# Intergenerational transmission of postpartum hemorrhage risk: analysis of 2 Scottish birth cohorts

# Accepted Manuscript

Intergenerational transmission of postpartum haemorrhage risk – analysis of two Scottish birth cohorts

Gemma C. Sharp, MSc Philippa TK. Saunders, PhD Stephen A. Greene, MD Andrew D. Morris, MD Jane E. Norman, MD

PII: S0002-9378(14)00023-4

DOI: 10.1016/j.ajog.2014.01.012

Reference: YMOB 9633

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 26 September 2013

Revised Date: 8 November 2013

Accepted Date: 7 January 2014

Please cite this article as: Sharp GC, Saunders PT, Greene SA, Morris AD, Norman JE, Intergenerational transmission of postpartum haemorrhage risk – analysis of two Scottish birth cohorts, *American Journal of Obstetrics and Gynecology* (2014), doi: 10.1016/j.ajog.2014.01.012.

# Intergenerational transmission of postpartum haemorrhage risk – analysis of two Scottish birth cohorts.

Ms Gemma C SHARP MSc, Edinburgh, United Kingdom MRC Centre for Reproductive Health, The University of Edinburgh

Prof Philippa TK SAUNDERS PhD, MRC Centre for Reproductive Health, The University of Edinburgh

Prof Stephen A GREENE MD, Tayside Children's Hospital, Maternal and Child Health Sciences (MACHS) Building, Ninewells Hospital & Medical School, Dundee, University of Dundee

Prof Andrew D MORRIS MD, Centre for Molecular Medicine, Clinical Research Centre, Level 7, Ninewells Hospital & Medical School, University of Dundee

Prof Jane E NORMAN MD, MRC Centre for Reproductive Health, The University of Edinburgh

**Conflicts of interest:** The authors GCS, PTKS, SAG and ADM have no conflict of interests to declare regarding this submission. JEN has received research grants from charities and governmental bodies for studies on understanding parturition and prevention of preterm parturition. On behalf of the University of Edinburgh, JEN has done some consultancy work for a small drug company interested in agents to prevent preterm parturition. Additionally JEN has received a lecture fee from an overseas academic institution for a lecture on preterm birth.

**Financial support:** This work was supported by the University of Edinburgh Principal's Research Fund (which co funded a PhD studentship for GCS), the Albert McKern Bequest, and Tommy's the baby charity.

**Reprint requests:** Gemma C Sharp, University of Edinburgh MRC Centre for Reproductive Health, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ, gemma.sharp@ed.ac.uk

**Correspondence related to the manuscript can be addressed to:** Gemma C Sharp, University of Edinburgh MRC Centre for Reproductive Health, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ, gemma.sharp@ed.ac.uk, work telephone: +44 131 242 6602

**Abstract word count: 245**

**Main text word count: 2766**

**One sentence condensation of paper:**

In two record-linked birth cohorts, the effects of family history of PPH are less than those conferred by risk factors associated with the index pregnancy.

**Short title:**

Intergenerational transmission of postpartum haemorrhage

**Abstract**

**Objective:** The purpose of this study was to determine risk factors for postpartum haemorrhage (PPH) including intergenerational transmission of risk of postpartum haemorrhage.

**Study Design:** We linked birth records of women, their daughters and granddaughters in two Scottish birth cohorts: the Walker cohort (collected from 1952 to 1966) and the Scottish Morbidity Records cohort (collected from 1975 to present). We determined clinical risk factors for PPH. We then quantified the risk of PPH in women whose mothers/grandmothers had postpartum haemorrhage before and after adjustment for these risk factors.

**Results:** The risk of PPH in women whose mothers/grandmothers had PPH was no greater than in those whose mothers/grandmothers did not have PPH. Our study had sufficient (80%) power to detect an odds ratio (OR) of 1.3, should such an increase in odds associated with familial history exist. In contrast, the adjusted ORs conferred by nulliparity, having a large baby, Caesarean section and genital tract trauma were 1.47, 1.84, 8.20 and 9.61 respectively.

**Conclusion:** Women whose mothers/grandmothers had PPH do not appear to be at increased risk themselves. We confirmed an increased risk of PPH associated with nulliparity, delivering a large baby, caesarean section and genital tract trauma. We were unable to demonstrate an effect of intergenerational transmission of PPH, although our study was underpowered to detect an OR less than 1.3. Thus we confirm that any risk conferred by familial history, should it exist, is less than that conferred by factors in the index pregnancy itself.

**Keywords:**

Birth cohort, epidemiology, intergenerational transmission, postpartum haemorrhage, record linkage.

## Introduction

Postpartum haemorrhage (PPH) is widely defined as ≥500ml blood loss from the genital tract in the first 24 hours after childbirth. It is the leading cause of maternal death worldwide, occurring in around 7-26% of all deliveries[1] and contributing to the deaths of an estimated 125,000 women each year.[2] The annual incidence of PPH appears to be rising steadily, even in high resource countries.[3] Known risk factors, causes and consequences of PPH are summarised in Figure 1, however the aetiology is often unclear and PPH may occur in women with no identifiable risk factors. PPH can be associated with a failure of the uterus to contract adequately after birth (atonic PPH; 90% of cases), trauma to the genital tract (traumatic PPH; 7% of cases), or bleeding due to retention of placental tissue or failure in the coagulation system (3% of cases).[4]

Previous PPH is a significant risk factor for subsequent PPH, with several studies finding women two to three times more likely to have PPH in their second pregnancy if they had PPH in their first.[5–8] If individual women are at increased risk, it is possible that this predisposition could be heritable, but to our knowledge no studies have previously addressed this. Understanding the biological and potentially heritable basis to PPH could be useful in understanding the aetiology of this important obstetric complication and developing better predictive and preventive tools. Additionally, it would help in the counselling of pregnant women, who are often aware of their family history of pregnancy related adverse events, including PPH.

We used Scottish population data in which quality and consistency has previously been confirmed, and where database linkage is possible. This allowed patient-based analysis and analysis of intergenerational transmission over three generations of women.

## Methods

### Record Linkage

Since the 1970's, people living in Scotland have been allocated a unique Community Health Identification (CHI) number, which allows record linkage across clinical databases and generations. We used the CHI number to record-link between the Walker Cohort and Scottish Morbidity Records maternity admissions data (SMR02). Data were provided and by the Health Informatics Centre (HIC) at the University of Dundee. The Information Services Division (ISD) Scotland provide SMR02 data to HIC. All data were anonymised prior to analyses.

### *The Walker Cohort*

The Walker cohort is a dataset of 48404 birth records that contains meticulously recorded details of pregnancy, labour and care before discharge for births in hospital in Dundee, Scotland between 1952 and 1966. The details of the Walker cohort have been previously published and will not be repeated here,[9] but there is information about PPH stored as a dichotomous variable for Walker births occurring between 1952-58. Information on later births was recorded on different cards that did not include details of PPH. The criteria used to define PPH is not described for the Walker cohort, but we have assumed it to be ≥500ml blood loss in the first 24 hours following delivery, as diagnosed by the doctor or midwife assessing the patient.

Maternities recorded in the Walker cohort account for 75% of all births in Dundee at this time. 34183 (73%) of these babies can be identified through their CHI number, and this presents the

opportunity to link this maternity or birth information with a large number of current health-outcome datasets covering both primary and secondary care for Walker mothers and babies.

*Scottish Morbidity Records – SMR02*

The Scottish Morbidity Records 02 (SMR02) dataset contains detailed information on hospital maternity admissions in Scotland collected from January 1975 to present. Outcomes are coded according to the International Classification of Diseases (ICD9 and ICD10). Table 1 shows the codes used to indicate PPH as an outcome. Again, we assume these codes were assigned based on observation of blood loss ≥500ml in the first 24 hours following delivery.

*The Generations*

We identified data on three generations of women, defined as follows:

- Generation 1 - Walker Mothers – Women who appear in the Walker cohort as mothers.
- Generation 2 - SMR02 Mothers – Women who appear in the Walker cohort as babies, and the SMR02 cohort as mothers.
- Generation 3 - SMR02 Daughters – Women who appear in the SMR02 cohort as babies, and also as mothers if they have had children themselves.

Data analysis

In SMR02, maternity admissions that were coded as not resulting in delivery of a child were removed. Stillbirths of a baby >500g were included.

We used IBM SPSS Statistics version 19 (IBM Corp., Armonk NY), to perform a univariate analysis of the pooled (Walker and SMR02) data. We calculated unadjusted odds ratios to assess the effects of each of: PPH in a previous pregnancy, multiple pregnancy, high birth weight (using the World Health Organisation (WHO) definition of ≥4kg), low birth weight (using the WHO definition of <2.5kg), maternal age under 20-years-old (previously identified as a risk factor for PPH[10]), maternal age over 40-years-old (previously identified as a risk factor for PPH[10]), parity, preterm birth (using the WHO definition of ≤37 weeks' gestation), post-term birth (using the WHO definition of ≥42 weeks' gestation), delivery by caesarean section, instrumental delivery and smoking status on risk of PPH in the index pregnancy. To calculate adjusted odds ratios, we built factors identified as significant in the univariate analyses into a multivariate logistic regression model using function glm() in the R package lme4[11] (R version 2.15.1[12]).

To assess intergenerational transmission of PPH, we used the CHI number to link records across generations as follows:

- Generation 1 was linked to Generation 2
- Generation 2 was linked to Generation 3
- Generation 1 was linked to Generation 3
- Pooled mother-daughter analysis: mothers from Generations 1 and 2 were linked to daughters in Generations 2 and 3.

To analyse intergenerational trends in PPH for each of these comparisons, we first calculated unadjusted odds ratios using logistic regression model, again using glm() in R package lme4.[11] These models assess the relationship between PPH in the younger generation (the dependent variable) and PPH in the older generation (the independent variable) without taking into account any other potential covariates. We then used function glmer() in R package lme4[11] to build generalised linear mixed models (GLMMs) using a binomial distribution with a logit link. These models incorporated any other covariates found to be significantly associated with PPH in the univariate analyses. The models also adjust for the 'random effects' introduced through the appearance of the same women in different mother-daughter/grandmother-granddaughter pairs (for example a woman could be a mother in the comparison of generations 2 and 3, but a daughter in the comparison in generations 1 and 2. Additionally, one woman could be a mother to more than one daughter). It is important to adjust for this non-independence, because it invalidates the assumptions of many statistical tests and can introduce bias that can mask exposure effects. Where we suspected low power, we used function fe.mdor() in the R package clinfun[13] to calculate the smallest effect size that our analyses would have been able to detect at 80% power based on our actual sample sizes.

**Results**

Figure 2 outlines how records were linked in this study and the number of records used in the final analysis.

The overall prevalence of PPH (1089/25322, 4.3%) was similar in both the Walker (176/3847, 4.6%) and SMR02 (913/21475, 4.3%) cohorts. 82.3% (751) of cases of PPH in SMR02 deliveries were caused by uterine atony. PPH was diagnosed as delayed or secondary in 8.9% (81) of SMR02 cases and associated with retained placenta (third stage) in 8.4% (77). Coagulation defect was the least common recorded cause of PPH (0.4%, 4 cases).

In univariate analyses of data pooled from Walker and SMR02 (Table 2), multiple pregnancy, baby birth weight over 4kg, maternal age over 40-years, preterm gestation ≤37 weeks, caesarean delivery, nulliparity, genital trauma/episiotomy and smoking during pregnancy were significant risk factors for PPH (ORs ranging from 1.17 to 6.02). Delivery by forceps or ventouse was associated with a small but significant lower risk of PPH. There were insufficient data on PPH in a previous pregnancy to determine if this was a risk factor for PPH in a subsequent pregnancy.

A logistic regression model incorporating significant risk factors from the univariate analysis allowed us to adjust for confounding and revealed that large birth weight, caesarean delivery, nulliparity and genital trauma/episiotomy were significant independent risk factors for PPH (adjusted ORs ranging from 1.47 to 9.61). After these adjustments (particularly for multiple pregnancy and Caesarean section, which are significant confounders), delivery at ≤37 weeks was associated with a significant decreased risk of PPH (OR 0.63 95% CI 0.55-0.97).

Table 3 shows that there is a small increased risk of PPH in women whose mothers and/or grandmothers had PPH across generations 1-2 and 1-3, but this trend did not reach statistical significance. Comparisons of generations 2 and 3 and pooling of mother and daughter comparisons showed a reverse trend, i.e a trend to a protective effect of maternal PPH on the risk of PPH in the daughter. GLMMs were used to adjust for non-independence between related mother-daughter pairs and most risk factors identified as significant by the multivariate analysis (delivery by caesarean

section was excluded due to incomplete data). These analyses again confirmed no statistically significant effect of maternal PPH on the risk of PPH in the daughter. These intergenerational analyses had 80% power at an alpha of 0.05 to detect the following odds ratios: 2.1 for generation 1 linked to generation 2; 1.3 for generation 2 linked to generation 3; 2.1 for generation 1 linked to generation 3; and 1.3 for the pooled mother to daughter analysis. Thus we can be reasonably confident that any intergenerational effect of maternal PPH, should it exist, increases the odds of PPH in the daughter by less than 1.3.

**Comment**

To our knowledge, this is the first attempt to investigate the intergenerational transmission of PPH. Our analyses do not support a large increased risk of PPH for women whose mothers/grandmothers had PPH. We identified caesarean delivery, genital trauma or episiotomy, high birth weight and nulliparity as risk factors for PPH, thus confirming the results of previous studies.[7,10,14–16] In particular, the odds of PPH in nulliparous women (odds ratio 1.47) was very similar to that reported by Combs et al. (odds ratio 1.45).[7] In both the SMR02 and Walker cohorts, the prevalence of PPH (4.3% and 4.6%, respectively) was lower than that reported for other populations. In a meta-analysis of 104 datasets, Calvert et al.[1] showed that PPH prevalence shows high regional variation, ranging from 7.2% in Oceania to 25.7% in Africa. In Europe, they found a prevalence of 12.7%, which is similar to the 13.2% incidence reported in the NHS maternity records for England and Wales in 2011-12.[17] However, the authors also found that the prevalence depends strongly on the method of diagnosis of PPH, with a subjective measurement of blood loss resulting in a lower prevalence compared to an objective measurement. A subjective measure is likely to have been used for the SMR02 and Walker cohorts, which may explain the relatively low prevalence of PPH in these datasets. Some authors have argued that the traditional definition of PPH is of little clinical relevance and should be revised so that PPH can be measured more easily and the diagnosis considers differences between individual patients.[18,19] For example, some authors have suggested PPH may be better defined by a fall in haematocrit or percentage of total blood.[20] Similarly, some authors have argued that using a definition of ≥500ml blood loss overestimates the prevalence of PPH associated with any increased risk of mortality or morbidity for the patient. Pritchard et al. found that 500ml is the average blood loss for a vaginal delivery, with 7% of women losing ≥1000ml of blood after vaginal delivery.[19] They identified the average blood loss for a caesarean delivery as ≥1000ml. Therefore it could be argued that using a definition of blood loss ≥500 ml for both vaginal and caesarean deliveries will result in an overestimation of the number of cases of PPH, especially following caesarean deliveries.[21] In SMR02 and Walker, PPH was recorded as a dichotomous variable with no information on the volume of blood loss postpartum, therefore we were unable to assess the clinical relevance of any of the cases of PPH. However, we do not consider this to be a major limitation of our study because PPH was diagnosed subjectively by trained doctors and midwives with experience of "clinically relevant" cases. In our study there were too few cases to perform subgroup analyses on vaginal and caesarean deliveries, although we did identify caesarean section as one of the strongest independent risk factors for PPH and adjusted for caesarean section in our multivariate analyses, where possible. In contrast to previous studies,[22–25] we saw no significant change in the prevalence of delivery by Caesarean section over time in either cohort. Therefore it is unlikely that between-generation differences in the Caesarean prevalence is masking any real trends in our data.

For SMR02 only, data were available on the cause or type of PPH through ICD codes. The data quality of SMR02 and Walker was not formally assessed for the purposes of this project, however previous studies have validated these datasets, including confirmation of a low error rate in the recording of ICD diagnostic codes in SMR02.[9,26–28] Therefore, we believe that the ICD coding used to identify cases of PPH is robust and any error in coding is not likely to introduce substantial bias. In line with previous studies,[10,29,30] the most frequent cause of PPH was uterine atony (82.3% of cases in SMR02), which prevents constriction of blood vessels during placental separation. Unfortunately there were insufficient data to analyse risk factors for different types of PPH individually. This is a limitation of our study, as we recognise that the different aetiologies of PPH, particularly coagulation defects, may be associated with different risk factors, including family history. We decided to include in our analyses the 4 women from SMR02 with PPH associated with coagulation defects because similar cases are likely to be included in the Walker cohort and it would have been impossible to identify and exclude these cases in this dataset.No previous reports have investigated family history of PPH as a risk factor for PPH. The historical Walker data linked to the more recent SMR02 data presented a unique opportunity to do this. SMR02 data collection began in 1975, so we were able to make the same comparison within this dataset. Special consideration was given to the appearance of the same women in more than one mother-daughter/grandmother-granddaughter pair. This is further complicated by the tendency for women to experience PPH in repeat pregnancies.[5–8] This non-independence invalidates the assumptions of many statistical tests and can lead to spurious conclusions. One option for dealing with this "clustering" is to restrict analysis to one pregnancy per woman (for example, the first pregnancy). However, this reduces statistical power and ignores a lot of potentially important information. It also changes the definition of the study population from "all births within the dataset" to "all first births within the dataset", so it may not be possible to generalise the results to "all births".[31] Another possible tactic is to include data on all pregnancies and ignore the non-independence. We used this approach to calculate our "unadjusted odds ratios" for intergenerational transmission of PPH. However, this will lead to incorrect standard errors and potentially incorrect conclusions. Therefore, we used a mixed model in our final, multivariate analysis to adjust for both covariates (fixed effects) and within-woman clustering (random effects). This protects against bias and allows us to estimate the size of the effect introduced by this clustering.[31]

We showed no significant association between PPH in the mother and the odds of PPH in daughters. Our study had 80% power to detect an OR of 1.29 for maternal influence on PPH in the daughter. This is a lower OR than conferred by birthweight > 4.0kg and nulliparity (1.87 and 1.47 respectively) and very much lower than conferred by maternal Caesarean section and genital tract trauma (8.20 and 9.61 respectively). Thus any effect of the pregnant woman's maternal history of PPH is (if it exists) much less significant than those of the index pregnancy. These data contrast with the known intergenerational transmission of pre-eclampsia and of preterm delivery.[32,33] Pregnant women whose mothers had PPH can be reassured that they are unlikely to be at any significantly increased risk, compared to those whose mothers did not have PPH.

**Conclusion**

The results have confirmed several statistically significant risk factors for PPH. They also suggest that women whose mothers/grandmothers had PPH are not at an increased risk themselves.

**Acknowledgments**

We acknowledge the support of the Health Informatics Centre, University of Dundee for managing and supplying the anonymised data and NHS Tayside, the original data source. Special thanks go to Professor Graham Horgan of Biostatistics Scotland for statistical advice and comments on the manuscript. We are also grateful to Daniel Ayoubkhani of the Office for National Statistics for statistical advice.

**References**

1. Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V. Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. *PloS one*. 2012;7(7):e41114.

2. Selo-Ojeme DO. Primary postpartum haemorrhage. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*. 2002;22(5):463–9.

3. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC pregnancy and childbirth*. 2009;9:55.

4. Carroli G, Cuesta C, Abalos E, Gulmezoglu a M. Epidemiology of postpartum haemorrhage: a systematic review. *Best practice & research. Clinical obstetrics & gynaecology*. 2008;22(6):999–1012.

5. Ford JB, Roberts CL, Bell JC, Algert CS, Morris JM. Postpartum haemorrhage occurrence and recurrence: a population-based study. *The medical journal of Australia*. 2007;187(7):391–3.

6. Magann EF, Evans S, Hutchinson M, Collins R, Howard BC, Morrison JC. Postpartum hemorrhage after vaginal birth: an analysis of risk factors. *Southern medical journal*. 2005;98(4):419–22.

7. Combs CA, Murphy EL, Laros RK. Factors associated with postpartum hemorrhage with vaginal birth. *Obstetrics and gynecology*. 1991;77(1):69–76.

8. Hall MH, Halliwell R, Carr-Hill R. Concomitant and repeated happenings of complications of the third stage of labour. *British journal of obstetrics and gynaecology*. 1985;92(7):732–8.

9. Libby G, Smith A, McEwan NF, et al. The Walker Project: a longitudinal study of 48,000 children born 1952-1966 (aged 36-50 years in 2002) and their families. *Paediatric and perinatal epidemiology*. 2004;18(4):302–12.

10. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesthesia and analgesia*. 2010;110(5):1368–73.

11. Bates D, Maechler M, Bolker B. lme4: Linear mixed-effects models using S4 classes. R package. 2012.

12. R Development Core Team. R: A language and environment for statistical computing. 2011.

13. Venkatraman ES. clinfun: Clinical Trial Design and Data Analysis Functions. R package. 2013.

14. Sosa CG, Althabe F, Belizán JM, Buekens P. Risk factors for postpartum hemorrhage in vaginal deliveries in a Latin-American population. *Obstetrics and gynecology*. 2009;113(6):1313–9.

15. Sheiner E, Sarid L, Levy A, Seidman DS, Hallak M. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*. 2005;18(3):149–54.

16. Brinsden PR, Clark AD. Postpartum haemorrhage after induced and spontaneous labour. *British medical journal*. 1978;2(6141):855–6.

17. National Health Service. Hospital Episode Statistics: NHS Maternity Statistics, 2011-12. *The Health and Social Care Information Centre*. 2012.

18. Andersen HF, Hopkins MP. Postpartum Hemorrhage. *The Global Library of Women's Medicine*. 2009.

19. Pritchard J, Baldwin R, Dickey J, Wiggins K. Blood volume changes in pregnancy and the puerperium: 2. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery cesarean section and cesarean section plus total hysterectomy. *American Journal of Obstetrics and Gynecology*. 1962;84(10).

20. Nelson GH. Consideration of blood loss at delivery as percentage of estimated blood volume. *American journal of obstetrics and gynecology*. 1980;138(8):1117–9.

21. Cameron M, Robson S. Vital Statistics: an overview. In: B-Lynch C, Keith LG, Lalonder AB, Karoshi M, eds. *A Textbook of PostPartum Hemorrhage*. Dumfrieshire: Sapiens Publishing; 2006.

22. Anderson GM, Lomas J. Determinants of the increasing cesarean birth rate. Ontario data 1979 to 1982. *The New England journal of medicine*. 1984;311(14):887–92.

23. Macfarlane A, Chamberlain G. What is happening to caesarean section rates? *Lancet*. 1993;342(8878):1005–6.

24. Treffers PE, Pel M. The rising trend for caesarean birth. *BMJ (Clinical research ed.)*. 1993;307(6911):1017–8.

25. Notzon FC, Placek PJ, Taffel SM. Comparisons of national cesarean-section rates. *The New England journal of medicine*. 1987;316(7):386–9.

26. Murphy DJ, Libby G, Chien P, Forsyth S, Greene S, Morris A. Cohort study of forceps delivery and the risk of epilepsy in adulthood. *American journal of obstetrics and gynecology*. 2004;191(2):392–7.

27. Norman JE, Morris C, Chalmers J. The effect of changing patterns of obstetric care in Scotland (1980-2004) on rates of preterm birth and its neonatal consequences: perinatal database study. *PLoS medicine*. 2009;6(9):e1000153.

28. Smith GC, Pell JP, Bobbie R. Caesarean section and risk of unexplained stillbirth in subsequent pregnancy. *The Lancet*. 2003;362(9398):1779–1784.

29. Oyelese Y, Ananth C V. Postpartum hemorrhage: epidemiology, risk factors, and causes. *Clinical obstetrics and gynecology*. 2010;53(1):147–56.

30. Lutomski JE, Byrne BM, Devane D, Greene R a. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. *BJOG : an international journal of obstetrics and gynaecology*. 2012;119(3):306–14.

31. Louis GB, Dukic V, Heagerty PJ, et al. Analysis of repeated pregnancy outcomes. *Statistical methods in medical research*. 2006;15(2):103–26.

32. Bhattacharya S, Raja EA, Mirazo ER, et al. Inherited predisposition to spontaneous preterm delivery. *Obstetrics and gynecology*. 2010;115(6):1125–33.

33. Mogren I, Högberg U, Winkvist A, Stenlund H. Familial occurrence of preeclampsia. *Epidemiology (Cambridge, Mass.)*. 1999;10(5):518–22.

346 **Tables**

| **Table 1. International Classification of Diseases (ICD) 9 and 10 codes used to identify postpartum haemorrhage (PPH) in SMR02 birth records.** | | |
|---|---|---|
| **Cause of PPH** | **ICD-9 code** | **ICD-10 code** |
| Third stage (associated with retained, trapped or adherent placenta) | 666.0 | O72.0 |
| Atonic (after placenta delivery) | 666.1 | O72.1 |
| Delayed and secondary PPH (associated with retained portions of placenta) | 666.2 | O72.2 |
| Coagulation defects | 666.3 | O72.3 |

347

348
349

| **Table 2. Analysis of risk factors associated with postpartum haemorrhage.** | | | | | |
|---|---|---|---|---|---|
| **Risk factor** | **(A) Number of births with information on PPH and risk factor** | **(B) Number of births with PPH (% of column A)** | **(C) Number of births with PPH where risk factor is present (% of column B)** | **Unadjusted odds ratio* (95% confidence interval)** | **Adjusted† odds ratio* (95% confidence interval)** |
| Multiple pregnancy | 25322 | 1089 (4.3%) | 58 (5.3%) | 2.09 (1.59 to 2.76) | 1.87 (0.77 to 4.53) *ns* |
| Low birth weight (≤2.5kg) | 24935 | 1059 (4.2%) | 81 (7.6%) | 1.11 (0.88 to 1.39) *ns* | n/a |
| High birth weight (≥4kg) | 24935 | 1059 (4.2%) | 199 (18.8%) | 2.37 (2.02 to 2.78) | 1.84 (1.27 to 2.67) |

| | | | | | |
|---|---|---|---|---|---|
| Maternal age ≤20-years-old | 20207 | 1015 (5.0%) | 136 (13.4%) | 1.34 (1.12 to 1.62) | 1.13 (0.77 to 1.65) *ns* |
| Maternal age ≥40-years-old | 20207 | 1015 (5.0%) | 44 (4.3%) | 2.73 (1.98 to 3.77) | 1.32 (0.73 to 2.38) *ns* |
| Nulliparity | 25293 | 1085 (4.3%) | 541 (49.9%) | 1.17 (1.03 to 1.32) | 1.47 (1.10 to 1.98) |
| Preterm birth (≤37 weeks' gestation) | 23741 | 1003 (4.2%) | 127 (12.7%) | 1.33 (1.1 to 1.61) | 0.63 (0.41 to 0.97) *ns* |
| Postterm birth (≥42 weeks' gestation) | 23741 | 1003 (4.2%) | 81 (8.1%) | 0.79 (0.63 to 1.00) *ns* | n/a |
| Delivery by caesarean section† | 3872 | 471 (12.2%) | 283 (60.1%) | 6.02 (4.92 to 7.38) | 8.20 (6.19 to 10.86) |
| Instrumental delivery (forceps or ventouse) | 3872 | 471 (12.2%) | 21 (4.5%) | 0.42 (0.27 to 0.66) *ns* | n/a |
| Genital trauma or episiotomy | 18890 | 885 (4.7%) | 25 (2.8%) | 1.61 (1.07 to 2.44) | 9.61 (2.15 to 43.02) |
| Mother smoked during pregnancy | 8833 | 573 (6.5%) | 140 (24.4%) | 1.40 (1.15 to 1.71) | 0.79 (0.57 to 1.08) *ns* |

*ns*: non significant.

* ratio of the odds of a birth being affected by PPH when the risk factor is present to the odds of a birth being affected by PPH when the risk factor is absent.

†adjusted for all factors identified as significant in the univariate (anadjusted) analysis.

**Table 3. Analysis of intergenerational trends in postpartum haemorrhage.**

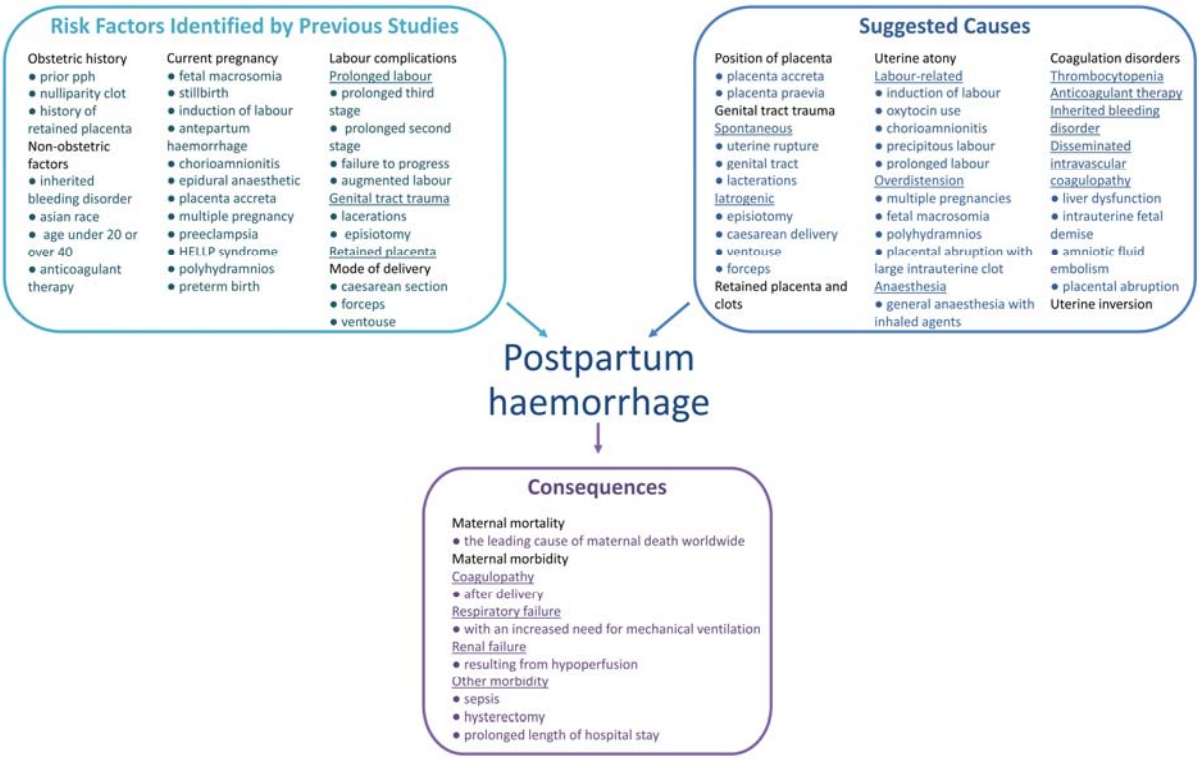
| Risk factor | (A) Number of linked births with information on PPH | (B) Number of linked births with PPH in younger generation (% of column A) | (C) Number of linked births with PPH in both generations (% of column B) | Unadjusted odds ratio (95% confidence interval) | Adjusted* odds ratio (95% confidence interval) |
|---|---|---|---|---|---|
| PPH in generation 1 as a risk factor for PPH in generation 2 | 2543 | 49 (1.9%) | 3 (6.1%) | 1.32 (0.41 to 4.32) | 1.20 (4.83e-3 to 296.0) |
| PPH in generation 2 as a risk factor for PPH in generation 3 | 2464 | 290 (11.8%) | 4 (1.4%) | 0.68 (0.24 to 1.90) | 0.58 (8.0e-3 to 41.61) |
| PPH in generation 1 as a risk factor for PPH in generation 3 | 519 | 65 (12.5%) | 6 (9.2%) | 2.21 (0.85 to 5.72) | 1.33 (9.43e-5 to 1.88e+4) |
| PPH in mothers as a risk factor for PPH in daughters (pooled analysis) | 5007 | 339 (6.8%) | 7 (2.1%) | 0.59 (0.27 to 1.27) | 0.69 (0.06 to 7.62) |

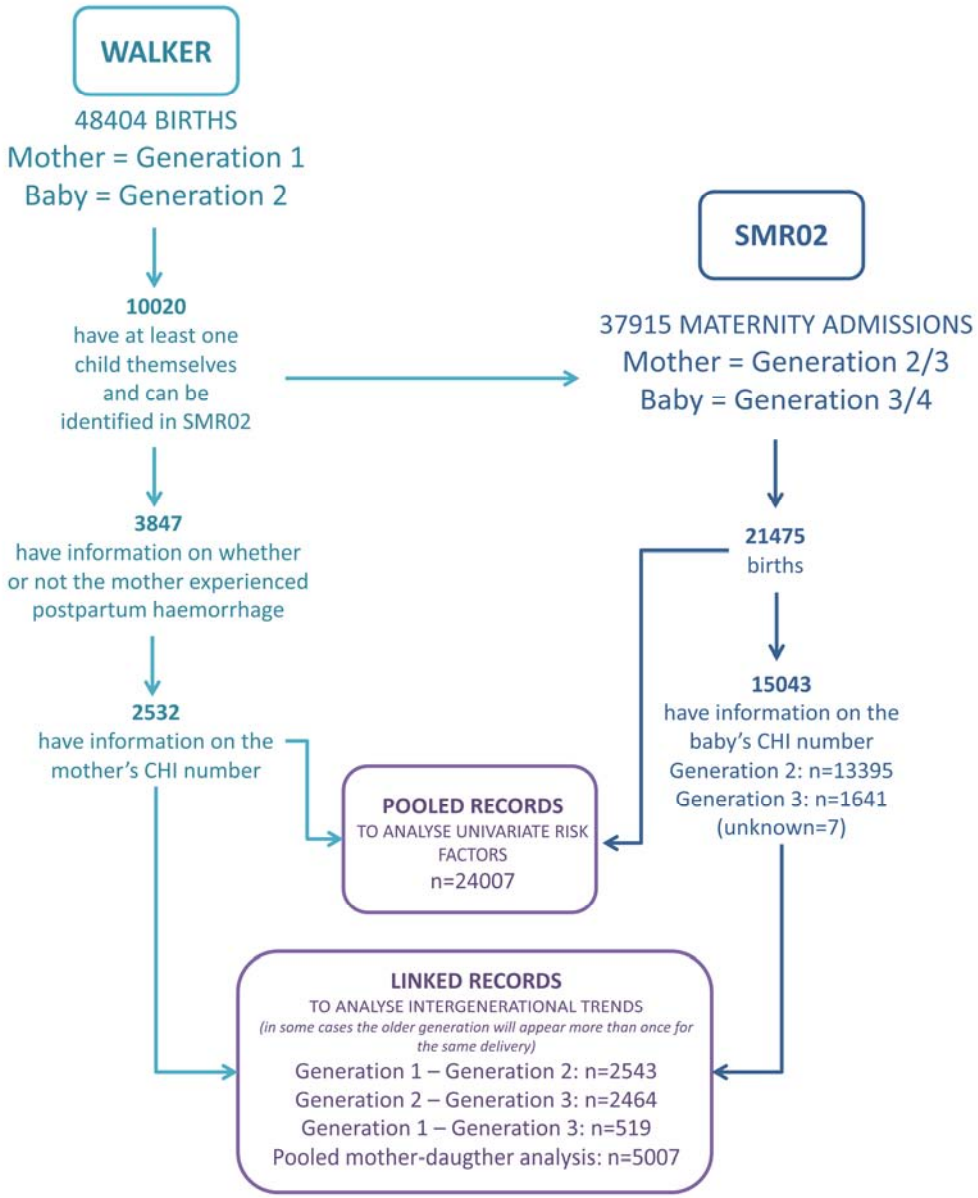
*calculated using a generalised linear mixed model to adjust for the non-independence between linked births and risk factors identified as significant in the multivariate analysis (excluding delivery by caesarean section because of incomplete data).

**Figure legends**

Figure 1. Causes, risk factors and consequences of postpartum haemorrhage, as identified previously.

Figure 2. Method of record linkage and number of records analysed.




WALKER
48404 BIRTHS
Mother = Generation 1
Baby = Generation 2
10020
have at least one child themselves and can be identified in SMR02
3847
have information on whether or not the mother experienced postpartum haemorrhage
2532
have information on the mother's CHI number
SMR02
37915 MATERNITY ADMISSIONS
Mother = Generation 2/3
Baby = Generation 3/4
21475
births
15043
have information on the baby's CHI number
Generation 2: n=13395
Generation 3: n=1641
(unknown=7)
POOLED RECORDS
TO ANALYSE UNIVARIATE RISK FACTORS
n=24007
LINKED RECORDS
TO ANALYSE INTERGENERATIONAL TRENDS
(in some cases the older generation will appear more than once for the same delivery)
Generation 1 – Generation 2: n=2543
Generation 2 – Generation 3: n=2464
Generation 1 – Generation 3: n=519
Pooled mother-daugther analysis: n=5007

W13-0897_SUM_Sharp_Intergen PPH Scottish_10dec13mr.docx

Obstetrics

# Intergenerational transmission of postpartum hemorrhage risk: analysis of 2 Scottish birth cohorts

Gemma C. Sharp, PhD; Philippa T. K. Saunders, PhD; Stephen A. Greene, MD; Andrew D. Morris, MD; Jane E. Norman, MD

From the MRC Center for Reproductive Health, University of Edinburgh, Edinburgh (Dr Sharp, Profs Saunders and Norman), and Tayside Children's Hospital (Prof Greene) and the Center for Molecular Medicine, Clinical Research Center (Prof Morris), Ninewells Hospital and Medical School, University of Dundee, Dundee, Scotland, UK.

J.E.N. has received research grants from charities and governmental bodies for studies on understanding parturition and prevention of preterm parturition. On behalf of the University of Edinburgh, she has done some consultancy work for a small drug company interested in agents to prevent preterm parturition. In addition, she has received a lecture fee from an overseas academic institution for a lecture on preterm birth. The other authors report no conflict of interest.

This work was supported by the University of Edinburgh Principal's Research Fund, which

cofunded a PhD studentship for G.C.S.; the Albert McKern Bequest; and Tommy's, the Baby Charity

.

Abstract will be inserted.

**Background and Objective**

Postpartum hemorrhage (PPH) is widely defined as ≥500 mL blood loss from the genital tract in the first 24 hours after childbirth. It is the leading cause of maternal death worldwide, occurring in around 7-26% of all deliveries and contributing to the death of an estimated 125,000 women each year.

Understanding the biological and potentially heritable basis of PPH could be useful in understanding the etiology of this important obstetric complication and developing better predictive and preventive tools. In addition, it would help in the counseling of pregnant women, who are often aware of their family history of pregnancy-related adverse events, including PPH.

**Materials and Methods**

We used the CHI number to record-link between the Walker Cohort and Scottish Morbidity Records maternity admissions data (SMR02). The Walker cohort is a dataset of 48,404 birth records that contains meticulously recorded details of pregnancy, labor, and care before discharge for births in hospital in Dundee, Scotland, in 1952-1966.

Maternities recorded in the Walker cohort account for 75% of all births in Dundee at this time. Among these babies, 34,183 (73%) can be identified through their CHI number.

This presents the opportunity to link this maternity or birth information with a large number of current health outcome datasets covering both primary and secondary care for Walker mothers and babies.

The Scottish Morbidity Records 02 (SMR02) dataset contains detailed information on hospital maternity admissions in Scotland collected from January 1975 to the present. We identified data on 3 generations of women.

**Results**

The overall prevalence of PPH (1089/25,322, 4.3%) was similar in both the Walker (176/3847, 4.6%) and SMR02 (913/21,475, 4.3%) cohorts. Among cases of PPH in SMR02 deliveries, 82.3% (751) were caused by uterine atony. PPH was diagnosed as delayed or secondary in 8.9% (81) of SMR02 cases and associated with retained placenta (third stage) in 8.4% (77). Coagulation defect was the least common recorded cause of PPH (0.4%, 4 cases).

In univariate analyses of data pooled from Walker and SMR02, multiple pregnancy, baby birthweight over 4kg, maternal age over 40 years, preterm gestation ≤37 weeks, cesarean delivery, nulliparity, genital trauma/episiotomy, and smoking during pregnancy were significant risk factors for PPH (ORs ranging from 1.17 to 6.02). Delivery by forceps or ventouse was associated with a small but significant lower risk of PPH. There were insufficient data on PPH in a previous pregnancy to determine whether this was a risk factor for PPH in a subsequent pregnancy.

A logistic regression model incorporating significant risk factors from the univariate analysis allowed us to adjust for confounding and revealed that high birthweight, cesarean

delivery, nulliparity, and genital trauma/episiotomy were significant independent risk factors for PPH (adjusted ORs ranging from 1.47 to 9.61). After these adjustments (particularly for multiple pregnancy and cesarean section, which are significant confounders), delivery at ≤37 weeks was associated with a significant decreased risk of PPH (OR 0.63; 95% CI, 0.55-0.97).

Women whose mothers and/or grandmothers had PPH had a small increased risk of PPH across generations 1-2 and 1-3, but this trend did not reach statistical significance (Table). We can be reasonably confident that any intergenerational effect of maternal PPH, should it exist, increases the odds of PPH in the daughter by less than 1.3.

**Comment**

To our knowledge, this is the first attempt to investigate the intergenerational transmission of PPH. Our analyses do not support a large increased risk of PPH for women whose mothers/grandmothers had PPH. We identified cesarean delivery, genital trauma or episiotomy, high birthweight, and nulliparity as risk factors for PPH, thus confirming the results of previous studies.

Some authors have argued that the traditional definition of PPH is of little clinical relevance and should be revised so that PPH can be measured more easily and the diagnosis considers differences between individual patients. In SMR02 and Walker, PPH was recorded as a dichotomous variable with no information on the volume of blood loss postpartum; therefore, we were unable to assess the clinical relevance of any of the cases of PPH. However, we do not consider this to be a major limitation of our study because PPH was diagnosed subjectively by trained doctors and midwives with experience of “clinically

relevant" cases.

In line with previous studies, the most frequent cause of PPH was uterine atony (82.3% of cases in SMR02), which prevents constriction of blood vessels during placental separation. Unfortunately, data were insufficient to analyze risk factors for different types of PPH individually.

No previous reports have investigated family history of PPH as a risk factor for PPH. The historical Walker data linked to the more recent SMR02 data presented a unique opportunity to do this. Special consideration was given to the appearance of the same women in more than one mother-daughter/grandmother-granddaughter pair. This is further complicated by the tendency for women to experience PPH in repeat pregnancies. This nonindependence invalidates the assumptions of many statistical tests and can lead to spurious conclusions.

Therefore, we used a mixed model in our final, multivariate analysis to adjust for both covariates (fixed effects) and within-woman clustering (random effects). This protects against bias and allows us to estimate the size of the effect introduced by this clustering. We showed no significant association between PPH in the mother and the odds of PPH in daughters. Our study had 80% power to detect an OR of 1.29 for maternal influence on PPH in the daughter. This is a lower OR than conferred by birthweight >4.0 kg and nulliparity (1.87 and 1.47, respectively) and very much lower than conferred by maternal cesarean section and genital tract trauma (8.20 and 9.61, respectively). Thus any effect of the pregnant woman's maternal history of PPH is (if it exists) much less significant than those of the index pregnancy.

**CLINICAL IMPLICATIONS**

• Pregnant women whose mothers experienced postpartum hemorrhage (PPH) can be reassured that they are unlikely to be at any significantly increased risk compared to those whose mothers did not experience PPH.

[Insert Table 3. Analysis of intergenerational trends in postpartum hemorrhage]