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Association between maternal haemoglobin at 27–29 weeks gestation and intrauterine growth restriction ☆

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ABSTRACT

Objective: To examine the relationship between maternal haemoglobin concentration (Hb) at 27–29 weeks' gestation and fetal growth restriction (FGR).
Design: This was a retrospective, case control study.
Setting: A University hospital in London, UK.
Population: Pregnant women attending for routine antenatal care at 27–29 weeks of pregnancy.
Methods: Maternal Hb, measured routinely at 27–29 weeks in pregnancies complicated by FGR ($n = 491$) was compared to normal controls ($n = 491$). Multiple regression analysis was used to examine the association between Hb and maternal characteristics.
Main outcome measures: Birthweight z-score, admission to the Neonatal Unit (NNU) and adverse perinatal outcome.
Results: Increased Hb at 27–29 weeks gestation is associated with reduced birthweight, with an inverse relationship between maternal Hb and fetal birthweight z-score ($R^2 = 0.10$, $p < 0.0001$). In addition, for the prediction of admission to the NNU ($R^2 = 0.24$, $p < 0.0001$) and serious adverse neonatal outcome ($R^2 = 0.10$, $p < 0.0001$), maternal Hb is an independent predictor with a linear and quadratic relationship, respectively. Therefore, both increased and decreased maternal Hb levels increase the risk of serious neonatal complications.
Conclusions: Raised Hb at 27–29 weeks gestation is associated with FGR and with an increased risk of admission to the NNU and adverse fetal outcome.

1. Introduction

The association between maternal blood viscosity and pregnancy outcome has been shown from the beginning of the previous century [1]. The changes in maternal blood viscosity throughout normal pregnancy have been investigated in the 1980's [2] and an association between hyperviscosity and poor pregnancy outcome has been described [3]. However, the measurement of blood viscosity is laborious and expensive and therefore, on everyday clinical practise and in many research reports the haemoglobin concentration (Hb) or the haematocrit levels (Ht) have been used as proxies in the assessment of blood viscosity [3,4]. Indeed, Ht is one of the most important determinants of blood viscosity and definitely the most important one in low shear flow systems [2]. Consequently, various observational studies have investigated the relationship between pregnancy outcome and maternal haemoglobin levels [5–16] and many of them, but not unexceptionally so, suggest a poorer outcome with higher haemoglobin levels. These studies have associated maternal Hb or haematocrit levels at different stages of pregnancy with reduced fetal growth but they have not presented clear evidence that the increased Hb or Ht levels are associated with poorer perinatal and neonatal outcome.

Abbreviations: CRH, corticotrophin releasing hormone; FGR, fetal growth restriction; Hb, haemoglobin; Ht, haematocrit; HIE, hypoxic ischaemic encephalopathy; IGF, insulin-like growth factor; IVH, intraventricular haemorrhage; IVF, in-vitro fertilisation; NNU, Neonatal Unit; NEC, necrotising enterocolitis; PE, pre-eclampsia; PVL, periventricular leucomalacia; RDS, respiratory distress syndrome.

Key message: Maternal haemoglobin concentration (Hb) at 27–29 weeks can be used as a continuous variable to predict adverse fetal outcome. The higher the maternal Hb, the higher the risk for FGR and the risk for admission to the NNU. Both high and low Hb increases the risk for adverse neonatal outcome.

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Hyperviscosity has a deleterious effect on the intervillous space with resultant poor maternal-fetal exchange [17] that could lead directly to fetal growth impairment by decreased nutrient transfer or indirectly by the effect of fetal corticosteroids that are released as a response to chronic hypoxia on the fetus [3]. Therefore, hyperviscosity can result in FGR and/or reduced fetal reserve with a consequent increased risk of antenatal and intrapartum fetal compromise and increased admissions to the neonatal unit (NNU).

More recently, the realisation that Hb has the ability to bind and inactivate nitric oxide (NO) [18] has generated interest on the potential of Hb to act as a mediator for cardiovascular disease. With increasing haematocrit and reducing oxygen levels this ability becomes counterproductive [19] leading to oxidative stress, vascular endothelial damage, vasoconstriction and placental ischaemia [20]. In addition, there is recent evidence of overproduction of fetal Hb at placental level [21], which leaks to the maternal circulation [22], and impairs further the placental function [23]. These changes have been shown to predate the clinical syndrome of pre-eclampsia and FGR [24].

During routine antenatal care testing of maternal Hb around 28 weeks gestation has been established as a screening test for maternal anaemia with a purpose of starting treatment [25]. However, there is little evidence regarding the value of increased maternal Hb at 28 weeks at predicting FGR and adverse perinatal outcomes.

The aim of our study is to assess the relationship between maternal Hb at 27–29 weeks gestation with fetal birthweight and its association with admission to the NNU and other indices of adverse perinatal outcome.

2. Materials and methods

2.1. Study population

This was a retrospective case-control study comparing maternal haemoglobin levels at 27–29 weeks' gestation between women whose pregnancies were complicated by FGR ($n = 491$) and a control group of women who had uncomplicated pregnancies ($n = 491$). 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. Pregnancies complicated with pre-eclampsia were excluded from both groups. Gestational age was estimated by first trimester ultrasound, which was performed routinely for first trimester screening for aneuploidies. FGR was defined as delivery of a baby with birthweight centile below the 5th percentile for the gestation. Each case of FGR was chronologically matched with the next case booked for care and having an uncomplicated pregnancy with delivery of a phenotypically normal neonate at term and birthweight above the 5th 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 locally. 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.

2.2. Outcome measures

Maternal and neonatal outcomes were obtained from the local maternity computerised records. The maternal haemoglobin concentration at 27–29 weeks' gestation was obtained from the local computerised pathology system. For women who were reported to have had pregnancies complicated by hypertension, the medical notes were reviewed to confirm the diagnosis. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [26].

The neonatal outcomes included Apgar score at 1 and 5 min, admission to the NNU, a composite outcome that comprised of sepsis, respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL), hypoxic ischaemic encephalopathy (HIE) and hypoglycaemia and fetal/neonatal death.

2.3. Sample analysis

The haematology analyser Bayer Advia 2120 (Siemens Healthcare Diagnostics) was used to measure maternal haemoglobin by a cyanide-free colourimetric method.

2.4. Statistical analysis

In order to control for the gestational age at delivery, the birthweight z-scores were calculated as described by Royston et al. [27] using locally derived birthweight reference ranges [28].

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. 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 haemoglobin with reducing fetal birthweight z-score, with admission or not to NNU and between controls and FGR pregnancies with and without adverse composite outcome. 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 haemoglobin levels at 27–29 weeks in the control and FGR groups, separately and in the total cohort. The variables used in the model were selected on the basis of our previous work where we created a prediction model for the risk of pre-eclampsia in pregnancy based on maternal demographic factors [29]. 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 birthweight. In the FGR group, apart from the above-mentioned factors, the following variables were also added to the model: Apgar score at 1 and 5 min, admission to the NNU (yes or no) and adverse composite outcome (yes or no).

In addition, multivariate logistic regression analysis was used to establish the factors that independently predict admission to the NNU and adverse composite outcome in the total cohort (controls and FGR together). The predictors were the same as those described above for the control group with the addition of maternal Hb.

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

3. Results

Maternal demographic characteristics, pregnancy outcome and routine haemoglobin levels at 27–29 weeks' gestation for the FGR and control groups are compared in Table 1. In the FGR group,