The Relationship Between Spiritual Well-Being, Stress Level and Serum Cystatin C Level in Preeclampsia

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KEYWORDS

preeclampsia, spiritual well being, Stress levels, cystatin C, pregnancy complications

ABSTRACT:

Background: Preeclampsia is a major complication of pregnancy characterized by hypertension and organ dysfunction, which can lead to severe maternal and fetal outcomes. Recent studies suggest that psychosocial factors, including spiritual well-being and stress levels, may influence the pathophysiology of preeclampsia. Additionally, Cystatin C, a biomarker of renal function and systemic inflammation, has been proposed as a potential predictor of disease severity. However, the interplay between these factors remains unclear.

Objective: This study aims to analyze the relationship between spiritual well-being, stress levels and serum cystatin C levels in preeclampsia (PE).

Methods: A comprehensive cross-sectional study involved pregnant women aged 20 weeks or greater who were examined at various healthcare facilities from November 2023 to March 2024. The study comprised 44 PE pregnant women and 44 non-PE pregnant women. Spiritual well-being, stress levels, and cystatin C levels were assessed using the Spiritual Well-Being Scale (SWBS), Perceived Stress Scale (PSS), and ELIAS kit. Statistical analyses employed chi-square, Mann-Whitney U, and multiple logistic regression tests.

Results: The level of spiritual well-being did not associate with preeclampsia (p value > 0.05). Stress levels and serum cystatin C levels associated with preeclampsia (p value < 005). Stress levels increased the risk of preeclampsia by 1.127 times greater than without preeclampsia (95% CI: 1.026-1.239, p=0.017). Serum cystatin C levels increased the risk of preeclampsia by 1.669 times greater than without preeclampsia (95% CI: 1.094-2.545. p=0.013).

Conclusion: High levels of stress and high serum cystatin C levels in mothers increase the incidence of preeclampsia. The present results can be the basis for consideration of examining stress levels and serum cystatin C levels to predict the incidence of preeclampsia in pregnant women.

1. Introduction

Preeclampsia (PE) is a complex systemic condition defined by the development of hypertension and proteinuria after 20 weeks of gestation.[1] It continues to be a significant cause of morbidity and mortality for mothers, fetuses, and neonates, especially in low- and middle-income countries. Globally, PE accounts for around 50,000 maternal fatalities and approximately 900,000 perinatal losses each year. In Indonesia, data from the Ministry of Health's family health program indicated that in 2020, there were 4,627 recorded maternal deaths, with 1,110 cases attributed specifically to hypertensive disorders in pregnancy.[2]

Preeclampsia is influenced by a range of factors, with psychological stress being a significant contributor. Recent research indicates that women who are experiencing stress face a 20-fold higher risk of developing preeclampsia. This association is thought to be mediated by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased levels of corticosteroids and

catecholamines hormones secreted by the adrenal glands in response to psychological and physiological stressors. Also, stress activates the sympathetic nervous system, adversely affecting immune system function. In women with PE, there have been consistent findings of elevated levels of corticotropin-releasing hormone and heightened sympathetic activity, implying that stress may significantly influence the pathophysiology of this condition.[3]

Stress is intricately related to an individual's spiritual well-being, with research indicating that higher levels of spirituality can effectively mitigate stress.[4],[5] Ahmadinezhad and Akbarzadeh found that women with PE often reported higher spiritual well-being. Furthermore, high-risk patients may enhance their spiritual health during pregnancy by actively seeking spiritual support and engaging in spiritual self-development practices.[6] Maintaining maternal health throughout pregnancy is crucial, as it significantly impacts fetal development and outcomes.[7] Maternal health encompasses a holistic approach incorporating physical, psychological, social, and spiritual dimensions. A deficiency in any of these aspects can adversely affect both the mother's and the fetus's health.[8]

Acute renal failure during pregnancy can arise in cases of PE and eclampsia, affecting up to 75% of patients. Therefore, monitoring renal function should be a primary focus in the management of PE. While serum creatinine has traditionally served as a routine marker for renal function, it is increasingly viewed as suboptimal due to its limitations. Cystatin C is emerging as a promising alternative biomarker for assessing renal function. This low-molecular-weight protein is continuously synthesized by all nucleated cells and is freely filtered at the glomerulus, with minimal secretion from the renal tubules. Unlike serum creatinine, cystatin C levels are not influenced by dietary factors, allowing for a more consistent evaluation of kidney function. After filtration, cystatin C is subsequently reabsorbed and metabolized by the proximal tubular cells.[1],[9] Recent studies indicate that the expression of cystatin C is influenced by extravillous trophoblast cells in the placenta of women with preeclampsia.[10]

Research has not been conducted on the interplay between spiritual well-being, stress levels, and serum cystatin C levels in PE. Understanding the relationship among these factors could enhance our ability to predict the onset of PE, thereby facilitating timely preventive measures. This study seeks to analyze the relationships between spiritual well-being, stress levels, and serum cystatin C levels in individuals with PE, potentially contributing valuable insights for clinical practice and early intervention strategies.

2. Objectives

This study aims to analyze the relationship between spiritual well-being, stress levels, and serum cystatin C levels in preeclampsia (PE). Preeclampsia is a serious pregnancy complication characterized by high blood pressure and organ dysfunction, often leading to adverse maternal and fetal outcomes. While physiological factors contributing to PE have been extensively studied, the role of psychological and spiritual factors remains less understood. This research seeks to explore whether spiritual well-being influences stress levels and how both factors correlate with serum cystatin C, a biomarker associated with kidney function and endothelial dysfunction in PE. Understanding these relationships is crucial for developing a more holistic approach to preeclampsia management. By identifying potential associations between spiritual well-being, stress, and cystatin C levels, this study may provide insights into the impact of psychological and emotional health on the progression of PE. The findings could contribute to improved prenatal care strategies, emphasizing not only medical interventions but also psychological and spiritual support for pregnant women at risk of developing preeclampsia.

3. Methods

Study design

This article is based on the guidelines set forth by STROBE 2007 (Strengthening the Reporting of Observational Studies in Epidemiology).11 The research was ethically approved by the Human Biomedical Research Ethics Commission, Faculty of Medicine, Hasanuddin University (No. 726/UN6.4.5.31/PP36/2023) on 25th September 2023.

A cross-sectional study was conducted across multiple healthcare facilities, which included all pregnant women with a gestational age of 20 weeks or more. These women underwent evaluation for PE based on specific criteria: the onset of gestational hypertension accompanied by at least one of the following: proteinuria, uterine dysfunction, or maternal organ dysfunction (including neurologic, hematologic, hepatic, or renal involvement),occurring at ≥ 20 weeks of gestation. The study period lasted from November 2023 to March 2024.

Population and samples

Sampling was conducted using consecutive sampling methodology, meaning all individuals within the study population who fulfilled the inclusion criteria were enrolled until the desired sample size was achieved. The criteria for eligibility to participate in the study included pregnant women with a gestational age of 20 weeks or more, singleton pregnancies, and a newly identified blood pressure measurement of 140/90 mmHg or above (supplementary criteria indicative of PE group). Participants were excluded from the study if they had any of the following conditions: diabetes mellitus, chronic hypertension, renal disease, active infections, a history of severe preeclampsia in previous pregnancies, or any diagnosed mental disorders prior to pregnancy.

Data collection

Patients who met the inclusion criteria were recruited for the study following the procurement of informed consent. Data collection involved completing a structured research questionnaire with demographic and clinical characteristics. Subsequently, participants underwent a thorough physical examination alongside the assessment of vital signs, including blood pressure. In addition, participants were administered two standardized questionnaires: the Spiritual Well-Being Scale (SWBS) to evaluate their spiritual well-being and the Perceived Stress Scale (PSS) to assess their stress levels. Additionally, venous blood samples were obtained using an ELISA kit to quantify Cystatin C levels.

The assessment of spiritual well-being is carried out utilizing the SWBS, which classifies scores into three distinct categories: low spiritual well-being (total score: 20-40), moderate spiritual well-being (total score: 41-99), and high spiritual well-being (total score: 100-120). Stress levels are assessed using the PSS, with outcomes categorized as mild stress (total score: 0-13), moderate stress (total score: 14-26), and severe stress (total score: greater than 27). Cystatin C levels are measured quantitatively in nanograms per millilitre (ng/mL).

Sampling size

A purposive sampling approach was utilized to gather the samples. The formula for calculating sample sizes in studies involving two independent population proportions was applied to estimate the required sample size. Consequently, a sample size of 28 was determined for each group, based on distinct proportions of 29% for PE and 71% for non-PE while maintaining a 95% confidence interval and a precision level of 10%.

Data analysis

Baseline data were analyzed using descriptive statistics, and Chi-Square tests were employed to assess differences in variables between the groups. Both Chi-Square and Fisher's Exact tests were applied as appropriate to compare the proportions of spiritual well-being, stress levels, and serum cystatin C levels between participants with PE and non-PE. A bivariate analysis was conducted using the Mann-Whitney U test to evaluate the differences in spiritual well-being scores, stress levels, and serum cystatin C levels between the PE and non-PE groups. The results of these preliminary analyses will be instrumental in informing the multivariate logistic regression model, which will incorporate variables with a p-value of less than 0.250. Statistical significance was established with a threshold of $p < 0.05$, and all analyses were executed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM, USA).

4. Results

Subject characteristics

This study involved 88 pregnant women with a gestational age of 20 weeks or more who were evaluated at the research facility. The cohort included 44 women diagnosed with preeclampsia and 44 without the condition. **Table 1** presents a comparative analysis of the characteristics of the study participants based on the presence of preeclampsia. Most participants were classified as low risk, had a normal body mass index (BMI), and were multigravida. The characteristics of both groups were homogeneous regarding age, BMI, and gravida status.

Table 1. Baseline characteristics of study participants

Characteristics	Non-Preeclampsia (N=44) n (%)	Preeclampsia (N=44) n (%)	p-value
Age			
Low Risk	36 (81.8)	31 (70.5)	0.211
High Risk	8 (18.2)	13 (29.5)	
Body Mass Index			
Underweight	3 (6.8)	2 (4.5)	0.111
Normal	31 (70.5)	22 (50.0)	
Overweight	6 (13.6)	8 (18.2)	
Obesity	4 (9.1)	12 (27.3)	
Gravidity			
Primigravid	14 (31.8)	10 (22.7)	0.338
Multigravid	30 (68.2)	34 (77.3)	
Gestational Age			
Preterm	0	33 (75.0)	N.A
Aterm	44 (100.0)	11 (25.0)	

Chi-square test

Comparison of spiritual well-being, stress level, and cystatin c level between preeclampsia and non-preeclampsia group

The comparison of spiritual well-being levels, stress levels, and serum cystatin C levels between mothers with PE and non-PE is summarized in **Table 2.** No statistically significant differences were observed in spiritual well-being and stress levels between the two groups. However, a significant difference was noted in serum cystatin C levels, with all mothers in the PE group exhibiting cystatin C levels of ≥ 1.49 ng/mL, whereas 84.1% of mothers in the non-PE group had cystatin C levels at or above this threshold.

Table 2. Comparison results of spiritual well-being. stress levels and serum cystatin C levels categories between preeclampsia and non-preeclampsia.

Variables	Non-Preeclampsia n (%)	Preeclampsia n (%)	p-value
Spiritual Well-Being			
Low	6 (13.7)	8 (18.2)	

Moderate	30 (68.2)	30 (68.2)	0.434
High	35 (6.8)	6 (13.6)	
Stress Level			
Mild	21 (47.7)	15 (34.1)	0.193
Moderate	23 (52.3)	29 (65.9)	
Cystatin C Level			
< 1.49 ng/mL	7 (15.9)	0 (0.0)	0.012*
≥ 1.49 ng/mL	37 (84.1)	44 (100.0)	

Fischer exact test, *significant at $p < 0.05$

Risk analysis of spiritual well-being, stress level, and cystatin c level toward preeclampsia

The comparison of spiritual well-being levels, stress levels, and serum cystatin C levels between the PE and non-PE groups is summarized in **Table 3**. The analysis revealed that spiritual well-being did not significantly impact the PE and non-PE cohorts. However, elevated stress levels and increased serum cystatin C levels were noted in the PE group compared to the non-PE group. These findings suggest a link between PE, heightened stress, and elevated cystatin C levels. Subsequently, these two variables were incorporated into a multiple logistic regression model for deeper statistical analysis.

Table 3. Relationship between spiritual well-being. stress levels and serum cystatin C levels in preeclampsia and non-preeclampsia.

Variables	Non-Preeclampsia	Preeclampsia	p-value
	Median (Min-Max)	Median (Min-Max)	
Spritual Well-Being	56.5 (34.0-101.0)	62.0 (38.0-104.0)	0.622
Stress Level	14.0 (8.0-24.0)	18.0 (10.0-26.0)	0.012*
Cystatin C Serum (ng/mL)	2.4 (0.1-5.3)	3.1 (1.6-5.8)	0.009*

Mann-Whitney test, *significant at $p < 0.05$

The findings of a multivariate analysis examining factors associated with PE are summarized in **Table 4**. Both stress levels and serum cystatin C levels showed significant associations with the incidence of PE. Increased stress levels were found to elevate the risk of PE by a factor of 1.127 compared to non-PE cases. Additionally, elevated serum cystatin C levels heightened the risk of PE by a factor of 1.669 compared to non-PE cases.

Table 4. Multivariate test results of factors associated with preeclampsia

Variables	OR	CI 95%	p-value
Stress Level	1.127	1.026-1.239	0.017
Cystatin C Serum Level	1.669	1.094-2.545	0.013

Multiple logistic regression test.

5. Discussion

This study showed no significant difference in spiritual well-being between PE and non-PE mothers. The belief in divine healing is recognized as a practical psychological approach to managing illness and alleviating pain, anxiety, depression, and stress in patients. Spiritual well-being is crucial

in effectively coping with stress, leading to positive health outcomes.[7] Significantly, spiritual well-being is influenced not only by the presence of illness, such as preeclampsia, but can also be enhanced through supportive interactions with healthcare professionals during antenatal care (ANC) visits. Such interactions can help mitigate pregnancy-related anxiety and stress, fostering healthier behaviours and improving overall health during pregnancy.[12]

High-risk pregnancies are characterized by a greater likelihood of complications, an increased level of danger, and the necessity for more intensive healthcare compared to low-risk pregnancies.[6] Research indicates that spirituality can play a significant role in providing support to individuals facing life's challenges. Positive psychological constructs core values, a sense of purpose, and faith are associated with improved physical and mental health outcomes.[13] For individuals with high-risk pregnancies, a strong faith in God or a higher power may facilitate coping mechanisms that enhance resilience, improve health, and potentially mitigate the onset of both physical and mental health disorders.[6] Furthermore, spiritual health often improves among high-risk patients during pregnancy as they actively seek spiritual support and engage in personal spiritual development. Enhanced spiritual well-being is linked to better overall well-being in pregnant women. Those who experience higher levels of spirituality are typically better equipped to manage stress, regulate their emotions effectively, and maintain a hopeful outlook on their future.[12]

The findings of this study reveal that mothers with preeclampsia exhibit significantly higher levels of stress compared to those without the condition. This observation aligns with previous research, which indicated that women experiencing preeclampsia report greater stress levels when contrasted with healthy pregnant women.[14] Additionally, similar outcomes were documented by another study, highlighting that women with preeclampsia experience significantly elevated stress levels compared to the control group. Furthermore, maternal distress, as assessed by the PSS, demonstrates a positive correlation with the incidence of preeclampsia.[15]

The connection between stress and preeclampsia can be understood through the framework of psychoneuroimmunology. Stress impacts the functioning of the HPA axis, resulting in increased cortisol levels and alterations in maternal-fetal cellular immune responses. Elevated cortisol concentrations in the bloodstream and placenta may lead to intermittent placental hypoxia, eventually progressing to placental ischemia. This ischemic state plays a crucial role in the pathophysiology of preeclampsia by stimulating the production of anti-angiogenic factors, particularly soluble fms-like tyrosine kinase-1 (sFlt-1). The heightened levels of sFlt-1 contribute to endothelial dysfunction, which is central to the clinical features of preeclampsia, such as hypertension and proteinuria.[15]

The immune dysregulation pathway can elucidate the relationship between stress and preeclampsia. In patients with preeclampsia, stress is associated with the release of abnormal cytokines, which elevates the levels of C-reactive protein (CRP) and neutrophil gelatinase-associated lipocalin (NGAL), contributing to placental or renal injury. Factors derived from the placenta activate neutrophils, increasing cytokine production that stimulates the immune response and facilitates the onset of preeclampsia. Evidence of immune dysregulation and relevant biomarkers indicate that alterations in autoimmune responses may result in abnormal placental implantation during the first trimester. This can lead to inadequate placental perfusion, resulting in ischemia, trophoblastic arterial shedding, and the release of various cytokines, ultimately causing significant damage to the vascular endothelium and manifesting clinically as preeclampsia.[16]

The results of this study indicate that preeclampsia mothers have significantly higher serum cystatin C levels than non-preeclampsia mothers. This result aligns with previous research that revealed higher Cystatin C levels in preeclampsia reflect early-stage kidney disorders even before conventional markers such as increased serum creatinine. Serum Cystatin C levels to detect kidney disorders in preeclampsia patients obtained a cut-off value of ≥1.49, showing the highest Youden index of 0.721 with a sensitivity of 77.78% and a specificity of 94.34%.[17]

Increased levels of cystatin C have been linked to PE development.[18] Cystatin C is produced at a stable rate by all nucleated cells. Due to its low molecular weight and an alkaline pH of approximately 9.0, it is effectively filtered through the glomeruli, primarily reabsorbed in the proximal tubules, and subsequently fully metabolized. Unlike creatinine, the concentration of cystatin C is not influenced by factors such as muscle mass, age, or sex, making it a more reliable biomarker for evaluating glomerular filtration rate (GFR). In pregnant individuals, variations in cystatin C levels indicate changes in renal function, highlighting its potential as a marker for renal performance, particularly during pregnancy. Furthermore, studies have shown that cystatin C concentrations tend to rise with advancing gestational age in patients with PE. Significantly, elevated cystatin C levels are associated with the severity of PE, irrespective of gestational age.[18]

Cystatin C is a protein predominantly produced by the placenta and released into maternal and fetal circulation through trophoblast cells.[19] Throughout pregnancy, it plays a crucial role in various physiological functions. The production of cysteine proteases is essential for angiogenesis within the decidua and for trophoblast invasion during placental development. Cystatin C is an inhibitor of cathepsin B, and together, they modulate trophoblast invasion. Importantly, cystatin C has emerged as a potential early PE biomarker.[20] In placentas affected by PE, the expression of cystatin C is affected by extravillous trophoblast cells, reflecting a complex interplay in the placentation process.[10] Furthermore, it is hypothesized that the decidua may inhibit trophoblast invasion through the action of cystatin C, which suppresses cysteine proteases.[20]

Cystatin C is recognized as a reliable biomarker for detecting kidney disorders, with its serum levels notably elevated in early preeclampsia. This protein indicates renal function alterations, which are hypothesized to contribute to elevated blood pressure and increased urinary albumin excretion. Consequently, Cystatin C may be a marker that delineates the transition from normal adaptive renal changes to the pathophysiological state of preeclampsia.[21] Furthermore, morphologic changes within the kidneys, such as endotheliosis, increase serum Cystatin C levels among women with preeclampsia by inhibiting glomerular filtration and reducing the glomerular filtration rate. Given its low molecular weight, Cystatin C can freely traverse the glomerular membrane; however, it is neither secreted by the renal tubules nor synthesized there. Instead, it is fully absorbed and catabolized by tubular epithelial cells. Therefore, serum Cystatin C levels are superior indicators for assessing reductions in glomerular filtration rate in the context of preeclampsia.[22]

Cystatin C plays a significant role in preeclampsia, particularly concerning the vascular endothelial injury that characterizes this condition. In patients with preeclampsia, there is an observed increase in antiangiogenic factors, specifically soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng). Conversely, levels of proangiogenic factors such as vascular endothelial growth factor (VEGF) are markedly decreased. This dysregulation in the balance of angiogenic factors leads to considerable endothelial damage, affecting placental implantation and glomerular filtration efficiency. As a result of these pathophysiological alterations, cystatin C levels are elevated, suggesting its potential as a biomarker for assessing renal function and endothelial health in the context of preeclampsia.[16]

The current study has several limitations that warrant consideration. It was conducted simultaneously and primarily focused on the association between spiritual well-being, stress levels, and serum cystatin C levels in individuals with PE compared to non-PE. Thus, further research is essential to explore the causal relationships among these variables and clarify the impact of spiritual well-being and stress on serum cystatin C levels in preeclampsia. This could enhance our understanding of the underlying mechanisms and inform holistic approaches to managing this condition.

6. Conclution

The level of spiritual well-being did not affect the non-PE or PE groups. On the contrary, high-stress levels and high serum cystatin C levels in mothers increased the incidence of PE. Therefore, an examination of stress levels and serum cystatin C levels can be carried out to predict the incidence of

PE in pregnant women. In addition, measurements of other factors related to serum cystatin C levels in pregnant women can be carried out in further studies. They can identify factors related to the spiritual well-being of pregnant women.

7. Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this literature review. No financial, institutional, or personal relationships influenced the research, analysis, or conclusions presented in this manuscript.

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9. Authors Contribution

Surgical and Medical Practices: Resky Yulianita, Elizabeth C. Jusuf, Susiawaty Susiawaty. Concept: Resky Yulianita. Design: Resky Yulianita, Elizabeth C. Jusuf, Susiawaty Susiawaty. Data Collection or Processing: Resky Yulianita. Analysis or Interpretation: Isharyah Sunarno. Literature Search: Resky Yulianita. Writing: Resky Yulianita. Validated of final manuscript: Elizabeth C Jusuf, Susiawaty Susiawaty, Isharyah Sunarno, A Mardiah Tahir, Eddy Hartono

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