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Iron, pre-eclampsia and hypoxia-inducible factor

Sir,

We read with interest the study by Ziaei *et al.*[1] in which they reported a higher incidence of pregnancy-related

hypertension disorder in nonanaemic women taking iron supplements. The authors speculated that this might have arisen from changes in blood viscosity causing impairment of uteroplacental blood flow. The purpose of this letter is to suggest an alternative potential explanation of their findings.

Pre-eclampsia is associated with a substantial elevation in serum indices of iron status.[2] This has been ascribed to increased haem catabolism resulting from mild continuing haemolysis. The increases in serum iron and ferritin are striking and may even have the potential to be used diagnostically to warn of incipient pre-eclampsia.[2] It is not known whether the rise in serum iron precedes or contributes to the clinical manifestations of pre-eclampsia, or is solely a result of the disease. There is some evidence to suggest that, through effects on formation of oxygen free radicals and subsequent lipid peroxidation, iron might be a significant aetiologic factor in the endothelial cell damage of pre-eclampsia.[2] Exogenous iron supplementation could exacerbate any such causal influence of iron, and for this reason it has been advised that, in the absence of iron deficiency, pregnant women at high risk for pre-eclampsia should not take iron supplements.[2]

We wish to propose that a further possible link between iron status and pre-eclampsia arises from the role that iron plays in the hypoxia-inducible factor (HIF) transcriptional activation pathway. It is now well established that HIF coordinates cellular responses to hypoxia by directly or indirectly regulating the expression of several hundred genes. HIF itself is synthesised continuously and is primarily regulated through its oxygen-dependent degradation. This degradation process is initiated by specific iron-dependent dioxygenase enzymes, and degradation of HIF is potentiated by supraphysiological iron supplementation in cell culture.[3] In theory, iron supplementation might similarly enhance HIF degradation in humans and thereby inhibit HIF-dependent processes. The uterine surface experiences low oxygen levels during early pregnancy, and HIF-mediated hypoxic gene regulation is essential for normal placental development.[4] Furthermore, it has been suggested that dysregulation of HIF-dependent placental angiogenesis underlies pre-eclampsia and that HIF activation protects against its pathogenesis.[5] In mice, knocking out functional HIF genes results in defective placental development,[4] and increasing iron availability may subtly phenocopy this effect. Thus, iron supplementation could conceivably promote the development of pre-eclampsia by potentiating HIF degradation and thereby preventing normal placental development. Should this be the case, it would provide an alternative explanation for the findings reported by Ziaei *et al.* and more generally would broaden their implications for understanding the pathophysiology of pre-eclampsia.

Supplementary material

The following supplementary material is available for this article:

Appendix S1. Full reference list.

These materials are available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1471-0528.2007.01490.x

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