COMMENT

Aetiology of pre-eclampsia and thrombophilic genetic mutations

ABSTRACT

Schlembach and co-workers in this issue of Clinical Science have studied the association of maternal and/or fetal factor V Leiden (FVL) and prothrombin G20210A gene mutation with HELLP syndrome and intrauterine growth restriction (IUGR) to confirm whether these genetic mutations are important risk factors for the pathogenesis of the HELLP syndrome, leading to an inadequate maternal–fetal circulation. Results showed that fetal FVL and prothrombin G20210A gene mutation were significantly associated with IUGR. The authors speculated that fetal thrombophilic mutations resulted in placental microthrombosis, leading to a disturbed fetoplacental blood flow. This study represents another important step in our understanding of the pathophysiological action of fetal thrombophilic mutations on fetal development. Regarding the aetiology of pre-eclampsia, one possible speculation is that systemic immune maladaptation, including systemic cytokine imbalance, contributes to placental ischaemia and systemic vessel abnormalities leading to pre-eclampsia.

Several studies have shown that inherited and acquired thrombophilias are associated with adverse pregnancy outcome, including thromboembolism [1] and severe pre-eclampsia [2] as maternal conditions; placental infarction and abruptio placenta [3] as placental conditions; and severe intrauterine growth restriction (IUGR) [3], neonatal stroke, cerebral palsy and thromboembolism as fetal consequences. Venous and possibly arterial diseases have resulted from many polymorphisms in various prothrombotic genes, including G1691A in factor V (factor V Leiden (FVL)), prothrombin G20210A, methylene-tetrahydrofolate reductase (MTHFR) C677T, plasminogen activator inhibitor-1 4G/5G and the platelet collagen receptor α2β1 C807T.

The aetiology and pathogenesis of hypertensive disorders of pregnancy, including pre-eclampsia, gestational hypertension and HELLP syndrome, remain unknown, but it is thought that genetic predisposition and immune maladaptation contribute to placental ischaemia and consequent abnormalities of the maternal vascular endothelium [4]. Activation of the coagulation systems is an important feature of these conditions [5]. Livingston et al. [6] investigated 110 women with severe pre-eclampsia and 97 controls and showed that maternal and/or fetal inherited thrombophilias, including FVL, MTHFR CC677TT and prothrombin G20210A gene mutation, were not associated with severe pre-eclampsia, HELLP syndrome or pre-eclampsia associated with IUGR. Morrison et al. [7] investigated five prothrombotic mutations described above in a case-control study of 404 women with pre-eclampsia, 303 with gestational hypertension and 164 unaffected controls, and showed that there were no significant differences in gene frequencies seen when any of the three groups were compared. Their study [7] did not support an association between any of these five polymorphisms and either pre-eclampsia or gestational hypertension, implying that it would not be useful or appropriate to attempt to predict the development of pre-eclampsia or gestational hypertension in pregnant women with these polymorphisms [7].

Regarding immune responses, a previous study [8] showed that peripheral blood leucocytes (PBL) were activated in pre-eclampsia in terms of basal changes in intracellular free Ca\(^{2+}\) and that monocytes in peripheral blood were primed to give greater responses after stimulation with \(n\)-formylmethionyl-leucyl-phenylalanine in pre-eclampsia. Another study [9] demonstrated that normal third trimester pregnancy had a remarkable activation of PBL, which was increased further in pre-eclampsia, due to increased levels of the surface markers CD11b, CD14 and CD64. Furthermore, endothelial

Key words: factor V Leiden, G20210A prothrombin mutation, HELLP syndrome, PCR, pregnancy complication, thrombophilic mutation.
cells co-cultured with syncytiotrophoblast microvillous membranes (STBM) released factors that can activate PBL in vitro in pre-eclampsia; these showed a possible mechanism for activation of PBL in pre-eclampsia as being secondary to endothelial cell activation caused by circulating STBM shed in excess amounts from the placenta [10]. Redman et al. [11] concluded that there was no specific cause for pre-eclampsia, which could be better considered as the extreme end of the range of maternal adaptation to pregnancy. Therefore Redman et al. [11] predicted that a single pre-eclampsia gene would not be found, nor would either a single specific predictive test or single preventive effective measure be devised. These studies reported that leucocytes and monocytes in peripheral blood are activated in pre-eclampsia. Activated monocytes in pre-eclampsia produce various cytokines, including macrophage colony-stimulating factor (M-CSF). We have demonstrated a significant increase in serum M-CSF levels in pre-eclampsia [12] and in normotensive pregnancies complicated by IUGR [13]. We have also shown a significant increase in M-CSF levels in the placenta relative to placental total protein levels in pre-eclampsia [14], and a similar phenomenon occurring in relation to granulocyte-macrophage colony-stimulating factor (GM-CSF). (M. Hayashi, Y. Hamada and T. Ohkura, unpublished results). Furthermore, we have confirmed a significant increase in blood M-CSF levels in women at 18 weeks of gestation who later developed pre-eclampsia [15]. Previous studies have shown an increased serum activity of interleukin-2 in pre-eclampsia [16], an elevation of plasma interleukin-12 in pre-eclampsia [17], and an elevation of serum interleukin-2 and tumour necrosis factor-α [18] before the clinical manifestations of pre-eclampsia. Based on these findings, one possible speculation is that immune maladaptation, including systemic endothelial cell activation, leucocyte and monocyte activation, leucocyte- and monocyte-derived cytokine secretion and cytokine imbalance in both the peripheral blood and the placenta, contributes to placent al ischaemia and systemic vessel abnormalities, leading to pre-eclampsia.

FVL arises from a point mutation R506Q at the cleavage site of factor V, leading to activated protein C (APC) resistance; its mean prevalence in Caucasian population is 4–5 % [19]. Acquired APC resistance without FVL is a common finding in patients with lupus anticoagulant or the antiphospholipid syndrome [20,21]. Prothrombin G20210A gene mutation causes high prothrombin formation and results in an elevated risk for thrombosis; its prevalence in the general population is 1 % [22]. FVL is independent of other known risk factors of thrombosis; in particular, it is independent of prothrombin G20210A gene mutation and the relative risk of venous thromboembolism among women with prothrombin G20210A gene mutation is at least as high as that among those with FVL [23]. Women having both FVL and prothrombin G20210A gene mutation show a disproportionately higher risk than with either defect alone.

Livingston et al. [6] reported that the three prothrombotic mutations did not predispose a patient to developing severe pre-eclampsia, HELLP syndrome or pre-eclampsia associated with IUGR. This finding is not consistent with the study by Schlembach and co-workers [24] in this issue of Clinical Science. This discrepancy may be explained, in part, by the genetic heterogeneity in the United States, as described by the authors of both papers. Morrison et al. [7] suggested that the five prothrombotic mutations were not predisposing to pre-eclampsia and gestational hypertension. Thus Schlembach and co-workers [24] might clarify the association of maternal and/or fetal FVL and prothrombin G20210A gene mutation with HELLP syndrome and IUGR, but not with pre-eclampsia and gestational hypertension. The study by Schlembach and co-workers [24] is based on a good concept that maternal and/or fetal prothrombotic mutations may be associated with HELLP syndrome and IUGR. The authors [24] described that the haemodynamic balance between maternal and fetal circulation was an important component of normal fetal development and pregnancy; a thrombophilic mutation in the fetus might disturb that balance, thereby contributing to the pathogenesis of these disorders. However, there was no information about the prevalence of these mutations in children born to mothers with HELLP syndrome. They demonstrated a strong association of fetal thrombophilic mutations with IUGR, indicating a fetal contribution to IUGR, and speculated that a fetal thrombophilic mutation might lead to placental microthrombosis, resulting in a disturbed fetoplacental blood flow.

In conclusion, fetal FVL and prothrombin G20210A gene mutation may contribute to intrauterine fetal growth restriction. The study by Schlembach and co-workers [24] represents another important step in our understanding of the pathophysiological action of fetal thrombophilic mutations on placental abnormalities and fetal development, although maternal and/or fetal thrombophilic genetic mutations may not be the cause of pre-eclampsia. One possible consideration is that systemic immune maladaptation, including endothelial cell activation, leucocyte and monocyte activation and cytokine imbalance in both the peripheral blood and the placenta, contributes to placent al ischaemia and systemic vessel abnormalities and leads to pre-eclampsia.

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(ON BEHALF OF THE EDITORIAL BOARD)
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Received 16 May 2003; accepted 2 June 2003
Published as Immediate Publication 2 June 2003, DOI 10.1042/CS20030181