risks of PPH recurrence in the Swedish population cannot be explained by known chronic conditions. This suggests the need for further research to define the basis for recurrence risk. We also show that a history of a specific subtype of PPH (i.e., atony, retained placenta, lacerations) increases the risk not only for that subtype, but other subtypes as well. This novel observation of recurrence risk across all PPH subtypes may point to shared pathological mechanisms; examining these mechanisms may be a fruitful direction for research aimed at elucidating the biological underpinnings of this complication.

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Table 1

ICD-10 diagnoses of PPH in the first three deliveries to 583 332 Swedish women between 1997–2009 (N=906 607)

	Specified PPH						Unspecified PPH			Any PPH
	Retained placenta	Atony	Lacerations	Unknown	Several specific	Late (>2hrs)	Leading to coagulopathy	Incomplete code	Peri-op bleeding	With blood transfusion
ICD-10	O72.0	O72.1A	O72.1B	O72.1X	O72.0 + O72.1A/B	O72.2	O72.3	O72.?	O67.8	Z51.3
Vaginal deliveries										
1st N (%)	8837 (2.01)	9872 (2.25)	4250 (0.97)	3536 (0.80)	461 (0.10)	788 (0.18)	23 (0.01)	40 (0.01)		4523 (1.03)
2nd N (%)	4069 (1.54)	5439 (2.05)	1174 (0.44)	1281 (0.48)	183 (0.07)	487 (0.18)	13 (0.00)	15 (0.01)		1771 (0.67)
3rd N (%)	676 (1.35)	1128 (2.26)	100 (0.20)	179 (0.36)	31 (0.06)	92 (0.18)	1 (0.00)	1 (0.00)		282 (0.56)
Cesarean deliveries										
1st N (%)	146 (0.15)	995 (1.00)	74 (0.07)	190 (0.19)	13 (0.01)	375 (0.38)	30 (0.03)	4 (0.00)	7996 (8.07)	1295 (1.31)
2nd N (%)	61 (0.14)	321 (0.72)	39 (0.09)	89 (0.20)	8 (0.02)	167 (0.37)	12 (0.03)		4025 (8.97)	615 (1.37)
3rd N (%)	13 (0.15)	63 (0.74)	6 (0.07)	18 (0.21)		34 (0.40)	4 (0.05)		709 (8.36)	101 (1.19)

Table 2

Distribution and odds ratios of PPH according to maternal characteristics

		Postpartum hemorrhage		
Maternal characteristics	**[N]**	**N**	**%**	**OR (95% CI)**
Age at delivery				
<20	20757	843	4.06	1.00
20–34	756554	46944	6.20	1.56 (1.46, 1.68)
>35	129262	10294	7.96	2.0 (1.90, 2.20)
Parity				
Primipara	538468	37651	6.99	1.00
Multipara	368139	20431	5.55	0.78 (0.77, 0.80)
Civil status				
Living with father	812033	52022	6.41	1.00
Living alone	15840	833	5.26	0.81 (0.76, 0.87)
Unknown	28207	1575	5.58	0.86 (0.82, 0.91)
Country of origin				
Scandinavian	771783	49814	6.45	1.00
Non-scandinavian	134069	8233	6.14	0.95 (0.92, 0.97)
Diabetes				
No	900986	57597	6.39	1.00
Yes	5621	485	8.63	1.38 (1.26, 1.52)
Chronic Hypertension				
No	901484	57667	6.40	1.00
Yes	5123	415	8.10	1.29 (1.16, 1.43)
Coagulopathy				
No	903221	57776	6.40	1.00
Yes	3386	306	9.04	1.45 (1.29, 1.64)
Fibroids				
No	905723	57956	6.40	1.00
Yes	884	126	14.25	2.43 (1.99, 2.97)

PPH, postpartum hemorrhage; OR odds ratio; CI confidence interval

NOTE numbers may not add up due to missingness (6% for civil status)

Table 3

Risk of subsequent PPH according to history of PPH, in all and restricted to vaginal deliveries

Pregnancy history of PPH		PPH recurrence in all deliveries				PPH recurrence in vaginal deliveries			
[First]	[Second]	[N]	%	RR (95% CI)	RR (95% CI) [a]	[N]	%	RR (95% CI)	RR (95% CI) [a]
No PPH	-	289982	5.0	1.0	1.0	226310	3.7	1.0	1.0
PPH	-	19853	15.0	3.0 (2.9, 3.1)	3.0 (2.9, 3.1)	13552	14.2	3.8 (3.6, 4.0)	3.7 (3.6, 3.9)
No PPH	No PPH	52847	4.4	1.0	1.0	41631	3.5	1.0	1.0
PPH	No PPH	2782	9.9	2.3 (2.0, 2.5)	2.3 (2.0, 2.6)	1937	9.4	2.7 (2.3, 3.1)	2.7 (2.3, 3.2)
No PPH	PPH	2405	15.0	3.4 (3.1, 3.8)	3.4 (3.0, 3.8)	1443	15.3	4.4 (3.8, 5.0)	4.2 (3.7, 4.9)
PPH	PPH	406	26.6	6.1 (5.1, 7.2)	6.2 (5.2, 7.3)	247	26.7	7.6 (6.2, 9.4)	7.6 (6.1, 9.5)

Abbreviations: PPH, postpartum hemorrhage; RR, relative risk; CI, confidence interval

[a] Adjusted for birth year, maternal age, civil status, country of origin, chronic hypertension, diabetes, coagulopathy and fibroids

Table 4

Risk of PPH in second pregnancy according to previous history and specific type, restricted to vaginal deliveries

Pregnancy history of PPH			PPH recurrence in vaginal deliveries									
			Any PPH		Retained placenta		Atony		Lacerations		Severe	
[First]	[Type]	[N]	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)
No PPH		226310	3.7	1.0	1.2	1.0	1.8	1.0	0.2	1.0	0.5	1.0
PPH	Any	13552	14.2	3.8 (3.6, 4.0)	6.1	5.3 (4.9, 5.7)	5.7	3.3 (3.0, 3.5)	0.8	3.4 (2.7, 4.1)	2.3	5.0 (4.4, 5.6)
	Retained placenta	4114	18.3	4.9 (4.6, 5.2)	12.0	10.4 (9.5, 11.4)	4.4	2.5 (2.2, 2.9)	0.4	1.9 (1.2, 3. 1)	3.9	8.4 (7.1, 9.9)
	Atony	4957	12.8	3.4 (3.2, 3.7)	3.6	3.1 (2.7, 3.6)	7.0	4.0 (3.6, 4.4)	0.7	2.9 (2.0, 4.1)	1.7	3.7 (3.0, 4.6)
	Lacerations	2007	12.6	3.4 (3.0, 3.8)	3.2	2.8 (2.2, 3.6)	5.7	3.2 (2.7, 3.9)	1.7	7.8 (5.5, 10.9)	1.4	2.9 (2.0, 4.3)
	Severe	2032	18.8	5.0 (4.6, 5.5)	6.2	5.4 (4.5, 6.4)	9.7	5.5 (4.8, 6.3)	0.8	3.5 (2.1, 5. 8)	4.2	9.1 (7.4, 11.3)