

## Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women

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Submitted 27 August 2003; Accepted 7 January 2004

### Abstract

**Objective:** Pregnancy and postpartum iron status is of great public health importance, yet few studies have examined predictors of haemoglobin (Hb) concentration during this time. We identified predictors of Hb from 24 weeks' gestation until delivery and from 4 to 25 weeks postpartum.

**Design:** Blood was drawn as many as four times during care: at the initial visit, at 24–29 weeks' gestation, at delivery and postpartum. A longitudinal, multivariable linear regression model was used to predict Hb concentration.

**Setting:** A public health clinic in Raleigh, North Carolina.

**Subjects:**  $n = 520$  women who participated in the Iron Supplementation Study.

**Results:** Hb concentration at the previous blood draw, short stature, non-Hispanic white ethnicity/race, > 12 years of education and smoking were positive predictors of pregnancy and postpartum Hb concentrations. Iron supplement use was a positive predictor, while inadequate weight gain and severe nausea/vomiting were negative predictors of gestational Hb. A high infant birth weight and postpartum haemorrhage were negative predictors of postpartum Hb. Pre-pregnancy body mass index had a slight positive relationship with gestational Hb, but had a strong negative relationship with postpartum Hb. The longitudinal model also confirmed the typical pattern of gestational Hb concentration. As the number of weeks between the initial visit and the 24- to 29-week visit increased, Hb at 24–29 weeks' gestation decreased. As gestational age increased from 24 weeks until delivery, Hb concentration increased as well.

**Conclusions:** The predictors identified here could be used in clinical settings to target high-risk women for intervention.

**Keywords**  
Pregnancy  
Postpartum  
Haemoglobin  
Iron  
Longitudinal data

Poor iron status, common among low-income pregnant and postpartum women in the United States<sup>1–3</sup>, is associated with reduced work capacity<sup>4</sup>, impaired cognition<sup>5,6</sup> and adverse birth outcomes<sup>7</sup>. Iron status is the most important biological determinant of haemoglobin (Hb) concentration among women of childbearing age in the USA<sup>8</sup>. Therefore, iron intake, iron stores, iron requirements and iron losses during and after pregnancy are likely to predict Hb concentrations. Hb concentrations during and after pregnancy are also greatly influenced by blood volume changes. Hb decreases by nearly  $20 \text{ g l}^{-1}$  during the first two trimesters of pregnancy as a result of normal plasma volume expansion<sup>9</sup> – even with adequate iron supplementation<sup>10</sup>. Among supplemented women, Hb concentration

rises from approximately 24 weeks' gestation to term<sup>10</sup>. By 6 weeks postpartum, Hb concentration is expected to return to first-trimester or pre-pregnancy levels<sup>11</sup>. Despite the public health importance of poor iron status and the vast changes to pregnancy and postpartum haematological status, few studies have assessed predictors of Hb concentration during this time<sup>12,13</sup>. Understanding the relative importance of these factors in the prediction of Hb concentration is important, because changes in Hb concentration are used to monitor response to iron interventions on both the individual<sup>14</sup> and the population level<sup>15</sup>. Our objective in the present study was to identify predictors of Hb concentration from 24 weeks' gestation until delivery and from 4 to 25 weeks postpartum.

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## Population and methods

Data came from the Iron Supplementation Study<sup>16</sup>, a randomised, double-blinded, placebo-controlled clinical trial of iron supplementation during pregnancy. The goal of the study was to determine the effect of selective versus universal iron supplementation during the first two trimesters on third-trimester iron status. The study recruited women initiating care at a public prenatal clinic in Raleigh, NC that serves women of mostly low socio-economic background. Women were approached in the clinic waiting area at their first prenatal visit by a study recruiter. Eligible women were those who were <20 weeks' gestation, carrying singletons, English-speaking, and had no known blood disorders. Eight hundred and sixty-seven women gave their informed, written consent.

Blood was drawn at recruitment and analysed for Hb and serum ferritin (SF) concentrations, which were used to randomise women into a supplementation group receiving a daily prenatal vitamin with 0, 30 or 60 mg of iron. Supplementation began immediately and continued until 24 to 29 weeks' gestation, when blood was drawn again and analysed for Hb and SF concentrations. Compliance to study supplements was measured indirectly through pill counts, questionnaires and clinic pharmacy records (date of dispensing and refill, dose of iron in each supplement). At 24 to 29 weeks' gestation active participation ended, and women received the standard clinic protocol, including prenatal vitamins containing 30 mg iron if not anaemic and a higher-dose supplement if anaemic.

Women were followed through the rest of pregnancy and into the early postpartum period, when clinic pharmacy records were again examined to assess supplement use during the remainder of pregnancy. Data from medical records were abstracted to ascertain information on reproductive history, pregnancy complications, health habits, Hb concentration before delivery and at the postpartum visit, and infant feeding method. The study was approved by the institutional review board.

For the 867 women randomised, Hb data were available for as many as four blood draws (initial visit, 24–29 weeks' gestation, before delivery and postpartum). We were interested in predicting Hb concentrations at the latter three visits for women who delivered a live birth. Of the 867 women randomised, 719 were known to deliver a live infant, while the remainder had a known spontaneous abortion, therapeutic abortion or foetal death ( $n = 64$ ), or were lost to follow-up ( $n = 84$ ). Of the 719 known to deliver a live birth, 520 (72%) had complete data on Hb concentration and corresponding predictors for at least one of the three aforementioned visits. About 57% of the 520 women had information at all three visits ( $n = 296$ ), while almost all remaining women had data at one of the three visits (42%;  $n = 218$ ). Missing data occurred because in this transient, low-income population, many women missed appointments, transferred to other clinics, moved,

delivered at other hospitals, or did not return for a postpartum visit. All 520 women were included in our final longitudinal model since it was built to accommodate such missing data (discussed below). The 520 women used in the analysis were similar to the 867 women randomised with respect to age, ethnicity/race, education, parity, marital status, gestational age at prenatal care entry, Hb concentration at the initial visit, and SF concentration at initial visit. Furthermore, among the 520 women in the analysis, there were no meaningful differences with respect to these maternal characteristics when comparing the 296 women with data available for all three visits with those 218 women contributing information from one visit.

### Main outcome measures and predictors

Venous blood samples taken by the prenatal clinic staff were routinely analysed for Hb concentration using a HemoCue technique. Medical records were used to ascertain Hb concentration no more than 7 days before delivery and at the postpartum visit. SF concentration was analysed using a radioimmunoassay technique by LabCorp of America (Burlington, NC, USA).

Gestational age (GA) was based on a reliable, self-reported estimate of last menstrual period (LMP) or an ultrasound done early in pregnancy if LMP was unknown. When both estimates were available and were within 14 days of one another, we used the LMP to estimate GA. When the difference in estimates exceeded 14 days, we used the ultrasound to estimate GA.

Cumulative dose of iron from supplements was estimated using a combination of pill-count and pharmacy data, as described previously<sup>17</sup>. Briefly, 31% of women had complete pill-count and pharmacy data, whereas the remaining 69% had pharmacy data only. Since pill-count data were considered our 'gold standard', we estimated percentage compliance (0–100%) using pill-count data for the 31% of women with such data. For the remaining 69%, clinic pharmacy records were used to estimate pill-count data. Specifically, we first used linear regression to quantify the association between pill-count and pharmacy data among the 31% with both types of data. Then we used simple regression imputation to impute pill-count data for the remaining 69%.

For each study supplement or clinic supplement picked up at the pharmacy, we calculated the therapeutic dose of iron received as:

$$\text{Amount of iron (mg day}^{-1}\text{) in the prescribed supplement} \times \text{number of days between dispensing and refill} \times \text{percentage compliance.}$$

We then summed these doses of iron to estimate the cumulative dose of iron from the initial visit to the 24- to 29-week blood draw and from the 24- to 29-week blood draw to delivery. Finally, we categorised cumulative dose

of iron in each time period into four groups reflecting iron intake relative to the  $30\text{ mg day}^{-1}$  dose that is recommended for non-anaemic pregnant women<sup>15</sup>. From the start of prenatal care until 24–29 weeks' gestation,  $30\text{ mg day}^{-1}$  corresponded to a cumulative dose of 2.0–3.5 g since most women in our study had the opportunity for 10–16 weeks of supplementation. Therefore, we categorised women into one of four groups: 0 g, 0.1–1.9 g (<prescribed), 2.0–3.5 g (prescribed) and >3.5 g (>prescribed). For the remainder of pregnancy, most women had the opportunity for 10–14 weeks of supplementation, so the categories were 0 g, 0.1–1.9 g (<prescribed), 2.0–3.0 g (prescribed) and >3.0 g (>prescribed). Comparable data on postpartum iron supplement use were unavailable.

Pre-pregnancy body mass index (BMI), calculated as weight (in kg) divided by the square of height (in m), was based on measured height and maternal report of pre-pregnancy weight at the initial visit. Maternal weight was measured at each prenatal visit. We calculated total weight gain by subtracting pre-pregnancy weight from weight at the last prenatal visit. To calculate each woman's expected gestational weight gain at 24–29 weeks and before delivery, we used the Institute of Medicine's (IOM) pre-pregnancy BMI-specific weight-gain recommendations<sup>9</sup> in combination with GA at the weight measurement at or before the blood draw. We used the following equation<sup>18</sup>:

$$\begin{aligned} &\text{Expected gestational weight gain} \\ &= \text{recommended first-trimester total weight gain} \\ &+ [(\text{GA at weight measurement at or before blood} \\ &\text{draw} - 13 \text{ weeks}) \times \text{recommended rate of gain} \\ &\text{in second and third trimesters}]. \end{aligned}$$

We then divided total weight gain by expected weight gain and multiplied by 100 to calculate the percentage of weight-gain recommendations met. Finally, in recognition that the IOM recommended a range of total gestational weight gain for each pre-pregnancy BMI group, we classified the percentage of weight-gain recommendations met as inadequate, adequate or excessive. For each BMI-specific range, therefore, we divided the lower and upper limits of recommended weight-gain range by expected weight gain at 40 weeks' gestation and multiplied by 100 to calculate corresponding ranges of recommended percentage of expected weight gain. We used these ranges as the basis for categorising weight-gain adequacy: inadequate (<lower cut-off of recommendations), adequate (within recommended range) or excessive (>upper cut-off of recommendations). See Appendix A for an example of this calculation.

Maternal race/ethnicity was self-reported. We classified women as having severe nausea and vomiting since the previous blood draw if it was documented in the medical record or cited as a reason for hospitalisation. Smoking status was self-reported at the first prenatal visit and at the

postpartum return visit. We classified route of delivery as vaginal or abdominal. High birth weight was defined as birth weight >4000 g. Postpartum haemorrhage was based on the physician's subjective opinion documented in the medical record. Breast-feeding initiation was classified as ever initiated or never initiated. Breast-feeding status at the postpartum visit was defined as exclusively breast-feeding, exclusively formula feeding or combination feeding.

### Statistical analysis

Initially, we screened a large set of variables with potential relevance to Hb concentration using bivariate linear regression analysis. Variables with a moderately low *P*-value ( $P < 0.25$ ) were considered further in multi-variable analysis. Some of these potential predictors of Hb concentration applied to all time periods (time-independent), while others were exclusive to pregnancy or postpartum. Time-independent factors that met the aforementioned criterion were ethnicity/race, marital status, education, parity, height and pre-pregnancy BMI. Pregnancy factors that met this criterion were GA at current blood draw, Hb concentration at the previous blood draw, number of weeks since previous Hb measurement, SF concentration at the previous blood draw, smoking status, iron supplement use, pre-eclampsia, severe nausea and vomiting, and adequacy of gestational weight gain. Postpartum factors that met the aforementioned criterion were number of weeks postpartum at current blood draw, Hb concentration at the previous blood draw, route of delivery, high birth weight, postpartum haemorrhage, breast-feeding initiation, and breast-feeding status at the postpartum visit.

To examine the longitudinal pattern of Hb concentration, we plotted pregnancy Hb concentrations by GA and plotted postpartum Hb concentrations by the number of weeks since delivery. After testing several transformations of GA in the model, we found the best fit with a continuous variable. Postpartum Hb concentration decreased from Week 4 to Week 6.5, and then appeared to level off. Thus, we used a linear spline with a knot at 6.5 weeks to capture this non-linear relationship.

We fit a longitudinal, multivariable fixed-effects model predicting Hb concentration from 24 weeks' gestation until delivery and from 4 to 25 weeks postpartum. We chose a fixed-effects regression model because we were interested in population averages rather than subject-specific parameters. All aforementioned predictors that met our *a priori* criteria were included in the full model. To build the longitudinal model, we used both PROC GENMOD and PROC MIXED in SAS software (SAS Institute, Cary, NC, USA). GENMOD uses generalised estimating equations, which account for intra-individual correlation of Hb measurements<sup>19</sup>. Because results from both procedures were similar, we used GENMOD to fit the final model. The longitudinal model accommodated

women without complete data at all three visits. Akaike's Information Criterion<sup>20</sup> was used to test several different covariance structures. We observed the best fit with the exchangeable covariance structure, so we used it for all models. The full model was reduced using backward deletion ( $P \leq 0.15$ ). Our final model is shown in Appendix B. The parameterisation we used allows us to predict Hb concentration during two different time periods, 24 weeks' gestation to delivery and 4 to 25 weeks postpartum, with the constraint that the intercept and the estimates for the time-independent parameters are the same for both time periods. This constraint was important because it allows the effect of the Hb measurements during pregnancy and postpartum periods to be estimated relative to the same pre-pregnancy Hb level. Hence, results from our model will be more easily implemented from a clinician's perspective. For clarity we present the modelling results in two tables (pregnancy and postpartum predictors) even though they were ultimately derived from the same model.

The distribution of residuals for delivery and postpartum visits was not normal. After excluding five outliers, however, normality at all visits was demonstrated. As this exclusion had minimal influence on the final parameter estimates (< 10% change), we included the outliers in the results presented here.

We explored non-linear relationships with splines and other transformations of the predictor variables. For categorical variables, adjacent categories were grouped if parameter estimates were similar. We also considered interactions with time by comparing parameter estimates in cross-sectional bivariate regressions. Interaction terms were maintained in the multivariable model if they had meaningfully different point estimates across strata of time.

SAS software was used for all data analysis.

## Results

Maternal characteristics, including sociodemographic factors, health habits, pregnancy and delivery complications, and mean Hb concentrations, are shown in Table 1 for all women in the final analysis. Some totals do not equal 520 in Table 1 since women only needed to have complete data for at least one of the three visits to contribute information to the longitudinal model. Most of the sample was 20 to 30 years of age, non-Hispanic black, multiparous and had < 12 years of education.

The final predictive model (Appendix B) was developed using 520 women who contributed 1112 measurements of Hb (460 from the third trimester, 299 at delivery, 353 at the postpartum visit). As stated above, data in Tables 2 and 3 were derived from the same final model but are presented separately for clarity. Timing of previous Hb measurement predicted Hb concentrations at 24 to 29 weeks' gestation (Table 2). When holding previous Hb concentration constant, the number of weeks since the previous

measurement was inversely associated with Hb concentration at 24 to 29 weeks. We observed an approximately linear relationship between Hb concentration and GA from 24 weeks until delivery, resulting in an increase of  $0.26 \text{ g l}^{-1}$  in Hb concentration with each increasing week. Cumulative iron intake through the previous Hb measurement was positively predictive of current Hb concentration; whereas, from the previous measurement to the current measurement, only women who took the prescribed amount of iron had higher concentrations than women who took no iron. Severe nausea and vomiting and inadequate gestational weight gain were negative predictors of Hb concentration from 24 weeks' gestation until delivery.

Hb concentration decreased by  $4.08 \text{ g l}^{-1}$  per week from 4 to 6.5 weeks postpartum but decreased only slightly with each week after 6.5 weeks (Table 3). Postpartum haemorrhage and high infant birth weight were independent predictors of reduced Hb concentrations. Eliminating BMI from the final model had the effect of making the coefficients for high birth weight ( $-6.52$ ; 95% confidence interval (CI)  $-11.6, -1.43$ ;  $P = 0.01$ ) and postpartum haemorrhage ( $-6.89$ ; 95% CI  $-14.3, 0.32$ ;  $P = 0.06$ ) stronger and more negative. When abdominal delivery was included in this model without BMI, it was negatively associated with postpartum Hb ( $-3.03$ ; 95% CI  $-6.68, 0.63$ ;  $P = 0.10$ ).

The effect of BMI on Hb concentration varied by the time period of interest. During pregnancy, BMI had a slight positive relationship with Hb concentration, whereas during the postpartum period, there was a strong inverse relationship between BMI and Hb concentration (Tables 2 and 3). Regardless of the time of Hb measurement, Hb concentration at the previous blood draw had a strong, positive, linear relationship with current Hb concentration, such that each increase of  $1 \text{ g l}^{-1}$  in prior Hb resulted in an increase of  $0.59 \text{ g l}^{-1}$  in current Hb. Maternal height was a negative predictor of Hb values. Non-Hispanic white ethnicity/race, smoking and > 12 years of education were positive predictors of Hb.

Table 4 shows predicted Hb concentrations at 28 weeks of gestation according to initial Hb, nausea/vomiting status, adequacy of weight gain and supplement use. Compared with women with Hb =  $125 \text{ g l}^{-1}$  at enrolment, borderline anaemic women (Hb =  $110 \text{ g l}^{-1}$ ) at enrolment had a substantially reduced Hb concentration at 28 weeks' gestation. Severe nausea and vomiting, inadequate weight gain and no iron supplement use since enrolment were predictive of Hb decreases similar in magnitude. Hb concentrations at 28 weeks were on average  $15 \text{ g l}^{-1}$  lower in borderline anaemic women who did not use iron and had both inadequate weight gain and severe nausea/vomiting, compared with women who used roughly 30 mg iron per day, had Hb of  $125 \text{ g l}^{-1}$  at the initial visit, adequate weight gain and no severe nausea/vomiting.

**Table 1** Characteristics of the 520 women who contributed data to the longitudinal model\*

Characteristic	<i>n</i>	% or mean (SD)
Age		
< 20 years	150	29.0
20–30 years	307	59.4
> 30 years	60	11.6
Ethnicity/race		
Non-Hispanic white	160	31.0
Non-Hispanic black	320	61.9
Other	40	7.1
Parity		
Nulliparous	247	47.8
Multiparous	270	52.2
Education		
≤ 12 years	416	79.9
> 12 years	104	20.1
Marital status		
Unmarried	423	81.8
Married	94	18.2
Pre-pregnancy BMI		
< 19.8 kg m <sup>-2</sup> (underweight)	86	16.5
19.8 to 25.9 kg m <sup>-2</sup> (normal weight)	228	43.9
26.0 to 29.0 kg m <sup>-2</sup> (overweight)	61	11.7
> 29.0 kg m <sup>-2</sup> (obese)	145	27.9
GA at prenatal care initiation (weeks)	520	12.0 (3.4)
Hb concentration at initial visit (g l <sup>-1</sup> )	520	123 (8.8)
SF concentration at initial visit (μg l <sup>-1</sup> )	520	52.3 (44.8)
Smoking status at the initial visit		
Smoker	160	31.0
Non-smoker	357	69.0
Severe nausea and vomiting prior to the 24- to 29-week blood draw		
Yes	101	21.4
No	370	78.6
Hb concentration at 24–29 weeks' gestation (g l <sup>-1</sup> )	506	113 (9.2)
GA at 24- to 29-week blood draw (weeks)	506	28.6 (2.0)
SF concentration at 24–29 weeks' gestation (μg l <sup>-1</sup> )	368	15.5 (13.6)
Severe nausea and vomiting between 24- to 29-week blood draw and delivery		
Yes	62	13.2
No	409	86.8
Inadequate gestational weight gain before delivery		
Yes	145	28.1
No	372	71.9
Estimated cumulative iron intake from supplements from 24 to 29 weeks of gestation until delivery		
0 g	76	15.2
0.1–1.9 g	196	39.1
2.0–3.0 g	155	30.9
> 3.0 g	74	14.8
Diagnosed with pre-eclampsia		
Yes	28	5.4
No	491	94.6
Hb concentration before delivery (g l <sup>-1</sup> )	461	117 (10.4)
GA at delivery Hb measurement (weeks)	461	39.4 (2.3)
Route of delivery		
Vaginal	432	86.4
Abdominal	68	13.6
Infant birth weight		
≤ 4000 g	477	92.8
> 4000 g	37	7.2
Presence of postpartum haemorrhage		
Yes	18	3.5
No	496	96.5
Smoking status at the postpartum visit to the clinic		
Smoker	130	25.2
Non-smoker	387	74.9
Hb concentration at the postpartum visit to the clinic (g l <sup>-1</sup> )	399	130 (13.1)
Number of weeks after delivery of postpartum Hb measurement	399	7.1 (2.2)
Ever initiated breast-feeding		
Yes	233	47.8
No	254	52.2
Infant feeding method at the postpartum visit to the clinic		
Exclusively breast-feeding	64	16.5
Exclusively formula feeding	253	65.2
Combination feeding	71	18.3

SD – standard deviation; BMI – body mass index; GA – gestational age; Hb – haemoglobin; SF – serum ferritin.  
 \* Some totals will not equal 520 due to missing data on some variables.

**Table 2** Predictors of Hb concentration ( $\text{g l}^{-1}$ ) from 24 weeks of gestation until delivery based on the final linear regression model\*†

Variable	Coefficient (95% CI)	P-value
<i>Pregnancy variables</i>		
Number of weeks since previous Hb measurement‡	-0.38 (-0.52, -0.24)	<0.001
GA (weeks)	0.26 (0.05, 0.47)	0.01
Estimated cumulative iron intake from supplements to the previous Hb measurement§		
> 0 g, < prescribed¶ (vs. 0 g)	1.78 (-0.67, 4.22)	0.21
Prescribed (vs. 0 g)	2.90 (0.29, 5.50)	0.05
> Prescribed (vs. 0 g)	3.59 (0.01, 7.16)	0.07
Estimated cumulative iron intake from supplements from the previous Hb measurement to the current Hb measurement		
> 0 g, < prescribed¶ (vs. 0 g)	0.02 (-1.70, 1.74)	0.98
Prescribed (vs. 0 g)	1.94 (0.26, 3.62)	0.05
> Prescribed (vs. 0 g)	0.46 (-1.93, 2.84)	0.72
Severe nausea and vomiting from the previous Hb measurement to the current Hb measurement (vs. none)	-1.80 (-3.31, -0.30)	0.01
Inadequate gestational weight gain to the current Hb measurement (vs. other)	-2.02 (-3.28, -0.76)	0.002
<i>Constrained time-independent variables  </i>		
Pre-pregnancy BMI ( $\text{kg m}^{-2}$ )	0.07 (-0.01, 0.15)	0.08
Hb concentration ( $\text{g l}^{-1}$ ) at the previous blood draw	0.59 (0.52, 0.67)	<0.001
Maternal height (cm)	-0.05 (-0.11, 0.01)	0.09
Non-Hispanic white (vs. other)	1.12 (-0.03, 2.28)	0.05
> 12 years of education (vs. $\leq 12$ years)	1.18 (-0.07, 2.43)	0.06
Smoker (vs. non-smoker)	1.38 (0.18, 2.57)	0.02
Intercept	45.5 (30.5, 60.3)	<0.001

Hb – haemoglobin; CI – confidence interval; GA – gestational age; BMI – body mass index.

\*Based on a fixed-effects longitudinal model (Appendix B).

† Unless otherwise indicated, each coefficient represents the change in Hb concentration ( $\text{g l}^{-1}$ ) for a one-unit increase in the  $\chi$  variable.

‡ Only applicable to second blood draw at 24 to 29 weeks' gestation.

§ Only applicable to the delivery blood draw.

¶ From the start of prenatal care until 24–29 weeks' gestation: 0.1–1.9 g (<prescribed), 2.0–3.5 g (prescribed), >3.5 g (>prescribed). From 24–29 weeks' gestation until delivery: 0.1–1.9 g (<prescribed), 2.0–3.0 g (prescribed), >3.0 g (>prescribed).

|| Time-independent parameters are constrained to be the same estimates for both pregnancy and postpartum time periods by the longitudinal model (Appendix B).

Table 5 shows predicted Hb concentrations at 8 weeks postpartum by race, haemorrhage, infant birth weight and pre-pregnancy BMI. High birth weight, postpartum haemorrhage and a BMI increase of  $15 \text{ kg m}^{-2}$  had negative impacts on postpartum Hb concentration similar

in magnitude, whereas ethnicity/race had a relatively small influence on Hb values. A pre-pregnancy BMI of  $36 \text{ kg m}^{-2}$  predicted a Hb concentration that indicated anaemia or borderline anaemia at 8 weeks postpartum when the delivery was complicated by either high infant

**Table 3** Predictors of Hb concentration ( $\text{g l}^{-1}$ ) from 4 to 25 weeks postpartum based on the final linear regression model\*†

Variable	Coefficient (95% CI)	P-value
<i>Postpartum variables</i>		
4 to 25 weeks postpartum‡ (vs. pregnant)	60.0 (35.8, 84.1)	<0.001
Number of weeks since delivery, if $\leq 6.5$ weeks	-4.08 (-7.67, -0.48)	0.02
Number of weeks since delivery, if > 6.5 weeks	-0.43 (-0.90, 0.38)	0.07
Postpartum haemorrhage (vs. no haemorrhage)	-6.40 (-13.3, 0.47)	0.06
Infant birth weight > 4000 g (vs. $\leq 4000$ g)	-5.17 (-10.1, -0.28)	0.03
Interaction: [Pre-pregnancy BMI ( $\text{kg m}^{-2}$ )] $\times$ (4–25 weeks postpartum‡)	-0.45 (-0.65, -0.26)	<0.001
<i>Constrained time-independent variables§</i>		
Pre-pregnancy BMI ( $\text{kg m}^{-2}$ )	0.07 (-0.01, 0.15)	0.08
Hb concentration ( $\text{g l}^{-1}$ ) at the previous blood draw	0.59 (0.52, 0.67)	<0.001
Maternal height (cm)	-0.05 (-0.11, 0.01)	0.09
Non-Hispanic white (vs. other)	1.12 (-0.03, 2.28)	0.05
> 12 years of education (vs. $\leq 12$ years)	1.18 (-0.07, 2.43)	0.06
Smoker (vs. non-smoker)	1.38 (0.18, 2.57)	0.02
Intercept	45.5 (30.5, 60.3)	<0.001

Hb – haemoglobin; CI – confidence interval; BMI – body mass index.

\*Based on a fixed-effects longitudinal model (Appendix B).

† Unless otherwise indicated, each coefficient represents the change in Hb concentration ( $\text{g l}^{-1}$ ) for a one-unit increase in the  $\chi$  variable.

‡ Coded as yes or no.

§ Time-independent parameters are constrained to be the same estimates for both pregnancy and postpartum time periods by the longitudinal model (Appendix B).

**Table 4** Predicted Hb concentration\* at 28 weeks of gestation by Hb concentration at the initial visit, adequacy of gestational weight gain to 28 weeks' gestation, nausea and vomiting status, and supplement use†‡

Hb at initial visit (g l <sup>-1</sup> )	Weight gain to 28 weeks' gestation	Severe nausea and vomiting	0 g cumulative supplement use from the initial visit to 28 weeks' gestation	2.0–3.0 g cumulative supplement use from the initial visit to 28 weeks' gestation
125	Adequate	No	114 (112, 116)	116 (114, 118)
		Yes	112 (110, 115)	114 (112, 116)
110	Inadequate	No	112 (110, 114)	114 (112, 116)
		Yes	110 (108, 113)	112 (110, 115)
	Adequate	No	105 (103, 107)	107 (105, 109)
		Yes	103 (101, 106)	105 (103, 108)
Inadequate	No	103 (101, 106)	105 (103, 107)	
	Yes	101 (99, 104)	103 (101, 106)	

Hb – haemoglobin; BMI – body mass index; CI – confidence interval.

\* Values are expressed as Hb concentration in g l<sup>-1</sup> (95% CI).

† Other variables held constant: initial visit at 12 weeks' gestation, non-Hispanic white ethnicity/race, 12 years of education or less, non-smoker, height = 163 cm (64 in), and pre-pregnancy BMI = 24 kg m<sup>-2</sup>.

‡ Predicted values are based on the final model shown in Table 2 and Appendix B.

birth weight or haemorrhage. Similarly, Hb concentrations indicating anaemia were predicted when both high infant birth weight and postpartum haemorrhage occurred in a woman with a BMI of 28 kg m<sup>-2</sup>, regardless of race.

## Discussion

Among women of childbearing age in the USA, iron status is recognised as the most important biological determinant of Hb concentration<sup>8</sup>. Poor iron status is associated with adverse functional consequences, so understanding the predictors of iron status is of great public health importance. Despite the plethora of publications on haemoglobin concentration, a Medline search using the key words 'hemoglobin' and 'pregnancy' or 'puerperium' suggests that this may be the first multivariable analysis of a wide selection of clinically relevant predictors of Hb concentration during and after pregnancy conducted in a non-malarial region.

We observed an inverse relationship between Hb concentration and both severe nausea and vomiting and inadequate weight gain – two conditions associated with inadequate intake of many nutrients, including iron.

Interestingly, these factors' relationships with Hb concentration or other iron status measures have not been studied previously.

Postpartum haemorrhage and high infant birth weight (macrosomia) were strong, negative predictors of postpartum Hb concentration. Women who have a clinically recognised haemorrhage may lose up to 1000 ml of blood<sup>21</sup> (the equivalent of 400 mg of iron<sup>22</sup>), which may impede the recovery of Hb concentration in the postpartum period. We lacked estimates of total blood loss, thus we could not evaluate how well blood loss, *per se*, predicts postpartum Hb concentration. Macrosomia can cause significant blood loss via a number of adverse maternal outcomes: abdominal delivery<sup>23</sup>, operative vaginal delivery<sup>24,25</sup> and perineal rupture and haemorrhage<sup>26</sup>. Macrosomia also lengthens duration of lochia, the vaginal discharge of blood following childbirth<sup>27</sup>, which may adversely affect postpartum iron status<sup>28</sup>. Pre-pregnancy overweight is a risk factor for macrosomia<sup>29</sup>, but in our data macrosomia predicted Hb concentrations independent of BMI.

Pre-pregnancy BMI was a modest positive predictor of pregnancy Hb concentration, but was a strong negative

**Table 5** Predicted Hb concentration\* at 8 weeks' postpartum by race, infant birth weight, postpartum haemorrhage, and pre-pregnancy BMI†‡

Race	Infant birth weight > 4000 g	Postpartum haemorrhage	BMI = 21 kg m <sup>-2</sup>	BMI = 28 kg m <sup>-2</sup>	BMI = 36 kg m <sup>-2</sup>
White	No	No	131 (130, 133)	129 (127, 130)	126 (123, 128)
		Yes	125 (120, 129)	122 (118, 127)	119 (115, 124)
	Yes	No	126 (122, 130)	123 (119, 127)	120 (116, 124)
		Yes	120 (114, 125)	117 (111, 123)	114 (108, 120)
Non-white	No	No	130 (129, 132)	127 (126, 129)	124 (123, 126)
		Yes	124 (119, 128)	121 (117, 125)	118 (114, 123)
	Yes	No	125 (121, 129)	122 (118, 126)	119 (115, 123)
		Yes	119 (113, 124)	116 (110, 121)	112 (107, 118)

Hb – haemoglobin; BMI – body mass index; CI – confidence interval.

\* Values are expressed as Hb concentration in g l<sup>-1</sup> (95% CI).

† Other variables held constant: 117 g l<sup>-1</sup> Hb concentration before delivery, 12 years of education or less, non-smoker, and height = 163 cm (64 in).

‡ Predicted values are based on the final model shown in Table 3 and Appendix B.

predictor of postpartum Hb; a  $15 \text{ kg m}^{-2}$  increase in BMI was associated with a  $5.7 \text{ g l}^{-1}$  decrease in postpartum Hb. BMI is most likely a marker of blood loss at delivery. Obesity is a well-documented risk factor for postpartum haemorrhage<sup>30</sup> and abdominal delivery<sup>31</sup>. In our model, pre-pregnancy BMI and haemorrhage were independent predictors of postpartum Hb concentration. Therefore, in our model BMI may account for the residual effect of blood loss on Hb concentration that is not specifically captured by haemorrhage, a dichotomous variable.

Estimated cumulative supplemental iron intake through the previous blood draw positively predicted Hb concentrations. However, only estimated intakes roughly equivalent to the prescribed amount from the previous blood draw to the current measurement were predictive of higher Hb levels than receiving no supplemental iron. Our methods of estimating iron supplement use were imperfect, however, because our study was not originally designed to collect such data after 24 weeks' gestation.

We observed a longitudinal pattern of Hb concentration during pregnancy that has been well documented. The number of weeks since the initial prenatal visit had a strong inverse relationship with Hb concentration at the 24- to 29-week blood draw, reflecting a decreasing Hb concentration through roughly the first two trimesters that results from plasma volume expansion and haemodilution<sup>9</sup>. Hb concentration increased from 24 weeks to delivery, marking the increased rate of red cell mass expansion<sup>9,10</sup>.

From 4 to 25 weeks postpartum, our data showed a downward trend in Hb concentration that was most pronounced from 4 to 6.5 weeks postpartum and was evident even after controlling for several factors suspected to influence Hb values. Randomised controlled trials that followed women after delivery have shown Hb levels to increase sharply from 1 week to 8 weeks postpartum, then either remain constant or increase to 25 weeks postpartum<sup>32–35</sup>. Our contrary findings are probably due to differences in menstruation status, which we did not measure. Prevalence of amenorrhoea decreases as time postpartum increases<sup>36</sup>. The majority of our sample was not lactating, and at 6 and 12 weeks postpartum, 40 and 65%, respectively, of non-lactating women return to menses<sup>36</sup>. Menstruation increases iron needs by  $0.5 \text{ mg day}^{-1}$  if averaged over the course of the month<sup>37</sup>, so Hb concentration may be depressed when menses resume if requirements are not being met by intake or iron stores.

The limitations of this study deserve attention. Missing data were a problem, but the loss to follow-up we experienced is not unlike real-life circumstances of women receiving care in public health clinics. In our low-income population, women missed appointments, transferred to other clinics, delivered at alternative hospitals, and/or did not return for postpartum care. None the less, the characteristics of the women contributing complete information to the longitudinal model for all

three visits were similar to those contributing data for one visit. Additionally, the 520 women used for this analysis were similar to the 867 women randomised. This suggests that the results may have good generalisability to the cohort.

Furthermore, we obtained similar parameter estimates when our model was run using two SAS procedures with different assumptions about missing data. The assumption underlying the results obtained from PROC GENMOD is that the outcome data are a random sub-sample of the target population (the data are missing completely at random), whereas results from PROC MIXED assume that the observed data explain the missing outcome data (the data are missing at random)<sup>38</sup>. The fact that results were similar when the model was run using both procedures supports the missing completely at random assumption for our data. These findings suggest that selection bias was unlikely to be a major concern in this analysis.

The Iron Supplementation Study was not designed with these analyses in mind. Therefore, misclassification may have been a problem in our analysis, specifically for iron exposure during pregnancy, which was found to be only a moderate predictor of Hb concentration. We estimated iron intake based on the relationship between pill counts from enrolment to 24–29 weeks and pharmacy data from enrolment to 24–29 weeks in a small sample of women who returned pill bottles, who may not be a representative group. Furthermore, pill-count data were based on pills containing up to 60 g of iron from the start of care to 24–29 weeks, whereas beyond 24–29 weeks, women in some cases were prescribed substantially higher doses. Our analysis assumed that the association between pill-count and pharmacy data was the same regardless of dose, which may not be the case. These factors probably underestimated the true magnitude with which iron exposure predicts Hb concentration.

In addition, since the Iron Supplementation Study was not designed to follow women into the postpartum period, we were missing several postpartum variables, including dietary intake, iron supplement use and blood loss. Other studies should collect such data to determine whether the postpartum predictors we have identified remain important throughout the postpartum period, once these other variables are accounted for.

Our study had adequate power to detect relatively small differences in Hb concentration for each predictor variable. Specifically, we had 80% power to detect a  $1.5 \text{ g l}^{-1}$  difference in Hb concentration, assuming  $\alpha = 0.05$  and standard deviation of  $13 \text{ g l}^{-1}$ . This sample size, however, was not large enough to develop the predictive model in one half and test its validity in the other half. Therefore, we encourage others to apply our predictive model to other populations to confirm or refute our results.

Our analysis demonstrated that, apart from the blood volume changes that accompany normal pregnancy, a

number of other factors predict gestational and postpartum Hb concentrations in our population. While these factors appear to be consistent with scientific knowledge, the current recommendations for preventing iron deficiency in pregnant and postpartum women do not make mention of many of the factors we have identified as putting women at high risk of adverse iron status<sup>14</sup>. Therefore, poor iron status among pregnant women who have inadequate weight gain or severe nausea and vomiting, for instance, may go unnoticed. In addition, women with a high pre-pregnancy BMI or a high-birth-weight infant would not be screened in the postpartum period according to the present policies. These data suggest that more attention should be paid to maternal factors and complications of pregnancy and delivery as risk markers of poor iron status. The results also highlight the importance of improving existing policies and developing new policies to ensure adherence to iron supplements during pregnancy. Iron supplement use in the postpartum period also deserves more attention, as our knowledge on this subject is currently limited.

Predictors of iron status that we have identified here should be tested in other populations. If our findings are replicated in other settings, the factors we have identified as predictors could be used in clinics to identify high-risk women who should be targeted for intervention. Such interventions would include counselling women with inadequate gestational weight gain on ways to improve iron and overall dietary intake. In addition to checking iron status frequently in these women, iron status among women with severe nausea and vomiting should also be carefully monitored, particularly if the nausea and vomiting inhibit adequate iron intake via diet and supplements. Iron supplementation after delivery may be beneficial to overweight women, women with a macrosomic infant or women who had a haemorrhage. Furthermore, postpartum anaemia screening for iron deficiency in these high-risk groups may be warranted. Such intervention strategies might prove useful in improving iron status, thereby preventing adverse functional outcomes of iron deficiency among pregnant and postpartum women.

### Acknowledgements

This research was funded by co-operative agreements from the Association of Schools of Public Health/Centers for Disease Control and Prevention (#S1326 and #S0454), a predoctoral traineeship from the National Institutes of Health and a Woodrow-Wilson Johnson & Johnson dissertation grant in women's health, and was supported by the Carolina Population Center. We thank Dr Mary E Cogswell and Dr Linda S Adair for providing insightful comments. We gratefully acknowledge the prenatal clinic staff of Wake County Human Services, and thank Mead-Johnson Pharmaceuticals for providing iron supplements.

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## Appendix A

### **Example of the adequacy of weight gain calculation for normal pre-pregnancy BMI**

The Institute of Medicine<sup>9</sup> recommends a weight-gain rate of 2.2 kg in the first trimester and 0.4 kg week<sup>-1</sup> in the second and third trimesters. Therefore, expected gestational weight gain at 40 weeks' gestation is:

$$2.2 \text{ kg} + [(40 \text{ weeks} - 13 \text{ weeks}) \times 0.4 \text{ kg week}^{-1}] \\ = 13 \text{ kg.}$$

The Institute of Medicine recommends a total weight-gain range of 11.5–16 kg, which corresponds to 88–123% of the 13-kg expected weight gain (i.e.  $(11.5 \text{ kg}/13 \text{ kg}) \times 100 = 88\%$ ). We classified inadequate, adequate and excessive weight gain as <88%, 88–123% and >123% of recommendations, respectively.

### **Example for a normal-weight woman who gained a total of 18 kg and whose weight was last measured at 38 weeks' gestation**

Expected gestational weight gain

$$= 2.2 \text{ kg} + [(38 \text{ weeks} - 13 \text{ weeks}) \times 0.4 \text{ kg week}^{-1}] \\ = 12.2 \text{ kg.}$$

Percentage of recommendations met

$$= (18 \text{ kg}/12.2 \text{ kg}) \times 100 = 148\%.$$

148% is greater than 123%, so this woman is classified as exhibiting excessive weight gain.

## Appendix B

The following equation represents our final predictive model:

$$E(\text{Hb}_{wt}) = \alpha + \sum_{i=1}^7 x_{iw} \beta_i + \sum_{j=1}^{10} y_{jw} \delta_j + \sum_{k=1}^5 z_{kw} \eta_k,$$

with working correlation matrix: exchangeable (compound symmetry)

$$R = \begin{bmatrix} 1 & \alpha & \alpha \\ \alpha & 1 & \alpha \\ \alpha & \alpha & 1 \end{bmatrix}.$$

In the above:

$w$  = subject

$t = 1$  if  $24 \leq \text{weeks' gestation} \leq 42$

$t = 2$  if  $4 \leq \text{week postpartum} \leq 25$ .

$x_{1w}$  = Hb concentration ( $\text{g l}^{-1}$ ) at the previous blood draw

$x_{2w}$  = maternal height (cm)

$x_{3w}$  = pre-pregnancy BMI ( $\text{kg m}^{-2}$ )

$x_{4w}$  = pre-pregnancy BMI ( $\text{kg m}^{-2}$ )  $\times$  (4–25 weeks postpartum)

$x_{5w}$  = non-Hispanic white (vs. other)

$x_{6w}$  = more than 12 years of education (vs.  $\leq 12$  years)

$x_{7w}$  = smoker (vs. non-smoker).

$y_{jw}$  = 0 if  $t = 2$ ; otherwise

$y_{1w}$  = number of weeks since previous Hb measurement

$y_{2w}$  = gestational age (weeks)

$y_{3w}$  = cumulative iron intake to the previous Hb measurement:  $>0$  g,  $<$ prescribed (vs. 0 g)

$y_{4w}$  = cumulative iron intake to the previous Hb measurement: prescribed (vs. 0 g)

$y_{5w}$  = cumulative iron intake to the previous Hb measurement:  $>$ prescribed (vs. 0 g)

$y_{6w}$  = cumulative iron intake from the previous Hb measurement to the current:  $>0$  g,  $<$ prescribed (vs. 0 g)

$y_{7w}$  = cumulative iron intake from the previous Hb measurement to the current: prescribed (vs. 0 g)

$y_{8w}$  = cumulative iron intake from the previous Hb measurement to the current:  $>$ prescribed (vs. 0 g)

$y_{9w}$  = severe nausea and vomiting from the previous Hb measurement to the current (vs. none)

$y_{10w}$  = inadequate gestational weight gain to the current Hb measurement (vs. other).

$z_{kwt} = 0$  if  $t = 1$ ; otherwise

$z_{1w} = 4$  to 25 weeks postpartum (vs. pregnant)

$z_{2w}$  = number of weeks since delivery

$z_{3w}$  = number of weeks since delivery minus 6.5, if weeks postpartum  $>6.5^*$

$z_{4w}$  = postpartum haemorrhage

$z_{5w}$  = infant birth weight  $>4000$  g.

\*In Table 2, the coefficient for 'Number of weeks since delivery, if  $>6.5$  weeks' represents a linear combination of the parameter estimates of  $z_{2w}$  and  $z_{3w}$ .