WHO recommendation on low-dose acetylsalicylic acid (aspirin) for pre-eclampsia prevention in high-risk women

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Recommendation

Low-dose acetylsalicylic acid (aspirin, 75 mg) is recommended for the prevention of pre-eclampsia in women at high risk of developing the condition. (Strong recommendation, moderate-quality evidence)

Publication history

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Remarks

- Women are regarded as being at high risk of developing pre-eclampsia if they have one or more of the following risk factors: previous preeclampsia; diabetes; chronic hypertension; renal disease; autoimmune disease; and multiple pregnancies. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.
- The guideline development group acknowledged that in settings where 75 mg aspirin tablets are not available, the available dose nearest to 75 mg should be used.
- While low-dose aspirin has been shown to be beneficial in women at high risk of preeclampsia, there is a paucity of evidence to suggest that any subset of women within the high-risk group would benefit from aspirin therapy.
- The guideline development group noted that it may be appropriate to initiate antiplatelet agents before 20 weeks of gestation, and, if possible, as early as 12 weeks of gestation.

Background

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths, whereas in Latin America and the Caribbean, they contribute to approximately 22% of all maternal deaths.(1)
Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. The majority of deaths due to pre-eclampsia and eclampsia are avoidable through the provision of timely and effective care to the women presenting with these complications.

Aspirin is an acetylated salicylate with anti-inflammatory, analgesic, antipyretic and antiplatelet properties. The pathogenesis of pre-eclampsia in early pregnancy involves abnormal platelet activation and vasoconstriction, which has led to a number of randomized controlled trials testing the efficacy of aspirin in preventing or delaying pre-eclampsia, or reducing the adverse effects of pre-eclampsia in women with the condition.(2)

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(3, 4) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of pre-eclampsia eclampsia (2011).(5)

A Cochrane systematic review was conducted, on the effects of antiplatelet agents (such as aspirin and dipyridamole) when used for the prevention of pre-eclampsia and its complications.(2) In the review, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting on recommendations for prevention and treatment of pre-eclampsia or eclampsia in April 2011, where this recommendation was developed. The GDG comprised of a group of independent experts, who used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Recommendation question

For this recommendation, we aimed to answer the following question/s:

- In pregnant women (P), does aspirin supplementation during pregnancy (I) compared to no supplementation or placebo (C) improve maternal and perinatal outcomes, including onset of pre-eclampsia and related complications?
- If so, what dosing regimen can optimize outcomes?

Evidence Summary

Evidence related to the effects of antiplatelet agents, such as aspirin and dipyridamole, when used for the prevention of pre-eclampsia and its complications came from a Cochrane systematic review of 60 RCTs involving 37 720 women.(2) Most of the trials were relatively small and only nine recruited 1000 or more women. Participants were pregnant women considered to be at moderate or high risk of developing pre-
eclampsia. Women were regarded as being at high risk if they were normotensive or had chronic hypertension in addition to one or more of the following risk factors: previous severe pre-eclampsia; diabetes; chronic hypertension; renal disease; or autoimmune disease. Those at moderate risk were those with any other known risk factors for pre-eclampsia, in particular, primigravity. Aspirin alone was compared with placebo or no treatment in majority of the trials.

**Antiplatelet agents versus placebo or no antiplatelet for primary prevention**

When any antiplatelet agent, regardless of the dose, duration of therapy and time of initiating treatment, was compared with placebo in women with normal blood pressure at trial entry, there was no statistically significant difference in the risk of gestational hypertension (33 trials, 20 701 women; RR 0.95, 95% CI 0.88–1.03). This finding remains consistent for women at moderate risk of pre-eclampsia, whereas for those at high risk the use of antiplatelet agents was associated with a significant reduction in the risk of gestational hypertension (moderate risk: 22 trials, 19 863 women; RR 1.00, 95% CI 0.92–1.08; high risk: 12 trials, 838 women; RR 0.54, 95% CI 0.41–0.70). There was a statistically significant risk reduction in the development of pre-eclampsia among women who received antiplatelet agents compared with placebo (44 trials, 32 750 women; RR 0.82, 95% CI 0.76–0.89). This risk reduction remains consistent across risk groups for pre-eclampsia although it was more marked among high-risk women (moderate risk: 26 trials, 28 629 women; RR 0.86, 95% CI 0.78–0.94; high risk: 18 trials, 4121 women; RR 0.75, 95% CI 0.66–0.85).

No statistically significant differences were observed between the two comparison groups for any other critical (or proxy) outcomes addressed in the trials: eclampsia (nine trials, 22 584 women; RR 0.94, 95% CI 0.59–1.48); maternal death (three trials, 12 709 women; RR 2.57, 95% CI 0.39–17.06); placental abruption (16 trials, 24 982 women; RR 1.10, 95% CI 0.89–1.37); perinatal death (15 trials, 16 550 women; RR 0.89, 95% CI 0.74–1.08); and admission to special care baby unit (15 trials, 28 298 women; RR 0.95, 95% CI 0.90–1.01) (EB Table 10).

In trials in which the gestational age at recruitment was specified, the above findings were consistent between women who commenced treatment before and after 20 weeks of pregnancy for gestational hypertension, pre-eclampsia and placental abruption. For fetal, neonatal or infant death, the use of antiplatelet agents was associated with statistically significant reduction in risk among women who commenced treatment before 20 weeks, although the reduction in risk remained statistically insignificant for those initiating treatment after 20 weeks (<20 weeks: 19 trials, 17 666 women, RR 0.82, 95% CI 0.69–0.98; >20 weeks: 19 trials, 11 057 women, RR 0.91, 95% CI 0.73–1.13) (EB Table 11).

Treatment effects of antiplatelet agents compared with placebo were evaluated across three dosage categories [low-dose aspirin (acetylsalicylic acid): 75 mg/day or lower; higher-dose aspirin: more than 75 mg/day; and aspirin more than 75 mg/day + dipyridamole] for the following critical (or proxy) outcomes: gestational hypertension; pre-eclampsia; placental abruption and fetal; and neonatal or infant death. While no statistically significant effect was demonstrated with low-dose aspirin, higher doses of aspirin and more than 75 mg/day aspirin plus dipyridamole were associated with statistically significant reduction in the risk of gestational hypertension.

The risk reduction effect of antiplatelet agent compared with placebo for pre-eclampsia was consistent across the three dosage categories and tend to increase with increasing dose (12% reduction with aspirin 75 mg/d or lower to 70% reduction with aspirin more than 75 mg/day + dipyridamole). Similar pattern was observed for fetal, neonatal or infant death across the three dosage categories. No statistically significant effect was demonstrated in any of the dosage categories for placental abruption (EB Table 12).

**Antiplatelet agents versus placebo or no antiplatelet for women with gestational hypertension**

Comparison of any antiplatelet agent with placebo in women with gestational hypertension at trial entry showed a statistically significant reduction in the risks of pre-eclampsia (five trials, 1643 women; RR 0.60, 95% CI 0.45–0.78) and severe pre-eclampsia (one trial, 94 women; RR 0.33, 95% CI 0.14–0.75). No
statistically significant differences were observed for any other critical (or proxy) outcomes addressed: eclampsia (three trials, 354 women; RR 0.25, 95% CI 0.03–2.24); placenta abruption (one trial, 94 women; RR 0.35, 95% CI 0.01–8.32); fetal, neonatal or infant death (four trials, 1728 women; RR 1.02, 95% CI 0.72–1.45); and admission to special care baby unit (one trial, 94 women; RR 0.52, 95% CI 0.05–5.56). Most of the trials providing these outcomes were small and at moderate risk of bias, thereby generating very-low- to low-quality evidence (EB Table 13).

### Implementation considerations

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of low-dose aspirin in antenatal care settings), and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

### Research implications

The 2011 GDG did not identify any high-priority research questions on this intervention.

### Related Links

- [Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice](https://www.who.int/mediacentre/factsheets/fs348/en/)
- [Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors](https://www.who.int/mediacentre/factsheets/fs349/en/)

### Supporting systematic review/s:


### References

2. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia


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