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ORIGINAL RESEARCH ARTICLE

Recurrence of postpartum hemorrhage in relatives: A population-based cohort study

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Abstract

Introduction: Studies on the family aggregation of postpartum hemorrhage (PPH) are scarce and with inconsistent results, and to what extent current birthweight influences recurrence between relatives remains to be studied. Further, family aggregation of PPH has been studied from an individual, but not from a public heath perspective. We aimed to investigate family aggregation of PPH in Norway, how birthweight influences these effects, and to estimate the proportion of PPH cases attributable to a family history of PPH and current birthweight.

Material and methods: Using data from the Medical Birth Registry of Norway, Statistics Norway, and Central Population Registry of Norway we identified individuals as newborns, parents, grandparents, and full and half-siblings, and studied 1 002 687 mother–offspring, 841 164 father–offspring, and 761 011 both-parents–offspring pairs. We used multilevel logistic regression to calculate odds ratios (OR) with 95% CI.

Results: If the birth of the mother but not of the father involved PPH, then the OR of PPH (>500 mL) in the next generation was 1.44 (95% CI 1.39–1.49). If the birth of the father but not of the mother involved PPH, then OR was 1.12 (95% CI 1.08–1.16). These effects were stronger in severe PPH. Recurrence between siblings was highest between full sisters (OR 1.47, 95% CI 1.41–1.52), followed by maternal half-sisters, paternal half-sisters, and partners of full brothers. A family history of PPH or birthweight of 4000 g or more accounted for ≤5% and 15% of the total number of PPH cases, respectively.

Conclusions: A history of PPH in relatives influenced the recurrence risk of PPH in a dose–response pattern consistent with the anticipated proportion of shared genes. The recurrence was highest through the maternal line.

KEYWORDS
adjusted population attributable fraction, birthweight, cohort studies, fathers, mothers, postpartum hemorrhage, recurrence, siblings

Abbreviations: OR, odds ratio; PPH, postpartum hemorrhage.

1 | INTRODUCTION

Postpartum hemorrhage (PPH) is an increasingly common obstetric complication in developed countries despite preventive measures implemented in clinical guidelines,[1,2] and is the leading direct cause of maternal death worldwide.[3,4] Main causes and risk factors for PPH are identified, including a woman's own history of PPH,[5–7] but studies on the family aggregation of PPH are scarce with inconsistent results.[8–10] The potential of PPH in a woman's mother or other relatives to predict PPH, with relevance especially for nulliparous women, needs to be clarified.

The paternal contribution to PPH, which is mediated through the fetus and placenta, has not been explored in generational studies and necessitates large data sets. If studies of family aggregation of PPH suggest a dose–response relation reflecting the anticipated number of shared genes among family members, this could strengthen a hypothesis of a genetic component in the causal pathway of PPH and encourage further study on cause-specific recurrence of PPH. Among common specific causes of PPH, both uterine atony and obstetric trauma are associated with increased distention of the uterus by a large fetus and placenta.[11] Fetal macrosomia also has environmental and genetic causes. However, to what extent current birthweight influences recurrence of PPH between relatives remains to be studied. Further, familial aggregation of PPH has been studied from an individual, but not from a population perspective.

The aim of the present study was to explore the recurrence risk between generations, between full and half-siblings and cousins, and the maternal and paternal contributions to the risk of PPH. Additionally, we explored how current birthweight influences recurrence, and quantified the population proportions of PPH cases attributable to a family history of PPH and high birthweight in the current delivery.

Key message

The recurrence risk of postpartum hemorrhage is highest among relatives with a close genetic relationship, is strongest through the maternal line and is strongly modulated by current birthweight.

2 | MATERIAL AND METHODS

2.1 | Data sources

In this study we use data from The Medical Birth Registry of Norway; this is a mandatory registry for all deliveries from its inception in 1967. Information on maternal and paternal country of birth and education was provided by Statistics Norway and linked with the research database through the unique national identification number. Information on parents was provided by the Central Population Registry of Norway for individuals born after 1954,[12] which allowed us to construct a population-based pedigree for family aggregation.

We included singleton births with gestational age at birth of at least 22 weeks. As this study included pregnancies before the introduction of ultrasound (recorded from 1999), gestational age was based on menstrual dates and on ultrasonography if information on menstrual date was lacking. We primarily analyzed deliveries with spontaneous onset or induction of labor, including cesarean deliveries after onset of labor. Cesarean delivery may strongly influence the risk of PPH, so we performed additional analyses of the population with these selections: (a) including all deliveries or (b) excluding cesarean deliveries.

2.2 | Record linkage

During the total study period (1967–2017), 3 003 025 births were registered. We identified individuals as newborns, parents, or grandparents. This approach allowed us to trace full- and half-siblings among newborns and parents.

Generational information was revealed by identifying the individual both as a newborn and as a mother or father (Figures S1 and S2). We restricted the generational files to the first three births in the second generation, yielding 1 002 687 mother–offspring pairs, 841 164 father–offspring pairs and 761 011 both-parents–offspring pairs.

To study recurrence between siblings as parents, we aligned the generational information of siblings (Figure S3). In this way, each record included birth registry data for four births: (a) the birth of the parent, (b) the birth of its offspring, (c) the birth of the parent's sibling, and (d) the birth of the sibling's offspring (ie, the parent's niece/nephew). A parent and its sibling's offspring constituted an aunt/uncle–niece/nephew pair sharing on average 25% of their genes, whereas pairs of siblings and pairs of their offspring (cousin pairs) share 50% and 12.5% of their genes, respectively. If the parent had more than one sibling, we selected the niece/nephew born immediately before the birth of the parents' offspring. Hence, each record in the file included the chronology of the family history. We restricted the analyses to fewer than six records for each pair of siblings. This left 909 584 pairs of sibling–offspring units available to explore whether the recurrence of PPH between siblings and the intergenerational recurrence of PPH is influenced by a history of PPH in other family members, and whether recurrence is transmitted through the maternal or paternal line. Similarly, maternal and paternal half-sisters were identified.

2.3 | Outcome variables

The primary outcome variable was loss of more than 500 mL blood during labor, or within 24 h postpartum (hereafter referred to as PPH). From 1999, severe PPH—defined as blood loss of more than 1500 mL or the need for blood transfusion (regardless of blood volume)—was also recorded.[13]

TABLE 1 Recurrence of postpartum hemorrhage (>500 mL) between generations; singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

	Second generation						
First generation	**Period**	**Total**	**PPH (*n*)**	**%**	**OR**	**95% CI**	
PPH >500 mL	PPH >500 mL						
No	1967–2017	805 702	110 860	13.8	1	Reference	
Yes		37 977	7170	18.9	1.44	1.40	1.49
No	1967–2001	239 590	18 330	7.7	1	Reference	
Yes		10 601	1194	11.3	1.52	1.42	1.62
No	2002–2010	343 191	46 965	13.7	1	Reference	
Yes		15 856	3007	19.0	1.47	1.40	1.53
No	2011–2017	222 921	45 565	20.4	1	Reference	
Yes		11 520	2969	25.8	1.35	1.29	1.41
PPH >500 mL	PPH >1500 mL						
No	1999–2017	630 555	11 079	1.8	1	Reference	
Yes		30 304	831	2.7	1.58	1.46	1.70

Abbreviations: OR, odds ratio; PPH, postpartum hemorrhage.

2.4 | Independent variables

The main independent variables were a history of PPH in relatives and the birthweight in the current delivery (<4000 g [reference], 4000–4499 g, 4500–4999 g, ≥5000 g). We used birthweight less than 4000 g as reference, because proportions of PPH stabilized with birthweights decreasing below 4000g. The data were stratified according to birth-year periods.

Variables available in our database,[13] were considered as possible confounders if they were associated with PPH in the current as well as in previous births of the relative: maternal age, parity, inter-delivery interval, marital status, mother's country of birth or eight WHO regions,[14] maternal smoking status before pregnancy, maternal body mass index before pregnancy,[14] length of education (available until 2013), and birth-year period. When analyzing recurrence between relatives, the period was divided into groups with approximately equal numbers of records, with unequal durations because of longer follow-up time in earlier than later years to attain sufficient numbers of relatives (between generations: 1967–2001, 2002–2010, and 2011–2017; between pairs of siblings: 1967–2002, 2003–2007, 2008–2011, 2012–2014, and 2015–2017).

Appendix S1 includes additional details on statistical analysis.

2.5 | Statistical analyses

We carried out logistic regression analyses to calculate odds ratios (OR) with 95% CI for PPH in the actual birth as the outcome, and a history of PPH in relatives as the main exposure variable. We accounted for the hierarchical nature of the family data by performing multilevel regression analyses in which the data were divided into different levels in generational analyses and in analysis of pairs of siblings.

We performed sensitivity analyses to assess the impact of unmeasured confounders on the recurrence of PPH between generations and siblings.[15]

To estimate the proportion of cases of PPH attributable to a history of PPH in relatives or current high birthweight (<4000 g (reference), 4000–4499 g, 4500–4999 g, and ≥5000 g) we calculated the adjusted population-attributable fraction.[16]

The statistical analyses were performed using SPSS (version 25) and MLwiN (version 3.05). Appendix S1 includes additional details.

2.6 | Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics on 19 September 2013 (2013/1484) and the registry owners (the Medical Birth Registry of Norway, the Norwegian Institute of Public Health, Statistics Norway and the Norwegian Tax Administration).

3 | RESULTS

In the regression analyses, possible confounders for recurrence between relatives had negligible effects on inter-generational recurrence and only the year of birth had significant effect on recurrence between siblings. When including the assumption of a strong unknown confounder in our sensitivity analyses, the OR of recurrence between relatives decreased by less than 5%. Therefore, in the final analyses we generally presented unadjusted OR of inter-generational recurrence and in analyses of recurrence between siblings we only adjusted for period of birth.

After we had excluded cesarean sections from our analysis, the OR of recurrence between relatives were slightly stronger (data not shown). Recurrence rates were similar in women born in Norway and in immigrants from different regions.

3.1 | Transgenerational recurrence of PPH

The odds ratio of PPH was increased with about 40% for women who themselves had been born in a labor with PPH, and the effect was stronger, (almost 60% increased), in severe PPH (>1500 mL) in the second generation (Table 1, Figure S1). When stratifying the second generation by year of birth into three groups of equal numbers of cases, we found that this effect decreased slightly during the study period, whereas the absolute risks increased (Table 1).

Analyzing PPH in the mother's and father's own births as exposure variable revealed that the transgenerational OR of recurrence was higher through the maternal than the paternal line (Table 2, Figure S2). Adjusting for possible confounders (including period) had negligible effects on the results, and so they were not included in the final analyses. We observed that the associations in the second generation were strongest for severe PPH (>1500 mL) with OR 2.0 (95% CI 1.4–2.8) if both parents were born in labors with PPH.

3.2 | Recurrence of PPH between siblings

Table 3 and Figure S3 present OR of recurrence of PPH between pairs of siblings (full and half-sisters, and brothers' partners). The OR of PPH increased if the mother's sister or brother's partner had experienced PPH. The strongest effects were observed between full sisters (50% increased OR), followed by (in decreasing order) maternal half-sisters, paternal half-sisters, and partners of full brothers (20% increase).

3.3 | Combined effects of PPH in relatives

The risk of PPH generally increased with the number of relatives previously exposed (Table S1). Adjusting for possible confounders had negligible effects on the results, and so they were not adjusted in the final analyses.

3.4 | The combined effect of birthweight in actual pregnancy and history of PPH in relatives

We explored if transgenerational OR of recurrence of PPH between siblings was influenced by birthweight in the current delivery (Table 4A and B and Figure S4).

As an example, if the mother herself was born in a delivery with PPH and gave birth to a neonate weighing 5000 g or more, her risk of PPH was five-fold compared with mothers without a generational history of PPH and a birthweight of less than 4000 g (Table 4A). Further, if the mother herself was born in a delivery with PPH and gave birth to a newborn weighing less than 4000 g, her OR of PPH was increased by about 40% compared with mothers without a generational history of PPH and a birthweight of less than 4000 g (Table 4A).

The results presented in Table 4B indicate that the recurrence of PPH between sisters was similarly influenced by the birthweight of the neonate: if the mother gave birth to a neonate weighing 5000 g or more and her sister had experienced PPH, her OR of PPH was four-fold higher than if the neonate weighed less than 4000 g and her sister had not experienced PPH. If the mother had a neonate weighing less than 4000 g and her sister experienced PPH, then her OR of PPH was increased by about 40% compared with a birthweight of less than 4000 g and no experience of PPH in her sister (Table 4B).

These findings indicate that the birthweight in the current delivery and a history of PPH in a mother's relatives (her mother or sisters) had independent effects on subsequent PPH.

3.5 | Population attributable fractions

Among PPH in deliveries in the second generation 1.9% was attributable to PPH in the previous generation (corresponding to 2230 cases), whereas 14.2% (17 023 cases) were attributable to high birthweight in the current delivery (4000–4499 g, 4500–4999 g or ≥5000 g, reference: <4000g). The adjusted population-attributable fraction for pairs of sisters was 5.0% (1555 cases) for a history of PPH in the first sister and 14.6% (4520 cases) for the birthweight in the current delivery.

4 | DISCUSSION

Women with a family history of PPH had an increased risk of PPH in a dose–response pattern consistent with the anticipated proportion of shared genes in relatives. This risk was strongly modified by current birthweight. The OR of PPH recurrence were higher through

TABLE 2 Occurrence of postpartum hemorrhage (>500 mL) in the second generation according to postpartum hemorrhage status in parents' births; singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

First generation		Second generation					
Mother	Father	Total	PPH (*n*)	%	OR	95% CI	
No	No	583 015	85 231	14.6	1	Reference	
Yes	No	27 415	5466	19.9	1.44	1.39	1.49
No	Yes	24 506	3936	16.1	1.12	1.08	1.16
Yes	Yes	1345	273	20.3	1.49	1.29	1.72

Abbreviations: OR, odds ratio; PPH, postpartum hemorrhage.

TABLE 3 Recurrence risk of postpartum hemorrhage (>500 mL) between pairs of siblings; singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

Recurrence between siblings	PPH in first sibling	PPH in second sibling								
		Total	PPH (*n*)	%	OR	95% CI		aOR	95% CI	
Full sisters	No	174 792	24 392	14.0	1	Reference		1	Reference	
	Yes	23 579	4721	20.0	1.62	1.56	1.68	1.47	1.41	1.52
Partners of full brothers	No	138 025	21 924	15.9	1	Reference		1	Reference	
	Yes	21 367	3805	17.8	1.17	1.12	1.21	1.08	1.04	1.13
Maternal half-sisters	No	12 176	1961	16.1	1	Reference		1	Reference	
	Yes	1601	335	20.9	1.48	1.29	1.69	1.39	1.22	1.59
Paternal half-sisters	No	15 287	2412	15.8	1	Reference		1	Reference	
	Yes	1939	364	18.8	1.30	1.15	1.47	1.22	1.08	1.39

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; PPH, postpartum hemorrhage.

aOR, OR adjusted for period in groups of approximately equal number of deliveries 1967–2002, 2003–2007, 2008–2011, 2012–2014 and 2015–2017.

TABLE 4 Impacts of birthweight in the current pregnancy on the occurrence and recurrence of postpartum hemorrhage (>500 mL) between generations (A) and between pairs of sisters (B). Singleton births ≥22 weeks of gestation and spontaneous onset or induction of labor

A. Inter-generational recurrence

Birthweight in second generation	PPH in mother's delivery (first generation)	PPH in delivery in second generation								
		Total	PPH (*n*)	%	OR	95% CI		aOR*	95% CI	
<4000 g	No	641 138	77 169	12.0	1	Reference		1	Reference	
4000–4499 g	No	133 916	25 746	19.2	1.71	1.68	1.74	1.84	1.81	1.87
4500–4999 g	No	27 376	6876	25.1	2.39	2.32	2.46	2.68	2.60	2.76
≥5000 g	No	3272	1069	32.7	3.43	3.17	3.71	3.92	3.62	4.24
<4000 g	Yes	28 444	4655	16.4	1.42	1.37	1.47	1.41	1.36	1.46
4000–4499 g	Yes	7578	1855	24.5	2.31	2.18	2.44	2.47	2.34	2.62
4500–4999 g	Yes	1700	558	32.8	3.41	3.06	3.80	3.82	3.42	4.27
≥5000 g	Yes	255	102	40.0	4.65	3.56	6.08	5.34	4.08	7.00

B. Recurrence between sisters

Birthweight in second sister's delivery	PPH in first sister's delivery	PPH in second sister's delivery								
		Total	PPH (*n*)	%	OR	95% CI		aOR**	95% CI	
<4000 g	No	137 782	16 975	12.3	1	Reference		1	Reference	
4000–4499 g	No	30 035	5639	18.8	1.63	1.57	1.68	1.70	1.64	1.76
4500–4999 g	No	6228	1540	24.7	2.30	2.16	2.45	2.52	2.36	2.68
≥5000 g	No	743	240	32.3	3.32	2.82	3.91	3.85	3.26	4.54
<4000 g	Yes	17 956	3198	17.8	1.43	1.37	1.49	1.32	1.26	1.38
4000–4499 g	Yes	4469	1157	25.9	2.25	2.09	2.42	2.18	2.03	2.35
4500–4999 g	Yes	1012	310	30.6	2.83	2.45	3.27	2.93	2.53	3.39
≥5000 g	Yes	146	58	39.7	4.22	2.96	6.01	4.64	3.25	6.64

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; PPH, postpartum hemorrhage.

*aOR, OR adjusted for marital status, period (1967–2001, 2002–2010 and 2011–2017), maternal age, parity and WHO region of maternal birth.;
**aOR, OR adjusted for marital status, period (1967–2002, 2003–2007, 2008–2011, 2012–2014 and 2015–2017), maternal age, parity and WHO region of maternal birth.

the maternal than the paternal line. Through the half-century study period, OR of recurrence between relatives decreased slightly, whereas the absolute risk of PPH increased. On a population level, a history of PPH in relatives accounted for a low number of PPH cases, whereas the current birthweight accounted for a more significant number of PPH cases.

The population-based cohort design, its large size and almost complete record linkage between relatives are the main strengths of the study. The prospective collection of the data reduced potential selection and recall bias. The long follow-up time allowed study of recurrence between relatives, including generations. Linking different data sources made adjusting for several potential confounders possible. The sensitivity analysis indicated that the effects of unmeasured confounders were not significant. As possible confounders for recurrence are associated with PPH in both the current and previous births in relatives (the criterion most rarely met), the models were robust to confounding. The variable of severe PPH in our database (>1500 mL) was found to be of adequate quality for epidemiological research,[17] and several independent variables in the Medical Birth Registry have been validated with the result of adequate quality.[18,19]

It cannot be ruled out that the implementation of activity-based financing in the Norwegian health care system in 1997 and the use of the new notification form from 1999 may have resulted in an increased rate of false positives. However, if this increased registration in the later period represents misclassification, it is likely that it is non-differential and does not significantly influence OR of recurrence between relatives.

The generalizability of our results to other part of the world may be limited by the relatively ethnically homogeneous Norwegian birth population. However, the population-based design affords generalizability to Western birth populations. Our finding that recurrence rates in immigrants from different regions were similar supports the generalizability of our results. The OR of recurrence seemed to follow a dose–response pattern, in that the OR increased with the anticipated number of shared genes and the severity of bleeding, which strengthens the biological plausibility of our results. Further, our results are in accordance with polygenic theory including higher recurrence rates between relatives of a trait with a severe phenotype or involving more than one family member.[20]

Extra-pair paternity most likely does not bias OR of PPH through the paternal line because it is reported to be low (<2%),[21] and likely has non-differential proportions in male infants born with, compared to without, PPH.

We have previously reported on the familial aggregation of maternal perinatal complications, such as placental abruption, preeclampsia, and obstetric anal sphincter injuries, which is mainly transmitted through the maternal line.[22–24] Our findings for recurrence of PPH between siblings are consistent with the results of a Swedish study.[9] Concerning the paternal contribution to the development of PPH, our finding of paternal transgenerational recurrence (Table 2) is consistent with increased recurrence risk between succeeding deliveries, if the father had changed partner.[9] However, our findings of increased recurrence between first-degree relatives do not corroborate the results of another study in which no significant inter-generational recurrence was found.[10] The cause of this interstudy difference is not known, but one may speculate that the unclear definition of PPH in the latter study attenuated the effects.

Although fetal macrosomia has been associated with PPH,[5] it has not previously been shown how birthweight of the neonate influences the OR of recurrence of PPH between relatives (Table 4).

We found the highest OR of PPH recurrence between relatives when the study population was restricted to include only vaginal deliveries, which is consistent with a Swedish study.[8] However, to increase the relevance for acute obstetric scenarios, we also included deliveries with spontaneous onset and induction of labor, which could end with acute cesarean delivery.

The patterns of OR for recurrence of PPH between relatives in this study were consistent with the average anticipated proportions of shared genes, and suggest a genetic susceptibility, in part related to high birthweight. This is also supported by the small effects of adjusting for sustained risk factors and unknown confounders, although it cannot be ruled out that environmental factors influence recurrence between relatives. The results of our study suggest that a hereditary component is mainly transmitted through the maternal line. We also found a paternal influence on recurrence, which was weaker than the maternal effect, presumably because paternal genes are limited to the fetus, placenta, and decidua (through trophoblast invasion).

The present study indicates that in women with a family history of PPH, anticipated fetal size is a useful, powerful additional predictor of recurrent PPH. Our results add to the understanding of the recurrence of PPH in families. Women with a family history of PPH can be reassured by the moderate effect (about 50% increased risk compared with the reference) of a family history. From a public health perspective, a family history of PPH accounted for a small proportion of all PPH cases (≤5%), and current birthweight of 4000 g or more for 15% of all cases. We did not study cause-specific recurrence of PPH between relatives, eg PPH caused by uterine atony or retained placenta, because it would be of limited clinical value, as most women are probably unaware of the cause of previous PPH in their relatives.

5 | CONCLUSION

The OR of recurrence of PPH between relatives was higher among relatives with a closer genetic relationship, was modulated by birthweight and was stronger through the maternal than the paternal line of transmission. Our results suggest that the etiology of PPH includes a genetic component, which should be disentangled from environmental causes in future studies.

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AUTHOR CONTRIBUTIONS

LEL prepared the analytic database under the supervision of SR. LEL also conducted the analyses and wrote the manuscript in

collaboration with CE and SR. DM, JK, EB and MG contributed by discussing the intellectual content and revising the manuscript. LEL is the guarantor of the manuscript.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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