

CLINICAL ARTICLE

Severity of maternal anemia and the risk of giving birth to a small vulnerable newborn: A cohort analysis of the WOMAN-2 trial in four countries

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Abstract

Objective: To investigate the association between maternal hemoglobin concentration and the risk of birth to a small vulnerable newborn (SVN).

Methods: We conducted a cohort analysis of women with moderate or severe anemia enrolled in the World Maternal Antifibrinolytic Trial-2 (WOMAN-2) across Nigeria, Pakistan, Tanzania, and Zambia (August 2019 to September 2023). Maternal hemoglobin concentration at admission for vaginal birth was categorized into six groups (<50, 50–59, 60–69, 70–79, 80–89, and 90–99 g/L). The primary outcome was SVN, defined as a liveborn or stillborn preterm (<37 weeks), low birthweight (<2500 g), or small for gestational age (birth weight below the average [unsexed] 10th-centile INTERGROWTH-21st standard for gestational age). Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) with 95% confidence intervals (CIs), controlling for potential confounders.

Results: Among 14 444 women, the median hemoglobin level was 85 g/L (interquartile range [IQR] 77–91 g/L), and 39.5% (5703/14 444) of newborns were classified as SVNs. A strong inverse relationship was observed between maternal hemoglobin and SVN. Compared with women with hemoglobin of 90–99 g/L, aOR values for SVN were 1.06 (95% CI 0.97–1.16) for 80–89 g/L; 1.27 (95% CI 1.15–1.41) for 70–79 g/L; 1.44 (95% CI 1.26–1.64) for 60–69 g/L; 2.00 (95% CI 1.64–2.43) for 50–59 g/L; and 2.51 (95% CI 1.85–3.41) for <50 g/L. Sensitivity analysis, including multiple pregnancies, yielded similar results.

Conclusions: Increasing severity of maternal anemia is associated with a marked increase in the risk of giving birth to SVNs. The disproportionately higher risk observed at lower hemoglobin levels supports prioritization of women with more severe anemia for intensified monitoring and treatment in high-burden settings.

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KEYWORDS

low birth weight, maternal hemoglobin anemia, preterm birth, small for gestational age, small vulnerable newborn

1 | INTRODUCTION

Reducing maternal mortality and improving neonatal survival are essential for achieving United Nations Sustainable Development Goals (SDGs) 3.1 and 3.2 on good health and well-being by 2030.¹ Neonatal deaths remain at 2.3 million per year, and sub-Saharan Africa (SSA) and South Asia accounted for over 80% of global neonatal deaths in 2022.² Over half of neonatal deaths worldwide occur among small vulnerable newborns (SVNs)—liveborn or stillborn babies who are preterm, low birth weight (LBW), and/or small for gestational age (SGA).^{3–5}

The term “SVN” was introduced in a 2023 Lancet Series to prevent underestimation of small newborns' prevalence and emphasize that the three categories—preterm birth, LBW, and SGA—frequently occur together.^{5–8} In 2020, an estimated 26% of global live births were SVN, with higher prevalence in low- and middle-income countries (LMICs, 38%) compared with high-income countries (12%).^{5,9,10} South Asia and SSA bear the highest burden at 52% and 35%, respectively.^{9,10} In addition to the higher likelihood of neonatal death reported in the BJOG series,^{11–13} SVN babies face increased risks of childhood undernutrition,¹⁴ neurodevelopmental delays,¹⁵ and chronic diseases in adulthood.^{16,17}

Maternal anemia is most prevalent in Asia (49%) and in Africa (46%)¹⁸ and is associated with preterm and SGA births.^{19,20} The World Health Organization (WHO) defines maternal anemia as hemoglobin <110 g/L, with further classifications of mild (100–109 g/L), moderate (70–99 g/L), and severe (<70 g/L) anemia.²¹ Previous studies have demonstrated a U-shaped relationship between maternal hemoglobin and newborn outcomes, with both low (<110 g/L) and high (>130 g/L) levels associated with increased risk of LBW, preterm birth, and SGA.^{22,23} However, the existing literature has focused on individual outcomes rather than the comprehensive SVN measure, often excluded stillbirths, and provided limited evidence from the highest-burden regions. This study investigated the association between maternal hemoglobin and the risk of birth to a SVN baby in this high-risk population.

2 | MATERIALS AND METHODS

2.1 | Study design, data source, and study population

We conducted a secondary cohort analysis of data from the WOMAN-2 trial, comprising women with moderate or severe anemia in Nigeria, Pakistan, Tanzania, and Zambia.²⁴ The trial recruited pregnant women with hemoglobin concentration <100 g/L upon hospital admission for vaginal birth between August 2019

and September 2023. The birth weight and newborn status were recorded after birth.²⁴ From the WOMAN-2 participants, we excluded women delivering before 24 or after 42 weeks of gestation (not included in the modified International Fetal and Newborn Growth Consortium for the 21st Century [INTERGROWTH-21st] charts) and those with missing birth weight data. Additionally, we excluded women with multiple pregnancies from the primary analysis for comparison with other studies.^{25,26}

2.2 | Variables and measurements

Maternal hemoglobin level was the primary exposure measured upon hospital admission using the HemoCue Hb 201 analyzer (HemoCue AB, Ängelholm, Sweden) with finger-prick blood samples. Thus, the exposure represents maternal hemoglobin status at admission for birth rather than longitudinal hemoglobin measurements during pregnancy. According to the COMPARE study, the HemoCue analyzer showed 82.8% sensitivity and 82.1% specificity against the gold standard automated hematology analyzer in women.²⁷ Another study found that capillary fingerstick HemoCue readings were systematically higher than venous blood (recommended) values from the gold standard.²⁸

The primary outcome was the birth of an SVN defined as a live or stillborn baby with LBW (<2500 g), preterm birth (<37 completed gestational weeks), or SGA, defined as birth weight below the average (unsexed) 10th-centile INTERGROWTH-21st standard for gestational age.^{5–7} Because data on newborn sex were unavailable, we used the average INTERGROWTH-21st standard rather than the sex-specific birth weight-for-gestational-age centile charts.²⁹

Covariates included maternal age, country, parity, pre-birth body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), previous cesarean sections, current infections (hepatitis, malaria, tuberculosis, HIV, syphilis, or others), previous postpartum hemorrhage, diabetes, hypertension, antepartum hemorrhage, placental abnormalities, polyhydramnios, labor induction, baby's status (live or stillborn), and congenital anomalies in the newborn, based on literature review and expert knowledge, as shown in the causal-directed acyclic graph (DAG) (Figure S1).

2.3 | Statistical analysis

We performed statistical analysis using STATA 18 (StataCorp LLC, College Station, TX, USA). With 15 068 WOMAN-2 participants

and assuming a 21% SVN incidence in the reference hemoglobin group (90–99 g/L), based on a South Asian study,³⁰ our analysis had 90% power at a 5% significance level to detect a 10% relative increase in SVN risk for each lower hemoglobin category. We conducted a complete case analysis. We summarized continuous variables using means and standard deviations or medians and IQRs as appropriate, while categorical variables were summarized as frequencies and percentages. We used logistic regression to assess the association between hemoglobin concentration and SVN. We used likelihood ratio tests to assess linear trend and departure from linearity. Based on the results, we modelled hemoglobin as categorical or continuous.

For adjusted analysis, the multivariable logistic regression model adjusted for age group, parity group, previous cesarean section, placental abnormalities, antepartum hemorrhage, country, pre-birth BMI groups, presence of current infections, hypertension in pregnancy, and diabetes in pregnancy.

In a sensitivity analysis, we included multiple pregnancies. This analysis compared characteristics between singleton and multiple pregnancies, and evaluated the hemoglobin–SVN association in a dataset including all pregnancies. Additionally, we examined whether the association between maternal hemoglobin and SVN was modified by the baby's status (live birth versus stillborn), as differences in survival status could reflect distinct biological mechanisms or reporting biases that influence the observed relationship.

The statistical analysis plan for this secondary analysis was finalized after access to the de-identified WOMAN-2 dataset had been granted but before any statistical analyses were undertaken. The analysis plan was reviewed during the scientific and ethical approval process but was not prospectively registered or published.

2.4 | Ethics

The WOMAN-2 trial was approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee (ref: 15194) on May 10, 2018; the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007-29/09/2019) on September 29, 2019; the National Bioethics Committee of Pakistan (NBC-340) on November 27, 2018; the National Institute for Medical Research of Tanzania (NIMR/HQ/R.8a/Vol. IX/3767) on August 19, 2021; and the University of Zambia Biomedical Research Ethics Committee (ref: 001-04-19) on February 2, 2019. Local site-specific ethical approvals were also obtained where required. All these approvals were obtained before the WOMAN-2 commencement. Fully competent women provided written consent, while proxy consent, deferred consent, or waivers (with later written consent) were used for incapacitated participants. For women under 18 years, consent was co-signed by a responsible adult witness. This secondary analysis was approved by the LSHTM's Master of Science (MSc) Ethics Committee (ref. 30094) on May 13, 2024.

3 | RESULTS

3.1 | Study participants

Among 15068 women enrolled in the WOMAN-2 trial, 14444 (95.9%) met the inclusion criteria for our primary analysis. We excluded women with multiple pregnancies ($n=583$, 3.9%), gestational age >42 weeks ($n=31$, 0.2%), gestational age <24 weeks ($n=8$, 0.05%) and those missing birth weight data ($n=2$, 0.01%). All included women were followed up to 42 days postpartum, discharge, or death, whichever came first, with complete follow-up data available for all included participants (Figure S2).

3.2 | Maternal hemoglobin levels

Severe anemia was observed in 13.8% of participants (Table 1). The median hemoglobin concentration was 85 g/L (IQR 77–91 g/L) (Figure S3).

3.3 | Small vulnerable newborns

Among newborns, 39.5% (5703/14444) were classified as SVN. Mean birth weight was 2841.9 g (SD 534.6), with LBW observed in 15.3%. Median gestational age was 38.0 weeks (IQR 37–39), with 21.7% of babies born preterm (<37 weeks) and 19.9% classified as SGA. Of the 5703 SVN babies, 6.7% were stillborn and 3.6% had congenital anomalies (Table 2). Nearly a third (29.9%) of the SVN babies were preterm, only 31.4% were SGA, only 19.8% were both LBW and preterm, 13.6% were both LBW and SGA, 5.3% met all three criteria (LBW, preterm, and SGA), and none were LBW only (Figure S4).

3.4 | Association between hemoglobin levels and SVN risk

The proportion of women giving birth to SVN babies increased as hemoglobin levels decreased: 35.0% in women with hemoglobin of 90–99 g/L, rising to 65.1% for women with hemoglobin levels <50 g/L. Compared with women with hemoglobin of 90–99 g/L, the crude odds of giving birth to a SVN baby (liveborn or stillborn) increased progressively with decreasing hemoglobin levels, ranging from a 10% increased odds for women with hemoglobin of 80–89 g/L (OR 1.10, 95% CI 1.02–1.20) to 246% increased odds among women with hemoglobin level <50 g/L (OR 3.46, 95% CI 2.59–4.63; $P<0.0001$) (Table 3). There was strong evidence of departure from linearity ($P=0.009$; Figure S5), so we included the hemoglobin level as a categorical variable (six groups: <50, 50–59, 60–69, 70–79, 80–89, 90–99 g/L) in the subsequent model.

After adjusting for age group, parity group, previous cesarean section, placental abnormalities, antepartum hemorrhage, country,

TABLE 1 Baseline characteristics of study participants with moderate/severe anemia in Nigeria, Pakistan, Tanzania, and Zambia (N = 14 444).

Characteristics	n (%) ^a
Hemoglobin level (g/L)	
Median (IQR)	85 (77–91)
90–99	4474 (31.0)
80–89	5381 (37.3)
70–79	2582 (17.9)
60–69	1302 (9.0)
50–59	495 (3.4)
<50	209 (1.4)
Age (years)	
Mean (SD)	27.2 (5.6)
<20	863 (6.0)
20–29	8593 (59.5)
30–39	4598 (31.8)
40+	390 (2.7)
Parity ^b	
Median (IQR)	2 (1–4)
0–1	4859 (33.6)
2–4	6957 (48.2)
5+	2628 (18.2)
Hypertension in pregnancy	
Present	1066 (7.4)
Absent	13 378 (92.6)
Pre-birth body mass index (Kg/m ²) ^c	
Mean (SD)	26.50 (3.80)
<18.5	112 (0.8)
18.5–24.9	5090 (35.2)
25.0–29.9	6934 (48.0)
30+	2308 (16.0)
Previous cesarean section	
Any	685 (4.7)
None	13 759 (95.3)
Current infection	
Any	522 (3.6)
None	13 922 (96.4)
Previous PPH history	
Yes	149 (1.0)
No	14 121 (97.8)
Unknown	174 (1.2)
Diabetes in pregnancy	
Present	86 (0.6)
Absent	14 358 (99.4)
Antepartum hemorrhage	
Present	421 (2.9)

TABLE 1 (Continued)

Characteristics	n (%) ^a
Absent	14 023 (97.1)
Placental abnormalities	
Any	459 (3.2)
None	13 985 (96.8)
Polyhydramnios	
Present	82 (0.6)
Absent	14 362 (99.4)
Labour induction	
Yes	1796 (12.4)
No	12 648 (87.6)
Country	
Pakistan	10 666 (73.8)
Zambia	629 (4.4)
Tanzania	1261 (8.7)
Nigeria	1888 (13.1)

Abbreviations: IQR, interquartile range; PPH, postpartum hemorrhage; SD, standard deviation.

^aPercentages may not add up to 100.0% due to rounding and missing data.

^bParity refers to previous pregnancies delivered alive or dead after 24 week of gestation.

^cBody mass index (calculated as weight in kilograms divided by the square of height in meters) categories: underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), obesity (30+).

pre-birth BMI groups, presence of current infections, hypertension in pregnancy, and diabetes in pregnancy, the strong association between maternal hemoglobin levels and the odds of giving birth to an SVN persisted. Compared with women with a hemoglobin level of 90–99 g/L, those with lower Hb had incrementally higher adjusted odds of SVN, ranging from 6% higher for women with a hemoglobin level of 80–89 g/L (OR 1.06, 95% CI 0.97–1.16) to 151% higher for those with hemoglobin <50 g/L (OR 2.51, 95% CI 1.85–3.41; [Table 4](#)).

3.5 | Sensitivity analysis

Women with multiple pregnancies had a similar SVN incidence to women with singleton births (41.5% vs. 39.5%). Women with multiple pregnancies had a higher risk of LBW, preterm births, and SGA babies ([Tables S1, S2](#)). After adjusting for potential confounders when including women with multiple pregnancies in the analysis, there remained strong evidence of an inverse relationship between maternal hemoglobin and SVN risk ($P < 0.0001$). Adjusted ORs ranged from 6% higher for women with a hemoglobin level of 80–89 g/L (OR 1.06, 95% CI 0.97–1.15) to 148% higher for those with hemoglobin <50 g/L (OR 2.48, 95% CI 1.81–3.36), as compared with the reference group (90–99 g/L), ([Table S3](#)). In analyses stratified by

TABLE 2 Small vulnerable newborns (SVNs) and their characteristics born to women with moderate/severe anemia in Nigeria, Pakistan, Tanzania, and Zambia (N = 14 444).

Characteristics	n (%) ^a
SVN	
Yes	5703 (39.5)
No	8741 (60.5)
Birth weight (g)	
Mean (SD)	2841.9 (534.6)
<2500	2212 (15.3)
≥2500	12 232 (84.7)
Gestational age (week)	
Median (IQR)	38.0 (37–39)
<37	3139 (21.7)
≥37	11 305 (78.3)
Size for gestational age	
Small	2869 (19.9)
Appropriate/large	11 575 (80.1)
Congenital anomalies	
Present	523 (3.6)
Absent	13 921 (96.4)
Status	
Liveborn	13 474 (93.3)
Stillborn	970 (6.7)

Note: SVN is a baby with low birth weight, who is small for gestational age, or preterm; low birth weight (<2500 g); preterm (<37 week of gestation); size for gestational age is classified as small if birth weight is below the average (unsexed) 10th-centile INTERGROWTH-21st standard for gestational age because newborn sex data were unavailable; stillbirth is defined as fetal death at or after 24 weeks of gestation.

Abbreviations: IQR, interquartile range; SD standard deviation.

^aPercentages may not add up to 100.0% due to rounding.

birth status (live birth vs. stillborn) there was no evidence of interaction; the association between maternal hemoglobin and SVN did not differ by whether the outcome was a live birth or a stillbirth. In an additional sensitivity analysis excluding women with antepartum hemorrhage, the hemoglobin–SVN association remained materially unchanged, with a clear dose–response pattern across hemoglobin categories (e.g. adjusted OR for <50 g/L: 2.54, 95% CI 1.87–3.45).

4 | DISCUSSION

4.1 | Main findings

In a large cohort of women giving birth with moderate or severe anemia across Nigeria, Pakistan, Tanzania, and Zambia, we found strong evidence of a dose–response relationship between maternal hemoglobin concentration and the odds of giving birth to a SVN (stillborn

or liveborn). Sensitivity analysis, including women with multiple pregnancies, yielded similar results.

4.2 | Strengths and limitations

A strength of our study was that it addressed a recommendation from the Lancet Series on SVN for more research investigating mechanisms for small newborns using the composite SVN outcome. This approach helps to prevent underestimation of newborn vulnerability and emphasizes that the three categories—preterm birth, LBW, and SGA—often co-occur in the same baby^{5–8} compared with individual outcomes alone. Second, this is the first study to investigate the association between maternal hemoglobin and both liveborn and stillborn SVN. By contrast, most previous studies limited their analyses to liveborn infants; our inclusion of stillbirths addressed the gap in earlier research.^{9,10} Third, although the observed incidence of SVN in the reference hemoglobin group was higher than assumed in the a priori power calculation (35% vs. 21%), the large sample size provided sufficient statistical power to detect associations while adjusting for several important potential confounders. The use of standardized data collection procedures across study sites implemented by well-trained research fellows as part of the WOMAN-2 trial protocol reduced the risk of information bias. In addition, the very low levels of missing data and loss to follow-up helped to reduce the potential for selection bias.

However, exposure misclassification was possible since the HemoCue 201 analyzer with capillary blood samples may have systematically underestimated maternal hemoglobin levels compared with the gold standard method of blood analysis.²⁸ This could have resulted in non-differential misclassification, likely biasing our observed odds ratios toward the null. In addition, maternal hemoglobin was measured only once, on admission for birth, and therefore reflects hemoglobin status at delivery rather than throughout pregnancy. Consequently, we were unable to assess the influence of changes in hemoglobin concentration across gestation on the risk of SVN. Second, outcome misclassification may have occurred due to gestational age estimation using the last menstrual period for some women (compared with the more accurate method using first-trimester ultrasound dates)³¹ and due to the use of average (unsexed) 10th-centile INTERGROWTH-21st birth weight standard (despite known differences in male and female fetal growth trajectories), necessitated by the lack of newborn sex data.³² Both issues likely introduced non-differential misclassification, biasing the true odds ratio for the hemoglobin–SVN relationship toward the null. Third, although we adjusted for several clinically relevant confounders identified a priori using a directed acyclic graph, residual confounding from unmeasured or incompletely measured factors, such as socioeconomic factors, genetic factors, or environmental exposures, cannot be excluded. Finally, findings should be interpreted in the context of the study population. The WOMAN-2 trial enrolled women with moderate or severe anemia who delivered in hospital

TABLE 3 Maternal hemoglobin level, other covariates, and their unadjusted association with small vulnerable newborn (SVN) delivery among women with moderate/severe anemia in Nigeria, Pakistan, Tanzania, and Zambia (N = 14 444).

Characteristics	N (%) ^a	SVN (n [%]) ^a	OR (95% CI)	P-value ^b
Hemoglobin level (g/L) ^c				
90–99	4474 (31.0)	1566 (35.0)	1	<0.0001
80–89	5381 (37.3)	2005 (37.3)	1.10 (1.02–1.20)	
70–79	2582 (17.9)	1095 (42.4)	1.37 (1.24–1.51)	
60–69	1302 (9.0)	619 (47.5)	1.68 (1.49–1.91)	
50–59	495 (3.4)	282 (56.9)	2.45 (2.03–2.95)	
<50	209 (1.4)	136 (65.1)	3.46 (2.59–4.63)	
Age (years)				
<20	863 (6.0)	379 (43.9)	1.16 (1.01–1.34)	0.0002
20–29	8593 (59.5)	3461 (40.3)	1	
30–39	4598 (31.8)	1710 (37.2)	0.88 (0.82–0.95)	
40+	390 (2.7)	153 (39.2)	0.96 (0.78–1.18)	
Parity				
0–1	4859 (33.6)	2115 (43.5)	1.34 (1.24–1.44)	<0.0001
2–4	6957 (48.2)	2543 (36.6)	1	
5+	2628 (18.2)	1045 (39.8)	1.14 (1.05–1.26)	
Hypertension in pregnancy				
Absent	13 378 (92.6)	5128 (38.3)	1	<0.0001
Present	1066 (7.4)	575 (53.9)	1.88 (1.66–2.14)	
Pre-birth body mass index (Kg/m ²)				
<18.5	112 (0.8)	66 (58.9)	1.84 (1.25–2.69)	<0.0001
18.5–24.9	5090 (35.2)	2233 (43.9)	1	
25.0–29.9	6934 (48.0)	2631 (37.9)	0.78 (0.73–0.84)	
30+	2308 (16.0)	773 (33.5)	0.64 (0.58–0.71)	
Previous cesarean section				
None	13 759 (95.3)	5398 (39.2)	1	0.006
Any	685 (4.7)	305 (44.5)	1.24 (1.07–1.45)	
Current infections				
None	13 922 (96.4)	5457 (39.2)	1	0.0003
Any	522 (3.6)	246 (47.1)	1.38 (1.16–1.65)	
Previous postpartum hemorrhage				
Yes	149 (1.0)	57 (38.3)	0.95 (0.68–1.32)	0.90
No	14 121 (97.8)	5575 (39.5)	1	
Unknown	174 (1.2)	71 (40.8)	1.06 (0.78–1.43)	
Diabetes in pregnancy				
Absent	14 358 (99.4)	5669 (39.5)	1	0.99
Present	86 (0.6)	34 (39.5)	1.00 (0.65–1.55)	
Antepartum hemorrhage				
Absent	14 023 (97.1)	5379 (38.4)	1	<0.0001
Present	421 (2.9)	324 (77.0)	5.37 (4.27–6.75)	
Placental abnormalities				
None	13 985 (96.8)	5340 (38.2)	1	<0.0001
Any	459 (3.2)	363 (79.1)	6.12 (4.88–7.69)	
Polyhydramnios				

TABLE 3 (Continued)

Characteristics	N (%) ^a	SVN (n [%]) ^a	OR (95% CI)	P-value ^b
Absent	14 362 (99.4)	5669 (39.5)	1	0.71
Present	82 (0.6)	34 (41.5)	1.09 (0.70–1.69)	
Labor induction				
No	12 648 (87.6)	4961 (39.2)	1	0.09
Yes	1796 (12.4)	742 (41.3)	1.09 (0.99–1.21)	
Country				
Pakistan	10 666 (73.8)	4328 (40.6)	1	<0.0001
Zambia	629 (4.4)	347 (55.2)	1.80 (1.53–2.12)	
Tanzania	1261 (8.7)	369 (29.3)	0.61 (0.53–0.69)	
Nigeria	1888 (13.1)	659 (34.9)	0.79 (0.71–0.87)	
Congenital anomalies				
Absent	13 921 (96.4)	5351 (38.4)	1	<0.0001
Present	523 (3.6)	352 (67.3)	3.30 (2.74–3.97)	
Status				
Alive	13 474 (93.28)	4915 (36.5)	1	<0.0001
Stillbirth ^d	970 (6.7)	788 (81.2)	7.54 (6.39–8.89)	

Abbreviations: CI confidence interval; IQR, interquartile range; OR, odds ratio; SD standard deviation.

^aPercentages may not add up to 100.0% due to rounding and missing data.

^bLikelihood ratio test (LRT) *P*-values.

^cTest for linear trend (LRT *P*-value <0.0001) and test for departure from linearity (LRT *P*-value = 0.009). LRT *P*-values.

^dStillbirth is defined as fetal death at or after 24 weeks of gestation.

across four LMICs. Therefore, the findings may not be directly applicable to women delivering outside health facilities or to populations in other settings. Additionally, our study did not have data for women with hemoglobin concentration above 100g/L to enable us to consider the association across the whole hemoglobin spectrum.

4.3 | Interpretation

The inverse hemoglobin–SVN relationship we observed among women with moderate and severe anemia aligns with findings from previous studies, also in LMICs, regarding maternal anemia, although this is the first paper to consider anemia with combined SVN outcomes for liveborn babies and stillbirths.^{22,26,33–35} A multi-country cohort found a U-shaped relationship between maternal hemoglobin level and preterm birth risk, with both low (<110g/L) and very high (>145g/L) hemoglobin levels associated with increased risk.²⁶ Similarly, a systematic review across multiple regions found that lower maternal hemoglobin (<110g/L) was consistently associated with increased odds of LBW, SGA, and preterm births.²² While the overall trends were similar, our study estimated the associations to be higher in magnitude than those in previous research. These variations may be due to different statistical methods, study populations (inclusion of women with mild anemia and normal hemoglobin levels in other studies), consideration of hemoglobin timing throughout pregnancy, use of individual outcomes rather than composite SVN measure, and the extent of

confounder adjustment. Although the composite SVN outcome captures the overall burden of newborn vulnerability and reflects the frequent co-occurrence of preterm birth, low birth weight, and SGA, these individual components may not contribute equally to the observed association with maternal hemoglobin.

An alternative explanation for part of the observed association is reverse causation. In some cases, intrauterine fetal death may precipitate disseminated intravascular coagulation, leading to antepartum hemorrhage and acute maternal blood loss, which could lower maternal hemoglobin concentration close to delivery. However, this mechanism is unlikely to fully explain our findings. We adjusted for antepartum hemorrhage and placental abnormalities in multivariable analyses, observed a clear dose–response relationship across hemoglobin categories, and found no evidence that the association differed by birth status (live birth versus stillbirth). Furthermore, in a sensitivity analysis excluding women with antepartum hemorrhage, the hemoglobin–SVN association remained nearly unchanged, with similar effect sizes across hemoglobin categories.

The observed relationship between low maternal hemoglobin and increased odds of having a SVN baby demonstrates a strength of association and consistency with previous studies.^{22,26,33–35} Additionally, the biological gradient was evident with lower hemoglobin levels associated with higher odds of SVN. Plausible causal mechanisms include preterm labor induced by altered placental production of nitric oxide and increased production of prostaglandin F_{2α}, cortisol, and oxytocin from the mother and fetus in response to stress from maternal anemia.³⁶ Additionally, fetal growth restriction

TABLE 4 Adjusted estimates of the odds ratio for maternal hemoglobin-small vulnerable newborn association estimated by logistic regression ($N = 14\,444$).

Variable	cOR (95% CI)	aOR (95% CI) ^a	P-value ^b
Maternal hemoglobin level (g/L)			
90–99	1	1	<0.0001
80–89	1.10 (1.02–1.20)	1.06 (0.97–1.16)	
70–79	1.37 (1.24–1.51)	1.27 (1.15–1.41)	
60–69	1.68 (1.49–1.91)	1.44 (1.26–1.64)	
50–59	2.45 (2.03–2.95)	2.00 (1.64–2.43)	
<50	3.46 (2.59–4.63)	2.51 (1.85–3.41)	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio.

^aOdds ratio adjusted for age group, parity group, previous cesarean section, placental abnormalities, antepartum hemorrhage, country, pre-birth body mass index groups, presence of current infections, hypertension in pregnancy, and diabetes in pregnancy.

^bP-value from likelihood ratio test for adjusted association.

may result from reduced oxygen delivery, increased oxidative stress and inflammation affecting placental function, and impaired placental angiogenesis, impacting fetal growth.^{8,37,38}

5 | CONCLUSIONS

This study demonstrates a clear gradient between maternal hemoglobin concentration and the odds of giving birth to a small vulnerable newborn among women with moderate or severe anemia in sub-Saharan Africa and South Asia. Lower hemoglobin levels were associated with progressively higher odds of adverse outcomes, supporting a clinically meaningful association between the severity of maternal anemia and newborn vulnerability.

These findings highlight the importance of preventing and effectively managing maternal anemia during pregnancy and provide evidence to inform future research on whether improving maternal hemoglobin concentrations can reduce the burden of SVN. Further research should evaluate whether targeted management of severe anemia can reduce the burden of SVN and stillbirths. Studies incorporating repeated hemoglobin measurements across pregnancy would help to clarify temporal relationships and strengthen causal inference.

AUTHOR CONTRIBUTIONS

HO, AB, JLei, and EW planned the analyses. HO, AB, JLei, EW, JLaw, and HB drafted the manuscript with input from all authors. HO performed the statistical analyses and generated the figures. All authors interpreted the data. IR and HSS were the co-lead investigators of the WOMAN-2 trial. RC was the lead coordinating investigator in Pakistan. FAB and OO were the lead coordinating investigators in Nigeria. PM was the lead coordinating investigator in Tanzania. AKay and KJ managed the trial in Pakistan. EB was responsible for overall study management. DP managed the data

collection. All members of the writing committee were involved in the development of the original manuscript and read and approved the final version submitted. All members of the writing committee had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the WOMAN-2 trial investigators and the London School of Hygiene & Tropical Medicine, but restrictions apply to the availability of these data, which were used under licence for the current study and are therefore not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the WOMAN-2 Trial Steering Committee.

CONSENT FOR PUBLICATION

The authors confirm this work is original and has not been published elsewhere in part or in whole.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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