REVIEW

Aspirin to prevent pre-eclampsia

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Key learning points

- High-quality evidence shows that aspirin at a dose of 75–100 mg daily reduces the risk of pre-eclampsia by 18% (number needed to treat for one woman to benefit [NNTB] 61) and preterm birth by 9% (NNTB 61). This is the recommended dose range advocated by most institutional guidelines.
- A major trial has shown that aspirin 150 mg daily is highly effective in preventing preterm pre-eclampsia (diagnosed <37 weeks' gestation); another large trial reported that a dose of 81 mg daily may be similarly effective at preventing preterm pre-eclampsia (diagnosed <34 weeks' gestation).
- Women should be offered aspirin if they have risk factors based on maternal history that puts them at elevated risk of developing pre-eclampsia, as defined by national and international guidelines.
- A first trimester screening algorithm that combines clinical and ultrasound information with a blood test is more sensitive at identifying those at risk of pre-eclampsia compared with screening using maternal risk factors such as those outlined in the National Institute of Health and Care Excellence guideline, but it is unclear whether it is cost effective.
- Aspirin should ideally be started at 12 weeks' gestation (and before 16 weeks' gestation) and taken until at least 36 weeks' gestation.
- Although aspirin is very safe, there is a 6%–25% relative risk increase of a postpartum haemorrhage.

Introduction

Pre-eclampsia complicates around 3%–5% of all pregnancies and is a condition where there is hypertension and multisystem organ injury to the mother. The pre-eclamptic placenta releases factors such as antiangiogenic proteins and inflammatory cytokines which incite endothelial dysfunction, vascular injury and can cause hypertension and maternal organ injury. The placental dysfunction often causes fetal growth restriction, which is a stillbirth risk. Furthermore, pre-eclampsia often ends in iatrogenic preterm birth for maternal indications, which exposes the neonate to the risks of prematurity. Hence, pre-eclampsia is a serious morbidity and mortality risk to mother and baby.[1]

For women who develop pre-eclampsia, no drug has been discovered that impacts on the underlying disease pathology to decrease its clinical impact. Therefore, prevention is highly worthwhile to help reduce the enormous global disease burden associated with pre-eclampsia.

There is now strong evidence that administering 75–150 mg of aspirin per day from early pregnancy (around 12 weeks' gestation) until 36 weeks' gestation or longer modestly decreases the relative risk of pre-eclampsia by around 18%, and can also decrease the risk of preterm birth, birth of a small for gestational age infant and even perinatal death.[2] The relative risk reduction for preterm pre-eclampsia (such as birth before 37 weeks' gestation) is significantly greater.[3 4]

This review provides a clinical update on prescribing aspirin to prevent pre-eclampsia; including who to give it to, the dose to give, when to give it and just how effective it is.

Effect of aspirin on pre-eclampsia and preterm pre-eclampsia

A recent Cochrane systematic review and meta-analysis concluded there is high-quality evidence showing that aspirin reduces the risk of proteinuric pre-eclampsia by around 18% (relative risk [RR] 0.82, 95% CI 0.77 to 0.82) with a number needed to treat for one woman to benefit [NNTB] of 61 (95% CI 45 to 92; 60 studies, 36 716 participants).[2]

Aspirin appears more effective at reducing the risk of preterm pre-eclampsia. Preterm pre-eclampsia has a far lower incidence but is more likely to cause significant perinatal morbidity and mortality, although disease arising at term gestation (>37 weeks' gestation) is still an important contributor to serious maternal morbidity. This effect on preterm pre-eclampsia was evident in the ASPRE trial, which included 1776 women between 11 and 14 weeks' gestation who had been identified as being at higher risk (>1 in 100) of developing pre-eclampsia based on a first trimester screening test.[3] Participants were randomised to 150 mg of aspirin or placebo once daily until 36 weeks' gestation. Aspirin reduced the risk of preterm pre-eclampsia (primary outcome) arising before 37 weeks' gestation by 62% (1.6% vs 4.3%; OR 0.38, 95% CI 0.20 to 0.74).[3] If false negatives are taken into account (where the primary screening test incorrectly assigned woman at low risk but who subsequently developed pre-eclampsia)[5] this 'screen and treat' approach may prevent just under half of all preterm pre-eclampsia. In contrast, pre-eclampsia at term (the most prevalent subtype) was not decreased in the ASPRE study (6.6% vs. 7.2%; OR 0.95, 99% CI 0.57 to 1.57).[3]

The recently published ASPIRIN trial further supports the contention that aspirin is effective in reducing rates of preterm pre-eclampsia.[4] With a primary outcome of preterm birth incidence, the ASPIRIN trial randomised 11 976 women between 6 and 13^{+6} weeks' gestation across six low-income and middle-income countries to receive 81 mg of aspirin or placebo once daily until 36^{+7} weeks' gestation or delivery. The primary outcome was lower in women who received aspirin (11.6% vs. 13.1%; RR 0.89, 95% CI 0.81 to

0.98). Aspirin also reduced the risk of women delivering <34 weeks' gestation with hypertensive disorders of pregnancy (secondary outcome) by 62% (0.1% vs 0.4%; RR 0.38, 95% CI 0.17 to 0.85). Like the ASPRE trial, the overall incidence of any pre-eclampsia in the entire cohort was unchanged (2.5% vs 2.4%; RR 1.06, 95% CI 0.85 to 1.33).

It is challenging to reconcile why ASPRE[3] and ASPIRIN[4] did not find that aspirin decreased the overall incidence of pre-eclampsia, and yet the overall incidence is lower in the Cochrane meta-analysis (which included the ASPRE trial but not the more recent ASPIRIN trial).[2] It may simply be an issue of power where individual trials were able to detect differences in preterm disease because the effect size was strong but were underpowered to detect the modest difference in term disease. In contrast, the Cochrane meta-analysis included enough women to show that aspirin decreases overall rates of pre-eclampsia.

Aspirin may also prevent other obstetric complications

The same Cochrane review found that aspirin resulted in a modest reduction in the risk of preterm birth before 37 weeks' gestation of 9% (RR 0.91, 95% CI 0.87 to 0.95; NNTB 61, 95% CI 42 to 114; 47 studies, 35 212 participants) corresponding to 16 fewer cases per 1000 women (95% CI 23 fewer to 9 fewer).[2] This finding is further supported by the ASPIRIN trial in which aspirin resulted in a relative risk reduction in preterm birth <37 weeks' gestation of 11% (11.6% vs 13.1%).[4] Aspirin has also been shown to produce a relative risk reduction in perinatal death of 14% (RR 0.85, 95% CI 0.76 to 0.95) though the number needed to treat to prevent one perinatal death will be very large (NNTB 197) as the prevalence is low.[2] Aspirin also reduces the risk of delivering a small for gestational age fetus by 16% (RR 0.84, 95% CI 0.76 to 0.92; NNTB 146).[2] These reductions in important clinical outcomes are presumably driven by decreased rates of pre-eclampsia, but this is unclear.

Table 1 Summary of recommendations from major guidelines for aspirin prophylaxis to prevent pre-eclampsia

Guideline	Criteria to start aspirin	Aspirin dose and duration of treatment
National Institute for Health and Care Excellence (NICE 2019)[6]	Presence of any 1 of the following high risk factors: ► *Hypertensive disease during a previous pregnancy* ► *Chronic kidney disease* ► *Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome* ► *Type 1 or type 2 diabetes* ► *Chronic hypertension* Presence of any 2 of the following moderate risk factors ► *First pregnancy* ► *Age 40 years or older* ► *Pregnancy interval >10 years* ► *Body mass index (BMI) ≥35 kg/m² at first visit* ► *Family history of pre-eclampsia* ► *Multifetal pregnancy*	75–150 mg daily from 12 weeks' gestation until the birth of the baby
American College of Obstetricians and Gynecologists (ACOG 2018)[10]	Similar to NICE guideline, except: ► *Multifetal pregnancy is listed as a high risk factor* ► *Sociodemographic characteristics are listed as a moderate risk factor (African American race, low socioeconomic status)* ► *Personal history is listed as a moderate risk factor (low birth weight or small for gestational age, previous adverse pregnancy outcome)* ► *Moderate risk factors include BMI>30 kg/m² and age ≥35 years*	81 mg* daily initiated between 12 and 28 weeks' gestation (optimally before 16 weeks' gestation) and continued until delivery.
International Society for the Study of Hypertension in Pregnancy (ISSHP 2018)[17]	Strong clinical risk factors for pre-eclampsia: ► *Prior pre-eclampsia* ► *Chronic hypertension* ► *Pregestational diabetes mellitus* ► *Maternal BMI >30 kg/m²* ► *Antiphospholipid syndrome* ► *Receipt of assisted reproduction* The guideline does not recommend universal first trimester screening and treating[3] but supports its use when it can be integrated into the local health system.	75–162 mg daily ideally before 16 weeks' gestation but definitely before 20 weeks' gestation. There is no recommendation when to cease aspirin.
The International Federation of Gynecology and Obstetrics (FIGO 2019)[18]	Women should be screened for pre-eclampsia using the first-trimester combined test with maternal risk factors, mean arterial pressure, uterine artery pulsatility index and placental growth factor as a one-step procedure. In low-income and middle-income countries, a variation of the first-trimester combined test should be considered where maternal risk factors are combined with mean arterial blood pressure and a risk score is calculated.	150 mg at night started between 11 and 14^{+6} weeks' gestation and continued until 36 weeks' gestation or when delivery occurs or pre-eclampsia is diagnosed.

*The ACOG guideline acknowledges that other doses have been studied but recommends 81 mg as it is the only dose available in the US.

Who should be offered aspirin?

Most international guidelines recommend offering aspirin to women at increased risk based on clinical history (see table 1). The National Institute of Health and Care Excellence (NICE) guideline, for instance, recommends aspirin is offered to those with one high risk factor, or two moderate risk factors.[6] These guidelines offer a sensible and pragmatic approach and are widely adopted.

The Fetal Medicine Foundation developed and validated a first trimester screening test that appears to be better at detecting more pregnancies at risk of pre-eclampsia.[7 8] It combines maternal history, blood pressure, ultrasound (uterine artery pulsatility index) and a blood test (measuring two proteins from the placenta). At a screen positive rate of 10% (ie, 10% of the population will be deemed at risk and offered aspirin) the test detected 42.5% destined to develop pre-eclampsia, compared with 30.4% if the NICE guideline was used.[8] It is particularly good at detecting preterm pre-eclampsia (<37 weeks' gestation), identifying 82.4% cases, compared with 40.8% using the NICE guideline (screen positive rate around 10%). Detecting preterm pre-eclampsia is useful as this is more likely to cause severe perinatal morbidity compared with term disease and seems more responsive to aspirin. The International Federation of Gynecology and Obstetrics (FIGO) has recommended using this first trimester screening test.[5]

It is not known whether this first trimester algorithm should be the preferred approach to select who is offered aspirin because of the expense of the test and the outcome we are trying to prevent—clinically significant morbidity and mortality caused by pre-eclampsia—is very uncommon. Its cost effectiveness might depend on the health system. For nationalised health systems such as the UK National Health Service, economic analyses might need to be done. It seems sensible to offer aspirin for those with high risk factors instead of performing first trimester screening (see NICE guideline recommendation in table 1). Conversely, for those with an exceptionally low risk of developing pre-eclampsia (eg, slim parous women who are young and have had prior pregnancies without pre-eclampsia) the likelihood of preventing significant morbidity by undertaking first trimester screening is likely to be vanishingly small.

When to start and stop aspirin

Current guidelines recommend starting aspirin before 16 weeks' gestation and this is supported by a meta-analysis and the ASPRE trial.[3 9] There is no strong evidence guiding clinicians as to the earliest week in pregnancy at which aspirin should be introduced but it is the authors' opinion that it may be sensible to commence aspirin at around 12 weeks' gestation as fetal organogenesis is mostly complete by this time.

It has been postulated that it is critical to administer aspirin before 16 weeks' gestation because it improves early placental development. However, there is little biological evidence supporting this and the drug may simply work via beneficial actions on the maternal blood vessel endothelium.[10] Of note, an individual participant meta-analysis found aspirin decreased rates of pre-eclampsia by 10% irrespective of whether it was begun before or after 16 weeks' gestation.[11] A sensible approach may be to start aspirin in early pregnancy but still offer it to women at high risk even if they have already progressed beyond 16 weeks' gestation.[12]

It is also important to encourage adherence to the aspirin regimen. A small study (220 women) that explored adherence with aspirin found that the 44% of participants who demonstrated inadequate adherence (<90%) had a higher incidence of early-onset pre-eclampsia, late-onset pre-eclampsia, intrauterine growth restriction and preterm delivery.[13]

Many clinicians cease aspirin at 36 weeks' gestation due to concerns that its effects on platelet function may increase bleeding risk during labour. The NICE guideline recommends continuing aspirin until delivery.[6]

What dose of aspirin?

Low-dose aspirin is available at a dose of 75 mg in the UK and in Europe, 81 mg in the USA and 100 mg in Australia. The evidence is strong that doses around 75–100 mg are effective. In the Cochrane meta-analysis, eight of the nine trials that contributed 80% of the total study cohort examined doses of aspirin within this range.[2] Thus, there is high-quality evidence that administering aspirin at these low doses is reasonable and effective.

The high-profile ASPRE trial (which used first trimester screening) randomly administered 150 mg of aspirin or placebo to selected women. As mentioned, at this dose the effect size on reducing preterm pre-eclampsia was impressive (preterm pre-eclampsia was reduced by 62%).[3] Anecdotally, many clinicians have moved to administering aspirin at 150 mg to prevent pre-eclampsia for anyone considered at risk, even on maternal history alone.

Although 150 mg of aspirin may be appropriate and safe, and potentially more efficacious compared with lower doses, there are caveats to exclusively using this higher dose. First, the recent ASPIRIN trial which used 81 mg of aspirin found the rate reduction of preterm birth arising from hypertensive disorders was similar to that found in the ASPRE trial (62% relative risk reduction), which suggests that a switch to the higher dose may not be more beneficial.[4 5] Second, no trials have evaluated whether 150 mg is an appropriate dose for those who are identified at high risk from screening using maternal history alone. Third, its efficacy has not been directly compared with lower doses. Lastly, as will be discussed in the next section, 75–100 mg of aspirin is associated with a bleeding risk and doubling the dose may increase this.

Given this uncertainty and that lower doses of 75–100 mg have not been directly compared with 150 mg, we suggest clinicians adhere to institutional guidelines (and do not routinely offer 150 mg of aspirin to unselected women). However, if first trimester screening is performed, administering 150 mg may be justified. This is because there is level 1 evidence to show that when using this specific 'screen and treat' approach, 150 mg decreases rates of preterm pre-eclampsia.[5]

Risk of bleeding

While aspirin appears very safe with no evidence of teratogenicity, it is associated with a slight bleeding risk. The Cochrane review, dominated by studies that used a dose of 75–100 mg, found a relative risk increase of 6% (RR 1.06, 95% CI 1.00 to 1.12; 19 studies, 23 769 participants) in postpartum haemorrhage (PPH) equivalent to nine more cases per 1000 women (95% CI 0 to 19) based on an assumed risk of 143 cases per 1000 women with placebo or no treatment.[2] Additionally, a recent population-based cohort study involving 313 624 women that investigated bleeding complications with aspirin 75 mg taken during pregnancy (4088 women), found that aspirin was associated with a higher rate of PPH (10.2% vs. 7.8%; adjusted OR 1.23, 95% CI 1.08 to 1.39). Reassuringly, no increased risk of major gastrointestinal bleeding was found (0.3% vs 0.2%).[14] A bleeding risk is biologically plausible because aspirin inhibits platelet function and it is unclear whether simply ceasing aspirin at 36 weeks' gestation mitigates this risk.

A 6% relative risk increase of an obstetric event that is relatively common—such as PPH—may be significant. For example, for an individual with a baseline risk of PPH that is greater than their risk of developing pre-eclampsia (eg, 12% PPH risk vs 4% pre-eclampsia risk), then the absolute increased risk of one adverse outcome (ie, 0.72% increase in the absolute risk of PPH from 12.00% to 12.72%), may roughly equate to the decreased risk of the other (4.0% absolute risk of pre-eclampsia reduced to 3.3%). In short, while aspirin only has a slight bleeding risk we suggest it should not be liberally offered to those with a low likelihood of developing pre-eclampsia.

Furthermore, it is plausible that the bleeding risk is even higher if the dose is increased to 150 mg. While the ASPRE trial

did not detect an increased risk of bleeding it may have been underpowered to do so.

Other considerations

A small clinical trial (350 women) reported that taking aspirin at night-time just before bed may decrease blood pressure and be more effective in decreasing blood pressure and preventing adverse outcomes.[15] The trial has some potential methodological concerns, for example, it does not appear to be registered, the power calculation was not based on the primary outcome and the reductions in adverse outcomes with aspirin were far greater than in other trials. These factors limit its generalisability and we suggest the findings should be considered preliminary. While the ASPRE trial administered aspirin at night, other trials did not. It is, therefore, difficult to be prescriptive as to whether night-time dosing is truly beneficial.

It is possible that the effects of aspirin may vary by maternal body mass index (BMI) and that adjusting the dose according to BMI may be beneficial. Indeed, a large meta-analysis in older non-pregnant populations showed low-dose aspirin becomes less effective in preventing cardiovascular events with increasing BMI.[16] However, aspirin is not offered in formulations that allows clinicians to refine dosing according to BMI. Given this, it is reasonable for clinicians to adhere with the dose recommended by local guidelines.

Conclusion

Taking aspirin at a dose of 75–150 mg per day during pregnancy appears to modestly reduce the risk of pre-eclampsia, fetal growth restriction and preterm birth. It should be ideally commenced in early pregnancy at around 12 weeks' gestation and taken until either 36 weeks' gestation, or delivery. Given there may be an increased risk of postpartum bleeding it should be prescribed to women who have been assessed as having an elevated risk of pre-eclampsia, such as those with maternal risk factors or screen positive from first trimester screening. It is unclear whether aspirin is more beneficial if taken at bedtime.

Information for patients

- For pregnant women who have risk factors placing them at increased risk of developing a condition called pre-eclampsia, taking a low dose of aspirin between 12 and 36 weeks of pregnancy can decrease their risk by around 20% (meaning if they had a 10% risk of developing pre-eclampsia to begin with, taking aspirin would drop it by 2% so their overall risk falls to 8%).
- Clinicians will use information from a woman's clinical history to determine whether she is at increased risk (eg, being a first-time mother, older and having a family history are things that increase the risk).
- Alternatively, the health professional may refer pregnant women to have a test done during the first trimester of pregnancy to determine whether they are at increased risk of developing pre-eclampsia. This test combines information from a blood test, ultrasound and clinical information to determine the risk of pre-eclampsia happening. This specialised test may not be available in all maternity services.
- The dose of aspirin that is offered will be 75 or 150 mg. It should be taken once a day from around 12 weeks of pregnancy, until at least 36 weeks.
- Aspirin at these low doses is very safe. There is a small risk of increased bleeding just after birth, but if it happens the maternity team can safely manage this.

Competing interests None declared. Refer to the online supplementary files to view the ICMJE form(s).

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