Prevention of preeclampsia with aspirin

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Preeclampsia is defined as hypertension arising after 20 weeks of gestational age with proteinuria or other signs of end-organ damage and is an important cause of maternal and perinatal morbidity and mortality, particularly when of early onset. Although a significant amount of research has been dedicated in identifying preventive measures for preeclampsia, the incidence of the condition has been relatively unchanged in the last decades. This could be attributed to the fact that the underlying pathophysiology of preeclampsia is not entirely understood. There is increasing evidence suggesting that suboptimal trophoblastic invasion leads to an imbalance of angiogenic and antiangiogenic proteins, ultimately causing widespread inflammation and endothelial damage, increased platelet aggregation, and thrombotic events with placental infarcts. Aspirin at doses below 300 mg selectively and irreversibly inactivates the cyclooxygenase-1 enzyme, suppressing the production of prostaglandins and thromboxane and inhibiting inflammation and platelet aggregation. Such an effect has led to the hypothesis that aspirin could be useful for preventing preeclampsia. The first possible link between the use of aspirin and the prevention of preeclampsia was suggested by a case report published in 1978, followed by the first randomized controlled trial published in 1985. Since then, numerous randomized trials have been published, reporting the safety of the use of aspirin in pregnancy and the inconsistent effects of aspirin on the rates of preeclampsia. These inconsistencies, however, can be largely explained by a high degree of heterogeneity regarding the selection of trial participants, baseline risk of the included women, dosage of aspirin, gestational age of prophylaxis initiation, and preeclampsia definition. An individual patient data meta-analysis has indicated a modest 10% reduction in preeclampsia rates with the use of aspirin, but later meta-analyses of aggregate data have revealed a dose-response effect of aspirin on preeclampsia rates, which is maximized when the medication is initiated before 16 weeks of gestational age. Recently, the Aspirin for Evidence-Based Preeclampsia Prevention trial has revealed that aspirin at a daily dosage of 150 mg, initiated before 16 weeks of gestational age, and given at night to a high-risk population, identified by a combined first trimester screening test, reduces the incidence of preterm preeclampsia by 62%. A secondary analysis of the Aspirin for Evidence-Based Preeclampsia Prevention trial data also indicated a reduction in the length of stay in the neonatal intensive care unit by 68% compared with placebo, mainly because of a reduction in births before 32 weeks of gestational age with preeclampsia. The beneficial effect of aspirin has been found to be similar in subgroups according to different maternal characteristics, except for the presence of chronic hypertension, where no beneficial effect is evident. In addition, the effect size of aspirin has been found to be more pronounced in women with good compliance to treatment. In general, randomized trials are underpowered to investigate the treatment effect of aspirin on the rates of other placental-associated adverse outcomes such as fetal growth restriction and stillbirth. This article summarizes the evidence around aspirin for the prevention of preeclampsia and its complications.

Key words: abruption, adverse pregnancy outcome, algorithm, aspirin, Aspirin for Evidence-Based Preeclampsia Prevention, blood pressure, competing risk, fetal growth restriction, Fetal Medicine Foundation, first trimester, hypertension, intrauterine growth restriction, mean arterial pressure, morbidity, mortality, number needed to screen, number needed to treat, perinatal, placental growth factor, placental insufficiency, prediction, preeclampsia, pregnancy, pregnancy complications, prematurity, preterm, prevention, prophylaxis, pulsatility index, resistant index, risk factor, safety, stillbirth, uterine artery, uterine artery mean pulsatility index

Introduction

Preeclampsia affects 2% to 8% of all pregnancies and is a significant cause of maternal and perinatal morbidity and mortality, particularly when of early onset. The disease is responsible for one-sixth of all premature births, which are a notable burden on healthcare systems.[1,2] One-third of all preeclampsia cases require preterm delivery, and its association with fetal growth restriction and prematurity often leads to lifelong consequences for the child, including higher risk of cerebral palsy and neurodevelopmental delay, respiratory disorders, hypertension, renal dysfunction, insulin resistance, obesity, cardiovascular disease, and impaired work capacity.[3,4] Furthermore, mothers affected by preeclampsia are 2 to 5 times more likely to develop hypertension and cardiovascular and cerebrovascular disease in the future when compared with mothers who do not have preeclampsia in their pregnancies.[5–7]

In recent years, a significant amount of research has been dedicated to

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elucidate the pathophysiology of the disorder, develop methods in identifying women at risk through the use of predictive models, and investigate possible preventive strategies to reduce the incidence of preeclampsia.[8–10] A robust predictive algorithm applied at 11 to 13 weeks of gestational age identifies about 75% of the cases of preterm preeclampsia (with delivery before 37 weeks of gestational age) and about 90% of the cases of early-onset disease preeclampsia (with delivery before 34 weeks of gestational age), at a 10% screen-positive rate.[11] This combined screening test utilizes maternal characteristics and medical and obstetrical history to calculate the a priori probability of delivery with preeclampsia vs that for any other cause at a given gestational age, which is then combined with the measurements of mean arterial pressure, uterine artery mean pulsatility index on Doppler ultrasound, and serum placental growth factor (PlGF) to estimate the posteriori adjusted probability of preeclampsia development.[11] Such predictive tests based on competing risks have been externally validated in prospective studies.[8,12–14]

Despite all these efforts, the prevalence of preeclampsia has remained relatively unchanged in the last few decades.[15] A large number of very heterogeneous studies have evaluated the possible benefit of aspirin intake in pregnancy to minimize the risk of preeclampsia, with large variations in included population risk profile, aspirin dosage, gestational age of prophylaxis initiation, and disease definition.[16] In this article, we review and summarize the evidence regarding the use of aspirin for the prevention of preeclampsia.

Summary of aspirin history

Aspirin is 1 of the oldest medications that is still in widespread use. A timeline of the history of aspirin is shown in Figure 1. Aspirin-related compounds were isolated from the willow tree (genus, *Salix*), and reports of willow bark use can be found in Egyptian papyrus scrolls with compilations of medical texts dating back to 1534 BCE.[19] Around 400 BC, Hippocrates also utilized extracts from the willow tree and its leaf tea to treat headache, pain, and fever.[20] In 1828, Johann Buchner extracted the active ingredient of the willow bark and called it salicin. A few years later, in 1853, sodium salicylate was treated with acetyl chloride to produce acetylsalicylic acid, and the first aspirin tablets were industrially produced in 1915.[21] The use of aspirin became widespread during the 1918 flu pandemic[22] and in the 1960s, the first studies on aspirin use for the prevention of myocardial infarction were published.[22,23]

In 1982, Vane, Samuelsson, and Bergström were awarded the Nobel Prize after elucidating the mechanism of action of the drug[24]: aspirin belongs to the family of nonsteroidal antiinflammatory drugs, and its analgesic, antipyretic, and antiinflammatory effects are due to the inactivation of the cyclooxygenase (COX)-1 and COX-2 enzymes, suppressing the production of prostaglandins and thromboxane. This thromboxane reduction also leads to an inhibition of platelet aggregation, producing an antithrombotic effect.[25,26] The mechanism of action of the drug is summarized in Figure 2.

There is increasing evidence suggesting that suboptimal trophoblastic invasion leads to an imbalance of angiogenic and antiangiogenic proteins, ultimately causing widespread inflammation and endothelial damage, increased platelet aggregation, and thrombotic events with placental infarcts.[27] It has been hypothesized, therefore, that the effect of aspirin in the inhibition of inflammation and platelet aggregation could be useful to prevent or treat preeclampsia.[28]

Nowadays, aspirin is 1 of the most commonly prescribed medications, taken by more than 50 million people in the United States for the prevention of cardiovascular disease, and about 40,000 tons are consumed every year worldwide.[29]

Effect of aspirin on preeclampsia rates

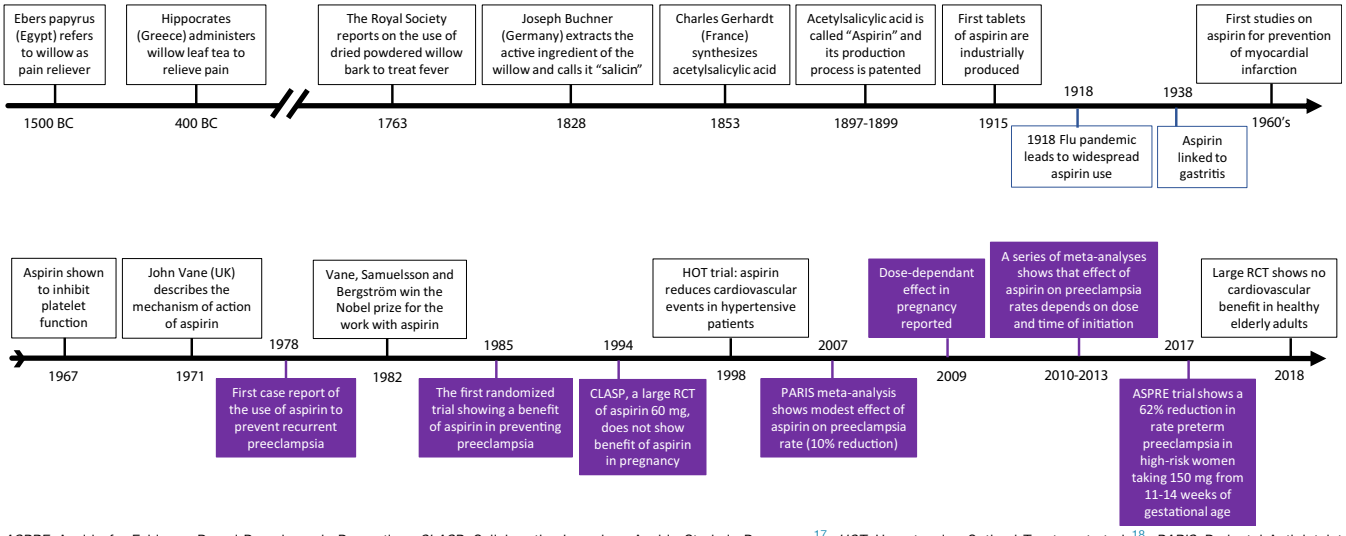
Conflicting results of randomized trials. The first possible link between the use of aspirin and the prevention of preeclampsia was suggested by a case report published in 1978, describing better outcomes with daily use of aspirin from midtrimester in the third pregnancy of a woman with 2 previous pregnancies severely affected by preeclampsia and fetal growth restriction.[30]

In the first randomized trial evaluating the effect of aspirin on placenta-mediated complications, Beaufils et al[31] randomized 102 women at high risk of preeclampsia and fetal growth restriction, mainly based on their obstetrical history, to receive daily doses of aspirin at 150 mg and dipyridamole at 300 mg from 12 weeks of gestational age or usual care. There were 6 cases of preeclampsia, 5 of perinatal death, and another 4 of fetal growth restriction in the control arm, and none of these events occurred in the treatment arm.[31]

Numerous randomized trials followed in the next few decades, with inconsistent results and conclusions, largely explained by a high degree of heterogeneity regarding the selection of trial participants, baseline risk of the included women, dosage of aspirin, gestational age of prophylaxis initiation, and preeclampsia definition. A large randomized trial performed in 1994, named Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), included 9364 women at risk of preeclampsia or fetal growth restriction because of medical history and pregnancies already diagnosed with these complications. Treatment with a daily dosage of 60 mg, initiated between 12 and 32 weeks of gestational age, was considered safe but did not lead to a reduction in preeclampsia rates. It was observed that there was correlation between rates of preeclampsia and gestational age at delivery; the lower the gestational age, the lower the rates of preeclampsia.[17]

Inconsistent effect of aspirin identified in meta-analyses. In 2007, Askie et al[16] published an individual patient data meta-analysis on the effect of antiplatelet agents (including 24 randomized controlled trials with aspirin alone) on the incidence of preeclampsia. A modest 10% risk reduction (relative risk [RR], 0.90; 95% confidence interval [CI], 0.84–0.97) was identified.[16] It is important to note that 15 definitions of

FIGURE 1
Timeline of events in aspirin history and specific aspects of its use in pregnancy (purple boxes)



ASPRE, Aspirin for Evidence-Based Preeclampsia Prevention; *CLASP*, Collaborative Low-dose Aspirin Study in Pregnancy[17]; *HOT*, Hypertension Optimal Treatment study[18]; *PARIS*, Perinatal Antiplatelet Review of International Studies; *RCT*, randomized controlled trial.

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preeclampsia were used in the different included trials; in most studies, trial medication was given at doses lower than 100 mg (ranging from 50−150 mg, with only 2 studies evaluating aspirin at a dosage of 150 mg)[16]; and in 59% of the included pregnancies, trial medication began after 20 weeks.

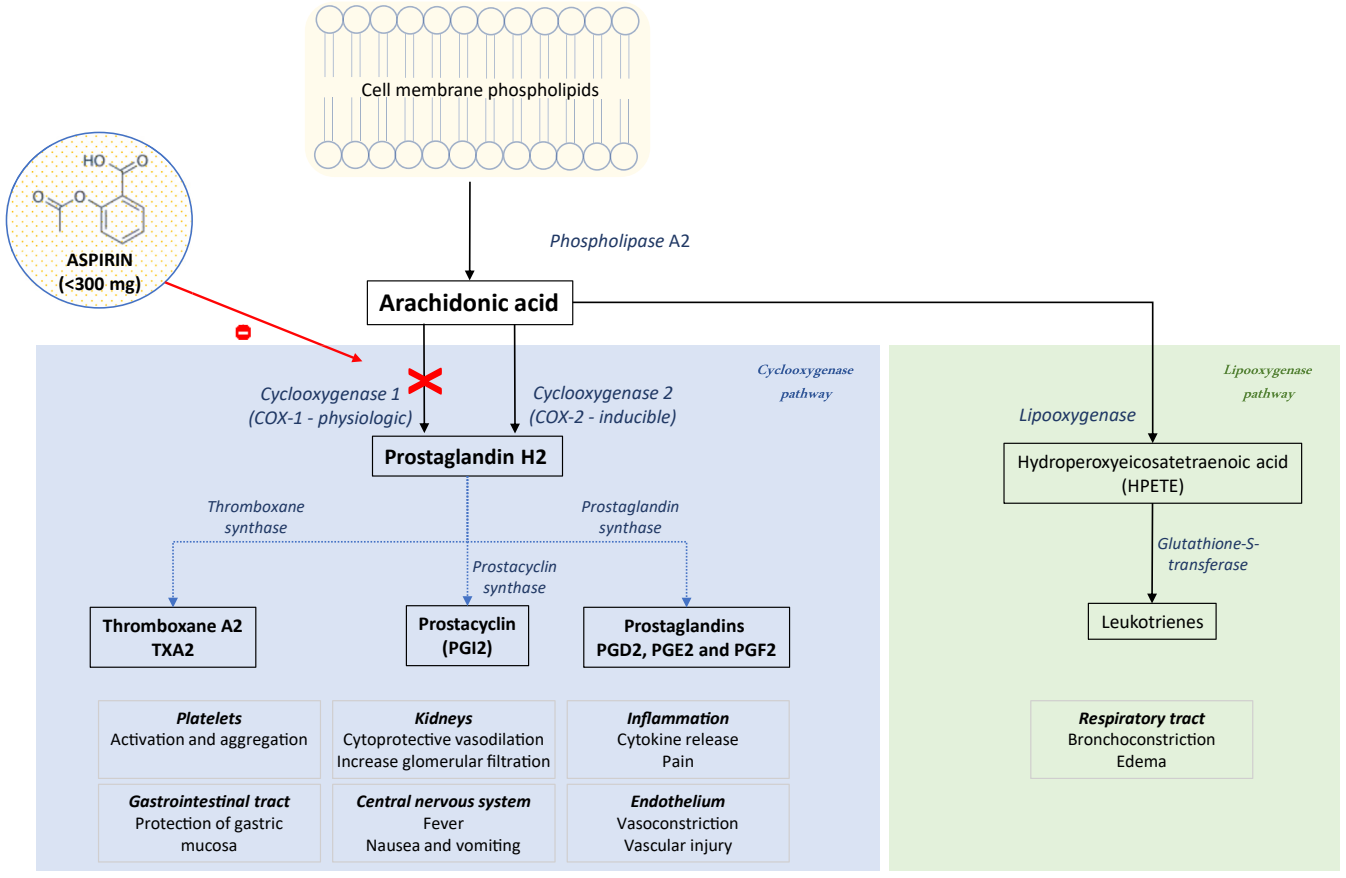
A series of subsequent meta-analyses of aggregate data has revealed that aspirin is highly effective in reducing preeclampsia rates if initiated before 16 weeks of gestational age (RR, 0.47; 95% CI, 0.34−0.65) but confers no beneficial effect when started after 16 weeks (RR, 0.81; 95% CI, 0.63−1.03)[32]; the effect on preeclampsia rates is mainly because of a reduction of the severe and preterm forms of the disorder (RR, 0.11; 95% CI, 0.04−0.33), with no significant beneficial effect on term preeclampsia (RR, 0.98; 95% CI, 0.42−2.33)[32,33]; and there is a dose-response effect when aspirin is initiated before 16 weeks of gestational age.[34]

The beneficial effect of aspirin is therefore optimized when initiated before 16 weeks, which corresponds to the time when placentation completes, and its action occurs in a dose-response fashion, with the effect maximized at daily doses above 100 mg. These later meta-analyses have been criticized because of the use of aggregate data, which may overestimate the effect size of aspirin as compared with individual patient data meta-analyses, the inclusion of a small number of heterogeneous studies, and the fact that the subgroup that received aspirin before 16 weeks of gestational age is likely to have a higher risk profile than the subgroup of women who received aspirin after 16 weeks of gestational age.[35]

The Aspirin for Evidence-Based Preeclampsia Prevention trial. Because of the conflicting results and significant heterogeneity of previous studies, and informed by the results of the aforementioned meta-analyses revealing that aspirin is highly effective in reducing preeclampsia rates if initiated before 16 weeks of gestational age, the Combined multimarker screening and randomized patient treatment with Aspirin for Evidence-Based Preeclampsia prevention (ASPRE) trial was proposed.[36] Based on previous data suggesting that approximately 30% of women are nonresponsive to the effect of aspirin at a daily dosage of 81 mg but only 5% are nonresponsive to its effects at a daily dosage of 162 mg, high-risk women were randomly and blindly allocated to receive 150 mg of the trial drug daily or placebo from 11 to 14 weeks of gestational age until 36 weeks of gestational age or delivery, whichever occurred first. Aspirin was given at bedtime, based on a previous chronotherapy trial including 350 high-risk women and comparing different administration times suggesting that the beneficial effects are dependent on the time of administration, with better regulation of ambulatory blood pressure when taken at night.[37]

Innovatively, high-risk women were identified by means of a combined algorithm that takes account of maternal characteristics, medical and obstetrical history, biophysical markers (mean arterial pressure and uterine artery Doppler) and biochemical markers (pregnancy-associated plasma protein A and PlGF).[38] Before initiating the randomized trial, the predictive algorithm was prospectively validated in an independent cohort, with similar predictive performance to that observed in the algorithm development studies.[11,14,38,39] Women with a predicted risk at or higher than 1 in 100 were deemed high

FIGURE 2
Mechanism of action of aspirin



At low doses (below 300 mg), the drug inhibits the COX-1 enzyme, particularly in platelets, leading to a reduction in the production of thromboxane A2 and, to a lesser degree, of prostaglandins and prostacyclin.

COX-1, cyclooxygenase 1; HPETE, hydroperoxyeicosatetraenoic acid; PGD2, prostaglandin D2, PGE2, prostaglandin E2, PGF2, prostaglandin F2; PGI2, prostacyclin; TXA2, Thromboxane A2.

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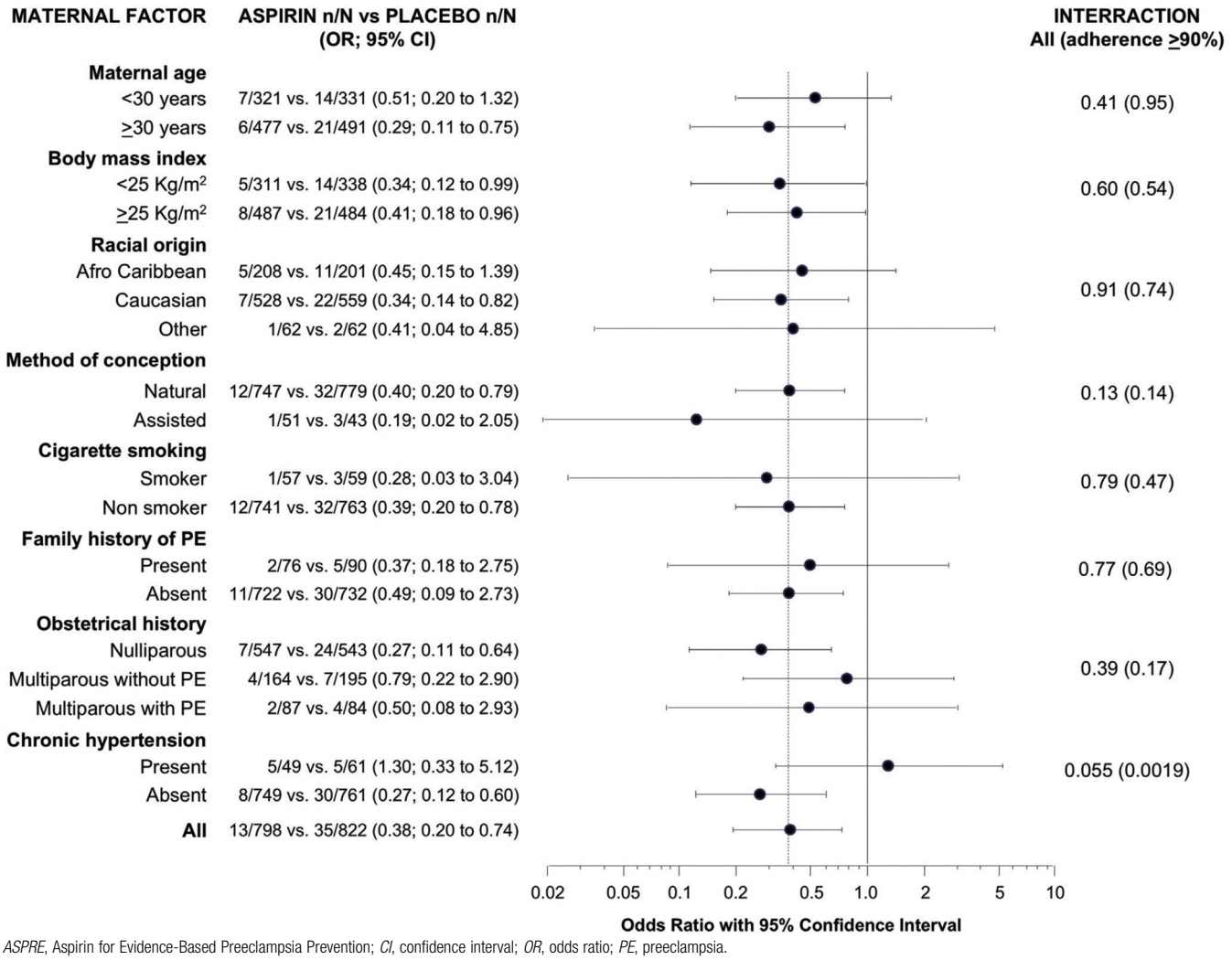
risk for developing preterm preeclampsia, resulting in a screen-positive rate of 11%. Eventually, 1776 high-risk women were recruited from 13 hospitals across 6 European countries, and treatment with aspirin was found to reduce the rate of preterm preeclampsia by 62% (1.6% vs 4.3%; odds ratio [OR] in the aspirin group, 0.38; 95% CI, 0.20−0.74; P=.004). There was a nonsignificant trend of greater reduction in the rate of preeclampsia the earlier the gestational age at delivery, and no significant reduction in the rate of term preeclampsia was observed.[40]

The effect of aspirin on the rate of preterm preeclampsia was subsequently confirmed by an updated meta-analysis.[41] A secondary analysis of the ASPRE data revealed a consistent effect size within subgroups according to recognized risk factors of preeclampsia (Figure 3), except in the subgroup of women with chronic hypertension, where no indication of beneficial effect was seen, possibly because of preexisting endothelial dysfunction or preestablished suboptimal cardiovascular function.[42] In addition, as expected, the beneficial effect of aspirin was clearly associated with good adherence to treatment.[43] At 90% compliance, the effect size of aspirin was even higher at 76% and could reach 90% when the high-risk woman did not have a history of chronic hypertension.[43]

Safety of aspirin in pregnancy

Aspirin use in pregnancy is considered safe. Large cohort and case-control studies, which have reported that the drug is not associated with an increase in risk of congenital heart defects or other structural or developmental anomalies.[44,45] Likewise, the theoretical risk of premature closure of the fetal arterial duct with aspirin use has not been reported.[46,47] A recent population-based study from Denmark reported an increased risk of cerebral palsy in children of mothers who used aspirin in pregnancy (adjusted OR [aOR], 2.4; 95% CI, 1.1−5.3, controlling for maternal socioeconomic status, respiratory infection, urinary infection,

FIGURE 3
Subgroup analysis of the ASPRE trial on the effect of aspirin on the rate of preterm preeclampsia[42]



ASPRE, Aspirin for Evidence-Based Preeclampsia Prevention; *CI*, confidence interval; *OR*, odds ratio; *PE*, preeclampsia.

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fever, and rheumatoid arthritis in pregnancy).[48] However, the use of aspirin was defined as "ever used" according to patient reporting, which not only introduced recall bias but also could not account for dose, frequency, timing, and indication of aspirin use. In addition, the authors did not adjust the analyses for preeclampsia, preterm birth, and small-for-gestational-age neonates. Prematurity is by far the main cause of cerebral palsy, and women who used aspirin were likely at higher baseline risk of pregnancy complications and preterm birth.

Although approximately 10% of women receiving low-dose aspirin in randomized trials have reported gastrointestinal symptoms, no other major side effects for the women have been confirmed. In the CLASP trial, there was no evidence of an increase in the rates of side effects or adverse events,[17] and no major complications were identified at 18 months of age in children born to mothers who took a daily dosage of 60 mg of aspirin during pregnancy.[49] Similarly, in the ASPRE trial, the incidence of untoward medication effects was similar between the intervention and the placebo groups.[40] Theoretical risks of intracranial bleeding for the neonate and postpartum hemorrhage for the mother have never been confirmed in randomized trials targeting high-risk populations, even if aspirin intake is continued until a few days before birth[17,40,49]; however, increased risk of hemorrhagic events and postpartum hemorrhage have been reported in studies evaluating universal aspirin prophylaxis in low-risk populations.[50,51]

An early randomized trial reported that, in 1570 nulliparous women who received 60 mg of daily aspirin and 1565

women who received placebo from 13 to 26 weeks of gestational age, the use of aspirin was associated with an increased risk of placental abruption (11 cases in the aspirin group and 2 cases in the placebo group).[52] This possible adverse event may have been attributed to the late initiation of aspirin therapy. Placentation is complete mostly by 16 to 18 weeks of gestational age, and it is plausible that late initiation of aspirin prophylaxis in women with impaired placentation leads to an increase in the risk of placental abruption. A recent meta-analysis has suggested a significantly higher risk of placental abruption when the onset of treatment occurs after 16 weeks of gestational age than with prophylaxis initiation before 16 weeks.[53]

Mechanism of action in the prevention of preeclampsia

Aspirin at doses below 300 mg selectively and irreversibly inactivates the COX-1 enzyme, suppressing the production of prostaglandins and thromboxane and inhibiting platelet aggregation[24] (Figure 2). The mechanism by which aspirin prevents preeclampsia is unknown, and proposed mechanisms are largely speculative and based on in vitro research, which is consistent with the lack of understanding of the disease pathophysiology. The following possible mechanisms have been proposed: (1) improvement in the placentation process, which is supported by the fact that early initiation of therapy indicates a more prominent reduction in the risk of preeclampsia; (2) inhibition of platelet aggregation and its antithrombotic effect, thereby leading to lower levels of placental infarct; and (3) antiinflammatory effects and endothelial stabilization.[54,55] In vitro research with human choriocarcinoma-derived (BeWo) cell line treated with serum from preeclamptic women and aspirin suggests that the drug modulates cytokine secretion, reduces apoptosis to levels seen in normotensive serum-treated trophoblast cells, upregulates trophoblast PlGF production, and prevents premature trophoblast differentiation commonly observed in preeclampsia.[54–56] These findings, however, have not been confirmed in human in vivo studies. Nonetheless, the beneficial effect of aspirin on preeclampsia is now evident, and subsequent modeling of the ASPRE data has revealed a significant interaction between the effect size of aspirin and the gestational age at delivery with preeclampsia, suggesting, first, that aspirin intake shifts the incidence distribution of preeclampsia to a later gestational age, and second, the delay in disease onset is gestational age–dependent, with greater delay and benefit in women destined to develop severe early-onset preeclampsia.[57]

Prevention of preeclampsia with aspirin in multiple pregnancies

Women with multiple pregnancy are at a significantly increased risk of preeclampsia when compared with those with a singleton pregnancy, with relative risks of 8.7 and 9.1 for preterm preeclampsia in dichorionic and monochorionic twin pregnancies, respectively.[58–60] However, because twin pregnancies are more likely to be delivered prematurely for other indications, these relative risks are underestimated when comparisons are made between twin and singleton pregnancies at the same gestational age.[60] The increased risk of preeclampsia in multiple pregnancies may be because of increased placental mass rather than true placental insufficiency, as suggested by the poorer predictive capability of uterine artery Doppler and the fact that expression of antiangiogenic factors is not increased in these pregnancies when compared with singleton gestations.[61] When the same combined screening algorithm for singleton pregnancies is applied to twin pregnancies, detection of preterm preeclampsia reaches 99%, at the expense of a high screen-positive rate of about 75%.[62]

Guidelines from professional organizations list multiple pregnancy as a risk factor for preeclampsia and therefore recommend aspirin prophylaxis in these cases.[35,63–65] Preliminary retrospective data from a single center has revealed that the incidence of preeclampsia in twin pregnancies with additional risk factors is significantly lower in those receiving aspirin 150 mg daily compared with 75 mg daily.[66] Furthermore, the issue of aspirin nonresponse appears more problematic in twin pregnancies, because rates of nonresponsiveness to aspirin have been reported to be as high as 65% at a daily dosage of 81 mg.[67] A systematic review and meta-analysis of 6 randomized controlled trials with 898 multiple pregnancies have reported a significant risk reduction in preeclampsia (RR, 0.67; 95% CI, 0.48–0.94) and mild preeclampsia (RR, 0.44; 95% CI, 0.24–0.82) but not severe preeclampsia (RR, 1.02; 95% CI, 0.61–1.72) with aspirin at doses between 60 mg and 100 mg. The reduction of preeclampsia is not significantly different between women randomized before (RR, 0.86; 95% CI, 0.41–1.81) or after 16 weeks of gestational age (RR, 0.64; 95% CI, 0.43–0.96; P=.50).[68] The authors conclude that there is a low level of evidence supporting the use of aspirin for the prevention of preeclampsia in multiple pregnancies and that further studies are required.

Effect of aspirin on other adverse pregnancy and cardiovascular outcomes

Given the common pathophysiology of preeclampsia and other placental-associated adverse outcomes, such as fetal growth restriction and stillbirth, it is reasonable to anticipate that treating women at high-risk of preeclampsia will also lead to a reduction in other pregnancy complications. However, because previous randomized controlled trials have focused on preeclampsia as the primary outcome, the evaluation of the treatment effect of aspirin on other pregnancy complications, particularly those that are infrequent, such as stillbirth, usually lacks statistical power.

Previous meta-analyses have suggested that aspirin prophylaxis initiated before 16 weeks of gestational age can halve the incidence of fetal growth restriction (RR, 0.46; 95% CI, 0.33–0.64), perinatal death (RR, 0.41; 95% CI, 0.19–0.92), and preterm birth (RR, 0.35; 95% CI, 0.22–0.57) when compared with placebo or no treatment.[32,69] As mentioned, these meta-analyses have been criticized

because they may have overestimated the effect size of the intervention. However, the results of the ASPRE trial also suggested a potential reduction in the rates of perinatal death (aOR, 0.59; 95% CI, 0.19−1.85, controlling for the effect of the estimated risk of preeclampsia at screening and the participating center) and birthweight below the 10th percentile (aOR, 0.77; 95% CI, 0.56−1.06). These reductions of slightly smaller magnitude were, however, not reaching statistical significance, and the trial was not powered to detect differences in these secondary outcomes. Investigating the effect of an intervention on the rates of rare perinatal outcomes in randomized controlled trials is problematic. To report a statistically significant reduction of 40% in perinatal death in a high-risk population and assuming a 1.7% baseline rate in the placebo group (estimates derived from the ASPRE trial) and a 60% recruitment uptake, about 170,000 pregnancies would have to be screened and 10,000 women recruited to the randomized trial, which would be practically unachievable.

A secondary analysis of 2 large multicenter studies reported that a policy of screening for preterm preeclampsia and daily treatment of high-risk women with aspirin 150 mg would potentially reduce the rate of small-for-gestational-age neonates born before 37 weeks by 20%.[70] Another secondary analysis of the ASPRE data revealed that neonates from the aspirin arm who required admission to the neonatal intensive care unit had a significantly shorter length of stay than that of neonates from the placebo arm who needed admission (11.1 vs 31.4 days), with a mean reduction of 20.3 days (95% CI, 7.0−38.6; P=.008). This finding was primarily driven by a significant decrease in the rate of preterm delivery before 32 weeks of gestational age (Figure 4), mainly because of the prevention of early-onset preeclampsia.[71]

Although previous meta-analyses have also suggested a reduction in the rate of preterm birth,[69] it is likely that this reduction is mediated via a reduction in the rate of preeclampsia and fetal growth restriction, which are the leading causes of medically indicated preterm delivery. A subset of pregnant women with spontaneous preterm birth has placental lesions associated with uteroplacental ischemia and abnormal uterine artery Doppler, findings that are frequently observed in women with preeclampsia, and therefore, it has been suggested that placental insufficiency may play a role in the spontaneous onset of preterm labor and be causally associated with spontaneous preterm birth.[72,73] However, the beneficial effect of aspirin on the rate of spontaneous preterm birth could not be confirmed in the ASPRE trial. A recent randomized trial indicated an 11% reduction in preterm deliveries with a policy of universal aspirin prophylaxis at 81 mg daily in low- and middle-income countries (RR, 0.89; 95% CI, 0.81−0.98; P=.012), but this reduction was likely as a result of prevention of preeclampsia, as the authors did not distinguish spontaneous from iatrogenic preterm birth.[74] Existing evidence is, thus, inconclusive regarding the effect of aspirin on spontaneous preterm birth rates.

The strength of the well-established association of preeclampsia, particularly of preterm and severe forms of the disease, with future cardiovascular morbidity and mortality led the American Heart Association in 2011 to consider a history of preeclampsia or pregnancy-induced hypertension a major risk factor for development of cardiovascular disease.[75] In a recently published advisory, the American College of Obstetricians and Gynecologists and the American Heart Association recommend cardiovascular disease risk factors screening for women with prior preeclampsia that was preterm (<37 weeks) or recurrent, with yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index.[76]

What remains to be determined is whether prevention of preeclampsia with aspirin will lead to lower rates of cardiovascular events later in life. If preeclampsia is caused by impaired placentation, which then leads to cardiovascular damage, then it is plausible that aspirin use during pregnancy will lead to a decrease in cardiovascular disease. However, if preeclampsia is primarily caused by a suboptimal cardiovascular adaptation during pregnancy, as suggested by recent studies,[77,78] aspirin intake for a short period during pregnancy is unlikely to modify cardiovascular outcomes in the future. Large population-based studies with long-term follow-up will be necessary to answer this question.

Based on the ASPRE trial results, 38 women at high risk of preterm preeclampsia need to be treated with aspirin at 150 mg to avoid 1 case. The RRs for the effect of aspirin on adverse pregnancy outcomes and the numbers needed to treat are summarized in the Table.

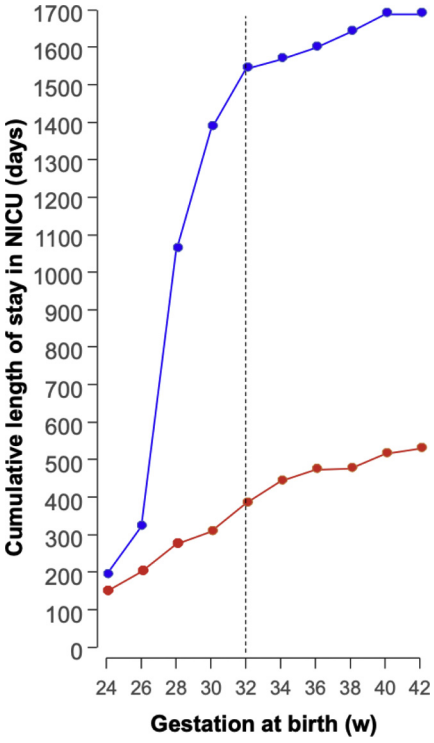
Identification of pregnancies at increased risk of preeclampsia

Because aspirin intake is highly effective and more than halves the risk of preterm and severe forms of preeclampsia in high-risk populations, an obvious and important question is how to best identify women at increased risk of developing the disorder and associated adverse outcomes. Approaches to prediction can be broadly divided in risk scoring methods and predictive models, and the details and performance of such prediction methods are discussed in a separate article in this issue. However, given that the effect of aspirin in reducing the risk of preterm preeclampsia is maximized when prophylaxis is initiated before 16 weeks of gestational age, screening should ideally be performed in the first trimester and target women at high risk of developing preterm disease.

Universal aspirin

Considering the clear benefit of aspirin in reducing the risk of preterm preeclampsia, its low cost, and safety profile, some authors advocate for universal aspirin prophylaxis for preeclampsia prevention. It has been suggested that this would be a more cost-effective strategy than the use of aspirin prophylaxis in women determined to be at high risk through a process of screening, which has been considered to be rather

FIGURE 4
Secondary analysis of the ASPRE trial[71]



Cumulative length of stay of neonates admitted to the NICU according to gestational age at birth for placebo (blue circles) and aspirin (red circles) groups.

NICU, neonatal intensive care unit.

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complex for implementation.[79–82] Nevertheless, possible benefits of a preventive strategy need to be balanced with potential harm because of hemorrhagic and other adverse events. Benefits of universal aspirin and long-term safety of this strategy have not been adequately studied in randomized trials. In addition, good adherence to treatment is paramount to successful prevention.[43] Compliance is likely to be lower when aspirin is given to the whole population than when recommended to a selected high-risk group of women counseled based on individual risk.[83] Earlier trials in which pregnant women received aspirin on the sole basis of being pregnant or nulliparous reported an increased frequency of bleeding episodes, low compliance with aspirin at only about 50%, and no reduction in the incidence of preeclampsia.[51,84] Analogously, universal aspirin for primary prevention of cardiovascular events in healthy older adults resulted in a significantly higher risk of major hemorrhage but did not significantly reduce the risk of cardiovascular disease.[85]

Cost effectiveness of aspirin for prevention of preeclampsia

Improving maternal and perinatal health is a development goal, and investing resources in preventing significant public health problems is key to achieving this goal. The prevalence and the cost of preeclampsia vary in different world regions. In the United States, the estimated average incremental cost for a pregnancy complicated by hypertensive disease was US $8200 in 2011.[86] Stevens et al[2] estimated the annual preeclampsia-associated costs in the United States at US $2.18 billion, and this was disproportionally driven by healthcare costs related to premature neonates, with a cost of US $1311 for a pregnancy with delivery at 36 weeks and US $150,000 for a pregnancy with delivery at 26 weeks of gestational age.

To date, 5 cost-effectiveness studies have been published on the economic aspects of preeclampsia prevention with aspirin. The first study performed an economic evaluation of a comprehensive combined first trimester screening algorithm (using maternal characteristics, medical and obstetrical history, serum biomarkers, and uterine artery Doppler) followed by treating high-risk women with aspirin prophylaxis, and the authors concluded that this approach to screening and prevention is cost effective in various disease prevalence scenarios in Israel.[87]

However, the low cost of the intervention has led to the comparison of a screening and treatment policy vs universal aspirin prophylaxis in 3 studies. Werner et al[80] have performed a cost-effectiveness study, with costs based on US healthcare prices. Treatment involved either no prophylaxis, provision of aspirin to women deemed high-risk in accordance with the American College of Obstetricians and Gynecologists guidelines or the United States Preventive Services Task Force recommendations,[88] or universal prophylaxis. The authors have suggested that a policy of screening by risk factors alone and a policy of universal prophylaxis would both lead to similar reductions in the rate of preeclampsia and cost savings of about US $370 million and that, with the screen and treat approach, 76.5% of the women would not be prescribed aspirin.[80]

Mone et al[81] have utilized data of 100,000 low-risk nulliparous women from Ireland and the United Kingdom to compare combined screening by the Fetal Medicine Foundation algorithm and daily aspirin at 75 mg in high-risk women vs universal treatment with aspirin at the same dose. The authors reported that universal aspirin use would lead to a cost saving of €14.9 million (equivalent to US $17.5 million) annually relative to no intervention, whereas the screen-and-treat strategy would save

TABLE
Relative risk and number needed to treat with 95% CIs for different adverse pregnancy outcomes with the use of aspirin initiated before 16 weeks compared with placebo or no treatment

Outcome	Relative risk (95% CI)	Number needed to treat (95% CI)
Preeclampsia <37 wk[a]	0.38 (0.20–0.72)	38 (24–102)
Preeclampsia <34 wk[a]	0.20 (0.06–0.71)	69 (41–233)
Birthweight <10th percentile[b]	0.77 (0.65–0.91)	16 (10–43)
Birthweight <5th percentile[b]	0.73 (0.59–0.91)	19 (12–63)
Birthweight <3rd percentile[b]	0.77 (0.59–0.99)	30 (15–846)
Neonatal intensive care unit >14 d[b]	0.34 (0.15–0.75)	51 (30–167)
Stillbirth or neonatal death[c]	0.26 (0.11–0.60)	34 (22–80)

ASPRE, Aspirin for Evidence-Based Preeclampsia Prevention; *CI*, confidence interval; *SPREE*, Screening Program for Preeclampsia.

[a] Estimates calculated based on the ASPRE trial data[35]; [b] Estimates based on secondary analysis of data from the ASPRE trial and the SPREE study[70,71]; [c] Estimates calculated based on reported numbers in random effects meta-analysis of aspirin use initiated before 16 weeks of gestational age.[69]

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only €3.1 million (equivalent to US $3.6 million).[82]

Another recent study has also suggested that universal aspirin prophylaxis would be the most cost-effective strategy.[81] A decision analysis was used to compare 4 strategies: no aspirin use, aspirin use initiated before 16 weeks of gestational age guided by biomarkers and ultrasound (estimates were based on the performance of combined screening and on the ASPRE trial results[11,40]), aspirin use initiated before 16 weeks of gestational age guided by the United States Preventive Services Task Force recommendations,[88] or universal aspirin initiated before 16 weeks of gestational age. The dose of aspirin was not specified. The authors reported that, compared with universal aspirin administration, the use of the United States Preventive Services Task Force guidelines was associated with US $8,011,725 higher healthcare costs and 346 additional cases of preeclampsia per 100,000 pregnant women; combined screening was associated with an additional US $19,216,551 and 308 additional cases.[81]

These 3 cost-effectiveness studies on universal aspirin prophylaxis have not, however, accounted for the likely lower compliance with treatment, presumed smaller effect size of aspirin on the rates of preeclampsia, and possible serious complications with universal prophylaxis.[83] Most importantly, the strategy of universal aspirin has not been adequately evaluated in randomized trials.

Finally, before implementing first trimester combined screening for preeclampsia, a Canadian group performed a cost-effectiveness study from the local healthcare system perspective using a decision-tree model to compare combined screening and treatment of high-risk women with aspirin 150 mg daily vs current practice in Canada (treatment with aspirin 81 mg daily based on identification of risk factors). First trimester screening led to a significant reduction in the rate of early-onset preeclampsia and a cost saving of CaD $14.4 million.[89] Screening cost has been estimated at CaD $668.84 per pregnancy, but where screening for fetal aneuploidy is performed, the cost of screening for preeclampsia is lower at approximately CaD $100.00 per pregnancy, leading to a further cost reduction of CaD $220 million.[89]

In the ASPRE trial, the shorter length of stay in the neonatal intensive care unit in women treated with aspirin resulted in significant estimated cost savings, which far outweigh the cost of screening.[71] Assuming a screen-positive rate of 10% and the daily cost of a stay in neonatal intensive care unit at US $4,000, the estimated cost savings from screening 10,000 pregnancies would be US $5,600,000 (US $560 per pregnancy screened), based on neonatal intensive care unit stay alone.[71]

None of the studies on cost effectiveness of selective or universal aspirin prophylaxis have adequately considered long-term consequences of preeclampsia for women and lifelong morbidity for children. Cost-effectiveness analyses investigating the value of the first trimester screen-and-prevent program in different populations, accounting for differences in prevalence and healthcare models, are needed, and future cost-effectiveness research should take into account not only the estimates of compliance with different strategies but also the full spectrum of long-term cardiovascular disease for women and prematurity-related complications for children.

Conclusion

Aspirin is highly effective in preventing preterm preeclampsia when administered to high-risk women at doses above 100 mg and initiated before 16 weeks of gestational age, reducing its incidence by more than 60%. Identification of high-risk women should, therefore, be performed in the first trimester of pregnancy, ideally with the use of predictive algorithms. Combined screening with maternal factors, mean arterial pressure, uterine artery Doppler, and serum PlGF for early prediction of preeclampsia has

the capability in identifying a group of high-risk women who are most responsive to aspirin prophylaxis for the prevention of preterm preeclampsia. Such a strategy will inherently reduce the burden of the disease and its associated adverse outcomes. ■

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