Implementation of combined screening for preeclampsia in the first trimester: cost-effectiveness and clinical outcomes

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Signed Declaration

‘I, Christina Ammari, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Abstract

Preeclampsia (PE) is a gestational hypertensive syndrome with a worldwide incidence of 3-5%. Globally, 76,000 women and 500,000 babies die each year from complications of PE. Its timely identification and prevention through effective screening and offer of treatment, can have a vital impact on reducing maternal and fetal mortality and morbidity. In addition, there are significant healthcare economic implications.

There are two primary methods for screening currently. Women can either be screened based solely on risk factors or through a combined approach that includes maternal characteristics alongside biophysical parameters such as mean arterial pressure (MAP) and uterine artery (UtA) blood flow, as well as biomarkers like pregnancy-associated plasma protein-A (Papp-A) and/or placental growth factor (PlGF). Administration of low dose aspirin (LDA) to women who screen as high-risk, using the combined screening approach has been shown to reduce the risk of PE by 62%. However, although the combined approach yields a higher detection rate for preterm PE, most international and national guidelines presently still recommend screening for PE based on maternal risk factors alone.

At University College London Hospital (UCLH), we initiated the implementation of the Fetal Medicine Foundation (FMF)-combined screening for all women in their first trimester. This new protocol aims to enhance the detection rates of preterm PE and fetal growth restriction (FGR), assessing the impact on our maternity service.

Our project began with a systematic review of clinical practice guidelines to understand global screening practices, revealing that despite its benefits, 74% of guidelines still recommend risk factor-based screening. We then conducted a retrospective analysis

of 5,957 patient episodes, evaluating the outcomes against a hypothetical implementation of the modified combined screening algorithm. This analysis confirmed the superior performance of the combined screening approach over the existing NICE protocol in detecting both PE and FGR in our population. Notably, the application of the modified combined algorithm was cost-effective with a cost saving of £9.06 per pregnancy screened and a marginal Quality Adjusted Life Years gain.

Further, we refined the clinical pathway post-first trimester screening by incorporating second trimester UtA Doppler assessments, significantly enhancing risk stratification. Our findings showed that screen-positive women with elevated UtA PI in the second trimester had an 18.8% risk of developing preterm PE, compared to just 6.5% for those with normal UtA PI. This trend was also observed in the FGR risk patterns, where the highest risk was noted in women with elevated second-trimester UtA PI.

We also assessed the PE risk in high-risk women who did not develop hypertension or growth restriction up until 37 weeks, finding a significantly higher risk of PE in women delivering after 40 weeks, leading us to advocate for earlier delivery policies.

Additionally, we evaluated the inter- and intra- observer variability of UtA PI measurements in the first trimester, confirming their reproducibility, which supported our decision to conduct periodic audits of sonographer performance.

A future direction for this project is the prospective evaluation of the effect of implementation of first trimester FMF combined-screening for PE at UCLH between February 2023-February 2024. In evaluating this prospective data, we aim to investigate potential strategies such as earlier delivery to reduce the incidence of term

PE. Finally, we plan to assess the qualitative performance of this screening approach and the associated clinical pathway by collecting patient feedback.

In conclusion, our project at UCLH represents a pivotal shift in the approach to screening, providing a means of substantially improving maternal and fetal outcomes. The adoption of this comprehensive screening during the first trimester, accompanied by targeted interventions such as LDA, appropriate antenatal follow-up and timely delivery strategies, not only offers the promise of reduced prevalence of severe complications associated with PE but also a potential cost benefit within maternity services. The project's ongoing assessment and refinement of clinical pathways, including the integration of second-trimester assessments and continuous performance evaluations of sonographic techniques, highlight our commitment to advancing clinical practice through evidence-based strategies. As we continue to collect and analyze prospective data, our goal is to establish a robust model that can be adopted widely, ensuring that every woman receives the most precise and effective care during her pregnancy.

Clinical Impact Statement

This study underscores a significant advancement in prenatal care through the implementation of the FMF-combined screening for PE at UCLH, representing a paradigm shift from the traditional risk factor-based screening recommended by the National Institute for Health and Care Excellence (NICE). By offering this combined screening approach to all women in their first trimester of pregnancy, we aim to significantly improve the early detection rates of PE, a condition for which early identification and management can significantly reduce maternal and fetal morbidity.

The routine administration of LDA to women who screen high-risk through this enhanced screening method has the potential to decrease the risk of developing PE by 62%. Our retrospective analysis of 5,957 patient episodes further validated the modified FMF-combined screening's superior performance in detecting not only PE but also FGR, compared to the standard NICE screening method. Moreover, the combined screening approach demonstrated cost-effectiveness, with a notable saving of £9.06 per pregnancy screened and a marginal increase in Quality Adjusted Life Years (QALY) by 0.00006.

Unlike with preterm PE, aspirin does not impact upon the development of term PE, which contributes to most of the health and economic burden of PE, and strategies to reduce the incidence of term PE are lacking. This study demonstrated that recommending delivery before 40 weeks in women who screen high risk in the first trimester could reduce the incidence of term PE, with a number needed to treat (NNT) of 7.

The findings of this project have considerable clinical and economic implications. Early and accurate prediction of PE and FGR can lead to tailored interventions that significantly improve maternal and perinatal outcomes.

In conclusion, the implementation of FMF-combined screening is a valuable development in prenatal care at UCLH, setting a new standard for early PE detection and management. This approach not only promises to enhance clinical outcomes for mothers and their babies but also presents a cost-effective strategy for healthcare systems, paving the way for its adoption in other healthcare settings globally.

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Christina Ammari contributed to data curation.

Diane Nzelu and Sara Hillman contributed to conceptualisation, data curation, methodology, formal analysis, and writing.

Tom Palmer contributed to the methodology, formal analysis of the data, review and editing of the paper.

Daniel Stott contributed to conceptualisation, review and editing of the paper.

Pranav Pandya, Raffaele Napolitano and Davide Casagradi contributed to project administration, review and editing of the paper.

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Table of Contents

Title Page	1
Signed Declaration	2
Abstract	3
Clinical Impact Statement	6
UCL Research Declaration Form	8
Acknowledgments	11
Table of Contents	12
Abbreviations	15
Chapter 1. Introduction	22
Preeclampsia	22
Preeclampsia Screening in the first trimester	24
The Fetal Medicine Foundation combined screening approach	27
Maternal Risk Factors	27
Mean Arterial Pressure	33
Uterine Artery Pulsatility Index	35
Biomarkers	37
Preventative strategies for Preeclampsia	40
Aspirin	41
Calcium	42
Economic Implications of Preeclampsia	44
Chapter 2. A systematic review of Clinical Practice Guidelines	46

Introduction 46

Methods 47

Results 51

A detailed review of the screening policies across the globe 51

Screening Policy as per International Societies 52

Screening Policy in Europe 60

Screening Policy in North America 77

Screening Policy in South America 83

Screening Policy in Africa 86

Screening Policy in Asia 87

Screening Policy in Australia and New Zealand 91

A summary of the results 97

Screening approach 97

Preventative approach 103

Quality Assessment 108

Discussion 114

Chapter 3. Data Analysis Prior to Implementation of the Combined Pre-eclampsia Screening Approach 120

3.1 Performance of First Trimester Combined Screening for Preeclampsia

Introduction 121

Methods 122

Results 125

Discussion 135

3.2 Stratification of women in the second trimester according to assessment of the uterine artery blood flow

Introduction 138

Methods 138

Results 140

Discussion 145

3.3 Investigation of adverse outcomes after 40 weeks of gestation in women who screen high risk for preterm preeclampsia in the first trimester

Introduction 150

Methods 151

Results 154

Discussion 161

Chapter 4. Cost-Effectiveness Evaluation of the Combined Screening Algorithm at UCLH 165

Introduction 168

Methods 166

Results 171

Discussion 173

Chapter 5. Key considerations prior to the new service implementation 177

Introduction 177

Methods 178

Results 179

Discussion 190

Chapter 6. Reproducibility of Uterine Arteries following the implementation of the Combined Screening Approach

Introduction 192

Methods 193

Results 194

Discussion 198

Chapter 7. Future Work 203

References 205

Abbreviations

ACR	Albumin: Creatinine Ratio
ACOG	American College of Obstetrics and Gynecology
AGREE	Appraisal of Guidelines for Research and Evaluation
AGREE-REX	Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence
AHA	American Heart Association
AKI	Acute Kidney Injury
APH	AntePartum Haemorrhage
APLS	Antiphospholipid syndrome
ARG	Argentina
ART	Assisted reproductive technologies
ASPRE	Combined multi-marker screening and randomized patient treatment with aspirin for evidence-based pre-eclampsia prevention
ATL	Aspirin-Triggered Lipoxins
AUC	Area under receiver operating characteristic curve
βhCG	β human chorionic gonadotrophin
BMI	Body mass index
BRA	Brazil
BW	Birthweight
CHN	China
CI	Confidence interval
CPG	Clinical Practice Guideline
CRL	Crown–rump length

dBP	Diastolic blood pressure
DIC	Disseminated Intravascular Coagulation
DR	Detection rate
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, i.e. German Society of Gynecology and Obstetrics
DSOG	Dansk Selskab for Obstetrik og Gynækologi, i.e. Danish Society of Obstetrics and Gynaecology
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ERA	European Renal Association
CNGOF	Collège national des gynécologues et obstétriciens français, i.e., French College of Obstetricians and Gynaecologists
FGR	Fetal Growth Restriction
FIGO	International Federation of Gynecology and Obstetrics
FIN	Finland
FPR	False Positive Rate
FSH	French Society of Hypertension
GDC	Guideline Development Committee
GI	Gastrointestinal
GWAS	Genome-wide association studies
HELLP	Haemolysis, elevated liver enzymes, low platelets
HR	Hazard ratio
HTN	Hypertension
IAD	Inter-arm difference
ICC	Intraclass Correlation

ICSI	Intracytoplasmic sperm injection
ICU	Intensive Care Unit
IGF	Insulin-like growth factor
IL-10	Interleukin-10
IPI	Interpregnancy interval
IQ	Intelligence quotient
IQR	Interquartile range
ISH	International Society of Hypertension
ISSHP	International Society for the Study of Hypertension in Pregnancy
ISUOG	International Society Of Ultrasound in Obstetrics and Gynaecology
IUFD	Intrauterine fetal death
IUI	Intrauterine insemination
IVF	In vitro fertilization
JAOG	Japanese Association of Obstetricians and Gynaecologists
JSOG	Japanese Society of Obstetrics and Gynaecology
LAGD	Lietuvos Akušerių Ginekologų Draugija, i.e., Lithuanian Society of Obstetricians and Gynaecologists
LCPUFA	Long chain polyunsaturated fatty acids
LCM	Lithuanian Union of Midwives
LDA	Low Dose Aspirin
LMWH	Low molecular weight heparin
LoA	Limits of Agreement
MAP	Mean arterial pressure
MoM	Multiple of median

NHFA	National Heart Foundation of Australia
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NGF	Norsk Gynekologisk Forening, i.e. Norwegian Gynaecological Association
NO	Nitric Oxide
NSAID	Nonsteroidal Anti-inflammatory Drug
NVOG	Nederlandse Vereniging voor Obstetrie en Gynaecologie, i.e., Dutch Association of Obstetrics and Gynaecology
NZL	New Zealand
OEGGG	Österreichische Gesellschaft für Gynäkologie und Geburtshilfe, i.e., Austrian Society of Gynecology and Obstetrics
OR	Odds ratio
Papp-A	Pregnancy-associated plasma protein A
PCR	Protein: Creatinine Ratio
PE	Pre-eclampsia
PGI2	Prostaglandin I2
PHL	Pakistan Hypertension League
PI	Pulsatility Index
PLGF	Placental growth factor
POC	Point of care
POL	Poland
PPH	Postpartum haemorrhage
PPI	Proton Pump Inhibitors
PTB	Preterm Birth

QALY	Quality-Adjusted Life-Years
QLD	Queensland
RCT	Randomised controlled trial
RDS	Respiratory Disease Syndrome
RR	Relative risk
sBP	Systolic blood pressure
SCBU	Special Care Baby Unit
SD	Standard deviation
SFHTA	Société Française d' HyperTension Artérielle- French Society of Arterial Hypertension
SFOG	Svensk Forening for Obstetrik & Gynekologi, i.e. Swedish Society for Obstetrics and Gynaecology
SGA	Small for gestational age
SGGG	Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe, i.e., Swiss Society of Gynecology and Obstetrics
SLE	Systemic lupus erythematosus
SMFM	Society of Maternal Fetal Medicine
SOGR	Society of Obstetrics and Gynaecology in Romania
SOMANZ	Society of Obstetric Medicine in Australia and New Zealand
SOP	Standard Operating Procedure
T&T	Trinidad and Tobago
TNF-a	Tumour Necrosis Factor- alpha
TXA2	Thromboxane 2
TUN	Tunisia
TWN	Taiwan

U.A	Umbilical artery
UCL	University College London
UCLH	University College London Hospital
USPSTF	United States Preventive Services Task Force
USU	Ultrasound Unit
UtA	Uterine artery
VEGF-R1	Vascular endothelial growth factor receptor 1
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

Chapter 1.

Introduction

Preeclampsia

Preeclampsia (PE) is a gestational hypertensive disorder that can impact both maternal and fetal wellbeing. The economic burden on healthcare is substantial and in the case of early PE estimated to cost 40-100 times that of a term pregnancy depending on the gestational age at delivery [1].

The definition of PE has changed over the years. In the past, PE was defined as new onset hypertension after 20 weeks of pregnancy accompanied by proteinuria. As our knowledge surrounding this disorder and its pathophysiology has increased, its definition has been expanded. When NICE updated its guidance [2], it defined PE as new onset hypertension and the co-existence of one or more of the following new-onset conditions: -proteinuria, - other maternal organ dysfunction, or – uteroplacental dysfunction including fetal growth restriction (FGR), abnormal umbilical artery (U.A) waveforms or stillbirth. Maternal organ dysfunction incorporates renal involvement (creatinine ≥90 μmol/lt), liver involvement (alanine aminotransferase or aspartate aminotransferase over 40 IU/lt), neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata), haematological complications (thrombocytopenia, disseminated intravascular coagulation or haemolysis. Women with a background of chronic hypertension may also develop superimposed PE. The diagnosis in this group of women is more challenging given that hypertension is present prior to the onset of the pregnancy and may already be accompanied by proteinuria. Approximately 10% of women with

chronic hypertension have proteinuria. Proteinuria is diagnosed either by using the protein: creatinine ratio (PCR) at a diagnostic threshold of 30 mg/mmol or the albumin: creatinine ratio (ACR) of 8 mg/mmol [2].

Pre-eclampsia screening in the first trimester

While the terms “screening” and “prediction” are often used interchangeably in the medical literature, they represent distinct concepts within the healthcare continuum [3]. Screening encompasses a comprehensive process that begins with the invitation of a population to participate and culminates in treatment for individuals identified as being at high risk for a condition. Prediction, on the other hand, refers specifically to the calculation of an individual's risk of developing a disease. It is a crucial component of the screening process but does not encapsulate the entirety of it. Screening distinguishes itself by including interventions for those at elevated risk, aiming to modify the course of the condition and enhance clinical outcomes. In the context of prenatal care, screening has historically facilitated the option of timely termination of pregnancies for parents of fetuses diagnosed with untreatable conditions. This application broadens the scope of screening as defined by the World Health Organization, which emphasizes disease prevention. For the guidelines discussed herein, particularly in relation to PE, “screening” is the term of choice when the identification of at-risk cases can lead to interventions that prevent the condition’s onset. Conversely, “prediction” is utilized when identifying women at risk does not necessarily translate to improved outcomes. This delineation ensures clarity and specificity in discussing strategies aimed at mitigating the impact of PE, reinforcing the importance of precise terminology in conveying the objectives and implications of prenatal care practices.

There are currently two main methods of screening for PE. The first relies on maternal risk factors alone. The second is a multi-variable method that combines maternal factors with MAP and/or UtA PI and/or serum biomarkers such as Papp-A or PLGF.

One of the landmark studies for screening and prevention of PE was the ASPRE trial (combined multi-marker screening and randomized patient treatment with aSpirin for evidence-based PREeclampsia prevention) [4-6]. The trial included 26,941 singleton pregnancies screened for PE in the first trimester. The reported detection rates of preterm and term PE were 77% and 43% respectively, after adjustment for the effect of aspirin, with a false positive rate (FPR) of 9.2%. In contrast, the respective detection rate based on the NICE screening recommendation, which relies on maternal factors alone, is 41% and 34% at a 10% FPR. The original algorithm was developed from a study of 58,884 singleton pregnancies at 11 to 13 weeks of pregnancy with detection rates of 77% and 54% for preterm PE and all cases of PE, respectively at a fixed FPR of 10%[7].

The FMF triple-combined test and the administration of 150 mg aspirin in screened women has been shown to reduce the rate of preterm PE by 62%. The number needed to screen to prevent one case of PE at any gestation is 143 [8]. The number needed to screen to prevent one case of early preterm PE (<34/40) is 400 and all preterm PE (<37/40) is 250. The number needed to treat with low dose aspirin to prevent 1 case of preterm PE is 38.

When we first started our project, PE screening at UCLH was performed by the midwife at the time of first contact, i.e., at the booking appointment by assessing maternal factors as per the NICE recommendation. The mother would then be advised

to obtain a prescription for LDA following their first trimester scan either by the Ultrasound Unit (USU) fellows or the Maternal-Fetal Assessment Unit fellows.

Our project was regarded as a quality improvement project and we were able to implement change in the service provision by offering combined screening for preterm PE to all women attending the Ultrasound Unit at the time of their first trimester scan from February 2023 onwards. Serum Papp-A was the biomarker selected for the combined PE screening given that this was already incorporated in the first trimester screening for chromosomal abnormalities, i.e., trisomies 13,18 and 21. Mothers who opted out of trisomy screening were still given the option to have the blood test for the sole purpose of PE screening.

The Fetal Medicine Foundation combined screening approach

Maternal Risk Factors

Parity

The risk of PE has been found to be approximately three-fold in nulliparous women. A meta-analysis of 26 studies found the risk to be 2.4-fold in nulliparous women [9]. Immune maladaptation, altered angiogenesis and a relatively elevated insulin resistance are amongst the proposed potential mechanisms for the development of PE in primiparous women.

Maternal Age

Maternal age, particularly at the extremes of the reproductive lifespan is a well-known risk factor for PE. Women who are 35 years or older appear to have a 1.2 to 3-fold increase risk of PE with an exponential increase after the age of 40 [10-13].

A number of theories behind maternal age and PE pathophysiology exist including those of oxidative stress, lower mitochondrial energy production and cytoplasmic quality, decreased androgen levels, placental senescence [14, 15].

Adolescent pregnancies are also associated with an increased risk of PE. Incomplete maternal physiological development secondary to lack of 'menstrual preconditioning' and uterine immaturity likely lead to 'progesterone resistance', defective placentation and impaired uterine decidualisation [16]. Additional factors such as the biological immaturity of the cardiovascular system and even socio-economic factors may also play a role in the increased susceptibility of younger mothers.

Assisted reproductive technologies (ART)

Women who undergo ART have been found to have a 2 to 3-fold higher incidence of PE compared to spontaneous pregnancies [17]. A recent meta-analysis of 27 studies showed that singleton pregnancies with oocyte donation were associated with the highest risk of PE amongst the ART pregnancies with a 5-fold increase compared to pregnancies from spontaneous conception [17]. The underlying mechanisms behind ART are thought to involve lack of immune priming, absence of corpus luteum and HLA mismatching leading to epigenetic modifications and impaired placentation [15]. Additionally, ART pregnancies often involve older maternal age and a higher prevalence of underlying fertility issues, both of which are independent risk factors for PE.

Previous history of Pre-eclampsia

Previous history of PE is a well-established and significant risk factor for its recurrence in subsequent pregnancies [18-20]. Women who have experienced PE in a prior pregnancy have a 7 to 10-fold risk of developing the condition again, depending on the severity and timing of onset in the initial pregnancy [21-27].

The pathophysiological basis for this increased risk is not fully understood, but it is thought to involve persistent cardiovascular and metabolic changes that predispose women to placental dysfunction [28, 29]. Additionally, genetic and environmental factors, alongside underlying conditions such as chronic hypertension and obesity, may contribute to the heightened risk.

Pregnancy Interval

The interval between pregnancies has emerged as a risk factor for PE, with both short and extended interpregnancy intervals associated with an increased risk of developing the condition. Two large meta-analyses published in 2016 [30] and in 2023 [31] reported that interpregnancy intervals of more than 72 months and more than 60 months, respectively, are associated with an increased risk of developing PE (OR of 1.1-1.3 and 1.35, respectively). The pathophysiological mechanism is likely multifactorial, involving, for example, the association with advanced maternal age, use of ART and different partner.

A population-based longitudinal cohort study of 711,252 pregnancies over a 35-year period reported that women with no previous history of PE and a short interpregnancy interval of less than 3 months have a higher chance of PE (RR:1.24) compared to women with an interpregnancy interval of 18 months [32]. However, recent meta-analyses have found no association between a short interpregnancy interval and PE [30, 33].

Family History of Pre-eclampsia

A family history of PE confers a 3 to 4-fold higher risk of developing this condition, underscoring the role of genetic and hereditary factors in its pathogenesis. [34] [35] The familial predisposition can be attributed to genetic predispositions that affect placental development and function, immune system interactions, and endothelial cell health, which are critical in maintaining normal pregnancy blood pressure and placental perfusion. A recent study on maternal DNA sequence variants identified 12 independent loci associated with PE/eclampsia. The identified loci play a role in natriuretic peptide signalling, angiogenesis, renal glomerular function, trophoblast development, and immune dysregulation. The authors of the study produced genome-

wide polygenic risk scores that could predict PE or eclampsia and gestational hypertension in external datasets, independent of first-trimester risk markers [36].

Body Mass Index

Several studies have demonstrated a significant association between obesity with an elevated risk of developing PE with the risk being 2 to 4 times higher compared to non-obese individuals [37-43].

Obesity is characterized by a state of chronic, low-grade inflammation, often referred to as “meta-inflammation” [44]. This ongoing inflammatory condition is thought to play a key role in the pathogenesis of various diseases, including PE [45-47]. In the context of pregnancy, low-grade inflammation associated with obesity can lead to endothelial dysfunction and placental ischemia through immune-mediated pathways. These disturbances in endothelial function and placental blood flow contribute to the production of inflammatory mediators within the maternal circulation. Subsequently, this heightened inflammatory response can trigger an exaggerated immune reaction in the mother, further exacerbating the inflammatory milieu and ultimately culminating in the development of PE [45-47]. In essence, the chronic inflammatory state characteristic of obesity sets the stage for endothelial dysfunction, placental ischemia, and an aberrant maternal immune response, all of which are central to the pathophysiology of PE. Additionally, obesity is associated with insulin resistance, which further exacerbates endothelial dysfunction.

Race and ethnicity

Extensive research findings indicate a clear link between race and ethnicity and the occurrence of PE. Large-scale population studies have revealed that Afro-Caribbean

women face a heightened risk of PE, with estimates ranging from a 20% to 50% increase compared to other groups [48-50]. Similarly, women of South Asian descent also exhibit a greater susceptibility to PE compared to non-Hispanic white women, with an adjusted O.R of 1.3 [24, 51, 52].

The increased risk of PE among certain racial and ethnic groups appears to be linked to metabolic profiles observed in non-pregnant women, which predispose them to cardiovascular diseases [53]. Both Afro-Caribbean and South Asian women tend to exhibit higher rates of chronic hypertension, diabetes mellitus, and cardiovascular issues even before pregnancy. A large prospective observational study, conducted in London, highlighted a significantly elevated risk of PE among women of Afro-Caribbean and South Asian racial backgrounds compared to Caucasian women [54]. Importantly, this increased risk persisted even after accounting for other known risk factors associated with PE, emphasizing the significant influence of race and ethnicity on the likelihood of developing this condition during pregnancy. This increased risk is possibly also influenced by systemic factors, including access to healthcare and socio-economic status.

Comorbidities

Medical comorbidities, including chronic hypertension, diabetes, renal disease, and autoimmune disorders such as systemic lupus erythematosus and antiphospholipid syndrome, significantly elevate the risk of developing PE [25, 55-58].

These conditions contribute to the pathophysiology of PE through various mechanisms, such as endothelial dysfunction, systemic inflammation, and alterations in immune response, which are central to the development of PE.

Existing cardiovascular risk factors, particularly chronic hypertension, can be exacerbated during pregnancy due to the heightened metabolic and vascular stress on the body. Women with chronic hypertension have approximately a 5-fold increased risk of developing superimposed PE [25, 55, 56]. Women have an approximately 3-fold and 4-fold elevated risk of PE in the background of renal disease or pregestational diabetes mellitus, respectively [25,57]. Women with APLS or SLE have a 2 to 3-fold increased risk [58].

Chronic hypertension predisposes to abnormal placentation, while diabetes mellitus and renal disease are associated with vascular dysfunction and oxidative stress, exacerbating the risk for placental insufficiency [59,60-62]. Furthermore, autoimmune disorders introduce additional immunological factors that may cause dysregulation of immune cells and disrupt the delicate balance required for normal placental development [63-65].

Mean Arterial Pressure (MAP)

There appears to be variation in the recommendations on the measurement of the blood pressure in adults and there is currently no standardized protocol for the measurement of the blood pressure in pregnancy.

For example, the National Heart Foundation of Australia (NHFA) recommends that the blood pressure is checked in both arms with two recordings or more until the point of stability can be reached, i.e until the difference in the systolic and diastolic blood pressure is less or equal to 10 mm Hg and 6 mm Hg, respectively [66]. This is in contrast to the American Society of Hypertension (ASC) and the International Society for Hypertension (ISC) who advise to take 2 consecutive readings 1-2 minutes apart in both arms and to use the arm with the highest blood pressure at follow up assessment [67].

In the United Kingdom, the British and Irish Hypertension Society endorse the NICE guideline NG136 on the diagnosis of hypertension in adults, which was updated in 2022, and advise to check the blood pressure in both arms. If the difference in the readings is more than 15 mmHg, the arm with the higher blood pressure reading should be used for subsequent readings. In a clinic setting, they recommend that if the blood pressure is initially greater than 140/90 mmHg and substantially different from a second measurement, a third measurement should then be taken and the lower of the last 2 measurements recorded [68].

Poon et al had published a protocol for measurement of MAP at 11-13 weeks for the prediction of PE [69]. The study's objective was to find a simple protocol for measurement of MAP that would perform similarly to the NHFA protocol for the prediction of PE based on MAP. They compared the area under the receiver operating

characteristic curve (AUC) for prediction of PE by MAP based on the NHFA protocol and compared it with 50 different combinations of MAP measurement. The blood pressure point of stability as per the NHFA protocol was reached after two, three, four, five or more recordings in 48.1%, 24%, 26.1% and 1.8%, respectively. The AUC was 0.773 (95% CI: 0.768- 0.778) with the MAP based on the NHFA protocol and 0.771 (95% CI: 0.766-0.777) with the MAP based on two recordings from each arm. The authors concluded that the high performance of screening for PE by MAP using the NHFA protocol can be achieved by the simpler approach of using the average of two recordings from each arm. In a later study by Roberts et al, MAP was assessed using the NHFA protocol at 10-40 weeks of gestation. The median MAP based on the average of two recordings from both arms was similar to the median MAP based on the NHFA protocol. The mean difference in z-score was 0.0194SD.

Uterine Artery Pulsatility Index

Uterine vascular remodeling during pregnancy occurs to facilitate the increase in the uteroplacental blood flow and consequently preserve the intrauterine environment and fetal growth [70]. The uterine vascular resistance is thought to mirror the degree of trophoblast invasion. This forms the rationale for using the uterine artery blood flow assessment in the screening test for preterm PE. Impaired trophoblast development and defective spiral artery re-modelling have been linked with PE. However, newer evidence suggest that maternal cardiovascular function can also affect the uterine artery blood flow [71].

Following successful implantation of the blastocyst, progesterone levels remain raised, the decidua is maintained and remodeling extends to the basal endometrial layer. During the first trimester, the placenta forms from trophectoderm on the outer layer of the blastocyst. The extravillous trophoblast (EVT) cells invade into the uterine epithelium and differentiate to form the villous structure of the placenta [72]. EVT cells migrate from the villi attached to the placenta to the decidual stroma cells (DSC) of the uterus and reach the inner third of the myometrium. The endovascular EVT migrate into the lumen of the uterine spiral arteries. EVT cells replace the arterial endothelial and vascular smooth cells of the transforming vessels, thus turning the small firm arteries into wide flaccid vessels and allowing high flow, low resistance circulation [73]. The DSC control the trophoblast invasion in order to ensure this is adequate but not excessive [74, 75].

There appears to be a mutual stimulation of chemotactic migration between trophoblast and endometrial stromal cells [72]. Endometrial stromal cell-derived Interleukin-11 and -15 (IL-11 and IL-15) are considered to play a key role in the regulation of decidualization and natural killer cell (NK) activity in the uterus [76].

Decidual NK (dNK) cells secrete factors that disrupt vascular cell interactions and allow for vascular smooth muscle cells to migrate out of the spiral arteries [77-79]. dNK cells have also been shown to increase EVT motility and support chemoattraction of the EVT to the sites of remodeling [80].

In pregnancies with high UtA doppler resistance indices in the first trimester, chemoattraction of trophoblast cells by the DSC appears to be impaired [81]. Decidual NK cells have decreased ability to chemoattract trophoblast cells and induce the outgrowth of the EVT from the villi in these pregnancies compared to pregnancies with normal uterine artery resistance in the first trimester [82]. The inhibition of EVT chemotaxis possibly contributes to the impaired invasion and spiral artery re-modelling. Furthermore, placental endothelial cells appear more sensitive to apoptotic stimuli and this may also contribute to poor placental vascular development.

In a study examining the sequential assessment of uterine artery (UtA) blood flow, it was observed that an elevated UtA pulsatility index (UtA PI) in the first trimester normalized by the second trimester in 73% of cases. Conversely, the findings also indicated that 95% of women with a normal UtA PI during the first trimester maintained normal levels in the second trimester [83].

Biomarkers

Placental Growth Factor (PlGF)

PlGF is a critical component of the vascular endothelial growth factor (VEGF) family, characterized as a glycosylated, dimeric glycoprotein produced by trophoblastic cells. Its primary function involves binding to the VEGF receptor 1 (VEGFR-1), which is known to proliferate during gestation [29, 84, 85]. Originating from both villous and extravillous cytotrophoblasts, PLGF contributes to vasculogenesis and angiogenesis, essential processes in normal pregnancy development [29, 85]. The role of PLGF in angiogenesis has been postulated to be significant in maintaining a healthy pregnancy, with alterations in its levels or the presence of inhibitory receptors being associated with the onset of PE [86-88]. Research indicates that lower maternal PLGF levels in the first trimester are significantly associated with the development of PE when compared to normal pregnancies. As a biomarker, PLGF has demonstrated a detection efficiency of 55% and 33% for early- and late-onset PE, respectively, at a 10% false-positive rate [88]. A systematic review and meta-analysis further highlighted PLGF's superiority over other biomarkers in predicting PE, showcasing a detection rate of 56% at a 9% false-positive rate specifically for early-onset PE [89].

Pregnancy-associated plasma protein (Papp-A)

Papp-A is a crucial metalloproteinase that mediates the bioavailability of insulin-like growth factor (IGF) by cleaving IGF binding proteins, primarily secreted by the placental syncytiotrophoblasts [90]. This action significantly contributes to placental development and growth by enhancing the proliferative effects of IGFs. PE is correlated with diminished Papp-A levels in the bloodstream, suggesting a limitation in the availability of free IGFs to execute their cellular functions. Papp-A serves as a

recognized biochemical indicator for screening chromosomal abnormalities such as trisomies 21, 18, and 13. In pregnancies without chromosomal abnormalities (euploid pregnancies), a Papp-A multiple of the median (MoM) value below the ^{5th} percentile (0.4 MoM) occurs in 8% to 23% of expectant mothers diagnosed with PE, indicating that Papp-A alone does not offer precise predictive capability for PE. However, a meta-analysis of eight studies with a combined cohort of 132,076 women in their first trimester revealed a significant association between low maternal Papp-A concentrations (<5^{th} percentile) and an increased risk of developing PE, with an odds ratio (OR) of 1.94 (95% CI: 1.63–2.30) and a detection rate of 16% for PE at an 8% false-positive rate [91,92].

For accurate interpretation, the measurements of both placental growth factor (PLGF) and Papp-A need to be adjusted to MoMs, considering the influence posed by maternal factors, the analysers used, and gestational age.

The debate over whether to prioritize PlGF over Papp-A for combined screening for PE focuses on the comparative effectiveness and reliability of these biomarkers. Proponents of PlGF argue that it offers superior sensitivity and specificity in detecting early-onset PE due to its direct involvement in placental angiogenesis and its marked decrease in cases of placental dysfunction[89]. Several studies have demonstrated that the use of PlGF in the combined screening algorithm enhances the early detection of PE by approximately 5-7% at a 10% false-positive rate compared to the use of Papp-A [93-96]. These studies included a total of 118,000 women, out of whom 945 developed preterm PE.

Conversely, advocates for Papp-A highlight its established role in prenatal screening and its utility in predicting adverse pregnancy outcomes. A recent study by Noel L. et al, showed that Papp-A was equally clinically effective as PlGF in first-trimester combined PE screening when used in conjunction with maternal characteristics, blood pressure, and UtA Doppler [97]. This was a retrospective cohort study, conducted in the UK and only included 1094 women, out of whom 30 developed preterm PE. Hu et al performed a prospective cohort study in the Chinese population (10,899 patients, 289 cases of preterm PE) and found Papp-A to be superior compared to the use of PlGF as the biomarker of choice in the combined algorithm with a detection rate of 64.96% compared to 56.41% at a 10% false positive rate [98]. Critics of relying solely on PlGF also point to the increased costs and the need for further validation in diverse populations. Consequently, the debate persists on whether to utilize Papp-A or PlGF or both in the combined screening approach. Ongoing research is essential to determine and refine the most effective and cost-efficient screening strategy.

Preventative strategies for Pre-eclampsia

Multiple pharmacological agents have been investigated for their potential benefits in preventing PE. Aspirin and calcium remain the most commonly recommended agents in CPGs and, consequently, are the only agents analysed further in the thesis.

Other pharmacological agents such as metformin, statins, proton pump inhibitors, low molecular weight heparin (LMWH), progesterone, magnesium, clopidogrel, nitric oxide, antioxidants (vitamin C/E), garlic supplements and omega-3 polyunsaturated fatty acids are generally not recommended outside the context of clinical research.

Non-pharmacological measures such as physical activity and dietary modification, including salt restriction have also been studied.

A Cochrane review published in 2006, which only included two trials with a total of 45 participants, found no statistically significant differences in the risk of PE between the intervention and control groups [99]. In contrast, a recent analysis of ten randomized controlled trials (RCTs) encompassing 3,410 women, showed that participants in the exercise intervention group had a lower risk of developing PE compared to those in the control group [100]. However, nine out of the ten studies involved women at low risk for developing PE and further research is necessary to evaluate the impact of exercise on high-risk women.

Studies on dietary modifications as a preventative measure have also yielded conflicting results [101-104].

Non-pharmacological interventions are beyond the scope of this thesis and, therefore, not explored further.

Aspirin

LDA is considered to reduce the risk of preterm PE by up to 70%, if commenced prior to 16 weeks [8, 105-107]. The appropriate dosage of aspirin and the time for discontinuing is not clear; recommendations tend to vary amongst national and international guidelines (chapter 2).

Aspirin is a non-selective, irreversible cyclooxygenase-1 (COX-1) inhibitor. Its likely mechanism of action involves the reduction in thromboxane A2 (TXA2) and subsequent imbalance between TXA2 and prostacyclin (PGI2) [108, 109]. The latter results in a reduction of platelet aggregation and inhibition of vasoconstriction, hence enhancing uterine blood flow. Additionally, aspirin appears to exhibit an anti-inflammatory role through the generation of aspirin-triggered lipoxins (ATL) [110, 111]. ATL can cause the upregulation of interleukin-10 (IL-10) and nitric oxide (NO), and downregulation of tumour necrosis factor-alpha (TNF-a) [112-114]. Aspirin is considered to reduce the risk of PE in women through its anti-platelet and anti-inflammatory effects.

Even though aspirin is generally regarded as safe for use during pregnancy, concerns had been raised in the past regarding the risk of haemorrhagic complications including ante-/post- partum haemorrhage, placental abruption and neonatal intracranial haemorrhage [105, 115, 116]. A Cochrane review on antiplatelet agents for preventing PE and its complications [105], concluded that aspirin probably, slightly increased the risk of postpartum blood loss of >500mls (23,769 women included, RR:1.06, CI: 1.0-1.12) and of placental abruption (30,775 women included, RR:1.2, 95% CI: 0.95-1.54). Both differences however, were not statistically significant. Only 1 of the trials included in the Cochrane review assessed women on an aspirin dose of 150mg, and there was no difference in the risk of haemorrhagic complications between the aspirin and placebo groups [107].

A more recent analysis of 38 randomised controlled trials (RCTs) with a combined sample size of approximately 23,000 women in each arm, assessed the risk of haemorrhagic complications [i.e. placental abruption, antenatal vaginal spotting/bleeding, antepartum haemorrhage (APH), postpartum haemorrhage (PPH) and neonatal intracerebral haemorrhage]. The study showed no difference in the risk of harm between those taking aspirin and those given placebo, irrespective of the aspirin dose (<100mg, 100mg or 150mg) [100].

Calcium

There are conflicting data on the role of calcium on PE prevention. A Cochrane review published in 2018, which included 13 trials, found that high dose calcium supplementation (≥ 1g/day) may reduce the risk of PE by 55%, especially in women with low dietary calcium intake [117]. However, a more recently published study by Wright et al. demonstrated that there was a disproportionate effect on the conclusions derived from the Cochrane review due to the inclusion of smaller studies with increased heterogeneity (I^2:70%). More specifically, the authors were able to show that, when only the 3 largest trials were included, which accounted for 88% of recruitment (I^2:0%), the reduction in the risk of PE was not statistically significant (CI: 0.8-1.06) [118].

Calcium's exact mechanism of action is not known. It is thought that low calcium can potentially stimulate the release of either parathyroid hormone (PTH) or renin and consequently promote angiotensin II and aldosterone synthesis. The subsequent increase in the intracellular calcium in vascular smooth muscle can lead to vasoconstriction and potentially an increase in blood pressure [119-123].

Calcium is considered overall safe for use in pregnancy. However, high-dose calcium has been linked to a higher risk of HELLP (Haemolysis, Elevated Liver enzyme, Low Platelets) syndrome, even though the absolute number of events remained low [117]. Furthermore, concerns have been raised regarding its potential impact on maternal bone health by disrupting metabolic adaptation[124, 125].

Economic Implications of Preeclampsia

PE is a multifaceted hypertensive disorder that imposes significant economic implications on healthcare systems globally. These include direct medical costs,

indirect costs associated with long-term health implications and broader societal impacts.

Women who develop PE require more frequent antenatal appointments, antihypertensive medications and ultrasound scans to assess fetal wellbeing. However, the main driving force of the economic burden is the presence of adverse outcomes. Stevens et al performed a retrospective study to quantify the annual epidemiological and health care cost burden of PE to both mothers and infants in the United States by combining state hospital discharge data with birth certificate data, commercial insurance claims data, and nationally representative Healthcare Cost and Utilization Project data [126].

Both the maternal and the fetal adverse outcomes were divided into (a) acute [i.e., intensive care unit (ICU) complications or death], (b) long-term associated with residual morbidity, and (c) maternal or fetal programming as a result of PE.

Maternal acute complications incorporated eclampsia/stroke, pulmonary oedema, myocardial ischaemia, admission to ICU, renal injury with or without dialysis, abruption/disseminated intravascular coagulation (DIC) and liver dysfunction/haematoma. Maternal long-term complications with residual morbidity included neurological deficit, renal failure requiring dialysis and cardiomyopathy. Maternal programming complications included coronary artery disease, chronic hypertension (HTN), metabolic syndrome, renal insufficiency, stroke, retinal dysfunction and premature death.

Fetal acute complications included respiratory distress syndrome (RDS)/ bronchopulmonary dysplasia, intraventricular haemorrhage/periventricular leukomalacia, necrotising enterocolitis/sepsis, retinopathy of prematurity and prolonged admission to the Neonatal intensive Care Unit (NICU). Fetal long-term

complications included cerebral palsy/neurological deficit, learning disabilities, blindness/hearing deficit, chronic lung disease and chronic heart disease. Fetal programming encompassed fetal origin- adult disease such as metabolic syndrome and cardiovascular disease.

According to the study, the cost of PE in the United States, within the first 12 months of delivery was estimated to be approximately $2.18 billion ($1.03 billion for mothers and $1.15 billion for infants), without including the loss on quality of life. Costs caused by the loss in quality-adjusted life year (QALY) could mount to a health burden of $20 billion per year (based on cost estimation in 2012) [126].

PE screening is hence, of paramount importance both for improving maternal and fetal outcomes in addition to ensuring a reduction in the economic burden.

Chapter 2.

A Systematic Review of Clinical Practice Guidelines

Introduction

Guidelines are carefully formulated statements that contain recommendations aimed at improving patient care pathways. These guidelines are essential for standardizing practices and ensuring that healthcare professionals are informed of the most current and unbiased clinical evidence. To achieve this, clinical guidelines must employ a rigorous and systematic methodology, which includes a thorough review of the latest research, expert consensus, and practical considerations for implementation in clinical settings.

The current recommendations for PE screening exhibit significant variability. This heterogeneity is evident both in the proposed predictive approaches to PE and in the preventive measures suggested. Notably, there is a lack of consensus among CPGs regarding the administration of aspirin. Discrepancies exist in the recommended dosage, the optimal timing for initiation and discontinuation of treatment. This inconsistency can lead to confusion among healthcare providers and variability in patient care.

This systematic review aims to critically evaluate the clinical variability present in the published national and international CPGs regarding first-trimester PE screening. Additionally, it assesses the quality of these guidelines and their feasibility for implementation in clinical practice. By scrutinizing these guidelines, the review seeks to identify areas of agreement and divergence, thereby highlighting opportunities for standardization and improvement in the management of PE. The ultimate goal is to

enhance patient outcomes by ensuring that clinical practices are based on the best available evidence and are uniformly applied across different healthcare settings.

Methods

We registered our systematic review on PROSPERO prior to the literature review [registration number: CRD42022378406]. The review included the following data sources: Ovid MEDLINE, EMBASE, Web of Science, Google Scholar and Tripdatabase. Furthermore, we searched clinical practice guidelines websites including: Guidelinecentral.com, HTA database, Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse (Link: https://www.ahrq.gov/gam/index.html), National Institute for Health and Care Excellence (NICE) National Library for Health (Link: https://www.nice.org.uk/guidance), Scottish Intercollegiate Guidelines Network (SIGN) (Link: http://www.sign.ac.uk/our-guidelines.html), EBSCO DynaMed Plus (Link: http://www.dynamed.com/home), Guidelines International Network Library (Link: https://www.g-i-n.net/home), Guidelines (https://www.guidelines.co.uk) and World Health Organisation (WHO) website (https://www.who.int).

Our search terms included: ‘hypertensive disorders of pregnancy’, ‘preeclampsia’, ‘screening for preeclampsia’, ‘guideline’, ‘clinical practice guideline’, ‘aspirin’, ‘uterine artery Doppler’, ‘PLGF’, ‘Papp-A’, ‘Pregnancy-associated plasma protein-A’, ‘Placental growth factor’. The CPGs were independently screened by two reviewers (CA, D.L) on Covidence (Figure 2.1) and conflicts were resolved after discussion and mutual agreement. CPGs with recommendations on screening / prediction and prevention of PE in the first trimester were considered eligible for inclusion.

In this thesis, the terms 'gynecology' and 'gynaecology' are used interchangeably to reflect the spelling differences based on regional preferences. 'Gynaecology' is the British English spelling, while 'gynecology' is the American English spelling. These variations are observed in the names and publications of professional societies and organisations.

The outcomes we evaluated were as follows:

-method of screening recommended

-risk factors used in the screening

-dose of aspirin recommended and whether the safety profile was discussed

-other pharmacological preventative measures recommended and

-non-pharmacological measures recommended

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument stands as the predominant tool for assessing the quality of CPGs, recognized as the benchmark for evaluation of CPG quality [127, 128]

The Appraisal of Guidelines for Research and Evaluation- Recommendations Excellence (AGREE-REX) tool acts an adjunct to AGREE II in order to appraise the clinical credibility and implementability of recommendations on a particular area of the guideline[128]. The methodological quality of each CPG was assessed by using both the AGREE II and the AGREE-REX tools.

The AGREE-II was used to assess the quality of the guideline by evaluating the following six domains:

-**Domain 1.** Scope and Purpose

-**Domain 2.** Stakeholder Involvement

-**Domain 3**. Rigour of Development

-**Domain 4**. Clarity of Presentation

-**Domain 5.** Applicability

-Domain 6. Editorial Independence

The AGREE-II tool comprised of a total of 23 questions spanning 6 domains followed by 2 global rating items for the overall assessment.

The AGREE-REX tool was used to appraise the clinical credibility and implementability of recommendations on a particular area of the guideline, and more specifically on prediction and prevention of PE.

The AGREE-REX domains assessed were:

-**Domain 1**. Clinical Applicability

-**Domain 2.** Values and Preferences

-**Domain 3.** Implementability

The AGREE-REX tool consisted of 9 questions for the assessment of each domain followed by 1 question for the overall rating of the guideline.

Each of the main questions included in AGREE II and AGREE-REX was scored on a 7-point scale ranging from 1: strongly disagree to 7: strongly agree.

Each domain score was then calculated by obtaining the scores of the individual items in each domain as assessed by two reviewers (C.A and D.N) followed by scaling the total as a percentage of the maximum score. More specifically, the domain score was calculated as follows:

$$\text{Domain score (\%)} = \frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100$$

Given that the domain scores are independent, these were not aggregated into a single score.

Quality was considered as high, moderate and low if the domain score thresholds overall were ≥70%, 50-69% and ≤49%, respectively.

Results

A detailed review of the screening policies across the globe

A total of 425 references were imported for screening onto Covidence: 365 studies were considered irrelevant and a total of 31 clinical practice guidelines/ statements, published from 2017 onwards were included (figure 2.1).

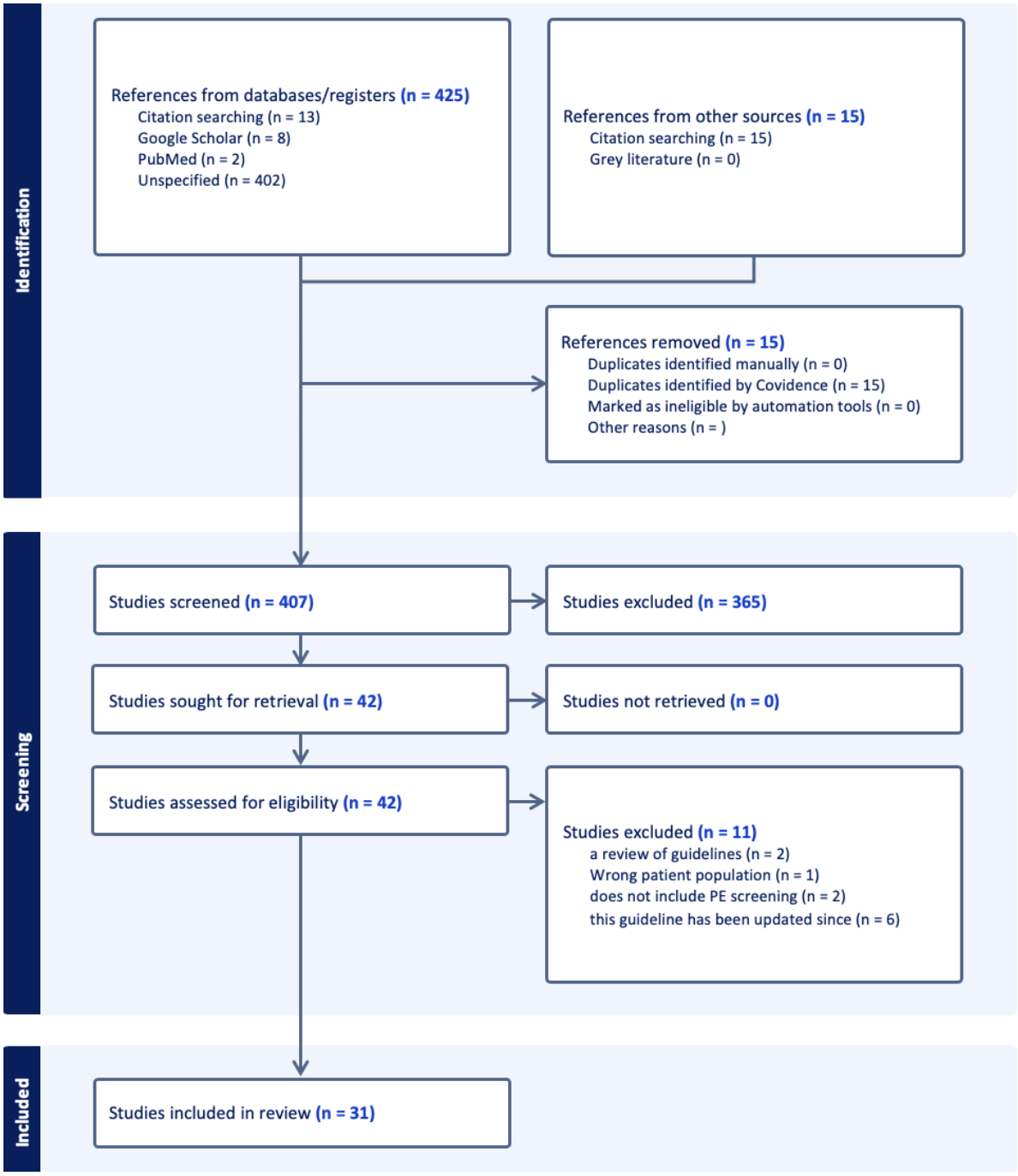


Figure 2.1: Covidence Flowchart representing the literature search results

Screening Policy amongst International Societies/Organisations

1. World Health Organisation (WHO)

Screening method

WHO released their guideline on '*Antiplatelet agents for the prevention of pre-eclampsia'* in 2021[129], which superseded the previous recommendations on antiplatelet agents in the 2011 guideline on "Prevention and treatment of pre-eclampsia and eclampsia"[130]. The 2021 guideline considers women at high risk of developing PE if they have at least one high-risk factor, and at moderate risk if they have two or more moderate-risk factors (table 2.1).

High Risk Factors	Moderate Risk Factors
Diabetes	Primiparity
Chronic or gestational hypertension	Family history of PE
Renal disease	Age greater than 40 years
Autoimmune disease	Multiple pregnancy
Positive uterine artery Doppler	
Previous history of PE	
Previous fetal or neonatal death associated with PE	

Table 2.1. PE screening as per WHO

The authors do recommend that the list is adapted or complemented based on the local epidemiology of PE, but have not proposed any further guidance on this. Furthermore, they have not specified what is meant by positive UtA doppler and which trimester this applies to.

Aspirin prophylaxis

Aspirin at a dose of 75 mg per day, or the nearest dose available, is recommended in women who are at high or at moderate risk of developing PE. The Guideline

Development Committee (GDC) recommended that women commence aspirin from 12 weeks of gestation, which is when antenatal care is ideally started. If this is not possible, then LDA should be commenced preferably before 16 weeks or at any time point antenatal care is started at, even if this is later than 20 weeks. Their recommendation applies to women who develop gestational hypertension during their current pregnancy. The GDC considers that there is not enough evidence to advise on the ideal timing for discontinuation of aspirin and suggest that this should be decided based on the local practice.

Aspirin safety profile

The CPG considers that there a potentially small increased risk of PPH and neuro-axial haemorrhage. The GDC states that, in some settings, the use of regional anaesthesia (epidural/spinal) may be precluded for women on LDA around the time of birth.

Additional preventative measures

WHO also recommends calcium supplementation (1.5-2gr oral elemental calcium) in women with low dietary intake (< 1gr/day) as stated in a separate CPG “Calcium supplementation during pregnancy for the prevention of pre-eclampsia” [131]. The recommendation targets populations with low dietary calcium intake, particularly those in geographical areas where calcium-rich foods are scarce. According to WHO, calcium intake at the population level can be estimated through methods such as dietary surveys, which may involve 24-hour recalls, food frequency questionnaires, or food weighing. The organisation has found no clear evidence on the timing of initiation

of calcium supplementation and suggests the option of commencing this at the first antenatal care contact, in order to improve compliance.

WHO advises against commencing calcium pre-pregnancy to reduce the risk of PE [132]. Additional preventative measures such as salt restriction, bed rest, vitamin C/D/E are only discussed in the 2011 CPG and recommended against [130].

2. International Society for the Study of Hypertension in Pregnancy (ISSHP)

Screening method

The ISSHP published the '*The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice'* in 2018 [133] and updated their recommendation in 2022 [134]. The Society supports first trimester combined screening for PE when this can be integrated into the local health system. The Society accepts that as a minimum, women should be screened by their risk factors. Women are considered at high risk if they have at least one clinical high-risk factor or two moderate risk factors (table 2.2).

High Risk Factors	Moderate Risk Factors
Previous PE	Advanced maternal age
Chronic hypertension	Family history of PE
Pre-gestational diabetes	Short duration of sexual relationship (< 6 months) prior to the pregnancy
APLS or SLE	Primiparity
BMI>30	Primipaternity or interpregnancy interval of more than 5 years
Chronic kidney disease	Connective Tissue disorders

Table 2.2: PE screening as per ISSHP

Aspirin prophylaxis

The Society recommends that high-risk women receive 150mg/day of LDA to be taken at night, if screened by the combined approach and 100-162mg/day, if screened by risk factors alone. No further specification for this range is given. This should be commenced ideally before 16 weeks and discontinued by 36 weeks of gestation.

Aspirin safety profile

No potential risks associated with aspirin use are discussed in the guideline.

Additional preventative measures

ISSHP advises on calcium supplementation (at least 500mg/d) for women with low dietary intake (<900mg/d). However, the Society acknowledges that there is no standardised method for assessing calcium intake among individual women.

Exercise in pregnancy is also recommended as means to reduce the risk for PE, unless there are contraindications.

The use of low-molecular weight heparin (LMWH), vitamins C/E, folic acid are not recommended as preventative measures for PE.

3. European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension

Screening method

The ESH CPG is endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA), and was published in 2023[135]. The Society recommends screening women based on their risk factors in the first trimester and,

similar to the WHO, considers women to be at high risk in the presence of a high risk factor and at moderate risk if they have more than one moderate risk factors (Table 2.3). ESH acknowledges that several biomarkers have been tested for the prediction of PE in the first trimester either separately or in combination with clinical characteristics. However, the Society considers that more studies are required to refine the role of these tests.

High Risk Factors	Moderate Risk Factors
Chronic hypertension	Nulliparity
Chronic kidney disease	Advanced maternal age (≥40)
Type1 or 2 diabetes	Multi-fetal pregnancy
Autoimmune disease	BMI ≥ 35 kg/m2 at first visit
Previous history of HDP	Pregnancy interval > 10 years
ART in the current pregnancy	Family history of PE

Table 2.3: PE screening as per ESH

Aspirin prophylaxis

The Society recommends that women at moderate or high risk of PE should be advised to take 100-150mg of aspirin at bedtime from week 11-14, and preferably before week 16, up until week 36.

Aspirin safety profile

No risks associated with LDA use in pregnancy are discussed in the CPG.

Additional preventative measures

Calcium supplementation of at least 1gr/day may be considered for women with low calcium intake (<600 mg/day). However, the criteria for the later have not been specified in the guideline. ESH also recommends lifestyle interventions such as aerobic exercise, unless contraindicated. A limited salt intake diet is considered reasonable but not specifically advised as a preventative measure.

4. International Federation of Gynaecology and Obstetrics (FIGO)

Screening method

'The International Federation of Gynecology and Obstetrics initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention' was released in 2019 [136]. FIGO supports screening for preterm PE by combining maternal risk factors with MAP, UtA PI and PlGF as per the FMF algorithm. The federation adapts their recommendation for the low/middle-income countries and recommends variations of the combined test depending on the resources available. As a minimum, baseline screening should be maternal risk factors and MAP. The risk factors taken into consideration are included in table 2.4.

Aspirin prophylaxis

FIGO advises that women who are considered high risk should be commenced on approximately 150mg of aspirin daily at 11-14^{+6} weeks of pregnancy and discontinued at 36 weeks or earlier as in the case of PE development or preterm labour.

Risk Factors
Advanced maternal age

Nulliparity
Previous history of PE
Short and long interpregnancy interval
Use of ART
Family history of PE
Obesity
Afro-Caribbean and South Asian racial origin
Co-morbid medical conditions (hyperglycemia in pregnancy, pre-existing chronic hypertension, renal disease and autoimmune diseases, such as SLE and APLS)

Table 2.4: Maternal Risk Factors incorporated in the Combined PE screening as per FIGO

Aspirin safety profile

Potential risks associated with aspirin are not discussed in the CPG.

Additional preventative measures

Women with low calcium intake (<800mg/d) are advised to receive calcium replacement (≤ 1g elemental calcium/d) or calcium supplementation (1.5-2g elemental calcium/d) to reduce the risk of preterm PE. The parameters for identifying low calcium intake are not specified. FIGO advises against the use of heparin, vitamins C/E, magnesium, folate, metformin and statin for the sole purpose of PE prevention.

5. International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG)

Screening method

The Society released the *'ISUOG Practice Guidelines: Role of ultrasound in screening for and follow-up of pre-eclampsia'* in 2019 [137]. They advise on a 'global assessment of risk' to include personal risk profile (age, ethnicity, parity, smoking, medical and obstetric history and conception method), metabolic risk profile (BMI and history of diabetes), cardiovascular risk profile (existing cardiovascular conditions and measurement of MAP) and placental risk profile (UtA PI and maternal serum biomarkers). ISUOG supports the FMF- combined screening strategy for PE prediction (maternal factors, MAP, UtA PI and PlGF).

Aspirin prophylaxis

The Society accepts that there is convincing evidence that LDA can significantly decrease the risk for development of preterm PE, when commenced at the time of first-trimester screening. ISUOG quotes the APRE randomised controlled trial and the reduction in the risk of PE by administering 150mg/d of aspirin at bedtime from 11-14 weeks to 36 weeks' gestation.

Aspirin safety profile

The potential of LDA-associated risks in pregnancy is not discussed in the guideline.

Additional preventative measures

No other pharmacological or non-pharmacological interventions are discussed in the guideline.

Screening Policy in Europe

1. National Institute for Health and Care Excellence (NICE), UK

Screening method

NICE recommends screening based on maternal factors that are considered either high-risk or moderate-risk for the development of PE[2]. Many hospitals in the UK follow this guidance, which was published in 2019. Women with at least one high-risk or two moderate-risk factors are considered at high risk for developing PE (Table 2.5).

High Risk Factors	Moderate Risk Factors
Hypertension in previous pregnancy	First pregnancy
Chronic kidney disease	Maternal age of ≥40
Autoimmune disease (SLE, APLS)	Interpregnancy interval > 10 years
Type 1 or type 2 diabetes	Family history of PE
Chronic hypertension	BMI of 35 kg/m^2 or more at first visit
	Multi-fetal pregnancy

Table 2.5: PE screening as per NICE

Aspirin prophylaxis

High-risk women are advised to commence low dose aspirin (75-150mg/d) from the 12th gestational week until birth.

Aspirin safety profile

The NICE CPG does not include any information on the safety profile of aspirin prophylaxis.

Additional preventative measures

Pharmacological agents other than LDA including nitric oxide donors, progesterone, diuretics, magnesium, folic acid, vitamin C/E and LMWH are not recommended for preventing hypertensive disorders in pregnancy (HDP). Non-pharmacological supplements such as fish/algal oils or garlic supplementation and salt restriction are not advised. The advice in NICE guidance on exercise and work as a preventative measure is the same as for all healthy pregnant women. All pregnant women are advised to aim for at least 150 minutes of moderate intensity activity every week.

The Royal College of Obstetricians and Gynaecologists (RCOG) endorses the NICE guideline and have released a patient information leaflet in order to support women who are at high risk [138]. **The Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and the Clinical Strategy and Programmes Division, Health Service Executive** published the Hypertension in Pregnancy guideline in 2016[139], which recommended the same screening method as NICE (table 2.5) and advised 75mg/d LDA from 12 weeks until the birth of the baby. They also advised to increase calcium intake either through diet or supplementation (1-2.5g/d) if the daily maternal calcium intake is low (<1g/d). However, this guideline is currently archived and a new CPG was commissioned in 2022, which has not yet been published.

2. French Society of Hypertension (Société Française d' HyperTension Artérielle, SFHTA)

Screening method

SFHTA published an expert consensus statement on Hypertension and Pregnancy in 2017 [140]. Women are considered to be at a higher risk for developing PE if they have any of the following risk factors included in table 2.6

Risk Factors
Previous history of PE
Chronic hypertension
Obesity
Pre-existing diabetes mellitus
Chronic kidney disease
ART
Abnormal UtA dopplers in the first trimester
Abnormal first trimester serum biomarkers

Table 2.6: PE screening as per SFHTA

However, the Society considered that the only cohort of women to benefit from administration of aspirin are those with previous history of PE.

Aspirin prophylaxis

The recommended dose of aspirin is 75-160mg per day, in the evening; this should be commenced prior to 20 weeks, optimally prior to the end of the first trimester and can be discontinued after 35 weeks of gestation.

Aspirin safety profile

LDA-associated risks are not discussed.

Additional preventative measures

SFHTA does not recommend LMWH, NO, antioxidants (Vitamin C and E) or physical exercise for the purpose of reducing the risk of PE.

3. French College of Obstetricians and Gynaecologists (Collège National des Gynécologues et Obstétriciens Français, CNGOF)

Screening method

CNGOF published the “Pre-eclampsia: recommendations for clinical practice” in 2024 [141]. The French College accepts that certain risk factors place women at a higher risk for developing PE and that these women would benefit from adapting the modality of care, antenatal monitoring, timing and place for delivery.

Risk Factors
Previous PE
Chronic hypertension
Pre-existing diabetes
Maternal age <17 or >40
Multi-fetal pregnancies
BMI > 30 kg/m^2
APLS
SLE
Primiparity
ART
Chronic nephropathy
History of retroplacental haematoma
Family history of PE
Non-Hispanic black ethnicity
Intrauterine death

Table 2.7: Maternal risk factors used for prediction of PE by the CNGOG

The use of LDA is only recommended in women with previous history of placental vascular pathology. Even though there is no further clarification on placental vascular pathology, the College discusses the outcomes of studies showing the reduction in the risk of PE from LDA administration in women with previous history of HDP, FGR and SB.

Aspirin prophylaxis

The recommended dose of LDA is 100-160mg/day to be taken in the evening or at bedtime, but there is no specification on which women would be more suitable for the higher or lower dose. LDA should be commenced prior to 20 weeks and ideally prior to 16 weeks of gestation and should be discontinued at 36 weeks.

Aspirin safety profile

CNGOF discusses risks of aspirin administration in pregnancy such as PPH and presents two studies with conflicting results [105, 115]. Furthermore, the CPG discusses the unknown potential clinical effect on the newborn; aspirin is known to cross the placental barrier and has been shown to exert antiplatelet effects in both the fetus and newborn [142].

Additional preventative measures

Other preventative measures such as calcium supplementation, LMWH, vitamin D, sodium restriction are not recommended. In contrast, physical activity in pregnancy is recommended to reduce the risk of PE and placental vascular pathologies.

4. Lithuanian Society of Obstetricians and Gynaecologists (Lietuvos Akušerių Ginekologų Draugija, LAGD)

Screening method

LAGD and the Lithuanian Union of Midwives recommend screening women based on their risk factors in their guideline on “Hypertension Induced by Pregnancy” [143]. The risk factor classification is almost identical to that used by NICE (table 2.5) with the addition of teenage pregnancy as a moderate risk factor. Similar to most other guidelines, women are considered at high risk if they have a minimum of one high risk or two moderate risk factors.

Aspirin prophylaxis

The daily administration of 75 mg of aspirin for women at high risk of PE is proposed from 12 weeks of gestation or at least, prior to 20 weeks up until delivery. The management of women at moderate risk is at the clinician’s discretion, depending on the individual circumstances, but there is no further guidance on this matter.

Aspirin safety profile

Risks associated with aspirin use are not discussed.

Additional preventative measures

Calcium is recommended in women who have low calcium diets (1.2-2g/d). However, the guideline does not provide further details on what defines low calcium intake.

Additionally rest, exercise and walks are also recommended to reduce the risk of PE. In contrast, other pharmacological measures such as the use of supplements including fish oil, vitamins C or E, folic acid, magnesium supplements, garlic products,

progesterone, LMWH and non-pharmacological measures such as salt restriction are not recommended.

5. German Society of Gynecology and Obstetrics (DGGG), Austrian Society of Gynecology and Obstetrics (OEGGG) and Swiss Society of Gynecology and Obstetrics (SGGG)

Screening method

The *"Guidelines for Hypertensive Disorders in Pregnancy: Diagnosis and therapy"* was published jointly by the German, Austrian and Swiss Societies in 2019 [144]. Their joint committee recommended screening for PE in the first trimester using the FMF-algorithm, combining the a-priori risk (age, medical history/risk factors, BMI, ethnicity) with biophysical factors (MoM-adjusted UtA PI and MAP) and biochemical factors (e.g. Papp-A, PlGF).

Aspirin prophylaxis

They endorse the administration of low dose aspirin (150mg/day) to be commenced in early pregnancy (before 16 weeks) in high-risk women. In Germany, LDA can be stopped at 34-36 weeks. The latter has not been specified for Switzerland and Austria.

Aspirin safety profile

LDA- associated risks are not discussed in the CPG.

Additional preventative measures

The Societies do not recommend the use of calcium, LMWH, magnesium, selenium, vitamin D or fish oil for the prevention of PE. The CPG also mentions the benefit of physical rest and exercise on maternal and fetal weight development and on the reduction of disease-related complications.

6. Society of Obstetrics and Gynaecology in Romania (SOGR)

Screening method

The Romanian Society recommends screening in the first trimester based on maternal risk factors applying the same criteria as per the ESH guideline (table 2.3). [144] However, the Society supports the option of using combined algorithms if available, incorporating data from patient's history (nulliparity and history of PE), BMI, MAP, UtA PI, Papp-A and PlGF.

Aspirin prophylaxis

The Society advises on the administration of LDA (150mg) daily to be commenced in the first trimester (prior to 16 weeks from amenorrhea) until 36 weeks.

Aspirin safety profile

Aspirin-associated risks are not included in the guideline.

Additional preventative measures

The OEGGG and SGGG societies do not recommend the use of heparin, antioxidants (Vitamin C/E) or salt restriction for the prevention of PE.

7. Dutch Association for Obstetrics and Gynaecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie, NVOG)

Screening method

NVOG developed the CPG on *"Hypertensive Disorders in Pregnancy"* under the Federation of Medical Specialists in 2022 [145]. They recommend screening based on maternal risk factors, the latter being based on recommendations from NICE [5], United States Preventive Services Task Force (USPSTF) [146] and the High Risk of Pre-eclampsia Identification Group [28].

LDA is recommended in women with any high-risk factors and considered in women with two or more moderate risk factors.

High Risk Factors	Moderate Risk Factors
Previous history of PE	Maternal age ≥40
Chronic kidney disease	Pregnancy interval > 10 years
Autoimmune disease (SLE, APLS)	Family history of PE
Type 1 or type 2 diabetes	BMI ≥35 kg/m^2
Nulliparity	Multiple pregnancy
	Pregnancy with egg donation
	Previous child with low birthweight or previous perinatal death

Table 2.8: PE screening as per NVOG

Aspirin prophylaxis

The dose recommended is 80-150mg/day in the evening from 12 weeks and preferably prior to 16 weeks up until 36 weeks or time of delivery should this occur earlier. There is no further clarification regarding the choice of the lower or upper range of LDA.

Aspirin safety profile

The NVOG accepts that LDA (up to 150mg) is not associated with an increased risk of placental abruption, postpartum haemorrhage or fetal intracranial haemorrhage, but expresses its concern that the risks of higher doses have not been extensively investigated. The criteria for dosage selection are not specified in the CPG.

Additional preventative measures

The Association also recommends calcium supplementation (1g/day) for women at high risk of developing PE, to be commenced prior to 16 weeks provided that the total intake of calcium does not exceed 2.5gr. Women with low calcium intake are also recommended 1g/day of calcium to be commenced from 20 weeks of gestation. Women are encouraged to assess their calcium intake by completing an online self-test (https://www.voedingscentrum.nl/nl/gezond-eten-met-de-schijf-van-vijf.aspx).

The Association advises against salt restriction for PE prevention.

8. Norwegian Gynaecological Association (Norsk Gynekologisk Forening, NGF)

Screening method

NGF developed the *"Hypertensive pregnancy complications and eclampsia"* guideline in 2020 and amended part of the guideline in 2022 [147]. They recommend screening based on risk factors as per NICE [5]. Even though they acknowledge the improved PE prediction with the use of the FMF combined screening algorithm, this does not constitute part of the public health screening.

Aspirin prophylaxis

They recommend daily use of 75mg of LDA from 12 weeks in the evening and definitely prior to 16 weeks up until delivery or 150mg if taken until 36 weeks.

Aspirin safety profile

The NGF also mentions that there is conflicting data in terms of LDA administration and bleeding as a risk.

Additional preventative measures

The Association recommends LMWH prophylaxis as means to reduce the PE risk for women with APLS or SLE. They also suggest that women with low calcium intake (<600mg/day) take calcium supplementation to a total dose of 1.2-2.5g/day. However, there is no information on how to assess calcium intake.

NGF also advises on exercise during pregnancy to reduce weight gain and incidence of HDP complications.

9. Danish Society for Obstetrics and Gynaecology (DSOG)

Screening method

The Danish Society for Obstetrics and Gynaecology (DSOG) published the "Acetylsalicylic acid in pregnancy" in 2022 [148]. The risk of PE is predicted based on maternal risk factors (table 2.9) with women who have ≥1 high risk factor(s) or ≥2 moderate risk factors being considered at high risk for the development of PE.

High risk factors	Moderate risk factors
Previous severe or early onset PE	Previous PE without severe disease
Essential Hypertension	BMI>30

Pre-gestational diabetes	Nulliparity
SLE/APLS	Maternal age over 40
Chronic kidney disease	Pregnancy interval > 10 years
ART with egg donation	

Table 2.9: PE screening as per DSOG

Aspirin prophylaxis

The Society recommends that high-risk women commence LDA ideally from 10-12 weeks and discontinue at 37 weeks or 5-7 days prior to delivery if less than 37/40. LDA should preferably be started prior to 16 weeks, but some effect is expected even if started prior to 20 weeks. The recommended dose is 150mg/day to be taken at night. The Society recently published a separate guideline on “Hypertension and Pre-eclampsia” in 2024 [149] and stated that the FMF combined screening approach was being planned for implementation, but this has not been included in the superseding guideline.

Aspirin safety profile

The guideline discusses all possible side effects associated with aspirin that include bleeding tendency, abdominal pain, gastro-oesophageal reflux, heartburn, flatulence, gastrointestinal bleeding, nausea, melena, vomiting, angioedema, urticaria, headache, insomnia, bronchospasm, anaphylactic reaction, hearing loss, gastro-intestinal perforation, cerebral haemorrhage, vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and renal function impairment. The CPG aknowledges LDA-associated risks during pregnancy such as an increased risk of intrapartum bleeding and of PPH in vaginal deliveries, without an increase in the risk of placental abruption.

Additional preventative measures

Additional recommendations on PE prevention are made. More specifically, high risk groups are advised to consume 500mls of milk daily or receive calcium supplements (500mg/day) if they have a low intake (<600mg/day). There is otherwise no further specification on assessing dietary calcium intake.

Furthermore, regular exercise, three times a week for approximately 50 minutes, is proposed as a preventative measure. The Society does not recommend vitamin D, metformin or statins for the prevention of PE.

10. Finnish Medical Association and Finnish Gynaecological Society (FIN)

Screening method

The Finnish Medical Association together with the Finnish Gynaecological Society developed a CPG on *"High Blood Pressure during pregnancy and pre-eclampsia"* in 2024[150]. They recommend screening based on maternal risk factors. They do include information on the combined screening approach, but recommend against it on the basis of conflicting evidence on applicability to the Finnish health system, the cost-effectiveness of screening, the high false positive results with the combined approach in addition to the overall low incidence of PE in the country (2%). Women are considered to be at high risk if they have either at least one of the with high-risk criteria or at least two of the moderate risk criteria as detailed in table 2.10.

High risk criteria	Moderate risk criteria
Chronic HTN	First pregnancy
SLE or phospholipid antibodies positive	Maternal age ≥ 40
Chronic kidney disease	BMI > 30kg/m^2
Type 1 or 2 diabetes	Family history of PE
Previous history of PE	ART with egg donation
Previous FGR caused by placental insufficiency; abnormal U.A or UtA blood flow or severe ischaemic changes in placenta	Interval between pregnancies of over 10 years
Fetal death secondary to severe placental ischaemia	Multiple pregnancy
	Papp-A level <0.4 MoM

Table 2.10: PE screening as per FIN

Aspirin prophylaxis

The aspirin dose recommended is 100mg/day (in the evening) to be commenced at 12^{+0} (-16^{+0}) and discontinued at 36^{+0} weeks or sooner if there are signs of preterm delivery.

Aspirin safety profile

The LDA- associated risks discussed include the risk of gastrointestinal bleeding and the risk of bleeding during childbirth, whilst mentioning the presence of conflicting research data around this.

Additional preventative measures

Calcium supplementation (≥ 1g/day) is recommended as a preventative measure only for women with low dietary intake. The guideline recognizes that, on average, the Finnish population meets the necessary calcium intake but advises that individuals adhere to the "Health and Welfare Institution's" guidelines for calcium supplementation based on personal dietary assessments (https://thl.fi/aiheet/elintavat-ja-ravitsemus).

Specifically, it recommends a supplement of 500 mg for those whose diets include few milk products or calcium-fortified foods, and 1,000 mg for those whose diets completely lack milk products or foods fortified with calcium.

Regular physical activity and exercise during pregnancy are also recommended as preventative measures.

Salt restriction and Vitamin B6/ C/ D/ E supplements are not recommended for the purpose of PE prevention.

11. Swedish Society of Obstetrics and Gynaecology (Svensk Forening For Obstetrik & Gynekolog, SFOG)

Screening method

SFOG [151] released a CPG on "Preeclampsia" in 2019 and appear to endorse screening in the first trimester based on maternal factors as per other international guidelines including those by ISSHP (table 2.2), NICE (table 2.5), DSOG (table 2.9), the American College of Obstetricians and Gynecologists (table 2.12), Society of Obstetricians and Gynecologists in Canada (table 2.13) and Queensland Health of the State (table 2.16). SFOG considers the scientific basis for the predictive capacity of maternal risk factors as moderately strong. However, the Society considers evidence behind the measurement of MAP and of biomarkers whether as a stand-alone test or in combined prediction models as insufficient. Women are considered at high risk in the presence of ≥1 high risk factor(s) or ≥2 moderate risk factors.

Aspirin prophylaxis

The Society recommends 75-100mg/day of LDA to women at high risk to be commenced no later than 12 weeks up until 36 weeks of gestation, with the exception

of women with SLE or APLS who are advised to commence LDA even prior to their pregnancy. They also remark that commencing LDA after 16/40 may still be effective.

High risk factors	Moderate risk factors
APLS / SLE	Nulliparity
Previous history of PE or eclampsia	Family history of PE
Previous hypertension in pregnancy with: -delivery prior to 34/40 or -FGR or intrauterine death or -abruption	Obesity (BMI >30kg/m^2),
Type1 or 2 diabetes	Maternal age >40
Chronic kidney disease	Family history of PE
Proteinuria at booking appointment	Interval between pregnancies > 4 years
Chronic Hypertension	Systolic BP>130 or Diastolic BP>80mmHg at booking
IVF with egg donation	African origin
	Obstructive sleep apnoea

Table 2.11: PE screening as per SFOG

Aspirin safety profile

Risks associated with aspirin use in pregnancy are not discussed.

Additional preventative measures

Prophylaxis using calcium, vitamin B6/ C/ D/ E, folic acid, fish oil, omega 3, l-arginine, magnesium or zinc supplementation, bed rest or salt reduction is not advised routinely. In contrast, daily physical activity of at least 30 minutes and a reduction in stress are proposed as preventative measures.

12. Polish Society of Hypertension, Polish Cardiac Society and Polish Society of Gynecologists and Obstetricians (POL)

Screening method

Three Polish medical societies created a joined position statement on *"Management of Hypertension in Pregnancy: prevention, diagnosis, treatment and long-term prognosis"* in 2019 [152]. The Joint Committee advises on screening for preterm PE by using the FMF combined algorithm and PlGF as biomarker of choice. A risk cut-off of 1:150 is proposed. If the combined screening is not feasible, then the Committee advises using risk factors to screen women and these are the same as the NICE CPG (table 2.5).

Aspirin prophylaxis

Women are recommended to receive 100-150mg of LDA daily up to 35 weeks of gestation.

Aspirin safety profile

Potential risks associated with aspirin are not discussed.

Additional preventative measures

There is no discussion regarding additional preventative measures with the exception of exercise.

Screening Policy in North America

1. American College of Obstetricians and Gynaecologists (ACOG) & Society for Maternal-Fetal Medicine (SMFM)

Screening method

In 2022, the ACOG together with the SMFM [153] released a Practice Advisory on "Low-dose Aspirin Use for Prevention of Preeclampsia and Related Morbidity and Mortality" to include the USPSTF guideline criteria for prediction of PE, which was published in the year prior [154]. According to this latest guidance, aspirin should be recommended in women with one or more high risk factors and it should be considered in women with more than one moderate risk factors (table 2.12).

High risk factors	Moderate risk factors
History of PE, especially when accompanied by an adverse outcome	Nulliparity
Multifetal gestation	Obesity (BMI greater than 30)
Chronic Hypertension	Family history of PE (mother or sister)
Type 1 or 2 diabetes	Black race
Renal disease	Lower income
Autoimmune disease (SLE, APLS)	Age 35 years or older
	Personal history factors (e.g. low birthweight or SGA, previous adverse pregnancy outcome, more than a 10-year pregnancy interval)
	IVF

Table 2.12: PE screening as per ACOG & SMFM

Aspirin prophylaxis

LDA (81mg daily) should be commenced between 12 and 28 weeks of gestation (ideally prior to 16 weeks) and continued until delivery [153]. The CPG also states that universal administration of LDA may be reasonable for those institutions and practices where the majority of patients may be at high or moderate risk for developing PE.

Aspirin safety profile

Information on aspirin safety is not included in the Practice Advisory or the ACOG Practice Bulletin number 222 on '*Gestational Hypertension and Preeclampsia'* .

Additional preventative measures

ACOG discusses preventative measures other than aspirin in their Practice Bulletin 222[155]. The College does not support the use of calcium, vitamins C/D/E, fish oil, folic acid or garlic supplementation for the prevention of PE. It also considers the use of sildenafil, statins and metformin as investigational and not to be recommended outside the context of clinical trials. ACOG advises against non-pharmacological preventative measures such as salt restriction and bed rest.

2. American Heart Association (AHA)

Screening method

AHA published the *"Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement from the American Heart Association"* in 2021[156]. The Association advises on screening based on risk factors as per the ACOG Committee Opinion No 743, which was published in 2018 [157]. However, in addition to the 'high' and 'moderate' risk factors used to advise on LDA prophylaxis,

the authors have identified 'other' risk factors. These include: white coat HTN, BMI>25kg/m^2, insulin resistance >75th centile, gestational diabetes, hyperthyroidism, hydatidiform mole, fetal trisomy 13, new paternity, pregnancy interval of more than 4 years and migraines.

Aspirin prophylaxis

The recommended dose of aspirin is 81-150 mg/day to be commenced at 12-16 weeks of pregnancy, without further clarification on criteria for choosing the dosage. The gestational cut-off for LDA to be discontinued is not included in the guidance.

Aspirin safety profile

Risks associated with LDA are not mentioned in this guidance.

Additional preventative measures

As an additional preventative measure, diet and exercise are also recommended to all women as means to reduce the risk of HDP and its associated complications. The use of pravastatin and metformin are discussed, but not advised outside an experimental setting.

3. Society of Obstetricians and Gynaecologists in Canada (SOGC)

Screening method

The SOGC released *"Guideline No 426: Hypertensive Disorders in Pregnancy: Diagnosis, Prediction, Prevention and Management in 2022"* [158] and have updated their recommendation on first trimester screening for PE to include the FMF combined algorithm. The latter involves clinical markers in addition to UtA PI and PlGF, if the

resources are available. Alternatively, women should be screened based on their risk factors as a minimum.

High risk factors	Moderate risk factors
Prior PE	Prior placental abruption
BMI >30	Prior stillbirth
chronic Hypertension	Prior FGR
Pre-gestational diabetes mellitus	Nulliparity
Chronic kidney disease	Multifetal pregnancy
SLE/APLS	
ART	

Table 2.13: PE screening as per SOGC

Women screened based on their clinical risk factors are considered high risk for development of PE in the presence of 1 or more high risk factor(s) or 2 or more moderate risk factors (table 2.13).

Aspirin prophylaxis

High risk women are advised to receive LDA at a dose of 81mg or 162 mg/day (at bedtime) preferably prior to 16 weeks up until 36 weeks. The SOGC does not provide any clarification over which women would benefit from the higher or lower dose.

Aspirin safety profile

According to the SOGC's guidance, LDA has not been associated with an increased risk of miscarriage but there may be adverse effects such as vaginal spotting, ante- and post- partum haemorrhage and postpartum haematoma. There is also a small absolute increase in the risk of neonatal intracranial haemorrhage following vaginal birth.

Additional preventative measures

High-risk women with low calcium intake (<900 mg/day) are recommended to commence calcium supplementation of at least 500mg/day. The CPG does not provide any guidance on calcium intake assessment for women. The length of calcium administration is not specified. Women with BMI over 25 are also advised to adjust their diet in order to reduce their calorie intake and select low glycaemic index food. Exercise is recommended to all pregnant women as a preventative measure for PE. The Society advises against salt restriction and the use of heparin, thiazide/thiazide-like diuretics, folic acid, vitamin C/ D/ E or omega-3 fatty acids for PE prevention.

4. Trinidad and Tobago (T&T)

Screening method

The Directorate of Women's Health of Trinidad and Tobago's Ministry of Health published a "Hypertension in Pregnancy" clinical guideline in 2018 [159]. The risk factors included in table 2.14 are considered in PE screening. The guideline considers women, "especially those with multiple risk factors" are at risk of developing PE.

Aspirin prophylaxis

They recommend that the aforementioned women should be commenced on LDA from 12 weeks until 37 weeks. It is unclear whether women with only one risk factor should also receive LDA or how the target user should come to the treatment decision. It is also not specified what the gestational cut-off is for commencing aspirin. The recommended dosage of LDA is 81mg/day.

Risk Factors
Type 1 or 2 diabetes

Previous PE or eclampsia
Family history of PE
Connective tissue disorder
APLS
Essential Hypertension
Obesity
Advanced maternal age
Nulliparity

Table 2.14: PE screening as per T&T

Aspirin safety profile

Risks associated with aspirin use are not discussed in the guideline.

Additional preventative measures

The Directorate recommends calcium supplementation of 1.2g/day in high-risk women and in those with low calcium intake. Assessment of calcium intake is not discussed. No other preventative pharmacological or non-pharmacological measures are discussed.

Screening Policy in South America

1. Department of Arterial Hypertension of the Brazilian Society of Cardiology, Brazilian Society of Hypertension, Brazilian Society of Nephrology (BRA)

Screening method

According to the "Brazilian guidelines of Hypertension- 2020" [160], women should receive combined screening for PE in the first trimester. The guideline prompts the target users to utilise the FMF's risk calculator for PE screening. The Brazilian Joint Committee acknowledges that there are additional promising biochemical parameters for the combined approach such as serum soluble endoglin, PlGF, sFlt-1 and sFlt-1/PlGF ratio that are not available in clinical practice.

If screening by maternal factors alone, then women are considered at high risk if they have any one of the high-risk factors or any two or more of the moderate risk factors detailed in table 2.15.

High Risk Factors	Moderate Risk Factors
Previous history of PE with adverse outcome	Nulliparity
Multifetal gestation	Obesity (BMI ≥30 kg/m^2)
Type 1 or type 2 diabetes	Family history of PE (mother/sister)
Renal Disease	Maternal age ≥35
Autoimmune disease (SLE, APLS)	Poor obstetric history (low BW/SGA or preterm birth)
	Pregnancy interval > 10 years

Table 2.15 PE screening as per BRA

Aspirin prophylaxis

LDA (75-150mg) is recommended for women at high risk of developing PE and should be considered for women at intermediate risk. LDA should be commenced prior to 16 weeks of gestation.

Aspirin safety profile

There is no discussion around the safety profile of aspirin.

Additional preventative measures

The only additional preventative measures recommended is calcium at a dose of 1-2gr/day in women with low calcium intake (<600mg/day) and at intermediate to high risk of developing PE. The CPG does not clarify how to assess calcium intake.

2. Argentinian Society of Cardiology, Argentinian Federation of Cardiology and Argentinian Arterial Hypertension Society (ARG)

Screening method

The *"Argentinian Consensus of Arterial Hypertension"* was formed by the aforementioned Societies and was published in 2018 [161]. According to the joint Committee, women are considered at high risk if they have any of the risk factors included in table 2.16.

There is no further clarification regarding certain risk factors and, most particularly, the definition of advanced maternal age and of autoimmune disease or on the interval between pregnancies for this to be considered long.

Risk Factors
Nulliparous
Advanced maternal age
Long interval between pregnancies
Low socio-economic level
Previous PE
Chronic Hypertension
Pre-gestational diabetes
Nephropathies
Twin pregnancy
Autoimmune disease
Obesity
APLS

Table 2.16 PE screening as per ARG

Aspirin prophylaxis

The CPG recommends LDA at a dose of 100mg/day for high-risk patients.

Aspirin safety profile

Risks associated with LDA use are not included in the guideline.

Additional preventative measures

Alternative or additional preventative measures for PE are not discussed.

Screening Policy in Africa

1. Tunisian Society of Cardiology (TUN)

Screening method

The *"Clinical Practice Guide. Management of Arterial Hypertension in Tunisian adults"* was created through the collaboration between the National Authority for Health Evaluation and Accreditation, the Tunisian Society of Cardiology and Cardiovascular Surgery and the National Fund of Health Insurance in 2021 [162]. Women are categorised as high risk with the same criteria as the ones used per NICE (table 2.5).

Aspirin prophylaxis

It is recommended that women at high or moderate risk, should receive LDA 100-150mg/day from 12 to 36 weeks of gestation. There is no further specification around the dose.

Aspirin safety profile

Potential risks associated with LDA use in pregnancy are not included in the guideline.

Additional preventative measures

There are no other preventative pharmacological or non-pharmacological measures discussed.

Screening Policy in Asia

1. Japanese Society of Obstetrics and Gynaecology (JSOG) and Japanese Association of Obstetricians and Gynaecologists (JAOG)

Screening method

The JSOG and JAOG joint committees published the Guideline for Obstetrical Practice in Japan in 2023 [163] consider women with previous history of PE as being at high-risk for recurrence of PE.

Aspirin prophylaxis

They recommend that these high-risk women should be advised to commence low dose aspirin to prevent recurrence, but do not include any further information on the aspirin dosage or the length of administration.

Aspirin safety profile

There is no discussion on potential risks associated with LDA use.

Additional preventative measures

Other preventative measures are not discussed in the guidance.

In contrast, the **Japanese Society for the Study of Hypertension in Pregnancy** endorses the recommendations set forth by the ISSHP's 2022 CPG[133], which primarily advocates for combined screening for PE if feasible, and risk factor- based screening if not (table 2.2).

2. Chinese Society of Cardiovascular Disease (CHN)

Screening method

The former Disease Control Bureau of National Health and Family Planning Commission of China, the Chinese Hypertension League, in partnership with Chinese Society of Cardiovascular Disease of the Chinese Medical Association, Hypertension Branch of the China International Exchange and Promotion Association for Medical and Healthcare, Hypertension Branch of the Chinese Geriatrics Society and the Hypertension Committee of Chinese Medical Doctor Association organised a committee for revising the Chinese Guidelines for the Management of Hypertension [164]. The risk factors and classification match the NICE guidance. According to the Joint Committee's 2018 "Guidelines for prevention and treatment for hypertension", women are considered at high risk as per NICE guidance (table 2.5).

Aspirin prophylaxis

High-risk women should be prescribed LDA from the 12th week of gestation until one week before delivery. The LDA dosage is not included.

Aspirin safety profile

No information is given on the risks associated with aspirin use in pregnancy.

Additional preventative measures

Preventative measures other than LDA are not discussed.

3. Task Force of the Hypertension Committee–- Guideline Committee of the Taiwan Society of Cardiology–- Taiwan Hypertension Society (TWN)

Screening method

The Taiwanese Joint Committee released a guideline for the Management of Hypertension in 2022 [165]. The Taiwanese CPG does not specify the risk factors they would recommend clinicians to screen for, but instead quotes the criteria applied by the ISSHP[133] (table 2.2) the ESH[166] (table 2.3) and the ACOG[155] (table 2.12) guidelines.

Aspirin prophylaxis

The recommended dosage of aspirin is 75mg-162mg per day for women at moderate or high risk from the 12th week of gestation until the 36th-37th week. Treatment should be initiated ideally before 16 weeks of gestation, but definitely before 20 weeks. Even though the criteria for the choice of dosage is not specified, it is suggested that the use of uterine artery doppler can select women who may benefit from 150mg/d of LDA.

Aspirin safety profile

LDA-associated risks are not discussed in the CPG.

Additional preventative measures

Calcium (1.2-2.5g/d) is also recommended if low intake (<600mg/d) or if the intake cannot be assessed/predicted. No specification is provided on assessment of calcium intake. LMWH is not recommended as means of PE prevention. Other preventative, non-pharmacological measures discussed and advised on is exercise to maintain health and appropriate weight in pregnancy. Salt restriction is not advised.

4. Pakistan Hypertension League (PHL)

Screening method

PHL released the "3rd National Hypertension Guideline for the Prevention, Detection, Evaluation and Management of Hypertension in 2018 [167]. They recommend screening based on maternal risk factors in the same approach as per the NICE guidance (table 2.5).

Aspirin prophylaxis

The authors recommend low dose aspirin of 75mg/day from 12 weeks until delivery unless women are at increased risk of suffering gastrointestinal haemorrhage.

Aspirin safety profile

There is no discussion on LDA safety profile in pregnancy.

Additional preventative measures

No other preventative pharmacological or non-pharmacological measures are discussed.

Screening Policy in Australia and New Zealand

1.Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)

Screening method

SOMANZ updated their guideline for the management of hypertensive disorders of pregnancy in 2023 [98]. Screening by maternal risk factors is strongly recommended by the Society and the combined screening approach is conditionally recommended depending on whether local access to validated resources and expertise is available. The combined PE screening approach is currently not widely available in Australia and New Zealand and it is not subsidised by Medicare in Australia. However, it can be accessed at some public and private healthcare facilities.

The criteria used to categorise women at high or moderate risk are the same as per NICE with the addition of systolic BP > 130mmHg or diastolic BP > 80mmHg as a moderate risk factor.

Aspirin prophylaxis

SOMANZ advise on the use of aspirin at a dose of 150mg/day (at bedtime) to be commenced prior to 16 weeks of pregnancy. They recommend cessation of LDA between 34 weeks of gestation and delivery with the exact timing to be individualised based on clinical judgment and shared decision making with the patient.

Aspirin safety profile

SOMANZ found evidence of no increased risk of complications such as abruption, vaginal bleeding, ante-/post-partum haemorrhage and neonatal intracerebral haemorrhage compared to placebo.

Additional preventative measures

They also advise on the use of supplemental high-dose calcium (≥1gr/day) in women with low dietary calcium intake (<1 gr/day). A clear dietary calcium intake assessment guide is included in the guideline. The Society acknowledges that the appropriate timing to commence or cease calcium is unclear and warrants further studies.

SOMANZ advises against omega-3 long chain polyunsaturated fatty acids (LCPUFA), oral garlic supplementation, Vitamin C, D or E supplementation, oral magnesium, progesterone, statins, LMWH, nitric oxide, metformin, proton pump inhibitors (PPI) and clopidogrel for PE prevention.

SOMANZ's CPG emphasizes the importance of exercise in pregnancy as a non-pharmacological, preventative measure. It recommends 2.5-5hrs of moderate intensity activities per week in the form of aerobic, stretching or muscle resistance exercises. Salt restriction, on the other hand, is not recommended.

2. Queensland Health of the State (QLD)

Screening method

Queensland Health of the State published a CPG on "Hypertension and Pregnancy" endorsed by the Clinical Guidelines Steering Committee and Statewide Maternity and Neonatal Clinical Network of Queensland [168] in 2021. The risk factors taken into account for PE screening are included in table 2.17. However, the advice on first trimester screening is slightly conflicting. The authors suggest that combined PE

screening may detect a higher risk of PE; healthcare professionals should in addition to maternal risk factors and MAP, consider additional testing if clinically indicated such as UtA PI, Papp-A, PLGF. According to the CPG, *"routine use in all women is not recommended",* in keeping with the guidance on Screening in Early Pregnancy for Adverse Perinatal Outcomes from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZOG) that was published in 2015 [169]. However, the latter CPG does recommend routine screening of all pregnant women by assessing their PE risk factors.

Risk Factors
Previous history of PE
Adolescent pregnancy
SLE
Chronic Hypertension
ART
Pre-existing diabetes
Family history of PE
Multiple pregnancy
BMI>30
APLS
Nulliparity
Pre-existing kidney disease
Maternal congenital heart defects
Maternal anxiety or depression
Inter-pregnancy interval of more than 10 years
Gestational trophoblastic disease
Fetal triploidy and fetal aneuploidy

Table 2.17 PE screening as per QLD

Aspirin prophylaxis

The LDA dosage recommended is 100-150mg per day (preferably to be taken at night). This should ideally be commenced prior to 16 weeks of gestation and discontinued at 36 weeks depending on the individualised risk. There is no recommendation on how to amend this in an individualised manner.

Aspirin safety profile

Information on the safety profile of aspirin in pregnancy is not included.

Additional preventative measures

The CPG also advises on calcium supplementation of 1.2-2.5 g/day for women with deficient calcium intake of less than 600mg/day. Assessment of calcium intake is not provided and the length of administration is not specified.

The use of heparin is only recommended in women with APLS. Magnesium, zinc and antioxidant supplementation is not advised. Non-pharmacological measures such as bed rest and dietary salt restriction are also not supported.

3. Te Whatu Ora- Health New Zealand (NZL)

Screening method

The Ministry of Health of New Zealand published the “Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand” in 2022 [170]. They recommend screening for PE by identifying individualised risk factors as early as possible in pregnancy or at booking. Women with any major risk factors or ≥2 non-major risk factors are considered at high risk for developing PE (table 2.18).

Major Risk Factors	Non-major risk factors
APLS/SLE	Nulliparity
Previous history of PE or HELLP	Multi-fetal pregnancy
ART with oocyte donation	Family history of PE including father of baby being born of PE-complicated pregnancy
Renal disease	Genetic ancestry if African, Indian, Māori, Pacific people
Chronic HTN	Change in partner
Pre-existing type 2 diabetes	BMI ≥35 kg/m^2
Family history of PE in mother or sibling	Maternal age ≥40
	Inter-pregnancy interval of over 10 years
	ART (other than egg donation)
	Diastolic BP≥80mmHg at booking

Table 2.18 PE screening as per NZL

Aspirin prophylaxis

LDA at a 100mg/day dose (to be taken at bedtime) is recommended for women with a major risk factor for developing PE. This should be commenced between 12 and 16 weeks and discontinued at approximately 36 weeks of gestation.

Aspirin safety profile

There is no discussion on the risks associated with aspirin use in pregnancy.

Additional preventative measures

Calcium supplementation is recommended for women with low dietary intake. However, there is no guidance on assessment of calcium intake. The calcium dosage recommended is 1.5-2 g/day from booking until birth.

Optimal weight gain and physical activity are also recommended. More specifically, the Ministry of Health recommends at least 2.5 hours of moderate physical activity on a weekly basis depending on the maternal age, intensity and capacity. Multivitamins,

vitamin C/E, fish oil and magnesium supplements are not recommended nor is salt restriction and bed rest.

A summary of the results

A total of 31 CPGs or statements, published between 2017 and 2024, were included in this systematic review.

Screening Approach

Out of the 31 guidelines, only 8 (25%) currently recommend the combined screening approach compared to 23 CPGs (75%) that recommend screening based on risk factors alone. Of those that recommend the combined screening approach, 4 made provisions so that when this method is not feasible due to lack of resources/skills, women can, at least, be screened by risk factors.

Figure 2.2 is a world map of the recommended screening approach, excluding the international societies/ organisations (i.e. WHO, ISSHP, ESH, FIGO and ISUOG), which could not be allocated to a specific country. Table 2.19 includes all the CPGs together with their primary PE screening recommendation and year of publication.

In the risk factor approach, previous history of PE is included in all the guidelines. Pregestational diabetes, chronic HTN, chronic kidney disease and autoimmune disease are included in 27 out of the 28 CPGs (93%). Nulliparity and obesity are included in 25 (89%), advanced maternal age in 23 (82%) and multifetal pregnancy in 21 (75%). Table 2.20 summarises the risk factors considered predictive of PE. The Taiwanese and the Swedish guidelines are not included in this table due to their slightly conflicting screening; they quote the criteria applied by multiple different guidelines. The FIGO and ISUOG guidelines are also not included as they support the combined screening approach only.

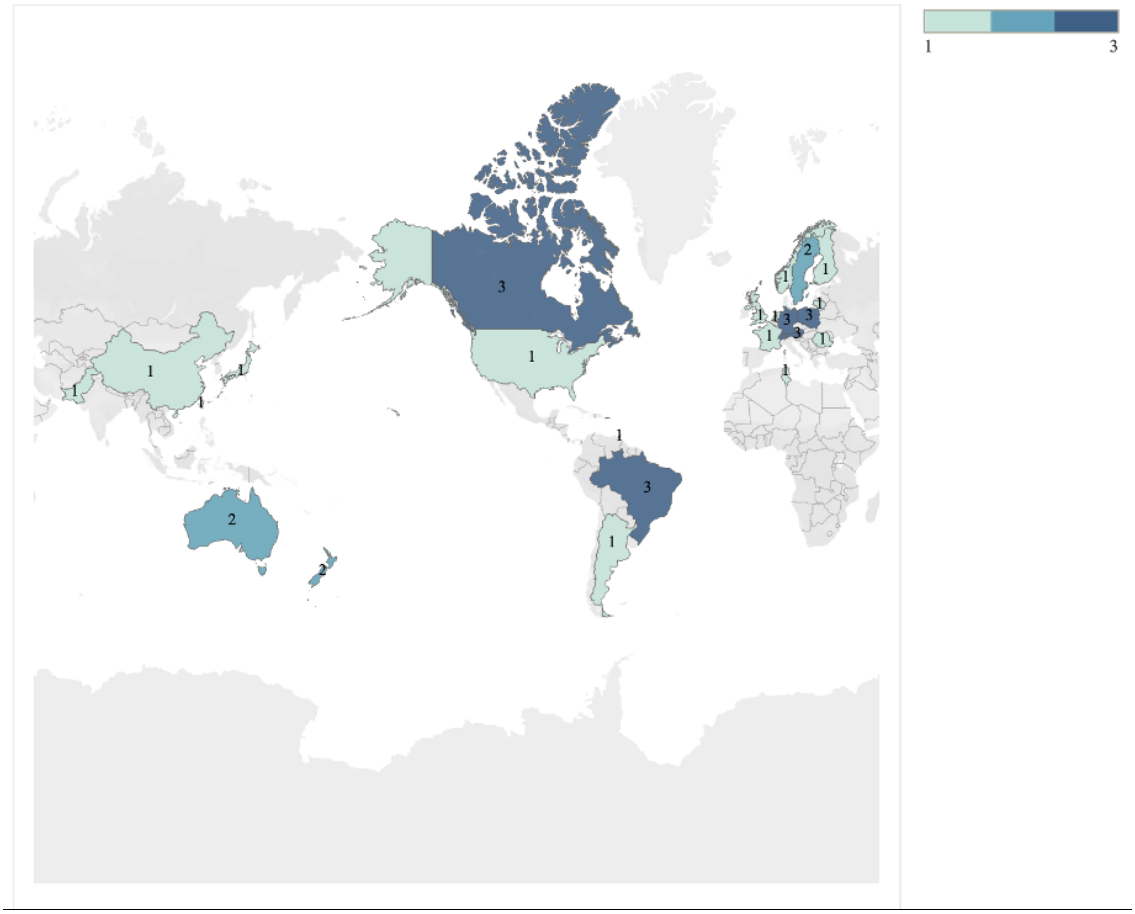


Figure 2.2: World map with recommended method of first trimester screening for PE (based on published clinical guidelines) *

1: Risk factor- Screening,

2. Either Risk factor- or Combined- screening,

3. Combined Screening

**International and National Guidelines* were not included*

International and National Guidelines	Preferred method of PE screening recommended	Year of Publication

International		
WHO	Risk factors	2019
ISSHP	Combined screening	2022
ESC	Risk factors	2023
FIGO	Combined screening	2019
ISUOG	Combined screening	2019
Europe		
NICE	Risk factors	2019
FSH	Risk factors	2017
CNGOF	Risk factors	2023
LAGD	Risk factors	2020
DGGG-OEGGG-SGGG	Combined screening	2019
SOGR	Risk factors	2019
NVOG	Risk factors	2022
NGF	Risk factors	2020
DSOG	Risk factors	2022
FIN	Risk factors	2024
SFOG	Risk factors	2019
POL	Combined screening	2019
North America		
ACOG	Risk factors	2021
AHA	Risk factors	2021
SOGC	Combined screening	2022
T&T	Risk factors	2018
South America		
BRA	Combined screening	2020
ARG	Risk factors	2018
Africa		
TUN	Risk factors	2021
Asia		
JSOG-JAOG	Risk factors	2023
CHN	Risk factors	2018
TWN	Risk factors	2022
PHL	Risk factors	2018
Australia		
SOMANZ	Combined screening	2024

QLD	Risk factors	2021
NZL	Risk factors	2022

Table 2.19: Screening policy recommended across the CPGs and year of publication

	WHO	ISSHP	ESC	NICE	SFHTA	CNGOF	LAGD	SOGR	NVOG	NGF	DSOG	FIN	SFOG	POL	ACOG	AHA	SOGC	T&T	BRA	ARG	TUN	JSOG	CHN	PHL	SOMANZ	QLD	NZL
Medical Background																											
Diabetes	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√
Essential HTN	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√
Chronic Kidney Disease	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√
Autoimmune Disease; SLE/APLS	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√
Connective tissue disorders		√																√								√	
Maternal congenital heart defect																										√	
Obstructive sleep apnoea													√														
Hyperthyroidism																√											
Migraine																√											
White coat syndrome																√											
Insulin resistance (>75th centile)																√											
Recovered Acute Kidney Injury																√											
Previous pregnancy complications																											
Previous history of PIH/PE	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Previous low BW/SGA						√			√			√			√	√	√		√									
Previous adverse outcome	√					√			√			√	√		√	√	√											
Previous PTB																			√								
Personal characteristics																											
Nulliparity	√	√	√	√		√	√	√	√	√		√	√	√	√	√	√	√	√		√		√	√	√	√	√
Advanced maternal age	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√		√	√	√	√		√	√	√		
Teenage pregnancy						√	√																			√	
Obesity		√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√
Race/ Ethnicity						√							√		√	√											√
Low socio-economic status															√	√				√							
Current pregnancy																											
ART			√					√	√		√	√	√		√	√	√									√	√
Multifetal pregnancy	√		√	√		√	√	√	√	√		√		√	√	√	√		√	√	√		√	√	√		√

Gestational diabetes																√												
Raised UtA PI	√																											
Abnormal Papp-A or bHCG												√																
sBP>130 or dBP>80mmHg													√													√		√
Gestational trophoblastic disease																√											√	
Fetal triploidy /aneuploidy																√											√	
History of retroplacental haematoma						√																						
Increased Pregnancy Interval		√	√	√			√	√	√	√	√	√	√	√	√	√			√	√	√		√	√	√			√
Short sexual relationship (<6m)		√																										
Family history																												
PE	√	√	√	√		√	√	√	√	√		√	√	√	√	√		√	√		√		√	√	√	√	√
Early onset cardiovascular disease																												
Paternal risk factors																												
Father being born from PE-complicated pregnancy																												√
New partner		√														√												√

Table 2.20: Risk factors for PE prediction per CPG

Preventative Approach

-Aspirin

All guidelines support the use of LDA in high-risk women (Table 2.21). The dose is not specified in two guidelines (6%). Six of the guidelines (19%) recommend a dose of 75mg or 81mg, two (6%) a dose of 100mg, five a dose of 150mg (16%) and fifteen (48%) recommend a range between 75/81 mg to 150/162mg. Amongst the latter, only three provide some specification over the dose selection. In particular, FIGO recommends 100mg for women who weigh less than 40 kg and 150mg for women over this weight cut-off. ISSHP recommends 150 mg for women who are screened by the combined algorithm and supports 100-162mg dose for those screened by risk factors, without further specifying the dose for these women. The Taiwanese guideline supports the administration of 150mg for women who are also screened by UtA dopplers and 75-162mg for all the other high-risk women, again with no further clarification on this range. Of note, the dose recommended also depends on the regional availability from the pharmaceutical companies.

Almost all CPGs recommend that LDA is commenced prior to 16 weeks. JSOG does not specify the gestational age and WHO advises high-risk women to commence aspirin whenever they first receive antenatal care, even if this occurs after 20/40. As regards the different recommendations around cessation of LDA, seventeen CPGs (55%) recommend discontinuation by 36/40, five at delivery (16%), two at 35/40 (6%), two at 37/40 (6%), one at 1 week prior to delivery (1%) and four do not specify (13%).

The safety profile of aspirin in pregnancy in not discussed in 22 guidelines (74%).

Clinical Practice Guideline	*LDA dose recommended (mg)*	*Ideal gestational age range to commence LDA*	*Gestational age to discontinue LDA*	*LDA- associated risks discussed (Y/N)*
International				
WHO	75	12/40	To be decided based on local practice	Y
ISSHP	100-162[@]	11-14/40	36/40	N
ESC	100-150	11-14/40	36/40	N
FIGO	100-150[^]	11-14+6/40	36/40	N
ISUOG	150	11-14/40	36/40	N
Europe				
NICE	75-150	12/40	Until delivery	N
SFHTA	75-160	<14/40	35/40	N
CNGOF	100-160	<16/40	36/40	Y
LAGD	75	12/40	Until delivery	N
DGGG-OEGGG-SGGG	150	11-14/40	34- 36/40	N
SOGR	150	11-14/40	36/40	N
NVOG	80-150	12/40	36/40	Y
NGF	75	12/40	36/40	Y
DSOG	150	10-12/40	37/40	Y
FIN	100	12/40	36/40	N
SFOG	75-100	12/40	36/40	N
POL	100-150	11-13+6/40	35/40	N

North America				
ACOG	81	12-16/40	Until delivery	N
AHA	81-150	12-16/40	N.S	N
SOGC	81-162	<16/40	36/40	Y
T&T	81	12/40	37/40	N
South America				
BRA	75-150	<16/40	N.S	N
ARG	100	N.S	N.S	N
Africa				
TUN	100-150	12/40	36/40	N
Asia				
JSOG-JAOG	N.S	N.S	N.S	N
CHN	N.S	12/40	Until 1 week prior to delivery	N
TWN	75-162∞	12/40	36-37/40	N
PHL	75	12/40	Until delivery	N
Australia				
SOMANZ	150	<16/40	34/40–- Delivery	Y
QLD	100-150	<16/40	36/40	N
NZL	100	12-16/40	36/40	N

Table 2.21: Recommendations on aspirin dose, length of administration and LDA-associated risks
@: 150mg if screened with combined algorithm, 100-162mg if screened by risk factors
^ : 100kg if patient weighs <40kg, ~150mg if patient weighs ≥40kg
∞: 150mg if raised UtA PI
N.S: Not Specified

-Calcium

Calcium is the only additional pharmacological intervention discussed and recommended in almost half of guidelines (15 out of 31, 48%). Amongst the guidelines that advise on calcium, in the vast majority, the recommendation only applies to women who have a low dietary intake of calcium (14 out of 15, 93%) (Table 2.22). The definition of low dietary intake ranges from <600mg to <1gr per day.

The dose of calcium recommended also ranges between 500 mg to 2.5 gr/day amongst the CPGs. Only 3 out of the 15 CPGs provide a recommendation on when to commence or discontinue calcium.

-Non-pharmacological measures

Non-pharmacological preventative measures are discussed in 12 guidelines (39%) (Table 2.22). Out of these, they all recommend exercise as means to reduce the risk of PE and the risk of PE-associated complications. Diet is only recommended in 2 of these (6% of all CPGs) and bed rest in 1 (3%).

Additional preventative recommendations	*Pharmacological interventions recommended (other than LDA)*	*Non-pharmacological measures recommended*
International		
WHO	Calcium*	N
ISSHP	Calcium*	Exercise
ESC	Calcium*	N
FIGO	Calcium*	N
ISUOG	N	N
Europe		
NICE	N	N
SFHTA	N	N
CNGOF	N	Exercise
LAGD	Calcium*	Rest Exercise
DGGG-OEGGG-SGGG	N	N
SOGR	N	N
NVOG	Calcium*	N
NGF	Calcium*	Exercise
DSOG	Calcium*	Exercise
FIN	Calcium*	Exercise
SFOG	N	Exercise
POL	N	Exercise
North America		
ACOG	N	N
AHA	N	Diet Exercise

SOGC	Calcium*	Diet Exercise
T&T	Calcium	N
South America		
BRA	Calcium*	N
ARG	N	N
Africa		
TUN	N	N
Asia		
JSOG-JAOG	N	N
CHN	N	N
TWN	Calcium*	N
PHL	N	N
Australia		
SOMANZ	Calcium*	Exercise
QLD	Calcium*	N
NZL	Calcium*	Exercise

Table 2.22: Recommendations on pharmacological and non-pharmacological preventative measures other than LDA
** : Calcium recommended in high risk women with low oral intake of calcium*
N: Nil

Quality Assessment

The domain score thresholds for quality assessment were selected by the appraisers (CA & DN). Quality was assessed as high, moderate and low with overall domain scores of ≥70%, 50-69% and ≤49%, respectively. The AGREE-II and AGREE-REX assessments for each domain are summarised in tables 2.23 and 2.24, respectively.

Based on the AGREE-II assessment, the guidelines published by SOMANZ and SOGC were considered of high quality. All other guidelines (29 out of 31, 94%) were assessed as moderate quality.

The AGREE-REX tool identified SOMANZ, ISSHP and ISUOG recommendations on first trimester screening for PE of high quality. Even though the latter two scored 67% in one of the items, their overall score was above 70%. The majority of the guidelines (22 out of 31, 71%) were of moderate quality and six of low quality (19%).

All CPGs included in our systematic review can be recommended for clinical application. However, four of the guidelines would be recommended with modifications.

AGREE II for each CPG	Domain 1 Scope and Purpose	Domain 2 Stakeholder Involvement	Domain 3 Rigour of Development	Domain 4 Clarity of Presentation	Domain 5 Applicability	Domain 6 Editorial Independence	Overall	Recommend for use (Y/YwM/N)
International								
WHO	83%	44%	63%	56%	63%	67%	58%	Y
ISSHP	56%	61%	60%	56%	54%	67%	67%	Y
ESC	89%	67%	73%	83%	67%	67%	83%	Y
FIGO	72%	67%	60%	83%	63%	50%	67%	Y
ISUOG	78%	67%	69%	72%	58%	50%	67%	Y
Europe								
NICE	83%	72%	69%	78%	71%	58%	67%	Y
SFHTA	78%	72%	69%	72%	54%	67%	67%	Y
CNGOF	78%	72%	69%	72%	54%	67%	67%	Y
LAGD	67%	56%	54%	72%	50%	33%	50%	Y
DGGG-OEGGG-SGGG	78%	67%	63%	72%	50%	42%	67%	Y
SOGR	72%	61%	52%	72%	54%	50%	50%	Y
NVOG	61%	56%	52%	56%	54%	58%	50%	Y
NGF	61%	56%	50%	50%	54%	42%	50%	Y
DSOG	67%	61%	69%	67%	50%	83%	67%	Y
FIN	67%	61%	60%	61%	46%	58%	67%	Y
SFOG	50%	50%	44%	44%	54%	42%	50%	YwM
POL	78%	67%	60%	72%	50%	50%	83%	Y
North America								
ACOG	83%	72%	65%	78%	50%	58%	67%	Y
AHA	72%	56%	58%	61%	50%	67%	50%	Y
SOGC	83%	83%	83%	83%	79%	83%	83%	Y

T&T	67%	56%	46%	67%	50%	33%	50%	YwM
South America								
BRA	72%	56%	58%	61%	50%	67%	67%	Y
ARG	89%	67%	71%	83%	67%	67%	67%	YwM
Africa								
TUN	78%	67%	69%	61%	58%	83%	83%	Y
Asia								
JSOG-JAOG	72%	56%	50%	50%	50%	67%	50%	Y
CHN	72%	56%	58%	61%	50%	67%	67%	Y
TWN	67%	56%	56%	61%	46%	58%	50%	YwM
PHL	72%	56%	50%	50%	50%	67%	50%	Y
Australasia								
SOMANZ	100%	100%	100%	78%	100%	92%	100%	Y
QLD	78%	72%	69%	67%	54%	67%	58%	Y
NZL	78%	72%	73%	67%	63%	67%	67%	Y

Table 2.23: AGREE-II assessment
Y: Yes
YwM: Yes with modifications
N: No
Highlighted in -green: high quality, -yellow: moderate quality

AGREE-REX	Item 1 Eviden-ce	Item 2 Applica-bility to Target Users	Item 3 Applica-bility to Patients/ Populations	Item 4 Values & Preferences of Target Users	Item 5 Values & Preferences of Patients/ Populations	Item 6 Values & Preferences of Policy/ Decision makers/	Item 7 Values & Preferences of Guideline Developers	Item 8 Purpose	Item 9 Local application and adoption	Recommend for use in the appropriate context (Y/YwM/N)
International										
WHO	67%	67%	50%	50%	33%	67%	67%	67%	83%	Y
ISSHP	83%	83%	83%	83%	83%	83%	67%	100%	83%	Y
ESC	67%	67%	50%	50%	50%	67%	67%	83%	83%	Y
FIGO	100%	100%	83%	83%	50%	83%	83%	83%	83%	Y
ISUOG	100%	100%	100%	83%	67%	83%	83%	100%	100%	Y
Europe										
NICE	50%	67%	67%	67%	50%	50%	67%	83%	83%	Y
SFHTA	67%	50%	50%	50%	50%	50%	67%	83%	83%	Y
CNGOF	83%	67%	83%	67%	33%	67%	67%	83%	83%	Y
LAGD	33%	50%	67%	33%	33%	33%	33%	83%	50%	Y
DGGG-OEGGG-SGGG	67%	67%	67%	67%	50%	67%	50%	67%	50%	Y
SOGR	67%	67%	67%	50%	33%	67%	67%	83%	83%	Y
NVOG	67%	67%	67%	67%	33%	33%	50%	83%	83%	Y
NGF	50%	67%	50%	67%	33%	33%	33%	67%	50%	Y
DSOG	67%	67%	67%	33%	33%	33%	33%	83%	67%	Y
FIN	50%	67%	67%	33%	33%	33%	33%	83%	83%	Y
SFOG	50%	50%	50%	50%	33%	50%	50%	67%	67%	YwM
POL	67%	50%	67%	50%	50%	50%	50%	83%	83%	Y
North America										

ACOG	67%	67%	67%	33%	33%	33%	50%	67%	50%	Y
AHA	67%	67%	67%	50%	33%	50%	67%	83%	83%	Y
SOGC	67%	83%	67%	67%	67%	67%	67%	83%	83%	Y
T&T	33%	50%	33%	33%	33%	33%	33%	33%	33%	YwM
South America										
BRA	50%	67%	67%	50%	33%	33%	33%	67%	33%	Y
ARG	33%	50%	50%	33%	33%	33%	33%	67%	50%	YwM
Africa										
TUN	50%	83%	83%	66.7%	33%	67%	67%	67%	67%	Y
Asia										
JSOG-JAOG	33%	33%	33%	33%	33%	33%	33%	33%	33%	N
CHN	33%	33%	33%	33%	33%	33%	33%	33%	33%	Y
TWN	50%	50%	50%	33%	33%	33%	83%	33%	33%	YwM
PHL	33%	50%	50%	50%	33%	33%	33%	67%	67%	Y
Australasia										
SOMANZ	100%	83%	100%	100%	83%	100%	83%	83%	83%	Y
QLD	83%	67%	83%	83%	50%	50%	67%	83%	83%	Y
NZL	67%	67%	67%	67%	67%	67%	67%	83%	83%	Y

Table 2.24: AGREE-REX assessment
Y: Yes
YwM: Yes with modifications
N: No
Highlighted in -green: high quality, -yellow: moderate quality, -orange: low quality

Discussion

Main Findings

Our systematic review included 31 CPGs published from 2017 onwards. We found a gradual, yet limited, increase in the number of CPGs in recent years recommending the FMF - combined screening method. Despite this shift, a significant majority (74%) of guidelines continue to advocate for risk factor-based screening. Our analysis revealed notable variations among the guidelines regarding the definition of maternal risk factors, although all uniformly recognized previous instances of PE and medical comorbidities as significant risk indicators.

Divergences were also evident in the recommended dosage and duration of low-dose aspirin (LDA) as a prophylactic intervention (Table 2.20). Approximately 48% of the CPGs suggest a dosage range between 75/80mg and 150/162mg, with only three guidelines offering specific criteria for selecting an appropriate dose within this range. A notable absence in the majority of guidelines is a discussion on potential risks associated with LDA usage during pregnancy, which could potentially impact maternal adherence to the prophylaxis, thereby affecting its preventative efficacy [171, 172].
The initiation and cessation of aspirin therapy vary across guidelines, which may further complicate the adherence to these recommendations. While all guidelines acknowledge the benefits of aspirin in reducing PE risk, and some highlight its potential in mitigating FGR and PTB, only a quarter explicitly address the potential side effects or complications of aspirin use.

Calcium supplementation is recommended by half of the CPGs for women with a low dietary intake of calcium, reflecting an increased recognition of its preventative role

against PE. However, there is inconsistency in the advised calcium dosage, ranging from 500mg to 2.5g daily, with most guidelines lacking clarity on the timing for starting and stopping calcium supplementation.

Recent years have also seen a growing endorsement of non-pharmacological interventions such as exercise and dietary modifications for PE risk reduction, indicating an evolving approach towards holistic preventive strategies in managing PE. However, these are outside the framework of the current review and cannot be commented further.

The AGREE-II instrument was used as a methodological resource to inform development, reporting and evaluation of each clinical guideline. The AGREE-REX tool was used as an adjunct to AGREE-II for the assessment of the clinical credibility and implementability of the recommendations on first trimester screening for PE.
The vast majority of the guidelines were considered of moderate quality (71% based on AGREE-II and 94% based on AGREE-REX). All guidelines can be recommended for clinical use, but we would recommend four of these with modifications. More specifically, the SFOG and the TWN CPGs both quote multiple other guidelines with different criteria used for risk-stratification of women. We would advise their modification in order to limit confusion amongst clinicians and thus create a more uniform policy. The T&T and the ARG guidelines could be further improved by clarifying the criteria for women to be considered at high risk.

Comparison to other studies

Bazzano et al [173] performed a systematic review on diagnosis, prevention and management of HDP in 2023. Their study included 12 CPGs with guidance on PE

screening, two of which have since been updated. The authors concluded that there was a lack of clear consensus and concordance across international guidelines. Similarly, Di Girolamo et al performed a systematic review on the use of aspirin in pregnancy [174] in 2023. The authors included a total of 16 guidelines; more than half (9) of these were published between 1995 and 2015. Three of the guidelines included have since been updated. The authors considered that there is general agreement in the reported indications for aspirin intake in pregnancy, with prior PE and maternal medical co-morbidity as the major indications for aspirin intake. However, they demonstrated heterogeneity in the recommended dose, gestational age at initiation and discontinuation of therapy among the different CPGs.

Sinkey et al performed a comparison of international guidelines on prevention, diagnosis and management of HDP in 2020 [175]. Information on PE prediction is not included and 6 of the 14 CPGs included have since been updated. The authors identified variations in the international guidelines for HDP regarding the dosage and initiation timing of aspirin. A structured validated tool (i.e., AGREE) for comparison of guideline content and concordance was not utilised, and there was no systematic review process described.

Scott et al published a systematic review of international CPGs for pregnancy hypertension in 2022 [176]. They included 14 CPGs with information on PE screening, 6 of which were published prior to 2016 and a total of 7 of the included guidelines have since been updated. The authors included information on the use of LDA and calcium supplementation as preventative measures without any discussion on other pharmacological or non-pharmacological preventative measures. They observed that

recent trends in recommendations advocate for the integration of multivariable models that incorporate biomarkers and ultrasonography with clinical risk markers in early pregnancy. Similarly to the other reviews, they established that all CPGs recommend aspirin for high-risk women despite persisting discrepancies regarding the specific dosages and the timing for initiating and discontinuing aspirin therapy.

Strengths and Limitations

The review's notable strengths lie in its thorough search strategy and careful methodology, which included evaluation of the CPGs by applying the AGREE II and AGREE-REX instruments. It covered a very wide geographical area with CPGs from all continents.

To our knowledge, this systematic review includes the most CPGs (31) in the area of prevention and prevention of PE and is the most up to date with the current guidance. We included multiple tables to make our results more comprehensive. Our review focussed only on CPGs after 2017 due to change in clinical practice motivated by the publication of the ASPRE randomised clinical trial.

A possible limitation in our study is the fact that we performed our literature search in English, introducing the possibility of selection bias. However, we were able to translate in multiple different languages such as French, Spanish, German and Romanian so that our review can be more inclusive and more representative of the different practices around the world.

Implications for clinical application and future research

Regardless of the method of screening, all national and international guidelines recognise the importance of prediction and prevention of PE. The FMF-combined screening algorithm provides an individualised risk assessment and has been reported to have superior predictive value when compared to screening on risk factors alone. However, the cost-effectiveness of the different screening approaches for PE has been less widely investigated.

Most guidelines support the use of LDA for high-risk women with the exception of the French CPGs. The latter (SFHTA and CNGOF) consider that only women with previous history of PE or placental vascular pathology would benefit from LDA. A recent metanalysis on LDA for the prevention of PE in women with chronic HTN found no evidence of significant change in the risk of superimposed PE or FGR [177]. However, they did find a difference in the risk of PTB. More research is required to find out whether LDA in certain subgroups would be of benefit.

Greater homogeneity amongst the recommendations and a more in-depth discussion of the risks and benefits of interventions could improve the counselling process for our patients in addition to improving aspirin compliance.

Additional research is essential to explore the feasibility of different PE screening approaches across diverse economic environments and healthcare infrastructures. Such studies would provide valuable insights into how effectively these strategies can be implemented globally, taking into account varying resource availabilities and medical practices. Moreover, there is a pressing need to establish more uniform agreement across national and international guidelines in the prediction and

prevention of PE. Achieving consensus would not only streamline clinical practices but also ensure that all pregnant women, regardless of their geographical location, receive optimal care. This concerted effort towards harmonization would significantly enhance the effectiveness of preventive measures and improve health outcomes for mothers and their babies worldwide.

Conclusion

The importance of screening for PE is recognised by all international and national CPGs. The majority of guidelines still advise on screening by risk factors. It is likely that this is influenced by concerns over cost-effectiveness and availability of the combined screening test. All CPGs consider LDA as an effective preventative measure. Following aspirin, supplemental calcium during pregnancy is the second most commonly cited preventative strategy for women considered at high risk of PE. Further research is required to explore feasibility of different screening approaches in different economic environments and healthcare infrastructures.

Chapter 3.

Data Analysis Prior to Implementation of the Combined Pre-eclampsia Screening Approach

One of the greatest challenges and a key objective for this project was to derive the evidence to create a clinical pathway, enabling a new service to be implemented. The first task was to ensure the superiority of the first trimester FMF screening over the NICE screening approach in the population of women receiving their antenatal care at University College London Hospital (UCLH). Our second task was to look at whether there was a requirement to further stratify the antenatal care for our patients in the second trimester by assessing the uterine artery dopplers mid-gestationally. Finally, our third task was to find out whether we could de-escalate care after 36 weeks of gestation if no complications associated with blood pressure or fetal growth had arisen for our screen-positive patients based on the first trimester FMF-combined algorithm.

The clinical pathway for women who did develop pregnancy complications associated with blood pressure or fetal growth was already set up with surveillance and management occurring through the ‘Hypertension in Pregnancy’ clinic and the FGR clinic, respectively with personalised management plans initiated.

3.1 Performance of First Trimester Combined Screening for Preeclampsia

Introduction

The efficacy of combined screening for PE is well-established, with numerous studies demonstrating its superiority in early detection and improved clinical outcomes[3, 7, 105, 171, 176-179]. This method significantly enhances the detection rates of PE compared to traditional screening based solely on maternal risk factors. Our initial objective was to determine whether these results could be replicated within the cohort of women receiving antenatal care at UCLH. Our cohort differed from the cohort in the ASPRE trial particularly in terms of their racial origin (e.g. Caucasian: 68% vs 79%, South Asian: 12.5% vs 4.6%), smoking rates (2% vs 8%) and the use of ART (7.1% vs 3.6%).

Prior to implementing the new screening service, it was crucial to validate the performance of the combined screening approach in our specific clinical context. This validation process entailed a retrospective, comprehensive assessment of screening data. We collected and analyzed maternal characteristics, biophysical measurements such as MAP taken at the booking appointment, and relevant biomarkers such as Papp-A.

By rigorously comparing our findings with established benchmarks from previous studies, we aimed to confirm our hypothesis that the combined screening protocol for our patient population at UCLH was superior to the risk factor screening approach. This thorough evaluation included not only the performance metrics of the screening process but also an analysis of its practical implementation within the existing clinical workflow.

In addition to validating the screening process, we assessed the potential for integrating this approach into routine clinical practice, considering factors such as resource allocation, staff training, and patient compliance. The comprehensive nature of this validation process underscores our commitment to adopting evidence-based practices that enhance patient care and outcomes.

Methods

Population

We performed a retrospective analysis on information collected between March 2019 and December 2022. Data were retrieved from the Ultrasound database (Viewpoint 5) and the Electronic Health Record System (EPIC). We collected data on maternal demographics, medical background, biomarkers (i.e., Papp-A) and MAP. MAP was standardised into MoM values after taking into consideration the maternal and pregnancy characteristics with the assistance of the FMF application on MAP performance (https://www.fetalmedicine.org/research/audit/map). Due to the retrospective nature of the study, the FMF algorithm did not take into consideration UtA PI or PlGF in the first trimester as this information was not available. Patient identifiable information was removed from the data sets for confidentiality purposes.

Definitions

We used the PE definition as set by the ISSHP 2014 guideline [180], which is also supported by NICE [5], i.e., new onset hypertension and the co-existence of one or more of the following new onset conditions including proteinuria, other maternal organ

dysfunction, utero-placental dysfunction including FGR, abnormal umbilical artery waveforms or stillbirth. Maternal organ dysfunction incorporates renal involvement (creatinine ≥90 μmol/lt), liver involvement (alanine aminotransferase or aspartate aminotransferase over 40IU/lt), neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata), haematological complications (thrombocytopenia, disseminated intravascular coagulation or haemolysis. We defined PIH as hypertension in pregnancy that developed after 20 weeks of gestation in the absence of symptoms/signs of PE. An estimated fetal weight or birthweight below the 3rd centile was used for the definition of FGR.

Screening for preeclampsia

Our cohort had already been screened based on the NICE methodology at the time of their booking appointment and advised on LDA accordingly. We retrospectively applied the combined screening for PE by combining their risk factors with MoMs of their first trimester MAP and Papp-A.

We considered women at high risk at a cut off of $\geq$ 1 in 100. Women only had the level of Papp-A measured as a biomarker, if they accepted screening for trisomies 13/18/21. Women with singleton pregnancies who had their first trimester scan with combined screening test for trisomy 13/18/21 and delivered at UCLH were included. We excluded women with confirmed fetal congenital anomalies identified at any point during their antenatal care and women whose pregnancy resulted in a miscarriage. Information was collected on a total of 5957 singleton pregnancy episodes.

Outcomes

Our primary outcome of interest was PE and our secondary outcomes included PIH, SGA, BW centile, EMCS, neonatal admission to NICU or SCBU and the length of admission.

Ethical approval

Ethical approval was not required given that our study was retrospective and did not alter the clinical pathway nor the outcomes for the mother or baby**.**

Statistical Analysis

Statistical analysis was performed with SPSS statistical software (version 29; SPSS Inc.). We used descriptive statistics for maternal demographic interpretation. Performance of screening comparisons were assessed by Area Under the Curve (AUC) Receiver Operating Characteristics (ROC). Categorical data were presented as proportions and compared by using chi-squared analyses. Continuous data were presented as median with interquartile ranges and compared by using Kruskal Wallis analyses with Bonferroni correction.

Results

A total of 5957 pregnancy episodes that met the inclusion criteria were recorded between March 2019 and December 2022.

Based on our cohort, 766 (12.9%) women were deemed high risk using NICE compared to 950 women (15.9%) had they been screened by the combined FMF algorithm (Table 3.1). A total of 391 women screened high risk in both groups. As a result, there were 559 women who would have screened positive based on the FMF algorithm that were missed through the NICE screening. 75% of NICE-screened high risk women were prescribed aspirin.

First trimester Screening	NICE	FMF
High Risk	766 (12.9%)	950 (15.9%)
Low Risk	5191 (87.1%)	5007 (84.1%)

Table 3.1: FMF-screened and NICE-screened high-risk and low-risk cohort

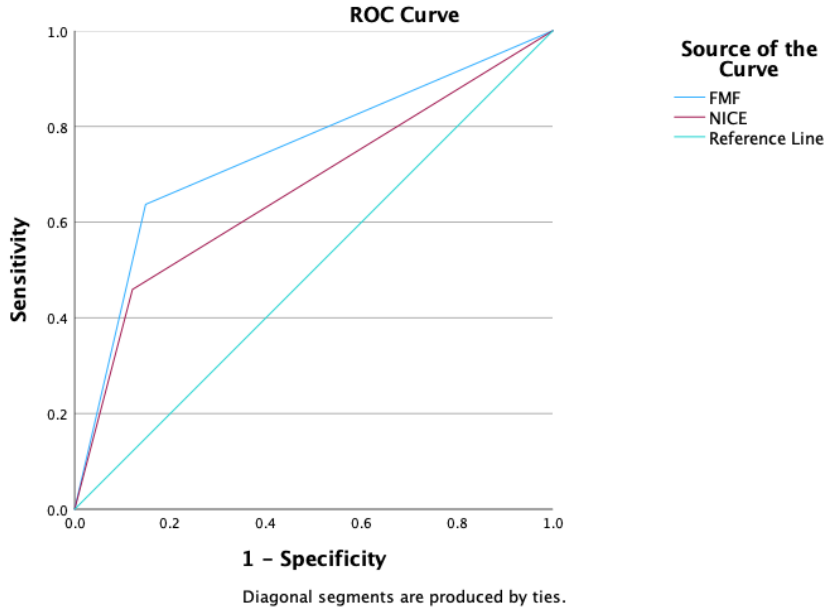
Retrospective application of the FMF algorithm identified 99% of high-risk women who had been prescribed aspirin. This is likely due to clinicians advising on LDA if the Papp-A level was low or if there was a previous complication in pregnancy such as FGR or poor obstetric outcome, thus deviating from the NICE guidance. Aspirin compliance was not assessed in our study. LDA can potentially reduce the risk of preterm PE by 62% but this assumption was not included in our data analysis [105], especially given the fact that more women in the FMF-screened group had been prescribed aspirin. As a consequence, we would, in theory, expect that our results on the efficacy from FMF screening approach would be less significant.

Approximately, half of our cohort of women (54.1%) were nulliparous. The majority were White (68.2%), followed by South Asian (12.5%) and Black (9.6%). Less than 8% of our cohort were older than 40 years. A minority of the pregnancies were achieved by means of assisted reproduction (7.1%). Women with class II or higher obesity (i.e., BMI ≥35) only consisted 4% of our cohort. Less than 2% had a previous

history of PE or medical comorbidities. The maternal characteristics of our population are shown in detail in table 3.2.

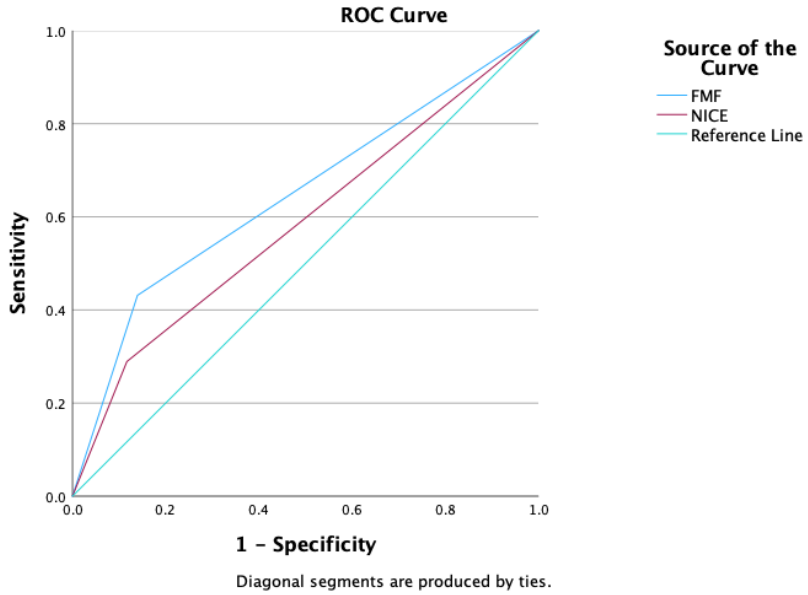
Parameter	Value
Maternal Characteristics	
Nulliparous, n (%)	3223 (54.1%)
Ethnicity, n (%) Black South Asian East Asian Mixed White	 569 (9.6%) 747 (12.5%) 309 (5.2%) 269 (4.5%) 4063 (68.2%)
Age, median (IQR) Age >40, n (%)	33 (IQR: 30-36) 463 (7.8%)
Body Mass Index, median (IQR) BMI >35, n (%)	23 (IQR: 21-27) 239 (4%)
Smoker, n (%)	119 (2%)
Previous PE, n (%)	119 (1.8%)
Family History of PE, n (%)	235 (3.9%)
Artificial Reproductive Technology, n (%)	420 (7.1%)
Chronic Hypertension, n (%)	125 (2.1%)
Diabetes Mellitus (Type 1 or 2), n (%)	59 (1%)
Systemic Lupus Erythematosus, n (%)	20 (0.4%)
Biophysical profile	
Mean Arterial Pressure, median	85 (IQR: 79-90.3)
Biomarkers	
Papp-A MoM, median (IQR) Papp-A≤0.4MoM, n (%)	1.01 (IQR: 0.69-1.43) 297 (5%)

Table 3.2: Baseline characteristics of the study population



PE < 37 weeks	AUC	p-value	95% CI
FMF	.744	.000	0.696 - 0.793
NICE	.669	.000	0.616 - 0.722

Figure 3.1: FMF and NICE ROC for prediction of preterm PE



PE at any gestation	AUC	p-value	95% CI
FMF	.646	.000	0.615 to 0.677
NICE	.586	.000	0.555 to 0.617

Figure 3.2: FMF and NICE ROC for prediction of PE at any gestation

Figure 3.3 shows the Odds Ratio (OR) for PE in the FMF- and NICE-screened women. The OR for preterm PE was 10.1(7.0-14.4) and 6.2 (4.4-8.7) for the FMF and NICE-screened women, respectively. The OR for PE at any gestation was 4.7 (95% CI:3.8-5.8) and 3.1 (95% CI: 2.4-3.9).

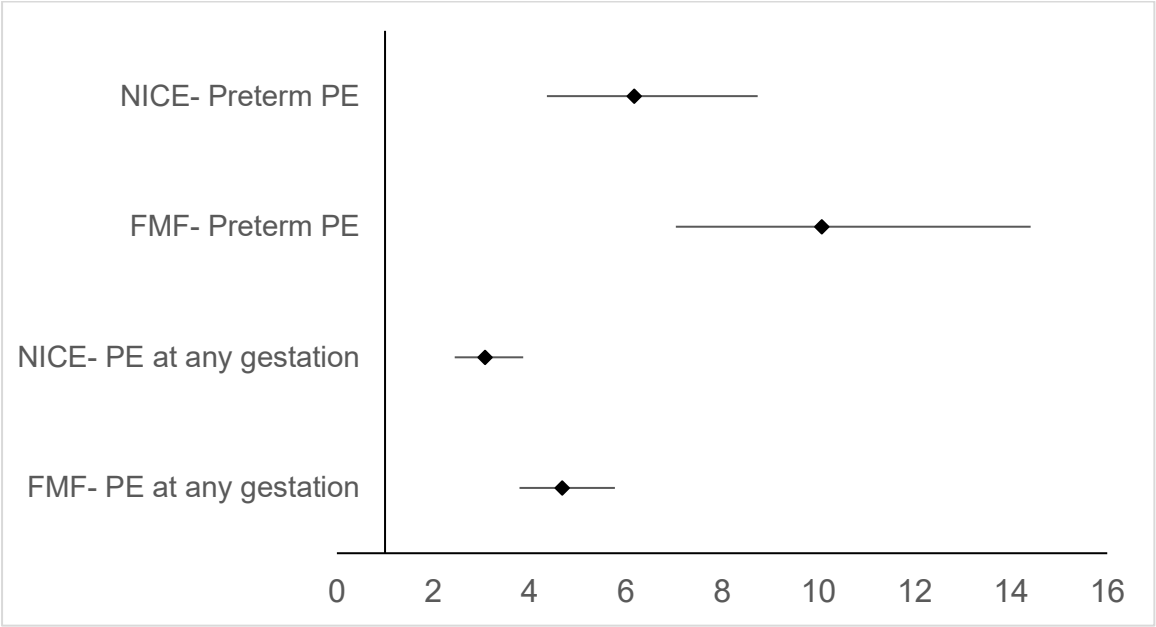


Figure 3.3: Forest plot on risk (Odds Ratio) of PE prior to 37 weeks or at any based on method of screening

Apart from PE, our secondary outcomes included PIH and small for gestational age (SGA) in women based on their NICE and FMF risk stratification.

Risk of PIH

We assessed the risk of PIH after excluding the women with essential HTN. There was a statistically significant correlation between women who screened high risk for preterm PE with either method of screening and the risk of PIH both prior to 37 weeks and at any gestation. The OR for PIH at any gestation was slightly higher for the NICE-screened women at a value of 2.1 (1.7-2.4) compared to the FMF-screened women at 1.7 (95% CI: 1.4-2.0). In contrast, the OR for preterm PIH was slightly higher for the FMF-screened women at 3.2 (95%CI: 2.5-4.1) compared to 2.6 (2.0-3.4) (Figure 3.4).

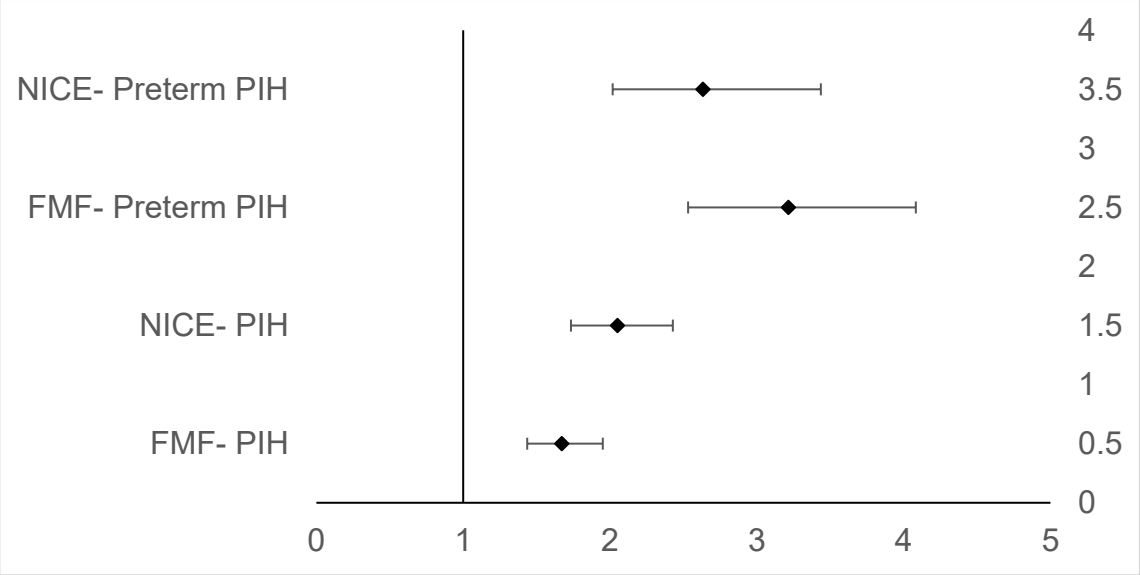


Figure 3.4. Forest plot on risk (Odds Ratio) of PIH in NICE- and in FMF-screened women

We also looked at the AUC for a more direct comparison between the two screening methods. The AUC for preterm PIH was only slightly greater for the FMF with almost no difference for PIH at any gestation (Table 3.4). However, the FMF- screening sensitivity for preterm PIH (Table 3.5) was noticeably higher compared to the NICE screening method but minimally higher for PIH at any gestation.

PIH	Screening Method	Area Under Curve	95% CI	p-value
Prior to 37 weeks	FMF	0.59	0.56-0.63	0.000
	NICE	0.56	0.53-0.59	0.000
At any gestation	FMF	0.53	0.52-0.55	0.000
	NICE	0.54	0.52-0.56	0.000

Table 3.4 FMF and NICE screening Area Under Curve values for PIH

	Women screened by NICE vs FMF	Number of high-risk women who developed PIH (n)	Sensitivity	Specificity	PPV	NPV	P - value
Preterm PIH (n= 373)	**NICE**	110	29.5%	88.3%	14.4%	94.9%	<.001
	FMF	142	38.1%	85.5%	14.9%	95.4%	<.001
PIH at any gestation (n=1651)	**NICE**	273	16.5%	91.2%	42.6%	73.4%	<.001
	FMF	316	19.1%	87.6%	37.1%	73.3%	<.001

Table 3.5: PIH-prediction performance of NICE and FMF screening methods

Risk of SGA

We found a statistically significant correlation between the FMF-screened positive women and the risk of having SGA (<3rd, <5th and <10th centiles) compared to FMF screened negative women (figures 3.5-3.8, table 3.6). This correlation was not statistically significant in NICE-screened positive women.

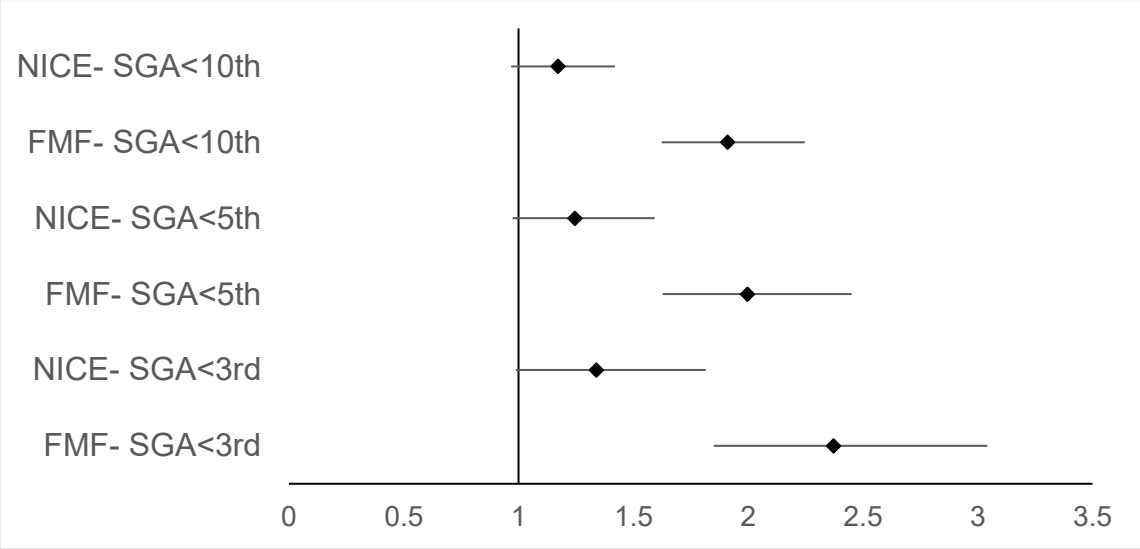
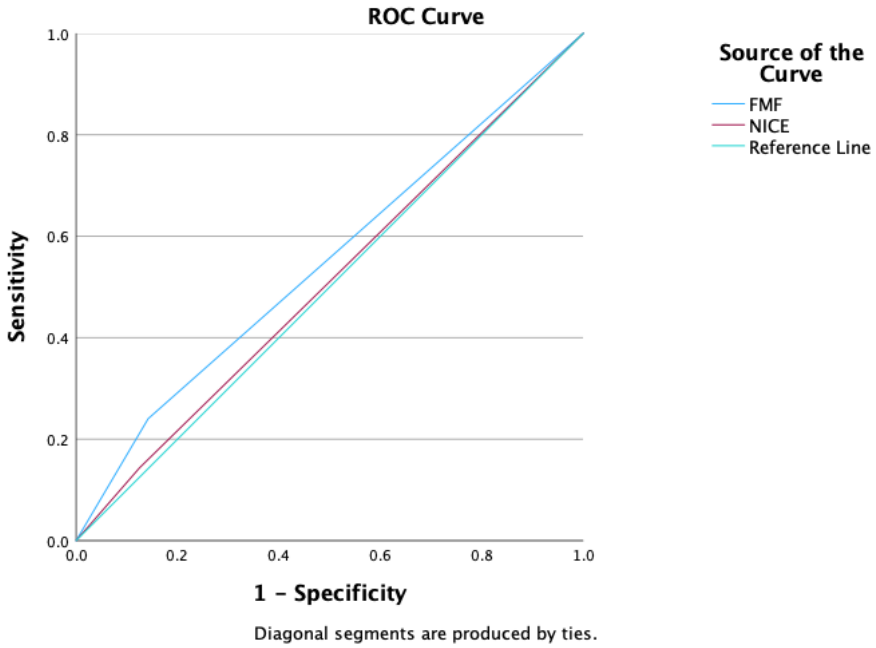


Figure 3.5: Forest plot on risk (OR) of SGA in NICE- and in FMF-screened women

	Women screened by NICE vs FMF	Number of high-risk women with SGA fetus (n)	Sensitivity	Specificity	PPV	NPV	P - value
SGA <10th (n=1057)	**NICE**	152	14.4%	87.5%	19.8%	82.6%	0.103
	FMF	254	24.0%	85.8%	26.7%	84%	<.001
SGA <5th (n=551)	**NICE**	84	15.2%	87.4%	11%	91%	0.079
	FMF	143	26%	85.1%	15.1%	91.9%	<.001
SGA <3rd (n=326)	**NICE**	53	16.3%	87.3%	6.9%	94.7%	0.059
	FMF	97	29.8%	84.9%	10.2%	95.4%	<.001

Table 3.6: SGA- prediction performance of NICE and FMF screening methods



SGA<10th	AUC	p-value	95% CI
FMF	.549	.000	0.529 - 0.569
NICE	.509	.345	0.490 - 0.529

Figure 3.6: Prediction performance for SGA <10th centile

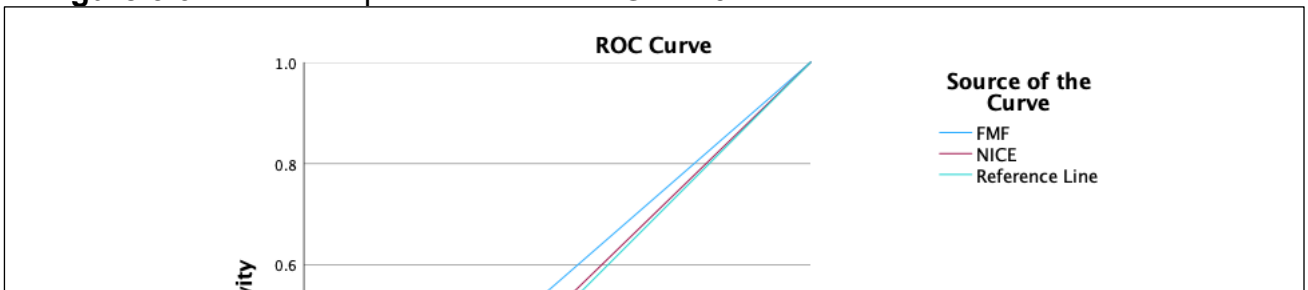
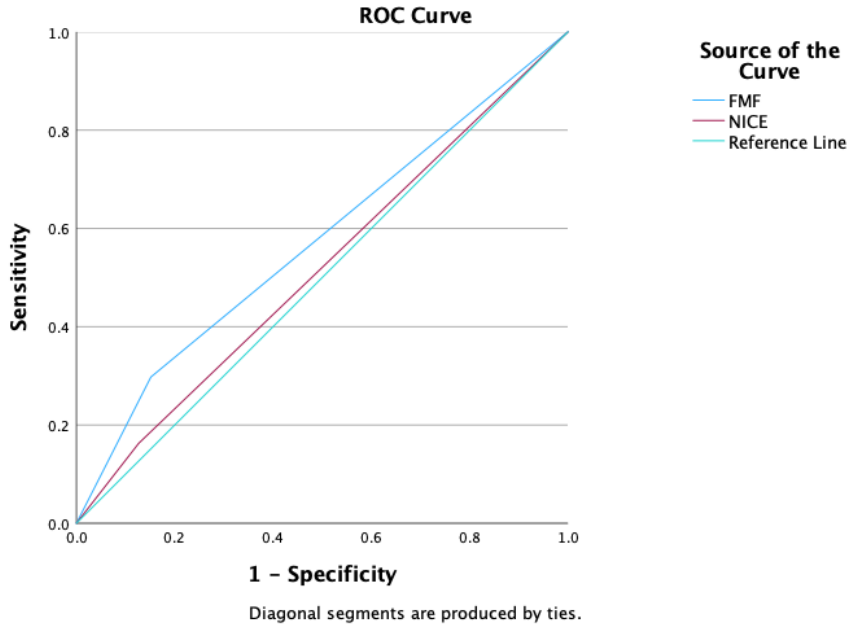


Figure 3.7: Prediction performance for SGA <5th centile



SGA<3rd	AUC	p-value	95% CI
FMF	.573	.000	0.539 - 0.607
NICE	.518	.274	0.485 - 0.551

Figure 3.8: Prediction performance for SGA <3rd centile

Furthermore, we looked at the correlation between the screening methods and the risk of other secondary outcomes including stillbirth, BW centile, emergency caesarean section, admission to the Neonatal intensive Care Unit (NICU) or Special Care Baby Unit (SCBU) and the length of neonatal admission (table 3.7).

	Screening method	Incidence in high risk group	P value
Stillbirth, n (%)	FMF	5 (0.5%)	0.13
	NICE	3 (0.4%)	0.56
BW centile, median (IQR)	FMF	25.9 (9.13-49.9)	<0.001
	NICE	31.19 (13.51-58.11)	0.21
Emergency C-section, n (%)	FMF	334 (63%)	0.007
	NICE	231 (53.2%)	0.029
Admission to NICU, n (%)	FMF	74 (7.8%)	0.07
	NICE	74 (9.7%)	<0.001
NICU admission duration (days), median (IQR)	FMF	4.84 (2.39-14.15)	0.01
	NICE	4.54 (2.16-13.68)	0.038
Admission to SCBU, n (%)	FMF	20 (2.1%)	0.016
	NICE	18 (2.3%)	0.006

Table 3.7: Risk of adverse outcomes in high-risk women depending on method of screening

Risk of stillbirth

The total number of stillbirths in our cohort was 17. There was no statistically significant correlation with stillbirth (table 3.7). The OR of stillbirth was 2.2 (95% CI: 0.8- 6.3) in the FMF-screened compared to 1.5 (95% CI: 0.4-5.1) in the NICE-screened groups.

Birthweight centile

There was no statistically significant difference in the birthweight centiles between high-risk and low-risk NICE- screened women (table 3.7). The birthweight was 9 centiles lower in high-risk FMF-screened women when compared to the low-risk FMF screened group, which was statistically significant. However, the median birthweight was still within the normal range. Due to the retrospective nature of our data and given that women did not have routine serial growth scans, we would not be able to show whether this decrease could actually be a reflection of a reduction in growth velocity.

Risk of Emergency Caesarean Section

We assessed the risk of requiring an EMCS after excluding the women who had an elective caesarean section (ELCS). Amongst the high risk FMF-screened, 63% required an emergency caesarean birth compared to 53% of high risk NICE-screened women. We found a statistically significant higher chance of requiring an EMCS for high-risk women independent of the method of screening (Table 3.7).

Neonatal admission

The vast majority (98%) of babies born to screen-positive mothers, regardless of the screening approach, did not require admission to NICU or SCBU. However, there was a statistically significant increase in the length of admission to NICU; 1.4 days longer for babies of FMF-screened positive mothers and 1.1 days longer for those of the NICE-screened positive mothers (table 3.7).

Discussion

Main Findings

Our study confirms that the first trimester modified FMF combined screening method (risk factors, MAP & Papp-A) has a superior performance compared to the NICE screening method over the prediction of PE and PIH, especially prior to 37 weeks.

Our study also shows that the use of the modified FMF combined screening can reliably identify women who have a higher risk of having an SGA (EFW<10^{th} or 5^{th} centile) or growth restricted (EFW <3^{rd} centile) baby.

Babies born to FMF-screen positive mothers are not at a higher risk of requiring admission to NICU compared to their screen negative counterparts. However, when these babies do require admission, the length of admission is increased by 1.4 days.

Finally, FMF- screened high risk women were significantly more likely to require a EMCS.

Strengths and Limitations

Strengths of our study include the large number include the large cohort with retrospective application of the FMF algorithm. The modified FMF algorithm did not take into consideration UtA PI or PlGF in the first trimester; this information was not available given the retrospective data collection. We would expect our FMF screening algorithm to perform even better if we did have this information. Another limitation was the MAP being calculated based on one measurement rather than multiple measurements as per the FMF recommendation.

Comparison to other studies

Our retrospective application of the FMF algorithm had an AUC of 0.773 for preterm PE. This is consistent with the predictive performance of the FMF algorithm using the same parameters (i.e. risk factors, MAP and Papp-A) that has been reported in external validation studies with an AUC ranging between 0.771 and 0.9 for preterm PE [181 96 182 183].

Implications for clinical application

In our study, we used a cut-off for preterm PE of 1 in 100. The FMF suggests that a risk of 1 in 150 can be considered in a primarily Caucasian population as was ours. This could have improved our DR for preterm PE but it would also simultaneously increase the FPR. Consequently, more women would be prescribed aspirin unnecessarily potentially leading to an increase in LDA- associated side effects or complications.

Our results support the implementation of the FMF-combined screening algorithm and the provision of fetal surveillance to our screen positive women. We found a significant association between the risk of SGA and FGR amongst high-risk women screened by the FMF-algorithm. We did not find a statistically significant difference in the risk of SB. However, this could be attributed to the size of our cohort and the small number of SBs.

Interestingly, screen-positive women, regardless of the method of screening, have an increased risk of requiring an EMCS. This difference was higher in FMF- screened women compared to NICE-screened women (63% vs 53%).

In the following chapter (chapter 3.2), we will investigate whether we should further adjust our surveillance for these women depending on the presence of raised UtA PI at the mid-trimester scan as this may further increase their risk of FGR and SB.

Conclusion

Our study confirms that the first trimester modified FMF combined screening method has a superior performance compared to the NICE screening method over the prediction of preterm PE, PIH, and SGA/FGR.

3.2 Stratification of women in the second trimester according to assessment of the uterine artery blood flow

Introduction

Women receiving their antenatal care at UCLH undergo routine assessment of uterine artery blood flow in the second trimester, at the time of the anomaly scan, in addition to screening for PE in the first trimester. Our objective was to refine our clinical approach by evaluating the risks of PE, PIH and SGA as our primary outcomes within these risk-stratified groups. Our secondary outcomes of interest included evaluation of the BW centile, requirement of EMCS, neonatal admission to NICU or SCBU and the length of admission.

This comprehensive assessment provided a critical foundation for stratifying care and tailoring fetal surveillance protocols to ensure that high-risk women receive appropriate monitoring and interventions. Our hypothesis was that maternal and fetal outcomes could be enhanced by enabling more personalized and precise medical management based on individual risk profiles.

Methods

This study included the same cohort of women from Chapter 3.1. However, patients were excluded if the uterine artery blood flow had not been assessed at the time of their anomaly scan.

We performed all statistical analyses on SPSS statistical software (version 29; SPSS Inc.). Categorical data were compared by using chi-squared analyses and numerical

data were compared by using Kruskal Wallis analyses with Bonferroni correction. Categorical data were presented as numbers and percentages and continuous data were presented as median values and interquartile ranges.

Definitions

We used the PE definition as in chapter 3.1. More specifically, PE was defined as hypertension in addition to at least one of the following conditions: renal involvement (i.e., proteinuria of 300 mg/24 hours and/or a creatinine level of 90 mmol/L or 1 mg/dL), liver impairment (i.e., transaminase levels exceeding 40IU/L), neurological complications (such as eclampsia), thrombocytopenia (platelet count below 150 $x10^3$/mL), or uteroplacental dysfunction (e.g., FGR).

An estimated fetal weight or birthweight below 3rd centile was used for the definition of FGR.

We divided our FMF-screened cohort into four groups (figure 3.9) as follows:

- H1H2; women who screened high-risk in the 1st trimester and had raised UtA PI in the second trimester
- H1L2; women who screened high-risk in the 1st trimester and had normal UtA PI in the second trimester
- L1H2; women who screened low-risk in the 1st trimester and had raised UtA PI in the second trimester
- L1L2; women who screened low-risk in the 1st trimester and had normal UtA PI in the second trimester

Results

Of the 5957 women retrospectively screened using the FMF-combined test (figure 3.9), 439 (7.4%) were excluded due to not having an assessment of the uterine artery Dopplers at the mid-trimester scan. The latter was the case either because the sonographers were unable to perform assessment of the uterine arteries or it was accidentally omitted.

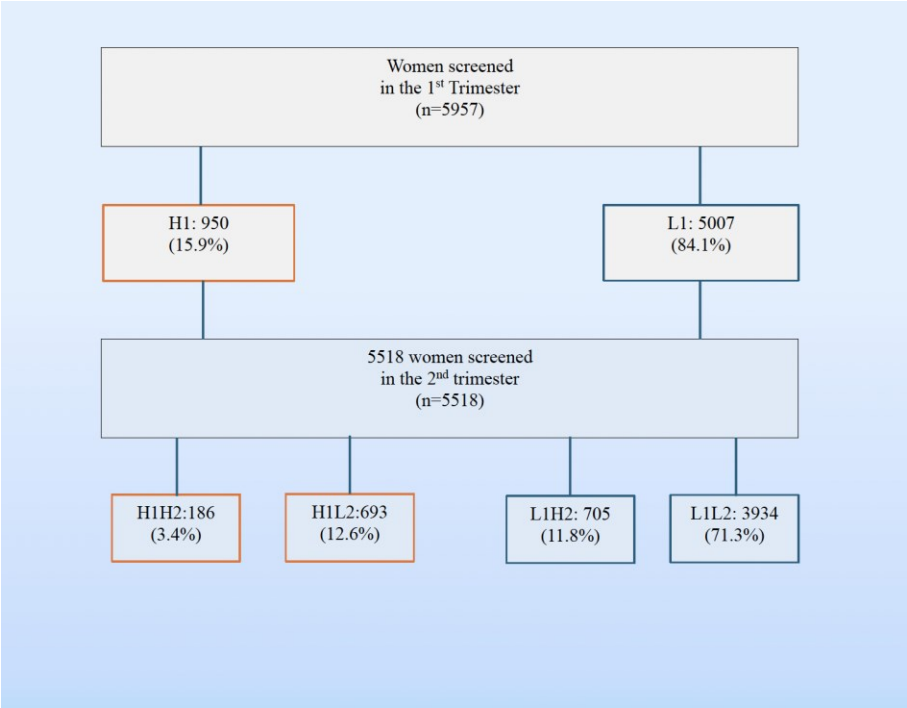


Figure 3.9: Stratification of women based on the risk calculation in the 1st and 2nd trimesters.
H1: High risk in the 1st trimester, H2: High risk in the 2nd trimester,
L1: Low Risk in the 1st trimester, L2: Low risk in the 2nd trimester

A total of 890 women (16.1%) had an increased UtA PI of ≥2.5. The median UtA PI in the FMF-screened high risk group was 1.9 (IQR: 1.51-2.37) and 1.86 in the low risk group (IQR: 1.54-2.25).

The proportion of women found to be at high risk in both the first and second trimesters were 16.3% and 19.5% according to the NICE and FMF algorithm, respectively. This resulted in an additional 60 women identified as high risk in both the 1st and 2nd trimester, when screened by FMF compared to NICE (table 3.8).

UtA PI in 2nd trimester	High risk NICE-screened women in 1st trimester	High risk FMF-screened in 1st trimester
High	125 (16.3%)	185 (19.5%)
Low	578 (75.5%)	694 (73.1%)
Missing values	63 (8.2%)	71 (7.5%)

Table 3.8: UtA PI risk assessment in the 2nd trimester in NICE- vs FMF- screened women in the 1st trimester

Risk of Preeclampsia

The risk of PE (preterm / at any gestation) was highest in the H1H2 group with a gradual decrease in the risk of preterm PE from H1H2 to H1L2 to L1H2 to L1L2 (Table 3.9).

Groups	Preterm PE, n (%)	PE at any gestation, n (%)
H1H2	35 (18.8) *^∝	59 (31.7) *^∝
H1L2	45 (6.5) *∈⊕	104 (15) *∈⊕
L1H2	24 (3.4) ɜ^	69 (9.8) ɜ^
L1L2	25 (0.6) ɜ∝⊕	151 (3.8) ɜ∝⊕

Table 3.9: Incidence of PE amongst the four FMF-screened risk groups
* *H1H2 statistically significant to H1L2*
^ *H1H2 statistically significant to L1H2*
∝ *H1H2 statistically significant to L1L2*
∈ *H1L2 statistically significant to L1H2*
⊕ *H1L2 statistically significant to L1L2*
ɜ *L1H2 statistically significant to L1L2*

Risk of PIH

A different pattern is noted when looking at the incidence of PIH prior to 37 weeks and at any gestation (Table 3.10) after excluding women with essential hypertension and women who developed PE. The incidence of preterm PIH appears to be highest in the H1L2 group followed by H1H2, L1H2 and L1L2. Similarly, the incidence of PIH at any gestation is higher in H1L2 group compared to the H1H2 group.

Groups	Preterm PIH	PIH
H1H2	14 (12.4%) *^	46 (40.7%) *
H1L2	91(17.3%) *∈⊕	247 (47%) *∈⊕
L1H2	34 (5.3%) ^∈	170 (26.7%) ∈
L1L2	183 (4.8%) ⊕	1072 (28.4%) ⊕

Table 3.10: Risk of preterm PIH and PIH at any gestation amongst the four risk groups
* *H1H2 statistically significant to H1L2*
^ *H1H2 statistically significant to L1H2*
∝ *H1H2 statistically significant to L1L2*
∈ *H1L2 statistically significant to L1H2*
⊕ *H1L2 statistically significant to L1L2*
ɔ *L1H2 statistically significant to L1L2*

Risk of SGA

The risk of SGA appears to be highest in the H1H2 group with a gradual decrease in the L1H2, H1L2 and L1L2 groups (Table 3.11).

The median BW centile appears to be lowest in the H1H2 group followed by the L1H2 group (table 3.11).

Groups	SGA< 10th n (%)	SGA <5th n (%)	SGA< 3rd n (%)	BW centile Median (IQR)
H1H2	88 *^ (47.3%)	57 *^ (30.6%)	45 *^ (24.2%)	12.52 *^∝ (IQR:3.01-28.91)
H1L2	143 *∈⊕ (20.6%)	68 *∈⊕ (9.8%)	38 *∈⊕ (5.5%)	30.73 *∈ (IQR:13.05-54.39)
L1H2	192 ɔ∈^ (27.2%)	114 ɔ∈^ (16.2%)	70 ^ɔ∈ (9.9%)	25.63 ^∈ɔ (IQR: 9.35-49.38)
L1L2	554 ɔ ⊕ (14.1%)	268 ɔ ⊕ (6.8%)	143 ɔ⊕ (3.6%)	36.5 ∝ɔ (IQR: 16.91- 62.02)

Table 3.11: Risk of SGA and BW centiles amongst the four risk groups
* *H1H2 statistically significant to H1L2*
^ *H1H2 statistically significant to L1H2*
∝ *H1H2 statistically significant to L1L2*
∈ *H1L2 statistically significant to L1H2*
⊕ *H1L2 statistically significant to L1L2*
ɔ *L1H2 statistically significant to L1L2*

Risk of stillbirth

The groups with high UtA PI appear to have higher risk compared to the low UtA PI groups, with a 2.2% risk in H1H2 followed by 0.6% in L1H2 (Table 3.12). These results were statistically significant ($p<0.05$).

Groups	Stillbirth
H1H2	4 (2.2%) *^∝
H1L2	0 (0%) *∈
L1H2	4 (0.6%)∈^
L1L2	8 (0.2%)∝

Table 3.12: Risk of SB amongst the four risk groups
* *H1H2 statistically significant to H1L2*
^ *H1H2 statistically significant to L1H2*
∝ *H1H2 statistically significant to L1L2*
∈ *H1L2 statistically significant to L1H2*
⊕ *H1L2 statistically significant to L1L2*
ɔ *L1H2 statistically significant to L1L2*

Risk of emergency caesarean section

The risk of emergency caesarean section appears highest in H1H2 group followed consecutively by groups H1L2, L1H2 and L1L2 (Table 3.13).

Groups	EMCS
H1H2	72 (45.9%) $^{\propto\wedge}$
H1L2	237 (43.6%)$^{\in\oplus}$
L1H2	160 (26.1%) $^{\wedge\in}$
L1L2	798 (24.1%) $^{\oplus\propto}$

Table 3.13: Risk of EMCS amongst the four risk groups
* *H1H2 statistically significant to H1L2*
$^{\wedge}$ *H1H2 statistically significant to L1H2*
$^{\propto}$ *H1H2 statistically significant to L1L2*
$^{\in}$ *H1L2 statistically significant to L1H2*
$^{\oplus}$ *H1L2 statistically significant to L1L2*
$^{\ni}$ *L1H2 statistically significant to L1L2*

Risk of Admission to NICU and/or SCBU & length of admission

The risk of requiring admission to NICU was similar between groups H1H2, H1L2 and L1H2. The risk was statistically significant higher in L1H2 compared to L1L2.

The length of admission was higher in group H1H2 (median: 4.98 days), followed by H1L2 (4.39 days), L1H2 (3.98 days) and L1L2 (3.25 days) (table 3.14). All pairwise comparisons were relatively small but statistically significant.

Groups	Admission to NICU n, %	Admission to SCBU n, %	Length of admission to NICU (in days) median (IQR)
H1H2	14 (7.5%)	8$^{*\propto}$ (4.3%)	4.98 $^{*\wedge\propto}$ (IQR: 2.69 - 29.79)
H1L2	53 (7.6%)	11* 1.6%)	4.39 $^{*\in\oplus}$ (IQR: 2.37 - 9.56)
L1H2	57 $^{\ni}$ (8.1%)	10 (1.4%)	3.98 $^{\wedge\in\ni}$ (IQR: 2.12 - 8.60)
L1L2	227 $^{\ni}$ (5.8%)	42$^{\propto}$ (1.1%)	3.25 $^{\propto\ni\oplus}$ (IQR: 1.71 - 6.89)

Table 3.14: Risk of Neonatal Admission amongst the four risk groups
* *H1H2 statistically significant to H1L2*
$^{\wedge}$ *H1H2 statistically significant to L1H2*
$^{\propto}$ *H1H2 statistically significant to L1L2*
$^{\in}$ *H1L2 statistically significant to L1H2*
$^{\oplus}$ *H1L2 statistically significant to L1L2*
$^{\ni}$*L1H2 statistically significant to L1L2*

Discussion

Main Findings

Our results indicate that incorporating assessment of the UtA dopplers during the second trimester can offer additional risk stratification for PE amongst women who underwent first-trimester combined screening using the FMF algorithm. Regarding composite adverse perinatal outcomes, including the risks of PIH, SGA and stillbirth, the level of care for women with low mid-gestational UtA PI in the second trimester should not be downgraded following a high risk combined screening result in the first trimester. Conversely, an intensification of care may be warranted for those initially deemed low-risk in the first trimester but demonstrate high UtA in the second trimester.

The incidence of preterm PE and of PE at any gestation was highest in the H1H2 group, followed by the H1L2, L1H2 and L1L2 groups. However, the downward trend

was different as regards the risk of PIH at any gestation; this was higher in H1L2 group compared to the H1H2 group. This may be partly attributed to the fact that the UtA assessment was not included in the 1st trimester PE screening algorithm may have played a role in these results. The trend in the incidence of SGA was also different, gradually descending from H1H2 to L1H2, H1L2 and L1L2 (Table 3.13). This may be due to a number of reasons. First of all, the uterine arteries were not assessed in our cohort during the 1st trimester. If they had been incorporated, it is possible that a higher number of patients might have been included in the H1H2 group. Secondly, several studies have shown that the increased resistance in the UtA is strongly associated with growth restriction and could be a direct sign of uteroplacental dysfunction.

Women who screened positive in the first trimester (H1H2 and H1L2) had a nearly 2-fold higher risk of requiring an EMCS compared to the women who screened negative in the first trimester (L1H2 and L1L2).

Babies born to women who screened negative in the first trimester but had a raised UtA PI in the second trimester had a higher risk of requiring admission to NICU compared to screen negative mothers who had a normal mid-gestational UtA PI assessment.

Comparison to other studies

The role of second trimester UtA assessment in the identification of pregnancies at higher risk of PE and placenta-mediated pathology is well established either in

isolation or as part of the combined screening approach in the second trimester. [184-192]. However, the only other study that has evaluated the value of mid-gestational UtA dopplers in the setting of routine first trimester PE combined screening is by Meroni et al.[193] This was a retrospective cohort study at a London tertiary hospital, which included 7793 patients. They found that the risk of preterm PE showed a consistent decrease across the different risk groups. More specifically, the incidence of preterm PE was 13.7% in the H1H2 group, 4.5% in the H1L2 group, 3.3% in the L1H2 group, and 0.2% in the L1L2 group. A similar downward trend was observed in other adverse outcomes including term HDP, SGA birth and stillbirth. However, the authors only included SGA below the 10th and below the 5th centiles in their analyses.

Their results are consistent with our own demonstrating the importance of the midgestational UtA doppler in further refining the risk stratification for PE and SGA .

Strengths and Limitations

The strengths of our study include the size of the cohort and the novelty of the results. Our study was limited by its single-centre retrospective nature, lack of uterine artery assessment in the first trimester and the possible impact of intervention bias.

The fact that the UtA assessment was not included in the 1st trimester PE screening algorithm may partly account for the incidence of preterm PIH and PIH at any gestation being higher in the H1L2 group compared to H1H2. However, a study on sequential assessment of the UtA blood flow found that an increased UtA PI in first trimester can normalise in the second trimester in 73% of cases [194]. Conversely, 95% of women with normal UtA PI in the first trimester also had normal UtA PI in the second trimester [194].

Furthermore, a proportion of women who were low risk in the first trimester would have taken aspirin on account of NICE. However, this would have resulted in an under- rather than over-estimation of the risk.

Given the relatively small number of stillbirths in our study (16 out of 5518, or 0.29%), the study was underpowered to robustly assess the risk of stillbirth.

Implications for clinical application

The rationale behind our project was to decide upon the follow-up clinical pathway once FMF-combined screening for PE in the first trimester was implemented. Our research provided good evidence to recommend increased fetal monitoring in mothers exhibiting elevated UtA PI levels during the second trimester. In view of our results, the decision was made to offer FMF-screened positive women serial growth scans at 28, 32 and 36 weeks if they also had raised mid-gestational UtA PI. For those with normal mid-gestational UtA PI, a single growth scan at 36 weeks of pregnancy was offered unless there were other obstetric or medical indications for earlier scans. Conversely, women who screened negative in the first trimester and then had raised mid-gestational UtA PI, had their care intensified by means of fetal growth scans at 28, 32 and 36 weeks of pregnancy. Women who screened negative in both trimesters, did not require any further scans following their anomaly scan in the absence of other indications. Our future work will focus on the collection of prospective data and the stratification of care based on the first and second trimester screening at UCLH.

Conclusion

The utilization of routine second-trimester UtA doppler assessment can enhance the stratification of PE risk among women who underwent first-trimester screening for PE

using the FMF- combined screening algorithm. Close fetal surveillance is of paramount importance for these women if they also develop raised mid-gestational UtA PI as they are at a higher risk of multiple adverse maternal and fetal outcomes including PE, PIH, SGA and SB.

3.3. Investigation of adverse outcomes after 40 weeks of gestation in women who screen positive for preterm preeclampsia in the first trimester

Introduction

Evidence is increasingly showing that women who screen positive through first trimester combined testing are at risk not just for preterm PE, but also for other adverse outcomes like SGA and term PE, compared to those who test negative [193, 195-198].

Consequently, following the introduction of first trimester screening for preterm PE, some practitioners have started offering routine labour induction from 39 weeks to those who tested positive but show no signs of PE, a practice not universally adopted [199]. This divergence stems from limited evidence supporting early induction for the screen-positive group.

Current guidelines in the UK as advised by NICE, recommend induction from 41 weeks unless earlier intervention is medically necessary [200]. However, research involving low-risk nulliparous women indicates that inducing labor at 39 weeks can decrease the incidence of hypertensive pregnancy disorders by 40% compared to awaiting the natural onset of labor [201].

While first trimester combined screening is superior to NICE screening, it is not designed to detect term PE and aspirin has not been shown to reduce the risk of PE at term. Observational studies in women screened for PE in the first trimester also suggest that planning an earlier delivery could decrease the occurrence of term PE. This highlights the need for more research to guide counselling before first trimester

PE screening and to support the recommendation of inducing labour from 39 weeks in women who test positive but do not exhibit PE symptoms.

We hypothesized that women screened for preterm preeclampsia (PE) in the first trimester and remained normotensive with normal fetal growth up to 37 weeks would exhibit a measurable incidence of term PE. Furthermore, we hypothesized that maternal and neonatal outcomes would differ between those delivering before 40 weeks compared to those delivering after 40 weeks.

Methods

Our study was a retrospective, observational study on the same cohort of women included in our first study (chapter 3.1). We retrospectively applied the modified FMF combined screening test to this cohort using the MAP and Papp-A levels at the time of their first trimester scan. Women with an estimated risk of preterm PE (<37/40) of ≥ 1 in 100 were considered high-risk based on the FMF algorithm. As the FMF algorithm was retrospectively applied to the cohort that had already been screened using the NICE method, a proportion of these women were at high risk for the development of preterm PE in both arms and had been prescribed low-dose aspirin prophylaxis.

Women included had singleton pregnancies resulting in the livebirth or stillbirth of an infant without any serious congenital anomalies at ≥ 37 weeks' gestation. We excluded women who, prior to 37 weeks, received a diagnosis of a hypertensive disorder in pregnancy (PIH/PE), had evidence of placental insufficiency on ultrasound (SGA/FGR or abnormal U.A PI) or an alternative medical indication for earlier induction of labour that included chronic HTN, pre-gestational diabetes or maternal age > 40 yrs. We also excluded women who did not receive a fetal growth scan in the third trimester.

Women received standard care as per the NICE guidance [200],[202]. They were offered aspirin prophylaxis of 150mg based on NICE-screening. Third trimester fetal growth surveillance or earlier induction of labour were routinely scheduled as recommended by NICE.

Patients were divided into four groups screened by FMF; groups 1 and 2 comprised of low-risk women who delivered at 37^{+0} - 39^{+6}/40 and 40^{+0} - 41^{+}/40, respectively and groups 3 and 4 of high-risk women who delivered at 37^{+0}-39^{+6}/40 and 40^{+0} - 41^{+}/40, respectively. We performed comparisons between the FMF- screened positive groups (3 vs 4) as well as the FMF-screened negative groups (1 vs 2).

In addition, we compared the risk of PE in NICE-screened high-risk women pre- and post- 40/40 at the time of delivery to find out whether similar conclusions could be drawn regardless of the method of screening.

Our primary outcome of interest was term PE amongst the FMF-screened positive groups, the FMF-screened negative groups and the NICE-screened positive groups. Our secondary outcomes of interest were term PIH, SGA/FGR, IOL, EMCS, neonatal admission to NICU/SCBU, BW centile amongst the FMF-screen positive groups (3 and 4).

Data on maternal characteristics and pregnancy outcomes were collected from the hospital maternity records. Patient identifiable information was removed from the data sets for confidentiality purposes. Ethical approval was not required given that our study was retrospective and did not alter the clinical pathway nor the outcomes for the mother or baby.

Definitions

PE was defined as hypertension in the presence of renal and/or liver and/or neurological complications and/or thrombocytopenia and/or uteroplacental dysfunction, similar to the definition used in chapters 3.1 and 3.2. However, we changed our definition of FGR to an estimated fetal weight or birthweight below the 10th centile after 37 weeks of gestation given that all the patients in our cohort previously had a normal growth scan (i.e. EFW>10th centile) in the third trimester. Consequently, a fetal/neonatal weight below the 10th centile would likely represent a noteworthy decline in the growth velocity.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software (version 29; SPSS Inc.). Categorical data were presented as numbers and percentages and compared with chi-squared analysis. Continuous data were presented as median with interquartile ranges and compared with Kruskal Wallis analysis and Bonferroni correction. We performed a chi-squared analysis of independence and a Kruskal-Wallis analysis for categorical and numerical data, respectively to find out whether there was homogeneity amongst the different groups being compared (table 3.30). The null hypothesis was that the groups were homogenous.

Results

Overall, there were 1802 pregnancies that met the inclusion criteria for our retrospective, observational study. The maternal characteristics for these women are shown in table 3.15.

Amongst the FMF-screened groups, there were more multiparous women delivering prior to 40/40 compared to nulliparous in both the low-risk (52.1% in group 1 vs 36.4% in group 2, p<0.00) and the high-risk groups (32.9% in group 3 vs 12% in group 4, p< 0.001)). In addition, there appeared to be more high-risk women with IVF pregnancies delivering prior to 40/40 (28.9% in group 3 vs 9.3% in group 4). Women had a slightly higher BMI in the groups delivering pre- rather than post- 40/40 (median of 23 vs 22.5 in groups 1 and 2, respectively, and median of 25.8 vs 26.45 in groups 3 vs 4, respectively).

Amongst the FMF-screened low-risk groups (groups 1 and 2), there were no statistically significant differences in IVF, smoking, previous history of PE, family history of PE and age.

Amongst the NICE-screened high-risk groups, there was homogeneity as regards all the maternal characteristics (table 3.16).

Maternal Characteristics	Group 1 (number=866)	Group 2 (number=712)	Group 3 (number=149)	Group 4 (number=75)
Primiparity, n (%)	415 (47.9%)	453 (63.6%)	100 (67.1%)	66 (88%)
History of PE, n (%)	3 (0.7%)	1 (0.4%)	14 (28.6%)	2 (22.2%)
Family history of PE, n (%)	36 (4.2%)	20 (2.8%)	13 (8.7%)	7 (9.3%)
IVF, n (%)	40 (4.6%)	33 (4.6%)	43 (28.9%)	7 (9.3%)
Smoker, n (%)	17 (2%)	8 (1.1%)	1 (0.7%)	3 (4%)
Ethnicity, n (%) White South Asian Black East Asian Mixed	 606 (70%) 118 (13.6%) 54 (6.2%) 56 (6.5%) 32 (3.7%)	 543 (76.3%) 49 (6.9%) 53 (7.4%) 36 (5.1%) 31 (4.4%)	 59 (39.6%) 37 (24.8%) 44 (29.5%) 5 (3.4%) 4 (2.7%)	 37 (49.3%) 16 (21.3%) 19 (25.3%) 0 (0%) 3 (4%)
Age, median (IQR)	33 (IQR: 31-36)	33 (IQR: 30-36)	34 (IQR: 30-37)	32 (IQR: 29-36)
BMI, median (IQR)	23 (IQR: 20.9-26.2)	22.5 (IQR: 20.4-24.9)	25.8 (IQR: 23.1-29.9)	26.45 (IQR: 23.4-30.1)

Table 3.15: Maternal characteristics across the FMF- screened groups

	Groups 3 vs 4 (FMF-screened)	Groups 1 vs 2 (FMF-screened)	HR <40/40 vs HR≥40/40 (NICE-screened)
Parity	S (<0.001)	S (<0.001)	NS (0.13)
IVF	S (<0.001)	NS (0.98)	NS (0.94)
Smoking	NS (0.07)	NS (0.18)	NS (0.53)
Ethnicity	NS (0.34)	S (<0.001)	NS (0.15)
Prior history of PE	NS (0.69)	NS (0.6)	NS (0.16)
Family history of PE	NS (0.88)	NS (0.15)	NS (0.9)
Age	NS (0.09)	NS (0.46)	NS (0.6)
BMI	NS (0.96)	S (<0.001)	NS (0.09)

Table 3.16: Maternal characteristics amongst low- and high- risk women pre- and post-40 weeks of gestation

S: statistically significant
NS: statistically non-significant

Primary Outcomes

In our cohort, 224 (12.4%) women screened positive based on the first trimester FMF-algorithm compared to 170 (9.4%) women who screened positive based on the NICE-screening. There were a total of 41 (18.3%) high-risk women screened by FMF who developed PE compared to 27 (15.8%) high-risk women screened by NICE.

There is an incremental increase in the risk of PE from 7% in group 1 to 7.6% in group 2 to 13.4% in group 3 to 28% in group 4 as shown in table 3.17.

Primary Outcomes	FMF-screened high risk (n=224)			FMF-screened low risk (n=1578)			NICE screened high risk (n=170)		
	Before 40 weeks (n=149)	After 40 weeks (n=75)	P value	Before 40 weeks (n=866)	After 40 weeks (n=712)	P value	Before 40 weeks (n=110)	After 40 weeks (n=60)	P value
PE	20 (13.4%)	21 (28%)	0.008	61 (7%)	54 (7.6%)	0.68	17 (15.5%)	10 (16.7%)	0.84
ARR	-14.6%			-0.6%			-1.2%		
NNT	1 in 7			1 in 166			1 in 69		

Table 3.17: Risk of PE in FMF-screened high-risk, FMF-screened low-risk and NICE-screened high-risk groups depending on whether they gave birth before or after 40 weeks.
ARR: absolute risk reduction
NNT: number needed to treat

There is an approximately two-fold increase in the risk of PE in FMF-screened positive women who delivered after 40 weeks of gestation compared to women who delivered prior to 40 weeks. The absolute risk difference between these two groups was approximately 15%. Therefore, we can estimate that for every 7 patients that we brought the delivery forward to prior to 40 weeks, we would be able to prevent 1 patient from developing PE (table 3.17).

These results cannot be generalised to all women regardless of their screening result, given that for their low-risk counterparts, there was a statistically non-significant increase in the risk of PE at a scale of 0.6%.

In addition, the results cannot be generalised to the NICE-screened high-risk women. The increase in the absolute risk of PE after 40/40 was only 1.2%, and this was not statistically significant (table 3.17).

Secondary Outcomes

As secondary outcomes, we evaluated the risk of PIH, SGA, IOL, EMCS, neonatal admission and BW centile in all of 4 groups (table 3.18). There was no statistically significant difference in the risk of PIH, SGA, EMCS and neonatal admission amongst the FMF-screened high risk groups (groups 3 vs 4), the FMF-screened low risk groups (groups 1 vs 2) and the NICE-screened high risk groups (HR<40/40 vs HR >40/40). We noticed a trend towards a higher risk of developing PIH and delivering prior to 40 weeks in the FMF high-risk groups and less so in the NICE-screened high-risk groups. There was also a trend towards a higher risk of having an SGA baby (<5th and <10th centile) in high risk groups delivering after 40 weeks compared to before (table 3.18).

There was a statistically significant increase in the women requiring an IOL after 40/40 both in the low-risk and the high-risk FMF-screened groups. However, this was not observed in the NICE-screened high-risk groups. Statistical analysis revealed a significant difference in BW, with the FMF-screened high-risk groups (groups 3 vs 4) exhibiting a reduction of approximately 12 centiles, and the FMF-screened low-risk groups (groups 1 vs 2) showing a reduction of 6 centiles. Despite these differences, the median birth weight remained within the normal range.

Secondary Outcomes	FMF-screened high risk (n=1578)			FMF-screened low risk (n=224)			NICE screened high risk (n=170)		
	<40/40 (n=866)	**≥40/40 (n=712)**	**p-value**	**<40/40 (n=149)**	**≥40/40 (n=75)**	**p-value**	**<40/40 (n=110)**	**≥40/40 (n=60)**	**p-value**
PIH n (%)	64 (49.5)	19 (35.2)	0.074	198 (24.6)	282 (27.5)	0.206	45 (48.4)	23 (46)	0.785
ARR	+14.3%			-2.9%			+2.4%		
NNT	1 in 7			1 in 34			1 in 42		
SGA<10th n (%)	27 (18.1)	22 (29.3)	0.055	121 (14)	118 (16.6)	0.15	21(19.2)	11 (18.3)	0.9
ARR	-11.2%			-2.6%			+1.1%		
NNT	1 in 9			1 in 38			1 in 91		
SGA<5th n (%)	10 (6.7)	9 (12)	0.18	57 (6.6%)	48 (6.7%)	0.89	9 (8.2)	3 (5)	0.43
ARR	-5.3%			-0.1%			-3.2%		
NNT	1 in 19			1 in 1000 patients			1 in 31		
IOL n (%)	43 (29.7)	27 (36.5)	0.01	154 (18)	174 (24.8)	<0.001	28 (25.5)	15 (25)	0.95
ARR	-6.8%			-6.8%			+0.5%		
NNT	1 in 15			1 in 15			1 in 200		
EMCS n (%)	39 (35.8)	26 (35.6)	0.98	169 (26.8)	175 (25)	0.46	27 (40.9)	17 (28.8)	0.16
ARR	+0.2%			+1.8%			+12.1%		
NNT	1 in 500			1 in 56			1 in 8		
Neonatal Admission n (%)	7 (4.7)	3 (4)	0.81	50 (5.8)	33 (4.6)	0.3	7 (6.4)	2 (3.3%)	0.39

ARR	+0.7%			-1.2%			+3.1%		
NNT	1 in 142			1 in 83			1 in 32		
BW centile median (IQR)	30.1 (13.7-51.29)	17.79 (9.39-34.82)	0.004	37.6 (16.79-63.87)	31.2 (15.47-55.18)	0.02	29.45 (16.06-52.54)	24.98 (12-55.36)	0.54

Table 3.18: Risk of secondary adverse outcomes in FMF-screened high-risk, FMF-screened low-risk and NICE-screened high-risk groups depending on whether they gave birth before or after 40 weeks
ARR: absolute risk reduction
NNT: number needed to treat

Discussion

Main Findings

In our study, using the modified first trimester FMF combined screening test, the incidence of term PE amongst those who screen high-risk is significantly increased if the pregnancy advances beyond 40 weeks (13% vs 28% for groups 3 and 4, respectively; p-value=0.008). The NNT analysis indicated that we would need to bring the delivery forward (e.g., by means of IOL) to prior to 40 weeks for seven FMF-screened high-risk women in order to prevent one case of term PE. In contrast, a policy of IOL at 40 weeks would confer no benefit in the prevention of term PE amongst women who are low-risk using the first trimester FMF combined screening method or high-risk when using the NICE maternal-characteristic screening method.

More women appeared to develop PIH and deliver prior to 40 weeks in the FMF high-risk groups (49.5% vs 35.2%), though this was not statistically significant (p-value:0.074). This may be iatrogenic, given that women who did develop PIH at term would have been advised to deliver prior to 40 weeks.

There were more women delivering a baby below the 10th centile after 40 weeks compared to prior to 40 weeks in all the groups compared, with the difference being more prominent in the FMF high-risk groups (29.1% vs 18%). However, these results did not reach statistical significance in any of the compared groups. Women in the FMF screened groups were significantly more likely to have baby with lower BW if they delivered after 40 weeks compared to prior to 40 weeks, regardless of their result of their screening (median of 17.79 vs 30.1 centiles in the high risk groups, 31.2 vs 37.6

centiles in the low risk groups). Nonetheless, the median BW centile was still within the normal range.

Comparison to previous studies

Our study confirms that, although the performance of the first trimester FMF combined test in the prediction of term PE is poor, women who screen high-risk for preterm PE remain at a significantly higher risk of term PE when compared to their low-risk counterparts. This is consistent with a retrospective cohort study of 29,618 women who underwent first trimester FMF combined screening. In this population, the incidence of total PE -of which term PE contributed to 63.8% of included patients- was 5.7% vs 0.9% in the high and low risk populations, respectively (risk ratio (RR) 0.36 (95% confidence interval (CI) 0.32–0.41; p value < 0.001) [203]. Similarly, in a cohort study of 7793 women, the incidence of HDP, of which preterm onset constituted 90%, was significantly higher in the first trimester high risk group compared to the low risk group with rates of 27% vs 3.8%, respectively [193]. However, in contrast to our study, the aforementioned studies did not stratify their cohort according to timing of birth and included women who developed PE prior to 37 weeks.

Having characterised the residual risk beyond 37 weeks in the high-risk population, the next question we sought to address was whether a policy of earlier delivery would confer benefit. Our findings have demonstrated that timed delivery prior to 40 weeks in women who screen as high risk would reduce the rate of term PE by 15%. There is only one other study that has similarly studied the impact of earlier timed delivery in women who screen high risk using the FMF combined test. In a cohort of 57,131 women, induction of labour by 40 weeks in high-risk women would have prevented 7.2% of term PE with a NNT of 18 [204]. Women with alternative medical indications

such as diabetes and chronic hypertension were not excluded from this population and may explain why in this latter study a smaller effect was observed. Well established guidelines to direct earlier timing of birth for these medical indications are already in place and, therefore, including these women in the analysis will only dilute the observed effect.

A third trimester combined screening test for the detection of term PE has been developed by FMF that combines maternal characteristics, MAP, placental growth factor (PlFG) and soluble Flt – 1 (sFlt-1). This has a reported detection rate of 75% for term PE at a SPR of 10% but has not yet been as extensively validated externally when compared to the first trimester screening test [205]. There is evidence to suggest timing of delivery between 37 to 40 weeks would be better guided by stratifying risk of term PE using this third trimester screening test, with delivery at 37 weeks for those in the highest risk strata. By using this approach, in a cohort of 29 035 pregnancies, approximately 54.2% of cases of term PE were prevented with an NNT of 8 [204].

Implications on clinical practice

Despite its superior performance in its prediction of preterm PE and rigorous validation across different populations, the first trimester FMF combined test is not currently endorsed by national and international guidelines. Implementation of third trimester screening with incorporation of angiogenic factors, PlGF and sFlt-1, to identify women at high risk of term PE seems even further away to becoming embedded into routine practice. Thus, we took a more pragmatic approach to our population focussing on clinical information that is more readily available at or around term, MAP and fetal growth as measured between 35 to 37 weeks. In doing so, we estimated that 7 additional women would require induction of labour to prevent one case of term PE. It

is well established that induction of labour between 38 to 40 weeks in the nulliparous low risk population is not associated with an increase in emergency caesarean deliveries or admission to NNU [206, 207]. This is further supported by our data.

A randomised controlled trial is clearly needed to determine appropriate timing of delivery in women who screen high risk for preterm PE in the first trimester of pregnancy. This trial should consider different strategies of re-evaluating risk in the third trimester to increase applicability across all economic settings both within the UK and beyond. Whilst understanding the clinical implications of these policy changes is important, as we move more towards women-centred care, evaluating their preferences in the context of screening for PE and earlier timing of delivery is also necessary.

Conclusion

Using the first trimester modified FMF combined test, women who screen high risk for preterm PE are at significantly higher risk for term PE when compared to their low-risk counterparts. A policy of earlier timed delivery by 40 weeks in all women who screen high risk would result in a reduction in term PE.

Chapter 4.

Cost-Effectiveness Evaluation of the Combined Screening Algorithm at UCLH

Introduction

PE poses significant risks to both maternal and perinatal health but it also may lead to higher healthcare costs. It is a leading cause of preterm birth, which, depending on the gestational age, may lead to admission to the Neonatal Intensive Care Unit, and is associated with a higher risk of neonatal complications such as respiratory distress syndrome, intraventricular haemorrhage and necrotizing enterocolitis. Babies born to mothers with PE are also more likely to have low birth weight, which increases their vulnerability to infections, developmental delays, and long-term health issues [208-212]. Mothers who had developed PE have an increased risk of developing diabetes mellitus, cardiovascular disease (e.g. essential hypertension, coronary artery disease or stroke) in addition to venous thromboembolic disease, vascular dementia and CKD later in life [213-216]. Moreover, newer evidence suggest that women who have experienced PE are at an increased risk of developing postpartum depression and other mental health disorders [217].

In the UK, NICE [5] and RCOG [137] support PE screening based on maternal risk factors and this was the approach that UCLH had adopted. In recent years, however, international societies or organisations such as ISSHP [133], FIGO [135] and ISUOG [136], recommend the combined screening approach. Both screening strategies categorize women into low- and high- risk groups and, it is based on this stratification that women will receive the standard care or a superior care pathway, which includes treatment

with LDA and more intensive monitoring (e.g. antenatal clinic appointments, growth scans).

The aim of this study was to evaluate the incremental cost-effectiveness of replacing the NICE screening method with the FMF screening method for PE at UCLH. An enhanced screening method that offers better predictive accuracy, combined with a preventative intervention such as aspirin, could potentially lead to significant cost savings for healthcare systems and improve patients' quality of life. However, we need to take into consideration that first trimester combined screening for PE would also result in additional obstetrical healthcare costs including additional monitoring during the pregnancy.

Methods

We performed a retrospective observational study on the same cohort of women whose data we had analysed with regard to PE and adverse outcome prediction (*as detailed in chapter 3.1*). Women had been screened based on risk factors and we retrospectively applied the modified FMF algorithm by including their MAP and Papp-A in their individualised screening. We considered the 1 in 100 cut-off for risk stratification of women and expected 10-15% of our included patients to have a high-risk result.

Definitions

The diagnosis or PE required, in addition to hypertension, the presence of at least one of the following conditions: renal involvement (i.e., proteinuria of 300 mg/24 hours and/or a creatinine level of 90 mmol/L or 1 mg/dL), liver impairment (i.e., transaminase levels exceeding 70IU/L), neurological complications (such as eclampsia), thrombocytopenia (platelet count below 150 $x10^3$/mL), or uteroplacental dysfunction (e.g., FGR). An estimated fetal weight or birthweight below the 3rd centile was used for the definition of FGR.

Outcomes

The primary outcome of interest was the development of PE either preterm or at any gestation. Secondary outcomes included: SGA (below the 3rd, 5th and 10th centiles), stillbirth, gestational age at delivery, mode of delivery, BW centile, admission to NICU and/or SCBU and length of neonatal admission.

Statistical analysis

Given the retrospective application of the FMF algorithm, a proportion of women in both groups (NICE- and FMF- screened) were deemed high risk for developing PE and had been prescribed aspirin prophylaxis accordingly. To adjust the reported effect size for the incidence of preterm PE using the FMF algorithm, the assumption that aspirin would reduce the risk of preterm PE by 62%, as evidenced in the ASPRE randomized controlled trial (RCT), was factored into the analysis. The ASPRE RCT [3] did not indicate any difference in the rate of term PE between those taking aspirin and the placebo group. Therefore, the model did not account for any effect of aspirin on term PE.

Continuous data and categorical data were presented as median (interquartile range) and percentages, respectively. Pregnancy outcomes were compared among groups without PE, with term PE, and with preterm PE using analysis of variance or Kruskal–Wallis tests (for numerical parametric or nonparametric data) with Bonferroni correction for post-hoc analysis. The Chi-square test was utilized for categorical variables and for trend analysis when proportions between groups showed an evident. The incremental cost-effectiveness of substituting the NICE screening method with the FMF screening method was assessed in the form of a decision-tree model. Model pathways for each screening outcome were established based on initial screening test results, aspirin prescription, rates of PE, and rates of preterm PE. Transition probabilities were derived from the statistical analysis of primary data. Aspirin prescription rates were determined from observed data for the NICE screening method and from scientific literature for the FMF screening method. Health outcomes were assessed solely for the mother in terms of quality-adjusted life-years (QALYs).

The prevalence of relevant health events was determined from primary data, while health utility values were derived from available secondary data (table 4.1). Both outcomes and costs considered varying probabilities of delivery modes and neonatal outcomes depending on PE status. Healthcare costs encompassed expenses related to PE screening, third-trimester ultrasound for fetal growth surveillance, aspirin prophylaxis, intrapartum and postpartum care for both mother and baby, stillbirth costs, and admission of a preterm neonate to the neonatal unit (table 4.1). Relevant probabilities were derived from primary data, and unit costs were based on the NHS England 2022/23 National Tariff Workbook and the British National Formulary. Incremental cost-effectiveness ratios were calculated to illustrate the additional cost

per QALY gained by adopting the FMF screening algorithm. To gauge model sensitivity to uncertainty in key parameters, a univariate sensitivity analysis was conducted, varying each input parameter in isolation based on its upper and lower 95% confidence limits. Additionally, a probabilistic sensitivity analysis was performed, simultaneously modelling variation in parameters based on assumed distributions 1000 times (i.e., Monte Carlo simulations). Parameters varied in the sensitivity analysis included healthcare costs, health-state utility values, and all transition probabilities (effectively the number of PE cases under each intervention). Beta distributions were assumed for probabilities and utility values, while gamma distributions were assumed for costs.

Cost-effectiveness analyses were conducted in R using the 'rdecision' package.

Parameter	Value	Unit Cost
Maternal		
LDA (150mg) effectiveness	62% [105]	£0.06 per 150mg of LDA
LDA prescription rate (NICE-screened women)	75%*	
LDA prescription rate (FMF-screened women)	99% [199]	
Third trimester scan		£96
PPH probability, no LDA	0.078 [113]	
Vaginal delivery probability, no PE	61.7%*	£2,028

Vaginal delivery probability, preterm PE	20.4%*	£2,471
Vaginal delivery probability, term PE	46.1%*	
ELCS probability, no PE	17.1%*	£4,778
ELCS probability, preterm PE	8.2%*	£3,298
ELCS probability, term PE	10.9%*	
EMCS probability, no PE	21.2%*	£4,778
EMCS probability, preterm PE	71.4%*	£6,017
EMCS probability, term PE	43%*	
Fetal/Neonatal		
Stillbirth probability, no PE	0.004 [218]	
Stillbirth probability, preterm PE	0.016 [218]	
Stillbirth probability, term PE	0.002 [218]	
NICU admission, no PE	5.9%*	£1,579 per day
NICU admission, preterm PE	41%*	
NICU admission, term PE	9.4%*	
Length of admission-NICU, no PE (days)	4*	
Length of admission-NICU, preterm PE (days)	13*	
Length of admission-NICU, term PE (days)	3*	
SCBU admission, no PE	1.4%*	£455 per day
SCBU admission, preterm PE (days)	12%*	
SCBU admission, term PE	2.6%*	
Length of admission-SCBU, no PE (days)	13*	
Length of admission-SCBU, preterm PE (days)	3*	
Length of admission-SCBU, term PE (days)	3*	
Health state utility values		
Maternal age (25-34)	0.911 [219]	
Vaginal delivery	-0.41 for 7 days [219]	
Caesarean delivery	-0.58 for 21 days [219]	
PPH	09.25 for 10 days [220]	
PE	-0.03 [221]	
Stillbirth	-0.08 [5]	
Neonatal care admission	-0.008 per day [222]	

Table 4.1: Health outcome values and unit cost inputs

* *Primary data, 2019-2022*

Results

All the pregnancy outcomes are included in detail in chapter 3.1.

In the deterministic analysis under the base case scenario, employing the FMF algorithm is linked with a total cost saving of £9.06 per screened pregnancy and a marginal gain of 0.00006 QALY compared to standard care using the NICE screening method. Consequently, the FMF algorithm is considered dominant in this scenario. With a cohort comprising 5957 pregnant women, utilizing the FMF algorithm led to an estimated reduction of seven cases of preterm PE (41 cases) compared to 48 preterm PE cases with the NICE algorithm. This translates to an approximate cost-saving of £54,000 across the cohort of 5957 women. Overall, the number of QALYs over a 1-year period was similar between the two interventions, reflecting the rarity of serious adverse events like stillbirth. Figure 4.1 illustrates the outcomes of the univariate sensitivity analysis, highlighting the top 10 model parameters with the most significant impact on results. The model's sensitivity was particularly influenced by the probability of PE cases occurring prematurely, whereas costs and health-state utility values had minimal impact on the findings. Figure 4.2 presents the incremental cost and QALY outcomes derived from the probabilistic sensitivity analysis on a cost-effectiveness graph, with each point symbolizing one simulation of the model that considers uncertainty in parameters. Most outcomes are concentrated in the southeast quadrant indicating that FMF screening results in higher cost savings and health benefits compared to the NICE (National Institute for Health and Care Excellence) guidelines.

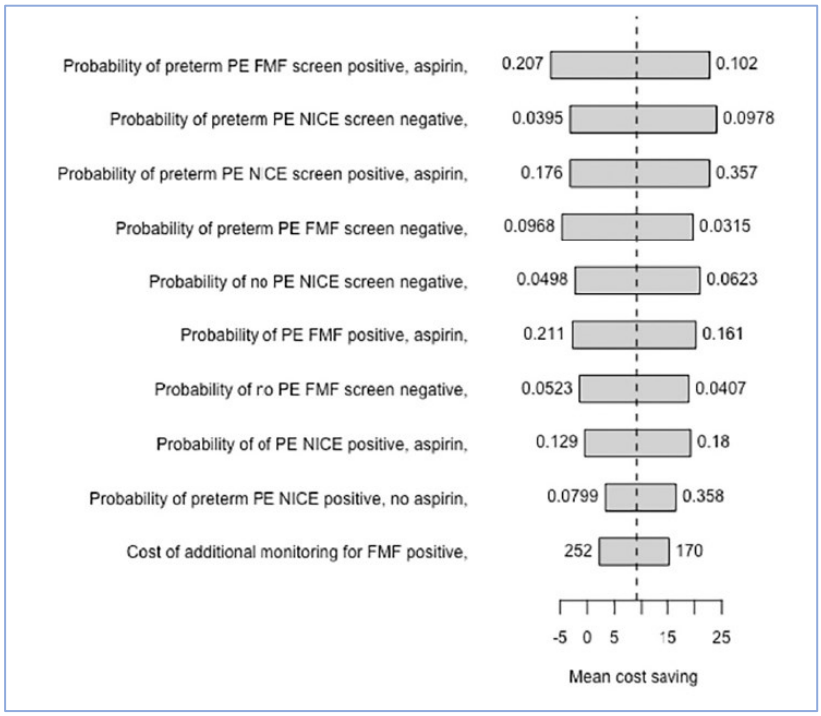


Figure 4.1 : Sensitivity analysis showing the ten model parameters that have the most significant influence on the outcomes [223]

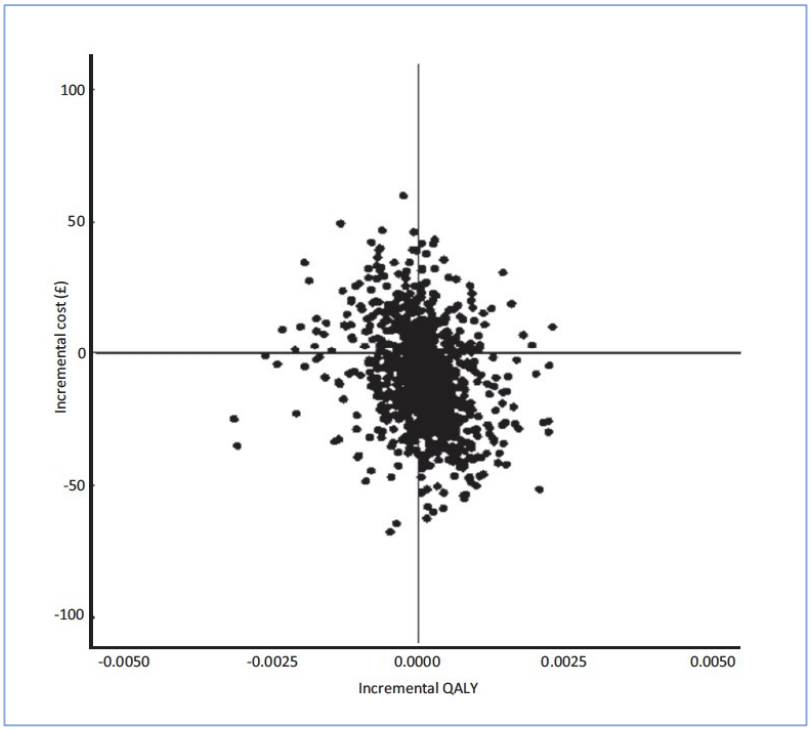


Figure 4.2 : Outcomes of the probabilistic sensitivity analysis displayed on a cost-effectiveness plane, comparing the incremental costs and QALY results between the FMF algorithm and standard care [223]

Discussion

Main Findings

Our findings support the adoption of the combined screening method for predicting PE at UCLH from a cost-effectiveness perspective. Employing the FMF algorithm does not only not lead to increased costs, but to cost savings of £9.06 and a marginal increase in quality-adjusted life years (QALY) of 0.00006 per screened pregnancy. Although the cost savings observed were slight, our cautious methodology still verified that FMF screening can be adopted without incurring extra expenses for the healthcare system, even when adherence by physicians is high. This approach allows for a more tailored antenatal care strategy by pinpointing a group at high risk. Such a group benefits not only from aspirin prophylaxis but also from a strategy on fetal growth surveillance in the third trimester and potentially earlier labour induction (chapter 3.3). Our study found a significantly higher occurrence of emergency caesarean sections and neonatal intensive care unit (NICU) admissions and longer NICU stays in cases of preterm PE compared to those from uncomplicated pregnancies or term PE. The adoption of the FMF protocol led to a reduction of seven instances of preterm PE.

Comparison to other studies

Park et al.'s study highlighted the cost-benefit of integrating first trimester screening for PE into the existing universal aneuploidy screening program in Australia, showing not only a decrease in preterm PE cases by 31 but also a significant reduction in overall health service costs by approximately $1.4 million (Australian dollars) [224]. The incremental costs for adding PE screening were found to be minimal due to the utilization of existing screening infrastructure. In Canada, theoretical models suggested a potential cost saving of $14.30 million (Canadian dollars), based on the

assumption of 387,516 births per year, by reducing the incidence of PE [225]. Studies from Germany and Switzerland have further investigated the cost implications of implementing first trimester PE screening. Mewes et al. found that while such screening could lead to cost savings in Switzerland, it would entail an additional healthcare cost of approximately €14 per woman in Germany [226].

Beernink et al found that the implementation of the combined screening test strategy in the Dutch heatlhcare setting is projected to save nearly €4 million annually while simultaneously preventing an extra 228 cases of preterm PE[227]. Sensitivity analyses identified the cost of monitoring high-risk pregnancies and the specificity of the tests as key factors influencing outcomes, with most model simulations indicating cost savings and a reduction in complications, primarily positioned in the southeast quadrant.

Strengths and Limitations

The robustness of our research lies in incorporating pragmatic population-based data, such as the adherence of physicians to aspirin prophylaxis protocols, into the model's structure and probability estimations for conducting the cost analysis. However, it is important to acknowledge that sourcing input parameters from a specific local population and healthcare context necessitates caution when extrapolating these findings to different populations or healthcare systems. Such generalizations require suitable modifications to account for varying demographic characteristics or healthcare costs. Our analysis primarily focused on the impact of the intervention on preterm PE rather than on the aggregate incidence of PE. Given the demonstrated potential benefits of the intervention on preterm PE, our cost-saving estimates likely

represent a conservative figure, suggesting the actual financial benefits could be more substantial.

This study did not assess the cost-effectiveness of alternative screening algorithms based on maternal characteristics, such as the comprehensive strategy recently recommended by American College of Obstetricians and Gynaecologists and the Society of Maternal Fetal Medicine.

Furthermore, our analysis did not incorporate the use of PLGF or UtA PI within the FMF screening algorithm. The inclusion of these biomarkers, as suggested by clinical effectiveness research, is expected to enhance the screening process's accuracy, potentially leading to a further decrease in the incidence of preterm PE [7,228].

Implications on clinical practice

Despite many studies showcasing the clinical efficacy of the FMF algorithm over screening based solely on maternal characteristics, obstacles remain regarding its broader application. Key among these hurdles are the financial implications, encompassing not only the cost of the screening itself but also the comprehensive care package required, which includes training for the measurement of uterine Doppler indices in the first trimester. Considering the proven effectiveness of aspirin and these barriers to implementation, especially in less resource-rich healthcare environments, several scholars have proposed the adoption of universal aspirin prophylaxis. However, a recent meta-analysis of 38 RCTs found that the use of universal aspirin in low-risk nulliparous women was not associated with a risk reduction in the rate of PE.

[98] The study found small benefit in the reduction of preterm birth rate, albeit with a moderate increase in the rate of postpartum haemorrhage. Adopting this approach would contradict our fundamental commitment to 'primum non nocere' – first, do no harm.

Conclusion

Within our study population, the conservative application of the FMF algorithm resulted in both clinical advantages and economic savings, underlining the value of this screening method in managing preterm PE risks.

Chapter 5.

Key considerations prior to the new service implementation

Introduction

Prior to the implementation of the FMF-combined screening for PE, women booking their antenatal care at UCLH would receive screening based on maternal risk factors as per NICE [5] at the time of their first midwifery appointment. Aspirin would then be prescribed following their first trimester scan depending on viability and the confirmed gestational age on scan. The FMF-screening approach would rely on the assessment of the MAP, UtA doppler, Papp-A and risk factors at the time of the first trimester scan. This process would be undertaken by the clinical fellows at the USU who would then prescribe aspirin to women identified as being high-risk.

The aim of our project was to implement the combined screening for PE algorithm. This would allow us to improve our recognition of women at high risk for developing preterm PE (<37 weeks of gestation) and tailor their antenatal care according to their individual risk.

Setting up the new service required an organised approach together with a multi-disciplinary team. Certain key steps needed to be undertaken to ensure the approval of the new service by the Clinical Governance Team and achieve a smooth transition from one screening method to the other. The new service was finally implemented in February 2023 and has been operating continuously since then.

Methods

Approval by the Clinical Governance team within Women's Health was required before the new service could be implemented. To secure approval, we developed a Standard Operating Procedure (SOP) on first trimester screening for PE and a patient information leaflet.

Standard operating procedure

For the new service to run smoothly, I first wrote a SOP on the screening process and the clinical pathway in order to ensure the process was clear for the healthcare professionals involved. The SOP is a document containing a set of step-by-step instructions to ensure efficiency and consistency among sonographers performing the first trimester screening for PE.

Patient information leaflet

Furthermore, I wrote a patient information leaflet following feedback from our expert Maternal-Fetal Medicine Team at UCLH. This ensured that patients had access to further information following a high-risk result and could be electronically sent to our patients through Epic, the online medical records system.

Training of sonographers

Subsequently to the above, individual training of all sonographers ensued. I personally trained all the senior clinical fellows working at USU on how to perform the MAP and Uterine artery blood flow assessment in the first trimester. The latter required multiple one-to-one sessions during the regular scanning appointments to ensure the fellows were appropriately trained and felt comfortable in their practice. As a Unit, we wanted to ensure that the quality of care we would provide met the required standards. All the clinical fellows were required to complete the FMF- online training course and submit three pictures to the FMF to obtain their certificate of competence in PE screening. In

addition, I gave two presentations on first trimester screening for PE in the department. Training was then maintained by the senior sonographers.

Results

Standard operating procedure

The SOP is depicted in figure 5.1.

Patient information leaflet

The patient information leaflet is shown in figure 5.2.

SOP ON FIRST TRIMESTER SCREENING FOR PRE-ECLAMPSIA

AIM AND SCOPE OF PROCEDURE

This SOP aims to provide guidance to all the clinical fellows performing the 11-13+6 week ultrasound scan at UCLH. The key objective is to offer combined screening for preterm preeclampsia (PE) to all women in their first trimester of pregnancy.

KEY STAFF RESPONSIBILITIES

Raffaele Napolitano & Davide Casagrandi: To ensure SOP is disseminated and followed by staff

DATE OF COMMENCEMENT: 01/02/23

INTRODUCTION

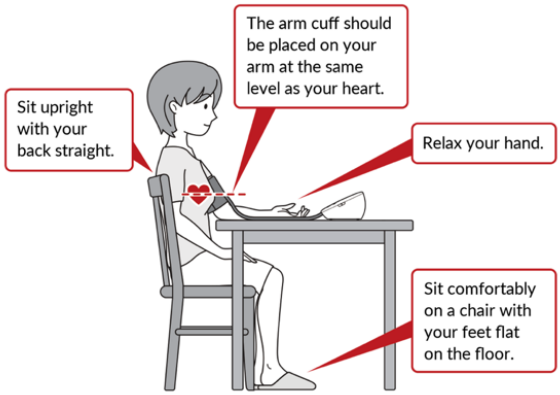
All women attending for their first trimester ultrasound scan at UCLH should be offered screening for preterm PE by means of the first trimester combined test. This includes mean arterial pressure (MAP), serum biomarkers and uterine artery pulsatility index (UtAPI) in addition to maternal risk factors. This is not part of the national screening programme. Women who decline the first trimester screening for chromosomal abnormalities should still be offered serum biochemistry for PE screening with a clear explanation that the screening for T13/18/21 would not be performed. Women who have had the Non Invasive Prenatal Testing (NIPT) should also be offered screening serum biochemistry for the prediction of PE. If the patient declines the screening, then this should be clearly documented on the Viewpoint report.

A woman is considered high risk if her risk of developing preeclampsia <37 weeks is 1 in 100 or more.

The use of low dose of aspirin (150mg) in these high risk women has been found to reduce the risk of preterm PE by 60%.

HOW TO MEASURE THE MEAN ARTERIAL PRESSURE

The patient should be seated in a chair with her back rested and her feet on the floor, relaxed and not speaking, ideally after the completion of the scan. The arm should be supported at the level of the heart. Ensure no tight clothing constricts the arm. Place the cuff on neatly 2cm above the brachial artery and aligning the 'artery mark'. The bladder should encircle at least 80% of the arm but not more than 100%. Use the cuff size recommended by the manufacturer of the monitor. Take one recording from each arm.



https://www.preeclampsia.org/accurate-blood-pressure

When to consider referral to the Maternal-Fetal Assessment Unit (MFAU):

-If the interarm BP difference is more than 20 mmHg.

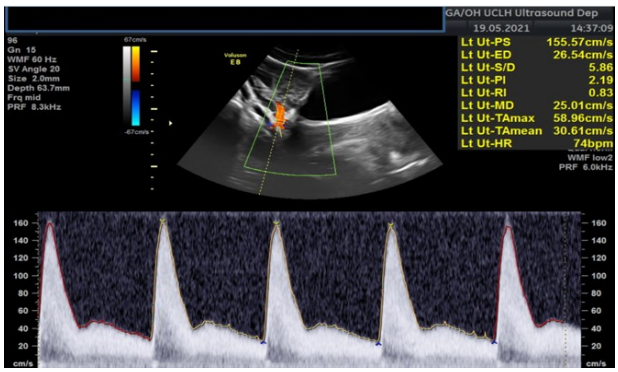
-If the systolic blood pressure is more than 140 mmHg or the diastolic more than 90 mmHg.

HOW TO MEASURE THE UTERINE ARTERY PULSATILITY INDEX

The measurement of the uterine artery pulsatility index (UtAPI) can be performed either transabdominally or transvaginally.

Transabdominal approach

1. Obtain a mid-sagittal view of the uterus and identify the cervical canal
2. Slide gently from side to side and place the colour doppler to identify the uterine artery at the level of the internal os.
3. Use high definition zoom once the uterine artery is identified
4. Use pulsed wave doppler and a sampling gate of 2mm.
5. Ensure that the angle of insonation is than 30º.
6. The UtAPI should be measured over three similar consecutive waveforms.



Transvaginal approach

1. The patient should have an empty bladder.
2. The ultrasound probe should be placed into the right and left lateral vaginal fornices to identify the respective uterine arteries at the level of the internal os.

Steps 3-7 are the same as per the transabdominal approach.

HOW TO CALCULATE THE RISK FOR PRETERM PREECLAMPSIA

Before you undertake the screening for preeclampsia, you should be FMF accredited. Please complete the FMF "Preeclampsia screening" internet-based course (https://fetalmedicine.org/education/preeclampsia-screening) and then submit three images that demonstrate colour flow mapping and waveforms of the uterine artery at 11-13+6/40. If you are not able to obtain the certificate or you need further training, then please inform your Manager who can arrange this.

The risk calculation can be performed on Viewpoint by completing the following fields:

Maternal Characteristics and History*;* If the patient is parous, then please also document the interpregnancy interval in the notes.

Maternal Serum-biochemistry*;* Papp-A level

Risk for Pregnancy Complications; In this field the MAP and the UtAPI should be documented.

Once all the required data are filled in, Viewpoint will allow you to calculate the risk.

Alternatively, the PE screening risk calculator can be accessed online at **https://fetalmedicine.org/research/assess/preeclampsia/first-trimester**

Once all the required data are filled in, Viewpoint will allow you to calculate the risk.

Alternatively, the PE screening risk calculator can be accessed online at **https://fetalmedicine.org/research/assess/preeclampsia/first-trimester**

WHAT TO DO IF A PATIENT HAS A HIGH RISK RESULT

If your patient has a risk of preterm preeclampsia of 1 in 100, then please inform her of the result either at the time of the scan (if the serum Papp-A is already available) or later during the day, when you have the result back. Reassure your patient that this is a screening, not a diagnostic test, and that aspirin can halve their risk. Additionally, offer the patient the information leaflet on "preeclampsia screening in the first trimester", which incorporates advice on aspirin prophylaxis. This can be sent through Epic. If you cannot reach the patient by phone, then use the smartphrase "*USU-high chance PET"* in order to communicate the results.

Please also prescribe low dose aspirin (150mg) for the patient to take in the evening unless there are any contraindications. If the patient is due to have an invasive test such as amniocentesis or chorionic villus sampling, please ask them to defer the use of aspirin until after they have had this performed and to discuss this with the team when she attends the Fetal Medicine Unit.

If you require any further information, please refer to our Trust's guideline on "Screening, Investigating and Managing Hypertensive Disorders in Pregnancy".

Figure 5.1: Standard Operating Procedure on PE screening

'ASSESING THE RISK OF PRE-ECLAMPSIA IN PREGNANCY

& TAKING ASPIRIN TO REDUCE THE RISK OF PREECLAMPSIA

- AN INFORMATION LEAFLET FOR PATIENTS

What is pre-eclampsia?

-If you have 2 or more of the following risk factors: (1) it is your first pregnancy, (2) you are 40 years old or older, (3) this pregnancy is more than 10 years since your last, (4) your body mass index is 35 kg/m^2 or more, (5) you have a family history of pre-eclampsia, (6) this is a multiple pregnancy (more than one baby).

Alternatively, you might have been recommended to take aspirin during your pregnancy by your Obstetric Team (including Professor Williams, Miss Whitten, Professor Siassakos and members of the Fetal Medicine team amongst others) in view of your previous obstetric or medical background

(b) an assessment of physical measurements, such as your blood pressure, the resistance in the blood flow through your uterine arteries (which supply the growing uterus) on ultrasound assessment and

(c) the measurement of a protein in your blood called pregnancy-associated placental protein (Papp-A). Papp-A is measured from the blood sample that is taken routinely in all women who have accepted to have combined screening for chromosomal abnormalities such as Down's syndrome.

If you have decided not to have the combined screening for chromosomal abnormalities, you will still be offered a blood test to calculate your preeclampsia risk. This is helpful,

Is aspirin safe for me and my baby?

Low-dose aspirin (150mg) is considered safe in pregnancy. Rarely, low dose aspirin may cause irritation of the stomach. Under these circumstances, LDA can be taken after food. If you are allergic to aspirin you should not take low dose aspirin.

You should not take aspirin if you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), if you have had previous gastric/ peptic ulcers/ inflammatory bowel disease or if you have severe asthma, especially if your asthma worsens when you take NSAIDs.

If your doctor had previously advised you to avoid NSAIDs outside of the pregnancy, then you should not take aspirin during the pregnancy.

Figure 5.2: Patient Information Leaflet on PE screening and aspirin use

Training of Sonographers

Every sonographer employed at the Ultrasound Unit is engaged in pursuing a Master of Science in Obstetric Ultrasound and Fetal Medicine at University College London (UCL). Junior sonographers are classified as such in their first year of the MSc program, progressing to senior status in their second year. A key duty of these senior

sonographers involves imparting training to the junior sonographers on conducting scans throughout the various stages of pregnancy. My specific role was to educate the senior sonographers on executing the combined screening test, with a particular focus on the UtA assessment during the first trimester. This was so they could adequately pass on this knowledge to their junior counterparts. Over a span of four months, I directly instructed all 17 senior sonographers in performing the UtA PI measurements during routine nuchal translucency scans at the USU. Following each session, I provided individualized feedback.

Concurrently, all senior sonographers were required to complete the Fetal Medicine Foundation's (FMF) online course on 'Preeclampsia Screening'. After the completion of their training, each senior sonographer submitted three images demonstrating their UtA assessments to the FMF. Upon meeting the FMF's quality standards with their images, they were awarded FMF certification in PE screening competence.

Discussion

The combined screening for PE service was successfully implemented in February 2023. We followed a staged and managed approach for the new service to be implemented. This required a period of two years and multiple challenges had to be overcome during this time.

Initially, we contemplated limiting the combined screening approach to a select proportion of women initiating their prenatal care at UCLH. The plan involved establishing a clinic within the USU, specifically for conducting first trimester scans and providing the combined PE screening. This arrangement would necessitate adjustments to the existing schedule at USU to ensure the uninterrupted flow of routine services. A significant challenge was to maintain the existing volume of scans at USU. Moreover, ethical concerns arose regarding the provision of an enhanced service to a subset of women, thereby creating disparity in service quality. After extensive deliberations among the multidisciplinary team, the initial plan was discarded and the decision was made to extend the combined screening method to all pregnant women under UCLH's care. This expansion required evidence demonstrating that (a) the new service would outperform the existing practice in predicting PE within the UCLH cohort (chapter 3.1) and (b) the approach would be cost-effective (chapter 4). It was also necessary to design a clinical pathway tailored to patients post-risk stratification in both the first and second trimesters (refer to chapter 3.2).

Indeed, we performed a decision analytic model on estimation of costs and outcomes for pregnancies screened with the FMF combined algorithm compared to the NICE screening method. The use of the combined screening algorithm would have correlated with seven fewer cases of preterm PE, an estimated cost-saving of £9.06 and a QALY gain of 0.00006 per pregnancy screened. Our study clearly supported the commencement of the combined screening algorithm for women booking their antenatal care at UCLH. We were also able to show that the utilization of routine second-trimester UtA doppler assessment could enhance the stratification of PE risk among women who underwent first-trimester combined screening for PE.

Another important aspect was training all sonographers in the assessment of uterine arteries during the first trimester as this formed part of the combined screening approach. This involved authoring a Standard Operating Procedure, creating a patient information leaflet, hands-on teaching on one-to-one basis with personalised feedback and delivering two presentations. Following the implementation of the new service, we performed a reproducibility analysis of the UtA doppler assessment among the sonographers (chapter 6). This allowed us to understand whether further training was required.

In the future, we plan to perform a patient satisfaction questionnaire from our new service in addition to a prospective data analysis on women who received the combined screening for PE at UCLH.

Chapter 6.

Reproducibility of Uterine Artery Pulsatility Index following the implementation of the Combined Screening Approach

Introduction

The measurement of the UtA PI plays an incremental role to the FMF algorithm and is the most operator-dependent marker. Differences in the UtA PI of 14% can result in a 7% difference in the PE screening performance[229].

The new service was implemented on the 1st of February 2023. Prior to the implementation date, I trained all the senior sonographers working at the Obstetric Ultrasound Unit of UCLH and provided personalised feedback to further improve their performance. The senior sonographers also had to complete an online learning course on PE screening [230] and then submit three images demonstrating colour flow mapping and waveform of the uterine artery in the first trimester. The images were submitted and reviewed by the FMF and if they met the standards, sonographers then obtained the FMF certificate of competence in PE screening. All the senior sonographers at our Unit were able to achieve the FMF accreditation on PE screening prior to the service implementation. Even though all the sonographers were officially certified to perform the PE screening, we wanted to ensure the accuracy and reproducibility of the UtA PI measurements.

The senior sonographers of the Unit had approximately 12 – 24 months of experience at UCLH and were into the 2nd year of the MSc in Obstetric Ultrasound and Fetal

Medicine at UCL. Junior sonographers had approximately 3 - 11 months of experience and were in the 1st year of the MSc.

We performed a prospective study over a period of 6 months to find out whether the sonographers were performing reproducible measurements by assessing both the intra-observer reproducibility as well as the inter-observer reproducibility. Different ultrasound scan machines were used for the measurements. If our results were to show discrepancy, then further training would be arranged for the team. If our results were reassuring, then periodic re-auditing would be ensued.

Methods

Prospective data on uterine artery blood flows were collected from 143 patients with singleton pregnancies. A total of 20 sonographers participated in the study. The UtA assessment was performed through the transabdominal route. The artery was sampled at the level of the internal cervical os in a midsagittal view with an angle of insonation of less than 30°, and measured over three similar consecutive waveforms. Both the intra- and the inter- observer reproducibility were assessed. Ethical approval was not required given that our study involved de-identified data for analysis and quality assurance purposes.

All the sonographers conducted the measurements independently and were blinded both to their own and to each other's measurements.

Statistical Analysis

Categorical data were presented in numbers and percentages and continuous data in median values and IQR. We performed one sample t-test analysis for the inter- and

the intra- observer mean differences. We then performed reliability analysis with Cronbach's alpha, intraclass correlation coefficient (ICC) with 2-way random effects model and absolute agreement. Results were analysed with Bland-Altman plots revealing limits of agreement (LoA). Statistical analysis was conducted on SPSS (version 29). Threshold of agreement was set at 14% given that this difference can result in the reclassification of PE prediction in 7% of women [229]. ICC was categorised as poor (0−0.2), fair (0.21−0.4), good (0.41−0.60), strong (0.61−0.8) or almost perfect (0.8−1) [231].

Results

A total of 143 patients were included in this study and had their uterine artery blood flow assessed twice and bilaterally by 2 sonographers All measurements were performed transabdominally. However, there were 3 measurements missing from the second sonographer. A total of 569 UtA PI comparisons were made for the intra-observer and the inter-observer reproducibility.

Table 6.1 summarises the maternal characteristics in detail. The median gestational age was 12^{+4} and the median CRL was 61mm (IQR: 55.9mm-67mm).

Maternal Characteristics	Population
Nulliparous, n (%)	79 (55.2%)
Age (in years), median (IQR)	35 (IQR: 29- 38)
BMI (in kg/m^2), median (IQR)	23.5 (IQR: 21.1-27.0)
Gestational age, median (IQR)	12^{+4} (IQR: 12^{+1}- 13^{+0})

Table 6.1: Maternal Characteristics

Intra-observer reproducibility

The mean difference between the two values taken by the same sonographer was equal to 0.0116 (95% CI: -0.002 to 0.026). The 95% limits of agreement (LoA) for intra-observer differences were -0.001 to 0.034. The Bland- Altman plot is shown in Figure 6.1. A linear regression analysis was also performed resulting in a p-value of 0.326, thus rejecting the null hypothesis and confirming that there is a level of agreement amongst the different measurements.

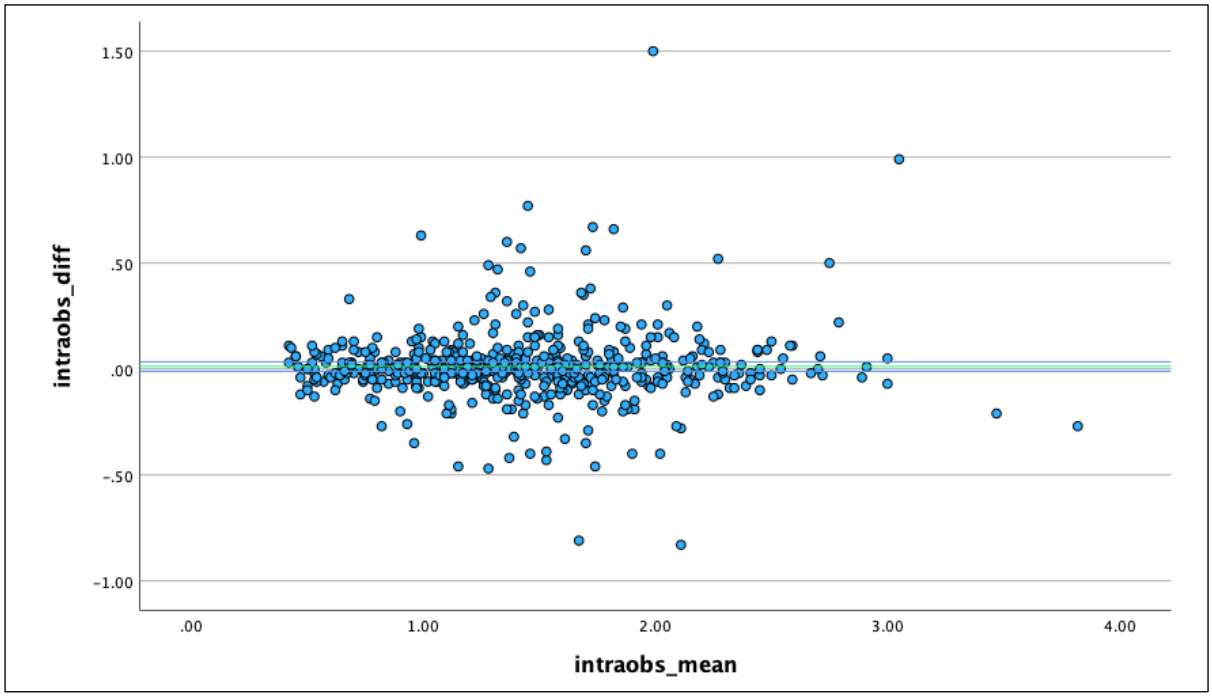


Figure 6.1: Bland-Altman plot of intra-observer differences
Green line: mean difference
Blue lines: 95% LoA

The ICC for single measures was 0.95 and for average measures 0.974 and both were statistically significant (p-value <0.001). The latter is also known as the Cronbach's alpha, and it assesses internal consistency. This can be interpreted as follows; 97.4% of the variance in the observed UtA PI measurements can be attributed to the variance in the sonographers' true measurements with 2.6% of the variance accounted for by measurement error (Table 6.2). 85.9% (489 out of 569) of the intra-observer measurements were within the threshold of agreement.

	Intraclass Correlation	95% Confidence Interval	p-value
Single Measures	.950	.941 -.957	<.001
Average Measures	.974	.970 - .978	<.001

Table 6.2: ICC for intra-observer reproducibility

Inter-observer reproducibility

The mean difference of the UtA PI values between the two sonographers was equal to -0.026 (95% CI: -0.048 to -0.0043). The 95% LoA were -0.077 to 0.025 as shown on the Bland-Altman plot (figure 6.2). The p-value on linear regression analysis was 0.364, rejecting the null hypothesis and thus verifying a level of agreement between the different measurements. The ICC was approximately 0.88 for single measures and 0.94 for average measures with p-values of <0.001 for both, proving excellent reliability.

	Intraclass Correlation	95% Confidence Interval	p-value
Single Measures	.884	.864 -.900	<.001
Average Measures	.938	.927 -.948	<.001

Table 6.3: ICC for inter-observer reproducibility (junior and senior sonographers)
Having set our threshold of agreement at a 14% difference, 73.6% (419 out of 569) of the measurements were within the agreement limit.

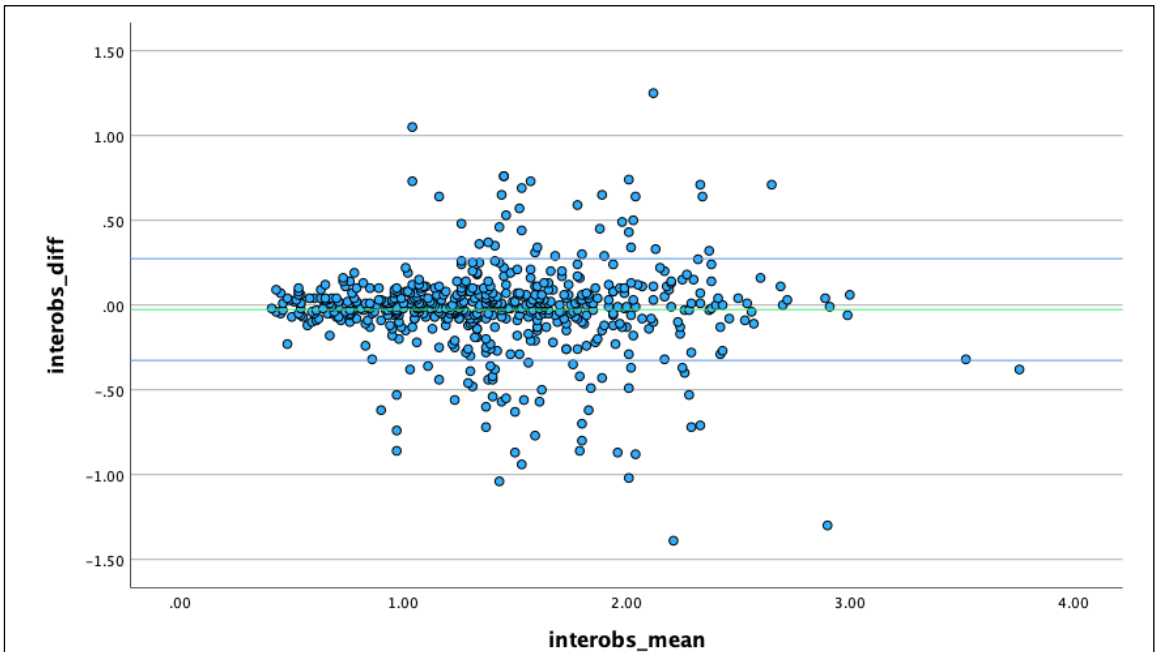


Figure 6.2: Bland-Altman plot for inter-observer differences
Green line: mean differences
Blue lines: 95% LoA

Our interobserver reproducibility results were slightly better if we were to exclude the junior sonographers from the analysis (table 6.4). A total of 496 measurements were compared. The mean difference was -0.013 (95% CI: -0.03 - 0.006) with LoA of -0.039 to 0.013.

The ICC was 0.926 and 0.962 for single and average measures, respectively. These results were statistically significant (p-value <0.001). 89.3% (419 out of 469) of the measurements were with the threshold of agreement.

	Intraclass Correlation	95% Confidence Interval	p-value
Single Measures	.926	. .912 -.938	<.001
Average Measures	.962	.954 -.968	<.001

Table 6.4 ICC for inter-observer reproducibility (senior sonographers only)

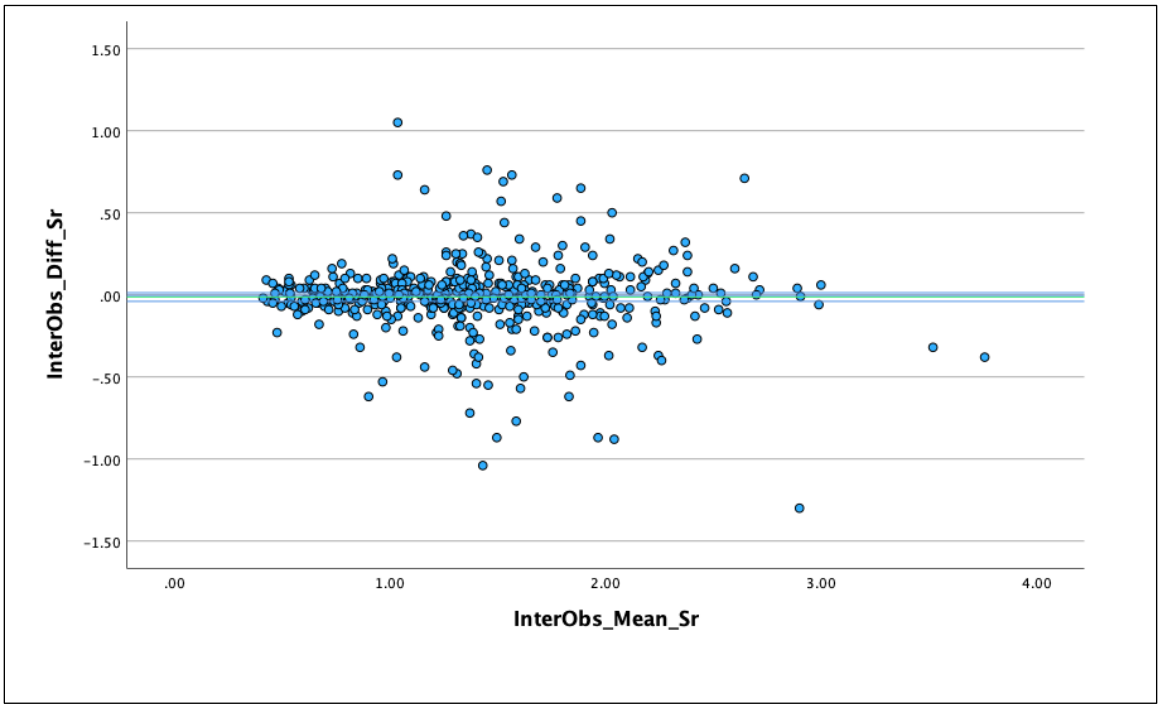


Figure 6.3 Bland-Altman plot for inter-observer differences between senior sonographers
Green line: mean differences
Blue lines: 95% LoA

Discussion

Main Findings

The assessment of the UtA blood flow plays an important role in the FMF algorithm for the prediction of PE as well as FGR. The first trimester UtA PI measurements performed at our Unit were reproducible with a good level of agreement.

We did acknowledge the work by Martins et al on assessing ultrasound measurements in reproducibility studies [232] who considered reliability very good if the value is greater than 0.99, good for values between 0.95 and 0.99, moderate for values of 0.9-0.95, poor for values of 0.70-0.90 and very poor for values less than 0.70. However, the authors did suggest that when only a narrow gestational age is included as in the case from 11 + 0 to 13 + 6 weeks, the more widely used lower cut-offs may be appropriate, which is the approach we followed. Consequently and based on the more widely acceptable ICC cut-offs to interpret our results [231], both the intra- and the inter-observer ICC values were almost perfect (0.97 and 0.94-0.96, respectively). The inter-observer reproducibility was evaluated both between senior and junior/senior sonographer as well as between solely senior sonographers, with a slight increase in the ICC from 0.94 to 0.96 as would be expected.

Approximately 86% of the intra-observer measurements were within the threshold of agreement compared to 89% of the senior inter-observer measurements.

Comparison to other studies

Our senior sonographers had up to 24 months of experience, which was less compared to other studies assessing reproducibility of UtA PI in the first trimester. Nonetheless our ICC results were comparable to other studies.

Chaemsaithong et al performed a reproducibility study including 52 women. UtA assessment was performed by senior sonographers with 10-15 years of experience. Their interobserver ICC was 0.72 for the left and 0.38 for the right UtA [229]. Marchi et al recruited a total of 101 women. A total of 202 measurements were taken transabdominally within 3 subgroups; these included a total of 50, 52 and 74 measurement comparisons, respectively in each subgroup. TAUSS assessment of the UtA PI was performed on included experienced sonographers who had between 6 months to over 3 years of holding the FMF certificate in PE screening [233]. They reported an ICC of 0.87 for intra-observer reproducibility and 0.79 to 0.92 for inter-observer reproducibility depending on the subgroup operators' experience and scanner (Voluson E8 vs Aloka alpha 6) used.

Hollis et al included 63 patients with a total of 126 measurements of the Rt UtA and 118 of the Lt UtA for intra-observer reproducibility [234]. The ICC was 0.78 and 0.80 for the Rt and Lt UtA PI, respectively. Inter-observer reproducibility was performed on a total of 90 measurements from the Rt Ut A and 94 from the Lt UtA. The ICC for inter-observer reproducibility was 0.6 and 0.58, respectively. The authors concluded that the UtA RI rather than the UtA PI was the most repeatable and reproducible measurement.

Strengths and limitations

Our study included a large number of measurements and was performed in an academic-hospital setting. The sonographers were blinded to the measurements as to reduce the risk of bias.

The senior sonographers received thorough training on a one-to-one basis, had the opportunity to study the SOP and an online learning course on PE screening. Measurements were thus performed using strict criteria as set by the FMF and our SOP recommendations. This likely contributed to the superior ICC achieved compared to other studies assessing reproducibility of UtA PI in the first trimester.

Our study was limited by the fact that we did not re-calculate the PE screening result based on the differences between the repeated measurements. This would have assisted us in setting a more clinically meaningful threshold of agreement for our statistical analysis. Furthermore, we did not include PE outcomes for the patients we included in our study.

Implications on clinical practice

Assessment of the UtA PI is an integral part of the combined screening algorithm. Our results showed that our Unit was thoroughly organised for the service implementation. We consider the transabdominal measurement of the UtA PI preferrable both in view of the patient acceptance as well as the lower values achieved compared to the transvaginal route. Despite this, there are no specific reference ranges depending on the method of UtA PI measurement (TA vs TV) and this is not taken into consideration

in the combined FMF algorithm. Another TA approach has also been described with comparable results to the recommended TA approach. More specifically, it is feasible and reliable to evaluate the UtAs at the level of the internal os in a transverse view of the cervix, whilst visualising both UtAs. [235] This is an alternative approach for assessing the UtA transabdominally prior to or instead of proceeding to a transvaginal assessment.

Conclusion

Our study was able to show that UtA PI was measured reliably by trained sonographers following implementation of the first trimester screening for PE in our clinical and academic setting. One-to-one teaching with provision of feedback and the completion of online learning prior to FMF accreditation helped our Unit achieve excellent reproducibility of the measurements, thus making the combined screening for PE more reliable. Individualised training of our sonographers was crucial prior to the new service implementation and we consider that periodic auditing will help maintain good standards of quality.

Chapter 7.

Future Work

To build upon the findings and successes of our project at UCLH, several future directions should be pursued. Firstly, it is crucial to evaluate prospective data on women who received first trimester FMF-combined screening for PE at UCLH from February 2023 to February 2024. This analysis will help validate our initial findings and provide insights into long-term outcomes. Additionally, we should investigate the potential benefits of earlier delivery to reduce the incidence of term PE, especially in high-risk women identified through combined screening, by comparing outcomes for those delivering before 40 weeks versus those delivering at term.

A qualitative performance evaluation, involving the collection of patient feedback, is necessary to assess the qualitative performance of the FMF combined screening approach and the associated clinical pathways. Understanding patient experiences and satisfaction can guide further improvements in care delivery. Additionally, continued periodic audits of sonographer performance are essential to ensure the accuracy and reproducibility of UtA PI measurements. Implementing additional training programs, if needed, will help maintain high standards.

Performing detailed cost-effectiveness studies is vital to quantify the economic benefits of implementing the FMF combined screening approach on a larger scale. This includes analyzing healthcare costs saved through early detection and intervention, as well as the long-term economic impacts on healthcare systems.

Investigating the potential integration of additional biomarkers such as PlGF with the FMF-combined screening to further enhance predictive accuracy for PE and FGR is another important future direction. Conducting longitudinal studies to follow up on children born to mothers who underwent the FMF-combined screening is also crucial. Assessing long-term health outcomes for both mothers and children will provide comprehensive insights into the benefits and any potential risks associated with this screening approach.

By focusing on these future directions, the project can continue to advance the understanding and management of PE, ultimately improving maternal and fetal outcomes. The integration of comprehensive screening methods, evidence-based interventions, and continuous quality assessments will help establish a new standard of care in prenatal medicine.

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