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Correspondence

QJM

Factor V Leiden, pregnancy complications and adverse outcomes

Sir,

In their recent paper, Nurk *et al*. nicely demonstrated an association between maternal factor V Leiden (FVL) mutation and pregnancy complications.[1] In addition, maternal smoking and the methylenetetrahydrofolate reductase (MTHFR) 677CT/TT genotype further increased the risk of stillbirth in mothers with FVL mutation. In another recent study,[2] Coulam *et al*. compared the prevalences of ten thrombophilic gene mutations (including FVL, MTHFR C677T, MTHFR A1298C and factor II G20210A) in 150 women with a history of recurrent miscarriage vs. a control group of fertile women with no history of miscarriage. The prevalence of homozygous mutations and total gene mutations, rather than the frequency of specific gene mutations, was significantly higher in the recurrent miscarriage group. These results suggest that complex interactions between a number of fairly common thrombophilic gene mutations are contributing to the multifactorial aetiology of placental insufficiency. As the factor II G20210A mutation is common, with a prevalence of approximately 1.7% in Northern Europe,[3] and has also been implicated as a contributory factor in obstetric complications,[4] it would be interesting to know why Nurk *et al*. chose not to examine the possible association of factor II G20210A mutation with pregnancy complications in their large retrospective cohort and, in particular, its possible interactions with some of the other measured risk factors such as MTHFR polymorphisms and cigarette smoking.

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Response

Sir,

We appreciate the letter from Dr Murphy, and read with interest the paper of Coulam *et al*.[1] In the latter study, the prevalences of ten thrombophilic gene mutations in 150 women with a history of recurrent miscarriage were compared to those in a control group of fertile women without a history of miscarriage. They found that when the total number of mutations was compared, counting a heterozygous mutation as one gene mutation and a homozygous mutation as two mutations, women experiencing recurrent pregnancy loss demonstrated significantly more total mutations than control women (68% versus 21%, $p = 0.02$), and the authors suggested that complex interactions between a number of fairly common thrombophilic gene mutations were contributing to the multifactorial etiology of placental insufficiency.

We have now performed a similar analysis, comparing the total number of mutations based on three polymorphisms (factor V Leiden, and methylenetetrahydrofolate reductase 677C → T and 1298A → C) in pregnancies with or without adverse outcomes. When all pregnancy complications and adverse outcomes were combined, the prevalence of pregnancies with three or more maternal mutations was 3.2% (84/2633) vs. 2.9% (330/11 362) in the group without pregnancy complications and adverse outcomes ($p = 0.45$). When evaluated separately, none of the observed pregnancy complications and adverse outcomes—pre-eclampsia (at any time during or before 37 weeks of pregnancy), placental abruption, premature delivery (<37 weeks), low birth weight (<2500 g), intrauterine growth restriction (<10th percentile for gestational age) and stillbirth—had significantly higher prevalence of having three or more maternal mutations than did pregnancies free of pathological outcome. The inconsistency between our findings and the results reported by Coulam *et al*.[1] may be explained by the smaller number of polymorphisms included in our study, and also by the different population sizes and outcomes studied.

The blood samples of >18 000 participants in the Hordaland Homocysteine Study[2] were collected from 1992 to 1993, and genotyping took place in the mid-1990s. We started with the three mentioned polymorphisms. Later on, we have identified other polymorphisms in various subsets of the cohort, but none of these is associated with thrombophilia. We have no current plans to study the factor II G20210A polymorphism.

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