

The Correlation Between Preeclampsia and Intracranial Hemorrhage: A Review of Current Literature

Viola Salsabila Faradisa¹, Asra Al Fauzi^{2*}, Muhammad Ilham Aldika Akbar³

¹Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia ²Departement of Neurosurgery, Dr. Soetomo General Hospital, Surabaya, Indonesia ³Departement of Obstetrics and Gynaecology, Universitas Airlangga General Academic Hospital, Surabaya, Indonesia

E-mail:viola.salsabila.faradisa-2021@fk.unair.ac.id; asra.al@fk.unair.ac.id; dokter_aldi@yahoo.com

*Corresponding author details: Asra Al Fauzi; asra.al@fk.unair.ac.id

ABSTRACT

Objective: This literature review aims to elucidate the relationship between preeclampsia and the occurrence of intracranial hemorrhage during pregnancy, highlighting the epidemiology, pathophysiological mechanisms, and risk factors. **Methods:** A systematic literature review was conducted using peer-reviewed articles, clinical studies, and guidelines related to preeclampsia patients with intracranial hemorrhage. **Results:** Pregnancy is a condition that can lead to alterations in the haemostatic system. The range of cerebral autoregulation may potentially vary during pregnancy, the elevated blood pressure associated with preeclampsia can lead to rupture of vessels at a lower pressure than in the non-pregnant women. In addition, high blood pressure consistently causes damage to the walls of blood vessels, resulting in its rupture and bleeding. Pregnancy-induced hypertension (PIH) may be a significant predictor of pregnancy-related intracranial hemorrhage (ICH). Hypertension is the primary risk factor for Intraparenchymal Hemorrhage. **Conclusion:** The evidence indicates a significant relationship between preeclampsia and intracranial hemorrhage (ICH), underscoring critical implications for maternal and fetal health. Future research could explore how age, BMI, parity, and the severity of hypertension, alongside socioeconomic factors, access to healthcare, and adherence to antenatal care, impact negative outcomes for mothers and children. , ultimately enhancing clinical outcomes for affected patients.

Keywords: preeclampsia; intracranial hemorrhage; pregnancy-induced hypertension.

INTRODUCTION

Preeclampsia is a condition characterized by having a systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, on two separate occasions at least 4 hours apart; or a shorter interval timing of systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mm Hg or higher, can also be used for diagnosis. Additional notable discoveries that may or may not be evident in the clinical manifestation encompass proteinuria and indications of damage to vital organs. These criteria must be identified after 20 weeks of gestation [1]. The prevalence of preeclampsia varies from 2% to 10% among pregnancies globally [2]. The underlying aetiology of pre-eclampsia is yet unknown [1]. Intracranial haemorrhage (ICH) is a rare yet severe and potentially fatal consequence of preeclampsia [3]. Given the serious complications of preeclampsia and intracerebral haemorrhage during pregnancy, including a high death rate and a poor prognosis, early identification of at-risk pregnant women is crucial in order to begin risk-specific treatment as soon as feasible.

REVIEW CONTENT

1. Pathophysiology Preeclampsia

The underlying aetiology of pre-eclampsia is yet unknown. The two-stage concept of pre-eclampsia suggests that pre-eclampsia occurs due to placental dysfunction, namely syncytiotrophoblast stress.

Syncytiotrophoblast stress then leads to the clinical symptoms of pre-eclampsia in the mother. Syncytiotrophoblast stress is characterized by the presence of oxidative stress, mitochondrial endoplasmic damage, reticulum stress, dysregulated metabolism, and apoptosis. The syncytiotrophoblast, under stress, produces proinflammatory cytokines, extracellular vesicles, reactive oxygen species, and anti-angiogenic substances into the maternal circulation. These factors contribute to maternal endothelial dysfunction and systemic multiorgan disorder that involves systemic inflammation, reduced vasodilation, and thrombosis. The consequences encompass hypertension, thrombocytopenia, liver and renal impairment, and coagulopathy [1].

2. Epidemiology of Preeclampsia

The occurrence of preeclamptic episodes is increasing globally, with a higher prevalence in developing countries compared to the developed world. The prevalence of preeclampsia varies from 2% to 10% among pregnancies globally. The incidence rate in developing ranges from 1.8% to 16.7%, whereas in developed countries it is 0.4% [4]. It accounts for 9% to 26% of maternal fatalities in low-income countries and 16% in high-income nations [2].

3. Risk Factor of Preeclampsia

A woman is considered to be at a high risk of developing preeclampsia if she has a history of hypertensive disease during a previous pregnancy or if she has a maternal disease such as chronic kidney disease, diabetes, or chronic hypertension. Women who have never given birth, are 40 years of age or older, have a body mass index (BMI) of 35 kg/m or above, have a family history of preeclampsia, a multiple pregnancy, or a pregnancy interval of more than 10 years are considered to be at intermediate risk [5]. Pregnancy-induced hypertension (PIH) may be a significant predictor of pregnancy-related intracranial hemorrhage (ICH) [6].

4. Definition of Intracranial Hemorrhage

Intracranial hemorrhage encompasses all instances of bleeding occurring within the intracranial vault, which includes the brain parenchyma as well as the adjacent meningeal spaces [13]. Intracranial hemorrhage refers to four main types of bleeding in the brain: epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, and intraparenchymal hemorrhage. Each bleeding type arises from distinct causes and the clinical manifestations, prognosis, and outcomes vary [11].

5. Classification of Intracranial Hemorrhage

Epidural Hemorrhage Epidural hematoma is characterised by haemorrhaging between the dura mater and the cranial bone. Subdural and epidural hematomas are frequently the result of a traumatic injury. An epidural hematoma can originate from either an artery or a vein. The classical arterial epidural hematoma occurs as a result of blunt trauma to the head, usually in the temporal area. Additionally, they can manifest following a serious cranial trauma. Usually, a fracture in the skull occurs together with injury to the main meningeal artery, resulting in bleeding from the artery into the possible epidural space. While the middle meningeal artery is commonly associated with arterial epidural hematoma, any meningeal artery has the potential to cause this condition. A venous epidural hematoma arises when a fracture in the skull causes bleeding from the veins, which then fills the space between the skull and the outermost protective layer of the brain, known as the epidural space. Venous epidural hematomas frequently occur in pediatric patients [11].

• Subdural Hemorrhage

A subdural hematoma occurs as a result of haemorrhaging between the dura mater and the

arachnoid mater. Subdural haemorrhage typically happens when a blood vessel connecting the brain and skull is strained, fractured, or ruptured, resulting in bleeding into subdural space. These are most prevalent after a blunt head injury, but they can also happen after a penetrating head injury or spontaneously [11].

• Subarachnoid Hemorrhage

Subarachnoid haemorrhage (SAH) is the term used to describe the occurrence of bleeding in the area between the pia and the arachnoid membranes. Nontraumatic factors that might lead to rupture include cerebral aneurysms, bleeding from arteriovenous malformations or tumours, cerebral amyloid angiopathy, and vasculopathies (such as vasculitis). A subarachnoid hemorrhage refers to the occurrence of bleeding within the subarachnoid space. Subarachnoid hemorrhage can be classified into two categories, traumatic and non-traumatic subarachnoid hemorrhage. A second categorization scheme divides subarachnoid hemorrhage into two categories, aneurysmal subarachnoid hemorrhage and non-aneurysmal subarachnoid hemorrhage. Aneurysmal subarachnoid hemorrhage arises when a cerebral aneurysm ruptures, resulting in the leakage of blood into the subarachnoid space. Nonaneurysmal subarachnoid hemorrhage refers to the occurrence of bleeding in the subarachnoid space, where no aneurysms can be identified. Nonaneurysmal subarachnoid hemorrhage typically arises following blunt head trauma, either with or without penetrating injury, or because of abrupt changes in head acceleration [11].

• Intraparenchymal Hemorrhage

Intraparenchymal haemorrhage is defined as bleeding into the brain parenchyma itself. Haemorrhage can develop for a variety of reasons, including but not limited to hypertension, aneurysm rupture, arteriovenous malformation, coagulopathy, amyloid angiopathy, vasculitis, tumour , infection, and trauma. Nontraumatic bleeding into the brain parenchyma is referred to as intraparenchymal haemorrhage (IPH) [11].

6. Etiology of Intraparenchymal Hemorrhage

Intraparenchymal bleeding comprises 10% to 20% of the total incidence of strokes. The incidence of intraparenchymal hemorrhage rises in those aged 55 and above, with a higher occurrence as age advances. Gender differences are a topic of contention, yet there may be a slight prevalence of males [11].

7. Pathophysiology of Intraparenchymal Hemorrhage

Non-traumatic intraparenchymal haemorrhage commonly arises as a result of hypertensive damage to cerebral blood vessels, leading to their burst and subsequent bleeding within the brain. Additional factors contributing to this condition encompass the rupture of an aneurysm, the rupture of an arteriovenous malformation, arteriopathy, tumour presence, infection, or restriction of venous outflow. Intraparenchymal haemorrhage can be caused by both non-penetrating and penetrating trauma [11].

High arterial pressures induce cellular-level vascular remodelling, leading to lipo hyalinosis and genuine arteriolar dissections known as Charcot-Bouchard aneurysms. These aneurysms burst, allowing high-pressure blood to escape into the deep parenchyma. Hypertensive haemorrhages typically manifest in the deep regions of the brain that receive blood from small capillaries, such as the brain stem, putamen, thalamus, caudate, and deep cerebellar nuclei [12].

8. Risk Factor of Intracranial Hemorrhage

Hypertension is the primary risk factor for IPH. Modifiable risk factors for this condition encompass hypertension, excessive alcohol consumption, cigarette smoking, low triglycerides, reduced levels of low-density lipoprotein cholesterol, and the use of medicines such as antithrombotic agents, anticoagulants, and sympathomimetics. Nonmodifiable risk factors encompass old age, cerebral amyloid angiopathy (CAA), male sex, and Asian ethnicity.

An increased incidence of childbirths may be linked to an elevated susceptibility to intracranial hemorrhage (ICH). Women who have given birth multiple times have a much greater risk of intracerebral hemorrhage (ICH) compared to women who have never given birth or have only given birth once. This risk increases as the number of pregnancies increases [7].

9. Correlation Between Preeclampsia and Intracranial Hemorrhage

Reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles is thought to be the initial event in preeclampsia. Placental ischemia is expected to cause extensive activation/dysfunction of the maternal vascular endothelium, resulting in increased endothelin and thromboxane formation, increased vascular sensitivity to angiotensin II, and decreased generation of vasodilators such as NO (Nitric Oxide) and prostacyclin. Endothelial abnormalities cause hypertension by impairing renal-pressure natriuresis and increasing total peripheral resistance [8].

Pregnancy is a condition that can lead to alterations in the haemostatic system. The range of cerebral autoregulation may potentially vary during pregnancy, the elevated blood pressure associated with preeclampsia can lead to rupture of vessels at a lower pressure than in the non-pregnant women [9]. In addition, high blood pressure consistently causes damage to the walls of blood vessels, resulting in its rupture and bleeding [6]. Hypertensive damage to cerebral blood vessels, leading to their burst and subsequent bleeding within the brain, is a pathophysiology that generally occurs in nontraumatic intraparenchymal hemorrhage. However, not all preeclampsia patients will develop into intracranial hemorrhage [10].

10. Molecular Mechanisms of Preeclampsia Which Induces Hypertension

• Nitric Oxide

A possible explanation for the decrease in pressure natriuresis and increase in arterial pressure in pregnant rats with a persistent decrease in uteroplacental perfusion pressure is a decrease in the synthesis of nitric oxide (NO) in the kidneys. Additional research has demonstrated that nitric oxide (NO) has a significant role in controlling kidney function and blood pressure in different physiological and pathological circumstances.

A potentially significant factor in preeclampsia is the discovery that decreased nitric oxide synthesis leads to an increase in blood pressure and a disruption in the body's ability to excrete sodium.

There is significant evidence to suggest that the synthesis of nitric oxide (NO) is increased during normal pregnancy. The increased level of nitric oxide (NO) production seems to have a significant impact on the dilation of blood vessels in the kidneys during pregnancy. Given that NO is a significant vasodilator in healthy pregnancies, it is possible that a lack of NO in preeclampsia could play a role in the development of the condition.

Research conducted by multiple laboratories has discovered that when pregnant rats are subjected to long-term inhibition of NO synthase, it leads to hypertension characterized by vasoconstriction in the peripheral and renal areas, proteinuria, impaired growth of the fetus in the womb, and higher fetal morbidity. These symptoms closely resemble those observed in human pregnancy-induced hypertension [14].

• Endothelin

The vasoconstrictor endothelin is another endothelial-derived factor that may play a role in preeclampsia. Because endothelial damage is a known stimulator of endothelin synthesis, increases in endothelin production may play a role in preeclampsia. Endothelin plasma concentrations have been measured in a number of studies involving both normal pregnant women and women with preeclampsia. The majority of researchers discovered 2- to 3-fold higher plasma endothelin concentrations in women with preeclampsia.

Endothelin levels in plasma are typically highest in the latter stages of the disease, implying that endothelin may not be involved in the onset of preeclampsia but rather in the progression of the disease into a malignant phase. Although plasma endothelin levels are only 2- or 3-fold higher than normal during preeclampsia, we discovered that this level of plasma endothelin can have long-term effects on systemic hemodynamics and arterial pressure regulation. Thus, long-term elevations in plasma endothelin levels comparable to those measured in preeclamptic patients could play a role in mediating the reductions in renal function and elevations in arterial pressure observed in preeclamptic women. These findings suggest that endothelin plays an important role in mediating the hypertension caused by chronic uterine perfusion pressure reductions in pregnant rats [14].

• Prostaglandins

Several lines of evidence suggest alterations in the prostaglandin system mediating renal impairment and an increase in arterial pressure during preeclampsia. Women with preeclampsia have significant changes in prostacyclin and thromboxane production. In women with preeclampsia, plasma, and urine thromboxane levels are high, although prostaglandin production, such as prostacyclin synthesis, is suppressed.

A study indicating that thromboxane receptor antagonism can prevent short-term elevations in systemic arterial pressure caused by acute reductions in uterine perfusion in pregnant dogs provides additional evidence for a potential function for thromboxane in preeclampsia. Human studies show that low-dose aspirin prevents the development of preeclampsia in women at risk for the condition, lending credence to thromboxane's probable function.

Although some studies suggest that thromboxane may play a role in preeclampsia, the quantitative importance of this substance in mediating the longterm reduction in renal hemodynamics and elevation in arterial pressure caused by chronic uterine perfusion pressure reductions in pregnant rats remains unknown. However, in preliminary investigations, we discovered that by day 19 of gestation, urine excretion of thromboxane B2 was higher in hypertensive pregnant rats with chronic deficits in uterine perfusion pressure than in normal pregnant rats [14].

• The Renin-Angiotensin System

The renin-angiotensin system (RAS) is crucial in regulating renal function and arterial pressure in many physiological and pathological situations. In a typical pregnancy, the levels of plasma renin concentration, renin activity, and angiotensin II (Ang II) are all increased. However, the blood vessels' ability to respond to Ang II seems to be decreased. The precise role of the renin-angiotensin system in controlling renal function and arterial pressure in the context of preeclampsia remains incompletely understood.

While the levels of Ang II in the bloodstream may appear normal in cases of preeclampsia, it is plausible that decreasing the pressure of blood flow between the uterus and placenta could heighten the kidneys' responsiveness to Ang II. This could occur due to a decrease in the synthesis of nitric oxide (NO) or prostacyclin, or an increase in the production of thromboxane.

In addition, prior research conducted by our laboratory and other researchers has discovered that the preglomerular vessels in the renal circulation exhibit heightened sensitivity to the vasoconstrictor effects of Ang II under abnormal conditions, such as reduced synthesis of NO or prostacyclin in the kidneys, or increased synthesis of thromboxane.

We have recently established the significance of Ang II in facilitating the sustained decrease in renal blood flow and the development of high blood pressure resulting from prolonged decreases in uterine perfusion pressure in pregnant rats [14].

CONCLUSIONS

The evidence presented in this literature review highlights a significant relationship between preeclampsia and intracranial hemorrhage (ICH), emphasizing the critical implications this association holds for both maternal and fetal health. Given the potentially severe consequences of these conditions, it is essential to further investigate the various factors that may influence outcomes. Future research could delve into how age, body mass index (BMI), parity, and the severity of hypertension interact with socioeconomic factors, access to healthcare, and adherence to antenatal By comprehensively examining these care. variables, we can better understand their impact on adverse outcomes for mothers and children. Ultimately, such investigations will contribute to the development of targeted interventions and strategies aimed at enhancing clinical outcomes for patients affected by these conditions.

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REFERENCES

- [1] Dimitriadis, E., Rolnik, D. L., Zhou, W., Estrada-Gutierrez, G., Koga, K., Francisco, R. P. V., Whitehead, C., Hyett, J., da Silva Costa, F., Nicolaides, K., & Menkhorst, E. (2023). Preeclampsia. Nature Reviews Disease Primers, 9(1). https://doi.org/10.1038/s41572-023-00417-6
- [2] Bartal, M. F., & Sibai, B. M. (2023). Preeclampsia. Protocols for High-Risk Pregnancies: An Evidence-Based Approach: Seventh Edition, 517–528. https://doi.org/10.1002/9781119635307.ch50
- [3] Keepanasseril, A., Subburaj, S. P., Nayak, D., Bojja, V., Chakkalakkoombil, S. V., & Nair, P. P. (2022). Risk factors of intracranial haemorrhage in preeclampsia: a case-control study. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 43(10).https://doi.org/10.1007/S10072-022-06286-3
- [4] Khan, B., Yar, R. A., Khakwani, A. khan, Karim, S., & Ali, H. A. (2022). Preeclampsia Incidence

and Its Maternal and Neonatal Outcomes With Associated Risk Factors. Cureus, 14(11). https://doi.org/10.7759/CUREUS.31143

- [5] Fox, R., Kitt, J., Leeson, P., Aye, C. Y. L., & Lewandowski, A. J. (2019). Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring. Journal of Clinical Medicine, 8(10). https://doi.org/10.3390/JCM8101625
- [6] Lin, L. Te, Tsui, K. H., Cheng, J. T., Cheng, J. S., Huang, W. C., Liou, W. S., & Tang, P. L. (2016). Increased Risk of Intracranial Hemorrhage in Patients With Pregnancy-Induced Hypertension: A Nationwide Population-Based Retrospective Cohort Study. Medicine,95(20). https://doi.org/10.1097/MD.00000000000 3732
- [7] An, S. J., Kim, T. J., & Yoon, B. W. (2017). Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. Journal of Stroke, 19(1), 3. https://doi.org/10.5853/JOS.2016.00864
- [8] Palei, A. C., Spradley, F. T., Warrington, J. P., George, E. M., & Granger, J. P. (n.d.). Pathophysiology of Hypertension in Preeclampsia: A Lesson in Integrative Physiology. https://doi.org/10.1111/apha.12106
- [9] Fairhall, J. M., & Stoodley, M. A. (2009). Intracranial haemorrhage in pregnancy. Obstetric Medicine, 2(4), 142. https://doi.org/10.1258/OM.2009.090030

- [10] Tenny, S., & Thorell, W. (2024, February 17). Intracranial Hemorrhage. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK 470242/
- [11] de Souza Lopes, D. N., de Almeida, J. H. C. L., & de Azevedo Gomes, M. C. (2023a). Intracranial Hemorrhage. Perinatology: Evidence-Based Best Practices in Perinatal Medicine, 1253– 1267. https://doi.org/10.1007/978-3-030-83434-0_66
- [12] Magid-Bernstein, J., Girard, R., Polster, S., Srinath, A., Romanos, S., Awad, I. A., & Sansing, L. H. (2022). Cerebral Hemorrhage: Pathophysiology, Treatment, and Future Directions. Circulation Research, 130(8), 1204–1229. https://doi.org/10.1161/CIRCRESAHA.121.3 19949
- [13] Caceres, J. A., & Goldstein, J. N. (2012). Intracranial Hemorrhage. Emergency Medicine Clinics of North America, 30(3), 771. https://doi.org/10.1016/J.EMC.2012.06.003
- [14] Palei, A. C., Spradley, F. T., Warrington, J. P., George, E. M., & Granger, J. P. (n.d.). Pathophysiology of Hypertension in Preeclampsia: A Lesson in Integrative Physiology. https://doi.org/10.1111/apha.12106