

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

First-Trimester Screening Program for the Risk of Pre-eclampsia Using a Multiple-Marker Algorithm: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Pre-eclampsia is when high blood pressure develops after 20 weeks of pregnancy and when one or more of the following are found: protein in the urine, maternal organ damage (kidneys, liver, blood, nervous system), or evidence of problems with the uterus and placenta. Risk factors for pre-eclampsia include long-term high blood pressure or kidney disease before pregnancy, having high blood pressure or pre-eclampsia in a previous pregnancy, obesity, age, in vitro fertilization, a multiple pregnancy (e.g., twins), certain ethnic backgrounds, a first pregnancy, and a family history of pre-eclampsia.

The most effective treatment for pre-eclampsia is delivery of the baby. Clinical guidelines recommend taking a low dose of acetylsalicylic acid (ASA [Aspirin]) as a preventive measure in those with heightened risk. Clinicians might assess a pregnant person for characteristics associated with pre-eclampsia to find out if they are high-risk. A new technique developed by the Fetal Medicine Foundation ("the FMF algorithm") uses the pregnant person's characteristics and other indicators to better identify people at high risk for pre-eclampsia. Once a person has been identified as high-risk, their doctor can start treating them with ASA.

This health technology assessment looked at the safety, effectiveness, and cost-effectiveness of a population-wide first-trimester screening program for pre-eclampsia risk that uses the FMF algorithm ("the population-wide FMF-based screening program") in reducing the risk of pre-eclampsia. It also looked at the accuracy of the FMF algorithm in predicting the risk of pre-eclampsia. Last, it looked at the budget impact of publicly the population-wide FMF-based screening program and at the experiences, preferences, and values of people who have had pre-eclampsia.

What Did This Health Technology Assessment Find?

The FMF-based screening program used between 11 weeks and 13 weeks plus 6 days of pregnancy likely reduces the risk of pre-eclampsia with delivery at less than 37 weeks' gestation compared with standard care. It may also reduce the risks of low birth weight and poor Apgar score in the first 5 minutes after birth. We also found that the FMF algorithm could more accurately detect pre-eclampsia with delivery at less than 37 weeks' gestation or at less than 34 weeks' gestation compared with conventional algorithms.

The population-wide FMF-based screening program might be more effective and more costly than standard care. We estimate that publicly funding this program in Ontario over the next 5 years would cost an additional \$8.50 million.

The population-wide FMF-based screening program, with its focus on education and equitable access, was seen as valuable by those who have experienced pregnancy and their family members.

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

A Note About Terminology

As a government agency, Ontario Health can play an active role in ensuring that people of all identities and expressions recognize themselves in what they read and hear from us. We recognize that gender identities are individual and that many people who give birth are not women, despite being assigned female sex at birth. Thus, in this health technology assessment, we use gender-inclusive pronouns and terms as much as possible. However, when citing published literature that uses the terms “woman,” “women,” “mother,” “pregnancy,” or “maternal,” we also use these terms for consistency with these cited studies.

Citation

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Abstract

Background

Pre-eclampsia is when high blood pressure develops after 20 weeks of pregnancy and either proteinuria, maternal end-organ dysfunction, or uteroplacental dysfunction causing fetal growth restriction also develops. The Fetal Medicine Foundation has created an algorithm ("the FMF algorithm") that uses maternal factors in combination with biophysical and biochemical markers to identify people at high risk for pre-eclampsia so that they can be offered acetylsalicylic acid (Aspirin) as a preventive measure. We conducted a health technology assessment to evaluate the safety, effectiveness, and cost-effectiveness of a first-trimester population-wide screening program for pre-eclampsia risk that uses the FMF algorithm ("the FMF-based screening program"). We also evaluated the accuracy of the FMF algorithm, the budget impact of publicly funding the population-wide FMF-based screening program, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each study using the Risk of Bias in Non-randomized Studies—of Interventions tool and the Quality Assessment of Diagnostic Accuracy Studies—Comparative tool, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost-effectiveness analysis comparing the FMF-based screening program to standard care (screening for risk of pre-eclampsia using maternal factors alone) from a public payer perspective. We also analyzed the budget impact of publicly funding a population-wide FMF-based screening program in Ontario. We spoke with people who have experience with pregnancy and pre-eclampsia and their family members through direct interviews to gather preferences and values surrounding pre-eclampsia and the potential screening program.

Results

We included nine studies in the clinical evidence review. The FMF-based screening program likely reduces the risk of pre-eclampsia with delivery at less than 37 weeks' gestation compared with standard care, when initiated at 11th to 13th weeks' gestation; risk ratios ranged from 0.64 (95% confidence interval [CI] 0.46–0.93) to 0.70 (95% CI 0.58–0.84) (GRADE: Moderate). It may reduce the risks of low birth weight (risk ratio 0.89 [95% CI 0.85–0.94]) and low Apgar score (risk ratio 0.73 [95% CI 0.63–0.85]) (GRADE: Low). Evidence on the effectiveness of the FMF-based screening program in reducing the risk of stillbirth and neonatal death was highly uncertain (GRADE: Very low). In addition, the FMF algorithm can improve the detection rate of pre-eclampsia with delivery at less than 37 weeks' gestation or at less than 34 weeks' gestation compared with conventional algorithms, although there are concerns about bias and applicability across studies. The population-wide FMF-based screening program is more effective and more costly than standard care. The incremental cost-effectiveness ratio of the population-wide FMF-based screening program compared with standard care is \$3,446 per prevented case of pre-eclampsia with delivery at less than 37 weeks. The annual budget impact of publicly funding the population-wide FMF-based screening program in Ontario ranges from an additional \$1.23 million in year 1 to \$3.56 million in year 5, for a total of \$8.50 million over the next 5 years. The population-wide FMF-based screening program was seen as valuable by those who have experienced pregnancy and their family members. Strong emphasis was placed on providing education and equitable access as part of any screening program, and

participants valued the potential clinical benefits that the population-wide FMF-based screening program could provide.

Conclusions

The FMF-based screening program is likely more effective than standard care in reducing the risk of pre-eclampsia with delivery at less than 37 weeks' gestation. Also, the FMF algorithm can improve the detection rate of pre-eclampsia with delivery at less than 37 weeks' gestation or at less than 34 weeks' gestation when compared with conventional algorithms. The population-wide FMF-based screening program is more effective and more costly than standard care. We estimate that publicly funding the population-wide FMF-based screening program in Ontario would result in additional costs of \$8.50 million over the next 5 years. Pregnant people and their family members valued the potential equitable access, information, and clinical benefits that the population-wide FMF-based screening program could provide.

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Objective

This health technology assessment evaluates the safety, effectiveness, and cost-effectiveness of a population-wide screening program for pre-eclampsia risk that uses a multiple-marker algorithm taken between 11¹⁰ and 13¹⁶ weeks' gestation, compared with standard care. It also evaluates the accuracy of the algorithm used in the screening program, the budget impact of publicly funding the program, and experiences, preferences, and values among pregnant people.

Background

Health Condition

Pre-eclampsia is characterized by the development of high blood pressure (> 140/90 mmHg) after 20 weeks' gestation and one of the following: proteinuria (presence of 0.3 g or more of protein in a 24-hour urine collection), maternal end-organ dysfunction (kidney, liver, hematologic, neurologic), or uteroplacental dysfunction causing fetal growth restriction.¹⁻³

Risk factors for pre-eclampsia include chronic high blood pressure or kidney disease before pregnancy, high blood pressure or pre-eclampsia in previous pregnancy, obesity, age, multiple gestation, African ancestry, first pregnancy, and family history of pre-eclampsia.⁴

The causes of pre-eclampsia are being actively pursued, and are thought to be multifactorial.⁵ It is thought to begin in the placenta, and mostly involves abnormal development of blood vessels early in the course of the pregnancy.³ In a normal pregnancy, the trophoblast cells of the embryo will invade the decidua (the specialized layer of the lining of the uterus that forms the base of the placental bed) and part of the myometrium (the smooth muscle tissue of the uterus) to reach and infiltrate the spiral arteries (the terminal branches of the uterine artery) to access oxygenated blood from the pregnant person.⁶ For this to work properly, the trophoblasts have to penetrate aggressively into the decidua, and the spiral arteries have to enlarge to allow large amounts of blood to flow through them. When this mechanism is compromised, the supply of oxygen to the placenta will be inadequate. This shortage of oxygen supply will cause the surrounding cells of the placenta to react inappropriately by releasing several factors, including inflammatory molecules, which will enter into the mother's bloodstream, causing damage in the endothelial cells that line the blood vessels.⁶ This damage is what leads to the characteristic signs and symptoms of pre-eclampsia.⁶ For example, when endothelial cells are damaged, they lose the ability to control the tone of the blood vessels and become stiff, leading to high blood pressure. Also, the blood vessels could become leaky, allowing protein to escape. When this leakiness occurs in the blood vessels of the kidneys, protein escapes from the glomerular capillaries and mixes with the urine (proteinuria). Throughout the rest of the body, the leakage in protein will go parallel with water oozing from the blood vessels into the surrounding tissues, leading to swelling in the body (edema). If the liver is affected, the destruction of liver cells causes breakdown of blood and the clotting system, a condition known as "HELLP syndrome" (HE for hemolysis, or breaking down of red blood cells; EL for elevated liver enzymes; and LP for low platelets). In the brain, edema can lead to headaches, seizures (eclampsia), and stroke. Dysfunction of blood vessels in the placenta can also result in fetal growth restriction.

The International Society for the Study of Hypertension in Pregnancy has subclassified pre-eclampsia outcomes based on the clinical diagnosis of the condition at time of delivery.⁷ Pre-eclampsia with delivery at less than 34 weeks' gestation and pre-eclampsia with delivery at less than 37 weeks' gestation are associated with a higher risk of adverse maternal and perinatal outcomes than

pre-eclampsia with delivery at 34 weeks' gestation or more and pre-eclampsia with delivery at 37 weeks' gestation or more (term pre-eclampsia).^{7,8} Sometimes the subclassification includes pre-eclampsia with delivery at less than 32 weeks' gestation.⁹

Pre-eclampsia with delivery at less than 37 weeks' gestation can result in severe infant and maternal morbidity and mortality. Most often the baby is delivered prematurely to spare the pregnant person additional complications. Some risks of pre-eclampsia for the baby include fetal growth restriction, lower mean birth weight, and potential physical and cognitive impairments throughout childhood. Some maternal risks of pre-eclampsia include progression to more severe conditions (such as HELLP syndrome or eclampsia), and a pregnancy complicated by pre-eclampsia is associated with a higher long-term risk of mortality from cardiovascular causes.¹⁰⁻¹² Last, pregnancies with pre-eclampsia with delivery at 28 weeks or less have the highest risk of maternal death.¹³ Worldwide each year, pre-eclampsia is responsible for 76,000 deaths in women and 500,000 deaths in babies.¹⁴

Clinical Need and Target Population

Pre-eclampsia affects 2% to 8% of all pregnancies globally.¹ In 2010/11, Canada had a pre-eclampsia rate of 11.5 per 1,000 deliveries.¹⁵ Among singleton births from Canada-born pregnant people, the rate of pre-eclampsia with delivery occurring between 24 and 36 weeks was estimated at 4 per 1,000 deliveries in the period covering April 1, 2003, through December 31, 2012.¹⁶ In 2009, there were more than 140,000 live births in Ontario.¹⁷ According to the data from Ontario's Better Outcomes Registry and Network (BORN), the prevalence of preeclampsia in Ontario is about 0.8%.

Current Screening Practices and Preventive Measures for Pre-eclampsia

Screening refers to the presumptive identification of unrecognized disease or defect through tests, examinations, or other procedures that can be applied rapidly.¹⁸ Screening tests sort out apparently well people who probably have or are at high risk of developing a disease from those who probably do not have disease or are at lower risk.¹⁸ A screening test is not intended to be diagnostic.¹⁸ A screening program is not just a single test but rather a pathway that starts by identifying people who are eligible for screening and stops when the outcomes are reported (can include re-evaluating and recalibrating test performance).¹⁸ The purpose of screening programs is to identify people who are at higher risk for a condition in a healthy population so that early treatment or intervention can be offered.¹⁸

Clinical societies, such as the United Kingdom's National Institute for Health and Care Excellence (NICE)¹⁹ and the American College of Obstetricians and Gynecologists (ACOG),²⁰ have developed guidelines for identifying people at high risk for pre-eclampsia based on maternal risk factors only²¹ so that they can be offered acetylsalicylic acid (ASA [Aspirin]) as a preventive measure.^{19,20} The use of ASA can decrease the risk of pre-eclampsia with delivery at less than 37 weeks' gestation, but not pre-eclampsia with delivery at 37 weeks' gestation or more, and only when initiated at less than 16 weeks' gestation and at a daily dose of 100 mg or more.²² Although there is no consensus across clinical societies on the minimum ASA dose,²³ clinical experts in Ontario deem a low daily dose of 162 mg to be reasonable.

The biggest potential harm of daily ASA use is bleeding complications; however, evidence suggests that the risk is very low for low-dose ASA.²⁴ Accurate screening for pre-eclampsia might further reduce this risk by identifying people at low risk of pre-eclampsia who would otherwise be advised to take ASA.

The UK's NICE²⁵ recommends assessing maternal risk factors for pre-eclampsia and advises those at risk to take 75 to 150 mg of ASA daily from 12 weeks' gestation until the birth of the baby for pregnant people with one of several conditions, including the following: previous hypertension in pregnancy, chronic kidney disease, autoimmune disease, type 1 or type 2 diabetes, or chronic hypertension. Treatment with ASA is also recommended if two or more of the following risk factors apply: first pregnancy, maternal age above 40 years, pregnancy interval more than 10 years, body mass index higher than 35 kg/m², family history of pre-eclampsia, multifetal gestation.

The ACOG²⁰ recommends beginning low-dose ASA (81 mg) before 16 weeks among pregnant people with one of the following factors: history of pre-eclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes, or chronic hypertension. The recommendation also applies if pregnant people have two or more of the following factors: first pregnancy, maternal age greater than 35 years, body mass index above 30 kg/m², a family history of pre-eclampsia, African American ethnicity, low socioeconomic status, low birth weight, previous delivery of an infant small for gestational age, previous adverse pregnancy outcomes, or interval between the current and most recent pregnancy of more than 10 years.

Several organizations have published a variety of guidelines for assessing risk of pre-eclampsia in the first trimester. The Society of Obstetricians and Gynaecologists of Canada published the most recent criteria for assessing risk of pre-eclampsia and recommending low-dose ASA in 2022²⁶:

- In early pregnancy, pregnant people should be screened, at a minimum, for clinical risk markers for pre-eclampsia
- If testing is available, pregnant people should be screened at 11 to 14 weeks' gestation using a combination of clinical risk markers, uterine artery pulsatility index (UtA-PI), and placental growth factor (PLGF) to individualize the risk of developing pre-eclampsia

For pregnant people at increased risk of pre-eclampsia, low-dose ASA (81 or 162 mg/d) is recommended, to be taken at bedtime, preferably begun before 16 weeks' gestation, and discontinued by 36 weeks' gestation.

In Ontario, people with multiple pregnancies are considered high-risk for pre-eclampsia and are prescribed low-dose ASA (telephone communication with N. Okun, MD, April 2022).

The International Federation of Gynecology and Obstetrics (FIGO) recommends that all pregnant people be screened for pre-eclampsia that could result in delivery at less than 37 weeks' gestation. Screening should take place during early pregnancy, using the first-trimester combined test with maternal risk factors and biomarkers as a one-step procedure and the algorithm from the Fetal Medicine Foundation (FMF).²⁷

Health Service Under Review

The health service under review is a population-wide pre-eclampsia screening program for pre-eclampsia risk that uses a multiple-marker algorithm by the Fetal Medicine Foundation ("the FMF algorithm"), taken between 11^o and 13^o weeks' gestation. This program, which we refer to throughout as "the FMF-based screening program," uses the FMF algorithm to identify people at high risk of developing pre-eclampsia that could necessitate delivery at less than 37 weeks' gestation. Pregnant

people classified as high-risk will be prescribed low-dose ASA to be taken once daily, starting at less than 16 weeks' gestation until the birth of the baby.

The FMF algorithm uses Bayes' theorem to combine prior risk from a combination of maternal risk factors and the results of various biophysical and biochemical measurements. Using these markers, an online risk calculator based on the FMF algorithm can be used to calculate pre-eclampsia risk. This risk calculator is available free at the website www.fetalmedicine.org.

Risk factors used in the FMF algorithm include maternal factors, mean arterial pressure (MAP), mean UtA-PI, and biochemical markers (the pregnancy-associated plasma protein A [PAPP-A] and PlGF). Not all risk factors are required for the FMF algorithm, but having more factors improves prediction accuracy. It has been demonstrated that screening the whole population using the FMF algorithm containing a subset of MAP, PlGF, and UtA-PI (triple test) followed by a confirmatory screening with a triple test on those identified as high-risk leads to similar accuracy but substantially lower costs than screening the whole population with all biomarkers.²⁸

Risk Factors Used in the FMF Algorithm

MATERNAL RISK FACTORS

Maternal risk factors are classified as demographic, medical history, and current pregnancy.

- Demographic: age, race or ethnicity, height, weight, smoking during pregnancy
- Medical history: chronic hypertension, type 1 diabetes, type 2 diabetes, systemic lupus erythematosus, anti-phospholipid syndrome, mother of patient had pre-eclampsia
- Current pregnancy: pregnancy type (twin vs. singleton pregnancy), fetal crown-rump length, conception method, nulliparous versus parous

MEAN ARTERIAL PRESSURE

MAP is measured on automated blood pressure monitoring devices and is calculated from measurements of the systolic and diastolic blood pressure taken twice from each arm.^{29,30}

MEAN UTERINE ARTERY PULSATILITY

Transabdominal ultrasonography by a qualified sonographer is used to assess the UtA-PI. The mean is calculated by taking the average measurements of the left and right uterine arteries.^{29,31}

BIOCHEMICAL MARKERS

The first biomarker, PAPP-A, is interpreted where a level lower than a 0.5 multiple of median (MOM) indicates a higher risk of pre-eclampsia.³² The second biomarker, PlGF, is interpreted where a level less than a 0.4 MOM indicates a higher risk of pre-eclampsia.³³

Conceptual Clinical Pathway

Figure 1 is a high-level conceptual clinical pathway for assessing pre-eclampsia risk with the FMF algorithm, where people considered high-risk are advised to take low-dose ASA.

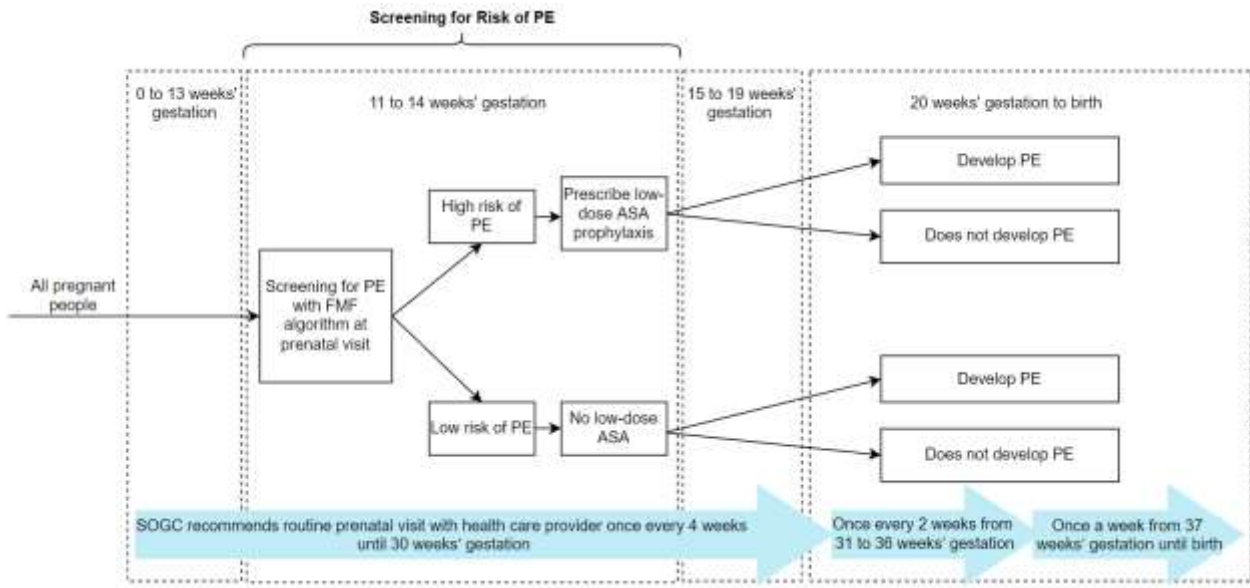


Figure 1: Conceptual Clinical Pathway for Pregnant People Assessed Using the FMF-Based Screening Program

A high-level conceptual clinical pathway for assessing pre-eclampsia risk with the FMF algorithm, where people considered high-risk are advised to take low-dose ASA.

Abbreviations: ASA, acetylsalicylic acid; PE, pre-eclampsia; SOGC, Society of Obstetricians and Gynaecologists of Canada.

Regulatory Information

The FMF algorithm does not require Health Canada approval.

Ontario, Canadian, and International Context

In Ontario there is no standardized way of assessing the risk of pre-eclampsia. According to clinical experts, guidelines from professional societies (see above) are followed to collect information on maternal risk factors alone to assess the risk of pre-eclampsia. Some academic hospitals in Ontario are evaluating the feasibility of implementing the FMF-based screening program, but neither the FMF algorithm nor guidelines from professional societies are used consistently across the province. An ongoing feasibility study across two hospital sites in Ontario is assessing the use of the FMF algorithm (email communication with N. Okun, MD, January 2022) to screen for pre-eclampsia. The FMF algorithm was chosen because it is the most validated internationally and is said to have greater accuracy than several other screening algorithms (telephone communication with N. Okun, MD, January 2022). A study conducted in Ontario by Vigiuliouk et al³⁴ found that the rate of ASA use in those classified as high-risk was actually very low (7.6%) using the current screening and prevention strategies.

According to clinical experts, the FMF algorithm is being used in Alberta and in several countries other than Canada, including China, Spain, and the United Kingdom.

Equity Context

There are disparities in incidence and outcomes of pre-eclampsia in certain subpopulations. For instance in the United States, where private health insurance is the predominant source of health

insurance coverage, the pre-eclampsia rate is estimated to be 60% higher in pregnant Black people (70 per 1,000 deliveries) than in White people (43 per 1,000 deliveries).³⁵ A 2016 study found that, compared with Canada-born people who have an estimated risk of pre-eclampsia and preterm birth of 4.0 per 1,000, the risk of pre-eclampsia and preterm birth was higher among pregnant people from Nigeria (relative risk [RR] 1.79, 95% confidence interval [CI] 1.12–2.84), the Philippines (RR 1.54, 95% CI 1.30–1.86), Colombia (RR 1.68, 95% CI 1.04–2.73), Jamaica (RR 2.06, 95% CI 1.66–2.57), and Ghana (RR 2.12, 95% CI 1.40–3.21).¹⁶ Estimates for pre-eclampsia in Indigenous populations in Canada are not readily available in the literature. However, a study from 2013 in First Nations people living in Southern Ontario found that 5.6% (n = 453) of people had pre-existing hypertension or developed hypertension during their pregnancy.³⁶ Unpublished data from BORN Ontario showed variability in the percentage of pregnant people diagnosed with pre-eclampsia across local health integration network regions in the year 2020, with four regions (South East, Champlain, North East, and North West) having the highest rates ranging from 1.2% to 1.9%. The rate in the rest of the regions was below 1%.

Historically in Ontario, rural regions have experienced substantially lower prenatal screening rates than urban regions.^{37,38} For instance, a study conducted in Ontario³⁷ found that, between 2007 and 2009, uptake of prenatal screening in the first trimester ranged from 40% in rural regions (such as Southwestern and Northern Ontario) to 80.3% in urban regions (such as central Toronto). Similarly, a recent report by BORN stated that, between 2019 and 2020, a greater proportion of pregnant people received prenatal screening in the first trimester in urban census divisions than in rural census divisions, ranging from 78.25% in Toronto, Kingston, London, and Ottawa, to 4.36% in Kenora and Temiskaming.³⁸ This finding indicates that this subpopulation could have a similarly low uptake of a population-wide FMF-based screening program. This variation could be the result of barriers of access, which in turn could contribute to fewer biomarkers collected under this screening program in this subpopulation. According to clinical experts, access to the UtA-PI (one of the parameters used to generate the FMF model) in Ontario is limited.

Expert Consultation

We engaged with experts in the specialty areas of family medicine, sonography, midwifery, and maternal fetal medicine to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD # 42022315346), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Questions

Question 1

What is the effectiveness of a population-wide screening program for pre-eclampsia risk that uses a multiple-marker algorithm between 11th and 13th weeks' gestation compared with standard care in improving maternal and infant outcomes?

Question 2

What is the accuracy of a multiple-marker algorithm screening test when used between 11th and 13th weeks' gestation compared with standard care in predicting pre-eclampsia with delivery at less than 37, less than 34, or less than 32 weeks' gestation?

Methods

Clinical Literature Search

We performed a clinical literature search on January 21, 2022, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment Database, the National Health Service Economic Evaluation Database (NHSEED). We used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer reviewed using the PRESS Checklist.³⁹

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until June 24, 2022. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published since database inception
- Randomized controlled trials and cohort/before–after studies (for the first research question), accuracy studies (for the second research question), health technology assessments, systematic reviews, and meta-analyses (for both research questions)

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

POPULATION, INTERVENTIONS, COMPARATORS, OUTCOMES

Question 1

- Population: pregnant people (singleton pregnancies) within the gestational age of 11^o and 13^o weeks
- Intervention: a screening program using a multiple-marker algorithm developed by the Fetal Medicine Foundation ("the FMF algorithm")
- Comparator(s): standard care (e.g., opportunistic screening programs, no screening programs, screening programs using guidelines from the National Institute for Health and Care Excellence [NICE], the American College of Obstetricians and Gynecologists [ACOG], or other similar methods)
- Outcomes:
 - Maternal morbidity (e.g., pre-eclampsia with delivery at less than 37 weeks' gestation, pre-eclampsia with delivery at less than 34 weeks' gestation, pre-eclampsia with delivery at less than 32 weeks' gestation, HELLP syndrome, postpartum bleeding, or postpartum hematoma)
 - Maternal mortality (peripartum until 42 days, late mortality within 1 year of birth or termination)
 - Infant morbidity (e.g., intrauterine growth restriction (less than 10th percentile for gestational age), low birthweight (weight less than 2,500 g), Apgar score less than 4 at 5 minutes after birth)
 - Infant mortality (perinatal to 28 days postpartum)
 - Neonatal hospital length of stay (including neonatal intensive care unit [NICU])
 - Maternal hospital length of stay
 - Psychological stress (e.g., patient stress and anxiety)
 - Measures of effect: mean difference, median difference, risk difference, risk ratio, rate difference, rate ratio, hazards ratio, and odds ratio
- Timing: screening done between 11^o and 13^o weeks' gestation
- Setting: outpatient settings for obstetric care (e.g., obstetrician–gynecologists, family physicians, nurse practitioners and registered midwives), experimental settings

Question 2

- Population: pregnant people (singleton pregnancies) within the gestational age of 11^o and 13^o weeks
- Index test: the FMF algorithm
- Comparator test: any other screening test for pre-eclampsia used as part of standard care (e.g., NICE or ACOG screening criteria)
- Reference standard: clinical diagnosis of pre-eclampsia *and* delivery at less than 37 weeks', less than 34 weeks', and less than 32 weeks' gestation
- Target outcome: pre-eclampsia with delivery at less than 37 weeks', less than 34 weeks', or less than 32 weeks' gestation
- Accuracy measures: detection rate (sensitivity), specificity, positive predictive value (PPV), negative predictive value (NPV)
- Timing: screening test done between 11^o and 13^o weeks' gestation
- Setting: outpatient settings for obstetric care (e.g., obstetrician–gynecologists, family physicians, nurse practitioners and registered midwives) or experimental settings.

Literature Screening

Two reviewers followed the Cochrane rapid review methods⁴⁰ to screen titles and abstracts using Covidence systematic review management software,⁴¹ and obtained the full text of studies that appear eligible for the review, according to the inclusion criteria. The primary reviewer examined the full-text articles and selected studies that met the inclusion criteria. Any disagreements between reviewers during screening were resolved by consensus. Reference lists of included studies were also examined by the primary reviewer for any additional relevant studies not identified through the search. Citation flow and reasons for exclusion for full-text articles were reported according to the Preferred Reporting of Items for Systematic Reviews and Meta-analyses (PRISMA) statement.⁴²

Data Extraction

The primary reviewer extracted relevant data on study design, population characteristics, and risk-of-bias items. These included the following:

- Source (e.g., citation information, country, funding)
- Methods (e.g., study design, study duration and years, sample size, inclusion and exclusion criteria)
- Baseline characteristics (e.g., age, weight, height, body mass index, gestational age, race, history of hypertension, diabetes and anti-phospholipid syndrome/systemic lupus erythematosus, smoking history, family history of pre-eclampsia, mode of conception, parity, pre-eclampsia history, and interpregnancy interval)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, unit of measurement, upper and lower limits [for scales])

The accuracy of data extraction was verified by the secondary reviewer.

Equity Considerations

We used PROGRESS-Plus, a health equity framework recommended by the Campbell and Cochrane Equity Methods Group,⁴³ to explore potential inequities for this health technology assessment. Factors that could lead to disadvantage or inequities in the framework include place of residence; race, ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

Using the search strategy designed to capture studies relevant to the clinical research questions, we sought but did not identify any evidence on equity issues relevant to how PROGRESS-Plus factors might affect inequity in screening for pre-eclampsia across different populations. Thus, equity issues could exist but were not identified in the studies included as part of our analysis.

Statistical Analysis

When possible, we reported the point estimates for each outcome along with confidence intervals. For the assessment of accuracy of the FMF algorithm versus other algorithms in studies where the false-positive rate was held fixed by investigators, we assessed only detection rates. This is the case because other measures of accuracy (such as specificity, PPV, or NPV) are all a function of the false-positive rate, which can vary across study populations if allowed to be data-dependent. We did not

conduct a meta-analysis owing to heterogeneity in outcomes, study population, how the effect of acetylsalicylic acid (ASA [Aspirin]) was handled in the assessment of accuracy, and whether the false- and screen-positive rates were allowed to be data-dependent. In situations where studies did not report confidence intervals but provided sufficient information to compute them, we used PropCIs library in R⁴⁴ to perform computations.

We were unable to undertake an analysis to evaluate disparity in access to pre-eclampsia screening by place of residence, race, ethnicity, culture or language, gender or sex, disability, occupation, religion, education, socioeconomic status, or social capital because this information was unavailable.

Critical Appraisal of Evidence

The primary reviewer assessed the risk of bias using the Risk of Bias in Non-randomized Studies—Intervention (ROBINS-I) tool⁴⁵ for the assessment of effectiveness and the Quality Assessment of Diagnostic Accuracy Studies—Comparative (QUADAS-C) tool⁴⁶ for the assessment of accuracy (Appendix 2). For the assessment of effectiveness, we evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook*.⁴⁷ The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence. The secondary reviewer undertook verification of all judgments (and support statements) made by the primary reviewer.

Results

Clinical Literature Search

The database search of the clinical literature yielded 4,977 citations published from database inception until January 21, 2022. We identified eight additional studies from other sources, for a total of 2,597 after removing duplicates. In total, we identified nine studies (two for the assessment of effectiveness and eight for the assessment of accuracy; one was eligible for both research questions) that met our inclusion criteria. See Appendix 3 for a list of selected studies excluded after full-text review. Figure 2 presents the PRISMA flow diagram for the clinical literature search.

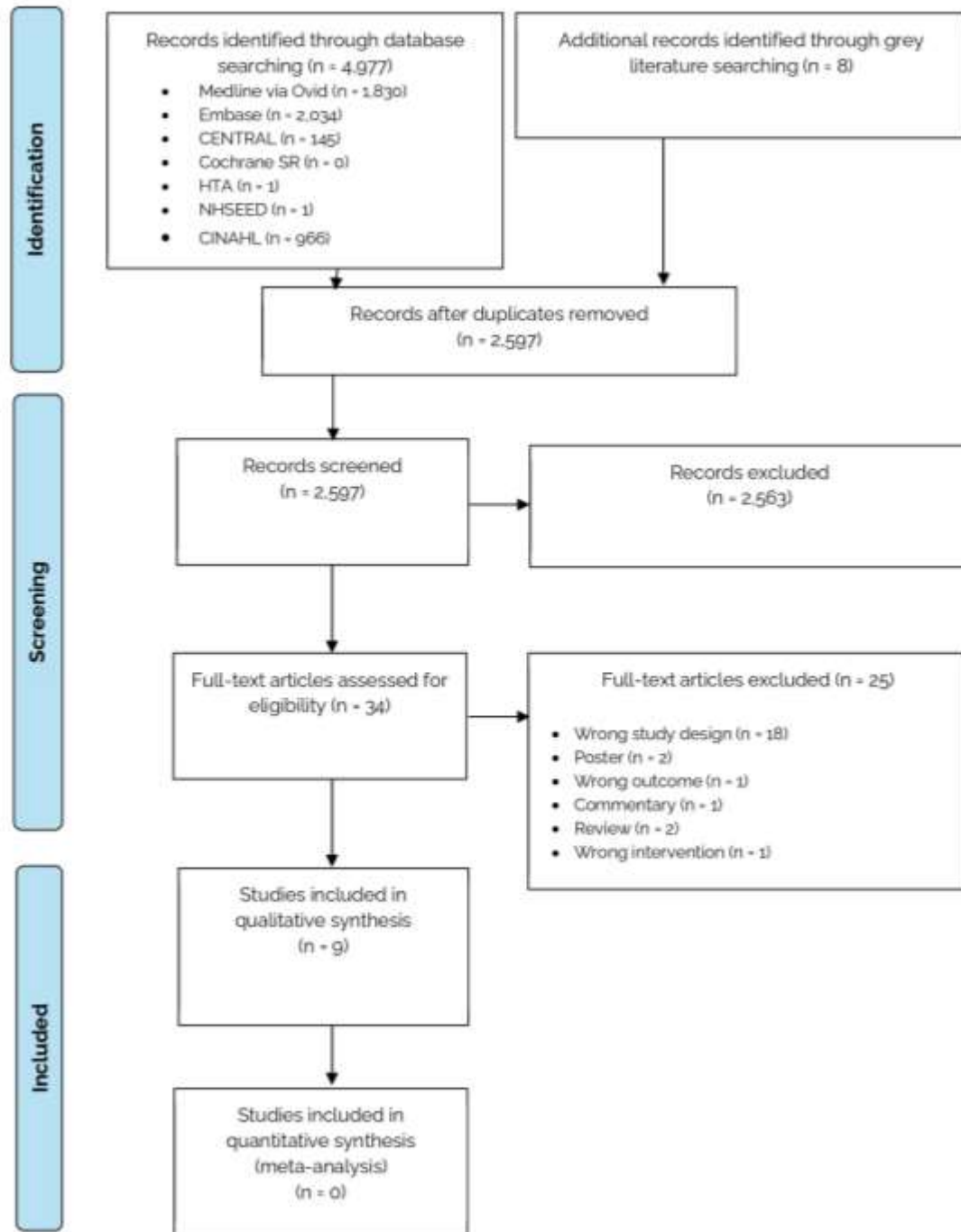


Figure 2: PRISMA Flow Diagram—Clinical Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 4,977 citations published between January 1, 2006, and January 21, 2022. We identified eight additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 2,597 studies and excluded 2,563. We assessed the full text of 34 articles and excluded a further 25. In the end, we included nine articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.⁴⁸

Characteristics of Included Studies

Nine studies met the inclusion criteria. Of these, two assessed the effectiveness of an FMF-based screening program^{49,50} and eight assessed the screening accuracy of the FMF algorithm^{49,51-57} (Table 1). One study assessed both the effectiveness and accuracy of the FMF algorithm.⁴⁹ With the exception of one study in which the authors mentioned only the use of local guidelines to identify maternal risk factors as standard care,⁵⁰ all other studies reported the UK's NICE, ACOG, or Sant Joan de Deu Barcelona Children's Hospital (BCNatal) screening algorithms as screening tests for the comparator. Five of eight studies that assessed screening accuracy did not account for the fact that the use of low-dose ASA to prevent pre-eclampsia following a positive screening result could have led to incorrectly regarding a test as producing false-negative results. Seven studies were done in Europe, and the remaining two were done in Asia and South America (Tables 1 to 7).

Table 1: Characteristics of Included Studies

Author, year, country	Study design	Participants	Intervention/ test	Outcomes/ target conditions
Chaemsithong et al, ⁵¹ 2019, Hong Kong, Japan, China, Thailand, Taiwan, India, and Singapore	Screening accuracy	10,935 singleton pregnancies Dec 2016–June 2018	FMF algorithm vs. NICE or ACOG	Pre-eclampsia with delivery at < 37 wk
Di Martino et al, ⁵² 2019, Italy	Screening accuracy	11,632 singleton pregnancies Jan 2014–May 2017	FMF algorithm vs. BCNatal	Pre-eclampsia with delivery at < 34 wk
Guy et al, ⁴⁹ 2021, United Kingdom	Cohort study/ screening accuracy	7,720 pregnant people screened per NICE and 4,841 per FMF	FMF-based screening program vs. NICE algorithm	Pre-eclampsia with delivery at < 37 wk or < 34 wk
O'Gorman et al, ⁵³ 2017, United Kingdom, Spain, Belgium, Greece, and Italy	Screening accuracy	8,775 singleton pregnancies Feb 2015–Sept 2015	FMF algorithm vs. NICE or ACOG	Pre-eclampsia with delivery at < 37 wk or < 32 wk
Poon et al (SPREE study), ⁵⁴ 2020, United Kingdom	Screening accuracy	16,747 pregnancies April–Dec 2016	FMF algorithm vs. NICE	Pre-eclampsia with delivery at < 37 wk
Rocha et al ⁵⁵ 2017, Brazil	Screening accuracy	733 pregnancies Aug 2009–Jan 2014	FMF algorithm vs. NICE or ACOG	Pre-eclampsia with delivery at < 37 wk
Rolnik et al, ⁵⁰ 2021, Australia	Cohort study	29,618 pregnant people screened per FMF and 30,1566 per standard care	FMF-based screening program vs. standard care	Pre-eclampsia with delivery at < 37 wk, birth weight < 2,500 g, Apgar score < 4 at 5 min after birth, stillbirth, neonatal death
Tan et al, ⁵⁶ 2018, United Kingdom	Screening accuracy	16,747 pregnancies April–Dec 2016	FMF algorithm vs. NICE	Pre-eclampsia with delivery at < 37 wk
Wright et al, ⁵⁷ 2015, United Kingdom	Screening accuracy	120,492 pregnancies Jan 2006–March 2014	FMF algorithm vs. NICE	Pre-eclampsia with delivery at < 37 or < 34 wk

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; BCNatal, Sant Joan de Deu Barcelona Children's Hospital; FMF, Fetal Medicine Foundation; NICE, National Institute for Health and Care Excellence; SPREE, Screening Programme for Preeclampsia.

Risk of Bias in the Included Studies

We noted the potential for residual confounding on the assessment of effectiveness for all outcomes evaluated in Rolnik et al.^{49,50} because the authors acknowledged that they were unable to adjust for ethnicity and mode of conception owing to lack of data. These outcomes were pre-eclampsia with delivery at less than 37 weeks' gestation, birth weight lower than 2,500 g, Apgar score less than 4 at 5 minutes after birth, stillbirth, and neonatal death. Thus we rated the risk of bias due to confounding on these outcomes as moderate, using the ROBINS-I tool. We determined that the risk of other types of bias was low (Appendix 2, Table A1). There were no major concerns of bias for all outcomes assessed in Guy et al.^{49,51-57} These outcomes were pre-eclampsia with delivery at less than 37 weeks' and less than 34 weeks' gestation.

In assessing accuracy, we identified potential risk of bias in five⁴⁹ of eight studies and applicability concerns in all eight studies. The most common type of bias was measurement errors; four studies failed to account for the effect of ASA when assessing accuracy (see Appendix 2, Table A2). Concerns about applicability include a distribution of ethnic groups that did not reflect Ontario's population, false-positive and screen-positive rates that were forced to be constant, not accounting for ASA effect, and lack of information about which biomarkers were used to construct the FMF algorithm.

Effectiveness of FMF-Based Screening Program

Two studies⁵⁰ evaluated the effectiveness of the FMF-based screening program versus standard care (Tables 2 and 3) in reducing the risk of pre-eclampsia with delivery at less than 37 weeks' gestation (GRADE: Moderate), pre-eclampsia with delivery at less than 34 weeks' gestation (GRADE: Very low), birth weight lower than 2,500 g (GRADE: Low), Apgar score less than 4 at 5 minutes after birth (GRADE: Low), stillbirth (GRADE: Very low), and neonatal death (GRADE: Very low). Both studies presented point estimates that showed the FMF-based screening program to be more effective than standard care. A combination of all or a subset of MAP, uterine artery pulsatility index (UtA-PI), PlGF, and PAPP-A biomarkers plus maternal factors were used to construct the FMF algorithm.

Table 2: Risk Differences, Risk Ratios, and Relative Linear Changes of the Effect of an FMF-Based Screening Program Versus Standard Care

Outcome	FMF-based screening program		Standard care		Risk difference (95% CI)	Risk ratio (95% CI)	Relative linear change in % with birth outcome
	FMF risk factors	n (%)	Screening algorithm	n (%)			
Pre-eclampsia with delivery at < 37 wk	Maternal factors + MAP, UtA-PI, PAPP-A	27 (0.56)	NICE	65 (0.84)	-0.28 (-0.64 to 0.00) ^a	0.64 (0.46 to 0.93) ^a	-80.0 ^b
Pre-eclampsia with delivery at < 34 wk	Maternal factors + MAP, UtA-PI, PAPP-A	7 (0.14)	NICE	18 (0.23)	-0.09 (-0.26 to 0.09) ^a	0.61 (0.09 to 4.80) ^a	-89.9 ^b

Abbreviations: CI, confidence interval; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; PAPP-A, pregnancy-associated plasma protein A; UtA-PI, uterine artery pulsatility index.

^a Point estimates and confidence intervals were computed by the authors of this health technology assessment.

^b The study provided neither confidence intervals nor sufficient information to compute them.

Source: Guy et al.⁴⁹

Table 3: Risk Ratios of the Effect of an FMF-Based Screening Program Versus Standard Care

Outcome	FMF-based screening program		Standard care, n (%)	Adjusted risk ratio (95% CI) ^a
	FMF risk factors	n (%)		
Pre-eclampsia with delivery at < 37 wk	Maternal factors + MAP, UtA-PI, PAPP-A, PlGF	134 (0.45)	2,096 (0.70)	0.70 (0.58 to 0.84)
Birth weight < 2,500 g	Maternal factors + MAP, UtA-PI, PAPP-A, PlGF	1,354 (4.57)	17,295 (5.74)	0.89 (0.85 to 0.94)
Apgar score < 4 at 5 min after birth	Maternal factors + MAP, UtA-PI, PAPP-A, PlGF	190 (0.64)	3,424 (1.13)	0.73 (0.63 to 0.85)
Stillbirth	Maternal factors + MAP, UtA-PI, PAPP-A, PlGF	76 (0.26)	1,049 (0.35)	0.90 (0.71 to 1.14)
Neonatal death	Maternal factors + MAP, UtA-PI, PAPP-A, PlGF	24 (0.08)	336 (0.11)	0.94 (0.61 to 1.45)

Abbreviations: CI, confidence interval; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

^a Adjusted for age, body mass index, parity, socioeconomic status as given by Index of Relative Socioeconomic Disadvantage, smoking, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, and pre-existing diabetes.

Source: Rolnik et al.⁵⁰

Screening Accuracy of the FMF Algorithm

Eight studies evaluated the screening accuracy of the FMF algorithm versus standard care in predicting pre-eclampsia with delivery at less than 34 or less than 32 weeks' gestation (Tables 4 to 7). Five studies^{51-54,57} 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, we did not use them to determine the accuracy of screening tests on these studies. Most studies used a combination of maternal factors and biomarkers MAP, UtA-PI, and PlGF to construct the FMF algorithm. At a fixed false-positive rate, the FMF algorithm was found to have a higher detection rate of pre-eclampsia with delivery at less than 37, less than 34, or less than 32 weeks' gestation than the NICE, ACOG, and BCNatal algorithms (see Table 4). Results remained mostly consistent when one study⁵³ fixed the false-positive rate for the FMF algorithm but not the comparators. The study also reported a higher detection rate for ACOG than FMF, but ACOG also had a much higher false-positive rate (73.3%).

Given the same screen-positive rate (the percentage of pregnant people who are classified as high-risk for pre-eclampsia with delivery at less than 37, less than 34, or less than 32 weeks' gestation by the screening test), four studies found that the detection rate was higher for FMF compared with the NICE algorithm (see Table 5). Only one study conducted in Brazil⁵⁰ allowed both the false- and screen-positive rates to be data-dependent (see Table 6). It reported that FMF had a higher detection rate and a lower false-positive rate (hence a higher specificity) than the NICE and ACOG algorithms. The PPVs and NPVs were derived from three studies that did not fix the false-positive rate (see Table 7). We found that all FMF, NICE, and ACOG algorithms had very poor PPVs (< 17%) but very large NPVs (98%), most likely reflecting the limitation of these measures, in that they can be highly influenced by the prevalence of the condition under investigation.

Table 4A: FMF Versus Conventional Screening Algorithms on Detection Rates at Fixed False-Positive Rates for Cases of Pre-eclampsia With Delivery at Less Than 37 Weeks' Gestation

Author, year, country	Fixed FPR	Adjusted for ASA use	FMF algorithm			Comparator			Difference in detection rate (95% CI), %
			FMF risk factors	True positives, n	Detection rate, %	Algorithm	True positives, n	Detection rate	
Chaemsaitong et al, ⁵¹ 2019, Hong Kong, Japan, China, Thailand, Taiwan, India, and Singapore	5.5%	Yes	Maternal + MAP, UtA-PI, PlGF	73	48.5	NICE	73	26.3	22.2 (6.2 to 36.9) ^a
Chaemsaitong et al, ⁵¹ 2019, Hong Kong, Japan, China, Thailand, Taiwan, India, and Singapore	20.4%	Yes	Maternal + MAP, UtA-PI, PlGF	73	75.8	ACOG	73	54.6	20.4 (5.0 to 35.5) ^a
O'Gorman et al, ⁵³ 2017, United Kingdom, Spain, Belgium, Greece, and Italy	10% (fixed only for FMF algorithm)	No	Maternal + MAP, UtA-PI, PlGF	59	75	NICE	59	39 (estimated FPR 10.2%)	36 ^b
O'Gorman et al, ⁵³ 2017, United Kingdom, Spain, Belgium, Greece, and Italy	10% (fixed only for FMF algorithm)	No	Maternal + MAP, UtA-PI, PlGF	59	75	ACOG	59	90 (estimated FPR 64.2%)	-15 ^b
Poon et al, ⁵⁴ 2020, United Kingdom	10%	Yes	Maternal + MAP, UtA-PI, PlGF	142	79.6	NICE	142	44.1	35.5 (25.2 to 45.8) ^c
Wright et al, ⁵⁷ 2015, United Kingdom	10.6%	No	Not described	786	47.6	NICE	786	39.9	7.7 (2.7 to 12.5) ^a

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASA, acetylsalicylic acid; BCNatal, Sant Joan de Deu Barcelona Children's Hospital; CI, confidence interval; FMF, Fetal Medicine Foundation; FPR, false-positive rate; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

^a Computed by the authors of this report.

^b FPR for comparator might be positively correlated with detection rate, requiring us to produce confidence curves for the bivariate pair of FPR and detection rate, which cannot be presented in a numeric format. Also the correlation value was not provided to allow plotting the confidence curves.

^c Results are based on the multiple imputation technique to account for the effect of ASA.

Table 4B: FMF Versus Conventional Screening Algorithms on Detection Rates at Fixed False-Positive Rates for Cases of Pre-Eclampsia With Delivery at Less Than 34 Weeks' Gestation

Author, year, country	Fixed FPR	Adjusted for ASA use	FMF algorithm			Comparator			Difference in detection rate (95% CI), %
			FMF risk factors	True positives, n	Detection rate, %	Algorithm	True positives, n	Detection rate, %	
Di Martino et al, ⁵² 2019, Italy	10%	No	Not described	67	44.1	BCNatal	67	38	6.1 (-9.6 to 24.1) ^a
Wright et al, ⁵⁷ 2015, United Kingdom	10.6%	No	Not described	370	53.5	NICE	370	43.5	10 (2.7 to 17.2) ^a

Abbreviations: ASA, acetylsalicylic acid; BCNatal, Sant Joan de Deu Barcelona Children's Hospital; CI, confidence interval; FMF, Fetal Medicine Foundation; FPR, false-positive rate; NICE, National Institute for Health and Care Excellence.

^aComputed by the authors of this report.

Table 4C: FMF Versus Conventional Screening Algorithms on Detection Rates at Fixed False-Positive Rates for Cases of Pre-Eclampsia With Delivery at Less Than 32 Weeks' Gestation

Fixed FPR	Adjusted for ASA use	FMF algorithm			Comparator			Difference in detection rate (95% CI), % ^a
		FMF risk factors	True positives, n	Detection rate, %	Algorithm	True positives, n	Detection rate, %	
10% (fixed only for FMF algorithm)	No	Maternal + MAP, UtA-PI, PlGF	17	100	NICE	17	41 (estimated FPR 10.2%)	59
10% (fixed only for FMF algorithm)	No	Maternal + MAP, UtA-PI, PlGF	17	100	ACOG	17	94 (estimated FPR 64.2%)	-

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASA, acetylsalicylic acid; CI, confidence interval; FMF, Fetal Medicine Foundation; FPR, false-positive rate; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

^aFPR for comparator might be positively correlated with detection rate, requiring us to produce confidence curves for the bivariate pair of FPR and detection rate, which cannot be presented in a numeric format. Also the correlation value was not provided to allow plotting the confidence curves.

Source: O'Gorman et al.^{53,58}

Table 5: FMF Versus Conventional Screening Algorithms on Detection and False-Positive Rates at Fixed Screen-Positive Rates for Cases of Pre-eclampsia With Delivery at Less Than 37 and Less Than 34 Weeks' Gestation

Author, year, country	Fixed SPR, %	Adjusted for ASA use	FMF algorithm			Comparator		Detection rate (FPR), %	Difference in detection rate (FPR), %
			Factors in model	TP/FP	Detection rate (FPR), %	Algorithm	TP/FP		
Pre-eclampsia with delivery at < 37 wk									
Guy et al, ⁴⁹ 2021, United Kingdom	10	No	Maternal + MAP, UtA-PI, PAPP-A	27/385	55.6 (8)	NICE	65/1,217	36.9 (15.9)	18.7 (-7.9)
Poon et al, ⁵⁴ 2020, United Kingdom	10.3	Yes	Maternal + MAP, UtA-PI, PlGF	142/1,611	79.6(9.7) ^a	NICE	142/1,611	44.1 (9.7) ^a	32.8 (0)
Tan et al, ⁵⁶ 2018, United Kingdom	10	Yes	Maternal + MAP, UtA-PI, PlGF	142	82.4 (5) ^b	NICE	142	40.8 (not reported)	35.1 (could not be estimated)
Wright et al, ⁵⁷ 2015, United Kingdom	11	No	Not described	786/12,689	48 (10.6) ^a	NICE	786/12,689	40 (10.6) ^a	8 (0)
Pre-eclampsia with delivery at < 34 wk									
Wright et al, ⁵⁷ 2015, United Kingdom	10	No	Not described	370	53.5 (10.6) ^a	NICE	370	43.5 (10.6) ^a	10 (0)

Abbreviations: ASA, acetylsalicylic acid; FMF, Fetal Medicine Foundation; FP, false positive; FPR, false-positive rate; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; PAPP-A, pregnancy-associated plasma protein A; PlGF, placental growth factor; SPR, screen-positive rate; TP, true positive; UtA-PI, uterine artery pulsatility index.

^a Fixed according to the NICE guidelines.

^b Approximated visually from the receiver operating characteristic curve.

Table 6: FMF Versus Conventional Screening Algorithms on Detection and False-Positive Rates at Unrestricted False- and Screen-Positive Rates for Cases of Pre-Eclampsia With Delivery at Less Than 37 Weeks' Gestation

Adjusted for ASA use	FMF algorithm		Detection rate (FPR), %	Comparator		Detection rate (FPR), %	Difference in detection rate (FPR), %
	FMF risk factors	TP/FP		Algorithm	TP/FP		
No	Maternal + MAP	21/71	67 (10)	NICE	21/115	47.6 (16.2)	19.4 (-6.2)
No	Maternal + MAP	21/71	67 (10)	ACOG	21/522	85.7 (73.3)	-18.7 (-63.3)

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASA, acetylsalicylic acid; FMF, Fetal Medicine Foundation; FP, false positive; FPR, false-positive rate; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; TP, true positive.

Source: Rocha et al.⁵⁵

Table 7: FMF Versus Conventional Screening Algorithms on Positive and Negative Predictive Values With Unrestricted False-Positive Rates for Cases of Pre-Eclampsia With Delivery at Less Than 37 Weeks' Gestation

Author, year, country	Adjusted for ASA use	FMF algorithm		PPV, NPV, %	Comparator Algorithm	Comparator		Difference in PPV, NPV, %
		FMF risk factors	No. test positive/No. test negative			No. test positive/No. test negative	PPV, NPV, %	
Guy et al, ⁴⁹ 2021, United Kingdom	No	Maternal + MAP, UtA-PI, PAPP-A	400/4,440	3.75, 99.73	NICE	1,241/6,478	1.93, 99.38	1.82, 0.35
Rocha et al, ⁵⁵ 2017, Brazil	No	Maternal + MAP	85/648	16.47, 98.92	NICE	125/608	8.00, 98.19	8.47, 0.73
Rocha et al, ⁵⁵ 2017, Brazil	No	Maternal + MAP	85/648	16.47, 98.92	ACOG	540/193	3.33, 98.45	14.98, 0.47
Wright et al, ⁵⁷ 2015, United Kingdom	No	Not described	13,066/10,7428	2.89, 99.62	NICE	13,003/17,491	2.41, 99.56	0.48, 0.06

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASA, acetylsalicylic acid; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; PAPP-A, pregnancy-associated plasma protein A; PPV, positive predictive value; UtA-PI, uterine artery pulsatility index.

Ongoing Studies

We are aware of the ongoing studies at two Ontario hospitals to assess the feasibility of implementing systematic prenatal screening and prevention of pre-eclampsia with delivery at less than 37 weeks, and to lay the foundation for scaling up this service in Ontario to promote equitable access to all people in Ontario (email communication with N. Okun, MD, May 2022). The study has also opened a new site in Alberta (email communication with N. Okun, MD, May 2022).

Discussion

Evidence from our assessment supports the effectiveness of the FMF-based screening program compared with standard care in reducing the risk of pre-eclampsia with delivery at less than 37 weeks' gestation. As well, the FMF algorithm can improve accuracy of predicting pre-eclampsia with delivery at less than 37 weeks' gestation more accurately than conventional algorithms. We did not identify any study evaluating the harms of being misclassified by the FMF algorithm as having a high or low risk of developing pre-eclampsia with delivery at less than 37 weeks' gestation. Being classified as high-risk would warrant initiating low-dose ASA treatment. Although low-dose ASA will not greatly increase serious bleeding complications, such as placental abruption or postpartum hemorrhage,⁵⁹ a small risk still remains,^{49,53,55,57} and it might be important to ensure that low-dose ASA prophylaxis is given only to those at high risk of developing pre-eclampsia. It should be noted, however, that a study conducted in Ontario by Vigiliouk et al³⁴ found that the rate of ASA use in those classified as high-risk was actually very low (7.6%) using the current screening and prevention strategies. Thus, scaling up use of low-dose ASA among those identified as high-risk is important. The ongoing implementation study on the FMF-based screening program has found a high adherence to ASA therapy (88.9%) if initiated at 16 weeks' gestation. However, it remains to be determined whether such high adherence is owing to the overall structure of the FMF-based screening program and structured interval data collection, the selected study population, or trust among clinicians in the accuracy of the screening test.

Most studies used the version of FMF that combines maternal factors and three biomarkers: MAP, UtA-P index, and PlGF (commonly known as the triple test). But access to all three biomarkers might not always be available especially in remote areas, and this could warrant further evaluation of whether using any combination of biomarkers listed in the FMF algorithm is still better than standard care. One such alternative is the mini combined test, which consists of maternal factors and two biomarkers: MAP and PAPP-A. It was used in Poon et al⁵⁴ and was shown to have a better performance than the NICE algorithm. Guy et al⁴⁹ replaced PlGF with PAPP-A in the triple test and found FMF to be superior to NICE, although the point estimates were too imprecise. Rocha et al⁵⁵ used the FMF model with only maternal factors and MAP. This reduced model performed better than NICE; however, comparison with the ACOG algorithm yielded mixed results where ACOG had a higher detection rate but a much higher false-positive rate (73.3% for ACOG vs. 10% for FMF). Given the well-known positive correlation between detection rate and false-positive rate, these findings likely reflect a high false-positive rate rather than a better performance of ACOG.

We derived PPVs and NPVs from three studies.^{49,55,57} Our calculations resulted in almost perfect PPVs but very poor NPVs on all screening tests (i.e., FMF, NICE, and ACOG). This is unsurprising, as PPVs and NPVs can be highly influenced by the prevalence of the condition under investigation. In our case, these findings could be explained by the low prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation; hence, they should be interpreted with caution.

We noted several limitations. First, the use of ASA after a positive screening test could have interfered with our ability to accurately interpret the results. Some studies tried to mitigate this problem by incorporating external knowledge to account for the effect of ASA, whereas others did not address the problem at all. We thus downrated all accuracy studies that did not correct for the effect of ASA. Second, several studies fixed the false- or screen-positive rate, making it difficult to estimate those parameters when they are allowed to vary depending on distribution of the data. However, the ongoing implementation study in Ontario (unpublished at the time of writing of this report) has observed the screen-positive rate of 10.4%, which is comparable to the fixed screen-positive rate reported in eligible studies for this review. Finally, our assessment on the effectiveness of FMF included several birth outcomes reported in only a single study. As a result, we were unable to determine the consistency of findings on these outcomes across populations.

Equity Issues

Pregnant people from groups most impacted by social determinants of health, such as Black and Indigenous communities, are widely reported to be disproportionately affected by pre-eclampsia. The genetic basis for the link between race and the pathophysiology of pre-eclampsia has not been identified.⁶⁰ This highlights the need to assess the extent to which gaps in access to health care have a role in pre-eclampsia rates across racial and ethnic groups. However, we did not identify any direct evidence on equity issues relevant to how gaps in access to screening affect pre-eclampsia rates across racial and ethnic populations. Although research in this area is limited, some studies have underscored the importance of this issue. For example, a case-control study by Haelterman et al⁶¹ found that the association between lack of access to national health insurance and the outcome of severe pre-eclampsia, eclampsia or HELLP was as strong as the association for obesity and chronic hypertension. They hypothesized that barriers to health care utilization play a major role in the occurrence of severe morbidity for women with hypertensive disorders of pregnancy. Similarly, Miao et al⁶² have explored the role of systemic racism and implicit bias in health care.

The Ontario Health Equity, Inclusion, Diversity and Anti-Racism Framework⁶³ identifies 11 areas of action, which bear consideration for the implementation of an FMF-based screening program in Ontario.

Conclusions

Our review found that an FMF-based screening program initiated at 11⁰ weeks' and 13⁶ weeks' gestation likely reduces the risk of pre-eclampsia with delivery at less than 37 weeks' gestation compared with standard care (GRADE: Moderate). An FMF-based screening program may reduce the risk of low birth weight and low Apgar score after birth (GRADE: Low). We are uncertain about the evidence for the comparative effectiveness of the FMF-based screening program on stillbirth and on neonatal death (GRADE: Very low).

We also found that the FMF algorithm initiated between 11⁰ and 13⁶ weeks' gestation can have a higher accuracy than conventional algorithms in detecting pre-eclampsia with delivery at less than 37 weeks' gestation or at less than 34 weeks' gestation, although there are concerns about risk of bias and applicability.

Economic Evidence

Research Question

What is the cost-effectiveness of a population-wide screening program for pre-eclampsia risk that uses a multiple-marker algorithm taken between 11⁰ and 13⁶ weeks' gestation, compared with standard care (or any other screening strategies)?

Methods

Economic Literature Search

We performed an economic literature search on January 26, 2022, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the clinical literature search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from inception to search date
- Cost-benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost-utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, and abstracts

POPULATION

- Pregnant people (singleton pregnancies) within the gestational age of 11⁰ weeks and 13⁶ weeks

INTERVENTION

- A population-wide screening program that uses a multiple-marker algorithm developed by the Fetal Medicine Foundation ("the population-wide FMF-based screening program")

COMPARATORS

- Standard care (e.g., opportunistic screening programs, no screening programs, screening programs using National Institute of Health and Clinical Excellence [NICE], American College of Obstetricians and Gynecologists [ACOG], or other similar methods)

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence⁴¹ and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria (Appendix 4). This reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, interventions, comparators)
- Outcomes (e.g., health outcomes, costs, ICERs)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality-appraisal checklist for economic evaluations originally developed by NICE in the United Kingdom to inform the development of NICE's clinical guidelines.⁶⁴ We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly or partially applicable.

Results

Economic Literature Search

The database search of the economic literature yielded 322 citations published from database inception to January 26, 2022. We identified three additional studies from other sources. In total, we identified six studies that met our inclusion criteria. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

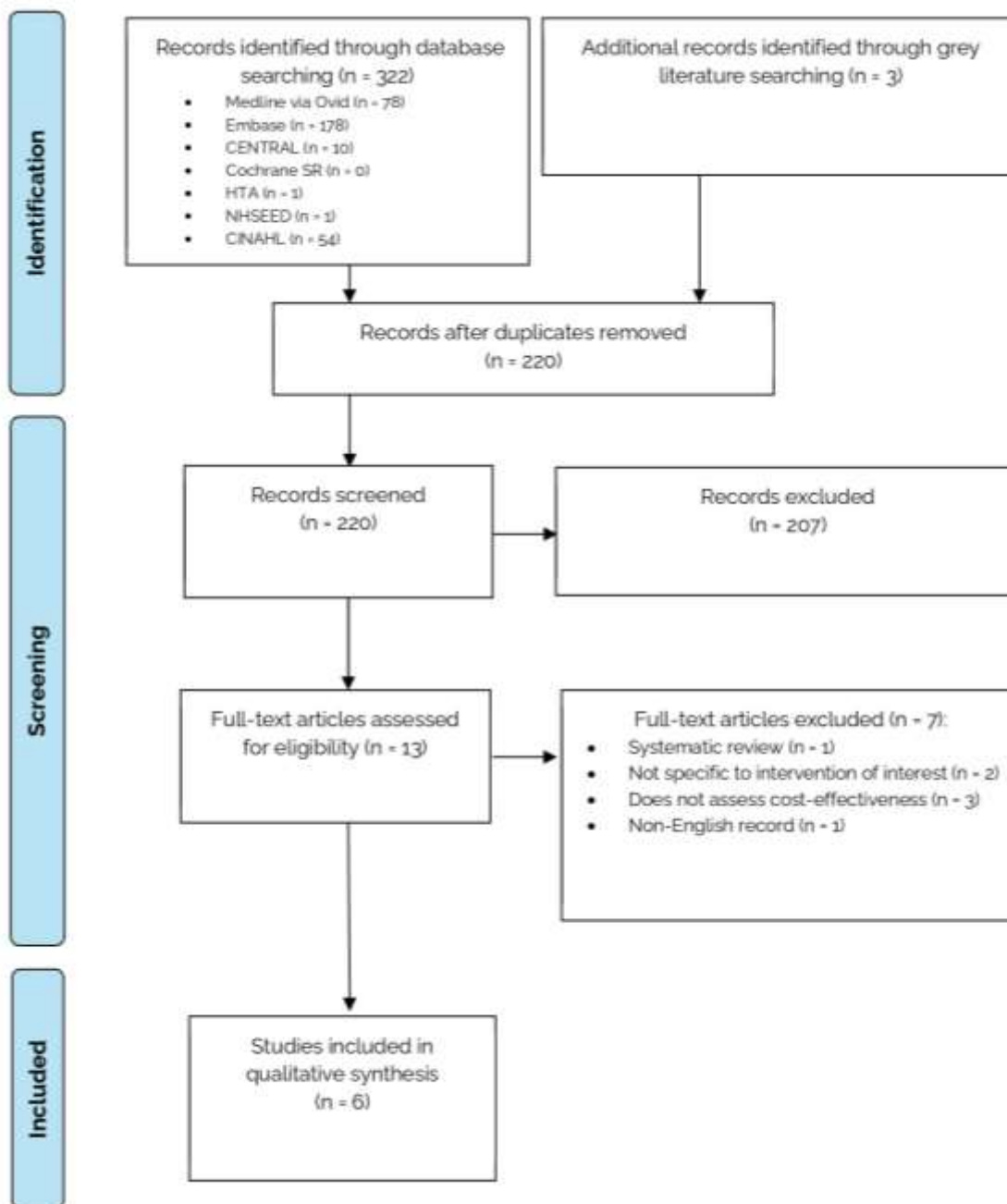


Figure 3: PRISMA Flow Diagram—Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 322 citations published from database inception to January 26, 2022. Records identified through database searching (n = 322) were MEDLINE via Ovid (n = 78); Embase (n = 178); CENTRAL (n = 10); Cochrane SR (n = 0); HTA (n = 1); NHSEED (n = 1); CINAHL (n = 54). We identified three additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 220 studies and excluded 207. We assessed the full text of 13 articles and excluded a further seven. In the end, we included 6 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.⁴⁸

Overview of Included Economic Studies

We identified a total of six studies that met our inclusion criteria (Table 8).⁶⁵⁻⁷⁰

Three of the studies were cost-effectiveness analyses^{65,67,68}; one study was a cost-utility analysis⁶⁹; and two studies conducted both cost-effectiveness and cost-utility analyses.^{66,70} All cost-effectiveness analyses reported outcomes as the number of pre-eclampsia cases prevented and the incremental costs arising from a population-wide FMF-based screening program compared with the alternatives.^{66,70}

One study was based in a Canadian setting.⁶⁷ The remaining were conducted in Australia,⁶⁵ Belgium,⁶⁶ Ireland,⁶⁹ Israel,⁷⁰ and the United States.⁶⁸ All studies used a decision tree structure to model the possible outcomes and associated costs. Two studies^{66,67} adopted a 12-month time horizon, one study⁶⁵ adopted a 24-month time horizon, and one study⁷⁰ conducted its analysis over a lifetime horizon. No time horizon was reported for the remaining three studies.^{68,69}

Comparators varied in the included studies. Three studies⁶⁵⁻⁶⁷ compared a population-wide FMF-based screening program with screening using maternal factors alone. This comparator is currently the standard care in Ontario. One study⁶⁸ compared a population-wide FMF-based screening program with three strategies: standard care, universal acetylsalicylic acid (ASA [Aspirin]) prophylaxis and no screening or prophylactic treatment for pre-eclampsia. The remaining two studies compared a population-wide FMF-based screening program with universal ASA prophylaxis or no screening and no prophylactic treatment for pre-eclampsia.

All three studies that compared a population-wide FMF-based screening program with standard care found the population-wide FMF-based screening program to be dominant (less costly and more effective) compared with standard care.⁶⁵⁻⁶⁷ For instance, Dubon Garcia et al⁶⁶ conducted the analyses using a 12-month time horizon from the Belgian health care payer's perspective. They found the population-wide FMF-based screening program provided an overall cost savings of €28.67 per person (2019 Euros) and prevented 337 cases of pre-eclampsia (of 51,309 pregnancies) annually compared with standard care, while the number of QALYs between the two strategies were similar. Orved et al⁶⁷ found that the population-wide FMF-based screening program resulted in 1,096 cases of pre-eclampsia prevented (of 387,516 pregnancies) and an annual cost saving of \$14.39 million in 2016 Canadian dollars. Similarly, Park et al⁶⁵ found that the population-wide FMF-based screening program resulted in 31 cases of pre-eclampsia prevented (of 6,822 pregnancies) and \$1.43 million in 2018 AUD saved over 2 years when compared with standard care.

Mallampati et al⁶⁸ also compared a population-wide FMF-based screening program with multiple strategies including standard care. It found that the population-wide FMF-based screening program resulted in fewer cases of pre-eclampsia (i.e., 3,780 vs. 3,818 cases in 100,000 pregnancies), but at an increased cost of \$11.2 million in 2018 USD yearly.

The remaining two studies^{69,70} both found that the population-wide FMF-based screening program was more effective and more costly than no screening and no prophylactic treatment. The analysis by Mone et al⁶⁹ also found that the universal ASA strategy dominated all other strategies. However, none of the comparators in these two studies were relevant to the standard care in Ontario.

Table 8: Results of Economic Literature Review—Summary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparators	Results		
				Health outcomes	Costs	Cost-effectiveness
Park et al, 2021, Australia ⁶⁵	Type of analysis: cost-effectiveness analysis Study design: decision tree Time horizon: 24 mo Perspective: Australian hospital Cost: calculated in 2018 AUD Discount rate: NR	Total N: 6,822 persons birthing at 2 centres in Australia	Intervention: population-wide FMF-based screening program Comparator: screening for risk of PE using maternal risk factors alone (standard care)	Mean: NR Mean difference: 31.30 cases of PE avoided	Mean: NR Mean difference: -\$1,431,186	Intervention vs. standard care: dominant (31.19 cases of PE prevented with cost savings of \$1,431,186)
Dubon Garcia et al, 2021, Belgium ⁶⁶	Type of analysis: cost-effectiveness analysis, cost-utility analysis Study design: decision tree Perspective: Belgian payers' perspective Time horizon: 12 mo Cost: calculated in 2019 Euros Discount rate: 0%	Total N: 51,309 nulliparous persons	Intervention: population-wide FMF-based screening program Comparator: screening for risk of PE using maternal risk factors alone (standard care)	<i>PE with delivery < 37 wk</i> Mean for intervention: 479 cases of PE with delivery < 37 wk/yr Mean for standard care: 816 cases of PE with delivery < 37 wk/yr Mean difference: 337 cases of PE with delivery < 37 wk prevented/yr <i>Total maternal and child QALYs</i> Mean for intervention: 1.8521 QALYs Mean for standard care: 1.8518 QALYs Mean difference: 0.0003 QALYs	Mean for intervention: €4,417.61/patient Mean for standard care: €4,446.28/patient Mean difference: -€28.67/patient	Intervention vs. standard care: dominant (337 cases of PE with delivery < 37 wk prevented per year, with cost savings of €28.67 per patient)

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparators	Results		
				Health outcomes	Costs	Cost-effectiveness
Ortved et al, 2019, Canada ⁶⁷	Type of analysis: Cost-effectiveness analysis Study design: decision tree Perspective: NR Time horizon: 12 mo Cost: Calculated in 2016 CAD Discount rate: NR	Total N: 387,516 live births	Intervention: population-wide FMF-based screening program Comparator: screening for risk of PE using maternal risk factors alone (standard care)	Mean for intervention: 705 cases of PE (with delivery < 34 wk) yearly Mean for standard care: 1,801 cases of PE (with delivery < 34 wk) yearly Mean difference: 1,096 (with delivery < 34 wk) prevented yearly	Mean for intervention: \$9,523,485/yr Mean for standard care: \$23,910,467/yr Mean difference: -\$14,386,982/yr	Intervention vs. standard care: dominant (1,096 cases of PE (with delivery < 34 wk gestation) prevented with cost savings of \$14,386,982)
Mallampati et al, 2019, US ⁶⁸	Type of analysis: Cost-effectiveness analysis Study design: decision tree Perspective: Societal Time horizon: NR Cost: Calculated in 2018 USD Discount rate: NR	Total N: NA	Strategy 1: no screening or ASA prophylaxis Strategy 2: population-wide FMF-based screening program Strategy 3: screening for risk of PE using maternal risk factors alone (standard care) Strategy 4: universal ASA prophylaxis (used as reference in this study)	<i>Mean per 100,000 pregnant persons</i> Strategy 1: 4,234 cases of PE/100,000 pregnant persons Strategy 2: 3,780 cases of PE/100,000 pregnant persons Strategy 3: 3,818 cases of PE/100,000 pregnant persons Strategy 4: 3,472 cases of PE/100,000 persons <i>Mean difference</i> Strategy 1 vs. Strategy 4: 762 additional cases of PE Strategy 2 vs. Strategy 4: 308 additional cases of PE Strategy 3 vs. Strategy 4: 346 additional cases of PE	<i>Mean per 100,000 pregnant women</i> Strategy 1: \$38,967,706 Strategy 2: \$39,433,876 Strategy 3: \$28,229,050 Strategy 4: \$20,217,325 <i>Mean difference</i> Strategy 1 vs. Strategy 4: \$18,750,381 Strategy 2 vs. Strategy 4: \$19,216,551 Strategy 3 vs. Strategy 4: \$8,011,725	At a threshold of \$90,843 per case of PE, Strategy 4 (universal ASA) dominated all other strategies Strategy 2 (population-wide FMF-based screening program) was more effective and more costly than Strategy 3 (standard care)

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparators	Results		
				Health outcomes	Costs	Cost-effectiveness
Mone et al, 2018, Ireland ⁶⁹	Type of analysis: cost-utility analysis Study design: decision tree Perspective: NR Time horizon: NR Cost: calculated in Euros (year NR) Discount rate: 5% on health outcomes only	Total N: 100,000 low-risk nulliparous persons	Strategy 1: population-wide FMF-based screening program Strategy 2: universal ASA prophylaxis Strategy 3: no screening or ASA prophylaxis (used as reference in this study)	Mean: NR Mean difference for Strategy 1 vs. Strategy 3: 108 QALYs/yr Mean difference for Strategy 2 vs. Strategy 3: 163 QALYs/yr	Mean for Strategy 1: €15,729,605/yr Mean for Strategy 2: €14,257,032/yr Mean for Strategy 3: €14,273,475/yr Mean difference for Strategy 1 vs. Strategy 3: -€3.1 million/yr Mean difference for Strategy 2 vs. Strategy 3: -€14.9 million/yr	Strategy 2 (universal ASA) dominated all other strategies

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Interventions and comparators	Results		
				Health outcomes	Costs	Cost-effectiveness
Shmueli et al, 2012, Israel ⁷⁰	Type of analysis: cost-effectiveness analysis, cost-utility analysis Study design: decision tree Perspective: payer's perspective Time horizon: lifetime Cost: Calculated in USD (year NR) Discount rate: 3% on costs and health outcomes	Total N: NA	Intervention: population-wide FMF-based screening program Comparator: no PE screening or ASA prophylaxis	<i>Prenatal period until admission for delivery</i> Mean for intervention: 0.015 expected cases of PE Mean for comparator: 0.017 expected cases of PE Mean difference for intervention vs. comparator: 0.00182 expected cases of PE <i>Prenatal period until discharge from hospital after delivery</i> Mean for intervention: NR Mean for comparator: NR Mean difference for intervention vs. comparator: NR <i>Prenatal period until death of offspring</i> Mean for intervention: 30.421 QALYs Mean for comparator: 30.426 QALYs Mean difference for intervention vs. comparator: 0.0056 QALYs	<i>Prenatal period until admission for delivery</i> Mean for intervention: \$633/person Mean for comparator: \$511/person Mean difference for intervention vs. comparator: \$122/person <i>Prenatal period until discharge from hospital after delivery</i> Mean for intervention: \$4,693 Mean for comparator: \$4,693 Mean difference for intervention vs. comparator: \$0 <i>Prenatal period until death of offspring</i> Mean for intervention: \$4,783 Mean for comparator: \$4,888 Mean difference for intervention vs. comparator: -\$105	<i>Prenatal period until admission for delivery</i> Intervention vs. comparator: \$66,949 per PE case prevented <i>Prenatal period until death of offspring</i> Reference case for intervention vs. comparator: \$18,919 per QALY (for offspring)

Abbreviations: ASA, acetylsalicylic acid; AUD, Australian dollars; CAD, Canadian dollars; NA, not applicable; NR, not reported; PE, pre-eclampsia; QALY, quality-adjusted life-years; USD, US dollars.

Applicability and Limitations of the Included Studies

Table A4 (Appendix 5) provides the results of the quality-appraisal checklist for economic evaluations applied to the included studies. One⁶⁷ of the included studies was deemed directly applicable to the research question, three^{65,66,68} were considered partially applicable, and the remaining two^{69,70} were inapplicable. Table A5 (Appendix 5) assesses the limitations of these studies. Of the included studies, two^{67,69} had potentially serious limitations and four^{65,66,68,70} had potentially minor limitations.

Discussion

Our literature review found six published economic evaluations⁶⁵⁻⁷⁰ on the population-wide FMF-based screening program, out of which four⁶⁵⁻⁶⁸ were directly or partially applicable to our research question. However, these studies had some common limitations.

The study by Ortvad et al⁶⁷ was conducted in Canada and was the only study directly applicable to our research question. However, this study focused on acute maternal health care costs associated with pre-eclampsia and did not consider the neonatal costs associated with preterm birth. Additionally, this study⁶⁷ also assumed that all pregnant people in Canada would participate in a first-trimester pre-eclampsia screening program. However, in practice, a proportion of pregnant people do not initiate their first prenatal visit with a health care provider in the first trimester and would therefore be unaffected by the screening program.⁷¹ Consequently, the number of pre-eclampsia cases that would be prevented by the screening program are likely overestimated. Further, this study⁶⁷ reported pre-eclampsia with delivery at less than 34 weeks' gestation as its only outcome, thereby not capturing outcomes of pre-eclampsia with preterm delivery between 34 and 36 weeks' gestation. Last, the accuracy or performance (i.e., sensitivity and specificity) of either screening strategy was not accounted for in the analysis.

The remaining three studies that were partially applicable to our research question had minor limitations. For instance, in the Australian study by Park et al,⁶⁵ the prenatal care management pathway modelled was different from current practice in Ontario. In the model, pregnant people identified as high-risk for pre-eclampsia were referred to an obstetrician, while those at low risk were referred to a midwife. In Ontario, however, pregnant people might choose an obstetrician, general practitioner, or midwife to be their prenatal health care provider. There is no recommended practice to change health care provider based on the results of screening for pre-eclampsia risk in the first trimester (N. Okun, MD, written communication, March 2022). Park et al⁶⁵ also assumed that pregnant people receiving standard care were screened systematically, whereas in Ontario, this is done opportunistically, or on an ad hoc basis, with variability in clinical practice across the province.⁶⁷

The Belgium study by Dubon Garcia et al⁶⁶ was one of the few studies that accounted for the screening accuracy of the FMF algorithm and screening using maternal risk factors alone. However, it derived the sensitivity and specificity of these screening strategies from studies^{56,58,72} that did not adjust for the treatment effect of low-dose ASA prophylaxis, which led to some uncertainty in its results.

Mallampati et al⁶⁸ assumed that all pregnant people who were identified as high-risk would be prescribed low-dose ASA prophylaxis. This assumption likely overestimated the uptake of ASA under both strategies. Similar to Ortvad et al,⁶⁷ Mallampati et al⁶⁸ accounted for only acute maternal health care costs and excluded neonatal costs of preterm birth, which are a significant consequence of pre-eclampsia and constitute a substantial cost to the health care system.⁷³⁻⁷⁵

Overall, most studies⁶⁶⁻⁷⁰ did not account for the additional costs of implementing and operationalizing a screening program, which could involve additional laboratory services, staff training, quality assurance, program coordination, and education and promotional resources for health care providers and patients. Finally, the prevalence of pre-eclampsia could be an important determinant to the evaluation, as higher prevalence would result in more favourable outcomes for a population-wide FMF-based screening program. The prevalence of pre-eclampsia varied across the studies. Hence, it is important to use a prevalence rate that is applicable to Ontario.

Equity Issues

None of the included studies identified equity issues in its assessment process or incorporated them as part of its analysis. None evaluated or discussed distribution of health benefits of the population-wide FMF-based screening program or its impact on health equity in Ontario.

Conclusions

We found six economic analyses that evaluated the population-wide FMF-based screening program. Three studies⁶⁵⁻⁶⁷ found the population-wide FMF-based screening program to be dominant (less costly and more effective) compared with standard care, and one study⁶⁸ found it to be more effective but more costly. Two studies^{69,70} were not applicable because they used comparators that were irrelevant to our research question.

Because of variations in study methods and results, we conducted a primary economic evaluation for Ontario.

Primary Economic Evaluation

Research Question

What is the cost-effectiveness of a population-wide screening program for pre-eclampsia risk that uses a multiple-marker algorithm between 11th and 13th weeks' gestation, compared with standard care, from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS) statement.⁷⁶

Type of Analysis

We conducted a cost-effectiveness analysis, whereby the outcome of effectiveness is the number of pre-eclampsia cases with delivery at less than 37 weeks' gestation. We did not focus on pre-eclampsia with delivery after 37 weeks' gestation, maternal mortality, stillbirths, or neonatal deaths as part of our outcomes because previous literature showed that administration of low-dose acetylsalicylic acid (ASA [Aspirin]) from 11th to 13th weeks' gestation did not greatly affect these outcomes.⁷⁷ Last, we did not conduct a cost-utility analysis or estimate health outcomes as quality-adjusted life-years (QALYs) because of a lack of health-related quality of life estimates for the impact of pre-eclampsia on maternal health.

Target Population

Our target population was all pregnant people with singleton pregnancies within the gestational age of 11th to 13th weeks' gestation. This was because in Ontario, people with multiple pregnancies are already considered high-risk and would be prescribed low-dose ASA (N. Okun, MD, phone communication, March 2022).

SUBGROUP

To support decision-making for concerns related to equity, we conducted a subgroup analysis of rural or remote populations in Ontario (e.g., northern and southwestern regions) and assumed lower uptake of a population-wide screening program that uses a multiple-marker algorithm developed by the Fetal Medicine Foundation ("the population-wide FMF-based screening program") in this subpopulation. This was because this subpopulation faces greater barriers to accessing routine prenatal care, including lack of infrastructure and health care resources, and greater emotional and financial burden associated with travelling for care or finding accommodations between appointments.⁷⁸

Historically in Ontario, rural regions have also been found to have significantly lower prenatal screening rates than urban regions.^{37,38} For instance, a retrospective cohort study³⁷ found that between 2007 and 2009, uptake of prenatal screening in the first trimester ranged from 40% in rural regions (such as Southwestern and Northern Ontario) to 80.3% in urban regions (such as central Toronto). A recent report by the Better Outcomes Registry and Network (BORN) similarly stated that between 2019 and 2020, a greater proportion of pregnant people received prenatal screening in the first trimester in urban census divisions than in rural census divisions, ranging from 78.25% in Toronto, Kingston, London, and Ottawa, to 4.36% in Kenora and Temiskaming.³⁸ This finding indicates that this subpopulation could have a similarly low uptake of a population-wide FMF-based screening program.

This variation could be the result of barriers to access, which in turn could contribute to fewer biomarkers collected under this screening program in this subpopulation.

As such, in addition to this subgroup analysis, we also conducted a scenario analysis in which we considered a population-wide FMF-based screening program based on a combination of fewer biomarkers—such as without uterine artery pulsatility index (UtA-PI) and the placental growth factor (PLGF).⁵⁴ The screening performance and program costs for this scenario were expected to be lower than that of the standard population-wide FMF-based screening program.

Perspective

We conducted the reference case analysis from the perspective of the Ontario Ministry of Health. This analysis included only direct medical costs borne by the public payer.

Interventions and Comparators

INTERVENTION

The intervention was the population-wide FMF-based screening program. The FMF algorithm used Bayes' theorem to combine previous risk from a combination of maternal risk factors and the results of various biophysical (i.e., mean arterial pressure [MAP], UtA-PI) and biochemical measurements (i.e., PLGF). Using these markers, a risk calculator based on the FMF algorithm can calculate pre-eclampsia risk. This risk calculator is available free online (<https://fetalmedicine.org/>). Pregnant people classified as high-risk will be prescribed low-dose ASA to be taken once daily, from less than 16 weeks' gestation until the birth of the baby.

STANDARD CARE

The current standard care in Ontario is opportunistic screening for risk of pre-eclampsia in the first trimester based on maternal risk factors alone, as recommended in several existing checklists.^{19,79,80} There is no standardized recommendation for any specific checklist, and there is substantial overlap in individual risk criteria comparing one with the others (N. Okun, MD, written communication, May 2022). Our analysis assumed that standard care is based on criteria from the National Institute of Health and Clinical Excellence (NICE) guideline¹⁹ only because our clinical model parameter inputs were obtained from studies in which standard care was based on the NICE guideline.¹⁹ The NICE guidelines for assessing pre-eclampsia risk in the first trimester are outlined in the clinical evidence review, above. In our model, pregnant people classified as high-risk are prescribed low-dose ASA to be taken once daily, from less than 16 weeks' gestation until the birth of the baby.

Time Horizon and Discounting

The time horizon of our reference case analysis is from the beginning of pregnancy to 2 years post-delivery. Although pre-eclampsia often has lifetime consequences for the health of both pregnant people and infants,⁸¹ we determined that a short time horizon would be sufficient to capture any meaningful differences relating to health effects and costs between our intervention (the population-wide FMF-based screening program) and comparator (standard care). We further considered that a longer time horizon was likely to be associated with uncertainties that might affect the validity of the model results. This was because the long-term consequences of pre-eclampsia included increased risk of diseases that can be attributed to multiple factors. For instance, pre-eclampsia is associated with increased risk of cardiovascular disease in pregnant people and increased risk of developing various diseases in the offspring, including stroke, hypertension, and type 2 diabetes.⁸¹⁻⁸⁴ In accordance

with the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines,⁸⁵ we applied a discount rate of 1.5% to costs exceeding 1 year.

Main Assumptions

The main assumptions were as follows:

- People who screened positive (considered high-risk) would take low-dose ASA if prescribed by a physician
- Physician adherence with prescribing ASA prophylaxis differed between strategies
- People who screened positive under either strategy would have additional ultrasound examinations as part of routine surveillance (N. Okun, MD, phone communication, January 2022):
 - Additional uterine-artery Doppler ultrasonography between 22 and 24 weeks' gestation
 - Additional monthly ultrasonography examining fetal growth from 24 weeks' gestation to the end of pregnancy (or an average of 3.5 additional ultrasound examinations of fetal growth)
- The screen-positive rate of the intervention and comparator was fixed at 10.3%. This predetermined rate was based on the Screening Programme for Preeclampsia (SPREE) study,⁵⁴ to allow for comparison of detection rate (sensitivity) between the FMF algorithm and standard care when the screen-positive rates were held at the same value
- Pregnant people who were not screened (under either strategy) would not be prescribed low-dose ASA, and their risk of developing pre-eclampsia with delivery at less than 37 weeks' gestation would be equal to the prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation in our target population
- Low-dose ASA prophylaxis would lower the risk of pre-eclampsia with delivery at less than 37 weeks' gestation only among people who were correctly classified as high-risk and were prescribed low-dose ASA prophylaxis by their health care providers
- We did not consider the risk of potential severe adverse effects of taking ASA in our model, because this risk is very low. For instance, a recent Swedish study found that ASA use in pregnancy is associated with increased risk of intrapartum bleeding (2.9% vs. 1.5%, adjusted odds ratio [OR] 1.63 [95% confidence interval (CI) 1.30–2.05]), postpartum hemorrhage (10.2% vs. 7.8%, adjusted OR 1.23 [95% CI 1.08–1.39]), postpartum hematoma (0.4% vs. 0.1%, adjusted OR 2.21 [95% CI 1.13–4.34]) and neonatal intracranial hemorrhage (0.07% vs. 0.01%, adjusted OR 9.66 [95% CI 1.88–49.48]). However, incidence was increased only in pregnant people who had vaginal birth and not in those who had caesarean delivery, which is more likely to occur in people with preterm delivery⁸⁶
- Last, our model did not consider the predictive value of biomarker tests (i.e., soluble fms-like tyrosine kinase 1 and PlGF ratio) in the diagnosis and misdiagnosis of people with suspected pre-eclampsia at greater than 20 weeks' gestation

Model Structure and Structure of Analysis

We developed a decision tree model (Figure 4) to estimate the costs and health outcomes associated with each strategy.

The standard care arm of the model represented current practice in Ontario, and the intervention arm simulated implementation of the population-wide FMF-based screening program. The two strategies shared the same model structure, but differed in parameter inputs and assumptions. Under both

strategies, health care providers screened a proportion of pregnant people for their risk of pre-eclampsia. The remainder were not screened or did not attend a prenatal care visit in the first trimester. Among those who were screened, some would be classified as high- or low-risk for pre-eclampsia. People classified as high-risk might then be prescribed or not prescribed low-dose ASA prophylaxis based on physician adherence. People classified as low-risk would not be prescribed ASA. All people in our model had a risk of developing pre-eclampsia with delivery at less than 37 weeks' gestation.

We also incorporated the screening performance of the FMF algorithm and the NICE criteria in our model using the positive predictive values (PPVs) and negative predictive values (NPVs) from the respective screening strategies. The PPV from each study determines the number of people correctly identified as high-risk who did not take ASA. The PPV multiplied by ASA treatment effect determined the number of people correctly identified as high-risk who took ASA, but still went on to develop pre-eclampsia with delivery at less than 37 weeks' gestation. Last, the NPV of the respective screening strategies determines the number of people correctly identified as low-risk.

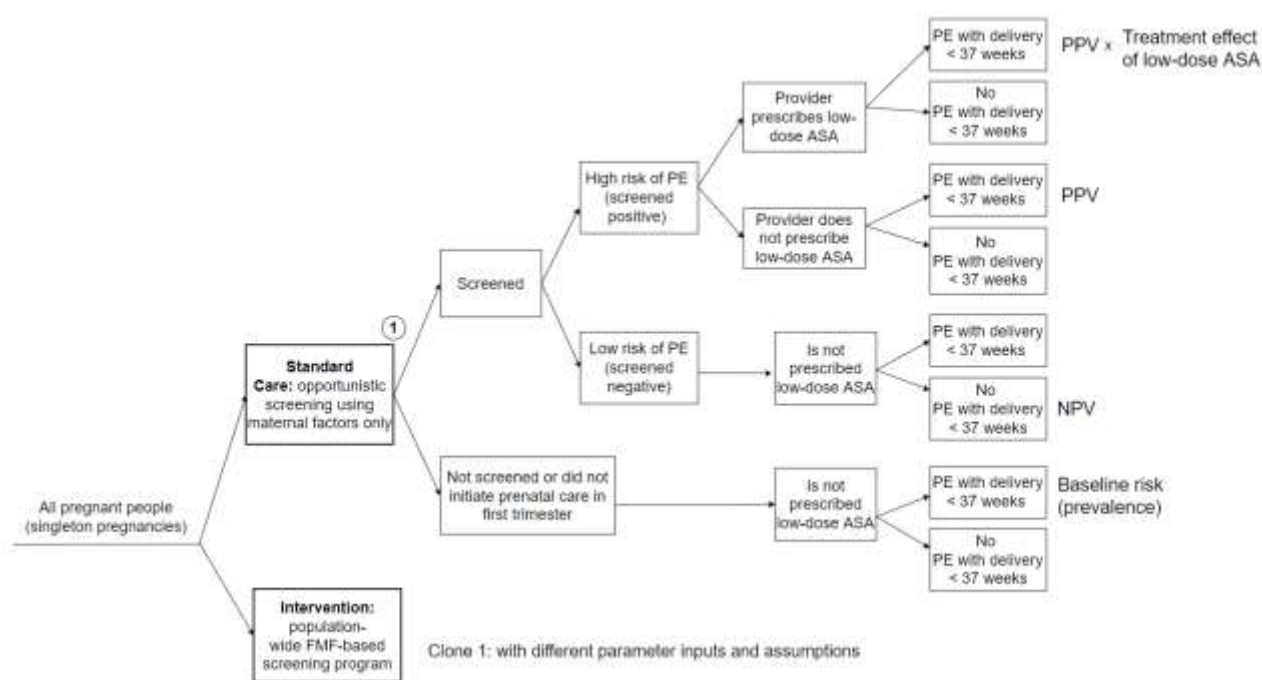


Figure 4: Model Structure

Decision tree structure showing the intervention and standard care arms of the economic model. The standard care arm of the model represents current practice in Ontario, and the intervention arm simulates implementation of the population-wide FMF-based screening program. The two strategies share the same model structure, but differ in parameter inputs and assumptions. Abbreviations: ASA, acetylsalicylic acid; NPV, negative predictive value; PE, pre-eclampsia; PPV, positive predictive value.

Clinical Outcomes Parameters

The clinical outcome parameters (Table 9) were obtained from our clinical evidence review whenever possible and validated by experts to ensure that they reflect Ontario clinical practice. The following clinical parameters were used:

- Baseline risk (prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation in the target population)
- Screening uptake (probability of being screened)
- Physician adherence with prescribing low-dose ASA prophylaxis
- Treatment effect of low-dose ASA prophylaxis on occurrence of pre-eclampsia with delivery at less than 37 weeks' gestation
- Screening performance of the FMF algorithm versus the NICE criteria

In summary, the risk of pre-eclampsia is influenced by baseline risk, screening uptake, provider adherence with prescribing low-dose ASA prophylaxis, treatment effect of ASA, and the screening performance of the respective screening strategies.

BASELINE RISK

For simplicity, we assumed that the risk of developing pre-eclampsia with delivery at less than 37 weeks' gestation in people who are not screened under either strategy was equal to the prevalence of this health outcome in our target population. No administrative or published data were available on the prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation in Canada. Consequently, we based the prevalence of this health outcome in our target population (of approximately 0.8%, or 8.0 per 1,000 people) on the Screening Program for Preeclampsia (SPREE) study.⁵⁴ This was a prospective UK multicentre cohort study that compared the predictive performance of standard care (i.e., NICE criteria for assessing pre-eclampsia risk¹⁹) to the FMF algorithm. We determined that deriving the prevalence of this health outcome from the SPREE study⁵⁴ was reasonable, because the prevalence of pre-eclampsia overall (with delivery before, at, and after 37 weeks' gestation) in Canada in 2010/11 was 1.15% (or 11.5 per 1,000 deliveries).¹⁵

SCREENING UPTAKE (PROBABILITY OF BEING SCREENED)

Our model applied a theoretical population of pregnant people with singleton pregnancies per year. We based our estimated cohort size ($n = 140,500$) on the total number of live births in the province in 2019.⁸⁷ We considered this reasonable because multiple fetal pregnancies constitute a very low percentage of the total number of live births.⁸⁸ We estimated the probability of being screened under either strategy based on the proportion of pregnant people in Ontario who initiate their routine prenatal care in the first trimester and are subsequently screened for pre-eclampsia risk at their first prenatal visit. We obtained the proportion of pregnant people in Ontario who attended a prenatal visit in their first trimester (86%) from published data from BORN.⁷¹ Under the standard care arm, some pregnant people were not screened for pre-eclampsia risk because, although screening for risk of pre-eclampsia is recommended as part of routine prenatal care, in practice, it occurs opportunistically. Clinical practice varies across Ontario.⁶⁷ However, data on the number of pregnant people screened for pre-eclampsia risk were unavailable in health administrative databases or from published literature. Therefore, we assumed that 50% of pregnant people would be screened at their first prenatal visit under standard care, based on clinical expert opinion (N. Okun, MD, written communication, March 2022). Under the intervention arm, some pregnant people might not be screened owing to patient preference. We assumed that 85% of pregnant people who had a first-trimester prenatal visit would agree to be screened based on the FMF algorithm. This estimate was based on the uptake of a screening program in a single-site feasibility study in Ontario (unpublished; N. Okun, MD, written communication, March 2022).

PROVIDER ADHERENCE WITH PRESCRIBING LOW-DOSE ASA PROPHYLAXIS

We derived the physician adherence rate for prescribing low-dose ASA prophylaxis for the two screening strategies from Guy et al.⁴⁹ a UK retrospective cohort study that compared screening performance and rate of pre-eclampsia between the population-wide FMF-based screening program and standard care (based on the NICE criteria). According to this study,⁴⁹ the physician adherence rate for prescribing low-dose ASA among those who screened positive was 99% under the population-wide FMF-based screening program and 28.9% under standard care.

EFFECTIVENESS OF LOW-DOSE ASA PROPHYLAXIS

We obtained an estimate of the effectiveness of low-dose ASA as a preventive measure for pre-eclampsia from the Aspirin for Evidence-Based Preeclampsia Prevention (ASPREE) trial.⁷⁷ This was a multicentre, double-blind, randomized controlled trial conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel. The study⁷⁷ compared low-dose ASA prophylaxis with placebo administered between 11^o to 13^o weeks' gestation in pregnant people classified as high-risk for pre-eclampsia based on the FMF algorithm. In this study, pre-eclampsia with delivery at less than 37 weeks' gestation occurred in the ASA and placebo group at 1.6% versus 4.3%, respectively (OR 0.38, 95% CI 0.20 to 0.74).

SCREENING PERFORMANCE AND PROBABILITY OF PRE-ECLAMPSIA WITH DELIVERY AT LESS THAN 37 WEEKS' GESTATION

We obtained screening performance outcomes for each strategy from the clinical evidence review, which identified eight studies that evaluated detection rates for pre-eclampsia with delivery at less than 37 weeks' gestation between the FMF algorithm and the NICE criteria. Of these eight studies, two^{49,50} reported the adjusted detection rates of each screening strategy after accounting for the treatment effect of low-dose ASA. Of these two studies, Chaemsaitong et al.⁵¹ focused on a large Asian population, while the SPREE study⁵⁴ focused on a UK-based population. Given that the Ontario population is more similar to that of the SPREE study⁵⁴ than that of Chaemsaitong et al.,⁵¹ we obtained our model parameters for screening performance outcomes from the SPREE study.⁵⁴ To allow for comparison of detection rates between the two screening strategies, the SPREE study⁵⁴ fixed the screen-positive rate at 10.3%. The predetermined screen-positive rate in the SPREE study⁵⁴ reflected the screen-positive rate of the FMF algorithm in the Ontario single-site feasibility study (currently unpublished) at 10.4%. We therefore applied the predetermined screen-positive rate to both strategies in our model.

We used the PPV, or the proportion of people who developed pre-eclampsia with delivery at less than 37 weeks' gestation among everyone who screened positive (high-risk), to determine the probability of this health outcome in pregnant people classified as high-risk under each screening strategy. We used the NPV, or the proportion of people who did not develop pre-eclampsia with delivery at less than 37 weeks' gestation of everyone who screened negative (low-risk), to determine the probability of this health outcome in pregnant people classified as low-risk under each screening strategy.

Using the total study population (n = 16,747), the number of observed cases of pre-eclampsia with delivery after less than 37 weeks' gestation (n = 142), the screen-positive rate, and the respective detection rates, we calculated the PPV and NPV for each screening strategy. Detection rates from the SPREE study⁵⁴ were 79.6% for the FMF algorithm and 44.1% for the NICE criteria (see the clinical evidence review). Using these outcome measures, we calculated that screening with the FMF algorithm yielded a PPV of 0.066 and a NPV of 0.998, and that screening using the NICE criteria yielded a PPV of 0.036 and a NPV of 0.995.

We estimated the probability of pre-eclampsia with delivery at less than 37 weeks' gestation in people who screened as high-risk and took low-dose ASA by multiplying the OR of developing pre-eclampsia with delivery at less than 37 weeks' gestation in the ASA versus placebo group from the ASPRE trial⁷⁷ and the probability of developing pre-eclampsia with delivery at less than 37 weeks' gestation among people at high risk who did not take ASA (or PPV) for each screening strategy. Using this method, we found that the probability of developing pre-eclampsia with delivery at less than 37 weeks' gestation in pregnant people who screened positive and took low-dose ASA was 0.025 (0.066×0.38) for the intervention arm and 0.014 (0.036×0.38) for the standard care arm.

Table 9: Clinical Inputs Used in the Economic Model

Model parameter	Probability, mean (SE) ^a	Distribution	Source
Probability of being screened			
Proportion of people who attended a prenatal visit in their first trimester	0.86	Fixed	BORN Ontario, 2013 ⁷¹
Screening uptake			
Standard care	0.5	Fixed	N. Okun, MD, written communication, March 2022
Intervention	0.85	Fixed	Ontario single-site feasibility study
ASA prophylaxis			
Physicians' ASA adherence rate			
Standard care	0.289	Beta (359, 883)	Guy et al, 2021 ⁴⁹
Intervention	0.99	Beta (393, 4)	Guy et al, 2021 ⁴⁹
Treatment effect of low-dose ASA prophylaxis			
Odds ratio	0.38 (0.138)	Log-normal (-0.97, 0.33)	Rolnik et al, 2017 ⁷⁷
Screening performance and probability of PE with delivery at less than 37 weeks' gestation			
Screen-positive rate	0.103	Fixed	Poon et al, 2020 ⁵⁴ (SPREE study)
Baseline risk (probability of PE with delivery < 37 wk in unscreened people)			
Standard care			
Probability of PE with delivery < 37 wk in people classified as high-risk who do not take ASA (PPV of NICE criteria)	0.036	Beta (63, 1,662)	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)

Model parameter	Probability, mean (SE) ^a	Distribution	Source
Probability of PE with delivery < 37 wk in people classified as high-risk who took ASA (PPV of NICE criteria × ASA treatment effect)	0.014	–	Calculated
Probability of PE with delivery < 37 wk in people classified as low-risk (1 – NPV of NICE criteria)	0.005	–	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)
NPV of NICE criteria	0.995	Beta (14,943, 79)	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)
Intervention			
Probability of PE with delivery < 37 wk in people classified as high-risk who do not take low-dose ASA (PPV of the FMF algorithm)	0.066	Beta (113, 1,612)	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)
Probability of PE with delivery < 37 wk in people classified as high-risk who took ASA (PPV of the FMF algorithm × ASA treatment effect)	0.025	–	Calculated
Probability of PE with delivery < 37 wk in people classified as low-risk (1 – NPV of the FMF algorithm)	0.002	–	Calculated
NPV of the FMF algorithm	0.998	Beta (14,993, 29)	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)

Abbreviations: ASA, acetylsalicylic acid; BORN, Better Outcomes Registry and Network; FMF, Fetal Medicine Foundation; NICE, National Institute of Health and Clinical Excellence; NPV, negative predictive value; PE, pre-eclampsia; PPV, positive predictive value; SE, standard error; SPREE, Screening Program for Preeclampsia Study.

^a Numbers might be inexact owing to rounding.

Cost Parameters

We derived our cost input parameters (Table 10) from the Ontario Health Insurance Plan (OHIP) schedule of benefits and fees, published literature, and preliminary results from an Ontario single-site feasibility study on predicting and preventing pre-eclampsia (unpublished at the time of writing of this report; N. Okun, MD, written communication, March 2022).

COSTS OF FIRST-TRIMESTER SCREENING PROGRAM FOR PRE-ECLAMPSIA

The cost of the population-wide FMF-based screening program includes the cost of additional markers that would be required as part of the screening program, such as MAP, UtA-PI, and the maternal serum pregnancy-associated marker PlGF. Other markers that are part of the population-wide FMF-based screening program are components of standard care that would remain the same. For instance, maternal medical and family history are currently taken as part of routine prenatal care.

We did not attribute additional costs associated with obtaining MAP measurements, because it is possible for them to be calculated from the systolic and diastolic blood pressure measurements currently taken as part of routine prenatal care. No billing code is currently associated with uterine-

artery Doppler ultrasonography. We therefore assumed that this cost would be similar to the cost of a fetal Doppler evaluation for middle cerebral artery or ductus venosus, which is another type of ultrasonography performed for complex pregnancies. Because this ultrasonography has established billing codes (J167 and J158),⁸⁹ we used it as a proxy for this cost in our analysis. We therefore estimated that uterine-artery Doppler ultrasonography would be \$111.75 (including technical and professional fees). We then derived the cost per PlGF test from an Ontario single-site feasibility study (currently unpublished), at \$22 per test. Using these markers, an online risk calculator based on the FMF algorithm can be used to calculate pre-eclampsia risk. This risk calculator is available for free at the FMF website (<https://fetalmedicine.org/>).

ADDITIONAL ULTRASONOGRAPHY COSTS FOR PREGNANT PEOPLE WHO SCREEN POSITIVE

Based on best clinical practice, additional ultrasound examinations should be performed as a baseline to monitor pregnant people who screen positive throughout the duration of their pregnancies (N. Okun, MD, written communication, March 2022). This includes one additional uterine-artery Doppler ultrasound examination at 22 and 24 weeks' gestation, followed by monthly ultrasound assessment of fetal growth until term (or an average of a further 3.5 additional fetal growth ultrasound examinations). We derived the cost of fetal growth ultrasonography from the OHIP schedule of benefits and fees, at \$49.65 per scan (including technical and professional fees). Altogether, the average cost of additional ultrasonography for pregnant people who screen positive under both strategies was estimated to be \$286 ($\$111.75 + [\$49.65 \times 3.5]$).

MATERNAL HEALTH CARE COSTS ATTRIBUTED TO PRE-ECLAMPSIA

We derived maternal health care costs associated with pre-eclampsia and uncomplicated pregnancies from a cost-of-illness study⁹⁰ that used primary case data in the United States to estimate medical costs associated with matched cohorts of people with pre-eclampsia and with uncomplicated pregnancies. Maternal medical costs included birth-related outcomes (i.e., at delivery) and frequency of adverse maternal outcomes during pregnancies such as renal failure, eclamptic seizure, thrombocytopenia, and severe intrapartum and postpartum hemorrhage.⁹⁰ This study⁹⁰ found that pregnancies in the pre-eclampsia cohort had a greater number of adverse events and caesarean deliveries (at 50%) than the uncomplicated cohort (at 29.6%). Mean maternal medical costs in the pre-eclampsia cohort were significantly higher than those in the uncomplicated cohort, at \$18,830 versus \$12,907 in 2022 Canadian dollars (after converting costs from 2015 USD and adjusting for inflation). Overall, we estimated that additional maternal health care costs attributed to pre-eclampsia were \$5,923.

NICU COSTS ATTRIBUTED TO PRETERM BIRTH

We derived neonatal costs associated with preterm birth from a Canadian study on the economic burden of premature births.⁹¹ This study⁹¹ reported the average cost of NICU stay stratified by gestational age for early preterm (less than 28 weeks), moderately preterm (28-32 weeks), and late preterm (33-36 weeks) infants. We obtained the average cost of NICU stay attributed to pre-eclampsia with delivery at less than 33 weeks' gestation by calculating the average NICU costs of infants born early and moderately preterm. We then obtained the average cost of NICU stay attributed to pre-eclampsia with delivery between 33 and 36 weeks directly from this Canadian study.⁹¹ After adjusting for inflation to 2022 Canadian dollars (using the Consumer Price Index for health and personal care), the average cost of NICU stay attributed to pregnancies with preterm birth from less than 33 weeks' gestation and from 33 to 36 weeks' gestation was \$52,805 and \$4,141, respectively.

We then estimated that approximately 42.25% of pregnant people with pre-eclampsia would deliver their baby at a gestational age of less than 33 weeks. This estimate was based on the proportion of pregnant people with pre-eclampsia who delivered at less than 34 weeks' gestation in the SPREE study.⁵⁴ We estimated that the average costs of NICU stay per pregnancy associated with pre-eclampsia when the infant was delivered at less than 37 weeks' gestation would be approximately \$24,702 ($[0.4225 \times \$52,805] + [0.5775 \times \$4,141]$).

COSTS FROM DISCHARGE TO 2 YEARS POST-DELIVERY

We further derived the average cost of health care resource utilization for preterm infants from discharge to 2 years post-delivery from the same Canadian study.⁹¹ These costs included inpatient and outpatient costs incurred between discharge and age 2 years. Similar to NICU costs, we obtained the average medical costs of an infant (from discharge to age 2 years) born at less than 33 weeks' gestation by calculating the average medical costs for infants who were early and moderately preterm. We then obtained the average medical costs for infants (from discharge to age 2 years) born between 33 and 36 weeks' gestation directly from this study.⁹¹ After adjusting for inflation to 2022 Canadian dollars and applying a discount of 1.5% to reflect society's preferences over time, the average medical costs attributed to infants (from discharge to age 2 years) who were born at less than 33 weeks' gestation and between 33 and 36 weeks' gestation was \$8,607 and \$2,419, respectively. Based on the estimate of the proportion of pregnant people with pre-eclampsia who would deliver their baby at a gestational age of less than 33 weeks, we calculated that average medical cost for infants (from discharge to age 2 years) born from pregnancies associated with pre-eclampsia and preterm birth would be approximately \$5,034 ($[0.4225 \times \$8,607] + [0.5775 \times \$2,419]$).

Last, we excluded the labour costs of routine prenatal care provided by general practitioners, midwives, and obstetricians, as these costs are identical under both strategies. Regardless of whether or not a person screened positive (high-risk) for pre-eclampsia, the health care provider they choose to oversee their prenatal care would not change until diagnosis of pre-eclampsia in late pregnancy (N. Okun, MD, phone communication, January 2022). In other words, responsibility for care could be transferred from a midwife or general practitioner to an obstetrician if pre-eclampsia were diagnosed from 20 weeks' gestation onward. We further excluded the cost of routine first-trimester dating ultrasonography and of routine second-trimester anatomical ultrasonography between 18 and 22 weeks' gestation, because they are also offered to all pregnant people in Ontario.^{92,93}

Table 10: Costs Used in the Economic Model

Variable	Total cost, mean (SE) ^a	Distribution	Source
Costs of population-wide FMF-based screening program			
Uterine artery Doppler ultrasonography ¹ (first trimester)	\$111.75 (28.00) ^b	Gamma (16, 6.98)	J158 and J167, OHIP (January 24, 2022) ⁸⁹ used as proxy ^c
PLGF Test	\$22	Fixed	Ontario single-site feasibility study
Additional ultrasound costs for pregnant people who screen positive (routine surveillance)			
Uterine-artery Doppler ultrasonography (second trimester)	\$111.75 (28.00) ^b	Gamma (16, 6.98)	J158 and J167, OHIP (January 24, 2022) ⁸⁹ used as proxy ^c
Fetal growth ultrasonography (average 3.5 examinations)	\$174.00	Fixed	J157, OHIP (January 24, 2022) ⁸⁹
Maternal health care costs attributed to PE			
Additional maternal health costs attributed to PE	\$5,923.00	–	Calculated
Maternal health costs associated with PE pregnancy ^d	\$18,830 (3,227) ^b	Gamma (16, 1,177)	Hao et al, 2019 ⁹⁰
Maternal health costs associated with uncomplicated pregnancy ^d	\$12,907 (4,708) ^b	Gamma (16, 807)	Hao et al, 2019 ⁹⁰
NICU costs attributed to preterm birth			
Average NICU stay associated with PE with delivery < 37 wk	\$24,702	–	Calculated
Average NICU stay for infants born at < 33 wk gestational age ^{e,f}	\$52,805 (13,201) ^b	Gamma (16, 3,300)	Johnston et al, 2014 ⁹¹
Average NICU stay for infants born at 33-36 wk gestational age ^e	\$4,141 (1,035) ^b	Gamma (16, 259)	Johnston et al, 2014 ⁹¹
Average costs from discharge to age 2 yr (discounted at 1.5%)	\$5,034	–	Calculated
Average costs from discharge to age 2 yr for infants born at < 33 wk gestational age ^{e,f}	\$8,607 (2,152) ^b	Gamma (16, 538)	Johnston et al, 2014 ⁹¹
Average costs from discharge to age 2 yr for infants born at 22-26 wk gestational age ^e	\$2,419 (605) ^b	Gamma (16, 151)	Johnston et al, 2014 ⁹¹

Abbreviations: FMF, Fetal Medicine Foundation; NICU, neonatal intensive care unit; OHIP, Ontario Health Insurance Plan; PE, pre-eclampsia; PLGF, placental growth factor; SE, standard error.

^a Figures might not be exact owing to rounding.

^b Assumed SE to be 25% of mean.

^c Currently OHIP has no billing code for uterine-artery Doppler ultrasonography. Fee codes J158 and JJ16 were used as proxies to approximate the cost of this cost component.

^d Converted costs from 2015 USD using purchasing power parities and adjusted for inflation to 2022 using the Consumer Price Index for health and personal care.

^e Adjusted for inflation from 2012 to 2022 using the Consumer Price Index for health and personal care.

^f Assumed 42.25% of pregnant people with PE will deliver their baby at gestational age less than 33 weeks. This estimate was based on the proportion of pregnant people with PE who delivered at less than 34 weeks' gestation in the Screening Programme for Preeclampsia (SPREE) study.⁵⁴

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

Our reference case and sensitivity analyses adhered to the CADTH guidelines⁸⁵ when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions. We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. When possible, we specified the distributions around input parameters using the mean and standard error. Selected cost parameters were characterized by gamma distributions; probabilities were characterized by beta distributions; and relative risks were characterized by log-normal distributions. We calculated mean costs with credible intervals and mean effect with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental effect with credible intervals, and ICERs for the population-wide FMF-based screening program versus standard care for pre-eclampsia.

Last, we presented the results of our probabilistic analysis in a scatter plot and also examined additional structural and parameter uncertainty by conducting several scenario analyses.

SCENARIO ANALYSES

We explored nine scenario analyses by modifying various parameter inputs and applying alternative assumptions (Table 11).

In scenario 1, we considered a screening strategy based on a reduced combination of biomarkers used by the FMF algorithm. Biomarkers used in this screening strategy included maternal risk factors, MAP, and PAPP-A. We explored this scenario because obtaining the full combination of biomarker measurements used in the FMF algorithm might be challenging in some health care regions across Ontario owing to access barriers and resource limitations. For instance, it might be more challenging to obtain UtA-PI measurements from pregnant people who live in rural or remote areas than from those who live in urban centres given the limited number of sonographers who service those areas. In addition, results from a PAPP-A serum test, which is currently part of aneuploidy screening in the first trimester, can be used in the FMF algorithm in lieu of the PIGF tests without requiring additional resources.³⁷

We obtained the screening performance of the screening strategy with a reduced combination of biomarkers from the SPREE study,⁵⁴ which found that the detection rate from using this reduced combination of markers was 53.5%. Using the total study population ($n = 16,747$), the number of observed pre-eclampsia cases with delivery at less than 37 weeks' gestation ($n = 142$), the screen-positive rate (10.3%), and the detection rate, we calculated that the PPV and NPV of the FMF algorithm when using a reduced combination of biomarkers would be 0.044 and 0.996, respectively. For this scenario, we also considered a reduced cost of screening owing to the reduced combination of biomarkers used. In other words, this analysis did not consider the cost of PIGF testing or UtA-PI.

In scenario 2, we explored an equity-related scenario analysis that considered the same screening strategy with a reduced combination of biomarkers, in addition to a lower screening uptake and a

reduced screening cost, including no additional ultrasound examinations for pregnant people who screened positive to account for the challenges of access barriers and resource limitations in rural or remote populations in Ontario. We obtained the screening uptake parameters from a population-based retrospective cohort study³⁷ that explored the rates of prenatal screening across Ontario. This study found that the first-trimester screening rate in rural areas was 24.9%, and that the ratio of pregnant people living in a rural versus urban areas who received screening was 0.64.

In scenario 3, we used a lower prevalence (0.4%, or 4 cases in 1,000 people) of pre-eclampsia with delivery at less than 37 weeks' gestation from an Ontario-based study¹⁶ to estimate the baseline risk and recalculate the screening performance of the FMF algorithm versus the NICE criteria. Specifically, we calculated the sensitivity and specificity of the FMF algorithm and the NICE criteria from the reference case to determine the new screen-positive rate, PPV, and NPV for the respective screening strategies using this lower prevalence rate. In this scenario, the screen-positive rate, PPV, and NPV were 9.99%, 0.032, and 0.999 for the intervention and 10.15%, 0.017, and 0.998 for standard care. It is important to note that the number of pre-eclampsia cases with delivery at less than 37 weeks' gestation in this Ontario-based study¹⁶ would likely be lower than the actual prevalence of this health outcome in the Ontario population. This is because the inclusion criterion of this study¹⁶ was singleton liveborn births from 24 weeks' gestation, and therefore it did not capture pre-eclampsia with delivery between 20 and 23 weeks' gestation.

We ran further scenarios that considered higher and lower screening uptake of both strategies (scenarios 4 and 5) and a higher physician adherence rate for prescribing ASA (scenario 6). We ran a scenario under a more cost-conservative assumption by not accounting for additional ultrasonography costs for pregnant people who screened positive (scenario 7) and a scenario that accounted for the cost of low-dose ASA prophylaxis, which is typically paid out-of-pocket (scenario 8).

Last, we ran a scenario that accounted for the operational costs of a population-wide FMF-based screening program in Ontario (scenario 9). We estimated that operational costs would be roughly \$16 per person screened, based on the current operational costs for aneuploidy screening in Ontario (S. Dougan, phone communication, June 2022). This estimate should be considered conservative, as it did not include costs associated with additional staff training, quality assurance support, and ongoing maintenance that could be required for some components of the FMF algorithm that are not part of aneuploidy screening, such as UtA-PI.

Table 11: Summary of Scenario Analyses

Parameter	Reference case ^a	Source	Scenario analysis ^a	Source
Scenario 1: Population-wide FMF-based screening program using a reduced combination of biomarkers (maternal factors, MAP, and PAPP-A)				
Probability of PE with delivery < 37 wk in people classified as high-risk who did not take low-dose ASA (PPV of the FMF algorithm)	0.066	Calculated from Poon et al, 2020 ⁵⁴	0.045	Calculated from Poon et al, 2020 ⁵⁴
Probability of PE with delivery < 37 wk in people classified as low-risk (1 - NPV of the FMF algorithm)	0.002	Calculated	0.004	Calculated
Probability of PE with delivery < 37 wk in people classified as high-risk who took low-dose ASA (PPV of the FMF algorithm × ASA treatment effect)	0.025	Calculated	0.017	Calculated
Uterine-artery Doppler ultrasound (first trimester)	\$111.75	OHIP (January 24, 2022) ⁸⁹ used as proxy	\$0	Assumption
PLGF test	\$22	Ontario single-site feasibility study	\$0	Assumption
Scenario 2: Rural/remote subpopulations (equity-related scenario)				
Screening uptake (standard care)	0.50	N. Okun, MD, written communication, March 2022	0.25	Hayeems et al, 2015 ³⁷
Screening uptake (the population-wide FMF-based screening program)	0.85	Ontario single-site feasibility study	0.54 (0.85 × 0.64)	Calculated from Hayeems et al, 2015 ³⁷
Additional ultrasonography for people who screen positive	\$286.00	OHIP (January 24, 2022) ⁸⁹	\$0	Assumption
Probability of PE with delivery < 37 wk in people classified as high-risk who did not take low-dose ASA (PPV of the FMF algorithm)	0.066	Calculated from Poon et al 2020 ⁵⁴ (SPREE study)	0.045	Calculated from Poon et al 2020 ⁵⁴ (SPREE study)
Probability of PE with delivery < 37 wk in people classified as low-risk (1 - NPV of the FMF algorithm)	0.002	Calculated	0.004	Calculated
Probability of PE with delivery < 37 wk in people classified as high-risk who took low-dose ASA (PPV of the FMF algorithm screening × ASA treatment effect)	0.025	Calculated	0.017	Calculated

Parameter	Reference case ^a	Source	Scenario analysis ^a	Source
Uterine-artery Doppler ultrasonography (first trimester)	\$111.75	OHIP (January 24, 2022) ⁸⁹ used as proxy	\$0	Assumption
PIGF test	\$22.00	Ontario single-site feasibility study	\$0	Assumption
Scenario 3: Lower baseline risk				
Baseline risk	0.008	Poon et al, 2020 ⁵⁴ (SPREE study)	0.004	Ray et al, 2016 ¹⁶
Standard care				
Probability of PE with delivery < 37 wk in people classified as high-risk who did not take ASA (PPV of NICE criteria)	0.036	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)	0.018	Calculated
Probability of PE with delivery < 37 wk in people classified as low-risk (1 - NPV of NICE criteria)	0.005	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)	0.002	Calculated
Intervention				
Probability of PE with delivery < 37 wk in people classified as high-risk who did not take low-dose ASA (PPV of the FMF algorithm)	0.066	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)	0.032	Calculated
Probability of PE with delivery < 37 wk in people classified as low-risk (1 - NPV of the FMF algorithm)	0.002	Calculated from Poon et al, 2020 ⁵⁴ (SPREE study)	0.001	Calculated
Scenario 4: Screening uptake at 100% in both strategies				
Standard care: proportion of pregnant people who were screened	0.50	N. Okun, MD, written communication, March 2022	1.0	Assumption
Intervention: proportion of pregnant people who were screened	0.85	Ontario single-site feasibility study	1.0	Assumption
Scenario 5: Screening uptake at 50% in both strategies				
Standard care: proportion of pregnant people who were screened	0.50	N. Okun, MD, written communication, March 2022	0.5	Assumption
Intervention: proportion of pregnant people who were screened	0.85	Ontario single-site feasibility study	0.5	Assumption

Parameter	Reference case ^a	Source	Scenario analysis ^a	Source
Scenario 6: Physician adherence with prescribing low-dose ASA prophylaxis at 100%				
Standard care	28.9%	Guy et al, 2021 ⁴⁹	100%	Assumption
Intervention	99%	Guy et al, 2021 ⁴⁹	100%	Assumption
Scenario 7: Not accounting for additional ultrasound costs for people who screen positive				
Additional ultrasonography for people who screen positive	\$286.00	OHIP (January 24, 2022) ⁸⁹	\$0	Assumption
Scenario 8: Accounting for low-dose ASA prophylaxis costs				
ASA (162 mg daily, 12-40 wk)	-	-	\$53.00 ^b	Ortved et al, 2019 ⁶⁷
Scenario 9: Accounting for operational costs of a screening program				
Cost per person screened	-	-	\$16.00	S. Dougan, phone communication, June 2022

Abbreviations: ASA, acetylsalicylic acid; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; NICE, National Institute of Health and Clinical Excellence; NPV, negative predictive value; OHIP, Ontario Health Insurance Plan; PAPP-A, pregnancy-associated plasma protein A; PE, pre-eclampsia; PlGF, plasma growth factor; PPV, positive predictive value; SPREE, Screening Programme for Preeclampsia.

^a Figures might not be exact owing to rounding.

^b Adjusted for inflation to 2022 using Consumer Price Index for health and personal care.

Results

Reference Case Analysis

For our estimated annual population of 140,500 pregnancies, total costs for the population-wide FMF-based screening program and standard care for pre-eclampsia were \$45.67 million (\$325/person) and \$44.39 million (\$316/person), respectively. Although the population-wide FMF-based screening program had a higher overall screening costs than standard care (at \$16.77 million vs. \$1.77 million) because of higher screening uptake, higher physician adherence with prescribing ASA, and higher screening costs (i.e., cost of PlGF, uterine-artery Doppler sonography), these costs were partially offset by the savings associated with cases of pre-eclampsia with delivery at less than 37 weeks' gestation prevented under the population-wide FMF-based screening program. For instance, the total costs of maternal and infant health care resource use attributed to pre-eclampsia and preterm birth was lower with the population-wide FMF-based screening program (at \$4.70 million and \$24.21 million, respectively) than with standard care (at \$6.92 million and \$35.70 million, respectively). Overall, the population-wide FMF-based screening program had an incremental cost of \$1.28 million compared with standard care.

The population-wide FMF-based screening program resulted in an estimated 781 cases of pre-eclampsia with delivery at less than 37 weeks' gestation, and standard care resulted in an estimated 1,152 cases of pre-eclampsia with delivery at less than 37 weeks' gestation. This screening program therefore could prevent 371 cases of pre-eclampsia with delivery at less than 37 weeks' gestation yearly compared with standard care.

Overall, compared with standard care, the population-wide FMF-based screening program had an ICER of \$3,446 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented. Table 12 provides results of the reference case analysis of our economic model.

Table 12: Reference Case Analysis Results

Parameter	Population-wide FMF-based screening program ^a	Standard care ^a
Average total costs, \$ millions (95% CrI)	\$45.67 (\$31.44 to \$63.48)	\$44.39 (\$26.71 to \$64.65)
Screening costs (95% CrI) ^b	\$16.77 (\$11.74 to \$23.25)	\$1.77 (\$1.47 to \$2.14)
Maternal health care costs attributed to PE (95% CrI) ^c	\$4.70 (-\$3.65 to \$14.49)	\$6.92 (-\$5.48 to \$20.35) ^c
Infant health care costs attributed to preterm birth (95% CrI)	\$24.21 (\$14.79 to \$37.63)	\$35.70 (\$23.24 to \$51.60)
Average total effects (95% CrI)	781 (615 to 1,035) PE with delivery < 37 wk	1,152 (1,020 to 1,293) PE with delivery < 37 wk
Incremental costs, \$ millions ^b (95% CrI) ^d	\$1.28 (-\$10.33 to \$12.53) ^c	
Screening costs (95% CrI)	\$14.99 (\$10.00 to \$21.50)	
Maternal health care costs attributed to PE (95% CrI) ^d	-\$2.22 (-\$7.19 to \$1.74) ^c	
Infant health care costs attributed to preterm birth (95% CrI) ^d	-\$11.49 (-\$19.75 to \$3.75) ^c	
Incremental effects (95% CrI) ^e	371 (128 to 552) PE with delivery < 37 wk prevented	
ICER (\$/PE with delivery < 37 wk prevented)	\$3,446/PE with delivery < 37 wk prevented	

Abbreviations: CrI, credible interval; FMF, Fetal Medicine Foundation; ICER, incremental cost-effectiveness ratio; PE, pre-eclampsia.

^a Results might appear inexact owing to rounding. Reference case results were derived from probabilistic analysis by running 5,000 simulations.

^b For the intervention arm, screening costs include cost of placental growth factor, uterine-artery Doppler ultrasonography, and additional ultrasonography for people who screen positive. For the standard care arm, screening costs include additional ultrasonography for people who screen positive.

^c Incremental cost = average cost (strategy B) - average cost (strategy A).

^d Negative costs indicate savings.

^e Incremental effect = average effect (strategy B) - average effect (strategy A).

Sensitivity Analysis

We conducted a cost-effectiveness analysis using the natural unit of pre-eclampsia with delivery at less than 37 weeks' gestation prevented rather than quality-adjusted life-years. Results of the probabilistic analysis are presented in a scatter plot in Figure 5. The results of our probabilistic analysis showed that 99.56% of simulations found the population-wide FMF-based screening program prevented more cases of pre-eclampsia with delivery at less than 37 weeks' gestation than standard care. Of these simulations, 58.80% also found the population-wide FMF-based screening program to be more costly, and 40.76% found it to be less costly than standard care.



Figure 5: Scatter Plot of Probabilistic Results

Scatter plot of probabilistic results with 5,000 iterations of the incremental cost-effectiveness ratio between the intervention and comparator arms. Each dot represents the joint distribution of incremental cost and effectiveness for one simulation.

Scenario Analyses

In scenario 1, we found that, while a population-wide FMF-based screening program that used a reduced combination of biomarkers had resulted in lower incremental effects than the FMF algorithm with the full set of biomarkers, when compared with standard care (at 236 vs. 371 cases of pre-eclampsia with delivery at less than 37 weeks' gestation prevented), it became the dominant strategy. Further, when we expanded this previous scenario in scenario 2 to also consider a lower screening uptake rate and reduced screening costs (including no additional ultrasound examinations for those who screened positive), similar results were produced. In this equity-related scenario (scenario 2), we found that the population-wide FMF-based screening program with a reduced combination of biomarkers resulted in a further reduced incremental effect compared with our reference case (at 156 vs. 371 cases of pre-eclampsia with delivery at less than 37 weeks' gestation prevented), but it also became the dominant strategy (Table 13).

Our scenario analyses also showed that some parameters affected the results of our reference case more substantially than others. For instance, assuming a lower prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation in scenario 3 resulted in an ICER of \$48,814 per case of

pre-eclampsia with delivery at less than 37 weeks' gestation prevented. The change in reference case results in this scenario was greater than varying parameters such as screening uptake (in scenarios 4 and 5), which resulted in ICERs of \$3,027 and \$3,065 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented, respectively, and physician adherence with prescribing ASA (scenario 6), which resulted in an ICER of \$16,850 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented.

Scenario 7 resulted in reduced incremental costs per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented, as it assumed lower screening costs than the reference case. Under this scenario, when no additional ultrasound costs were considered for pregnant people who screened positive, the incremental cost of the intervention was \$0.16 million, corresponding to an ICER of \$432 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented.

Last, scenarios 8 and 9 resulted in higher incremental costs per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented, as these scenarios accounted for additional screening cost components. For instance, when the cost of ASA prophylaxis was incorporated into our analysis (scenario 8), the incremental cost of the intervention was \$1.75 million, corresponding to an ICER of \$4,681 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented. When program operational costs were incorporated into our analysis (scenario 9), the incremental cost of the intervention was \$2.87 million, corresponding to an ICER of \$7,691 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented.

Table 13: Scenario Analysis Results

Strategy	Average total costs, \$ millions ^{a,b}			Average total effects ^{a,b}			
	Population-wide FMF-based screening program	Standard care	Incremental cost, \$ millions ^{a,b,d}	Population-wide FMF-based screening program	Standard care	Incremental effect ^{a,b,e}	ICER (\$/PE prevented) ^{a,b}
Reference case	45.67	44.39	1.28	781 PE	1,152 PE	371 PE prevented	3,446/PE prevented
Scenario 1: Population-wide FMF-based screening program using a reduced combination of biomarkers	36.84	44.28	-7.43	917 PE	1,153 PE	236 PE prevented	Dominant
Scenario 2: Rural/remote populations (equity-related scenario)	39.33	44.04	-4.71	1,016 PE	1,172 PE	156 PE prevented	Dominant
Scenario 3: Lower baseline risk of PE ^e	30.16	21.60	8.57	368 PE	543 PE	176 PE prevented	48,814/PE prevented
Scenario 4: Screening uptake at 100% in both strategies	45.73	44.51	1.23	707 PE	1,112 PE	405 PE prevented	3,027/PE prevented
Scenario 5: Screening uptake at 50% in both strategies	44.87	44.25	0.62	951 PE	1,052 PE	202 PE prevented	3,065/PE prevented
Scenario 6: Physician adherence with prescribing low-dose ASA prophylaxis at 100%	45.38	40.66	0.62	777 PE	1,057 PE	280 PE prevented	16,850/PE prevented
Scenario 7: Not accounting for additional ultrasound costs for people who screen positive	42.49	42.33	0.16	783 PE	1,154 PE	370 PE prevented	432/PE prevented
Scenario 8: Accounting for low-dose ASA prophylaxis costs	45.88	44.13	1.75	780 PE	1,153 PE	373 PE prevented	4,681/PE prevented
Scenario 9: Accounting for program operational costs	47.11	44.24	2.87	779 PE	1,153 PE	373 PE prevented	7,691/PE prevented

Abbreviations: ASA, acetylsalicylic acid; FMF, Fetal Medicine Foundation; ICER, incremental cost-effectiveness ratio; PE, pre-eclampsia.

^a Results might appear inexact owing to rounding.

^b PE with delivery less than 37 wk.

^c Incremental cost = average cost (strategy B) – average cost (strategy A).

^d Negative costs indicate savings.

^e Incremental effect = average effect (strategy B) – average effect (strategy A).

Discussion

Our reference case results showed that, despite being associated with higher screening costs, the overall costs of the population-wide FMF-based screening program were partially offset by the savings associated with preventing cases of pre-eclampsia with delivery at less than 37 weeks' gestation. This is because each case of pre-eclampsia with delivery at less than 37 weeks' gestation was associated with substantial maternal and infant health care resource use. For instance, every pregnancy for which pre-eclampsia with delivery at less than 37 weeks' gestation is averted attributes to \$35,659 (\$5,923 in maternal health care use and \$29,735 in average infant health care use) in cost savings.

In scenarios 1 and 2, we varied parameters to consider using fewer biomarkers in the population-wide FMF-based screening program. This screening strategy with a reduced combination of biomarkers does not require UtA-PI measurements, which could be challenging to obtain, because rural and remote regions of the province have limited access to ultrasound services.⁹⁴ Notably, we found that, although this screening strategy had lower screening performance than the full combination of biomarkers, and in turn prevented fewer pre-eclampsia cases with delivery at less than 37 weeks' gestation than the reference case, the strategy remained more attractive than standard care. This finding demonstrated that, even with a reduced combination of biomarkers, which could be most feasible in rural and remote regions of Ontario, the population-wide FMF-based screening program was still more effective than standard care. It is important to note that the driving factors behind the incremental cost savings in scenarios 1 and 2 were owing to the exclusion of measurements from the uterine-artery Doppler sonography and the PlGF test, so the additional costs of these markers were not applied to the intervention arm of these two scenarios.

Last, we also identified the prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation as the key driver of our results. For instance, when we assumed a lower rate of this health outcome in our target population (at 4 cases per 1,000 in scenario 3), the incremental cost increased from \$1.28 million in the reference case to \$8.57 million. On the other hand, the incremental effect was reduced from 371 to 176 pre-eclampsia cases with delivery at less than 37 weeks' gestation prevented compared with standard care. However, although we obtained the disease prevalence in this scenario from an Ontario-based study,¹⁶ the study reported outcomes for people with pre-eclampsia who delivered between 24 and 36 weeks' gestation, and did not capture those with pre-eclampsia who delivered between 20 and 23 weeks' gestation. This scenario could, therefore, underestimate the actual prevalence of pre-eclampsia with delivery at less than 37 weeks' gestation in Ontario. As such, the rate of pre-eclampsia with delivery at less than 37 weeks' gestation (at 8 cases per 1,000) used in the reference case was considered more reasonable for this parameter. Nevertheless, scenario 3 found that a lower prevalence of this health outcome resulted in an ICER of \$48,814 per case of pre-eclampsia with delivery at less than 37 weeks' gestation prevented.

Equity Issues

Implementation of the population-wide FMF-based screening program could reduce health inequities in pregnant people from groups most impacted by social determinants of health, such as Black and Indigenous communities, who are disproportionately affected by pre-eclampsia. This is because the current standard of using clinical guideline criteria for assessing pre-eclampsia risk based on maternal characteristics alone does not take maternal ethnicity into consideration. However, the rate of pre-eclampsia with delivery at less than 37 weeks' gestation is higher in these underrepresented groups than in pregnant people of European descent.⁹⁵ In contrast, the FMF

algorithm incorporates maternal ethnicity to adjust for their risk. This, along with its superior detection rates compared with standard care, could help reduce health disparities in these disadvantaged groups. However, implementation of a population-wide FMF-based screening program should ensure that all providers of prenatal care can order the PLGF test.

Strengths and Limitations

Our primary economic evaluation provides comprehensive cost-effectiveness analyses of the FMF based screening program versus opportunistic screening using maternal factors alone from the perspective of the Ontario Ministry of Health. To ensure the quality of evidence used, we derived key clinical parameters from our clinical evidence review, which included assessment of the quality of evidence. Our analysis further accounted for the screening performance of each screening strategy to more accurately reflect the clinical pathway of pregnant people who undergo pre-eclampsia screening. The screening performance of each screening strategy was accounted for in only two^{65,70} of the five studies in our economic evidence review.

Moreover, we obtained several key parameter inputs from local sources. For instance, we obtained the average cost of a NICU stay and the average medical costs accrued by an infant from discharge to age 2 years associated with preterm pregnancy from a Canadian study.⁹¹ Because this was the largest cost component in our analysis, it was important that this cost was directly applicable to Ontario. We also obtained both the likelihood of attending a prenatal care visit in the first trimester and screening uptake of a population-wide screening program from Ontario sources. Although we based our estimate of the current level of opportunistic screening of pre-eclampsia in the province on expert clinical opinion, this estimate was considered reasonable, because another Ontario-based study³⁷ had also found that 50% of pregnant people received prenatal screening in the first trimester.

Most notably, we included an equity-related scenario (scenario 2) to evaluate the cost-effectiveness of the population-wide FMF-based screening program compared with standard care for pre-eclampsia in rural or remote populations of Ontario. While all pregnant people (with singleton pregnancies) in Ontario are eligible to be screened for early risk of pre-eclampsia under a screening program, we acknowledge that there are geographic disparities in access to and availability of health care resources between those who live in rural and urban areas.⁹⁴ It might not be feasible for people in rural and remote regions of the province to obtain the full combination of biomarkers used by the FMF algorithm, particularly uterine-artery Doppler sonography measurements. Our equity-related scenario (scenario 2) therefore not only applied the screening performance of the FMF algorithm based on a reduced combination of biomarkers, but also varied our parameters to reflect local trends in the screening uptake of other prenatal screening programs in rural Ontario. These results could provide important insight to a decision-maker considering implementation of the population-wide FMF-based screening program.

Some limitations to our analysis should be noted. First, we determined the baseline risk of pre-eclampsia with delivery at less than 37 weeks' gestation in our model from an UK study,⁵⁴ because we were unable to obtain the rate of this health outcome in Ontario. Despite this, the baseline risk of pre-eclampsia with delivery at less than 37 weeks' gestation assumed in our model (at 8 cases per 1,000) is considered reasonable, as the prevalence of pre-eclampsia overall (with delivery before, at, and after 37 weeks) was 11.5 per 1,000 in Canada.¹⁵

Second, we did not identify any published Canadian costs on maternal health care resource utilization attributed to pre-eclampsia. We derived these costs from a US costing study.⁹⁰ However, we accounted for this uncertainty by assuming a standard error of this cost parameter at 25% of the mean when we ran our probabilistic analysis in the reference case.

Third, we applied predetermined screen-positive rates (10.3%) to both the FMF algorithm and standard care screening in our model. These rates were fixed by the SPREE study⁵⁴ to allow comparison of the detection rates between the two screening strategies. The predetermined screen-positive rate in the SPREE study⁵⁴ reflected the screen-positive rate of the FMF algorithm in the Ontario single-site feasibility study (currently unpublished) at 10.4%.

We also did not explore a long-term time horizon. There could be potential downstream cost savings over the long term, as pre-eclampsia is associated with lifelong health impacts, such as increased risk of cardiovascular disease in the pregnant person and increased risk of developing various diseases in the offspring, including stroke, hypertension, and type 2 diabetes.⁸¹⁻⁸⁴ Last, we applied a public payer perspective in our analysis, and therefore did not consider indirect costs, such as productivity loss and patients' out-of-pocket costs associated with pre-eclampsia and preterm birth. Given these last two limitations, our results should be considered conservative.

Conclusions

Our cost-effectiveness analysis showed that, compared with standard care, a population-wide FMF-based screening program would prevent 371 cases of pre-eclampsia with delivery at less than 37 weeks' gestation and cost an additional \$1.28 million in Ontario each year, resulting in an ICER of \$3,446 per prevented case of pre-eclampsia with delivery at less than 37 weeks. These results were most sensitive to the prevalence of this health outcome in the general population. Notably, we found that although a reduced combination of biomarkers from the FMF algorithm resulted in decreased screening performance and fewer cases prevented of pre-eclampsia with delivery at less than 37 weeks' gestation compared with the reference case, screening with the FMF algorithm still remained more attractive than standard care.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding a population-wide screening program for pre-eclampsia that uses a multiple-marker algorithm for all pregnant people (with singleton pregnancies) within the gestational age of 11⁺⁰ weeks and 13⁺⁶ weeks in Ontario?

Methods

Analytic Framework

We estimated the budget impact of publicly funding a population-wide screening program for pre-eclampsia (the Fetal Medicine Foundation [FMF]-based screening program) using the cost difference between two scenarios: 1) no public funding for the FMF-based screening program (the current scenario) and 2) public funding for the screening program (the new scenario). Figure 6 presents the budget impact model schematic.

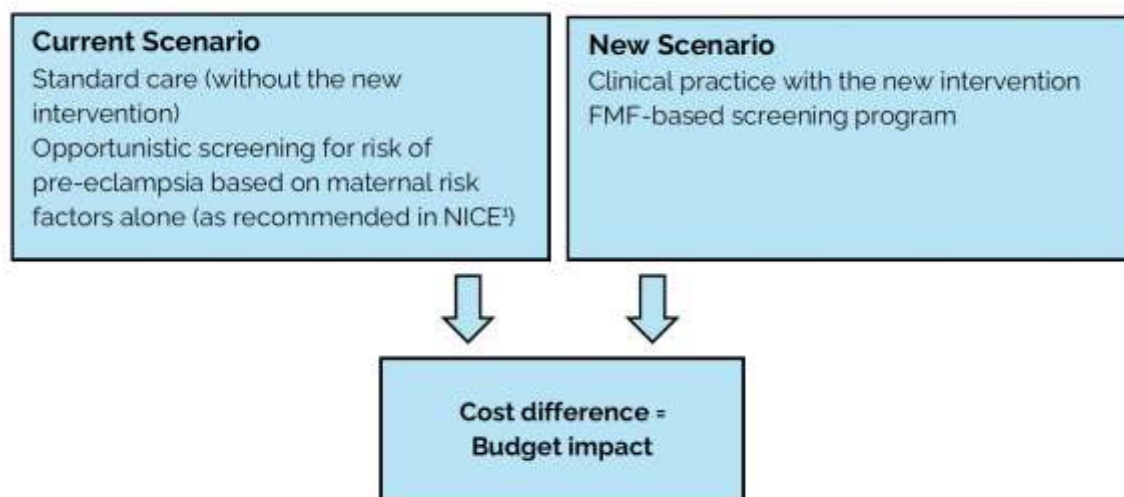


Figure 6: Schematic Model of Budget Impact

Schematic model of budget impact of current scenario, which involves standard care (without the new intervention) versus new scenario, which involves the population-wide FMF-based screening program. The cost difference between these scenarios gives us the budget impact.

Abbreviations: FMF, Fetal Medicine Foundation; NICE, National Institute for Health and Care Excellence.

Key Assumptions

- We assumed that the annual number of pregnancies ($n = 140,500$), proportion of pregnant people who attend a prenatal care visit in their first trimester, screening uptake, and physician adherence with prescribing low-dose ASA prophylaxis is the same as our model-based economic evaluation
- For simplicity, we assumed that these parameters would remain constant over the next 5 years

Target Population

We estimated our target population using both administrative and published data from the literature. Using the reported number of live births ($n = 140,500$) in Ontario in 2019 from Statistics Canada⁸⁷ and the proportion of pregnant people who initiate prenatal care in the first trimester (at 86%) from BORN,⁷¹ we calculated approximately 120,830 persons would be eligible for the population-wide FMF-based screening program in Ontario every year.

Current Intervention Mix

In the current scenario, the standard care to predict risk of pre-eclampsia among pregnant people in the first trimester is based on maternal risk factors alone, using criteria recommended by National Institute for Health and Care Excellence (NICE) guidelines or other authoritative medical or health organizations, such as the Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists (ACOG).⁷³⁻⁷⁵ People classified as high-risk for pre eclampsia are prescribed low-dose ASA as a preventive measure, to be taken daily and initiated at 16 weeks' gestation or less. People who screen positive will also receive additional ultrasound examinations throughout their second and third trimesters as part of routine surveillance. While screening for pre-eclampsia is recommended as part of routine prenatal care, in practice, it is currently done opportunistically. Clinical practice varies across Ontario.⁶⁷

Uptake of the New Intervention and New Intervention Mix

In the new scenario, standard care is expanded to the population-wide FMF-based screening program, which uses a combination of maternal factors, biophysical measurements (i.e., mean arterial pressure [MAP], uterine artery pulsatility index [UtA-PI]), and biochemical biomarkers (i.e., placental growth factor [PLGF]) taken between 11^{to} 13^{to} 16 weeks' gestation. People at high risk for pre-eclampsia will be prescribed low-dose ASA as a preventive measure, to be taken daily and initiated at 16 weeks' gestation or earlier. People who screen positive will also receive additional ultrasound examinations throughout their second and third trimesters as part of routine surveillance. Additional markers that would be required as part of first-trimester pre-eclampsia screening include the following:

- MAP: this measurement is not normally recorded by health care providers, but it can be calculated from systolic and diastolic blood pressure values
- UtA-PI: this measurement is taken via transabdominal ultrasonography by a qualified sonographer. The mean is calculated by taking the average measurement in the left and right uterine arteries.³¹ This measurement is not currently calculated in the first trimester as part of standard care
- Maternal serum pregnancy-associated marker PLGF: based on existing infrastructure, we expect that all PLGF serum tests will be sent and analyzed at the three centralized laboratories where aneuploidy testing takes place as part of the enhanced First Trimester Screening program (N. Okun, MD, phone communication, March 2022). The enhanced First Trimester Screening program provides prenatal genetic testing for trisomy 21 (Down syndrome) and trisomy 18 (Edwards syndrome) and is optional for all pregnant people in Ontario⁹⁶

Other components of standard care remain the same for the new scenario, including maternal risk factors, where maternal medical and obstetric characteristics and family history are routinely recorded as part of monitoring maternal and fetal health for the duration of the pregnancy.

We estimated the uptake of the population-wide FMF-based screening program based on the preliminary results of an Ontario single-site feasibility study on the prediction and prevention of early pre-eclampsia (currently unpublished).

Resources and Costs

We included both health technology-associated (screening program costs) and disease-associated resources and costs (all health care costs). For the health technology-associated (or screening-associated) resource use and costs, we included the mean costs associated with the population-wide FMF-based screening program (i.e., uterine-artery Doppler ultrasonography, PlGF, and additional ultrasound examinations for people who screened positive). For disease-associated costs, we ran the cost-effectiveness analyses previously described over the time horizon of the budget impact analysis (without discounting) to obtain relevant costs.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

In addition to the reference case, we also calculated the budget impact in several scenario analyses, including varying the parameters for uptake rate, the proportion of pregnant people who attended a prenatal care visit in the first trimester, and the costs associated with the population-wide FMF-based screening program. In total, we conducted the following five scenarios:

- Uptake rate of the population-wide FMF-based screening program was 100%
- Proportion of pregnant people who initiated their prenatal care in the first trimester and uptake rate of the population-wide FMF-based screening program were both 100%
- Not accounting for additional ultrasound costs for people who screened positive
- Accounting for low-dose ASA prophylaxis costs
- Accounting for program operational costs

Results

Reference Case

Table 14 summarizes the total costs associated with the population-wide FMF-based screening program for all singleton pregnancies over the next 5 years. The annual budget impact ranged from an additional \$1.23 million in year 1 to \$3.56 million in year 5, and the total 5-year budget impact was an additional \$8.50 million. When we accounted for only the direct costs of the screening program, the annual budget impact was an additional \$14.92 million, and the total 5-year budget impact was an additional \$74.58 million.

Table 14: Budget Impact Analysis Results—Reference Case

Scenario ^a	Budget impact, \$ millions ^{b,c}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^d
Current scenario	44.34	44.34	44.34	44.34	37.08	214.43
New scenario	45.57	45.57	45.57	45.57	40.65	222.92
Budget impact						
All health care costs	1.23	1.23	1.23	1.23	3.56	8.50
Screening costs only ^d	14.92	14.92	14.92	14.92	14.92	74.58

^a Costs were calculated using the mean cost from the probabilistic results of the primary economic evaluation.

^b In 2022 Canadian dollars.

^c Results might appear inexact owing to rounding.

^d Cost of the population-wide FMF-based screening program alone includes testing for placental growth factor, uterine artery pulsatility index, and additional ultrasonography for people who screen positive.

Sensitivity Analysis

Table 15 summarizes the results of the five scenario analyses conducted for the budget impact analysis of publicly funding the population-wide FMF-based screening program in Ontario. Compared with the reference case, scenarios that considered an increase in the number of people screened resulted in a higher budget impact. For instance, assuming a 100% uptake rate in population-wide pre-eclampsia screening (scenario 1) resulted in additional costs of \$1.29 million in year 1 to \$4.10 million in year 5. When this scenario was expanded to also assume that the proportion of pregnant people who attended a prenatal care visit in the first trimester was 100% (scenario 2), the annual cost was further increased to \$1.84 million in year 1 to \$5.04 million in year 5.

Scenarios that considered any increase or decrease in the cost of screening program components in turn resulted in a higher or lower budget impact, respectively. For instance, when we assumed no additional ultrasonography costs for people who screened positive (scenario 3), the annual cost was reduced to \$0.13 million in year 1 to \$2.43 million in year 5. On the other hand, when we incorporated low-dose ASA prophylaxis costs (scenario 4) and operational costs for the program (scenario 5) in our analyses, the annual budget impact increased to \$1.71 and \$2.82 million in year 1 to \$4.07 and \$5.17 million in year 5, respectively.

Table 15: Budget Impact Analysis Results—Sensitivity Analysis

Scenario	Budget impact, \$ millions ^{a,b}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Reference case						
Budget impact	1.23	1.23	1.23	1.23	3.56	8.50
Screening costs	14.92	14.92	14.92	14.92	14.92	74.58
Scenario 1: Uptake rate of the population-wide FMF-based screening program was 100%						
Budget impact	1.29	1.29	1.29	1.29	4.10	9.24
Screening costs	17.79	17.79	17.79	17.79	17.79	88.97
Scenario 2: Proportion of pregnant people who initiated their prenatal care in the first trimester and uptake rate of the population-wide FMF-based screening program were 100%						
Budget impact	1.84	1.84	1.84	1.84	5.04	12.40
Screening costs	20.81	20.81	20.81	20.81	20.81	104.04
Scenario 3: No additional ultrasonography for people who screened positive						
Budget impact	0.13	0.13	0.13	0.13	2.43	2.94
Screening costs	13.75	13.75	13.75	13.75	13.75	68.74
Scenario 4: Accounting for low-dose ASA prophylaxis costs						
Budget impact	1.71	1.71	1.71	1.71	4.07	10.91
Screening costs	15.42	15.42	15.42	15.42	15.42	77.08
Scenario 5: Accounting for operational costs of the program						
Budget impact	2.83	2.83	2.83	2.83	5.17	16.51
Screening costs	16.61	16.61	16.61	16.61	16.61	83.06

Abbreviation: ASA, acetylsalicylic acid; FMF, Fetal Medicine Foundation.

^a In 2022 Canadian dollars.

^b Results might appear inexact owing to rounding.

Discussion

The population-wide FMF-based screening program is associated with additional costs that are partially offset by the cost savings of preventing additional cases of pre-eclampsia with delivery at less than 37 weeks' gestation. This is apparent in the difference between the budget impact of disease-associated resources and costs (which resulted in annual costs of \$1.23 million in year 1 to \$3.56 million in year 5) and the budget impact of screening-associated resources and costs (which resulted in additional annual costs of \$14.92 million). When we accounted for a greater proportion of pregnant people to undertake screening (i.e., scenarios 1 and 2), the annual budget impact of both disease-associated and screening-associated resources and costs increased because of the program costs associated with each additional person who is screened. On the other hand, any reduction or increase to the cost of screening program components (scenarios 3, 4, and 5) would result in a lower or higher budget impact, respectively, in both the disease-associated and the screening-associated budget impact.

Strengths and Limitations

The estimates for our budget impact analysis were derived from running our cost-effectiveness analysis, which obtained its key parameters from the clinical evidence review as well as from several Canadian sources, including an Ontario single-site feasibility study (currently unpublished). Further, we validated our assumptions and estimates with clinical experts who have expertise in hypertension disorders during pregnancy in Ontario.

Our budget impact analyses assumed that uptake of the population-wide FMF-based screening program and ease of obtaining the full combination of biomarkers used in the FMF algorithm would be consistent across the province. We therefore did not consider that uptake of the population-wide FMF-based screening program could be lower in rural and remote regions of Ontario, or that a reduced combination of biomarkers might also be used in these regions under the screening program owing to access barriers and resource limitations. However, it is important to note that access to a population-wide screening program for pre-eclampsia might not be equitable across the province. The access barriers and the challenges around the availability of health resources need to be addressed to ensure that geographic disparities in maternal health do not continue to persist under a new province-wide prenatal screening program.

We also assumed that the number of pregnancies would remain stable over the next 5 years. We made this simplifying assumption because, although the COVID-19 pandemic has had an overall negative impact on fertility rates in Canada, the potential duration of this impact or whether this will continue to be a long-standing trend in Canada is currently unknown.⁹⁷ As such, there is some uncertainty surrounding the annual projected target population for the population-wide FMF-based screening program in our analyses.

Last, we did not include the initial implementation cost of establishing the population-wide FMF-based screening program. Accounting for these upfront costs could result in a higher budget impact in the first few years of implementing the screening program, and cost savings in later years.

Conclusions

We estimated that publicly funding the FMF-based screening program in Ontario would lead to an additional \$1.23 million in year 1 to \$3.56 million in year 5, for a total of \$8.50 million over the next 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience with pre-eclampsia as well as the preferences and perceptions of patients and family members of the population-wide FMF-based screening program.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).⁹⁸⁻¹⁰⁰ Additionally, lived experience can provide information and perspectives on the implications of ethical and social values on health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we might speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with lived experience of pre-eclampsia and may have undergone first-trimester screening for pre-eclampsia using the Fetal Medicine Foundation (FMF) algorithm. Ontario Health sought direct engagement with people who have lived experience with pre-eclampsia through interviews and written responses.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with pre-eclampsia and of their family members. We engaged people via phone interviews and through written submissions.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with pre-eclampsia, as well as those of their families.¹⁰¹ Additionally, a few people asked to submit written responses, as their schedules did not permit time for an interview. The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of these methods.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,¹⁰²⁻¹⁰⁵ which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed.

We approached a variety of partner organizations, to spread the word about this engagement activity and to contact people with pre-eclampsia and family members.

To explore equity issues related to inequities of access to screening programs and pregnancy care, we also reached out to community organizations to help us speak to members of specific populations affected by pre-eclampsia and pre-eclampsia screening.

Inclusion Criteria

We sought to speak with adults with lived experience of pre-eclampsia and various treatments. Participants did not need to have direct experience with pre-eclampsia to participate.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 17 people, including 15 with lived experience of pre-eclampsia and two family members. All participants had completed their pregnancy or were family members of those who had completed their pregnancies. We did not speak to any participants who were currently pregnant.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 6) if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 15 to 35 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.¹⁰⁶ Questions focused on the impact of pre-eclampsia on the quality of life of people, their experiences with treatments to manage or treat pre-eclampsia, and their perceptions of the benefits or limitations of first-trimester screening using the FMF algorithm. For family members, questions focused on their perceptions of the impact of pre-eclampsia and treatments on the quality of life of the person, as well as effects of the person's health condition and treatments on the family members themselves. See Appendix 7 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.^{107,108} We used the qualitative data analysis software program NVivo¹⁰⁹ to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of pre-eclampsia and treatments on the people with pre-eclampsia and family members we interviewed.

Results

AWARENESS OF PRE-ECLAMPSIA

Participants reported a variety of pre-existing knowledge around pre-eclampsia before their pregnancies or the pregnancies of family members. Some participants reported having little background medical knowledge; pre-eclampsia was simply unknown to them before they got pregnant. This was reported particularly in people whose pregnancy had occurred many years ago—they thought that little information was provided ahead of the pregnancy, and they did not feel well informed about such risks as pre-eclampsia:

My only education was that book at the time, What to Expect When You're Expecting, so no education from health care providers at all. [T]hey didn't say much, and they didn't ever tell me anything.

No, I didn't really know much about it going into pregnancy because ... I just didn't think it would affect me, to be honest—which is a stupid mindset looking back. Or not a stupid mindset, but a naive mindset.

Well, that's probably my biggest advocacy [now], the education and awareness. Because honestly, I didn't really have any, and my daughter and I really didn't have any awareness.

Other participants reported that they worked in a medical field, such as nursing. As such, they reported some general awareness of pre-eclampsia through their professional training or education, but some acknowledged that they did not necessarily transfer and apply this information directly to their own pregnancy:

I was aware of [pre-eclampsia] due to my background's nursing, but ... in the world of being a health care provider, you don't necessarily translate your knowledge to what's applicable for yourself. Do you know what I mean? So I think that gets disjointed, actually. So I was aware of it, but it wasn't on my radar to really watch closely.

I had some knowledge of it only because I am a nurse and I went to nursing school, but I did not do labour and delivery or any of that kind of thing. So it was very vague in my mind from when I had gone to school. Had I not studied nursing, it is not something that I knew about from the pregnancy books or anything like that. I did not have any knowledge and I did not have any high blood pressure, anything like that already existing. So I ... had no idea that this would be something that I could potentially ever experience.

Still other participants felt well versed in pre-eclampsia, reporting that their knowledge came from their own educational preparation for pregnancy, from family or friends who might have had experience with pre-eclampsia directly, or from their health care providers:

I know a lot about pre-eclampsia. I actually studied preterm labour in my master's degree and our lab specifically studied pre-eclampsia (that wasn't the focus of my project, but it was talked about often and was a topic in many of my courses in grad school and undergrad). So it was definitely something I was concerned with and thinking about during my pregnancies.

I knew about pre-eclampsia because my cousin had it with her first pregnancy in 2018, with no history of blood pressure issues. I knew that it leads to increased BP and water retention and can result in the baby needing to come early, which is what happened with my niece.

Yeah, pre-eclampsia was [on my radar] because I actually was on a blood pressure medication. I was taking 35 milligrams of [the drug], and I got pregnant when I was over 40. So I knew right off the bat I'm at high risk for diabetes, needing injections, and watching my blood pressure.

Generally, even participants who were aware of pre-eclampsia reported a tendency to underestimate its potential seriousness or the negative health consequences that could result from progressive pre-eclampsia:

I just thought, "OK, it's high blood pressure. My mother has high blood pressure. Maybe it just runs in the family." And no, I didn't know much about it at all. I didn't realize that it can cause seizures and all kinds of different things.

I just didn't worry about it because I didn't know any better. I didn't know anything about pre-eclampsia. I didn't know that, if it leads to eclampsia, you can die [and] your baby can die. I didn't know all those horrible things.

CARE JOURNEY WITH PRE-ECLAMPSIA

All participants interviewed or who responded through written submissions had either completed their pregnancy or were family members of those who had completed their pregnancy. Retrospectively, it was common for participants to report on potential early signs and symptoms of pre-eclampsia, but at the time they had considered these signs and symptoms a normal part of pregnancy. This was especially true for participants during their first pregnancy, not knowing precisely what symptoms were typical for pregnancy and what indicated pre-eclampsia. Some symptoms reported were large weight gain, swelling in certain parts of the body, difficulty breathing, and fatigue:

Yeah, it really wasn't quite on the radar until I started really having the symptoms, having problems actually breathing.

And I know from my own experience ... that there were warning signs and clues, maybe around the midpoint of the pregnancy. But there wasn't any active treatment of it until late in pregnancy.

It was awful. Like I just remember, it just felt so uncomfortable. And it's not [only] me who wasn't terribly worried. Even I'm thinking of my mother-in-law and my sister-in-law. Because we all lived very close and saw each other regularly. It's like nobody ever said, "Oh my gosh, what's going on? Like, are you OK?" People just didn't know back then.

Participants reported that the diagnosis of pre-eclampsia could come in a variety of circumstances and in various later stages of the pregnancy. For some participants, pre-eclampsia was diagnosed as part of a routine checkup with little warning that it was going to be a major concern. At that stage, participants could be monitored more closely, and some preventive measures could be taken to stop progression:

[At 5 months ... I had gone in just for a regular check, and my blood pressure, just all of a sudden [had] gone through the roof. I gained a ton of water weight, and they sent me ... the hospital was across the street. They sent me right over. And they started doing tests; they told me exactly what they were testing for. They're like, "We think you have pre-eclampsia. Like, you're in it. Right here, this is your blood pressure." It was really, really high.

No, I mean because I didn't feel it, right? High blood pressure wasn't something that you know ... I was fine; I was doing my stuff, living my life, doing my thing. And then I went in for one of the normal checkups that you go for. And they always do your pressure. And apparently mine was sky high, to the point that [the doctor] said, "I'm either admitting you or I'll send you home, but you need someone to come in every day." And I thought, "Oh my gosh. OK." And then I was on bed rest. I couldn't do anything for the last 6 weeks of my pregnancy with my daughter. I could get up to pee and I could shower. That's it.

For other participants it was a much more serious occurrence, and the diagnosis of pre-eclampsia might have come in hospital while seeking urgent medical care for the escalation of symptoms:

I was put on bed rest. And then I was back in the hospital at ... 37 weeks. ... Just because everything was going kind of crazy and ... I don't know exactly because I don't remember the testing [for pre-eclampsia], but I do remember my doctor saying my organs were starting to fail, whatever that means.

And the doctor came in and spoke to me and said, yeah, so ... I think it was creatine, maybe, that they detected; they were monitoring my urine. He said, "We're going to need you to stay here so we can get your blood pressure down and you have to be on strict bed rest because you do have it. You do have pre-eclampsia and here are the risks. Like if we can't get this down, the potentials are..."

No matter the precise time of diagnosis, most participants saw the progression of symptoms of pre-eclampsia, often requiring hospitalization. This had a large impact on patients and their family members.

IMPACT OF PRE-ECLAMPSIA

For participants, the diagnosis of pre-eclampsia and its risks for the pregnant person and the fetus could have a significant impact on the progression of the pregnancy and the circumstances of the birth. Many participants reported on the negative impact that pre-eclampsia caused for them, beyond experiencing uncomfortable or unpleasant symptoms. One of the most common immediate effects was that participants were admitted to hospital for close monitoring. This could be disruptive to participants' and families' daily activities, and some participants commented that this was not particularly restful and could increase their stress. Patients who lived in smaller communities also faced the possibility of being unable to remain at their local hospital, but being transferred to a different hospital to care for their serious condition:

Oh, it was brutal, right? And the hospital is like an hour away from where I live. And there's no food. And I was like, "I didn't just give birth, I'm hungry." I wasn't allowed to walk, so it was brutal.

Oh yeah, between 17 weeks to 22 weeks. So I was in like 5 weeks and then I went home. I begged to go home. I was put on complete bed rest, and I promised I would be on complete bed rest, but it didn't help at all.

And I was put on bed rest in the hospital. They monitored me for a week at that point. (Which was like nuts, because I was in the maternity ward and there were babies screaming all night, so I didn't really get to rest.)

So the doctor then said I had pre-eclampsia and then he said, because I was only 32 weeks pregnant, [this hospital] can't take babies until they're 35 [weeks' gestation]. So that's when they were like, "We're going to have to send you to [another hospital]."

Connected to this impact on daily life is the potential disruption to employment and a new financial burden placed on families by pre-eclampsia. Several women reported that their experience with pre-eclampsia required extended time in hospital, resulting in lost wages and reduced ability to see their other children:

And just some thought around not just the pre-eclampsia: what does that mean for a mother? You know, like I said, the loss of wages and what about the other kids?

Here's another [thing to consider] because I lost a lot of wages as well, right? And that was also detrimental, right? Because I had to go off work and yes, we have maternity, [leave] right. But I had to take sick leave benefits. You only get maternity leave once you have your baby. So if you don't have those benefits or they don't cover off what you need, that's a lot. I had a lot of lost income that put us in debt, so that's a huge factor.

The progression of pre-eclampsia, its symptoms, and the escalation of medical care could also affect patients and their families emotionally. Many participants spoke of increased levels of anxiety, stress, and concerns about well-being owing to pre-eclampsia. Some spoke of feelings of depression and fear simply from lack of knowledge about what was happening and how serious it was:

And I was very depressed. Very, very depressed because [I] wasn't really sure why I was there. I thought maybe I might die because they kept talking about having a stroke. It wasn't clear, like I didn't get a lot of information from them. I knew I had to be there, and I could explode probably. ... And I begged them to [let me] go home. I was in there for 8 days, and I begged them to [let me] go home and sleep in my own bed.

At that point I still didn't know that I would have to give birth to the baby. So I was just like, "oh, this is just a thing I have. And I might have to have it until he's born." So I didn't really think about it. I think my husband was panicking ... because I think he was probably looking at what [pre-eclampsia] was. And I wasn't. So I think he was panicking.

Naturally, these emotional concerns extended to the health and well-being of the unborn child. Pre-eclampsia could result in early delivery of the baby, requiring extended stays in the NICU and possible long-term health consequences for the infant. Many participants expressed concerns for their unborn child and their emotions on learning that pre-eclampsia could affect successful delivery of the child:

But it was really scary because I had no idea like exactly what [I had]. I did have pre-eclampsia and I didn't know it. They weren't very forthcoming about it. ... And I really didn't know what the hell ... I just thought, "Oh my God. I'm going to die or my baby's going to die. We're both going to die. What the hell's going to go on?" And my husband wasn't there yet, right? Because we lived an hour out.

So ... after [birth], I had major postpartum depression. I thought she was going to die for like, 6 months. I had my hand on her [as] she sat beside me [in] her little bassinet.

Oh, I was terrified. Very. Because it was the first one that I was successfully ... this was going to be an actual baby this time. So we had lost multiple pregnancies prior to that. ... We went through a lot of stuff to have our kids. And so when I when I got this news, I [thought], "Oh my gosh, are you serious? This is like a new thing; now I'm just I'm not going to get this baby?"

Beyond the immediacy of labour and delivery, some participants spoke about longer-term consequences of pre-eclampsia. For some, blood pressure issues needed to be treated with medication for an extended period. Others spoke about consequences for future pregnancies; some decided to avoid any future pregnancies given the potential for repeat pre-eclampsia. Others reported that their experience with pre-eclampsia made them more aware for future pregnancies; they made sure they were monitored much more closely or treated earlier to help prevent escalation of pre-eclampsia again:

And I went home afterwards, but my blood pressure never came down after that. I've been on high doses of blood pressure pills since. So I'm 63 years old and I'm still on blood pressure pills; from 34 all the way till now, I'm on blood pressure pills.

I mean for us, we're not [having another child]; it's a shame because it's too risky for us to have a second and that's just not. ... Right now the research is not there, and I know the doctor at [the hospital] said he would put me on a baby Aspirin, but for us it's just [not worth the risk]; we have our son. We're happy. It just is what it is.

So that awareness and then what I went through actually made me be a little bit more [careful about] adapting some screening application. And then also I found my family doctor also—because it was identified before—was actually taking my blood pressure or insisting I report [measurements to] the nurse. ... [They offered much more] tracking and attention, and, if there were any concerns, they were on it.

The most serious potential consequence of pre-eclampsia is loss of life. Tragically, we spoke to several people who had experienced death as a consequence of pre-eclampsia, where pre-eclampsia and further complications were so severe that the infant or the pregnant person did not survive. These tragedies had an enormous impact on the families involved. Several described the long-term emotional scars and effects of such a loss. These participants also lamented the lack of awareness or education around the potential seriousness of pre-eclampsia, wishing that more people were aware of it to prevent any further such tragedies:

And this is what I regret. We never had any conversations on pre-eclampsia or HELLP, and all I remember is the week before we had a whole day together getting the baby's room [ready], and that was the week before things happened or the week of.

Her mom, her sister, her dad. We were all just about as shocked as anybody, I think. And I don't really think anybody had any clue that it was going to be this serious.

I wouldn't wish this on my worst enemy, and ... I try to share it as much as I can to let people be more aware, like if people were more aware, you know, maybe they can help their loved ones and not have to go through this.

SCREENING PROGRAM FOR PRE-ECLAMPSIA

Participants were presented with basic information concerning the potential population-wide FMF-based screening program. Participants were informed that the FMF algorithm has been used to identify people who will benefit from low-dose ASA because of their high risk of developing preterm pre-eclampsia. Participants were asked to comment on their perceptions and values when it comes to a screening program and, based on their lived experience, what value or effect would a screening program for pre-eclampsia have for themselves, family members, or other pregnant people?

Almost all participants initially commented on the need for increased education and awareness of pre-eclampsia as part of screening. Informing pregnant people about the symptoms and risks of pre-eclampsia was seen as an essential and valuable part of any screening program. While some thought that written materials would be helpful in accomplishing this, others thought that written materials—such as pamphlets—were too easily ignored and not a good way of communicating essential information. Some participants emphasized that the information and education concerning pre-eclampsia in a screening program should come from family physicians or trusted health care professionals who are monitoring the pregnancy:

And when you look at what could have happened, I think it's really important that education is provided. Being able to identify these are the risk factors. If you're in your first trimester, these are the risk factors, and this is what you can do to hopefully prevent this from happening. I think that that's invaluable information to pregnant women for both them and their babies.

Another thing I think is huge is that people trust their health care providers, and if the health care provider didn't say something, they will often assume that means it's not a concern and that they don't need to think about it or be looking for things.

Where should this start? Well, from your first appointment; "Do you know what pre-eclampsia is?" And awareness. And your obstetrician or gynecologist saying, "I want you to know the signs of it. Please make sure you know the signs." I think it needs to be embedded in the whole process. Not just talked about it one day because their blood pressure is high or there's protein in the urine or something. They need to know what all those signs are.

Some participants commented that increased education and awareness of pre-eclampsia and the medical causes of the condition would be valuable for emotional and social reasons. They reported feeling a sense of blame or guilt for occurrences of pre-eclampsia, as if they had done something incorrect during pregnancy. A few participants also mentioned comments directed at them suggesting that their pre-eclampsia was caused by household factors or situations in their personal life. Some thought that better education and awareness of pre-eclampsia as part of a screening program could help to avoid these types of situations and emotional burden:

But they kept saying to me, "You must have a problem at home." I snapped at one because I went for the ultrasound twice a day, and she said to me, "Are you married?" And ... I said, "Of course I'm married." I looked at her. I was disgusted; just because somebody gets high blood pressure is not because of problems at home, and then afterwards they find it and they say "Oh, it's pre-eclampsia."

I remember specifically saying to [my doctor], "What did I do wrong? What could I have done?" And he said, "No, you didn't do anything. There's no way to know about this until you come and we check." That is in fact what he told me at the time. Because always your first thought is, "Did I eat something? Was it the yoga? What did this?" And he said, "No, it can just happen."

Participants also emphasized the potential clinical value of screening for prevention. Preventing pre-eclampsia from happening or detecting it early was seen as a significant benefit, as it could avoid downstream complications and negative consequences. Even if pre-eclampsia could not be prevented, some mentioned the belief that earlier screening for pre-eclampsia could help reduce its subsequent progression or the ultimate seriousness of the condition. This was seen as extremely valuable during pregnancy, allowing for a healthier pregnancy and a healthier baby:

I honestly think the prevention and the screening tool ... pushing that information and getting a support person ... makes a big difference.

When you say [screening at] 13 or 14 weeks, I'm like what!?! That would be amazing ... to know that soon, because then you can take steps, right? Even if it's not preventable, if you could slow it down, or if there were things you could do just to mitigate some of the stuff that's going to happen. ...

And just that snowball effect of potential interventions and complications and knowing that to really optimize health for my baby meant [having] as good and healthy a pregnancy as I could have. So that that would increase the chance that it would be not just a healthy pregnancy, but contribute to their own healthy development, but also then a birth that was less likely to have problems that could impact their health as well.

Additionally, participants did not express concern about the potential treatment of low-dose ASA as part of the population-wide FMF-based screening program. Many spoke of trusting their physician to provide appropriate care if required to mitigate the potential of developing pre-eclampsia. A few participants were familiar with this treatment, after experiencing pre-eclampsia previously and then receiving ASA in a subsequent pregnancy:

So I'm pregnant right now, for example, and because of my experience with HELLP syndrome, my OB [obstetrician] put me on baby Aspirin as soon as we met because I guess baby Aspirin is something that can reduce your risk of pre-eclampsia if you start it before I want to say 14 weeks. I didn't even ask questions when my doctor said, "Based on your last pregnancy, you were at higher risk of developing pre-eclampsia. So therefore, we would put you on baby Aspirin." I was like, "Cool." Didn't ask any more questions other than that.

But they would put you on a baby Aspirin at 12 weeks. So then people, if I did this test when I was pregnant and maybe because I was 35 when I gave birth, so that's geriatric pregnancy.

I should have probably been put on a baby Aspirin. Because they say it doesn't do any harm and they would be watching me. So I definitely agree that there should be a screening [tool].

BARRIERS AND EQUITY

When considering implementation of the population-wide FMF-based screening program, many participants commented on health equity around pre-eclampsia and the barriers to treatment that exist in the province. Several participants reflected that access to services is inequitable across the province and that a screening program would need to overcome these challenges to be accessible to all pregnant people. Others commented on the value of information and education as part of the population-wide FMF-based screening program, but reflected that this can be a challenge with such a diverse patient population:

The concern I would have is around accessibility and education, especially in communities [that] have more needs than upper middle class, predominantly White areas of our city and province.

If specific groups are more likely to have it, then how would education and resources target that group? Materials should be in multiple languages to increase accessibility. Connecting with specific community organizations who would know how to meet the needs of the community or at least connect with communities to understand their needs.

And even the educational piece because, if you were living in remote communities somewhere in Northern Ontario, and even if your doctor doesn't talk to you about it, at least if you're somehow provided with information, you can be aware of it, right?

Some participants reflected on the potential cost of this test and their hope that a provincial program would reduce this cost burden. Some thought that testing for risk of pre-eclampsia would be valuable even if they had to pay out-of-pocket, but they understood that this was not an option for all people in Ontario:

The barrier is going to be money, right? I personally would have paid for that, if someone said, "We can check you for this." I have insurance, but even if I didn't, for me personally it was so hard to have them and it was so important to me that I would have paid. I would have gotten the money and paid for any blood test that I needed. It's not the case for everybody. There's some not going to be able to do that. It could even be where it's covered for a certain population.

But something like that to me. I was like, "Yeah, I don't care." ... I can't say I don't care what the cost is, but like we were prepared to pay to have as much information about the health and well-being of our unborn child or children as soon as possible so that we could educate ourselves and make informed decisions.

Several participants commented on their hope that province-wide screening would help identify risk of pre-eclampsia and that earlier treatment would help to reduce health inequities that currently exist. Examples that were provided included the necessity of a hospital stay with pre-eclampsia and how that can adversely affect some patient populations in the province:

But right or wrong, the clinician might not think to ask or think about the client in the terms of "OK well, what else is going on for them?" Did [the clinician] know they had to take six buses to get here? And ... they've got seven other kids? ... Or do they know that, if you have to go on bed rest, that means that you can't get groceries for the next 5 weeks? And how does that play out for everybody? So something like this? I would love to see a full screening. Like through your maternal health [provider].

And although I think the care I got [in hospital] was a lot better, I still was like, "OK, So what? Do I call my work and say I'm never coming back?" ... I called my husband. And what happens for people who have zero family support? "So how do I get my kids from daycare today? I can't leave, but I have to." So then that's another whole stress and another whole conversation.

Along with comments around health equity, a few participants also expressed other concerns around potential implementation of the population-wide FMF-based screening program. One person commented that this screening program must be optional, rather than required, and people must understand what is done with data collected. Others commented on the potential for more false-positive or false-negative results if such a program were to be expanded across the province:

During my last pregnancy I did have a false positive and an ultrasound that turned out to be nothing; this was stressful, and I wish that my OB [obstetrician] had communicated more clearly about this to me. As long as there is timely and clear communication, I would appreciate having this extra layer of screening to ensure a healthy pregnancy.

I would assume it would be completely optional and it wouldn't be [introduced] like, "OK, in Ontario you got a 12-week ultrasound, and everybody gets that." I would assume this would be more akin to the NIPT [noninvasive prenatal testing], optional; if you want this information, go for it and if you decide you're going to have a baby regardless ... and you don't want to do any additional testing, then go for it. But I would assume this would be optional.

If it basically is, "Hey, you're at risk of developing pre-eclampsia. We think you're not going to carry your baby full term. You're probably going to have to deliver early." And it could open up a bit of a well toward, "OK, what do I do with this information and is there any kind of treatment for it?" That would be my only piece of [concern]. I'm all about collecting data, but what do you do with the data that you collect?"

Discussion

Participants were engaged directly through interviews or through written responses to interview questions. This flexibility allowed for additional engagement with people who had recent pregnancies, adding to the robustness of the engagement. Overall, this engagement was able to examine the experiences, preferences, and values of participants regarding pre-eclampsia and the population-wide FMF-based screening program.

All participants had experience with pregnancy (or were family members) and experience with or knowledge of pre-eclampsia. Most participants had direct experience with various treatments for pre-eclampsia and were able to comment on the impact and consequences of pre-eclampsia, for

themselves, family members, and their child. Participants were able to speak about changes to quality of life and both short-term and long-term effects of pre-eclampsia.

While only a few participants had direct experience with ASA as a preventive treatment for pre-eclampsia, all were able to comment on population-wide screening for pre-eclampsia and its value, whether for themselves or for family members. In this way, our engagement allowed for a thematic analysis of a variety of perspectives in consideration of the values and preferences related to a pre-eclampsia screening program.

Conclusions

Pre-eclampsia can be a serious health issue affecting both pregnant people and their unborn children. The population-wide FMF-based screening program was seen as valuable by those who have experienced pregnancy, and by their family members. Strong emphasis was placed on providing education and equitable access as part of any screening program, and participants valued the potential clinical benefits and increased awareness of pre-eclampsia that preventive screening could provide.

Conclusions of the Health Technology Assessment

A population-wide screening program for pre-eclampsia risk (the Fetal Medicine Foundation [FMF]-based screening program) that uses a multiple-marker algorithm (the FMF algorithm) initiated at 11^o and 13^o weeks' gestation likely reduces the risk of pre-eclampsia with delivery at less than 37 weeks' gestation compared with standard care (GRADE: Moderate). It may reduce the risks of low birth weight and low Apgar score (GRADE: Low). We are uncertain about the evidence for the comparative effectiveness of screening based on the FMF algorithm for stillbirth and neonatal death (GRADE: Very low).

We also found that screening using the FMF algorithm initiated between 11^o and 13^o weeks' gestation can have a higher accuracy than screening using conventional algorithms in detecting pre-eclampsia with delivery at less than 37 weeks' gestation or at less than 34 weeks' gestation, although there are concerns about risk of bias and applicability.

The population-wide FMF-based screening program was found to be more effective and more costly than standard care. We estimate that publicly funding this screening program in Ontario would result in additional costs of \$8.50 million over the next 5 years.

The population-wide FMF-based screening program was seen as valuable by those who have experienced pregnancy, and by their family members. Strong emphasis was placed on providing education and equitable access as part of any screening program, and participants valued the potential clinical benefits that preventive screening could provide.

Abbreviations

- ACOG:** American College of Obstetricians and Gynecologists
- ASA:** acetylsalicylic acid
- ASPREE:** Aspirin for Evidence-Based Preeclampsia Prevention
- BCNatal:** Saint Joan de Deu Barcelona Children's Hospital
- BORN:** Better Outcomes Registry and Network
- CADTH:** Canadian Agency for Drugs and Technologies in Health
- CHEERS:** Consolidated Health Economic Evaluation Reporting Standards
- CI:** confidence interval
- CINAHL:** Cumulative Index to Nursing & Allied Health Literature
- CrI:** credible interval
- FIGO:** Federation of Gynecology and Obstetrics
- FMF:** Fetal Medicine Foundation
- GRADE:** Grading of Recommendations Assessment, Development, and Evaluation
- HELLP:** Hemolysis, elevated liver enzymes, and low platelets
- ICER:** incremental cost-effectiveness ratio
- MAP:** mean arterial pressure
- MOM:** multiple of median
- NHSEED:** National Health Service Economic Evaluation Database
- NICE:** National Institute for Health and Care Excellence
- NICU:** neonatal intensive care unit
- NPV:** negative predictive value
- OHIP:** Ontario Health Insurance Plan
- OR:** odds ratio
- PAPP-A:** pregnancy-associated plasma protein A
- PLGF:** placental growth factor
- PPV:** positive predictive value
- PRESS:** Peer Review of Electronic Search Strategies
- PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis
- QALY:** quality-adjusted life-year
- RR:** relative risk
- SPREE:** Screening Program for Pre-eclampsia
- UtA-PI:** uterine artery pulsatility index

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Bayes' theorem: Bayes' theorem is used to update the prior probability distribution in light of the results of a study, to produce a posterior distribution. It can be used in a single study or in a meta-analysis. Statistical inference (point estimates, confidence intervals, etc.) is based on the posterior distribution. The posterior distribution can also be used as the prior distribution for the next study. This approach is controversial when it depends on opinions, which might vary. However, its use has become commonplace in economic evaluation, as it allows the creation of complex models with different evidence sources and the determination of uncertainty.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-benefit analysis: A cost-benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost-utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost-minimization analysis: In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.

Cost-utility analysis: A cost-utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost-utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done

using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost-utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Risk difference: Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost-utility analysis, the willingness-

to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: January 21, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database, and CINAHL

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 20, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 02>, Ovid MEDLINE(R) ALL <1946 to January 20, 2022>

Search Strategy:

-
- 1 Pre-Eclampsia/ (65721)
 - 2 (preeclamp* or pre eclamp* or ((early onset* or preterm* or pre term*) adj3 PE)).ti,ab,kf. (94802)
 - 3 (((pregnan* or gestat* or matern*) adj3 tox?emi*) or (edema adj3 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).ti,ab,kf. (7327)
 - 4 or/1-3 (115667)
 - 5 Pregnancy Trimester, First/ (61717)
 - 6 (early placenta* phase* or early pregnancy or first trimester* or 1st trimester* or "11 0 week*" or "13 6 week*" or ((11* week* or eleven* week* or 12* week* or twel* week* or 13* week* or thirteen* week* or 14* week* or fourteen* week* or "less than 16 week*" or "#16 week*" or "under 16 week*")) adj3 (pregnan* or gestat*))).ti,ab,kf. (117265)
 - 7 or/5-6 (131582)
 - 8 Mass Screening/ (171462)
 - 9 screen*.ti,ab,kf. (2136956)
 - 10 or/8-9 (2183078)
 - 11 Algorithms/ (517879)
 - 12 Bayes Theorem/ (79483)
 - 13 Logistic Models/ (303497)
 - 14 (algorithm* or (marker* adj3 multiple*) or multi marker* or multimarker* or bayes* theorem* or (multivaria* adj2 (logistic* or regression*))).ti,ab,kf. (1167388)
 - 15 ((f?etal medic* foundation* or FMF) adj4 (screen* or program* or test* or algorithm* or model* or multiple marker* or multimarker* or bayes* or theorem* or tool*)).ti,ab,kf. (613)
 - 16 *Models, Statistical/ (56159)
 - 17 nomograms/ (21072)
 - 18 nomogram*.ti,ab,kf. (34083)
 - 19 or/11-18 (1767907)
 - 20 Biomarkers/ (642355)
 - 21 (biomarker* or ((marker* or measurement* or parameter* or tool or tools) adj3 (biochemical or biologic or biological or biophysical or clinical or laboratory or serum))).ti,ab,kf. (1442727)
 - 22 (maternal risk factor* or maternal factor*).ti,ab,kf. (9225)
 - 23 Arterial Pressure/ (41946)

- 24 (mean adj2 (arterial pressure* or aortic pressure* or pulse pressure* or blood pressure*)).ti,ab,kf. (156536)
- 25 Uterine Artery/ (9839)
- 26 Pulsatile Flow/ph (2902)
- 27 (uterine artery pulsatil* or uterine artery doppler* or UtAPI or UtA PI or UTPI).ti,ab,kf. (3536)
- 28 Maternal Serum Screening Tests/ (883)
- 29 (maternal serum adj2 (screen* or test* or marker*)).ti,ab,kf. (3058)
- 30 Pregnancy-Associated Plasma Protein-A/ (5314)
- 31 (pregnan* associated plasma protein* or pregnan* associated alpha plasma protein* or PAPP-A* or PAPP-alpha*).ti,ab,kf. (6383)
- 32 Placenta Growth Factor/ (8258)
- 33 (placenta* growth factor* or PLGF).ti,ab,kf. (9673)
- 34 or/20-33 (1948555)
- 35 (screen* adj2 (preeclamp* or pre eclamp*)).ti,ab,kf. (950)
- 36 4 and 7 and (10 or 19) (2618)
- 37 4 and 10 and 19 (949)
- 38 4 and (10 or 19) and 34 (3569)
- 39 or/35-38 (5015)
- 40 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5986855)
- 41 39 not 40 (4937)
- 42 exp Animals/ not Humans/ (16623718)
- 43 41 not 42 (3803)
- 44 limit 43 to english language [Limit not valid in CDSR; records were retained] (3583)
- 45 44 use medall,coch,cctr,clhta,cleed (1977)
- 46 preeclampsia/ (94603)
- 47 (preeclamp* or pre eclamp* or ((early onset* or preterm* or pre term*) adj3 PE)).tw,kw,kf. (95272)
- 48 (((pregnan* or gestat* or matern*) adj3 tox?emi*) or (edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).tw,kw,kf. (7376)
- 49 or/46-48 (121582)
- 50 first trimester pregnancy/ (64450)
- 51 (early placenta* phase* or early pregnancy or first trimester* or 1st trimester* or "11 0 week*" or "13 6 week*" or ((11* week* or eleven* week* or 12* week* or twel* week* or 13* week* or thirteen* week* or 14* week* or fourteen* week* or "less than 16 week*" or "#16 week*" or "under 16 week*")) adj3 (pregnan* or gestat*)).tw,kw,kf. (117711)
- 52 or/50-51 (132535)
- 53 *screening/ (90352)
- 54 mass screening/ (171462)
- 55 prenatal screening/ (48166)
- 56 screening test/ (74660)
- 57 screen*.tw,kw,kf,dv. (2147491)
- 58 or/53-57 (2244516)
- 59 algorithm/ (590364)
- 60 bayes theorem/ (79483)
- 61 (algorithm* or (marker* adj3 multiple*) or multi marker* or multimarker* or bayes* theorem* or (multivaria* adj2 (logistic* or regression*))).tw,kw,kf,dv. (1170759)
- 62 ((f?etal medic* foundation* or FMF) adj4 (screen* or program* or test* or algorithm* or model* or multiple marker* or multimarker* or bayes* or theorem* or tool*)).tw,kw,kf,dv. (616)

- 63 *statistical model/ (59425)
- 64 nomogram/ (21072)
- 65 nomogram*.tw,kw,kf,dv. (34138)
- 66 or/59-65 (1566450)
- 67 biological marker/ (687584)
- 68 (biomarker* or ((marker* or measurement* or parameter* or tool or tools) adj3 (biochemical or biologic or biological or biophysical or clinical or laboratory or serum))).tw,kw,kf,dv. (1450959)
- 69 (maternal risk factor* or maternal factor*).tw,kw,kf,dv. (9269)
- 70 arterial pressure/ (41946)
- 71 (mean adj2 (arterial pressure* or aortic pressure* or pulse pressure* or blood pressure*)),tw,kw,kf,dv. (158041)
- 72 uterine artery/ (9839)
- 73 pulsatile flow/ (18019)
- 74 (uterine artery pulsatil* or uterine artery doppler* or UtAPI or UtA PI or UTPI).tw,kw,kf,dv. (3555)
- 75 maternal serum screening test/ (878)
- 76 (maternal serum adj2 (screen* or test* or marker*)),tw,kw,kf,dv. (3096)
- 77 pregnancy associated plasma protein A/ (5314)
- 78 (pregnan* associated plasma protein* or pregnan* associated alpha plasma protein* or PAPP-A* or PAPP-alpha*).tw,kw,kf,dv. (6410)
- 79 placental growth factor/ (6207)
- 80 (placenta* growth factor* or PLGF).tw,kw,kf,dv. (9701)
- 81 or/67-80 (1973768)
- 82 (screen* adj2 (preeclamp* or pre eclamp*)),tw,kw,kf,dv. (1139)
- 83 49 and 52 and (58 or 66) (2781)
- 84 49 and 58 and 66 (914)
- 85 49 and (58 or 66) and 81 (3778)
- 86 or/82-85 (5334)
- 87 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (12314665)
- 88 86 not 87 (4427)
- 89 (exp animal/ or nonhuman/) not exp human/ (11288368)
- 90 88 not 89 (4417)
- 91 limit 90 to english language [Limit not valid in CDSR; records were retained] (4150)
- 92 91 use emez (2034)
- 93 45 or 92 (4011)
- 94 93 use medall (1830)
- 95 93 use coch (0)
- 96 93 use cctr (145)
- 97 93 use clhta (1)
- 98 93 use cleed (1)
- 99 93 use emez (2034)
- 100 remove duplicates from 93 (2489)

CINAHL

#	Query	Results
S1	(MH "Pre-Eclampsia+")	9,872
S2	(preeclamp* or pre eclamp* or ((early onset* or preterm* or pre term*) N3 PE))	15,390
S3	((((pregnan* or gestat* or matern*) N3 (toxemi* or toxaemi*)) or (edema N2 proteinuria N2 hypertension) or EPH complex or EPH gestosis)	122
S4	S1 OR S2 OR S3	15,752
S5	(MH "Pregnancy Trimester, First")	5,633
S6	(early placenta* phase* or early pregnancy or first trimester* or 1st trimester* or "11 0 week*" or "13 6 week*" or ((11* week* or eleven* week* or 12* week* or twel* week* or 13* week* or thirteen* week* or 14* week* or fourteen* week* or "less than 16 week*" or "under 16 week*")) N3 (pregnan* or gestat*))	16,985
S7	S5 OR S6	16,985
S8	(MH "Health Screening+")	101,192
S9	screen*	238,450
S10	S8 OR S9	251,788
S11	(MH "Algorithms")	41,785
S12	(MM "Logistic Regression")	432
S13	(algorithm* or (marker* N3 multiple*) or multi marker* or multimarker* or bayes* theorem* or (multivaria* N2 (logistic* or regression*)))	131,137
S14	((fetal medic* foundation* or foetal medic* foundation* or FMF) N4 (screen* or program* or test* or algorithm* or model* or multiple marker* or multimarker* or bayes* or theorem* or tool*))	93
S15	nomogram*	3,264
S16	(MM "Models, Statistical+")	10,869
S17	S11 OR S12 OR S13 OR S14 OR S15 OR S16	142,454
S18	(MH "Biological Markers")	54,923
S19	(biomarker* or ((marker* or measurement* or parameter* or tool or tools) N3 (biochemical or biologic or biological or biophysical or clinical or laboratory or serum)))	329,315
S20	(maternal risk factor* or maternal factor*)	2,967
S21	(MH "Arterial Pressure")	3,437
S22	(mean N2 (arterial pressure* or aortic pressure* or pulse pressure* or blood pressure*))	11,012
S23	(uterine artery pulsatil* or uterine artery doppler* or UtAPI or UtA PI or UTPI)	830
S24	(maternal serum N2 (screen* or test* or marker*))	415
S25	(pregnan* associated plasma protein* or pregnan* associated alpha plasma protein* or PAPP-A* or PAPP-alpha*)	1,674
S26	(MH "Placenta Growth Factor")	25
S27	(placenta* growth factor* or PLGF)	1,241
S28	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	346,269
S29	(screen* N2 (preeclamp* or pre eclamp*))	325
S30	S4 AND S7 AND (S10 OR S17)	566
S31	S4 AND S10 AND S17	208
S32	S4 AND (S10 OR S17) AND S28	689
S33	S29 OR S30 OR S31 OR S32	1,012
S34	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,309,004
S35	S33 NOT S34	967
S36	S33 NOT S34	
	Limiters - English Language	966

Economic Evidence Search

Search date: January 26, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, National Health Service (NHS) Economic Evaluation Database, and CINAHL

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 20, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 03>, Ovid MEDLINE(R) ALL <1946 to January 25, 2022>

Search Strategy:

-
- 1 Pre-Eclampsia/ (65812)
 - 2 (preeclamp* or pre eclamp* or ((early onset* or preterm* or pre term*) adj3 PE)).ti,ab,kf. (94927)
 - 3 (((pregnan* or gestat* or matern*) adj3 tox?emi*) or (edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).ti,ab,kf. (7328)
 - 4 or/1-3 (115812)
 - 5 Pregnancy Trimester, First/ (61779)
 - 6 (early placenta* phase* or early pregnancy or first trimester* or 1st trimester* or "11 0 week*" or "13 6 week*" or ((11* week* or eleven* week* or 12* week* or twel* week* or 13* week* or thirteen* week* or 14* week* or fourteen* week* or "less than 16 week*" or "#16 week*" or "under 16 week*")) adj3 (pregnan* or gestat*))).ti,ab,kf. (117382)
 - 7 or/5-6 (131724)
 - 8 Mass Screening/ (171591)
 - 9 screen*.ti,ab,kf. (2140190)
 - 10 or/8-9 (2186320)
 - 11 Algorithms/ (518824)
 - 12 Bayes Theorem/ (79676)
 - 13 Logistic Models/ (303769)
 - 14 (algorithm* or (marker* adj3 multiple*) or multi marker* or multimarker* or bayes* theorem* or (multivaria* adj2 (logistic* or regression*))).ti,ab,kf. (1170125)
 - 15 ((f?etal medic* foundation* or FMF) adj4 (screen* or program* or test* or algorithm* or model* or multiple marker* or multimarker* or bayes* or theorem* or tool')).ti,ab,kf. (614)
 - 16 *Models, Statistical/ (56213)
 - 17 nomograms/ (21129)
 - 18 nomogram*.ti,ab,kf. (34220)
 - 19 or/11-18 (1771481)
 - 20 Biomarkers/ (643477)
 - 21 (biomarker* or ((marker* or measurement* or parameter* or tool or tools) adj3 (biochemical or biologic or biological or biophysical or clinical or laboratory or serum))).ti,ab,kf. (1445522)
 - 22 (maternal risk factor* or maternal factor*).ti,ab,kf. (9235)
 - 23 Arterial Pressure/ (41991)
 - 24 (mean adj2 (arterial pressure* or aortic pressure* or pulse pressure* or blood pressure*)).ti,ab,kf. (156648)

- 25 Uterine Artery/ (9844)
- 26 Pulsatile Flow/ph (2904)
- 27 (uterine artery pulsatil* or uterine artery doppler* or UtAPI or UtA PI or UTPI).ti,ab,kf. (3537)
- 28 Maternal Serum Screening Tests/ (889)
- 29 (maternal serum adj2 (screen* or test* or marker*)).ti,ab,kf. (3058)
- 30 Pregnancy-Associated Plasma Protein-A/ (5318)
- 31 (pregnan* associated plasma protein* or pregnan* associated alpha plasma protein* or PAPP-A* or PAPP-alpha*).ti,ab,kf. (6386)
- 32 Placenta Growth Factor/ (8273)
- 33 (placenta* growth factor* or PLGF).ti,ab,kf. (9682)
- 34 or/20-33 (1951972)
- 35 (screen* adj2 (preeclamp* or pre eclamp*)).ti,ab,kf. (950)
- 36 4 and 7 and (10 or 19) (2624)
- 37 4 and 10 and 19 (953)
- 38 4 and (10 or 19) and 34 (3576)
- 39 or/35-38 (5025)
- 40 39 use coch,clhta,cleed (2)
- 41 economics/ (263319)
- 42 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (966610)
- 43 economics.fs. (454094)
- 44 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmaco-economic* or pharmaco-economic*).ti,ab,kf. (1122293)
- 45 exp "costs and cost analysis"/ (645803)
- 46 (cost or costs or costing or costly).ti. (307437)
- 47 cost effective*.ti,ab,kf. (404644)
- 48 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (267805)
- 49 models, economic/ (15099)
- 50 markov chains/ or monte carlo method/ (97979)
- 51 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (56775)
- 52 (markov or markow or monte carlo).ti,ab,kf. (160878)
- 53 quality-adjusted life years/ (49534)
- 54 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (97533)
- 55 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (163622)
- 56 or/41-55 (3056367)
- 57 39 and 56 (275)
- 58 limit 57 to english language [Limit not valid in CDSR; records were retained] (259)
- 59 58 use medall,cctr (88)
- 60 or/40,59 (90)
- 61 preeclampsia/ (94693)
- 62 (preeclamp* or pre eclamp* or ((early onset* or preterm* or pre term*) adj3 PE)).tw,kw,kf. (95397)
- 63 (((pregnan* or gestat* or matern*) adj3 tox?emi*) or (edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).tw,kw,kf. (7377)
- 64 or/61-63 (121726)
- 65 first trimester pregnancy/ (64512)
- 66 (early placenta* phase* or early pregnancy or first trimester* or 1st trimester* or "11 0 week*" or "13 6 week*" or ((11* week* or eleven* week* or 12* week* or twel* week* or 13* week* or thirteen* week*

- or 14* week* or fourteen* week* or "less than 16 week*" or "#16 week*" or "under 16 week*") adj3 (pregnan* or gestat*)))tw,kw,kf. (117828)
- 67 or/65-66 (132677)
- 68 *screening/ (90400)
- 69 mass screening/ (171591)
- 70 prenatal screening/ (48189)
- 71 screening test/ (74717)
- 72 screen*.tw,kw,kf,dv. (2150727)
- 73 or/68-72 (2247781)
- 74 algorithm/ (591309)
- 75 bayes theorem/ (79676)
- 76 (algorithm* or (marker* adj3 multiple*) or multi marker* or multimarker* or bayes* theorem* or (multivaria* adj2 (logistic* or regression*)))tw,kw,kf,dv. (1173496)
- 77 ((f?etal medic* foundation* or FMF) adj4 (screen* or program* or test* or algorithm* or model* or multiple marker* or multimarker* or bayes* or theorem* or tool*))tw,kw,kf,dv. (617)
- 78 *statistical model/ (59479)
- 79 nomogram/ (21129)
- 80 nomogram*.tw,kw,kf,dv. (34275)
- 81 or/74-80 (1569851)
- 82 biological marker/ (688705)
- 83 (biomarker* or ((marker* or measurement* or parameter* or tool or tools) adj3 (biochemical or biologic or biological or biophysical or clinical or laboratory or serum)))tw,kw,kf,dv. (1453754)
- 84 (maternal risk factor* or maternal factor*).tw,kw,kf,dv. (9279)
- 85 arterial pressure/ (41991)
- 86 (mean adj2 (arterial pressure* or aortic pressure* or pulse pressure* or blood pressure*))tw,kw,kf,dv. (158153)
- 87 uterine artery/ (9844)
- 88 pulsatile flow/ (18059)
- 89 (uterine artery pulsatil* or uterine artery doppler* or UtAPI or UtA PI or UTPI).tw,kw,kf,dv. (3556)
- 90 maternal serum screening test/ (884)
- 91 (maternal serum adj2 (screen* or test* or marker*))tw,kw,kf,dv. (3096)
- 92 pregnancy associated plasma protein A/ (5318)
- 93 (pregnan* associated plasma protein* or pregnan* associated alpha plasma protein* or PAPP-A* or PAPP-alpha*).tw,kw,kf,dv. (6413)
- 94 placental growth factor/ (6219)
- 95 (placenta* growth factor* or PLGF).tw,kw,kf,dv. (9710)
- 96 or/82-95 (1977200)
- 97 (screen* adj2 (preeclamp* or pre eclamp*))tw,kw,kf,dv. (1139)
- 98 64 and 67 and (73 or 81) (2787)
- 99 64 and 73 and 81 (918)
- 100 64 and (73 or 81) and 96 (3784)
- 101 or/97-100 (5343)
- 102 Economics/ (263319)
- 103 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (140789)
- 104 Economic Aspect/ or exp Economic Evaluation/ (507752)
- 105 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1143058)
- 106 exp "Cost"/ (645803)

- 107 (cost or costs or costing or costly).ti. (307437)
- 108 cost effective*.tw,kw,kf. (414475)
- 109 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw,kf. (278085)
- 110 Monte Carlo Method/ (76405)
- 111 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (60181)
- 112 (markov or markow or monte carlo).tw,kw,kf. (164341)
- 113 Quality-Adjusted Life Years/ (49534)
- 114 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (101017)
- 115 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (184377)
- 116 or/102-115 (2616577)
- 117 101 and 116 (423)
- 118 limit 117 to english language [Limit not valid in CDSR; records were retained] (407)
- 119 118 use emez (178)
- 120 60 or 119 (268)
- 121 120 use medall (78)
- 122 120 use cctr (10)
- 123 120 use coch (0)
- 124 120 use cleed (1)
- 125 120 use clhta (1)
- 126 120 use emez (178)
- 127 remove duplicates from 120 (203)

CINAHL**# Query Results**

- S1 (MH "Pre-Eclampsia+") 9,896
- S2 (preeclamp* or pre eclamp* or ((early onset* or preterm* or pre term*) N3 PE)) 15,402
- S3 (((pregnan* or gestat* or matern*) N3 (toxemi* or toxaeimi*)) or (edema N2 proteinuria N2 hypertension) or EPH complex or EPH gestosis) 122
- S4 S1 OR S2 OR S3 15,764
- S5 (MH "Pregnancy Trimester, First") 5,638
- S6 (early placenta* phase* or early pregnancy or first trimester* or 1st trimester* or "11 0 week*" or "13 6 week*" or ((11* week* or eleven* week* or 12* week* or twel* week* or 13* week* or thirteen* week* or 14* week* or fourteen* week* or "less than 16 week*" or "under 16 week*") N3 (pregnan* or gestat*)) 17,004
- S7 S5 OR S6 17,004
- S8 (MH "Health Screening+") 101,257
- S9 screen* 238,838
- S10 S8 OR S9 252,188
- S11 (MH "Algorithms") 41,816
- S12 (MM "Logistic Regression") 432
- S13 (algorithm* or (marker* N3 multiple*) or multi marker* or multimarker* or bayes* theorem* or (multivaria* N2 (logistic* or regression*))) 131,450
- S14 ((fetal medic* foundation* or foetal medic* foundation* or FMF) N4 (screen* or program* or test* or algorithm* or model* or multiple marker* or multimarker* or bayes* or theorem* or tool*)) 93
- S15 nomogram* 3,283
- S16 (MM "Models, Statistical+") 10,886
- S17 S11 OR S12 OR S13 OR S14 OR S15 OR S16 142,787

S18	(MH "Biological Markers")	54,960
S19	(biomarker* or ((marker* or measurement* or parameter* or tool or tools) N3 (biochemical or biologic or biological or biophysical or clinical or laboratory or serum)))	329,732
S20	(maternal risk factor* or maternal factor*)	2,972
S21	(MH "Arterial Pressure")	3,442
S22	(mean N2 (arterial pressure* or aortic pressure* or pulse pressure* or blood pressure*))	11,018
S23	(uterine artery pulsatil* or uterine artery doppler* or UtAPI or UtA PI or UTPI)	830
S24	(maternal serum N2 (screen* or test* or marker*))	416
S25	(pregnan* associated plasma protein* or pregnan* associated alpha plasma protein* or PAPP-A* or PAPP-alpha*)	1,676
S26	(MH "Placenta Growth Factor")	25
S27	(placenta* growth factor* or PLGF)	1,241
S28	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	346,698
S29	(screen* N2 (preeclamp* or pre eclamp*))	325
S30	S4 AND S7 AND (S10 OR S17)	566
S31	S4 AND S10 AND S17	208
S32	S4 AND (S10 OR S17) AND S28	689
S33	S29 OR S30 OR S31 OR S32	1,012
S34	(MH "Economics")	14,686
S35	(MH "Economic Aspects of Illness")	10,694
S36	(MH "Economic Value of Life")	669
S37	MH "Economics, Dental"	148
S38	MH "Economics, Pharmaceutical"	2,360
S39	MW "ec"	193,822
S40	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmaco-economic* or pharmaco-economic*)	334,378
S41	(MH "Costs and Cost Analysis")	129,365
S42	TI cost*	59,028
S43	(cost effective*)	47,510
S44	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	37,648
S45	(decision N1 (tree* or analy* or model*))	10,281
S46	(markov or markow or monte carlo)	7,125
S47	(MH "Quality-Adjusted Life Years")	5,575
S48	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	13,820
S49	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analysis or sensitivity analyses)	22,585
S50	S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49	455,409
S51	S33 AND S50	54
S52	S33 AND S50	
	Limiters - English Language	54

Grey Literature Search

Performed on: January 28 – February 4, 2022

Websites searched: Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Québec-Université Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International Health Technology Assessment Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Health Council of Australian Governments Health Technologies, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, SickKids Paediatric Economic Database Evaluation (PEDE) Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used: preeclampsia, pre eclampsia, preeclampsia screening, prééclampsie, dépistage, first trimester, pre term, 11 week, 13 week, algorithm, multimarker, multi marker, biomarker, fetal medicine foundation, maternal risk factor, maternal factor, mean arterial pressure, uterine artery pulsatility, UtA-PI, maternal serum, pregnancy associated plasma protein, PAPP-A, placental growth factor, PLGF

Clinical results (included in PRISMA): 8

Economic results (included in PRISMA): 3

Ongoing HTAs (PROSPERO/EUnetHTA): 14

Ongoing RCTs (clinicaltrials.gov): 37

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias^a Among Nonrandomized Trials (ROBINS-I Tool)

Author, year	Pre-intervention		At intervention		Post-intervention		
	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Guy et al, 2021 ^{49,b}	Low	Low	Low	Low	Low	Low	Low
Rolnik et al, 2021 ^{50,c,d}	Moderate ^e	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

^a Possible risk-of-bias levels: low, moderate, serious, critical, and no information.

^b The assessment was for the following outcomes: pre-eclampsia with delivery at less than 37 weeks' gestation and pre-eclampsia with delivery at less than 34 weeks' gestation.

^c The assessment was for the following outcomes: preterm pre-eclampsia, birth weight less than 2500 g, Apgar score less than 4 at 5 minutes after birth, stillbirth, and neonatal death.

^d Models for each outcome were adjusted for age, body mass index, parity, socioeconomic status as given by Index of Relative Socioeconomic Disadvantage, smoking, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, and pre-existing diabetes.

^e The authors acknowledged that they did not adjust for ethnicity or mode of conception because data were not available.

Table A2: Risk of Bias and Applicability Concerns^a Among Screening Accuracy Studies (QUADAS-C Tool)

Author, year	Risk of bias					Applicability concerns			
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection	Index test	Comparator test	Reference standard
Chaemsaitong et al, 2019 ⁵¹	Low	Low	Low	Low	Low	High ^b	High ^c	Low	Low
Di Martino et al, 2019 ⁵²	Low	Low	Low	Low	Low	Low	High ^d	High ^d	Low
Guy et al, 2021 ⁴⁹	Low	Low	Low	High ^e	Low	Low	High ^f	High ^f	Low
O’Gorman et al, 2017 ⁵³	Low	Low	Low	High ^e	Low	Low	High ^c	Low	High ^e
Poon et al, 2020 ⁵⁴	Low	Low	Low	Low	Low	Low	High ^{d,f}	High ^{d,f}	Low
Rocha et al, 2017 ⁵⁵	Low	Low	Low	High ^e	Low	High ^b	Low	Low	High ^e
Tan et al, 2018 ⁵⁶	Low	Low	High ^g	Low	Low	Low	High ^f	High ^f	Low
Wright et al, 2015 ⁵⁷	Low	Low	Low	High ^e	Low	Low	High ^{d,f,h}	High ^{d,f}	High ^e

Abbreviation: FMF, Fetal Medicine Foundation; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

^aPossible risk-of-bias/applicability concerns levels: low, high, unclear.

^bThe population did not reflect Ontario.

^cFalse-positive rate for the FMF algorithm was fixed by design and might have been different if allowed to be data-dependent.

^dFalse-positive rates were fixed by design and might have been different if allowed to be data-dependent.

^eAssessment of occurrence of preterm pre-eclampsia did not account for the effect of acetylsalicylic acid.

^fScreen-positive rate was fixed by design and might have been different if allowed to be data-dependent.

^gFalse-positive rate for the NICE algorithm was not reported, so we could not fully assess its accuracy.

^hNo mention of which markers were used to construct the Fetal Medicine Foundation model.

Table A3: GRADE Evidence Profile for the Effect of an FMF-Based Screening Program

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Pre-eclampsia with delivery at < 37 wk							
2 (observational)	Serious limitations (-1) ^a	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Pre-eclampsia with delivery at < 34 wk							
1 (observational)	Very serious limitations (-2) ^a	Could not be assessed ^b	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Birth weight < 2500 g							
1 (observational)	Very serious limitations (-2) ^a	Could not be assessed ^b	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Apgar score < 4 at 5 minutes after birth							
1 (observational)	Very serious limitations (-2) ^a	Could not be assessed ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Stillbirth							
1 (observational)	Very serious limitations (-2) ^a	Could not be assessed ^a	No serious limitations	Very serious limitations (-2) ^c	Undetected	None	⊕ Very low
Neonatal death							
1 (observational)	Very serious limitations (-2) ^a	Could not be assessed ^a	No serious limitations	Very serious limitations (-2) ^b	Undetected	None	⊕ Very low

Abbreviations: FMF, Fetal Medicine Foundation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

^a Rolnik et al⁵⁰ acknowledged that ethnicity and mode of conception were potential confounders, but they had no data to adjust them.

^b We would not assess inconsistency with a single study.

^c The confidence interval was too wide to conclude whether the FMF-based screening program was effective.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Allen RE, Zamora J, Arroyo-Manzano D, Velauthar L, Allotey J, Thangaratinam S, et al. External validation of preexisting first trimester preeclampsia prediction models. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2017;217:119-25.	Wrong study design
Brunelli E, Seidenari A, Germano C, Prefumo F, Cavoretto P, Di Martino D, et al. External validation of a simple risk score based on the ASPRE trial algorithm for preterm pre-eclampsia considering maternal characteristics in nulliparous pregnant women: a multicentre retrospective cohort study. <i>BJOG.</i> 2020;127(10):1210-5.	Wrong outcome
Cabunac P, Karadzov Orlic N, Ardalic D, Damnjanovic Pazin B, Stanimirovic S, Banjac G, et al. Use of FMF algorithm for prediction of preeclampsia in high risk pregnancies: a single center longitudinal study. <i>Hypertens.</i> 2021;40(3):171-9.	Wrong study design
Cordisco A, Periti E, Antonioli N, Lozza V, Conticini S, Vannucci G, et al. Clinical implementation of pre-eclampsia screening in the first trimester of pregnancy. <i>Pregnancy Hypertens.</i> 2021;25:34-8.	Wrong study design
Cuckle H. Local validation and calibration of pre-eclampsia screening algorithms. <i>Ultrasound Obstet Gynecol.</i> 2019;53(6):724-8.	Wrong study design
Goto M, Koide K, Tokunaka M, Takita H, Hamada S, Nakamura M, et al. Accuracy of the FMF Bayes theorem-based model for predicting preeclampsia at 11-13 weeks of gestation in a Japanese population. <i>Hypertens Res.</i> 2021;44(6):685-91.	Wrong study design
Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia screening: evidence report and systematic review for the US Preventive Services Task Force. <i>JAMA.</i> 2017;317(16):1668-83.	Wrong study design
Herraiz I, Arbues J, Camano I, Gomez-Montes E, Graneras A, Galindo A. Application of a first-trimester prediction model for pre-eclampsia based on uterine arteries and maternal history in high-risk pregnancies. <i>Prenat Diagn.</i> 2009;29(12):1123-9.	Wrong study design
Hu J, Gao J, Liu J, Meng H, Hao N, Song Y, et al. Prospective evaluation of first-trimester screening strategy for preterm pre-eclampsia and its clinical applicability in China. <i>Ultrasound Obstet Gynecol.</i> 2021;58(4):529-39.	Wrong study design
Huang T, Rashid S, Dennis A, Mak-Tam E, Priston M, Gibbons C, et al. Early pregnancy screening for preeclampsia and preterm birth using maternal characteristics and biomarkers. <i>Am J Obstet Gynecol.</i> 2022;226(1):S638-S.	Poster
Huang T, Rashid S, Mak-Tam E, Priston M, Gibbons C, Bedford M, et al. Prenatal pre-eclampsia screening using maternal characteristics, maternal serum PAPP-A and PLGF in the first trimester. <i>Am J Obstet Gynecol.</i> 2022;226(1):S158-S.	Poster
Kagan KO, Sonek J, Wagner P, Hoopmann M. Principles of first trimester screening in the age of non-invasive prenatal diagnosis: screening for other major defects and pregnancy complications. <i>Arch Gynecol Obstet.</i> 2017;296(4):635-43.	Review
Lakovscek IC, Ulrich D, Jauk S, Csapo B, Kolovetsiou-Kreiner V, Mayer-Pickel K, et al. Risk assessment for preterm preeclampsia in first trimester: comparison of three calculation algorithms. <i>Eur J Obstet Gynecol Reprod Biol.</i> 2018;231:241-7.	Wrong study design

Citation	Primary reason for exclusion
Lin TY, Huang HY, Chan KS, Chen YT, Chu FC, Shaw SW. Current update of first trimester preeclampsia screening in Asia. <i>J Obstet Gynaecol Res.</i> 2021;47(1):26-33.	Review
Meertens Linda JE, Scheepers Hubertina CJ, van Kuijk Sander MJ, Aardenburg R, van Dooren Ivo MA, Langenveld J, et al. External validation and clinical usefulness of first trimester prediction models for the risk of preeclampsia: a prospective cohort study. <i>Fetal Diagn Ther.</i> 2019;45(6):381-93.	Wrong study design
O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. <i>Ultrasound Obstet Gynecol.</i> 2017;49(6):756-60.	Wrong study design
Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. <i>Aust N Z J Obstet Gynaecol.</i> 2013;53(6):532-9.	Wrong study design
Poon LC, Rolnik DL, Tan MY, Delgado JL, Tsokaki T, Akolekar R, et al. ASPRE trial: incidence of preterm preeclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. <i>Obstet Gynecol Survey.</i> 2018;73(11):623-5.	Wrong study design/duplicate
Poon LC, Rolnik DL, Tan MY, Delgado JL, Tsokaki T, Akolekar R, et al. ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. <i>Ultrasound Obstet Gynecol.</i> 2018;51(6):738-42.	Wrong study design
Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. <i>Ultrasound Obstet Gynecol.</i> 2017;50(4):492-5.	Wrong study design
Skråstad RB, Hov CG, Blaas H-GK, Romundstad PR, Salvesena KA. Risk assessment for preeclampsia in nulliparous women at 11–13 weeks gestational age: prospective evaluation of two algorithms. <i>Essentially MIDIRS.</i> 2015;6(1):39.	Wrong study design
Skråstad RB, Hov GG, Blaas HG, Romundstad PR, Salvesen KA. Risk assessment for preeclampsia in nulliparous women at 11-13 weeks gestational age: prospective evaluation of two algorithms. <i>BJOG.</i> 2015;122(13):1781-8.	Wrong study design/duplicate
Sovio U, Smith G. Evaluation of a simple risk score to predict preterm pre-eclampsia using maternal characteristics: a prospective cohort study. <i>BJOG.</i> 2019;126(8):963-70.	Wrong intervention
Tarca AL, Taran A, Romero R, Jung E, Paredes C, Bhatti G, et al. Prediction of preeclampsia throughout gestation with maternal characteristics and biophysical and biochemical markers: a longitudinal study. <i>Am J Obstet Gynecol.</i> 2022;226(1):126.e1-22.	Wrong study design
Thilaganathan B. The ASPRE pre-eclampsia trial: implications for basic research and clinical practice. <i>Cardiovasc Res.</i> 2018;114(8):e60-1.	Commentary

Appendix 4: Selected Excluded Studies—Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Hadker N, Garg S, Costanzo C, Miller JD, Foster T, van der Helm W, et al. Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective. <i>J Med Econ.</i> 2010;13(4):728-37.	Not specific to intervention of interest
Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. <i>Health Technol Assess.</i> 2008;12(6):iii-iv, 1-270.	Not specific to intervention of interest
Werner EF, Hauspurg AK, Rouse DJ. A cost-benefit analysis of low-dose Aspirin prophylaxis for the prevention of preeclampsia in the United States. <i>Obstet Gynecol.</i> 2015;126(6):1242-1250.	Not specific to intervention of interest
Zakiah N, Postma MJ, Baker PN, van Asselt ADI; IMPROVED Consortium. Pre-eclampsia diagnosis and treatment options: a review of published economic assessments. <i>Pharmacoeconomics.</i> 2015;33(10):1069-82.	Systematic review; no primary economic evaluation

Appendix 5: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A4: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of the FMF-Based Screening Program

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment ^a
Dubon Garcia et al, 2021, ⁶⁶ Belgium	Yes	Yes	Partially	Yes; Belgian payers' perspective	Yes	NA; study used a 1-year time horizon	Yes	No	Partially applicable
Park et al, 2021, ⁶⁵ Australia	Yes	Yes	No	Yes; Australian hospital	No; effects associated with impact on infant outcomes (i.e., NICU stay) not included	No	No	No	Partially applicable
Mallampati et al, 2019, ⁶⁸ United States	Yes	Partially; included comparators that were not relevant to standard care in Ontario	Partially	Yes; societal perspective	Yes	NR; study did not report a time horizon	No	No	Partially applicable
Ortved et al, 2019, ⁶⁷ Canada	Yes	Yes	Yes	No	No; effects associated with impact on infant outcomes (i.e., NICU stay) not included	NA; study used a 1-year time horizon	No	No	Directly applicable

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment ^a
Mone et al, 2018, ⁶⁹ Ireland	Yes? Only low risk	Partially: comparators were not relevant to standard care in Ontario	Partially	No	Yes	Yes	Yes	No	Not applicable
Shmueli et al, 2012, ⁷⁰ Israel	Yes	Partially: comparators were not relevant to standard care in Ontario	No	Yes; payer perspective	Yes	Yes; 3%	Yes	No	Not applicable

Abbreviations: FMF, Fetal Medicine Foundation; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

^aOverall judgment might be "directly applicable," "partially applicable," or "not applicable."

Table A5: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of the FMF-Based Screening Program

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment ^b
Dubon Garcia et al, 2021, ⁶⁶ Belgium	Yes	Partially; 1-year time horizon did not consider the long-term health effects of pre-eclampsia on maternal and infant health	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes; this study was funded by Roche Diagnostics; Roche was also involved in the study design, collection, analysis, and interpretation of data, as well as the writing of the report	Minor limitations
Park et al, 2021, ⁶⁵ Australia	Yes	Partially; 2 year time horizon did not consider the long-term health effects of pre-eclampsia on maternal and infant health	Partially; did not include QALYs	Yes	Yes	No; costs associated with infant care (e.g., NICU stay) not included	Yes	Yes	Partially; incremental analysis provided, but could not be calculated from reported data	Yes	No	Minor limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment ^b
Mallampati et al, 2019, ⁶⁸ United States	Yes	NR; study did not report a time horizon	Partially; did not include QALYs	Yes	Yes	No; costs associated with infant care (e.g., NICU stay) not included	Yes	Yes	Yes	Yes	No	Minor limitations
Ortved et al, 2019, ⁶⁷ Canada	Yes	Partially; 1-year time horizon did not consider the long-term health effects of pre-eclampsia on maternal and infant health	Partially; did not include QALYs, and only reported outcomes for pre-eclampsia with delivery < 34 weeks' gestation; did not report outcomes for pre-eclampsia with delivery between 34 and 37 weeks' gestation	Partially; some of the probability inputs were obtained by clinical expert opinion	Yes	No; costs associated with infant care (e.g., NICU stay) not included	Yes	Yes	Yes	Partially; probabilistic sensitivity analysis not conducted	NR	Potentially serious limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment ^b
Mone et al. 2018, ⁶⁹ Ireland	Yes	Unclear; authors did not report a time horizon; costs seemed to be for less than 12 months but study included lifetime QALYs gained from avoiding premature death	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially; probabilistic sensitivity analysis not conducted	NR; this study was supported by Health Research Board Mother and Baby Clinical Trials Network and Perinatal Ireland	Potentially serious limitations
Shmueli et al. 2012, ⁷⁰ Israel	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially; probabilistic sensitivity analysis not conducted	No	Minor limitations

Abbreviations: NICU, neonatal intensive care unit; NR, not reported; QALY, quality-adjusted life-year.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

^a Clinical inputs include relative treatment effects, natural history, and utilities.

^b Overall judgment might be "minor limitations," "potentially serious limitations," or "very serious limitations."

Appendix 6: Letter of Information

LETTER OF INFORMATION

Ontario Health is conducting a review of a **method of screening for Preeclampsia, a condition of high blood pressure during pregnancy**. The purpose is to better understand how this screening technique can be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed with preeclampsia and who may or may not have accessed a screening program.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 15-30 minutes of your time for a phone interview
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 15-30 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US:

Appendix 7: Interview Guide

Interview for Pop-wide Screening for Preeclampsia HTA

What are pregnant peoples' preferences and values around population-wide screening to predict preeclampsia risk, their decision-making around risk and potential impact of this screening program? To examine patient perceptions challenges or barriers to accessing screening and overall perceptions of a population-wide preeclampsia screening program.

Intro

Explain OH(Q) purpose, HTA process, and purpose of interview

Journey to Preeclampsia (if applicable)

Describe journey to findings of preeclampsia (if applicable)

Routine tests? Any signs or symptoms?

Barriers to access?

Other?

Information about Preeclampsia

What was awareness of preeclampsia prior to pregnancy? Was it a concern, why?

Thoughts/feelings on information

Source of info?

What is valued about info?

Impact of Finding of Preeclampsia

What next after discovery of preeclampsia?

Treatment and access to treatment.

COORDINATION OF CARE – Value in staying local, being treated locally and having care centralized.

Pop-wide Screening Program for Preeclampsia (mostly hypothetical)

What would be valuable to you in a supplemental screening program

(Would a preeclampsia screening program be valuable to you? Why/why not?)

Do you have any concerns about such a screening program?

(example: false positives, anxiety, access, etc)

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Ontario Health
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Toll Free: 1-877-280-8538
TTY: 1-800-855-0511
Email: OH-HQO_hqa@OntarioHealth.ca
hqontario.ca

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