Competing-risks model for prediction of small-for-gestational-age neonates from maternal characteristics, serum PAPP-A and PlGF at 11-13 weeks' gestation

I. PAPASTEFANOU,[1] D. WRIGHT,[2] M. LOLOS,[1] K. ANAMPOUSI,[1] M. MAMALIS,[1] K. H. NICOLAIDES.[1]

1. Fetal Medicine Research Institute, King's College Hospital, London, UK
2. Institute of Health Research, University of Exeter, Exeter, UK.

Corresponding author
Professor KH Nicolaides,
Fetal Medicine Research Institute, King's College Hospital,
16-20 Windsor Walk, Denmark Hill, London SE5 8BB
email: kypros@fetalmedicine.com

Running Head: New model in screening for small for gestational age neonates.

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What are the novel findings of this work?

The study describes the expansion of a new competing risk model with the addition of pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF), in a prior model according to maternal characteristics and medical history at 11-13 weeks' gestation, for the prediction of small for gestational age (SGA) neonates. The distribution of the biochemical markers depends on both gestational age at delivery and birth weight z - scores, in the same folded plane regression model.

What are the clinical implications of this work?

PlGF is better than PAPP-A in the prediction of all SGA, mainly because it is a better predictor of SGA with preeclampsia; PAPP-A performs equal to PlGF in predicting SGA without preeclampsia. The combination of PAPP-A with PlGF has an incremental value, however the most cost effective policy, in the framework of first trimester screening, is to use only PlGF. A single continuous model may determine an individualized timeline for predicting and managing SGA in the setting of a new inverted pyramid of prenatal care.

ABSTRACT

Objectives: To expand a new competing risks model for small for gestational age (SGA) neonates, by the addition of pregnancy associated plasma protein – A (PAPP-A) and placental growth factor (PlGF). To evaluate and compare PAPP-A and PlGF in predicting SGA.

Methods: This is a prospective observational study in 60,875 women with singleton pregnancies undergoing routine ultrasound examination at 11^{+0} - 13^{+6} weeks' gestation. We fitted a folded plane regression model for the PAPP-A and PlGF likelihoods. A previously developed history model and the likelihoods' models were combined, according to Bayes theorem, to obtain individualized distributions for gestational age at delivery (GA) and birth weight Z score (Z). We assessed the discrimination and calibration of the model. McNemar's test was used to compare the detection rates for SGA with, without or independently of preeclampsia (PE) existence, of different combinations of maternal history, PAPP-A and PlGF, for a fixed false positive rate.

Results: The distributions of PAPP-A and PlGF depend on both GA and Z, in the same continuous likelihood, according to a folded plane regression model. The new approach offers the capability for risk computation for any desired Z and GA cut-offs. PlGF was consistently and significantly better than PAPP-A in predicting SGA, especially in cases with co-existence of PE. These differences were more pronounced for preterm cases with higher severity of smallness. PAPP-A had similar performance independently of the PE occurrence. At a fixed false positive rate of 10%, the combination of maternal history, PlGF and PAPP-A predicted 33.8%, 43.8% and 48.4% of all cases of SGA neonates with birth weight <10^{th} percentile delivered

at ≥37, <37 and <32 weeks' gestation. The respective figures for birth weight <3rd percentile were 38.6%, 48.7% and 51.0%. The new model performed well in terms of risk calibration.

Conclusions: The combination of PAPP-A and PlGF values with maternal characteristics according to Bayes theorem, improves prediction of SGA. PlGF is a better predictor of SGA than PAPP-A, especially when PE is present. The new competing risks model for SGA, can be tailored to each pregnancy and to the relevant clinical requirements.

INTRODUCTION

Smallness at birth is a compounding factor whereby perinatal mortality and morbidity increases and it has been linked to metabolic and cardiovascular consequences in adult life.[1-5] The antenatal identification of small for gestational age (SGA) neonates may improve their outcome [6-8] There is considerable controversy as to the best way to recognize pregnancies at high risk for SGA, so that appropriate care is offered.[9] The traditional approach is to use scoring systems, as the one suggested by the Royal College of Obstetricians and Gynecologists (RCOG).[10] This method is simple to implement, but it does not provide patient-specific risks and the performance of screening is poor. Another approach is to use logistic regression models that produce individual patient specific risks for SGA, rather than categorize women into high- and low-risk groups.[11-14] The weaknesses of this method are: first, the conversion of a continuous outcome such as SGA to a binary one, as a prerequisite for logistic regression, and second, the inability to develop further a single model by adding biomarkers. Therefore, this approach is disadvantageous to altering SGA definition and/or adding a new biomarker, because the whole model must be refitted. The widespread application of logistic regression has also led to a fallible perception that SGA is a multiple-outcome disease.

We have developed a new method for SGA prediction, analogous to the competing risks model in the assessment of risks for preeclampsia (PE).[15-19] The first step of this novel methodology is a competing risk approach, based on the joint distribution of birth weight Z score (Z) and gestational age at delivery (GA), according to maternal factors and the second step is the process of updating this distribution by including the likelihood of biomarkers according to Bayes theorem.[20,21] The new model has clinical merits and it is supported by new methodological concepts: first, the severity of smallness and the burden of prematurity the two dimensions of SGA that define its outcome,[22-25] are expressed continuously and jointly in the same model; second, prediction of SGA for any chosen cut-offs is feasible and SGA is regarded as a two dimensional spectrum disorder rather than a fragmented disease;[20,21] third, the capacity of adding more biomarkers in the same model according to Bayes theorem is feasible; and fourth, the new model is superior and more stable compared to the RCOG green top guideline and the logistic regression models, a fact that has been proven in previous studies, through a process of vigorous internal validation.[20,21]

Two recent studies demonstrated that PlGF is better than PAPP-A in predicting PE and inferior to PAPP-A in screening for chromosomal abnormalities.[26,27] PlGF replacement by PAPP-A improves the early detection of PE and may sustain the detection rate for trisomies, with a small parallel increase in the false positive rate. [26,27] The clinical question that arises is whether the same pattern for the biochemical markers is evident in SGA prediction. In this study, we aim to expand further our new method for SGA prediction by combining the first trimester biochemical markers with

a prior history model in Bayesian framework. We compared PAPP-A and PlGF in predicting SGA with, without or independently of preeclampsia (PE) occurrence.

METHODS

Study population and design

The dataset for this study was derived from prospective screening for adverse obstetric outcomes in women attending for their routine first-trimester hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK. In this visit, at 11^{+0}- 13^{+6} weeks' gestation, we recorded maternal characteristics and medical history, we performed combined screening for aneuploidies[28] and we measured serum concentration of PLGF and PAPP-A. Serum PAPP-A was measured by DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, USA) during the whole study period in both hospitals. Serum PLGF was measured by DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, USA) between March 2006 and July 2012 and between August 2013 and March 2017 at King's College Hospital and between April 2010 and July 2012 and between August 2013 and March 2017 at Medway Maritime Hospital, it was also measured by Cobas e411 (Roche Diagnostics, Penzberg, Germany) between August 2012 and July 2012 in both hospitals. Gestational age was determined from the fetal crown-rump length.[29] Participants gave written informed consent to take part in the study, which was approved by the NHS Research Ethics Committee. The study population did not include women that participated in the ASPRE trial and during the study period we did not screen prospectively for PE using the competing risks model[19] and therefore did not treat women with aspirin based on first trimester risk of PE.[30] Singleton pregnancies undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at $\geq$24 weeks' gestation were included in the study. Pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage or fetal demise before 24 weeks' gestation were excluded from the analyses.

Outcome measures

Data on pregnancy outcome were collected from hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were birth of a neonate at or below different thresholds of birth weight percentile for different cut-offs of gestational age at delivery; with, without or independently of PE occurrence. The obstetric records of all women with pre-existing or pregnancy associated hypertension were reviewed, to determine if the condition was PE, as defined by the American College of Obstetricians and Gynecologists (ACOG).[31] According to this definition, diagnosis of PE requires the presence of new onset hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) at ≥ 20 weeks' gestation and either proteinuria (≥300 mg/24h or protein to creatinine ratio >30 mg/mmol or ≥2 + on dipstick testing) or evidence of renal dysfunction (serum creatinine >97 μmol/L), hepatic dysfunction (transaminases ≥65 IU/L) or hematological dysfunction (platelet count <100,000/μL).[31] The Fetal Medicine Foundation fetal and neonatal population weight charts were used to convert birth weight to percentiles and Z scores.[32]

Statistical analyses

The new approach for prediction of SGA neonates is based on a personalized joint distribution of GA and Z. The prior distribution for each pregnancy was defined by the history model as previously described.[20] We fitted likelihood functions for each biomarker, conditional to Z and GA. We adopted a folded regression plane method, as an extension of the broken stick regression, described in detail in a previous study.[21] The combination of PAPP-A and PlGF was achieved by a multivariable Gaussian distribution that was fitted to the log10 MoM values of the biomarkers, assuming a constant covariance matrix. Bayes theorem was applied to update the prior by the likelihood to obtain an individualized posterior joint distribution for Z and GA. This pregnancy specific posterior distribution was used to compute risks for different cut-offs.

We examined the predictive performance of the new model by means of detection rate (DR) of SGA neonates of different severities (<10th and <3rd percentiles) at different gestational age cut-offs (≥37, <37 and <32 weeks) with, without or independently of PE occurrence, at fixed false positive rates (FPR) of 5%, 10% and 20%. Calibration intercepts and slopes, using logistic regression analysis of outcome incidence against the logit of the respective risks, were obtained. McNemar's test was used to compare differences in DRs between screening with PAPP-A, PlGF or their combination, for FPR of 10%.

Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo (MCMC).[33] The statistical software package R was used for data analyses.[34]

RESULTS

The study population included 60,875 singleton pregnancies. The maternal and pregnancy characteristics are given in Table 1.

Likelihoods for PAPP-A and PlGF

Folded plane regression models for the mean $\log_{10}$ MoM PAPP-A and the mean $\log_{10}$ MoM PlGF conditional to Z and GA, were fitted. The inferences for the parameters of the models are given in Table 2. Residuals diagnostics have shown satisfactory fitting for the likelihood functions. The folded regression planes are depicted in a 3-dimensional representation in Figure 1. The new method operates in 2 dimensions namely birth weight and gestational age at delivery, in a continuous way. The originality of our approach is that it captures effectively the gradual decrease in PAPP-A and PlGF values for earlier gestations and lower birth weights. The folded regression plane (Figure 1), indicates that the model was fitted to the clinically relevant domain of the distribution. This would not be possible with a conventional regression analysis that is dominated by the term pregnancies with normal birth weight and normal biochemical values. Hence, biochemical indices, are positively related to gestational age at delivery and birth weight until the mean predicted by the model reaches a mean of one MoM (Figure 1). Figure 2 illustrates the joint distribution of Z and GA updated by the addition of PAPP-A and PlGF for a high risk and low risk case. For the high risk case the distorted contour lines, by the likelihood's effect, descend to earlier gestations and lower birth weights. Therefore, larger proportion of the joint distribution falls within the area defined by the chosen cut-offs, resulting in a higher risk for SGA.

Model evaluation

The discrimination for several SGA definitions for all cases, SGA with PE and SGA with no PE at fixed FPRs are given in Table 3. We found that the agreement between the predicted risks and the observed incidence for different SGA definitions was good (Table 4). Hence, we would expect realistic risks at the stage of clinical implementation of the model.

Overall the prediction improved for earlier gestations and increasing severity of SGA (Table 3). Serum PlGF was the best predictor for all SGA and SGA with PE (Table 5, 6). Serum PAPP-A performed equally well to PlGF in predicting SGA without PE (Table 5, 6). The combination of maternal history PAPP-A and PlGF resulted in an improvement that did not always reach statistical significance (Table 5, 6). Generally, the prediction was consistently better for SGA with PE and lower for SGA without PE, compared with all SGA (Table 3).

DISCUSSION

Main findings of the study

We present a competing risks approach whereby birth weight Z score merges with gestational age at delivery, in a continuous model for SGA prediction. This new method, is ideal to include various biomarkers because of its Bayesian nature. In this study, we have focused on the biochemical markers. We used appropriate birth weight charts that corrected the erroneous down shift of the previous ranges, due to the overrepresentation of preterm SGA in the birth weight distribution.[31] The new FMF charts by simply recognizing the self-evident truth that the birth weight and the ultrasonographically estimated fetal weight are measuring the same quantity in the same person, revealed that prematurity and smallness are related. In the new model SGA is now expressed as a continuous two dimensional outcome, consisted of gestational age at delivery and birth weight which are associated and jointly distributed.[20,21] Another manifestation of this association is the progressively lower level for PAPP-A and PlGF for both lower Z scores and gestational ages, described by the likelihoods of the model. This phenomenon is also reflected in the performance of screening that escalates to higher DRs, for preterm and more severe SGA. Therefore, the FMF birth weight ranges, the competing risks approach and the biomarkers likelihoods, justify that prematurity and smallness are linked as a continuous joint outcome. This new concept is now materialized into an integrated clinical tool for SGA prediction.

We confirm that PlGF and PAPP-A, which are established markers of impaired placentation, are predictive of SGA. Serum PlGF is better than PAPP-A in the prediction of all SGA, mainly because it is a better predictor of SGA with PE (Tables 3, 5, 6). Addition of PAPP-A in a test that already combines maternal history and PlGF results in an improvement that does not always reach statistical significance. Serum PAPP-A is equal to PlGF in predicting SGA without PE. The combination of PAPP-A with PlGF for the prediction of SGA without PE, has an incremental value. We have also recently demonstrated that PlGF outperforms PAPP-A in PE prediction.[26] All these observations regarding PE and SGA prediction, could be attributed to biological differences for the examined substances; PAPP-A is mainly a regulator of insulin like growth factors, whereas PlGF is directly involved in angiogenesis. Hence deteriorated angiogenesis reflected in PlGF values, maybe a step closer in the pathophysiology of PE and SGA.

The DRs are gradually better for earlier gestational ages and increasing severity of smallness. The prediction for term SGA is better than we would expect, providing that we screen at 37 weeks' gestatio and therefore excluding preterm cases. The folded plane regression model that we fitted describes the distribution of the biomarkers locally. For increasing gestational age the break line corresponds to progressively lower Z scores therefore the biomarkers are effective for the prediction of extreme smallness at term (Figure 1, Table 3).

PE is sometimes accompanied by SGA and the plausible explanation is the fact that both conditions are placental related. Occurrence of SGA is usually part of severe PE

and this may influence the decision for delivery, irrespective of a potentially stabilized maternal condition. On the other hand, isolated fetal growth restriction, requires different management and counseling. Therefore, it is of clinical importance to identify early SGA with or without PE coexistence. Our results demonstrate that the prediction of SGA with PE is consistently and significantly better for all the examined cut-offs (Tables 3, 5, 6).

Implications for clinical practice

Up until now, clinicians may choose between a vague risk scoring system and unstable probabilistic models with heterogeneous structure and fixed SGA definitions.[10-14] We introduce a new continuous approach that provides risks for any chosen cut-offs, at any stage of pregnancy. This methodology can be used repetitively during the pregnancy and it may include various biomarkers.

Accumulating evidence has led to an inverted pyramid of prenatal care.[35] Important characteristics of this new way of thinking are first; an integrated visit at around 12 weeks of pregnancy, which is the basis of any further action and second; the timeline of the necessary assessments that can be tailored to each woman. The new model for SGA prediction may effectively determine this individualized timeline, by the use of the gestational age component, as early as the first trimester of pregnancy. The other dimension in the same model is the severity of smallness, which is also an important factor that has an impact in prenatal management.

Placental profiling by PAPP-A and PlGF, has been used for first trimester screening for chromosomal abnormalities and PE prediction. We have recently demonstrated that a first trimester screening program would be cost effective and highly predictive for both PE and chromosomal abnormalities, by using PlGF instead of PAPP-A, with a small parallel increase in the FPR in screening for trisomies.[26,27] The same logic may also apply to SGA prediction, with PlGF being an alternative to PAPP-A, as the best cost effective policy, even if the SGA prediction can be maximized by using both PAPP-A and PlGF.

The new method is laying the groundwork for SGA prediction and management according to the principles of precision medicine. Contingency multistep protocols may be used to identify the high risk cases. These high risk pregnancies may benefit from an intense monitoring throughout the pregnancy. The goal is a customized antenatal assessment with a proper use of available resources and a better understanding of the disease.

Strengths and limitations

The strengths of this study are first, the large number of prospectively collected data as a part of a screening program; second, use of a folded surface model that best describes the distribution of PlGF and PAPP-A; third, use of a continuous joint probability model that allows estimation of patient-specific risks for any desired SGA definition; and fourth, use of Bayes rule in an update process that can be repeated at any stage of pregnancy. The new model is stable and better to other screening

methods as we have previously demonstrated.[20,21] Therefore, we opted not to carry out an internal validation in this study. However, external validation is important to show the clinical use of our model in other populations.

Conclusions

Serum PAPP-A and PlGF, which are already used in screening for chromosomal abnormalities and PE, provide effective prediction of SGA. Placental biochemical profile, substantiate the view that SGA is a two dimensional continuous joint outcome. In the context of this oneness, SGA prediction is reinvented as a part of the 11 to 13 weeks integrated clinic, which is the basis of the new pyramid of prenatal care.[35] A cohesive antenatal care design that is simultaneously tailored to each pregnancy is feasible. Customization according to health care systems and contingency pregnancy-specific plans, are vital characteristics of this new era of precision medicine.

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Data availability statement: Research data are not shared

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FIGURE LEGENTS

Figure 1. Three dimensional demonstration of the folded regression plane for the PlGF likelihood model from 2 different angles.

Figure 2. Contour plots of the joint distribution of birth weight Z scores and gestational age at delivery according to maternal factors, PlGF and PAPP-A for a high risk and a low risk case. The shaded area corresponds to the risk of delivery before 32 weeks' gestation with SGA below the 10^{th} percentile.

Table 1. Maternal and pregnancy characteristics in in the study population.

Variables	**Dataset (n=60875)**
Maternal age (years)	31 (8.2)
Maternal weight (kg)	67.1 (18.8)
Maternal height (cm)	165 (9)
Body mass index (kg/m^2)	24.7 (6.7)
Gestational age (weeks)	12.7 (0.8)
Racial origin	
White	44956 (73.9%)
Black	10389 (17.1%)
South Asian	2724 (4.5%)
East Asian	1254 (2.1%)
Mixed	1552 (2.6%)
Conception	
Natural	58902 (96.8%)
Ovulation induction	493 (0.8%)
In-vitro fertilization	1480 (2.4%)
Medical history	
Chronic hypertension	845 (1.4%)
Diabetes mellitus	560 (0.9%)
SLE/APS	122 (0.2)
Cigarette smokers	5768 (9.5%)
Family history of preeclampsia	2393 (3.9%)
Parity	
Nulliparous	28311 (46.5%)
Parous with previous PE or SGA <10th percentile	6005 (9.8%)
Parous with previous SGA <10th percentile	4666 (7.7%)

Parous with previous PE and SGA <10th percentile	479 (0.8%)
Pregnancy interval (years)	3 (2.9)
Gestation of last birth (weeks)	40 (1)

Values are given as median (IQR) or number (%)

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

Table 2. Fitted regression model for the mean log_{10} MoM PAPP-A and mean log10 MoM PlGF conditional to birth weight Z score (Z) and gestational age at delivery (GA). Posterior means, standard deviation (SD), lower (LCL) and upper (UCL) credibility limits for each parameter, are presented.

log_{10} MoM PAPP-A				
Term	**Estimate**	**SD**	**LCL**	**UCL**
Intercept	0.0167065204	0.0028180137	0.01148000	0.02225025
Birth weight Z score	0.0415211600	0.0018119964	0.03810000	0.04508025
GA - 40	0.0129835876	0.0014903081	0.01015000	0.01591000
(GA – 40)^2	0.0008288029	0.0001640010	0.00052940	0.00116000
SD for log10 MoM PAPP-A	0.2376927440	0.0006811669	0.23640000	0.23900000
log_{10} MoM PlGF				
Intercept	0.0396191116	0.0041962353	0.03146975	0.048160
Birth weight Z score	0.0353880640	0.0017549301	0.03214000	0.039030
GA - 40	0.0175942812	0.0015751119	0.01447000	0.020790
(GA – 40)^2	0.0009299725	0.0001369693	0.00066080	0.001207
SD for log10 MoM PlGF	0.1703244200	0.0004897085	0.16940000	0.171300
Correlation coefficient	0.3279437 (95% CI: 0.3208357- 0.3350148)			

PAPP-A = Pregnancy associated plasma protein A; PlGF=Placenta Growth factor; CI= confidence interval;

Table 3. Performance of screening by different combinations of maternal history, PAPP-A and PlGF, for all SGA cases, SGA with preeclampsia and SGA without preeclampsia.

Outcome measure	All SGA Al cases				**SGA with preeclampsia**				SGA without preeclampsia			
	AUC	FPR			**AUC**	**FPR**			AUC	FPR		
		5%	10%	20%		**5%**	**10%**	**20%**		5%	10%	20%
≥ 37 weeks SGA <10th												
H	0.724	19.1	31.1	48.7	**0.755**	**22.7**	**34.3**	**55.2**	0.725	19.2	31.2	48.7
H+PlGF	0.731	19.7	32.6	50.5	**0.783**	**26.0**	**39.7**	**58.4**	0.731	19.8	32.7	50.6
H+ PAPP-A	0.738	20.6	33.3	51.2	**0.775**	**27.1**	**39.4**	**57.8**	0.739	20.7	33.4	51.2
H+PlGF+PAPPA	0.740	21.4	33.8	51.9	**0.787**	**28.5**	**41.5**	**61.0**	0.740	21.5	33.8	51.8
≥ 37 weeks SGA <3rd												
H	0.747	21.6	34.2	52.6	**0.756**	**19.9**	**32.5**	**53.0**	0.749	21.9	34.3	52.8
H+ PlGF	0.760	23.0	37.1	55.6	**0.795**	**27.2**	**40.4**	**60.3**	0.760	23.1	37.2	55.8
H+ PAPP-A	0.767	24.0	38.1	55.9	**0.781**	**25.2**	**42.4**	**58.9**	0.768	24.7	38.1	55.8
H+PlGF+PAPPA	0.771	25.3	38.6	57.3	**0.799**	**31.1**	**43.7**	**62.9**	0.772	25.4	39.0	57.2
<37 weeks SGA <10th												
H	0.720	21.4	32.3	48.3	**0.716**	**22.9**	**32.4**	**48.0**	0.725	21.6	32.8	49.3
H+ PlGF	0.775	29.1	41.8	60.1	**0.828**	**39.2**	**51.2**	**69.2**	0.760	26.5	38.8	57.0
H+ PAPP-A	0.759	25.2	38.5	56.5	**0.756**	**29.2**	**38.4**	**54.5**	0.764	25.2	39.4	58.2
H+PlGF+PAPPA	0.786	29.8	43.8	62.0	**0.828**	**39.5**	**50.7**	**68.9**	0.774	28.3	43.0	60.0
<37 weeks SGA <3rd												
H	0.736	22.9	33.8	51.0	**0.726**	**22.8**	**34.2**	**49.3**	0.746	23.4	34.5	52.1
H+ PlGF	0.803	34.3	45.9	64.7	**0.838**	**42.6**	**53.4**	**70.5**	0.790	31.6	43.5	62.6
H+ PAPP-A	0.782	28.8	42.6	60.8	**0.769**	**30.9**	**41.6**	**57.1**	0.793	29.0	44.5	64.0
H+PlGF+PAPPA	0.813	35.3	48.7	68.0	**0.839**	**43.3**	**53.4**	**71.5**	0.805	33.8	47.5	66.7
<32 weeks SGA <10th												
H	0.725	22.7	31.8	45.1	**0.729**	**23.7**	**34.2**	**45.6**	0.728	22.2	31.4	46.4
H+ PlGF	0.799	37.0	47.7	63.3	**0.857**	**47.4**	**55.3**	**73.7**	0.772	31.4	45.4	57.7
H+ PAPP-A	0.758	26.6	38.3	56.5	**0.774**	**28.1**	**37.7**	**57.9**	0.755	27.8	39.2	57.2
H+PlGF+PAPPA	0.803	35.4	48.4	65.9	**0.859**	**47.4**	**57.0**	**73.7**	0.777	29.9	46.9	62.9

<32 weeks SGA <3rd												
H	0.716	22.5	30.6	44.9	**0.729**	**26.0**	**35.6**	**47.1**	0.713	20.0	28.4	43.3
H+ PlGF	0.815	40.8	51.4	64.5	**0.860**	**52.9**	**57.7**	**74.0**	0.789	32.6	47.5	58.9
H+ PAPP-A	0.761	26.9	37.6	56.7	**0.781**	**28.9**	**39.4**	**58.7**	0.753	25.5	37.6	56.0
H+PlGF+PAPPA	0.819	39.2	51.0	69.0	**0.866**	**50.0**	**59.6**	**75.0**	0.792	32.6	48.2	66.0

SGA = small for gestational age; FPR = False positive rate; AUC = Area under the curve; H= history alone; PAPP-A = Pregnancy associated plasma protein A; PlGF=Placenta Growth factor

Table 4. Calibration study for the new model for prediction of SGA neonates, by maternal history, PAPP-A, PlGF and their combination.

Outcome measure birth at:	Method of screening	Birth weight <10th percentile		Birth weight <3rd percentile	
		Calibration		Calibration	
		Slope	Intercept	Slope	Intercept
≥ 37 weeks	H+PlGF	1.19288	1.01941	1.13781	0.65260
	H+PAPP-A	1.20318	1.02379	1.14063	0.65580
	H+PlGF+PAPP-A	1.21238	1.02581	1.15384	0.65879
<37 weeks	H+PlGF	0.89873	0.09954	0.89411	0.18037
	H+PAPP-A	0.91167	0.11671	0.89407	0.20504
	H+PlGF+PAPP-A	0.91636	0.10163	0.91020	0.18304
<32 weeks	H+PlGF	0.86425	0.15255	0.85510	0.31227
	H+PAPP-A	0.79544	0.18606	0.75538	0.35654
	H+PlGF+PAPP-A	0.86590	0.15762	0.85427	0.31918

SGA = small for gestational age; PAPP-A = Pregnancy associated plasma protein A; PlGF=Placenta Growth factor; H= history alone

Table 5. Comparison of detection rate of all SGA (<10th percentile), SGA with preeclampsia (PE) or SGA without PE, with delivery at <32, <37 and ≥37 weeks' gestation, at a fixed false positive rate of 10%.

Method of screening	N	Comparison of detection by the two methods of screening n (%) vs. n (%)	Difference in detection between the two methods of screening n (%; 95% CI)	p-value
≥37 weeks				
All SGA <10th percentile				
H vs H + PAPP-A	6693	2081(31.1) vs. 2230(33.3)	149(2.2;1.9 to 2.6)	<0.0001
H vs H + PlGF	6693	2081(31.1) vs. 2181(32.6)	100(1.5;1.2 to 1.8)	<0.0001
H + PAPP-A vs H + PlGF	6693	2230(33.3) vs. 2181(32.6)	-49(-0.7; -0.9 to -0.5)	0.06193
H + PlGF vs H + PlGF + PAPP-A	6693	2181(32.6) vs. 2260(33.8)	79(1.2;0.9 to 1.4)	0.00092
SGA <10th percentile with PE				
H vs H + PAPP-A	277	95(34.3) vs. 109(39.4)	14(5.1;2.5 to 7.6)	0.01332
H vs H + PlGF	277	95(34.3) vs. 110(39.7)	15(5.4;2.8 to 8.1)	0.00534
H + PAPP-A vs H + PlGF	277	109(39.4) vs. 110(39.7)	1(0.4;-0.4 to 1.1)	0.87278
H + PlGF vs H + PlGF + PAPP-A	277	110(39.7) vs. 115(41.5)	5(1.8;0.2 to 3.4)	0.38408
SGA <10th percentile no PE				
H vs H + PAPP-A	6416	2003(31.2) vs. 2140(33.4)	137(2.1;1.8 to 2.5)	<0.0001
H vs H + PlGF	6416	2003(31.2) vs. 2096(32.7)	93(1.5;1.2 to1.7)	<0.0001
H + PAPP-A vs H + PlGF	6416	2140(33.4) vs. 2096(32.7)	-44(-0.7;-0.9 to -0.5)	0.08485
H + PlGF vs H + PlGF + PAPP-A	6416	2096(32.7) vs. 2166(33.8)	70(1.1;0.8 to 1.4)	0.00268
<37 weeks				
All SGA <10th percentile				
H vs H + PAPP-A	1328	429 (32.3) vs. 511 (38.5)	82 (6.2; 4.9 to 7.5)	<0.0001
H vs H + PlGF	1328	429 (32.3) vs. 555 (41.8)	126 (9.5; 7.9 to 11.1)	<0.0001
H + PAPP-A vs H + PlGF	1328	511 (38.5) vs. 555 (41.8)	44 (3.3; 2.3 to 4.3)	0.01054
H + PlGF vs H + PlGF + PAPP-A	1328	555 (41.8) vs. 582 (43.8)	27 (2.0; 1.3 to 2.8)	0.01744
SGA <10th percentile with PE				
H vs H + PAPP-A	367	119 (32.4) vs. 141 (38.4)	22(5.9; 3.6 to 8.4)	0.005206
H vs H + PlGF	367	119 (32.4) vs. 188 (51.2)	69(18.8;14.8 to 22.8)	<0.0001
H + PAPP-A vs H + PlGF	367	141 (38.4) vs. 188 (51.2)	47(12.8;9.4 to16.2)	<0.0001
H + PlGF vs H + PlGF + PAPP-A	367	188 (51.2) vs. 186 (50.7)	-2 (-0.5; -1.2 to 0.2)	0.7236736
SGA <10th percentile no PE				
H vs H + PAPP-A	961	315 (32.8) vs. 379 (39.4)	64 (6.6;5.1 to 8.2)	<0.0001
H vs H + PlGF	961	315 (32.8) vs. 373 (38.8)	58 (6;4.5 to 7.5)	0.0001401
H + PAPP-A vs H + PlGF	961	379 (39.4) vs. 373 (38.8)	-6 (-0.6 ; -1.1 to -0.1)	0.6884997
H + PlGF vs H + PlGF + PAPP-A	961	373 (38.8) vs. 413 (43.0)	40 (4.2; 2.9 to 5.4)	0.0000876
<32 weeks				
All SGA <10th percentile				
H vs H + PAPP-A	308	98(31.8) vs. 118(38.3)	20(6.5;3.7 to 9.2)	0.00467
H vs H + PlGF	308	98(31.8) vs. 147(47.7)	49(15.9;11.8 to 20.0)	<0.0001
H + PAPP-A vs H + PlGF	308	118(38.3) vs. 147(47.7)	29(9.4;6.2 to 12.6)	0.00095
H + PlGF vs H + PlGF + PAPP-A	308	147(47.7) vs. 149(48.4)	2(0.7;-0.3 to 1.6)	0.65472
SGA <10th percentile with PE				
H vs H + PAPP-A	114	39(34.2) vs. 43(37.7)	4(3.5;0.1 to 6.9)	0.28504
H vs H + PlGF	114	39(34.2) vs. 63(55.3)	24(21.1;13.6 to 28.5)	<0.0001
H + PAPP-A vs H + PlGF	114	43(37.7) vs. 63(55.3)	20(17.5;10.6 to 24.5)	0.00015
H + PlGF vs H + PlGF + PAPP-A	114	63(55.3) vs. 65(57.0)	2(1.8;-0.7 to 4.2)	0.52708
SGA <10th percentile no PE				
H vs H + PAPP-A	194	61(31.4) vs. 76(39.2)	15(7.7;4.0 to 11.5)	0.01630
H vs H + PlGF	194	61(31.4) vs. 88(45.4)	27(13.9;9.0 to 18.8)	0.00043
H + PAPP-A vs H + PlGF	194	76(39.2) vs. 88(45.4)	12(6.2;2.8 to 9.6)	0.08968

H + PlGF vs H + PlGF + PAPP-A	194	88(45.4) vs. 91(46.9)	3(1.6;-0.2 to 3.3)	0.43857

SGA = small for gestational age; H= history alone; PAPP-A = Pregnancy associated plasma protein A; PlGF=Placenta Growth factor

Table 6. Comparison of detection rate of all SGA (<3rd percentile), SGA with preeclampsia (PE) or SGA without PE, with delivery at <32, <37 and ≥37 weeks' gestation, at a fixed false positive rate of 10%.

Method of screening	N	Comparison of detection by the two methods of screening n (%) vs. n (%)	Difference in detection between the two methods of screening n (%; 95% CI)	p-value
≥37 weeks				
All SGA <3rd percentile				
H vs H + PAPP-A	2571	878(34.2) vs.979 (38.1)	101(3.9;3.2 to 4.7)	<0.0001
H vs H + PlGF	2571	878(34.2) vs. 955(37.1)	77(3.0;2.3 to3.7)	<0.0001
H + PAPP-A vs H + PlGF	2571	979 (38.1) vs. 955(37.1)	-24 (-0.9; -1.3 to -0.6)	0.18910
H + PlGF vs H + PlGF + PAPP-A	2571	955(37.1) vs. 992 (38.6)	37 (1.5;1.0 to 1.9)	0.02355
SGA <3rd percentile with PE				
H vs H + PAPP-A	151	49 (32.5) vs. 64 (42.4)	15 (9.9; 5.2 to 14.7)	0.00176
H vs H + PlGF	151	49 (32.5) vs. 61 (40.4)	12 (8.0; 3.6 to 12.3)	0.00729
H + PAPP-A vs H + PlGF	151	64 (42.4) vs. 61 (40.4)	-3(-2.0; -4.2 to 0.2)	0.54850
H + PlGF vs H+ PlGF + PAPP-A	151	61 (40.4) vs. 66 (43.7)	5 (3.3;0.5 to 6.2)	0.25134
SGA <3rd percentile no PE				
H vs. H+PAPP-A	2420	830 (34.3) vs. 921 (38.1)	91 (3.8; 3.0 to 4.5)	<0.0001
H vs. H + PlGF	2420	830 (34.3) vs. 901 (37.2)	71 (2.9; 2.3 to 3.6)	<0.0001
H + PAPP-A vs. H + PlGF	2420	921 (38.1) vs. 901 (37.2)	-20 (-0.8;-1.2 to -0.5)	0.26205
H +PlGF vs. H+PlGF+PAPP-A	2420	901 (37.2) vs. 943 (39.0)	42 (1.7;1.2 to 2.3)	0.00741
<37 weeks				
All SGA <3rd percentile				
H vs H + PAPP-A	887	300(33.8) vs. 378 (42.6)	78 (8.8;6.9 to10.7)	<0.0001
H vs H + PlGF	887	300(33.8) vs. 407 (45.9)	107 (12.1;9.9 to14.2)	<0.0001
H + PAPP-A vs H + PlGF	887	378(42.6) vs. 407 (45.9)	29 (3.3; 2.1 to 4.4)	0.04383
H + PlGF vs H+ PlGF+PAPP-A	887	407 (45.9) vs. 432 (48.7)	25 (2.8; 1.7 to 3.9)	0.01031
SGA <3rd percentile with PE				
H vs H + PAPP-A	298	102 (34.2) vs. 124 (41.6)	22 (7.4; 4.4 to 10.4)	0.00186
H vs H + PlGF	298	102 (34.2) vs. 159 (53.4)	57(19.1;14.7 to 23.6)	<0.0001
H + PAPP-A vs H + PlGF	298	124 (41.6) vs. 159 (53.4)	35(11.7; 8.1 to 15.4)	<0.0001
H + PlGF vs H+ PlGF + PAPP-A	298	159 (53.4) vs. 159 (53.4)	0 (0.01; -0.1 to 0.1)	1
SGA <3rd percentile no PE				
H vs H + PAPP-A	589	203 (34.5) vs. 262 (44.5)	59 (10.0; 7.6 to 12.4)	<0.0001
H vs H + PlGF	589	203 (34.5) vs. 256 (43.5)	53 (9.0; 6.7 to 11.3)	<0.0001
H + PAPP-A vs H + PlGF	589	262 (44.5) vs. 256 (43.5)	-6 (-1.0;-1.8 to -0.19)	0.61949
H + PlGF vs H+ PlGF + PAPP-A	589	256 (43.5) vs. 280 (47.5)	24 (4.1; 2.5 to 5.7)	0.00269
<32 weeks				
All SGA <3rd percentile				
H vs H + PAPP-A	245	75(30.6) vs. 92(37.6)	17(6.9;3.8 to 10.1)	0.01314
H vs H + PlGF	245	75(30.6) vs. 126(51.4)	51(20.8;15.7 to 25.9)	<0.0001
H + PAPP-A vs H + PlGF	245	92(37.6) vs. 126(51.4)	34(13.9;9.6 to 18.2)	<0.0001
H + PlGF vs H + PlGF + PAPP-A	245	126(51.4) vs. 125(51.0)	-1(-0.4;-1.2 to -0.4)	0.79625
SGA <3rd percentile with PE				
H vs H + PAPP-A	104	37(35.6) vs. 41(39.4)	4(3.9;0.2 to 7.5)	0.31731
H vs H + PlGF	104	37(35.6) vs. 60(57.7)	23(22.1;14.1 to 30.1)	<0.0001
H + PAPP-A vs H + PlGF	104	41(39.4) vs. 60(57.7)	19(18.3;10.8 to 25.7)	0.00025
H + PlGF vs H+ PlGF + PAPP-A	104	60(57.7) vs. 62(59.6)	2(1.9;-0.7 to 4.6)	0.47950
SGA <3rd percentile no PE				
H vs H + PAPP-A	141	40(28.4) vs. 53(37.6)	13(9.2;4.4 to 14.0)	0.02363
H vs H + PlGF	141	40(28.4) vs. 67(47.5)	27(19.2;12.7 to 25.6)	<0.0001
H + PAPP-A vs H + PlGF	141	53(37.6) vs. 67(47.5)	14(9.9;5.0 to 14.9)	0.03075

H + PlGF vs H+ PlGF + PAPP-A	141	67(47.5) vs. 68(48.2)	1(0.7;-0.7 to 2.1)	0.76302

SGA = small for gestational age; H= history alone; PAPP-A = Pregnancy associated plasma protein A; PlGF=Placenta Growth facto

Figure 1

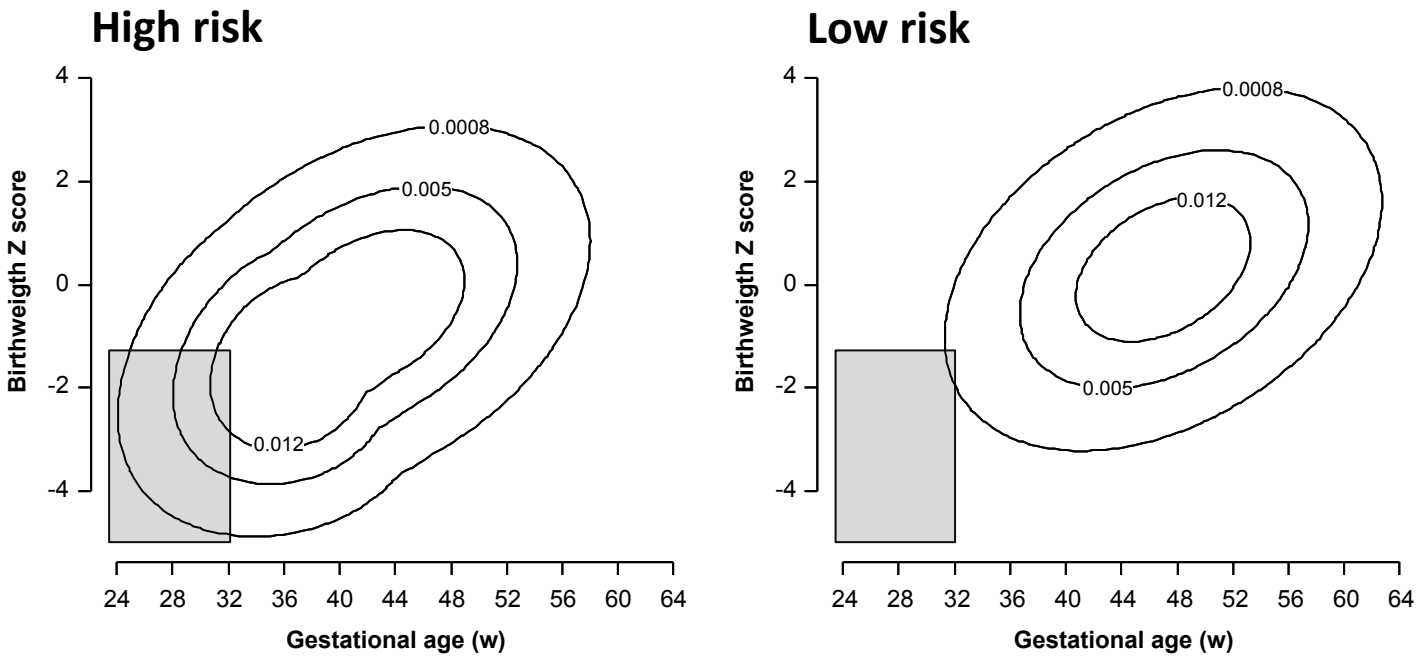

Figure 2