DOI: 10.1002/ijgo.12802

SUPPLEMENT ARTICLE

WILEY International Journal of Gynecology & Obstetrics FIGO

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

Liona C. Poon[1,*] | Andrew Shennan[2] | Jonathan A. Hyett[3] | Anil Kapur[4] | Eran Hadar[5] | Hema Divakar[6] | Fionnuala McAuliffe[7] | Fabricio da Silva Costa[8] | Peter von Dadelszen[2] | Harold David McIntyre[9] | Anne B. Kihara[10] | Gian Carlo Di Renzo[11] | Roberto Romero[12] | Mary D'Alton[13] | Vincenzo Berghella[14] | Kypros H. Nicolaides[15] | Moshe Hod[5]

[1]Department of Obstetrics and Gynecology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR

[2]Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

[3]Discipline of Obstetrics, Gynecology and Neonatology, Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

[4]World Diabetes Foundation, Bagsværd, Denmark

[5]Helen Schneider Hospital for Women, Rabin Medical Center, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[6]Divakars Speciality Hospital, Bangalore, India

[7]Department of Obstetrics and Gynecology, The National Maternity Hospital, Dublin, Ireland

[8]Department of Gynecology and Obstetrics, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil

[9]University of Queensland Mater Clinical School, Brisbane, QLD, Australia

[10]African Federation of Obstetrics and Gynaecology, Khartoum, Sudan

[11]Center of Perinatal and Reproductive Medicine, Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy

[12]Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, and Detroit, MI, USA

[13]Obstetrician and Gynecologist in-Chief, Columbia University Irving Medical Center, NewYork-Presbyterian

[14]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

[15]Fetal Medicine Research Institute, King's College Hospital London, London, UK

***Correspondence**
Liona C. Poon, Department of Obstetrics and Gynecology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR.
Email: liona.poon@cuhk.edu.hk

Funding Information
PerkinElmer Inc

[Correction added on 18 June 2019, after first online publication: the affiliation for Mary D'Alton has been corrected in this version.]

CONTRIBUTORS

In addition to the authors, the following people provided important contributions during the creation of the document. Thanks go to the following international experts: The Pregnancy and NCD Committee members: Moshe Hod, Hema Divakar, Mark Hanson, Anil Kapur, Harold David McIntyre, Mary D'Alton, Anne B. Kihara, Ronald Ma, Fionnuala McAuliffe, Gian Carlo Di Renzo, and CN Purandare. Special thanks for FIGO guidance and coordination go to President Carlos Fuchtner, Past-President CN Purandare, Past-Chair of the SMNH Committee Gerard Visser, along with Jessica Morris and Rachel Gooden (FIGO Project Manager and Coordinator). In addition to the FIGO Executive Board, various FIGO Committees and Working Groups contributed to and supported the document.

ACKNOWLEDGMENTS

This project was funded by an unrestricted educational grant from PerkinElmer Inc, Waltham, USA, represented by Yvonne Parker, VP Market Development, Reproductive Health, PerkinElmer Inc.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

CONTENTS

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Formulas for calculation of multiple of the median (MoM) values at 11–13 weeks of gestation. Algorithm for prediction of pre-eclampsia.

LIST OF ABBREVIATIONS/ACRONYMS

ACOG	American College of Obstetrics and Gynecology
APS	Antiphospholipid syndrome
ART	Assisted reproductive technologies
ASPRE	Combined multimarker screening and randomized patient treatment with aspirin for evidence-based pre-eclampsia prevention
AUC	Area under receiver operating characteristic curve
BMI	Body mass index
CI	Confidence interval
CRL	Crown–rump length
dBP	Diastolic blood pressure
DR	Detection rate
FGR	Fetal growth restriction
FIGO	International Federation of Gynecology and Obstetrics
GI	Gastrointestinal
GWAS	Genome-wide association studies
HELLP	Hemolysis, elevated liver enzyme, low platelet
HR	Hazard ratio
IAD	Interarm difference
ICSI	Intracytoplasmic sperm injection
IGF	Insulin-like growth factor
IQ	Intelligence quotient
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUFD	Intrauterine fetal death
IUI	Intrauterine insemination
IVF	In vitro fertilization
MAP	Mean arterial pressure
MoM	Multiple of median
NCDs	Noncommunicable diseases
NHFA	National Heart Foundation of Australia
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
OR	Odds ratio
PAPP-A	Pregnancy-associated plasma protein A
PE	Pre-eclampsia
PLGF	Placental growth factor
POC	Point of care
RR	Relative risk
sBP	Systolic blood pressure
SD	Standard deviation
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
UA	Umbilical artery
UTPI	Uterine artery pulsatility index
VEGF-R1	Vascular endothelial growth factor receptor 1
VEGF	Vascular endothelial growth factor

1 | EXECUTIVE SUMMARY

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 $\geq 34^{+0}$ weeks of gestation);
4. Term PE (with delivery at $\geq 37^{+0}$ 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.[1]

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.

2 | TARGET AUDIENCE OF THE FIGO INITIATIVE ON PRE-ECLAMPSIA

This document is directed at multiple stakeholders with the intention of bringing attention to PE, which is a preventable but common and potentially life-threatening complication of pregnancy with grave consequences for both the mothers and the offspring. This document proposes to create a global framework for action for early screening and prevention of PE.

The intended target audience includes:

- **Healthcare providers:** All those who are qualified to care for pregnant women and their newborns, but in particular those responsible for screening for high-risk women (obstetricians, maternal-fetal medicine specialists, internists, pediatricians, neonatologists, general practitioners/family physicians, midwives, nurses, advance practice clinicians, nutritionists, pharmacists, community health workers, laboratory technicians, etc.)
- **Healthcare delivery organizations and providers:** governments, federal and state legislators, healthcare management organizations, health insurance organizations, international development agencies, and nongovernmental organizations.
- **Professional organizations:** international, regional, and national professional organizations of obstetricians and gynecologists, internists, family practitioners, pediatricians, neonatologists, and worldwide national organizations dedicated to the care of pregnant women with PE.

3 | QUALITY ASSESSMENT OF EVIDENCE AND GRADING OF STRENGTH OF RECOMMENDATIONS

In assessing the quality of evidence and grading of strength of recommendations, the document follows the terminology proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (http://www.gradeworkinggroup.org/). This system uses consistent language and graphical descriptions for the strength and quality of the recommendations and the evidence on which they are based. Strong recommendations are numbered as 1 and conditional (weak) recommendations are numbered 2. For the quality of evidence, cross-filled circles are used: ⊕**OOO** denotes very low-quality evidence; ⊕⊕**OO** low quality; ⊕⊕⊕**O** moderate quality; and ⊕⊕⊕⊕ high-quality evidence (Tables 1 and 2).

TABLE 1 Interpretation of strong and conditional (weak) recommendations according to GRADE.[a,b]

Implications	1=Strong recommendation phrased as "we recommend"	2=Conditional (weak) recommendation phrased as "we suggest"
For patients	Nearly all patients in this situation would accept the recommended course of action. Formal decision aids are not needed to help patients make decisions consistent with their values and preferences	Most patients in this situation would accept the suggested course of action
For clinicians	According to the guidelines performance of the recommended action could be used as a quality criterion or performance indicator, unless the patient refuses	Decision aids may help patients make a management decision consistent with their values and preferences
For policy makers	The recommendation can be adapted as policy in most situations	Stakeholders need to discuss the suggestion

[a]Reprinted with permission of the American Thoracic Society. © 2019 American Thoracic Society. Schunemann HJ, Jaeschke R, Cook DJ, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605–614. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.
[b]Both caregivers and care recipients need to be involved in the decision-making process before adopting recommendations.

TABLE 2 Interpretation of quality of evidence levels according to GRADE.[a]

Level of evidence	Definition
High ⊕⊕⊕⊕	We are very confident that the true effect corresponds to that of the estimated effect
Moderate ⊕⊕⊕O	We are moderately confident in the estimated effect. The true effect is generally close to the estimated effect, but it may be slightly different
Low ⊕⊕OO	Our confidence in the estimated effect is limited. The true effect could be substantially different from the estimated effect
Very low ⊕OOO	We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect

[a]Adapted with permission from Balshem et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6. © Elsevier (2011).

4 | PRE-ECLAMPSIA: BACKGROUND, DEFINITION, RISK FACTORS, MATERNAL AND PERINATAL MORBIDITY AND MORTALITY ASSOCIATED WITH PRE-ECLAMPSIA

4.1 | Introduction

Pre-eclampsia (PE) is a multisystem disorder of pregnancy previously defined by the onset of hypertension accompanied by significant proteinuria after 20 weeks of gestation. Recently, the definition of PE has been broadened.[2–5] PE 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.[6,7] Globally, 76 000 women and 500 000 babies die each year from this disorder.[8] Furthermore, women in low-resource countries are at a higher risk of developing PE compared with those in high-resource countries.

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 $\geq 34^{+0}$ weeks of gestation);
4. Term PE (with delivery at $\geq 37^{+0}$ weeks of gestation).

These subclassifications are not mutually exclusive. Early-onset PE is associated with a substantial risk of both short- and long-term maternal and perinatal morbidity and mortality.[9,10]

Although a complete understanding of the pathogenesis 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.[11–13] 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.[11–13] In late-onset disease, placentation is usually normal; however, feto-placental demands exceed supply, resulting in a placental response that triggers the clinical phenotype. Whilst the placenta certainly plays an essential role in the development of PE, there is a growing body of evidence that the maternal cardiovascular system may have a significant contribution to the disorder.[14]

While knowledge of the complex pathophysiology of PE is improving, 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 to improve placentation and reduce the prevalence of the disease. Furthermore, identification of an "at risk" group will facilitate tailored prenatal surveillance to anticipate and recognize the onset of the clinical syndrome and manage it promptly.

4.2 | Definition of pre-eclampsia

PE is broadly defined as development of hypertension and proteinuria in a previously normotensive woman. The difficulty in interpreting epidemiological studies of PE is due to the wide variation in the definitions of the disease. There are several definitions for the diagnosis of PE that have been reported in published literature and proposed by various professional bodies. Consequently, this has resulted in several different guidelines produced by professional bodies worldwide for the diagnosis and management of PE.[2,15–17] However, an internationally agreed definition of PE is that of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[5] (Box 1), which is endorsed by FIGO.

Gestational hypertension is defined as systolic blood pressure (sBP) at ≥140 mm Hg and/or diastolic blood pressure (dBP) at ≥90 mm Hg on at least two occasions measured 4 hours apart developing after 20 weeks of gestation in previously normotensive women.

PE is defined as gestational hypertension accompanied by ≥1 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. 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).

FIGO adopts the definition of PE as provided by the International Society for the Study of Hypertension in Pregnancy (ISSHP).

4.3 | Risk factors

It is well established that a number of maternal risk factors are associated with the development of PE. These risk factors have been described by various professional organizations for the identification of women at risk of PE.[3,4,16,18,19]

4.3.1 | Maternal age

Advanced maternal age, defined as age greater than or equal to 35 years at the time of delivery, is associated with 1.2 to 3-fold increased risk of developing PE.[19–22] Predictive probability of PE increases when maternal age is greater than 35 years and the probability further increases rapidly when maternal age is greater than

40 years.[19] One study has evaluated the maternal age associated risk according to the severity of PE. Using multivariate logistic regression analysis, adjusting for confounders, the risk for late-onset PE has been shown to increase by 4% with every 1-year increase in maternal age above 32 years.[23] However, maternal age is not associated with increased risk of early-onset PE.[23]

4.3.2 | Parity

In nulliparous women, the increased risk of developing PE has been widely reported. One systematic review reported that the risk of PE is increased three-fold in nulliparous women.[24] Another systematic review that included 26 studies reported that this increased risk for PE persists even after adjusting for other risk factors, such as maternal age, race, and body mass index (BMI) and the summary adjusted odds ratio (OR) was 2.71 (95% CI, 1.96–3.74).[25] Parous women without prior history of PE have reduced risk of PE; however, this protective effect is lost when the conception partner is different.[26]

4.3.3 | Previous history of PE

A large population-based study including 763 795 nulliparous women with a first delivery between 1987 and 2004 showed that the risk of PE was 4.1% in the first pregnancy and 1.7% in later pregnancies overall. However, the risk was 14.7% in the second pregnancy for women with a history of PE in their first pregnancy and 31.9% for women who had PE in the previous two pregnancies. The risk of PE for parous women without a history of PE was 1.1%. These observations suggest that the risk of PE is greater in nulliparous than parous women without a prior history of PE. Among parous women, the risk of PE in subsequent pregnancies depends on a prior history of PE.[27] This relative risk for subsequent PE ranges from 7 to 10 times higher in a second pregnancy.[28–30]

A study focusing on PE according to severity of disease showed that a history of PE doubled the risk of developing early-onset PE (<32 weeks) in a subsequent pregnancy as opposed to late-onset PE.[31] Other studies have reported a 5% to 17% recurrence risk of early-onset PE (<34 weeks) in the index pregnancy for those with a prior history of early-onset PE.[32,33] A systematic review of 11 studies including 2377 women showed that the pooled recurrence risk of early-onset PE is approximately 8% in women who require delivery at less than 34 weeks following the development of early-onset PE in the first pregnancy.[33]

4.3.4 | Pregnancy interval

Both short and long interpregnancy intervals are associated with an increased risk of PE.[34–36] A recent large multicentric retrospective study of 894 479 women reported that interpregnancy intervals of less than 12 months or greater than 72 months are associated with higher risk of PE development compared with interpregnancy intervals of 12–23 months.[37] It has been observed that the longer the interval, the higher the risk of developing PE. The reasons for the association between short interpregnancy interval and PE are unclear, but several hypotheses have been proposed, including factors related to socioeconomic status, postpartum stress, malnutrition, and inadequate access to healthcare services. Meanwhile, the increased PE risk in women with long interpregnancy intervals might be attributed to advanced maternal age, infertility, and underlying maternal medical conditions.[38,39]

Box 1 Diagnosis of hypertensive disorders in pregnancy according to ISSHP.[a]

Gestational hypertension

- Persistent de novo hypertension (sBP ≥140 mm Hg and/or dBP ≥90 mm Hg after 20 weeks of gestation in the absence of features of PE.

PE de novo

- Gestational hypertension accompanied by ≥1 of the following new-onset conditions at or after 20 weeks of gestation:
  - Proteinuria: 24-h urine protein ≥300 mg/d or spot urine protein/creatinine ratio ≥0.30 mg/mg or urine dipstick testing ≥1+
  - Other maternal organ dysfunction:
    - Acute kidney injury (creatinine ≥90 μmol/L; 1 mg/dL)
    - Liver involvement (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric pain)
    - Neurological complications (including eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches, and persistent visual scotomata)
    - Hematological complications (thrombocytopenia–platelet count <150 000/μL, disseminated intravascular coagulation, hemolysis)
    - Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform or stillbirth).

Superimposed PE on chronic hypertension

- Women with chronic essential hypertension develop any of the above maternal organ dysfunctions consistent with PE
- Increase in blood pressure per se is not sufficient to diagnose superimposed PE
- In the absence of pre-existing proteinuria, new-onset proteinuria in the setting of a rise in blood pressure is sufficient to diagnose superimposed PE

In women with proteinuric renal disease, an increase in proteinuria during pregnancy is not sufficient per se to diagnose superimposed PE

[a] Source: Brown et al.[5]

4.3.5 | Assisted reproduction

Several studies have reported that the use of assisted reproductive technologies (ART) doubles the risk of PE.[40–43] In a cohort study of more than 1 million pregnant women, the risk of having PE was increased in women exposed to hyperestrogenic ovarian stimulation medications regardless of ART type compared with those with spontaneous conception (ORs ranging from 1.32 to 1.83).[44] In contrast, the use of nonhyperestrogenic ovarian stimulation drugs was

not associated with an increased risk of PE.[44] High estrogen levels during implantation may lead to impaired placentation and reduced uteroplacental circulation as well as decreased number of uterine spiral arteries with vascular invasion.[44–46] Women conceiving by intrauterine insemination, in particular by donor sperm, are at a greater risk of developing PE.[47–51] Those who have undergone donor ovum in vitro fertilization (IVF) appear to have a higher risk of PE than those who have had autologous ovum IVF.[52] Evidence from IVF pregnancies with ovum donation suggests that there are altered extravillous trophoblast and immunological changes in decidua basalis, which may impede the modification of the spiral arteries.[53]

4.3.6 | Family history of PE

Although most cases of PE are sporadic, a familial susceptibility to PE has been documented. Daughters or sisters of women with PE are 3–4 times more likely to develop the condition than women without a family history.[54–56] The mode of inheritance seems to be complex, including numerous variants, which individually have small effects, but collectively contribute to an individual's susceptibility to the disorder. Genome-wide association studies (GWAS) using sib-pair analysis have identified plausible, yet conflicting, positional candidate maternal susceptibility genes for PE. GWAS of PE affected families have demonstrated significant linkage to chromosomes 2p, 2q, 4p, 7p, 9p, 10q, 11q, and 22q.[57] However, no other study has reproduced these significant or suggestive loci.

4.3.7 | Obesity

There is substantial evidence to show that obesity (BMI ≥30 kg/m^2) confers a 2 to 4-fold higher risk for PE.[58–64] The exact mechanisms linking overweight/obesity and PE remain unclear. Obesity is known as a state of chronic, low-grade inflammation, also called "meta-inflammation".[65,66] Low-grade inflammation can induce endothelial dysfunction and placental ischemia by immune mediated mechanisms, which in turn lead to production of inflammatory mediators resulting in an exaggerated maternal inflammatory response and development of PE.[67]

4.3.8 | Race and ethnicity

There is extensive evidence in the literature demonstrating the association between race and ethnicity and PE. Large population studies suggest that the risk of PE in Afro-Caribbean women is increased by 20%–50%.[68–72] The risk of PE is also higher in women of South Asian origin than in those of non-Hispanic white women (adjusted OR 1.3; 95% CI, 1.2–1.4).[73] Increased risk of PE reflects the metabolic profiles of nonpregnant women associated with an increased susceptibility to cardiovascular disease.[74–76] Both Afro-Caribbean and South Asian women are more susceptible to developing chronic hypertension, diabetes mellitus, and cardiovascular disease. In a large prospective observational cohort study of more than 79 000 singleton pregnancies recruited in London, UK, the risk of PE was significantly higher in women of Afro-Caribbean and South Asian racial origin compared with white women.[77] The increased risk remains significant even after adjusting for other confounding risk factors for PE.

4.3.9 | Comorbidities

There are certain medical conditions that predispose women to developing PE. These include hyperglycemia in pregnancy (pre-pregnancy type 1 and type 2 diabetes mellitus, overt diabetes in pregnancy, and gestational diabetes requiring insulin treatment), pre-existing chronic hypertension, renal disease, and autoimmune diseases such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Recently, a systematic review and meta-analysis evaluated clinical risk factors at less than or equal to 16 weeks of gestation in 25 356 655 pregnant women in 27 countries.[78] Patients with a history of chronic hypertension have a higher risk of developing PE than those without this condition (relative risk [RR] 5.4; 95% CI, 4.0–6.5). Pre-existing diabetes mellitus, APS, SLE, and chronic kidney disease are also associated with an increased risk of developing PE (RR 3.7; 95% CI, 3.1–4.3; RR 2.8; 95% CI, 1.8–4.3; RR 2.5; 95% CI, 1.0–6.3; and RR 1.8; 95% CI, 1.5–2.1, respectively).[78]

Interestingly, pre-existing diabetes mellitus and PE share many risk factors including advanced maternal age, nulliparity, pre-pregnancy obesity, nonwhite racial propensity, and multiple pregnancy.[79,80] Several common pathological pathways are present in both conditions. These include endothelial dysfunction (e.g. lower flow-mediated dilatation),[81,82] imbalance of angiogenic factors,[81,83] increased oxidative stress (e.g. low total antioxidant status, high free radicals),[84] and dyslipidemia (e.g. increased triglycerides).[85,86] PE is a risk factor for future type 2 diabetes.[87–90] This relationship is still evident even when women who have PE with gestational diabetes are excluded. Both conditions are associated with insulin resistance[91–97] and women with PE have an increased risk of metabolic syndrome after delivery.[98–100]

FIGO acknowledges the many maternal risk factors that are associated with the development of pre-eclampsia, which must be taken into consideration for screening practices.

4.4 | Maternal and perinatal morbidity and mortality associated with pre-eclampsia

4.4.1 | Maternal morbidity and mortality

The most common cause of death in women with PE is intracranial hemorrhage.[101] Other serious complications include placental abruption, HELLP syndrome, acute pulmonary edema, respiratory distress syndrome, and acute renal failure.[102]

Chesley et al.[103] were the first to propose the concept that pregnancy is a stress test, based on the observation that pregnant women who have never developed PE have a lower risk of cardiovascular disease than the general female population; whereas women with eclampsia have a similar risk of cardiovascular disease in later life as

appropriately matched women with unknown pregnancy history. Therefore, while PE may not directly cause cardiovascular disease in later life, pregnancy itself acts as a challenge test to reveal underlying metabolic risk factors for atherosclerosis and cardiovascular disease.[103] Evidence in support of this hypothesis is that PE and cardiovascular disease share many risks factors, including obesity, insulin resistance, diabetes mellitus, underlying hypertension, and dyslipidemia.[103–106] A recent meta-analysis demonstrated that women with previous PE have a RR of 3.13 (95% CI, 2.51–3.89) for future development of chronic hypertension, an OR of 2.28 (95% CI, 1.87–2.78) for future cardiovascular disease, and an OR of 1.8 (95% CI, 1.43–2.21) for cardiovascular accident.[107] It has been observed that the earlier the onset of PE, the more severe the condition and the higher the risk of developing subsequent cardiovascular disease.[108]

Compared with normotensive women, women with PE are also more likely to have microalbuminuria (a marker of renal damage) at 3–5 years after delivery.[109] PE may adversely impact future kidney function since glomerular endotheliosis—a typical renal lesion in PE that was previously thought to resolve soon after delivery—can be observed long after pregnancy in some women who had PE.[110] A prospective cohort study reported an association between PE and subsequent end-stage renal disease (RR 4.7; 95% CI, 3.6–6.1).[111] Patients with a history of PE should be aware of the increased risk of future cardiovascular disease,[107,108] metabolic syndrome,[112,113] and chronic or end-stage renal disease.[111] It remains to be determined whether lifestyle modifications as well as close monitoring for signs and symptoms of metabolic syndromes after delivery among patients with PE can reduce these risks.[114]

4.4.2 | Perinatal morbidity and mortality

PE is associated with a number of short- and long-term perinatal and neonatal complications, including death (Table 3). These are mostly related to birth weight and gestational age at delivery and are therefore mainly attributed to early-onset PE.

PE is commonly associated with placental lesions. The underlying vascular manifestations and the presence of oxidative stress and endothelial damage can lead to fetal growth restriction (FGR) with underlying hypoxia and acidosis. A multicenter prospective study of 30 639 unselected women with singleton pregnancies demonstrated that in 614 (2%) women who developed PE there was an inverse significant association between the gestational age at delivery and prevalence of small for gestational age (SGA) (r=−0.99, P<0.0001). As would be expected, the prevalence of SGA with PE was 82%, 47%, and 30% in those delivered at less than 34 weeks, between 34 and 37 weeks, and greater or equal to 37 weeks, respectively. The frequency of SGA in pregnancies without PE was 44%, 21%, and 8%, respectively.[115]

TABLE 3 Short- and long-term perinatal and neonatal complications related to pre-eclampsia.

Short-term complications	Long-term complications
Fetal growth restriction (FGR)	Cerebral palsy
Oligohydramnios	Low IQ
Intrauterine fetal death (IUFD)	Hearing loss
Preterm birth	Visual impairment
Low Apgar score	Insulin resistance
Nonassuring FHR during labor	Diabetes mellitus
Need for NICU admission	Coronary artery disease
	Hypertension

Given the presence of underlying hypoxia in PE, and the frequent associations with FGR, the incidence of fetal distress before or during labor is also increased. This is partly related to the reduced fetal reserves available to withstand the stress of labor. This is supported by several studies in which levels of markers of chronic hypoxia (such as erythropoietin and nucleated red blood cells) in cord blood of fetuses born to women with PE were shown to be elevated.[116,117]

The most important complication that requires great attention through effective prediction and prevention of PE is intrauterine fetal death (IUFD). The risk of IUFD varies widely depending on the population, severity of PE, and the presence of comorbid factors.[118] For women with PE, infant mortality is three-times higher in low- and middle-income countries than in high-income countries.[119] The underlying causes of IUFDs related to PE include acute and chronic hypoxia, placental insufficiency, FGR, and placental abruption. A prospective study of 113 415 singleton pregnancies in the UK reported 396 (3.5 per 1000) prepartum IUFDs, of which 230 (58%) were secondary to impaired placentation (PE, FGR, placental abruption) and 166 (42%) were due to other or unexplained causes.[120]

Infants born to mothers suffering from PE are at risk of being born prematurely, as delivery is the only cure for PE. In women with early-onset or severe PE, the risk is much higher. About 25% of PE cases require delivery before 37 weeks of gestation. It is estimated that about one-third of preterm births are medically indicated, and that PE is the primary indication for iatrogenic preterm delivery.[121,122] Infants born prematurely are at higher risk of neonatal mortality and morbidity, including necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, and neurodevelopmental impairments compared with term infants. These tend to be inversely related to gestational age at birth.

In summary, several fetal complications are associated with PE, especially when the disease is severe or has an early onset. These include FGR, oligohydramnios, IUFD, preterm delivery, nonreassuring fetal heart rate (FHR) during labor, low Apgar scores, and need for admission to a neonatal intensive care unit (NICU).[118] Poor neonatal outcomes can be either related solely to prematurity or as a direct consequence of PE. More often than not, both are at play, particularly in cases of severe, early-onset PE.

Regarding early childhood and school-age neurodevelopmental impairment, several investigators have reported outcomes of large population-based or geographic cohorts of infants born extremely premature. The Epicure Study examined school age outcomes of all infants born at less than 26 weeks of gestation over a five-year period in England.[123] Cerebral palsy affected 6% of the survivors, whereas 41% had IQ tests that were more than two standard deviations (SDs) below the mean compared with schoolmates. Investigators

from British Columbia reported provincial outcomes for infants born between 22 and 25 weeks over 17 years (n=341).[124] Some 20% of survivors had moderate disability (defined as cerebral palsy, or IQ 2–3 SDs below the mean, or sensorineural hearing loss corrected with aids or visual impairment worse than 20/70), whereas 10% of survivors had severe disability (defined as nonambulatory cerebral palsy, IQ more than three SDs below the mean, hearing loss not corrected, or legal blindness).

Regarding impact in adult life, the publication by Osmond and Barker[125] suggested that the in-utero environment could influence adult health and disease state. Their hypothesis states that suboptimal in-utero nutrient supply, as seen in placental insufficiency, through metabolic and hormonal adaptations and altered organ morphology, leads to increased risks of insulin resistance, diabetes mellitus, coronary artery disease, and hypertension. Thus, both the short-term and long-term consequences of PE, in terms of impact on individual health, the financial costs in providing the needed acute intensive care, and the long-term consequences to health and human capital, justify efforts to find effective early prediction and preventive strategies.

FIGO recommends and supports the call for greater attention and focus on the links between maternal health and NCDs in the Sustainable Developmental Goals agenda, including efforts to ensure early screening for all pregnant women for pre-existing NCDs or their risk factors.

5 | FIRST TRIMESTER PREDICTION OF PRE-ECLAMPSIA

5.1 | Problems with existing methods of screening

The current approach to screening for PE is to identify risk factors from maternal demographic characteristics and medical history (maternal risk factors).[2–4,15,16,126,127] There are two key recommendations that have evolved over time. According to the National Institute for Health and Clinical Excellence (NICE) in the UK, women should be considered to be at high risk of developing PE if they have any one high-risk factor (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, or autoimmune disease) or any two moderate-risk factors (nulliparity, age ≥40 years, BMI ≥35 kg/m^2, family history of PE, or interpregnancy interval >10 years).[16] In the USA, the American College of Obstetricians and Gynecologists (ACOG) issued the Hypertension in Pregnancy Task Force Report recommending daily low-dose aspirin beginning in the late first trimester for women with a history of early-onset PE and preterm delivery at less than 34 weeks of gestation, or for women with more than one prior pregnancy complicated by PE.[128] The US Preventive Services Task Force published a similar guideline, although the list of indications for low-dose aspirin use was more expansive.[129] An updated version of the US Preventive Services Task Force guideline has now been endorsed by ACOG, the Society for Maternal-Fetal Medicine, and the American Diabetes Association.[130] Low-dose aspirin prophylaxis at 81 mg/d from 12 and 28 weeks of gestation (optimally at <16 weeks of gestation), continued daily until delivery, should be considered for women with one or more high-risk factors (history of PE, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) or more than one of several moderate-risk factors (first pregnancy, age of ≥35 years, BMI >30 kg/m^2, family history of PE, sociodemographic characteristics, and personal history factors).[128] The approach recommended by NICE and ACOG essentially treats each risk factor as a separate screening test with additive detection rate and screen-positive rate. Although recognition of maternal risk factors might be useful in identifying at-risk women in clinical practice, it is not a sufficient tool for the effective prediction of PE.[131] In screening with use of NICE guidelines, the detection rate is 39% for preterm PE and 34% for term PE at 10.3% false-positive rate. The respective detection rates in screening with use of the US Preventive Services Task Force recommendations were 90% and 89%, at 64.3% false-positive rate.[132]

5.2 | Screening with biomarkers

An alternative approach to screening for PE, which allows estimation of individual patient-specific risks of PE requiring delivery before a specified gestation, is to use Bayes theorem to combine the a priori risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements. Extensive research in the last decade has led to the identification of four potentially useful biomarkers at 11–13 weeks of gestation: mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum pregnancy-associated plasma protein A (PAPP-A), and serum placental growth factor (PLGF). The algorithm was originally developed from a study of 58 884 singleton pregnancies at 11–13 weeks of gestation, including 1426 (2.4%) that subsequently developed PE. The estimated detection rates of preterm PE and all cases of PE, at fixed false-positive rate of 10%, were 77% and 54%.[133] Subsequently, data from prospective screening in 35 948 singleton pregnancies, including 1058 pregnancies (2.9%) that experienced PE, were used to update the original algorithm. The detection rates of preterm PE and term PE were 75% and 47%, respectively, at false-positive rate of 10%.[134] The predictive performance of this algorithm was examined in a prospective multicenter study of 8775 pregnancies, including 239 (2.7%) cases that developed PE. The detection rates of preterm PE and term PE were 75% and 43%, respectively, at false-positive rate of 10%.[135] In the screened population in the ASPRE trial, involving 26 941 singleton pregnancies from 13 maternity hospitals in six countries (UK, Spain, Italy, Belgium, Greece, Israel), the detection rates of preterm PE and term PE, after adjustment for the effect of aspirin, were 77% and 43%, respectively, at false-positive rate of 9.2%.[136]

In the latest National Institute for Health Research (UK) commissioned prospective validation study of the Bayes-based model in 16 747 pregnancies, including 473 (2.8%) women who developed PE, the screen-positive rate by the NICE method was 10.3%, the detection rate for all PE was 30%, and for preterm PE it was 41%. The detection rate of the mini-combined test (maternal factors, MAP, and PAPP-A) for all PE was 43%, 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, UTPI, and PLGF, the detection rate was 82%, which was higher than that of the NICE method by 41.6% (95% CI, 33.2–49.9).[137] The addition of PAPP-A to this combined model did not improve the overall screening performance.

Data from three reported prospective nonintervention screening studies at 11–13 weeks of gestation in a combined total of 61 174 singleton pregnancies, including 1770 (2.9%) that developed PE, have demonstrated that screening by a combination of maternal risk factors, MAP, PLGF, and UTPI and using a risk cut-off of 1 in 100 for preterm PE in white women, the screen-positive rate was 10% and detection rates for early-onset, 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-onset, preterm, and term PE were 100%, 92%, and 75%, respectively.[138]

A secondary analysis of data from the ASPRE trial of a total of 34 573 women with singleton pregnancies who underwent prospective screening for preterm PE, including 239 (0.7%) cases of preterm PE, has shown that in ACOG or NICE screen-positive women who are screen negative by the Bayes-based method, the risk of preterm PE is reduced to within or below background levels. The study demonstrated that at least one of the ACOG criteria was fulfilled in 22 287 (64.5%) pregnancies and the incidence of preterm PE was 0.97% (95% CI, 0.85–1.11). In the subgroup that was Bayes-method screen positive, the incidence was 4.80% (95% CI, 4.14–5.55); in those that were screen negative it was 0.25% (95% CI, 0.18–0.33%), and the relative incidence in Bayes-method negative to Bayes-method positive was 0.051 (95% CI, 0.037–0.071). In 1392 (4.0%)

pregnancies at least one of the NICE high-risk criteria was fulfilled and in this group the incidence of preterm PE was 5.17% (95% CI, 4.13–6.46). In the subgroups of screen positive and screen negative by the Bayes method the incidence of preterm PE was 8.71% (95% CI 6.93–10.89%) and 0.65% (95% CI, 0.25–1.67), respectively, and the relative incidence was 0.075 (95% CI, 0.028–0.205). In 2360 (6.8%) pregnancies with at least two of the NICE moderate-risk criteria, the incidence of preterm PE was 1.74% (95% CI, 1.28–2.35). In the subgroups of screen positive and screen negative by the Bayes method the incidence was 4.91% (95% CI, 3.54–6.79) and 0.42% (95% CI, 0.20–0.86), respectively, and the relative incidence was 0.085 (95% CI, 0.038–0.192).[139] These results provide further evidence to support risk-based screening using biomarkers.

There is now a substantial body of evidence to support risk-based screening for preterm PE using various biomarkers. This approach to screening has also been validated prospectively in countries other than Europe.[140–143] A checklist-based method of screening using information from maternal history does not perform as well and can no longer be considered sufficient for predicting preterm PE effectively.

5.3 | Recommendations

FIGO recommends the following first-trimester screening procedures for singleton pregnancies.

5.3.1 | Maternal characteristics and medical history

Best practice recommendation: Maternal characteristics, medical history and obstetric history (as shown in Box 2) must be recorded accurately.

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Evidence to support the inclusion of the above-listed maternal risk factors in a multivariate regression algorithm originates from a screening study of 120 492 singleton pregnancies at 11–13 weeks of gestation, including 2704 (2.2%) pregnancies that experienced PE. A competing risk model has been utilized to produce risks for PE, based on a continuous model for the gestational age at delivery with PE, treating births from causes other than PE as censored observations.[144] This approach assumes that, if the pregnancy were to continue indefinitely, all women would experience PE and that whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE. The effect of variables from maternal characteristics and history is to modify the distribution of gestational age at delivery with PE so that in pregnancies at low risk for PE the gestational age distribution is shifted to the right with the implication that, in most pregnancies, delivery will actually occur before development of PE (Fig. 1). In high-risk pregnancies the distribution is shifted to the left and the smaller the mean gestational age then the higher the risk for PE (Fig. 1).

In this risk factor-based model, increased risk for PE, with a consequent shift in the Gaussian distribution of the gestational age at delivery with PE to the left, is related to advancing maternal age, increasing weight, Afro-Caribbean and South Asian origin, medical history of chronic hypertension, diabetes mellitus and SLE or APS, family history and personal history of PE, and conception by IVF. The risk for PE decreases with increasing maternal height and in parous women with no previous PE; in the latter, the protective effect, which is related inversely to the interpregnancy interval, persists beyond 15 years. At a screen-positive rate of 11%, as defined by NICE, the new model predicted 40% and 48% of cases of all PE and preterm PE, respectively.[144] The risk factor-based model has been further improved with the inclusion of gestational age at delivery in the previous pregnancy.[136]

Box 2 Maternal characteristics, medical history, and obstetric history for pre-eclampsia screening in the first trimester.

- Maternal age, y
- Maternal weight, kg
- Maternal height, cm
- Maternal ethnicity: white, Afro-Caribbean, South Asian, East Asian, Mixed
- Past obstetric history: nulliparous, parous without prior PE, parous with prior PE
- Interpregnancy interval in years between the birth of the last child
- Gestational age at delivery (weeks) and birthweight of previous pregnancy beyond 24 wk
- Family history of PE (mother)
- Method of conception: spontaneous, ovulation induction, in vitro fertilization
- Smoking habit
- History of chronic hypertension
- History of diabetes mellitus: type 1, type 2, insulin intake
- History of systemic lupus erythematosus or antiphospholipid syndrome

Abbreviation: PE, pre-eclampsia.

FIGO supports the use of risk-based screening using biomarkers for first-trimester prediction of pre-eclampsia over screening methods that use maternal demographic characteristics and medical history (maternal risk factors) only.

5.3.2 | Measurement of blood pressure

MAP is calculated from systolic (sBP) and diastolic blood pressure (dBP) readings. The measured sBP and dBP will be automatically converted to MAP by the risk calculator.

$$MAP = dBP + (sBP - dBP)/3$$

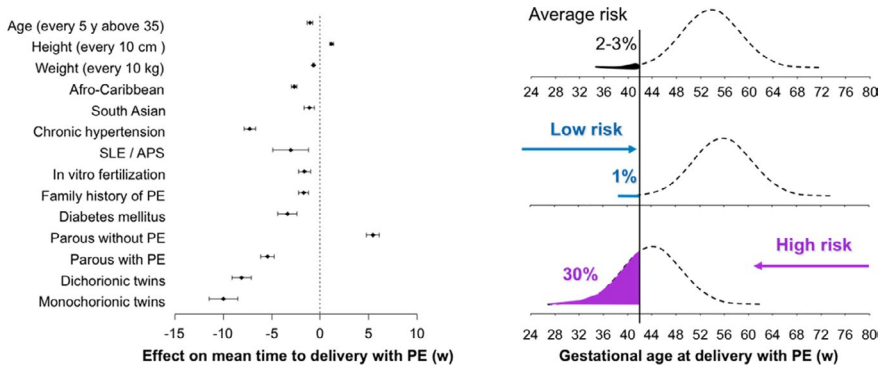

FIGURE 1 Competing risk model. Distribution of gestational age at delivery for PE. In pregnancies at low risk for PE the gestational age distribution is shifted to the right and, in most pregnancies, delivery will occur before the development of PE. In pregnancies at high risk for PE the distribution is shifted to the left. The risk of PE occurring at or before a specified gestational age is given by the area under the distribution curve. As an illustration, in the low-risk group the risk of PE at less than 34 wk of gestation is 0.01 or 1% and in the high-risk group the risk is 0.6 or 60%. Reprinted from Wright et al.[144] Copyright (2015), with permission from Elsevier. [Colour figure can be viewed at wileyonlinelibrary.com]

Best practice recommendation: MAP should be measured as part of the risk assessment for PE and it should be measured by validated automated and semiautomated devices (http://www.dableducational.org/sphygmomanometers/devices_1_clinical.html#ClinTable).

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Best practice recommendation: Women should be in a sitting position, with their arms well supported at the level of their heart and an appropriate-sized adult cuff (small <22 cm, normal 22–32 cm, or large 33–42 cm) used depending on the mid-arm circumference[145] (Fig. 2). After rest for 5 minutes, blood pressure is measured in both arms simultaneously and two sets of recordings are made at 1-minute intervals. The four sets of sBP and dBP measurements are needed for input into the risk calculator and the final MAP measurement (average of four sets of measurements) will be automatically calculated for the calculation of patient-specific risk.[145]

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Pragmatic practice recommendation: Women should be in the same position and posture as described above. Blood pressure is measured in one arm and two recordings are made at 1-minute intervals. The final MAP measurement (average of two measurements) will be used for the calculation of patient-specific risk.

Quality of evidence	Strength of recommendation
Moderate ⊕⊕⊕O	Conditional

Several factors can affect the values of MAP in pregnant women. A cohort study of nearly 70 000 pregnancies was conducted to evaluate the relationship between MAP and maternal characteristics.[146] Significant independent contributions to MAP are provided by gestational age, maternal weight, height, Afro-Caribbean racial origin, cigarette smoking, family history of PE,

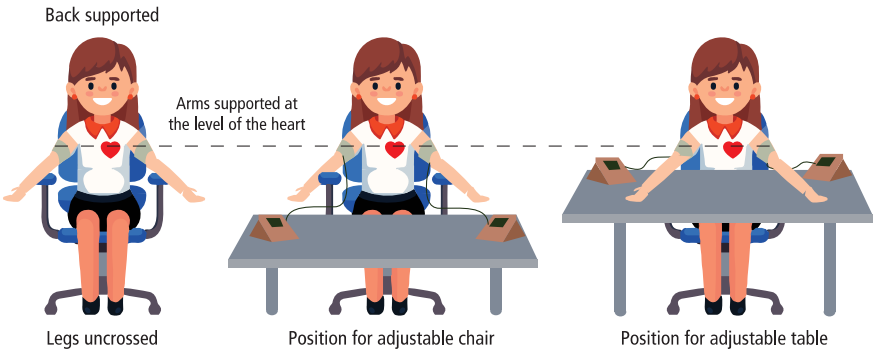

FIGURE 2 Correct positioning of a woman for blood pressure measurement. Courtesy of PerkinElmer Life and Analytical Sciences. [Colour figure can be viewed at wileyonlinelibrary.com]

history of PE in the previous pregnancy, interpregnancy interval, chronic hypertension, and diabetes mellitus. Consequently, the measurement of MAP is converted to a multiple of median (MoM), adjusting for these associated maternal characteristics and gestational age[146] (Appendix S1).

Poon et al.[147] first reported the value of MAP measured by validated automated blood pressure devices according to a standardized protocol at 11–13 weeks of gestation for the prediction of PE.[148] Maternal blood pressure was determined in 5590 singleton pregnant women by automated devices and appropriately trained doctors. For MAP alone and in combination with maternal history, the detection rates for PE, at 10% false-positive rate, were 38% and 63%, respectively. A follow-up study of more than 9000 pregnancies at 11–13 weeks of gestation compared the screening performance of sBP, dBP, and MAP.[149] Although sBP, dBP, and MAP were all found to be raised in women who subsequently developed PE, MAP performed best as a marker, with a detection rate for early-onset PE, increasing from 47% (based on maternal factors alone) to 76% (based on a combination of maternal factors and MAP) at a false-positive rate of 10%.[149]

Methodologically, based on the protocol of the National Heart Foundation of Australia (NHFA),[148] blood pressure is measured in both arms and a minimum of two recordings are made at one-minute intervals until variations between consecutive readings fall to within 10 mm Hg in sBP and 6 mm Hg in dBP in both arms.[148] When this point of stability is achieved, the average of the last two stable measurements of the left and right arms is calculated and the higher of these two measurements from the two arms is used. However, in order to achieve the necessary point of blood pressure stability according to the NHFA protocol, it has been shown that it is necessary to perform two measurements in both arms in about 50% of cases, three measurements in 25% of cases, and four measurements or more in 25%.[145] In addition, whether blood pressure should be taken on the left or right arm remains controversial. The evidence supporting simultaneous measurement of both arms is derived from the study published by Poon et al.[150] In this study, the prevalence of blood pressure interarm difference (IAD), defined as IAD of greater than 10 mm Hg of sBP and dBP was determined in 5435 women during the first trimester of pregnancy. The IAD of sBP and dBP was found in 8.3% and 2.3% of normal pregnant women, respectively.[150] A simplified protocol for blood pressure measurement (as described above) has been developed through a study of 25 505 singleton pregnancies where blood pressure measurements were made using a validated automatic device at 11–13 weeks of gestation.[145] The results demonstrated that performance of screening for PE by taking the average of two measurements from both arms is comparable with the NHFA protocol.

5.3.3 | Measurement of biochemical markers

Best practice recommendation: In first-trimester screening, the best biochemical marker is PLGF. PAPP-A is useful if measurements of PLGF and UTPI are not available.

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Maternal serum concentrations of PLGF and PAPP-A are measured by one of three commercially available automated devices. Quality control should be applied to achieve consistency of measurement of biomarkers.

5.3.3.1 | Placental growth factor

PLGF is a glycosylated dimeric glycoprotein secreted by trophoblastic cells and is part of the angiogenic vascular endothelial growth factor (VEGF) family. It binds to VEGF receptor 1 (VEGFR-1), which has been shown to increase during pregnancy. PLGF is synthesized in villous and extravillous cytotrophoblasts, and has both vasculogenic and angiogenetic functions. Its angiogenetic abilities have been speculated to play a role in normal pregnancy, and changes in the levels of PLGF or its inhibitory receptors have been implicated in the development of PE.[151–153] Several studies have shown that women who subsequently develop PE have significantly lower maternal PLGF concentrations in the first trimester than those with normal pregnancies.[154–157] This biomarker alone has a detection rate of 55% and 33%, respectively, at 10% false-positive rate, for the identification of both early- and late-onset PE.[158] A systematic review and meta-analysis demonstrated that PLGF is superior to the other biomarkers for predicting PE.[159] Specifically, maternal PLGF concentrations alone achieve a detection rate of 56% at 9% false-positive rate for the prediction of early-onset PE.[159]

Several factors affect the values of PLGF in pregnant women. A cohort study of more than 42 000 pregnancies, including 33 147 measured by the DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, MA, USA), 7065 measured by the Cobas e411 system (Roche Diagnostics, Risch-Rotkreuz, Switzerland), and 2143 measured by the B·R·A·H·M·S KRYPTOR compact PLUS (Thermo Fisher Scientific, Waltham, MA, USA), was conducted to evaluate the relationship of PLGF with analyzers and maternal characteristics.[138] Significant independent contributions to PLGF values are provided by the three analyzers as listed above, as well as by gestational age, maternal age, weight, racial origin, cigarette smoking, a history of PE in the previous pregnancy, diabetes mellitus, and IVF.

5.3.3.2 | Pregnancy-associated plasma protein A

PAPP-A is a metalloproteinase insulin-like growth factor (IGF) binding protein secreted by the syncytiotrophoblast that plays an important role in placental growth and development. It enhances the mitogenic function of the IGFs. PE has been shown to be associated with a low level of circulating PAPP-A, which is presumably due to the reduced availability of unbound IGFs to fulfil their functional role on a cellular level. PAPP-A is a well-established biochemical marker in the screening of trisomies 21, 18, and 13. In euploid pregnancies, a PAPP-A MoM value at less than the 5th percentile (0.4 MoM) is present in 8%–23% of women with PE. Therefore, as a single marker it is not an accurate predictive test for PE.[160–162] A recent systematic review and meta-analysis, including eight studies involving 132 076 pregnant women in

the first trimester, demonstrated that the maternal PAPP-A concentration of less than the 5th percentile is associated with the risk of developing PE with an OR of 1.94 (95% CI, 1.63–2.30). It has a detection rate of 16% (9%–28%) at 8% false-positive rate to predict PE.[163]

In a cohort study of more than 94 000 pregnancies, the relationship between PAPP-A, measured by the DELFIA Xpress system (PerkinElmer Life and Analytical Sciences), and maternal characteristics was evaluated.[164] Significant independent contributions to PAPP-A are provided by gestational age, maternal weight, height, racial origin, cigarette smoking, diabetes mellitus, method of conception, previous pregnancy with or without PE, and birth weight Z-score of the neonate in the previous pregnancy. The measurements of PLGF and PAPP-A should be converted to MoMs, adjusting for these associated maternal characteristics, analyzers, and gestational age[138] (Appendix S1).

5.3.4 | Measurement of uterine artery pulsatility index

Best practice recommendation: Where feasible UTPI should be measured. A transabdominal ultrasound scan should be done at 11^{+0} to 13^{+6} weeks of gestation (corresponding to fetal crown–rump length (CRL) of 42–84 mm). Gestational age must be determined from the measurement of the fetal CRL. The same scan is utilized for the measurement of fetal translucency thickness and diagnosis of any major fetal defects. For the measurement of UTPI, a sagittal section of the uterus is obtained and the cervical canal and internal cervical os are identified. Subsequently, keeping the transducer in the midline it is gently tilted to the side and color flow mapping is used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os (Fig. 3). Pulsed-wave Doppler is used with the sampling gate set at 2 mm to cover the whole vessel and care is taken to ensure that the angle of insonation is less than 30°. When three similar consecutive waveforms are obtained (Fig. 3), the UTPI is measured and the mean UTPI of the left and right arteries is calculated.[165] The measurement of UTPI must be carried out by sonographers who have received the appropriate certificate of competence from the Fetal Medicine Foundation (FMF) (www.fetalmedicine.org).

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

The Doppler ultrasound assessing the resistance to blood flow in the uterine arteries correlates with both histological studies and clinical severity of PE. This biophysical marker provides a useful noninvasive method for the assessment of the uteroplacental circulation. Studies have shown that a significant decrease of resistance in the spiral arteries occurs with advancing gestation, which is in keeping with physiological changes throughout pregnancy.[166,167] Persistent high impedance to flow in the uterine arteries is evidence of poor placentation that manifests itself in the form of abnormal uteroplacental flow velocity waveforms. Histological examination of placental bed biopsies of pregnancies affected by PE has shown that absence of physiological changes of the spiral arteries is found more commonly in cases with high UTPI.[168]

Methodologically, the measurement of UTPI at the level of the internal os during the first trimester is more reproducible than those obtained at the level of external iliac vessels crossover.[169] In addition, UTPI can be achieved at the level of the internal cervical os in a greater proportion of women than at the level of external iliac vessel crossover.[169]

Several factors can affect the values of UTPI in pregnant women. A cohort study of more than 83 000 pregnancies was conducted to evaluate the relationship between UTPI and maternal characteristics.[138] Significant independent contributions to UTPI are provided by gestational age, maternal age, weight, racial origin, a history of PE in the previous pregnancy, and type 1 diabetes. Hence, before comparing the values between affected and unaffected groups, the UTPI value needs to be adjusted for these associated maternal characteristics and gestational age by converting it to a MoM (Appendix S1).

A large meta-analysis of first-trimester UTPI measurement for the prediction of PE included eight studies for the prediction of early-onset PE (n=41 692 women) and eleven studies for the prediction of PE of any gestation (n=39 179 women).[170] The first-trimester abnormal UTPI is defined as greater than the 90th percentile, achieving a detection rate of 48%, at 8% false-positive rate, for the identification of early-onset PE. The detection rate for predicting late-onset PE reduces to 26% at a 7% false-positive rate.

[Correction added on 18 June 2019, after first online publication: Second last sentence 'The first-trimester abnormal UTPI is defined as greater than the 90th percentile' has been corrected for accuracy in this version.]

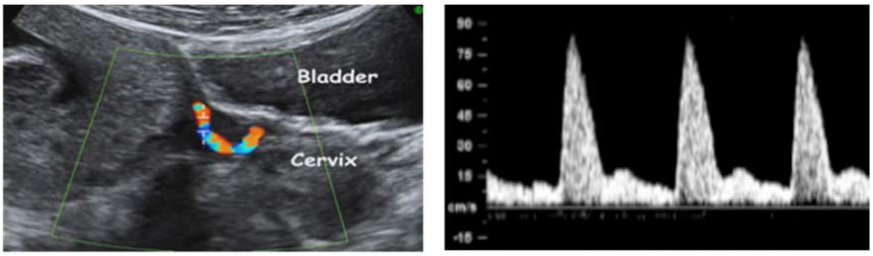

FIGURE 3 Identification of the uterine artery at the level of the internal os (left) and typical waveforms of the uterine artery Doppler in the first trimester of pregnancy. Courtesy of the Fetal Medicine Foundation. [Colour figure can be viewed at wileyonlinelibrary.com]

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has recently published its practice guideline on the role of ultrasound in screening for and follow-up of PE.[165]

FIGO acknowledges and endorses the guidance from ISUOG with regard to UTPI measurement methodology.

5.3.5 | Combined risk assessment

Best practice recommendation: Published algorithms should be used for converting the measured values of MAP, PLGF, and UTPI, with or without PAPP-A, into MoMs as detailed above. Patient-specific risk for preterm PE is calculated using the Bayes-based method. The risk calculator is available free of charge on the webpage https://fetalmedicine.org/research/assess/preeclampsia and on the FMF mobile app. It is also available on medical records software. A woman is considered high risk when the risk is greater than or equal to 1 in 100 based on the first-trimester combined test with maternal risk factors, MAP, PLGF, and UTPI.[1,136,171]

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Best practice recommendation: Based on existing evidence, the first-trimester combined test is most predictive of preterm PE but not term PE. The best model is the one that combines maternal risk factors with MAP, PLGF, and UTPI. The performance of screening for preterm PE of various combinations of the first-trimester test, based on data from three previously reported prospective nonintervention screening studies, including a combined total of 61 174 singleton pregnancies, including 1770 (2.9%) that developed PE, is illustrated in Table 4.

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Pragmatic practice recommendation: Where it is not possible to measure the biochemical markers and/or UTPI, the baseline screening test should be a combination of maternal risk factors with MAP, and not maternal risk factors alone. PAPP-A is useful if measurements of PLGF and UTPI are not available These variations to the combined test would lead to a reduction in the performance screening.

Quality of evidence	Strength of recommendation
Moderate ⊕⊕⊕O	Conditional

As demonstrated above, biomarkers are best used in the combination strategy for the prediction of PE. A recent systematic review has been conducted to evaluate the performance of simple risk models

TABLE 4 Detection rates, at screen-positive rate of 10%, of preterm PE and term PE by maternal factors, biomarkers, and their combination.[a]

Method of screening	Risk cut-off for PE <37 wk	Preterm PE		Term PE	
		AUC	DR % (95% CI)	AUC	DR % (95% CI)
Maternal risk factors	1 in 62	0.788	44.8 (40.5–49.2)	0.735	33.5 (31.0–36.2)
Maternal risk factors plus					
MAP (baseline)	1 in 61	0.841	50.5 (46.1–54.9)	0.776	38.2 (35.6–40.9)
UTPI	1 in 60	0.853	58.4 (54.0–62.7)	0.733	35.2 (32.6–37.8)
PAPP-A	1 in 61	0.810	48.5 (44.1–52.9)	0.734	35.2 (32.7–37.9)
PLGF	1 in 62	0.868	60.6 (56.3–64.9)	0.745	34.5 (32.0–37.2)
MAP, UTPI	1 in 61	0.891	68.4 (64.1–72.3)	0.772	41.4 (38.8–44.2)
MAP, PAPP-A	1 in 60	0.855	55.8 (51.4–60.1)	0.774	39.1 (36.4–41.8)
MAP, PLGF	1 in 65	0.895	66.1 (61.8–70.2)	0.777	39.3 (36.7–42.0)
UTPI, PAPP-A	1 in 60	0.861	59.2 (54.8–63.5)	0.735	36.3 (33.7–39.0)
UTPI, PLGF	1 in 62	0.892	66.9 (62.7–70.9)	0.744	36.9 (34.3–39.6)
PLGF, PAPP-A	1 in 62	0.869	63.5 (59.2–67.6)	0.745	35.7 (33.1–38.4)
MAP, UTPI, PAPP-A	1 in 61	0.896	68.2 (63.9–72.1)	0.773	40.6 (37.9–43.3)
MAP, PAPP-A, PLGF	1 in 65	0.896	67.3 (63.1–71.3)	0.777	39.3 (36.7–42.0)
MAP, UTPI, PLGF	1 in 66	0.915	74.8 (70.8–78.5)	0.776	41.0 (38.3–43.7)
UTPI, PAPP-A, PLGF	1 in 63	0.892	68.2 (63.9–72.1)	0.745	36.9 (34.3–39.6)
MAP, UTPI, PAPP-A, PLGF	1 in 66	0.916	74.8 (70.8–78.5)	0.777	41.3 (38.7–44.1)

Abbreviations: PE, pre-eclampsia; AUC, area under curve; DR, detection rate; MAP, mean arterial pressure; UTPI, uterine artery pulsatility index; PAPP-A, pregnancy-associated plasma protein A; PLGF, placental growth factor.

[a]Adapted with permission granted by Wiley, from Tan et al.[138]

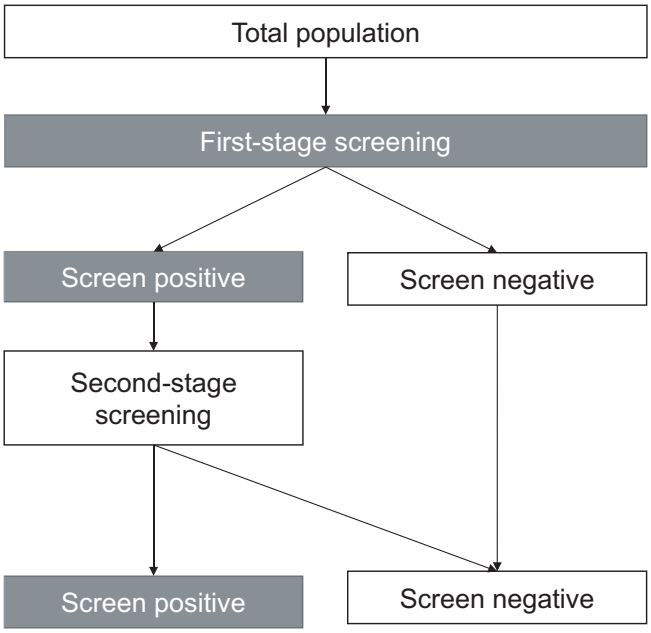

FIGURE 4 Two-stage screening strategy for preterm PE in which the whole population undergoes first-stage screening by maternal factors and MAP and a selected proportion of those considered to be at intermediate risk undergo second-stage screening by PLGF and UTPI. Adapted with permission granted by Wiley, from Wright et al.[173]

(maternal characteristics only) versus specialized models that include specialized tests such as the measurement of MAP, UTPI, and/or maternal biochemical markers for the prediction of PE. Seventy models from 29 studies have been identified (17 models to predict PE, 31 models to predict early-onset PE, and 22 models to predict late-onset PE). Among them, 22 were simple models while 48 were classified as specialized models. Comparing the simple and specialized models, the latter performed better than the simple models in predicting early- and late-onset PE, achieving an additional 18% (95% CI, 0–56) in detection rate for the prediction of PE at a fixed false-positive rate of 5% or 10%.[172] Therefore, a combination of various tests rather than a single test is recommended for the prediction of PE.

5.3.6 | Contingent screening

Pragmatic practice recommendation: 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 alone can be considered (Fig. 4).

Quality of evidence	Strength of recommendation
Moderate ⊕⊕⊕O	Conditional

In a prospective screening study including more than 120 000 singleton pregnancies, the performance of screening for preterm PE by this two-stage strategy was examined. At a fixed screen-positive rate of 10%, a detection rate of 71% was achieved by this two-stage screening, with screening by maternal factors and MAP, based on the above-described combined algorithm, at 11^{+0}–13^{+6} weeks of gestation in the first stage and reserving measurement of PLGF and UTPI for the second stage and for 30% of the population.[173]

5.3.7 | Multiple pregnancies

Pragmatic practice recommendation: The same first-trimester combined test for PE in singleton pregnancies can be adapted for screening in twin pregnancies. It leads to the detection of nearly all affected cases of PE but at a high screen-positive rate.

Quality of evidence	Strength of recommendation
Moderate ⊕⊕⊕O	Conditional

In a prospective screening study for PE in 2219 twin pregnancies undergoing routine first-trimester combined screening for aneuploidy and subsequently delivering two phenotypically normal live or stillborn babies at greater than or equal to 24 weeks of gestation, the incidence of PE in dichorionic and monochorionic twin pregnancies was shown to be increased by four-fold and three-fold, respectively.[174] In twin pregnancies that developed PE, the values of MAP and UTPI were increased and the values of PLGF and PAPP-A were decreased. The distributions of $\log_{10}$ MoM values of biomarkers with gestational age at delivery were similar to those that were previously reported in singleton pregnancies and it was therefore decided that the same first-trimester combined test for singleton pregnancies could be applicable to twin pregnancies. In a mixed population of singleton and twin pregnancies, combined screening by maternal factors, MAP, UTPI, and PLGF and at a risk cut-off of 1 in 75 for preterm PE, the detection rates of preterm PE and all PE in singleton pregnancies were 77% and 57%, respectively, at a screen-positive rate of 13%; the respective rates for twin pregnancies were 99% and 97%, at a screen-positive rate of 75%.[174] The addition of PAPP-A did not improve the performance of screening.

6 | FIRST TRIMESTER PREVENTION OF PRETERM PRE-ECLAMPSIA

The current approach to prevention of PE is to commence low-dose aspirin at 75 mg or 81 mg daily in high-risk women as locally defined.[2–4,16,128] Low-dose aspirin treatment in pregnancy is thought to prevent the development of PE by inhibiting the biosynthesis of placental thromboxane A_2 with minimal effects on vascular prostacyclin levels.[175] The enzyme cyclooxygenase plays a pivotal role in the production of both prostacyclin and thromboxane A_2. Aspirin inhibits endothelial cyclooxygenase[176] and this process is irreversible in platelets, where the enzyme is inhibited for their entire lifespan. In contrast, when the enzyme is resynthesized in endothelial cells, the prostacyclin production is re-established relatively rapidly. This selective inhibition of cyclooxygenase and the resulting alteration in the prostacyclin to thromboxane A_2 ratio in the placenta forms the basis of using aspirin to prevent or delay the onset of PE.

Crandon and Isherwood[177] demonstrated that nulliparous women who had taken aspirin more than once a fortnight throughout pregnancy had a lower risk of PE than those who had no reported history of aspirin consumption. In 1985, an open-label randomized trial showed that among women at risk for PE or FGR, based on obstetric history, pregnancies in women who received 300 mg of dipyridamole and 150 mg of aspirin beginning at 12 weeks of gestation until delivery were not complicated by PE, fetal loss, and severe FGR compared with those in the nonintervention group.[178] A landmark meta-analysis, including 31 randomized trials of PE prevention, including 32 217 pregnancies, showed that patients who received antiplatelet agents especially aspirin for the prevention of PE, had a 10% reduction of PE (RR 0.90; 95% CI, 0.84–0.97), preterm birth before 34 weeks of gestation, and serious adverse pregnancy outcomes (PE, delivery <34 weeks of gestation, SGA babies, fetal or maternal death).[179] Bujold et al.[180] showed that low-dose aspirin started at less than or equal to 16 weeks of gestation in women at risk of PE had a substantial reduction in the rate of PE (RR 0.47; 95% CI, 0.34–0.65). However, aspirin started after 16 weeks of gestation did not decrease the rate of PE (RR 0.81; 95% CI, 0.87–1.10).[180] Subsequent meta-analyses consistently showed that administration of low-dose aspirin (50–150 mg/d) at less than or equal to 16 weeks of gestation to women at risk of PE had a significant reduction in PE, in particular preterm PE (RR 0.22; 95% CI, 0.080–0.567).[181] Additionally, these meta-analyses highlighted that additional benefits from early aspirin prophylaxis include a 50% reduction in the risk of FGR and a 60% reduction in the risk of perinatal death.[180] These results have stimulated the need for a prospective randomized trial to evaluate the potential benefit of aspirin in preventing PE.

This evidence has been provided by the ASPRE trial (Project #601852; EudraCT number 2013-003778-29; ISRCTN13633058; www.aspre.eu). The ASPRE trial shows that the rate of delivery with preterm PE can be reduced by 62% by aspirin started at 11–14 weeks of gestation in high-risk women.[182] The ASPRE trial was designed to test the hypothesis that aspirin at a dose of 150 mg per night from 11 to 14 weeks until 36 weeks of gestation, compared with placebo, would result in halving the incidence of preterm PE. In this multicenter, double-blind, placebo-controlled trial, women with singleton pregnancies identified as being at high-risk of preterm PE by means of the first-trimester combined test were randomized to receive aspirin (150 mg per night) versus placebo from 11–14 weeks until 36 weeks of gestation. Preterm PE occurred in 1.6% (13/798) of participants in the aspirin group, compared with 4.3% (35/822) in the placebo group (OR in the aspirin group, 0.38; 95% CI, 0.20–0.74). However, there was no significant reduction in the rate of term PE with the use of aspirin prophylaxis (OR in the aspirin group, 0.95; 95% CI, 0.57–1.57). The proportion of prescribed tablets taken was used as an overall measure of adherence. Adherence was good, with reported intake of more than 85% of the required number of tablets in 80% of participants. There were no significant between-group differences in adverse events. There was no statistically significant difference in the rate of vaginal bleeding (3.6% vs 2.6%) and upper gastrointestinal (GI) symptoms (7.4% vs 7.1%) between placebo and aspirin groups. In particular, the rates of vaginal bleeding (4.8% vs 2.9%) and upper GI symptoms (6.8% vs 6.4%) were not significantly different in women who were of normal weight versus women who were overweight in the aspirin arm.

Further, a secondary analysis of data of 1620 participants with 1571 liveborn neonates showed that the total length of stay in NICU was substantially longer in the placebo than in the aspirin group (1696 vs 531 days). This reflected significantly shorter mean lengths of stay in babies admitted to the NICU in the aspirin group compared with the placebo group (11.1 vs 31.4 days; a reduction of 20.3 days).[183] Overall, in the whole population, including zero lengths of stay for those that were not admitted to the NICU, the mean length of stay was longer in the placebo than in the aspirin group (2.06 vs 0.66 days; reduction of 1.4 days). This corresponded to a reduction in length of stay by 68%.[183]

Results from the ASPRE trial provide definitive evidence that effective screening for preterm PE can be achieved with a combined test of maternal factors and biomarkers at 11–13 weeks and aspirin treatment from the first trimester of pregnancy can significantly reduce the risk of developing preterm PE. Furthermore, in pregnancies at high risk of preterm PE, administration of aspirin reduces the length of stay in the NICU by 68%. The findings have implications for both short- and long-term savings as well as infant survival, disability, and human capital.

FIGO makes the following recommendation for early prevention of preterm PE:

Best practice recommendation: Following the first-trimester screening and assessment 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 either 36 weeks of gestation, when delivery occurs, or when PE is diagnosed.[171]

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

This recommendation is supported by the evidence from the ASPRE trial.[182] The choice for recommending night-time consumption of low-dose aspirin is based on the results from a randomized, double-blind, placebo-controlled, chronotherapy trial on 350 high-risk women. This trial demonstrated that women taking low-dose aspirin at 100 mg, compared with placebo, had a significantly lower hazard ratio (HR) of serious adverse outcomes, a composite of PE, preterm birth, FGR, and IUFD (HR 0.35; 95% CI, 0.22–0.56) and that the event rate of serious adverse outcomes was significantly lower in women taking low-dose aspirin in the evening, compared with in the morning and afternoon (HR 0.19; 95% CI, 0.10–0.39).[184]

The latest systematic review and meta-analysis, which included 16 randomized controlled trial studies for a total of 18 907 participants, demonstrated that administration of aspirin was associated with a reduction in the risk of preterm PE (RR 0.62; 95% CI, 0.45–0.87). However, there was no significant effect on term PE (RR 0.92; 95% CI, 0.70–1.21). Only the subgroup in which aspirin was started at less than or equal to 16 weeks of gestation at a dose of greater than or equal to 100 mg/d was associated with a reduction in the frequency of preterm PE (RR 0.33; 95% CI, 0.19–0.57; *P*=0.0001). Aspirin started after 16 weeks or administered in a daily dose of less than 100 mg was not associated with a significant reduction in rates of preterm or term PE.[185] Suggested aspirin dosages are provided in Table 5.

Low-dose aspirin is defined as dosage of less than 300 mg/d. In 1979, Masotti et al.[186] demonstrated that aspirin 2.5–3.5 mg/kg is the required dosage to produce a consistent inhibition of platelet aggregation with slight inhibition of prostaglandin production. The recommended dosage of 150 mg/d would be sufficient for an average woman with a weight of 65 kg at booking.

Pragmatic practice recommendation: Where it is not possible to source the above suggested aspirin regime, the minimum dosage of aspirin to be prescribed to high-risk women should be 100 mg/d.

Quality of evidence	Strength of recommendation
Moderate ⊕⊕⊕O	Conditional

Best practice recommendation: High-risk women must be informed and counselled about the importance of treatment adherence and assessed for compliance at each prenatal visit.

Quality of evidence	Strength of recommendation
High ⊕⊕⊕⊕	Strong

In a secondary analysis of data from the ASPRE trial, the influence of adherence on the beneficial effect of aspirin in prevention of preterm PE was evaluated. The choice of cut-off for good compliance was redefined as greater than 90%, which was based on an exploratory analysis of the treatment effect. Preterm PE occurred in 5/555 (0.9%) participants in the aspirin group with adherence greater than or equal to 90%, in 8/243 (3.3%) of participants in the aspirin group with adherence less than 90%, in 22/588 (3.7%) of participants in the placebo group with adherence greater than or equal to 90%, and in 13/234 (5.6%) of participants in the placebo group with adherence less than 90%. The OR in the aspirin group for preterm PE was 0.24 (95% CI, 0.09–0.65) for adherence more than 90% and 0.59 (95% CI, 0.23–1.53) for adherence less than 90%. The beneficial effect of aspirin in preventing preterm PE is dependent on adherence.[187] In addition, there was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetric history, with the exception of chronic hypertension. In women with chronic hypertension, preterm PE occurred in 10.2% (5/49) in the aspirin group and in 8.2% (5/61) in the placebo group (adjusted OR 1.29; 95% CI, 0.33–5.12); the respective values in those without chronic hypertension were 1.1% (8/749) in the aspirin group and 3.9% (30/761) in the placebo group (adjusted OR 0.27; 95% CI, 0.12–0.60). Prophylactic aspirin may not be as effective in lowering preterm PE risk in women with chronic hypertension compared with other high-risk groups. Further, in women with adherence of more than 90% the adjusted OR in the aspirin group was 0.24 (95% CI, 0.09–0.65), in the subgroup with chronic hypertension it was 2.06 (95% CI, 0.40–10.71), and in those without chronic hypertension it was 0.05 (95% CI, 0.01–0.41).

TABLE 5 Proposed aspirin regime for preterm pre-eclampsia prevention.

Maternal weight, kg	Daily required dosage, mg	Administration, mg
<40	100	1 × 100
≥40	~150	2 × 60 2 × 75 2 × 81 1 × 100 + ½ × 100 (discard the other half) ½ × 300 (discard the other half)

Pragmatic practice recommendation: If vaginal spotting occurs it must be duly assessed but does not necessitate stopping aspirin prophylaxis.

Quality of EVIDENCE	Strength of recommendation
High ⊕⊕⊕⊕	Strong

Several systematic reviews of randomized controlled trials have demonstrated that the use of low-dose aspirin during pregnancy is not associated with hemorrhagic complications.[179,188,189] The study by the US Preventive Services Task Force, which included more than 23 000 pregnant women, showed that the risk of placental abruption (RR 1.17; 95% CI, 0.93–1.48) and postpartum hemorrhage (RR 1.02; 95% CI, 0.96–1.09) did not significantly increase with the use

of aspirin.[188] In addition, women who were exposed to low-dose aspirin during pregnancy had similar mean blood loss to those who were not exposed to low-dose aspirin.[188] A recent meta-analysis involving 12 585 pregnant women showed that the use of aspirin at less than 100 mg/d or greater than or equal to 100 mg/d, regardless of initiation time (≤16 or >16 weeks), was not associated with an increased risk of placental abruption or prepartum hemorrhage.[190] In the ASPRE trial, women exposed to aspirin did not have increased risk of bleeding adverse events.[136] During the trial, women with vaginal spotting were not advised to stop the trial medication.

Best practice recommendation: 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.[191]

Quality of evidence	Strength of recommendation
Low ⊕⊕OO	Conditional

PE was reduced consistently with low-dose calcium with or without co-supplements (nine trials, 2234 women, RR 0.38; 95% CI, 0.28–0.52), as well as for subgroups: low-dose calcium alone (four trials, 980 women, RR 0.36; 95% CI, 0.23–0.57); low-dose calcium plus linoleic acid (two trials, 134 women, RR 0.23; 95% CI, 0.09–0.60); low-dose calcium plus vitamin D (two trials, 1060 women, RR 0.49; 95% CI, 0.31–0.78); and a trend for low-dose calcium plus antioxidants (one trial, 60 women, RR 0.24; 95% CI, 0.06–1.01). Overall results were consistent with the single quality trial of low-dose calcium alone (171 women, RR 0.30; 95% CI, 0.06–1.38). For high-dose calcium, the average risk of high blood pressure was reduced with calcium supplementation versus placebo (12 trials, 15 470 women, RR 0.65; 95% CI, 0.53–0.81). There was a reduction in the average risk of PE associated with calcium supplementation (13 trials, 15 730 women, RR 0.45; 95% CI, 0.31–0.65). The effect was greatest for women with low baseline calcium intake (eight trials, 10 678 women, RR 0.36; 95% CI, 0.20–0.65) and those selected as being at high risk (five trials, 587 women, RR 0.22; 95% CI, 0.12–0.42). The variable methods of selecting women as being at high risk limit the clinical usefulness of these pooled results.[191]

Pragmatic practice recommendation: In high-risk women who are sensitive or allergic to aspirin, and in the absence of other proven interventions, close vigil and expectant management are appropriate. These include frequent clinic blood pressure and/or home blood pressure monitoring to ensure early diagnosis of PE. The purported benefit of other treatments, such as heparin, vitamins C and E, magnesium, folate, metformin, and statin for prophylaxis of preterm PE is not yet based on credible evidence and their use solely for the purpose of preventing preterm PE in pregnancy is neither justified nor recommended.[192–198]

Quality of evidence	Strength of recommendation
Very Low ⊕OOO	Conditional

Pragmatic practice recommendation: In women with multiple pregnancies, the use of low-dose aspirin for the prevention of PE may be considered; however, more research is required to demonstrate a high level of evidence.

Quality of evidence	Strength of recommendation
Very Low ⊕OOO	Conditional

The latest systematic review and meta-analysis of six randomized controlled trials, including 898 pregnancies, demonstrated a significant reduction in the risk of PE (RR 0.67; 95% CI, 0.48–0.94) and mild PE (RR 0.44; 95% CI, 0.24–0.82) but not severe PE (RR 1.02; 95% CI, 0.61–1.72) with low-dose aspirin. The risk of SGA was not changed (RR 1.09; 95% CI, 0.80–1.47). The reduction of PE was not different between women randomized before (RR 0.86; 95% CI, 0.41–1.81) or after 16 weeks of gestation (RR 0.64; 95% CI, 0.43–0.96; P=0.50). The authors concluded that there is a low level of evidence supporting the use of low-dose aspirin for the prevention of PE and SGA neonates in multiple gestations.[199]

The FIGO initiative for PE is meant to provide a practical and pragmatic guide for national associations to adopt and promote a uniform approach to predicting and preventing preterm PE for all countries and regions based on their financial, human, and infrastructure resources. A pathway for preterm PE prevention and screening is shown in Figure 5.

- FIGO adopts and supports the Fetal Medicine Foundation position that all pregnant women should be screened for preterm pre-eclampsia by the first-trimester combined test with maternal risk factors, mean arterial pressure, uterine artery pulsatility index, and placental growth factor as a one-step procedure.
- FIGO adopts and supports the Fetal Medicine Foundation position that in high-risk women, defined by the first-trimester combined test, aspirin ~150 mg/night should be commenced at 11–14^{+6} weeks of gestation until either 36 weeks of gestation, when delivery occurs, or when pre-eclampsia is diagnosed.
- Given the resource constraints in low/middle-income countries, variations of the first-trimester combined test should be considered but the baseline test should be maternal risk factors combined with mean arterial pressure.
- FIGO encourages all countries and its member associations to adapt and promote strategies to improve access to prenatal services and encourage early booking.
- FIGO encourages all countries and its member associations to ensure that risk assessment and resource-appropriate testing for preterm pre-eclampsia become an integral part of routine first-trimester evaluation protocol offered at all maternal health services.

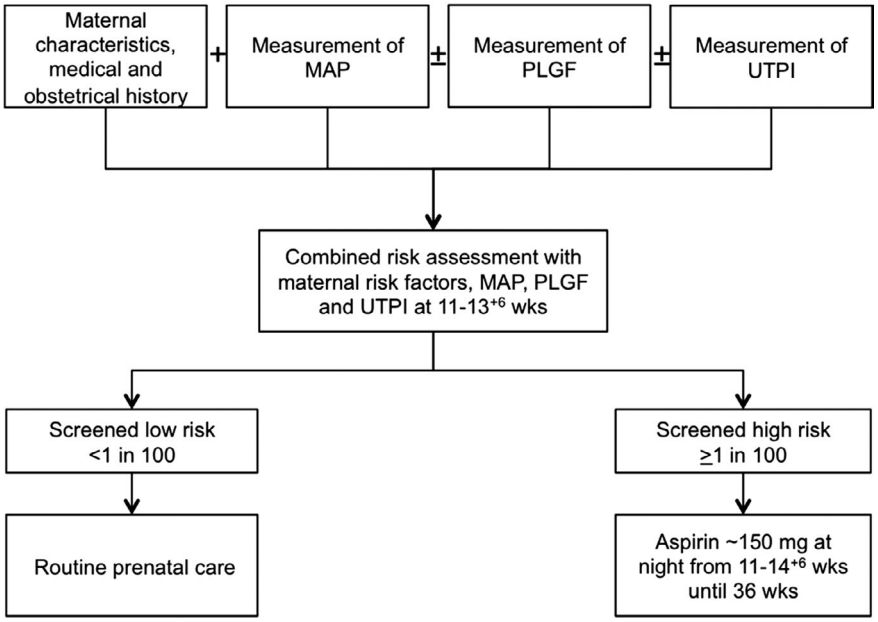

FIGURE 5 Pathway of preterm pre-eclampsia screening and prevention.

7 | RESOURCE-BASED APPROACH TO SCREENING

Implementation of guidelines is a constant challenge. The reality is that most low-resource countries around the world are unable to implement a first-trimester screening program for preterm PE based on the combined test.

Recommendations that are rigid and impractical in real-life settings are unlikely to be implemented and hence may produce little or no impact. On the other hand, pragmatic but less than ideal recommendations may produce significant impact owing to more widespread implementation.

The FIGO approach is three pronged: (1) to promote, encourage, and advocate ideal evidence-based guidance; (2) to offer pragmatic options for resource-constrained situations based on local experience backed by less than optimal evidence; and (3) to promote research aimed at improving the evidence base in both well-resourced and resource-constrained contexts.

FIGO recommendations are based on available resources at country level and evidence of local practice. Countries worldwide fall into four resource categories. There are also variations seen within any country. An affluent country may have pockets of poorly funded care and, conversely, a low- or middle-resource country may have "state of the art" care in the private sector for a selected few.

High-resource countries: Includes countries or regions like North America, Western Europe, Japan, South Korea, Australia, etc.

Upper/middle-resource countries: Includes countries like Brazil, China, Colombia, Hungary, Malaysia, Mexico, Romania, South Africa, Turkey, etc.

Low/middle-resource countries: Includes countries like India, Indonesia, Pakistan, Nigeria, Egypt, Vietnam, the Philippines, etc.

Low-resource countries: Includes countries like Bangladesh, Nepal, Cambodia, Kenya, Tanzania, Uganda, Ethiopia, Congo, Sierra Leone, etc.

In low- and middle-income countries where resources are limited, variations of the first-trimester combined test can be considered but the baseline test is one that combines maternal risk factors with MAP. In the absence of one or two of the biomarker(s), risk calculation can still be done but the detection rates for preterm PE will be reduced, in turn leading to a reduction in the treatment effect size by aspirin prophylaxis but may make the treatment economically feasible.

As 99% of serious morbidity occurs in low- and middle-income settings, any prediction and prevention strategies need to be applied in these settings to impact on the global burden. An estimated 70 000 women die each year from PE. Low- and middle-income countries are disproportionately affected by avoidable maternal deaths, with 84% of mortalities occurring in Sub-Saharan Africa and Southern Asia.[200] Regional variation in hypertension disorders in pregnancy as a cause of maternal mortality is also seen, with the highest burden in Latin America and the Caribbean, where these disorders are responsible for 22% of deaths compared with 14% globally. For every woman that dies, another 20 suffer life-altering morbidity.

Prediction and prevention of PE is an important goal in reducing avoidable mortality and morbidity on a global scale but enabling this in diverse health systems remains a challenge. Prediction models based on early maternal characteristics to improve risk stratification require contact with healthcare services in the first trimester. A systematic analysis of early prenatal care visits between 1990 and 2013 showed that although worldwide coverage increased by 40%, in 2013 only 24% of visits were in low-income countries compared with 82% in high-income countries.[201] Although progress in coverage of prenatal care is improving over time, it remains far from universal. Further understanding of contextual factors influencing barriers to prenatal care such as acceptability, affordability, and geographical accessibility is crucial when considering approaches to improve quality and coverage of care.

Community outreach strategies such as mobile clinics are an example of attempts to increase coverage; however, quality of care in these settings has rarely been evaluated. A cross-sectional study comparing quality of prenatal care between fixed and mobile clinics in Haiti found low referral rates, with 95% of women found to be hypertensive not being referred to a higher level of care to screen for proteinuria.[202] This highlights the need to focus on provider education, consistent adherence to clinical guidelines, and improvement in referral pathways.

A health systems approach must be advocated for, particularly in low- and middle-income countries where systems are weakest. Concentrating solely on delivery of health services or new technologies aimed at risk prediction is unlikely to work alone to reduce the burden of mortality and morbidity. However, it remains an important goal and must be accompanied by necessary pathways to deliver effective prophylaxis, such as with aspirin. Although affordable, education and prescribing/delivery pathways must be established if this strategy is to be effective. Workforce, availability of essential drugs, information systems, governance, and financing therefore must also be addressed.

Priorities for under-resourced settings may be focused around the availability of accurate, functional blood pressure monitoring devices; facility for assessment of risk such as proteinuria; training of staff (particularly if ultrasound is to be used for screening), including for appropriate escalation and management; ensuring reliable supply chains for the provision of aspirin, antihypertensives, and magnesium sulphate; and the availability of laboratory services. This will need to be in parallel with any strategy to implement prevention.

Cost-effectiveness of an early PE prediction and prevention approach has been evaluated in high-income countries and has shown substantial cost saving.[203] However, in low- and middle-income countries, multiple system-level barriers exist that impact implementation, evaluation, and sustainability of such approaches. Economic analysis of basic screening devices such as blood pressure monitors and urine dipsticks for use in low-resource settings has shown that simple devices are most cost-effective.[204] The more sophisticated tools for first-trimester screening must be evaluated in this context. More work is required to evaluate the balance between better detection versus cost of screening with current successful prediction algorithms, and treatment pathways when applied to a low-income setting.

A key barrier to early prediction and prevention of PE in low-resource settings is the delayed first prenatal visit or even contact with a healthcare worker. Further, in many places blood pressure is not being measured at all. More efforts to raise awareness of the benefits of an early prenatal visit (targeted at women of reproductive age, primary healthcare workers, women's self-help groups, etc.), coupled with skills development of primary healthcare providers on risk assessment, accurate blood pressure measurement, counselling skills, and ensuring aspirin availability and adherence to treatment and follow-up will have a far greater impact on PE outcomes than making more advanced testing technology and protocols available. Integrating PE risk assessment as an integral part of basic first-trimester evaluation protocol (measuring weight, blood pressure, hemoglobin, blood sugar, etc.) will go a long way to improve implementation.

- All countries have an obligation to implement the best pre-eclampsia testing and management practices they can.
- FIGO acknowledges that for global progress to be made, India, China, Nigeria, Pakistan, the Philippines, Indonesia, Bangladesh, Brazil, and Mexico must be key targets for focused pre-eclampsia attention.

8 | COST-EFFECTIVENESS OF PRE-ECLAMPSIA SCREENING

It is well established that significant healthcare resources have to be invested to prevent morbidity and mortality related to PE and that, as a consequence, both maternal and neonatal costs are inflated compared with an uncomplicated pregnancy. Given the relative frequency of PE, these costs are significant for the healthcare system and the widespread implementation of a prediction/prevention strategy would help ease this burden. As the best tests for prediction involve a multivariate model that includes several investigative tools, many consider screening to be complex and expensive. It is therefore important to first recognize the current costs of PE, and the potential benefit in spending a fraction of the sum that would be recouped through effective prevention on comprehensive screening.

The reported costs of PE do vary depending on the jurisdiction. Examples of costs include those reported within the USA and Irish healthcare systems. A review of billing data collected by the Californian Medi-Cal healthcare program estimated the cost of an uncomplicated vaginal delivery to be US $4500 in 2011 (US $4900 based on Consumer Price Index to 2017).[205] The average incremental cost for a pregnancy complicated by hypertensive disease was US $8200, with an estimated total incremental cost for all Californian births of more than US $200 million. Costs were highest for women who had severe disease requiring delivery at early (<34 weeks) gestations. In this cohort, the incremental cost was US $70 100 per pregnancy. Although costs for an uncomplicated delivery were reported to be lower in Ireland (US $3000) there was a similar increase in cost for pregnancies affected by PE (increment of US $3300).[206]

Through linkage of the maternal and neonatal datasets, it is possible to show that the predominant driver for increased costs in preterm birth is neonatal care.[207] While costs of maternal care rise 2.7-fold for women who need to be delivered before 32 weeks of gestation, costs of neonatal care increase 35-fold. Preterm birth impacts just 8% of the population but it is responsible for 61% of all costs. Delivery before 32 weeks of gestation affects just 1% of infants but is responsible for 36% of obstetric costs. A third Californian dataset showed that these margins hold true for PE as well as other adverse outcomes. In this series the cost burden was US $1311 at 36 weeks compared with US $150 000 at 26 weeks of gestation.[208] The authors suggested that the annual burden of PE to the USA in 2012, including care of mother and child for the first 12 months after delivery, was US $2.18 billion.

A systematic review of the literature showed that there are only four cost-effective analyses that focus on interventions for prevention of PE. Three of these examined the impact of aspirin, the fourth focused on the potential value of calcium supplementation.

The first paper to assess the economic value of a comprehensive first-trimester screening tool (using maternal characteristics, the biomarkers placental protein 13 and PLGF and UTPI) described three end points: the prevalence of PE, costs until discharge after delivery, and incremental cost per quality-adjusted life-year (QALY) to avoid perinatal death.[209] The authors were not prescriptive about the intervention, suggesting that low-dose aspirin, calcium, or vitamin supplementation could be used—either alone or in combination—and using sensitivity analysis to demonstrate differential effect. The authors defined costs based on the Israeli healthcare system and also demonstrated that cost benefit was affected by prevalence of disease. Using these models, the authors concluded that screening for PE was effective in various scenarios.

Werner et al.[210] used a decision model to determine which one of four potential strategies for prevention of PE was most cost-effective. Treatment involved either no prophylaxis, provision of aspirin to women deemed high risk in accordance with ACOG guidelines or the US Preventative Services Task Force recommendations, or universal prophylaxis.[17,129] Costs were based on US healthcare prices. The model showed that both the US Preventative Services Task Force approach and universal prophylaxis led to a similar and significant reduction in the prevalence of PE; the major difference being that 76.5% of women would not be prescribed aspirin using the former approach. The authors suggested rolling out either of these policies to all four million pregnant women in the USA as this would result in cost savings of approximately US $370 million (similar using either approach).

The cheap nature of the intervention (aspirin) makes a policy of universal screening attractive and easy to advocate. It is, however, important to recognize that although aspirin is currently recommended for prophylaxis, only a minority of high-risk women are treated, with medication starting at an appropriate time point.[211] Secondly, there is no high-quality evidence demonstrating that a policy of universal prophylaxis works. Thirdly, many pregnant women prefer to avoid taking medications when they are pregnant and compliance is likely to be poor. While the safety profile for aspirin is good, recent epidemiological data suggest that this drug may be associated with a small increase in the risk of having an infant affected by cerebral palsy.[212] The relative risk for cerebral palsy is much lower than that associated with preterm birth, so this does not impact pregnancies deemed to be high risk through formal multivariate screening programs, but it should make clinicians more circumspect about universal prescription.

The ASPRE trial did not show a significant reduction in admission rates to the NICU (6.8% in controls vs 6.2% in high-risk women who were prescribed aspirin) but did show a significant reduction in the length of stay (31.4 days vs 11.1 days, respectively).[183] This equated to a 68% reduction in the length of stay for the aspirin-treated group and an equivalent reduction in neonatal costs, which, as previously described, are the dominant costs in these models.

Prior to introducing first-trimester screening for PE, a Canadian group examined the potential cost benefit of screening with aspirin prophylaxis in high-risk women.[203] The group used a decision analysis model assigning probabilities and associated costs at each node based on local published data and public databases. The intervention mimicked that described in ASPRE and this was compared to current standard of care (prescription of 81 mg aspirin based on maternal history). Sensitivity analysis was performed to vary the uptake of screening and the probability of being prescribed aspirin if found to be in a high-risk group. The model showed that first-trimester screening and prescription of aspirin to high-risk women led to both a reduction

in prevalence of disease and a CAD $14.4 million cost saving to the Canadian healthcare system. This saving was demonstrated despite the conservative nature of some of the costings. The cost of a mother/infant being delivered at less than 34 weeks of gestation was only costed at CAD $13 268.21, therefore the cost savings from prevention of early-onset PE may be underestimated. The cost of first-trimester screening was estimated at CAD $668.84; however, in circumstances where first-trimester aneuploidy screening is performed this is likely lower (CAD $100 per test), which would lead to a cost reduction (and further saving to the health system) of an additional CAD $220 million per year.

A fourth cost-effectiveness analysis focused on calcium prophylaxis and used a decision analytic model to examine the impact of this treatment if prescribed to all pregnant women, to women identified as being high risk for PE, or to women with low dietary intake of calcium.[213] These three models led to corresponding reductions of disease prevalence of 25%, 8%, and 13%, respectively—all demonstrating cost savings ranging from €2 to 4.6 million per 100 000 pregnancies. Once again, the low cost of the intervention makes universal prophylaxis appealing.

None of these models have adequately considered the long-term health effects of PE. While maternal cerebrovascular events are rare, Pourat et al.[205] estimated a lifetime cost of US $659 156 for such an event in a 25-year-old woman. Similarly, women who had PE have higher risks of other cardiovascular pathologies in middle age that may be avoided through effective first-trimester screening and prophylaxis. Preterm infants have significant risk of cerebral palsy and neurodevelopmental delay—disabilities that have an associated estimated cost of US $38 250 per year.[205] These children/young adults also have higher risks of hypertension, type 2 diabetes, and metabolic syndrome—all associated with their own burdens and healthcare costs.

Further cost-effective analyses are needed to demonstrate the value of first-trimester screening in different populations, with different disease prevalence and different models/costs of medical care. To this point, all models have suggested that the introduction of first-trimester prediction and prevention dominates current screening strategies. This is largely driven by the cost savings associated with reduction of preterm delivery.

- FIGO considers early screening to be a measure that would most likely increase savings to the health system.
- FIGO calls for more cost-effective analyses to be conducted to show this benefit to policymakers.

REFERENCES

1. FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine. Good clinical practice advice: First trimester screening and prevention of pre-eclampsia in singleton pregnancy. *Int J Gynecol Obstet*. 2019;144:325–329.
2. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;4:97–104.
3. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens*. 2014;4:105–145.
4. Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol*. 2015;55:e1–e29.
5. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018;13:291–310.
6. Villar J, Say L, Gulmezoglu AM, et al. Eclampsia and pre-eclampsia: A health problem for 2000 years. In: Critchly H, MacLean A, Post L, Walk J, eds. *Pre-Eclampsia*. London: RCOG Press; 2003:189–207.
7. Ronsmans C, Graham WJ. Maternal mortality: Who, when, where, and why. *Lancet*. 2006;368:1189–1200.
8. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol*. 2009;113:1299–1306.
9. Lisonkova S, Joseph KS. Incidence of preeclampsia: Risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013;209:544.
10. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. *Obstet Gynecol*. 2014;124:771–781.
11. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308:1592–1594.
12. Jim B, Karumanchi SA. Preeclampsia: Pathogenesis, prevention, and long-term complications. *Semin Nephrol*. 2017;37:386–397.
13. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: Current understanding of its pathophysiology. *Nat Rev Nephrol*. 2014;10:466–480.
14. Thilaganathan B. Pre-eclampsia and the cardiovascular-placental axis. *Ultrasound Obstet Gynecol*. 2018;51:714–717.
15. World Health Organization. *WHO Recommendations for Prevention and Treatment of pre-Eclampsia and Eclampsia*. Geneva: WHO; 2011.
16. National Collaborating Centre for women's and Children's Health (UK). *Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy*. London: RCOG Press; 2010.
17. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122–1131.
18. Lowe SA, Brown MA, Dekker GA, et al. Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust N Z J Obstet Gynaecol*. 2009;49:242–246.
19. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: A cohort study. *Ultrasound Obstet Gynecol*. 2013;42:634–643.
20. Lamminpaa R, Vehvilainen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: A registry-based study on primiparous women in Finland 1997-2008. *BMC Pregnancy Childbirth*. 2012;12:47.
21. Yogev Y, Melamed N, Bardin R, Tenenbaum-Gavish K, Ben-Shitrit G, Ben-Haroush A. Pregnancy outcome at extremely advanced maternal age. *Am J Obstet Gynecol*. 2010;203:558.e1–558.e7.
22. Balasch J, Gratacos E. Delayed childbearing: Effects on fertility and the outcome of pregnancy. *Curr Opin Obstet Gynecol*. 2012;24:187–193.
23. Poon LC, Kametas NA, Chelemen T, Leal A, Nicolaides KH. Maternal risk factors for hypertensive disorders in pregnancy: A multivariate approach. *J Hum Hypertens*. 2010;24:104–110.
24. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. *BMJ*. 2005;330:565.
25. Luo Z-C, An N, Xu H-R, Larante A, Audibert F, Fraser WD. The effects and mechanisms of primiparity on the risk of pre-eclampsia: A systematic review. *Paediatr Perinat Epidemiol*. 2007;21(Suppl.1):36–45.
26. Robillard PY, Hulsey TC, Alexander GR, Keenan A, de Caunes F, Papiernik E. Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. *J Reprod Immunol*. 1993;24:1–12.
27. Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: Prospective cohort study. *BMJ*. 2009;338:b2255.
28. Campbell DM, MacGillivray I, Carr-Hill R. Pre-eclampsia in second pregnancy. *Br J Obstet Gynaecol*. 1985;92:131–140.
29. Sibai BM, el-Nazer A, Gonzalez-Ruiz A. Severe preeclampsia-eclampsia in young primigravid women: Subsequent pregnancy outcome and remote prognosis. *Am J Obstet Gynecol*. 1986;155:1011–1016.
30. Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: Population based study. *BMJ*. 1998;316:1343–1347.
31. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Risk factors and clinical manifestations of pre-eclampsia. *BJOG*. 2000;107:1410–1416.
32. van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW. Outcomes of subsequent pregnancy after first pregnancy with early-onset pre-eclampsia. *Am J Obstet Gynecol*. 2006;195:723–728.
33. Langenveld J, Jansen S, van der Post J, Wolf H, Mol BW, Ganzevoort W. Recurrence risk of a delivery before 34 weeks of pregnancy due to an early onset hypertensive disorder: A systematic review. *Am J Perinatol*. 2010;27:565–571.
34. Rousso D, Panidis D, Gkoutzioulis F, Kourtis A, Mavromatidis G, Kalahanis I. Effect of the interval between pregnancies on the health of mother and child. *Eur J Obstet Gynecol Reprod Biol*. 2002;105:4–6.
35. King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. *J Nutr*. 2003;133:1732S–1736S.
36. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Effects of birth spacing on maternal health: A systematic review. *Am J Obstet Gynecol*. 2007;196:297–308.
37. Mignini LE, Carroli G, Betran AP, et al. Interpregnancy interval and perinatal outcomes across Latin America from 1990 to 2009: A large multi-country study. *BJOG*. 2016;123:730–737.
38. Winikoff B. The effects of birth spacing on child and maternal health. *Stud Fam Plann*. 1983;14:231–245.
39. Klebanoff MA. The interval between pregnancies and the outcome of subsequent births. *N Engl J Med*. 1999;340:643–644.
40. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: A meta-analysis. *Obstet Gynecol*. 2004;103:551–563.
41. Trogstad L, Magnus P, Moffett A, Stoltenberg C. The effect of recurrent miscarriage and infertility on the risk of pre-eclampsia. *BJOG*. 2009;116:108–113.
42. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting

from IVF/ICSI: A systematic review and meta-analysis. *Hum Reprod Update*. 2012;18:485–503.
43. Thomopoulos C, Tsioufis C, Michalopoulou H, Makris T, Papademetriou V, Stefanadis C. Assisted reproductive technology and pregnancy-related hypertensive complications: A systematic review. *J Hum Hypertens*. 2013;27:148–157.
44. Martin AS, Monsour M, Kawwass JF, Boulet SL, Kissin DM, Jamieson DJ. Risk of preeclampsia in pregnancies after assisted reproductive technology and ovarian stimulation. *Matern Child Health J*. 2016;20:2050–2056.
45. Albrecht ED, Bonagura TW, Burleigh DW, Enders AC, Aberdeen GW, Pepe GJ. Suppression of extravillous trophoblast invasion of uterine spiral arteries by estrogen during early baboon pregnancy. *Placenta*. 2006;27:483–490.
46. Imudia AN, Awonuga AO, Doyle JO, et al. Peak serum estradiol level during controlled ovarian hyperstimulation is associated with increased risk of small for gestational age and preeclampsia in singleton pregnancies after in vitro fertilization. *Fertil Steril*. 2012;97:1374–1379.
47. Fisher SJ. Why is placentation abnormal in preeclampsia? *Am J Obstet Gynecol*. 2015;213:S115–S122.
48. Smith GN, Walker M, Tessier JL, Millar KG. Increased incidence of preeclampsia in women conceiving by intrauterine insemination with donor versus partner sperm for treatment of primary infertility. *Am J Obstet Gynecol*. 1997;177:455–458.
49. Hoy J, Venn A, Halliday J, Kovacs G, Waalwyk K. Perinatal and obstetric outcomes of donor insemination using cryopreserved semen in Victoria, Australia. *Hum Reprod*. 1999;14:1760–1764.
50. Salha O, Sharma V, Dada T, et al. The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. *Hum Reprod*. 1999;14:2268–2273.
51. Need JA, Bell B, Meffin E, Jones WR. Pre-eclampsia in pregnancies from donor inseminations. *J Reprod Immunol*. 1983;5:329–338.
52. Simeone S, Serena C, Rambaldi MP, Marchi L, Mello G, Mecacci F. Risk of preeclampsia and obstetric outcome in donor oocyte and autologous in vitro fertilization pregnancies. *Minerva Ginecol*. 2016;68:9–14.
53. Nakabayashi Y, Nakashima A, Yoshino O, et al. Impairment of the accumulation of decidual T cells, NK cells, and monocytes, and the poor vascular remodeling of spiral arteries, were observed in oocyte donation cases, regardless of the presence or absence of preeclampsia. *J Reprod Immunol*. 2016;114:65–74.
54. Arngrimsson R, Bjornsson S, Geirsson RT, Bjornsson H, Walker JJ, Snaedal G. Genetic and familial predisposition to eclampsia and pre-eclampsia in a defined population. *Br J Obstet Gynaecol*. 1990;97:762–769.
55. Cincotta RB, Brennecke SP. Family history of pre-eclampsia as a predictor for pre-eclampsia in primigravidas. *Int J Gynaecol Obstet*. 1998;60:23–27.
56. Williams PJ, Broughton PF. The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:405–417.
57. Zintzaras E, Kitsios G, Harrison GA, et al. Heterogeneity-based genome search meta-analysis for preeclampsia. *Hum Genet*. 2006;120:360–370.
58. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. *N Engl J Med*. 1998;338:147–152.
59. Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate – a population-based screening study. *Am J Obstet Gynecol*. 2004;190:1091–1097.
60. Leung TY, Leung TN, Sahota DS, et al. Trends in maternal obesity and associated risks of adverse pregnancy outcomes in a population of Chinese women. *BJOG*. 2008;115:1529–1537.
61. Syngelaki A, Bredaki FE, Vaikousi E, Maiz N, Nicolaides KH. Body mass index at 11-13 weeks' gestation and pregnancy complications. *Fetal Diagn Ther*. 2011;30:250–265.
62. Liu L, Hong Z, Zhang L. Associations of prepregnancy body mass index and gestational weight gain with pregnancy outcomes in nulliparous women delivering single live babies. *Sci Rep*. 2015;5:12863.
63. Rahman MM, Abe SK, Kanda M, et al. Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: A systematic review and meta-analysis. *Obes Rev*. 2015;16:758–770.
64. Wei Y-M, Yang H-X, Zhu W-W, et al. Risk of adverse pregnancy outcomes stratified for pre-pregnancy body mass index. *J Matern Fetal Neonatal Med*. 2016;29:2205–2209.
65. Catalano PM. Obesity, insulin resistance, and pregnancy outcome. *Reproduction*. 2010;140:365–371.
66. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol*. 2011;29:415–445.
67. Spradley FT, Palei AC, Granger JP. Immune mechanisms linking obesity and preeclampsia. *Biomolecules*. 2015;5:3142–3176.
68. Mittendorf R, Lain KY, Williams MA, Walker CK. Preeclampsia. A nested, case-control study of risk factors and their interactions. *J Reprod Med*. 1996;41:491–496.
69. Knuist M, Bonsel GJ, Zondervan HA, Treffers PE. Risk factors for preeclampsia in nulliparous women in distinct ethnic groups: A prospective cohort study. *Obstet Gynecol*. 1998;92:174–178.
70. Mostello D, Catlin TK, Roman L, Holcomb WLJ, Leet T. Preeclampsia in the parous woman: Who is at risk? *Am J Obstet Gynecol*. 2002;187:425–429.
71. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: Predictors of preeclampsia. *Obstet Gynecol*. 2005;106:156–161.
72. Ghosh G, Grewal J, Mannisto T, et al. Racial/ethnic differences in pregnancy-related hypertensive disease in nulliparous women. *Ethn Dis*. 2014;24:283–289.
73. Russell RB, Green NS, Steiner CA, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. *Pediatrics*. 2007;120:e1–e9.
74. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995;25:305–313.
75. Kestenbaum B, Seliger SL, Easterling TR, et al. Cardiovascular and thromboembolic events following hypertensive pregnancy. *Am J Kidney Dis*. 2003;42:982–989.
76. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. *BMJ*. 2007;335:974.
77. Khalil A, Rezende J, Akolekar R, Syngelaki A, Nicolaides KH. Maternal racial origin and adverse pregnancy outcome: A cohort study. *Ultrasound Obstet Gynecol*. 2013;41:278–285.
78. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. *BMJ*. 2016;353:i1753.
79. Mudd LM, Owe KM, Mottola MF, Pivarnik JM. Health benefits of physical activity during pregnancy: An international perspective. *Med Sci Sports Exerc*. 2013;45:268–277.
80. Schneider S, Freerksen N, Rohrig S, Hoeft B, Maul H. Gestational diabetes and preeclampsia–similar risk factor profiles? *Early Hum Dev*. 2012;88:179–184.
81. Conti E, Zezza L, Ralli E, et al. Growth factors in preeclampsia: A vascular disease model. A failed vasodilation and angiogenic challenge from pregnancy onwards?. *Cytokine Growth Factor Rev*. 2013;24:411–425.

82. Guimaraes MF, Brandao AHF, Rezende CA, et al. Assessment of endothelial function in pregnant women with preeclampsia and gestational diabetes mellitus by flow-mediated dilation of brachial artery. *Arch Gynecol Obstet*. 2014;290:441–447.
83. Kane SC, Costa Fda S, Brennecke S. First trimester biomarkers in the prediction of later pregnancy complications. *Biomed Res Int*. 2014;2014:807196.
84. Karacay O, Sepici-Dincel A, Karcaaltincaba D, et al. A quantitative evaluation of total antioxidant status and oxidative stress markers in preeclampsia and gestational diabetic patients in 24-36 weeks of gestation. *Diabetes Res Clin Pract*. 2010;89:231–238.
85. Wiznitzer A, Mayer A, Novack V, et al. Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: A population-based study. *Am J Obstet Gynecol*. 2009;201:482.e1–e8.
86. Zhou J, Zhao X, Wang Z, Hu Y. Combination of lipids and uric acid in mid-second trimester can be used to predict adverse pregnancy outcomes. *J Matern Fetal Neonatal Med*. 2012;25:2633–2638.
87. Engeland A, Bjorge T, Daltveit AK, et al. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. *Eur J Epidemiol*. 2011;26:157–163.
88. Feig DS, Shah BR, Lipscombe LL, et al. Preeclampsia as a risk factor for diabetes: A population-based cohort study. *PLoS Med*. 2013;10:e1001425.
89. Libby G, Murphy DJ, McEwan NF, et al. Pre-eclampsia and the later development of type 2 diabetes in mothers and their children: An intergenerational study from the Walker cohort. *Diabetologia*. 2007;50:523–530.
90. Mannisto T, Mendola P, Vaarasmaki M, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. *Circulation*. 2013;127:681–690.
91. Parretti E, Lapolla A, Dalfra M, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension*. 2006;47:449–453.
92. Sierra-Laguado J, Garcia RG, Celedon J, et al. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy-induced hypertension. *Am J Hypertens*. 2007;20:437–442.
93. Legro RS. Insulin resistance in women's health: Why it matters and how to identify it. *Curr Opin Obstet Gynecol*. 2009;21:301–305.
94. Ryan EA, Imes S, Liu D, et al. Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes*. 1995;44:506–512.
95. D'Anna R, Baviera G, Corrado F, et al. Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. *BJOG*. 2006;113:1264–1269.
96. Soonthornpun K, Soonthornpun S, Wannaro P, Setasuban W, Thamprasit A. Insulin resistance in women with a history of severe pre-eclampsia. *J Obstet Gynaecol Res*. 2009;35:55–59.
97. Fuh MM-T, Yin C-S, Pei D, et al. Resistance to insulin-mediated glucose uptake and hyperinsulinemia in women who had preeclampsia during pregnancy. *Am J Hypertens*. 1995;8:768–771.
98. Ray JG. Dysmetabolic syndrome, placenta-mediated disease and future risk of cardiovascular disease. *Fetal Matern Med Rev*. 2004;15:231–246.
99. Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2003;88:4116–4123.
100. Girouard J, Giguere Y, Moutquin J-M, Forest J-C. Previous hypertensive disease of pregnancy is associated with alterations of markers of insulin resistance. *Hypertension*. 2007;49:1056–1062.
101. Beck DW, Menezes AH. Intracerebral hemorrhage in a patient with eclampsia. *JAMA*. 1981;246:1442–1443.
102. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy*. 2003;22:203–212.
103. Chesley LC, Annitto JE, Cosgrove RA. The remote prognosis of eclamptic women. Sixth periodic report.. *Am J Obstet Gynecol*. 1976;124:446–459.
104. Kaaja R. Insulin resistance syndrome in preeclampsia. *Semin Reprod Endocrinol*. 1998;16:41–46.
105. Garovic VD, Hayman SR. Hypertension in pregnancy: An emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol*. 2007;3:613–622.
106. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: Formal risk factor or failed stress test? *Ther Adv Cardiovasc Dis*. 2008;2:249–259.
107. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: Systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28:1–19.
108. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses. *Am Heart J*. 2008;156:918–930.
109. McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: A systematic review and meta-analysis. *Am J Kidney Dis*. 2010;55:1026–1039.
110. Fisher KA, Luger A, Spargo BH, Lindheimer MD. Hypertension in pregnancy: Clinical-pathological correlations and remote prognosis. *Medicine (Baltimore)*. 1981;60:267–276.
111. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med*. 2008;359:800–809.
112. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, McIntyre HD. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: Findings from a prospective cohort study. *Am J Obstet Gynecol*. 2007;197:492.e1–e7.
113. Carr DB, Newton KM, Utzschneider KM, et al. Preeclampsia and risk of developing subsequent diabetes. *Hypertens Pregnancy*. 2009;28:435–447.
114. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. *J Hypertens*. 2010;28:1349–1355.
115. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH. Prediction of pre-eclampsia by uterine artery Doppler imaging: Relationship to gestational age at delivery and small-for-gestational age. *Ultrasound Obstet Gynecol*. 2008;31:310–313.
116. Teramo KA, Hiilesmaa VK, Schwartz R, Clemons GK, Widness JA. Amniotic fluid and cord plasma erythropoietin levels in pregnancies complicated by preeclampsia, pregnancy-induced hypertension and chronic hypertension. *J Perinat Med*. 2004;32:240–247.
117. Aali BS, Malekpour R, Sedig F, Safa A. Comparison of maternal and cord blood nucleated red blood cell count between pre-eclamptic and healthy women. *J Obstet Gynaecol Res*. 2007;33:274–278.
118. Yucesoy G, Ozkan S, Bodur H, et al. Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: A seven year experience of a tertiary care center. *Arch Gynecol Obstet*. 2005;273:43–49.
119. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130–137.
120. Yerlikaya G, Akolekar R, McPherson K, Syngelaki A, Nicolaides KH. Prediction of stillbirth from maternal demographic and pregnancy characteristics. *Ultrasound Obstet Gynecol*. 2016;48:607–612.
121. Moutquin J-M. Classification and heterogeneity of preterm birth. *BJOG*. 2003;110(Suppl):30–33.
122. Ilekis JV, Reddy UM, Roberts JM. Preeclampsia–a pressing problem: An executive summary of a National Institute of Child Health and Human Development workshop. *Reprod Sci*. 2007;14:508–523.
123. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med*. 2005;352:9–19.

124. Khashu M, Narayanan M, Bhargava S, Osiovich H. Perinatal outcomes associated with preterm birth at 33 to 36 weeks' gestation: A population-based cohort study. *Pediatrics*. 2009;123:109–113.
125. Osmond C, Barker DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ Health Perspect*. 2000;108(Suppl):545–553.
126. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for preeclampsia: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2017;317:1661–1667.
127. Committee Opinion No. 638: First-trimester risk assessment for early-onset preeclampsia. *Obstet Gynecol*. 2015;126:e25–e27.
128. ACOG Committee Opinion No. 743 Summary: Low-dose aspirin use during pregnancy. *Obstet Gynecol*. 2018;132:254–256.
129. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161:819–826.
130. American Diabetes Association. 13. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41:S137–S143.
131. Wallenburg HC. Prevention of pre-eclampsia: Status and perspectives 2000. *Eur J Obstet Gynecol Reprod Biol*. 2001;94:13–22.
132. O'Gorman N, Wright D, Poon LC, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: Comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol*. 2017;49:756–760.
133. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther*. 2013;33:8–15.
134. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol*. 2016;214:103.e1–103.e12.
135. O'Gorman N, Wright D, Poon LC, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2017;49:751–755.
136. Rolnik DL, Wright D, Poon LCY, et al. ASPRE trial: Performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol*. 2017;50:492–495.
137. Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: Results of SPREE. *Ultrasound Obstet Gynecol*. 2018;51:743–750.
138. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2018;52:186–195.
139. Poon LC, Rolnik DL, Tan MY, et al. ASPRE trial: Incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. *Ultrasound Obstet Gynecol*. 2018;51:738–742.
140. Park FJ, Leung CHY, Poon LCY, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. *Aust N Z J Obstet Gynaecol*. 2013;53:532–539.
141. Oliveira N, Magder LS, Blitzer MG, Baschat AA. First-trimester prediction of pre-eclampsia: External validity of algorithms in a prospectively enrolled cohort. *Ultrasound Obstet Gynecol*. 2014;44:279–285.
142. Lobo GA, Nowak PM, Panigassi AP, et al. Validation of Fetal Medicine Foundation algorithm for prediction of pre-eclampsia in the first trimester in an unselected Brazilian population. *J Matern Fetal Neonatal Med*. 2019;32:286–292.
143. Rocha RS, Alves JA, Maia E Holanda Moura SB, et al. Simple approach based on maternal characteristics and mean arterial pressure for the prediction of preeclampsia in the first trimester of pregnancy. *J Perinat Med*. 2017;45:843–849.
144. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol*. 2015;213:62.e1–62.e10.
145. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther*. 2012;31:42–48.
146. Wright A, Wright D, Ispas CA, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: Effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol*. 2015;45:698–706.
147. Poon LC, Kametas NA, Pandeva I, Valencia C, Nicolaides KH. Mean arterial pressure at 11(+0) to 13(+6) weeks in the prediction of preeclampsia. *Hypertension*. 2008;51:1027–1033.
148. National Heart Foundation of Australia. Hypertension Management Guide for Doctors. 2004. [website] www.heartfoundation.org.au. Accessed April 1, 2006.
149. Poon LC, Kametas NA, Valencia C, Chelemen T, Nicolaides KH. Hypertensive disorders in pregnancy: Screening by systolic diastolic and mean arterial pressure at 11-13 weeks. *Hypertens Pregnancy*. 2011;30:93–107.
150. Poon LC, Kametas N, Strobl I, Pachoumi C, Nicolaides KH. Inter-arm blood pressure differences in pregnant women. *BJOG*. 2008;115:1122–1130.
151. Maynard SE, Min J-Y, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111:649–658.
152. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350:672–683.
153. Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circ Res*. 2004;95:884–891.
154. Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. *J Hum Hypertens*. 2017;31:782–786.
155. Wortelboer EJ, Koster MP, Kuc S, et al. Longitudinal trends in feto-placental biochemical markers, uterine artery pulsatility index and maternal blood pressure during the first trimester of pregnancy. *Ultrasound Obstet Gynecol*. 2011;38:383–388.
156. Tidwell SC, Ho HN, Chiu WH, Torry RJ, Torry DS. Low maternal serum levels of placenta growth factor as an antecedent of clinical preeclampsia. *Am J Obstet Gynecol*. 2001;184:1267–1272.
157. Thadhani R, Mutter WP, Wolf M, et al. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for pre-eclampsia. *J Clin Endocrinol Metab*. 2004;89:770–775.
158. Akolekar R, Zaragoza E, Poon LC, Pepes S, Nicolaides KH. Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2008;32:732–739.
159. Zhong Y, Zhu F, Ding Y. Serum screening in first trimester to predict pre-eclampsia, small for gestational age and preterm delivery: Systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2015;15:191.
160. Smith GC, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein a and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth. *J Clin Endocrinol Metab*. 2002;87:1762–1767.
161. Spencer K, Yu CK, Cowans NJ, Otigbah C, Nicolaides KH. Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with second-trimester uterine artery Doppler. *Prenat Diagn*. 2005;25:949–953.
162. Dugoff L, Hobbins JC, Malone FD, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with

obstetric complications: A population-based screening study (the FASTER Trial). *Am J Obstet Gynecol*. 2004;191:1446–1451.
163. Morris RK, Bilagi A, Devani P, Kilby MD. Association of serum PAPP-A levels in first trimester with small for gestational age and adverse pregnancy outcomes: Systematic review and meta-analysis. *Prenat Diagn*. 2017;37:253–265.
164. Wright D, Silva M, Papadopoulos S, Wright A, Nicolaides KH. Serum pregnancy-associated plasma protein-A in the three trimesters of pregnancy: Effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol*. 2015;46:42–50.
165. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, et al. ISUOG Practice Guidelines: Role of ultrasound in screening for and follow-up of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2019;53:7–22.
166. Carbillon L, Perrot N, Uzan M, Uzan S. Doppler ultrasonography and implantation: A critical review. *Fetal Diagn Ther*. 2001;16:327–332.
167. Carbillon L, Challier JC, Alouini S, Uzan M, Uzan S. Uteroplacental circulation development: Doppler assessment and clinical importance. *Placenta*. 2001;22:795–799.
168. Olofsson P, Laurini RN, Marsal K. A high uterine artery pulsatility index reflects a defective development of placental bed spiral arteries in pregnancies complicated by hypertension and fetal growth retardation. *Eur J Obstet Gynecol Reprod Biol*. 1993;49:161–168.
169. Lefebvre J, Demers S, Bujold E, et al. Comparison of two different sites of measurement for transabdominal uterine artery Doppler velocimetry at 11-13 weeks. *Ultrasound Obstet Gynecol*. 2012;40:288–292.
170. Velauthar L, Plana MN, Kalidindi M, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: A meta-analysis involving 55,974 women. *Ultrasound Obstet Gynecol*. 2014;43:500–507.
171. Magee LA, Dadelszen PV, Stones WM. *The FIGO Textbook of Pregnancy Hypertension. An Evidence-Based Guide to Monitoring, Prevention and Management*. London: The Global Library of Woman's Medicine; 2016.
172. Al-Rubaie Z, Askie LM, Ray JG, Hudson HM, Lord SJ. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: A systematic review. *BJOG*. 2016;123:1441–1452.
173. Wright D, Gallo DM, Gil Pugliese S, Casanova C, Nicolaides KH. Contingent screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol*. 2016;47:554–559.
174. Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2017;50:589–595.
175. Sibai BM. Thrombophilia and severe preeclampsia: Time to screen and treat in future pregnancies? *Hypertension*. 2005;46:1252–1253.
176. Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. *Lancet*. 2001;357:209–215.
177. Crandon AJ, Isherwood DM. Effect of aspirin on incidence of pre-eclampsia. *Lancet*. 1979;1:1356.
178. Beaufils M, Uzan S, Donsimoni R, Colau JC. Prevention of pre-eclampsia by early antiplatelet therapy. *Lancet*. 1985;1:840–842.
179. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: A meta-analysis of individual patient data. *Lancet*. 2007;369:1791–1798.
180. Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. *Prenat Diagn*. 2014;34:642–648.
181. Roberge S, Giguere Y, Villa P, et al. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: A systematic review and meta-analysis. *Am J Perinatol*. 2012;29:551–556.
182. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377:613–622.
183. Wright D, Rolnik DL, Syngelaki A, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: Effect of aspirin on length of stay in the neonatal intensive care unit. *Am J Obstet Gynecol*. 2018;218:612.e1–612.e6.
184. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int*. 2013;30:260–279.
185. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: Systematic review and metaanalysis. *Am J Obstet Gynecol*. 2018;218:287–293.e1.
186. Masotti G, Galanti G, Poggesi L, Abbate R, Neri Serneri GG. Differential inhibition of prostacyclin production and platelet aggregation by aspirin. *Lancet*. 1979;2:1213–1217.
187. Wright D, Poon LC, Rolnik DL, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: Influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. *Am J Obstet Gynecol*. 2017;217:685.e1–685.e5.
188. Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. *Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force* [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US); 2014.
189. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2007;(2):CD004659.
190. Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. *Am J Obstet Gynecol*. 2018;218:483–489.
191. Hofmeyr GJ, Lawrie TA, Atallah AN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev*. 2018;(10):CD001059.
192. Rodger MA, Gris J-C, de Vries JIP, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: A meta-analysis of individual patient data from randomised controlled trials. *Lancet*. 2016;388:2629–2641.
193. Mastrolia SA, Novack L, Thachil J, et al. LMWH in the prevention of preeclampsia and fetal growth restriction in women without thrombophilia. A systematic review and meta-analysis. *Thromb Haemost*. 2016;116:868–878.
194. Chiswick C, Reynolds RM, Denison F, et al. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): A randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2015;3:778–786.
195. Kalafat E, Sukur YE, Abdi A, Thilaganathan B, Khalil A. Metformin for the prevention of hypertensive disorders of pregnancy in women with gestational diabetes and obesity: A systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2018;52:706–714.
196. Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy. *Cochrane Database Syst Rev*. 2015;(9):CD004072.
197. Rumbold A, Ota E, Hori H, Miyazaki C, Crowther CA. Vitamin E supplementation in pregnancy. *Cochrane Database Syst Rev*. 2015;(9):CD004069.
198. Wen SW, White RR, Rybak N, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): Double blind, phase III, randomised controlled, international, multicentre trial. *BMJ*. 2018;362:k3478.
199. Bergeron TS, Roberge S, Carpentier C, Sibai B, McCaw-Binns A, Bujold E. Prevention of preeclampsia with aspirin in multiple gestations: A systematic review and meta-analysis. *Am J Perinatol*. 2016;33:605–610.
200. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: A WHO systematic analysis. *Lancet Glob Health*. 2014;2:e323–e333.

201. Moller A-B, Petzold M, Chou D, Say L. Early antenatal care visit: A systematic analysis of regional and global levels and trends of coverage from 1990 to 2013. *Lancet Glob Health*. 2017;5:e977–e983.
202. Phillips E, Stoltzfus RJ, Michaud L, Pierre GLF, Vermeylen F, Pelletier D. Do mobile clinics provide high-quality antenatal care? A comparison of care delivery, knowledge outcomes and perception of quality of care between fixed and mobile clinics in central Haiti. *BMC Pregnancy Childbirth*. 2017;17:361.
203. Ortved D, Hawkins TL, Johnson JA, Hyett J, Metcalfe A. The cost-effectiveness of first trimester screening and early preventative use of aspirin in women at high risk of early onset pre-eclampsia. *Ultrasound Obstet Gynecol*. 2019;53:239–244.
204. McLaren ZM, Sharp A, Hessburg JP, et al. Cost effectiveness of medical devices to diagnose pre-eclampsia in low-resource settings. *Dev Eng*. 2017;2:99–106.
205. Pourat N, Martinez AE, Jones JM, et al. *Costs of Gestational Hypertensive Disorders in California: Hypertension, Preeclampsia, and Eclampsia*. Los Angeles, CA: UCLA Center for Health Policy Research; 2013.
206. Fox A, McHugh S, Browne J, et al. Estimating the cost of preeclampsia in the healthcare system: Cross-sectional study using data from SCOPE Study (screening for pregnancy end points). *Hypertension*. 2017;70:1243–1249.
207. Phibbs CS, Schmitt SK, Cooper M, et al. Birth Hospitalization Costs and Days of Care for Mothers and Neonates in California, 2009–2011. *J Pediatr*. 2019;204:118–125.e14.
208. Stevens W, Shih T, Incerti D, et al. Short-term costs of preeclampsia to the United States health care system. *Am J Obstet Gynecol*. 2017;217:237–248.e16.
209. Shmueli A, Meiri H, Gonen R. Economic assessment of screening for pre-eclampsia. *Prenat Diagn*. 2012;32:29–38.
210. Werner EF, Hauspurg AK, Rouse DJ. A cost-benefit analysis of low-dose aspirin prophylaxis for the prevention of preeclampsia in the United States. *Obstet Gynecol*. 2015;126:1242–1250.
211. Helou A, Walker S, Stewart K, George J. Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better? *Aust N Z J Obstet Gynaecol*. 2017;57:253–259.
212. Petersen TG, Liew Z, Andersen AN, et al. Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child. *Int J Epidemiol*. 2018;47:121–130.
213. Meertens LJE, Scheepers HCJ, Willemse JPMM, Spaanderman MEA, Smits LJM. Should women be advised to use calcium supplements during pregnancy? A decision analysis *Matern Child Nutr*. 2018;14:e12479.