DOI: https://doi.org/10.61841/df5j4g29 Publication URL: https://nnpub.org/index.php/MHS/article/view/2067

THE COMPREHENSIVE SYSTEMATIC REVIEW OF HYPERTENSIVE DISORDERS IN PREGNANCY AND LONG TERM RISK OF MATERNAL STROKE

[1*]Agung Supriyadi, [2]Zulfikar Andimapali, [3]Adina Fitria, [4]Rahadiyan Whisnu Dewanegara

[1]PKU Muhammadiyah Gamping General Hospital, Special Region of Yogyakarta, Indonesia
[2]Hermina General Hospital, Jakarta Special Capital Region, Indonesia
[3]Kanjuruhan Regional General Hospital, Malang, Indonesia
[4]Arvita Bunda Mother and Child Hospital, Special Region of Yogyakarta, Indonesia

Correspondence Author:
agungsupriadi299@gmail.com

ABSTRACT

Background: *Hypertensive disorders of pregnancy (HDP) are associated with a long-term risk for cardiovascular disease among parous patients later in life. However, relatively little is known about whether HDP are associated with an increased risk for ischaemic stroke (IS) or haemorrhagic stroke (HS) in later life.*

The aim: *This study aims to show about the comprehensive of hypertensive disorders in pregnancy and long term risk of maternal stroke.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 67 articles, whereas the results of our search on SagePub brought up 170 articles. The results of the search conducted for the last year of 2014 yielded a total 35 articles for PubMed and 58 articles for SagePub. The result from title screening, a total 15 articles for PubMed and 29 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Exposure to Hypertensive disorders of pregnancy (HDP), including PE and GH, seems to be associated with an increased risk for AS and IS among parous patients in later life. Preventive interventions may be warranted for patients who experience HDP to reduce their long-term risk for stroke.*

Keyword: *Hypertensive disorders of pregnancy, maternal stroke, cardiovascular disease.*

INTRODUCTION

Pregnancy has been established to be a state of physiological stress for patients. Hypertensive disorders of pregnancy (HDPs), such as preeclampsia (PE), place considerable strain on the body.1There is a growing body of evidence that HDPs induce endothelial changes that impact a patient's physiology.2,3 These endothelial changes have been linked to vascular pathologies throughout the body, including in the cardiovascular system, renal system, and neurologic system.4e8 A consensus has been reached about the risk that HDPs confer to the cardiovascular and renal systems.5,9 HDPs have been shown to be associated with an increased risk for cardiovascular disease (CVD). These conditions have also been associated with an increased risk for chronic kidney disease (CKD) and end-stage kidney disease (ESKD). However, the risk HDPs present to the neurovascular system is less established. If HDPs induce endothelial changes that have an impact on vascular efficacy, it is plausible that they may potentiate the risk for a cerebrovascular accident (CVA) in mothers later in life.[1,2]

Stroke is a major cause of severe maternal morbidity and mortality in the United States, accounting for 1 in 12 deaths in women who are pregnant and postpartum.[1] Even nonfatal strokes, including those considered "minor," can result in significant disability and have long-term physical, emotional, and financial consequences for maternal stroke survivors. The unique physiology and pathophysiology of pregnancy contribute to maternal stroke risk and can result in unusual stroke mechanisms and presentations. Neurologists must be familiar with the risk factors, pathophysiology, and mechanisms of maternal stroke to prevent, recognize, and effectively treat this potentially devastating group of diseases. The neurologist can play a key role both in acute recognition and treatment of maternal stroke and in primary and secondary prevention. This article summarizes the current understanding of the epidemiology, pathophysiology, and treatment of maternal stroke, with an emphasis on recent developments in the field.[3,4]

Preeclampsia is a hypertensive disorder that occurs during pregnancy and affects between 5 and 10% of all births in the United States each year. It is the leading cause of preterm births, morbidity, and mortality for both the mother and fetus during pregnancy. Preeclampsia is generally characterized as new-onset hypertension, with a blood pressure >140/90 mmHg that occurs during the 20th week of pregnancy. Different from gestational hypertension, preeclampsia is a disorder that can affect many organ systems of the body and can lead to decrease in renal function, liver dysfunction, and even stroke in more severe forms of preeclampsia, such as eclampsia. Preeclampsia is commonly associated with proteinuria, severe headaches, vomiting, abdominal pain, visual disturbances, and multiorgan dysfunction. Gestational hypertension typically is not associated with proteinuria or other organ dysfunction but can be a risk factor for the development of preeclampsia. Preeclampsia can be further broken down into two different diseases, mild and severe preeclampsia. A blood pressure of 140/90 mmHg on two different occasions after 20 wk of gestation with one of the major symptoms mentioned above is classified as mild preeclampsia. A blood pressure ≥160/110 mmHg with severe proteinuria (>5 g/day), severe headaches, and any of the associated side effects mentioned above is classified as severe preeclampsia. Severe preeclampsia is very dangerous and could result in eclampsia or death for both the mother and fetus.[5,6]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast the comprehensive of hypertensive disorders in pregnancy and long term risk of maternal stroke. It is possible to accomplish this by researching or investigating the comprehensive of hypertensive disorders in pregnancy and long term risk of maternal stroke. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the comprehensive of hypertensive disorders in pregnancy and long term risk of maternal stroke. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " the comprehensive of hypertensive disorders in pregnancy and long term risk of maternal stroke." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Hypertensive disorder*"[MeSH Subheading] OR "* Hypertensive disorders in pregnancy*"[All Fields] OR "*Maternal stroke*" [All Fields]) AND ("*Mechanism of hypertensive disorder in pregnancy*"[All Fields] OR "*

effects of hypertensive disorder in pregnancy*"[All Fields]) AND ("*Mechanism of maternal stroke*"[All Fields]) OR ("*hypertensive disorders in pregnancy and long term risk of maternal stroke" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

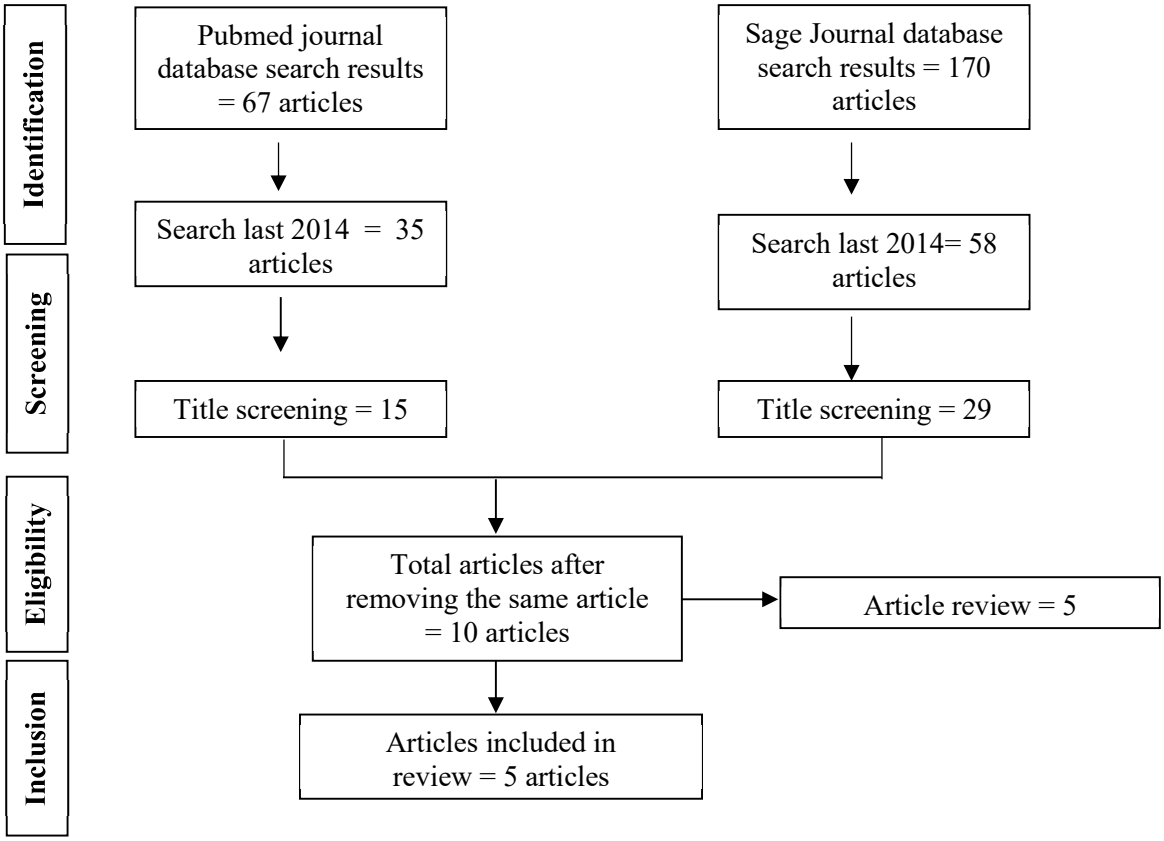

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 67 articles, whereas the results of our search on SagePub brought up 170 articles. The results of the search conducted for the last year of 2014 yielded a total 35 articles for PubMed and 58 articles for SagePub. The result from title screening, a total 15 articles for PubMed and 29 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Hung, SK *et al* (2022)[7] showed HDP increased the stroke risk, and its effect persisted for up to 17 years. The risk of both ischemic and hemorrhagic strokes persisted; however, their risk time-trends were different. Women with a previous HDP history should be aware that the risk of stroke may persist for even more than a decade and take appropriate precautionary measures or behavior modifications like regular blood pressure monitor, avoiding cigarette smoking and heavy drinking, or preventive medication such as aspirin, especially for women with multiple HDP combined with preeclampsia.

Fang, M *et al* (2023)[8] showed women with hypertension disorders of pregnancy did not show worse short-term outcomes of pregnancy-associated hemorrhagic stroke compared to those without but had poorer long-term functional outcomes. This underlines the importance of prevention, recognition, and treatment of hypertension disorders in these women.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Hung, SK *et al*., 2022[7]	Taiwan	Retrospective study	17588	HDP women had an adjusted hazard ratio (aHR) of 1.71 (95% CI, 1.46−2.00) for stroke, and 1.60 (1.35−1.89) and 2.98 (2.13−4.18) for ischemic and hemorrhagic stroke, respectively (P<0.001 for all). The overall stroke risk in the HDP group was still 2.04 times 10 to 15 years after childbirth (1.47−2.83, P<0.001). Although the risks of both ischemic and hemorrhagic stroke persisted, their risk time trends were different. The risk of ischemic stroke reached peak during 1 to 3 years after childbirth with an aHR of 2.14 (1.36–3.38), while hemorrhagic stroke risk gradually increased and had an aHR of 4.64 (2.47−8.73) after 10 to 15 years of childbirth (both P<0.001). Among the 4 HDP subtypes, chronic hypertension with superimposed preeclampsia had the highest stroke risk (aHR=3.86, 1.91−7.82, P<0.001), followed by preeclampsia–eclampsia (aHR=2.00, 1.63−2.45, P<0.001), and gestational hypertension (aHR=1.68, 1.13−2.52, P<0.05); chronic preexisting hypertension had the lowest stroke risk (aHR=1.27, 0.97−1.68, P>0.05). Furthermore, multiple HDP combined with preeclampsia had aHR of 5.48 (1.14−26.42, P<0.05).
Fang, M *et al*., 2023[8]	China	Retrospective study	94	Twenty-two HDP and 72 non-HDP pregnancy-associated HS patients were enrolled and follow-up after 4.7 ± 3.6 years. There was no significant difference between the two groups regarding short-term

				outcomes, but patients with HDP were more likely to reach poor functional outcomes at long-term follow-up (aOR = 4.47, 95% CI = 1.28–15.67, $p = 0.019$).
Huang, CC *et al*., 2022[9]	Taiwan	Case control study	41870	During the follow-up period, the Kaplan-Meier analysis indicated that patients with hypertensive pregnancy disorders had a significantly higher risk of developing stroke than did patients without hypertensive pregnancy disorders (log-rank test $P < 0.001$). Multivariate Cox regression analysis demonstrated that the case group had a 2.134-fold increased risk of stroke (HR = 2.134; 95% CI = 1.817–2.505; $P < 0.001$).
Miller, EC *et al*., 2019[10]	America	Prospective study	83749	Of 83,749 women included in the analysis, 4,070 (4.9%) had HDP. Women with prior HDP had increased risk of all stroke (adjusted HR 1.3, 95% CI 1.2–1.4) but no increased risk of stroke before age 60 (adjusted HR 1.2, 95% CI 0.9–1.7). There was an interaction ($p = 0.18$) between aspirin use and HDP history on risk of stroke before age 60: nonusers of aspirin had higher risk (adjusted HR 1.5, 95% CI 1.0–2.1) while aspirin users did not (adjusted HR 0.8, 95% CI 0.4–1.7). This effect was not seen with statins.
Garovic, VD *et al*., 2020[11]	USA	Cohort study	9862	Among 9,862 pregnancies, we identified 719 (7.3%) with HDP and 324 (3.3%) with preeclampsia. The incidence of HDP and preeclampsia doubled when assessed on a per-woman basis: 15.3% (281/1839) and 7.5% (138/1839), respectively. Women with a history of HDP were at increased risk for subsequent diagnoses of stroke (HR 2.27; 95% CI 1.37–3.76), coronary artery disease (1.89; 1.26–2.82), cardiac arrhythmias (1.62; 1.28–2.05), chronic kidney disease (2.41; 1.54–3.78), and multimorbidity (1.25; 1.15–1.35).

Huang, CC *et al* (2022)[9] showed provided evidence of the increased risk of stroke in patients with hypertensive pregnancy disorders. Compared with those without hypertensive pregnancy disorders, the patients who had experienced such disorders had a 2.134-fold ($P < 0.001$) higher risk of developing stroke in the future. The occurrence of stroke in younger

women is an important issue, especially among those who are in the childbearing stage. The results from this study will provide physicians with strong proof of the need for the cautious treatment of patients with hypertensive pregnancy disorders and awareness of possible future stroke problems.

Miller, EC *et al* (2019)[10] showed that women with a history of HDP are more likely than those without this history to develop future stroke. The risk of stroke before age 60, but not overall stroke, was mitigated in women who were taking aspirin. History of HDP should be considered an important risk factor for future stroke, and some women with this history may warrant primary preventive treatment with aspirin even in the absence of additional vascular risk factors. More research is needed to better understand the mechanisms by which preeclampsia and related disorders increase stroke risk, and randomized controlled trials may be warranted to establish the efficacy of aspirin for the primary prevention of stroke in selected women with a history of HDP.

Garovic, VD *et al* (2020)[11] showed a population based incidence of HDP and preeclampsia, both per pregnancy and per woman, and suggests that the former may underestimate the number of affected women with a history of this condition who may be at risk for future CVD and renal disease. These two measures are not mutually exclusive, but rather are complementary. Studies of HDP and preeclampsia should include incidence estimates, both per pregnancy and per woman, as these may facilitate assessments of risk for pregnancy-related complications and risks for future CVD and renal disease, respectively. Our data underscore the need for future research that will address the mechanisms of the multimorbidity burden in women with a history of HDP, as well as for sex-specific risk scores for prediction of CVD and renal disease that will include reproductive history.

DISCUSSION

The prevalence of hypertension in reproductive-aged women is estimated to be 7.7%. Hypertensive disorders of pregnancy, an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality. The terms, goals of therapy, and treatment agents have been long debated and remain controversial. We aimed to review the pathophysiology and treatment of hypertensive disorders of pregnancy.[12]

The European Society of Cardiology (ESC) suggests that gestational hypertension should resolve within 42 days postpartum, which is the puerperal period, and that preexisting hypertension persists beyond this period;[5] however, many investigators support the concept that pregnancy hypertension may be termed chronic hypertension if it persists beyond 12 weeks after delivery. ESC also includes a category “antenatally unclassifiable hypertension” as that which arises before 20 weeks, but has not yet been evaluated after 42 days postpartum for final classification. There are a few other discrepancies across guidelines as well. Several societies include “White Coat Hypertension” and the specific preeclampsia spectrum disorders (e.g. eclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP)). The Society of Obstetricians and Gynaecologists of Canada also characterize their chronic and gestational hypertension as “with” or “without comorbidities.”[12,13]

The third trimester lasts from 28 weeks and 0 days of gestation through delivery. There is a peak in cardiac output in the early third trimester and blood pressure begins to increase back to baseline levels. In addition, the ratio between plasma volume and red cell mass peaks at 30 to 34 weeks, resulting in a physiologic anemia. The resultant decrease in blood viscosity further decreases resistance to flow and in turn allows improved placental perfusion to support the growing fetus. In addition, plasma volume increases to 50% greater than nonpregnant values near term, allowing a reserve against blood loss during delivery. Heart rate peaks in the late third trimester, with a 20% to 25% increase relative to baseline.[7] During active labor, systolic and diastolic blood pressures can increase an additional 15% to 25% and 10% to 15% respectively. Cardiac output is increased by 15% in early labor and 25% during the active phase.[14]

In a healthy pregnancy, the spiral uterine arteries increase in diameter by losing their muscular walls and extending to the myometrium. This process, known as pseudovasculogenesis, transforms them into vessels with large capacitance vessels and low resistance, facilitating high placental blood flow. Failure of this remodeling leads to increased resistance in placental vasculature, causing placental hypoperfusion and ischemia, which forms the basis of preeclampsia.[15]

Placental ischemia and resultant oxidative stress soon cascade to widespread maternal endothelial dysfunction mediated by angiogenic imbalance and inflammatory reaction. Ischemic placenta releases soluble FMS-like tyrosine kinase 1 (sFlt-1) and soluble endoglin, which are antiangiogenic. sFlt-1 binds to vascular endothelial growth factor and placental growth factor (PlGF) and prevents their interaction with the receptors, thus antagonizing their proangiogenic biologic activity. The result is a series of downstream effects culminating in end-organ damage characteristics of preeclampsia.[15,16]

Women with a history of preeclampsia are at higher risk of having a stroke during the non-pregnant, postpartum period, than women with a history of normotensive pregnancies, and a history of (pre)eclampsia is associated with a two-fold increase in the likelihood of stroke later in life. Additionally, a 4-5 fold increased risk of stroke has been reported for women with a history of (pre)eclampsia compared to normotensive pregnant women. Of note, hemorrhagic strokes are the most frequent type of stroke affecting (pre)eclampsia patients. In a small study of 27 preeclampsia patients, 25 had hemorrhagic stroke while only two had ischemic strokes. This increased risk of hemorrhagic stroke has also been

documented with other hypertensive disorders of pregnancy such as chronic hypertension and gestational hypertension. It should be noted that not only is overall risk of stroke increased, but a history of preeclampsia is associated with an increased risk of fatal strokes as opposed to non-fatal stroke.[17,18]

In addition to hemorrhagic strokes, women with a history of preeclampsia also have an increased risk of ischemic stroke. In a population study, showed that women with a history of preeclampsia were over 60% more likely to suffer from ischemic stroke during the postpartum period than women without a history of preeclampsia (OR: 1.63; 95% CI: 1.02–2.62 after adjustment for age, race, education, and number of pregnancies). Another study looked specifically at the incidence and causes of stroke during the peripartum and postpartum periods and showed that although the incidence of intraparenchymal hemorrhages (4.6 per 1,00,000 deliveries) was similar to ischemic stroke (4.3 per 1,00,000 deliveries), eclampsia was the leading cause of intraparenchymal hemorrhage (44%) and ischemic stroke (47%). These findings suggest that (pre)eclampsia may increase the risk of stroke after childbirth due to hemodynamic dysfunction.[17]

CONCLUSION

Exposure to Hypertensive disorders of pregnancy (HDP), including PE and GH, seems to be associated with an increased risk for AS and IS among parous patients in later life. Preventive interventions may be warranted for patients who experience HDP to reduce their long-term risk for stroke.

REFERENCES

[1] Brohan MP, Daly FP, Kelly L, McCarthy FP, Khashan AS, Kublickiene K, et al. Hypertensive disorders of pregnancy and long-term risk of maternal stroke—a systematic review and meta-analysis. Am J Obstet Gynecol [Internet]. 2023;229(3):248–68. Available from: http://dx.doi.org/10.1016/j.ajog.2023.03.034

[2] Ijäs P. Trends in the Incidence and Risk Factors of Pregnancy-Associated Stroke. Front Neurol. 2022;13(April):1–7.

[3] Miller EC, Boehme AK, Chung NT, Wang SS, Lacey J V., Lakshminarayan K, et al. Aspirin reduces long-term stroke risk in women with prior hypertensive disorders of pregnancy. Neurology. 2019;92(4):E305–16.

[4] Karjalainen L, Tikkanen M, Rantanen K, Laivuori H, Gissler M, Ijäs P. Pregnancy-associated stroke -a systematic review of subsequent pregnancies and maternal health. BMC Pregnancy Childbirth. 2019;19(1):1–10.

[5] Cunningham MW, LaMarca B. Risk of cardiovascular disease, end-stage renal disease, and stroke in postpartum women and their fetuses after a hypertensive pregnancy. Am J Physiol - Regul Integr Comp Physiol. 2018;315(3):R521–8.

[6] Mureddu GF. How much does hypertension in pregnancy affect the risk of future cardiovascular events? Eur Hear J Suppl [Internet]. 2023;25(Supplement_B):B111–3. Available from: https://doi.org/10.1093/eurheartjsupp/suad085

[7] Hung SK, Lee MS, Lin HY, Chen LC, Chuang CJ, Chew CH, et al. Impact of Hypertensive Disorders of Pregnancy on the Risk of Stroke Stratified by Subtypes and Follow-Up Time. Stroke. 2022;53(2):338–44.

[8] Fang M, Wang J, Wang Z, Chen Y, Xu W, Tao C, et al. Impact of hypertensive disorders of pregnancy on short- and long-term outcomes of pregnancy-associated hemorrhagic stroke. Front Neurol. 2023;14.

[9] Huang CC, Huang CC, Lin SY, Chang CYY, Lin WC, Chung CH, et al. Association between hypertensive pregnancy disorders and future risk of stroke in Taiwan: A Nationwide population-based retrospective case-control study. BMC Pregnancy Childbirth. 2020;20(1):1–10.

[10] Miller EC. Maternal Stroke Associated with Pregnancy. Vol. 28, CONTINUUM Lifelong Learning in Neurology. 2022. 93–121 p.

[11] Dolgushina VF, Syundyukova EG, Chulkov VS, Ryabikina MG. Long-term outcomes of hypertensive disorders of pregnancy. Akusherstvo i Ginekol (Russian Fed. 2021;2021(10):14–20.

[12] Braunthal S, Brateanu A. Hypertension in pregnancy: Pathophysiology and treatment. Vol. 7, SAGE Open Medicine. SAGE Publications Ltd; 2019.

[13] Aronow WS. Hypertensive disorders in pregnancy. Ann Transl Med. 2017;5(12):12–4.

[14] Khedagi AM, Bello NA. Hypertensive Disorders of Pregnancy. Cardiol Clin. 2021;39(1):77–90.

[15] Bajpai D, Popa C, Verma P, Dumanski S, Shah S. Evaluation and Management of Hypertensive Disorders of Pregnancy. Kidney360. 2023;4(10):1512–25.

[16] Ying W, Catov JM, Ouyang P. Hypertensive disorders of pregnancy and future maternal cardiovascular risk. J Am Heart Assoc. 2018;7(17):1–9.

[17] Beckett AG, McFadden MD, Warrington JP. Preeclampsia history and postpartum risk of cerebrovascular disease and cognitive impairment: Potential mechanisms. Front Physiol. 2023;14(March):1–10.

[18] Leppert MH. Are strokes declining among pregnant women with hypertensive disorders of pregnancy? J Am Heart Assoc. 2020;9(15):9–11.