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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gaccioli F, Sovio U, Cook E, Hund M, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using ultrasound and the sFLT1/PlGF ratio in nulliparous women: a prospective cohort study. *Lancet Child Adolesc Health* 2018; published online June 7. http://dx.doi.org/10.1016/S2352-4642(18)30129-9.

Supplementary Appendix for Gaccioli F, Sovio U, Cook E, Hund M, Charnock-Jones DS, Smith GCS
Screening for fetal growth restriction using ultrasound and the sFLT1:PlGF ratio in a prospective cohort study of nulliparous women

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STARD checklist

Supplementary References

Panel S1. Diagnostic criteria

Diagnosis of preeclampsia (based on the 2013 ACOG Guideline(1))

Hypertension, for the purposes of diagnosis of preeclampsia, was defined as one or more of the following:

- 2x diastolic blood pressure (DBP) >89 mmHg at least 4 hours apart
- 1x DBP >89 mmHg + (new antihypertensive treatment AND/OR magnesium sulphate)
- 1x DBP>109 mmHg
- 2x systolic blood pressure (SBP) >139 mmHg at least 4 hours apart
- 1x SBP >139 mmHg + (new antihypertensive treatment AND/OR magnesium sulphate)
- 1x SBP >159 mmHg

Severe hypertension, for the purposes of diagnosis of preeclampsia with severe features, was defined as any one of the following:

- 2x DBP >109 mmHg at least 4 hours apart
- 2x SBP >159 mmHg at least 4 hours apart
- 1x DBP >109 mmHg + (new antihypertensive Rx AND/OR magnesium sulphate)
- 1x SBP >159 mmHg + (new antihypertensive Rx AND/OR magnesium sulphate)

Proteinuria was defined as one or more of the following:

- Greater than or equal to 300 mg per L in a 24 hour urine collection
- 2x dipstick reading of 1+ or greater 4 hours apart at >20 weeks gestational age

Low platelets was defined as:

- Platelets <100 at ≥ 24 weeks gestational age up to 48h after delivery in a woman with normal levels (>150) <20 weeks

Elevated creatinine was defined as:

- Creatinine >99mmol/L at ≥ 24 weeks gestational age up to 48h after delivery in women with normal levels or unrecorded <20 weeks. If the first onset of the hypertension was after delivery measurements up to 7d after birth were included in the definition.

Elevated alanine transaminase (ALT) was defined as:

- ALT >49 at ≥ 24 weeks gestational age up to 48h after delivery in a woman with normal levels or unrecorded <20 weeks

Pulmonary oedema was defined on the basis of whether it was documented as being present when reviewing the paper case record

Severe cerebral or visual disturbance was defined as:

- Severe cerebral or visual disturbance documented in the paper case record, plus evidence of significant clinical concern, including 2 or more measures of uric acid

Preeclampsia was defined as:

- Hypertension (defined above) AND (Proteinuria AND/OR low platelets AND/OR elevated ALT AND/OR elevated creatinine AND/OR pulmonary oedema AND/OR severe cerebral/visual symptoms)

Preeclampsia with severe features was defined as:

- Preeclampsia AND (severe hypertension AND/OR low platelets AND/OR elevated ALT AND/OR elevated creatinine AND/OR pulmonary oedema AND/OR severe cerebral/visual symptoms)

Gestational hypertension (GH) was defined as hypertension (as above) but not preeclampsia in a woman who was not hypertensive prior to 20 weeks and had no history of renal disease or essential hypertension.

Severe gestational hypertension was defined as GH AND severe hypertension

Pre-existing hypertension was defined as:

- Record of any documented history of essential hypertension or documented past or present use of anti-hypertensives when booking for antenatal care AND/OR any DBP>89 prior to 20 weeks gestational age AND/OR any SBP>139 prior to 20 weeks gestational age

Pre-existing renal disease was defined as:

- Record of any documented history of renal disease AND/OR heavy proteinuria prior to 20 weeks

Super-imposed preeclampsia

- If there is pre-existing hypertension or renal disease, then preeclampsia is defined as super-imposed. Diagnosis of superimposed preeclampsia required either new proteinuria or evidence of systemic involvement.

Diagnosis of fetal growth restriction (FGR) using estimated fetal weight (EFW) and abdominal circumference (AC) growth velocity (based on Sovio et al, 2015(2))

Early FGR:

EFW using Hadlock equation and normal range <10th percentile at 28 weeks

AND

Change in the fetal AC z score from 20 weeks to 28 weeks in the lowest decile (less than -1.3289)

Late FGR:

EFW using Hadlock equation and normal range <10th percentile at 36 weeks

AND

Change in the fetal AC z score from 20 weeks to 36 weeks in the lowest decile (less than -1.4808)

Diagnosis of FGR using criteria of the Delphi procedure, described by Gordijn et al, Ultrasound Obstet Gynecol 2016.(3)

Early FGR (GA < 32 weeks, diagnosed at ~28 weeks):

AC <3rd percentile using INTERGROWTH-21ST reference(4) AND/OR EFW <3rd percentile using Hadlock equation(5) and Hadlock reference(6) AND/OR absent end-diastolic flow in the umbilical artery (UA-AEDF)

AND/OR

(i) AC < 10th percentile AND/OR EFW <10th percentile
AND
(ii) Pulsatility index in the uterine artery above the 95th percentile using Gomez reference(7) AND/OR pulsatility in the umbilical artery above the 95th percentile using Acharya reference(8)

Late FGR (GA ≥ 32 weeks, diagnosed at ~36 weeks):

AC <3rd percentile using INTERGROWTH-21ST reference[4] AND/OR EFW <3rd percentile using Hadlock equation[5] and Hadlock reference[6]

AND/OR

Two out of three of the following:
(i) AC < 10th percentile AND/OR EFW <10th percentile
(ii) AC AND/OR EFW crossing percentiles >2 quartiles (crossing percentiles from 75th to 25th is equivalent to a change in z score of less than -1.35) from 20wkGA to 36wkGA visit or from 28wkGA to 36wkGA visit
(iii) Pulsatility index in the umbilical artery above the 95th percentile using Acharya reference[7]

Note: the original definition for late FGR (iii) also included "AND/OR cerebro-placental ratio below the 5th percentile" (this is the ratio of the pulsatility index of the middle cerebral artery (MCA) to the pulsatility index of the umbilical artery, as measured by Doppler flow velocimetry). However, this could not be measured as Doppler flow velocimetry of the MCA was not performed as part of the POP study.

Panel S2. Analysis plans

Analysis plan for assessing the diagnostic effectiveness of ultrasonic fetal biometry plus sFLT1 and PlGF at ~28 weeks of gestational age (wkGA) as a screening test for delivery of a small for gestational age (SGA) fetus, in the Pregnancy Outcome Prediction study (PMID 19019223 & 26360240).

1. Aim

To assess the diagnostic effectiveness of screening for SGA and associated complications using the combination of ultrasonic fetal biometry and measurement of sFLT1 and PlGF at ~28wkGA using data from the Pregnancy Outcome Prediction study (PMID 19019223 & 26360240).

2. Defining exposure

2.1 Primary exposure

The primary exposure will be the combination of ultrasonic diagnosis of SGA plus screen positive by biochemical testing at the 28wkGA visit. Ultrasonic diagnosis of SGA will be defined as lowest decile of estimated fetal weight (EFW), based on a previously published reference range (Hadlock et al, 1991), as previously described (PMID 26360240). Screen positive by biochemical testing: At 36 weeks, we used a previously defined cut off of >38 for the sFLT1:PlGF ratio, which was equivalent to >85th percentile using the distribution in our population. However, this threshold represents the 99.5th percentile at 28 weeks, hence we will use the cut point >5.78 at 28 weeks, which reflects the 85th percentile at 28 weeks.

2.2 Secondary exposures

2.2.1 Alternative classifications of the biochemical data

In order to compare different methods of characterising the biochemical data, we will explore the association between the outcome (see below) and the biochemical data on its own (i.e. without reference to US diagnosis of SGA). We will compare the sFLT1:PlGF ratio with sFLT1 on its own and PlGF on its own. In all of the following, analysis of the ratio will be on the basis of the absolute values of sFLT1 and PlGF, not on the derived multiples of the median. When using analysis of multiples of the median for values of sFLT1 or PlGF on their own, where the maternal weight is missing, the multiples of the median will be calculated using gestational age without correction for maternal weight.

Associations will be compared using:

(i) the highest decile of the sFLT1:PlGF ratio will be compared with the highest decile of sFLT1 and the lowest decile of PlGF, using study derived thresholds of the sFLT1:PlGF ratio and of the absolute concentrations of sFLT1 and PlGF.

(ii) the highest decile of the sFLT1:PlGF ratio will be compared with the highest decile of sFLT1 and the lowest decile of PlGF, using study derived thresholds of the sFLT1:PlGF ratio and study derived thresholds of sFLT1 and PlGF expressed as gestational age and maternal weight adjusted multiples of the median.

(iii) the sFLT1:PlGF ratio, sFLT1 and PlGF will all be compared as continuous variables, using the absolute concentrations of sFLT1 and PlGF.

(iv) the sFLT1:PlGF ratio, sFLT1 and PlGF will all be compared as continuous variables, using gestational age and maternal weight adjusted multiples of the median of sFLT1 and PlGF.

If one of the above approaches indicates that sFLT1 on its own or PlGF on its own are superior to the sFLT1:PlGF ratio, we will repeat the primary analysis using the given approach.

2.2.2 More inclusive classifications

We will repeat the main analysis using the threshold <20th percentile of EFW for the 28wkGA ultrasound and >80th percentile for the sFLT1:PlGF ratio.

3. Defining outcomes

3.1 Primary outcome

The primary outcome will be preterm delivery of an SGA infant defined by customised birth weight <10th percentile, using Gestation-Related Optimal Weight (GROW) calculator version 6.7.8.

3.2 Secondary outcomes

3.2.1. We will repeat the analysis using customised birth weight <5th percentile cut-off.

3.2.2. Population-based SGA using birth weight standard

We will repeat the analyses for the preterm delivery outcome where SGA is defined by birth weight <10th percentile for sex and gestational age, as previously described (PMID 26360240).

3.2.3. Population-based SGA using fetal weight standard

We will repeat the analysis using a fetal growth standard (Hadlock) adjusted only for sex and gestational age.

3.2.4. We will repeat the above analyses for any delivery of an SGA infant, whether preterm or term.

3.2.5. We will also compare the associations with complications at term, as described in our previous analysis plan, dated 14 May 2016.

4. Secondary analyses

4.1 Risk of perinatal morbidity in non-SGA infants

We will repeat the analyses relating biochemical data (i.e. without US) to the outcomes of subsequent delivery of a non-SGA infant (i) experiencing any perinatal complications, (ii) severe adverse perinatal outcome (both excluding cases with any pregnancy associated hypertensive morbidity, i.e. gestational hypertension or preeclampsia of any severity [this analysis will include women with pre-existing essential hypertension unless they also have super-imposed preeclampsia]).

4.2 Comparison of primary outcome in relation to presence or absence of preeclampsia, i.e. the main analyses above will be repeated separating the primary outcomes into those with or without a diagnosis of gestational hypertension or preeclampsia.

4.3 All preterm birth

We will also analyse the exposures in relation to the risk of any subsequent preterm birth. We will also analyse the association with sub-groups of preterm birth, as defined in PMID 27370790.

5. Analytic approach

Analysis will be performed using 2x2 tables and calculation of standard screening summary statistics (sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios). We will also describe the association between the outcomes and the sFLT1:PlGF ratio or PlGF as continuous variables by plotting the receiver operating characteristic (ROC) curve and estimating the c statistic (= the area under the ROC curve). C statistics will be compared using the method of De Long (PMID 3203132). Finally, we will analyse preterm birth by time to event methods, i.e. plot of cumulative incidence of birth from time of measurement, while accounting for competing risks (PMID 22906914).

6. Presentation of results.

In the publication, any analyses not described above will be clearly identified as not part of the original analysis plan.

7. Additional post hoc analyses:

7.1 We also calculated the area under the ROC curve for preeclampsia leading to preterm birth associated with delivery of a non-SGA infant.

7.2. We repeated the main analysis (primary exposure and primary outcome) excluding the women who had their research scan result revealed.

7.3 We performed ROC curve analysis of the sFLT1:PlGF ratio in women with an EFW $<10^{th}$ to assess the suitability of the $>85^{th}$ percentile threshold.

7.4. We analysed the Delphi procedure definition of early FGR in relation to the primary outcome. We also analysed the combination between the Delphi definition and the sFLT1:PlGF ratio in relation to the primary outcome.

8. Analyses included in the plan where data are not presented in the paper or Supplementary Appendix.

8.1 We did not report the comparison of primary outcome in relation to presence or absence of preeclampsia (4.2) since our numbers for this stratified analysis were inadequate.

8.2. We did not report the analysis by different subgroups of preterm birth (4.3) since our numbers for this analysis using the primary exposure were inadequate.

Analysis plan for assessing the diagnostic effectiveness of ultrasonic fetal biometry plus sFLT1 and PlGF at ~36 weeks of gestational age (wkGA) as a screening test for delivery of a small for gestational age (SGA) fetus with associated morbidity, in the Pregnancy Outcome Prediction study (PMID 19019223 & 26360240).

1. Aim

To assess the diagnostic effectiveness of screening for SGA and associated complications using the combination of ultrasonic fetal biometry and measurement of sFLT1 and PlGF at ~36wkGA using data from the Pregnancy Outcome Prediction study (PMID 19019223 & 26360240).

2. Defining exposure

2.1 Primary exposure

The primary exposure will be the combination of ultrasonic diagnosis of SGA plus screen positive by biochemical testing at the 36wkGA visit. Ultrasonic diagnosis of SGA will be defined as lowest decile of estimated fetal weight (EFW), based on a previously published reference range (Hadlock et al, 1991), as previously described (PMID 26360240). Screen positive by biochemical testing will be defined as an sFLT1:PlGF ratio of >38, as previously described for predicting the absence of preeclampsia among women who were clinically suspected to have the condition (PMID 26735990).

2.2 Secondary exposures

2.2.1 Analysis of more severe elevation of the ratio

We will also study the associations using a second threshold of the sFLT1:PlGF ratio, namely, >110.

2.2.2 Alternative classifications of the biochemical data

In order to compare different methods of characterising the biochemical data, we will explore the association between the outcome (see below) and the biochemical data on its own (i.e. without reference to US diagnosis of SGA). We will compare the sFLT1:PlGF ratio with sFLT1 on its own and PlGF on its own. In all of the following, analysis of the ratio will be on the basis of the absolute values of sFLT1 and PlGF, not on the derived multiples of the median. When using analysis of multiples of the median for values of sFLT1 or PlGF on their own, where the maternal weight is missing, the multiples of the median will be calculated using gestational age without correction for maternal weight.

Associations will be compared using:

(i) the highest decile of the sFLT1:PlGF ratio will be compared with the highest decile of sFLT1 and the lowest decile of PlGF, using study derived thresholds of the sFLT1:PlGF ratio and of the absolute concentrations of sFLT1 and PlGF.

(ii) the highest decile of the sFLT1:PlGF ratio will be compared with the highest decile of sFLT1 and the lowest decile of PlGF, using study derived thresholds of the sFLT1:PlGF ratio and study derived thresholds of sFLT1 and PlGF expressed as gestational age and maternal weight adjusted multiples of the median.

(iii) the sFLT1:PlGF ratio, sFLT1 and PlGF will all be compared as continuous variables, using the absolute concentrations of sFLT1 and PlGF.

(iv) the sFLT1:PlGF ratio, sFLT1 and PlGF will all be compared as continuous variables, using gestational age and maternal weight adjusted multiples of the median of sFLT1 and PlGF.

If one of the above approaches indicates that sFLT1 on its own or PlGF on its own are superior to the sFLT1:PlGF ratio, we will repeat the primary analysis using the given approach.

2.2.3 Comparison with abdominal circumference growth velocity (ACGV)

We previously demonstrated that lowest decile of ACGV discriminated between SGA infants who were or were not at increased risk of perinatal morbidity (PMID 26360240). We will compare the ability of the biochemical measures (expressed as deciles) to discriminate between ultrasonically diagnosed SGA infants at risk of the primary outcome, with the ability of lowest decile of ACGV. We will also compare the association between ultrasonic SGA + lowest decile of ACGV with or without sFLT1:PlGF ratio >38 and the risk of the primary outcome.

3. Defining outcomes

3.1 Primary outcome

The primary outcome will be subsequent delivery of an SGA infant (birth weight $<10^{th}$ percentile for sex and gestational age, as previously described (PMID 26360240) experiencing 1 or more of the following complications, (i) non-anomalous perinatal death (i.e. stillbirth or neonatal death), (ii) any neonatal morbidity, or (iii) maternal preeclampsia. The composite outcome "any neonatal morbidity" will be defined as per our previous publication (PMID 26360240) and preeclampsia will be defined as per the 2013 ACOG classification (PMID 24150027).

3.2 Secondary outcomes

3.2.1 SGA plus severe adverse outcome

We will also study the associations with the outcome of an SGA infant experiencing severe adverse outcome, and this will be defined as either severe adverse perinatal outcome (defined as previously described in PMID 26360240) or preeclampsia with severe features as per the 2013 ACOG classification (PMID 24150027).

3.2.2 Severe SGA ± adverse outcome

We will also study the association with severe SGA, defined as a birth weight percentile <3rd, irrespective of the presence or absence of neonatal or maternal morbidity.

4. Analytic approach

Analysis will be performed using 2x2 tables and calculation of standard screening summary statistics (sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios). We will also describe the association between the outcomes and the sFLT1:PlGF ratio or PlGF as continuous variables by plotting the receiver operating characteristic (ROC) curve and estimating the c statistic (= the area under the ROC curve). C statistics will be compared using the method of De Long (PMID 3203132). The ability of measurements to differentiate between ultrasonic diagnosis of SGA and the risk of morbidity will be assessed using stratified analysis and comparing associations using the Mantel-Haenszel test, as previously described for ACGV and a range of other markers of fetal growth restriction (PMID 26360240).

5. Secondary analyses

5.4.1 Comparison with ultrasonic diagnosis of FGR

A recent DELPHI consensus process (PMID 26909664) has described a widely accepted definition of late (>32 weeks) fetal growth restriction. The definition is as follows:

1: Abdominal circumference below the 3rd centile, or estimated fetal weight below the 3rd centile

OR

2: At least two out of three of the following:

(i) AC < 10th centile OR EFW <10th centile

(ii) AC OR EFW crossing centiles >2 quartiles (crossing centiles from 75th to 25th is equivalent to a decrease in z score of >1.35 which will be used as a basis of this definition) from 20wkGA to 36wkGA visit or from 28wkGA to 36wkGA visit.

(iii) Cerebro-placental ratio below the 5th centile OR pulsatility index in the umbilical artery above the 95th centile.

This definition will be applied using primarily the InterGrowth-21st normal range for AC (PMID 25209488), the Hadlock normal range for EFW (PMID 1887021), and the Acharya normal range for umbilical artery Doppler PI (PMID 15746695). We will also repeat the analysis using internally derived reference ranges (PMID 26360240). We are unable to include the cerebro-placental ratio in the definition as MCA Doppler was not performed in the POPs study.

We will determine the ability of the sFLT1:PlGF ratio to predict this ultrasonic diagnosis. We will also compare the ability of the findings above versus an sFLT1:PlGF ratio >38 or >110 to differentiate between SGA infants (on the basis of the 36wkGA research ultrasound) at risk of morbidity (same methods as described above for the AC growth velocity in section 2.2.3).

5.4.2 Customised birth weight percentile

We will repeat the analyses relating biochemical data (i.e. without US) to the primary and secondary outcomes where SGA birth weight is defined by customised birth weight percentile (defined as previously described in PMID 26360240).

5.4.3 Risk of perinatal morbidity in non-SGA infants

We will repeat the analyses relating biochemical data (i.e. without US) to the outcomes of subsequent delivery of a non-SGA infant (i) experiencing any perinatal complications, (ii) severe adverse perinatal outcome (both excluding cases with any pregnancy associated hypertensive morbidity, i.e. gestational hypertension or preeclampsia of any severity [this analysis will include women with pre-existing essential hypertension unless they also have super-imposed preeclampsia]).

5.4.4 Comparison of primary outcome in relation to presence or absence of preeclampsia, i.e. the main analyses above will be repeated separating the primary outcomes into those with or without a diagnosis of gestational hypertension or preeclampsia.

6. Presentation of results.

In the publication, any analyses not described above will be clearly identified as not part of the original analysis plan.

7. Statement

The above plan was drawn up prior to any analysis of the relationship between sFLT1, PlGF, or the ratio of sFLT1:PlGF and the maternal risk of adverse outcome in the Pregnancy Outcome Prediction study, with one exception. A previous analysis plan (23rd February 2016) included quantifying the association between the sFLT1: PlGF ratio and the risk of preeclampsia associated with SGA birth weight, and we further analysed the association between the ratio and the risk of preeclampsia associated with severe SGA. This analysis was confined to using the ROC curve and did not include ultrasonic assessment of SGA.

8. Additional post hoc analyses:

8.1 We also calculated the area under the ROC curve for preeclampsia associated with delivery of a non-SGA infant.

8.2. We repeated the main analysis (primary exposure and primary outcome) excluding the women who had their research scan result revealed.

8.3 We performed ROC curve analysis of the sFLT1:PlGF ratio in women with an EFW $<10^{th}$ to assess the suitability of the >38 threshold.

9. Analyses included in the plan where data are not presented in the paper or Supplementary Appendix.

9.1 We did not report the analysis of the Delphi procedure definition of FGR using internally derived references ranges as it had no effect on the results.

9.2 We did not report any analyses where SGA birth weight is defined by customised birth weight percentile as it had no effect on any of the results.

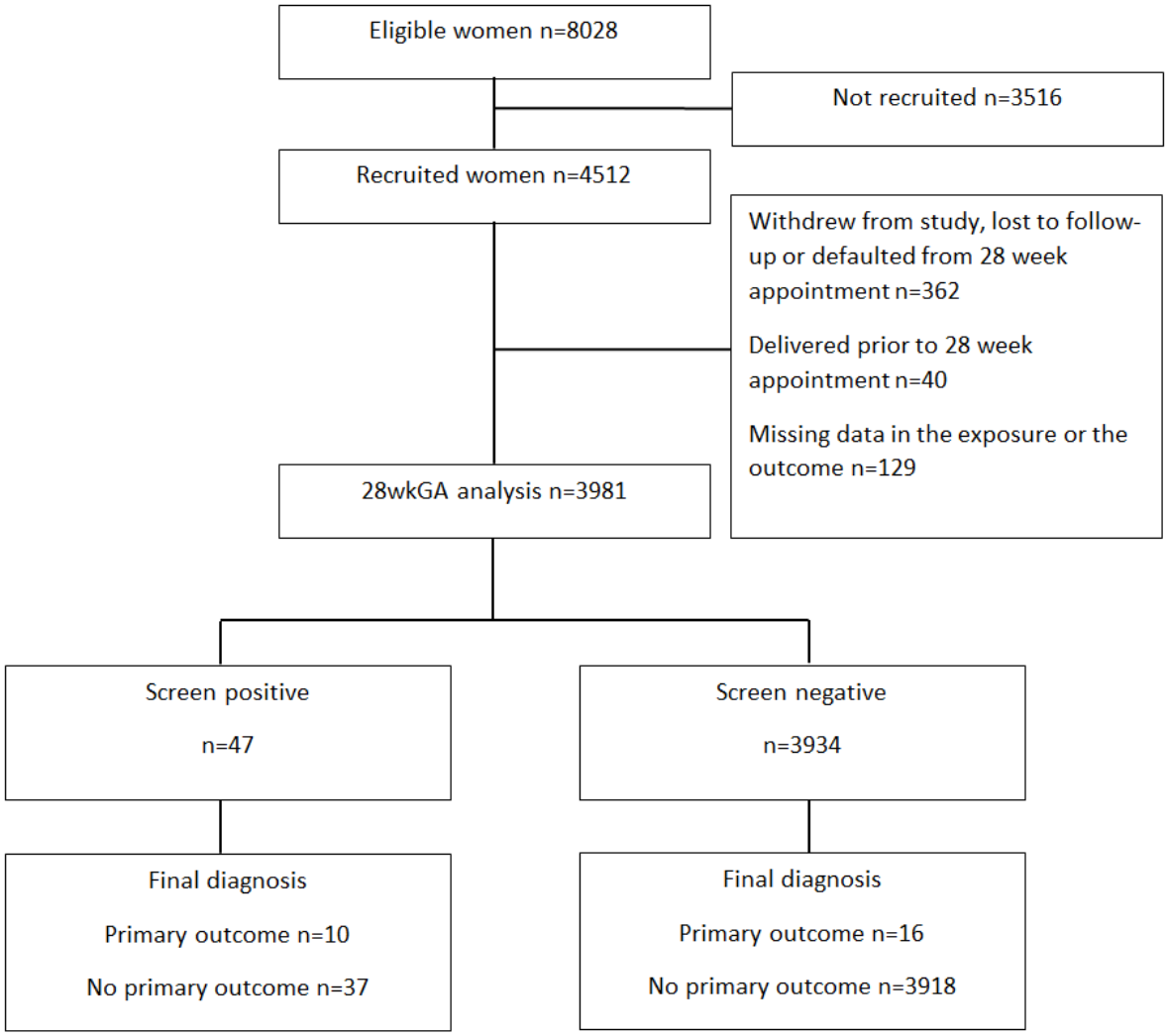

Figure S1. STARD flowchart for the primary analysis based on measurements at 28wkGA

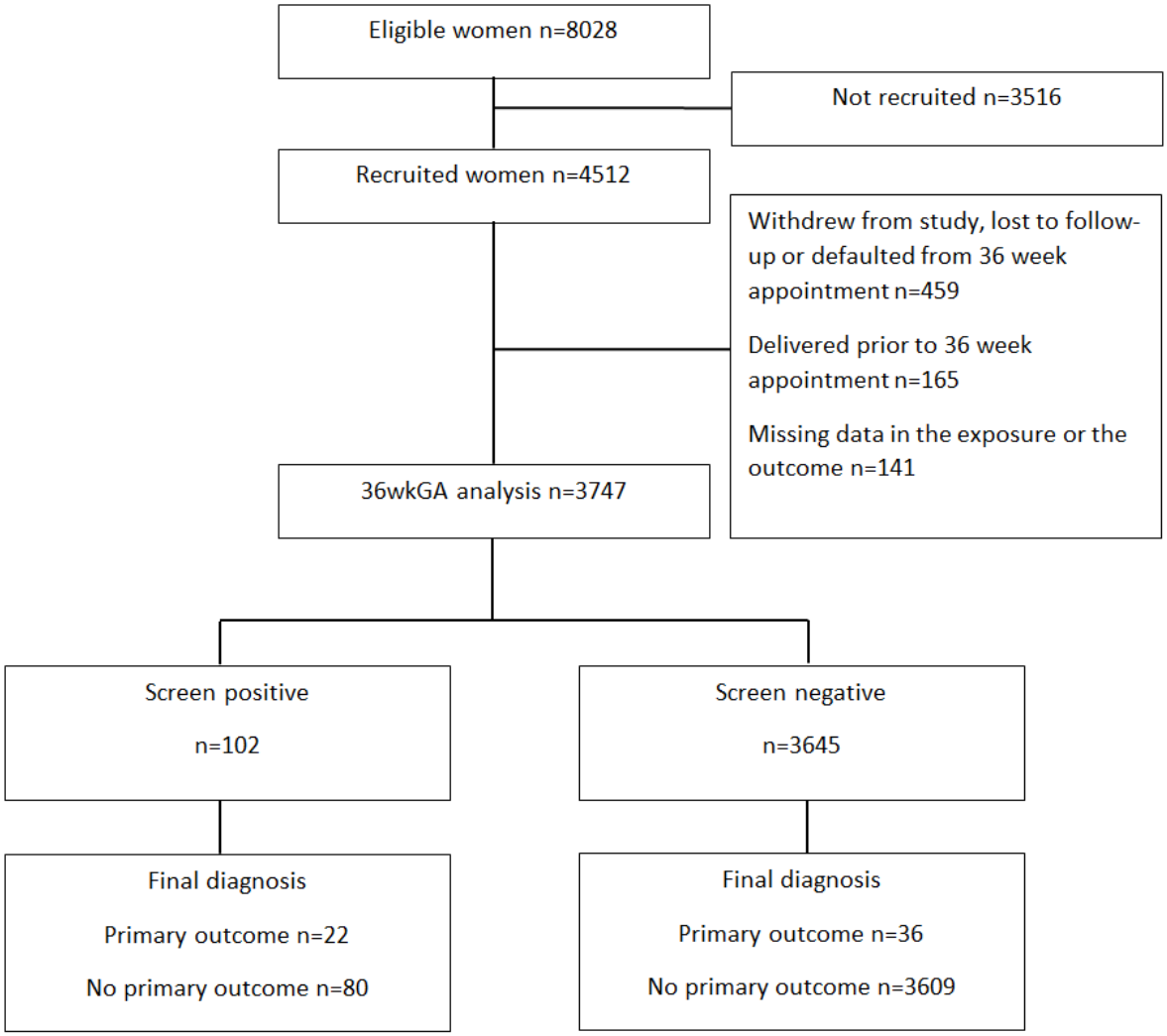

Figure S2. STARD flowchart for the primary analysis based on measurements at 36wkGA

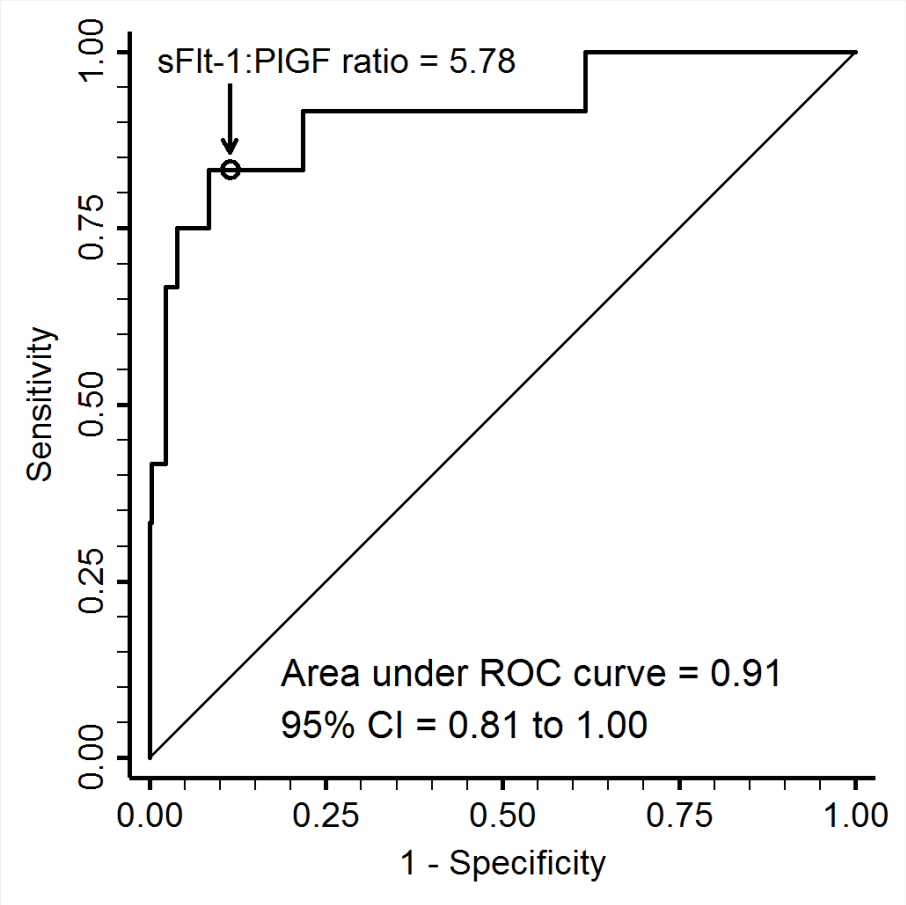

Figure S3. Receiver operating characteristic curve analysis of the relationship between the sFLT1:PlGF ratio and the risk of preterm delivery of an SGA infant (by customised birth weight standard, n=12) among women with an EFW <10th percentile at 28wkGA (total n=320)

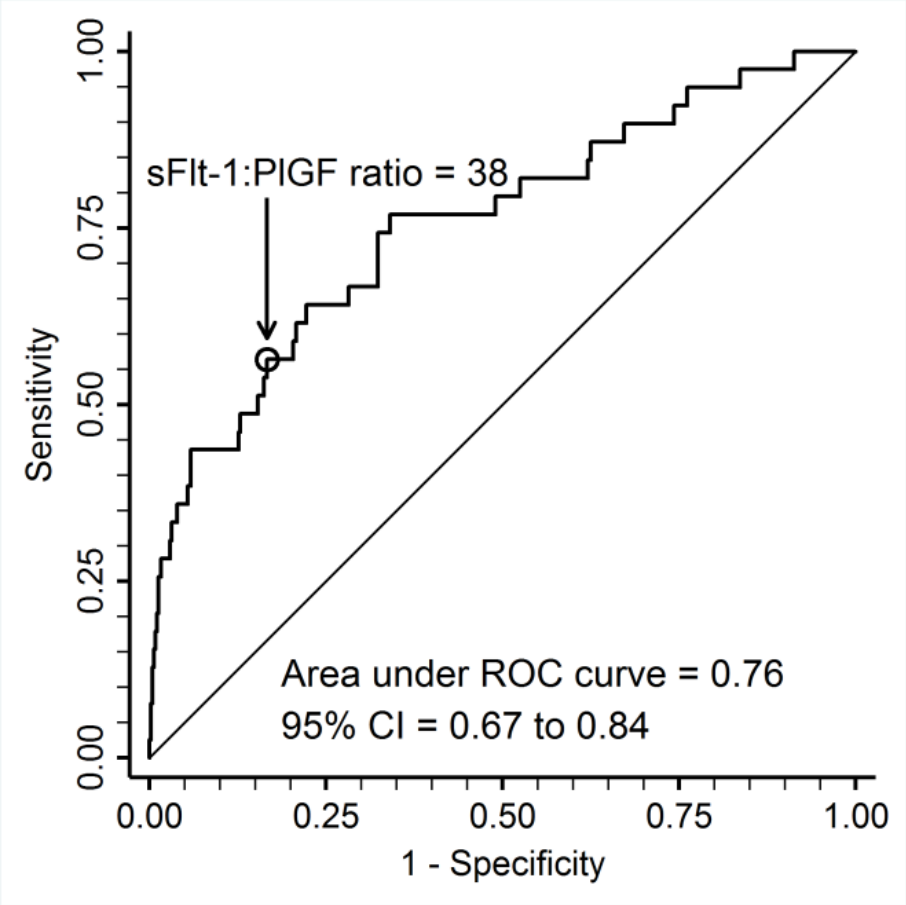

Figure S4. Receiver operating characteristic curve analysis of the relationship between the sFLT1:PlGF ratio and the subsequent risk of delivering an SGA infant with either maternal preeclampsia or perinatal morbidity or mortality (n=39) among women with an EFW <10th percentile at 36wkGA (total n=521)

Table S1. Screening performance of ultrasonic and biochemical screening at 28wkGA for preterm delivery of an SGA infant using population-based birth weight percentile

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th	9/311	3657/4	8.8 (6.1-12.9)	0.33 (0.15-0.75)	69.2	92.2	2.8	99.9
sFLT1:PlGF ratio >5.78	9/584	3384/4	4.7 (3.2-6.8)	0.36 (0.16-0.82)	69.2	85.3	1.5	99.9
Ultrasonic EFW <10th and sFLT1:PlGF ratio >5.78	7/40	3928/6	53.4 (29.6-96.4)	0.47 (0.26-0.84)	53.8	99.0	14.9	99.8
Ultrasonic EFW <10th and lowest decile of ACGV*	2/86	3864/11	7.1 (1.9-25.7)	0.86 (0.69-1.09)	15.4	97.8	2.3	99.7
Delphi procedure definition of early FGR*	9/109	3756/4	24.5 (16.3-36.9)	0.32 (0.14-0.72)	69.2	97.2	7.6	99.9

*See Panel S1 for definitions. Abbreviations: wkGA denotes weeks of gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.

Table S2. Screening performance of ultrasonic and biochemical screening at 28wkGA for preterm delivery of an SGA infant using partially customised birth weight percentile*

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th	15/305	3633/28	4.5 (3.0-6.9)	0.71 (0.57-0.87)	34.9	92.3	4.7	99.2
sFLT1:PlGF ratio >5.78	21/572	3366/22	3.4 (2.5-4.6)	0.60 (0.45-0.80)	48.8	85.5	3.5	99.4
Ultrasonic EFW <10th and sFLT1:PlGF ratio >5.78	10/37	3901/33	24.8 (13.2-46.5)	0.77 (0.66-0.91)	23.3	99.1	21.3	99.2
Ultrasonic EFW <10th and lowest decile of ACGV†	4/84	3836/39	4.3 (1.7-11.3)	0.93 (0.84-1.02)	9.3	97.9	4.5	99.0
Delphi procedure definition of early FGR†	14/104	3733/27	12.6 (7.9-20.1)	0.68 (0.54-0.84)	34.1	97.3	11.9	99.3

*Partially customised birth weight percentile used the Hadlock fetal weight standard (similarly to fully customised percentile), and customisation was performed only for fetal sex and gestational age. The partially customised birth weight percentile was calculated using the GROW v6.7.8.1(UK) bulk calculator (Perinatal Institute). †See Panel S1 for definitions. Abbreviations: wkGA denotes weeks of gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.

Table S3. Screening performance of ultrasonic and biochemical screening at 28wkGA for preterm delivery of an infant with a birth weight <5th percentile (customised)

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th	10/310	3653/8	7.1 (4.6-10.9)	0.48 (0.29-0.81)	55.6	92.2	3.1	99.8
sFLT1:PlGF ratio >5.78	14/579	3384/4	5.3 (4.1-6.9)	0.26 (0.11-0.62)	77.8	85.4	2.4	99.9
Ultrasonic EFW <10th and sFLT1:PlGF ratio >5.78	9/38	3925/9	52.1 (29.8-91.3)	0.50 (0.32-0.80)	50.0	99.0	19.1	99.8
Ultrasonic EFW <10th and lowest decile of ACGV†	2/86	3859/16	5.1 (1.4-19.1)	0.91 (0.77-1.07)	11.1	97.8	2.3	99.6
Delphi procedure definition of early FGR†	10/108	3752/8	19.9 (12.6-31.2)	0.46 (0.27-0.77)	55.6	97.2	8.5	99.8

The customised birth weight percentile was calculated using the GROW v6.7.8.1(UK) bulk calculator (Perinatal Institute). †See Panel S1 for definitions. Abbreviations: wkGA denotes weeks of gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.

Table S4. Outcome data of 47 women who screened positive with ultrasonic EFW <10th percentile and sFLT1:PlGF ratio >5.78 at 28wkGA

Characteristic	
Clinical scan between 22-27 completed weeks	
Performed, n (%)	7 (15)
Demonstrated EFW<10th, n (%)	4 (8.5)
Hypertensive before or at 28 week scan, n (%)	4 (8.5)
Induced labor, n (%)	14 (30)
Mode of delivery	
Spontaneous vaginal, n (%)	28 (60)
Operative vaginal, n (%)	7 (15)
Pre-labor caesarean, n (%)	10 (21)
Intrapartum caesarean, n (%)	2 (4.3)
Birth weight (g)	
Birth weight (IQR)	2800 (2190-3175)
Centile (IQR)	7.6 (1.3-20.7)
Birth weight <2,500g	16 (34)
Birth weight <10th percentile, n (%)	25 (53)
Birth weight <3rd percentile, n (%)	15 (32)
Gestational age at delivery (weeks)	
Median (IQR)	39.7 (37.4-40.7)
Preterm birth, n (%)	10 (21)
Preeclampsia, n (%)	
Any	7 (15)
With severe features	4 (8.5)
With birth weight <10th percentile	6 (13)
With birth weight <3rd percentile	5 (11)
Perinatal morbidity	
Any morbidity preterm or term	13 (28)
Apgar <7, n (%)	2 (4.3)
Metabolic acidosis, n (%)	1 (2.1)
Admission to neonatal unit, n (%)	12 (26)
Severe morbidity/mortality, n (%)	2 (4.3)*
Stillbirth, n (%)	0 (0.0)

Data are expressed as median (IQR) or n (%) as appropriate. Birth weight centile was calculated using the customised birth weight reference (GROW v6.7.8.1(UK) bulk calculator, Perinatal Institute). Abbreviations: wkGA denotes weeks of gestational age, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor.

*One of the two had severe metabolic acidosis and neonatal death at term.

Table S5. Screening performance of ultrasonic and biochemical screening at 28wkGA for subsequent delivery of an SGA infant (birth weight <10th customised centile) at any gestational age (preterm or term)

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th	96/224	3360/301	3.9 (3.1-4.8)	0.81 (0.76-0.86)	24.2	93.8	30.0	91.8
sFLT1:PlGF ratio >5.78	113/480	3104/284	2.1 (1.8-2.5)	0.83 (0.78-0.88)	28.5	86.6	19.1	91.6
Ultrasonic EFW <10th and sFLT1:PlGF ratio >5.78	25/22	3562/372	10.3 (5.8-18.0)	0.94 (0.92-0.97)	6.3	99.4	53.2	90.5
Ultrasonic EFW <10th and lowest decile of ACGV*	26/62	3504/371	3.8 (2.4-5.9)	0.95 (0.93-0.98)	6.5	98.3	29.5	90.4
Delphi procedure definition of early FGR*	55/62	3430/330	8.0 (5.7-11.4)	0.87 (0.84-0.91)	14.3	98.2	47.0	91.2

*See Panel S1 for definitions. Abbreviations: wkGA denotes weeks of gestational age, SGA denotes small for gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.

Table S6. Screening performance of ultrasonic and biochemical screening at 28wkGA for subsequent delivery of an SGA infant (birth weight <10th customised centile) with maternal preeclampsia or perinatal morbidity or mortality at any gestational age

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th	25/295	3589/72	3.4 (2.4-4.8)	0.80 (0.71-0.90)	25.8	92.4	7.8	98.0
sFLT1:PlGF ratio >5.78	55/538	3346/42	4.1 (3.4-5.0)	0.50 (0.40-0.63)	56.7	86.1	9.3	98.8
Ultrasonic EFW <10th and sFLT1:PlGF ratio >5.78	14/33	3851/83	17.0 (9.4-30.7)	0.86 (0.80-0.94)	14.4	99.2	29.8	97.9
Ultrasonic EFW <10th and lowest decile of ACGV†	8/80	3786/89	4.0 (2.0-8.0)	0.94 (0.88-0.99)	8.2	97.9	9.1	97.7
Delphi procedure definition of early FGR†	19/99	3688/72	8.0 (5.1-12.5)	0.81 (0.73-0.90)	20.9	97.4	16.1	98.1

†See Panel S1 for definitions. Abbreviations: wkGA denotes weeks of gestational age, SGA denotes small for gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.

Table S7. Screening performance of ultrasonic and biochemical screening at 36wkGA for subsequent risk of delivering an SGA infant with either maternal preeclampsia with severe features or severe adverse perinatal outcome

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th percentile	8/513	3222/4	4.9 (3.2-7.3)	0.39 (0.17-0.86)	66.7	86.3	1.5	99.9
sFLT1:PlGF ratio >38	8/555	3180/4	4.5 (3.0-6.7)	0.39 (0.18-0.87)	66.7	85.1	1.4	99.9
Ultrasonic EFW <10th percentile and sFLT1:PlGF ratio >38	5/97	3638/7	16.0 (8.0-32.2)	0.60 (0.37-0.97)	41.7	97.4	4.9	99.8
Ultrasonic EFW <10th percentile and lowest decile ACGV*	4/157	3564/8	7.9 (3.5-17.8)	0.70 (0.47-1.04)	33.3	95.8	2.5	99.8
Delphi procedure definition of late FGR*	7/405	3274/5	5.3 (3.3-8.6)	0.47 (0.24-0.91)	58.3	89.0	1.7	99.8

Abbreviations: wkGA denotes weeks of gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.
*See Panel S1 for definitions

Table S8. Screening performance of ultrasonic and biochemical screening at 36wkGA for subsequent delivery of an infant with a birth weight <3rd percentile (using population reference) irrespective of perinatal morbidity or preeclampsia

Screening test	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <10th percentile	60/461	3208/18	6.1 (5.3-7.1)	0.26 (0.18-0.40)	76.9	87.4	11.5	99.4
sFLT1:PlGF ratio >38	29/534	3135/49	2.6 (1.9-3.4)	0.74 (0.62-0.87)	37.2	85.4	5.2	98.5
Ultrasonic EFW <10th percentile and sFLT1:PlGF ratio >38	25/77	3592/53	15.3 (10.3-22.6)	0.69 (0.60-0.81)	32.1	97.9	24.5	98.5
Ultrasonic EFW <10th percentile & lowest decile ACGV*	22/139	3516/56	7.4 (5.0-11.0)	0.75 (0.65-0.86)	28.2	96.2	13.7	98.4
Delphi procedure definition of late FGR*	53/359	3254/25	6.8 (5.7-8.2)	0.36 (0.26-0.49)	67.9	90.1	12.9	99.2

Abbreviations: wkGA denotes weeks of gestational age, SGA denotes small for gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, ACGV denotes abdominal circumference growth velocity, and FGR denotes fetal growth restriction.
*See Panel S1 for definitions

Table S9. Outcome data of 102 women who screened positive with ultrasonic EFW <10th percentile and sFLT1:PlGF ratio >38 at 36wkGA

Characteristic	
Clinically-indicated scan between 24-35 weeks	
Performed, n (%)	38 (37)
Demonstrated EFW<10th, n (%)	14 (14)
Hypertensive before or at 36 week scan, n (%)	14 (14)
Induced labour, n (%)	
All, n (%)	37 (36)
Prior to 40 weeks, n (%)	22 (22)
Mode of delivery	
Spontaneous vaginal, n (%)	53 (52)
Operative vaginal, n (%)	22 (22)
Pre-labour caesarean, n (%)	16 (16)
Intrapartum caesarean, n (%)	11 (11)
Birth weight (g)	
Birth weight (IQR)	2710 (2390-3000)
Centile (IQR)	10.4 (3.3-21.2)
Birth weight <2,500g	33 (32)
Birth weight <10th percentile, n (%)	48 (47)
Birth weight <3rd percentile, n (%)	25 (25)
Gestational age at delivery (weeks)	
Median (IQR)	39 (38-40)
Preeclampsia, n (%)	
Any	23 (23)
With severe features	13 (13)
With birth weight <10th percentile	11 (11)
With birth weight <3rd percentile	6 (5.9)
Perinatal morbidity	
Any morbidity	19 (19)
Apgar <7, n (%)	0 (0.0)
Metabolic acidosis, n (%)	1 (1.0)
Admission to neonatal unit, n (%)	18 (18)
Severe morbidity/mortality, n (%)	1 (1.0)

Data are expressed as median (IQR) or n (%) as appropriate. Birth weight centile was calculated using a population-based UK reference range. Abbreviations: EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, wkGA denotes weeks of gestational age, and IQR denotes interquartile range.

Table S10. Screening performance for subsequent risk of delivering an SGA infant with either maternal preeclampsia or perinatal morbidity or mortality of biochemical screening versus ultrasonic measurements among women with EFW <10th at 36wkGA

Finding	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Highest decile sFLT1:PlGF ratio	17/60	422/22	3.5 (2.3-5.4)	0.64 (0.49-0.85)	43.6	87.6	22.1	95.0
sFLT1:PlGF ratio >38	22/80	402/17	3.4 (2.4-4.8)	0.52 (0.36-0.75)	56.4	83.4	21.6	95.9
Lowest decile ACGV*	18/143	337/21	1.5 (1.1-2.2)	0.77 (0.57-1.03)	46.2	70.2	11.2	94.1
Delphi procedure definition of late FGR*	34/330	150/5	1.3 (1.1-1.5)	0.41 (0.18-0.94)	87.2	31.3	9.3	96.8
Lowest decile ACGV & sFLT1:PlGF ratio >38	12/27	453/27	5.5 (3.0-9.9)	0.73 (0.59-0.91)	30.8	94.4	30.8	94.4
Lowest decile ACGV & sFLT1:PlGF ratio ≤38	6/116	364/33	0.6 (0.3-1.4)	1.12 (0.97-1.29)	15.4	75.8	4.9	91.7

Abbreviations: EFW denotes estimated fetal weight, wkGA denotes weeks of gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, FGR denotes fetal growth restriction, and ACGV denotes abdominal circumference growth velocity. The cut-off points were 49.82 for the highest decile of sFLT1:PlGF ratio and -1.4808 for the lowest decile of the ACGV.
*See Panel S1 for definitions

Table S11. Screening performance of ultrasonic and biochemical screening for subsequent risk of delivering an SGA infant with either maternal preeclampsia or perinatal morbidity or mortality using the sFLT1:PlGF ratio threshold of 110 at 36wkGA

Finding	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
sFLT1:PlGF ratio >110	13/56	3633/45	14.8 (8.6-25.5)	0.79 (0.69-0.90)	22.4	98.5	18.8	98.8
Ultrasonic EFW <10th percentile & sFLT1:PlGF ratio >110	10/8	3681/48	79.5 (32.6-194.1)	0.83 (0.74-0.93)	17.2	99.8	55.6	98.7

Abbreviations: sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, wkGA denotes weeks of gestational age, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, and EFW denotes estimated fetal weight.

Table S12. Screening performance of biochemical screening (sFLT1:PlGF ratio >5.78 at 28wkGA) for preterm non-SGA infants experiencing complications excluding preeclampsia and gestational hypertension*

Outcome	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Preterm non-SGA + perinatal complications	12/581	3344/44	1.45 (0.87-2.40)	0.92 (0.80-1.06)	21.4	85.2	2.0	98.7
Preterm non-SGA + severe adverse perinatal outcome	5/588	3383/5	3.38 (1.81-6.30)	0.59 (0.32-1.09)	50.0	85.2	0.84	99.9

*Complication is defined as perinatal morbidity or non-anomalous perinatal death excluding preeclampsia and gestational hypertension. Abbreviations: sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, wkGA denotes weeks of gestational age, non-SGA denotes not small for gestational age (birth weight $\geq 10^{th}$ percentile using customised standard), TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value and NPV denotes negative predictive value.

Table S13. Screening performance of biochemical screening (sFLT1:PlGF ratio >38 at 36wkGA) for non-SGA infants experiencing complications excluding preeclampsia and gestational hypertension*

Outcome	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Non-SGA + any perinatal complications	27/536	3034/150	1.02 (0.71-1.45)	1.00 (0.94-1.06)	15.3	85.0	4.8	95.3
Non-SGA + severe adverse perinatal outcome	5/558	3169/15	1.67 (0.78-3.58)	0.88 (0.68-1.14)	25.0	85.0	0.89	99.5

*Complication is defined as perinatal morbidity or non-anomalous perinatal death excluding preeclampsia and gestational hypertension. Abbreviations: sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placental growth factor, wkGA denotes weeks of gestational age, non-SGA denotes not small for gestational age (birth weight $\geq 10^{th}$ percentile using population based standard), TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value and NPV denotes negative predictive value.

Analyses requested by peer reviewers

A **B**

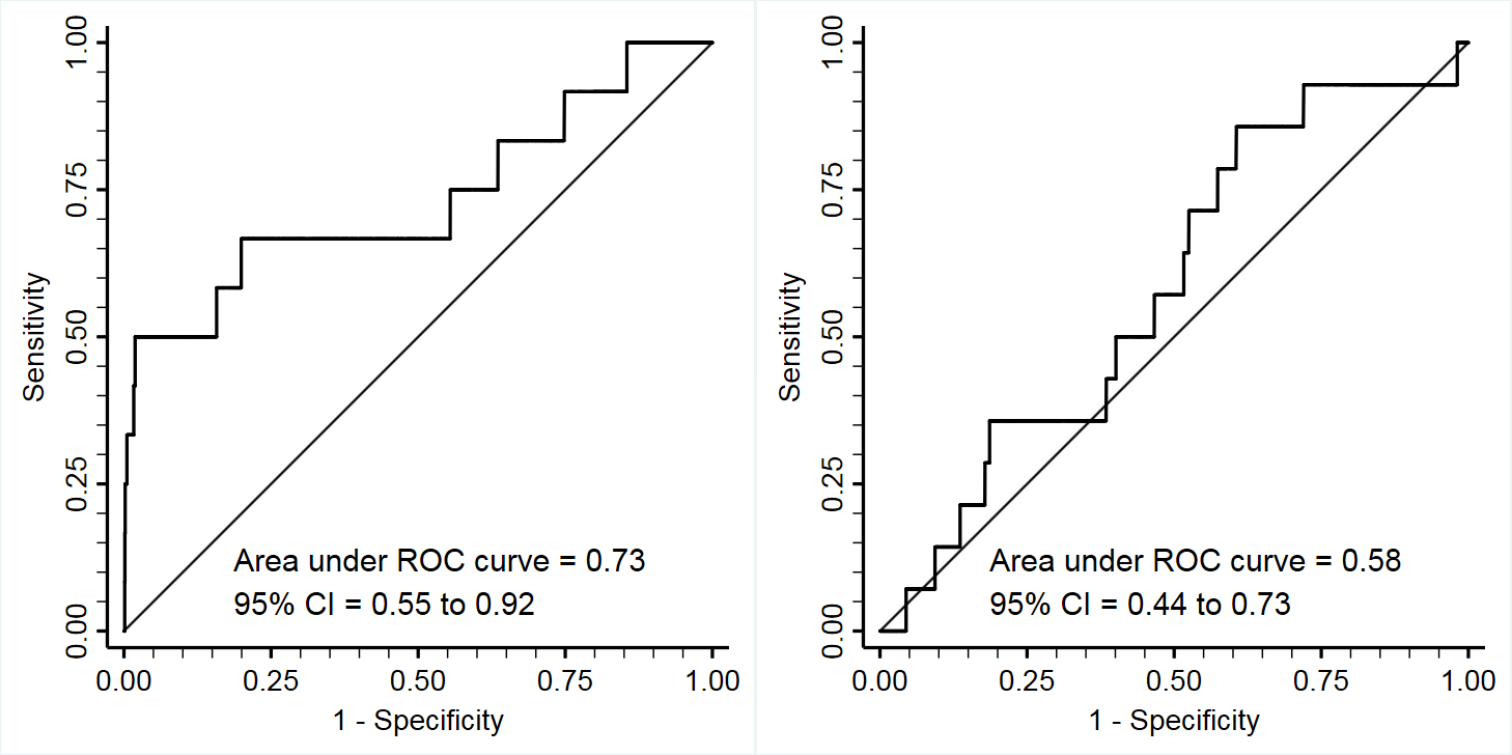

Figure S5. Receiver operating characteristic curve analysis of the relationship between sFLT1 at 28wkGA and **A**. the risk of preeclampsia with delivery of a preterm SGA infant (n=12 cases), **B**. the risk of preeclampsia with delivery of a preterm non-SGA infant (n=14 cases).

A **B**

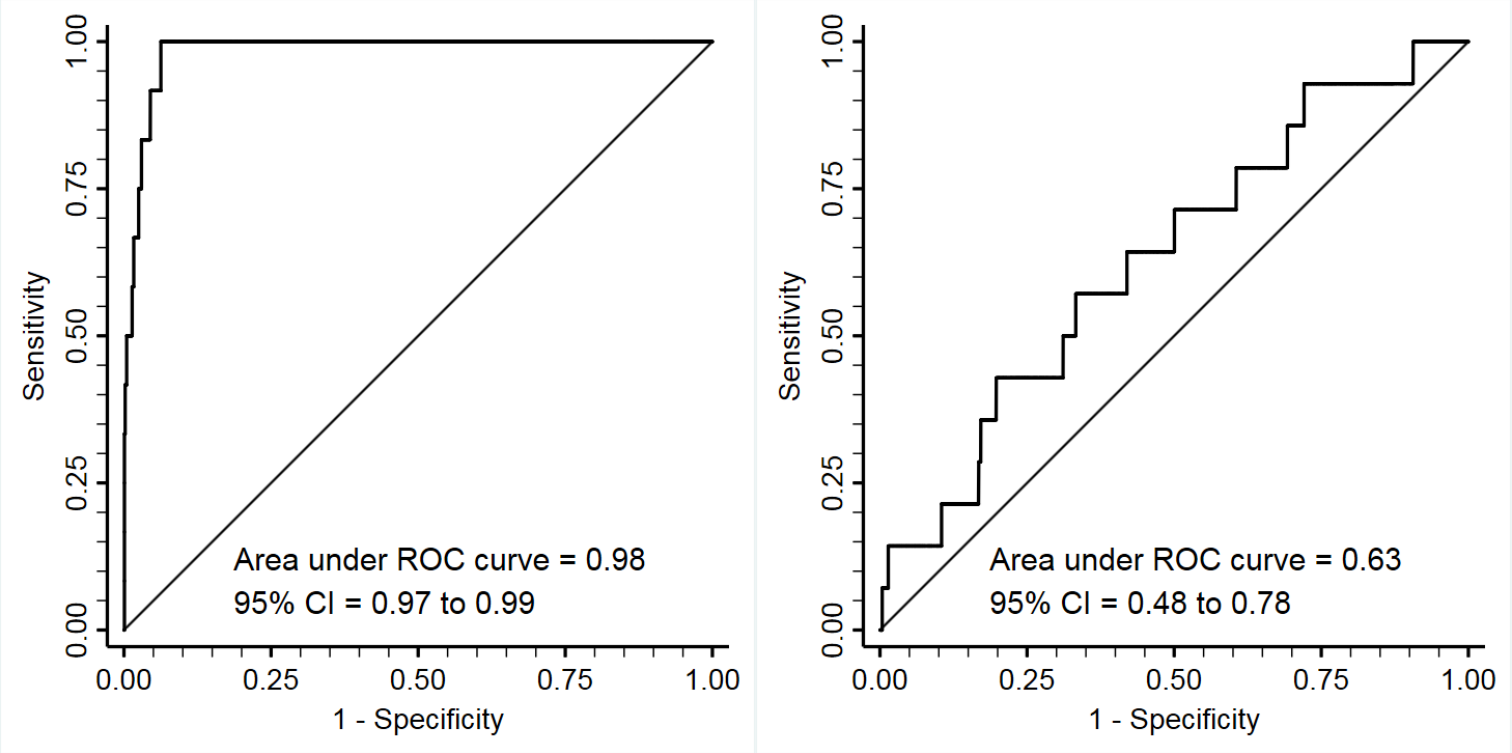

Figure S6. Receiver operating characteristic curve analysis of the relationship between PlGF at 28wkGA and **A**. the risk of preeclampsia with delivery of a preterm SGA infant (n=12 cases), **B**. the risk of preeclampsia with delivery of a preterm non-SGA infant (n=14 cases).

A **B**

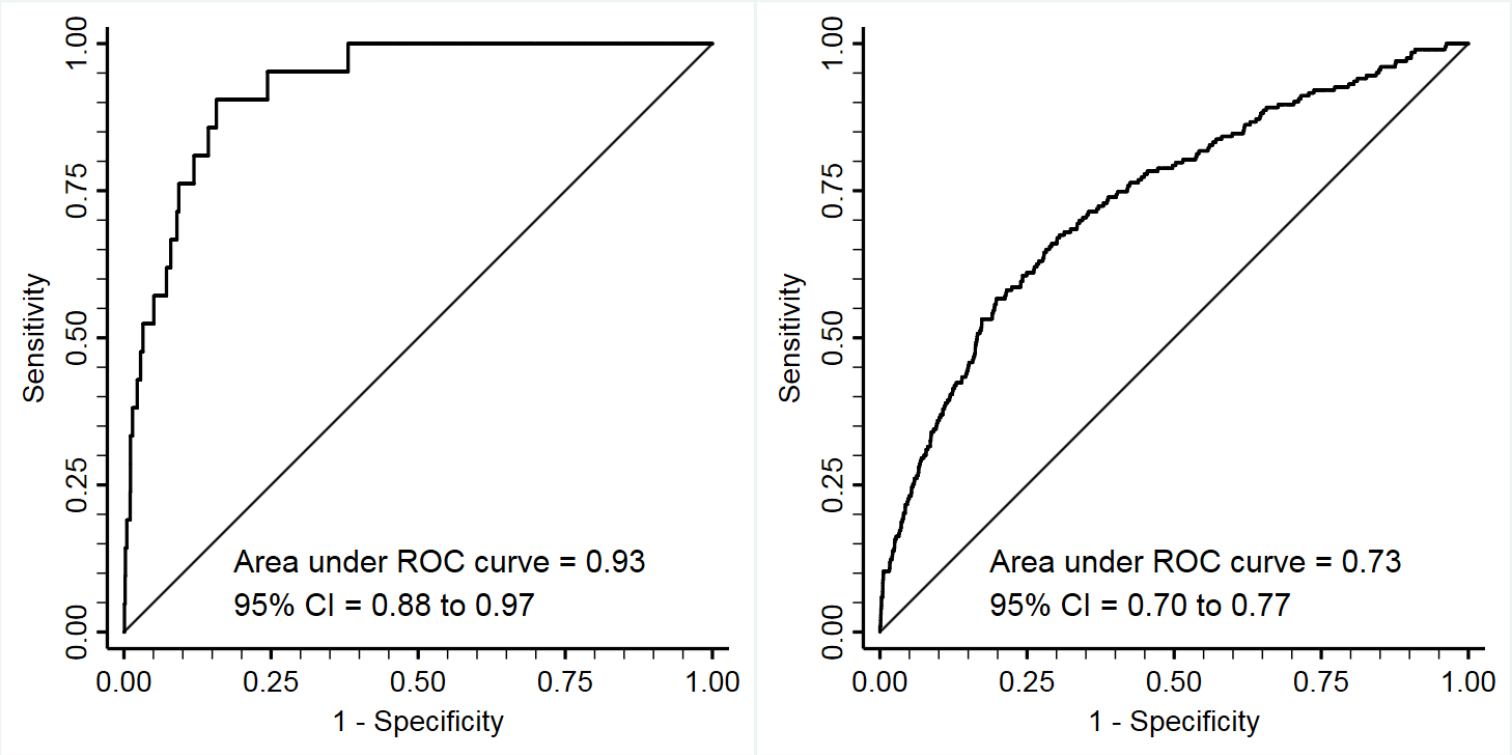

Figure S7. Receiver operating characteristic curve analysis of the relationship between sFLT1 at 36wkGA and **A**. the risk of preeclampsia with delivery of a SGA infant (n=21 cases), **B**. the risk of preeclampsia with delivery of a non-SGA infant (n=203 cases).

A **B**

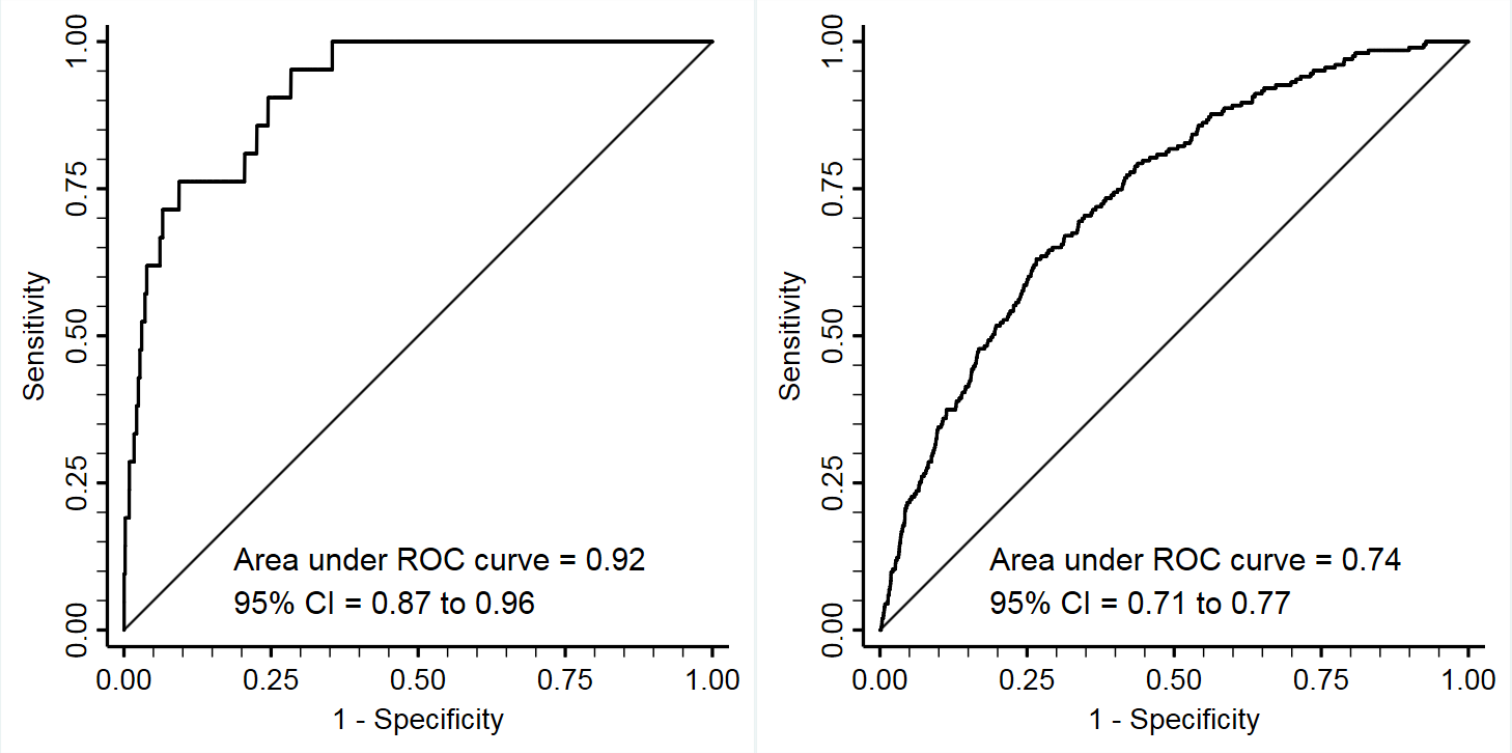

Figure S8. Receiver operating characteristic curve analysis of the relationship between PlGF at 36wkGA and **A**. the risk of preeclampsia with delivery of a SGA infant (n=21 cases), **B**. the risk of preeclampsia with delivery of a non-SGA infant (n=203 cases).

Table S14. Screening performance of ultrasonic and biochemical screening at 28wkGA for preterm delivery of an SGA infant within the whole cohort using customised birth weight percentile: comparison between the combination of EFW and sFLT1:PlGF ratio using different thresholds and the Delphi procedure

Screening test	Scr+ (%)	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <15th and sFLT1:PlGF ratio >5.78 (85th percentile)	2.5%	11/87	3868/15	19.2 (11.7-31.5)	0.59 (0.42-0.82)	42.3	97.8	11.2	99.6
Ultrasonic EFW <16.5th and sFLT1:PlGF ratio >5.53 (83.5th percentile)	3.0%	12/109	3846/14	16.7 (10.6-26.4)	0.55 (0.39-0.79)	46.2	97.2	9.9	99.6
Ultrasonic EFW <20th and sFLT1:PlGF ratio >4.94 (80th percentile)	5.0%	13/187	3768/13	10.6 (7.0-15.9)	0.52 (0.36-0.77)	50.0	95.3	6.5	99.7
Delphi procedure definition of early FGR†	3.0%	12/106	3747/13	17.4 (11.1-27.3)	0.53 (0.37-0.78)	48.0	97.2	10.2	99.7

*Customised birth weight percentile was calculated using the GROW v6.7.8.1(UK) bulk calculator (Perinatal Institute). †See appendix for definitions. Abbreviations: Scr+ denotes screen positive, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, and FGR denotes fetal growth restriction.

Table S15. Screening performance of ultrasonic and biochemical screening at 36wkGA for subsequent risk of delivering an SGA infant with either maternal preeclampsia or perinatal morbidity or mortality within the whole cohort using population-based birth weight percentile: comparison between the combination of EFW and sFLT1:PlGF ratio using different thresholds and the Delphi procedure

Screening test	Scr+ (%)	TP/FP	TN/FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity	Specificity	PPV	NPV
Ultrasonic EFW <20th and sFLT1:PlGF ratio >30.1 (80th percentile)	6.7	31/220	3469/27	9.0 (6.8-11.8)	0.50 (0.38-0.65)	53.4	94.0	12.4	99.2
Ultrasonic EFW <25th and sFLT1:PlGF ratio >25.3 (75th percentile)	9.8	35/333	3356/23	6.7 (5.3-8.4)	0.44 (0.32-0.60)	60.3	91.0	9.5	99.3
Ultrasonic EFW <26.5th and sFLT1:PlGF ratio >24.0 (73.5th percentile)	11.1	36/379	3310/22	6.0 (4.8-7.5)	0.42 (0.30-0.59)	62.1	89.7	8.7	99.3
Delphi procedure definition of late FGR*	11.2	35/377	3257/22	5.9 (4.7-7.4)	0.43 (0.31-0.60)	61.4	89.6	8.5	99.3

*See appendix for definitions. Abbreviations: Scr+ denotes screen positive, TP denotes true positive, FP denotes false positive, TN denotes true negative and FN denotes false negative, LR denotes likelihood ratio, CI denotes confidence interval, PPV denotes positive predictive value, NPV denotes negative predictive value, EFW denotes estimated fetal weight, sFLT1 denotes soluble fms-like tyrosine kinase 1, PlGF denotes placenta growth factor, and FGR denotes fetal growth restriction.

STARD checklist

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2-3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4-5
	4	Study objectives and hypotheses	5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6
Participants	**6**	Eligibility criteria	6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	6-7
	10b	Reference standard, in sufficient detail to allow replication	6-8
	11	Rationale for choosing the reference standard (if alternatives exist)	6-8
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6-8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	6-8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6,8
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6,8
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	8-9
	15	How indeterminate index test or reference standard results were handled	10
	16	How missing data on the index test and reference standard were handled	10
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	10-11
	18	Intended sample size and how it was determined	9
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Appendix
	20	Baseline demographic and clinical characteristics of participants	Table 1
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	Table 1
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Tables 2-5
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Tables 2-5

	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	13-14
OTHER INFORMATION			
	28	Registration number and name of registry	N/A
	29	Where the full study protocol can be accessed	6
	30	Sources of funding and other support; role of funders	3,10

Supplementary References

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