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TNF-α, TNF-R1, TNF-R2 levels in women with normal pregnancy, preeclampsia, and preeclampsia with sepsis

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Abstract

Preeclampsia (PE) is a disorder in pregnancy with a worldwide prevalence of about 5-8% of cases. TNF is the main physiological mediator of the inflammatory process. These membrane-bound and soluble cytokines are biologically active. They have different affinities for two types of TNF receptors, apoptotic receptors (TNFR1) and non-apoptotic receptors (TNFR2). This study reveals the levels of TNF-α, TNF-R1, TNF-R2 in women with normal pregnancy, preeclampsia, and preeclampsia with sepsis. An observational analytic cross sectional research design is applied. The minimum number of sample is 14 women for each group (group 1: women with normal pregnancy, group 2: preeclampsia, and group 3: preeclampsia with sepsis). The results show that

- There is an increase in TNF- levels in preeclamptic women and in preeclamptic women with sepsis
- There is an increase in TNF-R1 receptor levels in preeclamptic women and in preeclamptic women with sepsis
- There is an increase in TNF-R2 receptor levels in preeclamptic women and in preeclamptic women with sepsis.

Keywords: TNF level; Women; Preeclampsia; Preeclampsia with sepsis

1. Introduction

Preeclampsia (PE) is a disorder in pregnancy with a worldwide prevalence of about 5-8% of cases. PE is one of the leading causes of maternal death, causing about 50,000-60,000 deaths annually worldwide [1]. In Indonesia, based on the 2015 Indonesian Demographic and Health Survey (IDHS), the MMR is 161 per 100,000 live births. Meanwhile, the target of the National Medium Term Development Plan (RPJMN) is 102 per 100,000 live births. Maternal mortality in Indonesia is still dominated by the three main causes of death, namely bleeding, hypertension in pregnancy (preeclampsia) and infection.

In countries with advanced health care systems, sepsis remains a major preventable cause of maternal morbidity and mortality. Over the past decade, the incidence of maternal mortality due to severe maternal sepsis has increased in several European countries, especially the UK [2].

Sepsis was originally used as a term to indicate the presence of organisms that can be cultured from the host or samples from the host, also known as bacteremia. With the recognition that bacterial products can cause a cytokine storm which can be fatal, the term sepsis now refers to an early stage (based on the findings of infection) that can progress to septic shock and ultimately lead to mortality. Based on its development, it can be seen that preeclampsia in pregnancy has a process similar to the septic cascade in a mild form that involves an inflammatory process [3].

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In preeclampsia, the disordered immune system is the result of the predominance of the T1 subgroup, increased release of pro-inflammatory cytokines from the placenta, aberrant macrophage activation and a persistent dNK phenotype promoting a pro-inflammatory environment, which in turn activate other immune cells. Elevated levels of inflammatory cytokines, particularly Tumor Necrosis Factor Alpha (TNF-α) and Interleukin-6 (IL-6), result in widespread dysfunction of the maternal vascular endothelium that can lead to hypertension [4].

TNF is the main physiological mediator of the inflammatory process. These membrane-bound and soluble cytokines are biologically active. They have different affinities for two types of TNF receptors, apoptotic receptors (TNFR1) and non-apoptotic receptors (TNFR2), and thus may confer different biological properties [5].

TNF- in preeclampsia was found to increase vascular permeability, fibroblast proliferation and lymphocyte activation, and induce the production of IL-6 and IL-8. TNF-α downregulates eNOS and mitochondrial biogenesis, leading to mitochondrial dysfunction, oxidative stress and increased ROS. TNF- can also modify the expression of adhesion molecules in placental vessels and induce abnormal MMP production in PE [6].

In sepsis itself there is excessive inflammation and immune suppression, and many studies have shown that TNF is a major mediator of the inflammatory response seen in sepsis and shock, life-threatening conditions caused by circulatory and/or metabolic abnormalities [7].

Based on a search of the existing literature, there have been no studies that have detailed observations of changes in TNF- levels and its receptors in pregnancy, especially in women with preeclampsia and sepsis. Although there has been some literature that uses TNF inhibitors as therapy in several diseases such as Rheumatoid Arthritis, Inflammatory Bowel Disease, psoriasis, specific research on preeclampsia is still limited to date [8]. Based on this, the authors are interested in analyzing the differences in levels of TNF alpha and its types in the state of preeclampsia and sepsis.

Specific Problem Formulation

- Are there differences in TNF alpha levels in women with normal pregnancy, preeclampsia, and preeclampsia with sepsis?
- Are there differences in TNF R1 levels in women with normal pregnancy, preeclampsia, and preeclampsia with sepsis??
- Are there differences in TNF R2 levels in women with normal pregnancy, preeclampsia, and preeclampsia with sepsis?

2. Material and methods

The research design used was an observational analytic cross sectional research design. Observational analysis is research without giving treatment from the researcher to the subject. The researcher only observes the behavior or characteristics as well as the cause and effect of an event, then the researcher analyzes it further. Cross sectional study is a type of research in which the measurement of the variables is carried out only once in a period of time. In this study, blood samples were obtained from normal, pre-eclamptic, and pre-eclamptic pregnant women with sepsis. Data is displayed in descriptive form.

The location of this research is the Regional General Hospital dr. Saiful Anwar Malang to obtain blood samples of normal pregnant, preeclampsia, and preeclampsia patients with sepsis. Biomedical Laboratory, Faculty of Medicine, Universitas Brawijaya for sample examination.

This study uses blood samples of normal pregnant women, preeclampsia, and preeclampsia who have sepsis which has received approval from the Ethics Commission of the Faculty of Medicine, Universitas Brawijaya. All human subjects who participated in this study were explained about the research procedures to be carried out and asked to sign an informed consent form.

This study used venous blood samples with the following criteria

2.1. Inclusion criteria

2.1.1. Case

- Pre-eclamptic pregnant women (Pregnant at >28 weeks gestation)
- Pregnant women with preeclampsia who develop sepsis
- Willing to take part in research

2.1.2. Control

- Pregnant women who do not have preeclampsia or sepsis (Pregnant >28 weeks gestation)
- Willing to take part in research

2.2. Exclusion criteria

- Pregnant women who are suffering from infectious diseases
- Pregnant women with chronic hypertension
- Pregnant women with diabetes mellitus
- Not taking drugs for a long time (anti-inflammatory steroids or NSAIDs)

The minimum sample size is 13.11649 or rounded up to 14 people. This size is the minimum number of samples that must be met, the addition of the minimum number of samples is intended so that the sample can be more representative of the observed population.

Samples were given information and divided into 3 groups

- Group I : Normal pregnancy blood serum (control)
- Group II: Pregnancy blood serum with preeclampsia
- Group III: Blood serum for pregnancy with preeclampsia with sepsis

Research variable is something that is used as a characteristic, trait, or measure that is owned or obtained by the research unit about a certain concept of understanding. The variables used in this study are

2.2.1. Independent variables (Independent)

The independent variables in this study were levels of TNF-α, TNF-R1, TNF-R2.

2.2.2. Bound variable (Dependent)

The dependent variables in this study were normal pregnancy blood, preeclampsia and preeclampsia with sepsis.

The approach used was to observe the total levels of TNF-α, TNFR1, and TNF-R2 in blood serum of preeclampsia and sepsis pregnancy.

Observation of the expression of TNF-α, TNF-R1, and TNF-R2 using the Enzym-linked Immunosorbent Assay (ELISA) method.

3. Results and discussion

This study aims to determine the differences in levels of TNF alpha and its receptors in various conditions including normal pregnant women, mothers with preeclampsia and preeclampsia mothers with sepsis. Table 1 shows that women with preeclampsia showed higher levels of TNF-∝ when compared to normal pregnant women. There was a significant difference in the mean TNF-∝ levels between the normal pregnant women group (44.52±3.66a pg/mL) and the preeclampsia group (63.33±9.94b pg/mL). And preeclampsia mothers with sepsis showed higher TNF-∝ levels when compared to normal pregnant women. And there was a significant difference in the mean TNF-∝ level between the group of normal pregnant women (44.52±3.66a pg/mL) and the group of preeclamptic women with sepsis (117.18±20.63c pg/mL). Mothers with preeclampsia with sepsis showed higher levels of TNF-∝ when compared to women with preeclampsia. In other words, there was an increase in TNF-∝ levels in preeclamptic women and in preeclamptic women with sepsis. So the first research sub hypothesis has been proven, namely there is an increase in TNF-∝ levels in women with preeclampsia and sepsis. This was because monocytes exposed to PE plasma produced more TNF-∝ and IL-6 than cells exposed to plasma from normal pregnancy. This is probably due to the regulatory effect

of IL-10 on monocytes that regulates the inflammatory response that occurs during normal pregnancy by controlling TNF-∝ and IL-1β gene expression, and this IL-10-mediated regulatory activity may be lost in PE [9].

Table 1 Comparison of TNF-∝ levels (ng/mL**)**

Group	Mean + SD	p-value
Mothers with normal pregnancy	44.52+3.66a	0.000<α
Mothers with preeclampsia	63.33+9.94a	
Mothers with preeclampsia and sepsis	117.18+20.63a	

This secreted form of 17-kDa molecular weight TNF is produced by enzymatic cleavage of membrane-bound TNF by a metalloproteinase called the TNF- converting enzyme (TACE). Both TNF in dissolved and membrane form are considered as homotrimers held together by noncovalent interactions via trimerization domains. Both membrane-bound and soluble TNF are biologically active.

In preeclampsia, having a disordered immune system includes increased release of pro-inflammatory cytokines from the placenta, aberrant macrophage activation and a dNK phenotype that continuously promotes a pro-inflammatory environment, which in turn activates other immune cells. Elevated levels of inflammatory cytokines, particularly TNF- and IL-6, result in widespread dysfunction of the maternal vascular endothelium that can lead to hypertension [4]. Placental ischemia can increase the synthesis of inflammatory cytokines. Immediately following placental reperfusion injury, the regenerated blood stream releases cytokines and inflammatory factors such as TNF- and IL. TNF- is released from the hypoxic placenta and is a major modifier of the immune response.

TNF and IL 6 mediate immunological, inflammatory, and reparative responses from the host. In preeclampsia, placental ischemia can contribute to maternal endothelial cell dysfunction by increasing the synthesis of IL6, TNF and IL8 [10]. So if based on the existing theory it is proven that there is a significant increase in TNF- in preeclampsia mothers.

At the placental level, the cytokines IL-6 and TNF- were shown to induce excessive apoptosis as well as necrotic death of trophoblast cells; these cells were shown to induce endothelial activation when released. TNF- has potent effects on endothelial and platelet function, increasing coagulation, microvascular leakage, vasoconstrictive endothelial cell activation, and production of antiangiogenic factors such as tissue factor. TNF- and IL-1 cause increased production of thrombin, platelet activating factor, and cell adhesion molecule-1, increased endothelial cell permeability, and increased coagulation, and thereby trigger an inflammatory response. TNF- has been shown to induce endothelial cell activation and cause endothelial damage [11].

In preeclamptic women with sepsis showed a significant increase in TNF due to infection that occurs systemically induced by Toxoplasma gondii, Listeria monocytogenes, Yersinia pestis or other microbes, IL-12 secreted by DC induces NK cells to produce the broad immunosuppressive cytokine IL-10, TNF . And the widespread infection activates humoral elements (complements, acute-phase proteins and cytokines) and cellular elements (monocytes, macrophages, and anti-inflammatory mediators) resulting in greatly elevated levels of TNF- in the blood.

The main source of TNF is mononuclear phagocytes, this cytokine is also produced by T cells, NK cells, and mast cells. This can be considered as a potential biomarker for diagnosing sepsis. In addition, markers that have been used as routine clinical examinations include interleukin 6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP). Tumor necrotic factor (TNF) alpha was one of the first soluble factor proteins to be described in the context of septic disease. TNF has a close relationship with the pathogenesis of sepsis, and found an increase in TNF levels in the serum of patients diagnosed with sepsis [12]. Appropriate amounts of TNF are likely to have a beneficial effect on host survival against infection, but excessive levels of TNF can cause toxicity, which, at the cellular level, manifests as cell death.

Plasma TNF concentrations correlate with sepsis severity, and a meta-analysis of anti-TNF therapy in human sepsis trials suggests that inhibition of TNF or TNF-dependent signaling confer beneficial benefits. Thus, TNF remains an attractive target in studies on the pathobiology of sepsis, as well as a target in new human sepsis trials such as the one in this study.

TNF-∝ has been shown to directly stimulate endothelial cells in culture to secrete endothelin 1 and cell adhesion molecules that attract leukocytes to adhere to vascular tissue and play a role in edema and hypertension. TNF induces

oxidative damage by disrupting electron flow in mitochondria resulting in the release of oxidizing free radicals and the formation of peroxides that damage endothelial cells. TNF stimulates production

Angiotensin II in the female reproductive tract and IL6 regulates the expression of angiotensin II type 1 receptors in vascular smooth muscle. TNF has been shown to induce fever, activate the coagulation system, induce hypoglycemia, suppress cardiac contractility, reduce vascular resistance, induce cachexia, and activate acute-phase responses in the liver.

It has been proven in this study that the levels of TNF in preeclampsia mothers with sepsis increased significantly. With an increase in TNF will have an effect on overall cellular abnormalities that can cause a much decreased body condition so that it can be used as a prognosis for preeclampsia and preeclampsia mothers with sepsis.

3.1. Differences in TNF R1 levels in mothers with preeclampsia and preeclampsia with sepsis

TNF exerts its effects by activating cellular signaling pathways through two types of receptors, TNFR1 (p55) and TNFR2 (p75), both of which are released by the cell surface through proteolysis. TNF is essential for promoting a robust immune response through TNFR1. The 55-kDa TNF receptor (TNF-R1) plays a role in inducing apoptosis and the 75-kDa TNF receptor (TNF-R2) induces proliferation through the activation of transcription factor-κB. TNFR1 is expressed at various sites in almost all cells in the body and can be activated by mTNFα and sTNFα. Table 2 shows an increase in TNF-R1 receptor levels although only slightly increased in preeclamptic women compared to normal pregnant women. However, there was a significant difference in the mean TNF-R1 receptor level between the group of normal pregnant women (14.04±1.21a ng/L) and the group of preeclamptic women with sepsis (71.98±16.03b ng/L). This suggests that the function of serum concentrations of soluble TNF-R as a marker for TNF-overload biological activity is evident, as these receptors have longer half-lives than their ligands.

Table 2 Comparison of TNF-R1 receptor (ng/mL)

Group	**Mean ± SD**	***p-value***
Mothers with normal pregnancy	14.04±1.21[a]	0.000<α
Mothers with preeclampsia	16.79±1.48[a]	
Mothers with preeclampsia and sepsis	71.98±16.03[a]	

Soluble TNF and membrane TNF bind to two trans membrane receptor molecules: TNFR1 (also known as p55/p60) - a death domain-containing protein, and TNFR2 (also known as p75/p80). Intracellular molecular signaling pathway recruited on TNF R1 via TRADD (TNF receptor-associated death domain). The cytoplasmic domains of several receptors, including TNFR1, death receptor 3 (DR3), DR4, DR5, and FAS contain an 80-amino acid motif referred to as the death domain (DD). So that if it is found that TNF which is increased in eclampsia conditions, the level of TNF R1 in the serum will also increase. TNFR1 is required for the recruitment of DD-containing adapter molecules involved in the initiation of apoptotic cell death. For this reason, these receptors are referred to as "death receptors". As evidenced from previous studies, there was an increase in TNF-R1 levels in preeclamptic women.

In this study, it showed a significant increase in TNF-R1 levels in preeclamptic women with sepsis compared to normal pregnant women. With sepsis conditions increase TNF excessively so that TNF-R1 activation increases causing hepatocyte apoptosis, and thus causes organ damage. However, membrane-bound TNFR1 can be cleaved through the proteolytic release of its ectodomain, which is dependent on the activation of the TNF-converting enzyme (TACE, also known as ADAM17). Receptor release is thought to be a protective mechanism by reducing the cellular response to TNF and also by binding and releasing TNF to the extracellular space. TNFR1 release is a self-protective mechanism against the resulting effects of excessive amounts of TNF and blocking intracellular signaling by TNF [13], [6].

3.2. Differences in TNF R2 levels in preeclampsia and preeclampsia with sepsis

Table 3 shows that the mean value of TNF-R2 receptor levels in the group of preeclamptic women was found to increase compared to the average value of TNF-R2 receptor levels in the group of normal pregnant women, but not significant. Meanwhile, there was a significant difference in the mean TNF-R2 receptor level between the group of preeclamptic women (11.43±1.01a ng/mL) and the group of preeclamptic women with sepsis (28.96±7.99b ng/mL). It appears that the mean value of TNF-R2 receptor levels in the group of preeclamptic women with sepsis is greater than the average

value of TNF-R2 receptor levels in the group of preeclamptic women. This means that preeclampsia mothers with sepsis will show higher levels of TNF-R2 receptors when compared to preeclampsia mothers.

Table 3 Comparison of TNF-R2 receptor (ng/mL)

Group	Mean ± SD	*p-value*
Mothers with normal pregnancy	9.64±1.19[a]	0.000<α
Mothers with preeclampsia	11.43±1.01[a]	
Mothers with preeclampsia and sepsis	28.96±7.99[a]	

The 75-kDa TNF receptor (TNF-R2) functions to induce proliferation through activation of transcription factor-κB. TNFR2 is limited to thymic T lymphocytes, endothelial cells, microglia, and oligodendrocytes, and can only be fully activated by mTNFα. After mTNFα binds to TNFR2, the two bonds are too stable to be separated. This is not the case with sTNFα which induces weak signaling and exhibits low affinity for TNFR2. So far no one has evaluated sTNF-R2, before this disease shows clinical manifestations. In addition, in a previous study, elevated levels of sTNF-R2 had poor sensitivity and limited positive predictive value for the development of preeclampsia in later life. In contrast to previous studies, this study has demonstrated a significant increase in TNF R2 in women with preeclampsia compared to normal pregnant women. From the results of this study, there was a significant increase in TNF-R2 levels in preeclamptic women with sepsis compared to normal pregnant women. TNF-R2 levels increased in response to a significant increase in TNF- in septic conditions.

TNF-R2 contains TRAF protein that does not have Death Domain which will activate the NF-κB and MAPK pathways through recruitment and activation of protein complexes that stimulate this signaling cascade, which will lead to differentiation, inflammation, organogenesis and angiogenesis. TRAF2 will also increase the activation of Tregs which can provide inhibitory feedback on the TRADD pathway (death domain activation pathway in TNF) thereby inhibiting apoptosis.

TNFR2 in activated T cells provides costimulatory signals necessary for effector T cell expansion and differentiation. Several studies have demonstrated the immune modulating role of TNFR2 especially in Treg cells. TNFR2 activation is important for the proliferation, survival and stability of the Treg cell lineage, and the development of thymic Treg cells from Treg precursor cells. TNFR2 also limits CD8+ cells that mediate viral clearance and antitumor immunity. Several studies have shown that TNFR2 expression in CD8+ T cells reduces the accumulation of functional CD8+ T cells during viral or tumor attack. During acute influenza infection, the interaction between TNF and TNFR2 leads to rapid contraction of CD8+ T cells and reduces immunopathology by reducing levels of bioactive TNF due to an increase in soluble TNFR2 in the lung.

3.3. Ratio of TNF R1 levels compared to TNF R2 in normal pregnant women, preeclamptic women and preeclamptic women with sepsis

In this study, the results (Table 4) obtained mean TNF R1 levels in normal pregnant women (14.04 ± 1.20 ng/mL) and mean TNF R2 levels in normal pregnant women (9.6 ± 1.18 ng/mL). It appears that the average value of TNF-R1 receptor levels in normal pregnant women is greater than the average TNF-R2 receptor levels in normal pregnant women. This means that normal pregnant women will show an increase in the level of the TNF-R1 receptor as much as 1.4 times compared to the level of the TNFR2 receptor. And the mean TNF-R1 receptor level in preeclamptic women (16.79±1.48 ng/mL) with the mean TNF-R2 receptor level in preeclamptic mothers (11.43±1.01 ng/mL).

Table 4 Ratio of TNF-R1 compared to TNF-R2 in mother with normal pregnancy, mother with preeeclampsia, and mother woth preeclampsia and sepsis

Group	TNF-R1 Mean ± SD	TNF-R1 Mean ± SD	Ratio
Mothers with normal pregnancy	14.04±1.20[a]	9.64±1.19[a]	1.4x
Mothers with preeclampsia	16.79±1.48[a]	11.43±1.01[a]	1.4x
Mothers with preeclampsia and sepsis	71.98±16.03[a]	28.96±7.99[a]	2.5x

It appears that the mean TNF-R1 receptor level in preeclamptic mothers is greater than the mean TNF-R2 receptor level in preeclamptic mothers. This means that preeclampsia mothers will show an increase in TNF-R1 receptor levels as much as 1.4 times compared to TNF-R2 receptor levels. Similarly, in the group of preeclamptic women with sepsis, the mean TNF-R1 receptor level was (71.98±16.03 ng/mL) with the mean TNF-R2 receptor level (28.96±7.99 ng/mL). It appears that the mean value of TNF-R1 receptor levels in preeclamptic women with sepsis is greater than the mean TNF-R2 receptor levels in preeclamptic women with sepsis. This means that women with preeclampsia with sepsis will show an increase in TNF-R1 receptor levels as much as 2.5 times compared to TNF-R2 receptor levels.

TNFR1 is expressed at various sites on almost all cells in the body and can be activated by mTNFα and sTNFα. TNFR2, in contrast, is confined to thymic T lymphocytes, endothelial cells, microglia, and oligodendrocytes, and can only be fully activated by mTNFα [14], [15]. After mTNFα binds to TNFR2, the two bonds are too stable to be separated. This is not the case with sTNFα which induces weak signaling and exhibits low affinity for TNFR2. This causes TNF R1 levels to be higher than TNF R2 levels in preeclamptic women and in preeclamptic women with sepsis.

4. Conclusion and recommendations

- There is an increase in TNF-α levels in preeclamptic women and in preeclamptic women with sepsis.
- There is an increase in TNF-R1 receptor levels in preeclamptic women and in preeclamptic women with sepsis.
- There is an increase in TNF-R2 receptor levels in preeclamptic women and in preeclamptic women with sepsis.

Based on this study, it is necessary to carry out further research conducted on a larger number of samples so that it can increase the validity of this study and can be considered as a potential biomarker for diagnosing sepsis. Further testing is needed to examine other factors that play a role in the activity of TNF-α, TNF-R1 receptors, TNF-R2 such as TACE (TNF-converting enzyme), TRADD, TRAF, and Treg. It is necessary to conduct further research on factors that can block TNF -α so that therapeutic options can be found for preeclampsia and preeclampsia with sepsis conditions.

Compliance with ethical standards

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Statement of informed consent

Patients who have been designated as research samples based on inclusion and exclusion criteria prior to taking blood samples have been educated about the objectives and benefits of the research conducted before the patient expresses approval to be a research sample.

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