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Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously

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Hypertensive disorders of pregnancy and outcomes of persistent postpartum haemorrhage: a cohort study

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(submitted)

Abstract

Background Hypertensive disorders of pregnancy have been associated with postpartum hemorrhage, but it is unclear whether women with persistent postpartum hemorrhage and concurrent hypertensive disorders of pregnancy are also at increased risk of adverse maternal outcome associated with severe bleeding. The objective was to assess whether women with persistent postpartum hemorrhage and concurrent hypertensive disorders of pregnancy are at increased risk of maternal mortality, arterial embolization or hysterectomy to stop bleeding, as compared with women with persistent postpartum hemorrhage without concurrent hypertensive disorders of pregnancy.

Methods From a Dutch cohort of women with postpartum hemorrhage that received either ≥4 units of red blood cells or a multicomponent transfusion, we selected women with persistent postpartum hemorrhage. Persistent postpartum hemorrhage was defined as hemorrhage refractory to initial measures to stop bleeding. Adverse maternal outcome was a composite of maternal mortality, and arterial embolization or hysterectomy to stop bleeding. Associations were adjusted for patient and bleeding characteristics in multivariable analysis.

Results Out of 1260 women with persistent postpartum haemorrhage, 63 had concurrent chronic or gestational hypertension (5.0%) and 127 preeclampsia (10.1%). Adverse maternal outcomes occurred in 180 women (16.8%) with persistent postpartum haemorrhage without hypertensive disorders, in 5 women (7.9%) with concurrent hypertension and in 28 women (22.0%) with concurrent preeclampsia. Adjusted odds ratios were 0.3 (95% confidence interval 0.1-0.8) for women with hypertension and 1.8 (1.1-3.0) for women with preeclampsia.

Conclusion Our findings show an increased risk of haemorrhage-related adverse maternal outcome in women with persistent postpartum haemorrhage and concurrent preeclampsia, as compared with women without hypertensive disorders of pregnancy. This increased risk was not found for women with concurrent chronic or gestational hypertension.

Trial registration

Netherlands Trial Registry, http://www.trialregister.nl, identifier NTR4079.

Keywords

Adverse maternal outcome, postpartum hemorrhage, preeclampsia, maternal morbidity

Background

Obstetric haemorrhage poses a significant burden on women's health by being the principal cause of severe maternal morbidity and maternal mortality worldwide. It accounts for 27% of all maternal deaths, with severe postpartum haemorrhage as its main component. [1,2]

Interestingly, hypertensive disorders of pregnancy, the second most common cause of maternal death and severe maternal morbidity, [1,2] have been identified as one of many risk factors for postpartum haemorrhage. Women with hypertensive disorders of pregnancy have been reported to have a 1.5-5 fold increased risk of postpartum haemorrhage when compared to women without hypertensive disorders. [3-11]

Mechanisms for this interaction are not fully understood, [7,11,12] in line with uncertainties in the pathogenesis of in particular preeclampsia. Angiogenic factors of the vascular endothelial growth factor family (VEGF) in maternal circulation may be a common pathway in the development of both preeclampsia and postpartum haemorrhage. In preeclampsia, placental soluble fms-like tyrosine kinase 1 (sFlt-1) and other antiangiogenic factors seem to be upregulated, antagonising angiogenic factors VEGF and placenta growth factor (PlGF). [13-16] Angiogenesis on its turn, is thought to be closely related to the hemostatic system and activation of clotting. [17,18] In addition, impaired coagulation may also be induced by HELLP syndrome, placental abruption and disseminated intravascular coagulation, known complications of severe preeclampsia, [19,20] thereby increasing the risk of excessive bleeding after delivery.

While the association between hypertensive disorders of pregnancy and postpartum haemorrhage emphasises the importance of active management of the third stage of labour to prevent postpartum haemorrhage especially in women with concurrent hypertensive disorders of pregnancy, the implication of this association for management of postpartum haemorrhage in these women is unclear. Issues to be resolved are whether or not the course of postpartum

haemorrhage in women with concurrent hypertensive disorders is more severe than in women without hypertensive disorders, and if so, whether and how the management of postpartum haemorrhage in these women should differ from women without concurrent hypertensive disorders of pregnancy in order to prevent adverse maternal outcomes.

We set out to assess whether women with persistent postpartum haemorrhage and concurrent hypertensive disorders of pregnancy are at increased risk of maternal mortality, arterial embolisation or hysterectomy to stop bleeding, as compared with women with persistent postpartum haemorrhage without concurrent hypertensive disorders of pregnancy.

Methods

Patients

For the present study, we used data from the TeMpOH-1 study, a retrospective cohort study in the Netherlands on transfusion strategies in women with major obstetric haemorrhage comprising consecutive women from 61 Dutch hospitals who, from 1 January 2011 to 1 January 2013, received either ≥4 units of red blood cells or a multicomponent blood transfusion within 24 hours following delivery because of postpartum haemorrhage (≥1000 mL blood loss). Patients were selected from transfusion databases and birth registries of participating hospitals.

From this cohort, we selected women with persistent postpartum haemorrhage. We defined persistent postpartum haemorrhage as ongoing postpartum haemorrhage within 24 hours following delivery exceeding 1000 mL of blood loss, that continued in spite of initial measures to stop bleeding.[21] Initial measures depended on primary cause of haemorrhage, and included uterine massage, oxytocin, misoprostol, methylergometrine, manual placenta removal and removal of placental remnants in case of uterine atony, retained placenta, genital tract trauma, placenta praevia or placental abruption as primary cause of postpartum haemorrhage. Women with an abnormally invasive placenta as

primary cause of postpartum haemorrhage, a surgical cause (including uterine rupture) or a congenital or acquired coagulation disorder were regarded as having persistent postpartum haemorrhage irrespective of the firstly applied therapy, as these complex haemorrhage s require a series of therapeutic measures to control bleeding.

Approval and a waiver of informed consent was obtained from the Medical Ethics Research Committee of Leiden University Medical Center (reference number P12.273), and from the institutional review board of each study center. The study was registered in the Netherlands Trial Register (NTR4079).

Data collection

We collected detailed information concerning pregnancy, delivery and the course of bleeding from routinely documented medical information of selected patients. Comprehensive chart reviews were uniformly performed by well-trained medical students and research nurses. At the end of data collection, the first author and two data managers checked all data for completeness and inconsistencies, and whenever necessary, on-site chart review was repeated.

Collected data included maternal and pregnancy characteristics, bleeding characteristics and all interventions during the course of haemorrhage to stop bleeding. Maternal characteristics included age, ethnicity, weight, height, comorbidity, and pregnancy characteristics included parity, gestational age, type and severity of hypertensive disorder of pregnancy, medication because of hypertensive disorder, mode of delivery and primary cause of postpartum haemorrhage. Bleeding characteristics included blood loss, bleeding rate and signs of haemorrhagic shock at the moment of diagnosis of persistent (ongoing) haemorrhage, volume of clear fluids for volume resuscitation, and all uterotonic, surgical, radiological and hemostatic interventions to stop bleeding.

Outcomes

Women were followed up until end of bleeding. Adverse maternal outcome was a composite of maternal mortality, arterial embolisation and hysterectomy

to stop bleeding. Secondary outcomes were total blood loss, number of units of packed red blood cells transfused and admission to intensive care unit.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy included chronic hypertension, gestational hypertension and preeclampsia, and were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) [22]. Hypertension was defined as blood pressure ≥140/90 mmHg, measured on two separate occasions. Chronic hypertension was defined as hypertension occurring before pregnancy or before 20 weeks of gestation. Gestational hypertension was defined as de novo blood pressure ≥140/90 mmHg occurring for the first time after 20 weeks of gestation. Preeclampsia was defined as gestational hypertension with proteinuria ≥300 mg/24h and/or clinical signs and symptoms of preeclampsia, or chronic hypertension with de novo proteinuria ≥300 mg/24h or clinical signs and symptoms of preeclampsia after 20 weeks of gestation (superimposed preeclampsia) [22,23].

Bleeding characteristics at time of diagnosis of persistent postpartum haemorrhage

In the Netherlands, volume of blood loss during postpartum haemorrhage is determined by weighing of gauzes, cloths and surgical swabs and measured with suction canisters. Estimation of the volume of blood loss at time of diagnosis of persistent postpartum haemorrhage was performed by linearly interpolating blood loss from time of delivery until end of bleeding, using available consecutive estimations of blood loss during haemorrhage. Haemorrhage was considered ongoing until the last estimation of blood loss of last obstetric intervention to stop bleeding.

Bleeding rate at time of diagnosis of persistent postpartum haemorrhage was calculated by dividing total blood loss up till that moment by the time interval from delivery till diagnosis of persistent postpartum haemorrhage. For patients with abnormally invasive placenta, surgical cause or coagulation disorder as primary cause of postpartum haemorrhage, baseline bleeding rate was assessed 5 minutes after diagnosis of persistent postpartum haemorrhage, as persistent postpartum haemorrhage was diagnosed at time of delivery for

these patients.

At least one measurement of systolic blood pressure ≤90 mmHg and/ or a heart rate ≥120 beats per minute from time of delivery to diagnosis of persistent postpartum haemorrhage were considered signs of haemorrhagic shock up till moment of diagnosis of postpartum haemorrhage [24].

Statistical analysis

The association of concurrent chronic or gestational hypertension and of preeclampsia with maternal mortality, arterial embolisation and hysterectomy to stop bleeding in women with persistent postpartum haemorrhage was modelled using logistic regression models. We adjusted these associations in multivariable models for the following predefined confounders: age (categories: <35 years / ≥35 years), ethnicity (Caucasian / other), parity (0 / ≥1), gestational age (< 37 weeks / ≥37 weeks), mode of delivery (vaginal / caesarean), cause of haemorrhage (uterine atony/retained placenta/ other), total volume of clear fluids for resuscitation (<4L / ≥4L), blood loss at moment of diagnosis of persistent postpartum haemorrhage (<1L, ≥1 to 2L, ≥2L), bleeding rate at moment of diagnosis of persistent postpartum haemorrhage (<1L/h, ≥1 to 2L/h, ≥2L/h) and signs of haemorrhagic shock at moment of diagnosis of persistent postpartum haemorrhage (no / yes). In case of missing values in confounding variables, we estimated these values by using multiple imputation techniques. In the imputation models we included confounding variables, outcome measures and variables associated with missing variables [25,26].

Results

Out of 1391 women with postpartum haemorrhage meeting the TeMpOH-1 inclusion criteria, we identified 1260 women as having persistent postpartum haemorrhage (figure 1). A total of 63 women (5.0%) with persistent postpartum haemorrhage had concurrent chronic or gestational hypertension and 127 women (10.1%) had been diagnosed with preeclampsia (table 1). Median age of included women was 32 years (interquartile range, IQR 28-35), most women were of Caucasian ethnicity (N = 903, 71.7%), and 657 women (52.1%) were

nulliparous. Delivery before 37 weeks of gestation was seen in 162 women (12.9%), and the mode of delivery was predominantly vaginal (N = 967, 76.7%). More women with persistent postpartum haemorrhage and concurrent hypertensive disorders of pregnancy were nulliparous (67.9 versus 49.3%) and delivered before gestational age 37 weeks (27.4 versus 10.3%). Postpartum haemorrhage was caused by uterine atony in 805 women (63.9%), and at moment of diagnosis of persistent postpartum haemorrhage median blood loss and bleeding rate was similar between women with and without hypertensive disorders of pregnancy (table 2). Signs of haemorrhagic shock at moment of diagnosis of persistent postpartum haemorrhage were present in 434 women (34.4%) and median volume of crystalloids and colloids for resuscitation was 3.0L (IQR 2.5-4.4L).

Adverse maternal outcome was seen in 213 women (16.9%): 7 maternal deaths (0.6%), 165 arterial embolisations (13.1%) and 64 hysterectomies (5.1%) (table 3). Arterial embolisation was performed in one woman (0.1%) who died due to postpartum haemorrhage, and hysterectomy in 3 women (0.2%) prior to death. In 19 women (1.5%) hysterectomy was necessary after arterial embolisation. A total of 180 adverse maternal outcomes (16.8%) occurred in women with persistent postpartum haemorrhage without concurrent hypertensive disorders of pregnancy, 5 (7.9%) in women with concurrent chronic or gestational hypertension and 28 (22.0%) in women with concurrent preeclampsia (table 3). Compared with women with persistent postpartum haemorrhage without hypertensive disorders, women with concurrent chronic or gestational hypertension did not have increased odds for adverse maternal outcomes (adjusted odds ratio 0.3 (95% confidence interval (CI) 0.1-0.8)), whereas women with concurrent preeclampsia did have significantly higher odds of adverse maternal outcomes (1.8 (1.1-3.0)). Women with preeclampsia were also more often admitted to the intensive care unit (adjusted odds ratio 1.9 (1.3-3.0)). Total blood loss and number of transfused units of packed red blood cells did not differ between women with and without hypertensive disorders of pregnancy.

Discussion

Main findings

In this nationwide cohort study comparing maternal outcomes in 1260 women with persistent postpartum haemorrhage with and without hypertensive disorders of pregnancy, concurrent preeclampsia was associated with more haemorrhage-related adverse maternal outcomes when compared with women without concurrent hypertensive disorders of pregnancy. In contrast, this risk of adverse maternal outcomes was relatively lower in women with persistent postpartum haemorrhage and concurrent chronic or gestational hypertension.

Strengths and Limitations

We carefully reconstructed the course of every postpartum haemorrhage in this large observational study. Therefore, there were no losses to follow up and primary outcome after haemorrhage was known for every woman who experienced postpartum haemorrhage.

A limitation of our study was the study population, that comprised a selection of women with severe haemorrhage and thus high risk of severe maternal morbidity. Our results are therefore only applicable to women with severe postpartum haemorrhage. Nonetheless, for this specific group of women, our findings indicate that concurrent preeclampsia contributes significantly to the risk of adverse maternal outcome, possibly because of altered coagulation.

The observation that women with concurrent chronic or gestational hypertension had fewer advanced procedures to stop bleeding than women without concurrent hypertension is somewhat counterintuitive but can be explained as follows. Our study comprises women with severe postpartum haemorrhage. Each of the included women inherently has a number of risk factors that caused the haemorrhage. The women who did not have chronic or gestational hypertension as risk factors probably had other, more serious risk factors, explaining the observed relatively higher number of advanced procedures to stop bleeding.

Additionally, we had a proportion of 25-30% of missing values in the confounding variables haemorrhagic shock and volume resuscitation in all three groups of women in our analyses, due to the retrospective design of our study. For multivariable analysis, we imputed these missing values rather than excluding these women, avoiding selection bias that would be introduced by exclusion of women due to missing values. However, we cannot rule out residual confounding due to these missing values.

Interpretation

Several studies reported on hypertensive disorders of pregnancy as a risk factor for developing postpartum haemorrhage [3-11]. The LEMMoN study, a preceding, nationwide cohort study on severe maternal morbidity in the Netherlands in the period 2004-2006, identified concurrent preeclampsia in 11.2% of women with major obstetric haemorrhage [27], comparable to the 10.1% of women with persistent postpartum haemorrhage and concurrent preeclampsia in this study. An Australian population-based study showed an increased risk of severe maternal morbidity in women with postpartum haemorrhage and hypertension, with odds ratio 1.3 (95% confidence interval 1.2-1.4) [28]. The association between adverse outcome in women with severe postpartum haemorrhage and concurrent preeclampsia was also described in a cohort study in Finland, that calculated a 6.9-fold increased risk (95% confidence interval 4.4-10.7) of severe maternal complications [29]. Our study not only confirms the association between severe postpartum haemorrhage with concurrent hypertensive disorders of pregnancy and advanced procedures to stop bleeding, but it also clearly shows that this association is fully explained by concurrent preeclampsia, and not concurrent chronic or gestational hypertension. In addition, we found this association in women with concurrent preeclampsia, despite a remarkably lower rate of hysterectomies in these women compared with women without hypertensive disorders of pregnancy. An explanation for this lower rate would be a more aggressive management of women with severe haemorrhage and concurrent preeclampsia.

The similar total blood loss and total units of transfused packed red blood

cells between women with severe postpartum haemorrhage with and women without concurrent hypertensive disorders also suggest a more aggressive treatment of women with preeclampsia. Women with preeclampsia have a relatively small circulating blood volume [30], and thus, are able to tolerate smaller volumes of blood loss than women without preeclampsia. As a result, arterial embolisations may be performed relatively early in the course of postpartum haemorrhage in women with preeclampsia than in women without preeclampsia, to avoid further deterioration in clinical condition.

Associations between concurrent preeclampsia and haemorrhage-related adverse maternal outcome in women with persistent postpartum haemorrhage, may also be explained by alterations in angiogenic factors in maternal circulation and by impaired coagulation caused by complications of severe preeclampsia. As upregulation of placental sFLT-1 is also seen in pregnancies complicated by intra-uterine growth restriction and small for gestational age infants [31,32], pro-active management of haemorrhage to avoid adverse maternal outcome might be advisable not only in women with concurrent preeclampsia, but perhaps in all women with disturbed placental function.

Over the last decades, much effort has been put into early timing of haemostatic interventions to stop bleeding in women with severe postpartum haemorrhage. Apart from tranexamic acid, effects on clinically relevant maternal outcomes have been disappointing or inconclusive[33-36]. In view of our results, personalised haemostatic interventions need further study especially in women with concurrent preeclampsia, because of their high risk of haemostatic impairment.

Conclusion

In conclusion, our findings show a significantly higher risk of adverse maternal outcome in women with persistent postpartum haemorrhage and concurrent preeclampsia, as compared with women without hypertensive disorders of pregnancy. This increase in risk was not seen in women with concurrent chronic or gestational hypertension. Therefore, particularly in women with

preeclampsia who develop severe postpartum haemorrhage, complications of bleeding should be anticipated and haemorrhage should be managed proactively to prevent severe maternal morbidity and mortality.

Declarations

Ethics Approval

The study was approved by the research ethics committee of the Leiden University Medical Center, Leiden, the Netherlands (reference number P12.273) on 31 January 2013. A waiver for informed consent was granted, and all data were anonymised before being received by the research team.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

None.

Authors' contributions

DH, KB, JZ, JR and JB were responsible for study concept and design. DH monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data. RG collected data and helped development of the data collection tool. DH and JB drafted and revised the paper. RG, KB, JL, JZ and JR critically reviewed the manuscript and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global health 2014;2:e323-33.

2. Zwart JJ, Dupuis JR, Richters A, Ory F, van Roosmalen J. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. Intensive care medicine 2010;36:256-63.

3. Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. BJOG : an international journal of obstetrics and gynaecology 2008;115:1265-72.

4. Buzaglo N, Harlev A, Sergienko R, Sheiner E. Risk factors for early postpartum hemorrhage (PPH) in the first vaginal delivery, and obstetrical outcomes in subsequent pregnancy. 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 Obstet 2015;28:932-7.

5. Combs CA, Murphy EL, Laros RK, Jr. Factors associated with hemorrhage in cesarean deliveries. Obstetrics and gynecology 1991;77:77-82.

6. Combs CA, Murphy EL, Laros RK, Jr. Factors associated with postpartum hemorrhage with vaginal birth. Obstetrics and gynecology 1991;77:69-76.

7. Eskild A, Vatten LJ. Abnormal bleeding associated with preeclampsia: a population study of 315,085 pregnancies. Acta obstetricia et gynecologica Scandinavica 2009;88:154-8.

8. Naef RW, 3rd, Chauhan SP, Chevalier SP, Roberts WE, Meydrech EF, Morrison JC. Prediction of hemorrhage at cesarean delivery. Obstetrics and gynecology 1994;83:923-6.

9. Nyflot LT, Sandven I, Stray-Pedersen B, et al. Risk factors for severe postpartum hemorrhage: a case-control study. BMC pregnancy and childbirth 2017;17:17.

10. 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 Obstet 2005;18:149-54.

11. von Schmidt auf Altenstadt JF, Hukkelhoven CW, van Roosmalen J, Bloemenkamp KW. Pre-eclampsia increases the risk of postpartum haemorrhage: a nationwide cohort study in the Netherlands. PloS one 2013;8:e81959.

12. Koopmans CM, van der Tuuk K, Groen H, et al. Prediction of postpartum hemorrhage in women with gestational hypertension or mild preeclampsia at term. Acta obstetricia et gynecologica Scandinavica 2014;93:399-407.

13. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. The Journal of clinical investigation 2003;111:649-58.

14. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annual review of pathology 2010;5:173-92.

15. Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. The New England journal of medicine 2006;355:992-1005.

16. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. The New England journal of medicine 2004;350:672-83.

17. Browder T, Folkman J, Pirie-Shepherd S. The hemostatic system as a regulator of

angiogenesis. The Journal of biological chemistry 2000;275:1521-4.

18. Dvorak HF. Angiogenesis: update 2005. Journal of thrombosis and haemostasis : JTH 2005;3:1835-42.

19. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A Review. BMC pregnancy and childbirth 2009;9:8.

20. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet (London, England) 2010;376:631-44.

21. Abdul-Kadir R, McLintock C, Ducloy AS, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion 2014;54:1756-68.

22. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy hypertension 2014;4:97-104.

23. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet (London, England) 2016;387:999-1011.

24. Evaluating the quality of care for severe pregnancy complications. The WHO near-miss approach for maternal health. 2011. (Accessed January 10, 2018, at Availabel at: http://www.who.int/reproductivehealth/publications/monitoring/9789241502221/en/.)

25. Janssen KJ, Donders AR, Harrell FE, Jr., et al. Missing covariate data in medical research: to impute is better than to ignore. JClinEpidemiol 2010;63:721-7.

26. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. JClinEpidemiol 2006;59:1092-101.

27. Zwart JJ, Richters JM, Ory F, de Vries JI, Bloemenkamp KW, van Roosmalen J. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. BJOG : an international journal of obstetrics and gynaecology 2008;115:842-50.

28. Roberts CL, Ford JB, Algert CS, Bell JC, Simpson JM, Morris JM. Trends in adverse maternal outcomes during childbirth: a population-based study of severe maternal morbidity. BMC pregnancy and childbirth 2009;9:7.

29. Pallasmaa N, Ekblad U, Gissler M, Alanen A. The impact of maternal obesity, age, pre-eclampsia and insulin dependent diabetes on severe maternal morbidity by mode of delivery-a register-based cohort study. Archives of gynecology and obstetrics 2015;291:311-8.

30. Ganzevoort W, Rep A, Bonsel GJ, de Vries JI, Wolf H. Plasma volume and blood pressure regulation in hypertensive pregnancy. Journal of hypertension 2004;22:1235-42.

31. Nevo O, Many A, Xu J, et al. Placental expression of soluble fms-like tyrosine kinase 1 is increased in singletons and twin pregnancies with intrauterine growth restriction. The Journal of clinical endocrinology and metabolism 2008;93:285-92.

32. Spiel M, Salahuddin S, Pernicone E, et al. Placental soluble fms-like tyrosine kinase expression in small for gestational age infants and risk for adverse outcomes. Placenta 2017;52:10-6.

33. Collins P, Abdul-Kadir R, Thachil J. Management of coagulopathy associated with postpartum hemorrhage: guidance from the SSC of the ISTH. Journal of thrombosis and haemostasis : JTH 2016;14:205-10.

34. Collins PW, Cannings-John R, Bruynseels D, et al. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. British journal of anaesthesia 2017;119:411-21.

35. Wikkelso AJ, Edwards HM, Afshari A, et al. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. British journal of anaesthesia 2015;114:623-33.

36. WOMAN_Trial_Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2017;389:2105-16.

Table 1. Pregnancy characteristics of women with persistent postpartum haemorrhage according to the presence or absence of hypertensive disorders of pregnancy

Pregnancy characteristics	Women without concurrent hypertensive disorders of pregnancy (N = 1070)	Women with concurrent chronic or gestational hypertension (N = 63)	Women with concurrent preeclampsia (N = 127)
Age – no. (%)			
< 35 years	776 (72.5)	43 (68.3)	90 (70.9)
≥ 35 years	293 (27.4)	20 (31.7)	37 (29.1)
Unknown	1 (0.1)	-	-
Ethnicity – no. (%)			
Caucasian	756 (70.7)	54 (85.7)	93 (73.2)
Other/unknown	314 (29.3)	9 (14.3)	34 (26.8)
Nulliparous – no. (%)	528 (49.3)	39 (61.9)	90 (70.9)
Gestational age – no. (%)			
<32 weeks	33 (3.1)	-	6 (4.7)
≥32- <37 weeks	77 (7.2)	4 (6.3)	42 (33.1)
≥37 weeks	952 (89.0)	59 (93.7)	79 (62.2)
Unknown	8 (0.7)	-	-
Location of delivery – no. (%)			
University hospital	136 (12.7)	12 (19.0)	31 (24.4)
Non-university hospital	770 (72.0)	49 (77.8)	93 (73.2)
Home birth	161 (15.0)	2 (3.2)	2 (1.6)
Unknown	3 (0.3)	-	1 (0.8)
Mode of delivery – no. (%)			
Vaginal	828 (77.4)	47 (74.6)	92 (72.4)
Caesarean	235 (22.0)	16 (25.4)	34 (26.8)
Unknown	7 (0.7)	-	1 (0.8)

Table 2. Bleeding characteristics of women *at moment of diagnosing* persistent postpartum haemorrhage according to the presence or absence of hypertensive disorders of pregnancy

Bleeding characteristics	Women without concurrent hypertensive disorders of pregnancy (N = 1070)	Women with concurrent chronic or gestational hypertension (N = 63)	Women with concurrent preeclampsia (N = 127)
Cause of haemorrhage – no. (%)			
Uterine atony	673 (62.9)	45 (71.4)	87 (68.5)
Retained placenta	190 (17.8)	11 (17.5)	18 (14.2)
Abnormally invasive placenta	99 (9.3)	2 (2.3)	12 (9.4)
Placenta Praevia	12 (1.1)	-	-
Placental abruption	10 (0.9)	-	2 (1.6)
Surgical bleeding	82 (7.7)	5 (7.9)	5 (3.9)
Pre-existent coagulation disorder	4 (0.4)	-	3 (2.4)
Blood loss – no. (%)			
<1L	583 (54.5)	39 (61.9)	61 (48.0)
≥1-2L	339 (31.7)	17 (27.0)	46 (36.2)
≥2L	145 (13.6)	7 (11.1)	20 (15.7)
Unknown	3 (0.3)	-	-
Bleeding rate – no. (%)			
<1L/hr.	470 (43.9)	24 (38.1)	62 (48.8)
≥1-2L/hr.	269 (25.1)	16 (25.4)	24 (18.9)
≥2L/hr.	327 (30.6)	23 (36.5)	41 (32.3)
Unknown	4 (0.4)	-	-
Signs of haemorrhagic shock – no. (%)			
No	358 (33.5)	22 (34.9)	54 (42.5)
Yes	371 (34.7)	23 (36.5)	38 (29.9)
Unknown	341 (31.9)	18 (28.6)	35 (27.6)
Volume of clear fluids for resuscitation – no. (%)			
<4L	498 (46.5)	21 (33.3)	66 (52.0)
≥4L	283 (26.4)	24 (38.1)	26 (20.5)
Unknown	289 (27.0)	18 (28.6)	35 (27.6)

Table 3. Maternal outcomes in women with persistent postpartum haemorrhage			
Outcome	**Women without concurrent hypertensive disorders of pregnancy**	**Women with concurrent chronic or gestational hypertension**	**Women with concurrent preeclampsia**
	(N = 1070)†	**(N = 63)**	**(N = 127)**
Adverse maternal outcome* – no. (%)	180 (16.8)	5 (7.9)	28 (22.0)
Arterial embolisation	136 (12.7)	3 (4.8)	26 (20.5)
Hysterectomy	62 (5.8)	1 (1.6)	1 (0.8)
Maternal death	4 (0.4)	1 (1.6)	2 (1.6)
Crude odds ratio	**1**	**0.4 (0.2-1.1)**	**1.4 (0.9-2.2)**
Adjusted odds ratio‡	**1**	**0.3 (0.1-0.8)**	**1.8 (1.1-3.0)**
Secondary outcomes			
Total blood loss – median (IQR)	3.0 (2.5-4.0)	3.0 (2.5-4.0)	3.0 (2.2-4.0)
Units of red blood cells transfused – median (IQR)	4 (3-6)	4 (3-5)	4 (3-6)
Admission on intensive care unit – no. (%)	298 (27.9)	14 (22.2)	50 (39.4)

CI denotes confidence interval, IQR denotes interquartile range.

*Multiple endpoints per patient possible.

†Reference category.

‡ Adjusted for: age (<35 / ≥35 years), ethnicity (Caucasian / other), parity (0 / ≥1), gestational age (<37 / ≥37 weeks), mode of delivery (vaginal / caesarean), cause of haemorrhage (uterine atony / retained placenta / other), volume of clear fluids for resuscitation (< 4 / ≥4L), at moment of diagnosis of persistent postpartum haemorrhage: blood loss (<1L / ≥1-2L / ≥2L), bleeding rate (<1L/h. / ≥1-2L/h. / ≥2L/h.), signs of haemorrhagic shock (no / yes).

Figure 1. Flow chart of women with persistent postpartum haemorrhage without concurrent hypertensive disorder of pregnancy, with concurrent chronic or gestational hypertension and with concurrent preeclampsia.