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Subclinical infection as cause of inflammation in preeclampsia

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Abstract

Preeclampsia, a pregnancy-exclusive hypertensive disorder, is the major cause of maternal and perinatal mortality, with a greater importance in developing countries. The role of inflammation in the pathogenesis of preeclampsia has been the object of recent studies by our group. We have described elevated levels of inflammatory markers (TNFα, IL6 and CRP) in preeclamptic patients and demonstrated that Latin-American women present a higher degree of inflammation than women from developed countries. We have results that suggest that chronic subclinical infections and insulin resistance are the most probable causes of the increased inflammation in preeclampsia. Moreover, we showed that early treatment of urinary and vaginal infections decreased the incidence of preeclampsia. We also have evidences that suggest that inflammation leads to endothelial dysfunction, predisposing women to develop preeclampsia. Increased levels of inflammation markers and endothelial dysfunction are found in the early stages of pregnancy in women who later on develop preeclampsia. Appropriate prenatal care programs, including screening and treatment of urinary, vaginal and periodontal infections in early pregnancy and prevention of factors that predispose to insulin resistance, as excessive weight gain during pregnancy, may reduce the incidence of preeclampsia in Latin-American women.

Introduction

Hypertensive disorders during pregnancy are the principal cause of maternal and perinatal morbidity and mortality, preeclampsia (PE) being the most important among these alterations[1,2]. The etiology of PE comprises multiple risk factors[3,4], and we have proposed that the impact of each of them varies with the populations, with considerable differences between developed and developing countries[5]. In Latin-America, inappropriate nutrition, young maternal age and inadequate prenatal care programs, are important risk factors in the development of PE. In these countries, PE is the main cause of maternal mortality, which is 10 to 20 fold higher than in developed countries[2,5,6].

Excessive inflammation and risk of preeclampsia

Healthy pregnant women present a certain degree of inflammation, due in part to the activation of the immune system induced by the fetal allograft[7]. However, preeclamptic women have an excessive inflammatory response as demonstrated by increased concentrations of proinflammatory cytokines[8]. The role of these cytokines in normal pregnancy is not entirely understood. Some of them have been related to the mechanisms involved in the initiation and maintenance of gestation. For instance, TNF-α seems to regulate invasion and growth of the trophoblast into maternal spiral arteries[7]. However, women who

developed PE have significantly higher levels of TNF-α, IL2 and IL6[8,12].

In Andean population[13], we have confirmed the increased concentrations of proinflammatory cytokines in women with PE and demonstrated that our normal pregnant women have significantly higher concentrations of CRP, TNF-α and IL6, than those reported in studies conducted in pregnant women from developed countries[10,12,14].

The relationship of sub-clinical infection with preeclampsia

Asymptomatic bacteriuria is more frequently diagnosed in pregnant women with PE[15,16]. Various studies have described that urinary infection is associated with the development of preeclampsia, and that this association is more frequent among primigravidae women[17,18]. We have demonstrated that the early diagnosis and treatment of urinary and vaginal infections decreased the incidence of PE by 64 %[19].

Chronic subclinical infection appears as a factor that alters the endothelial production of nitric oxide (NO), substance which maintains a basal vessel dilator tone in the cardiovascular system[20,21]. An increased oxidative stress produced by infection impairs the bioactivity of NO and leads to endothelial dysfunction, event that is crucial in the development of PE[4,22]. In support of this view, PE-like manifestations have been induced in experimental models by blocking endothelial production of NO[20,23]. Moreover, in a randomized, double-blind, placebo controlled clinical trial, we included primigravidae women with family history of PE and abnormal Doppler ultrasound in uterine or arcuate arteries (diastolic notch). Women received daily elemental calcium and conjugated linoleic acid or lactose–starch placebo[24,25]. Endothelial function was evaluated by flow mediated dilation (FMD), method that has been validated in our population[26, 27]. Moreover, all women were screened for urinary and vaginal infections. The frequency of endothelial dysfunction was significantly higher among women with these infections and the antibiotic therapy improved FMD and decreased the risk of PE[24,25]. Recently, we established a cohort of 506 Colombian pregnant women with known risk factors for PE. FMD was realized in all women at 16 weeks of gestation and blood samples were withdrawn. All women were followed until delivery, 32 who developed PIH (Pregnancy induced hypertension) and 64 controls matched by body mass index and maternal and gestational age, were included in a nested case-control study[28]. CRP concentration and leukocyte counts were higher and FMD was lower in the women who developed PIH, suggesting that inflammation and endothelial dysfunction early in pregnancy precede the appearance of the clinical manifestations of PE. Furthermore, a correlation between the degree of inflammation and the severity of the hypertensive disorder was observed[28]. On the basis of these results we have suggested that inflammation secondary to chronic subclinical infection increases the risk of PIH[19].

Periodontal infection and risk of preeclampsia

Several studies have demonstrated a relationship between periodontitis and increased risk of PE, preterm delivery and low birth weight[29-31]. In Colombia we have reported[32] that chronic periodontal disease was more frequent in women with PE than in healthy pregnant controls (63.8% vs 36.6%), with a significant association between PE and chronic periodontitis (OR: 3.0; 95%-CI: 1.91-4.87). Two red complex microorganisms, Porphyromonas gingivalis and Tannerella forsythensis, and the green complex microorganism Eikenella corrodens were more frequently isolated in women with PE. These pathogens have also been isolated in atherosclerotic plaques in humans with coronary artery disease[33]. Moreover, we assessed the periodontal state and the CRP concentrations in 145 preeclamptic and 253 healthy pregnant controls[34]. Women with PE had a higher frequency of chronic periodontal disease (59% vs 36%; $p<0.001$) and in these women the CRP concentrations increased progressively depending on the severity of the periodontal disease. The CRP levels were significantly higher in the moderate/severe periodontitis group of women with PE [0.01]. Additionally P. gingivalis and E. corrodens were isolated more frequently in preeclamptic women[34]. These studies demonstrate a significant association between chronic periodontitis and PE, and suggest that the systemic inflammation observed in women that developed PE could be the result of periodontal infection.

Conclusión

Preeclampsia is the most important cause of maternal mortality in developing countries. Among the several conditions identified as risk factors for PE, sub-clinical infections have a major role in Latin-American population. Chronic inflammation induced by periodontal, vaginal and/or urinary infections causes endothelial dysfunction, a crucial alteration in the pathophysiology of PE. Early diagnosis and treatment of asymptomatic urinary and vaginal infections have been demonstrated to be an effective strategy to reduce the incidence of PE. Screening and treatment of common sub-clinical infections must be incorporated to the prenatal care programs, if we want to obtain a considerable reduction in maternal and perinatal mortality due to PE.

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