published: 1 Oktober 2026
doi: 10.21070/midwiferia.v12i2.1818

History of Preeclampsia and the Risk of Future Stroke: A Systematic Review

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OPEN ACCESS
ISSN 2548-2246 (online)
ISSN 2442-9139 (print)
Received: 12 Jun 2026
Accepted: 22 Sep 2026
Published: 9 Okt 2026
Citation:
Ovella Apri Rieza (2026) History of Preeclampsia and the Risk of Future Stroke: A Systematic Review
Midwiferia Jurnal Kebidanan. 12:2. doi: 10.21070/midwiferia.v12i2.1818

ABSTRACT

Introduction *Preeclampsia is a pregnancy complication that increases the risk of development of cardiovascular and cerebrovascular disease. The association of preeclampsia and future stroke risk is not entirely known yet. The purpose of this study is to assess and summarize the literature available about the association of history of preeclampsia with future stroke risk in women.*

Methods *This systematic review was performed following the PRISMA guideline. Searches were conducted for literature in PubMed, ScienceDirect, and Scopus from 2017 to 2026. Studies included in this study are retrospective cohort studies which have examined the relationship between preeclampsia and future stroke risk. The studies included for this research were conducted in Taiwan, the United States, Australia, and the United Kingdom. Methodological quality assessment of the selected studies was done by using the Critical Appraisal Tool provided by Joanna Briggs Institute.*

Results *It has been found that women with preeclampsia history have high chances of suffering from stroke in the future with an effect size range of aHR 1.71 to 2.05 and RR 3.79. More significant associations have been found for some types of strokes with aHR of 3.45 for hemorrhagic stroke and 1.90 to 4.76 for ischemic stroke.*

Discussion and Conclusion *This increased risk of stroke lasts at least for decades, particularly among women with recurrent hypertensive disorders of pregnancy or preterm preeclampsia. In conclusion, a history of preeclampsia is associated with an increased risk of future stroke, highlighting the importance of long-term cardiovascular and cerebrovascular risk monitoring and prevention.*

Keywords: *cerebrovascular disease, hypertension, long term outcomes, preeclampsia, stroke*

INTRODUCTION

According to the American College of Obstetricians and Gynecologists (ACOG), preeclampsia is a multisystem disorder characterized by new-onset hypertension after 20 weeks of gestation, defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, accompanied by proteinuria or evidence of maternal organ dysfunction. The condition may affect multiple organ systems, including the brain, kidneys, liver, lungs, and vascular system, and most commonly develops during the third trimester of pregnancy [1]. According to the World Health Organization (WHO), around 12% of maternal deaths are linked to preeclampsia. The rate of preeclampsia in developing countries is about seven times higher than in developed countries, at roughly 2.8% compared to 0.4%. In developing countries, the occurrence of preeclampsia ranges from about 1.8% to 16.7% [2], [3].

Preeclampsia is a condition that affects multiple systems. According to the two-stage placental model theory, the first stage of preeclampsia involves a failure of trophoblast invasion and spiral artery remodeling. This failure leads to poor blood flow in the uterus and placenta, causing low oxygen levels and oxidative stress in the placenta. This condition prompts the release of substances from the placenta into the mother's bloodstream, especially anti-angiogenic factors like sFlt-1 and sEng. These disrupt the balance of angiogenic factors, including PlGF. In the second stage, these substances cause systemic endothelial dysfunction. This dysfunction is marked by blood vessel constriction, higher vascular resistance, inflammation, and increased vessel permeability. These changes result in the symptoms of preeclampsia, which include high blood pressure, protein in the urine, and issues affecting various maternal organs like the kidneys, liver, and central nervous system [4]

Preeclampsia increases the risk of Ischemic Heart Disease (IHD), chronic hypertension, peripheral vascular disease, and stroke [5]. Globally, approximately 3.48 million women die from stroke each year, accounting for nearly 48% of all stroke-related deaths worldwide. Women also have a higher lifetime risk of stroke and poorer post-stroke outcomes than men because of sex-specific risk factors, including hypertensive disorders of pregnancy such as preeclampsia [6], [7].

Changes in the endothelium impact vascular function because of increased blood

pressure. This rise in blood pressure boosts the risk of cerebrovascular events, like stroke, in women as they age. Women who have a history of preeclampsia face a threefold higher risk of stroke. This heightened risk applies to both ischemic and hemorrhagic strokes, with the greatest risk seen in hemorrhagic strokes [8]. A hemorrhagic stroke occurs when a blood vessel ruptures, causing bleeding into the surrounding brain tissue [9]. An ischemic stroke, on the other hand, results from a blockage in an artery that supplies blood to a specific area of the brain [10]. An increase in carotid intima-media thickness is an indicator of subclinical atherosclerosis and is closely associated with an increased risk of stroke later in life [11].

The occurrence of strokes in the postpartum stage is greater, at a frequency of 7.77 per 100,000 pregnancies, than that observed in the antepartum stage, which was 5.67 per 100,000 pregnancies. Additional studies revealed that the highest risk for strokes occurs in the first six weeks after delivery at a frequency of 29.06 per 100,000, which is greater than the frequency in the 6 to 48-week period, which is 28.63 per 100,000. The figures suggest that the early postpartum period is a crucial time because there is great vascular susceptibility [12], [13].

Although there is ample evidence demonstrating that the presence of preeclampsia increases the risk of stroke in the future, the exact characteristics and timing of this increased risk of stroke are still unknown, and there is no guidance regarding long-term cardiovascular follow up after experiencing preeclampsia. There is no question that the women who have experienced preeclampsia should be aware of their higher risk of developing stroke in the future. However, the type of stroke, the time interval when the risk of having a stroke will be highest, and the degree of this risk are still unknown. This paper seeks to review the evidence regarding the long-term association of the history of preeclampsia and stroke risks in terms of the types of stroke, timing, and degrees of risk [5].

METHODS

This systematic review was conducted in accordance with the PRISMA 2020 Statement, and study selection was presented using the PRISMA flow diagram. The primary focus of this study is to collect and analyze relevant evidence regarding the risk of stroke in women with a history of preeclampsia. This systematic review was not registered in the International Prospective Register of Systematic Reviews (PROSPERO).

The search strategy for this study, designed to facilitate database searches, is based on the PICO framework (Population, Intervention, Comparison, Outcome). The research question in this study was formulated to evaluate whether a history of preeclampsia increases the risk of stroke later in life. The literature search was conducted in PubMed, Scopus, and ScienceDirect. The PubMed search strategy was: ("Preeclampsia"[MeSH] OR preeclampsia OR pre-eclampsia) AND ("Stroke"[MeSH] OR stroke OR "cerebrovascular disease" OR "cerebrovascular accident") AND (women OR "pregnant women" OR maternal).

Two independent reviewers (the first author and the second author) screened all titles, abstracts, and full-text articles according to the predefined eligibility criteria. Each reviewer independently assessed study eligibility. The reviewers were blinded to each other's decisions during the screening process. Any disagreement regarding study selection or eligibility was resolved through discussion between the first and second authors. If consensus could not be reached, the third author was consulted to make the final decision.

Table 1. PICO *Framework*

Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
Women who have been pregnant and given birth	Women with a history of preeclampsia	Women without a history of preeclampsia	Incidence of stroke

The quality of the following articles was assessed using the Critical Appraisal Tools (CAT) from the Joanna Briggs Institute (JBI). The assessment instrument was selected and adapted to the study design, specifically a retrospective cohort study. It consists of 11 questions to evaluate the quality of the research methodology, including the appropriateness of the study population, measurement of exposure, identification of confounding factors, validity of outcome measurement, and adequacy of the follow up period. Rather than applying a numerical cut off score, the methodological quality of each study was interpreted according to its overall risk of bias as low**,** moderate**,** or high, based on the reviewers judgment of the responses to the JBI checklist items.[14]

Table 2. Critical Appraisal Tools Retrospective Cohort Study

Authors	Question Number											Total
	1	2	3	4	5	6	7	8	9	10	11	
Chuang, et al, 2022	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓	10.5
Hung, et al, 2022	✓	✓	✓	✓	✓	✓	✓	✓	NA	NA	✓	10
Pipes, et al, 2023	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓	10.5
Kuo et al, 2018	✓	✓	✓	-	✓	✓	✓	✓	NA	NA	✓	9
Tooher, et al 2017	✓	✓	✓	✓	✓	✓	✓	✓	NA	NA	✓	10
Havenon, et al,2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Leon, et al, 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11

The risk of bias assessment considered five methodological domains, namely selection bias, exposure measurement bias, confounding, outcome measurement bias, and adequacy of follow-up. Overall, most included studies demonstrated a low risk of bias. The primary concern identified among several studies was incomplete adjustment for potential confounding variables. Nevertheless, the methodological quality was considered sufficient to support the synthesis of evidence.

A systematic literature search across three databases identified 11,008 articles. Subsequently, 82 duplicate articles were identified, and after reviewing the titles and abstracts, 10,926 were excluded for failing to meet the inclusion criteria; thus, 7 studies were determined to be eligible and included in this systematic review. The inclusion criteria for selecting articles to be reviewed included studies using a retrospective cohort design, the included articles were those published between 2017 and 2026 and were original research studies providing data on preeclampsia exposure and stroke incidence as the outcome. The articles excluded from this study were those on pregnant women who experienced a stroke, those that did not discuss women with a history of preeclampsia, articles that did not report stroke incidence as a research outcome, and articles that could not be accessed in full. Rayyan was used for screening. Subsequently, data extraction was performed using a form that included information regarding the authors, year of publication, study location, sample, sample size, and study results.

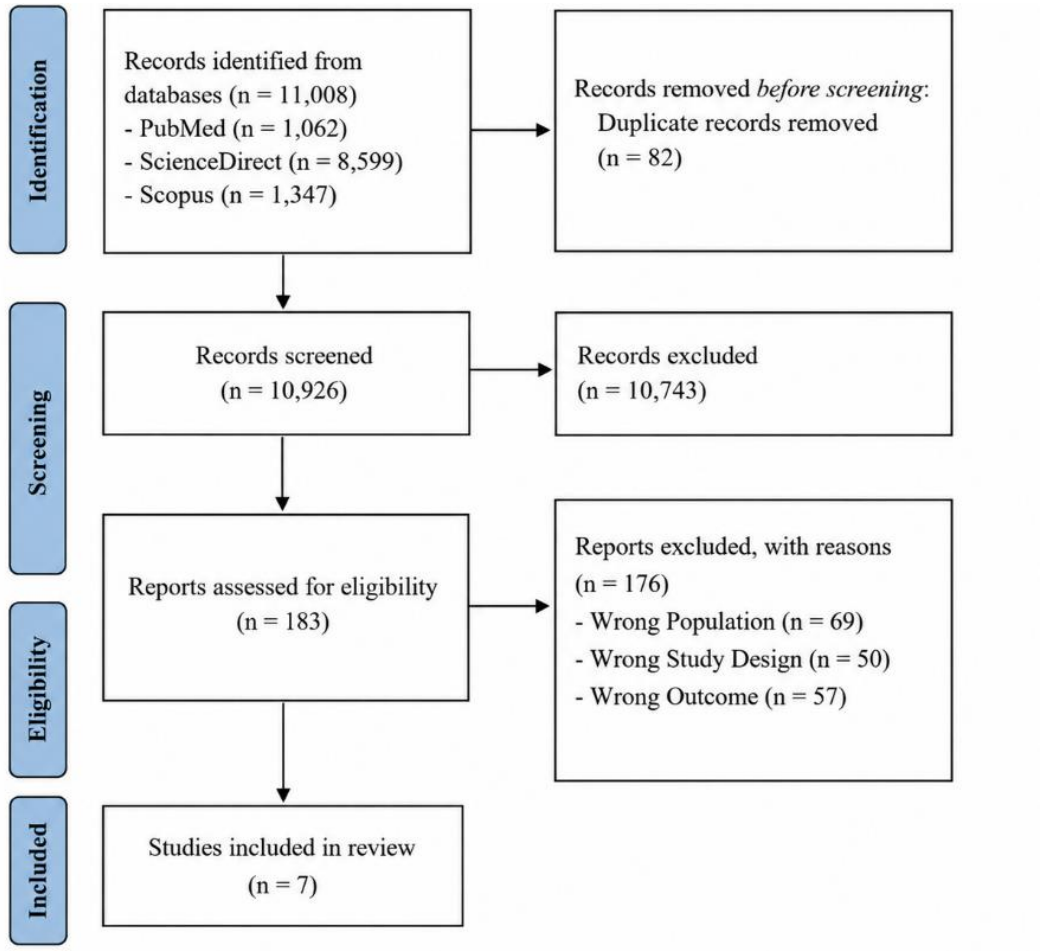


Figure 1. PRISMA flow chart

RESULT

Based on the selection process, seven articles met the established quality criteria and were therefore considered to have a relatively low risk of bias, making them appropriate for inclusion in the narrative synthesis. The features of these studies indicated great variation in the number of subjects involved, which were carried out in many countries, such as Taiwan, the United States, Australia, and the United Kingdom. Generally, all of these studies indicated that women who have experienced preeclampsia in their lives are more prone to suffer from stroke than those without preeclampsia. The results indicate a relationship between preeclampsia and risk of cerebrovascular disease.

The study **involved** a quantitative descriptive synthesis of the effect estimates that have been documented in the articles. The association between the two variables has been documented using the adjusted hazard ratio (aHR), hazard ratio (HR), relative risk (RR),

and odds ratio (OR) based on the article. In the case of the overall stroke outcomes, the adjusted hazard ratios were found to vary between 1.71 and 2.05. Havenon et al. reported a relative risk of 3.79 (95% CI 1.24-11.60) for future stroke among women with a history of preeclampsia. Leon et al. reported an HR of 1.90 (95% CI 1.53-2.35) for stroke. In addition, Chuang et al. reported an aHR of 2.05 (95% CI 1.67-2.52), while Hung et al. reported an aHR of 1.71 for stroke among women with hypertensive disorders of pregnancy.

The magnitude of risk was higher for specific stroke subtypes. Chuang et al. reported an aHR of 3.45 for hemorrhagic stroke and 1.98 for ischemic stroke, while Kuo et al. reported an HR of 4.76 for ischemic stroke associated with preeclampsia and an HR of 19.74 for hemorrhagic stroke associated with eclampsia. These findings indicate a generally positive trend toward an increased risk of future stroke following preeclampsia or hypertensive disorders of pregnancy. However, statistical pooling was not performed because of differences in study populations, definitions of exposure and outcomes, follow-up periods, and effect measures.

Table 3. Summary of Articles Included in the Review

Author	Country	Method	Sample	Findings
Chuang, et al, 2022 [15]	Taiwan	Retrospective Cohort Study	30.265	Women with a history of preeclampsia/eclampsia have a higher risk of stroke (aHR 2.05; 95% CI 1.67-2.52; p<0.001). The risk of hemorrhagic stroke (aHR 3.45) is higher than that of ischemic stroke (aHR 1.98). The peak risk of ischemic stroke occurs 1-3 years after childbirth, whereas the peak risk of hemorrhagic stroke occurs 3-5 years after childbirth.
Hung, et al, 2022 [16]	Taiwan	Retrospective Cohort Study	17.588	Women with HDP (hypertensive disorders of pregnancy) have an increased risk of stroke (aHR 1.71) compared to women without HDP. The risk of stroke remains elevated for up to 10-15 years postpartum. The highest risk was observed in cases of chronic hypertension with superimposed preeclampsia (aHR 3.86) and multiple HDP with preeclampsia (aHR 5.48).
Pipes, et al, 2023	United State	Retrospective Cohort Study	21.754.603	The incidence of postpartum stroke is 2,3 per 10,000 deliveries and shows no significant upward trend; most cases

Author	Country	Method	Sample	Findings
[17]				occur within the first 10 days postpartum, with the primary risk factors being preeclampsia/eclampsia, heart disease, chronic kidney disease, SLE, and maternal age ≥40 years.
Kuo et al, 2018 [18]	Taiwan	Retrospective Cohort Study	6.475	A history of preeclampsia/eclampsia increases the risk of long-term cardiovascular disease, including hypertension (HR 6.52-7.31), diabetes mellitus (HR 3.84-5.42), dyslipidemia (HR 2.75-3.40), heart failure (HR 7.39-9.07), and cerebrovascular disease (HR 3.47-10.71); eclampsia is strongly associated with hemorrhagic stroke (HR 19.74) and preeclampsia with ischemic stroke (HR 4.76).
Tooher, et al 2017 [19]	Australia	Retrospective Cohort Study	1.158	Women with pregnancy induced hypertension (PIH) have an increased risk of future cardiovascular disease, including hypertension (OR 2.78; 95% CI 2.47-3.13), ischemic heart disease (OR 2.16; 95% CI 1.98-3.84), stroke (OR 1.94; 95% CI 1.39-2.69), and kidney disease (OR 2.76; 95% CI 1.98-3.84) compared to normotensive women. However, preeclampsia (OR 2.03; 95% CI 0.75-5.49) and gestational hypertension (OR 0.57; 95% CI 0.14-2.31) did not show a statistically significant association when analyzed separately.
Havenon, et al, 2021 [20]	United State	Retrospective Cohort Study	1.435	This study found that 169 women had a history of preeclampsia and 231 experienced a stroke during the follow up period. After adjusting for all lifetime vascular risk factors, women with a history of preeclampsia had a risk of stroke later in life approximately 3.79 times higher than women without a history of preeclampsia (RR 3.79; 95% CI 1.24-11.60). These results indicate that preeclampsia is an independent risk factor contributing to an increased incidence of stroke in the future.
Leon, et al, 2019 [21]	United Kingdom	Retrospective Cohort Study	1.300.000	Women with a history of preeclampsia have an increased risk of cardiovascular disease, including stroke (HR 1.9; 95%

Author	Country	Method	Sample	Findings
				CI 1.53-2.35), heart failure (HR 2.13), atrial fibrillation (HR 1.73), and cardiovascular death (HR 2.12). This risk is evident as early as 1 year after pregnancy and is higher in cases of preterm preeclampsia.

Quantitative Synthesis

Overall, the quantitative descriptive synthesis demonstrated a consistent positive direction of association between a history of preeclampsia and the risk of future stroke. In general, most of the included studies reported a higher risk of stroke, but the strength of this association was inconsistent. We recorded adjusted hazard ratios (aHR), hazard ratios (HR), relative risks (RR) and odds ratios (OR). Due to differences in study populations, outcome definitions, follow up periods, and effect measures, a pooled statistical estimate was not calculated.

DISCUSSION

This is a systematic review highlighting an increased risk of subsequent stroke compared with women born without preeclampsia; in the UK, one study reported that women with previous preeclampsia had nearly double the risk of stroke [15]. One study carried out in the United Kingdom found that there is about twice the risk of having a stroke in women who have had preeclampsia [21]. Likewise, results from the Framingham Heart Study revealed that the relationship persisted even after adjusting for vascular risk factors acquired during the life course [20]. These results have indicated that preeclampsia can be considered not only a problem in pregnancy but also as a major indicator of long-term risk of cerebrovascular disease. Preeclampsia causes a disruption between the factors that expand blood vessels and those that constrict the vessels, causing increased vascular resistance and vasoconstriction. In cerebral arteries, preeclampsia prevents sufficient blood flow into the brain, thereby increasing its vulnerability due to lack of adequate blood supply. Consequently, there is a greater injury to the brain than in patients with no prior preeclampsia [22]. Moreover, we know that women who have had preeclampsia in their past are at higher risk for conditions such as hypertension, cholesterol abnormalities, and metabolic disorders. These are all factors that increase the

chances of having a stroke [12].

While most of the selected studies showed that preeclampsia is positively linked to stroke, the magnitude of the link differed greatly among the studies selected. The differences could be attributed to varying criteria for selecting participants of the study, definitions of the hypertensive disorders in pregnancy and stroke, duration of the follow up, and adjustment of the studies for confounding factors. Those studies that have longer follow up periods may capture more conventional cardiovascular risk factors while those with shorter follow up periods could be closer to the vascular effects of hypertension disorders during pregnancy.

All the included studies have shown a positive correlation between preeclampsia and risk of developing strokes in the future, but the degree to which the risks were expressed differed significantly. The hazard ratios varied between 1.7 and 3.8, which could possibly be attributed to the difference between definitions of hypertensive disorders of pregnancy. Studies involving longer follow up times have shown more associations, implying that the effects on the vasculature associated with preeclampsia may continue for several years following pregnancy.

Most studies show that the risk of stroke goes up. The number of strokes that actually happen can be different. In the United States, women who had preeclampsia are more likely to have a stroke. This is the common type of stroke for these women.[17] A study found that ischemic stroke is the type of stroke that is closely linked to preeclampsia. On the other hand, eclampsia is more closely linked to hemorrhagic stroke.[18] Ischemic stroke is more common than hemorrhagic stroke in women who're pregnant or have just given birth. The common subtype of ischemic stroke is cerebral venous thrombosis, especially in the six weeks, after giving birth. However, another study found that even though ischemic stroke is more common, preeclampsia actually increases the risk of hemorrhagic stroke more [15], [16]. High blood pressure can hurt the blood vessels in the brain. When blood pressure goes up suddenly and repeatedly, it can damage the blood vessels, the small ones. This can result in vascular rupture and intracerebral hemorrhage, which can lead to hemorrhagic stroke. Ischemic stroke and hemorrhagic stroke are both types of stroke, and preeclampsia can increase the risk of both, but in ways [23], [24].

A stroke can happen after preeclampsia, either after childbirth or suddenly. When

a woman is pregnant, her body gets ready for childbirth by making her blood clot more easily. This is a thing because it helps prevent too much bleeding during delivery. It also means that blood clots can form more easily in the wrong places. These abnormal blood clots can block blood vessels in the brain. Cause a stroke [17]. Changes in blood vessels and the stress on the body during pregnancy can also make them more likely to rupture. This can lead to a type of stroke called a hemorrhagic stroke. These changes can last for weeks after childbirth [25], [26]. In the run, women who had preeclampsia may have a stroke at an older age, usually more than 5 years after childbirth. The risk of stroke stays high for more than 10 years after childbirth. This shows that having preeclampsia is a risk factor for heart and blood vessel problems later in life. However, the risk of stroke is 1-3 years after childbirth. During this time, the body is going through changes after pregnancy, and new health problems like high blood pressure and insulin resistance may start to develop. A study found that strokes, which are caused by blood clots, peak earlier, within 1-3 years, after childbirth. The hemorrhagic stroke is different because it arises from a blood vessel rupture [15]. It is possible for someone to be at the risk of a stroke at any moment in time. Research done on women who have hypertension when they are pregnant including those with preeclampsia has shown that such women continue being at the risk of heart diseases even many years after the pregnancy. The research carried out focused on the risks associated with blood pressure and heart diseases and revealed that women with a history of high blood pressure while pregnant including preeclampsia are at the risk of heart diseases [19].

The study variability can be attributed to the difference in healthcare systems, the ethnicity of the population, and the preexisting cardiovascular risks. For instance, the studies done in Taiwan mainly used Asian subjects with access to national health insurance databases while studies from US and UK used ethnically diverse population. Variability in postpartum surveillance, access to prevention healthcare services, and management of chronic hypertension may have contributed to variability in risk of stroke reported.

Stroke is a disease which is multifactorial in origin and it is associated with various cardiovascular risks such as chronic hypertension, obesity, diabetes mellitus, smoking, dyslipidemia and advanced age of mothers. The included cohort studies adjusted for the above confounding factors by the use of multivariable regression analysis.

Notably, the studies by Havenon et al and Chuang et al showed the association between preeclampsia and stroke was statistically significant even after adjustment. This indicated that preeclampsia was an independent predictor of cerebrovascular disease and not the risk factors. However, the confounding factors were not entirely ruled out

The question at hand here is whether or not preeclampsia actually causes cerebrovascular disease or is simply an early indicator of an underlying predisposition to cardiovascular disease. It appears that there are probably elements of each of these two concepts. Preeclampsia causes dysfunction of the endothelium, vascular remodeling, inflammation, and chronic anti angiogenesis, all of which could lead to chronic vascular damage. That being said, those who suffer from preeclampsia also have an increased presence of cardiovascular risk factors prior to contribute directly to long term vascular injury. However, women who develop preeclampsia often have pre existing cardiovascular risk factors, including obesity, chronic hypertension, insulin resistance, and metabolic dysfunction, which may predispose them to both preeclampsia and future stroke. The several cohort studies that have been reviewed here have revealed that the relationship between preeclampsia and stroke has remained statistically significant even after controlling for major risk factors of cardiovascular disease, implying that the link between these conditions goes beyond being just a marker of an already existing condition to having a causative effect on cerebral vascular disease in the long run. Still, the possibility of confounding cannot be ruled out entirely.

The length of follow up is another factor that needs to be taken into account in analyzing the relation between preeclampsia and later risk of stroke. Stroke can develop several years after the first pregnancy, and the presence of the corresponding risk factors acquired with age can change the degree of the relation. Thus, the length of the follow up may affect the results of each study, leading to various estimates of the risk of stroke. A longer period may provide more opportunities for recognizing cerebrovascular problems, but it may also involve additional confounding due to age and other newly acquired risk factors.

The results obtained from the systematic review have significant practical applications for midwifery practice. First, midwives have an important responsibility to detect women with a history of preeclampsia among those at risk for developing cardiovascular and cerebrovascular disorders in the future. Despite the fact that the

preeclampsia is considered a pregnancy-specific condition, the findings presented in this review show that the vascular changes associated with this condition may remain for many years after the delivery. Consequently, the follow-up program for women after delivery should not be limited by the period of puerperium only; instead, a program that includes cardiovascular risk surveillance, control of blood pressure, and lifestyle modification, which involves such components as maintenance of normal body weight, physical activities, quitting smoking, and controlling other cardiovascular risk factors, should be developed. Moreover, it is necessary to inform women about the long term effects of preeclampsia and arrange timely referral to general practitioners or other specialists if there are any signs of cardiovascular risks.

The following are some of the strengths of the review. Firstly, a systematic literature search was carried out in PubMed, ScienceDirect, and Scopus and secondly, the inclusion criteria for the studies in the review was clear. Furthermore, quality assessment was done on the included studies.But there were some limitations which had to be taken into account. Firstly, the included studies differed in terms of population, definition of preeclampsia and stroke, follow up period, and adjustment for confounders, which led to significant methodological heterogeneity. The diversity in effect measures reported in different studies made it impossible to conduct a quantitative analysis. Thus, no statistical meta analysis was conducted and the results can be viewed as a descriptive analysis. Also, the review was confined to the studies published in English, which could cause some language bias.

CONCLUSIONS

In this systematic review, a history of preeclampsia was found to be strongly associated with a risk of developing stroke later on in life. The effect size for this association was roughly found to be twice or more the baseline risk with higher risks being noted for certain types of stroke. These findings highlight the importance of long term cardiovascular and cerebrovascular risk assessment and preventive follow up for women with a history of preeclampsia.

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