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Abstract

Background: Anaemia in pregnancy is a common condition associated with adverse maternal outcomes, including postpartum haemorrhage (PPH). However, the temporality of this relationship remains poorly understood, as most studies rely on haemoglobin values measured at delivery, making it difficult to distinguish cause from consequence.

Objective: To examine the association between haematologic and iron-related biomarkers measured at 36 weeks' gestation and the risk of PPH.

Methods: We conducted a secondary analysis of the IVON trial, a multicentre randomized controlled trial comparing intravenous versus oral iron therapy among pregnant women with moderate to severe anaemia in Nigeria. We included 787 women with biomarker data at 36 weeks and recorded estimated blood loss at delivery. Haemoglobin, serum ferritin, transferrin saturation, and platelet count were analysed. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using log-binomial or Poisson regression, adjusting for relevant sociodemographic and clinical covariates. Missing data were handled using multiple imputation. False discovery rate control was applied to account for multiple testing.

Results: The prevalence of anaemia was 76% at 36 weeks and 58% at delivery. The incidence of PPH was 13%. Haemoglobin concentration at 36 weeks was not significantly associated with PPH risk (adjusted RR: 0.92; 95% CI: 0.78, 1.08). Neither serum ferritin, iron deficiency, nor thrombocytopenia at 36 weeks showed statistically significant associations with PPH. In contrast, haemoglobin (RR: 0.87, 95% CI: 0.75, 0.92) and transferrin concentrations (RR: 0.52, 95% CI: 0.36, 0.75) measured at delivery were significantly associated with lower PPH risk, with every 1g/dl and 100µg/dl increase in haemoglobin and transferrin corresponding to 13% and 48% lower risk of PPH, respectively.

Conclusion: Haematologic and iron biomarkers measured at 36 weeks were not significantly associated with PPH, suggesting that prenatal anaemia may not be a strong independent predictor of bleeding risk, though women on the IVON trial had been treated with Iron, and therefore most of the anaemic women were not iron deficient.

Trial registration: International Standard Randomized Controlled Trial Number (ISRCTN) ISRCTN63484804 (<https://doi.org/10.1186/ISRCTN63484804>). Registered on: 10/12/2020

Keywords: anaemia in pregnancy, postpartum haemorrhage, iron deficiency, haemoglobin, temporality, transferrin, ferritin, randomized controlled trial, maternal outcomes

Introduction

Anaemia remains a major global health concern affecting women of reproductive age¹. In 2019, it affected 37% of pregnant and 30% of non-pregnant women worldwide². However, the burden remains particularly high in sub-Saharan Africa³. In Nigeria, the most populous African country, anaemia affects an estimated 20 – 40% of pregnant women⁴. Iron deficiency (ID) is the most common cause, but infections, infestations, haemoglobin disorders, and socio-environmental factors also contribute^{1,5}. Anaemia during pregnancy is associated with severe adverse feto-maternal outcomes, especially when haemoglobin levels reduce below 10 g/dl^{6,7}. One of the poor maternal outcomes associated with anaemia in pregnancy is postpartum haemorrhage (PPH)⁸. In addition to health consequences, anaemia in pregnancy can also have economic implications for families, communities, and countries. Every \$1 invested in reducing anaemia in women yields an estimated \$12 in economic returns⁹.

PPH is the leading cause of maternal mortality worldwide, accounting for 30-50% of maternal deaths¹⁰. Nigeria alone accounts for 23% of global maternal deaths¹⁰, and PPH is the leading direct cause. The most widely accepted definition of PPH is based on the amount of blood loss at birth; following vaginal birth, PPH is defined as blood loss of ≥ 500 ml, and severe PPH as blood loss of ≥ 1000 ml¹¹. Approximately ~80% of women with PPH have identifiable risk factors¹². Recent meta-analyses⁸ and many primary studies have shown a relationship between anaemia and PPH^{13,14}. However, these studies were largely conducted in developed country settings, raising questions about the applicability of the findings to Nigerian populations, where both anaemia and PPH have unique epidemiologic profiles.

Moreover, prior studies of anaemia and PPH have focused on either antenatal anaemia or delivery anaemia as the exposure. Because blood loss and haemoglobin measurements occur in close temporal proximity, such studies are practically cross-sectional, and the directionality of the relationship remains uncertain. It is unclear whether anaemia precedes and contributes to PPH risk, or whether it reflects early effects of blood loss. To address this gap, this study aimed to assess the association between hematologic parameters measured at 36 weeks' gestation (haemoglobin concentration, anaemia severity, iron status, and platelet count) and the risk of PPH among Nigerian women.

Methodology

Design

This study is a *post-hoc* analysis of the IVON trial, a multicentre open-label randomised controlled trial (RCT) of intravenous (IV) versus oral iron in the treatment of iron deficiency anaemia (IDA) among Nigerian pregnant women¹⁵. The trial was conducted between August 10, 2021, and December 15, 2022, at eleven antenatal clinics in Lagos and Kano, Nigeria's most populous states. These two states are in different geographical zones and vary substantially regarding culture, religion, and health system characteristics.

In the original trial, pregnant women with IDA were randomly assigned in a 1:1 ratio to receive intravenous iron or oral iron therapy. Participants in the IV iron group received a single dose of ferric carboxymaltose, 20 mg/kg in normal saline up to a maximum of 1,000 mg. Those in the oral iron group received 200 mg ferrous sulphate (containing 65 mg elemental iron) three times daily, consistent with standard clinical practice for anaemia treatment in Nigeria. Randomisation was performed using Sealed Envelope™ (London, UK), a web-based randomisation service, in balanced blocks of 4x4. Participants were followed monthly until delivery and again at six weeks postpartum. Blood samples were collected at study enrolment (baseline), 36 weeks' gestation, immediately following delivery, and six weeks' postpartum.

The parent trial enrolled 1,056 participants, with the sample size powered to detect a 14% absolute difference (16% vs. 30%) in anaemia prevalence at 36 weeks between the two arms, assuming a 5% significance level and 90% statistical power, with 15% loss to follow-up. Full details of the trial design⁴ and main findings¹⁵ have been published elsewhere.

The present analysis focuses on a subgroup of trial participants who had biomarker data available at the 36-week visit and within the first hour following delivery, to evaluate the relationship between hematologic parameters at these points and PPH.

Population

A total of 1056 eligible and consenting pregnant women aged 15 – 49 years with moderate or severe anaemia (haemoglobin <10g/dL) presenting to antenatal care between 20 and 32 weeks of gestation were recruited. Screening haemoglobin concentration was based on a point-of-care test using Hemocue 301 device (HemoCue America, Brea, CA, USA). Gestational age was determined based on the last menstrual period (LMP), or from an early ultrasound scan performed before 22 weeks' gestation.

Women were excluded if they had any of the following: significant vaginal bleeding defined as bleeding from the vagina greater than spotting, major surgery or blood transfusion in the last three months; symptomatic anaemia, anaemia from known causes such as sickle cell anaemia or HIV infection, clinically confirmed malabsorption syndrome, previous hypersensitivity to any form of iron, severe allergic reaction such as severe asthma, history of any autoimmune disease, or pre-existing maternal depression or other psychiatric illness.

Eligible and consenting participants were randomized in a 1:1 ratio to either the IV iron group, receiving a single dose of ferric carboxymaltose infusion (FCM), or the daily oral iron (FS) group, as described in the trial protocol⁴.

Study procedures

At enrolment, Interviewer-administered questionnaires were used to collect sociodemographic and obstetric history data, including age, parity, date of last menstrual period, and educational attainment. Research physicians and nurses performed detailed clinical assessments at each clinic visit.

All participants received standard antenatal care as per Nigerian national guidelines¹⁶, which included routine antenatal visits every 1 – 4 weeks depending on gestational age, intermittent preventive treatment twice for malaria, daily supplementation with 5 mg folic acid and 100 mg of vitamin C three times daily until delivery.

For participants in the oral iron group, adherence was assessed through pill counts and calculated as the percentage of dispensed pills that were consumed. To support retention and minimize loss to follow-up, participants were tracked using SMS appointment reminders, phone calls, and home visits as necessary. Blood samples were collected during clinic visits, or at participants' homes whenever necessary.

Laboratory procedures

At 36 weeks' gestation and within the first hour following delivery, venous blood samples were collected for laboratory analysis at a central laboratory, including a complete blood count (CBC), serum iron, total iron-binding capacity (TIBC), transferrin saturation, and serum ferritin concentration. The CBC was conducted using the Sysmex instruments, specifically the model XN550/XN350. All samples were processed at Synlab Nigeria. Serum iron levels were analysed using advanced Beckman instruments, specifically the AU 680 and DXC 700

models. The Abbott Architect i1000SR instrument was utilized for serum ferritin testing. Transferrin levels were measured using an immunoturbidimetric test, which is also conducted on the Beckman Coulter AU 680 and DXC 700 instruments. TIBC ($\mu\text{mol/L}$) was calculated by multiplying the serum transferrin concentration in g/L by 25.2, while the transferrin saturation was calculated by dividing serum iron ($\mu\text{mol/L}$) by the TIBC ($\mu\text{mol/L}$) and multiplying by 100¹⁷.

Anaemia at 36 weeks' gestation was defined as a haemoglobin concentration $< 11\text{g/dL}$ and was based on the CBC results. Anaemia severity was further categorized as $10 - 10.9\text{ g/dL}$ for mild, $7 - 9.9\text{g/dL}$ for moderate, and $<7\text{ g/dL}$ for severe categories. Iron deficiency (ID) was defined using serum ferritin $<30\text{ }\mu\text{g/L}$, and IDA was defined as the presence of both ID and anaemia. The following thresholds were used to determine abnormal biomarker values: $<35\%$ for packed cell volume (PCV), $\leq 70\text{ fL}$ for mean corpuscular volume (MCV), <4.0 or $>11.0\text{ cells/L}$ for white blood cell count, <150 or $>450\text{ cells/L}$ for platelet count, <250 or $>450\mu\text{g/dl}$ for serum transferrin, and $<30\text{ }\mu\text{g/L}$ for serum iron.

Case definitions and outcomes

On-call midwives documented delivery and birth outcomes and collected blood samples at the time of delivery (within the first hour). Postpartum blood loss was estimated using the gravimetric method, in which a standard predetermined under-pad was placed beneath the woman during the delivery. The difference in weight before and after delivery (in grams) was used to estimate the volume of blood loss in millilitres¹⁸. PPH was defined according to standard clinical criteria as $>500\text{ml}$ for vaginal delivery and $>1000\text{ml}$ for caesarean section¹⁹.

Statistical analysis

Sociodemographic and clinical parameters were summarized using frequencies and percentages and presented in tables and figures. Hematologic and iron status biomarkers at 36 weeks' gestation and at delivery were described using medians and interquartile ranges (IQR), as these do not require normally distributed data. The median of the differences between the levels of each biomarker at 36 weeks' vs delivery was calculated using the Hodges-Lehmann estimator, with accompanying 95% confidence intervals (CIs)²⁰. Biomarkers were also categorised into normal and abnormal based on pre-specified clinical thresholds, or in the case of haemoglobin, by anaemia severity. Categorical comparisons between the two timepoints were conducted using Chi-squared tests.

The association between selected sociodemographic and clinical variables and postpartum haemorrhage (PPH) was assessed using log-binomial regression models to estimate risk ratios (RRs) with 95% CIs. When log-binomial models failed to converge, we employed Poisson regression with robust standard errors, which yields consistent though not fully efficient RR estimates²¹. In cases where zero events occurred in a stratum, we either collapsed strata or applied Firth's penalized logistic regression²² to stabilize estimates. The models were adjusted for sociodemographic and clinical characteristics, including age (continuous, in years), state (Kano and Lagos), age group (<20, 20-35, and >35), and marital Status (married vs. unmarried). In some cases, models were scaled by multiplying by 10 or by 100 to improve interpretability. All *p*-values were two-sided, and statistical significance was set at <0.05. Throughout, we reported unadjusted 95% confidence intervals alongside *p*-values adjusted for multiple testing across several biomarker comparisons using the Benjamini-Hochberg method to control the false discovery rate²³.

Missing covariate data were addressed using Multiple Imputations by Chained Equations under the assumption that data were missing at random. We created 20 imputed datasets and combined their estimates using Rubin's rules. The imputation model included all the variables in the regression models, as well as study site, location (urban vs. rural), haemoglobin at antenatal enrolment, mode of delivery (caesarean vs. vaginal), estimated income in naira, occupation, ethnicity, gravidity and recent transfusion history. Statistical analysis was conducted in RStudio (version 1.0.153) using base R and supporting packages, including *tableone*, *mice*, *sandwich* and *logistf* package²⁴⁻²⁸.

Ethics

Participants gave written informed consent at enrolment. Ethical approval was obtained from National Health Research Ethics Committee (NHREC/01/01/200704/02/2021), Lagos University Teaching Hospital Health Research Ethics Committee (ADM/DCST/HREC/APP/3971), Kano State Ministry of Health (MOH/ Off/797/T.1/2102), and Aminu Kano Teaching Hospital (NHREC/28/01/2020/AKTH/EC/2955). Permission to conduct research in the secondary and primary health facilities in Lagos State was obtained from the Lagos State Health Service Commission (LSHSC/2222/VOLIII) and Lagos State Primary Health Care Board (LS/PHCB/ MS/1128/VOL.VII/100), respectively. This study was registered at the ISRCTN

registry (ISRCTN63484804) on Dec 10, 2020, and ClinicalTrials.gov (NCT04976179) on April 7, 2021.

Results

Among the 1,056 women randomized for the IVON trial study, 862 had complete blood count measured at 36 weeks' gestation. Of these, 787 also had blood loss quantified at delivery and were therefore included in this analysis (**Figure 1**).

The majority of the women were aged 20 – 35 years, and 83% completed at least secondary education. Approximately 38% were nulliparous, while 11% were grand multiparous. The majority (77%) delivered vaginally, and 13% had PPH (**Table 1**). The sociodemographic characteristics of the study population were broadly consistent with those of the overall IVON cohort (Table 1).

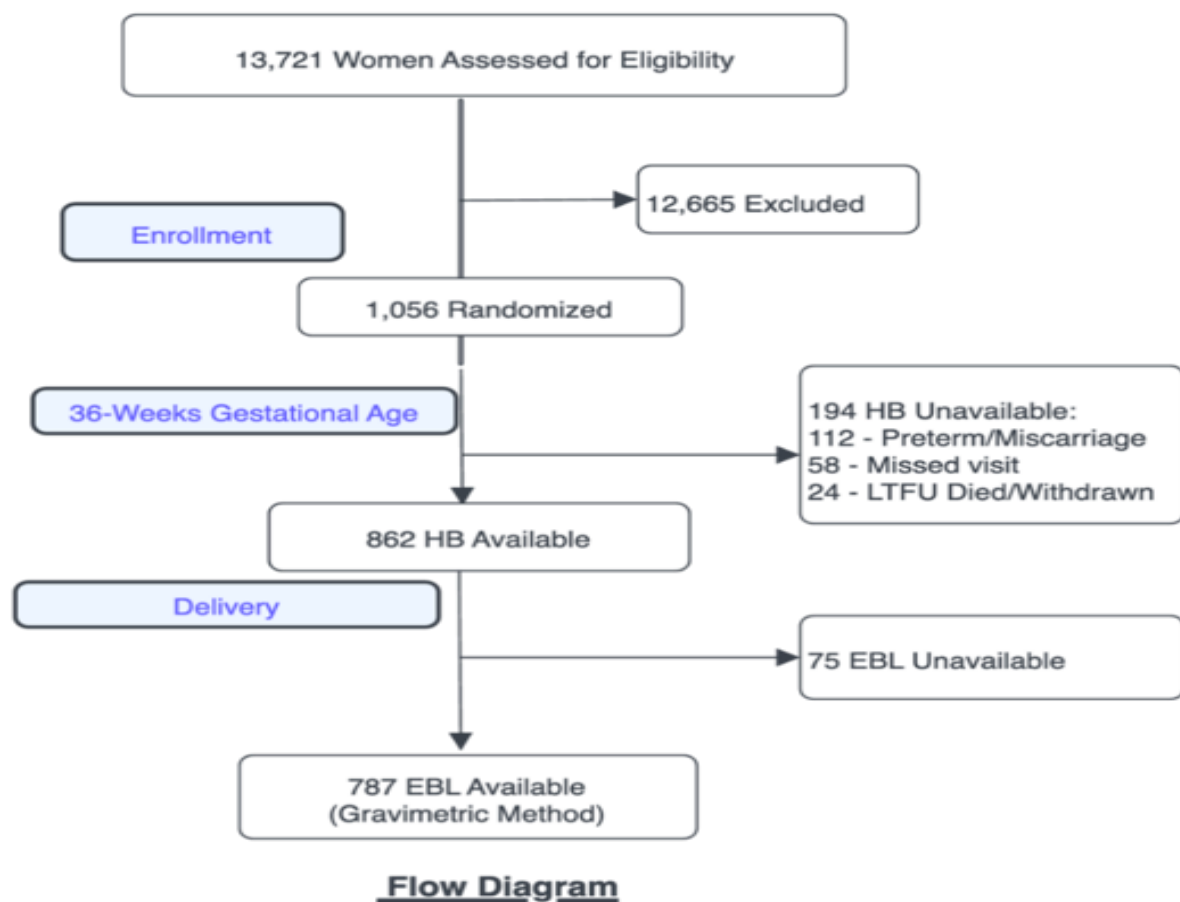


Figure 1. Flowchart of participant selection

Table 1: Sociodemographic & clinical characteristics of women who had measurements of full blood count at 36 Weeks GA and Estimated blood loss at delivery.

Characteristics	Included in this analysis, N = 787 ¹	IVON trial participants, N=1,056
Age	27.8 (5.8)	28.3 (6.02)
< 20	41 (5.2%)	55 (5.2%)
20-35	659 (84%)	875 (82.9%)
> 35	87 (11%)	126 (11.9%)
Marital status		
Married	756 (96%)	1010 (95.6%)
Others	31 (3.9%)	46 (4.2%)
Place of residence		
Rural	62 (7.9%)	93 (8.8%)
Urban	725 (92%)	963 (91.2%)
State		
Lagos	417 (53%)	519 (49.1%)
Kano	370 (47%)	537 (50.9%)
Highest level of education		
No formal education	35 (4.4%)	69 (6.5%)
Completed Primary	99 (13%)	125 (11.8%)
Completed Secondary	399 (51%)	544 (52%)
Completed Tertiary	254 (32%)	315 (29.8%)
Occupation		
Self-Employed	359 (46%)	478 (45.3%)
Private Employment	77 (9.8%)	89 (8.4%)
Government Employment	36 (4.6%)	42 (4.0%)
Unemployed	305 (39%)	432 (41.0%)
Not applicable	10 (1.3%)	11 (1.0%)
Unknown	0 (0%)	4 (0.4%)
Estimated family income		
Less than N20,000 (\$12)	154 (20%)	235 (22.3%)
N21,000 (\$13) – N50,000 (\$32)	264 (34%)	346 (32.8%)
N51,000 (\$33) – N100,000 (\$64)	134 (17%)	176 (16.7%)
N101,000 (\$65) – N200,000 (\$129)	63 (8.0%)	73 (6.9%)
> N200,000 (\$129)	17 (2.2%)	21 (2%)
Not applicable	153 (19%)	200 (18.9%)
Parity		
0	299 (38%)	384 (36.4%)
1-4	405 (51%)	538 (51%)
> 4	83 (11%)	134 (12.7%)
Gestational age at enrollment	25.1 (3.4)	25.2 (3.47)
Trial arm		
Intravenous ferric carboxymaltose (FCM)	362 (53%)	527 (50%)
Oral ferrous sulphate (FS)	324 (47%)	529 (50%)
Delivery method*		
Caesarean Section	154 (23%)	192 (18.2%)
Vaginal Delivery	528 (77%)	696 (66%)
Estimated blood loss**		
< 500 ml	685 (87%)	819 (77.6%)

Characteristics	Included in this analysis, N = 787 ¹	IVON trial participants, N=1,056
500 – 1000 ml	93 (12%)	108 (10.2%)
> 1000 ml	9 (1.1%)	12 (1.1%)

* In the IVON Trial, 168 participants did not have their method of delivery recorded, as some were miscarriages, pre-term delivery, term deliver (but at other facility or at home)

** Likewise, estimated blood loss (EBL) was recorded for some participants but their mode of delivery not recorded. Hence, the final cohort analysis for this study in Table 3, focused on participants that had both mode of delivery and EBL recorded.

Haemoglobin concentration increased between 36 weeks' gestation and delivery, from a median of 10.3 g/dl to 10.9 g/dL. The median of differences [MoD] was 0.6 g/dl (95% CI: 0.45 to 0.65, $p < 0.001$, **Table 2**). Correspondingly, the prevalence of anaemia declined from 76% at 36 weeks' gestation to 58% at delivery (**Figure 2**).

The median serum ferritin concentration increased modestly from 83.9 µg/L to 92.4 µg/L (MoD=3.2, 95% CI: -1.4 to 6.7, p -value = 0.46). However, the proportion of women classified as iron deficient rose slightly from 30% at 36weeks gestation to 43% at delivery. Other iron status-related measures, including serum iron, transferrin, and saturation percent, increased significantly (p -values < 0.05 for all comparisons). Platelet count remained relatively stable, with a median of 218×10^9 cells/L vs. 222×10^9 cells/L. However, the proportion of women with thrombocytopenia increased slightly from 12.2% vs 14.6%.

Table 2. Hematologic parameters of Nigerian women in the IVON trial

Parameter	36 weeks ^a	Delivery ^a	Effect estimate (95% CI) ^b	Adj. p-value ^c
Hematologic				
Haemoglobin, g/dL	10.30 (9.60–11.00)	10.90 (9.90–11.80)	0.60 (0.45 to 0.65)	< 0.001
Red Blood Cell, L	3.64 (3.32–3.96)	3.82 (3.45–4.22)	0.22 (0.16 to 0.24)	< 0.001
Abnormal	621 (79)	521 (66)		
MCV, fL	90.00 (84.00–96.40)	89.90 (84.57–96.80)	0.40 (0.10 to 0.85)	0.017
Abnormal	9 (1.1)	65 (8.3)		
MCH, pg	28.70 (26.80–30.50)	28.60 (26.90–30.50)	0.00 (-0.10 to 0.05)	0.33
MCHC, g/dL	32.10 (30.10–33.20)	31.80 (30.10–33.10)	-0.10 (-0.30 to -0.00)	0.026
RDW, %	14.50 (13.60–15.75)	14.50 (13.60–15.80)	0.00 (-0.10 to 0.10)	0.78
WBC, L	6.55 (5.45–7.88)	9.71 (6.88–12.73)	2.99 (2.83 to 3.46)	< 0.001
Abnormal	94 (12)	375 (48)		
Absolute Neutrophils, L	4.18 (3.35–5.39)	7.42 (4.38–10.46)	2.90 (2.77 to 3.38)	< 0.001
Absolute Lymphocytes, L	1.56 (1.30–1.87)	1.46 (1.00–1.94)	-0.10 (-0.15 to -0.04)	0.001
Absolute Monocytes, L	0.52 (0.41–0.64)	0.59 (0.42–0.86)	0.09 (0.08 to 0.13)	< 0.001
Absolute Eosinophils, L	0.08 (0.04–0.14)	0.03 (0.01–0.09)	-0.04 (-0.05 to -0.04)	< 0.001
Absolute Basophils, L	0.05 (0.03–0.09)	0.05 (0.04–0.09)	0.00 (0.00 to 0.01)	0.004
Platelet Count, L	218.00 (179.00–260.50)	221.50 (176.00–271.00)	3.00 (-0.50 to 8.50)	0.067
Abnormal	99 (12.6)	119 (16.3)		
Low	96 (12.2)	107 (14.6)		
Iron status markers				
Ferritin, µg/L	83.90 (46.93–157.85)	92.44 (53.33–153.30)	3.15 (-1.39 to 6.66)	0.20
Iron serum, µmol/L	16.50 (13.00–20.00)	10.10 (6.80–13.90)	5.80 (-6.45 to -5.35)	< 0.001
Transferrin, µg /dL	290.00 (251.00–323.00)	277.00 (246.00–325.00)	-4.00 (-10.50 to -2.00)	0.003
Saturation, %	22.70 (17.40–28.80)	14.25 (9.80–20.00)	-7.40 (-8.55 to -6.95)	< 0.001

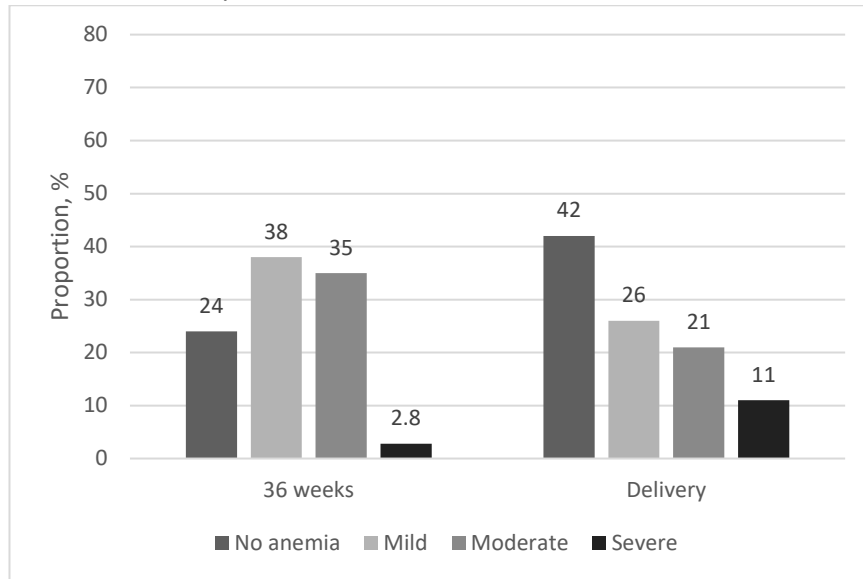
a. Values are median (IQR) for continuous variables and number (percentage) of participants who experience the outcome for categorical outcomes

b. Effect estimates are median of differences for continuous variables and risk ratios for categorical outcomes

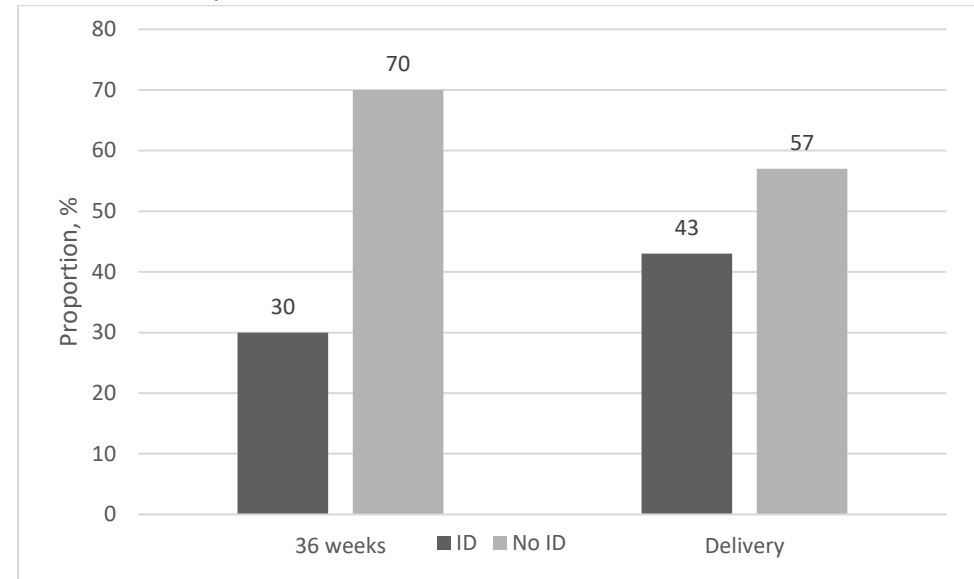
c. Adjusted p-values are based on the Benjamini-Hochberg correction

Figure 2. Trajectory of anaemia and iron deficiency

A] Anemia severity



B] Iron deficiency



Association of haematologic markers with PPH

Haemoglobin concentration at 36 weeks' gestation was not significantly associated with the risk of PPH (RR=0.92, 95% CI: 0.78, 1.08; p -value = 0.51; **Table 3**). Similarly, anaemia severity at 36 weeks' gestation showed no significant relationship with PPH. Compared to women with no anaemia, the risk of PPH was higher but non-significant among those with mild anaemia (RR: 1.17, 95% CI: 0.71, 1.91) and moderate to severe anaemia (RR: 1.44, 95% CI: 0.89, 2.33). Neither ferritin concentration (RR for every 100 $\mu\text{g/L}$ =0.82, 95% CI: 0.67, 0.99; p -value = 0.11) nor iron deficiency at 36 weeks' gestation (RR=0.77, 95% CI: 0.48, 1.22; p -value = 0.51) were significantly related to the risk of PPH. There were also no significant relationships of platelet count (RR=0.89, 95% CI: 0.68, 1.15; p -value = 0.53) and abnormal platelet count (RR=0.74, 95% CI: 0.40, 1.38; p -value = 0.51) with the risk of PPH.

In contrast, haemoglobin concentration at delivery was significantly related to the risk of PPH. For every 1g/dL increase in delivery haemoglobin, the risk of PPH decreased by 13% (RR: 0.87, 95% CI: 0.75, 0.92; p -value < 0.001; **Table 4**). Women with moderate to severe anaemia at delivery were 2.67 times more likely to have PPH (95% CI: 1.74, 4.09; p -value <0.001). Serum transferrin at delivery was also significantly associated with reduced PPH risk, with each 100 $\mu\text{g/dL}$ increase corresponding to a 48% lower risk (RR: 0.52, 95% CI: 0.36, 0.75; p -value < 0.001). There were no significant relationships with ferritin concentration (RR per 100 $\mu\text{g/L}$: 1.00, 95% CI: 0.95, 1.05; p -value = 0.99), iron deficiency (RR: 0.90, 95% CI: 0.60, 1.34; p -value = 0.74), platelet count (RR: 0.88, 95% CI: 0.70, 1.11; p -value = 0.51) or abnormal platelet count (RR: 1.25, 95% CI: 0.80, 1.96; p -value = 0.51).

Table 3: Hematologic parameters at 36 weeks gestation and the risk of postpartum haemorrhage among women in Nigeria

Outcome	PPH (N=102)	No PPH (N=685)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adj. p-value ^c
Haemoglobin, g/dL, mean (SD)	10.22 (1.03)	10.34 (1.18)	0.93 (0.80, 1.09)	0.92 (0.78, 1.08)	0.51
Anaemia at 36 weeks					
No anemia, %	22 (21.6)	184 (26.9)	Ref	Ref	
Mild, %	38 (37.3)	261 (38.1)	1.19 (0.73, 1.95)	1.17 (0.71, 1.91)	0.69
Moderate/Severe, %	42 (41.2)	240 (35.0)	1.39 (0.87, 2.31)	1.44 (0.89, 2.33)	0.36
MCV, fL, mean (SD)	91.4 (10.5)	90.6 (10.7)	1.01 (0.99, 1.02)	1.01 (0.99, 1.03)	0.51
Abnormal, %	1 (1.0)	8 (1.2)	0.86 (0.05, 3.18)	0.96 (0.16, 5.88)	0.99
RDW, fL, mean (SD)	15.2 (2.3)	15.0 (2.4)	1.04 (0.97, 1.11)	1.03 (0.96, 1.11)	0.54
Platelet count, cells/L ^b , mean (SD)	216 (68)	224 (73)	0.88 (0.67, 1.13)	0.89 (0.68, 1.15)	0.53
Abnormal, %	10 (9.8)	89 (13.0)	0.76 (0.38, 1.32)	0.74 (0.40, 1.38)	0.51
Ferritin, µg/L ^b , mean (SD)	101 (92)	147 (238)	0.82 (0.66, 0.96)	0.82 (0.67, 0.99)	0.11
Iron deficiency, %	38 (39.0)	282 (44.0)	0.75 (0.45, 1.17)	0.77 (0.48, 1.22)	0.51
Transferrin, µg/dL ^b , mean (SD)	292 (53)	295 (84)	0.96 (0.70, 1.31)	0.86 (0.60, 1.24)	0.55
Saturation percent ^c , mean (SD)	25.7 (12.4)	24.4 (11.5)	2.10 (0.46, 7.18)	2.25 (0.54, 9.44)	0.51
Iron serum, µmol/L, mean (SD)	18 (8)	17 (7)	2.05 (0.22, 19.46)	2.61 (0.28, 24.4)	0.54

a. Models were adjusted for age categories, marital status, level of education, gestational age, parity, and trial arm.

b. Scaled by 100. Thus, the RR is for every 100-unit increase in the biomarker, and not for every 1-unit increase.

c. Scaled by 10. Thus, the RR is for every 10-unit increase in the biomarker, and not for every 1-unit increase.

Table 4: Hematologic parameters at delivery and the risk of postpartum haemorrhage among women in Nigeria

Outcome	PPH (N=102)	No PPH (N=685)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adj. p-value ^c
Haemoglobin, g/dL, mean (SD)	10.04 (1.99)	10.93 (1.83)	0.80 (0.73, 0.89)	0.83 (0.75, 0.92)	<0.001
No anemia, %	30 (30.6)	317 (50.0)	Ref	Ref	
Mild, %	23 (23.5)	178 (28.1)	1.32 (0.78, 2.21)	1.29 (0.77, 2.15)	0.51
Moderate/Severe, %	45 (45.9)	139 (21.9)	2.83 (1.86, 4.39)	2.67 (1.74, 4.09)	<0.001
MCV, fL, mean (SD)	91.0 (9.2)	91.4 (13.2)	1.00 (0.98, 1.01)	1.00 (0.98, 1.02)	0.94
Abnormal, %	0 (0.0)	10 (1.6)	Not est	Not est	0.99
RDW, fL, mean (SD)	15.1 (2.1)	15.2 (3.7)	0.99 (0.93, 1.05)	0.99 (0.93, 1.05)	0.84
Platelet count, L ^b , mean (SD)	219 (89)	230 (86)	0.86 (0.68, 1.08)	0.88 (0.70, 1.11)	0.51
Abnormal, %	20 (20.4)	99 (15.6)	1.32 (0.82, 2.02)	1.25 (0.80, 1.96)	0.51
Ferritin, µg/L ^b , mean (SD)	153 (264)	153 (360)	1.00 (0.95, 1.05)	1.00 (0.95, 1.05)	0.99
Iron deficiency, %	31 (31.6)	229 (35.4)	0.86 (0.57, 1.27)	0.90 (0.60, 1.34)	0.74
Transferrin, µg/dL ^b , mean (SD)	261 (62)	289 (62)	0.52 (0.36, 0.75)	0.52 (0.36, 0.75)	<0.001
Saturation percent ^c , mean (SD)	16.8 (11.7)	15.8 (9.6)	2.37 (0.46, 12.2)	1.24 (0.23, 6.66)	0.89
Iron serum, µmol/L, mean (SD)	10.7 (6.5)	11.4 (7.0)	0.23 (0.01, 3.67)	0.15 (0.01, 3.30)	0.51

Not est: Not estimable (0 events)

- Models were adjusted for age categories, marital status, level of education, gestational age, parity, and trial arm.
- Scaled by 100. Thus, the RR is for every 100-unit increase in the biomarker, and not for every 1-unit increase.
- Scaled by 10. Thus, the RR is for every 10-unit increase in the biomarker, and not for every 1-unit increase.

Discussion

Anaemia in pregnancy is a well-established contributor to maternal morbidity and mortality, and postpartum haemorrhage (PPH) is one of its most devastating complications. Contrary to our hypothesis, haemoglobin concentration at 36 weeks was not significantly associated with the risk of PPH. Although women with anaemia showed a modest increase in risk, this was not statistically significant. These findings diverge from those reported by previous meta-analyses²⁹ and primary studies³⁰ which showed an increased risk of PPH in women with anaemia. One possible explanation for this discrepancy is that our participants received iron therapy as part of the IVON trial, which may have attenuated anaemia severity from 36 weeks to delivery. Moreover, prior studies often used haemoglobin measured at delivery, potentially reflecting early blood loss rather than a predisposing factor^{30,31}. These differences highlight the importance of considering timing when interpreting haemoglobin-PPH relationships.

In contrast to the 36-week findings, haemoglobin and transferrin concentrations measured within the first hour following delivery were significantly associated with PPH risk. There was a reduction in PPH risk with higher levels of haemoglobin and transferrin respectively, at delivery. These findings align with the previous studies that have been published on the subject^{8,29}, which also found a larger effect size for severe anaemia than for mild anaemia, strengthening the case for a likely true relationship between anaemia and PPH. Although these studies were often described as prospective longitudinal studies, they typically used haemoglobin assessed during or at admission for labour^{31,32}. Therefore, our findings underscore that delivery haemoglobin levels strongly correlate with bleeding severity, though the temporal direction is unclear. Since delivery haemoglobin is measured *post hoc* or concurrently with bleeding, these associations likely reflect reverse causality – PPH causing acute haemoglobin decline – rather than a protective role of high haemoglobin per se. Studies that carefully separate antenatal haemoglobin vs. intrapartum haemoglobin to predict PPH are needed.

We also found no significant associations between serum ferritin or iron deficiency at 36 weeks and PPH risk. Although ferritin levels were associated with numerically higher PPH risk, this did not reach statistical significance. This aligns with findings from Terence et al., who reported only marginal increases in PPH among women with low serum ferritin³². Given the widespread use of iron supplementation in our cohort, it is plausible that iron status alone

was insufficient to distinguish high-risk women. Taken together, these results suggest that antenatal iron deficiency may not independently predict PPH risk in women that have received iron supplementation.

We found no significant relationship of thrombocytopenia with PPH. This finding contrasts with previous reports that have consistently found significant relationships of thrombocytopenia and an increased risk of PPH^{32–34}. Differences in thrombocytopenia severity, sample size, or concurrent obstetric factors may explain these divergent results. Here, as well, temporality is an important concern. In the cited studies, thrombocytopenia was assessed shortly before or during labour.

Conclusion

In this prospective analysis nested within a randomized trial, we found no statistically significant association between prenatal anaemia, iron deficiency, or thrombocytopenia at 36 weeks' gestation and the risk of postpartum haemorrhage (PPH). Post-delivery haemoglobin and transferrin concentrations were significantly associated with PPH, but these likely reflect the consequences of bleeding rather than antecedent risk factors. These findings underscore the importance of accounting for temporality when evaluating haematologic predictors of PPH and highlight the need for additional prospective studies to clarify causal relationships.

Strengths

This study has several notable strengths. First, it leveraged prospectively collected data from a randomized controlled trial with repeated haemoglobin measurements, allowing us to evaluate antenatal and delivery-time biomarkers separately and to examine potential temporal relationships with PPH. Second, we addressed missing data through multiple imputations using chained equations, which helped minimize bias due to incomplete observations and retained statistical power. Third, we applied false discovery rate control using the Benjamini- Hochberg procedure to reduce the risk of false-positive findings in the context of multiple biomarker comparisons. Finally, blood loss was estimated using a gravimetric method, which, while imperfect and potentially still subject to measurement error, is more objective than visual estimation and is widely used in pragmatic obstetric studies.

Limitations

This study also has important limitations. First, some analyses were limited by small sample sizes, reducing the power to detect potentially meaningful associations. Second, the possibility of unmeasured confounding remains; factors such as uterine tone, placental pathology, provider skill, and undocumented comorbidities may have influenced PPH risk but were not captured in our dataset. Third, clinical interventions, including transfusions and iron supplementation provided as part of the trial, may have modified haemoglobin and iron indices, potentially minimizing true associations. Regression models accounted for these factors. Fourth, because the cohort received iron therapy, iron status at 36 weeks is not reflective of the natural history of untreated anaemia.

Ethical approval and consent to participate.

Ethical approval for the primary study (IVON trial) has been obtained from the Health Research and Ethics Committees of the Lagos University Teaching Hospital (ADM/DCST/HREC/APP/3971), Lagos State Health Service Commissions (LSHSC/2222/VOLIII), Lagos State Primary Health Care Board (LS/PHCB/MS/1128/VOL.VII/100), Aminu Kano Teaching Hospital, Kano (NHREC/28/01/2020/AKTH/EC/2955), Ministry of Health, Kano State (MOH/Off/797/T.1/2102), and National Health Research and Ethics Committee (NHREC/01/01/2007- 17/01/2021), all in Nigeria. Approval from the National Agency for Food and Drug Administration and Control (NAFDAC/DER/VCTD/IVON/VOL.2 OF 23/04/2021) was obtained. Written consent for participation was obtained from all eligible women before study enrolment. Pregnant women aged 15 to less than 18 years of age was considered able to provide independent consent, according to National Health Research Ethics Committee guidelines. This is due to their classification as emancipated minors for the purpose of this study, considering the 2016 World Health Organization's International Ethical Guidelines for Health-related Research Involving Humans. All amendments to the protocol were also submitted to the ethics committees for approval before implementation. The drug regulatory body was also notified. The revised protocols were circulated to various study sites for all research team members to study properly and implement. Where there is a need for additional training on the revised content, this was done before implementation. Information was also updated in the clinical trial registries according to the changes made in the latest protocol version.

Article type

This is a secondary analysis of data obtained from the IVON trial, the primary study (IVON trial) adheres to the CONSORT/SPIRIT guidelines with the checklist attached to this manuscript, the protocol of IVON trial has already been published.

Consent for publication

All authors gave consent for this manuscript to be published.

Declaration of interest

All authors declare no competing interests.

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Availability of data and materials

Data will be deposited in open science framework. Pending data deposition in the repository, data are available on reasonable request from the principal investigator of IVON trial who is one of the authors of this manuscript.

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BBA was the principal investigator of the primary study, BBA and HSG conceptualize the research idea, reviewed and corrected the manuscript. USS, AIA, SAG, JSG, AA, YS, HIB, KMA, and OSS, were the primary writers of the manuscript, AIA, HA, and USS drafted the analysis plan, AIA and HA conducted the analysis. All authors reviewed the manuscript.

Clinical trial registration

This manuscript reports a secondary analysis of the IVON randomized controlled trial. The IVON trial was prospectively registered in the ISRCTN registry under registration number

ISRCTN63484804 (DOI: <https://doi.org/10.1186/ISRCTN63484804>). The trial registration date is **10 December 2020**. The overall study start date was **1 November 2020** and the overall study end date was **15 June 2023**. The principal investigator listed on the registry is **Prof. Bosede B. Afolabi**, Department of Obstetrics and Gynaecology, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria. The trial is also registered on ClinicalTrials.gov under **NCT04976179**.

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Figure Legends

Figure 1. Flowchart of participant selection for this analysis. Flow diagram showing numbers enrolled in the IVON trial (N = 1,056), participants with complete blood count at 36 weeks (N = 862), and participants with estimated blood loss recorded at delivery included in this analysis (N = 787). Reasons for exclusion at each step are indicated. Abbreviations: CBC = complete blood count; EBL = estimated blood loss; PPH = postpartum haemorrhage.

Figure 2. Trajectory of anaemia and iron deficiency from 36 weeks' gestation to delivery. Panel A shows proportions by anaemia severity categories (no anaemia, mild, moderate, severe) at 36 weeks and at delivery. Panel B shows proportions classified as iron-deficient (serum ferritin <30 µg/L) versus not iron-deficient at 36 weeks and at delivery. Sample sizes reflect participants with both 36-week and delivery measurements (N = 787).

Table Legends

Table 1. Sociodemographic and clinical characteristics of women included in the analysis (N = 787) compared with all IVON trial participants (N = 1,056). Continuous variables are mean (SD); categorical variables are n (%). Missing data are described in Methods.

Table 2. Hematologic and iron-status parameters at 36 weeks' gestation and at delivery. Continuous variables are presented as median (IQR). Effect estimates are Hodges–Lehmann median differences with 95% confidence intervals. Adjusted p-values reflect Benjamini–Hochberg correction for multiple testing. Abbreviations: Hb = haemoglobin (g/dL); MCV = mean corpuscular volume (fL); RDW = red cell distribution width (%); WBC = white blood cell count ($\times 10^9/L$); Platelet count ($\times 10^9/L$); Ferritin = serum ferritin (µg/L); Transferrin (µg/dL); Saturation = transferrin saturation (%).

Table 3. Associations between hematologic parameters measured at 36 weeks' gestation and risk of postpartum haemorrhage (PPH). Risk ratios (RR) and 95% confidence intervals (CI) are shown for unadjusted and adjusted models. Adjusted models include age (continuous), state (Kano, Lagos), age group (<20, 20–35, >35), and marital status (married vs unmarried). Missing covariate data were handled using multiple imputation; see Methods for details.

Table 4. Associations between hematologic parameters measured at delivery and risk of postpartum haemorrhage (PPH). Risk ratios (RR) and 95% confidence intervals (CI) are shown

for unadjusted and adjusted models. Adjusted models include the same covariates as Table 3. Notes on model convergence and use of Poisson regression with robust standard errors or Firth's penalized logistic regression are provided in methods.