PREDICTION OF SMALL-FOR-GESTATIONAL-AGE NEONATES AT 30-34 WEEKS' GESTATION

Submitted by

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I, *Spyridon Bakalis* confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Small-for-gestational-age (SGA) fetuses and neonates are at increased risk of perinatal mortality and morbidity. There is evidence that these risks are reduced in cases identified antenatally, through close monitoring, timely delivery and prompt neonatal management, compared to those not detected. The current method of antenatal screening for SGA fetuses is by maternal characteristics and medical history and serial measurements of symphysis fundal height, but the performance of this method is poor.

This thesis aims to develop a model for the prediction of SGA neonates based on maternal characteristics, history, fetal biometry, uterine artery pulsatility index (PI), mean arterial pressure (MAP), and serum biochemical markers at 30-34 weeks' gestation (mean gestation at screening 32.3 weeks, IQR 32.0-32.9). The thesis also aims to examine the value of umbilical artery PI and fetal middle cerebral artery in the prediction of adverse perinatal outcome.

This screening study included biophysical measurements in 30,849 singleton pregnancies at 30-34 weeks with 1,727 (5.6%) that delivered SGA neonates. A subset of 9,003 cases with 469 (5.2%) delivering SGA neonates had biophysical and biochemical measurements recorded. The best prediction was provided by a combination of maternal factors, estimated fetal weight (EFW), uterine artery PI, MAP and serum placental growth factor (PlGF). This combination predicted, at 10% false positive rate, 89%, 94%, 96% of SGA neonates delivering at 32-36 weeks' gestation with BW <10th, <5th and <3rd centiles, respectively; the respective detection rates for SGA neonates delivering at $\geq$37 weeks were 57%, 65% and 72%. The use of umbilical artery PI and MCA in the prediction of adverse perinatal outcome was found to be poor.

In conclusion, combined screening by maternal factors and biophysical and biochemical markers at 30-34 weeks' gestation can identify a high proportion of pregnancies that subsequently deliver SGA neonates.

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Abbreviations

Abbreviation	
AC	Abdominal Circumference
AFP	α-fetoprotein
AGA	Appropriate for Gestational Age
AOR	Adjusted Odds Ratio
APS	Antiphospholipid Syndrome
BMI	Body Mass Index
BPD	Biparietal Diameter
BW	Birth Weight
CI	Confidence Intervals
CS	Caesarean Section
CTG	Cardiotocograph
DR	Detection Rate
DV	Ductus Venosus
EFW	Estimated Fetal Weight
FPR	False Positive Rate
GH	Gestational Hypertension
hCG	Human Chorionic Gonadotropin
IGF	Insulin Like Growth Factor
IGFBP-4	Insulin-Like Growth Factor Binding Protein-4
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
IVF	In Vitro Fertilisation
IVH	Intraventricular Haemorrhage
LBW	Low Birth Weight
LR-	Negative Likelihood Ratio
LR+	Positive Likelihood Ratio
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
NEC	Necrotizing Enterocolitis
NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal Intensive Care Unit
NNU	Neonatal Unit
NO	Nitric Oxide
OR	Odds Ratio
PAPP-A	Pregnancy Associated Plasma Protein-A
PE	Pre-eclampsia
PI	Pulsatility Index
PlGF	Placental Growth Factor
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
RR	Relative Risk
SD	Standard Deviation

SFH	Symphysis Fundal Height
sFlt-1	Soluble Vascular Endothelial Growth Factor Receptor-1
SGA	Small-for-Gestational Age
SLE	Systemic Lupus Erythematosus
sVEGFR-1	Soluble Vascular Endothelial Growth Factor Receptor-1
UAD	Umbilical Artery Doppler
UtAD	Uterine Artery Doppler
VEGF	Vascular Endothelial Growth Factor
VEGFR-1	Vascular Endothelial Growth Factor Receptor-1
VEGFR-2	Vascular Endothelial Growth Factor Receptor-2
VLBW	Very Low Birth Weight
β-hCG	β-human chorionic gonadotropin

Chapter 1: Introduction

Overview

Since the importance of birth weight's (BW) role in determining perinatal morbidity and mortality have been well documented (Lubcheno *et al.,* 1963; Thomson 1968). Multiple studies since have documented the increased early risks to neonates born with a low BW, such as the need for admission to the neonatal unit, low Apgar scores, umbilical artery pH <7 and need for intubation (McIntire *et al.,* 1999) and (Smith-Bindman *et al.,* 2003). The introduction of ultrasound, and its use in measuring fetal weight showed that the risks of SGA are not just in postnatal life, but also in antenatal and intrapartum. Studies have shown that there is an increased risk of a SGA fetus being stillborn (Lindqvist & Molin 2005; Smith-Bindman *et al.,* 2003), and have increased intrapartum risk of Caesarean section (CS) for fetal distress (Savchev *et al.,* 2012) and other adverse outcomes (Lindqvist & Molin 2005). There is also an increasing body of evidence suggesting that SGA neonates also have long term risks, with reduced neurobehavioral performance (Figueras *et al.,* 2009) which can persist beyond the first few weeks of life (Eixarch *et al.,* 2008).

The increased risk of perinatal mortality and morbidity associated with SGA neonates can be substantially reduced in cases identified antenatally, through close monitoring, timely delivery and prompt neonatal management, compared to those detected after birth (Lindqvist & Molin 2005; Mahsud-Dornan & Dornan 2009).

Over the years, many studies have attempted to find the most effective way to screen for SGA, from using abdominal palpation (Hall *et al.,* 1980), symphysis fundal height (Persson *et al.,* 1986), fetal biometry (Chang *et al.,* 1992) and uterine artery Doppler PI (Ghosh & Gudmundsson 2009). More recently, various biochemical markers have also been used in an attempt to predict at risk pregnancies (Morris *et al.,* 2008 and Conde-Agudelo *et al.,* 2013).

This thesis aims to develop a model for the prediction of SGA neonates based on maternal characteristics, medical history, fetal biometry, uterine artery PI, MAP, and serum biochemical markers at 30-34 weeks. The thesis also aims to examine the value of umbilical artery PI and fetal MCA PI at 30-34 weeks' gestation in the prediction of adverse perinatal outcome.

1.1 Definition and epidemiology of small for gestational age and fetal growth restriction

Small for gestational age (SGA) refers to either a fetus with an estimated fetal weight (EFW) or an abdominal circumference (AC) or a neonate with a birth weight (BW) under a predefined cut-off. Historically, a BW of under 2.5kg, and occasionally under 1.5kg, were used as the cut off for the definition of a SGA neonate. However, these became out-dated and with the development of population based gestational age dependent BW charts, originally by Lubcheno *et al.,* there was a move to the use of centiles (Lubcheno *et al.,* 1963). Several statistical definitions have been used and these include an EFW, AC or BW below the 10th centile, 5th centile, 3rd centile and 2 standard deviations (SD) below the mean for gestation. Therefore, the incidence of SGA depends on the cut-off that is used. The Royal College of Obstetrics and Gynaecology (RCOG) (Robson *et al.,* 2013) and the World Health Organisation (WHO) (WHO 2015) use the 10th centile from population centiles, therefore categorising 10 per cent of all infants as SGA.

The terms fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) are often incorrectly used synonymously with SGA. Unlike SGA that is statistically defined, IUGR and FGR suggest there is underlying pathology for the failure of the fetus to reach its genetically defined growth potential (Gardosi 2009; Robson *et al.,* 2013). Its incidence has been quoted as between 1-10% (Bryan & Hindmarsh 2006; Bamfo & Odibo 2011).

Of fetuses or neonates with a EFW or BW below the 10th centile for gestational age, 50–70% are normal (constitutionally) small, achieving expected growth for the maternal size and ethnicity (Alberry & Soothill 2007). These are associated with normal placental function and have a good prognosis. Lowering the cut-off for SGA below the 10th centile increases the likelihood of FGR being present (Bamfo & Odibo 2011). Those with a BW under the 2nd centile being the most likely to have FGR (de Jong *et al.,* 1998). However, FGR is present in fetuses or neonates with an EFW or BW >10th centile, or Appropriate for Gestational Age (AGA) fetuses or neonates, and the overall prevalence may be greater from this group rather than the SGA group (Chard 1984).

The antenatal differentiation between SGA and FGR remains an important and unresolved diagnostic challenge. Reduced velocity of the EFW can only be calculated

by serial ultrasound examinations (and less effectively by serial symphysis fundal height), a practice that is only supported by the RCOG in high risk cases and not as routine practice (Robson *et al.,* 2013). Other proposed markers for FGR, such as the use of abnormal umbilical artery Doppler (UAD) pulsatility index (PI), have not proved effective for use in screening studies. A study by Marconi *et al.,* (2009) showed that 47% of FGR (defined by a raised UAD PI) pregnancies had a BW above and 53% below the 10th centile (Marconi *et al.,* 2009).

1.2 Normal fetal growth

The factors that control the process of fetal growth are complex and dynamic, and involve bringing together three separate systems: the fetus, the mother and the placenta. These processes begin with effective placentation with associated development of the fetal vascular supply, appropriate changes to the maternal circulatory system, and adaptation of the placenta to maximise transport of oxygen and nutrients. Fetal growth can be broken down in to three phases, each of which requires different growth at a cellular level (Sankaran & Kyle 2009):

1. 0-16 weeks: cellular hyperplasia
2. 16~30 weeks: cellular hyperplasia and hypertrophy
3. 30 weeks-term: cellular hypertrophy

1.2.1 Placental contribution

Fetal growth begins with blastocyst implantation, which initiates the development of the placental vasculature. This leads to the development of placental transport systems and the activation of endocrine and paracrine signaling pathways between the mother, the placenta, and the fetus, which eventually coordinate fetal growth.

The cytotrophoblast migrates to form anchoring villi between the decidua and the uterus whilst vascular connections between the maternal circulation and the intervillous space are formed by hypoxia-stimulated angiogenesis (Baschat 2011; Pijnenborg *et al.,* 2011; Plaisier 2011). Fetal villous budding and trophoblastic invasion of the entire length of the maternal spiral artery, from their origin to their opening into the intervillous space, further enhances nutrient, waste and gas exchange.

Under trophoblast-induced vascular adaptation, the diameter of the spiral arteries increases from 15–20 to 300–500 μm during the second trimester (Nicolaides *et al.,* 2000). This process is termed *'physiological changes of pregnancy'*. It is this development that decreases the resistance to, and increases the volume of blood flow within the placenta and thereby optimising fetomaternal exchange in the intervillous space (Sheppard & Bonnar 1981; Y. Khong & Brosens 2011; Pijnenborg *et al.,* 2011; Plaisier 2011).

The continued growth of the placenta results in around 600 ml/min flow of maternal blood to be matched by 400 ml/kg/min of fetal flow with a term placental exchange area of $12m^2$. Once all the placental transport systems have been established, the substrate availability, placental perfusion from the maternal circulation, trans placental paracrine and endocrine signalling, and the perfusion of the fetal placental compartment determine growth (Sankaran & Kyle 2009) .

1.2.2 Parental contribution

Maternal factors that contribute to fetal size include parity, ethnicity, maternal height and weight (Dunger *et al.,* 2006). There is also a maternal metabolic component that enhances substrate availability to the placenta and therefore promotes fetal growth. These include maternal intravascular volume expansion, postprandial hyperglycemia, lipolysis, and increased fasting levels of free fatty acids, triglycerides, and cholesterol (Sankaran & Kyle 2009). Paternal factors have also been shown to affect fetal birthweight, however these seem to be less than maternal factors. In one study comparing the contribution of parental height and weight to neonatal birthweight, showed that maternal weight had a far greater influence than paternal weight on birthweight [coefficient for the difference between parents (95% CI): 0.15 (0.10–0.20)] (Griffiths et al. 2007). A large systematic review by (Shah 2003) studied the effects of paternal age, height, weight, birthweight, occupation, education, and alcohol use on neonatal birthweight. The study concluded that paternal characteristics including age, height, and birthweight are associated with LBW (Shah 2003). Low paternal birthweight contributing to low offspring birthweight has been shown by several other studies (Klebanoff et al. 1998). Another study examined the effects of paternal insulin resistance and cardiovascular risk factors on fetal growth and concluded that men who recently fathered growth restricted neonates had preclinical evidence of the insulin resistance syndrome and were more likely to smoke than fathers of normal grown offspring (Hillman et al. 2013).

1.2.3 Fetal contribution

Beyond its own genetic makeup, the fetus itself has certain features to aid growth, which favorably direct nutrients to vital organs.

The ductus venosus (DV) regulates fetal blood flow to the liver, allowing for glycogen storage and stimulation of the fetal pancreas to release insulin thereby increasing the release of Insulin Like Growth Factor (IGF) I and II, which are a major stimulus for fetal growth (Sankaran & Kyle 2009). The direction of blood flow in to the right atrium allows nutrient-rich blood from the ductus venosus to be preferentially distributed to the myocardium and cerebral circulation. This is aided by increased right ventricular and aortic isthmus afterload (Sankaran & Kyle 2009).

1.3 Aetiology and pathophysiology of growth restriction

The multiple factors involved in fetal growth results in a large number of causes that can cause constraint of growth, these are summarised in **Table 1.1.**

Table 1.1: Common causes of growth restriction (Sankaran and Kyle 2009).

Maternal Factors	**Placental factors**
Under nutrition	Abnormal placentation
Maternal low BW	Chronic abruption
Low maternal weight gain	Infarcts
Maternal age <16 years	Focal lesions
Low socio-economic status	Chronic inflammatory conditions (villitis)
Nulliparity	Single umbilical artery
Obesity	Velamentous cord insertion
Chronic Hypertension	Placental haemangioma
Systemic Lupus Erythematosus	Confined placental mosaicism
Pre-eclampsia	
Diabetes with vasculopathy	**Fetal factors**
Renal disease	Chromosomal anomalies
	Genetic conditions
Environmental factors	Congenital malformations
Drug use- smoking, alcohol, illicit drugs	Intrauterine infections
High altitude	Multiple pregnancy
Irradiation	

1.3.1 Maternal factors

Maternal characteristics

The extremes of maternal age (Geronimus 1996; Jacobsson *et al.,* 2004), short stature (Clausson *et al.,* 2001), lower maternal weight (Poon *et al.,* 2013) reduced body mass index (BMI) (Bhattacharya *et al.,* 2007) and ethnicity (Poon *et al.,* 2012) have all been associated with an increased risk of delivering a SGA fetus. This is partly thought to be due to the multifactorial elements for SGA being transmitted through the mother (Klebanoff *et al.,* 1997) rather than the father or from the environment.

Nutrition

The supply of oxygen and nutrients to the fetus are essential in influencing fetal growth. A decrease in the supply of nutrients due to maternal starvation, as indicated from the Dutch Hunger Winter famine of 1944–45 or poor weight gain during pregnancy have both been shown to decrease the BW (Bryan & Hindmarsh 2006; J. E. Harding 2001). A reduction in the maternal blood glucose, decreases the transplacental glucose gradient and therefore the transport of this and essential amino acids to the fetus increasing growth restriction (Alberry & Soothill 2007). Furthermore, a reduction in the maternal blood glucose causes the placenta to increase its metabolism of glucose from 50 to 80% of that obtainable, thus further decreasing the amount available to the fetus (Bryan & Hindmarsh 2006; Sankaran & Kyle 2009; and Dunger *et al.,* 2006).

Maternal disease

Maternal diseases that affect placental implantation and vasculature can increase the risk of delivering a SGA neonate. In one study of mothers with chronic hypertension, the odds ratio (OR) of delivering a SGA neonate was 2.9 (95% Confidence Interval (CI) 1.6-5.0). Type 1 diabetes can statistically significantly increase the risk of SGA, with one study of type I diabetic and matched control women showing that almost twice as many diabetics delivered a SGA neonate (20% vs. 11 %, $p < 0.001$) (Langer *et al.,* 1989). The mechanism for this is likely to be due to inconsistent glucose supply to the fetus. Autoimmune disorders which cause clots in small blood vessels are also know to affect growth. SLE has an OR of delivering a SGA of 5.6 (95% CI 4.1-7.8) (Yasmeen *et al.,* 2001). The relative risk (RR) of delivering a SGA neonate in the

presence of anticardiolipin antibodies is 6.22 (95% CI 2.43-16.0) (Empson *et al.,* 2005).

1.3.2 Environmental factors

Smoking

Smoking remains one of the most important factors in restricting fetal growth due to its hypoxic effects. Each cigarette smoked per day reducing the BW by 13g (Bryan & Hindmarsh 2006) and increasing the OR of delivering a SGA baby up to 3.24, (95% CI 2.32-4.54) (Horta *et al.,* 1997).

Alcohol, drug and maternal medication

Alcohol is known to increase the risk of delivering a SGA neonate by a RR of 7.48 (95 % CI 4.46-12.55), and appears to increase if the duration, amount and binge drinking are taken into account (Patra *et al.,* 2011). Alcohol's mechanism appears to be due to its ease at crossing the placenta and causing cellular damage. Illicit drugs are also known to affect fetal growth; for example, cocaine causes SGA by vaso constriction. A meta analysis by Holzman & Paneth 1994, showed that the mean adjusted BW deficit in cocaine users was significantly lower at 382g. A variety of pharmacological substances each with their own interaction have been implicated in causing growth restriction, these include bromides, beta blockers and steroids (Shah 2003).

1.3.3 Placental factors

Abnormal placentation leads to a reduction in fetal growth due to a reduced uteroplacental blood flow. The placental abnormalities leading to this are a decrease in the number of normal villi at the fetal-maternal interface, a decrease in the number of arterioles in the tertiary stem villi, reduced numbers of terminal capillary loops or reduced villous tree elaboration. All these have been implicated in studies of placentas of growth-restricted fetuses (Sankaran & Kyle 2009; Pijnenborg *et al.,* 2011; Plaisier 2011).

In pre-eclampsia (PE), FGR and some cases of SGA, there is histological evidence of impaired placentation characterized by inadequate trophoblastic invasion of the

maternal spiral arteries distal to the decidual segments of the utero-placental arteries. This failure of complete trophoblastic invasion of the maternal spiral arteries increase the resistance to blood flow and restricts fetomaternal exchange in the intervillous space (Sheppard & Bonnar 1981; T. Y. Khong *et al.,* 1986; Pijnenborg *et al.,* 2011; Plaisier 2011).

The size of the placenta equates to the size of the fetus; hence a small placenta has been associated with a small neonate. This relationship is not linear, as the placenta can lose 30-40% of its villi before affecting fetal growth (Teasdale 1984). The fetus and placenta are usually genetically identical, however confined placental moscaism occurs in up to 2% of pregnancies (Johnston *et al.,* 2002), and was found to be three times more common in SGA over AGA neonates (Wilkins-Haug *et al.,* 1995).

Any factor which can lead to a decrease in the uteroplacental transfer of nutrients, such as placental abruption, infarcts, haematomas or abnormalities (e.g. chorioangioma) can cause growth restriction (Sankaran & Kyle 2009).

1.3.4 Fetal factors

Fetal sex

Multiple studies have shown that male fetuses and neonates have larger EFW and BW than females, therefore increasing the risk that a female fetus may be deemed SGA (Bryan & Hindmarsh 2006).

Genetics

The three main common trisomy's, 21, 18 and 13, have all been associated with growth restriction. In addition to these, triploidy, unbalanced chromosome translocations and deletions (Cox & Marton 2009; Bamfo & Odibo 2011), and uniparental disomy have all been shown to contribute to poor fetal growth (Johnston *et al.,* 2002). These, and other rarer genetic causes will usually be accompanied with a structural abnormality, which would aid diagnosis (Cox & Marton 2009).

The parental contribution to BW via inherited genes is estimated to be between 30–70% (Dunger *et al.,* 2006), with animal studies suggesting that growth is modified toward the size of the mother (Bryan & Hindmarsh 2006). Antenatal and postnatal

growth disorders can be the result of various genetic polymorphisms, which in combination, can have significant effects on fetal growth (Sankaran & Kyle 2009). Several other genes have been associated with SGA and FGR including Igf-1, Igf-2, and H19 on chromosome 11, mitochondrial DNA 16189, G-protein beta 3 subunit, inducible cytochrome P450, genes encoding angiotensinogen, placental alkaline phosphatase and vitamin D receptor (Petry *et al.,* 2005; Sankaran & Kyle 2009; Johnston *et al.,* 2002).

Infections

All the common bacterial, viral and protozoal infections have been associated with growth restriction, with cytomegalovirus and rubella virus being the most frequent contributors (Cox & Marton 2009) .

1.4 Consequences of small for gestational age

1.4.1 Intrauterine programming

Programming is a process that alters gene expression due to an intrauterine insult, leading to tissue hyperplasia, abnormal cell type balance or incorrect timing of gene induction. These changes are part of a survival adaptation and are permanent and alter the metabolism, physiology or morphology of a fetus or neonate (Sankaran & Kyle 2009; Barker & Thornburg 2013). The risk of developing coronary artery disease, type 2 diabetes, hypertension and hyperlipidaemia is greater in SGA neonates. As placental insufficiency influences fetal growth, it can be said that the placenta has a major impact on childhood and adult onset diseases. Any organ can suffer damage due to placental insufficiency.

Brain

Brain sparing is a key feature of growth-restricted fetuses, allowing the brain's perfusion to be preserved during hypotension. Fetal compensatory mechanisms for brain sparing include a two- to threefold increase in cerebral blood flow, a reduction in the metabolic rate and the resulting cessation of growth (Sankaran & Kyle 2009).

Cardiovascular system

In FGR, the cardiac afterload is increased and the blood output to the placenta is decreased resulting in recirculation of deoxygenated to the fetus. DV shunting away from the liver, and towards the heart, increases in FGR (Kiserud *et al.,* 2006).

Lungs

Increase levels of adrenocorticotrophic hormone accelerate lung maturity, possibly to increase the chance of extra-uterine survival (Harding *et al.,* 2000).

Skeletal muscle

In FGR, there is reduction and finally ending, of fetal motor activity including fetal breathing movements, despite the possible structural and functional acceleration of the development of skeletal muscle (Sankaran & Kyle 2009).

Gastrointestinal tract

Reduced blood flow to the mesenteric artery can increase the risk of poor nutrient absorption and postnatal intestinal motility syndrome and is more common in FGR (Robel-Tillig *et al.,* 2004).

1.4.2 Antenatal, intrapartum and postpartum outcomes

Many studies have examined the antenatal, intrapartum and postpartum effects of SGA, focusing on the morbidity and mortality of such fetuses. The findings of such studies are consistent, in that they all find that the morbidity and mortality of this population is increased (Lindqvist & Molin 2005; Smith-Bindman *et al.,* 2003). One Swedish study of 589 fetal deaths amongst 71,171 livebirths finding that of those that were unexplained, 52% were SGA with an OR of 7.18 (95% CI 4.28-12.06) (Frøen *et al.,* 2004).

The term morbidity is covered by a wide range of findings, including, cerebral damage, fetal distress and neonatal hospitalisation (McIntire *et al.,* 1999; Lindqvist & Molin 2005; Smith-Bindman *et al.,* 2003). A large study of 122,754 deliveries from the USA showed that those born SGA were at a higher risk of seizures in the first 24 hours of

life (0.3% vs 0.1%, p=<0.05). As the BW centile decreased to the 3rd, the risk of Apgar scores of <3 at 5 minutes (0.2% vs 0.1%, p=<0.05), umbilical artery pH <7 (0.9% vs 0.4%, p=<0.05), intubation at delivery (2.2% vs 0.6%, p=<0.05), sepsis (0.5% vs 0.2%, p=<0.05) and death within the first 28 days of life (0.3% vs <0.1%, p=<0.05) all became significantly higher (McIntire *et al.,* 1999).

Similar results from a second study from the USA showed that SGA fetuses had a higher RR of long neonatal hospital stay 2.7 (95% CI 1.7-4.2), assisted ventilation at birth 4.2 (95% CI 2.3-7.8), NNU admission 3.2 (95% CI 2.2-4.8) and long NNU admission 5.1 (95% CI 3.0–8.6). The same study showed similar risks for neonates with a BW <5th and between 6-10th centiles. Interestingly, the RR of stillbirth in those with a BW <5th centile was 7.7 (95% CI 2.6-23.0) but was 0 (95% CI 0-6.5) in those with a BW between 6-10th centiles (Smith-Bindman *et al.,* 2003).

A study of 132 SGA fetuses by Savchev *et al.,* showed that SGA fetuses only had a higher risk for intrapartum CS due to fetal distress (15.9 v 5.3%; p=< 0.01) and longer neonatal hospitalization (1.39 v 0.87 days; p=< 0.05), however, smaller fetuses, below the 3rd centile, had statistically significantly higher incidence of intrapartum CS (30.0 v 15.3%; p=0.04), CS for fetal distress (25.0 v 8.3%; p=< 0.01) and longer neonatal hospitalisation (2.0 v 0.9 days; p=< 0.01) (Savchev *et al.,* 2012). One study examined the outcome of SGA fetuses, however this study not only looked at SGA fetuses (group 1), but also SGA with abnormal (raised) umbilical PI (group 2) and those with abnormal CTG and raised umbilical PI (group 3). The results, (**Table 1.2**), showed that those in group 3 had worse outcomes, than those in group 2, which were worse than group 1 (Marconi *et al.,* 2009).

The necessity in identifying SGA fetuses prior to delivery was highlighted in the study by Lindqvist & Molin, who showed that there was a four-fold increased risk of adverse fetal outcome (OR 4.1, 95% CI, 2.5-6.8) in those not recognised antenatally. A review of the results showed that there was an increase in the Adjusted Odds Ratio (AOR) for cerebral damage of 2.3 (95% CI 0.8-6.6), severe fetal distress 4.5 (95% CI 2.2-9.0) or fetal/infant death 4.2 (95% CI 2.1-8.5) (**see Table 1.3**) in SGA neonates not identified antenatally (Lindqvist & Molin 2005).

Lindqvist & Molin 2005 also studied the mode of deliveries between SGA and AGA neonates. The results showed that CS delivery (elective and emergency) were higher

amongst SGA neonates whether these were identified prior to delivery or not. The results also indicated that umbilical pH <7.0 and Apgar scores of <4 at 5 minutes were higher amongst the SGA group that the AGA group (OR 2.3 (95% CI 1.5-9.8) and OR 3.1 (1.8-5.4)) (Lindqvist & Molin 2005).

Table 1.2: Data of delivery and perinatal morbidity and mortality in 3 groups (Marconi *et al.,* 2009). SGA fetuses (group 1), SGA with raised umbilical PI (group 2) and those with abnormal CTG and raised umbilical PI (group 3).
*Statistical significance

Outcome	***Group 1 (n=251)***	***Group 2 (n=50)***	***Group 3 (n=35)***
GA (weeks)	38.1 + 1.4	35 + 2.4	29.6 + 3.2
BW g	2352 + 304	1701 + 534	796 + 398
CS (%)	99 (39.4%)*	42 (84%)	30 (86%)
Apgar score <7 at 5 min	6 (2.4%)*	6 (12%)	20 (57.1%)*
Intubation at 5 min	4 (1.6%)*	6 (12%)	22 (73.3%)*
NNU admission	6 (2.4%)*	18 (72%)	27 (90%)*
Mechanical ventilation	4 (1.3%)*	10 (20%)	25 (83.3%)*
Neonatal survival	215 (100%)	48 (96%)*	20 (57.1%)*
Perinatal mortality	-	1 (2%)	8 (22.9%)*
Late neonatal mortality	-	1 (2%)	7 (20%)*
RDS	-	4 (8%)*	12 (40%)*
ROP	-	-	5 (16.7%)*
Sepsis	-	2 (4%)*	2 (6.7%)*
NEC	-	1 (2%)	-
IVH II and III	-	3 (6%)*	6 (20%)*
Anemia	3 (1.2%)*	7 (14%)*	14 (46.7%)
Jaundice	13 (5.2%)*	9 (18%)	6 (20%)
Hypoglycemia	8 (3.2%)	1 (2%)	4 (13.3%)*
Neonatal hospital stay (days)	8.8 ± 8.1	24.5 ± 18.9	57.8 ± 72*

Table 1.3: Fetal outcome for pregnancies with not identified and identified as SGA fetuses.

Outcome	***Not identified as SGA* (n = *1291)* (n *(%))***	***Identified as SGA* (n = *24 585)* (n *(%))***	***Adjusted OR (95% CI)***
Adverse outcome	67 (11.7)	34 (5.0)	4.1 (3.2–5.0)
Cerebral damage	10 (1.7)	7 (1.0)	2.3 (0.8–6.6)
Severe fetal distress	34 (5.9)	12 (1.8)	4.5 (2.2–9.0)
Fetal or infant death	32 (5.6)	17 (2.5)	4.2 (2.1–8.5)

SGA neonates born with signs of perinatal asphyxia require relevant on going management. Hypoglycaemia, due to reduced hepatic glycogen storage, is more common in this group, especially in the first 3 days of life. Polycythaemia and associated hyperviscosity, due to a higher plasma volume and increased red cell

mass, is also common, and partial exchange transfusions can be required (Halliday 2009).

1.4.3 Long-term outcomes

SGA neonates are more likely to face poor postnatal growth, which can lead to long-term neurodevelopmental delay, however, it is worth noting that 90% of SGA infants catch up with their growth by 2 years of age Excessive promotion of growth at this stage can increase the risk, in later life, of cardiovascular disease (Halliday 2009).

The main area of concern regarding SGA neonates is neurodevelopmental outcome. A small study by (Sanz-Cortés *et al.,* 2010) showed that there are microstructural and metabolic brain changes visible on MRI at 37 weeks of gestation in utero in SGA fetuses. This suggests that there is abnormal brain development in these fetuses.

This antenatal finding is further backed up by postnatal outcomes. A Spanish study reviewed 202 infants after delivery: 102 were SGA and 100 were AGA. Neurobehavioral performance was studied at a corrected age of 40 weeks. In all the neurobehavioral areas studied, the SGA group performed worse than the AGA group, with statistical significant differences in the average mean differences for attention 0.77 (95% CI: 0.38-1.14), for habituation 0.64 (95% CI: 0.13-1.14), for motor 0.52 (95% CI: 0.31-0.74), for social-interactive 0.95 (95% CI: 0.54-1.37) and for regulation of state 0.68 (95% CI: 0.23-1.13) (Figueras *et al.,* 2009).

These differences in neurodevelopment persist beyond the first few weeks of life. A second study by the same Spanish group examined 125 SGA fetuses, of which 25 had redistribution of cerebral flow (defined as a PI <5th centile). In the subgroup with cerebral redistribution, neurodevelopmental outcome at 2 years of age was suboptimal compared to those without (52% vs. 31%; p=0.049), with a decrease in mean centile in problem-solving (39.7 vs. 47.4; p=0.04) and communication (53.1 vs. 67.4; p=0.006) (Eixarch *et al.,* 2008).

A study of 334 children, of more than 4 years old, with a diagnosis of cerebral palsy were compared with 668 matched children without the diagnosis (Jacobsson *et al.,* 2008). The results showed that those born at term who developed cerebral palsy were more likely to be born SGA OR of 5.2 (95% CI 2.7-10.1).

The concept of programming and the increased risk of various diseases in adulthood have already been discussed. One recent study comparing the hearts at 3 to 6 years old of children born SGA and those born AGA showed that those born SGA had more globular hearts, with impaired relaxation, reduced longitudinal motion and an increase in radial function, increased carotid intima-media thickness and raised blood pressure (Crispi *et al.,* 2012).

1.5 Screening for small for gestational age

'The object of screening for disease is to discover those among the apparently well who are in fact suffering from disease. They can then be placed under treatment and, if the disease is communicable, steps can be taken to prevent them from being a danger to their neighbours. In theory, therefore, screening is an admirable method of combating disease, since it should help detect it in its early stages and enable it to be treated adequately before it obtains a firm hold on the community' (Wilson & Jungner 1968).

These early ideas set by out by the WHO in 1968 still form the foundation of screening. The increased risk of perinatal mortality and morbidity associated with SGA neonates can be substantially reduced in cases identified antenatally, through close monitoring, timely delivery and prompt neonatal management, compared to those detected after birth (Lindqvist & Molin 2005). Therefore, accurate prenatal identification of SGA neonates, that decreases the associated morbidity and mortality, whilst not increasing unnecessary intervention (and by extension the preterm delivery rate) is vital. However, despite the benefits of screening for SGA, not all of Wilson's criteria for screening are met, for example, there is no easy test to perform that is easy interpret, acceptable, accurate, reliable, sensitive and specific.

Various methods have been devised in an attempt to screen for SGA, each with the aim of identifying a high-risk pregnancy and allowing appropriate management of the pregnancy (McCowan & Horgan 2009). In the UK, the RCOG recommends that at booking appointment all pregnancy's should be assessed for risk factors for a 'SGA fetus/neonate' and allow for increased surveillance in those deemed high risk (Robson *et al.,* 2013). The risks are set out in **Table 1.4** and the RCOG risk assessment strategy in **Figure 1.1**.

Table 1.4: RCOG risk factors for SGA fetus/neonate.

Summary of risk factors for a small for gestational age neonate				
Risk category	**Definition of risk**	**Outcome (BW centile)**	**Measure**	**Estimate (95% CI)**
Maternal risk factors				
Age	Age ≥ 35 years	< 10th population	OR	1.4 (1.1–1.8)
	Age > 40 years	< 10th population	OR	3.2 (1.9–5.4)
Parity	Nulliparity	< 10th population	OR	1.9 (1.8-2.0)
BMI	BMI < 20 kg/m^2	< 10th customised	OR	1.2 (1.1–1.3)
	BMI 25-29.9 kg/m^2	< 10th customised	RR	1.2 (1.1–1.3)
	BMI ≥ 30 kg/m^2	< 10th customised	RR	1.5 (1.3–1.7)
Maternal substance exposure	Smoker	< 10th customised	AOR	1.4 (1.2–1.7)
	1–10 cigarettes/day	< 9.9th population	OR	1.5 (1.4–1.7)
	≥ 11 cigarettes/day	< 9.9th population	OR	2.2 (2.0–2.4)
	Cocaine	< 10th population	OR	3.2 (2.4–4.3)
IVF conception	Singleton pregnancy	< 10th centile	OR	1.6 (1.3–2.0)
Vigorous exercise	Daily	< 10th customised	AOR	3.3 (1.5–7.2)
Pre pregnancy diet	Low fruit intake	< 10th customised	AOR	1.9 (1.3–2.8)
Previous pregnancy history				
SGA	Yes	< 10th customised	OR	3.9 (2.1–7.1)
Stillbirth	Yes	< 10th customised	OR	6.4 (0.8–52.6)
Preeclampsia	Yes	< 10th population	AOR	1.3 (1.2–1.4)
Pregnancy Interval	< 6 months	SGA not defined	AOR	1.3 (1.2–1.3)
	≥ 60 months	SGA not defined	AOR	1.39 (1.2–1.4)
Maternal medical history				
Maternal SGA	Yes	< 10th population	OR	2.6 (2.3–3.1)
Chronic hypertension	Yes	< 10th population	ARR	2.5 (2.1–2.9)
Diabetes	Yes	< 10th population	OR	6 (1.5–2.3)
Renal impairment	Yes	< 10th population	AOR	5.3 (2.8–10)
APS	Yes	No definition	RR	6.2 (2.43–16.0)
Paternal medical history				
Paternal SGA	Paternal SGA	< 10th population	OR	3.5 (1.2–10.3)
Current pregnancy complications				
Vaginal bleeding	Heavy: similar to menses	< 10th population	AOR	2.6 (1.2–5.6)
Ultrasound	Echogenic bowel	< 10th population	AOR	2.1 (1.5–2.9)
Preeclampsia	Yes	< 10th customised	AOR	2.3 (1.2–4.2)
Pregnancy induced hypertension	Mild	< 10th population	RR	1.3 (1.3–1.4)
	Severe	< 10th population	RR	2.5 (2.3–2.8)
Placental abruption	Yes	No definition	OR	- (1.3–4.1)
Unexplained APH	Yes	No definition	OR	5.6 (2.5–12.2)
Low weight gain	Yes	< 10th population	OR	4.9 (1.9–12.6)
Exposure to caffeine	≥300 mg/day (3rd trimester	< 10th population	OR	1.9 (1.3–2.8)
Serum PAPP-A	< 0.4 MoM	< 10th population	OR	2.6

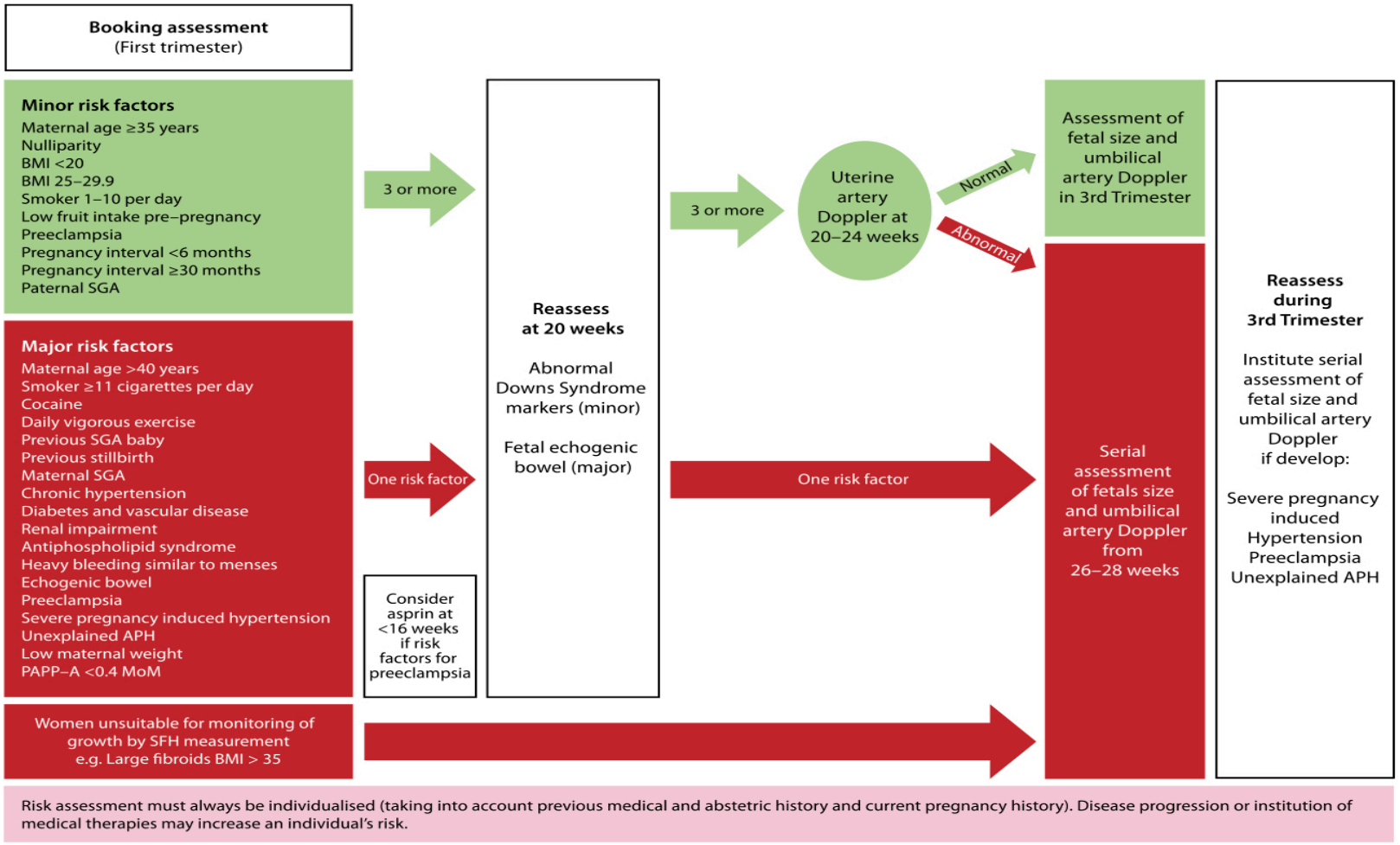

Figure 1.1: Risk assessment for SGA as set out by the RCOG.

1.5.1 Maternal characteristics

Maternal age

Extremes of maternal age have been associated with delivering an SGA neonate. A large Swedish study by Jacobsson *et al.,* examined the adverse perinatal outcome in mothers aged between 40 and 44 and those above 45 years old. Over 1.5 million women were recruited to the study during a 15-year period. Using an AOR of 1.00 for women aged between 20-29 years, the study showed that women aged 40-44 years old and >45 years old had a AOR 1.94 (95% CI 1.80-2.09) and 2.67 (95% CI 2.04-3.49) for delivering a neonate of BW <10th centile (Jacobsson *et al.,* 2004). Another large study (Swamy *et al.,* 2011) looked at various maternal characteristics, including maternal age, and their effects on BW. This study from North Carolina, USA, reviewed 510,288 women with singleton pregnancies. Its results revealed that mothers aged 30-34, 35-39 and 40-44 years old had neonates born with significantly lower BWs than mother's ages 25-29 years old. A case control study of 824 IUGR fetuses (defined as a BW below the 10th centile) and 1648 controls, showed that the OR for IUGR increased from 35 years old onwards reaching an AOR of 3.2 (1.9-5.4) for women aged over 40 years old. (Odibo *et al.,* 2006).

Two studies from the King's College Group (Poon *et al.,* 2010; Poon *et al.,* 2013) have shown that women delivering a SGA neonate were younger than those delivering an appropriate size baby. In the group's 2013 study of 65,960 patients, women delivering an SGA baby were statistically significantly younger than those delivering a normal size infant 31.0 years (IQR 27.7-35.6) versus 32.0 years (IQR 25.7-35.4) years. One study by Geronimus, compared 25 year old to 15 year old mothers. The results showed the OR of a low BW (defined as 2.5kg) neonate was 1.17 (95% CI 1.00-1.36) for African and 1.11 (95% CI 1.00-1.23) for Caucasian women, and for very low BW (defined as 1.5kg) neonates, the odds were 1.55 (95% CI 1.21-1.97) for African and 0.90 (95% CI 0.72-1.14) for Caucasian women (Geronimus 1996).

The reason behind the increased risk of delivering a SGA neonate with advancing maternal age is not completely understood. Lisonkova *et al.,* 2010 and Odibo *et al.,* 2006 postulated that this may be due in part to an increase in chronic diseases (such as chronic hypertension, anaemia or diabetes) within this group, however, both studies adjusted for such cofounders, yet the association persisted.

Height

The median height of women delivering an SGA baby is lower than in those delivering an appropriate size baby (De Paco *et al.,* 2008; Poon *et al.,* 2013; Poon *et al.,* 2010). A Swedish study in 96,662 pregnancies reported that the AOR for delivering a SGA neonate increased with deceasing maternal height (Clausson *et al.,* 2001).

Weight

The median weight of women delivering an SGA baby is lower than in those delivering an appropriate size baby (De Paco *et al.,* 2008; Poon *et al.,* 2013; Poon *et al.,* 2010). A study of 65,690 singleton pregnancies showed the average weight for women delivering a AGA and SGA baby were 65.5kg and 61.0kg (Poon *et al.,* 2013).

BMI

The majority of studies that have looked into maternal characteristics affecting the risk of delivering a SGA neonate use BMI rather than height or weight. Several studies have shown that as BMI decreases, the risk of delivering a SGA neonate increases (Bhattacharya *et al.,* 2007; Cnattingius *et al.,* 1998; Baeten *et al.,* 2001; Leung *et al.,* 2008).

Ethnicity

Multiple publications refer to the effects of ethnicity on the risk of SGA. In 2008, the Office of National Statistics (Moser 2008) released its data on all deliveries in in England and Wales from 2005 (**Table 1.5**). The data showed that babies born to white mothers were larger than those born to either south Asian or black. These ethnicities could be broken down to Pakistani, Indian and Bangladeshi and African or Caribbean. The lowest mean BW was in Bangladeshi mothers, however, the largest percentage of babies born either <2.5 kg or <1.5 kg was in the Caribbean group. Three further UK studies, (De Paco *et al.,* 2008) (SGA defined <5th centile), (Poon *et al.,* 2013) and (Poon *et al.,* 2010) (both defining SGA <10th centile) showed that Afro-Caribbean, South Asian, East Asian and mixed race women were statistically significantly more likely to deliver an SGA baby than white women.

These findings have not been limited to UK studies. In the USA, a large New York study (Rauh *et al.,* 2001) looked at the weight of the first or second deliveries of non Hispanic mothers. It showed that the AOR of an African mother, compared to a White mother, delivering a baby less than 2.5kg and less than 1.5kg was 2.10 (95% CI 1.95-2.25) and 3.08 (95% CI 2.64-3.60). Odibo *et al.,* work showed that Black ethnicity had an even more extreme effect on the risk of delivering a SGA baby (defined here as BW <10th centile). In this publication the AOR for Black women was 22.4 (95% CI 17.8-28) (Odibo *et al.,* 2006).

Table 1.5: The mean BW (and 95% CI) and percentages of babies born under 2.5kg and 1.5kg in different ethnicities in England and Wales in 2005. (Moser 2008).

Ethnicity	Mean BW (kg)	% <2.5kg	% <1.5kg
White other	3.393 (3,387-3,399)	4.9	0.9
White British	3.393 (3,391-3,394)	5.6	0.9
African	3.288 (3,279-3,297)	7.4	1.7
Pakistani	3.130 (3,123-3,137)	9.8	1.2
Bangladeshi	3.075 (3,063-3,086)	10.5	1.1
Indian	3.082 (3,073-3,090)	10.5	1.4
Caribbean	3.162 (3,147-3,176)	10.9	2.4

Smoking

Smoking has been associated with the increased risk of SGA since the 1950's. Butler *et al.,* (Butler & Alberman 2015) were amongst the first to notice the deleterious effects of smoking on pregnancy. Apart from showing the increase risk of stillbirth and neonatal death in patients who smoke, they also showed the downward trend of BW in neonates born to smoking mothers. Since then, repeated studies have confirmed the significant risk of smoking on delivering a SGA neonate (Horta *et al.,* 1997; Rauh *et al.,* 2001; Kleijer *et al.,* 2005; Papastefanou *et al.,* 2011).

Further studies have shown the risk of SGA is dose dependent, with the risk of SGA increasing with the number of cigarettes smoked. Clausson *et al.,* revealed that smoking from 1-9 cigarettes a day had an AOR of 1.7 (95% CI 1.60-1.90), and those above 10 per day 2.4 (95% CI 2.10-2.70) (Clausson *et al.,* 1998). Comparable results were presented by Kramer *et al.,* where women smoking up to 10 cigarettes per day

had an OR of 1.54 (95% CI 1.39-1.70) and those above 10, 2.21 (95% CI 2.03-2.40) (Kramer *et al.,* 1999).

There is evidence that smoking cessation during pregnancy can reduce the risk of SGA to that of a non-smoker. McCowan *et al.,* 2009 study indicated that stopping smoking prior to 15 weeks gestation reversed the risk of SGA to that of a non-smoker. The study found that the AOR of SGA was 1.06 (95% CI 0.67-1.68) in women who stopped smoking by 15 weeks gestation, and 1.76 (95% CI 1.03-3.02) in those who continued to smoke (McCowan *et al.,* 2009).

Alcohol

As with smoking, alcohol consumption has been known to increase the risk of SGA, and it has been shown that this is also dose dependent. Jaddoe *et al.,* examined the risks of alcohol consumption until pregnancy was known and late pregnancy (>25 weeks gestation) (Jaddoe *et al.,* 2007). They reported that consumption of more than 1 unit of alcohol per day, either before the pregnancy is known or in late pregnancy, significantly increase the risk of SGA. A meta-analysis by Patra *et al.,* looked into the effects of alcohol by comparing the risk of SGA in drinkers vs. non-drinkers and the dose effects. From 28 studies, after adjusting for cofounders, the results indicated that the RR for drinkers vs. non-drinkers was not significant, 1.06 (95% CI 0.99-1.13) (Patra *et al.,* 2011). However, the studies results on dose effect were similar to those of Jaddoe *et al.,* (2007). They both showed that there was not a significant increase in the risk of SGA until alcohol consumption exceeded one unit per day, reaching a RR of 7.48 (95 % CI 4.46-12.55) after 12 units per day (Jaddoe *et al.,* 2007).

Method of conception

Since the birth of the first in vitro fertilisation (IVF) baby in 1978, artificial reproductive techniques have been increasingly used for infertility of various causes. However, repeated studies have shown that there is a link between ART and obstetrics complications. SGA is statistically significantly more likely to occur in ART pregnancies (Koudstaal *et al.,* 2000). A meta-analysis by Jackson *et al.,* (2004), which compared over 12,000 IVF and 1.9 million spontaneous singletons found the OR for low BW (<2.5kg) was 1.8 (95% CI 1.40-2.20), very low BW (<1.5kg) 2.7 (95% CI 2.30-3.10), and SGA (<10th centile) 1.6 (95% CI 1.30-2.00). A smaller study showed similar results, with the RR for delivering a low BW (<2.5kg), very low BW (<1.5kg) and SGA

(<10th centile) neonate of 1.65 (95% CI 1.56-1.75), 1.93 (95% CI 1.72-2.17) and 1.39 (95% CI 1.27-1.52) (Pandey *et al.,* 2012).

Parity

Parity is an important risk factor for delivering a SGA neonate; increasing parity appears to be protective, whilst the highest risk is for nulliparous women. Several large studies, including two with over 500,000 patients each (Raymond *et al.,* 1994; Swamy *et al.,* 2011) and a large meta analysis (P. S. Shah 2010) have all published results which showed that nulliparous women were statistically significantly more likely to deliver a neonate with a BW under the 10th centile for gestational age. Two studies, based in South East London, (Poon *et al.,* 2013; Poon *et al.,* 2010) mirrored these findings, but for neonates with a BW under the 5th centile for gestational age. The reason behind the effects of nulliparity increasing the risk of SGA are incompletely understood, (Shah 2010).

Past obstetric history

Having a previous SGA delivery increases the subsequent risk of a further SGA neonate. Shiono *et al.,* 1997 showed that women with a previous LBW (low BW, defined as <2.5kg) baby delivered a statistically significantly smaller baby than those who had not. Raine *et al.,* 1994 calculated the RR of LBW in the subsequent birth after a previous LBW was RR 7.0 (95% CI 4.8-10.1). Similarly, Kleijer *et al.,* 2005, using a cut off of BW below the 10th centile, established the OR for a repeat SGA was 3.97 (95% CI 2.37-6.66). Finally, the King's College Group, in two prospective studies, (Poon *et al.,* 2013; Poon *et al.,* 2010), showed that women with a previous SGA neonate were statistically significantly more likely to deliver another SGA neonate than those who had previous normal babies, and in this latter study, found that this remained significant even if they had delivered a normal baby and an SGA baby.

Maternal medical disorders

A variety of maternal medical conditions have been associated with the delivery of a SGA neonate. These tend to affect placental implantation and vasculature and therefore trans placental nutrient transfer and thus fetal size. Common diseases include diabetes, hypertension and autoimmune disorders: systemic lupus erythematous (SLE) and antiphospholipid syndrome (APS). There are many other

diseases that have been shown to affect fetal growth, such as cyanotic heart disease, cardiac failure, renal disease, hyperthyroidism and asthma; however, it is usually the extreme, uncontrolled forms of these that have the greatest adverse effect on growth. Therefore, due to their relative rarity, their use a part of a screening tool for SGA is restricted.

Chronic hypertension

In 1996, an international study by McCowan *et al.,* investigated the effects of chronic hypertension on the perinatal morbidity rate in pregnancy. The study excluded PE. For those with chronic hypertension versus those without, the risk of preterm delivery, delivery by CS, placental abruption and admission of the neonate to the neonatal unit (NNU) was increased. The average BW was lower in the chronic hypertension group, and the OR of delivering a SGA neonate (BW <5th centile) was 2.9 (95% CI 1.6-5.0). The study also showed that those who had the severest hypertension (diastolic blood pressure ≥ 110mmHg) prior to 20 weeks of gestation had an OR for SGA of 3.8 (95% CI 1.0-13.7). A large Canadian study (Allen *et al.,* 2004), which analysed 135,466 pregnancies had very similar findings, in that the RR of delivering a SGA neonate (BW <10th centile) was 2.5 (95% CI 2.2-3.0). Due to the size of the study, it was also able to note that the RR of stillbirth in the same group was 3.2 (95% CI 1.9-5.4). A smaller UK study (Chappell *et al.,* 2008) found very similar results with the RR of delivering a SGA neonate 2.3 (95% CI 1.9-2.8). By far the largest study, with over half a million patients, has confirmed this independent increased risk of delivering a SGA neonate. Zetterström *et al.,* 2006 found the OR for delivering a SGA neonate (BW -2SD) was 3.1 (95% CI 2.7-3.7).

Diabetes mellitus

A 50 year review of experience of diabetes in pregnancy in 1977 (Hare & White 1977) showed that maternal survival was good except in those with ischaemic heart disease. Fetal survival was also lower in mothers with vascular disease:

'The effect of the maternal and placental vascular complications on the growth and development of the fetus was also evident. In contrast to the experience with infants of mothers without vascular lesions, fetal macrosomia did not occur. These infants were less cherubic in appearance and only moderately obese'.

The mean ultrasound derived EFW in the third trimester was examined by Reece *et al.,* 1990, who found that in diabetic affected pregnancies with no vasculopathy, the

EFW was higher than in controls, regardless of whether there was good or poor control of the diabetes. Though, similar to Hare & White's (1977) observation of the lack of macrosomia, the study showed that the mean EFW in those with vasculopathy was lower than controls (and lowest in the sub group with good control). Neither study refers to SGA, however, Langer *et al.,* (1989) did comment on SGA, and showed that women who had a low blood glucose level throughout pregnancy were statistically significant more likely to deliver a SGA neonate compared to a control group (20% vs. 11 %, $p < 0.001$).

A UK study of 138 women with Type 1 diabetes mellitus, showed that those with vascular disease, were more likely to have infants with a BW <10th centile, OR 6.0 (95% CI 1.54-23.33) and less likely to have macrosomic infants (BW >90th centile) with an OR 0.46 (95% CI 0.22-0.93) (Howarth *et al.,* 2007).

Autoimmune disorders

Autoimmune diseases cover a large spectrum of disorders. Systemic lupus erythematosus (SLE) is the autoimmune disease that compromises pregnancy most frequently (Cervera *et al.,* 2002). Many studies have looked into the adverse effects of this disease on pregnancy and the neonate, including the risk of delivering a SGA neonate. Using a control group of 600,000 women, Yasmeen *et al.,* 2001 found the OR of delivering a SGA neonate was statistically significantly higher in the group with SLE with an OR 5.6 (95% CI 4.1-7.8).

Anticardiolipin antibodies are present in many autoimmune diseases. Between 2.7% and 7% of women of child bearing age have anticardiolipin antibodies present, and its presence increasing the risk of fetal loss is well known (Lynch *et al.,* 1994; Lynch *et al.,* 1999; Empson *et al.,* 2005). However, it has also been associated with the risk of delivering a SGA neonate, with a RR of 6.22 (95% CI 2.43-16.0).

1.5.2 Clinical examination

Abdominal palpation

In terms of low cost and simplicity, abdominal palpation would be the ideal tool for detecting SGA, however, it has been consistently shown to be limited in its detection rate. A Lancet article from 1980 involving the review of 1907 pregnancies, showed that 44% (83 of 289) of IUGR (defined as a BW <10th centile) cases were detected

antenatally. However, using this method, there was substantial over diagnosis, and there were 206 falsely suspected cases of IUGR (Hall *et al.,* 1980). In 1982 a Glasgow based team looked at 226 cases of growth-restricted babies. Only half had been suspected of being growth restricted (defined as a BW <10th centile) antenatally, and, of these, 65% (73 cases) were suspected due to palpating small. Therefore, overall in this study, only 32% of IUGR neonates were detected antenatally (Rosenberg *et al.,* 1982). Finally, a cohort study in 6318 pregnancies by Bais *et al.,* reported that screening by abdominal palpation had a sensitivity of 28% for severe SGA (<2.3rd centile) and 21% for SGA (<10th centile) (Bais *et al.,* 2004). Though this study showed abdominal palpation to be better at predicting severe SGA, the sensitivities were still no better than maternal characteristics alone.

Symphysis fundal height

Symphysis Fundal Height (SFH) is considered an inexpensive method for screening for growth restricted fetuses (Morse *et al.,* 2009), however, the National Institute for Health and Clinical Excellence (NICE) 2008 guideline on routine antenatal care suggested that studies surrounding SFH are of limited use due to a wide variation in the results. The largest study by Persson *et al.,* of almost 3000 patients, revealed that the sensitivity of SFH in detecting neonates with a BW <10th centile was only 26.6%, with a specificity of 88% (Persson *et al.,* 1986). This compared with results from India (Grover *et al.,* 1991) where the sensitivity was 80.8% and specificity of 93.5% for the same outcome. The evidence summary from this document stated that when using SFH to predict SGA there was a *'wide variation in the results observed for predictive accuracy'* and that *'the results from a multicentre study, Persson et al., 1986 show that it does not have good diagnostic value for predicting and ruling out SGA babies'* (National Collaborating Centre for Women's and Children's Health (UK) 2008), (**Table 1.6**).

Despite this, in 2013 the RCOG released its updated guideline on the investigation and management of SGA. The recommendation of the RCOG is that 'serial measurement of SFH is recommended at each antenatal appointment from 24 weeks of pregnancy as this improves prediction of a SGA neonate' (Robson *et al.,* 2013). Six studies were analyzed by the RCOG with sensitivities from 27-86% and specificities 80-93% for the detection of a SGA neonate (Persson *et al.,* 1986; Bergman *et al.,* 2006; Belizan *et al.,* 1978; Cnattingius *et al.,* 1984; Mathai *et al.,* 1987). Apart from the significant intra– and inter–observer variation (Bailey *et al.,* 1989), the studies also

indicated that the measurement of SFH was affected by fetal lie, maternal habitus, fibroids, amniotic fluid levels and fetal head engagement. Finally, though there is evidence to suggest a one off measurement is sufficient to detect (up to 64% of) SGA by this method (Calvert *et al.,* 1982), there are indications that predictive accuracy is improved by serial measurements (Pearce & Campbell 1987).

Table 1.6 Characteristics of included studies on diagnostic value of SFH measurement (National Collaborating Centre for Women's and Children's Health (UK) 2008).

Study	n	Timing of screening	Performance (95% CI)
Persson *et al.,* 1986	2919	15 times approx. during the entire pregnancy.	Sensitivity 0.27 (0.22–0.32) Specificity 0.88 (0.87–0.89)
Harding 1995	28w: 747 34w: 913	Every 4 weeks from 20 to 38 weeks.	From 28 weeks: Sensitivity 0.32 (0.23–0.40) Specificity 0.88 (0.86–0.90) From 34 weeks: Sensitivity 0.31 (0.22–0.40) Specificity 0.87 (0.85–0.89)
Rosenberg *et al.,* 1982	753	From 20 weeks until delivery.	Sensitivity 0.56 (0.42–0.70) Specificity 0.85 (0.82–0.87)
Grover *et al.,* 1991	350	Every 2 weeks until 30 weeks and then weekly until term.	Sensitivity 0.81 (0.73–0.88) Specificity 0.94 (0.91–0.97)
Rogers *et al.,* 1985	250	Third trimester.	Sensitivity 0.73 (0.56–0.90) Specificity 0.92 (0.88–0.96)

1.5.3 Ultrasound scan for fetal biometry

The current RCOG guideline on 'The Investigation and Management of the Small-for-Gestational-Age Fetus' recommends that either ultrasound derived EFW or fetal AC less than the 10th centile for gestational age, be used to diagnose SGA (Robson *et al.,* 2013). This recommendation is based on two systematic reviews by Chang *et al.,* 1992 and Chauhan & Magann 2006. The first article by Chang *et al., (1992)* reviewed 15 years of literature so as to determine the most appropriate ultrasound measurements that best predict SGA neonates. After reviewing 117 articles, 36 biometric studies reached their required criteria and were selected for analysis. The conclusion of this review was that, in high risk patients, the OR for detecting of a SGA

neonates was 39.1 (95%CI 28.9-52.8) when using an EFW <10th centile and 18.4 (95% CI 9.8-34.3) when using an AC <10th centile. AC <10th centile had the highest sensitivity (84%) for predicting a SGA neonate. In routine low risk patients, the OR's were much lower, with that of AC dropping to 13.5 (95% CI 11.5-15.9) (no other results are stated) (Chang *et al.,* 1992). The second article by Chauhan & Magann (2006) aimed, firstly, to review randomized trials that have determined the value: *'of fundal measurements versus sonographic examinations to identify fetal growth restrictions'* and secondly *'to determine the accuracy of different diagnostic tests to identify a fetus with sub-optimal growth'.* Comparing studies using SFH measurements or ultrasound derived biometry or both, the study concluded that as randomized trials show that an EFW measured at 30-32 weeks and 36-37 weeks can: *'significantly decrease the rate of FGR among uncomplicated pregnancies, all patients should have sonographic examinations in the third trimester' (Chauhan & Magann 2006).* This study does not make a recommendation for SFH over ultrasound measured fetal biometry, but rather recommends ultrasound as the method for detecting SGA. This recommendation is different to the RCOG's, which suggests that '*routine measurement of fetal AC or EFW in the 3rd trimester does not reduce the risk of a SGA neonate nor does it improve perinatal outcome. Routine fetal biometry is thus not justified'.*

The *National Collaborating Centre for Women's and Children's Health* (National Collaborating Centre for Women's and Children's Health (UK) 2008) guideline's have a different position. This guideline combined the results of 5 studies that used a fetal AC measured in the third trimester to predict a BW of <10th centile. Using an AC cut off of less than the 10th centile, the guidelines state that the summary positive likelihood ratio (LR+) was 6.25 (95% CI 5.60-6.97) and summary negative likelihood ratio (LR−) was 0.55 (95% CI 0.52-0.58). The conclusion of the guidelines is that there is some evidence that, in the third trimester, a single measurement of fetal AC has some diagnostic value in predicting the birth of SGA neonates.

The potential value of sonographic examined fetal biometry during the third trimester, for the prediction of SGA neonates in low-risk singleton pregnancies has been studied many times, with consistent results. Skovron *et al.,* examined 768 pregnancies at 26-34 weeks' gestation and reported that the fetal AC and EFW, performed equally well in the prediction of SGA neonates with BW <10th centile; the detection rates (DR) were about 45% and 63%, at respective false positive rates (FPR) of 10% and 20% (Skovron *et al.,* 1991). David *et al.,* examined 1,000 pregnancies at 28-36 weeks' gestation and reported that the fetal AC and EFW performed equally well in the

prediction of SGA neonates with BW <10th centile; the DR's were about 46% and 54%, at respective FPR's of 10% and 20% (David *et al.,* 1996). De Reu *et al., (2008)* assessed the fetal AC at 27-33 weeks in the prediction of SGA neonates with BW <10th centile in 725 pregnancies and reported that the DR was 53% at FPR of 20% (De Reu *et al.,* 2008). Di Lorenzo *et al.,* assessed the EFW at 30-32 weeks in the prediction of SGA neonates with BW <10th centile in 1,868 pregnancies and reported that the DR was about 73% at FPR of 25% (Di Lorenzo *et al.,* 2013). Souka *et al.,* assessed fetal AC and EFW at 30-34 weeks in the prediction of SGA neonates with BW <5th centile in 2,310 pregnancies and reported that at FPR of 10%, the respective DRs were 57% and 60% (Souka *et al.,* 2012); similar results were obtained in an extended study of 3,690 pregnancies (Souka *et al.,* 2013). Finally, Rosendahl & Kivinen 1991 assessed a two-step screening approach combining maternal factors and symphysis-fundal height with the measurement of fetal AC and biparietal diameter in the detection of SGA in 1,122 unselected singleton pregnancies and demonstrated a DR of 70%, at FPR 5% (Rosendahl & Kivinen 1991).

1.5.4 Mean arterial pressure

There is evidence that in pregnancies affected by PE, prior to the onset of the clinical signs of PE, the mean arterial pressure (MAP) is increased. This has been shown at 11-13 (Poon *et al.,* 2009; Akolekar *et al.,* 2013; Poon *et al.,* 2012; Gallo *et al.,* 2014; Karagiannis *et al.,* 2011; Khalil *et al.,* 2012), 20-24 (Tayyar *et al.,* 2014; Gallo *et al.,* 2014) and 30-34 weeks (Lai *et al.,* 2013; Bamfo *et al.,* 2007).

In pregnancies delivering SGA neonates in the absence of PE, the MAP in the first trimester is significantly increased, (Karagiannis *et al.,* 2011; Khalil *et al.,* 2012). Karagiannis *et al.,* performed first trimester screening in 32,580 pregnancies, of which 1,536 had a SGA neonate. The MAP was measured between 11-13 weeks' in all the patients. In those delivering a SGA neonate the MAP was significantly increased above those who delivered an AGA neonate (1.01 MoM IQR 0.96-1.07 vs 1.00 MoM IQR 0.95-1.06). This was further increased in the SGA neonates delivered after 37 weeks (1.02 MoM IQR 0.96-1.07) (Karagiannis *et al.,* 2011). Two longitudinal studies reported that BW decreased as blood pressure increased between the second and early third trimester of pregnancy (Churchill *et al.,* 1997; Bakker *et al.,* 2011). Churchill *et al.,* showed that at 28 weeks gestation, a 1 SD (5mmHg) increase in diastolic blood pressure decreased the mean BW by 68g (95% CI 3-132) whilst at 36 weeks the same change reduced mean BW by 76g (Churchill *et al.,* 1997). Bakker *et al.,* study

of measuring blood pressure once in each trimester showed that only a rise in third trimester systolic blood pressure was associated with a lower BW (Bakker *et al.,* 2011).

1.5.5 Uterine artery Doppler

The anterior divisions of the internal iliac arteries give rise to the uterine arteries, which supply the uterus with the majority of its blood. A smaller proportion of blood is derived from the ovarian arteries. These arteries anastomose at the cornu and give rise to arcuate arteries that circumferentially run around the uterus and infiltrate into the outer third of the myometrium. In turn, these vessels divide into the basal arteries, which supply the myometrium, and the spiral arteries, which supply the intervillous space of the placenta.

Uterine artery Doppler is a non-invasive measure of the resistance of the uteroplacental circulation. In pathological processes, such as PE and FGR (Khong *et al.,* 1986), there is increased resistance in this circulation, which in turn causes increased resistance upstream in the uterine arteries. Therefore, uterine artery Doppler provides an indirect assessment of increased resistance in the uteroplacental circulation space (Gebb & Dar 2011). Furthermore, uterine artery Doppler studies also provide an indication of the extent of placental pathology. Madazli *et al.,* compared the uterine artery PI one week prior to delivery and the histomorphology of the placenta and the placental bed findings in IUGR and control pregnancies (Madazli *et al.,* 2003). Evidence from this study showed that the incidence of abnormal biopsies was highest in pregnancies with IUGR and abnormal uterine artery Doppler (79.3%), than in IUGR pregnancies with normal uterine artery Doppler (16.6%) and least (0%) in normal controls. This study did not compare these Doppler studies to any measured earlier in pregnancy, and consequently doies not equate late abnormal uterine artery Doppler findings to those in the first or second trimester. Ferrazzi *et al.,* compared hypoxic or ischaemic lesions in the placentas of normal fetuses and FGR fetuses with both normal and raised uterine artery PI. The number and severity of these lesions was found to be highest in FGR fetuses with abnormal and then normal uterine artery PI, and were lowest in normal pregnancies (Ferrazzi *et al.,* 1999). Another study compared products of conception from termination of pregnancy in pregnancies with high and low resistance uterine artery blood flow. Both types of pregnancy showed normal intradecidual endovascular trophoblast invasion, however the proportion of decidual vessels with endovascular trophoblast invasion was significantly higher in the low-resistance pregnancies (49%) compared with the high-resistance ones (34%,

p=0.02). The study concluded that the difference in uterine artery resistance in abnormal placentation can be seen as early as 9 weeks of gestation (Prefumo *et al.,* 2004).

A Swedish study by Ghosh & Gudmundsson 2009 showed that in 359 suspected cases of FGR (EFW <2SD below the mean gestational age), the UtAD's were abnormal in 120 cases (33.4%), and in these cases the number of SGA neonates was 93 (77.5%). This compared with 104 (44.6%) SGA neonates in those with normal UtAD's, with the difference being statistically significant (Ghosh & Gudmundsson 2009).

Extensive screening studies of pregnancies that develop PE have reported that the uterine artery PI is increased before the onset of the clinical signs of the disease. Studies carried out at 11-13 (Poon *et al.,* 2009; Akolekar *et al.,* 2013) 20-24 (Albaiges *et al.,* 2000; Yu *et al.,* 2005; Gallo *et al.,* 2013) and 30-34 (Lai *et al.,* 2013; Tayyar *et al.,* 2014) weeks' gestation.

Screening for SGA in the first (Karagiannis *et al.,* 2011; Pilalis *et al.,* 2007; Melchiorre *et al.,* 2009) and second trimester (Llurba *et al.,* 2009; Khalil *et al.,* 2012) have reported that in pregnancies that deliver SGA neonates in the absence of PE the uterine artery PI is increased. A large systematic review of 41,131 patients from 61 studies in the first and second trimesters of pregnancy, examined the predictive accuracy of uterine artery Doppler indices for the prediction of IUGR (BW <10th centile) (Cnossen *et al.,* 2008). In low risk patients, a second trimester increased PI with notching (LR+ 9.1, 95% CI 5.0-16.7; LR- 0.89, 95% CI 0.85-0.93) was the best predictor of IUGR. Severe IUGR (BW <5th or 3rd centile), in the same population at the same gestation, was best predicted by an increased PI (LR+ 13.7, 95% CI 10.3-16.9; LR- 0.34, 95% CI 0.23-0.48) or an increased PI with notching (LR+ 14.6, 95% CI 7.8-26.3; LR- 0.78, 95% CI 0.68-0.87).

The generation R study looked at increased uterine artery PI's in both the second and third trimester, and its results revealed that the OR for delivery of a SGA neonate was 1.28 (95% CI 1.14-1.43) in the second trimester and 1.56 (95% CI 1.40-1.73) in the third trimester. Furthermore, in the third trimester, the presence of unilateral and bilateral notching had an OR for delivery of a SGA neonate of 3.43 (95% CI 2.36-4.97) and 4.17 (95% CI 2.54-6.82) respectively. In addition to notching not being measurable, one study showed that the sensitivity of bilateral notches in predicting

SGA or PE was similar to that of increased PI, but had a higher screen-positive rate (9.3% vs 5.1%) (Papageorghiou *et al.,* 2001).

A small Italian study by Maroni *et al.,* compared 66 AGA pregnancies with increased uterine artery PI at 34 weeks with 66 AGA fetuses with a normal uterine artery PI, and revealed that those with increased uterine artery PI were statistically significantly more likely to deliver a SGA neonate (13/66 vs. 1/66, p=< 0.001) (Maroni *et al.,* 2011).

As part of a screening study for SGA, Di Lorenzo *et al.,* compared the detection rate of SGA between ultrasound derived EFW and EFW in combination with uterine artery Doppler studies. In SGA with a BW between the 5th and 10th centile, ultrasound derived EFW alone had a DR of 72.4% with a FPR of 25.2%, and when combined with UtAD's the DR was 72.4% with a FPR of 25.1%. In severe SGA, defined as a BW below the 5th centile, EFW alone has a DR of 74.3% with a FPR of 26.5% and when uterine artery Doppler was included; the DR was 71.4% with a FPR of 16.0%. The study's results indicated that the addition of UtAD's to an EFW improved the FPR, especially for severe cases of SGA (Di Lorenzo *et al.,* 2013).

Many third trimester studies have also examined the role of UtAD's in the prediction of adverse outcomes in cohorts of SGA fetuses. Studies by (Vergani *et al.,* 2002; Severi *et al.,* 2002; Ghi *et al.,* 2010; Vergani *et al.,* 2010; Jamal *et al.,* 2013) have consistently shown that abnormal uterine artery PI in a SGA fetus increases the risk of an adverse neonatal outcome such as delivery by CS, a lower BW centile, low Apgar score scores at delivery and admission to the NNU. Severi *et al.,* (2002) studied 231 SGA pregnancies (BW <10th centile) and found that those with abnormally raised UtAD had a had an increased risk of developing fetal distress and being delivered by emergency Caesarean section (Severi *et al.,* 2002;). Vergani *et al.,* (2002) showed that SGA fetuses with with abnormal UtAD waveforms were, compared to those with normal UtAD, more frequently born by Caesarean section, particularly for a pathological CTG (27% vs 10%, *p*=<0.001), had significantly lower GA at delivery (37.7 ± 2.0 vs 38.8 ± 1.6, *p*=<0.001), and lower BW percentiles (4.8 ± 5.1 vs 9.3 ± 10.2, *p*=<0.001) (Vergani *et al.,* 2002). A Swedish study by Ghosh & Gudmundsson 2009 showed that in 359 suspected cases of FGR (EFW <2SD below the mean gestational age), the UtAD's were abnormal in 120 cases (33.4%), and in these cases the number of SGA neonates was 93 (77.5%). This compared with 104 (44.6%) SGA neonates in those with normal UtAD's, with the difference being statistically significant (Ghosh & Gudmundsson 2009). Ghi *et al.,* (2010) examined UtAD at 20 and then 26-

28 weeks of gestation. Those with persistently raised UtAD PI, had a significantly higher risk of pre-eclampsia (p=0.047), SGA fetus (p=< 0.007) and admission to the NICU (p=< 0.001) compared to those whose UtAD had normalised. Those who initially had raised UtAD which normalised also had an increased risk of delivering a SGA neonate (p=0.03), but there were no significant differences for the other outcome measures (Ghi *et al.,* 2010).

A Cochrane review on *'Utero-placental Doppler ultrasound for improving pregnancy outcome'* with the objective of assessing *'the effects on pregnancy outcome, and obstetric practice, of routine utero-placental Doppler ultrasound in first and second trimester of pregnancy in pregnant women at high and low risk of hypertension complications'* concluded that *'present evidence failed to show any benefit to either the baby or the mother when utero-placental Doppler ultrasound was used in the second trimester of pregnancy in women at low risk for hypertensive disorders. More research is needed to investigate whether the use of utero-placental Doppler ultrasound may improve pregnancy outcome* (Alfirevic *et al.,* 2013)*'*. It is important to note that this review only looked at the second trimester screening, and both papers referenced were using uterine artery Doppler to categorise women in to high and low risk and treat high-risk women with aspirin to prevent adverse outcomes. Despite this selection of publications, both still showed that there were merits of using uterine artery Doppler studies to predict SGA. Subtil showed that an abnormal uterine artery Doppler measurement increased the risk of a SGA neonate, with a RR of delivering below the 10th centile 2.3 (95% CI 1.6-3.2) of and below the 3rd centile 3.6 (95% CI 1.6-8.1) (Subtil 2003), whilst Goffinet *et al.,* showed the RR was 1.14 (95% CI 0.85-1.52) for a neonate with a BW <10th centile and 1.15 (95% CI 0.60-2.22) for a neonate with a BW <3rd centile (Goffinet *et al.,* 2001).

1.5.6 Umbilical artery Doppler

The uteroplacental circulation has low resistance allowing easy flow of blood from the fetus to the placenta and therefore sufficient gas and nutrient exchange to take place. This flow is forward during the entire fetal cardiac cycle. As resistance within the placenta increases, the resistance to blood flow also rises. This is most evident during fetal diastole, where the passive flow of blood meets the increasing placental resistance, and its flow changes from forward, to absent and finally to reverse. In the UAD waveform, this is reflected as positive, absent, or reversed end diastolic flow. As the changes progress, the umbilical artery PI increases; and becomes raised when

around 30% fetal villous vasculature is abnormal and absent or reversed flow indicates that two-thirds of the villous vasculature is damaged (Sankaran & Kyle 2009; Baschat 2011). Many studies have attempted to use the measurement of the UAD to predict SGA and poor clinical outcomes.

A Cochrane review of the use of UAD ultrasound in pregnancy examined 5 studies and 14,185 patients (Alfirevic *et al.,* 2013) and, as a secondary outcome, looked at infant BW. There was no difference in the mean BW regardless of whether a single or multiple measurements of UAD were measured, however in one study within the review, by Newnham *et al.,* (1993) there were significantly more SGA neonates in pregnancies that had routine four weekly Doppler studies from 18 to 38 weeks (RR 1.66 95% CI 1.09-1.67) than in those that had a single 18 week measurement (Newnham *et al.,* 1993). However, despite these findings over 20 years ago, there has been no further research in to the routine use of UAD measurements to predict SGA. A small study of 90 patients, half AGA and half with an AC <10th centile, showed that 24 had an abnormal umbilical PI. Among these, 21 (87.5%) were SGA; therefore UAD had a sensitivity of 46.7% and specificity of 93.3% for detecting SGA (Bano *et al.,* 2010).

As early as 1996, a meta-analysis of randomized controlled trials that indicated that using an UAD measurement in high-risk pregnancies significantly decreased perinatal mortality without increasing inappropriate intervention (Divon 1996). Since then, many other studies have looked at the use of UAD measurement, usually in the third trimester of pregnancy, and mostly confined to detecting pregnancy adverse outcomes in 'high risk' cases, normally classified as SGA fetuses with an EFW <10th centile.

Adverse outcomes are usually stated as the need for CS delivery, NNU admission, low Apgar scores at delivery, poor umbilical artery cord pH at delivery and other related objective evidence of fetal or neonatal compromise. For example, Figueras *et al.,* (2008) looked at a large population of 7,645 women at 30-34 weeks. In the 369 cases of a SGA fetus that had been identified antenatally, those with an abnormal UAD were more to likely to have neonatal morbidity compared to those of normal BW (Figueras *et al.,* 2008). Vergani *et al.,* studied 481 FGR (AC <10th centile) fetuses after 34 weeks, and found that those with an adverse outcome or born SGA (<3rd centile) had an increased umbilical artery PI (Vergani *et al.,* 2010).

Ghosh & Gudmundsson examined the use of uterine artery Doppler and UAD studies in cases of antenatally suspected FGR. The results showed that as the umbilical PI increased the risk of delivering a SGA neonate increased from 44.6% in those with normal PI values to 100% in those with reversed end diastolic flow (Ghosh & Gudmundsson 2009). Morris *et al.,* found that in a high-risk population, fetal UAD is a moderately useful test with which to predict mortality and risk of compromise (Morris *et al.,* 2011). A correlation exists between UA PI, cerebroplacental ratio and perinatal outcome prior to 34 weeks' gestation. These studies are heterogeneous, and though they highlight a use for UAD measurements, they do not find a place for it within routine screening.

1.5.7 Middle cerebral artery Doppler

In chronic fetal hypoxia, effects on chemoreceptors and baroreceptors, initiates redistribution of blood flow to the brain and other vital organs. This *'brain-sparing effect'* is mediated by cerebral artery vasodilatation, thereby decreasing the resistance and increasing the velocity within these vessels, which can be detected clinically with a decrease in middle cerebral artery (MCA) PI (Cruz-Martínez & Figueras 2009).

Similarly, with research in to UAD's, there are no trials using MCA Doppler studies to predict SGA fetuses within a routine population. However, there is a large body of evidence focusing on the use of predicting adverse outcomes within SGA cohorts.

An early study by Hershkovitz *et al.,* looked at a small group of 47 SGA fetuses with an EFW <5th centile of which 16 had redistribution (MCA PI <5th centile). The study found that the BW was significantly lower in those with redistribution compared to those with a normal MCA PI (1745 ± 255.9 vs 2416 ± 306.8, p=<0.001). The chance of a spontaneous vaginal delivery was higher in the group with a normal MCA PI (65% vs 25%, p=<0.001) but the need for NNU admission was higher in the redistribution group (25% vs 0%, p=0.01) (Hershkovitz *et al.,* 2000).

A more detailed study by Nanthakomon & Uerpairojkit examined 297 SGA fetuses between 24-42 weeks, and reviewed the outcomes of those with normal (218) and abnormal (26) MCA Doppler, which was considered to be a PI <5th centile. The risk of an Apgar score <7 at both 1 (2.8% vs 23.1%, p=<0.001) and 5 (1.4% vs 11.5%, p=0.017) minutes, admission to the NNU (4.6% vs 30.8%, p=0.011) and perinatal

mortality (0% vs 3.8%, p=0.026) were statistically significantly higher in the group with an abnormal MCA measurement (Nanthakomon & Uerpairojkit 2010). The need for CS was also statistically higher in the group with abnormal MCA PI, (49.5% vs 69.2%, p=0.024) (Nanthakomon & Uerpairojkit 2010), with similar findings by Severi *et al.,* where the need for CS was 11% and 4% p=0.0078, OR 3.1250 (95% CI 1.3503–7.2319) in those with decreased MCA PI and normal MCA PI respectively (Severi *et al.,* 2002).

Another study assessed the risk of non-reassuring fetal status during labour and neonatal metabolic acidosis (Parra-Saavedra *et al.,* 2013). 193 SGA fetuses were monitored and showed that those found to have a non-reassuring fetal status during labour (abnormal CTG or abnormal fetal blood sampling) were more likely to have a lower MCA PI (PI 1.34±0.37 vs 1.58±0.36, p=<0.01). In addition, if the MCA PI was below the 5th centile, the risk of a non-reassuring fetal status during labour was increased further (12% vs 36% p=<0.01). This study also looked at neonatal metabolic acidosis in the same groups, and showed that those neonates found to have neonatal metabolic acidosis were more likely to have a lower MCA PI (1.55±0.37 1.32±0.37, p=0.02) and the risk of acidosis was higher in those with a MCA PI below the 5th centile (8% vs 26% p=<0.01).

Eixarch *et al.,* focused on neurodevelopmental outcome at 2 years of age in fetuses that had had a low MCA PI. The team monitored 125 SGA fetuses, 100 with normal blood flows and 25 with redistribution (defined as a MCA PI <5th centile). The results found that those with redistribution were statistically significantly more likely to have suboptimal neurodevelopment (52% vs. 31%; P=0.049), a lower mean centile in communication (53.1 vs. 67.4; P=0.006) and problem-solving (39.7 vs. 47.4; P=0.04) areas (Eixarch *et al.,* 2008).

1.5.8 Cerebroplacental ratio

The importance and difficulty in differentiating SGA and FGR has already been discussed, as has the use of Doppler assessment of the UA or MCA individually to predict adverse outcomes in pregnancy. However, it has been stated that combining the two in a ratio, the cerebroplacental ratio (CPR) reflects both the placental status and fetal response, and may be a more sensitive Doppler index for predicting perinatal outcome (Gramellini *et al.,* 1992). It has been used as early as 1987 by Arbeille *et al.,* who showed that, though in normal pregnancies the MCA PI was greater than UA PI

(CPR >1), in growth restricted pregnancies this was not the case and that the CPR ratio was <1 (Arbeille *et al.,* 1987). Gramellini *et al.,* (1992) studied 45 SGA and 45 normal fetuses and measured CPR in both groups during the last 10 weeks of gestation. Eighteen fetuses, all in the SGA group, had abnormal CPR, of which 16 required a Caesarean section. The umbilical vein pH was statistically lower than those with an abnormal CPR, whilst the incidence of a low 5 minute Apgar score, NICU admission and longer NICU stay were significantly higher (Gramellini *et al.,* 1992). Bahado-Singh *et al.,* (1998) aimed to determine whether CPR predicts perinatal outcome in fetuses at risk for intrauterine growth restriction. The team measured CPR in 123 SGA fetuses who delivered <3 weeks after their Doppler examination. The results showed that there was a statistically significant increase in perinatal complications in cases with an abnormal CPR. Perinatal complications were defined as: NND, CS for fetal distress, hypoglycemia, polycythemia, or stay in the neonatal intensive care unit for >24 hours. Prolonged neonatal intensive care unit stay was defined as a stay >10 days. As a screening tool for the prediction of perinatal complications in fetuses delivered <34 weeks with an assessment to delivery interval <3 weeks, the screening efficiency of CPR was sensitivity 54.2%, specificity 94.5%, and positive and negative predictive values 87%, and 76%, respectively (Bahado-Singh *et al.,* 1998). Odibo *et al.,* (2005) retrospectively identified 183 SGA pregnancies and retrieved data on CPR. the sensitivity, specificity, and positive and negative predictive values for predicting an adverse outcome were 65%, 73%, 73%, and 65%, respectively, with an OR of 5.2 (95% CI 1.4–19.4) (Odibo *et al.,* 2005).

More recent studies have shown that, regardless of fetal size, CPR may identify fetuses that are at risk of adverse obstetric and neonatal outcomes such as the necessity for operative delivery for presumed fetal compromise, low neonatal blood pH and NNU admission (Morales-Roselló *et al.,* 2014; Prior *et al.,* 2013; Morales-Roselló *et al.,* 2015; Khalil *et al.,* 2014a; Khalil *et al.,* 2014b). One group from London examined the use of CPR for various outcomes. In their first study, CPR was used to identify AGA fetuses that had failed to reach their growth potential, which was defined as a CPR <5th centile. The study showed that the percentage of AGA fetuses with a CPR <5th centile increased with decreasing BW: with 1% in the 75–90th BW centile group, 1.7% in the 50–75th centile group, 2.9% in the 25–50th centile group and 6.7% in the 10–25th centile group. The results suggested that CPR could be used in AGA pregnancies to detect those failing to reach their growth potential due to placental insufficiency and fetal hypoxia (Morales-Roselló *et al.,* 2014). The study also examined almost 3000 term pregnancies retrospectively and found that a low CPR

correlated with a reduced umbilical arterial and venous pH (p=<0.0001) in both SGA and AGA neonates. The study also showed that in AGA fetuses a low CPR was associated with acidaemia in both the umbilical artery (p=0.0359) and vein (p=0.0006) (Morales-Roselló *et al.,* 2015). When analysing 2518 pregnancies with a CPR recorded between 34-36 weeks gestation, those requiring admission to the NNU, had a statistically significantly lower CPR than those not admitted (p=<0.05), whilst the BW between the groups was not different (Khalil *et al.,* 2014a). Finally, the group examined the effect of a reduced CPR on the risk of intrapartum compromise and admission to the NNU. The results revealed that a reduced CPR increased the risk of an operative delivery and admission to the NNU (AOR 0.994; 95% CI, 0.992-0.997; p=0.001). Though a low BW increased the risk of an operative delivery and admission to the NNU (AOR 0.67; 95% CI 0.52-0.87; p=0.003), it was not an independent predictor (Khalil *et al.,* 2014b).

Prior *et al.,* examined 400 women prior to established labour, and found that CPR was significantly lower in those delivering by CS (1.52 vs 1.82, p=0.001), furthermore, those who had a CPR <10th centile had a six fold increase in risk of emergency CS due to fetal distress with an OR, 6.1; 95% CI 3.03-12.75). Those with a CPR >10th centile did not require a CS for fetal distress (Prior *et al.,* 2013).

These outcomes may be in part due to poor placentation, and therefore hypoxaemia, and thus CPR may have a role in identifying hypoxaemic fetuses irrespective of size.

1.5.9 Maternal serum biochemistry

Biochemical markers were initially used for screening for Down's syndrome and later for PE. Sub analysis of these studies incidentally identified markers that predicted SGA. Over the years there has been an increasing focus on developing biochemical markers specifically for SGA (**see Table 1.7**). There is now an increasing body of evidence highlighting the association between varying levels of several maternal serum biochemical markers and the birth of SGA neonates.

A large meta-analysis by Morris *et al.,* reviewed five markers used for aneuploidy screening in forty four studies testing 382,005 women including 20,339 SGA cases. All five biochemical markers were taken in the second trimester of pregnancy. The study reported that there was an increased risk for delivery of a SGA neonate in mothers with raised levels (>2.0MoM) of serum α-fetoprotein (AFP) or human

chorionic gonadotropin (hCG). For AFP, the LR+ was 27.96 (8.02-97.48), and LR- was 0.78 (0.55-1.11), whilst for hCG the LR+ 1.74 (1.48-2.04), LR- 0.95 (0.93-0.96), with neither ofd thse LR- being statistically significant (Morris *et al.,* 2008).

Table 1.7: Biomarkers for predicting small for gestational age identified in the literature.

Angiogenesis-related biomarkers	**Endothelial function/oxidative stress-related biomarkers**
Placental growth factor	Homocysteine
Soluble fms-like tyrosine kinase-1	Leptin
Soluble endoglin	Asymmetric dimethylarginine
Vascular endothelial growth factor	Soluble vascular cell adhesion molecule-1
Angiopoietin	Soluble intercellular adhesion molecule-1
Placental proteins/hormone-related biomarkers	Isoprostanes
Insulin-like growth factor binding protein-1 and -3	8-oxo-7,8-dihydro-2′-deoxyguanosine
A disintegrin and metalloprotease-12	Fibronectin
Placental protein-13	Lactate dehydrogenase
Activin A	Pentraxin 3
Placental growth hormone	Interferon-c
Pregnancy-specific b-1-glycoprotein	Interleukin-1 receptor antagonist
Annexin A5	Interleukin-12
Hepatocyte growth factor	Eotaxin
	Regulated on activation, normal T-cell expressed and secreted (RANTES)
Others	C-reactive protein
Urinary albumin:creatinine ratio	Folate
Vitamin D	
Thyroid function tests (thyroid-stimulating hormone, free thyroxine, free triiodothyronine)	
Metabolomics	
Genetic biomarkers	

A second meta-analysis looking at 37 *'novel biomarkers'* concluded that only placental growth factor (PlGF) and angiopoietin-2 had high predictive values for delivering a SGA neonate. The LR's for PlGF were LR + 1.7, range 1.0–19.8; and
LR- 0.8, range 0.0–1.0 (Conde-Agudelo *et al.,* 2013)

In clinical practice, a large first trimester screening study at 11-13 weeks' gestation reported that in the cases delivering SGA neonates, serum free β-human chorionic

gonadotropin (β-hCG) (MoM 0.89 (95% CI 0.58-1.40)), pregnancy associated plasma protein-A (PAPP-A) (MoM 0.82 (95% CI 0.55-1.12)), and PlGF (MoM 0.90 (95% CI 0.63-1.24)) were statistically significantly decreased, and in the latter two cases, further decreased in SGA neonates delivered prior to 37 weeks (Karagiannis *et al.,* 2011).

The following section summarises the evidence for biochemical markers used for the prediction of SGA, where automated machines that are used in clinical practice can undertake the required measurements.

Placental growth factor

PlGF is a 149 long amino acid dimeric proangiogenic glycoprotein (Maglione *et al.,* 1991) which, is involved in the regulation of maternal endothelial function, placental vascular development and the trophoblast invasion of the maternal spiral arteries (Savvidou *et al.,* 2008). Insufficient invasion of the trophoblast of the spiral arteries leads to reduced perfusion of the placenta, which is associated with SGA and PE (Cowans *et al.,* 2010).

Two studies have longitudinally examined the maternal serum concentrations of PlGF in normal pregnancy and those affected by delivery of a SGA neonate. Bersinger & Odegard's nested case-control study of 40 normal pregnancies and 9 delivering SGA neonates. PlGF was shown to increase throughout pregnancy, in both normal and pathological pregnancies. The results also showed that, though PlGF values were consistently lower in the SGA pregnancies, they were only statistically significantly lower at 33 weeks (2328 pg/ml vs 1667 pg/ml, p=<0.05) (Bersinger & Odegard 2005). A similar study by Rizos *et al.,* measured PlGF in 90 normal pregnancies and 14 with SGA neonates in each trimester. This study replicated the results by Bersinger & Odegard, in that PlGF was shown to increase in all pregnancies as GA increased, however, PlGF was only higher in the normal pregnancies from the second trimester (20 weeks) onwards (Rizos *et al.,* 2013).

Many other studies have analysed PlGF in specific trimesters (**Table 1.8**). Studies in the first trimester (10-14 weeks of gestation) by Smith *et al.,*; Poon *et al.,*; Karagiannis *et al.,*; Cowans *et al.,*; have all shown that PlGF is statistically significantly lower in pregnancies that go on to deliver SGA neonates (Smith *et al.,* 2007; Poon *et al.,* 2008; Karagiannis *et al.,* 2011; Cowans *et al.,* 2010).

Table 1.8: Studies showing the differences in PlGF in normal and pregnancies delivering a SGA neonate.

Author	GA (weeks)	Definition of SGA/FGR	Controls		SGA/FGR		P
			n	pg/mL	N	pg/mL	
Smith *et al.,* 2007	10-14	BW <3rd centile	937	-	333	-	0.02
Poon *et al.,* 2008	11-14	BW <5th centile	609	1.00 MoM	296	0.9 MoM	0.024
Karagiannis *et al.,* 2010	11-14	BW <5th centile	1869	1.00 MoM	274	0.90 MoM^{+}	<0.00001
Cowans *et al.,* 2010	11-14	BW <10th centile	452	1.00 MoM	8	0.51 MoM	<0.001
Krauss *et al.,* 2004	22-29	BW <10th centile	177	441	38	423	NS
Savvidou *et al.,* 2008	23-25	BW <5th centile	40	423.3	15	223.7	<0.05
Wallner *et al.,* 2007	38 & 33	BW <10th centile	16	245.74	15	48.4	0.0017
Shibata *et al.,* 2005	39-40	BW <10th centile	31	266	24	163	<0.0001
Bersinger *et al.,* 2005	17	BW <2 SD from expected	40	817	9	697	NS
	25		40	1518	9	1301	NS
	33		40	2328	9	1667	<0.005
Rizos *et al.,* 2013	11-14	BW <10th centile	88	57.8	14	59.9	0.645
	20-26		88	311	14	290	NS
	28-35		88	780	14	512	0.002

A second trimester study by Savvidou *et al.,* showed that levels of PlGF were statistically significantly lower in pregnancies affected by delivery of a SGA neonate than those delivering normal sized neonates (223.7 pg/ml vs 423.3 pg/ml, p=<0.05 (Savvidou *et al.,* 2008). A second study in this gestational period by *et al.,* showed no significant difference in levels of PlGF (Krauss *et al.,* 2004). Interestingly, this finding was also confirmed by Bersinger & Odegard in their longitudinal study (Bersinger & Odegard 2005).

Third trimester studies have consistently shown that the levels of PlGF are statistically lower in pregnancies delivering SGA neonates than in normal pregnancies (Bersinger & Odegard 2005; Wallner *et al.,* 2007; Shibata *et al.,* 2005; Rizos *et al.,* 2013).

Soluble vascular endothelial growth factor receptor-1

Vascular endothelial growth factor (VEGF) is a protein that regulates angiogenesis. It acts through two considerably different receptor tyrosine kinases, vascular endothelial

growth factor receptor-1 (VEGFR-1) and vascular endothelial growth factor receptor-2 (VEGFR-2). VEGFR-1 binds PlGF in addition to VEGF (Shibata *et al.,* 2005; Chaiworapongsa *et al.,* 2008; Ferrara *et al.,* 2003).

Soluble vascular endothelial growth factor receptor-1, also known as soluble fms-like tyrosine kinase-1 (sVEGFR-1 or sFlt-1) is an alternatively spliced, soluble variant of VEGFR-1 and, whilst containing the extracellular ligand-binding domain, lacks the tyrosine kinase signaling domain. Therefore, whilst sFlt-1 binds VEGF or PlGF, it inhibits their biological activities (Ferrara *et al.,* 2003; Chaiworapongsa *et al.,* 2008; Shibata *et al.,* 2005). It is these effects that lead to the conclusions that sFlt-1 levels in maternal blood could be used to predict the delivery of SGA neonates.

A longitudinal study of sFlt-1 levels in each trimester by Rizos *et al.,* for the prediction of the delivery of a SGA neonate, showed that, compared to normal pregnancies, levels were lower in each trimester in SGA pregnancies, however, the values did not reach significance (Rizos *et al.,* 2013) (**Table 1.9**). The results also confirmed that the levels of sFlt-1 increased between the first and third trimesters, with a dip in the second.

Table 1.9: Studies showing the differences in sFlt-1 in normal and pregnancies delivering a SGA neonate.

Author	GA (weeks)	Definition of SGA/FGR	Controls		SGA/FGR		P
			n	pg/mL	n	pg/mL	
Erez *et al.,* 2008	6-15	BW <10th	201	1788	145	1615.8	NS
	20-25		201	1799.5	145	1687	NS
Smith *et al.,* 2007	10-14	BW <3rd	937	-	333	-	<0.001
Rizos *et al.,* 2013	11-14	BW <10th	88	1530	14	1141	0.082
	20-26		88	1428	14	1023	0.139
	28-35		88	1616	14	1190	0.011
Savvidou *et al.,* 2006	23-25	EFW <5th and bilateral UA notches	42	463	15	1674	<0.0001
Romero *et al.,* 2008	25	BW <10th	46	-	56	-	0.147
	40		46	-	56	-	0.8285
Chaiworapongsa *et al.,* 2008.	20-40	EFW <10th	135	1445	53	3603	<0.001
		Normal Doppler's	135	1445	20	2059	0.9
		Abnormal UtAD	135	1445	14	6139	0.4
		Abnormal UmAD	135	1445	2	2467	0.9
		Abnormal UtAD and UmAD	135	1445	7	4482	0.006
Shibata *et al.,* 2005	39-40	BW <10th	31	2472	24	1987	0.56
Wallner *et al.,* 2007	Not given	AC <5th and BW <10th	16	2199.85	15	4479.17	0.0086

Similar, non significant results were found by Erez *et al.,* who examined sFlt-1 in the first and second trimesters only (Erez *et al.,* 2008). Smith *et al.,* study of first trimester patients only, did however show that SGA affected pregnancies had significantly lower levels of sFlt-1 (Smith *et al.,* 2007), as did a study by Savvidou *et al.,* who studied patients in the second trimester only (Savvidou *et al.,* 2006).

Third trimester studies have shown mixed results: Shibata *et al.,* suggested there was no significant difference in sFlt-1 between normal and SGA pregnancies (Shibata *et al.,* 2005), both Wallner *et al.,* and Chaiworapongsa *et al.,* revealed significantly higher results in pregnancies delivering SGA neonates (Wallner *et al.,* 2007; Chaiworapongsa *et al.,* 2008). Chaiworapongsa *et al.,* analysed the results by Doppler findings, and showed that sFlt-1 concentrations were highest in SGA fetuses with abnormal UtAD or abnormal UAD and UtAD artery Doppler studies.

Angiogenic and antiangiogenic factors ratio

It has been shown that the maternal levels of sFlt-1 (antiangiogenic factor) and PlGF (angiogenic factor) alter in pregnancies delivering SGA neonates and those delivering neonates of normal BWs. There is some evidence to suggest that an imbalance in the ratio in these factors is associated with delivery of a SGA neonate. Crispi *et al.,* showed that the sFlt-1/PlGF ratio was statistically significantly higher in PE/IUGR pregnancies, whether this was early or late onset, however, the study did not discriminate between the two conditions (Crispi *et al.,* 2008). Chaiworapongsa *et al.,* showed that the ratio of sFlt-1/PlGF was statistically lower at 34 weeks of gestation in pregnancies going onto deliver a SGA neonate (Chaiworapongsa *et al.,* 2013). Herraiz *et al.,* used a PlGF/SFlt-1 ratio, but found similar results with a higher significance found in those with a diagnosis of FGR prior to 34 weeks (Herraiz *et al.,* 2014) (see **Table 1.10**).

Table 1.10: Studies showing the differences in PlGF/sFlt-1 ratio in normal and pregnancies delivering a SGA neonate.

Author	GA (weeks)	Definition SGA/FGR	Controls		SGA/FGR		P
			n	sFlt-1/PlGF	n	sFlt-1/PlGF	
Chaiworapongsa *et al.,* 2013	30-34	BW <10th centile	886	1.0	108	0.53	<0.05
Herraiz *et al.,* 2014	24-33.6	EFW <10th centile + AFI <10th centile or PI UA >95th centile	171	2.8*	19	90.5*	0.001
	>34		171	11.0*	8	116.8*	<0.5

*PlGF/sFlt-1=

α-fetoprotein

α-fetoprotein (AFP) is a negatively charged sialylated glycoprotein, 590 amino acids long, protein released during fetal life from the yolk sac and fetal liver. Hay *et al.,* first measured maternal serum AFP in serial samples in normal pregnancies (Hay *et al.,* 1976). The study found that AFP increased from 10 to 32 weeks of gestation and then declined to term. In a small study of 63 patients, it was noted that there was no correlation between the value of AFP at 32 weeks and the BW.

Amongst second trimester findings, Waller *et al.,*'s study of 52,869 patients with AFP measurements as part of Down's screening at 15-19 weeks of gestation revealed a U-shaped relationship between AFP MoM and the risk of SGA (Waller *et al.,* 1996). The risk of delivering a SGA neonate was higher if the AFP level was <0.44 MoM (OR 2.3, 95% CI 1.7-3.0) and >2.5 MoM (OR 3.2, (95% CI 2.4-4.1). Spencer's study of 26,254 pregnancies found significance only in those with an AFP MoM >2.0 MoM (RR 1.640, p=0.0062) (Spencer 2000), which was also reflected by Chandra 2003 (RR 3.08, (95% CI 1.99-4.77) (Chandra 2003) (**Table 1.11**).

Table 1.11: Studies reporting on the risk of delivering a SGA neonate with an AFP measurement >2.0 MoM.

Author	GA	Controls	SGA	RR or OR (95% CI)	P
Spencer 2000	14-18 w	25,402	1,122	1.640	<0.0062
Waller *et al.,* 1996	15-19 w	44,663	2,429	3.2 (2.4-4.1)	<0.01
Simpson *et al., 1995*	15-20 w	650	68	2.7 (0.8-10.6)	<0.01
	24-36			1.9 (0.4-9.1)	NS
Chandra *et al.,* 2003	2nd tri	14,374	-	3.08 (1.99-4.77)	<0.01
Morris *et al.,* 2008	<25 w	361,666	20,339	LR + 8.80 (5.57-13.91)	

A large meta analysis found that an AFP level >2.0MoM's was the best cut-off used for the risk of delivering a SGA neonate, with LR+ 8.80 (95% CI 5.57-13.91) and LR- 0.02 (95% CI 0.00-0.34) (Morris *et al.,* 2008).

One study of 650 by Simpson *et al.,* in the second (15-20 weeks of gestation) and third (24-36 weeks of gestation) trimesters of pregnancy revealed an OR in the

second trimester of 2.7 (95% CI 0.8-10.6) and third of 1.9 (95% CI 0.4-9.1). The authors concluded that only second and not third trimester serum AFP was significantly elevated in SGA pregnancies (Simpson *et al.,* 1995). However, it is obvious that there is a wide range of dates of sampling in the third trimester.

Pregnancy associated plasma protein-A

Pregnancy associated plasma protein-A (PAPP-A) is a protein 1547 amino acids long, synthesised in the placenta, with its main function being cleavage of insulin-like growth factor binding protein-4 (IGFBP-4) thereby increasing the active levels of IGF to promote growth. It was first discovered in 1974, PAPP-A found early use as a marker for Down's syndrome (Boldt & Conover 2007).

One longitudinal study of PAPP-A at 17, 25 and 33 weeks of gestation showed that the maternal serum concentrations increased with gestation (Bersinger & Odegard 2004). This study showed that PAPP-A was significantly reduced in pregnancies delivering a SGA neonate at 17 weeks (p=0.0022), but not at 25 or 33 weeks. A second longitudinal study looked at serum concentrations in the first trimester (<15 weeks) and second trimester (15-21 weeks) and showed that levels increased, but not significantly between the two trimesters (Berry *et al.,* 1997). A third trimester longitudinal study measured concentrations from 30-40 weeks and found that concentrations rose steadily between 30-36 weeks and then rapidly from 37 weeks onwards (Smith *et al.,* 1979).

Three studies have compared first trimester concentration of PAPP-A in pregnancies delivering normal and SGA BW neonates (**Table 1.12).** A large study by Karagiannis *et al.,* of 31,314 pregnancies delivering normal BW and 1,536 SGA neonates found the concentration of PAPP-A neonates was statistically significantly lower in pregnancies delivering SGA neonates, 0.83 MoM (95% CI 0.58-1.40) and 1.03 MoM (95% CI 0.71-1.45), p=< 0.00001 (Karagiannis *et al.,* 2011). A smaller study by Poon *et al.,* showed similar results with the PAPP-A MoM being significantly lower in SGA, 0.78 MoM (95% CI 0.52-1.16), than normal pregnancies, 1.07 MoM (95% CI 0.74-1.46), p=< 0.00001 (Poon *et al.,* 2008).

One large meta analysis by Morris *et al.,* showed that the best predictor for delivery of a SGA neonate was a PAPP-A <1st centile in the first trimester, with a LR+ 3.50 (95% CI 2.53-4.82) and LR- 0.98 (95% CI 0.97-0.99) (Morris *et al.,* 2008).

Table 1.12: Studies showing the differences in PAPP-A in normal and pregnancies delivering a SGA neonate.

Author	Definition of SGA/FGR	GA (wks)	Controls		SGA		P
			n	MoM	n	MoM	
Smith *et al.,* 2002	BW <5th centile	8-14	8,469	-	370	AOR 2.8	<0.0001
Poon *et al.,* 2008	BW <5th centile	11-14	609	1.070	296	0.77*	<0.0001
Karagiannis *et al.,* 2011	BW <5th centile	11-13	31,314	1.03	1,373	0.83	<0.00001
Bersinger & Odegard 2004	BW ≥2 SD below expected weight	17	64	-	22	-	0.0022
		25	41	-	14	-	NS
		33	41	-	14	-	NS

Free βhCG

Human chorionic gonadotropin (hCG) is a glycoprotein made of 2 subunits: alpha and beta. It is synthesised by the syncytiotrophoblast and controls the invasion of the cytotrophoblast and supports the corpus luteum in early pregnancy (Cole 2009). Studies comparing values of free βhCG have shown mixed results. One study by Ong *et al.,* showed that, in the first trimester, there was no difference between free βhCG levels in normal or pregnancies that went on to deliver a SGA neonate, regardless whether the BW cut off for SGA was 10th, <5 or <3rd centile (Ong *et al.,* 2000). However, a much larger first trimester study of 32,850 women showed that the free βhCG was statistically significantly lower in pregnancies going on to deliver a SGA neonates than those delivering normal sized neonates: 0.89 MoM (95% CI 0.58-1.40) and 0.97 MoM (95% CI 0.66-1.47) respectively (Karagiannis *et al.,* 2011).

Only two small studies reviewed free βhCG in the third trimester and showed that though levels were higher in pregnancies delivering SGA neonates, the difference was not significant (Bartha *et al.,* 2003; Bartha *et al.,* 1997). Significance in these results was only seen in SGA fetuses with abnormal UmAD measurements and with a BW <10th centile (25256 IU/ml vs 45732 IU/ml, p=0.002) (Bartha *et al.,* 1997).

Several second trimester studies have examined the r*isk of delivering a SGA neonate* when using a cut off of free βhCG MoM of <0.5, >2.0, >2.5 or >3.0 (Spencer 2000; Benn et al., 1996; Chandra 2003; Morssink et al., 1995), with RR ranging form 0.99 to 3.01 (**see Table 1.13**). A large meta analysis showed that the best predictor for a

BW < 10th centile was bhCG >2.0MoM; LR+ 1.74 (1.48-2.04), LR- 0.95 (0.93-0.96) (Morris et al., 2008).

Table 1.13: Studies reporting on the risk of delivering a SGA neonate with a specified free βhCG measurement.

Authors	GA (wks)	Definition SGA/FGR	Controls	SGA	Cut off MoM	RR/OR (95% CI)	p
Spencer 2000	14-18	<10th centile	25,402	1,122	>2.0	0.986	0.8845
					<0.5	2.129	<0.0001
Benn *et al.,* 1996	15-19		44,663	2,429	>3.0	3.01 (1.49 - 6.06)	
Chandra *et al.,* 2003	2nd trimester		14,374	Not given	>2.0	1.37 (0.96-1.95)	
Morssink *et al.,* 1995	15-20	<2.3rd centile			>2.5	2.1	<0.01
		<10th centile			>2.5	1.5	<0.01

1.6 Objectives of the thesis

Despite the vast research carried out so far in screening for SGA, there is yet to be single trial combining all the above methods in to one single assessment. Therefore, the objectives of this thesis are:

1. To develop a model based on maternal characteristics and medical history for prediction of birth of SGA neonates and examine the performance of screening by maternal factors.

2. To develop a model based on a combination of maternal factors and fetal biometry at 30-34 weeks' gestation for prediction of birth of SGA neonates and examine the performance of screening by this method.

3. To develop a model based on a combination of maternal factors, fetal biometry, uterine artery PI and MAP at 30-34 weeks' gestation for prediction of birth of SGA neonates and examine the performance of screening by this method.

4. To develop a model based on a combination of maternal factors, fetal biometry and serum biochemical markers at 30-34 weeks' gestation for prediction of birth of SGA neonates and examine the performance of screening by this method.

5. To develop a model based on a combination of maternal factors, biophysical and biochemical markers at 30-34 weeks' gestation for prediction of birth of SGA neonates and examine the performance of screening by this method.

6. To examine the value of umbilical artery PI and fetal MCA PI at 30-34 weeks' gestation in the prediction of adverse perinatal outcome.

Chapter 2: Patients and Methods

2.1 Study population

A routine third trimester appointment intended for prospective screening for adverse obstetric outcomes was introduced at King's College Hospital and University College London Hospital, London, and Medway Maritime Hospital, Kent, between May 2011 and April 2014, providing the data for this study. The new appointment was held between 30^{+0}-34^{+6} weeks' gestation, which was determined at 11-13 weeks by measurement of fetal crown-rump length (Robinson & Fleming 1975) or at 20-24 weeks by the fetal head circumference (Hadlock *et al.,* 1985).

Information recorded included maternal characteristics and medical history and EFW (Hadlock *et al.,* 1985) from transabdominal ultrasound measurement of fetal head circumference (HC), AC and femur length (FL) (Snijders & Nicolaides 1994) and measurement of uterine artery PI, MAP by automated devices and measurement of maternal serum concentrations of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP (Cobas e411, Roche Diagnostics, Penzberg, Germany).

The patients included in the study were all pregnancies resulting in live birth or stillbirth of phenotypically normal babies.

2.2 Ethical committee approval

This project was part of a wider research programme on the third trimester prediction of PE and or SGA. Written informed consent, approved by the Ethics Committee of each participating hospital, was obtained from the women agreeing to participate in the study. See **Table 2.1**.

Table 2.1: Patient information leaflet

Patient information leaflet

Prediction of women at risk of preeclampsia and fetal growth restriction
We would like to invite you to take part in a research study. Before you decide whether to do so it is important for you to understand why the research is being done and what it will involve. Please take time to read this leaflet. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
We are looking for new ways through scientific research to improve the care of pregnant women and their unborn babies. As part of this work, we are inviting all women that attend for the 30-34 weeks scan to participate in a large study on preeclampsia (high blood pressure of pregnancy) and fetal growth restriction (poor fetal growth).

Preeclampsia and fetal growth restriction are two important complications of pregnancy, which can have serious implications for mother and baby. These problems can affect any pregnant woman, irrespective of previous healthy pregnancies and irrespective of how healthy the mother is.

Our aim is to try and identify the women who are at high risk of developing these problems and to do so as early in pregnancy as possible.

Why have I been chosen?
All pregnant women attending for the 30-34 weeks scan are welcome to take part in this study.

Do I have to take part?
It is up to you to decide whether you would like to take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. Once you have decided to take part you are still free to withdraw at any time without giving any reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
The study consists of three components which are done at the time of the 30-34 week scan:

1. Maternal blood markers
This involves us saving some of the blood that we take from you as part of the test to determine the risk for Down's syndrome. Since new tests may become available in the future we feel it would be prudent to store some of your blood sample for future studies.

2. Measurement of blood flow from the mother to the placenta
During your visit we will use ultrasound to examine your baby. We will also use ultrasound to look at the vessels that supply blood to the uterus and the placenta. This extra scan takes a couple of minutes to do. It is not uncomfortable and does not carry any risks to you or your baby.

3. Blood pressure measurement
During your visit we will measure your blood pressure. Usually this measurement is taken from your left arm. We are trying to find out if it is better to use the reading from the left or the right arm or the average one from both arms. We would take blood pressure measurements from both of your arms simultaneously.

What are the possible benefits of taking part?
If we find that you have high blood pressure we will arrange for any follow up tests and monitoring that would be necessary. This will have a direct benefit for you. In addition, the information we get from the study may help us to help you and/or other women in the future

What are the possible disadvantages and risks of taking part?
The blood pressure measurement may also be uncomfortable because of the inflation of the cuffs. If you find this examination intolerable please let us know, we will stop immediately.

Will my taking part in this study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential.

What if I want to complain?
If you have a concern about any aspect of this study, you can ask to speak with one of the researchers who will do their best to answer your questions. By agreeing to take part in the study you do not lose any legal rights. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital (Contact: Mr Tim Hiles on 0207 346 3983).

What will happen to the results of the research study?
It is hoped that the results will be published in medical journals and perhaps also in the press. You may request a copy of any published documents in relation to the study. You will not be identified in any of these reports.

Who is organising and funding the research?
This research is carried out by the team of Professor Kypros Nicolaides and it is funded by the Fetal Medicine Foundation (which is a registered charity).

We are requesting your permission to participate in the research study that essentially involves the following:
1. Maternal blood analysis
2. Measurement of blood flow to the placenta
3. Measurement of blood pressure

We hope that you find it worthwhile to take part in this study. If you should decide to participate, please sign the consent below. We would ask you to sign three copies of this form, one for your own records, one for our research, and one for your medical notes. Thank you.

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary, and that I am free to withdraw at any time, without affecting my medical care or legal rights.
• I agree / disagree to have a sample of my blood taken for current testing and storage for future tests

• I agree / disagree to the measurement of flow in the uterine arteries

• I agree / disagree to the measurement of my blood pressure.

Patient's name: ……
ID number: ……
Date: ……
Patient's signature: ……
Doctor's name: ……
Doctor's signature: ……

2.3 Recording of information

During a medical interview, the following information was recorded from each patient and documented electronically on computer software:

- Maternal age
- Race
- Method of conception
- Cigarettes smoking during pregnancy
- Chronic hypertension
- Pre-existing diabetes mellitus
- SLE
- APS
- Family history of PE in the mother of the patient
- Obstetric history including
- Parity
- Previous pregnancy with SGA
- Inter pregnancy time interval

The study population comprised 30,849 pregnancies, including 1,727 (5.6%) that delivered SGA neonates with a BW <5th centile (SGA <5th) in the absence of PE, and 29,122 (94.4%) cases that were unaffected by these outcomes. The characteristics of the study population are given in **Table 2.2**. The study population for biochemical markers and combined screening comprised of 9,003 pregnancies, with 469 (5.2%) that delivered SGA neonates with a BW <5th centile, in the absence of PE, and 8,534 (94.8%) cases that were unaffected by these outcomes, with the results given in **Table 2.3**.

2.4 Biophysical measurements

All women included in the study had the following measured and recorded:

1. Maternal height and weight and calculation of BMI in in Kg/m^2
2. Maternal blood pressure and calculation of MAP
3. Fetal HC, AC, FL and calculation of EFW
4. Umbilical artery Doppler PI
5. Middle Cerebral artery PI
6. Uterine artery PI in each artery

Table 2.2: Characteristics of the study population.

Characteristic	Normal (n=29,122)	SGA without PE (n=1,727)	P-value
Maternal age in years, median (IQR)	31.4 (26.9-35.1)	30.0 (25.3-34.5)	<0.0001*
Maternal weight in Kg, median (IQR)	75.6 (68.0-85.9)	69.3 (62.0-79.0)	<0.0001*
Maternal height in cm, median (IQR)	165 (160-169)	162 (157-166)	<0.0001*
GA at screening in weeks, median (IQR)	32.3 (32.0-32.9)	32.3 (32.0-33.0)	0.087
Racial origin			
Caucasian, n (%)	20,676 (71.0)	978 (56.6)	<0.0001*
Afro-Caribbean, n (%)	5,268 (18.1)	426 (24.7)	<0.0001*
South Asian, n (%)	1,587 (5.4)	204 (11.8)	<0.0001*
East Asian, n (%)	905 (3.1)	59 (3.4)	0.519
Mixed, n (%)	686 (2.4)	60 (3.5)	0.004*
Past obstetric history			
Nulliparous, n (%)	14,145 (48.6)	1,037 (60.0)	<0.0001*
Parous with no prior PE and SGA, n (%)	13,448 (46.2)	495 (28.7)	<0.0001*
Parous with prior PE no SGA, n (%)	720 (2.5)	37 (2.1)	0.435
Parous with prior SGA no PE, n (%)	734 (2.5)	137 (7.9)	<0.0001*
Parous with prior SGA and PE, n (%)	75 (0.3)	21 (1.2)	<0.0001*
Inter-pregnancy interval in years, median (IQR)	2.9 (1.9-4.8)	3.2 (2.1-5.6)	<0.0001*
Cigarette smoker, n (%)	2,501 (8.6)	343 (19.9)	<0.0001*
Conception			
Spontaneous, n (%)	28,017 (96.2)	1,668 (96.6)	0.462
Ovulation drugs, n (%)	307 (1.1)	23 (1.3)	0.332
In vitro fertilization, n (%)	798 (2.7)	36 (2.1)	0.120
Chronic hypertension (%)	321 (1.1)	36 (2.1)	0.0003*
Pre-existing diabetes mellitus, n (%)	288 (1.0)	12 (0.7)	0.281
Type 1, n (%)	109 (0.4)	2 (0.1)	0.125
Type 2, n (%)	179 (0.6)	10 (0.6)	0.980
SLE or APS, n (%)	54 (0.2)	5 (0.3)	0.497
GA at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	39.6 (38.4-40.6)	<0.0001*
BW in grams, median (IQR)	3,420 (3,125-3,730)	2,550 (2,324-2,730)	<0.0001*
BW in centile, median (IQR)	49.2 (26.2-74.4)	2.5 (1.3-3.7)	<0.0001*

SGA = small for gestational age; PE = preeclampsia; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; IQR = interquartile range.

Table 2.3: Characteristics of the study population for biochemical and combined screening.

Characteristic	Normal (n=9,003)	SGA without PE	
		Delivery <5w (n=51)	Delivery ≥5w (n=418)
Maternal age in years, median (IQR)	31.1 (26.8-34.8)	31.2 (26.1-36.1)	29.6 (25.0-33.9)*
Maternal weight in Kg, median (IQR)	76.9 (68.9-87.0)	72.4 (65.9-86.0)	70.0 (62.6-79.5)*
Maternal height in cm, median (IQR)	165 (160-169)	162 (158-167)*	162 (157-166)*
GA at screening in weeks, median (IQR)	32.2 (32.0-32.5)	32.1 (31.9-32.6)	32.1 (32.0-32.4)*
Racial origin			
Caucasian, n (%)	6,658 (74.0)	31 (60.8)	254 (60.8)*
Afro-Caribbean, n (%)	1,644 (18.3)	13 (25.5)	112 (26.8)*
South Asian, n (%)	332 (3.6)	2 (3.9)	33 (7.9)*
East Asian, n (%)	176 (2.0)	1 (2.0)	8 (1.9)
Mixed, n (%)	203 (2.3)	4 (7.8)	11 (2.6)
Past obstetric history			
- Nulliparous, n (%)	4,338 (48.2)	28 (54.9)	241 (57.7)*
Parous no prior PE and SGA, n (%)	4,139 (46.0)	17 (33.3)	136 (32.5)*
Parous prior PE no SGA, n (%)	271 (3.0)	1 (2.0)	7 (1.7)
Parous prior SGA no PE, n (%)	230 (2.6)	4 (7.8)	29 (6.9)*
Parous prior SGA and PE, n (%)	25 (0.3)	1 (2.0)	5 (1.2)*
Inter-pregnancy interval in years, median (IQR)	3.1 (2.1-5.1)	3.4 (2.4-8.2)	3.4 (2.3-5.6)*
Cigarette smoker, n (%)	844 (9.4)	9 (17.6)	94 (22.5)*
Conception			
Spontaneous, n (%)	8,712 (96.8)	48 (94.1)	406 (97.1)
Ovulation drugs, n (%)	81 (0.9)	2 (3.9)	4 (1.0)
In vitro fertilization, n (%)	210 (2.3)	1 (2.0)	8 (1.9)
Chronic hypertension (%)	97 (1.1)	2 (3.9)	5 (1.2)
Diabetes mellitus, n (%)	90 (1.0)	2 (4.0)	3 (0.7)
Type 1, n (%)	38 (0.4)	1 (2.0)	0 (0.0)
Type 2, n (%)	52 (0.6)	1 (2.0)	3 (0.7)
SLE or APS, n (%)	15 (0.2)	0 (0.0)	1 (0.2)
GA at delivery in weeks, median (IQR)	40.1 (39.0-40.9)	36.5 (35.1-37.0)*	40.0 (39.0-40.9)
BW in grams, median (IQR)	3,430 (3,144-3,750)	1,936 (1,770-2,198)*	2,604 (2,434-2,770)*
BW in centile, median (IQR)	50.6 (27.1-75.7)	2.2 (0.9-3.5)*	2.6 1.5-3.7)*

SGA = small for gestational age with BW <5th centile; PE = preeclampsia; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospolipid syndrome.

*Comparisons between outcome groups: Chi square test or Fisher exact test for categorical variables and Mann Whitney-U test or student t-test for continuous variables, with Bonferroni correction: * P<0.025

2.4.1 Maternal blood pressure and calculation of mean arterial pressure

Appropriately trained doctors used the 3BTO-A2 by Microlife (Microlife, Taipei, Taiwan) a validated automated device, to measure the maternal blood pressure. These devices were calibrated every 1,000 inflations. Patients were seated in a quite room, with a temperature set between 20°C and 24°C and allowed to rest for five minutes. Whilst in the seating position, patients had their arms supported at the level of the heart and appropriate cuffs were applied to each arm. Cuff size used was dependent on the mid-arm circumference, and cuffs of small (< 22 cm), medium (22-32 cm) or large (33-42 cm) were used (Pickering *et al.,* 2005). Simultaneous BP measurements were taken from both arms twice (**Figure 2.1**) and the MAP was calculated as the average of all four measurements (Poon *et al.,* 2012).

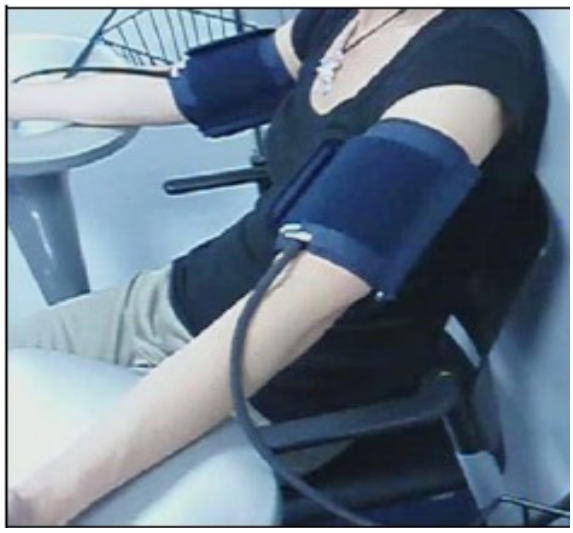

Figure 2.1: Simultaneous measurement of blood pressure in both arms.

2.4.2 Estimated fetal weight

The measurements of HC, BPD, AC and FL were conducted by operators trained and certified with the Certificate of Competence of The Fetal Medicine Foundation (https://fetalmedicine.org/the-18-23-weeks-scan).

The three-transabdominal images required to measure the fetal biometry are:

1. HC and biparietal diameter: Transverse view of the head at the level of the septum cavum pellucidum.
2. AC: Transverse view of the abdomen at the level of the stomach and umbilical vein.

3. FL: Longitudinal view of the femur.

The EFW was based on the formula by *et al.,* where the calculation follows the following formula (Hadlock *et al.,* 1985):

Log_{10} EFW =

1.3596 – 0.00386 (AC x FL) + 0.0064 (HC) + 0.00061 (BPD x AC) + 0.0425 (AC) + 0.174 (FL)

2.4.3 Uterine artery Doppler Pulsatility Index

UAD PI was measured by transabdominal ultrasound by obtaining a sagittal section of the uterus and with colour flow mapping moving on the probe laterally until the crossover of the uterine artery with the external iliac artery was visualised (see **Figure 2.2**) At this point pulsed-wave Doppler was used to obtain waveforms with the gate set at 2mm and with an angle of insonation of less than 30º. When three consecutively similar waveforms were attained the PI was measured and the mean PI of the two vessels was calculated (see **Figure 2.3**) (Albaiges *et al.,* 2000).

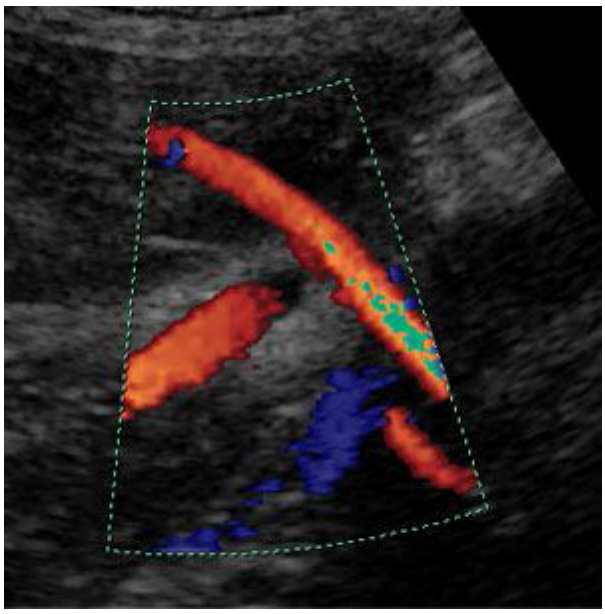

Figure 2.2: Image of sampling of the uterine artery via the transabdominal route

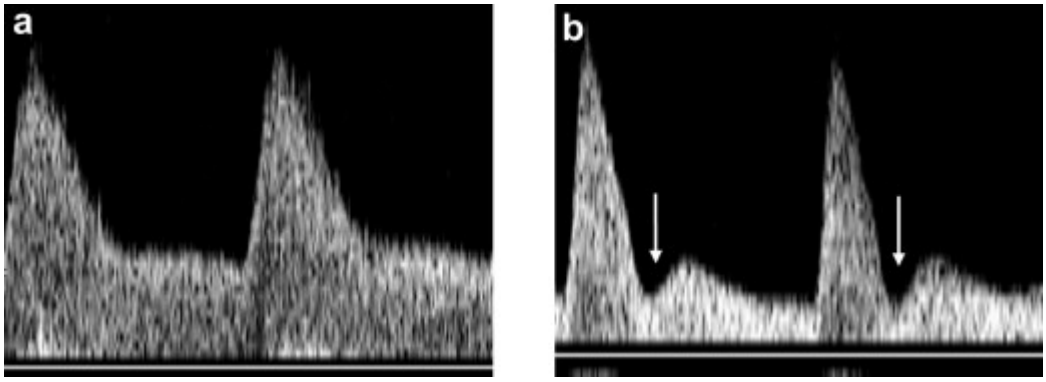

Figure 2.3: Uterine artery waveforms (a. normal resistance, b. increased resistance with notching).

2.4.4 Middle Cerebral artery Doppler PI

The MCA runs superior to the lesser wing of the sphenoid bone, hence, for its correct measurement, a transverse view of the fetal head at the level of the BPD is obtained and the transducer is then moved inferiorly. Using colour flow imaging, the circle of Willis can be visualised, and the MCA can be seen as a lateral branch of this, running in an anterolateral direction (**Figure 2.4**). The pulsed Doppler gate was placed over the central portion of this artery and, when three similar consecutive waveforms were obtained the PI was measured. Care was taken to ensure the angle of insonation was less than 30° and that minimal pressure was applied to the maternal abdomen to avoid compression of the fetal head (Nicolaides *et al.,* 2000; Vyas *et al.,* 1990).

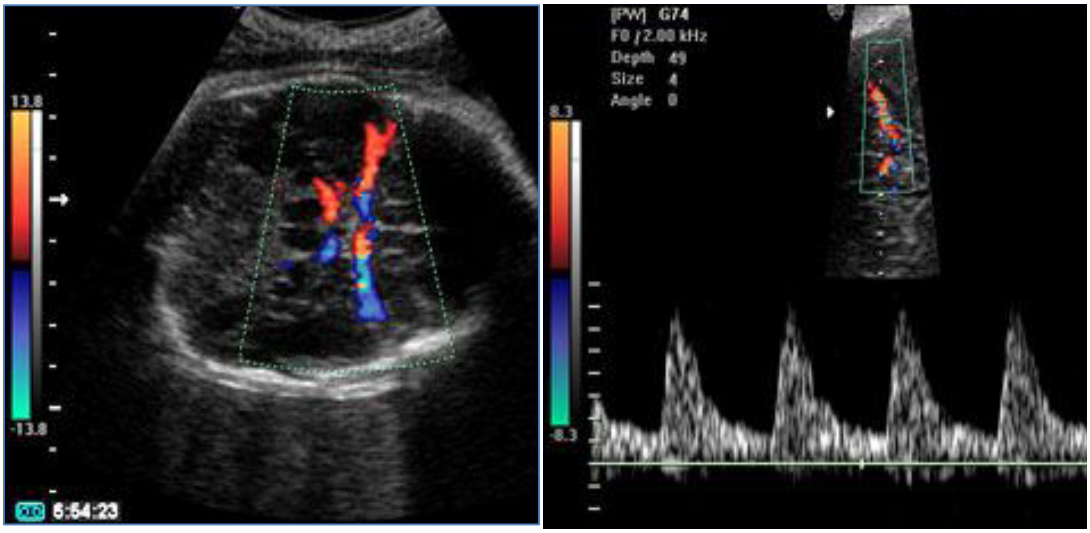

Figure 2.4: Transverse view of the fetal head with colour Doppler showing the circle of Willis (above). Flow velocity waveforms from the middle cerebral artery at 32 weeks of gestation (below).

2.4.5 Umbilical artery Doppler PI

A free-floating portion of the umbilical artery was identified transabdominally and using colour flow imaging the pulsed Doppler gate was placed over the central portion of this artery and, when three similar consecutive waveforms were obtained the PI was measured (see **Figure 2.5**) (Nicolaides *et al.,* 2000; Acharya *et al.,* 2005).

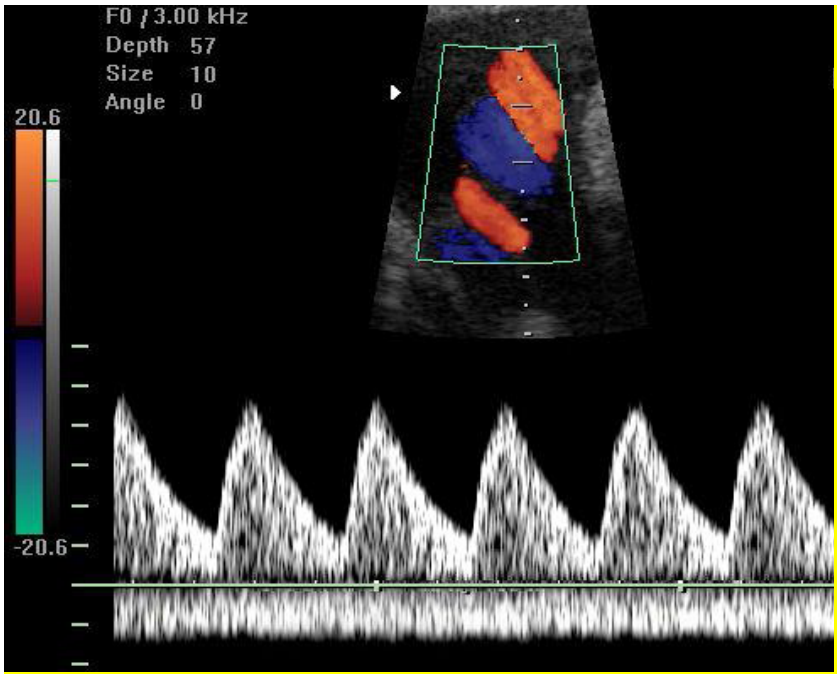

Figure 2.5: Normal flow velocity waveforms from the umbilical artery at 32 weeks of gestation.

2.5 Biochemical measurements

Using an automated electrochemiluminescence immunoassay system by Roche (Cobas e411, Roche Diagnostics, Penzberg, Germany), serum sFlt-1, IGF, PAPP-A, free ß-hCG and AFP were measured in parallel.

The inter-assay coefficients of variation for the low and high concentrations were 3.0 and 3.2% for sFlt-1 and 5.4 and 3.0% for PlGF. The intra-assay and inter-assay variations were 1.2% and 2.1%, respectively, at a PAPP-A concentration of 462 mU/L, 1.4% and 2.3% at 2124 mU/L and 1.3% and 2.5% at 5543 mU/L. The intra-assay and inter-assay variations were 1.8% and 3.2%, respectively, at a AFP concentration of 2.39 mU/L.

2.6 Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The primary outcome of the study was SGA without PE. Other outcomes measures of the study were stillbirth, CS for fetal distress in labour, umbilical artery cord blood pH $\leq$7.0, umbilical venous blood pH $\leq$7.1, Apgar score <7 at 5 minutes, admission to the NNU and admission to the Neonatal Intensive Care Unit (NICU).

The newborn was considered to be SGA if the BW was <5th centile after correction for gestational age at delivery (Poon, *et al.,* 2012).

The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy (Brown *et al.,* 2001). The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to confirm if the condition was chronic hypertension, PE or GH.

2.7 Statistical analysis

2.7.1 Analysis of fetal biometry, uterine artery Doppler's and maternal serum biochemistry

The observed measurements of fetal HC, AC, FL and EFW were expressed as the respective Z-score and centile, corrected for gestational age (Snijders & Nicolaides 1994) (Poon, Volpe, *et al.,* 2012). Mann Whitney-U test was used to compare the Z-score and centile values of HC, AC, FL and EFW between the SGA and unaffected groups. Linear regression analysis was used to determine the significance of association between HC Z-score, AC Z-score, FL Z-score and EFW Z-score with assessment to delivery interval.

The values of uterine artery PI and MAP and the values of serum PlGF, sFlt-1, PAPP-A, free β-hCG and AFP were $\log_{10}$ transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the $\log_{10}$ transformed value (Tayyar *et al.,* 2015; A. Wright

et al., 2015; Tsiakkas *et al.,* 2015; Tsiakkas *et al.,* 2015; D. Wright *et al.,* 2015; Bredaki *et al.,* 2015; McIntire *et al.,* 1999)

Mann Whitney-U test was used to compare the median MoM values of uterine artery PI, MAP and the serum metabolites between the outcome groups. Regression analysis was used to determine the significance of association between $\log_{10}$ MoM of uterine artery PI, MAP and each biochemical marker with assessment to delivery interval and BW Z-score.

The *a priori* risk for SGA<5th delivering at <5 weeks of assessment were calculated using multivariable logistic regression analysis with backward stepwise elimination to determine which of the factors among maternal characteristics and obstetric history had a significant contribution in predicting SGA<5th delivering at <5 weeks of assessment. The *a priori* risk for SGA<5th delivering at ≥5 weeks of assessment was determined using the algorithm derived from the multivariable logistic regression analysis for the prediction of SGA<5th delivering at <5 weeks of assessment.

Multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (*a priori* risks), HC Z-score, AC Z-score, FL Z-score, EFW Z-score $\log_{10}$ MoM uterine artery PI, $\log_{10}$ MoM MAP and $\log_{10}$ MoM value of each biochemical marker had a significant contribution in predicting SGA<5th delivering at <5 and at ≥5 weeks of assessment.

The performance of screening was determined by receiver operating characteristic (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by BW <10th centile (SGA<10th) and SGA with BW <3rd centile (SGA<3rd).

2.7.2 Statistical analysis for combined screening

The observed measurements of EFW were expressed as Z-scores, corrected for gestational age (Poon, Volpe, *et al.,* 2012). The values of uterine artery PI, MAP and serum PlGF and sFlt-1 were $\log_{10}$ transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the transformed $\log_{10}$ value (Tayyar *et al.,* 2015; A. Wright *et al.,* 2015; Tsiakkas, 2015; Tsiakkas, 2015b). Mann Whitney-U test was used to

compare the median MoM values of the biomarkers between the outcome groups and regression analysis was used to determine the significance of association between $\log_{10}$ MoM of each biomarker with assessment to delivery interval and BW Z-score.

The *a priori* risk for SGA <5th delivering at <5 weeks of assessment was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history as previously described (**section 2.7.1**). Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a priori* risk), EFW Z-score and $\log_{10}$ MoM value of each biomarker had a significant contribution in predicting SGA <5th delivering at <5 and at ≥5 weeks of assessment. The performance of screening was determined by receiver operating characteristic (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by BW <10th centile (SGA <10th) and SGA with BW <3rd centile (SGA <3rd).

2.7.3 Statistical analysis of umbilical and fetal middle cerebral artery

Comparison between the outcome groups was by χ2-test or Fisher's exact test for categorical variables and Mann Whitney-U test for continuous variables. Categorical data are presented as n (%) and continuous data as median and interquartile range (IQR).

The measured MCA PI and UA PI were expressed as multiples of the median (MoM) after adjustment for variables from maternal characteristics and medical history that affect these measurements (Akolekar *et al.,* 2015). The CPR was calculated by dividing MCA PI MoM with UA PI MoM.

Regression analysis was used to examine the association between CPR ($\log_{10}$ MoM) and BW Z-score in the study population as well as within each weekly interval from assessment to delivery. The slope of the regression line in each weekly interval was compared to the slope of the regression line in the subsequent interval using Potthoff analysis (Potthoff 2015).

The association between CPR ($\log_{10}$ MoM) and BW Z-score in each of the adverse outcome groups and those without the adverse outcome was examined in scatterplots. Univariable and multivariable logistic regression analysis was used to determine if CPR ($\log_{10}$ MoM) had a significant additional contribution to maternal characteristics,

medical history and obstetric factors in predicting adverse outcome. The DR, false positive rate (FPR) and positive predictive value (PPV) of screening by CPR were estimated for each adverse outcome.

2.7.4 Software

The statistical software package used through out this study was SPSS 22.0 (SPSS Inc.,Chicago, IL) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

Chapter 3: Maternal factors and fetal biometry at 30-34 weeks

ABSTRACT

Objective: To investigate the value of fetal biometry at 30-34 weeks' gestation in the prediction of delivery of SGA neonates, in the absence of PE.

Methods: Screening study in singleton pregnancies at 30-34 weeks, including 1,727 that delivered SGA neonates with BW <5th centile and 29,122 cases unaffected by SGA, PE or GH. Multivariable logistic regression analysis was used to determine if screening by a combination of maternal factors and Z-scores of fetal HC, AC and FL or EFW had significant contribution in predicting SGA neonates.

Results: Combined screening by maternal characteristics and history with EFW Z-scores at 30-34 weeks, predicted 80%, 87% and 92% of SGA neonates delivering at <5 weeks of assessment with BW <10th, <5th and <3rd centiles, respectively, at 10% false positive rate. The respective detection rates for prediction of SGA neonates delivering at ≥5 weeks of assessment were 52%, 58% and 61%. The performance of screening by a combination of Z-scores for fetal HC, AC and FL was similar to that achieved by the EFW Z-score.

Conclusion: Combined testing by maternal characteristics and fetal biometry at 30-34 weeks could identify a high proportion of pregnancies that deliver SGA neonates.

This chapter is based on:

Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 30-34 weeks. Ultrasound Obstet Gynecol. 2015 May;45(5):551-8.

3.1 Introduction

A few studies in small numbers of low-risk singleton pregnancies have examined the potential value of sonographic fetal biometry during the third trimester in the prediction of SGA neonates (Chapter 1, section 1.5.3). The studies reported that the fetal AC and EFW, performed equally well in the prediction of SGA neonates with BW <10th centile and the DR were about 45% at false positive rate (FPR) of 10% (Skovron *et al.,* 1991; David *et al.,* 1996; Souka *et al.,* 2012; Souka *et al.,* 2013), 53-63% at FPR of 20% (Skovron *et al.,* 1991; David *et al.,* 1996; De Reu *et al.,* 2008) and 73% at FPR of 25% (Di Lorenzo *et al.,* 2013). The performance of screening may be higher for prediction of SGA with BW <5th centile with DR of 60% at FPR of 10% (Rosendahl & Kivinen 1991).

3.1.1 Objectives

The objectives of this study in a large population of 30,849 singleton pregnancies undergoing routine antenatal care are firstly, to investigate further the potential value of fetal biometry at 30^{+0}-34^{+6} weeks' gestation in the prediction of delivery of SGA neonates in the absence of PE and secondly, combine these fetal biometric measurements with maternal characteristics and history to develop specific algorithms for the calculation of patient-specific risks for SGA.

3.2 Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at 30^{+0}-34^{+6} weeks' gestation. The methodology for recording of patient characteristics, sonographic estimation of EFW, outcome measures and statistical analysis was as described in Chapter 2.

3.3 Results

The study population comprised 30,849 pregnancies, including 1,727 (5.6%) that delivered SGA<5th neonates, in the absence of PE, and 29,122 (94.4%) cases that were unaffected by these outcomes. The characteristics of the study population are

given in Chaper 2. There were significant (P<0.0001) inter-correlations between Z-score values of HC, AC, FL and EFW in both the SGA and normal outcome groups (**Table 3.1**).

3.3.1 Normal pregnancy outcome

The normal ranges of Z-scores and centiles of HC, AC, FL and EFW are presented in **Table 3.2**. There was a significant polynomial association between HC Z-score with assessment to delivery interval (-0.481 + 0.110 * delivery interval – 0.014 * delivery interval^2 + 0.001 * delivery interval^3; r=0.070; P<0.0001), between AC Z-score with assessment to delivery interval (-0.370 + 0.097 * delivery interval – 0.014 * delivery interval^2 + 0.001 * delivery interval^3; r=0.031; P<0.0001), between FL Z-score with assessment to delivery interval (-0.351 + 0.075 * delivery interval – 0.004 * delivery interval^2; r=0.053; P<0.0001) and there was a significant linear association between EFW Z-score with assessment to delivery interval (0.257 + 0.027 * delivery interval; r=0.067; P<0.0001).

Table 3.2: Normal ranges of Z-scores of fetal head circumference, abdominal circumference, femur length and estimated fetal weight at 30-34 weeks' gestation

	Head circumference	Abdominal circumference	Femur length	Estimated fetal weight
Standard deviation	0.609	0.590	0.671	0.672
50th centile	-0.163	-0.152	-0.051	0.414
5th centile	-1.107	-1.076	-1.110	-0.534
10th centile	-0.908	-0.880	-0.885	-0.337
90th centile	0.648	0.618	0.829	1.312
95th centile	0.879	0.839	1.063	1.585

3.3.2 Small for gestational age

In the SGA<5th group, compared to the normal group, the median Z-score and centile values of HC AC, FL and EFW at 30-34 weeks were significantly lower (**Table 3.3**). There was a significant polynomial association between HC Z-score with assessment to delivery interval (-1.927 + 0.418 * delivery interval – 0.051 * delivery interval^2 + 0.002 * delivery interval^3; r=0.310; P<0.0001; **Figure 3.1**), between AC Z-score with assessment to delivery interval (-2.878 + 0.674 * delivery interval – 0.081 * delivery interval^2 + 0.004 * delivery interval^3; r=0.458; P<0.0001; **Figure 3.1**), between FL Z-score with assessment to delivery interval (-2.656 + 0.649 * delivery interval – 0.067

* delivery interval^2 + 0.003 * delivery interval^3; r=0.391; P<0.0001; **Figure 3.1**) and between EFW Z-score with assessment to delivery interval (-2.362 + 0.577 * delivery interval – 0.062 * delivery interval^2 + 0.003 * delivery interval^3; r=0.507; P<0.0001; **Figure 3.1**).

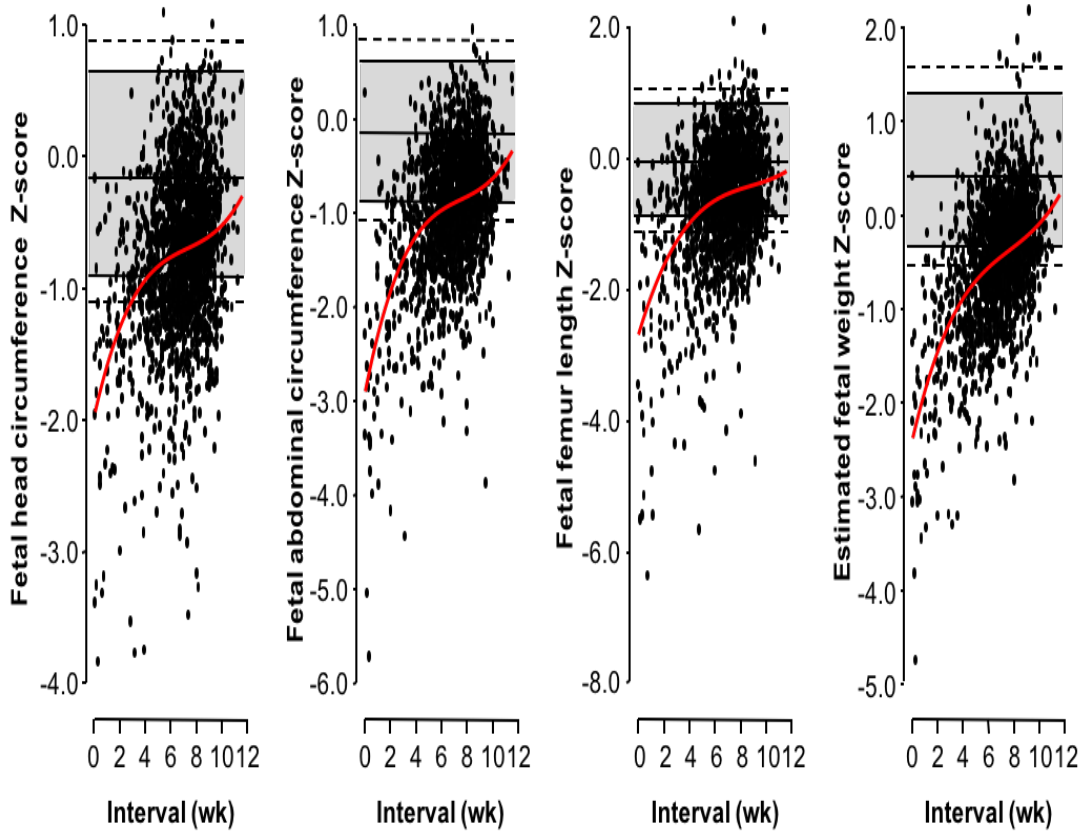

Figure 3.1: Z-scores for fetal head circumference, abdominal circumference, femur length and estimated fetal weight at 30-34 weeks' gestation with assessment to delivery interval in pregnancies delivering small for gestational age neonates with BW below the 5th centile, plotted on the 50th, 5th, 10th, 90th and 95th centile of the normal range. Red line indicates fitted mean from regression model.

The *a priori* risk for SGA<5th delivering at <5 weeks of assessment is calculated from the following formula: odds/(1+odds), where odds=e^{Y} and Y is derived from multivariable logistic regression analysis. Regression coefficients and AOR of each of the maternal factors in the prediction algorithms are presented in **Table 3.4** R2=0.063, P<0.0001).

Table 3.1: Pearson correlation between Z-score values of head circumference, abdominal circumference, femur length and estimated fetal weights at 30-34 weeks' gestation in the normal and small for gestational age groups.

Z-score values		Z-score values											
		Head circumference			Abdominal circumference			Femur length			Estimated fetal weight		
		Normal	SGA		Normal	SGA		Normal	SGA		Normal	SGA	
			<5w	>5w		<5w	>5w		<5w	>5w		<5w	>5w
Head circumference	r	1	1	1	0.331	0.500	0.280	0.171	0.449	0.147	0.549	0.639	0.502
	p	-	-	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Abdominal circumference	r	0.331	0.500	0.280	1	1	1	0.200	0.541	0.242	0.886	0.917	0.858
	p	<0.0001	<0.0001	<0.0001	-	-	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Femur length	r	0.171	0.449	0.147	0.200	0.541	0.242	1	1	1	0.516	0.778	0.554
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	-	-	-	<0.0001	<0.0001	<0.0001
Estimated fetal weight	r	0.549	0.639	0.502	0.886	0.917	0.858	0.516	0.778	0.554	1	1	1
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	-	-	-

r = Pearson correlation, SGA = small for gestational a

Table 3.3: Fetal head circumference, abdominal circumference, femur length and estimated fetal weight at 30-34 weeks' gestation in the normal and small for gestational age groups.

Biometry	Normal outcome (n=29,122)	Small for gestational age with BW <5th centile	
		Delivery at <5 weeks (n=277)	Delivery at ≥5 weeks (n=1,450)
Head circumference			
Value in mm	301.6 (295.0 to 308.5)	293.4 (285.0 to 299.8)*	293.9 (287.5 to 300.2)*
Z-score	-0.163 (-0.566 to 0.266)	-0.991 (-1.415 to -0.612)*	-0.661 (-1.069 to -0.273)*
Percentile in %,	43.5 (28.6 to 60.5)	16.1 (7.9 to 27.0)*	25.4 (14.2 to 39.2)*
<5th centile in Z-score,	1,456 (5.0, 4.8 to 5.3)	120 (43.3, 37.6 to 49.2)*	313 (21.6, 19.5 to 23.8)*
<10th centile in Z-score	2912 (10.0, 9.7 to 10.3)	157 (56.7, 50.8 to 62.4)*	504 (34.8, 32.4 to 37.2)*
Abdominal circumference			
Value in mm	284.3 (275.7 to 293.7)	265.8 (251.8 to 276.8)*	270.2 (262.3 to 278.1)*
Z-score	-0.152 (-0.540 to 0.251)	-1.385 (-1.944 to -0.901)*	-0.852 (-1.192 to -0.492)*
Percentile in %,	44.0 (29.5 to 59.9)	8.3 (2.6 to 18.4)*	19.7 (11.7 to 31.1)*
<5th centile in Z-score,	1,456 (5.0, 4.8 to 5.3)	184 (66.4, 60.7 to 71.7)*	477 (32.9, 30.5 to 35.4)*
<10th centile in Z-score	2912 (10.0, 9.7 to 10.3)	211 (76.2, 70.8 to 80.8)*	691 (47.7, 45.1 to 50.2)*
Femur length			
Value in mm	62.0 (60.5 to 63.7)	60.1 (57.1 to 62.6)*	60.7 (59.0 to 62.3)*
Z-score	-0.051 (-0.493 to 0.415)	-0.905 (-1.827 to -0.454)*	-0.488 (-0.936 to -0.016)*
Percentile in %,	48.0 (31.1 to 66.1)	18.3 (3.4 to 32.8)*	31.3 (17.5 to 49.4)*
<5th centile in Z-score,	1,456 (5.0, 4.8 to 5.3)	121 (43.7, 38.0 to 49.6)*	263 (18.1, 16.2 to 20.2)*
<10th centile in Z-score	2912 (10.0, 9.7 to 10.3)	144 (52.0, 46.1 to 57.8)*	393 (27.1, 24.9 to 29.4)*
Estimated fetal weight			
Value in g	2,202 (1,883-2,177)	1,735 (1,510 to 1,911)*	1,796 (1,678 to 1,917)*
Z-score	0.414 (-0.006 to 0.871)	-1.096 (-1.556 to -0.516)*	-0.382 (-0.716 to -0.009)*
Percentile in %,	66.1 (49.8 to 80.8)	13.6 (6.0 to 30.3)*	35.1 (23.7 to 49.6)*
<5th centile in Z-score,	1,456 (5.0, 4.8 to 5.3)	206 (74.4, 68.9 to 79.2)*	561 (38.7, 36.2 to 41.2)*
<10th centile in Z-score	2912 (10.0, 9.7 to 10.3)	232 (83.8, 79.0 to 87.6)*	782 (53.9, 51.4 to 56.5)*

Values in median (IQR) or n (%, 95% CI). IQR = interquartile range; GA = gestational age; CI = confidence interval; SGA = small for gestational age with BW below the 5th centile in the absence of preeclampsia. Comparisons between outcome groups: Chi square test or Fisher exact test for categorical variables and Mann Whitney-U test or student t-test, with Bonferroni correction: * P<0.025

The likelihood of SGA<5th delivering at <5 weeks of assessment decreased with maternal weight and height, and in parous women the risk increased with inter-pregnancy interval (**Figure 3.2**). The risk was higher in women of Afro-Caribbean, South Asian and mixed racial origins, in cigarette smokers, in nulliparous women, and in those with prior history of SGA, and in women with chronic hypertension. The risk was lower in parous women without prior history of SGA, with or without prior PE. The likelihood of SGA<5th delivering at <5 weeks of assessment was not significantly altered by maternal age (P=0.236), method of conception (P=0.229), SLE or APS (P=0.998) and pre-existing diabetes (P=0.991).

Table 3.4: Fitted regression model with maternal characteristics and history for the prediction of small for gestational age neonate with BW below the 5th centile delivering at <5 weeks of assessment in the absence of preeclampsia.

Independent variable	Coefficient	SE	OR	95% CI	P-value
Intercept	-1.24994	0.51502			
Weight in Kg – 75	-0.01446	0.00507	0.986	0.976-0.995	0.004
Height in cm – 165	-0.04609	0.01028	0.955	0.936-0.974	<0.0001
Racial origin					
Caucasian (reference)	0		1		
Afro-Caribbean	0.36948	0.16145	1.447	1.054-1.986	0.022
South Asian	0.59037	0.20960	1.805	1.197-2.721	0.005
Mixed	0.91974	0.20960	2.509	1.488-4.230	0.001
Cigarette smoking	1.00688	0.15833	2.737	2.007-3.733	<0.0001
Past obstetric history					
Nulliparous	1.03986	0.16132	2.829	2.062-3.881	<0.0001
Parous					
No previous SGA (reference)	-4.61445	0.15481	0.004		
Inter-pregnancy interval in years	0.08435	0.02120	1.107	1.062-1.154	<0.0001
Previous SGA	1.41074	0.22773	5.445	3.485-8.508	<0.0001
Previous SGA and PE	1.75066	0.52662	8.191	2.918-22.993	<0.0001
Chronic hypertension	1.36986	0.32568	3.935	2.078-7.450	<0.0001

SE = standard error; OR = odds ratio; CI = confidence interval; SGA = small for gestational age; PE = preeclampsia

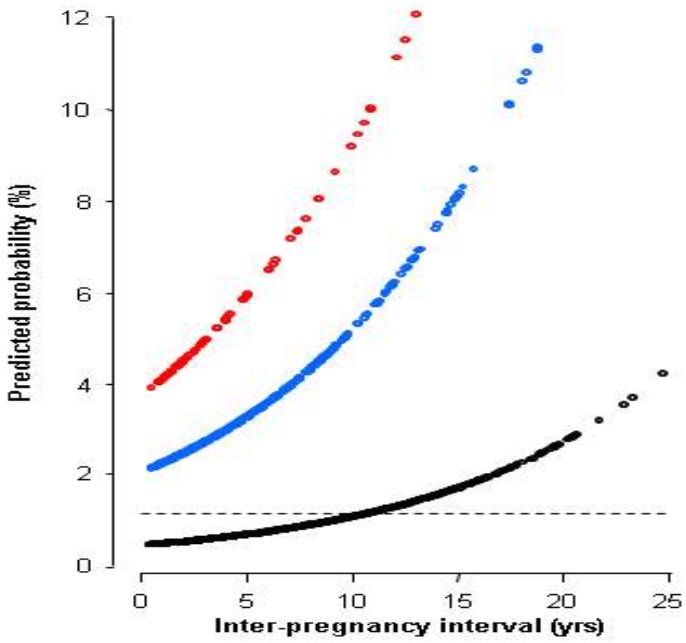

Figure 3.2: Relationship between predicted probability of delivering a small for gestational age (SGA) neonate, with BW below the 5th centile, within five weeks of assessment at 30-34 weeks' gestation and inter-pregnancy interval in parous women without previous SGA or preeclampsia (PE) (black circles), parous women with previous SGA in the absence of PE (blue circles) and parous women with previous SGA and PE (red circles). The black horizontal line represents the probability in nulliparous women.

Multivariable logistic regression analyses demonstrated that in the prediction of SGA<5th delivering at <5 weeks and ≥5 weeks of assessment there were significant contributions from maternal characteristics and a combination of HC Z-score, AC Z-score and FL Z-score or EFW Z-score (**Tables 3.5 and 3.6**).

Table 3.5: Fitted regression models with maternal characteristics and history, fetal head circumference Z-score, abdominal circumference Z-score, femur length Z-score or estimated fetal weight Z-score at 30-34 weeks' gestation for the prediction of small for gestational age with BW below the 5th centile delivering at <5 weeks of assessment in the absence of preeclampsia.

Independent variable	Coefficient	SE	OR	95% CI	P-value
HC Z-score, AC Z-score and FL Z-score (R2=0.433, P<0.0001)					
Intercept	-7.52720	0.20024			
HC Z-score	-2.42648	0.30044	0.088	0.049-0.159	<0.0001
HC Z-score^2	-0.81282	0.12461	0.443	0.347-0.566	<0.0001
AC Z-score	-2.26170	0.12708	0.104	0.081-0.134	<0.0001
FL Z-score	-0.86755	0.08926	0.420	0.353-0.500	<0.0001
EFW Z-score (R2=0.436, P<0.0001)					
Intercept	-5.67418	0.13538			
EFW Z-score	-4.34810	0.23556	0.013	0.008-0.021	<0.0001
EFW Z-score^2	-0.62383	0.09225	0.536	0.447-0.642	<0.0001
Maternal characteristics and history with HC Z-score, AC Z-score and FL Z-score (R2=0.458, P<0.0001)					
Intercept	-3.95175	0.42120			
Logit(*a priori* risks)	1.78036	0.19790	5.932	4.025-8.743	<0.0001
HC Z-score	-2.30839	0.30261	0.099	0.055-0.180	<0.0001
HC Z-score^2	-0.77613	0.12678	0.460	0.359-0.590	<0.0001
AC Z-score	-2.24418	0.12728	0.106	0.083-0.136	<0.0001
FL Z-score	-0.86874	0.09094	0.419	0.351-0.501	<0.0001
Maternal characteristics and history with EFW Z-score (R2=0.459, P<0.0001)					
Intercept	-2.31283	0.39855			
Logit(*a priori* risks)	1.67538	0.19715	5.341	3.629-7.860	<0.0001
EFW Z-score	-4.16178	0.24611	0.016	0.010-0.025	<0.0001
EFW Z-score^2	-0.54344	0.09969	0.581	0.478-0.706	<0.0001

SE = standard error; OR = odds ratio; CI = confidence interval

The areas under ROC and the detection rates of SGA<10th, SGA<5th and SGA<3rd delivering at <5 and ≥5 weeks of assessment for false positive rates of 5% and 10% in screening by maternal characteristics and a combination of HC Z-score, AC Z-score and FL Z-score or EFW Z-score are given in **Table 3.7 and 3.8 and Figure 3.3**. In the prediction of SGA<5th delivering at <5 and ≥5 weeks of assessment with a combination of maternal characteristics and EFW Z-score the negative predictive values were 99.9% (95% CI 99.8-99.9) and 97.8% (95% CI 97.6-97.9), respectively.

The respective numbers needed to screen were 1.29 (95% CI 1.24-1.36) and 2.07 (95% CI 2.00-2.14).

Table 3.6: Fitted regression models with maternal characteristics and history, fetal head circumference Z-score, abdominal circumference Z-score, femur length Z-score or estimated fetal weight Z-score at 30-34 weeks' gestation for the prediction of small for gestational age with BW below the 5th centile delivering at ≥5 weeks of assessment in the absence of preeclampsia.

Independent variable	Coefficient	SE	OR	95% CI	P-value
HC Z-score, AC Z-score and FL Z-score (R2=0.241, P<0.0001)					
Intercept	-4.36753	0.06268			
HC Z-score	-1.13491	0.09170	0.321	0.269-0.385	<0.0001
HC Z-score^2	-0.29444	0.05674	0.745	0.667-0.833	<0.0001
AC Z-score	-2.18002	0.11909	0.113	0.090-0.143	<0.0001
AC Z-score^2	-0.31439	0.06362	0.730	0.645-0.827	<0.0001
FL Z-score	-0.58240	0.05752	0.559	0.499-0.625	<0.0001
FL Z-score^2	-0.07834	0.03458	0.925	0.864-0.989	0.023
EFW Z-score (R2=0.231, P<0.0001)					
Intercept	-2.85683	0.03345			
EFW Z-score	-2.42887	0.07107	0.088	0.077-0.101	<0.0001
EFW Z-score^2	-0.40316	0.05735	0.668	0.597-0.748	<0.0001
Maternal characteristics and history with HC Z-score, AC Z-score and FL Z-score (R2=0.282, P<0.0001)					
Intercept	-0.70884	0.17935			
Logit(*a priori* risks)	1.77018	0.08558	5.872	4.965-6.944	<0.0001
HC Z-score	-1.00823	0.09241	0.365	0.304-0.437	<0.0001
HC Z-score^2	-0.24742	0.05794	0.781	0.697-0.875	<0.0001
AC Z-score	-2.05486	0.11932	0.128	0.101-0.162	<0.0001
AC Z-score^2	-0.26932	0.06421	0.764	0.674-0.866	<0.0001
FL Z-score	-0.49362	0.05809	0.610	0.545-0.684	<0.0001
FL Z-score^2	-0.07386	0.03443	0.929	0.868-0.994	0.033
Maternal characteristics and history with EFW Z-score (R2=0.272, P<0.0001)					
Intercept	0.68669	0.16661			
Logit(*a priori* risks)	1.76398	0.08464	5.836	4.944-6.889	<0.0001
EFW Z-score	-2.24402	0.07108	0.106	0.092-0.122	<0.0001
EFW Z-score^2	-0.34162	0.05818	0.711	0.634-0.796	<0.0001

SE = standard error; OR = odds ratio; CI = confidence interval

3.4 Discussion

3.4.1 Main findings of the study

The study shows that there are several maternal characteristics that influence the risk of delivering, in the absence of PE, a SGA neonate within five weeks of assessment at 30-34 weeks' gestation. The risk increases in cigarette smokers, in

Figure 3.3: Receiver operating characteristics curves of maternal characteristics (black line), combination of maternal characteristics with fetal head circumference, abdominal circumference and femur length Z-score (blue line) and the combination of maternal characteristics with estimated fetal weight Z-score (red line) at 30-34 weeks' gestation in the prediction of small for gestational age neonates with BW below the 10th the 5th and 3rd centile, delivering at <5 (left) and ≥5 (right) weeks of assessment.

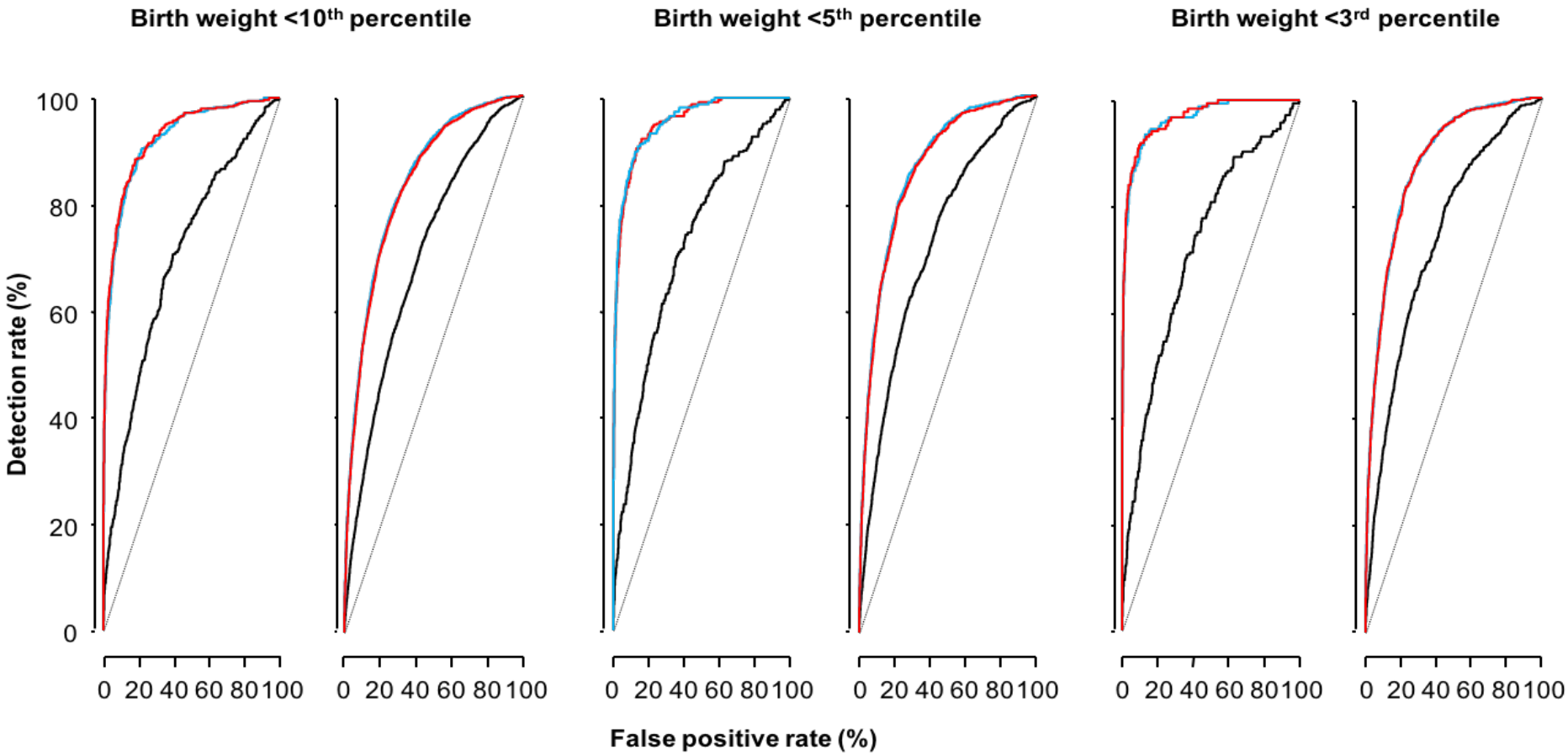

Table 3.7: Area under receiver operating characteristic curve, with 95% confidence interval, of screening for small for gestational age with BW <10th, <5th and <3rd centile in the absence of preeclampsia, delivering at <5 and ≥5 weeks of assessment with maternal characteristics and history, fetal head circumference Z-score, abdominal circumference Z-score, femur length Z-score or estimated fetal weight Z-score at 30-34 weeks' gestation.

Screening test	Small for gestational age	
	Delivery at <5 weeks	Delivery at ≥5 weeks
SGA <10th centile		
Maternal factors	0.699 (0.693-0.704)	0.698 (0.693-0.703)
HC Z-score	0.812 (0.807-0.816)	0.709 (0.703-0.714)
AC Z-score	0.884 (0.880-0.887)	0.785 (0.780-0.790)
FL Z-score	0.781 (0.777-0.786)	0.646 (0.641-0.652)
Z-scores for HC, AC, FL	0.910 (0.907-0.914)	0.815 (0.811-0.820)
EFW Z-score	0.917 (0.914-0.920)	0.810 (0.805-0.814)
Maternal factors plus		
HC Z-score	0.842 (0.838-0.847)	0.764 (0.759-0.769)
AC Z-score	0.899 (0.896-0.903)	0.818 (0.814-0.822)
FL Z-score	0.825 (0.820-0.829)	0.726 (0.721-0.731)
Z-scores for HC, AC, FL	0.920 (0.917-0.923)	0.837 (0.832-0.841)
EFW Z-score	0.925 (0.922-0.928)	0.831 (0.827-0.836)
SGA <5th centile		
Maternal factors	0.718 (0.712-0.723)	0.723 (0.718-0.728)
HC Z-score	0.854 (0.851-0.858)	0.732 (0.727-0.737)
AC Z-score	0.913 (0.910-0.917)	0.811 (0.807-0.815)
FL Z-score	0.822 (0.818-0.827)	0.677 (0.672-0.682)
Z-scores for HC, AC, FL	0.945 (0.942-0.947)	0.843 (0.838-0.847)
EFW Z-score	0.944 (0.941-0.947)	0.837 (0.833-0.841)
Maternal factors plus		
HC Z-score	0.882 (0.878-0.885)	0.792 (0.788-0.797)
AC Z-score	0.930 (0.927-0.933)	0.846 (0.841-0.850)
FL Z-score	0.866 (0.862-0.870)	0.760 (0.755-0.765)
Z-scores for HC, AC, FL	0.954 (0.951-0.956)	0.864 (0.860-0.868)
EFW Z-score	0.953 (0.950-0.955)	0.859 (0.855-0.863)
SGA <3rd centile		
Maternal factors	0.718 (0.713-0.724)	0.736 (0.731-0.741)
HC Z-score	0.887 (0.883-0.890)	0.739 (0.734-0.744)
AC Z-score	0.935 (0.932-0.938)	0.826 (0.822-0.830)
FL Z-score	0.846 (0.842-0.850)	0.695 (0.689-0.700)
Z-scores for HC, AC, FL	0.961 (0.959-0.963)	0.856 (0.852-0.860)
EFW Z-score	0.960 (0.957-0.962)	0.854 (0.850-0.858)
Maternal factors plus		
HC Z-score	0.900 (0.897-0.903)	0.803 (0.799-0.808)
AC Z-score	0.946 (0.943-0.949)	0.860 (0.856-0.864)
FL Z-score	0.887 (0.883-0.890)	0.779 (0.774-0.784)
Z-scores for HC, AC, FL	0.966 (0.964-0.968)	0.877 (0.873-0.881)
EFW Z-score	0.965 (0.963-0.967)	0.876 (0.872-0.880)

those with pre-existing chronic hypertension, in women with prior history of SGA with or without PE and with inter-pregnancy interval. The risk is also higher in women of Afro-Caribbean or South Asian racial origin than in Caucasian women. The risk

decreases with maternal weight and height. In parous women without previous history of SGA, with or without prior PE, the risk of delivering SGA neonates in the current pregnancy is reduced and remains so for a period of up to 10 years from the last pregnancy. Screening for SGA with BW <10th, <5th and <3rd

Table 3.8: Detection rate, with 95% confidence interval, of screening for small for gestational age with BW <10th, <5th and <3rd centile in the absence of preeclampsia, delivering at <5 and ≥5 weeks of assessment with maternal characteristics and history, fetal head circumference Z-score, abdominal circumference Z-score, femur length Z-score or estimated fetal weight Z-score at 30-34 weeks' gestation.

Screening test	Small for gestational age			
	Delivery at <5 weeks		Delivery at ≥5 weeks	
	Detection rate (%) for fixed false positive rate (95% CI)			
	5%	10%	5%	10%
SGA <10th centile				
Maternal factors	19.5 (15.9-23.4)	30.4 (26.2-34.9)	17.0 (15.7-18.4)	27.6 (26.0-29.3)
HC Z-score	37.1 (32.6-41.8)	51.0 (46.3-55.7)	19.0 (17.6-20.4)	30.2 (28.6-31.9)
AC Z-score	55.0 (50.3-59.7)	66.9 (62.3-71.2)	30.0 (28.3-31.6)	43.1 (41.4-44.9)
FL Z-score	36.0 (31.6-40.7)	47.9 (43.2-52.6)	14.3 (13.1-15.6)	23.3 (21.8-24.9)
Z-scores for HC, AC, FL	64.2 (59.6-68.7)	76.3 (72.1-80.2)	33.7 (32.0-35.5)	47.9 (46.5-50.1)
EFW Z-score	66.2 (61.6-70.6)	76.1 (71.8-79.9)	32.3 (30.7-34.0)	47.0 (45.2-48.8)
Maternal factors plus				
HC Z-score	41.4 (36.8-46.1)	57.1 (52.3-61.7)	24.5 (23.0-26.1)	37.9 (36.1-39.6)
AC Z-score	60.6 (55.9-65.2)	71.4 (66.7-75.5)	34.2 (32.5-35.9)	49.4 (47.6-51.2)
FL Z-score	42.5 (37.9-47.2)	55.5 (50.7-60.2)	21.3 (19.9-22.8)	33.6 (31.9-35.3)
Z-scores for HC, AC, FL	67.8 (63.2-72.1)	78.5 (74.4-82.2)	36.9 (35.1-38.6)	52.8 (51.0-54.6)
EFW Z-score	67.6 (63.0-71.9)	79.2 (75.1-82.9)	36.2 (34.5-38.0)	52.7 (50.9-54.5)
SGA <5th centile				
Maternal factors	22.4 (17.6-27.8)	31.1 (25.6-36.9)	19.7 (17.6-21.8)	31.9 (30.8-35.9)
HC Z-score	43.3 (37.4-49.4)	56.7 (50.6-62.6)	21.6 (19.5-23.8)	34.8 (32.3-37.3)
AC Z-score	66.4 (60.5-72.0)	76.2 (70.7-81.1)	32.9 (30.5-35.4)	47.7 (45.1-50.3)
FL Z-score	43.7 (37.8-49.7)	52.0 (45.9-58.0)	18.1 (16.2-20.2)	27.1 (24.8-29.5)
Z-scores for HC, AC, FL	72.9 (67.3-78.1)	82.8 (78.9-87.9)	38.6 (36.0-41.1)	54.4 (51.8-57.0)
EFW Z-score	74.4 (68.8-79.4)	83.8 (78.5-87.9)	38.8 (36.2-41.3)	54.0 (51.3-56.5)
Maternal factors plus				
HC Z-score	46.6 (40.6-52.6)	64.3 (58.3-69.9)	28.4 (26.0-30.8)	43.7 (41.2-46.3)
AC Z-score	72.2 (66.5-77.4)	79.8 (74.6-84.4)	38.4 (35.9-41.0)	53.5 (50.9-56.1)
FL Z-score	50.2 (44.1-56.2)	62.8 (56.8-68.5)	25.0 (22.8-27.3)	39.5 (36.9-42.0)
Z-scores for HC, AC, FL	78.3 (73.0-83.0)	86.3 (81.7-90.1)	42.6 (40.0-45.1)	59.2 (56.6-61.7)
EFW Z-score	79.8 (74.6-84.4)	87.4 (82.9-91.0)	42.1 (39.5-44.7)	58.4 (55.8-61.0)
SGA <3rd centile				
Maternal factors	22.2 (16.5-28.8)	31.8 (25.2-38.9)	21.6 (18.9-24.5)	33.9 (30.8-37.2)
HC Z-score	47.6 (40.3-55.0)	62.4 (55.1-69.4)	23.0 (20.2-25.9)	35.3 (32.1-38.6)
AC Z-score	79.9 (73.5-85.4)	85.2 (79.3-89.9)	35.5 (32.3-38.8)	50.2 (46.9-53.6)
FL Z-score	51.9 (44.5-59.2)	59.8 (52.4.66.8)	19.7 (17.1-22.5)	29.4 (26.4-32.6)
Z-scores for HC, AC, FL	82.0 (75.8-87.2)	87.8 (82.3-92.1)	41.7 (38.4-45.0)	57.1 (53.8-60.4)
EFW Z-score	82.0 (75.8-87.2)	88.4 (82.9-92.6)	42.2 (38.9-45.5)	57.4 (54.0-60.7)
Maternal factors plus				
HC Z-score	51.3 (44.0-58.6)	70.4 (63.3-76.8)	30.6 (27.5-33.8)	46.1 (42.7-49.5)
AC Z-score	79.9 (73.5-85.4)	85.2 (79.3-89.9)	41.4 (38.1-44.7)	56.3 (53.0-59.6)
FL Z-score	57.7 (50.3-64.8)	70.9 (63.9-77.3)	27.6 (24.6-30.7)	42.6 (39.3-46.0)
Z-scores for HC, AC, FL	85.7 (79.9-90.4)	90.5 (85.4-94.3)	45.8 (42.4-49.1)	61.5 (58.2-64.6)
EFW Z-score	86.2 (80.5-90.8)	92.1 (87.2-95.5)	45.2 (41.8-48.5)	61.0 (57.7-64.3)

centiles by maternal factors predicted 30%, 31% and 32% of those delivering at <5 weeks of assessment, at 10% FPR. The respective detection rates for prediction of SGA delivering at ≥5 weeks of assessment were 28%, 32% and 34%.

The study also demonstrates that the measurements of the fetal HC, AC, FL and the subsequent calculation of the EFW are, in the absence of PE, reduced in women at 30-34 weeks' gestation who proceed to deliver a SGA neonate. Furthermore, it has been shown that the alterations in fetal biometry are more pronounced in those with severe disease reflected as a lower BW (3^{rd} vs. 10^{th} centile) and earlier delivery (<5 vs. ≥5 weeks) from assessment. The selected intervals of <5 and ≥5 weeks from assessment correspond to <37 (preterm) and ≥37 (term) weeks of gestation.

Combined screening using maternal characteristics, history and EFW Z-scores calculated at 30-34 weeks had different predicitive values for SGA. These depended on the defintion of SGA ($<10^{th}$, $<5^{th}$ and $<3^{rd}$ centiles) and the assessment to delivery interval time (<5 and ≥5 weeks). For a FPR of 10% and in those delivering <5 weeks of from assessment, combined screening predicated 80% of SGA neonates with a BW <10th centile, 87% of those with a BW $<5^{th}$ and 92% of those with a BW $<3^{rd}$ centile. For those delivering the delivering ≥5 weeks after assessment, the prediction for SGA dropped to 52%, 58% and 61% for BW below the 10th, 5th and 3rd centiles. At either assessment interval and for each the prediction of SGA using the fetal AC was superior to that of HC or FL, but inferior to that of the combination of the three measurements. Finally, screening performance by a combination of Z-scores for fetal HC, AC and FL was similar to that achieved by the EFW Z-score.

3.4.2 Comparison with findings from previous studies

Previous studies on a small number of patients reported on the performance of fetal AC or EFW on the prediction of delivery of SGA neonates, commonly defined by BW $<10^{th}$ centile, irrespective of the gestational age at birth. However, most of these studies have wider inclusion gestations, commence at earlier gestations and do not make a clear distinction of assessment to delivery time. In three significantly smaller studies by Skovron *et al.,* (768 pregnancies) David *et al.,* (1,000 pregnancies) and De Reu *et al.,* (725 pregnancies) the gestation examined ranged from 26-34, 28-36 and 27-33 weeks respectively. Skovron *et al.,* and David *et al.,* used a FPR of 10%, and their detection rates of a SGA neonate born with a BW below the 10th centile were 45% and 46%. These results are still all lower than our DR of 52% in those delivering ≥5 weeks after assessment, and closer to De Reu *et al.,* who found a DR of 53%, but accepted a larger FPR of 20% (Skovron *et al.,* 1991; David *et al.,* 1996; De Reu *et al.,* 2008).

Two further studies have matched ours in terms of a narrow range of gestational age

for assessment. Di Lorenzo *et al.,* assessment at 30-32 weeks in 1,868 pregnancies, with outcome of BW <10th centile, reported a DR of 73% with a very large FPR of 25% (Di Lorenzo *et al.,* 2013).

Souka *et al.,* 2012., (2,310 pregnancies) assessment was carried out at between 30-34 weeks. For a FPR of 10% and examining the prediction of SGA neonates with a BW <5th centile the DR was 60%. This was similar to our prediction in those delivering ≥5 weeks after assessment which was 58%, but inferior to ours for those delivering within 5 weeks of assessment, where our DR was 87% (Souka *et al.,* 2012).

In our study of 30,849 pregnancies, we examined, in combination with maternal demographic characteristics and medical history, the value of fetal biometric measurements of the AC, HC, FL and EFW, and reported the performance of screening for SGA (in the absence of PE) of differing severities within and beyond five weeks from assessment. Our results have indicated that regardless of which BW centile cut-off is used, the prediction was better within 5 weeks of assessment than beyond.

Our results on the performance of individual biomarkers are in general agreement with or an improvement on previous studies and demonstrate that an early third trimester scan is by far superior to the traditional approach of symphyseal-fundal height-measurement (Lindhard *et al.,* 1990) in identifying pregnancies at high-risk of delivering SGA neonates.

The advantage of using Bayes theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry is that individual patient risks can be estimated for any predefined severity of SGA (e.g. BW <10^{th} centile) and any interval from assessment to delivery. This is an essential first step for the establishment of patient management protocols, and should be seen as further evidence for the need of implementing a third trimester scan as part of routine pregnancy care.

Chapter 4: Uterine artery Doppler and mean arterial pressure at 30-34 weeks

ABSTRACT

Objective: To investigate the potential value of UtA PI and MAP at 30-34 weeks' gestation in the prediction of SGA neonates, in the absence of PE.

Methods: Screening study in singleton pregnancies at 30-34 weeks, including 1,727 that delivered SGA neonates with BW <5th centile and 29,122 cases unaffected by SGA, PE or GH (normal group). Multivariable logistic regression analysis was used to determine if uterine artery PI and MAP improved the prediction of SGA neonates provided by screening with maternal characteristics and medical history (maternal factors), and EFW from fetal head circumference, abdominal circumference and femur length.

Results: Combined screening by maternal factors and EFW Z-scores predicted 80%, 87% and 92% of SGA neonates delivering at <5 weeks of assessment with BW <10^{th}, <5^{th} and <3^{rd} centiles, respectively, at 10% false positive rate. Addition of uterine artery PI and MAP improved the respective detection rates to 83%, 91% and 93%. Screening by maternal factors and EFW Z-scores, predicted 52%, 58% and 61% of SGA delivering at ≥5 weeks of assessment and these rates increased to 53%, 60% and 63% with the addition of uterine artery PI and MAP.

Conclusion: Combined testing by maternal factors, fetal biometry, uterine artery PI and MAP at 30-34 weeks could identify a high proportion of pregnancies that deliver SGA neonates.

This chapter is based on:

Bakalis S, Stoilov B, Akolekar R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 30-34 weeks. Ultrasound Obstet Gynecol. 2015 Jun;45(6):707-14.

4.1 Introduction

Histological studies reported that in pregnancies complicated by preeclampsia (PE) and in those delivering SGA neonates in the absence of PE there is evidence of impaired placentation characterized by inadequate trophoblastic invasion of the maternal spiral arteries [Chapter 1, section 1.3.3]. Extensive screening studies in the first-, second- and third-trimesters have reported that in pregnancies that develop PE the uterine artery PI is increased before the onset of the clinical signs of the disease (Poon *et al.,* 2009; Akolekar *et al.,* 2013; Albaiges *et al.,* 2000; Yu *et al.,* 2005; Gallo *et al.,* 2013; Lai *et al.,* 2013; Tayyar *et al.,* 2014). There is also evidence that in such pregnancies the MAP in the three trimesters is increased before the onset of the clinical signs of PE (Poon *et al.,* 2009; Akolekar *et al.,* 2013; Tayyar *et al.,* 2014; Poon *et al.,* 2012; Gallo *et al.,* 2014; Lai *et al.,* 2013). Screening studies in the first and second trimester have reported that in pregnancies that deliver SGA neonates in the absence of PE the uterine artery PI is increased (Karagiannis *et al.,* 2011; Khalil *et al.,* 2012). Although in the first trimester MAP is not significantly altered in pregnancies that deliver SGA neonates in the absence of PE (Karagiannis *et al.,* 2011; Khalil *et al.,* 2012), two longitudinal studies reported that an increase in blood pressure between the second and early third trimester of pregnancy was associated with a decrease in BW (Bakker *et al.,* 2011; Churchill *et al.,* 1997).

4.1.1 Objectives

The objectives of this study are firstly, to determine the distribution of uterine artery PI and MAP levels at 30-34 weeks' gestation in pregnancies that deliver SGA neonates in the absence of PE and secondly, to examine the potential value of these biomarkers in improving the performance of screening for SGA by maternal factors and fetal biometry.

4.2 Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at 30^{+0}-34^{+0} weeks' gestation. The methodology for recording of patient characteristics, sonographic estimation of EFW, uterine artery PI, MAP, outcome measures and statistical analysis was as described in Chapter 2.

4.3 Results

The study population comprised 30,849 pregnancies, including 1,727 (5.6%) that delivered SGA<5th neonates, in the absence of PE, and 29,122 (94.4%) cases that were unaffected by these outcomes. The characteristics of the study population are given in Chapter 2.

4.3.1 Normal pregnancy outcome

The mean, SD, 90th and 95th centile of log_{10} MoM uterine artery PI were 0.005, 0.111, 0.145 and 0.197, respectively. The mean, SD, 90th and 95th centile of log_{10} MoM MAP were 0.000, 0.034, 0.042 and 0.054, respectively.

There was no significant association between log_{10} MoM values of uterine artery PI and MAP (r=-0.010, P=0.095). There was a significant inverse association between log_{10} MoM uterine artery PI with assessment to delivery interval (r=-0.086, P<0.0001) and BW Z-score (r=-0.070, P<0.0001), and between log_{10} MoM MAP with assessment to delivery interval (r=-0.068, P<0.0001) and BW Z-score (r=-0.014, P=0.021).

4.3.2 Small for gestational age

In the SGA<5th group, compared to the normal group, the median MoM values of uterine artery PI and MAP at 30-34 weeks were significantly higher (**Table 4.1**).

There was a significant direct association between log_{10} MoM values of UtA PI and MAP (r=0.128, P<0.0001). There was a significant inverse association between log_{10} MoM uterine artery PI with assessment to delivery interval (r=-0.239, P<0.0001; **Figure 4.1** and BW Z-score (r=-0.138, P<0.0001; **Figure 4.1**), and between log_{10} MoM MAP with assessment to delivery interval (r=-0.198, P<0.0001; **Figure 4.1),** and BW Z-score (r=-0.084, P=0.001; **Figure 4.1**).

Table 4.1: Uterine artery pulsatility index and mean arterial pressure at 30-34 weeks' gestation in the small for gestational age neonates with BW below the 5th centile in the absence of preeclampsia and in the normal group.

	Value, Median (IQR)	MoM, median (IQR)	Log_{10} MoM, mean (SD)	>95th centile, n (%, 95% CI)	>90th centile, n (%, 95% CI)
Uterine artery pulsatility index					
Normal (n=28,620)	0.720 (0.615-0.855)	0.996 (0.854-1.176)	0.005 (0.111)	1,431 (5.0, 4.8-5.3)	2,862 (10.0, 9.7-10.4)
SGA total (n=1,683)	0.790 (0.665-0.990)*	1.101 (0.915-1.378)*	0.056 (0.134)*	224 (13.3, 11.8-15.0)*	402 (23.9, 21.9-26.0)*
SGA <5w (n=268)	0.925 (0.715-1.225)**	1.281 (0.994-1.690)**	0.116 (0.160)**	89 (33.2, 27.8-39.0)**	118 (44.0, 38.2-50.0)**
SGA ≥5w (n=1,415)	0.775 (0.655-0.960)**	1.077 (0.909-1.328)**	0.045 (0.126)**	155 (11.0, 9.4-12.7)**	284 (20.1, 18.1-22.2)**
Mean arterial pressure					
Normal (n=26,921)	87.0 (82.1-92.2)	0.999 (0.948-1.054)	0.000 (0.034)	1,346 (5.0, 4.7-5.3)	2,692 (10.0, 9.6-10.4)
SGA total (n=1,548)	87.3 (82.3-93.1)*	1.020 (0.962-1.079)*	0.009 (0.038)*	166 (10.7, 9.3-12.4)*	274 (17.7, 15.9-19.7)*
SGA <5w (n=227)	91.5 (84.8-97.1)**	1.054 (0.987-1.126)**	0.024 (0.045)**	51 (22.5, 17.5-28.3)**	68 (30.0, 24.4-36.2)**
SGA ≥5w (n=1,321)	87.0 (82.0-92.0)	1.013 (0.960-1.072)**	0.006 (0.036)**	115 (8.7, 7.3-10.3)**	206 (15.6, 13.7-17.7)**

IQR = interquartile range, MoM = multiple of the unaffected median, SD = standard deviation, SGA = small for gestational age, PE = preeclampsia.

Comparisons between normals and SGA total: Chi square test or Fisher exact test for categorical variables and Mann Whitney-U test or student t-test:*P<0.05. Comparisons between normals and SGA delivering at <5 and ≥5 weeks of assessment: Chi square test or Fisher exact test for categorical variables and Mann Whitney-U test or student t-test: **P<0.025

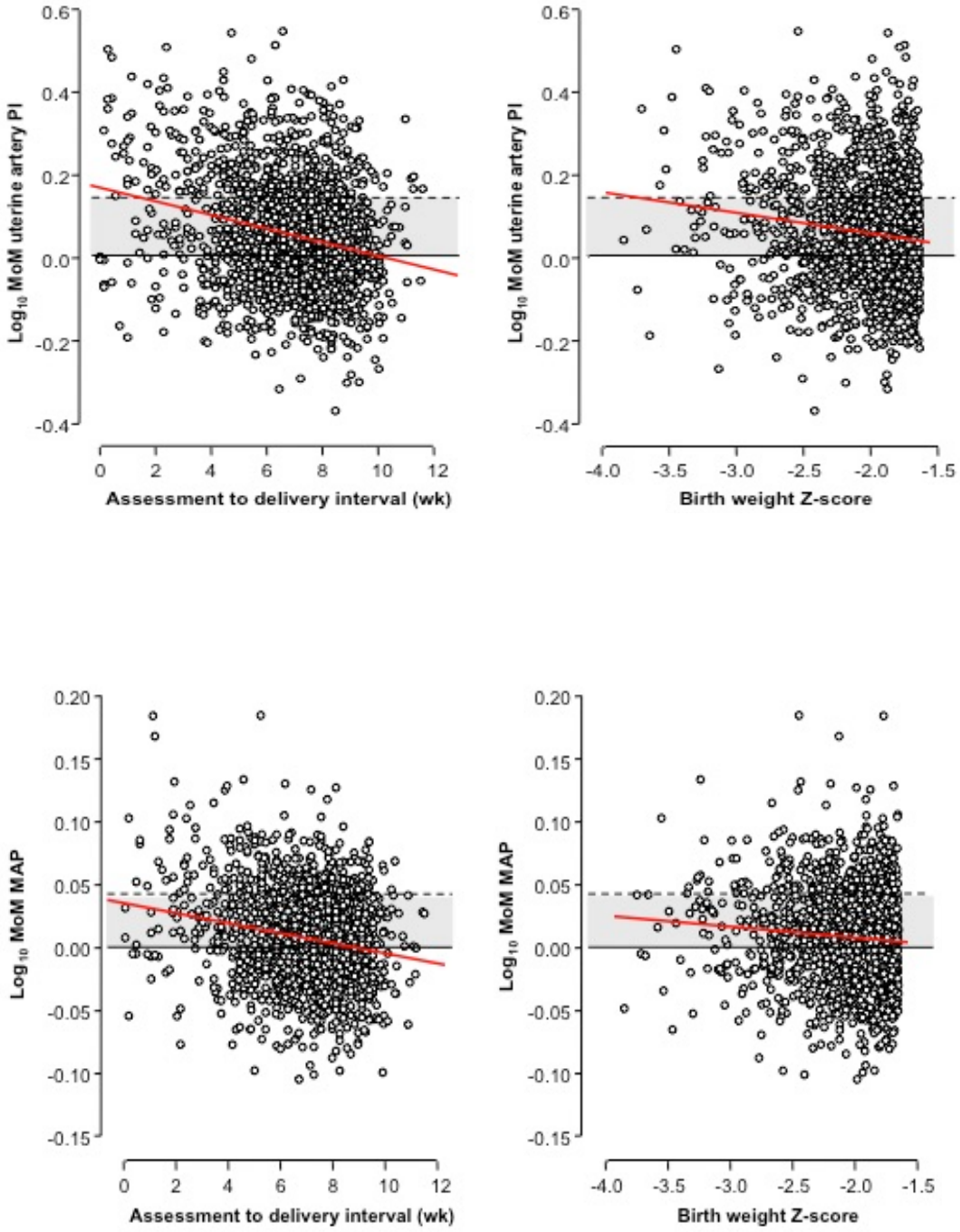

Figure 4.1: Relationship of uterine artery pulsatility index (PI) (top) and MAP (bottom) $\log_{10}$ multiple of median (MoM) at 30-34 weeks' gestation with assessment to delivery interval (left) and BW Z-score (right) in pregnancies delivering small for gestational age neonates with BW below the 5th centile, plotted on the range (grey box) between the 50th (horizontal black line) and 90th centile (interrupted horizontal black line) of the normal range. The regression lines are indicated in red.

Multivariable logistic regression analysis demonstrated that in the prediction of SGA<5th delivering at <5 and ≥5 weeks of assessment there were significant contributions from maternal characteristics, EFW Z-score, uterine artery PI and MAP (**Tables 4.2** and **4.3**). The areas under ROC and the detection rates of SGA<10th, SGA<5th and SGA<3rd delivering at <5 and at ≥5 weeks of assessment for false positive rates of 5% and 10% in screening by maternal characteristics, EFW Z-score, uterine artery PI, MAP and their combination are given in **Tables 4.4, 4.5** and **Figure 4.2**.

Table 4.2: Fitted regression models with maternal characteristics and history, uterine artery pulsatility index, mean arterial pressure and estimated fetal weight at 30-34 weeks' gestation for the prediction of small for gestational age neonates with BW below the 5th centile delivering at <5 weeks of assessment in the absence of preeclampsia.

Independent variable	Coefficient	SE	OR	95% CI
Uterine artery PI (R2=0.085, P<0.0001)				
Intercept	-5.21260	0.08910		
Log_{10} MoM uterine artery PI	5.35938	0.64276	212.593	60.316-749.313
Log_{10} MoM uterine artery PI^2	17.62251	3.26953	4.50×10^{7}	7.42×10^{4}-2.63×10^{10}
Log_{10} MoM uterine artery PI^3	-26.29431	7.33281	3.81×10^{-12}	2.18×10^{-18}-6.64×10^{-6}
MAP (R2=0.056, P<0.0001)				
Intercept	-5.13613	0.08223		
Log_{10} MoM MAP	13.18195	1.93106	6.31×10^{5}	1.21×10^{4}-2.34×10^{7}
Log_{10} MoM MAP^2	148.83063	24.97932	4.33×10^{64}	2.37×10^{43}-7.92×10^{85}
Uterine artery PI and MAP (R2=0.135, P<0.0001)				
Intercept	-5.63444	0.10947		
Log_{10} MoM uterine artery PI	5.27267	0.71452	194.937	48.050-790.854
Log_{10} MoM uterine artery PI^2	16.03626	3.66600	9.21×10^{6}	6.98×10^{3}-1.22×10^{10}
Log_{10} MoM uterine artery PI^3	-23.46618	8.12649	6.44×10^{-11}	7.79×10^{-18}-5.32×10^{-4}
Log_{10} MoM MAP	12.95900	2.04137	4.25×10^{5}	7.77×10^{3}-2.32×10^{7}
Log_{10} MoM MAP^2	135.68947	27.69743	8.50×10^{58}	2.25×10^{35}-3.20×10^{82}
Maternal characteristics and history with uterine artery PI (R2=0.143, P<0.0001)				
Intercept	-0.67860	0.32647		
Logit(*a priori* risk)	2.23254	0.16598	9.324	6.734-12.908
Log_{10} MoM uterine artery PI	5.05108	0.65562	156.191	43.211-564.571
Log_{10} MoM uterine artery PI^2	16.78366	3.38294	1.95×10^{7}	2.57×10^{4}-$1.1.47 \times 10^{10}$
Log_{10} MoM uterine artery PI^3	-23.09176	7.74248	9.36×10^{-11}	2.40×10^{-17}-3.65×10^{-4}
Maternal characteristics and history with MAP (R2=0.121, P<0.0001)				
Intercept	-0.34161	0.34388		
Logit(*a priori* risk)	2.37748	0.17879	10.778	7.592-15.301
Log_{10} MoM MAP	13.20796	1.88245	5.45×10^{5}	1.36×10^{4}-2.18×10^{7}
Log_{10} MoM MAP^2	146.42534	24.38193	3.91×10^{63}	6.88×10^{42}-2.22×10^{84}

Table 4.2 continued.

Independent variable	Coefficient	SE	OR	95% CI
Maternal characteristics and history with uterine artery PI and MAP (R2=0.193, P<0.0001)				
Intercept	-0.99912	0.36534		
Logit(*a priori* risk)	2.28401	0.18517	9.816	6.828-14.111
Log_{10} MoM uterine artery PI	4.77138	0.72968	118.082	28.254-493.504
Log_{10} MoM uterine artery PI^2	15.52451	3.85294	5.52×10^{6}	2.90×10^{3}-1.05×10^{10}
Log_{10} MoM uterine artery PI^3	-20.05878	8.68340	1.94×10^{-9}	7.89×10^{-17}-4.79×10^{-2}
Log_{10} MoM MAP	12.74716	2.01359	3.44×10^{5}	6.64×10^{3}-1.78×10^{7}
Log_{10} MoM MAP^2	132.48250	27.54525	3.44×10^{57}	1.23×10^{34}-9.62×10^{80}
Maternal characteristics and history with EFW and uterine artery PI (R2=0.506, P<0.0001)				
Intercept	-2.89942	0.42489		
Logit(*a priori* risk)	1.64446	0.20608	5.178	3.457-7.755
EFW Z-score	-4.30224	0.27879	0.014	0.008-0.023
EFW $Z\text{-score}^2$	-0.61313	0.11990	0.542	0.428-0.685
Log_{10} MoM uterine artery PI	4.66383	0.77417	106.041	23.254-483.554
Log_{10} MoM uterine artery PI^2	16.33555	4.23272	1.24×10^{7}	3.10×10^{3}-4.98×10^{10}
Log_{10} MoM uterine artery PI^3	-26.23235	10.20645	4.05×10^{-12}	8.31×10^{-21}-1.97×10^{-3}
Maternal characteristics and history with EFW and MAP (R2=0.463, P<0.0001)				
Intercept	-1.96109	0.42952		
Logit(*a priori* risk)	1.98481	0.21822	7.278	4.745-11.162
EFW Z-score	-3.88514	0.27104	0.021	0.012-0.035
EFW $Z\text{-score}^2$	-0.43020	0.12131	0.650	0.513-0.825
Log_{10} MoM MAP	12.87169	2.20280	3.89×10^{5}	5.19×10^{3}-2.92×10^{7}
Log_{10} MoM MAP^2	107.74511	31.47386	6.21×10^{46}	1.01×10^{20}-3.83×10^{73}
Maternal characteristics and history with EFW, uterine artery PI and MAP (R2=0.509, P<0.0001)				
Intercept	-2.43564	0.45730		
Logit(*a priori* risk)	1.97101	0.22876	7.178	4.584-11.239
EFW Z-score	-3.83936	0.29966	0.022	0.012-0.039
EFW $Z\text{-score}^2$	-0.38014	0.14521	0.684	0.514-0.909
Log_{10} MoM uterine artery PI	4.23275	0.83682	68.906	13.365-355.275
Log_{10} MoM uterine artery PI^2	15.74416	4.61491	6.88×10^{6}	8.12×10^{2}-5.83×10^{10}
Log_{10} MoM uterine artery PI^3	-20.80408	10.46579	9.22×10^{-10}	1.14×10^{-18}-7.47×10^{-1}
Log_{10} MoM MAP	12.30128	2.37779	2.20×10^{5}	2.08×10^{3}-2.32×10^{7}
Log_{10} MoM MAP^2	91.82516	35.00953	7.57×10^{39}	1.20×10^{10}-4.78×10^{69}

OR = odds ratio; CI = confidence interval; PI = pulsatility index; MAP = mean arterial pressure; EFW = estimated fetal weight

Table 4.3: Fitted regression models with maternal characteristics and history, uterine artery pulsatility index, mean arterial pressure and estimated fetal weight at 30-34 weeks' gestation for the prediction of small for gestational age neonates with BW below the 5th centile delivering at ≥5 weeks of assessment in the absence of preeclampsia.

Independent variable	Coefficient	SE	OR	95% CI
Uterine artery PI (R2=0.019, P<0.0001)				
Intercept	-3.14569	0.03468		
Log_{10} MoM uterine artery PI	3.08941	0.31788	21.964	11.780-40.954
Log_{10} MoM uterine artery PI^2	6.23237	1..66224	508.961	19.579-13,230.702
Log_{10} MoM uterine artery PI^3	-14.80584	5.04328	3.71×10^{-7}	1.893×10^{-11}-7.29×10^{03}
MAP (R2=0.006, P<0.0001)				
Intercept	-3.08008	0.03390		
Log_{10} MoM MAP	5.06497	0.80204	158.375	32.885-762.750
Log_{10} MoM MAP^2	49.73175	14.53183	3.96×10^{21}	1.69×10^{9}-9.28×10^{33}
Uterine artery PI and MAP (R2=0.024, P<0.0001)				
Intercept	-3.22479	0.04090		
Log_{10} MoM uterine artery PI	3.02088	0.33176	20.509	10.704-39.296
Log_{10} MoM uterine artery PI^2	5.81852	1.73793	336.473	11.159-10,145.566
Log_{10} MoM uterine artery PI^3	-13.83585	5.22976	9.80×10^{-7}	3.46×10^{-11}-2.77×10^{-2}
Log_{10} MoM MAP	5.17866	0.81877	177.444	35.655-883.087
Log_{10} MoM MAP^2	47.36155	14.89047	3.71×10^{20}	7.84×10^{7}-1.75×10^{33}
Maternal characteristics and history with uterine artery PI (R2=0.106, P<0.0001)				
Intercept	1.48765	0.15416		
Logit(*a priori* risk)	2.28429	0.07844	9.819	8.420-11.451
Log_{10} MoM uterine artery PI	2.86305	0.32832	17.515	9.203-33.333
Log_{10} MoM uterine artery PI^2	5.66152	1.70768	287.587	10.120-8,172.452
Log_{10} MoM uterine artery PI^3	-12.55930	5.28689	3.51×10^{-6}	1.11×10^{-10}-1.11×10^{-1}
Maternal characteristics and history with MAP (R2=0.094, P<0.0001)				
Intercept	1.58304	0.16021		
Logit(*a priori* risk)	2.30031	0.08150	9.977	8.504-11.705
Log_{10} MoM MAP	5.07954	0.81785	160.700	32.349-798.304
Log_{10} MoM MAP^2	39.13956	14.94142	9.96×10^{15}	1.91×10^{4}-5.20×10^{29}

Table 4.3 continued.

Independent variable	Coefficient	SE	OR	95% CI
Maternal characteristics and history with uterine artery PI and MAP (R2=0.110, P<0.0001)				
Intercept	1.41486	0.16426		
Logit(*a priori* risk)	2.28148	0.08275	9.791	8.325-11.515
Log_{10} MoM uterine artery PI	2.77788	0.34237	16.085	8.222-31.466
Log_{10} MoM uterine artery PI^2	5.37092	1.79048	21.5.060	6.434-7,188.205
Log_{10} MoM uterine artery PI^3	-11.65344	5.49300	8.69×10^{-6}	1.83×10^{-10}-4.12×10^{-1}
Log_{10} MoM MAP	5.14888	0.83517	172.239	33.515-885.171
Log_{10} MoM MAP^2	37.80562	15.25683	2.62×10^{16}	2.70×10^{3}-2.54×10^{29}
Maternal characteristics and history with EFW and uterine artery PI (R2=0.287, P<0.0001)				
Intercept	0.48519	0.17129		
Logit(*a priori* risk)	1.75183	0.08615	5.765	4.869-6.826
EFW Z-score	-2.34273	0.07251	0.096	0.083-0.111
EFW $Z\text{-score}^2$	-0.21913	0.04513	0.803	0.735-0.878
EFW $Z\text{-score}^3$	0.10964	0.01125	1.116	1.092-1.141
Log_{10} MoM uterine artery PI	2.68720	0.34674	14.691	7.445-28.986
Log_{10} MoM uterine artery PI^2	6.11466	1.78810	452.444	13.600-15,052.159
Log_{10} MoM uterine artery PI^3	-14.32716	5.49919	6.00×10^{-7}	1.25×10^{-11}-2.88×10^{-2}
Maternal characteristics and history with EFW and MAP(R2=0.279, P<0.0001)				
Intercept	0.61468	0.17618		
Logit(*a priori* risk)	1.76066	0.08941	5.816	4.881-6.930
EFW Z-score	-2.32901	0.07436	0.097	0.084-0.113
EFW $Z\text{-score}^2$	-0.18105	0.04816	0.834	0.759-0.917
EFW $Z\text{-score}^3$	0.10197	0.01230	1.107	1.081-1.134
Log_{10} MoM MAP	5.02861	0.87901	152.721	27.270-855.290
Maternal characteristics and history with EFW, uterine artery PI and MAP(R2=0.290, P<0.0001)				
Intercept	0.48223	0.18027		
Logit(*a priori* risk)	1.76323	0.09080	5.831	4.881-6.967
EFW Z-score	-2.30958	0.07582	0.099	0.086-0.115
EFW $Z\text{-score}^2$	-0.16429	0.05039	0.848	0.769-0.937
EFW $Z\text{-score}^3$	0.09748	0.01292	1.102	1.075-1.131
Log_{10} MoM uterine artery PI	2.51815	0.35932	12.406	6.134-25.088
Log_{10} MoM uterine artery PI^2	5.92248	1.87684	363.336	9.430-14,779.866
Log_{10} MoM uterine artery PI^3	-12.27826	5.61886	4.65×10^{-6}	7.67×10^{-11}-2.82×10^{-1}
Log_{10} MoM MAP	4.93779	0.89478	139.462	24.145-805.548

Table 4.4: Area under receiver operating characteristic curve, with 95% confidence interval, of screening for small for gestational age neonates with BW <10th, <5th and <3rd centile in the absence of preeclampsia, delivering at <5 and at ≥5 weeks of assessment with maternal characteristics and history, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and their combination at 30-34 weeks' gestation.

Screening test	Small for gestational age	
	Delivery at <5 weeks	Delivery at ≥5 weeks
SGA <10th centile		
Maternal factors	0.699 (0.693-0.704)	0.698 (0.693-0.703)
Uterine artery PI	0.669 (0.664-0.675)	0.575 (0.569-0.581)
Mean arterial pressure	0.634 (0.628-0.639)	0.537 (0.531-0.542)
Uterine artery PI and mean arterial pressure	0.705 (0.699-0.711)	0.583 (0.578-0.589)
Estimated fetal weight	0.917 (0.914-0.920)	0.810 (0.805-0.814)
Maternal factors plus		
Uterine artery PI	0.760 (0.755-0.765)	0.709 (0.704-0.714)
Mean arterial pressure	0.750 (0.745-0.755)	0.700 (0.695-0.705)
Uterine artery PI, mean arterial pressure	0.787 (0.782-0.792)	0.710 (0.705-0.716)
Estimated fetal weight	0.925 (0.922-0.928)	0.831 (0.827-0.836)
Maternal factors, estimated fetal weight plus		
Uterine artery PI	0.937 (0.934-0.940)	0.836 (0.832-0.841)
Mean arterial pressure	0.929 (0.926-0.932)	0.833 (0.828-0.837)
All markers	0.940 (0.937-0.943)	0.837 (0.833-0.841)
SGA <5th centile		
Maternal factors	0.718 (0.712-0.723)	0.723 (0.718-0.728)
Uterine artery PI	0.702 (0.696-0.707)	0.595 (0.589-0.600)
Mean arterial pressure	0.661 (0.655-0.666)	0.550 (0.544-0.556)
Uterine artery PI and mean arterial pressure	0.739 (0.733-0.744)	0.605 (0.599-0.611)
Estimated fetal weight	0.944 (0.941-0.947)	0.837 (0.833-0.841)
Maternal factors plus		
Uterine artery PI	0.798 (0.793-0.802)	0.741 (0.736-0.746)
Mean arterial pressure	0.780 (0.775-0.785)	0.729 (0.724-0.734)
Uterine artery PI, mean arterial pressure	0.823 (0.819-0.828)	0.745 (0.740-0.750)
Estimated fetal weight	0.953 (0.950-0.955)	0.859 (0.855-0.863)
Maternal factors, estimated fetal weight plus		
Uterine artery PI	0.965 (0.963-0.967)	0.865 (0.861-0.869)
Mean arterial pressure	0.959 (0.956-0.961)	0.862 (0.858-0.866)
All markers	0.968 (0.966-0.970)	0.867 (0.863-0.871)
SGA <3rd centile		
Maternal factors	0.718 (0.713-0.724)	0.736 (0.731-0.741)
Uterine artery PI	0.721(0.715-0.726)	0.611 (0.606-0.617)
Mean arterial pressure	0.671 (0.665-0.676)	0.568 (0.562-0.574)
Uterine artery PI and mean arterial pressure	0.749 (0.744-0.754)	0.630 (0.624-0.636)
Estimated fetal weight	0.960 (0.957-0.962)	0.854 (0.850-0.858)
Maternal factors plus		
Uterine artery PI	0.809 (0.804-0.813)	0.757 (0.753-0.762)
Mean arterial pressure	0.784 (0.779-0.789)	0.746 (0.741-0.751)
Uterine artery PI, mean arterial pressure	0.831 (0.827-0.836)	0.765 (0.760-0.770)
Estimated fetal weight	0.965 (0.963-0.967)	0.876 (0.872-0.880)
Maternal factors, estimated fetal weight plus		
Uterine artery PI	0.974 (0.972-0.976)	0.882 (0.879-0.885)
Mean arterial pressure	0.968 (0.966-0.970)	0.879 (0.875-0.883)
All markers	0.974 (0.972-0.976)	0.884 (0.880-0.888)

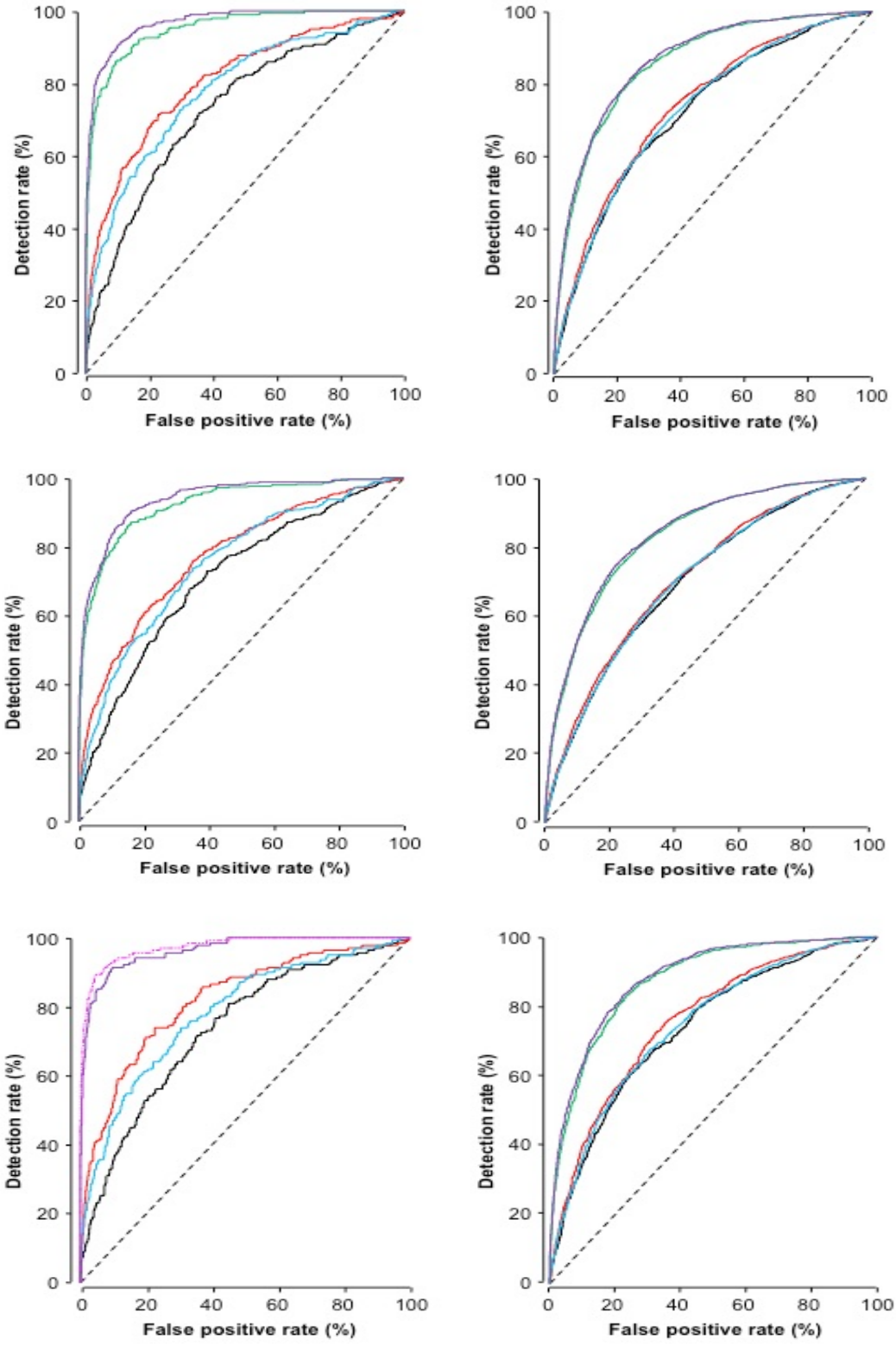

Figure 4.2: Receiver operating characteristics curves of maternal factors (black line) and maternal factors with uterine artery pulsatility index (red line), mean arterial pressure (blue line), estimated fetal weight Z-core (green line) and the combination of all (purple line), at 30-34 weeks' gestation, in the prediction of small for gestational age neonates with BW below the 10th centile (top), below the 5th centile (middle) and below the 3rd centile (bottom) delivering at <5 (left) and at ≥5 (right) weeks of assessment.

Table 4.5: Detection rate, with 95% confidence interval, of screening for small for gestational age neonates with BW <10th, <5th and <3rd centile, delivering at <5 and at ≥5 weeks of assessment with maternal factors, estimated fetal weight, uterine artery pulsatility index and mean arterial pressure and their combination.

Screening test	Delivery at <5 weeks		Delivery at >5 weeks	
	Detection rate (%) for fixed false positive rate (95% CI)			
	5%	10%	5%	10%
SGA <10th centile				
Maternal factors	19.5 (15.9-23.4)	30.4 (26.2-34.9)	17.0 (15.7-18.4)	27.6 (26.0-29.3)
Uterine artery PI	26.5 (22.4-31.0)	36.5 (32.0-41.3)	10.1 (9.1-11.3)	18.3 (16.9-19.8)
MAP	16.8 (13.1-20.9)	24.5 (20.2-29.1)	7.6 (6.6-8.6)	13.9 (12.6-15.2)
Uterine artery PI, MAP	30.4 (25.7-35.4)	39.0 (33.9-44.2)	10.3 (9.2-11.5)	18.1 (16.7-19.6)
Estimated fetal weight	66.2 (61.6-70.6)	76.1 (71.8-79.9)	32.3 (30.7-34.0)	47.0 (45.2-48.8)
Maternal factors plus				
Uterine artery PI	33.3 (28.8-37.9)	44.4 (39.7-49.3)	18.0 (16.6-19.4)	30.5 (28.8-32.2)
MAP	25.8 (21.4-30.5)	39.9 (34.9-45.0)	17.0 (15.6-18.4)	27.8 (26.1-29.5)
Uterine artery PI, MAP	36.7 (31.8-41.9)	47.2 (42.0-52.5)	19.5 (18.0-21.0)	29.8 (28.0-31.5)
EFW	67.6 (63.0-71.9)	79.2 (75.1-82.9)	36.2 (34.5-38.0)	52.7 (50.9-54.5)
Maternal factors, EFW plus				
Uterine artery PI	70.0 (65.4-74.3)	81.6 (77.6-85.2)	37.4 (35.7-39.2)	52.4 (50.6-54.2)
MAP	69.7 (64.8-74.3)	79.5 (75.1-83.5)	36.8 (35.0-38.6)	52.0 (50.1-53.8)
All markers	70.2 (65.2-74.8)	82.6 (78.3-86.4)	37.3 (35.5-39.2)	52.8 (50.9-54.7)
SGA <5th centile				
Maternal factors	22.4 (17.6-27.8)	31.1 (25.6-36.9)	19.7 (17.6-21.8)	31.9 (30.8-35.9)
Uterine artery PI	33.2 (27.6-39.2)	44.0 (38.0-50.2)	11.0 (9.4-12.7)	20.1 (18.0-22.3)
MAP	22.5 (17.2-28.5)	30.0 (24.1-36.4)	8.7 (7.2-10.4)	15.6 (13.7-17.7)
Uterine artery PI, MAP	38.9 (32.4-45.7)	46.6 (39.9-53.4)	13.0 (11.2-15.0)	20.9 (18.7-23.2)
Estimated fetal weight	74.4 (68.8-79.4)	83.8 (78.5-87.9)	38.8 (36.2-41.3)	54.0 (51.3-56.5)
Maternal factors plus				
Uterine artery PI	40.7 (34.7-46.8)	51.5 (45.3-57.6)	21.1 (19.0-23.3)	35.7 (33.2-38.2)
MAP	33.9 (27.8-40.5)	46.7 (40.1-53.4)	19.5 (17.4-21.8)	31.6 (29.1-34.2)
Uterine artery PI, MAP	44.8 (38.1-51.6)	54.8 (47.9-61.4)	23.0 (20.7-25.4)	35.0 (32.4-37.7)
EFW	79.8 (74.6-84.4)	87.4 (82.9-91.0)	42.1 (39.5-44.7)	58.4 (55.8-61.0)
Maternal factors, EFW plus				
Uterine artery PI	84.0 (79.0-88.1)	88.8 (84.4-92.3)	44.6 (42.0-47.2)	59.4 (56.8-61.9)
MAP	79.3 (73.4-84.4)	88.6 (83.2-92.0)	43.2 (40.5-45.9)	58.1 (55.4-60.8)
All markers	83.7 (78.2-88.3)	90.5 (85.8-94.0)	45.1 (42.3-47.8)	60.2 (57.4-63.0)
SGA <5th centile				
Maternal factors	22.2 (16.5-28.8)	31.8 (25.2-38.9)	21.6 (18.9-24.5)	33.9 (30.8-37.2)
Uterine artery PI	34.1 (27.2-41.4)	47.3 (39.8-54.8)	12.2 (10.1-14.6)	22.2 (19.4-25.1)
MAP	23.3 (16.7-31.0)	30.1 (22.8-38.3)	9.7 (7.7-12.0)	17.3 (14.7-20.2)
Uterine artery PI, MAP	38.7 (30.7-47.3)	48.6 (40.1-57.1)	14.5 (12.0-17.1)	23.3 (20.4-26.5)
Estimated fetal weight	82.0 (75.8-87.2)	88.4 (82.9-92.6)	42.2 (38.9-45.5)	57.4 (54.0-60.7)
Maternal factors plus				
Uterine artery PI	41.2 (34.0-48.7)	53.3 (45.8-60.7)	23.4 (20.6-26.3)	39.0 (35.7-42.3)
MAP	33.6 (26.0-41.8)	46.6 (38.3-55.0)	21.3 (18.5-24.3)	35.9 (32.6-39.4)
Uterine artery PI, MAP	46.5 (38.1-55.0)	55.6 (47.1-64.0)	25.5 (22.5-28.8)	40.2 (36.7-43.8)
EFW	86.2 (80.5-90.8)	92.1 (87.2-95.5)	45.2 (41.8-48.5)	61.0 (57.7-64.3)
Maternal factors, EFW plus				
Uterine artery PI	90.1 (84.8-94.0)	92.3 (87.4-95.7)	47.9 (44.5-51.3)	62.2 (58.9-65.5)
MAP	85.6 (78.9-90.9)	91.8 (86.1-95.7)	47.1 (43.6-50.7)	61.3 (57.8-64.7)
All markers	89.4 (83.2-94.0)	93.0 (87.4-96.6)	49.0 (45.4-52.6)	63.3 (59.8-66.7)

MAP = mean arterial pressure; EFW = estimated fetal weight; PI = pulsatility index; CI = confidence intervals

4.4 Discussion

4.4.1 Main findings of the study

The findings of this study demonstrate that in women that deliver SGA neonates in the absence of PE, uterine artery PI and MAP at 30-34 weeks' gestation are increased and the increase is inversely related to the severity of the disease reflected in the gestational age at delivery and the BW Z-score. The selected intervals of <5 and ≥5 weeks from assessment correspond to <37 (preterm) and ≥37 (term) weeks of gestation.

Predictive values for SGA using maternal factors alone differed depending on the definition of SGA (BW <10th, <5th and <3rd centiles) and the assessment to delivery interval time (<5 and ≥5 weeks) are shown in section 3.4.1.

Screening for SGA by maternal factors improved when combined with uterine artery PI and MAP. For a BW of <10th, <5th and <3rd centiles predicted 47%, 55% and 56% of those delivering within 5 weeks of assessment and 30%, 35% and 40% of those delivering beyond 5 weeks of assessment. The prediction of SGA neonates provided by uterine artery PI was superior to that of MAP, but for delivery within five weeks of assessment, combined screening was superior to that achieved by either biophysical marker alone.

In Chapter 3, it was shown that the best performance of screening for SGA was by combining maternal factors and EFW Z-score where the DR for BW <10th, <5th and <3rd centiles were 80%, 87% and 92%, with a FPR of 10%, for delivery at <5 weeks of assessment and 52%, 58% and 61% for delivery at ≥5 weeks. This screening was improved when uterine artery PI and MAP were added. The DR for SGA with a BW <10th, <5th and <3rd centiles increased to 83%, 91% and 93% for delivery at within 5 weeks of assessment and 53%, 60% and 63% for delivery beyond 5 weeks of assessment or the same 10% FPR.

4.4.2 Comparison with findings from previous studies

A few first trimester studies have shown that, in the absence of PE, pregnancies delivering SGA neonates have a significantly increased MAP (Karagiannis *et al.,* 2011, Khalil *et al.,* 2012). Two longitudinal studies, including blood pressure measurements

in the third trimester, have shown a reduction in the BW, however, neither of these studies looked at the change in blood pressure (Bakker *et al.,* 2011) and change in diastolic blood pressure (Churchill *et al.,* 1997). Our data is the first large-scale measurement of BP in the third trimester correlating the results with BW centiles and showed a small but significant increase in MAP, regardless of the assessment to delivery time, in those delivering a SGA neonate.

Several first and second trimester studies on screening for SGA have reported that, in the absence of PE, the uterine artery PI is increased in those delivering a SGA neonate (Karagiannis *et al.,* 2011, Pilalis *et al.,* 2007, Melchiorre *et al.,* 2009 and Khalil *et al.,* 2012). Systematic meta-analysis have echoed these findings, with one study showing that, in the presence of raised uterine artery PI the OR of delivering a SGA neonate was 1.28 (95% CI 1.14-1.43) in the second and 1.56 (95% CI 1.40-1.73) in the third trimester (Gaillard *et al.,* 2013). These studies all rely on measurement of uterine artery PI alone on prediction of SGA, rather than in combination with other markers.

Third trimester studies that have also examined the use of UtAD in predicting SGA neonates. The generation R study looked at increased uterine artery PI's in both the second and third trimester, and its results revealed that the OR for delivery of a SGA neonate was 1.28 (95% CI 1.14-1.43) in the second trimester and 1.56 (95% CI 1.40-1.73) in the third trimester. A small Italian study by Maroni *et al.,* revealed that those with increased uterine artery PI were statistically significantly more likely to deliver a SGA neonate (p=< 0.001) (Maroni *et al.,* 2011).

One third trimester study combined EFW with uterine artery PI, and showed that for the prediction of a SGA neonate with a BW between the 5th and 10th centile, the DR was 72.4% with a FPR of 25.1%. For a SGA neonate with a BW <5th centile, the DR was 71.4% with a FPR of 16.0% (Di Lorenzo *et al.,* 2013). Though this latter study has a much better DR of SGA than our own, it is off set by a larger FPR.

Previous studies that examined pregnancies with SGA fetuses in the third trimester reported that the outcome was worse in cases with Doppler evidence of increased, impedance to flow in the uterine arteries (Severi *et al.,* 2002; Vergani *et al.,* 2002; Ghosh & Gudmundsson 2009; Ghi *et al.,* 2010; Vergani *et al.,* 2010 and Jamal *et al.,* 2013). These adverse neonatal outcome include delivery by CS, a lower BW centile, low Apgar score scores at delivery and admission to the NNU, however.

Prediction of PE has been studied more often than SGA, with two studies examining women at 30-34 weeks' and combining maternal factors, uterine artery PI and MAP in their prediction of PE (Lai *et al.,* 2013 and Tayyar *et al.,* 2014). The larger cohort studied 13,878 normal pregnancies and 350 cases of PE, using a FPR of 5% detected 90% of those requiring delivery within four weeks of assessment, but less than half requiring delivery after this (Tayyar *et al.,* 2014). In comparison to these results, uterine artery PI and MAP perform better in the screening for PE than for SGA in the absence of PE, however, in a one stop clinical assessment for adverse pregnancy outcomes in the third trimester, these measurements can be used for prediction of both PE and SGA.

Chapter 5: Serum biochemistry at 30-34 weeks

ABSTRACT

Objective: To investigate the potential value of serum PlGF, sFlt-1, PAPP-A, free β-hCG and AFP at 30-34 weeks' gestation in the prediction of small for gestational age (SGA) neonates, in the absence of preeclampsia (PE).

Methods: Screening study in singleton pregnancies at 30-34 weeks including 490 that delivered SGA neonates and 9,850 cases that were unaffected by SGA, PE or GH (normal). Multivariable logistic regression analysis was used to determine if serum PlGF, sFlt-1, PAPP-A, free β-hCG and AFP, individually or in combination, improved the prediction of SGA neonates provided by screening with maternal characteristics and medical history (maternal factors), and estimated fetal weight (EFW) from fetal head circumference, abdominal circumference and femur length.

Results: In the SGA group with BW <5th centile (SGA <5th) delivering at <5 weeks of assessment, compared to the normal group, the mean log_{10} multiple of the median (MoM) values of PlGF and AFP were significantly lower and the mean log_{10} MoM values of sFlt-1 and free β-hCG were significantly higher. The best model for prediction of SGA was provided by a combination of maternal factors, EFW and serum PlGF. Such combined screening, predicted, at 10% false positive rate, 84%, 93% and 92% of SGA neonates delivering at <5 weeks of assessment with BW <10th, <5th and <3rd centiles, respectively; the respective detection rates of combined screening for SGA neonates delivering at ≥5 weeks of assessment were 57%, 64% and 71%.

Conclusion: Combined screening by maternal factors, EFW and serum PlGF at 30-34 weeks' gestation can identify a high proportion of pregnancies that subsequently deliver SGA neonates.

This chapter is based on:

Bakalis S, Gallo DM, Mendez O, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by maternal biochemical markers at 30-34 weeks. Ultrasound Obstet Gynecol. 2015 Aug;46(2):208-15.

5.1 Introduction

Several studies have reported on the association between low or high levels of several maternal serum biochemical markers and the birth of SGA neonates. A large screening study at 11-13 weeks' gestation reported that in the cases delivering SGA neonates serum PAPP-A, free β-hCG were decreased (Karagiannis et al., 2011).

A meta-analysis of studies on the association between second trimester biochemical markers of aneuploidy reported that increased risk for delivery of SGA neonates was associated with high levels of serum (AFP and hCG (Morris *et al.,* 2008). Several studies, mainly case-control, reported that in pregnancies delivering SGA neonates maternal serum PlGF is decreased and sFlt-1 is increased both in the second- and third-trimesters of pregnancy (Crispi *et al.,* 2008; Herraiz *et al.,* 2014; Rizos *et al.,* 2013; Romero *et al.,* 2008; Savvidou et al., 2006)

5.1.1 Objectives

The objectives of this study are firstly, to determine the distribution of maternal serum concentrations of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP at 30-34 weeks' gestation in pregnancies that deliver SGA neonates in the absence of PE and secondly, to examine the potential value of these biomarkers in improving the performance of screening for SGA by maternal factors and fetal biometry.

5.2 Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at 30^{+0}-34^{+6} weeks' gestation. The methodology for recording of patient characteristics, sonographic estimation of EFW, measurement of maternal serum concentrations of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP, outcome measures and statistical analysis was as described in Chaper 2.

5.3 Results

The characteristics of the study population are given in Chaper 2. Serum PlGF was measured in 9,850 pregnancies, including 490 (5.0%) with SGA neonates, but for the other metabolites a smaller number of cases was examined because of limited availability of samples or reagents.

5.3.1 Normal pregnancy outcome

In the unaffected pregnancies with BW >5th centile, the mean, standard deviation and 5th, 10th, 90th and 95th centiles of log_{10} MoM values of each biochemical marker are shown in **Table 5.1**.

Correlations between log_{10} MoM values of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP in the normal pregnancy outcome group are shown in **Table 5.2**. Correlations between log_{10} MoM values of each metabolite with gestational age at delivery, assessment to delivery interval and BW Z-score are shown in **Table 5.3**.

Table 5.1. Mean, standard deviation and 5th, 10th, 90th and 95th centiles of log_{10} multiple of the median values of placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein in the unaffected pregnancies with BW >5th centile.

Measure	Log_{10} multiple of the median values				
	PlGF	sFlt-1	PAPP-A	free β-hCG	AFP
Mean	0.032	-0.037	-0.002	0.001	-0.019
Standard deviation	0.308	0.203	0.276	0.359	0.182
5th centile	-0.498	-0.360	-0.470	-0.614	-0.316
10th centile	-0.380	-0.288	-0.358	-0.466	-0.247
90th centile	0.409	0.218	0.337	0.438	0.200
95th centile	0.511	0.299	0.424	0.548	0.256

PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; PAPP-A = pregnancy associated plasma protein-A; β-hCG = β-human chorionic gonadotropin; AFP = α-fetoprotein.

Table 5.2. Pearson correlation between log_{10} multiple of the median values of placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein in the normal group and in the small for gestational age groups delivering at <5 and ≥5 weeks from assessment.

		Log_{10} MoM PlGF			Log_{10} MoM sFlt-1			Log_{10} MoM PAPP-A			Log_{10} MoM free β-hCG			Log_{10} MoM AFP		
		Normal	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**
Log_{10} MoM PlGF	r	1	1	1	-0.105	-0.578	-0.332	0.138	-0.235	-0.035	-0.004	0.085	-0.103	0.072	-0.048	0.093
	p	-	-	-	<0.0001	<0.0001	<0.0001	<0.0001	0.145	0.519	0.719	0.603	0.053	<0.0001	0.763	0.086
Log_{10} MoM sFlt-1	r	-0.105	-0.578	-0.332	1	1	1	0.676	0.727	0.697	0.203	0.176	0.224	0.056	-0.024	0.133
	p	<0.0001	<0.0001	<0.0001	-	-	-	<0.0001	<0.0001	<0.0001	<0.0001	0.276	<0.0001	<0.0001	0.909	0.031
Log_{10} MoM PAPP-A	r	0.138	-0.235	-0.035	0.676	0.727	0.697	1	1	1	0.088	0.165	0.106	0.104	-0.189	0.253
	p	<0.0001	0.145	0.519	<0.0001	<0.0001	<0.0001	-	-	-	<0.0001	0.308	0.049	<0.0001	0.366	<0.0001
Log_{10} MoM free β-hCG	r	-0.004	0.085	-0.103	0.203	0.176	0.224	0.088	0.165	0.106	1	1	1	0.034	-0.079	0.107
	p	0.719	0.603	0.053	<0.0001	0.276	<0.0001	<0.0001	0.308	0.049	-	-	-	0.008	0.709	0.086
Log_{10} MoM AFP	r	0.072	-0.048	0.093	0.056	-0.024	0.133	0.104	-0.189	0.253	0.034	-0.079	0.107	1	1	1
	p	<0.0001	0.763	0.086	<0.0001	0.909	0.031	<0.0001	0.366	<0.0001	0.008	0.709	0.086	-	-	-

r = Pearson Correlation.

Table 5.3. Pearson correlation between log_{10} multiple of the median values of placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein with gestational age at delivery, assessment to delivery interval and BW Z-score in the small for gestational age and normal outcome groups.

Outcome	r/p	Log_{10} multiple of the median values									
		PlGF		sFlt-1		PAPP-A		free β-hCG		AFP	
		Normal	SGA <5th	Normal	SGA <5th	Normal	SGA <5th	Normal	SGA <5th	Normal	SGA <5th
Gestational Age at delivery	r	0.155	0.301	-0.115	-0.307	-0.027	-0.125	-0.084	-0.130	-0.012	0.078
	p	<0.0001	<0.0001	<0.0001	<0.0001	0.020	0.014	<0.0001	0.010	0.289	0.122
Assessment to delivery interval	*r*	0.148	0.300	-0.098	-0.284	-0.025	-0.119	-0.080	-0.155	0.006	0.111
	p	<0.0001	<0.0001	<0.0001	<0.0001	0.030	0.019	<0.0001	0.002	0.594	0.027
BW Z-score	r	0.176	0.142	-0.057	-0.113	0.078	-0.038	0.009	-0.154	0.071	0.011
	p	<0.0001	0.002	<0.0001	0.025	<0.0001	0.453	0.442	0.002	<0.0001	0.824

SGA = small for gestational age with BW <5th centile; r = Pearson Correlation; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; PAPP-A = pregnancy associated plasma protein-A; β-hCG = β-human chorionic gonadotropin; AFP = α-fetoprotein.

5.3.2 Small for gestational age

In the SGA <5th group delivering at <5 weeks of assessment, compared to the normal group, the mean log_{10} MoM values of PlGF and AFP were significantly lower and the mean log_{10} MoM values of sFlt-1 and free β-hCG were significantly higher but mean log_{10} MoM value of PAPP-A was not significantly different (**Table 5.4**). In the SGA <5th group delivering at ≥5 weeks of assessment, compared to the normal group, the mean log_{10} MoM values of PlGF, PAPP-A and AFP were significantly lower and the mean log_{10} MoM sFlt-1 was significantly higher but the mean log_{10} MoM free β-hCG was not significantly different (**Table 5.4)**. Correlations between log_{10} MoM values of each metabolite with gestational age at delivery, assessment to delivery interval and BW Z-score are shown in **Table 5.3** and **Figures 5.1 and 5.2**.

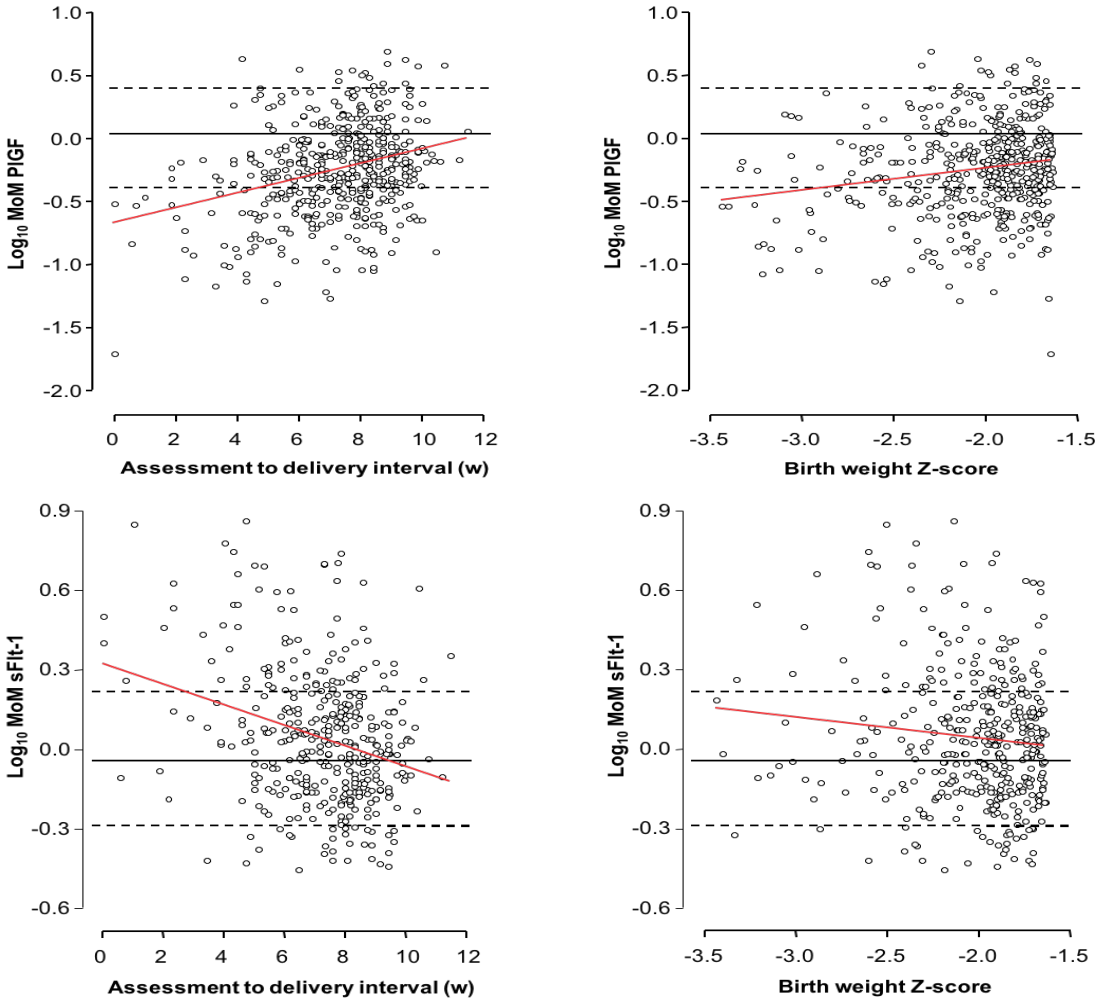

Figure 5.1. Placental growth factor (PlGF) and Soluble vascular endothelial growth factor receptor-1 (sFlt-1) log_{10} multiple of median (MoM) with assessment to delivery interval (left) and birth weight Z-score (right) in pregnancies complicated by small for gestational age neonates, plotted on the 50th and 90th centile of the normal range.

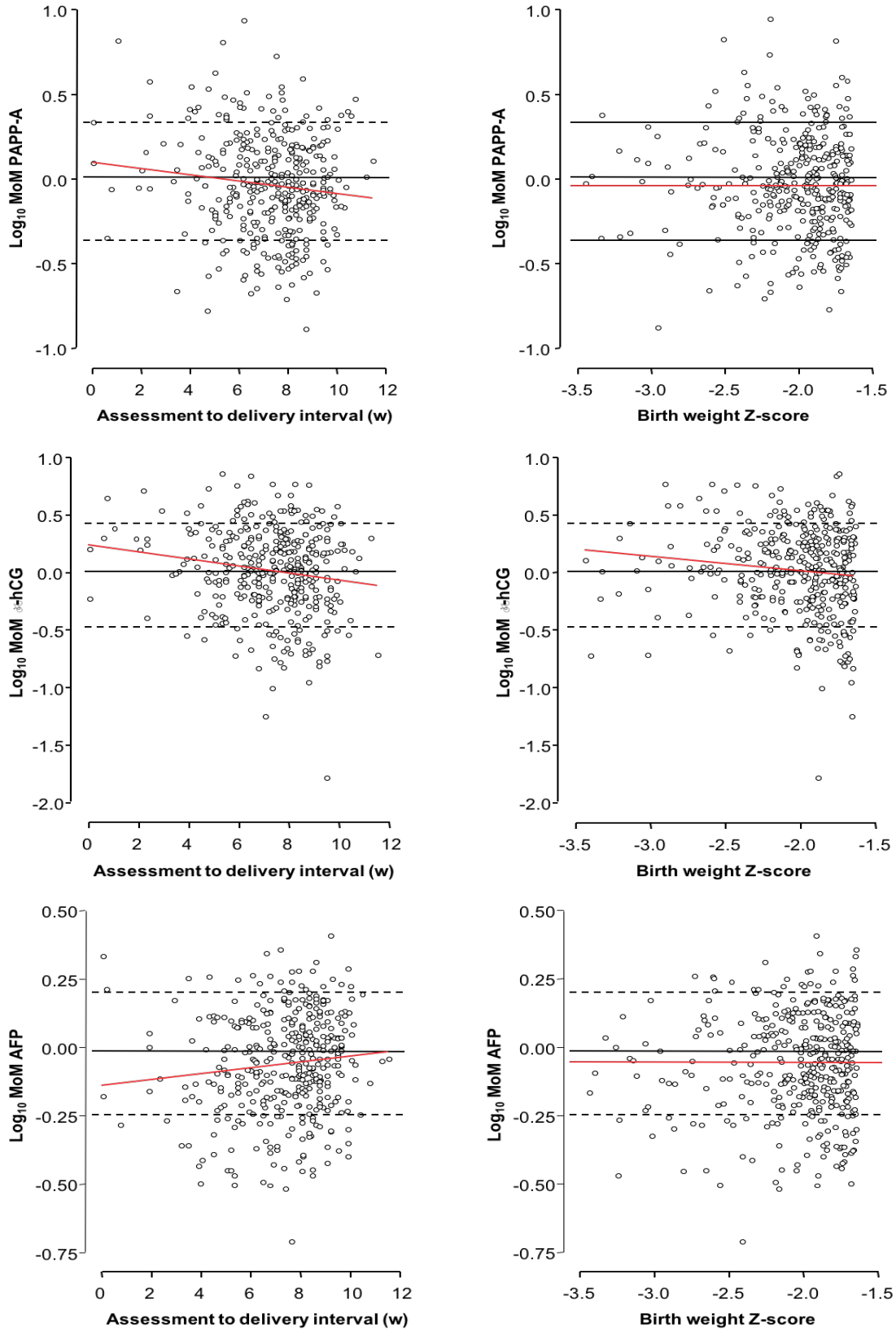

Figure 5.2. Pregnancy associated plasma protein-A (PAPP-A) (top), Free β-human chorionic gonadotropin (β-hCG) (middle) and α-fetoprotein (AFP)(bottom) $\log_{10}$ multiple of median (MoM) with assessment to delivery interval (left) and birth weight Z-score (right) in pregnancies complicated by small for gestational age neonates, plotted on the 5th, 10th, 50th, 90th and 95th centile of the normal range.

Table 5.4: Maternal serum placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein in the small for gestational age and normal outcome groups.

Biomarker	Normal outcome	SGA (BW <5th centile)	
		Delivery at <5 wks	Delivery at ≥5 wks
PlGF			
N (%)	9,360	57 (0.6%)	433 (4.4%)
pg/mL, median (IQR)	580.1 (348.5-930.8)	166.4 (89.3-277.9)*	369.8 (211.5-668.0)*
MoM, median (IQR)	1.112 (0.686-1.771)	0.304 (0.146-0.619)*	0.649 (0.386-1.027)*
Log_{10} MoM, mean (SD)	0.032 (0.308)	-0.510 (0.443)*	-0.197 (0.341)*
<5th centile, n (%, 95% CI)	468 (5.0, 4.6-5.5)	32 (56.1, 43.3-68.2)*	75 (17.3, 14.0-21.1)*
<10th centile, n (%, 95% CI)	936 (10.0, 9.4-10.6)	35 (61.4, 48.4-72.9)*	122 (28.2, 24.1-32.6)*
sFlt-1			
N (%)	7,646	40 (0.5%)	351 (4.4%)
pg/mL, median (IQR)	1,729 (1,275-2,371)	3,211 (1,993-5,858)*	1,913 (1,363-2,713)*
MoM, median (IQR)	0.905 (0.669-1.242)	1.777 (1.067-3.121)*	0.990 (0.711-1.417)*
Log_{10} MoM, mean (SD)	-0.037 (0.203)	0.246 (0.335)*	0.022 (0.231)*
>95th centile, n (%, 95% CI)	382 (5.0, 4.5-5.5)	17 (42.5, 28.5-57.8)*	37 (10.5, 7.7-14.2)*
>90th centile, n (%, 95% CI)	764 (10.0, 9.3-10.7)	21 (52.5, 37.5-67.1)*	63 (17.9, 14.3-22.3)*
PAPP-A			
N (%)	7,524	40 (0.5%)	346 (4.4%)
IU/L, median (IQR)	64.1 (39.8-100.3)	77.9 (48.9-137.6)	61.7 (40.9-108.0)
MoM, median (IQR)	1.031 (0.659-1.544)	1.166 (0.771-2.076)	0.906 (0.600-1.437)*
Log_{10} MoM, mean (SD)	-0.002 (0.276)	0.059 (0.340)	-0.042 (0.283)*
<5th centile, n (%, 95% CI)	376 (5.0, 4.5-5.5)	3 (7.5, 2.6-19.9)	24 (6.9, 4.7-19.1)
<10th centile, n (%, 95% CI)	752 (10.0, 9.3-10.7)	4 (10.0, 4.0-23.1)	50 (14.5, 11.1-18.5)*
Free β-hCG			
N (%)	7,649	40 (0.5%)	351 (4.4%)
IU/L, median (IQR)	5.700 (3.200-9.800)	8.500 (5.025-13.225)*	6.200 (3.400-11.000)
MoM, median (IQR)	1.047 (0.591-1.769)	1.521 (0.920-2.419)*	1.081 (0.621-1.876)
Log_{10} MoM, mean (SD)	0.001 (0.359)	0.145 (0.335)*	0.013 (0.377)
>95th centile, n (%, 95% CI)	382 (5.0, 4.5-5.5)	5 (12.5, 5.5-26.1)	23 (6.6, 4.4-9.6)
>90th centile, n (%, 95% CI)	764 (10.0, 9.3-10.7)	7 (17.5, 8.7-31.9)	41 (11.7, 8.7-15.5)
AFP			
N (%)	7,801	45 (0.5%)	348 (4.3%)
IU/mL, median (IQR)	185.6 (139.8-245.8)	145.8 (115.4-221.7)*	179.1 (129.9-243.3)
MoM, median (IQR)	0.966 (0.739-1.270)	0.736 (0.597-1.185)*	0.902 (0.672-1.203)*
Log_{10} MoM, mean (SD)	-0.019 (0.182)	-0.099 (0.200)*	-0.057 (0.185)*
<5th centile, n (%, 95% CI)	390 (5.0, 4.5-5.5)	7 (15.6, 7.7-28.8)*	32 (9.2, 6.6-12.7)*
<10th centile, n (%, 95% CI)	780 (10.0, 9.4-10.7)	10 (22.2, 12.5-36.3)*	52 (14.9, 11.6-19.1)*

SGA = Small for gestational age; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; PAPP-A = pregnancy associated plasma protein-A; β-hCG = β-human chorionic gonadotropin; AFP = α-fetoprotein; IQR = interquartile range; MoM = multiple of the unaffected median; SD = standard deviation.

Comparisons by Mann Whitney-U test or student t-test between outcome groups: *P<0.025

Multivariable logistic regression analysis demonstrated that the best model for prediction of SGA <5th delivering at <5 weeks and at >5 weeks of assessment was provided by a combination of maternal factors, EFW and PlGF (**Table 5.5 and 5.6**). The areas under ROC (AUROC) and the DRs, at FPRs of 5% and 10%, of SGA <10th, SGA <5th and SGA <3rd delivering at <5 and at ≥5 weeks of assessment in screening by maternal factors, EFW Z-score, PlGF, sFlt-1, PAPP-A, free β-hCG, AFP and their combinations are given in **Tables 5.7** and **5.8** and **Figures 5.3**.

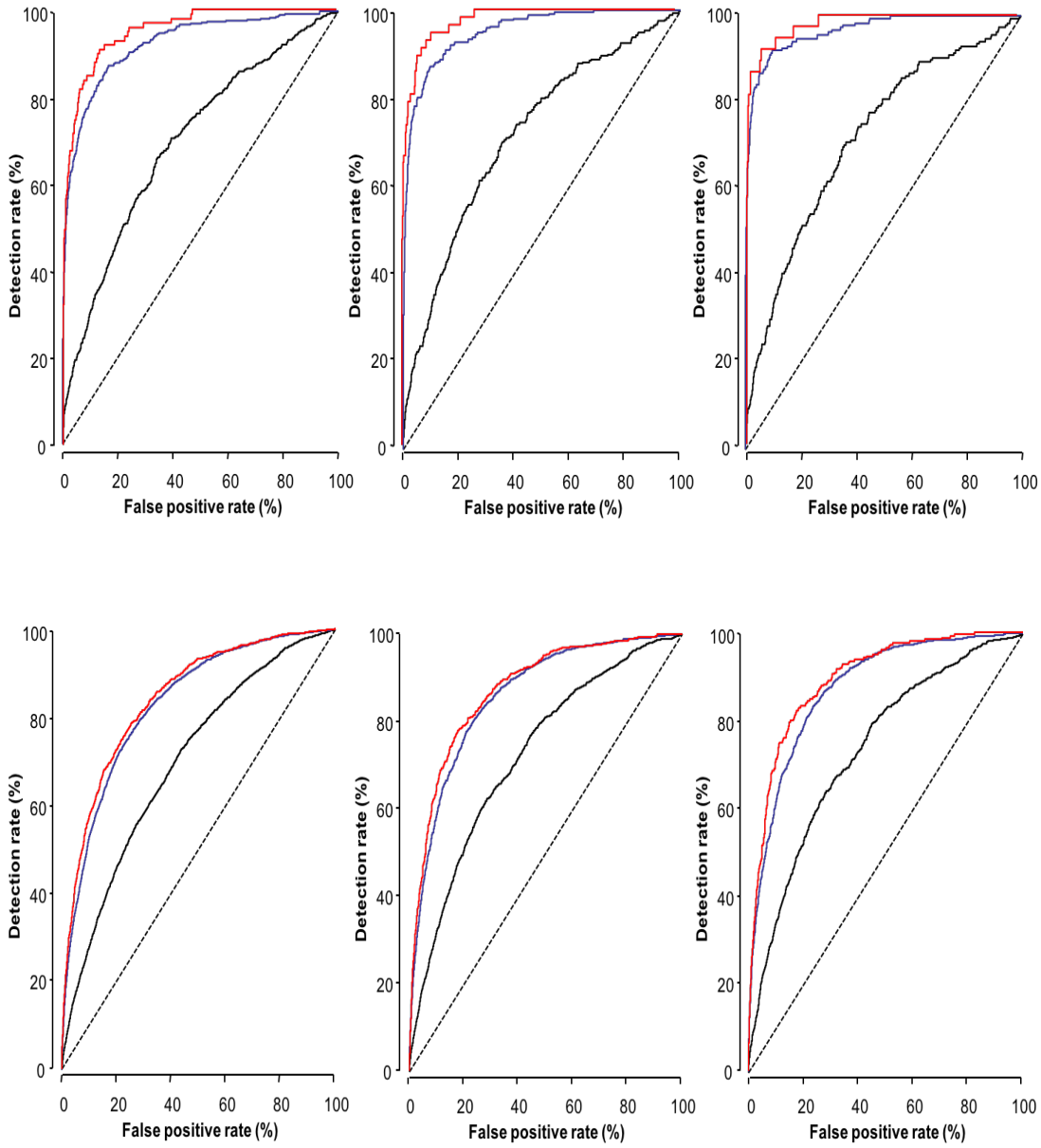

Figure 5.3. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight and serum PlGF (red line) in the prediction of small for gestational age neonates with birth weight 10th (left) <5th (middle) and 3rd (right) centile delivering at <5 weeks (above) and ≥5 weeks (below) of assessment.

Table 5.5. Fitted regression models with maternal characteristics and history, placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein for the prediction of small for gestational age <5th centile without preeclampsia delivering at <5 weeks of assessment.

Independent variable	Coefficient	Standard error	OR	95% CI	P-value
Maternal factors with PlGF (R2=0.258, P<0.0001)					
Intercept	-2.24449	0.72952			
Logit (*a priori* risk)	1.83739	0.36289	6.280	3.084-12.790	<0.0001
Log_{10} MoM PlGF	-2.98629	0.68527	0.050	0.013-0.193	<0.0001
Log_{10} MoM $PlGF^2$	1.73038	0.71530	5.643	1.389-22.928	0.016
Maternal factors with sFlt-1 (R2=0.170, P<0.0001)					
Intercept	-3.06330	0.89187			
Logit (*a priori* risk)	1.32649	0.43559	3.768	1.604-8.848	0.002
Log_{10} MoM sFlt-1	2.70848	0.73404	15.006	3.560-63.254	0.0002
Log_{10} MoM $sFlt\text{-}1^2$	4.74733	1.19916	115.276	10.990-1,209.120	<0.0001
Maternal factors with free β-hCG (R2=0.047, P<0.0001)					
Intercept	-1.70125	0.82389			
Logit (*a priori* risk)	1.76331	0.41235	5.832	2.600-13.085	<0.0001
Log_{10} MoM free β-hCG	1.10544	0.46632	3.021	1.211-7.534	0.018
Maternal factors with AFP (R2=0.055, P<0.0001)					
Intercept	-1.16221	0.78757			
Logit (*a priori* risk)	2.00165	0.40192	7.401	3.367-16.271	<0.0001
Log_{10} MoM AFP	-1.85456	0.60564	0.157	0.048-0.513	0.002
Maternal factors with PlGF and sFlt-1 (R2=0.309, P<0.0001)					
Intercept	-3.77967	0.88471			
Logit (*a priori* risk)	1.30966	0.42865	3.705	1.599-8.583	0.0002
Log_{10} MoM PlGF	-4.17493	0.52884	0.015	0.005-0.043	<0.0001
Log_{10} MoM sFlt-1	2.50301	0.73429	12.219	2.897-51.531	0.0007
Maternal factors with EFW and PlGF (R2=0.538, P<0.0001)					
Intercept	-3.45773	0..89822			
Logit (*a priori* risk)	1.56789	0.44809	4.797	1.993-11.544	0.0005
EFW Z-score	-2.76508	0.23973	0.063	0.039-0.101	<0.0001
Log_{10} MoM PlGF	-2.86569	0.61516	0.057	0.017-0.190	<0.0001
Log_{10} MoM $PlGF^2$	3.54748	1.24836	34.726	3.006-401.108	0.004
Log_{10} MoM $PlGF^3$	1.95148	0.94040	7.039	1.114-44.462	0.038
Log_{10} MoM PlGF	-1.85599	0.16408	0.156	0.113-0.216	<0.0001
Maternal factors with EFW and sFlt-1 (R2=0.253, P<0.0001)					
Intercept	0.18137	0.33279			
Logit (*a priori* risk)	1.48482	0.16665	4.414	3.184-6.119	<0.0001
EFW Z-score	-2.19093	0.13259	0.112	0.086-0.145	<0.0001
EFW $Z\text{-score}^2$	-0.27571	0.09055	0.759	0.636-0.906	0.002
EFW $Z\text{-score}^3$	0.13427	0.02498	1.144	1.089-3.166	<0.0001
Log_{10} MoM sFlt-1	0.62474	0.26929	1.868	1.102-3.166	0.020
Log_{10} MoM $sFlt\text{-}1^2$	1.70281	0.73074	5.489	1.311-22.990	0.020

Table 5.6. Fitted regression models with maternal characteristics and history, placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein for the prediction of small for gestational age <5th centile without preeclampsia delivering at ≥5 weeks of assessment.

Independent variable	Coefficient	Standard error	OR	95% CI	P-value
Maternal factors with PlGF (R2=0.138, P<0.0001)					
Intercept	0.91884	0.27949			
Logit (*a priori* risk)	2.03291	0.14061	7.636	5.797-10.059	<0.0001
Log_{10} MoM PlGF	-2.03872	0.15476	0.130	0.096-0.176	<0.0001
Maternal factors with sFlt-1 (R2=0.083, P<0.0001)					
Intercept	1.04697	0.30408			
Logit (*a priori* risk)	2.05242	0.15325	7.787	5.766-10.515	<0.0001
Log_{10} MoM sFlt-1	0.64961	0.25631	1.915	1.159-3.164	0.011
Log_{10} MoM sFlt-1^2	1.57216	0.67297	4.817	1.288-18.014	0.019
Maternal factors with PAPP-A (R2=0.081, P<0.0001)					
Intercept	1.29242	0.30195			
Logit (*a priori* risk)	2.14382	0.15341	8.532	6.316-11.525	<0.0001
Log_{10} MoM PAPP-A	-0.53180	0.19359	0.588	0.402-0.859	0.006
Maternal factors with AFP (R2=0.079, P<0.0001)					
Intercept	1.13072	0.30091			
Logit (*a priori* risk)	2.09592	0.15297	8.133	6.026-10.976	<0.0001
Log_{10} MoM AFP	-1.00016	0.28220	0.368	0.212-0.640	0.0004
Maternal factors with PlGF and AFP (R2=0.129, P<0.0001)					
Intercept	0.72886	0.31473			
Logit (*a priori* risk)	1.96339	0.15786	7.123	5.228-9.706	<0.0001
Log_{10} MoM PlGF	-1.90257	0.17329	0.149	0.106-0.210	<0.0001
Log_{10} MoM AFP	-0.68658	0.28976	0.503	0.285-0.888	0.018
Maternal factors with EFW and PlGF (R2=0.301, P<0.0001)					
Intercept	0.17729	0.30534			
Logit (*a priori* risk)	1.53663	0.15286	4.649	3.445-6.273	<0.0001
EFW Z-score	-2.20694	0.12283	0.110	0.086-0.140	<0.0001
EFW Z-score^2	-0.23938	0.08286	0.787	0.669-0.926	0.004
EFW Z-score^3	0.12917	0.02315	1.138	1.087-1.191	<0.0001
Log_{10} MoM PlGF	-1.85599	0.16408	0.156	0.113-0.216	<0.0001
Maternal factors with EFW and sFlt-1 (R2=0.253, P<0.0001)					
Intercept	0.18137	0.33279			
Logit (*a priori* risk)	1.48482	0.16665	4.414	3.184-6.119	<0.0001
EFW Z-score	-2.19093	0.13259	0.112	0.086-0.145	<0.0001
EFW Z-score^2	-0.27571	0.09055	0.759	0.636-0.906	0.002
EFW Z-score^3	0.13427	0.02498	1.144	1.089-3.166	<0.0001
Log_{10} MoM sFlt-1	0.62474	0.26929	1.868	1.102-3.166	0.020
Log_{10} MoM sFlt-1^2	1.70281	0.73074	5.489	1.311-22.990	0.020

Table 5.7. Area under receiver operating characteristic curve and detection rate for false positive rates of 5% and 10%, with 95% confidence interval, of screening for small for gestational age with BW <10th, <5th and <3rd centile in the absence of preeclampsia, delivering at <5 weeks after assessment with maternal factors, estimated fetal weight and various biochemical markers.

Screening test	SGA delivery at <5 weeks of assessment		
	AUROC	DR for FPR 5%	DR for FPR 10%
SGA <10th centile			
Maternal factors	0.699 (0.693-0.704)	19.5 (15.9-23.4)	30.4 (26.2-34.9)
Maternal factors plus			
PlGF	0.838 (0.830-0.845)	48.5 (38.3-58.7)	57.6 (47.2-67.5)
sFlt-1	0.763 (0.754-0.773)	30.1 (19.9-42.0)	39.7 (28.5-51.9)
PAPP-A	-	-	-
Free β-hCG	0.692 (0.681-0.702)	16.4 (8.8-27.0)	32.9 (22.3-44.9)
AFP	0.725 (0.714-0.735)	15.9 (8.7-25.6)	32.9 (22.9-44.2)
PlGF and sFlt-1	0.841 (0.832-0.849)	50.7 (38.7-62.6)	61.6 (49.5-72.8)
PlGF and AFP	-	-	-
EFW	0.925 (0.922-0.928)	67.6 (63.0-71.9)	79.2 (75.1-82.9)
Maternal factors, EFW plus			
PlGF	0.953 (0.948-0.957)	75.8 (66.1-83.8)	84.9 (76.2-91.3)
sFlt-1	-	-	-
SGA <5th centile			
Maternal factors	0.718 (0.712-0.723)	22.4 (17.6-27.8)	31.1 (25.6-36.9)
Maternal factors plus			
PlGF	0.887 (0.881-0.893)	52.6 (39.0-66.0)	71.9 (58.5-83.0)
sFlt-1	0.815 (0.806-0.824)	50.0 (33.8-66.2)	60.0 (43.3-75.1)
PAPP-A	-	-	-
Free β-hCG	0.703 (0.693-0.714)	15.0 (5.7-29.8)	30.0 (16.6-46.5)
AFP	0.735 (0.725-0.745)	17.8 (8.0-32.1)	42.2 (27.7-57.8)
PlGF and sFlt-1	0.891 (0.884-0.898)	65.0 (48.3-79.4)	80.0 (64.4-90.9)
PlGF and AFP	-	-	-
EFW	0.953 (0.950-0.955)	79.8 (74.6-84.4)	87.4 (82.9-91.0)
Maternal factors, EFW plus			
PlGF	0.975 (0.972-0.978)	84.2 (72.1-92.5)	93.0 (83.0-98.1)
sFlt-1	-	-	-
SGA <3rd centile			
Maternal factors	0.718 (0.713-0.724)	22.2 (16.5-28.8)	31.8 (25.2-38.9)
Maternal factors plus			
PlGF	0.887 (0.880-0.893)	50.0 (33.4-66.6)	76.3 (59.8-88.6)
sFlt-1	0.783 (0.773-0.792)	48.3 (29.5-67.5)	55.2 (35.7-73.6)
PAPP-A	-	-	-
Free β-hCG	0.723 (0.713-0.733)	17.2 (5.8-35.8)	31.0 (15.3-50.8)
AFP	0.773 (0.764-0.783)	16.7 (5.6-34.7)	46.7 (28.3-65.7)
PlGF and sFlt-1	0.899 (0.893-0.906)	69.0 (49.2-84.7)	82.8 (64.2-94.2)
PlGF and AFP	-	-	-
EFW	0.965 (0.963-0.967)	86.2 (80.5-90.8)	92.1 (87.2-95.5)
Maternal factors, EFW plus			
PlGF	0.980 (0.977-0.983)	89.5 (75.2-97.1)	92.1 (78.6-98.3)
sFlt-1	-	-	-

AUROC = area under receiver operating characteristic curve; DR = detection rate; FPR = false positive rate; SGA = small for gestational age; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; β-hCG = β-human chorionic gonadotropin; PAPP-A = pregnancy associated plasma protein-A, AFP = α-fetoprotein.

Table 5.8. Area under receiver operating characteristic curve and detection rate for false positive rates of 5% and 10%, with 95% confidence interval, of screening for small for gestational age with BW <10th, <5th and <3rd centile in the absence of preeclampsia, delivering at ≥5 weeks after assessment with maternal factors, estimated fetal weight and various biochemical markers.

Screening test	SGA delivery at ≥5 weeks of assessment		
	AUROC	DR for FPR 5%	DR for FPR 10%
SGA <10th centile			
Maternal factors	0.698 (0.693-0.703)	17.0 (15.7-18.4)	27.6 (26.0-29.3)
Maternal factors plus			
PlGF	0.742 (0.733-0.750)	20.8 (18.2-23.5)	34.0 (30.9-37.1)
sFlt-1	0.692 (0.682-0.703)	14.1 (11.7-16.8)	27.9 (24.7-31.2)
PAPP-A	0.696 (0.686-0.706)	16.5 (13.9-19.4)	28.4 (25.2-31.8)
Free β-hCG	-	-	-
AFP	0.686 (0.676-0.696)	16.1 (13.6-18.9)	25.6 (22.6-28.9)
PlGF and sFlt-1	-	-	-
PlGF and AFP	0.737 (0.727-0.747)	20.6 (17.8-23.7)	32.5 (29.1-36.0)
EFW	0.831 (0.827-0.836)	36.2 (34.5-38.0)	52.7 (50.9-54.5)
Maternal factors, EFW plus			
PlGF	0.844 (0.836-0.851)	42.0 (38.7-45.2)	57.2 (53.9-60.4)
sFlt-1	0.815 (0.806-0.824)	34.1 (30.7-37.6)	49.5 (45.9-53.2)
SGA <5th centile			
Maternal factors	0.723 (0.718-0.728)	19.7 (17.6-21.8)	31.9 (30.8-35.9)
Maternal factors plus			
PlGF	0.771 (0.762-0.779)	25.4 (21.4-29.8)	40.4 (35.8-45.2)
sFlt-1	0.717 (0.707-0.727)	19.4 (15.4-23.9)	33.3 (28.4-38.5)
PAPP-A	0.714 (0.704-0.724)	19.4 (15.3-23.9)	33.5 (28.6.38.8)
Free β-hCG	-	-	-
AFP	0.709 (0.699-0.718)	19.3 (15.2-23.8)	30.2 (25.4-35.3)
PlGF and sFlt-1	-	-	-
PlGF and AFP	0.761 (0.752-0.770)	25.7 (21.2-30.7)	39.5 (34.3-44.9)
EFW	0.859 (0.855-0.863)	42.1 (39.5-44.7)	58.4 (55.8-61.0)
Maternal factors, EFW plus			
PlGF	0.874 (0.867-0.880)	46.4 (41.6-51.2)	64.2 (59.7-68.9)
sFlt-1	0.851 (0.843-0.859)	40.2 (35.0-45.5)	57.6 (52.2-62.8)
SGA <3rd centile			
Maternal factors	0.736 (0.731-0.741)	21.6 (18.9-24.5)	33.9 (30.8-37.2)
Maternal factors plus			
PlGF	0.792 (0.783-0.800)	29.9 (24.5-35.8)	44.7 (38.6-50.9)
sFlt-1	0.732 (0.722-0.742)	23.4 (17.9-29.6)	37.9 (31.3-44.7)
PAPP-A	0.723 (0.713-0.733)	22.9 (17.4-29.1)	38.1 (31.5-45.0)
Free β-hCG	-	-	-
AFP	0.714 (0.704-0.724)	21.9 (16.5-28.1)	34.3 (27.9-41.1)
PlGF and sFlt-1	-	-	-
PlGF and AFP	0.780 (0.770-0.789)	30.2 (24.0-37.0)	43.9 (37.0-51.0)
EFW	0.876 (0.872-0.880)	45.2 (41.8-48.5)	61.0 (57.7-64.3)
Maternal factors, EFW plus			
PlGF	0.895 (0.889-0.901)	51.1 (44.9-57.3)	70.5 (64.6-75.9)
sFlt-1	0.871 (0.863-0.878)	43.0 (36.3-49.9)	60.3 (53.4-66.9)

AUROC = area under receiver operating characteristic curve; DR = detection rate; FPR = false positive rate; SGA = small for gestational age; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; β-hCG = β-human chorionic gonadotropin; PAPP-A = pregnancy associated plasma protein-A, AFP = α-fetoprotein.

5.4 Discussion

5.4.1 Main findings of the study

This study illustrates how the levels of a variety of biomarkers varies in the third trimester in those pregnancies that go on to deliver a SGA neonate. In those delivering a SGA (BW <5th centile) neonate within five weeks of assessment at 30-34 weeks' gestation maternal serum PlGF and AFP are statistically significantly decreased and serum sFlt-1 and free β-hCG are statistically significantly increased. In those that deliver beyond five weeks of their assessment, maternal serum PlGF, PAPP-A and AFP are statistically significantly decreased and serum sFlt-1 is statistically significantly increased. There was no difference in the free β-hCG levels in this group. The alterations in serum metabolites were related to the severity of the disease reflected in the BW Z-score.

Screening for SGA by maternal factors improved when combined with PlGF. For a FPR of 10% and a BW of <10^{th}, <5^{th} and <3^{rd} centiles predicted 58%, 72% and 76% of those delivering within 5 weeks of assessment and 34%, 40% and 45% of those delivering beyond 5 weeks of assessment. Screening for SGA by maternal factors and EFW improved when combined with PlGF. For a FPR of 10% and a BW of <10^{th}, <5^{th} and <3^{rd} centiles predicted 85%, 93% and 92% of those delivering within 5 weeks of assessment and 57%, 64% and 71% of those delivering beyond 5 weeks of assessment.

Screening for SGA by maternal factors improved when combined with sFlt-1. For a FPR of 10% and a BW of <10^{th}, <5^{th} and <3^{rd} centiles predicted 40%, 60% and 55% of those delivering within 5 weeks of assessment and 30%, 33% and 38% of those delivering beyond 5 weeks of assessment. Screening for SGA by maternal factors and EFW improved when combined with sFlt-1. For a FPR of 10% and a BW of <10^{th}, <5^{th} and <3^{rd} centiles the prediction rate was not significant for those delivering within 5 weeks of assessment and 50%, 58% and 60% of those delivering beyond 5 weeks of assessment.

Screening for SGA by maternal factors improved when combined with PAPP-A. For a FPR of 10% and a BW of <10^{th}, <5^{th} and <3^{rd} centiles the prediction rate was not significant for delivering within 5 weeks of assessment and 28%, 36% and 38% of those delivering beyond 5 weeks of assessment.

Screening for SGA by maternal factors did not improve when combined with free β-hCG. For a FPR of 10% and a BW of <10th, <5th and <3rd centiles predicted 33%, 30% and 31% of those delivering within 5 weeks of assessment and not significant for those delivering beyond 5 weeks of assessment.

Screening for SGA by maternal factors improved when combined with AFP. For a FPR of 10% and a BW of <10th, <5th and <3rd centiles predicted 33%, 42% and 47% of those delivering within 5 weeks of assessment and 26%, 30% and 34% of those delivering beyond 5 weeks of assessment.

In addition to using maternal factors and fetal biometry to predict SGA at 30-34 weeks, only PlGF made a significant contribution.

5.4.2 Comparison with findings from previous studies

One large first trimester screening study for delivery of SGA neonates measured the maternal serum levels of PlGF, PAPP-A and free ß-hCG at 11-13 week', and found that all three markers were decreased in affected pregnancies (Karagiannis *et al.,* 2011). This differed with our third trimester findings of decreased levels of PlGF and PAPP-A and increased levels of free ß-hCG. Other studies have looked at individual biochemical markers.

Previous third trimester studies of PlGF in pregnancies going on to deliver SGA neonates have been in agreement with our findings (Wallner *et al.,* 2007; Shibata *et al.,* 2005; Bersinger *et al.,* 2005 and Rizos *et al.,* 2013) and have consistently shown that the decrease is statistically significant.

Similarly, mainly small case-control studies in the third trimester, have consistently shown that sFlt-1 is decreased in pregnancies delivering a SGA neonate, however some trials have shown a significant decrease (Rizos *et al.,* 2013, Chaiworapongsa *et al.,* 2008 and Wallner *et al.,* 2007) whilst others a non-significant decrease (Romero *et al.,* 2008 and Shibata *et al.,* 2005).

One small longitudinal study (41 normal and 14 SGA pregnancies) of PAPP-A at 17, 25 and 33 weeks of gestation showed that the maternal serum concentrations of PAPP-A were significantly reduced in pregnancies delivering a SGA neonate at 17 weeks (p=0.0022), but not at 25 or 33 weeks. (Bersinger & Odegard 2004). The

significant difference seen in our results, in those delivering beyond five weeks of assessment at 30-34 weeks of gestation may be due to the large numbers in our study.

Free βhCG has not been shown to be statistically significantly higher in the third trimester in pregnancies going on to deliver SGA neonates (Bartha *et al.,* 2003; Bartha *et al.,* 1997). One study that did find a significant difference in SGA pregnancies was only found to be significant in those with abnormal UmAD measurements (Bartha *et al.,* 1997).

A large meta-analysis of second trimester markers showed reported the association of delivery of SGA neonates with increased levels of AFP (Morris *et al.,* 2008), whereas in our third-trimester study AFP was decreased. This may be due to the natural levels of the protein which increase until 32 weeks and then decline to term (Hay *et al.,* 1976). This is in keeping with the study by Simpson *et al.,* in third (24-36 weeks of gestation) trimester of pregnancy which revealed a non significant OR in the third of 1.9 (95% CI 0.4-9.1) and a conclusion by the authors that only second and not third trimester serum AFP was significantly elevated in SGA pregnancies (Simpson *et al.,* 1995).

Chapter 6: Screening by biophysical and biochemical markers at 30-34 weeks

ABSTRACT

Objective: To investigate the potential value of combined screening by maternal characteristics and medical history (maternal factors), EFW, uterine artery PI, MAP and serum PlGF and soluble fms-like tyrosine kinase-1 (sFlt-1) at 30-34 weeks' gestation in the prediction of SGA neonates, in the absence of PE.

Methods: Screening study in singleton pregnancies at 30-34 weeks including 469 that delivered SGA neonates and 9,003 cases that were unaffected by SGA, PE or GH (normal). Multivariable logistic regression analysis was used to determine if uterine artery PI, MAP and serum PlGF or sFlt-1, individually or in combination, improved on the prediction of SGA neonates provided by screening with maternal factors and EFW.

Results: In the SGA group, compared to the normal group, the mean $\log_{10}$ multiple of the median (MoM) values of uterine artery PI, MAP and serum sFlt-1 were significantly higher and $\log_{10}$ MoM PlGF was lower. Multivariable logistic regression analysis demonstrated that in the prediction of SGA $<5^{th}$ delivering at <5 weeks and at $\geq$5 weeks of assessment there were significant independent contributions from maternal factors, EFW, uterine artery PI, MAP, serum PlGF and serum sFlt-1, but the best prediction was provided by a combination of maternal factors, EFW, uterine artery PI, MAP and serum PlGF without inclusion of sFlt-1 Combined screening predicted, at 10% false positive rate, 89%, 94%, 96% of SGA neonates delivering at 32-36 weeks' gestation with BW $<10^{th}$, $<5^{th}$ and $<3^{rd}$ centiles, respectively; the respective detection rates of combined screening for SGA neonates delivering at $\geq$37 weeks were 57%, 65% and 72%.

Conclusion: Combined screening by maternal factors and biophysical and biochemical markers at 30-34 weeks' gestation can identify a high proportion of pregnancies that subsequently deliver SGA neonates.

This chapter is based on:
Bakalis S, Peeva G, Gonzalez R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by biophysical and biochemical markers at 30-34 weeks. Ultrasound Obstet Gynecol. 2015 Mar 31 [Epub]

6.1 Introduction

The traditional approach of identifying pregnancies at high-risk of delivering SGA neonates is maternal abdominal palpation and/or serial measurements of symphysial-fundal height, but the performance of such screening is poor with detection of <30% of affected fetuses (Bais *et al.,* 2004; Lindhard *et al.,* 1990).

Chapter 3 shows that by a combination of maternal characteristics, medical history (maternal factors) and EFW at 30-34 weeks' gestation, screening can predict, at 10% FPR, 87% and 58% of SGA neonates with BW <5th centile (SGA<5th) delivering at <5 and at ≥5 weeks of assessment, respectively. Chapter 4 demonstrates that in pregnancies going on to deliver a SGA neonate, the uterine artery PI and MAP are increased. Screening by maternal factors, EFW, uterine artery PI and MAP predicted 91% and 60% of SGA <5th, at 10% FPR, delivering at <5 and at ≥5 weeks of assessment, respectively. Finally, chapter 5 shows that in pregnancies delivering a SGA neonate, the maternal serum PlGF is decreased and sFlt-1 increased. Combined screening with maternal factors, EFW and serum biochemistry predicted 93% and 64% of SGA <5th centile, at 10% FPR, delivering at <5 and at ≥5 weeks of assessment, respectively.

6.1.1 Objectives

The objective of this study is to examine the potential value of combined screening by maternal factors, EFW, uterine artery PI, MAP, serum PlGF and serum sFlt-1 at 30-34 weeks' gestation in the prediction of pregnancies that deliver SGA neonates in the absence of PE.

6.2 Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit at 30^{+0}-34^{+6} weeks' gestation at King's College Hospital, London, and Medway Maritime Hospital, Kent, between June 2011 and December 2013. The methodology for recording of patient characteristics, sonographic estimation of EFW, measurement of maternal serum concentrations of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP, outcome measures and statistical analysis was as described in Chapter 2.

6.3 Results

The characteristics of the study population are presented in Table 2.3. Uterine artery PI, MAP and serum PlGF were measured in 9,472 pregnancies, including 469 (5.0%) with SGA neonates.

6.3.1 Normal pregnancy outcome

In the unaffected pregnancies with BW >5th centile, the mean, standard deviation and 5th, 10th, 90th and 95th centiles of log_{10} MoM values of each biomarker are shown in **Table 6.1**.

Table 6.1. Mean, standard deviation and 5th, 10th, 90th and 95th centiles of log_{10} multiple of the median values of uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and soluble fms-like tyrosine kinase-1 in the unaffected pregnancies with BW >5th centile.

Measure	Log_{10} multiple of the median values			
	Uterine PI	MAP	PlGF	sFlt-1
Mean	0.001	-0.001	0.032	-0.037
Standard deviation	0.111	0.034	0.307	0.203
5th centile	-0.166	-0.057	-0.498	-0.360
10th centile	-0.131	-0.045	-0.380	-0.289
90th centile	0.140	0.041	0.409	0.218
95th centile	0.195	0.053	0.510	0.299

Uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Correlations between log_{10} MoM values of uterine artery PI, MAP, PlGF and sFlt-1 in the normal group are shown in **Table 6.2** and correlations between log_{10} MoM values of each biomarker with gestational age at delivery, assessment to delivery interval and BW Z-score are shown in **Table 6.3**.

6.3.2 Small for gestational age

In the SGA <5th group delivering at <5 weeks and ≥5 weeks of assessment, compared to the normal group, the mean log_{10} multiple of the median (MoM) values of uterine artery PI, MAP and serum sFlt-1 were significantly higher and log_{10} MoM PlGF was lower (**Table 6.4**). Correlations between log_{10} MoM values of each biomarker with gestational age at delivery, assessment to delivery interval and BW Z-score are shown in **Table 6.3**.

Table 6.2. Pearson correlation between log_{10} multiple of the median values of uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and soluble fms-like tyrosine kinase-1 in the small for gestational age and normal outcome groups.

		Log_{10} MoM uterine PI			**Log_{10} MoM MAP**			**Log_{10} MoM PlGF**			**Log_{10} MoM sFlt-1**		
		Normal	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**	**Normal**	**SGA <5w**	**SGA ≥5w**
Log_{10} MoM uterine PI	r	1	1	1	-0.029	0.260	0.052	-0.069	-0.230	-0.199	-0.057	0.061	-0.016
	p	-	-	-	0.006	0.065	0.287	<0.0001	0.104	<0.0001	<0.0001	0.733	0.767
Log_{10} MoM MAP	r	-0.029	0.260	0.052	1	1	1	-0.135	-0.116	-0.170	0.051	-0.003	0.149
	p	0.006	0.065	0.287	-	-	-	<0.0001	0.419	<0.0001	<0.0001	0.988	0.006
Log_{10} MoM PlGF	r	-0.069	-0.230	-0.199	-0.135	-0.116	-0.170	1	1	1	-0.101	-0.584	-0.330
	p	<0.0001	0.104	<0.0001	<0.0001	0.419	<0.0001	-	-	-	<0.0001	<0.0001	<0.0001
Log_{10} MoM sFlt-1	r	-0.057	0.061	-0.016	0.051	-0.003	0.149	-0.101	-0.584	-0.330	1	1	1
	p	<0.0001	0.733	0.767	<0.0001	0.988	0.006	<0.0001	<0.0001	<0.0001	-	-	-

r = Pearson Correlation; MoM = multiple of the median; Uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; SGA = small for gestational age.

Table 6.3. Pearson correlation between log_{10} multiple of the median values of uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and soluble fms-like tyrosine kinase-1 with gestational age at delivery, assessment to delivery interval and BW Z-score in the small for gestational age and normal

Outcome	r/p	Log_{10} multiple of the median values							
		Uterine PI		MAP		PlGF		sFlt-1	
		Normal	SGA <5th	Normal	SGA <5th	Normal	SGA <5th	Normal	SGA <5th
Gestational age at delivery	r	-0.079	-0.192	-0.074	-0.185	0.153	0.290	-0.110	-0.304
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Assessment to delivery interval	*r*	-0.084	-0.195	-0.079	-0.180	0.147	0.292	-0.095	-0.282
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BW Z-score	r	-0.073	-0.120	0.013	-0.138	0.174	0.176	-0.056	-0.099
	p	<0.0001	0.009	0.208	0.003	<0.0001	<0.0001	<0.0001	0.057

outcome groups.

r = Pearson Correlation; Uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Table 6.4. Uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and soluble fms-like tyrosine kinase-1 in the small for gestational age and normal outcome groups.

Biomarker	Normal outcome (n=9,003)	SGA (BW <5th centile)	
		Delivery at <5 wks (n=51)	Delivery at ≥5 wks (n=418)
Uterine artery PI			
median (IQR)	0.715 (0.615-0.850)	0.865 (0.725-1.200)*	0.760 (0.655-0.946)*
MoM, median (IQR)	0.990 (0.848-1.166)	1.161 (0.993-1.636)*	1.045 (0.909-1.305)*
Log_{10} MoM, mean (SD)	0.001 (0.111)	0.098 (0.153)*	0.040 (0.127)*
$>95^{th}$ centile, n (%, 95% CI)	450 (5.0, 4.6-5.5)	14 (27.5, 17.1-40.9)*	45 (10.8, 8.1-14.1)*
$>90^{th}$ centile, n (%, 95% CI)	900 (10.0, 9.4-10.6)	20 (39.2, 27.0-52.9)*	83 (19.9, 16.3-23.9)*
MAP			
mmHg, median (IQR)	87.2 (82.1-92.4)	93.4 (87.8-102.3)*	87.4 (82.6-92.7)
MoM, median (IQR)	0.998 (0.946-1.052)	1.094 (1.017-1.146)*	1.015 (0.965-1.079)*
Log_{10} MoM, mean (SD)	-0.001 (0.034)	0.033 (0.043)*	0.008 (0.036)*
$>95^{th}$ centile, n (%, 95% CI)	450 (5.0, 4.6-5.5)	17 (33.3, 22.0-47.0)*	41 (9.8, 7.3-13.0) *
$>90^{th}$ centile, n (%, 95% CI)	900 (10.0, 9.4-10.6)	22 (43.1, 30.5-56.7)*	75 (17.9, 14.6-21.9)*
PlGF			
pg/mL, median (IQR)	579.5 (348.0-930.6)	166.4 (87.1-302.9)*	369.0 (209.1-654.3)*
MoM, median (IQR)	1.111 (0.685-1.773)	0.267 (0.145-0.635)*	0.647 (0.386-1.020)*
Log_{10} MoM, mean (SD)	0.032 (0.307)	-0.513 (0.459)*	-0.198 (0.343)*
$<5^{th}$ centile, n (%, 95% CI)	450 (5.0, 4.6-5.5)	29 (56.9, 43.3-69.5)	73 (17.5, 14.1-21.4)*
$<10^{th}$ centile, n (%, 95% CI)	900 (10.0, 9.4-10.6)	31 (60.8, 47.1-73.0)	120 (28.7, 24.6-33.2)*
	Normal outcome (n=7,340)	**SGA (BW <5th centile)**	
		Delivery at <5 wks (n=34)	**Delivery at ≥5 wks (n=337)**
sFlt-1			
pg/mL, median (IQR)	2,371 (1,276-2,371)	3,355 (1,996-6,522)*	1,909 (1,368-2,709)*
MoM, median (IQR)	0.903 (0.671-1.242)	1.840 (1.067-3.454)*	0.990 (0.711-1.417)*
Log_{10} MoM, mean (SD)	-0.037 (0.203)	0.263 (0.355)*	0.023 (0.231)*
$>95^{th}$ centile, n (%, 95% CI)	367 (5.0, 4.5-5.5)	16 (47.1, 31.5-63.3)*	36 (10.7, 7.8-14.4)*
$>90^{th}$ centile, n (%, 95% CI)	734 (10.0, 9.3-10.7)	19 (55.9, 39.5-71.1)*	60 (17.8, 14.1-22.2)*

Uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; IQR = interquartile range; MoM = multiple of the unaffected median; SD = standard deviation. Comparisons by Mann Whitney-U test or student t-test between outcome groups: *P<0.025

Table 6.5. Fitted regression models with maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and soluble fms-like tyrosine kinase-1 for the prediction of small for gestational age neonates with BW <5th centile delivering at <5 weeks of assessment without preeclampsia.

Independent variable	Coefficient	Standard error	OR	95% CI	P-value
Maternal factors with uterine artery PI and PlGF (R2=0.281, P<0.0001)					
Intercept	-2.62194	0.78132			
Logit (*a priori* risk)	1.75325	0.38957	5.773	2.690-12.389	<0.0001
Log_{10} MoM uterine artery PI	4.16713	1.11107	64.530	7.312-569.515	0.0002
Log_{10} MoM PlGF	-2.47115	0.66785	0.084	0.023-0.313	0.0002
Log_{10} MoM $PlGF^2$	2.04541	0.71210	7.732	1.915-31.221	0.0004
Maternal factors with uterine artery PI and sFlt-1 (R2=0.224, P<0.0001)					
Intercept	-3.95822	1.01181			
Logit (*a priori* risk)	1.09980	0.48899	3.004	1.152-7.832	0.025
Log_{10} MoM uterine artery PI	5.68840	1.33892	295.421	21.416-4,075.070	<0.0001
Log_{10} MoM sFlt-1	2.59822	0.73798	13.440	3.164-57.091	0.0004
Log_{10} MoM $sFlt\text{-}1^2$	5.49748	1.20370	244.076	23.064-2,582.936	<0.0001
Maternal factors with MAP and PlGF (R2=0.305, P<0.0001)					
Intercept	-2.79195	0.78851			
Logit (*a priori* risk)	1.77698	0.39229	5.912	2.740-12.754	<0.0001
Log_{10} MoM MAP	12.42561	4.79554	$2.49x10^5$	$2.06x10^1$-$3.01x10^9$	0.010
Log_{10} MoM MAP^2	162.07547	65.65366	$2.45x10^{70}$	$3.19x10^{14}$-$1.87x10^{126}$	0.014
Log_{10} MoM PlGF	-2.35756	0.65464	0.095	0.026-0.341	0.0003
Log_{10} MoM $PlGF^2$	2.04145	0.70998	7.702	1.915-30.969	0.004
Maternal factors with MAP and sFlt-1 (R2=0.234, P<0.0001)					
Intercept	-4.09257	1.01573			
Logit (*a priori* risk)	1.06977	0.48445	2.915	1.128-7.533	0.027
Log_{10} MoM MAP	24.37075	5.47976	$3.84x10^{10}$	$8.31x10^5$-$1.77x10^{15}$	<0.0001
Log_{10} MoM sFlt-1	2.18393	0.75327	8.881	2.029-38.873	0.004
Log_{10} MoM $sFlt\text{-}1^2$	5.56881	1.23220	262.122	23.424-2,933.289	<0.0001
Maternal factors with uterine artery PI, MAP and PlGF (R2=0.323, P<0.0001)					
Intercept	-2.92716	0.80577			
Logit (*a priori* risk)	1.75402	0.39929	5.778	2.642-12.637	<0.0001
Log_{10} MoM uterine artery PI	3.78879	1.12679	44.203	4.856-402.326	0.0008
Log_{10} MoM MAP	12.99747	4.90222	$4.41x10^5$	$2.96x10^1$-$6.57x10^9$	0.008
Log_{10} MoM MAP^2	148.55851	70.45710	$3.30x10^{64}$	$3.51x10^4$-$3.10x10^{124}$	0.035
Log_{10} MoM PlGF	-2.13041	0.64357	0.119	0.034-0.419	0.0009
Log_{10} MoM $PlGF^2$	1.99944	0.68225	7.385	1.939-28.124	0.0003
Maternal factors with uterine artery PI, MAP and sFlt-1 (R2=0.269, P<0.0001)					
Intercept	-4.24894	1.00409			
Logit (*a priori* risk)	1.08653	0.48262	2.964	1.151-7.633	0.024
Log_{10} MoM uterine artery PI	5.47521	1.37251	238.700	16.202-3,516.732	<0.0001
Log_{10} MoM MAP	23.12414	5.43885	$1.10x10^{10}$	$2.59x10^5$-$4.70x10^{14}$	<0.0001
Log_{10} MoM sFlt-1	2.17186	0.76749	8.775	1.950-39.492	0.005
Log_{10} MoM $sFlt\text{-}1^2$	5.58406	1.27440	266.149	21.895-3,235.184	<0.0001

Table 6.5 continued

Independent variable	Coefficient	Standard error	OR	95% CI	P-value
Maternal factors with uterine artery PI, PIGF and sFlt-1 (R2=0.331, P<0.0001)					
Intercept	-4.48357	0.98483			
Logit (*a priori* risk)	1.08912	0.47402	2.972	1.174-7.525	0.022
Log_{10} MoM uterine artery PI	3.21940	1.35750	25.013	1.748-357.828	0.018
Log_{10} MoM PlGF	-3.94445	0.57646	0.019	0.006-0.060	<0.0001
Log_{10} MoM sFlt-1	2.93288	0.80007	18.782	3.915-90.107	0.0002
Maternal factors with MAP, PIGF and sFlt-1 (R2=0.339, P<0.0001)					
Intercept	-4.58182	0.99462			
Logit (*a priori* risk)	1.07305	0.47303	2.924	1.157-7.390	0.023
Log_{10} MoM MAP	15.99888	5.44778	$8.88x10^{6}$	$2.05x10^{2}$-$3.85x10^{11}$	0.003
Log_{10} MoM PlGF	-3.96068	0.58119	0.019	0.006-0.060	<0.0001
Log_{10} MoM sFlt-1	2.57170	0.79778	13.088	2.740-62.510	0.001
Maternal factors with uterine artery PI, MAP, PIGF and sFlt-1 (R2=0.351, P<0.0001)					
Intercept	-4.56169	0.98840			
Logit (*a priori* risk)	1.10150	0.47480	3.009	1.185-7.630	0.020
Log_{10} MoM uterine artery PI	3.18315	1.37098	24.123	1.642-354.328	0.020
Log_{10} MoM MAP	15.71448	5.45309	$6.68x10^{6}$	$1.52x10^{2}$-$2.93x10^{11}$	0.004
Log_{10} MoM PlGF	-3.67425	0.58309	0.025	0.008-0.080	<0.0001
Log_{10} MoM sFlt-1	2.71360	0.80680	15.083	3.103-73.324	0.0008
Maternal factors with EFW, uterine artery PI and PIGF (R2=0.530, P<0.0001)					
Intercept	-3.57426	0.90440			
Logit (*a priori* risk)	1.46304	0.45530	4.319	1.760-10.542	0.001
EFW Z-score	-2.94953	0.26541	0.052	0.031-0.088	<0.0001
Log_{10} MoM uterine artery PI	3.05318	1.19129	21.183	2.051-218.782	0.010
Log_{10} MoM PlGF	-3.50376	0.49086	0.030	0.011-0.079	<0.0001
Maternal factors with EFW, MAP and PIGF (R2=0.546, P<0.0001)					
Intercept	-3.40484	0.90510			
Logit (*a priori* risk)	1.62320	0.46313	5.069	2.045-12.565	0.0005
EFW Z-score	-3.03101	0.27528	0.048	0.028-0.083	<0.0001
Log_{10} MoM MAP	19.25106	4.88855	$2.29x10^{8}$	$1.58x10^{4}$-$3.32x10^{12}$	<0.0001
Log_{10} MoM PlGF	-3.35886	0.48537	0.035	0.013-0.090	<0.0001
Maternal factors with EFW, uterine artery PI, MAP and PIGF (R2=0.553, P<0.0001)					
Intercept	-3.55561	0.91124			
Logit (*a priori* risk)	1.56000	0.46423	4.759	1.916-11.821	<0.0001
EFW Z-score	-3.02445	0.27920	0.049	0.028-0.084	<0.0001
Log_{10} MoM uterine artery PI	2.67801	1.23705	14.556	1.288-164.445	0.030
Log_{10} MoM MAP	18.17900	4.89587	$7.85x10^{7}$	$5.34x10^{3}$-$1.15x10^{12}$	0.0002
Log_{10} MoM PlGF	-3.15184	0.49666	0.043	0.016-0.113	<0.0001

OR = odds ratio; CI = confidence interval; MoM = multiple of median; EFW = estimated fetal weight; uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Table 6.6. Fitted regression models with maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure, serum placental growth factor and soluble fms-like tyrosine kinase-1 for the prediction of small for gestational age neonates with BW <5th centile delivering at ≥5 weeks of assessment without preeclampsia.

Independent variable	Coefficient	Standard error	OR	95% CI	P-value
Maternal factors with uterine artery PI and PlGF (R2=0.144, P<0.0001)					
Intercept	0.80143	0.28497			
Logit (*a priori* risk)	1.98754	0.14293	7.298	5.515-9.657	<0.0001
Log_{10} MoM uterine artery PI	1.85797	0.42621	6.411	2.780-14.781	<0.0001
Log_{10} MoM PlGF	-1.96016	0.15827	0.141	0.103-0.192	<0.0001
Maternal factors with uterine artery PI and sFlt-1 (R2=0.093, P<0.0001)					
Intercept	0.84778	0.31200			
Logit (*a priori* risk)	1.97548	0.15642	7.210	5.306-9.797	<0.0001
Log_{10} MoM uterine artery PI	2.42037	0.47765	11.250	4.411-28.690	<0.0001
Log_{10} MoM sFlt-1	0.72056	0.26497	2.056	1.223-3.4555	0.007
Log_{10} MoM sFlt-1^2	1.54632	0.70638	4.694	1.176-18.743	0.029
Maternal factors with MAP and PlGF (R2=0.142, P<0.0001)					
Intercept	0.88102	0.28482			
Logit (*a priori* risk)	2.01847	0.14318	7.527	5.685-9.965	<0.0001
Log_{10} MoM MAP	5.03367	1.52942	153.495	7.660-3,075.673	0.001
Log_{10} MoM PlGF	-1.97169	0.15936	0.139	0.102-0.190	<0.0001
Maternal factors with MAP and sFlt-1 (R2=0.091, P<0.0001)					
Intercept	0.96939	0.31108			
Logit (*a priori* risk)	2.02559	0.15646	7.581	5.579-10.301	<0.0001
Log_{10} MoM MAP	7.61579	1.67880	$2.03x10^3$	$7.56x10^1$-$5.45x10^4$	<0.0001
Log_{10} MoM sFlt-1	0.57221	0.26568	1.772	1.053-2.983	0.031
Log_{10} MoM sFlt-1^2	1.54336	0.71185	4.680	1.160-18.888	0.030
Maternal factors with uterine artery PI, MAP and PlGF (R2=0.148, P<0.0001)					
Intercept	0.78517	0.28559			
Logit (*a priori* risk)	1.98442	0.14320	7.275	5.495-9.632	<0.0001
Log_{10} MoM uterine artery PI	1.88494	0.42619	6.586	2.857-15.184	<0.0001
Log_{10} MoM MAP	5.17059	1.53256	176.019	8.731-3,547.755	0.0007
Log_{10} MoM PlGF	-1.86942	0.16009	0.154	0.113-0.211	<0.0001
Maternal factors with uterine artery PI, MAP and sFlt-1 (R2=0.102, P<0.0001)					
Intercept	0.81649	0.31341			
Logit (*a priori* risk)	1.97084	0.15705	7.177	5.275-9.763	<0.0001
Log_{10} MoM uterine artery PI	2.42725	0.47791	11.328	4.440-28.903	<0.0001
Log_{10} MoM MAP	7.65816	1.68185	$2.12x10^3$	$7.84x10^1$-$5.72x10^4$	<0.0001
Log_{10} MoM sFlt-1	0.63354	0.26700	1.884	1.117-3.180	0.018
Log_{10} MoM sFlt-1^2	1.49583	0.71536	4.463	1.098-18.136	0.037
Maternal factors with EFW, uterine artery PI and PlGF (R2=0.308, P<0.0001)					
Intercept	0.03546	0.31311			
Logit (*a priori* risk)	1.48661	0.15610	4.422	3.257-6.005	<0.0001
EFW Z-score	-2.24097	0.12861	0.106	0.083-0.137	<0.0001
EFW Z-score^2	-0.18896	0.08824	0.828	0.696-0.984	0.032
EFW Z-score^3	0.14003	0.02937	1.150	1.086-1.218	<0.0001
Log_{10} MoM uterine artery PI	1.52684	0.45118	4.604	1.901-11.147	0.0007
Log_{10} MoM PlGF	-1.76712	0.16922	0.171	0.123-0.238	<0.0001

Table 6.6 continued.

Independent variable	Coefficient	Standard error	OR	95% CI	P-value
Maternal factors with EFW, uterine artery PI and sFlt-1 (R2=0.264, P<0.0001)					
Intercept	-0.03601	0.34182			
Logit (*a priori* risk)	1.41058	0.17029	4.098	2.935-5.722	<0.0001
EFW Z-score	-2.23446	0.13869	0.107	0.082-0.140	<0.0001
EFW Z-score^2	-0.22485	0.09412	0.799	0.664-0.960	0.017
EFW Z-score^3	0.14776	0.03086	1.159	1.091-1.232	<0.0001
Log_{10} MoM uterine artery PI	2.15242	0.49719	8.606	3.248-22.803	<0.0001
Log_{10} MoM sFlt-1	0.62600	0.27709	1.870	1.086-3.219	0.024
Log_{10} MoM sFlt-1^2	1.72598	0.74936	5.618	1.293-24.403	0.021
Maternal factors with EFW, MAP and PlGF (R2=0.308, P<0.0001)					
Intercept	0.10614	0.31164			
Logit (*a priori* risk)	1.51631	0.15578	4.555	3.357-6.182	<0.0001
EFW Z-score	-2.24455	0.12810	0.106	0.082-0.136	<0.0001
EFW Z-score^2	-0.18885	0.08866	0.828	0.696-0.985	0.033
EFW Z-score^3	0.13942	0.02977	1.150	1.084-1.219	<0.0001
Log_{10} MoM MAP	5.30605	1.59886	201.552	8.779-4,627.457	0.0009
Log_{10} MoM PlGF	-1.77027	0.16937	0.170	0.122-0.237	<0.0001
Maternal factors with EFW, MAP and sFlt-1 (R2=0.263, P<0.0001)					
Intercept	0.14460	0.34046			
Logit (*a priori* risk)	1.45106	0.17064	4.268	3.055-5.963	<0.0001
EFW Z-score	-2.22784	0.13790	0.108	0.082-0.141	<0.0001
EFW Z-score^2	-0.22548	0.09571	0.798	0.662-0.963	0.018
EFW Z-score^3	0.14645	0.03166	1.158	1.088-1.232	<0.0001
Log_{10} MoM MAP	7.55916	1.72608	$1.92x10^3$	$6.51x10^1$-$5.65x10^4$	<0.0001
Log_{10} MoM sFlt-1	0.65725	0.28611	1.929	1.101-3.380	0.022
Maternal factors with EFW, uterine artery PI, MAP and sFlt-1 (R2=0.270, P<0.0001)					
Intercept	0.02219	0.34250			
Logit (*a priori* risk)	1.41176	0.17108	4.103	2.934-5.738	<0.0001
EFW Z-score	-2.21483	0.13830	0.109	0.083-0.143	<0.0001
EFW Z-score^2	-0.21358	0.09605	0.808	0.669-0.975	0.026
EFW Z-score^3	0.14289	0.03194	1.154	1.084-1.228	<0.0001
Log_{10} MoM uterine artery PI	2.13888	0.49717	8.490	3.204-22.496	<0.0001
Log_{10} MoM MAP	7.47687	1.72867	$1.77x10^3$	$5.97x10^1$-$5.23x10^4$	<0.0001
Log_{10} MoM sFlt-1	0.68283	0.28685	1.979	1.128-3.473	0.017
Maternal factors with EFW, uterine artery PI, MAP and PlGF (R2=0.312, P<0.0001)					
Intercept	-0.03623	0.31286			
Logit (*a priori* risk)	1.49274	0.15606	4.449	3.277-6.041	<0.0001
EFW Z-score	-2.23360	0.12838	0.107	0.083-0.138	<0.0001
EFW Z-score^2	-0.18087	0.08898	0.835	0.701-0.994	0.042
EFW Z-score^3	0.13694	0.02994	1.147	1.081-1.216	<0.0001
Log_{10} MoM uterine artery PI	1.52707	0.45105	4.605	1.902-11.146	0.0007
Log_{10} MoM MAP	5.31788	1.60204	203.951	8.828-4,711.774	0.0009
Log_{10} MoM PlGF	-1.67582	0.17136	0.187	0.134-0.262	<0.0001

OR = odds ratio; CI = confidence interval; MoM = multiple of median; EFW = estimated fetal weight; uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Prediction of SGA delivering at <5 and ≥5 weeks from screening

Multivariable logistic regression analysis demonstrated that in the prediction of SGA <5th delivering at <5 weeks and at ≥5 weeks of assessment there were significant independent contributions from maternal factors, EFW, uterine artery PI, MAP, serum PlGF and serum sFlt-1, but the best prediction was provided by a combination of maternal factors, EFW, uterine artery PI, MAP and serum PlGF without inclusion of sFlt-1 (**Tables 6.5, 6.6, 6.7, 6.8** and **6.9**).

The areas under ROC (AUROC) and the DRs, at FPRs of 5% and 10%, of SGA <10th, SGA <5th and SGA <3rd delivering at <5 and at ≥5 weeks of assessment in screening by maternal factors, EFW Z-score, uterine artery PI, MAP and serum PlGF are given in **Tables 6.7, 6.8** and **6.9**.

Performance of screening for SGA delivering at <5 and ≥5 weeks from screening

In combined screening by maternal factors, EFW, uterine artery PI, MAP and serum PlGF at 30-34 weeks' gestation, the DRs at FPR of 5% and 10% and FPR for DR of 80%, 90% and 100%, of SGA neonates with BW <10th, <5th and <3rd centiles delivering at <5 and ≥5 weeks from screening are shown in **Table 6.10** and the ROC curves are shown in **Figures 6.1** and **6.2**.

6.4 Discussion

6.4.1 Main findings of the study

Our study has shown that when screening for SGA neonates at 30-34 weeks' gestation with the combination of maternal factors, fetal biometry, MAP, uterine artery PI, and serum PlGF predicted, in those delivering between 32-36 weeks' gestation and at 10% FPR, 89% for those with a BW <10th centile, 94% for those with a BW <5th centile, and 96% for those with a BW <3rd centile. Using the same combination of factors and for the same 10% FPR, the DR for those delivering after 37 weeks of gestation were 57% for those with a BW <10th centile, 65% for those with a BW <5th centile, and 72% for those with a BW <3rd centile.

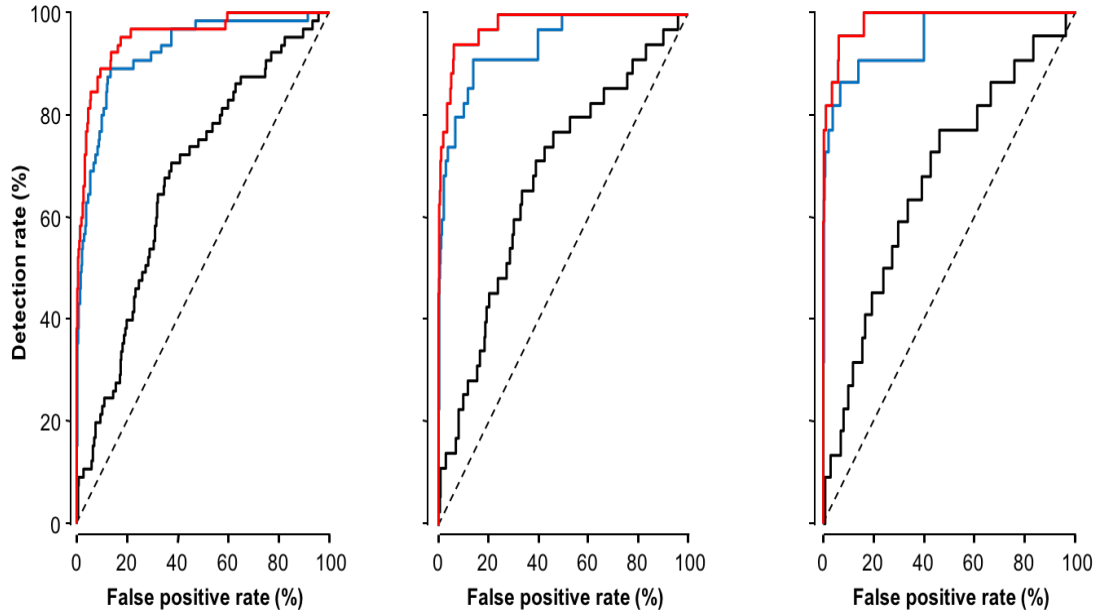

Figure 6.1. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor (red line) in the prediction of small for gestational age neonates with BW 10th (left) <5th (middle) and 3rd (right) centile delivering at 32-36 weeks' gestation.

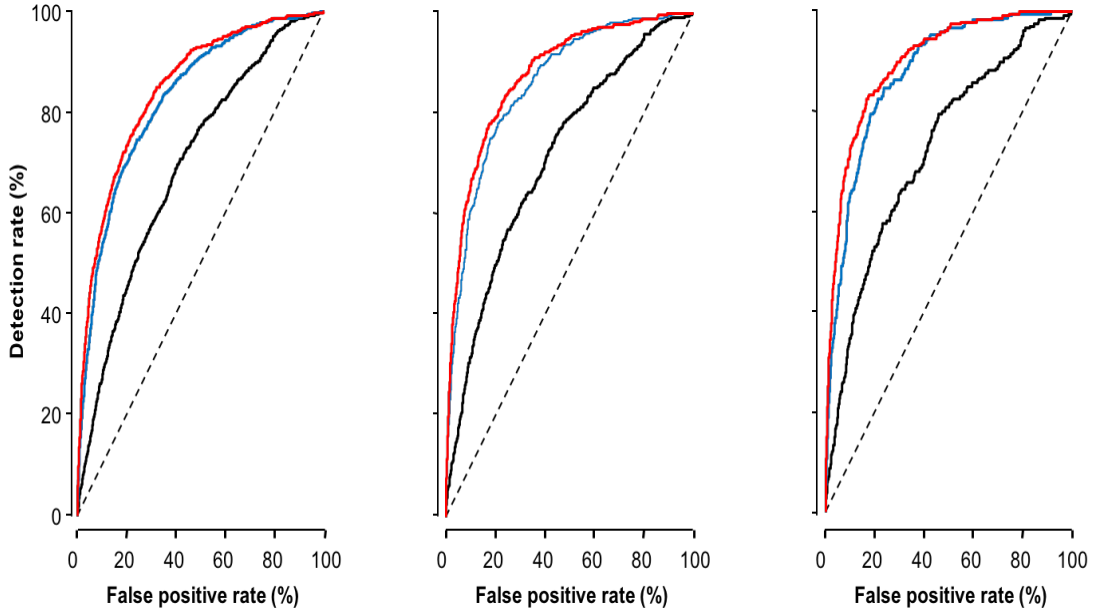

Figure 6.2. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor (red line) in the prediction of small for gestational age neonates with BW 10th (left) <5th (middle) and 3rd (right) centile delivering at ≥37 weeks' gestation.

Table 6.7. Area under receiver operating characteristic curve and detection rate for false positive rates of 5% and 10%, with 95% confidence interval, of screening for small for gestational age with BW <10th centile in the absence of preeclampsia, delivering at <5 and at ≥5 weeks after assessment with maternal factors, estimated fetal weight and various biomarkers.

Screening test	SGA delivery at <5 weeks of assessment			SGA delivery at ≥5 weeks of assessment		
	AUROC	DR for FPR 5%	DR for FPR 10%	AUROC	DR for FPR 5%	DR for FPR 10%
Maternal factors	0.678 (0.668-0.687)	12.5 (6.4-21.3)	22.7 (14.5-32.9)	0.693 (0.683-0.702)	14.4 (12.1-16.9)	27.0 (24.1-30.0)
Maternal factors plus						
EFW	0.914 (0.908-0.920)	63.6 (52.7-73.6)	76.1 (65.9-84.6)	0.828 (0.820-0.836)	34.9 (31.8-38.2)	53.3 (49.9-56.6)
Uterine artery PI, PlGF	0.849 (0.841-0.856)	51.1 (40.2-61.9)	60.2 (49.2-70.5)	0.746 (0.737-0.755)	21.6 (18.9-24.4)	36.3 (33.1-39.5)
Uterine artery PI, sFlt-1	0.804 (0.795-0.813)	43.6 (31.0-56.7)	52.2 (40.1-66.0)	0.703 (0.693-0.713)	15.2 (12.7-18.1)	29.9 (26.6-33.4)
MAP, PlGF	0.855 (0.847-0.862)	52.3 (41.4-63.0)	60.2 (49.2-70.5)	0.741 (0.732-0.750)	26.7 (19.0-24.5)	33.7 (30.6-36.9)
MAP, sFlt-1	0.801 (0.792-0.810)	35.5 (23.7-48.7)	48.4 (35.5-61.4)	0.692 (0.681-0.702)	15.7 (13.1-18.5)	27.6 (24.3-31.0)
Uterine artery PI, MAP, PlGF	0.863 (0.856-0.870)	54.6 (43.6-65.2)	62.5 (51.5-72.6)	0.746 (0.737-0.754)	22.5 (19.8-25.4)	35.8 (32.7-39.1)
Uterine artery PI, MAP, sFlt-1	0.831 (0.822-0.840)	43.6 (31.0-56.7)	54.8 (41.7-67.5)	0.703 (0.693-0.714)	16.6 (14.0-19.5)	28.5 (25.3-32.0)
Uterine artery PI, PlGF, sFlt-1	0.858 (0.849-0.866)	56.5 (43.3-69.0)	64.5 (51.3-76.3)	-	-	-
MAP, PlGF, sFlt-1	0.859 (0.850-0.867)	53.2 (40.1-66.0)	62.9 (49.7-74.8)	-	-	-
Uterine artery PI, MAP, PlGF, sFlt-1	0.867 (0.859-0.875)	54.8 (41.7-67.5)	61.3 (48.1-73.4)	-	-	-
Maternal factors, EFW plus						
Uterine artery PI, PlGF	0.957 (0.952-0.961)	75.0 (64.6-83.6)	87.5 (78.7-93.6)	0.848 (0.841-0.855)	43.3 (40.0-46.6)	58.3 (55.0-61.6)
Uterine artery PI, sFlt-1	-	-	-	0.822 (0.814-0.831)	34.5 (31.0-38.1)	52.2 (48.5-55.9)
MAP, PlGF	0.953 (0.948-0.957)	76.1 (65.9-84.6)	86.4 (77.4-92.8)	0.846 (0.838-0.853)	42.9 (39.6-46.2)	56.5 (53.2-59.8)
MAP, sFlt-1	-	-	-	0.818 (0.809-0.827)	35.0 (31.6-38.6)	51.8 (48.1-55.5)
Uterine artery PI, MAP, PlGF	0.957 (0.953-0.961)	79.6 (69.6-87.4)	89.8 (81.5-94.2)	0.848 (0.840-0.855)	43.8 (40.5-47.2)	57.4 (54.1-60.7)
Uterine artery PI, MAP, sFlt-1	-	-	-	0.822 (0.814-0.831)	36.3 (32.8-39.9)	53.6 (49.3-56.7)

AUROC = area under receiver operating characteristic curve; DR = detection rate; FPR = false positive rate; SGA = small for gestational age; EFW = estimated fetal weight; uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Table 6.8. Area under receiver operating characteristic curve and detection rate for false positive rates of 5% and 10%, with 95% confidence interval, of screening for small for gestational age with BW <5th centile in the absence of preeclampsia, delivering at <5 and at ≥5 weeks after assessment with maternal factors, estimated fetal weight and various biomarkers.

Screening test	SGA delivery at <5 weeks of assessment			SGA delivery at ≥5 weeks of assessment		
	AUROC	DR for FPR 5%	DR for FPR 10%	AUROC	DR for FPR 5%	DR for FPR 10%
Maternal factors	0.680 (0.670-0.690)	15.7 (7.0-28.6)	25.5 (14.3-39.6)	0.712 (0.703-0.721)	17.0 (13.5-20.9)	31.6 (27.1-36.3)
Maternal factors plus						
EFW	0.941 (0.936-0.945)	72.6 (58.3-84.1)	80.4 (66.9-90.2)	0.857 (0.850-0.864)	41.2 (36.4-46.0)	60.3 (55.4-65.0)
Uterine artery PI, PlGF	0.881 (0.874-0.888)	58.8 (44.2-72.4)	70.6 (56.2-82.5)	0.774 (0.765-0.782)	24.6 (20.6-29.1)	41.4 (36.6-46.3)
Uterine artery PI, sFlt-1	0.839 (0.831-0.848)	55.9 (37.9-72.8)	64.7 (46.5-80.3)	0.727 (0.717-0.737)	19.0 (14.9-23.6)	33.5 (28.5-38.8)
MAP, PlGF	0.905 (0.898-0.911)	62.8 (48.1-75.9)	70.6 (56.2-82.5)	0.773 (0.764-0.781)	27.0 (22.8-31.6)	39.5 (34.8-44.3)
MAP, sFlt-1	0.858 (0.850-0.866)	52.9 (35.1-70.2)	64.7 (46.5-80.3)	0.725 (0.715-0.735)	20.8 (16.6-25.5)	34.1 (29.1-39.5)
Uterine artery PI, MAP, PlGF	0.905 (0.898-0.911)	56.9 (42.2-70.7)	70.6 (56.2-82.5)	0.777 (0.768-0.785)	28.2 (24.0-32.8)	42.3 (37.6-47.2)
Uterine artery PI, MAP, sFlt-1	0.873 (0.866-0.881)	52.9 (35.1-70.2)	67.7 (49.5-82.6)	0.736 (0.726-0.746)	23.2 (18.7-28.0)	31.8 (26.8-37.0)
Uterine artery PI, PlGF, sFlt-1	0.881 (0.874-0.889)	70.6 (52.5-84.9)	76.5 (58.8-89.3)	-	-	-
MAP, PlGF, sFlt-1	0.897 (0.890-0.904)	70.6 (52.5-84.9)	76.5 (58.8-89.3)	-	-	-
Uterine artery PI, MAP, PlGF, sFlt-1	0.897 (0.890-0.904)	67.7 (49.5-82.6)	76.5 (58.8-89.3)	-	-	-
Maternal factors, EFW plus						
Uterine artery PI, PlGF	0.977 (0.974-0.980)	82.4 (69.1-91.6)	94.1 (83.8-98.8)	0.877 (0.870-0.883)	47.6 (42.7-52.5)	64.8 (60.0-69.4)
Uterine artery PI, sFlt-1	-	-	-	0.856 (0.848-0.864)	43.0 (37.7-48.5)	59.1 (53.6-64.3)
MAP, PlGF	0.976 (0.973-0.979)	84.3 (71.4-93.0)	76.5 (58.8-89.3)	0.877 (0.870-0.884)	46.7 (41.8-51.6)	65.1 (60.3-69.6)
MAP, sFlt-1	-	-	-	0.857 (0.849-0.865)	42.4 (37.1-47.9)	59.6 (54.2-64.9)
Uterine artery PI, MAP, PlGF	0.979 (0.976-0.982)	84.3 (71.4-93.0)	94.1 (83.8-98.8)	0.878 (0.871-0.885)	49.3 (44.4-54.2)	65.3 (60.5-69.9)
Uterine artery PI, MAP, sFlt-1	-	-	-	0.859 (0.851-0.867)	43.6 (38.3-49.1)	60.8 (55.4-66.1)

AUROC = area under receiver operating characteristic curve; DR = detection rate; FPR = false positive rate; SGA = small for gestational age; EFW = estimated fetal weight; uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Table 6.9. Area under receiver operating characteristic curve and detection rate for false positive rates of 5% and 10%, with 95% confidence interval, of screening for small for gestational age with BW <3rd centile in the absence of preeclampsia, delivering at <5 and at ≥5 weeks after assessment with maternal factors, estimated fetal weight and various biomarkers.

Screening test	SGA delivery at <5 weeks of assessment			SGA delivery at ≥5 weeks of assessment		
	AUROC	DR for FPR 5%	DR for FPR 10%	AUROC	DR for FPR 5%	DR for FPR 10%
Maternal factors	0.710 (0.700-0.719)	15.6 (5.3-82.8)	28.1 (13.7-46.7)	0.722 (0.712-0.731)	19.8 (15.1-25.3)	34.5 (28.7-40.7)
Maternal factors plus						
EFW	0.952 (0.947-0.956)	81.3 (63.6-92.8)	84.4 967.2-94.7)	0.878 (0.871-0.884)	42.1 (35.9-48.4)	63.1 (56.8-69.1)
Uterine artery PI, PlGF	0.878 (0.871-0.885)	62.5 (43.7-78.9)	75.0 (56.6-88.5)	0.793 (0.784-0.801)	29.4 (23.8-35.4)	46.0 (39.8-52.4)
Uterine artery PI, sFlt-1	0.842 (0.833-0.850)	60.9 (38.5-80.3)	69.6 (47.1-86.8)	0.744 (0.734-0.754)	22.7 (17.1-29.0)	37.4 (30.8-44.5)
MAP, PlGF	0.906 (0.900-0.912)	59.4 (40.6-76.3)	71.9 (53.3-86.3)	0.795 (0.786-0.803)	33.3 (27.5-39.5)	44.4 (38.2-50.8)
MAP, sFlt-1	0.844 (0.836-0.852)	47.8 (26.8-69.4)	60.9 (38.5-80.3)	0.746 (0.736-0.756)	26.6 (20.7-33.2)	39.9 (33.1-47.0)
Uterine artery PI, MAP, PlGF	0.903 (0.897-0.909)	50.0 (31.9-68.1)	71.9 (53.3-86.3)	0.799 (0.790-0.807)	33.7 (27.9-39.9)	46.8 (40.5-53.2)
Uterine artery PI, MAP, sFlt-1	0.862 (0.853-0.869)	52.2 (30.6-73.2)	65.2 (42.7-83.6)	0.761 (0.751-0.770)	26.6 (20.7-33.2)	39.4 (32.6-46.5)
Uterine artery PI, PlGF, sFlt-1	0.885 (0.878-0.892)	78.3 (56.3-92.5)	78.3 (56.3-92.5)	-	-	-
MAP, PlGF, sFlt-1	0.903 (0.896-0.910)	69.6 (47.1-86.8)	78.3 (56.3-92.5)	-	-	-
Uterine artery PI, MAP, PlGF, sFlt-1	0.901 (0.894-0.909)	65.2 (42.7-83.6)	78.3 (56.3-92.5)	-	-	-
Maternal factors, EFW plus						
Uterine artery PI, PlGF	0.983 (0.980-0.986)	87.5 (71.0-96.5)	93.8 (79.2-99.2)	0.898 (0.892-0.904)	52.4 (46.0-58.7)	71.0 (65.-76.6)
Uterine artery PI, sFlt-1	-	-	-	0.877 (0.869-0.884)	46.8 (39.8-53.9)	63.1 (56.0-69.7)
MAP, PlGF	0.982 (0.979-0.985)	87.5 (71.0-96.5)	93.8 (79.2-99.2)	0.901 (0.895-0.907)	52.4 (46.0-58.7)	71.8 (65.8-77.3)
MAP, sFlt-1				0.881 (0.873-0.888)	45.8 (38.8-52.9)	63.1 (56.0-69.7)
Uterine artery PI, MAP, PlGF	0.984 (0.982-0.987)	87.5 (71.0-96.5)	93.8 (79.2-99.2)	0.901 (0.895-0.907)	54.8 (48.4-61.0)	71.4 (65.4-76.9)
Uterine artery PI, MAP, sFlt-1	-	-	-	0.882 (0.875-0.890)	47.3 (40.3-54.4)	65.0 (58.0-71.6)

AUROC = area under receiver operating characteristic curve; DR = detection rate; FPR = false positive rate; SGA = small for gestational age; EFW = estimated fetal weight; uterine PI = uterine artery pulsatility index; MAP = mean arterial pressure; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.

Table 6.10. Performance of screening for small for gestational age neonates with BW <10th, <5th and <3rd centile delivering at 32-36 and ≥37 weeks' gestation in the absence of preeclampsia by a combination of maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor at 30-34 weeks' gestation.

Outcome	DR (%)		FPR (%)		
	FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
Delivery at 32-36 weeks					
SGA <10th centile	81.5 (70.0-90.1)	89.2 (79.1-95.6)	59.8 (58.7-60.8)	13.5 (12.8-14.2)	4.7 (4.2-5.1)
SGA <5th centile	82.9 (66.4-93.4)	94.3 (80.8-99.3)	24.0 (23.1-24.9)	6.0 (5.5-6.5)	3.6 (3.2-4.0)
SGA <3rd centile	86.4 (65.1-97.1)	95.5 (77.2-99.9)	16.1 (15.3-16.8)	6.0 (5.5-6.5)	1.1 (0.9-1.4)
Delivery at ≥37 weeks					
SGA <10th centile	43.9 (40.6-47.2)	57.4 (54.1-60.7)	99.9 (99.8-100.0)	42.2 (41.1-43.3)	27.2 (26.2-28.1)
SGA <5th centile	49.4 (44.5-54.3)	65.3 (60.5-69.9)	89.6 (88.9-90.2)	34.5 (33.6-35.5)	20.8 (20.0-21.7)
SGA <3rd centile	55.0 (48.6-61.3)	71.5 (65.4-77.0)	78.6 (77.8-79.5)	30.2 (29.3-31.2)	15.3 (14.5-16.0)

DR = detection rate; FPR = false positive rate; SGA = small for gestational age.

6.4.2 Comparison with findings from previous studies

In the previous chapters we have reported the performance of screening for SGA neonates by maternal factors and fetal biometry (chapter 3) and how this performance is improved by the addition of uterine artery PI and MAP (chapter 4) or serum PlGF and sFlt-1 (chapter 5). In this chapter we have combined screening using biophysical and biochemical markers to produce this final result.

There are no other studies that combine both biophysical and biochemical markers in the third trimester to compare our findings to. However, two studies are similar. An Italian study did examine the use of AC, EFW and uterine artery Doppler to identify SGA neonates in the third trimester. The study was much smaller (1848 pregnancies), was carried out slightly earlier, 30-33 weeks', and did not use MAP or biochemical profiles and only looked at deliveries beyond 37 weeks' gestation. For a FPR of 17% the study identified 71% of SGA neonates with a BW <5th centile and for a FPR of 27% the study identified 72% of SGA neonates with a BW <between the 5th and 10th centile (di Lorenzo *et al.,* 2012). The DR for those with a BW <5th centile was similar to ours, albeit with an increased FPR, however the DR for those with a BW between the 5th and 10th centile was better. This could be explained by the much larger FPR of 27%. It is not possible to extrapolate this study's results back to a FPR of 10% to make a direct comparison; however, the similar results enhance the validity of our study.

A very similar study in the first trimester, which combined maternal characteristics, fetal nuchal translucency thickness, PAPP-A, and free βhCG, MAP, uterine artery PI, PlGF, placental protein 13 (PP13) and A Disintegrin And Metalloprotease (ADAM12). For a FPR of 10%, and in neonates with a BW <5th centile, this study detected 73% of those needing delivery before 37 weeks and 46% of those delivering after 37 weeks (Karagiannis *et al.,* 2010). The early gestation and accuracy of this screening test, especially in those delivered preterm is impressive, however, its ability to detect those delivered at term is weaker. Regardless, though this screening test is less accurate, it does allow time to implement an earlier surveillance scheme in those who screen positive and to implement any treatment at an early gestation.

Chapter 7: Umbilical and fetal middle cerebral artery Doppler at 30–34 weeks' gestation in the prediction of adverse perinatal outcome

ABSTRACT

Objective: To investigate the potential value of cerebroplacental ratio (CPR) at 30-34 weeks' gestation in the prediction of adverse perinatal outcome.

Methods: Screening study in 30,780 singleton pregnancies at 30-34 weeks. UA and MCA PI were measured, the values were converted to MoM after adjustment from variables in maternal characteristics and medical history that affect the measurements and the CPR was calculated by dividing MCA PI MoM with UA PI MoM. Multivariable logistic regression analysis was used to determine if CPR had a significant additional contribution to maternal characteristics, medical history and obstetric factors in predicting adverse outcome. The DR and FPR of screening by CPR were estimated for stillbirth, CS for fetal distress, umbilical artery cord blood pH <7.0, umbilical venous pH <7.1, Apgar score <7 at 5 minutes and admission to the NNU and neonatal intensive unit (NICU).

Results: There was a significant association between CPR and BW Z-score. Significant contribution, in addition to maternal characteristics, medical history and obstetric factors, was provided by CPR in the prediction of arterial blood pH ≤7.0, venous blood pH ≤7.1 and admission to NNU. The performance of CPR in screening for each adverse outcome was poor with DR of 5-11% and FPR of about 5%. In the small subgroup of the population delivering within two weeks of assessment, the DR improved to 20-50%, but with a simultaneous increase in FPR to 10-23%.

Conclusion: The performance of CPR in routine screening for adverse perinatal outcome at 30-34 weeks' gestation is poor.

This chapter is based on:

Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2015 Apr;45(4):409-20.

7.1 Introduction

SGA neonates can be separated in to two groups: constitutionally small or growth restricted. The latter can be due to a variety of causes such as impaired placentation, fetal abnormalities or adverse environmental effects, such as congenital infection. In FGR the perinatal outcome and long-term neurodevelopment are worse than in constitutionally small fetuses (Cruz-Martínez *et al.,* 2011; Eixarch *et al.,* 2008; Gramellini *et al.,* 1992; Odibo, *et al.,* 2005).

Due to these differences in outcomes, it is important to distinguish, whether a structurally normal SGA fetus belongs to the FGR group, and if so, determine the best time, place and mode of delivery. Currently, assessment is by measurement of the UA and MCA Doppler PI and calculation of the CPR. It has been established, by fetal blood sampling, for more than twenty five years that increased impedance to flow in the UA and decreased impedance in the MCA are associated with fetal hypoxemia and acidaemia (Nicolaides *et al.,* 1986; Soothill *et al.,* 1987; Nicolaides *et al.,* 1988; Vyas *et al.,* 1990). UA PI is a direct measurement of placental resistance, whilst MCA measures the fetal compensatory *'brain-sparing effect'*. CPR reflects both the placental status and fetal response, and may be a more sensitive Doppler index for predicting perinatal outcome (Gramellini *et al.,* 1992).

If adverse outcomes are due to impaired placentation, and, if this is better reflected by CPR rather than SGA, then prenatal screening for fetal hypoxia may be preferable. There is an increasing body of evidence suggesting that a low CPR is associated with the need for operative delivery for presumed fetal compromise and poor perinatal outcomes such as low neonatal blood pH and NNU admission (Khalil *et al.,* 2014b; Morales-Roselló *et al.,* 2015; 2014; Prior *et al.,* 2013).

If prenatal care is to be adjusted from screening for SGA to screening for fetal hypoxia then a third-trimester ultrasound examination should be implemented for all women in lieu of current serial measurements of SFH.

7.1.1 Objectives

The objective of this screening study is to investigate the potential value of CPR at 30-34 weeks' gestation in the prediction of adverse perinatal outcome by examining the relationship between CPR with BW Z-score and the rates of stillbirth, CS for fetal

distress, umbilical artery cord blood pH <7.0, umbilical venous blood pH <7.1, Apgar score <7 at 5 minutes and admission to the NNU or the NICU.

7.2 Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at 30^{+0}-34^{+6} weeks' gestation. The methodology for recording of patient characteristics, transabdominal sonographic assessment by colour Doppler of the UA and MCA, outcome measures and statistical analysis was as described in Chapter 2.

7.3 Results

7.3.1 Study population

During the study period we prospectively examined and measured MCA PI and UA PI in 32,370 singleton pregnancies. We excluded 213 (0.7%) for major fetal abnormalities or genetic syndromes diagnosed prenatally or postnatally and 1,377 (4.3%) for no follow-up. The study population comprised of 30,780 pregnancies and included 30,698 with live births and 82 with stillbirths.

In the 30,698 pregnancies with live births, there were 22,801 with vaginal delivery following spontaneous (n=19,647) or induction of labour (n=3,154), 3,689 with elective CS for a variety of indications and 4,208 with CS following spontaneous or induced labour; in the latter group the indication for CS was fetal distress in 1,912 cases. In the elective CS group (n=3,689) there were a variety of indications, including breech or transverse lie, placenta previa, previous CS or traumatic birth, maternal medical disorder or maternal request and fetal compromise diagnosed by abnormal Doppler findings or fetal heart rate patterns, mainly in SGA fetuses. The latter group included 94 cases with low CPR <5^{th} centile and in 51 of these delivery was undertaken within two weeks of the initial assessment at 30-34 weeks. The characteristics of the study population and the various subgroups according to outcome are given and compared in **Tables 7.1-7.3**.

Table 7.1. Maternal and pregnancy characteristics of the study population and subgroups of stillbirths and fetal distress in labour leading to CS. In each group the data are compared to the cohort without the outcome measure.

Variable	Population (n=30,780)	Stillbirth (n=82)	Fetal distress (n=1,912)
GA at assessment (w)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	32.3 (32.0-32.9)
Assessment to delivery inretval (w)	7.4 (6.3-8.4)	6.4 (4.1-8.3)*	8.0 (6.6-9.0)*
Maternal characteristics			
Maternal age (y)	31.3 (26.8-35.0)	30.0 (25.7-36.2)	31.1 (26.7-35.4)**
Maternal weight (Kg)	75.5 (67.8-85.7)	83.5 (70.1-95.2)**	78.5 (69.4-90.0)**
Maternal height (m)	1.65 (1.60-1.69)	1.65 (1.62-1.68)	1.63 (1.58-1.68)**
Cigarette smoker	2791 (9.1)	11 (13.4)	160 (8.4)
Racial origin			
Caucasian	21619 (70.2)	47 (57.3)	1187 (62.1)
Afro-Caribbean	5708 (18.5)	27 (32.9)**	501 (26.2)**
South Asian	1775 (5.8)	5 (6.1)	130 (6.8)
East Asian	959 (3.1)	2 (2.4)	58 (3.0)
Mixed	719 (2.3)	1 (1.2)	36 (1.9)
Conception			
Spontaneous	29614 (96.2)	78 (95.1)	1827 (95.6)
Ovulation drugs	332 (1.1)	2 (2.4)	23 (1.2)
In vitro fertilization	834 (2.7)	2 (2.4)	62 (3.2)**
Medical disorder			
Chronic hypertension	413 (1.3)	2 (2.4)	31 (1.6)*
SLE / APS	58 (0.2)	0 (0.0)	7 (0.4)
Diabetes mellitus			
Type 1	107 (0.3)	0 (0.0)	13 (0.7)**
Type 2	185 (0.6)	0 (0.0)	15 (0.8)*
Obstetric history			
Parous	15332 (49.8)	40 (48.8)	513 (26.8)
Nulliparous	15448 (50.2)	42 (51.2)	1399 (73.2)**
Pregnancy complication			
Preeclampsia	686 (2.2)	3 (3.7)	97 (5.1)**
Gestational diabetes	756 (2.5)	2 (2.4)	57 (3.0)**
Obstetric cholestasis	147 (0.5)	0 (0.0)	14 (0.7)
Spontaneous rupture of membranes	1601 (5.2)	1 (1.2)	210 (11.0)**
Onset of labour and mode of delivery			
Spontaneous labour, vaginal delivery	19676 (63.9)	24 (29.3)	
Spontaneous labour, CS	2955 (9.6)	0 (0.0)	1261 (66.0)
Induced labour, vaginal delivery	3206 (10.4)	52 (63.4)**	
Induced labour, CS	1248 (4.1)	0 (0.0)	651 (34.0)**
Elective CS	3695 (12.0)	6 (7.3)	
Outcome			
GA at delivery (w)	40.0 (39.0-40.9)	38.9 (37.0-40.7)**	40.5 (39.3-41.4)**
BW (g)	3388 (3,060-3710)	3000 (2619-3567)**	3351 (3020-3700)**
BW (centile)	46.4 (22.3-72.7)	28.0 (7.7-75.7)**	37.9 (14.6-67.9)**

Data for continuous variables are presented as median (interquartile range) and for categorical variables as n (%). NNU = Neonatal unit; NICU = Neonatal intensive care unit; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome; * = $p<0.05$; ** = $p<0.01$

Table 7.2. Maternal and pregnancy characteristics of the subgroups of low Apgar score at 5 minutes and low umbilical arterial or venous cord blood pH. In each group the data are compared to the cohort without the outcome measure.

Variable	Arterial pH ≤7.0 (n=203)	Venous pH ≤7.1 (n=199)	5 min Apgar <7 (n=259)
GA at assessment (w)	32.2 (32.0-32.6)**	32.3 (32.0-32.8)**	32.3 (32.0-32.9)
Delivery interval (w)	7.6 (6.3-8.7)	7.3 (5.9-8.6)	7.6 (5.9-8.6)
Maternal characteristics			
Maternal age (y)	30.0 (26.0-34.1)**	30.4 (26.2-34.8)	30.7 (26.5-34.5)
Maternal weight (Kg)	78.0 (71.0-85.0)	77.7 (69.2-86.0)	76.0 (68.0-87.0)
Maternal height (m)	1.63 (1.58-1.67)**	1.63 (1.58-1.68)*	1.63 (1.59-1.68)*
Cigarette smoker	18 (8.9)	25 (12.6)	22 (8.5)
Racial origin			
Caucasian	135 (66.5)	120 (60.3)	149 (57.5)
Afro-Caribbean	42 (20.7)*	51 (25.6)**	87 (33.6)**
South Asian	19 (9.4)	18 (9.0)	16 (16.2)
East Asian	2 (1.0)	2 (1.0)	2 (0.8)*
Mixed	5 (2.5)	8 (4.0)	5 (1.9)
Conception			
Spontaneous	200 (98.5)	193 (97.0)	252 (97.3)
Ovulation drugs	1 (0.5)	1 (0.5)	2 (0.8)
In vitro fertilization	2 (1.0)	5 (2.5)	5 (1.9)
Medical disorder			
Chronic hypertension	3 (1.5)	6 (3.0)	4 (1.5)
SLE / APS	0 (0.0)	0 (0.0)	3 (1.2)*
Diabetes mellitus			
Type 1	1 (0.5)	3 (1.5)	2 (0.8)
Type 2	0 (0.0)	1 (0.5)	3 (1.2)
Obstetric history			
Parous	85 (41.9)	88 (44.2)	106 (40.9)
Nulliparous	118 (58.1)	111 (55.8)	153 (59.1)
Pregnancy complication			
Preeclampsia	8 (3.9)	13 (6.5)	12 (4.6)*
Gestational diabetes	15 (7.4)**	9 (4.5)**	10 (3.9)
Obstetric cholestasis	1 (0.5)	0 (0.0)	0 (0.0)
SROM	8 (3.9)*	7 (3.5)*	12 (4.6)
Onset of labour and mode of delivery			
Spontaneous labour, VD	105 (51.7)	83 (41.7)	115 (44.4)
Spontaneous labour, CS	44 (21.7)	52 (26.1)**	51 (19.7)**
Induced labour, VD	23 (11.3)	18 (9.0)	32 (12.4)
Induced labour, CS	16 (7.9)	25 (12.6)**	34 (13.1)**
Elective CS	15 (7.4)**	21 (10.6)	27 (10.4)
Outcome			
GA at delivery (w)	40.2 (38.7-41.1)	39.7 (38.4-40.9)*	40.0 (38.5-41.4)
BW (g)	3445 (3020-3790)	3342 (2785-3720)*	3370 (2965-3775)
BW (centile)	48.8 (17.7-74.6)	40.8 (14.2-73.9)	48.2 (15.2-75.9)

Data for continuous variables are presented as median (interquartile range) and for categorical variables as n (%). SROM = Spontaneous rupture of membranes; NNU = Neonatal unit; NICU = Neonatal intensive care unit; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome; VD = vaginal delivery; CS = CS; GA = gestational age; * = $p<0.05$; ** = $p<0.01$

Table 7.3. Maternal and pregnancy characteristics of the subgroups of admission to the neonatal unit or neonatal intensive care unit. In each group the data are compared to the cohort without the outcome measure.

Variable	NNU admission (n=2,043)	NICU admission (n=445)
GA at assessment (w)	32.3 (32.0-32.9)	32.3 (32.0-33.0)
Delivery interval (w)	6.4 (4.0-8.0)**	6.0 (2.4-8.0)**
Maternal characteristics		
Maternal age (y)	31.2 (27.0-35.0)	31.3 (27.6-35.2)
Maternal weight (Kg)	77.0 (68.5-88.0)**	77.3 (69.0-88.9)**
Maternal height (m)	1.64 (1.60-1.68)**	1.64 (1.59-1.68)*
Cigarette smoker	230 (11.3)**	34 (7.5)
Racial origin		
Caucasian	1,366 (66.9)	286 (62.9)
Afro-Caribbean	460 (22.5)**	133 (29.2)**
South Asian	123 (6.0)	20 (4.4)
East Asian	42 (2.1)**	9 (2.0)
Mixed	52 (2.5)	7 (1.5)
Conception		
Spontaneous	1,952 (95.5)	438 (96.3)
Ovulation drugs	26 (1.3)	6 (1.3)
In vitro fertilization	65 (3.2)	11 (2.4)
Medical disorder		
Chronic hypertension	57 (2.8)**	17 (3.7)**
SLE / APS	5 (0.2)	3 (0.7)
Diabetes mellitus		
Type 1	37 (1.8)**	5 (1.1)*
Type 2	41 (2.0)**	7 (1.5)*
Obstetric history		
Parous	878 (43.0)	205 (45.1)
Nulliparous	1165 (57.0)**	250 (54.9)*
Pregnancy complication		
Preeclampsia	148 (7.2)**	46 (10.1)**
Gestational diabetes	120 (5.9)**	22 (4.8)**
Obstetric cholestasis	8 (0.4)	0 (0.0)
SROM	211 (10.3)**	44 (9.7)**
Onset of labour and mode of delivery		
Spontaneous labour, VD	952 (46.6)**	174 (38.3)
Spontaneous labour, CS	352 (17.2)	98 (21.6)**
Induced labour, VD	203 (9.9)**	32 (7.0)*
Induced labour, CS	170 (8.3)**	40 (8.8)**
Elective CS	365 (17.9)**	110 (24.2)**
Outcome		
GA at delivery (w)	39.0 (36.5-40.5)**	38.7 (34.9-40.6)**
BW (g)	3150 (2550-3648)**	3000 (2300-3590)**
BW (centile)	42.6 (15.1-75.8)**	39.2 (14.4-73.7)**

Data for continuous variables are presented as median (interquartile range) and for categorical variables as n (%). SROM = Spontaneous rupture of membranes; NNU = Neonatal unit; NICU = Neonatal intensive care unit; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome; VD = vaginal delivery; CS = CS; GA = gestational age; * = $p<0.05$; ** = $p<0.01$

7.3.2 Relationship of Doppler finding and BW Z-score

There was a significant association between $\log_{10}$ MoM CPR and BW Z-score (r=0.131, p<0.0001), with the lower the BW Z-Score, the lower the CPR. The steepness of the regression line was inversely related to the interval from assessment to delivery (**Figure 7.1, and Table 7.4**). Consequently, the proportion of abnormal Doppler findings observed in small babies is higher for those with a short, as compared to a long, assessment-to-delivery interval.

In the group delivering at ≤2 weeks of assessment the CPR was <5th centile in 49.6% (57/115) and 11.2% (28/250) of cases with BW ≤10th and >10th centile, respectively (p<0.0001); the rates for those delivering at >2 weeks of assessment were 8.6% (287/3331) and 4.6% (1244/27084), respectively (p<0.0001).

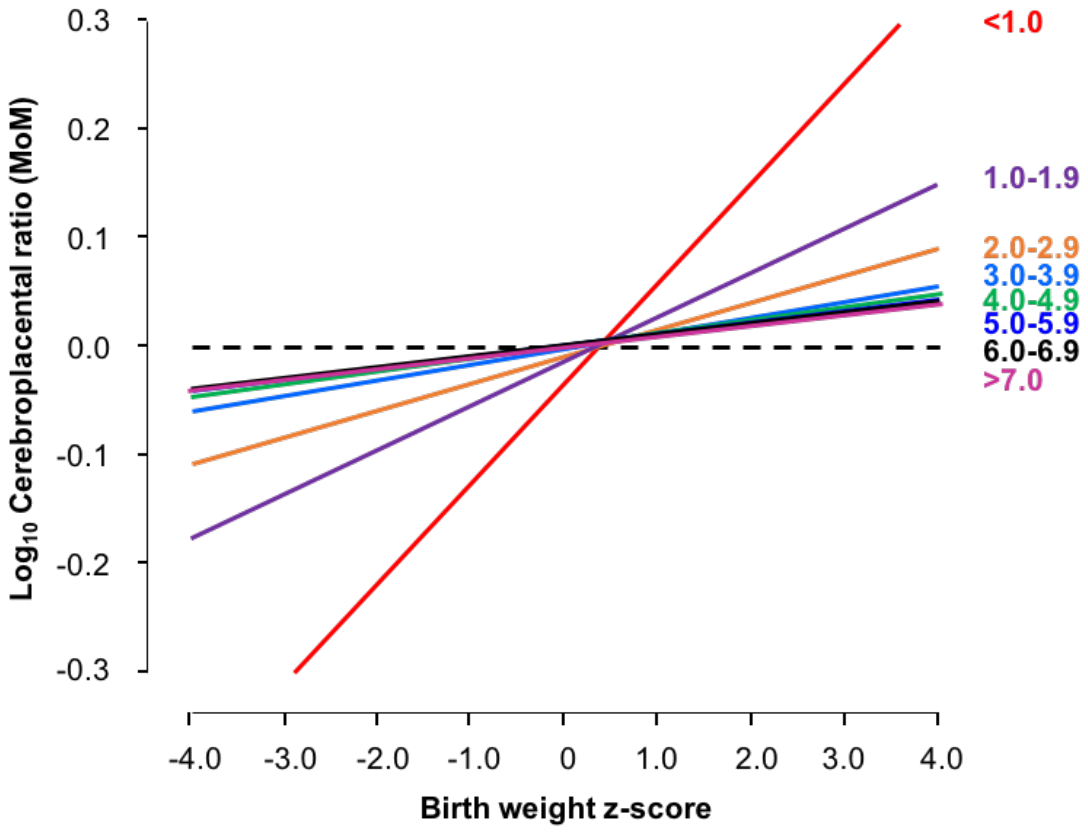

Figure 7.1. Association between $\log_{10}$ multiple of the median (MoM) cerebroplacental ratio and BW Z-score according to interval in weeks between assessment and delivery.

Table 7.4. Relationship of log_{10} transformed cerebroplacental ratio (CPR) multiple of median (MoM) with BW z-score in weekly intervals from time of assessment to delivery. The significance of difference in the slope of the regression line within each interval is compared to the slope of the intercept in the subsequent interval.

Interval (weeks)	Intercept (z-score) (95% CI)	Slope (95% CI)	Significance (p value)	
			Association	Slope comparison
< 1.0	-0.069 (-0.103 to -0.035)	0.056 (0.036 to 0.075)	<0.0001	0.019
1.0 to 1.9	-0.031 (-0.049 to -0.013)	0.030 (0.018 to 0.042)	<0.0001	0.197
2.0 to 2.9	-0.012 (-0.022 to -0.001)	0.021 (0.013 to 0.029)	<0.0001	0.988
3.0 to 3.9	0.001 (-0.007 to 0.008)	0.021 (0.015 to 0.027)	<0.0001	0.051
4.0 to 4.9	-0.003 (-0.008 to 0.001)	0.014 (0.010 to 0.018)	<0.0001	0.139
5.0 to 5.9	-0.001 (-0.004 to 0.002)	0.010 (0.008 to 0.013)	<0.0001	0.933
6.0 to 6.9	0.003 (0.001 to 0.005)	0.010 (0.008 to 0.012)	<0.0001	0.192
> 7.0	0.002 (0.001 to 0.003)	0.009 (0.007 to 0.010)	<0.0001	-

7.3.3 Prediction of stillbirth

There were 82 stillbirths, including 75 antepartum and seven intrapartum. The maternal and pregnancy characteristics of the stillbirths are compared to those of live births in **Table 7.5**. The distribution of BW according to gestational age of the stillbirths is shown in **Figure 7.2**. The BW was <10th and <50th centile in 24 (29.3%) and 53 (64.6%) of the cases, respectively.

The results of univariable and multivariable regression analysis for the prediction of stillbirth are given in **Table 7.6**. Multivariable regression analysis demonstrated that significant contribution to prediction of stillbirth was provided by maternal weight, Afro-Caribbean race, PE and gestational diabetes mellitus in the current pregnancy, gestational age at delivery, BW Z-score, but not $\log_{10}$ MoM value of CPR (R^2=0.048, p<0.0001).

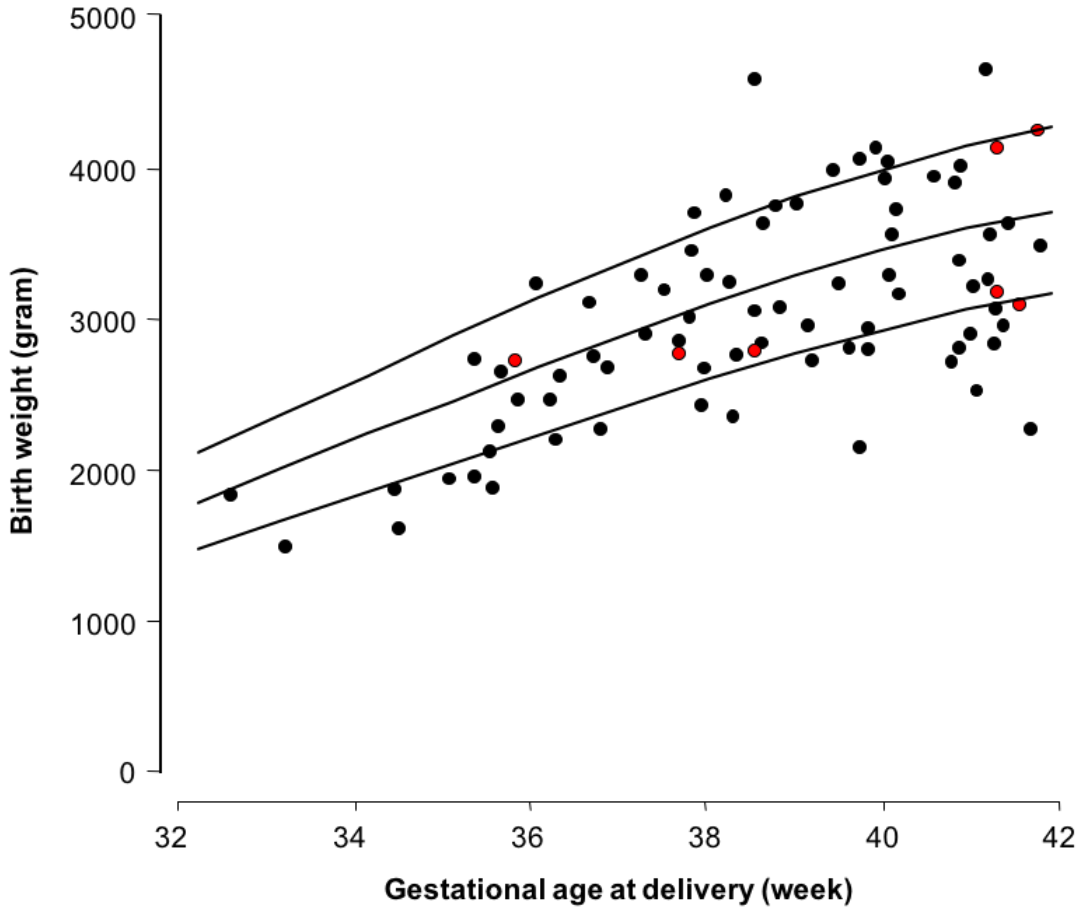

Figure 7.2. BW of antepartum (black dots) and intrapartum (red dots) stillbirths plotted on the reference range (50th, 90th and 10th centile) with gestational age.

Table 7.5. Maternal and pregnancy characteristics of women who had stillbirth compared to those with live birth.

Maternal and pregnancy characteristics	Live births (n=30,698)	Stillbirths (n=82)	P-value
Gestation at assessment in weeks, median (IQR)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	0.621
Interval from assessment to delivery (w)	7.4 (6.3-8.4)	6.4 (4.1-8.3)	<0.0001
Maternal characteristics			
Maternal age in years, median (IQR)	31.3 (26.8-35.0)	30.0 (25.7-36.2)	0.724
Maternal weight in Kg, median (IQR)	75.5 (67.8-85.7)	83.5 (70.1-95.2)	<0.0001
Maternal height in meters, median (IQR)	1.65 (1.60-1.69)	1.65 (1.62-1.68)	0.669
Cigarette smoker, n (%)	2,780 (9.1)	11 (13.4)	0.238
Racial origin			
Caucasian, n (%)	21,572 (70.3)	47 (57.3)	
Afro-Caribbean, n (%)	5,681 (18.5)	27 (32.9)	0.001
South Asian, n (%)	1,770 (5.8)	5 (6.1)	0.898
East Asian, n (%)	957 (3.1)	2 (2.4)	0.972
Mixed, n (%)	718 (2.3)	1 (1.2)	0.761
Conception			
Spontaneous, n (%)	29,536 (96.2)	78 (95.1)	
Ovulation drugs, n (%)	330 (1.1)	2 (2.4)	0.510
In vitro fertilization, n (%)	832 (2.7)	2 (2.4)	0.880
Medical disorder			
Chronic hypertension, n (%)	411 (1.3)	2 (2.4)	0.301
SLE / APS, n (%)	58 (0.2)	0 (0.0)	-
Diabetes mellitus, n (%)			
Type 1, n (%)	107 (0.3)	0 (0.0)	-
Type 2, n (%)	185 (0.6)	0 (0.0)	-
Obstetric history			
Parous, n (%)	15,292 (49.8)	40 (48.8)	
Nulliparous, n (%)	15,406 (50.2)	42 (51.2)	0.939
Pregnancy complication			
Preeclampsia, n (%)	683 (2.2)	3 (3.7)	0.433
Gestational diabetes, n (%)	754 (2.5)	2 (2.4)	1.000
Obstetric cholestasis, n (%)	147 (0.5)	0 (0.0)	1.000
Spontaneous rupture of membranes, n (%)	1,600 (5.2)	1 (1.2)	0.132
Onset of labour and mode of delivery			
Spontaneous labour, vaginal delivery	19,652 (64.0)	24 (29.3)	
Spontaneous labour, CS	2,955 (9.6)	0 (0.0)	-
Induced labour, vaginal delivery	3,154 (10.3)	52 (63.4)*	<0.0001
Induced labour, CS	1,248 (4.1)	0 (0.0)	-
Elective CS	3,689 (12.0)	6 (7.3)	0.255
Outcome			
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	38.9 (37.0-40.7)	<0.0001
BW in grams, median (IQR)	3,390 (3,064-3,710)	3,000 (,2619-3,567)	<0.0001
BW in centile, median (IQR)	46.5 (22.4-72.7)	28.0 (7.7-75.7)	0.002

IQR = interquartile range; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome. *All stillbirths undergo induction of labour, falsely increasing this number.

Table 7.6. Univariable and multivariable regression analysis in prediction of stillbirth based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	0.99 (0.96-1.03)	0.608		
Maternal weight in Kg - 78	1.03 (1.01-1.04)	<0.0001	1.03 (1.02-1.04)	<0.0001
Maternal height in meters -1.64	3.16 (0.12-84.4)	0.493		
Cigarette smoker	1.56 (0.82-2.94)	0.173		
Racial origin				
Caucasian (Reference)	1.00			
Afro-Caribbean	2.18 (1.36-3.51)	<0.0001		
South Asian	1.30 (0.52-3.26)	0.581		
East Asian	0.96 (0.23-3.96)	0.954		
Mixed	0.64 (0.09-4.64)	0.658		
Conception				
Spontaneous (Reference)	1.00			
Assisted conception	1.30 (0.48-3.57)	0.606		
Medical disorders				
Chronic hypertension	1.84 (0.45-7.52)	0.395		
SLE / APS	-	-		
Diabetes mellitus	-	-		
Obstetric history				
Parous (Reference)	1.00			
Nulliparous	1.04 (0.68-1.61)	0.852		
Pregnancy complication				
Preeclampsia	1.67 (0.53-5.30)	0.385		
Gestational diabetes	0.99 (0.24-4.05)	0.992		
Obstetric cholestasis	-	-		
Spontaneous rupture of membranes	0.23 (0.03-1.61)	0.138		
Onset of labour				
Spontaneous (reference)	1.00			
Induced	10.35 (6.60-16.25)	<0.0001		
Outcome				
Gestation at delivery in weeks	0.74 (0.67-0.82)	<0.0001	0.78 (0.70-0.86)	<0.0001
BW z-score	0.70 (0.57-0.87)	0.001	0.70 (0.57-0.85)	0.001
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.57 (0.05-6.70)	0.653		

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome; MoM=multiple of median

The relationship between $\log_{10}$ MoM CPR and BW Z-score in stillbirths and live births is shown in **Figure 7.3**. The performance of screening of low CPR for stillbirth is shown in **Table 7.7**. In total, the DR and FPR were 8.5% and 5.2%, respectively.

On the basis of the results the following conclusions can be drawn concerning the adverse event of stillbirth:

1. Only 6.0% (5/82) of the events occurred at ≤2 weeks.
2. Only 40.0% of the events at ≤2 weeks and 28.5% of those at >2 weeks had a BW <10th centile.
3. The DR and FPR of low CPR were 20.0% (1/5) and 23.3% (84/360), respectively, for deliveries at ≤2 weeks and 7.8% (6/77) and 5.0% (1,525/30,338), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 0.4% (7/1,616) for all cases, 1.2% (1/85) for those delivering at ≤2 weeks and 0.4% (6/1,531) for deliveries at >2 weeks. In the total group, the PPV was higher in those with BW <10th than ≥10th centile [1.2% (4/364) vs. 0.2% (3/1,272), p<0.05].

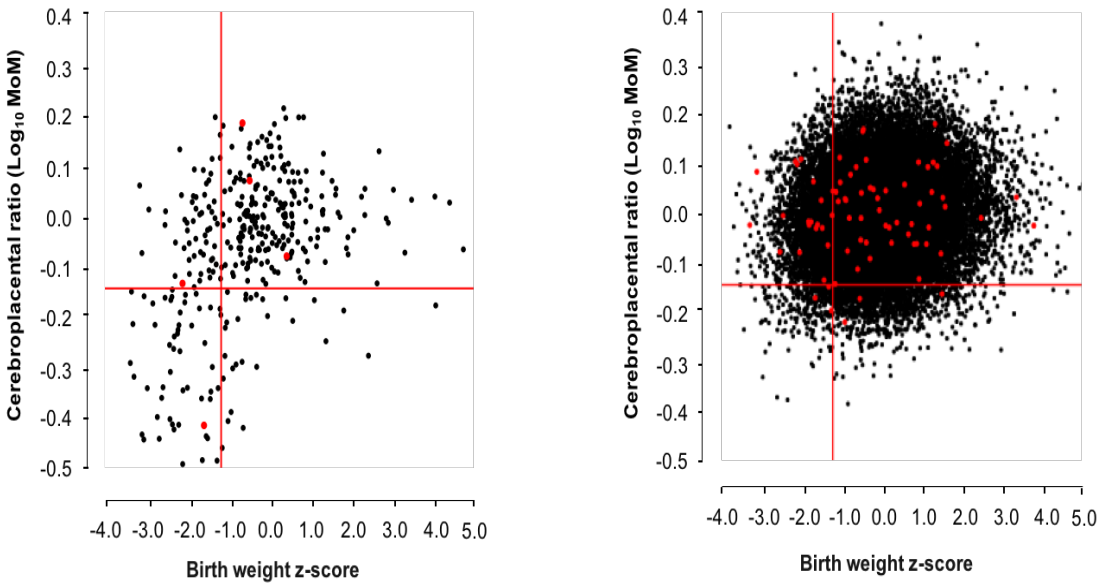

Figure 7.3. Relationship between $\log_{10}$ multiple of the median (MoM) cerebroplacental ratio and BW Z-score in stillbirths (red dots) and live births (black dots) in pregnancies delivering at ≤2 weeks (left) and >2 weeks (right) from assessment. The vertical red line corresponds to the 10th centile for BW and the horizontal red line corresponds to the 5th centile for the cerebroplacental ratio.

7.3.4 Prediction of fetal distress in labour leading to Caesarean section

In this section we compare the outcome of the 22,801 pregnancies with vaginal delivery and the 1,912 with CS for fetal distress during labour. The maternal and pregnancy characteristics of the two groups are compared in **Table 7.8**. The results of univariable and multivariable regression analysis for the prediction of fetal distress are given in **Table 7.9**. Multivariable regression analysis demonstrated that significant contribution to prediction of fetal distress was provided by maternal age, weight, height, Afro-Caribbean racial origin, nulliparity, PE in the current pregnancy, prelabour spontaneous rupture of membranes, induction of labour, gestational age at delivery and BW Z-score, but not $\log_{10}$ MoM value of CPR (R^2=0.150, p<0.0001).

The relationship between $\log_{10}$ MoM CPR and BW Z-score in the group of CS for fetal distress and those with vaginal delivery is shown in **Figure 7.4**. The performance of screening of low CPR for fetal distress in labour leading to CS is shown in **Table 7.7**.

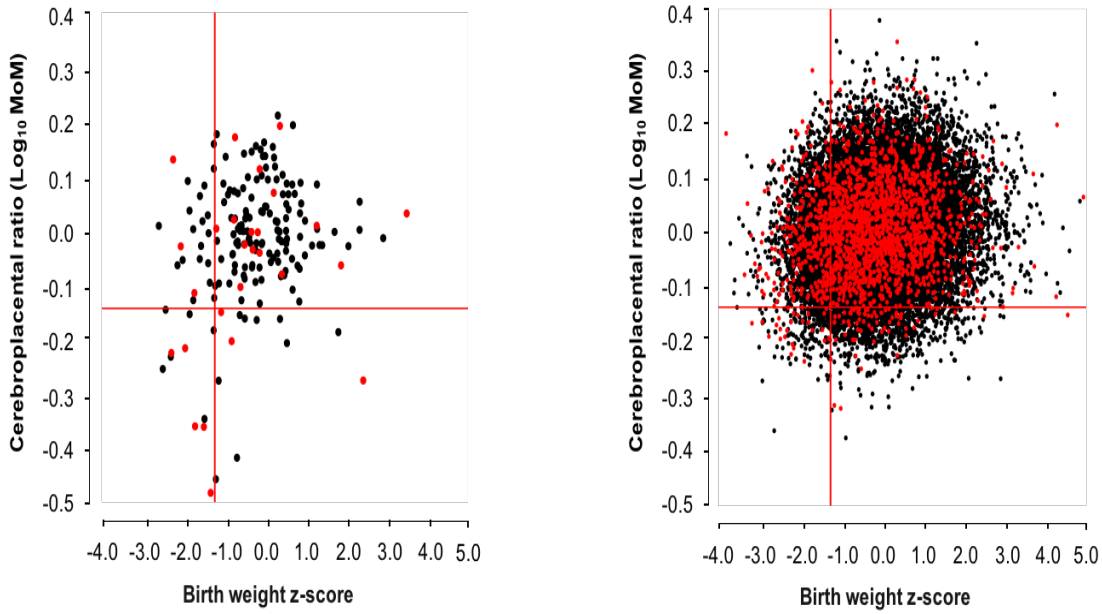

Figure 7.4. Relationship between $\log_{10}$ multiple of the median (MoM) cerebroplacental ratio and BW Z-score in pregnancies delivering by CS for fetal distress (red dots) and those delivering vaginally (black dots) in those delivering at ≤2 weeks (left) and >2 weeks (right) from assessment. The vertical red line corresponds to the 10th centile for BW and the horizontal red line corresponds to the 5th centile for the cerebroplacental ratio.

Table 7.7. Performance of screening of cerebroplacental ratio <5th centile in the prediction of adverse perinatal outcome.

Adverse event	BW centile	Total		Delivery at ≤ 2 wks		Delivery at > 2 wks	
		DR, n/n (%)	FPR, n/n (%)	DR, n/n (%)	FPR, n/n (%)	DR, n/n (%)	FPR, n/n (%)
Stillbirth (n=82)	≤ 10th centile	4/24 (16.7)	340/3422 (9.9)	1/2 (50.0)	56/113 (49.6)	3/22 (13.6)	284/3309 (8.6)
	> 10th centile	3/58 (5.2)	1269/27276 (4.7)	0/3 (0.0)	28/247 (11.3)	3/55 (5.5)	1241/27029 (4.6)
	Total	7/82 (8.5)	1609/30698 (5.2)	1/5 (20.0)	84/360 (23.3)	6/77 (7.8)	1525/30338 (5.0)
Fetal distress (n=1912)	≤ 10th centile	31/347 (8.9)	208/2493 (8.3)	5/8 (62.5)	7/26 (26.9)	26/339 (7.7)	201/2467 (8.2)
	> 10th centile	69/1565 (4.4)	929/20308 (4.6)	3/19 (15.8)	9/134 (6.7)	68/1546 (4.4)	920/2017 (4.6)
	Total	100/1912 (5.2)	1137/22801 (5.0)	8/27 (29.6)	16/160 (10.0)	94/1885 (5.0)	1121/22641 (5.0)
Arterial pH ≤7.0 (n=203)	≤ 10th centile	4/26 (15.4)	107/1111 (9.6)	2/3 (66.7)	17/48 (35.4)	2/23 (8.7)	90/1063 (8.5)
	> 10th centile	8/177 (4.5)	356/8034 (4.4)	0/3 (0.0)	10/119 (8.4)	8/174 (4.6)	346/7915 (4.4)
	Total	12/203 (5.9)	463/9145 (5.1)	2/6 (33.3)	27/167 (16.2)	10/197 (5.1)	436/8978 (4.9)
Venous pH ≤7.1 (n=199)	≤ 10th centile	6/38 (15.8)	142/1478 (9.6)	2/4 (50.0)	25/64 (39.1)	4/34 (11.8)	117/1414 (8.3)
	> 10th centile	7/161 (4.3)	509/11064 (4.6)	0/3 (0.0)	13/140 (9.3)	7/158 (4.4)	496/10924 (4.5)
	Total	13/199 (6.5)	651/12542 (5.2)	2/7 (28.6)	38/204 (18.6)	11/192 (5.7)	613/12338 (5.0)
5 min Apgar <7 (n=259)	≤ 10th centile	4/44 (9.1)	266/2768 (9.6)	2/4 (50.0)	32/75 (42.7)	2/40 (5.0)	234/2693 (8.7)
	> 10th centile	14/215 (6.5)	1015/21889 (4.6)	1/2 (50.0)	19/195 (9.7)	13/213 (6.1)	996/21694 (4.6)
	Total	18/259 (7.0)	1281/24657 (5.2)	3/6 (50.0)	51/270 (18.9)	15/253 (5.9)	1230/24387 (5.0)
NNU admission (n=2,043)	≤ 10th centile	77/403 (19.1)	263/3019 (8.7)	38/75 (50.7)	18/38 (47.4)	39/328 (11.9)	245/2981 (8.2)
	> 10th centile	92/1640 (5.6)	1177/25636 (4.6)	20/163 (12.3)	8/84 (9.5)	72/1477 (4.9)	1169/25552 (4.6)
	Total	169/2043 (8.3)	1440/28655 (5.0)	58/238 (24.4)	26/122 (21.3)	111/1805 (6.2)	1414/28533 (5.0)
NICU admission (n=445)	≤ 10th centile	25/97 (25.8)	315/3325 (9.5)	20/30 (66.7)	36/83 (43.4)	5/67 (7.5)	279/3242 (8.6)
	> 10th centile	23/358 (6.4)	1246/26918 (4.6)	8/68 (11.8)	20/179 (11.2)	15/290 (5.2)	1226/26739 (4.6)
	Total	48/455 (10.6)	1561/30243 (5.2)	28/98 (28.6)	56/262 (21.4)	20/357 (5.6)	1505/29981 (5.0)

BW = BW; DR = detection rate; FPR = false positive rate; NNU = Neonatal unit; NICU = Neonatal intensive care unit

Table 7.8. Maternal and pregnancy characteristics in women who required a CS for fetal distress following labour compared to women who had vaginal delivery

Maternal and pregnancy characteristics	Vaginal deliveries (n=22,801)	CS for fetal distress (n=1,912)	P-value
Gestation at assessment in weeks, median (IQR)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	0.410
Interval from assessment to delivery (w)	7.6 (6.4-8.5)	8.0 (6.6-9.0)	<0.0001
Maternal characteristics			
Maternal age in years, median (IQR)	30.8 (26.2-34.5)	31.1 (26.7-35.4)	<0.0001
Maternal weight in Kg, median (IQR)	75.0 (67.0-84.5)	78.5 (69.4-90.0)	<0.0001
Maternal height in meters, median (IQR)	1.65 (1.60-1.69)	1.63 (1.58-1.68)	<0.0001
Cigarette smoker, n (%)	2181 (9.6)	160 (8.4)	0.094
Racial origin			
Caucasian, n (%)	16,208 (71.1)	1,187 (26.2)	
Afro-Caribbean, n (%)	4,025 (17.7)	501 (26.2)	<0.0001
South Asian, n (%)	1,304 (5.7)	130 (6.8)	0.0588
East Asian, n (%)	707 (3.1)	58 (3.0)	0.925
Mixed, n (%)	557 (2.4)	36 (1.9)	0.145
Conception			
Spontaneous, n (%)	22,094 (96.9)	1,827 (95.6)	
Ovulation drugs, n (%)	233 (1.0)	23 (1.2)	0.526
In vitro fertilization, n (%)	474 (2.1)	62 (3.2)	0.001
Medical disorder			
Chronic hypertension, n (%)	230 (1.0)	31 (1.6)	0.016
SLE / APS, n (%)	34 (0.1)	7 (0.4)	0.052
Diabetes mellitus, n (%)			
Type 1, n (%)	41 (0.2)	13 (0.7)	<0.0001
Type 2, n (%)	94 (0.4)	15 (0.8)	0.029
Obstetric history			
Parous, n (%)	11,423 (50.1)	513 (26.8)	
Nulliparous, n (%)	11,378 (49.9)	1,399 (73.2)	<0.0001
Pregnancy complication			
Preeclampsia, n (%)	336 (1.5)	97 (5.1)	<0.0001
Gestational diabetes, n (%)	423 (1.9)	57 (3.0)	0.001
Obstetric cholestasis, n (%)	118 (0.5)	14 (0.7)	0.283
Spontaneous rupture of membranes, n (%)	1,095 (4.8)	210 (11.0)	<0.0001
Onset of labour			
Spontaneous	19,647 (86.2)	1,261 (66.0)	
Induced	3154 (13.8)	651 (34.0)	<0.0001
Outcome			
Gestation at delivery in weeks, median (IQR)	40.1 (39.2-40.9)	40.5 (39.3-41.4)	<0.0001
BW in grams, median (IQR)	3,390 (3,078-3,700)	3,351 (3,020-3,700)	0.005
BW in centile, median (IQR)	45.1 (22.0-70.7)	37.9 (14.6-67.9)	<0.0001

IQR = interquartile range; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.9. Univariable and multivariable regression regression analysis in prediction of CS for fetal distress based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	1.02 (1.01-1.03)	<0.0001	1.04 (1.03-1.05)	<0.0001
Maternal weight in Kg - 78	1.02 (1.01-1.02)	<0.0001	1.03 (1.02-1.03)	<0.0001
Maternal height in meters -1.64	0.01 (0.01-0.02)	<0.0001	$4.3e^{-04}$ ($1.8e^{-04}$-0.001)	<0.0001
Cigarette smoker	0.86 (0.73-1.02)	0.086		
Racial origin				
Caucasian	1.00			
Afro-Caribbean	1.70 (1.52-1.90)	<0.0001	1.74 (1.55-1.96)	<0.0001
South Asian	1.36 (1.13-1.65)	0.001		
East Asian	1.12 (0.85-1.47)	0.417		
Mixed	0.88 (0.63-1.24)	0.474		
Conception				
Spontaneous	1.00			
Assisted conception	1.45 (1.16-1.83)	0.001		
Medical disorders				
Chronic hypertension	1.62 (1.11-2.36)	0.013		
SLE / APS	2.46 (1.09-5.56)	0.030		
Diabetes mellitus	2.50 (1.66-3.76)	<0.0001		
Obstetric history				
Parous	1.00			
Nulliparous	2.74 (2.45-3.04)	<0.0001	3.37 (3.00-3.78)	<0.0001
Pregnancy complication				
Preeclampsia	3.57 (2.84-4.50)	<0.0001	1.63 (1.26-2.11)	<0.0001
Gestational diabetes	1.63 (1.23-2.15)	0.001		
Obstetric cholestasis	1.42 (0.81-2.47)	0.218		
Spontaneous rupture of membranes	2.45 (2.09-2.86)	<0.0001	2.93 (2.48-3.47)	<0.0001
Onset of labour				
Spontaneous	1.00			
Induced	3.22 (2.91-3.56)	<0.0001	2.69 (2.40-3.02)	<0.0001
Outcome				
Gestation at delivery in weeks	1.12 (1.08-1.15)	<0.0001	1.12 (1.08-1.16)	<0.0001
BW z-score	0.84 (0.80-0.88)	<0.0001	0.94 (0.90-0.99)	0.022
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.86 (0.50-1.48)	0.582		

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome; MoM=multiple of median

In total, the DR and FPR were 5.2% and 5.0%, respectively. On the basis of the data presented in **Table 7.7** the following conclusions can be drawn concerning the adverse event of CS for fetal distress:

1. Only 1.4% (27/1912) of the events occurred at ≤2 weeks.
2. Only 29.6% (8/27) of the events at ≤2 weeks and 18.0% (339/1885) of those at >2 weeks had a BW <10th centile.
3. The DR and FPR of low CPR were 29.6% (8/27) and 10.0% (16/160), respectively, for deliveries at ≤2 weeks and 5.0% (94/1885) and 5.0% (1121/22641), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 8% (100/1237) for all cases, 33.3% (8/24) for those delivering at ≤2 weeks and 7.7% (94/1215) for deliveries at >2 weeks. In the total group, the PPV was higher in those with BW <10th than ≥10th centile [13% (31/239) vs. 6.9% (69/998), p<0.01].

7.3.5 Prediction of low cord blood pH

In the 30,698 pregnancies with live births, the umbilical artery and vein cord blood pH was recorded in 9,348 and 12,741 cases, respectively. The umbilical artery cord blood pH was ≤7.0 in 203 (2.2%) cases and the umbilical vein cord blood pH was ≤7.1 in 199 (1.6%) cases. The maternal and pregnancy characteristics of cases with low cord blood pH are compared to those with normal pH in **Tables 7.10** and **7.11**.

The results of univariable and multivariable regression analysis for the prediction of low cord blood pH are given in **Tables 7.12** and **7.13**. Multivariable regression analysis demonstrated that significant contribution to prediction of umbilical artery cord blood pH ≤7.0 was provided by maternal weight, Afro-Caribbean race, height, assisted conception, gestational diabetes mellitus during the current pregnancy, pre-labour spontaneous rupture of membranes, onset of labour and method of delivery and gestational age at delivery, and $\log_{10}$ MoM CPR (adjusted R^2=0.027, p<0.0001). Similarly, multivariable regression analysis demonstrated that significant contribution to prediction of umbilical vein cord blood pH ≤7.1 was provided by maternal weight, Afro-Caribbean racial origin, cigarette smoking, pre-labour spontaneous rupture of

membranes, onset of labour and method of delivery and $\log_{10}$ MoM CPR (adjusted R^2=0.037, p<0.0001).

The relationship between $\log_{10}$ MoM CPR and BW Z-score in those with arterial blood pH ≤7.0 and pH >7.0 and venous blood pH ≤7.1 and pH >7.1 are shown in **Figure 7.5**. In both the arterial and venous pH groups there was a significant association between CPR MoM and BW Z-score (r=0.148, p<0.0001 and r=0.137, p<0.0001, respectively).

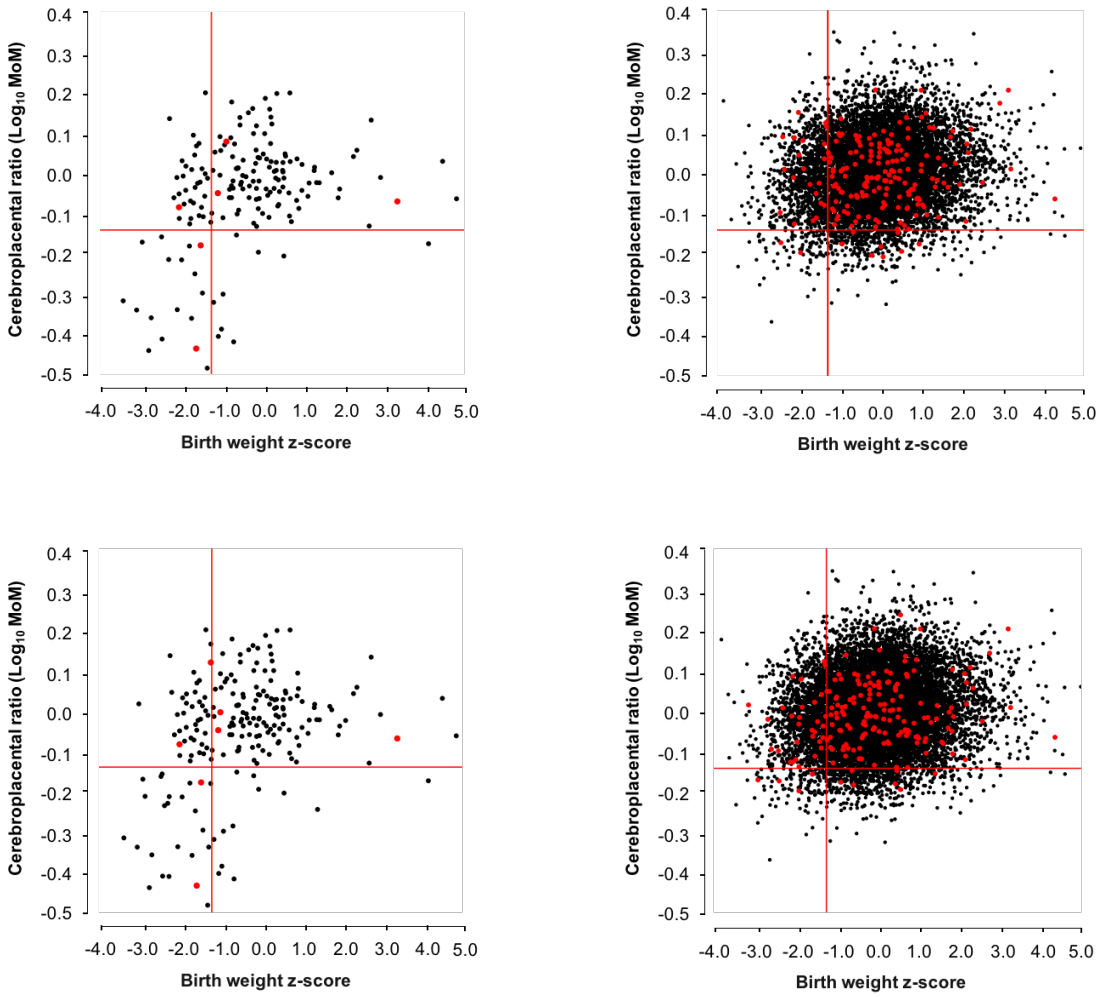

Figure 7.5. Relationship between $\log_{10}$ multiple of the median (MoM) cerebroplacental ratio and BW Z-score in those with arterial cord blood pH ≤7.0 (red dots) and pH >7.0 (black dots) (top panel) and those with venous cord blood pH ≤7.1 (red dots) and pH >7.1 (black dots) (bottom panel) in pregnancies delivering at ≤2 weeks (left) and >2 weeks (right) from assessment. The vertical red line corresponds to the 10th centile for BW and the horizontal red line corresponds to the 5th centile for the cerebroplacental ratio.

Table 7.10. Maternal and pregnancy characteristics of women who delivered neonates with arterial cord blood pH ≤7.0 compared to those with pH >7.0

Maternal and pregnancy characteristics	Arterial cord pH > 7.0 (n=9,145)	Arterial cord pH ≤ 7.0 (n=203)	P-value
Gestation at assessment in weeks, median (IQR)	32.4 (32.1-33.1)	32.2 (32.0-32.6)	<0.001
Interval from assessment to delivery (w)	7.3 (6.1-8.4)	7.6 (6.3-8.7)	0.081
Maternal characteristics			
Maternal age in years, median (IQR)	31.4 (27.0-35.1)	30.0 (26.0-34.1)	0.009
Maternal weight in Kg, median (IQR)	76.0 (67.9-86.3)	78.0 (71.0-85.0)	0.128
Maternal height in meters, median (IQR)	1.64 (1.60-1.68)	1.63 (1.58-1.67)	0.008
Cigarette smoker, n (%)	844 (9.2)	18 (8.9)	0.957
Racial origin			
Caucasian, n (%)	6,685 (73.1)	135 (66.5)	
Afro-Caribbean, n (%)	1,404 (15.4)	42 (20.7)	0.048
South Asian, n (%)	564 (6.2)	19 (9.4)	0.087
East Asian, n (%)	322 (3.5)	2 (1.0)	0.050
Mixed, n (%)	170 (1.9)	5 (2.5)	0.283
Conception			
Spontaneous, n (%)	8,687 (95.0)	200 (98.5)	
Ovulation drugs, n (%)	128 (1.4)	1 (0.5)	0.533
In vitro fertilization, n (%)	330 (3.6)	2 (1.0)	0.051
Medical disorder			
Chronic hypertension, n (%)	131 (1.4)	3 (1.5)	0.768
SLE/APLA, n (%)	14 (0.2)	0 (0.0)	1.000
Diabetes mellitus, n (%)			
Type 1, n (%)	55 (0.6)	1 (0.5)	1.000
Type 2, n (%)	85 (0.9)	0 (0.0)	0.267
Obstetric history			
Parous, n (%)	3,574 (39.1)	85 (41.9)	
Nulliparous, n (%)	5,571 (60.9)	118 (58.1)	0.464
Pregnancy complication			
Preeclampsia, n (%)	282 (3.1)	8 (3.9)	0.623
Gestational diabetes, n (%)	249 (2.7)	15 (7.4)	<0.0001
Obstetric cholestasis, n (%)	52 (0.6)	1 (0.5)	1.000
Spontaneous rupture of membranes, n (%)	713 (7.8)	8 (3.9)	0.045
Onset of labur and mode of delivery			
Spontaneous labour, vaginal delivery	4,486 (49.1)	105 (51.7)	
Spontaneous labour, CS	1,603 (17.5)	44 (21.7)	0.184
Induced labour, vaginal delivery	1,046 (11.4)	23 (11.3)	0.962
Induced labour, CS	675 (7.4)	16 (7.9)	0.893
Elective CS	1,335 (14.6)	15 (7.4)	0.005
Outcome			
Gestation at delivery in weeks, median (IQR)	40.0 (38.9-41.0)	40.2 (38.7-41.1)	0.811
BW in grams, median (IQR)	3,392 (3,040-3,740)	3,445 (3,020-3,790)	0.828
BW in centile, median (IQR)	47.8 (22.3-74.9)	48.8 (17.7-74.6)	0.694

IQR = interquartile range; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.11. Maternal and pregnancy characteristics of women who delivered neonates with a venous cord blood pH ≤7.1 compared to those with pH >7.1

Maternal and pregnancy characteristics	Venous cord pH > 7.1 (n=12,542)	Venous cord pH ≤ 7.1 (n=199)	P-value
Gestation at screening in weeks, median (IQR)	32.4 (32.0-33.0)	32.3 (32.0-32.8)	0.004
Interval from assessment to delivery (w)	7.4 (6.2-8.6)	7.3 (5.9-8.6)	0.203
Maternal characteristics			
Maternal age in years, median (IQR)	31.5 (27.1-35.2)	30.4 (26.2-34.8)	0.064
Maternal weight in Kg, median (IQR)	76.0 (68.0-86.0)	77.7 (69.2-86.0)	0.397
Maternal height in meters, median (IQR)	1.64 (1.60-1.69)	1.63 (1.58-1.68)	0.011
Cigarette smoker, n (%)	1104 (8.8)	25 (12.6)	0.084
Racial origin			
Caucasian, n (%)	8,856 (70.6)	120 (60.3)	
Afro-Caribbean, n (%)	2,233 (17.8)	51 (25.6)	0.006
South Asian, n (%)	753 (6.0)	18 (9.0)	0.102
East Asian, n (%)	426 (3.4)	2 (1.0)	0.071
Mixed, n (%)	274 (2.2)	8 (4.0)	0.133
Conception			
Spontaneous, n (%)	11,948 (95.3)	193 (97.0)	
Ovulation drugs, n (%)	160 (1.3)	1 (0.5)	0.524
In vitro fertilization, n (%)	434 (3.5)	5 (2.5)	0.692
Medical disorder			
Chronic hypertension, n (%)	195 (1.6)	6 (3.0)	0.176
SLE/APLA, n (%)	22 (0.2)	0 (0.0)	1.000
Diabetes mellitus, n (%)			
Type 1, n (%)	72 (0.6)	3 (1.5)	0.215
Type 2, n (%)	108 (0.9)	1 (0.5)	0.875
Obstetric history			
Parous, n (%)	5,020 (40.0)	88 (44.2)	
Nulliparous, n (%)	7,522 (60.0)	111 (55.8)	0.260
Pregnancy complication			
Preeclampsia, n (%)	370 (3.0)	13 (6.5)	0.006
Gestational diabetes, n (%)	342 (2.7)	9 (4.5)	0.188
Obstetric cholestasis, n (%)	69 (0.6)	0 (0.0)	0.630
Spontaneous rupture of membranes, n (%)	944 (7.5)	7 (3.5)	0.046
Onset of labour and mode of delivery			
Spontaneous labour, vaginal delivery	6,553 (52.2)	83 (41.7)	
Spontaneous labour, CS	1,945 (15.5)	52 (26.1)	<0.0001
Induced labour, vaginal delivery	1,490 (11.9)	18 (9.0)	0.264
Induced labour, CS	852 (6.8)	25 (12.6)	0.002
Elective CS	1,702 (13.6)	21 (10.6)	0.258
Outcome			
Gestation at delivery in weeks, median (IQR)	40.1 (39.0-41.0)	39.7 (38.4-40.9)	0.014
BW in grams, median (IQR)	3,410 (3,058-3,730)	3,342 (2,785-3,720)	0.024
BW in centile, median (IQR)	47.9 (22.7-72.8)	40.8 (14.2-73.9)	0.056

IQR = interquartile range; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.12. Univariable and multivariable regression analysis in prediction of an arterial cord blood pH ≤7.0 based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	0.97 (0.95-1.00)	0.023		
Maternal weight in Kg - 78	1.01 (1.00-1.01)	0.298		
Maternal height in meters -1.64	0.04 (0.01-0.36)	0.004	0.05 (0.01-0.45)	0.007
Cigarette smoker	0.96 (0.59-1.56)	0.860		
Racial origin				
Caucasian	1.00			
Afro-Caribbean	1.48 (1.04-2.10)	0.028		
South Asian	1.67 (1.02-2.72)	0.040		
East Asian	0.31 (0.08-1.25)	0.099		
Mixed	1.46 (0.59-3.60)	0.416		
Conception				
Spontaneous	1.00			
Assisted conception	0.29 (0.09-0.89)	0.031	0.30 (0.10-0.94)	0.039
Medical disorders				
Chronic hypertension	1.03 (0.33-3.27)	0.957		
SLE / APS	-	-		
Diabetes mellitus	0.32 (0.04-2.29)	0.255		
Obstetric history				
Parous	1.00			
Nulliparous	0.89 (0.67-1.18)	0.421		
Pregnancy complication				
Preeclampsia	1.29 (0.63-2.64)	0.487		
Gestational diabetes	2.85 (1.66-4.90)	<0.0001	2.84 (1.65-4.91)	<0.0001
Obstetric cholestasis	0.87 (0.12-6.29)	0.887		
Spontaneous rupture of membranes	0.49 (0.24-0.99)	0.046	0.44 (0.21-0.89)	0.022
Onset of labour				
Spontaneous labour, vaginal delivery	1.00			
Spontaneous labour, CS	1.17 (0.82-1.68)	0.381		
Induced labour, vaginal delivery	0.94 (0.60-1.48)	0.788		
Induced labour, CS	1.01 (0.60-1.72)	0.963		
Elective CS	0.48 (0.28-0.83)	0.008	0.43 (0.25-0.73)	0.002
Outcome				
Gestation at delivery in weeks	0.99 (0.91-1.07)	0.76		
BW z-score	0.99 (0.87-1.12)	0.868		
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.18 (0.04-0.85)	0.030	0.17 (0.04-0.83)	0.028

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome; MoM=multiple of median

Table 7.13. Univariable and multivariable regression analysis in prediction of a venous cord blood pH ≤7.1 based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	0.98 (0.96-1.00)	0.107		
Maternal weight in Kg - 78	1.00 (0.99-1.01)	0.492		
Maternal height in meters -1.64	0.04 (0.01-0.37)	0.004		
Cigarette smoker	1.49 (0.97-2.27)	0.066	1.58 (1.03-2.43)	0.038
Racial origin				
Caucasian	1.00			
Afro-Caribbean	1.69 (1.21-2.35)	0.002	1.60 (1.14-2.23)	0.006
South Asian	1.76 (1.07-2.91)	0.026	1.79 (1.08-2.96)	0.024
East Asian	0.35 (0.09-1.41)	0.138		
Mixed	2.16 (1.04-4.45)	0.038	2.17 (1.05-4.49)	0.038
Conception				
Spontaneous	1.00			
Assisted conception	0.63 (0.28-1.42)	0.260		
Medical disorders				
Chronic hypertension	1.97 (0.86-4.49)	0.108		
SLE / APS	-			
Diabetes mellitus	1.41 (0.52-3.83)	0.502		
Obstetric history				
Parous	1.00			
Nulliparous	0.84 (0.64-1.12)	0.231		
Pregnancy complication				
Preeclampsia	2.30 (1.30-4.07)	0.004		
Gestational diabetes	1.69 (0.86-3.33)	0.129		
Obstetric cholestasis	-	-		
Spontaneous rupture of membranes	0.45 (0.21-0.96)	0.038	0.34 (0.16-0.73)	0.006
Onset of labour				
Spontaneous labour, vaginal delivery	1.00			
Spontaneous labour, CS	2.11 (1.49-3.00)	<0.0001	2.35 (1.68-3.28)	<0.0001
Induced labour, vaginal delivery	0.95 (0.57-1.59)	0.856		
Induced labour, CS	2.32 (1.47-3.64)	<0.0001	2.31 (1.48-3.60)	<0.0001
Elective CS	0.97 (0.60-1.58)	0.915		
Outcome				
Gestation at delivery in weeks	0.89 (0.83-0.95)	0.001	0.88 (0.82-0.95)	<0.0001
BW z-score	0.90 (0.79-1.03)	0.112		
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.13 (0.03-0.63)	0.011	0.19 (0.04-0.85)	0.030

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome

The performance of screening of low CPR for arterial blood pH ≤7.0 and venous blood pH ≤7.1 is shown in **Table 7.7**. In total, the DR and FPR were 5.9% and 5.1%, respectively, for arterial blood pH ≤7.0 and 6.5% and 5.2% for venous blood pH ≤7.1. On the basis of the data presented in **Table 7.7** the following conclusions can be drawn concerning the adverse event of arterial bood pH ≤7.0:

1. Only 3.0% (6/203) of the events occurred at ≤2 weeks.
2. 50.0% of the events at ≤2 weeks and 11.7% of those at >2 weeks had a BW <10th centile.
3. the DR and FPR of low CPR were 33.3% (2/6) and 16.2% (27/167), respectively, for deliveries at ≤2 weeks and 5.1% (10/197) and 4.9% (436/8,978), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 2.5% (12/475) for all cases, 6.9% (2/29) for those delivering at ≤2 weeks and 2.2% (10/446) for deliveries at >2 weeks. In the total group, the PPV was not significantly different in those with BW <10th than ≥10th centile [3.6% (4/111) vs. 2.2% (8/364), p=0.490].

Similarly, the following conclusions can be drawn concerning the adverse event of venous blood pH ≤7.1:

1. Only 3.5% (7/199) of the events occurred at ≤2 weeks.
2. 57.7% of the events at ≤2 weeks and 17.7% of those at >2 weeks had a BW <10th centile.
3. The DR and FPR of low CPR were 28.6% (2/7) and 18.6% (38/204), respectively, for deliveries at ≤2 weeks and 5.7% (11/192) and 5.0% (613/12,338), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 2.0% (13/664) for all cases, 5.0% (2/40) for those delivering at ≤2 weeks and 1.8% (11/624) for deliveries at >2 weeks. In the total group, the PPV was not significantly different in those with BW <10th than ≥10th centile [4.1% (6/148) vs. 1.4% (7/516), p=0.089].

7.3.6 Prediction of low Apgar score

In the 30,698 pregnancies with live births, the Apgar score at 5 minutes was recorded in 27,742 cases and it was <7 in 259 (0.9%) cases. The maternal and pregnancy characteristics of cases with low Apgar score are compared to those with normal Apgar score in **Table 7.14**.

The results of univariable and multivariable regression analysis for the prediction of 5 minute Apgar <7 are given in **Table 7.15**. Multivariable regression analysis demonstrated that significant contribution to prediction of Apgar <7 was provided by maternal height, Afro-Caribbean racial origin, history of SLE or APS and onset of labour and method of delivery, but not $\log_{10}$ MoM CPR (adjusted R^2=0.042, p<0.0001).

The relationship between CPR MoM and BW Z-score in those with Apgar score <7 and ≥7 is shown in **Figure 7.6**. The performance of screening of low CPR for 5 minute Apgar <7 is shown in **Table 7.7**. In total, the DR and FPR were 7.0% and 5.2%, respectively. On the basis of the data presented in **Table 7.7** the following conclusions can be drawn concerning the adverse event of 5 minute Apgar <7:

1. Only 2.3% (6/259) of the events occurred at ≤2 weeks.
2. 66.7% (4/6) of the events at ≤2 weeks and 15.8% (40/253) of those at >2 weeks had a BW <10th centile.
3. The DR and FPR of low CPR were 50.0% (3/6) and 18.9% (51/270), respectively, for deliveries at ≤2 weeks and 5.9% (15/253) and 5.0% (1,230/24,387), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 1.4% (18/1,297) for all cases, 5.6% (3/54) for those delivering at ≤2 weeks and 1.2% (15/1,245) for deliveries at >2 weeks. In the total group, the PPV was not significantly different in those with BW <10th than ≥10th centile [1.5% (4/270) vs. 1.4% (14/1,029), p=0.777].

Table 7.14. Maternal and pregnancy characteristics of women whose neonates had an Apgar score <7 at five minutes compared to those with Apgar score of ≥7.

Maternal and pregnancy characteristics	Apgar <7 (n=24,657)	Apgar ≥7 (n=259)	P-value
Gestation at assessment in weeks, median (IQR)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	0.360
Interval from assessment to delivery (w)	7.4 (6.3-8.4)	7.6 (5.9-8.6)	0.514
Maternal characteristics			
Maternal age in years, median (IQR)	31.3 (26.8-35.0)	30.7 (26.5-34.5)	0.328
Maternal weight in Kg, median (IQR)	75.6 (67.8-85.6)	76.0 (68.0-87.0)	0.342
Maternal height in meters, median (IQR)	1.65 (1.60-1.69)	1.63 (1.59-1.68)	0.002
Cigarette smoker, n (%)	2,281 (9.3)	22 (8.5)	0.756
Racial origin			
Caucasian, n (%)	17,550 (71.2)	149 (57.5)	
Afro-Caribbean, n (%)	4,361 (17.7)	87 (33.6)	<0.0001
South Asian, n (%)	1,413 (5.7)	16 (6.2)	0.862
East Asian, n (%)	778 (3.2)	2 (0.8)	0.019
Mixed, n (%)	555 (2.3)	5 (1.9)	0.892
Conception			
Spontaneous, n (%)	23,651 (95.9)	352 (97.3)	
Ovulation drugs, n (%)	274 (1.1)	2 (0.8)	0.826
In vitro fertilization, n (%)	732 (3.0)	5 (1.9)	0.437
Medical disorder			
Chronic hypertension, n (%)	346 (1.4)	4 (1.5)	0.787
SLE/APLA, n (%)	41 (0.2)	3 (1.2)	0.011
Diabetes mellitus, n (%)			
Type 1, n (%)	91 (0.4)	2 (0.8)	0.585
Type 2, n (%)	148 (0.6)	3 (1.2)	0.454
Obstetric history			
Parous, n (%)	11,609 (47.1)	106 (40.9)	
Nulliparous, n (%)	13,048 (52.9)	153 (59.1)	0.056
Pregnancy complication			
Preeclampsia, n (%)	558 (2.3)	12 (4.6)	0.020
Gestational diabetes, n (%)	596 (2.4)	10 (3.9)	0.194
Obstetric cholestasis, n (%)	126 (0.5)	0 (0.0)	0.645
Spontaneous rupture of membranes, n (%)	1,383 (5.6)	12 (4.6)	0.587
Onset of labur and mode of delivery			
Spontaneous labour, vaginal delivery	15,715 (63.7)	115 (44.4)	
Spontaneous labour, CS	2,407 (9.8)	51 (19.7)	<0.0001
Induced labour, vaginal delivery	2,566 (10.4)	32 (12.4)	0.358
Induced labour, CS	1,038 (4.2)	34 (13.1)	<0.0001
Elective CS	2,931 (11.9)	27 (10.4)	0.531
Outcome			
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	40.0 (38.5-41.1)	0.659
BW in grams, median (IQR)	3390 (3065-3710)	3370 (2965-3775)	0.350
BW in centile, median (IQR)	46.3 (22.6-72.5)	48.2 (15.2-75.9)	0.579

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.15. Univariable and multivariable regression analysis in prediction of 5 minute Apgar score <7 based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	0.99 (0.97-1.01)	0.477		
Maternal weight in Kg - 78	1.01 (1.00-1.01)	0.260		
Maternal height in meters -1.64	0.06 (0.01-0.41)	0.004	0.13 (0.02-0.84)	0.033
Cigarette smoker	0.91 (0.59-1.41)	0.676		
Racial origin				
Caucasian	1.00			
Afro-Caribbean	2.35 (1.80-3.07)	<0.0001	2.14 (1.65-2.78)	<0.0001
South Asian	1.33 (0.79-2.24)	0.276		
East Asian	0.30 (0.08-1.22)	0.094		
Mixed	1.06 (0.43-2.60)	0.897		
Conception				
Spontaneous	1.00			
Assisted conception	0.65 (0.31-1.39)	0.268		
Medical disorders				
Chronic hypertension	1.10 (0.41-2.98)	0.848		
SLE / APS	7.04 (2.17-22.87)	0.001	6.02 (1.82-19.20)	0.003
Diabetes mellitus	2.01 (0.82-4.92)	0.126		
Obstetric history				
Parous	1.00			
Nulliparous	1.28 (1.00-1.65)	0.049		
Pregnancy complication				
Preeclampsia	2.10 (1.17-3.77)	0.013		
Gestational diabetes	1.62 (0.86-3.07)	0.137		
Obstetric cholestasis	-	-		
Spontaneous rupture of membranes	0.82 (0.46-1.46)	0.498		
Onset of labour				
Spontaneous labour, vaginal delivery	1.00			
Spontaneous labour, CS	2.89 (2.08-4.04)	<0.0001	2.60 (1.88-3.60)	<0.0001
Induced labour, vaginal delivery	1.70 (1.15-2.53)	0.008	1.65 (1.12-2.44)	0.011
Induced labour, CS	4.48 (3.04-6.60)	<0.0001	4.10 (2.78-6.04)	<0.0001
Elective CS	1.26 (0.83-1.92)	0.284		
Outcome				
Gestation at delivery in weeks	0.92 (0.86-0.99)	0.031	0.92 (0.85-0.98)	0.015
BW z-score	0.99 (0.88-1.12)	0.910		
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.87 (0.21-3.53)	0.841		

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome

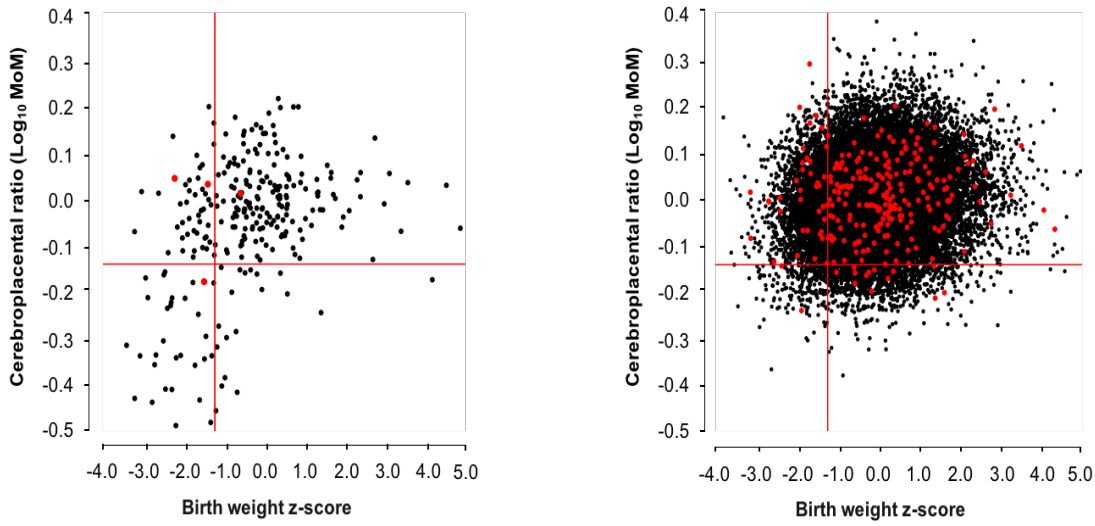

Figure 7.6. Relationship between $\log_{10}$ multiple of the median (MoM) cerebroplacental ratio and BW Z-score in those with a 5 minute Apgar score <7 (red dots) and Apgar ≥7 (black dots) in pregnancies delivering at ≤2 weeks (left) and >2 weeks (right) from assessment. The vertical red line corresponds to the 10th centile for BW and the horizontal red line corresponds to the 5th centile for the cerebroplacental ratio.

7.3.7 Prediction of admission to the neonatal unit and neonatal intensive care unit

In the 30,698 pregnancies with live births, there were 2,043 admissions to the NNU and 445 admissions to the NICU. The maternal and pregnancy characteristics of neonates admitted to these units are compared to those that were not admitted in **Tables 7.16 and 7.17**.

The results of univariable and multivariable regression analysis for the prediction of admission to NNU and NICU are given in **Tables 7.18** and **7.19**. Multivariable regression analysis demonstrated that significant contribution to prediction of admission to NNU was provided by maternal weight, height, East Asian racial origin, smoking, diabetes mellitus, nulliparity, PE, gestational diabetes mellitus and obstetric cholestasis during the current pregnancy, onset of labour and method of delivery and $\log_{10}$ MoM CPR (adjusted R^2=0.148, p<0.0001). Similarly, multivariable regression analysis demonstrated that in the prediction of admission to the NICU significant contributions were provided by Afro-Caribbean racial origin, nulliparity, onset of labour and method of delivery, but not by $\log_{10}$ MoM CPR (adjusted R^2=0.149, p<0.0001).

Table 7.16. Maternal and pregnancy characteristics of women whose neonates were admitted to the neonatal unit (NNU) compared to those not admitted.

Maternal and pregnancy characteristics	No admission (n=28,655)	Admission (n=2,043)	P-value
Gestation at screening in weeks, median (IQR)	32.3 (32.0-32.9)	32.3 (32.0-32.9)	0.130
Interval from assessment to delivery (w)	7.4 (6.4-8.4)	6.4-4.0-8.0)	<0.0001
Maternal characteristics			
Maternal age in years, median (IQR)	31.3 (26.8-35.0)	31.2 (27.0-35.0)	0.843
Maternal weight in Kg, median (IQR)	75.3 (67.6-85.4)	77.0 (68.5-88.0)	<0.0001
Maternal height in meters, median (IQR)	1.65 (1.60-1.69)	1.64 (1.60-1.68)	<0.0001
Cigarette smoker, n (%)	2,550 (8.9)	230 (11.3)	<0.0001
Racial origin			
Caucasian, n (%)	20,206 (70.5)	1,366 (66.9)	
Afro-Caribbean, n (%)	5,221 (18.2)	460 (22.5)	<0.0001
South Asian, n (%)	1,647 (5.7)	123 (6.0)	0.644
East Asian, n (%)	915 (3.2)	42 (2.1)	0.005
Mixed, n (%)	666 (2.3)	52 (2.5)	0.573
Conception			
Spontaneous, n (%)	27,584 (96.3)	1,952 (95.5)	
Ovulation drugs, n (%)	304 (1.1)	26 (1.3)	0.432
In vitro fertilization, n (%)	767 (2.7)	65 (3.2)	0.198
Medical disorder			
Chronic hypertension, n (%)	354 (1.2)	57 (2.8)	<0.0001
SLE / APS, n (%)	53 (0.2)	5 (0.2)	0.592
Diabetes mellitus, n (%)			
Type 1, n (%)	70 (0.2)	37 (1.8)	<0.0001
Type 2, n (%)	144 (0.5)	41 (2.0)	<0.0001
Obstetric history			
Parous, n (%)	14,414 (50.3)	878 (43.0)	
Nulliparous, n (%)	14,241 (49.7)	1,165 (57.0)	<0.0001
Pregnancy complication			
Preeclampsia, n (%)	535 (1.9)	148 (7.2)	<0.0001
Gestational diabetes, n (%)	634 (2.2)	120 (5.9)	<0.0001
Obstetric cholestasis, n (%)	139 (0.5)	8 (0.4)	0.739
Spontaneous rupture of membranes, n (%)	1,389 (4.8)	211 (10.3)	<0.0001
Onset of labour and mode of delivery			
Spontaneous labour, vaginal delivery	18,695 (65.3)	952 (46.6)	
Spontaneous labour, CS	2,603 (9.1)	352 (17.2)	<0.0001
Induced labour, vaginal delivery	2,951 (10.3)	203 (9.9)	0.629
Induced labour, CS	1,078 (3.8)	170 (8.3)	<0.0001
Elective CS	3,323 (11.6)	365 (17.9)	<0.001
Outcome			
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	39.0 (36.5-40.5)	<0.0001
BW in grams, median (IQR)	3400 (3084-3714)	3150 (2550-3648)	<0.0001
BW in centile, median (IQR)	46.7 (22.8-72.5)	42.6 (15.1-75.8)	0.001

IQR = interquartile range; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.17. Maternal and pregnancy characteristics comparing women whose neonates were admitted and not admitted to the neonatal intensive care unit (NICU).

Maternal and pregnancy characteristics	No admission (n=30,243)	Admission (n=455)	P-value
Gestation at screening in weeks, median (IQR)	32.3 (32.0-32.9)	32.3 (32.0-33.0)	0.155
Interval from assessment to delivery (w)	7.4 (6.3-8.4)	6.0 (2.4-8.0)	<0.0001
Maternal characteristics			
Maternal age in years, median (IQR)	31.3 (26.8-35.0)	31.3 (27.6-35.2)	0.329
Maternal weight in Kg, median (IQR)	75.4 (67.7-85.6)	77.3 (69.0-88.9)	0.001
Maternal height in meters, median (IQR)	1.65 (1.60-1.69)	1.64 (1.59-1.68)	0.035
Cigarette smoker, n (%)	2,746 (9.1)	34 (7.5)	0.236
Racial origin			
Caucasian, n (%)	21,286 (70.4)	286 (62.9)	
Afro-Caribbean, n (%)	5,548 (18.3)	133 (29.2)	<0.0001
South Asian, n (%)	1,750 (5.8)	20 (4.4)	0.245
East Asian, n (%)	948 (3.1)	9 (2.0)	0.203
Mixed, n (%)	711 (2.4)	7 (1.5)	0.326
Conception			
Spontaneous, n (%)	29,098 (96.2)	438 (96.3)	
Ovulation drugs, n (%)	324 (1.1)	6 (1.3)	0.780
In vitro fertilization, n (%)	821 (2.7)	11 (2.4)	0.809
Medical disorder			
Chronic hypertension, n (%)	394 (1.3)	17 (3.7)	<0.0001
SLE/APS, n (%)	55 (0.2)	3 (0.7)	0.074
Diabetes mellitus, n (%)			
Type 1, n (%)	102 (0.3)	5 (1.1)	0.020
Type 2, n (%)	178 (0.6)	7 (1.5)	0.022
Obstetric history			
Parous, n (%)	15,087 (49.9)	205 (45.1)	
Nulliparous, n (%)	15,156 (50.1)	250 (54.9)	0.046
Pregnancy complication			
Preeclampsia, n (%)	637 (2.1)	46 (10.1)	<0.0001
Gestational diabetes, n (%)	732 (2.4)	22 (4.8)	0.001
Obstetric cholestasis, n (%)	147 (0.5)	0 (0.0)	0.136
Spontaneous rupture of membranes, n (%)	1556 (5.1)	44 (9.7)	<0.0001
Onset of labour and mode of delivery			
Spontaneous labour, vaginal delivery	19,473 (64.4)	174 (38.3)	
Spontaneous labour, CS	2,857 (9.4)	98 (21.6)	<0.0001
Induced labour, vaginal delivery	3,122 (10.3)	32 (7.0)	0.027
Induced labour, CS	1,208 (4.0)	40 (8.8)	<0.0001
Elective CS	3,578 (11.8)	110 (24.2)	<0.0001
Outcome			
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	38.7 (34.9-40.6)	<0.0001
BW in grams, median (IQR)	3390 (3070-3710)	3000 (2300-3590)	<0.0001
BW in centile, median (IQR)	46.7 (22.5-72.7)	39.2 (14.4-73.7)	0.002

IQR = interquartile range; SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.18. Univariable and multivariable regression analysis in prediction of all admissions to the neonatal unit based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	1.00 (0.99-1.01)	0.993		
Maternal weight in Kg - 78	1.01 (1.01-1.02)	<0.0001	1.01 (1.00-1.01)	0.001
Maternal height in meters -1.64	0.20 (0.10-0.40)	<0.0001	0.35 (0.16-0.76)	0.008
Cigarette smoker	1.30 (1.13-1.50)	<0.0001	1.23 (1.06-1.43)	0.008
Racial origin				
Caucasian	1.00			
Afro-Caribbean	1.30 (1.17-1.46)	<0.0001		
South Asian	1.11 (0.91-1.34)	0.307		
East Asian	0.68 (0.50-0.93)	0.016	0.66 (0.47-0.91)	0.011
Mixed	1.16 (0.87-1.54)	0.326		
Conception				
Spontaneous	1.00			
Assisted conception	1.20 (0.97-1.49)	0.101		
Medical disorders				
Chronic hypertension	2.30 (1.73-3.05)	<0.0001		
SLE / APS	1.32 (0.53-3.32)	0.549		
Diabetes mellitus	5.28 (4.01-6.86)	<0.0001	2.27 (1.70-3.04)	<0.0001
Obstetric history				
Parous	1.00			
Nulliparous	1.34 (1.23-1.47)	<0.0001	1.45 (1.32-1.61)	<0.0001
Pregnancy complication				
Preeclampsia	4.11 (3.40-4.95)	<0.0001	1.33 (1.06-1.67)	0.013
Gestational diabetes	2.76 (2.26-3.37)	<0.0001	1.52 (1.22-1.90)	<0.0001
Obstetric cholestasis	0.81 (0.40-1.65)	0.555	0.40 (0.19-0.83)	0.013
Spontaneous rupture of membranes	2.26 (1.94-2.63)	<0.0001	1.38 (1.16-1.64)	<0.0001
Onset of labour				
Spontaneous labour, vaginal delivery	1.00		1.00	
Spontaneous labour, CS	2.66 (2.33-3.02)	<0.0001	2.10 (1.83-2.42)	<0.0001
Induced labour, vaginal delivery	1.35 (1.16-1.58)	<0.0001	1.33 (1.12-1.59)	0.001
Induced labour, CS	3.10 (2.60-3.69)	<0.0001	3.27 (2.67-4.00)	<0.0001
Elective CS	2.16 (1.90-2.45)	<0.0001	1.29 (1.12-1.49)	<0.0001
Outcome				
Gestation at delivery in weeks	0.63 (0.62-0.65)	<0.0001	0.65 (0.64-0.67)	<0.0001
BW z-score	0.94 (0.90-0.98)	0.004		
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.17 (0.10-0.28)	<0.0001	0.48 (0.29-0.80)	0.005

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome

Table 7.19. Univariable and multivariable regression analysis in prediction of admission to the neonatal intensive care unit based on maternal and pregnancy characteristics

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal characteristics				
Maternal age in years - 30	1.01 (0.99-1.03)	0.256		
Maternal weight in Kg - 78	1.01 (1.01-1.02)	<0.0001		
Maternal height in meters -1.64	0.18 (0.04-0.75)	0.018		
Cigarette smoker	0.81 (0.57-1.15)	0.237		
Racial origin				
Caucasian	1.00			
Afro-Caribbean	1.78 (1.45-2.20)	<0.0001	1.59 (1.28-1.97)	<0.0001
South Asian	0.85 (0.54-1.34)	0.487		
East Asian	0.71 (0.36-1.38)	0.307		
Mixed	0.73 (0.35-1.56)	0.419		
Conception				
Spontaneous	1.00			
Assisted conception	0.99 (0.61-1.61)	0.956		
Medical disorders				
Chronic hypertension	2.94 (1.79-4.82)	<0.0001		
SLE / APS	3.64 (1.14-11.69)	0.030		
Diabetes mellitus	2.89 (1.61-5.21)	<0.0001		
Obstetric history				
Parous	1.00			
Nulliparous	1.21 (1.01-1.46)	0.041	1.30 (1.07-1.58)	0.009
Pregnancy complication				
Preeclampsia	5.23 (3.82-7.16)	<0.0001		
Gestational diabetes	2.05 (1.33-3.16)	0.001		
Obstetric cholestasis	-	-		
Spontaneous rupture of membranes	1.97 (1.44-2.71)	<0.0001		
Onset of labour				
Spontaneous labour, vaginal delivery	1.00			
Spontaneous labour, CS	3.84 (2.99-4.93)	<0.0001	2.87 (2.23-3.70)	<0.0001
Induced labour, vaginal delivery	1.15 (0.79-1.68)	0.478		
Induced labour, CS	3.71 (2.62-5.25)	<0.0001	4.06 (2.84-5.78)	<0.0001
Elective CS	3.44 (2.70-4.38)	<0.0001	1.86 (1.45-2.39)	<0.0001
Outcome				
Gestation at delivery in weeks	0.60 (0.58-0.63)	<0.0001	0.62 (0.60-0.65)	<0.0001
BW z-score	0.88 (0.80-0.96)	0.005		
Doppler findings				
Log_{10} cerebroplacental ratio MoM	0.14 (0.05-0.39)	<0.0001		

OR=odds ratio; CI=confidence interval; SLE=systemic lupus erythematosus; APS = anti-phospholipid syndrome

The relationship between CPR MoM and BW Z-score in those with and without admision to the NNU or NICU is shown in **Figure 7.7**. The performance of screening of low CPR for admision to the NNU or NICU is shown in **Table 7.7**. In total, the DR and FPR were 8.3% and 5.0%, respectively, admision to the NNU and 10.6% and 5.2% for admision to the NICU. On the basis of the data presented in **Table 7.7** the following conclusions can be drawn concerning the adverse event of admission to the NNU:

1. Only 11.6% (238/2,043) of the events occurred at $\leq$2 weeks.
2. Only 31.5% of the events at $\leq$2 weeks and 18.2% of those at >2 weeks had a BW <10th centile.
3. The DR and FPR of low CPR were 24.4% (58/238) and 21.3% (26/122), respectively, for deliveries at $\leq$2 weeks and 6.2% (111/1,805) and 5.0% (1,414/28,533), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 10.5% (169/1,609) for all cases, 69.0% (58/84) for those delivering at $\leq$2 weeks and 7.3% (111/1,525) for deliveries at >2 weeks. In the total group, the PPV was higher in those with BW <10th than $\geq$10th centile [22.6% (77/340) vs. 7.2% (92/1,269), p<0.001].

Similarly, the following conclusions can be drawn concerning the adverse event of admission to the NICU (**Table 7.7**):

1. Only 22.0% (98 of 445) of the events occurred at $\leq$2 weeks.
2. Only 30.6% of the events at $\leq$2 weeks and 18.8% of those at >2 weeks had a BW <10th centile.
3. The DR and FPR of low CPR were 28.6% (28/98) and 21.4% (56/262), respectively, for deliveries at $\leq$2 weeks and 5.6% (20/357) and 5.0% (1,505/29,981), respectively, for deliveries at >2 weeks.

The PPV of low CPR for the adverse event was 3.0% (48/1,609) for all cases, 33.3% (28/84) for those delivering at $\leq$2 weeks and 1.3% (20/1,525) for deliveries at >2 weeks. In the total group, the PPV was higher in those with BW <10th than $\geq$10th centile [7.4% (25/340) vs. 1.8% (23/1,269), p<0.001].

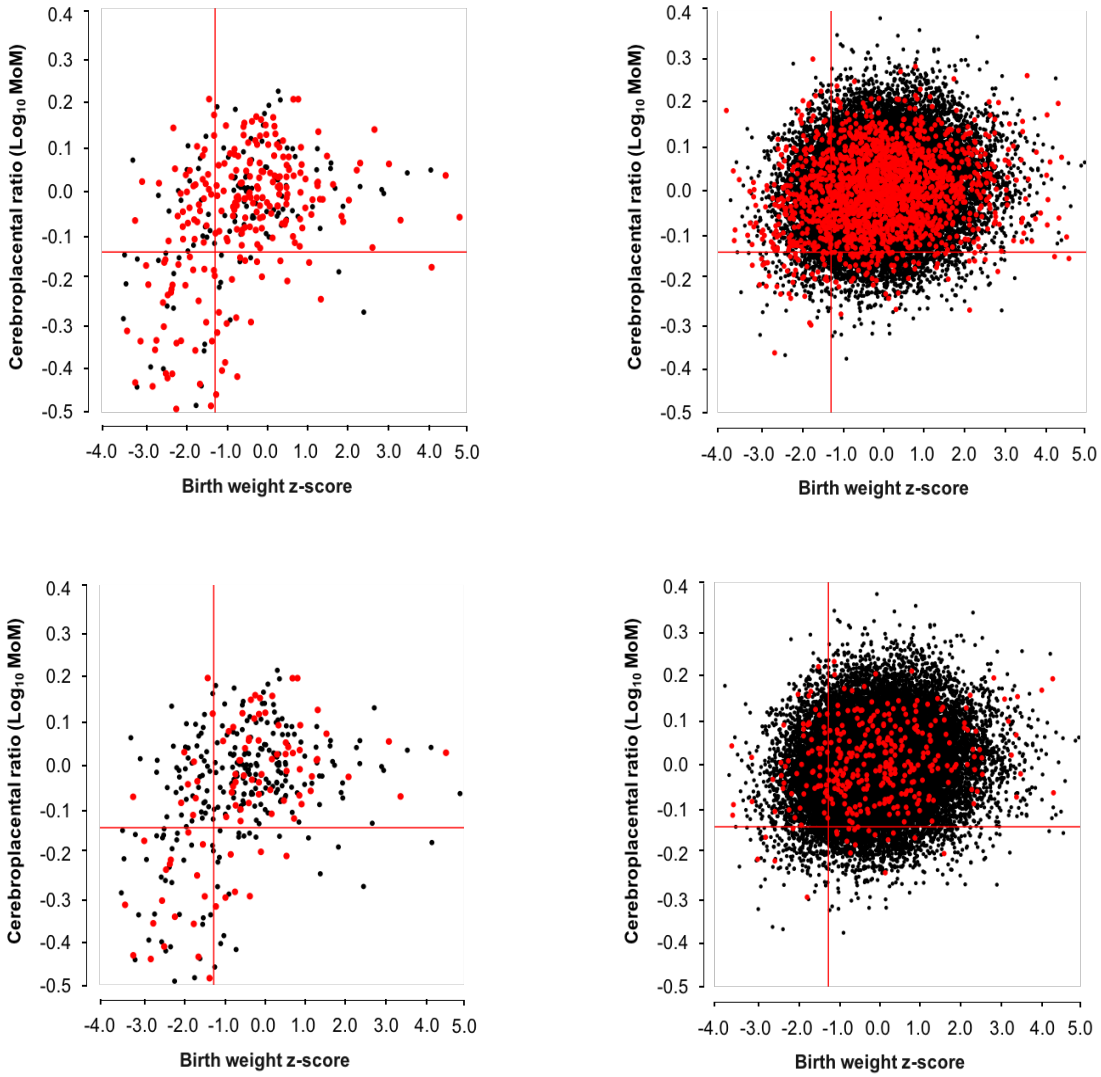

Figure 7.7. Relationship between $\log_{10}$ multiple of the median (MoM) cerebroplacental ratio and BW Z-score in those with admission to the neonatal unit (red dots) and those without admission (black dots) in pregnancies delivering at ≤2 weeks (left) and >2 weeks (right) from assessment. The vertical red line corresponds to the 10th centile for BW and the horizontal red line corresponds to the 5th centile for the cerebroplacental ratio. In the bottom panel admissions to the neonatal intensive care unit are considered.

7.4 Discussion

7.4.1 Main findings of the study

The findings of this study demonstrate that the incidence of adverse perinatal outcome is higher in SGA than non-SGA fetuses, including stillbirth (0.7% vs. 0.2%),

CS for fetal distress in labour (13.0% vs. 6.9%), arterial blood pH ≤7.0 (2.3% vs. 2.1%), venous blood pH ≤7.1 (2.5% vs. 1.4%), 5 minute Apgar score <7 (1.6% vs. 1.0%), admission to NNU (11.8% vs. 6.0%) and admission to NICU (2.8% vs. 1.3%). However, the non-SGA group contains the greater proportion of cases including around 71% of stillbirths, 82% of cases of CS for fetal distress, 87% of those with arterial blood pH ≤7.0, 81% with venous blood pH ≤7.1, 83% with 5 minute Apgar score <7, 80% of admissions to NNU and 79% of admissions to NICU.

The rationale for the study was that if adverse outcomes are the consequence of impaired placentation, then the focus of prenatal care should be moved away from detecting SGA and towards detecting hypoxaemic fetuses, currently done by calculating the CPR.

We have shown that at 30-34 weeks' gestation, a low CPR is poor at predicting adverse outcomes, with a DR of 5-11% for a FPR of about 5%. The DR improved to 20-50% in the small number of pregnancies that delivered within two weeks of their assessment, however, there was a simultaneous increase in FPR to 10-23%. Combining CPR with maternal characteristics, medical history and obstetric factors significantly improved the prediction of arterial blood pH ≤7.0, venous blood pH ≤7.1 and admission to NNU, but not in the prediction of all adverse outcomes.

In the predicition of adverse outcomes, a low CPR had a higher PPV in SGA than in AGA fetuses, especially in the subset of preganncies going on to deliver within two weeks of assessment.

There was a linear association between CPR and BW Z-score and the steepness of the regression line was inversely related to the interval from assessment to delivery. Thus, low CPR <5th centile was observed in about 50% of the SGA neonates delivering within two weeks of assessment, but in less than 10% of SGA neonates delivering at >2 weeks.

7.4.2. Comparison with findings from previous studies

UAD are not of use to predict SGA neonates (Alfirevic *et al.,* 2013), however, they have been shown to be useful in reducing perinatal mortality in high-risk pregnancies

(Divon 1996). Two studies have shown that SGA fetuses with an increased UAD were at greater risk of neonatal morbidity compared to AGA fetuses (Figueras *et al.,* 2008; Vergani *et al.,* 2010).

MCA Doppler PI has been used to predict adverse outcomes within SGA cohorts. Hershkovitz *et al.,* showed that in SGA fetuses a lower MCA PI increased the need for NNU admission, whilst Nanthakomon & Uerpairojkit showed that adverse perinatal outcomes were higher in those with an abnormal MCA measurement (Hershkovitz *et al.,* 2000; Nanthakomon & Uerpairojkit 2010). They have also been shown to be significant in predicting the long-term neurodevelopmental outcome in SGA fetuses, with those with a low MCA PI having suboptimal neurodevelopment at 2 years of age (Eixarch *et al.,* 2008).

Relationship of Doppler finding and BW Z-score

The association of low BW and low CPR has been demonstrated in previous studies (Gramellini *et al.,* 1992, Khalil *et al.,* 2014). Both have been independently associated with adverse fetal and neonatal outcomes. The higher proportion of abnormal CPR in SGA neonates with a shorter assessment-to-delivery interval has also been noted by Bahado-Singh *et al.,* (1998). This publication also showed that the risk of adverse outcomes was higher in preterm SGA neonates with an assessment-to-delivery interval of <3 weeks, and the sensitivity of CPR to identify these neonates increased as the BW decreased from the 10^{th} to the 5^{th} centile (Bahado-Singh *et al.,* 1998).

Prediction of stillbirth

Many studies have excluded stillbirths from their analysis, either because they assess the risk of intrapartum fetal compromise (Prior *et al.,* 2013, Khalil *et al.,* 2014a), or because they assess postnatal outcomes such as admission the NICU (Khalil *et al.,* 2014b). Therefore, it is not possible to directly compare our results with other studies.

Prediction of fetal distress in labour leading to Caesarean section

Most studies of CPR have used CS, whether for fetal distress or not, as a measure of an adverse outsome. Bahado-Singh et al., Odibo et al., Khalil *et al.,* 2014a; Khalil *et al.,* 2014b; and Morales-Roselló *et al.,* have all shown a significant increase in the

CS rate as the CPR rises. The significance of this was greater amongst SGA neonates and increased with decreasing BW (Bahado-Singh et al., 1998, Odibo et al., 2005, Khalil *et al.,* 2014a; Khalil *et al.,* 2014b; Morales-Roselló *et al.,* 2014). In one study of AGA fetuses, a low CPR was associated with an increased risk of CS for fetal compromise (Prior *et al.,* 2013). Our results were similar in that fetuses requiring CS for fetal distress were smaller, and more likely to have an assessment to delivery interval of <2 weeks rather than >2 weeks. This risk increased further if there was an IOL rather than a spontaneous onset of delivery.

Prediction of low cord blood pH

A low cord pH, whether an arterial or venous sample, is another commonly used adverse pregnancy outcome measure. Morales-Roselio *et al.,* (2014) showed that there was a significant correlation between BW and venous pH (p=<0.001), but not arterial pH (p=0.180). However, a decreasing CPR was significantly correlated with both a decreasing arterial (p=<0.0001) and venous pH (p=<0.0001). This remained true for both SGA and AGA fetuses. (Morales-Roselló *et al.,* 2014). Gramellini *et al.,* study of 45 SGA and 45 AGA fetuses revealed that the umbilical vein pH was statistically lower than those with an abnormal CPR (7.25 ± 0.03 and 7.33 ± 0.04, p=<0.01), however the pH used here was higher than our cutoff of <7.1. Odibo et al., showed that CPR was a good predicator of all adverse pregnancy outcomes in SGA fetuses, including an arterial pH <7.0, with an OR of 5.2 (95% CI 1.4–19.4) and 3.9 (95% CI 1.2–13.6) respectively, for SGA below the 10th and 5th centiles. This study also showed a statistically significant increase in adverse outcomes in those delivering <34 weeks' gestation, and within 2 weeks' of assessment (numbers not given). This is similar to our study, where the DR of a low arterial pH was greater in those delivering within rather than after 2 weeks of assessment (66.7% vs 8.7%).

Prediction of low Apgar score

Prediction of a low Apgar score has been used by some publications as a measure of an adverse outcome that could be predicted by a low CPR. Gramellini *et al.,* found that those with a low CPR were statistically significantly more likely to be born with a low Apgar score (16.6% vs 2.7%; p=<0.05) (Gramellini *et al.,* 1992). Two further studies have only commented that CPR can be for predicting adverse outcomes,

including a low Apgar score, however, they have not given individual results for this (Bahado-Singh *et al.,* 1998, Odibo *et al.,* 2005).

Prediction of admission to the neonatal unit and neonatal intensive care unit

A low CPR as a prediction tool for admission to NNU or NICU has been shown to be significant in several studies (Gramellini *et al.,* 1992, Bahado-Singh *et al.,* 1998, Odibo *et al.,* 2005). Two publications by the same author, have analysed the prediction of admission to the NNU and NICU using CPR. The first study showed that CPR recorded at 34-36 weeks in 2518 pregnancies was statistically significantly lower in those requiring admission to the NNU than those not admitted (p=<0.05) (Khalil *et al.,* 2014a). In the second study, an analysis of 9772 pregnancies, showed that a reduced CPR increased the risk of admission to the NNU (OR 0.54; 95% CI, 0.35-0.81; p=0.003) (Khalil *et al.,* 2014b).

Summary

Despite the interesting findings of these studies, ours remains unique as it evaluated CPR as part of routine screening for adverse perinatal outcome in all pregnant women at 30^{+0}-34^{+6} weeks' gestation rather than within a select population. Our study shows that a low CPR is poor at predicting adverse outcomes at this gestation, even though combining CPR with maternal characteristics, medical history and obstetric factors significantly improved the prediction of arterial blood pH $\leq$7.0, venous blood pH $\leq$7.1 and admission to NNU, but not in the prediction of all adverse outcomes. Further studies within routine populations at later gestations are required to determine CPR's use as a screening tool for entire populations, or whether it should remain as a measurement in high risks pregnancies only.

Chapter 8: Conclusion

8.1 Summary of results

This study has shown that screening by maternal factors can detect 30%, 31% and 32%, at 10% FPR, of SGA neonates with a BW <10th, <5th and <3rd centile delivering at <5 weeks of assessment. The respective DRs for prediction of SGA delivering at ≥5 weeks of assessment are 28%, 32% and 34%. We have shown that when combining maternal factors with fetal biometry, uterine artery PI, MAP and serum PlGF the DRs for SGA delivering at <5 weeks of assessment increase to 89%, 94%, 96% of SGA neonates, and the respective values for those delivering at ≥5 weeks of assessment are 57%, 65% and 72%.

Such performance of screening is superior to that achieved by the current method which is based on maternal characteristics and measurement of SFH (Lindhard *et al.,* 1990). This study should now lead to further studies, including a randomized controlled trial of SFH versus third trimester ultrasound derived EFW, ideally with with uterine artery PI, MAP and serum PlGF.

8.2 Strengths and limitations

This study has several strengths. Firstly, this was a large, routine screening study carried out at a gestational age that much of the current literature recommends for assessing fetal growth and wellbeing. Secondly, the study ensured that appropriately trained sonographers using specific methodology undertook the measurements of HC, AC FL, MAP, uterine artery PI, MCA PI and UA PI. Thirdly, we assessed several biochemical markers, which associated with impaired placentation. Fourthly, the study used Bayes theorem to combine the prior risk from maternal characteristics and medical history with biomarkers to estimate patient-specific risks and the performance of screening for SGA of different severities delivering at selected intervals from the time of assessment.

The main limitation of the study is that the patient's obstetricians were made aware of the screening results. This would have led to further monitoring of identified SGA fetuses and possible delivery. Such intervention would positively bias the

performance of screening, especially for severe SGA delivering at <5 weeks from assessment.

A second important limitation is that as this was a cross-sectional study, we do not have any data on prenatal markers of fetal hypoxia, such as abnormal fetal MCA PI and UA PI, that may have become apparent between assessment and delivery and would have helped to categorise SGA fetuses into FGR and constitutionally small. This would be more evident in those delivering ≥5 weeks after screening, and likely to have been more important in the SGA neonates with BW <5th and 3rd centiles, rather than those with BW <10th centile.

8.3 Implications for clinical practice

This study has the potential to influence clinical practice. Since completion of the studies in this thesis, colleagues from the same department have examined the potential value of screening for SGA neonates at 35-37 weeks' gestation. They reported that the DRs, at a FPR of 10%, of SGA neonates with BW <10th, <5th and<3rd centiles delivering ≥37 weeks were 66%, 70%, and 77.2% compared with our study's results of 53%, 58%, 61% (Fadigas *et al.,* 2015). These results suggest that 35-37 week's routine ultrasound scan, using EFW alone, is a better screening test, however, the lack of Doppler studies, maternal blood pressure measurements and biochemistry make like for like comparisons difficult.

If third trimester screening for SGA was to be implemented this can either be performed at around 32 or 36 weeks' gestation. The advantage of screening at 32 weeks is detection of severe SGA delivering at <36 weeks. In contrast, the advantage of screening at 36 weeks is the improved performance in identifying SGA at term. From our study, there were 14 (17.0%) of the 82 stillbirths in this study occurred prior to 36 weeks. All these cases would be missed, however, it is unclear from this study whether this would increase the chance of identifying the other 83% by planning the routine scan at 35-37 week's.

One option in clinical practice would be to undertake assessment at both 32 and 36 weeks. An alternative strategy for countries with limited resources is to carry out screening at 32 weeks in all pregnancies and on the basis of findings divide the population into firstly, a very-high risk group in need for close monitoring, secondly,

an intermediate risk group in need of further assessment at 36 weeks and thirdly, a low risk group that may not require further monitoring.

It is important to note that the introduction of a third trimester scan increases the total number of routine obstetric scans by more than 50%. An audit of 8,562 patients in one of our hospitals showed that 6,924 (80.9%) did not require any follow up scans resulting from their routine 30-34 weeks' scan. A total of 1,091 (12.7%) had one further scan, and 547 (6.4%) required two or more. SGA requiring follow up was found in 474 (5.5%) patients. Two hundred patients required a further ultrasound due to either an EFW or AC >95th centile. There were 101 (1.2%) cases of polyhydramnios. Importantly, there were a total of 70 (0.8%) new fetal abnormalities detected; these included neurological, cardiac, renal and GI anomalies. This routine scan can therefore be seen as both a growth scan but also an opportunity to identify other anatomical abnormalities. All these findings require appropriate follow up, and create extra workload for both an antenatal scanning unit and its associated fetal medicine unit.

The financial implications, though beyond the scope of this study, are an important aspect of the implementation of an additional routine third trimester ultrasound scan. It has not been possible to carry out a full analysis of the cost benefit of introduction of a 30-34 weeks' routine scan. The main costs of the scan are ultrasound machines and appropriately trained sonographers along with creating clinical space and time for these patients to be seen. It remains to be seen whether the antenatal detection of SGA would decrease the cost of care for these neonates. If the introduction of a third trimester scan decreases the number of stillbirth, whether directly by action on ultrasound findings or by increasing the antenatal surveillance of women, financial effects may not be realised, however the emotional distress of such outcomes will be greatly reduced.

8.4 New pyramid of pregnancy care

Nicolaides (2011) proposed that all women should be assessed at 11-13 weeks' gestation by a combination of maternal characteristics and medical history with biophysical and biochemical markers to identify pregnancies at high-risk of developing PE or delivering SGA neonates. Low dose aspirin would then be prescribed to help

reduce these complications (Bujold *et al.,* 2010; Roberge *et al.,* 2012; Roberge *et al.,* 2012); such treatment should be initiated prior to 16 weeks, otherwise there is no effect in reducing risks (Roberge *et al.,* 2012; Yu *et al.,* 2003).

In the context of the new pyramid of care, an integrated clinic at 30-34 weeks' gestation would allow reassessment of risks to identify pregnancies that despite prophylactic low-dose aspirin can develop PE and / or deliver SGA neonates (Lai et al., 2013; Lai et al., 2013; Lai et al., 2014).

8.5 Future studies

The proposed model from this thesis for prediction of SGA neonates requires prospective intervention studies that would firstly, evaluate the predicted performance of such screening and secondly, examine the extent to which such assessment and appropriate management of the high-risk pregnancies can reduce the high perinatal mortality and morbidity associated with SGA fetuses.

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