Inflammatory Cytokines in the Pathophysiology of Hypertension during Preeclampsia

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Reduced uterine perfusion pressure during pregnancy is an important initiating event in preeclampsia. Inflammatory cytokines are thought to link placental ischemia with cardiovascular and renal dysfunction. Supporting a role for cytokines are findings of elevated tumor necrosis factor (TNF)-α and interleukin (IL)-6 plasma levels in preeclamptic women. Blood pressure regulatory systems (eg, renin-angiotensin system [RAS] and sympathetic nervous system) interact with proinflammatory cytokines, which affect angiogenic and endothelium-derived factors regulating endothelial function. Chronic reductions in placental perfusion in pregnant rats are associated with enhanced TNF-α and IL-6 production. Chronic infusion of TNF-α or IL-6 into normal pregnant rats significantly increases arterial pressure and impairs renal hemodynamics. TNF-α activates the endothelin system in placental, renal, and vascular tissues, and IL-6 stimulates the RAS. These findings suggest that inflammatory cytokines elevate blood pressure during pregnancy by activating multiple neurohumoral and endothelial factors.

Introduction

Preeclampsia is defined as new-onset hypertension with proteinuria during pregnancy. Preeclampsia occurs in 5% to 7% of all pregnancies and is a multisystemic disorder affecting most organs of the body [1]. The hypertension develops during the third trimester of gestation and remits after delivery, implicating the placenta as a central culprit in the disease. Inadequate invasion of the cytotrophoblast is one important initiating event in preeclampsia. Insufficient invasion of trophoblasts in the uterine spiral arteries prevents normal vascular remodeling and markedly attenuates placental perfusion [2••]. Subsequent placental release of circulating factors—such as soluble vascular endothelial growth factor (VEGF) receptors (sFlt-1), angiotensin II type 1 receptor autoantibodies (AT1-AA), and inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6—may be important mediators of maternal endothelial activation and/or dysfunction [3,4]. The mechanisms linking placental ischemia, immune activation, endothelial dysfunction, and dysregulation of angiogenic factors with the development of hypertension during pregnancy are the main focus of this review (Fig. 1).

Immune Activation and Cytokine Production in Pregnancy and Preeclampsia

Preeclampsia has long been considered an immunologically based disease [3,4]. During normal pregnancy, TNF-α promotes expression of adhesion molecules in maternal endothelial cells and activates phagocytic cells that are important mediators of morphologic changes in the uterine arteries. Under normal conditions, the cytotrophoblasts undergo endovascular invasion, allowing the cells to replace the endothelial and muscular linings of the uterine arterioles. As a result of this invasion, the vessel diameter of spiral arteries increases, allowing enhanced perfusion to meet the uteroplacental unit's metabolic needs. By the end of the second trimester, the cytotrophoblasts completely line the decidua and endothelial cells are no longer visible. During preeclampsia, however, cytotrophoblast invasion of the uterus is shallow and endovascular invasion is incomplete, thus inhibiting essential morphologic changes of the maternal uterine vasculature [1,2••]. As a result, the mean arterial diameter of the first third of myometrial vessels is less than half that of vessels isolated from placentas in normal pregnancies. Furthermore, the endothelial lining of the maternal vasculature remains, thereby inhibiting maternal cellular protein expression in women with preeclampsia.

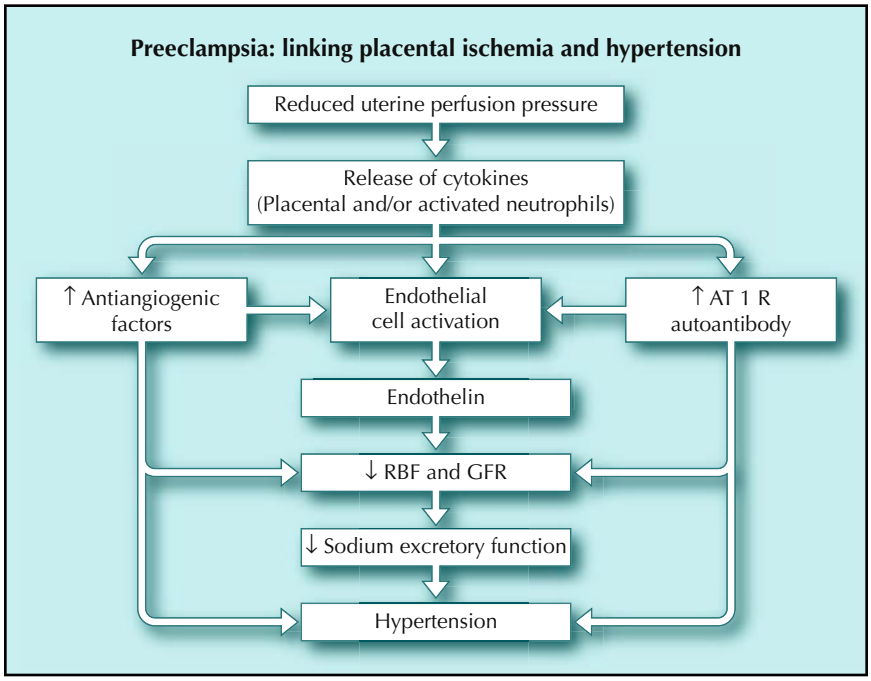

Figure 1. Potential mechanism linking placental ischemia with the development of hypertension during pregnancy. AT 1 R—angiotensin II type 1 receptor; GFR—glomerular filtration rate; RBF—renal blood flow.

This could allow interactions between activated immune cells and proinflammatory cytokines to persist, leading to elevations in cytokines and immune infiltrates, characteristic of a chronic inflammatory condition.

Many inflammatory cells are activated in the circulation and infiltrate into renal and placental tissues. Macrophages, neutrophils, and T lymphocytes of the T helper (Th)-1 subset are the predominant cell types mediating the inflammatory cascade in women with preeclampsia [1,3,4]. Furthermore, the cytokine profile of these women is consistent with a cell-mediated immune response that uses neutrophils, macrophages, and $CD4^+$ Th1 cells as a defense mechanism against microbial infections. As a result, elevated inflammatory cytokines and the oxidative burst of phagocytic cells persist, resulting in vascular oxidative stress during preeclampsia [4].

Preeclampsia is characterized by compromised vascular remodeling, which results in decreased placental perfusion, creating a hypoxic environment for placental and fetal tissues. Under hypoxic conditions, placental explants from preeclamptic women exhibit a twofold increase in TNF-α compared with explants from normal pregnant women. Preeclamptic women have a twofold elevation in placental and plasma TNF-α protein levels. Circulating levels of other proinflammatory cytokines (eg, IL-8, IL-6) are also significantly elevated in these women. Levels of circulating IL-10, an anti-inflammatory cytokine, are decreased in the same women [4].

Role of Cytokines in Mediating Blood Pressure Response to Placental Ischemia

Although inflammatory cytokines have been reported as elevated in preeclamptic women, their importance in mediating the cardiovascular and renal dysfunction in response to placental ischemia during pregnancy has yet to be fully elucidated [3]. It is becoming increasingly evident that proinflammatory cytokines interact with important blood pressure regulatory systems, such as the renin-angiotensin system (RAS), sympathetic nervous system, and endothelial and angiogenic factors [4,5,6•,7,8]. We reported that chronic reductions in uterine perfusion pressure (RUPP) in pregnant rats increase arterial pressure and reduce renal plasma flow and glomerular filtration rate [9••]. Moreover, we reported that serum levels of TNF-α and IL-6 are elevated during RUPP in pregnant rats and chronic infusion of TNF-α or IL-6 into pregnant rats increases arterial pressure and decreases renal plasma flow and glomerular filtration rate [6•,7,10•]. These findings indicate that TNF-α and IL-6 may play a part in mediating the hypertension and impaired renal hemodynamics observed during RUPP in pregnant rats.

Endothelin and Inflammatory Cytokines

Endothelial damage is a known stimulus for endothelin (ET)-1 synthesis; therefore, increases in the production of ET-1 and activation of ET receptor type A (ETA) may participate in the pathophysiology of hypertension during preeclampsia. [1,7]. Although several studies have reported no significant changes in ET-1 circulating levels during moderate forms of preeclampsia, possible paracrine or autocrine actions of ET-1 in preeclampsia remain worthy of consideration. Recent evidence implicates a role for ET-1 in mediating the hypertension in a placental ischemic rat model of preeclampsia. Preproendothelin mRNA was significantly elevated in both the renal medulla and cortex of pregnant rats with chronic RUPP, compared

with control pregnant rats. Moreover, chronic administration of a selective ETA receptor antagonist markedly attenuated the increase in mean arterial pressure in pregnant rats with RUPP. In contrast to the response in RUPP rats, ETA receptor blockade had no significant effect on blood pressure in the normal pregnant animal [7]. These findings suggest that ET-1 has a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats.

The exact mechanism linking enhanced renal production of ET-1 to placental ischemia in pregnant rats or in preeclamptic women is unknown. One potential mechanism is via transcriptional regulation of the ET-1 gene by TNF-α. Chronic infusion of TNF-α in pregnant rats, at a rate to mimic plasma levels (two- to threefold increase) observed in women with preeclampsia, significantly increased blood pressure [7]. The increase in arterial pressure produced by TNF-α in pregnant rats is associated with significant increases in local production of ET-1 in the kidney, placenta, and vasculature. Moreover, the increase in mean arterial pressure in response to TNF-α is completely abolished in pregnant rats treated with an ETA-receptor antagonist [7]. Collectively, these findings suggest that endothelin, via ETA-receptor activation, has an important role in mediating TNF-α–induced hypertension in pregnant rats.

Angiogenic Factors and Inflammatory Cytokines

Expression of angiogenic factors such as VEGF, placental growth factor (PlGF), and their respective receptors is essential for normal placental development in pregnancy. The balance between pro- and antiangiogenic factors has recently become an area of interest in cancer, autoimmune, and preeclampsia research. Although numerous factors are recognized as important for angiogenesis, the VEGF system has gained the most attention with respect to preeclampsia [12••,13–15,16••,17]. Recent evidence illustrates the importance of VEGF in regulation and maintenance of blood pressure and renal function during various forms of hypertension and/or renal injury [18–20], including pregnancy-induced hypertension and preeclampsia [13,15,21–23]. Evidence suggests that high serum levels of the VEGF antagonist sFlt-1 and low serum levels of free PlGF and VEGF play a key role in the pathogenesis of preeclampsia [13–15,22,24–27]. A recent study in pregnant rats demonstrated that adenovirus-mediated increases in circulating sFlt-1 produced hypertension, proteinuria, and glomerular endotheliosis—the classic pathologic renal lesion of preeclampsia [28]. In contrast to cytokine-mediated hypertension during pregnancy, increased serum sFlt-1 produced hypertension in nonpregnant animals, suggesting that the effects of sFlt-1 on the vasculature were direct and not restricted to pregnancy.

Although evidence increasingly supports the concept that elevated levels of sFlt-1 are important in the pathogenesis of preeclampsia, much less is known about mechanisms that result in its dysregulated expression. Two putative stimulatory pathways for sFlt-1 are hypoxia and angiotensin II. Nevo et al. [29] recently suggested that hypoxia may be a primary stimulus for excess placental production of sFlt-1, based on evidence from pregnancies at high altitudes and from in vitro cytotrophoblast primary cultures exposed to hypoxia. These data suggest that poor trophoblast invasion might lead to a hypoxic placenta and ultimately to pathogenic levels of sFlt-1.

Another factor contributing to altered regulation of angiogenic factors may be inflammatory cytokines. Cytokines have been shown to increase angiogenic factors and promote angiogenesis in chronic systemic diseases such as rheumatoid arthritis [8] and cancer; however, the relationship between inflammation and dysregulation of angiogenic factors in pregnancy is unknown. The elevation of inflammatory mediators that occurs with preeclampsia may prevent VEGF-induced angiogenesis by stimulating sFlt-1. Girardi et al. [4] was able to directly trigger sFlt-1 by stimulating monocytes with products of the complement cascade. Subsequently, the authors demonstrated that inhibiting complement activation blocked increases in sFlt-1 and rescued pregnancies in a mouse model of immunologically mediated perimplantation pregnancy loss [4]. In addition, recent studies have found that the cytokine granulocyte-macrophage colony-stimulating factor increases sFlt-1 expression in monocytes and inhibits angiogenesis in mice [30]. Monocyte-derived sFlt-1 also inhibits endothelial cell migration and tube formation [30]. Collectively, these studies support a role for various immune mechanisms as contributors to pregnancy loss and fetal growth restriction. Further studies addressing monocyte activation will be essential in determining their importance as mediators of angiogenic dysregulation and abnormal placental development during preeclampsia.

Renin-Angiotensin System and Cytokines

The RAS is one of the most powerful endocrine systems involved in regulating arterial pressure. In addition to renal, vascular, and central effects, evidence now supports a proinflammatory mechanism for angiotensin II in hypertension. Angiotensin II enhances synthesis of TNF-α and IL-6 from immune cells; furthermore, it appears that in mice, IL-6 may be instrumental in mediating hypertension produced by angiotensin II [5]. Whether cytokines directly activate the RAS is not yet clear.

Recent data show that IL-6–treated pregnant rats had significantly higher plasma renin activity when compared with control pregnant animals [6•]. This effect of IL-6 on plasma renin activity could potentially lead to enhanced vasoconstriction, reduced pressure natriuresis, and hypertension [2••]; however, the quantitative importance of the RAS in mediating in vivo effects of IL-6

during pregnancy is unknown, and remains an important area of investigation.

Recent studies suggested that agonistic autoantibodies to the angiotensin II type I (AT1) receptor may play a role in the pathogenesis of preeclampsia [31]. Activation of Th1 cells and macrophages, both important mediators of inflammation during preeclampsia, leads to proliferation of specific antibody-producing cells or B lymphocytes, a potential source of AT1-AA [31]. These autoantibodies are thought to bind to the AT1 receptor and initiate a conformational change, leaving the binding site more freely accessible to angiotensin II. Autoantibody-mediated activation of AT1 causes overproduction of reactive oxygen species in trophoblasts or vascular smooth muscle via activation of NADPH oxidase or nuclear factor-κB and activation protein-1, which are transcriptional regulators of many immunomodulatory proteins [31]. Preeclamptic women producing AT1-AA also had significantly increased levels of sFlt-1 and reduced VEGF when compared with autoantibody-negative women [32]. Recent work by Zhou et al. [33] proposed that activating the AT1 receptor may induce sFlt-1 expression [33] and link AT1-AA and increased sFlt-1, characteristic of preeclamptic pregnancies [32–35]. Hubel et al. [32] recently demonstrated that AT1-AA production diminishes, but does not cease completely, and therefore may be a link among AT1-AA, preeclampsia, and subsequent cardiovascular disease.

Inflammatory Cytokines and the Nervous System

Some studies show that activity of the sympathetic branch of the autonomic nervous system is no different among women with normal pregnancies, normotensive nonpregnant women, and hypertensive nonpregnant women. To the contrary, other reports suggest that sympathetic nerve activity is increased as a mechanism contributing to normalization of blood pressure during the third trimester of pregnancy for many women. In preeclamptic pregnancies, however, sympathetic activity is clearly increased even beyond levels observed in normal late-term pregnancy [35]. Therefore, enhanced sympathetic activity likely has an important role in the pathophysiology of preeclampsia. Several factors may promote increased sympathetic activation during preeclampsia. For example, it is well known that the RAS and endothelin system are activated during preeclampsia, and that each can enhance sympathetic activity. Another putative contributor to sympathetic activation during preeclampsia is the presence of elevated inflammatory cytokines.

Few studies have examined the effect of specific inflammatory cytokines on blood pressure and sympathetic activity. One experiment demonstrated that an acute forebrain infusion of TNF-α increased arterial pressure, heart rate, and renal sympathetic nerve activity in rats. These effects were mediated by prostaglandins in the paraventricular nucleus [36]. Similarly, another study in rats showed that intracisternal or intravenous infusion of IL-1β increased blood pressure in a prostaglandin-dependent manner [35]. The authors proposed that likely sites of action for IL-1β in the brain were the circumventricular organ, area postremus, and choroid plexus because these regions lack a blood-brain barrier. In contrast to these studies, evidence also supports a role of centrally administered cytokines in lowering blood pressure and inhibiting sympathetic activity. For example, IL-1β has been reported to tonically reduce sympathetic activity [37]. In support of this, infusion of IL-1β into the lateral ventricle of rats lowers blood pressure—an effect that is prevented with a neutralizing antibody to IL-1β [37]. Whether chronic elevations in inflammatory cytokines contribute to increased sympathetic activity during preeclampsia remains to be determined.

Conclusions

The initiating event in preeclampsia is postulated to be reduced uteroplacental perfusion, leading to widespread dysfunction of the maternal vascular endothelium (Fig. 1). Inflammatory cytokines such as IL-6 and TNF-α are thought to be important links between placental ischemia and cardiovascular and renal dysfunction. Supporting a potential role of cytokines are findings that plasma levels of TNF-α and IL-6 are elevated in women with preeclampsia. Chronic reductions in placental perfusion in pregnant animals are associated with enhanced production of TNF-α and IL-6. In addition, chronic infusion of either TNF-α or IL-6 into normal pregnant rats results in significantly increased arterial pressure and decreased renal hemodynamics. TNF-α activates the endothelin system in placenta, renal, and vascular tissues, whereas IL-6 stimulates the RAS. Inflammatory mediators have also been shown to induce production of soluble proteins having antiangiogenic actions, and may thereby help cause the placental insufficiency accompanying preeclampsia. Proinflammatory cytokines may also activate the sympathetic nervous system. Collectively, these findings suggest that inflammatory cytokines may have an important role in causing hypertension and diminishing placental development in response to chronic reductions in uterine perfusion during pregnancy by activating multiple neurohumoral, antiangiogenic, and endothelial factors.

Although recent studies have shown that inflammatory cytokines (eg, TNF-α and IL-6) may have a part in mediating arterial pressure elevation in response to uterine perfusion reduction, their importance in mediating cardiovascular and renal alterations during preeclampsia in humans remains unclear. Furthermore, it is unknown whether drugs that inhibit the actions of inflammatory cytokines may be beneficial for women at high risk of developing preeclampsia. These important questions will

not be answered until well-controlled clinical studies using specific inhibitors of cytokines are performed in women with preeclampsia.

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