Correspondence

A Role for Vitamin D in Placental Immunology

To the Editor—We were excited to read the article by Mehta and colleagues [1] that described the association between the vitamin D status of pregnant women and the risk of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV). The authors suggested that the lower incidence of MTCT in vitamin D–sufficient women (with a serum 25-hydroxyvitamin D [25OHD] level of >80 nmol/L) may be due to improved innate immune response to infection, as described elsewhere by our group [2]. Studies to date have focused primarily on immunomodulatory responses to vitamin D in peripheral blood mononuclear cells. However, given the fundamental role of the placenta in the vertical transmission of HIV from the mother to the fetus [3], it seems likely that this organ also plays a key role in defining innate immune responses to vitamin D. We have shown elsewhere that placental expression of the vitamin D–activating enzyme 1α-hydroxylase and the nuclear vitamin D receptor is elevated early in gestation [4]. The resulting capacity for autocrine and paracrine activity of vitamin D does not appear to be essential for classical responses such as skeletal homeostasis. Instead, we have suggested that local activation of vitamin may function to promote placental immunity. In recent ex vivo studies with human tissue, we have demonstrated vitamin D–dependent induction of the antimicrobial protein cathelicidin in decidual [5] and trophoblastic [6] cells, with the latter supporting enhanced bacterial killing. Crucially, these responses correlated with levels of 25OHD, the form of vitamin D that defines vitamin D status. Thus, we would predict that low maternal levels of 25OHD would lead to dysregulation of placental immune responses, whereas maternal vitamin D supplementation would improve placental immunity.

At present, studies of innate immune responses to 25OHD have focused on antibacterial activity, and this alone may be important, given the link between Mycobacterium tuberculosis infection and fetal mortality associated with HIV infection. However, it is also possible that placental conversion of 25OHD to 1,25-dihydroxyvitamin D [1,25(OH)2D] acts to support antiviral activity. In monocytes, 1,25(OH)2D has been shown to promote autophagy, a key component of cytoplasmic homeostasis that has also been linked to cellular handling of pathogens including viruses. Autophagic vacuoles have been detected in cytotrophoblasts and syncytiotrophoblasts of the human placenta, and trophoblastic cells are known to express autophagy proteins [7]. It is, therefore, tempting to speculate that the autophagy effects of locally synthesized 1,25(OH)2D may not be restricted to monocytes but may also involve cells from the placenta. Like monocytes, cells from the placenta also express the HIV coreceptors CXCR4 and CCR5, and early pregnancy trophoblasts are permissive for HIV infection [3]. Results of studies with monocytes and dendritic cells suggest that 1,25(OH)2D can modulate expression of CXCR4 [8] and CCR5 [9], which may provide another mechanism by which vitamin D is able to influence placental responses to HIV.

The data of Mehta et al [1] were equally striking with respect to the circulating levels of 25OHD that were associated with different rates of MTCT. The mean serum concentration of 25OHD among women designated as having low vitamin D levels was 24.2 ng/mL (60 nmol/L), whereas the mean serum 25OHD concentration in the group of women with adequate vitamin D levels was 43.1 ng/mL (108 nmol/L). These values are considerably higher than those observed in previous studies of vitamin D status during pregnancy. In an analysis of a cohort of pregnant women in Pittsburgh, Pennsylvania, Bodnar and colleagues [10] reported that >90% of black women had serum levels of 25OHD of <80 nmol/L, with 46% having levels of <37.5 nmol/L. Of white women, 66% had 25OHD levels of <80 nmol/L. These observations may have important ramifications for MTCT in other populations across that globe in which vitamin D status is universally lower than that reported for the Tanzanian population described by Mehta and colleagues [1]. Moreover, we suggest that under these conditions, other adverse pregnancy outcomes such as preterm and severe preterm birth may also be influenced by vitamin D status. This is particularly relevant for cases of preterm birth associated with maternal infection, in which chronic vitamin D deficiency, as opposed to insufficiency, may impair maternal and fetal immune function.

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