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## LOW-DOSE ASPIRIN FOR PRE-ECLAMPSIA PREVENTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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### 1. INTRODUCTION

Pre-eclampsia, the new onset of hypertension with organ dysfunction after twenty weeks of gestation, complicates a few per cent of pregnancies worldwide and is a major contributor to maternal death, stillbirth and preterm delivery [1, 2]. Delivery remains the only cure. Prevention has therefore drawn constant interest, and among the candidates tested, low-dose aspirin has the longest record and the broadest support from guideline bodies [3, 4]. It is cheap, taken by mouth, and familiar to every clinician. The question for this review is how strong the supporting evidence really is, what dose and timing the

### Abstract

Pre-eclampsia is a leading cause of maternal and perinatal morbidity, and low-dose aspirin is the most widely recommended preventive drug. This narrative review, which reports no new data, summarises what published randomised trials and meta-analyses show about aspirin for pre-eclampsia prevention, including mechanism, dose, timing, risk selection and safety. Syntheses consistently report a modest overall reduction in pre-eclampsia, with larger effects for preterm disease when treatment starts early in pregnancy at doses of about 100 mg or more in women at increased risk. Serious maternal bleeding has not been shown to increase. Uncertainties remain about optimal dose, duration, adherence and use in low-resource settings, and heterogeneity limits pooled estimates.

studies back, and who is likely to benefit. The review draws on published trials, systematic reviews and guidelines, and reports no new data.

The idea is older than many assume. Small trials in the 1980s reported that low doses of aspirin lowered blood pressure and the rate of pre-eclampsia in women with raised vascular sensitivity to angiotensin [5]. Larger trials followed, and the picture became less clear: the CLASP trial of more than nine thousand women found only a modest and statistically uncertain reduction in pre-eclampsia, and meta-analyses of the 1990s and 2000s gave small, sometimes disputed, benefits [6, 7]. What changed later was not the drug but the way trials were designed, with more attention to who was recruited, when treatment started and what dose was used [8, 9].

Because the field is large, the review is arranged in a sequence. Mechanism and the biology of pre-eclampsia come first, followed by the main trials and syntheses, summarised in table 1 and grouped by type in fig. 1. A section on dose, timing and risk selection comes next, then safety and guideline recommendations, and finally the limits of current knowledge. One caution applies throughout: pooled estimates from meta-analyses are only as good as the trials entering them, and the trials differ in population, dose, start time and adherence, so heterogeneity needs weighing before any pooled number is accepted [10, 11].

**Table 1: Selected published trials, syntheses and guidance on low-dose aspirin for pre-eclampsia prevention**

| Source or topic                        | Reported finding or recommendation                                                    | Ref. |
|----------------------------------------|---------------------------------------------------------------------------------------|------|
| CLASP trial<br>9364 women              | Large early trial found a modest, statistically uncertain fall in pre-eclampsia.      | [6]  |
| ASPRE trial<br>150 mg, high risk       | Preterm pre-eclampsia fell by more than half; term disease not significantly changed. | [12] |
| ASPIRIN trial<br>low-resource settings | Modest reduction in preterm birth with 81 mg in first-time mothers.                   | [13] |
| PARIS individual data<br>meta-analysis | Average reduction of about a tenth in pre-eclampsia across subgroups.                 | [7]  |
| Cochrane review<br>antiplatelet agents | Roughly one fifth fewer cases of pre-eclampsia; moderate certainty for most outcomes. | [14] |

| Source or topic                              | Reported finding or recommendation                                                  | Ref.        |
|----------------------------------------------|-------------------------------------------------------------------------------------|-------------|
| Dose meta-analysis<br>100 mg or more         | Larger reductions at higher doses, with fewer growth-restricted infants.            | [8]         |
| Early versus late start<br>16 weeks          | Greater reduction when started by 16 weeks; later analyses less clear-cut.          | [9, 15, 16] |
| USPSTF evidence review<br>safety             | No clear rise in abortion, haemorrhage or perinatal death.                          | [3]         |
| ACOG recommendation<br>81 mg                 | Daily aspirin for high-risk women from 12 weeks, ideally before 16 weeks.           | [4, 17]     |
| NICE and WHO guidance<br>75–150 mg           | Daily aspirin for women at high risk, started in first or early second trimester.   | [18, 19]    |
| Competing-risks screening<br>first trimester | Combined maternal factors and biomarkers detect more preterm cases than checklists. | [20, 21]    |

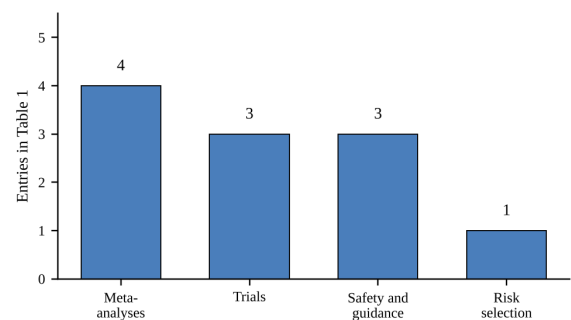


**Fig. 1: Number of entries in table 1 by type of evidence**

## 2. PATHOPHYSIOLOGY AND MECHANISM OF ASPIRIN

Pre-eclampsia is commonly described in two stages. In the first, shallow invasion of the uterine spiral arteries by trophoblast cells leaves the placenta poorly perfused and stressed. In the second, placental factors reach the maternal circulation and provoke widespread endothelial dysfunction, with hypertension, proteinuria and microvascular injury as the clinical result [22, 23]. Not every case follows the model neatly, and some authors argue that maternal cardiovascular and metabolic susceptibility matters as much as placental pathology [24, 25]. The model nonetheless guides prevention: if the defect arises early in placental development, effective drugs should act early, which is one reason timing features so heavily in aspirin

trials.

Aspirin acts by irreversibly acetylating a serine residue in cyclooxygenase, chiefly cyclooxygenase-1 in platelets. Because platelets lack a nucleus, they cannot make new enzyme, so the effect lasts for the life of the platelet and thromboxane A<sub>2</sub> production is suppressed until new platelets are released [26]. Pre-eclampsia is associated with an imbalance in which thromboxane, a vasoconstrictor that promotes platelet aggregation, is raised relative to prostacyclin, a vasodilator produced by endothelium. Low doses of aspirin tip the balance back by inhibiting platelet thromboxane to a greater degree than vascular prostacyclin, which is the classical argument for using low rather than analgesic doses [26, 27].

The prostanoid story is probably incomplete. Experimental work suggests that aspirin may also improve trophoblast invasion and spiral artery remodelling, reduce placental inflammation and oxidative stress, and modify endothelial function, effects that would fit better with the observed benefit of early treatment [23, 28]. Evidence for these actions in human pregnancy is mostly indirect. Whether effects at the placenta need higher doses than those required to block platelets is another unresolved point, and some authors have suggested this as an explanation for the better performance of doses at or above 100 mg in the meta-analyses [8, 29].

Maternal susceptibility helps explain who develops the disease. Chronic hypertension, pregestational diabetes, kidney disease, autoimmune conditions, obesity, a previous affected pregnancy and multiple gestation all raise the risk, and a first pregnancy and older age add a smaller increment [24, 30]. Many of these features also predispose to cardiovascular disease later in life, which has led to the suggestion that pre-eclampsia exposes underlying vascular vulnerability as much as it causes damage itself [22, 25]. For prevention research the point is practical. Women with several risk factors form the group in which a drug of modest effect gives the largest absolute benefit, which is why trials and guidelines concentrate on selecting them [1, 20].

### 3. EVIDENCE FROM TRIALS AND SYNTHESSES

The most up-to-date broad synthesis is the Cochrane review of antiplatelet agents, which pooled dozens of trials involving many thousands of women. It reported a relative reduction in pre-eclampsia of roughly one fifth, along with smaller reductions in preterm birth, fetal or neonatal death and small-for-gestational-age infants, with moderate certainty for most outcomes [14]. The earlier individual participant analysis by the PARIS collaboration had reported a smaller average effect of about ten per cent for pre-eclampsia, similar across subgroups defined by risk, gestation at entry and dose [7]. The difference between the two analyses reflects the trials added in the interval and the methods used, and neither found strong evidence of harm [3].

Subgroup analyses by timing and dose give a clearer view. Meta-analyses of trials in which aspirin was started at or before sixteen weeks reported larger reductions in pre-eclampsia, particularly preterm disease, than those starting later [9, 15]. Daily doses of at least 100 mg were linked to greater reductions than lower doses in a dose-based meta-analysis, which also reported lower rates of fetal growth restriction [8]. These analyses depend on comparing trials rather than randomising dose or timing directly, so confounding is possible. An individual participant data meta-analysis found no clear difference by gestational age at initiation, and the authors urged caution about overinterpreting subgroup contrasts [16, 31].

The most influential single trial is the ASPRE study, which enrolled women identified at first-trimester screening as being at high risk of preterm pre-eclampsia and randomised them to 150 mg of aspirin nightly or placebo from about eleven to fourteen weeks until thirty-six weeks. Preterm pre-eclampsia was reduced by more than half in the aspirin group, a striking result, although the effect on term disease was not significant [12]. The screening method used a competing-risks algorithm combining maternal factors, blood pressure, uterine artery Doppler and placental biomarkers, which is more sensitive than risk factor checklists [20, 21]. Replication in other

settings has been uneven, partly because few units run the same screening algorithm.

A recent trial in low-resource settings makes a useful contrast. The ASPIRIN trial, conducted in several low- and middle-income countries, tested 81 mg of aspirin started between six and twenty-eight weeks in first-time mothers, and found a modest reduction in preterm birth before thirty-seven weeks, rather than a dramatic effect on pre-eclampsia as such [13]. The population, the dose and the outcome were all different from those in ASPRE. Put simply, the results suggest that benefit exists across settings but varies in size, and that conclusions from screening-selected high-income populations may not apply directly elsewhere [14, 29].

Outcomes beyond pre-eclampsia itself bear on the value of treatment. Aspirin has been associated with fewer preterm births, fewer small-for-gestational-age infants and a lower risk of fetal or neonatal death in the Cochrane synthesis, though the absolute reductions are small and certainty varies between outcomes [3, 14]. The dose-based analysis reported lower rates of fetal growth restriction at 100 mg or more, and the ASPIRIN trial focused on preterm delivery as its primary outcome [8, 13]. For parents and clinicians, avoiding an early birth often matters more than the label given to the hypertensive complication, so these secondary findings may carry as much weight as the headline reduction [7, 9].

The principal findings are brought together in table 1. Three themes emerge. Overall effects are modest and consistent in direction, with no signal that aspirin makes outcomes worse for mothers [3, 14]. Larger effects are seen for preterm disease and in women treated early at adequate dose [8, 12]. And the strongest trials either selected women at high risk or tested a defined dose and start time, which suggests that the benefit is real but depends on matching treatment to the patient [9, 21]. No single trial answers every question, and combined evidence is needed to interpret each.

Methodological quality of the evidence deserves comment. Earlier trials differed so much in design that heterogeneity in pooled analyses was often considerable, and standard measures of inconsistency should be

examined before a single summary effect is quoted [11]. Reporting of adherence, a major determinant of benefit, was inconsistent, and some trials counted women who stopped aspirin early in the same group as those who continued. Publication bias is difficult to exclude with small early studies. The broad agreement of independent syntheses is reassuring, but readers should treat precise numerical estimates as approximate, and favour the direction and rough size of effect over false precision [10, 14].

#### 4. DOSE, TIMING AND RISK SELECTION

Dose recommendations vary by body. The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force (USPSTF) recommend 81 mg daily, the common low-dose tablet strength in the United States, for women at high risk, beginning between twelve and twenty-eight weeks, ideally before sixteen [4, 17]. The National Institute for Health and Care Excellence (NICE) recommends 75 to 150 mg daily from twelve weeks until birth [18]. The World Health Organization (WHO) suggests 75 mg daily started before twenty weeks for women at high risk [19]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends doses of 75 to 162 mg, taken at night, from the end of the first trimester [32, 33]. The differences are modest, and mostly reflect available tablet strengths.

Evidence that higher doses work better has led several authorities to favour 100 to 150 mg where available, and the ASPRE trial used 150 mg [8, 12]. Authors of dose-response analyses are frank that the evidence is observational at the level of between-trial comparison, and a large head-to-head randomised comparison of 81 mg and 162 mg has been called for to resolve the question [28, 29]. At present, a pragmatic approach is to use the dose recommended by the local guideline and to consider a higher dose in women who are heavier or at especially high risk, while recognising that this practice rests more on biological reasoning than on direct evidence.

Timing is the second variable. Starting before sixteen weeks appears more effective than later initiation in several syntheses, which fits the biology of early placentation [9, 15]. Studies of initiation before eleven weeks suggest that earlier is not necessarily better, though the evidence base is small [31]. Stopping time is less well studied. Many protocols continue to thirty-six weeks or delivery, while some propose discontinuing earlier in women whose risk is judged to have fallen, and trial data on early discontinuation, though suggestive, are not decisive [21, 29]. Practicality matters: starting soon after booking and avoiding gaps in supply are likely to be more important than fine adjustments of a few weeks.

Who should receive aspirin is the third question. Guidelines in the United States and the United Kingdom use lists of risk factors, which are classed as high or moderate: previous pre-eclampsia, chronic hypertension, diabetes, kidney or autoimmune disease and multiple pregnancy are high-risk features, while first pregnancy, older maternal age, obesity and family history count as moderate [4, 18]. Systematic review of cohort data shows that most of these factors raise risk, though none is strongly predictive alone, and checklists detect only a minority of women who go on to develop preterm disease [20, 30]. Combined first-trimester screening with competing-risks models gives better detection at the same false-positive rate [12, 21].

Universal aspirin for all pregnant women has been debated. An argument in favour is that risk-factor approaches miss many cases and that aspirin is cheap and safe; against it are the small absolute benefit in low-risk women, the burden of treating many for few gains and the small but real bleeding risk [34, 35]. Modelling and policy papers have suggested that universal treatment might be cost-effective in some settings, while others call for better screening first. The question is unlikely to be resolved by theory. Pragmatic trials comparing universal and screened strategies would be informative, but have not yet been done on a scale that settles matters [21, 29].

Aspirin is not the only preventive measure, and guidelines place it alongside others.

Calcium supplementation is advised by the World Health Organization for women whose dietary intake is low, a common situation in parts of Africa and Asia, and has a separate evidence base [19, 25]. Management of chronic conditions before and during pregnancy, such as control of blood pressure and diabetes, remains central. Other agents including low-molecular-weight heparin, vitamins C and E and metformin have been tested with disappointing or inconclusive results, and none has displaced aspirin [21, 24]. In practice aspirin is added to a package of antenatal care and does not replace it.

## 5. SAFETY, GUIDELINES AND PRACTICE

Safety data from the trials are largely reassuring. The systematic evidence review for the US Preventive Services Task Force found no increase in placental abruption, postpartum haemorrhage or perinatal mortality attributable to low-dose aspirin, and the Cochrane review reported a small increase in postpartum haemorrhage in some analyses, with no clear rise in severe bleeding events [3, 14]. Neonatal outcomes did not appear to worsen in the reviewed trials, and there was no sign of premature closure of the ductus arteriosus at low doses, a concern that is raised with non-steroidal anti-inflammatory drugs given late in pregnancy [4, 17]. The trial populations were selected, and rare adverse events could be missed, so pharmacovigilance after wider use remains worthwhile.

Practical points are worth restating. Aspirin should generally be avoided in women with a history of aspirin-sensitive asthma, active peptic ulceration, a bleeding disorder or severe liver or kidney disease, and combined use with anticoagulants or other non-steroidal drugs requires a specialist decision [4, 18]. Epidural or spinal anaesthesia is not contraindicated in women taking low-dose aspirin, according to most guidance. Women should be told to continue the tablet unless advised otherwise and to report unusual bleeding. Gastrointestinal upset can be reduced by taking the tablet with food, and a coated or dispersible preparation can be used if swallowing is difficult [3, 28].

Implementation is where evidence often falters. Even when guidelines are clear, aspirin may not be offered because risk factors are not recorded, because clinicians doubt the benefit for moderate-risk women or because the tablet is available over the counter and the prescription never enters the record [34, 35]. Cost is small for the drug and larger for screening. Programmes that automate risk assessment at booking, supply tablets at the visit and follow up adherence appear to deliver better coverage than those relying on individual clinician recall, though most published data are descriptive [21, 29]. Evaluation of implementation, not only of efficacy, should be part of research on this intervention.

Taken as a whole, guideline recommendations converge on the same practice despite small differences in dose. Women at high risk should be offered aspirin early in the second trimester at the latest and preferably in the first, continued to late pregnancy [4, 18, 19]. The evidence base supporting these statements has strengthened since the earliest recommendations, though the certainty of evidence for many details, such as dose above 100 mg or discontinuation timing, is still moderate to low [14, 33]. Pharmacists and midwives can help by checking for interacting drugs, confirming that the woman understands how long to continue and making sure she can obtain the tablets [21, 29].

## 6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations affect what can be concluded. Trials differ in the populations recruited, the dose and timing used, adherence and the definitions of pre-eclampsia, so pooled estimates describe an average that may not apply to any individual woman [11, 14]. Subgroup contrasts for dose and timing are based on between-trial comparisons and subject to confounding. Few trials come from low- and middle-income countries, where the burden is greatest, and screening methods like those in ASPRE are not available in many places [1, 13]. Long-term follow-up of children exposed to aspirin in utero is limited, though available data are reassuring [3].

Priorities for future work are fairly clear. A randomised comparison of different doses, such as 81 mg against 150 mg, would resolve the dose question, and trials that randomise the start time or stop time would address timing [8, 29]. Studies of screening strategies in routine practice, including low-cost approaches suited to resource-poor settings, are needed alongside work on adherence [13, 21]. Individual participant data meta-analyses with prespecified subgroups will provide firmer estimates than aggregate data [7, 16]. Until then, current guidelines offer a reasonable course of action based on consistent, if imperfect, evidence.

## 7. CONCLUSION

Published evidence supports low-dose aspirin as a safe and moderately effective way to lower the risk of pre-eclampsia in women at increased risk. Pooled analyses show an overall reduction of around a tenth to a fifth, with larger effects on preterm disease when treatment begins early in pregnancy at doses of about 100 mg or more [7, 8, 9, 14]. The ASPRE trial gave the clearest demonstration of benefit in a screened high-risk group [12], while trials in low-resource settings suggest smaller but still useful gains [13]. Reassuring safety data from large reviews support routine use under guideline criteria, and the drug costs little compared with the burden of the disease it helps prevent [3, 4].

The picture is not complete. Optimal dose, stopping time and the best way to select women remain uncertain, adherence in everyday practice is imperfect, and most evidence comes from high-income settings [1, 21, 29]. Comparisons of 81 mg and 150 mg, studies of universal and screened strategies and better individual participant data analyses are the main needs [16, 34]. Until they arrive, clinicians and pharmacists can rely on guideline advice, explain the purpose and duration of treatment to women, and support adherence, since a tablet left in the cupboard prevents nothing [18, 19, 33].

## 8. ABBREVIATIONS

ACOG-American College of Obstetricians and Gynecologists, ASPRE-Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia

Prevention, CLASP-Collaborative Low-dose Aspirin Study in Pregnancy, ISSHP-International Society for the Study of Hypertension in Pregnancy, NICE-National Institute for Health and Care Excellence, PARIS-Perinatal Antiplatelet Review of International Studies, USPSTF-US Preventive Services Task Force, WHO-World Health Organization

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All the authors have contributed equally.

## 11. CONFLICT OF INTERESTS

Declared none

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