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Original Research

Maternal Anemia during Pregnancy and Infant Birth Outcomes: A Prospective Cohort Study in Eastern Maharashtra, India

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A B S T R A C T

Background: Anemia during pregnancy may be associated with poor infant outcomes, although its consequences may vary based on etiology and timing.

Objectives: We examined the associations between anemia and anemia-related biomarkers during pregnancy and infant outcomes [birthweight, gestational age at birth, birthweight-for-gestational age percentile, and infant hemoglobin (Hb) at 6 wk of age] in Nagpur, Eastern Maharashtra, India.

Methods: We conducted a prospective cohort study of 200 pregnant women. In the first trimester, venous blood was collected to assess Hb via cyanmethemoglobin analysis, micronutrient status (ferritin, vitamin B12, and folate), and inflammation (C-reactive protein). Hb was also assessed in capillary samples using a hemoglobinometer in the first and third trimesters for mothers and at 6 wk for infants. Associations were assessed using generalized linear models controlling for background characteristics.

Results: In the first trimester, high (compared with normal) venous Hb was significantly associated with lower gestational age at birth [β: −1.0 wk, 95% confidence interval (CI): −1.9, −0.2] and higher birthweight-for-gestational age percentile (β: 20.1, 95% CI: 9.0, 31.2). Mild anemia, moderate anemia, and high (compared with normal) capillary Hb were significantly associated with lower birthweight (β: −147.7 g, 95% CI: −243.4, −51.7; β: −77.7 g, 95% CI: −123.9, −31.4; and β: −236.0 g, 95% CI: −478.0, −48.1) and birthweight-for-gestational age percentile (β: −7.3, 95% CI: −13.7, −0.9; β: −8.4, 95% CI: −14.1, −2.8; and β: −8.9, 95% CI: −15.9, −1.9). Higher serum ferritin was significantly associated with higher birthweight (β: 2.0 g, 95% CI: 0.1, 3.9) and gestational age at birth (β: 0.01 wk, 95% CI: 0.00, 0.01). In the third trimester, mild anemia was significantly associated with lower gestational age at birth (β: −0.5 wk, 95% CI: −0.7, −0.3).

Conclusions: Associations between maternal anemia during pregnancy and infant outcomes were mixed indicating further studies are needed to better understand these relationships.

Keywords: anemia, iron deficiency, hemoglobin, pregnancy, birth outcomes, India

Introduction

Anemia is defined as a hemoglobin (Hb) concentration and/or red blood cell numbers that are too low to meet an individual's physiological needs [1]. Although the optimal Hb concentration required to meet physiological needs varies by numerous factors, including age, sex, altitude, smoking habits, and pregnancy status, the WHO considers Hb concentration of <12.0 g/dL in nonpregnant women to be anemic [2]. As of 2016, anemia during pregnancy is defined using trimester-specific cutoffs, or Hb concentration <11.0 g/dL in the first and third trimesters and <10.5 g/dL in the second trimester, to account for the expanded plasma volume of pregnant women [2].

Abbreviations: ANC, antenatal care; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; ID, iron deficiency; IFA, iron and folic acid; LBW, low birth weight; LMIC, low- and middle-income country; LMP, last menstrual period; MNHR, Maternal and Newborn Health Registry; PHC, primary health center.

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The causes of anemia are complex, multifactorial, and often overlapping, particularly in low- and middle-income countries (LMICs). Iron deficiency (ID), primarily due to inadequate dietary intake, is thought to be the most common nutritional deficiency leading to anemia, responsible for approximately half of cases [3]. Notably, however, the proportion of anemia due to ID differs according to factors such as population group, geographical setting, infectious disease burden, and prevalence of other anemia causes [4]. In many contexts, other nutritional deficiencies, including folate and vitamin B12, are also important causes due to their specific roles in the synthesis of Hb and/or erythrocyte production. Common non-nutritional causes include infection, inflammation, impaired absorption, blood loss, and genetic conditions such as sickle-cell [5].

Women of reproductive age are particularly prone to anemia due to inadequate dietary intake and iron loss during menstruation and pregnancy [6]. In 2012, the World Health Assembly endorsed Global Nutrition Target 2, to achieve a 50% reduction in anemia among women of reproductive age by 2025 [5,7]. In 2015, the Sustainable Development Goals also included the goal of anemia reduction among women of reproductive age by 50% by 2030 [8]. However, despite these resolutions, it is estimated that ~30% of women of reproductive age (15–49 y) are anemic—representing over half a billion women—and ~37% of pregnant women are anemic [9].

In India, approximately half of pregnant women (or 7.5 million women) are anemic, representing the largest burden of anemia among pregnant women globally [10]. India was the first country to launch a National Nutritional Anemia Prophylaxis Program in 1970, which prioritized iron and folic acid (IFA) supplementation [11]. However, because of a number of programmatic challenges such as stock-outs, insufficient training and support for frontline workers, and limited program coverage, adherence to IFA supplementation remains low, and there have been limited reductions in the prevalence of anemia in pregnant women in India [12]. According to the National Family Health Survey-5, only 44% of pregnant women in India took IFA for ≥100 d [13]. Furthermore, the estimated prevalence of anemia among pregnant women was 58.7% in 2005–2006, 50.4% in 2015–2016, and 52.2% in 2019–2021 [13–15]. In Eastern Maharashtra, we have previously reported a prevalence of anemia in pregnant women of 79% from 2014 to 2018, measured in the first trimester of pregnancy [16].

Anemia has significant consequences for human health as well as for social and economic development. In young women of reproductive age, anemia has been shown to reduce cognitive capacity, educational achievement, and labor productivity as well as negatively impact mental health [17]. Research also suggests that the consequences of anemia during pregnancy may vary based on etiology [18,19] as well as timing during pregnancy [20,21]. According to several recent systemic reviews and meta-analyses, anemia during pregnancy is associated with a number of poor maternal and infant outcomes, including impaired fetal growth and increased risk of low birth weight (LBW), preterm birth, reduced neonatal iron stores, and future development delays [22–25]. Notably, however, high iron status during pregnancy is also a risk factor for such adverse birth outcomes, indicating the existence of a U-shaped relationship [26]. Finally, deficiencies in anemia-related biomarkers during pregnancy, including vitamin B12 and folate, have also been linked to a number of adverse birth outcomes, including LBW and preterm birth [27,28].

Two retrospective cohort studies using hospital records from India have demonstrated an association between maternal anemia during pregnancy and poor infant birth outcomes, including LBW and preterm birth [29,30]. However, to date, there remain few prospective studies on anemia and associated micronutrient deficiencies over the course of pregnancy among rural Indian women and their associations with infant birth outcomes. The aim of this study was to examine the associations between maternal anemia and anemia-related micronutrient biomarkers during pregnancy and infant outcomes, namely birthweight, gestational age at birth, birthweight-for-gestational age percentile, and infant Hb at 6 wk of age, in Nagpur, Eastern Maharashtra, India.

Methods

Ethical approval

The study was approved by the Institutional Review Boards of the Lata Medical Research Foundation, Nagpur, India and the Boston University Medical Center, Boston, MA. All women provided informed consent for themselves and their infants to participate. The Maternal Newborn Health Registry and anemia study are registered at clinicaltrials.gov (NCT04708665 and NCT01073475).

Study participants

Participants ($n = 200$) in this substudy were enrolled from the Nagpur, India site of the Global Network for Women's and Children's Health Research's Maternal and Newborn Health Registry (MNHR). The MNHR methods have previously been published [31]. Pregnant women who reside in or receive healthcare in select communities and provide informed consent are enrolled in the MNHR of the Global Network. The Nagpur site includes 8 clusters in 4 districts (Nagpur, Bhandara, Chandrapur, and Wardha) in Eastern Maharashtra, India. Each cluster is the geographic area surrounding a single primary health center (PHC). For the anemia substudy, 2 health facilities (1 PHC and 1 subcenter) were selected from 4 clusters (Nagardhan and Kondhali in Nagpur district, Bhuyar in Bhandara district, and Mandgaon in Wardha district). To select these facilities, a convenience sample of 4 PHCs was initially selected with a focus on ensuring representation from multiple districts as well as that fresh blood could be transported to the laboratory on the day of collection. After selecting the PHCs, a randomly selected rural subcenter for each cluster was chosen to ensure representation from rural areas. All women who presented for antenatal care (ANC) at a selected facility before 13 wk gestation were invited to participate in the substudy until a sample size of 200 was reached. This sample size has 99% power to detect an effect size of 0.15 (medium), assuming a significance level (alpha) of 0.05, 1 tested predictor, and 6 additional independent covariates [32]. Women were enrolled from November 2020 through April 2021, with follow-up continued through February 2022.

Data collection

During the first-trimester visit, a trained research administrator (that is, a medical officer or auxiliary nurse-midwife

employed at a PHC or subcenter) collected background information from women, including age, education, parity, height, weight, and asset ownership, as well as consumption of meat and animal products in the past 3 mo. Gestational age was assessed based on recall of last menstrual period (LMP).

Hb concentrations were measured using a digital hemoglobinometer (HemoCue201+, Ängelholm, Sweden) using the finger-prick method and after discarding first 2 drops of blood. For the anemia substudy, 7 mL of venous blood were also drawn. If a woman was enrolled into the study on a day when venous blood samples were not being collected, she was asked to return to the clinic at a scheduled time within 1 wk of enrollment.

After collection, venous blood samples were stored on ice-packs and transported to Nagpur city where they were shipped by air to SRL Diagnostics within 12 h of collection. A complete blood count with Erythrocyte Sedimentation Rate and peripheral smear test were conducted on all samples. Hb concentrations were assessed on whole blood using the Cyanmethemoglobin method (Horiba Micros ES 60). Ferritin, vitamin B12, and folate concentrations were assessed via electrochemiluminescence immunoassay. C-reactive protein (CRP) concentrations were assessed via turbidimetry.

The anemia substudy included an additional visit in the third trimester of pregnancy (>27 wk gestation). During this visit, women completed a questionnaire specifically focused on anemia, including information on diet and exposure to IFA supplementation. At this visit, an additional finger-prick was conducted for the assessment of capillary Hb using the same hemoglobinometer methods as at enrollment. Infant birthweight was measured to the nearest 10 g within 24 h of birth using a pan digital weighing scale as part of standard MNHR procedures (Bd-590, Tanita). Finally, women were reminded 1–2 d prior regarding a 6-wk post-partum visit. For infants who attended this visit, a heel-prick was conducted for Hb assessment via hemoglobinometer.

Details on data collection and management for the Nagpur site of MNHR have been published previously [33]. Briefly, trained registry administrators collected data on standardized, paper forms, which were manually reviewed prior to data entry at the Lata Medical Research Foundation (Nagpur, India). Data were also reviewed by the Global Network data management center (Research Triangle Institute), which was responsible for data monitoring, cleaning, and management. Anemia substudy data were collected and managed using REDCap electronic data capture tools hosted at Boston University [34,35].

Data preparation and analysis

In accordance with the WHO cutoffs for women in their first or third trimester of pregnancy, anemia was defined as Hb <11 g/dL [2]. Mild anemia was defined as Hb 10.0–10.9 g/dL, moderate anemia was defined as 7.0–9.9 g/dL, and severe anemia was defined as Hb < 7.0 g/dL [2]. High maternal Hb concentrations were defined as >13.0 g/dL as levels above this cut point have been associated with poor birth outcomes in the literature [36]. Although only women who presented for an ANC visit in their first trimester of pregnancy were invited to participate in the study, occasionally blood draws occurred after enrollment to ensure that samples could be transported on the day of collection. As such, 8 women had their blood drawn between 13.0- and 15.2-wk gestation. For these women, the second trimester cut-off of 10.5 g/dL was used to define anemia.

Serum ferritin was adjusted for inflammation (CRP) using the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) linear regression technique with internal data-driven reference levels [37]. ID was defined as inflammation-adjusted serum ferritin <15 μg/L [38]. ID anemia was defined as ID plus anemia. Vitamin B12 deficiency was defined as serum vitamin B12 <203 pg/mL, without adjustment for inflammation [39]. Folate deficiency was defined as folate <3ng/mL [40]. Inflammation, or elevated CRP, was defined as CRP >5mg/L [41].

All birthweights were confirmed to be biologically plausible (range: 1500–4500 g), and LBW was defined as <2500 g. Gestational age at birth was calculated by subtracting the date of birth from the report of LMP. Birthweight-for-gestational age percentiles, which adjust infant birthweight-for-gestational age at birth and infant sex, were calculated based on the INTERGROWTH-21 standards [42,43]. Maternal BMI was calculated by dividing weight in kg by squared height in m. Principal component analysis was used to derive asset tertiles based on ownership of the following (% owned): bicycle (44.5%), scooter (86.0%), automobile (8.5%), electricity (99.0%), television (96.0%), refrigerator (58.5%), and smart phone (72.5%).

Statistical analyses

Summary statistics, including frequencies and percentages or medians with interquartile ranges, were calculated for key demographic and health characteristics. Histograms showing the first trimester distributions of Hb concentrations from the capillary specimens assessed via hemoglobinometer compared with laboratory-based cyanmethemoglobin assessment of venous blood specimens have previously been reported [44]. Univariable linear regression models were used to assess relationships between demographic characteristics and 4 different infant outcomes, including birthweight, gestational age at birth, birthweight-for-gestational age percentile, and infant Hb at 6 wk of age. Characteristics significant at the $P \leq 0.10$ level for any infant outcome were selected for inclusion into multivariable models.

Separate generalized linear models, accounting for correlated errors within clusters using an exchangeable covariance structure, were developed to assess the association between maternal anemia and anemia-related micronutrient biomarkers (both continuous and categorical) and infant outcomes. Models were adjusted for maternal characteristics, including age, height, BMI, education, parity, and enrollment location (PHC compared with subcenter). Models with categorical anemia classifications compare high Hb, mild anemia, and moderate anemia to normal concentrations. Given the rapid changes in Hb concentration in the first weeks of life, models for infant Hb were also adjusted for infant age at Hb assessment. Those with missing outcome data were excluded from regression analyses. P values < 0.05 were considered statistically significant.

Results

Figure 1 presents the flow diagram for the anemia substudy. A total of 200 women were enrolled in the first trimester. Of these, 181 attended a third trimester visit, and 185 singleton, live births were recorded. Of these, 161 infants had Hb assessed at 6 wk.

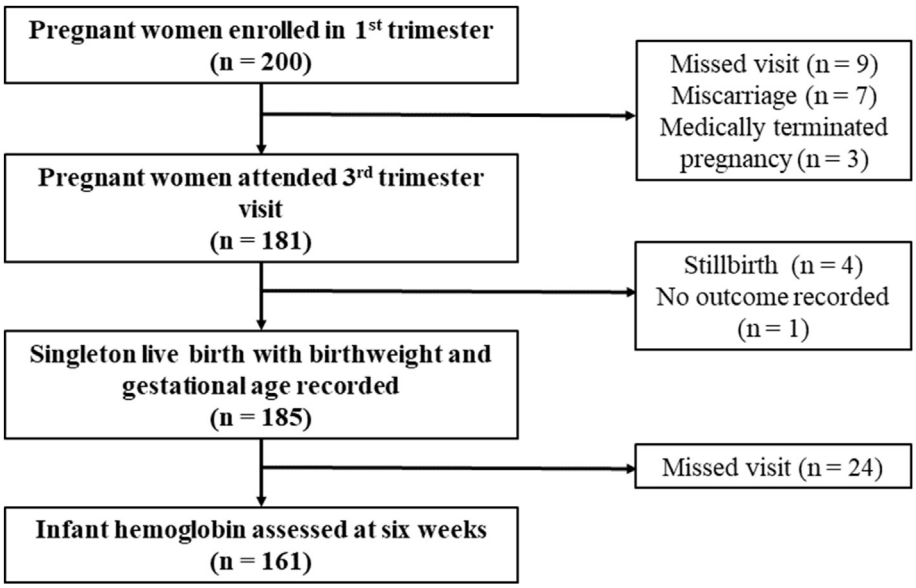

FIGURE 1. Flow diagram of women enrolled in the anemia study in Nagpur, India.

Table 1 presents the demographic, health, and nutrition characteristic of pregnant women and infants in the anemia substudy. Median age of women at enrollment was 24 y, and approximately half were nulliparous. Median height of women was 153 cm, and median BMI was 20 kg/m^2. The prevalence of anemia in the first trimester was 38% when assessed via cyanmethemoglobin analysis of venous samples and 51% when assessed via HemoCue analysis of capillary samples. The prevalence of high Hb in the first trimester was 7% when assessed via cyanmethemoglobin analysis of venous samples and 9% when assessed via HemoCue analysis of capillary samples. Only 15% of women had elevated CRP, resulting in little difference in median unadjusted (21.1 μg/L) and BRINDA-adjusted (19.3 μg/L) ferritin concentrations. Overall, in the first trimester, 40% of women were deficient in iron, 30% were deficient in vitamin B12, and 0% were deficient in folate.

Between the first and third trimester, HemoCue assessments indicated a median reduction of Hb concentration of −0.7 g/dL and an increase in the prevalence of anemia to 71%. Furthermore, among women with HemoCue assessments in both the first and third trimesters, 30% were not anemic in the first trimester but progressed to anemia by the third trimester, 40% were anemic in both trimesters, 20% were not anemic in both trimesters, and 10% were anemic in the first trimester but not in the third trimester. Notably, only 1 woman in the third trimester had high Hb, and thus this category was omitted from multivariable regression models. At the third trimester visit, 80% of women reported receiving IFA for free from either a PHC or community health worker. Furthermore, 95% of women reported receiving IFA supplements in the last 30 d, and 83% reported consuming IFA in the last day. Over three-quarters (76%) reported consuming ≥7 IFA tablets in the previous week. Nearly all women reported consuming animal products during pregnancy, and approximately half reported consuming meat in the past 3 mo. However, the frequency of consumption was limited with only 7%–13% and 64%–73% of women reporting consuming meat and animal products ≥3 times/wk, respectively.

Supplemental Table 1 presents maternal and infant characteristics and their association with infant outcomes, including birthweight, gestational age at birth, birthweight-for-gestational age percentile, and infant Hb at 6 wk. All maternal (age, height, BMI, education, parity, enrollment location) and infant (sex and age at Hb assessment) predictors were significantly ($P \leq 0.10$) associated with ≥1 infant outcome with the exception of asset tertile and consumption of meat, which were omitted from multivariable regression models.

Table 2 presents maternal anemia and anemia-related micronutrient biomarkers and their association with infant outcomes adjusting for the significant predictors mentioned above and accounting for clustering. Unadjusted associations can be found in Supplemental Table 2. In adjusted analyses, compared with normal Hb concentrations, high venous Hb in the first trimester was associated with lower gestational age at birth [β: −1.0 wk, 95% confidence interval (CI): −1.9, −0.2, $P = 0.01$] and higher birthweight-for-gestational age percentile (β: 20.1, 95% CI: 9.0, 31.2, $P = 0.0004$). Higher capillary Hb concentrations in the first trimester were significantly associated with lower gestational age at birth (β: −0.1 wk, 95% CI: −0.2, −0.0, $P = 0.002$) and infant Hb at 6 wk of age (β: −0.2 g/dL, 95% CI: −0.3, −0.1, $P < 0.0001$). Compared with normal Hb concentrations, mild anemia, moderate anemia, and high capillary Hb concentrations in the first trimester were significantly associated with lower birthweight (β: −147.7 g, 95% CI: 243.4, −51.7, $P = 0.003$; β: −77.7 g, 95% CI: −123.9, −31.4, $P = 0.001$; and β: −236.0 g, 95% CI: −478.0, −48.1, $P = 0.02$) and birthweight-for-gestational age percentile (β: −7.3, 95% CI: −13.7, −0.9, $P = 0.03$; β: −8.4, 95% CI: −14.1, −2.8, $P = 0.004$; and β: −8.9, 95% CI: −15.9, −1.9, $P = 0.01$, respectively). Mild anemia in the third trimester was significantly associated with lower gestational age at birth (β: −0.5 wk, 95% CI: −0.7, −0.3, $P < 0.0001$).

With regard to anemia-related micronutrient biomarkers, higher serum ferritin concentrations in the first trimester were significantly associated with higher infant birthweight (β: 2.0 g, 95% CI: 0.1, 3.9, $P = 0.04$) and gestational age at birth (β: 0.01

TABLE 1
Characteristics of pregnant women and their infants in Nagpur, India.

	$N = 200$[1]
Demographics	
Cluster	
Nagardhan	55 (27.5)
Kondhali	50 (25.0)
Bhuyar	52 (26.0)
Mandgaon	43 (21.5)
Enrollment location	
Primary health center	76 (38.0)
Subcenter	124 (62.0)
Maternal age (y), median (IQR)	24 (22, 26)
Maternal education (y), median (IQR)	12 (10,12)
Parity	
Nulliparous	103 (51.5)
Parous	97 (48.5)
Asset tertile[2]	
Tertile 1 (most)	63 (31.5)
Tertile 2	74 (37.0)
Tertile 3 (fewest)	63 (31.5)
Maternal health and nutrition assessment at first trimester visit	
Gestation (wk), median (IQR)	9.6 (7.9, 11.0)
Height (cm), median (IQR)	153 (150, 156)
Height <150 cm	45 (22.5)
Weight (kg), median (IQR)	45.0 (41.0, 50.5)
BMI (kg/m^2), median (IQR)	19.7 (17.5, 21.8)
<18.5 kg/m^2	70 (35.0)
18.5–22.9 kg/m^2	98 (49.0)
≥23 kg/m^2	32 (16.0)
Anemia and ID prevalence[3]	
IDA	42 (21.0)
ID in the absence of anemia	38 (19.0)
Anemia in the absence of ID	33 (16.5)
No anemia or ID	87 (43.5)
Hb from venous blood + Cyanmethemoglobin (g/dL), median (IQR)[4]	11.4 (10.4, 12.2)
Hb >13.0 g/dL	13 (6.5)
Hb <11.0 g/dL	75 (37.5)
Hb from capillary blood + HemoCue (g/dL), median (IQR) ($n = 190$)[4]	10.9 (10.0, 11.8)
Hb >13.0 g/dL	14 (8.9)
Hb <11.0 g/dL	97 (51.1)
Serum ferritin (μg/L), median (IQR)	21.1 (10.9, 38.6)
Serum ferritin <15 μg/L	76 (38.0)
Serum ferritin (BRINDA-adjustment for inflammation) (μg/L), median (IQR)[5]	19.3 (10.0, 34.6)
Inflammation-adjusted ferritin <15 μg/L	80 (40.0)
CRP (mg/L), median (IQR)	1.5 (0.7, 3.5)
CRP >5 mg/L[5]	30 (15.0)
Vitamin B12 (pmol/L), median (IQR)	276.4 (191.0, 448.0)
B12 <150 pmol/L[5]	60 (30.0)
Folate (ng/mL), median (IQR)	17.7 (11.5, 30.0)
Folate <3 ng/mL[5]	0 (0.0)
Consumption of meat in the last 3 mo ($n = 196$)	
None	96 (48.0)
1–3× per wk	74 (37.8)
≥3× per wk	26 (13.3)
Consumption of animal products in the last 3 mo ($n = 195$)	
None	6 (3.1)
1–3× per wk	64 (32.8)
≥3× per wk	125 (64.1)
Maternal health and nutrition assessment at third trimester visit[6]	
Gestation (wk), median (IQR)	31.4 (29.6, 33.6)
Hb from capillary blood + HemoCue (g/dL), median (IQR)[4]	10.1 (9.4, 11.1)
Hb >13.0 g/dL	1 (0.0)
Hb <11.0 g/dL	128 (70.7)
Change in Hb from first to third trimester (capillary + HemoCue), median (IQR)	−0.7 (−1.9, 0.4)
Received IFA for free	144 (80.0%)
Received IFA in the last 30 d	171 (94.5)
Consumed IFA in the last day	151 (83.4)
Consumption of IFA tablets in the last week	
None	17 (9.4)
1–6 tablets	26 (14.4)
≥7 tablets	138 (76.2)
Consumption of meat in the last 3 mo	
None	75 (41.4)
1–3× per wk	84 (46.5)
≥3× per wk	22 (7.1)
Consumption of animal products in the last 3 mo	
None	2 (1.0)
1–3× per wk	48 (26.5)
≥3× per wk	131 (72.5)
Pregnancy and infant outcomes[7]	
Pregnancy outcome	
Singleton live birth	185 (93.0)
Miscarriage	7 (3.5)
Medically terminated pregnancy	3 (1.5)
Still birth	4 (2.0)
Infant sex, male	107 (57.8)
Birthweight (g), median (IQR)	2740 (2500, 3008)
<2500 g	35 (18.9)
Gestational age at birth (wk), median (IQR)	39.6 (38.1, 40.3)
≤37 wk	21 (11.4)
Birthweight-per-gestational age percentile, median (IQR)[8]	12.7 (3.0, 32.9)
Infant age at Hb assessment (wk), median (IQR)	6.7 (6.0, 7.4)
Infant Hb (capillary + HemoCue) (g/dL), median (IQR)	10.6 (9.7, 11.6)

Abbreviations: CRP, C-reactive protein; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; IFA, iron folic acid; IQR, interquartile range.

[1] Values are frequency (%) except where specified as median (IQR).

[2] Asset tertile calculated from a principal components analysis of ownership of the following items (% owned): bicycle (44.5%), scooter (86.0%), automobile (8.5%), electricity (99.0%), television (96.0%), refrigerator (58.5%), and smart phone (72.5%).

[3] Anemia is defined as venous blood Hb <11.0 g/dL. Iron deficiency is defined as serum ferritin <15 μg/L after inflammation adjustment using the BRINDA linear regression technique [37].

[4] "Venous + Cyanmethemoglobin" Hb estimates were derived from venous blood samples analyzed in a laboratory using the Cyanmethemoglobin method. "Capillary + HemoCue" Hb estimates were drawn using the finger-prick method and a HemoCue201+ machine.

[5] Inflammation defined as CRP >5 mg/L. Vitamin B12 deficiency defined as serum B12 <203 pg/mL without adjustment for inflammation. Folate deficiency defined as serum folate <3 ng/mL [39,40].

[6] $n = 181$ with a third trimester visit.

[7] $n = 185$ with a pregnancy outcome; $n = 161$ with a 6-wk visit.

[8] Birthweight-for-gestational age percentile calculated using the INTERGROWTH-21 standards [42,43].

wk, 95% CI: 0.00, 0.01 $P < 0.0001$). Finally, vitamin B12 deficiency in the first trimester was significantly associated with lower infant Hb concentrations at 6 wk of age (β: −0.5 g/dL, 95% CI: −0.7, −0.3, $P < 0.0001$). We found no other statistically significant associations between maternal anemia and anemia-related micronutrient biomarkers and infant outcomes.

TABLE 2
Maternal anemia and anemia-related micronutrient biomarkers and their adjusted association with birthweight, gestational age at birth, birthweight-for-gestational age percentile, and infant Hb at 6 wk in Nagpur, India[1].

	Birthweight (g) ($n = 185$)		Gestational age at birth (wk) ($n = 185$)		Birthweight-for-gestational age percentile ($n = 185$)		Infant Hb at 6 wk (g/dL) ($n = 161$)	
	B (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*
First trimester								
Hb (venous)	14.0 (−40.0, 68.1)	0.61	0.0 (−0.2, 0.2)	0.93	0.5 (−1.6, 2.6)	0.61	−0.1 (−0.4, 0.1)	0.25
Anemia classification (venous)								
High Hb	134.0 (−84.4, 352.4)	0.23	−1.0 (−1.9, −0.2)	0.01*	20.1 (9.0, 31.2)	0.0004***	0.1 (−0.7, 1.0)	0.76
Mild anemia	23.2 (−27.1, 73.4)	0.37	0.2 (−0.4, 0.8)	0.58	3.2 (−1.15, 7.5)	0.15	0.3 (−0.0, 0.6)	0.09
Moderate anemia	52.7 (−93.7, 199.2)	0.48	0.1 (−0.8, 1.1)	0.80	1.8 (−2.4, 6.0)	0.41	0.5 (−0.2, 1.2)	0.18
Hb (capillary, HemoCue)	−3.6 (−35.2, 27.9)	0.82	−0.1 (−0.2, 0.0)	0.002**	0.7 (−0.6, 2.0)	0.30	−0.2 (−0.3, −0.1)	<0.0001***
Anemia classification (capillary, HemoCue)[2]								
High Hb	−263.0 (−478.0, −48.1)	0.02*	−0.9 (−2.2, 0.3)	0.13	−8.9 (−15.9, −1.9)	0.01*	−0.3 (−1.8, 1.2)	0.68
Mild anemia	−147.7 (−243.4, −51.7)	0.003**	0.0 (−0.6, 0.6)	0.97	−7.3 (−13.7, −0.9)	0.03*	0.1 (−0.3, 0.5)	0.66
Moderate anemia	−77.7 (−123.9, −31.4)	0.001**	0.4 (−0.2, 1.1)	0.28	−8.4 (−14.1, −2.8)	0.004**	0.5 (−0.2, 1.2)	0.20
Serum ferritin (μg/L)	2.0 (0.1, 3.9)	0.04*	0.0 (0.0, 0.0)	<0.0001***	0.0 (−0.2, 0.1)	0.84	0.0 (0.0, 0.0)	0.86
ID	−27.0 (−143.4, 89.4)	0.65	−0.6 (−1.1, −0.1)	0.03*	3.3 (−3.5, 10.1)	0.34	0.2 (−0.3, 0.8)	0.41
Vitamin B12 (pmol/L)	0.1 (0.0, 0.3)	0.15	0.0 (0.0, 0.0)	0.22	0.0 (0.0, 0.0)	0.10	0.0 (0.0, 0.0)	0.22
Vitamin B12 deficiency	−81.2 (−166.9, 4.5)	0.06	−0.2 (−0.7, 0.3)	0.36	−1.2 (−6.4, 3.9)	0.64	−0.5 (−0.7, −0.3)	<0.0001***
Folate (ng/mL)	−0.1 (−5.2, 5.0)	0.96	0.0 (0.0, 0.0)	0.08	0.0 (−0.2, 0.3)	0.87	0.0 (0.0, 0.0)	0.91
CRP (mg/L)	7.7 (−10.4, 25.8)	0.40	0.0 (0.0, 0.1)	0.17	−0.1 (−0.7, 0.4)	0.60	0.0 (0.0, 0.1)	0.61
Elevated CRP	122.7 (−42.4, 287.7)	0.15	0.7 (−0.1, 1.6)	0.09	−0.8 (−11.2, 9.5)	0.87	0.0 (−0.9, 0.9)	0.96
Third trimester								
Hb (capillary, HemoCue)	20.5 (−23.2, 64.2)	0.36	0.0 (−0.1, 0.2)	0.69	0.4 (−1.6, 2.3)	0.72	0.0 (−0.1, 0.2)	0.67
Anemia classification (capillary, HemoCue)[3]								
Mild anemia	−39.4 (−165.8, 87.1)	0.54	−0.5 (−0.7, −0.3)	<0.0001***	3.2 (−5.3, 11.8)	0.46	0.0 (−0.5, 0.6)	0.87
Moderate anemia	−61.9 (152.8, 28.9)	0.18	0.1 (−0.4, 0.6)	0.72	−1.9 (−6.9, 3.0)	0.44	−0.1 (−0.5, 0.3)	0.70

Abbreviations: CRP, C-reactive protein; Hb, hemoglobin, ID, iron deficiency. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[1] Values derived from multivariable regression analyses adjusted for maternal characteristics, including age, height, BMI, education, parity, and enrollment location (primary health center vs. subcenter) and accounting for cluster.

[2] There were no women with severe anemia in the first trimester so this category was not included in regression models.

[3] There were no women with severe anemia and only 1 woman with high Hb in third trimester so these categories were not included in regression models.

Discussion

In our sample of 200 pregnant women in Nagpur, Eastern Maharashtra, India, we found that the prevalence of anemia in the first trimester from venous and capillary samples was high and increased throughout pregnancy, reaching 71% by the third trimester, when only capillary samples were available. Overall, we found mixed associations between maternal anemia during pregnancy and infant outcomes. Maternal anemia assessed via HemoCue during the first trimester was significantly associated with lower birthweight and lower birthweight-for-gestational age percentile, and in the third trimester it was significantly associated with lower gestational age at birth. High venous Hb concentrations (compared with normal concentrations) in the first trimester were significantly associated with higher birthweight-for-gestational age percentile but lower gestational age at birth. Higher capillary Hb concentrations in the first trimester were significantly associated with lower gestational age at birth and lower Hb concentrations in infants at 6 wk of age. With regard to anemia-related micronutrient biomarkers, maternal serum ferritin concentrations in the first trimester were significantly associated with both higher infant birthweight as well as gestational age at birth, and vitamin B12 deficiency in the first trimester was significantly associated with lower infant Hb concentrations at 6 wk of age.

Maternal anemia in the first trimester being significantly associated with lower birthweight and birthweight-for-gestational age percentile is supported by several recent systematic reviews and meta-analyses that draw similar conclusions about such relationships [22–25]. With regard to mechanisms, it is thought that reduced concentrations of Hb result in changes in placental angiogenesis, which limits the availability of oxygen to the fetus and, ultimately, causes restriction of intrauterine growth and LBW [45]. Furthermore, the fact that this relationship was not seen with maternal anemia in the third trimester supports the hypothesis that the link with adverse infant outcomes is more evident when Hb concentrations are measured in early pregnancy [26]. However, in our study we did find mild maternal anemia in the third trimester to be associated with reduced gestational age at birth.

The fact that higher Hb concentrations in the first trimester were significantly associated with lower gestational age at birth and infant Hb at 6 wk supports the existence of a U-shaped relationship between maternal Hb concentrations during pregnancy and the risk of adverse birth outcomes. Several studies have also shown there to be a higher risk of LBW and preterm birth observed among women with both low and high Hb concentrations [26,46–49]. According to Dewey et al. [26], there are several mechanisms through which higher Hb concentrations during pregnancy may cause adverse effects including increased blood viscosity and compromised placental blood flow. Furthermore, excess iron intake may contribute to oxidative stress, which can result in lipid peroxidation and DNA damage of placental cells, and it may also impair systematic response to inflammation and infection. As a result, the effect of iron supplementation during pregnancy may depend on initial iron status and may not be beneficial for women who are iron replete, although further research is needed.

Anemia in our study was assessed in the first trimester using both venous and capillary assessment methods. Although the gold standard for Hb assessment is cyanmethemoglobin analysis [50], the most common protocol for Hb assessment in field and many clinic settings in LMICs consists of capillary blood obtained via finger-prick assessed with a hemoglobinometer. The extensive use of hemoglobinometers in these settings is due to the fact that these devices are portable, easy to use, relatively inexpensive, and provide immediate results. However, recent research has highlighted the differences in estimates of Hb from venous blood specimens compared with single-drop capillary specimens, as well as differences based on whether Hb is assessed with hemoglobinometers compared with laboratory methods [51,52]. Overall, we found that the prevalence of anemia was higher (and Hb concentrations were lower) in capillary samples compared with venous samples. This finding differs from the literature that shows that most, but not all, studies find capillary Hb concentrations to be higher than venous Hb concentrations [51,52]. We have previously speculated that these differences may be due to biological differences between capillary and venous blood and/or techniques in specimen collection [44].

In our analyses, we found that maternal background characteristics—particularly maternal anthropometry—were significant and perhaps more influential predictors of birthweight, gestational age at birth, birthweight-for-gestational age percentile, and infant Hb at 6 mo compared with anemia and anemia-related micronutrient biomarkers. The lack of more significant associations between anemia and anemia-related micronutrient biomarkers with birth outcomes may also be due to timing of venous blood collection. Although we analyzed venous blood from the first trimester, many women initiated IFA after their first trimester; furthermore, the third trimester is particularly important for the accumulation of fetal iron stores, fetal weight gain, and fat deposition [53,54].

Overall, our study has several limitations as well as strengths. With regard to limitations, the sample size of our study was relatively small and may not be representative of all pregnant women in Nagpur, India. In the end, however, our estimates of anemia and other sociodemographic characteristics from our sample are comparable with other studies from Eastern Maharashtra, India [16,33]. Furthermore, because of a relatively small sample size, we were unable to examine the associations between maternal anemia and binary outcomes such as LBW and preterm birth as well as rare outcomes such as still birth and neonatal mortality. We must also acknowledge the fact that that there may be unmeasured covariates, associated with both anemia and infant outcomes, affecting the associations (for example, maternal depression). Finally, additional limitations include the collection of venous samples in the first trimester only, the lack of testing for non-nutritional causes of anemia, and the potential for error in measuring using LMP recall in the first trimester to estimate gestational age.

Our study also has several strengths including the inclusion of women from urban, peri-urban, and rural communities around Nagpur city. In addition, there have been few prospective studies from India where Hb concentrations and anemia were assessed in >1 trimester along with infant outcomes. Furthermore, detailed survey data collected during both the first and third trimesters allowed us to control for a number of potential confounding variables. In the first trimester we were able to examine the association between Hb concentrations as well as anemia classification and infant birth outcomes using 2 assessment

methods, namely cyanmethemoglobin analysis and digital hemoglobinometer. Finally, in addition to Hb concentrations and anemia, to our knowledge, this is the first study to assess micronutrient deficiencies in pregnant women in Eastern Maharashtra and their association with infant outcomes.

In conclusion, maternal anemia during pregnancy was found to have a negative association with certain infant outcomes although higher Hb concentrations also appeared to have negative consequences on certain infant outcomes. These findings underscore the complex relationship between anemia and birth outcomes that must continue to be investigated. Future studies may wish to consider including a larger and/or more at-risk sample as well as assess anemia and anemia-related micronutrient biomarkers at multiple time points to better understand the relationship between the timing of anemia during pregnancy and infant outcomes.

Author contributions

The authors' responsibilities were as follows – JML, LML, AP, PH, SB, VD: designed the study and oversaw data collection; JML, LML, AG, MS: analyzed the data; JML, LML: wrote the first draft of the paper; and all authors: read, edited, and approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdnut.2024.104476.

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