

Prediction of small for gestational age neonates: screening by biophysical and biochemical markers at 19–24 weeks

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Abstract

Objective: To investigate the potential value of combined screening, by maternal characteristics and medical history, fetal biometry and biophysical and biochemical markers at 19-24 weeks' gestation, for prediction of delivery of small for gestational age (SGA) neonates in the absence of preeclampsia (PE) and examine the potential value of such assessment in deciding whether the third-trimester scan should be at 32 and / or 36 weeks' gestation.

Methods: Screening study in 7,816 singleton pregnancies, including 389 (4.9%) that delivered SGA neonates with birth weight <5th percentile (SGA <5th) in the absence of PE. Multivariable logistic regression analysis was used to determine if screening by a combination of maternal factors, fetal biometry, uterine artery pulsatility index (PI), and maternal serum concentration of placental growth factor (PIGF) and α -fetoprotein (AFP) had significant contribution in predicting SGA neonates. A model was developed in selecting the gestational age for third-trimester assessment, at 32 and / or 36 weeks, based on the results of screening at 19-24 weeks.

Results: Significant independent contributions to the prediction of SGA <5th were provided by maternal factors, fetal biometry, uterine artery PI and serum PIGF and AFP. The detection rate (DR) of such combined screening at 19-24 weeks, was 100%, 78% and 42% for SGA <5th delivering at <32, at 32-36 and at \geq 37 weeks' gestation, respectively, at 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, it would be necessary at the 19-24 weeks assessment to select 11% of the population to be reassessed at 32 weeks, 43% to be reassessed at 36 weeks and 57% that do not require a third-trimester scan.

Conclusion: Prenatal prediction of a high proportion of SGA neonates necessitates the undertaking of screening in the third-trimester of pregnancy, in addition to assessment in the second-trimester, and the timing of such screening, at 32 and / or 36 weeks, should be contingent on the results of the assessment at 19-24 weeks.

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 or measurement of the symphysial-fundal height, but such screening detects less than 30% of affected cases [2,3]. A routine third-trimester scan is by far superior to abdominal palpation in identifying pregnancies at high-risk of delivering SGA neonates [4,5]. However, the timing of such scan is uncertain. About 90% of SGA neonates with birth weight below the 5th percentile (SGA <5th), are born at ≥ 37 weeks' gestation and 10% at <37 weeks [6]. Screening at 36 weeks is superior to screening at 32 weeks in the prediction of SGA delivering at ≥ 37 weeks, but at the inevitable expense of missing most cases delivering at <37 weeks [4,5]. We have proposed that the decision on whether the third-trimester scan should be at 32 and / or 36 weeks should be based on the findings of the assessment at 19-24 weeks [6-8].

In previous studies we reported that the overall performance of screening for SGA by assessment in the second- and third-trimesters is improved if at 19-24 weeks uterine artery pulsatility index (PI) [7] or maternal serum placental growth factor (PIGF) and α -fetoprotein (AFP) [8] are used, in addition to the combination of maternal characteristics and medical history (maternal factors) with fetal biometry [6].

The objectives of this study in singleton pregnancies undergoing routine antenatal care are firstly, to investigate the potential value of combined screening by maternal factors, fetal biometry and both biophysical and biochemical markers at 19-24 weeks' gestation in the prediction of delivery of SGA neonates in the absence of PE and secondly, examine the potential value of such assessment in deciding whether the third-trimester scan should be at 32 and / or 36 weeks' gestation.

Methods

The data for the study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the second-trimester of pregnancy at King's College Hospital, London and Medway Maritime Hospital, Kent, between October 2011 and January 2014. This visit, which was held at 19⁺⁰-24⁺⁶ weeks' gestation, included first, recording of maternal characteristics and medical history, second, estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) [9], third, measurement of uterine artery PI at the level of the internal os by transvaginal color Doppler ultrasound [10], and fourth, measurement of serum concentrations of PIGF and AFP (Cobas e411, Roche Diagnostics, Penzberg, Germany). Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks [11] or the fetal HC at 19-24 weeks [9].

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 second-trimester prediction of PE and or SGA. In this publication we present the results on combined screening in the prediction of SGA in the absence of PE. The pregnancies included in the study were those resulting in live birth or stillbirth of phenotypically normal babies at ≥ 24 weeks' gestation.

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 ≥ 24 weeks' gestation), previous pregnancy with PE (yes or no), neonatal birth weight of previous pregnancy expressed as a Z-score corrected for gestational age [12] 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) [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 and FL were expressed as the respective Z-score for gestational age [9]. The observed values of uterine artery PI, PIGF 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 [14-16]. Regression analysis was used to determine the significance of association between \log_{10} MoM of each biomarker with gestational age at delivery and birth weight Z-score.

The *a priori* risk for SGA <5th delivering at <37 weeks' gestation was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history for the prediction of SGA <5th delivering at <37 weeks' gestation [6].

Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a priori* risk), the Z-scores for HC, AC and FL and \log_{10} MoM values of uterine artery PI, PIGF and AFP had significant contributions in predicting SGA <5th delivering at <37 weeks' gestation in the absence of PE. The algorithm was used to determine the performance of screening for SGA <5th delivering at <32, 32-36 and at ≥ 37 weeks' gestation and SGA defined by birth weight <10th percentile (SGA <10th) and SGA with birth weight <3rd percentile (SGA <3rd).

The datasets from our previous studies of fetal biometry, biophysical and biochemical markers at 30-34 weeks' gestation [17] and fetal biometry at 35-37 weeks [18] were used to combine the maternal factor-derived logit (*a priori* risk), using the algorithm derived from the previously reported multivariable logistic regression analysis [6], with fetal biometry, biophysical and biochemical markers at 30-34 [6,17] and fetal biometry at 35-37 weeks [6,18] to determine the performance of screening for SGA <5th delivering at 32-36 weeks and at ≥ 37 weeks, respectively. At 35-37 weeks the performance of screening by maternal

factors and fetal biometry is not improved by the addition of biophysical and biochemical markers [19,20].

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 of 7,816 pregnancies, including 389 (4.9%) with SGA <5th neonates, are presented in Table 1.

The mean, standard deviation and 5th, 10th, 90th and 95th percentiles of log₁₀ MoM values of each biomarker in the unaffected pregnancies with birth weight >5th percentile were reported previously [7,8]. In the SGA <5th group delivering at <37 weeks, compared to the normal group, the mean log₁₀ MoM value of uterine artery PI and AFP were significantly higher and log₁₀ MoM PIGF was lower [7,8].

Correlations between log₁₀ MoM values of uterine artery PI, PIGF and AFP in the normal and SGA <5th groups are shown in sTable 1. Multivariable logistic regression analysis demonstrated that in the prediction of SGA <5th delivering at <37 weeks' gestation there were significant contributions from maternal factors, fetal biometry, uterine artery PI, serum PIGF and AFP (sTable 2).

Performance of screening at 19-24 weeks

The performance of combined screening for SGA <10th, SGA <5th and SGA <3rd delivering at <32, 32-36 and ≥37 weeks' gestation by maternal factors, fetal biometry, uterine artery PI and serum PIGF and AFP is shown in sTable 3 and Table 2. The areas under the receiver operating characteristic curves (AUROC) and the DRs, at FPRs of 5% and 10%, of SGA <10th, SGA <5th and SGA <3rd delivering at <32, 32-36 and ≥37 weeks' gestation in screening by a combination of maternal factors, fetal biometry and serum PIGF and AFP are given in Table 2 and illustrated in Figure 1.

Performance of screening at 32 and 36 weeks

The fitted regression models of maternal factors, fetal biometry, uterine artery PI, mean arterial pressure (MAP) and serum PIGF at 30-34 weeks' gestation for the prediction of SGA <5th, in the absence of PE, are shown in sTable 4. The fitted regression model of maternal factors and fetal biometry at 35-37 weeks' gestation for the prediction of SGA <5th in the absence of PE has been previously published [6,18].

The ROC curves for prediction of SGA <5th delivering at 32-36 weeks by combined screening from this study at 19-24 weeks and our previous study at 30-34 weeks [17] are shown in Figure 1. Similarly, the ROC curves for prediction of SGA <5th delivering at ≥37 weeks by combined screening from this study at 19-24 weeks and our previous studies at 30-34 weeks [17] and at 35-37 weeks [18] are shown in Figure 2.

Selection of the gestation for third-trimester screening

In this section we develop a hypothetical model for the follow up of pregnancies after the assessment at 22 weeks with the aim of detecting prenatally a high proportion of cases of SGA <5th. The concept is illustrated in Figure 1. All pregnancies are assessed at 22 weeks and stratified into four groups: low-risk, moderate-risk, high-risk and very-high-risk.

- The low-risk group would not require any further assessment.

- The moderate-risk group would be assessed at 36 weeks for risk of delivery of SGA <5th at ≥ 37 weeks. On the basis of such assessment they would be further stratified into a high-risk group in need of close monitoring and a low-risk group that would not have further assessment.
- The high-risk group would be assessed at 32 weeks for risk of delivery of SGA <5th at 32-36 weeks. On the basis of such assessment they would be further stratified into a high-risk group in need of close monitoring and a low-risk group that would be reassessed at 36 weeks. The management after the assessment at 36 weeks would be the same as in the moderate-risk group above.
- The very high-risk group would require further assessment at around 26 weeks to distinguish between the SGA <5th that would deliver at <32 weeks and the unaffected pregnancies; on the basis of such assessment they would be further stratified into a high-risk group in need of close monitoring and a low-risk group that would be reassessed at 32 weeks. The management after the assessment at 32 weeks would be the same as in the high-risk group above.

For the model, we assumed that if 100,000 pregnancies are examined there will be 5,000 cases of SGA <5th, including 135, 465 and 4,400 that would deliver at <32, at 32-36 and at ≥ 37 weeks' gestation, respectively [7]. The model is also based on the findings of this study that the performance of screening for SGA <5th delivering at 32-36 weeks is higher if screening is at 32 than at 22 weeks and the performance for SGA <5th delivering at ≥ 37 weeks is higher if screening is at 36 than at 22 or 32 weeks.

Prediction of SGA delivering at <32 weeks

In a population of 100,000 pregnancies there are 135 cases of SGA <5th delivering at <32 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 0.03% to 0.09% and the total number of pregnancies classified at 22 weeks as being very high-risk requiring follow-up scans at around 26 weeks would vary from 96 to 221, respectively (sTable 5).

Prediction of SGA delivering at 32-36 weeks

In a population of 100,000 pregnancies there are 465 cases of SGA <5th delivering at 32-36 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 1.48% to 30.25% and the total number of pregnancies classified at 22 weeks as being very high-risk or high-risk requiring assessment at 32 weeks would vary from 1,639 to 29,203, respectively (sTable 6).

On the basis of the data from combined screening at 30-34 weeks, the estimated FPR to detect between 50% and 100% of the cases of SGA <5th that deliver at 32-36 weeks would vary from 0.32 to 17.44% (sTable 6). Consequently, the number of pregnancies requiring follow-up scans at around 34 weeks would vary from 324 to 5,477, respectively.

In sTable 6 we provide the necessary data to estimate the number of assessments at 22 and 32 weeks to achieve a desired DR of SGA <5th delivering at 32-36 weeks. There are several approaches that can be used to achieve a desired prenatal DR. For example, one option for DR of about 50% of SGA <5th that deliver at 32-36 weeks, is to identify at 22 weeks the pregnancies that contain 100% of this SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 50% of the affected cases. Another option is to identify at 22 weeks the pregnancies that contain 50% of the SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 100% of the affected cases. Since the performance of screening at 32 weeks is superior to that at 22 weeks, the second option would be preferable because the same overall DR can be achieved with the

need for a considerably lower number of assessments at 32 weeks.

Prediction of SGA delivering at ≥ 37 weeks

In a population of 100,000 pregnancies there are 4,400 cases of SGA $< 5^{\text{th}}$ delivering at ≥ 37 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 15.26% to 95.88% and the total number of pregnancies classified at 22 weeks as being very high-risk, high-risk or moderate-risk requiring assessment at 36 weeks would vary from 16,697 to 95,486, respectively (sTable 7).

On the basis of the data from combined screening at 35-37 weeks by maternal factors and fetal biometry, the estimated FPR to detect between 50% and 100% of the cases of SGA $< 5^{\text{th}}$ that deliver at ≥ 37 weeks would vary from 3.37% to 77.48% (sTable 7). Consequently, the number of pregnancies requiring follow-up scans or early delivery at around 38 weeks would vary from 5,270 to 74,973, respectively.

There are several approaches that can be used to achieve a desired prenatal DR of SGA $< 5^{\text{th}}$ delivering at ≥ 37 weeks' gestation. As in the case of prediction of SGA delivering at 32-36 weeks described above, the preferred strategy would be to select at 22 weeks the group for assessment at 36 weeks and then define the FPR necessary to detect 100% of the affected cases. In sTable 7 we provide all the necessary data to estimate the number of assessments at 22 and 36 weeks to achieve a desired DR of SGA $< 5^{\text{th}}$ delivering at ≥ 37 weeks.

Prenatal prediction of 80% of SGA delivering at any gestational age

On the basis of data in sTables 5-7, it was estimated that if the desired objective of prenatal screening is to predict 100% of SGA $< 5^{\text{th}}$ delivering at < 32 weeks and about 80% of SGA $< 5^{\text{th}}$ delivering at ≥ 32 weeks in a population of 100,000 pregnancies, the following steps would be necessary (Figure 3). First, at 22 weeks identify a very high-risk group of 221 pregnancies which would contain 100% of cases of SGA delivering at < 32 weeks' gestation; these pregnancies would require monitoring which would include at least one scan at around 26 weeks. Second, at 22 weeks identify a group of 10,965 pregnancies which would contain 80% of cases of SGA delivering at 32-36 weeks' gestation and provide combined screening at 32 weeks; such screening will identify 2,219 of pregnancies which would require monitoring, including at least one scan at around 34 weeks. Third, at 22 weeks identify a group of 43,458 pregnancies which would contain 80% of cases of SGA delivering at ≥ 37 weeks' gestation and provide combined screening at 36 weeks; such screening will identify 34,464 pregnancies which would require monitoring, including at least one scan at around 38 weeks. Fourth, at 22 weeks identify a low-risk group of 56,542 pregnancies which would not require any further scans.

Discussion

Main findings of the study

The findings of this study confirm that in pregnancies that deliver SGA neonates in the absence of PE, uterine artery PI and serum AFP at 19-24 weeks' gestation are increased and fetal biometry and serum PLGF are decreased [6-8]. Combined screening by maternal factors, fetal biometry, uterine artery PI and serum PIGF and AFP at 19-24 weeks, predicted, at 10% FPR, 100%, 78%, 42% of SGA $< 5^{\text{th}}$ neonates delivering at < 32 , 32-36 and ≥ 37 weeks' gestation in the absence of PE.

The performance of the combined test in screening for SGA was poorer in the second- than

in the third-trimester. Thus, the DR at 10% FPR, of SGA <5th delivering at 32-36 weeks improved from 78% with screening at 19-24 weeks to 95% with screening at 30-34 weeks [17]. Similarly, the DR of SGA <5th delivering at ≥ 37 weeks improved from 42% with screening at 19-24 weeks, to 67% with screening at 30-34 weeks [17] and 76% with screening at 35-37 weeks [18].

Prenatal detection of a high proportion of SGA neonates necessitates assessment in the third-trimester and the timing of such assessment, at 32 and / or 36 weeks, could be determined from the findings of combined screening at 22 weeks.

Strengths and limitations

The strengths of this second-trimester screening study for SGA in the absence of PE are firstly, examination of a population of pregnant women attending for routine care in a gestational age range which is widely used for the assessment of fetal anatomy and growth, secondly, measurement of uterine artery PI and serum PLGF and AFP that have been shown to be altered in pregnancies associated with impaired placentation, thirdly, expression of the values of biomarkers 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 fetal biometry and 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.

A limitation of the study is that the diagnosis of SGA was based on the birth weight percentile and no distinction was made 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 preterm 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

The finding of this study on combined biophysical and biochemical testing and proposal for the use of the second-trimester assessment to define the timing of a third-trimester assessment for maximizing the prenatal detection of SGA neonates, are an extension of our previous studies which examined the value of biophysical and biochemical tests separately [6-8].

Implications for clinical practice

In most developed countries routine ultrasound examination is carried out at 11-13 and at 19-24 weeks and in some countries a third scan is offered at 30-34 weeks. The implication of our findings, in the context of prenatal prediction of SGA, is that either all women should be offered two third-trimester scans at 32 and 36 weeks or if only one scan is to be offered the decision as to whether this is carried out at 32 and / or 36 weeks should be contingent on the results of the assessment at 22 weeks. The performance of screening for SGA at 22 weeks' gestation achieved by a combination of maternal factors and fetal biometry is improved by the addition of uterine artery PI and serum PLGF and AFP. Measurement of uterine artery PI can be easily carried out at the time of the scan and serum PLGF and AFP can be measured by automated machines within 30 minutes of blood sampling. It is therefore possible to obtain these measurements during the routine visit for the second-trimester ultrasound scan and estimate the combined patient specific risk for SGA.

In a previous study we reported that the distribution of SGA <5th that deliver at <32, 32-36 and at ≥ 37 weeks' gestation is 3%, 9% and 88%, respectively [7]. This study provides the

necessary data for development of policies to achieve prenatal prediction of a desired percentage of SGA neonates. In a hypothetical model, the desired objective to predict about 100% of the cases of SGA <5th delivering at <32 weeks and 80% of the cases of SGA <5th delivering at 32-36 and at ≥ 37 weeks, would necessitate that at 22 weeks the population is divided into four groups (Figure 1). A very high-risk group, comprising of 0.2% of pregnancies, requiring assessment at 26-28 weeks and then again at 32 and 36 weeks if not delivered; a high-risk group, comprising of 10.8% of pregnancies, requiring assessment at 32 and 36 weeks; a moderate-risk group, comprising of 32.5% of pregnancies, requiring assessment at 36 weeks; and a low-risk group, comprising of 56.5% of pregnancies in no need for further scans. In the 11.0% of the total population having assessment at 32 weeks, 20.2% (2,219 of 10,965) would require close monitoring at 32-36 weeks; monitoring would include assessment of fetal growth, biophysical profile, fetal heart rate patterns and fetal Doppler studies. Similarly, in the 43.5% of the total population having assessment at 36 weeks, 79.3% (34,464 of 43,458) would require further monitoring at ≥ 37 weeks to define the best plan for delivery.

The study provides the necessary data for development of policies to achieve prenatal prediction of a desired percentage of SGA neonates. Future studies will define management protocols for the high-risk pregnancies and examine whether the implementation of such protocols could reduce the high perinatal mortality and morbidity associated with SGA.

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Figure legends

Figure 1. Receiver operating characteristics curves of maternal factors with fetal biometry (black line) and maternal factors, fetal biometry, uterine artery pulsatility index and serum placental growth factor and α -fetoprotein (red line) at 19-24 weeks in the prediction of small for gestational age neonates with birth weight below the 5th percentile, delivering at <32 (left), 32-36 (middle) and at ≥ 37 (right) weeks' gestation. The vertical and horizontal interrupted red lines indicate the detection rate (DR) at 10% false positive rate (FPR) and the necessary FPR to achieve a DR of 90%, respectively.

Figure 2. Receiver operating characteristics curves of maternal factors, fetal biometry, uterine artery pulsatility index and serum placental growth factor and α -fetoprotein at 19-24 weeks in the prediction of small for gestational age neonates with birth weight below the 10th (black line), 5th (blue line) and 3rd (red line) percentile, delivering at <32 (left), 32-36 (middle) and at ≥ 37 (right) weeks' gestation. The vertical and horizontal interrupted red lines indicate the detection rate (DR) at 10% false positive rate (FPR) and the necessary FPR to achieve a DR of 90%, respectively.

Figure 3. Flow chart demonstrating the application of combined screening at 22 weeks' gestation in stratifying risk for delivery of small for gestational age neonates and the subsequent management of pregnancies according to this risk.

Table 1. Characteristics of the study population.

Characteristic	Normal (n=7,427)	SGA <37w (n=37)	SGA ≥37w (n=352)
Maternal age in years, median (IQR)	31.1 (26.6-34.8)	31.4 (26.5-35.1)	29.7 (25.3-34.1)*
Maternal weight in Kg, median (IQR)	71.0 (63.5-81.7)	66.3 (59.0-80.3)	65.6 (58.5-74.0)*
Maternal height in cm, median (IQR)	165 (160-169)	163 (157-167)	162 (157-166)*
Gestation at screening in weeks, median (IQR)	21.9 (21.1-22.1)	21.9 (21.4-22.1)	21.9 (21.1-22.1)
Racial origin			
Caucasian, n (%)	5,509 (74.2)	18 (48.6)*	224 (63.6)*
Afro-Caribbean, n (%)	1,333 (17.9)	10 (27.0)	85 (24.1)*
South Asian, n (%)	290 (3.9)	4 (10.8)	21 (6.0)
East Asian, n (%)	141 (1.9)	3 (8.1)	11 (3.1)
Mixed, n (%)	154 (2.1)	2 (5.4)	11 (3.1)
Past obstetric history			
Nulliparous, n (%)	3,484 (46.9)	19 (51.4)	199 (56.5)*
Parous with no prior PE and SGA, n (%)	3,516 (47.3)	13 (35.1)	112 (31.8)*
Parous with prior PE no SGA, n (%)	218 (2.9)	0 (0.0)	9 (2.6)
Parous with prior SGA no PE, n (%)	188 (2.5)	5 (13.5)*	28 (8.0)*
Parous with prior SGA and PE, n (%)	21 (0.3)	0 (0.0)	4 (1.1)
Inter-pregnancy interval in years, median (IQR)	2.9 (1.8-4.8)	4.3 (2.6-5.5)	3.5 (2.5-6.3)*
Cigarette smoker, n (%)	677 (9.1)	9 (24.3)*	99 (28.1)*
Conception			
Spontaneous, n (%)	7,180 (96.7)	35 (94.6)	339 (96.3)
Ovulation drugs, n (%)	68 (0.9)	0 (0.0)	4 (1.1)
<i>In vitro</i> fertilization, n (%)	179 (2.4)	2 (5.4)	9 (2.6)
Chronic hypertension	72 (1.0)	2 (5.4)	6 (1.7)
Pre-existing diabetes mellitus, n (%)	70 (0.9)	2 (5.4)	4 (1.2)
Type 1, n (%)	30 (0.4)	0 (0.0)	2 (0.6)
Type 2, n (%)	40 (0.5)	2 (5.4)	2 (0.6)
SLE / APS, n (%)	10 (0.1)	0 (0.0)	2 (0.6)
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	34.9 (33.3-35.6)*	39.9 (39.0-40.9)
Birth weight in grams, median (IQR)	3,140 (3,440-3,760)	1,772 (1,530-1,877)*	2,597 (2,431-2,755)*
Birth weight in percentile, median (IQR)	51.3 (27.8-76.3)	2.4 (0.7-3.9)*	2.6 (1.4-3.7)*

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

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. Performance of screening for small for gestational age with birth weight <10th, <5th and <3rd percentile in the absence of preeclampsia, delivering at <32, at <32-36 and at ≥37 weeks' gestation with a combination of maternal factors, fetal biometry, uterine artery pulsatility index, placental growth factor and α -fetoprotein at 19-24 weeks' gestation.

Screening test	Small for gestational age without preeclampsia		
	<32 weeks	32-36 weeks	≥37 weeks
SGA <10th percentile			
AUROC (95% CI)	0.978 (0.953-0.962)	0.874 (0.866-0.882)	0.733 (0.723-0.743)
DR, % (95% CI) at FPR of:			
5%	89.9 (51.8-99.7)	49.1 (35.4-62.9)	21.5 (18.6-24.6)
10%	89.9 (51.8-99.7)	63.6 (49.6-76.2)	33.1 (29.7-36.6)
SGA <5th percentile			
AUROC (95% CI)	0.999 (0.999-1.000)	0.941 (0.936-0.947)	0.767 (0.757-0.776)
DR, % (95% CI) at FPR of:			
5%	100.0 (47.8-100.0)	62.5 (43.7-78.9)	27.0 (22.4-31.9)
10%	100.0 (47.8-100.0)	78.1 (60.0-90.7)	41.9 (36.0-46.5)
SGA <3rd percentile			
AUROC (95% CI)	0.999 (0.999-1.000)	0.969 (0.964-0.972)	0.777 (0.767-0.786)
DR, % (95% CI) at FPR of:			
5%	100.0 (47.8-100.0)	70.6 (44.0-89.7)	39.3 (23.2-36.0)
10%	100.0 (47.8-100.0)	88.2 (63.6-98.5)	43.3 (36.4-50.3)

SGA = small for gestational age; AUROC = area under receiver operating characteristics curve; CI = confidence intervals; DR = detection rate; FPR = false positive rate

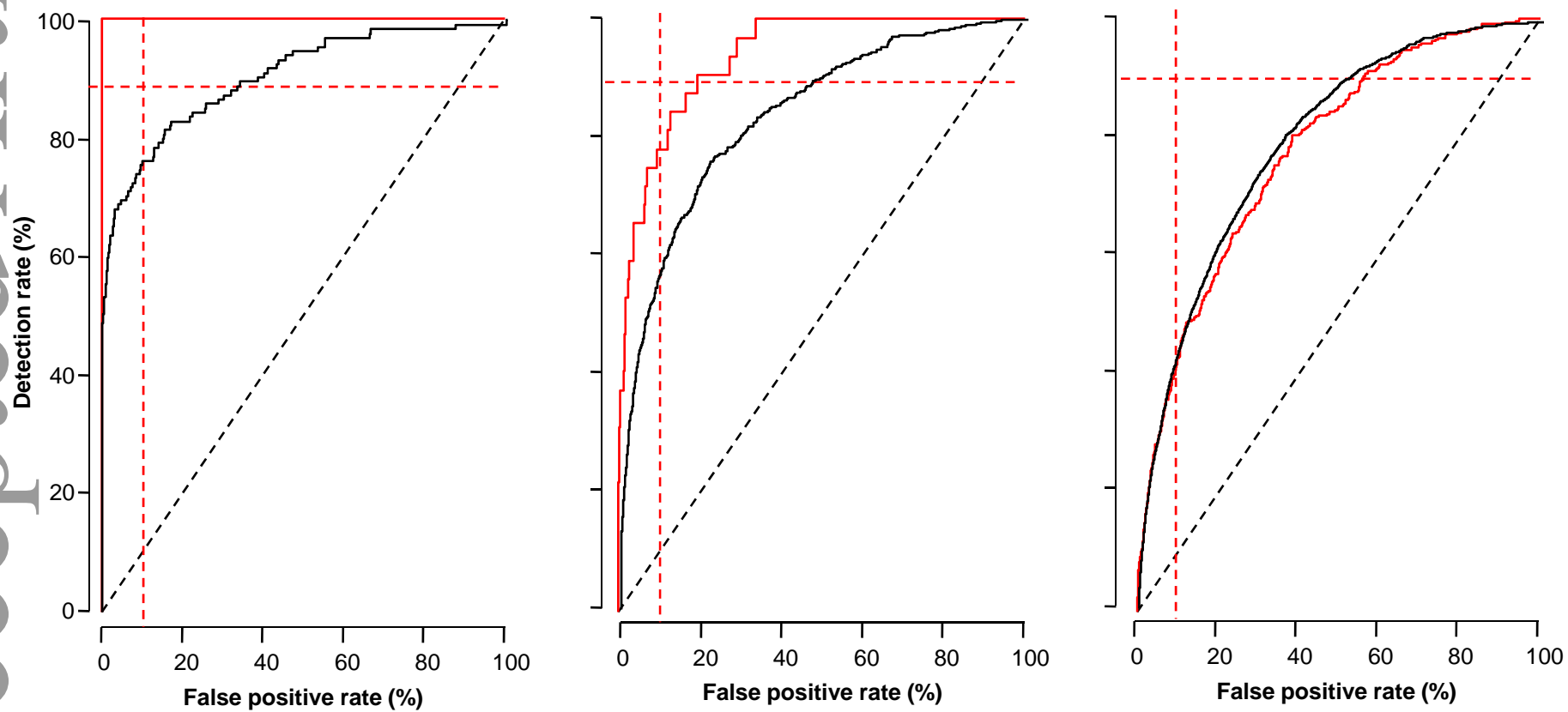


Figure 1

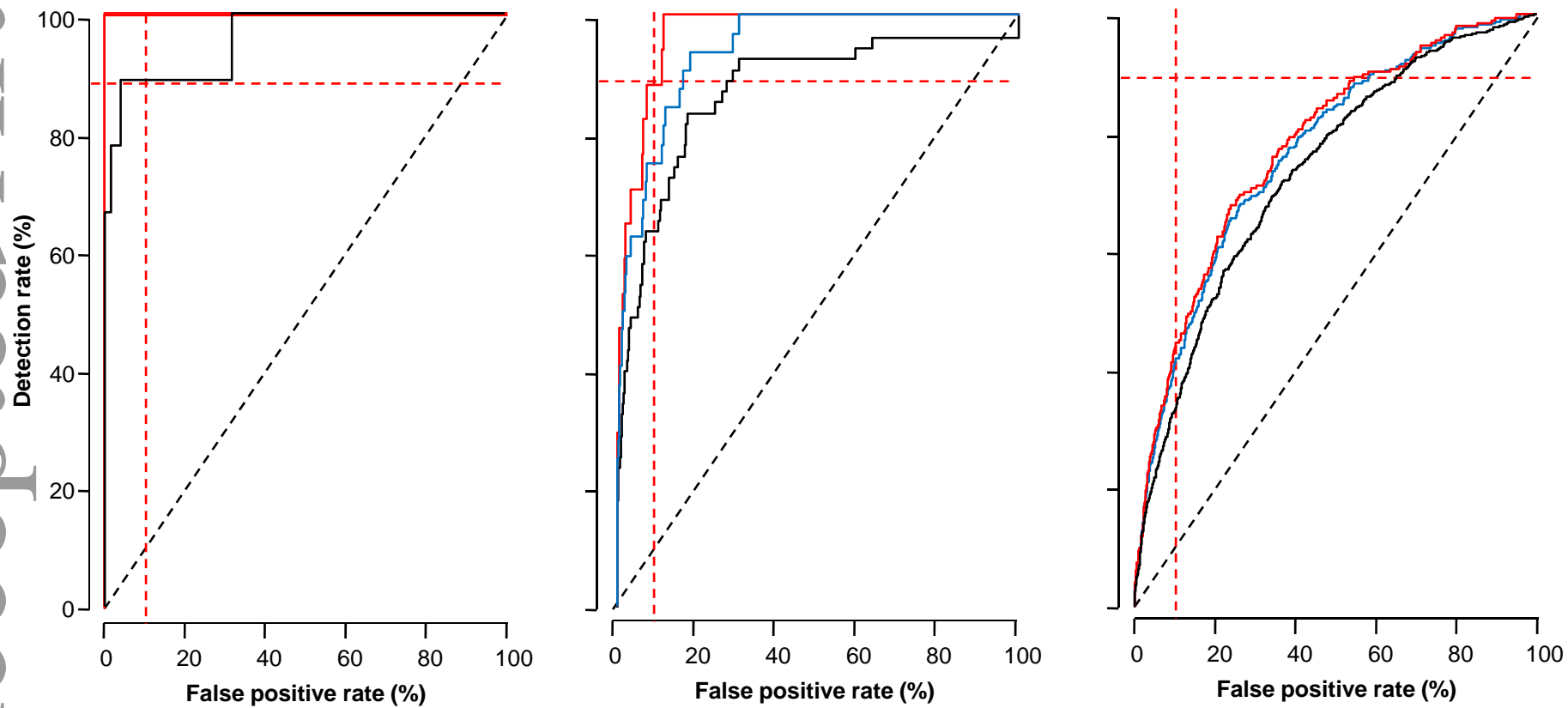


Figure 2

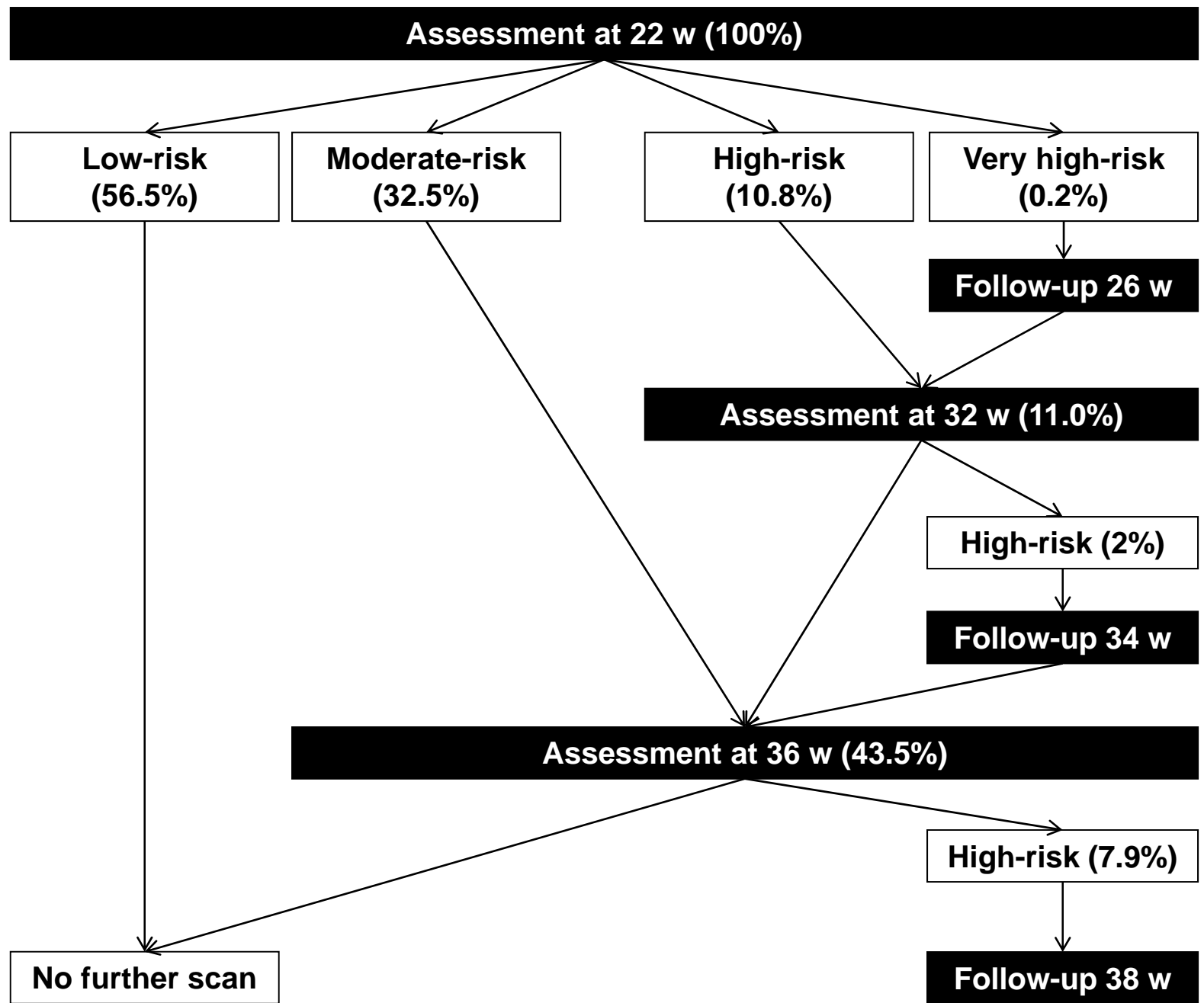


Figure 1