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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

Table 1
Immune-mediated models of pregnancy complications.

Model	Observations	References
TNF infusion *(rat)*	Pregnancy-specific ↑ MAP	[66–68]
IL-6 infusion *(rat)*	Pregnancy-specific ↑ MAP	[145,146]
RUPP-induced $CD4^+$ T cell adoptive transfer *(rat)*	Pregnancy-specific ↑ MAP, ↑ TNF, ↑ sFlt-1	[147]
Low-dose (1 μg/kg) LPS infusion *(rat)*	↑ MAP, ↑ TNF, ↑ IL-8, glomerular inflammation, platelet coagulopathy, albuminuria	[46,148,149]
Repeated, low-dose (10–40 μg/kg) LPS injections *(rat)*	FGR, fetal death, ↓ trophoblast invasion, ↓ SA remodelling, ↑ SA resistance index, placental nitrosative stress, altered placental morphometrics, ↑ coagulopathy Pregnancy-specific findings: ↑ MAP, ↑ TNF, renal alterations, proteinuria	[10,11,14]
High-dose (100 μg/kg) LPS injection *(rat)*	Fetal death, FGR, ↑ TNF, ↓ utero-placental perfusion, ↑ coagulopathy, placental hypoxia	[12,13,150]
aPL antibody injection *(mouse)*	Fetal death, decidual fibrin deposition	[47,151]
ATP infusion *(rat)*	↓ Trophoblast invasion, ↓SA remodelling, proteinuria, placental ischemia	[15,152]
CBA/J × DBA/2J matings *(mouse)*	Fetal death, FGR ↓SA remodelling, ↑ s-Flt-1, ↓VEGF, albuminuria, glomeruloendotheliosis	[153–155]
Intrauterine LPS injection *(mouse)*	100% PTL within 24 h	[35]

TNF, tumour necrosis factor; IL-6, interleukin-6; IL-8, interleukin-8; RUPP, reduced uterine perfusion pressure; LPS, lipopolysaccharide; aPL, anti-phospholipid; ATP, adenosine triphosphate; MAP, mean arterial pressure; sFlt-1, soluble fms-like tyrosine kinase-1; SA, spiral artery, VEGF, vascular endothelial growth factor; PTL, pre-term labour; h, hours.

inflammation plays a causal role in the pathogenesis of pregnancy complications, and is not just a consequence of altered utero-placental perfusion.

3. Factors contributing to alterations in utero-placental perfusion

3.1. Maternal hemostasis and pregnancy

Uncomplicated pregnancy has been described as a state of low-grade, well-compensated, intravascular coagulation [70–73]. Contributing to pregnancy-induced hypercoagulability is an increase in circulating levels of pro-coagulant clotting factors [72] and a reduction in fibrinolysis [74]. There is evidence that the shift towards hypercoagulability observed in uncomplicated pregnancy is magnified during pathological pregnancy. For example, histological examination of placentas revealed thrombotic lesions associated with PE [75], FGR [76] and fetal death [77]. While some studies describe a link between thrombophilia and increased risk for adverse pregnancy outcomes including PE [78], FGR [79] and fetal loss [80,81], other studies do not reveal such associations [82–84]. Nonetheless, alterations in maternal hemostasis may lead to insufficient utero-placental perfusion and/or poor placental development, thereby contributing to the pathogenesis of pregnancy complications [85,86]. Work from our laboratory revealed that inflammation-induced coagulopathies (ranging from hypercoagulability, hypocoagulability, hyperfibrinolysis and disseminated intravascular coagulation) are associated with altered utero-placental hemodynamics and fetal death in rat models [12–14]. Importantly, administration of the TNF inhibitor etanercept prevented inflammation-induced hemostatic alterations resulting in normalized utero-placental perfusion and reduced incidence of fetal loss [13].

It is well established that cells of the immune system play a critical role in the regulation of normal and pathological hemostasis and that coagulation and fibrinolytic factors have immunomodulatory functions [87]. In support of this concept, the pro-coagulant serine protease thrombin was shown to regulate the release of MCP-1 from vascular smooth muscle cells [88]. Moreover, apart from playing an important role in anti-coagulation, activated protein C (APC) was found to attenuate endotoxin-induced release of cytokines from immune cells both *in vivo* [89] and *in vitro* [90]. It is likely that the natural state of APC resistance characteristic of uncomplicated pregnancy [91] contributes to the spectrum of increased inflammation and thrombogenic potential observed during gestation. Amplification of APC resistance is observed in complications of pregnancy, where there is a strong link between inflammation, coagulation and adverse outcomes [92].

Tissue factor (TF) is one of the most important links between inflammation and hemostasis given that immune cells are capable of initiating coagulation, often as a result of TF activation [93,94]. Indeed, inhibition of TF was shown to prevent inflammation-induced coagulation [95]. While some reports reveal increased plasma levels of TF in women with adverse pregnancies [96,97], others do not [98]. However, syncytiotrophoblast microvesicles (STBMs) released from pre-eclamptic placentas exhibit increased TF activity [99]. Since the placenta is a known source of TF [100], it is possible that increased local release of TF contributes to placental pathology associated with adverse outcomes. Interestingly, Girardi and colleagues showed that fetal loss in a mouse model of APS was not a result of thrombosis despite the fact that inhibition of TF prevented fetal demise [101]. Instead TF was found to mediate the release of reactive oxygen species (ROS) from inflammatory cells, thereby leading to the development of anti-phospholipid antibody-induced fetal death. STBMs collected from pregnancies complicated by PE stimulate the production of pro-inflammatory cytokines including TNF [102], IL-6 and IL-8 [103]. These circulating STBMs may therefore contribute to pathological activation of the inflammatory and coagulation cascades associated with complications of pregnancy.

3.2. Maternal vasoconstriction

The role of vasoconstriction in utero-placental oxidative stress is often overlooked. Endothelin-1 is one of the most potent vasoconstrictors and has been associated with the pathogenesis of PE [67,104]. Using the reduced uterine perfusion pressure (RUPP) rat model, LaMarca and colleagues showed that the hypertension induced by TNF was mediated by ET-1 [67]. Moreover, impaired endothelium-dependent NO-cGMP-mediated relaxation and enhanced reactivity was shown in aortic strips isolated from rats infused with either TNF [105] or IL-6 compared with controls [106]. It remains to be determined whether spiral arteries *in vivo* respond similarly to ET-1, TNF or IL-6.

In the past, studies using *ex vivo* wire myography led to the concept that remodelled spiral arteries lacking vascular smooth muscle are incapable of responding to vasoactive molecules [3]. However, using intravital microscopy on mouse uterine vessels it was recently demonstrated that remodelling does not necessarily impair drug-induced vasoconstrictive responses *in vivo* [107]. Though the mechanism by which these vessels retain vasoactive properties remains undetermined, these findings provide evidence that the network of uterine vessels contributing to utero-placental blood flow may remain sensitive to vasoactive factors throughout

gestation, even when spiral artery remodelling has occurred. Though it is not known whether human remodelled spiral arteries fully retain vasoactivity, factors that perturb the local vascular tone prior to completion of vascular remodelling could potentially contribute to hypoxia or I/R injury leading to oxidative and nitrosative stress. Indeed, some inflammatory mediators are known to possess vasoactive properties.

4. Hypoxia, oxidative and nitrosative stress

An oxidatively stressed placenta is a common feature of complications of pregnancy [108]. Hypoxia and or/ischemia are known to contribute to the development of oxidative stress, however these terms are not synonymous [109]. In particular, a hypoxic placenta is a placenta exposed to low oxygen while an oxidatively stressed placenta is a placenta exposed to high levels of damaging ROS. Importantly, though ROS can arise as a consequence of hypoxia, a variety of endogenous and exogenous factors, including inflammatory cytokines, have been shown to regulate the production of these damaging molecules [110].

Hypoxia-inducible factor-1 (HIF-1) is an oxygen-sensitive transcription factor that bridges hypoxia, oxidative stress pathways and inflammation. HIF-1, is activated under low oxygen levels as a result of increased accumulation of its alpha (α) subunit (HIF-1α). Importantly, ROS have been shown to also increase HIF-1α levels through activation of NFκB [111]. It was commonly thought that hypoxia-induced responses and inflammatory pathways were mutually exclusive. However, it is now known that there is a strong link between inflammation and hypoxia-response pathways [112,113]. In support of this relationship are findings revealing that the transcription factors NFκB and HIF-1 regulate each other [112,114]. Hypoxia-induced HIF-1α accumulation was found to depend on basal NFκB activity, suggesting that inflammation is tightly linked to the hypoxic response [112]. Moreover, it is well established that during complications of human pregnancy, the placenta is exposed to pathological ischemia [115,116]. Importantly, levels of HIF-1α were found to be increased in placentas from pregnancies complicated by PE [117,118]. Given the intimate association between HIF-1, NFκB and ROS, it is reasonable to link the exaggerated maternal inflammatory response that characterizes adverse pregnancies, with local oxidative stress.

Complicated pregnancies are also associated with placental nitrosative stress. Altered utero-placental hemodynamics and local oxidative damage were shown to contribute to the increased levels of nitrotyrosine in placental vessels of women with PE [119]. Thus, it is likely that local ROS production and subsequent peroxynitrite formation results in the reduction of bioavailable NO and NO-mediated cGMP signalling. Moreover, since oxygen is required for NO synthesis, NO production is decreased under conditions of hypoxia and oxidative stress [120–122]. Deficiencies in NO production or bioavailability have been linked to the pathogenesis of PE [10,123–125], FGR [10,126], and fetal loss [127] in humans and animals models.

4.1. Activation of classical NO-signalling: a novel therapeutic target for pregnancy complications?

There have been recent attempts to determine whether activation of classical cGMP-mediated NO signalling improves pregnancy success in women afflicted by adverse complications. Sildenafil citrate is a pharmacological inhibitor of phosphodiesterase-5 (PDE-5) and therefore inhibits PDE-5-mediated cGMP degradation. The beneficial effects of sildenafil in the treatment of erectile dysfunction are commonly attributed to its vasodilatory properties. Studies have revealed that sildenafil improves utero-placental perfusion in animal models and therefore may be beneficial in the treatment of complicated pregnancies [128–131].

Our studies demonstrated that increases in spiral artery resistance index induced by inflammation were attenuated by the NO-mimetic glyceryl trinitrate (GTN) [10]. Since GTN is a well-known vasodilator, it is likely that some of its beneficial effects are due to maintenance of adequate utero-placental perfusion. Interestingly, we also reported that white blood cell counts in LPS-treated rats were normalized by GTN [10]. It is possible that GTN restores utero-placental hemodynamics, thereby preventing placental damage induced by I/R and widespread maternal systemic inflammation. Furthermore, our studies revealed that GTN prevented inflammation-induced fetal death associated with a spectrum of maternal coagulopathies [14]. Low concentrations (<1 μM) of NO are known to induce anti-aggregating effects in platelets by activating cGMP signalling [132], and low concentrations of GTN (<10 ηm) are known to reverse platelet aggregation [133]. Therefore, through the activation of cGMP signalling, GTN may function to inhibit or reverse platelet aggregation, thereby preventing the development of maternal coagulopathies and fetal death. It remains unknown whether the beneficial effects of GTN on preventing inflammation-induced FGR and features of PE [10] are attributable to cGMP signalling.

Though the precise mechanisms of GTN action have not been fully characterized, it is known that GTN functions as an NO-mimetic through the activation of cGMP [134]. Traditionally, GTN was believed to function as an NO-donor [135,136]. However, though GTN activity requires biotransformation [137], there is evidence that NO is released only when supraphysiological concentrations of GTN are present [136,138]. Interestingly, GTN is used to induce uterine relaxation and has tocolytic properties [139]. Together, these data indicate that GTN, via activation of classical NO signalling, may be beneficial in the treatment of inflammation-associated pregnancy complications due to its vasodilatory, anti-inflammatory and/or platelet anti-aggregating effects.

In recent years, much research has focused on angiogenic imbalance as a cause for PE and FGR. In 2003, Maynard and colleagues reported that women with PE have increased serum levels of soluble fms-like tyrosine kinase-1 (s-Flt1) and reduced levels of vascular endothelial growth factor (VEGF) and placental growth factor (PGF) [140]. By acting as an antagonist of VEGF and PGF, placental-derived sFlt-1 (released as a result of placental underperfusion) may contribute to the widespread endothelial dysfunction that characterizes PE. There is further evidence that increased maternal levels of soluble endoglin (sEng), the soluble receptor for transforming growth factor-beta (TGF-β), also contribute to endothelial dysfunction via a mechanism linked to impaired nitric oxide synthase (NOS) activity [141].

Interestingly, a correlation between maternal sFlt-1 levels and MAP in the RUPP model has been shown [142]. Etanercept administration to RUPP rats significantly reduced sFlt-1 levels, thereby implicating TNF in the modulation of sFlt-1 and MAP [143]. Additionally, studies using human placental explants have shown that placental release of sFlt-1 [144] and TNF [57] increases under hypoxic conditions. We reported that administration of GTN to human term placental explants reduced the hypoxia-induced release of sFlt-1 and sEng via inhibition of HIF-1α accumulation [144]. It is not known whether the use of a cGMP analogue would mimic these beneficial effects of GTN. However, the pre-clinical studies presented here provide a rationale to investigate whether activators of classical NO signalling (*i.e.* GTN, cGMP-mimetics, PDE-5 inhibitors) have therapeutic value in the prevention of pregnancy complications.

5. Conclusion

The studies presented here provide a rationale to further elucidate the contribution of abnormal maternal inflammation to altered utero-placental perfusion and the development of adverse pregnancy outcomes. We propose that inflammation-induced alterations in maternal hemostasis, local vasoconstriction and/or oxidative/nitrosative stress, are linked to the pathogenesis of negative pregnancy outcomes. Gaining mechanistic insight into the cellular and molecular mediators associated with complications of human pregnancy will be essential to developing successful intervention/prevention strategies. The additional benefits of preventing pregnancy complications extend beyond the immediate protection afforded to mother and child such that the risk of developing adult-onset diseases as a result of fetal programming may be ameliorated.

Conflict of interest

The authors declare no conflict of interest.

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