Eur. Cytokine Netw. Vol. 31, n° 1, *March 2020* 18-31

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>

Accepted for publication December 21, 2019

To cite this article: Guney G, Taskin MI, Tokmak A. Increase of circulating inflammatory molecules in preeclampsia, an update. *Eur. Cytokine Netw.* 2020; 31(1): 18-31. doi: 10.1684/ecn.2020.0443

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].

doi: 10.1684/ecn.2020.0443

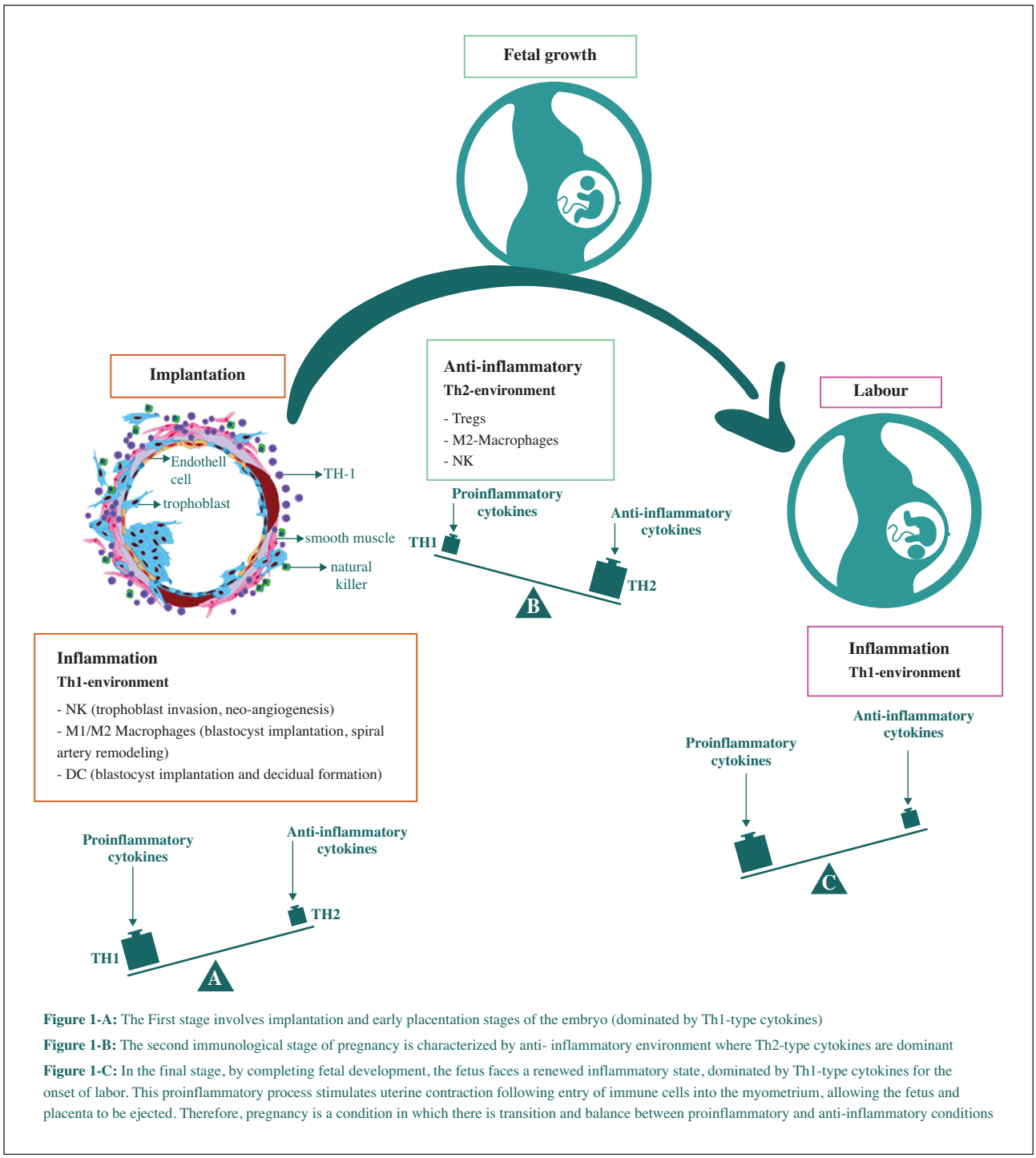

Figure 1-A: The First stage involves implantation and early placentation stages of the embryo (dominated by Th1-type cytokines)

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

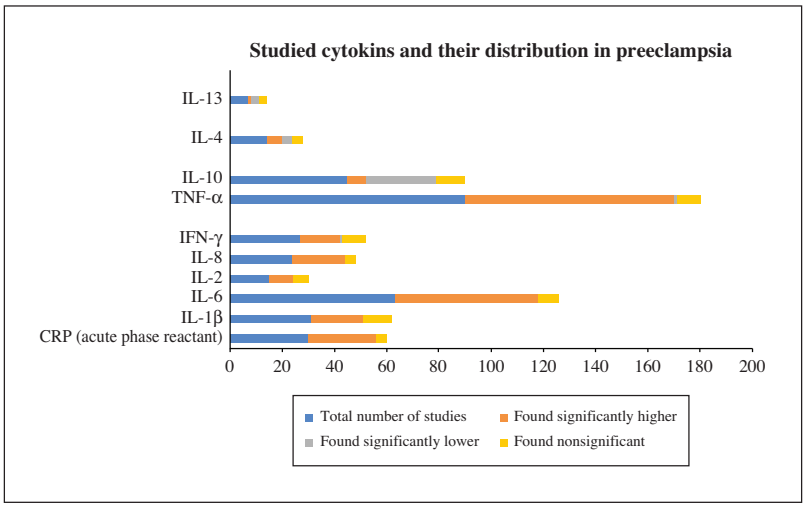

Figure 2
Shematic distribution of cytokins studied in preeclampsia.

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.

REFERENCES

1. Bonney EA. Immune regulation in pregnancy: a matter of perspective? *Obstet Gynecol Clin North Am* 2016; 43(4):679-98.
2. Kutteh WH, Stanic AK, Schust DJ. Immunology and reproduction. *Yen and Jaffe's reproductive endocrinology (eighth edition) physiology, pathophysiology and clinical management* 2019; 13 : 301-321.e3.
3. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. *Ann N Y Acad Sci* 2011; 1221(1):80-7.
4. Ander SE, Diamond MS, Coyne CB. Immune responses at the maternal-fetal interface. *Sci Immunol* 2019; 4(31).
5. Romero R, Espinoza J, Kusanovic JP, *et al.* The preterm parturition syndrome. *BJOG* 2006; 113(Suppl 3):17-42.
6. Romero R, Espinoza J, Gonçalves LF, Kusanovic JP, Friel LA, Nien JK. Inflammation in preterm and term labour and delivery. *Semin Fetal Neonatal Med* 2006; 11 : 317-26.
7. Kamity R, Sharma S, Hanna N. MicroRNA-mediated control of inflammation and tolerance in pregnancy. *Front Immunol* 2019; 10 : 718.
8. Phillips TA, Ni J, Pan G, *et al.* TRAIL (Apo-2L) and TRAIL receptors in human placentas: implications for immune privilege. *J Immunol* 1999; 162 : 6053.
9. Phillips TA, Ni J, Hunt JS. Death-inducing tumour necrosis factor (TNF) superfamily ligands and receptors are transcribed in human placentae, cytotrophoblasts, placental macrophages and placental cell lines. *Placenta* 2001; 22 : 663.
10. Austgulen R, Johnsen H, Kjøllesdal AM, *et al.* Soluble receptors for tumor necrosis factor: occurrence in association with normal delivery at term. *Obstet Gynecol* 1993; 82 : 343.
11. Payne SG, Smith SC, Davidge ST, *et al.* Death receptor Fas/Apo-1/CD95 expressed by human placental cytotrophoblasts does not mediate apoptosis. *Biol Reprod* 1999; 60 : 1144.
12. Yao Y, Xu XH, Jin L. Macrophage polarization in physiological and pathological pregnancy. *Front Immunol* 2019; 10 : 792.
13. Somerset DA, Zheng Y, Kilby MD, *et al.* Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T cell subset. *Immunology* 2004; 112 : 38.
14. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. *Nat Immunol* 2004; 5 : 266.
15. Zenclussen AC, Gerlof K, Zenclussen ML, *et al.* Abnormal T cell reactivity against paternal antigens in spontaneous abortion: adoptive transfer of pregnancy induced CD4 + CD25+ T regulatory cells prevents fetal rejection in a murine abortion model. *Am J Pathol* 2005; 166 : 811.
16. Schumacher A, Wafula PO, Bertoja AZ, *et al.* Mechanisms of action of regulatory T cells specific for paternal antigens during pregnancy. *Obstet Gynecol* 2007; 110 : 1137.
17. Rolle L, Memarzadeh Tehran M, MorellGarcía A, *et al.* Cutting edge: IL10 producing regulatory B cells in early human pregnancy. *Am J Reprod Immunol* 2013; 70 : 448.
18. Ober C, Karrison T, Odem RR, *et al.* Mononuclear cell immunisation in prevention of recurrent miscarriages: a randomised trial. *Lancet* 1999; 354 : 365.
19. Lu HQ, Hu R. The role of immunity in the pathogenesis and development of pre-eclampsia. *Scand J Immunol* 2019; 90(5): e12756.
20. Amash A, Weintraub AY, Sheiner E, Zeadna A, Huleihel M, Holcberg G. Possible therapeutic effect of magnesium sulfate in pre-eclampsia by the down-regulation of placental tumor necrosis factor-alpha secretion. *Eur Cytokine Netw* 2010; 21 (1):58-64.
21. Santulli G, Al-Mallah MH. Pre-eclampsia and future cardiovascular diseases: how to assess the risk? *Atherosclerosis* 2019; 290 : 136-7.
22. Kushner I. The phenomenon of the acute phase response. *Ann N Y Acad Sci* 1982; 389 : 39.
23. Raio L, Bersinger NA, Malek A, *et al.* Ultra-high sensitive C-reactive protein during normal pregnancy and in preeclampsia: a pilot study. *J Hypertens* 2019; 37(5):1012-7.
24. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: from physiopathology to therapy. *J Hepatol* 2016; 64(6):1403-15.
25. Nichols DC, Flannery AH, Magnuson BL, Cook AM. Prealbumin is associated with in-hospital mortality in critically ill patients. *Nutr Clin Pract* 2019;. [Epub ahead of print].
26. Syriou V, Papanikolaou D, Kozyraki A, Goulis DG. Cytokines and male infertility. *Eur Cytokine Netw* 2018; 29(3):73-8.
27. Stavropoulos-Kalinoglou A, Kitas GD. Could IL-6 inhibition prevent exercise-induced fat loss in RA? *Nat Rev Rheumatol* 2019; 15 : 192-4.
28. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol* 2018; 9 : 754.
29. Mohaupt MG. C-reactive protein and its role in preeclampsia. *Hypertension* 2015; 65(2):285-6.
30. Kara AE, Guney G, Tokmak A, Ozaksit G. The role of inflammatory markers hs-CRP, sialic acid and IL-6 in the pathogenesis of preeclampsia and intrauterine growth restriction. *Eur Cytokine Netw* 2019; 30(1):29-33.
31. Ali Z, Bokhari FA, Zaki S, Zargham U, Tauseef A, Khakan S. Correlation of CRP levels in third trimester with fetal birth

weight in preeclamptic and normotensive pregnant women. *J Coll Physicians Surg Pak* 2015; 25(2):111-4.

32. Gandevani SB, Banaem LM, Mohamadi B, Moghadam NA, Asghari M. Association of high-sensitivity C-reactive protein serum levels in early pregnancy with the severity of preeclampsia and fetal birth weight. *J Perinat Med* 2012; 40 (6):601-5.
33. Chen H, Zhang J, Qin F, Chen X, Jiang X. Evaluation of the predictive value of high sensitivity C-reactive protein in pregnancy-induced hypertension syndrome. *Exp Ther Med* 2018; 16(2):619-22.
34. Rebelo F, Schlüssel MM, Vaz JS, *et al*. C-reactive protein and later preeclampsia: systematic review and meta-analysis taking into account the weight status. *J Hypertens* 2013; 31(1):16-26.
35. Jannesari R, Kazemi E. Level of high sensitive C-reactive protein and procalcitonin in pregnant women with mild and severe preeclampsia. *Adv Biomed Res* 2017; 6 : 140.
36. Mihu D, Costin N, Mihu CM, Blaga LD, Pop RB. C-reactive protein, marker for evaluation of systemic inflammatory response in preeclampsia. *Rev Med Chir Soc Med Nat Iasi* 2008; 112(4):1019-25.
37. Stefanović M, Vukomanović P, Milosavljević M, Kutlesić R, Popović J, Tubić-Pavlović A. Insulin resistance and C-reactive protein in preeclampsia. *Bosn J Basic Med Sci* 2009; 9(3):235-8.
38. Von Versen-Hoeynck FM, Hubel CA, Gallaher MJ, Gammill HS, Powers RW. Plasma levels of inflammatory markers neopterin, sialic acid, and C-reactive protein in pregnancy and preeclampsia. *Am J Hypertens* 2009; 22(6):687-92.
39. Aalami-Harandi R, Karamali M, Asemi Z. The favorable effects of garlic intake on metabolic profiles, hs-CRP, biomarkers of oxidative stress and pregnancy outcomes in pregnant women at risk for pre-eclampsia: randomized, double-blind, placebo-controlled trial. *J Matern Fetal Neonatal Med* 2015; 28(17):2020-7.
40. Guven MA, Coskun A, Ertas IE, Aral M, Zencirci B, Oksuz H. Association of maternal serum CRP, IL-6, TNF-alpha, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birth weight. *Hypertens Pregnancy* 2009; 28(2):190-200.
41. Ertas IE, Kahyaoglu S, Yilmaz B, *et al*. Association of maternal serum high sensitive C-reactive protein level with body mass index and severity of pre-eclampsia at third trimester. *J Obstet Gynaecol Res* 2010; 36(5):970-7.
42. Kashanian M, Aghbali F, Mahali N. Evaluation of the diagnostic value of the first-trimester maternal serum high-sensitivity C-reactive protein level for prediction of pre-eclampsia? *J Obstet Gynaecol Res* 2013; 39(12):1549-54.
43. Farzadnia M, Ayatollahi H, Hasan-Zade M, Rahimi HR. A comparative study of serum level of vascular cell adhesion molecule-1 (sVCAM-1), intercellular adhesion molecule-1 (ICAM-1) and high sensitive C - reactive protein (hs-CRP) in normal and pre-eclamptic pregnancies. *Iran J Basic Med Sci* 2013; 16(5):689-93.
44. Swellam M, Samy N, Wahab SA, Ibrahim MS. Emerging role of endothelial and inflammatory markers in preeclampsia. *Dis Markers* 2009; 26(3):127-33.
45. García RG, Celedón J, Sierra-Laguado J, *et al*. Raised C-reactive protein and impaired flow-mediated vasodilation precede the development of preeclampsia. *Am J Hypertens* 2007; 20(1):98-103.
46. Belo L, Santos-Silva A, Caslake M, *et al*. Neutrophil activation and C-reactive protein concentration in preeclampsia. *Hypertens Pregnancy* 2003; 22(2):129-41.
47. Qiu C, Luthy DA, Zhang C, Walsh SW, Leisenring WM, Williams MA. A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia. *Am J Hypertens* 2004; 17(2):154-60.
48. Mihalceanu E, Nemescu D, Gavriluţ M, Dimitriu DC, Pangal A, Onofriescu M. The correlation between markers of systemic inflammation and angiogenic markers in pre-eclampsia. *Rev Med Chir Soc Med Nat Iasi* 2015; 119(2):473-83.
49. Ouyang YQ, Li SJ, Zhang Q, Cai HB, Chen HP. Interactions between inflammatory and oxidative stress in preeclampsia. *Hypertens Pregnancy* 2009; 28(1):56-62.
50. Sarween N, Drayson MT, Hodson J, *et al*. Humoral immunity in late-onset pre-eclampsia and linkage with angiogenic and inflammatory markers. *Am J Reprod Immunol* 2018; 80(5): e13041.
51. Kucukgoz Gulec U, Tuncay Ozgunen F, Baris Guzel A, *et al*. An analysis of C-reactive protein, procalcitonin and D-dimer in pre-eclamptic patients. *Am J Reprod Immunol* 2012; 68(4):331-7.
52. Best LG, Saxena R, Anderson CM, *et al*. Two variants of the C-reactive protein gene are associated with risk of pre-eclampsia in an American Indian population. *PLoS One* 2013; 8(8): e71231.
53. Paternoster DM, Fantinato S, Stella A, *et al*. C-reactive protein in hypertensive disorders in pregnancy. *Clin Appl Thromb Hemost* 2006; 12(3):330-7.
54. Jääskeläinen T, Heinonen S, Hämäläinen E, Pulkki K, Romppanen J, Laivuori H. Impact of obesity on angiogenic and inflammatory markers in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort. *Int J Obes* 2019; 43 (5):1070-81.
55. Srinivas SK, Sammel MD, Bastek J, *et al*. Evaluating the association between all components of the metabolic syndrome and pre-eclampsia. *J Matern Fetal Neonatal Med* 2009; 22 (6):501-9.
56. Gammill HS, Powers RW, Clifton RG, *et al*. Does C-reactive protein predict recurrent preeclampsia? *Hypertens Pregnancy* 2010; 29(4):399-409.
57. Donker RB, Molema G, Faas MM, *et al*. Absence of *in vivo* generalized pro-inflammatory endothelial activation in severe, early-onset preeclampsia. *J Soc Gynecol Investig* 2005; 12 (7):518-28.
58. Ustün Y, Engin-Ustün Y, Kamaci M. Association of fibrinogen and C-reactive protein with severity of preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2005; 121(2):154-8.
59. Tjoa ML, van Vugt JM, Go AT, Blankenstein MA, Oudejans CB, van Wijk IJ. Elevated C-reactive protein levels during first trimester of pregnancy are indicative of preeclampsia and intrauterine growth restriction. *J Reprod Immunol* 2003; 59 (1):29-37.
60. Chekaoui A, Lahmar K, Belguendouz H, *et al*. Increased IL-1β levels are associated with an imbalance of "oxidant/antioxidant" status during Behçet's disease. *Eur Cytokine Netw* 2018; 29(3):95-102.
61. Duan L, Liu Z, Wang L, *et al*. C1q and tumor necrosis factor related protein 4 (CTRP4) suppresses caspase-1/IL-1β inflammatory pathway in trophoblasts of rat models with preeclampsia. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2016; 32(11):1441-5.
62. Wang X, Jiang F, Liang Y, *et al*. Interleukin-1β-31C/T and -511T/C polymorphisms were associated with preeclampsia in Chinese Han population. *PLoS One* 2014; 9(9):e106919.
63. Weel I, Romão-Veiga M, Matias ML, *et al*. Increased expression of NLRP3 inflammasome in placentas from pregnant women with severe preeclampsia. *J Reprod Immunol* 2017; 123 : 40-7.
64. Van Rijn BB, Bruinse HW, Veerbeek JH, *et al*. Postpartum circulating markers of inflammation and the systemic

acute-phase response after early-onset preeclampsia. *Hypertension* 2016; 67(2):404-14.

65. Mulla MJ, Myrtolli K, Potter J, *et al*. Uric acid induces trophoblast IL-1β production via the inflammasome: implications for the pathogenesis of preeclampsia. *Am J Reprod Immunol* 2011; 65(6):542-8.
66. Matias ML, Romão M, Weel IC, *et al*. Endogenous and uric acid-induced activation of NLRP3 inflammasome in pregnant women with preeclampsia. *PLoS One* 2015; 10(6):e0129095.
67. Wang J, Huang Y, Huang Y, Zhou J, Liu X. Effect of lipoxin A on IL-1β production of monocytes and its possible mechanism in severe preeclampsia. *J Huazhong Univ Sci Technolog Med Sci* 2010; 30(6):767-70.
68. Álvarez-Cabrera MC, Barrientos-Galeana E, Barrera-García A, *et al*. Secretion of heat shock -60, -70 kD protein, IL-1β and TNFα levels in serum of a term normal pregnancy and patients with pre-eclampsia development. *J Cell Mol Med* 2018; 22(11):5748-52.
69. Giorgi VS, Witkin SS, Bannwart-Castro CF, *et al*. Elevated circulatingadenosine deaminase activity in women with preeclampsia: association with pro-inflammatory cytokine production and uric acid levels. *Pregnancy Hypertens* 2016; 6 (4):400-5.
70. Romão-Veiga M, Matias ML, Ribeiro VR, *et al*. Induction of systemic inflammation by hyaluronan and hsp70 in women with pre-eclampsia. *Cytokine* 2018; 105 : 23-31.
71. Alanbay I, Coksuer H, Ercan CM, *et al*. Chitotriosidase, interleukin-1 beta and tumor necrosis factor alpha levels in mild preeclampsia. *Arch Gynecol Obstet* 2012; 285(6):1505-11.
72. Kalinderis M, Papanikolaou A, Kalinderi K, *et al*. Elevated serum levels of interleukin-6, interleukin-1β and human chorionic gonadotropin in pre-eclampsia. *Am J Reprod Immunol* 2011; 66(6):468-75.
73. Amash A, Holcberg G, Sapir O, Huleihel M. Effect placental secretion of interleukin-1 and interleukin-1 receptor antagonist in preeclampsia of magnesium sulfate. *J Interferon Cytokine Res* 2012; 32(9):432-41.
74. Liu L, Zhang Y, Wang Y, Peng W, Zhang N, Ye Y. Progesterone inhibited endoplasmic reticulum stress associated apoptosis induced by interleukin-1β via the GRP78/PERK/CHOP pathway in BeWo cells. *J Obstet Gynaecol Res* 2018; 44(3):463-73.
75. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. *Am J Reprod Immunol* 1998; 40(2):102-11.
76. Pinheiro MB, Martins-Filho OA, Mota AP, *et al*. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. *Cytokine* 2013; 62 (1):165-73.
77. Szarka A, , Rigó Jr J, Lázár L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. *BMC Immunol* 2010; 11 : 59.
78. Munno I, Chiechi LM, Lacedra G, *et al*. Spontaneous and induced release of prostaglandins, interleukin (IL)-1beta, IL-6, and tumor necrosis factor-alpha by placental tissue from normal and preeclamptic pregnancies. *Am J Reprod Immunol* 1999; 42(6):369-74.
79. Greer IA, Lyall F, Perera T, Boswell F, Macara LM. Increased concentrations of cytokines interleukin-6 and interleukin-1 receptor antagonist in plasma of women with preeclampsia: a mechanism for endothelial dysfunction? *Obstet Gynecol* 1994; 84(6):937-40.
80. Mosimann B, Wagner M, Poon LC, Bansal AS, Nicolaides KH. Maternal serum cytokines at 30-33 weeks in the prediction of preeclampsia. *Prenat Diagn* 2013; 33(9):823-30.
81. Benyo DF, Smarason A, Redman CW, Sims C, Conrad KP. Expression of inflammatory cytokines in placentas from women with preeclampsia. *J Clin Endocrinol Metab* 2001; 86(6):2505-12.
82. Benyo DF, Miles TM, Conrad KP. Hypoxia stimulates cytokine production by villous explants from the human placenta. *J Clin Endocrinol Metab* 1997; 82(5):1582-8.
83. Siljee JE, Wortelboer EJ, Koster MP, *et al*. Identification of interleukin-1 beta, but no other inflammatory proteins, as an early onset pre-eclampsia biomarker in first trimester serum by bead-based multiplexed immunoassays. *Prenat Diagn* 2013; 33(12):1183-8.
84. Moreno-Eutimio MA, Tovar-Rodríguez JM, Vargas-Avila K, *et al*. Increased serum levels of inflammatory mediators and low frequency of regulatory T cells in the peripheral blood of preeclamptic Mexican women. *Biomed Res Int* 2014; 2014 : 413249.
85. Lockwood CJ, Huang SJ, Krikun G, *et al*. Decidual hemostasis, inflammation, and angiogenesis in pre-eclampsia. *Semin Thromb Hemost* 2011; 37(2):158-64.
86. Jabalie G, Ahmadi M, Koushaeian L, *et al*. Metabolic syndrome mediates proinflammatory responses of inflammatory cells in preeclampsia. *Am J Reprod Immunol* 2019; 81(3): e13086.
87. Giorgi VS, Peracoli MT, Peracoli JC, Witkin SS, Bannwart-Castro CF. Silibinin modulates the NF-κb pathway and pro-inflammatory cytokine production by mononuclear cells from preeclamptic women. *J Reprod Immunol* 2012; 95(1-2):67-72.
88. Van Nieuwenhoven AL, Moes H, Heineman MJ, Santema J, Faas MM. Cytokine production by monocytes, NK cells, and lymphocytes is different in preeclamptic patients as compared with normal pregnant women. *Hypertens Pregnancy* 2008; 27 (3):207-24.
89. Kronborg CS, Gjedsted J, Vittinghus E, Hansen TK, Allen J, Knudsen UB. Longitudinal measurement of cytokines in pre-eclamptic and normotensive pregnancies. *Acta Obstet Gynecol Scand* 2011; 90(7):791-6.
90. Djurovic S, Clausen T, Wergeland R, Brosstad F, Berg K, Henriksen T. Absence of enhanced systemic inflammatory response at 18 weeks of gestation in women with subsequent pre-eclampsia. *BJOG* 2002; 109(7):759-64.
91. Giorgi VS, Bannwart-Castro CF, Peracoli JC, Peracoli MT. PP062 Silibinin modulates NF-kB pathway and proinflammatory cytokines production by mononuclear cells of preeclamptic women. *Pregnancy Hypertens* 2012; 2(3):275-6.
92. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity and disease. *Cold Spring Harb Perspect Biol* 2014; 6 (10):a016295.
93. Taylor BD, Tang G, Ness RB, *et al*. Mid-pregnancy circulating immune biomarkers in women with preeclampsia and normotensive controls. *Pregnancy Hypertens* 2016; 6 : 72-8.
94. Bernardi FC, Guolo F, Bortolin T, Petronilho F, Dal-Pizzol F. Oxidative stress and inflammatory markers in normal pregnancy and preeclampsia. *J ObstetGynaecol Res* 2008; 34 : 948-51.
95. Bernardi FC, Felisberto F, Vuolo F, *et al*. Oxidative damage, inflammation, and toll-like receptor 4 pathway are increased in preeclamptic patients: a case–control study. *Oxidat Med Cell Long* 2012; 2012 : 636419.
96. Catarino C, Santos-Silva A, Belo L, *et al*. Inflammatory disturbances in preeclampsia: relationship between maternal and umbilical cord blood. *J Pregnancy* 2012; 2012 : 684384.
97. Daneva AM, Hadži-Lega M, Stefanovic M. Correlation of the system of cytokines in moderate and severe preeclampsia. *Clin Exp Obstet Gynecol* 2016; 43 : 220-4.

98. Jonsson Y, Rubèr M, Matthiesen L, *et al*. Cytokine mapping of sera from women with preeclampsia and normal pregnancies. *J Reprod Immunol* 2006; 70 : 83-91.

99. Luppi P, Deloia JA. Monocytes of preeclamptic women spontaneously synthesize pro-inflammatory cytokines. *Clin Immunol* 2006; 118 : 268-75.

100. Molvarec A, Szarka A, Walentin S, *et al*. Serum leptin levels in relation to circulating cytokines, chemokines, adhesion molecules and angiogenic factors in normal pregnancy and preeclampsia. *Reprod Biol Endocr* 2011; 9 : 124.

101. Pinheiro MB, Martins-Filho OA, Mota AP, *et al*. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. *Cytokine* 2013; 62 : 165-173.

102. Sharma A, Satyam A, Sharma JB. Leptin, IL-10 and inflammatory markers (TNF-alpha, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. *Am J Reprod Immunol* 2007; 58 : 21-30.

103. Silva DM, Marreiro Ddo N, Moita Neto JM, *et al*. Oxidative stress and immunological alteration in women with preeclampsia. *Hypertens Pregnancy* 2013; 32 : 304-11.

104. Singh A, Sharma D, Raghunandan C, Bhattacharjee J. Role of inflammatory cytokines and eNOS gene polymorphism in pathophysiology of pre-eclampsia. *Am J Reprod Immunol* 2010; 63 : 244-51.

105. Teran E, Escudero C, Moya W, Flores M, Vallance P, Lopez-Jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with preeclampsia. *Int J Gynaecol Obstet* 2001; 75 : 243-9.

106. Toldi G, Bíró E, Szalay B, *et al*. Soluble urokinase plasminogen activator receptor (suPAR) levels in healthy pregnancy and preeclampsia. *Clin Chem Lab Med* 2011; 49 : 1873-6.

107. Wang B, Koga K, Osuga Y, *et al*. High mobility group box 1 (HMGB1) levels in the placenta and in serum in preeclampsia. *Am J Reproductive Immunol* 2011; 66 : 143-8.

108. Xiao JP, Yin YX, Gao YF, *et al*. The increased maternal serum levels of IL-6 are associated with the severity and onset of preeclampsia. *Cytokine* 2012; 60(3):856-60.

109. Xie F, Hu Y, Speert DP, *et al*. Toll-like receptor gene polymorphisms and preeclampsia risk: a case–control study and data synthesis. *Hypertens Pregnancy* 2010; 29 : 390-8.

110. Wu LZ, Xiao XM. Evaluation of the effects of Uncaria rhynchophylla alkaloid extract on LPS-induced preeclampsia symptoms and inflammation in a pregnant rat model. *Braz J Med Biol Res* 2019; 52(6):e8273.

111. Ma Y, Ye Y, Zhang J, Ruan CC, Gao PJ. Immune imbalance is associated with the development of preeclampsia. *Medicine* 2019; 98(14):e15080.

112. Gu S, Shen H, Zhou Y, *et al*. Tetramethylpyrazine reduces the consequences of nitric oxide inhibition in pregnant rats. *J Cell Physiol* 2019; 234(11):19799-806.

113. Zák P, Souček M. Correlation of tumor necrosis factor alpha, interleukin 6 and interleukin 10 with blood pressure, risk of preeclampsia and low birth weight in gestational diabetes. *Physiol Res* 2019; 68(3):395-408.

114. Sljivancanin Jakovljevic T, Kontic-Vucinic O, Nikolic N, Carkic J, Soldatovic I, Milasin J. Glutathione-S-transferase M1 polymorphism and pro-inflammatory cytokines tumour necrosis factor-α and interleukin-1β are associated with preeclampsia in Serbian women. *Am J Reprod Immunol* 2019; 81(5): e13105.

115. Aggarwal R, Jain AK, Mittal P, Kohli M, Jawanjal P, Rath G. Association of pro- and anti-inflammatory cytokines in preeclampsia. *J Clin Lab Anal* 2019; 33(4):e22834.

116. Zhang JY, Cao XX, Wen HX, Zhang HY. Correlation analysis of levels of inflammatory cytokines and nitric oxide in peripheral blood with urine proteins and renal function in patients with gestational hypertension. *Exp Ther Med* 2019; 17 (1):657-62.

117. Cottrell JN, Amaral LM, Harmon A, *et al*. Interleukin-4 supplementation improves the pathophysiology of hypertension in response to placental ischemia in RUPP rats. *Am J Physiol Regul Integr Comp Physiol* 2019; 316(2):R165-71.

118. Chen J, Zhao L, Wang D, *et al*. Contribution of regulatory T cells to immune tolerance and association of microRNA-210 and Foxp3 in preeclampsia. *Mol Med Rep* 2019; 19(2):1150-8.

119. Ding H, Dai Y, Lei Y, *et al*. Upregulation of CD81 in trophoblasts induces an imbalance of Treg/Th17 cells by promoting IL-6 expression in preeclampsia. *Cell Mol Immunol* 2019; 16(1):302-12.

120. Eghbal-Fard S, Yousefi M, Heydarlou H, *et al*. The imbalance of Th17/Treg axis involved in the pathogenesis of preeclampsia. *J Cell Physiol* 2019; 234(4):5106-16.

121. Heydarlou H, Eghabl-Fard S, Ahmadi M, *et al*. Investigation of follicular helper T cells, as a novel player, in preeclampsia. *J Cell Biochem* 2019; 120(3):3845-52.

122. Tanz LJ, Stuart JJ, Missmer SA, *et al*. Cardiovascular biomarkers in the years following pregnancies complicated by hypertensive disorders or delivered preterm. *Pregnancy Hypertens* 2018; 13 : 14-21.

123. Sagrillo-Fagundes L, Assunção Salustiano EM, Ruano R, Markus RP, Vaillancourt C. Melatonin modulates autophagy and inflammation protecting human placental trophoblast from hypoxia/reoxygenation. *J Pineal Res* 2018; 65(4):e12520.

124. Yang MY, Diao ZY, Wang ZY, *et al*. Pravastatin alleviates lipopolysaccharide-induced placental TLR4 over-activation and promotes uterine arteriole remodeling without impairing rat fetal development. *J Biomed Res* 2018; 32(4):288-97.

125. Valencia-Ortega J, Zárate A, Saucedo R, Hernández-Valencia M, Cruz JG, Puello E. Placental Proinflammatory State and Maternal Endothelial Dysfunction in Preeclampsia. *Gynecol Obstet Invest* 2019; 84(1):12-9.

126. Sun J, Zhang H, Liu F, Tang D, Lu X. Ameliorative effects of aspirin against lipopolysaccharide-induced preeclampsia-like symptoms in rats by inhibiting the pro-inflammatory pathway. *Can J Physiol Pharmacol* 2018; 96(11):1084-91.

127. Ding L, Bai C, Liu Y. Interleukin-6 contributes to myocardial damage in pregnant rats with reduced uterine perfusion pressure. *Braz J Med Biol Res* 2018; 51(8):e6921.

128. Ciampa E, Li Y, Dillon S, *et al*. Cerebrospinal fluid protein changes in preeclampsia. *Hypertension* 2018; 72(1):219-26.

129. Krasnyi AM, Gracheva MI, Sadekova AA, *et al*. Complex analysis of total and fetal DNA and cytokines in blood plasma of pregnant women with preeclampsia. *Bull Exp Biol Med* 2018; 164(6):721-5.

130. Bashir SO, Morsy MD, Elkarib AO, *et al*. Impact of high altitude on maternal serum leptin level and its correlation with oxidative stress and endothelial inflammatory markers in preeclamptic women. *Chin J Physiol* 2018; 61(1):50-6.

131. Freitas NA, Santiago LTC, Kurokawa CS, Meira Junior JD, Corrente JE, Rugolo LMSS. Effect of preeclampsia on human milk cytokine levels. *J Matern Fetal Neonatal Med* 2019; 32 (13):2209-13.

132. Martinez-Fierro ML, Castruita-De La Rosa C, Garza-Veloz I, *et al*. Early pregnancy protein multiplex screening reflects circulating and urinary divergences associated with the development of preeclampsia. *Hypertens Pregnancy* 2018; 37 (1):37-50.

133. Allam HIG, Masri AAA. The potential therapeutic role of peroxisome proliferatoractivated receptors agonist in pre-eclamptic pregnant rats. *J Coll Physicians Surg Pak* 2018; 28 (1):31-5.

134. Kemse N, Sundrani D, Kale A, Joshi S. Maternal micronutrients, omega-3 fatty acids and gene expression of angiogenic and inflammatory markers in pregnancy induced hypertension rats. *Arch Med Res* 2017; 48(5):414-22.

135. Charkiewicz K, Jasinska E, Goscik J, *et al*. Angiogenic factor screening in women with mild preeclampsia – New and significant proteins in plasma. *Cytokine* 2018; 106 : 125-30.

136. Xu J, Gu Y, Sun J, Zhu H, Lewis DF, Wang Y. Reduced CD200 expression is associated with altered Th1/Th2 cytokine production in placental trophoblasts from preeclampsia. *Am J Reprod Immunol* 2018; 79(1).

137. Chen Q, Wang Y, Li Y, Zhao M, Nie G. Serum podocalyxin is significantly increased in early-onset preeclampsia and may represent a novel marker of maternal endothelial cell dysfunction. *J Hypertens* 2017; 35(11):2287-94.

138. Huda SS, Jordan F, Bray J, *et al*. Visceral adipose tissue activated macrophage content and inflammatory adipokine secretion is higher in pre-eclampsia than in healthy pregnancys. *Clin Sci* 2017; 131(13):1529-40.

139. Ribeiro VR, Romao-Veiga M, Romagnoli GG, *et al*. Association between cytokine profile and transcription factors produced by T-cell subsets in early- and late-onset pre-eclampsia. *Immunology* 2017; 152(1):163-73.

140. Hannan NJ, Brownfoot FC, Cannon P, *et al*. Resveratrol inhibits release of soluble fms-like tyrosine kinase (sFlt-1) and soluble endoglin and improves vascular dysfunction - implications as a preeclampsia treatment. *Sci Rep* 2017; 7(1):1819.

141. Yin Y, Feng Y, Zhao H, *et al*. SIRT1 inhibits releases of HMGB1 and HSP70 from human umbilical vein endothelial cells caused by IL-6 and the serum from a preeclampsia patient and protects the cells from death. *Biomed Pharmacother* 2017; 88 : 449-58.

142. Al-Othman S, Omu AE, Diejomaoh FM, Al-Yatama M, Al-Qattan F. Differential levels of interleukin 6 in maternal and cord sera and placenta in women with preeclampsia. *Gynecol Obstet Investig* 2001; 52 : 60-5.

143. Boij R, Svensson J, Nilsson-Ekdahl K, *et al*. Biomarkers of coagulation, inflammation and angiogenesis are independently associated with preeclampsia. *Am J Reprod Immunol* 2012; 68 : 258-70.

144. Carty DM, Anderson LA, Freeman DJ, *et al*. Early pregnancy soluble E-selectin concentrations and risk of preeclampsia. *J Hypertens* 2012; 30 : 954-9.

145. Montagnana M, Lippi G, Albiero A, Salvagno GL, Franchi M, Guidi GC. Serum pro-inflammatory cytokines in physiological and pre-eclamptic pregnancies. *Gynecol Endocr* 2008; 24 : 113-116.

146. Ozkan ZS, Simsek M, Ilhan F, Deveci D, Godekmerdan A, Sapmaz E. Plasma IL-17, IL-35, interferon-γ, SOCS3 and TGF-β levels in pregnant women with preeclampsia, and their relation with severity of disease. *J Matern Fetal Neonat Med* 2014; 27 : 1513-7.

147. Vitoratos N, Economou E, Iavazzo C, Panoulis K, Creatsas G. Maternal serum levels of TNF-alpha and IL-6 long after delivery in preeclamptic and normotensive pregnant women. *Mediat Inflamm* 2010; 2010 : 908649.

148. Maharaj NR, Phulukdaree A, Nagiah S, Ramkaran P, Tiloke C, Chuturgoon AA. Pro-inflammatory cytokine levels in HIV infected and uninfected pregnant women with and without preeclampsia. *PLoS One* 2017; 12(1):e0170063.

149. Keaton SA, Heilman P, Bryleva EY, *et al*. Altered tryptophan catabolism in placentas from women with pre-eclampsia. *Int J Tryptophan Res* 2019; 12 : 1178646919840321.

150. Capobianco MP, Cassiano GC, da Cruz Furini AA, *et al*. Human interleukin 2 (IL-2) promotion of immune regulation and clinical outcomes: a review. *J Cytokine Biol* 2016; 1 : 10.

151. Sharma D, Singh A, Trivedi SS, Bhattacharjee J. Role of endothelin and inflammatory cytokines in preeclampsia–A pilot North Indian study. *Am J Reprod Immunol* 2011; 65 : 428-32.

152. Sharma D, Singh A, Trivedi SS, Bhattacharjee J. Intergenotypic variation of nitric oxide and inflammatory markers in preeclampsia: A pilot study in a north indian population. *Hum Immunol* 2011; 72 : 436-9.

153. Ibrahim T, Przybyl L, Harmon AC, *et al*. Proliferation of endogenous regulatory T cells improve the pathophysiology associated with placental ischaemia of pregnancy. *Am J Reprod Immunol* 2017; 78(5).

154. Maharaj NR, Ramkaran P, Pillay S, Chuturgoon AA. MicroRNA-146a rs2910164 is associated with severe pre-eclampsia in Black South African women on HAART. *BMC Genet* 2017; 18(1):5.

155. Brünnert D, Piccenini S, Ehrhardt J, Zygmunt M, Goyal P. Sphingosine 1-phosphate regulates IL-8 expression and secretion via S1PR1 and S1PR2 receptors-mediated signaling in extravillous trophoblast derived HTR-8/SVneo cells. *Placenta* 2015; 36(10):1115-21.

156. Cemgil Arikan D, Aral M, Coskun A, Ozer A. Plasma IL-4, IL-8, IL-12, interferon-γ and CRP levels in pregnant women with preeclampsia, and their relation with severity of disease and fetal birth weight. *J Matern Fetal Neonat Med* 2012; 25(9):1569-73.

157. Luppi P, Deloia JA. Monocytes of preeclamptic women spontaneously synthesize pro-inflammatory cytokines. *Clin Immunol* 2006; 118 : 268-75.

158. Molvarec A, Szarka A, Walentin S, *et al*. Serum heat shock protein 70 levels in relation to circulating cytokines, chemokines, adhesion molecules and angiogenic factors in women with preeclampsia. *Clinica Chimica Acta* 2011; 412 : 1957-62.

159. Sahin S, Ozakpinar OB, Eroglu M, *et al*. The impact of platelet functions and inflammatory status on the severity of preeclampsia. *J Matern Fetal Neonat Med* 2015; 28 : 643-8.

160. Berryman K, Buhimschi CS, Zhao G, Axe M, Locke M, Buhimschi IA. Proteasome levels and activity in pregnancies complicated by severe preeclampsia and hemolysis, elevated liver enzymes, and thrombocytopenia (HELLP) syndrome. *Hypertension* 2019; 73(6):1308-18.

161. Williamson RD, McCarthy FP, Kenny LC, McCarthy CM. Activation of a TLR9 mediated innate immune response in preeclampsia. *Sci Rep* 2019; 9(1):5920.

162. Khanabdali R, Shakouri-Motlagh A, Wilkinson S, *et al*. Low-dose aspirin treatment enhances the adhesion of preeclamptic decidual mesenchymal stem/stromal cells and reduces their production of pro-inflammatory cytokines. *J Mol Med* 2018; 96 (11):1215-25.

163. Arlier S. Endothelial cell leptin receptors, leptin and interleukin-8 in the pathogenesis of preeclampsia: an *in vitro* study. *Turk J Obstet Gynecol* 2017; 14(4):220-7.

164. Docheva N, Romero R, Chaemsaithong P, *et al*. The profiles of soluble adhesion molecules in the "great obstetrical syndromes". *J Matern Fetal Neonat Med* 2019; 32(13):2113-36.

165. Salazar Garcia MD, Mobley Y, Henson J, *et al*. Early pregnancy immune biomarkers in peripheral blood may predict preeclampsia. *J Reprod Immunol* 2018; 125 : 25-31.

166. Al-Ofi EA, Anumba DO. Ligands of toll-like receptors 2/4 differentially alter markers of inflammation, adhesion and angiogenesis by monocytes from women with pre-eclampsia in co-culture with endothelial cells. *J Reprod Immunol* 2017; 121 : 26-33.

167. Adela R, Borkar RM, Mishra N, *et al*. Lower serum vitamin D metabolite levels in relation to circulating cytokines/chemokines and metabolic hormones in pregnant women with hypertensive disorders. *Front Immunol* 2017; 8 : 273.

168. Sun L, Mao D, Cai Y, *et al*. Association between higher expression of interleukin-8 (IL-8) and haplotype -353A/-251A/+ 678T of IL-8 gene with preeclampsia: a case-control study. *Medicine* 2016; 95(52):e5537.

169. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines and their receptors. *Immunol Rev* 2004; 202 : 8-32.

170. Huang SJ, Chen CP, Buchwalder L, *et al*. Regulation of CX3CL1 expression in human first-trimester decidual cells: implications for preeclampsia. *Reprod Sci* 2019; 26(9):1256-65.

171. Lee CL, Veerbeek JHW, Rana TK, Van Rijn BB, Burton GJ, Yung HW. Role of endoplasmic reticulum stress in proinflammatory cytokine-mediated inhibition of trophoblast invasion in placenta-related complications of pregnancy. *Am J Pathol* 2019; 189(2):467-78.

172. Sharma K, Singh R, Kumar M, Gupta U, Rohil V, Bhattacharjee J. First-trimester inflammatory markers for risk evaluation of pregnancy hypertension. *J Obstet Gynaecol* 2018; 68(1):27-32.

173. Scroggins SM, Santillan DA, Lund JM, *et al*. Elevated vasopressin in pregnant mice induces T-helper subset alterations consistent with human preeclampsia. *Clin Sci* 2018; 132 (3):419-36.

174. Elfarra J, Amaral LM, McCalmon M, *et al*. Natural killer cells mediate pathophysiology in response to reduced uterine perfusion pressure. *Clin Sci* 2017; 131(23):2753-62.

175. Li X, Li T, Liu Y, *et al*. Association of IFNG gene polymorphisms with susceptibility to preeclampsia among pregnant woman from Shaanxi. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2017; 34(5):726-30.

176. Hashemi V, Dolati S, Hosseini A, Gharibi T, Danaii S, Yousefi M. Natural killer T cells in preeclampsia: an updated review. *Biomed Pharmacother* 2017; 95 : 412-8.

177. Bueno-Sánchez JC, Peña-Alzate S, Peña RB, *et al*. Sera from early-onset, severely preeclamptic women directly modulate HLA-E expression in the EA. hy296 endothelial cell line. *J Reprod Immunol* 2014; 104-105 : 68-79.

178. Giurgescu C, Sanguanklin N, Engeland C G, *et al*. Relationships among psychosocial factors, biomarkers, preeclampsia, and preterm birth in African American women: a pilot. *Appl Nurs Res* 2015; 28 : e1-6.

179. Cemgil Arikan D, Aral M, Coskun A, Ozer A. Plasma IL-4, IL-8, IL-12, interferon-γ and CRP levels in pregnant women with preeclampsia and their relation with severity of disease and fetal birth weight. *J Matern Fetal Neonat Med* 2012; 25 : 1569-73.

180. Haedersdal S, Salvig JD, Aabye M, *et al*. Inflammatory markers in the second trimester prior to clinical onset of preeclampsia, intrauterine growth restriction and spontaneous preterm birth. *Inflammation* 2013; 36 : 907-13.

181. Soobryan N, Murugesan S, Phoswa W, Gathiram P, Moodley J, Mackraj I. The effects of sildenafil citrate on uterine angiogenic status and serum inflammatory markers in an L-NAME rat model of pre-eclampsia. *Eur J Pharmacol* 2017; 795 : 101-7.

182. Ren M, Li X, Hao L, Zhong J. Role of tumor necrosis factor alpha in the pathogenesis of atrial fibrillation: a novel potential therapeutic target? *Ann Med* 2015; 47(4):316-24.

183. Cackovic M, Buhimschi CS, Zhao G, *et al*. Fractional excretion of tumor necrosis factor-alpha in women with severe preeclampsia. *Obstet Gynecol* 2008; 112 : 93-100.

184. Ferguson KK, McElrath TF, Chen YH, Mukherjee B, Meeker JD. Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. *Am J Reprod Immunol* 2014; 72(3):326-36.

185. Hou L, Zhu Y, Ma X, Li J, Zhang W. Serum protein microarray analysis of patients with preeclampsia. *Mol Med Rep* 2012; 6 : 83-7.

186. Shu C, Yan D, Chen C, *et al*. Metformin exhibits its therapeutic effect in the treatment of pre-eclampsia *via* modulating the Met/H19/miR-148a-5p/P28 and Met/H19/miR-216-3p/EBI3 signaling pathways. *Int Immunopharmacol* 2019; 74 : 105693.

187. Liu Z, Zhao X, Shan H, Gao H, Wang P. microRNA-520c-3p suppresses NLRP3 inflammasome activation and inflammatory cascade in preeclampsia by downregulating NLRP3. *Inflamm Res* 2019; 68(8):643-54.

188. Doganlar ZB, Güçlü H, Öztopuz Ö, *et al*. The role of melatonin in oxidative stress, DNA damage, apoptosis and angiogenesis in fetal eye under preeclampsia and melatonin deficiency stress. *Curr Eye Res* 2019; 44 : 1-13.

189. Cox AG, Gurusinghe S, Abd Rahman R, *et al*. Sulforaphane improves endothelial function and reduces placental oxidative stress *in vitro*. *Pregnancy Hypertens* 2019; 16 : 1-10.

190. Matias ML, Gomes VJ, Romao-Veiga M, *et al*. Silibinin Downregulates the NF-κB Pathway and NLRP1/NLRP3 Inflammasomes in Monocytes from Pregnant Women with Preeclampsia. *Molecules* 2019; 24(8):E1548.

191. Ahmed M, Alqosaibi A, Mohamed MA, Soliman MG. Evaluation of some cytokines and gene expressions in preeclampsia. *Pak J Biol Sci* 2019; 22(3):148-53.

192. Zhang QL, Wang L, Xu MJ, Wang TL. Protective effect of dexmedetomidine on kidney injury of parturients with preeclampsia undergoing cesarean section: a randomized controlled study. *Biosci Rep* 2019; 39(5):BSR20190352.

193. Harmon AC, Ibrahim T, Cornelius DC, *et al*. Placental CD4 T cells isolated from preeclamptic women cause preeclampsia-like symptoms in pregnant nude-athymic rats. *Pregnancy Hypertens* 2019; 15 : 7-11.

194. Ampey AC, Boeldt DS, Clemente L, *et al*. TNF-alpha inhibits pregnancy-adapted Ca signaling in uterine artery endothelial cells. *Mol Cell Endocrinol* 2019; 488 : 1424.

195. Li ZH, Wang LL, Liu H, *et al*. Galectin-9 alleviates LPS-induced preeclampsia-like impairment in rats *via* switching decidual macrophage polarization to M2 subtype. *Front Immunol* 2019; 9 : 3142.

196. Turbeville HR, Taylor EB, Garrett MR, Didion SP, Ryan MJ, Sasser JM. Superimposed preeclampsia exacerbates postpartum renal injury despite lack of long-term blood pressure difference in the dahl salt-sensitive rat. *Hypertension* 2019; 73 (3):650-8.

197. Lin Y, Wang L, Yan Y, Zhou W, Chen Z. A meta-analysis of tumor necrosis factor-α and FAS/FASL polymorphisms with risk of pre-eclampsia. *Hypertens Pregnancy* 2019; 38(1):20-31.

198. Wang Z, Wang P, Wang Z, *et al*. MiRNA-548c-5p downregulates inflammatory response in preeclampsia *via* targeting PTPRO. *J Cell Physiol* 2019; 234(7):11149-55.

199. Kim S, Lee KS, Choi S, *et al*. NF-κB-responsive miRNA-31-5p elicits endothelial dysfunction associated with preeclampsia *via* down-regulation of endothelial nitric-oxide synthase. *J Biol Chem* 2018; 293(49):18989-9000.

200. Feng J, Wang X, Li H, Wang L, Tang Z. Silencing of Annexin A1 suppressed the apoptosis and inflammatory response of preeclampsia rat trophoblasts. *Int J Mol Med* 2018; 42(6):3125-34.

201. Canfield J, Arlier S, Mong EF, *et al*. Decreased LIN28B in preeclampsia impairs human trophoblast differentiation and migration. *FASEB J* 2019; 33(2):2759-69.

202. Wang L, Qu G, Wu W, Tang X, Sun Y. Association between tumor necrosis factor-α-308G/A gene polymorphism and susceptibility to pre-eclampsia: an updated meta-analysis. *Cytokine* 2018; 111 : 278-86.

203. Chen Y, Xue F, Han C, *et al*. Ferulic acid ameliorated placental inflammation and apoptosis in rat with preeclampsia. *Clin Exp Hypertens* 2019; 41(6):524-30.

204. Wen Z, Chen Y, Long Y, Yu J, Li M. Tumor necrosis factor-alpha suppresses the invasion of HTR-8/SVneo trophoblast cells through microRNA-145-5p-mediated downregulation of Cyr61. *Life Sci* 2018; 209 : 132-9.

205. Zou AX, Chen B, Li QX, Liang YC. MiR-134 inhibits infiltration of trophoblast cells in placenta of patients with preeclampsia by decreasing ITGB1 expression. *Eur Rev Med Pharmacol Sci* 2018; 22(8):2199-206.

206. Li G, Ma L, Lin L, Wang YL, Yang H. The intervention effect of aspirin on a lipopolysaccharide-induced preeclampsia-like mouse model by inhibiting the nuclear factor-κB pathway. *Biol Reprod* 2018; 99(2):422-32.

207. Brunacci F, Rocha VS, De Carli E, Espósito BP, Ruano R, Colli C. Increased serum iron in preeclamptic women is likely due to low hepcidin levels. *Nutr Res* 2018; 53 : 32-9.

208. Agostinis C, Rami D, Zacchi P, *et al*. Pre-eclampsia affects procalcitonin production in placental tissue. *Am J Reprod Immunol* 2018; 79(4):e12823.

209. Quan LM, Xu QL, Zhang GQ, Wu LL, Xu H. An analysis of the risk factors of preeclampsia and prediction based on combined biochemical indexes. *Kaohsiung J Med Sci* 2018; 34 (2):109-12.

210. Uckan K, Sahin HG. Serum amyloid A, procalcitonin, highly sensitive C reactive protein and tumor necrosis factor alpha levels and acute inflammatory response in patients with hemolysis, elevated liver enzymes, low platelet count (HELLP) and eclampsia. *J Obstet Gynaecol Res* 2018; 44(3):440-7.

211. Shi DD, Wang Y, Guo JJ, Zhou L, Wang N. Vitamin D enhances efficacy of oral nifedipine in treating preeclampsia with severe features: a double blinded, placebo-controlled and randomized clinical trial. *Front Pharmacol* 2017; 8 : 865.

212. Bakrania BA, Spradley FT, Satchell SC, *et al*. Heme oxygenase-1 is a potent inhibitor of placental ischemia-mediated endothelin-1 production in cultured human glomerular endothelial cells. *Am J Physiol Regul Integr Comp Physiol* 2018; 314(3):R427-32.

213. Gurusinghe S, Cox AG, Rahman R, *et al*. Resveratrol mitigates trophoblast and endothelial dysfunction partly *via* activation of nuclear factor erythroid 2-related factor-2. *Placenta* 2017; 60 : 74-85.

214. Amaral LM, Faulkner JL, Elfarra J, *et al*. Continued investigation into 17-OHPC: results from the preclinical RUPP rat model of preeclampsia. *Hypertension* 2017; 70(6):1250-5.

215. Xu B, Shanmugalingam R, Chau K, Pears S, Hennessy A, Makris A. The effect of acetyl salicylic acid (Aspirin) on trophoblast-endothelial interaction *in vitro*. *J Reprod Immunol* 2017; 124 : 54-61.

216. Yu J, Jia J, Guo X, Chen R, Feng L. Modulating circulating sFlt1 in an animal model of preeclampsia using PAMAM nanoparticles for siRNA delivery. *Placenta* 2017; 58 : 1-8.

217. Kaitu'u-Lino TJ, Brownfoot FC, Hastie R, *et al*. Activating transcription factor 3 is reduced in preeclamptic placentas and negatively regulates sFlt-1 (soluble fms-like tyrosine kinase 1), soluble endoglin, and proinflammatory cytokines in placenta. *Hypertension* 2017; 70(5):1014-24.

218. Li W, Cui N, Mazzuca MQ, Mata KM, Khalil RA. Increased vascular and uteroplacental matrix metalloproteinase-1 and -7 levels and collagen type I deposition in hypertension in pregnancy: role of TNF-α. *Am J Physiol Heart Circ Physiol* 2017; 313(3):H491-507.

219. Kim J, Lee KS, Kim JH, *et al*. Aspirin prevents TNF-α-induced endothelial cell dysfunction by regulating the NF-κB-dependent miR-155/eNOS pathway: Role of a miR-155/eNOS axis in preeclampsia. *Free Radic Biol Med* 2017; 104 : 185-98.

220. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, Llurba E, Gris JM. Tumor necrosis factor-alpha and pregnancy: focus on biologics, an updated and comprehensive review. *Clin Rev Allergy Immunol* 2017; 53(1):40-53.

221. Ferguson KK, Meeker JD, McElrath TF, Mukherjee B, Cantonwine DE. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. *Am J Obstet Gynecol* 2017; 216(5):527.e1-527.e9.

222. Tavakkol Afshari Z, Rahimi HR, Ehteshamfar SM, Ganjali R, Tara F, Shapouri Moghadam A. Tumor necrosis factor-α and interleukin-1-β polymorphisms in pre-eclampsia. *Iran J Immunol* 2016; 13(4):309-16.

223. Xu B, Bobek G, Makris A, Hennessy A. Antihypertensive methyldopa, labetalol, hydralazine and clonidine reversed tumour necrosis factor-α inhibited endothelial nitric oxide synthase expression in endothelial-trophoblast cellular networks. *Clin Exp Pharmacol Physiol* 2017; 44(3):421-7.

224. Taylor BD, Ness RB, Klebanoff MA, *et al*. First and second trimester immune biomarkers in preeclamptic and normotensive women. *Pregnancy Hypertens* 2016; 6(4):388-93.

225. Song J, Li Y, An R. Vitamin D restores angiogenic balance and decreases tumor necrosis factor-α in a rat model of preeclampsia. *J Obstet Gynaecol Res* 2017; 43(1):42-9.

226. Dong X, Shi D. Simvastatin alleviates pathology in a rat model of preeclampsia involving ERK/MAPK pathway. *Reprod Sci* 2017; 24(7):1053-61.

227. Shaw J, Tang Z, Schneider H, Saljé K, Hansson SR, Guller S. Inflammatory processes are specifically enhanced in endothelial cells by placental-derived TNF-α: Implications in preeclampsia (PE). *Placenta* 2016; 43 : 1-8.

228. Weel IC, Baergen RN, Romão-Veiga M, *et al*. Association between placental lesions, cytokines and angiogenic factors in pregnant women with preeclampsia. *PLoS One* 2016; 11(6): e0157584.

229. Zhou L, Cheng L, He Y, Gu Y, Wang Y, Wang C. Association of gene polymorphisms of FV, FII, MTHFR, SERPINE1, CTLA4, IL10 and TNF alpha with preeclampsia in Chinese women. *Inflamm Res* 2016; 65(9):717-24.

230. Mohammadpour-Gharehbagh A, Jahantigh D, Eskandari M, *et al*. The role of TNF-α and TLR4 polymorphisms in the placenta of pregnant women complicated by preeclampsia and *in silico* analysis. *Int J Biol Macromol* 2019; 134 : 1205-15.

231. Artunc-Ulkumen B, Guvenc Y, Goker A, Gozukara C. Relationship of neutrophil gelatinase-associated lipocalin (NGAL) and procalcitonin levels with the presence and severity of the preeclampsia. *J Matern Fetal Neonat Med* 2015; 28 : 1895-900.

232. Couper KN, Blount DG, Riley EM. IL-10: the master regulator of immunity to infection. *J Immunol* 2008; 180(9):5771-7.

233. Bachmayer N, Rafik Hamad R, Liszka L, Bremme K, Sverremark-Ekström E. Aberrant uterine natural killer (NK)-cell expression and altered placental and serum levels of the NK-cell promoting cytokine interleukin-12 in pre-eclampsia. *Am J Reprod Immunol* 2006; 56 : 292-301.

234. Makris A, Xu B, Yu B, Thornton C, Hennessy A. Placental deficiency of interleukin-10 (IL-10) in preeclampsia and its

relationship to an IL-10 promoter polymorphism. *Placenta* 2006; 27 : 445-51.

235. Yu J, Qian L, Wu F, Li M, Chen W, Wang H. Decreased frequency of peripheral blood CD8CD25FoxP3regulatory T cells correlates with IL-33 levels in pre-eclampsia. *Hypertens Pregnancy* 2017; 36(2):217-25.

236. Cui S, Gao Y, Zhang L, *et al*. Combined use of serum MCP-1/IL-10 ratio and uterine artery Doppler index significantly improves the prediction of preeclampsia. *Clin Chim Acta* 2017; 473 : 228-36.

237. Azizieh FY, Raghupathy R. IL-10 and pregnancy complications. *Clin Exp Obstet Gynecol* 2017; 44(2):252-8.

238. Cubro H, Kashyap S, Nath MC, Ackerman AW, Garovic VD. The role of interleukin-10 in the pathophysiology of pre-eclampsia. *Curr Hypertens Rep* 2018; 20(4):36.

239. Raguema N, Gannoun MBA, Zitouni H, *et al*. Interleukin-10 rs1800871 (-819C/T) and ATA haplotype are associated with preeclampsia in a Tunisian population. *Pregnancy Hypertens* 2018; 11 : 105-10.

240. Zhang Z, Liu H, Shi Y, *et al*. Increased circulating Th22 cells correlated with Th17 cells in patients with severe preeclampsia. *Hypertens Pregnancy* 2017; 36(1):100-7.

241. Xu H, Shi Q, Mo Y, Wu L, Gu J, Xu Y. Downregulation of α7 nicotinic acetylcholine receptors in peripheral blood monocytes is associated with enhanced inflammation in preeclampsia. *BMC Pregnancy Childbirth* 2019; 19(1):188.

242. Nunes PR, Romão-Veiga M, Peraçoli JC, *et al*. Downregulation of CD163 in monocytes and its soluble form in the plasma is associated with a pro-inflammatory profile in pregnant women with preeclampsia. *Immunol Res* 2019; 67(2–3):194-201.

243. Yang SW, Cho EH, Choi SY, *et al*. DC-SIGN expression in Hofbauer cells may play an important role in immune tolerance in fetal chorionic villi during the development of preeclampsia. *J Reprod Immunol* 2017; 124 : 30-7.

244. Heyward CY, Sones JL, Lob HE, *et al*. The decidua of preeclamptic-like BPH/5 mice exhibits an exaggerated inflammatory response during early pregnancy. *J Reprod Immunol* 2017; 120 : 27-33.

245. Cornelius DC, Cottrell J, Amaral LM, LaMarca B. Inflammatory mediators: a causal link to hypertension during preeclampsia. *Br J Pharmacol* 2019; 176(12):1914-21.

246. Choi P, Reiser H. IL-4: role in disease and regulation of production. *Clin Exp Immunol* 1998; 113 : 317-9.

247. Chen J, Zhong M, Yu YH. Association between interleukin-4 polymorphisms and risk of pre-eclampsia in a population of Chinese pregnant women. *Genet Mol Res* 2017; 16(2).

248. Chatterjee P, Chiasson VL, Seerangan G, *et al*. Cotreatment with interleukin 4 and interleukin 10 modulates immune cells and prevents hypertension in pregnant mice. *Am J Hypertens* 2015; 28(1):135-42.

249. Salimi S, Mohammadoo-Khorasani M, Yaghmaei M, Mokhtari M, Moossavi M. Possible association of IL-4 VNTR polymorphism with susceptibility to preeclampsia. *Biomed Res Int* 2014; 2014 : 497031.

250. Omu AE, Makhseed M, Al-Qattan F. The comparative value of interleukin-4 in sera of women with preeclampsia and cord sera. *Nutrition* 1995; 11(5):688-91.

251. Hwang JH, Lee MJ, Seok OS, *et al*. Cytokine expression in placenta-derived mesenchymal stem cells in patients with pre-eclampsia and normal pregnancies. *Cytokine* 2010; 49(1):95-101.

252. Chatterjee P, Kopriva SE, Chiasson VL, *et al*. Interleukin-4 deficiency induces mild preeclampsia in mice. *J Hypertens* 2013; 31(7):1414-23.

253. Fraser R, Walker JJ, Ekbote UV, Martin KL, McShane P, Orsi NM. Interleukin- 4-590 (C > T), toll-like receptor-2 +2258 (G > A) and matrix metalloproteinase-9-1562 (C > T) polymorphisms in pre-eclampsia. *BJOG* 2008; 115(8):1052-6.

254. Azizieh F, Raghupathy R, Makhseed M. Maternal cytokine production patterns in women with pre-eclampsia. *Am J Reprod Immunol* 2005; 54(1):30-7.

255. Kang L, Chen CH, Yu CH, Chang CH, Chang FM. An association study of interleukin-4 gene and preeclampsia in Taiwan. *Taiwan J Obstet Gynecol* 2014; 53(2):215-9.

256. Henriques CU, Rice GE, Wong MH, Bendtzen K. Immunolocalisation of interleukin-4 and interleukin-4 receptor in placenta and fetal membranes in association with pre-term labour and pre-eclampsia. *Gynecol Obstet Invest* 1998; 46 (3):172-7.

257. Omu AE, Makhseed M, Al-Qattan F. Effect of antihypertensive therapy in preeclampsia on levels of serum interleukin-4. *Gynecol Obstet Invest* 1996; 42(4):230-6.

258. Shima Y. The benefits and prospects of interleukin-6 inhibitor on systemic sclerosis. *Mod Rheumatol* 2019; 29(2):294-301.

259. Tangerås LH, Austdal M, Skråstad RB, *et al*. Distinct first trimester cytokine profiles for gestational hypertension and preeclampsia. *Arterioscler Thromb Vasc Biol* 2015; 35(11): 2478-2485.

260. Peixoto AB, Araujo Júnior E, Ribeiro JU, *et al*. Evaluation of inflammatory mediators in the deciduas of pregnant women with pre-eclampsia/eclampsia. *J Matern Fetal Neonatal Med* 2016; 29(1):75-9.

261. Bueno-Sánchez JC, Agudelo-Jaramillo B, Escobar-Aguilerae LF, *et al*. Cytokine production by non-stimulated peripheral blood NK cells and lymphocytes in early-onset severe pre-eclampsia without HELLP. *J Reprod Immunol* 2013; 97(2):223-31.

262. Brewster JA, Orsi NM, Gopichandran N, Ekbote UV, Cadogan E, Walker JJ. Host inflammatory response profiling in preeclampsia using an *in vitro* whole blood stimulation model. *Hypertens Pregnancy* 2008; 27(1):1-16.

263. Jonsson Y, Matthiesen L, Berg G, Ernerudh J, Nieminen K, Ekerfelt C. Indications of an altered immune balance in preeclampsia: a decrease in in vitro secretion of IL-5 and IL-10 from blood mononuclear cells and in blood basophil counts compared with normal pregnancy. *J Reprod Immunol* 2005; 66 (1):69-84.