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REVIEW

Increase of circulating inflammatory molecules in preeclampsia, an update

Gurhan Guney[1], Mine Islimye Taskin[1], Aytekin Tokmak[2]

[1] Balikesir University Medical Faculty, Department of Obstetrics and Gynecology, Balikesir, Turkey
[2] University of Health Sciences Ankara Dr. Zekai Tahir Burak Women's Health, Training and Research Hospital, Ankara, Turkey

Correspondence: Dr. Gurhan Guney, Balikesir University Medical Faculty, Department of Obstetrics and Gynecology, Balikesir, Turkey
<gurhanguney@yahoo.com>

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ABSTRACT. Special hormonal and immunological changes are required for normal pregnancy continuation. To escape from rejection by the maternal immune system, pregnancy needs an optimum environment with the integration and the balance of immune factors. As an immunologically unique site that permits allogenic fetus to be tolerated by mother, the maternal–fetal interface has a vital role. Microorganisms may trigger innate immune responses at the maternal–fetal interface and this may have a significant impact on the success of pregnancy. While the presence of inflammatory markers are slightly increased in healthy pregnancies, their significant increase in preeclampsia suggests that the balance between the inflammatory and antiinflammatory mechanisms may be disrupted by a shift towards inflammation. Based on these immunological observations, we aimed to review the literature for the link between the inflammatory response and preeclampsia since its etiology has not yet been clarified.

Key words: inflammation, plasma, preeclampsia

INTRODUCTION

Pregnancy entails a unique immune program which requires that conceptus should be tolerated and supported by maternal organism, although half of its genetic traits come from the father. Placenta should be rejected under normal immunological conditions because it expresses paternal antigens. Since there is no rejection response to the fetus, the placenta may function as a functional and anatomical barrier that protects the fetal components from the maternal immune response. The immune system dynamically modulates inflammatory responses to prevent rejection, allowing the basic events of pregnancy to develop correctly [1].

Many immune mechanisms that are effective from the menstrual cycle to the formation of normal pregnancy are still not fully understood. Some agents, such as immunological factors, cytokines, and growth factors, regulate a nonpathological inflammation at important stages such as endometrial decidualization, embryo implantation, and the onset of labor [2].

Pregnancy has three immunological stages characterized by different biological processes. The first stage involves implantation and early placentation stages of the embryo, which includes the beginning of pregnancy. This stage, which resembles an open wound, leads to a strong inflammatory response due to implantation, invasion, and vascularization of trophoblast cells into the maternal endometrium. In fact, the presence of an inflammatory environment is essential because cellular debris must be removed and the uterine epithelium and tissue adequately reconstructed. In this regard, the first trimester of pregnancy can be considered a proinflammatory stage dominated by Th1-type cytokines [3, 4].

The second immunological stage of pregnancy is characterized by rapid fetal growth. At this stage, the mother, placenta, and fetus have a mutual harmonic relationship in an antiinflammatory environment where Th2-type cytokines are dominant. In the final stage, by completing fetal development, the fetus faces a renewed inflammatory state, dominated by Th1-type cytokines for the onset of labor. This proinflammatory process stimulates uterine contraction following entry of immune cells into the myometrium, allowing the fetus and placenta to be ejected. Therefore, pregnancy is a condition in which there is a transition and balance between the proinflammatory and antiinflammatory conditions. This balance between the proinflammatory and antiinflammatory reactions at the maternal fetal interface is controlled by various regulatory mechanisms. Epigenetic regulation of DNA methylation, imprinting, and microRNAs play an important role in these equilibrium mechanisms. MicroRNAs play a role in the development of placenta, and changes in its expression are associated with many pregnancy complications [5-7].

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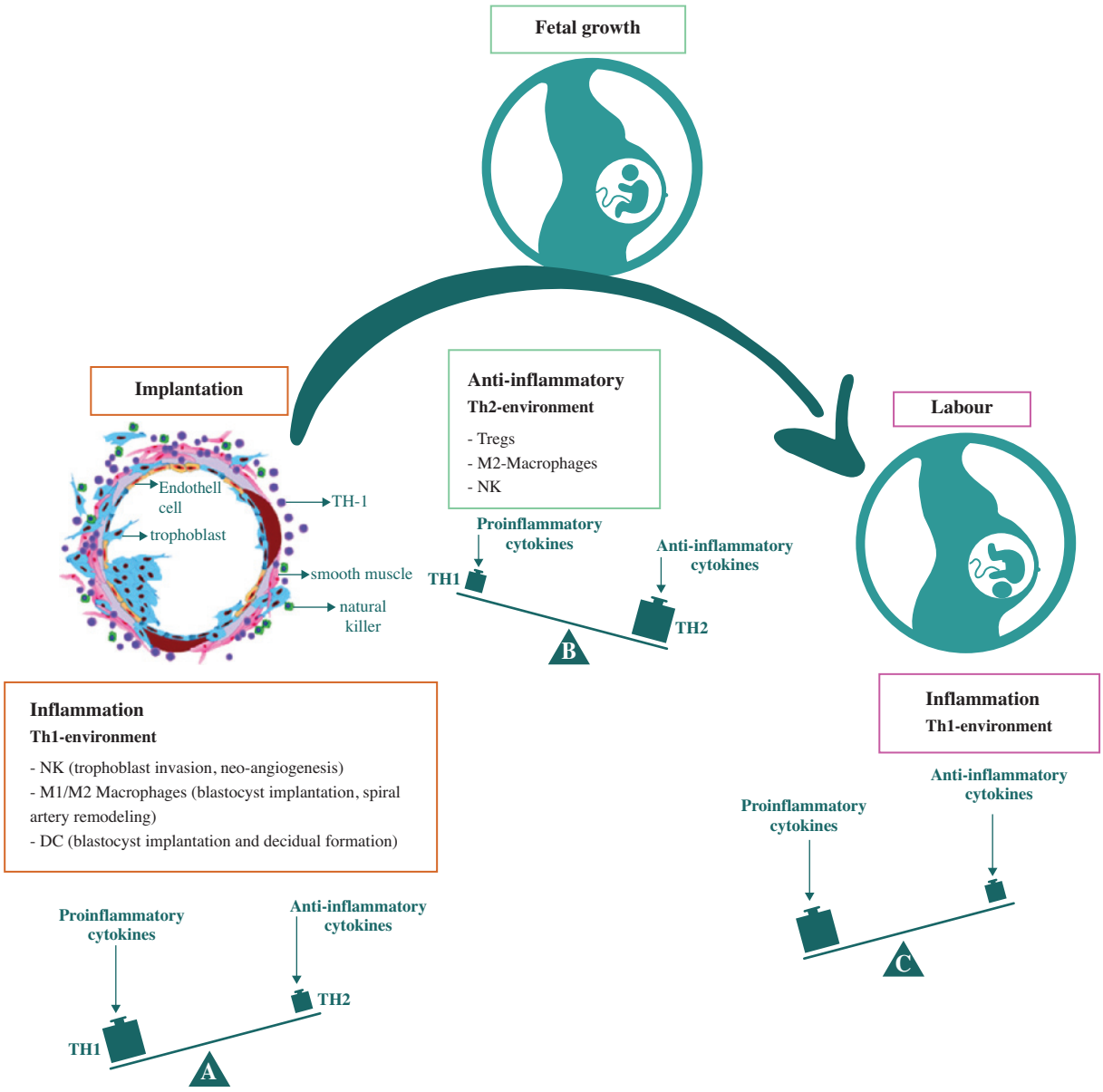

Figure 1-A: The First stage involves implantation and early placentation stages of the embryo (dominated by Th1-type cytokines)

Figure 1-B: The second immunological stage of pregnancy is characterized by anti- inflammatory environment where Th2-type cytokines are dominant

Figure 1-C: In the final stage, by completing fetal development, the fetus faces a renewed inflammatory state, dominated by Th1-type cytokines for the onset of labor. This proinflammatory process stimulates uterine contraction following entry of immune cells into the myometrium, allowing the fetus and placenta to be ejected. Therefore, pregnancy is a condition in which there is transition and balance between proinflammatory and anti-inflammatory conditions

Figure 1
Schematic representation of the inflammatory-antiinflammatory balance in different stages of pregnancy from the implantation to the delivery.

INFLAMMATORY CYTOKINES

Immunology of pregnancy and inflammation

Normal pregnancy is characterized by hormonal and immunological changes. Immune factors are thought to be integrated into the hormonal system and prevent the fetus from rejection by the maternal immune system. For example, the degree of immune response to infectious agents on the maternal fetal interface has an important effect on success of pregnancy because intrauterine infections are associated with some serious complications during pregnancy. It has been reported that immune system disorders may be responsible for some adverse pregnancy outcomes such as preeclampsia (PE), HELLP syndrome, recurrent spontaneous abortion (RSA), and intrauterine growth retardation. However, it is clear that the placenta is protected from killing functions of maternal cells. This protection may be achieved by synthesis of various soluble receptors and their interaction with many other cytokines [8-11].

During pregnancy, some dramatic changes occur in the uterus to advance a successful pregnancy. The interaction between the fetus and the placenta contributes to the immune system's acceptance of

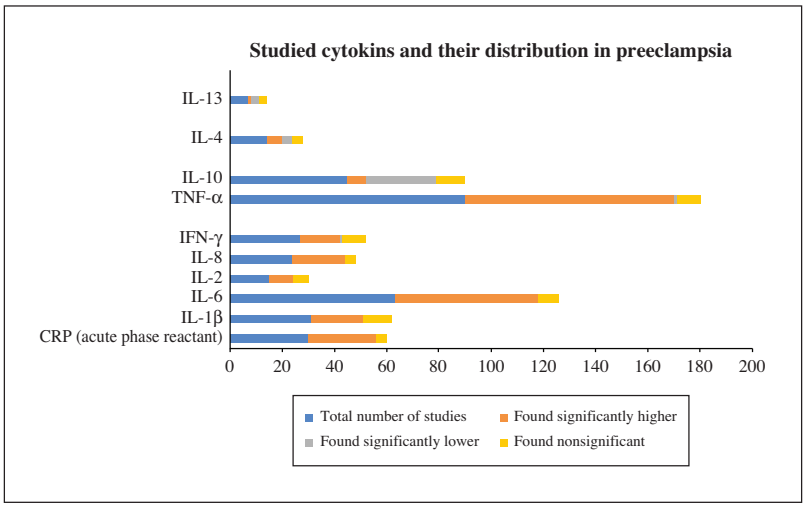

Figure 2
Shematic distribution of cytokins studied in preeclampsia.

the product of pregnancy. For example, the first histological response of the mother to the presence of the embryo is the changes in the leukocyte subpopulation of the uterus. While the natural killer cell population in the endometrium turns into decidual NK cells, decidual macrophages show phenotypic elasticity such as M1 (inflammatory) type during the peri-implantation period, both M1 (inflammatory) and M2 (antiinflammatory) in the placentation period and completely M2 fenotype after the placentation period. The predominance of M1 phenotype again at birth suggests that the placenta may be responsible for these transitions between phenotypes [12].

Some studies have shown that the mutual interaction between decidual macrophages and trophoblasts can regulate implantation, placental development, immunregulation, vascular remodeling, and tissue homeostasis. As a result of this interaction, macrophages, whose number and activations have increased significantly, are likely to be associated with some complications such as preeclampsia, IUGR, and preterm labor. Other than this, it is thought that the decrease in the number of natural lymphoid cells, decidual dendritic cells (dDC), Gamma-delta T cells, cells of the double-negative T lymphocytes (CD4- / CD8-) population, CD 24, CD 25 pošitive TREGS cells in peripheral blood and decidua may be associated with preeclampsia and therefore responsible for maternal tolerance against fetus. In normal pregnancies, the number of regulatory T cells (TREGS) has been shown to increase considerably due to introduction of fetal or paternal antigens [13-16].

These Tregs cells are thought to be responsible for the production of IL-10, which ensures the continuation of pregnancy. In animal studies, it was observed that blocking of IL 10 increased the abortion rates. IL-10 producing CD 19, CD 24, CD 27 positive regulatory B cells are thought to increase in number during normal pregnancy and have a duty to suppress unwanted immune responses that maternal T cells can produce [17]. Infections at the maternal fetal interface affect trophoblasts, decidual stroma, or chorioamniotic membranes, resulting in a proinflammatory or proapoptotic response, disrupting the balance between phenotype, distribution, and function of decidual immune cells. One of the examples of this imbalance is poor pregnancy outcomes in women with autoimmune diseases. Other examples are recurrent pregnancy loss and a late pregnancy complication such as preeclampsia. Antiphospholipid antibodies (APL), one of the major causes of recurrent pregnancy loss, directly affect trophoblast function, induce placental inflammation, and ultimately change the immune cell profile at the maternal fetal interface, making it difficult for pregnancy to continue successfully. In multicenter studies based on the effects of immunity in pregnancy, it was shown that immunization of potential mothers with other paternal and third class leukocytes did not yield any positive results; on the contrary, it even exacerbated the results [18].

In the future, genomics, proteomics, immunophenotype techniques, and immunomodulators are likely to be a guide in treatment of various diseases. Prevention of immune rejection of the fetus requires presence of local immunological adaptations within the mother. Trophoblast cells protect the embryo and some components of the extraembryonic membrane from antipaternal cytotoxic antibodies formed in the mother [19].

Preeclampsia and Inflammation (figures 1, 2)

Preeclampsia is a multisystemic progressive disease characterized by hypertension and proteinuria or hypertension and end organ dysfunction in the last half of pregnancy or postpartum period. Since there is a significant cause of fetal and maternal morbidity and mortality, many theories have been proposed to clarify the etiology, but a clear result has not been obtained yet. Defective invasion of the uterus by trophoblasts, subsequent inadequate spiral artery dilatation, and impaired placentation are the most recent of these theories. It is known that some mechanisms in which angiogenic factors and proinflammatory cytokines are involved play a role in preeclampsia that may develop in or after placentation [20].

Risk factors for atherosclerosis (such as excessive weight, hypertension, dyslipidemia) trigger oxidative stress and inflammation causing arterial aging. The

Table 1
Number of studies about cytokins in preeclampsia.

Inflammation Type	Cytokine Type	Total Number of Studies	Found significantly higher in preeclampsia cases	Found significantly lower in preeclampsia cases	Found nonsignificant in preeclampsia cases
Proinflammatory	CRP (acute phase reactant)	30	26	-	4
Proinflammatory	IL-1β	31	20	-	11
Proinflammatory	IL-6	63	55	-	8
Proinflammatory	IL-2	15	9	-	6
Proinflammatory	IL-8	24	20	-	4
Proinflammatory	IFN-γ	27	15	1	9
Proinflammatory	TNF-α	90	80	1	9
Antiinflammatory	IL-10	45	7	27	11
Antiinflammatory	IL-4	14	6	4	4
Antiinflammatory	IL-13	7	1	3	3

presence of the same risk factors in preeclampsia has brought to mind the question of whether these inflammatory markers are the cause or the result of preeclampsia. While some inflammatory markers have a slight elevation in healthy pregnancies, their significant increase in preeclampsia suggests that some mechanisms that we do not know yet may have caused the tendency of preeclampsia by shifting the immune balance between inflammatory and antiinflammatory toward the direction of inflammation [21].
When we look at the literature, we observed that there are very few review type publications that question the relationship between the preeclampsia and inflammatory markers. Therefore, we planned to present this relationship in a comprehensive way in our review. Detection of preeclampsia with inflammatory markers by screening tests or early diagnosis may help us to prevent complications by timely intervention (*table 1*).

INFLAMMATORY MARKERS

Inflammatory markers secreted in response to inflammation and tissue damage with varying concentrations are known as acute phase reactants. Although they are named as acute phase reactants, they are also secreted secondary to chronic inflammatory conditions. By definition acute phase protein includes proteins whose concentrations in the serum vary at least by 25 % percent during the inflammatory process. These proteins are called positive or negative acute phase proteins [22, 23].
Changes in APR levels occur largely in response to cytokines secreted by hepatocytes from macrophages, monocytes, and various other cells. IL 6 is the major stimulator of most acute phase reactants [24]**.** Other major cytokines are IL-1 beta, TNF-alpha, and interferon gamma. These cytokines also suppress albumin synthesis. Therefore, albumin is called negative acute phase reactant because its levels decrease with inflammation. Other negative acute phase reactants are albumin, transferrin, and transthyretin [25].
Cytokines are peptides that allow the immune system to communicate within and with other tissues. They bind to the receptors and transmit messages to the receiving cell. Cytokines are a large family but have structurally common features such as TNF receptor family, IL-1 superfamily, and IL-6 superfamily. Most cytokine-targeted therapeutic treatments have been found to be effective in rheumatologic diseases for example those which inhibit TNF or IL-6. Therefore, other cytokines are being investigated for treatment [26, 27].

C-Reactive Protein

CRP has both proinflammatory and antiinflammatory activities, but its primary effect is antiinflammatory. CRP promotes recognition and destruction of pathogens while accelerating clearing of necrotic and apoptotic cells [28]. In preeclampsia, high blood pressure, ischemia, and oxidative stress cause endothelial damage similar to those of atherosclerosis. In the literature, it is thought that immune system may have an effect on the pathogenesis and subsequent complications of atherosclerosis such as abdominal aortic aneurysm and myocardial infarction and this may be correlated with CRP levels. CRP levels in pregnant women are higher than those in nonpregnant women [29].
Levels were higher in preeclampsia patients compared to normal pregnant women. Mechanisms involving angiogenic factors and proinflammatory cytokines play a key role in the development of placentation and preeclampsia. IL-6 is a strong inducer of hepatic CRP production. Endothelial activation is an integral component of the inflammatory response. Endothelium that is activated secondary to local endothelial trauma, attracts inflammatory leukocytes to itself and binds to them. It has been hypothesized that the inflammatory state seen in normal pregnancy increases in preeclampsia and maternal immune regulatory conditions may facilitate preeclampsia formation as they may have been decompansated [30].
When we reviewed the literature about the relationship between CRP and preeclampsia, we observed that there are 30 studies so far. In 26 of them, there was a significant relationship between preeclampsia and CRP levels but in 4 studies no significant relationship was found. When studies in which significant correlation was found were evaluated generally, it was found that in some of those studies that some diagnostic

markers should be added to CRP to predict the severity of preeclampsia, but the majority emphasized that the CRP alone is enough. In 3 of these studies, where no significant relationship was found, CRP levels turned out to be insignificant when adjustments were made according to BMI, as obesity itself increased inflammation. In another study, there was a positive correlation between insulin resistance and preeclampsia, but no correlation was found between CRP and preeclampsia. In a different study in which the result was found to be insignificant, CRP levels were evaluated in recurrent preeclampsia cases, but no statistically significant difference was found [23, 31-59].

IL-1β (Proinflammatory Cytokine)

Another cytokine that has been investigated for preeclampsia is IL-1β which is a potent proinflammatory cytokine particularly cells of the natural immune system. Secondary to inflammation, it is secreted from monocytes and macrophages [60]. In the literature, we found that there were 31 studies investigating the relationship between preeclampsia and IL-1β. In 20 of them, we observed that the levels of PE patients were significantly higher when compared with the control groups and in the remaining 11 studies there was no significant difference. When we examined the studies in which correlation was found, we observed that the number of studies investigating the relationship only between preeclampsia and IL-1β was quite small [61-91].

In one of these studies, it was observed that high levels of IL-1β and its natural inhibitor, IL-1Ra, were released in the same amounts from the preeclamptic placentas to the maternal circulation and the ratio between them did not change. However, when MgSO4 was given to preeclamptic placentas, it was observed that only IL-1β levels secreted by the placenta into the maternal circulation were decreased. Since MgSO4 is an agent used in preeclampsia patients, it may be considered that demonstrating this relationship may guide the determination of other treatment modalities [73].

In another study, monocytes from women with severe preeclampsia and normal pregnancy were left in the culture medium and the relationship between IL-1β levels which is an indicative of monocyte activation and LXA4, which could inhibit its release from monocytes were investigated. As a result of the study, it was shown that IL-1β levels were high in preeclampsia patients and LXA4 might have decreased L-1β levels by decreasing Ca secretion. Further studies are needed for LXA4 to be a clinically used agent [67].

In another interesting study, it was shown that secreted IL-1β activated some signaling pathways in preeclampsia patients and induced stress-related apoptosis in the endoplasmic reticulum, whereas progesterone inhibited this stimulation. In all other studies that found the relationship between preeclampsia and IL-1β to be significant or insignificant, IL-1β were evaluated together with other cytokines [74].

IL-6 (Proinflammatory Cytokine)

IL-6 is a soluble cytokine with effects on inflammation, immune response, and hematopoiesis. After being synthesized in a local lesion in the first stage of inflammation, it moves to the liver by circulation and enables the synthesis of many acute phase proteins such as CRP, SAA, Fibrinogen, etc. Owing to its pleiotropic activity, irregular continuous production of IL-6 can lead to the onset or development of various diseases [92]. In our review, we observed a total of 63 studies so far investigating the relationship between IL-6 and preeclampsia. In 55 of them, the results were significantly high, while in 8 of them there were no significant differences. We did not find any reports in which IL-6 levels decreased in preeclamptic cases [23, 44, 72, 75, 77, 86, 93-149].

In one of the studies with significant differences, the inflammatory picture of preeclampsia persisted even years after the disease and posed a risk for cardiovascular disease. Chronic inflammation, endothelial dysfunction, and dyslipidemia were associated with elevation of IL-6. In a rat study performed to confirm the increase in CVD risk, it was shown that the increase in IL-6 levels increased the myocardial damage rate and the decreases in its levels lowered the damage rate [126].

Glomeruli are one of the most affected sites of endothelial damage in preeclampsia. In a study confirming this issue, it was shown that the glomerular podocyte protein, podocalyxin, increased in secondary to IL-6 release, especially in early stage of severe preeclampsia cases [136]. Since the number of studies showing no relationship between IL-6 and preeclampsia is relatively small, there is a need for more studies to claim that there is no relation between IL-6 and preeclampsia.

IL-2 (Proinflammatory Cytokine)

IL-2 is a proinflammatory cytokine secreted by Th-1 cells, which stimulates both helper and cytotoxic T cells for their reproduction. It also stimulates T cells to produce tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN- γ). IL-2 has been shown to control the immune response by playing a critical role in the differentiation and survival of regulatory T cells. IL-2 may also increase cytolytic activity of natural killer cells (NK), IL-2 plays multiple roles in immune function by contributing to generation and progression of antigen-specific immune responses [150]. The relation of a cytokine that plays such a role with preeclampsia is quite important. However, when we look at the literature, we found that there are only 15 studies investigating the relationship between preeclampsia and IL-2. In 9 of these studies, IL-2 levels were found to be high in preeclamptic patients whereas not significant in other 6 studies [77, 93, 97, 98, 100, 104, 109, 129, 143, 144, 148, 151-154].

IL-8 (Proinflammatory Cytokine)

IL-8, a proinflammatory cytokine, plays a role in the development of placenta as well as regulating various cellular functions such as neutrophil movement, cell adhesion, and tumor growth. IL-8 also stimulates migration and invasion of trophoblastic cells [155]. In the literature, we observed a total of 24 studies so far investigating the relationship between IL-8 and preeclampsia. While IL-8 levels were elevated in 20 of

them, no significant relationship was detected in 4 cases [76, 77, 93, 97, 98, 102, 111, 125, 136, 143, 144, 156-168].

Interferon γ (Proinflammatory Cytokine)

Interferons are a heterogeneous group of glycoproteins produced by human and other animal cells after exposure to viral infection or some other stimulants. They inhibit the production of viruses by blocking the translation of viral proteins. Interferons are divided into 3 groups according to the source. These are alpha, beta, and gamma interferons, respectively. Gamma interferon is stimulated by antigens and is an effective means of cellular immunity. Alpha and beta interferons are stimulated by viruses [169].

To date, we have seen 27 studies investigating the relationship between preeclampsia and interferon gamma. In 15 of them, gamma interferon levels were elevated in preeclamptic cases, whereas in 3 studies it was found to be low. In other 9 studies, no relationship was found between them. In one of the studies where the interferon gamma level was low, plasma proteasome levels and activity were elevated in severe preeclampsia and Hellp cases together with the increased IL-8 and IL-10 levels. In a study with insignificant results, preeclampsia model was created in pregnant rats and sildenafil was given to them and no increase was observed in IFN-gamma level. As a result, since the number of studies with significant results was higher, gamma interferon levels seem to be increasing in preeclampsia cases [76, 77, 93, 98, 109, 110, 135, 143-147, 151, 152, 157, 159, 170-180].

Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF-α), a proinflammatory cytokine, plays an important role in various immune and inflammatory processes, such as cellular activation, survival and proliferation, as well as necrosis and apoptosis resulting in cellular death [182].

We have found 90 studies in the literature that have investigated the relationship between preeclampsia and TNF alpha. In 80 of these studies, TNF alpha levels were high, 9 of them were insignificant and 1 of them was low. In one study, it was found that the incidence of preeclampsia decreased in patients with TNF alpha polymorphism [63, 69, 70, 77, 86, 93, 94, 96, 98, 102-105, 109, 110, 113-117, 125, 130, 134, 138, 139, 143-147, 151, 152, 157, 158, 171, 172, 174, 177, 183-231]. When patients who have higher TNF alpha levels were evaluated, it was thought that TNF alpha may be responsible for the antiangiogenic effect by inhibiting NO release from endothelium in some cases, while in other cases the elevation of other inflammatory markers accompanied high TNF alpha levels. The only study that has low levels of TNF alpha was preeclampsia cases receiving antiviral HIV treatment. Since HIV itself is also an inflammatory condition, significant decrease in TNF alpha levels with antiinflammatory treatment in preeclampsia cases with HIV infection clearly demonstrates the role of the inflammatory process in preeclampsia [148].

Antiinflammatory markers

The antiinflammatory markers are a series of immunoregulatory molecules that control the proinflammatory response. The most well known of these major antiinflammatory markers are IL-10, IL-4, and IL 13.

IL-10

As an antiinflammatory cytokine; IL-10 inhibits the activity of Th1 cells, NK cells, and macrophages during infection. All of these cells are required for optimal pathogen clearance but may also contribute to tissue damage. As a result, IL-10 can both inhibit pathogen clearance and improve immunopathology [232].

Up to now, we have detected 45 studies investigating the IL-10 and preeclampsia relationship. In 11 of these studies, IL-10 levels were insignificant, in 27 of them low and in the remaining 7 studies were elevated. In general, it is understood that IL 10 is low in preeclampsia and may be responsible for the deviation of the inflammatory-antiinflammatory balance to the direction of inflammation [75, 77, 93, 94, 97, 98, 101–103, 109, 113, 115, 118, 120, 129, 134, 136, 139, 143, 144, 146, 153, 158-160, 165, 184, 187, 190, 203, 211, 226, 233-245].

IL-4

As a potent regulator of immunity, IL-4 is a cytokine that is secreted primarily by mast cells, Th2 cells, eosinophils, and basophils. A balance between the Th1 and Th2 subsets is required for the development of successful immune responses as inappropriately skewed responses are associated with pathology. A clear role for IL-4 in driving Th2 differentiation and inhibiting development of Th1 cells was established in many in vivo and in vitro studies [246].

To date, we have identified 14 studies in the literature which directly investigate the relationship between IL-4 and preeclampsia. While IL 4 levels were elevated in 6 of them, low levels were found in 4 of them. In the remaining 4 studies, no significant relationship was found between IL 4 levels and preeclampsia [117, 156, 176, 247-257]. Since the numbers of significant and insignificant results are close to each other, further studies are needed to explain the role of IL-4 in preeclampsia.

IL 13

IL 13 is an antiinflammatory cytokine primarily secreted by TH 2 lymphocytes. IL 13 is typically associated with allergic inflammations, particularly asthma. Its profibrotic properties have also been demonstrated on multiple animal models [258].

The number of studies investigating the relationship with preeclampsia is 7 in total and quite few. In 3 of these studies, IL-13 levels were low and only 1 of them had high levels. The remaining 3 studies did not show any significant differences [98, 251, 259-263]. Further studies are needed to explain the role of IL-13 in preeclampsia.

CONCLUSIONS

This review paper collected and evaluated well-designed studies focusing on involvement of pro-inflammatory and antiinflammatory cytokines in preeclampsia. Since its etiology cannot be elucidated yet, preeclampsia as an important cause of maternal-fetal morbidity and mortality, the number and type of studies performed on this subject are so many and quite different. Therefore, the reviews about pre-eclampsia will be informative, necessary, and directive for other studies. In preeclampsia, the fetus carrying the paternal antigens should be accepted by the mother's body similar to organ transplantation and should not be rejected during continuation of pregnancy.

Therefore, maternal immune status and concomitant and / or subsequent inflammatory events before conception become important. If the response to inflammation is not adjusted or stabilized by the body's own antiinflammatory mechanisms, it can be harmful to the mother and therefore to the fetus. The interplay of inflammatory and antiinflammatory cytokines appears to be effective in the development of preeclampsia both before and during pregnancy. As a conclusion, in cases where the inflammatory-antiinflammatory balance deteriorates toward the direction of inflammation both before and during pregnancy, attempting to provide homeostasis by both medical and surgical methods will contribute to the life of the mother and the fetus positively.

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