THE IMMUNOLOGICAL ASPECTS OF PREECLAMPSIA

Maya Khaerunnisa Puspitasari[1,2], Anita Deborah Anwar[2], Akhmad Yogi Pramatirta[2], Budi Handono[2]

[1] Department of Obstetrics and Gynecology, Dr. Drajat Prawiranegara Serang Hospital, [2]Maternal Fetal Medicine Division of Department of Obstetrics and Gynecology, Faculty of Medicine Padjadjaran University, Bandung, Indonesia

* Correspondence Email: maya22004@mail.unpad.ac.id

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ABSTRACT
The pathogenesis of preeclampsia remains uncertain; nevertheless, endothelial dysfunction, aberrant angiogenesis, trophoblastic invasion, and insufficient remodeling of the spiral artery have been recognized as significant factors. The appropriate remodeling of the spiral artery into dilated, elastic, and low-resistance blood capillaries facilitates an unobstructed delivery of oxygen and nutrients to the fetus. This necessitates the appropriate infiltration of extravillous trophoblasts and the substitution of maternal endothelial cells. Inappropriate activation of the innate immune system and persistent inflammation might result in placental malfunction or inadequate maternal vascular adaptation, hence contributing to the onset of preeclampsia. Immune cells are essential for effective implantation and the formation of the maternal-fetal interaction. Nonetheless, immunological dysregulation and inflammation contribute to the onset of preeclampsia. The decidua contains several types of immune cells, including distinct subtypes of T cells, B cells, NK cells, and macrophages. During a healthy pregnancy, these cells are controlled to facilitate fetal tolerance; nevertheless, they may become disordered, leading to inflammation, oxidative stress, and endothelial dysfunction, as observed in preeclampsia. The etiology of preeclampsia is multifaceted; nonetheless, therapies aimed at the immune system has therapeutic potential. Consequently, comprehending the interplay between the innate and adaptive immune systems in facilitating maternal-fetal tolerance is essential for the advancement of innovative therapeutic strategies for hypertensive diseases during pregnancy.

Introduction

Preeclampsia (PE) is a unique disease of pregnancy and affects many organ systems. PE can cause maternal and fetal death. The incidence rate is about 2-8%. PE is referred to as one of thenGreat Obstetrical Syndromes. Approximately 50,000-60,000 pregnant women worldwide die each year due to PE, and the highest mortality rate occurs in developing countries, including Indonesia.[1]

Preeclampsia is defined as hypertension (systolic blood pressure ≥ 140mmHg and or diastolic blood pressure ≥ 90mmHg), which occurs for the first time after 20 weeks of gestation and may include one or more of the following clinical manifestations: proteinuria (≥ 300mg/day), maternal organ damage (liver, kidney, or nervous system), blood system involvement (such as thrombocytopenia), or evidence of placental dysfunction (such as stunted fetal growth and/or abnormal uterine artery doppler). Severe preeclampsia is characterized by significantly elevated blood pressure (≥ 160/110 mmHg), proteinuria, pulmonary edema, severe neurological deficit symptoms, liver and kidney dysfunction, or thrombocytopenia. Preeclampsia can gradually progress to eclampsia, emergent hypertension, acute renal failure, hepatic subcapsular hematoma, heart failure, and can also lead to placental abruption and fetal death in utero. Furthermore, the risk of developing cardiovascular disease later in life is 12x higher in preeclamptic women. [1]

Preeclampsia can be classified into early-onset preeclampsia or late-onset preeclampsia, depending on whether the onset occurs before or after 34 weeks. Although the features of both conditions are similar, they have different maternal and fetal outcomes, heritability, biochemical markers and clinical features. Another difference between the two is that early-onset preeclampsia is complicated by the presence of stunted fetal growth. Eclampsia is a severe, life-threatening complication of pregnancy that occurs in 0.8% of pregnant women diagnosed with high blood pressure and causes seizures during and after delivery. Hemolysis, elevated liver enzymes and platelets (HELLP) syndrome is a severe complication of preeclampsia that causes blood hemolysis, liver dysfunction and thrombocytopenia. The incidence is 0.1-0.6% in all pregnancies and 4-12% in patients with preeclampsia. [2]

The etiology of preeclampsia is unclear, but endothelial dysfunction, inappropriate angiogenesis, trophoblastic invasion and inadequate remodeling of the spiral artery have all been identified as major contributors. Proper remodeling of the spiral artery into dilated, elastic and low resistance blood vessels allows for an unrestricted supply of fetal oxygen and nutrients. This requires proper invasion of extravillous trophoblasts and replacement of maternal endothelial cells. Inappropriate activation of the innate immune system and continued inflammation, however, can lead to placental dysfunction or poor maternal vascular adaption and contribute to the development of preeclampsia. [1–3]

The human embryo is a maternal *semiallograft*. Interactions between various immune cells, decidual stromal cells, and fetal trophoblasts in the maternal decidua begin at embryo implantation and continue throughout pregnancy. This interaction is known as the *maternal-fetal interface*. This interface is the first place the maternal immune system comes into contact with fetal alloantigens and is also an important site for placenta formation. The success of a pregnancy is highly dependent on the immune tolerance of the maternal immune system to the embryo. Imbalance between immunity and tolerance at the *maternal-fetal interface* has been confirmed to be associated with spontaneous abortion in early pregnancy, preeclampsia and stunted fetal growth. Many studies have shown the association of preeclampsia with systemic or local immune abnormalities. Both the innate and adaptive immune systems, such as neutrophils, monocytes, natural killer cells and T cells, contribute to the onset and progression of preeclampsia.[1,4] This study aims to elucidate the mechanism of immune tolerance at the *maternal-fetal interface* and its role in the pathogenesis of preeclampsia to provide new insights to explore the pathogenesis of preeclampsia and its prevention strategies from the perspective of immunity.

Immune System in Normal Pregnancy

In normal pregnancy, the maternal immune system must balance the fetus' semi-allogenic immune tolerance to prevent the mother from disease. However, disruption to this balance is associated with the development of preeclampsia. During pregnancy, women experience time-dependent shifts in the activation of the innate and adaptive immune systems, and this immune system dysregulation leads to adverse effects for both mother and fetus.[5]

The immune system encompasses all organ systems and provides protection from pathogens and foreign bodies. This defense mechanism is influenced by the success of well-organized responses by innate and adaptive immune responses. The innate immune response is present at birth and acts as the first line of defense by rapidly engaging in protective actions against pathogens. The adaptive immune response acts as a secondary antigen-specific response. It is organized by innate immune cells with the ability to retain antigen memory, correlating with a rapid response in future encounters (Figure 1).[3,6]

The overall maternal innate immune system plays an important role during pregnancy to ensure protection from pathogens, while inducing tolerance to semi-allogeneic fetal and placental development. This is achieved in a complex way through the balance of various cell functions and interactions between cells of the innate immune system and trophoblast cells at the right time.

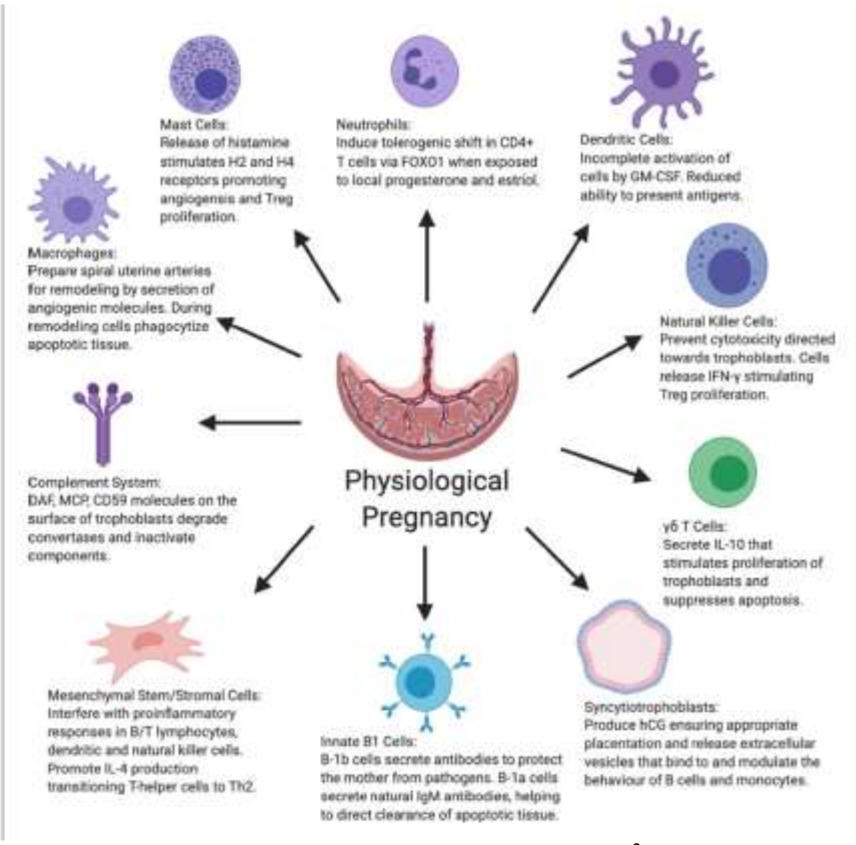

Figure 1. Different types of immune cells in pregnancy physiology[3]

Desidualization is one of the critical events to achieve a successful pregnancy. The decidua provides the embryo with an adequate supply of nutrients and a privileged immunological site before placentation. In addition to the decidual stromal cells, the decidua is enriched with several immune cells such as, NK cells, macrophages and T cells. The decidual immune cells jointly contribute to the remodeling of the decidual immune homeostasis, further promoting the establishment and maintenance of a good pregnancy. Dysfunction of decidual immune cells is closely related to pregnancy complications, including failure of placentation, recurrent miscarriage, preeclampsia, and stunted fetal growth. Therefore, the maternal immune system is an important key to placental homeostasis.

Pathologic Changes in Preeclampsia

The cause of gestational hypertension, preeclampsia, eclampsia, or HELLP syndrome is still unknown, but several underlying conditions such as pre-existing hypertension, renal disease, and diabetes increase the risk of preeclampsia or gestational hypertension. The main mechanisms underlying the occurrence of hypertensive disorders in pregnancy include endothelial dysfunction, angiogenesis, impaired remodeling of the spiral artery, and inadequate trophoblastic invasion. Notably, immune system dysregulation and inflammation are important contributors to placental and renal dysfunction leading to hypertension (figures 2 and 3). [2]

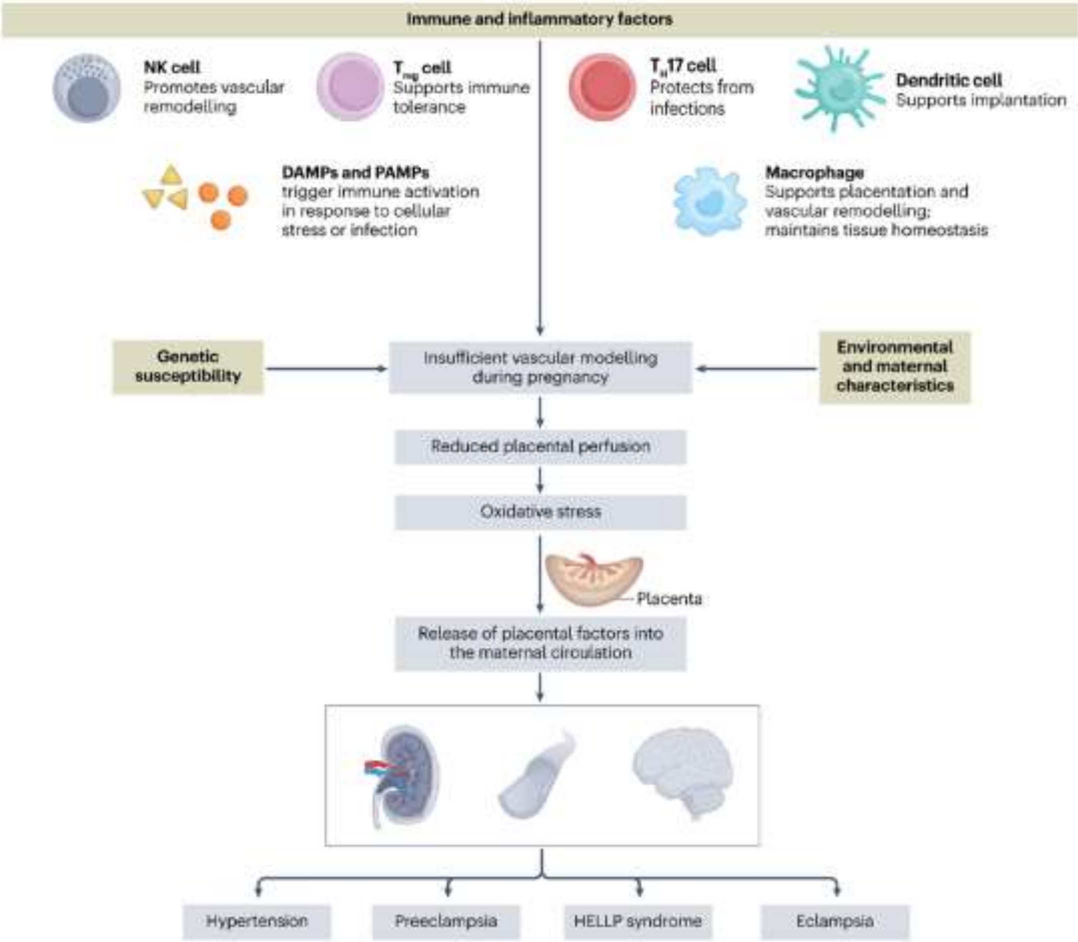

Figure 2. Illustration of Immunologic factors in preeclampsia[2]

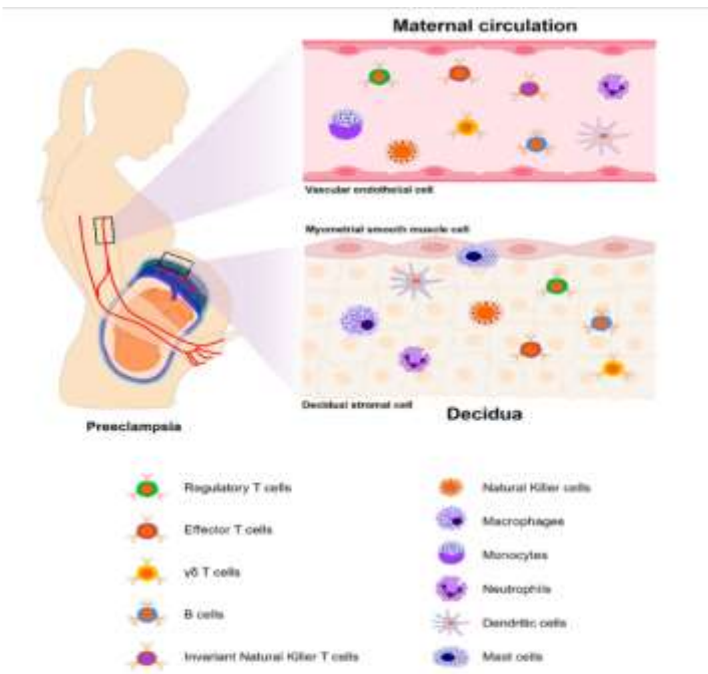

Figure 3. Immunologic aspects in preeclampsia

Placentation and the formation of the *maternal-fetal interface* are complex processes that involve careful regulation by trophoblasts and immune cells. For example, fetal trophoblast invasion of the maternal endometrium is essential to establish the maternal-fetal blood supply in pregnancy. These trophoblasts promote remodeling of the maternal spiral artery into a low-resistance blood vessel throughout pregnancy by replacing the endothelial cells of the spiral artery; smooth muscle cells and their autonomic innervation are also lost, further reducing vascular resistance. In preeclampsia, extravillous trophoblast invasion into the myometrium is insufficient, leading to the formation of smaller vessels with higher resistance than in normal pregnancies. In addition, the spiral artery in preeclampsia fails to maintain adequate perfusion to support fetal growth, leading to progressive placental damage due to ischemia and hypoxia. The hypoxic placenta releases vasoactive factors such as tumor necrosis factor (TNF), sFLT-1 (also called VEGFR1 receptor), and *soluble endoglin*. These factors cause endothelial dysfunction and increased vascular resistance (figure 4). [2]

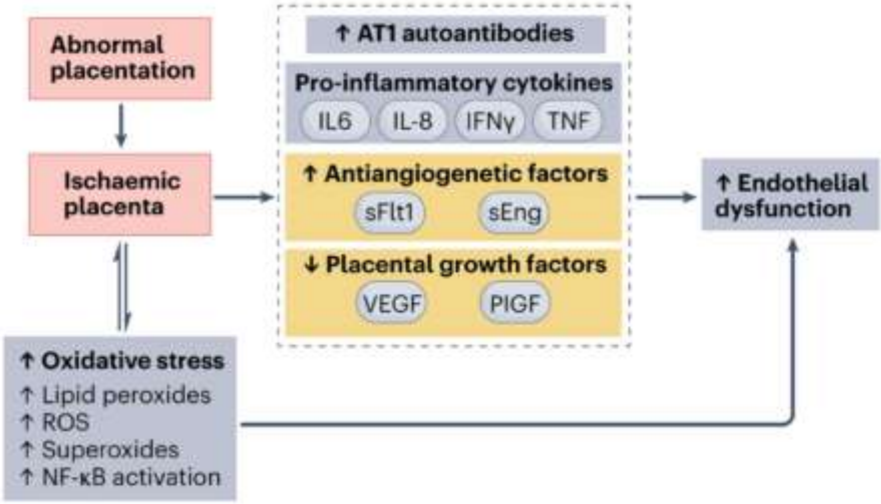

Figure 4. Endothelial Dysfunction in Preeclampsia[2]

In a healthy pregnancy, the immune response must be balanced to achieve successful implantation while protecting the fetus from immune compromise. Chronic immune activation of CD4+ T cells, se;B, NK cells, and macrophages, as well as activation of inflammatory pathways involving the complement system and agonistic anti-angiotensin II type 1 receptor autoantibodies (AT1-AAs) are associated with placental ischemia and have been implicated in the pathogenesis of preeclampsia. These immunological factors are thought to sensitize women with preeclampsia to vasoconstrictors. The immune cell profile in pregnancy is dynamic but early remodeling of the spiral artery, for example, relies on an anti-inflammatory environment to ensure maternal-fetal tolerance. However, in contrast to normal pregnancy, pro-inflammatory cytokines such as TNF, IL-6 and IL-17 increase during preeclampsia and promote a cytotoxic inflammatory response. For example, in decidual tissue from chorionic villus sampling, women with preeclampsia had high levels of IL6 mRNA38. TNF and IL-6 are involved in endothelial dysfunction through decreased nitric oxide (NO) production and increased endothelin, and also modulate vascular resistance by increasing the production of anti-angiogenic phacoes such as sFlt-1.

Preeclampsia is also associated with pathological release of free radicals by the placenta. In a healthy pregnancy, maternal and fetal oxygen demand increases oxygen metabolism at the mitochondrial level, which generates free radicals, including superoxide ions. Importantly, reactive oxygen species (ROS) control energy metabolism, cell proliferation and apoptosis, intracellular and intercellular signaling pathways, and biochemical recombination through oxidative-reductive processes. Therefore, palsenta ROS are present in healthy pregnancies and are necessary for cell replication, proliferation, and maturation processes that support embryonic development and maintenance of pregnancy. However, in preeclampsia there is impaired uteroplacental blood flow creating an imbalance between ROS and antioxidant production, leading to oxidative stress, inflammation, and syncytiotrophoblast apoptosis (figure 5). This oxidative stress affects the vascular response, causing inadequate vascular remodeling, smooth muscle hypertrophy, and cellular apoptosis.

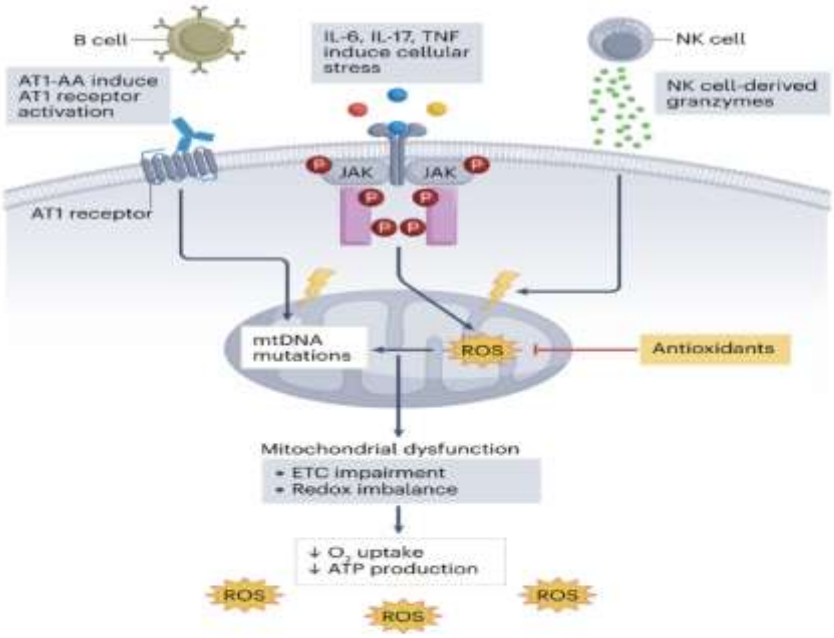

Figure 5. Mitochondrial dysfunction and pathogenesis of preeclampsia[2]

Circulating factors such as sFLT-1 and VEGF contribute to endothelial dysfunction triggered by excessive ROS and oxidative stress in preeclampsia (figure 7). VEGF is important for the growth of new blood vessels and maintenance of endothelial cell health. In healthy pregnancy, sFLT-1, which acts as an inhibitor of VEGF, regulates angiogenesis and vasculogenesis. However, in hypoxic conditions, Flt-1 cleavage increases and elevated levels of sFLT-1 lead to endothelial dysfunction. Women with preeclampsia have increased levels of sFlt-1 compared to normal blood pressure pregnant women. Collectively, an environment of anti-angiogenic factors, endothelial dysfunction, and oxidative stress and chronic inflammation lead to cardiovascular dysfunction and hypertension as seen in preeclampsia. [2]

In *early onset preeclampsia* (*EOPE*), inflammatory macrophages, dendritic cells, NK cells and Th cells disrupt spiral artery formation leading to placental hypoxia. Hypoxia then causes cell death leading to placental dysfunction and fetal antigen shedding. In *late onset preeclampsia* (*LOPE*), spiral artery formation initially occurs normally, but eventually placental demand exceeds uterine perfusion capacity, causing placental hypoxia and subsequently creating an inflammatory environment similar to that in early onset preeclampsia (figure 6).[2,5]

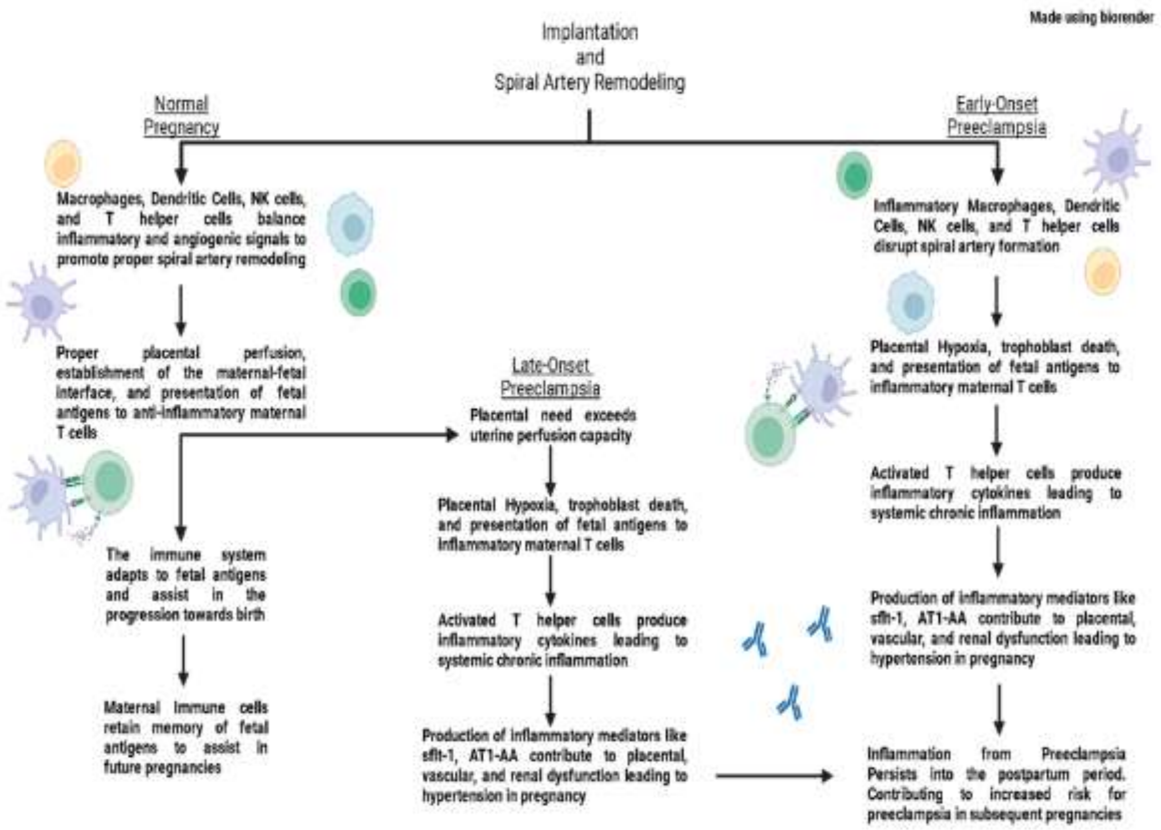

Figure 6. Various immune mediators impact the 2 stages of preecalmsia[5]

Immune System Pathogenesis in Preeclampsia

a. Congenital Immune System in Preeclampsia

The innate immune system - including complement, neutrophils, and NK cells - not only protects the mother and fetus from infection but also contributes to the establishment of the maternal-fetal interface (figure 7). For example, macrophages and NK cells help establish implantation and remodeling of the spiral artery. Innate immune cells also eliminate apoptosis in the uterus and are combined with natural antibodies from innate B1 cells. [2]

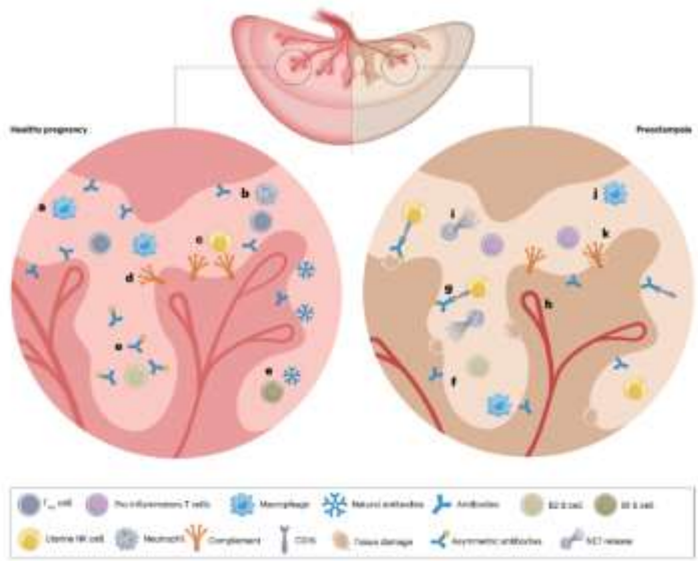

Figure 7. Immunologic system changes in preeclampsia[2]

b. NK (Natural Killer) Cells

Accumulating evidence suggests that dNK cells are beneficial from early pregnancy through several methods (Figure 8). First, several studies have shown that dNK cells promote spiral artery remodeling by producing angiogenic growth factors in early pregnancy, such as interleukin 8 (IL-8), angiopoietin-1/2, and *VEGF* (*vascular endothelial growth* factor), and initiate spiral artery transformation. In addition, dNK cells express various matrix metloproitenases (MMPs), which can initiate extracellular matrix breakdown. To prevent excessive extravillous trophoblast invasion, dNK cells can also produce cytokines, such as *transforming growth factor b* (TGF-b), *tumor necrosis factor a* (TNF-a), and *interferon g* (IFN-g), which inhibit excessive trophoblast invasion at a later stage. The important role of dNK cells in spiral artery remodeling is further demonstrated in the presence of comorbid pregnancy. The number of dNK cells was shown to be reduced in women with FGR and preeclampsia, both of which are pathological and characterized by poor spiral artery remodelling and superficial trophoblastic invasion. The capacity of dNK cells to promote fetal growth and development has been reported. Notably, CD49a+dNK cells have been identified as having the ability to promote fetal development by producing growth-promoting factors, such as pleiotropin and osteoglycine, prior to placental formation.[1,7]

Second, dNK cells act as immunomodulators at the *maternal-fetal interface* by suppressing Th17 inflammatory cells through IFN-g to promote maternal immune tolerance. Third, dNK cells resist the invasion of ptogens in the placenta, such as Listeria and Zika virus, through the expression of the antimicrobial peptide granulisin. Thus, dNK cells play an important role in modulating placental blood vessel remodeling and contribute to an immunomodulatory microenvironment in facilitating fetal growth in early pregnancy.[1,7]

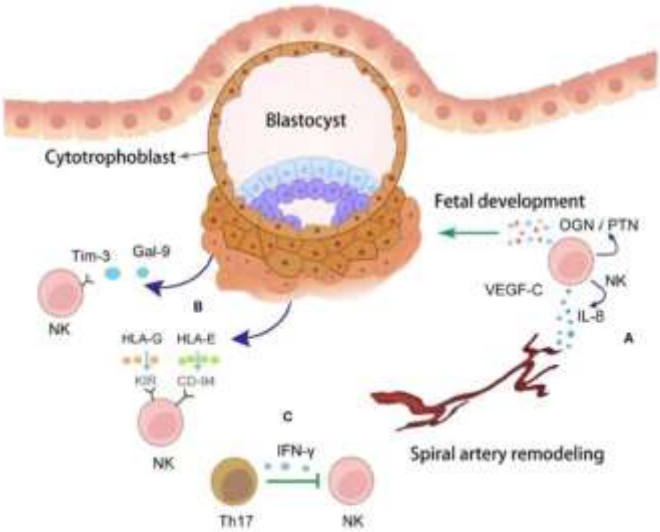

Figure 8. Immunologic work process of decidual dNK cells in fetal development.[7]

c. Macrophage Cells

During reproduction, decidual macrophages account for 20-30% of total decidual immune cells. Based on their antigen surface, cytokine profile, and function, macrophages are classified into *classically activated* (M1, CD14+CD86+) and *alternatively activated* (M2, CD14+CD206+) subtypes, although this is still controversial. To adapt to different stages of fetal development, the macrophage phenotype changes dynamically with changes in the microenvironment that vary with gestational age. During the embryo implantation period, macrophages exhibit an M1 phenotype. With implantation and trophoblast invasion into the endometrium, macrophages change to a mixed M1/M2 type, which persists into the first trimester and early stages of the second trimester. In the second trimester, macrophages polarize with maternal immune tolerance and trigger fetal growth until delivery. Although many studies have shown the role of macrophages, their classification and phenotypes are still controversial.[7]

Macrophages play many important roles during pregnancy (Figure 9). Firstly, macrophages serve a regulatory/homeostatic function through phagocytosis, by performing apoptotic 'clearance' of trophoblasts, preventing activation of pro-inflammatory pathways. They also secrete *indoleamine 2,3-dioxygenase* (IDO) which catabolizes tryptophan and further inhibits T helper cell activation. Second, macrophages perform an antimicrobial role to protect the fetus from infection through pattern recognition receptors, e.g. CD206, CD209 and CD163. Third, macrophages promote spiral artery remodeling, angiogenesis, and trophoblast invasion through the production of *MMP9* and *VEGF*. Previous studies have also shown that macrophages regulate vascular remodeling by secreting *placental growth factor* (*PlGF*) and its receptor, *FMS-like tyrosine kinase* (*sFlt-1*).[2,7,8]

Compared to the M1 subtype, M2 macrophages have a higher angiogenic potential. M2 macrophages produce higher levels of granulocyte colony stimulating factor (G-CSF) and are able to increase G-CSFR expression. Macrophage-derived G-CSF promotes epithelial to mesenchymal transition, trophoblast migration and invasion through activating the PI3K/Akt/Erk1/2 signaling pathway.[7]

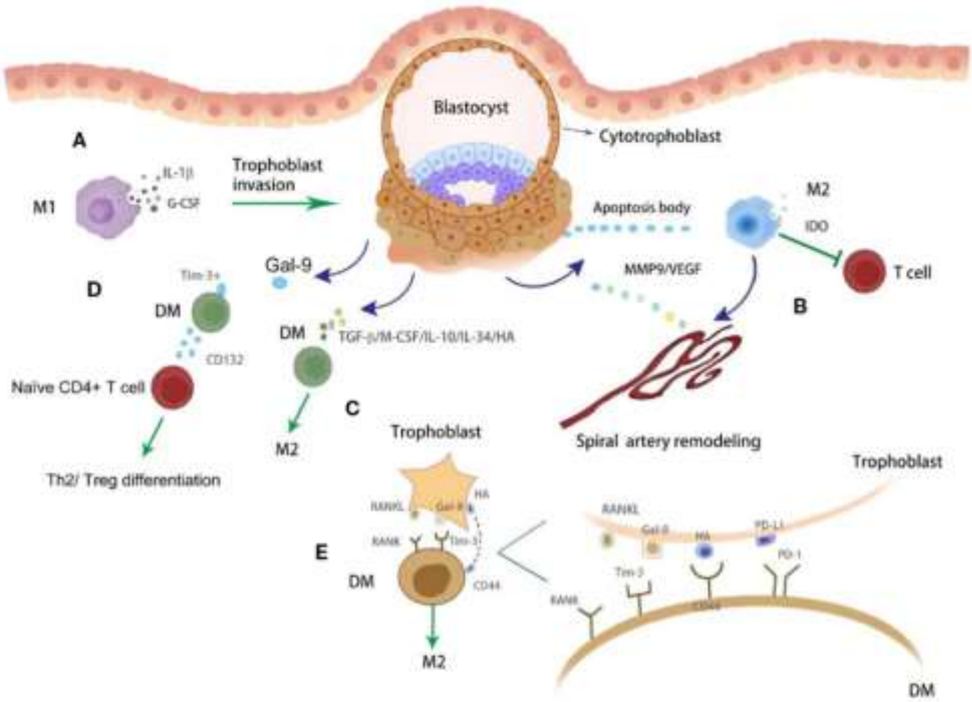

Figure 9. The mechanism of action of decidual macrophages in the process of fetal development.[7]

d. Complement System

The complement system is an integral component of innate immunity and, although complement activation is increased during normal pregnancy, it is further increased in preeclampsia. Complement can be activated through three pathways: the classical pathway, the lectin pathway and the alternative pathway. Alternative complement activation in early pregnancy is associated with an increased risk of developing preeclampsia. In an animal model of placental ischemia, inhibition of complement receptor 1 attenuated hypertension, further suggesting that activation of both classical and alternative complement pathways may be involved in the pathogenesis of hypertension in preeclampsia.[2]

Complement activation leads to target opsonization via C3b, recruitment of proinflammatory cells via C3a and C5a, and formation of membrane attack complex (MAC; otherwise known as C5b-9). Soluble C5b-9 levels are significantly higher in women with hypertensive disorders of pregnancy, including preeclampsia, than in healthy pregnant ones. MAC signaling induces apoptosis in placental cytotrophoblasts, and potentially reduces the effectiveness of trophoblast invasion and spiral artery remodeling. C3a, C5a, and MAC are highly expressed in plasma during preeclampsia, and patients who develop preeclampsia have high levels of complement factor (CFB), CFH, and C1q in early pregnancy.[2,9]

e. Adaptive Immune System in Preeclampsia

Adaptive immune responses driven by T and B cells can be directed against pathogens, but also against allo- and autoantigens, and are characterized by the formation of immune memory that enhances the immune response to subsequent encounters with the same antigen. Of note, preeclampsia is more common in first than subsequent pregnancies and the use of barrier contraception that prevents sperm exposure is associated with a higher risk of preeclampsia. Similarly, lack of prior contact with sperm or oocyte donor alloantigens in medically assisted reproduction increased the risk of preeclampsia compared with natural conception; repeated exposure to donor semen reduced sperm donation-associated risk. Collectively, these observations suggest that seminal fluid may induce adaptive immune tolerance to paternal antigens, thereby reducing the risk of preeclampsia. Therefore, impaired tolerance to paternal antigens may result in inappropriate immune activation that causes inflammation and triggers preeclampsia.[2,8]

f. Cell B

During normal pregnancy, B cells promote a tolerant immune environment for the fetus. However, these lymphocytes can also produce antibodies against paternal antigens, as well as autoantibodies, which can cause pregnancy complications. B cells consist not only of classical B2 cells, but also innate B1 cells, which are associated with T cell independent antibody responses and produce natural antibodies with low specificity, which are usually igM class specific for lipid antigens. B2 cells are derived from generalized lymphoid progenitor cells and represent the dominant classical B cells associated with T cell-dependent antibody responses. B1 cells, on the other hand, develop from progenitor cells in the fetal liver and are only dominant in early pregnancy (Figure 10). [2,8]

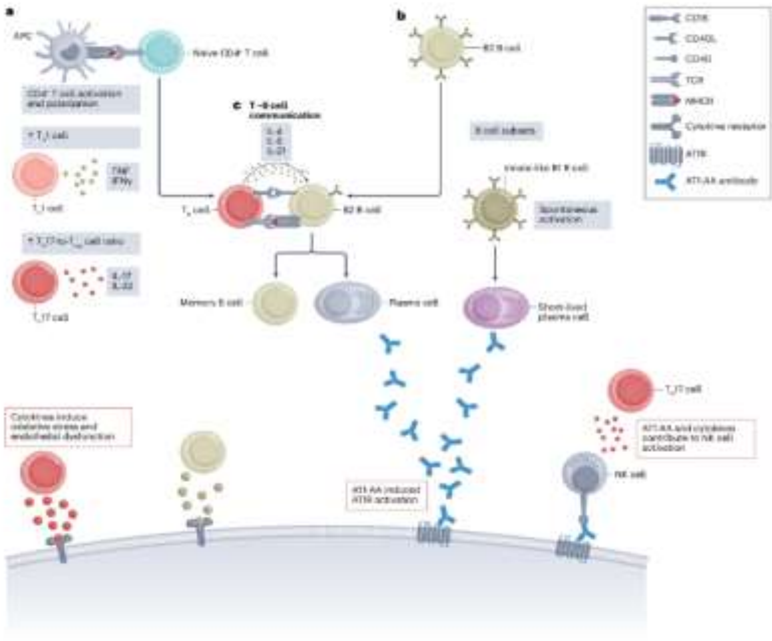

Figure 10. Role of T cells and B cells in preeclampsia[2]

g. T cells

Compared to dNK cells and macrophages, T cells account for a smaller proportion (10-20%), but they are also important for implantation and placentation. Although several subtypes of adaptive immune cells play a role in pregnancy, the key cell mediators are Treg cells and Th cells. At the maternal-fetal interface, approximately 10-20% of CD4+ T cells are Treg cells, which exhibit immunomodulatory effects on immunity through the transcription factor *Forkhead box protein 3*. Without the presence of Treg cells, the allogeneic fetus will be rejected by the mother, who is most vulnerable in the pre- and peri-implantation period.[2,4,8]

Treg cells facilitate placental implantation and development through at least three mechanisms. First, Treg cells have a profound inhibitory effect on CD4+T and CD8+T effector cells. Uncontrolled Treg cells have adverse effects on placental development in an antigen-independent manner, possibly through the release of inflammatory cytokines and *antigen-dependent trophoblast* cytotoxicity. Treg cells secrete TGF-b and IL-10 and express CD25, *cytoyoxic T lymphocyte-associated antigen-4* (*CTLA-4*), and *programmed cell death ligand 1* (*PD-L1*), all of which are specific mediators of Treg cell inhibition and likely contribute to Treg action in early pregnancy. Second, Treg cells regulate other immune cells in the decidua, by facilitating anti-inflammatory and tolerogenic phenotypes in M2 macrophages and tolerogenic decidual cells through TGF-b and IL-10, and CTLA-4. Treg cells may be important modulators of NK cell phenotype and function during implantation by controlling the release of Il-15 from decidual cells and inhibiting NK cell cytolytic activity. These coordinated interactions allow Treg cells to control inflammatory responses and oxidative stress associated with trophoblast invasion. Third, Treg cells are critical modulators of spiral artery remodeling, which is important for normal placental development. A study in pregnant mice that permanently lacked Treg cells caused damage to the spiral artery remodeling, decreased placental blood flow and FGR. The rapid decline of Treg cells in the first trimester of pregnancy leads to uterine artery dysfunction in late pregnancy, which is closely associated with increased production of the vasoconstrictor endhotelin-1. The ability of Treg cells to transition between pro- and anti-inflammatory cell types provides therapeutic opportunities for inflammatory pregnancy complications (figure 11).[7,8,9]

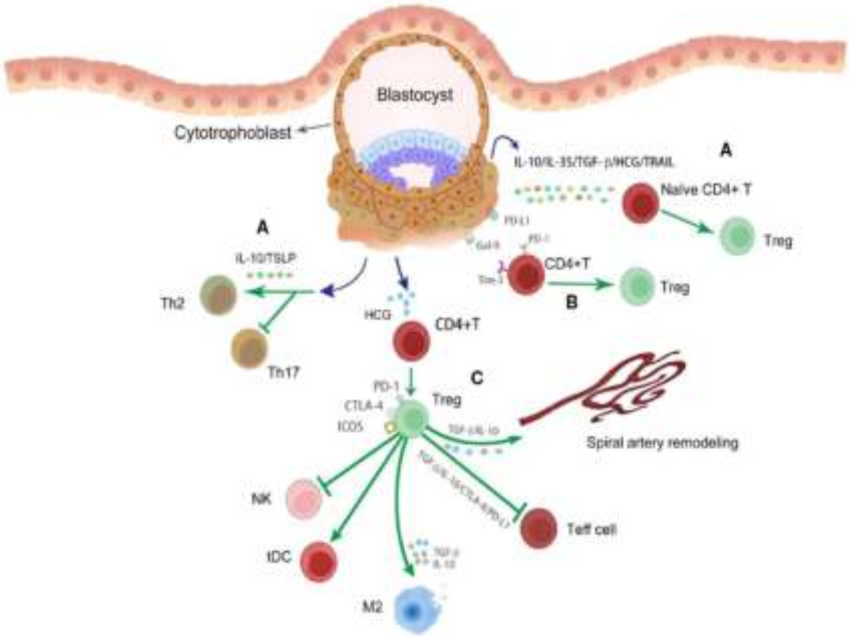

Figure 11. The process of decidual T cell mechanism of action in the process of fetal development[7]

Conclusion

During a typical pregnancy, the maternal immune system must maintain a balance of semi-allogenic immunological tolerance towards the fetus to avert maternal illness. Nonetheless, disruption of this equilibrium is linked to the onset of preeclampsia. Pregnant women undergo temporal alterations in the activation of the innate and adaptive immune systems, and this immunological dysregulation results in detrimental repercussions for both the mother and the fetus.Immune cells are essential for successful implantation and the establishment of the maternal-fetal interface. However, immune dysregulation and inflammation also play a role in the occurrence of preeclampsia. Several types of immune cells are present in the decidua, including different subtypes of T cells, B cells, NK cells and macrophages. In a healthy pregnancy, these cells are regulated to enable fetal tolerance, but they can also become disorganized and instead trigger inflammation, oxidative stress and endothelial dysfunction, as occurs in preeclampsia. Although the pathophysiology of preeclampsia is multifactorial, interventions that target the immune system have therapeutic potential. Therefore, understanding how the innate and adaptive immune systems work together to ensure maternal-fetal tolerance is critical to enable the development of novel therapeutic approaches for hypertensive disorders in pregnancy.

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