

Aspirin for pre-eclampsia

Pre-eclampsia may lead to poor intrauterine growth, premature birth and maternal death. There have been many clinical trials of aspirin and other antiplatelet agents as prevention of pre-eclampsia but their findings have been contradictory.

The shortcomings of individual studies have been addressed by conducting a systematic review of good quality clinical trials (updated in 2007).¹ This review concluded that antiplatelet agents, mainly aspirin, offered moderate benefits as prevention of pre-eclampsia and its complications. However, this analytical approach could not identify which subgroups of women would benefit from treatment and which would not. The PARIS (Perinatal Antiplatelet Review of International Studies) Collaborative group has therefore carried out a more exhaustive meta-analysis using patient-level data from good quality trials² and provides the most definitive evidence to date on the use of aspirin and other antiplatelet agents in preventing pre-eclampsia.

What is pre-eclampsia?

Pre-eclampsia is hypertension associated with proteinuria; it occurs during the second half of pregnancy and affects 2 - 8 percent of pregnancies. Maternal complications include disorders of the liver and kidneys, convulsions (eclampsia) and abnormal clotting. The placenta may be damaged, restricting blood supply to the foetus; this causes complications including poor growth and premature delivery. Pre-eclampsia is asymptomatic until blood pressure increases above 170 mmHg systolic or 110 mmHg diastolic, when headache, epigastric pain or visual disturbances may occur.

Approximately 10 percent of women have raised blood pressure during pregnancy. It is not possible to predict who will go on to develop pre-eclampsia. The outcome in

developed countries is usually good but hypertensive disorders of pregnancy cause 10 - 15 percent of maternal deaths in the developing world. Infant mortality is also high.

What causes pre-eclampsia?

A layer of cells that ultimately forms part of the placenta (trophoblast) invades arteries in the uterus, restricting blood flow through them to the placenta. The resulting placental damage activates maternal platelets and the clotting system. These changes are associated with excessive production of thromboxane, a vasoconstrictor derived from platelets and a stimulant of platelet aggregation, and deficient production of prostacyclin, a vasodilator. This imbalance in the mechanisms that regulate clotting provides the rationale for treatment with antiplatelet agents such as aspirin.

The PARIS meta-analysis

The PARIS study included 31 randomised trials involving a total of 32,217 women and 32,819 infants in which an antiplatelet agent was evaluated in the prevention of pre-eclampsia. Ninety percent of the women had at least one risk factor for pre-eclampsia. Treatment began before the twentieth week of pregnancy in 59 percent of women; aspirin 50 - 150 mg/day was the sole treatment in 27 of these trials and was taken by 98 percent of the women.

The main results were:

- Antiplatelet agents were associated with a 10 percent reduction in the relative risk of both pre-eclampsia ($p < 0.004$) and preterm birth (before 34 weeks) ($p = 0.011$)

- There were similar reductions in risk of the baby being small for gestational age or stillbirth/death before discharge, but these were not statistically significant
- There was a 10 percent reduction in the relative risk of any serious adverse outcome (any of: maternal death, pre-eclampsia, preterm birth, small for gestational age or stillbirth/death before discharge) (p=0.001)

Other findings included:

- There was no difference between antiplatelet agents and placebo (or no treatment) in adverse effects such as postpartum or antepartum haemorrhage, or placental abruption
- The relative risks of birth before 28 or 37 weeks, or admission to a special care baby unit, were also reduced but the differences were not consistently statistically significant
- The benefit of treatment was potentially greater in women with a history of hypertension during pregnancy

There was no evidence that:

- antiplatelet agents were more or less effective in different subgroups of women
- aspirin doses greater than 75 mg/day were more effective than lower doses
- beginning treatment before the twentieth week of pregnancy was more beneficial than later treatment

Interpreting these findings

The benefit a mother would derive from treatment with an antiplatelet agent depends on her level of risk: women at higher risk would derive greater benefit. Overall, the PARIS study suggests that:

- 51 women would need to be treated to prevent a serious outcome in one pregnancy
- 114 women would need to be treated to prevent one case of pre-eclampsia
- 78 infants would need to be treated (via their mothers) to prevent one from needing assisted ventilation

A commentary published in the same issue of *The Lancet* concluded that:

- the use of aspirin to prevent pre-eclampsia is justified for women who are almost certainly going to develop it - examples include women who have developed pre-eclampsia in more than one pregnancy or with hypertension and pre-eclampsia in a previous pregnancy
- in women with the more usual risk of 20 percent of developing pre-eclampsia (e.g. due to chronic hypertension, multiple gestations, pre-pregnancy diabetes, pre-eclampsia in one previous pregnancy), the decision to use aspirin must be made in consultation with an informed mother

Summary

Meta-analysis of patient-level data from clinical trials of antiplatelet agents (almost exclusively aspirin) as prevention of pre-eclampsia shows that these agents moderately reduce the risk of pre-eclampsia and its complications with no apparent increase in the risk of haemorrhage.

It is not possible to identify which women will benefit from treatment. Aspirin is indicated for women at high risk of pre-eclampsia. For others, the decision to treat depends on the balance of risk and benefits for each individual and should be made in consultation with an informed mother.

References

1. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD004659. DOI: 10.1002/14651858.CD004659.pub2.
2. Askie LM, Duley L, Henderson-Smart D, Stewart LA on behalf of the PARIS Collaborative group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet published online May 17, 2007. doi:10.1016/S0140-6736(07)60712-0