IMMUNE MECHANISM OF PREECLAMPSIA

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Abstrak: Sampai saat ini etiologi preeklamsi masih belum jelas. Faktor-faktor imun diduga terlibat dalam mekanisme terjadinya preeklamsi. Faktor-faktor tersebut berperan penting dalam terjadinya preeklamsi tidak sebagai penyebab tunggal tetapi sebagai bagian dalam jalur yang sangat rumit. Peran faktor imun paternal, respons imun dini maternal (terutama yang berhubungan dengan sel NK), korelasi antara faktor imun dan angiogenik terhadap peran autoantibodi (AT-1) merupakan hal-hal penting untuk ditelusuri lanjut. Pemahaman yang detil terhadap patomekanisme sangat bermanfaat dalam penatalaksanaan preeklamsi.
Kata kunci: preeklamsi, faktor imun, mekanisme

Abstract: The etiology of preeclampsia remains unclear so far. It seems immunological factors are involved in preeclampsia mechanism. These factors play some important roles in the mechanism, not as a single factor but as a part in a complex pathway. The role of paternal immunological factors, early maternal immune response (especially related to NK cells), the correlation between immunological and angiogenic factors to the role of autoantibodies (AT-1) are the important points that are needed to be explored further. Thorough understanding about the patho-mechanism would be very useful in the management of preeclampsia itself.
Keywords: preeclampsia , immunological factors, mechanism

Preeclampsia is a disease or complication in pregnancy characterized by hypertension and proteinuria, usually occurs in late pregnancy (second to third trimesters). This condition occurs in about 5% of pregnancies, and can manifest as a maternal or fetal syndrome (intrauterine growth retardation/IUGR, oligohydramnion and impaired oxygenation). Until now preeclampsia is a major cause of maternal and fetal mortality, particularly in developing countries.[1]

The etiology of preeclampsia is unknown, but it can be assumed that the development of preeclampsia is due to genes to genes complex and genes to environment interactions between the mother and the fetus. Previous studies provides evidence that supports the existence of preeclampsia risk factors such as nulliparity, familial history of pre-eclampsia or eclampsia, history of previous pregnancy with preeclampsia, increase in trophoblastic mass (multiple pregnancy, molar pregnancy), maternal age over 40 years, obesity, and some chronic states such as maternal diabetes and chronic hypertension.[1,2]

THEORIES OF PREECLAMPSIA

There are several theories associated with the incidence of preeclampsia, namely:

1. Placental ischaemia: An increase in trophoblast deportation as a consequence of ischemia can cause endothelial cell dysfunction.[3,4]
2. Counter-activity of very low density lipoprotein in preventing toxicity. In

order to compensate the increased energy needdd during pregnancy, unconjugated fatty is mobilized. In women with low albumin concentrations, extra transport of fatty acids from adipose tissue to the liver seems to reduce the antitoxic activity of albumin to the point where VLDL toxicity is expressed.[2]

3. Immune maladaptation: Interactions between decidual leukocytes and cytotrophoblast cell invasion is essential for normal trophoblast invasion and development. Immune maladaptation can cause shallow invasion of spiral arteries by endovascular cytotrophoblast cells and dysfunction of endothelial cell mediated by increased release of cytokines, proteolytic enzymes, and free radicals from decidual layer.[2,5]
4. Genetic factors: The development of preeclampsia-eclampsia may be based on a single recessive gene or a dominant gene associated with fetal genotype.[1,2]

The current hypothesis about the etiology of preeclampsia focuses on the immune response maladaptation and damage of trophoblast invasion. The possibility of a link of the immune maladaptation as the cause of preeclampsia is based on a number of observations and previous studies, such as:[5,6]

- The incidence of preeclampsia is often related to the time interval between pregnancies.
- Exposure to sperms seems to have protective effect on preeclampsia

Thus this disease is excessive maternal inflammatory response, possible of the immune response against foreign antigens of the fetus, resulting in a series of events including shallow invasion of trophoblasts, damage of spiral artery formation, placental infarction, and release of proinflammatory cytokines from the fetus that enter the systemic circulation.[5,6]

In this regard, it is necessary to understand about the current development mechanism or immunologic factors associated with the incidence of preeclampsia.

IMMUNOLOGY IN EARLY PREGNANCY

The main factors of immune-modulation are embryo, uterine natural killer cells (uNK cells of endometrium), and the progesterone. At the time of implantation, a lot of these uNK cells from late luteal phase are activated to control the trophoblast invasion and to increase changes in the blood vessels that provide adequate feto-maternal perfusion.[6,7]

The immune response is controlled by progesterone induced blocking factor (PIBF) due to increased progesterone that tends to increase humoral responses and suppress cytotoxic response. All of these processes are likely to fail in the state of abortion and obstetric complications such as intrauterine growth disorders, preeclampsia, and placental abruption.[6,8]

Implantation

Maternal tolerance to the fetus can be explained by the theory of allogenic reactions that are bipolar, i.e destructive reactions and amplifying reactions. Destructive effects such as adverse reactions encountered in transplantation. Production of antibodies that are cytotoxic and damage the antigenic targets. Amplifier effect works by humoral response that can offset adverse reaction that causes a positive effect on antigenic targets. The amplifying reaction in pregnancy are more dominant than the destructive reaction.[6,7]

Pregnancy is not a transplant reaction but a combination of conceptus and immune reaction of immune response modulation. The presence of peptides with low molecular weight which is only found in pregnancy and in all species of mammals has been identified as the pre-implantation factor (PIF). This factor is derived from embryo that seems to contribute to the main immunomodulator that appears at the beginning of pregnancy before the implantation as the basis of a successful pregnancy. This event occurs and is detected at the beginning of fertilization

which is before implantation. PIF is a base to start immunomodulation (not suppression) and allows the endometrium to prepare implantation.[6,7,9]

Uterine NK cells

Endometrium has decidual changes in the late luteal phase of the menstrual cycle. uNK cells are the predominant cell population in the first trimester of pregnancy. The fact is that at the time of blastocyst implantation, uNK cells are activated by a number of molecules that control trophoblast invasion due to cytotoxic activity and also by early changes in decidual arteries to increase blood supply to the fetoplacental unit.[10,11]

Through the expression of Th2 type cytokines and growth factors, NK cells play a role in placental aggregation as well as local immunosuppression and modulation. The increase of Th1 cytokines (adverse effect on pregnancy) will cause NK cells to express CD16 that can impair trophoblasts directly through cytolytic activity or indirectly through the formation of inflammatory cytokines.[10,12]

NK cell activity appears to be important in achieving an optimal balance of trophoblast invasion. Polymorphic HLA-C fetal gene expressed by trophoblast cells and modulated through killer immunomodulating receptors (KIR) is found on NK cells. Trophoblasts do not express HLA - A or B gene.[11,13]

Progesterone

Progesterone has a major function in modulating the immune response to maintain pregnancy and prevent miscarriage. Progesterone Induced Blocking Factor is a 34 kDa protein that can inhibit mediated NK cell lysis from K562 tumor cells. Expression of this protein through CD 8 T lymphocytes (gamma/delta T cells) require progesterone and therefore called PIBF. PIBF is only synthesized in places that connect fetal and maternal side because the area containing adequate concentrations of progesterone to stimulate the synthesis of PIBF. If the amount of endogenous progesterone is sufficient to establish PIBF then this will protect the fetus by preventing secondary inflammatory and secondary thrombotic reactions toward trophoblasts through 3 real actions:[6-8]

1. Asymmetric induction, antibody protection.
2. Blocking NK cell degranulation.
3. Induction of Th2-dependent cytokines by shifting the balance towards a Th2 dominated, cytoprotective immune response.

Progesterone receptors (PgR) are not shown in the normal T lymphocytes but are found in gamma/delta T-lymphocytes and high progesterone concentrations at the site that links fetus-mother, inducing PIBF expression that will increase PIBF on immunomodulating of pregnancy especially in the location that connects the fetus-mother which is the most important.[6-8]

Trophoblast invasion

Adequate trophoblast invasion may take place only if there is adequate decidualization of endometrial lining of the uterus. Decidualization starts soon after ovulation, so that the embryo can be accepted. Corpus luteum produces progesterone to stimulate decidual vascularization and increase secretory activity of the adrenal gland. Decidual leukocytes consist mainly of uNK cells (65-70%) and monocytes /macrophages (15-20%); the exact function is still unknown. A number of T cells are also found, while B cells are not existent. In endometrial extracellular matrix (composed of various types of collagen, proteoglycans, and glycoproteins), the changes facilitate trophoblast invasive nature, so placenta can implant in the decidual layer and remodel spiral artery vascularization.[3.5]

The invading cytotrophoblasts belong to a subpopulation of villous cytotrophoblast, which then differentiate into the outer layer of multinuclear cells,

syncytiotrophoblast. This syncytiotrophoblast surround the fetal mesenchymal tissue and blood vessels as well as in direct contact with maternal blood circulation. On the surface of the syncytiotrophoblast cell membrane nutrients and oxygen are delivered to the fetus and waste products are delivered back to the maternal circulation.[3.5]

The cytotrophoblasts that differentiate into extravillous cytotrophoblast are designed to have migration capacity to invade maternal decidual matrix and spiral arteries. The musculoelastic tissue of tunica media of spiral arteries is replaced by cytotrophoblasts and fibrinoid material. Spiral arteries then modulate the low resistant flow that increases the blood flow to the space between villi. The cytotrophoblast invasion relies on cell adhesion molecule expression and secretion of proteolytic enzymes, the matrix metalloproteinases (MMP). Integrins are membrane cell adhesion receptors that adhere with different glycoprotein matrix depending on the tissue-specific expression of α and β subunits. When the trophoblasts migrate along the basal membrane and into decidua then spiral arteries, integrin expression is modulated by the structure of the surrounding tissue. The surrounding matrix is digested by proteolytic enzymes secreted by the trophoblasts. Integrins and protease together provide migrating capacity for the trophoblast, which is a significant physiological adaptation. Shallow trophoblast invasion leads to poor placental vascularization and insufficient placental attachment to the tissue matrix. It is associated with an increased risk of placenta, intra uterine growth retardation (IUGR), and placental abruption.[3.5]

EARLY PREGNANCY TO SYSTEMIC INFLAMATION AND ANGIOGENIC IMBALANCE

Systemic inflammation

Excessive maternal inflammatory response to foreign fetal antigens leads to a series of events: impairment of the trophoblast invasion, defects of spiral artery remodeling, placental infarction, and release of pro-inflammatory cytokines and placental fragments into the systemic circulation. In normal pregnancy, the trophoblasts in decidua interact with NK cells resulting in modification of cytokines as well as regulating adhesion molecules and matrix metalloproteinases. Some cytokines, produced in the maternal-fetal interface, affect the trophoblast invasion.[3,5,14]

Balance between inflammatory immune response and anti-inflammation

The trophoblast invasion is influenced by some cytokines produced in the maternal-fetal interface by some immune and non-immune cells, i.e. leukocytes, NK cells, trophoblasts, stromal cells, and endothelial glandular cells Thus, the current hypothesis regarding the etiology of preeclampsia should focus on immune responses maladaption and trophoblast invasion defect. Activation of the adaptive immune response is specifically based on cytokine secretion pattern phenomenon by the by T-helper cells (Th). Th cells consist of Th1 and Th2 cells. Th1 cells secrete inflammatory cytokines such as interferon-γ (IFN-γ) and TNF-α, whereas Th2 cells secrete anti-inflammatory cytokines such as interleukin (IL) 4, IL-5, and IL-9. Th1 cells and Th2 as well as non-lymphoid cells, including macrophages, secrete IL-10. Although Th1 and Th2 cells explanation is too simple, but it can be a basic description of immune and non-immune cells response.[5,9]

According to Jianjun et al,[15] decreased expression of FOXP3 mRNA and increased expression of T-bet mRNA may contribute to the predominantly Th1 in preeclampsia. Important determinant for the induction of Th1 or Th2 pathway is the presence of certain cytokines in the beginning when the antigen is recognized. IL-4 determines Th2 immune response and the effects of IL-4 are greater than of IFN-γ. The presence of trophoblasts in the uterine cavity which has

a low anti-inflammatory effect causes inadequate activation of decidual immune cells that directs local immune activities into inflammation. Systemic cytokine production and immune response initiate their inflammatory functions that cause preeclampsia.[5,9]

PATHOPHYSIOLOGY

Vasoconstriction

Vasoconstriction is the basic of preeclampsia pathogenesis. Vasoconstriction causes an increase in total peripheral resistance and hypertension. The existence of vasoconstriction will also cause hypoxia in local endothelium, resulting in endothelial damage and arterioles' leakage accompanied by micro bleeding at the site of the endothelial cells. The existence of spiral artery vasoconstriction will lead to a further decrease in uteroplacental perfusion and eventually causes maladaptation of placenta. Hypoxia/anoxia hyperoxidase tissue is a source of lipid peroxidase, while hyperoxidation process itself requires increased oxygen consumption, and thus disrupts cell metabolism. Lipid peroxidase, a free radical, is the result of the peroxidation of unsaturated lipid oxidase which produces hyperoxidated saturated fat. If the balance between cells is disrupted where peroxidase and oxidants become more dominant, then there will be a condition called oxidative stress.[5,9]

In preeclampsia serum anti-oxidants levels decrease and placenta becomes the source of lipid peroxidase. While in normal pregnant women, their serum contain transferrin, copper ions, and sulfhydryl which act as strong antioxidants. Lipid peroxidase circulates in the blood stream through the lipoprotein bond. This lipid peroxidase will get into all cell components that it passes including endothelial cells. In these cells, lipid peroxidase causes damages that will lead to, among others:[5,9]

1. Adhesion and aggregation of platelets
2. Disruption of endothelial permeability to plasma layer
3. Release of lysosomal enzymes, thromboxane, and serotonin as a result of platelet destruction
4. Ceased prostacyclin production
5. Disruption of the balance of prostacyclin and thromboxane.
6. Placental hypoxia due to oxygen consumption by the lipid peroxidase

Role of prostacyclin and thromboxane

In preeclampsia there are some vascular endothelial damages resulting in decreased production of prostacyclin (PGI 2) which is normally increased in pregnancy, clotting activation, and fibrinolysis which will be replaced by thrombin and plasmin. Thrombin will consume antithrombin III, resulting in fibrin deposits. Activation of platelets causes the release of thromboxane (TXA2) and serotonin resulting in vasospasm and endothelial damage.[2,4]

Role of Renin-Angiotensin-Aldosterone system (RAAS)

AT1-AA becomes the basis of preeclampsia through its interaction with the AT1 receptor. AT1-AA in preeclamptic patients serves as angiotensin II to activate AT1 receptors at the cell surface. Activation of AT1 autoantibody-induced receptor causes increased heart muscle contraction, production of NADPH oxidase by trophoblasts and vascular smooth muscle cells, PAI-1, sFlt-1, which play some important roles in preeclampsia pathophysiological condition. Besides that, there is an increase of reactive oxygen species.[16-18]

Role of cytokines

Tumor necrosis factor-α (TNF-α)

TNF-α is a pro-inflammatory cytokine produced by NK cells, monocytes/ macrophages, and trophoblasts. TNF-α causes endothelial apoptosis and vascular leakage resulting in systemic endothelial activation that causes preeclampsia. In preeclampsia, in addition to the excess of expression and secretion of TNF-α in the

placenta and plasma, there is also an increased expression of IL-1. These IL-1 and TNF-α cause structural and functional changes in endothelial cells which lead to oxidative stress, activation of the complement cascade, secretion of vasoconstrictor, microthrombosis and infarction, and elevated levels of thromboxane; all changes are found in preeclampsia. The increased expression effect of TNF-α is involved in the pathophysiological mechanism resulting in clinical symptoms. Thus, TNF-α is a major factor of specific local and systemic changes in preeclampsia. TNF-α also increases leptin level which is linked to preeclampsia. TNF-α also activates endothelin system in the placenta, kidney, and vascular tissue.[1,5,19]

Transforming growth factor-β

Transforming growth factor-β (TGF-β) is secreted by decidual stromal cells, macrophages, and T cells, and is found in the maternal-fetal interface. The role of regulatory cytokines with potent negative effects is on the induction of the invasive properties of trophoblastic tissue inhibitor of matrix proteases and the increase of matrix protein adhesion. However, the impact of excessive expression of TGF-β on shallow cytotrophoblast invasion in the fetal placental unit remains controversial since there is no difference in the placental bed or in the placenta between patients with preeclampsia and with normal pregnancy.[3,5]

Interferon- γ

IFN-γ is released by activated T cells. IFN-γ activates uNK cells which regulate physiologically the trophoblast invasion into the decidua. However, excessive IFN-γ along with TNF-α and IL-1 can cause apoptosis of the trophoblasts. This situation also takes place in idiopathic spontaneous abortion. In an inflammatory environment, macrophages secrete IL-12 in a large amount which stimulates the secretion of IFN-γ by NK cells resulting in inhibition of angiogenesis.[5,20,21]

According to Banerjee et al,[20] IFN-γ expression and placental receptors IFN-γR2 failed to convert early hypoxia into the development of normotensive in preeclampsia,[20]

Interleukin-6

IL-6 plasma level is elevated in preeclampsia. Infusion of IL-6 (or TNF-α resulted in a significant increase in arterial pressure and a decrease in renal hemodynamics. It is hypothesized that IL-6 stimulates the RAS.[22.23]

Interleukin-10

IL-10 is an anti-inflammatory cytokine that is important in pregnancy. It inhibits the increased regulation of MMP-2 and MMP-9 and causes the termination of Th1 inflammatory rejection reaction against the fetal placental unit. In some cases of preeclampsia, levels of IL-10 were higher in the placenta and peripheral blood as a compensatory response of increased levels of IFN-γ, TNF-α, IL-2, and IL-12. On the other hand, IL-10 deficiency and increased expression of TNF-α in the placenta and decidua are found in preeclampsia. It is defined as an imbalance of the immune system inflammatory response in preeclampsia.[5,12,24]

Other cytokines

Recently, several other preeclampsia immunopathology cytokine cascades have been found. These cytokines are different and can not be included in the concept of Th2 which is beneficial for pregnancy and Th1 that disrupts pregnancy; therefore, they are categorized differently. These cytokines are still under investigation since there is still no ascertained mechanism of their functions.[5,12,24]

Human leucocyte antigen (HLA)

In the uterus cavity, extravillous cytotrophoblast cells are recognized from typical HLA class I molecule expression: HLA-E, HLA-G, and HLA-C. Currently there are receptors that link with HLA class I molecules located in uterine NK cells

(uNK cells). The syncytiotrophoblasts, which circle placental villi exposed to maternal blood do not express HLA molecules.[5,13,19]

uNK cells varies based on the period of menstruation. In the luteal phase until mid-gestation, uNK cells increase in number and accumulate around the invading cytotrophoblasts. After the placental formation, the uNK cells decrease in number and disappear during term pregnancy.[5.14]

Interactions between extravillous cytotrophoblasts and uNK cells, possibly after stimulation of IFN-γ, affect the spiral artery remodeling. High expression of inhibited uNK cytotoxic activity receptor signals interact with HLA-E, HLA-C, and HLA-G.[1,5,19]

Inability of cytotrophoblasts to modify the order of uNK cells, the regulation of adhesion molecules, MMP, and inadequate neovascularization is an important factor in the onset of pregnancy complications, especially preeclampsia.[5.14]

Nevertheless, Biggar et al.[13] research, did not support the associated HLA-adaptive immune interaction between the mother and fetus as an important factor that induces preeclampsia.

Leukocytes activation and lymphocyte population

The mechanisms underlying the activation of leukocytes in preeclampsia is still unknown. However, these changes are found similar to those found in humans after viral or bacterial infection. Low-dose bacterial endotoxins were injected to pregnant mice led to a state that resembled preeclampsia including the T cell activation markers. The results of these studies indicated that preeclampsia was associated with innate and adaptive immune activity in the peripheral blood. This means that interleukin-10 deficiency causes an increase in inflammatory responses induced by trophoblastic TNF-α and interferon-γ. As a result, distressed throphoblast due to apoptosis have impaired capacity resulting in defect of spiral arteries, hypoxia, thrombosis, and placental infarction. This placental infarction causes leakage of placental fragments and cytokines into the maternal circulation causing systemic endothelial activation resulting in preeclampsia.[5.22]

Preeclampsia is also characterized by systemic changes in distribution of peripheral blood lymphocyte populations. Elevated levels of activated/memory cells ($CD4^+$ $CD45RO^+$ and $CD4^+$ $CD29^+$) and decreased levels of naive cells /suppressor ($CD4^+$ $CD45RA^+$) are found. This means that antigens that activate T cells can be found in preeclampsia. Lymphocytes in normal pregnancy turn into naive T cells/suppressor $CD4^+$ $CD45RA^+$. Cytotoxic T cells $CD8^+$ that express the marker S6F show killer effector function and are increased in preeclamptic pregnancies compared with normal pregnancies; this shows an inflammatory activity.[5,25]

Apoptosis

Apoptosis plays an important role in cell homeostasis and tissue remodeling, especially in the development of placenta. Most importantly, plasental degeneration is found in preeclampsia caused by unscheduled trophoblast apoptosis. Remodeling of spiral arteries associated with pregnancy is caused by local ischemia, thrombosis, and infarction. The exact cause of increased apoptosis in preeclampsia is still unknown. Increased apoptosis of syncytiotrophoblasts increase the syncitial debris which leak into the maternal circulation and cause systemic endothelial activation reaction. In vitro, trophoblast debris activates TNF-α and IL-12 sources in monocytes which further encourages systemic immune response towards systemic inflammation and abnormal innate immune reactivity caused by syncitial nodes; this condition is common in pregnancy. The cause of apoptosis is still unknown, but it is found that pro-inflammatory cytokine gene regulation can boost Fas/FasL, while anti-

inflammatory cytokines protect trophoblast against Fas-induced apoptosis.[5,26]

Free radicals

Other inflammatory mediators are also important in the pathogenesis of preeclampsia including reactive oxygen species, particularly the superoxide anion. This agent is increased in preeclampsia, in which the balance of antioxidants (vitamin E, ascorbic acid, gluthatione peroxidase, superoxide catalase/mutase, and caeruloplasmin) is disrupted. Antioxidants is produced by many kinds of cells, including trophoblasts and leukocytes to protect them from free radicals or as part of the cellular homeostasis and aging. Free radicals and lipid peroxidation levels are increased in preeclampsia and may cause systemic endothelial activation, including platelet consumption, changes in the ratio of thromboxane/prostacyclin, increased production of TNF-α, and promotion of the coagulation cascade.[5.9]

In normal pregnancy, increased detected antioxidants in the blood are due to the growing pregnancy. However, if there is a severe inflammatory process or low antioxidant production, more free radicals will be expressed. This occurs in preeclampsia where free radicals are found in higher levels than in normal pregnancies. In HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), hemolysis of erythrocytes due to the high degree of glutathione oxidation which causes cell damage. Cyclooxygenase inhibitor therapy aiming to inhibit erythrocyte oxidative stress, nutritional supplements with antioxidants, vitamin E and C, can reduce the incidence of preeclampsia in high-risk pregnancies.[5.9]

Complement system

The complement system is activated via the classical pathway and/or lectin with increased terminal complex formation in the third trimester of normal pregnancy, and further in preeclampsia which is characterized by an increase in the number of markers of activation of the systemic circulation. Excessive activation of the terminal pathway is associated with fetal growth inhibition in patients with preeclampsia.[27]

Immunoglobulins

Ahsan et al[28] stated that elevated levels of immunoglobulin IgG, IgA, IgM in preeclampsia and eclampsia women might be caused by an increase in B-lymphocytes. IgM was found higher in eclampsia rather than in preeclampsia, but there was no significant difference in the IgA and IgD.

Toll like receptor

Xie et al[29] explained that there was a possibility of an infectious agent to increase the risk of preeclampsia. Innate immune defence mechanisms might interact with pro-inflammatory pathways that are contributed to the development of preeclampsia. It is estimated that the relationship is mediated through TLR activation.

Angiogenic factors, angiotensin, and autoantibodies

Soluble fms-like tyrosine kinase-1 (sFlt-1) as an angiogenic factors now are accepted as one of the important markers associated with preeclampsia development. Xu et al[30] showed that exogenous sFlt-1 increased production of TNF-α and IL-10 in the placenta, whereas the Th1/Th2 cytokine changes might be mediated by intracellular free calcium.

Expression and secretion of s-Flt-1 in the trophoblast cells are also apparently induced by AT-1, giving rise to the hypothesis: increased expression of sFLT-1 in preeclampsia was associated with activation of AT1 combined receptor by Ang II and AT1-AA.[31]

Zhou et al[32] also suggested that an autoantibody in preeclamptic women induces the production of sFlt-1. Increased sFlt-1 in preeclampsia is also expected to reduce thyroid function.[33]

Toxic substances

What kind of toxic substance produced by disturbed placenta that can cause overall organ damages in preeclampsia? Currently there is no final conclusion about it although there are suspicions from paternal cytokines and antigens carried by the fetus. Moreover, a recall antigen (purified protein derivative of Mycobacterium tuberculosis or tetanus toxoid) that causes secretion of IL-4, IL-10, IL-12, and IFN-γ, are also found in preeclampsia. However, the basic is essentially the same, namely pre-eclampsia, which is a complex inflammatory phenomenon.[5]

CONCLUSION

Preeclampsia is a multisystem disorder based on a cascade of immunopathology events derived from the placenta. There is no single mechanism that can explain the complex pathogenesis. Albeit, a deeper understanding of the mechanisms and the involvement of immunological factors could enshroud the mechanisms of preeclampsia.

The role of paternal immunological factors, early maternal immune response (especially related to NK cells), the correlation between immunological and angiogenic factors (such as sFlt-1), to the role of autoantibodies (AT-1) are the important points that are needed to be explored further through research. An understanding of more established patho-mechanism would be very useful in the treatment of preeclampsia itself.

REFERENCES

1. **Serrano NC**. Immunology and genetic of preeclampsia. Clinical & Developmental Immunology. 2006;13(2-4):197–201.
2. **Dekker GA, Sibai BM**. Etiology and pathogenesis of preeclampsia : Current concepts. Am J Obstet Gynecol. 1998;179:1359-75
3. **Moffett A, Hiby SE**. Immunological factors and placentation: implications for preeclampsia. In: Lyall F, Belfort M, editors. Preeclampsia Etiology and Clinical Practice (7th ed.). New York: Cambridge University Press, 2007; p. 92-102.
4. **Blum A, Shenhav M, Baruch R, Hoffman M**. Endothelial dysfunction in preeclampsia and eclampsia: Current etiology and future non invasive assessment. IMAJ. 2003;5:724-6.
5. **Matthiesen L, Berg G, Ernerudh J, Ekerfelt C, Jonsson Y, Sharma S**. Immunology of preeclampsia. Chem Immunol Allergy. Basel, Karger, 2005; 89: 49-61.
6. **Formosa M**. The paradox of pregnancy: an update on immunology of early pregnancy. Malta Med J. 2008; 20(2): 10-4.
7. **Manyonda I**. The Immunolgy of Human Reproduction. London: The Taylor & Francis Group, 2006; p. 21-52.
8. **Blois SM, Joachim R, Kandil J, Margni R, Tometten M, Klapp BF, et al**. Depletion of $CD8^+$ cells abolishes the pregnancy protective effect of progesterone substitution with dydrogesterone in mice by altering the Th1/Th2 cytokine profile. The Journal of Immunology. 2004;172:5893-9.
9. **Bonney EA**. Preeclampsia: A view through the danger model. J Reprod Immunol. 2007;76(1-2):68-74.
10. **Parham P**. NK Cells and trophoblasts - partners in pregnancy. JEM 2004; 200(8): 951-5.
11. **Smith SD, Dunk CE, Aplin JD, Harris LK, Jones RL**. Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy. Am J Pathol. 2009;174:1959-71.
12. **LaMarca BD, Ryan MJ, Granger JP**. Patophysiology of hypertension during preeclampsia: role of inflammatory cytokines. Current Hypertension Review 2007;3:69-74
13. **Biggar RJ, Poulsen, G, Ng J, Melbye M, Boyd HA**. HLA antigen sharing between mother and fetus as a risk factor for eclampsia and preeclampsia. Human Immunology. 2010;71:263-7.
14. **Kopcow HD, Karumanchi A**. Angiogenic factors and natural killer (NK) cells in the pathogenesis of preeclampsia. J Reprod Immunol. 2007;76(1-2):23-9.
15. **Jianjun Z, Yali H, Zhiqun W, Mingming**

Z, Xia Z. Imbalance of T-cell transcription factors contributes to the Th1 type immunity predominant in preeclampsia. Am J Repro Immunol. 2010;63:38-45.

16. **Xia Y, Zhou CC, Ramin SM, Kellems RE**. Angiotensin receptors, auto-immunity and preeclampsia. The Journal of Immunology. 2007;179:3391-5.
17. **Irani RA, Xia Y**. The functional role of the renin- angiotensin system in pregnancy and preeclampsia. Placenta 2008;29(9):763-71.
18. **Xia Y, Ramin SM, Kellems RE**. Potential roles of angiotensin receptor-activating autoantibody in the pathophysiology of preeclampsia. Hypertension. 2007;50:269-75.
19. **Kilpatrick DC**. Influence of human leukocyte antigen and tumour necrosis factor genes on the development of pre-eclampsia. Human Reproduction Update. 1999;5(2):94-102.
20. **Banerjee S, Smallwood A, Moorhead J, Chambers AE, Papageorghiou A, Campbell S, et al**. Placental expression of interferon-γ (IFN-γ) and its receptor IFN-γ R2 fail to switch from early hypoxic to late normotensive development in preeclampsia. J of Clin Endocrinol & Metab. 2005;90(2):944-52.
21. **Murphy SP, Tayade C, Ashkar AA, Hatta K, Zhang J**. Interferon gamma in successful pregnancy. Biology of Reproduction. 2009;80:848-59.
22. **Gu Y, Lewis DF, Deere K, Groome LJ, Wang Y**. Elevated maternal IL-16 levels, enhanced IL-16 expressions in endothelium and leukocytes, and increased IL-16 production by placental trophoblasts in women with preeclampsia. The Journal of Immunology. 2008;181(6):4418-22.
23. **Guven MA, Coskun A, Ertas IE, Aral M, Zencirci, Oksuz H**. Association of maternal serum CRP, IL-6, TNF-a, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birth weight. Hypertension in Pregnancy. 2009;28: 190-200.
24. **Mansouri R, Akbari F, Vodjgani M, Mahboudi F, Kalantar F, Mirahmadian M**. Serum cytokines profiles in Iranian Patients with preeclampsia. Iran J Immunol. 2007;4(3):179-85.
25. **Grill S, Rusterholz, Zanetti-Dallenbach, Tercanli S, Holzgreve W, Hahn S, et al**. Potential markers of preeclampsia – a review. Reproductive Biology and Endocrinology. 2009;7:70.
26. **Levy R**. The role of apoptosis in preeclampsia. IMAJ. 2005;7:178-81.
27. **Derzsy Z, Prohaszka Z, Rigo J, Fust G, Molvarec A**. Activation of the complement system in normal pregnancy and preeclampsia. Molecular Immunology. 2010;47:1500-6.
28. **Ahsan T, Wahab F, Kamal M, Islam S**. Serum immunoglobulins (IgG, IgA, IgM) levels in preeclampsia and eclampsia pregnancies. The Internet Journal of Third World Medicine. 2009; 8(1):16.
29. **Xie F, Turvey SE, Williams MA, Mor G, Dadelszen P**. Toll-like receptor signaling and preeclampsia. Am J Reprod Immunol. 2010;63:7-16.
30. **Xu B, Thornton C, Tooher J, Hennessy A**. Exogenous soluble VEGF receptor-1 (sFLT-1) regulates Th1/Th2 cytokine production from normal placental explants via intracellular calcium. Hypertension in Pregnancy. 2009; 28:448-56.
31. **Herse F, Staff AC, Hering L, Müller DN, Luft FC, Dechend R**. AT1-receptor autoantibodies and uteroplacental RAS in pregnancy and pre-eclampsia. J Mol Med. 2008;86:697-703.
32. **Zhou CC, Ahmad S, Mi T, Abbasi S, Xia L, Day M, Ramin SM, et al**. Autoantibody from women with preeclampsia induces soluble Fms-like tyrosine kinase-1 production via angiotensin type 1 receptor and calcineurin/nuclear factor of activated T-cells signaling**.** Hypertension. 2008;51:1010-9.
33. **Levine RJ, Vatten LJ, Horowitz GL, Qian C, Romundstad PA, Yu KF, et al**. Preeclampsia, soluble fms like tyrosin kinase 1, and the risk of reduced thyroid function: nested case and population based study. BMJ. 2009;339:b4336.