Screening for preeclampsia risk and prophylaxis with acetylsalicylic acid

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Preeclampsia affects 2%–8% of pregnancies, and preterm preeclampsia 0.5%–2% of pregnancies.[1] Preeclampsia, particularly when it occurs before 32 weeks' gestation, remains a leading cause of maternal and perinatal morbidity and mortality.[1] Acetylsalicylic acid (ASA) is highly effective in preventing preterm preeclampsia but is grossly underutilized in people at risk of the condition in Canada. Despite accumulating evidence that multifactorial screening can predict early-onset preeclampsia, and level-1 evidence for the efficacy of ASA, protocols used in most Canadian jurisdictions are disjointed and inadequate. We discuss how the burden of preterm preeclampsia could be reduced in Canada through widespread appropriate risk screening.

Use of ASA for preeclampsia prevention was first described in 1978[2] and supported by a randomized trial in 1985.[3] In 2017, the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial showed 62% reduction in preterm preeclampsia (80% for preeclampsia < 32 wk) at a compliance rate of 80%.[4] A subsequent meta-analysis confirmed a substantial reduction in preterm preeclampsia with ASA at a dose of 100–162 mg/d, when initiated before 16 weeks of gestation.[5] Whereas ASA is effective for prevention of preterm preeclampsia, the impact on term preeclampsia may be less pronounced.[4,5] Preeclampsia prophylaxis has also been explored for all pregnant people,[6] with a lower associated cost,[7] but the most compelling evidence for its efficacy is in pregnant people at high risk of preeclampsia.

Despite the evidence in favour of ASA prophylaxis, it appears to be used in only a minority of pregnant people at risk of developing preeclampsia.[8] For example, in a population-based study in Ontario, only 39% of pregnant people with diabetes, obesity and hypertension used ASA.[8] Among those with only diabetes, obesity or hypertension, the rate of ASA use was 17%, 7% and 28%, respectively.[8] Possible reasons for these low rates of prophylaxis use include a lack of awareness among most practitioners, lack of access to multifactorial screening and, to a smaller extent, perceived risks of medication use in pregnancy.

The current approach by many in Canada is to identify people at higher risk of preeclampsia around 12 weeks of gestation, based on clinical risk factors such as previous preeclampsia, diabetes, obesity or chronic hypertension. People at risk are advised to take ASA (80–162 mg/d) starting at 12 weeks, and to continue until 36 weeks of gestation.[14] Uterine artery Doppler and biochemical markers have also been used for screening, but when used in isolation have suboptimal screening performance. Risk stratification based on individual factors alone has high false-positive rates. Most individuals screening positive are not truly at risk, which results in unnecessary ASA use.[9] Further, screening with individual factors has low sensitivity for the development of early-onset preeclampsia and results in most patients at high risk not receiving ASA. Given the efficacy, low risk and low financial cost of ASA prophylaxis in pregnancy, the greatest harm lies in missing those in whom ASA is indicated, but who are missed by insensitive screening methods.

A recently developed multifactorial screening algorithm that utilizes all available clinical, uterine artery Doppler ultrasonography and biochemical factors in combination has nearly 100% (95% confidence interval 80%–100%) sensitivity for predicting early-onset preeclampsia (< 32 wk) at a relatively low screen-positive rate of 10% and appears cost effective.[10] When ASA was used by people who have positive multifactorial screening, the cost savings from a reduction in neonatal intensive care of their infants far outweighed the cost of preeclampsia screening.[11] This multifactorial approach, also validated in a cohort in Quebec, Canada, may further identify fetuses at risk of intrauterine growth restriction and death, as well

Key points

- Multifactorial early-pregnancy screening for preeclampsia can identify most patients at risk, particularly of early-onset, severe disease.
- Prophylaxis with acetylsalicylic acid (ASA) can prevent 80%–94% of early-onset, severe preeclampsia.
- Most pregnant people in Canada do not have access to preeclampsia screening, and a large majority are not offered ASA prophylaxis when indicated.
- Consideration should be given to multifactorial early-pregnancy screening for preeclampsia, as well as timely initiation of ASA in patients who are identified to be at risk.

as preterm birth.[12] In a cost effectiveness analysis in Alberta, Canada, the potential savings of a multifactorial screening algorithm were estimated to approach $140 million over a 10-year period.[13] Further, the long-term burden of preeclampsia, such as maternal cardiovascular diseases and impaired child development also require further study and consideration.

Multifactorial risk assessment for preeclampsia and use of ASA in individuals at risk was endorsed in 2022 by the Society of Obstetricians and Gynaecologists of Canada.[14] Optimally, each centre that provides pregnancy care could consider a multifactorial screening tool applied at 11–13 weeks' gestation that incorporates clinical risk factors, maternal blood pressure, uterine artery Doppler and biochemical placental function assessment (placental growth factor and pregnancy-associated plasma protein A) is essential.[15] However, such a coordinated approach requires technical training in uterine artery Doppler ultrasonography and access to standardized laboratory measurement of placental growth factor. Further, such screening programs need to be done in a timely manner, to alert the practitioner that their patient is eligible for ASA prophylaxis initiation.[15] Currently the guidelines state that people who screen positive should use 150 mg/d, and ideally should be started before 16 weeks of gestation.[16] In Canada, given the 80 or 81 mg pill that is available, this would translate to the use of 160–162 mg/d.

A centralized, coordinated and standardized multifactorial risk assessment for preeclampsia is virtually nonexistent in most Canadian jurisdictions, though Alberta, Ontario and Quebec are working toward it. Until such universal screening programs become readily available, the process for identifying those at high risk for preeclampsia will be fragmented. Early pregnancy care is largely completed by family physicians, some of whom may not be familiar with or equipped to perform preeclampsia screening. Thus, to assist early prenatal care providers, the Fetal Medicine Foundation has a freely accessible online tool for multifactorial preeclampsia screening that can be tailored to local resources (https://fetalmedicine.org/research/assess/preeclampsia). Not all factors (clinical, uterine artery Doppler and biochemical) must be input to generate a risk estimate, which is especially relevant given the regional availability of these resources. This easy-to-use online tool also facilitates shared decision-making for the initiation of ASA in people at risk.

Considering the effectiveness of a multifactorial screening approach tied to ASA prophylaxis can prevent 80%–94% of early-onset severe preeclampsia,[4,5] an opportunity exists in Canada to reduce the burden of preterm preeclampsia. Until such programs become available, every early prenatal care provider should perform assessment of preeclampsia risk in every pregnant person at 11–13 weeks' gestation using the tools available to them and initiate ASA in individuals at risk. Without such a concerted effort, some pregnant people, and their fetuses, may be being denied protection against preeclampsia, prematurity and related morbidity.

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