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REVIEW ARTICLE

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Cytokines in the perinatal period – Part II

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ABSTRACT
A contemporary, robust immunologic explanation for common obstetric conditions remains elusive; why some pregnant women are more susceptible to developing preeclampsia or preterm labor is not completely understood. We explore the immunology behind four important and commonly encountered pregnancy-related conditions: preeclampsia, recurrent miscarriage, preterm labor and gestational diabetes. For each condition, we summarize the current understanding of cytokines implicated in the pathogenesis, discuss the impact of anesthesia and analgesia on selected cytokine profiles, and suggest potential opportunities for clinical and research interventions.

Preeclampsia

Preeclampsia is a systemic, pregnancy-specific syndrome characterized by intrauterine growth restriction (IUGR), maternal hypertension, renal insufficiency/proteinuria, thrombocytopenia, liver dysfunction, generalized edema and cerebral disturbances culminating in seizures. Occurring in approximately 8% of pregnancies, preeclampsia is a leading cause of maternal morbidity and mortality.[1] Although the exact etiology of preeclampsia remains unclear, an imbalance in cytokines has been used to explain the pathogenesis and associated adverse pregnancy outcomes (Fig. 1). Paternal specificity and preponderance in the first pregnancy suggest an association with an antigen-specific maternal inflammatory response. An inciting event may be a partial breakdown of maternal immune tolerance to allogeneic fetal-derived cells within the uterus.[2]

The placenta is a chimeric organ composed of maternal and fetal cells anchored in the decidua, the post-implantation lining of the uterus. During the first trimester, invasion of fetal placental trophoblast cells into the decidua places them in direct contact with maternal cells; in a normal healthy pregnancy, these trophoblastic cells eventually line the walls of maternal decidual spiral arteries. In preeclampsia, placental histopathology specimens demonstrate incomplete decidual spiral artery remodeling and more shallow placental invasion into the uterus;[3] these alterations result in decreased placental bed blood flow and IUGR. The oxidative stress within the placental bed releases mediators, such as soluble fms-like tyrosine kinase-1 (sFlt-1), which likely cause additional maternal endothelial dysfunction and incite further clinical sequelae.[4]

Approximately half of all maternal decidual cells are leukocytes, which include a large population of unique natural killer (NK) cells, macrophages, regulatory T cells, and NK cell-derived cytokines, including interferon-gamma (IFN-γ), that promote the trophoblastic invasion of spiral arteries.[5] The innate and adaptive immune cell interactions observed in preeclampsia at the decidual and systemic levels have been extensively detailed.[2] During the second trimester, an accentuated maternal systemic inflammatory response with distinct cytokine mediators accompanies the signs and symptoms of preeclampsia. A convincing role for tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in preeclampsia has been demonstrated, as an infusion of either cytokine into pregnant rats causes an elevation of mean arterial pressure; non-pregnant rats do not exhibit the same response.[6,7]

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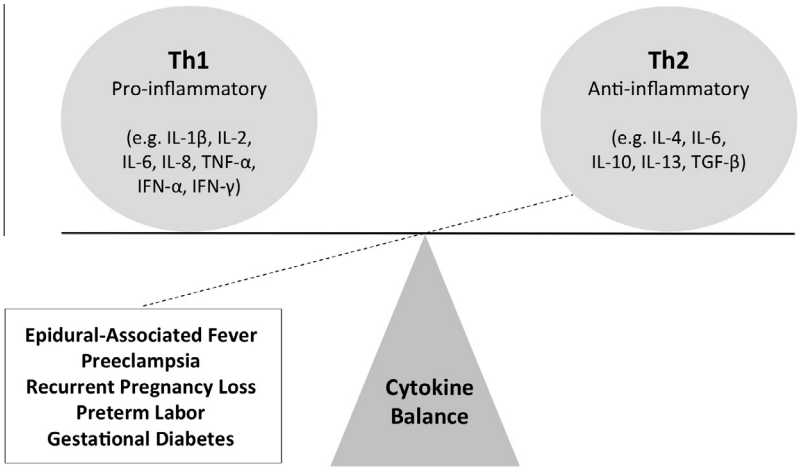

Fig. 1 Cytokine balance during pregnancy. The pro-inflammatory Th1 response is essential for maternal host defenses whereas the Th2 reaction is important for inducing fetal immune tolerance. Imbalance of the immune responses may lead to adverse pregnancy outcomes such as gestational diabetes, preeclampsia, recurrent pregnancy loss, preterm labor and development of labor epidural-associated fever

Increases in TNF-α, induced by exogenous lipopolysaccharide (LPS), have also been associated with elevations in mean arterial pressure and an abnormal inflammatory response in the rat placenta; these processes were reversed with the administration of anti-inflammatory agents or nitric oxide.[8]

Normal human pregnancy involves a progressive mild inflammatory state with oxidative stress characterized by leukocytosis, activation of innate immune cells, elevation of serum IL-6 and TNF-α levels,[9] and resistance to insulin, when compared to non-pregnant controls. During preeclampsia, the pro-inflammatory response is of greater intensity,[9] with certain cytokine levels correlating with the progression and severity of the disease. Serum analysis of preeclamptic patients indicates elevated IL-6, TNF-α, and other acute phase proteins compared to normotensive controls, with no differences in IL-1β and IL-10 levels.[10,11] Bernardi et al.[10] reported undetectable IL-6 levels in normotensive controls compared to 20 pg/mL in preeclamptic patients; Catarino et al.[11] reported a more modest doubling of IL-6 levels, from 1.9 pg/mL in normotensive patients to 4 pg/mL in preeclamptic patients. Similar differences between normotensive and preeclamptic women in circulating maternal TNF-α have been observed, with Bernardi et al.[10] reporting undetectable levels compared to 37 pg/mL and Catarino et al.[11] reporting 1.2 pg/mL vs. 1.9 pg/mL, respectively. By contrast, Vitoratos et al.[12] demonstrated no difference between normotensive and preeclamptic patients in IL-6 levels (2.44 pg/mL vs. 2.66 pg/mL) and a small, but statistically significant difference in TNF-α levels (0.6 pg/mL vs. 0.8 pg/mL). Interestingly, levels of these cytokines are similar to those detected in umbilical cord blood samples, indicating that an independent fetal inflammatory response likely does not occur.[11]

Serum cytokine measurements show promise in identifying women at risk for preeclampsia. Chemokines, a class of cytokines named for their leukocyte-attracting ability, are increased in the sera and decidual tissues of preeclamptic patients; increased IFN-γ-induced protein 10 (IP-10) in the sera of first trimester pregnant women has been strongly correlated with preeclampsia.[13] In the second trimester sera of women who later developed preeclampsia, Kumar et al.[14] reported significantly decreased levels of IL-10, IFN-γ, and TNF-α, when compared to normal healthy controls. An analysis of cytokines from third trimester women has yielded no clinically useful predictors of preeclampsia, with the possible exception of reduced and elevated serum levels of IL-1β and TNF-R1, respectively, when compared to first trimester measurements.[15] These investigations likely highlight the diversity in the etiology and expression of preeclampsia. Future prospective studies should correlate multiplex cytokine analyses with disease onset and outcomes; the development of a yet elusive diagnostic biomarker panel for preeclampsia will likely include a cytokine marker.

Delivery of the fetus does not immediately alleviate preeclampsia in all cases, with 6% of cases presenting in the postpartum period[16] and approximately 26% of eclamptic seizures occurring between two and 42 days after delivery.[17] Inflammation appears to persist following preeclampsia. In preeclamptic patients IL-6 levels were higher at 12–14 weeks postpartum than in normotensive controls (3.53 pg/mL vs. 1.69 pg/mL);[12] similarly, in postpartum preeclamptic patients, TNF-α levels were higher than in normotensive controls