About the Authors

Mary Alexandra Murphy, MD, MASc, FRCSC

Dr. Alix Murphy is a practicing obstetrician-gynecologist and recent graduate of the Complex Obstetric Surgery Fellowship at Mount Sinai Hospital in Toronto. She completed her medical degree at the University of Queensland in Brisbane, Australia, and residency at the University of Toronto. She is currently pursuing a Master's degree in Health Quality at Queen's University. Dr. Murphy holds both undergraduate and master's degrees in chemical engineering, a background that informs her interest in systems thinking, surgical safety, and quality improvement. Her clinical and academic work focuses on health system innovation and improving outcomes in complex obstetric care. She has worked in a range of health care environments globally, which has shaped her perspective on equitable access to reproductive and surgical care.

Affiliations: Mount Sinai Hospital, Department of Obstetrics & Gynecology, Toronto, Ontario

Sebastian Rupert Hobson, MD, PhD, MPH, FRANZOG, FACOG, FRCSC

Dr. Sebastian Hobson is a Maternal-Fetal Medicine Specialist who has particular clinical and research interests in labour and delivery care, complex obstetric surgery and placenta accreta spectrum disorders. He attended medical school and residency training at Monash University in Melbourne whilst concurrently completing a Master's in Public Health and PhD in preeclampsia. After further subspecialty training in Australia, Dr. Hobson moved to Canada to join the Maternal-Fetal Medicine Division at the University of Toronto. He is currently the Head of Labour and Delivery at Mount Sinai Hospital and Co-Chair of the Clinical Practice Obstetrics Committee for SOGC.

Affiliations: Mount Sinai Hospital, Department of Obstetrics & Gynecology, Toronto, Ontario

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Risk Reduction In Pregnancy: Evidence-Based Use Of Aspirin For Prevention Of Preeclampsia

Mary Alexandra Murphy, MD, MASc, FRCSC
Sebastian Rupert Hobson, MD, PhD, MPH, FRANZOG, FACOG, FRCSC

Introduction

Preeclampsia is a multisystem disorder that emerges in the second half of pregnancy, characterized by the onset of hypertension and end-organ dysfunction. Globally, hypertensive disorders of pregnancy are the second leading cause of direct maternal death.[1] Preeclampsia alone it is estimated to affect up to 5% of all pregnancies.[2] This condition poses serious risks to both mother and fetus, including increasing the likelihood of complications such as preterm birth, fetal growth restriction, and long-term cardiovascular consequences.

Given the severity of complications associated with preeclampsia, prevention strategies are essential, particularly for individuals at high risk. One of the most well-established interventions is the use of low-dose aspirin, which has been shown to significantly reduce the risk of preeclampsia in select high-risk populations. Leading obstetric organizations, including the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) have issued guidelines recommending aspirin prophylaxis for individuals with specific risk factors for the development of preeclampsia.[3,4] Despite this, awareness and implementation of these guidelines vary, highlighting the need for continued education and standardization of care.

This article explores the current evidence and guidelines supporting the use of aspirin for preventing preeclampsia. By understanding the benefits of aspirin, identifying appropriate candidates most likely to benefit, and ensuring proper administration, healthcare providers can improve maternal and fetal outcomes and reduce the burden of this serious condition.

Understanding Preeclampsia

Preeclampsia is defined as new-onset hypertension occurring after 20 weeks of gestation, with maternal end-organ dysfunction or uteroplacental insufficiency.[4] Maternal end-organ complications include the central nervous system (e.g., severe headache, eclampsia, stroke, retinal detachment), cardiorespiratory symptoms (e.g., pulmonary edema, myocardial infarction), hematological abnormalities (e.g., thrombocytopenia, coagulopathy), renal impairment (e.g., acute kidney injury, renal failure), and/or hepatic involvement (e.g., Hemolysis, Elevated Liver enzymes, Low Platelet count [HELLP] syndrome, severe liver dysfunction, hepatic hematoma or rupture). Uteroplacental insufficiency may manifest as fetal growth restriction, atypical or abnormal fetal heart rate patterns, oligohydramnios, abnormal Doppler studies, placental abruption, or intrauterine fetal death.[4]

While the underlying etiology of preeclampsia remains unclear, placental dysfunction and maternal cardiovascular maladaptation to pregnancy are recognized as central mechanisms of the disease. The prevailing theory is that defective placental implantation through abnormal trophoblast invasion and abnormal spiral artery remodelling lead to poor placental perfusion. This ischemic environment triggers systemic maternal endothelial dysfunction, inflammation, and an imbalance of vasoactive factors, ultimately leading to the clinical manifestations of preeclampsia.

Several risk factors have been identified that increase the likelihood of developing preeclampsia. Among them, chronic hypertension is considered one of the strongest predictors.[5] Other significant risk factors include advanced maternal age, obesity, diabetes, multiple gestation, use of assisted reproductive technologies, autoimmune

High-risk factors*	Moderate-risk factors**
• History of preeclampsia in a previous pregnancy • Pre-pregnancy body mass index >30 kg/m² • Chronic hypertension • Pre-gestational diabetes mellitus (i.e., type 1 or type 2 diabetes) • Chronic kidney disease • Autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid antibody syndrome) • Assisted reproductive technology (e.g., in vitro fertilization)	• Nulliparity • Multiple gestation • Maternal age >40 years • Prior placental abruption • Prior stillbirth • Prior fetal growth restriction

Table 1. Risk factor-based criteria for aspirin use in pregnancy; *courtesy of Mary Alexandra Murphy, MD, MASc, FRCSC and Sebastian Rupert Hobson, MD, PhD, MPH, FRANZOG, FACOG, FRCSC*

* Presence of one is sufficient to recommend aspirin
** Consider aspirin if presence of two or more

disorders, kidney disease, and a personal or family history of preeclampsia.

Preeclampsia is a major contributor to adverse pregnancy outcomes, including preterm birth, fetal growth restriction, and low birth weight.[6] Furthermore, it remains a major cause of direct maternal mortality worldwide, with deaths primarily due to stroke, organ failure, and other complications related to severe hypertensive crises.[1] In addition to its immediate risks, preeclampsia carries long-term implications for both mother and child. Patients with a history of preeclampsia face an increased risk of chronic hypertension, cardiovascular disease, and stroke later in life.[7] Similarly, children born to mothers with preeclampsia may be at higher risk of developing cardiovascular, metabolic, and neurological disorders. Globally, it is estimated that more than 300 million people are at an increased risk of chronic health conditions due to prior exposure to preeclampsia.[8] Given these significant maternal and fetal complications, primary prevention remains a key priority in obstetric care.

The Role Of Aspirin In Preventing Preeclampsia

The preventive use of low-dose aspirin for preeclampsia has been widely studied over several decades. Initial evidence emerged from a 1979 retrospective cohort study, which found that frequent aspirin use during pregnancy was associated with a lower incidence of preeclampsia in primigravidas.[9] This finding led to the hypothesis that platelet activation played a role in the development of preeclampsia, and aspirin, as an antiplatelet agent, could help mitigate this effect.

Aspirin exerts its effects by irreversibly inhibiting cyclooxygenase-1 (COX-1), which reduces thromboxane A2 production, a potent vasoconstrictor and promoter of platelet aggregation.[3] This mechanism ultimately improves placental blood flow and reduces systemic inflammation, both of which contribute to the pathophysiology of preeclampsia.[10] By decreasing placental ischemia and endothelial dysfunction, aspirin may prevent or delay the onset of the disorder in high-risk individuals.

Contemporary evidence supporting the use of aspirin in pregnancy derives from the renowned ASPRE trial, a multicenter, randomized controlled trial that investigated aspirin's role in preventing preeclampsia. The study found that administering low-dose aspirin (150 mg daily) from 11–14 weeks of gestation until 36 weeks in high-risk pregnancies led to a 62% reduction in the incidence of preterm (<37 weeks gestation) preeclampsia compared to placebo.[11] Furthermore, the risk of developing preeclampsia <34 weeks gestation was reduced by 82% in the aspirin group compared to placebo. Additional meta-analyses, including reviews by the United States Preventive Services Task Force (USPSTF), have further confirmed the efficacy of aspirin in reducing the risk of preeclampsia, particularly when started before 16 weeks gestation.[12]

Despite these findings, questions remain regarding the optimal dosage and timing of aspirin administration. These considerations are explored in more detail in the following sections. Current guidelines generally advise starting aspirin before 16 weeks of gestation, as earlier initiation has been associated with greater benefit in some studies.[13] However, patients who present from 16–20 weeks may still derive benefit from daily low-dose aspirin and should be offered therapy when appropriate.[12]

Despite strong evidence supporting aspirin's role in reducing preeclampsia risk, its implementation in clinical practice depends on identifying patients who are most likely to benefit. Given the multifactorial nature of preeclampsia, a risk-based approach is necessary to ensure that aspirin prophylaxis is targeted to those who are most at-risk.

Guidelines For Aspirin Use In Pregnancy

In Canada, the SOGC recommends the use of daily low-dose aspirin (81 or 162 mg) for individuals at high risk of developing preeclampsia, ideally starting before 16 weeks of gestation and continuing until 36 weeks.[4] These recommendations align with international guidelines from organizations such as the ACOG,[3] the USPSTF,[12] and the National Institute for Health and Clinical Excellence (NICE),[14] all of which advocate for a risk-based approach to aspirin prophylaxis. These recommendations are based on extensive research demonstrating that aspirin is most effective when used in high-risk populations and initiated early in pregnancy.

Criteria For Aspirin Prophylaxis

Risk assessment for preeclampsia is based on a combination of pre-pregnancy demographics, pre-existing medical conditions, previous pregnancy complications, and current pregnancy features. Based on recommendations from the International Society for the Study of Hypertension in Pregnancy, the SOGC classifies risk factors into high-risk and moderate-risk categories to guide aspirin use,[4] as outlined in **Table 1**.

Given Canada's diverse population, it is important to recognize disparities in maternal health outcomes. Studies indicate that individuals of African, South Asian, and Indigenous backgrounds may have an elevated risk of hypertensive disorders in pregnancy. Some guidelines consider racial disparities along with other sociodemographic factors (e.g., low socioeconomic status) as moderate-risk factors for preeclampsia.[3] Ensuring equitable access to aspirin prophylaxis is essential to improving maternal and neonatal outcomes across the country and for all.

Dosing Recommendations

Canadian guidelines currently lack consensus regarding the recommended dose of aspirin for preeclampsia prevention. Traditionally, it was believed that a higher daily dose of aspirin, such as 162 mg or similar, would maximize effectiveness, whereas a lower daily dose of 81 mg or similar would maximize maternal safety. However, a recent large cohort study by Kupka *et al*.[15] compared daily doses of 150-160 mg versus 75 mg during pregnancy for preeclampsia prevention and showed no significant differences in preeclampsia incidence or adverse bleeding outcomes. These findings suggest that both dosing strategies may be appropriate. Clinicians should consider individual patient characteristics, risk profiles, and tolerance when selecting the most suitable dosage. Additionally, practical considerations such as cost, pill burden, and availability may influence decision-making regarding dose selection.

Safety And Contraindications

Low-dose aspirin is considered safe and well-tolerated in pregnancy. Large-scale studies have not shown an increased risk of congenital anomalies, excessive bleeding at delivery, or other major complications when taken at recommended doses.[16] However, aspirin should be avoided in individuals with the following conditions:

- Known allergy or hypersensitivity to aspirin
- Active peptic ulcer disease or gastrointestinal bleeding
- Severe bleeding disorders
- Any contraindication to aspirin therapy, such as contraindication to NSAIDs, severe renal or hepatic disease, and gout

Practical Considerations For Healthcare Providers

To effectively reduce the incidence of preeclampsia, early identification of at-risk patients is essential. Healthcare providers should conduct a comprehensive risk assessment at the first prenatal visit to determine which patients qualify for aspirin prophylaxis. The SOGC recommends a multifactorial screening approach,

which combines maternal history, biophysical markers, and biochemical tests to improve early detection of preeclampsia risk.[4]

Screening And Risk Assessment

All pregnant patients should be screened for preeclampsia risk factors between 11–14 weeks gestation. Where available, the SOGC endorses the use of combined first-trimester screening algorithms that integrate:

- Maternal risk factors (as outlined in **Table 1**)
- Mean arterial pressure (measured at the first prenatal visit)
- Uterine artery Doppler studies (assessment of placental blood flow)
- Biochemical markers (e.g., placental growth factor, pregnancy-associated plasma protein-A)

Studies have shown that using this multifactorial approach, when available, is more effective than relying on clinical history alone for identifying individuals at high risk for preterm preeclampsia.[4,11] This method allows for more precise risk stratification, ensuring aspirin is prescribed to those most likely to benefit. At the very least, risk factor assessment should be conducted at the first antenatal visit.

For individuals at high risk, aspirin prophylaxis should be initiated before 16 weeks of gestation and continue until 36 weeks. Given the multifactorial nature of preeclampsia, a tailored, patient-centred approach is necessary.

Counselling Patients On Aspirin Use

Clear, evidence-based counselling can improve adherence to aspirin prophylaxis. Many patients have concerns about taking medication during pregnancy, and addressing misconceptions is crucial. Key points to emphasize include:

- Aspirin is safe in pregnancy and does not increase the risk of congenital anomalies.[3]
- Aspirin does not cause excessive bleeding at delivery when taken at recommended doses.[16]
- Low-dose aspirin significantly reduces the risk of preeclampsia, particularly in those with high-risk factors.[11]
- As a good practice point, aspirin administration is generally suspended during episodes of antepartum hemorrhage and resumed based on the advice of the most responsible pregnancy care provider.

Shared decision-making is essential, ensuring that patients are well-informed and comfortable with their treatment plan.

Addressing Barriers To Access

Despite strong recommendations, some patients may face barriers to accessing aspirin prophylaxis, including financial constraints, lack of awareness, or limited access to prenatal care. In Canada, efforts should be made to improve accessibility, particularly for individuals from underserved communities, including Indigenous, Black, and low-income communities. Incorporating aspirin prescribing into standard prenatal care protocols can help bridge these gaps.

By prioritizing early risk screening, proactive counselling, and equitable access, healthcare providers play a key role in the effective implementation of aspirin prophylaxis. These efforts are essential to reducing the burden of preeclampsia and improving maternal and fetal outcomes.

Conclusion

Preeclampsia remains a serious threat to maternal and perinatal health in Canada and worldwide, contributing to acute complications, such as seizures, stroke, and maternal death as well as long-term health risks for both mother and child. Given its complex pathophysiology and the limited treatment options once it develops, prevention is critical.

Low-dose aspirin has emerged as a safe, low-cost, and highly-effective evidence-based intervention to reduce the risk of preeclampsia in high-risk pregnancies. Large trials, such as the ASPRE study, have demonstrated its effectiveness, especially when started early in pregnancy. Reflecting this evidence, many guidelines, including those from the SOGC, recommend early screening using multifactorial risk assessment tools to identify candidates for aspirin prophylaxis.

For healthcare providers, the opportunity lies in early identification, patient-centred counselling, and equitable implementation of care. As clinical tools and risk prediction models continue to evolve, integrating these strategies into routine prenatal care can lead to significant improvements in maternal and fetal outcomes.

Continued research, education, and supportive health policies will be key to ensure that all pregnant individuals at risk have access to preventive strategies like aspirin.

Correspondence

Sebastian Rupert Hobson, MD, PhD, MPH, FRANZOG, FACOG, FRCSC
Email: sebastian.hobson@sinaihealth.ca

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