Literature Review

First trimester pre-eclampsia screening

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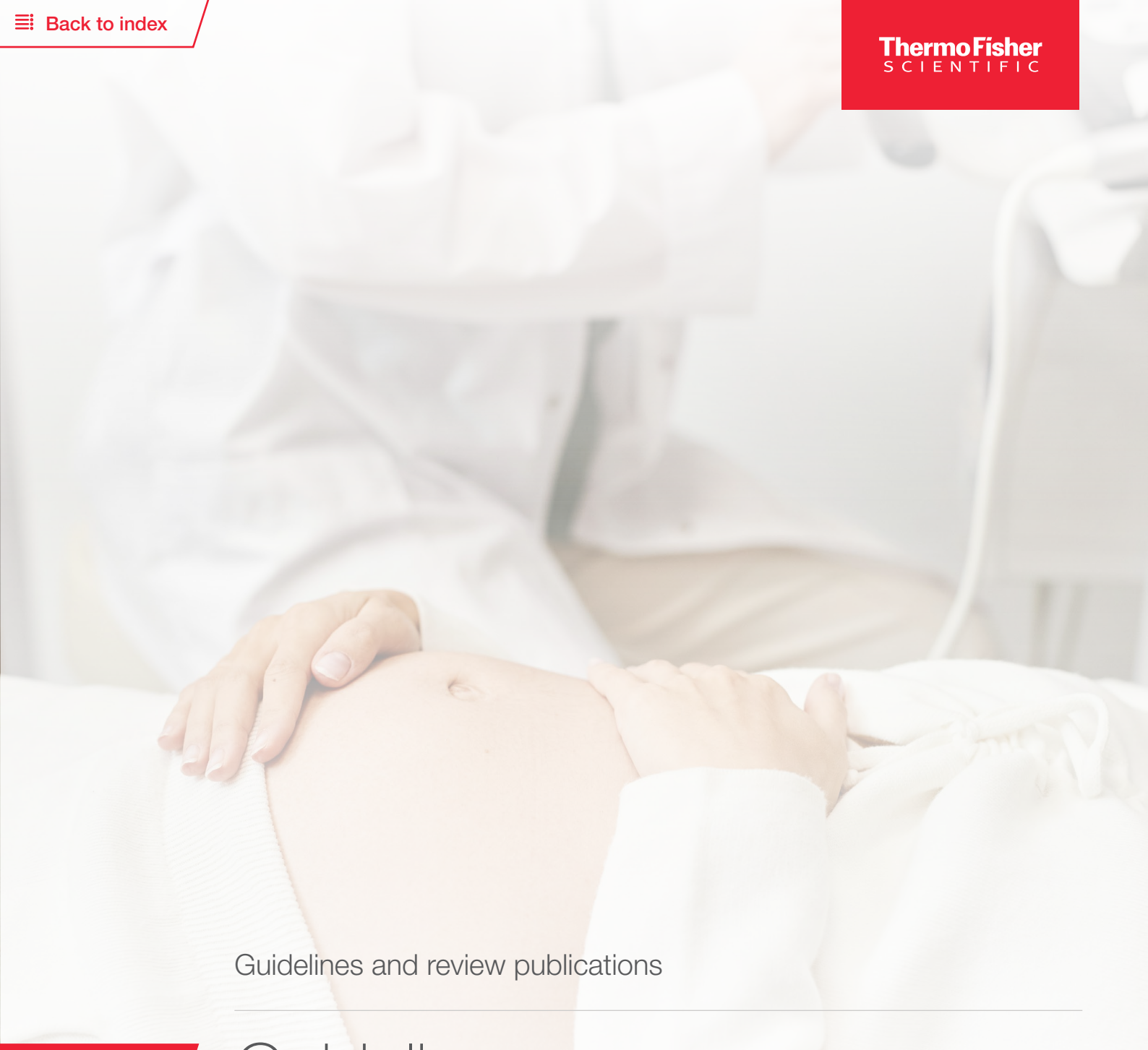


Guidelines and review publications

Guidelines

2018 ESC/ESH Guidelines for the management of arterial hypertension

B. Williams, G. Mancia, W. Spiering, E. Agabiti Rosei, M. Azizi, M. Burnier et al.

Eur Heart J 2018 Vol. 39 Issue 33 Pages 3021-3104

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) and by the European Society of Hypertension (ESH), 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/ClinicalPractice-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 and ESH 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 and approved by the ESH. 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 ESH and updated. The Task Force received its entire financial support from the ESC and ESH without any involvement from the healthcare industry. The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by ESH appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG and ESH for publication in the European Heart Journal and in the Journal of Hypertension as well as Blood Pressure. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating. The task of developing ESC and ESH Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC AND ESH websites and hosted on the EHJ AND JOURNAL OF HYPERTENSION websites. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations. Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice. Health professionals are encouraged to take the ESC and ESH Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC and ESH Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention

L. Poon, A. Shennan, J. Hyett, A. Kapur, E. Hadar, H. Divakar, et al.

Int J Gynaecol Obstet 2019 Vol. 145 Suppl 1 Issue Suppl 1 Pages 1-33

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 (thrombocytopenia–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.

ISUOG Practice guidelines: Role of ultrasound in screening for and follow-up of pre-eclampsia

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

Ultrasound Obstet Gynecol 2019 Vol. 53 Issue 1 Pages 7-22

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) is a scientific organization that encourages sound clinical practice, and high-quality teaching and research related to diagnostic imaging in women's healthcare. The ISUOG Clinical Standards Committee (CSC) has a remit to develop Practice Guidelines and Consensus Statements as educational recommendations that provide healthcare practitioners with a consensus-based approach, from experts, for diagnostic imaging. They are intended to reflect what is considered by ISUOG to be the best practice at the time at which they were issued. Although ISUOG has made every effort to ensure that Guidelines are accurate when issued, neither the Society nor any of its employees or members accepts any liability for the consequences of any inaccurate or misleading data, opinions or statements issued by the CSC. The ISUOG CSC documents are not intended to establish a legal standard of care, because interpretation of the evidence that underpins the Guidelines may be influenced by individual circumstances, local protocol and available resources. Approved Guidelines can be distributed freely with the permission of ISUOG (info@isuog.org).

The 2021 International Society for the Study of Hypertension in Pregnancy classification, Diagnosis & management recommendations for international practice

L. Magee, M. Brown, D. Hall, S. Gupte, A. Hennessy, S. Karumanchi, et al.

Pregnancy Hypertens 2022 Vol. 27 Pages 148-169

All units managing hypertensive pregnant women should maintain and review uniform departmental management protocols and conduct regular audits of maternal & fetal outcomes. The cause(s) of pre-eclampsia and the optimal clinical management of the hypertensive disorders of pregnancy remain uncertain; therefore, we recommend that every hypertensive pregnant woman be offered an opportunity to participate in research, clinical trials and follow-up studies.

Guideline no. 426 - Hypertensive disorders of pregnancy: Diagnosis, prediction, prevention, and management

L. Magee, G. Smith, C. Bloch, A. Côté, V. Jain, K. Nerenberg, et al.

J Obstet Gynaecol Can 2022 Vol. 44 Issue 5 Pages 547-571.e1

Objective
This guideline was developed by maternity care providers from obstetrics and internal medicine. It reviews the diagnosis, evaluation, and management of the hypertensive disorders of pregnancy (HDPs), the prediction and prevention of preeclampsia, and the postpartum care of women with a previous HDP.

Target population
Pregnant women

Benefits, Harms, and Costs
Implementation of the recommendations in these guidelines may reduce the incidence of the HDPs, particularly preeclampsia, and associated adverse outcomes.

Evidence
A comprehensive literature review was updated to December 2020, following the same methods as for previous Society of Obstetricians and Gynaecologists of Canada (SOGC) HDP guidelines, and references were restricted to English or French. To support recommendations for therapies, we prioritized randomized controlled trials and systematic reviews (if available), and evaluated substantive clinical outcomes for mothers and babies.

Validation Methods
The authors agreed on the content and recommendations through consensus and responded to peer review by the SOGC Maternal Fetal Medicine Committee. The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, along with the option of designating a recommendation as a “good practice point. The Board of the SOGC approved the final draft for publication.

Intended Users
All health care providers (obstetricians, family doctors, midwives, nurses, and anesthesiologists) who provide care to women before, during, or after pregnancy.

Prediction and prevention of preeclampsia: FEBRASGO position statement

F. Peixoto-Filho, F. Costa, S. Kobayashi, P. Beitune, A. Garrido, A. Carmo, et al.

Rev Bras Ginecol Obstet 2023 Vol. 45 Issue 1 Pages 49-54

The National Specialized Commission on Ultrasonography in GO of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorses this document. The production of content is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

SOMANZ - Hypertension in pregnancy guidelines

A. Makris, R. Shanmugalingam. H. Barrett. A Beech, L. Bowyer et al.,

Aust N Z J Obstet Gynaecol, (TBC)

This guideline document is based upon literature searches last conducted in December 2020, and updated in December 2022. It is designed to assist with decision-making in matter related to the care of women with hypertension in pregnancy. It is not intended to define the standard of care but rather should be interpreted by clinicians based on the individual needs, preferences and values of their patient, the resources available to them and other constraints to practice that be unique to an institution. It is not compulsory to apply these guidelines and they do not override the responsibility of the clinician to make decisions appropriately. The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) has made every effort to ensure there were no conflicts of interest between the members of the working group and their personal, professional or business interests. All members of the working group were required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as, or are actual conflicts of interest. Disclosures are published in the appendix of this document and are also held on file at SOMANZ. These are the recommendations of a multidisciplinary working party convened by SOMANZ. They reflect a thorough assessment of the current medical literature and the clinical experience of members of the working party.

Guidelines and review publications

Reviews on pre-eclampsia

First-trimester maternal factors and biomarker screening for preeclampsia

L. Poon and K. Nicolaides

Prenat Diagn 2014 Vol. 34 Issue 7 Pages 618-27

Preeclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality. PE can be subdivided into early onset PE with delivery <34 weeks' gestation and late onset PE with delivery ≥34 weeks. Early onset PE is associated with a higher incidence of adverse outcome. This review illustrates that effective screening for the development of early onset PE can be provided in the first-trimester of pregnancy. Screening by a combination of maternal risk factors, mean arterial pressure, uterine artery Doppler, maternal serum pregnancy-associated plasma protein-A and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%.

Pre-eclampsia: Pathophysiology and clinical implications

G. Burton, C. Redman, J. Roberts and A. Moffett

Bmj 2019 Vol. 366 Pages l2381

Pre-eclampsia is a common disorder that particularly affects first pregnancies. The clinical presentation is highly variable but hypertension and proteinuria are usually seen. These systemic signs arise from soluble factors released from the placenta as a result of a response to stress of syncytiotrophoblast. There are two sub-types: early and late onset pre-eclampsia, with others almost certainly yet to be identified. Early onset pre-eclampsia arises owing to defective placentation, whilst late onset pre-eclampsia may center around interactions between normal senescence of the placenta and a maternal genetic predisposition to cardiovascular and metabolic disease. The causes, placental and maternal, vary among individuals. Recent research has focused on placental-uterine interactions in early pregnancy. The aim now is to translate these findings into new ways to predict, prevent, and treat pre-eclampsia.

Preeclampsia: Recent advances in predicting, preventing, and managing the maternal and fetal life-threatening condition

K. Chang, K. Seow and K. Chen

Int J Environ Res Public Health 2023 Vol. 20 Issue 4

Preeclampsia accounts for one of the most common documented gestational complications, with a prevalence of approximately 2 to 15% of all pregnancies. Defined as gestational hypertension after 20 weeks of pregnancy and coexisting proteinuria or generalized edema, and certain forms of organ damage, it is life-threatening for both the mother and the fetus, in terms of increasing the rate of mortality and morbidity. Preeclamptic pregnancies are strongly associated with significantly higher medical costs. The maternal costs are related to the extra utility of the healthcare system, more resources used during hospitalization, and likely more surgical spending due to an elevated rate of cesarean deliveries. The infant costs also contribute to a large percentage of the expenses as the babies are prone to preterm deliveries and relevant or causative adverse events. Preeclampsia imposes a considerable financial burden on our societies. It is important for healthcare providers and policy-makers to recognize this phenomenon and allocate enough economic budgets and medical and social resources accordingly. The true cellular and molecular mechanisms underlying preeclampsia remain largely unexplained, which is assumed to be a two-stage process of impaired uteroplacental perfusion with or without prior defective trophoblast invasion (stage 1), followed by general endothelial dysfunction and vascular inflammation that lead to systemic organ damages (stage 2). Risk factors for preeclampsia including race, advanced maternal age, obesity, nulliparity, multi-fetal pregnancy, and co-existing medical disorders, can serve as warnings or markers that call for enhanced surveillance of maternal and fetal well-being. Doppler ultrasonography and biomarkers including the mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum pregnancy-associated plasma protein A (PAPP-A) can be used for the prediction of preeclampsia. For women perceived as high-risk individuals for developing preeclampsia, the administration of low-dose aspirin on a daily basis since early pregnancy has proven to be the most effective way to prevent preeclampsia. For preeclamptic females, relevant information, counseling, and suggestions should be provided to facilitate timely intervention or specialty referral. In pregnancies complicated with preeclampsia, closer monitoring and antepartum surveillance including the Doppler ultrasound blood flow study, biophysical profile, non-stress test, and oxytocin challenge test can be arranged. If the results are unfavorable, early intervention and aggressive therapy should be considered. Affected females should have access to higher levels of obstetric units and neonatal institutes. Before, during, and after delivery, monitoring and preparation should be intensified for affected gravidas to avoid serious complications of preeclampsia. In severe cases, delivery of the fetus and the placenta is the ultimate solution to treat preeclampsia. The current review is a summary of recent advances regarding the knowledge of preeclampsia. However, the detailed etiology, pathophysiology, and effect of preeclampsia seem complicated, and further research to address the primary etiology and pathophysiology underlying the clinical manifestations and outcomes is warranted.

Pre-eclampsia

E. Dimitriadis, D. Rolnik, W. Zhou, G. Estrada-Gutierrez, K. Koga, R. Francisco, et al.

Nat Rev Dis Primers 2023 Vol. 9 Issue 1 Pages 8

Pre-eclampsia is a life-threatening disease of pregnancy unique to humans and a leading cause of maternal and neonatal morbidity and mortality. Women who survive pre-eclampsia have reduced life expectancy, with increased risks of stroke, cardiovascular disease and diabetes, while babies from a pre-eclamptic pregnancy have increased risks of preterm birth, perinatal death and neurodevelopmental disability and cardiovascular and metabolic disease later in life. Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction. Pre-eclampsia is found only when a placenta is or was recently present and is classified as preterm (delivery <37 weeks of gestation), term (delivery ≥37 weeks of gestation) and postpartum pre-eclampsia. The maternal syndrome of pre-eclampsia is driven by a dysfunctional placenta, which releases factors into maternal blood causing systemic inflammation and widespread maternal endothelial dysfunction. Available treatments target maternal hypertension and seizures, but the only 'cure' for pre-eclampsia is delivery of the dysfunctional placenta and baby, often prematurely. Despite decades of research, the aetiology of pre-eclampsia, particularly of term and postpartum pre-eclampsia, remains poorly defined. Significant advances have been made in the prediction and prevention of preterm pre-eclampsia, which is predicted in early pregnancy through combined screening and is prevented with daily low-dose aspirin, starting before 16 weeks of gestation. By contrast, the prediction of term and postpartum pre-eclampsia is limited and there are no preventive treatments. Future research must investigate the pathogenesis of pre-eclampsia, in particular of term and postpartum pre-eclampsia, and evaluate new prognostic tests and treatments in adequately powered clinical trials.

Guidelines and review publications

Reviews on PlGF and sFlt-1 biochemistry

Circulating angiogenic factors and the risk of preeclampsia

R. Levine, S. Maynard, C. Qian, K. Lim, L. England, K. Yu, et al.

N Engl J Med 2004 Vol. 350 Issue 7 Pages 672-83

Background

The cause of preeclampsia remains unclear. Limited data suggest that excess circulating soluble fms-like tyrosine kinase 1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), may have a pathogenic role.

Methods

We performed a nested case-control study within the Calcium for Preeclampsia Prevention trial, which involved healthy nulliparous women. Each woman with preeclampsia was matched to one normotensive control. A total of 120 pairs of women were randomly chosen. Serum concentrations of angiogenic factors (total sFlt-1, free PlGF, and free VEGF) were measured throughout pregnancy; there were a total of 655 serum specimens. The data were analyzed cross-sectionally within intervals of gestational age and according to the time before the onset of preeclampsia.

Results

During the last two months of pregnancy in the normotensive controls, the level of sFlt-1 increased and the level of PlGF decreased. These changes occurred earlier and were more pronounced in the women in whom preeclampsia later developed. The sFlt-1 level increased beginning approximately five weeks before the onset of preeclampsia. At the onset of clinical disease, the mean serum level in the women with preeclampsia was 4382 pg per milliliter, as compared with 1643 pg per milliliter in controls with fetuses of similar gestational age ($P<0.001$). The PlGF levels were significantly lower in the women who later had preeclampsia than in the controls beginning at 13 to 16 weeks of gestation (mean, 90 pg per milliliter vs. 142 pg per milliliter, $P=0.01$), with the greatest difference occurring during the weeks before the onset of preeclampsia, coincident with the increase in the sFlt-1 level. Alterations in the levels of sFlt-1 and free PlGF were greater in women with an earlier onset of preeclampsia and in women in whom preeclampsia was associated with a small-for-gestational-age infant.

Results

Increased levels of sFlt-1 and reduced levels of PlGF predict the subsequent development of preeclampsia.

Total versus free placental growth factor levels in the pathogenesis of preeclampsia

E. Lecarpentier, Z. Zsengellér, S. Salahuddin, A. Covarrubias, A. Lo, B. Haddad, et al.

Hypertension 2020 Vol. 76 Issue 3 Pages 875-883

Elevated circulating sFLT-1 (soluble fms-like tyrosine kinase) and low levels of its ligand, PlGF (placental growth factor), are key characteristics of preeclampsia. However, it is unclear if the low levels of plasma PlGF noted during preeclampsia are due to decreased placental production of PlGF or due to binding of PlGF by increased circulating sFLT-1. Here, we describe a biochemical procedure to dissociate PlGF-sFLT-1 complex ex vivo and when used in conjunction with an immunoassay platform, demonstrate a method to measure total and free PlGF in human blood samples. Using this method, we noted that plasma free PlGF levels were significantly lower in preeclampsia (N=22) than in nonhypertensive controls (N=24; mean, 314 versus 686 pg/mL, P<0.05), but total PlGF levels were not different (mean, 822 versus 800 pg/mL, P=0.49). In contrast, total sFLT-1 levels were significantly higher in preeclampsia than in nonhypertensive controls (mean, 16 957 versus 3029 pg/mL, P<0.01) and sFLT-1 levels correlated with bound PlGF levels (bound PlGF=total PlGF-free PlGF) in these samples (r(2)=0.68). We confirmed these findings in an independent cohort of subjects (N=49). Furthermore, we did not detect any difference in PlGF mRNA by quantitative polymerase chain reaction or in PlGF protein expression by immunohistochemistry in preeclamptic placentas when compared with nonhypertensive controls. In contrast, sFLT-1 mRNA and protein levels were upregulated in placentas from women with preeclampsia. Taken together with prior studies, our results provide evidence that decrease in circulating PlGF noted during preeclampsia is largely mediated by excess circulating sFLT-1.

From biomarkers to the molecular mechanism of preeclampsia. A comprehensive literature review

M. Rybak-Krzyszkowska, J. Staniczek, A. Kondracka, J. Bogusławska, S. Kwiatkowski, T. Góra, et al

Int J Mol Sci 2023 Vol. 24 Issue 17

Preeclampsia (PE) is a prevalent obstetric illness affecting pregnant women worldwide. This comprehensive literature review aims to examine the role of biomarkers and understand the molecular mechanisms underlying PE. The review encompasses studies on biomarkers for predicting, diagnosing, and monitoring PE, focusing on their molecular mechanisms in maternal blood or urine samples. Past research has advanced our understanding of PE pathogenesis, but the etiology remains unclear. Biomarkers such as PlGF, sFlt-1, PP-13, and PAPP-A have shown promise in risk classification and preventive measures, although challenges exist, including low detection rates and discrepancies in predicting different PE subtypes. Future perspectives highlight the importance of larger prospective studies to explore predictive biomarkers and their molecular mechanisms, improving screening efficacy and distinguishing between early-onset and late-onset PE. Biomarker assessments offer reliable and cost-effective screening methods for early detection, prognosis, and monitoring of PE. Early identification of high-risk women enables timely intervention, preventing adverse outcomes. Further research is needed to validate and optimize biomarker models for accurate prediction and diagnosis, ultimately improving maternal and fetal health outcomes.

1st trimester pre-eclampsia screening with ~~Thermo Scientific~~ B·R·A·H·M·S KRYPTOR Assays

1st trimester pre-eclampsia screening with Thermo Scientific B·R·A·H·M·S KRYPTOR Assays

Key screening publications

Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: A meta-analysis

E. Bujold, S. Roberge, Y. Lacasse, M. Bureau, F. Audibert, S. Marcoux, et al.

Obstet Gynecol 2010 Vol. 116 Issue 2 Pt 1 Pages 402-414

Objective

To estimate the effect of low-dose aspirin started in early pregnancy on the incidence of preeclampsia and intrauterine growth restriction (IUGR).

Data Sources

A systematic review and meta-analysis were performed through electronic database searches (PubMed, Cochrane, Embase).

Methods of Study Selection

Randomized controlled trials of pregnant women at risk of preeclampsia who were assigned to receive aspirin or placebo (or no treatment) were reviewed. Secondary outcomes included IUGR, severe preeclampsia and preterm birth. The effect of aspirin was analyzed as a function of gestational age at initiation of the intervention (16 weeks of gestation or less, 16 weeks of gestation or more).

Tabulation, Integration, and Results

Thirty-four randomized controlled trials met the inclusion criteria, including 27 studies (11,348 women) with follow-up for the outcome of preeclampsia. Low-dose aspirin started at 16 weeks or earlier was associated with a significant reduction in preeclampsia (relative risk [RR] 0.47, 95% confidence interval [CI] 0.34-0.65, prevalence in 9.3% treated compared with 21.3% control) and IUGR (RR 0.44, 95% CI 0.30-0.65, 7% treated compared with 16.3% control), whereas aspirin started after 16 weeks was not (preeclampsia: RR 0.81, 95% CI 0.63-1.03, prevalence in 7.3% treated compared with 8.1% control; IUGR: RR 0.98, 95% CI 0.87-1.10, 10.3% treated compared with 10.5% control). Low-dose aspirin started at 16 weeks or earlier also was associated with a reduction in severe preeclampsia (RR 0.09, 95% CI 0.02-0.37, 0.7% treated compared with 15.0% control), gestational hypertension (RR 0.62, 95% CI 0.45-0.84, 16.7% treated compared with 29.7% control), and preterm birth (RR 0.22, 95% CI 0.10-0.49, 3.5% treated compared with 16.9% control). Of note, all studies for which aspirin had been started at 16 weeks or earlier included women identified to be at moderate or high risk for preeclampsia.

Conclusion

Low-dose aspirin initiated in early pregnancy is an efficient method of reducing the incidence of preeclampsia and IUGR.

A competing risks model in early screening for preeclampsia

D. Wright, R. Akolekar, A. Syngelaki, L. Poon and K. Nicolaides

Fetal Diagn Ther 2012 Vol. 32 Issue 3 Pages 171-8

Objective

It was the aim of this study to develop models for the prediction of preeclampsia (PE) based on maternal characteristics and biophysical markers at 11-13 weeks' gestation in which gestation at the time of delivery for PE is treated as a continuous variable.

Methods

This was a screening study of singleton pregnancies at 11-13 weeks including 1,426 (2.4%) cases that subsequently developed PE and 57,458 cases that were unaffected by PE. We developed a survival time model for the time of delivery for PE in which Bayes' theorem was used to combine the prior information from maternal characteristics with the uterine artery pulsatility index (PI) and the mean arterial pressure (MAP), using multiple of the median values.

Results

The risk for PE increased with maternal age, weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with PE, conception by in vitro fertilization and a medical history of chronic hypertension, type 2 diabetes mellitus as well as systemic lupus erythematosus or antiphospholipid syndrome. In pregnancies with PE, there was an inverse correlation between multiple of the median values of the uterine artery PI and MAP with gestational age at delivery. Screening by maternal characteristics, uterine artery PI and MAP detected 90% of PE cases requiring delivery before 34 weeks and 57% of all PE cases at a fixed false-positive rate of 10%.

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

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

Ultrasound Obstet Gynecol 2015 Vol. 46 Issue 4 Pages 419-23

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 ($P = 0.03$).

Conclusions

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.

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

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

Ultrasound Obstet Gynecol 2017 Vol. 49 Issue 6 Pages 756-760

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 (PlGF) 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.

Conclusions

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

Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia (ASPRE)

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

N Engl J Med 2017 Vol. 377 Issue 7 Pages 613-622

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.

Conclusions

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).

Serum PlGF compared with PAPP-A in first trimester screening for preterm pre-eclampsia: Adjusting for the effect of aspirin treatment

D. Wright, M. Tan, N. O'Gorman, A. Syngelaki and K. Nicolaides

Bjog 2022 Vol. 129 Issue 8 Pages 1308-1317

Objective
To compare the predictive performance for preterm-pre-eclampsia (PE) in first-trimester screening by serum placental growth factor (PlGF) versus pregnancy associated plasma protein-A (PAPP-A), in combination with maternal risk factors, mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI), after adjustment for the effect of aspirin in women receiving this treatment. DESIGN: Non-intervention multicentre screening studies for PE in singleton pregnancies.

Setting
Maternity hospitals.

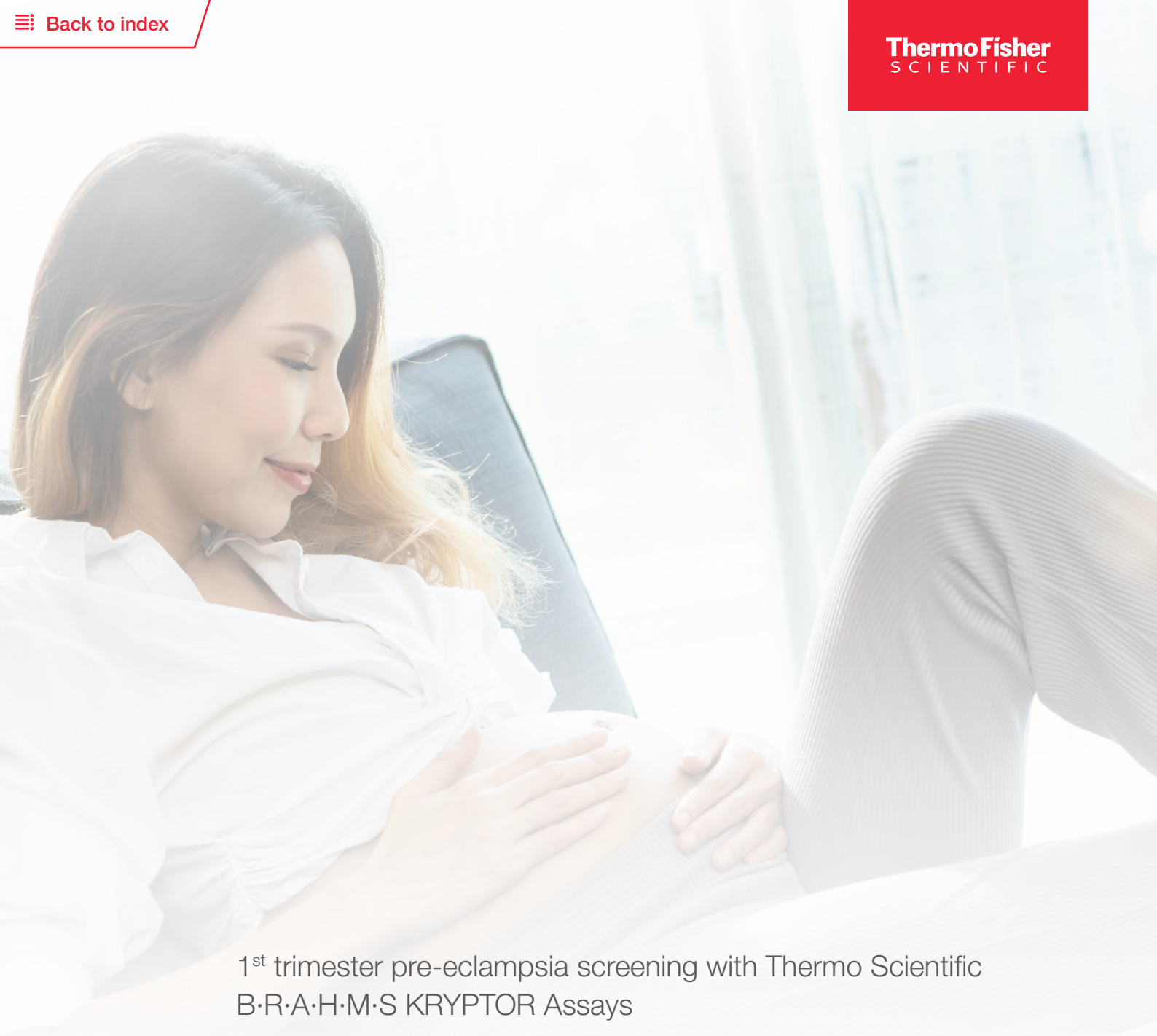
Population
Two independent prospective studies of 8775 and 16451 women with singleton pregnancies attending for routine assessment at 11(+0) -13(+6) weeks' gestation.

Methods
The competing risks model was used to estimate patient-specific risks of delivery with PE at <37 weeks' gestation based on maternal risk factors and combinations with MAP, UtA-PI and either PlGF or PAPP-A. McNemar's test was used to compare the detection rate (DR) of preterm-PE of screening utilising PlGF versus PAPP-A, after adjustments for the effects of aspirin.

Main Outcome Measure
Predictive performance for preterm-PE.

Results
In the combined data of 25226 women, including 678 (2.7%) who developed PE, there were 194(0.8%) with preterm-PE. Addition of PlGF improved the DR of preterm-PE, at 10% screen positive rate, by 18.4% (95% CI 12.2-24.6) in screening by maternal risk factors, by 19.9% (95% CI 13.6-26.2) in screening by maternal factors and MAP, and by 7.0% (95% CI 2.3-11.6) in screening by maternal factors, MAP and UtA-PI. PAPP-A did not significantly improve the DR provided by any combination of biomarkers.

Conclusion
The predictive performance of first trimester PlGF for preterm-PE is superior to that of PAPP-A.



1st trimester pre-eclampsia screening with Thermo Scientific B·R·A·H·M·S KRYPTOR Assays

Country publications Asia

Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population

P. Chaemsaithong, R. Pooh, M. Zheng, R. Ma, N. Chaiyasit, M. Tokunaka, et al.

Am J Obstet Gynecol 2019 Vol. 221 Issue 6 Pages 650.e1-650.e16

Background

The administration of aspirin <16 weeks gestation to women who are at high risk for preeclampsia has been shown to reduce the rate of preterm preeclampsia by 65%. The traditional approach to identify such women who are at risk is based on risk factors from maternal characteristics, obstetrics, and medical history as recommended by the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence. An alternative approach to screening for preeclampsia has been developed by the Fetal Medicine Foundation. This approach allows the estimation of patient-specific risks of preeclampsia that requires delivery before a specified gestational age with the use of Bayes theorem-based model.

Objective

The purpose of this study was to examine the diagnostic accuracy of the Fetal Medicine Foundation Bayes theorem-based model, the American College of Obstetricians and Gynecologists, and the National Institute for Health and Care Excellence recommendations for the prediction of preterm preeclampsia at 11-13+6 weeks gestation in a large Asian population

Study Design

This was a prospective, nonintervention, multicenter study in 10,935 singleton pregnancies at 11-13+6 weeks gestation in 11 recruiting centers across 7 regions in Asia between December 2016 and June 2018. Maternal characteristics and medical, obstetric, and drug history were recorded. Mean arterial pressure and uterine artery pulsatility indices were measured according to standardized protocols. Maternal serum placental growth factor concentrations were measured by automated analyzers. The measured values of mean arterial pressure, uterine artery pulsatility index, and placental growth factor were converted into multiples of the median. The Fetal Medicine Foundation Bayes theorem-based model was used for the calculation of patient-specific risk of preeclampsia at <37 weeks gestation (preterm preeclampsia) and at any gestation (all preeclampsia) in each participant. The performance of screening for preterm preeclampsia and all preeclampsia by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index, and placental growth factor (triple test) was evaluated with the adjustment of aspirin use. We examined the predictive performance of the model by the use of receiver operating characteristic curve and calibration by measurements of calibration slope and calibration in the large. The detection rate of screening by the Fetal Medicine Foundation Bayes theorem-based model was compared with the model that was derived from the application of American College of Obstetricians and Gynecologists and National Institute for Health and Care Excellence recommendations.

Results

There were 224 women (2.05%) who experienced preeclampsia, which included 73 cases (0.67%) of preterm preeclampsia. In pregnancies with preterm preeclampsia, the mean multiples of the median values of mean arterial pressure and uterine artery pulsatility index were significantly higher (mean arterial pressure, 1.099 vs 1.008 [P<.001]; uterine artery pulsatility index, 1.188 vs 1.063[P=.006]), and the mean placental growth factor multiples of the median was significantly lower (0.760 vs 1.100 [P<.001]) than in women without preeclampsia. The Fetal Medicine Foundation triple test achieved detection rates of 48.2%, 64.0%, 71.8%, and 75.8% at 5%, 10%, 15%, and 20% fixed false-positive rates, respectively, for the prediction of preterm preeclampsia. These were comparable with those of previously published data from the Fetal Medicine Foundation study. Screening that used the American College of Obstetricians and Gynecologists recommendations achieved detection rate of 54.6% at 20.4% false-positive rate. The detection rate with the use of National Institute for Health and Care Excellence guideline was 26.3% at 5.5% false-positive rate.

Conclusion

Based on a large number of women, this study has demonstrated that the Fetal Medicine Foundation Bayes theorem-based model is effective in the prediction of preterm preeclampsia in an Asian population and that this method of screening is superior to the approach recommended by American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence. We have also shown that the Fetal Medicine Foundation prediction model can be implemented as part of routine prenatal care through the use of the existing infrastructure of routine prenatal care.

First-trimester pre-eclampsia biomarker profiles in Asian population: Multicenter cohort study

P. Chaemsaithong, D. Sahota, R. Pooh, M. Zheng, R. Ma, N. Chaiyasit, et al.

Ultrasound Obstet Gynecol 2020 Vol. 56 Issue 2 Pages 206-214

Objective

To (i) evaluate the applicability of the European-derived biomarker multiples of the median (MoM) formulae for risk assessment of preterm pre-eclampsia (PE) in seven Asian populations, spanning the east, southeast and south regions of the continent, (ii) perform quality-assurance (QA) assessment of the biomarker measurements and (iii) establish criteria for prospective ongoing QA assessment of biomarker measurements.

Methods

This was a prospective, non-intervention, multicenter study in 4023 singleton pregnancies, at 11 to 13+6 weeks' gestation, in 11 recruiting centers in China, Hong Kong, India, Japan, Singapore, Taiwan and Thailand. Women were screened for preterm PE between December 2016 and June 2018 and gave written informed consent to participate in the study. Maternal and pregnancy characteristics were recorded and mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI) and maternal serum placental growth factor (PlGF) were measured in accordance with The Fetal Medicine Foundation (FMF) standardized measurement protocols. MAP, UtA-PI and PlGF were transformed into MoMs using the published FMF formulae, derived from a largely Caucasian population in Europe, which adjust for gestational age and covariates that affect directly the biomarker levels. Variations in biomarker MoM values and their dispersion (SD) and cumulative sum tests over time were evaluated in order to identify systematic deviations in biomarker measurements from the expected distributions.

Results

In the total screened population, the median (95% CI) MoM values of MAP, UtA-PI and PlGF were 0.961 (0.956-0.965), 1.018 (0.996-1.030) and 0.891 (0.861-0.909), respectively. Women in this largely Asian cohort had approximately 4% and 11% lower MAP and PlGF MoM levels, respectively, compared with those expected from normal median formulae, based on a largely Caucasian population, whilst UtA-PI MoM values were similar. UtA-PI and PlGF MoMs were beyond the 0.4 to 2.5 MoM range (truncation limits) in 16 (0.4%) and 256 (6.4%) pregnancies, respectively. QA assessment tools indicated that women in all centers had consistently lower MAP MoM values than expected, but were within 10% of the expected value. UtA-PI MoM values were within 10% of the expected value at all sites except one. Most PlGF MoM values were systematically 10% lower than the expected value, except for those derived from a South Asian population, which were 37% higher.

Conclusion

Owing to the anthropometric differences in Asian compared with Caucasian women, significant differences in biomarker MoM values for PE screening, particularly MAP and PlGF MoMs, were noted in Asian populations compared with the expected values based on European-derived formulae. If reliable and consistent patient-specific risks for preterm PE are to be reported, adjustment for additional factors or development of Asian-specific formulae for the calculation of biomarker MoMs is required. We have also demonstrated the importance and need for regular quality assessment of biomarker values.

Routine first trimester combined screening for preterm preeclampsia in Australia: A multicenter clinical implementation cohort study

D. Rolnik, R. Selvaratnam, D. Wertaschnigg, S. Meagher, E. Wallace, J. Hyett, et al.

Int J Gynaecol Obstet 2021

Objective

To assess pregnancy outcomes following first trimester combined screening for preterm preeclampsia in Australia.

Methods

We compared pregnancy outcomes of women with singleton pregnancies who underwent first trimester combined preeclampsia screening with the Fetal Medicine Foundation algorithm between 2014 and 2017 in Melbourne and Sydney, Australia, with those from women who received standard care. The primary outcomes were preterm preeclampsia and screening performance. Effect estimates were presented as risk ratios with 95% confidence intervals.

Results

A total of 29 618 women underwent combined screening and 301 566 women received standard care. Women who had combined screening were less likely to have preeclampsia, preterm birth, small neonates, and low Apgar scores than the general population. Women with high-risk results (≥1 in 100) were more likely to develop preterm preeclampsia (2.1% vs. 0.7%, risk ratio [RR] 3.04, 95% CI 2.46-3.77), while low-risk women (risk <1 in 100) had lower rates of preterm preeclampsia (0.2% vs. 0.7%, RR 0.26, 95% CI 0.19-0.35) and other pregnancy complications. Screening detected 65.2% (95% CI 56.4-73.2%) of all preterm preeclampsia cases, with improved performance after adjustment for treatment effect.

Conclusion

First trimester screening for preeclampsia in clinical practice identified a population at high risk of adverse pregnancy outcomes and low-risk women who may be suitable for less intensive antenatal care.

Impact of replacing or adding pregnancy-associated plasma protein-A at 11-13 weeks on screening for preterm pre-eclampsia

Y. Wah, D. Sahota, P. Chaemsaithong, L. Wong, A. Kwan, Y. Ting, et al.

Ultrasound Obstet Gynecol 2022 Vol. 60 Issue 2 Pages 200-206

Objective

To assess whether pregnancy-associated plasma protein-A (PAPP-A) alters or provides equivalent screening performance as placental growth factor (PlGF) when screening for preterm pre-eclampsia (PE) at 11-13 weeks of gestation.

Methods

This was a secondary analysis of a non-intervention screening study of 6546 singleton pregnancies that were screened prospectively for preterm PE in the first trimester between December 2016 and June 2018. Patient-specific risks for preterm PE were estimated by maternal history, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), PlGF and PAPP-A. A competing-risks model with biomarkers expressed as multiples of the median was used. All women and clinicians were blinded to the risk for preterm PE. The performance of screening for preterm PE using PlGF vs PAPP-A vs both PAPP-A and PlGF was assessed by comparing areas under the receiver-operating-characteristics (AUC) curves. McNemar's test was used to compare detection rate at a fixed false-positive rate (FPR) of 10%.

Results

PlGF and PAPP-A were measured in 6546 women, of whom 37 developed preterm PE. The AUC and detection rate at 10% FPR using PlGF in combination with maternal history, MAP and UtA-PI were 0.854 and 59.46%, respectively. The respective values were 0.813 and 51.35% when replacing PlGF with PAPP-A and 0.855 and 59.46% when using both PAPP-A and PlGF. Statistically non-significant differences were noted in AUC when replacing PlGF with PAPP-A (ΔAUC, 0.04; P = 0.095) and when using both PAPP-A and PlGF (ΔAUC, 0.002; P = 0.423). However, on an individual case basis, screening using PlGF in conjunction with maternal history, MAP and UtA-PI identified three (8.1%) additional pregnancies that developed preterm PE and that were not identified when replacing PlGF with PAPP-A. Screening using PAPP-A in addition to maternal history and other biomarkers did not identify any additional pregnancies.

Conclusion

On an individual case basis, adoption of a screening strategy that uses PAPP-A instead of PlGF results in reduced detection of preterm PE, consistent with previous literature.

1st trimester pre-eclampsia screening with Thermo Scientific B·R·A·H·M·S KRYPTOR Assays

Country publications Canada

Does low PAPP-A predict adverse placenta-mediated outcomes in a low-risk nulliparous population? The Great Obstetrical Syndromes (GOS) study

A. Boutin, C. Gasse, S. Demers, G. Blanchet, Y. Giguère and E. Bujold

J Obstet Gynaecol Can 2018 Vol. 40 Issue 6 Pages 663-668

Objective

First-trimester low concentration of pregnancy-associated plasma protein A (PAPP-A) has been associated with adverse perinatal outcomes in high-risk populations. This study aimed to estimate the ability of PAPP-A to identify adverse outcomes in a low-risk population.

Methods

The study investigators recruited nulliparous women with singleton pregnancy at their 11-13-week ultrasound scan. Serum samples were collected, and maternal PAPP-A concentration was measured using the B·R·A·H·M·S PAPP-A KRYPTOR (ThermoFisher Scientific, Hennigsdorf, Germany) automated assay. PAPP-A was reported in multiple of median (MoM) adjusted for GA. Participants were followed until delivery for pregnancy outcomes including preeclampsia (PE), SGA <3rd percentile, and fetal death. Receiver operating characteristic curves with the area under the curve (AUC) were used to evaluate the predictive value of PAPP-A. The investigators calculated the detection rates (DRs) and positive predictive values (PPVs) of a PAPP-A < 0.4 MoM.

Results

The study investigators recruited 4739 eligible participants at a mean GA of 13 ± 6 weeks. The investigators observed 232 (4.9%) cases of PE, 84 (1.8%) cases of SGA, and 14 (0.3%) fetal deaths. PAPP-A was moderately associated with PE (AUC 0.57; 95% CI 0.53-0.61) and SGA (AUC 0.62; 95% CI 0.56-0.69), but not with fetal death (AUC 0.43; 95% CI 0.23-0.63). PAPP-A < 0.4 MoM was observed in 364 (7.7%) participants and had poor predictive values for PE (DR 9.8%; PPV 6.3%), SGA (DR 18.1%; PPV 4.4%), and fetal death (DR 21.4%; PPV 0.9%).

Conclusion

Isolated first trimester PAPP-A has a limited predictive value for adverse pregnancy outcomes (other than trisomies). Low PAPP-A (<0.4 MoM) should be used in combination with other markers for the prediction of PE, SGA, or fetal death, and it does not constitute an indication for low-dose aspirin.

First-trimester placental growth factor for the prediction of preeclampsia in nulliparous women: The Great Obstetrical Syndromes cohort study

A. Boutin, S. Demers, C. Gasse, Y. Giguère, A. Tétu, G. Laforest, et al.

Fetal Diagn Ther 2019 Vol. 45 Issue 2 Pages 69-75

Background

First-trimester maternal serum markers have been associated with preeclampsia (PE). We aimed to evaluate the performance of first-trimester placental growth factor (PlGF) for the prediction of PE in nulliparous women.

Subjects and Methods

We conducted a prospective cohort study of nulliparous women with singleton pregnancy at 11-13 weeks. Maternal serum PlGF concentration was measured using B·R·A·H·M·S PlGFplus KRYPTOR automated assays and reported in multiple of the median adjusted for gestational age. We used proportional hazard models, along with receiver operating characteristic curves and areas under the curve (AUC).

Results

Out of 4,652 participants, we observed 232 (4.9%) cases of PE including 202 (4.3%) term and 30 (0.6%) preterm PE. PlGF was associated with the risk of term (AUC = 0.61, 95% confidence interval [CI] 0.57-0.65) and preterm PE (AUC = 0.73, 95% CI 0.64-0.83). The models were improved with the addition of maternal characteristics (AUC for term PE 0.66, 95% CI 0.62-0.71; AUC for preterm PE 0.81, 95% CI 0.72-0.91; $p < 0.01$). At a false-positive rate of 10%, PlGF combined with maternal characteristics could have predicted 26% of term and 55% of preterm PE. The addition of pregnancy-associated plasma protein A did not significantly improve the prediction models.

Conclusion

First-trimester PlGF combined with maternal characteristics is useful to predict preterm PE in nulliparous women.

First-trimester preterm preeclampsia screening in nulliparous women: The Great Obstetrical Syndrome (GOS) study

A. Boutin, C. Gasse, P. Guerby, Y. Giguère, A. Tétu and E. Bujold

J Obstet Gynaecol Can 2021 Vol. 43 Issue 1 Pages 43-49

Objectives

To estimate the ability of a combination of first-trimester markers to predict preterm preeclampsia in nulliparous women.

Methods

We conducted a prospective cohort study of nulliparous women with singleton gestations, recruited between 11(0) and 13 (6) weeks gestation. Data on the following were collected: maternal age; ethnicity; chronic diseases; use of fertility treatment; body mass index; mean arterial blood pressure (MAP); serum levels of pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), alpha fetoprotein (AFP), free beta human chorionic gonadotropin (ß-hCG); and mean uterine artery pulsatility index (UtA-PI). We constructed a proportional hazard model for the prediction of preterm preeclampsia selected based on the Akaike information criterion. A receiver operating characteristic curve was created with the predicted risk from the final model. Our primary outcome was preterm preeclampsia and our secondary outcome was a composite of preeclampsia, small for gestational age, intrauterine death, and preterm birth.

Results

Among 4659 nulliparous women with singleton gestations, our final model included 4 variables: MAP MoM, log(10) PlGF MoM, log(10) AFP MoM and log(10) UtA-PI MoM. We obtained an area under the curve of 0.84 (95% CI 0.75-0.93) with a detection rate of preterm preeclampsia of 55% (95% CI 37%-73%) and a false-positive rate of 10%. Using a risk cut-off with a false-positive rate of 10%, the positive predictive value for our composite outcome was 33% (95% CI 29%-37%).

Conclusion

The combination of MAP, maternal serum PlGF and AFP, and UtA-PI are useful to identify nulliparous women at high risk of preterm preeclampsia but also at high risk of other great obstetrical syndromes.

Pregnancy outcomes in nulliparous women with positive first-trimester preterm preeclampsia screening test: The Great Obstetrical Syndromes cohort study

A. Boutin, P. Guerby, C. Gasse, S. Tapp and E. Bujold

Am J Obstet Gynecol 2021 Vol. 224 Issue 2 Pages 204.e1-204.e7

Background

The Fetal Medicine Foundation proposed a competing risks model for early identification of women at a high risk of preterm preeclampsia, typically associated with deep placentation disorders. The Great Obstetrical Syndromes include a spectrum of pregnancy complications (preeclampsia, intrauterine growth restriction, preterm birth, late spontaneous abortion, and abruptio placentae) that are also associated with deep placentation disorders.

Objective

This study aimed to estimate the rate of placenta-mediated pregnancy complications in nulliparous women with a positive first-trimester Fetal Medicine Foundation preterm preeclampsia screening test.

Study Design

We conducted a prospective cohort study of nulliparous women recruited at 11 to 14 weeks of gestation. Maternal characteristics, mean arterial blood pressure, levels of maternal serum biomarkers (pregnancy-associated plasma protein-A, placental growth factor, and soluble fms-like tyrosine kinase-1), and mean uterine artery pulsatility index were obtained to calculate the risk of preterm preeclampsia according to the Fetal Medicine Foundation algorithm. The predicted risks were dichotomized as a positive or negative test according to 2 risk cutoffs (1 in 70 and 1 in 100). The detection rate, false-positive rate, and positive and negative predictive values were calculated for placenta-mediated complications, including preeclampsia, small for gestational age (birthweight <10th percentile), fetal death, preterm birth, and a composite outcome, including any of the foregoing. The same analyses were computed for a composite of severe outcomes, including preterm preeclampsia, severe small for gestational age (less than third percentile), and fetal death.

Results

We included 4575 participants with complete observations, of whom 494 (10.8%) had an estimated risk of preterm preeclampsia of ≥1 in 70 and 728 (15.9%) had a risk of ≥1 in 100. The test based on a risk cutoff of 1 in 70 could have correctly predicted up to 27% of preeclampsia, 55% of preterm preeclampsia, 18% of small for gestational age, 24% of severe small for gestational age, and 37% of fetal deaths at a 10% false-positive rate. The test based on a cutoff of 1 in 100 could have predicted correctly up to 35% of preeclampsia, 69% of preterm preeclampsia, 25% of small for gestational age, 30% of severe small for gestational age, and 53% of fetal deaths at a 15% false-positive rate. The positive predictive value of a screening test for preterm preeclampsia of ≥1 in 70 was 3% for preterm preeclampsia, 32% for the composite outcome, and 9% for the severe composite outcome.

Conclusion

Nulliparous women with a first-trimester positive preterm preeclampsia Fetal Medicine Foundation screening test are at a higher risk of both preterm preeclampsia and other severe placenta-mediated pregnancy complications. Approximately 1 woman of 10 identified as high risk by the Fetal Medicine Foundation algorithm developed at least 1 severe placenta-mediated pregnancy complication.

1st trimester pre-eclampsia screening with Thermo Scientific B·R·A·H·M·S KRYPTOR Assays

Country publications Europe

Screening for pre-eclampsia and fetal growth restriction by uterine artery doppler and PAPP-A at 11-14 weeks' gestation

A. Pilalis, A. Souka, P. Antsaklis, G. Daskalakis, N. Papantoniou, S. Mesogitis, et al.

Ultrasound Obstet Gynecol 2007 Vol. 29 Issue 2 Pages 135-40

Objective

To assess the role of maternal demographic characteristics, uterine artery Doppler velocimetry, maternal serum pregnancy-associated plasma protein-A (PAPP-A) and their combination in screening for pre-eclampsia and small-for-gestational age (SGA) fetuses at 11-14 weeks.

Methods

This was a prospective study of 878 consecutive women presenting for a routine prenatal ultrasound examination at 11-14 weeks. Pulsed wave Doppler was then used to obtain uterine artery flow velocity waveforms and the mean pulsatility index (PI) of the uterine arteries was calculated. Maternal serum samples for PAPP-A were assayed. Along with maternal history, these measurements were compared in their ability to predict adverse outcome, defined as pre-eclampsia and/or SGA and/or placental abruption.

Results

Mean uterine artery PI > or = 95(th) centile and PAPP-A < or = 10(th) centile each predicted 23% of the women that developed pre-eclampsia and 43% of cases of placental abruption. For SGA < or = 5(th) centile, mean uterine artery PI > or = 95(th) centile predicted 23% of cases and PAPP-A < or = 10(th) centile predicted 34%. Independent predictors for subsequent development of pre-eclampsia were increased mean uterine artery PI > or = 95(th) centile (OR, 2.76; 95% CI, 1.11-6.81) and maternal history of pre-eclampsia/hypertension (OR, 50.54; 95% CI, 10.52-242.73). The predicting factors for SGA < or = 5(th) centile were increased mean uterine artery PI > or = 95(th) centile (OR, 2.0; 95% CI, 1.07-3.74) and low PAPP-A (OR, 0.43; 95% CI, 0.20-0.93). Increased uterine artery PI was the only independent factor in the prediction of placental abruption (OR, 8.49; 95% CI, 2.78-25.94). The combination of uterine artery PI and maternal history of pre-eclampsia/hypertension was better than was using uterine artery Doppler alone in predicting pre-eclampsia. Similarly, for the prediction of SGA < or = 5(th) centile, combining uterine artery Doppler and maternal serum PAPP-A was better than was uterine artery Doppler alone. In both cases, the difference approached statistical significance.

Conclusion

The combination of maternal history with abnormal uterine artery Doppler and low PAPP-A level at 11-14 weeks achieves better results than does either test alone in the prediction of pre-eclampsia and SGA.

Maternal serum placental growth factor (PlGF) isoforms 1 and 2 at 11-13 weeks' gestation in normal and pathological pregnancies

M. Nucci, L. Poon, G. Demirdjian, B. Darbouret and K. Nicolaides

Fetal Diagn Ther 2014 Vol. 36 Issue 2 Pages 106-16

Objective

To compare the maternal serum concentration of placental growth factor-1 (PlGF-1) and PlGF-2 at 11-13 weeks' gestation in normal pregnancies and in those complicated by preeclampsia (PE), delivery of small for gestational age (SGA) neonates and fetal trisomies 21, 18 and 13.

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 (MoM) 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) and trisomy 13 (0.373 and 0.699 MoM).

Conclusion

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.

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

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

Swiss Med Wkly 2017 Vol. 147 Pages w14498

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.

Materials 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.

Conclusion

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..

Targeted screening for pre-eclampsia in the first trimester of pregnancy at Toulouse University Hospital

A. Genoux, P. Guerby, M. Morin, B. Perret, C. Vayssière and S. Hamdi

Ann Cardiol Angeiol (Paris) 2018 Vol. 67 Issue 3 Pages 111-118

Goals

Preeclampsia (PE) is a leading cause of maternal and neonatal morbidity and mortality. Early treatment by aspirin has been shown to significantly reduce PE risk before 37weeks supporting the implementation of first-trimester screening.

Subjects and Methods

A targeted screening was recently implemented at Toulouse University Hospital for women in their first pregnancy or those with personal or familial history of PE. It uses Fetal Medicine Foundation (FMF) algorithm that combines maternal characteristics, clinical, biophysical and biochemical (PAPP-A, Pregnancy Associated Plasma Protein-A, and PlGF, Placental Growth Factor) data. We describe this first population of pregnant women and compare our results with those of a mini-test that excludes PlGF and biophysical data.

Results

Between October 2016 and September 2017, 500women have benefited from this screening. In such targeted population, we identified 3,6 % (n=18) of women at high risk to develop PE before 34 weeks and 9,6 % (n=48) of women at high risk to develop PE between 34 and 37 weeks. When we recalculated the risk using the mini-test, only 10 women (56 %) were identified at high risk of early PE.

Conclusion

For the first time in France, we report the result of a targeted screening of PE during the first trimester using the FMF algorithm. We describe the screened population and show that it is more efficient than the mini-test.

Prediction and prevention of small-for-gestational-age neonates: Evidence from SPREE and ASPRE

M. Tan, L. Poon, D. Rolnik, A. Syngelaki, C. de Paco Matallana, R. Akolekar, et al.

Ultrasound Obstet Gynecol 2018 Vol. 52 Issue 1 Pages 52-59

Objectives

To examine the effect of first-trimester screening for pre-eclampsia (PE) on the prediction of delivering a small-for-gestational-age (SGA) neonate and the effect of prophylactic use of aspirin on the prevention of SGA.

Methods

The data for this study were derived from two multicenter studies. In SPREE, we investigated the performance of screening for PE by a combination of maternal characteristics and biomarkers at 11-13 weeks' gestation. In ASPRE, women with a singleton pregnancy identified by combined screening as being at high risk for preterm PE (>1 in 100) participated in a trial of aspirin (150 mg/day from 11-14 until 36 weeks' gestation) compared to placebo. In this study, we used the data from the ASPRE trial to estimate the effect of aspirin on the incidence of SGA with birth weight <10(th) , <5(th) and <3(rd) percentile for gestational age. We also used the data from SPREE to estimate the proportion of SGA in the pregnancies with a risk for preterm PE of >1 in 100.

Results

In SPREE, screening for preterm PE by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor identified a high-risk group that contained about 46% of SGA neonates <10(th) percentile born at <37 weeks' gestation (preterm) and 56% of those born at <32 weeks (early); the overall screen-positive rate was 12.2% (2014 of 16 451 pregnancies). In the ASPRE trial, use of aspirin reduced the overall incidence of SGA <10(th) percentile by about 40% in babies born at <37 weeks' gestation and by about 70% in babies born at <32 weeks; in babies born at ≥37 weeks, aspirin did not have a significant effect on incidence of SGA. The aspirin-related decrease in incidence of SGA was mainly due to its incidence decreasing in pregnancies with PE, for which the decrease was about 70% in babies born at <37 weeks' gestation and about 90% in babies born at <32 weeks. On the basis of these results, it was estimated that first-trimester screening for preterm PE and use of aspirin in the high-risk group would potentially reduce the incidence of preterm and early SGA by about 20% and 40%, respectively.

Conclusion

First-trimester screening for PE by the combined test identifies a high proportion of cases of preterm SGA that can be prevented by the prophylactic use of aspirin.

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

M. Tan, A. Syngelaki, L. Poon, D. Rolnik, N. O'Gorman, J. Delgado, et al.

Ultrasound Obstet Gynecol 2018 Vol. 52 Issue 2 Pages 186-195

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.

Conclusion

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

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

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

Ultrasound Obstet Gynecol 2018 Vol. 51 Issue 6 Pages 743-750

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%).

Conclusion

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

Two-stage screening for preterm preeclampsia at 11-13 weeks' gestation

A. Wright, D. Wright, A. Syngelaki, A. Georgantis and K. Nicolaides

Am J Obstet Gynecol 2019 Vol. 220 Issue 2 Pages 197.e1-197.e11

Background

Screening for preeclampsia at 11-13 weeks' gestation by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor (triple test) can predict about 90% of preeclampsia, with delivery at <32 weeks (early-preeclampsia), and 75% of preeclampsia with delivery at <37 weeks (preterm preeclampsia), at a screen-positive rate of 10%. In pregnancies identified as being at high risk for preeclampsia by such screening, administration of aspirin (150 mg/d from 11 to 14 weeks' gestation to 36 weeks) reduces the rate of early preeclampsia by about 90% and preterm preeclampsia by about 60%. Recording of maternal history and blood pressure are part of routine prenatal care, but measurement of uterine artery pulsatility index and placental growth factor require additional costs.

Objective

To explore the possibility of carrying out first-stage screening in the whole population by maternal factors alone or a combination of maternal factors, mean arterial pressure and uterine artery pulsatility index or maternal factors, mean arterial pressure, and placental growth factor and proceeding to second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

Study Design

The data for this study were derived from prospective nonintervention screening for preeclampsia at 11(+0) to 13(+6) weeks' gestation in 61,174 singleton pregnancies. Patient-specific risks of delivery with preeclampsia at <37 and <32 weeks' gestation were calculated using the competing risks model to combine the prior distribution of the gestational age at delivery with preeclampsia, obtained from maternal characteristics and medical history, with various combinations of multiple of the median values of mean arterial pressure, uterine artery pulsatility index, and placental growth factor. We estimated the detection rate of preterm-preeclampsia and early-preeclampsia at overall screen-positive rate of 10%, 15%, and 20% from a policy in which first-stage screening of the whole population is carried out by some of the components of the triple test and second-stage screening by the full triple test on women selected on the basis of results from first-stage screening.

Results

If the method of first-stage screening is maternal factors, then measurements of mean arterial pressure, uterine artery pulsatility index, and placental growth factor can be reserved for only 70% of the population, achieving similar detection rate and screen-positive rate as with screening the whole population with the triple test. In the case of first-stage screening by maternal factors, mean arterial pressure, and uterine artery pulsatility index, then measurement of placental growth factor can be reserved for only 30-40% of the population, and if first-stage screening is by maternal factors, mean arterial pressure, and placental growth factor, measurement of uterine artery pulsatility index can be reserved for only 20-30% of the population. Empirical results were consistent with model-based performance.

Conclusion

Two-stage screening and biomarker testing for only part of the population will have financial benefits over conducting the test for the entire population.

Predictive performance of the competing risk model in screening for preeclampsia

D. Wright, M. Y. Tan, N. O'Gorman, L. Poon, A. Syngelaki, A. Wright, et al.

Am J Obstet Gynecol 2019 Vol. 220 Issue 2 Pages 199.e1-199.e13

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.

Conclusion

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.

First trimester serum angiogenic and anti-angiogenic factors in women with chronic hypertension for the prediction of preeclampsia

D. Nzelu, D. Biris, T. Karampitsakos, K. Nicolaides and N. Kametas

Am J Obstet Gynecol 2020 Vol. 222 Issue 4 Pages 374.e1-374.e9

Background

An imbalance between angiogenic and antiangiogenic factors is thought to be a central pathogenetic mechanism in preeclampsia. In pregnancies that subsequently experience preeclampsia, the maternal serum concentration of the angiogenic placental growth factor is decreased from as early as the first trimester of pregnancy, and the concentration of the antiangiogenic soluble fms-like tyrosine kinase-1 is increased in the last few weeks before the clinical presentation of the disease. Chronic hypertension, which complicates 1-2% of pregnancies, is the highest risk factor for the development of preeclampsia among all other factors in maternal demographic characteristics and medical history. Two previous studies in women with chronic hypertension reported that first-trimester serum placental growth factor and soluble fms-like tyrosine kinase-1 levels were not significantly different between those who experienced superimposed preeclampsia and those who did not, whereas a third study reported that concentrations of placental growth factor were decreased.

Objective

The purpose of this study was to investigate whether, in women with chronic hypertension, serum concentrations of placental growth factor and soluble fms-like tyrosine kinase-1 and soluble fms-like tyrosine kinase-1/placental growth factor ratio at 11(+0)-13(+6) weeks gestation are different between those women who experienced superimposed preeclampsia and those who did not and to compare these values with those in normotensive control subjects.

Study Design

The study population comprised 650 women with chronic hypertension, which included 202 women who experienced superimposed preeclampsia and 448 women who did not experience preeclampsia, and 142 normotensive control subjects. Maternal serum concentration of placental growth factor and soluble fms-like tyrosine kinase-1 were measured by an automated biochemical analyzer and converted into multiples of the expected median with the use of multivariate regression analysis in the control group. Comparisons of placental growth factor and soluble fms-like tyrosine kinase-1 levels and soluble fms-like tyrosine kinase-1/placental growth factor ratio in multiples of the expected median values between the 2 groups of chronic hypertension and the control subjects were made with the analysis of variance or the Kruskal-Wallis test.

Results

In the group of women with chronic hypertension who experienced preeclampsia compared with those women who did not experience preeclampsia, there were significantly lower median concentrations of serum placental growth factor multiples of the expected median (0.904 [interquartile range, 0.771-1.052] vs 0.948 [interquartile range, 0.814-1.093]; P=.014) and soluble fms-like tyrosine kinase-1 multiples of the expected median (0.895 [interquartile range, 0.760-1.033] vs 0.938 [interquartile range, 0.807-1.095]; P=.013); they were both lower than in the normotensive control subjects (1.009 [interquartile range, 0.901-1.111] and 0.991 [interquartile range, 0.861-1.159], respectively; P<.01 for both). There were no significant differences among the 3 groups in soluble fms-like tyrosine kinase-1/placental growth factor ratios. In women with chronic hypertension, serum placental growth factor and soluble fms-like tyrosine kinase-1 levels provided poor prediction of superimposed preeclampsia (area under the curve, 0.567 [95% confidence interval, 0.537-0.615] and 0.546 [95% confidence interval, 0.507-0.585], respectively).

Conclusion

Women with chronic hypertension, and particularly those who subsequently experienced preeclampsia, have reduced first-trimester concentrations of both placental growth factor and soluble fms-like tyrosine kinase-1

Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: The SPREE diagnostic accuracy study

L. Poon, D. Wright, S. Thornton, R. Akolekar, P. Brocklehurst and K. Nicolaides
Southampton (UK): NIHR Journals Library; 2020 Nov.
Efficacy and Mechanism Evaluation.

Background
The traditional method of risk assessment for pre-eclampsia recommended by the National Institute for Health and Care Excellence is based on maternal factors and it recommends that high-risk women should be treated with aspirin. An alternative method of screening is based on the competing risk model, which uses Bayes' theorem to combine maternal factors with mean arterial pressure, the uterine artery pulsatility index, serum placental growth factor and pregnancy-associated plasma protein-A at 11–13 weeks' gestation.

Objective
The primary aim was to compare the performance of screening by risks obtained using the competing risk model with risk assessment using the National Institute for Health and Care Excellence guidelines.

Design
This was a prospective multicentre observational study.

Setting
The setting was seven NHS maternity hospitals in England.

Participants
Participants were women with singleton pregnancy attending for a routine hospital visit at 11(+0)–13(+6) weeks' gestation between April and December 2016.

Main Outcome Measures
The performance of screening for pre-eclampsia by the competing risk model was compared with the National Institute for Health and Care Excellence method. Relative reductions in risk with aspirin prophylaxis of 30% and 60% were assumed for all pre-eclampsia and preterm pre-eclampsia, respectively. The primary comparison was the detection rate of the National Institute for Health and Care Excellence method with the detection rate of a mini-combined test (including maternal factors, mean arterial pressure and pregnancy-associated plasma protein-A) in the prediction of all pre-eclampsia for the same screen-positive rate determined by the National Institute for Health and Care Excellence method.

Results
In 473 (2.8%) of the 16,747 pregnancies there was development of pre-eclampsia, including 142 (0.8%) women with preterm pre-eclampsia. The screen-positive rate by the National Institute for Health and Care Excellence method was 10.3%. For all pre-eclampsia, the false-positive and detection rates by the National Institute for Health and Care Excellence method were 9.7% and 31.6%, respectively. For preterm pre-eclampsia, the false-positive and detection rates were 10.0% and 42.8%, respectively. Compliance with the National Institute for Health and Care Excellence recommendation that high-risk women should be treated with aspirin from the first trimester was 23%. For the same screen-positive rate, the detection rate of the mini-combined test for all pre-eclampsia was 42.8%, which was superior to that of the National Institute for Health and Care Excellence method by 11.2% (95% confidence interval 6.9% to 15.6%). The increase in detection for the same screen-positive rate was accompanied by a reduction in false-positive rate of 0.3%. For the same screen-positive rate as National Institute for Health and Care Excellence, the detection rate for preterm pre-eclampsia by combining maternal factors, mean arterial pressure and placental growth factor was 67.3% compared with 44.1% with the National Institute for Health and Care Excellence method. With the addition of the uterine artery pulsatility index, the detection rate was 78.6%. This was higher than that of the National Institute for Health and Care Excellence method by 35.5% (95% confidence interval 25.2% to 45.8%). Calibration of risks for pre-eclampsia was generally good, with the calibration slope very close to 1.0. The feasibility of incorporating a new biomarker was demonstrated. However, the addition of inhibin A to the full combined test did not improve the detection rates for all pre-eclampsia and preterm pre-eclampsia (61% and 80%, respectively). The same screening model for preterm pre-eclampsia by a combination of maternal factors, mean arterial pressure, the uterine artery pulsatility index and placental growth factor achieved detection rates of 45.8% and 56.3%, respectively, for preterm small for gestational age and early small for gestational age neonates.

Limitation
The study did not include a health economic assessment.

Conclusion
The findings suggest that performance of screening for pre-eclampsia provided by a combination of maternal factors and biomarkers is superior to that achieved by current National Institute for Health and Care Excellence guidelines.

Future Work
Future work is required to identify potential biomarkers for further improvement of the competing risk model and to carry out a health economic assessment.

Trial Registration
Current Controlled Trials ISRCTN83611527.

Funding
This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in Efficacy and Mechanism Evaluation; Vol. 7, No. 8. See the NIHR Journals Library website for further project information.
This study demonstrated that the performance of first-trimester screening for pre-eclampsia by a combination of maternal factors and biomarkers was superior to that achieved by current NICE guidelines.

Prediction of pre-eclampsia in twin pregnancy by maternal factors and biomarkers at 11-13 weeks' gestation: Data from EVENTS trial

Z. Benkő, A. Wright, A. Rehal, B. Cimpoca, A. Syngelaki, J. Delgado, et al.

Ultrasound Obstet Gynecol 2021 Vol. 57 Issue 2 Pages 257-265

Objectives

First, to validate a previously developed model for screening for pre-eclampsia (PE) by maternal characteristics and medical history in twin pregnancies; second, to compare the distributions 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) in twin pregnancies that delivered with PE to those in singleton pregnancies and to develop new models based on these results; and, third, to examine the predictive performance of these models in screening for PE with delivery at <32 and <37 weeks' gestation.

Methods

Two datasets of prospective non-intervention multicenter screening studies for PE in twin pregnancies at 11+0 to 13+6 weeks' gestation were used. The first dataset was from the EVENTS (Early vaginal progesterone for the preVention of spontaneous prEterm birth iN TwinS) trial and the second was from a previously reported study that examined the distributions of biomarkers in twin pregnancies. Maternal demographic characteristics and medical history from the EVENTS-trial dataset were used to assess the validity of risks from our previously developed model. The combined data from the first and second datasets were used to compare the distributional properties of log(10) multiples of the median (MoM) values of UtA-PI, MAP, PlGF and PAPP-A in twin pregnancies that delivered with PE to those in singleton pregnancies and develop new models based on these results. The competing-risks model was used to estimate the individual patient-specific risks of delivery with PE at <32 and <37 weeks' gestation. Screening performance was measured by detection rates (DR) and areas under the receiver-operating-characteristics curve.

Results

The EVENTS-trial dataset comprised 1798 pregnancies, including 168 (9.3%) that developed PE. In the validation of the prior model based on maternal characteristics and medical history, calibration plots demonstrated very good agreement between the predicted risks and the observed incidence of PE (calibration slope and intercept for PE <32 weeks were 0.827 and 0.009, respectively, and for PE <37 weeks they were 0.942 and -0.207, respectively). In the combined data, there were 3938 pregnancies, including 339 (8.6%) that developed PE and 253 (6.4%) that delivered with PE at <37 weeks' gestation. In twin pregnancies that delivered with PE, MAP, UtA-PI and PlGF were, at earlier gestational ages, more discriminative than in singleton pregnancies and at later gestational ages they were less so. For PAPP-A, there was little difference between PE and unaffected pregnancies. The best performance of screening for PE was achieved by a combination of maternal factors, MAP, UtA-PI and PlGF. In screening by maternal factors alone, the DR, at a 10% false-positive rate, was 30.6% for delivery with PE at <32 weeks' gestation and this increased to 86.4% when screening by the combined test; the respective values for PE <37 weeks were 24.9% and 41.1%.

Conclusions

In the assessment of risk for PE in twin pregnancy, we can use the same prior model based on maternal characteristics and medical history as reported previously, but in the calculation of posterior risks it is necessary to use the new distributions of log(10) MoM values of UtA-PI, MAP and PlGF according to gestational age at delivery with PE. © 2020 International Society of Ultrasound in Obstetrics and Gynecology.

Clinical implementation of pre-eclampsia screening in the first trimester of pregnancy

A. Cordisco, E. Periti, N. Antoniolli, V. Lozza, S. Conticini, G. Vannucci, et al.

Pregnancy Hypertens 2021 Vol. 25 Pages 34-38

Objectives

Early identification of preeclampia in the first trimester of pregnancy represents one of the major challenges of modern fetal medicine. The primary aim of our study was to evaluate the effectiveness of implementation of preeclampsia screening in Tuscany, Italy. The secondary aim was to evaluate pregnancy/neonatal outcome in the positive screening group compared with the negative screening group.

Study Design

Retrospective study including singleton pregnancies undergoing screening for preeclampsia. The screening test was a multiparametric algorithm based on maternal history, biochemical and biophysical parameters (Fetal Medicine Foundation algorithm).

Main Outcome Measures

The overall performance of the test was calculated, in terms of sensitivity, specificity, positive and negative predictive value and in relation to gestational age at onset (primary aim). Pregnancy and neonatal outcomes were then compared between the positive and negative population at preeclampsia screening test (secondary aim).

Results

Of the 5719 patients enrolled, 4797 were included in the analysis. The sensitivity for early onset of preeclampsia (≤34 weeks) was 0.75 (CI:0.41-0.93) and specificity 0.93 (CI:0.92-0.94) for a false positive rate of 7%. The population that tested positive for preeclampsia screening showed a higher incidence of deliveries at lower gestational ages ($p < 0.001$), preeclampsia onset despite prophylaxis with aspirin ($p < 0.001$), emergency caesarean section ($p < 0.001$), low fetal birth weight ($p < 0.001$) and neonatal admission in intensive care unit ($p < 0.001$).

Conclusions

Our data confirm the validity of first trimester screening test in identifying a category of patients at greatest risk for preeclampsia even in the presence of a post-test pharmacological prophylaxis.

Performance of first-trimester combined screening of preterm pre-eclampsia: Results from cohort of 10 110 pregnancies in Spain

D. Gómez, C. De Paco Matallana, V. Rolle, N. Valiño, R. Revello, B. Adiego, et al.

Ultrasound Obstet Gynecol 2023

Objective

To evaluate the diagnostic accuracy of the Fetal Medicine Foundation (FMF) competing risk model (the triple test) for the prediction of preterm pre-eclampsia (PE) in a Spanish population.

Methods

This was a prospective cohort study performed in eight fetal-medicine units in five different regions of Spain between September 2017 and December 2019. All pregnant women with singleton pregnancies and non-malformed live fetuses attending their routine ultrasound examination at 11(+0) -13(+6) weeks' gestation were invited to participate in the study. We recorded maternal demographic characteristics and medical history and measured MAP, UtA-PI, and serum PlGF and PAPP-A following standardized protocols. We also recorded whether the women were treated with aspirin during pregnancy. The raw values of the biomarkers were converted into multiples of the median (MoM), and audits were periodically performed for the operators and laboratories to receive continuous feedback. Risks for term and preterm PE were calculated according to the FMF competing risks model blinded to outcome. The performance of screening for PE, taking account of aspirin, was assessed by calculating the areas under the receiver-operating-characteristics curve (AUROC) and detection rates (DRs) with 95% confidence intervals (CI) at different fixed screen-positive rates (SPRs). Risk calibration was also assessed.

Results

The study population comprised 10,110 singleton pregnancies, including 72 (0.7%) that developed preterm PE. Compared to those without PE, the median MAP and UtA-PI were significantly higher in the preterm PE group, and the median serum PlGF and pregnancy-associated plasma protein A (PAPP-A) were significantly lower. In the PE group, the deviation in biomarkers from normal was inversely related to the gestational age at delivery. In screening by a combination of maternal characteristics and medical history with MAP, UtA-PI, and PlGF, at an SPR of 10%, the DR of preterm PE was 72.7 (95% CI, 62.9-82.6). An alternative strategy of replacing PlGF with PAPP-A in the triple test was associated with poorer screening performance; the DR was 66.5% (95% CI, 55.8-77.2). Calibration plots showed good agreement between predicted and observed cases of preterm PE, with a slope of 0.983 (0.846-1.120) and an intercept of 0.154 (-0.091 to 0.397). Our DR of preterm PE at 10% SPR by the triple test was lower than that reported by the FMF (72.7% vs. 74.8%).

Conclusions

The FMF model is effective in predicting preterm PE in the Spanish population. This method of screening is feasible and easy to implement in routine clinical practice, but it must be accompanied by a good audit and monitoring system, which helps ensure the quality of the screening.

Screening for pre-eclampsia with competing risks model using placental growth factor measurements in blood samples collected before 11 weeks' gestation

I. Riishede, C. Ekelund, L. Sperling, M. Overgaard, C. Knudsen, T. Clausen, et al.

Ultrasound Obstet Gynecol 2023

Objectives

To describe the distributional properties and assess the performance of placental growth factor (PlGF) measured in blood samples collected before 11 weeks' gestation in prediction of preeclampsia.

Methods

The study population consisted of pregnant women included in the PRESIDE study (Preeclampsia Screening in Denmark) with a PlGF measurement from the routine combined first trimester screening (cFTS) blood sample collected at 8-14 weeks' gestation. PRESIDE was a prospective multicenter study investigating the predictive performance of the Fetal Medicine Foundation (FMF) first trimester screening algorithm for preeclampsia in a Danish population. For the current study, serum concentration of PlGF in the cFTS blood samples was analyzed in batches between January and June 2021.

Results

A total of 8,386 pregnant women were included. The incidence of preeclampsia was 0.7% <37 weeks and 3.0% ≥37 weeks. In blood samples collected at 10 weeks' gestation, multiples of the median (MoM) of PlGF were significantly lower in pregnancies with preeclampsia <37 weeks. However, PlGF MoM did not differ significantly between pregnancies with preeclampsia and unaffected pregnancies in samples collected before 10 weeks' gestation.

Conclusions

Gestational age for PlGF samples might be expanded from 11-14 weeks to 10-14 weeks in risk assessment for preeclampsia using the FMF first trimester screening model. There is little evidence to support the use of PlGF collected before 10 weeks' gestation.

Pre-eclampsia screening in Denmark (PRESIDE): National validation study

I. Riishede, L. Rode, L. Sperling, M. Overgaard, J. Ravn, P. Sandager, et al.

Ultrasound Obstet Gynecol 2023

Objectives

To investigate the predictive performance of the Fetal Medicine Foundation (FMF) first trimester screening algorithm for pre-eclampsia in a Danish population and compare screening performance with the current Danish strategy, which is based on maternal risk factors.

Methods

Women with singleton pregnancies, attending for their first trimester ultrasound scan and screening for aneuploidies, were included at six Danish university hospitals between May 2019 and December 2020. Prenatal data on maternal characteristics and medical history were recorded, and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtPI), serum pregnancy-associated plasma protein-A (PAPP-A), and serum placental growth factor (PlGF) were collected without performing a risk assessment for pre-eclampsia. Acetylsalicylic acid use was registered. After delivery, pregnancy outcome including gestational age at delivery and pre-eclampsia diagnoses were collected. Pre-eclampsia risk assessment for each woman was calculated blinded to outcome using the FMF screening algorithm, preceded by adjustments to the Danish population. Detection rates (DRs) of the FMF algorithm were calculated for a fixed screen-positive rate (SPR) of 10% and for the SPR achieved in the current Danish screening.

Results

A total of 8,783 pregnant women were included with a median age of 30.8 years (IQR, 28.1-33.9). The majority were white (95%), naturally conceiving (90%), non-smokers (97%), who had no family history of pre-eclampsia (96%). The median Body Mass Index was 23.4 kg/m(2) (IQR, 21.2-26.6). UtPI was measured bilaterally with a median value of 1.58 (IQR, 1.27-1.94) and the median resting MAP was 80.5 mmHg (IQR, 76.1-85.4) in two consecutive measurements. A complete risk assessment including maternal characteristics, MAP, UtPI, PlGF, and PAPP-A was available for 8,156 women (92.9%). Among these, 303 (3.7%) developed pre-eclampsia including 55 (0.7%) cases of pre-eclampsia with delivery <37 weeks of gestation and 16 (0.2%) cases of pre-eclampsia with delivery <34 weeks. At a SPR of 10%, the DR for pre-eclampsia <34 weeks was 77.4% (95% CI, 57.6-97.2%), the DR for pre-eclampsia <37 weeks was 66.8% (95% CI, 54.4-79.1%), and the DR for pre-eclampsia at any gestational age was 44.1% (95% CI, 38.5-49.7%). The current Danish screening strategy using maternal risk factors detected 25.0% of women with pre-eclampsia <34 weeks and 19.6% of women with pre-eclampsia <37 weeks at a SPR of 3.4%.

Conclusion

In a large Danish multicenter study, the FMF algorithm predicted 77.4% of pre-eclampsia <34 weeks and 66.8% of pre-eclampsia <37 weeks at a SPR of 10%, suggesting that performance of the algorithm in a Danish cohort matches that in other populations.

Implementing Preeclampsia Screening In Switzerland (IPSISS): First results from a multicentre registry

F. Trottmann, P. Challande, G. Manegold-Brauer, S. Ardabili, I. Hösli, H. Schönberger, et al.

Fetal Diagn Ther 2023 Vol. 50 Issue 6 Pages 406-414

Introduction

The Fetal Medicine Foundation (FMF) London developed a first trimester combined screening algorithm for preterm preeclampsia (pPE) that allows a significantly higher detection of pregnancies at risk compared to conventional screening by maternal risk factors only. The aim of this trial is to validate this screening model in the Swiss population in order to implement this screening into routine first trimester ultrasound and to prescribe low-dose aspirin 150 mg (LDA) in patients at risk for pPE. Therefore, a multicentre registry study collecting and screening pregnancy outcome data was initiated in 2020; these are the preliminary results.

Methods

Between June 1, 2020, and May 31, 2021, we included all singleton pregnancies with pPE screening at the hospitals of Basel, Lucerne, and Bern. Multiple of medians of uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), placental growth factor (PlGF), and pregnancy-associated plasma protein A (PAPP-A) as well as risks were analysed as calculated by each centre's software and recalculated on the FMF online calculator for comparative reasons. Statistical analyses were performed by GraphPad Version 9.1.

Results

During the study period, 1,027 patients with singleton pregnancies were included. 174 (16.9%) had a risk >1:100 at first trimester combined screening. Combining the background risk, MAP, UtA-PI, and PlGF only, the cut-off to obtain a screen positive rate (SPR) of 11% is ≥1:75. Outcomes were available for 968/1,027 (94.3%) of all patients; 951 resulted in live birth. Fifteen (1.58%) developed classical preeclampsia (PE), 23 (2.42%) developed PE according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition.

Conclusion

First trimester combined screening for PE and prevention with LDA results in a low prevalence of PE. The screening algorithm performs according to expectations; however, the cut-off of >1:100 results in a SPR above the accepted range and a cut-off of ≥1:75 should be considered for screening. More data are needed to evaluate, if these results are representative for the general Swiss population.

Validation of machine-learning model for first-trimester prediction of pre-eclampsia using cohort from PREVAL study

M. Gil, D. Cuenca-Gómez, V. Rolle, M. Pertegal, C. Díaz, R. Revello, et al.

Ultrasound Obstet Gynecol 2024 Vol. 63 Issue 1 Pages 68-74

Objective

Effective first-trimester screening for pre-eclampsia (PE) can be achieved using a competing-risks model that combines risk factors from the maternal history with multiples of the median (MoM) values of biomarkers. A new model using artificial intelligence through machine-learning methods has been shown to achieve similar screening performance without the need for conversion of raw data of biomarkers into MoM. This study aimed to investigate whether this model can be used across populations without specific adaptations.

Methods

Previously, a machine-learning model derived with the use of a fully connected neural network for first-trimester prediction of early (<34 weeks), preterm (<37 weeks) and all PE was developed and tested in a cohort of pregnant women in the UK. The model was based on maternal risk factors and mean arterial blood pressure (MAP), uterine artery pulsatility index (UtA-PI), placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A). In this study, the model was applied to a dataset of 10 110 singleton pregnancies examined in Spain who participated in the first-trimester PE validation (PREVAL) study, in which first-trimester screening for PE was carried out using the Fetal Medicine Foundation (FMF) competing-risks model. The performance of screening was assessed by examining the area under the receiver-operating-characteristics curve (AUC) and detection rate (DR) at a 10% screen-positive rate (SPR). These indices were compared with those derived from the application of the FMF competing-risks model. The performance of screening was poor if no adjustment was made for the analyzer used to measure PlGF, which was different in the UK and Spain. Therefore, adjustment for the analyzer used was performed using simple linear regression.

Results

The DRs at 10% SPR for early, preterm and all PE with the machine-learning model were 84.4% (95% CI, 67.2-94.7%), 77.8% (95% CI, 66.4-86.7%) and 55.7% (95% CI, 49.0-62.2%), respectively, with the corresponding AUCs of 0.920 (95% CI, 0.864-0.975), 0.913 (95% CI, 0.882-0.944) and 0.846 (95% CI, 0.820-0.872). This performance was achieved with the use of three of the biomarkers (MAP, UtA-PI and PlGF); inclusion of PAPP-A did not provide significant improvement in DR. The machine-learning model had similar performance to that achieved by the FMF competing-risks model (DR at 10% SPR, 82.7% (95% CI, 69.6-95.8%) for early PE, 72.7% (95% CI, 62.9-82.6%) for preterm PE and 55.1% (95% CI, 48.8-61.4%) for all PE) without requiring specific adaptations to the population.

Conclusions

A machine-learning model for first-trimester prediction of PE based on a neural network provides effective screening for PE that can be applied in different populations. However, before doing so, it is essential to make adjustments for the analyzer used for biochemical testing.

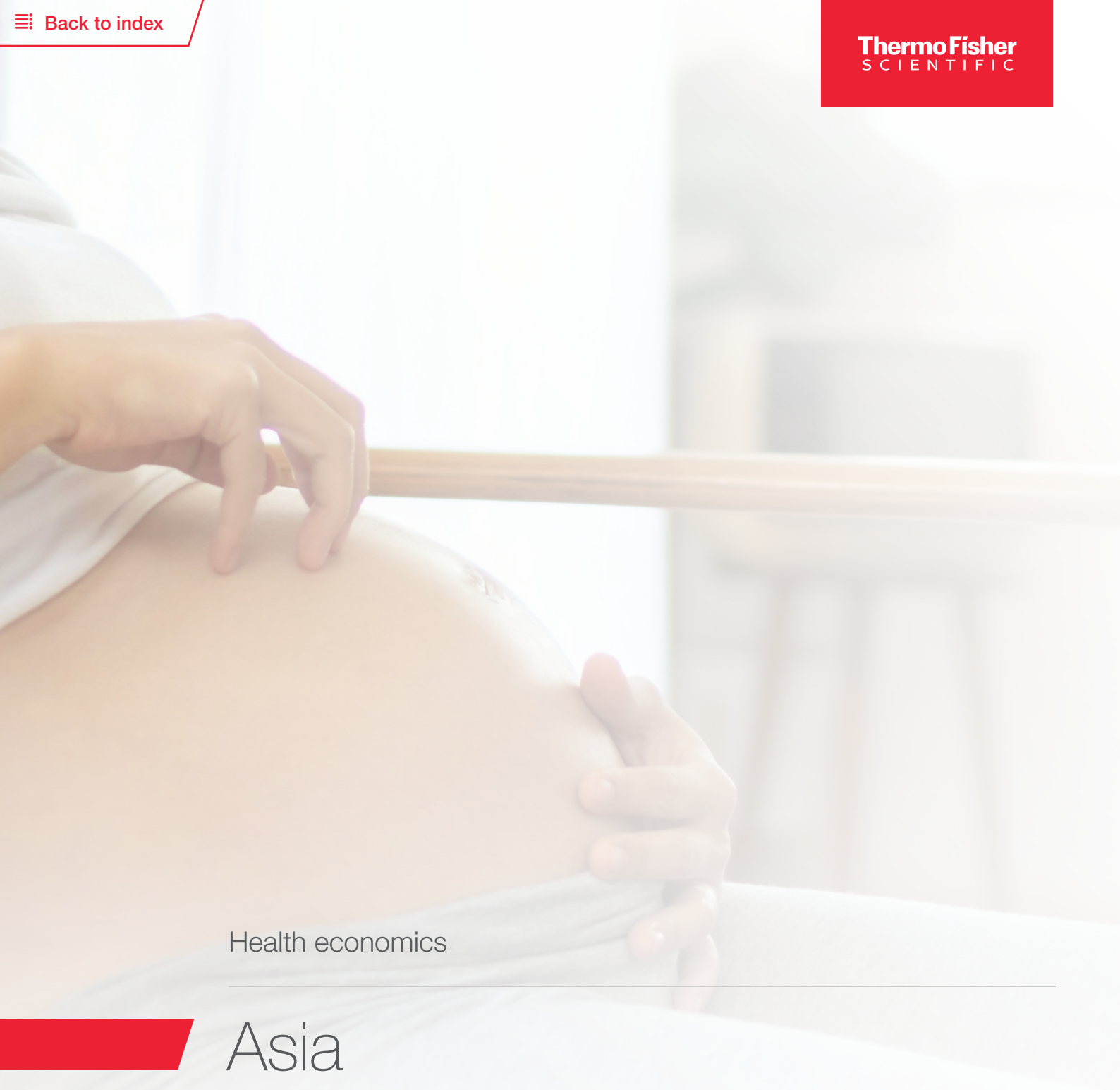
Health economics

Pregenesys pre-eclampsia markers consensus meeting: What do we require from markers, risk assessment and model systems to tailor preventive strategies?

I. Cetin, B. Huppertz, G. Burton, H. Cuckle, R. Gonen, O. Lapaire, et al.

Placenta 2011 Vol. 32 Suppl Pages S4-16

The Pregenesys Consensus Meeting held in Cambridge on 13 July 2009 was organized by the Pregenesys Consortium to review and critically discuss current knowledge regarding early markers of preeclampsia, to identify priorities and opportunities for future research, to consider issues that may need to be addressed in future recommendations and to highlight key issues in cost effectiveness and national policies concerning prediction and early screening for the risk of developing preeclampsia. This report summarizes the outcome of the Consensus Meeting and draws attention to issues for further investigation with specific regard to single versus multiple markers, early versus late risk identification, and the long-term effects on both maternal and perinatal health and the need to include these in any future cost-benefit assessment.



Health economics

Asia

Cost-effectiveness analysis of a model of first-trimester prediction and prevention of preterm pre-eclampsia compared with usual care

F. Park, S. Deeming, N. Bennett and J. Hyett

Ultrasound Obstet Gynecol 2021 Vol. 58 Issue 5 Pages 688-697

Objectives

Pre-eclampsia (PE) causes substantial maternal and neonatal mortality and morbidity. In addition to the personal impact on women, children and their families, PE has a significant economic impact on our society. Recent research suggests that a first-trimester multivariate model is highly predictive of preterm (<37 weeks' gestation) PE and can be combined successfully with targeted prophylaxis (low-dose aspirin), resulting in an 80% reduction in prevalence of disease. The aim of this study was to examine the potential health outcomes and cost implications following introduction of first-trimester prediction and prevention of preterm PE within a public healthcare setting, compared with usual care, and to conduct a cost-effectiveness analysis to inform health-service decisions regarding implementation of such a program.

Methods

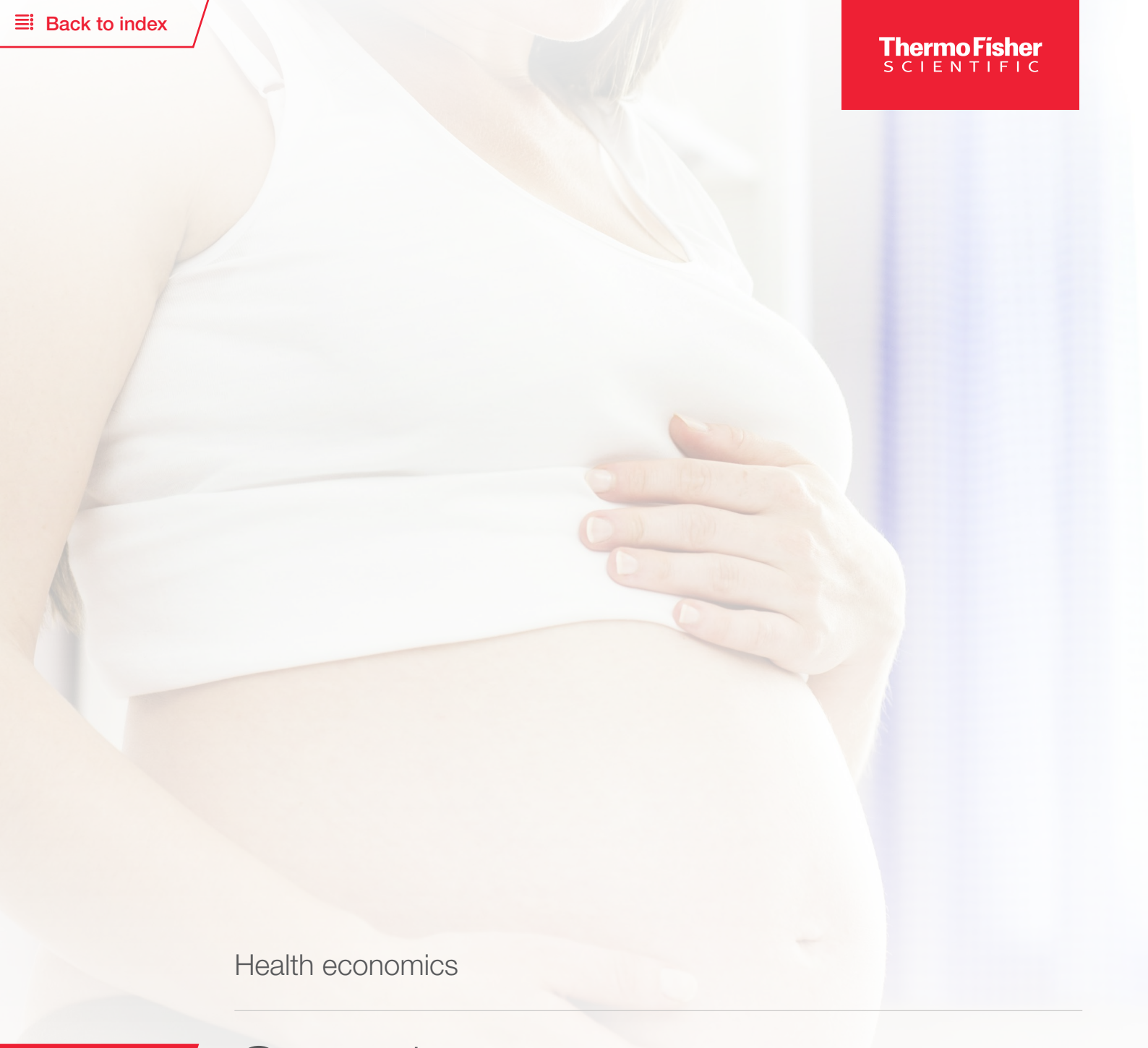
A decision-analytic model was used to compare usual care with the proposed first-trimester screening intervention within the obstetric population (n = 6822) attending two public hospitals within a metropolitan district health service in New South Wales, Australia, between January 2015 and December 2016. The model, applied from early pregnancy, included exposure to a variety of healthcare professionals and addressed type of risk assessment (usual care or first-trimester screening) and use of (compliance with) low-dose aspirin prescribed prophylactically for prevention of PE. All pathways culminated in six possible health outcomes, ranging from no PE to maternal death. Results were presented as the number of cases of PE gained/avoided and the incremental increase/decrease in economic costs arising from the intervention compared with usual care. Significant assumptions were tested in sensitivity/uncertainty analyses.

Results

The intervention produced, across all gestational ages, 31 fewer cases of PE and reduced aggregate economic health-service costs by 1 431 186 Australian dollars over the 2-year period. None of the tested iterations of uncertainty analyses reported additional cases of PE or higher economic costs. The new intervention based on first-trimester screening dominated usual care.

Conclusions

This cost-effectiveness analysis demonstrated a reduction in prevalence of preterm PE and substantial cost savings associated with a population-based program of first-trimester prediction and prevention of PE, and supports implementation of such a policy. .



Health economics

Canada

Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia

D. Ortved, T. Hawkins, J. Johnson, J. Hyett and A. Metcalfe

Ultrasound Obstet Gynecol 2019 Vol. 53 Issue 2 Pages 239-244

Objective

Pre-eclampsia (PE) remains a leading cause of maternal and fetal morbidity and mortality. A first-trimester screening algorithm predicting the risk of early-onset PE has been developed and validated. Early prediction coupled with initiation of aspirin at 11-13 weeks in women identified as high risk is effective at reducing the prevalence of early-onset PE. The aim of this study was to evaluate the cost-effectiveness of this first-trimester screening program coupled with early use of low-dose aspirin in women at high risk of developing early-onset PE, in comparison to current practice in Canada.

Methods

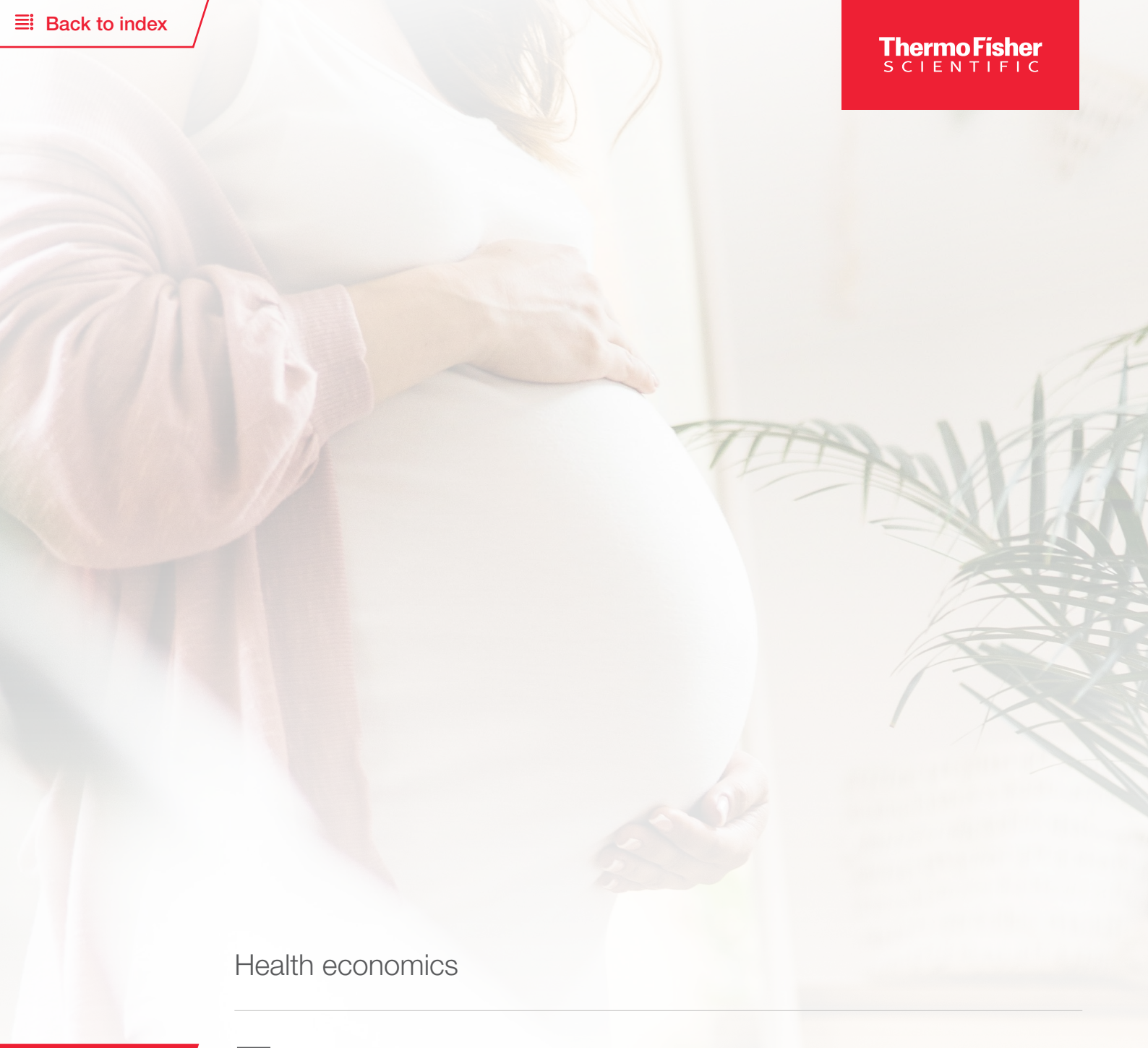
A decision analysis was performed based on a theoretical population of 387 516 live births in Canada in 1 year. The clinical and financial impact of early preventative screening using the Fetal Medicine Foundation algorithm for prediction of early-onset PE coupled with early (< 16 weeks) use of low-dose aspirin in those at high risk was simulated and compared with current practice using decision-tree analysis. The probabilities at each decision point and associated costs of utilized resources were calculated based on published literature and public databases.

Results

Of the theoretical 387 516 births per year, the estimated prevalence of early PE based on first-trimester screening and aspirin use was 705 vs 1801 cases based on the current practice. This was associated with an estimated total cost of C$9.52 million with the first-trimester screening program compared with C$23.91 million with current practice for the diagnosis and management of women with early-onset PE. This equals an annual cost saving to the Canadian healthcare system of approximately C$14.39 million.

Conclusions

The implementation of a first-trimester screening program for PE and early intervention with aspirin in women identified as high risk for early PE has the potential to prevent a significant number of early-onset PE cases with a substantial associated cost saving to the healthcare system in Canada.



Health economics

Europe

Estimating the cost of preeclampsia in the healthcare system: Cross-sectional study using data from SCOPE study (screening for pregnancy end points)

A. Fox, S. McHugh, J. Browne, L. Kenny, A. Fitzgerald, A. Khashan, et al.

Hypertension 2017 Vol. 70 Issue 6 Pages 1243-1249

To estimate the cost of preeclampsia from the national health payer's perspective using secondary data from the SCOPE study (Screening for Pregnancy End Points). SCOPE is an international observational prospective study of healthy nulliparous women with singleton pregnancies. Using data from the Irish cohort recruited between November 2008 and February 2011, all women with preeclampsia and a 10% random sample of women without preeclampsia were selected. Additional health service use data were extracted from the consenting participants' medical records for maternity services which were not included in SCOPE. Unit costs were based on estimates from 3 existing Irish studies. Costs were extrapolated to a national level using a prevalence rate of 5% to 7% among nulliparous pregnancies. Within the cohort of 1774 women, 68 developed preeclampsia (3.8%) and 171 women were randomly selected as controls. Women with preeclampsia used higher levels of maternity services. The average cost of a pregnancy complicated by preeclampsia was €5243 per case compared with €2452 per case for an uncomplicated pregnancy. The national cost of preeclampsia is between €6.5 and €9.1 million per annum based on the 5% to 7% prevalence rate. Postpartum care was the largest contributor to these costs (€4.9-€6.9 million), followed by antepartum care (€0.9-€1.3 million) and peripartum care (€0.6-€0.7 million). Women with preeclampsia generate significantly higher maternity costs than women without preeclampsia. These cost estimates will allow policy-makers to efficiently allocate resources for this pregnancy-specific condition. Moreover, these estimates are useful for future research assessing the cost-effectiveness of preeclampsia screening and treatment.

Aspirin for evidence-based preeclampsia prevention trial: Effect of aspirin on length of stay in the neonatal intensive care unit

D. Wright, D. Rolnik, A. Syngelaki, C. de Paco Matallana, M. Machuca, M. de Alvarado, et al.

Am J Obstet Gynecol 2018 Vol. 218 Issue 6 Pages 612.e1-612.e6

Background

Preeclampsia is a major pregnancy complication with adverse short- and long-term implications for both the mother and baby. Screening for preeclampsia at 11-13 weeks' gestation by a combination of maternal demographic characteristics and medical history with measurements of biomarkers can identify about 75% of women who develop preterm preeclampsia with delivery at <37 weeks' gestation and 90% of those with early preeclampsia at <32 weeks, at a screen-positive rate of 10%. A recent trial (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) has reported that in women identified by first-trimester screening as being at high risk for preeclampsia, use of aspirin (150 mg/d from the first to the third trimester), compared to placebo, reduced the incidence of preterm preeclampsia, which was the primary outcome, by 62% (95% confidence interval, 26-80%) and the incidence of early preeclampsia by 89% (95% confidence interval, 53-97%). The surprising finding of the trial was that despite the reduction in preeclampsia the incidence of admission to the neonatal intensive care unit, which was one of the secondary outcomes, was not significantly affected (odds ratio, 0.93; 95% confidence interval, 0.62-1.40).

Objective

We sought to examine the effect of prophylactic use of aspirin during pregnancy in women at high risk of preeclampsia on length of stay in the neonatal intensive care unit.

Study Design

This was a secondary analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention trial to assess evidence of differences in the effect of aspirin on length of stay in neonatal intensive care. Bootstrapping was used for the comparison of mean length of stay between the aspirin and placebo groups. Logistic regression was used to assess treatment effects on stay in the neonatal intensive care unit.

Results

In the trial there were 1620 participants and 1571 neonates were liveborn. The total length of stay in neonatal intensive care was substantially longer in the placebo than aspirin group (1696 vs 531 days). This is a reflection of significantly shorter mean lengths of stay in babies admitted to the neonatal intensive care unit from the aspirin than the placebo group (11.1 vs 31.4 days), a reduction of 20.3 days (95% confidence interval, 7.0-38.6; P = .008). Neonatal intensive care of babies born at <32 weeks' gestation contributed 1856 (83.3%) of the total of 2227 days in intensive care across both treatment arms. These occurred in 9 (1.2%) of the 777 livebirths in the aspirin group and in 23 (2.9%) of 794 in the placebo group (odds ratio, 0.42; 95% confidence interval, 0.19-0.93; P = .033). Overall, in the whole population, including 0 lengths of stay for those not admitted to the neonatal intensive care unit, the mean length of stay was longer in the placebo than aspirin group (2.06 vs 0.66 days; reduction of 1.4 days; 95% confidence interval, 0.45-2.81; P = .014). This corresponds to a reduction in length of stay of 68% (95% confidence interval, 20-86%).

Conclusion

In pregnancies at high risk of preeclampsia administration of aspirin reduces the length of stay in the neonatal intensive care unit by about 70%. This reduction could essentially be attributed to a decrease in the rate of births at <32 weeks' gestation, mainly because of prevention of early preeclampsia. The findings have implications for both short- and long-term health care costs as well as infant survival and handicap.

Cost-utility of a first-trimester screening strategy versus the standard of care for nulliparous women to prevent pre-term pre-eclampsia in Belgium

A. Dubon Garcia, R. Devlieger, K. Redekop, K. Vandeweyer, S. Verlohren and L. Poon

Pregnancy Hypertens 2021 Vol. 25 Pages 219-224

Objectives

To assess the cost-effectiveness of the Fetal Medicine Foundation (FMF) combined first-trimester pre-eclampsia (PE) screening algorithm, coupled with low-dose aspirin treatment in high-risk patients, compared to the standard of care (SOC; screening based on maternal risk factors) for nulliparous pregnancies in Belgium.

Study Design

A decision analytic model was used to estimate the costs and outcomes for patients screened using the SOC and for those using the FMF screening algorithm, from the Belgian payers' perspective. Where possible, the probabilities and associated costs at each decision point were calculated based on published literature and public databases.

Main Outcome Measures

Cost-effectiveness was assessed using an incremental cost-effectiveness ratio. One-way sensitivity analyses were performed to assess the impact of independent variations in each model parameter. A probabilistic sensitivity analysis was used to estimate the impact of the overall uncertainty of the model on the estimated cost-effectiveness.

Results

Considering an estimated 51,309 pregnancies in nulliparous women in Belgium per year, the FMF screening algorithm resulted in fewer cases of pre-term PE compared with the SOC (479 versus 816 cases) and a cost saving of €28.67 per patient. The outcome in quality-adjusted life-years was similar for both screening approaches (FMF screening algorithm 1.8521 versus SOC 1.8518). The FMF screening algorithm was cost-saving and more effective in 99.4% of simulations.

Conclusions

The FMF screening algorithm coupled with early intervention using low-dose aspirin has the potential to prevent an additional 337 cases of pre-term PE per year compared with the current SOC in this population, along with a cost saving.

Cost-effectiveness analysis of implementing screening on preterm pre-eclampsia at first trimester of pregnancy in Germany and Switzerland

J. Mewes, M. Lindenberg and H. J. M. Vrijhoef

PLoS One 2022 Vol. 17 Issue 6 Pages e0270490

Objective

To assess the cost-effectiveness of preterm preeclampsia (PE) screening versus routine screening based on maternal characteristics in Germany and Switzerland.

Methods

A health economic model was used to analyse the cost-effectiveness of PE screening versus routine screening based on maternal characteristics. The analysis was conducted from the healthcare perspective with a time horizon of one year from the start of pregnancy. The main outcome measures were incremental health care costs and incremental costs per PE case averted.

Results

The incremental health care costs for PE screening versus routine screening per woman were €14 in Germany, and -CHF42 in Switzerland, the latter representing cost savings. In Germany, the incremental costs per PE case averted were €3,795. In Switzerland, PE screening was dominant. The most influential parameter in the one-way sensitivity analysis was the cost of PE screening (Germany) and the probability of preterm PE in routine screening (Switzerland). In Germany, at a willingness-to-pay for one PE case avoided of €4,200, PE screening had a probability of more than 50% of being cost-effective compared to routine screening. In Switzerland, at a willingness-to-pay of CHF0, PE screening had a 78% probability of being the most cost-effective screening strategy.

Conclusion

For Switzerland, PE screening is expected to be cost saving in comparison to routine screening. For Germany, the additional health care costs per woman were expected to be €14. Future cost-effectiveness studies should be conducted with a longer time horizon.

Early cost-effectiveness analysis of screening for preeclampsia in nulliparous women: A modelling approach in European high-income settings

N. Zakiyah, R. Tuytten, P. Baker, L. Kenny, M. Postma and A. van Asselt

PLoS One 2022 Vol. 17 Issue 4 Pages e0267313

Background

Preeclampsia causes substantial maternal and perinatal morbidity and mortality and significant societal economic impact. Effective screening would facilitate timely and appropriate prevention and management of preeclampsia.

Objectives

To develop an early cost-effectiveness analysis to assess both costs and health outcomes of a new screening test for preeclampsia from a healthcare payer perspective, in the United Kingdom (UK), Ireland, the Netherlands and Sweden.

Methods

A decision tree over a 9-month time horizon was developed to explore the cost-effectiveness of the new screening test for preeclampsia compared to the current screening strategy. The new test strategy is being developed so that it can stratify healthy low risk nulliparous women early in pregnancy to either a high-risk group with a risk of 1 in 6 or more of developing preeclampsia, or a low-risk group with a risk of 1 in 100 or less. The model simulated 25 plausible scenarios in a hypothetical cohort of 100,000 pregnant women, in which the sensitivity and specificity of the new test were varied to set a benchmark for the minimum test performance that is needed for the test to become cost-effective. The input parameters and costs were mainly derived from published literature. The main outcome was incremental costs per preeclampsia case averted, expressed as an incremental cost-effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analyses were conducted to assess uncertainty.

Results

Base case results showed that the new test strategy would be more effective and less costly compared to the current situation in the UK. In the Netherlands, the majority of scenarios would be cost-effective from a threshold of €50,000 per preeclampsia case averted, while in Ireland and Sweden, the vast majority of scenarios would be considered cost-effective only when a threshold of €100,000 was used. In the best case analyses, ICERs were more favourable in all four participating countries. Aspirin effectiveness, prevalence of preeclampsia, accuracy of the new screening test and cost of regular antenatal care were identified as driving factors for the cost-effectiveness of screening for preeclampsia.

Conclusion

The results indicate that the new screening test for preeclampsia has potential to be cost-effective. Further studies based on proven accuracy of the test will confirm whether the new screening test is a cost-effective additional option to the current situation.

Cost-effectiveness analysis of a first-trimester screening test for preterm preeclampsia in the Netherlands

R. Beernink, S. Scherjon, T. Cremers and A. van Asselt

J Reprod Immunol 2023 Vol. 160 Pages 104141

Objectives

The risk of preterm preeclampsia (PT PE) can significantly be reduced by starting acetylsalicylic acid ≤ 16 weeks of gestational age. First trimester predictive models based on maternal risk factors to effectively start this therapy lacked sufficient power, but recent studies showed that these models can be improved by including test results of biochemical and/or -physical markers. To investigate whether testing a biochemical marker in the first trimester is cost-effective in the Netherlands, a cost-effectiveness analysis was performed in this study.

Study Design

The outcome of this study was expressed as an incremental cost-effectiveness ratio (ICER) with as effect prevented PT PE cases. To evaluate the impact of each model parameter and to determine model uncertainties, both univariate and probabilistic sensitivity analyses were performed.

Results

When compared to the baseline strategy, the test strategy is estimated to save almost 4 million euros per year on a national scale and at the same time this would prevent an additional 228 PT PE cases. The sensitivity analyses showed that the major drivers of the result are the costs to monitor a high-risk pregnancy and the specificity and that most of the model simulations were in the southeast quadrant: cost saving and more prevented complications.

Conclusions

This study showed that a first-trimester test strategy to screen for PT PE in the first trimester is potentially cost-effective in the Dutch healthcare setting. The fact that the specificity is a major driver of the ICER indicates the importance for a (new) screening model to correctly classify low-risk pregnancies.

Which first-trimester risk assessment method for preeclampsia is most suitable? A model-based impact study

L. Strijbos, M. Hendrix, S. Al-Nasiry, L. Smits and H. Scheepers

Am J Obstet Gynecol MFM 2023 Vol. 5 Issue 7 Pages 100974

Background
Low-dose aspirin treatment reduces the risk of preeclampsia among high-risk pregnant women. Internationally, several first-trimester risk-calculation methods are applied.

Objective
This study aimed to assess the costs and benefits of different first-trimester preeclampsia risk estimation algorithms: EXPECT (an algorithmic prediction model based on maternal characteristics), National Institute for Health and Care Excellence (a checklist of risk factors), and the Fetal Medicine Foundation (a prediction model using additional uterine artery Doppler measurement and laboratory testing) models, coupled with low-dose aspirin treatment, in comparison with no risk assessment.

Study Design
We constructed a decision analytical model estimating the number of cases of preeclampsia with each strategy and the costs of risk assessment for preeclampsia and early aspirin treatment, expressed in euros (€) in a hypothetical population of 100,000 women. We performed 1-way sensitivity analyses to assess the impact of adherence rates on model outcomes.

Results
Application of the EXPECT, National Institute for Health and Care Excellence, and Fetal Medicine Foundation models results in respectively 1.98%, 2.55%, and 1.90% of the women developing preeclampsia, as opposed to 3.00% of women in the case of no risk assessment. Overall, the net financial benefits of the EXPECT, National Institute for Health and Care Excellence, and Fetal Medicine Foundation models relative to no risk assessment are €144, €43, and €38 per patient, respectively. The respective percentages of women receiving aspirin treatment are 18.6%, 10.2%, and 6.0% for the 3 risk assessment methods.

Conclusion
The EXPECT and Fetal Medicine Foundation model are comparable with regard to numbers of prevented preeclampsia cases, and both are superior to the National Institute for Health and Care Excellence model and to no risk assessment. EXPECT is less resource-demanding and results in the highest cost savings, but also requires the highest number of women to be treated with aspirin. When deciding which strategy is preferable, cost savings and easier use have to be weighed against the degree of overtreatment, although low-dose aspirin has no clear disadvantages during pregnancy.

First trimester screening for pre-eclampsia and targeted aspirin prophylaxis: A cost-effectiveness cohort study

D. Nzelu, T. Palmer, D. Stott, P. Pandya, R. Napolitano, D. Casagrandi, et al.

Bjog 2024 Vol. 131 Issue 2 Pages 222-230

Objective
Investigate cost-effectiveness of first trimester pre-eclampsia screening using the Fetal Medicine Foundation (FMF) algorithm and targeted aspirin prophylaxis in comparison with standard care.

Design
Retrospective observational study.

Setting
London tertiary hospital.

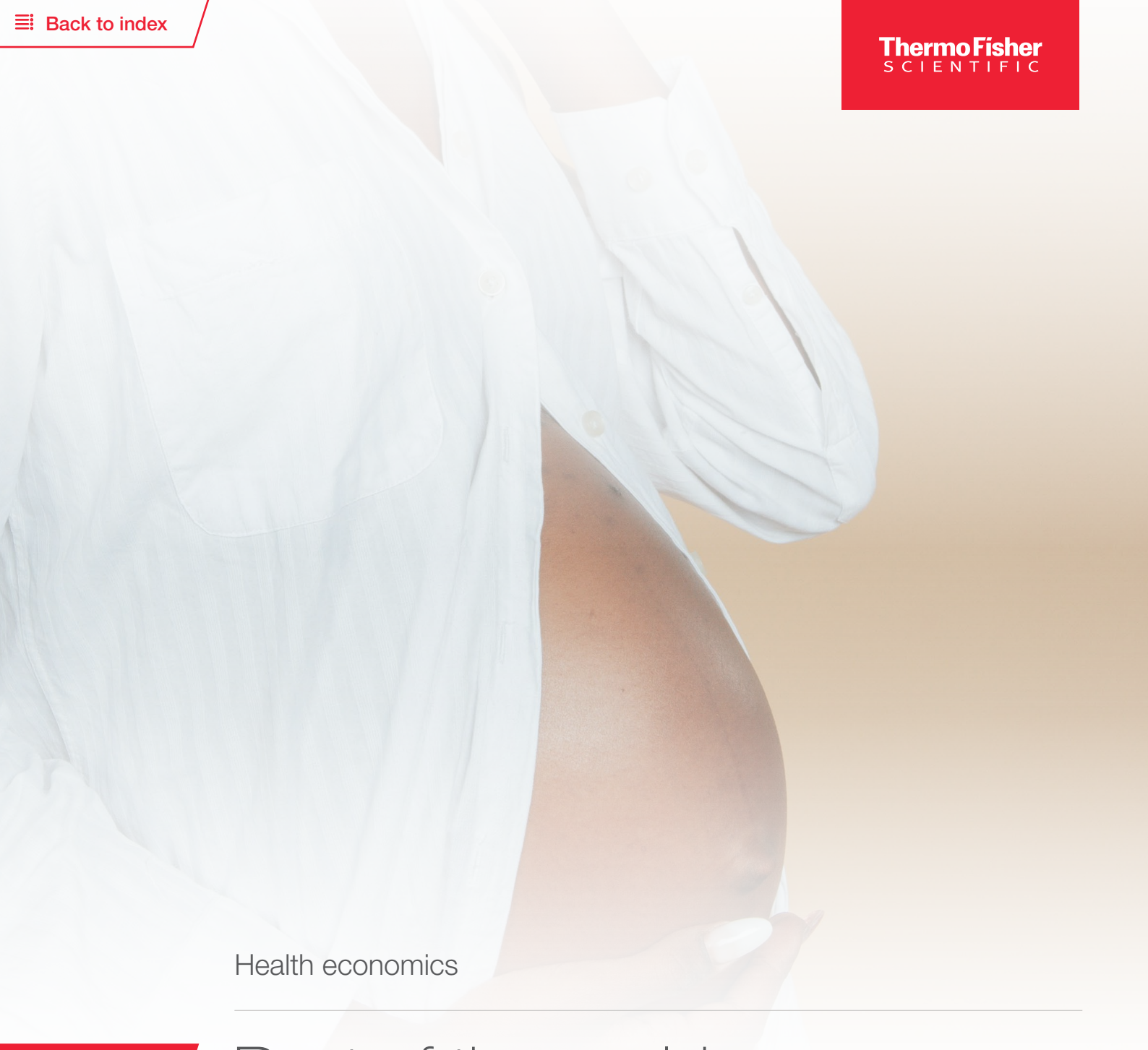
Population
5957 pregnancies screened for pre-eclampsia using the National Institute for Health and Care Excellence (NICE) method.

Methods
Differences in pregnancy outcomes between those who developed pre-eclampsia, term pre-eclampsia and preterm pre-eclampsia were compared by the Kruskal-Wallis and Chi-square tests. The FMF algorithm was applied retrospectively to the cohort. A decision analytic model was used to estimate costs and outcomes for pregnancies screened using NICE and those screened using the FMF algorithm. The decision point probabilities were calculated using the included cohort.

Main Outcome Measures
Incremental healthcare costs and QALY gained per pregnancy screened.

Results
Of 5957 pregnancies, 12.8% and 15.9% were screen-positive for development of pre-eclampsia using the NICE and FMF methods, respectively. Of those who were screen-positive by NICE recommendations, aspirin was not prescribed in 25%. Across the three groups, namely, pregnancies without pre-eclampsia, term pre-eclampsia and preterm pre-eclampsia there was a statistically significant trend in rates of emergency caesarean (respectively 21%, 43% and 71.4%; $P<0.001$), admission to neonatal intensive care unit (NICU) (5.9%, 9.4%, 41%; $P<0.001$) and length of stay in NICU. The FMF algorithm was associated with seven fewer cases of preterm pre-eclampsia, cost saving of £9.06 and QALY gain of 0.00006/pregnancy screened.

Conclusion
Using a conservative approach, application of the FMF algorithm achieved clinical benefit and an economic cost saving.



Health economics

Rest of the world

Economic assessment of screening for pre-eclampsia

A. Shmueli, H. Meiri and R. Gonen

Prenat Diagn 2012 Vol. 32 Issue 1 Pages 29-38

Backgroung

Pre-eclampsia is a major contributor to maternal and neonatal morbidity and mortality. Our objectives in this study are to economically assess, from the payer perspective, routine screening for pre-eclampsia using placental markers -placental protein 13 and placental growth factor - and uterine artery Doppler compared with standard care.

Methods

A decision model was developed, which progresses through three sequential endpoints, and compares screening with no screening: (1) Pre-eclampsia yes/no: calculation of the incremental cost of pre-eclampsia-case averted; (2) Hospital discharge: calculation of the mean accumulated costs until discharge after delivery; and (3) Offspring death: calculation of the incremental cost per quality of life-adjusted life-year gained by screening. Data used includes: (1) Obstetrical data of 14 500 births; (2) cost data from the Israeli Ministry of Health and the literature; and (3) screening performance and outcome from the literature.

Results

(1) The incremental cost of pre-eclampsia-case averted is $66,949 and $24,723 when the prevalence is 1.7 and 5% respectively. (2) With test cost of $112, the total cost until discharge with/without screening is equal. With pre-eclampsia prevalence of 3%, screening is cheaper. (3) The cost per quality of life-adjusted life-year with screening is $18,919 and < $10,000 with pre-eclampsia prevalence of 1.7 and 3%, respectively.

Conclusions

Screening for pre-eclampsia is cost-effective under various scenarios.

Cost-effectiveness of first trimester screening for preterm pre-eclampsia in Lebanon

J. Karaki, R. Chahine, M. Kharoubi, H. Cuckle

J. Fetal Med 2020 Vol. 7 Pages 119–123

To estimate, for Lebanon, the financial benefit of screening for preterm pre-eclampsia (PE) at 11–13 weeks gestation combining risk factors with mean arterial pressure and maternal serum placental growth factor. Preterm PE cases delivered during 2010–2018 at Rafik Hariri University Hospital were identified from electronic records. Manual nursing notes were reviewed to confirm the diagnosis using international criteria. For each case, adverse maternal and infant events were noted and billing information extracted. A series of 1000 non-PE pregnancies were identified and billing information recorded. Published screening detection rates for a 10% false-positive rate and the proportion prevented by aspirin prophylaxis were applied to estimate the reduced cost following screening. There were a total of 17,131 deliveries including 486 (2.84%) PE and 223 (1.30%) preterm PE cases. The caesarean section rate was substantially higher for preterm PE (74%) than non-PE deliveries (36%) and 76% of infants were admitted to the Newborn Intensive Care Unit, where the average stay was 32, 21 and 8 days for deliveries before 32, 32–33 and 34–36 weeks respectively. The total cost of maternal and infant care for preterm PE was $881,206 and the average cost of an unaffected delivery $599. It was estimated that following screening the saving in treatment costs including aspirin would have been $431,665, which is $24 per woman delivering at the hospital over the nine year period. The financial savings are more than sufficient to pay for the screening test in those who are screen-positive.

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Automated immunofluorescent assay for the quantitative determination of Placental Growth Factor (PlGF) in human serum and plasma (EDTA). The assay is specific for the measurement of human free PlGF-1.

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- **29 min incubation time**
- **Single-point calibration**
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- **Excellent precision**

With a lower and upper detection limits of 4.91pg/ mL and 7 000 pg/mL B·R·A·H·M·S PlGF plus KRYPTOR provides the high sensitivity needed for **measuring PlGF levels in first trimester** as well as a wide measuring range to reliably **measure clinical values throughout pregnancy.**[1]

Thermo Scientific B·R·A·H·M·S PAPP-A KRYPTOR

Automated immunofluorescent assay for the quantitative determination of pregnancy associated plasma protein-A (PAPP-A) in human serum.

- **75 determinations per kit**
- **19 min incubation time**
- **Single-point calibration**
- **Linear direct measuring range: 0.010-6 IU/L**
- **Excellent precision**

With the lower and upper detection limits of 0.0054 IU/L and 6 IU/L, B·R·A·H·M·S PAPP-A KRYPTOR provides the measuring range needed for a **reliable detection of clinical PAPP-A values in first trimester of pregnancy**.[2]

References

1. IFU B·R·A·H·M·S PlGF plus KRYPTOR
2. IFU B·R·A·H·M·S PAPP-A KRYPTOR

Clinical Diagnostics

Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf, Germany

+49 (0)3302 883 0
+49 (0)3302 883 100 fax
info.brahms@thermofisher.com
www.thermoscientific.com/brahms
https://eifu.thermofisher.com/BMK

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