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# Effects of anemia at different stages of gestation on infant outcomes

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ABSTRACT

*Objectives:* Maternal anemia is a public health challenge worldwide. The present study aims to explore the effects of maternal anemia at different stages of gestation on postnatal growth and neurobehavioral development in infants.
*Methods:* A cohort of pregnant Indian women were followed from 13 to 22 wk gestation (i.e., second trimester; n = 211), 29 to 42 wk gestation (i.e., third trimester; n = 178); their infants were followed to ∼3 wk (n = 147) postpartum. Data collected included information on sociodemographic and health-related factors, including anemia (i.e., low hemoglobin status), maternal and infant anthropometric data, and infant neurobehavioral data. A mixed logistic regression model was used to examine the impact of anemia during pregnancy on maternal and infant outcomes (i.e., anthropometric growth parameters and infant neurobehavioral development).
*Results:* The prevalence of maternal anemia was 41% and 55% ($P < 0.001$), and iron deficiency anemia was 3.6% and 5.6%, respectively, in the second trimester and third trimester. Infants of pregnant women who were not anemic in the second trimester were 0.26 standard deviations (SD) heavier ($P = 0.029$), 0.50 SD taller ($P = 0.001$), and had 0.26 SD larger head circumference ($P = 0.029$) compared with infants of anemic pregnant women. Infants of pregnant women who were not anemic in the third trimester had orientation scores 3.88 higher ($P = 0.004$) than infants of women who were anemic.
*Conclusions:* Our findings indicate that maternal anemia in the second trimester of gestation influences postnatal infant growth and underscores the necessity of alleviating anemia in young women in the early stages of gestation.



## Introduction

Maternal anemia is a health issue worldwide. Despite most developing countries having national programs to combat anemia, the proportion of anemic pregnant women remains higher than developed countries (56% versus 16%) [1]. In general, the effects of anemia during pregnancy include poor gestational weight gain, complications during delivery, preterm delivery, maternal mortality, and morbidity [2]. Similarly, the effects of maternal anemia on infant outcomes include low birth weight, preterm birth, and irreversible or partially reversible neurobehavioral and cognitive deficits [3].

Emerging evidence indicates the timing of maternal anemia during pregnancy may have different implications for the infant [4]. A few human studies from developed countries that have investigated the impact of maternal nutrient intake, blood levels of micronutrients, and iron deficiency anemia (IDA) at different stages of gestation on brain development on newborns have shown mixed results [5–7]. In developed countries, pregnant

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women have good nutritional status and maternal anemia is predominantly because of iron deficiency (ID). The results from these studies are less relevant than they are to developing countries, in which women are undernourished and the majority have coexisting micronutrient deficiencies. Maternal anemia often develops because of concurrent deficiencies of iron, folic acid, and vitamin $B_{12}$, especially when dietary intakes of animal sources of foods are limited [8]. In such settings, it is unclear whether maternal anemia at different trimesters of gestation affects brain and physical growth, as well as development of neonates or older infants.

The aim of the present study was to investigate the implications of anemia at 13 to 22 wk (i.e., second trimester) and 29 to 42 wk (i.e., third trimester) of gestation on the physical and neurobehavioral development of ∼3 wk old infants.

## Materials and methods

The study investigated the iron and iodine deficiencies in pregnant Indian women in tribal villages of Ramtek block, Nagpur, Maharashtra State, India. We present data from this cohort of pregnant women recruited and first visited at 13 to 22 wk gestation (i.e., second trimester; n = 211), visited a second time at 29 to 42 wk gestation (i.e., third trimester; n = 178), and again when their infants reached ∼3 wk postpartum (n = 147). Details of data collection including study design, participant recruitment, sociodemographic status, and anthropometric measurements are available elsewhere [9,10]. Written informed consent was obtained from the study subjects in accordance with the guidelines from the Institutional Research Ethics Committee, Health and Family Welfare Training Center. All healthy pregnant women ages 18 to 30 y self-reported thyroid disease, tuberculosis, fever for more than 2 weeks, and human immunodeficiency virus/AIDS status were recruited from home after obtaining prior written and verbal consent.

Data on sociodemographic, socioeconomic, and health status of participants were collected using pretested interviewer-administered questionnaires. The information included gestational age at recruitment and at the third trimester, maternal age, annual household income, caste, education (i.e., number of completed years of schooling), family size (i.e., number of family members in the household), parity, food habits (non-vegetarian [i.e., likely to use animal sources of foods] versus vegetarian), women nursing their babies at the time of recruitment, use of pan (chewing of Betel leaves with dry Areca nut), and chewing tobacco at the second trimester.

Fasting venous blood samples were obtained to estimate hemoglobin, serum ferritin (SF), soluble transferrin receptor (sTfR), C-reactive protein concentrations, and sickle cell trait [10]. Maternal anemia (hemoglobin concentration <105 g/L at the second trimester and <110 g/L at the third trimester), IDA (SF concentration ≤15 mg/L or sTfR concentration >4.4 mg/L, in the presence of anemia), non-iron deficiency anemia (NIDA; SF concentration >15 mg/L, or sTfR concentration <4.4 mg/L in the presence of anemia), and infection (i.e., CRP >10 mg/L) were determined at the second trimester and the third trimester, and the sickle cell trait at the second trimester [10]. Pregnant women with positive sickle cell trait and twin pregnancies were excluded from the statistical analysis. The proportion of women with maternal anemia, IDA, and NIDA at the second trimester (n = 195) and the third trimester (n = 161) are presented in Figure 1 (adapted from Menon et al. [10]).

Maternal weight and height were recorded at both visits using standard protocols and equipment [11]. Weight gain during pregnancy was calculated as the difference between the maternal weights at the second trimester and the third trimester. Body mass index (BMI) was computed. Nude infant weight, recumbent length, and head circumference were collected at ∼3 wk postpartum [12]. Because World Health Organization growth standards are less reliable for

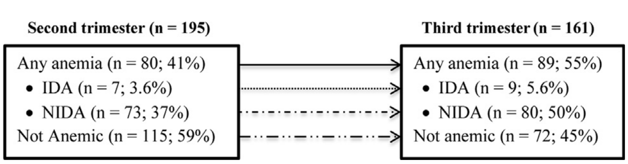


**Fig. 1.** Changes in anemia (low hemoglobin status), iron deficiency anemia (IDA; serum ferritin concentration ≤15 mg/L, or soluble transferrin receptor concentration >4.4 mg/L, in the presence of anemia), and non-iron deficiency anemia (NIDA; serum ferritin concentration >15 mg/L or soluble transferrin receptor concentration <4.4 mg/L, in the presence of anemia) status between the second and the third trimesters in pregnant Indian women.

∼3 wk old infants, weight-for-age, length-for-age, weight-for-length, and head circumference-for-age Z-scores were estimated using the Centers for Disease Control and Prevention growth charts [13]. Underweight, stunting, wasting, and smaller head size-for-age was defined as Z-score <−2 SD of weight-for-age, length-for-age, weight-for-length, and head circumference-for-age, respectively [11].

A senior pediatrician administered the neonatal behavioral assessment scale (NBAS) to assess the neurobehavioral development of infants at ∼3 wk postpartum [14]. The NBAS has 28 behavioral items and 18 neurologic reflex items that assess capacity of infants to interactively respond to external manipulations [14]. The scores elicited were reduced to seven behavior dimensions as per data reduction scheme [15], namely, abnormal reflexes, habituation, orientation, range of state, regulation of state, motor maturity, and autonomic stability. The orientation cluster scores reflect the quality of infants' attention and interactive abilities (i.e., social interaction capacities) measured via the degree of alertness and responses to animate and inanimate visual and auditory stimuli [14]. Higher cluster scores indicated better behavioral development.

Descriptive statistics were used to summarize the baseline characteristics of pregnant women. Mixed logistic regression model with a random participant effect was used to examine the impact of anemia (i.e., low hemoglobin status) during pregnancy on maternal (i.e., premature delivery, duration of gestation, and weight gain) and infant outcomes (i.e., anthropometric growth parameters, and infant neurobehavioral development). Potential confounders investigated included maternal age, education, annual household income, weight gain (except when it is an outcome), BMI at the second trimester (except when it is an outcome), family size, caste, parity, women nursing their babies while pregnant, likely to use animal sources of foods, use of pan, and chewing tobacco at the second trimester. None of the women consumed alcohol in this region. Interactions between the potential predictors and trimester of pregnancy were investigated (second and third trimesters of pregnancy). All variables with $P < 0.250$ were included in the final adjusted model. Stata (versions 12.1 and 13.1; Stata Corporation, 2013, StataCorp LP, TX, USA) and SAS (version 9.1.3; SAS Institute Inc., Cary, NC, USA) for Windows were used for all analyzes. In all cases, two-sided $P < 0.05$ was considered statistically significant.

## Results

A total of 228 pregnant women consented, 5 women dropped out, 223 were recruited, and 178 completed the study. Of the 223 pregnant women recruited at the second trimester, 12 women were excluded from the analysis (positive sickle cell trait [n = 9], twin pregnancies [n = 2], and human immunodeficiency virus–positive [n = 1]), resulting in data available for 211 women (Table 1). The present cohort of women were young (mean SD: 23.0 [2.7] y), about a third had families with fewer than five members, and three-quarters were non-vegetarians. About half of the women were first-time mothers, and 18% were currently nursing children from the preceding birth (Table 1).

Third trimester data were available for 178 pregnant women. For others, data were unavailable (n = 33); lost to follow-up (n = 9); delivered before the second visit (n = 16). We obtained postpartum data for 2 infants from these women. Out of 180 possible infants, data are presented for 147 (excluded/unavailable [n = 33]): premature infants born <37 wk gestation (n = 28), 2 sets of twins (n = 4), infant death (n = 1). The mean (SD) age of infants at the postpartum visit was 2.5 (0.4) weeks. The proportion of underweight, stunted, wasted, and smaller head size for-age infants were 18%, 10%, 8%, and 13% (Table 1). The mean (SD) NBAS cluster scores for abnormal reflex, orientation, habituation, range of state, state of regulation, motor performance, and autonomic stability were 8.5 (4.1), 33.2 (7.3), 18.7 (3.3), 17.2 (2.0), 19.4 (4.3), 22.3 (3.1), and 20.1 (3.3), respectively (Table 1).

A significantly higher proportion of women were anemic at the third trimester (i.e., second visit) compared with the second trimester (41% and 55%; $P < 0.001$), and 37%, and 50% at the second trimester and third trimester, respectively, had non-iron deficiency anemia (Fig. 1) [10]. Additionally, 22%, 2%, and 18% of pregnant women had anemia, IDA, and NIDA at both trimesters, respectively.

**Table 1**
Characteristics of pregnant women and their infants from Ramtek, Nagpur, Maharashtra, India

| Variables | n | % |
|---|---|---|
| Gestation weeks at recruitment* | 211 | 17.3 (2.3) |
| Gestation weeks at the third trimester* | 178 | 34.7 (1.5) |
| Age (y)* | 211 | 23.0 (2.7) |
| Annual Household income (1000 INR)† | 210 | 30.5 (27.4, 34.2) |
| Caste | | |
| Scheduled Tribes | 141 | 67 |
| Scheduled Caste | 13 | 6 |
| Minorities | 46 | 22 |
| Others | 11 | 5 |
| Maternal education (y)* | 211 | 7.2 (3.4) |
| Number of family members | | |
| >5 members | 69 | 33 |
| Non-vegetarian | 155 | 74 |
| Nursing mothers | 38 | 18 |
| Anthropometry* | | |
| BMI ($kg/m^2$) | 211 | 19.3 (1.9) |
| Weight gain (kg) | 178 | 4.9 (2.2) |
| Infant anthropometry* | | |
| Weight-for-age | 146 | −1.53 (0.69) |
| % Underweight (Z-scores <−2 SD) | 37 | 18 |
| Length-for-age | 146 | −1.04 (0.85) |
| % Stunted (Z-scores <−2 SD) | 22 | 10 |
| Weight-for-length | 146 | −0.92 (0.89) |
| % Wasted (Z-scores <−2 SD) | 16 | 8 |
| Head circumference-for-age | 145 | −1.38 (0.68) |
| % Infants with smaller heads (Z-scores <−2 SD) | 27 | 13 |

BMI, body mass index; INR, Indian Rupees
* Mean (SD).
† Geometric mean (GI).

The impact of anemia at the second trimester and the third trimester on maternal and infant outcomes is reported in Table 2. In the unadjusted analysis, maternal anemia at the second trimester was positively associated with infant length-for-age Z-scores and after adjustment it was also positively associated with weight-for-age and head circumference-for-age Z-scores. In the adjusted analysis, it was found that infants of women who were not anemic at 13 to 22 wk gestation (i.e., at the second trimester) were 0.26 SD heavier ($P = 0.029$); 0.50 SD taller ($P = 0.001$); and had 0.26 SD larger head circumference ($P = 0.029$) compared with infants of anemic women. Anemia at the third trimester was not significantly associated with infant anthropometric Z-scores, but it was positively associated with orientation NBAS cluster scores (both adjusted and not adjusted) at ∼3 wk postpartum. Infants of women who were not anemic at the third trimester had orientation scores 3.88 higher ($P = 0.004$) than infants of anemic women.

## Discussion

The present study reports two important findings that add to the growing body of literature in the area of maternal anemia and infant outcomes. Firstly, infants born to women who were not anemic during early gestation had better physical growth at ∼3 wk postpartum than the infants of women who were anemic. Secondly, infants of women who were not anemic later in gestation had higher attention and social interaction abilities (measured via the degree of alertness and responses to animate and inanimate visual and auditory stimuli) at ∼3 wk postpartum than the infants of women who were anemic at this stage of gestation. These findings have important implications given that rural and tribal Indian women have a high prevalence of anemia [16]. This calls for a greater focus on improving the nutritional status of Indian women during early gestation or even before conception, as most childbearing is unplanned in these women.

Maternal anemia is a major public health challenge and is, in developing countries including India, a major risk factor for low birth weight [17]. To address this issue, pregnant women in this research area were actively supplemented with multiple micronutrients including iron-folic acid from early gestation [10]. Two meta-analyses, one examining 13 intervention studies of daily iron and/or folic acid supplementation and the second considering 15 interventions that used multiple micronutrient supplementation in pregnant women, reported 42 g and 53 g higher birth weight in infants, respectively, of pregnant women who used supplements compared with infants born to women who were not supplement users [18]. Furthermore, a meta-analysis that included cohort studies measuring maternal anemia in different stages of pregnancy showed significantly higher risk (adjusted odds ratio 1.29; 95% confidence interval: 1.09–1.53) of low birth weight with first or second trimester anemia compared with the third trimester anemia [19,20]. In addition, Tanner [20] showed that fetal linear growth rate peaks in velocity at ∼16 wk gestation, followed by a decline. Additionally, ultrasound measurements of the growth velocity for femur length on healthy fetuses showed that peak growth velocity occurs during the early second trimester followed by a gradual decline to the third trimester [21,22]. It is possible that in this study, maternal anemia during this crucial phase of fetal linear growth might have a pronounced influence the fetal linear growth than anemia in the third trimester. Non-pregnant women in this area had concurrent micronutrient deficiencies of iron, zinc, and vitamin $B_{12}$ [16] whereas the same pregnant women had a poor iodine status [9].

In addition to the better physical growth, the present study also found improved attention and social interactive skills in infants ∼3 wk postpartum born to women who were not anemic during late gestation compared with infants of anemic women. We speculate that the non-anemic women had better iron and folate stores in late pregnancy because the majority used iron and folic acid supplements throughout gestation.

Recent electrophysiological studies evaluated the potential effects of ID on offspring brain maturation. ID in utero, especially at the last trimester, a period of rapid neurogenesis, neuron myelination, and synthesis of neurotransmitters, decreased brain iron concentration, and adversely influenced neurodevelopment [23]. In their study, Amin and coworkers showed that ID in utero is associated with abnormal auditory neural myelination in infants born at ≥35 gestation because of hypomyelination or delayed maturation of neurons resulting in latencies in pathway transmission [24]. Such neurologic changes may influence attention, audio-visual responses, and other higher cognitive and behavioral functions [25].

Although not previously reported in infants, similar observations have been observed in older children, suggesting there are permanent damaging neurologic impairments from ID. Tamura et al. [26] reported that the five-year-old children of mothers with ID in the last trimester of pregnancy (i.e., cord serum ferritin <76 mcg/L) had significantly lower scores on tests of auditory language comprehension and ability to follow instructions compared with children whose mothers did not have ID.

In an Indonesian study, children of undernourished mothers who were supplemented with multiple micronutrient supplements from ∼3 mo of gestation had improved visual attention and spatial ability at 42 mo of age compared with infants of iron and folic acid-only supplemented mothers [27]. The effect of

**Table 2**
The effects of gestational anemia (non-anemic vs anemic) on maternal and infant outcomes in Indian women from Ramtek, Nagpur, India

| Determinants | Unadjusted effect of maternal anemia | | | | Unadjusted effect of maternal anemia[*,†] | | | |
|---|---|---|---|---|---|---|---|---|
| | Second trimester (n = 211) | | Third trimester (n = 178) | | Second trimester (n = 211) | | Third trimester (n = 178) | |
| **Maternal outcomes** | | | | | | | | |
| *Categorical outcomes* | OR (CI) | *P* | OR (CI) | *P* | | | | |
| Premature delivery (<37 wk) gestation) | 1.36 (0.55 to 3.37) | 0.510 | 3.86 (0.98 to 15.18) | 0.053 | — | — | — | —[‡] |
| *Continuous outcomes* | Differences of means (CI) | *P* | Differences of means (CI) | *P* | Differences of means (CI) | *P* | Differences of means (CI) | *P* |
| Duration of gestation (week)[§] | 0.32 (−0.41 to 1.05) | 0.391 | −0.37 (−0.93 to 0.19) | 0.196 | 0.15 (−0.45 to 0.75) | 0.623 | −0.17 (−0.77 to 0.43) | 0.579 |
| Weight gain[‖] | −0.11 (−0.27 to 0.05) | 0.190 | −0.03 (−0.18 to 0.13) | 0.714 | −0.07 (−0.24 to 0.09) | 0.390 | −0.02 (−0.18 to 0.14) | 0.817 |
| **Infant outcomes at ∼3 wk postpartum** | (n = 147) | | | | (n = 147) | | | |
| *Infant anthropometry (Z-scores)*[¶] | | | | | | | | |
| Weight-for-age | 0.19 (−0.04 to 0.43) | 0.108 | 0.13 (−0.11 to 0.36) | 0.286 | 0.26 (0.03 to 0.50) | 0.029 | 0.17 (−0.06 to 0.41) | 0.152 |
| Length-for-age | 0.40 (0.11 to 0.69) | 0.008 | 0.18 (−0.11 to 0.47) | 0.217 | 0.50 (0.20 to 0.79) | 0.001 | 0.26 (−0.04 to 0.56) | 0.087 |
| Weight-for-length | −0.20 (−0.51 to 0.11) | 0.195 | −0.05 (−0.36 to 0.27) | 0.778 | −0.19 (−0.51 to 0.14) | 0.255 | −0.08 (−0.41 to 0.25) | 0.624 |
| Head circumference-for-age | 0.21 (−0.01 to 0.42) | 0.061 | 0.17 (−0.04 to 0.38) | 0.117 | 0.26 (0.03 to 0.49) | 0.029 | 0.16 (−0.07 to 0.39) | 0.180 |
| *NBAS cluster scores*[**,¶] | | | | | | | | |
| Abnormal reflex | −0.34 (−1.79 to 1.10) | 0.642 | −0.72 (−2.15 to 0.70) | 0.317 | −0.70 (−2.18 to 0.78) | 0.350 | −1.43 (−2.90 to 0.04) | 0.057 |
| Habituation | 0.06 (−1.10 to 1.21) | 0.919 | −0.21 (−1.30 to 0.88) | 0.700 | 0.18 (−1.03 to 1.39) | 0.772 | −0.13 (−1.29 to 1.02) | 0.818 |
| Orientation | 0.89 (−1.77 to 3.55) | 0.508 | 3.58 (1.08 to 6.08) | 0.005 | 1.16 (−1.66 to 3.98) | 0.417 | 3.88 (1.23 to 6.53) | 0.004 |
| Range of state | −0.82 (−1.52 to −0.13) | 0.021 | 0.20 (−0.51 to 0.92) | 0.573 | −0.83 (−1.56 to −0.09) | 0.029 | 0.34 (−0.43 to 1.10) | 0.390 |
| Regulation of state | −0.57 (−2.09 to 0.95) | 0.463 | 0.03 (−1.45 to 1.52) | 0.963 | −0.30 (−1.97 to 1.37) | 0.720 | 0.23 (−1.42 to 1.88) | 0.782 |
| Motor maturity | −0.76 (−1.84 to 0.31) | 0.162 | 0.25 (−0.80 to 1.31) | 0.636 | −0.41 (−1.54 to 0.72) | 0.475 | 0.44 (−0.69 to 1.56) | 0.442 |
| Autonomic stability | 1.17 (−0.32 to 2.66) | 0.121 | 0.20 (−1.37 to 1.77) | 0.798 | 1.35 (−0.47 to 3.18) | 0.143 | 0.20 (−1.68 to 2.08) | 0.831 |

OR, odds ratio; CI, confidence interval; NBAS, neonatal behavioral assessment scores; BMI, body mass index

* Model adjusted for maternal age, maternal education, annual household income, weight gain (except when weight gain is the outcome), BMI at the second trimester (except when weight gain is the outcome), family size, caste, parity, nursing mothers, likely or unlikely to use animal sources of foods, use of pan, and chewing tobacco at the second trimester; model excludes women with infection (CRP > 10 mg/L).

† Maternal anemia: hemoglobin values <105 g/L in the second trimester and <110 g/L in the third trimester.

‡ Adjusted models not examined because of small number of events (n = 25 at the second trimester and n = 11 at the third trimester).

§ Gestation week adjusted by 1 mo backwards for participants with >44 wk to <46 wk and by 2 mo for >46 wk gestation estimated based on their self-reported last menstrual period (n = 6).

‖ Ratio of geometric means (95% CI).

¶ Differences of means (95% CI).

** Scores from Neonatal Behavioral Assessment in full term infants at ∼3 wk postpartum.

maternal folate status on infant cognition is emerging. A higher maternal folate concentration in pregnant Indian women at the third semester was found to be associated with better cognition in their children at 9 to 10 y, including attention, concentration, and visual-spatial abilities [28]. Collectively, these studies support our findings of higher attention and better responses to audio-visual stimuli (i.e., social interaction) in infants of women who were not anemic compared with anemic women at late gestation.

## Conclusions

The findings from the present study underpin the necessity of alleviating maternal anemia, both iron and non-iron deficiency anemia, to improve infant outcomes with regard to physical growth and behavior. Additionally, it is important that women use supplements that contain iron, folic acid, and vitamin $B_{12}$ even before conception to ensure adequate micronutrient status during early stages of gestation. It may be prudent to promote the World Health Organization strategy to prevent anemia in reproductive age women via the use of weekly iron–folic acid supplements with added vitamin $B_{12}$.

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