DOI: 10.30651/jqm.v8i02.20427

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Research Article

Exploring cytokine levels in pregnancy, preeclampsia, and sepsis-complicated preeclampsia

Mira Kusuma Wardhani[1*], Harry Kurniawan Gondo[2]

1, 2) Faculty of Medicine, Wijaya Kusuma University, Surabaya

ARTICLE INFO

Submitted : 03rd October 2023
Accepted : 08 th March 2024
Published : 25th July 2024

Keywords:

TNF levels, healthy pregnancy, preeclampsia, sepsis-complicated preeclampsia

Correspondence:
mirakw@uwks.ac.id

ABSTRACT

Around the world, preeclampsia (PE) influences five to eight percent of pregnancies and contributes significantly to maternal mortality. This study applies a scientific observational cross-sectional review to examine how TNF-α, TNF-R1, and TNF-R2 play their roles in healthy pregnancy, preeclampsia, and preeclampsia associated with sepsis. Blood tests were gathered from subjects at a local medical clinic in Malang, Indonesia, and TNF-α, TNF-R1, and TNF-R2 levels were surveyed utilizing the Enzyme-Linked Immunosorbent Assay (ELISA) strategy. The results demonstrate raised TNF-α levels in both preeclampsia and preeclampsia with sepsis, along with expanded TNF-R1 and TNF-R2 receptor levels, signifying their association in these circumstances. Validation through more extensive scope studies is basic, possibly situating TNF-α as an early indicative biomarker for sepsis. This study highlights the importance of TNF-α in pregnant mothers with preeclampsia and preeclampsia muddled by sepsis, uncovering possible analytic and remedial avenues.

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

INTRODUCTION

Preeclampsia (PE) poses a significant threat to global maternal health, affecting 5-8% of pregnant women and contributing substantially to maternal mortality (Gathiram & Moodley, 2016). Despite efforts, the 2015 Indonesia Demographic and Health Survey (IDHS) indicates a maternal death rate exceeding the national target (RPJMN) of 102 per 100,000 live births, with preeclampsia, hemorrhage, and infection identified as leading causes. Moreover, advanced healthcare settings continue to witness unnecessary maternal deaths from sepsis, with rising mortality rates observed in the UK and European countries (Acosta, et al., 2013).

Understanding the evolution of sepsis and its connection to preeclampsia is crucial. Preeclampsia during pregnancy is considered a minor form of sepsis, sharing inflammatory processes (Kell & Kenny, 2016). Elevated inflammatory cytokines, such as TNF-α and IL-6, damage the maternal vascular endothelium and contribute to hypertension (Geldenhuys, Rossouw, Lombaard, Ehlers, & Kock, 2018).

This study delves into the physiological mediator of inflammation, TNF, and its receptors (TNFR1 and TNFR2), particularly in pregnant women with healthy pregnancy, preeclampsia, and sepsis-complicated preeclampsia. Current research on TNF-α levels and receptors in pregnant women, especially those with preeclampsia and sepsis, is limited, necessitating further exploration (Yang, Wang, Brand, & Zheng, 2018).

In preeclampsia, TNF-α, a type-1 cytokine, has negative consequences, causing trophoblast death and inhibiting differentiation and invasion crucial for implantation and placental development (Acosta, et al., 2013). Dysregulation of TNF-α can hinder cytotrophoblast penetration into uterine spiral arteries, contributing to preeclampsia's pathogenesis.

The study investigates the complex relationship between TNF-α, TNFR1, and TNFR2 levels in pregnant women facing different situations. This exploration aims to unravel novel insights into the inflammatory dynamics of preeclampsia and sepsis, paving the way for targeted interventions and therapeutic strategies in maternal health.

METHODS

This cross-sectional observational study, conducted from August to October 2019 at Malang's Regional General Hospital Dr. Saiful Anwar, utilized blood samples from pregnant women meeting specific criteria. Inclusion criteria encompassed willingness to participate and being diagnosed with preeclampsia (>28 weeks) or sepsis. Exclusion criteria included ongoing infections, severe hypertension, diabetes, or the use of long-term medications like steroids or NSAIDs. The sample size was determined using a formula by Xiong et al. (2023) with a significance level (α) of 0.05 and 80% power, resulting in a minimum of 14 participants. Three observation groups were established: Group I (control) from healthy pregnant women, Group II from preeclampsia patients, and Group III from preeclampsia with sepsis patients.

The study focused on independent variables (TNF-α, TNF-R1, TNF-R2) and dependent variables (blood samples from healthy pregnancy, preeclampsia, and sepsis-complicated preeclampsia). ELISA was employed to quantify TNF-α, TNF-R1, and serum TNF-R2 levels in serum. Parametric tests, including independent ones, were used for comparison sample t-tests for normally distributed data, and non-parametric tests like the Mann-Whitney test for non-normally

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

distributed data were used to compare assessed data normality. Variable correlations were examined using the Pearson correlation test for normally distributed data and the Spearman rho test for non-normally distributed data. This study aimed to determine relationships by analyzing TNF-α, TNF-R1, and TNF-R2 levels in pregnant women with various illnesses.

Ethical clearance statement: This research has obtained ethical clearance from the Ethiersity of Wijaya Kusuma Surabaya, as the Ethics Committee indicated by the official letter with reference number 32/SLE/FK/UWKS/2019.

RESULTS

Table 1 displays sample characteristics. One-way ANOVA results for age and BMI yield p-values of 0.018 and 0.000, respectively, indicating significance ($p < 0.05$). Age data reveals older patients with preeclampsia (32.50±5.57) and preeclampsia with sepsis (30.36±6.23), with Table 1 showing a significant p-value of 0.018 for age differences among the three groups. Similarly, BMI data has a significant p-value of 0.000, indicating different group differences in preeclampsia and preeclampsia, with sepsis patients having higher BMIs (32.02±1.24 and 30.65±1.83).

The Chi-Square test for pregnancy age in Table 1 shows no significant difference ($p=0.921>\alpha$). The most common pregnancy age in all groups is 28-36 weeks, followed by 37-40 weeks. Pregnancy age >40 weeks is the least common. Parity distribution also shows no significant difference ($p=0.484>\alpha$), with each group evenly distributed in parities (0, 1, 2, 3, and 4).

Table 1. Characteristics of age, BMI (Body Mass Index), gestational age, and parity

Variable	Group			p-value
	Healthy Pregnancy	Preeclampsia	Preeclampsia + sepsis	
Age	25.79±6.35	32.50±5.57	30.36±6.23	0.018*
BMI	26.54±1.03	32.02±1.24	30.65±1.83	0.000*
Gestational age:				
28 – 36 weeks	8 (57.1%)	10 (71.4%)	8 (57.1%)	
> 36 – 40 weeks	5 (35.7%)	3 (21.4%)	5 (35.7%)	0.921
≥ 40 weeks	1 (7.1%)	1 (7.1%)	1 (7.1%)	
Parity:				0.484
0	5 (35.7%)	2 (14.3%)	5 (35.7%)	
1	5 (35.7%)	6 (42.9%)	7 (50.0%)	
2	3 (16.7%)	5 (35.7%)	1 (7.1%)	
3	1 (7.1%)	1 (7.1%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	1 (7.1%)	

Note: If the p-value is <0.05, there is a significant difference, and if the p-value is >0.05, it means there is no significant difference.

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Table 2 displays the mean TNF-α levels, revealing a significant difference between healthy pregnant women (44.52±3.66a ng/mL) and preeclampsia patients (63.33±9.94b ng/mL) using the LSD test. Research indicates that pregnant women with preeclampsia had elevated TNF-α levels relative to healthy individuals. Patients with preeclampsia and sepsis have significantly higher TNF-α levels (117.18±20.63c ng/mL) than those with healthy pregnancies. Women with preeclampsia and sepsis had elevated TNF-α levels compared to those without these illnesses. TNF-α levels differ significantly between preeclampsia (63.33±9.94b ng/mL) and sepsis (117.18±20.63c ng/mL). Women with both preeclampsia and sepsis have enhanced TNF-α levels compared to those with only preeclampsia. Table 3 indicates elevated TNF-α levels in women with preeclampsia and sepsis, particularly in advanced cases.

As can be seen in Figure 1, the lowest mean TNF-α level belongs to healthy pregnant women, followed by preeclampsia and preeclampsia with sepsis. One-way ANOVA was used to compare TNF-R1 levels in healthy pregnant women with preeclampsia with or without sepsis. The one-way ANOVA specified meaningful differences (p-value 0.000, below α).

Table 2. Comparison of TNF-a levels (ng/mL)

Observation group	Mean ± SD	p-value
Healthy pregnancies	44.52±3.66a	
Preeclampsia	63.33±9.94b	0.000 < a
Preeclampsia with sepsis	117.18±20.63b	

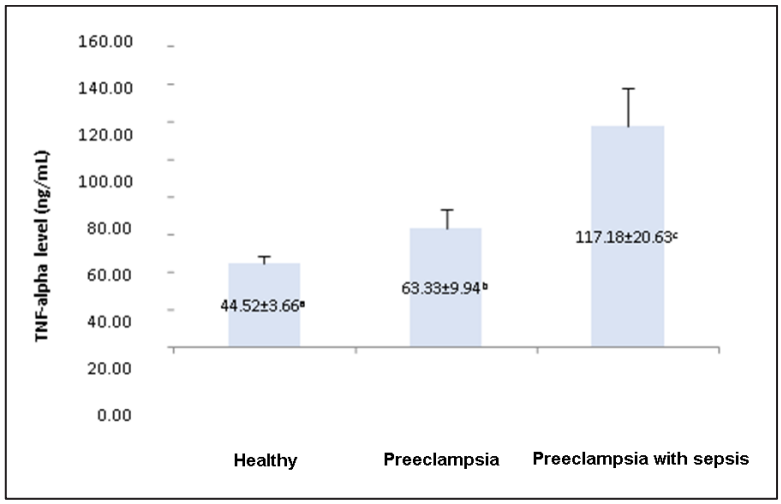

Figure 1. Histogram of mean TNF-a levels

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Table 3 shows no significant difference in TNF-R1 levels between healthy pregnant women (14.04±1.21a ng/mL) and preeclampsia women (16.79±1.48a ng/mL). Preeclampsia patients had higher mean TNF-R1 levels than healthy pregnant women, but not significantly. Mean TNF-R1 levels differed considerably between healthy pregnant women and those with preeclampsia and sepsis (71.98±16.03b ng/mL). Both preeclampsia and sepsis patients had far higher TNF-R1 levels than healthy pregnant women. Mean TNF-R1 levels differed considerably between preeclampsia (16.79±1.48a ng/mL) and sepsis (71.98±16.03b ng/mL). This suggests that preeclampsia and sepsis increase TNF-R1 levels considerably.

Table 4 demonstrates that preeclampsia and sepsis increase TNF-R1. Preeclampsia and sepsis mothers have higher TNF-R1 levels, supporting the second sub-hypothesis.

The histogram in Figure 2 reveals that healthy pregnant women had the lowest mean TNF-R1 levels, followed by preeclampsia and sepsis, supporting the findings.

In this research, preeclampsia women with and without sepsis were tested for TNF-R2. TNF-R2 levels were compared using a one-way ANOVA test between healthy pregnant women and preeclampsia with and without sepsis. A p-value of 0.000 indicates significant differences in a one-way ANOVA below the significance level α.

Table 3. Comparison of TNF-R1 receptor levels (ng/mL)

Observation group	Mean ± SD	p-value
Healthy pregnancies	14.04±1.21a	
Preeclampsia	16.79±1.48a	0.000<a
Preeclampsia with sepsis	71.98±16.03b	

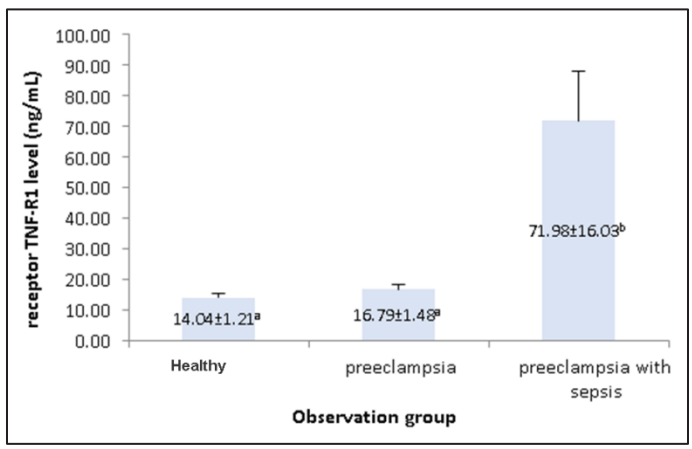

Figure 2. Histogram of mean TNF-R1 receptor levels

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Table 4 shows no significant difference in mean TNF-R2 levels between healthy pregnant and preeclampsia women. Although not statistically higher, preeclampsia patients showed higher mean TNF-R2 levels than healthy pregnant women. Compared to healthy pregnant women, individuals with preeclampsia and sepsis had significantly higher mean TNF-R2 levels (28.96±7.99b ng/mL Healthy pregnant women exhibited far lower TNF-R2 levels than preeclampsia and sepsis patients. The mean TNF-R2 levels in women differed significantly between preeclampsia (11.43±1.01a ng/mL) and sepsis (28.96±7.99b ng/mL). Preeclampsia coupled with sepsis increases TNF-R2 levels more than alone. Table 5 shows increased TNF-R2 levels in preeclampsia and sepsis patients. TNF-R2 elevations in preeclampsia and sepsis mothers support the final sub-hypothesis.

The histogram in Figure 3 demonstrates that healthy pregnant women had the lowest mean TNF-R2 levels, followed by preeclampsia and sepsis.

In this study section, the research aimed to determine the ratio of TNF-R1 to TNF-R2 levels in healthy pregnant women, women with preeclampsia, and women with preeclampsia and sepsis. The researchers calculated the ratio between TNF-R1 and TNF-R2 levels within each group, as presented in Table 5.

Table 4. Comparison of TNF-R2 receptor levels (ng/mL)

Observation group	Mean ± SD	p-value
Healthy pregnancies	9.64±1.19a	
Preeclampsia	11.43±1.01a	0.000<a
Preeclampsia with sepsis	28.96±7.99b	

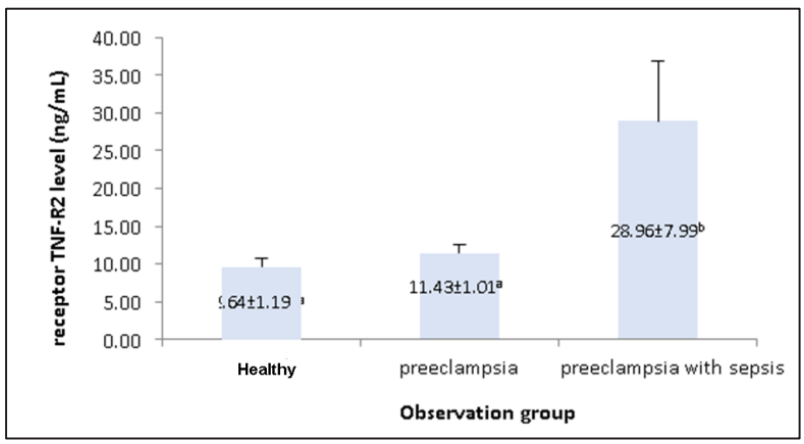

Figure 3. Histogram of mean TNF-R2 receptor levels

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Table 5. The ratio of TNF-R1 to TNF-R2 in healthy pregnant women, preeclamptic women, and preeclamptic women with sepsis

Observation group	TNF-R1	TNF-R2	Ratio
	Mean ± SD	Mean ± SD	
Healthy pregnancies	14.04±1.20	9.60±1.20	1.4x
Preeclampsia	16.79±1.48	11.43±1.01	1.4x
Preeclampsia with sepsis	71.98±16.03	28.96±7.99	2.5x

Table 5 displays the mean TNF-R1 and TNF-R2 levels and the resulting ratio for each group. In the group of healthy pregnant women, the mean TNF-R1 level was 14.04±1.20 ng/mL, and the mean TNF-R2 level was 9.6±1.19 ng/mL. Notably, the mean TNF-R1 level in healthy pregnant women was 1.4 times greater than the mean TNF-R2 level. This result indicates that healthy pregnant women exhibit a 1.4-fold increase in TNF-R1 levels compared to TNF-R2.

Similarly, in the group of women with preeclampsia, the mean TNF-R1 level was 16.79±1.48 ng/mL, and the mean TNF-R2 level was 11.43±1.01 ng/mL. Here, the mean TNF-R1 level in women with preeclampsia was also 1.4 times greater than the mean TNF-R2 level, indicating a 1.4-fold increase in TNF-R1 levels compared to TNF-R2 levels.

In the women with preeclampsia and sepsis group, the mean TNF-R1 level was 71.98±16.03 ng/mL, while the mean TNF-R2 level was 28.96±7.99 ng/mL. In this case, the mean TNF-R1 level in women with preeclampsia and sepsis was 2.5 times greater than the mean TNF-R2 level, signifying a substantial 2.5-fold increase in TNF-R1 levels compared to TNF-R2 levels in these patients.

The Chi-Square test revealed no significant differences in gestational age or parity among the groups. Normality tests confirmed that TNF-a, TNF-R1, and TNF-R2 levels were within the normal range for all groups. Mean TNF-a levels showed a significant increase in preeclampsia (63.33±9.94b ng/mL) and further elevation in preeclampsia with sepsis (117.18±20.63c ng/mL) compared to healthy pregnancy (44.52±3.66a ng/mL). TNF-R1 levels were significantly higher in both preeclampsia (16.79±1.48a ng/mL) and preeclampsia with sepsis (71.98±16.03b ng/mL) compared to healthy pregnancy (14.04±1.21a ng/mL). TNF-R2 levels showed no significant difference between preeclampsia and healthy pregnancy but significantly increased in preeclampsia with sepsis (28.96±7.99b ng/mL). The ratio of TNF-R1 to TNF-R2 increased in preeclampsia and, more prominently, in preeclampsia with sepsis, indicating a potential correlation with disease severity. The study contributes novel insights into the inflammatory dynamics of preeclampsia and sepsis, emphasizing the importance of TNF-related markers.

DISCUSSION

TNF-alpha levels and receptors are compared in healthy, preeclampsia, and preeclampsia with sepsis pregnant women. In preeclampsia, TNF-alpha levels were higher than in healthy pregnant women. TNF-alpha levels differed significantly between groups. Healthy

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

pregnancy levels of TNF-alpha were 44.52±3.66a pg/mL, while preeclampsia patients had 63.33±9.94b pg/mL. A 2015 study by Guillemette et al. (2015) reported that pregnant women with preeclampsia and sepsis had higher TNF-alpha levels (117.18±20.63c pg/mL) than those with healthy and preeclampsia increased TNF-alpha. Due to abnormal immune cell activation and placenta cytokine synthesis, preeclampsia may increase TNF-alpha. Overactive TNF-alpha and IL-6 might damage blood vessels and elevate blood pressure. Placental ischemia—reduced blood flow—can also boost inflammatory cytokines (Minuz, et al., 2015). The restored blood flow following placental reperfusion injury produces cytokines and inflammatory substances such as TNF-alpha and IL, the main immune response modulator.

TNF-alpha and IL-1 mediate host immunological, inflammatory, and reparative responses. Preeclampsia can result from IL6, TNF-alpha, and IL8 affecting the mother's blood vessel cells in ischemic placentas. These chemicals also kill placenta cells and activate blood vessel cells. In particular, TNF-alpha increases small blood vessel blood clotting leaks, tightens blood vessel cells, and produces tissue factors, influencing blood vessel and platelet function (Singh, Raghun, & Bhattacharjee, 2015).

Toxoplasma gondii, Listeria monocytogenes, Yersinia pestis, and other bacteria can raise TNF-alpha levels in preeclampsia and sepsis patients. When there is a broad infection, NK cells release IL-10 and TNF-alpha, suppressing the immune response. This widespread infection increases blood TNF-alpha by triggering complement, acute-phase proteins, cytokines, monocytes, and macrophages (Possomato-Vieira & Khalil, 2016).

Mononuclear phagocytes, T, NK, and mast cells produce most TNF-alpha. In addition to clinical signs, including IL-6, PCT, and CRP, TNF-alpha may be a biomarker for sepsis. TNF-alpha is crucial to sepsis pathogenesis and increases in sepsis patients. This debate compares TNF R1 levels in preeclampsia and sepsis. TNFR1 (p55) and TNFR2 (p75), released from the cell surface via proteolysis, activate cellular signaling pathways. Through TNFR1, TNF boosts immunity (Wardhani, 2022). TNF-R1, a 55-kDa receptor, promotes apoptosis, while TNF-R2, a 75-kDa receptor, activates transcription factor-κB to promote proliferation. This study found that preeclampsia patients had higher TNF-R1 levels than healthy pregnant women.

However, the mean TNF-R1 levels differ significantly between healthy pregnant women (14.04±1.21a ng/L) and preeclampsia with sepsis (71.98±16.03b ng/L). Since soluble TNF-Rs have a longer half-life than their ligands, their serum levels can indicate excessive physiologic TNF activity. TNF is soluble and membrane-bound and binds to two transmembrane receptor molecules: TNFR1 (p55/p60), a death domain protein, and TNFR2 (p75/p80). TNF R1 recruits intracellular signaling pathways via TRADD (Rahardjo, Nurseta, & Sinaga, 2023).

Several receptors, including TNFR1, DR3, DR4, DR5, and FAS, have a ≈80-amino acid motif called the death domain (DD) in their cytoplasmic domains. Serum TNF R1 rises with TNF alpha in preeclampsia. Apoptosis cell death requires TNFR1 to recruit DD-containing adaptor molecules. Thus, it is called the "death receptor" (Walczak, 2013). Preeclampsia increases TNF-R1 levels. TNF-R1 levels were significantly higher in preeclampsia and sepsis patients than in healthy pregnant women. Hepatocyte apoptosis and organ damage result from increased TNF and TNF-R1 activation in sepsis (e Holanda Moura, et al., 2016). TNF-converting enzyme (TACE) activation is

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

needed to remove membrane-bound TNFR1's ectodomain proteolytically.

Receptor shedding protects cells from TNF by binding and releasing it into the extracellular environment. TNFR1 shedding limits intracellular TNF signaling and protects against excessive TNF (Steeland, Libert, & Vandenbroucke, 2018). This section compares TNF R2 levels in preeclampsia and sepsis. In the study, preeclampsia patients had higher mean TNF-R2 levels than healthy pregnant women, although the difference was insignificant. A substantial difference in mean TNF-R2 levels was found between the preeclampsia group (11.43±1.01a ng/mL) and the sepsis group (28.96±7.99b ng/mL). The preeclampsia with sepsis group has higher mean TNF-R2 levels. It means women with preeclampsia and sepsis had higher TNF-R2 levels than those with it alone (Minuz, et al., 2015). TNF-R2, a 75-kDa receptor, activates transcription factor-κB to promote proliferation. Only mTNFα can fully activate TNFR2, which is only found in thymus T lymphocytes, endothelial cells, microglia, and oligodendrocytes (Wardhani, 2022). TNFR2 and mTNFα form a stable connection that cannot be severed.

The phenomenon is not observed with sTNFα, which has poor affinity for TNFR2 and weak signaling. sTNF-R2 has not been tested before this disease's clinical onset. In previous investigations, elevated sTNF-R2 levels demonstrated low sensitivity and minimal positive predictive value for preeclampsia. TNF-R2 was much higher in preeclampsia patients than in healthy pregnant women, contrary to earlier research. TNF-R2 levels are also much higher in preeclampsia and sepsis patients than in healthy pregnant women. The rise in TNF-α levels during sepsis leads to an increase in TNF-R2 levels (Yang, Wang, Brand, & Zheng, 2018). TNF-R2's TRAF proteins, lacking a Death Domain, stimulate NF-κB and MAPK pathways, recruiting and activating protein complexes, triggering signaling cascades for differentiation, inflammation, organogenesis, and angiogenesis. TRAF2 boosts Treg activation, blocking the TRADD pathway (TNF death domain activation pathway) and apoptosis (Kong, Chen, Fan, & Chen, 2020).

TNFR2 activation in T cells offers co-stimulatory signals for T effector cell growth and differentiation. According to several studies, TNFR2 modulates Treg cell immunity (Minuz, et al., 2015). Treg cell proliferation, survival, lineage stability, and thymic formation from Treg precursors need TNFR2 activation. TNFR2 limits CD8+ cell accumulation, which helps remove viruses and fight cancer. Studies demonstrate that TNFR2 expression in CD8+ T cells inhibits functional CD8+ T cell expansion after viral or tumor assaults (Kong, Chen, Fan, & Chen, 2020). TNF and TNFR2 interact to rapidly contract CD8+ T cells during acute influenza infection, lowering immunopathology by decreasing bioactive TNF due to increased soluble TNFR2 in the lungs. Healthy pregnant women, preeclampsia patients, and sepsis patients are investigated for TNF R1 and R2 levels.

The mean TNF R1 level in typical pregnancy was 14.04±1.20 ng/mL, while the mean TNF R2 level was 9.6±1.18 ng/mL. TNF-R1 increased 1.4 times over TNF-R2 in healthy pregnancy. In women with preeclampsia, TNF-R1 levels were substantially higher (16.79±1.48 ng/mL) than TNF-R2 levels (11.43±1.01 ng/mL). TNF-R1 was 1.4 times greater in preeclampsia, leading to a high TNF-R1/TNF-R2 ratio. On average, women with preeclampsia and sepsis had greater TNF R1 levels (71.98±16.03 ng/mL) than TNF R2 levels (28.96±7.99 ng/mL). Preeclampsia and sepsis patients had 2.5 times more TNF-R1 than TNF-R2.

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Research shows that TNFR1 is present in various bodily cells and triggered by mTNFα and sTNFα. T lymphocytes in the thymus, endothelial cells, microglia, and oligodendrocytes express TNFR2. TNFR2 requires mTNFα for optimum activation. Rahardjo et al. (2023) found that TNF R1 levels are more significant in preeclampsia and sepsis due to mTNFα binding to TNFR2 and inconsistent sTNFα signaling activation.

CONCLUSION

The study found a substantial increase in TNF-α levels in pregnant women with preeclampsia and preeclampsia with sepsis, suggesting its significance as a biomarker in the pathophysiology of these disorders. The study found higher TNF-R1 and TNF-R2 receptor levels in these patients, indicating a complex interplay between TNF-α and its receptors. More study with more significant sample numbers is needed to confirm and generalize these findings, potentially establishing TNF-α as an effective sepsis biomarker. Further research should examine elements affecting TNF-α, TNF-R1, and TNF-R2 activity, including TACE, TRADD, TRAF, and Treg cells, to better comprehend their complex pathways in many medical diseases. Prioritizing research on TNF-α suppression could improve preeclampsia and sepsis treatments, improving maternal and fetal health.

REFERENCES

Gathiram, P., & Moodley, J. (2016). Pre-eclampsia: Its Pathogenesis and Pathophysiology. *Cardiovascular Journal of Africa, 27(2)*, 71-78. https://doi.org/10.5830/CVJA-2016-00.

Kell, D. B., & Kenny, L. C. (2016). A Dormant Microbial Component in the Development of Preeclampsia. *Frontiers in Medicine*, 3, 60. https://doi.org/10.3389/fmed.2016.00060.

Geldenhuys, J., Rossouw, T. M., Lombaard, H. A., Ehlers, M. M., & Kock, M. M. (2018). Disruption in the Regulation of Immune Responses in the Placental Subtype of Preeclampsia. *Frontiers in Immunology*, 9, 1659. https://doi.org/10.3389/fimmu.2018.01659.

Kong, C., Chen, M., Fan, X., & Chen, X. (2020). Associations between Hepatocellular Carcinoma Risk and rs3212227 and rs568408 Polymorphisms: A Systematic Review and Meta-Analysis. *Journal of International Medical Research*, 48(8). https://doi.org/10.1177/0.

Possomato-Vieira, J. S., & Khalil, R. A. (2016). Mechanisms of Endothelial Dysfunction in Hypertensive Pregnancy and Preeclampsia. *Advances in Pharmacology*, 77, 361-431. https://doi.org/10.1016/bs.apha.2016.04.008.

Steeland, S. L., Libert, C., & Vandenbroucke, R. E. (2018). A New Venue of TNF Targeting. *International Journal of Molecular Sciences*, 19(5), 1442-1496. https://doi.org/10.3390/ijms19051442.

Yang, S., Wang, J., Brand, D. D., & Zheng, S. G. (2018). Role of TNF–TNF Receptor 2 Signal in Regulatory T Cells and Its Therapeutic Implications. *Frontiers in Immunology*, https://doi.org/10.3389/fimmu.2018.00784.

Minuz, P., Fava, C., Hao, S., Pedraza, P., Amen, G., Meneguzzi, A., . . . Ferreri, N. (2015). Differential regulation of TNF receptors in maternal leukocytes is associated with severe preterm preeclampsia. *The Journal of Maternal-Fetal & Neonatal Medicine*, 28, 869 - 875. https://doi.org/10.3109/14767058.2014.937695.

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Singh, A., Raghun, C., & Bhattacharjee, J. (2015). Endothelin: Link between the Primary Placental Causes and the Secondary Systemic Endothelial Dysfunction in Pathophysiology of Pre-Eclampsia. *Obstetrics & Gynecology International Journal*, 2. https://medcraveonline.com/OGIJ/OGIJ-02-00042.pdf.

Wardhani, M. (2022). TNF-α, TNF-R1, TNF-R2 levels in women with normal pregnancy, preeclampsia, and preeclampsia with sepsis. *World Journal of Advanced Research and Reviews*, https://doi.org/10.30574/wjarr.2022.15.3.0948.

Rahardjo, B., Nurseta, T., & Sinaga, A. (2023). Profile Tumor Necrosis Factor Alpha and Procalcitonin in Preeclampsia and Preeclampsia with Sepsis. Open Access Macedonian . *Journal of Medical Sciences*, https://doi.org/10.3889/oamjms.2023.11644.

Walczak, H. (2013). Death receptor–ligand systems in cancer, cell death, and inflammation. *Cold Spring Harbor perspectives in biology*, 5(5), a008698.

Guillemette, L., Lacroix, M., Allard, C., Patenaude, J., Battista, M. C., Doyon, M., & Hivert, M. F. (2015). Preeclampsia is associated with an increased pro-inflammatory profile in newborns. *Journal of reproductive immunology*, 112, 111-114. https://doi.org/10.1016/j.jri.2015.09.003.

e Holanda Moura, S. B., Park, F., Murthi, P., Martins, W. P., Kane, S. C., Williams, P., & Silva Costa, F. D. (2016). TNF-R1 as a first trimester marker for prediction of pre-eclampsia. . *The Journal of Maternal-Fetal & Neonatal Medicine,*, 29(6), 897-https://doi.org/10.3109/14767058.2015.1022865.

Minuz, P., Fava, C., Hao, S., Pedraza, P., Amen, G., Meneguzzi, A., & Ferreri, N. R. (2015). Differential regulation of TNF receptors in maternal leukocytes is associated with severe preterm preeclampsia. *The Journal of Maternal-Fetal & Neonatal Medicine*, 28(8), 869-875. https://doi.org/10.3109/14767058.2014.937695.