Commentary: On the clinical prediction of pre-eclampsia and its enigmatic aetiology

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Even if pre-eclampsia has been considered a nosological entity way back in the history of medicine, its main diagnostic criteria, proteinuria and hypertension, were ascertained only during the last two centuries, proteinuria around 1840 and hypertension in the first decades of the 20th century. However, its aetiology and pathogenesis still represent enigmas and challenges to everyone engaged in perinatal health problems. Issues needing clarification comprise the clinical prediction of pre-eclampsia and its long-term consequences. The increasing evidence suggesting that women experiencing pre-eclampsia are at increased risk of cardiovascular disease and even kidney disorder later in life may represent an aetiological clue. Likewise, increased risk of pre-eclampsia is well-established for women with chronic hypertension, diabetes mellitus and obesity. These associations, together with patterns in pre-eclampsia and severe pre-eclampsia observed in biomarkers such as angiogenic (placental growth factor) and anti-angiogenic (sFlt-1) proteins have prompted studies aimed at clinical prediction but with conflicting results. Even the nosological entity has been questioned. Thus, most studies are now performed on severe/early and mild/late pre-eclampsia as two different conditions.

In this issue, Catov et al. have used the Danish National Birth Cohort to quantify the increased burden of disease in terms of pre-eclampsia and severe pre-eclampsia observed in nulliparous women with hypertension, diabetes mellitus, obesity and multiple gestation. In multiparous women, the effects of previous pre-eclampsia were included as well.

The effects of these conditions in nulliparous women, on the occurrence of pre-eclampsia ranged between a relative risk of 1.6 for overweight to a relative risk of 3.4 for definite chronic hypertension. In multiparous women, the relative risk for previous pre-eclampsia of 15.9 dominated. These associations support previously established hypotheses involving aetiological relations between the conditions and pre-eclampsia. However, fairly wide confidence intervals precluded further assessment as to whether early and late pre-eclampsia are aetiologically different conditions.

Attributable risks are of particular interest from a preventive point of view, indicating how large a fraction of the total incidence rate could have been prevented if an aetiological factor had been eliminated. In this study, it appeared that in nulliparous women, approximately 30% of the cases were attributable to the conditions included while in multiparous women, the fraction was higher, 50%, due to the high recurrence risk. This means that if a causal path exists between these conditions and pre-eclampsia, 30–50% of the cases would have been prevented if these conditions had been eliminated in the population.

Here, the aetiological mechanism involved is essential. For example if blood pressure, blood glucose or obesity per se are elements in a causal path, adequate individual control of these conditions would seem beneficial, representing effective preventive strategies. If, on the other hand, both the conditions analysed and pre-eclampsia were caused by a third factor of genetic or more permanent environmental origin, the benefits of individual control of the conditions would be limited.

From a preventive point of view, overweight would seem to represent the most promising factor. As the authors point out, one might speculate whether pre-pregnancy weight loss would be beneficial. Conversely, one would expect to see an increased rate of pre-eclampsia as the prevalence of obesity increases. Although the epidemic of overweight has also reached Norway, the rate of pre-eclampsia has remained fairly stable during the last 6 years. The occurrence of birth weights >4500 g, which also is thought to be associated with obesity, increased dramatically in the 1990s from 3.1 to 4.9%, but peaked in the year 2000, leaving us with conflicting secular trends. These findings raise the possibility that obesity is partly genetically determined and this genetic factor is related to pre-eclampsia as well.

Similarly, in diabetes and chronic hypertension, adequate clinical control of these conditions will not necessarily contribute to lowering of the risk of pre-eclampsia. Either the pathogenetic mechanism is related to a genetic factor or the high recurrence risk may be due to pathological processes, initiated in a previous pregnancy.

The associations discussed above have bearings on prediction and prevention. However, they have also implications for the long-term prognosis of the woman after pre-eclampsia, which may be affected by the same main pathogenetic mechanisms. The high long-term risk of cardiovascular disease and kidney disease observed after pre-eclampsia may either be related to a permanent (possibly genetic) background or (and) pathological processes perhaps initiated by the conditions and possibly aggravated by the pre-eclamptic event.

The study represents an interesting output of the Danish birth cohort project. However, the number of variables involved...
is rather low. If data on body mass index were available in the Nordic medical birth registries, similar studies based on far larger numbers would have been feasible, clarifying important interactions impossible to address in the present set of data.

References