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Current opinion

Aberrant maternal inflammation as a cause of pregnancy complications: A potential therapeutic target?

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ABSTRACT

Pre-eclampsia (PE), fetal growth restriction (FGR), pre-term labour and fetal death are common complications of pregnancy often associated with abnormal maternal inflammation. Though the precise causes of these complications remain obscure, altered maternal blood flow to the placenta is an underlying hallmark, especially with respect to the pathogenesis of PE, FGR and fetal demise. Furthermore, deficient trophoblast-mediated spiral artery remodelling is often cited as the primary cause of impaired utero-placental perfusion. Considerably less attention has been directed towards investigating other factors, including maternal vasoconstriction or hemostatic alterations, as contributors to poor utero-placental perfusion. This review provides a rationale for investigating the role of abnormal maternal inflammation in the pathophysiology of pregnancy complications including PE, FGR and fetal demise. In particular, the association between aberrant maternal inflammation and inadequate utero-placental perfusion is considered in the context of inflammation-associated alterations in maternal hemostasis and vasoconstriction. Finally, the role of aberrant maternal inflammation as a cause of local oxidative/nitrosative stress is examined and the possibility of targeting deficient nitric oxide signalling as a therapeutic intervention for the treatment of inflammation-associated pregnancy complications is discussed.

1. Introduction

While women can experience a variety of reproductive complications ranging from infertility to pre-term labour (PTL), common adverse pregnancy outcomes associated with poor fetal and maternal health include pre-eclampsia (PE), fetal growth restriction (FGR) and fetal loss. Shared features of PE, FGR and fetal loss include an abnormal maternal inflammatory response [1], impaired placentation [2,3], poor utero-placental perfusion [2], alterations in maternal hemostasis [4] and utero-placental oxidative/nitrosative stress [5]. Though PTL is associated with an abnormal inflammatory response [6], a link between altered utero-placental perfusion and the onset of PTL has not been well characterised. Therefore, this review examines the role of aberrant maternal inflammation as a key factor leading to altered utero-placental perfusion in the context of PE, FGR and fetal demise.

1.1. Pathogenesis of pregnancy complications

The two-stage model of PE initially proposed that deficient spiral artery remodelling (stage one) leads to local placental ischemia, oxidative stress and the systemic release of placental-derived factors that contribute to the pathophysiology of the maternal disease (stage two) [2,7]. This paradigm has been recently modified to explain negative fetal outcomes (*i.e.* FGR and fetal death) arising secondary to insufficient utero-placental perfusion [1]. The current model proposes that alterations of utero-placental perfusion are key to the disease process as it results in placental pathology including local oxidative/nitrosative stress. However, the literature emphasises impaired spiral artery remodelling and the subsequent deficit in utero-placental perfusion as the main, if not exclusive, mechanism contributing to placental ischemia and oxidative stress. It was commonly thought that the pathological reduction in spiral artery vessel diameter results in decreased blood volume reaching the fetal–maternal interface [3]. However, Burton and colleagues demonstrated that blood volume is only moderately affected by reductions in vessel diameter and proposed that the consequences of poor spiral artery modification are local tissue

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damage due to ischemia/reperfusion (I/R) and high-momentum blood entering the intervillous space [8].

Because placental damage is secondary to altered utero-placental perfusion and is important to the pathogenesis of pregnancy complications [8,9], factors that disrupt utero-placental hemodynamics (*i.e.* deficient spiral artery remodelling, local vasoconstriction and/or disruption of local maternal hemostasis) should be investigated in order to identify therapeutic targets. Recent work has highlighted the importance of exaggerated maternal inflammation in the development of pregnancy complications [10–16].

2. Inflammation and pregnancy

2.1. Immunological phases of uncomplicated pregnancy

Uncomplicated pregnancy induces a state of low-grade inflammation [17,18]. Compared with their non-pregnant counterparts, pregnant women exhibit leukocytosis [17], increased complement activation [19] and alterations in peripheral blood leukocyte populations reminiscent of sepsis [18]. In the past, successful pregnancy was considered to be a state of immune tolerance requiring a global Th-2 or anti-inflammatory cytokine shift [20–22]. New evidence indicates that this paradigm is too simplistic and that pregnancy is not a single immunological entity, but a dynamically modulated immunological state [23,24]. In particular, three distinct immunological phases of uncomplicated pregnancy have been described [24]. The biological processes that characterize early pregnancy [25] and parturition [26,27] rely on mild and finely regulated sterile inflammatory processes and are hallmarks of the first and third immunological phases of pregnancy, respectively [23]. Conversely, the rapid fetal growth occurring during the third trimester occurs optimally under anti-inflammatory conditions and constitutes the second immunological phase of pregnancy [24]. Dysregulation of these immunological phases can lead to complications including PTL, fetal death, FGR and PE as discussed below.

2.2. Role of abnormal maternal inflammation in pregnancy complications

Uncontrolled, exaggerated inflammation has been linked with poor perinatal and placental development [28]. Certain complications of human pregnancy, including PE [18,29,30], FGR [31,32], fetal demise [28,33,34], and PTL [6,35] are associated with an abnormal maternal inflammatory response, both systemically and locally at the placenta. This response is characterised by increased levels of cytokines and chemokines including tumour necrosis factor (TNF), interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, interferon (INF) gamma and monocyte chemotactic protein (MCP-1) [29,30,36–41].

There is evidence that an ordinarily non-pathological inflammatory stimulus results in the manifestation of pregnancy complications when superimposed on the pro-inflammatory state of pregnancy [1,42]. For example, PTL was suggested to occur as a result of the exaggerated or premature activation of inflammatory pathways associated with labour [6]. Moreover, the degree of inflammation during pregnancy was shown to correlate with the severity of the complication [1]. This implies that inflammation and pregnancy complications exist along a continuum, such that PE, FGR and fetal death occur only after the severity of inflammation surpasses a threshold [1]. Indeed, non-pregnant women with a history of recurrent miscarriage exhibit a heightened state of inflammation compared with non-pregnant women who later experience healthy pregnancies [43]. Moreover, women with obesity prior to pregnancy are at an increased risk of developing PE during their pregnancy in a 'dose-dependent' manner. Compared with women with a pre-pregnancy normal BMI of 21, the adjusted risk of PE in women with a BMI of 26 and 31, is doubled and tripled, respectively [44]. It is likely, therefore, that pregnancy complications are not isolated conditions. Instead, they develop as a result of dysregulation of physiological processes leading to exacerbation of the inflammatory response [17,45]. Adding to this paradigm is the concept that the systemic maternal inflammation that characterizes pregnancy complications exists at the higher end of the continuum of inflammation associated with pregnancy [17], with the most severe complications, such as fetal demise and severe PE, occurring at the extreme end of the spectrum [29].

Various animal models have provided insight into the role of abnormal inflammation in the development of adverse pregnancy outcomes (Table 1). Faas and colleagues described the use of intravenous low-dose lipopolysaccharide (LPS) infusion to pregnant rats on gestational day 14.5 to induce features of PE including glomerular pathology, elevated blood pressure, albuminuria, and platelet coagulopathy [46]. In another study, intrauterine infusion of LPS into pregnanct mice induced PTL in 100% of cases within a 24-h period [35]. Moreover, studies using a mouse model of the autoimmune disorder anti-phospholipid syndrome (APS) revealed a causal role for complement activation in FGR and fetal loss [47–49]. Complement activation results in the systemic release of TNF, a potent pro-inflammatory cytokine involved in the recruitment of leukocytes and propagation of the immune response [50]. TNF is produced mainly by activated macrophages [51]; however, neutrophils [52], lymphocytes [53], monocytes [54], endothelial cells [55], and trophoblasts [56,57] also release this cytokine. Our laboratory established a causal role for TNF in the pathogenesis of inflammation-induced pregnancy complications including fetal loss [12,13], FGR and PE [10] in rat models.

Many studies have described increased circulating TNF levels in women with pathological pregnancy [29,30,38,58]. There are conflicting reports on TNF expression in placentas from complicated pregnancies, with some studies showing increased levels [59,60] and others finding no difference in TNF levels between normal and pathological placentas [61,62]. Differences in specimen collection or timing of specimen acquisition (*i.e.* early *versus* late pregnancy) may explain the discordance in the data [63]. Whether increased TNF levels are a cause or a consequence of adverse pregnancy outcomes has yet to be conclusively determined. Although the current paradigm suggests that maternal levels of pro-inflammatory cytokines increase as a result of placental damage subsequent to inadequate spiral artery remodelling and deficient placental perfusion, there is also a potential role for TNF as a cause of the poor placentation that characterizes these diseases. For example, TNF released from activated macrophages was shown to inhibit the migration and invasion of trophoblast cells *in vitro* [64,65]. Our work revealed a causal role for TNF in deficient trophoblast invasion and spiral artery remodelling in a rat model of low-dose LPS-induced FGR and PE [10]. Moreover, infusion of TNF to pregnant rats was shown to increase arterial pressure and cause vasoconstriction through a mechanism involving endothelin-1 (ET-1) and/or reduced nitric oxide (NO) production [66–68]. Finally, TNF is a potent stimulator of the coagulation cascade [69] and has been linked to hemostatic changes associated with adverse pregnancy outcomes [12,13].

A pathological placenta, and in particular a placenta with altered utero-placental hemodynamics, is important to the development of adverse pregnancy outcomes. In addition to deficient trophoblast invasion and spiral artery remodelling, other factors may contribute to altered utero-placental perfusion such as maternal hemostatic alterations and/or local vasoconstriction. As discussed below, aberrant maternal inflammation may be linked to each of these events. Therefore, we propose that abnormal maternal