

## Research Article

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# Incidence and risk factors associated with the occurrence of encephalic vascular accident in the pregnancy-puerperal cycle: an integrative review

## Abstract

**Background:** The encephalic vascular accident (EVA), also called stroke, is a complication that leads to high morbidity during the gestational period. The incidence of encephalic stroke is three times higher in pregnant women compared to non-pregnant women, with an increase in rates in recent years. Considering the impacts of this comorbidity on the maternal-fetal health, this review aims to compile data regarding the incidence and risk factors related to the occurrence of EVA in the pregnancy-puerperal cycle, in order to facilitate the identification of risk factors and the prevention of an unfavorable outcome.

**Methodology:** This is an integrative review of the literature. The research was conducted using the databases from the *Medical Literature and Retrieval System onLine* (MEDLINE), *Scientific Electronic Library Online* (SciELO) and *Latin American and Caribbean Literature on Health Sciences* (LILACS). The information was systematized based on the guiding question: "What is the incidence and risk factors related to the occurrence of encephalic vascular accident in the pregnancy-puerperal period?". The descriptors used were: "Pregnant Women" AND "Stroke". Original and complete articles, with free access, in English or Portuguese language, published in the last five years and with a detailed description on the subject were included in this review.

**Results and discussion:** The incidence of pregnancy hospitalizations due to EVA ranged from 7.3 to 42.8 per 100,000 pregnant in the studies evaluated. Related to risk factors, a relationship was found with physiological changes during pregnancy, especially the state of hypercoagulability due to the increase in levels of prothrombotic factors. Additionally, hypertensive disorders during the pregnancy, such as eclampsia and pre-eclampsia, and traditional cardiovascular risk factors such as smoking, sedentary lifestyle, dyslipidemia and advanced age, were also considered risk factors for stroke.

**Conclusion:** Despite being an uncommon complication during the pregnancy-puerperal cycle, stroke has a severe impact in women and fetus health, this condition is being related to physiological alterations inherent to pregnancy, pathological alterations and modifiable risk factors.

**Keywords:** encephalic vascular accident, pregnancy, puerperal, obstetrics, neurology

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## Introduction

The encephalic vascular accident (EVA), also called stroke, is an uncommon event during the pregnancy, however represents a severe complication with high morbidity during the pregnancy-puerperal period.<sup>1</sup> The EVA is characterized by a sudden and dimidiated neurological deficit, and can have an ischemic origin (iEVA) with reduced blood flow to a certain brain area; or hemorrhagic (hEVA) that is associated with extravasation of blood due to vascular rupture.<sup>2,3</sup>

The global incidence of stroke is increasing in the last years. In this perspective, a Canadian population-based study reported an increase of 60.0% in the incidence of EVA during pregnancy and puerperium, between 2003 and 2016.<sup>4</sup> In addition, the incidence rates of stroke are three times higher in pregnant women in relation to non-pregnant women.<sup>5</sup> Therefore, there is a global tendency towards an increase in the incidence of stroke, with women in the pregnancy-puerperal cycle being a susceptible population.

This predisposing for the occurrence of vascular events during pregnancy is related to the physiological conditions in this period that involves changes in the circulatory system, coagulability, connective tissue integrity and immune responses. Despite these are necessary

adaptations to the biological requirements of pregnancy, they are also aspects that slightly increase the chance of stroke.<sup>6</sup>

In addition to these physiological changes associated to pregnancy, the overlapping of pathological conditions during pregnancy, as the elevation of blood pressure levels and endothelial dysfunction associated with pre-eclampsia and eclampsia, contribute significantly to the increased incidence of EVA in affected women.<sup>7</sup> Furthermore, the global increasing of comorbidities prior to pregnancy, such as obesity, heart disease and chronic hypertension, are risk factors for cerebrovascular disease.<sup>6</sup>

It is known that stroke represents a relevant public health problem due to high levels of morbidity and mortality.<sup>8,9</sup> It is estimated that occurs 1.4 maternal deaths attributed to EVA in every 100,000 births.<sup>10</sup> A study carried out with the objective of evaluating gestational deaths due to stroke identified that approximately 50% of the cases were related to conditions that could be identified and followed up in the prenatal care to avoid unfavorable outcomes.<sup>11</sup>

In addition to maternal mortality, stroke can lead to neurological deficits that can affect woman's ability to take care of herself and of her child and to be professionally productive.<sup>1</sup> The most affected pregnant

women have residual weakness and/or cognitive dysfunction after the event. Furthermore, EVA can affect the health of the conceptus and the maternal well-being, and these are also drastic conditions to deal with during the puerperium, period of significant psychological fragility.<sup>6</sup> Thus, this review aims to compile data regarding the incidence and risk factors related to the occurrence of EVA in the pregnancy-puerperal cycle.

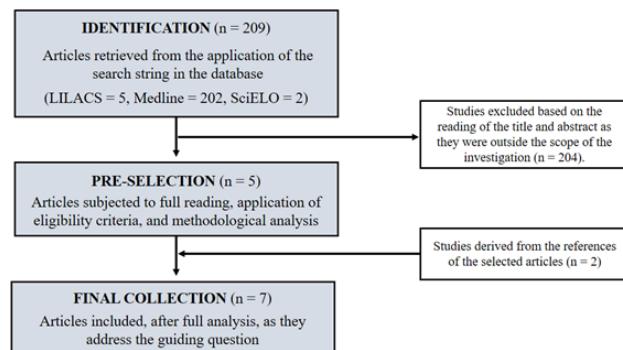
## Methodology

The present study is an integrative literature review that was conducted with the objective of systematizing the search results on the specific theme. Through a previous literature search, the following research guiding question was defined: "What is the incidence and risk factors related to the occurrence of encephalic vascular accident in the pregnancy-puerperal cycle?". The methodological process was consisted of the following steps: (1) Definition of eligibility criteria; (2) Research strategy design; (3) Data collection and sample delimitation by two reviewers; (4) Critical analysis of data, discussion and synthesis of results by two reviewers.

The data collection was made from June to October 2022, by consulting the databases *Medical Literature and Retrieval System onLine* (MEDLINE), *Scientific Electronic Library Online* (SciELO) and *Latin American and Caribbean Literature on Health Sciences* (LILACS). The controlled descriptors were selected from the records of the *Descriptors in Health Sciences/Medical Subject Headings* (DeCS/MeSH), in the English language and combined with each other by the Boolean operator "AND", determining the following search strategy: "Pregnant Women" AND "Stroke".

The eligibility criteria established were original and complete manuscripts with free access, in English or Portuguese, published within the last five-year and that presented a detailed description of the relationship between cerebrovascular disease and the pregnancy-puerperal cycle. Review articles, meta-analyses, theses, dissertations, books or documents were not included in this research. Duplicated studies in different databases and articles outside of the scope of

the investigation were also excluded. After applying the selection process, screening and eligibility criteria, as described in Figure 1, five articles relevant to the research guiding question remained. In addition, two other manuscripts obtained from the references of the articles previously selected in the search strategy were included, aiming to reach all the writings on the proposed theme.



**Figure 1** Flowchart.

**Source:** The authors, 2023.

In order to ensure the ethical aspects of this literature review, the authorship and citations of each publication presented were formally referenced. This study did not directly involve research with human beings, so the present work does not require a Research Ethics Committee agreeing, considering the Resolution 510/2016 of the National Health Council.

## Results

The studies that were selected, show descriptions of the incidence and risk factors associated with the occurrence of EVA in the pregnancy-puerperal cycle. Data were extracted and processed using the tool designed by the authors considering the following fields: authors and year of publication, objective, methodology and results. The synthesis of each study is presented in Table 1.

**Table 1** Original Manuscripts about Encephalic Vascular Accident during pregnancy-puerperium cycle included in the integrative review

Reference	Aim	Methodology	Main results
Ban et al. <sup>16</sup>	To identify the risk of a first encephalic vascular accident (EVA) in women of childbearing age and compare with the risk during pregnancy and in the early postpartum period.	Cohort study with a sample of 2,046,048 pregnant women hospitalized between 1997 and 2014, based on the analysis of secondary data from the Hospital Episode Statistics.	It was identified that 10.7 of 100,000 pregnancy-related hospitalizations occurred due to acute EVA. The main risk factors associated to EVA during pregnancy were preeclampsia, eclampsia and prothrombotic state.
Ban et al. <sup>12</sup>	To quantify the incidence of EVA during pregnancy compared to baseline risk in women of childbearing age.	Population-based cohort study with a sample of 1,124,541 pregnant women who had their children between 1992 and 2011, based on the analysis of secondary data from the Swedish Medical Birth Registry.	It was identified that 7.3 of 100,000 pregnancy-related hospitalizations occurred due to acute EVA. The main risk factors associated to EVA during pregnancy were pre-eclampsia, thrombophilia and the peripartum period.
Elgendi et al. <sup>13</sup>	To investigate the incidence and outcome of EVA and transient ischemic attack (TIA) during pregnancy.	Retrospective cohort study with a sample of 37,360,772 pregnant women hospitalized between 2007 and 2015 based on the analysis of secondary data from The National Inpatient Sample.	It was identified that 42.8 of 100,000 pregnancy-related hospitalizations occurred due to acute EVA or TIA. The main risk factors associated with EVA during pregnancy were pre-eclampsia, eclampsia, obesity, smoking, hyperlipidemia, migraine and atrial septal defect.
Liu et al. <sup>4</sup>	To quantify the incidence, temporal trends and risk factors associated with EVA in pregnancy.	Retrospective cohort study, with a sample of 3,907,262 pregnant women hospitalized between 2003 and 2016, based on the analysis of secondary data from the Canadian Institute of Health Information.	It was identified that 13.4 of 100,000 pregnancy-related hospitalizations occurred due to acute EVA. The main risk factors associated with stroke during pregnancy were age equal to or greater than 40 years, gestational hypertensive disorders, congenital heart disease, connective tissue disorders, sepsis, severe postpartum hemorrhage and thrombophilia. Gestational hypertension was associated with a 60.0% higher risk of stroke.

Table Continued...

Reference	Aim	Methodology	Main results
Lorenzano et al. <sup>14</sup>	To evaluate the frequency, clinical management, pathophysiological mechanisms and outcomes of EVA in pregnant and postpartum women.	Case-control study based on the selection of a case of a pregnant woman affected by EVA for two controls of unaffected pregnant women for follow-up for 24 months.	It was identified that 40.0 of 100,000 pregnancy-related hospitalizations occurred due to acute EVA. The main risk factors associated with stroke during pregnancy were pre-eclampsia, eclampsia and gestational prothrombotic status.
Miller et al. <sup>17</sup>	To evaluate the EVA risk in women with pre-eclampsia compared to age- and race-matched controls.	Case-control study with a sample of 3,373,114 pregnant women hospitalized between 2003 and 2012, based on the analysis of secondary data from the New York State Department of Health.	The incidence was not investigated. The main risk factors associated with EVA during pregnancy were severe preeclampsia, eclampsia, nosocomial infections, prothrombotic states, coagulopathies and chronic hypertension.
Yoshida et al. <sup>15</sup>	To characterize the pattern of EVA involvement related to pregnancy in Japan.	Retrospective cohort study with a sample of 1,510,000 pregnant women hospitalized between 2012 and 2013, based on the retrospective analysis of clinical records in 736 hospitals specializing in EVA care.	An incidence of 10.2 per 100,000 of pregnancy-related hospitalizations that occurred due to EVA was identified. The main risk factor associated with stroke during pregnancy was gestational hypertensive disorders.

Source: The authors, 2023.

All selected articles were written in English and compiled data from different countries, such as the United States (28.5%), Canada (14.3%), Sweden (14.3%), England (14.3%) and Japan (14.3%). In addition to these, an international multicenter study was included (14.3%).

## Discussion

### Incidence, etiology and time relation of eva in pregnant woman

According to the data of the selected articles, the incidence of hospitalizations associated to acute EVA during the pregnancy ranged between 7.3 and 42.8 per 100,000 hospitalized pregnant.<sup>12,13</sup> Despite being uncommon, stroke represents a drastic impact when it occurs during pregnancy or in the postpartum period.<sup>14</sup>

Regarding the stroke etiology, it was observed that most pregnant women were affected by hEVA.<sup>4,15</sup> This data differs from the cases in general population, in which 87.0% of the cases are attributable to iEVA and only 13.0% to hEVA.<sup>2</sup> The higher incidence of hemorrhagic stroke in pregnant women may be related to the occurrence of gestational hypertensive disorders.<sup>16</sup> Given the above, it is suggested that health professionals stay aware of this epidemiological difference in order to facilitate the clinical management.

Related to the period of occurrence, EVA seems to be more common in the peripartum and postpartum period. According to Miller et al.<sup>17</sup> 22.3% of strokes occurred after hospitalization, without specifying if they were pre- or postpartum. In the same study, 44.5% of strokes reported occurred in the postpartum period, being 70.1% after hospital discharge. A Canadian study that analyzed secondary data from 3,907,262 pregnant women identified that 51.5% of EVA occurred in the postpartum period.<sup>4</sup> In view of these findings, it is emphasized that postpartum follow-up is essential.<sup>17</sup>

### Gestational hypertensive disorders

Hypertensive disorders are known are risk factors for the outcome of cerebrovascular diseases during pregnancy and the puerperium.<sup>16</sup> The study conducted by Liu et al.<sup>4</sup> showed that the presence of hypertension during pregnancy is associated with a 60.0% greater chance of EVA. In addition, Elgendi et al.<sup>13</sup> demonstrated that 22.1% of pregnant women hospitalized for EVA or transient ischemic attack (TIA) had some hypertensive disorder during pregnancy. Regarding to preeclampsia and eclampsia conditions, 37.5% of women affected by stroke in the peripartum were diagnosed during prenatal care.<sup>16</sup>

From this perspective, Miller et al.<sup>17</sup> demonstrated that women with pre-eclampsia were six times more likely to have a stroke event than pregnant women without hypertensive disorder. Additionally, other recent studies indicated that women with blood pressure changes during pregnancy have an independent twice times high for EVA.<sup>18,19</sup> The pregnancy that presents a hypertensive condition has a significantly greater chance of developing cerebrovascular disease, being this condition considerate a higher attributable risk than traditional cardiovascular risk factors for the occurrence of EVA.<sup>20</sup>

The pathophysiology of this association is still not well defined.<sup>20</sup> It is accepted that endothelial dysfunction and disruption of the blood-brain barrier represent a central role in brain dysfunction. Furthermore, it is suggested that vasodilation and reduced cerebral vascular resistance, observed in hypertensive disorders during pregnancy, impair vascular self-regulation.<sup>21</sup>

Another point to take under consideration is that pre-eclampsia and EVA have some risk factors in common, such as obesity, metabolic syndrome, increased inflammatory responses and hypercoagulable states, that may be associated with the pathophysiology of the event.<sup>20</sup> In addition, women with pre-eclampsia and stroke were more likely to have infections on hospital admission, coagulopathies and chronic hypertension than women affected only by the hypertensive disorder.<sup>17</sup>

In this context, the study conducted by Liu et al.<sup>4</sup> demonstrated that 20.3% of EVA cases could be avoided if hypertensive disorders were properly managed during the prenatal period. Similarly, a study carried out in Japan identified that early detection and hospitalization can reduce the chance of hEVA in pregnant women and the authors suggested a reduction in the interval period between prenatal visits in that country.<sup>22</sup>

Given the above, it is imperative that health professionals are aware of the risk of EVA in women with blood pressure changes during pregnancy, aiming at the early identification and proper management of these disorders.<sup>12</sup> This attention should be given especially in prenatal care during the third trimester and peri-partum, because these are the common times of occurrence of pre-eclampsia and eclampsia conditions.<sup>16</sup>

### Pro-thrombotic status

During pregnancy, thrombophilia is a known risk factor for iEVA and cerebral venous thrombosis. This condition is due to a confluence of aspects that provide a favorable environment for the formation of clots, both arterial and venous, including an increase in the levels of

coagulation proteins and a decrease in natural anticoagulants agents.<sup>13</sup> Corroborating with this perspective, the study by Liu *et al.* (2019) showed that thrombophilia is strongly associated with EVA.

The hypercoagulable state is explained by an increase in clotting factors, specially factor I (fibrinogen), VII, VIII and XII. Fibrinogen, which is involved in the construction of the fibrin network and in platelet aggregation, has its concentration increased from the twentieth week of gestation, reaching levels of 400mg/100ml. From this perspective, high fibrinogen concentration can be identified as an independent risk factor for recurrent EVA.<sup>6,7</sup>

In addition, there is a decrease in the Spike protein (S), glycoprotein that is responsible for interrupting the coagulation cascade. The deficiency of this protein is a condition that facilitates the thrombosis process. Other factor that favors the hypercoagulability state during pregnancy is the higher resistance to activated protein C, that is associated with poor obstetric outcomes, given that this protein is also responsible for regulating hemostasis by degrading coagulation proteins.<sup>7</sup> Thus, prothrombotic states are risk factors of both, arterial thrombosis and hEVA.<sup>17</sup>

## Cardiovascular risk

As numerous as they are, physiological changes during pregnancy are not the only aspects that contribute to the increased incidence of EVA. The advancement of maternal age and the decrease in practice of physical activities during the pregnancy progress, are also configured as agents that facilitate the neurological outcomes.<sup>13,20</sup>

Furthermore, other traditional cardiovascular risk factors, such as obesity, smoking, sedentary lifestyle, hyperlipidemia and race, are also related to cerebrovascular disease in the pregnancy<sup>13</sup>. It is described that almost two thirds of women who are affected by EVA during pregnancy are smokers, and has been observed that African-American women over 35 years old have an increased probability of EVA when compared to Hispanic and white women of the same age group.<sup>6</sup>

## Final considerations

Despite still being considered an uncommon event, an increase in the incidence of cerebrovascular diseases linked to the gestational period has been observed, causing a deep impact on maternal health. In this sense, acute EVA is related to high morbidity and mortality rates and represents a relevant proportion of hospitalizations during pregnancy.

The physiological adaptations in the maternal organism during the pregnancy period, such as changes in coagulability, blood volume and pressure, are factors that increase the risk for EVA. In addition, pathological changes during pregnancy, such as pre-eclampsia and eclampsia, are also related to the increased incidence of stroke cases. Thus, in view of the differences in management between the different etiologies of EVA, it is recommended that health professionals remain alert to a higher incidence of hEVA in pregnant women. Furthermore, it is suggested that more studies must be conducted aiming determine which groups of women deserve more special attention in the pregnancy-puerperal cycle, including possible prophylactic measures. Thus, it is expected to facilitate the identification of pregnant women at risk, with the aim to prevent an unfavorable outcome for the mother and the fetus. This study has no financial interests or affiliations with any organization that could be perceived as having a potential conflict of interest with the content discussed in this manuscript.

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## Conflicts of interest

The authors declare no conflict of interests.

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