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ORIGINAL ARTICLE

Maternal hemoglobin at 27–29 weeks' gestation and severity of pre-eclampsia

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Abstract

Objective: To examine the relationship between maternal hemoglobin concentration (Hb) at 27–29 weeks' gestation and severity of pre-eclampsia (PE).

Methods: This was a retrospective study of maternal Hb at 27–29 week in 497 pregnancies that developed PE and 497 healthy controls with normal pregnancy outcomes. Multiple regression analysis was used to examine the association between HB and maternal characteristics and severity of PE classified according to gestation at delivery, birth weight and prevalence of abnormal peripartum maternal creatinine, aspartate transaminase and platelet count.

Results: There was no significant difference in median Hb between the PE and control groups. Multiple regression analysis in the PE group showed that significant prediction for Hb was provided by Afro-Caribbean race, gestation at delivery, maternal platelet count <2.5th percentile and birth weight, but not serum creatinine or aspartate transaminase above the 97.5th percentile. Increased Hb was observed in both small and large for gestational age neonates.

Conclusion: In PE, Hb at 27–29 weeks is influenced by birth weight, maternal characteristics and platelet count.

Keywords

Hemoglobin, pre-eclampsia, pregnancy

History

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Introduction

In normal pregnancy, plasma volume increases with gestation to about 40% above pre-pregnancy levels at 30 weeks followed by a small decrease at term [1]. Red cell mass increases linearly with gestation to about 25% above pre-pregnancy levels at term [2]. Consequently, hemoglobin (Hb) decreases with gestation reaching a nadir of about 15% below pre-pregnancy levels at 30 weeks [3]. The purpose of this physiological hemodilution is to create a low-viscosity intravascular system that allows an optimal red cell circulation in the low-velocity placental circulation [4] and a low-resistance system for the maternal left ventricle to contract against. Failure to achieve this low blood viscosity milieu during pregnancy is likely to decompensate both the maternal and fetal/placental homeostasis. It is therefore not surprising that there is an association between adverse pregnancy outcome with increasing Hb levels (and thus whole blood viscosity) [5,6] and a strong correlation between the prevalence of pre-eclampsia (PE) and plasma volume restriction and hemorheological disorders [7,8].

Previous large observational studies have reported on the differences of maternal Hb levels between normal and pregnancies with PE [6,9–15], treating the PE group as a homogeneous population. However, PE has a spectrum of clinical presentations, with differences as to the degree of maternal and fetal involvement. The purpose of this study was to compare normal and PE pregnancies and to examine whether maternal somatometric and demographic factors or differences in disease presentation between maternal and/or fetal involvement present different subgroups in terms of maternal Hb at 27–29 weeks.

Methods

Study population

This was a retrospective case–control study comparing maternal Hb levels at 27–29 weeks gestation between women who developed PE ($n = 497$) and a control group of women who had uncomplicated pregnancies ($n = 497$). Both groups consisted of women with singleton pregnancies who booked for routine antenatal care at King's College Hospital, London, between March 2006 and September 2011. Each case of PE was matched with the next case booked for care and

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having an uncomplicated pregnancy with delivery of a phenotypically normal neonate at term and birth weight between the 5th and 95th percentile for gestational age. The demographic, clinical and outcome characteristics were previously recorded as part of a large prospective observational study for the prediction of pregnancy complications, for which Ethics Committee approval had been granted. For the current study, the advice of our Local Research and Development Committee and the Local Research Ethics Committee (London-Dulwich NRES Committee) was sought regarding the study, and we were advised that formal consideration would not be required.

Outcome measures

Maternal and neonatal outcomes were obtained from the local maternity computerized records or from their General Practitioners. The maternal Hb concentration at 27–29 weeks' gestation and the highest (for serum creatinine and aspartate transaminase) and lowest (for platelet count) peripartum values were obtained from the local computerized pathology system. For women who were reported to have had pregnancies complicated by hypertension, the medical notes were reviewed to confirm the diagnosis and classify the condition as PE, pregnancy-induced hypertension or chronic hypertension with or without superimposed PE.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [16]. The systolic blood pressure should be 140 mm Hg or more and/or the diastolic blood pressure should be 90 mmHg or more on at least two occasions 4 h apart developing after 20 weeks' gestation in previously normotensive women and there should be proteinuria of 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of mid- stream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' of gestation in the absence of trophoblastic disease).

Sample analysis

The hematology analyzer Bayer ADVIA 2120 Hematology System (Siemens AG, Eschborn, Germany) was used to measure maternal Hb by a cyanide-free colorimetric method.

Statistical analysis

In order to control for the gestational age at delivery, the z-scores of birth weight were calculated as described by Royston et al. [17] using locally derived birth weight reference ranges [18]. Similarly, the maternal peripartum levels of creatinine, aspartate transaminase and platelets were classified as abnormal (above the 97.5th percentile for creatinine and aspartate transaminase and below the 2.5th percentile for platelets) based on trimester specific normal ranges [19,20].

The normality of the distribution of the data was assessed by the Kolmogoroff–Smirnoff test. The distribution of maternal weight was normalised by the Box–Cox transformation as follows: TransfWeight = (weight**–8) – 1/−8. For continuous numerical data, the Mann–Whitney U test and the unpaired *t*-test were used to compare non-normally and normally distributed data, respectively. The Jonckheere–Terpstra Test, a non-parametric test for ordered differences among subgroups, was used to assess the significance of increase of Hb with reducing fetal birth weight z-score. For categorical variables, the chi-square test or the Fisher's exact test, where appropriate, were used to assess the differences in proportions between groups.

Multivariate regression analysis was used to establish the factors that independently predict the maternal Hb levels at 27–29 weeks in the control and PE groups. In the control group, the variables assessed in the multivariate model were gestational age of test, gestational age of delivery, maternal age, height, weight (Box-Cox transformation), maternal racial origin (Caucasian, Afro-Caribbean, East Asian, Southeast Asian or mixed), conception (spontaneous, ovulation drugs or IVF), family history of PE (yes or no), smoking (yes or no), previous pregnancy (nulliparous, multiparous-previous PE or multiparous-no PE) and z-score birth weight. In the PE group, apart from the above-mentioned factors, the following variables were also added to the model: maternal creatinine above the 97.5th percentile (yes or no), maternal aspartate transaminase above the 97.5th percentile (yes or no) and maternal platelet count below the 2.5th percentile (yes or no).

The statistical software package SPSS (SPSS Inc, Chicago, IL) was used for data analysis.

Results

Maternal demographic characteristics, pregnancy outcome and routine Hb levels at 27–29 weeks' gestation for the PE and control groups are compared in Table 1. In the PE, compared to the control group, the mean maternal height and median maternal weight were higher, more women were nulliparous or had PE in a previous pregnancy, required assisted reproduction techniques or had a family history of PE, the prevalence of Afro-Caribbean origin was higher, gestational age at delivery was earlier and birth weight was lower. The gestation of measurement of maternal Hb was similar between the two groups and there was no significant difference in median Hb.

In the PE group, there was no significant difference in median Hb between those with serum creatinine above or below the 97.5th percentile ($p = 0.475$), serum aspartate transaminase above or below the 97.5th percentile ($p = 0.300$) and platelet count below or above the 2.5th percentile ($p = 0.073$). The median Hb was higher in those delivering babies with birth weight below than above the 5th percentile ($p = 0.002$). There was an inverse correlation between median Hb and birth weight z-score ($p = 0.009$; Figure 1).

In the control group, independent predictors of maternal Hb were nulliparity, Afro-Caribbean origin and the maternal Box-Cox transformed weight (Hb = −9.84 − 0.5 for Afro-Caribbean race +0.17 for Nulliparity + (17.5 × TransfWeight); R^2 0.09, $p < 0.0001$). In the PE group independent predictors of maternal Hb were gestational age at delivery, Afro-Caribbean race, maternal platelet count below or above the 2.5th percentile and birth weight z-score

Table 1. Demographic characteristics and pregnancy outcome in the women with uncomplicated pregnancies (Controls) and in those complicated by pre-eclampsia (PE).

	Controls ($n = 497$)	Pre-eclampsia ($n = 497$)	p value
Maternal age in years, median (IQR)	31.8 (27.3–35.5)	31.6 (26.5–35.9)	0.9
Maternal height (cm), mean (SD)	164.3 (6.87)	163.3 (6.8)	0.02
Maternal weight in kg, median (IQR)	65.0 (58.1–74.0)	73.6 (64.0–86.9)	<0.0001
Racial origin, *n* (%)			
Caucasian	292 (58.8)	198 (39.8)	<0.0001
Afro-Caribbean	150 (30.2)	256 (51,5)	<0.0001
South Asian	19 (3.8)	18 (3.6)	0.8
East Asian	15 (4.2)	6 (1.2)	0.047
Mixed	21 (4.2)	19 (3.8)	0.7
Parity, *n* (%)			
Nulliparous	212 (42.7)	297 (59.8)	<0.0001
Parous-no previous pre-eclampsia	275 (55.3)	134 (27.0)	<0.0001
Parous-previous pre-eclampsia	10 (2.0)	66 (13.3)	<0.0001
Family history of pre-eclampsia, *n* (%)	14 (2.8)	41 (8.2)	<0.0001
Cigarette smokers, *n* (%)	24 (4.8)	24 (4.8)	1.0
Conception, *n* (%)			
Spontaneous	489 (98.4)	467 (94)	<0.0001
In vitro fertilization	4 (0.8)	22 (4.4)	<0.0001
Ovulation drugs	4 (0.8)	8 (1.6)	0.2
History of chronic hypertension, *n* (%)	0 (0)	60 (12.1)	–
Birth weight in g, median (IQR)	3486.0 (3213.0–3774.0)	2968.0 (2402.0–3403.0)	<0.0001
Birth weight percentile, median (IQR)	48.9 (28.3–74.7)	25.5 (7.4–40.0)	<0.0001
Birth weight z-score, mean (SD)	0.076 (0.9)	−0.5998 (1.2)	<0.0001
Gestation at delivery in weeks, median (IQR)	40.3 (39.49–41.0)	38.6 (36.7–40.0)	<0.0001
Hemoglobin in g/dL, mean (SD)	11.23 (0.90)	11.344 (1.00)	0.08
Gestation at test in weeks, median (IQR)	28.2 (27.7–28.8)	28.3 (27.9–28.9)	0.07

SD, standard deviation; IQR, interquartile range.

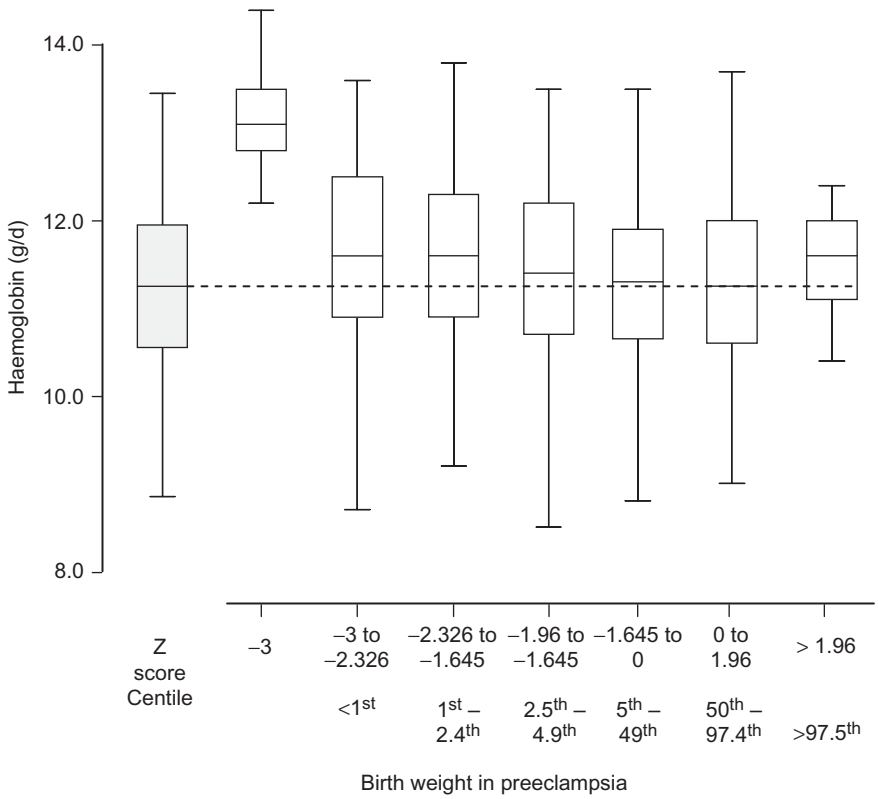

Figure 1. Box and whiskers comparing maternal haemoglobin levels between controls (box on the left) and the PE group. The PE group data are split between subgroups with reducing birth weight z-score. On the x-axis birth weight is represented as z-scores (top) and birth weight centiles (bottom). The dashed line represents the median Hb for the control group.

(Hb = 13.1 − 0.49 for Afro-Caribbean race − 0.3 for platelet count <2.5th percentile − (0.04 × gestational week at delivery) − (0.28 × birth weight z-score) + (0.07 × birth weight z-score 2); R^2 0.11, $p < 0.0001$).

Discussion

This study has demonstrated that maternal Hb at 27–29 weeks' gestation is influenced by maternal characteristics and pregnancy outcome. In uncomplicated pregnancies, Hb

increased with maternal weight, it was higher in nullips compared to multips and was lower in women of Afro-Caribbean compared to Caucasian origin. In women with PE, Hb was lower in women of Afro-Caribbean origin compared to Caucasians and in those with platelet count below the 2.5th percentile, decreased with gestational age at delivery and had a quadratic relationship with birth weight. Increased Hb was observed in association with both growth restriction and macrosomia.

In both the PE group and controls maternal Hb was lower in women of Afro-Caribbean race compared to Caucasians. This is in agreement with previously published data that showed 4.5% lower Hb and higher ferritin levels in non-pregnant black compared to white women in the USA, even after controlling for dietary iron intake [21]. The literature is consistent with differences in Hb levels of about 5–10% between black and white populations, which cannot be explained for by socioeconomic status [22], hereditary disorders such as sickle cell disease or copper or zinc levels [23]. More recently, investigators reporting from the third National Health and Nutrition Examination Survey (NHANES III) in the USA have hypothesized that the combination of lower Hb and higher ferritin levels in black compared to white populations, in association with similar differences in infection markers, may be a sign of anemia of chronic disease and it was suggested that future research associates the differences in Hb levels with inflammatory markers [24].

In the control group maternal Hb increased with maternal weight while in the PE group the Hb increased with high birth weight. It is possible that these two associations of maternal Hb reflect a similar background, that of ensuing maternal glucose intolerance and insulin resistance. In non-pregnant individuals, high Hb levels are related to insulin resistance [25] and compensatory hyperinsulinaemia [26]. In normotensive and hypertensive premenopausal women there is a negative correlation between the insulin sensitivity index and hematocrit, even after adjustment for BMI [27]. Consequently, there is a link between raised Hb, obesity and insulin insensitivity and it is likely that in our data the positive association between maternal Hb and weight is a reflection of a gradual reduction in insulin sensitivity with increasing maternal weight. In addition, maternal pre-pregnancy weight, weight-gain during pregnancy and insulin sensitivity are independent predictors of birth weight and maternal weight and weight gain are associated with delivery of large-for-gestational age babies [28,29]. It is therefore likely, that similar to the association between maternal Hb and maternal weight, the positive association between maternal Hb and LGA babies reflects the interplay between the increase in maternal weight and the resulting increase in the prevalence of glucose intolerance and fetal macrosomia.

The largest observational studies describing changes in maternal Hb in PE are summarized in Table 2. Apart from two prospective studies all other are retrospective. Most

Table 2. Summary of studies in singleton pregnancies examining the association of maternal hemoglobin concentration and pre-eclampsia.

Reference	*n*	Study details	Definition of hypertensive disease	Results/comments
[12]	285 484	– Retrospective study – Women at sea level and high altitude in Peru with low (<10.9 g/dL), normal (11.0–14.5 g/dL) and high (>14.5 g/dL) booking HB – Hb in 2nd or 3rd trimester	BP ≥140/90 and proteinuria >300 mg/24 h	Increased risk for PE with low (<10.9 g/dL) and high (>14.5 g/dL) Hb
[10]	142	– Retrospective study – Women with PE – Maximal pre-delivery Hb	BP ≥140/90 on 2 separate occasions 6 h apart, proteinuria >300 mg in 24 h	Hb increased in PE and inversely related to birth weight percentile
[30]	4985	– Retrospective study – Routine population – Mean 2nd trimester Hb	BP ≥140/90 and proteinuria >300 mg/24 h	Hb <13 g/dL in 67% of women developing PE and 90% of women with normal outcome
[15]	920	– Retrospective study – 1st trimester Hb, low risk women – Hb >12.5 g/dL ($n = 426$) compared to Hb <12.5 g/dL ($n = 448$)	PE defined as per the Report of the National High Blood Pressure Education program working group on high blood pressure in pregnancy	Hb >12.5 g/dL increased risk for PE
[11]	918	– Retrospective study – African American teenagers (<17 yrs old) – Hb in 1st, 2nd and 3rd trimesters	BP ≥140/90 on 2 separate occasions 6 h apart, proteinuria 2+	Hb increased in women developing PE
[14]	796	– Prospective study – Low-risk pregnancies – Hb at 31–32 weeks	BP >140/90 or a rise in SBP of 30 and DBP by 15 mmHg.	Hb increased in women developing PIH
[6]	53 382	– Retrospective study – Low–risk pregnancies – Hb at booking visit (<24 weeks)	PIH and PE according to Cardiff classification	Hb increased in women developing hypertensive disease
[13]	1535	– Retrospective study – Low-risk pregnancies – Hb in 2nd trimester	PIH before 37 weeks (defined as diastolic BP ≥90 mmHg on one or more occasions)	Hb increased in women developing PIH

BP, blood pressure in mmHg; Hb, hemoglobin in g/dL; Ht, hematocrit (%); PIH, pregnancy-induced hypertension; PE: pre-eclampsia.

studies have used maternal Hb as a dichotomous variable and they reported the performance of Hb as a screening tool above a specific threshold. In general, there appears to be an agreement that higher maternal Hb levels at different stages of pregnancy increase the risk of PE. Older reports have also addressed the issue of low maternal Hb levels and PE and this was thought to be a reflection of low socio-economic and poor nutritional status in developing countries [4].

We found that in pregnancies developing PE maternal Hb is higher in cases with fetal growth restriction, compared to women with PE and normal fetal growth. The gradual increase in maternal Hb with reducing birth weight suggests that the maternal and fetal components of this association are demonstrating a parallel shift rather than a ''threshold'' response where fetal growth is reducing above a specific cut-off of maternal Hb, as described by previous studies [31]. In the PE group maternal Hb at 27–29 weeks was not significantly different between those with abnormal and normal renal and liver function, but it was inversely related to low platelet count. This association between low Hb and platelet count below the 2.5th percentile is observed in pregnancies with PE irrespective of the gestational age at delivery. Although many of these pregnancies had platelet counts that we would consider acceptable on everyday clinical practise, one cannot ignore the fact that 15% (75 of 497) of women that developed PE, compared to 2.5% in the controls, had lower platelet counts and also lower Hb, contrary to the general trend of PE being associated with high Hb. It is possible that variations in what we consider HELLP syndrome take place at a sub-clinical stage, earlier than an obvious need for delivery and present a different subgroup of women to the one that is characterized by high Hb. Furthermore, the fact that the PE group comprises of subgroups with divergent Hb levels, i.e. high Hb in the PE with fetal growth restriction and low Hb in the low platelet group and Afro-Caribbean women, may explain the lack of statistical significance in the difference in Hb between controls and PE group.

A limitation of our study is that we could not examine the association of raised maternal Hb and SGA or LGA in the control group because we predefined this group to have birth weight between the 5th and 95th percentiles. Additionally, as this was a retrospective study, we did not have information on maternal iron supplementation and thus we were not able to control for this in our regression models for prediction of maternal Hb. However, iron supplementation cannot increase Hb levels above what is an ideal level for an individual and therefore it cannot account for the increased levels noticed in the SGA and LGA groups [31]. Rather, this is important information for defining the median level of the ''control'' or normal group, so that differences with the raised Hb groups are not artificially inflated.

In conclusion, this study has demonstrated that in women developing PE maternal Hb levels at 27–29 weeks' gestation are influenced by maternal characteristics, platelet count, gestational age of delivery and fetal growth. The interplay between these factors may affect maternal Hb and further studies are needed before this is used as a screening tool for pregnancy complications.

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Declaration of interest

The authors report no declarations of interest. Advice regarding ethics approval was sought from the chairman of the Local Research Ethics Committee (London-Dulwich NRES Committee) and the Local Research and Development Committee. After consideration by the chairman of the committee and the Local R&D Committee, it was advised that this project did not require formal review under the terms of the Governance Arrangements for Research Ethics Committees in the UK.

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