Original Article

Risk of stillbirth in relation to maternal haemoglobin concentration during pregnancy

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Abstract

The authors determined the association between maternal haemoglobin concentration measured at <28 weeks' gestation and late fetal death at ≥28 weeks' gestation (stillbirth). Data were derived from the National Maternal and Infant Health Survey – a nationally representative survey of US deliveries in 1988. Analysis was restricted to women with a singleton live birth ($n = 4199$) or a stillbirth ($n = 1375$) for whom maternal prenatal care, haemoglobin, smoking status and gestational age data were available. Haemoglobin concentrations during first and second trimesters, respectively, were classified as mild (10.0 to <11.0 and 9.5 to <10.5 g dL^{-1}) or moderate (9.0 to <10.0 and 8.5 to <9.5 g dL^{-1}) anaemia, or high haemoglobin (≥14.6 g dL^{-1} in either trimester). Hazard ratios (HR) and 95% confidence intervals (CI) for stillbirth were derived from discrete proportional hazards regression models after adjusting for confounders. Stillbirth was not associated with mild anaemia or high haemoglobin in either the first or second trimester of pregnancy. Moderate anaemia measured before 28 weeks' gestation was significantly associated with an increased risk of stillbirth among non-black women (adjusted HR: 4.4; 95% CI: 1.02, 19.01). Moderate anaemia was not associated with stillbirths among black women. Further investigation regarding causal mechanisms for this association is warranted.

Keywords: anaemia, fetal death, pregnancy outcome, stillbirth.

Maternal anaemia and high haemoglobin concentration have been associated with a number of adverse pregnancy outcomes (Lu *et al*., 1991; Zhou *et al*., 1998; Scanlon *et al*., 2000; Scholl & Reilly, 2000; Rasmussen, 2001). Few studies have examined the association of maternal haemoglobin concentration with fetal death (Garn *et al*., 1981a; Lister *et al*., 1985; Stephansson *et al*., 2000) and perinatal mortality (Murphy *et al*., 1986; Xiong *et al*., 2003). Many of

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these studies, however, are limited in that they either failed to adjust for important confounding variables (e.g. timing of haemoglobin assessment) (Garn *et al*., 1981a; Lister *et al*., 1985; Murphy *et al*., 1986), or may not be generalizable to US populations because they were conducted in developing countries where the aetiology of anaemia or high haemoglobin concentrations may differ (Lister *et al*., 1985; Xiong *et al*., 2003). One recent Swedish study found an increased risk of late fetal death (≥28 weeks' gestation) among women with high haemoglobin concentration (≥14.6 g dL^{-1}) at first prenatal measurement (Stephansson *et al*., 2000), but the study lacked sufficient power to detect an association between maternal anaemia and late fetal death.

Several biologic mechanisms have been postulated through which maternal anaemia or iron deficiency anaemia, and high haemoglobin (Dallman, 1986; Cnattingius *et al*., 1998; Allen, 2001; Cnattingius & Stephansson, 2002) may be associated with adverse pregnancy outcomes. Preterm delivery and fetal growth retardation, major determinants of stillbirth (Cnattingius *et al*., 1998; Wilcox, 2001; Cnattingius & Stephansson, 2002), have been associated with maternal anaemia or iron deficiency, and high haemoglobin (Lu *et al*., 1991; Steer *et al*., 1995; Scanlon *et al*., 2000; Scholl & Reilly, 2000). Anaemia, iron deficiency or both can activate a stress response in the mother and fetus through elevations in corticotrophin-releasing hormone or cortisol resulting in preterm labour, pregnancy-induced hypertension, eclampsia, premature rupture of membranes or restricted fetal growth. While the aetiology of the high haemoglobin is uncertain, it may be due to either increased red cell production due to residence at a high altitude, smoking, polycythaemia vera, chronic respiratory or cyanotic heart disease, or high haemoglobin can be an indication of a failure in adequate plasma volume expansion (Yip, 2000). Regardless of aetiology, high haemoglobin concentrations cause high blood viscosity which leads to placental infarction/thrombosis and compromised oxygen delivery to the fetus and may lead to restricted fetal growth and preterm delivery (Naeye, 1977; Steer *et al*., 1995; Steer, 2000). Using the most recent national data in the USA that contains information on both maternal haemoglobin concentrations during pregnancy and subsequent fetal death, we evaluated the relationship between maternal anaemia and high haemoglobin concentration as measured at the first prenatal visit at <28 weeks' gestation and late fetal death at ≥28 weeks' gestation (stillbirth). Because of the survey's sampling design and because US black women have higher rates of both anaemia and stillbirths (Barfield *et al*., 2002; Looker *et al*., 2002) than US white women, we evaluated risks of anaemia and stillbirth separately among black and non-black women.

Methods

National Maternal and Infant Health Survey 1988

The National Maternal and Infant Health Survey (NMIHS), conducted by the US Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), is a nationally representative survey of live births, fetal deaths and infant deaths that is based on a multistage probability sample of the 1988 US vital statistics records (Sanderson *et al*., 1991, 1998a, 1998b). The NMIHS contains information from live birth and fetal death certificates, infant death certificate, and questionnaires administered to a sample of mothers with live births, stillbirths and infant deaths during 1988 and to physicians, hospitals and other medical care providers associated with those outcomes. It is the only national data available that contain information about maternal haemoglobin concentrations during pregnancy and subsequent fetal deaths. Very-low-birthweight and moderately-low-birthweight infants and black infants (classified according to the mother's self-identified race) were over-sampled in the live birth component. Black infants were over-sampled in the fetal death component. Sampling weights were assigned to each record to allow nationally representative estimates. A more detailed description of the sampling strategy and survey methodology is provided elsewhere (Sanderson *et al*., 1998a, 1998b).

The full sample included in our analysis was restricted to women who delivered a singleton live birth or fetal death greater than or equal to 28 weeks'

gestation and for whom primary care provider information was available. We defined a stillbirth as a fetal death greater than or equal to 28 weeks' gestation because the survey was designed to restrict fetal deaths to ≥28 weeks' gestation to minimize bias due to under-registration or under-reporting of fetal deaths 20–27 weeks' gestation in the United States vital records (Sanderson *et al*., 1998a, 1998b). The original NMIHS study included 8384 live births and 2803 stillbirths. The final study sample was restricted to only those women who had prenatal care information including a haemoglobin or haematocrit measurement taken before 28 weeks' gestation and information on maternal smoking (from the mother's questionnaire). Women whose first haemoglobin or haematocrit measurement occurred at or after 28 weeks' gestation were not included in the study. Our final study sample included 4199 live births and 1375 stillbirths.

We determined gestational age using an algorithm developed at the US Centers for Disease Control and Prevention which used NMIHS data from the birth certificate, hospital questionnaire and mother's questionnaire (Blackmore-Prince *et al*., 1999). Gestational age was largely based on last menstrual period (LMP). When LMP on the birth certificate was unavailable, LMP as recorded on the hospital questionnaire was used. This computed gestational age was compared with the non-imputed gestational age reported on the birth certificate. If the discrepancy between the two gestational age measures were within 2 weeks, the computed gestational age was used. Otherwise, the gestational age reported on the mother's questionnaire was used. When the gestational age on the birth certificate was imputed, the calculated gestational ages from both the hospital questionnaire and birth certificate LMP were compared with each other for concordance within 2 weeks before comparing them with the gestational age reported on the mother's questionnaire.

Haemoglobin assessment

We used data on haemoglobin (g dL^{-1}) or haematocrit (%) concentrations from the prenatal care provider component of the survey. Because women may have multiple haemoglobin or haematocrit measurements over the course of their pregnancy, we selected only the first measurement provided that this occurred at <28 weeks' gestation. If a hematocrit was assessed instead of a haemoglobin concentration, we converted it to haemoglobin by dividing the haematocrit by 2.97 (Yip *et al*., 1984). Since haemoglobin values are influenced by maternal smoking status (CDC, 1998), we adjusted haemoglobin concentrations for smoking (discussed below).

Anaemia was evaluated by its presence and by level of severity. Anaemia was defined by established Centers for Disease Control and Prevention criteria as a haemoglobin concentration of <11.0 g dL^{-1} if measured in the first 12 weeks' gestation and <10.5 g dL^{-1} if measured between 13 and 27 completed weeks' gestation (CDC, 1998). Severity of anaemia was defined as mild (10.0 to <11.0 g dL^{-1} in the first 12 weeks' gestation and 9.5 to <10.5 g dL^{-1} between 13 and 27 completed weeks' gestation) or moderate (9.0 to <10.0 g dL^{-1} in the first 12 weeks' gestation and 8.5 to <9.5 g dL^{-1} between 13 and 27 completed weeks' gestation) (IOM, 1993). There were three women in the study sample who had severe anaemia (i.e. <9.0 g dL^{-1} in the first 12 weeks' gestation and <8.5 g dL^{-1} between 13 and 27 completed weeks' gestation). They were combined with the group of women who had moderate anaemia. All haemoglobin concentrations were adjusted for smoking status according to the guidelines proposed by the Centers for Disease Control and Prevention (1998).

High haemoglobin was defined as a haemoglobin concentration of ≥14.6 g dL^{-1} at first antenatal measurement at <28 weeks' gestation. This definition was used by a Swedish study that evaluated the association between maternal haemoglobin concentration and fetal death at ≥28 weeks' gestation (Stephansson *et al*., 2000) and corresponds to ≥2 standard deviations from the reference mean (Scanlon *et al*., 2000).

Confounding variables

The following variables were considered as potential confounders on the basis of a review of the literature: maternal age (categorized as <20, 20–24, 25–29, 30–34 or ≥35 years), parity (0, 1, ≥2), maternal education

(≤12, 13–16 or ≥17 years of completed schooling), marital status (yes or no), alcohol, cocaine and marijuana use before and during pregnancy (yes or no), pre-pregnancy body mass index (BMI) defined as self-reported pre-pregnancy weight (in kilograms) divided by height (in meters squared), and was categorized as <19.8, 19.8 to <26.0 and ≥26.0 (NAS *et al.*, 1990), physician diagnosed/reported pre-eclampsia and eclampsia, and iron supplement use (defined by reported use of either multivitamin/mineral supplements or iron supplements during pregnancy).

Statistical analysis

The rate of stillbirths (per 1000 live births plus stillbirths at ≥28 weeks' gestation) was derived for women with or without anaemia and for those with mild anaemia, moderate anaemia or high haemoglobin concentrations. Sampling weights were incorporated in all analyses to account for non-response and post-stratification adjustment of the original NMIHS study (Sanderson *et al.*, 1998a, 1998b). All statistical analyses were performed with SUDAAN (Research Triangle Institute, Cary, NC) version 8.0, operating on a UNIX platform. Associations between anaemia and stillbirth risk were based on hazard ratios (HR) derived from fitting discrete proportional hazards regression models (Stokes *et al.*, 2001). A discrete proportional hazards regression model was deemed appropriate for this analysis since (i) it allows the hazard of stillbirth to vary as gestation advances, and (ii) due to the presence of 'ties' in the event (i.e. stillbirth) at each week in gestation. The assumption of proportionality was tested by examining plots of Schoenfeld residuals (Schoenfeld, 1983), and found to be satisfied. Adjustment for potential confounding factors was accomplished by including the confounders in the regression model either if their presence changed the crude hazard ratio by at least 10% or if they were variables of a priori interest. In order to ensure that confounders were not omitted in a multivariable setting, we forced all confounders in to the final model. The final model is presented in Tables 2 and 3. The confounders used in the final model are listed in the footnote of each table. No formal effect modification was evaluated in this analysis. The interaction between race and haemoglobin concentration was not tested since all statistical analyses were performed separately for black and non-black women because of the NMIHS sampling methodology.

Results

Our final sample was comparable to the original sample of NMIHS with regard to the distributions of maternal age, education, parity, smoking, alcohol use other substance use, pre-pregnancy BMI and iron supplement use (Table 1). However, our final sample had lower proportions of black women and single women. Inclusion in the final sample depended on prenatal care use and measurement of haemoglobin or haematocrit before 28 weeks' gestation, and so those differences were in the expected direction (Martin *et al.*, 2002).

Mild maternal anaemia was not associated with the risk of stillbirth (Tables 2 and 3). Moderate anaemia was associated with an increased risk of stillbirth among non-black women, but not among black women. The association between moderate anaemia and stillbirth among non-black women was significant overall [adjusted HR: 4.4; 95% confidence intervals (CI): 1.02, 19.01] but more strongly among those who had moderate anaemia measured at 13–27 completed weeks' gestation (adjusted HR: 9.40; 95% CI: 1.50, 58.97).

There was a twofold, but not statistically significant, greater risk of stillbirth among black women with a high haemoglobin concentration measured at <28 weeks' gestation compared with black women with a normal haemoglobin concentration (adjusted HR: 2.02; 95% CI: 0.96, 4.23), and a more than 3.5-fold greater risk of stillbirth among those with a high haemoglobin concentration measured at 0–12 weeks' gestation (adjusted HR: 3.67; 95% CI: 0.92, 14.63). High haemoglobin was not associated with stillbirth among non-black women.

Discussion

Our study suggests that moderate anaemia measured within the first 27 completed weeks' gestation may be associated with an increased risk of stillbirth among

Table 1. Maternal characteristics of the full and final sample*: National Maternal and Infant Health Survey 1988, United States (Sanderson *et al.*, 1991)

Maternal characteristics	Full sample		Final sample	
	Live births $n = 8384$	Stillbirths $n = 2803$	Live births $n = 4199$	Stillbirths $n = 1375$
Maternal age (years) (%)				
<20	12.1	12.5	11.1	10.7
20–24	27.5	27.4	25.9	26.3
25–29	31.6	28.5	33.0	30.6
30–34	20.6	20.0	21.7	21.4
≥35	8.1	11.1	8.3	11.0
Maternal education (years) (%)				
≤12	60.3	65.4	54.7	61.3
13–16	34.1	30.3	36.3	34.2
≥17	5.6	4.3	6.3	4.5
Primiparity (%)	30.4	35.0	31.2	36.4
Black race (%)	15.8	24.2	12.1	19.5
Single marital status (%)	25.1	22.0	20.5	17.8
Cigarette smoking (%)	22.0	24.8	20.9	23.8
Alcohol use (%)	20.9	15.5	22.5	15.3
Cocaine use (%)	1.7	1.9	1.2	2.1
Marijuana use (%)	5.5	6.6	5.4	6.1
Iron use 3 months before pregnancy (%)	9.2	9.5	9.2	8.8
Iron use during pregnancy (%)	33.0	33.1	31.2	32.0
Pre-pregnancy body mass index†	22.8 (5.5)	24.0 (5.8)	22.8 (5.2)	23.9 (7.0)
Gestational age at delivery†	39.5 (2.7)	35.7 (5.3)	39.5 (2.6)	36.0 (4.4)
Week prenatal care initiated†	12.4 (9.1)	12.4 (5.8)	12.5 (7.1)	12.4 (5.9)
Week first haemoglobin drawn†			12.7 (5.8)	12.4 (6.3)

*Full and final samples were restricted to women who delivered a singleton at ≥28 weeks' gestation. The final sample is similar to the full sample, but is restricted to women for whom a haemoglobin or haematocrit measurement and smoking information were available.

†Data expressed as mean (standard deviation).

Table 2. Association between maternal haemoglobin status at <28 weeks' gestation and risk of stillbirth at ≥28 weeks' gestation: National Maternal and Infant Health Survey 1988, United States (Sanderson *et al.*, 1991)

Haemoglobin status*	Black women					Non-black women				
	Total deliveries†	Stillbirth at ≥28 weeks' gestation‡				Total deliveries†	Stillbirth at ≥28 weeks' gestation‡			
		Risk	95% CI	cHR	95% CI		Risk	95% CI	cHR	95% CI
Any anaemia	250	0.40	0.26, 0.54	0.87	0.58, 1.30	72	0.26	0.25, 0.27	0.97	0.50, 1.47
Mild	199	0.42	0.26, 0.58	0.94	0.61, 1.45	60	0.22	0.09, 0.35	0.84	0.44, 1.57
Moderate or severe	51	0.31	0.01, 0.61	0.64	0.23, 1.73	12	0.63	0.01, 14.4	3.82	1.00, 14.6
Normal haemoglobin	1832	0.52	0.48, 0.56	1.00	Ref	3158	0.29	0.15, 0.43	1.00	Ref
High haemoglobin	48	1.20	0.42, 1.98	1.94	0.94, 3.98	214	0.30	0.21, 0.39	0.95	0.68, 1.35

*Maternal haemoglobin concentrations during the first and second trimesters were classified as anaemia (haemoglobin <11.0 g dL^{-1} and <10.5 g dL^{-1}, respectively), mild anaemia (10.0 to <11.0 g dL^{-1} and 9.5 to <10.5 g dL^{-1}), moderate anaemia (9.0 to <10.0 g dL^{-1} and 8.5 to <9.5 g dL^{-1}) and high haemoglobin (≥14.6 g dL^{-1} in either trimester). Normal haemoglobin includes women with neither anaemia nor high haemoglobin.

†Unweighted number of deliveries.

‡Risk of stillbirth is expressed per 1000 live births plus stillbirths (≥28 weeks' gestation).

cHR, crude hazards ratio; CI, confidence intervals; Ref, reference.

Table 3. Adjusted hazard ratio* for stillbirth at ≥28 weeks' gestation by haemoglobin status at <28 weeks' gestation: National Maternal and Infant Health Survey 1988, United States (Sanderson *et al.*, 1991)

Timimng of haemoglobin measurement	Haemoglobin status†														
	Any anaemia			Mild anaemia			Moderate or severe anaemia			Normal haemoglobin			High haemoglobin		
	Total deliveries†	HR	95% CI	Total deliveries†	HR	95% CI	Total deliveries†	HR	95% CI	Total deliveries†	HR	95% CI	Total deliveries†	HR	95% CI
Black women															
<28 weeks	250	1.05	0.68, 1.61	199	1.09	0.68, 1.74	51	0.86	0.32, 2.34	1832	1.00	Ref	48	2.02	0.96, 4.23
<13 weeks	106	0.99	0.16, 2.12	56	1.07	0.50, 2.31	16	‡		696	1.00	Ref	18	3.67	0.92, 14.6
13–27 weeks	144	1.12	0.65, 1.92	143	1.11	0.61, 2.04	35	1.14	0.41, 3.17	1136	1.00	Ref	30	2.69	0.69, 10.5
Non-black women															
<28 weeks	72	0.80	0.41, 1.56	60	0.65	0.31, 1.34	12	4.41	1.02, 19.0	3158	1.00	Ref	214	0.95	0.63, 1.43
<13 weeks	31	0.67	0.25, 1.77	26	0.49	0.16, 1.54	5	2.87	0.33, 25.2	994	1.00	Ref	109	0.70	0.39, 1.25
13–27 weeks	41	1.09	0.46, 2.59	34	0.90	0.35, 2.27	7	9.40	1.50, 59.0	2164	1.00	Ref	105	1.62	0.72, 3.65

*Hazard ratios were adjusted for maternal age, parity, marital status, maternal education, cocaine use during pregnancy, pre-pregnancy body mass index, prenatal iron supplementation, and iron/multivitamin use during pregnancy, and pre-eclampsia/eclampsia.

†Maternal haemoglobin concentrations during the first and second trimesters were classified as anaemia (haemoglobin <11.0 g dL^{-1} and < 10.5 g dL^{-1}, respectively), mild anaemia (10.0 to <11.0 g dL^{-1} and 9.5 to <10.5 g dL^{-1}), moderate anaemia (9.0 to <10.0 g dL^{-1} and 8.5 to < 9.5 g dL^{-1}) and high haemoglobin (≥14.6 g dL^{-1} in either trimester). Normal haemoglobin includes women with neither anaemia nor high haemoglobin.

‡Number of stillbirths was too few for meaningful analysis.

HR, hazard ratios; CI, confidence intervals; Ref, reference.

non-black women, and this association is most pronounced for moderate anaemia detected between 13 and 27 completed weeks' gestation. However, we cannot be sure that this association did not happen by chance because of the few observations in the subgroup examined. High haemoglobin also may be a risk factor for stillbirth, but in our study the association between high haemoglobin and stillbirth risk was not statistically significant.

Our study is not the first study to show an association between maternal anaemia and fetal death. Previous studies have shown a crude association between maternal anaemia and fetal death (Garn *et al*., 1981a; Lister *et al*., 1985; Stephansson *et al*., 2000) and between maternal anaemia and perinatal mortality (Murphy *et al*., 1986; Xiong *et al*., 2003). The strength of our study was the fact that we used a nationally representative sample that enabled us to adjust for the timing of haemoglobin measurement in weeks' gestation among a sample of pregnant women with both mild and moderate anaemia. We were also able to adjust for socio-economic status, pre-pregnancy BMI and environmental exposures. The results of three of these studies may have been positively biased as they did not control for positive confounders such as age, pre-pregnancy BMI, socio-economic indicators (Garn *et al*., 1981a; Lister *et al*., 1985; Murphy *et al*., 1986) or timing of measurement of haemoglobin (Lister *et al*., 1985). Moreover, one of the studies (Garn *et al*., 1981a) used the lowest haemoglobin or haematocrit which may obscure the association between anaemia and stillbirth, as has been shown for preterm birth and low birthweight (Zhou *et al*., 1998) as this shifts the haemoglobin distribution toward the lowest value and the timing of the measurement is not taken into account. However, when the authors stratified the association by trimester, they found a somewhat similar U-shaped distribution with the highest rate of fetal death at the lowest and highest values of haematocrit (Garn *et al*., 1981a). In the study conducted by Lister in Zaire, maternal anaemia (defined as a haematocrit <30%) was associated with a fourfold greater risk of fetal death [odds ratio (OR): 4.29; 95% CI: 3.66, 5.02] (Lister *et al*., 1985), but maternal haematocrit was determined within 2 weeks of delivery. Because haematocrit reaches a nadir in the second trimester and then gradually increases during the third trimester, women who deliver earlier and are at greater risk of stillbirth are also at greater risk of having low haematocrit.

The other two studies that did control for positive confounders did not find a significant association after adjusting for confounding variables (Stephansson *et al*., 2000; Xiong *et al*., 2003). However, one of these studies did not examine haemoglobin levels over the range of anaemia and used a relatively high threshold for anaemia (<11.5 g dL^{-1}) thus including women with haemoglobin levels in the normal range in the anaemic group (Stephansson *et al*., 2000).

Studies have shown that the distribution of haemoglobin concentration is shifted to the left for blacks, and that black women may have up to 1.0 g dL^{-1} lower haemoglobin concentration than white women in the United States (Johnson-Spear & Yip, 1994; Scanlon *et al*., 2000). This shift in haemoglobin distribution has not been explained by maternal iron intake, iron status or demographic factors, and it may be a physiologic difference (Perry *et al*., 1992). Moreover, a few studies (Garn *et al*., 1981b; Blankson *et al*., 1993; Steer *et al*., 1995), but not all (Scanlon *et al*., 2000), have suggested differential effects of maternal anaemia on birth outcomes by race such that at the same low haemoglobin level white women have an increased risk for poor pregnancy outcomes. Our finding that non-black women with moderate anaemia had an increased risk of stillbirth whereas black pregnant women with moderate anaemia were not at increased risk was consistent with this theory that optimal haemoglobin levels differ for black and white women. In addition, our results are consistent with data from the US Collaborative Perinatal Project which showed that fetal death rates among white women increased at haemoglobin concentrations <9.5 g dL^{-1}, while rates among black women increased at haemoglobin concentrations <8.5 g dL^{-1} (Garn *et al*., 1981b).

Several biologic mechanisms have been postulated through which anaemia or iron deficiency may be associated with adverse pregnancy outcomes (Dallman, 1986; Cnattingius *et al*., 1998; Allen, 2001; Cnattingius & Stephansson, 2002). Fetal growth

restriction and maternal infections are major determinants of stillbirth and may be the mechanisms by which maternal anaemia is associated with an increased risk of stillbirth. Anaemia, iron deficiency or both can activate a stress response in the mother and the fetus by causing chronic fetal hypoxia and increased levels of norepinephrine, respectively (Allen, 2001; Dallman, 1986). The stress response results in elevated levels of cortisol, corticotrophin-releasing hormone, and decreased insulin-like growth factors, both of which effects may lead to restricted fetal growth. Maternal immune function may also be adversely affected by iron deficiency directly or through the activation of the hypothalamic-pituitary-adrenal axis, thereby leading to an increased risk of maternal infection among anaemic women (Viteri, 1994; Allen, 2001).

In our study a high haemoglobin concentration measured at <28 weeks' gestation was not significantly associated with an increased risk of stillbirths. Three previous studies found that high maternal haemoglobin concentrations were associated with an increased risk for perinatal mortality (Murphy *et al.*, 1986) or, specifically, fetal death (Garn *et al.*, 1981a; Stephansson *et al.*, 2000). Two of these studies were large cohort studies (over 50 000 pregnancies) conducted in the USA (Garn *et al.*, 1981a) and Wales (Murphy *et al.*, 1986). However, as mentioned earlier, both studies may be limited by their design. The third study, a recent Swedish population-based, matched case-control study of primiparous women, adjusted for confounding factors and the week of first haemoglobin measurement, as was carried out in our study (Stephansson *et al.*, 2000). Those investigators found that women with a first antenatal haemoglobin measurement of ≥14.6 g dL^{-1} had a greater risk of fetal death at ≥28 weeks' than did women with a haemoglobin of 12.6–13.5 g dL^{-1} (OR: 1.8; 95% CI: 1.0, 3.3). Although our results did not reach statistical significance, the magnitude of the OR among black women, was comparable with this study. Other recent studies suggest the need to examine high haemoglobin as a marker for poor pregnancy outcomes among black women (Garn *et al.*, 1981b; Blankson *et al.*, 1993; Steer *et al.*, 1995; Chang *et al.*, 2003). Further investigation is warranted of the racial disparities in the association between low and high haemoglobin concentrations and adverse pregnancy outcomes.

Our findings are subject to potential limitations. Self-reported information on maternal exposures, such as cocaine use or mineral/vitamin use during pregnancy, may be subject to recall bias given that the maternal questionnaire was completed after delivery and women who had fetal deaths may recall exposures differently (Jacobson *et al.*, 1991; Sanderson *et al.*, 1998a, 1998b). However, this should not affect our results unless recall is also associated with maternal anaemia. Second, non-response rates for mothers with fetal deaths were substantial, and response rates in all three components of the NMIHS are known to have varied by maternal characteristics (Sanderson *et al.*, 1998b). Respondents were more likely to be white, be married, be 20–39 years of age, reside in the midwest, have <4 children, have had more prenatal visits, have entered prenatal care earlier and have more years of education. This may have resulted in weaker associations. However, post-sampling adjustments were made at NCHS prior to the public release of the data to account for non-response (Sanderson *et al.*, 1998b). Third, in some of our comparisons the sample size may have limited our ability to detect a significant association. Fourth, timing or the dose of the mineral/vitamin supplements was unknown, and we did not have access to information on the aetiology of the anaemia. Studies have found iron deficiency anaemia but not anaemia due to other causes to be associated with an increased risk for adverse pregnancy outcomes such as preterm delivery and low birthweight (Lu *et al.*, 1991; Zhou *et al.*, 1998; Scanlon *et al.*, 2000; Scholl & Reilly, 2000; Stephansson *et al.*, 2000; Rasmussen, 2001). Fifth, the lack of information about the aetiology of the stillbirth and on other potential confounders such as the women's diet, other micronutrient levels and environmental exposures limits the interpretation of our findings. Finally, our study may have been underpowered to examine the purported associations between haemoglobin status and the risk of stillbirth.

In spite of its limitations, this study suggests that among non-black women, moderate anaemia at <28 weeks' gestation may be associated with an increased risk of stillbirth. It is recommended that

pregnant women take low-dose iron supplements from the first prenatal visit to meet the daily recommended allowances for iron and to prevent anaemia (CDC, 1998; Stokes *et al*., 2001; AAP & ACOG, 2002) and women with anaemia should be treated with iron supplements (NAS *et al*., 1990; CDC, 1998; AAP & ACOG, 2002). When possible, randomized controlled trials of interventions to prevent anaemia during pregnancy (e.g. iron supplements) should include measures of the potential mechanisms through which anaemia could cause adverse pregnancy outcomes (e.g. cortisol or corticotrophin-releasing hormone concentrations). Maternal nutritional status, including haemoglobin concentration, should be investigated in studies that evaluate racial disparities in adverse pregnancy outcomes such as the National Children's Study.

Acknowledgements

Dr Ananth is partially supported by a grant (R01-HD038902) awarded to him by the National Institutes of Health.

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