

patients suffering from severe autoimmune diseases such as rheumatoid arthritis, systemic sclerosis, and multiple sclerosis. The initial results have been encouraging, with some patients going into clear remission.<sup>2,4</sup> Allogeneic transplants (where the recipient receives haemopoietic stem cells from another person) have a procedural mortality rate of up to 20%, but in some cases have resulted in a two year remission of the autoimmune disease. Autologous transplants (harvesting and reinfusing the patient's own cells) have a much safer procedural record, but patients tend to relapse faster.

As yet there is no definitive explanation for these observations. Some haematologists argue that peripheral blood stem cell transplantation simply allows more intensive immunosuppression than is conventionally used by rheumatologists, with the stem cell transplant being used as a rescue vehicle. Another theory is that the stem cell transplantation "stirs up" the immune system enough to re-educate the way it works, so that even putting back the patient's own cells is likely to work. Early relapse with autologous transplantation may be explained by assuming that residual colonies of T lymphocytes (thought to play an important part in autoimmune diseases) are either left behind, or reinfused back, and that these are in some way responsible for triggering self reactivity again.

But perhaps more interesting are the patients with autoimmune disease who relapse after allogeneic transplantation. In such cases the disease appears to recur despite the new immune system. It is as if the same "mistakes" are being learnt by the new system, mediated perhaps by as yet unidentified antigens.

The rationale for the use of peripheral blood stem cell transplantation in autoimmune disease is questionable, and it is certainly too early to call it a curative procedure. Many rheumatologists argue that even with intensive immunosuppression and bone marrow rescue, this approach is unlikely completely to cure diseases such as systemic sclerosis, which is also mediated by fibroblast dysfunction. It is also unlikely to benefit patients who already have severe joint destruction from rheumatoid arthritis, for example. Thus peripheral blood stem cell transplantation may be able to tackle some of the important mechanisms of autoimmune disease, but it certainly cannot deal with them all. Several longer term risks also render the decision to undergo a stem cell transplant more difficult. Total body irradiation and high dose

chemotherapy, for example, are associated with an increased risk of solid tumours and other haematological malignancies, and infertility in both men and women is also common.

At present the evidence for peripheral blood stem cell transplantation as a therapeutic option in autoimmune disease relies on a small number of transplantations performed at a few centres around the world. Since September 1996, when the first international meeting took place in Basel, work has started on producing consensus guidelines and European protocols for treating several autoimmune diseases, including systemic sclerosis and multiple sclerosis.<sup>3</sup> Most patients who are offered peripheral blood stem cell transplantation are those with highly progressive disease, where there is a significant threat to life but as yet no severe end organ damage and where there are few therapeutic options. For these people the high risks of the procedure must be weighed against the higher risk of dying from the disease itself. It is therefore highly unlikely that peripheral blood stem cell transplantation will ever become a routine treatment for people with stable rheumatoid arthritis, where adequate control is achieved with more moderate immunosuppressing drugs.

This year when the European group meet again in October, there may be enough collective experience to start a large prospective clinical trial. Over forty cases have already been registered in Europe since 1994. The chronicity of all autoimmune diseases, however, means that the true efficacy of this approach will take many years to assess.

Michael Potter *Senior lecturer in haematology*

Carol Black *Professor of rheumatology*

Royal Free Hospital, London NW3 2QG

Abi Berger *Science editor, BMJ*

- 1 Snowden JA, Brooks PM, Biggs JC. Haemopoietic stem cell transplantation for autoimmune diseases. *Br J Haematol* 1997;99:9-22.
- 2 Fassas A, Anagnostopoulos A, Kazis A, Kapinas A, Sakellari I, Kimiskidis V, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. *Bone Marrow Transplant* 1997;20:631-8.
- 3 Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in autoimmune disease: a consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1997;19:643-5.
- 4 Snowden JA, Milliken ST, Brooks PM, Biggs JC. Autografting in severe active rheumatoid arthritis—mobilisation and dose escalation studies. *Br J Haematol* 1988;101(suppl 1):70.

## Aspirin for preventing and treating pre-eclampsia

*Large trials continue to show no benefit*

Pre-eclampsia is a multisystem disorder usually associated with raised blood pressure and proteinuria. A relatively common complication of the second half of pregnancy, it affects 2-8% of pregnancies.<sup>1</sup> Although outcome is often good, pre-eclampsia remains a major cause of morbidity and mortality for both woman and child. For example, the woman may

develop renal or hepatic failure or disseminated intravascular coagulation or have a cerebrovascular haemorrhage. The baby may have intrauterine growth restriction, suffer the consequences of prematurity, or die in utero. The causes of pre-eclampsia remain obscure, but women with the condition produce excess thromboxane, and thus aspirin has long been tried for

both prevention and treatment. Early trials were promising, but more recent ones have shown little benefit.

Although the causes of pre-eclampsia are unknown, it is primarily a placental disorder.<sup>2</sup> During implantation, deficient trophoblast invasion of the maternal spiral arteries leads to underperfusion of the uteroplacental circulation and placental ischaemia. The resulting placental damage is thought to be responsible for the release of, as yet unknown, factors into the maternal circulation, which then alter endothelial cell function and cause widespread circulatory changes.<sup>2</sup> Women with pre-eclampsia have deficient intravascular production of prostacyclin, a vasodilator, and excessive production of thromboxane, a vasoconstrictor and platelet agonist. The potential antiplatelet effect of aspirin derives from inhibition of the platelet production of thromboxane. Early trials of low dose aspirin (60-150 mg/day) for preventing and treating pre-eclampsia were small but suggested a considerable reduction in the risk of pre-eclampsia. The hope was that there would be comparable reductions in more substantive outcomes, such as perinatal death and intrauterine growth restriction. Several large studies were initiated to test these hypotheses. Excitement quickly turned to disappointment as, one after another, these failed to confirm any clinically worthwhile benefits associated with aspirin.

Much data now exist on the effects of low dose aspirin in pre-eclampsia. A recent search of the register of trials maintained by the Cochrane pregnancy and childbirth group (as part of an ongoing systematic review, to be published in the Cochrane Library<sup>3</sup>) yielded over 100 citations referring to around 60 studies. The largest to date is the collaborative low dose aspirin study in pregnancy (CLASP).<sup>4</sup> Despite recruiting nearly 10 000 women, this study failed to detect any significant differences in the incidence of proteinuric pre-eclampsia, intrauterine growth restriction, or perinatal death. In March this year three more trials were published, providing data on a further 12 000 women and bringing the total number of participants to around 30 000.

Two of the new studies were conducted in the Caribbean and recruited relatively low risk women.<sup>5,6</sup> The third was conducted in the United States and recruited women at higher risk (with insulin dependent diabetes, chronic hypertension, multiple pregnancy, or pre-eclampsia in a previous pregnancy).<sup>7</sup> BLASP, the Barbados trial,<sup>5</sup> used a new 75 g slow release aspirin; the others used standard 60 g aspirin.<sup>6,7</sup> Overall, aspirin was associated with a 10% reduction in the incidence of pre-eclampsia but this was not reflected in more substantive benefit, such as a reduction in perinatal death.<sup>7</sup> Aspirin does seem to be reasonably safe, however. Early fears that it might be associated with an increased risk of bleeding have not been confirmed, and we now know more about the short term safety of aspirin than about most other drugs used during pregnancy. Further reassurance comes from follow up by postal questionnaire, at the age of 12-18 months, of 8500 of the infants in CLASP. This failed to detect any differences between the two groups.<sup>8</sup>

CLASP showed a trend towards a greater reduction in pre-eclampsia the more preterm the delivery.<sup>5</sup> Additional post hoc analyses also suggested a trend towards

a more protective effect of aspirin the earlier the gestational age at trial entry.<sup>9</sup> These data perpetuated the hope that starting aspirin at 12-20 weeks might have benefits for the small, but important, subgroup of women at high risk of severe early onset disease. This has not been confirmed in the later studies, however.<sup>5-7</sup>

Why did the small trials have such different results from the larger trials? Those who still believe in aspirin argue that the pragmatic approach of the large trials led us all astray as the effects were diluted by too many low risk women and that the high risk women in the small trials really did benefit<sup>10</sup>; this interpretation is not, however, supported by separate analyses of high risk groups within the large trials.<sup>11</sup> Others argue that 60 mg was too low a dose and that 150 mg aspirin might still be beneficial.<sup>12</sup> Another possibility is publication bias. The early positive trials were promptly published in high profile journals. Unpublished studies have long been known about, and these might have had results that differed from those of the trials that were published.<sup>4, 13</sup>

Nevertheless, there is now a consensus that, although low dose aspirin appears to be safe, for most women it is not effective at preventing or treating pre-eclampsia and its complications.<sup>5-7,9</sup> A few issues continue to provoke controversy. Anecdotally, aspirin continues to be used for women at risk of early onset pre-eclampsia.<sup>12</sup> Although it seems unlikely that this confers any benefit, at least we can reassure these women that it is probably doing no harm.

Lelia Duley *Obstetric epidemiologist*

Magpie Trial Coordinating Centre, Institute of Health Sciences, Oxford OX3 7LF

Competing interest: I was on the steering group for BLASP and am one of the authors of the report. I am also one of the reviewers for the ongoing systematic review.

- 1 World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. *Am J Obstet Gynecol* 1988;158:80-3.
- 2 Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993;341:1447-51.
- 3 Knight M, Duley L, Henderson-Smart D, King J. The effectiveness and safety of antiplatelet agents for the prevention and treatment of pre-eclampsia (Cochrane protocol). In: Cochrane Collaboration. *Cochrane Library*, Issue 3. Oxford: Update Software, 1998.
- 4 CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 women. *Lancet* 1992;343:619-29.
- 5 Rotchell YE, Cruickshank JK, Gay MP, Griffiths J, Stewart A, Farrell B, et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol* 1998;105:286-92.
- 6 Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. *Br J Obstet Gynaecol* 1998;105:293-9.
- 7 Cartis S, Sibai B, Hauth J, Lindheimer M, Klebanoff M, Thom E, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. *N Engl J Med* 1998;338:701-5.
- 8 CLASP Collaborative Group. Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. *Br J Obstet Gynaecol* 1995;102:861-8.
- 9 Pipkin FB, Crowther C, de Swiet M, Duley L, Judd A, Lilford RJ, et al. Where next for prophylaxis against pre-eclampsia? *Br J Obstet Gynaecol* 1996;103:603-7.
- 10 Grant JM. Multicentre trials in obstetrics and gynaecology. Smaller explanatory trials are required. *Br J Obstet Gynaecol* 1996;103:599-602.
- 11 Kyle PM, Buckley D, Kissane RN, de Swiet M, Redman CWG. The angiotensin sensitivity test and low-dose aspirin are ineffective methods to predict and prevent hypertensive disorders in nulliparous pregnancy. *Am J Obstet Gynaecol* 1995;173:865-72.
- 12 Bower H. Studies reject aspirin for prevention of pre-eclampsia. *BMJ* 1998;316:885.
- 13 Collins R. Antiplatelet agents for IUGR and pre-eclampsia. In: Chalmers I, ed. *Oxford database of perinatal trials*. Oxford: OUP, 1990. Version 1.2, disk issue 4.