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PREDICTION OF SMALL FOR GESTATION NEONATES FROM BIOPHYSICAL AND BIOCHEMICAL MARKERS AT 35-37 GESTATIONAL WEEKS

Cristina Maria Patronilho Fadigas

Orientador: Prof. Luís Fernando Pacheco Mendes da Graça

Co-Orientador: Prof. Kypros Herodotou Nicolaides

Tese especialmente elaborada para obtenção do grau de Doutor em Medicina, especialidade de Ginecologia e Obstetrícia

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As opiniões expressas nesta publicação são da exclusiva responsabilidade da sua autora.

Contents

Preface

The studies described in this thesis comprise work performed at the Fetal Medicine Units of King's College Hospital and Medway Maritime Hospital (United Kingdom). The project was guided by Professor Kypros Nicolaides and funded by The Fetal Medicine Foundation.

According to "Artigo 4º, Diário da República, 2ª série, N.º 111, 9th June 2015 (Regulamento n.º 320/2015)" and "Artigo 19º, Diário da República, 2ª série, nº 153, 7th August 2015 (Regulamento n.º 519/2015)", the results presented and discussed in this thesis were published in the following scientific peer-reviewed journals:

- **Fadigas C**, Saiid Y, Gonzalez R, Poon LC, Nicolaides KH. **Prediction of small-for-gestational-age neonates: screening by fetal biometry at 35-37 weeks**. Ultrasound Obstet Gynecol. 2015 May;45(5):559-65. doi: 10.1002/uog.14816. Epub 2015 Apr 9. Impact factor: 5.654. Cited by 29 (Google Scholar, 28 Jan 2019).

- **Fadigas C,** Guerra L, Garcia-Tizon Larroca S, Poon LC, Nicolaides KH. **Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 35–37weeks.** Ultrasound Obstet Gynecol. 2015 June;45(6):715–721. doi: 10.1002/uog.14847. Epub 2015 May 4. Impact factor: 5.654. Cited by 15 (Google Scholar, 28 Jan 2019).

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Partial results of this thesis were presented at international congresses, as part of a wider project, also lead by Prof. Kypros Nicolaides and funded by the Fetal Medicine Foundation. The referred research project aims to predict appropriate timing for third trimester growth scan, contingent to the second trimester scan. The meetings were the following:

- Poon C, Lesmes C, Bakalis S, **Fadigas C**, Nicolaides KH. **Prediction of Fetal Growth Restriction.** Advances in Fetal Medicine Course 2014, London, United Kingdom, 6-7 Dec 2014. [Oral presentation]

- Poon C, Lesmes C, Bakalis S, **Fadigas C**, Nicolaides KH. **Small for gestional age: Timing for 3rd trimester scan.** 14th World Congress in Fetal Medicine, Crete, Greece, 21-25 Jun 2015. [Oral presentation]

- Poon C, Gallo D, Bakalis S, **Fadigas C**, Nicolaides KH. **Contingent model for the prediction of delivery of small-for-gestational-age neonates**. 26th World Congress on Ultrasound in Obstetrics and Gynecology, Rome, Italy, 24-28 September 2016 [Oral presentation]. Abstract available in Ultrasound in Obstetrics and Gynecology, 48, Suppl 1:2, September 2016. DOI: 10.1002/uog.16029.

Abstract

Small for gestational age (SGA) is common in pregnancy and it has been associated with an increase in adverse perinatal outcomes, predisposition for neurological and cognitive delay in childhood and cardiovascular and endocrine diseases in adulthood.

The classification is not consensual, having been defined in different studies as estimated fetal weight, abdominal circumference or birthweight below the 10th, 5th or 3rd percentiles, with the prevalence varying with the definition that is used.

The increased risk of perinatal mortality and morbidity can be substantially reduced in cases identified prenatally, as close monitoring, timely delivery and prompt neonatal care can be undertaken, in comparison to those cases detected after birth.

Over time, several screening methods have been introduced, in order to optimize the detection rate for SGA. These approaches range from abdominal palpation, symphyseal-fundal height measurement, fetal biometries, uterine artery doppler assessment and, more recently, biochemical markers.

The aim of this thesis is to develop a model for prediction of SGA neonates in the absence of pre-eclampsia, based on maternal characteristics, clinical history, fetal biometry, uterine pulsatility index (Ut PI), mean arterial blood pressure (MAP) and serum biochemical markers (serum placental growth factor: PlGF; Soluble fms-like tyrosine kinase-1: sFlt-1) at 35-37 gestational weeks.

This was a prospective screening project for detection of SGA neonates, in women attending for their third-trimester hospital visit in pregnancy at King's College Hospital (London) and Medway Maritime Hospital (Kent). The project comprised three studies.

The first study included biophysical measurements of 5515 pregnant women, including 278 that delivered SGA (<5th) neonates. A SGA predictive model was developed based on the combination of maternal factors, clinical history and estimated fetal weight.

In the second study, a subset of 5121 pregnant women was evaluated, 245 of which had SGA (<5th) newborns. A model was developed based on the combination of maternal factors, clinical history, estimated fetal weight, mean arterial pressure and uterine artery

dopplers. It was found that the additional use of mean arterial pressure and pulsatility index of the uterine arteries did not significantly improve the performance of screening for delivery of SGA neonates in comparison to the first study.

In the third study, a subset of 3859 pregnant women was evaluated, comprising 158 SGA newborns. The SGA prediction model combined the following parameters: maternal factors, estimated fetal weight and biochemical values (serum placental growth factor, PlGF; fms-like soluble tyrosine kinase-1, sFlt-1). It was found that sFlt-1, when combined with maternal factors and fetal biometries, did not remain an independent factor in this predictive model. Additionally, serum PlGF only marginally improved the SGA screening performance when compared to the model of the first study.

Hence, based on the findings, the best prediction was provided by the combination of maternal factors, estimated fetal weight and serum placental growth factor (PlGF). This combined screening predicted, at a 10% false positive rate, 88, 96 and 94% of SGA neonates with birth weight below the 10^{th}, 5^{th} and 3^{rd} percentiles delivering at <2 weeks following assessment. The respective values for SGA delivering ≥37 weeks were 64, 75 and 80%.

In conclusion, combined screening by maternal factors, biophysical and biochemical markers at 35-37 weeks can identify a high percentage of pregnancies that will deliver SGA neonates.

Keywords: Small-for-gestational age; Late third trimester screening; Fetal biometry; Placental growth factor; Soluble fms-like tyrosine kinase-1.

Resumo

Ser leve para a idade gestacional (LIG) é comum na gravidez e tem sido associado a um aumento nos resultados perinatais adversos, predisposição para défices neurológico e cognitivo na infância e doenças cardiovascular e endocrinológica na vida adulta.

A classificação não é consensual, tendo sido definida em diferentes estudos como peso fetal estimado, circunferência abdominal fetal ou peso à nascença abaixo dos percentis 10, 5 ou 3. Deste modo, a prevalência de LIG varia com a definição utilizada.

O aumento do risco de mortalidade e morbilidade perinatal pode ser substancialmente reduzido nos casos identificados no período pré-natal, uma vez que a vigilância apertada da gravidez, com programação do parto na altura adequada e um atendimento neonatal apropriado podem ser oferecidos, em comparação com os casos apenas detectados após o parto.

Ao longo do tempo, vários métodos de triagem foram introduzidos, a fim de optimizar a taxa de detecção de LIG. Essas abordagens incluem a palpação abdominal, a medição da altura uterina, a avaliação da biometria fetal, a medição dos dopplers das artérias uterinas e, mais recentemente, a utilização de marcadores bioquímicos.

O objectivo desta tese é desenvolver um modelo para previsão de recém-nascidos LIG na ausência de pré-eclâmpsia, baseado em factores maternos, história clínica, biometrias fetais, índice de pulsatilidade das artérias uterinas, pressão arterial média e marcadores bioquímicos (factor de crescimento placentário sérico: PlGF; FMS-like tirosina cinase solúvel-1: sFlt-1) às 35-37 semanas de gestação.

Este foi um trabalho prospectivo de rastreio de gestações simples às 35-37 semanas gestacionais, que decorreu no Reino Unido, no King's College Hospital em Londres e no Medway Maritime Hospital em Kent. O projecto foi organizado em 3 estudos distintos.

No primeiro estudo foram incluídas medidas biofísicas de 5515 gestantes, em que 278 grávidas tiveram recém-nascidos LIG (<p5) e foi desenvolvido um modelo de previsão de LIG com base na combinação de factores maternos, história clínica e peso fetal estimado.

No segundo estudo avaliou-se um subgrupo de 5121 gestantes, das quais 245 tiveram recém-nascidos LIG (<p5) e desenvolveu-se um modelo com base na combinação dos factores maternos, história clínica, peso fetal estimado, pressão arterial média e fluxometria das artérias uterinas. Constatou-se que a utilização adicional da pressão arterial média e do índice de pulsatilidade das artérias uterinas não melhorou significativamente a taxa de detecção de recém-mascidos LIG face ao primeiro estudo.

No terceiro estudo, avaliou-se um subconjunto de 3859 grávidas, incluindo 158 recém-nascidos LIG. O modelo de previsão de recém-nascido LIG combinou os seguintes parâmetros: factores maternos, peso fetal estimado e valores bioquímicos (factor de crescimento placentário sérico, PlGF; fms-like tirosina cinase solúvel-1, sFlt-1). Verificou-se que o sFlt-1, quando combinado com os factores maternos e biometrias fetais, não permaneceu como um factor independente neste modelo de previsão. Adicionalmente, observou-se que o PlGF sérico apenas melhorou marginalmente a taxa de detecção de LIG face ao modelo do primeiro estudo.

Assim, dos vários modelos avaliados, aquele com melhor taxa de detecção de recém-nascidos LIG foi fornecido pela combinação de factores maternos, peso fetal estimado e factor de crescimento placentário sérico (PlGF). Este modelo previu, com uma taxa de falsos positivos de 10%, 88, 96 e 94% dos recém-nascidos LIG com peso ao nascer inferior aos percentis 10, 5 e 3, respectivamente, e que nasceram <2 semanas após a avaliação em consulta. A taxa de detecção para LIG com nascimento ≥37 semanas foi de 64, 75 e 80%.

Em conclusão, o rastreio pelo modelo combinado de factores maternos, marcadores biofísicos e bioquímicos às 35-37 semanas pode identificar uma percentagem elevada de gestações com recém-nascidos LIG.

Acknowledgements

The studies described here in comprise work performed at the Fetal Medicine Units of King's College Hospital and Medway Maritime Hospital (United Kingdom).

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The study was funded by a grant from The Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme - FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project #601852). Roche Diagnostics Limited provided the machine and reagents for the assays.

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Abbreviations

Abbreviation	
AC	Abdominal Circumference
ACOG	American College of Obstetricians and Gynecologists
ADAM12	Metalloprotease Domain-Containing Protein-12
AGA	Appropriate for Gestational Age
aOR	Adjusted Odds Ratio
APH	Antepartum haemorrhage
APLS	Antiphospholipid Syndrome
aRR	Adjusted Relative Risk
ART	Assisted Reproductive Technology
AUC	Area Under ROC (Receiver Operating Characteristic)
β-hCG	free β-human chorionic gonadotropin
BMI	Body Mass Index
BPD	Biparietal Diameter
BW	Birth Weight
CI	Confidence Intervals
CPR	Cerebro-Placental Ratio
CS	Cesarean section
DR	Detection Rate
EFW	Estimated Fetal Weight
FGR	Fetal Growth Restriction
FL	Femur Length
FPR	False Positive Rate
GH	Gestational Hypertension
HC	Head Circumference
IGF	Insulin Like Growth Factor
IQR	Interquartile Range
iSUA	Isolated Single Umbilical Artery
IVF	In Vitro Fertilization
LGA	Large for Gestational Age
LR+	Positive Likelihood Ratio
LR-	Negative Likelihood Ratio

MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MCI	Marginal Cord Insertion
MoM	Multiple of the Median
MRI	Magnetic Resonance Imaging
NBAS	Neonatal Behavioral Assessment Scale
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
PAPP-A	Pregnancy Associated Plasma Protein-A
PE	Pre-eclampsia
PI	Pulsatility Index
PlGF	Placental Growth Factor
PP-13	Placental Protein-13
RCOG	Royal College of Obstetricians and Gynaecologists
RI	Resistance Index
ROC	Receiver Operating Characteristic
RR	Relative Risk
SD	Standard Deviation
SGA	Small for Gestational Age
SFH	Symphyseal-Fundal Height
sFlt-1	Soluble fms-like tyrosine kinase-1
SGA	Small-for-Gestational Age
SLE	Systemic Lupus Erythematosus
SUA	Single Umbilical Artery
UA	Umbilical Artery
UK	United Kingdom
UtA	Uterine Artery
VCI	Velamentous Cord Insertion
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

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CHAPTER 1

Introduction

Chapter 1. Introduction

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

Small for gestational age (SGA) is usual in pregnancy[1]. It is associated with increased adverse perinatal outcomes[2], predisposition for neurological and cognitive delay in childhood and cardiovascular and endocrine diseases in adulthood[3, 4].The classification is not consensual and the prevalence will vary with the definition that is used.

Historically, a birthweight (BW) below 2500g and, occasionally, under 1500g, was used as a cut-off for the definition of SGA. The World Health Organization still uses the definition of SGA as neonatal weight below 2500g at term[5]. This definition is especially useful in developing countries, as it eliminates the impact of accurate pregnancy dating and since low birthweight has long been used as an important public health indicator.

However, with the introduction of population based gestational age dependent BW charts since Lubchenco[6], there was a move to the use of percentiles, which has been widely adopted in developed countries. The definition of SGA is not consensual and various cut-off limits have been proposed, including estimated fetal weight (EFW), BW, abdominal circumference (AC) or, more recently, BW charts comprising babies still in utero[7] below the 10th, 5th or 3rd percentiles or -2 standard deviations (SD) below the mean for gestational age. The ideal cut-off remains uncertain.

The differentiation between constitutionally small and fetal growth restriction (FGR) and the subsequent obstetric management is challenging. The distinction is important, since SGA fetus have a good prognosis compared to FGR fetus. Some authors use the terms SGA and FGR interchangeably, although the majority of SGA are constitutionally small. FGR suggests an underlying pathology and refers to a fetus that has failed to achieve its optimal growth potential [8, 9]. It affects up to 5-10% of all pregnancies[10]. Fetus with a BW below the 10th percentile may not be growth restricted, but rather constitutionally small. The incidence of FGR and SGA are approximately 10%[11, 12]. Although they are not the same population, there is an overlap, as FGR concentrates in the SGA population. Using the 10th percentile as cut-off, it is estimated that in the SGA population, 40% neonates are constitutionally small and 60% are growth restricted[12, 13]. The lower the weight percentile, the higher the chances of pathology and, thus, growth restriction and problems after birth. Lowering the threshold for SGA, increases the likelihood of the fetus being fetal growth

restricted and lowers the false positive rate (FPR)[14]. Nevertheless, this definition fails to recognize the fetus that have fallen across the percentiles, but still remain above the 10th percentile[14].

The challenge is to differentiate constitutionally SGA from FGR fetus and to define FGR fetuses in the group of appropriate for gestational age (AGA) or large for gestational age (LGA). The risks of inaccurate definition of FGR within these different growth groups are overtreatment of healthy SGA and undertreatment of FGR fetus with normal growth.

The traditional approach for identifying pregnancies with SGA fetuses by maternal abdominal palpation and serial measurements of symphisis-fundal height has a detection rate of 30-85%[15-21], as obesity and leyomiomas limit its accuracy.

A few studies comprising low-risk singleton pregnancies have examined the potential value of sonographic fetal biometry during the third trimester in the prediction of SGA neonates [22-28].Of these, only one study[27], up until the end of the studies of this thesis, examined the value of EFW in a late third trimester-ultrasound examination in low risk pregnancies

The use of mathematical models, as well as customized charts[10] adjusted for physiological variables, might improve the classification of fetal growth. They would help to identify fetuses that are small because of constitutional reasons and not because of FGR, reducing unnecessary investigations and interventions [29-32].

The advantage of serial ultrasound examinations for longitudinal growth assessment has not been clearly demonstrated[33, 34].

Doppler studies of maternal and fetal circulation have also shown to improve the diagnosis of SGA and FGR, as often SGA have normal doppler studies, whereas FGR show doppler abnormalities, due to placental insufficiency[35].

Histological studies report that in preeclampsia (PE) and SGA without PE there is impaired placentation, with inadequate trophoblastic invasion of the maternal spiral arteries. This leads to an altered placental production and systemic release of antiangiogenic (soluble fms-like tyrosine kinase-1: sFlt-1) and proangiogenic (placental growth factor: PlGF) factors[36]. Several studies, mainly case-control, reported that, in pregnancies delivering SGA neonates, maternal PlGF is decreased and sFlt-1 is

increased, both in the second and third trimesters of pregnancy. This translates into an increase in the sFlt-1/PlGF ratio[37-39], which is not as high in late-onset FGR as in early onset FGR[37, 40]. There has been a positive correlation in between sFlt-1/PlGF ratio and the likelihood of complications[41, 42].

1.2. ETIOLOGY AND PATHOPHYSIOLOGY OF GROWTH RESTRICTION

At a cellular level, fetal growth has three different stages [43]:

- 0-16 weeks: Hyperplasia
- 16-30 weeks: Hyperplasia and hypertrophy
- 30 week - term: Hypertrophy

An exponential curve translates fetal growth between the end of the first trimester and the last part of the third trimester, with only a slight tailing off around term. However, if we consider the percentage of mass gained per week rather than absolute mass gain, the greatest growth rate occurs in the early stages of pregnancy (in between conception and middle of second trimester), whilst organogesis occurs, in a period of very rapid cell division. From that point onwards, growth occurs mainly due to organs' maturation and hypertrophy[44].

Normal fetal growth relies on the coordination of several components, namely, the genetic growth potential of the fetus, the ability of the placenta to transfer nutrients and oxygen to the fetus and the capacity of the maternal body to deliver these nutrients to the placenta. All of which, are influenced by the surrounding environment[44].

Hence, the etiology of fetal FGR can be categorized into maternal, fetal, placental and environmental factors (Table 1.1)[45]. Even though the pathophysiology of the various underlying conditions is different, the majority of the cases will lead to sub-optimal placental perfusion and fetal nutrition[1, 9].

Table 1.1: Common causes of growth restriction (Sankaran et al [45])

Common causes for FGR
Maternal factors
• Undernutrition • Low maternal weight gain • Low maternal BW • Extremes of maternal age • Low socio-economic status • Nulliparity • Medical conditions (eg, pregestational diabetes, renal insufficiency, systemic lupus erythematosus, antiphospholid antibody syndrome, hypertensive disease pregestational or pregnancy-related, cyanotic cardiac disease)
Environmental factors
• Substance use and abuse (tobacco, alcohol, cocaine or narcotics) • Teratogen exposure • Daily vigorous exercise • High altitude (above 1500m) • Irradiation
Fetal factors
• Chromosomal abnormalities • Genetic diseases • Congenital malformations • Intrauterine infections • Multiple gestation
Placental factors
• Abnormal placentation • Chronic abruption, infarcts and focal lesions • Chronic inflammatory conditions • Chorioangioma • Single umbilical artery, velamentous cord insertion • Confined placental mosaicism

1.2.1. Maternal factors

Nutrition

Animal studies have shown that both maternal undernutrition and overnutrition reduce placental-fetal blood flows and reduce fetal growth, by decreasing placental synthesis of nitric oxide (a major vasodilator and angiogenic factor) and polyamines (key regulators of DNA and protein synthesis). There is some evidence that maternal nutrition status can alter the epigenetic state of the fetal genome, which may provide a molecular mechanism for the impact of maternal nutrition on both fetal programming and genomic imprinting[46].

Studies of pregnant women during famine times have shown an association between SGA and maternal undernutrition. However, the American College of Obstetricians and Gynecologists (ACOG)[47-49] reports that there is no high-quality evidence to support that an

additional nutrient intake will improve the outcome of FGR, in the absence of true malnutrition.

Weight, height, body mass index and low maternal weight gain

The median weight and the median height of women delivering an SGA fetus is lower than those delivering an AGA fetus[50, 51]. More often, the studies have assessed maternal characteristics on the basis of body mass index (BMI) and several of these have shown that the lower the BMI, the higher the risk of delivering a SGA neonate[52, 53].

Low maternal weight gain has been shown to be associated with SGA, even when adjusted for confounding factors as height, BMI, parity, race, toxemia and diabetes. The relative risk (RR) was 1.8 (95% CI, 1.3-2.6) in the second trimester and 1.7 (95% CI 1.3-2.3) in the third trimester[54]. This increased risk was observed across the spectrum of maternal BMI[54]. Regardless, the Royal College of Obstetricians and Gynaecologists (RCOG)[9] no longer recommends that women are routinely weighted during pregnancy as a form of screening for SGA.

Low maternal birthweight

Parental contribution for fetal birthweight through inherited genes is estimated to be around 30-70%[55]. Potential interaction in between fetal genes and uterine environment influences fetal size, with animal studies suggesting that growth is modified towards maternal size. In general, fetal growth tends to be restrained by maternal environment and this is more evident in the first pregnancy. This trace appears to be inherited through the maternal line, with several genes being potentially associated, namely mitochondrial DNA 16189 variant and common variants of maternally only expressed genes, such as H19. Several other genes have been reported to be in association with SGA and FGR (insulin-like growth factor IGF-1, IGF-2, G-protein beta 3 subunit, inducible cytochrome P450, genes encoding angiotensinogen, placental alkaline phosphatase and vitamin D receptor[45, 56, 57]. Paternally inherited genes seem to play a role when the maternal component of restraining fetal growth is less evident. With paternal birthweight history of SGA, a study[58] reports a 3.47 fold increase risk of the fetus being SGA (95% CI, 1.17-10.27)

Maternal age

Extremes of maternal age have been associated with a higher risk of SGA.

Women<17 years: A study[59] reports the highest incidence of SGA in mothers <17 years of age (3.2%). Nevertheless, young age did not remain as an independent risk factor, when it was adjusted to other maternal factors, such as race, education, parity, marital status and prenatal care. These results indicate that the higher incidence of SGA in younger mothers apparently reflects their poor sociodemographic and prenatal care status.

Advanced maternal age: Women over 35 years are at higher risk of many pregnancy complications, mainly because they are more likely to have pre-existing medical conditions than their younger counterparts, predisposing them to develop pregnancy complications[60]. It was observed that women over 40 years of age were at increased risk of pregnancy complications and this risk persisted even when the data was adjusted for preexisting maternal disease[61]. Hence, maternal age 40 years or older constitutes a major risk factor for having a small-for-gestational-age neonate, with an odd ratio (OR) of 3.2 (95% CI 1.9-5.4) having been reported[62].

Ethnicity

It has been referred that birthweight is affected by ethnicity. Gardosi's study[31] to assess the factors that affect fetal growth and birthweight in the population to derive the coefficients to obtain customized charts, shows that african babies can weight less than 218g less than European babies, whereas Chinese babies can weight 100g more (Table 1.2).

Table 1.2 - Birthweight comparison (in grams) based on standard mother being defined as of European origin, height 163 cm, weight 64 kg, first pregnancy, with baby sex averaged between male and female (Gardosi et al [31])

Ethnic origin	United States	England	New Zealand	Australia
African American	-161.0	—	—	—
African Caribbean	—	-127.5	—	—
African	—	-218.5	—	-297.4
Hispanic	-38.6	—	—	—
Middle Eastern.	—	-89.9	—	-110.0
Bangladeshi	—	-79.3	—	—
Indian/Pakistani	—	—	—	-162.0
Indian	—	-149.4	-149.5	—
Pakistani	—	-187.3	—	—
Chinese	—	—	100.9	—
Maori	—	—	—	-66.8
Samoan	—	—	—	84.2
Tongan	—	—	—	124.1
Other	-140.8	—	—	—

This also impacts on the incidence of SGA neonates. In 2008, the Office of National Statistics[63] released its data on all deliveries in England and Wales from 2005. The data showed that babies born to white mothers were larger than those of south Asian or black mothers. Further dividing those two groups into Pakistani, Indian, Bangladeshi, African and Caribbean, showed that 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. Further United Kingdom (UK) studies, documented that Afro-Caribbean, South Asian, East Asian and mixed race women were statistically significantly more likely to deliver an SGA baby than white women[50-51, 64].

Parity

Nulliparity - The biological mechanisms by which parity and SGA are correlated are not quite understood. Nulliparous women have significant associations with adverse outcomes, particularly, when women are also of young age (<18 years). A review[65] has shown an association with term SGA and nulliparity. For nulliparous aged under 18 years, the adjusted odds ratio (aOR) was 1.80 (95% CI: 1.62-2.01)[65]. For nulliparous aged 18-34, the association was not as strong, but still significant, with aOR of 1.51 (95% CI: 1.39-1.64)[65]. Several studies have hypothesized that in young mothers, maternal-fetal competition for nutrients and/or the mother's incomplete physical growth might contribute to adverse neonatal outcomes[65, 66].

Grand Multiparity - Multiple studies have shown an association in between grand multiparous and medical, obstetric and placental complications. Biological mechanisms have been used to explain this association (eg: chronic hypertension for abruption or atrophy of the endometrium for placenta previa)[65]. A study[67] reports that grand multiparity in an economically stable population is not a major risk factor and that previous studies reflect socio-economic factors and not parity itself. This was also shown in a meta-analysis, where a higher risk of SGA was identified in the subgroup of less developed countries, whereas the increase in uterine blood flow associated with increasing multiparity leads to an higher BW in subsequent newborns[65].

Maternal medical conditions

Medical conditions that are associated with vascular disease and interfere with utero-placental circulation increase the risk of FGR. These include hypertensive disorders, pregestational diabetes, auto-immune diseases (eg: systemic lupus erythematosus - SLE), renal insufficiency and antiphospholid syndrome. As for hereditary thrombophilias (eg, factor V Leiden or prothrombin gene mutations), the association with FGR is not consistent[1]. The effects of placental underperfusion vary, whether the placental insufficiency has early or late onset. Early onset insufficiency leads to the underdevelopment of terminal villi, with terminal villous hypoplasia. Late onset insufficiency leads to advanced maturation of the villi, with increased capillary branching, which only compensates the degree of hypoxia temporarily[45, 68]. Where the maternal supply of the placenta has been completely occluded, there will be infarctation of the associated area.

The risks of SGA associated with pathology that affect placental perfusion are significant. The adjusted relative risk (aRR) for chronic hypertension is 2.5 (95% CI 2.1-2.9) [69], being associated with the inadequate conversion of the spiral arteries in the decidua and myometrium. Diabetes with vascular disease has an OR of 6 (95% CI1.5-2.3)[70], the underlying mechanism involving small ischaemic villi, immature/dysmature villi and inconsistent glucose supply to the fetus. For renal impairment, the aOR is 5.3 (95% CI 2.8-10)[71]. SLE has an OR of SGA of 5.6 (95% CI 4.1-7-8)[72]. The presence of anticardiolipin antibodies gives a RR of SGA 6.22 (95% CI 2.42-16.0)[73].

Previous pregnancy history

Having a previous SGA neonate, increases up until three-fold the risk of having another SGA, using a cut-off of BW below the 10th percentile (OR 3.9; 95% CI 2.14-7.12)[9, 74]. This risk is further increased, after two SGA deliveries[75]. The King's College Group, in two prospective studies[51, 64], showed, not only that women with a previous SGA neonate were more likely to deliver another SGA baby than those who had previous normal babies, but also that this risk remained significantly higher even if they had delivered a normal baby after an SGA baby.

Method of conception

In comparison with naturally conceived children, singletons born after assisted reproductive technology (ART) have a higher risk of FGR and other adverse outcomes, with studies reporting a risk of 40-60% of SGA in ART neonates[61, 76]. Regarding singleton pregnancies after in vitro fertilization (IVF), a review[76] reports an OR of 1.59 for SGA (OR 1.59; 95% CI 1.20-2.11). The results were in consistency with a meta-analysis[77], which reported an OR of 1.8 (95% CI 1.4, 2.2) for low birth weight (<2500g), an OR of 2.7 (95% CI 2.3, 3.1) for very low birth weight (<1500g) and an OR of 1.6 (95% CI 1.3, 2.0) for small for gestational age (<10th percentile). Nevertheless, according to a study[78], the increased risk of SGA observed among infertile couples, with or without infertility treatment, suggests that infertility may be a risk factor itself for FGR.

1.2.2. Environmental factors

Substance use and abuse

Smoking tobacco, both active and passive exposures, leads to SGA through its hypoxic effect. A variety of factors has been considered, including poor nutritional state of the mother, toxins and carbon monoxide disruption of oxygen binding. The use during pregnancy has been associated with a 3.5 fold increase of SGA[79]. Further studies have shown that the risk is dose dependent, increasing with the number of cigarettes smoked. A study[80] reported that women smoking up to 10 cigarettes per day have an OR of 1.54 of having a SGA fetus (95% CI, 1.39-1.70) and those who smoke more than 10 cigarettes have an OR of 2.21 (95% CI, 2.03-2.40). A Cochrane review[81] of fifty-six randomised controlled trials (over 20,000 pregnant women) and nine cluster-randomised trials (over 5000 pregnant women) has shown that smoking cessation interventions reduced low birthweight (RR 0.83, 95% CI 0.73 to 0.95). Another study[82] indicated that stopping smoking prior to 15 weeks reversed the risk of SGA to that of a non smoker, showing aOR of SGA of 1.06 (95% CI 0.67-1.68) in women who stopped smoking by 15 weeks vs 1.76 (96% CI 1.03-3.02) in those who kept smoking.

Second and third trimester consumption of alcohol may result in SGA, with the impact being dose dependent[83]. A meta-analysis[84] of 28 studies indicated an overall pooled RR of SGA of 1.12 (95% CI 1.04–1.20) for mothers drinking before or during pregnancy. However, this result was not significant when adjusted for confounders. The risk of SGA

only becomes apparent when the consuption of alcohol exceeds an average of one drink per day. The risk becomes two-fold for an average of four to five units per day, reaching a maximum RR of 7.48 (95% CI 4.46–12.55)[84] for 12 units of alcohol per day. Conversely, consuming less than one drink per day has a minimal effect on intrauterine growth and birth weight[84].

Cocaine acts on the central nervous system and, through its sympathomimetic vasoconstritive effects, can cause hypertension in the mother and fetus, leading to infarcts or hemorrhages in the placenta, at any time in gestation. Due to its high water content, lipid solubility, low molecular weight, and low ionization at physiologic pH, it is believed that it crosses the placenta by simple diffusion[85]. Cocaine use during pregnancy is associated with SGA, with an OR of 3.66 (95% CI, 2.90-4.63)[86].

Teratogen exposure

A variety of pharmacological substances has been implicated with FGR, with the teratogenicity being dependent not only on the substance itself, but also on the dosage, timing and duration of exposure and on the individual genetic predisposition[1].

Vigorous exercise

Exercise is recommended in pregnancy. However, high intensity exercise is associated SGA, with an aOR of 3.3 (95% CI, 1.5-7.2%)[87]. The mechanism in uncertain, but it can be related with flow reduction in the uterine arteries during vigorous exercise[88].

1.2.3. Fetal factors

Chromosomal abnormalities and genetic diseases

Growth potential is adversely influenced by genetic disorders and chromosomal abnormalities. Genetic diseases affect the rate of cellular division, leading to poor growth early in pregnancy. This growth restriction will be enhanced in later stages of pregnancy. On the other hand, in fetus with chromosomal abnormalities, not only the rate of cell

division is reduced, but also placental development is affected, resulting in an additional factor of poor nutrient supply later in pregnancy[44].

Congenital malformations

Fetus with congenital malformations (with a normal karyotype), are at an increased risk of being SGA. Gastroschisis is frequently associated with FGR, being up to 25% of these fetuses growth restricted[1, 89]. Congenital heart problems also are correlated to SGA, having being hypothesized that fetal hemodynamics impact on suboptimal fetal growth[1].

Intrauterine infections

Intrauterine infections are responsible for around 5-10% of FGR cases[1]. All the common bacterial, viral and protozoal infections have been associated with FGR. Cytomegalovirus, toxoplasmosis, rubeolla, varicella, syphilis and malaria are the infections most commonly involved with FGR, with the latter accounting for most of the cases of infection related FGR worldwide. Infections in pregnancy can affect fetal growth not only at a fetal cellular level, but also at a placental level, as inflammation and scarring of the placenta can interfere with nutrient supply[1, 44].

Multiple gestation

The risk of SGA in multiple gestations is increased, having been reported as high as 25% in twin pregancies and reaching 60% for triplets and quadruplets[1]. The prevalence will vary, not only according to the number of fetus, but also in regard to chorionicity, as complications as twin-to-twin transfusion and selective fetal growth restriction tend to arise due to the uneven share of the placenta in monochorionic fetus.

Fetal gender

It has been shown that male fetuses and neonates have both an EFW and a BW larger than females. Thus, the risk of a female being considered SGA is higher[90].

1.2.4. Placental factors

Placenta is the interface between maternal and fetal circulation. The development of placental transport systems and the activation of endocrine and paracrine signaling pathways between the mother, the placenta, and the fetus, will eventually coordinate fetal growth.

The blastocyst implantation triggers the development of the placental vasculature. The migration of the cytotrophoblast forms anchoring villi among the decidua and the uterus. At the same time, hypoxia-stimulated angiogenesis forms vascular connections between the maternal circulation and the intervillous space[43, 68, 91]. Fetal villous budding and trophoblastic invasion of the maternal spiral artery, promotes further nutrient, waste and gas exchange.

Trophoblast-induced vascular adaptation induces an increase in the diameter of the spiral arteries from 15–20 to 300–500 mm during the second trimester[92]. This process is designated *'physiological changes of pregnancy'*, decreases the resistance to, and increases the volume of blood flow within the placenta. Hence, it optimizes fetal-maternal exchange in the intervillous space[68, 91].

Further growth of the placenta results in a term placental exhange area of 12 m^2, with around 600 ml/min flow of maternal blood to be matched by 400 ml/kg/min of fetal flow. Once all the placental transport systems have been established, growth is determined by substrate availability, placental perfusion from the maternal circulation, transplacental paracrine and endocrine signaling, and the perfusion of the fetal placental compartment[45].

Abnormal placentation

Abnormal placentation, with impaired placental vessels development, can lead to a reduction in fetal growth. The reduction in utero-placental blood flow can occur by a reduction in the number the following structures: normal villi at the fetal-maternal interface, arterioles in the tertiary stem villi, terminal capillary loops and villous tree elaboration[44].

The rate of DNA synthesis is decreased in the trophoblasts in FGR and the placental cotyledon's cross-sectional area is reduced. These findings are suggestive of alterations in placental development[45].

A small placenta has been associated with a small neonate[93]. However, this evidence is not consistent, as the placenta can hold up unto 30-40% functional inactivation of the villous population without affecting fetal growth[94]. Clinically, the severity of placental dysfuntion is assessed by Doppler ultrasound. Uterine artery (UtA) dopplers assess the maternal blood flow to the uterus and umbilical artery (UA) doppler assesses the response of the fetus to placental function. UA doppler resistance will only be raised when approximately 30% of the villous are affected[43]. That occurs due to the placenta's potential for compensatory growth[43,45].

Placental disorders

Also, SGA can be caused by any factor that leads to a decrease in utero-placental transfer of nutrients, such as placental abruption, infarcts, haematomas or abnormalities (eg: chorioangioma)[45].

Umbilical cord abnormalities

Single umbilical artery (SUA) is a common finding, which is found in nearly 1% of liveborn fetuses. Still, the association with SGA with isolated SUA (iSUA) is not consensual. Regardless, it is reported an almost two fold increased risk of FGR for iSUA, even after adusting for smoking, gestational diabetes, African-American race and pre-eclampsia (aOR 1.9, 95% CI 1.4-2.5)[95].

Regarding abnormal cord insertion (velamentous cord insertion - VCI; marginal cord insertion - MCI), in singleton pregnancies, it is stated that FGR neonates (BW<3rd percentile) are at higher risk for poor neurological outcomes. Namely, for cerebral palsy the OR is of 10.1 (95% CI 2.4-41.5) for VCI and 4.3 (95% CI 1.6-11.9) for MCI[96]. As for developmental disorders, the OR is of 6.7 (95% CI 1.7-26) for VCI[96]. Also, for SUA it is reported an increased risk for development problems, with an OR of 3.9 (95% CI 1.1-14.2)[96].

Confined placental mosaicism

Confined placental mosaicism occurs in up to 2% of pregnancies[57] and was found to be three times more common in SGA rather than in AGA fetus[97].

1.3. ADVERSE OUTCOMES OF SMALL FOR GESTATIONAL AGE

In case of placental insufficiency, the fetus adjusts and adapts to the inadequate supply of nutrients, in order to optimize its chances of postnatal survival. The adaptive mechanism consists of several strategies, which lead to adjustment in fetal circulation, to spare the brain and the axial skeleton[45].

A catabolic state, with consumption of subtracts to provide energy, is the immediate response to malnutrition. If insufficient supply of nutrients persists, alterations in metabolism occur, which are mediated by changes in hormonal synthesis, such as a decrease the production of IGF-1 and the sensitivity of the tissues to it[98]. The initial response to late fetal growth restriction, does not necessarily translate into a weight change, but typically there is an increase in the brain-to-liver weight. This is followed by fetal adrenal hypertrophy, with increased glucocorticoid activity and a decrease in thymus weight. Further ahead, there will be a reduction in fetal growth and amniotic fluid, as well as myocardium hypertrophy[99]. If the compensatory mechanisms reach their limits, fetal distress occurs and, ultimately, there may be intrauterine demise[45, 100].

1.3.1. Impact of placental insufficiency on organ functions

Brain

Sparing mechanisms aim to compensate oxygen brain supply during hypotensive episodes. These mechanisms include an increased cerebral blood flow and a decreased metabolic rate, by electrophysiological and behavioral states changes[101]. However, in case of chronic placental insufficiency, it is uncertain whether these mechanisms of protection are enough to ensure enough oxygen supply[45].

Cardiovascular

In FGR, there is cardiac hypertrophy as a result of increased cardiac afterload. Also, there is a decreased cardiac output to the placenta. Both result in an increased recirculation of deoxygenated umbilical flow within the fetus. The shunting through the ductus-venosus is higher, with a reduction of the fraction of blood directed to the fetal liver[102].

Lungs

In response to the increased levels of adrenocorticotrophic, there is accelerated lung maturation, as an adaptative mechanism, for increasing the chances of extra-uterine survival[103].

Skeletal muscle

The DNA synthesis is reduced in skeletal muscle. Hence, growth-restricted fetus have a reduction in muscle mass, with a reduction in muscle fiber number, when compared with their appropriate grown counterparts. Muscle hypertrophy can only partially compensate for this limitation in fiber number[104, 105].

Gastrointestinal tract

Reduction of the mesenteric blood flow can be associated with the poor nutrient absorption and postnatal intestinal motility syndrome, more frequently seen in FGR[106].

1.3.2. Adverse perinatal outcomes

FGR is associated with stillbirth, neonatal death, cesarean section (CS) delivery for fetal distress, neonatal acidosis and neonatal unit admission[1, 100, 107-110].

The risk of stillbirth for SGA (EFW <10th) is of 1.5%, which is twice as high as reported for AGA[1]. This is consistent with the findings in one study[100], which reported a higher

incidence of neonatal death (1.1 vs 0.4/1000 births) in a cohort of uncomplicated term pregnancies with SGA (BW <10th percentile), with an aOR of 2.56 (95% CI, 1.83–3.57). The more severely affected the fetuses are, the higher the risk is[1].

It is also reported an association between SGA (BW<10th percentile) and hypoxic composite neonatal morbidity (5-minute Apgar score, hypoxic-ischemic encephalopathy, seizures and neonatal death)[107]. After adjusting for potential confounders, hypoxic composite neonatal morbidity was significantly higher in SGA (1.1%) compared with normally grown babies (0.7%), with an aRR of 1.44 (95% CI, 1.07–1.93)[107].

Another study showed that SGA (EFW<5th) had a higher risk of long neonatal hospital stay (RR 2.7; 95%, CI 2.3-7.8), neonatal unit admission (RR 3.2; 95% CI, 2.2-4.8) and stillbirth (RR 7.7; 9% CI 2.6-23)[108].

The higher risk for having a CS for SGA fetus (EFW<10th percentile) with normal dopplers was shown by Savchev et al[109]. The risk for CS due to fetal distress was higher (22.0 vs 15.9%; p=0.21), but not the risk for intrapartum CS[109]. However, for fetus with EFW<3rd percentile, the risk was both higher for CS for fetal distress (25.0 vs 8.3%; p<0.01) and for intrapartum CS (30.0 vs 15.3%; p 0.04)[109].

In order to prevent potential adverse outcomes, it is important to identify SGA, as there is a four-fold increase of adverse fetal outcome (OR 4.1; 95% CI, 2.5-6.8) in SGA fetuses not recognised antenatally[110]. Breaking down the outcomes, considering SGA not identified antenatally vs SGA identified antenatally, the risks are higher for the first, with an aOR of 2.3 (95% CI, 0.8-6.6; not statistically significant) for cerebral damage, 4.5 (95% CI, 2.1-8.5) for severe fetal distress and 4.2 (95% CI, 2.1-8.5) for fetal/infant death[110]. In the same study, by comparing the SGA group with the AGA group, it was observed that the risk for umbilical pH<7 (OR 2.3; 95% CI 1.5-9.8) and Apgar score<4 at 5 minutes (OR 3.1; 95% CI, 1.8-5.4) was higher for the SGA fetuses[110].

1.3.3. Long-term adverse outcomes

Intrauterine remodeling 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, that are part of a survival strategy, not only have short-term impact, but also have long-term consequences[45, 111].

It is described that FGR fetus have predisposition for neurological and cognitive delay in childhood and cardiovascular and endocrine diseases in adulthood

Neurological and cognitive development

The main long-term concern regardind SGA, is the neurodevelopment outcome. A small study[112] showed that microstructural and metabolic brain changes are identifiable by fetal Magnetic Resonance Imaging (MRI) spectroscopy and diffusion weighted imaging at 37 weeks in SGA fetuses. This suggests that the brain development of this population is different.

A cohort[113] was designed to assess term SGA infants, with normal dopplers. Neurobehavioral performance was evaluated at corrected age of 40 weeks, with the Neonatal Behavioral Assessment Scale (NBAS). The results showed that there was a trend to all of the neurobehavioral areas studied to be poorer in the SGA group. Namely, the average mean differences in scores between the study groups were 0.77 (95% CI 0.38-1.14) for attention, 0.64 (95% CI 0.13-1.14) for habituation, 0.52 (95% CI 0.31-0.74) for motor, 0.95 (95% CI 0.54-1.37) for social-interactive, and 0.68 (95% CI 0.23-1.13) for regulation of state[113].

These differences persist in infants. Another study[114] assessed the neurodevelopmental outcome at 2 years of age of children who had been SGA with cerebral blood flow redistribution (middle cerebral artery pulsatility index MCA PI<5th percentile). These children had a higher incidence of suboptimal neurodevelopmental outcome when compared with those with normal MCA PI (52% vs. 31%; P = 0.049)[114]. They also had a lower mean percentile in communication (53.1 vs. 67.4; P = 0.006) and problem-solving (39.7 vs. 47.4; P = 0.04) areas[114].

The differences persist later in life, being reported that all SGA groups (severe BW <-3SD; moderate -3<BW<-2SD; mild -2<BW<-1 SD) were associated with increased risk of poor school performance at time of graduation from compulsory school[115]. The aOR at a 95% CI ranged from 1.85 (1.65–2.07) for severe, to 1.5 (1.43–1.58) for moderate and 1.25 (1.22–1.28) for mild SGA[115].

A meta-analysis[116] including 28 studies on neurodevelopment of term SGA babies showed that SGA had a poorer performance in standardized neurodevelopment tests than AGA (SD 0.31; 95% CI 0.25-0.38), though there was heterogeneity among studies.

Endocrine diseases

Studies[117, 118] suggest that SGA babies are predisposed in adulthood to metabolic syndrome and adult-onset diabetes (OR, 2.42; 95% CI, 1.44–4.07)[118], when adjusted for body mass index and parental history of diabetes.

A proposed model[119], whereby permanent structural and functional changes in organs and tissues are followed by intrauterine remodeling, may help to explain the relationship between FGR and development of diabetes later in life. In the pancreas, a decrease in beta cell mass and beta cell insulin secretion is observed. In the liver, there is increased gluconeogenesis. In the skeletal muscle, muscle mass is decreased, with decreased insulin sensitivity and increased lipid oxidation. Adipose tissue has decreased insulin inhibition of lipolysis and decreased insulin stimulated glucose uptake. All these four factors, in association with increasing age and obesity, potentiate impaired glucose tolerance, insulin resistance and type 2 diabetes.

Cardiovascular diseases

Primary cardiovascular changes are already present in the SGA fetus and persist at 6 months of age. Both, pre and postnatally, when compared with controls, the SGA group showed a more globular cardiac shape, as well as signs of systolic longitudinal dysfunction, tricuspid annular plane systolic excursion and diastolic dysfunction. In addition, infants in the SGA group had increased mean blood pressure[120, 121].

1.4. SCREENING FOR SMALL FOR GESTATIONAL AGE

The increased risk of perinatal mortality and morbidity of SGA can be substantially reduced in cases identified prenatally, as close monitoring, timely delivery and prompt neonatal care can be undertaken. For that, several methods of screening have been attempted, to optimize the outcomes.

1.4.1. Medical and obstetric history

In the United Kingdom, where a third trimester growth scan is not offered routinely, the RCOG recommends that all women should be assessed at booking for risk factors for SGA and, based on medical history, it will be determined who requires increased surveillance[9].

The strategy of risk assessment is based on OR associated with risk factors for SGA. Risk factors from booking history and current pregnancy complications are taken into account (Tables 1.3 and 1.4).

Table 1.3 RCOG risk factors for SGA fetus/neonate from history at booking[9].

Risk category	Definition of risk	Outcome (BW percentile)	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 percentile	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)
Antiphospholipid Syndrome	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)

Table 1.4: RCOG risk factors for SGA fetus/neonate from current pregnancy complications[9].

Risk category	Definition of risk	Outcome (BW percentile)	Measure	Estimate (95% CI)
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

Based on this factors, RCOG uses the following risk assessment strategy (Fig 1.1)[9]:

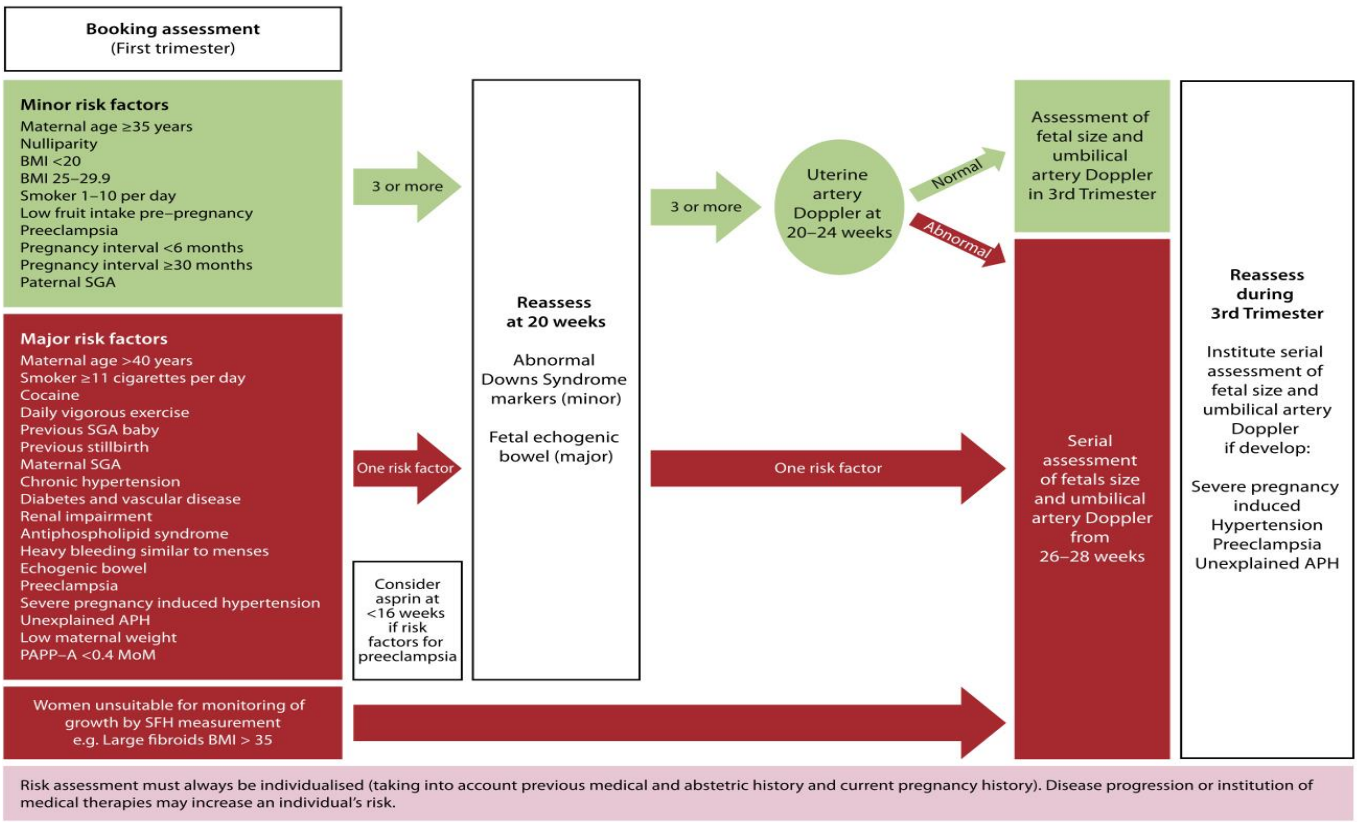

Figure 1.1 - Risk assessment for SGA as set out by the RCOG[9].

1.4.2. Clinical examination

Screening for SGA by clinical examination is considered an inexpensive and effective method[122]. However, the National Institute for Health and Clinical Excellence (NICE) 2008 guidelines on routine antenal care suggest that this can be of limited use, due to a wide variation in study results.

Abdominal palpation

Abdominal palpation has limited accuracy in the detection of SGA both in high and low risk population. In low risk population, the detection rate (DR) rounds 19-21%, whereas in high risk population the DR is of 37%[19, 20]. The results improve for severe SGA (<3rd percentile), with a DR of 28% in the low risk group and 53% in the high risk group[19, 20]. Regardless, RCOG advises not to perform routinely abdominal palpation as a method of screening[9]. On the other hand, in Low and/or Middle Income Countries, the World Health Organization (WHO) does not recommend replacing abdominal palpation with symphysis-fundal height measurement for assessing fetal growth in order to improve perinatal outcomes, due to the lack of clear evidence of accuracy or superiority of either method[123].

Symphysis-Fundal Height Measurement

Studies vary widely, with a symphysis-fundal height (SFH) measurement DR for SGA ranging from 27-86%[124-127]. The measurement is affected by fetal lie, maternal habitus, fibroids, amniotic fluid and fetal head engagement. Serial SFH measurements might improve the predictive accuracy[128]. Currently, RCOG[9] recommends serial measurements of SFH, from 24 gestational weeks onwards, at each antenatal appointment. A single SFH below the 10th percentile or serial SFH measurements suggesting slow or static growth should be referred for further investigation.

Plotting the measurements against customised charts might improve the prediction of SGA[129].

However, the impact of SFH measurement on perinatal outcome still remains uncertain[130].

1.4.3. Mean arterial blood pressure

Two studies reported that, as blood pressure increases between second and third trimester of pregnancy, BW decreases[131, 132]. At 28 weeks, an increase of 5mmHg (1 SD) in diastolic blood pressure decreases BW by 68g, whereas at 36 weeks, the same change reduced BW by 76g[131]. Also, a study showed that lower BW was only associated with a rise in blood pressure in the third trimester[132].

1.4.4. Ultrasound fetal biometry

RCOG guidelines recommend that either EFW or AC <10th percentile can be used to diagnose SGA[9]. On the other hand, ACOG[1] supports only the use of EFW<10th percentile. In fact, a study reports that after 24 weeks, AC and EFW < 10th percentile have similar ability to predict SGA[133].

Some studies have examined the potential value of third trimester sonographic fetal biometry in low-risk singleton pregnancies in the prediction of SGA neonates[22-28]. Three studies examined 725-1000 pregnancies each at 26-36 weeks' gestation and reported that the EFW predicted 54-63% of SGA neonates with birth weight <10th percentile, at false positive rate (FPR) of 20%[22-24]. A study of 1868 pregnancies at 30-32 weeks reported that EFW predicted 73% of SGA neonates with birth weight <10th percentile, at FPR of 25%[25]. Another study of 2310 pregnancies at 30-33 weeks, reported that EFW predicted 60% of SGA neonates with birth weight <5th percentile, at FPR of 10%[26].

Up until the publication of the articles of this thesis, only one study examined the value of a late third trimester scan in low-risk pregnancies; the EFW in 2288 pregnancies at 34-37 weeks' gestation predicted 75% of SGA neonates with birth weight <5th percentile, at screen positive rate of 10%, which was superior to the detection rate of 58% in 3690 pregnancies examined at 30-33 weeks[27].

The use of customised charts adjusted for physiological variables might improve the classification of fetal growth. They help identifying fetuses that are small because of constitutional reasons and not because of FGR, reducing unnecessary investigations and interventions, as well as improving the prediction of adverse outcomes[8, 29]. It is reported that the risks of stillbirth, neonatal death and Apgar score below four at five minutes were higher if SGA was classified by a customised, rather than by the population-based

birthweight standard. For stillbirth, the OR were 6.1 (95% CI 5.0-7.5) for SGA by customised standard only and 1.2 (95 % CI 0.8-1.9) for small for gestational age by population standard in comparison to infants who were AGA / LGA for both standards[134].

1.4.5. Uterine artery dopplers

The uterine arteries (UtA) rise from the anterior divisions of the internal iliac arteries, which supply the uterus with the majority of its blood. A smaller amount of blood is provided from the ovarian arteries. These arteries anastomose at the level of the uterine cornu and originate the arcuate arteries, that run around the uterus and infiltrate into the outer third of the myometrium. Then, these vessels divide into the basal arteries and spiral arteries, which respectively supply blood to the myometrium and intervillous space of the placenta.

The doppler assessment of the UtA provide a non-invasive measurement of the resistance of the uteroplacental circulation, which is increased in FGR[135]. According to a study, UtA doppler studies provide an indication of the extent of placental pathology[136].

Screening for SGA, both in first[137-140] and second trimesters[141], have reported an increase in UtA PI in pregnancies that deliver SGA neonates.

A review of 41131 patients from 61 studies has shown that UtA Dopplers perform more accurately in the second trimester rather than in the first trimester. An increased pulsatility index with notching was the best predictor for overall (positive likelihood ratio: LR+ 9.1) and severe (LR+ 14.6) FGR among low risk patients[142].

Second-trimester UtA resistence index (UtA RI) was associated with the risk of delivering an SGA infant (OR = 1.45; 95% CI: 1.27-1.65)[143]. A stronger association was observed in the third trimester, not only for UtA RI (OR = 1.66; 95% CI: 1.46- 1.89), but also for the presence of unilateral (OR 3.43; 95% CI, 2.36-4.97) and bilateral notching (OR 4.17; 95% CI, 2.54-6.82)[143].

Studies have shown that abnormal UtA Doppler is associated with an increased risk of adverse neonatal outcome, namely, delivery by CS, lower BW, low apgar scores and admission into Neonatal Unit[144-147]. Also, at diagnosis of abnormal UtA, a late SGA fetus has a two-fold increased risk of developing abnormal brain dopplers before induction of labour[148].

1.4.5. Fetal Doppler

Umbilical artery doppler

The placenta is a structure of low resistance, in order to facilitate the blood exchanges. Hence, the fetus blood flow from the umbilical arteries (UA) to the placenta is forward. Once resistance in the placenta starts to increase, the resistance in the UA starts to increase and progressively the blood flow changes from forward during the diastole, to absent or even reversed. The UA PI starts to rise when 30% of the placenta is affected and absent or reversed end-diastolic flow translate a damage of the villous vasculature of at least around 60%[43].

A review in a high-risk population has shown that UA doppler has moderate accuracy to diagnose SGA (LR+ 3.76; 95% CI 2.96-4.76; LR- 0.52; 95% CI 0.45-0.61)[149].

Figueras *et al*[150], studied a large population of 7645 women at 30-34 weeks. In the 369 cases of a SGA fetus identified antenatally, those who had an abnormal UA doppler were more to likely to have neonatal morbidity compared to those of normal BW[150]. If EFW is below the 10th percentile, perinatal death rate can be reduced as much as 29% when the UA doppler is added in fetal assessment[151-154].

However, UA is not reliable to assess placental insufficiency in late-onset FGR. Hence, other doppler studies need to be examined[33].

Middle cerebral artery doppler

When chronic fetal hypoxia is installed, there is redistribution of the blood flow to the brain and other vital organs (heart, adrenals). The brain sparing mechanism translates into cerebral artery vasodilation, with decreased resistance and increased velocity. Therefore, this clinically translates into a low middle cerebral artery (MCA) PI.

There are no trials using MCA doppler to predict SGA fetuses in routine population. On the other hand, the studies have focused on the use of MCA to predict adverse outcomes.

Focusing on late-onset FGR, studies have shown that of all term fetuses, with late-onset FGR and normal UA doppler, 15-20% had low MCA PI and that this was associated with poorer perinatal outcome and neurobehaviour[145, 155]. Namely, a six fold increase in risk of

CS for fetal distress (29% vs 4.8%; p<0.001) and a three fold increase in risk for neonatal acidosis (7.6 vs 2.4%; p=0.01)[156].

Cerebro-placental ratio

It has been stated that combining UA and MCA in a ratio (cerebro-placental ratio - CPR), reflects both the placental status and fetal response, being a more sensitive doppler index for predicting perinatal outcome, as it is already decreased when both of its components are still within normal range[157]. In late SGA, CPR is abnormal in 20% of cases[158, 159]. A review of 9 studies regarding SGA delivered after 32 weeks, has shown that calculating the CPR with MCA Doppler might add value to UA Doppler assessment in the prediction of adverse perinatal outcome in women with a singleton pregnancy. However, this is not consensual and it is unclear to which subgroup of pregnant women this applies[160].

1.4.6. Biochemical markers

The placenta plays a crucial role in SGA development because of multiple biological processes underlying fetal growth. However, valid and reliable placental biomarkers have not yet been determined. In late third trimester, placental growth factor and soluble fms-like tyrosine kinase-1 are the most commonly studied biomarkers of fetal growth. However, findings related to these and other biomarkers are often contradictory in their relation to SGA. Thus, none of the biomarkers has yet been confirmed as reliable for predicting SGA.

Placental growth factor

Placental growth factor (PlGF) is a member of the vascular endothelial family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries[161-163]. Some studies, mainly case-control, have reported that maternal serum PlGF is decreased both in the second and third trimesters[164-169]. Focusing in the studies[170-172] that include late third trimester, the findings are the following (Table 1.5):

Table 1.5: 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	
Wallner *et al.*, 2007[170]	38 & 33	AC <5th and BW <10th	16	245.74	15	48.4	0.0017
Shibata *et al.*, 2005[171]	39-40	BW <10th	31	266	24	163	<0.0001
Rizos *et al.*, 2013[172]	28-35	BW <10th	88	780	14	512	0.002

These studies consistently show that the levels of PlGF are lower in SGA rather than in their counterparts and the difference is statistically significant.

Soluble fms-like tyrosine kinase-1

Soluble fms-like tyrosine kinase-1 (sFlt-1) is a circulating antiangiogenic protein. It binds to vascular endothelial growth factor (VEGF), a protein that regulates angiogenesis, and PlGF. Thus, it inhibits their biological activity and has an antiangiogenic effect[171, 173, 174].

Focusing in the studies[170-172, 174, 175] that include late third trimester, the results are mixed and not consistent, as stated below (Table 1.6):

Table 1.6: 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	
Wallner *et al.*, 2007[170]	38 & 33	AC <5th and BW <10th	16	2199.85	15	4479.17	0.0086
Shibata *et al.*, 2005[171]	39-40	BW <10th	29	2472	22	1987	0.56
Rizos *et al.*, 2013[172]	28-35	BW <10th	88	1616	14	1190	0.011
Chaiworapongsa *et al.*, 2008[174]	20-40	EFW <10th	135	1445	53	3603	<0.001
Romero *et al.*, 2008[175]	40	BW <10th	46	-	56	-	0.8285

Both Wallner *et al*[170] and Chaiworapongsa *et al*[174] have shown that sFlt-1 is significantly higher in pregnancies delivering SGA. Also, by breaking down the results by Doppler findings, it was seen that the concentration of sFlt-1 was highest in SGA fetuses with abnormal UtA Doppler or abnormal UA and UtA dopplers.

sFlt-1/PlGF ratio

As studies show a decrease in PlGF and an increase in sFlt-1 in SGA fetuses[164-169], there is a potential to use the ratio sFlt-1/PlGF to improve the detection of SGA. The data refering to late SGA, without PE is scarce and not significant, as shown in the table below.

Table 1.7: Difference 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	
Herraiz *et al.*, 2014[169]	>34	EFW <10th percentile + AFI <10th percentile or UA PI>95th percentile	171	11.0	8	116.8	<0.5

1.4.7. Combination models

Combination models for SGA fetuses without pre-eclampsia have focused mainly in the first, second and early third trimester.

For first trimester, the algorithms combining maternal characteristics, biophysical and biochemical tests have shown an improvement in the early detection of SGA. A screening study at 11-13 weeks established an algorithm for the prediction of SGA in absence of PE based on maternal characteristics, biochemical (PAPP-A, free ß-hCG, PlGF, PP13, ADAM12) and biophysical markers (UtA PI, MAP and Nuchal translucency). It concluded that half the pregnancies with SGA neonates, in the absence of PE, could be identified at 11-13 weeks[137].

Models developed for the second trimester also showed an improvement in the detection SGA without PE. A study using maternal characteristics, EFW and UtA PI on the second trimester was predictive for SGA (R^2 0.225, AUC 0.815). It also demonstrated that the additional use of a third trimester scan (EFW, UtA PI, UA PI) and maternal characteristics, improved the prediction of SGA (combined model: R^2 0.423, AUC 0.896)[176].

For early third trimester, a study comparing the detection rate for SGA between EFW and EFW combined with uterine artery doppler showed that adding Doppler velocimetry to 30-32 weeks EFW improves the specificity (84%) regarding SGA newborns, maintaining a good detection rate (71%). Thus reducing the population needed to be rescreened from 27 to 17% according to the study model[25].

There is very limited data screening for SGA in late third trimester with combination models. Regarding late-onset FGR, Crispi et al, developed a combination model of UtA Doppler with PlGF, for identifying late-onset PE/IUGR. However, besides not discriminating SGA with and without PE, it did not perform well, with a detection rate below 11% for all parameters analyzed, for a specificity of 95% (UtA PI and sFlt1 - DR 5.3; PlGF and sFlt1 - DR 5.3; UtA PI and sFlt1/PlGF ratio - DR 10.5)[167].

Despite lack of models for late SGA screening, there is more data involving prediction of adverse outcomes. Namely, a model combining SGA (EFW<3rd percentile) with Doppler studies (CPR <10th percentile and UtA>95th percentile) increased the risk of predicting adverse neonatal outcomes. The algorithm had a detection rate of 82.8% (95% CI, 75.1-88.6%) for prediction of adverse outcomes[177].

1.5. OBJECTIVES OF THE THESIS

Up until the publication of the articles of this thesis, only one study examined the value of a late third trimester scan in low-risk pregnancies to predict SGA neonates. Furthermore, there is not a single trial that combined all the above described methods to predict SGA late in pregnancy.

Hence, the objective of this thesis is to assess the combination of maternal factors and biophysical and biochemical markers at 35-37 gestational weeks to predict SGA neonates in the absence of preeclampsia.

This will facilitate targeted surveillance and early intervention. In order to develop a clinically useful screening test, algorithms should be derived from multivariable logistic regression analysis combining maternal characteristics, biophysical and biochemical markers. Therefore, a new approach to antenatal care can be proposed, whereby the patient-specific risk for a wide variety of pregnancy complications is estimated at 35-37 weeks, at the same time we perform the routine growth scan. This will be followed by an individualized patient and disease specific approach, both in terms of the schedule and content of subsequent antenatal care.

CHAPTER 2

Patients and Methods

Chapter 2. Patients and Methods

2.1 Study population

This is a prospective screening study for detection of SGA, in women attending for their routine third-trimester hospital visit in pregnancy at King's College Hospital (London) and Medway Maritime Hospital (Kent), between February and December 2014. This visit, at 35-37 gestational weeks (gestational age being determined by the measurement of fetal crown-rump length at 11-13 weeks or fetal head circumference after that), includes:

- Recording of information regarding maternal characteristics and medical history;
- Assessment of blood pressure and mean arterial blood pressure (MAP) by automated devices;
- Ultrasound examination for estimation of fetal weight[178] from transabdominal measurement of fetal biparietal diameter (BPD), head circumference (HC), abdominal circumference and femur length (FL)[179], as well as mesurement of UtA PI;
- Measurement of maternal serum metabolites PlFG and sFlt-1.

The entry criteria for the study are singleton pregnancies that resulted in live birth or stillbirth of phenotypically normal babies.

2.2. Ethical comittee approval

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital.

2.3. Data collection

2.3.1. Maternal characteristics and history

The following information was recorded from a medical interview:

- Maternal age
- Racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed)

- Method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or in vitro fertilisation (IVF))
- Cigarette smoking during pregnancy (yes or no)
- History of chronic hypertension (yes or no)
- History of type 1 or 2 diabetes mellitus (yes or no)
- History of systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APLS) (yes or no)
- Family history of PE in the mother of the patient (yes or no)
- Obstetric history:
    - ✓ Parity (parous or nulliparous, if no previous pregnancies at or after 24 weeks)
    - ✓ Previous pregnancy with PE (yes or no)
    - ✓ Previous pregnancy with SGA babies (yes or no)
    - ✓ Inter-pregnancy interval.

Maternal weight and height were also recorded.

2.3.2. Mean arterial blood pressure

Blood pressure (BP) was taken by automated devices (3BTO-A2, Microlife, Taipei, Taiwan), which were calibrated before and at regular intervals during the study. Doctors who have received appropriate training on the use of these machines made the record. The women were in sitting position, with their arms supported at the level of the heart and either a small (<22 cm), normal (22-32 cm) or large (33-42 cm) adult cuffs were used depending on the mid-arm circumference. After rest for five minutes, two recordings of MAP were made in both arms simultaneously. Final MAP was calculated as the average of all four measurements.

2.3.3. Estimated fetal weight

Ultrasound was performed by operators trained by the Fetal Medicine Foundation and who had a Certificate of Competence both for anomaly scan and fetal doppler assessment.

The images recquired for assessing fetal biometry were:
- BPD and HC: Transverse view of the head at the level of the septum pellucidum cavum

- AC: Transverse view of the abdomen at the level of the umbilical vein and stomach
- FL: Longitundinal view of the femur

EFW was calculated using Hadlock's formula[178]:

$$\text{Log}_{10}\,\text{EFW} = 1.3596 - 0.00386\,(\text{AC} \times \text{FL}) + 0.0064\,(\text{HC}) + 0.00061\,(\text{BPD} \times \text{AC}) + 0.0425\,(\text{AC}) + 0.174\,(\text{FL})$$

2.3.4. Measurement of uterine artery doppler

Transabdominal colour Doppler ultrasound is used to visualize the left and right uterine arteries at the apparent crossover with the external iliac arteries. Pulsed-wave Doppler is then used with the sampling gate set at 2 mm to cover the whole vessel. Care is taken to ensure that the angle of insonation is less than 30º and the peak systolic velocity is greater than 60 cm/s to ensure that the uterine artery, rather than the arcuate artery, is examined. When three similar consecutive waveforms are obtained the PI is measured and the mean PI of the left and right arteries calculated.

2.3.5. Biochemical measurements

Maternal venous blood is processed within 15 minutes of blood sampling. Serum PlGF and sFlt-1 are measured in parallel, using an automated electrochemiluminescence immunoassay system (Cobas e411, Roche Diagnostics, Penzberg, Germany).

The interassay coefficients of variation for the low and high concentrations were 5.4% and 3.0% for PlGF and 3.0% and 3.2% for sFlt-1, respectively. The Cobas e411 covers a measurement range from 3 to 10 000 pg/mL for PlGF and from 10 to 85 000 pg/mL for sFlt-1.

2.3.6. Outcome measures

Data on pregnancy outcome was collected from the hospital maternity records or the general medical practitioners of the women.

The primary outcome of the study was SGA without PE. The newborn was considered to be SGA if the birth weight was less than the 5th percentile after correction for gestational age at delivery (SGA<5th)[180]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[181]. 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. The patients who developed pre-eclampsia were excluded.

2.4. STATISTICAL ANALYSIS

The observed measurements of fetal HC, AC, FL and EFW were expressed as the respective Z-score and percentile, corrected for gestational age[179, 182]. Mann Whitney-U test was used to compare the Z-score and percentile values of HC, AC, FL and EFW between the SGA and unaffected groups. 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 the time interval between assessment and delivery.

The values of uterine artery PI, MAP, 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 $\log_{10}$ transformed value[183-186]. Mann Whitney-U test was used to compare the median MoM values of uterine artery PI and MAP between the outcome groups. Regression analysis was used to determine the significance of association between $\log_{10}$ MoM of uterine artery PI, MAP, PlGF and sFlt-1 with assessment to delivery interval and birth weight Z-score.

The *a priori* risk for SGA<5th 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.

Multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (*a priori* risk), Z-score of biometries (HC, AC, FL or EFW) or $\log_{10}$MoM value of the remaining biophysical and biochemical markers (MAP, UtA PI, PlGF and sFlt-1) had significant contribution in predicting SGA<5th. 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 birth weight <10th percentile (SGA<10th) and SGA with birth weight <3rd percentile (SGA<3rd) delivering <2 weeks following assessment and delivering ≥37 weeks' gestation.

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

CHAPTER 3

Screening by maternal charateristics and fetal biometry at 35-37 weeks

Chapter 3: Screening by maternal charateristics and fetal biometry at 35-37 weeks

ABSTRACT

Objective: To investigate the value of fetal biometry at 35-37 weeks' gestation in the prediction of delivery of small for gestational age (SGA) neonates, in the absence of preeclampsia (PE).

Methods: Screening study in singleton pregnancies at 35-37 weeks, including 278 that delivered SGA neonates with birth weight <5th percentile and 5237 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if screening by a combination of maternal factors and Z-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) or estimated fetal weight (EFW) had a significant contribution in predicting SGA neonates.

Results: Combined screening by maternal characteristics and history with EFW Z-scores at 35-37 weeks, predicted 89% of SGA neonates with birth weight <5th percentile delivering<2 weeks following assessment, at 10% false positive rate (FPR). The detection rate for the prediction of SGA neonates delivering after 37 weeks was 70%. 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 35-37 weeks could identify, at a 10% FPR, 90% of pregancies that subsequently deliver SGA neonates within 2 weeks of assessment and 70% of those that deliver after 37 weeks.

This chapter is based on: Fadigas C, Saiid Y, Gonzalez R, Poon LC and Nicolaides KH. Prediction of small-for-gestational age neonates: screening by fetal biometry at 35-37 weeks. Ultrasound Obstet and Gynecol. 2015; 45: 559-65.

3.1. INTRODUCTION

Small for gestational age (SGA) neonates are at increased risk of perinatal mortality and morbidity, but the risks can be substantially reduced if the condition is identified prenatally, because in such cases close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken[110].

A few studies have examined the potential value of sonographic fetal biometry in low-risk singleton pregnancies during the third trimester in the prediction of SGA neonates[22-28]. The studies report that the estimated fetal weight (EFW) at 26-36 gestational weeks predicted 54-63% of SGA neonates with BW <10th percentile, at false positive rate (FPR) of 20%[22-24] and 73% of SGA at FPR of 25% with an ultrasound at 30-32 weeks[25]. For SGA defined with neonate with BW<5th percentile, it was reported that EFW at 30-33 weeks had a DR of 60%, at FPR of 10%[26]. Only one study examined the value of a late third trimester scan in low-risk pregnancies. For that, the EFW 34-37 weeks' gestation, in 2288 pregnancies, predicted 75% of SGA neonates with BW <5th percentile, at a FPR of 10%, which was superior to the detection rate of 58%, in 3690 pregnancies examined at 30-33 weeks[27].

Since completion of this thesis studies, colleagues from the same department reported the findings from a screening study at 30-34 weeks in 30849 singleton pregnancies[28]. Combined screening by maternal characteristics and history with EFW Z-scores, predicted 79%, 87% and 92% of SGA neonates in the absence of PE delivering at <5 weeks following assessment with birth weights <10th, <5th and <3rd percentiles, respectively, at a 10% FPR. The respective detection rates for prediction of SGA neonates delivering at $\geq$5 weeks following assessment were 53%, 58% and 61%. Consequently, the performance of screening for SGA at 30-34 weeks is acceptably high for those delivering preterm, but disappointingly low for those delivering at term.

3.1.1. Objectives

The objectives of this study in a large cohort of singleton pregnancies undergoing routine antenatal care are firstly, to investigate further the potential value of fetal biometry at 35-37 weeks' gestation in the prediction of delivery of SGA neonates in the absence of PE and secondly, combine these biomarkers 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 was derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at 35^{+0}-37^{+6} weeks' gestation. The methodology for recording of patient characteristics, sonographic estimation of EFW, mean arterial blood pressure (MAP), UtA PI, maternal serum metabolites, outcome measures and statistical analysis was as described in Chapter 2.

3.3. RESULTS

The study population comprised of 5515 pregnancies, including 278 (5.0%) that delivered SGA<5th neonates in the absence of PE and 5237 (95.0%) cases that were unaffected by these outcomes. The characteristics of the study population are given in Table 3.1.

Table 3.1 Characteristics of the study population of women with a singleton pregnancy with normal outcome or with a small-for-gestational-age (SGA) neonate, in the absence of pre-eclampsia (PE).

Characteristic	Normal (n=5237)	SGA without PE (n=278)	P-value
Maternal age in years, median (IQR)	31.2 (26.5-35.0)	30.1 (24.8-35.3)	0.067
Maternal weight in Kg, median (IQR)	79.0 (70.9-89.9)	73.2 (64.2-83.5)	<0.0001
Maternal height in cm, median (IQR)	164 (160-168)	162 (157-165)	<0.0001
Gestation at screening in weeks, median (IQR)	36.1 (36.0-36.4)	36.3 (36.0-36.4)	0.916
Racial origin			
Caucasian, n (%)	3720 (71.0)	161 (57.9)	<0.0001
Afro-Caribbean, n (%)	1034 (19.7)	64 (23.0)	0.190
South Asian, n (%)	199 (3.8)	34 (12.2)	<0.0001
East Asian, n (%)	109 (2.1)	6 (2.2)	0.830
Mixed, n (%)	175 (3.3)	13 (4.7)	0.233
Past obstetric history			
Nulliparous, n (%)	2537 (48.4)	172 (61.9)	0.001
Parous with no prior PE and SGA, n (%)	2481 (47.4)	73 (26.3)	<0.0001
Parous with prior PE no SGA, n (%)	82 (1.6)	5 (1.8)	0.459
Parous with prior SGA no PE, n (%)	127 (2.4)	27 (9.7)	0.002
Parous with prior SGA and PE, n (%)	10 (0.2)	1 (0.4)	>0.999
Inter-pregnancy interval in years, median (IQR)	3.1 (2.1-5.1)	2.9 (2.1-5.5)	0.965
Cigarette smoker, n (%)	503 (9.6)	62 (22.3)	<0.0001
Conception			
Spontaneous, n (%)	5110 (97.6)	266 (95.7)	0.072
Ovulation drugs, n (%)	23 (0.4)	2 (0.7)	0.362
***In vitro* fertilization, n (%)**	104 (2.0)	10 (3.6)	0.079
Chronic hypertension	72 (1.4)	2 (0.7)	0.588
Pre-existing diabetes mellitus, n (%)	65 (1.2)	3 (1.1)	>0.999
Type 1, n (%)	31 (0.6)	2 (0.7)	>0.999
Type 2, n (%)	34 (0.6)	1 (0.4)	>0.999
SLE / APS, n (%)	13 (0.2)	0 (0.0)	>0.999
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	39.4 (38.4-40.4)	<0.0001
Birth weight in grams, median (IQR)	3430 (3140-3745)	2550 (2347-2721)	<0.0001
Birth weight in percentile, median (IQR)	50.3 (26.6-75.6)	2.7 (1.2-3.7)	<0.0001

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

In the SGA group, compared with the normal group, there was a lower median maternal weight and height, a higher prevalence of South Asian racial origin, nulliparous women, parous women with a prior history of SGA and cigarette smokers, and a lower prevalence of Caucasian racial origin and parous women without prior history of SGA and PE. The median gestational age at delivery and neonatal birth weight were significantly lower in the SGA group than in the normal group.

There were significant (p<0.0001) intercorrelations between Z-score values of HC, AC, FL and EFW in both SGA and normal outcome groups (Table 3.2).

Table 3.2 Pearson correlation between Z-score values of head circumference, abdominal circumference, femur length and estimated fetal weights at 35-37 weeks' gestation in the normal and small for gestational age groups.

Z-score values		Head circumference		Abdominal circumference		Femur length		Estimated fetal weight	
		Normal	SGA	Normal	SGA	Normal	SGA	Normal	SGA
Head circumference	r	1	1	0.373	0.381	0.146	0.234	0.592	0.545
	p	-	-	<0.0001	<0.0001	<0.0001	0.001	<0.0001	<0.0001
Abdominal circumference	r	0.373	0.381	1	1	0.238	0.254	0.916	0.867
	p	<0.0001	<0.0001	-	-	<0.0001	<0.0001	<0.0001	<0.0001
Femur length	r	0.146	0.234	0.238	0.254	1	1	0.469	0.622
	p	<0.0001	0.001	<0.0001	<0.0001	-	-	<0.0001	<0.0001
Estimated fetal weight	r	0.592	0.545	0.916	0.867	0.469	0.622	1	1
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	-	-

r = Pearson correlation, SGA = small for gestational age

3.3.1. Normal pregnancy outcome

There was a significant linear association between HC Z-score and the assessment to delivery interval (-0.298 + 0.040 x delivery interval; r=0.087; P<0.0001) and between EFW Z-score with assessment-to-delivery interval (0.281 + 0.025 x delivery interval; r=0.047; P=0.001) and there was a significant polynomial association between AC Z-score with assessment-to-delivery interval (-0.146 + 0.077 x delivery interval – 0.010 x delivery interval ^{2}; r=0.040; P=0.015) and between FL Z-score with assessment-to-delivery interval (-0.215 + 0.194 x delivery interval – 0.053 x delivery interval ^{2} + 0.005 x delivery interval ^{3}; r=0.043; P=0.022).

3.3.2. Small for gestational age

In the SGA<5th group, the median Z-score values of HC, AC, FL and EFW at 35-37 weeks were significantly lower (p<0.0001). There was a significant linear association between HC Z-score with assessment-to-delivery interval (-1.147 + 0.098 x delivery interval; r=0.249; P<0.001 (Figure 3.1.a); AC Z-score with assessment-to-delivery interval (-1.684 + 0.214 x delivery interval; r=0.481; P<0.0001; Figure 3.1.b); FL Z-score with assessment-to-delivery interval (-1.263 + 0.190 x delivery interval; r=0.314; P<0.0001; Figure 3.1.c); and EFW Z-score with assessment-to-delivery interval (-1.572 + 0.234 x delivery interval; r=0.505; P<0.0001; Figure 3.1.d).

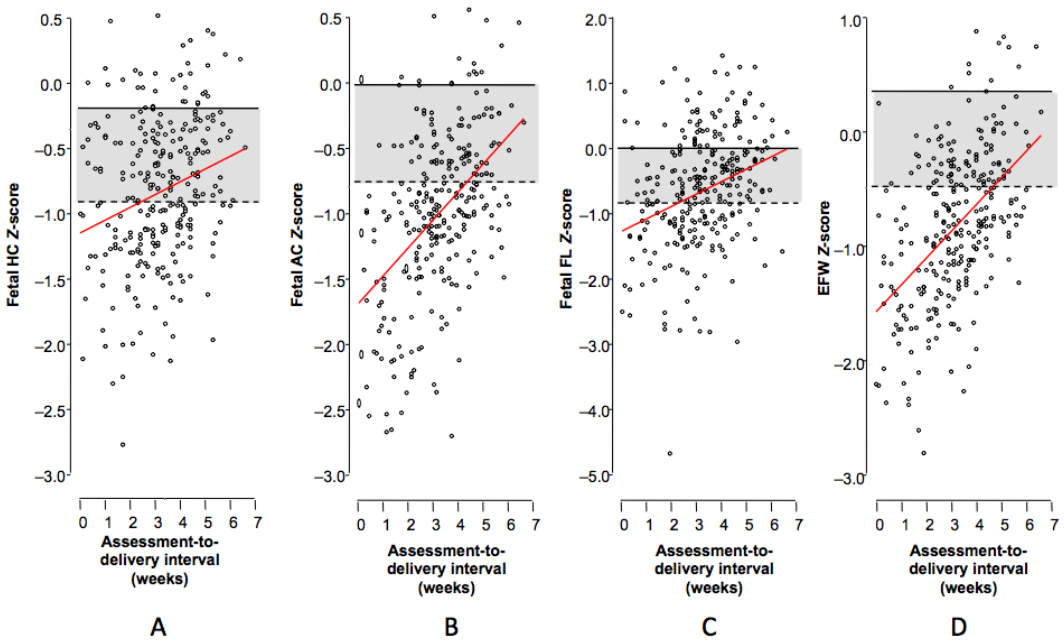

Figure 3.1 Z-scores for fetal head circumference (A), abdominal circumference (B), femur length (C) and estimated fetal weight (D) at 35-37 weeks

The *a priori* risk for SGA<5th 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 adjusted odds ratios of each of the maternal factors in the prediction algorithms are presented in Table 3.3 (R^2=0.106, p<0.0001).

Table 3.3 Fitted regression model with maternal characteristics and history for the prediction of small for gestational age with birth weight below the 5th percentile in the absence of preeclampsia.

Independent variable	Coefficient	SE	OR (95% CI)	P-value
Intercept	-0.89206	0.39700	-	-
Weight (-75)†	-0.02012	0.01094	0.980 (0.970-0.990)	<0.0001
Height (- 165)§	-0.03839	0.01094	0.962 (0.942-0.983)	0.0004
Racial origin				
Caucasian, East Asian, mixed (reference)	0		1	
Afro-Caribbean	0.56782	0.15750	1.764 (1.296-2.403)	0.0003
South Asian	1.08597	0.21540	2.962 (1.942-4.518)	<0.0001
Cigarette smoking	1.08264	0.16094	2.952 (2.154-4.047)	<0.0001
Past obstetric history and pregnancy interval				
Nulliparous	1.06018	0.16341	2.887 (2.096-3.977)	<0.0001
Parous				
No previous SGA, with or without PE (reference)	-3.23409	0.17404	0.021	
Interpregnancy interval in years	0.06583	0.02655	1.081 (1.026-1.139)	0.003
Previous SGA, with or without PE	1.59429	0.23809	6.639 (4.163-10.587)	<0.0001

Subtracted from maternal weight in kg†. Subtracted from maternal height in cm§. SE, standard error.

The likelihood of SGA<5th decreased with maternal weight and height, and in parous women the risk increased with inter-pregnancy interval. The risk was higher in women of Afro-Caribbean and South Asian racial origin, in cigarette smokers, in nulliparous women, and in those with prior history of SGA, with or without prior PE. The risk was lower in parous women without prior history of SGA, with or without prior PE. The likelihood of SGA<5th was not significantly altered by maternal age (p=0.911), method of conception (p=0.083), chronic hypertension (p=0.502), diabetes mellitus (p=0.645) and SLE or APS (P=0.998).

Multivariable logistic regression analyses demonstrated that, in the prediction of SGA<5th, 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 (Table 3.4).

Table 3.4 Fitted regression models with maternal characteristics and history, fetal head circumference (HC) *Z*-score, abdominal circumference (AC) *Z*-score, femur length (FL) *Z*-score or estimated fetal weight (EFW) *Z*-score at 35–37 weeks' gestation, for the prediction of small-for-gestational age with birth weight < 5th percentile in the absence of pre-eclampsia

Independent variable	Coefficient	SE	OR	95% CI	*P*
HC *Z*-score, AC *Z*-score, FL *Z*-score (R^2 = 0.385, *P* < 0.0001)					
Intercept	-4.63644	0.17774	-	-	-
HC *Z*-score	-1.69241	0.38801	0.184	0.086-0.394	<0.0001
HC *Z*-score^2	-1.38647	0.58648	0.250	0.079-0.789	0.018
HC *Z*-score^3	-0.57469	0.24992	0.563	0.345-0.919	0.021
AC *Z*-score	-2.70720	0.31467	0.067	0.036-0.124	<0.0001
AC *Z*-score^2	-0.42986	0.15646	0.651	0.479-0.884	0.006
FL *Z*-score	-0.58584	0.10142	0.557	0.456-0.679	<0.0001
EFW *Z*-score (R^2 = 0.382, *P* < 0.0001)					
Intercept	-3.54921	0.10191	-	-	-
EFW *Z*-score	-2.69024	0.12566	0.068	0.053-0.087	<0.0001
Maternal characteristics and history with HC *Z*-score, AC *Z*-score and FL *Z*-score (R^2=0.404, *P* < 0.0001)					
Intercept	-2.96574	0.30796	-	-	-
Logit (*a-priori* risk)	1.23133	0.19699	3.426	2.329-5.040	<0.0001
HC *Z*-score	-1.58736	0.39123	0.204	0.095-0.440	<0.0001
HC *Z*-score^2	-1.43277	0.59159	0.239	0.075-0.761	0.015
HC *Z*-score^3	-0.60812	0.25210	0.544	0.332-0.892	0.016
AC *Z*-score	-2.59686	0.31677	0.075	0.040-0.139	<0.0001
AC *Z*-score^2	-0.41541	0.15819	0.660	0.484-0.900	0.009
FL *Z*-score	-0.55642	0.10197	0.573	0.469-0.700	<0.0001
Maternal characteristics and history with EFW *Z*-score (R^2=0.402, *P* < 0.0001)					
Intercept	-1.93604	0.25984	-	-	-
Logit (*a-priori* risk)	1.25042	0.19651	3.492	2.376-5.132	<0.0001
EFW *Z*-score	-2.54708	0.12867	0.078	0.061-0.101	<0.0001

OR, odds ratio; SE, standard error.

The areas under the ROC curves (AUC) and the DRs at a false-positive rate (FPR) of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA<10th, SGA<5th and SGA<3rd delivering <2 weeks after assessment and ≥ 37 weeks' gestation, when screening by maternal characteristics and a combination of HC, AC and FL Z-scores or EFW Z-scores are given in Table 3.5, 3.6 and 3.7 in and Figure 3.2.

Table 3.5 Performance of screening for small for gestational age (SGA) neonates with birthweight <10th, <5th and <3rd percentiles, delivering within 2 weeks of assessment and ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal characteristics and history, fetal biometry or estimated fetal weight at 35-37 weeks' gestation

Screening test	AUC	Detection rate (%)		FPR (%)		
		FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
SGA delivering <2 weeks following assessment						
Small for gestational age <10th percentile						
Maternal characteristics and history	0.735 (0.722-0.747)	26.5 (18.1-36.4)	41.8 (31.9-52.2)	98.4 (98.0-98.7)	71.0 (69.7-72.3)	52.1 (50.7-53.5)
Plus EFW z-score	0.961 (0.955-0.966)	77.6 (68.0-85.4)	87.8 (79.6-93.5)	53.5 (52.1-54.9)	11.9 (11.0- 12.8)	5.8 (5.1-6.5)
Small for gestational age <5th percentile						
Maternal characteristics and history	0.804 (0.793-0.815)	35.9 (23.1-50.2)	50.0 (36.6-64.9)	73.6 (72.4-74.8)	57.9 (56.6-59.3)	44.8 (43.5-46.2)
Plus EFW z-score	0.972 (0.967-0.976)	84.9 (72.4-93.3)	88.7 (77.0-95.7)	34.6 (33.3-35.9)	11.1 (10.2-12.0)	3.0 (2.5-3.5)
Small for gestational age <3rd percentile						
Maternal characteristics and history	0.807 (0.796-0.818)	38.9 (23.1-56.5)	50.0 (32.9-67.1)	62.4 (61.1-63.7)	57.9 (56.6-59.3)	40.5 (39.1-41.8)
Plus EFW z-score	0.983 (0.979-0.986)	91.7 (77.5-98.2)	91.7 (77.5-98.2)	17.1 (16.1-18.2)	3.8 (3.3-4.3)	0.9 (0.7-1.3)
SGA delivering ≥37 weeks' gestation						
Small for gestational age <10th percentile						
Maternal characteristics and history	0.709 (0.697-0.721)	19.7 (16.6-23.1)	32.2 (28.5-36.1)	99.9 (99.8-99.9)	70.5 (69.2-71.7)	53.4 (52.0-54.8)
Plus EFW z-score	0.887 (0.879-0.895)	46.9 (42.9-51.0)	66.0 (62.0-69.7)	88.5 (87.6-89.4)	32.9 (31.6-34.2)	19.5 (18.4-20.6)
Small for gestational age <5th percentile						
Maternal characteristics and history	0.734 (0.722-0.746)	22.4 (17.5-28.0)	35.7 (29.9-41.9)	98.1 (97.7-98.5)	68.8 (67.5-70.0)	49.7 (48.3-51.0)
Plus EFW z-score	0.906 (0.898-0.913)	53.6 (47.4-59.8)	70.0 (64.0-75.4)	83.4 (82.4-84.4)	25.0 (23.9-26.2)	13.5 (12.6-14.5)
Small for gestational age <3rd percentile						
Maternal characteristics and history	0.772 (0.761-0.784)	24.8 (18.1-32.6)	37.6 (29.8-45.9)	90.7 (89.9-91.5)	56.3 (54.9-57.6)	41.7 (40.4-43.1)
Plus EFW z-score	0.928 (0.921-0.935)	63.8 (55.5-71.5)	77.2 (69.6-83.7)	69.3 (68.0-70.5)	19.6 (18.5-20.7)	10.6 (9.8-11.5)

Table 3.6 Detection rates (DR) in screening for small-for-gestational-age neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal characteristics and history, fetal biometry or estimated fetal weight at 35–37 weeks' gestation

Screening test	AUC	DR (%)		FPR (%)		
		FPR = 5%	FPR = 10%	DR = 100%	DR = 90%	DR = 80%
Small for gestational age <10th percentile						
Maternal characteristics and history	0.735 (0.722–0.747)	26.5 (18.1–36.4)	41.8 (31.9–52.2)	98.4 (98.0–98.7)	71.0 (69.7–72.3)	52.1 (50.7–53.5)
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.954 (0.948–0.959)	77.6 (68.0–85.4)	82.7 (73.7–89.6)	48.1 (46.7–49.5)	16.4 (15.4–17.4)	5.8 (5.2–6.5)
EFW *Z*-score	0.959 (0.953–0.964)	79.6 (70.3–87.1)	86.7 (78.4–92.7)	59.5 (58.1–60.9)	13.8 (12.9–14.8)	5.4 (4.9–6.2)
Maternal characteristics and history plus						
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.957 (0.952–0.963)	77.6 (68.0–85.4)	85.7 (77.2–92.0)	43.6 (42.2–45.0)	13.3 (12.3–14.3)	6.7 (6.0–7.4)
EFW *Z*-score	0.961 (0.955–0.966)	77.6 (68.0–85.4)	87.8 (79.6–93.5)	53.5 (52.1–54.9)	11.9 (11.0–12.8)	5.8 (5.1–6.5)
Small for gestational age <5th percentile						
Maternal characteristics and history	0.804 (0.793–0.815)	35.9 (23.1–50.2)	50.9 (36.8–64.9)	73.6 (72.4–74.8)	57.9 (56.6–59.3)	44.8 (43.5–46.2)
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.960 (0.954–0.965)	81.1 (68.0–90.6)	86.8 (74.7–94.5)	45.4 (44.1–46.8)	13.8 (12.9–14.8)	4.8 (4.3–5.4)
EFW *Z*-score	0.964 (0.959–0.969)	83.0 (70.2–91.9)	86.8 (74.7–94.5)	43.4 (42.0–44.7)	13.1 (12.2–14.0)	3.7 (3.2–4.3)
Maternal characteristics and history plus						
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.969 (0.964–0.973)	81.1 (68.0–90.6)	90.6 (79.3–96.9)	38.1 (36.8–39.4)	10.0 (9.2–10.8)	3.9 (3.4–4.4)
EFW *Z*-score	0.972 (0.967–0.976)	84.9 (72.4–93.3)	88.7 (77.0–95.7)	34.6 (33.3–35.9)	11.1 (10.2–12.0)	3.0 (2.5–3.5)
Small for gestational age <3rd percentile						
Maternal characteristics and history	0.807 (0.796–0.818)	38.9 (23.1–56.5)	50.0 (32.9–67.1)	62.4 (61.1–63.7)	57.9 (56.6–59.3)	40.5 (39.1–41.8)
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.973 (0.969–0.978)	86.1 (70.5–95.3)	88.9 (73.9–96.9)	20.0 (18.9–21.1)	13.7 (12.7–14.6)	1.6 (1.2–1.9)
EFW *Z*-score	0.980 (0.976–0.984)	88.9 (73.9–96.9)	91.7 (77.5–98.2)	18.6 (17.5–19.7)	8.4 (7.6–9.2)	1.7 (1.3–2.1)
Maternal characteristics and history plus						
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.979 (0.975–0.983)	83.3 (67.2–93.6)	91.7 (77.5–98.2)	17.4 (16.4–18.4)	9.1 (8.4–10.0)	1.1 (0.8–1.4)
EFW *Z*-score	0.983 (0.979–0.986)	91.7 (77.5–98.2)	91.7 (77.5–98.2)	17.1 (16.1–18.2)	3.8 (3.3–4.3)	0.9 (0.7–1.3)

Table 3.7 Detection rates (DR) in screening for small-for-gestational-age neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal characteristics and history, fetal biometry or estimated fetal weight at 35–37 weeks' gestation

Screening test	AUC	DR (%)		FPR (%)		
		FPR = 5%	FPR = 10%	DR = 100%	DR = 90%	DR = 80%
Small-for-gestational age <10th percentile						
Maternal characteristics and history	0.709 (0.697–0.721)	19.7 (16.6–23.1)	32.2 (28.5–36.1)	99.9 (99.8–99.9)	70.5 (69.2–71.7)	53.4 (52.0–54.8)
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.874 (0.865–0.883)	44.6 (40.6–48.7)	61.2 (57.1–65.1)	98.8 (98.5–99.1)	34.1 (32.8–35.5)	21.9 (20.7–23.0)
EFW *Z*-score	0.876 (0.867–0.885)	46.1 (42.1–50.2)	63.1 (59.2–67.0)	93.8 (93.1–94.4)	33.8 (32.5–35.1)	21.9 (20.8–23.1)
Maternal characteristics and history plus						
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.885 (0.876–0.893)	46.9 (42.9–51.0)	64.5 (60.5–68.3)	98.6 (98.3–98.9)	33.5 (32.2–34.9)	19.1 (18.0–20.3)
EFW *Z*-score	0.887 (0.879–0.895)	46.9 (42.9–51.0)	66.0 (62.0–69.7)	88.5 (87.6–89.4)	32.9 (31.6–34.02)	19.5 (18.4–20.6)
Small-for-gestational age <5th percentile						
Maternal characteristics and history	0.734 (0.722–0.746)	22.4 (17.5–28.0)	35.7 (29.9–41.9)	98.1 (97.7–98.5)	68.8 (67.5–70.0)	49.7 (48.3–51.0)
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.899 (0.890–0.907)	53.2 (47.0–59.4)	65.8 (59.7–71.5)	80.0 (78.9–81.0)	26.7 (25.5–27.9)	16.9 (15.9–17.9)
EFW *Z*-score	0.895 (0.887–0.903)	54.8 (48.5–60.9)	65.8 (59.7–71.5)	77.3 (76.1–78.4)	29.1 (27.8–30.3)	16.7 (15.7–17.8)
Maternal characteristics and history plus						
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.908 (0.900–0.916)	54.0 (47.8–60.1)	69.2 (63.2–74.7)	84.9 (83.9–85.8)	23.0 (21.9–24.2)	13.8 (12.8–14.7)
EFW *Z*-score	0.906 (0.898–0.913)	53.6 (47.4–59.8)	70.0 (64.0–75.4)	83.4 (82.4–84.4)	25.0 (23.9–26.2)	13.5 (12.6–14.5)
Small-for-gestational age <3rd percentile						
Maternal characteristics and history	0.772 (0.761–0.784)	24.8 (18.1–32.6)	37.6 (29.8–45.9)	90.7 (89.9–91.5)	56.3 (54.9–57.6)	41.7 (40.4–43.1)
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.919 (0.912–0.926)	61.1 (52.8–68.9)	73.2 (65.3–80.1)	67.4 (66.1–68.7)	20.0 (18.9–21.1)	13.7 (12.7–14.6)
EFW *Z*-score	0.918 (0.911–0.925)	62.4 (54.1–70.2)	72.5 (64.6–79.5)	71.2 (69.9–72.4)	20.2 (19.1–21.3)	13.5 (12.5–14.4)
Maternal characteristics and history plus						
HC *Z*-score, AC *Z*-score, FL *Z*-score	0.928 (0.921–0.935)	64.4 (56.2–72.1)	77.2 (69.6–83.7)	63.5 (62.2–64.8)	17.4 (16.4–18.4)	10.4 (9.6–11.3)
EFW *Z*-score	0.928 (0.921–0.935)	63.8 (55.5–71.5)	77.2 (69.6–83.7)	69.3 (68.0–70.5)	19.6 (18.5–20.7)	10.6 (9.8–11.5)

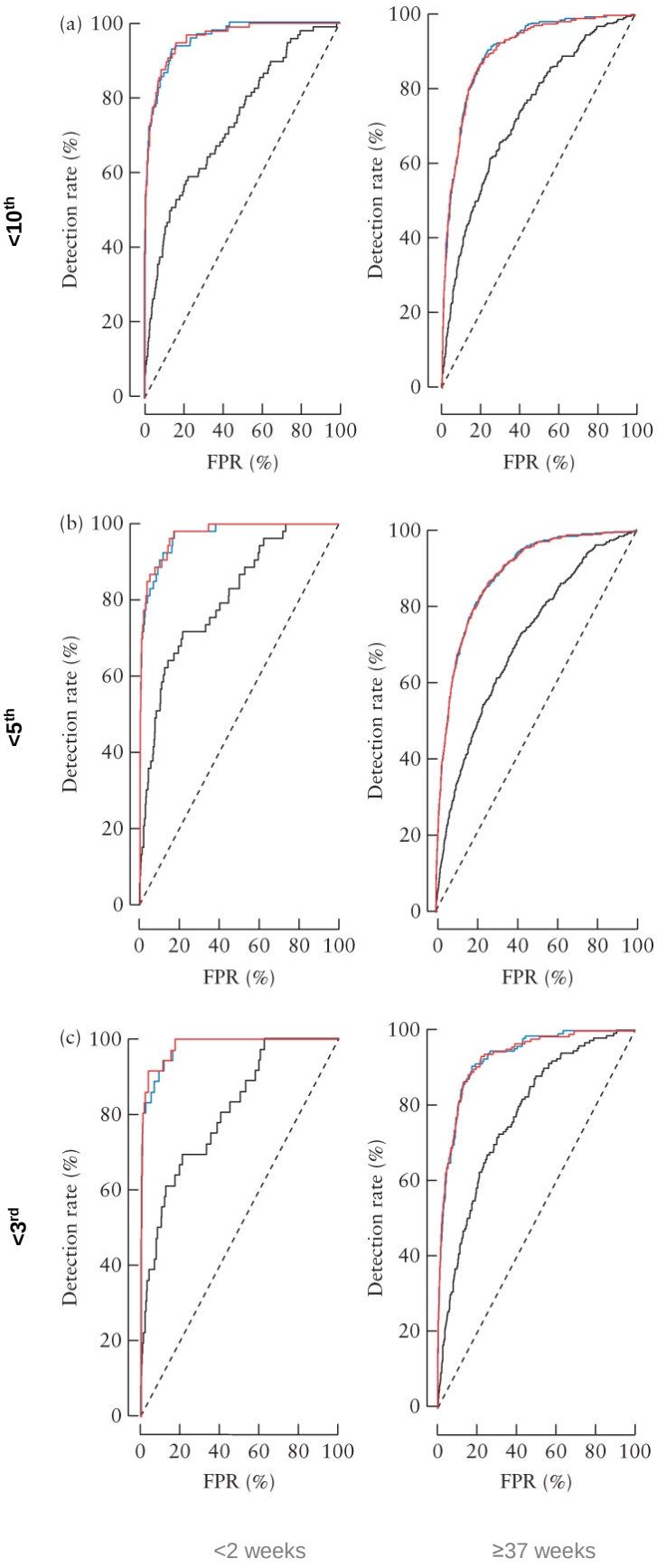

Figure 3.2 Receiver-operating characteristic curves of maternal characteristics (black line), combination of maternal characteristics of HC, AC and FL z-score (blue line) and the combination of maternal characteristics with EFW z-score (red line) at 35-37 gestational weeks in the prediction of SGA with BW below the 10th (a), the 5th (b) and the 3rd (c) percentile, delivering < 2 weeks following assessment (left) or ≥37 weeks' gestation.

Prediction of small for gestational age delivering <2 or ≥2 weeks following screening at 35-37 weeks

The DRs, at a FPR of 10%, of combined screening by maternal characteristics and history with EFW Z-scores for the prediction of SGA neonates with BW <10th, <5th and <3rd percentiles, delivering ≥2 weeks following assessment, were 62.6% (95% CI, 58.3-66.7; AUC 0.875 (95% CI, 0.866-0.884)), 67.1% (95% CI, 60.6-73.2; AUC 0.895 (95% CI, 0.886-0.903)) and 74.4% (95% CI, 65.6-81.9; AUC 0.916 (95% CI, 0.909-0.924)), respectively. The performance of screening was better for the prediction of SGA delivering within 2 weeks of assessment with respective DRs of 87.8% (95% CI, 79.6-93.5; AUC 0.961 (95% CI, 0.955-0.966)), 88.7% (95% CI, 77.0-95.7; AUC 0.972 (95% CI, 0.967-0.976)) and 91.7% (95% CI, 77.5-98.2; AUC 0.983 (95% CI, 0.979-0.986)).

Prediction of small for gestational age delivering ≥37 weeks with screening at 35-37 weeks compared to 30-34 weeks

In combined screening by maternal characteristics and history with EFW Z-scores at 35-37 weeks the DRs, at a FPR of 10%, of SGA neonates with BW<10th, <5th and <3rd percentiles delivering ≥ 37 weeks were 66.0% (95% CI, 62.0-69.7; AUC 0.887 (95% CI, 0.879-0.895)), 70.0% (95% CI, 64-75.4; AUC 0.906 (95% CI, 0.898-0.913)) and 77.2% (95% CI, 69.6-83.7; AUC 0.928 (95% CI, 0.921-0.935)), respectively. Using data from a simultaneuos publication of colleagues, from the same Department, in combined screening by maternal characteristics and history with EFW Z-scores at 30-34 weeks[28], the respective detection rates were 53.0% (95% CI, 51.3-54.8; AUC 0.833 (95% CI, 0.829-0.837)), 58.3% (95% CI, 55.7-60.9; AUC 0.859 (95% CI, 0.855-0.863)) and 60.8% (95% CI, 62.6-85.0; AUC 0.875 (95% CI, 0.871-0.879)).

3.4. DISCUSSION

3.4.1. Main findings of the study

The findings of this study demonstrate that the risk of delivering SGA neonates in the absence of PE, increases with a longer interpregnancy interval, decreases with maternal weight and height, it is higher in women of Afro-Caribbean or South Asian racial origin

than in Caucasian women, in cigarette smokers, nulliparous women and in parous women with history of SGA.

In women who deliver SGA neonates in the absence of PE, the fetal HC, AC, FL and EFW at 35-37 weeks' gestation are reduced. The prediction of SGA provided by the fetal AC is superior to that of HC or FL, but inferior to that of the combination of the three measurements. The performance of screening by a combination of Z-scores for fetal HC, AC and FL is similar to that achieved by the EFW Z-score.

Combined screening by maternal characteristics and history with EFW Z-scores at 35-37 weeks, predicted about 70% of pregnancies that subsequently delivered SGA <5th neonates, at a FPR of 10%. This was superior to the DR of 58% achieved by screening at 30-34 weeks. The performance of screening was better in the prediction of SGA delivering within 2 weeks of assessment, with DR of about 90%.

3.4.2. Comparison with findings of previous studies

Our findings, that the prediction of SGA neonates with BW<5th percentile at 35-37 gestational weeks by sonographic estimation of EFW Z-scores is superior to that of screening at 30-34 weeks (70% vs 58%), at a FPR of 10%, are similar to those of a previous study that reported rates of 75% and 58% with screening at 34-37 weeks and 30-33 weeks, respectively[27]. In the latter study, all cases of SGA were included, whereas is this study, the cases with associated PE were excluded.

A routine third trimester scan is by far superior to the traditional approach of abdominal palpation in identifying pregnancies at high-risk of delivering SGA neonates. A population based observational study of 6318 consecutive low risk singleton pregnancies reported that abdominal palpation predicted only 21% and 28% of SGA neonates with birth weight <10th and 2.3rd percentiles respectively, at FPR of about 5%[20]. One randomized study compared the effectiveness of abdominal palpation to that of serial measurements of symphysial-fundal height in the prediction of SGA neonates with birth weight <10th percentile and reported no significant difference between the two methods (28% vs. 48%, both at FPR of about 4%)[21].

The advantage of using Bayes theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry is that individual patient-specific

risks and the performance of screening for SGA of different severities, delivering at term, can be estimated. This is an essential first step for establishing patient management protocols.

CHAPTER 4

Screening by maternal characteristics, fetal biometry, uterine artery Doppler and mean arterial blood pressure at 35-37 weeks

Chapter 4: Screening by maternal characteristics, fetal biometry, uterine artery Doppler and mean arterial blood pressure at 35-37 weeks

ABSTRACT

Objective: To investigate the potential value of uterine artery pulsatility index (PI) and mean arterial pressure (MAP) at 35-37 weeks' gestation in the prediction of delivery of small for gestational age (SGA) neonates, in the absence of preeclampsia (PE).

Methods: Screening study in singleton pregnancies at 35-37 weeks, including 245 that delivered SGA neonates with birth weight <5th percentile and 4,876 cases unaffected by SGA, PE or gestational hypertension (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 estimated fetal weight (EFW) from fetal head circumference, abdominal circumference and femur length.

Results: In the SGA<5th group, compared to the normal group, the median multiple of the median (MoM) values of uterine artery PI and MAP were significantly higher. Combined screening by maternal factors, EFW Z-score, uterine artery PI and MAP at 35-37 weeks, predicted at 10% false positive rate, 90%, 86% and 90% of SGA neonates with birth weight <10th, <5th and <3rd percentiles, respectively, delivering at <2 weeks following assessment and the respective values for SGA delivering at ≥37 weeks were 66%, 74% and 80%. Such performance was not significantly different from screening by maternal factors and EFW Z-score alone.

Conclusion: Addition of uterine artery PI and MAP to combined testing using maternal factors and fetal biometry at 35-37 weeks does not improve the performance of screening for delivery of SGA neonates.

This chapter is based on: Fadigas C, Guerra L, Garcia-Tizon Larroca S, Poon LC and Nicolaides KH. Prediction of small-for-gestational age neonates: screening by uterine artery Doppler and mean arterial pressure at 35-37 weeks. Ultrasound Obstet and Gynecol 2015; 45: 715-21.

4.1. INTRODUCTION

Small for gestational age (SGA) neonates are at increased risk of perinatal mortality and morbidity, but the risks can be substantially reduced if the condition is identified prenatally, because in such cases close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken[110]. The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysial-fundal height, but the detection rate (DR) of this approach is less that 30%[20,21]. A higher performance in screening for SGA is achieved by a third-trimester assessment which includes ultrasound examination for fetal biometry and the timing of such assessment, at 32 or 36 weeks' gestation, could be defined by the results of assessment at 22 weeks[187, 188].

Screening by a combination of maternal characteristics and medical history with estimated fetal weight (EFW), uterine artery (UtA) pulsatility index (PI) and mean arterial pressure (MAP) at 32 weeks' gestation, predicted, at false positive rate (FPR) of 10%, 83%, 91% and 93%, of SGA neonates delivering within five weeks of assessment with respective birth weight <10th, <5th and <3rd percentiles in the absence of preeclampsia (PE)[189]. However, the respective values for delivery at $\underline{\geq}$5 weeks of assessment were only 53%, 60% and 63%.

4.1.1. Objectives

The objectives of this study in singleton pregnancies undergoing routine antenatal assessment at 35-37 weeks' gestation are firstly, to investigate the potential value of uterine artery PI and MAP on their own and in combination with maternal characteristics, medical history and EFW in the prediction of delivery of SGA neonates in the absence of PE and secondly, to develop specific algorithms for the calculation of patient-specific risks for SGA.

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 35-37 weeks' gestation. The methodology for recording of patient

characteristics, sonographic estimation of EFW, UtA PI, MAP, serum metabolites, outcome measures and statistical analysis was as described in Chapter 2.

4.3. RESULTS

The characteristics of the study population of 5121 pregnancies, including 245 delivering SGA <5th neonates in the absence of PE, are presented in Table 4.1.

Table 4.1. Characteristics of the study population of women with a singleton pregnancy with normal outcome or with a small-for-gestational-age (SGA) neonate, in the absence of pre-eclampsia (PE).

Characteristic	Normal (n=4876)	SGA without PE (n=245)	P-value
Maternal age in years, median (IQR)	31.2 (26.5-35.0)	30.1 (24.6-35.3)	0.061
Maternal weight in Kg, median (IQR)	79.0 (70.8-89.8)	73.5 (63.9-84.1)	<0.0001
Maternal height in cm, median (IQR)	164 (160-168)	162 (158-165)	<0.0001
Gestation at screening in weeks, median (IQR)	36.1 (36.0-36.4)	36.3 (36.0-36.4)	0.848
Racial origin			
Caucasian, n (%)	3495 (71.7)	140 (57.1)	<0.0001
Afro-Caribbean, n (%)	941 (19.3)	57 (23.3)	0.137
South Asian, n (%)	178 (3.7)	30 (12.2)	<0.0001
East Asian, n (%)	101 (2.1)	6 (2.4)	0.644
Mixed, n (%)	161 (3.3)	12 (4.9)	0.200
Past obstetric history			
Nulliparous, n (%)	2352 (48.2)	148 (60.4)	0.0002
Parous with no prior PE and SGA, n (%)	2318 (47.5)	67 (27.3)	<0.0001
Parous with prior PE no SGA, n (%)	77 (1.6)	4 (1.6)	0.795
Parous with prior SGA no PE, n (%)	121 (2.5)	25 (10.2)	<0.0001
Parous with prior SGA and PE, n (%)	8 (0.2)	1 (0.4)	0.357
Inter-pregnancy interval in years, median (IQR)	3.1 (2.1-5.1)	2.9 (2.1-5.5)	0.965
Cigarette smoker, n (%)	464 (9.5)	59 (24.1)	<0.0001
Conception			
Spontaneous, n (%)	4758 (97.6)	235 (95.9)	0.136
Ovulation drugs, n (%)	20 (0.4)	2 (0.8)	0.284
***In vitro* fertilization, n (%)**	98 (2.0)	8 (3.3)	0.167
Chronic hypertension	64 (1.3)	2 (0.8)	0.770
Pre-existing diabetes mellitus, n (%)	57 (1.2)	2 (0.8)	>0.999
Type 1, n (%)	27 (0.6)	1 (0.4)	>0.999
Type 2, n (%)	30 (0.6)	1 (0.4)	>0.999
SLE / APLS, n (%)	13 (0.3)	0 (0.0)	>0.999
Gestation at delivery in weeks, median (IQR)	40.0 (39.1-40.9)	39.4 (38.6-40.4)	<0.0001
Birth weight in grams, median (IQR)	3435 (3,140-3,745)	2550 (2,350-2,718)	<0.0001
Birth weight in percentile, median (IQR)	50.6 (26.8-75.6)	2.7 (1.2-3.8)	<0.0001

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

4.3.1. Normal pregnancy outcome

In the unaffected pregnancies with birth weight ≥5th percentile, the mean ± SD, 90th and 95th percentile of log_{10} MoM UtA PI were -0.009 ± 0.113, 0.134 and 0.187, respectively. The mean ± SD, 90th and 95th percentile of log_{10} MoM MAP were 0.002 ± 0.033, 0.044 and 0.056, respectively (Table 4.2). There was no significant association between log_{10} MoM values of UtA PI and MAP (r=-0.004, P=0.893). There was a significant inverse association between log_{10} MoM UtA PI with assessment to delivery interval (r=-0.096, P<0.0001) and birth weight Z-score (r=-0.096, P<0.0001), and between log_{10} MoM MAP with assessment to delivery interval (r=-0.080, P<0.0001) but not birth weight Z-score (r=-0.022, P=0.113).

Table 4.2 Uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation in pregnancies that delivered small-for-gestational-age (SGA) neonates with birth weight < 5th percentile, in the absence of pre-eclampsia, and in unaffected pregnancies

Outcome group	Median (IQR)	MoM (median (IQR))	Log_{10} MoM (mean ± SD)	> 95th percentile (*n* (%, 95% CI))	> 90th percentile (*n* (%, 95% CI))
UtA-PI					
Normal	0.690 (0.590–0.820)	0.967 (0.824–1.146)	–0.009 ± 0.113	243 (5.0, 4.4–5.6)	487 (10.0, 9.2–10.9)
SGA	0.785 (0.620–0.978)*	1.104 (0.873–1.385)*	0.050 ± 0.137*	42 (17.1, 12.9–22.4)*	65 (26.5, 21.4–32.4)*
MAP					
Normal	89.0 (83.9–93.8)	1.008 (0.955–1.059)	0.002 ± 0.033	243 (5.0, 4.4–5.6)	487 (10.0, 9.2–10.9)
SGA	90.3 (85.2–95.6)*	1.045 (0.969–1.101)*	0.014 ± 0.037*	25 (10.2, 7.0–14.6)*	53 (21.6, 16.9–27.2)*

Comparison between normal outcome and SGA by Chi square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test or student's *t*-test for continuous variables:*$P < 0.05$. IQR, interquartile range, MoM, multiples of the unaffected median.

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 35-37 weeks were significantly higher (Table 4.2). There was no significant association between log_{10} MoM values of uterine artery PI and MAP (r=0.109, P=0.088). There was a significant inverse association between log_{10} MoM uterine artery

PI with assessment to delivery interval (r=-0.232, P<0.0001; Figure 4.1.a) and birth weight Z-score (r=-0.157, P=0.011; Figure 4.1.b). There was no significant association between log_{10} MoM MAP with assessment to delivery interval (r=-0.100, P=0.107; Figure 4.1.c) and birth weight Z-score (r=-0.057, P=0.354; Figure 4.1.d).

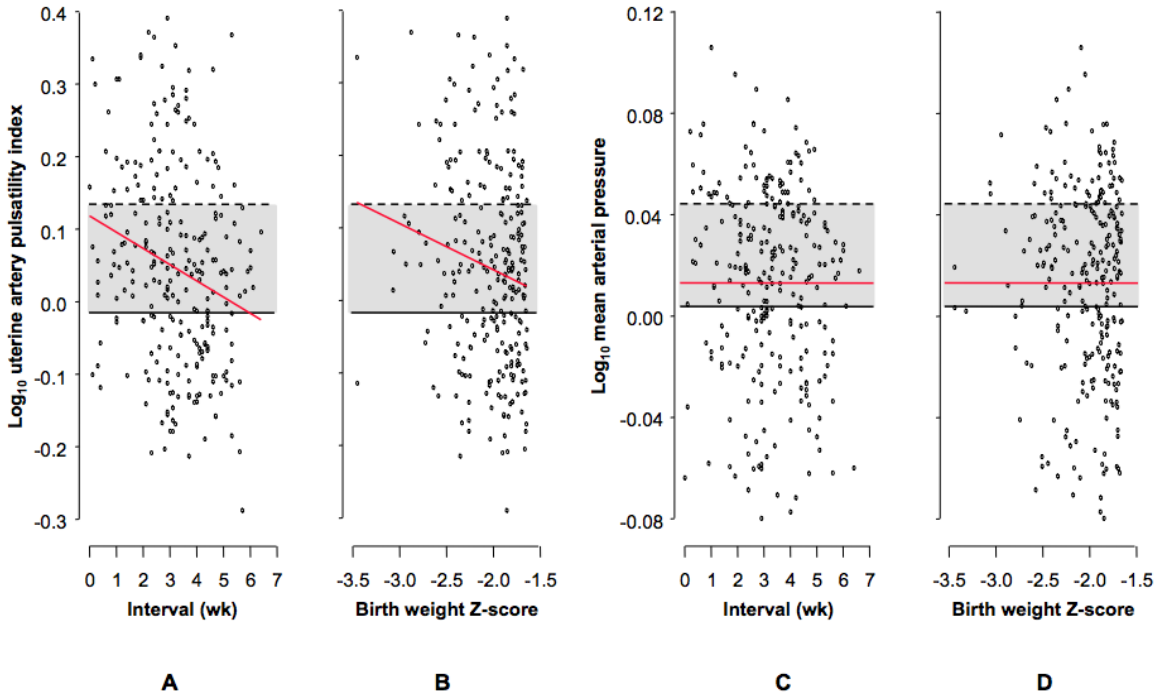

Figure 4.1 Log_{10} uterine artery pulsatility index (UtA-PI) (A, B) and log_{10} mean arterial pressure (MAP) (C, D) multiples of median according to assessment-to-delivery interval (A, C) and birth-weight *Z*-score (B, D) in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile, plotted on the 50th (solid line), 90th and 95th (dashed line) percentile of the appropriate normal range.

Multivariable logistic regression analysis demonstrated that in the prediction of SGA <5th there were significant contributions from maternal characteristics, EFW Z-score, uterine artery PI and MAP (Table 4.3). Combined screening by maternal characteristics and history with EFW Z-scores, uterine artery PI and MAP detected 66%, 74% and 80% of SGA neonates with birth weight <10th, <5th and <3rd percentiles, respectively, at 10% FPR.

Table 4.3 Fitted regression models with maternal characteristics and history, estimated fetal weight (EFW) *Z*-score, uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation for the prediction of small-for-gestational-age neonates with birth weight < 5th percentile, in the absence of pre-eclampsia

Independent variable	Coefficient	SE	OR	95% CI	*P*
Maternal characteristics and history with UtA-PI (R^2 = 0.140, P < 0.0001)					
Intercept	–0.14600	0.21172	-	-	-
Logit (*a-priori* risk)	2.35253	0.17513	10.512	7.458–14.817	< 0.0001
Log_{10} MoM UtA-PI	2.78497	0.60186	16.199	4.980–52.699	< 0.0001
Log_{10} MoM UtA-PI^2	7.78026	2.65846	2.39×10^3	1.31×10^1 to 4.38×10^5	0.003
Maternal characteristics and history with MAP (R^2 = 0.122, P < 0.0001)					
Intercept	–0.19178	0.21290	-	-	-
Logit (*a-priori* risk)	2.29773	0.17204	9.952	7.103–13.942	< 0.0001
Log_{10} MoM MAP	7.24939	1.85688	1.41×10^3	3.70×10^1 to 5.36×10^4	< 0.0001
Log_{10} MoM MAP^2	86.92506	32.41269	5.64×10^{37}	1.45×10^{10} to 2.19×10^{65}	0.007
Maternal characteristics and history with UtA-PI and MAP (R^2 = 0.157, P < 0.0001)					
Intercept	–0.32312	0.22619	-	-	-
Logit (*a-priori* risk)	2.34318	0.18198	10.414	7.290–14.878	< 0.0001
Log_{10} MoM UtA-PI	3.00152	0.63232	20.116	5.825–69.466	< 0.0001
Log_{10} MoM UtA-PI^2	6.37356	2.76860	5.86×10^2	2.58 to 1.33×10^5	0.021
Log_{10} MoM MAP	6.98422	1.96456	1.08×10^3	2.30×10^1 to 5.08×10^4	0.0004
Log_{10} MoM MAP^2	80.60922	34.82041	1.02×10^{35}	2.34×10^5 to 4.44×10^{64}	0.021
Maternal characteristics and history with EFW and UtA-PI (R^2 = 0.410, P < 0.0001)					
Intercept	–1.99167	0.27112	-	-	-
Logit (*a-priori* risk)	1.32430	0.20436	3.760	2.519–5.612	< 0.0001
EFW *Z*-score	–2.49459	0.13358	0.083	0.064–0.107	< 0.0001
Log_{10} MoM UtA-PI	1.58376	0.66640	4.873	1.320–17.991	0.017
Log_{10} MoM UtA-PI^2	7.22373	3.02151	1.37×10^3	3.68 to 5.12×10^5	0.017
Maternal characteristics and history with EFW and MAP (R^2 = 0.408, P < 0.0001)					
Intercept	–2.09259	0.27670	-	-	-
Logit (*a-priori* risk)	1.23907	0.20366	3.452	2.316–5.146	< 0.0001
EFW *Z*-score	–2.53483	0.13339	0.079	0.061–0.103	< 0.0001
Log_{10} MoM MAP	5.57999	2.11732	2.65×10^2	4.18 to 1.68×10^4	0.008
Log_{10} MoM MAP^2	79.80021	40.15720	4.54×10^{34}	2.98 to 6.90×10^{68}	0.047
Maternal characteristics and history with EFW, UtA-PI and MAP (R^2 = 0.413, P < 0.0001)					
Intercept	–1.95863	0.27992	-	-	-
Logit (*a-priori* risk)	1.31289	0.21184	3.717	2.454–5.630	< 0.0001
EFW *Z*-score	–2.48639	0.13877	0.083	0.063–0.109	< 0.0001
Log_{10} MoM UtA-PI	2.48618	0.63132	12.015	3.486–41.410	< 0.0001
Log_{10} MoM MAP	5.90022	2.27286	3.65×10^2	4.24 to 3.14×10^4	0.009

The areas under ROC (AUC), the detection rates (DRs) at FPRs of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA <10th, SGA <5th and SGA <3rd delivering at <2 weeks of assessment and at ≥37 weeks' gestation in screening by maternal characteristics, EFW Z-score, uterine artery PI, MAP and their combination are given in Table 4.4, 4.5 and 4.6 and Figure 4.2.

Table 4.4. Performance of screening for small for gestational age neonates with birth weight <10th, <5th and <3rd percentile delivering within two weeks of assessment and at >37 weeks' gestation in the absence of preeclampsia, with maternal factors, estimated fetal weight, uterine artery pulsatility index and mean arterial pressure at 35-37 weeks' gestation.

Screening test	AUC curve	DR (%)		FPR (%)		
		FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
Delivery within 2 weeks						
SGA <10th percentile						
Maternal factors	0.744 (0.731-0.756)	25.9 (16.8-36.9)	40.7 (29.9-52.2)	79.8 (78.6-80.9)	64.4 (63.0-65.7)	48.6 (47.2-50.1)
Maternal factors, EFW	0.961 (0.955-0.967)	77.8 (67.2-86.3)	86.4 (79.6-93.5)	53.4 (51.9-54.8)	11.6 (10.7-12.6)	5.6 (5.0-6.3)
Maternal factors, EFW, UtA PI, MAP	0.963 (0.957-0.968)	76.5 (65.8-85.2)	90.1 (81.5-95.6)	51.2 (49.8-52.7)	9.3 (8.4-10.1)	5.7 (5.0-6.4)
SGA <5th percentile						
Maternal factors	0.800 (0.788-0.811)	34.1 (20.5-49.9)	50.0 (34.6-65.4)	73.5 (72.2-74.7)	57.6 (56.2-59.0)	44.7 (43.3-46.1)
Maternal factors, EFW	0.969 (0.964-0.974)	84.1 (69.9-93.4)	86.4 (72.6-94.8)	34.0 (32.7-35.4)	13.4 (12.5-14.4)	3.6 (3.1-4.1)
Maternal factors, EFW, UtA PI, MAP	0.972 (0.967-0.976)	84.1 (69.9-93.4)	86.4 (72.6-94.8)	34.3 (32.9-35.6)	12.0 (11.1-12.9)	3.0 (2.6-3.6)
SGA <3rd percentile						
Maternal factors	0.813 (0.802-0.824)	36.7 (19.9-56.1)	50.0 (32.9-67.1)	60.2 (58.8-61.6)	52.8 (51.4-54.2)	38.1 (37.7-39.4)
Maternal factors, EFW	0.982 (0.978-0.985)	90.0 (73.5-97.9)	90.0 (73.5-97.9)	16.7 (15.6-17.7)	3.6 (3.1-4.1)	0.9 (0.7-1.2)
Maternal factors, EFW, UtA PI, MAP	0.985 (0.981-0.988)	90.0 (73.5-97.9)	90.0 (73.5-97.9)	13.1 (12.2-14.1)	2.8 (2.4-3.3)	0.6 (0.4-0.9)
Delivery at ≥37 weeks						
SGA <10th percentile						
Maternal factors	0.712 (0.700-0.725)	20.1 (16.8-23.7)	33.2 (29.2-37.3)	98.6 (98.2-98.9)	69.9 (68.5-71.2)	53.5 (52.0-54.9)
Maternal factors, EFW	0.887 (0.878-0.896)	47.3 (43.1-51.6)	66.1 (62.0-70.1)	82.5 (81.3-83.6)	32.6 (31.3-34.0)	20.2 (19.0-21.4)
Maternal factors, EFW, UtA PI, MAP	0.888 (0.879-0.897)	48.6 (44.3-52.9)	66.1 (62.0-70.1)	84.8 (83.7-85.8)	31.4 (30.1-32.8)	19.1 (18.0-20.3)
SGA <5th percentile						
Maternal factors	0.741 (0.729-0.753)	23.5 (18.2-29.5)	38.0 (31.8-44.6)	98.1 (97.7-98.5)	68.6 (67.3-69.9)	48.8 (47.4-50.2)
Maternal factors, EFW	0.908 (0.900-0.916)	54.3 (47.7-60.8)	71.4 (65.1-77.1)	83.5 (82.4-84.5)	24.6 (23.4-25.8)	13.4 (12.5-14.4)
Maternal factors, EFW, UtA PI, MAP	0.910 (0.902-0.917)	55.6 (48.9-62.0)	73.9 (67.8-79.4)	83.2 (82.1-84.2)	25.2 (24.0-26.5)	14.1 (13.1-15.1)
SGA <3rd percentile						
Maternal factors	0.775 (0.764-0.787)	26.2 (18.8-34.6)	39.2 (30.8-48.2)	90.8 (90.0-91.6)	53.4 (52.0-54.8)	41.4 (40.0-42.8)
Maternal factors, EFW	0.929 (0.922-0.936)	64.6 (55.5-71.5)	79.2 (71.2-85.8)	69.1 (67.8-70.4)	17.8 (16.7-18.9)	10.1 (9.3-11.0)
Maternal factors, EFW, UtA PI, MAP	0.929 (0.921-0.936)	64.6 (55.8-72.8)	80.0 (72.1-86.5)	70.2 (68.9-71.4)	20.1 (19.0-21.3)	9.9 (9.0-10.7)

Values in parenthesis are 95% CIs. AUC, area under receiver operating characteristic curve. FPR, false positive rate. DR, detection rate.

Table 4.5. Detection rates (DR) in screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation

Screening test	AUC	DR (%)		FPR (%)		
		FPR = 5%	FPR = 10%	DR = 100%	DR = 90%	DR = 80%
SGA < 10th percentile						
Maternal factors	0.744 (0.731-0.756)	25.9 (16.8-36.9)	40.7 (29.9-52.2)	79.8 (78.6-80.9)	64.4 (63.0-65.7)	48.6 (47.2-50.1)
Maternal factors plus						
EFW *Z*-score	0.961 (0.955-0.967)	77.8 (67.2-86.3)	86.4 (79.6-93.5)	53.4 (51.9-54.8)	11.6 (10.7-12.6)	5.6 (5.0-6.3)
UtA-PI	0.798 (0.787-0.810)	34.6 (24.3-46.0)	45.7 (34.6-57.1)	84.3 (83.2-85.3)	61.6 (60.2-63.1)	39.3 (37.9-40.8)
MAP	0.743 (0.731-0.756)	33.3 (23.2-44.7)	42.0 (31.1-53.5)	81.9 (80.7-83.0)	64.7 (63.3-66.1)	52.1 (50.6-53.6)
UtA-PI and MAP	0.795 (0.783-0.807)	22.3 (18.6-26.1)	32.4 (28.2-36.8)	86.6 (85.6-87.6)	54.6 (53.1-56.0)	34.9 (33.5-36.3)
Maternal factors and EFW plus						
UtA-PI	0.965 (0.959-0.970)	77.8 (67.2-86.3)	87.7 (78.5-93.9)	46.3 (44.8-47.7)	10.5 (9.7-11.5)	5.4 (4.8-6.2)
MAP	0.958 (0.952-0.964)	76.5 (65.8-85.2)	87.7 (78.5-93.9)	56.9 (55.5-58.3)	12.2 (11.3-13.2)	6.6 (5.9-7.4)
UtA-PI and MAP	0.963 (0.957-0.968)	76.5 (65.8-85.2)	90.1 (81.5-95.6)	51.2 (49.8-52.7)	9.3 (8.4-10.1)	5.7 (5.0-6.4)
SGA < 5th percentile						
Maternal factors	0.800 (0.788-0.811)	34.1 (20.5-49.9)	50.0 (34.6-65.4)	73.5 (72.2-74.7)	57.6 (56.2-59.0)	44.7 (43.3-46.1)
Maternal factors plus						
EFW Z-score	0.969 (0.964-0.974)	84.1 (69.9-93.4)	86.4 (72.6-94.8)	34.0 (32.7-35.4)	13.4 (12.5-14.4)	3.6 (3.1-4.1)
UtA-PI	0.866 (0.856-0.875)	47.7 (32.5-63.3)	59.1 (43.2-73.7)	69.3 (67.9-70.6)	42.0 (40.6-43.4)	22.1 (20.9-23.4)
MAP	0.804 (0.793-0.815)	45.5 (30.4-61.2)	54.6 (38.8-69.6)	81.3 (80.1-82.3)	59.6 (58.2-61.0)	46.5 (45.1-47.9)
UtA-PI and MAP	0.860 (0.850-0.870)	43.2 (28.3-59.0)	59.1 (43.2-73.7)	73.6 (72.3-74.8)	35.3 (34.0-36.7)	25.5 (24.3-26.8)
Maternal factors and EFW plus						
UtA-PI	0.971 (0.966-0.975)	84.1 (69.9-93.4)	86.4 (72.6-94.8)	31.7 (30.4-33.1)	13.1 (12.2-14.1)	3.5 (3.0-4.1)
MAP	0.968 (0.962-0.972)	84.1 (69.9-93.4)	86.4 (72.6-94.8)	38.0 (36.6-39.4)	10.8 (10.0-11.7)	3.3 (2.8-3.8)
UtA-PI and MAP	0.972 (0.967-0.976)	84.1 (69.9-93.4)	86.4 (72.6-94.8)	34.3 (32.9-35.6)	12.0 (11.1-12.9)	3.0 (2.6-3.6)
SGA < 3rd percentile						
Maternal factors	0.813 (0.802-0.824)	36.7 (19.9-56.1)	50.0 (32.9-67.1)	60.2 (58.8-61.6)	52.8 (51.4-54.2)	38.1 (37.7-39.4)
Maternal factors plus						
EFW Z-score	0.982 (0.978-0.985)	90.0 (73.5-97.9)	90.0 (73.5-97.9)	16.7 (15.6-17.7)	3.6 (3.1-4.1)	0.9 (0.7-1.2)
UtA-PI	0.875 (0.866-0.884)	50.0 (32.4-67.6)	60.0 (40.6-77.3)	63.0 (61.6-64.4)	27.2 (26.0-28.5)	18.6 (17.5-19.7)
MAP	0.823 (0.812-0.833)	50.0 (31.9-68.1)	56.7 (37.4-74.5)	69.5 (68.2-70.8)	54.7 (53.3-56.1)	43.7 (42.4-45.1)
UtA-PI and MAP	0.873 (0.863-0.882)	46.7 (28.3-65.7)	63.3 (43.9-80.1)	69.1 (67.8-70.4)	33.9 (32.6-35.2)	25.5 (24.3-26.8)
Maternal factors and EFW plus						
UtA-PI	0.984 (0.980-0.987)	90.0 (73.5-97.9)	90.0 (73.5-97.9)	13.8 (12.8-14.8)	2.7 (2.3-3.2)	0.5 (0.4-0.8)
MAP	0.981 (0.977-0.985)	90.0 (73.5-97.9)	90.0 (73.5-97.9)	20.0 (18.9-21.2)	2.6 (2.2-3.1)	0.9 (0.7-1.2)
UtA-PI and MAP	0.985 (0.981-0.988)	90.0 (73.5-97.9)	90.0 (73.5-97.9)	13.1 (12.2-14.1)	2.8 (2.4-3.3)	0.6 (0.4-0.9)

Table 4.6. Detection rates (DR) in screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering ≥ 37 weeks, in the absence of pre-eclampsia, using maternal factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation

Screening test	AUC curve	DR (%)		FPR (%)		
		FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
SGA <10th percentile						
Maternal factors	0.712 (0.700–0.725)	20.1 (16.8–23.7)	33.2 (29.2–37.3)	98.6 (98.2–98.9)	69.9 (68.5–71.2)	53.5 (52.0–54.9)
Maternal factors plus						
EFW Z-score	0.887 (0.878–0.896)	47.3 (43.1–51.6)	66.1 (62.0–70.1)	82.5 (81.3–83.6)	32.6 (31.3–34.0)	20.2 (19.0–21.4)
UtA-PI	0.725 (0.713–0.738)	23.4 (19.9–27.2)	33.7 (29.7–37.9)	99.0 (98.7–99.3)	68.8 (67.4–70.1)	50.4 (48.9–51.8)
MAP	0.719 (0.707–0.731)	21.2 (17.8–24.9)	32.4 (28.5–36.5)	99.1 (98.8–99.3)	69.8 (68.5–71.2)	52.3 (50.9–53.8)
UtA-PI and MAP	0.728 (0.716–0.740)	23.9 (20.4–27.8)	34.1 (30.1–38.2)	99.3 (99.0–99.5)	69.1 (67.7–70.4)	49.6 (48.1–51.1)
Maternal factors and EFW plus						
UtA-PI	0.889 (0.880–0.897)	47.5 (43.2–51.8)	66.3 (62.1–70.3)	84.0 (82.9–85.0)	31.8 (30.5–33.2)	18.7 (17.6–19.8)
MAP	0.888 (0.879–0.896)	47.0 (42.7–51.3)	66.5 (62.3–70.3)	84.5 (83.4–85.6)	32.5 (31.2–33.9)	19.2 (18.0–20.3)
UtA-PI and MAP	0.888 (0.879–0.897)	48.6 (44.3–52.9)	66.1 (62.0–70.1)	84.8 (83.7–85.8)	31.4 (30.1–32.8)	19.1 (18.0–20.3)
SGA <5th percentile						
Maternal factors	0.741 (0.729–0.753)	23.5 (18.2–29.5)	38.0 (31.8–44.6)	98.1 (97.7–98.5)	68.6 (67.3–69.9)	48.8 (47.4–50.2)
Maternal factors plus						
EFW Z-score	0.908 (0.900–0.916)	54.3 (47.7–60.8)	71.4 (65.1–77.1)	83.5 (82.4–84.5)	24.6 (23.4–25.8)	13.4 (12.5–14.4)
UtA-PI	0.762 (0.751–0.774)	28.2 (22.5–34.4)	39.3 (33.0–45.9)	98.7 (98.4–99.0)	61.8 (60.5–64.4)	44.0 (42.6–45.4)
MAP	0.756 (0.744–0.768)	26.1 (20.6–32.2)	39.3 (33.0–45.9)	97.2 (96.7–97.6)	65.3 (64.0–66.6)	45.2 (46.6–43.8)
UtA-PI and MAP	0.770 (0.758–0.781)	28.6 (22.9–34.9)	41.5 (35.1–48.1)	94.1 (93.4–94.7)	61.9 (60.6–63.3)	43.8 (42.4–45.2)
Maternal factors and EFW plus						
UtA-PI	0.909 (0.901–0.917)	56.4 (49.8–62.9)	70.9 (64.7–76.7)	82.2 (81.1–83.3)	22.5 (21.3–23.7)	13.8 (13.9–14.8)
MAP	0.910 (0.902–0.918)	57.3 (50.7–63.7)	69.7 (63.3–75.5)	85.5 (84.5–86.5)	21.4 (20.2–22.6)	13.1 (12.2–14.1)
UtA-PI and MAP	0.910 (0.902–0.917)	55.6 (48.9–62.0)	73.9 (67.8–79.4)	83.2 (82.1–84.2)	25.2 (24.0–26.5)	14.1 (13.1–15.1)
SGA <3rd percentile						
Maternal factors	0.775 (0.764–0.787)	26.2 (18.8–34.6)	39.2 (30.8–48.2)	90.8 (90.0–91.6)	53.4 (52.0–54.8)	41.4 (40.0–42.8)
Maternal factors plus						
EFW Z-score	0.929 (0.922–0.936)	64.6 (55.5–71.5)	79.2 (71.2–85.8)	69.1 (67.8–70.4)	17.8 (16.7–18.9)	10.1 (9.3–11.0)
UtA-PI	0.797 (0.786–0.808)	30.0 (22.3–38.7)	40.8 (32.2–49.7)	87.8 (86.8–88.7)	53.3 (51.9–54.7)	33.4 (32.1–34.8)
MAP	0.791 (0.779–0.802)	30.8 (23.0–39.5)	42.3 (33.7–51.3)	86.5 (86.5–87.5)	57.0 (55.6–58.4)	35.9 (34.6–37.3)
UtA-PI and MAP	0.804 (0.793–0.815)	33.1 (25.1–41.9)	43.9 (35.2–52.8)	84.2 (83.2–85.2)	52.1 (50.7–53.5)	33.2 (31.9–34.5)
Maternal factors and EFW plus						
UtA-PI	0.929 (0.921–0.936)	66.2 (57.3–74.2)	79.2 (71.2–85.8)	68.3 (67.0–69.6)	21.0 (19.9–22.2)	10.1 (9.3–11.0)
MAP	0.930 (0.923–0.937)	66.9 (58.1–74.9)	76.9 (68.7–83.9)	71.5 (70.2–72.7)	20.0 (18.9–21.1)	10.9 (10.0–11.7)
UtA-PI and MAP	0.929 (0.921–0.936)	64.6 (55.8–72.8)	80.0 (72.1–86.5)	70.2 (68.9–71.4)	20.1 (19.0–21.3)	9.9 (9.0–10.7)

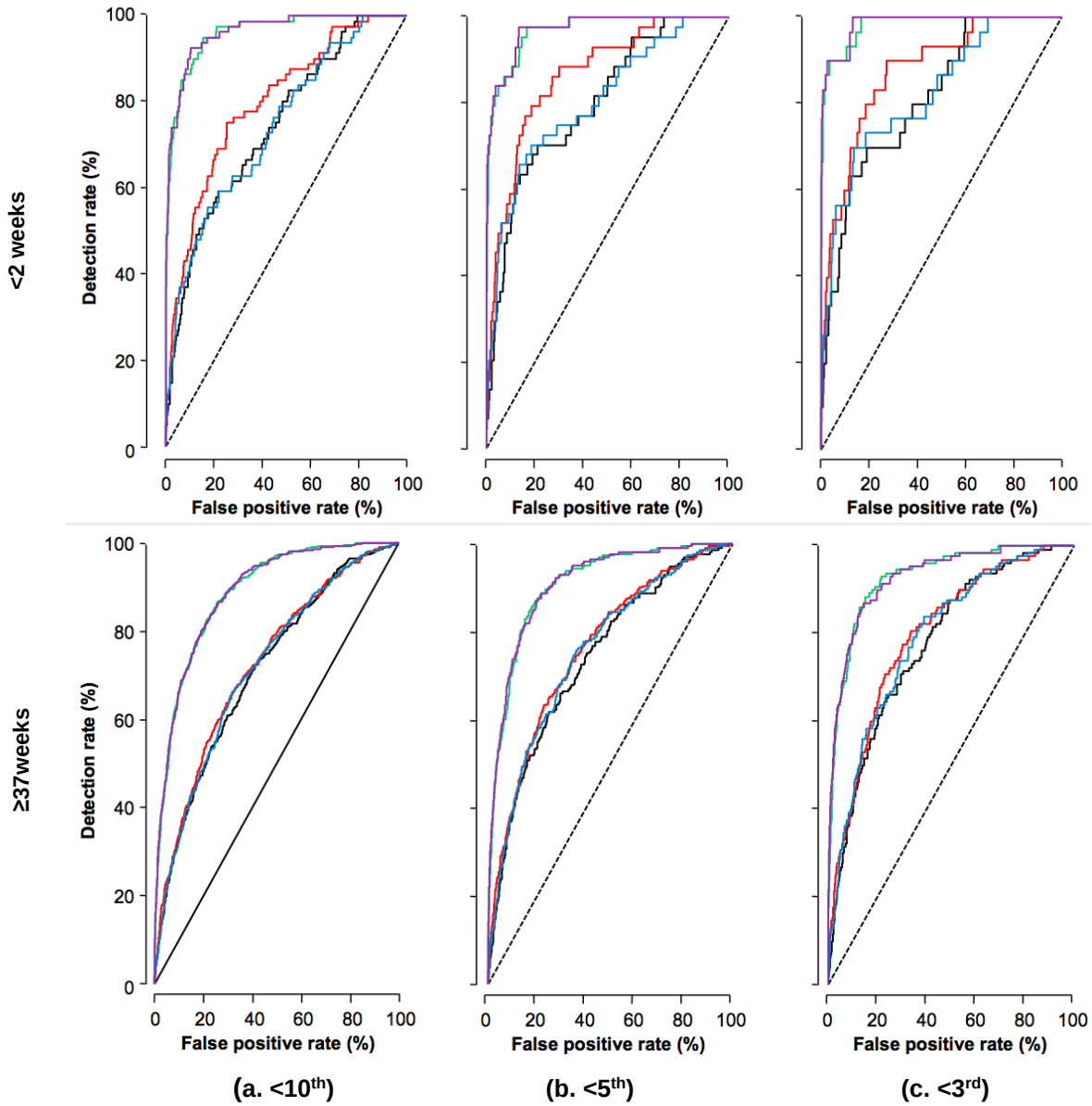

Figure 4.2. Receiver–operating characteristics curves of maternal factors (black) and maternal factors with uterine artery pulsatility index (red), mean arterial pressure (blue), estimated fetal weight *Z*-score (green) and their combination (purple), at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) or < 3rd (c) percentile, delivering < 2 weeks following assessment (top) or ≥ 37 weeks' gestation (bottom).

The DRs, at FPR of 10%, of combined screening by maternal characteristics and history with EFW Z-scores for the prediction of SGA neonates with birth weight <10th, <5th and <3rd percentiles, delivering at <2 weeks of assessment, were 86.4% (95% CI, 79.6-93.5%; AUC 0.961 (95% CI, 0.955-0.967)), 86.4% (95% CI, 72.6-94.8; AUC 0.969 (95% CI, 0.964-0.974)) and 90.0% (95% CI, 73.5-97.9; AUC 0.982 (95% CI, 0.978-0.985)), respectively. The respective values for SGA delivering at ≥37 weeks, were 66.1% (95% CI, 62.0-70.1; AUC 0.887 (95% CI, 0.878-0.896)), 71.4% (95% CI, 65.1-77.1; AUC 0.908

(95% CI, 0.900-0.916)) and 79.2% (95% CI, 71.2-85.8; AUC 0.929 (95% CI, 0.922-0.936)).

In combined screening by maternal characteristics and history with EFW Z-scores, UtA PI and MAP at 35-37 weeks' gestation, the DRs, at FPR of 10%, of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment were 90.1% (95% CI, 81.5-95.6; AUC 0.963 (95% CI, 0.957-0.968)), 86.4% (95% CI, 72.6-94.8; AUC 0.972 (95% CI, 0.967-0.976)) and 90.0% (95% CI, 73.5-97.9; AUC 0.985 (95% CI, 0.981-0.988)), respectively. The respective values for SGA delivering at ≥37 weeks, were 66.1% (95% CI, 62.0-70.1; AUC 0.888 (95% CI, 0.879-0.897)), 73.9% (95% CI, 67.8-79.4; AUC 0.910 (95% CI, 0.902-0.917)) and 80.0% (95% CI, 72.1-86.5; AUC 0.929 (95% CI, 0.921-0.936)).

4.4. Discussion

4.4.1. Main findings of the study

The findings of the study demonstrate that in women who deliver SGA neonates in the absence of PE, uterine artery PI and MAP at 35-37 weeks' gestation are increased and EFW is reduced. The deviation from normal for uterine artery PI is inversely related to the severity of the disease reflected in the gestational age at delivery and the birth weight Z-score.

Combined screening by maternal factors, EFW Z-score, uterine artery PI and MAP at 35-37 weeks, predicted, at FPR of 10%, 90%, 86% and 90% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment and the respective values for SGA delivering at ≥37 weeks were 66%, 74% and 80%. The addition of uterine artery PI and MAP at 35-37 weeks does not improve the performance of screening for delivery of SGA neonates achieved by combined testing using maternal factors and fetal biometry alone.

4.4.2. Comparison with findings from previous studies

Previous studies examining pregnancies with SGA fetuses in the third-trimester reported that the outcome was worse in cases with Doppler evidence of increased, rather than normal impedance to flow in the uterine arteries[145, 190].

A screening study involving 1848 singleton pregnancies at 30-32 weeks' gestation reported that uterine artery PI improved the prediction of SGA neonates provided by fetal biometry alone with reduction in FPR from 27% to 16% for the same DR of about 71%[25].

Simultaneously to this study, colleagues from the same Departments have done a screening study of 30849 singleton pregnancies at 30-34 weeks' gestation. Combined screening by maternal factors, fetal biometry, uterine artery PI and MAP at 30-34 weeks predicted 91% and 60% of SGA<5th neonates delivering at <5 and at $\geq$5 weeks of assessment, respectively, at FPR of 10%[189].

CHAPTER 5

Screening by maternal characteristics, fetal biometry, placental growth factor and soluble fms-like tyrosine kinase-1 at 35-37 weeks

Chapter 5: Screening by maternal characteristics, fetal biometry, placental growth factor and soluble fms-like tyrosine kinase-1 at 35-37 weeks

ABSTRACT

Objective: To investigate the potential value of maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35-37 weeks' gestation in the prediction of delivery of small for gestational age (SGA) neonates, in the absence of preeclampsia (PE).

Methods: Screening study in singleton pregnancies at 35-37 weeks, including 158 that delivered SGA neonates with birth weight <5th percentile and 3,701 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if serum PlGF and sFlt-1 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, compared to the normal group, the median PlGF multiple of the median (MoM) was significantly lower and the median sFlt-1 MoM was significantly higher. Combined screening by maternal factors and EFW Z-score at 35-37 weeks, predicted 90%, 92% and 94% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment, at 10% false positive rate; the respective values for SGA delivering at ≥37 weeks were 66.0%, 73% and 80%. When PlGF and sFlt-1 were added to a model that combines maternal factors and EFW Z-score, sFlt-1 did not remain as a significant independent predictor of SGA <5th. Combined screening by maternal factors, EFW Z-score and serum PlGF, predicted 88%, 96% and 94% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment and the respective values for SGA delivering at ≥37 weeks were 64%, 75% and 80%.

Conclusion: sFlt-1 does not provide significant independent prediction of SGA, in the absence of PE, in addition to combined testing by maternal factors and fetal biometry at 35-37 weeks. Whilst addition of serum PlGF only marginally improves the performance of screening.

This chapter is based on: Fadigas C, Peeva G, Mendez O, Poon LC and Nicolaides KH. Prediction of small-for-gestational age neonates: screening by placental growth factor and soluble fms-like tyrosine kinase-1 at 35-37 weeks. Ultrasound Obstet and Gynecol. 2015; 46: 191-97.

5.1. INTRODUCTION

The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysial-fundal height, but the detection rate (DR) of this approach is less that 30%[20, 21].

Chapter 3 shows that a higher performance in screening for SGA is achieved by a combination of maternal characteristics and medical history (maternal factors) with EFW from ultrasonographic measurements of HC, AC and FL. Such combined screening at 35-37 weeks, predicted 66%, 70% and 77% of SGA neonates with respective birth weight <10th, <5th and <3rd percentiles delivering at ≥37 weeks in the absence of preeclampsia (PE), at 10% false positive rate (FPR), The performance of screening was better for prediction of SGA delivering within two weeks of assessment with respective DRs of 88%, 89% and 92%.

Placental growth factor (PlGF) is a member of the vascular endothelial growth factor family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries[161-163]. Soluble fms-like tyrosine kinase-1 (sFlt-1) is a circulating anti-angiogenic protein implicated in the pathogenesis of PE; the concentration of sFlt-1 is increased in the placenta and serum of women with PE and exogenous sFlt-1 administered to pregnant rats induces hypertension, proteinuria, and glomerular endotheliosis[191]. 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 [164-169].

5.1.1. Objectives

The objective of this study, in singleton pregnancies undergoing routine antenatal assessment at 35-37 weeks' gestation, was to investigate the potential value of serum PlGF and sFlt-1 in improving the prediction of delivery of SGA neonates, in the absence of PE, achieved by the combination of maternal factors and EFW.

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 35^{+0}-37^{+6} weeks' gestation. The methodology for recording of patient characteristics, sonographic estimation of EFW, MAP, UtA IP, maternal serum metabolites

(PlGF and sFlt-1), outcome measures and statistical analysis was as described in Chapter 2.

5.3. RESULTS

The characteristics of the study population of 3859 pregnancies, including 158 delivering SGA <5th neonates in the absence of PE, are presented in Table 5.1.

Table 5.1. Characteristics of the study population of women with a singleton pregnancy with normal outcome or with a small-for-gestational-age (SGA) neonate, in the absence of pre-eclampsia (PE)

Characteristic	Normal (n=3701)	SGA without PE (n=158)	P-value
Maternal age in years, median (IQR)	31.6 (26.9-35.2)	29.9 (24.2-35.3)	0.012
Maternal weight in Kg, median (IQR)	78.8 (70.9-89.4)	72.7 (63.2-82.7)	<0.0001
Maternal height in cm, median (IQR)	164 (160-168)	161 (158-165)	<0.0001
Gestation at screening in weeks, median (IQR)	36.1 (36.0-36.4)	36.3 (36.0-36.4)	0.594
Racial origin			
Caucasian, n (%)	2762 (74.6)	95 (60.1)	<0.0001
Afro-Caribbean, n (%)	615 (16.6)	38 (24.1)	0.022
South Asian, n (%)	132 (3.6)	16 (10.1)	0.0003
East Asian, n (%)	82 (2.2)	3 (1.9)	>0.999
Mixed, n (%)	110 (3.0)	6 (3.8)	0.476
Past obstetric history			
Nulliparous, n (%)	1789 (48.3)	94 (59.5)	0.007
Parous with no prior PE and SGA, n (%)	1761 (47.6)	43 (27.2)	<0.0001
Parous with prior PE no SGA, n (%)	59 (1.6)	0 (0.0)	0.175
Parous with prior SGA no PE, n (%)	86 (2.3)	20 (12.7)	<0.0001
Parous with prior SGA and PE, n (%)	6 (0.2)	1 (0.6)	0.254
Inter-pregnancy interval in years, median (IQR)	3.1 (2.1-5.0)	3.9 (2.1-6.2)	0.026
Cigarette smoker, n (%)	325 (8.8)	37 (23.4)	<0.0001
Conception			
Spontaneous, n (%)	3599 (97.2)	151 (95.6)	0.214
Ovulation drugs, n (%)	15 (0.4)	1 (0.6)	0.488
***In vitro* fertilization, n (%)**	87 (2.4)	6 (3.8)	0.279
Chronic hypertension	49 (1.3)	1 (0.6)	0.722
Pre-existing diabetes mellitus, n (%)	43 (1.1)	1 (0.6)	>0.999
Type 1, n (%)	20 (0.5)	1 (0.6)	0.585
Type 2, n (%)	23 (0.6)	0 (0.0)	>0.999
SLE / APS, n (%)	11 (0.3)	0 (0.0)	>0.999
Gestation at delivery in weeks, median (IQR)	40.0 (39.1-40.9)	39.6 (38.8-36.4)	0.002
Birth weight in grams, median (IQR)	3450 (3,160-3,760)	2587 (2,350-2,755)	<0.0001
Birth weight in percentile, median (IQR)	51.6 (27.4-76.2)	2.8 (1.2-3.7)	<0.0001

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

5.3.1. Normal pregnancy outcome

In the unaffected pregnancies with birth weight ≥5th percentile, the mean ± SD, 5th and 10th percentiles of log_{10} MoM PlGF were -0.019 ± 0.343, -0.588 and -0.470, respectively. The mean ± SD, 90th and 95th percentiles of log_{10} MoM sFlt-1 were -0.081 ± 0.210, 0.199 and 0.285, respectively.

There was a significant inverse association between log_{10} MoM values of PlGF and sFlt-1 (r=-0.400, P<0.0001). There was a significant positive association between log_{10} MoM PlGF with assessment to delivery interval (r=0.152, P<0.0001) and birth weight Z-score (r=0.179, P<0.0001). There was a significant inverse association between log_{10} MoM sFlt-1 with assessment to delivery interval (r=-0.168, P<0.0001) and birth weight Z-score (r=-0.042, P=0.011).

5.3.2. Small for gestational age

In the SGA <5th group, compared to the normal group, the median MoM PlGF at 35-37 weeks was significantly lower and the median MoM value of sFlt-1 was significantly higher (Table 5.2).

Table 5.2. Placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35-37 weeks' gestation in small for gestational age (SGA) neonates with birth weight below the 5th percentile, in the absence of preeclampsia and in the normal group.

Biochemical markers	pg/mL, Median (IQR)	MoM, median (IQR)	Log_{10} MoM, mean (SD)	<5th (or >95th) percentile, n (%, 95% CI)	<10th (or >90th) percentile, n (%, 95% CI)
Serum PlGF					
Normal	320.2 (181.2-576.6)	0.946 (0.548-1.654)	-0.019 (0.343)	185 (5.0, 4.3-5.7)	370 (10.0, 9.1-11.0)
SGA	195.6 (106.8-377.6)*	0.568 (0.301-0.933)*	-0.228 (0.362)*	31 (19.6, 14.2-26.5)*	50 (31.6, 24.9-39.3)*
Serum sFlt-1					
Normal	2,460.0 (1,831.0-3,447.5)	0.806 (0.598-1.122)	-0.081 (0.210)	185 (5.0, 4.3-5.7)	370 (10.0, 9.1-11.0)
SGA	2,908.5 (2,023.5-4,470.0)*	0.956 (0.654-1.435)*	0.005 (0.251)*	22 (13.9, 9.4-20.2)*	34 (21.5, 15.8-28.6)*

Comparisons between pregnancies with normal outcome and those with SGA: Chi square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test or student's *t*-test: *$P < 0.05$. IQR, interquartile range; MoM, multiples of the unaffected median.

There was a significant inverse association between log_{10} MoM values of PlGF and sFlt-1 (r=-0.375, P<0.0001). There was a significant positive association between log_{10} MoM PlGF with assessment to delivery interval (r=0.300, P<0.0001; Figure 5.1.a) and birth

weight Z-score (r=0.208, P=0.009). There was a significant inverse association between log_{10} MoM sFlt-1 with assessment to delivery interval (r=-0.260, P=0.001; Figure 5.1.b) but not birth weight Z-score (r=-0.085, P=0.287).

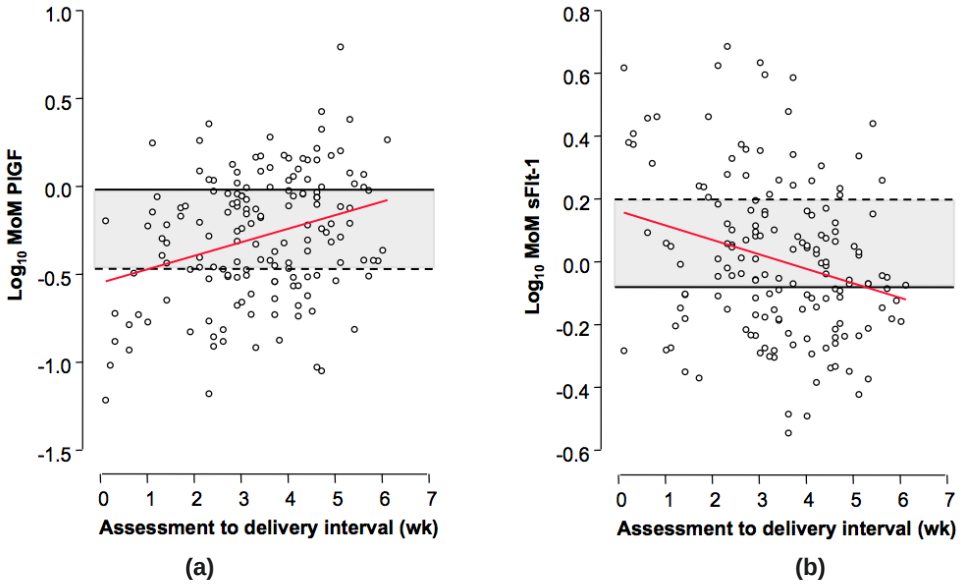

Figure 5.1. Log_{10} placental growth factor (a) and log_{10} soluble fms-like tyrosine kinase-1 (b) multiples of the median (MoM) according to assessment-to-delivery interval in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile, plotted on the 50th (solid line) and 10th (dashed line) percentile of the normal range.

Multivariable logistic regression analysis demonstrated that in the prediction of SGA <5th there were significant contributions from maternal characteristics and history, EFW Z-score, and PlGF or sFlt-1 (Table 5.3). When PlGF and sFlt-1 were added to maternal factors and a model that combines maternal factors and EFW Z-score, sFlt-1 (P=0.509; R^2=0.921) did not remain as a significant independent predictor of SGA <5th. Combined screening by maternal factors with EFW Z-scores and PlGF detected 64.1%, 75.3% and 80.2% of SGA neonates with birth weight <10th, <5th and <3rd percentiles, respectively, at 10% FPR.

The areas under ROC (AUC), the detection rates (DRs) at FPRs of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA <10th, SGA <5th and SGA <3rd delivering at <2 weeks of assessment and at ≥37 weeks' gestation when screening by maternal characteristics, EFW Z-score, PlGF and sFlt-1 are given in (Table 5.4, Table 5.5, Figure 5.2 and Figure 5.3).

Table 5.3. Fitted regression models with maternal characteristics and history (maternal factors), estimated fetal weight (EFW) *Z*-score, placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation for the prediction of small-for-gestational-age neonates with birth weight < 5th percentile, in the absence of pre-eclampsia

Independent variable	Coefficient	SE	OR	95% CI	*P*
Maternal factors with PIGF (R^2 = 0.182, P < 0.0001)					
Intercept	–0.42984	0.27889	-	-	-
Logit (*a-priori* risk)	2.38807	0.22459	10.892	7.014–16.916	< 0.0001
Log_{10} MoM PIGF	–2.06182	0.25619	0.127	0.077–0.210	< 0.0001
Maternal factors with sFlt-1 (R^2 = 0.136, P < 0.0001)					
Intercept	–0.09724	0.26777	-	-	-
Logit (*a-priori* risk)	2.49572	0.22265	12.130	7.841–18.767	< 0.0001
Log_{10} MoM sFlt-1	0.92718	0.35454	2.527	1.261–5.064	0.009
Log_{10} MoM sFlt-1^2	2.93094	1.08731	18.745	2.225–157.912	0.007
Maternal factors, EFW and PIGF (R^2 = 0.418, P < 0.0001)					
Intercept	–2.10909	0.34712	-	-	-
Logit (*a-priori* risk)	1.40611	0.25842	4.080	2.459–6.771	< 0.0001
EFW Z-score	–2.52481	0.17865	0.080	0.056–0.114	< 0.0001
Log_{10} MoM PIGF	–1.58096	0.28125	0.206	0.119–0.357	< 0.0001
Maternal factors, EFW and sFlt-1 (R^2 = 0.397, P < 0.0001)					
Intercept	–1.80207	0.33685	-	-	-
Logit (*a-priori* risk)	1.43451	0.25889	4.198	2.527–6.972	< 0.0001
EFW Z-score	–2.61927	0.17698	0.073	0.052–0.103	< 0.0001
Log_{10} MoM sFlt-1	1.05551	0.41636	2.873	1.271–6.498	0.011

Table 5.4. Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal characteristics and history, estimated fetal weight (EFW), placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation

Screening test	AUC	DR (%)		FPR (%)		
		FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
SGA <10th percentile						
Maternal factors	0.818 (0.805-0.831)	30.6 (18.3-45.4)	53.1 (38.3-67.5)	77.6 (76.2-79.0)	47.1 (45.4-48.8)	34.9 (33.4-36.6)
Maternal factors plus						
EFW Z-score	0.965 (0.958-0.971)	83.7 (70.3-92.7)	89.8 (77.8-96.6)	53.4 (51.7-55.0)	10.8 (9.8-11.9)	3.0 (2.5-3.6)
PlGF	0.862 (0.850-0.873)	38.8 (25.2-53.8)	63.3 (48.3-76.6)	77.3 (75.9-78.7)	43.0 (41.4-44.7)	22.9 (21.5-24.4)
sFlt-1	0.836 (0.823-0.848)	38.8 (25.2-53.8)	53.1 (38.3-67.5)	76.3 (74.9-77.7)	44.2 (42.5-45.8)	28.0 (26.5-29.5)
Maternal factors, EFW plus						
PlGF	0.969 (0.963-0.974)	83.7 (70.3-92.7)	87.8 (75.2-95.4)	46.5 (44.9-48.2)	11.6 (10.5-12.7)	3.6 (3.0-4.3)
sFlt-1	0.967 (0.960-0.972)	83.7 (70.3-92.7)	87.8 (75.2-95.4)	50.5 (48.9-52.2)	12.5 (11.4-13.7)	2.8 (2.3-3.5)
SGA <5th percentile						
Maternal factors	0.890 (0.879-0.900)	40.0 (21.1-61.3)	64.0 (42.5-82.0)	48.7 (47.0-50.3)	31.5 (30.0-33.1)	16.0 (14.9-17.2)
Maternal factors plus						
EFW Z-score	0.977 (0.972-0.982)	92.0 (74.0-99.0)	92.0 (74.0-99.0)	32.9 (31.3-34.4)	2.5 (2.0-3.0)	0.8 (0.5-1.1)
PlGF	0.944 (0.936-0.951)	56.0 (34.9-75.6)	84.0 (63.9-95.5)	19.0 (17.8-20.4)	16.6 (15.4-17.8)	9.8 (8.8-10.8)
sFlt-1	0.912 (0.902-0.921)	52.0 (31.3-72.2)	60.0 (38.7-78.9)	42.9 (41.3-44.5)	23.7 (22.3-25.1)	13.8 (12.7-14.9)
Maternal factors, EFW plus						
PlGF	0.987 (0.983-0.991)	88.0 (68.8-97.5)	96.0 (79.6-99.9)	13.9 (12.8-15.4)	5.2 (3.5-6.0)	0.3 (0.1-0.5)
sFlt-1	0.980 (0.975-0.984)	92.0 (74.0-99.0)	92.0 (74.0-99.0)	20.1 (18.8-21.4)	3.3 (2.8-4.0)	0.5 (0.3-0.8)
SGA <3rd percentile						
Maternal factors	0.904 (0.894-0.913)	44.4 (21.5-69.2)	66.7 (41.0-86.7)	36.6 (35.1-38.2)	31.5 (30.0-33.1)	16.0 (14.9-17.2)
Maternal factors plus						
EFW Z-score	0.990 (0.987-0.993)	94.4 (72.7-99.9)	94.4 (72.7-99.9)	13.5 (12.5-14.7)	0.8 (0.5-1.1)	0.7 (0.4-1.0)
PlGF	0.948 (0.941-0.955)	61.1 (35.7-82.7)	83.3 (58.6-96.4)	19.0 (17.8-20.4)	16.6 (15.3-17.8)	9.8 (8.8-10.8)
sFlt-1	0.906 (0.896-0.915)	61.1 (35.7-82.7)	61.1 (35.7-82.7)	42.9 (41.3-44.5)	24.2 (22.9-25.7)	18.3 (17.1-19.6)
Maternal factors, EFW plus						
PlGF	0.991 (0.988-0.994)	94.4 (72.7-99.9)	94.4 (72.7-99.9)	13.9 (12.8-15.1)	0.3 (0.1-0.5)	0.2 (0.1-0.4)
sFlt-1	0.988 (0.984-0.991)	94.4 (72.7-99.9)	94.4 (72.7-99.9)	18.4 (17.2-19.7)	0.5 (0.3-0.8)	0.4 (0.2-0.7)

Table 5.5. Performance of screening for small for gestational age (SGA) neonates with birth weight <10th, <5th and <3rd percentile delivering at ≥37 weeks' gestation in the absence of preeclampsia, with maternal characteristics and history, estimated fetal weight, placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35-37 weeks' gestation.

Screening test	AUC	DR (%)		FPR (%)		
		FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
SGA <10th percentile						
Maternal factors	0.730 (0.716-0.744)	21.3 (17.2-25.8)	34.6 (29.8-39.6)	99.9 (99.8-99.9)	68.0 (66.4-69.5)	48.7 (47.0-50.4)
Maternal factors plus						
EFW Z-score	0.888 (0.878-0.898)	47.3 (42.2-52.8)	66.0 (60.9-70.7)	82.2 (80.9-83.5)	32.2 (30.7-33.8)	19.8 (18.5-21.2)
PlGF	0.762 (0.748-0.775)	23.1 (19.0-27.7)	35.9 (31.1-41.0)	99.8 (99.6-99.9)	59.2 (57.6-60.9)	44.0 (42.4-45.7)
sFlt-1	0.731 (0.717-0.745)	20.0 (16.0-24.3)	33.0 (28.2-38.0)	99.6 (99.3-99.8)	67.2 (65.7-68.8)	47.6 (45.9-49.3)
Maternal factors, EFW plus						
PlGF	0.893 (0.883-0.903)	47.9 (42.7-53.1)	64.1 (59.0-68.9)	73.7 (72.2-75.2)	29.8 (28.3-31.4)	18.0 (16.7-19.3)
sFlt-1	0.886 (0.875-0.896)	48.1 (43.0-53.3)	63.8 (58.7-68.7)	81.9 (80.6-83.2)	32.5 (30.9-34.1)	20.4 (19.1-21.8)
SGA <5th percentile						
Maternal factors	0.769 (0.756-0.782)	23.4 (16.9-30.9)	40.9 (33.1-49.1)	97.9 (97.3-98.3)	58.2 (56.6-59.8)	41.4 (39.8-43.0)
Maternal factors plus						
EFW Z-score	0.918 (0.909-0.926)	53.9 (45.7-61.9)	72.7 (65.0-79.6)	79.1 (77.7-80.4)	19.9 (18.7-21.3)	12.2 (11.2-13.3)
PlGF	0.807 (0.794-0.819)	26.6 (19.8-34.3)	44.2 (36.2-52.4)	98.6 (98.2-98.9)	51.5 (49.8-53.1)	32.5 (31.0-34.0)
sFlt-1	0.769 (0.756-0.783)	25.3 (18.7-33.0)	38.3 (30.6-46.5)	96.1 (95.4-96.7)	60.5 (59.0-62.1)	42.9 (41.3-44.5)
Maternal factors, EFW plus						
PlGF	0.922 (0.913-0.930)	56.5 (48.3-64.5)	74.7 (67.0-81.0)	75.3 (73.9-76.7)	21.4 (20.1-22.8)	13.8 (12.7-15.0)
sFlt-1	0.918 (0.909-0.927)	53.9 (45.7-61.9)	74.7 (67.0-81.0)	81.0 (79.7-82.3)	20.4 (19.1-21.7)	13.1 (12.0-14.2)
SGA <3rd percentile						
Maternal factors	0.806 (0.793-0.818)	28.6 (19.2-39.5)	46.4 (35.5-57.6)	90.2 (89.2-91.1)	47.3 (45.6-48.9)	38.0 (36.4-39.6)
Maternal factors plus						
EFW Z-score	0.942 (0.934-0.949)	63.1 (51.9-73.4)	79.8 (69.6-87.7)	42.9 (41.3-44.5)	13.9 (12.8-15.1)	10.9 (9.9-11.9)
PlGF	0.828 (0.816-0.840)	32.1 (22.4-43.2)	53.6 (42.4-64.5)	84.8 (83.6-86.0)	51.5 (49.9-53.1)	29.9 (28.4-31.4)
sFlt-1	0.803 (0.790-0.816)	32.1 (22.4-42.0)	44.1 (33.2-55.3)	91.8 (90.9-92.7)	49.4 (47.8-51.0)	40.1 (38.6-41.8)
Maternal factors, EFW plus						
PlGF	0.943 (0.935-0.950)	65.5 (54.3-75.5)	79.8 (69.6-87.7)	41.1 (39.6-42.8)	16.1 (15.0-17.4)	11.7 (10.7-12.8)
sFlt-1	0.942 (0.934-0.949)	60.7 (49.5-71.2)	79.8 (69.6-87.7)	40.8 (39.2-42.4)	16.2 (15.0-17.4)	10.8 (9.9-11.9)

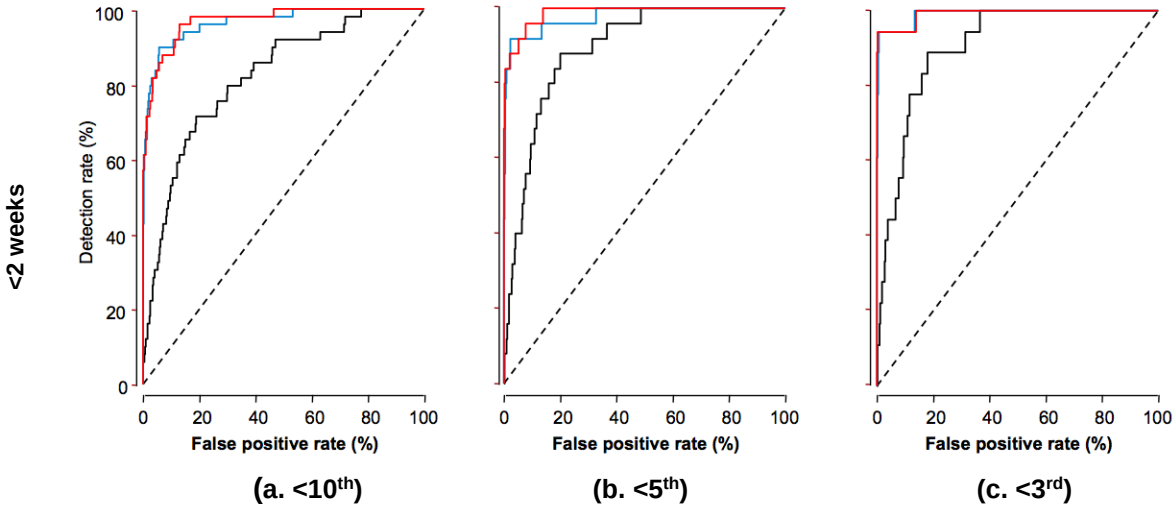

Figure 5.2. Receiver–operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (EFW) (blue line), maternal factors with EFW and placental growth factor (red line) at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) and < 3rd (c) percentile, delivering within 2 weeks of assessment.

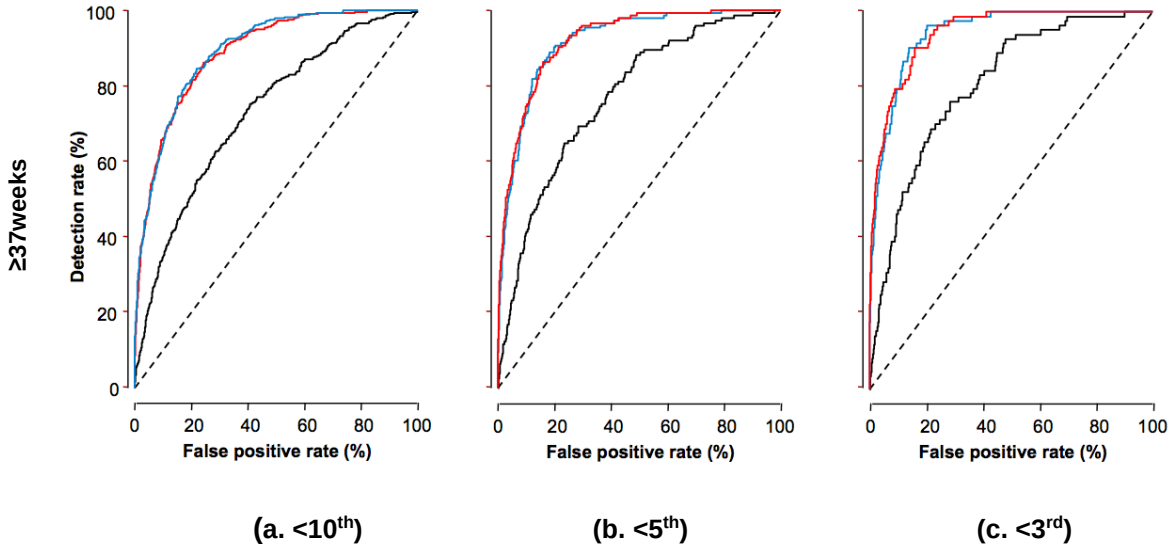

Figure 5.3. Receiver–operating characteristics curves of maternal factors (black line), maternal factors with EFW (blue line), maternal factors with EFW and placental growth factor (red line) at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) and < 3rd (c) percentile, delivering ≥ 37 weeks' gestation.

The DRs, at FPR of 10%, of combined screening by maternal factors with EFW Z-scores for the prediction of SGA neonates with birth weight <10th, <5th and <3rd percentiles, delivering at <2 weeks of assessment, were 89.8% (95% CI, 77.8-96.6; AUC 0.965 (95% CI, 0.958-0.971)), 92.0% (95% CI, 74.0-99.0 AUC 0.977 (95% CI, 0.972-0.982)) and 94.4% (95% CI, 72.7-99.9; AUC 0.990 (95% CI, 0.987-0.993)), respectively. The

respective values for SGA delivering at ≥37 weeks, were 66.0% (95% CI, 60.9-70.7; AUC 0.888 (95% CI, 0.878-0.898)), 72.7% (95% CI, 65.0-79.6; AUC 0.918 (95% CI, 0.909-0.926)) and 79.8% (95% CI, 69.6-87.7; AUC 0.942 (95% CI, 0.934-0.949)).

In combined screening by maternal factors with EFW Z-scores and serum PlGF at 35-37 weeks' gestation, the DRs, at FPR of 10%, of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment were 87.8% (95% CI, 75.2-95.4; AUC 0.969 (95% CI, 0.963-0.974)), 96.0% (95% CI, 79.6-99.9; AUC 0.987 (95% CI, 0.983-0.991)) and 94.4% (95% CI, 72.7-99.9; AUC 0.991 (95% CI, 0.988-0.994)). The respective values for SGA delivering at ≥37 weeks, were 64.1% (95% CI, 59.0-68.9; AUC 0.893 (95% CI; 0.883-0.903)), 74.7% (95% CI, 67.0-81.0; AUC 0.922 (95% CI, 0.913-0.930)) and 79.8% (95% CI, 69.6-87.7; AUC 0.943 (95% CI, 0.935-0.950)).

5.4. Discussion

5.4.1. Main findings of the study

The findings of this study demonstrate that at 35-37 weeks' gestation, in pregnancies that deliver SGA neonates in the absence of PE maternal serum PlGF is reduced and sFlt-1 is increased. The alterations in serum biochemistry are more pronounced in those with severe disease reflected at lower birth weight (3rd vs. 10th percentile) and delivery within two weeks from assessment.

Combined screening by maternal factors and EFW Z-score at 35-37 weeks, predicted 90%, 92% and 94% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment, at FPR of 10%; the respective values for SGA delivering at ≥37 weeks were 66%, 73% and 80%. Combined screening by maternal factors, EFW Z-score and serum PlGF, predicted 88%, 96% and 94% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment and the respective values for SGA delivering at ≥37 weeks were 64%, 75% and 80%. Consequently, addition of serum PlGF only marginally improves the screening performance for the delivery of SGA neonates, in the absence of PE, achieved by maternal factors and fetal biometry alone.

5.4.2. Comparison with findings from previous studies

Most previous reports on maternal serum PlGF and sFlt-1 in pregnancies with SGA fetuses / neonates were based on case-control studies involving a small number of affected pregnancies[164-169]. Such studies compared the median serum concentration of the angiogenic and anti-angiogenic factors or their ratio in affected and unaffected pregnancies or the percentage of cases above or below certain concentration cut-offs. Our study involved screening of all pregnancies attending for a routine scan at 35-37 weeks and assessed the value of serum PlGF and sFlt-1 both individually and in combination with maternal factors and fetal biometry in screening for SGA delivering at term in the absence of PE.

The advantage of using Bayes theorem to combine the prior risk from maternal characteristics and medical history, fetal biometry and biomarkers is that individual patient risks can be estimated for any predefined severity of SGA and any interval from testing to delivery. This is an essential first step for the establishment of patient management protocols.

CHAPTER 6

Conclusion

Chapter 6: Conclusion

6.1. SUMMARY OF RESULTS

This study has shown that combined screening by maternal factors and EFW Z-score at 35-37 weeks, predicted 90%, 92% and 94% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment, at 10% false positive rate; the respective values for SGA delivering at ≥37 weeks were 66%, 73% and 80%.

Addition of UtA PI and MAP to combined testing using maternal factors and fetal biometry at 35-37 weeks has not improved the performance of screening.

When PlGF and sFlt-1 were both added to a model that combines maternal factors and EFW Z-score, sFlt-1 did not remain as a significant independent predictor of SGA <5th. Combined screening by maternal factors, EFW Z-score and serum PlGF, predicted 88%, 96% and 94% of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at <2 weeks of assessment and the respective values for SGA delivering at ≥37 weeks were 64%, 75% and 80%. Hence, addition of serum PlGF only marginally improves the performance of screening.

Such performance of screening is superior to that achieved by the current method in the UK, which is based on maternal characteristics and measurement of SFH[21].

6.2. STRENGTHS AND LIMITATIONS

This study has several strengths. Firstly, this was the largest routine screening study carried out at 35-37 weeks, a gestational age when there was few literature regarding assessing fetal growth and wellbeing. Secondly, the study ensured that only appropriately trained doctors, certified by the Fetal Medicine Foundation, using specific methodology undertook the measurements of HC, AC FL, MAP and uterine artery PI. Thirdly, it assessed two biochemical markers (PlGF and sFlt-1), which have been associated with impaired placentation at late third trimester. 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, which is an essential step for establishing patient management protocols.

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, particularly those delivering within 2 weeks of assessment.

6.3. 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 30-34 weeks' gestation. They compared screening at 30-34 weeks, also with biophysical and biochemical markers, namely, maternal factors, EFW, UtA PI, MAP and the PlGF (sFlt-1 was not included, as the use of PlGF alone was better predictor than PlGF and sFlt-1). The DRs, at a FPR of 10%, of SGA neonates with BW <10th, <5th and<3rd percentiles delivering ≥37 weeks were 57%, 65%, 71%[192] compared with our study's results of 64%, 75%, and 80%. Thus, the 35-37 weeks scan performed better for detection of SGA ≥ 37 weeks.

In the proposed new pyramid of pregnancy care[193], an integrated clinic at 11-13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high-risk of developing PE and/or SGA[137, 194] and through pharmacological intervention (eg, aspirin) to reduce the prevalence of these complications[195-198].

The objective of subsequent visits, at around 22 and 32 or 36 weeks' gestation, are to identify the high-risk group and through close monitoring of such pregnancies to minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery. It was proposed that all women should be offered a third-trimester scan for assessment of fetal growth and wellbeing and that the timing of such scan, at 32 and/or 36 weeks, should be contingent on the results of assessment at around 22 weeks[187-188,199].

The 19-24 gestational weeks' model, simultaneously proposed by colleagues of the same Department[199], uses maternal factors, fetal biometry, UtA-PI and serum PlGF and AFP as

significant independent contributions to the prediction of SGA (< 5th percentile). The detection rate (DR) of such combined screening at 19-24 weeks was 100%, 78% and 42% for SGA (< 5th percentile) delivering < 32, at 32-36 and ≥ 37 weeks' gestation, respectively, at a false-positive rate (FPR) of 10%. In a hypothetical model, it was estimated that if the desired objective of prenatal screening is to predict about 80% of the cases of SGA < 5th, at a FPR of 10%, it would be necessary to select 11% of the population at the 19-24-week assessment to be reassessed at 32 weeks and 44% to be reassessed at 36 weeks; 57% would not require a third-trimester scan.

Following a 35-37 weeks scan, on the basis of results from this thesis study, if the assessment includes a combination of maternal factors, fetal biometry and serum PlGF, potentially 80%, 90% and 100% of cases of SGA <5th without PE could be detected at respective FPRs of 14%, 21% and 75%. The subsequent management of the screen positive group with the objective of reducing perinatal death and handicap remains to be determined.

Regarding the timing of the 35-37 weeks routine appointment, which up until the publication of the studies of this thesis there was very scarce information on, it can also be useful, not only to predict SGA without PE, but also to predict term pre-eclampsia. Colleagues from the same department[200] developed a model for prediction of term pre-eclampsia (PE) based on a combination of maternal factors and late third-trimester biomarkers. Screening for term PE by a combination of maternal factors, MAP, PlGF and sFlt-1 at 35–37 weeks' gestation predicted about 85% of affected pregnancies, at a FPR of 10%. Hence, the screening performance at 35-37 weeks for late PE is also superior to that achieved by screening at 11–13, 19–24 or 30–34 weeks, with respective DRs of 47%, 46% and 66%.

Since the publication and presentation of the data in this thesis, late third trimester routine growth scans have been progressively implemented and further studies have been being pursued in this field.

6.4. 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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APPENDICES

Appendix A.1. Paper **"Prediction of small-for-gestational-age neonates: screening by fetal biometry at 35-37 weeks"**, published in Ultrasound in Obstetrics & Gynecology, May 2015.

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Prediction of small-for-gestational-age neonates: screening by fetal biometry at 35–37 weeks

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KEYWORDS: abdominal circumference; estimated fetal weight; fetal biometry; pre-eclampsia; pyramid of antenatal care; small-for-gestational age; third-trimester screening

ABSTRACT

Objective *To investigate the value of fetal biometry at 35–37 weeks' gestation in the prediction of delivery of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE).*

Methods *This was a screening study in singleton pregnancies at 35–37 weeks' gestation, comprising 278 that delivered SGA neonates with a birth weight < 5th percentile and 5237 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if screening by a combination of maternal factors and Z-scores of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) or estimated fetal weight (EFW) had a significant contribution to the prediction of SGA neonates.*

Results *Multivariable logistic regression analysis demonstrated that the likelihood of delivering a SGA neonate with a birth weight < 5th percentile decreased with maternal weight and height, and in parous women the risk increased with a longer interpregnancy interval. The risk was higher in women of Afro-Caribbean and South Asian racial origins, in cigarette smokers, nulliparous women and in those with history of SGA, with or without prior PE. Combined screening by maternal characteristics and history with EFW Z-scores at 35–37 weeks predicted 89% of SGA neonates with birth weight < 5th percentile delivering < 2 weeks following assessment, at a 10% false-positive rate (FPR). The respective detection rate for the prediction of SGA neonates delivering ≥ 37 weeks' gestation was 70%. The performance of screening by a combination of Z-scores of 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 35–37 weeks could identify, at a 10% FPR, about 90% of pregnancies that subsequently deliver SGA neonates within 2 weeks of assessment and 70% of those that deliver ≥ 37 weeks.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified prenatally, as close monitoring, timely delivery and prompt neonatal care can be undertaken[1].

A few studies comprising low-risk singleton pregnancies have examined the potential value of sonographic fetal biometry during the third trimester in the prediction of SGA neonates[2–8]. Three studies each examined a range of 725 to 1000 pregnancies at 26–36 weeks' gestation and reported that the estimated fetal weight (EFW) predicted 54–63% of SGA neonates with birth weight < 10th percentile, at a false-positive rate (FPR) of 20%[2–4]. Di Lorenzo *et al.*[5] assessed EFW at 30–32 weeks in the prediction of SGA neonates < 10th percentile in 1868 pregnancies, and reported that the detection rate (DR) was 73% at a FPR of 25%. Souka *et al.*[6] assessed EFW at 30–33 weeks in 2310 pregnancies and reported that, at a FPR of 10%, the DR of SGA neonates with birth weight < 5th percentile was 60%. Only one study examined the value of EFW in a late third-trimester ultrasound examination in low-risk pregnancies; EFW at 34–37 weeks' gestation in 2288 pregnancies predicted 75% of SGA neonates with birth weight < 5th percentile, at a FPR of 10%, which was superior to the DR of 58% in 3690 pregnancies examined at 30–33 weeks[7].

We have reported recently our findings from a screening study at 30–34 weeks in 30 849 singleton pregnancies[8]. Combined screening by maternal characteristics and history with EFW Z-scores predicted 79%, 87% and 92%

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of SGA neonates in the absence of PE delivering < 5 weeks following assessment with birth weights < 10th, < 5th and < 3rd percentiles, respectively, at a 10% FPR. The respective DRs for prediction of SGA neonates delivering ≥ 5 weeks following assessment were 53%, 58% and 61%. Consequently, the performance of screening for SGA at 30–34 weeks is acceptably high for those delivering preterm, but disappointingly low for those delivering at term.

The objectives of this study in a large cohort of singleton pregnancies undergoing routine antenatal care were, first, to investigate the potential value of fetal biometry at 35–37 weeks' gestation in the prediction of delivery of SGA neonates in the absence of PE, and second, to combine these biomarkers with maternal characteristics and history to develop specific algorithms for the calculation of patient-specific risks for SGA.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcome in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, and Medway Maritime Hospital, Kent, between February 2014 and September 2014. This visit, which was held at 35 + 0 to 37 + 6 weeks' gestation, included recording of maternal factors and EFW[9] from trans-abdominal ultrasound measurement of the fetal head circumference (HC), abdominal circumference (AC) and femur length (FL)[10], and measurement of uterine artery pulsatility index, mean arterial pressure and maternal serum metabolites. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[10,11].

Written informed consent was obtained from the women agreeing to participate in this study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. This study is part of a research program on the late third-trimester prediction of PE and/or SGA. In this study, we present the results on combined screening with maternal factors and fetal biometry in the prediction of SGA in the absence of PE. The pregnancies included in this study all resulted in live birth or the stillbirth of phenotypically normal babies.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), obstetric history including parity (parous/nulliparous if no previous pregnancy ≥ 24 weeks' gestation), previous pregnancy with PE (yes/no), previous pregnancy with SGA (yes/no) and the time interval (years) between last delivery and conception of the current pregnancy. Maternal weight and height were also measured.

Outcome measures

Data on pregnancy outcomes 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. The newborn was considered to be SGA if the birth weight was < 5th percentile after correction for gestational age at delivery (SGA < 5th)[12]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[13]. 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.

Statistical analysis

The observed measurements of fetal HC, AC, FL and EFW were expressed as the respective *Z*-score and percentile, corrected for gestational age[9,10]. Mann–Whitney *U*-test was used to compare the *Z*-scores of HC, AC, FL and EFW between the SGA and unaffected groups. 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 the time interval between assessment and delivery.

The *a-priori* risk for SGA < 5th 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.

Multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (*a-priori* risk), HC *Z*-score, AC *Z*-score, FL *Z*-score or EFW *Z*-score had significant contribution in predicting SGA < 5th. The performance of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight < 10th percentile (SGA < 10th) and birth weight < 3rd percentile (SGA < 3rd).

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

RESULTS

The study population comprised of 5515 pregnancies, including 278 (5.0%) that delivered SGA < 5th neonates in the absence of PE and 5237 (95.0%) cases that were unaffected by these outcomes. The characteristics of the study population are given in Table 1. In the SGA group, compared with the normal group, there was a lower median maternal weight and height, a higher prevalence of South Asian racial origin, nulliparous women, parous women

Table 1 Characteristics of the study population of pregnant women with normal outcomes and those with small-for-gestational-age (SGA) neonates without pre-eclampsia (PE)

Characteristic	*Normal* (n = *5237*)	*SGA without PE* (n = *278*)	P
Maternal age (years)	31.2 (26.5–35.0)	30.1 (24.8–35.3)	0.067
Maternal weight (kg)	79.0 (70.9–89.9)	73.2 (64.2–83.5)	< 0.0001
Maternal height (cm)	164 (160–168)	162 (157–165)	< 0.0001
GA at screening (weeks)	36.1 (36.0–36.4)	36.3 (36.0–36.4)	0.916
Racial origin			
Caucasian	3720 (71.0)	161 (57.9)	< 0.0001
Afro-Caribbean	1034 (19.7)	64 (23.0)	0.190
South Asian	199 (3.8)	34 (12.2)	< 0.0001
East Asian	109 (2.1)	6 (2.2)	0.830
Mixed	175 (3.3)	13 (4.7)	0.233
Obstetric history			
Nulliparous	2537 (48.4)	172 (61.9)	0.001
Parous with no prior PE or SGA	2481 (47.4)	73 (26.3)	< 0.0001
Parous with prior PE, no SGA	82 (1.6)	5 (1.8)	0.459
Parous with prior SGA, no PE	127 (2.4)	27 (9.7)	0.002
Parous with prior SGA and PE	10 (0.2)	1 (0.4)	> 0.999
Interpregnancy interval (years)	3.1 (2.1–5.1)	2.9 (2.1–5.5)	0.965
Cigarette smoker	503 (9.6)	62 (22.3)	< 0.0001
Mode of conception			
Spontaneous	5110 (97.6)	266 (95.7)	0.072
Ovulation drugs	23 (0.4)	2 (0.7)	0.362
In-vitro fertilization	104 (2.0)	10 (3.6)	0.079
Chronic hypertension	72 (1.4)	2 (0.7)	0.588
Pre-existing diabetes mellitus	65 (1.2)	3 (1.1)	> 0.999
Type 1	31 (0.6)	2 (0.7)	> 0.999
Type 2	34 (0.6)	1 (0.4)	> 0.999
SLE or APS	13 (0.2)	0 (0.0)	> 0.999
GA at delivery (weeks)	40.0 (39.0–40.9)	39.4 (38.4–40.4)	< 0.0001
Birth weight (g)	3430 (3140–3745)	2550 (2347–2721)	< 0.0001
Birth-weight percentile	50.3 (26.6–75.6)	2.7 (1.2–3.7)	< 0.0001

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus.

with a history of SGA and cigarette smokers, and a lower prevalence of Caucasian racial origin and parous women with no history of SGA and PE. The median gestational age at delivery and neonatal birth weight were significantly lower in the SGA group than in the normal group.

There were significant ($P < 0.0001$) intercorrelations between Z-score values of HC, AC and FL in both the SGA and normal outcome groups with *r*-values ranging from 0.146 to 0.381.

Normal pregnancy outcome

There was a significant linear association between HC Z-score and the assessment-to-delivery interval ($-0.298 + (0.040 \times$ delivery interval); $r = 0.087$; $P < 0.0001$) and between EFW Z-score and the assessment-to-delivery interval ($0.281 + (0.025 \times$ delivery interval); $r = 0.047$; $P = 0.001$), and there was a significant polynomial association between AC Z-score and the assessment-to-delivery interval ($-0.146 + (0.077 \times$ delivery interval) $- (0.010 \times$ delivery interval^2); $r = 0.040$; $P = 0.015$) and between FL Z-score and the assessment-to-delivery interval ($-0.215 + (0.194 \times$ delivery interval) $- (0.053 \times$ delivery interval^2) $+ (0.005 \times$ delivery interval^3); $r = 0.043$; $P = 0.022$).

Small-for-gestational age

In the SGA < 5th group, the median Z-score values of HC, AC, FL and EFW at 35–37 weeks were significantly lower ($P < 0.0001$) than those of the normal group. There was a significant linear association between HC Z-score and the assessment-to-delivery interval ($-1.147 + (0.098 \times$ delivery interval); $r = 0.249$; $P < 0.0001$; Figure S1a); AC Z-score and assessment-to-delivery interval ($-1.684 + (0.214 \times$ delivery interval); $r = 0.481$; $P < 0.0001$; Figure S1b); FL Z-score and assessment-to-delivery interval ($-1.263 + (0.190 \times$ delivery interval); $r = 0.314$; $P < 0.0001$; Figure S1c); and EFW Z-score and assessment-to-delivery interval ($-1.572 + (0.234 \times$ delivery interval); $r = 0.505$; $P < 0.0001$; Figure S1d).

The *a-priori* risk for SGA < 5th 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 adjusted odds ratios of each of the maternal factors in the prediction algorithms are presented in Table 2 ($R^2 = 0.106$, $P < 0.0001$). The likelihood of SGA < 5th decreased with maternal weight and height, and in parous women the risk increased with interpregnancy interval. The risk was higher in women of Afro-Caribbean and South Asian racial origin, in

Table 2 Fitted regression model with maternal characteristics and history for the prediction of small-for-gestational age (SGA) with birth weight < 5th percentile in the absence of pre-eclampsia (PE)

Independent variable	*Coefficient*	*SE*	*OR (95% CI)*	P
Intercept	−0.89206	0.39700		
Weight (−75)*	−0.02012	0.01094	0.980 (0.970–0.990)	< 0.0001
Height (−165)†	−0.03839	0.01094	0.962 (0.942–0.983)	0.0004
Racial origin				
Caucasian, East Asian, mixed (reference)	0		1	
Afro-Caribbean	0.56782	0.15750	1.764 (1.296–2.403)	0.0003
South Asian	1.08597	0.21540	2.962 (1.942–4.518)	< 0.0001
Cigarette smoker	1.08264	0.16094	2.952 (2.154–4.047)	< 0.0001
Obstetric history				
Nulliparous	1.06018	0.16341	2.887 (2.096–3.977)	< 0.0001
Parous				
No previous SGA ± PE (reference)	−3.23409	0.17404	0.021	
Interpregnancy interval in years	0.06583	0.02655	1.081 (1.026–1.139)	0.003
Previous SGA ± PE	1.59429	0.23809	6.639 (4.163–10.587)	< 0.0001

*Subtracted from maternal weight in kg. †Subtracted from maternal height in cm. OR, odds ratio; SE, standard error.

cigarette smokers, nulliparous women and in those with a prior SGA pregnancy, with or without prior PE. The risk was lower in parous women with no history of SGA, with or without prior PE. The likelihood of SGA < 5th was not altered significantly by maternal age ($P = 0.911$), method of conception ($P = 0.083$), chronic hypertension ($P = 0.502$), diabetes mellitus ($P = 0.645$) and SLE or APS ($P = 0.998$).

Multivariable logistic regression analyses demonstrated that, in the prediction of SGA < 5th, 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 ($R^2 = 0.407$, $P < 0.0001$; Table S1).

The areas under the ROC curves (AUC) and the DRs at FPRs of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA < 10th, SGA < 5th and SGA < 3rd, delivering < 2 weeks after assessment and ≥ 37 weeks' gestation, when screening by maternal characteristics and a combination of HC, AC and FL Z-scores or EFW Z-score are given in Tables 3, S2 and S3 and Figure 1.

Prediction of SGA delivering < 2 or ≥ 2 weeks following screening at 35–37 weeks

The DRs, at a FPR of 10%, of combined screening by maternal characteristics and history with EFW Z-scores for the prediction of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, delivering ≥ 2 weeks following assessment, were 62.6% (95% CI, 58.3–66.7; AUC: 0.875 (95% CI, 0.866–0.884)), 67.1% (95% CI, 60.6–73.2; AUC: 0.895 (95% CI, 0.886–0.903)) and 74.4% (95% CI, 65.6–81.9; AUC: 0.916 (95% CI, 0.909–0.924)), respectively. The performance of screening was better for the prediction of SGA delivering within 2 weeks of assessment with respective DRs of 87.8% (95% CI, 79.6–93.5; AUC: 0.961 (95% CI, 0.955–0.966)), 88.7% (95% CI, 77.0–95.7; AUC: 0.972 (95% CI, 0.967–0.976)) and 91.7% (95% CI, 77.5–98.2); AUC: 0.983 (95% CI, 0.979–0.986)) (Tables 3 and S2).

Prediction of SGA delivering ≥ 37 weeks with screening at 35–37 compared to 30–34 weeks

In combined screening by maternal characteristics and history with EFW Z-scores at 35–37 weeks' gestation, the DRs, at a FPR of 10%, of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles delivering ≥ 37 weeks were 66.0% (95% CI, 62.0–69.7; AUC: 0.887 (95% CI, 0.879–0.895)), 70.0% (95% CI, 64.0–75.4; AUC: 0.906 (95% CI, 0.898–0.913)) and 77.2% (95% CI, 69.6–83.7; AUC: 0.928 (95% CI, 0.921–0.935)), respectively (Tables 3 and S3). Using data from our recent publication in combined screening by maternal characteristics and history with EFW Z-scores at 30–34 weeks[8], the respective DRs were 53.0% (95% CI, 51.3–54.8; AUC: 0.833 (95% CI, 0.829–0.837)), 58.3% (95% CI, 55.7–60.9; AUC: 0.859 (95% CI, 0.855–0.863)) and 60.8% (95% CI, 62.6–85.0; AUC: 0.875 (95% CI, 0.871–0.879)).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that the risk for delivering SGA neonates in the absence of PE, increases with a longer interpregnancy interval, decreases with maternal weight and height, it is higher in women of Afro-Caribbean or South Asian racial origin than in Caucasian women, in cigarette smokers, nulliparous women and in parous women with a history of SGA.

In women who deliver SGA neonates in the absence of PE, the fetal HC, AC, FL and EFW at 35–37 weeks' gestation are reduced. The prediction of SGA provided by the fetal AC is superior to that of HC or FL, but inferior to that of the combination of the three measurements. The performance of screening by a combination of Z-scores for fetal HC, AC and FL is similar to that achieved by the EFW Z-score.

Combined screening by maternal characteristics and history with EFW Z-scores at 35–37 weeks predicted

Table 3 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering within 2 weeks of assessment and ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal characteristics and history, fetal biometry or estimated fetal weight at 35–37 weeks' gestation

		DR (%)		FPR (%)		
Screening test	*AUC*	*FPR = 5%*	*FPR = 10%*	*DR = 100%*	*DR = 90%*	*DR = 80%*
SGA delivering < 2 weeks following assessment						
SGA < 10th percentile						
Maternal characteristics and history	0.735 (0.722–0.747)	26.5 (18.1–36.4)	41.8 (31.9–52.2)	98.4 (98.0–98.7)	71.0 (69.7–72.3)	52.1 (50.7–53.5)
Plus EFW Z-score	0.961 (0.955–0.966)	77.6 (68.0–85.4)	87.8 (79.6–93.5)	53.5 (52.1–54.9)	11.9 (11.0–12.8)	5.8 (5.1–6.5)
SGA < 5th percentile						
Maternal characteristics and history	0.804 (0.793–0.815)	35.9 (23.1–50.2)	50.9 (36.8–64.9)	73.6 (72.4–74.8)	57.9 (56.6–59.3)	44.8 (43.5–46.2)
Plus EFW Z-score	0.972 (0.967–0.976)	84.9 (72.4–93.3)	88.7 (77.0–95.7)	34.6 (33.3–35.9)	11.1 (10.2–12.0)	3.0 (2.5–3.5)
SGA < 3rd percentile						
Maternal characteristics and history	0.807 (0.796–0.818)	38.9 (23.1–56.5)	50.0 (32.9–67.1)	62.4 (61.1–63.7)	57.9 (56.6–59.3)	40.5 (39.1–41.8)
Plus EFW Z-score	0.983 (0.979–0.986)	91.7 (77.5–98.2)	91.7 (77.5–98.2)	17.1 (16.1–18.2)	3.8 (3.3–4.3)	0.9 (0.7–1.3)
SGA delivering ≥ 37 weeks' gestation						
SGA < 10th percentile						
Maternal characteristics and history	0.709 (0.697–0.721)	19.7 (16.6–23.1)	32.2 (28.5–36.1)	99.9 (99.8–99.9)	70.5 (69.2–71.7)	53.4 (52.0–54.8)
Plus EFW Z-score	0.887 (0.879–0.895)	46.9 (42.9–51.0)	66.0 (62.0–69.7)	88.5 (87.6–89.4)	32.9 (31.6–34.02)	19.5 (18.4–20.6)
SGA < 5th percentile						
Maternal characteristics and history	0.734 (0.722–0.746)	22.4 (17.5–28.0)	35.7 (29.9–41.9)	98.1 (97.7–98.5)	68.8 (67.5–70.0)	49.7 (48.3–51.0)
Plus EFW Z-score	0.906 (0.898–0.913)	53.6 (47.4–59.8)	70.0 (64.0–75.4)	83.4 (82.4–84.4)	25.0 (23.9–26.2)	13.5 (12.6–14.5)
SGA < 3rd percentile						
Maternal characteristics and history	0.772 (0.761–0.784)	24.8 (18.1–32.6)	37.6 (29.8–45.9)	90.7 (89.9–91.5)	56.3 (54.9–57.6)	41.7 (40.4–43.1)
Plus EFW Z-score	0.928 (0.921–0.935)	63.8 (55.5–71.5)	77.2 (69.6–83.7)	69.3 (68.0–70.5)	19.6 (18.5–20.7)	10.6 (9.8–11.5)

AUC, area under receiver–operating characteristics curve; DR, detection rate; EFW, estimated fetal weight; FPR, false-positive rate.

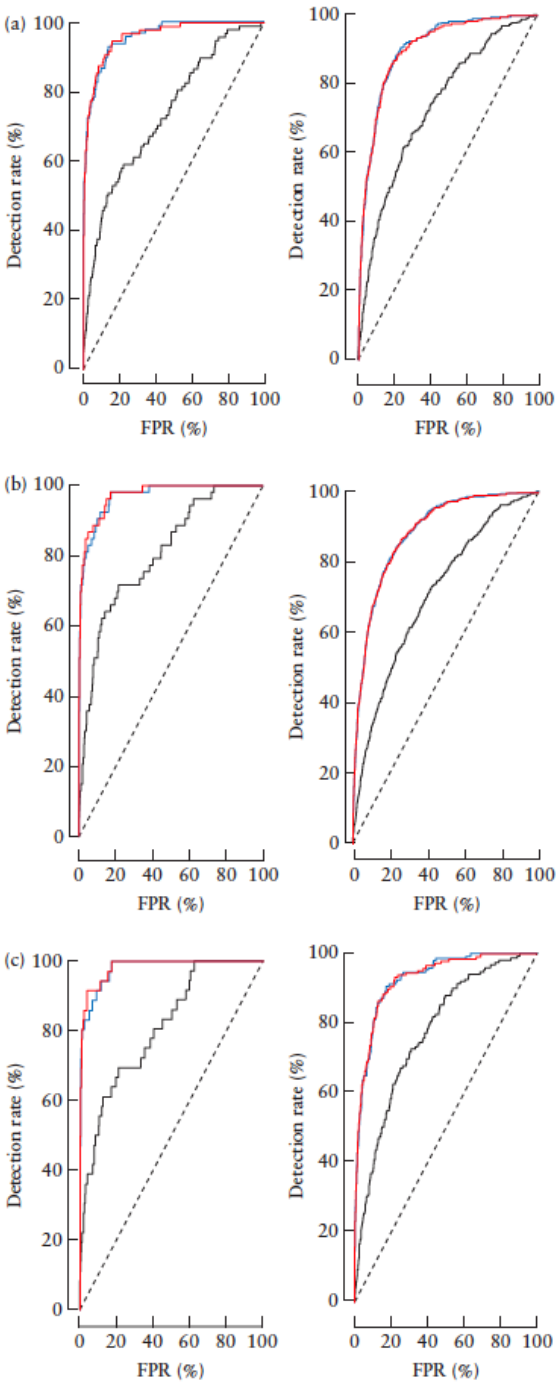

Figure 1 Receiver–operating characteristics curves of maternal characteristics (—), combination of maternal characteristics with fetal head circumference, abdominal circumference and femur length Z-score (—) and combination of maternal characteristics with estimated fetal weight Z-score (—) at 35–37 weeks' gestation in the prediction of small-for-gestational-age neonates with birth weight < 10th percentile (a), < 5th percentile (b) and < 3rd percentile (c), delivering < 2 weeks following assessment (left) or ≥ 37 weeks' gestation (right). FPR, false-positive rate.

about 70% of pregnancies that subsequently delivered SGA < 5th neonates ≥ 37 weeks, at a FPR of 10%. This was superior to the DR of 58% achieved by screening at 30–34 weeks[8]. The performance of screening was better in the prediction of SGA delivering within 2 weeks of assessment, with DR of about 90%.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are first, examination of a population of pregnant women attending for routine assessment of fetal growth and wellbeing and second, use of Bayes' theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry to estimate patient-specific risks and the performance of screening for SGA of different severities, delivering at term.

The main limitation of the study is that the results of the 35–37 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring of the cases of suspected SGA. Consequently, the performance of screening would be positively biased.

Comparison with findings from previous studies

Our findings, that the prediction of SGA neonates with birth weight < 5th percentile at 35–37 weeks' gestation by sonographic estimation of EFW Z-scores is superior to that of screening at 30–34 weeks (70% *vs* 58%), at a FPR of 10%, are similar to those of a previous study that reported rates of 75% and 58% with screening at 34–37 and 30–33 weeks, respectively[7]. In the previous study[7], all cases of SGA were included, whereas in our study those associated with PE were excluded.

A routine third-trimester scan is by far superior to the traditional approach of abdominal palpation in identifying pregnancies at high risk of delivering SGA neonates. A population-based observational study of 6318 consecutive low-risk singleton pregnancies reported that abdominal palpation predicted only 21% and 28% of SGA neonates with birth weight < 10th and 2.3rd percentiles, respectively, at a FPR of about 5%[14]. One randomized study compared the effectiveness of serial measurements of symphysis–fundal height to that of abdominal palpation in the prediction of SGA neonates with birth weight < 10th percentile and reported no significant difference between the two methods (28% *vs* 48%, both at a FPR of about 4%)[15].

Implications for clinical practice

In the proposed new pyramid of pregnancy care[16], an integrated clinical assessment at 11–13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high risk of developing PE and/or SGA[17,18] and, through pharmacological intervention, reduce the prevalence of these complications[19,20].

The objectives of subsequent visits, at around 22 and 32 or 36 weeks' gestation, are to identify the high-risk group and, through close monitoring of such pregnancies, to minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery. We found that screening at 32 weeks can identify, at a FPR of 10%, about 90% of SGA < 5th delivering preterm, but < 60% of those delivering at term[8]. Although a third-trimester scan at 36 weeks, rather than at 32 weeks, would improve the prediction of SGA < 5th delivering ≥ 37 weeks from 58% to 70%, this would be at the inevitable expense of missing preterm SGA. Future studies will investigate the extent to which selection of the timing of the third-trimester scan can be defined by the findings of screening at 12 and 22 weeks; women at high risk of early-onset SGA would be offered a scan at 32 weeks and those at low risk would be offered a scan at 36 weeks.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Z-scores for fetal head circumference (HC) (a), abdominal circumference (AC) (b), femur length (FL) (c) and estimated fetal weight (EFW) (d) at 35–37 weeks' gestation, according to assessment-to-delivery interval, in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile. Horizontal solid and dashed lines indicate the 50th and 10th percentiles of the normal range. Red line indicates fitted mean from regression model.

Table S1 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 35–37 weeks' gestation, for the prediction of small-for-gestational age with birth weight < 5th percentile in the absence of pre-eclampsia.

Table S2 Detection rates in screening for small-for-gestational-age neonates with birth weight < 10th, < 5th or < 3rd percentile, delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal characteristics and history, fetal biometry or estimated fetal weight at 35–37 weeks' gestation.

Table S3 Detection rates in screening for small-for-gestational-age neonates with birth weight < 10th, < 5th or < 3rd percentile, delivering ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal characteristics and history, fetal biometry or estimated fetal weight at 35–37 weeks' gestation.

Appendix A.2. Paper **"Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 35-37 weeks"**, published in Ultrasound in Obstetrics & Gynecology, June 2015.

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Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 35–37 weeks

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KEYWORDS: mean arterial pressure; pre-eclampsia; pyramid of antenatal care; small-for-gestational age; third-trimester screening; uterine artery Doppler

ABSTRACT

Objective *To investigate the potential value of uterine artery (UtA) pulsatility index (PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation in the prediction of delivery of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE).*

Methods *This was a screening study in singleton pregnancies at 35–37 weeks, including 245 that delivered SGA neonates with birth weight < 5th percentile and 4876 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if UtA-PI and MAP 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 *Compared to the normal group, the median multiple of the median (MoM) values of UtA-PI and MAP were significantly higher in the SGA < 5th group. Combined screening by maternal factors, EFW Z-score, UtA-PI and MAP at 35–37 weeks predicted, at a 10% false-positive rate, 90%, 86% and 90% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, respectively, delivering < 2 weeks following assessment; the respective values for SGA delivering ≥ 37 weeks were 66%, 74% and 80%. Such performance was not significantly different from screening by maternal factors and EFW Z-score alone.*

Conclusion *Addition of UtA-PI and MAP to combined testing by maternal factors and fetal biometry at 35–37 weeks does not improve the performance of screening for delivery of SGA neonates.* Copyright © 2015 ISUOG. *Published by John Wiley & Sons Ltd.*

INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified prenatally, as close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken[1]. The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysis–fundal height, but the detection rate (DR) of this approach is less than 30%[2,3]. A higher performance in screening for SGA is achieved by third-trimester assessment which includes ultrasound examination for fetal biometry and the timing of such assessment, at 32 or 36 weeks' gestation, could be defined by the results of assessment at 22 weeks[4,5].

Screening by a combination of maternal characteristics and medical history with estimated fetal weight (EFW), uterine artery (UtA) pulsatility index (PI) and mean arterial pressure (MAP) at 32 weeks' gestation, predicted 83%, 91% and 93% of SGA neonates delivering within 5 weeks of assessment, at a false-positive rate (FPR) of 10%, with respective birth weight < 10th, < 5th and < 3rd percentiles, in the absence of pre-eclampsia (PE)[6]. However, the respective values for delivery ≥ 5 weeks following assessment were only 53%, 58% and 61%.

The objectives of this study, in singleton pregnancies undergoing routine antenatal assessment at 35–37 weeks'

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gestation, were first, to investigate the potential value of UtA-PI and MAP on their own and in combination with maternal characteristics, medical history and EFW in the prediction of delivery of SGA neonates in the absence of PE and second, to develop specific algorithms for the calculation of patient-specific risks for SGA.

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 King's College Hospital, London, and Medway Maritime Hospital, Kent, between February 2014 and September 2014. This visit, which is held at 35 + 0 to 37 + 6 weeks' gestation, included the recording of maternal characteristics and medical history and estimation of fetal weight (EFW)[7] from transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length[8] and measurement of UtA-PI, MAP and maternal serum metabolites. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[8,9].

Transabdominal color Doppler ultrasound was used to visualize the left and right UtA at the apparent crossover with the external iliac arteries[10]. Pulsed-wave Doppler was then used to obtain waveforms and, when three similar consecutive waveforms were obtained, the PI was measured and the mean PI of the two vessels was calculated. The scans were carried out by sonographers who had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com).

The MAP was measured by validated automated devices (3BTO-A2, Microlife, Taipei, Taiwan), which were calibrated before, and at regular intervals during, the study. Recordings were made by doctors who had received appropriate training on the use of these machines. During measurements, women were in the sitting position with their arms supported at the level of the heart and a small (22 cm), normal (22–32 cm) or large (33–42 cm) adult cuff was used, depending on the mid-arm circumference. After 5 min of rest, two recordings of blood pressure were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements[11].

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. This study is part of a research program on the late third-trimester prediction of PE and/or SGA. In this publication, we present the results of combined screening with maternal factors and biophysical markers in the prediction of SGA in the absence of PE. The patients included in the study were all pregnancies resulting in live birth or stillbirth of phenotypically normal babies.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), and obstetric history including parity (parous/nulliparous if no previous pregnancy ≥ 24 weeks' gestation), previous pregnancy with PE (yes/no), previous pregnancy with SGA (yes/no) and the time interval between the last delivery and conception of the current pregnancy in years. Maternal weight and height were also measured.

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. The newborn was considered to be SGA if the birth weight was < 5th percentile after correction for gestational age at delivery (SGA < 5th)[12]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[13]. 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.

Statistical analysis

The observed measurements of EFW were expressed as *Z*-scores, corrected for gestational age[12]. The values of UtA-PI and MAP 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 adjusting for those characteristics found to provide substantial contribution to the $\log_{10}$ transformed value[14,15]. Mann–Whitney *U*-test was used to compare the median MoM values of UtA-PI and MAP between the outcome groups. Regression analysis was used to determine the significance of association between $\log_{10}$MoM of UtA-PI and MAP with the assessment-to-delivery interval and birth-weight *Z*-score.

The *a-priori* risk for SGA < 5th was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history, as described previously[16]. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a-priori* risk), $\log_{10}$MoM UtA-PI, $\log_{10}$MoM MAP and EFW *Z*-score had a significant contribution in predicting SGA < 5th. The performance of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined

Table 1 Characteristics of the study population of women with a singleton pregnancy with normal outcome or with a small-for-gestational-age (SGA) neonate, in the absence of pre-eclampsia (PE)

Characteristic	*Normal (n = 4876)*	*SGA without PE (n = 245)*	P
Maternal age (years)	31.2 (26.5–35.0)	30.1 (24.6–35.3)	0.061
Maternal weight (kg)	79.0 (70.8–89.8)	73.5 (63.9–84.1)	< 0.0001
Maternal height (cm)	164 (160–168)	162 (158–165)	< 0.0001
GA at screening (weeks)	36.1 (36.0–36.4)	36.3 (36.0–36.4)	0.848
Racial origin			
Caucasian	3495 (71.7)	140 (57.1)	< 0.0001
Afro-Caribbean	941 (19.3)	57 (23.3)	0.137
South Asian	178 (3.7)	30 (12.2)	< 0.0001
East Asian	101 (2.1)	6 (2.4)	0.644
Mixed	161 (3.3)	12 (4.9)	0.200
Obstetric history			
Nulliparous	2352 (48.2)	148 (60.4)	0.0002
Parous with no prior PE and SGA	2318 (47.5)	67 (27.3)	< 0.0001
Parous with prior PE no SGA	77 (1.6)	4 (1.6)	0.795
Parous with prior SGA no PE	121 (2.5)	25 (10.2)	< 0.0001
Parous with prior SGA and PE	8 (0.2)	1 (0.4)	0.357
Interpregnancy interval (years)	3.1 (2.1–5.1)	2.9 (2.1–5.5)	0.965
Cigarette smoker	464 (9.5)	59 (24.1)	< 0.0001
Mode of conception			
Spontaneous	4758 (97.6)	235 (95.9)	0.136
Ovulation drugs	20 (0.4)	2 (0.8)	0.284
In-vitro fertilization	98 (2.0)	8 (3.3)	0.167
Chronic hypertension	64 (1.3)	2 (0.8)	0.770
Pre-existing diabetes mellitus	57 (1.2)	2 (0.8)	> 0.999
Type 1	27 (0.6)	1 (0.4)	> 0.999
Type 2	30 (0.6)	1 (0.4)	> 0.999
SLE or APS	13 (0.3)	0 (0.0)	> 0.999
GA at delivery (weeks)	40.0 (39.1–40.9)	39.4 (38.6–40.4)	< 0.0001
Birth weight (g)	3435 (3140–3745)	2550 (2350–2718)	< 0.0001
Birth-weight percentile	50.6 (26.8–75.6)	2.7 (1.2–3.8)	< 0.0001

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus.

by birth weight < 10th percentile (SGA < 10th) and < 3rd percentile (SGA < 3rd).

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

RESULTS

The characteristics of the study population of 5121 pregnancies, including 245 delivering SGA < 5th neonates in the absence of PE, are presented in Table 1.

Normal pregnancy outcome

In the unaffected pregnancies with birth weight ≥ 5th percentile, the mean ± SD, 90th and 95th percentile of $\log_{10}$MoM UtA-PI were −0.009 ± 0.113, 0.134 and 0.187, respectively. The mean ± SD, 90th and 95th percentile of $\log_{10}$MoM MAP were 0.002 ± 0.033, 0.044 and 0.056, respectively (Table S1).

There was no significant association between $\log_{10}$MoM values of UtA-PI and MAP ($r = -0.004$, $P = 0.893$). There was a significant inverse association between $\log_{10}$MoM UtA-PI and the assessment-to-delivery interval ($r = -0.096$, $P < 0.0001$) and birth-weight Z-score ($r = -0.096$, $P < 0.0001$), and between $\log_{10}$MoM MAP and assessment-to-delivery interval ($r = -0.080$, $P < 0.0001$), but not birth-weight Z-score ($r = -0.022$, $P = 0.113$).

Small-for-gestational age

In the SGA < 5th group, compared to the normal group, the median MoM values of UtA-PI and MAP at 35–37 weeks were significantly higher (Table S1). There was no significant association between $\log_{10}$MoM values of UtA-PI and MAP ($r = 0.109$, $P = 0.088$). There was a significant inverse association between $\log_{10}$MoM UtA-PI and assessment-to-delivery interval ($r = -0.232$, $P < 0.0001$; Figure S1a) and birth-weight Z-score ($r = -0.157$, $P = 0.011$; Figure S1b). There was no significant association between $\log_{10}$MoM MAP and assessment-to-delivery interval ($r = -0.100$, $P = 0.107$; Figure S1c) and birth-weight Z-score ($r = -0.057$, $P = 0.354$; Figure S1d).

Multivariable logistic regression analysis demonstrated that, in the prediction of SGA < 5th, there were significant contributions from maternal characteristics, EFW Z-score, UtA-PI and MAP (Table S2). Combined screening by maternal characteristics and history with

EFW Z-scores, UtA-PI and MAP detected 66.6%, 74.7% and 80.9% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, respectively, at 10% FPR.

The areas under ROC (AUC) curves, detection rates (DRs) at FPRs of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA < 10th, SGA < 5th and SGA < 3rd delivering < 2 weeks following assessment and ≥ 37 weeks' gestation when screening by maternal characteristics, EFW Z-score, UtA-PI, MAP and their combination are given in Tables 2, S3 and S4 and Figure 1.

The DRs, at FPR of 10%, of combined screening by maternal characteristics and history with EFW Z-scores for the prediction of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, delivering < 2 weeks following assessment, were 86.4% (95% CI, 79.6–93.5%; AUC: 0.961 (95% CI, 0.955–0.967)), 86.4% (95% CI, 72.6–94.8%; AUC: 0.969 (95% CI, 0.964–0.974)) and 90.0% (95% CI, 73.5–97.9%; AUC: 0.982 (95% CI, 0.978–0.985)), respectively. The respective values for SGA delivering ≥ 37 weeks, were 66.1% (95% CI, 62.0–70.1%; AUC: 0.887 (95% CI, 0.878–0.896)), 71.4% (95% CI, 65.1–77.1%; AUC: 0.908 (95% CI, 0.900–0.916)) and 79.2% (95% CI, 71.2–85.8%; AUC: 0.929 (95% CI, 0.922–0.936)).

In combined screening by maternal characteristics and history with EFW Z-scores, UtA-PI and MAP at 35–37 weeks' gestation, the DRs, at FPR of 10%, of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, delivering < 2 weeks following assessment were 90.1% (95% CI, 81.5–95.6%; AUC: 0.963 (95% CI, 0.957–0.968)), 86.4% (95% CI, 72.6–94.8%; AUC: 0.972 (95% CI, 0.967–0.976)) and 90.0% (95% CI, 73.5–97.9%; AUC: 0.985 (95% CI, 0.981–0.988)), respectively. The respective values for SGA delivering ≥ 37 weeks were 66.1% (95% CI, 62.0–70.1%; AUC: 0.888 (95% CI, 0.879–0.897)), 73.9% (95% CI, 67.8–79.4%; AUC: 0.910 (95% CI, 0.902–0.917)) and 80.0% (95% CI, 72.1–86.5%; AUC: 0.929 (95% CI, 0.921–0.936)).

DISCUSSION

Main findings of the study

The findings of the study demonstrate that, in women who deliver SGA neonates in the absence of PE, UtA-PI and MAP at 35–37 weeks' gestation are increased and EFW is reduced, compared to women with a normal pregnancy outcome. The deviation from normal for UtA-PI is inversely related to the severity of the disease, reflected in the gestational age at delivery and the birth-weight Z-score.

Combined screening by maternal factors, EFW Z-score, UtA-PI and MAP at 35–37 weeks, predicted 90%, 86% and 90% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, at FPR of 10%, delivering < 2 weeks following assessment and the respective values for SGA delivering ≥ 37 weeks were 66%, 74% and 80%. The addition of UtA-PI and MAP at 35–37 weeks does not improve the performance of screening for delivery of SGA neonates achieved by combined testing using maternal factors and fetal biometry alone.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are, first, examination of a population of pregnant women attending for routine assessment of fetal growth and wellbeing at 35–37 weeks' gestation and, second, use of Bayes' theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry, UtA-PI and MAP 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 results of fetal biometry at the 35–37-week scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring of the cases of suspected SGA and, consequently, the performance of screening, particularly those delivering within 2 weeks of assessment, would be positively biased.

Comparison with findings from previous studies

Previous studies examining pregnancies with SGA fetuses in the third trimester reported that the outcome was worse in cases with Doppler evidence of increased, rather than normal, impedance to flow in the UtAs[17,18]. A screening study involving 1848 singleton pregnancies at 30–32 weeks' gestation reported that UtA-PI improved the prediction of SGA neonates provided by fetal biometry alone, with reduction in FPR from 27% to 16%, with the same DR of about 71%[19]. In our screening study of 30 849 singleton pregnancies at 30–34 weeks' gestation, combined screening by maternal factors, fetal biometry, UtA-PI and MAP predicted 91% and 60% of SGA < 5th neonates delivering < 5 and ≥ 5 weeks following assessment, respectively, at FPR of 10%[6].

Implications for clinical practice

In the proposed new pyramid of pregnancy care[20], an integrated clinical assessment at 11–13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high risk of developing PE and/or SGA[21,22] and, through pharmacological intervention, reduce the prevalence of these complications[23,24].

The objective of subsequent visits, at around 22 and 32 or 36 weeks' gestation, are to identify the high-risk group and, through close monitoring of such pregnancies, minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery. We have proposed recently that all women should be offered

Table 2 Performance of screening for small-for-gestational-age (SGA) neonates, with birth weight < 10th, < 5th and < 3rd percentile, delivering within 2 weeks of assessment or ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation

		DR (%)		*FPR (%)*		
Screening test	*AUC*	*FPR = 5%*	*FPR = 10%*	*DR = 100%*	*DR = 90%*	*DR = 80%*
Delivery within 2 weeks						
SGA < 10th percentile						
Maternal factors	0.744 (0.731–0.756)	25.9 (16.8–36.9)	40.7 (29.9–52.2)	79.8 (78.6–80.9)	64.4 (63.0–65.7)	48.6 (47.2–50.1)
Maternal factors plus EFW	0.961 (0.955–0.967)	77.8 (67.2–86.3)	86.4 (79.6–93.5)	53.4 (51.9–54.8)	11.6 (10.7–12.6)	5.6 (5.0–6.3)
Maternal factors and EFW plus UtA-PI and MAP	0.963 (0.957–0.968)	76.5 (65.8–85.2)	90.1 (81.5–95.6)	51.2 (49.8–52.7)	9.3 (8.4–10.1)	5.7 (5.0–6.4)
SGA < 5th percentile						
Maternal factors	0.800 (0.788–0.811)	34.1 (20.5–49.9)	50.0 (34.6–65.4)	73.5 (72.2–74.7)	57.6 (56.2–59.0)	44.7 (43.3–46.1)
Maternal factors plus EFW	0.969 (0.964–0.974)	84.1 (69.9–93.4)	86.4 (72.6–94.8)	34.0 (32.7–35.4)	13.4 (12.5–14.4)	3.6 (3.1–4.1)
Maternal factors and EFW plus UtA-PI and MAP	0.972 (0.967–0.976)	84.1 (69.9–93.4)	86.4 (72.6–94.8)	34.3 (32.9–35.6)	12.0 (11.1–12.9)	3.0 (2.6–3.6)
SGA < 3rd percentile						
Maternal factors	0.813 (0.802–0.824)	36.7 (19.9–56.1)	50.0 (32.9–67.1)	60.2 (58.8–61.6)	52.8 (51.4–54.2)	38.1 (37.7–39.4)
Maternal factors plus EFW	0.982 (0.978–0.985)	90.0 (73.5–97.9)	90.0 (73.5–97.9)	16.7 (15.6–17.7)	3.6 (3.1–4.1)	0.9 (0.7–1.2)
Maternal factors and EFW plus UtA-PI and MAP	0.985 (0.981–0.988)	90.0 (73.5–97.9)	90.0 (73.5–97.9)	13.1 (12.2–14.1)	2.8 (2.4–3.3)	0.6 (0.4–0.9)
Delivery ≥ 37 weeks						
SGA < 10th percentile						
Maternal factors	0.712 (0.700–0.725)	20.1 (16.8–23.7)	33.2 (29.2–37.3)	98.6 (98.2–98.9)	69.9 (68.5–71.2)	53.5 (52.0–54.9)
Maternal factors plus EFW	0.887 (0.878–0.896)	47.3 (43.1–51.6)	66.1 (62.0–70.1)	82.5 (81.3–83.6)	32.6 (31.3–34.0)	20.2 (19.0–21.4)
Maternal factors and EFW plus UtA-PI and MAP	0.888 (0.879–0.897)	48.6 (44.3–52.9)	66.1 (62.0–70.1)	84.8 (83.7–85.8)	31.4 (30.1–32.8)	19.1 (18.0–20.3)
SGA < 5th percentile						
Maternal factors	0.741 (0.729–0.753)	23.5 (18.2–29.5)	38.0 (31.8–44.6)	98.1 (97.7–98.5)	68.6 (67.3–69.9)	48.8 (47.4–50.2)
Maternal factors plus EFW	0.908 (0.900–0.916)	54.3 (47.7–60.8)	71.4 (65.1–77.1)	83.5 (82.4–84.5)	24.6 (23.4–25.8)	13.4 (12.5–14.4)
Maternal factors and EFW plus UtA-PI and MAP	0.910 (0.902–0.917)	55.6 (48.9–62.0)	73.9 (67.8–79.4)	83.2 (82.1–84.2)	25.2 (24.0–26.5)	14.1 (13.1–15.1)
SGA < 3rd percentile						
Maternal factors	0.775 (0.764–0.787)	26.2 (18.8–34.6)	39.2 (30.8–48.2)	90.8 (90.0–91.6)	53.4 (52.0–54.8)	41.4 (40.0–42.8)
Maternal factors plus EFW	0.929 (0.922–0.936)	64.6 (55.5–71.5)	79.2 (71.2–85.8)	69.1 (67.8–70.4)	17.8 (16.7–18.9)	10.1 (9.3–11.0)
Maternal factors and EFW plus UtA-PI and MAP	0.929 (0.921–0.936)	64.6 (55.8–72.8)	80.0 (72.1–86.5)	70.2 (68.9–71.4)	20.1 (19.0–21.3)	9.9 (9.0–10.7)

Values in parentheses are 95% CIs. AUC, area under receiver–operating characteristics curve; DR, detection rate; FPR, false-positive rate.

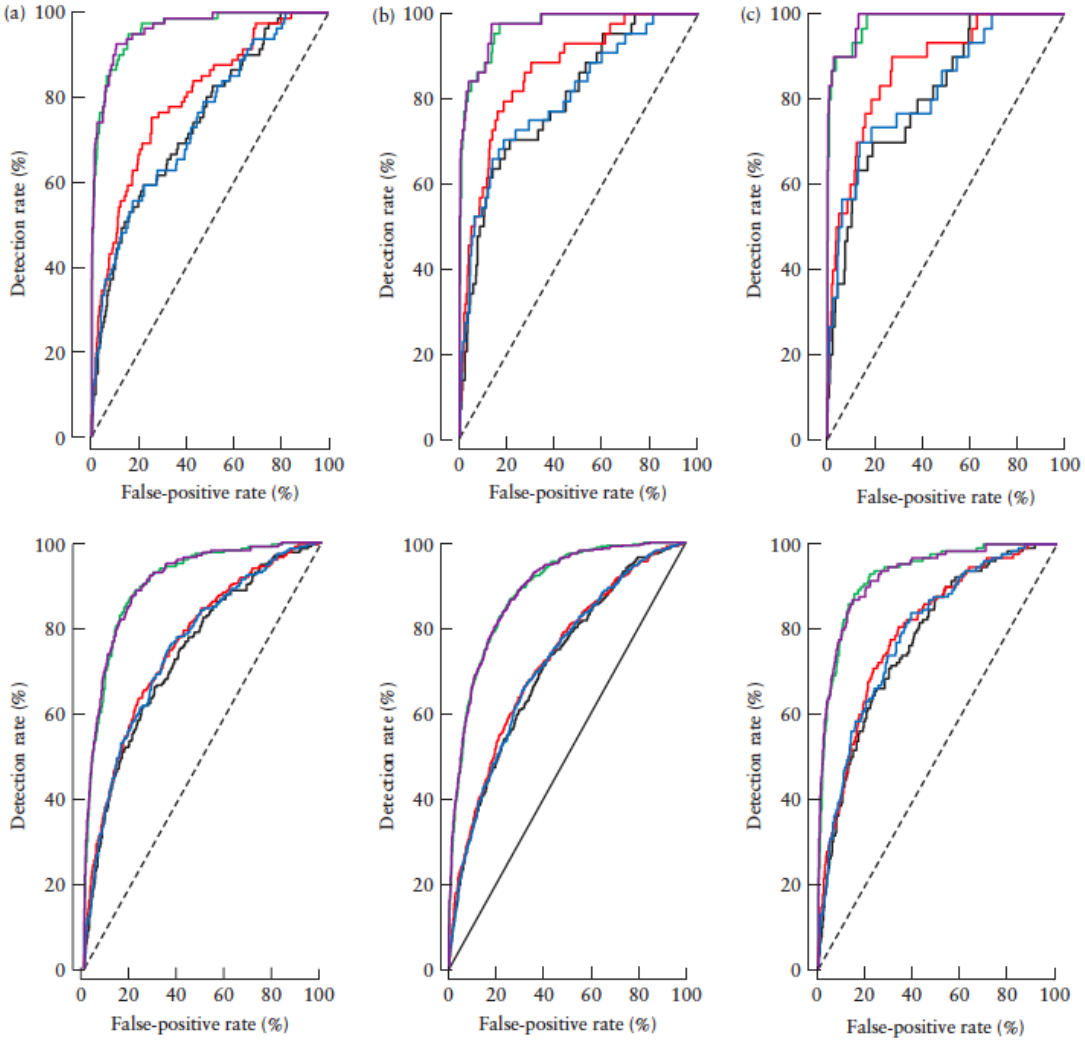

Figure 1 Receiver–operating characteristics curves of maternal factors (——) and maternal factors with uterine artery pulsatility index (——), mean arterial pressure (——), estimated fetal weight Z-score (——) and their combination (——), at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) or < 3rd (c) percentile, delivering < 2 weeks following assessment (top) or ≥ 37 weeks' gestation (bottom).

a third-trimester scan for assessment of fetal growth and wellbeing and that the timing of such a scan, at 32 or 36 weeks, should be contingent on the results of the assessment made at around 22 weeks[4,5]. On the basis of the results from this study, screening for SGA at 36 weeks does not benefit from measurement of UtA-PI and MAP.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Log_{10} uterine artery pulsatility index (UtA-PI) (a,b) and log_{10} mean arterial pressure (MAP) (c,d) multiples of median according to assessment-to-delivery interval (a,c) and birth-weight *Z*-score (b,d) in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile, plotted on the 50th (solid line), 90th and 95th (dashed line) percentile of the appropriate normal range.

Table S1 Uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation in pregnancies that delivered small-for-gestational-age (SGA) neonates with birth weight < 5th percentile, in the absence of pre-eclampsia, and in unaffected pregnancies

Table S2 Fitted regression models with maternal characteristics and history, estimated fetal weight (EFW) *Z*-score, uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation for the prediction of small-for-gestational-age neonates with birth weight < 5th percentile, in the absence of pre-eclampsia

Table S3 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation

Table S4 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile, delivering ≥ 37 weeks, in the absence of pre-eclampsia, using maternal factors, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 35–37 weeks' gestation

Appendix A.3. Paper **"Prediction of small-for-gestational-age neonates: screening by placental growth factor and soluble fms-like tyrosine kinase-1 at 35-37 weeks"**, published in Ultrasound in Obstetrics & Gynecology, August 2015.

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Prediction of small-for-gestational-age neonates: screening by placental growth factor and soluble fms-like tyrosine kinase-1 at 35–37 weeks

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KEYWORDS: late third-trimester screening; placental growth factor; pre-eclampsia; pyramid of antenatal care; small-for-gestational age; soluble fms-like tyrosine kinase-1

ABSTRACT

Objective *To investigate the potential value of maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation in the prediction of delivery of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE).*

Methods *This was a screening study in singleton pregnancies at 35–37 weeks, including 158 that delivered SGA neonates with birth weight < 5th percentile and 3701 cases unaffected by SGA, PE or gestational hypertension. Multivariable logistic regression analysis was used to determine if measuring serum levels of PlGF and sFlt-1 improved the prediction of delivery 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 *Compared to the normal group, the median PlGF multiples of the median (MoM) was significantly lower and the median sFlt-1 MoM was significantly higher in the SGA group. Combined screening by maternal factors and EFW at 35–37 weeks predicted, at 10% false-positive rate (FPR), 90%, 92% and 94% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, respectively, delivering < 2 weeks following assessment; the respective values for SGA delivering ≥ 37 weeks were 66%, 73% and 80%. When PlGF and sFlt-1 were added to a model that combines maternal factors and EFW, sFlt-1 did not remain as a significant independent predictor of SGA < 5th. Combined screening by maternal factors, EFW and serum PlGF, predicted, at a 10% FPR, 88%, 96% and 94% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, respectively, delivering < 2 weeks following assessment and the respective values for SGA delivering ≥ 37 weeks were 64%, 75% and 80%.*

Conclusion *sFlt-1 does not provide significant independent prediction of SGA, in the absence of PE, in addition to combined testing by maternal factors and fetal biometry at 35–37 weeks; whilst the addition of PlGF alone marginally improves the performance of screening.* Copyright © 2015 ISUOG. *Published by John Wiley & Sons Ltd.*

INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified prenatally, as close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken[1]. The traditional approach of identifying pregnancies with SGA fetuses is maternal abdominal palpation and serial measurements of symphysis–fundal height, but the detection rate (DR) of this approach is less than 30%[2,3]. A higher performance in screening for SGA is achieved by a combination of maternal characteristics and medical history (maternal factors) with estimated fetal weight (EFW) from ultrasonographic measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL). We have reported recently that such combined screening at 35–37 weeks predicted, at a 10% false-positive rate (FPR), 66%, 70% and 77% of SGA neonates with respective birth weight < 10th, < 5th and < 3rd percentiles delivering ≥ 37 weeks, in the absence of pre-eclampsia (PE)[4]. The performance of screening was better for prediction of SGA delivering within 2 weeks of assessment, with respective DRs of 88%, 89% and 92%[4].

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Placental growth factor (PlGF) is a member of the vascular endothelial growth factor family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries[5–7]. Soluble fms-like tyrosine kinase-1 (sFlt-1) is a circulating antiangiogenic protein implicated in the pathogenesis of PE; the concentration of sFlt-1 is increased in the placenta and serum of women with PE and administration of exogenous sFlt-1 to pregnant rats induces hypertension, proteinuria and glomerular endotheliosis[8]. 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[9–14].

The objective of this study, in singleton pregnancies undergoing routine antenatal assessment at 35–37 weeks' gestation, was to investigate the potential value of measuring serum PlGF and sFlt-1 in improving the prediction of delivery of SGA neonates, in the absence of PE, achieved by the combination of maternal factors and EFW.

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 King's College Hospital, London, and Medway Maritime Hospital, Kent, between February 2014 and December 2014. This visit, which is held at 35 + 0 to 37 + 6 weeks' gestation, included the recording of maternal characteristics and medical history and EFW[15] from transabdominal ultrasound measurement of fetal HC, AC and FL[16] and measurement of uterine artery pulsatility index, mean arterial pressure and maternal serum metabolites. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal HC at 19–24 weeks[16,17].

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. This study is part of a research program on the late third-trimester prediction of PE and/or SGA. In this publication, we present the results on combined screening with maternal factors and biochemical markers in the prediction of SGA in the absence of PE. The pregnancies included in the study all resulted in live birth or stillbirth of phenotypically normal babies.

Sample analyses

Serum levels of PlGF and sFlt-1 were measured in parallel, using an automated Electro ChemiLuminescence immunoassay system (Cobas e411, Roche Diagnostics, Penzberg, Germany). The interassay coefficients of variation for the low and high concentrations were 5.4% and 3.0% for PlGF, and 3.0% and 3.2% for sFlt-1, respectively. The cobas e411 analyzer assay covers a measurement range from 3 to 10 000 pg/mL for PlGF and from 10 to 85 000 pg/mL for sFlt-1.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), and obstetric history including parity (parous/nulliparous if no previous pregnancies ≥ 24 weeks' gestation), previous pregnancy with PE (yes/no), previous pregnancy with SGA (yes/no) and the time interval between the last delivery and conception of the current pregnancy in years. The maternal weight and height were also measured.

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. The newborn was considered to be SGA if the birth weight was < 5th percentile after correcting for gestational age at delivery (SGA < 5th)[18]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[19]. 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.

Statistical analysis

The observed measurements of EFW were expressed as *Z*-scores, corrected for gestational age[18]. The values of 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 $\log_{10}$ transformed value[20,21]. Mann–Whitney *U*-test was used to compare the median MoM values of PlGF and sFlt-1 between the outcome groups. Regression analysis was used to determine the significance of association between $\log_{10}$MoM of PlGF and sFlt-1 with assessment-to-delivery interval and birth-weight *Z*-score.

The *a-priori* risk for SGA < 5th was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history, as described previously[4]. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a-priori* risk), EFW *Z*-score, $\log_{10}$MoM PlGF and $\log_{10}$MoM sFlt-1 had a significant contribution in predicting SGA < 5th. The performance

Table 1 Characteristics of the study population of women with a singleton pregnancy with normal outcome or with a small-for-gestational-age (SGA) neonate, in the absence of pre-eclampsia (PE)

Characteristic	*Normal (n = 3701)*	*SGA without PE (n = 158)*	P
Maternal age (years)	31.6 (26.9–35.2)	29.9 (24.2–35.3)	0.012
Maternal weight (kg)	78.8 (70.9–89.4)	72.7 (63.2–82.7)	< 0.0001
Maternal height (cm)	164 (160–168)	161 (158–165)	< 0.0001
GA at examination (weeks)	36.1 (36.0–36.4)	36.3 (36.0–36.4)	0.594
Racial origin			
Caucasian	2762 (74.6)	95 (60.1)	< 0.0001
Afro-Caribbean	615 (16.6)	38 (24.1)	0.022
South Asian	132 (3.6)	16 (10.1)	0.0003
East Asian	82 (2.2)	3 (1.9)	> 0.999
Mixed	110 (3.0)	6 (3.8)	0.476
Obstetric history			
Nulliparous	1789 (48.3)	94 (59.5)	0.007
Parous with no prior PE and SGA	1761 (47.6)	43 (27.2)	< 0.0001
Parous with prior PE, no SGA	59 (1.6)	0 (0.0)	0.175
Parous with prior SGA, no PE	86 (2.3)	20 (12.7)	< 0.0001
Parous with prior SGA and PE	6 (0.2)	1 (0.6)	0.254
Interpregnancy interval (years)	3.1 (2.1–5.0)	3.9 (2.1–6.2)	0.026
Cigarette smoker	325 (8.8)	37 (23.4)	< 0.0001
Mode of conception			
Spontaneous	3599 (97.2)	151 (95.6)	0.214
Ovulation drugs	15 (0.4)	1 (0.6)	0.488
In-vitro fertilization	87 (2.4)	6 (3.8)	0.279
Chronic hypertension	49 (1.3)	1 (0.6)	0.722
Pre-existing diabetes mellitus	43 (1.1)	1 (0.6)	> 0.999
Type 1	20 (0.5)	1 (0.6)	0.585
Type 2	23 (0.6)	0 (0.0)	> 0.999
SLE or APS	11 (0.3)	0 (0.0)	> 0.999
GA at delivery (weeks)	40.0 (39.1–40.9)	39.6 (36.4–38.8)	0.002
Birth weight (g)	3450 (3160–3760)	2587 (2350–2755)	< 0.0001
Birth-weight percentile	51.6 (27.4–76.2)	2.8 (1.2–3.7)	< 0.0001

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus.

of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight < 10^{th} percentile (SGA < 10^{th}) and < 3^{rd} percentile (SGA < 3^{rd}) delivering < 2 weeks following assessment and delivering ≥ 37 weeks' gestation.

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

RESULTS

The characteristics of the study population of 3859 pregnancies, including 158 (4.1%) delivering SGA < 5^{th} neonates in the absence of PE, are presented in Table 1.

Normal pregnancy outcome

In the unaffected pregnancies with birth weight ≥ 5^{th} percentile, the mean ± SD and 5^{th} and 10^{th} percentiles of $\log_{10}$MoM PlGF were −0.019 ± 0.343, −0.588 and −0.470, respectively. The mean ± SD and 90^{th} and 95^{th} percentiles of $\log_{10}$MoM sFlt-1 were −0.081 ± 0.210, 0.199 and 0.285, respectively.

There was a significant inverse association between $\log_{10}$MoM values of PlGF and sFlt-1 ($r = -0.400$, $P < 0.0001$). There was a significant positive association between $\log_{10}$MoM PlGF with assessment-to-delivery interval ($r = 0.152$, $P < 0.0001$) and birth-weight Z-score ($r = 0.179$, $P < 0.0001$). There was a significant inverse association between $\log_{10}$MoM sFlt-1 with assessment-to-delivery interval ($r = -0.168$, $P < 0.0001$) and birth-weight Z-score ($r = -0.042$, $P = 0.011$).

Small-for-gestational age

In the SGA < 5^{th} group, compared to the normal group, the median MoM value of PlGF at 35–37 weeks was significantly lower and the median MoM value of sFlt-1 was significantly higher (Table S1). There was a significant inverse association between $\log_{10}$MoM values of PlGF and sFlt-1 ($r = -0.375$, $P < 0.0001$). There was a significant positive association between $\log_{10}$MoM PlGF with assessment-to-delivery interval ($r = 0.300$, $P < 0.0001$; Figure S1a) and birth-weight Z-score ($r = 0.208$, $P = 0.009$). There was a significant inverse association between $\log_{10}$MoM sFlt-1 with assessment-to-delivery interval ($r = -0.260$, $P = 0.001$;

Figure S1b) but not birth-weight Z-score ($r = -0.085$, $P = 0.287$).

Multivariable logistic regression analysis demonstrated that, in the prediction of SGA < 5th, there were significant contributions from maternal characteristics and history, EFW Z-score and PlGF or sFlt-1 (Table S2). When PlGF and sFlt-1 were added to screening by maternal factors and a model that combines maternal factors and EFW Z-score, sFlt-1 ($P = 0.509$; $P = 0.921$) did not remain as a significant independent predictor of SGA < 5th. Combined screening by maternal factors with EFW Z-scores and PlGF detected 64.1%, 75.3% and 80.2% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, respectively, at a 10% FPR.

The areas under the ROC (AUC), the detection rates (DRs) at FPRs of 5% and 10% and FPRs for DRs of 100%, 90% and 80% of SGA < 10th, < 5th and < 3rd delivering < 2 weeks following assessment and ≥ 37 weeks' gestation when screening by maternal characteristics, EFW Z-score, PlGF and sFlt-1 are given in Tables 2 and S3 and Figures 1 and S2.

The DRs, at a FPR of 10%, of combined screening by maternal factors with EFW for the prediction of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles, delivering < 2 weeks following assessment, were 89.8% (95% CI, 77.8–96.6; AUC: 0.965 (95% CI, 0.958–0.971)), 92.0% (95% CI, 74.0–99.0; AUC: 0.977 (95% CI, 0.972–0.982)) and 94.4% (95% CI, 72.7–99.9; AUC: 0.990 (95% CI, 0.987–0.993)), respectively. The respective values for SGA delivering ≥ 37 weeks, were 66.0% (95% CI, 60.9–70.7; AUC: 0.888 (95% CI, 0.878–0.898)), 72.7% (95% CI, 65.0–79.6; AUC: 0.918 (95% CI, 0.909–0.926)) and 79.8% (95% CI, 69.6–87.7; AUC: 0.942 (95% CI, 0.934–0.949)).

In combined screening by maternal factors, EFW and serum PlGF at 35–37 weeks' gestation, the DRs, at a FPR of 10%, of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles delivering < 2 weeks following assessment were 87.8% (95% CI, 75.2–95.4; AUC: 0.969 (95% CI, 0.963–0.974)), 96.0% (95% CI, 79.6–99.9; AUC: 0.987 (95% CI, 0.983–0.991)) and 94.4% (95% CI, 72.7–99.9; AUC: 0.991 (95% CI, 0.988–0.994)). The respective values for SGA delivering ≥ 37 weeks, were 64.1% (95% CI, 59.0–68.9; AUC: 0.893 (95% CI, 0.883–0.903)), 74.7% (95% CI, 67.0–81.0; AUC: 0.922 (95% CI, 0.913–0.930)) and 79.8% (95% CI, 69.6–87.7; AUC: 0.943 (95% CI, 0.935–0.950)).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that, in pregnancies that deliver SGA neonates in the absence of PE, maternal serum PlGF is reduced and sFlt-1 is increased at 35–37 weeks' gestation. The alterations in serum biochemistry are more pronounced in those with severe disease reflected as a lower birth weight (3rd *vs* 10th percentile) and delivery within 2 weeks of assessment.

Combined screening by maternal factors and EFW at 35–37 weeks predicted, at a 10% FPR, 90%, 92% and 94% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles delivering < 2 weeks following assessment; the respective values for SGA delivering ≥ 37 weeks were 66%, 73% and 80%. Combined screening by maternal factors, EFW and serum PlGF predicted, at a 10% FPR, 88%, 96% and 94% of SGA neonates with birth weight < 10th, < 5th and < 3rd percentiles delivering < 2 weeks of assessment and the respective values for SGA delivering ≥ 37 weeks were 64%, 75% and 80%. Consequently, addition of serum PlGF at 35–37 weeks only marginally improves the performance of screening for delivery of SGA neonates, in the absence of PE, achieved by combined testing using maternal factors and fetal biometry alone.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are, first, examination of a population of pregnant women attending for routine assessment of fetal growth and wellbeing at 35–37 weeks' gestation and, second, use of Bayes' theorem to combine the prior risk from maternal characteristics and medical history with fetal biometry and maternal serum biochemistry 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 results of fetal biometry at the 35–37 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring of cases of suspected SGA and, consequently, the performance of screening, particularly those delivering within 2 weeks of assessment, would be positively biased.

Comparison with findings from previous studies

Most previous reports on maternal serum PlGF and sFlt-1 in pregnancies with SGA fetuses/neonates were based on case–control studies involving a small number of affected pregnancies[9–14]. Such studies compared the median serum concentration of the angiogenic and antiangiogenic factors or their ratio in affected and unaffected pregnancies, or the percentage of cases above or below certain concentration cut-offs. Our study involved screening of all pregnancies attending for a routine scan at 35–37 weeks and assessed the value of serum PlGF and sFlt-1 both individually and in combination with maternal factors and fetal biometry in screening for SGA delivering at term in the absence of PE.

The advantage of using Bayes' theorem to combine the prior risk from maternal characteristics and medical history, fetal biometry and biomarkers is that individual patient risks can be estimated for any predefined severity

Table 2 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile delivering ≥ 37 weeks' gestation, in the absence of pre-eclampsia, using maternal characteristics and history, estimated fetal weight (EFW), placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation

		DR (%)		*FPR (%)*		
Screening test	*AUC*	*FPR = 5%*	*FPR = 10%*	*DR = 100%*	*DR = 90%*	*DR = 80%*
SGA < 10th percentile						
Maternal factors	0.730 (0.716–0.744)	21.3 (17.2–25.8)	34.6 (29.8–39.6)	99.9 (99.8–99.9)	68.0 (66.4–69.5)	48.7 (47.0–50.4)
Maternal factors plus:						
EFW Z-score	0.888 (0.878–0.898)	47.3 (42.2–52.8)	66.0 (60.9–70.7)	82.2 (80.9–83.5)	32.2 (30.7–33.8)	19.8 (18.5–21.2)
PlGF	0.762 (0.748–0.775)	23.1 (19.0–27.7)	35.9 (31.1–41.0)	99.8 (99.6–99.9)	59.2 (57.6–60.9)	44.0 (42.4–45.7)
sFlt-1	0.731 (0.717–0.745)	20.0 (16.0–24.3)	33.0 (28.2–38.0)	99.6 (99.3–99.8)	67.2 (65.7–68.8)	47.6 (45.9–49.3)
Maternal factors and EFW plus:						
PlGF	0.893 (0.883–0.903)	47.9 (42.7–53.1)	64.1 (59.0–68.9)	73.7 (72.2–75.2)	29.8 (28.3–31.4)	18.0 (16.7–19.3)
sFlt-1	0.886 (0.875–0.896)	48.1 (43.0–53.3)	63.8 (58.7–68.7)	81.9 (80.6–83.2)	32.5 (30.9–34.1)	20.4 (19.1–21.8)
SGA < 5th percentile						
Maternal factors	0.769 (0.756–0.782)	23.4 (16.9–30.9)	40.9 (33.1–49.1)	97.9 (97.3–98.3)	58.2 (56.6–59.8)	41.4 (39.8–43.0)
Maternal factors plus:						
EFW Z-score	0.918 (0.909–0.926)	53.9 (45.7–61.9)	72.7 (65.0–79.6)	79.1 (77.7–80.4)	19.9 (18.7–21.3)	12.2 (11.2–13.3)
PlGF	0.807 (0.794–0.819)	26.6 (19.8–34.3)	44.2 (36.2–52.4)	98.6 (98.2–98.9)	51.5 (49.8–53.1)	32.5 (31.0–34.0)
sFlt-1	0.769 (0.756–0.783)	25.3 (18.7–33.0)	38.3 (30.6–46.5)	96.1 (95.4–96.7)	60.5 (59.0–62.1)	42.9 (41.3–44.5)
Maternal factors and EFW plus:						
PlGF	0.922 (0.913–0.930)	56.5 (48.3–64.5)	74.7 (67.0–81.0)	75.3 (73.9–76.7)	21.4 (20.1–22.8)	13.8 (12.7–15.0)
sFlt-1	0.918 (0.909–0.927)	53.9 (45.7–61.9)	74.7 (67.0–81.0)	81.0 (79.7–82.3)	20.4 (19.1–21.7)	13.1 (12.0–14.2)
SGA < 3rd percentile						
Maternal factors	0.806 (0.793–0.818)	28.6 (19.2–39.5)	46.4 (35.5–57.6)	90.2 (89.2–91.1)	47.3 (45.6–48.9)	38.0 (36.4–39.6)
Maternal factors plus:						
EFW Z-score	0.942 (0.934–0.949)	63.1 (51.9–73.4)	79.8 (69.6–87.7)	42.9 (41.3–44.5)	13.9 (12.8–15.1)	10.9 (9.9–11.9)
PlGF	0.828 (0.816–0.840)	32.1 (22.4–43.2)	53.6 (42.4–64.5)	84.8 (83.6–86.0)	51.5 (49.9–53.1)	29.9 (28.4–31.4)
sFlt-1	0.803 (0.790–0.816)	32.1 (22.4–42.0)	44.1 (33.2–55.3)	91.8 (90.9–92.7)	49.4 (47.8–51.0)	40.1 (38.6–41.8)
Maternal factors and EFW plus:						
PlGF	0.943 (0.935–0.950)	65.5 (54.3–75.5)	79.8 (69.6–87.7)	41.1 (39.6–42.8)	16.1 (15.0–17.4)	11.7 (10.7–12.8)
sFlt-1	0.942 (0.934–0.949)	60.7 (49.5–71.2)	79.8 (69.6–87.7)	40.8 (39.2–42.4)	16.2 (15.0–17.4)	10.8 (9.9–11.9)

Values in parentheses are 95% CIs. AUC, area under receiver–operating characteristics curve; DR, detection rate; FPR, false-positive rate.

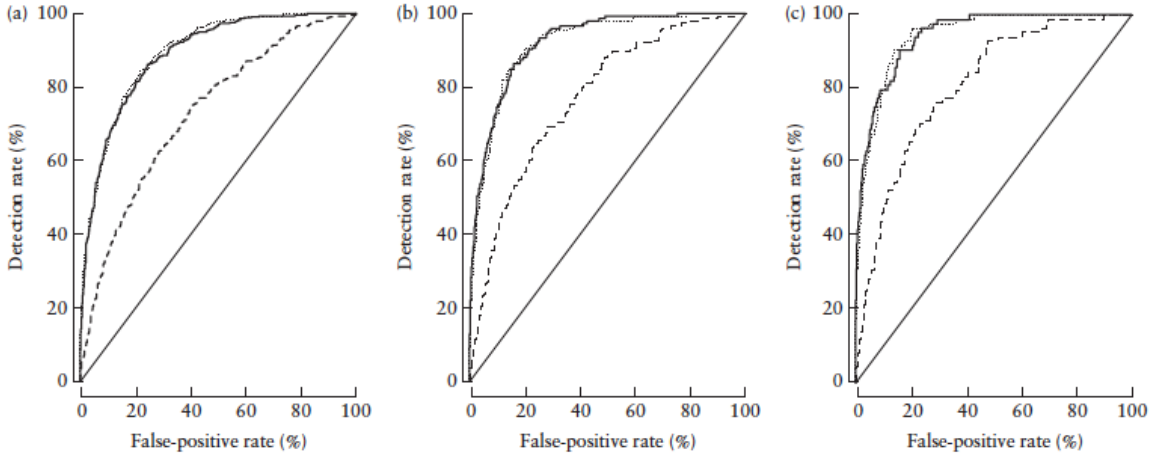

Figure 1 Receiver–operating characteristics curves of maternal factors (- - - -), maternal factors with estimated fetal weight (EFW) (·····), maternal factors with EFW and placental growth factor (——) at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) and < 3rd (c) percentile, delivering ≥ 37 weeks' gestation.

of SGA and any interval from time of testing to delivery. This is an essential first step for the establishment of patient management protocols.

Implications for clinical practice

In the proposed new pyramid of pregnancy care[22], an integrated clinical assessment at 11–13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high risk of developing PE and/or SGA[23,24] and, through pharmacological intervention, reduce the prevalence of these complications[25,26].

The objective of subsequent visits, at around 22 and 32 or 36 weeks' gestation, are to identify the high-risk group and, through close monitoring of such pregnancies, minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery. We have proposed recently that all women should be offered a third-trimester scan for assessment of fetal growth and wellbeing and that the timing of this scan, at 32 and/or 36 weeks, should be contingent on the results of assessment at around 22 weeks[27,28]. On the basis of results from this study, if screening for SGA at 36 weeks includes a combination of maternal factors, fetal biometry and serum PlGF, potentially 80%, 90% and 100% of cases of SGA < 5th delivering ≥ 37 weeks could be detected at respective FPRs of 14%, 21% and 75%. The subsequent management of the screen-positive group, with the objective of reducing perinatal death and disability, remains to be determined.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Log_{10} placental growth factor (a) and log_{10} soluble fms-like tyrosine kinase-1 (b) multiples of the median (MoM) according to assessment-to-delivery interval in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile, plotted on the 50th (solid line) and 10th (dashed line) percentile of the normal range

Figure S2 Receiver–operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (EFW) (blue line), maternal factors with EFW and placental growth factor (red line) at 35–37 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) and < 3rd (c) percentile, delivering within 2 weeks of assessment.

Table S1 Placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation in pregnancies that delivered small-for-gestational-age (SGA) neonates with birth weight < 5th percentile, in the absence of pre-eclampsia, and in unaffected pregnancies

Table S2 Fitted regression models with maternal characteristics and history (maternal factors), estimated fetal weight (EFW) Z-score, placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation for the prediction of small-for-gestational-age neonates with birth weight < 5th percentile, in the absence of pre-eclampsia

Table S3 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile delivering within 2 weeks of assessment, in the absence of pre-eclampsia, using maternal characteristics and history, estimated fetal weight (EFW), placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 35–37 weeks' gestation