

Stroke in Pregnancy and Perinatal Period

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Introduction

Stroke is a rare illness in pregnancy; nevertheless, it is one of the main causes of morbidity in young women of childbearing age. During pregnancy, a woman's body undergoes a number of pathophysiological changes that promote thrombus formation and increase the risk of stroke in comparison to women of the same age who are not pregnant. At that time, estrogens increase renin activity leading to increased sodium and water retention; heart rate goes up by 30-50%; cardiac output and arrhythmia index increase, venous capacity raises; venous return decreases; the vessel walls undergo remodeling; and the amount of elastin and collagen fibers decrease. The coagulation system presents a natural predominance of coagulation processes over fibrinolysis [1,2]. Factors increasing the risk of stroke include: the age of the pregnant woman (over 35), hypertension, obesity, smoking, systemic lupus, migraine with aura, diabetes, thrombophilia, pre-eclampsia and eclampsia, prolonged delivery, pregnancy intoxication, infection after delivery [2]. A meta analysis of Swartz et al. [3] covering the period from 1990 to 2017 showed that the prevalence of all strokes in pregnancy was 30.00 per 100,000 pregnant women (with a 95% confidence interval; 18.8-47); for ischemic strokes - 19.9 (10.7-36.9); for hemorrhagic strokes - 12.20 (6.7-2.2); and for strokes after delivery - 14.7 (8.3-26.1). Ischemic and haemorrhagic strokes are most commonly observed in the last trimester of pregnancy and in the postpartum period [4].

Types of stroke in pregnancy

In pregnant woman, as in other groups of risk, two main types of strokes may occur: ischemic stroke or hemorrhagic stroke.

Pre-eclampsia and eclampsia, as well as other brain disorders, are among the most important risk factors for both hemorrhagic and ischemic stroke.

Pre-eclampsia and eclampsia

Pre-eclampsia is characterized by: 1. an increase in systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg found at least two times at four-hour intervals in woman without previous hypertension in the 20th week of pregnancy or over, 2. proteinuria [2,5]. If these symptoms are accompanied by epileptic seizures, eclampsia can be diagnosed [2,5]. The prevalence of stroke in eclampsia ranges from 25% to 75% of pregnant women [5]. Eclampsia occurs not only during pregnancy, but may also appear in the puerperium up to 48 hours after delivery. Pre-eclampsia and eclampsia are associated with significantly higher mortality of both mothers and children [5]. In addition, these are important risk factors for the development of hypertension and stroke not only in pregnancy, but also in the later years of women's lives [5-8].

In eclampsia, both hemorrhagic and ischemic focus, as well as brain edema, may be found in the same woman at the same time. Pre-eclampsia and eclampsia frequently coexist with HELLP syndrome. It is characterized by the simultaneous occurrence of H-hemolysis (which may manifest as anemia in laboratory tests), EL-elevated liver enzymes and LP-low platelets. In HELLP syndrome, intravascular coagulation is increased and disseminated intravascular coagulation (DIC) may develop with subsequent hemorrhagic diathesis, resulting in intracerebral bleeding [1,2,5].

Management of pre-eclampsia and eclampsia with stroke

It is necessary to lower blood pressure. Magnesium sulfate is the first drug administered immediately after diagnosis of pre-eclampsia or eclampsia (high strength of recommendations and quality of evidence). The drug is administered as a 20-minute intravenous infusion with 0.9% sodium chloride (NaCl) at a dose of 4-6 g, and then the infusion is continued (1-2 g per hour). In the absence of an effect, labetalol or another beta blocker (e.g. Betaloc, intravenously, initially 5 mg at a rate of 1-2 ml / min; amp. 5 mg / 5 ml) is added. Other drugs used to rapidly lower blood

pressure include: urapidil, furosemide, calcium channel blockers (nicardipine, nimodipine, sodium nitroprusite) administered intravenously and angiotensin converting enzyme inhibitor (ACE inhibitor), such as captopril, administered orally. Patients with eclampsia need immediate gynecologist consultation for any pregnancy-related decisions (frequently, a decision to terminate the pregnancy by cesarean section under general anaesthesia within 48 hours is taken) [2,5,6,9,10]. In cerebral edema that may accompany eclampsia and pre-eclampsia, mannitol, furosemide or decomposing hemispherectomy are used, if necessary [11].

Eclampsia may be associated with hypertensive encephalopathy (posterior reversible encephalopathy syndrome - PRES or reversible cerebral vasoconstriction syndrome - RCVS). The main symptoms include headaches and blurred vision. The neuroimaging test of choice is the magnetic resonance (MR) without contrast. In case it is not available, the computed tomography (CT) without contrast is performed. Typical changes shown in MR include: symmetrical, hyperintense focus in both occipital and parietal lobes, more intense in the white matter, with accompanying vascular edema. In the treatment of PRES, in the case of elevated blood pressure, antihypertensive drugs are administered. Calcium channel blockers with vasodilatation effect, beta blockers (e.g. Labetalol, Betaloc - administered intravenously) are among the most commonly used. Magnesium sulfate ($MgSO_4$) used for intravenous infusion 4-6 g in 0.9% NaCl for 20 minutes (according to the Zaks' method) plays an important role. $MgSO_4$ slightly reduces blood pressure and shows anticonvulsant effects. Vasodilatation drugs are also administered. In some cases, steroids may be used, although they are not encouraged (steroids are not widely recommended in the literature). The prognosis for encephalopathy is good, but the condition may lead to the progression of symptoms and even death. It is usually a monophasic disease, after which there are no contraindications for another pregnancy [12,13,14].

Ischemic stroke

The causes of ischemic stroke in pregnancy and the postpartum period include:

- Cardiogenic embolism
- Aortic dissection (AD)
- Pre-eclampsia and eclampsia
- Coagulopathy and cerebral thrombosis
- Cerebral venous thrombosis
- Reversible cerebral vasoconstriction syndrome (RCVC)

Among rare causes there are: amniotic fluid embolism, choriocarcinoma, air embolism, fat embolism and Sheehan syndrome.

In the case of suspicion of a stroke, a neuroimaging examination should be performed without delay. The preferred test is MR angiography without contrast, but more often CT scan without contrast (with cover for the mother's abdomen) is performed, because this type of examination is more easily accessible and faster [15].

Unless contraindicated, intravenous rt-PA may be considered and administered in accordance with the existing guidelines. Pregnancy is not an absolute contraindication to treat acute ischemic stroke with rt-PA, as there is no clear evidence that rt-PA cannot be administered during pregnancy [1,16,17]. In recent years, there are more reports of the cases of pregnant women with ischemic stroke in whom rt-PA was used (most often intravenously) at a typical dose administered to other patients, in accordance with the guidelines [1,16-24]. On occasions, the drug is administered intra-arterially and, in some cases, endovascular treatment (thrombectomy) is performed according to generally applicable rules, either without intravenous rt-PA or with intravenous rt-PA before endovascular thrombectomy [1,23,25]. It should be emphasized that less pregnant women receive rtPA intravenously compared to those who are not pregnant (4.4% vs. 7.9%). The main reason for this is that pregnant women themselves do not agree to be subjected to this procedure or they have recently undergone a surgery, which is a contraindication to thrombolysis [26].

In addition, more than half of strokes occur after delivery and during delivery (52.4% and 2.8%, respectively), and labour is a contraindication to thrombolytic therapy for up to 10 days. What is more, pregnant women more often than non-pregnant women are admitted to the intensive care units, where they undergo life-saving procedures and usually thrombolysis is not administered [26]. Eclampsia and stroke with amniotic fluid embolism are a contraindication to administering rt-PA. Pregnant women after thrombolysis are more likely to have symptomatic intracranial haemorrhage compared to other women of the respective age [26]. Individual case reports show that systemic (intravenous) thrombolytic therapy was also administered in the early stages of pregnancy with good effect: pregnancies were maintained and fetuses developed properly [20,24]. Despite various restrictions and an increased risk of haemorrhage, rt-PA shall be administered to pregnant woman after stroke, unless there are contraindications [1,16,24]. Each woman should be approached individually, considering the possible benefits of treatment and potential complications. If the benefits are greater than the possible complications, administering the drug is worth considering, with patient's permission, because thrombolytic treatment gives a better chance for full or significant recovery. Experts point out that in pregnant women with stroke, more attention should be given to the type of stroke in terms of its etiology, severity, and time passed since the onset of the disease and whether the patient meets the criteria for rt-PA administration or for endovascular therapy, instead of focusing on the pregnancy itself [1,16,24].

Stroke caused by coagulopathy

During pregnancy, there is a predominance of coagulation processes over fibrinolysis and this condition is most expressed in the third trimester and after delivery. Hypercoagulability may cause both arterial stroke and venous thrombosis. The procedure in the acute period is the same as in arterial or venous ischemic stroke in non-pregnant women in accordance with the guidelines, but it is important to determine whether the patient's hypercoagulability is only a transient, pregnancy-induced condition or the patient suffers

from thrombophilia, which showed in pregnancy. It is advisable to conduct tests for congenital thrombophilia and for antiphospholipid syndrome (APS), which is the most common type of acquired thrombophilia. In the latter, the test should be repeated after 12 weeks or later (after the puerperium period) and only a second positive result (if at least one antiphospholipid antibody is found) authorizes to diagnose APS [1,2,4,27]. It is very important to apply appropriate prevention [28]. If the thrombosis is caused by:

- transient hypercoagulability associated with pregnancy, anticoagulant treatment is carried out for 3-6 months (only heparin is allowed in pregnancy; however, it is switched to warfarin in the puerperium),
- idiopathic, mild thrombophilia (heterozygote: factor V Leiden gene mutation, G20210A prothrombin gene mutation, elevated level of factor VII), anticoagulant therapy is carried out for 6-12 months,
- severe thrombophilia (e.g. homozygous mutation of the G20210A prothrombin gene, factor V Leiden mutation, protein C and S deficiency, APS), anticoagulant treatment is applied for life.

These women are not advised to take hormonal contraceptives and for the next pregnancy, LMWH is administered from the beginning, including ASA 75mg in APS [29].

Venous stroke

Pregnancy increases the risk of suffering from venous stroke and is recognized as an important risk factor for cerebral venous thrombosis. A total of 5-20% of all cerebral blood clots in women in developed countries is caused by venous thrombosis [1-3,30,31].

Management in pregnant woman who has previously suffered from ischemic stroke

Experts believe that if a woman suffered from an ischemic cerebral stroke in the past, if she gets pregnant, consideration should be given to administering low molecular weight heparin (LMWH) in the first trimester, and low dose acetylsalicylic acid (ASA) starting in the second trimester (75-100mg) [32,33].

If the stroke was caused by cardiogenic embolism, anticoagulant treatment should be administered during pregnancy, but only using LMWH or unfractionated heparin (UFH). Warfarin is contraindicated in pregnancy because it is teratogenic. However, it is safe to start administering it after delivery, as it does not pass into the breast milk. Anticoagulants, which are direct antagonists of coagulation factors (dabigatran - factor II inhibitor, rivaroxaban and apixaban - factor X inhibitors), are currently not recommended during the puerperium period. The use of vitamin K antagonists (warfarin) is still advised [33,34].

Artery dissection

This is a rare cause of stroke. Only around 6% of pregnancy-related strokes are caused by dissection of the artery and they usually occur after delivery [2,33,35,36]. In women, there is a relation between migraine and non-traumatic dissection [35,36]. Dissection can be caused by fibromuscular dysplasia and it can

affect the carotid and renal arteries at the same time. It can be present in the following syndroms: Marfan, Ehlers-Danlos or Loeys-Dietz. Most frequently, however, these syndromes are not found. Headache and neck pain are characteristic for dissection [2,35,36]. The risk factors for dissection include older age of the mother and the prolonged second phase of delivery. A stroke in this case may be a consequence of an arteriovenous embolism, where the embolic material breaks away from the dissection site or the formation of a clot in the dissected artery. The treatment consists of anti-aggregation drugs, for example: ASA or anticoagulant administered after delivery (it can be warfarin for 6 months if the prolonged delivery was the only reason of dissection) [2,33,35].

Recommendations	Remarks / Strength of recommendations and quality of evidence
Stroke in pregnancy is rare, but it is a major cause of disability in this population of female.	-----
In pregnant women, if there is a suspicion of stroke, the following neuroimaging examination should be performed: CT of the head without contrast with the cover on the mother's abdomen or vascular MR without contrast.	High strength of recommendations Moderate quality of evidence
Women with acute ischemic stroke should be evaluated for thrombolytic or endovascular thrombectomy in the same way as non-pregnant patients.	High strength of recommendations Moderate quality of evidence
Pregnant women who suffered from a stroke should be evaluated for the cause of the stroke and appropriate prevention should be undertaken.	High strength of recommendations Moderate quality of evidence
Stroke in pregnancy is a risk factor for developing hypertension and subsequent stroke later in life, which is why these women require close monitoring for six months and then strict control for risk factors of stroke	High strength of recommendations Moderate quality of evidence

Table 1: Suggestion on the treatment of ischemic stroke in pregnant women.

Hemorrhagic stroke

Pregnant woman are 2.5 times more likely to suffer from hemorrhagic stroke. In the postpartum period, the risk is 28.5 times higher [27]. Hemorrhagic stroke in pregnancy occurs due to: hypertension, rupture of the aneurysm, rupture of other arteriovenous malformation or brain injury. Types of hemorrhages include:

- interstitial bleeding, intraventricular bleeding
- subarachnoid, epidural and subdural bleeding

Hemorrhagic stroke in pregnancy is a common cause of death in pregnant woman [1]. The most common causes of gestational hemorrhagic stroke are pre-eclampsia and eclampsia, followed by arteriovenous malformations and aneurysms [1,2].

Bleeding from a ruptured aneurysm or arteriovenous malformation

Recent observations indicate that the risk of aneurysm rupture

during pregnancy amounts to 1.4% and is not higher than in non-pregnant women of the same age [37]. This study shows that the caesarean section is performed twice as often in women with an unruptured aneurysm compared to pregnant women without aneurysm. Only one study [38] indicates that the risk of aneurysm rupture increases significantly during natural delivery, but nevertheless the authors believe that some women with aneurysm could give birth naturally and further research shall be conducted. Despite this, delivery by caesarean section is always justified in women with aneurysm, as it guarantees greater safety to the woman.

Ruptured aneurysm should be treated as soon as possible, because the greatest risk of another bleeding occurs within the first 24 hours and it amounts to 4.1%. This risk drops to 1.5% after 48 hours and remains at this level until the 14th day [39]. Mortality in pregnant women with ruptured aneurysm who were treated with neurosurgery amounts to 11%, whereas in those who were not subjected to a surgery - to 63% [40]. Similarly, higher mortality occurred in children if the aneurysm was not treated (27% vs. 11%) [40]. Therefore, in a pregnant woman, a ruptured aneurysm needs to be closed as soon as possible by neurosurgery (clamping) or, optionally, by endovascular procedure carried out in a neurosurgical center that performs this type of intervention. Aneurysm in a young woman who is planning pregnancy should be closed before she gets pregnant in order to protect the woman and child from complications during childbirth [1].

Subarachnoid or intracerebral bleeding is the most common manifestation of arteriovenous (A-V) malformation [41]. The risk of bleeding due to malformation during pregnancy without prior bleeding amounts to 3.5% and increases to 5.8% in women with previous bleeding [1,2,41]. The risk of bleeding from A-V malformation reaches the highest-level during delivery [41]. Experts propose the following: 1) planned closure of A-V malformation in young women before they get pregnant, if possible, 2) if the malformation is detected during pregnancy and it does not bleed, it should be observed and closed after the termination of pregnancy 3) ruptured A-V malformation with bleeding during pregnancy requires immediate surgical or endovascular treatment to the extent it is necessary and safe, while comprehensive treatment can be postponed after delivery and spread over time [1,42].

Summary

A stroke in pregnancy is a medical emergency for both the mother and the child. Neuroimaging shall be performed with caution in order to establish a diagnosis. Subsequently, appropriate treatment should be implemented with a view to the well-being of the mother and the child, and preventive measures should be taken to prevent another stroke.

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