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EDITORIAL COMMENT

Preeclampsia: A fascinating syndrome due not only to oxidative stress☆

Pré-eclâmpsia: uma síndroma fascinante com *stress* oxidativo, mas não só

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Preeclampsia (PE) is a clinical syndrome specific to pregnancy, diagnosed in the presence of hypertension (blood pressure ≥140/90 mmHg) and proteinuria (>300 mg/24 h) after the 20th week of pregnancy or, exceptionally, immediately after childbirth. It occurs in 4-8% of pregnancies and is the leading cause of perinatal morbidity and mortality. PE is a systemic disease with a marked inflammatory and antiangiogenic component and increased autoantibody production.[1–3] Reduced blood flow to the placenta is central to PE. If there is no placenta (or placental remains) there can be no PE, but PE can occur without a fetus, as in hydatidiform mole. It is generally accepted[4] that placental ischemia is the main finding in PE and results from alterations in the physiological process of extravillous trophoblast invasion of the uterine wall associated with immunological imbalance between proinflammatory and regulatory CD4 T cells. Among other disturbances, this imbalance triggers a chronic inflammatory process characterized by the release of proinflammatory cytokines and autoantibodies, as well as the development of oxidative stress and endothelial dysfunction. The proinflammatory and antiangiogenic process perpetuates placental ischemia, leading to the formation and release of syncytial material and free oxygen radicals. In the absence of adequate tissue antioxidant capacity, the latter exacerbate the proinflammatory cycle and tissue damage, as well as causing inappropriate leukocyte activation, platelet aggregation and vasoconstriction, leading to systemic injury to various maternal tissues. Some authors[5] have shown that from the 16th week of pregnancy women with PE present elevated malondialdehyde and glutathione peroxidase levels, reduced superoxide dismutase, and lower placental expression of glutathione and glutathione peroxidase, indicating increased oxidative stress. Although oxidative stress always appears to be involved in the deterioration of homeostatic mechanisms, endothelial dysfunction and production of placental antiangiogenic factors such as sFlt1[6] seen in PE, as well as in its pathophysiology, there is still uncertainty as to whether it is a cause, an epiphenomenon or a consequence of the disease. If a cause, free oxygen radicals could well be responsible and are therefore a potential therapeutic target for interventions to neutralize them.

It is against this background that an interesting paper by Menezes de Oliveira et al. is published in this issue of the *Journal*.[7] The authors start from the premise that oxidative stress has a crucial role in the etiopathogenesis of PE and that a diet deficient in antioxidant nutrients is a factor in susceptibility to and exacerbation of the disease that can be corrected. Setting out to determine whether increasing dietary intake of these nutrients could have a protective effect by neutralizing excess free oxygen radicals, they analyzed the consumption of antioxidant nutrients and

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coefficients of variation in 90 women with and 90 women without PE, using two food recalls, nutrients and calories being adjusted using the estimated average requirement, and a validated food frequency questionnaire to assess antioxidant intakes.

Overall, women both with and without PE had inadequate intakes of the antioxidants vitamins A and E, selenium, zinc and copper and high intakes of milk, tomatoes and eggs; vitamin A intake was even lower in those with PE. The study concludes that intake of antioxidant nutrients in women with PE is inadequate and that there is considerable daily variation in consumption.

However, the fact is that oxidative stress is only one of several etiopathological mechanisms put forward for PE. The fact that biomarkers of oxidative stress are found in PE, in the placenta and/or in maternal blood, is only suggestive of an etiopathogenic role, not proof. Furthermore, a meta-analysis of 15 randomized trials[8] showed no convincing evidence that increased intake of antioxidants, in the form of supplements, medication or food sources, prevents or delays PE or reduces associated maternal and fetal morbidity. Evidence that oxidative stress in PE can be corrected by medication or diet is as yet weak or nonexistent. Some studies[9] even suggest that supplementation with vitamins C and E actually has harmful effects in pregnant women. However, the fact that antioxidant treatment is unsuccessful in treating PE does not necessarily mean that oxidative stress plays no part in the disease.

Another question that is not fully answered in the article is whether the dietary deficiencies in antioxidant nutrients are specific to women with PE or are common to all women of low socioeconomic status in the region studied. Low mean intakes of antioxidants (vitamin A, selenium, zinc and copper) and high coefficients of variation were found in both groups of women, although intakes of vitamin A and selenium were higher in those without PE. The differences in antioxidant intakes between women with and without PE were only slight.

It is a pity that there is no detailed data are provided on the anthropometric or clinical characteristics of the study population such as body mass index or blood pressure, gestation time, gestational week in which PE was diagnosed, or obstetric history. It would also have been useful to know maternal and infant outcomes (blood pressure, albuminuria, edema, seizures, prematurity, rates of cesarean delivery, perinatal maternal and infant morbidity, etc.) as a function of different levels of intake of antioxidant nutrients. Supplementation with L-arginine, a precursor of nitric oxide, appears to prevent PE in high-risk pregnancies,[10] probably by reversing endothelial dysfunction, but this obviously does not prove that antioxidant effects are responsible.

To summarize, various findings indicate that oxidative stress is present in PE. There is a body of at least experimental evidence that relates the increased oxidative stress in PE and the low antioxidant capacity of the trophoblast to inflammation, apoptosis, endothelial dysfunction, and antiangiogenic factors, among others, but the fact remains that to date the available means of improving antioxidant status have not proved beneficial at any stage of the development of PE. Even so, given of the risk of maternal and fetal complications due to PE, the complexity of its pathophysiology, the considerable interest in modeling the disease and the lack of measures to treat or prevent it, there is ample justification for studies such as this, in order to open up new research paths that could lead to understanding and controlling the disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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