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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,

Table 1
Demographic characteristics and pregnancy outcome in the women with uncomplicated pregnancies (Controls) and in those complicated by fetal growth restriction (FGR).

	Controls (N = 491)	FGR (N = 491)	p-Value
Maternal demographics			
Maternal age in years, median (IQR)	31.9 (27.3–35.5)	30.5 (25.2–35.0)	0.009
Maternal height (cm), mean (SD)	164.3 (6.8)	161.2 (6.7)	<0.0001
Maternal weight in kg, median (IQR)	65.0 (58.1–74.3)	61.0 (54.6–70.0)	<0.0001
Racial origin, *n* (%)			
Caucasian	287 (58.5)	206 (42.0)	0.06
Afro-Caribbean	150 (30.5)	210 (42.8)	0.06
South Asian	19 (3.9)	32 (6.5)	0.06
East Asian	14 (2.9)	18 (3.7)	0.47
Mixed	21 (4.3)	25 (5.1)	0.5
Parity, *n* (%)			
Nulliparous	207 (42.2)	292 (59.5)	<0.0001
Parous-no previous preeclampsia	274 (55.8)	187 (38.1)	<0.0001
Parous-previous preeclampsia	10 (2.0)	12 (2.4)	0.6
Family history of preeclampsia, *n* (%)	14 (2.9)	27 (5.5)	0.03
Cigarette smokers, *n* (%)	24 (4.9)	79 (16.1)	<0.0001
Conception, *n* (%)			
Spontaneous	483 (98.4)	471 (95.9)	0.02
In vitro fertilisation	4 (0.8)	12 (2.4)	0.04
Ovulation drugs	4 (0.8)	8 (1.6)	0.2
History of chronic hypertension, *n* (%)	0 (0)	6 (1.2)	–
Fetal outcome			
Birthweight in g, median (IQR)	3484.5 (3209.0–3773.0)	2594.0 (2348.0–2760.0)	<0.0001
Birthweight percentile, median (IQR)	48.7 (28.2–74.7)	2.6 (1.3–3.7)	<0.0001
Birthweight *z*-score, mean (SD)	0.074 (0.9)	−2.06 (0.4)	<0.0001
Gestation at delivery in weeks, median (IQR)	40.3 (39.4–41.0)	39.3 (38.5–40.7)	<0.0001
Admission to the Neonatal Unit, *n* (%)	4 (0.8)	43 (8.7)	<0.0001
Fetal/neonatal death, *n* (%)	0	8 (1.6)	0.005
Composite adverse outcome, *n* (%)	0	24 (4.9)	<0.0001
Haemoglobin test details			
Haemoglobin in g/dL, mean (SD)	11.21 (0.87)	11.34 (1.04)	0.03
Gestation at test in weeks, median (IQR)	28.2 (27.7–28.8)	28.4 (27.9–28.8)	0.07

compared to the control group, the mean maternal height and median maternal age and weight were lower, more women were nulliparous or had PE in a previous pregnancy, more women were smokers, required assisted reproduction techniques or had a family history of PE and birthweight was lower. The gestation of measurement of maternal haemoglobin was similar between the two groups and mean Hb was higher in the FGR group. The FGR group, compared to the control group had a higher rate of admission to the NNU, fetal/neonatal death rate and adverse composite outcome.

There is a progressive increase in maternal Hb levels with reducing birthweight *z*-score ($p < 0.0001$, Fig. 1). Maternal Hb was higher in patients with babies admitted compared to those not admitted to NNU ($p = 0.03$, Fig. 2) and there was a progressive increase in maternal Hb levels between controls, pregnancies with FGR without and with adverse composite outcome ($p = 0.008$, Fig. 3).

In the control group independent predictors of maternal Hb were Afro-Caribbean origin and maternal transformed weight (Hb = 12.1−(0.5**Afro-Caribbean*)−(21.4**TransfWeight*); R^2 0.08, $p < 0.0001$). In the FGR group independent predictors of maternal Hb were Afro-Caribbean and South East Asian race, maternal weight, Apgar score at 1 min and birthweight *z*-score (Hb = 11.2−(0.75**Afro-Caribbean*)−(0.41**SE_Asian*)-(0.073**Apgar_1*)−(21.2**TransfWeight*)−(0.32**Birthweight_z-score*); R^2 0.15, $p < 0.0001$). When the total cohort (controls and FGR) was analysed as one group (Fig. 1), independent predictors of maternal Hb were Afro-Caribbean race and South East Asian race, maternal weight and birthweight *z*-score ((Hb = 12.2−(0.66**Afro-Caribbean*)−(0.31**SE_Asian*)−(23.6**TransfWeight*)−(0.12**birthweight_z-score*); $R^2 = 0.10$, $p < 0.0001$).

For the prediction of admission to the NNU independent predictors were maternal Hb, maternal age, Afro-Caribbean and South-East Asian origin, smoking, in vitro fertilisation, the use of ovulation drugs and gestation at delivery (Admission to NNU = 1.99 + (0.14**Hb*)−(0.05**Gestation_delivery*) + (0.002**maternal_age*) + (0.05**smoking*) + (0.03**AfroCaribbean*) + (0.1**SE_Asian*) + (0.1**IVF*) + (0.1**Ovulation_drugs*); $R^2 = 0.24$, $p < 0.0001$). For the prediction of composite adverse neonatal outcome, maternal Hb is an independent predictor with a quadratic relationship. In addition, South-East Asian origin and gestation at delivery were independent predictors of composite adverse outcome (Composite adverse outcome = 9.2 + (20.1*Hb)−(0.8Hb^2)−(0.6**Gestation_delivery*) + (1.3**SE_Asian*) + (0.27**IVF*); $R^2 = 0.10$, $p < 0.0001$).

4. Discussion

The results of our study demonstrate that increased maternal Hb concentration at 27–29 weeks gestation is associated with reduced birthweight and that there is an inverse relationship between maternal Hb and fetal birthweight *z*-score. In addition, for the prediction of admission to the NNU and serious adverse neonatal outcome, 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.

Our results confirm previous observational studies that have shown a relationship between high Hb or haematocrit levels and FGR [5–16]. Some of these studies examined the maternal Hb in the second or third trimester [6,15] and some longitudinally throughout pregnancy [8,9,11–13]. In some manuscripts the timing of the maternal Hb is not clear and the authors report the "highest or lowest Hb vales in pregnancy" or at the first hospital visit [5,7,10,16,30]. The populations include Europeans [5,6,10,12,14,15], North Americans [8,9,11,13,16] and Asians [7] and were usually low risk pregnancies. In many studies, attention

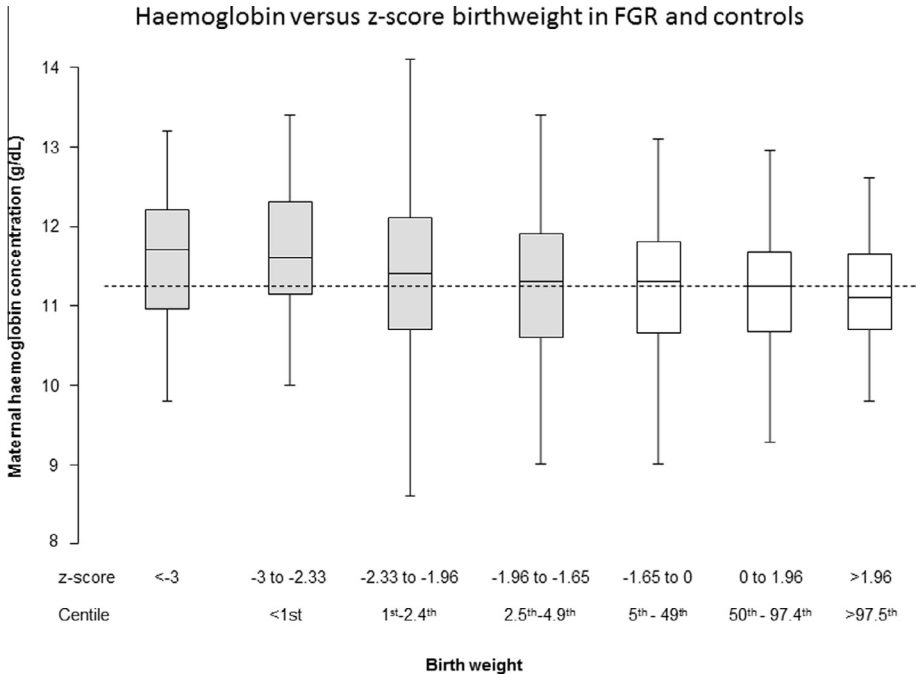

Fig. 1. Maternal haemoglobin versus birthweight in FGR (grey-shaded box and whiskers) and control (white-shaded box and whiskers) pregnancies. Birthweight is presented on the *x*-axis both as *z*-scores (top line) and centiles (bottom line).

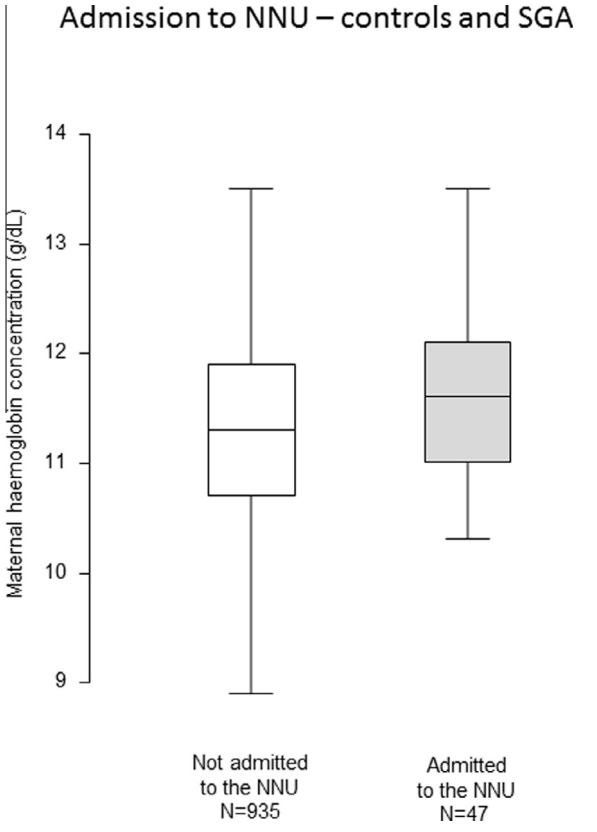

Fig. 2. Maternal haemoglobin levels in pregnancies with babies that were not admitted to the NNU (white-shaded box and whiskers) and those who were admitted to the NNU (grey-shaded box and whiskers).

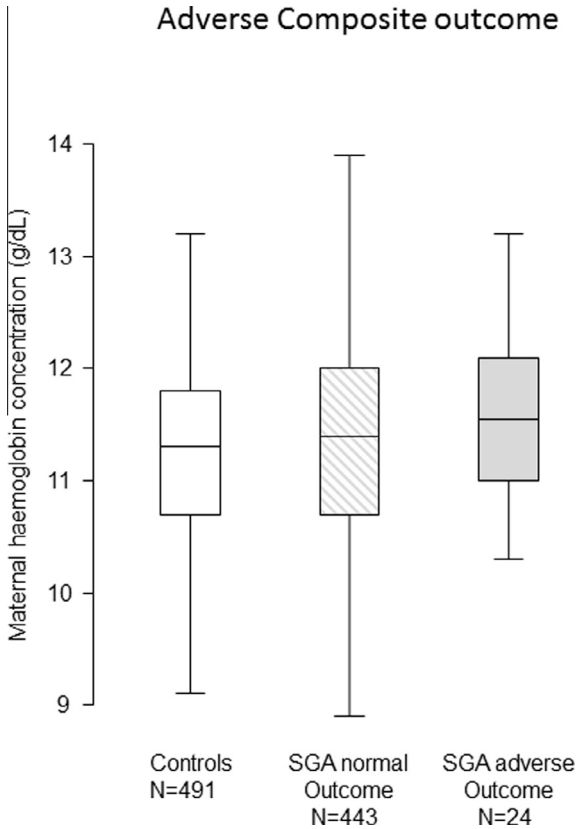

Fig. 3. Maternal haemoglobin levels in control pregnancies (white-shaded box and whiskers), FGR pregnancies with babies without adverse composite outcome (box and whiskers with diagonal lines) and FGR pregnancies with babies with adverse composite outcome (grey-shaded box and whiskers).

was initially focused to low Hb levels and anaemia was recognised as a significant risk factor for preterm delivery and poor pregnancy outcome. Progressively, the association between raised Hb and pregnancy outcome was also highlighted and it has been hypothesised that on the background of an antenatal care system that targets anaemia, high as opposed to low Hb will be more prevalent

and therefore in developed countries, where malnutrition and social deprivation is less prevalent raised Hb is more reflective of the underlying pathology of FGR [10]. This explains why many of the pre-mentioned studies that have examined populations in developing countries [7] have related a decrease in fetal weight to the extremes of maternal Hb or haematocrit level (a U-shaped relationship). It is of interest, however, that some studies have not shown such a relationship between the haemoglobin concentration and fetal weight [7].

As previously discussed, we examined maternal Hb as a surrogate marker for blood viscosity, since the relationship between haemoglobin concentration and blood viscosity is linear if the Ht is <0.5 [31,32], an assumption which is usually met in pregnancy. In our study, we used a very short time frame for the Hb measurement at 27–29 weeks. This is a point of pregnancy where the regression line for Hb reaches a plateau and therefore there is no change with gestation and it is an established point of screening for antenatal care obviating extra cost for the healthcare system. In fact, a major disadvantage of many of the previous studies is that most of them did not control for the effect of gestational age in Hb levels. It is known that Hb decreases by about 8% by mid-pregnancy [33] and increases thereafter until term. Hence, this explains the wide range of variation in the suggested ideal Hb, with some authors quoting optimal levels between 8.6 and 9.5 g/dL [10] and others between 10.7 and 13.8 g/dL [8]. It is not surprising therefore, that despite so many reports on the value of Hb as a predictor of FGR, little has been achieved for its incorporation in a prediction model for FGR.

A limitation of our study is that this being a retrospective study, we did not correct for iron supplementation. However, iron supplementation can improve low haemoglobin levels but would not cause abnormally high ones since its absorption is self-limiting with normalisation of iron stores [34]. Therefore, iron supplements would not be important for the raised haemoglobin levels in the FGR group but would be beneficial in establishing an accurate reference range for the controls [8,31].

The pathophysiology of the association between maternal Hb and fetal growth is difficult to elucidate but it is most likely explained by the known deleterious effects of haemoconcentration, a process that in normal pregnancy nature is trying to avoid. During pregnancy there is a dramatic increase in maternal metabolism, necessitating an effective mechanism for heat loss and metabolite excretion at the same time as supplying oxygen and nutrients to the conceptus and herself. This is achieved by an increase in cardiac output and a concomitant haemodilution (known as physiological anaemia), that is achieved through an increase of 45% in plasma volume and 25% in red cell mass by about 32 weeks [30,35]. The increase in cardiac output increases the oxygen carrying capacity whilst the lower blood viscosity improves flow in the low pressure – low velocity intervillous circulation and decreases the risk of thrombosis in an already hypercoaguable state which already predisposes for thrombosis in the microvilli [10]. The importance of this exaggerated plasma volume expansion appears to be more linked with the fetus rather than the mother, since it is reported that the degree of haemodilution and plasma volume expansion are associated with size of conception (and hence birthweight) rather than maternal weight [10,30]. When this haemodilution is not achieved, there is an increased risk of adverse pregnancy outcome with a rise in the rates of pre-eclampsia, FGR and a higher perinatal morbidity [3,17].

Although an association between hyperviscosity and FGR appears to be well established in the literature, there is little understanding regarding the mechanisms that may be involved. One possible mechanism is that the hyperviscosity leads directly to reduction in perfusion and oxygenation of the placental and the fetal tissues. The effect of viscosity on flow and perfusion is dependent on kinetic forces propelling the blood. In major arteries, these kinetic forces far outdo the viscous forces, with viscosity playing minimal effect on the flow, whereas as the vessels decrease in size, viscous forces increase in importance. Viscous forces in arterioles are much more important than in arteries, whilst in the low kinetic force microvasculature, such as the placenta, blood flow is determined by blood viscosity [36,37]. It is therefore, possible that in the low velocity placental circulation, the increase in maternal blood viscosity reduces blood flow and the efficiency of the processes of nutrient exchange as a result of abnormal red cell aggregation with a subsequent tissue hypoxia as a direct result of a reduction in oxygen supply.

A second possible mechanism is that the reduction in nutrient transfer, leads to a decline in availability in substrate substances necessary for the action of the placental hormones that are stimulating fetal growth. Insulin-like growth factor (IGF) I and II are placental-derived proteins playing an important role in cell proliferation and hence growth and development [38]. Substrate availability is the limiting factor for IGF metabolism [38] and this may be impaired due to decreased intravillous perfusion secondary to the increased blood viscosity [39]. Another possible mechanism for impaired IGF function is its inhibition from corticotrophin releasing hormone (CRH). Animal studies on rat-granulosa cells by Calogero et al. suggest that CRH can inhibit IGF at a receptor level [40] and with the presence of hypoxia, there is increased norepinephrine release [41] which stimulates CRH [42] and cortisol [43]. The fetus is responsive to these stress hormones [44] and elevated CRH at 33 weeks gestation has been associated with a threefold increase in the risk of FGR [45]. In addition, cortisol slows fetal growth, stimulates catabolism of fetal tissues and promotes cell differentiation [46]. The relationship between high levels of CRH and FGR was also described by Goland et al. who showed that the level of CRH in cord blood is four-times higher in FGR versus normally grown babies [47]. The rate of growth in selective organs can also decrease (e.g. the kidneys), and there is a capacity to lose integral components for organ well-being including nephrons, pancreatic B-cells and cardiomyocytes [46] and this organ specific impairment could be a possible link between our results on raised Hb and increased admission to NNU and adverse neonatal outcome rates.

An alternative explanation for the negative association between Hb levels and fetal growth may be provided by the direct role of Hb on NO regulation and endothelial function. Hb binds and inactivates NO, an endothelium-derived smooth-muscle relaxation factor [18], leading to vasoconstriction [20]. Hb exists mostly in a compartmentalised form in the red blood cells (RBC) and to a lesser degree in a free plasma form. Free haemoglobin has a deleterious effect on the endothelium either via direct oxidant injury or via the atherogenic effects of an oxidised low-density lipoprotein [48]. In addition, it has a significant ability of scavenging NO, but in healthy organisms its plasma concentration is about 200 times less than that of red-cell Hb, limiting thus its toxic effect. An increase in free Hb levels that usually happens as a result of haemolysis, trauma or infection has been associated with pulmonary hypertension, renal dysfunction and thrombosis [49]. Red-cell encapsulated Hb has 1000 times less potential for NO binding and this is due to the protective effect of the red-cell membrane and the flow properties of the blood [19]. However, these protective mechanisms are dependent on haematocrit and oxygenation levels with increasing haematocrit and reducing oxygen levels been associated with increase in RBC membrane permeability to NO [19]. It is therefore, possible that with progressively increasing Hb levels, there is an increase in NO scavenging with a consequent vasoconstriction at the maternal and placental milieu leading to hypertension and placental ischaemia. Moreover, there is recent evidence that oxidative/ischaemic damage to the placenta is

associated with over production of fetal Hb at placental level [21] and leaking to the maternal circulation [22], which in turn worsens the oxidative stress, vascular endothelial damage and vasoconstriction, exacerbates further the placental dysfunction [23] and can lead to haemolysis and renal impairment [24]. It is of interest that this increase in fetal Hb in the maternal blood of pre-eclamptic women is evident from the first trimester of pregnancy [50].

5. Conclusion

Raised maternal haemoglobin levels at 27–29 weeks gestation are associated with FGR and with an increased risk of admission to the NNU and adverse fetal outcome. There have been reports that haemodilution may have a beneficial effect to placental function demonstrated either as increased birthweight or improved Doppler studies [51–53] and new drugs are been trialled for the treatment of pre-eclampsia targeting NO and endothelial dysfunction [54]. Further work is warranted in order to assess the value of maternal haemorheology parameters in screening for FGR and the impact of its correction in pregnancy outcome.

Conflicts of Interest

There were no conflicts of interest.

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