Biochemical tests of placental function versus ultrasound assessment of fetal size for stillbirth and small-for-gestational-age infants

Heazell, Alexander E P; Hayes, Dexter JL ; Whitworth, Melissa; Takwoingi, Yemisi; Bayliss, Susan; Davenport, Clare

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Diagnostic accuracy of biochemical tests of placental function versus ultrasound assessment of fetal size for stillbirth and small-for-gestational-age infants

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Authors

Alexander EP Heazell[1], Dexter JL Hayes[1], Melissa Whitworth[1], Yemisi Takwoingi[2], Susan E Bayliss[2], Clare Davenport[2]

[1]Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK
[2]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

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Contact person

Alexander EP Heazell

Clinical Lecturer in Obstetrics
Maternal and Fetal Health Research Centre
University of Manchester
5th floor (Research), St Mary's Hospital, Oxford Road
Manchester
M13 9WL
UK

E-mail: alexander.heazell@manchester.ac.uk
E-mail 2: alex_heazell@talk21.com

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Abstract

Background

Stillbirth affects 2.6 million pregnancies worldwide each year. Whilst the majority of cases occur in low- and middle-income countries, stillbirth remains an important clinical issue for high-income countries (HICs) - with both the UK and the USA reporting rates above the mean for HICs. In HICs, the most frequently reported association with stillbirth is placental dysfunction. Placental dysfunction may be evident clinically as fetal growth restriction (FGR) and small-for-dates infants. It can be caused by placental abruption or hypertensive disorders of pregnancy and many other disorders and factors

Placental abnormalities are noted in 11% to 65% of stillbirths. Identification of FGA is difficult in utero. Small-for-gestational age (SGA), as assessed after birth, is the most commonly used surrogate measure for this outcome. The degree of SGA is associated with the likelihood of FGR; 30% of infants with a birthweight < 10th centile are thought to be FGR, while 70% of infants with a birthweight < 3rd centile are thought to be FGR. Critically, SGA is the most significant antenatal risk factor for a stillborn infant. Correct identification of SGA infants is associated with a reduction in the perinatal mortality rate. However, currently used tests, such as measurement of symphysis-fundal height, have a low reported sensitivity and specificity for the identification of SGA infants.

Objectives

The primary objective was to assess and compare the diagnostic accuracy of ultrasound assessment of fetal growth by

estimated fetal weight (EFW) and placental biomarkers alone and in any combination used after 24 weeks of pregnancy in the identification of placental dysfunction as evidenced by either stillbirth, or birth of a SGA infant. Secondary objectives were to investigate the effect of clinical and methodological factors on test performance.

Search methods

We developed full search strategies with no language or date restrictions. The following sources were searched: MEDLINE, MEDLINE In Process and Embase via Ovid, Cochrane (Wiley) CENTRAL, Science Citation Index (Web of Science), CINAHL (EBSCO) with search strategies adapted for each database as required; ISRCTN Registry, UK Clinical Trials Gateway, WHO International Clinical Trials Portal and ClinicalTrials.gov for ongoing studies; specialist abstract and conference proceeding resources (British Library's ZETOC and Web of Science Conference Proceedings Citation Index). Search last conducted in Ocober 2016.

Selection criteria

We included studies of pregnant women of any age with a gestation of at least 24 weeks if relevant outcomes of pregnancy (live birth/stillbirth; SGA infant) were assessed. Studies were included irrespective of whether pregnant women were deemed to be low or high risk for complications or were of mixed populations (low and high risk). Pregnancies complicated by fetal abnormalities and multi-fetal pregnancies were excluded as they have a higher risk of stillbirth from non-placental causes. With regard to biochemical tests, we included assays performed using any technique and at any threshold used to determine test positivity.

Data collection and analysis

We extracted the numbers of true positive, false positive, false negative, and true negative test results from each study. We assessed risk of bias and applicability using the QUADAS-2 tool. Meta-analyses were performed using the hierarchical summary ROC model to estimate and compare test accuracy.

Main results

We included 91 studies that evaluated seven tests — blood tests for human placental lactogen (hPL), oestriol, placental growth factor (PlGF) and uric acid, ultrasound EFW and placental grading and urinary oestriol — in a total of 175,426 pregnant women, in which 15,471 pregnancies ended in the birth of a small baby and 740 pregnancies which ended in stillbirth. The quality of included studies was variable with most domains at low risk of bias although 59% of studies were deemed to be of unclear risk of bias for the reference standard domain. Fifty-three per cent of studies were of high concern for applicability due to inclusion of only high- or low-risk women.

Using all available data for SGA (86 studies; 159,490 pregnancies involving 15,471 SGA infants), there was evidence of a difference in accuracy ($P < 0.0001$) between the seven tests for detecting pregnancies that are SGA at birth. Ultrasound EFW was the most accurate test for detecting SGA at birth with a diagnostic odds ratio (DOR) of 21.3 (95% CI 13.1 to 34.6); hPL was the most accurate biochemical test with a DOR of 4.78 (95% CI 3.21 to 7.13). In a hypothetical cohort of 1000 pregnant women, at the median specificity of 0.88 and median prevalence of 19%, EFW, hPL, oestriol, urinary oestriol, uric acid, PlGF and placental grading will miss 50 (95% CI 32 to 68), 116 (97 to 133), 124 (108 to 137), 127 (95 to 152), 139 (118 to 154), 144 (118 to 161), and 144 (122 to 161) SGA infants, respectively. For the detection of pregnancies ending in stillbirth (21 studies; 100,687 pregnancies involving 740 stillbirths), in an indirect comparison of the four biochemical tests, PlGF was the most accurate test with a DOR of 49.2 (95% CI 12.7 to 191). In a hypothetical cohort of 1000 pregnant women, at the median specificity of 0.78 and median prevalence of 1.7%, PlGF, hPL, urinary oestriol and uric acid will miss 2 (95% CI 0 to 4), 4 (2 to 8), 6 (6 to 7) and 8 (3 to 13) stillbirths, respectively. No studies assessed the accuracy of ultrasound EFW for detection of pregnancy ending in stillbirth.

Authors' conclusions

Biochemical markers of placental dysfunction used alone have insufficient accuracy to identify pregnancies ending in SGA or stillbirth. Studies combining U and placental biomarkers are needed to determine whether this approach improves diagnostic accuracy over the use of ultrasound estimation of fetal size or biochemical markers of placental dysfunction used alone. Many of the studies included in this review were carried out between 1974 and 2016. Studies of placental substances were mostly carried out before 1991 and after 2013; earlier studies may not reflect developments in test technology.

Plain language summary

Blood tests in late pregnancy to identify small babies and those at risk of stillbirth

Background

Placental dysfunction describes when the placenta does not meet the demands of the growing baby; it may result in a baby that is smaller than expected or is stillborn. Currently, it is not easy to detect placental dysfunction before birth; ultrasound scans are most often used to identify small babies. However, tests can measure substances made by the placenta in mothers' blood and urine which may detect a placenta that is not functioning well. We aimed to find the best test to identify placental dysfunction.

What we did

We searched for studies in October 2016 and identified and total of 24,059 studies - with 91 of those studies providing us with information that we could include in this review. We looked at ultrasound scanning and six different tests of placental substances, including proteins and hormones. These studies involved 175,426 women in total of which 15,471 pregnancies

ended in the birth of a small baby and 740 pregnancies which ended in stillbirth.

What we found

Of the 91 included studies, 86 had information on small babies, of which 18 also looked at stillbirth; another five studies only looked at stillbirth. The most accurate test for detecting a small baby was ultrasound scan to estimate a baby's weight. Of the substances measured in mother's blood, human placental lactogen (hPL), a hormone produced by the placenta during pregnancy, was the most accurate. There was only one study which looked at both ultrasound scanning and measurement of a placental substance. Placental growth factor (PlGF) was the most accurate test of a placental substance to identify a baby that would be stillborn; there were no studies of ultrasound scanning to detect a baby that would be stillborn. Tests of placental substances were better at identifying a baby at risk of stillbirth than detecting a small baby.

Other important information to consider

Many of the studies included in this review were carried out between 1974 and 2016. Studies of placental substances were mostly carried out before 1991 and after 2013; earlier studies may not reflect developments in test technology. More studies are needed to find out whether a combination of ultrasound scans and mother's blood tests could improve identification of pregnancies which end in the birth of a small baby or in a stillborn baby. No studies were identified for this review that looked at the accuracy of ultrasound and blood tests used together.

Background

Stillbirth affects 2.6 million pregnancies worldwide each year (Lawn 2016). Whilst the majority of cases occur in low- and middle-income countries, stillbirth remains an important clinical issue for high-income countries (HICs) - with both the UK and the USA reporting rates above the mean for HICs (Flenady 2016).

In HICs, the most frequently reported association with stillbirth is placental dysfunction, which may be clinically evident as fetal growth restriction (FGR), small-for-gestational-age (SGA) infants, placental abruption or hypertensive disorders of pregnancy. Placental abnormalities are noted in 11% to 65% of stillbirths (Ptacek 2014). Identification of FGR is difficult in utero and even after birth, with SGA being most commonly used as a surrogate measure (Worton 2014). The degree of SGA is associated with the likelihood of FGR; 30% of infants with a birthweight < 10th centile are thought to be FGR, while 70% of infants with a birthweight < 3rd centile are thought to be FGR. Critically, SGA is the most significant antenatal risk factor for a stillborn infant (Flenady 2011; Gardosi 2013; McCowan 2007). Correct identification of SGA infants is associated with a reduction in the perinatal mortality rate (Gardosi 2013). However, currently used tests, such as measurement of symphysis-fundal height, have a low reported sensitivity and specificity for the identification of SGA infants (RCOG 2014).

Due to the importance of the placenta in FGR and stillbirth there is growing interest in antenatal placental evaluation in an attempt to identify pregnancies at increased risk of stillbirth or fetal compromise (Heazell 2015a). A systematic review of biochemical tests of placental function found insufficient evidence to conclude whether these interventions had any effect on perinatal mortality or fetal compromise (Heazell 2015b). In contrast, a single trial of placental grading assessed by ultrasound demonstrated reduced perinatal mortality (Proud 1987). Systematic reviews of other methods employed to identify fetal compromise such as ultrasound assessment of fetal growth or umbilical artery Doppler (measurement of blood flow through the umbilical artery) in late pregnancy have also found insufficient evidence to conclude whether these interventions reduce perinatal mortality in a low-risk maternity population (Alfirevic 2015; Bricker 2015), although both are effective in women deemed to be at high risk of pregnancy complications (Alfirevic 2013). The efficacy of umbilical artery Doppler in high-risk populations may be due to its prognostic accuracy; a systematic review found this test predicted SGA infants with a positive likelihood ratio of 3.76 and stillbirth with a positive likelihood ratio of 4.37 (Morris 2011).

Two components are necessary to reduce perinatal mortality and minimise unwarranted intervention. Firstly, the test must accurately identify fetal compromise and secondly, the intervention must be effective in preventing the adverse outcome. There is now strong evidence that planned delivery (by induction of labour) after 37 weeks of pregnancy is associated with a reduction in perinatal mortality (Stock 2012). Therefore, the most accurate test to identify fetal compromise needs to be determined so that it may be combined with planned delivery where appropriate.

Target condition being diagnosed

The target condition of interest is placental dysfunction – which describes the condition in which the placenta does not meet the demands of the fetus (Heazell 2015a). As with other organ dysfunction, there are multiple pathways that can result in placental dysfunction including vascular, inflammatory, infective and genetic disorders. These various processes may lead to changes in placental structure and/or function that may lead to two clinical outcomes i) stillbirth or ii) the birth of an SGA infant. As placental dysfunction cannot easily be quantified, this review will use these two clinical outcomes as the target conditions of interest.

Index test(s)

This review evaluated tests used in late pregnancy (after 24 weeks) to identify pregnancies with placental dysfunction to inform decisions to continue with the pregnancy or institute intervention. Tests that were included in this review assessed placental structure or biochemical function by one or more of ultrasound scan or measurement of placental products in maternal blood (plasma or serum) or urine.

Biochemical tests of placental function measure placental products (proteins, peptides, metabolites, hormones) in maternal biofluids (serum, plasma, urine); it is hypothesised that levels of such products in maternal fluids reflect endocrine and

metabolic functions of the placenta. Many placental products can be detected in maternal biofluids including protein hormones: human chorionic gonadotrophin (hCG), human placental lactogen (hPL), human placental growth hormone (hPGH), placental growth factor (PlGF), placental protein-13 (PP-13), pregnancy specific glycoproteins and steroid hormones including oestrogens and progesterone with their related metabolites. Ultrasonography has been used to measure the size, shape, and echotexture of the placenta; the majority of such studies have used 2D ultrasound to evaluate placental morphology, although newer studies have utilised 3D techniques.

Clinical Pathway

Antenatal care differs between countries; the clinical pathway described here applies to the UK and follows guidance from the Royal College of Obstetricians and Gynaecologists (RCOG 2014) and the National Institute for Health and Social Care Excellence (NICE 2008).

Prior test(s)

Currently, in the UK women are grouped into high risk and low risk for SGA in early pregnancy at the booking-visit by assessing a woman's past medical history, obstetric history and risk factors for an SGA infant (RCOG 2014). All women are offered screening for Down's syndrome (which is currently based on measurement of nuchal translucency by ultrasound scan and measurement of serum analytes between 11 and 13 + 6 weeks of pregnancy) and for fetal anomaly (by ultrasound scan from 18 to 20 + 6 weeks).

In clinical practice, placental dysfunction is suspected by identification of an SGA infant. However, testing for SGA currently depends upon the risk status of the woman (RCOG 2014). The National Institute for Health and Care Excellence do not recommend routine measurement of fetal growth by ultrasound scan in late pregnancy (NICE 2008). Fetal growth is assessed in women deemed to be at low risk of an SGA infant by measurement of symphysis-fundal height with a tape measure (RCOG 2014). Women at increased risk of SGA are recommended to have a uterine artery Doppler (to assess blood flow through both uterine arteries) at 20 weeks' gestation and regular scans to measure fetal biometry with assessment of liquor volume and umbilical artery Doppler. Umbilical artery Doppler is the most frequently employed test to predict fetal outcome; the relationship between umbilical artery Doppler indices and placental function is not clear. In addition to recommendations for the diagnosis and management of an SGA fetus, ultrasound assessment of fetal growth, liquor volume and umbilical artery Doppler are recommended following maternal presentation with reduced fetal movements, as this may be a symptom of placental insufficiency (RCOG 2011). The current clinical pathway is shown in Figure 1.

When an SGA infant is identified by tests, clinical management is dependent upon gestation. Prior to 37 weeks' gestation, identification of SGA prompts further assessment of fetal well-being, primarily by measurement of Doppler waveforms in the umbilical artery, but may also include the middle cerebral artery and ductus venosus. Delivery is recommended when evidence of fetal compromise is identified (RCOG 2014). After 39 weeks' gestation, delivery of the baby may be offered as this is associated with a reduction in stillbirth, avoids potential hazards of early term birth (MacKay 2010), and is not associated with an increase in obstetric intervention (Stock 2012).

There are currently no routinely used measures of placental function after 16 weeks of pregnancy. There is evidence that measurement of placental analytes as part of screening for aneuploidy may identify fetuses at high risk of early-onset FGR (Smith 2002; Smith 2006). Assessment of these analytes is incorporated into the current clinical pathway (RCOG 2014); women with low pregnancy-associated plasma protein A (PAPP-A) levels are managed as high risk for SGA. Therefore, we wish to focus on placental tests performed in late pregnancy (after 24 weeks' gestation).

Role of index test(s)

Due to the established use of ultrasound in obstetric practice, we envisage that additional tests of placental function would most likely be added to an ultrasound measurement of fetal size rather than replacing it (Figure 1); this is certainly true of the intervention trials of placental assessment (by biochemical tests) that have been conducted (Duenholter 1976; Heazell 2013; Sharf 1984). It is hypothesised that the addition of a placental function test to an ultrasound scan would improve identification of an SGA infant and consequently focus intervention on those pregnancies at the greatest risk of stillbirth or fetal compromise, thereby reducing the burden of perinatal mortality and morbidity. It is also possible that a placental function test could be used to triage infants who were SGA to identify which were constitutionally small and which had placental dysfunction. This would allow the pregnancy to continue in otherwise healthy constitutionally small infants, reducing unnecessary intervention.

The importance of specific aspects of test performance will depend upon the context in which it is used in late pregnancy. From the perspective of reducing perinatal mortality and morbidity in a high-risk population (e.g. triage of women with a small baby on ultrasound scan or women presenting with reduced fetal movements, Figure 1), a false negative test would be more harmful than a false positive test as pregnant women may be deprived of further monitoring or intervention which may mitigate some of the increased risk. In women at low risk of SGA or stillbirth then a false negative test would mean that the mother continued upon the pathway of care she would have otherwise received, whereas a false positive result would mean she may be exposed to monitoring or intervention which was unnecessary, which may have negative medical and economic consequences. Thus, it is important to consider the clinical group being studied and how this impacts upon test performance.

Alternative test(s)

Presently, there are no tests in widespread clinical use that directly assess placental biochemical function. Umbilical artery Doppler is often used in clinical practice to identify placental dysfunction but has not been included in this analysis as a systematic review and meta-analysis has already been conducted (Morris 2011).

Rationale

There are several tests of placental structure and function. Systematic reviews of the measurement of biochemical placental factors and the effectiveness of ultrasound in late pregnancy found that few tests of placental structure or function have been evaluated in robust intervention studies (Bricker 2015; Heazell 2015a). This review aims to identify and evaluate tests of placental structure and function, not restricted to those evaluated in intervention studies, to determine which measurement(s) have the greatest diagnostic accuracy for detection of placental dysfunction leading to stillbirth and SGA. The most accurate test(s) can then be taken forward into intervention studies to determine whether performing investigations can reduce perinatal morbidity or mortality.

Objectives

The primary objective of this review was to assess and compare the diagnostic accuracy of ultrasound assessment of fetal growth and placental biomarkers alone and in any combination used after 24 weeks of pregnancy in the identification of placental dysfunction as evidenced by either stillbirth or born small-for-gestational age (SGA). Accuracy is described by the proportion of fetuses who are subsequently stillborn or who have an SGA baby detected by a positive test result (the presence of placental dysfunction) (sensitivity) and by the proportion of fetuses that have an uncomplicated pregnancy following a negative index test result (absence of placental dysfunction) (specificity).

Secondary objectives

We investigated the effect of clinical (patient and test characteristics) and methodological factors (study design, threshold used to define SGA) on test performance. The clinical factors include patient group (low-risk or high-risk pregnancies), gestation at measurement, ethnicity, maternal age and method of testing. With regard to methodological variation, studies may include an intervention (delivery or additional fetal surveillance for index test positive cases) which impacts on the outcome; therefore we assessed whether this is a source of heterogeneity.

Methods

Criteria for considering studies for this review

Types of studies

Presently, there are no effective interventions to reverse placental dysfunction *in utero*. This means that an intervention cannot be employed to reverse the small-for-gestational age (SGA) phenotype following a positive test result. Delivery may be indicated, although at earlier gestations this does not affect perinatal mortality (GRIT 2003).

We included prospective and retrospective cross-sectional or cohort studies in which all women received one or more index tests and the outcome of their pregnancy was known. Case-control studies were excluded.

We included studies which measured index tests on one occasion (cross-sectional design).

We excluded studies where it was not possible to derive a 2 x 2 table of the number of true positives, false positives, false negatives and true negatives, or studies that reported preliminary experimental findings, i.e. laboratory-based studies.

Participants

We included studies of pregnant women after 24 weeks' gestation that recorded relevant outcomes of pregnancy (live birth/stillbirth; SGA infant).

We included studies of pregnant women of any reproductive age, who were deemed to be low or high risk for complications (e.g. who had pre-existing medical disorders or previous stillbirth) or studies of mixed populations (of low and high risk for complications).

We excluded pregnancies complicated by fetal abnormalities, as they often have a higher risk of stillbirth from non-placental causes. We excluded studies of women with multi-fetal pregnancies.

Index tests

We included, but were not restricted to, the following index tests of placental biochemical function, placental structure or assessment of fetal biometry to identify an SGA infant:

- human placental lactogen (hPL) in maternal urine/blood;
- oestriol in maternal urine/blood;
- placental growth factor (PlGF) in maternal blood;
- ultrasound assessment of placental echogenicity;
- ultrasound assessment of fetal size.

With regard to biochemical tests, we included assays that were performed using different techniques, including: immunoassay, enzyme-linked immunosorbent assay (ELISA), chromatography or point of care test in any combination and at any threshold used to determine test positivity. Examples of current commercially available tests are listed in Appendix 1.

Target conditions

The target conditions were stillbirth and delivery of a SGA infant at the centile or threshold used by each study, as clinical manifestations of placental dysfunction.

Reference standards

The outcome of pregnancy was considered as the reference standard. A “positive” result was either i) a stillbirth – an infant born with no signs of life after 24 weeks’ gestation, or ii) a birthweight classified as SGA. A “negative” result was a live birth after 24 weeks’ gestation or a birthweight classified as appropriate for gestational age.

The classification of SGA was determined according to the definition used in the study. Where possible, the definition of an infant with a birthweight ≤ 10th centile using a customised birthweight calculator was used (Clausson 2001). Where this was not possible, the definition of SGA from the manuscript was used and recorded. The effects of different definitions of SGA were addressed as a potential source of heterogeneity.

Search methods for identification of studies

We conducted a comprehensive search for existing systematic reviews and primary studies relevant to the prevention of adverse pregnancy outcome in women at increased risk of stillbirth by detecting placental dysfunction. A scoping search was undertaken in the bibliographic databases MEDLINE, MEDLINE In Process, Embase, the Cochrane Library (CDSR, DARE, HTA, NHS EED and Central Register of Controlled Trials (CENTRAL) databases), HTA and relevant web sites in order to identify existing reviews and to gauge the nature and number of relevant studies to inform the protocol.

Electronic searches

We developed full search strategies based on the scoping searches, expert advice, and consultation with the Cochrane Pregnancy and Childbirth Group’s Information Specialist. Search strategies included a combination of text words and index terms. Methodological search filters for diagnostic test accuracy were avoided as they have been shown to miss relevant studies (Whiting 2011a). We did not apply any language or date restrictions. We searched the following sources:

- bibliographic databases - MEDLINE, MEDLINE In Process and Embase via Ovid, Cochrane (Wiley) CENTRAL, Science Citation Index (Web of Science), CINAHL (EBSCO) with search strategies adapted for each database as required;
- ISRCTN Registry, UK Clinical Trials Gateway, WHO International Clinical Trials Portal (ICTRP) and ClinicalTrials.gov for ongoing studies;
- specialist abstract and conference proceeding resources (British Library’s ZETOC and Web of Science Conference Proceedings Citation Index).

Searches were last conducted on 27 Ocober 2016. The full search strategy is provided in Appendix 2.

Searching other resources

We checked citation lists of included studies and relevant reviews. We examined grey literature by searching websites of companies producing biochemical tests of placental function (Alere 2015; Perkin Elmer 2015; Roche 2015). We also undertook consultation with experts in the field to access relevant unpublished data.

Data collection and analysis

We used the methods advocated by the *Cochrane Screening and Diagnostic Test Methods Group.*

Selection of studies

Two review authors (DH and AH) independently screened the titles and abstracts of all studies identified by the search strategy. We obtained full-text versions of all potentially relevant studies. Two review authors (DH and AH) independently assessed studies for inclusion using pre-specified inclusion criteria stated earlier. We included studies of pregnant women after 24 weeks’ gestation that recorded relevant outcomes of pregnancy (live birth/stillbirth; SGA infant), and presented data to construct a 2 x 2 table. We resolved any disagreement between the two review authors or by discussion with a third party (CD) if needed. Reasons for study exclusion were documented.

Data extraction and management

We developed a customised form to ensure reproducible collection of data items. Data collection was piloted on five manuscripts then reviewed by the review authors. Data were extracted independently by two review authors (DH and AH). We resolved discrepancies, where they occurred, through discussion or if required we consulted a third author (CD or MW), drawing on clinical and methodological expertise in the team as appropriate to the content of the query. We extracted characteristics of participants, index tests or test combinations (including thresholds used), and details of the reference standard in terms of pregnancy outcome (live birth or stillbirth) and whether the infant was SGA. For studies that reported data at multiple thresholds for a test, we extracted a 2 x 2 table at each reported threshold. Where possible we recorded the frequency of obstetric intervention and infant admission to neonatal intensive care. If reported, we also recorded data on outcomes including harms of testing, need for further testing, and the effects of the test. We did not address women’s experiences of testing, caregivers' satisfaction with testing or economic evaluation of testing as this is beyond the scope of this review.

We attempted to contact the authors of included studies where information considered key to assessment of methodological quality, investigation of heterogeneity, or completion of a 2 x 2 table was unclear or missing. Studies published only as conference abstracts were followed up to identify whether a subsequent full paper had been published.

Assessment of methodological quality

We used the QUADAS-2 tool (Whiting 2011b) to assess the risk of bias and applicability of included studies. We tailored the tool to our review question using the operational criteria detailed in Appendix 3 to answer signalling questions and make the overall judgement of risk of bias and applicability concerns for each domain of the tool. Two review authors (DH and AH)

assessed each included study separately. We resolved differences in assessment through discussion and if required, by discussion with a third person (CD). We assessed each criteria in QUADAS-2 as “yes”, “no” or “unclear” and summarised the results graphically or in tables.

We included all signalling questions of QUADAS-2 assessment including the time interval between testing and the outcome and any intervention as these may alter the outcome. We have operationalised the domains of the QUADAS-2 tool for the clinical context of this review. For example, the domain concerning patient selection was amended to reflect review exclusion criteria including women with multiple pregnancies or with fetal abnormalities. However, other criteria that might be expected to alter the accuracy of tests in universal populations (e.g. ethnicity, maternal age and income) would be inappropriate exclusions. Studies restricted to specific high-risk groups, e.g. maternal hypertension, will reduce the applicability of review findings. We also tailored the target condition domain to assess the quality of measures of SGA used in studies, some of which may not be related to gestation, e.g. low birthweight (< 2.5 kg). Studies using a threshold which alters with sex and gestation, e.g. individualised birthweight centile, were rated more highly than those which did not.

Statistical analysis and data synthesis

From here on we use the term SGA for SGA defined as birthweight ≤ 10th centile, and SGA3 for SGA defined as birthweight < 3rd centile. We performed separate analyses for each target condition (SGA, SGA3 and stillbirth). For each test and target condition, estimates of sensitivity and specificity from each study were plotted in receiver operating characteristic (ROC) space and forest plots for preliminary investigations of the data. Since studies used different thresholds to determine test positivity, we performed meta-analyses using the hierarchical summary ROC (HSROC) model (Rutter 2001) to estimate and compare the SROC curves of the tests. Methods that allow joint synthesis of sensitivities and specificities at multiple thresholds have been proposed, but are not yet used routinely in practice and require further evaluation before they can be used in diagnostic test accuracy reviews (Ensor 2018; Riley 2015; Steinhauser 2016). As such, where a study reported multiple thresholds for a test, we selected the threshold most frequently reported across studies so that only one 2 x 2 table was included in a meta-analysis. In separate analyses of each test, where studies reported common thresholds for the test, we estimated summary sensitivities and specificities using functions of HSROC model parameters.

Before performing meta-analyses to compare test accuracy, we performed meta-analysis of each test separately for preliminary investigation of the shape of the SROC curve of each test and to explore if assuming common variances across tests for the random effects would be reasonable. The main test comparison was an indirect comparison pooling all relevant studies that assessed at least one of the index tests. In secondary analyses, we performed direct comparisons by restricting the analyses to only studies that compared tests head-to-head in the same study population. This analytical strategy was adopted because of the paucity of comparative studies of diagnostic accuracy (Takwoingi 2013). We limited the indirect comparison to only tests with at least four studies because of potential model complexity given the number of tests included and number of model parameters to be estimated. For direct comparisons, we performed pair-wise comparisons of tests. Test comparisons were performed by adding a covariate for test type to the HSROC model to estimate differences in accuracy, threshold, and/or shape of SROC curves. When there were adequate data, we also allowed the variance parameters for accuracy and threshold to depend on test type, i.e. differences in accuracy and threshold modelled as random effects. We assessed the statistical significance of differences between tests using likelihood ratio tests comparing models with and without the covariate terms. The NLMIXED procedure in the SAS software package (version 9.4; SAS Institute, Cary, NC, USA) was used for meta-analyses.

To quantify differences in accuracy between tests, we computed ratios of diagnostic odds ratios when SROC curves were symmetric or a common shape was assumed. Using the estimate statement within NLMIXED, we also estimated sensitivities along the SROC curves at fixed values of specificity that correspond to the median and interquartile range of specificities from the studies included in the comparative meta-analysis. We used these values along with the median and interquartile range of the prevalence estimated from the studies to compute numbers of missed cases and false positives in a hypothetical cohort of 1000 pregnant women. We used these frequencies to illustrate the accuracy of the tests in absolute terms.

Investigations of heterogeneity

We initially examined heterogeneity between studies by visually inspecting forest plots of sensitivity and specificity and SROC plots. Where a sufficient number of studies assessed the same index test and there were at least four studies per subgroup of a categorical covariate, we performed meta-regression by adding the potential source of heterogeneity as a covariate to the HSROC model. We assessed the effect of the covariate on test accuracy by using likelihood ratio tests to compare models with and without the covariate terms.

Sensitivity analyses

We planned to perform sensitivity analyses by restricting analyses to studies that:

- were without an intervention that may have altered outcome;
- were at low risk of bias in each of the four domains of the QUADAS-2 tool;
- specifically described histological evidence of placental insufficiency.

These analyses were not possible due to limited data.

Assessment of reporting bias

We did not undertake any formal assessment of reporting bias in our review due to current uncertainty about how to assess

reporting bias in diagnostic accuracy reviews, especially in the presence of heterogeneity (Macaskill 2010).

Results

Results of the search

Our literature searches identified a total of 24,059 papers after duplicates were removed (Figure 2) After initial screening based on title and abstract, we obtained full-text copies of 472 papers, of which 91 were included. The included studies evaluated seven tests — blood tests for human placental lactogen (hPL), oestriol, placental growth factor (PlGF) and uric acid, ultrasound EFW and placental grading and urinary oestriol — in a total of 175,426 pregnant women, in which 15,471 pregnancies ended in the birth of a small baby and 740 pregnancies which ended in stillbirth.

In total, seven different tests were evaluated, as well as two combinations of these tests. Included studies are described in Table 1. We described the studies that were excluded after full-text assessment in Characteristics of excluded studies. Some papers could not be obtained, index tests used in these papers are stated in Characteristics of studies awaiting classification where possible.

Methodological quality of included studies

Figure 3 shows the summary risk of bias and applicability concerns for included studies. Risk of bias and applicability concerns for individual index tests are in Appendix 5. The quality of included studies was judged to be mostly high, with most domains at low risk of bias, although risk of bias for the reference standard domain was mostly unclear (59% of studies) due to definitions of small-for-gestational age (SGA) not being reported or uncertainty as to whether index test results were blinded. In terms of applicability concerns; 53% of studies were at high concern for patient selection, mostly due to inclusion of only high- or low-risk women rather than an unselected population of pregnant women where both are likely to be included. Fourteen studies (15%) were of high concern regarding the reference standard due to differing definitions of SGA, for example if gestation was not taken into account or centiles were based on the study population only. Eighty-four per cent of studies were judged to be at low risk of bias for flow and timing as testing was mostly performed with an appropriate interval between testing and delivery.

Findings

Small-for-gestational age (SGA) (birthweight ≤ 10th centile)

The findings are summarised in Summary of findings table 1. SGA was the outcome assessed in 86 studies involving 159,490 pregnancies (included 15,471 SGA infants). The study specific estimates of sensitivity and specificity for each test are shown for structural tests (ultrasound assessment of fetal size and placental grading) in Figure 4, and for biochemical tests (human placental lactogen (hPL), serum oestriol, urinary oestriol, placental growth factor (PlGF), uric acid, and a combination of serum oestriol and hPL) in Figure 5.

1) Ultrasound assessment of fetal size (estimated fetal weight (EFW))

There were 32 studies of estimated fetal weight (EFW) with a total of 51,702 pregnancies involving 6169 SGA infants (Figure 4). Of these, 20 studies (Baird 2016; Barel 2016; Ben-Haroush 2007; Callec 2015; Chauhan 1999; Chauhan 1999a; Chauhan 2003; Christensen 2015; Freire 2010; Gabbay-Benziv 2016; Geerts 2016; Gupta 2008; Hammad 2015; Hendrix 2000; Roma 2015; Sekar 2016; Sovio 2015; Takeuchi 1985; Turitz 2014; Weiner 2016) used the Hadlock formula, two (Laurin 1987; Palo 1989) used the Eik-Nes formula, and four (Berkowitz 1988; Chervenak 1984; Ott 1984; Skovron 1991) used the Shepard formula to estimate fetal weight. The formula used in the remaining six studies (Bikmetova 2013; Griffin 2015; Hatfield 2010; MacLeod 2013; Mahran 1988; Valino 2016) was not stated. There were two, 10 and 19 studies in low-, high- and mixed-risk cohorts; the patient group was unknown in one study. Six (18.8%) studies (Berkowitz 1988; Callec 2015; Chauhan 2003; Roma 2015; Turitz 2014; Valino 2016) intervened based on test results, which may have altered the outcome of the pregnancy, while index test results did not affect management in four (12.5%) studies (Hammad 2015; Hendrix 2000; Sekar 2016; Weiner 2016). The remaining 22 (68.8%) studies did not provide information on whether the test results led to intervention(s). Sovio 2015 blinded clinicians to the results of the universal ultrasonography and Weiner 2016 blinded clinicians to results of all ultrasound methods other than the one they conducted, but in the majority of studies clinicians either were not blinded to test results or this was not reported. The same ultrasound threshold (10th centile) was used to determine test positivity in 25 studies, one study did not report the threshold used, and each of the six remaining studies used a different threshold (Figure 4). For the 10th centile ultrasound threshold, the summary sensitivity (95% CI) and specificity (95%) were 0.54 (0.43 to 0.65) and 0.95 (0.92 to 0.97) from meta-analysis of the 25 studies (47,057 pregnancies involving 5650 SGA infants) (Figure 6).

2) Ultrasound placental grading

Twelve studies assessed placental grading (by ultrasound echogenicity for identifying SGA infants (Figure 4). The studies included 4940 pregnancies involving 520 SGA infants. There were two, six and four studies in low-, high- and mixed-risk cohorts, respectively. One study (McKenna 2005) intervened based on test results, a grade III placenta was used to identify pregnancies to be induced for suspected fetal compromise, and one study did not (Chen 2012a). Three studies fall beneath the diagonal, two of these are small studies of nine and 55 participants, respectively (Altmann 1978; Estel 1989), while the other study examined placental grading in late pregnancy (36 to 38 weeks) (Miller 1988). The remaining 10 studies did not report this information. All the studies used Grannum grading based on placental calcification and set a grade III threshold; the summary sensitivity (95% CI) and specificity (95%) were 0.38 (0.23 to 0.55) and 0.79 (0.62 to 0.90) (Figure 7).

3) Human placental lactogen (hPL)

Figure 5 shows the 20 studies that assessed hPL. A total of 3486 pregnancies involving 624 SGA infants were included. There were one, 11, and eight studies in low-, high- and mixed-risk cohorts, respectively. Most of the studies (14/20, 70%) did not report whether or not interventions were affected by index test results, four (20%) studies (Granat 1977; Nice 2016; Odendaal 1981; Zhang 1990) did not intervene based on test results, and in two (10%) studies (Sagen 1984; Siebert 1974) index test results led to interventions. The studies used different test thresholds (Figure 5), but eight studies used the 10th centile test threshold. The meta-analysis of the eight studies (1124 pregnancies involving 303 SGA infants) gave summary sensitivity (95% CI) and specificity (95% CI) of 0.38 (0.23 to 0.55) and 0.88 (0.78 to 0.94) (Figure 8).

4) Serum oestriol

Nine studies of 2773 pregnancies involving 373 SGA infants were included (Figure 5). Five of the studies were in high-risk cohorts while the remaining four were in mixed-risk cohorts. Five studies (Cedard 1979; Chard 1985; Nisbet 1982; Palo 1987; Spernol 1989) did not intervene based on index test results, three studies (Gerhard 1986 ; Nielsen 1985 ; Odendaal 1981) did not intervene based on index test results, while one study (Sagen 1984) did, described above. Five studies (Cedard 1979; Chard 1985; Gerhard 1986; Odendaal 1981; Sagen 1984) used the 10th centile test threshold and included a total of 1248 pregnancies (involving 204 SGA infants). Based on the five studies, the summary sensitivity (95% CI) and specificity (95% CI) were 0.39 (0.27 to 0.54) and 0.86 (0.79, 0.91).

5) Urinary oestriol

Urinary oestriol was assessed in nine studies with a total of 92,406 pregnancies involving 7076 SGA infants (Figure 5). Seven of the studies were in high-risk cohorts and two were in mixed-risk cohorts. Five studies (Campbell 1972; Kunz 1976; Oats 1979; Steiner 1991; Weerasinghe 1977) did not state whether or not index test results led to interventions, three studies (Chew 1976; Fliegner 1979; Odendaal 1981) did not intervene based on index test results and one study (Beischer 1991) stated that oestriol levels were an indicator for early delivery, although no numbers were given. Studies used different index test positivity thresholds (Figure 5) but four studies (Beischer 1991; Fliegner 1979; Oats 1979; Steiner 1991) used a threshold of 8 mg per 24 hours (at 30 weeks) to 12 mg per 24 hours (at 40 weeks). The summary sensitivity (95% CI) and specificity (95% CI) from the four studies (84,737 pregnancies involving 6886 SGA infants) were 0.31 (0.18, 0.49) and 0.84 (0.72, 0.91).

6) Placental growth factor (PlGF)

The seven studies of PlGF are shown in Figure 5. A total of 6405 pregnancies (involving 837 SGA infants) were included in the studies. Three of the studies were in high-risk cohorts while four were in mixed-risk cohorts. Two studies (Chaiworapongsa 2013; Kienast 2016) did not state whether index test results led to interventions, four studies (Benton 2016; Molvarec 2013; Nice 2016; Shawkat 2015) did not intervene based on test results and one study (Valino 2016) used the results of the EFW scan to determine whether suspected SGA pregnancies should be delivered by caesarean section. Three studies (Benton 2016; Nice 2016; Shawkat 2015) used a 12 pg/mL threshold, while each of the four remaining studies used a different threshold (Figure 5). Due to the limited number of studies at a common threshold and substantial heterogeneity, meta-analysis to obtain summary estimates of sensitivity and specificity was not performed.

7) Uric acid

Eight studies with a total of 2884 pregnancies (involving 605 SGA infants) assessed uric acid (Figure 5). The studies were in high-risk cohorts except for one study in a mixed-risk cohort. Five studies (Amini 2014; Bellomo 2011; Jauniaux 1996; Voto 1988; Yassaee 2003) did not state whether interventions were made based on index test results and three studies (Hawkins 2012; Odendaal 1997; Williams 2002) had no interventions. The studies used various thresholds (Figure 5).

8) Combination of serum oestriol and human placental lactogen (hPL)

Lenstrup 1982 (88 pregnancies) assessed this combination in a mixed-risk cohort (Figure 5). The sensitivity (95% CI) and specificity (95%) were 0.56 (0.21 to 0.86) and 0.95 (0.88 to 0.99). The specific measurement used as a threshold in this study was not stated; a low hPL and/or E3 level was classified as a positive test result. In this study, one patient was hospitalised after a cardiotocography (CTG) investigation due to a low plasma oestriol level.

Comparative analyses of seven tests for identifying small-for-gestational-age infants (SGA) (birthweight ≤ 10th centile)

Using all available data (86 studies), we compared the accuracy of EFW, hPL, serum oestriol, urinary oestriol, PlGF and uric acid in a single model. Based on the preliminary assessments and likelihood ratio tests comparing different HSROC meta-regression models, in the final model fitted, we modelled differences in accuracy and threshold as random effects with symmetric curves for all tests, i.e. parallel SROC curves such that each curve can be described using a diagnostic odds ratio (DOR) (Figure 9, Table 2). There was a statistically significant ($P < 0.0001$) difference in accuracy between the tests, with EFW being more accurate than all the other tests. For example, the DOR (95% CI) of EFW was 21.3 (13.1 to 34.6) while that of hPL, the biochemical test with the highest DOR, was 4.78 (3.21 to 7.13). Comparing EFW to hPL, the ratio of DORs (95% CI) was 4.45 (2.38 to 8.25) with statistical evidence of a difference in accuracy ($P < 0.0001$). Pairwise comparisons of the seven tests are shown in Table 2.

The sensitivities estimated along the SROC curves at fixed values of specificity are shown in Table 3 for different values of prevalence. Table 3 also shows the numbers of missed SGA infants and false positives in a hypothetical cohort of 1000 pregnant women. At the median specificity of 0.88 and median prevalence of 19%, EFW, hPL, oestriol, urinary oestriol, uric acid, PlGF, and placental grading will miss 49, 116, 123, 128, 139, 144, and 145 SGA infants, respectively.

Ten studies (Altmann 1978; Chard 1985; Geerts 2016; Kunz 1976; Nice 2016; Nisbet 1982; Sagen 1984; Spernol 1989; Steiner 1991; Valino 2016) evaluated two tests and one study (Odendaal 1981) evaluated three tests (hPL, serum oestriol, and urinary oestriol). Of the 11 studies, five (Chard 1985; Nisbet 1982; Odendaal 1981; Sagen 1984; Spernol 1989) evaluated hPL and serum oestriol (Figure 10). From the comparative meta-analysis of the five studies, the DOR (95% CI) for hPL was 5.60 (2.84 to 11.0) and that of serum oestriol was 4.06 (1.81 to 9.07); ratio of the DORs was 1.29 (0.58 to 2.86), P = 0.40. Due to limited data we did not perform meta-analyses for other pair-wise comparisons but summarised individual study results in Appendix 6.

Small-for-gestational age (birthweight < third centile) (SGA3)

SGA3 was evaluated in four studies (Chaiworapongsa 2013; Griffin 2015; Roma 2015; Sovio 2015) involving 6953 pregnancies (235 cases). The four studies assessed PlGF and/or EFW in high- or mixed-risk cohorts (Figure 11). One study (Griffin 2015) of 592 pregnancies evaluated EFW, PlGF, and a combination of the two. The other three studies (5678 pregnancies) assessed EFW and used the 10th centile as the threshold. The summary sensitivity (95% CI) and specificity (95% CI) were 0.66 (0.56 to 0.76) and 0.87 (0.80 to 0.91). The two PlGF studies (1861 pregnancies) used different thresholds (< 0.3 MoM (multiple of the median) and fifth centile); sensitivities were 0.52 (0.31 to 0.73) and 0.37 (0.26 to 0.49) and specificities were 0.83 (0.81 to 0.85) and 0.89 (0.86 to 0.91) respectively. The sensitivity (95% CI) and specificity (95% CI) from the single study of the PlGF and EFW combination were 0.69 (0.55 to 0.81) and 0.72 (0.67 to 0.77).

Stillbirth

1) Ultrasound placental grading

Three studies assessed placental grading for stillbirth (Figure 12) with a total of 15,2236 pregnancies involving 114 stillbirths. Two of the studies (Altmann 1978; Chen 2012) were in high-risk cohorts and the third (Chen 2015) was in a low-risk cohort. Chen 2015 contributed most of the data (15,122/15,236, 99%). The sensitivity and specificity of placental grading in this study was 0.35 (0.26 to 0.46) and 0.94 (0.93 to 0.94). None of the studies stated whether or not there were any interventions based on test results and all used a grade III threshold.

2) Human placental lactogen

Six studies of 544 pregnancies involving 36 stillbirths were included (Figure 12). One study (Siebert 1974) was in a low-risk cohort while the others were in high-risk cohorts. Three studies (Altmann 1978; Trudinger 1979; Ylikorkala 1973) did not report whether or not there were interventions based on index test results, two studies (Leader 1980; Zhang 1990) did not intervene while one study (Siebert 1974) intervened based on test results; both false positive results were caesarean sections prompted by falling hPL values. The studies used various thresholds with sensitivities ranging from 0.50 to 1.00, and specificities from 0.48 to 0.89 (Figure 12).

3) Urinary oestriol

Seven urinary oestriol studies included 92,186 pregnancies involving 651 stillbirths (Figure 12). Five studies were in high-risk cohorts and two were in mixed-risk cohorts. Three studies (Campbell 1972; Oats 1979; Weerasinghe 1977) did not report whether there were any interventions based on index test results, two studies (Chew 1976; Fliegner 1979) did not intervene due to index test results while in two studies (Beischer 1991; Elliott 1970) index test results affected pregnancy management; in the Elliott study there were five caesarean sections that were performed due to greatly reduced oestriol excretion. The studies used different thresholds with sensitivities ranging from 0 to 1, and specificities from 0.60 to 1.00.

4) Placental growth factor

A total of 5894 pregnancies (involving 16 stillbirths) were included in three studies (Figure 12). Two studies were in high-risk cohorts and two were in mixed-risk cohorts. One study (Chaiworapongsa 2013) did not report whether or not index test results could lead to interventions, two studies (Benton 2016; Shawkat 2015) did not intervene based on index test results and one study (Valino 2016) did intervene, described earlier. The studies used different thresholds with sensitivities ranging from 0.67 to 1.00, and specificities from 0.63 to 0.95.

5) Uric acid

Four studies included 2063 pregnancies (involving 37 stillbirths) (Figure 12). Three of the studies were in high-risk cohorts and the remaining study was in a mixed-risk cohort. Intervention status was unknown for one study (Yassaee 2003) while there were no interventions in three studies (Hawkins 2012; Odendaal 1997; Redman 1976). None of the studies used the same threshold. The sensitivities ranged from 0.17 to 1.00, and specificities ranged from 0.40 to 0.90.

Comparative analyses of four biochemical tests for predicting stillbirth

In an indirect test comparison based on 21 studies (including 100,687 pregnancies involving 740 stillbirths), we compared the accuracy of hPL, urinary oestriol, PlGF and uric acid. As there were several tests and only three placental grading studies, to reduce model complexity, we did not include this test in the model. We fitted a model with symmetric curves for the four biochemical tests (Figure 13) and the DORs and ratio of DORs are shown in Table 4. There was a statistically significant (P < 0.0001) difference in accuracy between the tests, with PlGF being the most accurate. For

example, the DOR (95% CI) of PlGF was 49.2 (12.7 to 191) while that of urinary oestriol was 5.83 (4.91 to 6.92). The ratio of the DORs (95% CI) of PlGF and urinary oestriol was 8.44 (2.15 to 33.1) with statistical evidence of a difference in accuracy (P = 0.004). Pair-wise comparisons of the four tests are shown in Table 5.

Using sensitivities estimated at fixed values of specificity, Table 5 shows the numbers of missed stillbirths and false positives in a hypothetical cohort of 1000 pregnant women. At the median specificity of 0.78 and median prevalence of 1.7%, PlGF, hPL, urinary oestriol and uric acid will miss 2, 5, 7 and 8 stillbirths, respectively.

There were no comparative studies of biochemical tests; one study (Altmann 1978) evaluated hPL and placental grading in a small cohort of 10 pregnancies.

Studies with evaluations of both small-for-gestational-age infants (birthweight ≤ 10th centile) and stillbirth

Biochemical tests were assessed for both SGA and stillbirth in 18 studies (Appendix 7). In addition, Chen 2012 assessed placental grading for both outcomes. As it is only possible to show one outcome per study on the forest plot, we chose to display only biochemical tests for clarity. Results for Altmann 1978 and Chen 2012 can be seen in Figure 4 for SGA and in Figure 12 for stillbirth.

Investigation of heterogeneity

Where the number of studies allowed, we investigated the effect of the formula used to estimate fetal weight based on ultrasound examination on test accuracy in a meta-regression. We compared the 20 studies (41,104 pregnancies) that used the Hadlock formula with the four studies (1710 pregnancies) that used the Shepard formula. The DORs (95% CI) for the Shepard and Hadlock formulas were 28.3 (6.60 to 121) and 24.2 (12.3 to 47.7). There was no statistical evidence of a difference in accuracy; the ratio of DORs (95%) was 1.17 (0.23 to 5.79), P = 0.55. Due to limited data, we were unable to formally investigate the effect of other potential sources of heterogeneity as outlined in the Secondary objectives.

Discussion

Summary of main results

Small-for-gestational age (SGA) (birthweight ≤ 10th centile)

The main findings of this review are that ultrasound estimated fetal weight (EFW) is the most accurate test available to detect an SGA infant, but still only detects about 50% of infants born SGA. There are more studies of ultrasound EFW than any biochemical marker of placental dysfunction in this review. Overall, ultrasound EFW is better at predicting SGA < 3rd centile than SGA < 10th centile, which suggests that the more severe the phenotype of SGA, the better the accuracy of ultrasound EFW to identify that baby as SGA. Analysis of the biochemical tests found that human placental lactogen (hPL) was best for identifying an infant that would be SGA at birth, although it was inferior to the performance of ultrasound EFW.

Stillbirth

Fewer studies investigated the prediction of pregnancies that would end in stillbirth and only three studies examined abnormal placental structure or function directly (Benton 2016, Jauniaux 1996, Ylikorkala 1973) by pathological examination.

Placental histopathology data were available for 213 women from the Benton 2016 study; 55 of 94 women with low placental growth factor (PlGF) had Grannum grade II or III placentas, as did one of the 119 with normal PlGF values. Jauniaux 1996 found extended vascular lesions after histopathological examination in 12 complicated cases and Ylikorkala 1973 found evidence of degenerative placental changes and dysmature placenta in 50% of cases; we did not use data from the entire cohort so cannot know numbers from these but there was no relationship found between placental calcification and serum hPL level.

There were no studies that presented data to allow estimation of the diagnostic accuracy of EFW measurement for stillbirth; Sovio 2015 included stillbirths but data were presented as part of a severe adverse perinatal outcome group meaning that stillbirth could not be assessed separately. Included studies measured hPL, PlGF, placental grading, uric acid, and urinary E3. Of the biochemical tests for detecting pregnancies that would end in stillbirth, PlGF had the best diagnostic accuracy.

Critically, very few studies investigated the accuracy of different tests in the same study population, which would allow direct comparison of diagnostic test accuracy, and only one study (Lenstrup 1982) investigated combinations of biomarkers. Indirect comparison suggests that biochemical tests of placental function performed better in identification of pregnancies that would end in a stillbirth compared to detection of a pregnancy that would end in the birth of an SGA infant.

Strengths and weaknesses of the review

This review is the first comprehensive review of biochemical markers in maternal blood or serum in late pregnancy in comparison with the performance of ultrasound to detect pregnancies that end in stillbirth and SGA births. We examined papers from different countries and published in languages other than English, allowing us to cover a wide range of populations of pregnant women. We contacted authors where necessary to clarify or obtain data (although this was not always successful) and were able to include unpublished data in some cases. However, some papers were also unobtainable, meaning it is possible that some usable data may not have been included (see Characteristics of studies awaiting classification). Furthermore, the nomenclature of some of the biochemical factors has changed meaning that the search strategies may not have included all possible studies.

There are some limitations which need to be considered.

- Limitations in the availability and variability in reporting of data prevented us from undertaking comparisons and

investigations of heterogeneity as originally set out in the protocol. Measurements were taken at many different gestational ages and these were often not comparable. Studies often took measurements over a fixed range of time rather than at one time point so there were few studies that used the exact same gestation; a comparison of studies that tested before and after term (37 weeks) was not possible, due to the amount of overlap of this time point.

- Studies used many different measurement techniques for the same index tests, for example measurement of different isoforms of the biochemical factor of interest, which could have had an impact on test performance. Definitions of index test positivity thresholds for individual tests varied and were often not prespecified; they were frequently based on optimally performing thresholds in the study population itself rather than on externally validated thresholds. This meant that it was not practical to perform a formal comparison of all measurements at the 10th centile, for example, as exact measurements differed across studies. If there were common thresholds between studies then these are the ones for which data were extracted, especially if these were in clinical use (e.g. < 12 pg/mL for PlGF). Defined externally-validated thresholds are needed before recommendations for clinical practice can be made.
- Few papers made direct comparisons between index tests (comparison of index test in the same population) or investigated the accuracy of testing strategies (combining several index tests for the same woman). Due to differences between study populations, such as risk factors, it is unclear how useful comparisons between studies are.
- Due to variation between study populations we decided to use fairly broad definitions of patient risk; high risk was defined as all women at high risk due to various factors (pre-eclampsia, hypertension, suspected fetal growth restriction (FGR), history of SGA or stillbirth), mixed risk was where some but not all women were affected by these conditions (including unselected populations), and low-risk was where all complications were excluded. It was not possible to look at test performances in only hypertensive women or only women with suspected FGR, for example.
- With the exception of uric acid, the studies of biochemical markers were performed in two distinct time periods, before 1991 (for hPL and E3) and after 2013 (for PlGF), whereas the accuracy of ultrasound scan has been studied continuously since the 1970s. Earlier studies tended to be smaller and less rigorously conducted and reported as required by contemporary standards of study reporting. In addition, methods of biochemical analysis have also developed over the time frame of the review from radioimmunoassay to enzyme-linked immunosorbent assay (ELISA) or chemiluminescent assays.

Applicability of findings to the review question

Ultrasound EFW is a well-established technique in contemporary obstetric practice and is at the centre of screening for FGR (RCOG 2013) and strategies to reduce stillbirth (NHS England 2016). Many of the studies were conducted in women who were at increased risk of FGR or stillbirth, so these findings cannot necessarily be generalised to a mixed- or low-risk population. This is particularly important because the risk status of the woman alters the importance of specific aspects of test performance. In mothers at high risk of stillbirth, a false negative result would potentially deprive the woman of additional monitoring or intervention which may mitigate the increased risk of adverse outcome, thus sensitivity would be prioritised over specificity. However, women in low- or mixed-risk populations, a false positive result may increase monitoring and/or intervention which is unnecessary and could have short- and long-term consequences (Peters 2018). Unfortunately, limitations in data meant that the impact of the potential sources of heterogeneity described above (including risk status of the mother) on test accuracy could not be explored. We were not able to find all of the information we had intended to, particularly about the outcome of testing and potential harms of testing because data were unavailable. The search was completed in October 2016 and it is possible that new studies, particularly regarding PlGF, have been added since then.

Authors' conclusions

Implications for practice

Ultrasound estimated fetal weight (EFW) appears to be the most accurate method to identify a baby that will be small-for-gestational age (SGA) at birth. However, clinicians should be aware that the estimates of sensitivity (the range of sensitivity for included studies was 0.07 to 0.93) that ultrasound EFW does not detect a significant proportion of babies who have a birthweight < 10th centile. Importantly, EFW has a high specificity (pooled estimate 0.95) which avoids implications of false positive results (e.g. maternal anxiety, further testing, or unwarranted intervention). This review could not find a significant difference between two of the formulae used to derive EFW on diagnostic accuracy (Shepard or Hadlock). This review also suggests that biochemical markers of placental function cannot be used alone to identify which pregnancies will end with the birth of an SGA baby. Biochemical markers show promise in identifying babies who go on to be stillborn, although data are largely confined to women at increased risk of stillbirth. Furthermore, the performance of biochemical markers in comparison to ultrasound EFW for stillbirth is unknown.

Implications for research

Further research studies of ultrasound are required to determine whether an EFW under a specific threshold, e.g. 10th centile identifies pregnancies that end in stillbirth. This could be achieved by including stillbirth as an outcome measure in all studies; stillbirths were frequently excluded from many of the studies examining the accuracy of ultrasound EFW. While individual studies of the accuracy of ultrasound EFW are likely to be underpowered to evaluate the prediction of a pregnancy that ends in stillbirth, this aim could be achieved by meta-analysis of such studies. Further studies are also needed of biochemical markers alone and in combination with ultrasound EFW. Such studies would facilitate direct comparison of test performance and whether a combination of tests would be more effective than a single means of assessment for detection of SGA infants at birth and pregnancies that end in stillbirth.

Ideally, future studies should have an adequate sample size to study their outcome of interest or when this is unlikely

to be possible, e.g. in studies of stillbirth a range of important pregnancy outcomes should be reported to facilitate future meta-analyses. Similarly, studies should also have standardised reporting using the STARD guidelines (Bossuyt 2015) to ensure that information can be extracted for future meta-analyses. In addition, researchers should consider using direct assessment of placental pathology as the reference standard. For practical reasons, this review used two clinical endpoints which are associated with placental pathology. However, the use of clinical endpoints rather than evidence of placental pathology could account for the apparent suboptimal test performance. For example, 70% of SGA infants (< 10th percentile) are “constitutionally small”, with no evidence of underlying placental dysfunction, so would not be expected to have a positive test result. This may also explain why biochemical markers of placental function appear to have a greater accuracy in predicting stillbirth compared to SGA, as stillbirth is more frequently associated with placental abnormalities (in up to 60% of cases). Further studies are needed to determine whether ultrasound EFW, biochemical markers of placental function, and other measurements such as fetal and maternal Doppler measurements accurately identify placental pathology.

Initial research studies may wish to focus on women at highest risk of placental dysfunction, and by association the birth of an SGA infant and stillbirth, e.g. women who are suspected to have a SGA infant by symphysis-fundal height (SFH) measurement, or who present with reduced fetal movements or have hypertension. Studies could then explore the diagnostic accuracy of biochemical factors alone, or in association with ultrasound measurements, in a low- or mixed-risk population where the background risk of adverse outcome is lower. In either case

Test evaluation studies need to consider the implications of revealing index test results as this could have adverse consequences such as increased intervention by induction of labour or increased frequency of birth by caesarean section and admission to neonatal units, all of which may impact upon mothers’ experience of care and fetal outcome. The clinical role of biochemical markers of placental dysfunction needs to be revisited using robust study designs with adequate sample sizes and standardised reporting. Ultimately, clinical efficacy will need to be demonstrated by intervention studies before any test is adopted into clinical practice.

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Contributions of authors

AEP Heazell (AEPH) and Clare Davenport (CD) conceived the idea for the systematic review. All authors contributed to the design of the review and writing the protocol. Susan Bayliss (SEB) undertook the literature searches. AEPH, Dexter Hayes (DH) and Melissa Whitworth (MKW) screened the titles and abstracts and extracted data from included studies. Yemisi Takwoingi (YT) performed the statistical analysis. All authors contributed to the final manuscript. AEPH is the guarantor for the review.

Declarations of interest

Susan Bayliss: none known.

Clare Davenport's employer (The University of Birmingham) received funding for her participation in this review as part of an NIHR clinical fellowship awarded to Alexander Heazell (the lead author and contact person).

Dexter Hayes: none known.

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Alexander Heazell has received research grants from Alere (UK) and Action Medical Research to investigate placental factors in maternal serum in women with reduced fetal movements. He is also a Supervisor for a Clinical Research Fellowship from Action Medical Research which incorporates projects to detect placental factors in maternal serum. In addition, he holds a Clinician Scientist Award from National Institute of Health Research (NIHR) (CS-2013-13-009) and this review is part of that programme of work. The views expressed here are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Differences between protocol and review

There are some minor differences between our published protocol (Heazell 2016) and this review.

- **Methods/investigation of heterogeneity:** in our protocol we stated "Where a sufficient number of studies assess the same index test, potential sources of heterogeneity will be separated into clinical (e.g. population studied, test type) and methodological (as appropriate) sources". In the review, we clarified this and edited the methods to "Where a sufficient number of studies assessed the same index test and there were at least four studies per subgroup of a categorical covariate, we performed meta-regression by adding the potential source of heterogeneity as a covariate to the HSROC model".
- **Statistical analysis and data synthesis**
  - We clarified the use of the terms SGA (for SGA defined as birthweight ≤ 10th centile) and SGA3 for SGA defined as birthweight < 3rd centile.
  - We added "Before performing meta-analyses to compare test accuracy, we performed meta-analysis of each test separately for preliminary investigation of the shape of the SROC curve of each test and to explore if assuming common variances across tests for the random effects would be reasonable".
  - We added "When there were adequate data, we also allowed the variance parameters for accuracy and threshold to depend on test type, i.e. differences in accuracy and threshold modelled as random effects"
  - We also added "To quantify differences in accuracy between tests, we computed ratios of diagnostic odds ratios when SROC curves were symmetric or a common shape was assumed. Using the estimate statement within NLMIXED, we also estimated sensitivities along the SROC curves at fixed values of specificity that correspond to the median and interquartile range of specificities from the studies included in the comparative meta-analysis. We used these values along with the median and interquartile range of the prevalence estimated from the studies to compute numbers of missed cases and false positives in a hypothetical cohort of 1000 pregnant women. We used these frequencies to illustrate the accuracy of the tests in absolute terms"

Published notes

Characteristics of studies

Characteristics of included studies

Altmann 1978

Patient Selection

A. Risk of Bias	
Patient Sampling	Case reports of 10 high-risk pregnancies
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 10 women **Gestation at sampling:** > 26 weeks **Risk:** high risk
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL measured in serum, values classifies as normal/borderline/abnormal, from a reference group of 242 pregnant women. Grade III used as threshold for placental grading.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight under the 10th percentile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	Paper translated from German

Amini 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective multicentric cohort study of singleton pregnancies between 28 and 42 weeks.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size**: 404 **Gestation at sampling:** 24 hours before delivery **Risk:** mixed (some exclusions due to hypertension) **Setting:** Vali-Asr and Akbar-Abadi teaching hospitals of Tehran University of Medical Sciences, Iran **NICU admission:** 79 neonates required NICU admission, 31 from women with hyperuricaemia
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Blood samples taken within 24 hours preceding delivery and uric acid levels were determined using the enzymatic colorimetric method. Hyperuricemia defined as serum uric acid level 1 SD greater than the appropriate for gestational age as defined by Lind and colleagues.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight < 10th percentile for gestational age according to Fenton growth charts
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	559 women were asked to participate, 404 met inclusion criteria
Was there an appropriate interval between index test and reference standard?	No
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Baird 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective cohort study, consecutive enrolment of women clinically suspected of FGR
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 107 **Gestation at sampling:** 35-38 weeks (within 2 weeks of birth) **Risk:** high risk (suspected FGR, previous FGR, maternal medical conditions, decreased fetal movements) **Setting:** university teaching hospital in Victoria, Australia **Mode of delivery:** 45.8% normal vaginal delivery, 14.1% instrumental delivery, 12.1% elective caesarean section, 28% emergency caesarean section
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW calculated using Hadlock charts

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight < 10th centile for gestational age using the most recent Australian birthweight centiles
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	107 pregnancies met the inclusion criteria over a 12-month study period; all were included
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Barel 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Women referred to the gynaecologic ultrasound unit for SEFW 1 week prior to delivery
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 14,089 **Gestation at sampling:** 1 week before delivery (24-41 weeks) **Risk:** mixed **Setting:** Assaf Harofe Medical Centre
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as less than the 10th percentile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	53 cases (4.3%) of SGA were delivered before 34 weeks of gestation

Beischer 1991

Patient Selection

A. Risk of Bias	
Patient Sampling	Consecutive patients from 1971-1984 and 1985-1989
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 72,062 **Gestation at sampling**: 30-34 weeks **Risk:** mixed **Setting:** Mercy Maternity Hospital, Melbourne **Mode of delivery:** 13.6% delivered by caesarean section (12.7% of normal UE3 group and 21.5% of low UE3 group)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	24-hour urinary oestriol excretion, threshold 10th centile according to gestational age

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias
B. Concerns regarding applicability

PIGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias
B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	FGR defined as birthweight below 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	51,427 patients tested from 1971-1984 and 20,635 tested from 1985-1989. Not all patients who delivered were tested due to emergency admissions, premature deliveries, and administrative failures (there were 85,000 total deliveries).
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	High oestriol levels were an indicator for early delivery

Bellomo 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort of women admitted for suspected hypertension during pregnancy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 163 **Gestation at sampling:** 30.4+/- 4.1 weeks **Risk:** high (all suspected hypertension, 44.7% developed pre-eclampsia) **Mode of delivery:** 39% delivered by caesarean section **Setting:** San Giovanni Battista Hospital, Foligno, Italy
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Uric acid measured in serum, hyperuricemia defined as > 309 umol/L

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as those weighing less than the 10th centile based on nationwide derived centile charts for singleton births
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Some patients did not complete the study due to not meeting the BP criteria on entry, elevated proteinuria, incomplete data, insufficient BP recordings, or withdrawal of consent.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Ben-Haroush 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	Women with healthy singleton pregnancies recruited at time of delivery
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size**: 259 **Gestation at sampling:** 28-34 weeks **Risk:** low (no obstetric complications, hypertensive and diabetic pregnancies were excluded)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Estimated fetal weight calculated using Hadlock's formula and converted to percentiles using locally developed growth charts

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as < 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	259 women were included in the study
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Benton 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort of suspected FGR pregnancies from 3 centres
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 411 **Age:** 18-45 **Gestation at sampling:** 20-41 weeks (IQR 29.8, 36) **Risk:** high (suspected FGR, hypertension and pre-eclampsia excluded) **Setting:** 3 sites in Canada, New Zealand, UK **Mode of delivery:** 92 inductions, 38 caesarean, 7 instrumental **NICU admission:** 36 admission, 26 of these from the low PIGF group
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	PIGF measured using Triage immunoassay, very low PIGF defined as < 12 pg/mL

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below the 3rd centile. Birthweight centile determined by the Canadian standard for multi-ethnicity.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	Women recruited from inpatient and outpatient centres at BC Women's Hospital, Vancouver and Ottawa Hospital; cohort of FGR pregnancies from Auckland, New Zealand with banked maternal blood samples; cohort of FGR pregnancies from the UK (PELICAN-FGR Study)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Placental pathology data were available for 213 women; 55 of 94 with a low PlGF were grade II or III, as was one of the 119 with a normal PlGF.

Berkowitz 1988

Patient Selection

A. Risk of Bias	
Patient Sampling	Women with singleton pregnancies selected on the basis of known risk factors or clinical suspicion of IUGR
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 168 **Gestation at sampling**: 30 to 42 weeks (all last measurements used) **Risk:** high (clinical suspicion of IUGR, previous infant with IUGR, complications associated with IUGR, smoking, alcohol/drug abuse, postdates) **Setting:** Mount Sinai Medical Centre, New York
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW calculated using Shepard formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below 10th centile for gestational age at birth on the basis of the nomogram by Brenner and colleagues
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Bikmetova 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective cohort study
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 518 **Gestation at sampling:** 3rd trimester **Risk:** unknown
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	Ultrasound formula not known

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR definition unknown
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Callec 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study across 2 centres between 2003 and 2006, diabetes and illiteracy excluded, as well as intention to deliver outside the hospital or to move outside the region within 3 years.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1897 **Gestation at sampling**: 30-35 weeks **Risk:** mixed **Setting:** EDEN study, 2 university maternity centres, France **Mode of delivery:** 1404 normal vaginal deliveries, 195 instrumental, 298 caesarean sections **NICU admission:** 128 admissions, 20 of these from the EFW < 10 group
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	EFW measured using Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	2002 women originally included in the cohort; 80 were lost to follow-up, declined to continue participation, or experienced fetal death. 1 woman with a stillbirth was also excluded.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Some elective caesarean sections and inductions were performed due to reduced fetal growth; there were higher rates in the FP compared with the FN group.

Campbell 1972

Patient Selection

A. Risk of Bias	
Patient Sampling	All women at risk of FGR
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 284 **Gestation at sampling**: unknown **Risk:** high (268 women clinically suspected of having a small uterus, 16 diabetic or with a bad obstetric history) **Setting:** Queen Charlotte's Maternity Hospital **Mode of delivery:** 43 instrumental deliveries, 26 EmCS, 29 ElCS
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Oestrogens measured as oestriol in 26 cases and total oestrogens in the rest. One or no abnormal measurements classed as normal, 2+ classed as abnormal; measurements did not have to be consecutive.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight below the 5th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Cedard 1979

Patient Selection

A. Risk of Bias	
Patient Sampling	All patients were clinically suspected of IUGR due to lower than expected SFH on 2 consecutive visits
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 64 **Gestation at sampling:** 37-39 weeks **Risk:** high (all clinically suspected of IUGR due to lower than expected SFH on 2 consecutive visits) **Setting:** Maternite de Port-Royal, France
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Oestriol measured in plasma using the oestriol RIA kit IM 82, levels for normal pregnancies established from 301 values obtained from 88 judged to be free of complications and low defined as < 10th percentile

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below the 10th centile, birthweights calculated using Lubchenko curve
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Plasma total oestriol was studied in 222 pregnancies, 64 of these had measurements at 37-39 weeks
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chaiworapongsa 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort between November 2003 and August 2006
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1269 **Gestation at sampling:** 30-34 weeks **Risk:** mixed (PE excluded in early pregnancy, otherwise mixed) **Setting:** Sotero del Rio Hospital, Santiago, Chile
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PlGF/sVEGFR-1 and PlGF/sEng

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below 10th centile for gestational age according to the Chilean birthweight distribution of a Hispanic population. Stillbirth defined as death of a fetus before delivery that was not a consequence of an induced termination of pregnancy (including intrapartum and antepartum stillbirth)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Patients were excluded if they delivered < 34 weeks (n = 29) and did not have a plasma sample collected at 30-34 weeks (n = 326)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chard 1985

Patient Selection

A. Risk of Bias	
Patient Sampling	Antenatal patients with 3 or more blood samples at weekly intervals from the 36th week onwards
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 392 **Gestation at sampling:** 36 weeks onwards **Risk:** mixed (144 with varying degrees of pre-eclampsia) **Setting:** Solihull Hospital, Birmingham UK
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	hPL and oestriol measured in serum using well-established commercial kits

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as a delivered weight below the 10th percentile for the group (2775 g)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chauhan 1999

Patient Selection

A. Risk of Bias	
Patient Sampling	162 patients with oligohydramnios and 162 patients with adequate amniotic fluid
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 324 **Gestation at sampling:** 3rd trimester, mean 34 weeks **Risk:** mixed **Setting:** Spartanburg Regional Medical Center, Jackson, Mississippi
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW, Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chauhan 1999a

Patient Selection

A. Risk of Bias	
Patient Sampling	287 women with pre-eclampsia and 287 healthy controls
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 574 **Gestation at sampling:** average 35 weeks **Risk:** mixed **Setting:** Spartanburg Regional Medical Center, Jackson, Mississippi
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below the 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chauhan 2003

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective identification of all pregnant patients with hypertension delivered during a 5-year period at 3 centres.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 264 **Gestation at sampling:** within 21 days of delivery **Risk:** high (all women had chronic hypertension) **Setting:** centres in Australia (1) and the USA (2)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW estimated using Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as birthweight < 10% for gestational age using the fetal growth curve by Alexander and colleagues in the USA and an Australian growth curve in the other centre
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	All women with chronic hypertension defined according to ACOG criteria who delivered within 5-year period, had a reliable gestational age, and a SEFW within 3 weeks of delivery. Known fetal anomalies, multiple gestations, gestational hypertension, pre-eclampsia, diabetes mellitus were excluded.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chen 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study of 105 women with hypertension
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 105 **Gestation at sampling:** 28-36 weeks **Risk:** high
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as poor fetal growth. Perinatal death.
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chen 2012a

Patient Selection

A. Risk of Bias	
Patient Sampling	High-risk women
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 113 **Gestation at sampling:** 28-36 weeks **Risk:** high **Setting:** tertiary hospital with an average of 200 or more deliveries per month
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Grannum grade III used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Low birthweight defined as below 2500 g, gestational age not taken into account
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chen 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study of patients in a routine obstetric clinic
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 15,122 **Gestation at sampling:** 28 weeks **Risk:** low (hypertension, diabetes mellitus, placenta praevia, anaemia excluded) **Setting:** tertiary teaching hospital
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Placental grading classified using Grannum grading, measured with ultrasound

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Stillbirth between 28 and 41 weeks' gestation
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	19,338 women received examinations at the clinics; 17,991 of these were eligible for further analysis; 15,112 of these met the inclusion criteria
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chervenak 1984

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients referred with a clinical suspicion of IUGR
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 179 **Gestation at sampling:** within 15 days of delivery **Risk:** high
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW calculated using Shepard formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as birthweight 2 SD below the mean
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chew 1976

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients with high-risk pregnancies
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 43 **Gestation at sampling:** 30-40 weeks **Risk:** high (hypertension, poor obstetric history, suspected IUGR) **Setting:** Kandang Kerbau Hospital, Singapore
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Urinary oestriol measured as oestradiol-17-beta

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Some samples taken after fetal death
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Chitlange 1990

Patient Selection

A. Risk of Bias	
Patient Sampling	270 pregnant women with single uncomplicated pregnancies
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 270 **Gestation at sampling:** 31-34 weeks **Risk:** low (only normal antenatal women were selected) **Setting:** Nowrisjee Wadia Maternity Hospital **Mode of delivery:** 3 emergency caesarean sections due to intrapartum fetal distress
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Placental grading

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight < 2500 g (combined data of IUGR, BW < 2 kg, and LBW, 2 kg- to 2.49 kg). No adjustments for gestational age
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Christensen 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective chart review cohort study from 2000 to 2009 in a single academic centre
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 157 **Gestation at sampling:** 3rd trimester **Risk:** high (all pregnancies with SUA) **Setting:** University of Utah School of Medicine
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW calculated using the Hadlock equation

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight < 2500 g, gestational age was not taken into account
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	425 pregnancies identified, anomalies present in 165,35 multiple gestations, birth information unavailable in 27, 7 ended in stillbirth.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Elliott 1970

Patient Selection

A. Risk of Bias	
Patient Sampling	22 pregnancies where all delivered babies with a birthweight lower than 2500g after 37 weeks, part of a series of 104 pregnancies
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 22 **Gestation at sampling**: 3rd trimester **Risk:** high (all fetuses weighed under 2500 g) **Setting:** King George V Memorial Hospital, Sydney
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Oestriol was measured using either Brown and Coyle's method or the semi-automatic method of Brown. Low was defined as a reduction of more than the SD. Measurements were taken at daily intervals and the values used for diagnosis were the means of the values from the final week before pregnancy

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Stillbirth; intrauterine death after 37 weeks
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	We used data for the incidence of stillbirth in this SGA cohort. 5 elective caesarean sections were performed for greatly reduced oestriol excretion.

Estel 1989

Patient Selection

A. Risk of Bias	
Patient Sampling	All women with reduced amniotic fluid measured with ultrasound between 38 and 40 weeks
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 41 **Gestation at sampling:** 38-40 weeks **Risk**: high (reduced amniotic fluid)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Placental grading measured using ultrasound, grade III used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below the 10th weight percentile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	From translation notes

Fliegner 1979

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients in whom simultaneous serial oestriol and pregnanediol measurements were performed after 30 weeks
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 329 **Gestation at sampling:** after 30 weeks **Risk:** mixed (unselected population) **Setting:** Royal Women's Hospital, Melbourne, Australia **Mode of delivery:** 76 inductions, 42 caesarean sections (22 normal E3, 20 subnormal)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Urinary oestriol assays were measured by the method of Brown and colleagues and considered to be subnormal if below a line joining 8 mg/24 hours at 30 weeks' gestation to 12 mg/24 hours at 40 weeks.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	FGR, diagnosed when the infant's weight was less than the 10th percentile for gestational age as seen in patients in the community
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Some pregnancies were terminated if hypertension or pre-eclampsia developed, or if a clinical diagnosis of placental insufficiency was supported by a failure to obtain clear amniotic fluid. Oestriol values were not used to influence treatment.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Freire 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Cross-sectional study of 122 pregnant women who had EFW calculated by ultrasonography up to 7 days before delivery
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 122 **Gestation at sampling:** 29-41 weeks **Risk:** mixed (unselected population, some prior caesareans) **Setting:** Joao Pessoa, Paraiba, Brazil
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW, Hadlock formula

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined using Alexander curve
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Gabbay-Benziv 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective cohort study of all women presenting with sonographic EFW performed within 3 days prior to delivery, July 2007-December 2014
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 6126 **Gestation at sampling:** within 3 days of delivery **Risk:** mixed (malformations and abnormalities, multiple births, stillbirths, missing measurements excluded) **Setting:** single tertiary university-affiliated medical centre
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	EFW calculated using Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as an actual birth weight below the 10th percentile for gestational age, using local growth reference values controlled for gestational age and sex
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	6322 women had fetal weight estimation performed within 3 days of delivery, 133 were excluded due to anomalies and abnormalities, 63 were exclude due to lack of measurements.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Geerts 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study of women who had been referred for umbilical artery RI assessment after 32 weeks of pregnancy and the RI found to be normal between February 11th and October 21st 2013
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 210 **Gestation at sampling:** after 32 weeks **Risk:** high (all women referred due to: reduced SFH, hypertension, diabetes, previous fetal loss, previous abruption or FGR) **Setting:** Tygerberg Hospital (a secondary and tertiary referral centre), Cape Town, South Africa, February 11th to October 21st 2013
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW calculated using Hadlock formula. Grade II used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	228 eligible patients were enrolled during the study period, 18 were excluded (3 did not meet criteria, anomalies detected in 10, 3 left before being scanned, 2 withdrew consent)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Gerhard 1986

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study including all women who visited the outpatient department for the first time before 20 weeks of pregnancy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 869 **Gestation at sampling:** 28-40 weeks **Risk:** mixed (unselected population) **Setting:** University Women's Hospital, Heidelberg, Germany **Mode of delivery:** 130 caesarean sections, 678 spontaneous onset of labour, 61 instrumental **NICU admission:** 122 admissions (20% sensitivity and 91% specificity of oestriol screening for predicting NICU admission)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Serum assay

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight < 10th percentile for age and sex
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	1140 women were included in the study, 260 were eliminated on account of miscarriages, insufficient examinations, and missed appointments, 11 multiple births were not studied.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Test results were examined up until the time of delivery but did not affect management

Gohari 1978

Patient Selection

A. Risk of Bias	
Patient Sampling	All patients studies as they either exhibited subnormal uterine growth clinically or had pregnancy complications often associated with IUGR
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 111 **Gestation at sampling:** after 30 weeks **Risk:** high (suspected IUGR) **Setting:** Department of Obstetrics and Gynaecology, Yale University School of Medicine, New Haven, Connecticut
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL measured using the Placgest immunodiffusion technique or radioimmunoassay

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA diagnosed if birthweight was in or below the 10th percentile of mean weight for gestation, gestational age was determined by Dubowitz examination
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Granat 1977

Patient Selection

A. Risk of Bias	
Patient Sampling	29 severely hypertensive patients from a cohort of 373 women who had hPL measurements in the 3rd trimester
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 29 **Gestation at sampling:** after 30 weeks **Risk:** high (severe hypertension) **Setting:** Rothschild Univeristy Hospital, Israel **Mode of delivery:** 10 deliveries by caesarean section
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Serum hPL measured using a radioimmunoassay technique, low hPL defined as < 1 SD below the normal means

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SFD defined as those infants whose weights were below the 10th percentile for gestational age, according to Battaglia and colleagues.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	2 x 2 table could only be extracted for the severely hypertensive group

Griffin 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Women with singleton pregnancies and reduced SFH across 11 sites in the UK and Canada
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 592 **Gestation at sampling:** 24-37 weeks **Risk:** high **Setting:** PELICAN FGR study **Mode of delivery:** 68.2% spontaneous vaginal delivery, 15% assisted vaginal delivery, 16.7% caesarean section
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	PIGF measured by plasma assay, EFW formula unclear

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined using customised BW centiles
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	9 women excluded from the analysis due to lack of PlGF/outcome/ultrasound data
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	The EFW and PLGF test included AFI measurements but these did not have much of an effect on the overall results

Gupta 2008

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective cohort
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size**: 38 **Gestation at sampling:** 28-32 weeks **Risk:** high (all patients with severe preterm pre-eclampsia) **Mode of delivery:** 19 normal vaginal deliveries, 19 caesarean sections
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW, formula unknown

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Hammad 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	71 women with uncomplicated pregnancies and confirmed gestational dates recruited across 3 sites and randomised to an additional ultrasound group
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 71 **Gestation at sampling:** after 30 weeks **Risk:** low (autoimmune disorders, diabetes, hypertension, history of IUGR, preterm birth, stillbirth, or pre-eclampsia excluded) **Mode of delivery:** 53 spontaneous vaginal deliveries, 2 operative deliveries, 16 caesarean sections **NICU admission:** 2 admissions
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW using Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight < 10th centile using Alexander curves
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	234 women were approached for randomisation, 149 were recruited and 97% of these had follow-up data.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	The extra ultrasound group was used, this had the latest measurements taken (36 to 37 weeks)

Hatfield 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective cohort study from 1999 to 2007
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 659 **Gestation at sampling:** after 26 weeks **Risk:** high (all patients had elevated hCG levels) **Setting:** Saddleback Memorial Medical Centre
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW < 10th centile, formula unknown

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below the 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Hawkins 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective analysis of 2 databases of hypertensive pregnancies
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1306 **Gestation at sampling:** after 34 weeks (value closest to delivery was used) **Risk:** high (all hypertensive pregnancies, excluding chronic hypertension and renal disease) **Setting:** St George Hospital, Australia **NICU admissions:** 226 of 1880 NICU or SCN transfer
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Uric acid measured in serum, values used to determine hyperuricaemia were corrected for gestational age. Elevated uric acid defined as being 1 SD above the gestation-specific mean.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	n =1880 after databases were combined and duplicates were excluded.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	The presence of hyperuricaemia was not a component in the diagnosis of pre-eclampsia nor in the decision to deliver any pregnancy. Authors were contacted for data.

Hendrix 2000

Patient Selection

A. Risk of Bias	
Patient Sampling	Randomised clinical trial of singleton pregnancies with reliable gestational age of 37 weeks or more.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 367 **Gestation at sampling:** > 37 weeks **Risk:** mixed (unselected population) **Setting:** Spartanburg Regional Medical Centre, South Carolina & Medical College of Georgia, Augusta, Georgia
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW calculated using Hadlock formula

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Birthweight < 2500 g, not adjusted for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	758 of 2541 eligible patients were randomised to groups for the trial, 367 assigned to the sonographic estimate group
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Howell 1985

Patient Selection

A. Risk of Bias	
Patient Sampling	501 unselected women with a singleton pregnancy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 501 **Gestation at sampling:** 36-41 weeks **Risk:** mixed (unselected population; 45 patients with pre-eclampsia, 2 with hypertension, 4 with antepartum haemorrhage, 2 diabetics) **Setting:** St Bartholomew's Hospital Medical College & London Hospital Medical College
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	hPL measured by serum radioimmunoassay, 10th centile used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Low birthweight defined as below the 10th centile for the whole population
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Jauniaux 1996

Patient Selection

A. Risk of Bias	
Patient Sampling	Women with abnormal uterine artery Doppler features and/or an increased pulsatility index
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 41 **Gestation at sampling**: 25-28 weeks **Risk:** high (abnormal Doppler, increased pulsatility)
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	Serum levels of uric acid measured by an enzymatic method using uricase, > 4.0 mg/dL considered to be elevated

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as birthweight < 10th centile for local standards
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Measurements taken from 41 women who consented
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Placental histopathological examination revealed extended vascular lesions in 12 complicated cases. These lesions were often combined in cases complicated by PIH and IUGR and by placental abruption.

Kazzi 1983a

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective observational study of placental grade and fetal maturity
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 109 **Gestation at sampling:** within 7 days of delivery **Risk:** high (pregnancies with birthweight < 2700 g) **Setting:** Cleveland Metropolitan General Hospital
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Placental grading determined according to Grannum classification, grade III used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight less than the 10th percentile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	109 pregnancies from a cohort of 224 women with birthweight < 2700 g who were examined sonographically within 7 days of delivery
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

Notes	2700 g was chosen as it was the maximum weight at which infants could be considered SGA

Kienast 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort of women who attended for routine obstetrical care between April and December 2010
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 346 **Gestation at sampling:** 28-32 weeks **Risk:** mixed (unselected population although there is a high incidence of PE in the highlands of Ecuador) **Setting:** Hospital Isidro Ayora, Quito, Ecuador
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Plasma sFlt-1 and PlGF measured using a commercial Roche Elecsys System.Threshold was not pre-specified; the optimal cutoff in terms of maximising both sensitivity and specificity was reported.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	FGR was defined as a birthweight less than the 10th percentile of a reference group
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Klebe 1990

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients with renal transplants from 4 different centres
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 13 **Gestation at sampling:** after 32 weeks **Risk:** high **Setting:** 4 centres in Denmark
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	hPL measured in serum, 5th centile used as threshold

All tests

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

E3

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

EFW

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

PlGF

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Uric acid

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Urinary E3

A. Risk of Bias
Could the conduct or interpretation of the index test have introduced bias?

B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as outside of normal reference area (below 5th percentile); unclear if this threshold was prespecified
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Kunz 1976

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients presently hospitalised because of, or with history of, suspected placental insufficiency
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 83 **Gestation at sampling:** third trimester **Risk:** high (suspected placental insufficiency or a case history)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL and oestriol determinations both performed in serum. 10 measurements of oestriol were taken but only the last 2 values were used for diagnosis. Biochemical parameters were considered to be pathological if they were below 95% of the normal values, with 2 values being outside this normal range or with 3 or more values being continuously below the 95% normal range.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined if birthweight was below the 10th percentile on the Lubchenko curve
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Twin pregnancies and those with doubtful duration were excluded
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Laurin 1987

Patient Selection

A. Risk of Bias	
Patient Sampling	All singleton births without major malformations in Malmö in 1983
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 2205 **Gestation at sampling:** 32 weeks **Risk:** mixed (94% of the population, malformations and multiple births excluded) **Setting:** Malmö General Hospital, Sweden
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	EFW using formula of Eik-Nes, IUGR defined as a -15% deviation for gestational age

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight - 2 SD for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	2322 singleton births in Malmö in 1983, 2205 of which participated in at least 2 ultrasound examinations. 137 of these were lost to follow-up.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Leader 1980

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients admitted antenatally with hypertension, suspicion of IUGR or postmaturity.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 135 **Gestation at sampling:** 30-42 weeks **Risk:** high (hypertension, suspected IUGR, postmaturity) **Setting:** Groote Schuur Hospital, Cape Town
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL estimations done by radioimmunoassay using the Amersham hPL kit, levels were known but not used to influence treatment

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Stillbirth after 30 weeks
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Lenstrup 1982

Patient Selection

A. Risk of Bias	
Patient Sampling	Consecutive series of patients examined with CTG in the 35th-36th week of pregnancy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 88 **Gestation at sampling:** 35-36 weeks **Risk:** mixed (unselected population) **Setting:** Herlev Hospital, Denmark **NICU admission:** 4 admissions, 3 of these from the reduced variability group
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Oestriol and hPL analyses were performed on blood, threshold unclear ('low levels')

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SFD defined as birthweight below 10th centile for Danish children
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	1 patient was hospitalised after CTG because of a low plasma oestriol level and low EFW. Some incorrect data in Table 5; 2 normal E3/hPL reduced variability and normal for date assumed to be 6 instead.

Lilford 1983

Patient Selection

A. Risk of Bias	
Patient Sampling	Unselected women with a singleton pregnancy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 527 **Gestation at sampling:** 36-40 weeks **Risk**: mixed (unselected population; 27 women with pre-eclampsia, 7 with antepartum haemorrhage)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Serum assay for hPL, 10th centile used as threshold. The effect of changing centiles on the sensitivity and specificity was looked at.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	FGR defined as a birthweight < 2740 g; the 10th centile for birthweight in the sample studied
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	Stillbirths were excluded from the calculations as they all occurred before the onset of labour and birthweight would be unrelated to the remainder of the group.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

MacLeod 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study of term, cephalic, singleton pregnancies
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 90 **Gestation at sampling:** term **Risk:** mixed (unselected population) **Setting:** Mbarara Regional Referral Hospital, Uganda
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW, Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Low birthweight defined as < 2500 g, not adjusted for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Mahran 1988

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients selected at random from obstetric population who attended the Ultrasound Unit in 1983, only those who had sure dates confirmed by early ultrasonic examination.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 828 **Gestation at sampling:** after 24 weeks **Risk:** mixed (unselected population)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW, below 2 SD of normal parameters

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile, evaluated by tables constructed by Thomson and colleagues
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Marin 1979

Patient Selection

A. Risk of Bias	
Patient Sampling	Antenatal patients with amniotic fluid samples
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 47 **Gestation at sampling:** after 33 weeks **Risk:** mixed
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Serum hPL assayed using radioimmunoassay kits, 5th centile used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	10th centile for gestational age used to define IUGR
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

McKenna 2005

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort of singleton pregnancies with known gestational age
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1802 **Gestation at sampling:** 36 weeks **Risk:** low (known maternal medical problems, obstetric complications in present or prior pregnancy, fetal abnormalities excluded) **Setting:** Royal Jubilee Maternity Hospital, Belfast **Mode of delivery:** 1190 normal vaginal deliveries, 71 inductions **NICU admission:** 33 admissions, 1 of these from the grade III group
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Placental maturity was determined using the Grannum classification, grade III used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Low birthweight defined as below the 10th centile at birth
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Some pregnancies were induced for suspected fetal compromise, grade III placentas helped to identify these pregnancies

Miller 1988

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients who delivered beyond 37 weeks with known dates, early examination, confirmatory ultrasound, and who delivered within 7 days of study were selected from all referrals
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 246 **Gestation at sampling:** 36-38 weeks **Risk:** mixed (unselected apart from no preterm delivery) **Setting:** Louisiana State University Medical Centre
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Placental grade established from the most mature view of the placenta and assigned in accordance with established criteria, grade III used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA classified as birthweight below 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Molvarec 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Study group selected from groups of hypertensive women based on availability of Doppler ultrasound results
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 89 **Gestation at sampling:** mean 32 weeks **Risk**: high (all women had hypertensive disorders of pregnancy) **Mode of delivery:** 78 caesarean sections
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	PIGF measured using the Alere Triage test, 12 pg/mL used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability	

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th percentile for gestational age and sex according to a Hungarian birthweight percentile table. All neonates with SGA had an asymmetric size, indicating that they had intrauterine growth restriction and were not constitutionally small.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	PIGF values were not an indicator for early delivery

Montan 1986

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study of 645 consecutive pregnancies over a 4-month period
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 307 **Gestation at sampling:** 37 weeks **Risk:** mixed (unselected pregnancies, 40 admitted due to pregnancy induced hypertension) **Setting:** University Hospital of Lund
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Placental grading was made according to the classification of Grannum and colleagues, grade III used as threshold

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA not defined
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	654 women were recruited for the study, of which 621 had a scan in weeks 32 to 33. 146 gave birth before weeks 38 to 29, and 96 objected to further examinations.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Nice 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Blood collected from healthy pregnancies, women with reduced fetal movements, or a suspected SGA fetus after 28 weeks of gestation
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 77 **Gestation at sampling:** after 28 weeks **Risk:** mixed **Setting:** St. Mary's Hospital, Manchester UK **NICU admission:** 12
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	hPL measured by ELISA (threshold 0.8 MoM), PlGF by Alere Triage, ELISA, and Roche automated immunoassay (threshold 12 pg/mL)

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight < 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Authors contacted for data

Nielsen 1985

Patient Selection

A. Risk of Bias	
Patient Sampling	All births that took place in a geographically well-defined area in the course of 1 year that met the inclusion criteria (expected date of delivery, all measurements, measurements not known to the physicians)
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1018 **Gestation at sampling:** 26th and 35th **Risk:** mixed (unselected pregnancies)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Oestriol measured with a radioimmunoassay kit, 2.5th centile used as a threshold

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias
B. Concerns regarding applicability

PlGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias
B. Concerns regarding applicability

Urinary E3

A. Risk of Bias
B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as bodyweight below the 10th centile, referring to the Danish National Board of Health
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	1702 births took place; 1660 of these were registered on a form (8 outside hospital and 34 not registered, these were omitted). 13 twin pregnancies, 153 with uncertain date of expected delivery, 213 without measurements, 263 where monitoring was prescribed were all excluded.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Nisbet 1982

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients with singleton pregnancies attending routine antenatal clinic
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 166 **Gestation at sampling:** 3rd trimester (34.3 +/- 3.1) **Risk:** high (all considered clinically to have small for dates fetuses) **Setting:** Aberdeen Maternity Hospital
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Measurements taken from serum or plasma, oestriol was only measured when there was sufficient sample volume. - 2 SD used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as birthweight below the 10th centile according to gestation, sex, and parity.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	166 patients were included in the study, only 103 could be assayed for oestriol (25 SGA and 38 AGA not included)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Oats 1979

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients in a 7-year period
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 19,119 **Gestation at sampling:** from 30 weeks **Risk:** mixed (unselected population) **Setting:** Mercy Maternity Hospital, Melbourne
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Urinary oestriol excretion was measured by the method of Brown and colleagues, which accounts for gestation. Low E3 patients are from 2 groups, persistently low (2 or more consecutive low values) and transiently low (only 1 low value out of the total number of measurements). Values were regarded as low when below a line joining 8 mg/24 hours at 30 weeks and 12 mg/24 hours at 40 + weeks.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SFD defined as birthweight < 10th centile for gestational age in the community. Stillbirths defined according to the criteria used in the Commonwealth of Australia.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	The test was performed as a routine at 30 and 36 weeks and at other times when indicated by complications of pregnancy or by poor past obstetrical history. Study looks at 400 patients with low oestriol in a subsequent pregnancy but also gives results for the whole study population so these were used.

Obiekwe 1983

Patient Selection

A. Risk of Bias	
Patient Sampling	Unselected women with singleton pregnancies
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 522 **Gestation at sampling:** 36-40 weeks **Risk:** mixed (unselected population; 27 women with pre-eclampsia, 7 antepartum haemorrhage)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	hPL measured in serum by immunoassay, 10th centile used as threshold.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as birthweight below 10th centile of study population (2740 g)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	Stillbirths (n = 5) excluded from original cohort
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Odendaal 1981

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients with positive stress tests
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 148 **Gestation at sampling:** 25-43 weeks **Risk:** high (positive stress tests, various indications) **Setting:** Tygerberg Hospital, South Africa
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL and oestriol immunoassay kit used to measure both, 10th centile used to define low levels. Centiles derived from curves used by Tygerberg hospital derived from 432 patients.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th percentile for the specific duration of pregnancy, gestational age estimated using a Dubowitz score and weight charts used to assess growth
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Serum oestriol and hPL studies were not performed on all patients as these tests were not initially available; intrauterine deaths were also not included in the estimations of IUGR.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Odendaal 1997

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study of women with severe pre-eclampsia.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 196 **Gestation at sampling:** the week before delivery (blood taken twice a week from admission until delivery, last sample used) **Risk:** high (all women with severe pre-eclampsia, all were delivered once 34 weeks was reached) **Setting:** Tygerberg Hospital, South Africa - a tertiary hospital to which many patients with severe pre-eclampsia are referred
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Plasma uric acid was assessed by the automated urokinase method on a Technician SMAC machine, high levels denoted as 1 SD above the mean

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Tygerberg Hospital growth curves were used to assess whether newborns were SGA
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	229 women were included but 33 delivered before 28 weeks and so their weights for gestational age could not be assessed.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Patients were delivered once a gestational age of 34 weeks has been reached or when maternal reasons or abnormal fetal heart rate patterns were an indication for earlier delivery.

Ott 1984

Patient Selection

A. Risk of Bias	
Patient Sampling	All patients undergoing ultrasonic examination within 72 hours before delivery
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 595 **Gestation at sampling:** after 30 weeks **Risk:** mixed (the study population was composed of both high- and low-risk patients) **Setting:** St Mary's Health Centre, St. Louis, Missouri
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW calculated using the formula of Shepard and colleagues

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA classified based on birthweight from gestational age percentile obtained from the normogram of Altman and Coles
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Palo 1987

Patient Selection

A. Risk of Bias	
Patient Sampling	Admissions due to short SFH measurement
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 90 **Gestation at sampling:** 1 week before delivery (28-40 weeks) **Risk:** high (reduced SFH) **Setting:** University Central Hospital, Turku
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Oestriol measured by radioimmunoassay according to Kaihola, - 2 SD used as threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as below 10th percentile by weight
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	The study combined prospective and retrospective data; prospective population derived from mothers with reduced SFH plus 'controls' (women without IUGR after screening the whole cohort), retrospective part was mothers with low E3 only so was not included
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Palo 1989

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study, women admitted based on clinical suspicion of poor fetal growth.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 186 **Gestation at sampling:** 31-42 weeks (mean 38.6) **Risk:** high **Setting:** Maternity Clinic of University Central Hospital, Turku
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	EFW calculations were performed using the calculations of Eik-Nes and colleagues.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	206 women admitted, 20 excluded because exact BPD or AD data were not available
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Patterson 1983

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective selection of patients that demonstrated a Grade II or III placenta (Spanish-surnamed patients only)
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 398 **Gestation at sampling:** 26-39 weeks **Risk:** high **Setting:** Medical Center Hospital, San Antonio, Texas
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Placental grade assessed according to the criteria of Grannum and associates

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile for gestational age.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	431 patients were identified, 398 of these underwent delivery at Medical Center Hospital and were included in the study.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Redman 1976

Patient Selection

A. Risk of Bias	
Patient Sampling	All patients with hypertension. Patients do not comprise a single cohort since new patients entered the study up to 32 weeks of gestation and premature delivery removed other patients from the later periods of the study.
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 281 **Gestation at sampling:** 36 weeks **Risk**: high
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Plasma urate was assayed by the routine automated hydroxylamine method

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias
B. Concerns regarding applicability

PlGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Stillbirths defined as fetuses born dead after the 24th week of gestation
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Hypertension was confirmed in 332 pregnant patients, 238 of which were participating in a trial of antihypertensive treatment. Some women delivered early; hyperuricaemia was never used as an indicator. 281 women had uric acid measurements at 36 weeks.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Roma 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Women were non-selectively enrolled into a randomised trial. Some exclusions based on medical history and history of FGR/PE/stillbirth.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1115 **Gestation at sampling:** 36 weeks **Risk:** mixed **Mode of delivery:** 400 inductions, 86 instrumental deliveries and 47 caesarean sections (both for non reassuring fetal status) **NICU admission:** 1 admission
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	EFW calculated using Hadlock formula

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	1314 women were assigned to US at 36 weeks, 1115 were analysed (1 stillbirth, 13 preterm births, 185 lost to follow up)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Suspected cases of SGA prompted weekly monitoring and elective induction at 37 + 1 weeks if UA-PI values were abnormal (> 95th centile); otherwise, monitoring was carried out every 2 weeks and delivery was induced at 40 + 1 weeks. Data for US at 36 weeks were used as the last test before delivery.

Sagen 1984

Patient Selection

A. Risk of Bias	
Patient Sampling	Women with severe pre-eclampsia
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 74 **Gestation at sampling:** 1-3 days before birth **Risk:** high **Mode of delivery:** 54 caesarean sections, 15 instrumental deliveries, remaining 5 were IUDs
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Oestriol measured in plasma using a radioimmunoassay, hPL measured in plasma using an immunoassay. Threshold defined as the 10th centile from a reference group of 40 healthy pregnant women. Measurements taken twice a day but only the last measurement before delivery was used.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias
B. Concerns regarding applicability

PIGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias
B. Concerns regarding applicability

Urinary E3

A. Risk of Bias
B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Low birthweight defined as under the 10th centile, weight of the newborn related to a centile scale based on 416,756 liveborn infants without congenital malformations and after normal singleton pregnancy in Norway from 1967-1977
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Indication for delivery was based on case history, clinical findings, and results of hormonal, biochemical, ultrasonographic, and cardiotocographic tests

Sekar 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study of all women booked for induction of labour or elective caesarean section during February to December 2013
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 150 **Gestation at sampling:** 1 week prior to delivery **Risk:** mixed
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	EFW calculated using Hadlock formula

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias
B. Concerns regarding applicability

Urinary E3

A. Risk of Bias
B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile for gestational age. Doctors and women were both aware of EFWs
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Shawkat 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	High-risk cohort of women < 35 weeks gestation
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 261 **Gestation at sampling:** test nearest delivery **Risk:** high (suspected FGR, superimposed PE)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	PlGF measured using Alere Triage; threshold used was very low (< 12 pg/mL)

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PIGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as < 10th centile, fetal death
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Surveillance was adjusted according to test results

Siebert 1974

Patient Selection

A. Risk of Bias	
Patient Sampling	A group of 166 pregnant women
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 67 **Gestation at sampling:** 1-3 days before birth **Risk:** low
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Serum assay, some multiple measurements and samples analysed in duplicate

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA, intrauterine death
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	166 women were recruited but data could only be extracted for the 67 normal pregnancies where hPL data were given for all SGA babies, and 20 diabetic patients for intrauterine death
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Test results facilitated management - 2 caesareans were performed in the diabetic pregnancy group (excluded) due to falling values

Skovron 1991

Patient Selection

A. Risk of Bias	
Patient Sampling	Patients with a singleton gestation who had ultrasound for determination of fetal size between 26 and 34 weeks, 1985-1987. Gestational diabetes, placenta praevia, premature labour excluded.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 768 **Gestation at sampling:** 26-34 weeks **Risk:** mixed
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW calculated using the formula of Shepard and colleagues.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as below the 10th centile of birthweight for gestational age and sex using the nomogram developed by Brenner and colleagues.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	996 patients recruited, 768 met the inclusion criteria (37 excluded because of incomplete ultrasound data)
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Sovio 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort of nulliparous women attending for their dating ultrasound scan between January 2008 and July 2012.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 3977 **Gestation at sampling:** 28 or 36 weeks (last scan before delivery) **Risk:** mixed (the only exclusion criterion was multiple pregnancy) **Mode of delivery:** 1924 normal vaginal deliveries, 949 instrumental, 1089 caesarean sections (data missing for mode of delivery for 15 births) **NICU admission:** 229 admissions
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Ultrasound EFW calculated using Hadlock equations

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight of less than the 10th percentile for sex and gestational age, calculated from a UK reference
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	8028 women eligible, 4512 enrolled, 3977 attended all third trimester scans and delivered a liveborn infant after 26 weeks.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	We used universal ultrasonography as these were all single measurements (the last scan before birth) and the data for selective ultrasonography includes women who did not have a scan. Results of routine clinical scans were reported but results of research scans were masked.

Spernol 1989

Patient Selection

A. Risk of Bias	
Patient Sampling	Women screened prospectively; 30 with suspected IUGR, 5 with infants below the 10th centile for weight who were not suspected SGA, 75 low-risk pregnancies.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 110 **Gestation at sampling:** unclear, likely to be 3rd trimester **Risk:** mixed
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Steiner 1991

Patient Selection

A. Risk of Bias	
Patient Sampling	113 pregnant women with suspected IUGR
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 113 **Gestation at sampling:** 28-40 weeks **Risk:** high (all suspected IUGR)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Serum assay for hPL, urinary assay for E3; mean value from 3 measurements was used for diagnosis. Threshold unclear.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as a birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	From translation notes - no details
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Takeuchi 1985

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 210 **Gestation at sampling:** within 7 days of delivery (36-41 weeks) **Risk:** mixed **Mode of delivery:** 20 out of 60 LFD fetuses were delivered by CS, 8 for fetal distress
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	LFD mean BW was 2186 +/- 452 g so was likely adjusted for gestation
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	36-41 weeks' gestation was chosen as it is closest to delivery but not al women had measurements at this time.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Trudinger 1979

Patient Selection

A. Risk of Bias	
Patient Sampling	Consecutive series of inpatients studied within 14 days of delivery where the fetus was considered to be at high risk
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 59 **Gestation at sampling:** after 33 weeks **Risk:** high (31 hypertensive, 20 suspected FGR, 2 antepartum haemorrhage, 3 previous stillbirth, 1 diabetes mellitus, 3 other)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL measured using radioimmunoassay, 10th centile for a pregnancy of the same maturity used as a threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	The clinician was aware of the E3 and ultrasound results but not hPL. SGA below 10th centile for gestational age.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Turitz 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective cohort of all singleton pregnancies presenting for at least 1 growth ultrasound between 26 and 36 weeks gestational age, January 2008 and December 2011
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 10,642 **Gestation at sampling:** 26-36 weeks **Risk:** mixed (all pregnancies; only exclusions were fetal anomalies, multiple pregnancies, twins with 1 fetal loss)
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	EFW centiles calculated using Hadlock formula C

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile using the Alexander curve
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Fetuses with growth restriction were delivered at 37 weeks, or sooner as indicated for abnormal fetal testing or Doppler studies.

Valino 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective study of screening for adverse obstetric outcomes in women attending for a routine third trimester hospital visit
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 3953 **Gestation at sampling:** after 35 weeks **Risk:** mixed (normal population, no exclusion criteria, some women with pre-eclampsia) **Setting:** King's Hospital, London & Medway Maritime Hospital, Gillingham, Kent **Mode of delivery:** 3016 normal vaginal deliveries, 436 elective caesarean sections, 500 emergency caesarean sections (mode of delivery not given for 1 stillbirth) **NICU admission:** 232 admissions, 13 of these from the EFW < 5 group
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PIGF measured in serum using Roche kit, EFW formula unclear; 5th centile used as a threshold for both tests

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

PIGF

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile after correcting for gestational age at delivery
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Included women are those who consented, had data available on all biomarkers, and resulted in the live birth or stillbirth of a phenotypically normal baby at > 24 weeks' gestation.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	The results of the scan were made available to the obstetricians who would have taken specific actions of further monitoring and delivery of the cases of SGA.

Voto 1988

Patient Selection

A. Risk of Bias	
Patient Sampling	Hypertensive pregnant women during the third trimester of pregnancy
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 215 **Gestation at sampling:** third trimester **Risk:** high (all hypertensive)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Threshold > 6 mg%

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias
B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Definition of low birthweight not explicitly stated but it was adjusted for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Walker 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Only Caucasian women were included (represent approximately 60% of pregnant women at University College London Hospitals)
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 1238 **Gestation at sampling:** 30-34 weeks **Risk:** mixed (exclusion criteria were having a single anatomically normal fetus, normal health status, and uncomplicated obstetrical history) **Mode of delivery:** 300 caesarean sections
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Placental grading measured using Grannum classification, grade II used as a threshold

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight below the 10th centile using UK-WHO growth charts
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	1650 women were recruited to the study, of whom 1238 had the 30-34 week ultrasound examination and detailed pregnancy and perinatal outcome available
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Weerasinghe 1977

Patient Selection

A. Risk of Bias	
Patient Sampling	327 patients with antenatal complications, including pre-eclampsia, hypertension, clinical FGR, antepartum haemorrhage, threatened abortion, diabetes mellitus, and premature labour.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 327 **Gestation at sampling:** between 30 weeks and term **Risk:** high
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	Urinary E3 measured using Lever's method; 920 assays were obtained from 327 patients and a low index test result was defined as 1 or more low values (- 2 SD of mean values)

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as a birthweight below 2500 g; no adjustment for gestational age
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Weiner 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	All women were recruited in the active phase of labour (mean cervical dilatation at enrolment 5.5 +/- 2.1 cm).
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size**: 405 **Gestation at sampling:** after 37 weeks **Risk:** mixed **Setting:** Wolfson Medical Centre, Holon, Israel
Are there concerns that the included patients and setting do not match the review question?	Unclear

Index Test

Index tests	EFW calculated using Hadlock formula, sensitivity and specificity were calculated for detection (+/- 10%)

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	FGR defined as actual birthweight below the 10th centile
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	

Westergaard 1984

Patient Selection

A. Risk of Bias	
Patient Sampling	Women that were considered to have a normal singleton pregnancy plus women with a normal singleton pregnancy and abnormal past obstetric history
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 392 **Gestation at sampling:** 35 weeks **Risk:** mixed
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	hPL measured by electroimmunoassay, confidence limits of normal ranges were derived from 3648 samples from 721 normal pregnancies.

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	IUGR defined as birthweight below the 10th centile for gestational age in the Odense populations and assessment based on phenotypic features
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	816 women were invited to participate, of which 611 were recruited. 24 infants with birthweights under the 10th centile but no obvious phenotypic features of IUGR were excluded from the analysis. hPL was determined in 392 women at 35 weeks
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

Notes	Unclear if results were blinded and/or affected management

Williams 2002

Patient Selection

A. Risk of Bias	
Patient Sampling	All hypertensive women who presented for care between 1992 and 1996
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 456 **Gestation at sampling:** after 20 weeks **Risk:** high (patients with gestational hypertension, pre-eclampsia, eclampsia; diabetes and chronic hypertension excluded) **Setting:** British Columbia Women's Hospital
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	450 umol/L used as a threshold

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias
B. Concerns regarding applicability

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias
B. Concerns regarding applicability

PlGF

A. Risk of Bias
B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA infants were defined as being less than the 10th percentile based on the Canadian birthweight percentile figures
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Data for combined GH and PE from all tables add to 452 (258 GH and 194 PE) except table 5 (258 GH and 198 PE) but this is the only place that presents totals of SGA so these numbers have to be used. Management was not based on uric acid levels but unclear as to whether this was because measurements were blinded or not.

Yassaee 2003

Patient Selection

A. Risk of Bias	
Patient Sampling	Cohort study of women with severe pre-eclampsia between 1986 and 2001
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 103 **Gestation at sampling:** unknown **Risk:** high **Mode of delivery:** 59 caesarean sections **Setting:** Taleghani Hospital, Tehran, Iran
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	No description of when tests were performed

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias

B. Concerns regarding applicability

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Unclear whether index test results were known. IUGR not defined.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

Flow and Timing

A. Risk of Bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Ylikorkala 1973

Patient Selection

A. Risk of Bias	
Patient Sampling	Series of pregnancies between 1971 and 1972
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 199 **Gestation at sampling:** third trimester **Risk:** high (mixture of hypertensive, preeclamptic, diabetic, previous IUD) **Setting:** Department of Obstetrics and Gynaecology, Oulu University
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL determined using a double antibody radioimmunoassay (HCS Sclavo-Sorin kit), 2.5th centile used as a threshold (calculated according to Herrera 1958)

All tests

A. Risk of Bias
B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias
B. Concerns regarding applicability

E3

A. Risk of Bias
B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	SGA defined as birthweight below the 10th centile for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	687 patients in the series, only data from high-risk patients could be used
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	
Notes	Placentas were examined microscopically and 46 were found to have degenerative placental changes, 32 had a dysmature placenta, and 78 had normal placental structure. No relationship was found between microscopic calcifications and serum hPL level.

Zhang 1990

Patient Selection

A. Risk of Bias	
Patient Sampling	381 pregnant women recruited
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample size:** 121 **Gestation at sampling:** after 36 weeks **Risk:** high (mixture of hypertension and postterm pregnancy)
Are there concerns that the included patients and setting do not match the review question?	High

Index Test

Index tests	hPL analysed in serum; threshold - 2 SD for each week of gestation, 4.0 mg/L for 36-41 weeks

All tests

A. Risk of Bias

B. Concerns regarding applicability

hPL

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Placental grading

A. Risk of Bias

B. Concerns regarding applicability

E3

A. Risk of Bias

B. Concerns regarding applicability

EFW

A. Risk of Bias

B. Concerns regarding applicability

PlGF

A. Risk of Bias

B. Concerns regarding applicability

Uric acid

A. Risk of Bias

B. Concerns regarding applicability

Urinary E3

A. Risk of Bias

B. Concerns regarding applicability

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Low birthweight defined as < 2501 g, no adjustments made for gestational age
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High

Flow and Timing

A. Risk of Bias	
Flow and timing	Patients were tested at random so not all recruited patients were included, hPL measured using hPL-SRID method
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	2 x 2 table derived from high-risk patients only

Footnotes

ACOG: American College of Obstetricians and Gynecologists; **AFI:** amniotic fluid index; **AGA:** appropriate-for-gestational age; **BP:** blood pressure; **BPD:** biparietal diameter; **BW:** birthweight; **CTH:** cardiotocography; **EFW:** estimated fetal weight**;** **ELISA**: enzyme-linked immunosorbent assay**; FGR:** fetal growth restriction; **FN:** false negative; **FP:** false positive; **hCG:** human chorionic gonadotrophin;**hPL:** human placental lactogen; **IQR:** interquartile range; **IUD:** intrauterine death; **IUGR:** Intrauterine growth restriction; **LFD:** light-for-dates; **NICU:** neonatal intensive care unit; **PE***:* pre-eclampsia; **PIGF:** placental growth factor **; PIH:** pregnancy induced hypertension; **RI:** resistance index; **SCN:** special care nursery; **SD:** standard deviation; **SEFW:** sonographic estimated fetal weight; **SFD:** small-for-dates; **SFH:** symphysis fundal height **SGA:** small-for-gestational age; **SUA:** single umbilical artery; **sVEGFR-1:** soluble vascular endothelial growth factor receptor-1.

Characteristics of excluded studies

Adekanle 2013

Reason for exclusion	Relevant reference standard not recorded

Agboola 1978

Reason for exclusion	2 x 2 table could not be extracted

Aggarwal 2006

Reason for exclusion	Relevant reference standard not recorded

Agorastos 2014

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Ahmad 1979

Reason for exclusion	Relevant reference standard not recorded

Aickin 1983

Reason for exclusion	2 x 2 table could not be extracted

Al-Amin 2015

Reason for exclusion	Relevant index test not included

Alahakoon 2014

Reason for exclusion	Data presented in another paper

Alberry 2009

Reason for exclusion	2 x 2 table could not be extracted

Algeri 2013

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Alvarez-Fernandez 2014

Reason for exclusion	2 x 2 table could not be extracted

Alwasel 2013

Reason for exclusion	Relevant reference standard not recorded

Anastasakis 2008

Reason for exclusion	Participants do not match population of interest

Anderson 1978

Reason for exclusion	Relevant index test not included

Arabin 1993

Reason for exclusion	2 x 2 table could not be extracted

Arabin 1995

Reason for exclusion	2 x 2 table could not be extracted

Arias 1977

Reason for exclusion	Relevant index test not included

Ariyuki 1995

Reason for exclusion	Participants do not match population of interest

Atzeni 2012

Reason for exclusion	2 x 2 table could not be extracted

Aviram 2015

Reason for exclusion	2 x 2 table could not be extracted

Axelsson 1978

Reason for exclusion	Relevant reference standard not recorded

Baeza Valenzuela1995

Reason for exclusion	2 x 2 table could not be extracted

Bahado-Singh 1998

Reason for exclusion	Relevant reference standard not recorded

Bainbridge 2008

Reason for exclusion	2 x 2 table could not be extracted

Bakketeig 1984

Reason for exclusion	2 x 2 table could not be extracted

Baltajian 2016

Reason for exclusion	2 x 2 table could not be extracted

Barden 1999

Reason for exclusion	2 x2 table could not be extracted

Bardien 2016

Reason for exclusion	Relevant reference standard not recorded

Baron 1996

Reason for exclusion	Index test performed continuously over time

Barrilleaux 2007

Reason for exclusion	Relevant reference standard not recorded

Bartha 2003

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Bashir 1982

Reason for exclusion	Relevant index test not included

Bastek 2009

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Battaglia 1995

Reason for exclusion	Relevant reference standard not recorded

Beischer 1975

Reason for exclusion	Data presented in another study

Bell 1967

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Benton 2010

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Benton 2011

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Benton 2011a

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Benton 2012

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Benton 2012a

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Benton 2014

Reason for exclusion	Participants do not match population of interest

Benton 2014a

Reason for exclusion	Relevant reference standard not recorded

Benz 1980

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Berendtsen 1985

Reason for exclusion	Index test measured continuously over time

Bergsjo 1973

Reason for exclusion	2 x2 table could not be extracted

Berle 1973

Reason for exclusion	2 x 2 table could not be extracted

Berle 1973a

Reason for exclusion	2 x 2 table could not be extracted

Berle 1973b

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Berle 1975

Reason for exclusion	2 x 2 table could not be extracted

Bernardes 2013

Reason for exclusion	Relevant reference standard not recorded

Bernatavicius 2013

Reason for exclusion	Participants do not match population of interest

Bersinger 2004

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Bersinger 2005

Reason for exclusion	2 x 2 table could not be extracted

Bhansali 1975

Reason for exclusion	Review

Bian 1992

Reason for exclusion	2 x 2 table could not be extracted

Biberoglu 2016

Reason for exclusion	Relevant reference standard not recorded

Bieglmayer 1981

Reason for exclusion	2 x 2 table could not be extracted

Bila 1980

Reason for exclusion	2 x 2 table could not be extracted

Bitzer 1985

Reason for exclusion	2 x 2 table could not be extracted

Blaskova 1977

Reason for exclusion	Relevant index test not included

Bligh 2015

Reason for exclusion	Relevant reference standard not recorded

Blitz 2016

Reason for exclusion	Review

Blumenfeld 2007

Reason for exclusion	2 x 2 table could not be extracted

Bobrow 2002

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Bock 1976

Reason for exclusion	2 x 2 table could not be extracted

Boij 2012

Reason for exclusion	2 x 2 table could not be extracted

Borges 2005

Reason for exclusion	2 x 2 table could not be extracted

Botasheva 2016

Reason for exclusion	2 x 2 table could not be extracted

Boucoiran 2012

Reason for exclusion	2 x 2 table could not be extracted

Branconi 1981

Reason for exclusion	2 x 2 table could not be extracted

Brush 1970

Reason for exclusion	Participants do not match population of interest

Bukowski 2014

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Butcher 2012

Reason for exclusion	Participants do not match population of interest

Buyon 2011

Reason for exclusion	Relevant reference standard not recorded

Cage 2009

Reason for exclusion	2 x 2 table could not be extracted

Calabrese 2012

Reason for exclusion	Relevant reference standard not recorded

Calderon 2011

Reason for exclusion	2 x 2 table could not be extracted

Campobasso 1967

Reason for exclusion	Participants do not match population of interest

Camus-Bablon 1990

Reason for exclusion	Relevant reference standard not recorded

Carne 1987

Reason for exclusion	Data presented in another study

Castren 1966

Reason for exclusion	Relevant reference standard not recorded

Cavazza 2015

Reason for exclusion	2 x 2 table could not be extracted

Ceccarello 1980

Reason for exclusion	Relevant index test not included

Cefalo 2005

Reason for exclusion	Commentary

Cetin 2014

Reason for exclusion	2 x 2 table could not be extracted

Cetin 2016

Reason for exclusion	Relevant reference standard not recorded

Chaiworapongsa 2008

Reason for exclusion	2 x 2 table could not be extracted

Chaiworapongsa 2012

Reason for exclusion	Data presented in another study

Chaiworapongsa 2013a

Reason for exclusion	2 x 2 table could not be extracted

Chaiworapongsa 2013b

Reason for exclusion	2 x 2 table could not be extracted

Chambers 1989

Reason for exclusion	Relevant index test not included

Chang 1993

Reason for exclusion	Relevant index test not included

Chang 1994

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Chapman 1978

Reason for exclusion	2 x 2 table could not be extracted

Chapman 1981

Reason for exclusion	Participants do not match population of interest

Chappell 2002

Reason for exclusion	2 x 2 table could not be extracted

Chard 1982

Reason for exclusion	Review

Chauhan 2012

Reason for exclusion	2 x 2 table could not be extracted

Chawengsettakul 2015

Reason for exclusion	Relevant reference standard not recorded

Chew 2014

Reason for exclusion	Relevant reference standard not recorded

Church 2016

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Clelia 2013

Reason for exclusion	Relevant reference standard not recorded

Clowse 2011

Reason for exclusion	Relevant reference standard not recorded

Cody 2013

Reason for exclusion	2 x 2 table could not be extracted

Cody 2016

Reason for exclusion	2 x 2 table could not be extracted

Cooley 2011

Reason for exclusion	2 x 2 table could not be extracted

Cordano 1988

Reason for exclusion	Participants do not match population of interest

Craigo 1996

Reason for exclusion	2 x 2 table could not be extracted

Crane 1979

Reason for exclusion	2 x 2 table could not be extracted

Crawford 1985

Reason for exclusion	2 x 2 table could not be extracted

D'Anna 2000

Reason for exclusion	Relevant reference standard not recorded

Daikoku 1979

Reason for exclusion	2 x2 table could not be extracted

Darling 2014

Reason for exclusion	Participants do not match population of interest

Dave 2016

Reason for exclusion	Relevant index test not included

Dawood 1976

Reason for exclusion	Participants do not match population of interest

De Marchi 1977

Reason for exclusion	Participants do not match population of interest

Del Moral 2015

Reason for exclusion	Relevant reference standard not recorded

Deter 2016

Reason for exclusion	Relevant reference standard not recorded

Di Lorenzo 2013

Reason for exclusion	2 x 2 table could not be extracted

Dombrowski 1992

Reason for exclusion	Participants do not match population of interest

Dombrowski 1992a

Reason for exclusion	Participants do not match population of interest

Ducarme 2012

Reason for exclusion	2 x 2 table could not be extracted

Duff 1986

Reason for exclusion	Relevant index test not included

Dutton 2012

Reason for exclusion	Relevant reference standard not recorded

Dutton 2012a

Reason for exclusion	Relevant reference standard not recorded

Eik-Nes 1984

Reason for exclusion	Participants do not match population of interest

El-Ahmady 1997

Reason for exclusion	2 x 2 table could not be extracted

Elchalal 2000

Reason for exclusion	Participants do not match population of interest

Ernst 2016

Reason for exclusion	2 x 2 table could not be extracted

Fadigas 2015

Reason for exclusion	2 x 2 table could not be extracted

Falkner 1995

Reason for exclusion	Relevant index test not included

Ferrazzi 1986

Reason for exclusion	Relevant index test not included

Fioretti 1986

Reason for exclusion	2 x 2 table could not be extracted

Fischer-Rasmussen 1971

Reason for exclusion	2 x 2 table could not be extracted

Fisteag-Kiprono 2006

Reason for exclusion	Relevant reference standard not recorded

Forger 2016

Reason for exclusion	2 x 2 table could not be extracted

Fotiou 2015

Reason for exclusion	2 x 2 table could not be extracted

Furuhashi 1984

Reason for exclusion	2 x 2 table could not be extracted

Gabbay-Benziv 2016a

Reason for exclusion	2 x 2 table could not be extracted

Gabbay-Benziv 2016b

Reason for exclusion	Abstract for another study

Gaillard 2014

Reason for exclusion	2 x 2 table could not be extracted

Gao 2008

Reason for exclusion	2 x 2 table could not be extracted

Garcia-Flores 2015

Reason for exclusion	Relevant reference standard not recorded

Garoff 1976

Reason for exclusion	2 x 2 table could not be extracted

Gaziano 1988

Reason for exclusion	Participants do not match population of interest

Geerts 2007

Reason for exclusion	Relevant reference standard not recorded

Gerhard 1987

Reason for exclusion	2 x 2 table could not be extracted

Gernand 2015

Reason for exclusion	2 x 2 table could not be extracted

Gherzi 1981

Reason for exclusion	Index test measured continuously over time

Giambanco 1986

Reason for exclusion	Review

Giardini 2014

Reason for exclusion	Relevant reference standard not recorded

Gloning 1991

Reason for exclusion	Relevant index test not included

Goetzinger 2013

Reason for exclusion	Relevant index test not included

Goldenberg 1993

Reason for exclusion	Relevant reference standard not recorded

Goldenberg 1997

Reason for exclusion	Relevant reference standard not recorded

Gomez-Roig 2015

Reason for exclusion	2 x 2 table could not be extracted

Gordon 1978

Reason for exclusion	Relevant reference standard not recorded

Grantz 2016

Reason for exclusion	Relevant reference standard not recorded

Gravett 2015

Reason for exclusion	2 x 2 table could not be extracted

Griffin 2014

Reason for exclusion	Data presented in another study

Gris 2015

Reason for exclusion	2 x 2 table could not be extracted

Habib 2002

Reason for exclusion	2 x 2 table could not be extracted

Hargreaves 2011

Reason for exclusion	2 x 2 table could not be extracted

Harper 2014

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Hassan 1987

Reason for exclusion	Relevant index test not included

Hawkins 2014

Reason for exclusion	Relevant index test not included

Heazell 2014

Reason for exclusion	Review

Henrichs 2016

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Hensleigh 1977

Reason for exclusion	Participants do not match population of interest

Herraiz 2014

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Hinkle 2015

Reason for exclusion	2 x 2 table could not be extracted

Hughes 1980

Reason for exclusion	2 x 2 table could not be extracted

Husse 2014

Reason for exclusion	2 x 2 table could not be extracted

Jabeen 1999

Reason for exclusion	Participants do not match population of interest

James-Todd 2015

Reason for exclusion	Relevant reference standard not recorded

Johnson 2011

Reason for exclusion	Relevant reference standard not recorded

Johnstone 2015

Reason for exclusion	Participants do not match population of interest

Karjalainen 1975

Reason for exclusion	Relevant reference standard not recorded

Karlsen 2016

Reason for exclusion	2 x 2 table could not be extracted

Kase 2012

Reason for exclusion	2 x 2 table could not be extracted

Kase 2012a

Reason for exclusion	2 x 2 table could not be extracted

Kazzi 1983

Reason for exclusion	Participants do not match population of interest

Khalil 2015

Reason for exclusion	2 x 2 table could not be extracted

Khalil 2016

Reason for exclusion	2 x 2 table could not be extracted

Kihaile 1988

Reason for exclusion	Participants do not match population of interest

Kim 2009

Reason for exclusion	2 x 2 table could not be extracted

Kim 2014

Reason for exclusion	2 x 2 table could not be extracted

Kim 2016

Reason for exclusion	Participants do not match population of interest

Kjos 2015

Reason for exclusion	2 x 2 table could not be extracted

Kneitel 2016

Reason for exclusion	2 x 2 table could not be extracted

Kolovetsiou-Kreiner 2014

Reason for exclusion	2 x 2 table could not be extracted

Kolovetsiou-Kreiner 2015

Reason for exclusion	2 x 2 table could not be extracted

Krochik 2010

Reason for exclusion	Participants do not match population of interest

Kulkarni 1981

Reason for exclusion	2 x 2 table could not be extracted

Kulkarni 2010

Reason for exclusion	2 x 2 table could not be extracted

Kullander 1982

Reason for exclusion	Relevant index test not included

Kundu 1978

Reason for exclusion	2 x 2 table could not be extracted

Kunzig 1975

Reason for exclusion	2 x 2 table could not be extracted

Kunzig 1980

Reason for exclusion	2 x 2 table could not be extracted

Lai 2014

Reason for exclusion	Relevant reference standard not recorded

Larkin 2015

Reason for exclusion	2 x 2 table could not be extracted

Larsen 1992

Reason for exclusion	2 x 2 table could not be extracted

Larsen 1997

Reason for exclusion	Relevant reference standard not recorded

Laurin 1987a

Reason for exclusion	2 x 2 table could not be extracted

Lean 2016

Reason for exclusion	2 x 2 table could not be extracted

Leanos-Miranda 2013

Reason for exclusion	2 x 2 table could not be extracted

Lechner 1987

Reason for exclusion	2 x 2 table could not be extracted

Levine 2005

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Li 2014

Reason for exclusion	2 x 2 table could not be extracted

Little 2016

Reason for exclusion	2 x 2 table could not be extracted

Lobmaier 2014

Reason for exclusion	2 x 2 table could not be extracted

London 1983

Reason for exclusion	Relevant reference standard not recorded

MacDonald 1983

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Macmillian 1976

Reason for exclusion	2 x 2 table could not be extracted

Maly 1987

Reason for exclusion	Relevant reference standard not recorded

March 2015

Reason for exclusion	2 x 2 table could not be extracted

Margossian 2016

Reason for exclusion	2 x 2 table could not be extracted

Markestad 1997

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Martins 2005

Reason for exclusion	Relevant index test not included

Masoura 2014

Reason for exclusion	2 x 2 table could not be extracted

Matthews 2017

Reason for exclusion	2 x 2 table could not be extracted

Mazzocco 2014

Reason for exclusion	Relevant reference standard not recorded

McKenna 2003

Reason for exclusion	Relevant index test not included

Melamed 2015

Reason for exclusion	2 x 2 table could not be extracted

Melamed 2016

Reason for exclusion	2 x 2 table could not be extracted

Melamed 2016a

Reason for exclusion	2 x 2 table could not be extracted

Merriam 2014

Reason for exclusion	Participants do not match population of interest

Mertens 1975

Reason for exclusion	Participants do not match population of interest

Mirza 2015

Reason for exclusion	Participants do not match population of interest

Miwa 2014

Reason for exclusion	Relevant reference standard not recorded

Mlynarczyk 2015

Reason for exclusion	2 x 2 table could not be extracted

Mlynarczyk 2015a

Reason for exclusion	2 x 2 table could not be extracted

Mone 2016

Reason for exclusion	2 x 2 table could not be extracted

Moore 2012

Reason for exclusion	Relevant reference standard not recorded

Morrison 1980

Reason for exclusion	Participants do not match population of interest

Muraguchi 1981

Reason for exclusion	Participants do not match population of interest

Myatt 2013

Reason for exclusion	2 x 2 table could not be extracted

Nadal 2015

Reason for exclusion	2 x 2 table could not be extracted

Nair 2016

Reason for exclusion	2 x 2 table could not be extracted

Nelson 2015

Reason for exclusion	Participants do not match population of interest

Nice 2014

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Nice 2014a

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Nieder 1976

Reason for exclusion	2 x 2 table could not be extracted

Nielsen 1981

Reason for exclusion	2 x 2 table could not be extracted

Niknafs 2001

Reason for exclusion	Relevant index test not included

O'Connor 2015

Reason for exclusion	Participants do not match population of interest

Obiekwe 1982

Reason for exclusion	Relevant index test not included

Odibo 2014

Reason for exclusion	2 x 2 table could not be extracted

Okonofua 1986

Reason for exclusion	Participants do not match population of interest

Pal 2015

Reason for exclusion	Participants do not match population of interest

Palomaki 2015

Reason for exclusion	Participants do not match population of interest

Palomaki 2015a

Reason for exclusion	Participants do not match population of interest

Papastefanou 2014

Reason for exclusion	2 x 2 table could not be extracted

Papastefanou 2015

Reason for exclusion	2 x 2 table could not be extracted

Parra Saavedra 2015

Reason for exclusion	Relevant reference standard not recorded

Parrish 2010

Reason for exclusion	2 x 2 table could not be extracted

Partap 2015

Reason for exclusion	Relevant reference standard not recorded

Pavelka 1982

Reason for exclusion	Participants do not match population of interest

Pecks 2015

Reason for exclusion	2 x 2 table could not be extracted

Peixoto 2016

Reason for exclusion	2 x 2 table could not be extracted

Perez-Cruz 2015

Reason for exclusion	2 x 2 table could not be extracted

Perry 1986

Reason for exclusion	2 x 2 table could not be extracted

Persson 1978

Reason for exclusion	2 x 2 table could not be extracted

Persson 1980

Reason for exclusion	2 x 2 table could not be extracted

Peyronnet 2016

Reason for exclusion	2 x 2 table could not be extracted

Pfeiffer 1990

Reason for exclusion	2 x 2 table could not be extracted

Pinheiro 2014

Reason for exclusion	2 x 2 table could not be extracted

Pledger 1984

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Pluta 1979

Reason for exclusion	Participants do not match population of interest

Ponce 1995

Reason for exclusion	2 x 2 table could not be extracted

Powers 2010

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Prakash 2012

Reason for exclusion	2 x 2 table could not be extracted

Qublan 2005

Reason for exclusion	2 x 2 table could not be extracted

Raghuramulu 1978

Reason for exclusion	2 x 2 table could not be extracted

Rajasingam 2009

Reason for exclusion	2 x 2 table could not be extracted

Rasanen 2015

Reason for exclusion	Relevant reference standard not recorded

Reck 1987

Reason for exclusion	Relevant index test not included

Ris-Stalpers 2012

Reason for exclusion	2 x 2 table could not be extracted

Riss 1982

Reason for exclusion	Relevant reference standard not recorded

Rizos 2013

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Rocca 1995

Reason for exclusion	2 x 2 table could not be extracted

Romero 2008

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Ronin-Walknowska 1984

Reason for exclusion	2 x 2 table could not be extracted

Rosendahl 1988

Reason for exclusion	Relevant index test not included

Rosendahl 1991

Reason for exclusion	Relevant index test not included

Rothenbacher 2016

Reason for exclusion	2 x 2 table could not be extracted

Ruozi Berretta 1967

Reason for exclusion	Participants do not match population of interest

Sabbagha 1979

Reason for exclusion	Review

Salahuddin 2016

Reason for exclusion	2 x 2 table could not be extracted

Salas 1993

Reason for exclusion	2 x 2 table could not be extracted

Salas 1998

Reason for exclusion	2 x 2 table could not be extracted

Salas 2006

Reason for exclusion	2 x 2 table could not be extracted

Saleh 2015

Reason for exclusion	Relevant reference standard not recorded

Salkie 1977

Reason for exclusion	2 x 2 table could not be extracted

Samanta 1989

Reason for exclusion	2 x 2 table could not be extracted

Sanchez Fernandez 2015

Reason for exclusion	2 x 2 table could not be extracted

Sarandakou 1989

Reason for exclusion	2 x 2 table could not be extracted

Sato 1974

Reason for exclusion	Participants do not match population of interest

Secher 1986

Reason for exclusion	2 x 2 table could not be extracted

Secher 1987

Reason for exclusion	2 x 2 table could not be extracted

Sekar 2015

Reason for exclusion	2 x 2 table could not be extracted

Selbing 1984

Reason for exclusion	Relevant index test not included

Semczuk-Sikora 2007

Reason for exclusion	2 x 2 table could not be extracted

Shaarawy 2001

Reason for exclusion	2 x 2 table could not be extracted

Shah 1996

Reason for exclusion	2 x 2 table could not be extracted

Sharf 1984

Reason for exclusion	Participants do not match population of interest

Sheth 2016

Reason for exclusion	Relevant reference standard not recorded

Shibata 2005

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Sibiude 2012

Reason for exclusion	2 x 2 table could not be extracted

Sichinava 2014

Reason for exclusion	2 x 2 table could not be extracted

Singer 1970

Reason for exclusion	2 x 2 table could not be extracted

Smith 2014

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Smith-Bindman 2002

Reason for exclusion	Participants do not match population of interest

Smith-Bindman 2003

Reason for exclusion	Participants do not match population of interest

Soler 1975

Reason for exclusion	Index test performed continuously over time

Sood 1988

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Sorensen 2000

Reason for exclusion	2 x 2 table could not be extracted

Souka 2012

Reason for exclusion	2 x 2 table could not be extracted

Souka 2013

Reason for exclusion	2 x 2 table could not be extracted

Sovio 2014

Reason for exclusion	Abstract for an included study

Spellacy 1967

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Spellacy 1975

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Spellacy 1976

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Spona 1971

Reason for exclusion	2 x 2 table could not be extracted

Spona 1972

Reason for exclusion	2 x 2 table could not be extracted

Stefanelli 2014

Reason for exclusion	Participants do not match population of interest

Stefanidis 1998

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Strizhakov 2013

Reason for exclusion	2 x 2 table could not be extracted

Strom 1983

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Sucak 2010

Reason for exclusion	2 x 2 table could not be extracted

Sudik 1982

Reason for exclusion	Participants do not match population of interest

Sundrani 2013

Reason for exclusion	2 x 2 table could not be extracted

Tajik 2012

Reason for exclusion	2 x 2 table could not be extracted

Takeuchi 1988

Reason for exclusion	2 x 2 table could not be extracted

Tammemae 2016

Reason for exclusion	2 x 2 table could not be extracted

Tayama 1983

Reason for exclusion	2 x 2 table could not be extracted

Taylor 2003

Reason for exclusion	2 x 2 table could not be extracted

Teoh 1971

Reason for exclusion	Index test performed continuously over time

Tonari 1987

Reason for exclusion	2 x 2 table could not be extracted

Torok 1987

Reason for exclusion	Index test performed continuously over time

Triunfo 2014

Reason for exclusion	2 x 2 table could not be extracted

Triunfo 2016

Reason for exclusion	2 x 2 table could not be extracted

Triunfo 2016a

Reason for exclusion	2 x 2 table could not be extracted

Tsiakkas 2015

Reason for exclusion	Relevant reference standard not recorded

Tsiakkas 2016

Reason for exclusion	Relevant reference standard not recorded

Turpin 2015

Reason for exclusion	2 x 2 table could not be extracted

Van Rijn 2015

Reason for exclusion	2 x 2 table could not be extracted

Varma 1979

Reason for exclusion	Relevant index test not included

Varma 1982

Reason for exclusion	2 x 2 table could not be extracted

Vatten 2012

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Vinayagam 2015

Reason for exclusion	2 x 2 table could not be extracted

Wallner 2007

Reason for exclusion	2 x 2 table could not be extracted

Watson 1973

Reason for exclusion	2 x 2 table could not be extracted

Weissbach 1985

Reason for exclusion	2 x 2 table could not be extracted

Whigham 1980

Reason for exclusion	2 x 2 table could not be extracted

White 2016

Reason for exclusion	Relevant reference standard not recorded

Woelkers 2016

Reason for exclusion	Relevant reference standard not recorded

Woo 2016

Reason for exclusion	Relevant index test not included

Woods 2015

Reason for exclusion	2 x 2 table could not be extracted

Wurz 1983

Reason for exclusion	Participants do not match population of interest

Xing 2016

Reason for exclusion	2 x 2 table could not be extracted

Xu 2015

Reason for exclusion	2 x 2 table could not be extracted

Yamaguchi 1979

Reason for exclusion	2 x 2 table could not be extracted

Yanaihara 1984

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Zail 1975

Reason for exclusion	2 x 2 table could not be extracted

Zera 2011

Reason for exclusion	2 x 2 table could not be extracted

Zhang 2011

Reason for exclusion	2 x 2 table could not be extracted

Zhao 2010

Reason for exclusion	Not a prospective or retrospective cross-sectional or cohort study

Zlatnik 1979

Reason for exclusion	Participants do not match population of interest

Zuckerman 1974

Reason for exclusion	Participants do not match population of interest

Footnotes

Characteristics of studies awaiting classification

Bracali 1968

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Urinary oestriol
Target condition and reference standard(s)	Unknown
Flow and timing	Unknown
Comparative	
Notes	

Fuks 1990

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Placental grading
Target condition and reference standard(s)	Fetal and neonatal outcomes - unclear
Flow and timing	Unknown
Comparative	
Notes	

Jain 2000

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Placental grading
Target condition and reference standard(s)	IUGR
Flow and timing	Unknown
Comparative	
Notes	

Khan 2004

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Ultrasound EFW?
Target condition and reference standard(s)	IUGR
Flow and timing	Unknown
Comparative	
Notes	

Ruseva 1983

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Unknown
Target condition and reference standard(s)	Unknown
Flow and timing	Unknown
Comparative	
Notes	

Ruseva 1985

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Ultrasound EFW
Target condition and reference standard(s)	Unknown
Flow and timing	Unknown
Comparative	
Notes	

Ruseva 1985a

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Ultrasound EFW
Target condition and reference standard(s)	Unknown
Flow and timing	Unknown
Comparative	
Notes	

Ruseva 1988

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	Ultrasound EFW
Target condition and reference standard(s)	Unknown
Flow and timing	Unknown
Comparative	
Notes	

Serban 1971

Patient Sampling	Unknown
Patient characteristics and setting	Unknown
Index tests	hPL
Target condition and reference standard(s)	Unknown
Flow and timing	Unknown
Comparative	
Notes	

Footnotes

EFW: estimated fetal weight; **hPL:** human placental lactogen; **IUGR:** Intrauterine growth restriction

Characteristics of ongoing studies

Footnotes

Summary of results tables

1 Summary of findings table

Review question	To assess and compare the diagnostic accuracy of ultrasound assessment of fetal growth and placental biomarkers alone and in any combination used after 24 weeks of pregnancy in the identification of placental dysfunction as evidenced by either stillbirth or born small-for-gestational age (SGA).
Population	Pregnant women of any reproductive age after 24 weeks' gestation with relevant outcomes of pregnancy recorded.
Settings	All settings
Numbers of studies, pregnancies, SGA births, and stillbirths	Ninety-one studies were included; 86 studies involving 159,490 pregnancies with 15,471 SGA infants and 23 studies involving 115,911 pregnancies with 851 stillbirths (18 of these also looked at SGA).
Index tests	Human placental lactogen (hPL), oestriol (in blood or urine), placental grading, placental growth factor (PlGF), ultrasound estimated fetal weight (EFW), uric acid
Reference standards	Small for gestational age (SGA), stillbirth
Study limitations	Full-text papers of some studies were unobtainable; comparisons of testing at different gestational ages were not possible; comparisons of tests in the same population were not possible; broad definitions of patient risk were used.
Conclusions	Biochemical markers of placental dysfunction alone are not sufficiently accurate to identify pregnancies ending in SGA or stillbirth. Studies combining ultrasound and placental biomarkers are needed to determine whether this approach improves diagnostic accuracy.

Test strategy	Studies	Number of women (cases)	Sensitivity (95% CI) [a]	Specificity (95% CI) [a]	Number of missed cases in a hypothetical cohort of 1000 pregnant women [b]	Number of false positives in a hypothetical cohort of 1000 pregnant women [b]
SGA defined as birthweight ≤ 10th centile						
Comparison of ultrasound EFW and biochemical tests						
Ultrasound EFW	32	51,702 (6169)	0.74 (0.64 to 0.83)	0.88	50 (32 to 68)	97
Placental grading	12	4940 (520)	0.24 (0.15 to 0.36)		144 (122 to 161)	
hPL	20	3486 (624)	0.39 (0.30 to 0.49)		116 (97 to 133)	
Serum oestriol	9	2773 (373)	0.35 (0.28 to 0.43)		124 (108 to 137)	
Urinary oestriol	9	92,406 (7076)	0.33 (0.20 to 0.50)		127 (95 to 152)	
PlGF	8	6997 (1029)	0.24 (0.15 to 0.38)		144 (118 to 161)	
Uric acid	8	2884 (605)	0.27 (0.19 to 0.38)		139 (118 to 154)	
Combination of biochemical tests						
Serum oestriol and hPL	1	88 (9)	0.56 (0.21 to 0.86)	0.95 (0.88 to 0.99)	45 (14 to 91)	45
SGA3 defined as birthweight < 3rd centile						
EFW[c]	3	5678 (212)	0.66 (0.56 to 0.76)	0.87 (0.80 to 0.91)	16 (11 to 20)	124
PlGF	2	1861 (101)	-	–	–	
EFW & PlGF	1	343 (52)	0.69 (0.55 to 0.81)	0.72 (0.67 to 0.77)	42 (35 to 50)	237
Stillbirth						
Comparison of biochemical tests [d]						
hPL	6	544 (36)	0.76 (0.55 to 0.90)	0.78	4 (2 to 8)	216
Urinary oestriol	7	92,186 (651)	0.62 (0.58 to 0.66)		6 (6 to 7)	
PlGF	4	5894 (16)	0.93 (0.78 to 0.98)		2 (0 to 4)	
Uric acid	4	2063 (37)	0.53 (0.21 to 0.83)		8 (3 to 13)	
Ultrasound						
Placental grading	3	15,236 (114)	–	–	–	-

Footnotes

[a]For SGA and stillbirth, the sensitivities were estimated from the SROC curves at fixed values of specificity that correspond to the median of the specificities reported in the studies included in each comparative meta-analysis. For SGA3, the estimates are the pooled sensitivity and specificity from the only meta-analysis that was possible. All other estimates are the sensitivity and specificity from a single study.

[b]To calculate the number of missed cases and false positives for SGA and stillbirth in a hypothetical cohort of 1000 pregnant women, we used the median prevalence of 19% and 1.7% from the studies included in the comparative meta-analysis of SGA and stillbirth, respectively. For SGA3, we used the median prevalence of 4.6% to calculate the number of missed cases

from the pooled estimates of sensitivity and specificity from the only meta-analysis that was possible. For all single studies, we used the prevalence derived from the study.

[c]Meta-analysis was not possible for EFW. For the three studies, the sensitivities were between 0.58 and 0.77, and the specificities were between 0.79 and 0.91.

[d]This comparison was limited to only biochemical tests because there were several tests and only three placental grading studies. Including placental grading increased model complexity and made the comparative meta-analysis model impossible to fit. Therefore, placental grading was excluded. The sensitivities of the three placental grading studies ranged between 0.35 and 0.69, and the specificities between 0.14 and 0.94.

Additional tables

1 Characteristics of included studies table

Study	Target condition	Test	Sample size	Cases	Threshold	EFW formula	Risk	Interventions	Gestational age	Low RoB all
Altmann 1978	SGA	hPL	10	6	Abnormal value		High	Unknown		No
Altmann 1978	SGA	Placental grading	9	6	Grade III		High	Unknown		No
Altmann 1978	Stillbirth	hPL	10	3	Abnormal value		High	Unknown		No
Altmann 1978	Stillbirth	Placental grading	9	2	Grade III		High	Unknown		No
Amini 2014	SGA	UA	404	46	+1 SD		Mixed	Unknown		No
Baird 2016	SGA	EFW	107	78	Below 10th centile	Hadlock	High	Unknown		No
Barel 2016	SGA	EFW	14089	1218	Below 10th centile	Hadlock	Mixed	Unknown		No
Beischer 1991	SGA	Urinary E3	72062	5390	8 mg per 24 hour (30 w) to 12 mg/24 hours (40 w)		High	Yes	Before 37 weeks	No
Beischer 1991	Stillbirth	Urinary E3	72062	452	8 mg per 24 hours (30 w) to 12 mg/24 hours (40 w)		High	Yes	Before 37 weeks	No
Bellomo 2011	SGA	UA	163	43	309 µmol/L		High	Unknown	Before 37 weeks	No
Ben-Haroush 2007	SGA	EFW	259	19	Below 10th centile	Hadlock	Low	Unknown	Before 37 weeks	No
Benton 2016	SGA	PlGF	411	159	12 pg/mL		High	No		Yes
Benton 2016	Stillbirth	PlGF	411	7	12 pg/mL		High	No		Yes
Berkowitz 1988	SGA	EFW	168	42	Below 10th centile	Shepard	High	Yes		No
Bikmetova 2013	SGA	EFW	518	185	Unknown	Unknown	Unknown	Unknown		No
Callec 2015	SGA	EFW	1897	156	Below 10th centile	Hadlock	Mixed	Yes	Before 37 weeks	No
Campbell 1972	SGA	Urinary E3	284	87	Unknown		High	Unknown		Yes
Campbell 1972	Stillbirth	Urinary E3	284	11	Unknown		High	Unknown		Yes
Cedard 1979	SGA	E3	64	17	Below 10th centile		High	Unknown	37 weeks onwards	No

Chaiworapongsa 2013	SGA	PlGF	1269	108	< 0.3 MoM		Mixed	Unknown	Before 37 weeks	No
Chaiworapongsa 2013	SGA3	PlGF	1269	23	< 0.3 MoM		Mixed	Unknown	Before 37 weeks	No
Chaiworapongsa 2013	Stillbirth	PlGF	1269	5	< 0.12 MoM		Mixed	Unknown	Before 37 weeks	No
Chard 1985	SGA	E3	392	39	Below 10th centile		Mixed	Unknown		No
Chard 1985	SGA	hPL	392	39	Below 10th centile		Mixed	Unknown		No
Chauhan 1999	SGA	EFW	324	44	Below 10th centile	Hadlock	Mixed	Unknown		No
Chauhan 1999a	SGA	EFW	574	59	Below 10th centile	Hadlock	Mixed	Unknown		No
Chauhan 2003	SGA	EFW	264	58	Below 10th centile	Hadlock	High	Yes		No
Chen 2012	SGA	Placental grading	105	36	Grade III		High	Unknown		No
Chen 2012	Stillbirth	Placental grading	105	13	Grade III		High	Unknown		No
Chen 2012a	SGA	Placental grading	113	23	Grade III		High	No	Before 37 weeks	Yes
Chen 2015	Stillbirth	Placental grading	15122	99	Grade III		Low	Unknown	Before 37 weeks	Yes
Chervenak 1984	SGA	EFW	179	17	L99CL	Shepard	High	Unknown		No
Chew 1976	SGA	Urinary E3	43	15	Below 2.5th centile		High	No		Yes
Chew 1976	Stillbirth	Urinary E3	43	6	-2SD		High	No		Yes
Chitlange 1990	SGA	Placental grading	270	72	Grade III		Low	Unknown	Before 37 weeks	No
Christensen 2015	SGA	EFW	157	7	Below 10th centile	Hadlock	High	Unknown		No
Elliott 1970	Stillbirth	Urinary E3	22	2	-2 SD		High	Yes		Yes
Estel 1989	SGA	Placental grading	55	21	Grade III		High	Unknown	37 weeks onwards	No
Fliegner 1979	SGA	Urinary E3	329	37	8 mg per 24 hours (30 w) to 12 mg/24 hours (40 w)		Mixed	No		Yes
Fliegner 1979	Stillbirth	Urinary E3	329	5	8 mg per 24 hours (30 w) to 12 mg/24 hours (40 w)		Mixed	No		Yes
Freire 2010	SGA	EFW	122	21	Below 10th centile	Hadlock	Mixed	Unknown		No
Gabbay-Benziv 2016	SGA	EFW	6126	638	Below 10th centile	Hadlock	Mixed	Unknown		No
Geerts 2016	SGA	EFW	210	60	Below 10th centile	Hadlock	High	Unknown		Yes
Geerts 2016	SGA	Placental grading	188	51	Grade III	Hadlock	High	Unknown		Yes
Gerhard 1986	SGA	E3	869	78	Below 10th centile		Mixed	No	Before 37 weeks	Yes

Gohari 1978	SGA	hPL	111	38	5 µg/mL		High	Unknown		No
Granat 1977	SGA	hPL	29	10	4 µg/mL		High	No		No
Griffin 2015	SGA	EFW	586	192	Below 10th centile	Unknown	High	Unknown	Before 37 weeks	No
Griffin 2015	SGA3	EFW	586	78	Below 10th centile	Unknown	High	Unknown	Before 37 weeks	No
Griffin 2015	SGA	PlGF	592	192	Below 5th centile	Unknown	High	Unknown	Before 37 weeks	
Griffin 2015	SGA3	PlGF	592	78	Below 5th centile	Unknown	High	Unknown	Before 37 weeks	No
Griffin 2015	SGA	PlGF or EFW	343	115	Below 10th centile/below 5th centile	Unknown	High	Unknown	Before 37 weeks	
Griffin 2015	SGA3	PlGF or EFW	343	52	Below 10th centile/below 5th centile	Unknown	High	Unknown	Before 37 weeks	No
Gupta 2008	SGA	EFW	38	15	Below 10th centile	Hadlock	High	Unknown		No
Hammad 2015	SGA	EFW	71	9	Below 10th centile	Hadlock	Low	No		No
Hatfield 2010	SGA	EFW	659	48	Below 10th centile	Unknown	High	Unknown		No
Hawkins 2012	SGA	UA	1306	224	+1 SD		High	No		Yes
Hawkins 2012	Stillbirth	UA	1483	5	+ 1SD		High	No		Yes
Hendrix 2000	SGA	EFW	367	22	SEFW < 2500 g	Hadlock	Mixed	No		No
Howell 1985	SGA	hPL	501	50	2.5 µg/mL		Mixed	Unknown		Yes
Jauniaux 1996	SGA	UA	41	16	4 mg/dL		High	Unknown	Before 37 weeks	No
Kazzi 1983a	SGA	Placental grading	109	42	Grade III		Mixed	Unknown		No
Kienast 2016	SGA	PlGF	346	40	Below 5th centile		Mixed	Unknown	Before 37 weeks	No
Klebe 1990	SGA	hPL	13	3	Below 10th centile		High	Unknown		
Kunz 1976	SGA	hPL	83	15	Below 5th centile		High	Unknown		No
Kunz 1976	SGA	Urinary E3	83	15	Below 5th centile		High	Unknown		No
Laurin 1987	SGA	EFW	2068	78	Predicted BW deviation for GA of -15% or more	Eik-Nes	Mixed	Unknown	Before 37 weeks	No
Leader 1980	Stillbirth	hPL	135	8	4 mg/mL		High	No		Yes
Lenstrup 1982	SGA	E3 and/or hPL	88	9	Below 10th centile		Mixed	No	Before 37 weeks	No
Lilford 1983	SGA	hPL	522	52	Below 10th centile		Mixed	Unknown		No
MacLeod 2013	SGA	EFW	90	8	< 2500 g (+/- 10%)	Unknown	Mixed	Unknown		No
Mahran 1988	SGA	EFW	828	98	-2 SD	Unknown	Mixed	Unknown		No

Marin 1979	SGA	hPL	47	13	Below 5th centile		Mixed	Unknown		No
McKenna 2005	SGA	Placental grading	1902	109	Grade III		Low	Yes	Before 37 weeks	No
Miller 1988	SGA	Placental grading	246	29	Grade III		Mixed	Unknown		Yes
Molvarec 2013	SGA	PlGF	89	22	3.9:1		High	No	Before 37 weeks	No
Montan 1986	SGA	Placental grading	307	6	Grade III		Mixed	Unknown	37 weeks onwards	No
Nice 2016	SGA	hPL	77	23	< 0.8 MoM		Mixed	No		No
Nice 2016	SGA	PlGF	76	23	12 pg/mL		Mixed	No		No
Nielsen 1985	SGA	E3	1018	61	Below 2.5th centile		Mixed	No	Before 37 weeks	Yes
Nisbet 1982	SGA	E3	103	46	-2 SD		High	Unknown		No
Nisbet 1982	SGA	hPL	166	71	-2 SD		High	Unknown		No
Oats 1979	SGA	Urinary E3	19119	1391	8 mg/24 hours (30 w) to 12 mg/24 hours (40 w)		Mixed	Unknown		No
Oats 1979	Stillbirth	Urinary E3	19119	172	8 mg/24 hours (30 w) to 12 mg/24ours hours (40 w)		Mixed	Unknown		No
Obiekwe 1983	SGA	hPL	522	29	4.8 µg/mL		Mixed	Unknown	37 weeks onwards	No
Odendaal 1981	SGA	E3	53	30	Below 10th centile		High	No		No
Odendaal 1981	SGA	hPL	77	43	Below 10th centile		High	No		No
Odendaal 1981	SGA	Urinary E3	46	28	Below 10th centile		High	No		No
Odendaal 1997	SGA	UA	196	100	520 µmol/L		High	No	Before 37 weeks	No
Odendaal 1997	Stillbirth	UA	196	18	520 µmol/L		High	No	Before 37 weeks	No
Ott 1984	SGA	EFW	595	111	-1.5 SD	Shepard	Mixed	Unknown	Before 37 weeks	No
Palo 1987	SGA	E3	90	40	-2 SD		High	Unknown		Yes
Palo 1989	SGA	EFW	186	97	Below 10th centile	Eik-Nes	High	Unknown		No
Patterson 1983	SGA	Placental grading	398	21	Grade III		High	Unknown		No
Redman 1976	Stillbirth	UA	281	2	360 µmol/L		Unknown	No	Before 37 weeks	No
Roma 2015	SGA	EFW	1115	134	Below 10th centile	Hadlock	Mixed	Yes	Before 37 weeks	No
Roma 2015	SGA3	EFW	1115	49	Below 10th centile	Hadlock	Mixed	Yes	Before 37 weeks	No
Sagen 1984	SGA	E3	74	40	Below 10th centile		High	Yes		No

Sagen 1984	SGA	hPL	74	40	Below 10th centile		High	Yes		No
Sekar 2016	SGA	EFW	150	15	Below 10th centile	Hadlock	Mixed	No		No
Shawkat 2015	SGA	PlGF	261	106	12 pg/mL		High	No		Yes
Shawkat 2015	Stillbirth	PlGF	261	3	12 pg/mL		High	No		Yes
Siebert 1974	SGA	hPL	67	11	Below 10th centile		Low	Yes		No
Siebert 1974	Stillbirth	hPL	20	2	Below 10th centile		Low	Yes		No
Skovron 1991	SGA	EFW	768	69	Below 10th centile	Shepard	Mixed	Unknown	Before 37 weeks	No
Sovio 2015	SGA	EFW	3977	352	Below 10th centile	Hadlock	Mixed	Unknown	Before 37 weeks	No
Sovio 2015	SGA3	EFW	3977	87	Below 10th centile	Hadlock	Mixed	Unknown	Before 37 weeks	No
Spernol 1989	SGA	E3	110	22	Below 5th centile		Mixed	Unknown		No
Spernol 1989	SGA	hPL	110	22	Below 10th centile		Mixed	Unknown		No
Steiner 1991	SGA	hPL	113	68	Below 10th centile		High	Unknown		No
Steiner 1991	SGA	Urinary E3	113	68	8 mg per 24 hours (30 w) to 12 mg/24 hours (40 w)		High	Unknown		No
Takeuchi 1985	SGA	EFW	210	39	Below 10th centile	Hadlock	Mixed	Unknown		No
Trudinger 1979	SGA	hPL	59	25	Below 10th centile		High	Unknown		No
Trudinger 1979	Stillbirth	hPL	59	1	Below 10th centile		High	Unknown		No
Turitz 2014	SGA	EFW	10642	1876	Below 10th centile	Hadlock	Mixed	Yes	Before 37 weeks	No
Valino 2016	SGA	EFW	3953	379	Below 10th centile	Unknown	Mixed	Yes		No
Valino 2016	SGA	PlGF	3953	379	Below 10th centile	Unknown	Mixed	Yes		No
Valino 2016	Stillbirth	PlGF	3953	1	Below 10th centile	Unknown	Mixed	Yes		No
Voto 1988	SGA	UA	215	30	6 mg%		High	Unknown		No
Walker 2010	SGA	Placental grading	1238	104	Grade III		Mixed	Unknown	Before 37 weeks	No
Weerasinghe 1977	SGA	Urinary E3	327	45	-2 SD		High	Unknown		No
Weerasinghe 1977	Stillbirth	Urinary E3	327	3	-2 SD		High	Unknown		No
Weiner 2016	SGA	EFW	405	30	Below 10th centile	Hadlock	Mixed	No	37 weeks onwards	No
Westergaard 1984	SGA	hPL	392	28	Abnormal value		Mixed	Unknown	Before 37 weeks	No
Williams 2002	SGA	UA	456	87	450 µmol/L		High	No		No
Yassaee 2003	SGA	UA	103	59	6 mg/dL		High	Unknown		No

Yassaee 2003	Stillbirth	UA	103	12	6 mg/dL		High	Unknown		No
Ylikorkala 1973	Stillbirth	hPL	199	14	Below 2.5th centile		High	Unknown		No
Zhang 1990	SGA	hPL	121	38	4 µg/mL		High	No		No
Zhang 1990	Stillbirth	hPL	121	8	4 µg/mL		High	No		No

Footnotes

EFW: estimated fetal weight**; hPL:** human placental lactogen; **MoM:** multiple of the median; **PIGF:** Placental growth factor **;** **SD:** standard deviation; **SEFW:** sonographic estimated fetal weight; **SGA:** small-for-gestational age; **UA:** uric acid

2 Indirect comparison of tests for assessment of small-for-gestational-age infants ≤tenth centile outcome

Ratio of diagnostic odds ratios (95% CI), P value			Estimated fetal weight	Human placental lactogen	Oestriol	Urinary oestriol	Placental growth factor	Uric acid
	Studies; participants (SGA cases)	DOR (95% CI)	21.3 (13.1 to 34.6)	4.78 (3.21 to 7.13)	4.00 (2.91 to 5.49)	3.59 (1.78 to 7.23)	2.73 (1.67 to 4.48)	2.36 (1.25 to 4.46)
Estimated fetal weight	32; 51,702 (6169)	21.3 (13.1 to 34.6)						
Human placental lactogen	20; 3486 (624)	4.78 (3.21 to 7.13)	4.45 (2.38 to 8.25), P < 0.0001					
Oestriol	9; 2773 (373)	4.00 (2.91 to 5.49)	5.33 (2.98 to 9.52), P < 0.0001	1.20 (0.72 to 1.99), P = 0.48				
Urinary oestriol	9; 92,406 (7076)	3.59 (1.78 to 7.23)	5.93 (2.53 to 13.9), P < 0.0001	1.33 (0.59 to 2.98), P = 0.48	1.11 (0.52 to 2.40), P = 0.78			
Placental growth factor	7; 6405 (837)	2.73 (1.67 to 4.48)	7.79 (3.90 to 15.6), P < 0.0001	1.75 (0.93 to 3.30), P = 0.08	1.46 (0.81 to 2.63), P = 0.26	1.31 (0.56 to 3.09), P = 0.53		
Uric acid	8; 2884 (605)	2.36 (1.25 to 4.46	9.02 (4.05 to 20.1), P < 0.0001	2.03 (0.96 to 4.29), P = 0.06	1.69 (0.83 to 3.44), P = 0.14	1.52 (0.59 to 3.92), P = 0.38	1.16 (0.52 to 2.59), P = 0.72	
Placental grading	12; 4940 (520)	2.34 (1.33 to 4.12)	9.09 (4.32 to 19.2), P < 0.0001	2.04 (1.02 to 4.08), P = 0.04	1.71 (0.89 to 3.26), P = 0.10	1.53 (0.62 to 3.77), P = 0.35	1.17 (0.55 to 2.47), P = 0.68	1.01 (0.43 to 2.36), P = 0.98

Footnotes

All available data were used for indirect comparison of the accuracy of the tests. The ratio of diagnostic odds ratios is the DOR of the test in the column divided by the DOR of the test in the row. If the ratio of DORs is greater than one, then the diagnostic accuracy of the test in the column is higher than that of the test in the row; if the ratio is less than one, the diagnostic accuracy of the test in the row is higher than that of the test in the column.

3 Comparison of test accuracy at different levels of prevalence of small-for-gestational-age (birthweight ≤tenth centile) infants

Prevalence (%)	Specificity	False positives	Test	Sensitivity (95% CI)	Missed SGA infants

10	0.74	234	EFW	0.88 (0.82 to 0.92)	12
			hPL	0.63 (0.53 to 0.71)	38
			Oestriol	0.58 (0.51 to 0.66)	42
			Urinary oestriol	0.56 (0.39 to 0.72)	45
			PlGF	0.49 (0.37 to 0.61)	52
			Uric acid	0.45 (0.31 to 0.61)	55
			Placental grading	0.45 (0.32 to 0.59)	55
19	0.74	211	EFW	0.88 (0.82 to 0.92)	23
			hPL	0.63 (0.53 to 0.71)	71
			Oestriol	0.58 (0.51 to 0.66)	80
			Urinary oestriol	0.56 (0.39 to 0.72)	84
			PlGF	0.49 (0.37 to 0.61)	97
			Uric acid	0.45 (0.31 to 0.61)	104
			Placental grading	0.45 (0.32 to 0.59)	105
35	0.74	169	EFW	0.88 (0.82 to 0.92)	42
			hPL	0.63 (0.53 to 0.71)	131
			Oestriol	0.58 (0.51 to 0.66)	146
			Urinary oestriol	0.56 (0.39 to 0.72)	155
			PlGF	0.49 (0.37 to 0.61)	179
			Uric acid	0.45 (0.31 to 0.61)	192
			Placental grading	0.45 (0.32 to 0.59)	193
10	0.88	108	EFW	0.74 (0.64 to 0.83)	26
			hPL	0.39 (0.30 to 0.49)	61
			Oestriol	0.35 (0.28 to 0.43)	65
			Urinary oestriol	0.33 (0.20 to 0.50)	68
			PlGF	0.24 (0.15 to 0.38)	76
			Uric acid	0.27 (0.19 to 0.38)	73
			Placental grading	0.24 (0.15 to 0.36)	76
19	0.88	97	EFW	0.74 (0.64 to 0.83)	49
			hPL	0.39 (0.30 to 0.49)	116
			Oestriol	0.35 (0.28 to 0.43)	123
			Urinary oestriol	0.33 (0.20 to 0.50)	128
			PlGF	0.24 (0.15 to 0.38)	144
			Uric acid	0.27 (0.19 to 0.38)	139
			Placental grading	0.24 (0.15 to 0.36)	145
35	0.88	78	EFW	0.74 (0.64 to 0.83)	90
			hPL	0.39 (0.30 to 0.49)	212
			Oestriol	0.35 (0.28 to 0.43)	227
			Urinary oestriol	0.33 (0.20 to 0.50)	235
			PlGF	0.24 (0.15 to 0.38)	265
			Uric acid	0.27 (0.19 to 0.38)	255
			Placental grading	0.24 (0.15 to 0.36)	266

10	0.96	36	EFW	0.47 (0.35 to 0.59)	53
			hPL	0.17 (0.12 to 0.23)	84
			Oestriol	0.14 (0.11 to 0.19)	86
			Urinary oestriol	0.13 (0.07 to 0.23)	87
			PlGF	0.10 (0.07 to 0.16)	90
			Uric acid	0.09 (0.05 to 0.16)	92
			Placental grading	0.09 (0.05 to 0.15)	92
19	0.96	23	EFW	0.47 (0.35 to 0.59)	101
			hPL	0.17 (0.12 to 0.23)	159
			Oestriol	0.14 (0.11 to 0.19)	163
			Urinary oestriol	0.13 (0.07 to 0.23)	166
			PlGF	0.10 (0.07 to 0.16)	171
			Uric acid	0.09 (0.05 to 0.16)	173
			Placental grading	0.09 (0.05 to 0.15)	174
35	0.96	26	EFW	0.47 (0.35 to 0.59)	186
			hPL	0.17 (0.12 to 0.23)	292
			Oestriol	0.14 (0.11 to 0.19)	301
			Urinary oestriol	0.13 (0.07 to 0.23)	305
			PlGF	0.10 (0.07 to 0.16)	315
			Uric acid	0.09 (0.05 to 0.16)	319
			Placental grading	0.09 (0.05 to 0.15)	319

Footnotes

EFW: estimated fetal weight; **hPL:** human placental lactogen; **PlGF:** placental growth factor.

The sensitivities were estimated from the SROC curves at quartiles of the observed specificity in the included studies. Using these sensitivities and specificities, along with quartiles of prevalence from the included studies, the numbers of missed SGA infants and false positives were calculated based on a hypothetical cohort of 1000 pregnant women predicted to have a small-for-gestational-age infant.

4 Indirect comparison of biochemical tests for predicting stillbirth

Ratio of diagnostic odds ratios (95% CI), **P value**			**Placental growth factor**	**Human placental factor**	**Urinary oestriol**
	Studies; **participants (stillbirths)**	**DOR (95% CI)**	49.2 (12.7 to 191)	11.4 (4.29 to 30.2)	5.83 (4.91 to 6.92)
Placental growth factor	4; 5894 (16)	49.2 (12.7, 191)			
Human placental lactogen	6; 544 (36)	11.4 (4.29, 30.2)	4.32 (0.81 to 23.0), P = 0.08		
Urinary oestriol	7; 92,186 (651)	5.83 (4.91, 6.92)	8.44 (2.15 to 33.1), P = 0.004	1.95 (0.72 to 5.27), P = 0.17	
Uric acid	4; 2063 (37)	4.02 (0.95, 17.0)	12.2 (1.69 to 88.5), P = 0.016	2.83 (0.50 to 16.1), P = 0.22	1.45 (0.34 to 6.19), P = 0.60

Footnotes

All available data were used for the indirect comparison of the accuracy of the tests. The ratio of diagnostic odds ratios is the

DOR of the test in the column divided by the DOR of the test in the row. If the ratio of DORs is greater than one, then the diagnostic accuracy of the test in the column is higher than that of the test in the row; if the ratio is less than one, the diagnostic accuracy of the test in the row is higher than that of the test in the column.

5 Comparison of test accuracy at different levels of prevalence of stillbirth

Prevalence (%)	Specificity	False positives	Test	Sensitivity (95% CI)	Missed stillbirths
0.9	0.63	367	PlGF	0.97 (0.88 to 0.99)	1
			hPL	0.87 (0.72 to 0.95)	2
			Urinary oestriol	0.77 (0.74 to 0.80)	3
			Uric acid	0.70 (0.36 to 0.91)	3
1.7	0.63	364	PlGF	0.97 (0.88 to 0.99)	1
			hPL	0.87 (0.72 to 0.95)	3
			Urinary oestriol	0.77 (0.74 to 0.80)	4
			Uric acid	0.70 (0.36 to 0.91)	6
9.1	0.63	336	PlGF	0.97 (0.88 to 0.99)	4
			hPL	0.87 (0.72 to 0.95)	12
			Urinary oestriol	0.77 (0.74 to 0.80)	21
			Uric acid	0.70 (0.36 to 0.91)	28
0.9	0.78	218	PlGF	0.93 (0.78 to 0.98)	1
			hPL	0.76 (0.55 to 0.90)	3
			Urinary oestriol	0.62 (0.58 to 0.66)	4
			Uric acid	0.53 (0.21 to 0.83)	5
1.7	0.78	216	PlGF	0.93 (0.78 to 0.98)	2
			hPL	0.76 (0.55 to 0.90)	5
			Urinary oestriol	0.62 (0.58 to 0.66)	7
			Uric acid	0.53 (0.21 to 0.83)	8
9.1	0.78	200	PlGF	0.93 (0.78 to 0.98)	7
			hPL	0.76 (0.55 to 0.90)	22
			Urinary oestriol	0.62 (0.58 to 0.66)	35
			Uric acid	0.53 (0.21 to 0.83)	43
0.9	0.89	109	PlGF	0.86 (0.61 to 0.96)	2
			hPL	0.58 (0.35 to 0.79)	4
			Urinary oestriol	0.42 (0.38 to 0.46)	6
			Uric acid	0.33 (0.11 to 0.68)	7
1.7	0.89	108	PlGF	0.86 (0.61 to 0.96)	3
			hPL	0.58 (0.35 to 0.79)	8
			Urinary oestriol	0.42 (0.38 to 0.46)	10
			Uric acid	0.33 (0.11 to 0.68)	12
9.1	0.89	100	PlGF	0.86 (0.61 to 0.96)	13
			hPL	0.58 (0.35 to 0.79)	38
			Urinary oestriol	0.42 (0.38 to 0.46)	53
			Uric acid	0.33 (0.11 to 0.68)	61

Footnotes

hPL: human placental lactogen; **PlGF:** placental growth factor.

The sensitivities were estimated from the SROC curves at quartiles of the observed specificity in the included studies. Using these sensitivities and specificities, along with quartiles of prevalence from the included studies, the numbers of missed

stillbirths and false positives were calculated based on a hypothetical cohort of 1000 pregnant women predicted to have a stillbirth.

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Classification pending references

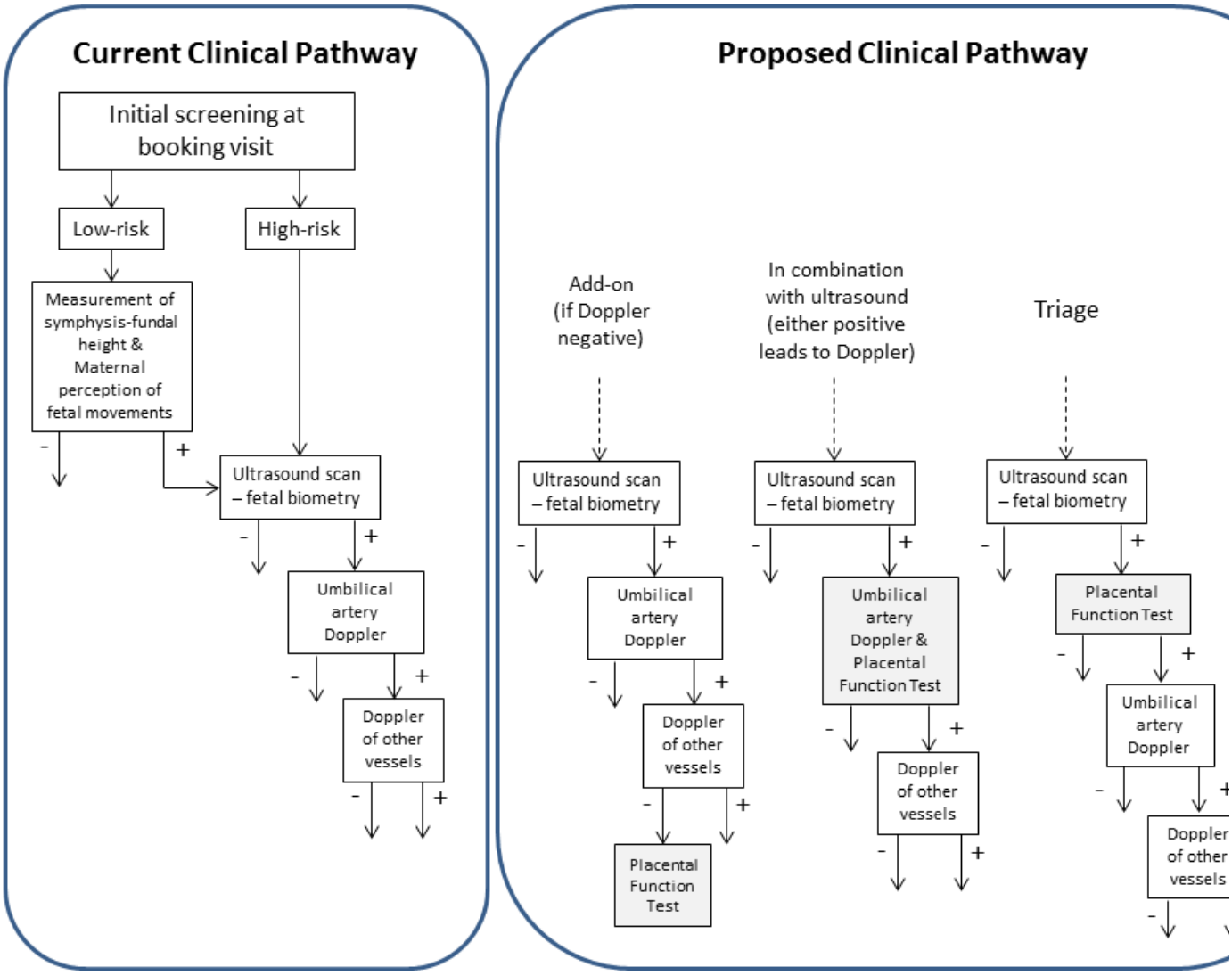
Data and analyses

Data tables by test

Test	Studies	Participants
1 EFW and SGA	32	51702
2 Placental grading and SGA	12	4940
3 hPL and SGA	20	3486
4 E3 and SGA	9	2773
5 Urinary E3 and SGA	9	92406
6 PlGF and SGA	8	6997
7 UA and SGA	8	2884
8 E3 AND/OR hPL and SGA	1	88
9 EFW for SGA - 10th centile threshold only	25	47057
10 hPL for SGA - 10th centile threshold only	8	1414
11 EFW and SGA3	3	5678
13 PlGF and SGA3	2	1861
14 hPL and stillbirth	6	544
15 Urinary E3 and stillbirth	7	92186
16 PlGF and stillbirth	4	5894
17 UA and stillbirth	4	2063
18 Placental grading and stillbirth	3	15236
19 SGA data from studies with both SGA infants and stillbirths	17	99920
20 Stillbirth data from studies with both SGA infants and stillbirths	17	100050
22 PlGF or EFW and SGA	1	343
23 PlGF or EFW and SGA3	1	343

Figures

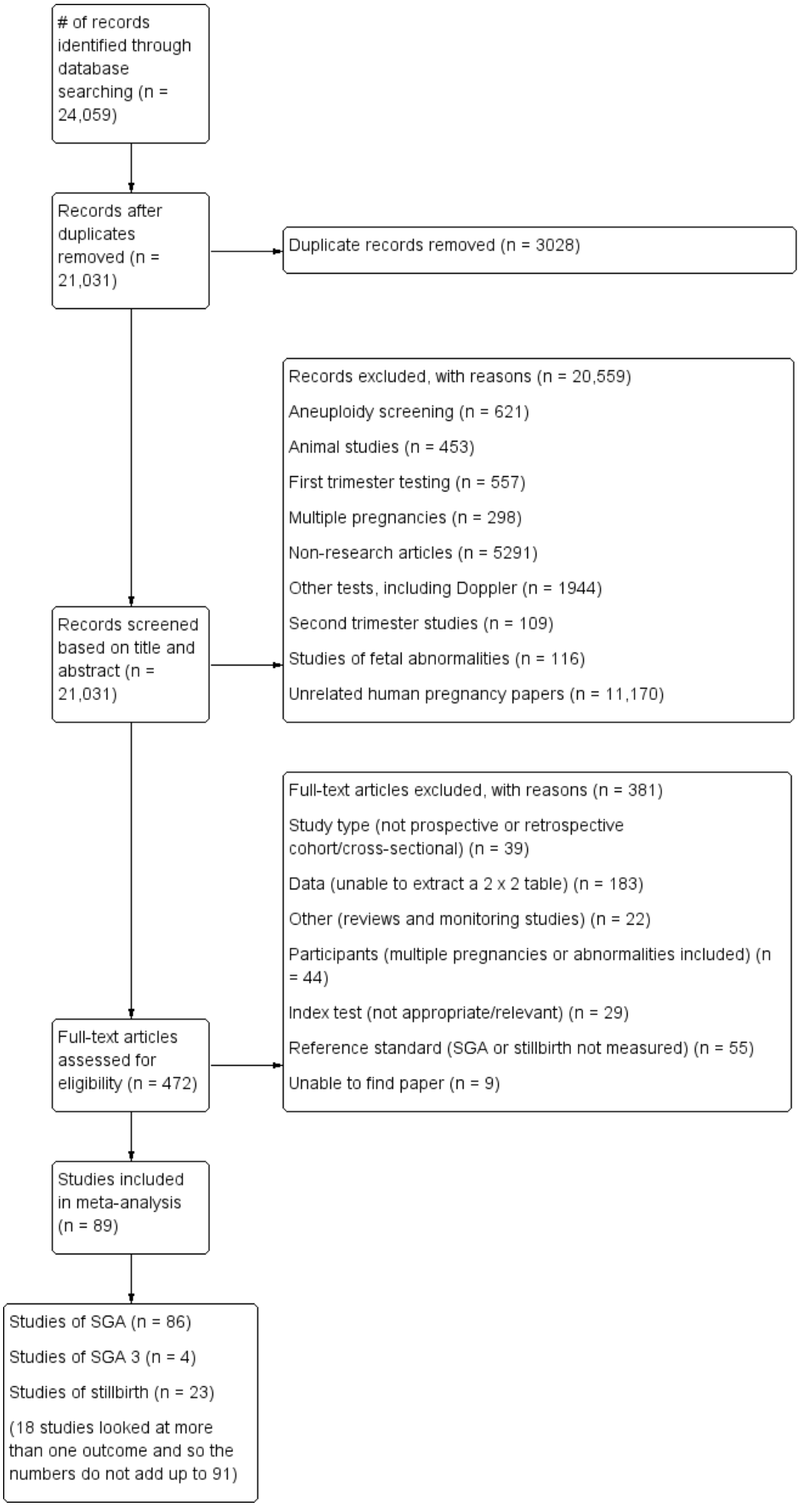
Figure 1



Caption

Current clinical pathway and three proposed uses of a placental function test. Currently, women are screened for a small-for-gestational age fetus (as a proxy for placental dysfunction) using symphysis-fundal height and maternal awareness of fetal movements. Women deemed to be at increased risk are screened using ultrasound measurement of fetal biometry. We propose three different clinical pathways for placental function tests. Firstly, they could be used as an additional test when Doppler measurements are normal. They could be used in combination with currently used tests, and finally they could be used as a triage test to differentiate infants who are constitutionally small from those with placental dysfunction. Although treatment decisions would be tailored to individual cases, a positive test would be expected to lead to increased surveillance or intervention (planned delivery) and a negative test would lead to continuing with the pregnancy.

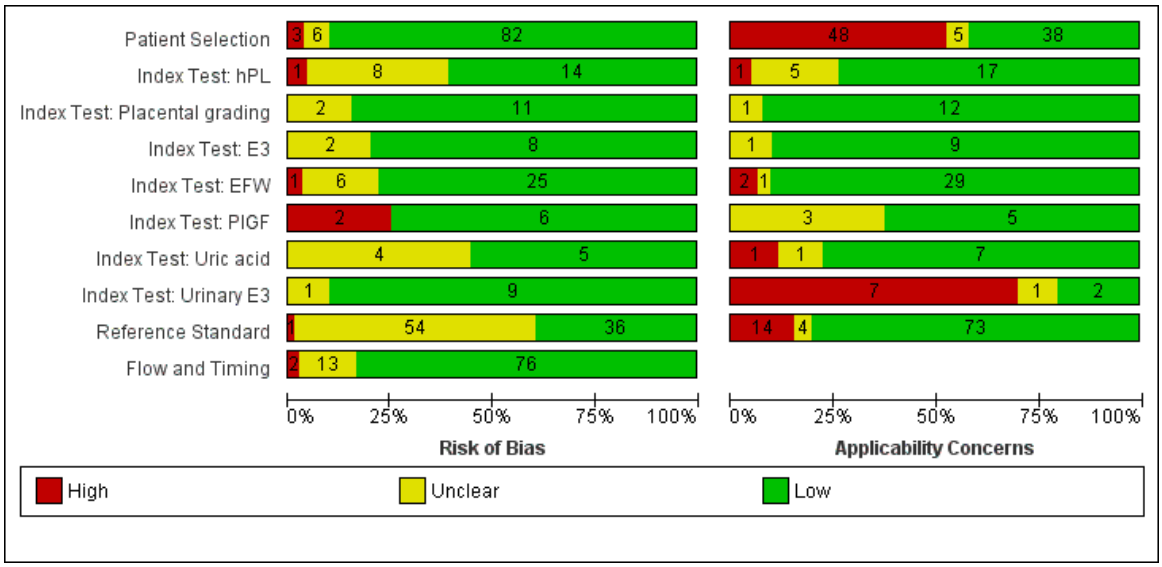
Figure 2


# of records identified through database searching (n = 24,059)
Records after duplicates removed (n = 21,031)
Duplicate records removed (n = 3028)
Records excluded, with reasons (n = 20,559)
Aneuploidy screening (n = 621)
Animal studies (n = 453)
First trimester testing (n = 557)
Multiple pregnancies (n = 298)
Non-research articles (n = 5291)
Other tests, including Doppler (n = 1944)
Second trimester studies (n = 109)
Studies of fetal abnormalities (n = 116)
Unrelated human pregnancy papers (n = 11,170)
Records screened based on title and abstract (n = 21,031)
Full-text articles excluded, with reasons (n = 381)
Study type (not prospective or retrospective cohort/cross-sectional) (n = 39)
Data (unable to extract a 2 x 2 table) (n = 183)
Other (reviews and monitoring studies) (n = 22)
Participants (multiple pregnancies or abnormalities included) (n = 44)
Index test (not appropriate/relevant) (n = 29)
Reference standard (SGA or stillbirth not measured) (n = 55)
Unable to find paper (n = 9)
Full-text articles assessed for eligibility (n = 472)
Studies included in meta-analysis (n = 89)
Studies of SGA (n = 86)
Studies of SGA 3 (n = 4)
Studies of stillbirth (n = 23)
(18 studies looked at more than one outcome and so the numbers do not add up to 91)

Caption

PRISMA flow diagram for selection of studies.

Figure 3



Caption

Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

E3 = oestriol; EFW = estimated fetal weight; hPL = human placental lactogen; PIGF = placental growth factor. Each bar shows the number of studies in each category for a domain. The index test domain was evaluated separately for each test. Of the 91 included studies, 9 studies evaluated more than one test and so the numbers of studies shown for the 7 index test domains do not add up to 91 across tests.

Figure 4 (Analysis 10)

EFW and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Ott 1984	99	67	12	417	-1.5SD	Mixed	Unknown	0.89 [0.82, 0.94]	0.86 [0.83, 0.89]
Mahran 1988	88	235	10	495	-2SD	Mixed	Unknown	0.90 [0.82, 0.95]	0.68 [0.64, 0.71]
MacLeod 2013	4	4	4	78	<2500g (+/- 10%)	Mixed	Unknown	0.50 [0.16, 0.84]	0.95 [0.88, 0.99]
Palo 1989	80	8	17	81	Below tenth centile	High	Unknown	0.82 [0.73, 0.89]	0.91 [0.83, 0.96]
Hatfield 2010	15	19	33	592	Below tenth centile	High	Unknown	0.31 [0.19, 0.46]	0.97 [0.95, 0.98]
Gupta 2008	6	3	9	20	Below tenth centile	High	Unknown	0.40 [0.16, 0.68]	0.87 [0.66, 0.97]
Christensen 2015	6	24	1	126	Below tenth centile	High	Unknown	0.86 [0.42, 1.00]	0.84 [0.77, 0.89]
Griffin 2015	88	64	99	335	Below tenth centile	High	Unknown	0.47 [0.40, 0.54]	0.84 [0.80, 0.87]
Geerts 2016	34	0	26	150	Below tenth centile	High	Unknown	0.57 [0.43, 0.69]	1.00 [0.98, 1.00]
Baird 2016	60	16	18	13	Below tenth centile	High	Unknown	0.77 [0.66, 0.86]	0.45 [0.26, 0.64]
Chauhan 2003	40	42	18	164	Below tenth centile	High	Yes	0.69 [0.55, 0.80]	0.80 [0.73, 0.85]
Berkowitz 1988	33	19	9	107	Below tenth centile	High	Yes	0.79 [0.63, 0.90]	0.85 [0.77, 0.91]
Hammad 2015	6	1	3	61	Below tenth centile	Low	No	0.67 [0.30, 0.93]	0.98 [0.91, 1.00]
Ben-Haroush 2007	4	8	15	232	Below tenth centile	Low	Unknown	0.21 [0.06, 0.46]	0.97 [0.94, 0.99]
Weiner 2016	26	114	4	261	Below tenth centile	Mixed	No	0.87 [0.69, 0.96]	0.70 [0.65, 0.74]
Sekar 2016	14	1	1	134	Below tenth centile	Mixed	No	0.93 [0.68, 1.00]	0.99 [0.96, 1.00]
Skovron 1991	17	21	52	678	Below tenth centile	Mixed	Unknown	0.25 [0.15, 0.36]	0.97 [0.95, 0.98]
Sovio 2015	199	363	153	3262	Below tenth centile	Mixed	Unknown	0.57 [0.51, 0.62]	0.90 [0.89, 0.91]
Takeuchi 1985	21	3	18	168	Below tenth centile	Mixed	Unknown	0.54 [0.37, 0.70]	0.98 [0.95, 1.00]
Chauhan 1999a	4	8	55	507	Below tenth centile	Mixed	Unknown	0.07 [0.02, 0.16]	0.98 [0.97, 0.99]
Gabbay-Benziv 2016	441	159	197	5329	Below tenth centile	Mixed	Unknown	0.69 [0.65, 0.73]	0.97 [0.97, 0.98]
Freire 2010	18	0	3	101	Below tenth centile	Mixed	Unknown	0.86 [0.64, 0.97]	1.00 [0.96, 1.00]
Barel 2016	373	90	845	12781	Below tenth centile	Mixed	Unknown	0.31 [0.28, 0.33]	0.99 [0.99, 0.99]
Chauhan 1999	30	19	14	261	Below tenth centile	Mixed	Unknown	0.68 [0.52, 0.81]	0.93 [0.90, 0.96]
Roma 2015	52	63	82	918	Below tenth centile	Mixed	Yes	0.39 [0.31, 0.48]	0.94 [0.92, 0.95]
Turitz 2014	593	254	1283	8512	Below tenth centile	Mixed	Yes	0.32 [0.30, 0.34]	0.97 [0.97, 0.97]
Valino 2016	104	55	275	3519	Below tenth centile	Mixed	Yes	0.27 [0.23, 0.32]	0.98 [0.98, 0.99]
Callec 2015	45	101	111	1640	Below tenth centile	Mixed	Yes	0.29 [0.22, 0.37]	0.94 [0.93, 0.95]
Chervenak 1984	14	13	3	149	L99CL	High	Unknown	0.82 [0.57, 0.96]	0.92 [0.87, 0.96]
Laurin 1987	50	69	28	1921	Predicted BW deviation for GA of ≥15%	Mixed	Unknown	0.64 [0.52, 0.75]	0.97 [0.96, 0.97]
Hendrix 2000	15	79	7	266	SEFW<2500g	Mixed	No	0.68 [0.45, 0.86]	0.77 [0.72, 0.81]
Bikmetova 2013	26	38	159	295	Unknown	Unknown	Unknown	0.14 [0.09, 0.20]	0.89 [0.85, 0.92]

Placental grading and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2012a	13	29	10	61	Grade III	High	No	0.57 [0.34, 0.77]	0.68 [0.57, 0.77]
Altmann 1978	4	3	2	0	Grade III	High	Unknown	0.67 [0.22, 0.96]	0.00 [0.00, 0.71]
Chen 2012	20	24	16	45	Grade III	High	Unknown	0.56 [0.38, 0.72]	0.65 [0.53, 0.76]
Estel 1989	4	14	17	20	Grade III	High	Unknown	0.19 [0.05, 0.42]	0.59 [0.41, 0.75]
Geerts 2016	21	5	30	132	Grade III	High	Unknown	0.41 [0.28, 0.56]	0.96 [0.92, 0.99]
Patterson 1983	11	166	10	211	Grade III	High	Unknown	0.52 [0.30, 0.74]	0.56 [0.51, 0.61]
Chitlange 1990	26	38	46	160	Grade III	Low	Unknown	0.36 [0.25, 0.48]	0.81 [0.75, 0.86]
McKenna 2005	12	56	97	1737	Grade III	Low	Yes	0.11 [0.06, 0.18]	0.97 [0.96, 0.98]
Kazzi 1983a	26	18	16	49	Grade III	Mixed	Unknown	0.62 [0.46, 0.76]	0.73 [0.61, 0.83]
Montan 1986	4	84	2	217	Grade III	Mixed	Unknown	0.67 [0.22, 0.96]	0.72 [0.67, 0.77]
Miller 1988	10	87	19	130	Grade III	Mixed	Unknown	0.34 [0.18, 0.54]	0.60 [0.53, 0.66]
Walker 2010	3	15	101	1119	Grade III	Mixed	Unknown	0.03 [0.01, 0.08]	0.99 [0.98, 0.99]

Caption

Forest plot of structural tests for identifying small-for-gestational age (birthweight ≤tenth centile) infants. EFW = estimated fetal weight; FN = false negative; FP = false positive; SGA = small-for-gestational-age; TN = true negative; TP = true positive. For each test, the forest plot shows the estimates of sensitivity and specificity from each study, the threshold used to define test positivity, risk of SGA pregnancy and whether there was an intervention that may have altered outcome. Studies are sorted by threshold, risk and intervention status.

Figure 5 (Analysis 11)

hPL and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Nisbet 1982	25	13	46	82	-2SD	High	Unknown	0.35 [0.24, 0.47]	0.86 [0.78, 0.93]
Howell 1985	12	44	38	407	2.5µg/ml	Mixed	Unknown	0.24 [0.13, 0.38]	0.90 [0.87, 0.93]
Obiekwe 1983	5	50	24	443	4.8µg/ml	Mixed	Unknown	0.17 [0.06, 0.36]	0.90 [0.87, 0.92]
Granat 1977	10	4	0	15	4µg/ml	High	No	1.00 [0.69, 1.00]	0.79 [0.54, 0.94]
Zhang 1990	25	42	13	41	4µg/ml	High	No	0.66 [0.49, 0.80]	0.49 [0.38, 0.61]
Gohari 1978	25	11	13	62	5µg/ml	High	Unknown	0.66 [0.49, 0.80]	0.85 [0.75, 0.92]
Nice 2016	10	5	13	49	<0.8MoM	Mixed	No	0.43 [0.23, 0.66]	0.91 [0.80, 0.97]
Altmann 1978	3	4	3	0	Abnormal value	High	Unknown	0.50 [0.12, 0.88]	0.00 [0.00, 0.60]
Westergaard 1984	15	38	13	326	Abnormal value	Mixed	Unknown	0.54 [0.34, 0.72]	0.90 [0.86, 0.93]
Kunz 1976	8	16	7	52	Below fifth centile	High	Unknown	0.53 [0.27, 0.79]	0.76 [0.65, 0.86]

Klebe 1990	1	0	2	10	Below fifth centile	High	Unknown	0.33 [0.01, 0.91]	1.00 [0.69, 1.00]
Marin 1979	11	6	2	28	Below fifth centile	Mixed	Unknown	0.85 [0.55, 0.98]	0.82 [0.65, 0.93]
Odendaal 1981	35	16	8	18	Below tenth centile	High	No	0.81 [0.67, 0.92]	0.53 [0.35, 0.70]
Trudinger 1979	10	4	15	30	Below tenth centile	High	Unknown	0.40 [0.21, 0.61]	0.88 [0.73, 0.97]
Steiner 1991	25	17	43	28	Below tenth centile	High	Unknown	0.37 [0.25, 0.49]	0.62 [0.47, 0.76]
Sagen 1984	28	6	12	28	Below tenth centile	High	Yes	0.70 [0.53, 0.83]	0.82 [0.65, 0.93]
Siebert 1974	1	2	10	54	Below tenth centile	Low	Yes	0.09 [0.00, 0.41]	0.96 [0.88, 1.00]
Chard 1985	13	29	26	324	Below tenth centile	Mixed	Unknown	0.33 [0.19, 0.50]	0.92 [0.88, 0.94]
Lilford 1983	15	41	37	429	Below tenth centile	Mixed	Unknown	0.29 [0.17, 0.43]	0.91 [0.88, 0.94]
Spernol 1989	5	3	17	85	Below tenth centile	Mixed	Unknown	0.23 [0.08, 0.45]	0.97 [0.90, 0.99]

E3 and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Palo 1987	9	0	31	50	-2SD	High	Unknown	0.23 [0.11, 0.38]	1.00 [0.93, 1.00]
Nisbet 1982	9	4	37	53	-2SD	High	Unknown	0.20 [0.09, 0.34]	0.93 [0.83, 0.98]
Nielsen 1985	11	40	50	917	Below 2.5th centile	Mixed	No	0.18 [0.09, 0.30]	0.96 [0.94, 0.97]
Spernol 1989	2	3	20	85	Below fifth centile	Mixed	Unknown	0.09 [0.01, 0.29]	0.97 [0.90, 0.99]
Odendaal 1981	13	3	17	20	Below tenth centile	High	No	0.43 [0.25, 0.63]	0.87 [0.66, 0.97]
Cedard 1979	9	13	8	34	Below tenth centile	High	Unknown	0.53 [0.28, 0.77]	0.72 [0.57, 0.84]
Sagen 1984	22	6	18	28	Below tenth centile	High	Yes	0.55 [0.38, 0.71]	0.82 [0.65, 0.93]
Gerhard 1986	18	71	60	720	Below tenth centile	Mixed	No	0.23 [0.14, 0.34]	0.91 [0.89, 0.93]
Chard 1985	11	32	28	321	Below tenth centile	Mixed	Unknown	0.28 [0.15, 0.45]	0.91 [0.87, 0.94]

Urinary E3 and SGA

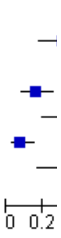
Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Weerasinghe 1977	36	98	9	184	-2SD	High	Unknown	0.80 [0.65, 0.90]	0.65 [0.59, 0.71]
Steiner 1991	9	17	59	28	8mg at 30w to 12mg at 40w (per 24h)	High	Unknown	0.13 [0.06, 0.24]	0.62 [0.47, 0.76]
Beischer 1991	1454	5621	3936	61051	8mg at 30w to 12mg at 40w (per 24h)	High	Yes	0.27 [0.26, 0.28]	0.92 [0.91, 0.92]
Fliegner 1979	22	57	15	235	8mg at 30w to 12mg at 40w (per 24h)	Mixed	No	0.59 [0.42, 0.75]	0.80 [0.75, 0.85]
Oats 1979	497	2064	894	15664	8mg at 30w to 12mg at 40w (per 24h)	Mixed	Unknown	0.36 [0.33, 0.38]	0.88 [0.88, 0.89]
Chew 1976	0	0	15	28	Below 2.5th centile	High	No	0.00 [0.00, 0.22]	1.00 [0.88, 1.00]
Kunz 1976	10	12	5	56	Below fifth centile	High	Unknown	0.67 [0.38, 0.88]	0.82 [0.71, 0.91]
Odendaal 1981	6	1	22	17	Below tenth centile	High	No	0.21 [0.08, 0.41]	0.94 [0.73, 1.00]
Campbell 1972	46	34	41	163	Unknown	High	Unknown	0.53 [0.42, 0.64]	0.83 [0.77, 0.88]

PlGF and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Shawkat 2015	18	43	88	112	12pg/ml	High	No	0.17 [0.10, 0.26]	0.72 [0.65, 0.79]
Benton 2016	87	70	72	182	12pg/ml	High	No	0.55 [0.47, 0.63]	0.72 [0.66, 0.78]
Nice 2016	4	4	19	49	12pg/ml	Mixed	No	0.17 [0.05, 0.39]	0.92 [0.82, 0.98]
Molvarec 2013	16	25	6	42	3.9:1	High	No	0.73 [0.50, 0.89]	0.63 [0.50, 0.74]
Chaiworapongsa 2013	38	184	70	977	<0.3MoM	Mixed	Unknown	0.35 [0.26, 0.45]	0.84 [0.82, 0.86]
Griffin 2015	47	40	145	360	Below fifth centile	High	Unknown	0.24 [0.19, 0.31]	0.90 [0.87, 0.93]
Kienast 2016	29	80	11	226	Below fifth centile	Mixed	Unknown	0.72 [0.56, 0.85]	0.74 [0.69, 0.79]
Valino 2016	48	150	331	3424	Below tenth centile	Mixed	Yes	0.13 [0.09, 0.16]	0.96 [0.95, 0.96]

UA and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Hawkins 2012	168	621	56	461	+1SD	High	No	0.75 [0.69, 0.81]	0.43 [0.40, 0.46]
Amini 2014	14	89	32	269	+1SD	Mixed	Unknown	0.30 [0.18, 0.46]	0.75 [0.70, 0.80]
Bellomo 2011	36	34	7	86	309µmol/l	High	Unknown	0.84 [0.69, 0.93]	0.72 [0.63, 0.80]
Williams 2002	14	42	73	327	450µmol/l	High	No	0.16 [0.09, 0.26]	0.89 [0.85, 0.92]
Jauniaux 1996	7	4	9	21	4mg/dl	High	Unknown	0.44 [0.20, 0.70]	0.84 [0.64, 0.95]
Odendaal 1997	8	13	92	83	520µmol/l	High	No	0.08 [0.04, 0.15]	0.86 [0.78, 0.93]
Voto 1988	10	47	20	138	6mg%	High	Unknown	0.33 [0.17, 0.53]	0.75 [0.68, 0.81]
Yassaee 2003	41	12	18	32	6mg/dl	High	Unknown	0.69 [0.56, 0.81]	0.73 [0.57, 0.85]



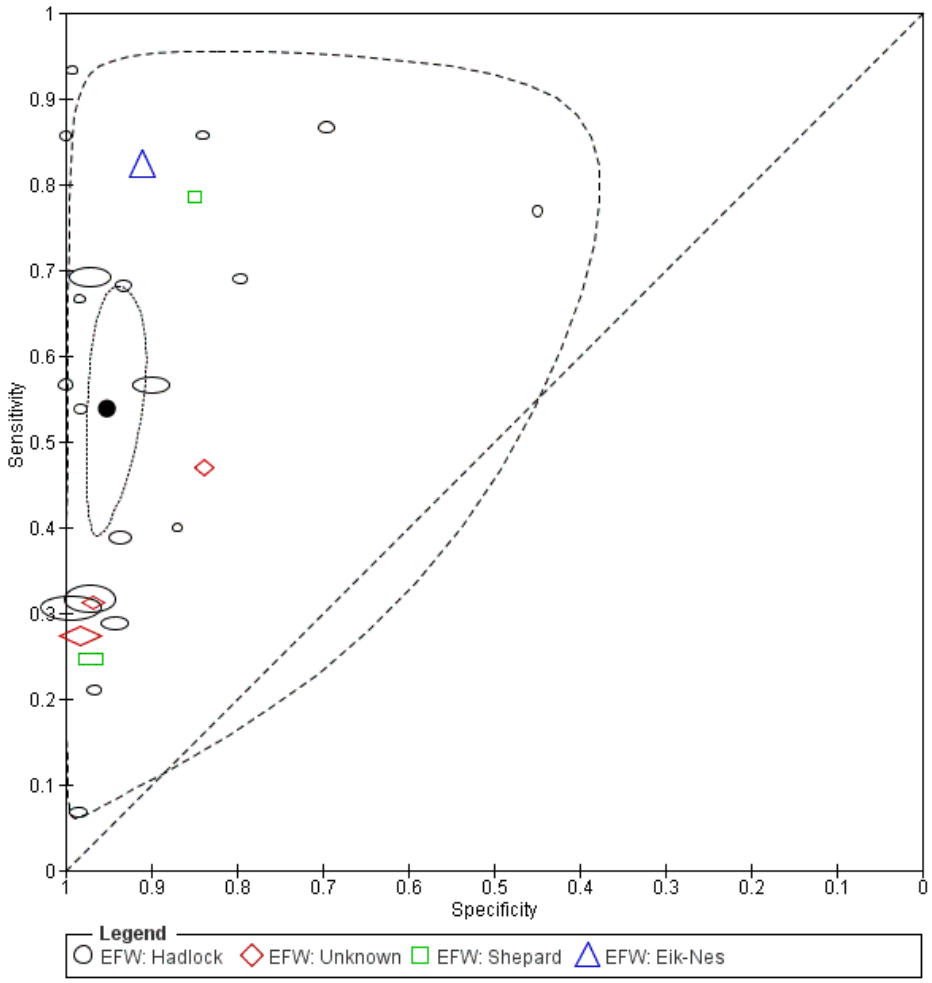
E3 AND/OR hPL and SGA

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Lenstrup 1982	5	4	4	75	Below tenth centile	Mixed	No	0.56 [0.21, 0.86]	0.95 [0.88, 0.99]

Caption

Forest plot of biochemical tests for identifying small-for-gestational-age (birthweight ≤tenth centile) infants. E3 = oestriol; FN = false negative; FP = false positive; hPL = human placental lactogen; PlGF = placental growth factor; SGA = small-for-gestational-age; TN = true negative; TP = true positive; UA = uric acid. For each test, the forest plot shows the estimates of sensitivity and specificity from each study, the threshold used to define test positivity, risk of SGA pregnancy and whether there was an intervention that may have altered outcome. Studies are sorted by threshold, risk and intervention status.

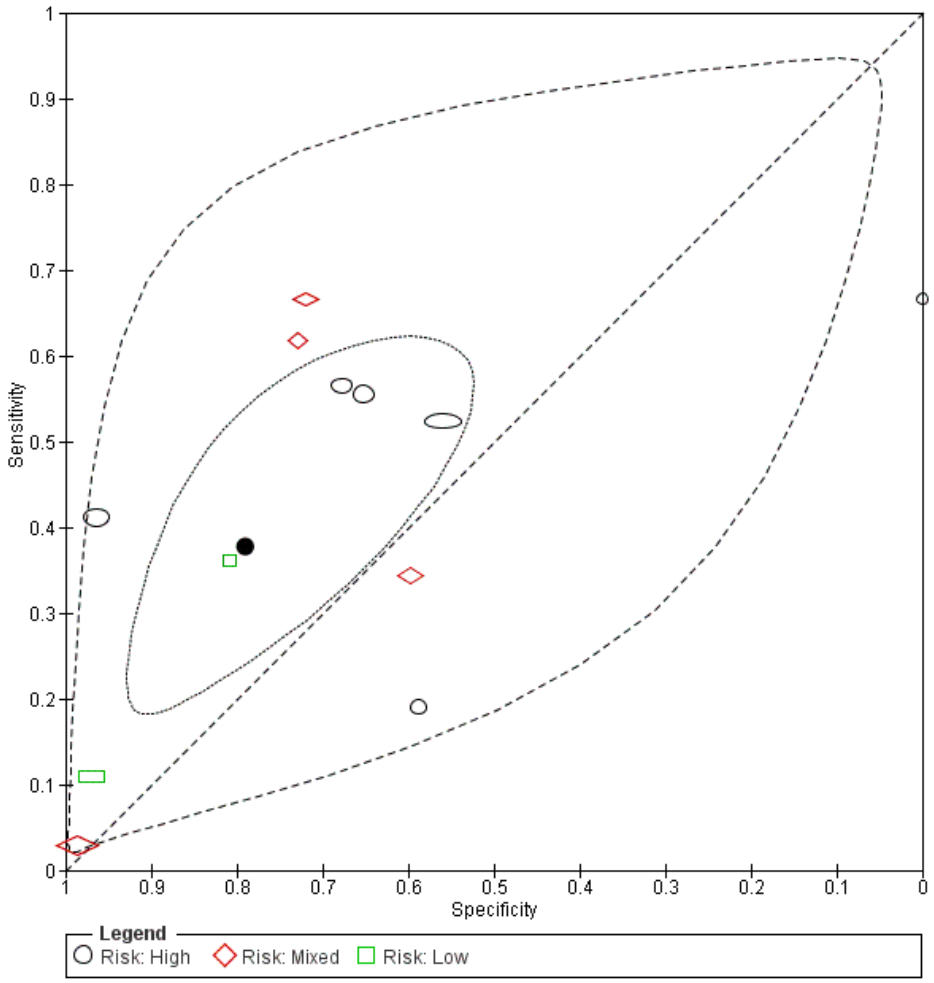
Figure 6 (Analysis 2)



Caption

Summary ROC plot of ultrasound estimated fetal weight (EFW) at a tenth centile threshold for identifying small-for-gestational-age (birthweight ≤tenth centile) infants. The study points are shown using different symbols for the formulas used. The study points were scaled according to the precision of sensitivity and specificity in the studies. The solid circle (summary point) represents the summary estimate of sensitivity and specificity for all 25 studies, and is surrounded by a dotted line representing the 95% confidence region and a dashed line representing the 95% prediction region. The 95% prediction region is the region within which one is 95% certain the results of a new study will lie.

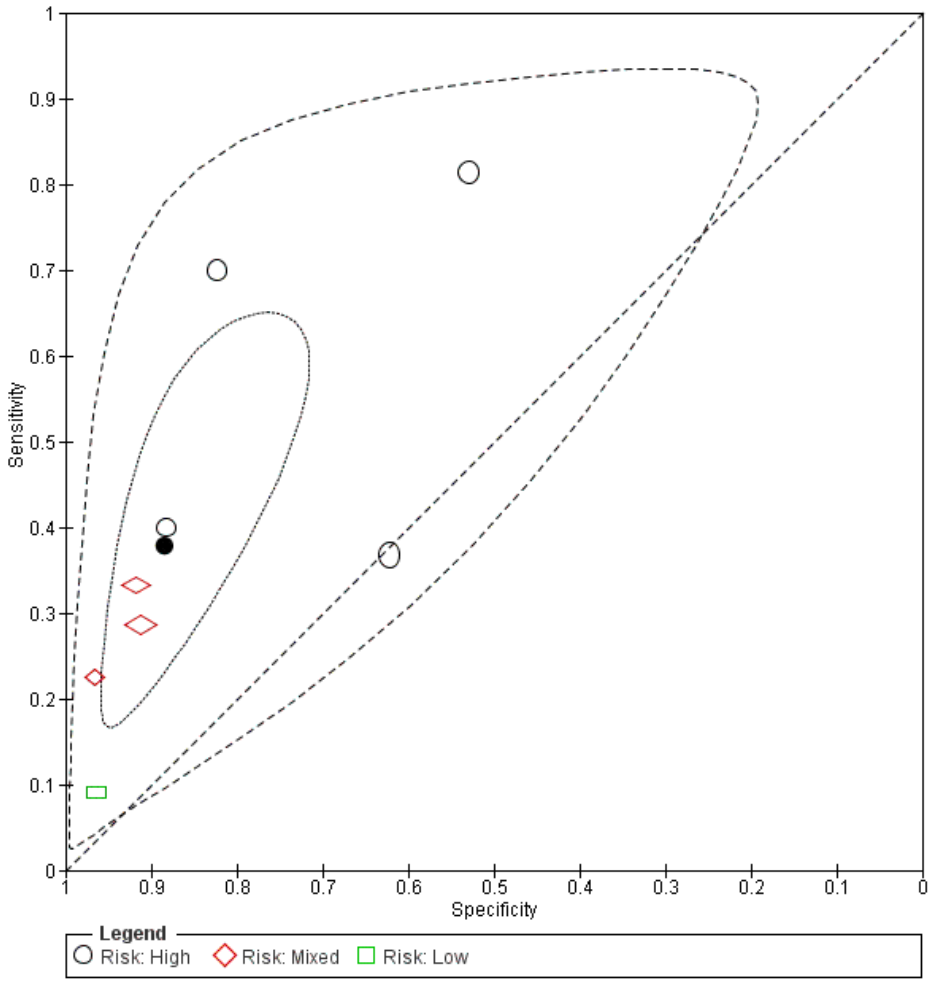
Figure 7 (Analysis 6)



Caption

Summary ROC plot of placental grading for identifying small-for-gestational-age (birthweight ≤tenth centile) infants. The study points are shown using different symbols for different risk groups. The study points were scaled according to the precision of sensitivity and specificity in the studies. The solid circle (summary point) represents the summary estimate of sensitivity and specificity for all 12 studies, and is surrounded by a dotted line representing the 95% confidence region and a dashed line representing the 95% prediction region. The 95% prediction region is the region within which one is 95% certain the results of a new study will lie.

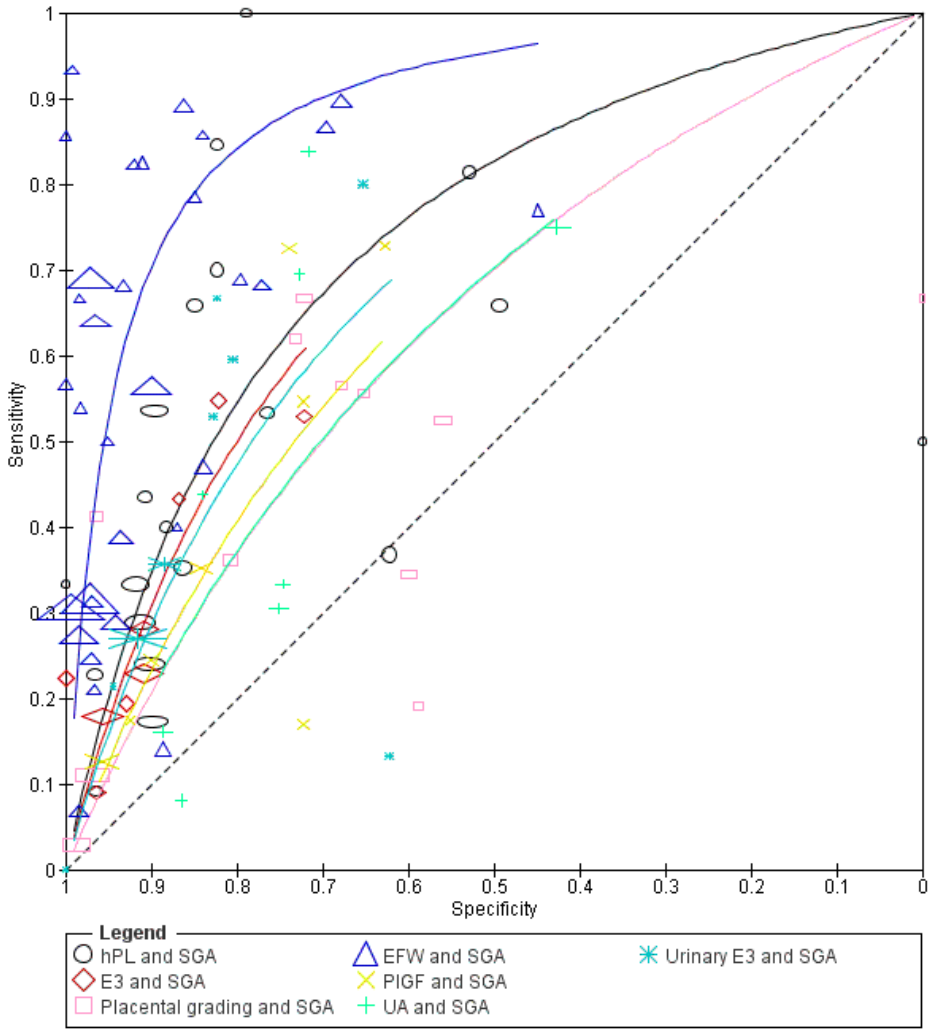
Figure 8 (Analysis 4)



Caption

Summary ROC plot of human placental lactogen (hPL) for identifying small-for-gestational-age (birthweight ≤tenth centile) infants. The study points are shown using different symbols for different risk groups. The study points were scaled according to the precision of sensitivity and specificity in the studies. The solid circle (summary point) represents the summary estimate of sensitivity and specificity for all nine studies, and is surrounded by a dotted line representing the 95% confidence region and a dashed line representing the 95% prediction region. The 95% prediction region is the region within which one is 95% certain the results of a new study will lie.

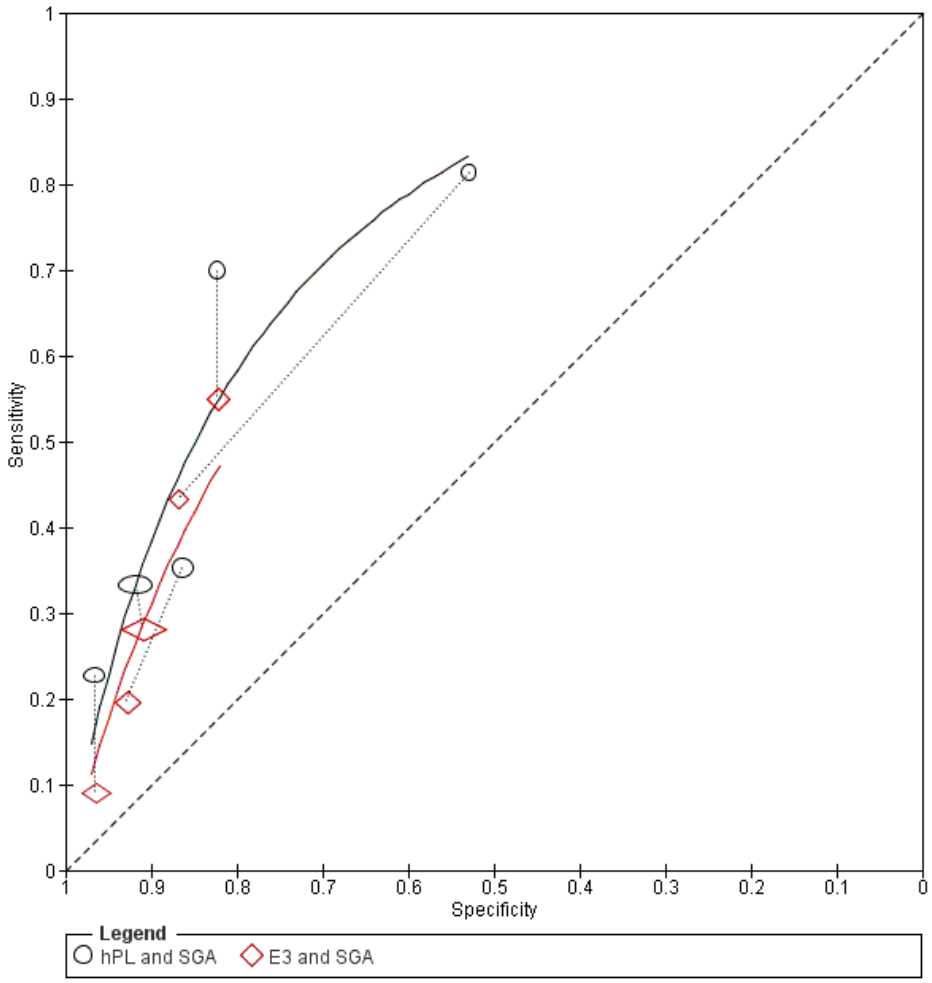
Figure 9 (Analysis 12)



Caption

Summary ROC plot of structural and biochemical tests for identifying small-for-gestational-age (birthweight ≤tenth centile) infants. E3 = oestriol; EFW = estimated fetal weight; hPL = human placental lactogen; PIGF = placental growth factor; SGA = small-for-gestational-age; UA =uric acid. The curve for each test is drawn within the range of estimates of specificity from the studies included for the test. Compared to the other curves, the curve for EFW lies closest to the top left hand corner (ideal position where sensitivity and specificity both equal 1). The position of the curves for UA and placental grading is very similar. The SROC curve for UA is the green curve lying above the pink curve for placental grading.

Figure 10 (Analysis 13)



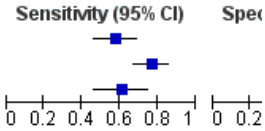
Caption

Summary ROC plot of direct comparisons of human placental lactogen and oestriol for identifying small-for-gestational-age (birthweight ≤tenth centile) infants. E3 = oestriol; hPL = human placental lactogen; SGA = small-for-gestational-age. Each symbol represents the pair of sensitivity and specificity for one test from a study. The pair of points for the two tests from a study are connected by a dotted line. The size of each symbol was scaled according to the precision of sensitivity and specificity in the study. Each summary curve was restricted to the range of specificities for each test from the five studies that evaluated both tests in the same patients.

Figure 11 (Analysis 15)

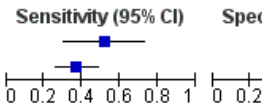
EFW and SGA3

Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Griffin 2015	44	108	32	402	Below tenth centile	High	Unknown	0.58 [0.46, 0.69]	0.79 [0.75, 0.82]
Sovio 2015	67	495	20	3395	Below tenth centile	Mixed	Unknown	0.77 [0.67, 0.85]	0.87 [0.86, 0.88]
Roma 2015	30	91	19	975	Below tenth centile	Mixed	Yes	0.61 [0.46, 0.75]	0.91 [0.90, 0.93]



PIGF and SGA3

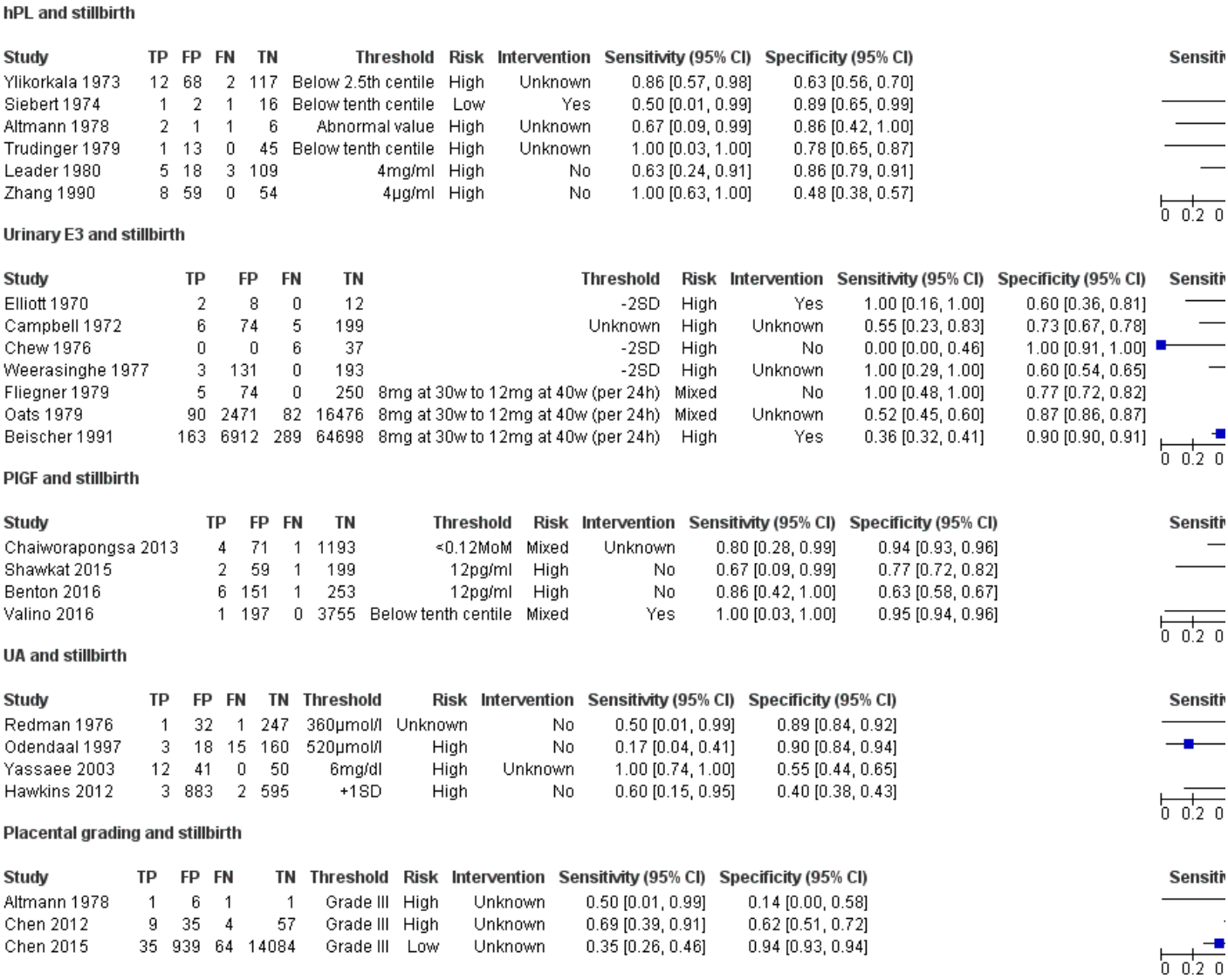
Study	TP	FP	FN	TN	Threshold	Risk	Intervention	Sensitivity (95% CI)	Specificity (95% CI)
Chaiworapongsa 2013	12	210	11	1036	<0.3MoM	Mixed	Unknown	0.52 [0.31, 0.73]	0.83 [0.81, 0.85]
Griffin 2015	29	58	49	456	Below fifth centile	High	Unknown	0.37 [0.26, 0.49]	0.89 [0.86, 0.91]



Caption

Forest plot of ultrasound estimated fetal weight (EFW) and placental growth factor (PlGF) for identifying small-for-gestational age (birthweight <third centile) infants. FN = false negative; FP = false positive; SGA3 = small-for-gestational-age birthweight <third centile; TN = true negative; TP = true positive. For each test, the forest plot shows the estimates of sensitivity and specificity from each study, the threshold used to define test positivity, risk of SGA pregnancy and whether there was an intervention that may have altered outcome. Studies are sorted by threshold, risk and intervention status.

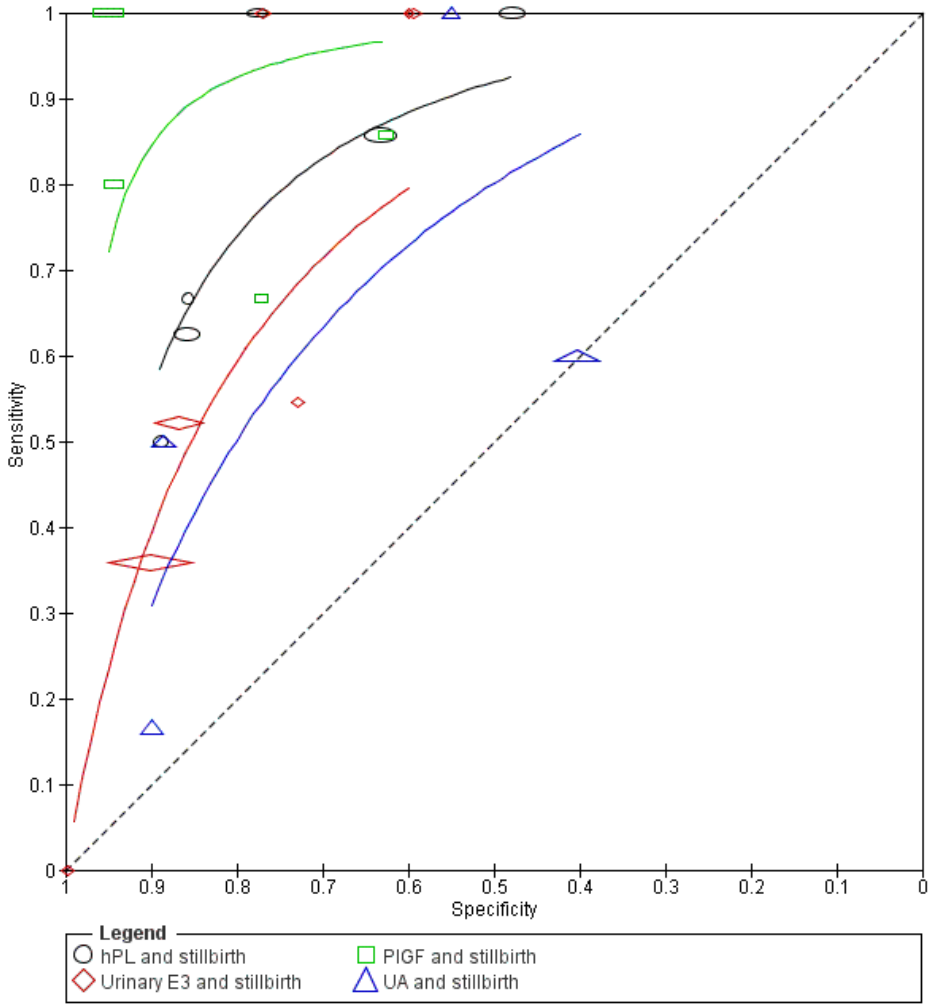
Figure 12 (Analysis 17)



Caption

Forest plot of structural and biochemical tests for predicting stillbirth. E3 = oestriol; FN = false negative; FP = false positive; hPL = human placental lactogen; PlGF = placental growth factor; TN = true negative; TP = true positive; UA = uric acid. For each test, the forest plot shows the estimates of sensitivity and specificity from each study, the threshold used to define test positivity, risk of stillbirth and whether there was an intervention that may have altered outcome. Studies are sorted by threshold, risk and intervention.

Figure 13 (Analysis 18)



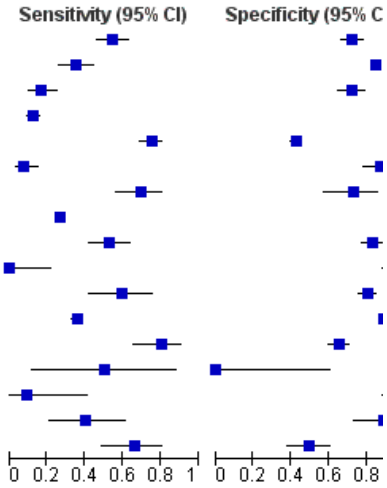
Caption

Summary ROC plot of biochemical tests for predicting stillbirth. E3 = Oestriol; hPL = human placental lactogen; PlGF = placental growth factor; SGA = small-for-gestational-age; UA =uric acid. The SROC curves for the four tests are parallel. The curve for each test is drawn within the range of estimates of specificity from the studies included for the test. Compared to the other curves, the curve for PlGF lies closest to the top left hand corner (ideal position where sensitivity and specificity both equal 1).

Figure 14 (Analysis 19)

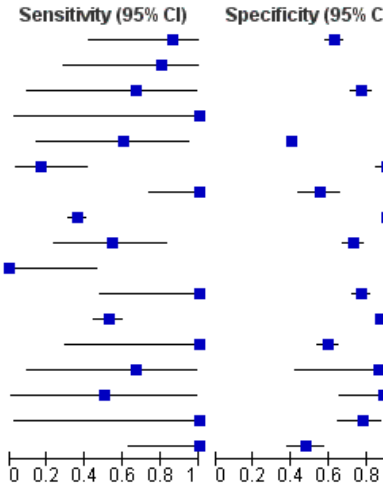
SGA data from studies with both SGA infants and stillbirths

Study	TP	FP	FN	TN	Risk	Test	Sensitivity (95% CI)	Specificity (95% CI)
Benton 2016	87	70	72	182	High	PlGF	0.55 [0.47, 0.63]	0.72 [0.66, 0.78]
Chaiworapongsa 2013	38	184	70	977	Mixed	PlGF	0.35 [0.26, 0.45]	0.84 [0.82, 0.86]
Shawkat 2015	18	43	88	112	High	PlGF	0.17 [0.10, 0.26]	0.72 [0.65, 0.79]
Valino 2016	48	150	331	3424	Mixed	PlGF	0.13 [0.09, 0.16]	0.96 [0.95, 0.96]
Hawkins 2012	168	621	56	461	High	UA	0.75 [0.69, 0.81]	0.43 [0.40, 0.46]
Odendaal 1997	8	13	92	83	High	UA	0.08 [0.04, 0.15]	0.86 [0.78, 0.93]
Yassaee 2003	41	12	18	32	High	UA	0.69 [0.56, 0.81]	0.73 [0.57, 0.85]
Beischer 1991	1454	5621	3936	61051	High	Urinary E3	0.27 [0.26, 0.28]	0.92 [0.91, 0.92]
Campbell 1972	46	34	41	163	High	Urinary E3	0.53 [0.42, 0.64]	0.83 [0.77, 0.88]
Chew 1976	0	0	15	28	High	Urinary E3	0.00 [0.00, 0.22]	1.00 [0.88, 1.00]
Fliegner 1979	22	57	15	235	Mixed	Urinary E3	0.59 [0.42, 0.75]	0.80 [0.75, 0.85]
Oats 1979	497	2064	894	15664	Mixed	Urinary E3	0.36 [0.33, 0.38]	0.88 [0.88, 0.89]
Weerasinghe 1977	36	98	9	184	High	Urinary E3	0.80 [0.65, 0.90]	0.65 [0.59, 0.71]
Altmann 1978	3	4	3	0	High	hPL	0.50 [0.12, 0.88]	0.00 [0.00, 0.60]
Siebert 1974	1	2	10	54	Low	hPL	0.09 [0.00, 0.41]	0.96 [0.88, 1.00]
Trudinger 1979	10	4	15	30	High	hPL	0.40 [0.21, 0.61]	0.88 [0.73, 0.97]
Zhang 1990	25	42	13	41	High	hPL	0.66 [0.49, 0.80]	0.49 [0.38, 0.61]



Stillbirth data from studies with both SGA infants and stillbirths

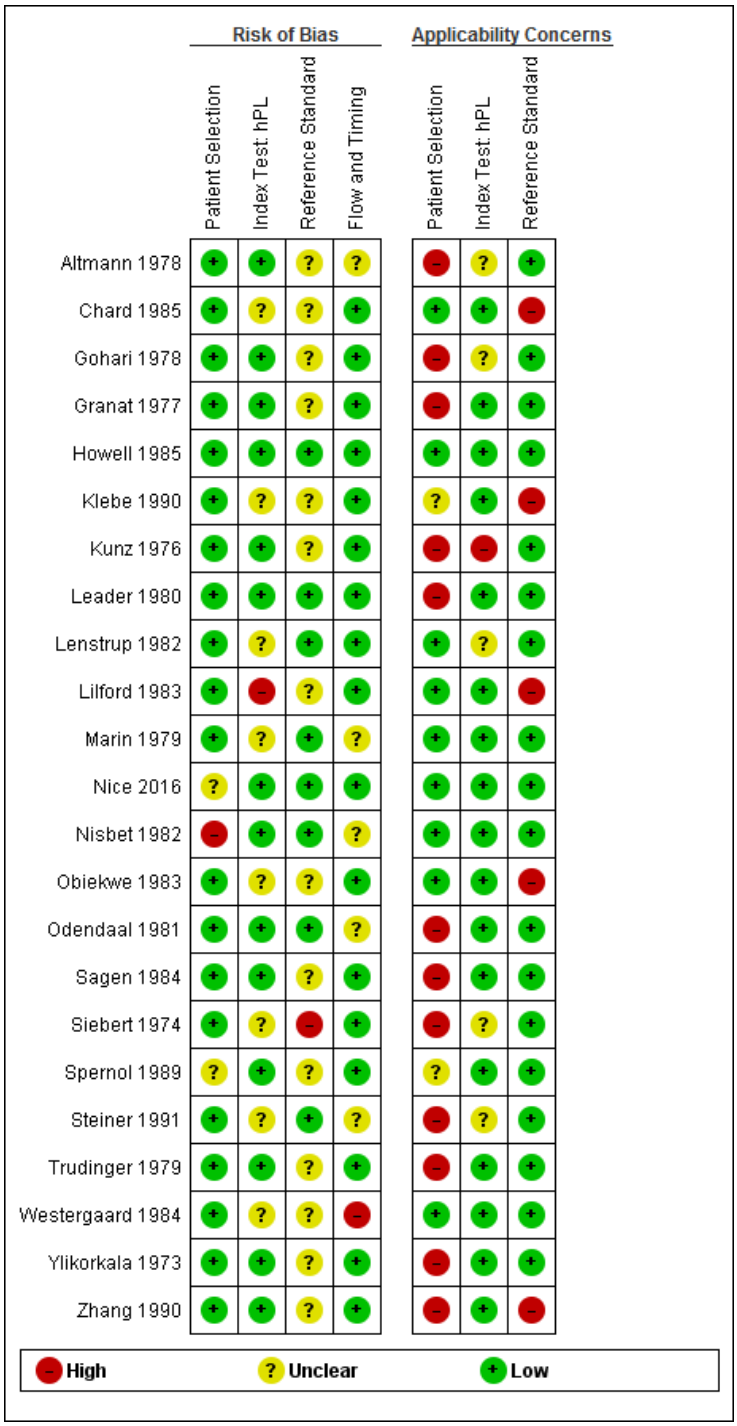
Study	TP	FP	FN	TN	Risk	Test	Sensitivity (95% CI)	Specificity (95% CI)
Benton 2016	6	151	1	253	High	PlGF	0.86 [0.42, 1.00]	0.63 [0.58, 0.67]
Chaiworapongsa 2013	4	71	1	1193	Mixed	PlGF	0.80 [0.28, 0.99]	0.94 [0.93, 0.96]
Shawkat 2015	2	59	1	199	High	PlGF	0.67 [0.09, 0.99]	0.77 [0.72, 0.82]
Valino 2016	1	197	0	3755	Mixed	PlGF	1.00 [0.03, 1.00]	0.95 [0.94, 0.96]
Hawkins 2012	3	883	2	595	High	UA	0.60 [0.15, 0.95]	0.40 [0.38, 0.43]
Odendaal 1997	3	18	15	160	High	UA	0.17 [0.04, 0.41]	0.90 [0.84, 0.94]
Yassaee 2003	12	41	0	50	High	UA	1.00 [0.74, 1.00]	0.55 [0.44, 0.65]
Beischer 1991	163	6912	289	64698	High	Urinary E3	0.36 [0.32, 0.41]	0.90 [0.90, 0.91]
Campbell 1972	6	74	5	199	High	Urinary E3	0.55 [0.23, 0.83]	0.73 [0.67, 0.78]
Chew 1976	0	0	6	37	High	Urinary E3	0.00 [0.00, 0.46]	1.00 [0.91, 1.00]
Fliegner 1979	5	74	0	250	Mixed	Urinary E3	1.00 [0.48, 1.00]	0.77 [0.72, 0.82]
Oats 1979	90	2471	82	16476	Mixed	Urinary E3	0.52 [0.45, 0.60]	0.87 [0.86, 0.87]
Weerasinghe 1977	3	131	0	193	High	Urinary E3	1.00 [0.29, 1.00]	0.60 [0.54, 0.65]
Altmann 1978	2	1	1	6	High	hPL	0.67 [0.09, 0.99]	0.86 [0.42, 1.00]
Siebert 1974	1	2	1	16	Low	hPL	0.50 [0.01, 0.99]	0.89 [0.65, 0.99]
Trudinger 1979	1	13	0	45	High	hPL	1.00 [0.03, 1.00]	0.78 [0.65, 0.87]
Zhang 1990	8	59	0	54	High	hPL	1.00 [0.63, 1.00]	0.48 [0.38, 0.57]



Caption

Forest plot of studies with evaluations of both small-for-gestational-age (SGA birthweight ≤tenth centile) infants and stillbirth. E3 = oestriol; hPL = human placental lactogen; PlGF = placental growth factor; UA = uric acid. Two studies (Altmann 1978; Chen 2012) evaluated placental grading for both SGA and stillbirth but not possible to include them on the plot. Studies are sorted by test and study identifier.

Figure 15



Caption

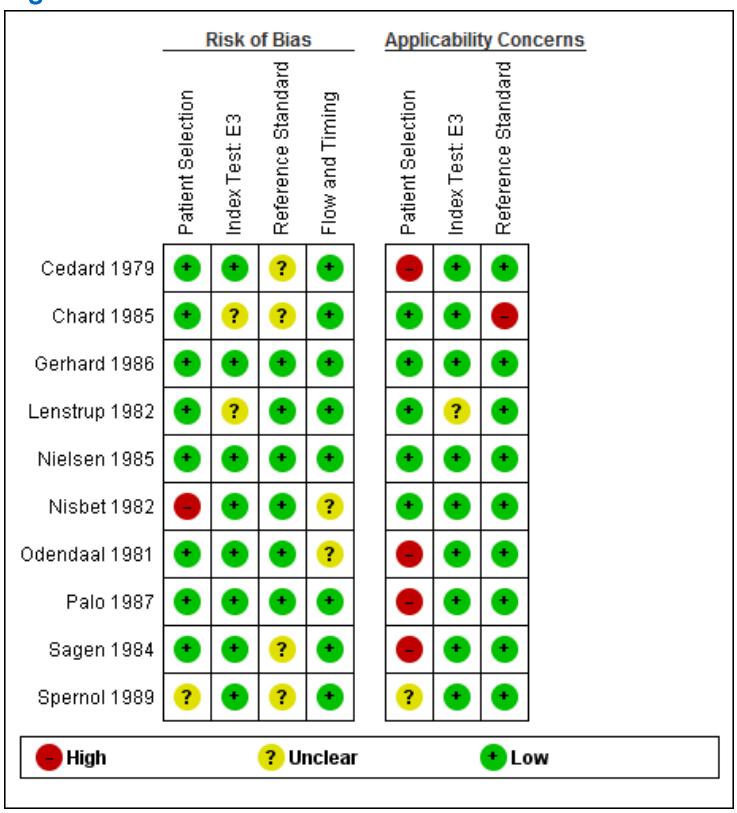
Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of human placental lactogen (hPL)

Figure 16

Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of placental grading.

Figure 17



Caption

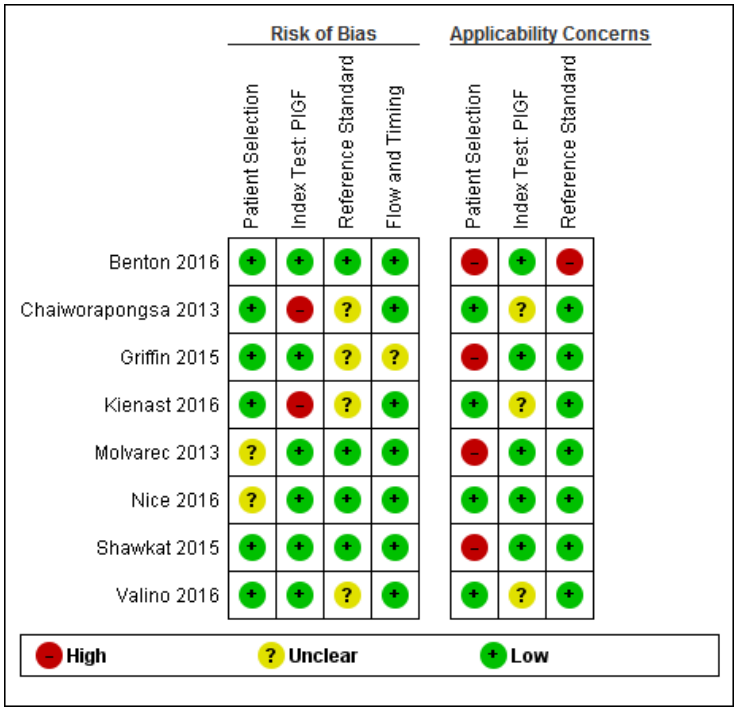
Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of serum oestriol (E3).

Figure 18

Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of estimated fetal weight (EFW).

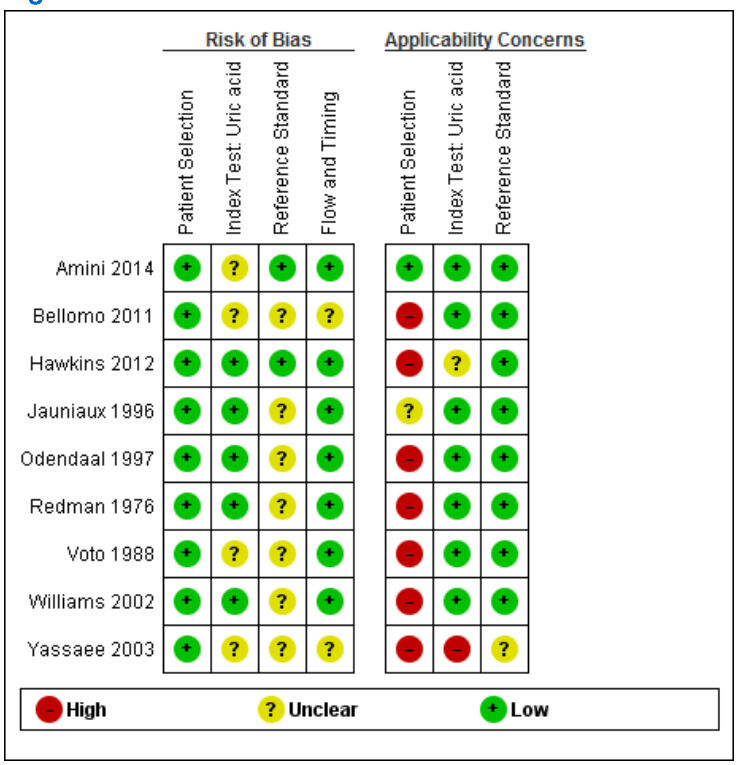
Figure 19



Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of placental growth factor (PlGF).

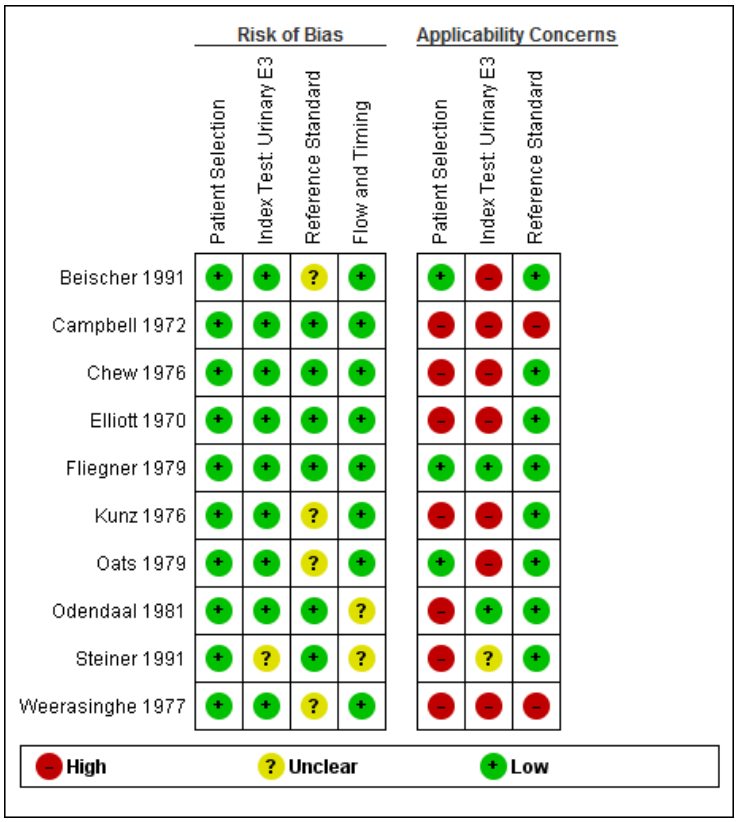
Figure 20



Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of uric acid.

Figure 21



Caption

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study of urinary oestriol (UE3).

Sources of support

Internal sources

- No sources of support provided

External sources

- National Insitute of Health Research, UK
  Alexander Heazell is funded by a Clinician Scientist Award from the National Institute of Health Research (CS-2013-009). This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Feedback

Appendices

1 Examples of placental function tests available for diagnostic use (compiled 29th March 2016)

Placental growth factor (PlGF)

Triage PlGF (Alere, San Diego) – point of care fluorescence immunoassay (http://www.plgf.com/home/proposed-clinical-use-of-plgf/alere-triage-plgf.html)

Elecsys™ Preeclampsia (sFlt-1 & PlGF) – automated immunoassay performed on Roche platform

(http://www.cobas.com/home/product/clinical-and-immunochemistry-testing/elecsys-preeclampsia-assays-sFlt-1-PlGF.html)

Oestriol (E3)

AutoDELFIA Unconjugated Estriol (Perkin Elmer) – automated fluorescence immunoassay performed on Perkin-Elmer platform. (http://www.perkinelmer.co.uk/product/autodelfia-unconjugated-estriol-ue3-ki-b083-301)

Beckman Coulter – automated immunoassay performed on Beckman Coulter platform (https://www.beckmancoulter.com/wsrportal/bibliography?docname=DS14764A%20Access%20Unconjugated%20Estriol%20U)

Elecsys™ Estradiol – automated immunoassay performed on Roche platform (http://www.cobas.com/content/dam/cobas_com/pdf/lists/parameter-list-swa.pdf)

2 Search strategy

Database: Ovid MEDLINE(R) 1946 to October Week 3 2016 (October 26th 2016)

Search Strategy:

1 Placental insufficiency/
2 ((placenta$ or f?etoplacental or uteroplacental) adj2 (insufficien$ or fail$ or function$)).ti,ab.
3 fetal movement/
4 fetal growth retardation/
5 ((reduc$ or decline$) adj2 f?etal movement).ti,ab.
6 (stillborn or stillbirth).ti,ab.
7 Stillbirth/
8 ((f?etal or intrauterine or intra-uterine) adj2 (growth or death$ or loss$)).ti,ab.
9 IUGR.ti,ab.
10 (small adj2 gestational age).ti,ab.
11 ((neonatal or perinatal or fetal or birth$ or deliver$) adj2 outcome$).ti,ab.
12 f?etal move$.ti,ab.
13 or/1-12
14 oestradiol.ti,ab.
15 estradiol.ti,ab.
16 exp Estradiol/
17 oestriol.ti,ab.
18 exp progesterone/
19 progesterone.ti,ab.
20 exp pregnenolone/
21 pregnenolone.ti,ab.
22 exp Chorionic Gonadotropin/
23 human chorionic gonadotrophin.ti,ab.
24 hCG.ti,ab.
25 placental lactogen/
26 hPL.ti,ab.
27 human placental lactogen.ti,ab.
28 human placental growth hormone.ti,ab.
29 placental protein 13.ti,ab.
30 placental growth factor.ti,ab.
31 plasma placental protein.ti,ab.
32 pregnancy specific glycoprotein$.ti,ab.
33 Pregnancy-Specific beta 1-glycoproteins/
34 schwangerschaft protein 1.ti,ab.
35 pregnancy specific beta 1-glycoprotein.ti,ab.
36 exp ultrasonography, Prenatal/
37 (sonograph$ or ultraso$).ti,ab.
38 Grannum grading.ti,ab.
39 biomarkers/
40 biomarker$.mp. or marker$.ti,ab.
41 or/14-40
42 13 and 41
43 limit 42 to humans

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (October 25, 2016)

Search Strategy:

1 (placenta$ or f?etoplacental or uteroplacental) adj2 (insufficien$ or fail$ or function$)).ti,ab.
2 ((reduc$ or decline$) adj2 fe?tal movement).ti,ab.
3 (stillborn or stillbirth).ti,ab.
4 ((f?etal or intrauterine or intra-uterine) adj2 (growth or death$ or loss$)).ti,ab.
5 IUGR.ti,ab.
6 (small adj2 gestational age).ti,ab.
7 ((neonatal or perinatal or fetal or birth$ or deliver$) adj2 outcome$).ti,ab.
8 f?etal move$.ti,ab.
9 or/1-8
10 oestradiol.ti,ab.
11 estradiol.ti,ab.
12 oestriol.ti,ab.
13 progesterone.ti,ab.
14 pregnenolone.ti,ab.
15 human chorionic gonadotrophin.ti,ab.
16 hCG.ti,ab.
17 hPL.ti,ab.
18 human placental lactogen.ti,ab.
19 human placental growth hormone.ti,ab.
20 placental protein 13.ti,ab.
21 placental growth factor.ti,ab.
22 plasma placental protein.ti,ab.
23 pregnancy specific glycoprotein$.ti,ab.
24 schwangerschaft protein 1.ti,ab.
25 pregnancy specific beta 1-glycoprotein.ti,ab.
26 (sonograph$ or ultraso$).ti,ab.
27 Grannum grading.ti,ab.
28 placental lactogen.ti,ab.
29 biomarker$.ti,ab.
30 marker$.ti,ab.
31 or/10-30
32 9 and 31

Database: Embase (Ovid) 1974 to week 4 October 2016

Search Strategy:

1 ((placenta$ or fetoplacental or foetoplacental or uteroplacental) adj2 (insufficien$ or fail$ or function$)).ti,ab.
2 ((reduc$ or decline$) adj2 (fetal or foetal) adj movement)).ti,ab.
3 (stillborn or stillbirth).ti,ab.
4 ((fetal or foetal or intrauterine or intra-uterine) adj2 (growth or death$ or loss$)).ti,ab.
5 IUGR.ti,ab.
6 (small adj2 gestational age).ti,ab.
7 ((neonatal or perinatal or fetal or foetal or birth$ or deliver$) adj2 outcome$).ti,ab.
8 (fetal or foetal) adj move$.ti,ab.
9 exp placenta insufficiency/
10 exp fetus movement/
11 exp intrauterine growth retardation/
12 exp stillbirth/
13 oestradiol.ti,ab.

14 estradiol.ti,ab.

15 exp estradiol/

16 exp estriol/

17 oestriol.ti,ab.

18 exp progesterone/

19 progesterone.ti,ab.

20 exp pregnenolone/

21 pregnenolone.ti,ab.

22 exp chorionic gonadotropin/

23 human chorionic gonadotropin.ti,ab.

24 hCG.ti,ab.

25 placental lactogen.ti,ab.

26 exp placenta lactogen/

27 hPL.ti,ab.

28 human placental growth hormone.ti,ab.

29 exp placenta protein/

30 placental protein 13.ti,ab.

31 placental growth factor.ti,ab.

32 plasma placental protein.ti,ab.

33 pregnancy specific glycoprotein$.ti,ab.

34 exp pregnancy specific beta1 glycoprotein/

35 schwangerschaft protein 1.ti,ab.

36 pregnancy specific beta 1-glycoprotein.ti,ab.

37 exp fetus echography/

38 sonograph$ or ultrason$.ti,ab.

39 Grannum grading.ti,ab.

40 biological marker/

41 biomarker$ or marker$.ti,ab.

42 or/13-41

43 or/1-12

44 42 and 43

45 limit 44 to human

Database: Cochrane Library (Wiley) (CENTRAL) Issue 7 of 12 2016 (DARE, HTA,EED) Issue 2 of 4 2015, (CDSR) Issue 7 of 12 2016

Search strategy:

#1 MeSH descriptor: [Placental Insufficiency] explode all trees

#2 (placenta* or fetoplacental or foetoplacental or uteroplacental) near/2 (insufficienc* or fail* or function*)

#3 MeSH descriptor: [Fetal Movement] explode all trees

#4 MeSH descriptor: [Fetal Growth Retardation] explode all trees

#5 (reduc* or declin*) near/2 ("fetal move*") or (("foetal move*")

#6 stillborn or stillbirth

#7 MeSH descriptor: [Stillbirth] explode all trees

#8 (fetal or foetal or intrauterine or intra-uterine) near/2 (growth or death* or loss*)

#9 IUGR

#10 small near/2 (gestational next age)

#11 (neonatal or perinatal or fetal or birth* or deliver*) near/2 (outcome*)

#12 fetal next move*

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 oestradiol

#15 estradiol

#16 oestriol

#17 progesterone

#18 MeSH descriptor: [Estradiol] explode all trees

#19 MeSH descriptor: [Progesterone] explode all trees

#20 pregnenolone

#21 MeSH descriptor: [Pregnenolone] explode all trees

#22 MeSH descriptor: [Chorionic Gonadotropin] explode all trees

#23 "human chorionic gonadotrop*"

#24 hCG

#25 hPL

#26 MeSH descriptor: [Placental Lactogen] explode all trees

#27 "human placental lactogen"

#28 "human placental growth hormone"

#29 "placental protein 13"

#30 "placental growth factor"

#31 "plasma placental protein"

#32 "pregnancy specific glycoprotein*"

#33 MeSH descriptor: [Pregnancy-Specific beta 1-Glycoproteins] explode all trees

#34 "schwangerschaft protein 1"

#35 "pregnancy specific beta 1-glycoprotein"

#36 MeSH descriptor: [Ultrasonography, Prenatal] explode all trees

#37 sonograph* or ultraso*

#38 "Grannum grading"

#39 MeSH descriptor: [Biological Markers] explode all trees

#40 biomarker* or marker*

#41 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40

#42 #13 and #41

Database: CINAHL (Ebsco) 1937 – present (28 October 2016)

Search strategy:

S1 (placenta* or fetoplacental or foetoplacental or uteroplacental) N2 (insufficienc* or fail* or function*)

S2 (MH”Placental Insufficiency”)

S3 (MH”Fetal Movement”)

S4 (MH”Fetal Growth Retardation”)

S5 (reduc* or decline) N2 (fetal move* or foetal move*)

S6 stillborn or stillbirth

S7 (MH”Perinatal Death”)

S8 (fetal or foetal or intrauterine or intra-uterine) N2 (growth or death* or loss*)

S9 IUGR

S10 (small) N2 (gestational age)

S11 (neonatal or perinatal or fetal or birth* or deliver*) N2 (outcome*)

S12 fetal move* or foetal move*

S13 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12

S14 oestradiol or estradiol or oestriol or progesterone or pregnenolone

S15 (MH"Estradiol")

S16 (MH"Progesterone+")

S17 (MH "Gonadotropins, Chorionic")

S18 human chorionic gonadotrophin

S19 hCG

S20 placental lactogen

S21 human placental growth hormone

S22 placental protein 13

S23 placental growth factor

S24 plasma placental protein

S25 pregnancy specific glycoprotein*

S26 schwangerschaft protein 1

S27 pregnancy specific beta 1-glycoprotein*

S28 (MH"Ultrasonography, Prenatal")

S29 sonograph* or ultraso*

S30 Grannum grading

S31 S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30

S32 S13 and S31

S33 S13 and S31 Limiters exclude MEDLINE records

3 QUADAS 2 tool for assessing methodological quality of included studies

Domain	Signalling question	Signalling question	Signalling question	Risk of bias	Concerns about applicability
Patient selection	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?	Are there concerns that the included patients and setting do not match the review question?
	Yes *if participants were consecutively enrolled or if all eligible participants were enrolled or participants were randomly sampled.* No *if participants were selected from those eligible.* Unclear *if participant selection was not clear from the report.*	Yes *if a case control design was avoided.* No *if a case control design was used.* Unclear *if the study design could not be determined from the report.*	Yes *if the study avoided inappropriate exclusions (e.g. only excluded multiple pregnancy, congenital abnormalities).* No *if participants were excluded inappropriately (e.g. ethnicity, age, income).* Unclear *if appropriateness of exclusions could not be assessed from report.*	Low risk *if yes to all of the signalling questions.* High or unclear risk *if "no" or "unclear" was reported for at least one signalling question.*	Low concern *if the sample of pregnant women represent the women indicated by the review question and if inappropriate exclusions were avoided.* High concern *if the sample of pregnant women are different from those indicated in the review question.* Unclear concern *if insufficient information was available.*
Index test – test of placental function	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used was it pre-specified?		Could the conduct or interpretation of the index test have introduced bias?	Are there concerns that the index test, its conduct or its interpretation differ from the review question?

	Yes *if the result(s) of the test of placental function was interpreted without knowledge of the reference standard.* No *if the result(s) of the test of placental function was interpreted with knowledge of the reference standard.* Unclear *if this was not clear in the report.*	Yes *if the criteria for a positive result of the placental function test were pre-specified.* No *if the criteria for a positive result were not pre-specified or deviated from that specified.* Unclear *if this was not clear from the report.*		Low risk *if yes to all of the signalling questions.* High or unclear risk *if "no" or "unclear" was reported for at least one signalling question.*	Low concern *if the placental function test was performed as described in the review question (e.g. after 24 weeks of pregnancy to assess placental function).* High concern *if the placental function test was performed in a different way to that described in the review question.* Unclear concern *if insufficient information was available.*
Reference standard and target condition	Is there reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?		Could the reference standard, its conduct or interpretation have introduced bias?	Are there concerns that the target condition as defined by the reference standard does not match the question?
	Yes *if an acceptable reference standard was used (e.g. SGA = birthweight < 10th centile, Stillbirth = baby born with no signs of life after 24 weeks' gestation).* No *if pregnancy outcome was not classified by an acceptable reference standard (e.g. low birthweight < 2.5 kg).* Unclear *if this was not clear from the report.*	Yes *if pregnancy outcome (live or stillbirth), and a diagnosis of a small for gestational age infant was made without the knowledge of results of the placental function test.* No *if pregnancy outcome and a diagnosis of a small for gestational age infant were made with the knowledge of the results of the placental function test.* Unclear *if this was not clear from the report.*		Low risk *if yes to all of the signalling questions.* High or unclear risk *if "no" or "unclear" was reported for at least one signalling question.*	Low concern *if acceptable reference standards were used and if the reference standard was interpreted without the knowledge of the placental function test.* High concern *if an acceptable reference standard was not used or the results were interpreted with knowledge of the result of the placental function test.* Unclear concern *if insufficient information was available.*
Flow and Timing	Was there an appropriate interval between the index test and reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?	Could the patient flow have introduced bias?	
	Yes *If acquisition of the index test occurred prior to birth (reference standards both determined after birth).* No *if sample acquired after delivery of the infant (i.e. known reference standard).* Unclear *if this was not clear from the report.*	Yes *if all participants had the outcome of pregnancy and birthweight recorded.* No *if some participants do not have the outcome of pregnancy and birthweight recorded.* Unclear *if this was not clear from the report.*	Yes *if all participants recruited to the study were included in the final analysis.* No *if all participants were not included in the final analysis.* Unclear *if this was not clear from the report.*	Low risk *if yes to all of the signalling questions.* High or unclear risk *if "no" or "unclear" was reported for at least one signalling question.*	

4 Glossary

Aneuploidy: a condition where there are an abnormal number of chromosomes in a cell

Centile: percentile, below the tenth centile means in the bottom 10%

Ductus venosus: a fetal blood vessel that helps carry oxygenated blood to the heart

Echotexture: the appearance of human tissue when looked at using ultrasound

Efficacy:efficiency, the ability of a test to produce the desired result

False negative: a negative test result in an individual with the condition of interest

False positive: a positive test result in an individual without the condition of interest

Heterogeneity: variation, diversity

Fetal growth restriction (FGR: a condition where a fetus fails to attain its growth potential, i.e. is smaller than expected for its genetic potential.

hPL - human placental lactogen - a protein made by the trophoblast layer of the placenta.

Morphology: appearance, structure

Placental analyte: a substance produced by the placenta that can be measured and analysed

PlGF: placental growth factor- a protein made by the trophoblast layer of the placenta.

Small-for-gestational-age infant (SGA infant): the condition where the fetal weight or birthweight is beneath a specific threshold, generally considered to be the 10th centile.

SROC plot: summary receiver operator characteristic plot - a scatterplot of estimates of sensitivity and specificity from included studies.

Umbilical artery Doppler: a measurement of fetal blood flow through the umbilical artery using Doppler ultrasound.

Uterine artery Doppler: a measurement of maternal blood flow through the uterine artery using Doppler ultrasound.

5 Risk of bias and applicability concerns summary for each study, by index test

Figure 15, Figure 16, Figure 17, Figure 18, Figure 19, Figure 20, Figure 21

6 Within study comparisons of tests for identifying small-for-gestational age (birthweight ≤ 10th centile) infants

Study	Sensitivity (true positives/cases)		Difference (95% CI)	P value	Specificity (true negatives/non-cases)		Difference (95% CI)	P value
Estimated fetal weight (EFW) versus placental grading								
	EFW	**Placental grading**			**EFW**	**Placental grading**		
Geerts 2016	0.57 (34/60)	0.41 (21/51)	0.15 (-0.03 to 0.34)	P = 0.13	1.00 (150/150)	0.96 (132/137)	0.04 (0.01 to 0.07)	P = 0.02
Estimated fetal weight versus placental growth factor (PlGF)								
	EFW	**PlGF**			**EFW**	**PlGF**		
Valino 2016	(104/379)	(48/379)	0.15 (0.09 to 0.20)	P < 0.0001	(3519/3574)	(3424/3574)	0.03 (0.02 to 0.03)	P < 0.0001
Human placental lactogen (hPL) versus placental grading								
	hPL	**Placental grading**			**hPL**	**Placental grading**		
Altmann 1978	0.50 (3/6)	0.67 (4/6)	-0.17 (-0.72 to 0.38)	P = 1.00	0 (0/4)	0 (0/4)	0 (– to –)	–
Human placental lactogen versus placental growth factor								
	hPL	**PlGF**			**hPL**	**PlGF**		
Nice 2016	0.43 (10/23)	0.17(4/23)	0.26 (0.01 to 0.52)	P = 0.11	0.91 (49/54)	0.92 (49/53)	-0.02 (-0.12 to 0.09)	P = 1.0.
Human placental lactogen versus urinary oestriol (UE3)								
	hPL	**UE3**			**hPL**	**UE3**		
Kunz 1976	0.53 (8/15)	0.67 (10/15)	-0.13 (-0.48 to 0.21)	P = 0.71	0.76 (52/68)	0.82 (56/68)	-0.06 (-0.19 to 0.08)	P = 0.53
Odendaal 1981	0.81 (35/43)	0.21 (6/28)	0.60 (0.41 to 0.79)	P < 0.0001	0.53 (18/34)	0.94 (17/18)	-0.42 (-0.61 to -0.22)	P = 0.002
Steiner 1991	0.37 (25/68)	0.13 (9/68)	0.24 (0.10 to 0.38)	P = 0.003	0.62 (28/45)	0.62 (28/45)	0 (-0.20 to 0.20)	P = 1.0
Serum oestriol (E3) versus urinary oestriol								
	E3	**UE3**			**E3**	**UE3**		
Odendaal 1981	0.43 (13/30)	0.21 (6/28)	0.22 (-0.01 to 0.45)	P = 0.10	0.87 (20/23)	0.94 (17/18)	-0.07 (-0.25 to 0.10)	P = 0.62

Differences in sensitivities and specificities between tests evaluated within each study are presented in the table. Five studies that evaluated hPL and oestriol were not included in this table as meta-analysis was performed (see Figure 10). The three studies of hPL versus urinary oestriol used different thresholds (see Figure 5).

7 Studies with evaluations of both small-for-gestational age (birthweight ≤ 10th centile) infants and stillbirths

Estimates of sensitivity and specificity from studies that evaluated biochemical tests for both SGA infants and stillbirths (Figure 14)