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Research Article

Factors associated with severe postpartum haemorrhage: systematic review using Bradford Hill's causality framework

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Background

Severe postpartum haemorrhage (S-PPH) is the leading cause of maternal death worldwide. We aimed to provide an up-to-date summary about S-PPH determinants.

Methods

We performed a systematic review following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines. We searched the terms “risk factor”, “determinant”, “post-partum haemorrhage” and “severe”, within Web of Science, Scopus, Science Direct, Medline, Cochrane, and Clinical [Trials.gov](http://trials.gov) databases. The primary endpoint was S-PPH, defined as a blood loss $\geq 1,000$ mL a second-line treatment, a PPH-related blood transfusion, a peripartum decrease in haemoglobin level or a PPH-related maternal death. All interventional and observational studies about risks factors for S-PPH published in English or French between January 1, 2004 and August 31, 2018 were eligible. Because studies used very different definitions of S-PPH, meta-analysis was ruled out and we gauged the risk factors using the Bradford Hill's criteria causality framework.

Results

Amongst 1,193 identified abstracts, we selected fourteen studies that collected information on 9,271,519 parturient women (35,825 with S-PPH). Key established determinants of S-PPH were previous PPH, previous caesarean, multiple pregnancy, abnormal placentation, preeclampsia, labour induction, prolonged labour, placental retention, uterine rupture, uterine atony, uterine fibroids, macrosomia, birth canal injuries, instrumental vaginal and caesarean deliveries. Most of associated factors of uncertain significance belonged to socio-environmental characteristics. Biological parameters were all classified as indicators of risk.

Conclusions

The key established determinants of S-PPH are of primarily obstetrical nature. New avenues of research, including contextual studies, are needed to improve the management of severe obstetrical morbidity.

Despite global effort to reduce maternal mortality, post-partum haemorrhage (PPH) is the leading cause of maternal death worldwide. PPH accounts for a large majority of obstetrical haemorrhages and severe obstetrical morbidity.¹

PPH is usually defined as blood loss of at least 500 mL, 700 mL, or 1,000 mL, according to its different guidelines.¹⁻³ At population level, the incidence of PPH is estimated about 5% of total live births—this number varying greatly between regions and obstetric centres. Severe PPH (S-PPH), currently defined as blood loss of more than 1,000 mL accounts for about 1% of total deliveries (~20% of all parturient women).¹⁻³

Several individual risk factors for PPH and S-PPH have been reported in the literature, including non-obstetrical and obstetrical determinants.^{4,5} Thus, greater attention has been paid during the last decade to the medical management of S-PPH, as it may lead to further improvements with an important impact on the disease burden.

In accordance, studies have been conducted to establish recommendations for clinical practice in managing child-birth. Nevertheless, most of these studies have focused on the period of labour and did not fully account, either for non-obstetrical individual or antepartum obstetrical individual risk factors.^{6,7} Furthermore, the quality of care in

obstetrics is a major global health concern that requires continuous improvements. In this sense, conducting regular updates of the literature on the determinants of S-PPH can help to account for the evolution of knowledge and practices, quality emergency obstetric care (EmOC) while in turn it may also contribute to mitigating maternal risks through improving the triage and treatment of parturient women.

In this framework, we provided an up-to-date summary about the determinants for S-PPH. Our first hypothesis was that certain maternal conditions (age at first parity, grand multiparity, obesity, stress, depression, etc.) which are increasing in western countries and are classically associated with some PPH determinants (pre-eclampsia, caesarean section, instrumental extractions) could contribute to an increase in the incidence of PPH. Our second hypothesis was that the lack of identification, upstream of organizational measures aimed at preventing PPH, pushed to focus efforts on individual obstetrical care, which could be hampered by the deterioration of socio-economic conditions and access to prevention, thus facilitating the risk of S-PPH at presentation. We deduced from the above the possibility that determinants of PPH upstream of childbirth could emerge, with a strong probability that those which are not very dependent on obstetrical care, could be also associated with progression from PPH to S-PPH. Our primary objective was to identify and classify the determinants of S-PPH for decision-making purposes.

METHODS

SEARCH STRATEGY AND STUDY SELECTION

This systematic review was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Appendix S1 in the **Online Supplementary Document**).⁸

Using the terms “risk factor”, OR “determinant”, AND “post-partum haemorrhage” AND “severe”, we searched Web of Science, Scopus, Science Direct, Medline, Cochrane (Pregnancy and Childbirth Group's Register), ClinicalTrials.gov databases, for both interventional and observational studies (randomized controlled trials; either cross-sectional, case-control or cohort studies, respectively) published in English language, between January 1, 2004 and August 31, 2018.

The full search strategy is detailed in the protocol provided in Appendix S2 of the **Online Supplementary Document**.

Abstracts of identified articles were screened independently by two reviewers (TS, PG) to verify whether they matched the selection criteria. Inter-observer discrepancies were resolved by arbitration of a third reviewer (MS). Searches were complemented by consulting with experts in the field.

Study eligibility criteria targeted women who planned for a vaginal delivery or those who underwent an unplanned, emergency caesarean. All interventional and observational studies were deemed eligible.

Our primary endpoint was S-PPH, defined as a composite of blood loss of at least 1,000 mL, or a second-line treat-

ment (uterine suture, pelvic vessel ligation, arterial embolization, hysterectomy), PPH-related blood transfusion, peripartum decrease in haemoglobin level, PPH-related maternal death. This outcome definition was selected because it was consistent with the WHO definition of S-PPH.¹

QUALITY ASSESSMENT AND DATA EXTRACTION

The quality of studies was assessed using both the STROBE and CONSORT checklists, as appropriate for observational studies and RCTs.^{9,10}

Data extraction was performed in duplicate using a standardized form by two independent researchers (TS and PG). Inter-observer discrepancies were again resolved by arbitration of the same third reviewer (MS).

DATA ANALYSIS

BIAS ASSESSMENT

Bias analysis was adapted from both interventional and observational study designs. It was conducted with reference to the classic biases identified in the Cochrane Handbook or in Jean Bouyer's epidemiology textbook (selection, performance, detection, attrition, classification, evaluation, and confusion biases).^{11,12} We rated biases in each study as “absent” (-), “possible” (+), “probable” (++) , “highly probable” (+++), or “not applicable” (N/A).

EVALUATION OF RISK FACTORS FOR S-PPH

Risk factors for S-PPH were gauged using odds ratios (OR) and their 95% confidence interval (CI). Strength was defined for OR>2.0. They were classified as “key established” or of “uncertain significance” determinants using the Bradford Hill criteria's framework for causal inference, under a pragmatic approach devised to comply with modern-day issues.^{13,14} Concretely, each of the factors identified through data extraction was gauged using the Bradford Hill criteria (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy) causality framework to determine the causative nature of the pathway between exposure to this factor and S-PPH. Causation and mediation were investigated using directed acyclic graphs, as done routinely in epidemiological practice.

Factors matching at least three of the abovementioned criteria, or two criteria while being linked to a known cause of bleeding (well-known aetiology of PPH, inherited or acquired haemorrhagic disease) were considered as “key established” determinants (involving the probability of a “causal pathway”, based on this abovementioned composite definition).

Factors matching one or two criteria without being linked to a known cause of bleeding were classified as of “associated uncertain status” and recommended for being explored in further study.

Factors accompanying development or progression of S-PPH, without matching any of the abovementioned criteria, nor being linked to a known cause of bleeding, were considered as indicators (or markers) of risk. By this, we mean fac-

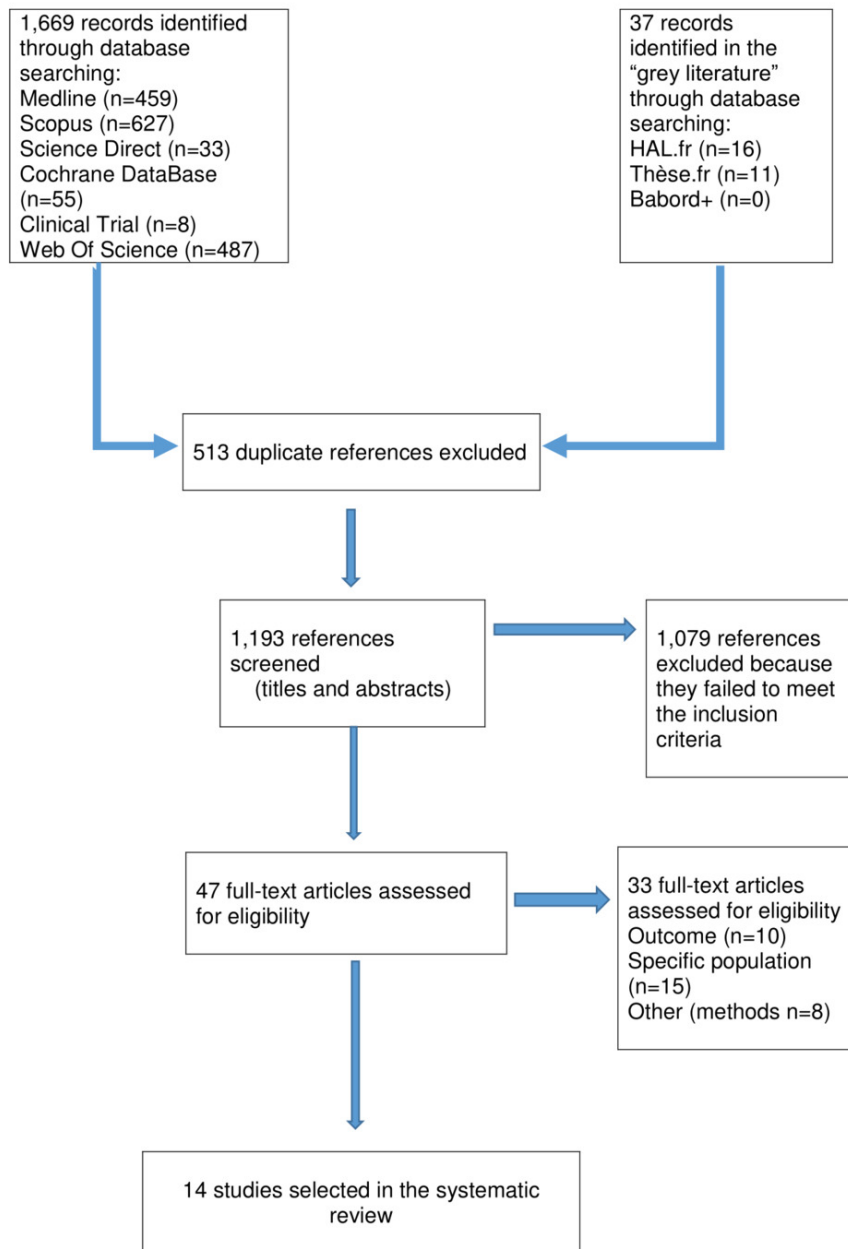


Figure 1. PRISMA flowchart.

Summarizes the selection of the articles included in this literature review.

tors indicating a risk of PPH without necessarily intervening in the causal chain between exposure and event.

RESULTS

The selection process of the articles fulfilling the eligibility criteria for our systematic review is presented in [Figure 1](#).

SELECTED STUDIES

We identified 1,193 potentially relevant, non-duplicate studies. After reviewing the full text of these publications, we found a total of eleven articles that met our inclusion criteria.

CHARACTERISTICS OF SELECTED STUDIES

The descriptive characteristics of the retrieved studies^{15–28} including the period, location, study design, duration of enrolment, and the monocentric or multi-centric organisation of the fourteen selected studies, as well as the statistical method used for classifying risk factors in each of them, are summarized in [Table 1](#).

The selected studies belonged to several study designs, as follows: cohort study (n=10), case-control study (n=3), and cluster randomized clinical trial (n=1). Inclusion periods ranged from ten months to nine years.

The total study population was composed of 9,271,519 parturient women (including 146,781 participants of the Pithagore-6 cluster randomized clinical trial). The number of cases of S-PPH was of 35,825 representing 3.9% of all child-births.

In studies for which the proportion of S-PPH among all cases of PPH could be measured, the average proportion of S-PPH was of 25%. This figure differs slightly from the usually accepted ratio of one S-PPH for five PPH (20%).

The primary endpoint of each study fulfilled the outcome measure previously established in our review protocol. However, the definition of S-PPH varied across studies according to whether the selected outcome was single or composite.

RISK OF BIAS IN SELECTED STUDIES

Biases were independently evaluated for each study. Their analysis is summarized in [Table 2](#).

For example, the study by Briley *et al.* was deemed to be potentially prone to a moderate selection bias given the small representativeness of this bicentric study and the use of secondary subsampling withdrawing the majority of PPH cases.¹⁷ Together with a 14% error rate in estimated blood loss, we considered it was also affected by a highly probable classification bias, while other biases were considered negligible.

FACTORS ASSOCIATED WITH S-PPH

The full assessment of risk factors using Bradford Hill's criteria is displayed in Appendix S3 of the **Online Supplementary Document**.

INDIVIDUAL RISK FACTORS

AGE

Six studies showed that maternal age of 35 years or above were associated with PPH in a significant, consistent, and coherent manner.^{15,17,24–27} In addition, Kramer *et al.* also showed a significant association between PPH and maternal age less than 19 years and the role of first pregnancy at older age on risk of S-HPP was highlighted.²⁷ Indeed, the risk of S-PPH appears to be U-shaped, being higher before 19 and after 35 years.

BODY MASS INDEX

In the study by Briley *et al.*, the body Mass Index (BMI) was associated with a linear increase of the S-PPH risk (OR 1.04,

95% CI=1.01–1.06, per one-unit increase).¹⁷ In the study by Nyfløt *et al.*, obese women (BMI>30) were slightly more at risk of S-PPH (OR 1.29, 95% CI=1.02–1.63),¹⁶ while in turn, Paglia *et al.* found a higher risk of S-PPH when the parturient had a BMI less than 30 kg/m².²⁰

These seemingly contradictory results do not allow us to conclude about the risk's direction between BMI and S-PPH.

ETHNICITY

The risk of S-PPH was lower among patients from the Middle East (OR 0.60, 95% CI=0.45–0.81) but was higher among patients from Southeast Asia (OR 1.77, 95% CI=1.48–2.12) than it was among European patients.¹⁵ Another study found a strong risk (OR>2.0) of PPH in Hispanic populations (OR 3.14, 95% CI=1.23–9.32), as compared with Caucasians.²⁰

SOCIAL CONTEXT

The study by Briley *et al.* was the only to focus on the impact of patients' neighbourhood, income level, and educational skills (these variables feeding an "index of multiple deprivation") on PPH.¹⁷ Importantly, it showed that a disadvantaged neighbourhood was associated with an increased risk of severe PPH (OR 1.82, 95% CI=1.10–3.00).

OBSTETRICAL HISTORY

PREVIOUS CAESAREAN

The studies by Al Zirqi *et al.* (OR 1.46, 95% CI=1.02–2.20), Helman *et al.* (OR 2.75, 95% CI=1.42–5.33), and Kramer *et al.* (OR 1.3, 95% CI=1.2–1.3) found an association between a history of caesarean and S-PPH.^{15,18,27}

These results are consistent, plausible, and coherent. They also met the criterion of temporality, according to which exposure precedes the effect. In agreement, a history of previous caesarean section was deemed a key established determinant of S-PPH.

PREVIOUS PPH

The strength of the association between a history of previous PPH and subsequent postpartum bleeding was consistent.^{16,17,22,24} Ditto, the criterion of temporality was met. In agreement, a history of previous PPH was deemed a key established determinant of S-PPH.

PARITY

Al Zirqi *et al.* (OR 1.10, 95% CI=1.02–1.19), Driessen *et al.* (OR 1.88, 95% CI=1.51–2.33) and Dupont *et al.* (OR 1.71, 95% CI=1.43–2.05), reported an association between primiparity and S-PPH.^{15,22,24} It was less clear for multiparity. Given these discrepancies through parity, we concluded that regarding S-PPH, parity was a factor of uncertain significance.

COURSE OF PREGNANCY

MULTIPLE PREGNANCY

Eight studies showed a strong association between multiple pregnancy and severe bleeding.^{15–18,22–25} These results

Table 1. Descriptive characteristics of selected studies

Authors	Study location, period	Study design	Inclusion (months)	Population (inclusion criteria)	Outcome measure	Analysis
Al Zirqi et al, Sep. 2008 ¹⁵	Norway, 1999 - 2004	Multicentric retrospective cohort study	48	Cohort n= 307,415 (SPPH n=3,501) "Medical Birth Registry of Norway"	1: SPPH: >1,500 mL or blood transfusion	Multivariate logistic regression
Briley et al, Feb. 2014 ¹⁷	United Kingdom, 08/2008 - 07/2009	Bicentric prospective Cohort study	12	Cohort n=10,213-> 9,937 (PPH n=3,349; SPPH n=936)	1: PPH: >500 mL 2: SPPH: >1,500 mL (measure not specified)	Multivariate logistic regression
Deneux-Tharaux et al, Jun. 2010 ²¹	France 09/2004 - 11/2005, 09/2005 - 11/2006	Multicentric cluster randomized controlled trial	27	Trial population n=146,781 (SPPH n=2,414) Pithagore	1: SPPH: blood transfusion, second-line treatment, decrease in Hb \geq 4 g/dL, ICU transfer, death 2: Ratio of SPPH to total number of deliveries	Multivariate logistic regression (random intercept mixed model)
Driessen et al, Jan. 2011 ²²	France, 12/2004 - 11/2006	Multicentric prospective cohort study	24	PPH from uterine atony n=4,550 Including SPPH n=952 Pithagore 6	SPPH: decrease in Hb \geq 4g/dL	Multivariate random-intercept hierarchical logistic regression
Dupont et al, May 2014 ²⁴	France, 12/2005 - 11/2006	Multicentric Prospective cohort study	27	Cohort n=146,781 (PPH n=9,364; SPPH n=2,494) Pithagore 6	1: PPH: >500mL, decrease in Hb \geq 2g/dL, 2: SPPH: >1,000mL, decrease in Hb \geq 4g/dL, uterine embolization, uterine surgery, blood transfusion, ICU transfer, death (measure not standardized)	Multivariate logistic regression
Gayat et al, Jul. 2011 ²³	France, 01/2004 - 12/2005	Monocentric retrospective cohort study	24	PPH n=257 including SPPH n=110 Cohort Lariboisière	SPPH: uterine embolization, balloon tamponade, pelvic vessel ligation and/or hysterectomy	Multivariate logistic regression
Marocchini et al, May 2017 ²⁵	France, 2006-2014	Multicentric rétrospective Cohort		Cohort n=156047 including SPPH n=1136	Blood transfusion	Multivariate logistic regression
Helman et al, Apr. 2015 ¹⁸	Israel, 07/2005- 02/2014	Monocentric case-control (1/4) study	24	n=113,342 (SPPH n=122) "Medical DataBase"	SPPH: blood transfusion (5 RBCs)	Multivariate logistic regression
Karlsson et al, Jul. 2015 ¹⁹	Sweden, 06/2013 - 03/2014	Multicentric prospective cohort study	10	n=1,951 (SPPH n=250)	SPPH: >1,000mL (measure not specified)	Multivariate logistic regression
Kramer et	Canada,	Multicentric	108	PPH n=240,472, SPPH n=25,906	SPPH: -PPH + blood transfusion, -PPH + hysterectomy and/	Multivariate

Authors	Study location, period	Study design	Inclusion (months)	Population (inclusion criteria)	Outcome measure	Analysis
al, Jul. 2013 ²⁷	Montreal, USA, Atlanta, 1999 - 2008	retrospective cohort study		"NIS Database"	or blood transfusion and/or uterine surgery, - PPH + uterine surgery w/o hysterectomy and/or blood transfusion	logistic regression
Nyflot et al, Jan.2017 ¹⁶	Norway, 2008-2011	Bicentric retrospective, Case control	48	Population n=43105,SPPH=1064	SPPH: >1,500 mL or blood transfusion	Multivariate logistic regression
Paglia et al, 2012 ²⁰	USA, Durham, 2000 - 2004	Monocentric case-control study	60	n=218 deliveries in the case-control group (12,476 in the source population), PPH n=671 including SPPH n=109 "Duke University Medical Center, ICD 9"	SPPH: PPH + blood transfusion	Multivariate logistic regression
Sosa et al, Jun. 2009 ²⁸	Uruguay, Argentina, 12/10/2003 -12//0/2005	Multicentric prospective cohort Secondary analysis	24	Cohort n=11,323 (PPH n=1,221; SPPH n=209)	PPH: >500 mL SPPH: >1,000 mL + blood transfusion (measure not specified)	Multivariate cluster logistic regression
Tort et al, Nov.2016 ²⁶	Benin Mali, 2013-2014	Multicentric prospective cohort	17	Cohort:22666,PPH:223,SPPH:88	SPPH:PPH+surgery or blood transfusion or death	Multivariate logistic regression

SPPH – severe postpartum haemorrhage, PPH – postpartum haemorrhage

Table 2. Evaluation of study quality with bias analysis

Study/bias	Selection	Performance	Detection	Attrition	Classification	Evaluation	Confounding
Al Zirqi et al. ¹⁵	+	N/A	N/A	-	+	++	+
Briley et al. ¹⁷	++	N/A	N/A	-	++	+++	+
Deneux-Tharaux et al. ²¹	-	++	+	-	N/A	+	+
Driessen et al. ²²	+	N/A	N/A	-	+	+	++
Dupont et al. ²⁴	++	N/A	N/A	+	+	+	+
Gayat et al. ²³	+++	N/A	N/A	+	++	++	+++
Marocchini et al. ²⁵	++	N/A	N/A	+	++	+++	+++
Helman et al. ¹⁸	+++	N/A	N/A	-	++	+++	+++
Karlsson et al. ¹⁹	+++	N/A	N/A	+	++	+++	+++
Kramer et al. ²⁷	++	N/A	N/A	-	++	++	++
Nyflot et al. ¹⁶	++	N/A	N/A	-	+	++	+
Paglia et al. ²⁰	++	N/A	N/A	-	++	+++	+++
Sosa et al. ²⁸	+	N/A	N/A	-	+	++	++
Tort et al. ²⁶	+	N/A	N/A	-	++	+++	++

no bias (-), possible bias (+), probable bias (++), highly probable bias (+++), N/A – not applicable

met the criteria of strength, consistency, plausibility, and coherence. Multiple pregnancy was considered as a key established determinant of S-PPH.

EMBRYONIC ANNEXES (PLACENTA, AMNIOTIC MEMBRANES, UMBILICAL CORD)

Abnormal placentation led to S-PPH (OR 7.05, 95% CI=2.26-22.03).²³ Kramer *et al.* confirmed this association with placenta praevia and placenta abruption (OR 7.00, 95% CI=6.60-7.30),²⁷ though Marocchini *et al.* found a very strong association between placenta praevia and S-PPH (OR 22.00).²⁵ In addition, Briley *et al.* specified that the risk of S-PPH was the higher with anterior placental presentation (OR 5.55, 95% CI=1.29-23.90).¹⁷ Kramer *et al.* showed a significant increase in the risk of PPH in the presence of polyhydramnios and chorioamnionitis.²⁷

Given the strength, consistency, and plausibility of these results, we considered abnormal placentation as a key established determinant for S-PPH.

PREGNANCY-INDUCED HYPERTENSIVE DISORDERS

Although no association was found between preeclampsia and PPH, the strength and the dose-response relationship between pregnancy-induced hypertensive disorders and S-PPH found consistently in the literature support a causal association.^{17,20} Moreover, eclampsia complicated by a HELLP Syndrome (Haemolysis, Elevated Liver enzyme levels, Low Platelet count) was strongly and consistently associated with life-threatening haemorrhages.^{15,25}

Given the coherence of these results, we classified preeclampsia as a key established determinant for S-PPH and low platelet counts as a key established indicator.

UTERINE FIBROIDS

Uterine fibroids increased the risk of PPH in the study by Nyfløt *et al.* (OR 2.51, 95% CI=1.36-4.64)¹⁶ and in the study by Kramer *et al.* (OR 2.00, 95% CI=1.80-2.20).²⁷ Given uterine fibroids are known to cause bleeding in other circumstances (eg, menstruations), this association was found coherent, strong, and in accordance, uterine fibroids were considered as a key established obstetrical determinant of S-PPH.

ASSISTED REPRODUCTION

In vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) increased the risk of S-PPH in the study by Nyfløt *et al.* (OR 2.72, 95% CI=1.93-3.85).¹⁶

MEDICATIONS

Two studies assessed the impact of medications taken during pregnancy on S-PPH.^{17,20}

The use of corticosteroids for foetal lung maturation was associated with an increased risk of S-PPH (OR 2.0, 95% CI=1.2-3.4).¹⁷ Magnesium injection, as used for alleviating preeclampsia, was also associated with S-PPH (OR 5.4, 95% CI=1.8-20.1).²⁰ Both were deemed as indicators (markers of risk) of S-PPH.

GESTATIONAL AGE

An increased risk of S-PPH was shown for deliveries occurring before 37 weeks gestation (OR 5.0) (²⁵), or after 41 weeks gestation (OR 1.30, 95% CI=1.08-1.56).²⁴ Women whose infant was very small-for-gestational age (< 3rd percentile) were more likely to be transfused for S-PPH.²⁵ These two studies did not allow us to draw a firm conclusion and this factor was classified as of uncertain significance.

ACTIVE PHASE OF LABOUR

OXYTOCIC DRUGS

Eight studies assessed the role of oxytocic drugs, used for labour induction, in S-PPH.^{15-18,20,24,27,28} Two was inconclusive,^{17,20} four of these showed a weak association (OR between 1.1 and 1.7),^{15,16,24,27} whereas two found a strong association (OR>2.0).^{18,28}

The consistency, the coherence with current knowledge and temporality led us to consider labour induction as a key established determinant of S-PPH.

LABOUR DURATION

Prolonged active phase of labour, known to alter muscle contractility, was associated with an increased risk of S-PPH.^{15,16,22,24} In addition, Dupont *et al.* emphasised that bleeding risk was higher when the active phase of labour exceeded six hours (OR 1.70, 95% CI=1.143-2.01).²⁴

Given the consistency and plausibility of these results, we concluded that prolonged labour is a key established determinant for S-PPH, without further confirming the six-hour time limit.

UTERINE RUPTURE

Uterine rupture, a complication that occurs mostly during the active phase of labour, has been recognised as cause of obstetric haemorrhage. The study by Kramer *et al.* confirmed a very strong association between uterine rupture and S-PPH (OR 11.6, 95% CI=9.7-13.8).²⁷

CHILDBIRTH

MODE OF DELIVERY

Eight studies found that instrumental vaginal delivery and emergency caesarean were both associated with S-PPH.^{15-19,24,25,27}

Given consistency and coherence of these results, we concluded that instrumental vaginal delivery and caesarean were key established determinants of S-PPH.

FOETAL PRESENTATION

Kramer *et al.* showed that breech presentation increased the risk of S-PPH (OR 1.2, 95% CI=1.1-1.2).²⁷ However, this single study did not allow us to draw a firm conclusion conducting this factor to be considered as of uncertain significance.

DELIVERY COMPLICATIONS

Sosa *et al.* found a strong association between placenta retention and S-PPH (OR 16.0, 95% CI=7.1-36.0).²⁸ Karlsson *et al.* highlighted a strong association between uterine exploration (usually an indicator of placenta retention) and risk of S-PPH (OR 23.0, 95% CI=14.3-37.1).¹⁹ These findings are highly coherent with current knowledge and recommendations.

LESIONS IN THE BIRTH CANAL

Cervical laceration was shown strongly associated with bleeding risk (OR 94.0, 95% CI=87.3-101.2).²⁷

Together with the plausibility and coherence of these results, this strong association led us to conclude that if such a birth canal injury (cervical or vaginal laceration, episiotomy) was not sutured in the shortest time possible, blood loss would be substantial. In agreement, cervical injury was considered as a key established determinant of S-PPH.

BIRTHWEIGHT

Five studies an association between foetal macrosomia and the risk of S-PPH.^{15,16,24,27,28}

The consistency and the coherence of these results with current knowledge led us to propose foetal macrosomia as a key established determinant of S-PPH, even though it may not be causal, this increasing the risk of other contributors on the causal pathway to S-PPH like, for instance, the lesions of birth canal.

BIOLOGICAL PARAMETERS

Low pre-pregnancy or low prepartum haemoglobin levels (<9 g/dL), prothrombin time (PT) below 50%, fibrinogen level below 2 g/L, and detectable level of Troponin-I before delivery, were considered as indicators of S-PPH.^{15,16,23}

EPIDURAL ANALGESIA

Several studies examined the relationships between epidural analgesia during labour and S-PPH.^{17,22,24} Only two of these showed a weakly protective role ($0.5 < OR < 1.0$) of analgesia against S-PPH. Further studies are needed to draw a firm conclusion.

MANAGEMENT OF SEVERE PPH

Only four studies reported the impact of the medical management of labour on the incidence and prevalence of S-PPH.^{21,22,24,26}

Importantly, Deneux-Tharaux *et al.* found no risk reduction in women exposed to a multifaceted intervention for reducing the incidence of S-PPH.²¹ In the Pithagore-6 cluster RCT similar incidence rates of S-PPH were observed in both the intervention arm (discussion of recommendations, reminders, audit) and the control group (passive diffusion of information). With respect to oxytocin injected during labour, one study found a protective effect when injected within 10 minutes.²⁶ By contrast, Dupont *et al.* found an overall increased risk of S-PPH (OR 1.26, 95%

CI=1.06-1.50),²⁴ while the study by Driessen *et al.*, within the same Pithagore-6-trial framework, established that this risk was actual when given beyond 20 minutes after birth (OR 1.49, 95% CI=1.14-1.94).²² Given this inconsistency, oxytocin during labour was deemed as a factor of S-PPH of uncertain significance.

SUMMARY OF FINDINGS

We distinguished the factors associated with S-PPH into key established determinants, associated factors of uncertain significance, and indicators to guide the obstetrical decision. This classification is summarized in [Table 3](#).

DISCUSSION

Based on a critical and pragmatic analysis of the literature, we propose that the key established determinants of S-PPH be identified, as follows: previous caesarean, previous PPH, multiple pregnancy, abnormal placentation, pregnancy-induced hypertensive disorders, labour induction, prolonged labour, uterine rupture, uterine fibroids, instrumental vaginal delivery and caesarean, uterine atony, placental retention, macrosomia and birth canal injuries. In addition, we require further studies to confirm the relevance of reproductive assistance technics (IVF/ICSI), epidural analgesia, gestational age, as well as social factors.

Together with the heterogeneity in the outcome measure definition, the very different study designs, population sizes, and definitions of exposure factors, prevented us to use meta-analysis for providing quantitative estimates of the associations between the candidate determinants and S-PPH.

Despite these limitations, we believe that the pragmatic approach that we used ensures internal validity of our results while minimising publication bias.

We confirm the primarily obstetrical nature of the key determinants of S-PPH. This observation fits current knowledge on the pathogenesis of postpartum bleeding.^{4,29} Among these, we distinguish causes and risk factors according to whether there are no or not mediators on the causal pathway linking exposure to severe bleeding. In agreement, uterine fibroids, abnormal placentation, preeclampsia, uterine rupture, uterus atony, placental retention, and birth canal injuries, are likely causes of PPH by different pathomechanisms (*fibrinolysis and consumption of clotting factors) and should prompt active management to prevent evolution into S-PPH. By contrast, history of previous caesarean, history of previous PPH, multiple pregnancy, labour induction, prolonged labour, instrumental vaginal delivery and caesarean, require intermediate factors (abnormal placentation or uterus atony) are favouring conditions to severe bleeding in the third stage of labour or after delivery, which motivates additional explorations and interventions (e.g., timely reinjection of oxytocin,³⁰ sublingual misoprostol,³¹ sulprostone,³² or early tranexamic acid³³) to contain blood losses.

Along with uncertain significance of their predictive value, the non-modifiable character of most socio-demographic factors does not support them for guiding obstetrical decisions.

Table 3. Summary of determinants of severe postpartum haemorrhage

S-PPH determinants	Socio-demographic	Obstetrical	Delivery	Indicators (biological, medical statements)
Key established		Previous caesarean, or PPH,	Instrumental vaginal delivery,	Hb<9g/dL,
		Multiple pregnancy,	Caesarean,	Low platelets,
		Abnormal placentation	Placental retention,	PT<50%,
		Preeclampsia, eclampsia,	Uterine exploration,	Fibrinogen<2g/dL,
		Cervical maturation,	Cervical injury,	Troponin I (detectable)
		Labour induction,	Macrosomia.	
		Prolonged duration of labour,		
		Uterine fibroids, Uterine rupture.		
Uncertain significance	Age	Parity	Breech presentation	Corticosteroid
	BMI	IVF	Epidural analgesia*	Magnesium intake
	Ethnicity	Gestational age		
	Socio-educational level	Oxytocin infusion during labour		
	Maternal education			

PPH - postpartum haemorrhage, Hb - Haemoglobin level, TP - Prothrombin time, BMI - Body Mass Index, IVF - In vitro Fertilization

*Protective factor.

However, the U-shaped curves of S-PPH risk observed both for maternal age and parity, should prompt caregiver's awareness to young *nulliparae* and elderly grand *multiparae* at the top of the risk of S-PPH, while women with one single of these factors could be considered at an intermediate risk. Interestingly, these U-shaped curves are coherent with those observed in several other perinatal outcomes, such as preterm birth and small-for-gestational age for maternal age, but also with all-cause mortality later in life for parity.³⁴

It is recognised that severely obese women with a pre-pregnancy BMI > 35 kg/m² face multiple perinatal risks.³⁵ Briley et al. have confirmed the existence of a positive association between maternal weight and S-PPH in a large prospective cohort.¹⁷ The evidence of a biological gradient between an increasing BMI and a higher risk of S-PPH likely supports causality. Actually, the finding suggest that maternal obesity has a modest effect on haemorrhage risk: the direction of the association may differ by delivery mode.³⁶

The role of ethnicity in S-PPH is less clear and may differ according to both socio-environmental context and genetic factors. Briley et al. have suggested that Black African women were more likely to have PPH.¹⁷ In other studies, Southeast Asian¹⁵ and Hispanic²⁰ women were the more at-risk of S-PPH, while Middle Eastern women seemed protected.¹⁵ Importantly, these ethnic groups at-risk have been confirmed recently in a large hospital-based study conducted in the US, in comparison to Non-Hispanic White, the lower-risk group, independently of confounding factors, including insurance status.³⁷ Interestingly, among seven can-

didate genes, promoter polymorphism of the tissue factor gene (F3-603A>G) showed a significant association with PPH after adjustment for known risk factors, fuelling the idea of a genetic background that supports role of ethnicity in S-PPH.³⁸ However, this hypothesis is challenged by another observation in low-income American women of increased risks of PPH with antidepressants uptake, independently of numerous confounders including race.³⁹

During the last decade, the growing interest in reviews of clinical practices and the commitment to identifying sub-optimal care has led to investigate the factors related to the management of PPH, both collectively and individually.

At maternity level, despite the inconclusive Pithagore-6 cluster RCT,²¹ community-based multifaceted interventions, aimed at improving the translation into clinical practices of the guidelines for PPH management, have gained attention in recent years and even proved effectiveness in low-middle income countries.⁴⁰

At individual level, oxytocin infusion is mandatory for the prevention of third-stage labour and postpartum bleeding risks. In the presence of PPH, re-administration of oxytocin should be prompt, as it was shown ineffective when performed more than 20 min after onset of PPH to avoid progression towards S-PPH.²² In addition, caution should be the rule as treatment with oxytocin was associated with a harmful dose-response in a population-based nested case-control study (*i.e.*, the higher the dose, the more severe the bleeding), which emphasises the need for more evidence-based indications and the minimal useful regimens.⁴¹

Epidural analgesia was found protective for the risk of S-PPH in two studies.^{22,24} This practice ensures comfort to parturient women and allows effective and rapid intervention in life-threatening obstetric emergencies. However, its benefits must be weighed against a potential decrease in uterine contractility, and hence against increased duration of labour, with expected difficulties in foetus expulsion.

We found four biological parameters, Troponin-I, haemoglobin, PT, and fibrinogen that seemed mere indicators of S-PPH as they are not clearly located on the causal pathway between exposure and disease. Among these, given that fibrinolysis may be important in S-PPH pathogenesis,²² only fibrinogen has paid attention so far, and multicenter trials testing the effectiveness of fibrinogen concentrates are currently underway.

Our systematic review has strengths and limitations. The attachment to the PRISMA statement throughout the different steps of this systematic review adds scientific rigour in the reporting of the results.

In the absence of consensual definition, we defined S-PPH as primary endpoint using the WHO definition. As a consequence, we excluded from our systematic review studies that used the former definition of S-PPH, such as Canadian and Italian studies.^{42,43}

Our systematic review covers a wide range of geographic areas including North and South America,^{20,27,28} Southern and Northern Europe,^{15–17,19,21–25} West Africa²⁶ and Israel.¹⁸ It gathers a very large population, which provides external validity and ensures extrapolations.

In a global context in which S-PPH remains the leading cause of maternal mortality, we rigorously gauged factors associated with S-PPH and distinguished key established determinants, as well as associated factors (especially contextual factors) and indicators that warrant further studies. We highlight socio-environmental factors and propose new studies to specify the impact of emerging factors on PPH, to take into account the context in which the disease occurs, and organise emergency obstetric care distribution and accessibility. In the field of obstetrical care, in which practices move faster than the pace of new publications, we endorse the concept of “living” systematic reviews and encourage regular updates of the current knowledge on S-PPH determinants combining rigour with timeliness.⁴⁴

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