Pre-eclampsia Screening

Study overview on first trimester risk assessment with Placental Growth Factor (PIGF)
Content

### 1st trimester pre-eclampsia screening

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**Glossary**
Placental Growth Factor (PIGF) in first trimester pre-eclampsia screening

Pre-eclampsia is a leading cause of maternal morbidity and mortality. First trimester screening with Placental Growth Factor (PIGF) allows early detection of women at risk for pre-eclampsia before first clinical symptoms such as hypertension and proteinuria occur.

Low PIGF levels indicate an increased risk for pre-eclampsia
In normal pregnancy, the concentration of PIGF increases progressively, reaching a peak during weeks 29-32 and declining thereafter. Compared to controls, the PIGF concentrations of those women who later develop pre-eclampsia are significantly lower. [Levine RJ et al. N Engl J Med 2004; 350: 672-83]

Several maternal clinical characteristics have been identified as risk factors for developing pre-eclampsia. Algorithms have been established that include biomarker values, biophysical measurements as well as maternal characteristics to enhance the prediction rate to about 95% at a false positive rate of 10%. [Poon et al, 2014]

An identification of women at high risk for pre-eclampsia in first trimester allows an intensified maternal and fetal monitoring and offers the potential of reducing adverse outcome for mother and child.

Figure  Mean PIGF concentrations of healthy women and those women who later developed pre-eclampsia
Optimal first trimester pre-eclampsia prediction: a comparison of multimarker algorithm, risk profiles and their sequential application
Gabbay-Benziv R, Oliveira N, Baschat AA

Objective
To compare performance of multimarker algorithm, risk profiles and their sequential application in prediction of pre-eclampsia and determining potential intervention targets.

Study design
Maternal characteristics, ultrasound variables and serum biomarkers were collected prospectively at first trimester. Univariate analysis identified pre-eclampsia associated variables followed by logistic regression analysis to determine the prediction rule. Combined characteristics of the cardiovascular, metabolic and the personal risk factors were compared to the multimarker algorithm and the sequential application of both methods.

Results
Out of 2433 women, 108 developed pre-eclampsia (4.4%). Probability scores considering nulliparity, prior pre-eclampsia, body mass index, diastolic blood pressure and placental growth factor had an area under the receiver operating characteristic curve 0.784 (95% CI = 0.721-0.847).

While the multimarker algorithm had the lowest false negative rate, sequential application of cardiovascular and metabolic risk profiles in screen positives reduced false positives by 26% and identified blood pressure and metabolic risk in 49/54 (91%) women with subsequent pre-eclampsia as treatable risk factors.

KEY FACTS
Sequential application of a multimarker algorithm followed by determination of treatable risk factors in screen positive women is the optimal approach for first trimester pre-eclampsia prediction and identification of women that may benefit from targeted metabolic or cardiovascular treatment.
First trimester prediction of HELLP syndrome
Oliveira N, Poon LC, Nicolaides KH, Baschat AA
Prenat Diagn. 2016 Jan;36(1):29-33

Objective
The aim of this study was to evaluate first-trimester maternal characteristics and biomarkers in pregnancies that subsequently develop HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.

Method
Maternal history, biochemical, and biophysical parameters were compared between women who developed HELLP, pre-eclampsia (PE) without HELLP and controls. After determination of significant variables through univariate analysis a first-trimester prediction model was obtained by applying logistic regression analysis. Performance of the model was evaluated.

Results
Twenty participants with HELLP were compared with 147 patients that developed PE without HELLP and 2810 controls. Women with HELLP were more likely Caucasian, nulliparous and presented a higher mean arterial pressure (MAP) when compared with controls. As opposing to women who developed HELLP, women who developed PE without HELLP were more likely of African-American origin and presented an even higher first-trimester MAP.

Enrollment biochemical and biophysical parameters were similar between HELLP and PE or controls. Ethnicity, nulliparity, history of previous PE, history of previous HELLP syndrome, and first-trimester MAP were primary risk factors. A prediction rule for HELLP syndrome had an area under the curve of 0.80, with 75% sensitivity for 79% specificity.

KEY FACTS
The majority of pregnancies that develop HELLP syndrome can be predicted in the first trimester.
Competing risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks gestation
O’Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH

Background
Pre-eclampsia affects approximately 3% of all pregnancies and is a major cause of maternal and perinatal morbidity and death

Objective
The purpose of this study was to develop a model for pre-eclampsia based on maternal demographic characteristics and medical history (maternal factors) and biomarkers.

Study design
The data for this study were derived from prospective screening for adverse obstetric outcomes in women who attended for their routine first hospital visit at 11-13 weeks gestation in 2 maternity hospitals in England. We screened 35,948 singleton pregnancies that included 1058 pregnancies (2.9%) that experienced pre-eclampsia. Bayes theorem was used to combine the a priori risk from maternal factors with various combinations of uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A, and placental growth factor multiple of the median values. Five-fold cross validation was used to assess the performance of screening for pre-eclampsia that delivered at <37 weeks gestation (preterm-pre-eclampsia) and ≥37 weeks gestation (term-pre-eclampsia) by models that combined maternal factors with individual biomarkers and their combination with screening by maternal factors alone.

Results
In pregnancies that experienced pre-eclampsia, the values of uterine artery pulsatility index and mean arterial pressure were increased, and the values of serum pregnancy-associated plasma protein-A and placental growth factor were decreased. For all biomarkers, the deviation from normal was greater for early than late pre-eclampsia; therefore, the performance of screening was related inversely to the gestational age at which delivery became necessary for maternal and/or fetal indications. Combined screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor predicted 75% (95% confidence interval, 70-80%) of preterm-pre-eclampsia and 47% (95% confidence interval, 44-51%) of term-pre-eclampsia, at a false-positive rate of 10%; inclusion of pregnancy-associated plasma protein-A did not improve the performance of screening. Such detection rates are superior to the respective values of 49% (95% confidence interval, 43-55%) and 38% (34-41%) that were achieved by screening with maternal factors alone.

KEY FACTS
Combination of maternal factors and biomarkers provides effective first-trimester screening for preterm-pre-eclampsia.
Objective
To determine the diagnostic accuracy of pre-eclampsia (PE) screening test offered in early pregnancy for the prediction of the risks for early-onset (requiring delivery <32 weeks gestation) and late-onset (requiring delivery ≥32 weeks gestation) disease.

Methods
In a retrospective study of 615 women with singleton pregnancy, the risk for PE was calculated by the combined effect of multiple variables: serum placental growth factor (PLGF) and pregnancy-associated plasma protein-A (PAPP-A), maternal age, parity, ethnicity, mean arterial pressure (MAP), body mass index (BMI), uterine artery-pulsatility index, and previous history of PE or hypertension (HT). The results of the screening test in three different groups of women were validated by pregnancy outcome: (i) control group - without any history of PE/HT; (ii) history of PE without HT; and (iii) history of HT without PE. The performance of the screening test was evaluated for early- and late-onset PE.

Results
The multivariate screening effectively identified cases of PE with >97% specificity. The detection rate (DR) was 93.8% for late-onset PE at a false positive rate (FPR) of 2.3% and 44.4% for early-onset PE at an FPR of 0.0%. The incidence of PE was 7% overall, with 1.52% and 5.43% for early- and late-onset PE, respectively.

KEY FACTS
The study demonstrated 96.6% diagnostic accuracy of the multi-variable screening test to predict the risk of PE in the first trimester. The negative predictive value (>98%) reinforces the utility of cost-effective noninvasive screening test for the early detection of PE.
First- and second-trimester maternal serum markers of pre-eclampsia in twin pregnancy
Svirsky R, Levinsohn-Tavor O, Feldman N, Klog E, Cuckle H, Maymon R
Ultrasound Obstet Gynecol. 2016 May;47(5):560-4

Objective
To evaluate the distribution of first- and second-trimester maternal serum markers in twin pregnancy with and without pre-eclampsia.

Methods
One-hundred and forty-four twin and 109 unaffected singleton pregnancies were recruited from the same institution. First- and second-trimester maternal blood samples were stored and measured retrospectively for serum placental growth factor (PlGF), pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP). All had measurement of first-trimester serum markers, and 167 (66%) had second-trimester tests. Values were expressed in multiples of the gestation-specific median (MoMs) in singletons, adjusted for maternal weight, as appropriate.

Results
Pre-eclampsia was diagnosed in 12 (9.0%) twin pregnancies of 133 continuing beyond 22 weeks. In unaffected twin pregnancies, all serum markers were statistically significantly increased (P < 0.0001), consistent with a doubling of concentration.

Among twin pregnancies, those with pre-eclampsia had a significantly reduced median PlGF compared with surviving unaffected twin pregnancies (0.96 MoM vs 1.46 MoM; P < 0.0002, two-tailed), whilst median PAPP-A, which is known to be reduced in affected singleton pregnancies, was increased (3.91 MoM vs 2.43 MoM; P < 0.0005, two-tailed). The levels of free β-hCG (P < 0.02) and AFP (P < 0.05) were also significantly raised, but to a lesser extent than was the level of PAPP-A.

Using a logistic regression algorithm based on first- and second-trimester PlGF and PAPP-A, together with previously published uterine artery Doppler and mean arterial pressure measurements in the same series, the predicted pre-eclampsia detection rate was 65% for a 10% false-positive rate.

KEY FACTS
In twin pregnancy, the predicted detection rate of pre-eclampsia using first- and second-trimester maternal serum and biophysical markers is good. In contrast to singleton pregnancy, PAPP-A levels are raised in the first trimester of twin pregnancies destined to develop pre-eclampsia and therefore a different prediction algorithm is needed.
First trimester prediction of pre-eclampsia
Anderson UD, Gram M, Åkerström B, Hansson SR
Curr Hypertens Rep. 2015 Sep;17(9):584

Abstract
Pre-eclampsia (PE) is a serious pregnancy-related condition that causes severe maternal and fetal morbidity and mortality. Within the recent years, there has been an increasing focus in predicting PE at the end of the first trimester of pregnancy. In this review, literature published between 2011 and 2015 was evaluated.

In a total of six biomarker algorithms, for first and early second trimester, the prediction of pre-eclampsia is discussed. In addition, one randomized clinical trial was included. Several algorithms were based on placental biomarkers such as pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PLGF), and soluble FMS-like tyrosine kinase 1 (s-FLT-1).

The algorithms containing these biomarkers showed a high prediction rate (PR) for early onset PE, ranging from 44 to 92 % at 5 % false positive rate (FPR). New biomarkers suggest an alternative model based on free HbF and the heme scavenger alpha-1-microglobulin (A1M) with a prediction rate of 69 % at an FPR of 5 %.

Interestingly, this model performs well without uterine artery Doppler pulsatility index (UtAD-PI), which is an advantage particularly if the screening method were to be implemented in developing countries.

The randomized clinical trial showed a clear reduction in early onset PE as well as reducing preterm PE if identified high-risk pregnancies were treated with low-dose aspirin. In conclusion, PE prediction is now possible through several prediction algorithms and prophylaxis is beneficial in high-risk cases.
First-trimester uterine artery Doppler analysis in the prediction of later pregnancy complications
Khong SL, Kane SC, Brennecke SP, da Silva Costa F
Dis Markers 2015;2015:679730

Abstract
Uterine artery Doppler waveform analysis has been extensively studied in the second trimester of pregnancy as a predictive marker for the later development of pre-eclampsia and fetal growth restriction. The use of Doppler interrogation of this vessel in the first trimester has gained momentum in recent years. Various measurement techniques and impedance indices have been used to evaluate the relationship between uterine artery Doppler velocimetry and adverse pregnancy outcomes.

Overall, first-trimester Doppler interrogation of the uterine artery performs better in the prediction of early-onset than late-onset pre-eclampsia. As an isolated marker of future disease, its sensitivity in predicting pre-eclampsia and fetal growth restriction in low risk pregnant women is moderate, at 40-70%.

Multiparametric predictive models, combining first-trimester uterine artery pulsatility index with maternal characteristics and biochemical markers, can achieve a detection rate for early-onset pre-eclampsia of over 90%. The ideal combination of these tests and validation of them in various patient populations will be the focus of future research.
Objective
The aim of this article is to develop the best first-trimester screening model for pre-eclampsia (PE) based on maternal characteristics, biophysical parameters, and angiogenic factors in a low-risk population.

Methods
A prospective cohort of 9462 pregnancies undergoing first-trimester screening is used. Logistic regression predictive models were developed for early and late PE (cut-off of 34 weeks' gestation at delivery). Data included the a priori risk (maternal characteristics), mean arterial pressure (MAP), and uterine artery (UtA) Doppler (11-13 weeks) in all cases.

Plasma levels (8-11 weeks) of human chorionic gonadotrophin, pregnancy-associated plasma protein A, placental growth factor (PIGF), and soluble Fms-like tyrosine kinase-1 (sFlt-1) were analyzed using a nested case-control study design.

Results
The best model for early PE (n = 57, 0.6%) included a priori risk, MAP, UtA Doppler, PIGF, and sFlt-1 achieving detection rates of 87.7% and 91.2% for 5% and 10% false-positive rates, respectively (AUC: 0.98 [95% CI: 0.97-0.99]).

For late PE (n = 246, 2.6%), the best model included the a priori risk, MAP, UtA Doppler, PIGF, and sFlt-1 achieving detection rates of 68.3% and 76.4% at 5% and 10% of false-positive rates, respectively (AUC: 0.87 [95% CI: 0.84-0.90]).

KEY FACTS
Pre-eclampsia can be predicted with high accuracy in general obstetric populations with a low risk for PE, by combined algorithms. Angiogenic factors substantially improved the prediction.
Psychological impact of first-trimester prevention for pre-eclampsia on anxiety
Prenat Diagn 2015 Jan;35(1):60-4

Objective
This study aims to examine whether a first-trimester strategy of secondary prevention for pre-eclampsia increases anxiety in pregnant women.

Methods
The anxiety levels of a cohort of women screened for pre-eclampsia at first trimester were measured by the Spielberg State-Trait Anxiety Inventory (STAI-S) and compared between women screened as low and high risk. In a subgroup of women, the anxiety levels were additionally measured at second and third trimester. A General Linear Model (GLM) for repeated measurements was performed to adjust for potential confounders (age, nulliparity and socio-economic level).

Results
A total of 255 women (135 low-risk and 120 high-risk) were evaluated. No differences were found in the mean STAI-S scores between low-risk and high-risk women: 35 (SD 9.9) and 34.6 (SD 10.1); p = 0.77.

The proportion of women with high anxiety was not significantly different between groups (28/134 [20.7%] vs 24/120 [20%]; p = 0.88).

No differences were found in the subgroups (51 low-risk and 50 high-risk) in which the anxiety levels were also measured at second and third trimester: 35.8 (SD 8.8) vs 35.2 (SD 9.7), p = 0.74, and 37.2 (SD 9.4) vs 35.3 (SD 8.6), p = 0.3. These differences remained non-significant after adjustment for potential confounders.

KEY FACTS
A strategy of first-trimester screening for pre-eclampsia does not increase maternal anxiety.
Use of first or second trimester serum markers, or both, to predict pre-eclampsia
Lambert-Messerlian G, Eklund EE, Chien EK, Rosene-Montella K et al. 

Objective
Pre-eclampsia is a serious complication of pregnancy, threatening fetal and maternal health. The aim of our study is to examine the association between pre-eclampsia and biochemical markers, in matched first and second trimester maternal serum samples.

Study design
This is a nested case/control study derived from the cohort of pregnancies delivering at Women & Infants Hospital. Cases were identified at a clinic or by hospital codes, and individually confirmed by record review. Stored samples were available from 'integrated' Down syndrome screening. Results were expressed as multiples of the median (MoM).

Main outcome measures
Pre-eclampsia was classified as early/severe, late/severe, or mild based on professional guidelines. An additional adverse outcome group had only gestational hypertension.

Results
Ninety-eight cases were each matched with five control pregnancies. Population distribution parameters and within and between trimester correlations were derived for cases and controls for six markers, as well as in case subgroups.

The strongest associations were for early/severe pre-eclampsia with second trimester PAPP-A (rank sum test 2.30, p<0.01); PlGF (2.60, p<0.05) inhibin A (4.45, p<0.05) and endoglin (4.25, p<0.05).

No strong associations were found for sVEGF-R and FLRG. Second trimester associations were stronger than those in the first (e.g., PAPP-A 2.45, p<0.01). No between-trimester associations were found that would provide important improvements in prediction.

KEY FACTS
This matched analysis of the serum markers in early pregnancy allows for direct comparison of first and second trimester associations with pre-eclampsia. PAPP-A and PlGF are equally and highly predictive of early/severe pre-eclampsia.
Early prediction of pre-eclampsia
Poon LC, Nicolaides KH
*Obstet Gynecol Int* 2014;2014:297397

**Abstract**
Effective screening for the development of early onset pre-eclampsia (PE) can be provided in the first-trimester of pregnancy. Screening by a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum pregnancy-associated plasma protein-A, and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%.

First-trimester maternal factors and biomarker screening for pre-eclampsia
Poon LC, Nicolaides KH
*Prenat Diagn. 2014 Jul;34(7):618-27*

**Abstract**
Pre-eclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality. PE can be subdivided into early onset PE with delivery <34 weeks’ gestation and late onset PE with delivery ≥34 weeks. Early onset PE is associated with a higher incidence of adverse outcome.

This review illustrates that effective screening for the development of early onset PE can be provided in the first-trimester of pregnancy. Screening by a combination of maternal risk factors, mean arterial pressure, uterine artery Doppler, maternal serum pregnancy-associated plasma protein-A and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%.
Prediction of pre-eclampsia utilizing the first trimester screening examination
Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG
*Am J Obstet Gynecol* 2014 Apr 15

**Objective**
To derive a prediction rule for pre-eclampsia and early onset pre-eclampsia requiring delivery <34 weeks using first trimester maternal, ultrasound, and serum markers.

**Study design**
Prospective cohort study of women enrolled at first trimester screening. Maternal history, demographics, anthropometry, ultrasound parameters, and serum analytes were compared between women with pre-eclampsia and normal outcome. The prediction rule was derived by Lasso logistic regression analysis.

**Results**
In 2441 women, 108 (4.4%) women developed pre-eclampsia, and 18 (0.7%) early pre-eclampsia. Nulliparity, prior hypertension, diabetes, prior pre-eclampsia, mean arterial pressure, and the log pregnancy-associate pregnancy protein-A multiples of the median were primary risk factors.

Prediction rules for pre-eclampsia/early pre-eclampsia had an area under the curve of 0.82/0.83 respectively. Pre-eclampsia was predicted with 49% sensitivity and early pre-eclampsia with 55% sensitivity for a 10% false positive rate.

**KEY FACTS**
First trimester prediction rules using parameters currently available at first trimester screening identify a significant proportion of women with subsequent pre-eclampsia.
Pre-eclampsia part 2: prediction, prevention and management
Chaiworapongsas T, Chaemsaiithong P, Korzeniewski SJ, Yeo L, Romero R
Nat Rev Nephrol 2014 Jul 8

Abstract
An antiangiogenic state might constitute a terminal pathway for the multiple aetiologies of pre-eclampsia, especially those resulting from placental abnormalities. The levels of angiogenic and antiangiogenic proteins in maternal blood change prior to a diagnosis of pre-eclampsia, correlate with disease severity and have prognostic value in identifying women who will develop maternal and/or perinatal complications.

Potential interventions exist to ameliorate the imbalance of angiogenesis and, hence, might provide opportunities to improve maternal and/or perinatal outcomes in pre-eclampsia.

Current strategies for managing pre-eclampsia consist of controlling hypertension, preventing seizures and timely delivery of the fetus.

Prediction of pre-eclampsia in the first trimester is of great interest, as early administration of aspirin might reduce the risk of pre-eclampsia, albeit modestly. Combinations of biomarkers typically predict pre-eclampsia better than single biomarkers; however, the encouraging initial results of biomarker studies require external validation in other populations before they can be used to facilitate intervention in patients identified as at increased risk.

Angiogenic and antiangiogenic factors might also be useful in triage of symptomatic patients with suspected pre-eclampsia, differentiating pre-eclampsia from exacerbations of pre-existing medical conditions and performing risk assessment in asymptomatic women.

KEY FACTS
This Review article discusses the performance of predictive and prognostic biomarkers for pre-eclampsia, current strategies for preventing and managing the condition and its long-term consequences.
Placental pathology, first-trimester biomarkers and adverse pregnancy outcomes
Odibo AO, Patel KR, Spitalnik A, Odibo L, Huettner P

Objective
We investigated the relationship between placental pathological findings in pregnancies with adverse pregnancy outcomes and first-trimester serum analytes and uterine artery Doppler results.

Study design
This is a secondary analysis of a prospective study of first-trimester screening for adverse pregnancy outcomes, including preterm birth (PTB (delivery<37 weeks)), pre-eclampsia (PE), gestational hypertension, and small for gestational age (SGA) infants (birth weight <10th percentile).

We compared the mean levels of serum analytes (pregnancy-associated plasma protein A (PAPP-A), placental protein 13 (PP13), a-disintegrin and metalloproteinase 12 (ADAM12), placental growth factor (PLGF)) and uterine artery Doppler pulsatility index (UADPI) obtained between 11 and 14 weeks gestation in cases with adverse outcomes and abnormal placental histology to a control group without adverse outcome or abnormal placental pathology.

Placental findings were classified as: lesions of maternal under perfusion, lesions causing reduced placental reserve, infections/inflammatory lesions, and fetal vascular lesions.

Result
Among 193 cases, lesions of maternal under perfusion were seen in 50 cases (25.9%), lesions causing reduced placental reserve in 63 cases (32.8%), infection/inflammation in 65 cases (34.2%) and fetal vascular lesions in 23 cases (11.9%). There were 123 pregnancies with no adverse pregnancy outcome or placental lesion used as controls. Pregnancies with PE had a significant association with lesions of maternal under perfusion (P=0.005) and placental infection/inflammation (P=0.003). Significant differences were seen in mean levels of PAPP-A, ADAM12 and PLGF in cases with PE, PTB and SGA with specific placental histological findings when compared with controls. UADPI was not significantly different between the cases with adverse pregnancy outcomes and abnormal histology.

KEY FACTS
Our findings provide evidence linking placental pathology with suboptimal secretion of analytes in the first trimester in pregnancies with adverse outcomes, especially PE.
Maternal Serum PIGF Isoforms 1 and 2 at 11-13 Weeks’ Gestation in Normal and Pathological Pregnancies
Nucci M, Poon LC, Demirdjian G, Darbouret B, Nicolaides KH
Fetal Diagn Ther 2014 Jan 23

Rationale
To compare the maternal serum concentration of PIGF-1 and PIGF-2 at 11-13 weeks’ gestation in normal pregnancies and in those complicated by pre-eclampsia, delivery of small for gestational age neonates and fetal trisomies 21, 18 and 13.

Patients/Methods
Serum PIGF-1 and PIGF-2 were measured in 270 pathological pregnancies (PE, n = 80; SGA, n = 80; trisomy 21, n = 44; trisomy 18, n = 38; trisomy 13, n = 28) and 590 normal controls. The values were expressed as multiple of the median after adjustment for maternal characteristics and corrected for adverse pregnancy outcomes and the median MoM values in each pathological pregnancy were compared to the normal group.

Results
There were significant contributions to PIGF-1 and PIGF-2 from gestational age, smoking and racial origin. In addition, there were significant contributions to PIGF-1 from parity and method of conception.

The median MoM of PIGF-1 and PIGF-2 was significantly decreased in

- PE (0.783 and 0.916 MoM)
- SGA (0.891 and 0.851 MoM)
- trisomy 21 (0.609 and 0.749 MoM)
- trisomy 18 (0.529 and 0.730 MoM)
- trisomy 13 (0.373 and 0.699 MoM)

KEY FACTS
In pathological pregnancies, except SGA, the decrease in serum PIGF-1 at 11-13 weeks’ gestation is more marked than the decrease in PIGF-2.
Maternal characteristics, mean arterial pressure and serum markers in early prediction of pre-eclampsia
Kuc S, Koster MP, Franx A, Schielen PC, Visser GH

**Objective**
In a previous study, we have described the predictive value of first-trimester Pregnancy-Associated Plasma Protein-A (PAPP-A), free β-subunit of human Chorionic Gonadotropin (fβ-hCG), Placental Growth Factor (PIGF) and A Disintegrin And Metalloprotease 12 (ADAM12) for early onset pre-eclampsia (EO-PE; delivery <34 weeks).

The objective of the current study was to obtain the predictive value of these serum makers combined with maternal characteristics and first-trimester maternal mean arterial blood pressure (MAP) in a large series of patients, for both EO-PE and late onset PE (LO-PE; delivery ≥ 34 weeks).

**Methods**
This was a nested case-control study, using stored first-trimester maternal serum from women who developed EO-PE (n=68) or LO-PE (n=99), and 500 uncomplicated singleton pregnancies. Maternal characteristics, MAP, and pregnancy outcome were collected for each individual woman and used to calculate prior risks for PE in a multiple logistic regression model.

Models containing prior PE risks, serum markers, and MAP were developed for the prediction of EO-PE and LO-PE. The model-predicted detection rates (DR) for fixed 10% false-positive rates were calculated for EO-PE and LO-PE with or without the presence of a small-for-gestational age infant (SGA, birth weight <10(th) centile).

**Results**
The best prediction model included maternal characteristics, MAP, PAPP-A, ADAM12, and PIGF, with DR of 72% for EO-PE and 49% for LO-PE. Prediction for PE with concomitant SGA was better than for PE alone (92% for EO-PE and 57% for LO-PE).

**KEY FACTS**
First-trimester MAP, PAPP-A, ADAM12, and PIGF combined with maternal characteristics and MAP are promising markers in the risk assessment of PE, especially for EO-PE complicated by SGA.
Competing risks model in early screening for pre-eclampsia by biophysical and biochemical markers
Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH
Fetal Diagn Ther 2013;33(1):8-15

Objective
To develop models for prediction of pre-eclampsia (PE) based on maternal characteristics, biophysical and biochemical markers at 11-13 weeks’ gestation in which the gestation at the time of delivery for PE is treated as a continuous variable.

Methods
This was a screening study of singleton pregnancies at 11-13 weeks including 1,426 (2.4%) that subsequently developed PE and 57,458 that were unaffected by PE.

We developed a survival time model for the time of delivery for PE in which Bayes’ theorem was used to combine the prior information from maternal characteristics with uterine artery pulsatility index (PI), mean arterial pressure (MAP), serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PLGF) multiple of the median (MoM) values.

Results
In pregnancies with PE, there was a linear correlation between MoM values of uterine artery PI, MAP, PAPP-A and PLGF with gestational age at delivery and therefore the deviation from normal was greater for early than late PE for all four biomarkers.

Screening by maternal characteristics, biophysical and biochemical markers detected 96% of cases of PE requiring delivery before 34 weeks and 54% of all cases of PE at a fixed false-positive rate of 10%.

KEY FACTS
A new model has been developed for effective first-trimester screening for PE.
Combined screening for pre-eclampsia and small for gestational age at 11-13 weeks
Poon LC, Syngelaki A, Akolekar R, Lai J, Nicolaides KH
Fetal Diagn Ther 2013;33(1):16-27

Objective
To combine a specific algorithm for small for gestational age (SGA) without pre-eclampsia (PE) and another algorithm for PE in the prediction of SGA and PE.

Methods
This was a screening study of singleton pregnancies at 11-13 weeks including
• 1,426 (2.3%) that subsequently developed PE,
• 3,168 (5.1%) that delivered SGA neonates and
• 57,458 that were unaffected by PE and SGA.

We developed a prediction algorithm for SGA requiring delivery before 37 weeks' gestation (preterm-SGA) from maternal characteristics, uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A and placental growth factor multiple of the median values.

We then examined the performance of this algorithm individually and in combination with a previously reported algorithm for early-PE in the prediction of SGA and PE.

Results
When screen positivity was defined by risk cutoff of 1:200 using the algorithm for early-PE and the risk cutoff of 1:150 using the algorithm for preterm-SGA, the false positive rate was 10.9% and the detection rates of early-PE, late-PE, preterm-SGA and term-SGA were 95.3, 45.6, 55.5 and 44.3%, respectively.

KEY FACTS
Effective first-trimester screening for early-PE and preterm-SGA can be provided by the combined use of the specific algorithms.
Early detection of maternal risk for pre-eclampsia
Mikat B, Gellhaus A, Wagner N, Birdir C, Kimmig R, Königer A
ISRN Obstet Gynecol 2012;2012:172808

Abstract
Pre-eclampsia is one of the leading causes of maternal and fetal morbidity and mortality.


Preventive and effective therapeutic agents like acetylsalicylic acid can be started in the early second trimester.

This article reviews the diagnostic possibilities of early risk calculation to detect women having high risk for pre-eclampsia and the potential benefits for them, the offspring and health care systems. We provide risk calculation for pre-eclampsia as an important and sensible part of first trimester screening.
First trimester maternal serum PlGF, free β-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of pre-eclampsia

**Objective**
To evaluate the detection of pregnancy hypertensive disorders by integrating maternal history, serum biomarkers and uterine artery Doppler in the first trimester.

**Methods**
We prospectively recruited 2118 women that underwent an 11-13 weeks aneuploidy screening. We gathered information on maternal history, uterine artery Doppler and serum biomarkers (PAPP-A, PlGF, PP-13 and free β-hCG).

Models were developed for the prediction of overall pre-eclampsia (PE), early-onset PE, late-onset PE and gestational hypertension (GH). For each outcome, we performed a multivariate logistic regression starting from the saturated model: adopting a step-down procedure we excluded all factors not statistically significant (p > 0.05). Sensitivity models only for statistically significant parameters were calculated from the ROC curves for fixed false-positive rates (FPR).

**Results**
Among 2118 women, 46 (2.17%) developed GH and 25 (1.18%) were diagnosed with PE, including 12 (0.57%) early-onset PE and 13 (0.61%) late-onset PE.

For a fixed FPR of 10 and 5%, serum PlGF, free β-hCG and chronic hypertension identified respectively 67 and 75% of women who developed early-onset PE. In the model for the prediction of overall PE the combination of the uterine artery Doppler pulsatility index (UtA PI) with PlGF and chronic hypertension reached a sensitivity of 60% for a 20% of FPR.

**KEY FACTS**
An integration of maternal characteristics and first trimester maternal serum biomarkers (free β-hCG and PlGF) provided a possible screening for early-onset PE. In the overall PE model, UtA PI turned out to be statistically significant but did not improve the detection rate.
Angiogenic factors in pre-eclampsia and related disorders
Cerdeira AS, Karumanchi SA
Cold Spring Harb Perspect Med 2012 Nov 1;2(11)

Abstract
During fetal development, the human placenta undergoes high levels of both angiogenesis and vasculogenesis. Additionally, the developing placenta undergoes a process of vascular mimicry (referred to as pseudovasculogenesis) as cytotrophoblasts convert from an epithelial to an endothelial phenotype.

The initiation, maturation, and maintenance of the placental vasculature are of critical importance. Failure to do so can lead to adverse obstetric outcomes such as pre-eclampsia and/or intrauterine growth restriction (IUGR).

Furthermore, the foundation of many aspects of adult health is laid in utero. In this context, normal placental function is not only critical for normal fetal development but can also permanently influence long-term health and disease. Understanding the mechanisms that regulate placental vasculogenesis and angiogenesis is therefore of critical importance.

This chapter will focus on placental vascular development with a particular emphasis on the role of angiogenic factors in the pathogenesis of the maternal syndrome of pre-eclampsia and related disorders.
Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks
Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH
_Prenat Diagn_ 2011 Jan;31(1):66-74

**Objective**
To develop models for prediction of pre-eclampsia (PE) based on maternal factors and biophysical and biochemical markers at 11-13 weeks’ gestation.

**Methods**
Screening study of singleton pregnancies at 11-13 weeks including 752 (2.2%) that subsequently developed PE and 32,850 that were unaffected by PE. Models were developed for the prediction of early PE, requiring delivery before 34 weeks, intermediate PE with delivery at 34-37 weeks and late PE delivering after 37 weeks.

The data used for the models were firstly, maternal characteristics and history, uterine artery pulsatility index, mean arterial pressure and serum pregnancy-associated plasma protein-A obtained from the screening study and secondly, maternal serum or plasma concentration of placental growth factor, placental protein-13, inhibin-A, activin-A, soluble endoglin, pentraxin-3 and P-selectin obtained from case-control studies.

**Results**
In screening for PE by maternal factors only at a fixed false positive rate of 5%, the estimated detection rates were 33.0% for early PE, 27.8% for intermediate PE and 24.5% for late PE.

The respective detection rates in screening by a combination of maternal factors, biophysical and biochemical markers were 91.0, 79.4 and 60.9%.

**KEY FACTS**
Effective prediction of PE can be achieved at 11-13 weeks’ gestation.
Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11-13 weeks
Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH

Objective
To examine the performance of screening for pre-eclampsia (PE) and gestational hypertension (GH) by a combination of maternal factors and various biophysical and biochemical markers at 11-13 weeks' gestation.

Methods
This was a case-control study of 26 cases of early PE, 90 of late PE, 85 of GH and 201 unaffected controls. Maternal history was recorded, the uterine artery with the lowest pulsatility index (L-PI) and mean arterial pressure (MAP) were measured and stored plasma and serum were analyzed for placental growth factor (PIGF), inhibin-A, activin-A, tumor necrosis factor receptor-1, matrix metalloproteinase-9, pentraxin-3 and P-selectin.

Results
Multivariate logistic regression analysis demonstrated that significant prediction for early PE was provided by maternal factors, MAP, uterine artery L-PI and serum PIGF.

Significant prediction of late PE was provided by maternal factors, MAP, uterine artery L-PI, PIGF, activin-A and P-selectin.

For GH significant prediction was provided by maternal factors, MAP, uterine artery L-PI and activin-A.

In screening by a combination of maternal factors, biophysical and biochemical markers the estimated detection rates, at a 5% false-positive rate, were 88.5% (95% CI, 69.8-97.4%) for early PE, 46.7% (95% CI, 36.1-57.5%) for late PE and 35.3% (95% CI, 25.2-46.4%) for GH.

KEY FACTS
Combined biophysical and biochemical testing at 11-13 weeks could effectively identify women at high risk for subsequent development of hypertensive disorders in pregnancy.
Objective
We sought to estimate the impact of aspirin dosage on the prevention of pre-eclampsia, severe pre-eclampsia, and fetal growth restriction.

Study Design
We performed a systematic review and meta-analysis of randomized controlled trials comparing the effect of daily aspirin or placebo (or no treatment) during pregnancy. We searched MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials up to December 2015, and study bibliographies were reviewed. Authors were contacted to obtain additional data when needed. Relative risks for pre-eclampsia, severe pre-eclampsia, and fetal growth restriction were calculated with 95% confidence intervals using random-effect models. Dose-response effect was evaluated using meta-regression and reported as adjusted R2. Analyses were stratified according to gestational age at initiation of aspirin (≤16 and >16 weeks) and repeated after exclusion of studies at high risk of biases.

Results
In all, 45 randomized controlled trials included a total of 20,909 pregnant women randomized to between 50-150 mg of aspirin daily. When aspirin was initiated at ≤16 weeks, there was a significant reduction and a dose-response effect for the prevention of pre-eclampsia (relative risk, 0.57; 95% confidence interval, 0.43-0.75; P < .001; R2, 44%; P = .036), severe pre-eclampsia (relative risk, 0.47; 95% confidence interval, 0.26-0.83; P = .009; R2, 100%; P = .008), and fetal growth restriction (relative risk, 0.56; 95% confidence interval, 0.44-0.70; P < .001; R2, 100%; P = .044) with higher dosages of aspirin being associated with greater reduction of the 3 outcomes. Similar results were observed after the exclusion of studies at high risk of biases. When aspirin was initiated at >16 weeks, there was a smaller reduction of pre-eclampsia (relative risk, 0.81; 95% confidence interval, 0.66-0.99; P = .04) without relationship with aspirin dosage (R2, 0%; P =.941). Aspirin initiated at >16 weeks was not associated with a risk reduction or a dose-response effect for severe pre-eclampsia (relative risk, 0.85; 95% confidence interval, 0.64-1.14; P = .28; R2, 0%; P = .838) and fetal growth restriction (relative risk, 0.95; 95% confidence interval, 0.86-1.05; P = .34; R2, not available; P = .563).

KEY FACTS
Prevention of pre-eclampsia and fetal growth restriction using aspirin in early pregnancy is associated with a dose-response effect. Low-dose aspirin initiated at >16 weeks’ gestation has a modest or no impact on the risk of pre-eclampsia, severe pre-eclampsia, and fetal growth restriction. Women at high risk for those outcomes should be identified in early pregnancy.
Aspirin for the Prevention of Pre-eclampsia and Intrauterine Growth Restriction
Roberge S, Odibo AO, Bujold E

Abstract
Low-dose aspirin (LDA) has been used for several years for the prevention of pre-eclampsia (PE). LDA started in early pregnancy is associated with improvement of placental implantation. The best evidence suggests that LDA can prevent more than half of PE cases in high-risk women when started before 16 weeks of gestation. Moreover, LDA started in early pregnancy reduces the risk of other placenta-mediated complications such as intrauterine growth restriction (IUGR) and perinatal death. The efficacy of LDA has been demonstrated in women with abnormal first-trimester uterine artery Doppler or with prior history of chronic hypertension or pre-eclampsia.

Low-Dose Aspirin in Early Gestation for Prevention of Pre-eclampsia and Small-for-Gestational-Age Neonates: Meta-analysis of Large Randomized Trials
Roberge S, Sibai B, McCaw-Binns A, Bujold E

Abstract
Objectives Meta-analyses of small to moderate size randomized controlled trials (RCTs) suggested that aspirin started before 17 weeks' gestation reduces the risk of pre-eclampsia and small-for-gestational-age (SGA) neonates. We evaluated data from large randomized trials originally excluded from meta-analyses. Methods We performed meta-analyses of RCTs including more than 350 participants that compared aspirin to placebo during pregnancy. Corresponding authors were contacted to obtain data according to gestational age. Outcomes included pre-eclampsia, severe pre-eclampsia, and SGA. Relative risks (RRs) with their 95% confidence intervals (CIs) were calculated. Results Data for women recruited before 17 weeks' gestation were obtained for three (50%) of the six eligible trials for a total of 11,949 participants including 3,293 recruited before 17 weeks' gestation with available data. We observed no impact of low-dose aspirin (60 mg) started before 17 weeks' gestation on the risk of pre-eclampsia (RR: 0.93; 95% CI: 0.75-1.15), severe pre-eclampsia (RR: 0.96; 95% CI: 0.71-1.28), or SGA (RR: 0.84; 95% CI: 0.56-1.26) and it was not statistically different than when started at or after 17 weeks' gestation. Conclusion Data from large randomized trials do not support greater benefits of low-dose aspirin (at 60 mg daily) when started before 17 weeks' gestation for the prevention of pre-eclampsia or SGA.
Objective
To examine the effect of a combination of screening and treatment with low-dose aspirin on the prevalence of early-onset pre-eclampsia (PE).

Methods
This was a retrospective analysis of two consecutive cohorts of women screened for early PE. The first cohort was observed to determine whether algorithms developed to screen for PE at 11 to 13 + 6 weeks' gestation could be applied to our population. High-risk women in the second cohort were advised on their risk and offered aspirin (150 mg at night), with treatment starting immediately after screening. The prevalence of early PE and the proportion of women with PE delivering at 34-37 weeks' gestation were compared between the cohorts.

Results
In the observational and interventional cohorts, 3066 and 2717 women, respectively, were screened.

There were 12 (0.4%) cases of early PE in the observational cohort and one (0.04%) in the interventional cohort (P < 0.01).

Among all women with PE delivering before 37 weeks, 25 (0.83%) were in the observational cohort and 10 (0.37%) in the interventional cohort (P = 0.03).

KEY FACTS
A strategy of first-trimester screening for early PE coupled with prescription of aspirin to the high-risk group appears to be effective in reducing the prevalence of early PE.
Low-dose aspirin use for the prevention of morbidity and mortality from pre-eclampsia: U.S. Preventive Services Task Force recommendation statement
LeFevre ML; U.S. Preventive Services Task Force
Ann Intern Med 2014 Dec 2;161(11):819-26

Description
Update of the 1996 U.S. Preventive Services Task Force (USPSTF) recommendation on aspirin prophylaxis in pregnancy.

Methods
The USPSTF reviewed the evidence on the effectiveness of low-dose aspirin in preventing pre-eclampsia in women at increased risk and in decreasing adverse maternal and perinatal health outcomes, and assessed the maternal and fetal harms of low-dose aspirin during pregnancy.

Population
This recommendation applies to asymptomatic pregnant women who are at increased risk for pre-eclampsia and who have no prior adverse effects with or contraindications to low-dose aspirin.

Recommendation
The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for pre-eclampsia. (B recommendation).
Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation
Bujold E, Roberge S, Nicolaides KH
Prenat Diagn 2014 Jul;34(7):642-8

Abstract
Meta-analysis of randomized studies on the use of low-dose aspirin in women at high risk of pre-eclampsia (PE) has demonstrated that if treatment is initiated at \( \leq 16 \) weeks’ gestation, there is significant reduction in the risk of

- PE [relative risk (RR) 0.47, 95% confidence interval (CI) 0.36-0.62]
- fetal growth restriction (RR 0.46, 95% CI 0.33-0.64)
- preterm birth (RR 0.35, 95% CI 0.22-0.57)
- and perinatal death (RR 0.41, 95% CI 0.19-0.92)

Whereas the effect of treatment after 16 weeks is substantially less (RR 0.78, 95% CI 0.61-0.99; RR 0.98, 95% CI 0.88-1.08; RR 0.90, 95% CI 0.83-0.97; and RR 0.93, 95% CI 0.73-1.19, respectively).

Moreover, the decrease in the risk of PE from early onset treatment seems to be related to the dose of aspirin, and a dose of \( >80 \) mg daily should be considered for optimal benefits.
Early administration of low-dose aspirin for the prevention of severe and mild pre-eclampsia: a systematic review and meta-analysis

**Objective**
To determine whether early administration of aspirin prevents severe and mild pre-eclampsia.

**Study design**
A systematic review and meta-analysis of randomized controlled trials were performed. Studies in which women were randomized at or before 16 weeks' gestation to low-dose aspirin versus placebo or no treatment were included. The outcomes of interest were severe pre-eclampsia and mild pre-eclampsia. Pooled relative risks with their 95% confidence intervals (CIs) were calculated.

**Results**
Among 7941 citations retrieved, 352 were completely reviewed and four studies (392 women) fulfilled the inclusion criteria and were analyzed.

When compared with controls, aspirin started at ≤16 weeks was associated with a significant reduction in severe (relative risk: 0.22, 95% CI: 0.08 to 0.57) but not mild (relative risk: 0.81, 95% CI: 0.33 to 1.96) pre-eclampsia.

**KEY FACTS**
Low-dose aspirin initiated at or before 16 weeks reduces the risk of severe pre-eclampsia, but not mild pre-eclampsia.
### Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADAM12</td>
<td>A disintegrin and metalloprotease 12</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DR</td>
<td>Detection rate</td>
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<tr>
<td>FPR</td>
<td>False-positive rate</td>
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<tr>
<td>GA</td>
<td>Gestational age</td>
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<tr>
<td>GH</td>
<td>Gestational hypertension</td>
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<tr>
<td>IUGR</td>
<td>Intrauterine growth restriction</td>
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<tr>
<td>LR</td>
<td>Likelihood ratio</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MoM</td>
<td>Multiple of the median</td>
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<tr>
<td>PAPP-A</td>
<td>Pregnancy-associated plasma protein A</td>
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<tr>
<td>PE</td>
<td>Pre-eclampsia</td>
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<tr>
<td>PI</td>
<td>Pulsatility index</td>
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<tr>
<td>PIGF/PGF</td>
<td>Placental growth factor</td>
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<tr>
<td>PP13</td>
<td>Placental protein 13</td>
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<tr>
<td>PTB</td>
<td>Preterm birth</td>
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<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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<tr>
<td>sFlt-1</td>
<td>Soluble fms-like tyrosine kinase</td>
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<tr>
<td>UAPI/UADPI/UtAPI</td>
<td>Uterine artery (Doppler) pulsatility index</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>β-hCG</td>
<td>Human chorionic gonadotropin</td>
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Automated immunofluorescent assay for the quantitative determination of human Placental Growth Factor (PIGF) in human serum
- Excellent precision
- Very low detection limit: 3.6 pg/mL
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► Reliable detection of clinical values throughout pregnancy

Clinical Interest

Screening for pre-eclampsia in first trimester of pregnancy in conjunction with other biological and clinical data to assess the risk of developing pre-eclampsia.

Screening for fetal chromosomal abnormalities in first trimester in conjunction with other biological and clinical findings for assessing the risk of fetal trisomy 21.

Aid in diagnosis and short-term prognosis of pre-eclampsia together with B·R·A·H·M·S sFlt-1 KRYPTOR and additional clinical data in pregnant women with suspicious pre-eclampsia

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<tr>
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