Association between maternal haemoglobin and stillbirth: a cohort study among a multi-ethnic population in England

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Summary

The study objectives were to examine the association of maternal haemo-
globin with stillbirth and perinatal death in a multi-ethnic population in
England. We conducted a retrospective cohort analysis using anonymised
maternity data from 14 001 women with singleton pregnancies ≥24 weeks'
gestation giving birth between 2013 and 2015 in two hospitals - the Royal
Wolverhampton NHS Trust and Guy's and St Thomas' NHS Foundation
Trust. Multivariable logistic regression analyses were undertaken to analyse
the associations between maternal haemoglobin at first visit and at
28 weeks with stillbirth and perinatal death, adjusting for 11 other risk fac-
tors. Results showed that 46% of the study population had anaemia (hae-
moglobin <110 g/l) at some point during their pregnancy. The risk of
stillbirth and perinatal death decreased linearly per unit increase in haemo-
globin concentration at first visit (adjusted odds ratio [aOR] still-
birth = 0·70, 95% confidence interval [CI] 0·58–0·85, aOR perinatal
death = 0·71, 95% CI 0·60–0·84) and at 28 weeks (aOR stillbirth = 0·83,
95% CI 0·66–1·04; aOR perinatal death = 0·86, 95%CI 0·67–1·12). Com-
pared with women with haemoglobin ≥110 g/l, the risk of stillbirth and
perinatal death was five- and three-fold higher in women with moderate-
severe anaemia (haemoglobin <100 g/l) at first visit and 28 weeks, respec-
tively. These findings have clinical and public health importance.

Keywords: haemoglobin concentration, pregnancy, stillbirth, perinatal
death, maternal anaemia.

There is increasing acceptance that anaemia affects patient
outcomes. Pre-operative anaemia has an adverse impact on
surgical outcomes, and this has driven changes in patient
care pathways to attempt optimisation of a patient's haemo-
globin before surgery (Musallam *et al*, 2011). Anaemia is also
highly prevalent in pregnancy, and is by far most commonly
caused by iron deficiency. Arguably, a lack of clarity on the
full clinical consequences of anaemia has contributed to the
lack of a comprehensive systematic approach to address this
public health issue during pregnancy. One recent study in
the UK showed that 24% of women developed anaemia at
some point during their pregnancy (Barroso *et al*, 2011). A
systematic review of 48 randomised controlled trials and 44
cohort studies provided evidence about the benefits of rou-
tine iron supplementation for selected outcomes, including
improving maternal haemoglobin concentration and child
birth-weight, but there was considerable uncertainty about
the magnitude of the effects on most other maternal and
infant outcomes including stillbirth and perinatal death due
to a lack of studies (Haider *et al*, 2013).

It is thought that most stillbirths are preventable and the causes are considered to be inextricably linked with the health of the mother (Frøen *et al*, 2016). In the UK, 3252 babies were stillborn in 2014, giving an incidence of 4·16 per 1000 total births (Manktelow *et al*, 2016). The stillbirth rate in the UK appears high compared with other high income countries (Lawn *et al*, 2016). One potential aetiological factor in the cause of stillbirth is iron deficiency anaemia, however, there is discussion in the literature about the strength of data supporting any association between haemoglobin concentration and stillbirth or levels of evidence on the effects of iron supplementation (Lawn *et al*, 2011).

The objective of this study was to further examine the association of maternal haemoglobin concentration at first antenatal visit and at 28 weeks with stillbirth and perinatal death by using very recent maternity data from large multiethnic populations at two urban hospitals in England.

Methods

We conducted a retrospective cohort analysis using anonymised maternity data from 14 001 women with singleton pregnancies ≥24 weeks of gestation giving birth in two hospitals between 2013 and 2015 (7175 from Royal Wolverhampton NHS Trust, 2013–2014 and 6826 from Guy's and St Thomas' NHS Foundation Trust, 2014–2015). We examined the association between maternal haemoglobin and both stillbirth and perinatal death. These two outcomes clearly overlap, perinatal death being a composite of stillbirths and neonatal deaths in the first 7 days of life. However, both are frequently used as outcome measures.

Information on infant outcomes, live-birth, stillbirth at or after 24^{+0} weeks' gestation, and neonatal death in the first week of life were used to generate the outcome variables 'stillbirth' and 'perinatal death'. Information on maternal haemoglobin concentration at first visit and at 28 weeks was extracted from the hospital pathology systems and then paired with the maternity data. The datasets were then anonymised. We tested this exposure variable for deviations from linearity by fitting functional polynomials in the univariable logistic regression models with multiple transformations of the continuous variable (Royston *et al*, 1999). Results did not show the presence of any significant non-linear associations between maternal haemoglobin and the outcomes. We therefore used maternal haemoglobin as a continuous variable for the analysis.

Other known risk factors for stillbirth and perinatal mortality are advanced maternal age (>35 years), low socioeconomic status, ethnicity, high body mass index (BMI), nulliparity, smoking, antepartum haemorrhage, gestational diabetes, maternal infection and pregnancy-induced hypertensive disorders during the index pregnancy, pre-existing diabetes mellitus, and other pre-existing medical co-morbidities (such as mental health problems, hypertension, haemoglobinopathies), placental dysfunction, fetal growth restriction and spontaneous preterm labour (Di Mario *et al*, 2007; Flenady *et al*, 2011; Lawn *et al*, 2016). Major confounders identified from the literature include hypertensive disorders of pregnancy, which are associated with a decreased plasma volume and therefore a relatively higher haemoglobin concentration, antepartum haemorrhage, which can lead to a fall in haemoglobin, low socioeconomic status, which could result in a low haemoglobin from poor nutrition, and other medical comorbidities, such as haemoglobinopathies (Di Mario *et al*, 2007; Flenady *et al*, 2011; Lawn *et al*, 2016).

Information on socio-demographic characteristics, obstetric history, current pregnancy problems, and medical co-morbidities were used to generate variables for potential confounders and other risk factors for stillbirth and perinatal death. Information on ethnicity was not available for about 16% of the study sample. In another study Knight *et al* (2009) included women with unknown ethnicity in the 'white' group because the re-distributed proportions matched more accurately with the estimated ethnic profiles in the UK population census (NHS England, 2006). The same was done in this study. Tests for deviations from linearity showed that maternal age had a linear association with the outcomes, but a non-linear association was observed for maternal BMI. Women were therefore divided into four standard groups: normal ($18·5$–$24·9$ kg/m^2), underweight (<$18·5$ kg/m^2), overweight (25-$29·9$ kg/m^2) and obese (≥30 kg/m^2). Parity was used as a continuous variable and women were divided into smokers and non-smokers based on their smoking status at booking.

Maternal records relating to problems during the index pregnancy were used to generate binary variables for antepartum haemorrhage, gestational diabetes and hypertensive disorders of pregnancy. Three binary variables were generated from the history of medical co-morbidities; pre-existing haemoglobinopathies, pre-existing diabetes mellitus and any other medical comorbidities (excluding obesity).

Statistical analysis

We compared the characteristics of the study population with that of the general pregnant population in England using available data on maternal characteristics from the Hospital Episode Statistics (HES) database of the Health and Social Care Information Centre (HSCIC) [http://www.hscic.gov.uk/hes (Accessed 12 August 2015)]. We then undertook univariable analysis to examine the crude associations of the outcomes (stillbirth and perinatal death) with maternal haemoglobin concentration at first visit, usually in the first trimester, and at 28 weeks' gestation. Both these time points coincide with routine haematology measurements during pregnancy. Multivariable logistic regression models were built to analyse the association of maternal haemoglobin concentration with stillbirth and perinatal death separately for the first visit and at 28 weeks adjusting

for 11 other risk factors (maternal age, ethnicity, BMI, parity, smoking status, gestational diabetes, antepartum haemorrhage and hypertensive disorders of pregnancy, pre-existing diabetes mellitus, haemoglobinopathies, and other medical comorbidities). We did not find any significant moderate to strong correlations among the independent variables. However haemoglobin concentrations at first visit and at 28 weeks were highly correlated (correlation coefficient 0·54, $P < 0·001$), hence we did not adjust for baseline haemoglobin status in the 28 weeks multivariable model. Studies have shown that maternal haemoglobin concentration is associated with fetal growth restriction and preterm birth, precursors for stillbirth and early neonatal mortality (Haider *et al*, 2013; Nair *et al*, 2016a). Therefore, fetal growth restriction and preterm birth were not included in the regression models.

Additional logistic regression analyses were conducted by dividing the women into categories of anaemia according to their haemoglobin concentration using the cut-offs suggested by the World Health Organisation (WHO) (no anaemia ≥110 g/l (reference group), mild anaemia 100–109 g/l; moderate-severe anaemia <100 g/l) (WHO 2011). The multivariable models for anaemia at first visit and at 28 weeks adjusted for the 11 other risk factors. The categorical variables for maternal anaemia at first visit and at 28 weeks were not highly correlated, hence the 28 weeks multivariable model also adjusted for baseline anaemia status.

We tested for plausible interactions between haemoglobin concentration and mother's ethnicity, and haemoglobin concentration and BMI by fitting interaction terms into each of the multivariable models followed by likelihood ratio testing (LR-test). No significant interactions were observed. Missing information was <2% for most variables, except BMI and smoking. Data were not assumed to be missing at random and a proxy variable was generated by categorising the missing data as a separate group for each variable. All analyses were performed using Stata version 13·1, SE (StataCorp, College Station, TX, USA).

Sensitivity analyses

Data on index of multiple deprivation (IMD) quintiles, a measure of socioeconomic status, was available only in the Wolverhampton dataset, hence a sensitivity analysis was conducted using this data to measure the effect of IMD quintiles on the association between haemoglobin concentration and the outcomes by testing two models, one with IMD quintiles in addition to the other 11 variables and one without. The results did not vary with the inclusion and exclusion of IMD quintiles. Sensitivity analysis was conducted for variables with >1% missing information by redistributing the missing observations into the different categories of the variables; this did not materially change the results. A complete case analysis was also performed. Again the results did not differ from the original models.

Study power

A logistic regression of the binary response variables, stillbirth and perinatal death, on a continuous variable of maternal haemoglobin concentration with a fixed sample size of 14 001 observations and 0·4% prevalence of stillbirth in the UK (Manktelow *et al*, 2016) had 80% power at a 0·05 significance level to detect an odds ratio (OR) of ≤0·69 or ≥1·46 per unit increase in haemoglobin concentration. For the anaemia analysis, the minimum sub-group sample of 279 with a prevalence range of 0·4% to 0·7% for the outcomes in the unexposed had 80% power to detect an OR of 3·30 or greater at a *P*-value of <0·05 (two-tailed), and the maximum sub-sample 2976 for the same range of prevalence had 80% power to detect an OR of 1·60 or greater at $P < 0·05$ (two-tailed).

Results

Characteristics of the women with singleton pregnancies delivering at or after 24^{+0} weeks of gestation in relation to the study outcomes are shown in Table I. The median age of pregnant women in the study population was 30 years (range 14–53 years) and median BMI was 25 kg/m^2 (range 10–74 kg/m^2). More than a third of the pregnant women had a BMI ≥25 kg/m^2 (21% of the pregnant women were overweight and 17% were obese), 48% were multiparous, 13% smoked during pregnancy and 30% belonged to ethnic minority groups. Nearly a quarter of the women had one or more pre-existing medical problems and 18% had problems during the index pregnancy (0·4% antepartum haemorrhage, 5% gestational diabetes, 5% hypertensive disorders of pregnancy and approximately 7% had other problems).

In the study population, median haemoglobin concentration at first visit was 125 g/l (range 51·6– 191 g/l) and at 28 weeks it was 113 g/l (range 64–174 g/l). The prevalence of mild anaemia increased, from 5% at the first visit to 22% at 28 weeks, and the proportion of women with moderate-severe anaemia increased from 2% at first visit to 7% at 28 weeks. In 26% of the women who had a normal haemoglobin at first visit, the concentrations decreased to <110 g/l at 28 weeks and 23% of the women who had mild anaemia at first visit became moderate to severely anaemic at 28 weeks. For 18% of the women with anaemia at first visit, the haemoglobin concentrations improved to normal pregnancy concentrations at 28 weeks. Overall, 46% of the women were identified to have developed anaemia at some point during their pregnancy.

In total, 0·5% of singleton babies were stillborn (14 before 28 weeks of gestation and 62 after 28 completed weeks of gestation) and a further 34 (20 of which were born before 28 weeks) died during the first seven days after birth, leading to an overall 0·8% perinatal mortality rate in the study population. The proportions of stillbirths and perinatal deaths did not vary across the categories of age, parity, smoking

Table I. Characteristics of the study population in relation to the outcomes.

Maternal characteristics (N = 14 001)	Women with live born babies (%) n = 13 925	Women with stillborn babies (%) n = 76	Women with infants who were alive at seven completed days after birth (%) n = 13 891	Women whose babies were stillborn or died at <7 days after birth (%) n = 110
Age (years)				
<20	535 (3·8)	5 (6·6)	530 (3·8)	10 (9·1)
20–24	2,240 (16·1)	14 (18·4)	2,235 (16·1)	19 (17·3)
25–29	3,656 (26·3)	14 (18·4)	3,649 (26·3)	21 (19·1)
30–34	4,152 (29·8)	25 (32·9)	4,141 (29·8)	36 (32·7)
35–39	2,453 (17·6)	15 (19·7)	2,449 (17·6)	19 (17·3)
40–44	644 (4·6)	3 (4·0)	642 (4·6)	5 (4·5)
≥45	52 (0·4)	0 (0)	52 (0·4)	0 (0)
Missing	193 (1·4)	0 (0)	193 (1·4)	0 (0)
Parity				
Nulliparous	7,231 (51·9)	36 (47·4)	7,211 (51·9)	56 (50·9)
Multiparous	6,693 (48·1)	40 (52·6)	6,679 (48·1)	54 (49·1)
Missing	1 (0·01)	0 (0)	1 (0·01)	0 (0)
Body mass index categories (kg/m^2)*,†				
Underweight (<18·5)	361 (2·6)	1 (1·3)	360 (2·6)	2 (1·8)
Normal (18·5–24·9)	4,801 (34·5)	23 (30·3)	4,788 (34·5)	36 (32·7)
Overweight (25–29·9)	2,978 (21·4)	17 (22·4)	2,970 (21·4)	25 (22·7)
Obese (≥30)	2,333 (16·7)	23 (30·3)	2,325 (16·7)	31 (28·2)
Missing	3,452 (24·8)	12 (15·8)	3,448 (24·8)	16 (14·6)
Smoking status				
Smoker	1,808 (13·0)	11 (14·5)	1,803 (13·0)	16 (14·5)
Non-smoker	10,430 (74·9)	60 (78·9)	10,404 (74·9)	86 (78·2)
Missing	1,687 (12·1)	5 (6·6)	1,684 (12·1)	8 (7·3)
Ethnicity				
White	9,722 (69·8)	47 (61·8)	9,698 (69·8)	71 (64·6)
Non-white	4,203 (30·2)	29 (38·2)	4,193 (30·2)	39 (35·4)
Problems in current pregnancy				
Antepartum haemorrhage†				
No	13,825 (99·3)	74 (97·4)	13,792 (99·3)	107 (97·3)
Yes	53 (0·4)	1 (1·3)	53 (0·4)	1 (0·9)
Missing	47 (0·3)	1 (1·3)	46 (0·3)	2 (1·8)
Gestational diabetes mellitus†				
No	13,167 (94·6)	69 (90·8)	13,135 (94·6)	101 (91·8)
Yes	711 (5·1)	6 (7·9)	710 (5·1)	7 (6·4)
Missing	47 (0·3)	1 (1·3)	46 (0·3)	2 (1·8)
Hypertensive disorders of pregnancy†				
No	13,177 (94·6)	69 (90·8)	13,147 (94·6)	99 (90·0)
Yes	694 (5·0)	6 (7·9)	691 (5·0)	9 (8·2)
Missing	54 (0·4)	1 (1·3)	53 (0·4)	2 (1·8)
Pre-existing medical problems				
Diabetes mellitus*,†				
No	13,693 (98·3)	73 (96·1)	13,661 (98·3)	105 (95·5)
Yes	219 (1·6)	2 (2·6)	217 (1·6)	4 (3·6)
Missing	13 (0·1)	1 (1·3)	13 (0·1)	1 (0·9)
Haemoglobinopathies*,†				
No	13,832 (99·3)	75 (98·7)	13,798 (99·3)	109 (99·1)
Yes	80 (0·6)	0 (0)	80 (0·6)	0 (0)
Missing	13 (0·1)	1 (1·3)	13 (0·1)	1 (0·9)
Others (except obesity)*,†				
No	11,033 (79·2)	52 (68·4)	11,009 (79·2)	76 (69·1)
Yes	2,879 (20·7)	23 (30·3)	2,869 (20·7)	33 (30·0)
Missing	13 (0·1)	1 (1·3)	13 (0·1)	1 (0·9)

*$P < 0.05$ for chi square test for difference in proportion of stillbirths across the sub-groups.
†$P < 0.05$ for chi square test for difference in proportion of perinatal deaths across the sub-groups.

status and ethnicity, but a higher proportion of stillbirth and perinatal death were observed among obese women and women with pre-existing medical comorbidities (Table I).

A comparison of the study population with that of the general population of pregnant women in England using routine national data showed that the age distribution, and proportions of multiparous women in the study population were comparable with that of the general pregnant population in England. However, the study population had a higher proportion of women from ethnic minority groups, particularly Indian, black Caribbean and black African (Table S1).

Maternal haemoglobin concentration and stillbirth

The associations between maternal haemoglobin concentration and stillbirth are shown in Table II. In singleton babies born at or after 24^{+0} weeks of gestation, the crude odds of stillbirth decreased by 25% per unit increase in the haemoglobin concentration at first visit [OR = 0·75, 95% confidence interval (CI) 0·62–0·92, $P = 0.004$]. After adjusting for 11 other risk factors, the odds of stillbirth decreased by 30% per unit increase in the haemoglobin concentration (i.e. per 10 g/l increase in haemoglobin concentration) [adjusted odds ratio (aOR) = 0·70, 95% CI 0·58–0·85, $P = 0.001$]. The association between maternal haemoglobin concentration at 28 weeks and stillbirth was not statistically significant at $P < 0.05$, but an inverse linear association was observed (OR = 0·86, 95% CI 0·65–1·14, $P = 0.277$); aOR = 0·83, 95% CI 0·63–1·11, $P = 0.207$).

Maternal haemoglobin concentration and perinatal death

As shown in Table II, the association between maternal haemoglobin concentration and perinatal death was comparable with the association between haemoglobin concentration and stillbirth. In singleton babies born at or after 24^{+0} weeks of gestation, the crude odds of perinatal death decreased by 25% per unit increase in the haemoglobin concentration at first visit (OR = 0·75, 95% CI 0·64–0·88, $P = 0.001$). After adjusting for the 11 risk factors, the odds of perinatal death

decreased by 29% per unit increase in the haemoglobin concentration (aOR = 0·71, 95% CI 0·60–0·84, $P < 0.001$). The adjusted odds of perinatal death decreased by 13% per unit increase in haemoglobin concentration at 28 weeks, but the association was not statistically significant at $P < 0.05$ (OR = 0·87, 95% CI 0·68–1·13, $P = 0.290$; aOR = 0·86, 95% CI 0·67–1·12, $P = 0.272$).

Maternal anaemia and infant outcomes

An examination of the association between maternal anaemia and the adverse outcomes further substantiated the results of the inverse association between haemoglobin concentration and the outcomes at both the first and 28 week visits. The odds of stillbirth and perinatal death were five-fold higher among pregnant women with moderate-severe anaemia compared with women who had no anaemia at first visit (Table III) after adjusting for the 11 other risk factors (aOR stillbirth = 4·97, 95% CI 2·09–11·79, $P < 0.001$; aOR perinatal death = 5·16, 95% CI 2·53–10·52, $P < 0.001$). The odds of stillbirth and perinatal death were more than two and a half times higher among pregnant women with moderate-severe anaemia at 28 weeks of gestation after adjusting for the baseline anaemia status and 11 other risk factors compared with women with normal haemoglobin concentration at 28 weeks (aOR stillbirth = 2·81, 95% CI 1·25–6·30, $P = 0.012$; aOR perinatal death = 2·60, 95% CI 1·23–5·51, $P = 0.012$). The crude and adjusted odds ratios for stillbirth and perinatal death among women with mild anaemia were not significantly different compared to women who had no anaemia at first visit (aOR stillbirth = 0·56, 95% CI 0·13–2·30, $P = 0.416$; aOR perinatal death = 0·58, 95% CI 0·18–1·85, $P = 0.354$) or at 28 weeks (aOR stillbirth = 1·30, 95% CI 0·64–2·61, $P = 0.457$; aOR perinatal death = 1·27, 95% CI 0·68–2·38, $P = 0.446$).

Discussion

This study confirms that the burden of anaemia is high: nearly half of the women (46%) in the study population had

Table II. Association of maternal haemoglobin concentration with adverse fetal and infant outcomes.

Exposure	Stillbirth	Perinatal death
Maternal haemoglobin at first visit (g/l)		
Unadjusted odds ratio (95% CI) per unit increase in haemoglobin concentration	0·75 (0·62–0·92)	0·75 (0·64–0·88)
Adjusted odds ratio† (95% CI) per unit increase in haemoglobin concentration	0·70 (0·58–0·85)	0·71 (0·60–0·84)
Maternal haemoglobin at 28 weeks (g/l)*		
Unadjusted odds ratio (95% CI) per unit increase in haemoglobin concentration	0·86 (0·65–1·14)	0·83 (0·66–1·04)
Adjusted odds ratio† (95% CI) per unit increase in haemoglobin concentration	0·83 (0·63–1·11)	0·86 (0·67–1·12)

$N = 14001$ singleton babies born at or after 24 weeks of gestation.

*The model at 28 weeks excludes women who had a stillbirth or perinatal death before 28 weeks.

†Model adjusted for maternal age, body mass index, parity, smoking status, gestational diabetes, antepartum haemorrhage and pregnancy-induced hypertension during index pregnancy, pre-existing diabetes mellitus, haemoglobinopathies, other medical comorbidities and ethnicity; CI, Confidence Interval.

Table III. Association of maternal anaemia with adverse infant outcomes.

Maternal anaemia	Stillbirth (n = 14001 singleton babies born at or after 24^{+0} of gestation)					
	Stillborn (%)	Live born (%)	Unadjusted OR (95% CI)	P-value for trend	†Adjusted OR (95% CI)	P-value for trend
First visit (Hb, g/l)						
Normal Hb (≥110)	59 (77·6)	11 529 (82·8)	1 (ref)	0·025	1 (ref)	0·018
Mild (100–109)	2 (2·6)	767 (5·5)	0·51 (0·12–2·09)		0·56 (0·13–2·30)	
Moderate-severe (<100)	6 (7·9)	273 (2·0)	4·29 (1·84–10·03)		4·97 (2·09–11·79)	
Missing	9 (11·8)	1356 (9·7)	1·29 (0·64–2·62)		1·50 (0·73–3·11)	
28 weeks (Hb, g/l)*						
Normal Hb (≥110)	26 (41·9)	7833 (56·6)	1 (ref)	0·008	1 (ref)	0·059
Mild (100–109)	12 (19·4)	3007 (21·7)	1·20 (0·61–2·39)		1·30 (0·64–2·61)	
Moderate-severe (<100)	10 (16·1)	988 (7·1)	3·05 (1·47–6·34)		2·81 (1·25–6·30)	
Missing	14 (22·6)	2014 (14·6)	2·09 (1·09–4·02)		1·84 (0·91–3·74)	

Maternal anaemia	Perinatal death (n = 14001 singleton babies born at or after 24^{+0} weeks)					
	Perinatal death (%)	Alive at 7 completed days after birth (%)	Unadjusted OR (95% CI)	P-value for trend	†Adjusted OR (95% CI)	P-value for trend
First visit (Hb, g/l)						
Normal Hb (≥110)	83 (75·5)	11,505 (82·8)	1 (ref)	0·003	1 (ref)	0·003
Mild (100–109)	3 (2·7)	766 (5·5)	0·54 (0·17–1·72)		0·58 (0·18–1·85)	
Moderate-severe (<100)	9 (8·2)	270 (1·9)	4·62 (2·29–9·28)		5·16 (2·53–10·52)	
Missing	15 (13·6)	1,350 (9·7)	1·54 (0·88–2·67)		1·85 (1·05–3·26)	
28 weeks (Hb, g/l)*						
Normal Hb (≥110)	32 (42·1)	7,827 (56·6)	1 (ref)	0·013	1 (ref)	0·059
Mild (100–109)	15 (19·7)	3,004 (21·7)	1·17 (0·67–2·05)		1·27 (0·68–2·38)	
Moderate-severe (<100)	11 (14·5)	987 (7·1)	2·57 (1·37–4·82)		2·60 (1·23–5·51)	
Missing	18 (23·7)	2,010 (14·5)	3·75 (2·41–5·84)		1·99 (1·06–3·71)	

Hb- Haemoglobin; CI, Confidence Interval.

*Excludes 14 women with stillbirth and 34 women with perinatal death before 28 weeks.

†Model for first visit adjusted for maternal age, body mass index, parity, smoking status, gestational diabetes, antepartum haemorrhage and pregnancy-induced hypertension during index pregnancy, pre-existing diabetes mellitus, haemoglobinopathies, other medical comorbidities and ethnicity; Model for 28 weeks is adjusted for baseline anaemia status in addition to the other variables included in the first visit model.

anaemia at some point during their pregnancy. The need for haematologists and obstetricians to optimise local care pathways for recognition and management of anaemia is further reinforced by our main study findings suggesting that the risk of stillbirth and perinatal death decreased linearly per unit increase in haemoglobin concentration at first visit and at 28 weeks after accounting for 11 other known risk factors. Compared with women with normal haemoglobin concentrations, the risk of stillbirth and perinatal death was five-fold and three-fold higher in women with moderate-severe maternal anaemia at first visit and 28 weeks, respectively.

The inverse linear association of stillbirth and perinatal death with maternal haemoglobin concentration at 28 weeks of gestation was not statistically significant, possibly due to a low study power, however, the higher risk of adverse outcomes was still present among pregnant women with moderate-severe anaemia (haemoglobin <100 g/l) at 28 weeks. Overall, we believe our findings are important in the broader haematology, obstetric and public health context as it suggests that, given anaemia is most commonly related to iron

deficiency, iron supplementation during pregnancy could have an incremental benefit on reducing the risk of stillbirth and perinatal death for all women.

Iron deficiency anaemia during pregnancy has been explored as a risk factor for stillbirth although the evidence is limited and conflicting (Lawn *et al*, 2011). A few studies from low-to-middle income countries have shown an association of maternal anaemia with stillbirth and perinatal death (Lone *et al*, 2004; Watson-Jones *et al*, 2007; Nair *et al*, 2016a), but others from high-income countries have not reported a significant association (Stephansson *et al*, 2000; Little *et al*, 2005). However, a study from the USA that used National Maternal and Infant Health Survey data from deliveries in 1988 (Tomashek *et al*, 2006) found a significantly higher risk of stillbirth among non-black women who have moderate anaemia. A prospective study from China (Zhang *et al*, 2009) found that haemoglobin <90 g/l in the third trimester of pregnancy was associated with a reduced risk of stillbirth. The authors did not adjust for important pregnancy complications, such as hypertensive disorders of

pregnancy, which can result in reduced plasma volume (and thereby an increase in haemoglobin concentration). Hypertensive disorders of pregnancy are known risk factors for stillbirth with a well-recognised aetiology. These disorders, particularly the pre-eclampsia syndrome, are associated with a reduced maternal intravascular volume and, consequently, a relatively higher haemoglobin concentration compared to unaffected pregnancies. Not adjusting for these important groups of disorders results in the potential for confounding and bias.

A study among Swedish pregnant women found a U-shaped association between stillbirth and haemoglobin concentration at first visit or at 28 weeks (Stephansson et al, 2000). In contrast to our findings, the Swedish study did not show a significant association between anaemia and stillbirth. One possible reason for this difference could be because the Swedish study did not account for the effect of important risk factors for stillbirth, including gestational diabetes and medical comorbidities; instead the multivariable models adjusted for small-for-gestational age, which has been hypothesised to be in the pathway mediating the effect of haemoglobin concentration on stillbirth (Stephansson et al, 2000). Another study using data from St Mary's Maternity Information System database (London) did not find a significant association between perinatal mortality and haemoglobin concentration at first antenatal visit, but showed a risk associated with lowest and highest haemoglobin concentrations recorded at any point during the pregnancy after the first visit (Little et al, 2005). A limitation of this study, as acknowledged by the authors, was that information for haemoglobin concentration was missing for more than a third of the study population. In addition, the authors did not adjust for important potential confounders.

The present study addresses a gap in the UK to explore evidence on the association between haemoglobin concentration and adverse fetal and infant outcomes. In addition to the already known association of low haemoglobin during pregnancy and maternal anaemia with poor maternal outcomes in the UK (Nair et al, 2016b), this study identified a significant association with stillbirth and perinatal death. The study population appears comparable with that of the general pregnant population in England in terms of age distribution, multiparity and multiple pregnancies, suggesting generalisability, although the study sample had a higher proportion of women from ethnic minority groups. We did not have information on BMI, smoking status and pregnancy problems in national data, and were unable to comment on the comparability of these factors to the general population. We did not have information on whether women in the study population were taking multivitamin or iron supplementation and therefore could not account for this in the analysis. However, according to the recommended guidance, in the study hospitals all pregnant women who are diagnosed with anaemia at any point during pregnancy should be prescribed iron supplementation.

There are several limitations to recognise in our analysis. We have defined haemoglobin thresholds during pregnancy as commonly reported in textbooks, but it is unclear to what degree these thresholds are validated reference ranges during pregnancy, even allowing for the effects of changes in plasma volume. Inability to adjust for socioeconomic status in the main multivariable models was a limitation, but sensitivity analysis using the Wolverhampton data did not show any significant effect of socioeconomic status on the association we observed between haemoglobin concentration and the outcomes. Another limitation was missing information on haemoglobin concentration at first visit and at 28 weeks for about 9·7% and 15·6% of the women, respectively, which could have biased the study results. However, the results of sensitivity analyses by redistributing the missing observations into the different categories of the anaemia variable, and complete case analysis were not materially different from that of the original models. We did not have information about the causes of stillbirth in the study population and were therefore not able to examine the association between maternal haemoglobin and stillbirth stratified by causes of stillbirth (for example, congenital anomalies).

Conclusion

This study provides clear evidence of an association of stillbirth and perinatal death with maternal haemoglobin concentration at first visit and at 28 weeks of pregnancy in a multi-ethnic population in England. The risk of these adverse outcomes was significantly higher among women who had moderate-severe anaemia during pregnancy, but more importantly, this risk decreased linearly per unit increase in maternal haemoglobin concentration. This finding is of clinical and public health importance, given that high rates of stillbirth are a major issue globally and a high burden of anaemia is a common finding during pregnancy.

Anaemia is most commonly caused by iron deficiency. Current approaches to the management of anaemia during pregnancy are described in national guidelines (Pavord et al, 2012), based on reactive treatment following case identification. It is of note that nearly half of women in our study population developed anaemia at some point during their pregnancy, which is higher than that reported several years earlier in an epidemiological study (Barroso et al, 2011), suggesting significant on-going challenges in delivering the current policies for case identification and treatment. Alternative strategies to better manage anaemia during pregnancy appear to be an attractive option to improve maternal and fetal outcomes, alongside attention to factors such as obesity and smoking cessation. Routine iron supplementation during pregnancy can maintain normal haemoglobin concentrations and prevent many cases of maternal anaemia. Further experimental studies are required to investigate the effect of iron supplementation during pregnancy on fetal outcomes, assessing appropriate dosing and factors such as adherence and tolerability.

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Author contribution

MN contributed to the design of the study, carried out the data analysis, interpreted the data, and wrote the first draft of the manuscript. DC designed the study, facilitated the process of data extraction from the hospital records, contributed to the data analysis plan and interpretation of the results, and edited the manuscript. SR facilitated the process of data extraction from the hospital records, contributed to interpretation of the results and edited the manuscript. CNP contributed to interpretation of the results and edited the manuscript. SS designed the study, contributed to the data analysis plan and data interpretation, and edited the manuscript. MK designed the study, contributed to the data analysis plan, data interpretation, and edited the manuscript.

Ethical approval

Ethics approval was not required since this was a secondary analysis of anonymous hospital data.

Disclosure of interest

The authors declare that they have no competing interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of characteristics of women giving birth in the study hospitals with that of the general population of pregnant women in England

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