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Prenatal anemia and postpartum hemorrhage risk: A systematic review and meta-analysis

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Abstract

Introduction: Postpartum hemorrhage (PPH) has remained the leading cause of maternal mortality. While anemia is a leading contributor to maternal morbidity, molecular, cellular and anemia-induced hypoxia, clinical studies of the relationship between prenatal-anemia and PPH have reported conflicting results. Therefore, our objective was to investigate the outcomes of studies on the relationships between prenatal anemia and PPH-related mortality.

Materials and Methods: Electronic databases (MEDLINE, Scopus, ClinicalTrials.gov, PROSPERO, EMBASE, and the Cochrane Central Register of Controlled Trials) were searched for studies published before August 2019. Keywords included “anemia,” “hemoglobin,” “postpartum hemorrhage,” and “postpartum bleeding.” Only studies involving the association between anemia and PPH were included in the meta-analysis. Our primary analysis used random effects models to synthesize odds-ratios (ORs) extracted from the studies. Heterogeneity was formally assessed with the Higgins’ I^2 statistics, and explored using meta-regression and subgroup analysis.

Results: We found 13 eligible studies investigating the relationship between prenatal anemia and PPH. Our findings suggest that severe prenatal anemia increases PPH risk (OR = 3.54; 95% CI: 1.20, 10.4, p-value = 0.020). There was no statistical association with mild (OR = 0.60; 95%

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Conflict of interest

The authors have nothing to disclose.

Supporting information

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CI: 0.31, 1.17, *p*-value = 0.130), or moderate anemia (OR = 2.09; 95% CI: 0.40, 11.1, *p*-value = 0.390) and the risk of PPH.

Conclusion: Severe prenatal anemia is an important predictive factor of adverse outcomes, warranting intensive management during pregnancy. PROSPERO Registration Number: CRD42020149184; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=149184.

Keywords

maternal mortality; meta-analysis; obstetric emergency; postpartum hemorrhage risk factors; postpartum hemorrhage-related mortality; prenatal anemia; systematic review

Introduction

Postpartum hemorrhage (PPH) is a critical and significant public health problem, and a leading cause of maternal mortality in developing countries.[1] In 2017, an estimated 38 000 deaths were due to PPH (19% of all maternal deaths).[2] Disturbingly, the incidence of PPH has been increasing in the United States. In the United States, a nationwide study reported that the incidence of PPH increased by 100% between 1998 and 2008.[3]

The management of PPH starts in the prenatal period, with identification of women who are at the highest risk for PPH from placental abnormalities, trauma to vaginal/cervical tissue, anemia, uterine atony, scarred uterus, and coagulation disorders. However, during labor, the mainstay of global PPH control is the active management of the third stage of labor with prophylactic use of uterotonics (AMSTL).[4–6] While AMSTL is estimated to prevent over half of PPH cases, there are many cases of pregnant women who lose potentially deleterious amounts of blood despite AMSTL, warranting therapeutic administration of uterotonics.[7] In a subset of women with PPH, uterine atony and bleeding remains refractory despite uterotonic administration, warranting surgical or other invasive interventions.[8] It is plausible that the underlying cause and pathogenesis of PPH in this subset of women might differ from those due to atony, responsive to uterotonics. In addition, mechanistic studies suggest that anemia through its effect on nitric oxide synthesis might play a role in uterine atony.[9–18]

Anemia, one of the most frequent complications of pregnancy, is a leading contributor to maternal morbidity globally. Mechanistic, clinical and population studies suggest that preexisting anemia might also be a risk factor for PPH incidence.[14–19] Although few clinical studies have compared the risk of PPH among pregnant women with anemia to pregnant women without anemia, findings from these studies have been conflicting, and there have been no systematic review and/or meta-analysis summarizing findings of these clinical studies that have examined the relationship between anemia in pregnancy and PPH risk. Therefore, the objective of this study was to synthesize the evidence regarding the relationship of prenatal anemia and the risk of PPH. We also sought to summarize the clinical studies that have examined the relationship of prenatal anemia and the risk of mortality among patients with PPH.

Methods

Database search, study criteria eligibility, and search strategy

The protocol for this review was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020149184), and we followed the PRISMA guidelines for protocols (PRISMA-P; Supporting Information, Appendix S1)[20] for data extraction. We searched the literature for retrospective cohort studies, prospective cohort studies, and randomized clinical trials, and identified studies examining the association of prenatal anemia and PPH risk. Original peer-reviewed research articles published up to August 2019 in PUBMED/Medline (US National Library of Medicine), ClinicalTrials.Gov, EMBASE (Elsevier), PROSPERO and Web of Science (Clarivate Analytics) were examined. Our search included controlled vocabulary terms (MeSH and free text keywords) for anemia (exposure), PPH (outcome), pregnancy and postpartum (study population), and cohort/randomized clinical trial (study design). Relevant synonyms and alternative spellings were identified via EMBASE's controlled vocabulary (Emtree). Hand searching of references was also done. The search strategy for the association between anemia and PPH included Boolean operators "OR" (for related terms) and "AND" (for a combination of different concepts). Our ClinicalTrials.Gov search strategy incorporated a very similar search strategy, without including the "cohort" and "randomized controlled trial" terms in the search. In finalth analysis, we included studies of pregnant women any gestational age or parity, in any trimester of pregnancy, of any maternal age, and from any country that met our inclusion criteria. No restrictions by age, year of publication, or language were implemented.

Outcome measures

Our primary outcome of interest was the proportion of women with anemia who developed PPH. We assessed the following secondary outcomes: the proportion of women with developed mild anemia, moderate anemia, and severe anemia, and the associations between these classes of anemia severity with PPH. All primary and secondary outcomes were assessed as odds ratios (ORs) and adjusted odds ratios.

Data extraction, exposure, and outcome definitions and descriptions

The title and abstract of each study were screened and full-texts examined in duplicate by AIA and MK (Table 1). Discrepancies were resolved by a third author (Moshood O. Omotayo). The final inclusion–exclusion decisions were made after the articles were reviewed in full. Studies were excluded if they did not examine exposure-outcome relationship of interest, were nonhuman studies, cross-sectional studies or systematic reviews. Data extraction from full-text articles was done using a comprehensive extraction sheet. Information on study design, population, intervention, covariates, and findings were extracted. Anemia, defined as a decrease in red-cell mass below 11 g/dL, was diagnosed using hemoglobin testing. A number of different cutoffs were used by the included studies: 7,[21,26,34] 9,[27] 10,[29] and 11 g/dL.[21,23,31,33] In the main analysis, we restricted to studies that defined anemia based on the World Health Organization's (WHO) classification.[35] In sensitivity analysis, we included the most appropriate estimate from each study, and compared the impact of that approach on the results. We employed the definition of PPH used by the primary studies (>500 or >1000 mL—with or without modification based on

clinical scenario). Severe PPH was regarded as estimated blood loss >1500 mL or requiring transfusion.[21,27]

Risk of bias assessment

We assessed the risk of bias of individual studies using the Newcastle Ottawa Scale which permits distinct quality scales for case–control and cohort studies, and assess the quality of nonrandomized studies with particular focus on study content, study design, and applicability.[36] Using the Newcastle Ottawa Scale, the quality of the individual studies were assessed and interpreted, before they are incorporated into the meta-analysis. Two investigators (Ajibola I. Abioye and Moshood Kuyebi) independently assessed the studies and disagreements were resolved by consensus with a third author (Moshood O. Omotayo). This ranking did not influence decisions concerning exclusion of studies or analytic approach.

Statistical analysis

The primary analysis included OR estimates from each included study evaluating the relationship of anemia and PPH. For studies that reported more than one estimate, the estimate that incorporated the largest possible sample was included. If studies reported separate estimates for anemia categories or other subgroups, they were included separately if the individual participants in the subgroups were distinct. For studies reporting no OR estimates, we calculated them if sufficient information was provided. [21,23,25,26] In some cases, there were no exposed or nonexposed cases or noncases, and we imputed 0.5 to permit the estimation of the ORs.[26,31]

Random effects models based on the restricted maximum likelihood (REML), which explicitly model the between study variation, were selected a priori for the meta-analyses.[37] The REML is superior to the more commonly used Der-Simonian Laird method, and allows inclusion of study-level covariates.[38] Heterogeneity was formally assessed with the Higgins' I^2 statistics, a measure of the total variability that is due to between study variations. I^2 was regarded as low if <50%, substantial if 50%–90% and considerable is >90%, in accordance with the general guidelines for Cochrane reviews, and p-values for Q-statistic reported.[39] Heterogeneity was further assessed using meta-regression approaches and analysis within subgroups defined by age, baseline iron status, country income classification, and timing of prenatal hemoglobin assessment. The impact of an individual study on the findings was evaluated by removing one or more studies sequentially and comparing the pooled estimates obtained. Possible publication bias was visualized using funnel plots, quantitatively evaluated with the Egger's tests based on mixed effects regression model, and explored with trim and fill analysis.[40,41]

p-Values are two sided and significance set at $p < 0.05$. Statistical analyses were conducted using Stata version 15.0 (College Station, TX) and R-Studio (1.0.153). Values presented in the text are means (±SD), means (95% CI), and means (±SE).

Results

Description of included studies

We identified 13 papers from an initial set of 2012 unique titles and abstracts reporting on the relationship of anemia and PPH (Appendix S2), and the PRISMA flowchart of the study selection is as described in Appendix S3. There were nine cohort studies and four case–controls studies. The studies were conducted in multiple different countries spanning Africa,[22,24,30,31,33] Asia,[26,28] Europe,[25,27,29] North America,[21] and South America.[23] The prevalence of prenatal anemia varied widely, from 4% to 88%. The individual studies defined PPH differently: as estimated blood loss >500 mL,[22,23,29–31] > 1000 mL[21] or used different cutoffs depending on whether delivery was vaginal or by cesarean section,[25] or whether vaginal bleeding was associated with features of hemodynamic deterioration such as hypotension or shock, or need for blood transfusion.[33] Other studies defined PPH based on clinician diagnosis, without specifying how it was made. [24,28,32] One study only reported on severe PPH based on estimated blood loss >1500 mL. [27] Another study did not specify how PPH was defined.[26] Only one study from Senegal and Mali [32] reported on PPH-related mortality. The studies were of poor [21,22,26,30,31,33] or moderate [24,25,27–29,32] quality based on the Newcastle-Ottawa Scale.

Anemia and PPH

Observational studies evaluating the relationship of anemia and PPH have reported inconsistent findings. We pooled estimates from eight studies that defined anemia as hemoglobin <11 g/dL per WHO recommendations,[21,23,24,26,30,31,33] and found that anemia was not associated with PPH (OR: 1.39; 95% confidence interval [CI]: 0.64–3.01; *p*-value = 0.400, Figure 1). Visual inspection of the funnel plot did not suggest publication bias (Figure SS1), and the *p*-value for the Egger's test of publication bias was 0.24. The OR did not considerably change on excluding any of the studies. The Higgins' I^2 statistic was 97%, suggestive of considerable heterogeneity (p-heterogeneity <0.0001). Heterogeneity was not influenced by year of study publication (*p*-value = 0.970), mean age (*p*-value = 0.240), or country income classification (*p*-value = 0.180). Heterogeneity did not also differ by whether PPH was defined using a 1000 mL cutoff (*p*-value = 0.100) or other criteria (*p*-value = 0.570), compared to 500 mL cutoff. The pooled OR estimate among cohort studies was 0.88 (95% CI: 0.52–1.49). Only one study [30] had a case–control design and its OR was 1.29 (95% CI: 0.39–4.36).

In sensitivity analysis, we pooled estimates from 12 studies regardless of how anemia was defined, but the magnitude and direction of the association did not substantially change (OR: 1.63, 95% CI: 0.93–2.86).

Anemia severity and PPH

Five cohort studies from Egypt, India, Pakistan Peru, and United States reported estimates across multiple categories of anemia severity in relation to the odds of PPH, allowing visualization (Figure 2) of the possible nonlinear relationship of anemia severity and PPH risk.[21,23,26,28,31] The estimates from one study [31] were extreme and are not shown—though the direction of its estimates was consistent with the other studies. Overall, the scatter plot

shows a possible inverted J-shape relationship of prenatal hemoglobin concentration and the risk of PPH. The plot suggests an increased risk of PPH when anemia is severe, but no increased risk at other hemoglobin levels.

Neither mild nor moderate anemia was significantly associated with the PPH. When we pooled the estimates for the relationship of mild anemia and PPH from four studies [21,23,26,31], we obtained a pooled OR of 0.60; (95% CI: 0.31, 1.17, *p*-value = 0.130, Figure SS2). There was low heterogeneity (I^2 = 46%, p-heterogeneity = 0.240) and visual inspection of the funnel plot did not suggest publication bias (Figure SS3). The pooled OR for moderate anemia from five studies was 2.09 (95% CI: 0.40, 11.1, *p*-value = 0.390, Figure SS4). There was considerable heterogeneity (I^2 = 97%, p-heterogeneity <0.0001). Visual inspection of the funnel plot suggested possible publication bias (Figure SS5), and the *p*-value for funnel plot asymmetry (Egger's test) was 0.04. Imputing one study using trim and fill reduced the magnitude of the OR considerably (OR: 1.18; 95% CI: 0.16–8.68) but the direction did not change.

Severe anemia was associated with higher odds of PPH, unlike mild and moderate anemia. The pooled OR for severe anemia from five studies [22,23,25,26,31] was 3.54 (95% CI: 1.20, 10.4, *p*-value = 0.020, Figure 3). There was substantial heterogeneity (I^2 = 83%, p-heterogeneity = 0.0001). Visual inspection of the funnel plot did not suggest possible publication bias (Figure SS6). The confidence intervals (CIs) were, however, much wider when the large Peruvian study [23] was excluded (OR: 3.37; 95% CI: 0.69–16.6).

Severe PPH

Two studies reported estimates for severe PPH and their findings were contradictory. A case–control study in Norway[27] only reported estimates for severe PPH. It considered moderate anemia (<90 g/L) as a risk factor for severe PPH and found considerably higher odds (OR = 4.27; 95% CI: 2.79–6.54). This estimate was adjusted for multiple covariates including previous PPH, uterine fibromas, birthweight, parity, mode of delivery, and induction of labor. The second study was a US cohort study. The reported estimates for severe PPH were unadjusted for any confounders, and restricted to women with severe postpartum anemia.[21] They found that anemia is associated with a considerably lower odds of PPH (OR: 0.35; 95% CI: 0.27, 0.47).

PPH-related mortality

One study from Senegal and Mali[32] evaluated the predictors of PPH-related mortality in 46 referral hospitals in a 1-year period and found that severe prenatal anemia was associated with a considerably higher odds of mortality (OR: 6.65; 95% CI: 3.77–11.7). Estimates were adjusted for country, location in relation to hospital, age, number of prenatal visits, preexisting disease, gestational hypertensive disorders, referral, prolonged labor, mode of delivery, and birthweight.

Discussion

In this systematic review, we pooled estimates from studies that evaluated the relationship between prenatal anemia and PPH risk. Our findings suggest that prenatal anemia might

increase PPH risk, but only when anemia is severe. Only one study investigated the relationship between anemia and PPH-related mortality and it indicated that severe prenatal anemia increases the risk of PPH-related mortality. However, the body of studies evaluating this relationship remains weak. Nevertheless, the likelihood that severe anemia increases the risk of PPH is another important motivation to address the underlying drivers of anemia risk among women of reproductive age, particularly in low- and middle-income countries where there is high prevalence of anemia.

Molecular and cellular studies provide plausible scientific premise for a direct relationship between prenatal anemia and risk of PPH-related mortality. Among adolescents, iron deficiency anemia has been associated with a 700% increase in nitric oxide production compared to adolescents with normal hemoglobin range.[18] During pregnancy, NO produced by the trophoblast and placenta could play a significant role in maintaining uterine quiescence by paracrine effect since there is marginal activity of NO synthase (NOS) in the myometrium.[10] It is known that NO participates in responses to acute hypoxia via inducing HIF but contributes to a negative feedback process in chronic hypoxia.[9] In accordance, eNOS expression was shown to be increased in the placental tissue of pregnancies complicated by IUGR or preeclampsia, which could be an adaptive response to the increased resistance and poor trophoblastic invasion.[11,12] Moreover, NO production in IUGR placenta was reported to be increased and this increase was more pronounced in those with compromised fetal oxygenation.[13] It has not been reported whether placental NOS activity and NO production is increased in pregnancies complicated by severe anemia. However, it is reasonable to assess PPH with reference to placental NO production in pregnancies complicated by severe anemia. The body of clinical studies directly examining this relationship does not provide conclusive evidence of this relationship, although this meta-analysis suggests that severe prenatal anemia is associated with increased risk of PPH.

The WHO estimates that approximately 27% of maternal deaths are due to obstetric hemorrhages.[42] It is plausible that preexisting anemia and consequent hypoxia can complicate the cardio-vascular compromise resulting from postpartum hemorrhage. This review shows that there is limited empirical evaluation from clinical studies. We found only one study that has examined the influence of prenatal anemia on PPH-related mortality. Given the high prevalence of anemia and public health significance of PPH, further empirical testing of this relationship, and quantification of the association may be important to guide maternal health policy decisions. Thus, more studies are warranted.

Anemia during the prenatal care period is an important predictive factor of adverse outcomes, possibly for PPH and mortality, warranting intensive follow-up. One study reported 6.7-fold higher odds of mortality among individuals with PPH if they had severe prenatal anemia.[32] Preventive and therapeutic interventions for prenatal anemia might prevent PPH or PPH-related mortality although more studies are needed to evaluate effectiveness. There are different causes underlying prenatal anemia. Thus, the appropriate preventative and therapeutic interventions should be personalized, taking into consideration the hemoglobin electrophoresis, dietary history, infections, and inflammatory conditions. Potential interventions for averting deleterious consequences of anemia in pregnancy include early and routine screening with complete blood counts and hemoglobin electrophoresis

during the initial prenatal visit, iron supplementation in women with iron deficiency anemia, and multiple micronutrient supplementation and transfusion of blood and blood products in women with severe or symptomatic anemia during pregnancy. At the population level, nutritional and educational interventions for improving dietary intake and reducing recurrent infections and inflammation among women of reproductive age can reduce the prevalence of severe anemia in low- and middle-income countries.[43]

This systematic review has multiple strengths. Anemia has high global prevalence and PPH is the leading cause of maternal mortality. The rarity of studies that have synthesized evidence on the relationship of these two conditions despite their importance to global maternal health, adds to the significance of this work. Second, we followed the PRISMA guidelines, registered the review in PROSPERO and followed rigorous methodological standards in the synthesis and reporting of evidence on this important question. Third, our analytical plan and interpretation focused on the clinical and public health implications of the body of work that has examined this relationship.

The implications for future research are enormous. There is need to design and implement prospective studies to examine the direct association between mild, moderate, and severe anemia and the risk and severity of PPH in diverse settings. Since PPH and PPH-related mortality are relatively rare outcomes, large cohort studies or well-designed case–control studies would be appropriate study designs.

This systematic review is limited by the scarcity and low quality of the primary studies, as well as inconsistency of measurement approaches across studies. Few studies have considered the relationship of anemia and PPH, and it was not possible to comprehensively evaluate the relationship of anemia severity and PPH using statistical techniques such as generalized least squares for trend estimation.[44] Many studies did not report the mean gestational age at which anemia testing was done, especially in developing countries where third trimester labs are not done routinely, making it impossible to comprehensively explore heterogeneity using meta-regression. Some of the included studies were also restricted to patients who delivered via cesarean section or who developed postpartum anemia, likely limiting the external validity of the studies, or introducing selection bias.

The studies were of low or moderate quality as assessed by the Newcastle-Ottawa Scale. For many of the studies included, PPH was a secondary outcome and no adjustment for confounding was considered. There was also considerable unmeasured confounding due to factors such as gestational age for some of the studies that controlled for any confounders. The threat of unmeasured confounding is particularly great due to the wide CIs seen in the various analyses. For instance, the point estimates and CIs could be explained away by unmeasured confounding related to the exposure and the outcome by an E-value of 6.54, and a lower confidence limit of 1.69, but weaker confounding could not do so.[45] An E-value greater than 3.0 tends to suggest that the identified association is more likely to represent a true causal relationship, and unlikely to be spurious. Nonetheless, future studies should carefully control for important confounding variables that may reasonably exert substantial influence on the association between anemia and PPH, including socioeconomic status, nutrition, and health insurance coverage.

Conclusion

Severe anemia during prenatal care is an important predictive factor of PPH, warranting early diagnosis and treatment. Published studies did not comprehensively control for confounders. Therefore, larger, well-designed prospective cohort studies with careful control for confounding are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. As this is a systematic review and meta-analysis of already published studies, we do not have any stored data.

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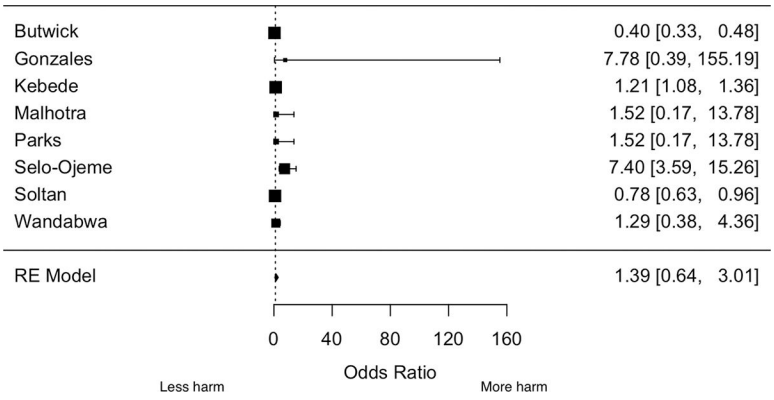

Figure 1.
Forest plot of the association between anemia and postpartum hemorrhage

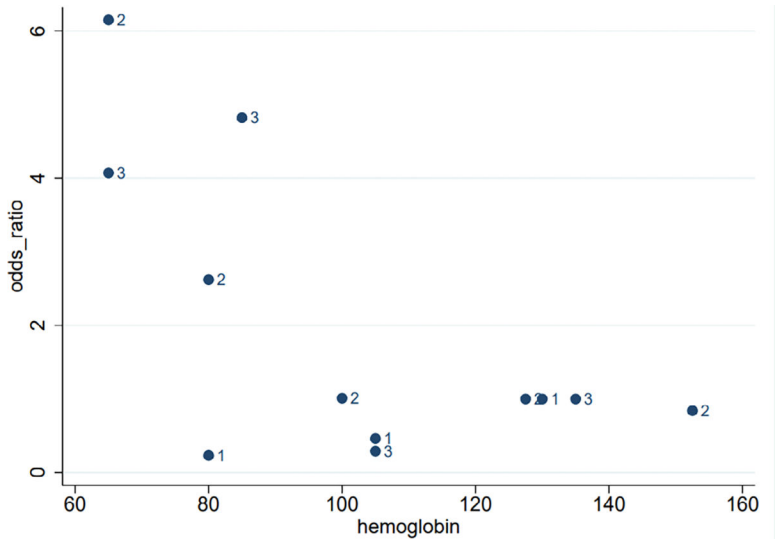

Figure 2.
Scatterplot of the association between categories of anemia severity and PPH

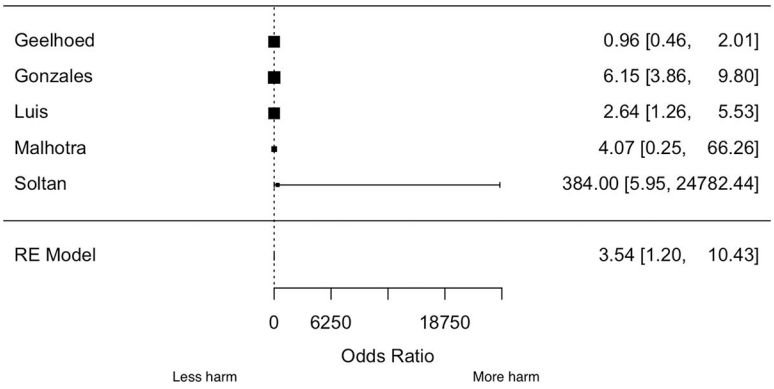

Figure 3.
Forest plot of the association between severe anemia and PPH

Table 1

Description of included studies

Study	Study type	Sample size	Mean age, years	Country	Baseline anemia, %	Exposure cutoff for hemoglobin, g/L	Outcome, definition	Lindings, Odds ratio (95% CI)	*p*-Value	Confounders adjusted	Study quality
Butwick et al.[21]	Cohort	1789	NA	United States	43	<110 ≥110 <100 ≥100 ≥110 100—<110 <100	PPH, estimated blood loss >1000 mL	0.40 (0.33, 0.48) Ref 0.92 (0.71, 1.17) Ref Ref 0.50 (0.39, 0.64) 0.25 (0.19, 0.32)	<0.0001 0.48 <0.0001 <0.0001	None	Poor
						<110 ≥110	Severe PPH, estimated blood loss >1500 mL	Ref 0.35 (0.27, 0.45)	<0.0001		
						<100 ≥100		Ref 0.28 (0.19, 0.41)	<0.0001		
						≥110 100—<110 <100		Ref 0.46 (0.34, 0.63) 0.23 (0.15, 0.34)	<0.0001 <0.0001		
Geethoed et al.[22]	Cohort	309	22	Ghana	51	<80 ≥110	PPH, estimated blood loss >500 mL	0.96 (0.46, 2.01) Ref	0.93	None	Poor
Gonzales et al.[23]	Cohort	379, 816	NA	Peru	18	<110 ≥110 <70 70 to <90 90 to <110 110 to 145 >145	PPH, estimated blood loss >500 mL	1.21 (1.08, 1.36) Ref 6.15 (3.86, 9.78) 2.62 (2.03, 3.38) 1.01 (0.88, 1.15) Ref 0.84 (0.67, 1.05)	0.0008 0.002 0.002 >0.05 - >0.05	None Age, education, marital status, BMI, prenatal care, parity, gestational diabetes mellitus, cardiopathy in current pregnancy, gestational age at which hemoglobin was first measured, and recent migration	Poor
Kebede et al.[24]	Cohort	422	NA	Ethiopia	14	<110 ≥110	PPH, based on clinician diagnosis	7.4 (3.6, 15.3) Ref	<0.05	Confounders adjusted for but list not provided	Moderate
Luis et al.[25]	Case–control	212	27	UK	50	<80 ≥110	PPH, estimated blood loss >500 mL if vaginal delivery and >1000 mL if cesarean	2.64 (1.26, 5.55) Ref	0.01	None	Moderate
Malhotra et al.[26]	Cohort	447	27	India	7	<110 ≥110 ≥110 100—<110 70—<100 <70	PPH, definition not specified	1.53 (0.17, 13.8) Ref Ref 0.29 (0.01, 8.56) 4.82 (0.49, 47.1) 4.07 (0.25, 66.9)	0.70 0.47 0.18 0.33	None	Poor

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Study	Study type	Sample size	Mean age, years	Country	Baseline anemia, %	Exposure cutoff for hemoglobin, g/L	Outcome, definition	Lindings, Odds ratio (95% CI)	*p*-Value	Confounders adjusted	Study quality
Nyflot et al.[27]	Case–control	3123	33	Norway	4	<90 ≥90	Severe PPH, estimated blood loss >1500 mL or requiring blood transfusion	4.27 (2.79, 6.54) Ref	<0.001	Previous PPH, anticoagulant medication, severe preeclampsia, uterine fibromas, multiple pregnancy, mode of delivery, IVF, fever, induction of labor, birthweight >4500 g, parity	Moderate
Parks et al[28]	Cohort	92 247	NA	India and Pakistan	88	<110 ≥110 ≥110 100—<110 70—<100 <70	PPH, based on clinician diagnosis	0.78 (0.63, 0.96) Ref Ref 0.65 (0.52, 0.82) 0.82 (0.66, 1.02) 5.31 (3.51, 8.02)	0.018 0.0003 0.07 <0.0001	None	Moderate
Rukuni et al.[29]	Cohort	80 422	29	Scotland	9	<100 ≥100	PPH, estimated blood loss >500 mL	0.92 (0.86, 0.98) Ref	0.007	Age, parity, smoking status, ethnicity, socioeconomic status, BMI and CKD	Moderate
Selo-Ojeme et al.[30]	Case–control	208	NA	Nigeria	5	<110 ≥110	PPH, estimated blood loss >500 mL	1.29 (0.38, 4.36) Ref	0.68	None	Poor
Soltan et al.[31]	Cohort	152	25	Egypt	76	<110 ≥110 ≥110 100—<110 70—<100 <70	PPH, estimated blood loss >500 mL	7.78 (0.45, 134) Ref Ref 0.38 (0.01, 19.2) 80 (4.36, 1468) 384 (5.95, 24 784)	0.16 0.63 0.003 0.005	None None	Poor
Tort et al[32]	Cohort	3278	NA	Senegal and Mali	NA	<70 ≥70	Mortality among women with PPH; PPH defined based on clinician diagnosis	6.65 (3.77, 11.7) Ref	NA	Country, location in relation to hospital, age, number of prenatal visits, preexisting disease, gestational hypertensive disorders, referral, prolonged labor, mode of delivery and birthweight	Moderate
Wandabwa et al.[33]	Case–control	606	24	Uganda	8	<110 ≥110	PPH, estimated blood loss >500 mL, or any vaginal bleeding with hemodynamic deterioration	6.10 (1.10, 35.4) Ref	0.05	Age, distance from home to hospital, marital status, educational level, job, spouse job, type of house, need to request permission to visit hospital, who pays for treatment, previous CS, PPH, number of pregnancies	Poor

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; IVF, in vitro fertilization; NA, not available.