Prediction of small-for-gestational-age neonates: maternal biochemical markers at 30–34 weeks

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Abstract

Objective: To investigate the potential value of serum placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), pregnancy associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) at 30-34 weeks' gestation in the prediction of small for gestational age (SGA) neonates, in the absence of preeclampsia (PE).

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

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

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

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 [1]. The traditional approach of identifying pregnancies at high-risk of delivering SGA neonates is maternal abdominal palpation and/or serial measurements of symphysial-fundal height, but the performance of such screening is poor with detection of <30% of affected fetuses [2,3]. A routine third-trimester scan is by far superior to abdominal palpation in identifying pregnancies at high-risk of delivering SGA neonates. A study in 30,849 singleton pregnancies, examined the performance of routine screening for delivery of SGA neonates by a combination of maternal characteristics and medical history (maternal factors) and estimated fetal weight (EFW) from the measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) at 30-34 weeks' gestation [4]. Combined screening predicted, at 10% false positive rate (FPR), 80%, 87% and 92% of SGA neonates delivering at <5 weeks of assessment with birth weight $<10^{th}$, $<5^{th}$ and $<3^{rd}$ percentiles, respectively; the respective detection rates (DR) for SGA neonates delivering at $\geq$5 weeks of assessment were 52%, 58% and 61% [4].

Several studies have reported on the association between low or high levels of several maternal serum biochemical markers and the birth of SGA neonates. A large screening study at 11-13 weeks' gestation reported that in the cases delivering SGA neonates serum pregnancy associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG) were decreased [5]. A meta-analysis of studies on the association between second trimester biochemical markers of aneuploidy reported that increased risk for delivery of SGA neonates was associated with high levels of serum α-fetoprotein (AFP) and hCG [6]. Several studies, mainly case-control, reported that in pregnancies delivering SGA neonates maternal serum placental growth factor (PlGF) is decreased and soluble fms-like tyrosine kinase-1 (sFlt-1) is increased both in the second- and third-trimesters of pregnancy [7-12].

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

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 June 2011 and December 2013. This visit, which is held at 30^{+0}-34^{+6} weeks' gestation, included recording of maternal characteristics and medical history, calculation of EFW from ultrasound measurements of fetal HC, AC and FL, and measurement of maternal serum concentrations of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP (Cobas e411, Roche Diagnostics, Penzberg, Germany). 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 [13,14].

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 programme on the 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.

Patient characteristics

Patient characteristics recorded included 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), cigarette smoking during pregnancy (yes or no), medical history of chronic hypertension (yes or no), diabetes mellitus (yes or no), systemic lupus erythematosus (SLE) or anti-phospholipid syndrome (APS), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at $\geq$ 24 weeks' gestation), previous pregnancy with PE (yes or no), previous pregnancy with SGA (yes or no) and the time interval between the last delivery and conception of the current pregnancy in years. The maternal weight and height were 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 less than the 5th percentile after correction for gestational age at delivery (SGA <5th) [15]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy [16]. 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 [15]. The values of serum PlGF, sFlt-1, PAPP-A, free β-hCG and AFP were $\log_{10}$ transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the $\log_{10}$ transformed value [17-21]. Mann Whitney-U test was used to compare the median MoM values of the serum metabolites between the outcome groups. Regression analysis was used to determine the significance of association between $\log_{10}$ MoM of each biochemical marker with assessment to delivery interval and birth weight Z-score.

The *a priori* risk for SGA <5th delivering at <5 weeks of assessment was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history as previously described [4]. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a priori* risk), EFW Z-score and $\log_{10}$ MoM value of each biochemical marker had a significant contribution in predicting SGA <5th delivering at <5 and at $\geq$5 weeks of assessment. The performance of screening was determined by receiver operating characteristic (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight <10th percentile (SGA <10th) and SGA with birth weight <3rd percentile (SGA <3rd).

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

Results

The characteristics of the study population are presented in Table 1. Serum PlGF was measured in 9,850 pregnancies, including 490 (5.0%) with SGA neonates, but for the other metabolites a smaller number of cases was examined because of limited availability of samples or reagents.

Normal pregnancy outcome

In the unaffected pregnancies with birth weight >5th percentile, the mean, standard deviation and 5th, 10th, 90th and 95th percentiles of log_{10} MoM values of each biochemical marker are shown in sTable 1.

Correlations between log_{10} MoM values of PlGF, sFlt-1, PAPP-A, free β-hCG and AFP in the normal group are shown in sTable 2 and correlations between log_{10} MoM values of each metabolite with gestational age at delivery, assessment to delivery interval and birth weight Z-score are shown in sTable 3.

Small for gestational age

In the SGA <5th group delivering at <5 weeks of assessment, compared to the normal group, the mean log_{10} MoM values of PlGF and AFP were significantly lower and the mean log_{10} MoM values of sFlt-1 and free β-hCG were significantly higher but mean log_{10} MoM value of PAPP-A was not significantly different (Table 2). In the SGA <5th group delivering at ≥5 weeks of assessment, compared to the normal group, the mean log_{10} MoM values of PlGF, PAPP-A and AFP were significantly lower and the mean log_{10} MoM sFlt-1 was significantly higher but the mean log_{10} MoM free β-hCG was not significantly different (Table 2). Correlations between log_{10} MoM values of each metabolite with gestational age at delivery, assessment to delivery interval and birth weight Z-score are shown in sTable 3 and sFigures 1-5.

Multivariable logistic regression analysis demonstrated that the best model for prediction of SGA <5th delivering at <5 weeks and at >5 weeks of assessment was provided by a combination of maternal factors, EFW and PLGF (sTable 4). The areas under ROC (AUROC) and the DRs, at FPRs of 5% and 10%, of SGA <10th, SGA <5th and SGA <3rd delivering at <5 and at ≥5 weeks of assessment in screening by maternal factors, EFW Z-score, PlGF, sFlt-1, PAPP-A, free β-hCG, AFP and their combinations are given in Table 3 and Figures 3-5.

Discussion

Main findings of the study

The findings of this study demonstrate that in pregnancies that deliver SGA neonates in the absence of PE within five weeks of assessment at 30-34 weeks' gestation, maternal serum PlGF and AFP are decreased and serum sFlt-1 and free β-hCG are increased. In SGA delivering at ≥5 weeks, serum PlGF, PAPP-A and AFP are decreased and serum sFlt-1 is increased. The alterations in serum metabolites were related to the severity of the disease reflected in the birth weight Z-score. In the prediction of SGA the only biochemical marker with significant contribution, in addition to maternal factors and fetal biometry, was PLGF.

Combined screening by maternal factors, fetal biometry and serum PlGF at 30-34 weeks' gestation, predicted, at 10% FPR, 84%, 93%, 92% of SGA neonates delivering at <5 weeks of assessment with birth weight <10th, <5th and <3rd percentiles, respectively; the respective DRs of combined screening for SGA neonates delivering at ≥5 weeks of assessment were 57%, 64% and 71%.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are firstly, examination of a large population of pregnant women attending for routine care in a gestational age range which is widely used for the assessment of fetal growth and wellbeing, secondly, measurement of maternal serum concentration of metabolites that have been shown to be altered in pregnancies associated with impaired placentation, thirdly, expression of the values of metabolites as MoMs after adjustment for factors that affect the measurements and fourthly, use of 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.

There are two major limitations to the study. Firstly, the results of the 30-34 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring for the cases of suspected SGA and consequently the performance of screening, especially for severe SGA delivering at <5 weeks from assessment, would be positively biased. Secondly, this was a cross-sectional study and in most cases of SGA, especially those delivering at ≥5 weeks after screening, the diagnosis was made after birth. Consequently, we do not have complete data on prenatal markers of fetal hypoxia, such as abnormal fetal Doppler, that would help distinguish between fetal growth restriction (FGR) due to impaired placentation and constitutionally small fetuses. However, the proportion of FGR to constitutional SGA is likely to be higher in SGA<5th and SGA<3rd than in the SGA<10th groups and in those delivering at <5 than at ≥5 weeks of assessment and this is reflected in the higher performance of screening for the earlier and more severe forms of SGA.

Comparison with findings from previous studies

Previous large screening studies for delivery of SGA neonates examined the value of serum PAPP-A and free ß-hCG in the first-trimester and reported that the levels of both metabolites were decreased in affected pregnancies [5]. In our third-trimester screening study, the delivery of SGA neonates was associated with decreased levels of PAPP-A and increased levels of free ß-hCG. Similarly, screening studies in the early second-trimester reported the association of delivery of SGA neonates with increased levels of AFP [6], whereas in our third-trimester study AFP was decreased. The finding of our third-trimester screening study that in pregnancies delivering SGA neonates serum PLGF is decreased and sFlt-1 is increased, is compatible with the results of several, mainly case-control studies, in the second- and third-trimesters of pregnancy [7-12].

Implications for clinical practice

In the proposed new pyramid of pregnancy care [22], 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 and through pharmacological intervention, with such medications as low-dose aspirin, to reduce the prevalence of these complications [23,24]. In pregnancies with impaired placentation the use of low-dose aspirin beyond 16 weeks' gestation does not prevent the subsequent development of PE and / or SGA [23-25]. Consequently, the objective of screening at around 32 weeks' gestation is not to prevent SGA, but rather 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. This study has shown that in the assessment at 30-34 weeks, measurement of

serum PlGF improves the performance of screening for SGA achieved by the combination of maternal factors and fetal biometry.

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Figure legends

Figure 1. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight and serum PlGF (red line) in the prediction of small for gestational age neonates with birth weight 10th (left) <5th (middle) and 3rd (right) percentile delivering at <5 weeks of assessment.

Figure 2. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight and serum PlGF (red line) in the prediction of small for gestational age neonates with birth weight 10th (left) <5th (middle) and 3rd (right) percentile delivering at $\geq$5 weeks of assessment.

Table 1. Characteristics of the study population.

Characteristic	Normal (n=9,360)	SGA without PE	
		Delivery <5w (n=57)	Delivery ≥5w (n=433)
Maternal age in years, median (IQR)	31.1 (26.8-34.8)	30.5 (26.1-35.5)	29.5 (24.9-33.8)*
Maternal weight in Kg, median (IQR)	76.9 (68.9-87.0)	72.0 (65.3-84.7)	70.0 (62.7-79.5)*
Maternal height in cm, median (IQR)	165 (160-169)	162 (157-167)*	162 (157-166)*
Gestation at screening in weeks, median (IQR)	32.2 (32.0-32.5)	32.1 (31.9-32.7)	32.1 (32.0-32.4)*
Racial origin			
Caucasian, n (%)	6,917 (73.9)	37 (64.9)	263 (60.7)*
Afro-Caribbean, n (%)	1,714 (18.3)	13 (22.8)	117 (27.0)*
South Asian, n (%)	334 (3.6)	2 (3.5)	33 (7.6)*
East Asian, n (%)	182 (1.9)	1 (1.8)	8 (1.8)
Mixed, n (%)	213 (2.3)	4 (7.0)	12 (2.8)
Past obstetric history			
Nulliparous, n (%)	4,494 (48.0)	32 (56.1)	252 (58.2)*
Parous with no prior PE and SGA, n (%)	4,318 (46.1)	17 (29.8)*	138 (31.9)*
Parous with prior PE no SGA, n (%)	282 (3.0)	2 (3.5)	8 (1.8)
Parous with prior SGA no PE, n (%)	240 (2.6)	5 (8.8)*	30 (6.9)*
Parous with prior SGA and PE, n (%)	25 (0.3)	1 (1.8)	5 (1.2)*
Inter-pregnancy interval in years, median (IQR)	3.1 (2.1-5.1)	3.4 (2.4-8.2)	3.4 (2.3-5.6)*
Cigarette smoker, n (%)	880 (9.4)	10 (17.5)	98 (22.6)*
Conception			
Spontaneous, n (%)	9,056 (96.8)	54 (94.7)	421 (97.2)
Ovulation drugs, n (%)	84 (0.9)	2 (3.5)	4 (0.9)
In vitro fertilization, n (%)	220 (2.4)	1 (1.8)	8 (1.8)
Chronic hypertension	102 (1.1)	2 (3.5)	5 (1.2)
Diabetes mellitus, n (%)	93 (1.0)	2 (3.6)	3 (0.7)
Type 1, n (%)	38 (0.4)	1 (1.8)	0 (0.0)
Type 2, n (%)	55 (0.6)	1 (1.8)	3 (0.7)
SLE or APS, n (%)	15 (0.2)	0 (0.0)	1 (0.2)
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	36.4 (35.0-36.9)*	40.1 (39.0-40.9)
Birth weight in grams, median (IQR)	3,433 (3,145-3,750)	1,920 (1,756-2,181)*	2,610 (2,436-2,770)*
Birth weight in percentile, median (IQR)	50.6 (27.1-75.9)	1.9 (0.7-3.4)*	2.6 (1.4-3.7)*

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

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

Table 2. Maternal serum placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein-A, β-human chorionic gonadotropin and α-fetoprotein in the small for gestational age and normal outcome groups.

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

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

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

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

Screening test	SGA delivery at <5 weeks of assessment			SGA delivery at ≥5 weeks of assessment		
	AUROC	DR for FPR 5%	DR for FPR 10%	AUROC	DR for FPR 5%	DR for FPR 10%
SGA <10th percentile						
Maternal factors	0.699 (0.693-0.704)	19.5 (15.9-23.4)	30.4 (26.2-34.9)	0.698 (0.693-0.703)	17.0 (15.7-18.4)	27.6 (26.0-29.3)
Maternal factors plus						
PlGF	0.838 (0.830-0.845)	48.5 (38.3-58.7)	57.6 (47.2-67.5)	0.742 (0.733-0.750)	20.8 (18.2-23.5)	34.0 (30.9-37.1)
sFlt-1	0.763 (0.754-0.773)	30.1 (19.9-42.0)	39.7 (28.5-51.9)	0.692 (0.682-0.703)	14.1 (11.7-16.8)	27.9 (24.7-31.2)
PAPP-A	-	-	-	0.696 (0.686-0.706)	16.5 (13.9-19.4)	28.4 (25.2-31.8)
Free β-hCG	0.692 (0.681-0.702)	16.4 (8.8-27.0)	32.9 (22.3-44.9)	-	-	-
AFP	0.725 (0.714-0.735)	15.9 (8.7-25.6)	32.9 (22.9-44.2)	0.686 (0.676-0.696)	16.1 (13.6-18.9)	25.6 (22.6-28.9)
PlGF and sFlt-1	0.841 (0.832-0.849)	50.7 (38.7-62.6)	61.6 (49.5-72.8)	-	-	-
PlGF and AFP	-	-	-	0.737 (0.727-0.747)	20.6 (17.8-23.7)	32.5 (29.1-36.0)
EFW	0.925 (0.922-0.928)	67.6 (63.0-71.9)	79.2 (75.1-82.9)	0.831 (0.827-0.836)	36.2 (34.5-38.0)	52.7 (50.9-54.5)
Maternal factors, EFW plus						
PlGF	0.953 (0.948-0.957)	75.8 (66.1-83.8)	84.9 (76.2-91.3)	0.844 (0.836-0.851)	42.0 (38.7-45.2)	57.2 (53.9-60.4)
sFlt-1	-	-	-	0.815 (0.806-0.824)	34.1 (30.7-37.6)	49.5 (45.9-53.2)
SGA <5th percentile						
Maternal factors	0.718 (0.712-0.723)	22.4 (17.6-27.8)	31.1 (25.6-36.9)	0.723 (0.718-0.728)	19.7 (17.6-21.8)	31.9 (30.8-35.9)
Maternal factors plus						
PlGF	0.887 (0.881-0.893)	52.6 (39.0-66.0)	71.9 (58.5-83.0)	0.771 (0.762-0.779)	25.4 (21.4-29.8)	40.4 (35.8-45.2)
sFlt-1	0.815 (0.806-0.824)	50.0 (33.8-66.2)	60.0 (43.3-75.1)	0.717 (0.707-0.727)	19.4 (15.4-23.9)	33.3 (28.4-38.5)
PAPP-A	-	-	-	0.714 (0.704-0.724)	19.4 (15.3-23.9)	33.5 (28.6.38.8)
Free β-hCG	0.703 (0.693-0.714)	15.0 (5.7-29.8)	30.0 (16.6-46.5)	-	-	-
AFP	0.735 (0.725-0.745)	17.8 (8.0-32.1)	42.2 (27.7-57.8)	0.709 (0.699-0.718)	19.3 (15.2-23.8)	30.2 (25.4-35.3)
PlGF and sFlt-1	0.891 (0.884-0.898)	65.0 (48.3-79.4)	80.0 (64.4-90.9)	-	-	-
PlGF and AFP	-	-	-	0.761 (0.752-0.770)	25.7 (21.2-30.7)	39.5 (34.3-44.9)
EFW	0.953 (0.950-0.955)	79.8 (74.6-84.4)	87.4 (82.9-91.0)	0.859 (0.855-0.863)	42.1 (39.5-44.7)	58.4 (55.8-61.0)
Maternal factors, EFW plus						
PlGF	0.975 (0.972-0.978)	84.2 (72.1-92.5)	93.0 (83.0-98.1)	0.874 (0.867-0.880)	46.4 (41.6-51.2)	64.2 (59.7-68.9)
sFlt-1	-	-	-	0.851 (0.843-0.859)	40.2 (35.0-45.5)	57.6 (52.2-62.8)
SGA <3rd percentile						
Maternal factors	0.718 (0.713-0.724)	22.2 (16.5-28.8)	31.8 (25.2-38.9)	0.736 (0.731-0.741)	21.6 (18.9-24.5)	33.9 (30.8-37.2)
Maternal factors plus						
PlGF	0.887 (0.880-0.893)	50.0 (33.4-66.6)	76.3 (59.8-88.6)	0.792 (0.783-0.800)	29.9 (24.5-35.8)	44.7 (38.6-50.9)
sFlt-1	0.783 (0.773-0.792)	48.3 (29.5-67.5)	55.2 (35.7-73.6)	0.732 (0.722-0.742)	23.4 (17.9-29.6)	37.9 (31.3-44.7)
PAPP-A	-	-	-	0.723 (0.713-0.733)	22.9 (17.4-29.1)	38.1 (31.5-45.0)
Free β-hCG	0.723 (0.713-0.733)	17.2 (5.8-35.8)	31.0 (15.3-50.8)	-	-	-

AFP	0.773 (0.764-0.783)	16.7 (5.6-34.7)	46.7 (28.3-65.7)	0.714 (0.704-0.724)	21.9 (16.5-28.1)	34.3 (27.9-41.1)
PlGF and sFlt-1	0.899 (0.893-0.906)	69.0 (49.2-84.7)	82.8 (64.2-94.2)	-	-	-
PlGF and AFP	-	-	-	0.780 (0.770-0.789)	30.2 (24.0-37.0)	43.9 (37.0-51.0)
EFW	0.965 (0.963-0.967)	86.2 (80.5-90.8)	92.1 (87.2-95.5)	0.876 (0.872-0.880)	45.2 (41.8-48.5)	61.0 (57.7-64.3)
Maternal factors, EFW plus						
PlGF	0.980 (0.977-0.983)	89.5 (75.2-97.1)	92.1 (78.6-98.3)	0.895 (0.889-0.901)	51.1 (44.9-57.3)	70.5 (64.6-75.9)
sFlt-1	-	-	-	0.871 (0.863-0.878)	43.0 (36.3-49.9)	60.3 (53.4-66.9)

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

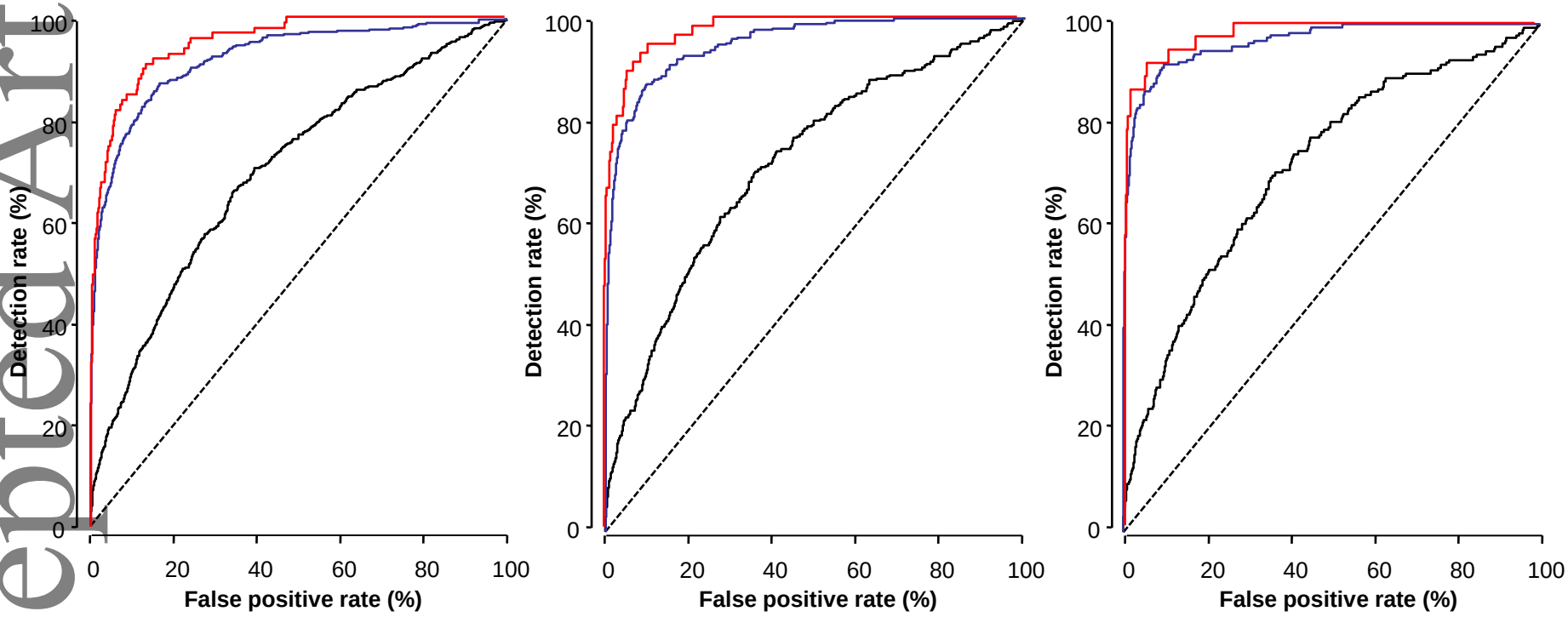

Figure 1

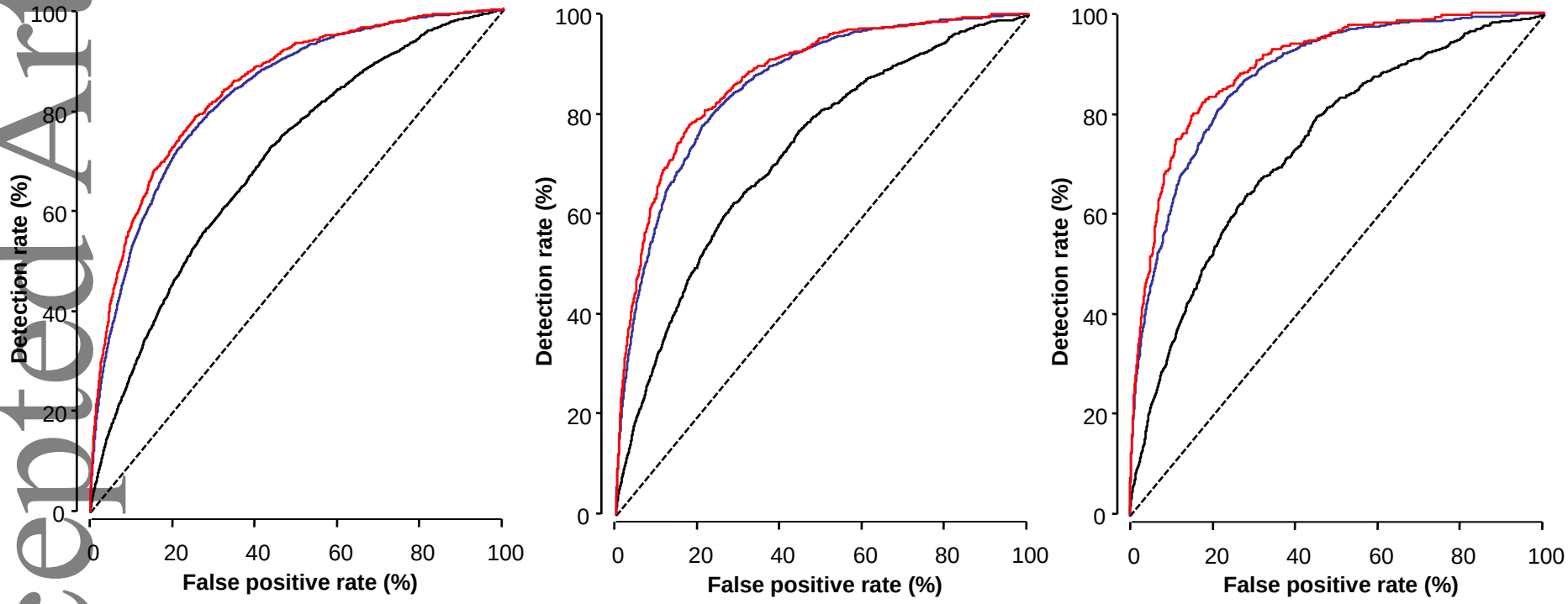

Figure 2