

# Low-molecular-weight heparin to prevent pre-eclampsia: there is no evidence and potential harm

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Pre-eclampsia is a serious complication of pregnancy that threatens both the mother and her foetus. Pre-eclampsia is characterised by early and late vascular dysfunction with many known and unknown factors interacting that ultimately lead to the classical clinical syndrome which lies in a spectrum that ranges from gestational hypertension toward HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome.<sup>1</sup>

At least two aspects make pre-eclampsia a disease of interest for both obstetricians and internists focused on vascular medicine. First, many case-control studies have shown an association between the occurrence of pre-eclampsia and inherited thrombophilia, although in a meta-analysis this could only be demonstrated for severe, early-onset pre-eclampsia.<sup>2</sup> Second, gestational hypertensive complications, such as other vascular diseases, have a tendency to recur. For instance, in a large series of Dutch women with HELLP syndrome, the recurrence rate in the subsequent pregnancy was as high as 29%.<sup>3</sup> Third, aspirin has been found to have a small beneficial effect on the prevention of pre-eclampsia, as well as preterm delivery and infant death, with statistically significant risk reductions of 15%, 8% and 14% respectively.<sup>4</sup> It is attractive to hypothesise that anticoagulant treatment with (low-molecular-weight) heparin may have a beneficial effect on pregnancy outcome in women with a history of pre-eclampsia and a known thrombophilic defect. This has been demonstrated for women with recurrent foetal losses and antiphospholipid antibody syndrome in one of the rare randomised controlled trials that have been performed in this field.<sup>5</sup> However, an adequate trial has not been completed in women with hereditary thrombophilia and obstetric complications such as pre-eclampsia.<sup>6</sup> Only

uncontrolled series have been published in which low-molecular-weight heparin suggested an improved outcome of subsequent pregnancies in women with a history of various obstetric complications.<sup>7,8</sup> In these series, outcome was compared with the patients' previous pregnancies, which by definition was poor, as this was a selection criterion for inclusion.

Why should we not implement anticoagulant treatment to prevent (recurrent) pre-eclampsia in women with hereditary thrombophilia? No pharmacological therapy, especially in pregnant patients, should be applied without solid evidence from appropriate clinical studies. Although the use of aspirin and/or low-molecular-weight heparin is considered safe and is being applied for prophylaxis of thromboembolic complications during pregnancy,<sup>9,10</sup> there is a significant burden of low-molecular-weight heparin treatment induced by the daily subcutaneous injections, as well as a high incidence of skin reactions, in particular in higher doses.<sup>11</sup> In this issue of the Netherlands Journal of Medicine, Kalk and colleagues present a retrospective analysis of 58 women with a history of pre-eclampsia out of a large cohort of women who were tested for thrombophilia. They observed a risk reduction of 45% in women who were treated with both aspirin and low-molecular-weight heparin, which did not reach statistical significance. However, as the authors discuss, this study has serious limitations. These concern issues of patient selection, the small number of observations, inadequate follow-up of the original cohort of tested women, the fact that the allocation of interventions was not randomised, and the potential of inferior quality of data recording due to the retrospective character of the study.

What this study does demonstrate is the urgent need for

results from adequate, placebo-controlled trials in women with hereditary thrombophilia and pre-eclampsia, as well as other clearly defined obstetric histories.<sup>12</sup> In the meantime we should not implement therapies for which we have no evidence, or in other words, *in dubio, abstinae*.

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On the occasion of the 'Internistendagen' in Maastricht (22 and 23 April), the editors of

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will award three prizes: one for the best *original article*, one for the best *review* and one for the best *case report* published in the Journal in 2003.

For their prize, the winners may choose an original graphic print from the series published on the covers of last year's issues of the Journal. These covers are on exhibit at the booth of the Netherlands Journal of Medicine in the exposition area of the Internistendagen. So visit our booth!

The editors of the Netherlands Journal of Medicine will be giving two practical workshops at the Internistendagen on 'How to write a biomedical paper'. We look forward seeing you there!

**The editors**

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