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Innate immunity, coagulation and placenta-related adverse pregnancy outcomes

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Abstract

Maternal immunity undergoes subtle adjustment in order to tolerate the semi-allogeneic embryo and maintain the host defense against potential pathogens. Concomitantly, coagulation systems change from an anti-coagulant state to a pro-coagulant state to meet the hemostatic challenge of placentation and delivery. Innate immunity and blood coagulation systems are the first line of defense to protect a host against exogenous challenges, including alloantigens and mechanical insults, and preserve the integrity of an organism. The interactions between coagulation and immune systems have been extensively studied. Immune cells play a pivotal role in the initiation of the coagulation cascade, whereas coagulation proteases display substantial immunomodulatory effects. Upon exogenous challenges, the immune and coagulation systems are capable of potentiating each other leading to a vicious cycle. Natural killer (NK) cells, macrophages (Mϕs) and dendritic cells (DCs) are three major innate immune cells that have been demonstrated to play essential roles in early pregnancy. However, immune maladaptation and hemostatic imbalance have been suggested to be responsible for adverse pregnant outcomes, such as preeclampsia (PE), miscarriage, recurrent spontaneous abortion (RSA) and intrauterine growth restriction (IUGR). In this review, we will summarize the mutual regulation between blood coagulation and innate immune systems as well as their roles in the maintenance of normal pregnancy and in the pathogenesis of adverse pregnancy outcomes.

Introduction

Inflammatory response and hemostasis are multi-factorial host defensive processes to infectious or noxious insults. When an organism is exposed to microbial invasion or trauma, innate immune cells will be recruited to the foci and initiate a series of immune responses to confine the damage. The host response to immune challenges requires coordination between innate and adaptive elements. As the first line of defense against exogenous challenges, the innate immune system generates an initial, nearly instantaneous, relatively non-specific response to potential pathogens [1]. The subsequent highly specific, albeit slower, adaptive immune response provides a far more efficient and long-term suppression of pathogens. While

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the innate immunity does not require the presence of an adaptive arm, the latter requires an intact innate immune system.

Mechanical trauma not only induces tissue damage but also generates vascular injury. Over the past two decades, an increasing body of evidence shows that the activation of coagulation is an integral part of inflammatory response. In addition to innate immune cells, the coagulation system also participate host defense and wound healing processes. Although immune system and coagulation system are not usually associated in time, emerging evidence indicates that there are extensive interactions between these two systems throughout vertebrae evolution [2]. Immune cells and inflammatory mediators are capable of modifying hemostasis, while molecules in coagulation pathway have considerable immuno-modulatory effects.

Pregnancy is a complex and well-regulated process, which leads to systemic changes, including hormonal homeostasis, cardiovascular kinetics and metabolism. The placenta is the first organ that develops immediately after implantation. Abnormal development of a placenta will result in adverse pregnancy outcomes. Preeclampsia is a multi-system disorder characterized by maternal hypertension, proteinuria and edema that complicates 5% to 10% of pregnancies [3]. It may be associated with IUGR and preterm delivery, and is a leading cause of maternal and fetal morbidity and mortality worldwide [4]. In addition to PE, preterm birth and abortion are common abnormal pregnancy outcomes. Preterm birth occurs in approximately 13% of all pregnancies, accounts for 75% of neonatal [5]. In all human conceptions, only 30% of fetuses are viable and more than 50% of which are lost prior to the first missed menstruation [6]. Furthermore, the risk of subsequent abortion is increased as the frequency of failed pregnancy increases; for example, the approximate failure rates in the index pregnancy are 24% after two, 30% after three and 50% after four spontaneous abortions [7]. RSA is defined as three or more consecutive spontaneous abortions, which affects about 1% of the childbearing women. Although the pathogenesis of PE, preterm birth and spontaneous abortion is thought to be related to the placenta, the exact mechanisms of these adverse pregnancy outcomes remain unclear. An increasing body of evidence indicates that the foundations of lifelong health are established *in utero* [8-11]. Prematurity contributes significantly to such major long-term morbidity as chronic lung disease, hearing and visual impairment, developmental delay and cerebral palsy. Prematurity and IUGR are also associated with subtle intellectual and behavioral problems during development [12,13]. Thus, placenta-related abnormal pregnancy is a source of stress and financial burden for affected families and society. While numerous factors, such as gene polymorphisms, dysregulated immune responses, aberrant angiogenesis and excessive coagulopathy have been postulated to be associated with adverse pregnancy outcomes, this review will highlight the role of immunity in conjunction with coagulation during the pathogenesis of placenta-related adverse pregnancy outcomes.

Regulation of coagulation by the immune system

The host response to outside challenges requires coordination between innate and adaptive immunity. When pathogens successfully invade an organism, innate immune system is the first line of host defense to encounter these intruders. The pathogens are first recognized and engulfed by professional phagocytes (e.g. Mϕs, DCs and neutrophils), among which DCs and Mϕs are major antigen-presenting cells (APCs). Chemokines are then secreted by pathogen-stimulated APCs and chemoattract more innate immune cells to the foci. Subsequently, the adaptive immunity takes place in the peripheral lymph nodes that is characterized by APC-mediated activation of naïve T- and B-lymphocytes, the key cell types of the adaptive immune system. Eventually, activated T- and B-lymphocytes are recruited back to the site of inflammation that augments the host defense.

In addition to immune system, coagulation pathway serves as another survival mechanism for an organism. Coagulation immediately fills up the wound to preserve the integrity of the tissues and plugs up the opening of the circulatory system to prevent further loss of blood. Coagulation involves both platelets and coagulation factors and is activated instantaneously after an injury. The coagulation cascade is classified to tissue factor (TF) (extrinsic) and contact activation (intrinsic) pathways that activate a final common pathway of factor X, thrombin and fibrin. Platelets immediately aggregate at the site of injury. Simultaneously, a complex cascade mediated by coagulation factors is initiated to form a fibrin meshwork, which reinforces the platelet plug. Interestingly, most of the inflammatory signals also trigger pro-coagulant signals to the coagulation cascade. Phylogenetically, many of the inflammatory cytokines of innate immune system and coagulation molecules, such as CD40 ligand from platelets versus tumor necrosis factor (TNF) family members [14] and TF versus cytokine receptors [15], share structural homologies, indicating the crosstalk between innate immune system and coagulation. Based on the observation of septic shock, the actions of the innate system and coagulation system are remarkably homologous.

When pathogens trigger innate immune response, inflammatory cytokines are secreted by innate immune cells. Microbial components and pro-inflammatory cytokines, including endotoxin, IL-6, TNF-α, IL-1, IL-2 and C5a, can induce the de novo synthesis of TF in endothelial cells and leukocytes, especially monocytes [16-19]. The coagulation cascade is then activated by exposure of TF to the blood. The coagulation can also be enhanced by complement-activated formation of plasma membrane enriched in negatively charged phospholipids [20]. Furthermore, platelet activating factor, L- and P-selectin as well as Mac-1 integrin production in endothelial cells is up-regulated, that either synergistically increase the monocyte TF response or potentially amplify the pro-coagulant response [21-24]. Meanwhile, the chemotaxis and activation of neutrophils and monocytes are promoted via the generation of thrombin and fibrinogen/fibrin degradation product [25,26]. Thus, a vicious cycle between immune response and coagulation is established. Coagulation is counterbalanced by natural anti-coagulant pathways, including protein C anti-coagulant pathways, anti-thrombin-heparin and tissue factor pathway inhibitor (TFPI) [27]. During acute inflammatory response, anti-thrombin is consumed and inactivated [28]. The vascular heparin-like molecules and protein C pathway appear to be inhibited by endotoxin and inflammatory cytokines, such as IL-1β and TNF-α, through down-regulation of thrombomodulin and the endothelial protein C receptor (EPCR) [29-31]. Fibrinolysis is also suppressed by increased production of plasminogen activator inhibitor-1 (PAI-1) [32,33].

Regulation of immune system by coagulation

Fibrin/platelet deposition is one of the characteristics of inflammation that helps an organism to wall off infection and accelerate wound healing. Several molecules in the coagulation cascade, such as thrombin and factor Xa have been shown to be pro-inflammatory [34,35]. Both molecules activate mast cells to induce degranulation with the secretion of bioamines [34,36]. Thrombin is a serine protease, which cleaves fibrinogen to fibrin and promotes platelet aggregation and degranulation for clot formation. However, thrombin also mediates different cellular events in a catalytic activity-independent manner [15,37]. After binding to its receptor, protease-activated receptors (PARs), thrombin is able to induce cytokine expression, including IL-6, IL-8, MCP-1 and MIF production in various cell types [38-42]. Acting through NFκB, thrombin, factor Xa and TF-VIIa complex enhance the expression of adhesion molecules in leukocytes [43-45]. Binding of TF-VIIa complex to PAR-2 also affects neutrophils infiltration and TNF-α and IL-1β expression [46]. Besides, thrombin and fibrin/fibrinogen degradation products also exhibit chemotactic activity for neutrophils and monocytes [37,47].

On the contrary, anti-thrombin down-regulates factor X receptor, CD11b/CD18, on leukocytes and leads to decrease in leukocyte adhesion [27]. The treatment of endothelial cells with anti-thrombin increases prostacyclin formation [48] and decreases NFκB signaling and IL-6 expression [49,50]. Both thrombomodulin and activated protein C attenuate NFκB signaling [51,52]. In recent years, the role of activated protein C in anti-inflammatory response has been inspired by the studies in human sepsis. Activated protein C was demonstrated to reduce leukocyte infiltration [51-54], suppress TNF-α and NFκB expression, inhibit cytokine signaling, interfere with cytokine-induced up-regulation of leukocyte adhesion molecules as well as inflammation- and apoptosis-related genes [55-57].

Immediately after a blood vessel injury, platelets form a hemostatic plug at the site of injury and secrete factors to initiate inflammatory response that chemoattracts and activates leukocytes. Due to their early role in coagulation in response to injury, platelets can act as a sentinel cell and provide information transfer in host defense similar to such innate immune cells as mast cells, Mϕs and DCs. Interestingly, the interaction between platelets and innate defensive cells, including polymorphonuclear cells, monocytes, mast cells, Mϕs and DCs, has been well-recognized. Activated platelets release inflammatory and immune-modulating factors, which can affect the cells of the innate and adaptive immune systems [58-60]. For instance, CXCL4 and CXCL7 secreted by platelets [58] in the early response to injury are recognized by neutrophils and modulate their activities [61]. In addition to CXC chemokines, platelets also secrete such CC chemokines as CCL3, CCL5 and CCL7 displaying similar diverse functions in regulating monocyte activities [62,63]. Platelets also produce pro-inflammatory lipids and cytokines, such as cyclooxygenase-1 (COX-1), COX-2, thromboxane A_2 (TXA_2) [64] and IL-1β [65]. Besides the ability to modulate immune cell activity via secreted molecules, platelets also interact with target cells through cell-cell adhesion. P-selectin on the surface of platelets mediates the induction of chemokine and urokinase plasminogen activator receptor expression in neutrophils and monocytes by binding P-selectin glycoprotein-1 (PSGL-1) [66,67]. Furthermore, binding of CD40 ligand on platelets and CD40 on B cells, monocytes, Mϕs, DCs and endothelial cells induces multiple inflammatory responses [68]. Thus, platelets can be considered as one of the cell types bridging inflammation and coagulation.

Dendritic cells are the major antigen-presenting cell links innate and adaptive immune systems. Normally, platelets and tissue DCs do not interact with each other. However, the CD40 ligand and IL-1β produced by activated platelets in bleeding tissue can serve as an endogenous danger signal to DCs and quickly initiate DC maturation [1,68]. DC recruitment can also be facilitated by platelets [69]. Platelets form tight aggregates with monocytes. P-selectin on activated platelets may induce differentiation of DCs from monocytes [70,71]. In a recent report, coagulation was shown to amplify inflammation through PAR1 signaling in DCs [72]. Conversely, activated platelets may suppress secretion of pro-inflammatory cytokines from DCs [73].

Coagulation and placenta-related abnormal pregnancy

During normal pregnancy, there is a marked increase in the pro-coagulant activity and a down-regulation in levels of physiological anti-coagulants. Such changes meet the hemostatic challenge of placentation and delivery but may account for adverse pregnancy outcomes in women [74]. Blood coagulation and platelet abnormalities may lead to hemorrhagic and thrombotic defects. Thrombophilic defects are extremely common in RSA compared to hemorrhagic defects [75]. The insufficient fibrin formation leads to hemorrhage, thus precluding adequate implantation of the fertilized ovum into the uterus. Patients having hemorrhagic defects, including factor XIII, XII, X, VII, V, II deficiency, von Willebrand disease, carriers of hemophilia and fibrinogen defects, are susceptible to RSA [76-79].

Inherited thrombophilic conditions have been associated a variety of pregnancy complications including fetal loss, preeclampsia, abruption and intrauterine growth restriction [80,81], although other studies have not confirmed the association [82,83]. While initial case control studies have confirmed a positive association between inherited thrombophilic conditions and pregnancy complications [84], larger prospective evaluations have not confirmed the association [85], suggesting that larger prospective studies are still needed to confirm the association between inherited thrombophilias and pregnancy complications [86].

Thrombosis associated with fetal wastage is most common in the first trimester. The earlier this presents in pregnancy, the smaller the placental and uterine vessels will be, therefore, the propensity to undergo partial or total occlusion by thrombus formation will be greater [75]. Despite the strong association between thrombosis and adverse pregnancy outcomes, its pathogenic role in the development of adverse pregnant has not been elucidated. Moreover, it is not clear why adverse pregnancies only occur in some of the women having thrombophilia. The involvement of additional factors in the regulation of coagulation and immune response in placenta need to be further scrutinized.

Recent data suggest that trophoblasts produce endothelial regulators of hemostasis, such as thrombomodulin (TM), endothelial protein C receptor (EPCR) and tissue factor pathway inhibitor (TFPI) [87,88]. Sood, et al. identified some candidate fetal genes expressed by trophoblasts that were potential promoters of thrombophilia-associated pregnancy complications [89].

Innate immunity and placenta-related abnormal pregnancy

In non-pregnant women, the allogeneic tissues will be rejected by maternal immune system. However, the semi-allogeneic fetus survives in normal pregnancy. Robertson et al. [3] proposed that pregnancy was a state of “altered immune competence”. Indeed, peripheral blood mononuclear cells isolated from pregnant women were found to elicit stronger Th-2 immune response compared to non-pregnant women [90,91]. High levels of estradiol, HCG and progesterone during the pregnancy can inhibit secretion of such NFkB-induced inflammatory cytokines as IL-1, -2, -3, -5, -8, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) by Mϕs and T cells, while enhance the secretion of the monocyte-deactivating cytokine, IL-10 [92-94]. Decidual cells, syncytiotrophoblasts and cytotrophoblasts can secrete an array of pregnancy-associated molecules to suppress pro-inflammatory activation of decidual Mϕs and NK cells [95]. Therefore, there must be a balance between Th-1 and Th-2 immune responses during normal pregnancy.

After implantation, extravillous cytotrophoblasts penetrate and traverse the underlying decidua and myometrium [96]. During this invasive process, cytotrophoblasts surround, breach and transform the smooth muscle and endothelium of endometrial spiral arteries and arterioles to produce large-bore, low-resistance vessels [97]. The resulting increased uterine blood flow to the intervillous space is required for growth, development and survival of the fetal-placental unit [98,99].

Shallow cytotrophoblast invasion [98-100] will lead to incomplete uterine vascular conversion, an inadequate fetal blood supply, and a pathological hypoxic milieu [101]. This placental defect is associated with persistence of a pro-inflammatory environment and is considered as a failure of maternal immune tolerance required for normal cytotrophoblast invasion [91,100].

Mϕs and DCs initiate innate and adaptive immunity and are involved in developing immune tolerance. These antigen-presenting cells are uniquely capable of modulating the balance between the innate and adaptive immune systems to provide protection against pathogens yet confer immune tolerance to the semi-allogeneic embryo [102,103]. A marked excess of Mϕs

in the preeclamptic decidua has been observed [104]. Other than Mϕs, mature and immature DC infiltration in preeclamptic decidua was also reported [105]. Although uterine NK (uNK) cells have been suggested to be required for the success of pregnancy and shown to be the main immune cells in the implantation site [106,107], an increase of uNK cells has been shown in decidual parietalis in patients with miscarriage [108]. Interestingly, an increase of Mϕs, tissue factor and coagulation factor IX around anchoring villi in recurrent abortion was demonstrated [109], suggesting the role of Mϕs and coagulopathy as well as their potential relationship during the pathogenesis of miscarriage. The link between abnormal pregnancy and aberrant maternal immune responses [107] and the versatility exhibited by uNK cells, Mϕs and DCs in mediating both immune activation and tolerance reveal the importance of the study of the regulation of uNK cell, Mϕ and DC infiltration and activation in the decidua of placenta-related pregnant complications.

The role of NK cells in adverse pregnancy outcomes

NK cells play a fundamental role in the innate immune response through their ability to secrete cytokines and kill target cells without prior sensitization. uNK cells constitute approximately 70 - 75% of the decidual immune cells during early pregnancy but undergo extensive apoptosis upon the onset of trophoblast infiltration and are virtually absent at term [110,111]. Uterine NK cells are thought to support remodeling of the uterine spiral arteries and to facilitate successful placentation through the regulation of trophoblast invasion [106,112]. Mouse studies demonstrated that mice deficient in uNK cells displayed incomplete widening of uterine vessels and significant decidual pathology [113]. In peripheral blood, 95% of NK cells are $CD56^{dim}CD16^{bright}$ and approximately 5% are $CD56^{bright}CD16^{dim}$, however, the majority of uNK cells are $CD56^{bright}CD16^{dim}$ [114,115]. Basically, $CD56^{dim}CD16^{bright}$ NK cells are highly cytotoxic whereas the $CD56^{bright}CD16^{dim}$ uNK cells have low cytotoxic capacity but effectively secrete cytokines, such as IFN-γ, vascular endothelial growth factor (VEGF), angiopoietin-2 (Ang-2) and placental growth factor (PlGF) which may facilitate vascular remolding and normal endometrial decidualization [116-118].

NK cell functions, specifically cytokine production and cytotoxicity, are tightly regulated by the inhibitory and excitatory receptors which can recognize the ubiquitously expressed major histocompatibility complex class I (MHC-I) proteins on target cells [119]. Functionally, inhibitory receptors can block NK cell activation signals originated from excitatory receptors and leave NK cells in a quiescent state. In early development, the blastocyst divides into two cell lineages. The inner cells give rise to the embryo while the outer cells develop into the fetal portion of the placenta, including trophoblasts, some of which have direct contact with the maternal immune system [120]. Human and murine trophoblasts are devoid of MHC-II molecules and only express limited MHC-I [110] which renders them the potential target of an allogeneic immune response. In humans, the studies of maternal KIRs (on NK cells) and fetal HLA-C genes (on extravillous trophoblasts) pairing in PE indicate that strong KIR-HLA-C inhibitory signals predispose women to PE by inhibiting the expression of growth factors. This inhibition in turn impairs trophoblast invasion, spiral artery remodeling and thus, the overall quality of placentation. By contrast, in women with unexplained RSA, the relatively lower inhibitory receptor expression or higher MHC-I-specific excitatory receptor expression results in hyperactivation and cytotoxicity of uNK cells [121].

The role of macrophages in adverse pregnancy outcomes

Mϕs comprise 20 – 25% of decidual leukocytes in early pregnancy. Unlike uNK cells, the number of Mϕs remains relatively constant throughout gestation [122]. They are recruited to the cytotrophoblast shell in close association with invading extravillous trophoblasts through expression of a variety of receptor-ligand pairs. During placentation, apoptotic bodies are removed by Mϕs [123-125]. Ingestion of low levels of apoptotic debris has been shown to

reinforce the secretion of Th2 cytokines by Mϕs [126]. Although apoptosis is required for normal placentation, excess apoptosis and insufficient clearance of apoptotic bodies enhance the secretion of pro-inflammatory cytokines, such as TNF-α and IFN-γ, by activated Mϕs [127]. Consequently, these pro-inflammatory cytokines will induce excess trophoblast apoptosis and lead to adverse pregnant outcomes, including PE, IUGR and abortion [128, 129].

Shallow trophoblast invasion and impaired spiral artery remodeling as well as decreased placental vascularity [130] were found in pregnancies complicated by PE and in some cases of IUGR and abortion [131-133]. Excess inflammation is postulated to be associated with PE [134], IUGR and abortion, suggesting that altered behavior of uterine leukocytes may account for the defective placentation.

An increased infiltration of Mϕs was found in decidua complicated by PE and IUGR. Mϕs were also shown to mediate fetal demise in a mouse model of abortion [135]. In addition, the expression of such cytokines involved in the recruitment and development of Mϕs as M-CSF, GM-CSF, IL-8, MCP-1, MIP-1b, RANTES and MCP-3 are increased in preeclamptic decidua [95,105]. The production of TNF-α [136], plasminogen activator inhibitor 1 (PAI-1) [137]and inducible nitric oxide synthase (iNOS) [138] by activated Mϕs may result in impaired trophoblast invasion and spiral artery remodeling. In addition, Mϕs are key mediators of all steps during angiogenesis due to their ability to secrete VEGF, matrix metalloproteinases (MMPs), fibroblast growth factor, fibronectin and collagen [139]. Girardi et al. found that decreased levels of free VEGF in a mouse model of IUGR and abortion coincided with increased levels of sFlt-1 and an influx of Mϕs in the decidua [140]. However, the role of Mϕs in the impaired placental angiogenesis remains unclear.

The role of dendritic cells in adverse pregnancy outcomes

DCs are specialized antigen-presenting and phagocytic cells that play important role in mediating both innate and subsequent adaptive immune responses. The maternal–fetal interface is an immunologically privileged site that provides immune tolerance to the semi-allogeneic fetus while maintains host defense against possible pathogens. Immature myeloid DCs are found in tissues and may maintain tolerance via induction of T-cell anergy or regulatory T-cells, whereas mature DCs may promote a Th1 immune response. Gardner suggested that decidual DCs in the proximity of extravillous trophoblasts at the implantation site are HLA-DR$^+$, CD11c$^+$, DEC-205$^+$, CD40$^+$, DC-SIGN$^+$, CD1a$^+$, CD123$^+$, indicating that the majority of the decidual DCs in normal pregnancy are immature DCs [141]. Normal pregnant mice show an expansion of CD4$^+$CD25$^+$ and IL-10$^+$ Treg cells at the periphery compared to non-pregnant mice [142]. Significantly decreased CD4$^+$CD25^{bright} T cells and elevated mature DCs in RSA or PE indicate that mature DCs may induce inflammatory response in decidua. Our study demonstrated that the recruitment of DCs as well as the expression of their recruiting-chemokines was significantly higher in preeclamptic decidua compared to gestational age-matched control [105]. However, unlike Mϕs, DCs did not directly impede trophoblast invasion. Plaks et al. suggested that DCs might regulate tissue remodeling and angiogenesis via such important blood vessel maturing factors as sFlt1 and TGF-β [143].

Conclusions

Normal pregnancy is a mild inflammatory state and the adverse pregnancy outcomes seem to be an exaggeration of the norm. This deteriorated inflammatory state is associated with maternal leukocyte activation, especially as related to local uterine innate immunity (Fig. 1). In addition, the release of cytokines from immune cells and uteroplacental tissues, endothelial cell activation as well as immune/coagulation interaction are also observed. As indicated, the inflammatory signals may induce the synthesis of TF in endothelial cells and monocytes to

trigger the coagulation cascade [16-19]. The coagulation system then in turn enhances the chemoattraction and activation of the leukocytes by thrombin or factors released from activated platelets. Through this vicious cycle between immune response and coagulation, the inflammatory state is therefore worsened. The enhanced expression of such molecules as TNF-α, IL-1, IFN-γ, sFlt1 and iNOS by activated immune cells was shown to be important during the formation of a dysfunctional placenta in complications of pregnancy through the induction of excessive trophoblast apoptosis, shallow trophoblast invasion, and impaired spiral artery remodeling [127,136,138,144]. Consequently, this leads to various adverse pregnancy outcomes. Moreover, Lockwood reported that thrombin, a critical coagulation factor activated by tissue factor, could block the angiogenic effects of VEGF and placental growth factor by enhancing the expression of sFlt-1 in first trimester decidual cells that might result in incomplete remodeling of the spiral arteries [144]. Given the pivotal roles of the coagulation and inflammatory cascades in the etiopathogenesis of PE, IUGR, abruption, fetal loss, and preterm delivery, their precise interaction in this placenta mediated complications still requires further scrutinization.

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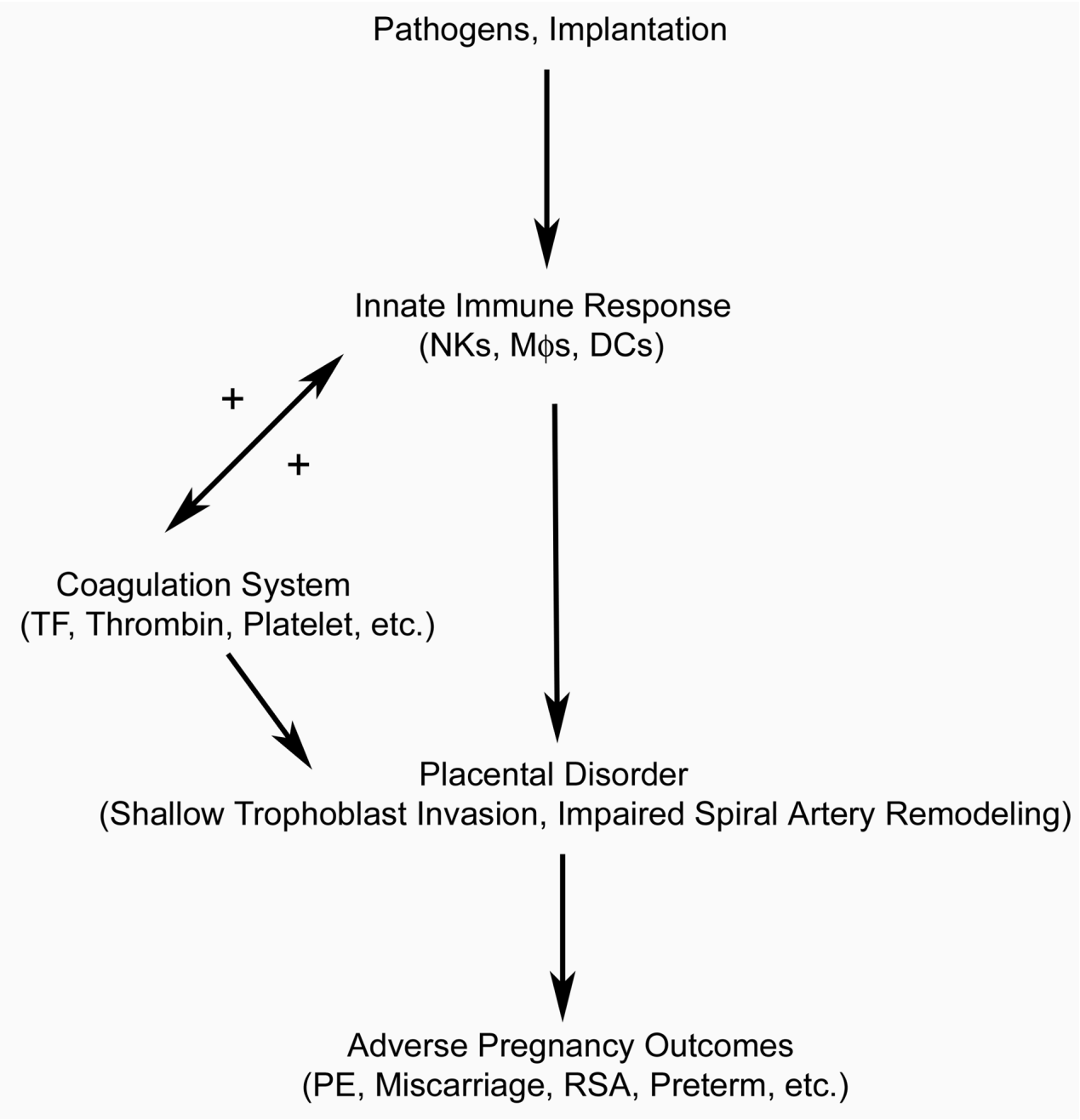

Fig. 1.
Hypothesized effects of immune-coagulation interaction on pregnancy