Prediction of small for gestational age neonates: screening by uterine artery Doppler and mean arterial pressure at 19–24 weeks

Cristina Lesmes, Dahiana M. Gallo, Youssef Saiid, Leona C. Poon, Kypros H. Nicolaides.

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK.

Key words: Second trimester screening, Small for gestational age, Preeclampsia, Uterine artery Doppler, Mean arterial pressure, Pyramid of antenatal care.

Correspondence to: Dr Leona C. Poon, Harris Birthright Research Centre for Fetal Medicine, Division of Women's Health, King's College London, Denmark Hill, London SE5 9RS, UK (e-mail: chiu_yee_leona.poon@kcl.ac.uk)

Acknowledgments: This study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme - FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852). This study is part of the PhD thesis of Cristina Lesmes for Universitat de Barcelona, Spain.

Abstract

Objective: To investigate the potential value of uterine artery pulsatility index (PI) and mean arterial pressure (MAP) at 19-24 weeks' gestation, in combination with maternal characteristics and medical history (maternal factors) and fetal biometry 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 63,975 singleton pregnancies, including 3,702 (5.8%) 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 head circumference (HC), abdominal circumference (AC) and femur length (FL) and uterine artery PI and MAP 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: The detection rate (DR) of combined screening by maternal factors, fetal biometry and uterine artery PI at 19-24 weeks, was 88%, 66% and 43% for SGA <5th delivering at <32, 32-36 and ≥37 weeks' gestation, respectively, at false positive rate (FPR) of 10%. The performance of screening was not improved by the addition of MAP. The DR of SGA <5th delivering at 32-36 weeks improved from about 66% to 89% with screening at 32 rather than at 19-24 weeks. Similarly, the DR of SGA <5th delivering at ≥37 weeks improved from about 43% to 59% and 70% with screening at 19-24, 32 and 36 weeks, respectively. 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 about 36% of the population to be reassessed at 32 weeks and 56% to be reassessed at 36 weeks.

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 the performance of such screening is poor with a detection rate (DR) of less than 30% [2,3]. A routine third-trimester scan is by far superior to abdominal palpation in identifying pregnancies at high-risk of delivering SGA neonates [4-7]. 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 $\geq$37 weeks' gestation and 10% at <37 weeks [7]. Screening at 36 weeks is superior to screening at 32 weeks in the prediction of SGA delivering at $\geq$37 weeks, but at the inevitable expense of missing most cases delivering at <37 weeks [5-7]. We have proposed that the decision on whether the third-trimester scan should be at 32 or 36 weeks should be based on the findings of the assessment at 19-24 weeks [7]. It was estimated that if the method of screening at 19-24 weeks is a combination of maternal characteristics and medical history (maternal factors) with fetal biometry and 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 about 50% of the population to be reassessed at 32 weeks and 60% to be reassessed at 36 weeks [7].

Extensive studies at 19-24 weeks' gestation have reported that screening by measurement of uterine artery pulsatility index (PI) can identify a high proportion of pregnancies that develop preeclampsia (PE), especially those with severe early-onset disease that is commonly associated with fetal growth restriction [8-16]. These studies have also reported that increased uterine artery PI is observed in pregnancies with SGA fetuses / neonates in the absence of PE. A screening study investigating 3,347 pregnancies at 22-24 weeks' gestation, reported that the performance of screening for PE was improved by the addition of mean arterial pressure (MAP) to uterine artery PI, but in SGA without PE the MAP was not significantly altered [11].

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, uterine artery PI and MAP 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 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, between April 2006 and June 2014, Medway Maritime Hospital, Kent, between February 2007 and June 2014 and at University College London Hospital, London, between May 2009 and September 2013.

This visit, which was held at 19^{+0}-24^{+6} weeks' gestation, included recording of maternal characteristics and medical history and estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) [17]. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal HC at this visit [17,18]. Transvaginal color Doppler ultrasound

was used to visualize the left and right uterine arteries at the level of the internal os [19]. Pulsed-wave Doppler wa then used to obtain waveforms and when three similar consecutive waveforms are obtained the PI is measured, and the mean PI of the two vessels is calculated. The scans are carried out by sonographers who had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com). Women with a mean uterine artery PI greater than 1.6 were followed up with growth scans at 28, 32 and 36 weeks' gestation. Women with normal uterine artery Doppler received routine antenatal care.

In the second part of the study, we measured the MAP in addition to the measurement of uterine artery PI. The MAP was measured by validated automated devices (3BTO-A2, Microlife, Taipei, Taiwan), which were calibrated before and at regular intervals during the study. The recordings were made by doctors who had received appropriate training on the use of these machines. The women were in the sitting position, their arms were supported at the level of the heart, and a small (22 cm), normal (22 to 32 cm), or large (33 to 42 cm) adult cuff was used depending on the mid-arm circumference. After rest for five minutes, two recordings of blood pressure were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements [20].

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 with maternal factors and biophysical markers 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 $\geq$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 $\geq$ 24 weeks' gestation), 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 5^{th} percentile after correction for gestational age at delivery (SGA<5^{th}) [21]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy [22]. 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 corrected for gestational age [17]. The observed values of uterine artery PI and MAP were $\log_{10}$ transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the $\log_{10}$ transformed value [23,24]. Mann Whitney-U test was used to compare the median MoM values of uterine artery PI and MAP between the outcome groups. Regression analysis was used to determine the significance of association between $\log_{10}$ MoM of uterine artery PI and MAP 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 factors for the prediction of SGA <5th delivering at <37 weeks' gestation [7].

Multivariable logistic regression analysis was 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 and MAP had significant contributions in predicting SGA <5th delivering at <37 weeks' gestation. 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 <5th delivering at <32, at 32-36 and at $\geq$37 weeks' gestation and 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 study population, in which maternal factors and uterine artery PI were recorded, comprised of 63,975 pregnancies, including 60,273 (94.2%) cases that were unaffected by SGA, PE or GH, and 447 and 3,255 delivering SGA <5th neonates in the absence of PE at <37 and $\geq$37 weeks' gestation, respectively. In 29,404 of the pregnancies, including 195 and 1,529 delivering SGA <5th neonates in the absence of PE at <37 and $\geq$37 weeks' gestation, respectively, the MAP was also recorded. In 27,817 of the pregnancies, including 185 and 1,438 delivering SGA <5th neonates in the absence of PE at <37 and $\geq$37 weeks' gestation, respectively, both uterine artery PI and MAP were recorded. The characteristics of the study population are given in Table 1.

Normal pregnancy outcome

The mean, SD, 90th and 95th percentile of $\log_{10}$ MoM uterine artery PI were 0.001, 0.111, 0.141 and 0.181, respectively. The mean, SD, 90th and 95th percentile of $\log_{10}$ MoM MAP were -0.003, 0.036, 0.043 and 0.057, respectively.

There was a negative linear significant association between $\log_{10}$ MoM values of uterine artery PI and MAP (r=-0.050, P<0.0001). There was a significant inverse association between $\log_{10}$ MoM uterine artery PI with gestational age at delivery (r=-0.036, P<0.0001) and birth weight Z-score (r=-0.111, P<0.0001), and between $\log_{10}$ MoM MAP with gestational age at delivery (r=-0.038, P<0.0001), but not birth weight Z-score (r=0.004, P=0.461).

Small for gestational age

In the SGA<5th group, compared to the normal group, the median MoM values of uterine artery PI and MAP at 19-24 weeks' gestation were significantly higher (sTable 1). There was no significant association between log_{10} MoM values of uterine artery PI and MAP (r=0.020, P=0.410). There was a significant inverse association between log_{10} MoM uterine artery PI with gestational age at delivery (r=-0.254, P<0.0001; sFigure 1) and birth weight Z-score (r=-0.176, P<0.0001; sFigure 1), and between log_{10} MoM MAP with gestational age at delivery (r=-0.148, P<0.0001; sFigure 2) and birth weight Z-score (r=-0.066, P=0.006; sFigure 2).

Multivariable logistic regression analysis demonstrated that in the prediction of SGA <5th delivering at <37 weeks' gestation, there were significant contributions from maternal factors [7], the Z-scores for HC, AC and FL and log_{10} MoM values of uterine artery PI and MAP (sTable 2). However, 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 and uterine artery PI was not improved by the addition by MAP sTable 3. The performance of screening for SGA <5th delivering at <32, 32-36 and at ≥37 weeks' gestation is illustrated in sFigure 3 and sFigure 4.

The ROC curves for prediction of SGA <5th delivering at 32-36 weeks by combined screening with maternal factors, fetal biometry and uterine artery PI from this study at 19-24 weeks and our previous study at 30-34 weeks [25] are shown in sFigure 5. 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 [25] and at 35-37 weeks [6] are shown in sFigure 5. At 35-37 weeks, the performance of screening for SGA by maternal factors and fetal biomery was not improved by the addition of uterine artery PI and MAP [26].

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 19-24 weeks with the aim of detecting about 80% of the cases of SGA <5th. 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 (Figure 1) [7].

SGA delivering at <32 weeks

On the basis of the data from this study of combined screening at 19-24 weeks by maternal factors, fetal biometry and uterine artery PI the estimated FPR for detection of 80% of the cases of SGA <5th that delivered at <32 weeks was 2.6% (Table 2); consequently, 2,578 (108 true positive and 2,470 false positive) pregnancies would require a minimum of one follow up scan at 26-28 weeks to distinguish between the SGA <5th and the unaffected pregnancies that would deliver at <32 weeks (Figure 1).

SGA delivering at 32-36 weeks

To detect 80% of SGA <5th that deliver at 32-36 weeks, it would be necessary to identify at 19-24 weeks the pregnancies that contain about 90% of this SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 90% of the affected cases. At 19-24 weeks, the estimated FPR for detection of 90% of the cases of SGA <5th that deliver at 32-36 weeks was about 37% (Table 2); consequently, 35,569 (419 true positive and 35,150 false positive) of the total population of 100,000 pregnancies would require

reassessment at 32 weeks (Figure 1).

On the basis of the data from our previous study of combined screening at 30-34 weeks by maternal factors, fetal biometry and uterine artery PI [25], the estimated FPR for detection of 90% of the cases of SGA <5th that delivered at 32-36 weeks was 12% (12.4, 95% CI 12.0-12.7); consequently, 4,595 (377 true positive and 4,218 false positive) pregnancies would require a minimum of one follow up scan at around 34 weeks to distinguish between the SGA <5th and the unaffected pregnancies that would deliver at 32-36 weeks (Figure 1).

SGA delivering at ≥37 weeks

To detect 80% of SGA <5th that deliver at ≥37 weeks, it would be necessary to identify at 19-24 weeks the pregnancies that contain about 90% of the SGA group, reassess these pregnancies at 36 weeks and then define the FPR necessary to detect 90% of the affected cases. At 19-24 weeks, the estimated FPR for detection of 90% of the cases of SGA <5th that deliver at ≥37 weeks was about 55% (Table 2); consequently, 56,210 (3,960 true positive and 52,250 false positive) of the total population of 100,000 pregnancies would require reassessment at 36 weeks (Figure 1).

On the basis of the data from our previous study of combined screening at 35-37 weeks by maternal factors and fetal biometry [6], the estimated FPR for detection of 90% of the cases of SGA <5th that deliver at ≥37 weeks was about 27% (27.2, 95% CI 25.5-28.9); at 35-37 weeks, uterine artery PI and MAP do not improve the prediction provided by maternal factors and fetal biometry alone. Consequently, 17,672 pregnancies (3,564 true positive and 14,108 false positive) would require a minimum of one follow up scan at around 38 weeks to distinguish between the SGA <5th and the unaffected pregnancies that would deliver at ≥37 weeks (Figure 1).

Overall results in the study population

In our study of 63,975 pregnancies, screening at 19-24 weeks by maternal factors, fetal biometry and uterine artery PI would identify a high-risk group for SGA <5th requiring reassessment at 32 weeks. The high-risk group would comprise of 22,485 (35.1%) cases, including 90% (304/337) of the SGA <5th group delivering at 32-36 weeks and 36.8% (22,181/60,273) unaffected cases.

On the assumption that no pregnancies deliver at <37 weeks, the assessment at 19-24 weeks would also identify a high-risk group for SGA <5th requiring reassessment at 36 weeks. The high-risk group would comprise of 36,080 (56,4%) cases, including 90% (2,930/3,255) of the SGA <5th group delivering at ≥37 weeks and 55.0% (33,150/60,273) unaffected cases.

Consequently, the objective of prenatal prediction of about 80% of pregnancies delivering SGA <5th neonates would necessitate an ultrasound scan at 32 and 36 weeks in about 35% of pregnancies, one scan at 36 weeks in about 20% and no third-trimester assessment in about 45% (Figure 2).

Discussion

Main findings of the study

The findings of this study demonstrate that in women who deliver SGA neonates in the absence of PE, uterine artery PI and MAP at 19-24 weeks' gestation are increased and the increase is inversely related to the severity of the disease reflected in the gestational age at delivery and the birth weight Z-score. Screening by a combination of maternal factors, fetal biometry and uterine artery PI at 19-24 weeks, predicted at 10% FPR, 88% 66% and 43% of SGA <5th neonates delivering at <32, 32-36 and at >37 weeks' gestation. The performance of screening was not improved by the addition by MAP.

The performance of combined screening for SGA with maternal factors, fetal biometry and uterine artery PI is 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 66% with screening at 19-24 weeks to 89% with screening at 30-34 weeks. Similarly, the DR of SGA <5th delivering at ≥37 weeks improved from 43% with screening at 19-24 weeks, to 59% with screening at 30-34 weeks and 70% with screening at 35-37 weeks.

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 of the study

The major strengths of the study are firstly, prospective examination of a large number of pregnancies attending for routine care in a gestational age range which is widely used for the assessment of fetal anatomy and growth, secondly, use of appropriately trained doctors and a specific protocol to measure uterine artery PI and MAP and expression of values as MoMs after adjustment for factors that affect the measurements, and thirdly, use of Bayes theorem to combine the *prior* risk from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for SGA of different severities delivering at selected gestational age cut-offs.

The main limitation of the study is that the uterine artery PI results of the 19-24 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring for the cases of high PI and consequently the performance of screening, especially for SGA delivering at <32 and at <37 weeks' gestation, would be positively biased.

Comparison with previous studies

Our finding that in pregnancies delivering SGA neonates in the absence of PE uterine artery PI at 19-24 weeks' gestation is increased, is compatible with the results of previous smaller screening studies [8,10,14]. In our study, MAP was significantly increased in pregnancies that delivered SGA neonates in the absence of PE, but in a previous small study of 3,347 pregnancies at 22-24 weeks' gestation, the MAP was not significantly altered [11].

Implications for clinical practice

Extensive studies have established that screening by a combination of maternal factors and uterine artery PI, at the time of the routine second-trimester ultrasound examination at 19-24 weeks' gestation, can identify a high proportion of pregnancies that subsequently develop PE. This study, demonstrates that second-trimester combined screening can also be used for detection of pregnancies which deliver SGA neonates in the absence of PE.

In the proposed new pyramid of pregnancy care [27], combined screening at 11-13 weeks' gestation aims to identify pregnancies at high-risk of developing PE and / or SGA and through pharmacological intervention to reduce the prevalence of these complications [28,29]. In contrast to the evidence of beneficial effect of low-dose aspirin started at <16 weeks' gestation, a major randomized study in pregnancies with impaired placentation demonstrated that the daily administration of 150 mg of aspirin after 23 weeks does not prevent the subsequent development of PE and / or SGA [30]. Consequently, the objective of screening at around 22 weeks and in the third-trimester is not prevention of PE and / or 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 [1,31].

The best approach for identifying the high-risk group for SGA is to carry out screening in the whole population by a combination of maternal factors, fetal biometry and uterine artery PI at around 22 weeks' gestation. In addition, women should be offered third-trimester assessment and the decision as to whether this is carried out at 32 and / or 36 weeks would be contingent on the results of the assessment at 22 weeks. In a previous study we reported that the distribution of SGA $<5^{th}$ that deliver at <32, 32-36 and at $\geq$37 weeks' gestation is 3%, 9% and 88%, respectively [7]. In a hypothetical model, the desired objective to predict about 80% of the cases of SGA $<5^{th}$ at <32, 32-36 and at $\geq$37 weeks by screening with maternal factors, fetal biometry and uterine artery PI would be achieved by assessment of 100% pregnancies at 22 weeks, about 36% at 32 weeks and 56% at 36 weeks. The respective values from our previous model of screening by maternal factors and fetal biometry alone were 100%, 48% and 60% [7].

Following identification of the high-risk groups, close monitoring of such pregnancies would be needed to minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery; monitoring would include assessment of fetal growth, biophysical profile, fetal heart rate patterns and fetal Doppler studies. As suggested from our model a minimum of 2.6%, 4.6% and 17.7% of the total population would require such monitoring of the high-risk pregnancies identified at 22, 32 and 36 weeks, respectively; the values from our previous model of screening by maternal factors and fetal biometry alone were 15.3%, 6.3% and 18.7%, respectively [7].

Future studies will firstly, investigate the potential improvement in performance of screening for SGA at 22, 32 and 36 weeks by combining biophysical with biochemical markers with consequent increase in DR and / or decrease in the total number of necessary scans, secondly, define management protocols for pregnancies identified by screening as being at high-risk for SGA and thirdly, examine whether the implementation of such protocols could reduce the high perinatal mortality and morbidity associated with SGA.

References

1. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005; **25**: 258-264.

2. Bais JMJ, Eskes M, Pel M, Bonsel GJ, Bleker OP. Effectiveness of detection of intrauterine retardation by abdominal palpation as screening test in a low-risk population: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2004; **116**: 164-169.

3. Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sørensen HU, Rosenø H. The implications of introducing the symphyseal-fundal height-measurement. A prospective randomized controlled trial. *Br J Obstet Gynaecol* 1990; **97**: 675-680.

4. Souka AP, Papastefanou I, Pilalis A, Michalitsi V, Kassanos D. Performance of third-trimester ultrasound for prediction of small-for-gestational-age neonates and evaluation of contingency screening policies. *Ultrasound Obstet Gynecol* 2012; **39**: 535–542.

5. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by fetal biometry at 30–34 weeks. *Ultrasound Obstet Gynecol* 2015; in press

6. Fadigas C, Saiid Y, Gonzalez R, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by fetal biometry at 35-37 weeks *Ultrasound Obstet Gynecol* 2015; in press

7. Lesmers C, Gallo D, Panaiotova J, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by fetal biometry at 19-24 weeks *Ultrasound Obstet Gynecol* 2015; in press

8. Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KN. Multicentre screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441-449.

9. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2005; **193**: 429-436

10. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH; for The Fetal Medicine Foundation Second Trimester Screening Group. Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. *Ultrasound Obstet Gynecol* 2008; **31**: 310-313.

11. Onwudiwe N, Yu CK, Poon LC, Spiliopoulos I, Nicolaides KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. *Ultrasound Obstet Gynecol* 2008; **32**: 877-883.

12. Plasencia W, Maiz N, Poon L, Yu C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2008; **32**: 138-146.

13. Llurba E, Carreras E, Gratacós E, Juan M, Astor J, Vives A, Hermosilla E, Calero I, Millán P,

García-Valdecasas B, Cabero L. Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. *Obstet Gynecol Int* 2009; **2009**: 275613.

14. Espinoza J, Kusanovic JP, Bahado-Singh R, Gervasi MT, Romero R, Lee W, Vaisbuch E, Mazaki-Tovi S, Mittal P, Gotsch F, Erez O, Gomez R, Yeo L, Hassan SS. Should bilateral uterine artery notching be used in the risk assessment for preeclampsia, small-for-gestational-age, and gestational hypertension? *J Ultrasound Med* 2010; **29**: 1103–1115.

15. Gallo DM, Poon LC, Akolekar R, Syngelaki A, Nicolaides KH. Prediction of preeclampsia by uterine artery Doppler at 20-24 weeks' gestation. *Fetal Diagn Ther* 2013; **34**: 241-247.

16. Gallo D, Poon LC, Fernandez M, Wright D, Nicolaides KH. Prediction of preeclampsia by mean arterial pressure at 11-13 and 20-24 weeks' gestation. *Fetal Diagn Ther* 2014; **36**: 28-37.

17. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34-48.

18. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702-710.

19. Papageorghiou AT, To MS, Yu CK, Nicolaides KH. Repeatability of measurement of uterine artery pulsatility index using transvaginal color Doppler. *Ultrasound Obstet Gynecol* 2001; **18**: 456-459.

20. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42-48.

21. Poon LCY, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156-165.

22. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX-XIV.

23. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history *Ultrasound Obstet Gynecol* 2015; in press

24. Wright A, Wright D, Ispas A, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; in press

25. Bakalis S, Stoilov B, Akolekar R, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by uterine artery Doppler and mean arterial pressure at 30–34 weeks. *Ultrasound Obstet Gynecol* 2015; in press

26. Fadigas C, Guerra L, Garcia-Tizon Larroca S, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: Screening by uterine artery Doppler and mean arterial pressure at 35-37 weeks. *Ultrasound Obstet Gynecol* 2015; in press

27. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183-196.

28. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguere Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402-414.

29. Roberge S, Nicolaides K, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; **41**: 491-499.

30. Yu CK, Papageorghiou AT, Parra M, Palma DR, Nicolaides KH. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol* 2003; **22**: 233-239.

31. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM,Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG; HYPITAT study group. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; **374**: 979-988.

Figure legends

Figure 1. Flow chart demonstrating the potential value of the 19-24 weeks assessment in identifying about 80% of pregnancies delivering small for gestational age neonates with birth weight below the 5th percentile.

Figure 2. Flow chart for prenatal prediction of about 80% of pregnancies delivering small for gestational age neonates with birth weight below the 5th percentile. At 22 weeks the patient-specific risk for SGA is determined by combined screening with maternal factors, fetal biometry and uterine artery pulsatility index and the patients are divided into three risk categories. The high-risk group, which constitutes 35% of the population, is reassessed at 32 and 36 weeks and the moderate-risk group, which constitutes 20% of the population, is reassessed at 36 weeks. The low-risk group, which constitutes 45% of the population, does no require a third-trimester scan.

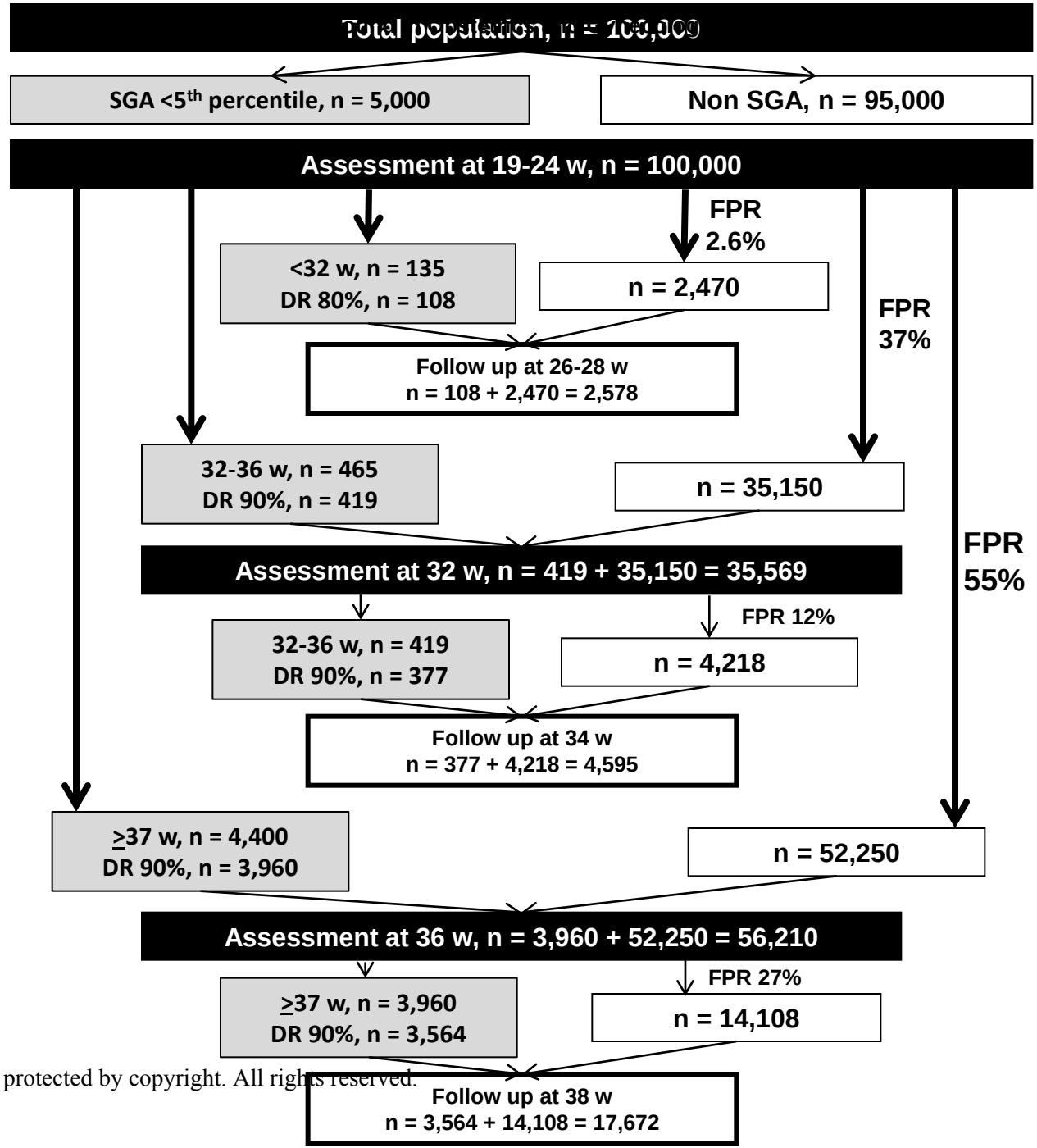

Figure 1

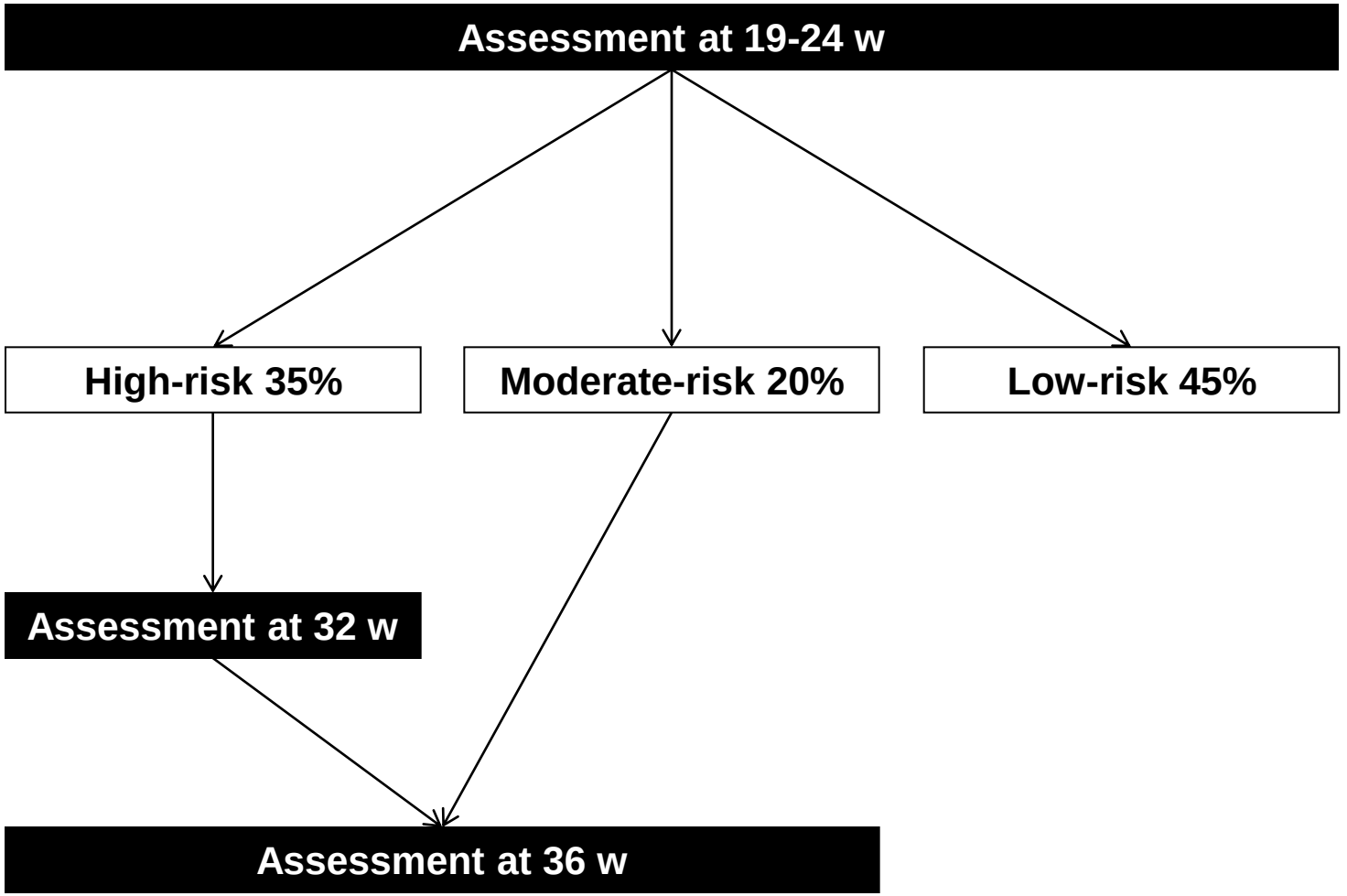

Figure 2

Table 1. Characteristics of the study population.

	Uterine artery pulsatility index			Mean arterial pressure		
Characteristic	**Normal (n=60,273)**	**SGA <37w (n=447)**	**SGA ≥37 w (n=3,255)**	**Normal (n=27,680)**	**SGA <37w (n=195)**	**SGA ≥37 w (n=1,529)**
Maternal age in years, median (IQR)	30.8 (26.2-34.7)	30.7 (25.5-35.7)	29.5 (58.4-74.6)*	31.0 (26.3-34.8)	30.8 (25.3-36.0)	29.5 (24.6-34.0)*
Maternal weight in Kg, median (IQR)	70.0 (63.0-80.3)	68.0 (60.1-81.0)*	65.0 (58.4-74.4)*	71.0 (63.5-81.9)	67.0 (60.0-77.0)*	65.0 (58.3-75.1)*
Maternal height in cm, median (IQR)	164 (160-169)	162 (157-167)*	162 (157-166)*	165 (160-169)	162 (157-167)*	162 (157-166)*
Gestation at screening in weeks, median (IQR)	22.2 (21.6-22.7)	22.1 (21.4-22.7)	22.2 (21.6-22.7)	22.1 (21.4-22.6)	22.0 (21.2-22.6)	22.1 (21.4-22.7)
Racial origin						
Caucasian, n (%)	42,960 (71.3)	253 (56.6)*	1,882 (57.8)*	18,960 (68.5)	102 (52.3)*	851 (55.7)*
Afro-Caribbean, n (%)	11,626 (19.3)	122 (27.3)*	867 (26.6)*	6,223 (22.5)	60 (30.8)*	456 (29.8)*
South Asian, n (%)	2,766 (4.6)	36 (8.1)*	298 (9.2)*	1,159 (4.2)	13 (6.7)	124 (8.1)*
East Asian, n (%)	1,463 (2.4)	16 (3.6)	108 (3.3)*	613 (2.2)	8 (4.1)	40 (2.6)
Mixed, n (%)	1,458 (2.4)	20 (4.5)*	100 (3.1)*	725 (2.6)	12 (6.2)*	58 (3.8)*
Past obstetric history						
Nulliparous, n (%)	29,831 (49.5)	251 (56.2)*	2,013 (61.8)*	12,726 (46.0)	103 (52.8)	920 (60.2)*
Parous with no prior PE and SGA, n (%)	27,193 (45.1)	134 (30.0)*	878 (27.0)*	13,407 (48.4)	68 (34.9)*	434 (28.4)*
Parous with prior PE no SGA, n (%)	1,527 (2.5)	17 (3.8)	66 (2.0)	715 (2.6)	6 (3.1)	30 (2.0)
Parous with prior SGA no PE, n (%)	1,531 (2.5)	33 (7.4)*	269 (8.3)*	743 (2.7)	16 (8.2)*	127 (8.3)*
Parous with prior SGA and PE, n (%)	191 (0.3)	12 (2.7)*	29 (0.9)*	89 (0.3)	2 (1.0)	18 (1.2)*
Inter-pregnancy interval in years, median (IQR)	2.9 (1.9-4.9)	4.4 (2.4-7.1)*	3.4 (2.1-6.1)*	3.0 (2.0-5.0)	4.0 (2.1-6.7)*	3.4 (2.1-5.9)*
Cigarette smoker, n (%)	5,719 (9.5)	111 (24.8)*	697 (21.4)*	2,651 (9.6)	47 (24.1)*	344 (22.5)*
Conception						
Spontaneous, n (%)	58,346 (96.8)	424 (94.9)	3,142 (96.5)	26,832 (96.9)	184 (94.4)	1,479 (96.7)
Ovulation drugs, n (%)	609 (1.0)	12 (2.7)*	43 (1.3)	295 (1.1)	5 (2.6)	21 (1.4)
In vitro fertilization, n (%)	1.318 (2.2)	11 (2.5)	70 (2.2)	553 (2.0)	6 (3.1)	29 (1.9)
Chronic hypertension	674 (1.1)	23 (5.1)*	50 (1.5)	321 (1.2)	9 (4.6)*	24 (1.6)
Pre-existing diabetes mellitus, n (%)	482 (0.8)	8 (1.8)	19 (0.6)	251 (0.9)	2 (1.0)	10 (0.7)
Type 1, n (%)	215 (0.4)	0 (0.0)	5 (0.2)	108 (0.4)	0 (0.0)	4 (0.3)
Type 2, n (%)	267 (0.4)	8 (1.8)*	14 (0.4)	143 (0.5)	2 (1.0)	6 (0.4)
SLE / APS, n (%)	99 (0.2)	3 (0.7)	10 (0.3)	39 (0.1)	0 (0.0)	4 (0.3)

Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	34.9 (32.1-36.3)*	39.9 (38.9-40.9)*	40.0 (39.0-40.9)	34.9 (32.5-36.4)*	39.9 (38.9-40.8)*
Birth weight in grams, median (IQR)	3,426 (3,128-3,740)	1,674 (1,160-1,930)*	2,600 (2,410-2,760)*	3,426 (3,130-3,744)	1,720 (1,280-1,980)*	2,600 (2,403-2,752)*
Birth weight in percentile, median (IQR)	49.5 (26.6-74.7)	1.2 (0.3-2.8)*	2.5 (1.3-3.8)*	49.9 (26.5-75.1)	1.8 (0.4-3.6)*	2.6 (1.4-3.8)*

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

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 and uterine artery pulsatility index 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)	0.901 (0.899-0.904)	0.841 (0.838-0.844)	0.759 (0.756-0.762)
DR, % (95% CI) at FPR of:			
5%	72.4 (64.4-79.5)	47.2 (42.9-51.4)	26.0 (24.9-27.0)
10%	77.9 (70.3-84.4)	57.7 (53.5-61.9)	37.8 (36.6-39.0)
FPR, % (95% CI) to achieve DR of:			
100%	87.9 (87.7-88.2)	97.9 (97.8-98.0)	99.9 (99.9-100.0)
90%	45.4 (45.0-45.9)	46.6 (46.2-47.0)	60.3 (59.9-60.7)
80%	13.5 (13.2-13.8)	27.9 (27.5-28.3)	44.0 (43.6-44.4)
SGA <5th percentile			
AUROC (95% CI)	0.943 (0.941-0.945)	0.876 (0.874-0.879)	0.788 (0.785-0.791)
DR, % (95% CI) at FPR of:			
5%	85.3 (77.3-91.4)	55.2 (49.7-60.6)	29.8 (28.2-31.4)
10%	88.1 (80.5-93.5)	65.6 (60.2-70.6)	43.0 (41.3-44.8)
FPR, % (95% CI) to achieve DR of:			
100%	76.3 (75.9-76.6)	98.0 (97.9-98.1)	99.9 (99.9-100.0)
90%	11.3 (11.1-11.6)	36.8 (36.4-37.1)	55.0 (54.6-55.4)
80%	2.6 (2.5-2.8)	20.6 (20.3-20.9)	38.3 (37.9-38.6)
SGA <3rd percentile			
AUROC (95% CI)	0.958 (0.957-0.960)	0.891 (0.889-0.894)	0.736 (0.733-0.740)
DR, % (95% CI) at FPR of:			
5%	89.1 (80.9-94.7)	59.8 (53.5-66.0)	23.2 (21.4-25.2)
10%	91.3 (83.6-96.2)	69.9 (63.8-75.5)	35.0 (32.9-37.2)
FPR, % (95% CI) to achieve DR of:			
100%	65.4 (65.1-65.8)	98.0 (97.9-98.1)	99.4 (96.7-97.2)
90%	5.0 (4.9-5.2)	30.8 (30.5-31.2)	65.0 (64.7-65.4)
80%	2.1(1.9-2.2)	17.2 (18.9-19.8)	47.8 (47.5-48.3)

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