Do acetylsalicylic acid and other antiplatelet drugs prevent preeclampsia?

Rohan Maharaj, MB, MHSC

Duley L, Henderson-Smart D, Knight M, King J. Anti-platelet drugs for prevention of pre-eclampsia and its consequences: systematic review. *BMJ* 2001;322:329-33.

Research question

How effective and safe are antiplatelet drugs in preventing preeclampsia and its consequences?

Type of article and design

Systematic review and meta-analysis of 39 trials.

Relevance to family physicians

Family physicians providing obstetric care are on the front line for screening and managing patients with preeclampsia. Preeclampsia is defined as elevated blood pressure and associated proteinuria during pregnancy. During late pregnancy, preeclampsia is associated with hyperreflexia and seizures and increased maternal and fetal morbidity and mortality.

The condition is similar to gestational hypertension with proteinuria and adverse conditions as defined by the Report of the Canadian Hypertension Society Consensus Conference.[1] Appropriate management by family physicians should include screening and primary and secondary prevention. The ideal management protocol would allow primary care physicians to choose when to initiate therapy for prevention of preeclampsia in low-, moderate-, and high-risk patients, and would recommend types of therapy and indicate their dosages and safety profiles. Antihypertensive therapies have been unsatisfactory in the past because they did not address underlying pathology: deficient intravascular production of prostacyclin; a vasodilator; or the excessive production of thromboxane, a vasoconstrictor that stimulates platelet aggregation. Antiplatelet drugs could address these underlying factors; initial results of studies using acetylsalicylic acid and dipyridamole have been positive.

Previous meta-analyses of early studies of using ASA for preeclampsia strongly supported these positive results,[2,3] but subsequent large multicentre studies, such as the Collaborative Low dose Aspirin Study in Pregnancy (CLASP),[4] did not support them. Citing publication bias as a possible reason for discrepancies, this new meta-analysis sets out to reassess the effectiveness and safety of antiplatelet drugs for prevention of preeclampsia and its consequences. The Society of Obstetricians and Gynaecologists of Canada's webpage (**sogc.medical.org**/) has no guideline addressing this issue.

Overview of study and outcomes

The reviewers searched the Cochrane Pregnancy and Childbirth Group Register of Trials, the Cochrane Controlled Trials Register, EMBASE (1994-1999), and, by hand, conference abstracts. The entire search strategy is described in detail in another article.[5]

Randomized trials comparing antiplatelet agent(s) with placebo or no antiplatelet agents for women at risk of developing preeclampsia were included. In their synthesis of the data, the authors divided women groups based on whether they were at high or moderate risk of developing preeclampsia at trial entry, were more or less than 20 weeks' gestation at trial entry, were taking more or less than

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail **michael.evans@utoronto.ca** or by fax (416) 603-5821.

Dr Maharaj, *a family physician and lecturer at the University of the West Indies in St Augustine, Trinidad, received his MHSC in family medicine at the University of Toronto in Ontario and recently participated in the Teaching Evidence-Based Medicine Workshop at Oxford University in England.*

75 mg of ASA, and were in studies where placebo was given to the control group.

High risk of preeclampsia was defined as history of preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease. Moderate risk of preeclampsia was defined as any other risk. Trials with quasi-random designs were excluded. Main outcomes were preeclampsia, preterm delivery, stillbirth or neonatal death, and small-for-gestational-age babies.

There was no blinding of study results or authors, but two independent pairs of researchers assessed the studies using data extraction forms. Each pair assessed the trials independently; differences were resolved by discussion. If differences remained unresolved, the other pair was consulted. Each trial was assessed for whether concealment of allocation[6] was adequate, unclear, or clearly inadequate. Inadequately concealed randomization could lead to overestimating odds ratios by 40%.[7] Only one of the 39 trials included was graded inadequate; 14 were adequate; and 24 were unclear. All data were double-checked for discrepancies.

Results

Of 310 articles identified, 153 were excluded: 109 did not meet the eligibility criteria; 44 were duplicate articles. Of the remaining 157 articles, 99 referred to 39 included trials, and 58 referred to 45 excluded trials. The 39 included trials recruited a total of 30 563 women. The women's risk status varied widely among the various trials and often within the same trial. Most studies compared ASA alone with placebo (28 802 women). Other antiplatelet drugs used were dipyridamole, heparin, and ozagrel hydrochloride.There was no overall difference in risk of pregnancy-induced hypertension in the 27 trials reporting this outcome.

In the 32 trials (29 331 women) with preeclampsia as an end point, there was a 15% risk reduction with ASA (relative risk [RR] 0.85, 95% confidence interval [CI] 0.78 to 0.92; number needed to treat [NNT] 100, 95% CI 55 to 167). This result was consistent regardless of the risk status of the women in the various trials, the dose of ASA used, gestation at trial entry, or whether placebo or no treatment was used.

As to outcomes for babies in the 23 trials using preterm birth as an end point (28 268 women), there was an 8% risk reduction with ASA (RR 0.92, 95% CI 0.88 to 0.97; NNT 72, 95% CI 44 to 100). Overall, there was a 14% reduction in deaths in the antiplatelet group compared with the control group (30 trials, 30 093 women).

Analysis of methodology

This review has only one apparent methodologic weakness: the two pairs of reviewers were not blinded to the trial authors or the location of the study. Another issue for primary care physicians is that it is not clear where patients were recruited from and, therefore, not clear whether these results can be generalized to our practices. Stratification of patients into high- and moderate-risk groups means many factors are applicable to primary care settings. Further, review of the characteristics of the 39 trials reveals that patients were recruited from a mix of primary, secondary, and tertiary care settings. In many of the studies with large patient populations, patients appear similar to those seen in primary care.

Application to clinical practice

Analysis of the subgroups looked extensively at outcomes and less at time of gestation when ASA was initiated or how ill patients were at initiation of therapy. We are left with uncertainty about how to use this intervention in primary care.

An interesting issue for further analysis is the value of using higher doses of ASA. This review notes that, although the studies were small, when women were given >75 mg of ASA, results suggest greater reduction in risk of preeclampsia (RR 0.35, 95% CI 0.24 to 0.52); greater reduction in risk of preterm birth (RR 0.58, 95% CI 0.38 to 0.88); and a clear reduction in risk of small-for-gestational-age babies (RR 0.68, 95% CI 0.52 to 0.88).

Bottom line

- Acetylsalicylic acid is ineffective for primary prevention of hypertension during pregnancy.
- Low-dose ASA (75 mg) and antiplatelet drugs are associated with a 15% decrease in risk of preeclampsia.
- This 15% risk reduction is consistent regardless of women's risk status or gestation at time of entry into the trial.
- Antiplatelet drugs and ASA are associated with a 14% decrease in risk of stillbirths and neonatal death and an 8% decrease in risk of preterm birth.
- Previous meta-analyses have suggested that low-dose ASA is safe for use during pregnancy.
- Family physicians can use this information to offer ASA to patients with a history of preeclampsia, diabetes mellitus, chronic hypertension, renal disease, or autoimmune disease for prevention of preeclampsia during pregnancy.

References

1. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference. 1. Definition, evaluation and classification of hypertensive disorders in pregnancy. *Can Med Assoc J* 1997;157:715-25.

Points saillants

- L'acide acétylsalicylique (AAS) n'est pas efficace dans la prévention primaire de l'hypertension durant la grossesse.
- L'AAS à faible dose (75 mg) et les anti-agrégants plaquettaires sont associés à une réduction de 15% du risque d'éclampsisme.
- Cette réduction du risque de 15% demeure constante qu'importe la situation de risque ou la gestation de la femme au moment de commencer à participer à l'étude.
- Le recours aux anti-agrégants plaquettaires et à l'AAS est relié à une réduction de 14% des accouchements de morts-nés ou des décès néonatal et à une réduction de 8% des naissances avant terme.
- Des méta-analyses antérieures faisaient valoir l'innocuité de l'AAS à faible dose durant la grossesse.
- Les médecins de famille peuvent se fonder sur ces renseignements pour offrir de prendre de l'AAS à leurs patientes ayant des antécédents d'éclampsisme, de diabète sucré, d'hypertension chronique, de néphropathies ou de maladies auto-immunes pour prévenir l'éclampsisme durant la grossesse.

2. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive states. *JAMA* 1991;266:260-4.
3. Sanchez-Ramos L, Wears R, Del Valle GO, Gaudier FL, Adair D. Low dose aspirin for the prevention of pregnancy-induced hypertension: a meta-analysis. *Am J Obstet Gynecol* 1994;170:408.
4. CLASP Collaborative Group. Low dose aspirin in pregnancy and early childhood: follow up of the Low dose Aspirin Study in Pregnancy. *Br J Obstet Gynaecol* 1995;102:861-8.
5. Knight M, Duley L, Henderson-Smart D, King J. Antiplatelet drugs for preventing and treating pre-eclampsia. The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration. Issue 3. Oxford, Engl: Update Software; 2000. Updated quarterly.
6. Mulrow CD, Oxman AD, editors. The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration. Issue 1. Oxford, Engl: Update Software; 1999. Updated quarterly.
7. Schultz KF, Chalmers I, Haynes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.

...