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## Headache in Preeclampsia: Review Article

Mulia Dian Sumbawati<sup>1</sup>, Hanik Badriyah Hidayati<sup>2</sup>, Ernawati<sup>3</sup>

<sup>1</sup> Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>2</sup> Department of Neurology, Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

<sup>3</sup> Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

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### ABSTRACT

Preeclampsia is a multisystem vascular disease characterized by systemic disturbances in maternal endothelial function and symptoms such as arterial hypertension and organ dysfunction, including the kidneys, liver, and brain. A headache is defined as pain or discomfort localized in the head region. Pregnancy-related headaches may have primary causes, such as migraines, but they can also indicate potentially life-threatening secondary causes, including preeclampsia. Pregnant women with high blood pressure have a 17-fold increased risk of developing secondary headaches. Headaches associated with preeclampsia can adversely affect pregnancy and labor, increasing the risk of complications. Preeclampsia headaches can predict eclampsia or seizures 56% sensitivity and 83% specificity. According to research conducted in Indonesia, the majority of preeclampsia patients experienced severe headaches (65.2%), followed by moderate (19.6%), mild (13%), and no headaches (2.2%). Therefore, based on the existing literature, this article intends to compile scientific data on headache pain in preeclampsia patients.

### Corresponding Author

Hanik Badriyah Hidayati

Department of Neurology, Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

email: hanikhidayati@fk.unair.ac.id

Available at <https://e-journal.unair.ac.id/index.php/aksona>



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## INTRODUCTION

The IASP defines headache as a painful and disabling neurological condition that can manifest in several forms, including idiopathic persistent facial pain, cluster headaches, primary stabbing headaches, primary sex-related headaches, migraines, or tension-type headaches. Headaches are typically classified into two types: primary and secondary. A primary headache refers to pain unaccompanied by structural abnormalities, while a secondary headache occurs as a result of underlying organ dysfunction.<sup>1</sup> Pregnancy is considered a risk factors for secondary headache. The high frequency of secondary headaches during pregnancy can be attributed to several factors, including hypercoagulability, hormonal changes, and anesthetic post-delivery. Red flags warranting attention include the presence of atypical symptoms such as confusion, impaired alertness, and reduced consciousness with the headache.<sup>2</sup> Preeclampsia is defined as hypertension after 20 weeks of pregnancy and more than 300 mg of protein every day.<sup>3</sup> Preeclampsia is a multisystem disease that causes systemic disturbances in maternal endothelial function. It is a vascular disease characterized by arterial hypertension and dysfunction of organs such as the kidneys, liver, and brain.<sup>4</sup>

A recent study by Robbins *et al.* involving 140 pregnant women with acute headaches found that 35% had secondary headaches. Preeclampsia was the most common cause, accounting for 51% of the total followed by posterior reversible encephalopathy syndrome (PRES) and eclampsia.<sup>5</sup> Research in Indonesia showed that, in cases of preeclampsia, headaches were severe in 65.2% of patients, moderate in 19.6%, mild in 13%, and no headaches in 2.2%.<sup>6</sup> Headaches in preeclampsia may adversely affect pregnancy and labor. Headache in preeclampsia may serve as a predictor of eclampsia or seizure, with a sensitivity of 56% and specificity of 83%.<sup>7</sup> Therefore, this study was created to collect scientific data on headache pain in preeclampsia.

## REVIEW

### Definition

condition associated with a potential or current tissue injury.<sup>8</sup> A headache is defined as pain or discomfort in the head region. A headache without any warning signs is typically considered low-risk and is often classified as a primary headache. In contrast, the presence of warning signs, such as prolonged headache, seizures, or neurological symptoms, needs further evaluation through laboratory testing and imaging.<sup>9</sup> Women who experience headaches or

migraines during pregnancy have a lower health-related quality of life than those who don't. This condition significantly impacts maternal quality of life.<sup>10</sup>

Preeclampsia is a pregnancy-related disorder characterized by the onset of hypertension, typically occurring after 20 weeks of pregnancy and often near term.<sup>11</sup> It is clinically defined as hypertension after 20 weeks of pregnancy, accompanied by proteinuria exceeding 300 mg per day.<sup>3</sup> It is a multisystem disorder that disrupts maternal endothelial function. This vascular dysfunction results in symptoms such as arterial hypertension and end-organ involvement, particularly affecting the kidneys, liver, and brain.<sup>4</sup>

### Characteristics and Causes of Headache in Pregnancy:

#### 1. Primary headache

Primary headaches are more prevalent during pregnancy. Migraine-type headaches are the most common form of primary headache during pregnancy, affecting around 5% of pregnant women.<sup>12</sup> In addition to migraines, tension-type headaches are also quite common. In late pregnancy, migraine frequency and intensity tend to decline due to a shift in the ration between maternal estrogen and progesterone.<sup>13</sup> Pregnancy is associated with is physiological changes that impact neurological function and could result in many neurological symptoms.<sup>5</sup> Clinically, the most significant primary headaches consist of cluster headaches, tension-type headaches, and migraines.

#### 2. Secondary headache

Secondary headaches are frequently connected to cerebrovascular disease during pregnancy, particularly in its latter stages.<sup>14</sup> Pregnancy is associated with cerebrovascular disorders that may result in headaches. Studies on headaches during pregnancy indicate that secondary headaches are the most common type, accounting for 86% of cases.<sup>12</sup> According to Robbins *et al.*, preeclampsia is the leading cause of frequent headaches during pregnancy. Secondary headaches may result from medical conditions such as preeclampsia, eclampsia, idiopathic intracranial hypertension, cerebral venous thrombosis, posterior reversible encephalopathy syndrome, subarachnoid hemorrhage, ischemic stroke, and reversible cerebral vasoconstriction syndrome.<sup>15</sup>

### Pathogenesis of headache in preeclampsia

Pregnant women with high blood pressure are 17 times more likely to develop subsequent headaches.<sup>15</sup> Women with a history of migraine have a higher prevalence of hypertensive disorder.<sup>16</sup> Immediate evaluation is warranted for individuals exhibiting headache pain symptoms (fever, changed

mental status, thunderclap episodes, etc.) accompanied by hypertension. Pregnant women with a history of hypertension should be closely monitored for disease progression and related symptoms, as they represent an at-risk population.<sup>17</sup>

Preeclampsia causes various neurological disorders, including headaches, blurred vision, seizures, posterior reversible encephalopathy syndrome, and hemorrhagic stroke. Typical preeclampsia headaches are progressive, throbbing, bilateral (frontal or occipital), accompanied by vision problems, worsened by high blood pressure and exercise, and resistant to over-the-counter medications. Additionally, these symptoms are characteristic of tension-type headaches. Headaches associated with posterior reversible encephalopathy syndrome (PRES) are typically bilateral, dull, occipital, and without a prodrome. A pathophysiological explanation for headache pain in preeclampsia is the loss of fenestrae in the choroid plexus due to VEGF and TGF- $\beta$  inhibition, leading to endothelial cell instability and periventricular edema. Seizures and posterior reversible encephalopathy syndrome, defined as neurological abnormalities and vasogenic edema in the posterior cerebral circulation, may result from these changes.<sup>18</sup>

### Changes in the brain after preeclampsia and eclampsia

Proximal muscle weakness, autonomic the brain imaging results of moms with eclampsia reveal a condition known as PRES, a kind of cerebral edema that is thought to be reversible and has no long-term effects. However, there has recently been debate about the reversibility of eclampsia's effects on the brain or severe preeclampsia, since women who have previously had preeclampsia are at a higher risk of vascular dementia and stroke, epilepsy, and cognitive impairment.<sup>19</sup> Magnetic resonance imaging (MRI) investigations have found that women with preeclampsia and eclampsia have abnormal brain shape and function. For example, women with eclampsia or severe preeclampsia in previous pregnancies had more white matter lesions (WML) few years later.<sup>20</sup>

Types of headache disorders in preeclampsia patients:

#### 1. Preeclampsia and cerebral autoregulation

Cerebral autoregulation refers to the process by which cerebral arterioles dynamically react and adapt to variations in systemic blood pressure, thereby ensuring steady cerebral blood flow and preventing hyperperfusion injury. Impaired dynamic cerebral autoregulation has been demonstrated in women with chronic hypertension and preeclampsia, but not in

those with normal pregnancy or gestational hypertension.<sup>21</sup>

#### 2. Blood-Brain barrier dysfunction

Increased permeability of the blood-brain barrier can lead to cerebral edema, which is common in women with eclampsia and sporadically in preeclamptic women, especially those with neurological symptoms. Radiographically, the edema pattern has some similarities with PRES. This condition is typically curable with prompt and intensive treatment.<sup>22</sup> Although the exact cause of blood-brain barrier disruption in preeclampsia is unknown, neuroinflammation may play a role. Preeclampsia is associated with increased serum markers of inflammation, such as C-reactive protein, platelets, complement activity, and elevated proinflammatory cytokines, including interleukin (IL)-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , and IL-17.<sup>23</sup> Proteomic analysis of cerebrospinal fluid (CSF) from women with preeclampsia has shown clear differences from those of normotensive women, including increased markers of neuroinflammation and binding proteins.<sup>24</sup>

#### 3. Migraine and preeclampsia

Women with migraines are more likely to develop preeclampsia. A retrospective case study revealed that expecting moms with migraine had a preeclampsia rate of 21.3%, which is five times higher than the general population, especially among those with a favourable phenotype.<sup>25</sup> The risk of preeclampsia appears to be increased in women with migraines, even in the presence of an aura. Women who frequently get migraines or have active attack during pregnancy may exhibit a higher-risk phenotype. The relationship between migraine and preeclampsia is not fully understood. While migraine is primarily thought to be a brain disorder, there is evidence that peripheral components are involved. Migrain pain is caused by a combination of cells, including vascular endothelial cells, dural immune cells, and trigeminal nerve afferents.<sup>26</sup> The mechanisms that initiate migraine pain continue to be elusive and probably complex and multifaceted. Overlapping clinical and pathophysiological features of migraine and preeclampsia include inflammation, vascular endothelial dysfunction, and changes in vasoreactivity.<sup>27</sup>

Sterile neurogenic inflammation is believed to play a critical role contributes to migraine headaches by increasing meningeal vascular permeability, arterial vasodilatation, and local immune cell activity, as well as extravasation of dural plasma protein. Adjacent Trigeminal nerve activity near meningeal blood vessels releases neuropeptides and vasoactive

neurotransmitters such as substance P and calcitonin gene-related peptide. These vasoactive neurotransmitters and neuropeptides cause mast cells to activate and degranulation, dural plasma protein extravasation, and meningeal artery vasodilation. Animal models have shown neurogenically induced dural plasma protein extravasation following trigeminal ganglion activation. This theory is supported by the elevation of proinflammatory mast cell components TNF- $\alpha$ , IL-1 $\beta$ , IL-10, and histamine during migraine attacks. Migraine has diverse underlying etiologies and may arise secondary to hormonal treatments or manifest as an isolated symptom during the menstrual cycle or pregnancy, with variations in intensity and duration.<sup>28</sup>

#### 4. Posterior reversible encephalopathy syndrome (PRES)

PRES is a neuroradiological entity that was initially described as a pathological condition characterized by headache, visual disturbances, seizures, and decreased consciousness. MR imaging frequently detects vasogenic edema in the white matter and subcortical cortex, especially affecting the bilateral parieto-occipital lobes. Similar to headache pathophysiology, preeclampsia is partially mediated by blood-brain barrier dysfunction, neuroinflammation, altered angiogenic pathways, endothelial cell dysfunction, and changes in vascular reactivity. Preeclampsia syndrome has also been linked with abnormal platelet activity. Randomized trials have indicated that aspirin-induced platelet activity lowers the chances of developing early preeclampsia.<sup>29</sup>

Several mechanisms are thought to contribute to preeclampsia-associated headaches, including alterations in vasoreactivity, inflammation, and vascular endothelial dysfunction, but none of them has yet been fully established.<sup>27</sup> Brain endothelial dysfunction in preeclampsia, may increase blood-brain barrier (BBB) permeability, leading to intracerebral edema, increased intracerebral inflammation, and intracerebral hypoxia.<sup>30</sup> Preeclampsia can have serious consequences for maternal blood vessels. Both short- and long-term cerebrovascular complications associated with preeclampsia include PRES, ischemic and hemorrhagic stroke, and cerebral small vessel disease (CVSD).<sup>27</sup>

## CONCLUSION

Based on this review, scientific evidence suggests that pregnant women with preeclampsia are more vulnerable to headaches. Typical preeclampsia headaches are progressive, bilateral (frontal or

occipital), throbbing, linked to visual abnormalities, worsening with elevated blood pressure and exercise, and resistant to over-the-counter drugs. The putative mechanisms underlying preeclampsia-associated headaches include inflammation, vascular endothelial dysfunction, and altered vasoreactivity, but no mechanism has yet been fully defined.

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## Conflict of Interest

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## Author Contributions

MS, HH, and E contributed to the acquisition of research data, analysis, and writing of the manuscript. The submitted version of the manuscript has been read and approved by all authors.

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