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Review

Pregnancy Risk Factors in Cerebrovascular Disease

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Abstract

Cerebrovascular diseases such as strokes and cerebral hemorrhages are important causes of death in the world, which increase during pregnancy due to physiological conditions. This study investigated risk factors such as diabetes mellitus, hypertension and other factors by searching in databases. After searching, 35 articles were reviewed based on the inclusion criteria. The inclusion criteria included articles from 2014-2024 related to the words "pregnancy" AND "cerebrovascular disease." The obtained results were evaluated based on risk factors. Diabetes and hypertension were among the aggravating factors of stroke in pregnancy and were recognized as essential factors. Other factors, such as migraine smoking and alcohol consumption, were also investigated, although they had a low prevalence. According to the obtained results, it can be said that all the risk factors, even if they are less risky, are essential during pregnancy to prevent neurological diseases.

Keywords

Pregnancy; cerebrovascular disease; stroke; hypertension; diabetes

1. Introduction

Cerebrovascular diseases, which are the second leading cause of death in the world, include cerebral hemorrhages such as subarachnoid hemorrhage-cerebral ischemia and stroke [1]. The prevalence of stroke has increased as a cause of global disability and mortality in young people, especially pregnant women [2]. A stroke is a neurological defect that may be caused by problems such as damage to the vessels of the nervous system or venous sinus thrombosis [3]. Important risk factors in cerebrovascular diseases include gender, age, alcohol consumption, smoking, and blood pressure. A high prevalence of these diseases has been reported in women [1]. The prevalence of stroke in pregnant women increases three times compared to other women, so that its prevalence reaches 48% in the postpartum period [3].

In addition to the mentioned risk factors, other practical factors include diabetes, increased consumption of estradiol, high-risk pregnancy with diabetes and pregnancy blood pressure, and heart diseases such as atrial fibrillation [4]. During pregnancy, the increase in blood volume venous stasis and thrombotic factors cause more ischemic stroke and thrombosis [2]. Pregnancy is associated with increased coagulability. An increase in fibrinogen and factors VII, IX, X, XII, and XIII and a decrease in fibrinolysis provide favorable conditions for thrombosis and stroke. Pressure on the inferior vena cava in the third trimester worsens this condition [5]. Pregnancy along with diabetes and blood pressure increases the risk of cardiovascular and cerebrovascular diseases [4]. Gestational blood pressure is defined as (≥140 mmHg diastolic or ≥90 mmHg diastolic or both) in the 20th week of pregnancy, which increases the risk of heart disease, stroke, kidney disease, and pulmonary edema [6]. Hemolysis, increase in liver enzymes and decrease in platelets, which is introduced as HELLP syndrome, is a malignant type of preeclampsia, which related neurological factors can cause subarachnoid hemorrhage and stroke [7].

It is predicted that from 2000 to 2030, the number of people with type 2 diabetes will increase by 1.6 times. In the Siren study, a high risk of stroke was seen in people under 50 years old with type 2 diabetes [8]. Many women in America take hormonal pills. Although the incidence of stroke with the use of these drugs is very low, in various studies, a 25-fold increase has been seen with birth control pills. The risk of stroke increases in women with high blood pressure, diabetes, smoking and obesity [4].

The prevalence of tobacco use in pregnant women varies from 1 to 18%. In a hospital study in America, the ratio of stroke in pregnant people was reported as 1.7 odds ratio [7].

The type of delivery, especially cesarean section, can be considered adequate for stroke, although this relationship has not yet been determined. Although cesarean section is effective for postpartum stroke, doctors prefer cesarean section for cerebral hemorrhages [9].

Considering that pregnant women are one of the sensitive groups of society and identifying the risk factors of neurological deficits can have good results in the treatment and recovery of these people, in this study, we will investigate these risk factors.

2. Method

The study selection process has been done according to PRISMA requirements. The search for this study was done in PubMed, Springer, web of Science, and Google Scholar search engines. The search in PubMed was done with MESH "PREGNANCY" AND "CEREBROVASCULAR DISEASE". The entry criteria included articles from 2014-2024 and accessible and systematic review articles. Finally,

9 articles were found out of 45 articles due to their relevance in terms of title and topic chosen. The search in Springer was done based on the said entry criteria and two articles were examined out of 35559 articles. According to the requirements and the presence of at least one of the words PREGNANCY or CEREBROVASCULAR, out of 185 articles searched in Google Scholar, 14 were included in the study. The search continued on the Web of Science and reviewed articles in English, and the last ten years were searched. From about 44 articles, after reviewing their titles and abstracts, 14 related articles were selected.

Two studies from Springer, 14 articles from Google Scholar, 14 articles from Web of Science and nine articles from PubMed were selected, and after reviewing their content, 35 articles were reviewed (Figure 1).

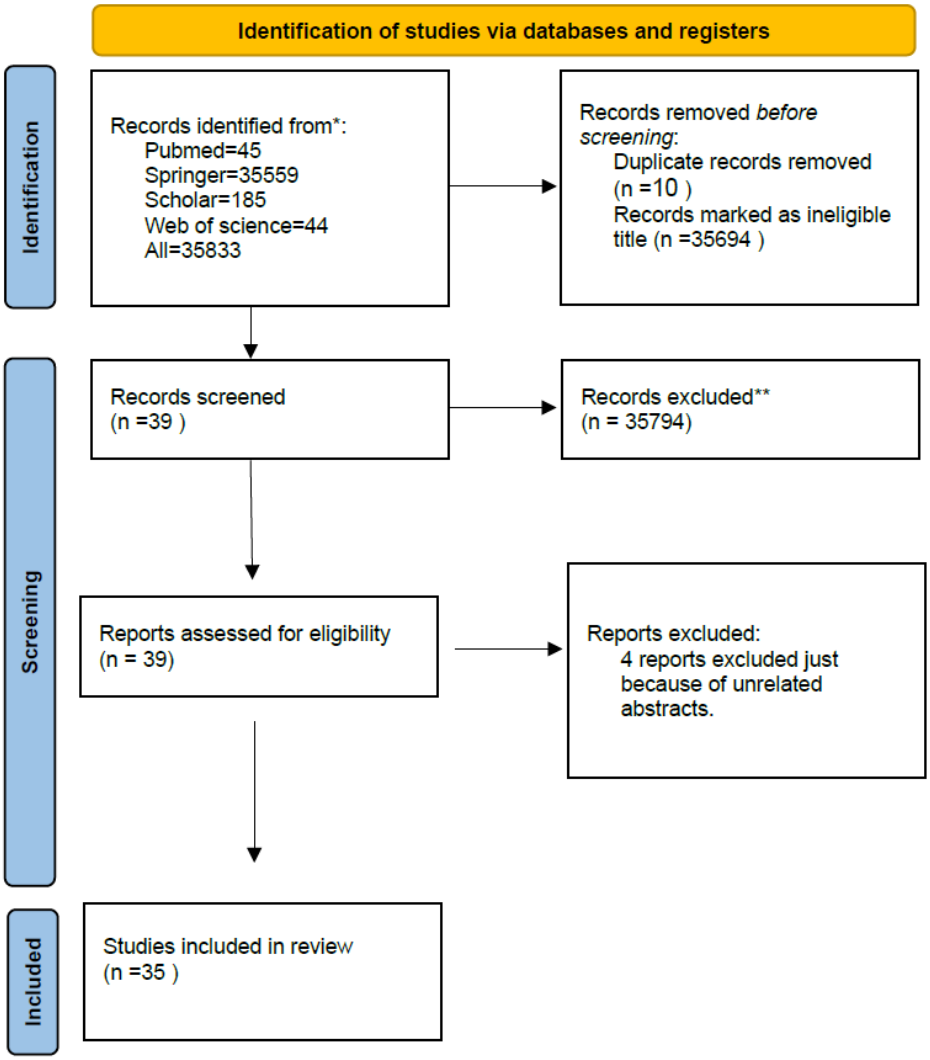

Figure 1 PRISMA 2020 flow diagram for new systematic reviews included database searches [10].

To ensure the search, this process was repeated by another author. The articles were categorized based on the standard variables like diabetes, hypertension, etc., that are mentioned in the reviewed articles.

This research was approved by regional committee of research of Tabriz University of medical sciences with no.: IR.TBZMED.REC.1402.658.

3. Result

3.1 Blood Pressure

The possibility of the effect of pregnancy blood pressure on diseases is not yet known definitively. Still, blood pressure can cause changes in the endothelium of blood vessels, disorders in the self-regulation of blood vessels, and the blood-brain barrier. In the study of Brohan et al. About 24 studies on pregnancy blood pressure and stroke were reviewed. From the results of this study, it can be pointed out that blood pressure during pregnancy is not related to the types of stroke (adjusted risk ratio, 1.23; 95% confidence interval, 1.20 and 1.26). But chronic blood pressure is closely related to types of stroke such as hemorrhagic stroke (adjusted risk ratio, 2.66; 95% confidence interval, 1.02 and 6.98) [11]. In the studies reviewed by Kumar, the risk of stroke and its dangerousness is higher in pre-eclampsia after delivery. The onset of pre-eclampsia before 32 weeks increases the risk of stroke by 5 times compared to earlier onset [4].

In the study of Ciampa, et al., TGF-beta, VEGF, angiotensin, and IL-6 molecules were seen on the cerebrospinal fluid drawn from pregnant women with preeclampsia. The necessary receptors for VEGF create a condition of anti-vascular imbalance in maternal blood.

In the study by Bean, et al, endoglin was used as a TGF-beta receptor, which caused cerebral edema in the posterior brain regions. Some factors in the smooth muscles and pericytes of the brain cause vascular changes, for example, in the research conducted by Warrington, et al. al TNF-alpha factor in pregnant rats increases cerebrospinal fluid and disturbs the permeability of cerebrospinal fluid [12].

A review study by B. Miller et al. was conducted with the aim of cognitive diseases in women. For example, in the Rochester Epidemiology Project medical study, which is a large cohort study, carotid thickness was increased in women with preeclampsia, and these changes are associated with extensive vascular changes. In women over 35 years old who had recently given birth, the relationship between cognitive diseases and blood pressure was seen [13]. Women with gestational hypertension are at a higher risk of hospitalization for pulmonary infection and need a ventilator and death. In data from the Global Burden of Disease 2019 Study, gestational hypertension increased by about 10.92% from 1990-2019, but the age of affected people decreased [14].

In people with pre-eclampsia, pregnancy can change the sensitivity of the vascular system and cause brain damage and lesions in the white matter of the brain. Damaged areas can be seen in MRI as hypertensive areas. A review of studies by Beckett has shown that Alzheimer's has damaged white areas and these areas are closely related to women with high blood pressure during pregnancy [15] in the study. Hammer and colleagues about 34-37% and 41% of pregnant women with high blood pressure have lesions of white brain areas in the imaging. Women under 37 weeks who have high blood pressure are more likely to suffer from heart disease and white matter damage than people with high blood pressure over 37 weeks [16].

Cerebral autoregulation is a mechanism that creates enough blood for the brain by regulating vascular resistance and cerebral flow pressure. Pregnancy with high blood pressure disrupts autoregulation. Normal pregnancy is associated with an increase in autoregulation, while blood pressure has destructive effects on cerebral arterioles. When cerebral autoregulation is insufficient, it can lead to brain edema and neurological problems such as seizures and strokes [17]. In the studies reviewed by C. Miller, pregnant women with preeclampsia who have headaches have

disorders in vascular resistance, cerebral blood flow pressure, and vascular response to carbon dioxide inhalation and autoregulation. The effects of preeclampsia on the mother can be years later. Continue from childbirth, for example, increasing the thickness of the carotid sheath, which is an essential indicator of future stroke. No trial has investigated the preventive method, but a retrospective cohort study found aspirin use useful in these people [18].

In the study of Etter et al., by examining 12 pregnant women, 25% of whom had high blood pressure and 8.3% of whom had preeclampsia, it was found that upon entering the hospital, their GCS was 15. 7 of these women had a cerebral hemorrhage. The size of the aneurysm rupture was 5 mm in three [19]. Pregnancy is a risk factor for bleeding, especially in arteriovenous malformations. In 12 studies reviewed by Che Yusof et al., the rate of AVM bleeding in pregnancy was from 0.01 to 0.89%, which was the lowest rate in Asian people. In this study, the risk of AVM bleeding in pregnant people was reported to be low. However, due to the limitations of this study, such as the lack of reviewed articles, it cannot be cited [20].

3.2 Diabetes

Gestational diabetes is defined as glucose intolerance in pregnant women. In 14 articles reviewed by Xie et al., it has been determined that 45% of diabetic pregnant women have a higher risk of developing cerebrovascular disease. The risk percentage of stroke (95% confidence interval 1.29 to 1.63, I^2 = 31%) - ischemic stroke (1.29 to 1.71, I^2 = 40%) and hemorrhagic stroke (1.16 to 1.78, I^2 = 0%) is reported in this way [21]. The risk of cerebrovascular diseases associated with gestational diabetes may continue even after delivery. In the study by Hromadnikova et al., microRNAs related to cerebrovascular diseases were investigated in children born to women with diabetes. MicroRNAs except miR-92a-3p, miR-155-5p, and miR 3p-210 were increased in children of diabetic mothers, which shows the relationship between gestational diabetes and cardiovascular and cerebrovascular diseases [22].

3.3 Migraine

Migraine is a neurological disorder that affects women more than men. Migraine is an independent risk factor for stroke and heart attack, and women under the age of 55 suffer from these complications about 2.5 times more than other people. Many studies have investigated the role of sex hormones in migraine. Even menstruation increases the frequency of migraine in women, but the improvement of migraine during pregnancy has been reported. During menstruation or discontinuation of contraceptives, estrogen, and oxytocin decrease, the 5^{th} cranial nerve is activated, and migraine attacks begin. In a Dutch study reviewed by Welie et al., which examined women's MRI, it was found that women who have migraines have a higher probability of damage to the white matter of the brain and cerebellum [23]. Jung Kwon, by examining 45,246 patients in the years 2002-2009, found the connection between migraine and vascular and heart diseases, so that 10.25% of every 1000 patients examined had a stroke [24]. In the study conducted in the Nationwide Inpatient Sample database, it was determined that people with acute stroke had obesity and migraine [14].

3.4 Other Important Risk Factors

Risk factors such as maternal age, abortion, diabetes and intrauterine growth restriction can cause cardiovascular and cerebrovascular problems in babies even after birth. In the study of Roy et al., by examining studies related to infants weighing 450-3500 grams, it has been determined that only 3% of them suffered cerebral sinus thrombosis. In this case, there were no significant risk factors between the control group and the patient [25].

Studies have shown that the use of estradiol increases the risk of stroke, especially in postmenopausal women. In a study in Sweden on 49,259 women, no significant relationship was found between stroke and the use of birth control pills. Although the use of birth control pills is an old risk factor, Studies have shown that high-risk women with a history of blood lipids and diabetes can increase the risk of cerebrovascular diseases by taking these pills [4]. In the studies reviewed by Miller et al., it has been shown that in ovarian removal surgery, which reduces hormones such as estradiol, cognitive problems such as dementia increase in women under 48 years of age [26]. An increase in progesterone during pregnancy causes dilation of blood vessels and decreases venous return. After childbirth, when the amount of this hormone decreases, the contraction of cerebral vessels leads to brain ischemia and stroke [27].

Abortion during pregnancy can be considered a risk factor for stroke. In the meta-analysis reviewed by Liang et al., the risk of stroke in these people is 7% (95% CI, 1.00-1.14; I^2 = 52.6%). In these studies, the number of abortions was also investigated, and women with more than 3 abortions have a higher risk of stroke [28]. Although studies have reported the same rate of miscarriage in pregnant women with stroke as in the general population, a prospective study reported a higher rate of miscarriage and higher mortality in pregnant women with stroke [29].

The study conducted by Bushnell et al. investigated gender and ischemia. The results show that the response to cerebral ischemia differs in women and men. In women, cell death occurs more due to the activation of caspases and cytochrome c. Caspases: By initiating inflammation and activating microRNAs, they play an essential role in stroke. In the study of Li et al., the drug that was used was minocycline; the protective effects of this drug were more in men than in women. This drug is one of the inhibitors of PARP-1, which plays a vital role in cell death [30].

Kivelä et al.'s study was conducted to investigate the weight of the mother and the baby and its effect on cerebrovascular diseases. In babies with low birth weight, the probability of vascular diseases increases (95% CI, 1.07-1.97), but also in babies with high birth weight. This relationship was seen [95% CI, 1.03-2.04]. The mother's weight affects the baby's weight [31]. There is a linear relationship between stroke and body weight, but the mechanism is unknown. Impairment of immune activity and platelets and vascular endothelium function and increase of lipoproteins can be considered effective [4].

In 2020, the World Health Organization warned about the risk of Covid-19 in pregnant women, especially those with diabetes and high blood pressure. Magalhães et al.'s study was conducted to investigate this virus and its neurological complications in pregnant women. Out of 18 investigated cases, two cases suffered from cerebrovascular diseases with headache symptoms, in which movement symptoms were seen with delay. It can be said that the changes in the physiological and immune systems during pregnancy aggravate the symptoms of COVID-19 and increase the possibility of neurological damage [32].

Although placental abruption occurs in about 1% of pregnancies, it is associated with more neurological complications and mortality. According to studies by Ananth et al., the risk of stroke increases in placental abruption (RR = 1.32, 95% CI: 0.91, 1.92; $I^2 = 93\%$; $\tau^2 = 0.15$). Placental ischemia and oxidative stress activity and vascular damage and activation of defective trophoblasts lead to separation of the placenta. This vascular disorder can also activate stroke pathways [33].

Cesarean section also affects the prevalence of stroke. A retrospective study in Taiwan showed that 44% of people who had a cesarean section had a higher risk of stroke than those who experienced a vaginal delivery. Changes during surgery, such as increased protein C and cardiac output, and hemodynamic changes in spinal anesthesia can be considered effective [34].

4. Discussion

In the studies reviewed in this article, it can be said that seemingly unimportant factors are also crucial in increasing the risk of vascular and brain diseases. Simple things such as the mother's weight and even cesarean section are also practical, but still, in pregnancy studies, blood pressure and diabetes are two Important factors that are checked. Neurological diseases are significant during pregnancy, especially stroke, which causes disability after delivery. In epidemiological studies, the prevalence of stroke in pregnant women has increased in different countries [35]. In our study, pregnancy blood pressure was mentioned as an essential stroke risk factor, as hypertension increases the risk of all types of stroke. With the increase in exposure to blood pressure, the amount of elastic fibers in the vessel wall decreases, causing vascular destruction and a decrease in nitric oxide (NO). Finally, in the brain, it causes a disturbance in the self-regulation of vessels and vascular resistance [36]. The primary mechanism of eclampsia in pregnant people is not known. It can be said that the insufficient invasion of trophoblast cells into the spiral arteries of the uterus causes changes in the shape of the vascular endothelium and hypoxia in the uterus, causing inflammatory reactions and reducing essential factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) and reducing nitric oxide [37].

Today, eclampsia is known as a gender-related risk factor, as it increases the risk of heart disease and diabetes in women. In pregnant rats, where placental ischemia conditions were created in the laboratory, it was seen that the permeability of the blood-brain barrier increased and the self-regulation of blood vessels decreased.

In high-risk pregnancies, the risk of cerebral hemorrhage and aneurysm or AVM increases. Still, there are not enough studies to say whether eclampsia is effective on aneurysm rupture or not. The amount of VEGF increases in AVM conditions, but if the AVM ruptures, the amount of VEGF is decreased as it is in eclampsia [18].

The second most important risk factor is diabetes. Diabetes doubles the risk of stroke. Although the exact cause is unknown, diabetes affects both large and small vessels and indirectly causes vasoconstriction by increasing triglycerides in the ship [38]. The increase in blood sugar in the long term activates the oxidative stress pathway and produces (ROS), which reduces nitric oxide. In a study, Pinto et al observed that the risk of cerebrovascular diseases increases in people with diabetic foot. Arterial occlusion was also seen in these people. The most common type of stroke in diabetics is a lacunar type [39]. Diabetes can reduce vascular dilation markers, such as endothelin-1. This molecule can cause contraction by affecting smooth muscles, and by involving the renin-angiotensin system, it causes water and sodium retention. In a stroke, high blood sugar can reduce the blood

flow to the ischemic area, disrupt calcium entry through N-methyl-D-aspartate (NMDA) receptors, and worsen ischemic conditions. By activating p47phox, which is a part of the NADPH oxidase system, diabetes causes an increase in oxygen free radicals. It ultimately damages DNA, releases nitric oxide, and reduces the local blood supply [40].

One of the most common causes of death in young people and the cause of aneurysms and brain hemorrhages is smoking. The chemicals present in the smoke cause damage to the vascular endothelium activation of the inflammatory pathway [41] and increase coagulability and arteriosclerosis [42]. Smoking increases the risk of stroke by reducing the vascular response to changes in blood flow pressure and, not having the necessary tension in the vessels and destroying the endothelium. As mentioned, smoking is associated with changes in coagulability conditions. There is a substance called thrombin that converts fibrinogen into fibrin strands. In the case of tobacco, the amount of thrombin increases immediately, and the coagulability increases. Nicotine also increases tissue plasminogen activator (tPA) inhibitor and prevents the breakdown of fibrin [43].

During these 40 years, the relationship between migraine and stroke has been discussed a lot, and both are neurological diseases [44]. Anti-migraine drugs themselves are also effective in the development of stroke. Drugs such as triptans and ergotamine cause vasoconstriction and ultimately stroke and cerebral hemorrhages. Important coagulation factors such as t-PA, high-sensitivity C-reactive protein, von Willebrand factor, vascular endothelial growth factor, and nitric oxide metabolites are increased in migraine, and migraine causes a decrease in the function of endothelial productive cells [45].

Some risk factors are specific to young women, such as pregnancy and the use of contraceptives. With the use of birth control pills, smoking, and migraines, the risk of stroke in young women increases about 9 times compared to other people. Although stroke in pregnancy is not reported in some articles, there is a possibility of stroke even after cesarean section [46]. Caesarean section is directly related to increased risk of stroke. Infections such as influenza and lung infection during pregnancy increase the risk of neurological diseases. Electrolyte disorders in pregnancy such as a decrease in fluid volume, a decrease or an increase in sodium and potassium play a role in the prevalence of stroke [47].

Alcohol consumption is one of the important risk factors related to gender, which linearly increases the risk of stroke with increasing alcohol consumption. Alcohol reduces the risk of ischemic stroke and increases the risk of hemorrhagic stroke by reducing the accumulation of platelets, increasing the breakdown of fibrins, and increasing lipoproteins [48]. Today, SARS-CoV-2, or COVID-19, is one of the risk factors for stroke, which has been discussed in the present study. By disrupting angiotensin-converting enzyme-2 (ACE-2), this virus causes vasoconstriction and blood pressure reduction, thrombosis, and nerve cell death. In general, viruses increase thrombin and inhibit fibrin breakdown. Hypoxia with covid 19 worsens the condition [49].

The study's limitations include the small number of articles in this field, and most of the articles are in the form of reviews. It can also be said that due to the conditions of pregnant people, more risk factors cannot be examined in these people.

5. Conclusion

In recent years, many studies have been conducted on the risk factors of cerebrovascular diseases during pregnancy. Pregnancy is one of the most critical and sensitive periods in women's

lives, which is accompanied by many physiological changes, which sometimes have negative results, especially if diseases such as hypertension and diabetes are present. The current study has tried to look at the critical risk factors from different aspects, as well as examine the less critical risk factors. In most of the articles, blood pressure and diabetes are still known as essential markers in increasing the risk of stroke. At the same time, seemingly unimportant factors such as alcohol consumption, smoking, and even the age of pregnancy are as important as these two factors.

Author Contributions

Project development: Samad Shams Vahdati. Study conduct: Alireza Ala. Article identification: Mina Zeinalzadeh. Article screening: Elyar Sadeghi Hokmabadi, Samad Shams Vahdati. Writing: Mina Zeinalzadeh. Critic: Alireza Ala.

Competing Interests

The authors have declared that no competing interests exist.

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