Category: Clinical Guideline

Early pregnancy screening and prevention of preterm preeclampsia and related complications (C-Obs 61)

This guideline has been developed by the C-Obs 61 Early pregnancy screening and prevention of preterm preeclampsia and related complications Guideline Development Group and reviewed by the Women's Health Committee in April 2024. Final approval is now sought from RANZCOG Council.

A list of the Women's Health Committee membership can be found in Appendix A: Women's Health Committee Membership. A list of the Guideline Development Group Membership can be found in Appendix B: Guideline Development Group Membership.

Conflict of interest disclosures have been received from members of this Guideline Development Group. See Appendix C: Overview of the development and review process for this guideline.

Disclaimer: This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances (Appendix D: Full Disclaimer)

Objectives:	To provide advice to registered health professionals providing maternity care on early-pregnancy screening for and prevention of preeclampsia to improve maternal and perinatal outcomes.
Target audience:	This guideline was developed primarily for use by registered health professionals providing maternity care, and consumers. See: RANZCOG's Interim guideline on gendered language (below).[1]
Background:	This guideline was first developed by the RANZCOG Women's Health Committee in July 2015. The guideline was most recently updated by the C-Obs 61 Early pregnancy screening and prevention of preterm preeclampsia and related complications Guideline Development Group, a working group of the Women's Health Committee in April 2024.
Funding:	The development and review of this guideline was funded by RANZCOG.

[1] *RANZCOG currently uses the term 'woman' in its documents to include all individuals needing obstetric and gynaecological healthcare, regardless of their gender identity. The College is firmly committed to inclusion of all individuals needing O&G care, as well as all its members providing care, regardless of their gender identity.*

Contents

1. Plain language summary

Preeclampsia is a serious pregnancy complication. It can begin any time after a woman is 20 weeks pregnant and usually does not go away until after birth. The features of this condition are very high blood pressure and problems with other organs such as the kidneys, liver, blood, brain, and placenta. As preeclampsia can be dangerous for both mother and baby, pregnancies complicated by preeclampsia may need to be monitored more closely than those without.

Some women have a higher chance of developing preeclampsia than others. While no treatment completely prevents preeclampsia and women at higher risk still require extra monitoring during pregnancy, current research suggests screening all women to help understand who is at most risk and who should receive medication is an approach that is likely to improve outcomes for women and babies. Evidence shows if women at increased risk of preeclampsia are identified early in their pregnancy, common medications (such as aspirin) can be offered by registered health professionals and may help to lower the risk of developing preeclampsia (particularly preterm preeclampsia) and other adverse pregnancy and birth outcomes.

2. Purpose and scope

In 2023, under the auspices of RANZCOG's Women's Health Committee, a Guideline Development Group (GDG) was convened to update the existing guideline on Screening in Early Pregnancy for Adverse Perinatal Outcomes (C-Obs 61). The GDG, consisting of members in both Australia and Aotearoa New Zealand, determined the scope of the guideline would be limited to screening for preterm preeclampsia. A change of the guideline title to reflect the revised scope was also approved.

Scope: Screening for preterm preeclampsia in any type of pregnancy (plurality, any parity) before 16 weeks gestation, with acknowledgment that 11^{+0}-14^{+1} weeks gestation is the ideal window for screening. Prophylaxis for women who screen at increased risk of preterm preeclampsia is also addressed in this guideline. This includes recommended medications, dosage, timing of treatment and when to cease treatment.

Out of scope: Screening algorithms for other placental conditions and complications, including small for gestational age, fetal growth restriction (SGA/FGR) and preterm birth; gestational diabetes mellitus (GDM); placenta accreta spectrum (see College guideline C-Obs 20 PAS); long term maternal outcomes associated with preeclampsia; management of preeclampsia >20 weeks gestation; antiplatelet therapy aside from aspirin; non-pharmacological prevention strategies.

3. Terminology

This Clinical Guideline uses the following terms throughout this document. Definitions are provided to assist the reader with interpretation of evidence and recommendations.

Odds Ratio (OR)- measures association between two events (i.e., intervention and outcome). An OR of 1 is indicative of no difference in the odds of an outcome with the intervention. An OR < 1 demonstrates reduced odds of an outcome. An OR > 1 shows increased odds of an outcome.

Relative Risk (RR)- provides a ratio between the risk or probability of an outcome with the intervention, divided by the risk for the same outcome with the comparator. Like the OR, a RR of 1 suggests no difference. An RR > 1 suggests increased risk. An RR < 1 suggests decreased risk. The term Hazard Ratio (HR) may also be used and is similarly equivalent.

Sensitivity- the proportion of people with the target condition who test positive.

A test with high sensitivity will be positive in a high proportion of participants who have the target condition and may be used to rule out the presence of that target condition: false negatives are not likely, so any negative is probably a true negative.

Specificity- the proportion of people without the target condition who test negative.

A test with high specificity will be negative in most of those without the target condition and may be used for ruling in the target condition. As false positives are unlikely, most positive index test results will be true positives.

Positive Predictive Value (PPV)- the proportion of those with a positive index test who have (or will go on to develop) the target condition.

Negative Predictive Value (NPV)- the proportion of those with a negative index test result who do not have (or will not go on to develop) the target condition.

Screen positive rate (SPR)- the proportion of people who were tested who received a positive result (i.e., increased risk of preterm preeclampsia).

Number needed to treat (NNT)- equates to the number of patients who must be exposed to a treatment/intervention to prevent one additional poor outcome.

4. List of recommendations

Screening

Recommendation 1	Evidence based recommendation
Strong: Offer routine screening in early pregnancy for preterm preeclampsia to all women. Screening algorithms that include clinical history, blood pressure (MAP), ultrasound with mean uterine artery pulsatility index (UtPI), and maternal serum biochemical markers (PAPP-A, and/or PlGF) are recommended as they more accurately predict which women are at risk for developing preterm preeclampsia compared to risk assessment by history alone. GRADE of evidence: Moderate	
Good Practice Point 1	
GPP: In settings where the complete algorithm may not be feasible, consideration may be given to the use of some but not all components of the algorithm. Evidence suggests that any additional components to maternal history and BP are likely to improve the ability to detect women who will go on to develop preterm preeclampsia. When screening for preterm preeclampsia, maternal risk factors and BP measurements are the minimum requirements to identify women at risk of developing preterm preeclampsia using the Fetal Medicine Foundation (FMF) algorithm (Available online - The Fetal Medicine Foundation).	
Good Practice Point 2	
GPP: The GDG recommend a risk cut off of 1:100 (which approximates a screen positive rate of 10% in a typical pregnant population) be used to offer prophylaxis.	

Prophylaxis for women identified at increased risk

Recommendation 2	Evidence based recommendation
Strong: Women with an increased risk of preeclampsia (identified by screening) should be offered low-dose aspirin (at least 100mg daily) starting before 16 weeks pregnancy as it reduces the likelihood of preterm preeclampsia, preterm birth, and other associated complications. GRADE of evidence: Moderate	

Recommendation 3	Evidence based recommendation
Conditional: Women with an increased risk of preeclampsia (identified by screening) could be offered high-dose calcium (>1000mg or more), as it may reduce the likelihood of preeclampsia and preterm birth. GRADE of evidence: Low	

Recommendation 4	Consensus-based recommendation
Where calcium is offered for preeclampsia prevention, it should be in addition to low-dose aspirin and not as a sole agent.	

5. Introduction

Rationale

Preeclampsia (Māori: pēhanga toto i te hapūtanga) is a multi-system condition which occurs at or above 20 weeks gestation, characterised by new-onset hypertension (systolic blood pressure at ≥140 mm Hg and/or diastolic blood pressure at ≥90 mm Hg on at least two occasions, measured four hours apart in a previously normotensive woman).[1] This elevation in blood pressure is further accompanied by one or more of new-onset proteinuria, evidence of other maternal end-organ dysfunction, and/or placental dysfunction. A complete definition, including clinical conditions and markers can be found in Appendix G-Classification of preeclampsia: list of clinical features (ISSHP).

Preeclampsia is associated with significant adverse maternal and perinatal outcomes. While most cases of preeclampsia develop at term (after 37 weeks), preterm preeclampsia (resulting in birth before 37 weeks gestation) may result in substantial morbidity for both mother and neonate. Preeclampsia is also a known risk factor for other related complications including preterm birth, fetal growth restriction (FGR), and placental abruption.

Early identification of women at increased risk for preeclampsia is critical in reducing the burden of this condition. Development of screening algorithms and the efficacy of associated prophylactic treatment for women at increased risk have been the focus of a substantial volume of research in the past five years and prior. Systematic review of this evidence demonstrating the benefits of screening and treatment has resulted in updates to international guidelines, many of which now recommend the routine use of screening and prophylaxis to reduce preterm preeclampsia and related complications. Furthermore, severe complications of preeclampsia, such as eclampsia, HELLP syndrome, and stillbirth may be largely preventable through early detection and management of preeclampsia, which is enhanced in women previously identified as being at increased risk.

Improvements in identifying women at risk of preterm preeclampsia and targeted prophylaxis in early pregnancy may lessen the incidence of such complications. This has provided further impetus to facilitate the translation of this evidence into clinical practice for health professionals in Australia and Aotearoa New Zealand. In addition to summarising the evidence base for three key clinical questions, this Clinical Guideline considers practical issues and challenges which may arise for practitioners in the implementation of updated evidence and recommendations into clinical practice, particularly for those working in rural and remote settings in both countries.

NB: Occasionally in this document a further subgroup of preeclampsia is referred to as early-onset preeclampsia which is variably defined in the literature as preeclampsia diagnosed and leading to birth before 32 or 34 weeks gestation.[2]

Epidemiology

Preeclampsia complicates approximately 3% of pregnancies. It remains a significant contributor to maternal and perinatal morbidity and mortality globally, accounting for more than 76,000 maternal deaths and 500,000 infant deaths worldwide annually.3 Preeclampsia is a contributory factor for other adverse pregnancy and perinatal outcomes, including preterm birth, FGR, and neonatal admissions to intensive care (NICU).

Australian studies estimate the prevalence of preterm preeclampsia (diagnosed or requiring delivery before 37 weeks' pregnancy) as 0.7% and early-onset preeclampsia (diagnosed or requiring delivery before 34 weeks' pregnancy) as 0.4%.4 Although the occurrence of preterm preeclampsia is less common than term preeclampsia, the impact on maternal and neonatal morbidity and mortality is substantial due to generally more severe maternal disease and the impact of prematurity upon the neonate.

Preeclampsia is associated with short- and long-term morbidity in mothers and babies. In Australia, hypertension is a leading cause of maternal and neonatal illness and death.5, 6 In Aotearoa New Zealand, hypertensive disorders of pregnancy (HDP), including preeclampsia, accounted for 31% of maternity admissions to an intensive care or high-dependency unit in 2018/2019.7 Women whose pregnancies are complicated by preeclampsia are at increased risk of cardiovascular disease in the long term.8

Equity

Preeclampsia rates are reportedly higher in Aboriginal and Torres Strait Islander women and Māori and Pacific Islands women, however comprehensive national data are lacking in both Australia and Aotearoa New Zealand.

Australia: In 2021, a greater proportion of Aboriginal and Torres Strait Islander women were diagnosed with hypertensive disorders of pregnancy (inclusive of preeclampsia) than non-Indigenous women in Australia (3.4% compared to 2.3% respectively). Studies have reported that Aboriginal and Torres Strait Islander women more commonly have risk factors associated with hypertensive disorders of pregnancy, including elevated pre-pregnancy blood pressure, a known risk factor for preeclampsia.9, 10 Other pregnancy complications which may be related to preeclampsia, including preterm birth, are experienced at higher rates for Aboriginal and Torres Strait Islander women.11, 12

Aotearoa New Zealand: In an Auckland based study in 2012, the risk of preeclampsia was found to be nearly 50% higher among Māori wāhine hapū (pregnant women) compared to European women.13 Māori wāhine more commonly have risk factors associated with hypertensive disorders of pregnancy, including elevated pre-pregnancy blood pressure, a known risk factor for preeclampsia.13 Of further relevance to preeclampsia screening, the proportion of women who register with a Lead Maternity Carer (LMC) in first trimester is reported as lower in Māori and Pacific Islands populations (59.8% and 49.4% in 2021

respectively).14 Factors associated with this difference may include limited availability to culturally appropriate antenatal care and other social determinants of health.

Two consecutive reports from the Perinatal and Maternal Mortality Review Committee (PMMRC 2021 and 2022), have highlighted that women and babies with Indian ethnicity in Aotearoa New Zealand also experience adverse pregnancy outcomes, including preeclampsia, at disproportionate rates to New Zealand women with European ethnicity.7, 15 The causes of this inequity are likely to be multifactorial, may be related to the availability of culturally appropriate care and remain subject to ongoing research.7, 15, 16

An equity tool, developed to understand the experiences and barriers Māori populations may encounter in accessing the health system was applied to this guideline and can be found in Appendix F- Māori Equity toolkit.

6. Methods

The guideline was developed according to approved RANZCOG processes, available in the Handbook for the development of evidence-based guidelines and statements. Following these processes, including the development of three clinical questions, the Research and Policy Team identified several local and international guidelines published within the past five years. These included:

- The International Federation of Gynaecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention (2019).[3]
- ISUOG Practice Guidelines: Role of ultrasound in screening for and follow-up of preeclampsia (2019).[17]
- Te Whatu Ora: Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand (2023).[18]
- Queensland Clinical Guidelines: Hypertension and pregnancy (2021).[5]
- Hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice (2018).[1]
- The 2021 ISSHP classification, diagnosis & management recommendations for international practice.[19]
- NICE: NG 133 Hypertension in pregnancy: diagnosis and management (2019).[20]
- Society of Obstetric Medicine Australia and New Zealand (SOMANZ) Hypertension in Pregnancy Guideline (2023).[21]

For each clinical question, further literature searches were performed to identify additional peer-reviewed studies where relevant and in accordance with RANZCOG evidence processes. For the complete search strategy and results, see Search strategies.

Assessment of the rigour, certainty and quality of evidence was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

The terms and phrases used in recommendations and Good Practice Points (GPPs) are dependent on the strength and certainty of the body of evidence - further explanation of recommendation types and classifications can be found in the Handbook.

7. Clinical Questions and Recommendations

Detailed summaries of evidence and Evidence to Decision frameworks for each clinical question, including the study results, absolute effect estimates and certainty of evidence for the reported outcomes, can be found in Appendix E- Evidence to Decision framework.

Clinical Question 1

Does screening in early pregnancy for preeclampsia improve maternal and perinatal outcomes?

P[ii]- All women in early pregnancy up to 16 weeks

I- Screening algorithm (combination and each in individually)- maternal risk factors + blood pressure or mean arterial pressure (MAP), +/- PAPP-A, PlGF, UtPI) plus treatment (if screen high risk)

C- Standard screening (history-based screening) +/- MAP plus treatment if high risk from history-based screening

O- Maternal- Diagnosis of preterm and term preeclampsia/ hypertensive disorder of pregnancy, maternal mortality or serious morbidity, need for antihypertensive medication, antenatal secondary/tertiary care admission, mode of birth, ICU admission, placental abruption, stress/anxiety

Neonatal- Perinatal mortality or serious morbidity, preterm birth (<37+0 weeks), gestation at delivery, birthweight, Apgar score (at 5mins), NICU admission

Clinical Question 2

In pregnant women up to 14 weeks, are UtPI and biomarkers compared with usual care or other combinations, more accurate in identifying women at risk of preeclampsia < 37 weeks?

P- Women in first trimester pregnancies up to 14 weeks, any parity.

I- Combined ultrasound (UtPI) and biomarkers (PAPP-A, PIGF)

C- Maternal risk factors, MAP, individual components of combined ultrasound (UtPI) and different biomarkers (PAPP-A, PIGF)

O- Sensitivity and specificity for identifying women at risk of preterm preeclampsia (<37^{+0} weeks) detection rates

Background

One recent systematic review of six studies was included as the primary source of evidence.[22] Of the six, one high-quality randomised control trial (RCT) and five observational cohort studies reported a first trimester approach to screening accompanied with prophylactic aspirin for prevention of preterm preeclampsia (30,192 women in all studies).[23]

Screening algorithms reported in the review were either the Fetal Medicine Foundation (FMF) algorithm (four studies) or alternative (two studies) compared with provision of standard maternity care.

The FMF algorithm is a publicly available online calculator which uses a combination of prior risk factors (maternal and medical history) with biophysical (MAP, uterine artery pulsatility index (UtPI)) and biochemical (pregnancy-associated plasma protein A (PAPP-A) and/or placental growth factor (PlGF)) markers to estimate the risk of preterm preeclampsia. The FMF calculator is validated to calculate risk for women who are 11^{+0} – 14^{+1} weeks pregnant, however measurement of UtPI must be taken between 11^{+0}- 13^{+6} weeks gestation. The

[ii] Please note, PICO is a framework for developing a focused clinical question. The letters represent Population, Intervention, Comparator, Outcome. See RANZCOG Manual on Developing and Updating Clinical Guidance Statements- pp. 10 for further detail.

completion of every measurement is not required to calculate a risk; however, test performance is improved with each additional measure included in the algorithm.

Summary of evidence for Clinical Questions 1 & 2

For women who screened at high risk and commenced taking aspirin before 16 weeks gestation:

- First trimester screening followed by aspirin prophylaxis **most likely reduces** the risk of early-onset preeclampsia diagnosed at or resulting in birth <32-34 weeks gestation (Five studies, OR 0.38, 95% CI 0.22- 0.64. Certainty of evidence- Moderate).

- First trimester screening followed by aspirin prophylaxis **may reduce** the risk of preterm preeclampsia diagnosed at or resulting in birth <37 weeks gestation (Six studies, OR 0.61, 95% 0.52- 0.70. Certainty of evidence- Low).

- First trimester screening followed by aspirin prophylaxis **may reduce** the rate of stillbirth, defined variably as an in-utero fetal death after 20-24 weeks gestation (Three studies, OR 0.71, 95% CI 0.56-0.89. Certainty of evidence- Very low).

- First trimester screening followed by aspirin prophylaxis may have **little or no effect** on the risk of term preeclampsia ≥37 weeks gestation (Five studies, OR 0.80, 95% CI 0.62- 1.03. Certainty of evidence- Low).

Included evidence identified that the FMF first trimester screening algorithm was the most effective at identifying women who either would or would not go on to develop preterm preeclampsia in their pregnancy when compared with screening by maternal history-based risk factors alone.

The FMF algorithm consisted of clinical history, MAP, plus ultrasound factors (UtPI) and/or biochemical maternal serum markers (PAPP-A and/or PlGF), or a combination of all four of these components. Outcome data demonstrated the sensitivity of the FMF algorithm improved with each addition of clinical markers (ultrasound and biochemistry) to maternal history and MAP.

All screening algorithms were most effective at identifying women who were unlikely to develop preterm preeclampsia and therefore, could be safely assessed as not requiring prophylactic aspirin (a high negative predictive value).

Screening by history-based maternal risk factors alone, as defined by ACOG and NICE guidelines reported the lowest sensitivity of any screening approach. Screening by history-based maternal risk factors alone, as defined by the FMF reported a small improvement in test sensitivity, however use of a combined screening algorithm was the superior approach for all measures of diagnostic test accuracy. Screening by history-based maternal risk factors without the addition of MAP or any other component of the algorithm likely impedes the accuracy of detecting women with an increased risk of developing preterm preeclampsia.

For detailed evidence tables presenting screening test accuracy results, see Table 2- Clinical Question 2: Screening test accuracy in identifying women at risk of preterm preeclampsia (≤37 weeks gestation) and Table 3- Clinical Question 2: Screening test accuracy in identifying women at risk of early onset preeclampsia (≤ 34 weeks gestation).

Analysis of outcome data stratified by each study is reported in Appendix E Evidence to Decision framework.

Clinical considerations and practice issues for Clinical Questions 1 & 2

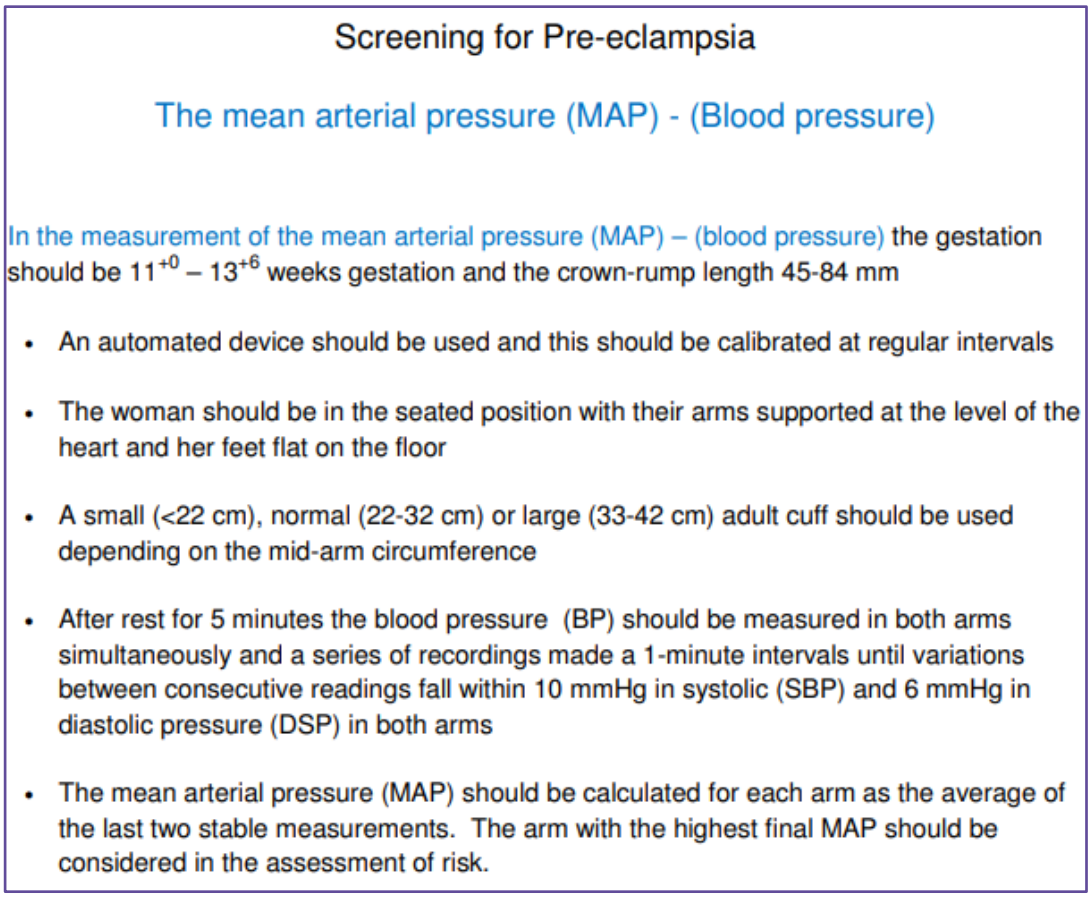
To assist with implementation of the minimum advisable components of the algorithm in clinical practice, the following advice is offered:

- The FMF calculator for first-trimester risk assessment of preeclampsia can be accessed here- https://fetalmedicine.org/research/assess/preeclampsia/first-trimester.

- There are several key maternal characteristics required for the algorithm, including pregnancy type, maternal age, height, weight, racial origin, conception method, smoking during pregnancy, history of mother with preeclampsia, maternal medical history (risk factors) including chronic hypertension, diabetes type 1 and 2, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS); obstetric history (parity). Pregnancy dating (fetal crown-rump length) and the examination date is also required. Accuracy of data submitted affects both test performance and interpretation of results.

- Standardized measurement of MAP is required for best performance of the algorithm, as outlined below. [24] The applicability of using a single BP measurement (systolic/diastolic) within the algorithm is the subject of current and ongoing implementation research.

Figure 1- RANZCOG Protocol for measuring mean arterial pressure (MAP)[iii]



Screening for Pre-eclampsia

The mean arterial pressure (MAP) - (Blood pressure)

In the measurement of the mean arterial pressure (MAP) – (blood pressure) the gestation should be 11^{+0} – 13^{+6} weeks gestation and the crown-rump length 45-84 mm

- An automated device should be used and this should be calibrated at regular intervals
- The woman should be in the seated position with their arms supported at the level of the heart and her feet flat on the floor
- A small (<22 cm), normal (22-32 cm) or large (33-42 cm) adult cuff should be used depending on the mid-arm circumference
- After rest for 5 minutes the blood pressure (BP) should be measured in both arms simultaneously and a series of recordings made a 1-minute intervals until variations between consecutive readings fall within 10 mmHg in systolic (SBP) and 6 mmHg in diastolic pressure (DSP) in both arms
- The mean arterial pressure (MAP) should be calculated for each arm as the average of the last two stable measurements. The arm with the highest final MAP should be considered in the assessment of risk.

[iii] as per RANZCOG Nuchal Translucency Education Program for UAPI Certification (originally published by the Fetal Medicine Foundation).

- Registered health professionals (including obstetricians, general practitioners (GPs), midwives, radiologists, and sonographers) using a combined algorithm to screen for preterm preeclampsia should, applicable to their role:
    - Undertake training or formal accreditation (RANZCOG NTUMP) to ensure proficiency in performing UtPI.
    - Follow a standardised protocol for measuring MAP (see *Figure 1- RANZCOG Protocol for measuring mean arterial pressure (MAP)*).
    - Provide pre and post-test counselling to women, including discussion of what the algorithm tests for, limitations of screening and interpretation of results, including management options for ongoing pregnancy care following an increased chance risk calculation.
    - Ensure responsibility for reporting of test results and the overall risk calculation is clear and consistent.
    - Audit performance of the components of the algorithm they are responsible for collecting.

- The FMF algorithm has limited accuracy as a screening test for term preeclampsia (>37 weeks gestation).

- When women are assessed to be low risk (1 in 100 cut off) based on the screening algorithm result, the risk calculation is sufficient and accurate enough to disregard maternal history-based risk factors in isolation. Recent implementation studies reporting women with a risk of less than 1 in 100 have lower preterm preeclampsia rates than that of the general population and it is acceptable to not recommend prophylactic aspirin even in the presence of history-based risk factors.[4]

There are several considerations of note for collection of biophysical and biochemical markers:

- For a description of conducting other biophysical and biochemical components of the algorithm, please see FMF protocol.

- While UtPI may not be widely performed routinely in the first trimester, clinicians already accredited to perform nuchal translucency (NT) scans can be trained to incorporate UtPI into practice, as additional time to complete the examination is modest. Clinicians performing UtPI should receive formal training, either through accreditation with the RANZCOG NTUEMP program or similar.

- In the absence of combined first trimester aneuploidy screening due to NIPT, PAPP-A may not have already been collected. Additionally, a first trimester ultrasound at which UtPI could be performed may not have also been conducted. Therefore, these components of the FMF algorithm may need to be arranged within the ideal screening window for preeclampsia screening (11^{+0}- 14^{+1} weeks pregnant, while noting the FMF protocol still requires UtPI to be performed at 11^{+0}- 13^{+6} weeks).

- The FMF recommends practitioners and laboratories undertake regular auditing of the distribution of both biophysical and biochemical components of the algorithm. This enables clinicians to verify the accuracy of their individual data collection and technique against an average trend and defined acceptable limits. If measurements are not meeting the accepted standard, review of technique is advised.
    - To view the FMF guide for auditing MAP performance- click here
    - To view the FMF guide for auditing UtPI performance- click here
    - Auditing of biochemical marker analysis (PAPP-A, PlGF) should occur by the pathology service reporting the result.

It is acknowledged that use of a screening algorithm may not be currently a component of routine maternity care for all providers. Informed by the latest evidence, the FMF algorithm to screen for preeclampsia risk is free and easily accessible for clinicians online, and thus is recommended. Although other algorithms exist, the FMF algorithm has been the subject of rigorous research and has been implemented internationally. It is also noted there are some software programs which have incorporated the algorithm into internal systems. Furthermore, all biophysical and biochemical markers required for risk calculation can be ordered or performed by registered health professionals providing antenatal care, including obstetricians, GPs, midwives, radiologists, and sonographers, although there are potential logistic, geographic, and financial barriers to equitable access to some components. This includes variance in laboratory reporting of first trimester combined screening results, in which PAPP-A is obtained from. Solutions to these potential barriers may vary between jurisdictions.

While the screening algorithm performed marginally better when both PAPP-A and PlGF were included as clinical biomarkers and any combination of maternal serum biomarkers remained superior to maternal history and MAP alone,[25] accessibility to PlGF (pathology services capacity, cost of test) may currently be limited in some settings, particularly in rural and remote areas of Australia. Furthermore, while PAPP-A is subsidised and collected in both Australia and Aotearoa New Zealand as part of first-trimester aneuploidy screening (CFTS, MSS1), raw data for PAPP-A is no longer reported to clinicians in New Zealand. Although the FMF algorithm provides an option for providers to enter either raw data or a calculated multiple of the mean (MoM) value to perform the risk calculation, this is a limitation in the implementation of this recommendation in the context of Aotearoa New Zealand. Efforts to resolve this situation are in progress.

In circumstances where elements of the screening algorithm are not routinely collected and multiple barriers to implementation (i.e., NZ- PAPP-A) exist, jurisdictions will need to consider mechanisms and strategies to mitigate these challenges.

Cost effectiveness

Several studies have demonstrated the cost effectiveness of screening with an algorithm followed by prophylaxis for women at increased risk, compared with history-based screening. Algorithm based screening methods were associated with an improved prediction of who will go on to develop preterm preeclampsia and subsequent cost savings, largely driven by a reduction in need for neonatal care. For further detail, see Table 7- Clinical Question 3: Cost effectiveness of preeclampsia screening with FMF algorithm compared to history-based screening using decision models:.

The FMF algorithm permits screening in twin pregnancies, albeit with lesser quality evidence to support this compared to singleton pregnancies.[26]

While the primary outcome for all included evidence was preterm preeclampsia, greater use of the FMF screening algorithm and aspirin prophylaxis for women at increased risk may have further benefit in reducing incidence of other related complications, such as preterm birth, SGA/FGR, and stillbirth. There are also likely to be resource advantages as a reduction in screen-positive rate compared to risk factor-based approaches will reduce the proportion of women requiring enhanced third trimester surveillance and obstetric intervention.

Equity

The FMF algorithm currently does not include an ethnicity category specific to Aboriginal and Torres Strait Islander or Māori populations. Appropriate modification of biochemical risks is considered an important factor in maximising the effectiveness of the algorithm in varied populations. Trialling and adaptation of preeclampsia prediction tools within First Nations and Māori populations has also been recognised as a priority area for further study- see Recommendations for future research.[11]

To use the FMF algorithm, early antenatal care attendance is vital. While data included in the evidence review did not consider outcomes related to ethnicity, it is acknowledged that Aboriginal and Torres Strait Islander women and Māori and Pacific Islands women face many barriers to accessing culturally safe care and have reported lower rates of antenatal care attendance compared to non-Indigenous women.[14, 27] Issues in accessing timely and appropriate care may also be hindered for women from culturally and linguistically diverse backgrounds (particularly women of Indian ethnicity in Aotearoa New Zealand) and those who experience other forms of social and economic disadvantage.[15] Thus, consideration should be given to implementing culturally appropriate initiatives which support women to access first trimester antenatal care where screening can occur.[28]

Limitations in the evidence for Clinical Questions 1 & 2

- The primary systematic review consisted of one high-quality RCT and six observational studies. Although the study design reduces the certainty of evidence/GRADE assessment (potential selection bias and confounding), the included observational studies provided evidence in geographically relevant clinical settings. This was considered to be important in broadening implementation into routine clinical practice.
- Two studies included in the review where history-based screening was used, followed with prophylactic aspirin for high-risk women. The remaining studies did not perform screening or prescribe aspirin in the control group.
    - The primary systematic review grouped studies with and without aspirin use in the standard care group together, as there is evidence that history-based screening and intervention is poorly adhered to in many clinical settings (including Australia where an audit of care at a secondary care unit found 24.3% of women at high risk of preeclampsia on history-based screening received aspirin.[29]
- Several identified outcomes listed in the PICO were not reported in the included systematic review.
    - Only two studies reported rates of severe preeclampsia, small for gestational age, FGR, or placental abruption, with differing definitions, preventing further interpretation.
    - One study only reported small for gestational age infants born <37 weeks gestation. As the other two studies reporting this outcome reported small for gestational age infants across all gestations, this precluded analysis.
- Although all screening algorithms reported low positive predictive values (PPV), these results are expected for a test of this nature and indicative of the prevalence of preeclampsia, rather than efficacy or test performance.
- A change in the ISSHP definition of preeclampsia (updated in 2017) may have had an effect on the classification of data in the included systematic reviews reported on prior to this change.

Final summary for Clinical Questions 1 & 2

While a preventative effect was observed for all preterm preeclampsia, the greatest certainty and confidence in reduction was reported for preterm preeclampsia <32-34 weeks gestation. Although this outcome is rarer in its occurrence, the impact on maternal and neonatal outcomes is particularly significant. Hence, this result is important in informing the strength and wording of the evidence-based recommendation.

Recommendation 1	Evidence based recommendation

Strong: Offer routine screening in early pregnancy for preterm preeclampsia to all women.

Screening algorithms that include clinical history, blood pressure (MAP), ultrasound with mean uterine artery pulsatility index (UtPI), and maternal serum biochemical markers (PAPP-A, and/or PlGF) are recommended as they more accurately predict which women are at risk for developing preterm preeclampsia compared to risk assessment by history alone.
GRADE of evidence: Moderate

Good Practice Point 1

GPP: In settings where the complete algorithm may not be feasible, consideration may be given to the use of some but not all components of the algorithm. Evidence suggests that any additional components to maternal history and BP are likely to improve the ability to identify women who will go on to develop preterm preeclampsia.

When screening for preterm preeclampsia, maternal risk factors and BP measurements are the minimum requirements to identify women at risk of developing preterm preeclampsia using the Fetal Medicine Foundation (FMF) algorithm (Available online - The Fetal Medicine Foundation).

Good Practice Point 2

GPP: The GDG recommend a risk cut off of 1:100 (which approximates a screen positive rate of 10% in a typical pregnant population) be used to offer prophylaxis.

Clinical Question 3

When women are identified as high-risk with early pregnancy screening, what prophylaxis regimen is most effective at reducing preeclampsia?

P- Pregnant women up to 16 weeks gestation, with preeclampsia risk factors/identified as higher risk on combined first trimester screening or with maternal risk factors where combined screening has not been undertaken.

I- Aspirin vs placebo + sub-analyses of dose, timing, and with/without calcium supplementation

C-

Part A	Part B	Part C	Part D
I- Aspirin	I- Aspirin dose A	I- Aspirin < 16 weeks	I-Aspirin (any dose) + calcium
C- placebo	C- Aspirin dose B or placebo	C- Aspirin > 16 weeks	C- Aspirin (any dose) without calcium, or placebo

O- Maternal- Diagnosis of preterm and term preeclampsia, HELLP, maternal mortality/other morbidity, antenatal secondary/tertiary care admission, mode of birth, ICU admission, adverse events from medications

Neonatal- Perinatal mortality or serious morbidity, pre-term birth, birthweight, Apgar score (at 5mins), NICU admission.

Background

Five large systematic reviews of randomised studies considering the benefits and harms of aspirin (and calcium) for the main outcomes of preterm and term preeclampsia were identified.[30-34] The certainty of evidence varied from high to low, with several factors confounding the strength/GRADE of evidence. Reasons for downgrading and GRADE results can be found in Evidence to Decision tables- EtD- Clinical Question 3.

Five additional studies published since the Cochrane review were identified. All studies were assessed as having very low certainty/GRADE of evidence. In keeping with RANZCOG processes, the sources of best available evidence were determined to be published within the included systematic reviews, and additional studies were therefore excluded.

Thus, the studies can be used as indirect evidence taking into account these limitations. The evidence should be interpreted considering these limitations.

Summary of evidence for Clinical Question 3

Aspirin

A Cochrane review of 39 studies reported on the efficacy of antiplatelet therapies (primarily aspirin) for women at risk of developing preeclampsia.[30] The review included both individual participant data (IPD) (where this was available) and aggregated data (where IPD was not available). Subgroup analyses by risk category (low, moderate, and high risk), dosage (<75mg and ≥75mg) and gestation of commencement (<20 weeks and ≥20 weeks) were all provided.

For women who screened as high risk of developing preeclampsia (including both history-based and algorithms):

- Aspirin **may decrease** preeclampsia (RR 0.83, 95% CI 0.77-0.90. Certainty of evidence- Low).

- Aspirin **most likely decreases** rates of preterm birth <37 weeks (RR 0.87, 95% CI 0.81- 0.94), a composite outcome of fetal death, neonatal death, or death before hospital discharge (RR 0.77, 95% CI 0.64- 0.93), and SGA (RR 0.83, 95% CI 0.73- 0.94.) compared to placebo. Certainty of evidence- Moderate.

- For women of any risk category, aspirin **may decrease** preeclampsia slightly more when prescribed at doses ≥75mg (RR 0.78, 95% CI 0.66- 0.92) than <75mg (RR 0.92, 95% CI 0.85- 1.0). Certainty of evidence- Low.

- For women of any risk category, there was **little or no difference** found for the following outcomes: severe maternal morbidity, antepartum haemorrhage, placental abruption, postpartum haemorrhage, neonatal intraventricular haemorrhage and gestation of onset of proteinuria. Certainty of evidence- Low.

A recent United States Preventive Services Task Force (USPSTF) systematic review also conducted a similar analysis of 16 studies, however applied different definitions to what constitutes a high-risk category (by either history-based screening, ultrasound, or algorithm methods).[31] The USPSTF review reported outcomes for aspirin at <75mg, ≥75mg, in addition to <100mg and ≥100mg dosage. For women who screened at increased risk of preeclampsia:

- Aspirin doses ≥100mg **most likely reduces** preeclampsia (RR 0.74, 95% 0.58- 0.94. Certainty of evidence- Moderate).

- Aspirin doses <100mg have **little or no effect** on preeclampsia (RR 0.88, 95% CI 0.74- 1.05. Certainty of evidence- Moderate).

- Aspirin doses ≥100mg **most likely reduces** preterm birth (RR 0.68, 95% CI 0.51- 0.90) more than doses <100mg (0.91, 95% CI 0.84- 1.0. Certainty of evidence- Moderate).

The timing of commencement was also reported by < 16 weeks and ≥16 weeks gestation. For women who screened at increased risk of preeclampsia:

- Aspirin commenced <16 weeks pregnancy **most likely decreases** preeclampsia (RR 0.68, 95% CI 0.53- 0.89. Certainty of evidence- Moderate).

- Aspirin commenced <16 weeks **most likely decreases** preterm birth (RR 0.49, 95% CI 0.26- 0.95. Certainty of evidence- Moderate).

A 2021 systematic review of 23 studies also reported outcomes for different dosages of aspirin for women identified at moderate or increased risk of developing preeclampsia.[32] Women were classified at risk if they had any moderate or high-risk factors in line with history-based screening as detailed in USPSTF and ACOG guidelines.[35, 36] Furthermore, this systematic review specifically reported on the primary outcome of interest- preterm preeclampsia (diagnosed at <37 weeks gestation). For women with moderate or increased risk factors for preeclampsia:

- Aspirin **may decrease** preterm preeclampsia (RR 0.70, 95% CI 0.53- 0.92. Certainty of evidence- Low).

Uncategorised risk

Two further systematic reviews reported outcome data by dosage of aspirin for women who commenced aspirin before 16 weeks, however, they did not undertake analysis by risk.[33, 34] Results demonstrated:

- Aspirin ≥100mg, taken at or before 16 weeks **most likely reduces** preterm preeclampsia (RR 0.33, 95% CI 0.19-0.57. Certainty of evidence- Moderate), yet aspirin <100mg has **little or no effect** on preterm preeclampsia (RR 0.59, 95% CI 0.29- 1.19. Certainty of evidence- Low).[33]

- Aspirin 150-162mg **may reduce** preterm preeclampsia compared to aspirin 75-81mg (RR 0.34, 95% CI 0.15- 0.79. Certainty of evidence- Low).[34]

Further detail of the evidence and outcomes is presented in Table 4 and Table 5.

.**Outcomes not reported:** side effects of medication, maternal satisfaction with the medication.

Calcium

No literature was identified where a combination of calcium and aspirin were compared with aspirin alone. A Cochrane review of 27 studies analysing the effect of calcium supplementation compared to placebo during pregnancy on maternal and neonatal outcomes, including hypertensive disorders of pregnancy was identified.[37] For women who screened[iv] at high risk for preeclampsia:

- High-dose calcium (≥1g/day) **most likely reduces** preeclampsia when compared to placebo (RR 0.22, 95% CI 0.12- 0.42). Certainty of evidence- Moderate.

- High-dose calcium (≥1g/day) **may reduce** preterm birth when commenced at any time in pregnancy and compared to placebo (RR 0.45, 95% CI 0.24- 0.83). Certainty of evidence- Low.

- High-dose calcium (≥1g/day) may have **little or no difference** on babies' admission to NICU (RR 0.29, 95% CI 0.03- 2.48, Certainty of evidence- Low) and perinatal death when compared to placebo (few instances of outcome- RR 0.39, 95% CI 0.02- 9.20). Certainty of evidence- Very low.

- Low-dose calcium (<1g/day) may have **little or no difference** on preeclampsia (RR 0.8, 95% CI 0.61-1.06), early onset preeclampsia 32-34 weeks when compared to placebo (RR 0.93, 95% CI 0.61- 1.42). Certainty of evidence- Very low.

- Low-dose calcium (<1g/day) may have **little or no difference** on severe maternal morbidity or mortality, preterm birth <37 weeks, pregnancy loss/stillbirth at any gestational age, perinatal death, or babies' admission to NICU >24hrs, Apgar score <7 at 5mins and low birthweight (<2500g) when compared to placebo. Certainty of evidence- Very low.

While this component of Clinical Question 3 considered oral calcium supplements only, the included Cochrane review also reported outcomes by sub-group analysis of dietary intake. For all women (unscreened for risk of preeclampsia) with low calcium diets, high dose calcium (≥1g/day) supplements **may reduce** preeclampsia (RR 0.36, 95% CI 0.20- 0.65. Certainty of evidence- Low), however the same effect was not observed for women with adequate dietary intake or when calcium supplementation was decreased to ≤1g/day (low dose) (RR 0.62, 95% CI 0.32- 1.20). Thus, it could be interpreted that calcium supplementation to reduce risk of preeclampsia may be most beneficial for women who do not consume sufficient dietary calcium.

A 2022 network meta-analysis of 25 trials reporting the effect of high and low-dose calcium for women with low and adequate dietary intake reported similar findings.[38] There were six studies not included in the original Cochrane review and three studies published since the Cochrane review searches were undertaken. The network meta-analysis reported:

[iv] Screening was undertaken using history-based screening alone (no application of a risk assessment algorithm).

- Any calcium supplementation **most likely reduces** incidence of any preeclampsia when compared to placebo/no therapy (RR 0.49, 95% CI 0.39- 0.61). Certainty of evidence- Moderate.

- For women with an increased risk for preeclampsia[v], calcium supplementation **most likely reduces** incidence of preeclampsia when compared with placebo/no therapy (RR 0.41, 95% CI 0.29- 0.57). Certainty of evidence- Moderate.

- For women with low baseline calcium intake, calcium supplementation **most likely reduces** incidence of preeclampsia when compared with placebo/no therapy (RR 0.45, 95% CI 0.35- 0.58). Certainty of evidence- Moderate.

- For women with adequate baseline calcium intake, calcium supplementation may have **little or no difference** on incidence of preeclampsia when compared with placebo/no therapy (RR 0.62, 95% CI 0.37- 1.06). Certainty of evidence- Moderate.

A sub-group analysis by level of preeclampsia risk for the outcome of preterm birth was not performed in this analysis. The assessment of calcium intake varied significantly across included studies in both reviews.

Clinical considerations and practice issues for Clinical Question 3

Aspirin

Potential benefits

There is evidence to suggest a dose-response of aspirin on reduction of preterm preeclampsia. The largest randomised clinical trial (ASPRE) compared 150mg aspirin with placebo,[23] however no studies have compared 100mg with 150mg.[33] Although 150mg of aspirin has been recommended by several international guidelines (FIGO, ISUOG, SOMANZ),[3, 17] and it may be that this dose is superior to 100mg, [23] the RANZCOG GDG has recommended an aspirin dose of **at least** 100mg for the following reasons:

- The absence of studies directly comparing 100mg with 150mg aspirin daily.
- The lack of a specific 150mg aspirin preparation available in Australia or Aotearoa New Zealand. Splitting a 300mg aspirin tablet would be required to achieve this higher dose.

Potential harms

- A possibility of increased gastrointestinal side effects with 150mg of aspirin, as this dose is not enteric coated. However, this risk should be balanced with evidence indicating non-responsiveness to 100mg of enteric coated aspirin.[39,vi]
- A possibility of increased risk of pregnancy-related bleeding and neonatal intracranial haemorrhage.[39]
- The additional task of splitting tablets could reduce compliance.

It is acknowledged that clinicians may choose to prescribe 150mg of aspirin and provide women with the potential benefits and harms of both options. The wording of this recommendation allows for such a possibility.

Gestation of initiation

Indirect evidence suggests low-dose aspirin should not commence until 11^{+0} weeks gestation in women who screen at increased risk, as earlier prophylaxis has not shown an effect on development of preeclampsia.[40]

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[v] High risk was determined by presence of at least one of the following preeclampsia risk factors- adolescent pregnancy, maternal age over 35 years, chronic underlying medical conditions, a family history and/or past history of preeclampsia, positive roll-over test or angiotensin sensitivity, abnormal uterine artery Doppler and/or high mean arterial pressure.

[vi] Resistance to aspirin is defined as platelet function response, as measured by PFA-100 (Caron et al 2009, ref 26).

While the FMF calculator is not validated for pregnancies after 14^{+1} weeks gestation, there may still be some value in prescribing aspirin to women deemed high risk using traditional (history-based or other) screening processes. At present, aspirin initiation after 16 weeks gestation is not reported to have the same effect on reducing risk of developing preterm preeclampsia. Potential harms, including risk of bleeding complications, are also unknown. Therefore, aspirin for women who present to antenatal care later than 16 weeks gestation should be considered on a case-by-case basis, taking into account maternal history, risk factors and the potential harms and benefits of later prophylaxis.

Time of day

There is limited evidence regarding the best time of day to take aspirin relevant to this population of women. Studies in the Cochrane review either advised women to ingest aspirin in the evening or did not report this detail. One small RCT assessing the effect of low-dose aspirin for prevention of pregnancy complications, including preeclampsia, reported a significant reduction in BP when aspirin was ingested at bedtime, compared with a dose in the morning (upon awakening).[41] These findings are also consistent with evidence for aspirin use for non-pregnant cardiovascular indications.

Gestation of cessation

A recent RCT reported no difference in preterm preeclampsia when aspirin was discontinued at 24-28 weeks gestation, compared with continuation of aspirin up to 37 weeks gestation, however this finding was limited to women identified at decreased risk for the outcome with normal sFLT-1:PlGF ratio of 38 or less between 24-28 weeks.[42] However, for the population outlined in the Clinical Question 3, there is limited evidence available to provide a definitive recommendation on when to discontinue aspirin. Furthermore, on the basis the risk of preeclampsia is most marked for early-onset (<32-34 weeks gestation) and preterm preeclampsia (<37 weeks gestation), the GDG have concluded that clinicians may advise women to stop aspirin at 36 weeks gestation (or earlier if delivery precedes). This advice is consistent with other high-quality clinical trials and the FMF.[23] Discontinuation of aspirin in this population is also noted as the subject of ongoing research.

Calcium

High-dose calcium supplements (>1g/day) are widely available in both Australia and Aotearoa New Zealand. In Australia, calcium carbonate is available as a 600mg tablet. In Aotearoa New Zealand, calcium supplements are funded as a 500mg calcium carbonate tablet, so women would be required to take at least two tablets to achieve the recommended dose of at least 1g/day.

In the absence of evidence comparing aspirin to a combination of aspirin and calcium supplements, the effect of calcium alone on risk reduction of preterm preeclampsia cannot be confidently determined. The GDG recommends that if calcium supplements are prescribed, aspirin is too. This practice is supported by evidence demonstrating a likely preventative effect on preeclampsia, particularly preterm preeclampsia, with aspirin (see Recommendation 2 for specifics).

It is generally accepted women with low dietary intake of calcium should be recommended calcium supplements in pregnancy. However, there is no standardised method to quantify calcium consumption. Inconsistency in measurement of dietary intake and the definition of dietary deficiency may affect implementation of this consensus-based recommendation into clinical practice. The use of a dietary calculator to ascertain daily calcium intake has been suggested by other guidelines,[3] although this level of detail was determined to be out of scope for this Clinical Guideline.

Potential harms

There is insufficient evidence to determine whether an association between calcium supplementation <1g or >1g and an adverse side effect profile exists. A network meta-analysis reported high and low-dose calcium

supplementation did not appear to be associated with any short-term harms, however did not conclude the same for longer-term outcomes.

Small studies have reported some women find the texture and taste of supplements >1g as intolerable and this may impact on regimen adherence. Furthermore, it is unclear whether high-dose calcium >1g a day increases the likelihood of side effects. Additional research is required.

Limitations in the evidence for Clinical Question 3

- No evidence was identified that included all components of the stated clinical question and PICO. The relationship between the data sources and their analyses is presented in the Appendix E- Evidence to Decision framework.
- The change in the ISSHP definition of preeclampsia (updated in 2021) may have had an effect on the classification of data in the included systematic reviews.
- There was some inconsistency in the definition of risk categories across the reported evidence, this included:
    - Of the 18 studies identified by the USPSTF review as being of increased risk of developing preeclampsia, three of these studies were classified in the Cochrane review (Hofmyer et al 2018) as low risk (See Table 1).
    - Only seven studies met the population of interest as identified in the PICO- studies in increased risk pregnancies with aspirin commenced before 16 weeks.
    - Of the 16 included studies in the systematic review Roberge et al 2018, five were categorized as at increased risk in the USPSTF review and 13 were categorized as at moderate or high risk of preeclampsia in the Cochrane review.
- Clinical Question 3, Part D (calcium):
    - A high degree of heterogeneity, indirectness of the data to the clinical question and possible publication bias precluded higher certainty/GRADE of evidence and strength of the recommendation relating to calcium supplementation.
    - Small sample sizes of some studies part of the Hofmyer 2018 Cochrane review meta-analyses affected the ability to draw definitive conclusions on calcium efficacy and risk reduction of preeclampsia for women who screen at high risk from this data.
    - Publication bias is also possible. A recent secondary sensitivity analysis of the 2018 Cochrane review data identified that small clinical trials accounted for 88% of the observed preventative effect of calcium for women with low dietary intake.[43] In this sub-group, when analysis was restricted to inclusion of larger trial data only, risk reduction of preeclampsia was not observed. While this specific analysis did not stratify by risk level, as the smallest RCTs only included women at increased risk for preeclampsia, it is possible the preventative effect of calcium at any dose, as reported by Hofmyer 2018, may have been due to inclusion of high-risk populations. As the population identified in Clinical Question 3, Part D were women who screen at increased risk for preeclampsia, the findings of the secondary sensitivity analysis are of less concern, however results should still be interpreted accordingly.
    - No included studies in either systematic review compared women by baseline calcium intake who also screened at increased risk for developing preeclampsia.

Final summary

Overall, the included evidence suggests that low-dose aspirin of at least 100mg, commenced before 16 weeks gestation in high-risk women, is associated with a reduction in preterm preeclampsia. There may be increased effectiveness with increasing dose, with some evidence reporting a regimen of 150mg may have greater effect on the outcome. However, the exact upper limit of this dose effect is currently unknown, as are the

possible adverse effects, impeding a recommendation of a specific ideal dose. Although the evidence base is limited, there may be further benefit if prophylactic aspirin is accompanied with calcium supplementation (>1g/day), specifically for women identified at increased risk for preeclampsia (by screening) and women with low baseline calcium intake.

Recommendation 2	Evidence based recommendation
Strong: Women with an increased risk of preeclampsia (identified by screening) should be offered low-dose aspirin (at least 100mg daily) starting before 16 weeks pregnancy as it reduces the likelihood of preterm preeclampsia, preterm birth, and other associated complications. GRADE of evidence: Moderate	

Recommendation 3	Evidence based recommendation
Conditional: Women with an increased risk of preeclampsia (identified by screening) could be offered high-dose calcium (>1000mg or more), as it may reduce the likelihood of preeclampsia and preterm birth. GRADE of evidence: Low	

Recommendation 4	Consensus-based recommendation
Where calcium is offered for preeclampsia prevention, it should be in addition to low-dose aspirin and not as a sole agent.	

8. Legal and ethical considerations

It is important to ensure clinicians understand the screening algorithm is a risk assessment only. Caution should be taken to prevent iatrogenic premature birth based on the result or risk profile alone.

In all areas of maternity care, shared decision making about interventions and treatment options should occur. In using the screening algorithm (and prophylaxis for women identified at increased risk), women have a right to be provided with clear information on the potential benefits and harms of this intervention to make an informed choice about their care preferences. This includes an explanation of benefits and harms which may be associated with aspirin or a combination of aspirin and calcium supplements. It is the clinician's responsibility to ensure informed consent is obtained and this is recognised as an interactive process between the patient, her family (*whānau*), and the clinician.

9. Recommendations for future research

- Comparison of 100mg of aspirin to 150mg to assess impact on rate of preterm preeclampsia and other maternal and neonatal outcomes including adverse effects.
- Application of FMF algorithm to personalised risk assessment and care clinical decision tools to facilitate wider implementation and reduce adverse outcomes, such as preeclampsia and preterm birth.[44]
    - Application of the FMF screening algorithm to Aboriginal and Torres Strait Islander and Māori populations.[11]

- Test performance of combined screening algorithm by meta-analysis of area under the curve (AUC) from existing diagnostic accuracy data.
- It is acknowledged that there are ongoing studies relating to the application of the ASPRE clinical trial data to other subgroups, including twin pregnancies.
- Timing of birth for women who have screened at increased risk of preeclampsia. It is noted limited evidence exists for recommendations on the upper limits of delivery (i.e., no later than 39 or 40 weeks gestation).
- Timing of cessation of aspirin prophylaxis and time of day in which greatest benefit to reduction of BP/risk of preeclampsia is observed.
- Effectiveness of aspirin and calcium prophylaxis in Aboriginal and Torres Strait Islander and Māori pregnant populations.
- Comparison of a combined prophylaxis regimen of daily low-dose aspirin and calcium supplementation, versus low-dose aspirin alone for prevention of preeclampsia (particularly preterm preeclampsia) and related complications.
    - Including sub-group analysis of combination prophylaxis for women who screen at increased risk (based on FMF algorithm assessment), women with low dietary intake of calcium and women with adequate dietary intake of calcium.

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11. Links to relevant College Guidelines

- Routine antenatal assessment in the absence of pregnancy complications (C-Obs 3b)
- Timing of elective caesarean section at term (C-Obs 23) (specifically for 4- Preterm planned caesarean delivery (pp.5), in which preeclampsia is noted as a potential indicator to warrant earlier planned delivery on balance of risk-benefits of preterm birth versus continuation of the pregnancy).
- Management of obesity in pregnancy (C-Obs 49)
- Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions (C-Obs 59) (Under review)
- Prenatal Assessment of Fetal Structural Conditions (C-Obs 60) (Under review)
- Exercise during pregnancy (C-Obs 62)

12. Links to relevant Consumer resources

- Pregnancy and High Blood Pressure During Pregnancy- RANZCOG Patient Information Pamphlet, available for order via RANZCOG PIP Print Portal.
- Health Navigator NZ/Healthify He Puna Waiora: Pre-eclampsia | Healthify

13. Links to relevant ATMs and learning modules

- RANZCOG Nuchal Translucency ultrasound education and monitoring program. Visit- https://nuchaltrans.edu.au/

Appendices

Appendix A: Women's Health Committee Membership

Name	Position on Committee
Dr Scott White	Chair
Dr Anna Clare	Deputy Chair (Gynaecology) and Councillor
Associate Professor Amanda Henry	Deputy Chair (Obstetrics) and Councillor
Dr Samantha Scherman	Member and Councillor
Dr Marilla Druitt	Member and Councillor
Dr Kasia Siwicki	Member and Councillor
Associate Professor Jared Watts	Member and Councillor
Dr Victoria Carson	Member
Dr Nisha Khot	Vice President, Specialist International Medical Graduate (SIMG) Representative
Dr Marilyn Clarke	Aboriginal and Torres Strait Islander Representative
Dr Angela Beard	He Hono Wāhine Representative
Dr Martina Mende	DRANZCOG Representative
Dr Pallavi Desai	SIMG Representative
Professor Kirsten Black	Sexual and Reproductive Health Committee Representative
Dr Frank Clark	State Representative- TAS
Dr Elizabeth Gallagher	Territory Representative- ACT
Dr James Brown	State Representative- VIC
Dr Kathy Saba	State Representative- QLD
Dr Divya Viswanathan	Trainee Representative
Adrienne Priday	Midwifery Representative, Aotearoa New Zealand
Dr Angela Brown	Midwifery Representative, Australia
Ms Leigh Toomey	Community Representative
Dr Steve Resnick	Co-opted member: Neonatologist

Appendix B: Guideline Development Group Membership

Name	Position
Dr Scott White	GDG Chair, CMFM
Dr Ailsa Borbolla Foster	Member, CMFM
Professor Sue Walker AO	Member, CMFM
Professor Fabricio da Silva Costa	Member, COGU
Professor Jonathan Hyett	Member
A/Prof Daniel Rolnik	Member
A/Prof Gino Pecoraro	Member
Dr Sue Belgrave	Member, Aotearoa New Zealand Representative
Dr Linda Mann	Member, GP Obstetrician Representative
Dr Emmeline Lee	Member, Consultant Radiologist (FRANZCR, DRANZCOG)

Dr Jessica Little	Member, FRANZCOG Trainee Representative
Ms Paula Dillon	Member, Midwifery Representative
Research & Policy Team	**Position**
Professor Cindy Farquhar	Dean of Research & Policy
Ms Jinty Wilson	Head of Research & Policy
Ms Katie Coulthard	Senior Coordinator, Research & Policy
Research evidence	**Position**
Professor Cindy Farquhar	Dean of Research & Policy
Dr Karyn Anderson	Research Fellow, University of Auckland

Appendix C: Overview of the development and review process for this guideline

i. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of RANZCOG Women's Health Committee or working groups.

A declaration of interest form specific to guidelines and guidelines (approved by the RANZCOG Board in September 2012). All members of the Guideline Development Groups, Statement and Guideline Advisory Group (SaGG) and Women's Health Committee were required to declare their relevant interests in writing on this form prior to participating in the review of this guideline.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

Conflict of interest declaration details are provided in the following table. All GDG members named have given approval for this information to be made transparent and published.

Member	Declaration type	Details
Dr Scott White	Ownership interests, Participation in previous guideline development	• Co-owner private obstetric ultrasound practice providing early pregnancy U/S including first trimester screening
Prof Jonathan Hyett	Consultancy (past), Research funding, Participation in previous guideline development	• Previous research work with Perkin Elmer (unrelated to preterm PE) • Lead applicant for MSAC Application 1705 • Project involvement- bedside analysis PlGF in third trimester pregnancies • Guideline involvement- FIGO, ISUOG • Trustee- Fetal Medicine Foundation UK (charity).
Prof Fabricio da Silva Costa	Research funding, Honoraria (past), participation in previous guideline development	• Research device and kits for sFlt1/PlGF ratio study • Previous lectures supported by biomarker companies • Guideline involvement- FIGO, ISUOG, FEBRASGO
A/Prof Daniel Rolnik	Honoraria, participation in previous guideline development	• Lecture fees from Perkin-Elmer • Guideline involvement and endorsement- Monash Health, National Preterm Birth Prevention Alliance

ii. Steps in developing and updating this guideline

The guideline Screening in Early Pregnancy for Adverse Perinatal Outcomes (C-Obs 61) was published in July 2015 and updated in 2018. An updated guideline was developed from July 2023 to November 2023 by the C-Obs 61 Early pregnancy screening and prevention of preterm preeclampsia and related complications Guideline Development Group (GDG), a working group established by the Women's Health Committee. It was most recently reviewed by the Women's Health Committee in April 2024 (final review). The Women's Health Committee carried out the following steps in reviewing this guideline:

- Declarations of interest were sought from all members prior to reviewing this guideline.
- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken (Research and Policy Team/Guideline Development Group)
- At the November 2023 meeting of the Women's Health Committee, the existing consensus-based recommendations were reviewed and updated based on the current available body of evidence and clinical expertise, as set out in the Methodology section below.

RANZCOG guidelines are developed according to the standards of the Australian National Health and Medical Research Council (NHMRC), which includes the use of GRADE methodology. The Evidence to Decision framework embedded within the MAGIC (Making GRADE the Irresistible Choice) digital platform (https://magicevidence.org) is used to publish the updated guideline recommendations. The recommendations published by RANZCOG are approved by the RANZCOG Women's Health Committee, Council and Board respectively. The processes used to develop RANZCOG Clinical Guidelines are described in detail at: https://ranzcog.edu.au/wp-content/uploads/2022/08/Manual-for-developing-and-updating-clinical-guidance-statements.pdf

iii. Developing recommendations using GRADE methodology

The relevant GRADE assessments for each recommendation are presented within the online platform used to structure the Clinical Guideline (MAGICapp; https://magicevidence.org/magicapp/).

Appendix D: Full Disclaimer

Purpose

This Guideline has been developed to provide general advice to practitioners about women's health issues concerning early pregnancy screening and prevention of preterm preeclampsia and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any person. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual person and the particular circumstances of each case.

Quality of information

The information available in this guideline is intended as a guide and provided for information purposes only. The information is based on the Australian/New Zealand context using the best available evidence and information at the time of preparation. While the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) has endeavoured to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available. The use of this information is entirely at your own risk and responsibility.

For the avoidance of doubt, the materials were not developed for use by patients, and patients must seek medical advice in relation to any treatment. The material includes the views or recommendations of third parties and does not necessarily reflect the views of RANZCOG or indicate a commitment to a particular course of action.

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Exclusion of warranties

To the maximum extent permitted by law, RANZCOG makes no representation, endorsement or warranty of any kind, expressed or implied in relation to the materials within or referred to throughout this guideline being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages and costs incurred.

These terms and conditions will be constructed according to and are governed by the laws of Victoria, Australia.

Appendix E- Evidence to Decision frameworks

Search strategies

Clinical Question 1

Database: Medline (ovid) <1966 to current>

Search date: 17th August 2023

#	Query
1	hypertension, pregnancy induced.mp. or maternal hypertension/
2	Pre-eclampsia/ or preeclampsia.mp.
3	eclampsia/ or eclampsia.mp.
4	gestational hypertension.mp.
5	hypertension in pregnancy.mp.
6	1 or 2 or 3 or 4 or 5
7	algorithm/ or algorithm.mp.
8	Risk assessment/ or "risk algorithm".mp.
9	Biomarkers/ or biomarkers.mp.
10	predictive model.mp.
11	logistic model/ or statistical model/
12	maternal serum/ or prenatal screening/ or maternal serum screening.mp. or maternal serum screening test/
13	prediction.mp.
14	screening.mp.
15	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	first trimester.mp. or pregnancy trimester, first/
17	"11 to 13 weeks" or "11-13 weeks".mp.
18	16 or 17
19	prevention.mp. or secondary prevention/ or primary prevention/
20	risk reduction.mp.
21	prophylaxis.mp.
22	19 or 20 or 21
23	6 and 15 and 18 and 22

Clinical Question 3, Part A, B and C

Database: Medline (ovid) <1966 to current>

Search date: 4th August 2023

#	Query
1	hypertension, pregnancy induced.mp. or maternal hypertension/
2	Pre-eclampsia/ or preeclampsia.mp.
3	eclampsia/ or eclampsia.mp.
4	gestational hypertension.mp.
5	hypertension in pregnancy.mp.
6	1 or 2 or 3 or 4 or 5
7	Aspirin/ or aspirin.mp.
8	Acetylsalicylic acid.mp.
9	7 or 8

10	prevention.mp. or secondary prevention/ or primary prevention/
11	risk reduction.mp.
12	prophylaxis.mp.
13	10 or 11 or 12
14	6 and 9 and 13
23	Limit 14 to "systematic review"

Clinical Question 3, Part D

Database: Medline (ovid) <1966 to current>

Search date: 1st August 2023

#	Query
1	hypertension, pregnancy induced.mp. or maternal hypertension/
2	Pre-eclampsia/ or preeclampsia.mp.
3	eclampsia/ or eclampsia.mp.
4	gestational hypertension.mp.
5	hypertension in pregnancy.mp.
6	1 or 2 or 3 or 4 or 5
7	calcium/ or calcium.mp.
8	prevention.mp. or secondary prevention/ or primary prevention/
9	risk reduction.mp.
10	prophylaxis.mp.
11	8 or 9 or 10
12	9 and 7 and 11
13	Limit 12 to "systematic review"

Benefits and harms

A shared Evidence to Decision framework was used for CQ1 and 2 leading to one set of recommendations which cover diagnostic accuracy and clinical outcomes of screening.

CQ1:

Foster, Park, Hyett systematic review:

First-trimester screening algorithms linked to preventative therapy with aspirin (150mg initiated prior to 16 weeks gestation in response to a high-risk screening algorithm result) reduced the risk of pre-term preeclampsia (diagnosed before or requiring delivery prior to 37 weeks) compared to standard maternity care (six studies, 30,192 women; OR 0.61, 95% CI 0.52- 0.70); NNT 384; low quality evidence).

The effect is most marked for the prevention of preeclampsia diagnosed at or resulting in birth <32–34 weeks (five studies, 371,041 women; OR 0.38; 95% CI: 0.22–0.64; moderate quality evidence). Little to no difference was found in the risk of term preeclampsia between first-trimester screening algorithms linked to preventative therapy with aspirin and standard maternity care.

Rates of stillbirth (in-utero fetal death after 20 - 24 weeks) were reduced in pregnancies undergoing first-trimester screening algorithms linked to preventative therapy with aspirin compared to standard maternity care (three studies, 338,339; OR 0.71: 95% CI 0.56–0.89; very-low quality evidence).

No results were reported for other outcomes of interest.

Among RCT evidence:

A single RCT was identified in the Foster 2023 systematic review, the ASPRE trial (Rolnick 2017). This RCT compared screening with the FMF algorithm and aspirin prophylaxis if identified at high risk with screening with the algorithm but no aspirin prophylaxis (placebo) if high risk. Whilst the RCT publication reports outcomes only in the high risk group, Foster 2023 used published screening accuracy data from the same study (Rolnick 2017a) to calculate event rates across the entire unselected cohort.

First-trimester screening with the FMF algorithm linked to preventative therapy with aspirin (150mg initiated prior to 16 weeks gestation in response to a high-risk screening algorithm result 1:100) reduced the risk of pre-term preeclampsia (delivery prior to 37 weeks) compared to screening with the FMF algorithm linked to placebo (OR 0.53; 95% CI: 0.33–0.87; NNT = 334; high quality evidence).

Among Australian studies:

An Australian clinical implementation study was reported by Rolnik 2021. 29,618 women underwent first trimester combined preeclampsia screening and 301,566 women received standard care. Women who were screened with the FMF algorithm and assessed as being high risk for preterm preeclampsia (1 in 100 cut-off) were recommended to take aspirin for preterm preeclampsia prophylaxis. Screened women had lower rates of preterm preeclampsia compared to standard care (OR 0.64; 95% CI 0.54-0.76; low quality evidence). Rates of birthweight <2500g (aOR 0.89; 95% CI 0.85–0.94), and birthweight <3rd centile (a OR 0.91; 95% CI 0.83–0.99) were lower in the screened group than standard care. Little to no difference was found in rates of neonatal death and birthweight <10th centile between groups.

CQ2:

Meta-analysis not performed for this data by any review sources owing to heterogeneity in:

- Outcomes – early onset (<34 weeks), and preterm preeclampsia (<37 weeks)
- Study population – different countries, different ethnicity make ups, different prevalence of preterm/early onset preeclampsia
- How the effect of aspirin was handled in the assessment of accuracy – preventative effect of aspirin will turn some of the true positives into false positives making the sensitivity and specificity appear lower
- Whether the false and screen-positive rates were allowed to be data-dependent.

Current history-based screening determines a large percentage of women as high risk.

Overall, the sensitivity of the FMF algorithm increases with the addition of UtPI, PAPP-A, or PlGF to MAP and maternal history.

PPVs and NPVs were calculated for studies that did not fix the false-positive rate. All FMF algorithms had a PPVs < 10% but very large NPVs (98%), meaning if one receives a negative result women can be reassured they are unlikely to develop preterm preeclampsia and could safely not take aspirin. However, even in the complete algorithm including all biomarkers and UtPI, low PPVs mean that only one in every 11-23 women placed in a high-risk group would actually develop preterm pre-eclampsia.

In places where access to both biomarkers and/or UtPI might not always be available, especially in remote areas, using any combination of biomarkers/UtPI listed in the FMF algorithm is still better than maternal history + MAP.

Certainty of the Evidence

CQ1:

AMSTAR-2 of systematic review - moderate quality.

This systematic review consisted primarily of observational studies (6/7), thus a starting point of low for GRADE was applied. Outcomes were downgraded for high risk of bias due to lack of blinding and confounding, and upgraded for dose response and size of effect, resulting in low-moderate certainty of evidence.

- The single RCT included in this systematic review (Rolnik et al 2017) is of high quality - looking at outcomes of this study in isolation evidence GRADED as high certainty.
- Australian implementation study (Rolnik et al 2021) was assessed as having a risk of bias from confounding. Results were based on large cohorts of women (29,618 receiving structured screening with the FMF algorithm and 301,566 receiving standard care). The results of the Australian clinical impact study are considered to be highly applicable to the Australian population. The certainty of evidence according to GRADE was low.

CQ2:

Risk of bias for diagnostic test accuracy studies assessed using QUADAS tool.

Values and preferences

Qualitative studies by the Ontario Health Technology Assessment group (2022), Silang et al (2023), and Crombag (2017) across a variety of countries report high satisfaction with algorithm-based screening for preeclampsia. Preterm preeclampsia was seen as a significant pregnancy complication with maternal and neonatal health impacts, as well as social impacts on individuals and families. Although receiving a high-risk result may generate feelings of anxiety, high NPVs associated with screening using algorithms may lessen levels of anxiety overall, as less women would receive a high-risk result overall.

Resources

In most economic evaluations use of an FMF algorithm in a preeclampsia screening programme is the dominant strategy over standard care using history-based screening. Inconsistencies in the literature are likely the result of variations in methodology, prevalence of preeclampsia and healthcare costs across different countries. In sensitivity analyses, results were most sensitive to the prevalence of this health outcome in the general population. In many studies cost savings were driven by the reduction of neonatal intensive care costs by avoiding cases of preterm preeclampsia. See Table 7- Clinical Question 3: Cost effectiveness of preeclampsia screening with FMF algorithm compared to history-based screening using decision models:

Equity

Preeclampsia rates are higher among Indigenous populations and thus improved screening may better identify those at high risk, so appropriate preventative therapies (aspirin +/- calcium) can be commenced. This effect was seen following the introduction of FMF screening to a teaching hospital in London, where the perinatal death rate among non-white women (previously much higher than white women) fell to such a degree that it was no longer significantly different from the perinatal mortality rate in white women.

However, if barriers to the uptake of screening such as access to ultrasound and laboratory services for rural and remote populations, and the ability to book with a maternity care provider within the screening window are not addressed, current inequities in the development of preeclampsia are likely to be perpetuated.

Although the FMF algorithm accounts for ethnicity, the categories were developed for the UK context, and do not align well with the Indigenous/First Nations populations of Australia and Aotearoa New Zealand. Clinicians may vary in which ethnicity category they place an individual based on their own racial biases, potentially altering the risk assessment calculation.

Furthermore, if a predictive test for pre-eclampsia is acted on inappropriately (for example, by considering it to be a diagnostic test), there is potential to cause substantial morbidity through iatrogenic premature birth of an infant. Indigenous populations already experience higher rates of preterm birth. Screening algorithms have greatest value in accurately determining who can safely not take aspirin, but clinicians should understand that a at risk result is still limited in its ability to predict women who will go on to develop preterm preeclampsia.

Acceptability

No safety concerns related to screening were identified. ISUOG note that scanning of the maternal uterine arteries (UtA) at any point in the first trimester is unlikely to have any fetal safety implications, as long as the embryo/fetus lies outside the Doppler ultrasound beam.

Implementation of a version of the FMF algorithm including MAP, UtPI, and PAPP-A is likely to be acceptable to most women. Addition of serum markers not already measured, necessitating an additional laboratory appointment may reduce acceptability of screening, particularly for those who are required to travel long distances, or face other constraints in accessing such services.

- The ultrasound performed for nuchal translucency would be increased by approximately six minutes with the addition of measurement of UtPI.
- PAPP-A is already included in combined first trimester screening for aneuploidies (CFTS).
- Measurement of MAP would require measurement of BP on both arms at the time of registration with a maternity care provider, in addition to current single arm measurement performed to identify chronic hypertension and establish a baseline BP for comparison in later pregnancy.

Feasibility

A FMF algorithm-based screening programme for preeclampsia is feasible but would require the establishment of quality control process and credentialing/training of sonographers and healthcare providers to measure algorithm variables (MAP and UtPI).

Health practitioners who perform CFTS screening for aneuploidy would require modest additional training to be credentialled for UtPI measurement for preeclampsia screening. There is an existing accreditation process for UtPI through RANZCOG.

Early pregnancy structural ultrasound scans for those that had NIPT rather than CFTS for aneuploidy should occur in the 13th, not 14th week to accommodate UtPI measures to be taken within the FMF screening window and prevent the need for multiple early pregnancy scans.

PAPP-A is currently included in combined first trimester screening for aneuploidy, thus requires minimal additional laboratory capability to implement. PlGF testing is not routinely performed in Australia or Aotearoa New Zealand and thus would require additional resourcing to establish. It may be preferable that, at least initially, an FMF algorithm without PlGF inclusion be selected for implementation.

Benefits and harms

Aspirin (any dosage) commenced at any point in pregnancy vs placebo in women at increased risk of preeclampsia

Maternal outcomes:

- Preterm pre-eclampsia: Aspirin may reduce the risk of preterm pre-eclampsia among women at moderate to high risk for preeclampsia (van Doorn SR: low certainty evidence: 23 studies, 24,351 women; RR 0.70, 95% CI 0.53 to 0.92)
- Pre-eclampsia: Antiplatelet agents may reduce the risk of pre-eclampsia among women at high risk for preeclampsia (CR: low certainty evidence: 39 studies, 14,082 women; RR 0.83, 95% CI 0.77 to 0.90)
- Severe maternal morbidity: antiplatelet agents probably make little or no difference for pregnant women (regardless of level of risk at trial entry) developing or experiencing the composite outcome of severe maternal morbidity (eclampsia, renal failure, liver failure, HELLP, stroke) (CR: moderate certainty evidence: 16 studies, 28,065 women; RR 1.00, 95% CI 0.72 to 1.39).
- Antiplatelet agents may make little or no difference for pregnant women (regardless of level of risk at trial entry) developing or experiencing placental abruption (CR: low certainty evidence: 29 studies, 30,775 women; RR 1.21, 95% CI 0.95 to 1.54)
- Preterm birth (< 37 weeks): Antiplatelet agents probably reduce the risk of preterm birth among women at high risk for preeclampsia (CR: moderate certainty evidence: 31 studies, 13,089 women; RR 0.87, 95% CI 0.81 to 0.94)
- Adverse effects of interventions: Antiplatelet agents probably make little or no difference for pregnant women (regardless of level of risk at trial entry) experiencing antepartum haemorrhage (moderate certainty evidence: 25 trials, 30,513 women; RR 1.04, 95% CI 0.92 to 1.1; individual patient data only).
- The Cochrane review reported a possible small increase in women experiencing postpartum haemorrhage, however the confidence interval touches the line of no effect (> 500ml; moderate certainty evidence: 19 trials, 23,769 women; RR 1.06, 95% CI 1.00 to 1.12).
- The Cochrane review did not report on side effects of medication nor maternal satisfaction with the medication.

Neonatal outcomes:

- Small for gestational age (SGA): Antiplatelet agents probably reduce the risk of SGA among pregnancies at high risk for preeclampsia (moderate certainty evidence: 35 studies, 13,431 women; RR 0.83, 95% CI 0.73 to 0.94).
- Mean birth weight: Antiplatelet agents probably increase mean birth weight for pregnancies (regardless of level of risk at trial entry) (CR: moderate certainty evidence: 11 studies, 3,442 women; MD 126.88g, 95% CI 39.78g to 213.97g).
- Fetal or neonatal death: antiplatelet agents reduce the risk of the composite outcome fetal death, neonatal death, or death before hospital discharge among pregnancies at high-risk of preeclampsia (CR: moderate certainty evidence: 37 studies, 13,399 babies; RR 0.77, 95% CI 0.64 to 0.93).
- The Cochrane review found that antiplatelet agents given to women during pregnancy (regardless of level of risk at trial entry) may not have any effect on the risk of intraventricular haemorrhage (CR: low certainty evidence: 20 studies, 32,224 babies; RR 0.99, 95%CI 0.72 to 1.36)

Aspirin higher dosage (150-162mg) vs aspirin lower dosage (75-81mg) commenced at any point in pregnancy in women at unselected risk of preeclampsia

A direct comparison of higher (150-162mg) and lower (75-81mg) dosages of aspirin was performed in the Ghesquiere 2023 systematic review.

- Preterm pre-eclampsia: Higher dose aspirin (150-162mg) may reduce the risk of preterm pre-eclampsia compared to lower dose aspirin (75-81mg) (Ghesquiere SR: low certainty evidence: 4 studies, 552 women; RR 0.34, 95% CI 0.15 to 0.79)
- Severe pre-eclampsia: Higher dose aspirin (150-162mg) may reduce the risk of preterm pre-eclampsia compared to lower dose aspirin (75-81mg) (Ghesquiere SR: low certainty evidence: 4 studies, 552 women; RR 0.23, 95% CI 0.09 to 0.62)
- We are uncertain if higher dose aspirin (150-162mg) has any effect on term pre-eclampsia compared to lower dose aspirin (75-81mg) as the confidence interval is very wide (Ghesquiere SR: low certainty evidence: 4 studies, 552 women; RR 0.57, 95% CI 0.12 to 2.64)

Aspirin dosage (< 75mg, ≥ 75mg, < 100mg, ≥ 100mg) vs placebo commenced at any point in pregnancy in women at increased risk of preeclampsia

Maternal outcomes:

- Dosage of <75mg vs ≥75 mg of aspirin:
  - Preeclampsia risk: among women at an increased risk of preeclampsia, reduction in development of preeclampsia with ≥75 mg of aspirin (USPSTF SR: moderate certainty evidence: 12 studies, 3,375 women; RR, 0.72, 95% CI, 0.56, 0.93) was slightly greater compared with <75 mg (USPSTF SR: moderate certainty evidence: 4 studies, 10,718 women; RR, 0.89, 95% CI, 0.74, 1.07). Test for subgroup differences: $Chi^2 = 2.74$, df = 1 (P = 0.10), $I^2 = 0\%$ - no significant difference
  - Preterm birth risk: among women at an increased risk of preeclampsia, reduction in development of preterm birth with ≥75 mg of aspirin (USPSTF SR: moderate certainty evidence: 9 studies, 3,065 women; RR 0.68, 95% CI 0.52- 0.88) was slightly greater compared with <75 mg (USPSTF SR: moderate certainty evidence: 4 studies, 10,554 women; RR, 0.91, 95% CI 0.81- 1.02). Test for subgroup differences: $Chi^2 = 4.85$, df = 1 (P = 0.03), $I^2 = 48.71\%$ - significant difference
  - In the Cochrane review there was some evidence that higher doses of aspirin among women (regardless of level of risk at trial entry) may conferred a greater benefit than lower doses (≥75 mg: low certainty evidence; 35 trials, 12,612 women; RR 0.69, 95% CI 0.61 to 0.78;)(< 75 mg: low certainty evidence; 17 trials, 23,204 women; RR 0.90, 95% CI 0.83 to 0.98;) in terms of reducing the risk of developing pre-eclampsia. Test for subgroup differences: $Chi^2 = 13.51$, df = 1 (P = 0.0002), $I^2 = 92.6\%$) - significant difference
- Dosage of <100mg vs ≥100 mg of aspirin:
  - Preeclampsia risk among women at an increased risk of preeclampsia, reduction in development of preeclampsia with ≥100 mg of aspirin (USPSTF SR: high certainty evidence: 10 studies, 3,157 women; RR, 0.72, 95% CI, 0.56, 0.93) was slightly greater compared with <100 mg (USPSTF SR: high certainty evidence: 6 studies, 10,936 women; RR, 0.89, 95% CI, 0.74, 1.07). Test for subgroup differences: $Chi^2 = 1.93$, df = 1 (P = 0.16), $I^2 = 0\%$ - no significant difference
  - In the Roberge 2018 review among women at unselected risk of preeclampsia, reduction in development of preterm preeclampsia with ≥100 mg of aspirin commended at or before 16 weeks (Roberge SR: moderate certainty evidence: 6 studies, 2,259 women; RR, 0.33, 95% CI, 0.19, 0.57) was greater compared with <100 mg (Roberge SR: low certainty evidence: 7 studies, 3,599 women; RR, 0.59, 95% CI, 0.29, 1.19). No test for subgroup differences was reported

- Preterm birth risk among women at an increased risk of preeclampsia, reduction in development of preterm birth with ≥100 mg of aspirin (USPSTF SR: moderate certainty evidence: 8 studies, 2,947 women; RR, 0.72, 95% CI, 0.56, 0.93) was slightly greater compared with <100 mg (USPSTF SR: moderate certainty evidence: 5 studies, 10,672 women; RR, 0.89, 95% CI, 0.74, 1.07). Test for subgroup differences: $Chi^2 = 4.90$, df = 1 (P = 0.03), $I^2 = 48.71\%$ - significant difference
- No difference in SGA/IUGR related to the dosage of aspirin was seen in either the 75mg or 100mg comparisons (p=0.38; p=0.14 respectively)
- No difference in placental abruption related to the dosage of aspirin was seen in either the 75mg or 100mg comparisons (p=0.71; p=0.65 respectively).
- Adverse effects of interventions: No difference in postpartum haemorrhage related to the dosage of aspirin was seen in either the 75mg or 100mg comparisons (p=0.78; p=0.65 respectively).

Neonatal outcomes:

- No difference in SGA/IUGR related to the dosage of aspirin was seen in either the 75mg or 100mg comparisons (p=0.38; p=0.14 respectively)

Aspirin (any dosage) timing of commencement (< 16 weeks, ≥ 16 weeks) vs placebo in women at increased risk of preeclampsia

Maternal outcomes:

- Preeclampsia risk: among women at an increased risk of preeclampsia, there may be little to no reduction in development of preeclampsia with commencement of aspirin ≥16 weeks (USPSTF SR: moderate certainty evidence: 11 studies, 11,747 women; RR, 0.88, 95%CI, 0.77 to 1.00). However, with commencement of aspirin <16 weeks a reduction was noted (USPSTF SR: moderate certainty evidence: 5 studies, 2,346 women; RR, 0.68, 95% CI, 0.53, 0.89). Test for subgroup differences: $Chi^2 = 3.17$, df = 1 (P = 0.08), $I^2 = 0\%$ - no significant difference
- Preterm birth risk: among women at an increased risk of preeclampsia, a smaller reduction in preterm birth with commencement of aspirin ≥16 weeks (USPSTF SR: moderate certainty evidence: 9 studies, 11,516 women; RR, 0.91, 95%CI, 0.85 to 0.96) was noted when compared with commencement of aspirin <16 weeks (USPSTF SR: moderate certainty evidence: 4 studies, 2,103 women; RR, 0.49, 95% CI, 0.26, 0.95). Test for subgroup differences: $Chi^2 = 5.50$, df = 1 (P = 0.02), $I^2 = 48.71\%$ - significant difference
- No difference in placental abruption related to the timing of commencement of aspirin was seen among women at increased risk of preeclampsia (p = 0.59).
- Adverse effects of interventions: No difference in postpartum haemorrhage related to the timing of commencement of aspirin was seen among women at increased risk of preeclampsia (p = 0.91).

Neonatal outcomes:

SGA/IUGR: among women at an increased risk of preeclampsia, there may be little to no reduction in development of SGA/IUGR with commencement of aspirin ≥16 weeks (USPSTF SR: moderate certainty evidence: 10 studies, 12,034 women; RR, 0.95, 95%CI, 0.80 to 1.13). However, with commencement of aspirin <16 weeks a reduction was noted (USPSTF SR: moderate certainty evidence: 6 studies, 2,351 women; RR, 0.59, 95% CI, 0.41, 0.86). Test for subgroup differences: $Chi^2 = 4.80$, df = 1 (P = 0.03), $I^2 = 41.24\%$ - significant difference

Certainty of the Evidence

Range: High to low quality of evidence

Both Cochrane and the USPSTF noted to be high quality systematic reviews.

An AMSTAR II score was performed on all other systematic reviews:

- Roberge 2018 review - Moderate quality review.
- van Doorn 2021 review - Moderate quality review
- Ghesquiere 2023 review - Moderate quality review

Outcomes were downgraded for indirectness due to dissimilarity with the population of interest (high risk women for preeclampsia, commenced aspirin before 16 weeks) and/or intervention of interest (differing aspirin dosages, other antiplatelet therapies). Where multiple dissimilarities were noted, studies were only downgraded by one level in the indirectness domain. Other reasons for downgrading included imprecision due to wide confidence intervals, inconsistency due to high statistical heterogeneity, and suspicion of publication bias due to asymmetric funnel plots.

Values and preferences

Preeclampsia can increase the risk of adverse pregnancy outcomes including placental abruption, renal failure, liver failure, cerebrovascular accident, HELLP syndrome, and/or admission to the ICU, fetal or neonatal death, admission to the NICU. Preeclampsia may also increase the use of additional interventions and hospital admission. Considering these risks, it is likely that most women would want aspirin as a preventative therapy if it were shown to reduce the risk of developing preterm preeclampsia.

Resources

A literature review conducted for the WHO (Recommendations on antiplatelet agents for the prevention of pre-eclampsia) found that aspirin use in pregnancy is a cost-effective intervention to prevent pre-eclampsia. Cost-effectiveness of screening in selecting the population of women to which to prescribe aspirin was addressed in Clinical Question 1.

Equity

Preeclampsia is more prevalent in Indigenous populations. Any intervention that reduces the risk of preeclampsia is likely to increase equity. However, the later aspirin is started the less effective it may be. Women who do not have access to antenatal care <16 weeks pregnant will not be screened or offered aspirin and thus are likely to receive less benefit from this intervention. This is likely to occur more often for Māori and Aboriginal and Torres Strait Islander women, and women who live in rural and remote areas. In some low-income settings, the indirect costs associated with procuring the medication, travelling to clinics for additional check-ups or both may also restrict access to the intervention.

Acceptability

Aspirin is likely an acceptable intervention for women. Studies of aspirin use for preeclampsia prevention have reported high adherence rates (>80%). Adherence may be further enhanced by improved patient-healthcare provider communication as to its importance, and introduction of reminder strategies to reduce unintentional missed doses. Side effects are reported to occur in approximately 25% of pregnant women taking aspirin, however, most studies of aspirin in pregnancy are underpower to detect rare adverse events

associated with aspirin use, such as major gastrointestinal bleeding. Among the relatively healthy population of people taking aspirin for primary prevention of stroke, a systematic review of three studies found there was an increased risk of major gastrointestinal bleeds in the aspirin group as compared with the placebo (no aspirin) group (OR was 1.41; 95% CI 1.09–1.82). No sub-analysis was conducted by aspirin dose or by enteric coated aspirin or immediate release.

Aspirin use as a prophylactic medication to reduce the risk of preeclampsia is well established in obstetric practice; thus its use is likely to be highly acceptable to registered health professionals providing maternity care.

Feasibility

No feasibility issues are identified. Aspirin is available over the counter and by prescription in both Australia and Aotearoa New Zealand. Dosages available differ by country. Both countries have a 100mg dose registered with their medication's regulatory authority. A dosage of 150mg could be achieved by splitting a 300mg tablet in half if this was the only dose available.

Benefits and harms

High dose calcium (1g or more/day) commenced at any point in pregnancy vs placebo in women at increased risk of preeclampsia

Maternal outcomes:

- Pre-eclampsia: Moderate certainty evidence suggests high-dose calcium supplementation (1g or more per day) reduces preeclampsia in those at high risk of developing hypertensive disorders (CR: five studies, 587 women; RR 0.22, 95% CI 0.12 to 0.42).
- Preterm birth: Moderate certainty evidence suggests high-dose calcium supplementation (1g or more per day) reduces preterm birth in those at high risk of developing hypertensive disorders (CR: four studies, 568 women; RR 0.45, 95% CI 0.24 to 0.83).
- The Cochrane review did not report on side effects of medication nor maternal satisfaction with the medication.

Neonatal outcomes:

- Very low certainty evidence suggests we are uncertain whether high-dose calcium supplementation has any effect on perinatal death (stillbirth or infant death prior to discharge from hospital) for those born to women at high risk of developing hypertension as very there were very few instances of this outcome (three studies; 512 infants; 0/248 vs 1/264; RR 0.39, 95% CI 0.02 to 9.20).
- Very low certainty evidence suggests we are uncertain whether high-dose calcium supplementation has any effect on NICU admission for those born to women at high risk of developing hypertension (CR: one trial; 63 infants; RR 0.29, 95% CI 0.03 to 2.48)

Low dose calcium (< 1g/day) commenced at any point in pregnancy vs placebo in women at increased risk of preeclampsia

Maternal outcomes:

- Preeclampsia: Very low certainty evidence suggests we are uncertain whether low dose calcium supplementation (500mg/ day) has any effect on preeclampsia for women at high risk of developing hypertension (CR: one trial; 579 women; RR 0.8, 95% CI 0.61 to 1.06)
- Early onset preeclampsia: Very low certainty evidence suggests we are uncertain whether low dose calcium supplementation (500mg/ day) has any effect on early onset preeclampsia for women at high risk of developing hypertension (CR: one trial; 579 women; RR 0.93, 95% CI 0.61 to 1.42)
- Very low certainty evidence was identified for severe maternal morbidity or mortality, preterm birth < 37 weeks, and pregnancy loss/stillbirth at any gestational age thus we are uncertain if low dose calcium has any effect on these outcomes.
- The Cochrane review did not report on side effects of medication nor maternal satisfaction with the medication.

Neonatal outcomes:

Very low certainty evidence suggests we are uncertain whether high-dose calcium supplementation has any effect on perinatal death or NICU admission >24hrs for those born to women at high risk of developing hypertension (one study; 508 infants; RR 1.11, 95% CI 0.77 to 1.6).

Very low certainty evidence was identified for Apgar score < 7 at 5 minutes, stillbirth, and birthweight < 2500g, thus we are uncertain if low dose calcium has any effect on these outcomes.

Certainty of the Evidence

Range: Moderate to very low quality of evidence

GRADE taken from Cochrane. Outcomes were further downgraded for indirectness as the population of interest different to the inclusion criteria for the Cochrane review. Most outcomes were GRADEd as very low due to a serious risk of bias, serious indirectness, and serious imprecision.

Values and preferences

Similar to aspirin use to prevent preterm preeclampsia, women are likely to value a therapy that may prevent preeclampsia given the significant impacts this condition can have for mother and baby.

Resources

No studies were identified that assessed the cost effectiveness of the addition of calcium to aspirin in the prevention of preeclampsia.

Indirect evidence from a cost analysis by means of a decision-analytic model in the Netherlands supports the use of calcium supplementation as a cost-effective prevention strategy, but did not include aspirin in addition to calcium in prevention. Actual healthcare costs are likely to vary in Australia and Aotearoa New Zealand from those in cost analyses from other jurisdictions.

Equity

A substantial proportion of pregnant women do not meet the recommended daily calcium intake, even in developed countries. Women from some cultural backgrounds may have lower dietary calcium intake than others and thus may receive greater benefit from supplementation.

Similar to aspirin for preeclampsia prevention, the greatest benefit is likely to be derived if prophylaxis is commenced before 16 weeks. Māori and Aboriginal and Torres Strait Islander women, and women who live in rural and remote areas, face significant access issues to antenatal care, and thus may be more likely to have their first consultation with their maternity care provider beyond this period, potentially limiting the benefit derived from calcium supplementation.

Acceptability

Calcium carbonate tablets used for calcium supplementation might be unpalatable to some women, as they can be large and have a powdery texture. To obtain high dose (>1000mg/day) women usually need to take two to three tablets a day, which significantly increases the total number of tablets a woman is required to take on a daily basis (in addition to other supplements such as iron and folic acid). These factors could have implications for both acceptability and compliance.

Feasibility

No feasibility issues identified. Calcium supplements are funded in Aotearoa New Zealand as a 500mg tablet. In Australia Caltrate 600mg is available. Both would require taking at least two tablets to achieve high dose.

Table 1- Clinical Question 1: Screening algorithms compared with routine care, by outcome

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Summary
		History-based screening + aspirin or no screening or prophylaxis.	Screening algorithm (combination and each in individually)		
Preterm preeclampsia (diagnosis of or requiring delivery <37 weeks) - first trimester screening algorithm + aspirin vs routine maternity care [SR: FOSTER 2023]	Odds ratio: 0.61 (CI 95% 0.52 - 0.7) Based on data from 371041 participants in 6 studies	7 per 1000	4 per 1000	**Low** Due to serious risk of bias	A first trimester screening algorithm + aspirin (if high risk) may decrease preterm preeclampsia compared to routine maternity care
		Difference: **3 fewer per 1000** (CI 95% 3 fewer - 2 fewer)			
Preeclampsia diagnosed prior to 32-34 weeks - first trimester screening algorithm + aspirin vs routine maternity care [SR: FOSTER 2023]	Odds ratio: 0.38 (CI 95% 0.22 - 0.64) Based on data from 30192 participants in 5 studies	4 per 1000	2 per 1000	**Moderate** Due to serious risk of bias	A first trimester screening algorithm + aspirin (if high risk) probably decreases preeclampsia prior to 32-34 weeks compared to routine maternity care
		Difference: **2 fewer per 1000** (CI 95% 3 fewer - 1 fewer)			
Term Preeclampsia - first trimester screening algorithm + aspirin vs routine maternity care [SR: FOSTER 2023]	Odds ratio: 0.8 (CI 95% 0.62 - 1.03) Based on data from 365542 participants in 5 studies	18 per 1000	14 per 1000	**Low** Due to serious risk of bias	A first trimester screening algorithm + aspirin (if high risk) may have little or no effect on term preeclampsia compared to routine maternity care.
		Difference: **4 fewer per 1000** (CI 95% 7 fewer - 1 more)			
Any Preeclampsia - first trimester screening algorithm + aspirin vs routine maternity care [SR: FOSTER 2023]	Odds ratio: 0.73 (CI 95% 0.63 - 0.85) Based on data from 371039 participants in 6 studies	25 per 1000	18 per 1000	**Low** Due to serious risk of bias	A first trimester screening algorithm + aspirin (if high risk) may decrease preeclampsia (at any gestation) compared to routine maternity care
		Difference: **7 fewer per 1000** (CI 95% 9 fewer - 4 fewer)			
Stillbirth - first trimester screening algorithm + aspirin vs routine maternity care [SR: FOSTER 2023]	Odds ratio: 0.71 (CI 95% 0.56 - 0.89) Based on data from 338339 participants in 3 studies	3 per 1000	2 per 1000	**Very low** Due to serious risk of bias	We are uncertain whether a first trimester screening algorithm + aspirin (if high risk) increases or decreases stillbirth compared to
		Difference: **1 fewer per 1000** (CI 95% 1 fewer - 0 fewer)			

					routine maternity care due to very low certainty evidence.
Preterm preeclampsia (requiring delivery <37 weeks) - first trimester screening algorithm + aspirin vs routine maternity care [RCT: ROLNIK 2017]	Odds ratio: 0.53 (CI 95% 0.33 - 0.87) Based on data from 15152 participants in 1 studies	6 per 1000	3 per 1000	**Moderate** Due to indirectness	A first trimester screening algorithm + aspirin (if high risk) probably decreases preterm preeclampsia compared to routine maternity care
		Difference: **3 fewer per 1000** (CI 95% 4 fewer - 1 fewer)			

Table 2- Clinical Question 2: Screening test accuracy in identifying women at risk of preterm preeclampsia (≤37 weeks gestation)

Study	N (country)	Developed preterm PE in study N (%)	Risk cut off	Screen positive rate %	Sensitivity % (95% Confidence Interval)	Specificity % (95% Confidence Interval)	Positive predictive value % (PPV)[1]	Negative predictive value % (NPV)[1]	Fixed variable	Adjust for aspirin
Maternal history-based screening by NICE, or ACOG guidelines										
Tan 2018[7]	61,174 (Multicentre)	493 (0.8)	NICE	11.5	42.0 (37.7 – 46.4)	88.8	2.9	99.5	Risk cut-off	Yes
			ACOG	66.1	89.2 (86.2 – 91.7)	34.0	1.1	99.7	Risk cut-off	Yes
Guy 2021	7,720 (UK)	65 (0.8)	NICE	16.1	36.9 (25.3–49.8)	84.1 (83.6–84.9)	1.9	99.4	Risk cut-off	No
Poon 2018 (ASPRE)	34,573 (Multicentre)	239 (0.7)	ACOG	64.5	90.8	35.8	1.0	100.0	Risk cut-off	Yes
Maternal history-based screening by FMF risk factors										
Tan 2018	61,174 (Multicentre)	493 (0.8)	1:100	19.1	59.4	81.2	2.6	98.5	Risk cut-off	Yes
			1:70	11.8	48.3	88.5	3.3	99.5	Risk cut-off	Yes
Maternal risk factors (FMF) + MAP										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	18.3	66.7 (62.5 – 70.8)	82.1	2.9	99.7	Risk cut-off	Yes
			1:70	12.0	55.8 (51.4 – 60.1)	88.4	3.7	99.6	Risk cut-off	Yes

[7] Tan 2018 includes data from: Tan et al 2018a (SPREE), O'Gorman et al 2017, and O'Gorman et al 2015

Akolekar 2013	58,884 (UK)	568 (1.0)	1:52	10.6	59.3	90			FPR	?No
Maternal risk factors (FMF) + MAP + UtPI										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	16.9	77.7 (73.8 – 81.1)	83.6	3.7	99.8	Risk cut-off	Yes
			1:70	11.7	70.6 (66.4 – 74.4)	88.8	4.9	99.7	Risk cut-off	Yes
Akolekar 2013	58,884 (UK)	568 (1.0)	1:57	10.7	71.5	90			FPR	?No
Maternal risk factors (FMF) + MAP + PAPP-A										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	17.7	69.0 (64.8 – 72.9)	82.7	3.1	99.7	Risk cut-off	Yes
			1:70	11.9	58.6 (54.2 – 62.9)	88.4	4.0	99.6	Risk cut-off	Yes
Maternal risk factors (FMF) + MAP + PlGF										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	15.3	77.9 (74.0 – 81.3)	85.2	4.1	99.8	Risk cut-off	Yes
			1:70	10.8	68.6 (64.3 – 72.5)	89.7	5.1	99.7	Risk cut-off	Yes
Maternal risk factors (FMF) + MAP + UtPI + PAPP-A										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	16.7	79.7 (75.9 – 83.0)	83.8	3.8	99.8	Risk cut-off	Yes
			1:70	11.5	71.6 (67.5 – 75.4)	88.9	5.0	99.7	Risk cut-off	Yes

Akolekar 2013	58,884 (UK)	568 (1.0)	1:65	10.7	74.6	90			FPR	?No
Guy 2021	4,841 (UK)	27 (0.6)	1:50	8.2	55.6 (35.3–74.5)	92.0 (91.2–92.8)	3.8	99.7	Risk cut-off	No
Maternal risk factors (FMF) + MAP + UtPI + PlGF										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	14.7	79.9 (76.2 – 83.2)	85.9	4.4	99.8	Risk cut-off	Yes
			1:70	10.6	75.5 (71.5 – 79.1)	90.0	5.8	99.8	Risk cut-off	Yes
Chaemsaithong 2019	10,935 (Multicentre Asia)	73 (0.7)	1:93	10.4	64.0 (53.3 – 74.7)	90			FPR	Yes
Akolekar 2013	58,884 (UK)	568 (1.0)	1:67	10.7	77.3	90			FPR	?No
Maternal risk factors (FMF) + MAP + UtPI + PAPP-A + PlGF										
Tan 2018[1]	61,174 (Multicentre)	493 (0.8)	1:100	14.7	80.7 (77.0 – 84.0)	85.9	4.4	99.8	Risk cut-off	Yes
			1:70	10.6	76.1 (72.1 – 79.6)	90.0	5.8	99.8	Risk cut-off	Yes
Akolekar 2013	58,884 (UK)	568 (1.0)	1:67	10.7	76.6 (73 – 80)	90			FPR	?No
Zwertbroek 2021	362 (Netherlands)	10 (2.8)	1:64	20.7	70.0	80.7	9.3	99.0	Risk cut-off	Yes
			1:100	25.1	70.0	76.1	7.7	98.9	Risk cut-off	Yes

Rolnik 2017 (ASPRE)	25 797 (Multicentre Europe)	180 (0.7)	1:100	10.5	76.7	90.8	5.1	99.8	Risk cut-off	Yes

[1] Three studies assessed the detection rate of the FMF algorithm versus standard care, when the false-positive rate is fixed at the same value, to allow a comparison of detection rate (sensitivity) when the false-positive rate (1 minus specificity) is held at the same value. Since specificity, PPV, and NPV are all a function of a false-positive rate that is predetermined by investigators, PPV and NPV were not calculated nor used to determine the accuracy of screening tests on these studies.

Table 3- Clinical Question 2: Screening test accuracy in identifying women at risk of early onset preeclampsia (≤ 34 weeks gestation)

Study	N (country)	Developed preterm PE in study N (%)	Risk cut off	Screen positive rate %	Sensitivity % (95% Confidence Interval)	Specificity % (95% Confidence Interval)	Positive predictive value % (PPV)[1]	Negative predictive value % (NPV)[1]	Fixed variable	Adjusted for Aspirin effect
Maternal risk factors + MAP										
Park 2013[2]	3,014 (Australia)	12 (0.4)	Not reported	10.2	58.3 (27.8 – 84.7)	90			FPR	Yes
Poon 2009[2]	8,366 (UK)	37 (0.4)	Not reported	10.3	75.7 (58.8 – 88.2)	90			FPR	No
Akolekar 2013	58,884 (UK)	214 (0.4)	1:159	10.3	72.9	90			FPR	?No
Maternal risk factors + MAP + UtPI										
Park 2013[2]	3,014 (Australia)	12 (0.4)	Not reported	10.3	75.0 (42.8 – 94.2)	90			FPR	Yes
Poon 2009[2]	8,366 (UK)	37 (0.4)	Not reported	10.4	89.2 (74.6 – 96.6)	90			FPR	No
Akolekar 2013	58,884 (UK)	214 (0.4)	1:197	10.3	89.7	90			FPR	?No
DiMartino 2019	11,632 (Italy)	67 (0.6)	1:226	-	58.2 (45.5–70.2)	90			FPR	No
Maternal risk factors + MAP + PAPP-A										
Park 2013[2]	3,014 (Australia)	12 (0.4)	Not reported	10.1	41.7 (15.3 – 72.2)	90			FPR	Yes
Poon 2009[2]	8,366 (UK)	37 (0.4)	Not reported	10.3	73.0 (55.9 – 86.2)	90			FPR	No
Maternal risk factors + MAP + UtPI + PAPP-A										

Park 2013[2]	3,014 (Australia)	12 (0.4)	Not reported	10.3	91.7 (61.5 – 98.6)	90			FPR	Yes
Poon 2009[2]	8,366 (UK)	37 (0.4)	Not reported	10.4	94.6 (81.8 – 99.2)	90			FPR	No
		37 (0.4)	1:100	10.3	86.5	93.5			Risk cut-off	No
Akolekar 2013	58,884 (UK)	214 (0.4)	1:216	10.3	92.5	90			FPR	?No
Maternal risk factors + MAP + UtPI + PlGF										
Akolekar 2013	58,884 (UK)	214 (0.4)	1:261	10.3	95.8	90			FPR	?No
Maternal risk factors + MAP + UtPI + PAPP-A + PlGF										
Zwertbroek 2021	362 (Netherlands)	5 (1.4)	1:150	16.0	40.0	84.3	3.4	99.0	Risk cut-off	Yes
			1:250	20.0	80.0	80.6	5.6	99.7	Risk cut-off	Yes
Akolekar 2013	58,884 (UK)	214 (0.4)	1:269	10.3	96.3	90			FPR	?No

[1] Four studies assessed the detection rate of the FMF algorithm versus standard care, when the false-positive rate is fixed at the same value, to allow a comparison of detection rate (sensitivity) when the false-positive rate (1 minus specificity) is held at the same value. Since specificity, PPV, and NPV are all a function of a false-positive rate that is predetermined by investigators, PPV and NPV were not calculated nor used to determine the accuracy of screening tests on these studies.

[2] Measurement of UtPI included in algorithm is lowest measured UtPI not mean UtPI as included in standard FMF algorithm

Table 4- Clinical Question 3: Summary of systematic review evidence- aspirin with placebo for women at moderate to high risk of preeclampsia based on screening (varying gestation at starting aspirin)

Outcome (Source)	Source	Aspirin (all doses)	Placebo	Relative Risk (95% confidence intervals)	Plain language summary
Preeclampsia	CR: Duley 2019	13.0%	15.7%	0.83 (0.77-0.90)	Aspirin may decrease development of PE compared to placebo. **NNT 37** (37 women need to be treated with aspirin to avoid one woman developing preeclampsia) **GRADE of evidence:** Low[3]
Preterm preeclampsia	SR: Van Doorn 2021	2.8%	4.0	0.7 (0.53-0.92)	Aspirin may decrease development of preterm PE compared to placebo. **NNT 83** **GRADE of evidence:** Low[5]
Composite outcome for perinatal death[6]	CR: Duley 2019	2.8%	3.6%	0.77 (0.64-0.93)	Aspirin likely decreases fetal death, neonatal death or death before hospital discharge compared to placebo. **NNT 125 GRADE of evidence:** Moderate[7]
Preterm birth	CR: Duley 2019	17.1%	19.7%	0.87 (0.81-0.94)	Aspirin likely decreases preterm birth compared to placebo. **NNT 38** **GRADE of evidence:** Moderate[7]
Preterm birth < 34 weeks	CR: Duley 2019	6.3%	7.0%	1.0 (0.72-1.39)	Aspirin likely decreases preterm birth < 34 weeks compared to placebo. **NNT 142 GRADE of evidence:** Moderate[7]
Small for gestational age	CR: Duley 2019	6.0%	7.2%	0.83 (0.73-0.94)	Aspirin likely decreases SGA compared to placebo. **NNT 83 GRADE of evidence:** Moderate[7]
Severe maternal morbidity[6]	CR: Duley 2019	0.5%	0.5%	1.0 (0.72-1.39)	Aspirin likely decreases severe maternal morbidity compared to placebo. **GRADE of evidence:** Moderate[7]

1. Number needed to treat (100/risk difference)
2. *Cochrane Review Duley, number of patients varies according to the outcome*
3. Downgraded for serious publication bias, serious indirectness (included patients who started aspirin>16 weeks)
4. *van Doorn 2021*
5. Downgraded for serious inconsistency, serious indirectness (included patient who started aspirin>16 weeks)
6. Fetal death, neonatal death or death before hospital discharge
7. Downgraded for serious indirectness (included >16 weeks at time of starting aspirin)
8. Eclampsia, renal and liver failure, HELLP, stroke

Table 5- Clinical Question 3: Women at varying risks of preeclampsia and grouped by timing of commencement of aspirin and doses of aspirin

Outcome (Source)	Source	Aspirin (all doses)	Placebo	Relative Risk (95% confidence intervals)	Plain language summary
Prophylaxis started before 16 weeks pregnant – moderate to high risk of PE, all doses of aspirin					
Preeclampsia Aspirin started < 16 weeks pregnancy	USPSTF 2021	7.9%	11.6	0.68 (0.53-89)	Aspirin commenced before 16 weeks likely decreases development of PE compared to placebo. **NNT 27** **GRADE of evidence:** Moderate[8]
Preterm birth	USPSTF 2021	5.8%	11.9%	0.49 (0.26-0.95)	Aspirin commenced before 16 weeks likely decreases preterm birth compared to placebo. NNT 16 (16 women need to be treated with aspirin to avoid one woman having a preterm birth) **GRADE of evidence:** Moderate
Small for gestational age	USPSTF 2021	12.3%	20.8%	0.59 (0.41-0.86)	Aspirin commenced before 16 weeks likely decreases SGA compared to placebo. NNT 12 (12 women need to be treated with aspirin to avoid one woman having a SGA baby) **GRADE of evidence:** Moderate
Prophylaxis started before 16 weeks pregnant – moderate to high risk of PE, varying doses of aspirin					
Preeclampsia Aspirin < 75mg	USPSTF 2021	9.4%	10.6	0.89 (0.74-1.07)	Aspirin < 75mg commenced before 16 weeks has little or no difference on the development of PE compared to placebo. **GRADE of evidence:** Moderate

[8] All outcomes graded as Moderate received downgrading for serious indirectness or for other reasons as indicated by footnotes.

Preeclampsia Aspirin >=75mg	USPSTF 2021	9.6%	13.3	0.72 (0.56-93)	Aspirin >=75mg commenced before 16 weeks likely decreases the development of PE compared to placebo. **NNT - 27** **GRADE of evidence:** Moderate
Preeclampsia Aspirin >=100mg	USPSTF 2021	9.7%	13.1	0.74 (0.58-0.94)	Aspirin >=75mg commenced before 16 weeks likely decreases the development of PE compared to placebo. **NNT - 29** **GRADE of evidence:** Moderate
Preterm birth Aspirin <75mg	USPSTF 2021	22.6%	24.8	0.91 (0.81-1.02)	Aspirin >=75mg commenced before 16 weeks has little or no effect on preterm birth compared to placebo. **GRADE of evidence:** Moderate
Preterm birth Aspirin >=75mg	USPSTF 2021	9.6%	14.1	0.68 (0.52-0.88)	Aspirin >=75mg commenced before 16 weeks likely decreases the preterm birth compared to placebo. **NNH - 22** **GRADE of evidence:** Moderate
Preterm birth Aspirin >=100mg	USPSTF 2021	9.9 %	14.6	0.91 (0.81-1.02)	Aspirin >=75mg commenced before 16 weeks likely decreases the preterm birth compared to placebo. **NNT 21** **GRADE of evidence:** Moderate
Small for gestational age	USPSTF 2021	21.4%	16.3%	0.76 (0.59-0.96)	Aspirin >= 100mg commenced before 16 weeks likely decreases SGA compared to placebo. **NNT 19** (19 women need to be treated with aspirin to avoid one woman having a SGA baby) **GRADE of evidence:** Moderate
Prophylaxis started at or after 16 weeks pregnant - moderate to high risk of PE – varying doses of aspirin					
Preeclampsia Aspirin started >= 16 weeks pregnancy	USPSTF 2021	9.9%	11.2	0.88 (0.77-1.0)	Aspirin commenced at >= 16 weeks likely decreases development of PE compared to placebo. **NNT 77** **GRADE of evidence:** Moderate

Preterm birth	USPSTF 2021	22.3%	24.5%	0.91 (0.85-0.96)	Aspirin commenced before 16 weeks likely decreases preterm birth compared to placebo. NNT 45 (45 women need to be treated with aspirin to avoid one woman having a preterm birth) **GRADE of evidence:** Moderate
Small for gestational age	USPSTF 2021	7.9%	8.3%	0.95 (0.8-1.13)	Aspirin commenced before 16 weeks has little or no effect on SGA compared to placebo **GRADE of evidence:** Moderate
Prophylaxis started before 16 weeks pregnant – women with unselected risk of PE – varying doses of aspirin					
Preeclampsia Aspirin < 75mg	Duley 2019	4.7%	5.1	0.92 (0.85-1.0)	Aspirin < 75mg commenced before 16 weeks has little or no difference on the development of PE compared to placebo. **GRADE of evidence:** Moderate
Preeclampsia Aspirin >= 75mg	Duley 2019	5.2%	6.7	0.78 (0.66-0.92)	Aspirin < 75mg commenced before 16 weeks likely decreases the development of PE compared to placebo. **NNT - 66** **GRADE of evidence:** Moderate
Preterm birth Aspirin < 75mg	Duley 2019	17.9%	19.3%	0.93 (0.89-0.98)	Aspirin < 75mg commenced before 16 weeks likely decreases preterm birth compared to placebo. **NNT -71** **GRADE of evidence:** Moderate
Preterm birth Aspirin >=75mg	Duley 2019	11.2%	13.0%	0.86 (0.73-1.01)	Aspirin >= 75mg commenced before 16 weeks likely decreases preterm birth compared to placebo. **NNT -55 GRADE of evidence:** Moderate (downgraded for serious indirectness)
Preterm preeclampsia Aspirin < 100mg	Roberge 2021	3.3%	5.6%	0.59 (0.29-1.19)	Aspirin < 100mg commenced before 16 weeks has little or no difference on the development of PPE compared to placebo. **GRADE of evidence:** Low
Preterm preeclampsia Aspirin >= 100mg	Roberge 2021	1.7%	5.1%	0.33 (0.19-0.57)	Aspirin < 100mg commenced before 16 weeks likely reduces the development of PPE compared to placebo. **NNT - 29** **GRADE of evidence:** Moderate[9]

[9] Downgraded for serious indirectness and publication bias

Preterm preeclampsia Aspirin >= 100mg versus 75-81mg	Roberge 2021 (includes ASPRE + 5 other RCTs)	3.0%	8.8%	0.34 (0.15-0.79)	Aspirin < 100mg commenced before 16 weeks likely reduces the development of PPE compared to placebo. **NNT - 17** **GRADE of evidence:** Moderate[10]
Prophylaxis started before 16 weeks pregnant – women with moderate to high risk of PE – 150mg Aspirin only					
Preterm preeclampsia Aspirin 150mg versus placebo	ASPRE Rolnik	1.6	4.3%	0.38 (0.20 to 0.74)	Aspirin < 100mg commenced before 16 weeks likely reduces the development of PPE compared to placebo. **NNT - 37** **GRADE of evidence:** Moderate[11]

[10] Downgraded for serious indirectness and publication bias
[11] Downgraded for imprecision

Table 6- Clinical Question 3, Part D (Calcium): Summary of systematic review evidence

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Placebo (or aspirin alone)	Calcium (+/- aspirin)		
Development of preeclampsia - high dose calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.22 (CI 95% 0.12 - 0.42) Based on data from 587 participants in 5 studies[3]	**176** per 1000	**39** per 1000	**Moderate** Due to serious indirectness[4]	High dose calcium probably decreases development of preeclampsia in women at high risk of preeclampsia based on screening compared to placebo.
		Difference: **137 fewer per 1000** (CI 95% 155 fewer - 102 fewer)			
Preterm birth - high dose calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.45 (CI 95% 0.24 - 0.83) Based on data from 568 participants in 4 studies	**107** per 1000	**48** per 1000	**Low** Due to serious indirectness, Due to serious imprecision[6]	High dose calcium probably decreases preterm birth in women at high risk of preeclampsia based on screening compared to placebo.
		Difference: **59 fewer per 1000** (CI 95% 81 fewer - 18 fewer)			
Preeclampsia (any)- high dose calcium supplementation in women at high risk of preeclampsia [SR: Woo Kinshella 2022]	Risk ratio: 0.23 (CI 95% 0.10- 0.42) Based on data from 929 participants in 9 studies	**187** per 1000[12]	**43** per 1000	**Moderate**	High dose calcium probably decreases preeclampsia (any) in women at high risk of preeclampsia compared to placebo.
		Difference: 144 **fewer per 1000** (CI 95% 114 fewer - 108 fewer)			
Preeclampsia (any)- low dose calcium supplementation in women at high risk of preeclampsia [SR: Woo Kinshella 2022]	Risk ratio: 0.38 (CI 95% 0.21- 0.64) Based on data from 2234 participants in 9 studies	**187** per 1000	71 per 1000	**Moderate**	Low dose calcium probably decreases preeclampsia (any) in women at high risk of preeclampsia compared to placebo.
		Difference: 116 **fewer per 1000** (CI 95% 148 fewer - 67 fewer)			

[12] High risk subgroup from Woo Kinshella 2022 applied as baseline risk with placebo.

Admission to NICU - high dose calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2018]	Relative risk: 0.29 (CI 95% 0.03 - 2.48) Based on data from 63 participants in 1 studies[1]	**118** per 1000	**34** per 1000	**Low** Due to serious indirectness, Due to serious imprecision	We are uncertain whether high dose calcium supplementation in women at high risk of preeclampsia based on screening has an effect on admission to NICU due to wide confidence intervals
		Difference: **84 fewer per 1000** (CI 95% 114 fewer - 175 more)			
Admission to NICU- any dose calcium supplementation in women at any risk for preeclampsia [SR: Woo Kinshella 2022]	Risk ratio: 0.86 (CI 95% 0.66- 1.13) Based on data from 13,825 participants in 6 studies	**118** per 1000[13]	**101** per 1000	**Low**	We are uncertain whether high dose calcium supplementation in women at high risk of preeclampsia has an effect on admission to NICU due to wide confidence intervals
		Difference: **17 fewer per 1000** (CI 95% 40 fewer - 15 more)			
Stillbirth or death prior to discharge from hospital - high dose calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.39 (CI 95% 0.02 - 9.2) Based on data from 512 participants in 3 studies[7]	**4** per 1000	**0** per 1000	**Very low** Due to serious indirectness, Due to very serious imprecision	There were too few who experienced stillbirth or death prior to discharge from hospital, to determine whether high dose calcium supplementation in women at high risk of preeclampsia based on screening made a difference
		Difference: **4 fewer per 1000** (CI 95% 4 fewer - 33 more)			
Preeclampsia - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.8 (CI 95% 0.61 - 1.06) Based on data from 579 participants in 1 studies[9]	**290** per 1000	**232** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases preeclampsia due to very low quality data
		Difference: **58 fewer per 1000** (CI 95% 113 fewer - 17 more)			
Early onset preeclampsia - 500mg calcium supplementation in women at high risk of	Relative risk: 0.93 (CI 95% 0.61 - 1.42)	**134** per 1000	**125** per 1000	**Very low**	We are uncertain whether calcium supplementation in women at high risk of early

[13] No baseline risk reported for this outcome in Woo Kinshella 2022. Baseline risk from Hofmeyr 2018 applied instead.

preeclampsia based on screening [CR: Hofmeyr 2019]	Based on data from 579 participants in 1 studies	Difference: **9 fewer per 1000** (CI 95% 52 fewer - 56 more)	Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	onset preeclampsia based on screening increases or decreases preeclampsia due to very low quality data
Severe maternal morbidity or mortality - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.93 (CI 95% 0.68 - 1.26) Based on data from 579 participants in 1 study	**230** per 1000 / **214** per 1000 Difference: **16 fewer per 1000** (CI 95% 74 fewer - 60 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases severe maternal morbidity or mortality due to very low quality data
Pregnancy loss or stillbirth at any gestational age - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.83 (CI 95% 0.61 - 1.14) Based on data from 633 participants in 1 study	**216** per 1000 / **179** per 1000 Difference: **37 fewer per 1000** (CI 95% 84 fewer - 30 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases pregnancy loss or stillbirth at any gestational age due to very low quality data
Birthweight < 2500 g - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 1.0 (CI 95% 0.76 - 1.3) Based on data from 507 participants in 1 study	**300** per 1000 / **300** per 1000 Difference: **0 fewer per 1000** (CI 95% 72 fewer - 90 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases birthweight < 2500 g due to very low quality data
Preterm birth < 37 weeks - 500mg calcium supplementation in women at high risk of	Relative risk: 0.9 (CI 95% 0.74 - 1.1)	**420** per 1000 / **378** per 1000	**Very low**	We are uncertain whether calcium supplementation in women at high risk of

preeclampsia based on screening [CR: Hofmeyr 2019]	Based on data from 579 participants in 1 study	Difference: **42 fewer per 1000** (CI 95% 109 fewer - 42 more)	Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	preeclampsia based on screening increases or decreases preterm birth < 37 weeks due to very low quality data
Apgar < 7 at 5 minutes - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.43 (CI 95% 0.15 - 1.21) Based on data from 494 participants in 1 study	**46** per 1000 / **20** per 1000 Difference: **26 fewer per 1000** (CI 95% 39 fewer - 10 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases Apgar < 7 at 5 minutes due to very low quality data
Perinatal death or NICU admission > 24 hrs - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 1.11 (CI 95% 0.77 - 1.6) Based on data from 508 participants in 1 study	**177** per 1000 / **196** per 1000 Difference: **19 more per 1000** (CI 95% 41 fewer - 106 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases perinatal death or NICU admission > 24 hrs due to very low quality data
Stillbirth - 500mg calcium supplementation in women at high risk of preeclampsia based on screening [CR: Hofmeyr 2019]	Relative risk: 0.78 (CI 95% 0.48 - 1.27) Based on data from 579 participants in 1 study	**117** per 1000 / **91** per 1000 Difference: **26 fewer per 1000** (CI 95% 61 fewer - 32 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain whether calcium supplementation in women at high risk of preeclampsia based on screening increases or decreases stillbirth due to very low quality data

Table 7- Clinical Question 3: Cost effectiveness of preeclampsia screening with FMF algorithm compared to history-based screening using decision models: Adapted from Table Ontario Health Technology Assessment 2022

	Park et al 2021 (CEA)	Dubon Garcia et al 2021 (CUA)	Mewes et al 2022 (Germany) (CEA)	Mewes et al 2022 (Germany) (CEA)	Ortved et al 2019 (CEA)	Ontario Health Technology Assessment 2022 (CEA)	Nzelu et al 2023 (CUA)
Country (currency, reference year)	Australia (AUD, 2018)	Belgium (Euros, 2019)	Germany (Euros, 2021)	Germany (Euros, 2021) Switzerland (Swiss Francs, 2021)	Canada (CAD, 2016)	Canada (CAD, 2022)	UK (GBP, 2022)
Population	N = 6,822	N = 51,309	Germany N = 763,732	Switzerland N = 84,759	N = 387,516	N = 140,500	N = 5,957
Perspective	Australian public hospital	Belgian payers' perspective - costs for the government and patient	Health care perspective	Health care perspective	Not reported	Ontario Ministry of Health	Provider perspective
Time horizon	2 years	1 year	9 months	9 months	1 year	2 years	1 year
What tests included in algorithm	Maternal history, MAP, UtPI, PAPP-A	Maternal history, MAP, UtPI, PlGF	Maternal history, MAP, UtPI, PAPP-A, PlGF	Maternal history, MAP, UtPI, PAPP-A, PlGF	Maternal history, MAP, UtPI, PAPP-A, PlGF	Maternal history, MAP, UtPI, PlGF	Maternal history, MAP, UtPI, PAPP-A
Prevalence of preterm preeclampsia used	0.4% (<34 weeks)	0.4%	0.7%	0.7%	0.4% (<34 weeks)	0.8%	0.8%
Effectiveness (cases with and without preeclampsia)	31.19 fewer cases of early onset preeclampsia	337 fewer cases of preterm preeclampsia	Germany – 2,891 fewer cases of preterm preeclampsia	Switzerland - 321 fewer cases of preterm preeclampsia	1,096 fewer cases of early onset preeclampsia	371 fewer cases of preterm preeclampsia	7 fewer cases of preterm preeclampsia

Cost per pregnancy screened with FMF algorithm	Not reported	€4,417.61	Germany - €5,916	Switzerland - CHF14,800	$24.58	$325.05	Not reported
Cost per pregnancy screened with history-based screening	Not reported	€4,446.28	Germany - €5,901	Switzerland - CHF14,842	$61.70	$315.94	Not reported
Mean cost difference between screening strategies	$-209.79/ pregnancy screened	€-28.67/ pregnancy screened	Germany €14/pregnancy screened	Switzerland – CHF-42/ pregnancy screened.	$-37.12/ pregnancy screened	$9.11/pregnancy screened	£-9.06
Quality of life outcome	-	Mean difference: 0.0003 QALYs/patient (mother and child – assessed by EQ-5D)	-	-	-	-	Mean difference: 0.00006 QALYs/patient screened (assessed by EQ-5D)
Dominant strategy	**FMF dominant**	**FMF dominant**	**Germany – ICER-Cost of €3,795/case of preeclampsia prevented**	**Switzerland – FMF dominant**	**FMF dominant**	**ICER - Cost of $3,446/ case of preeclampsia prevented** When PAPP-A used instead of PlGF, FMF is dominant	**FMF dominant**

CEA = Cost effectiveness analysis; CUA = cost utility analysis

Appendix F- Māori Equity toolkit

At recommendation of He Hono Wāhine of RANZCOG Aotearoa New Zealand, the College is committed to applying an equity tool and lens to Clinical Guidelines, including C-Obs 61.

The following tool was developed by Dr Maira Patu, Dr Angela Beard and Professor Suzanne Pitama- Māori Indigenous Health Innovation, University of Otago, Christchurch. The toolkit seeks to identify any differences in how Māori patients receive and experience care within health systems, particularly as it relates to the principles of Te Whare Tapa Whā (a model/understanding of the concept of Māori health).

Questions within each domain also provide opportunity to highlight ways to address or mitigate these gaps and work towards reducing health inequities between Māori and non-Māori in Aotearoa New Zealand.

1. Marginalisation data

What is the prevalence for this condition for Māori compared to non-Māori?

- A study of 26,254 women in Aotearoa New Zealand demonstrated a univariate association with ethnicity. The evidence showed that, compared with European women, the risk of preeclampsia is nearly 50% lower among Chinese women (adjusted OR 0.56; 95% CI 0.41–0.76) and nearly 50% higher among Māori women (adjusted OR 1.51; 95% CI 1.16–1.96).[13] .
- However, no association between ethnicity and preeclampsia was found in a recent cohort study.[45]

What are the morbidity and mortality rates for Māori compared to non-Māori?

- There is limited population-wide data, stratified by ethnicity, available reporting mortality and morbidity associated with preeclampsia. However, the Perinatal and Maternal Mortality Review Committee of Aotearoa New Zealand have consistently found that Māori and Pacific Island wāhine and pēpi experience higher rates of the following outcomes in general, when compared with women and babies from New Zealand European ethnicity:
    - Maternal mortality rate (2006-2020)- higher among Māori (26.3 deaths/100,000 maternities) and Pacific women (23.8 deaths/100,000 maternities) compared to women of New Zealand European ethnicity (13.5 deaths/100,000 maternities) in combined data.
    - Neonatal mortality (2016-2020):
        - Neonatal death per 1000 births- higher for Māori (3.82) and Pacific Islands (3.98) compared with New Zealand European ethnicity (2.36).
        - Stillbirth per 1000 births- higher for Māori (5.22) and Pacific peoples (6.53) compared with New Zealand European ethnicity (4.44).
- Death due spontaneous preterm labour was the leading classification of death for Māori and Pacific Islands pēpi. Unexplained antepartum fetal death was the primary cause of death for babies of mothers in other ethnic groups.

2. Racism (including personally-mediated racism (unintentional and intentional), institutionalised racism causing inequity, internalised racism

Is there any evidence that Māori do not receive best practice for this condition?

Do rates of diagnosis for Māori match the prevalence, age of onset, and severity for the condition?

Do rates of treatment, referral, and intervention for Māori match the prevalence, age of onset, and severity for the condition?

- No data was identified which stratified either screening rates for preeclampsia or aspirin prescription rates if identified at increased risk by ethnicity for Māori populations in Aotearoa New Zealand.

- Access issues with primary care for Indigenous populations may mean that pre-pregnancy chronic hypertension is not picked up. Undiagnosed chronic hypertension can be masked in early pregnancy due to physiological changes that may cause initial decreases in blood pressure, then misdiagnosed later in the pregnancy as a gestational disorder when abnormal readings re-surface. Disparities in the broader social determinants of health impact this for Indigenous groups.
- Screening algorithms currently used were developed in the UK and do not include ethnicity categories for Māori or Pacific Islands populations. Outputs from the algorithm may differ depending on the ethnicity category selected (which may be informed by a healthcare provider's racial biases). Selecting the most accurate ethnicity category further impacts on the risk calculation result – for example, Black and African-American women consistently screen at higher risk of preeclampsia and experience greater morbidity, and mortality associated with the condition than their white counterparts, while Asian women are consistently at lower risk of preeclampsia.[46]
- Māori people (not limited to wāhine / wāhine hapū) are less likely to receive antihypertensive treatment when appropriate (38.1% untreated compared with 18.5% in European) (2020-2021/21 Ministry of Health New Zealand Health Survey)
- Women from culturally and linguistically diverse backgrounds, including Māori wāhine, who report experiencing racial discrimination during antenatal care have been found to self-rate their health poorly. Possible associations between exposure to increased stress during pregnancy and cortisol reactivity of both mother and newborn have also been reported.

3. Colonisation

What barriers to health care might a Māori patient with this condition encounter?

Independent associations with preeclampsia were observed in Māori (aOR 1.51, [1.16-1.96]) compared with European women. Other independent risk factors for pre-eclampsia were overweight and obesity, nulliparity, type 1 diabetes, chronic hypertension and pre-existing medical conditions.[13]

Access to care - five aspects of access (approachability, acceptability, availability and accommodation, affordability, and appropriateness) as defined by Penchansky and Thomas

- Māori and Pacific Islands wāhine are reported to have lower registration rates with a Lead Maternity Carer in the first trimester of pregnancy (Indicator 1- Maternity clinical indicator trends, Te Whatu Ora) and are more likely to attend antenatal care at later gestations.[14] The reasons for this difference are likely to be multifactorial, however may include a lack of trust of healthcare provider and system, avoidance of health services due to associations with intergenerational trauma, limited availability of culturally specific and appropriate services and cost-related barriers.
- Timely engagement with first trimester antenatal care is critical to successful facilitation of universal screening for preeclampsia. It is also key for correct determination of gestational age by ultrasound. Later attendance after 13^{+6} weeks gestation is likely to limit the window of opportunity to use biomarkers and ultrasound data for calculating risk of preeclampsia. Attendance after 16 weeks gestation is likely to limit the effectiveness of aspirin prophylaxis for women who screen at increased risk for preeclampsia.
- Furthermore, undiagnosed chronic hypertension can be masked in early pregnancy due to physiological changes that may cause initial decreases in blood pressure, then misdiagnosed later in the pregnancy as a gestational disorder when abnormal readings re-surface. Inequities in the broader social determinants of health impact this for Māori and Pacific Islands women. This includes higher rates of pre-existing hypertension and diabetes, both risk factors for preeclampsia.[13]

Health literacy

- There was no specific research identified relating to the impact of health literacy on Māori women who may be accessing antenatal care, including screening for preeclampsia.

- Kōrero Mārama, a publication summarising results from the 2006 Adult Literacy and Life Skills Survey for Māori adults in Aotearoa New Zealand reported Māori women scored less than the minimum required score to meet the threshold for complex demands of everyday life. This was also observed for non-Māori women at the time. This included participation in health activities (i.e., engagement in screening or diagnostic tests) and understanding concepts such as risk of a particular condition.[47]
- Broader evidence not specific to Māori or Indigenous populations has reported an association between low levels of health literacy and uptake of preventative health programs, including but not limited to screening and taking medications as prescribed.[48]

4. Ratonga hauora (Barriers to health)

How can these barriers be mitigated at the point of care, including: Actions by clinician

- Provision of culturally safe and competent care to foster improved clinician-patient trust and rapport in provision of antenatal care, where screening for risk of preeclampsia would occur. This could include.[49]
    - Use of te reo Māori in interactions with wāhine hapū and their whānau
    - Incorporating principles of a Māori health framework (i.e., Meihana model and the Hui process) in clinical assessment, including:[49, 50]
        - Mihimihi (greeting/engagement)
        - Whakawhānaungatanga (making connections)
        - Kaupapa (purpose/reason for the encounter)
        - Poroporoaki (closing the session)
    - Self-awareness of unconscious bias
    - Consideration of the impact of colonisation, racism and marginalisation may have had on a patient's prior experiences of the healthcare system.
    - Identification and involvement of whanau and other support networks in decision-making and care discussions (if patient's preference).
- Awareness of Recommendation 4, 15th Annual Report of the PMMRC, which communicates the importance of healthcare practitioners working at an individual and collective level to identify women with risk factors for perinatal related death and ensure that care is accessible and appropriate to their needs. Access to appropriate antenatal care is highlighted as a risk factor which requires particular focus.[15]

Funding streams available for Māori Available hauora Māori and non-Māori services

- Resources and funding are out of scope for this Clinical Guideline. The availability of funding streams and services for Māori women in early pregnancy is likely to differ within each jurisdiction.
- The Te Whatu Ora directory provides a search tool to assist clinicians and patients with a search tool to help identify services offered by Kaupapa Māori organisations and practitioners (by Māori, for Māori). The directory enables searches to filter by health service type (including maternity services and pregnancy ultrasound), provider (including Lead Maternity Carers), region and language spoken (including Māori). See- https://www.adhb.health.nz/your-health/find-a-midwife/
- Greater availability of Māori LMCs may have a positive effect on earlier engagement in antenatal care, including improvement in earlier booking with LMC in the first trimester. This in turn may facilitate opportunities for administer universal screening for preeclampsia, and prophylaxis for Māori women at increased risk.

5. Te reo Māori and whakawhanaungatanga

What opportunities are there to use te reo Māori headings?

Are key Māori concepts communicated using suitable, respectful language? Is te reo included if appropriate, with correct translation where necessary?

What terms in the SNOMED NZ edition Te Reo Māori language reference set are relevant to this page?

- Pēhanga toto i te hapūtanga (preeclampsia)– added to Introduction section of guideline. Te reo Māori terms used throughout guideline where suitable.

Appendix G- Classification of preeclampsia: list of clinical features (ISSHP)

Citation: Magee, L. A., Brown, M. A., Hall, D. R., Gupte, S., Hennessy, A., Karumanchi, S. A., Kenny, L. C., McCarthy, F., Myers, J., Poon, L. C., Rana, S., Saito, S., Staff, A. C., Tsigas, E., & von Dadelszen, P. (2022). The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy hypertension, 27, 148–169. https://doi.org/10.1016/j.preghy.2021.09.008

Table 1
Classification of the HDPs.

Type of hypertensive disorder	Definition
Pre-pregnancy or at < 20 weeks	
Chronic hypertension	Hypertension detected pre-pregnancy or before 20 weeks' gestation
Essential	Hypertension without a known secondary cause
Secondary	Hypertension with a known secondary cause (e.g., renal disease)
White-coat hypertension	sBP ≥ 140 and/or dBP ≥ 90 mmHg when measured in the office or clinic, and BP < 135/85 mmHg using HBPM or ABPM readings
Masked hypertension	BP that is <140/90 mmHg at a clinic/office visit, but ≥135/85 mmHg at other times outside the clinic/ office
≥20 weeks	
Gestational hypertension	Hypertension arising *de novo* at ≥ 20 weeks' gestation in the absence of proteinuria or other findings suggestive of pre-eclampsia
Transient gestational hypertension	Hypertension arising at ≥20 weeks' gestation in the clinic, which resolves with repeated BP readings
Pre-eclampsia*	
De novo	Pre-eclampsia (de novo) is gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation: 1. Proteinuria 2. Other maternal end-organ dysfunction, including: • Neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata) • Pulmonary oedema • Haematological complications (e.g., platelet count < 150,000/μL, DIC, haemolysis) • AKI (such as creatinine ≥ 90 μmol/L or 1 mg/dL) • Liver involvement (e.g., elevated transaminases such as ALT or AST > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain) 3. Uteroplacental dysfunction (e.g., placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death).
Superimposed on chronic hypertension	Among women with chronic hypertension, development of new proteinuria, another maternal organ dysfunction(s), or evidence of uteroplacental dysfunction (as above).

ABPM (ambulatory 24-hour BP monitoring), AKI (acute kidney injury), ALT (alanine aminotransferase), AST (aspartate aminotransferase), BP (blood pressure), dBP (diastolic BP), DIC (disseminated intravascular coagulation), HBPM (home BP monitoring), HDPs (hypertensive disorders of pregnancy), sBP (systolic BP).

* Some components of the definition will require use of locally-accepted definitions (such as fetal growth restriction) and clinical judgement. Also, the term 'severe pre-eclampsia' should not be used in clinical practice, as all women with pre-eclampsia are at risk of developing severe features.

Version	Date of Version	Pages revised / Brief Explanation of Revision
V1.0	July / 2015	Screening in Early Pregnancy for Adverse Perinatal Outcomes (C-Obs 61) published.
V2.0	July / 2018	Working party (Prof S Walker, Dr N Nassar, Dr S White) review and update
V3.0	April / 2024	GDG update: Early pregnancy screening and prevention of preterm preeclampsia and related complications (C-Obs 61), approved by RANZCOG WHC and Council
V3.1	September /2024	Document title and associated phrasing changed from Clinical Guidance Statement to Clinical Guideline, as per approval of terminology change by Dean of Research and Policy and RANZCOG Board

Policy Version:	Version 3.1
Policy Owner:	Women's Health Committee
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