PREVENTION OF PREECLAMPSIA

Gustaaf A. Dekker MD PhD.
Chef-de-Clinique Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Free University Hospital, De Boolelaan 1117, 1081 HV, Amsterdam, The Netherlands, Extended Abstract 4th Perinatology Congress, Istanbul, 26th-30th April, 1994

Preeclampsia-eclampsia is the largest single cause of perinatal mortality and maternal death in most developed and developing countries. The ultimate goal in the management of preeclampsia is to be able to detect the disease in the early stages and have an available therapy that either cures it or at least ameliorates its progression in an attempt to achieve fetal maturity. The term "prevention" not only points at averting the occurrence of disease (primary prevention), but also at breaking off the disease process before the emergence of clinically recognizable disease (secondary prevention), and at prevention of complications caused by the disease process (tertiary prevention). This presentation concerns secondary prevention of preeaclampsia.

Whether the endothelial cell injury in preeclampsia causes primarily a decrease in prostacyclin synthesis or a decrease in for example EDRF platelets play a central role in the disease process. Redman stated "preeclampsia is a trophoblast-dependent process mediated by platelet dysfunction and prevented at least in part by antiplatelet agents". On the virtually non-endothelialized surface of the spiral arteries in the absence of an adequate production of antiaggregatory prostacyclin and/or EDRF by the uteroplacental vasculature and/or endovascular trophoblast, surface mediated platelet activation may be expected to occur. Platelets will adhere and release alpha- and dense granule constituents. Thromboxane A2 and serotonin will be generated, contributing to platelet aggregation and inducing the formation of fibrin to stabilize the platelet thrombus that may occlude maternal blood flow to a placental cotyledon, thus leading to placental infarction. Based on the hypothesis that preeclampsia is at least partially caused by an increase in platelet-derived thromboxane-A2, several investigators have attempted to correct this pathology by pharmacologic manipulation with low-dose Aspirin.

Acetylsalicylic acid (Aspirin) as an antiplatelet agent: Aspirin prolongs the bleeding time through its inhibition of platelet cyclo-oxygenase activity and the resultant platelet secretory reaction. Aspirin acetylates the alanine residue at the active site of the cyclo-oxygenase enzyme. Because the acetyl group of Aspirin is covalently bound to the active size of cyclo-oxygenase, the inhibition of the enzyme is irreversible. Platelets lack nuclei and are unable to resynthesize cyclo-oxygenase. Therefore, following Aspirin administration, thromboxane A2 synthesis in platelets remains impaired for the duration of their lifespan. The optimal antithrombotic dose of Aspirin remains disputed. Doses as high as 3.5 g/day and as low as 20-40 mg/day have been reported to be effective in preventing thrombotic events. In the case of Aspirin, it is of particular importance to use the lowest effective dose, because of its concomitant effect on vessel-wall cyclo-oxygenase. Aspirin inhibits endothelial cyclo-oxygenase, but the vessel wall may be less sensitive and has the capacity to synthesize new cyclo-oxygenase when Aspirin is removed from the system. Another major mechanisms involved in the causation of the "paradoxical" selectivity of low-dose Aspirin on platelet cyclo-oxygenase is based on the pharmacokinetic characteristics of this drug. Platelets passing though the gut capillaries, while an oral dose of Aspirin is undergoing presystemic hydrolysis, are exposed to significantly higher concentrations of Aspirin than platelets in the peripheral circulation. Absorption of a low oral dose of Aspirin causes relatively high concentrations in the portal circulation leading to a cumulative inhibition of cyclo-oxygenase in platelets passing through the gut capillaries, whereas the concentration in the peripheral circulation (after deacetylation of Aspirin in the liver) remains too low to affect endothelial cyclo-oxygenase.

Safety aspects: The current literature suggests that the use of low-dose Aspirin during pregnancy is safe with regard to congenital anomalies and fetal, neonatal, and maternal cardiovascular physiology and hemostasis. Secondary prevention of preeclampsia with low-dose Aspirin:

Up to the 8th World Congress for the Study on Hypertension in Pregnancy in November '92 in Buenos Aires the results of low-dose Aspirin in randomized trials, all concerning small groups of selected high-risk patients, demonstrated, 30 % reduction in the incidence of gestational hypertension, 85 % reduction in the incidence of preeclampsia, and a significant reduction in the incidence of adverse perinatal outcome in the Aspirin treated group as compared to the placebo-group. The results of the more recent Italian Aspirin study, the N.I.H study, the Birmingham study and the results of the CLASP study will be discussed in some detail during the congress.

The results of the N.I.H study, reported by Sibai et al in January '93 at the Society of perinatal Obstetricians in San Francisco, and the results of the CLASP study reported by Chris Redman at the IXth ISSHP World Congress in March of this year suggest that low-dose Aspirin should not be adopten in routine prenatal care. Over all the effect of

low-dose Aspirin appears to be modest. The major benifit of low-dose Aspirin appears to be delaying the onset of severe preeclampsia. However, because perinatal mortality or serious morbidity is mainly associated with early-onset preeclampsia, this effect of low-dose Aspirin makes the use of this safe antiplatelet durg worthwhile in high-risk patients. Based on the available literature and an 8 year personal experience with low-dose Aspirin I advocate the use of low-dose Aspirin only in women considered at high-risk of developing preeclampsia and/or fetal growth retardation. Because of the reported high recurrence rates of preeclampsia, we recommend use of low-dose Aspirin in all patients with severe early-onset preeclampsia in the previous pregnancy. Other indications for the use of low-dose Aspirin will be discussed during the congress. The optimal time to initiate low-dose Aspirin is 10-14 weeks amenorrhea.

Low-dose Aspirin has been demonstrated not to influence the clinical course and perinatal outcome of women with mild pregnancy-induced hypertensive disorders (tertiary prevention). Low-dose Aspirin is not curative, but is essentially a preventive treatment which, in order to be effective, should be started weeks before clinical signs of preeclampsia are present.