BIBLIO

1 2 3 4 5 6 7 8 9

Pre-eclampsia screening (1ˢᵗ Trim.)

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

Thermo Fisher
SCIENTIFIC

Content

3. Prevention with low-dose aspirin

Placental Growth Factor (PlGF) in first trimester pre-eclampsia screening

Pre-eclampsia is a leading cause of maternal morbidity and mortality. First trimester combined screening including Placental Growth Factor (PlGF) allows early detection of women at high risk for preterm pre-eclampsia and offers the possibility of prevention before first clinical symptoms such as hypertension and proteinuria are seen.

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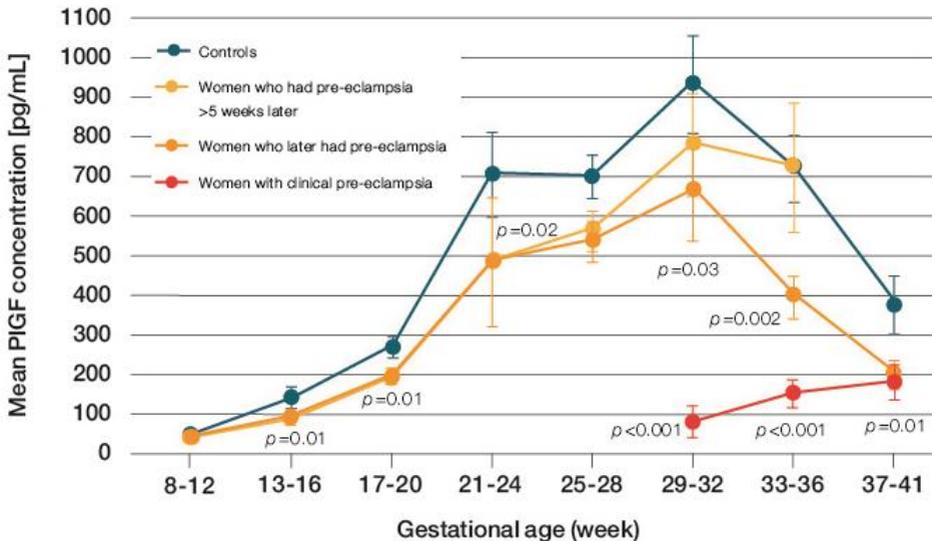
Figure Mean PlGF concentrations of healthy women and those women who later developed pre-eclampsia

According to latest FIGO guidelines all pregnant women should be screened for preterm PE during early pregnancy by the first-trimester combined test with maternal risk factors and biomarkers.

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

1. Guidelines

The FIGO initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention

Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, McAuliffe F et al.

Abstract

Pre-eclampsia (PE) is a multisystem disorder that typically affects 2%–5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early onset. Globally, 76 000 women and 500 000 babies die each year from this disorder. Furthermore, women in low-resource countries are at a higher risk of developing PE compared with those in high-resource countries. Although a complete understanding of the pathogenesis of PE remains unclear, the current theory suggests a two-stage process. The first stage is caused by shallow invasion of the trophoblast, resulting in inadequate remodeling of the spiral arteries. This is presumed to lead to the second stage, which involves the maternal response to endothelial dysfunction and imbalance between angiogenic and antiangiogenic factors, resulting in the clinical features of the disorder.
Accurate prediction and uniform prevention continue to elude us. The quest to effectively predict PE in the first trimester of pregnancy is fueled by the desire to identify women who are at high risk of developing PE, so that necessary measures can be initiated early enough to improve placentation and thus prevent or at least reduce the frequency of its occurrence. Furthermore, identification of an "at risk" group will allow tailored prenatal surveillance to anticipate and recognize the onset of the clinical syndrome and manage it promptly.

PE has been previously defined as the onset of hypertension accompanied by significant proteinuria after 20 weeks of gestation. Recently, the definition of PE has been broadened. Now the internationally agreed definition of PE is the one proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP). According to the ISSHP, PE is defined as systolic blood pressure at ≥140 mm Hg and/or diastolic blood pressure at ≥90 mm Hg on at least two occasions measured 4 hours apart in previously normotensive women and is accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation:

1. **Proteinuria** (i.e. ≥30 mg/mol protein:creatinine ratio; ≥300 mg/24 hour; or ≥2 + dipstick);
2. **Evidence of other maternal organ dysfunction**, including: acute kidney injury (creatinine ≥90 μmol/L; 1 mg/dL); liver involvement (elevated transaminases, e.g. alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain; neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); or hematological complications (thrombo-cytopenia–platelet count <150 000/μL, disseminated intravascular coagulation, hemolysis); or

3. **Uteroplacental dysfunction** (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth). It is well established that a number of maternal risk factors are associated with the development of PE: advanced maternal age; nulliparity; previous history of PE; short and long interpregnancy interval; use of assisted reproductive technologies; family history of PE; obesity; Afro-Caribbean and South Asian racial origin; co-morbid medical conditions including hyperglycemia in pregnancy; pre-existing chronic hypertension; renal disease; and autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid syndrome.

These risk factors have been described by various professional organizations for the identification of women at risk of PE; however, this approach to screening is inadequate for effective prediction of PE.

PE can be subclassified into:
1. **Early-onset PE** (with delivery at <34+0 weeks of gestation);
2. **Preterm PE** (with delivery at <37+0 weeks of gestation);
3. **Late-onset PE** (with delivery at ≥34+0 weeks of gestation);
4. **Term PE** (with delivery at ≥37+0 weeks of gestation).

These subclassifications are not mutually exclusive. Early-onset PE is associated with a much higher risk of short- and long-term maternal and perinatal morbidity and mortality. Obstetricians managing women with preterm PE are faced with the challenge of balancing the need to achieve fetal maturation in utero with the risks to the mother and fetus of continuing the pregnancy longer. These risks include progression to eclampsia, development of placental abruption and HELLP (hemolysis, elevated liver enzyme, low platelet) syndrome. On the other hand, preterm delivery is associated with higher infant mortality rates and increased morbidity resulting from small for gestational age (SGA), thrombocytopenia, bronchopulmonary dysplasia, cerebral palsy, and an increased risk of various chronic diseases in adult life, particularly type 2 diabetes, cardiovascular disease, and obesity. Women who have experienced PE may also face additional health problems in later life, as the condition is associated with an increased risk of death from future cardiovascular disease, hypertension, stroke, renal impairment, metabolic syndrome, and diabetes. The life expectancy of women who developed preterm PE is reduced on average by 10 years. There is also significant impact on the infants in the long term, such as increased risks of insulin resistance, diabetes mellitus, coronary artery disease, and hypertension in infants born to pre-eclamptic women.

The International Federation of Gynecology and Obstetrics (FIGO) brought together international experts to discuss and evaluate current knowledge on PE and develop a document to frame the issues and suggest key actions to address the health burden posed by PE. FIGO's objectives, as outlined in this document, are: (1) To raise awareness of the links between PE and poor maternal and perinatal outcomes, as well as to the future health risks to mother and offspring, and demand a clearly defined global health agenda to tackle this issue; and (2) To create a consensus document that provides guidance for the first-trimester screening and prevention of preterm PE, and to disseminate and encourage its use. Based on high-quality evidence, the document outlines current global standards for the first-trimester screening and prevention of

preterm PE, which is in line with FIGO good clinical practice advice on first trimester screening and prevention of pre-eclampsia in singleton pregnancy.

It provides both the best and the most pragmatic recommendations according to the level of acceptability, feasibility, and ease of implementation that have the potential to produce the most significant impact in different resource settings. Suggestions are provided for a variety of different regional and resource settings based on their financial, human, and infrastructure resources, as well as for research priorities to bridge the current knowledge and evidence gap. To deal with the issue of PE, FIGO recommends the following:

- **Public health focus:** There should be greater international attention given to PE and to the links between maternal health and noncommunicable diseases (NCDs) on the Sustainable Developmental Goals agenda. Public health measures to increase awareness, access, affordability, and acceptance of preconception counselling, and prenatal and postnatal services for women of reproductive age should be prioritized. Greater efforts are required to raise awareness of the benefits of early prenatal visits targeted at reproductive-aged women, particularly in low-resource countries.

- **Universal screening:** All pregnant women should be screened for preterm PE during early pregnancy by the first-trimester combined test with maternal risk factors and biomarkers as a one-step procedure. The risk calculator is available free of charge at https://fetalmedicine.org/research/assess/preeclampsia. FIGO encourages all countries and its member associations to adopt and promote strategies to ensure this. The best combined test is one that includes maternal risk factors, measurements of mean arterial pressure (MAP), serum placental growth factor (PLGF), and uterine artery pulsatility index (UTPI). Where it is not possible to measure PLGF and/or UTPI, the baseline screening test should be a combination of maternal risk factors with MAP, and not maternal risk factors alone. If maternal serum pregnancy-associated plasma protein A (PAPP-A) is measured for routine first-trimester screening for fetal aneuploidies, the result can be included for PE risk assessment. Variations to the full combined test would lead to a reduction in the performance screening. A woman is considered high risk when the risk is 1 in 100 or more based on the first-trimester combined test with maternal risk factors, MAP, PLGF, and UTPI.

- **Contingent screening:** Where resources are limited, routine screening for preterm PE by maternal factors and MAP in all pregnancies and reserving measurements of PLGF and UTPI for a subgroup of the population (selected on the basis of the risk derived from screening by maternal factors and MAP) can be considered. Prophylactic measures: Following first-trimester screening for preterm PE, women identified at high risk should receive aspirin prophylaxis commencing at 11–14+6 weeks of gestation at a dose of ~150 mg to be taken every night until 36 weeks of gestation, when delivery occurs, or when PE is diagnosed. Low-dose aspirin should not be prescribed to all pregnant women. In women with low calcium intake (<800 mg/d), either calcium replacement (≤1 g elemental calcium/d) or calcium supplementation (1.5–2 g elemental calcium/d) may reduce the burden of both early- and late-onset PE.

Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice

Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP et al.

Abstract

These recommendations from the International Society for the Study of Hypertension in Pregnancy (ISSHP) are based on available literature and expert opinion. It is intended that this be a living document, to be updated when needed as more research becomes available to influence good clinical practice. Unfortunately, there is a relative lack of high-quality randomized trials in the field of hypertension in pregnancy compared with studies in essential hypertension outside of pregnancy, and ISSHP encourages greater funding and uptake of collaborative research in this field. Accordingly, the quality of evidence for the recommendations in this document has not been graded although relevant references and explanations are provided for each recommendation. The document will be a living guideline, and we hope to be able to grade recommendations in the future.

Guidelines and recommendations for management of hypertension in pregnancy are typically written for implementation in an ideal setting. It is acknowledged that in many parts of the world, it will not be possible to adopt all of these recommendations; for this reason, options for management in less-resourced settings are discussed separately in relation to diagnosis, evaluation, and treatment.

ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia

Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A et al.

Abstract

Hypertensive disease of pregnancy affects up to 10% of pregnant women and the pooled global incidence of pre-eclampsia (PE) is approximately 3%. Significant variations between developed and developing countries can be attributed to true differences or differences arising from data acquisition. PE and its complications are a major contributor to maternal and perinatal morbidity and mortality worldwide. Given that timely and effective care can improve the outcome of PE, the development of effective prediction and prevention strategies has been a major objective of prenatal care and of research.

PE is a multisystemic disease of multifactorial origin: it involves defective placentation, oxidative stress, autoimmunity, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction, an imbalance in angiogenesis and maternal cardiac maladaptation. Defective placental invasion is associated strongly with most cases of early and severe PE. In contrast, defective placentation seems to be less important for the development of PE that manifests later in pregnancy, for example after 34 weeks. Compared with pregnancies affected by early-onset disease, in those complicated with PE at or near term, placentae have a significantly lower frequency of histological abnormalities, and maternal factors (e.g. metabolic syndrome or chronic hypertension) have a relatively greater significance. Differences between early- and late-onset PE are also seen in risk factors, maternal vascular responsiveness, screening performance and prevention effectiveness.

Increasing insight into the pathophysiology of PE is reflected in current screening strategies, which are based on history, demographics, biomarkers (including blood pressure) and uterine artery Doppler.

There are currently more than 10 000 PubMed-indexed articles related to PE screening, illustrating the vast interest in this topic. Fewer than one-fifth of these deal with early screening, this being a development of the last decade. The aim of these Guidelines is to review the latest evidence and, when possible, provide evidence-based recommendations regarding the role of ultrasound in screening and follow-up of PE. The Guidelines focus on the technical/clinical aspects of screening, without extending to health economics and policy issues including the advisability and cost-effectiveness of screening. Moreover, these Guidelines were developed with the assumption that the resources required for implementation of screening and follow-up (equipment, examiners, expertise) are available. The steps and procedures described in these Guidelines are not intended to act as a legal standard for clinical service.

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C et al.

Abstract

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.
A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated. Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

2. 1st trimester pre-eclampsia screening

Prenatal screening for pre-eclampsia: Frequently asked questions

Wertaschnigg D, Reddy M, Mol BWJ, Rolnik DL, da Silva Costa F

Abstract
The current approach to screening for pre-eclampsia is based on guidelines that rely on medical and obstetric history in early pregnancy to select a high-risk group that might benefit from low-dose aspirin. However, combined screening tests with the addition of biophysical and biochemical measurements have shown significantly better detection rates for preterm pre-eclampsia. Furthermore, the administration of aspirin for the 10% screen-positive group can lead to a significant reduction in severe and preterm forms of pre-eclampsia. This review aims to answer frequently asked questions related to the clinical implementation of screening and the management of screening results.

Predictive performance of the competing risk model in screening for preeclampsia

Wright D, Tan MY, O'Gorman N, Poon LC, Syngelaki A, Wright A, Nicolaides KH

Background

The established method of screening for preeclampsia is to identify risk factors from maternal demographic characteristics and medical history; in the presence of such factors the patient is classified as high risk and in their absence as low risk. However, the performance of such an approach is poor. We developed a competing risks model, which allows combination of maternal factors (age, weight, height, race, parity, personal and family history of preeclampsia, chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, method of conception and interpregnancy interval), with biomarkers to estimate the individual patient-specific risks of preeclampsia requiring delivery before any specified gestation. The performance of this approach is by far superior to that of the risk scoring systems.

Objective

The objective of the study was to examine the predictive performance of the competing risks model in screening for preeclampsia by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor, referred to as the triple test, in a training data set for the development of the model and 2 validation studies.

Study design

The data for this study were derived from 3 previously reported prospective, nonintervention, multicenter screening studies for preeclampsia in singleton pregnancies at 11+0 to 13+6 weeks' gestation. In all 3 studies, there was recording of maternal factors and biomarkers and ascertainment of outcome by appropriately trained personnel. The first study of 35,948 women, which was carried out between February 2010 and July 2014, was used to develop the competing risks model for prediction of preeclampsia and is therefore considered to be the training set. The 2 validation studies were comprised of 8775 and 16,451 women, respectively, and they were carried out between February and September 2015 and between April and December 2016, respectively. Patient-specific risks of delivery with preeclampsia at <34, <37, and <41+3 weeks' gestation were calculated using the competing risks model and the performance of screening for preeclampsia by maternal factors alone and the triple test in each of the 3 data sets was assessed. We examined the predictive performance of the model by first, the ability of the model to discriminate between the preeclampsia and no-preeclampsia groups using the area under the receiver operating characteristic curve and the detection rate at fixed screen-positive rate of 10%, and second, calibration by measurements of calibration slope and calibration in the large.

Results

The detection rate at the screen-positive rate of 10% of early-preeclampsia, preterm-preeclampsia, and all-preeclampsia was about 90%, 75%, and 50%, respectively, and the results were consistent between the training and 2 validation data sets. The area under the receiver operating characteristic curve was >0.95, >0.90, and >0.80, respectively, demonstrating a very high discrimination between affected and unaffected pregnancies. Similarly, the calibration slopes were very close to 1.0, demonstrating a good agreement between the predicted risks and observed incidence of preeclampsia. In the prediction of early-preeclampsia and preterm-preeclampsia, the observed incidence in the training set and 1 of the validation data sets was consistent with the predicted one. In the other validation data set, which was specifically designed for evaluation of the model, the incidence was higher than predicted, presumably because of better ascertainment of outcome. The incidence of all-preeclampsia was lower than predicted in all 3 data sets because at term many pregnancies deliver for reasons other than preeclampsia, and therefore, pregnancies considered to be at high risk for preeclampsia that deliver for other reasons before they develop preeclampsia can be wrongly considered to be false positives.

KEY FACTS

The competing risks model provides an effective and reproducible method for first-trimester prediction of early preeclampsia and preterm preeclampsia as long as the various components of screening are carried out by appropriately trained and audited practitioners. Early prediction of preterm preeclampsia is beneficial because treatment of the high-risk group with aspirin is highly effective in the prevention of the disease.

Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation

Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL et al.

Objective

To examine the performance of screening for early, preterm and term pre-eclampsia (PE) at 11-13 weeks' gestation by maternal factors and combinations of mean arterial pressure (MAP), uterine artery (UtA) pulsatility index (PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A).

Methods

The data for this study were derived from three previously reported prospective non-intervention screening studies at 11 + 0 to 13 + 6 weeks' gestation in a combined total of 61 174 singleton pregnancies, including 1770 (2.9%) that developed PE. Bayes' theorem was used to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics, with various combinations of biomarker multiples of the median (MoM) values to derive patient-specific risks of delivery with PE at < 37 weeks' gestation. The performance of such screening was estimated.

Results

In pregnancies that developed PE, compared to those without PE, the MoM values of UtA-PI and MAP were increased and those of PAPP-A and PlGF were decreased, and the deviation from normal was greater for early than late PE for all four biomarkers. Combined screening by maternal factors, UtA-PI, MAP and PlGF predicted 90% of early PE, 75% of preterm PE and 41% of term PE, at a screen-positive rate of 10%; inclusion of PAPP-A did not improve the performance of screening. The performance of screening depended on the racial origin of the women; on screening by a combination of maternal factors, MAP, UtA-PI and PlGF and using a risk cut-off of 1 in 100 for PE at < 37 weeks in Caucasian women, the screen-positive rate was 10% and detection rates for early, preterm and term PE were 88%, 69% and 40%, respectively. With the same method of screening and risk cut-off in women of Afro-Caribbean racial origin, the screen-positive rate was 34% and detection rates for early, preterm and term PE were 100%, 92% and 75%, respectively.

KEY FACTS

Screening by maternal factors and biomarkers at 11-13 weeks' gestation can identify a high proportion of pregnancies that develop early and preterm PE.

The first-trimester of pregnancy - A window of opportunity for prediction and prevention of pregnancy complications and future life

Poon LC, McIntyre HD, Hyett JA, da Fonseca EB, Hod M; FIGO Pregnancy and NCD Committee

Abstract

The International Federation of Gynecology and Obstetrics (FIGO) has identified non communicable maternal diseases (NCDs) as a new focus area. NCDs and exposures as related to pregnancy complications and later impairment of maternal and offspring health will form the basis for action in the forthcoming years.

This paper summarizes recent advances, centered on the use of first-trimester testing, as a window of opportunity to predict and prevent many pregnancy complications; and for potential future prevention of NCDs in mother and offspring.

Recent results from a large-scale randomized control trial have provided definitive proof that effective screening for preterm preeclampsia (preterm-PE), requiring delivery before 37 weeks' gestation, can be achieved with a combined test of maternal factors and biomarkers at 11-13 weeks and that aspirin, given to high-risk women, is effective in reducing the risk of preterm-PE and the length of stay in neonatal intensive care unit. This is the first successful example to illustrate that pregnancy complications is predictable and preventable in early pregnancy.

Similar prediction and prevention strategies are being developed for hyperglycemia in pregnancy and preterm birth, with the intention for longer lasting interventions leading to significant downstream impact in improving long-term health in both mothers and babies.

Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE

Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, Singh M et al.

Objective

To test the hypothesis that the performance of first-trimester screening for pre-eclampsia (PE) by a method that uses Bayes' theorem to combine maternal factors with biomarkers is superior to that defined by current National Institute for Health and Care Excellence (NICE) guidelines.

Methods

This was a prospective multicenter study (screening program for pre-eclampsia (SPREE)) in seven National Health Service maternity hospitals in England, of women recruited between April and December 2016. Singleton pregnancies at 11-13 weeks' gestation had recording of maternal characteristics and medical history and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A). The performance of screening for PE by the Bayes' theorem-based method was compared with that of the NICE method. Primary comparison was detection rate (DR) using NICE method vs mini-combined test (maternal factors, MAP and PAPP-A) in the prediction of PE at any gestational age (all-PE) for the same screen-positive rate determined by the NICE method. Key secondary comparisons were DR of screening recommended by the NICE guidelines vs three Bayes' theorem-based methods (maternal factors, MAP and PAPP-A; maternal factors, MAP and PlGF; and maternal factors, MAP, UtA-PI and PlGF) in the prediction of preterm PE, defined as that requiring delivery < 37 weeks.

Results

All-PE developed in 473 (2.8%) of the 16 747 pregnancies and preterm PE developed in 142 (0.8%). The screen-positive rate by the NICE method was 10.3% and the DR for all-PE was 30.4% and for preterm PE it was 40.8%. Compliance with the NICE recommendation that women at high risk for PE should be treated with aspirin from the first trimester to the end of pregnancy was only 23%. The DR of the mini-combined test for all-PE was 42.5%, which was superior to that of the NICE method by 12.1% (95% CI, 7.9-16.2%). In screening for preterm PE by a combination of maternal factors, MAP and PlGF, the DR was 69.0%, which was superior to that of the NICE method by 28.2% (95% CI, 19.4-37.0%) and with the addition of UtA-PI the DR was 82.4%, which was higher than that of the NICE method by 41.6% (95% CI, 33.2-49.9%).

> **KEY FACTS**
>
> **The performance of screening for PE as currently recommended by NICE guidelines is poor and compliance with these guidelines is low. The performance of screening is substantially improved by a method combining maternal factors with biomarkers.**

ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm

Poon LC, Rolnik DL, Tan MY, Delgado JL, Tsokaki T, Akolekar R, Singh M et al.

Objective

To report the incidence of preterm pre-eclampsia (PE) in women who are screen positive according to the criteria of the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG), and compare the incidence with that in those who are screen positive or screen negative by The Fetal Medicine Foundation (FMF) algorithm.

Methods

This was a secondary analysis of data from the ASPRE study. The study population consisted of women with singleton pregnancy who underwent prospective screening for preterm PE by means of the FMF algorithm, which combines maternal factors and biomarkers at 11-13 weeks' gestation. The incidence of preterm PE in women fulfilling the NICE and ACOG criteria was estimated; in these patients the incidence of preterm PE was then calculated in those who were screen negative relative to those who were screen positive by the FMF algorithm.

Results

A total of 34 573 women with singleton pregnancy delivering at ≥ 24 weeks' gestation underwent prospective screening for preterm PE, of which 239 (0.7%) cases developed preterm PE. At least one of the ACOG criteria was fulfilled in 22 287 (64.5%) pregnancies and the incidence of preterm PE was 0.97% (95% CI, 0.85-1.11%); in the subgroup that was screen positive by the FMF algorithm the incidence of preterm PE was 4.80% (95% CI, 4.14-5.55%), and in those that were screen negative it was 0.25% (95% CI, 0.18-0.33%), with a relative incidence in FMF screen negative to FMF screen positive of 0.051 (95% CI, 0.037-0.071). In 1392 (4.0%) pregnancies, at least one of the NICE high-risk criteria was fulfilled, and in this group the incidence of preterm PE was 5.17% (95% CI, 4.13-6.46%); in the subgroups of screen positive and screen negative by the FMF algorithm, the incidence of preterm PE was 8.71% (95% CI, 6.93-10.89%) and 0.65% (95% CI, 0.25-1.67%), respectively, and the relative incidence was 0.075 (95% CI, 0.028-0.205). In 2360 (6.8%) pregnancies fulfilling at least two of the NICE moderate-risk criteria, the incidence of preterm PE was 1.74% (95% CI, 1.28-2.35%); in the subgroups of screen positive and screen negative by the FMF algorithm the incidence was 4.91% (95% CI, 3.54-6.79%) and 0.42% (95% CI, 0.20-0.86%), respectively, and the relative incidence was 0.085 (95% CI, 0.038-0.192).

KEY FACTS

In women who are screen positive for preterm PE by the ACOG or NICE criteria but screen negative by the FMF algorithm, the risk of preterm PE is reduced to within or below background levels. The results provide further evidence to support the personalized risk-based screening method that combines maternal factors and biomarkers.

First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume

Sonek J, Krantz D, Carmichael J, Downing C, Jessup K, Haidar Z, Ho S et al.

Background

Preeclampsia is a major cause of perinatal morbidity and mortality. First-trimester screening has been shown to be effective in selecting patients at an increased risk for preeclampsia in some studies.

Objective

We sought to evaluate the feasibility of screening for preeclampsia in the first trimester based on maternal characteristics, medical history, biomarkers, and placental volume.

Study design

This is a prospective observational nonintervention cohort study in an unselected US population. Patients who presented for an ultrasound examination between 11-13+6 weeks' gestation were included. The following parameters were assessed and were used to calculate the risk of preeclampsia: maternal characteristics (demographic, anthropometric, and medical history), maternal biomarkers (mean arterial pressure, uterine artery pulsatility index, placental growth factor, pregnancy-associated plasma protein A, and maternal serum alpha-fetoprotein), and estimated placental volume. After delivery, medical records were searched for the diagnosis of preeclampsia. Detection rates for early-onset preeclampsia (<34 weeks' gestation) and later-onset preeclampsia (≥34 weeks' gestation) for 5% and 10% false-positive rates using various combinations of markers were calculated.

Results

We screened 1288 patients of whom 1068 (82.99%) were available for analysis. In all, 46 (4.3%) developed preeclampsia, with 13 (1.22%) having early-onset preeclampsia and 33 (3.09%) having late-onset preeclampsia. Using maternal characteristics, serum biomarkers, and uterine artery pulsatility index, the detection rate of early-onset preeclampsia for either 5% or 10% false-positive rate was 85%. With the same protocol, the detection rates for preeclampsia with delivery <37 weeks were 52% and 60% for 5% and 10% false-positive rates, respectively. Based on maternal characteristics, the detection rates for late-onset preeclampsia were 15% and 48% for 5% and 10%, while for preeclampsia at ≥37 weeks' gestation the detection rates were 24% and 43%, respectively. The detection rates for late-onset preeclampsia and preeclampsia with delivery at >37 weeks' gestation were not improved by the addition of biomarkers.

> **KEY FACTS**
>
> **Screening for preeclampsia at 11-13+6 weeks' gestation using maternal characteristics and biomarkers is associated with a high detection rate for a low false-positive rate. Screening for late-onset preeclampsia yields a much poorer performance. In this study the utility of estimated placental volume and mean arterial pressure was limited but larger studies are needed to ultimately determine the effectiveness of these markers.**

First trimester combined screening for preeclampsia and small for gestational age - a single centre experience and validation of the FMF screening algorithm

Mosimann B, Pfiffner C, Amylidi-Mohr S, Risch L, Surbek D, Raio L

Aim of the study

Preeclampsia (PE) is associated with severe maternal and fetal morbidity in the acute presentation and there is increasing evidence that it is also an important risk factor for cardiovascular disease later in life. Therefore, preventive strategies are of utmost importance. The Fetal Medicine Foundation (FMF) London recently developed a first trimester screening algorithm for placenta-related pregnancy complications, in particular early onset preeclampsia (eoPE) requiring delivery before 34 weeks, and preterm small for gestational age (pSGA), with a birth weight <5th percentile and delivery before 37 weeks of gestation, based on maternal history and characteristics, and biochemical and biophysical parameters. The aim of this study was to test the performance of this algorithm in our setting and to perform an external validation of the screening algorithm.

Material and methods

Between September 2013 and April 2016, all consecutive women with singleton pregnancies who agreed to this screening were included in the study. The proposed cut-offs of ≥1:200 for eoPE, and ≥1:150 for pSGA were applied. Risk calculations were performed with Viewpoint® program (GE, Mountainview, CA, USA) and statistical analysis with GraphPad version 5.0 for Windows.

Results

1372 women agreed to PE screening; the 1129 with complete data and a live birth were included in this study. Nineteen (1.68%) developed PE: 14 (1.24%) at term (tPE) and 5 (0.44%) preterm (pPE, <37 weeks), including 2 (0.18%) with eoPE. Overall, 97/1129 (8.6%) screened positive for eoPE, including both pregnancies that resulted in eoPE and 4/5 (80%) that resulted in pPE. Forty-nine of 1110 (4.41%) pregnancies without PE resulted in SGA, 3 (0.27%) of them in pSGA. A total of 210/1110 (18.9%) non-PE pregnancies screened positive for pSGA, including 2/3 (66.7%) of the pSGA deliveries and 18/46 (39.1%) of term SGA infants.

KEY FACTS

Our results show that first trimester PE screening in our population performs well and according to expectations, whereas screening for SGA is associated with a high false positive rate.

First-Trimester Combined Multimarker Prospective Study for the Detection of Pregnancies at a High Risk of Developing Preeclampsia Using the Fetal Medicine Foundation-Algorithm

Guizani M, Valsamis J, Dutemeyer V, Kang X, Ceccotti V, Khalife J, Duiella SF et al.

Objective

To evaluate the Fetal Medicine Foundation (FMF) algorithm prospectively at 11-13 weeks' gestation in the prediction of preeclampsia (PE).

Methods

Single-center prospective screening study for PE of singleton pregnancies at 11-13 weeks. The FMF algorithm takes into account maternal characteristics and biomarkers. Detection rate (DR) for a 10% false-positive rate (FPR) for delivery with preterm and term PE was estimated.

Results

Between January 2011 and December 2013, of 3,239 patients available for final analysis, 36 (1.1%) subsequently developed preterm and 44 (1.4%) term PE. In combined screening by maternal factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor, the DR was 80.6% (95% CI 64.0-91.8) for PE at <37 weeks and 31.8% (95% CI 18.6-47.6) for PE at ≥37 weeks, at a 10% FPR.

KEY FACTS

Our data suggest that the FMF algorithm provides effective first-trimester screening for preterm PE.

Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11-13 weeks' gestation

Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH

Objective

To develop a model for screening for pre-eclampsia (PE) in twin pregnancies based on maternal demographic characteristics and medical history and biomarkers at 11-13 weeks' gestation.

Methods

This was a screening study in twin pregnancies at 11-13 weeks' gestation. Bayes theorem was used to combine the a-priori risk from maternal factors with various combinations of uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) multiples of the median (MoM) values. The performance of screening for PE requiring delivery at < 32, < 37 and < 42 weeks' gestation was estimated in 1100 twin pregnancies and 35 948 singleton pregnancies with complete data on UtA-PI, MAP, PlGF and PAPP-A.

Results

In twin pregnancies that developed PE, the values of MAP and UtA-PI were increased and the values of PlGF and PAPP-A were decreased. The distributions of log10 MoM values of biomarkers with gestational age at delivery were similar to those that were previously reported in singleton pregnancies and it was therefore assumed that the same model could be used for both singleton and twin pregnancies.

The performance of screening for PE by maternal factors was improved by the addition of MAP, UtA-PI and PlGF; there was no further improvement with the addition of PAPP-A. In a mixed population of singleton and twin pregnancies, combined screening by maternal factors, MAP, UtA-PI and PlGF and risk cut-off of 1 in 75 for PE at < 37 weeks, the detection rate of PE at < 32, < 37 and < 42 weeks in singleton pregnancies was 91%, 77% and 57%, respectively, at a screen-positive rate (SPR) of 13%; the respective rates for twin pregnancies were 100%, 99% and 97%, at a SPR of 75%.

KEY FACTS

First-trimester combined screening for PE in singleton pregnancies can be adapted for screening in twins, leading to detection of nearly all affected cases but at a high SPR.

Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations

O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M et al.

Objective

To compare the performance of screening for pre-eclampsia (PE) based on risk factors from medical history, as recommended by NICE and ACOG, with the method proposed by The Fetal Medicine Foundation (FMF), which uses Bayes' theorem to combine the a-priori risk from maternal factors, derived by a multivariable logistic model, with the results of various combinations of biophysical and biochemical measurements.

Methods

This was a prospective multicenter study of screening for PE in 8775 singleton pregnancies at 11-13 weeks' gestation. A previously published FMF algorithm was used for the calculation of patient-specific risk of PE in each individual. The detection rates (DRs) and false-positive rates (FPRs) for delivery with PE < 32, < 37 and ≥ 37 weeks were estimated and compared with those derived from application of NICE guidelines and ACOG recommendations. According to NICE, all high-risk pregnancies should be offered low-dose aspirin. According to ACOG, use of aspirin should be reserved for women with a history of PE in at least two previous pregnancies or PE requiring delivery < 34 weeks' gestation.

Results

In the study population, 239 (2.7%) cases developed PE, of which 17 (0.2%), 59 (0.7%) and 180 (2.1%) developed PE < 32, < 37 and ≥ 37 weeks, respectively. Screening with use of the FMF algorithm based on a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PIGF) detected 100% (95% CI, 80-100%) of PE < 32 weeks, 75% (95% CI, 62-85%) of PE < 37 weeks and 43% (95% CI, 35-50%) of PE ≥ 37 weeks, at a 10.0% FPR. Screening with use of NICE guidelines detected 41% (95% CI, 18-67%) of PE < 32 weeks, 39% (95% CI, 27-53%) of PE < 37 weeks and 34% (95% CI, 27-41%) of PE ≥ 37 weeks, at 10.2% FPR. Screening with use of ACOG recommendations detected 94% (95% CI, 71-100%) of PE < 32 weeks, 90% (95% CI, 79-96%) of PE < 37 weeks and 89% (95% CI, 84-94%) of PE ≥ 37 weeks, at 64.2% FPR. Screening based on the ACOG recommendations for use of aspirin detected 6% (95% CI, 1-27%) of PE < 32 weeks, 5% (95% CI, 2-14%) of PE < 37 weeks and 2% (95% CI, 0.3-5%) of PE ≥ 37 weeks, at 0.2% FPR.

KEY FACTS

Performance of screening for PE at 11-13 weeks' gestation by the FMF algorithm using a combination of maternal factors, MAP, UtA-PI and PIGF, is by far superior to the methods recommended by NICE and ACOG.

Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation

O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, Akolekar R et al.

Objective

To examine the diagnostic accuracy of a previously developed model for prediction of pre-eclampsia (PE) by a combination of maternal factors and biomarkers at 11-13 weeks' gestation.

Methods

This was a prospective first-trimester multicenter study of screening for PE in 8775 singleton pregnancies. A previously published algorithm was used for the calculation of patient-specific risk of PE in each individual. The detection rates (DRs) and false-positive rates (FPRs) for delivery with PE < 32, < 37 and ≥ 37 weeks were estimated and compared with those for the dataset used for development of the algorithm.

Results

In the study population, 239 (2.7%) cases developed PE, of which 17 (0.2%), 59 (0.7%) and 180 (2.1%) developed PE < 32, < 37 and ≥ 37 weeks, respectively. With combined screening by maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor, the DR was 100% (95% CI, 80-100%) for PE < 32 weeks, 75% (95% CI, 62-85%) for PE < 37 weeks and 43% (95% CI, 35-50%) for PE ≥ 37 weeks, at a 10% FPR. These DRs were similar to the estimated rates for the dataset used for development of the model: 89% (95% CI, 79-96%) for PE < 32 weeks, 75% (95% CI, 70-80%) for PE < 37 weeks and 47% (95% CI, 44-51%) for PE ≥ 37 weeks.

KEY FACTS

Assessment of a combination of maternal factors and biomarkers at 11-13 weeks provides effective first-trimester screening for preterm PE.

Validation of a first-trimester screening model for pre-eclampsia in an unselected population

Scazzocchio E, Crovetto F, Triunfo S, Gratacós E, Figueras F

Objective

To validate the performance of a previously constructed first-trimester predictive model for pre-eclampsia (PE) in routine care of an unselected population.

Methods

A validation cohort of 4621 consecutive women attending their routine first-trimester ultrasound examination was used to test a prediction model for PE that had been developed previously in 5170 women. The prediction model included maternal factors, uterine artery Doppler, blood pressure and pregnancy-associated plasma protein-A. Model performance was evaluated using receiver-operating characteristics (ROC) curve analysis and ROC curves from both cohorts were compared unpaired.

Results

Among the 4203 women included in the final analysis, 169 (4.0%) developed PE, including 141 (3.4%) cases of late-onset PE and 28 (0.7%) cases of early-onset PE. For early-onset PE, the model showed an area under the ROC curve of 0.94 (95% CI, 0.88-0.99), which did not differ significantly ($P = 0.37$) from that obtained in the construction cohort (0.88 (95% CI, 0.78-0.99)). For late-onset PE, the final model showed an area under the ROC curve of 0.72 (95% CI, 0.66-0.77), which did not differ significantly ($P = 0.49$) from that obtained in the construction cohort (0.75 (95% CI, 0.67-0.82)).

KEY FACTS

The prediction model for PE achieved a similar performance to that obtained in the construction cohort when tested on a subsequent cohort of women, confirming its validity as a predictive model for PE.

The use of ultrasound and other markers for early detection of preeclampsia

O'Gorman N, Nicolaides KH, Poon LC

Abstract

Preeclampsia (PE) is a multisystem disorder of pregnancy classically characterized with the onset of hypertension after 20 weeks gestation in the presence of proteinuria. PE typically affects 2-8% of pregnancies and is a leading cause of maternal and perinatal morbidity and mortality.

This article reviews the most effective biomarkers used in first trimester screening for PE. It explores their use both in isolation and as part of an algorithm to yield the best detection rates. Screening by a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum PAPP-A and PlGF can identify about 75% of cases of preterm PE for a false-positive rate of 10%.

By identifying these patients at high risk for PE, appropriately tailored antenatal surveillance can be instigated and prophylactic pharmacological interventions can be prescribed to improve placentation and ultimately, the outcome for both the mother and fetus.

Contingent screening for preterm pre-eclampsia

Wright D, Gallo DM, Gil Pugliese S, Casanova C, Nicolaides KH

Objective

Effective screening for pre-eclampsia resulting in delivery < 37 weeks' gestation (preterm PE) is provided by assessment of a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) at 11-13 or 19-24 weeks' gestation. This study explores the possibility of carrying out routine screening for preterm PE by maternal factors and MAP in all pregnancies and reserving measurements of UtA-PI and PlGF for a subgroup of the population, selected on the basis of the risk derived from screening by maternal factors and MAP alone.

Methods

Study data were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit at 11-13 and/or 19-24 weeks' gestation. Bayes' theorem was used to derive the a-priori risk for preterm PE from maternal factors and MAP. The posterior risk was obtained by the addition of UtA-PI and PlGF. We estimated the detection rate (DR) of preterm PE, at an overall false-positive rate (FPR) of 10%, from a policy in which first-stage screening by a combination of maternal factors and MAP defines screen-positive, screen-negative and intermediate-risk groups, with the latter undergoing second-stage screening by UtA-PI and PlGF.

Results

At 11-13 weeks' gestation, the model-based DR of preterm PE, at a 10% FPR, when screening the whole population by maternal factors, MAP, UtA-PI and PlGF was 74%. A similar DR was achieved by two-stage screening, with screening by maternal factors and MAP in the first stage and reserving measurement of UtA-PI and PlGF for the second stage and for only 50% of the population. If second-stage screening was offered to 30% of the population, there would be only a small reduction in DR from 74% to 71%. At 19-24 weeks, the model-based DR of preterm PE, at a 10% FPR, when screening the whole population by maternal factors, MAP, UtA-PI and PlGF was 84%. A similar DR was achieved by two-stage screening with measurements of UtA-PI and PlGF in only 70% of the population; if second-stage screening was offered to 40% of the population, the DR would be reduced from 84% to 81%.

KEY FACTS

High DR of preterm PE can be achieved by two-stage screening in the first and second trimesters with maternal factors and MAP in the whole population and measurements of UtA-PI and PlGF in only some of the pregnancies.

First trimester prediction and prevention of adverse pregnancy outcomes related to poor placentation

D'Silva A, Fyfe R, Hyett J

Purpose of the review

To summarize recent research findings related to first trimester prediction and prevention of adverse pregnancy outcomes associated with poor placentation. Recent publications related to prediction and prevention of preeclampsia, intrauterine growth restriction (IUGR) and stillbirth were reviewed.

Recent findings

Researchers continue to identify markers that will help predict pregnancies that go on to develop preeclampsia through screening at 11-13 weeks. A number of multivariate algorithms describing risks for preeclampsia have been published and some of these have been validated in independent populations. A large randomized controlled trial has proven the efficacy of a first trimester prediction - prevention programme for preeclampsia with an 80% reduction in prevalence of disease leading to delivery less than 34 weeks. Screening tools for IUGR and stillbirth are less advanced and require further validation in other populations. The value of these models in preventing disease still needs to be demonstrated.

KEY FACTS

Significant progress has been made in developing predictive and preventive strategies which can affect the prevalence of severe early-onset preeclampsia. This approach could be adopted for population-based screening aiming to prevent this disease.

ASPRE trial: performance of screening for preterm pre-eclampsia

Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C et al

Objective

To examine the performance of screening for preterm and term pre-eclampsia (PE) in the study population participating in the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial.

Methods

This was a prospective first-trimester multicenter study on screening for preterm PE in 26 941 singleton pregnancies by means of an algorithm that combines maternal factors, mean arterial pressure, uterine artery pulsatility index and maternal serum pregnancy-associated plasma protein-A and placental growth factor at 11-13 weeks' gestation. Eligible women with an estimated risk for preterm PE of > 1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg per day) vs placebo from 11-14 until 36 weeks' gestation, which showed that, in the aspirin group, the incidence of preterm PE was reduced by 62%. In the screened population, the detection rates (DRs) and false-positive rates (FPRs) for delivery with PE < 37 and ≥ 37 weeks were estimated after adjustment for the effect of aspirin in those receiving this treatment. We excluded 1144 (4.2%) pregnancies because of loss to follow-up or study withdrawal (n = 716), miscarriage (n = 243) or termination (n = 185).

Results

The study population of 25 797 pregnancies included 180 (0.7%) cases of preterm PE, 450 (1.7%) of term PE and 25 167 (97.6%) without PE. In combined first-trimester screening for preterm PE with a risk cut-off of 1 in 100, the DR was 76.7% (138/180) for preterm PE and 43.1% (194/450) for term PE, at screen-positive rate of 10.5% (2707/25 797) and FPR of 9.2% (2375/25 797).

KEY FACTS

The performance of screening in the ASPRE study was comparable with that of a study of approximately 60 000 singleton pregnancies used for development of the algorithm; in that study, combined screening detected 76.6% of cases of preterm PE and 38.3% of term PE at a FPR of 10%.

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

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.

Methods

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.

MoM cutoffs for variables, an important tool for multivariate analysis and accurate interpretation of pre-eclampsia risk in high-risk pregnancy at 11-13+6 weeks gestation

Verma J, Thomas DC, Jhingan G, Puri RD, Verma IC

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

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

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

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.

First trimester screening for early and late pre-eclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors

Crovetto F, Figueras F, Triunfo S, Crispi F, Rodriguez-Sureda V et al.

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 (PlGF), 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, PlGF, 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, PlGF, 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

Simeone S, Lojo C, Garcia-Esteve L, Triunfo S, Crovetto F, Arranz A et al.

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.

Prediction of pre-eclampsia utilizing the first trimester screening examination

Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG

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.

Maternal Serum PlGF Isoforms 1 and 2 at 11-13 Weeks' Gestation in Normal and Pathological Pregnancies

Nucci M, Poon LC, Demirdjian G, Darbouret B, Nicolaides KH

Rationale

To compare the maternal serum concentration of PlGF-1 and PlGF-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 PlGF-1 and PlGF-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 PlGF-1 and PlGF-2 from gestational age, smoking and racial origin. In addition, there were significant contributions to PlGF-1 from parity and method of conception.

The median MoM of PlGF-1 and PlGF-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 PlGF-1 at 11-13 weeks' gestation is more marked than the decrease in PlGF-2.

3. Prevention with low-dose aspirin

Aspirin delays the development of preeclampsia

Wright D, Nicolaides KH

Background
In the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial, risks of preterm preeclampsia were obtained from the competing risk model. Consenting women with risks of greater than 1 in 100 were randomized to treatment with aspirin or placebo. The trial showed strong evidence of an effect (odds ratio, 0.38, 95% confidence interval, 0.20-0.74) on the incidence of preterm preeclampsia, which was the primary outcome of Aspirin for Evidence-Based Preeclampsia Prevention. There was a small and insignificant effect on the incidence of term preeclampsia, which was a secondary outcomes (odds ratio, 0.95, 95% confidence interval, 0.64-1.39). These differential effects on term and preterm preeclampsia could reflect a mechanism in which the action of aspirin is to delay the delivery with preeclampsia, thereby converting what would be, without treatment, preterm preeclampsia to term preeclampsia.

Objective
The objective of the study was to examine the hypothesis that the effect of aspirin is to delay the time of delivery in women who have preeclampsia.

Study design
This was an unplanned exploratory analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention trial. The delay hypothesis predicts that in groups for which preterm preeclampsia, without aspirin, were infrequent relative to term preeclampsia, a reduction in term preeclampsia would be expected because few cases of preterm preeclampsia would be converted to term preeclampsia. In contrast, in groups for which preterm preeclampsia were frequent relative to term preeclampsia, the conversion of preterm preeclampsia to term preeclampsia by aspirin would reduce or even reverse any effect on the incidence term preeclampsia. This is examined using the Aspirin for Evidence-Based Preeclampsia Prevention trial data by analysis of the effect of aspirin on the incidence of term preeclampsia stratified according to the risk of preterm preeclampsia at randomization. Given that women were included in Aspirin for Evidence-Based Preeclampsia Prevention with risks of preterm preeclampsia >1 in 100, a risk cutoff if 1 in 50 was used to define higher risk and lower risk strata. A statistical model in which the effect of aspirin is to delay the gestational age at delivery was fitted to the Aspirin for Evidence-Based Preeclampsia Prevention trial data and the consistency of the predictions from this model with the observed incidence was demonstrated.

Results

In the lower-risk group (<1 in 50), there was a reduction in the incidence of term preeclampsia (odds ratio, 0.62, 95% confidence interval, 0.29-1.30). In contrast, in the higher risk group (≥1 in 50) there was a small increase in the incidence of term-preeclampsia (odds ratio 1.11, 95% confidence interval, 0.71- .75). Although these effects fail to achieve significance, they are consistent with the delay hypothesis. Within the framework of the aspirin-related delay hypothesis, the effect of aspirin was to delay the gestational age at delivery with preeclampsia by an estimated 4.4 weeks (95% confidence interval, 1.4-7.1 weeks) for those that in the placebo group would be delivered at 24 weeks and the effect decreased by an estimated 0.23 weeks (95% confidence interval, 0.021-0.40 weeks) for each week of gestation so that at 40+0 weeks, the estimated delay was by 0.8 weeks (95% confidence interval, -0.03 to 1.7 weeks).

KEY FACTS

The Aspirin for Evidence-Based Preeclampsia Prevention trial data are consistent with the hypothesis that aspirin delays the gestational age at delivery with preeclampsia.

Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis

Objective data

Metaanalyses of randomized controlled trials have reported contradictory results about the effect of aspirin in the prevention of preeclampsia, both in terms of the gestational age at the onset of treatment and the dose of the drug. The controversy may be resolved by a metaanalysis that includes several recently published trials and particularly the large Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-based Preeclampsia Prevention trial and by examination of whether there is a difference of the effect of aspirin on preterm vs term preeclampsia.

Study

We performed a systematic review and metaanalysis that evaluated the prophylactic effect of aspirin during pregnancy.

Study appraisal and synthesis methods

We completed a literature search through PubMed, Cinhal, Embase, Web of Science, and Cochrane library from 1985 to June 2017. Relative risks with random effect were calculated with their 95% confidence intervals.

Results

Sixteen trials that included 18,907 participants provided data for preterm and term pre-eclampsia. Eight of the included studies were evaluated as being of good quality, and the other 8 studies were deemed to be of poor or uncertain quality. There was high heterogeneity within studies ($I2 > 50\%$) for preterm and term preeclampsia, but no heterogeneity was found in the subgroup of preterm preeclampsia when the onset of treatment was ≤16 weeks of gestation and the daily dose of aspirin was ≥100 mg ($I2=0\%$). Administration of aspirin was associated with reduction in the risk of preterm preeclampsia (relative risk, 0.62; 95% confidence interval, 0.45-0.87), but there was no significant effect on term preeclampsia (relative risk, 0.92; 95% confidence interval, 0.70-1.21). The reduction in preterm preeclampsia was confined to the subgroup in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg (relative risk, 0.33; 95% confidence interval, 0.19-0.57). This effect was also observed in the high-quality studies. The reduction in preterm preeclampsia that was observed in the largest trial (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-based Preeclampsia Prevention; n=1620; relative risk, 0.38; 95% confidence interval, 0.20-0.72) was similar to that in the 5 smaller trials in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg (n=639; relative risk, 0.22; 95% confidence interval, 0.07-0.66).

> **KEY FACTS**
>
> **Aspirin reduces the risk of preterm preeclampsia, but not term preeclampsia, and only when it is initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg.**

Aspirin for Evidence-Based Preeclampsia Prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia

Wright D, Poon LC, Rolnik DL, Syngelaki A, Delgado JL, Vojtassakova D et al.

Background

The Aspirin for Evidence-Based Preeclampsia Prevention trial was a multicenter study in women with singleton pregnancies. Screening was carried out at 11-13 weeks' gestation with an algorithm that combines maternal factors and biomarkers (mean arterial pressure, uterine artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor). Those with an estimated risk for preterm preeclampsia of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg/d) vs placebo from 11-14 until 36 weeks' gestation. Preterm preeclampsia with delivery at <37 weeks' gestation, which was the primary outcome, occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74).

Objective

We sought to examine the influence of compliance on the beneficial effect of aspirin in prevention of preterm preeclampsia in the Aspirin for Evidence-Based Preeclampsia Prevention trial.

Study design

This was a secondary analysis of data from the trial. The proportion of prescribed tablets taken was used as an overall measure of compliance. Logistic regression analysis was used to estimate the effect of aspirin on the incidence of preterm preeclampsia according to compliance of <90% and ≥90%, after adjustment for the estimated risk of preterm preeclampsia at screening and the participating center. The choice of cut-off of 90% was based on an exploratory analysis of the treatment effect. Logistic regression analysis was used to investigate predictors of compliance ≥90% among maternal characteristics and medical history.

Results

Preterm preeclampsia occurred in 5/555 (0.9%) participants in the aspirin group with compliance ≥90%, in 8/243 (3.3%) of participants in the aspirin group with compliance <90%, in 22/588 (3.7%) of participants in the placebo group with compliance ≥90%, and in 13/234 (5.6%) of participants in the placebo group with compliance <90%. The odds ratio in the aspirin group for preterm preeclampsia was 0.24 (95% confidence interval, 0.09-0.65) for compliance ≥90% and 0.59 (95% confidence interval, 0.23-1.53) for compliance <90%. Compliance was positively associated with family history of preeclampsia and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian racial origin, and history of preeclampsia in a previous pregnancy.

> **KEY FACTS**
>
> **The beneficial effect of aspirin in the prevention of preterm preeclampsia appears to depend on compliance.**

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A et al.

Background

Preterm preeclampsia is an important cause of maternal and perinatal death and complications. It is uncertain whether the intake of low-dose aspirin during pregnancy reduces the risk of preterm preeclampsia.

Methods

In this multicenter, double-blind, placebo-controlled trial, we randomly assigned 1776 women with singleton pregnancies who were at high risk for preterm preeclampsia to receive aspirin, at a dose of 150 mg per day, or placebo from 11 to 14 weeks of gestation until 36 weeks of gestation. The primary outcome was delivery with preeclampsia before 37 weeks of gestation. The analysis was performed according to the intention-to-treat principle.

Results

A total of 152 women withdrew consent during the trial, and 4 were lost to follow up, which left 798 participants in the aspirin group and 822 in the placebo group. Preterm preeclampsia occurred in 13 participants (1.6%) in the aspirin group, as compared with 35 (4.3%) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004). Results were materially unchanged in a sensitivity analysis that took into account participants who had withdrawn or were lost to follow-up. Adherence was good, with a reported intake of 85% or more of the required number of tablets in 79.9% of the participants. There were no significant between-group differences in the incidence of neonatal adverse outcomes or other adverse events.

KEY FACTS

Treatment with low-dose aspirin in women at high risk for preterm preeclampsia resulted in a lower incidence of this diagnosis than placebo. (Funded by the European Union Seventh Framework Program and the Fetal Medicine Foundation; EudraCT number, 2013-003778-29; Current Controlled Trials number, ISRCTN13633058).

Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history

Poon LC, Wright D, Rolnik DL, Syngelaki A, Delgado JL, Tsokaki T et al.
Am J Obstet Gynecol. 2017 Nov;217(5):585.e1-585.e5

Background
The Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial demonstrated that in women who were at high risk for preterm preeclampsia with delivery at <37 weeks' gestation identified by screening by means of an algorithm that combines maternal factors and biomarkers at 11-13 weeks' gestation, aspirin administration from 11 to 14 until 36 weeks' gestation was associated with a significant reduction in the incidence of preterm preeclampsia (odds ratio 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004).

Objective
We sought to examine whether there are differences in the effect of aspirin on the incidence of preterm preeclampsia in the Aspirin for Evidence-Based Preeclampsia Prevention trial in subgroups defined according to maternal characteristics and medical and obstetrical history.

Study design
This was a secondary analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention trial. Subgroup analysis was performed to assess evidence of differences in the effect of aspirin on incidence of preterm preeclampsia in subgroups defined by maternal age (<30 and ≥30 years), body mass index (<25 and ≥25 kg/m2), racial origin (Afro-Caribbean, Caucasian and other), method of conception (natural and assisted), cigarette smoking (smoker and non-smoker), family history of preterm preeclampsia (present and absent), obstetrical history (nulliparous, multiparous with previous preterm preeclampsia and multiparous without previous preterm preeclampsia), history of chronic hypertension (present and absent). Interaction tests were performed on the full data set of patients in the intention to treat population and on the data set of patients who took ≥ 90% of the prescribed medication. Results are presented as forest plot with P values for the interaction effects, group sizes, event counts and estimated odds ratios. We examined whether the test of interaction was significant at the 5% level with a Bonferroni adjustment for multiple comparisons.

Results

There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetrical history. In participants with chronic hypertension preterm preeclampsia occurred in 10.2% (5/49) in the aspirin group and 8.2% (5/61) in the placebo group (adjusted odds ratio, 1.29; 95% confidence interval, 0.33-5.12). The respective values in those without chronic hypertension were 1.1% (8/749) in the aspirin group and 3.9% (30/761) in the placebo group (adjusted odds ratio, 0.27; 95% confidence interval, 0.12-0.60). In all participants with adherence of ≥90% the adjusted odds ratio in the aspirin group was 0.24 (95% confidence interval, 0.09-0.65); in the subgroup with chronic hypertension it was 2.06 (95% confidence interval, 0.40-10.71); and in those without chronic hypertension it was 0.05 (95% confidence interval, 0.01-0.41). For the complete data set the test of interaction was not significant at the 5% level (P = .055), but in those with adherence ≥90%, after adjustment for multiple comparisons, the interaction was significant at the 5% level (P = .0019).

KEY FACTS

The beneficial effect of aspirin in the prevention of preterm preeclampsia may not apply in pregnancies with chronic hypertension. There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetrical history.

The role of aspirin dose on the prevention of pre-eclampsia and fetal growth restriction: systematic review and meta-analysis

Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E

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.**

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
Am J Perinatol. 2016 Jul;33(8):781-5

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.

KEY FACTS

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.

Prediction and prevention of early-onset pre-eclampsia: impact of aspirin after first-trimester screening

Park F, Russo K, Williams P, Pelosi M, Puddephatt R, Walter M, Leung C et al.

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.

Glossary

ADAM12	A disintegrin and metalloprotease 12
AUC	Area under the curve
CI	Confidence interval
DR	Detection rate
FPR	False-positive rate
GA	Gestational age
GH	Gestational hypertension
IUGR	Intrauterine growth restriction
LR	Likelihood ratio
MAP	Mean arterial pressure
MoM	Multiple of the median
PAPP-A	Pregnancy-associated plasma protein A
PE	Pre-eclampsia
PI	Pulsatility index
PlGF/PGF	Placental growth factor
PP13	Placental protein 13
PTB	Preterm birth
SGA	Small for gestational age
sFlt-1	Soluble fms-like tyrosine kinase
UAPI/UADPI/UtAPI	Uterine artery (Doppler) pulsatility index
VEGF	Vascular endothelial growth factor
β-hCG	Human chorionic gonadotropin

thermoscientific

Thermo Scientific™
B·R·A·H·M·S™ PlGF plus KRYPTOR™

Automated immunofluorescent assay for the quantitative determination of human Placental Growth Factor (PlGF) in human serum

- Excellent precision
- Very low detection limit: 3.6 pg/mL
- Best functional assay sensitivity (FAS): 6.7 pg/mL

► 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

Find out more at **thermoscientific.com/brahms**

Thermo Fisher
SCIENTIFIC

900228.4