Review: antiplatelet agents (particularly aspirin) reduce the incidence of pre-eclampsia in women at risk

Duley L, Henderson-Smart DJ, Knight M, *et al.* Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2004;(1):CD004659.

Clinical impact ratings FP/GP/Obstetrics ★★★★★★☆ Obstetrics ★★★★★★☆

Q In pregnant women at risk, is prophylactic use of antiplatelet agents (such as aspirin and dipyridamole) effective for preventing or delaying the development of pre-eclampsia as well as other related maternal and child outcomes?

METHODS

Data sources: the Cochrane Pregnancy and Childbirth Group trials register (September 2003), the Cochrane Central Register of Controlled Trials (*Cochrane Library*, Issue 2, 2003), EMBASE/Excerpta Medica (1994–2003), and congress proceedings of the International and European Societies for the Study of Hypertension in Pregnancy (up to 2002).

Study selection and assessment: randomised controlled trials (RCTs) that compared any antiplatelet agent (such as low dose aspirin or dipyridamole) with a control condition comprising placebo or no antiplatelet agent in pregnant women considered to be at risk of developing pre-eclampsia. Exclusion criteria included comparisons of 1 antiplatelet agent with another, and of antiplatelets with other interventions. Study quality was assessed using criteria outlined in the Cochrane Handbook.

Outcomes: maternal outcomes including pre-eclampsia, eclampsia, death, elective delivery (induction of labour or elective caesarean section), caesarean section (emergency plus elective), bleeding episodes (such as abruption of the placenta, antepartum haemorrhage, and postpartum haemorrhage); and child outcomes including death (stillbirth, neonatal, or infant), gestational age at birth, small for gestational age, intraventricular haemorrhage, and infant and child development disorders (such as cerebral palsy, cognitive delay, deafness, and blindness).

MAIN RESULTS

51 RCTs (36 500 women) met the selection criteria. Comparisons included aspirin alone with placebo or no treatment (44 RCTs), aspirin plus dipyridamole or dipyridamole alone with a control (4 RCTs), heparin plus dipyridamole with a control (1 small RCT), aspirin plus vitamins C and E and fish oil (1 small RCT), and ozagrel hydrochloride with placebo (1 RCT). Meta-analysis was done using a fixed effects model. The rates of pre-eclampsia, delivery before 37 weeks of gestation, child deaths (stillbirth, neonatal, or infant death), and small for gestational age were lower in the antiplatelet group than in the control group (table). The groups did not differ for all other outcomes.

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CONCLUSIONS

In pregnant women at risk, prophylactic use of antiplatelet agents (particularly aspirin) is effective for reducing the risk of pre-eclampsia and delivery before 37 weeks of gestation.

Commentary

No other intervention in obstetric practice has been subjected to the degree of trial investigation that antiplatelet agents have in the prevention of pre-eclampsia. This is not surprising because pre-eclampsia is a relatively common, and occasionally devastating, disease. The beneficial reduction in pre-eclampsia with antiplatelet agents is modest, but is associated with a corresponding reduction in the sequelae of early delivery, intrauterine growth restriction, and perinatal mortality; therefore this intervention is clinically important. The small relative risk reduction in adverse outcome and the low prevalence of pre-eclampsia in the studies included in the meta-analysis by Duley *et al* (6–7%) mean that considerable numbers of women need to be treated to prevent each adverse event. Seventy women would need to be treated to prevent 1 case of pre-eclampsia. Many women would not be prepared to take a "drug" while pregnant under these circumstances, even though these trials have confirmed the safety of antiplatelet agents, particularly as pre-eclampsia is usually mild. The risk of "baby death," however, may convince 250 women to take the medication to prevent a single death. Risk status is key when introducing prophylactic measures in pregnancy. Many clinical risk factors (eg, previous pre-eclampsia, multiple pregnancies, chronic hypertension, or diabetes) are associated with a higher prevalence of pre-eclampsia (approximately 20%). An abnormal uterine Doppler at 20 weeks gestation can indicate a similar risk, about 1 in 5, in both low and high risk women, and the treatment benefit may even be greater in this group.[1] The clinical value of agents such as aspirin increase considerably in higher risk women and the numbers needed to treat reduce considerably. Routine prescription of low dose aspirin can be justified in such women.

Controversy still exists over which population to target, what dose to prescribe, and the optimal gestation to treat. However, the benefit of antiplatelet agents has been shown across a wide range of all these variables. Low dose aspirin for the prevention of pre-eclampsia is safe and here to stay.

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1 Shennan AH. Recent developments in obstetrics. *BMJ* 2003;**327**:604–8.

Prophylactic use of antiplatelet agents (largely low dose aspirin) *v* control (placebo or no antiplatelet agent) in women at risk of developing pre-eclampsia*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Antiplatelet agents	Control		
Pre-eclampsia	43 (33 439)	6.3%	7.7%	19% (12 to 25)	69 (51 to 109)
Preterm birth (<37 wks)	28 (31 845)	16.1%	17.3%	7% (2 to 11)	83 (50 to 238)
Fetal and neonatal deaths	38 (34 010)	2.4%	2.8%	16% (4 to 26)	250 (125 to ∞)
Small for gestational age	32 (24 310)	7.6%	8.6%	8% (0 to 15)	100 (100 to ∞)

*Abbreviations defined in glossary; weighted event rates calculated from data in article using a fixed effects model.