



Cerebral Vascular Accident in Young Women: A Problem for Pregnancy and Contraception? Report of Two Cases

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Abstract

Cerebrovascular disease (CVD) is a neurological medical emergency and one of the main causes of death worldwide; it is classified as ischemic or hemorrhagic. The disease is one of the most severe clinical events related to pregnancy due to thrombogenesis and thrombophilia; there is an incidence of 25 to 34 CVD per 100 thousand births. The current research reports two cases of stroke episode, one previous and another during pregnancy, as well as their associated complications. The first patient had hereditary thrombophilia caused by PAI 4G/5G polymorphism and previous stroke; however, she had regular pregnancy. The second patient had hereditary thrombophilia caused by protein C deficit, had a stroke during pregnancy, and preeclampsia in the first gestational semester; therefore, she was subjected to the cesarean section on the 35th week of pregnancy. Stroke episodes during pregnancy can be very aggressive because it can lead to death or disabilities, not only in the mother but also in the fetus. Based on the association between thrombotic processes and complications, prophylactic anticoagulant therapy is recommended for women with thrombophilia who had a stroke and/or certain adverse pregnancy outcomes, such as recurrent miscarriages.

Keywords

Cerebrovascular Disease, Stroke, Eclampsia, Pregnancy, Hemorrhagic, Ischemic

Introduction

Cerebrovascular disease (CVD) is a neurological medical emergency and one of the main causes of death worldwide; it is classified as ischemic (the most common type) or hemorrhagic. Moreover, it is one of the most severe clinical events related to pregnancy, since it leads to maternal death rates close to 20% and incidence from 25 to 34 CVDs per 100 thousand births [1].

Ischemic stroke, which is the most common type of it, happens due to the blockage of a blood vessel supplying the brain. It is often caused by atherosclerosis or embolic process when thrombi of cardiac or arterial origin migrate to brain arteries. Hemorrhagic stroke can manifest itself as subarachnoid hemorrhage due to blood leakage commonly related to the rupture of an intracranial aneurysm or to intraparenchymal hemorrhage. Bleeding overlapping neoplasms, rupture of arteriovenous malformations and CVT (cerebral venous thrombosis – often associated with young women) are other causes of a cerebral hemorrhage. Ischemic stroke is more frequent (80%) than hemorrhagic stroke (15%) [2,3].

Several physiological changes take place in cardiovascular and clotting processes during pregnancy. There is hypercoagulability state throughout pregnancy since pregnant women have all three etiopathogenic components of the Virchow triad, namely: blood stasis, hypercoagulability, and endothelial damage. Blood stasis results from the compression of the left common vena cava and of iliac veins by the uterus. Hypercoagulability is secondary to the induction of hepatic synthesis of coagulation factors (VII, VIII, and X) caused by the action of placental estrogen and increased fibrinogen, plasminogen activator inhibitor type I and II and decreased protein synthesis. Recent studies have shown that the number of pregnant women who underwent a stroke episode has increased due to late motherhood, obesity, diabetes mellitus, and high blood pressure; all these factors are increasingly more common in pregnant women and directly contribute to the occurrence of vascular events [2,4]. It is possible observing associated thrombophilia along with the

pregnancy factors of thrombogenesis, and it increases the risk of complications during pregnancy [5-7].

Hereditary (protein C S deficit, or antithrombin; plasminogen activator inhibitor - PAI, Factor V Leiden mutation - FVL, and mutation in the prothrombin gene) or acquired (antiphospholipid syndrome) changes in coagulation, which lead, to a prothrombotic state, are the causes of thrombophilia. Such a state predisposes patients to venous or arterial thrombosis; both risk factors are mostly associated with stroke development [5-7]. Blood flow obstruction can happen anywhere in the vascular system, rather than just in brain blood vessels; it causes fetal growth restrictions and even intrauterine fetal death. Another relevant aspect lies in the fact that thrombophilia increases the risk of recurrent miscarriages, premature birth, and preeclampsia development. Therefore, patients who had recurrent miscarriages and fetal loss in previous pregnancies must undergo thrombophilia investigation [8-13].

Cerebrovascular disease diagnosis in pregnant women is challenging because of restrictions in using some imaging methods in pregnant patients. Nuclear magnetic resonance imaging (NMRI) is the favorite method since it does not expose the fetus to ionizing radiation. Detailed laboratory evaluation to identify possible triggering causes of the disease is also important to be performed. Pregnant patients should receive individualized treatment to ensure mother and fetus' safety [1,8], including careful evaluation of the pregnant women at the beginning of prenatal care through anamnesis, obstetric history investigation and possible previous comorbidities since these factors can be aggravated by the pregnancy cycle and lead to unfavorable outcomes [8]. Authors in the current study have herein reported two clinical cases of patients who underwent stroke episodes, one before pregnancy and the other one in the first semester of pregnancy.

Case Presentation

Case-1:

D.M.S., aged 34 years, GoPoAo, with hereditary thrombophilia (PAI polymorphism 4G/5G) reported to the gynecologic appointment due to hypermenorrhea.

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She was recommended for hysterectomy because of difficulty in hormonal medication control. The patient had an ischemic stroke episode, which was confirmed through nuclear magnetic resonance imaging carried out on July 12, 2017. The exam showed an obstruction in the posterior cerebral artery, which was compromising the right hippocampus, the cortical and subcortical region of the cuneus and the lateral occipital-temporal gyrus of the right occipital lobe. There was a millimetric lesion in the ipsilateral thalamus. Since she was a young patient, we prescribed micronized natural progesterone (Utrogestan 200 mcg on a daily basis) for 14 days, starting from the 14th day of the menstrual cycle in order to regulate it. The patient had satisfactory evolution and reported 28-day menstrual cycles in follow-ups performed 30, 90, 120, and 180 days later. She continued to use the anticoagulant medication for 6 months. There were no other stroke episodes or sequelae and the patient fully recovered - she was able to perform her work activities as usual.

Two years after the beginning of the gynecologic control, the patient returned to the clinic. She was approximately 5 weeks pregnant. Treatment started with enoxaparin sodium at a dose of 40 mg, on a daily basis. There were no complications during prenatal care. **Fig-1** and **Fig-2** shows the patient's clinical

evolution and **Table-1** shows the evolution of her laboratory exams. She was subjected to a cesarean section at 39 weeks of pregnancy; she gave birth to one live fetus, with adequate weight for its gestational age. The patient is well; there was no recurrence of her previous condition, she is breastfeeding and using only progesterone as contraception procedure.

Case-2:

T.M.A, aged 21 years, G1PoA1, reported to a routine obstetric appointment with a 7-week menstrual delay. She was looking to start prenatal care, without any complaints or comorbidities. Three days after the appointment, she had intense cephalalgia and went several times to the local hospital in her city. The patient had a sensory loss and motor deficit; therefore, she had to be hospitalized. NMRI identified thrombosis in the left internal cerebral vein (vein of Galen); she had to stay in the ICU (Intensive Care Unit) for 5 days to be treated with enoxaparin sodium anticoagulant - supportive measures were also provided. She was discharged from hospitalization after full recovery and did not present any sequelae. The patient continued to use sodium enoxaparin (120 mg) on a daily basis throughout the prenatal period. She stopped taking the other medications after one month (dexamethasone 8 mg/day; 4 mg 12/12 hours, clopidogrel 75 mg 12/12, and phenytoin 100 mg/day) and presented satisfactory

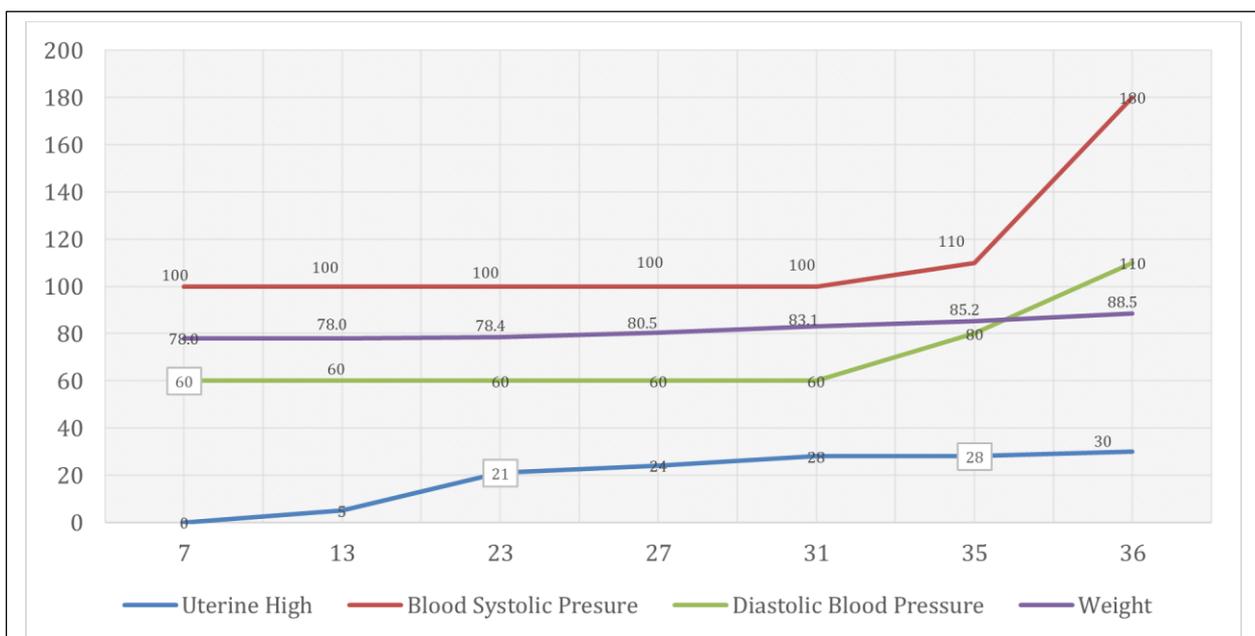


Fig-1: Evolution of patient's clinical data 1 according to the weeks of pregnancy

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Table-1: Laboratory and ultrasound data of the studied patients						
	Case 1			Case 2		
	Quartier					
Laboratory data	First	Second	Third	First	Second	Third
Hemoglobin (g/dl)	12,4	12,9	13,2	13,1	12,8	-
Hematocrit 9%)	37,3	40,1	41	39	34	-
Glucose	86	70	92	76	68	-
Dextrosol 75g	-			-	68/100/77	-
Syphilis	N	N	N	N	N	N
C Hepatitis	N	N	N	N	N	N
HIV	N	N	N	N	N	N
Urynalisis	N	N	N	N	N	N
D Vitamin	28,9	26,9	22,4	31,4	81,3	-
Ferritin	64,8	66,9	54	53,9	73,4	-
Free Thyroxin	-	0,99	1,4	0,68	-	-
Thyreotrophic Hormone	-	1,89	1,65	3,90	-	-
Toxoplasmosis	Immune			N	N	N
Rubella	Immune			Immune		
B Hepatitis	Immune			Immune		
Cytomegalovirus	Immune			Immune		
Hospitalization exams						
Hematocrit (%)	-			41,10		
Hemoglobin (g'dl)	-			13,8		
Creatinine (mg/dl)	-			0,81		
Transaminasis (U/L)	-			19/15		
Index protein/creatinine (mg/dl)	-			0,99		
Urea	-			28		
Uric acid	-			4		
Ultrasound	Gestational age 36 weeks, fetal wight 2600g, amniotic fluid = normal, placentae grade 3.					
Ultrasound						
First Quartier	Gestational age 11 weeks, nuchal translucency= 0,9 mm			Gestational age 13 weeks, nuchal translucency= 1,9 mm		
Second Quartier	Gestational age 22 weeks, fetal morphology normal, uterine doppler normal (pulsatility index)			Gestational age 23 weeks, fetal morphology normal, uterine doppler normal (pulsatility index)		
Third Quartier	Gestational age 29 weeks, uterine doppler normal (pulsatility index), umbilical doppler normal, fetal wight 1480g, amniotic fluid normal, placentae grade 0			Gestational age 32 weeks, uterine doppler normal (pulsatility index), umbilical doppler normal, fetal wight1900g, amniotic fluid normal, placentae grade 0		
	Gestational age 35 weeks, fetal wight 2552g, amniotic fluid = 9,4, placentae grade					

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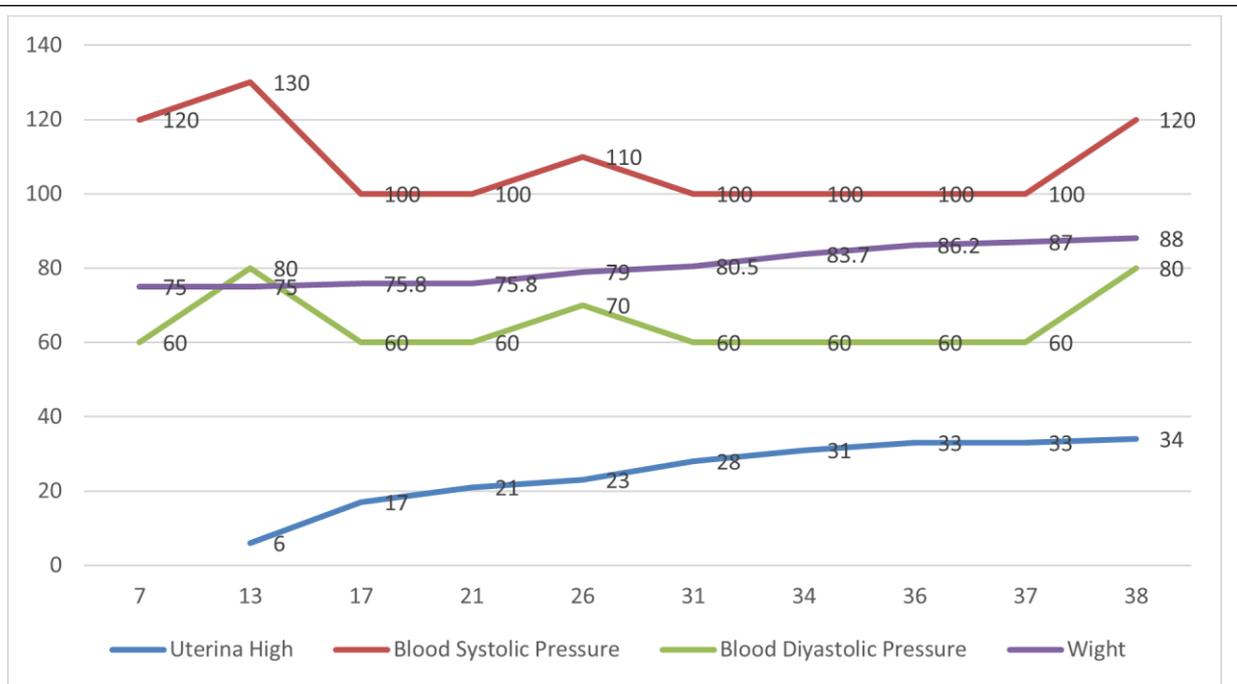


Fig-2: Evolution of patient's clinical data 2 according to the weeks of pregnancy

evolution - no further complications. Blood pressure and fetus growth were regular until the 35th week of pregnancy when she presented high blood pressure (180 x 120 mmHg) during prenatal care appointment and was referred to the hospital. The patient's blood pressure remained high, even after medication; she had cephalalgia and visual scotomas. She was subjected to the cesarean section and gave birth to a single live female fetus, without complications. The patient kept on using enoxaparin for 6 weeks after labor. She is well, without any complications, and is only taken progesterone as a contraceptive method. A recent investigation has shown that the protein C deficit is the cause of thromboembolic events, and this outcome corroborates the hypothetical diagnostic of thrombophilia.

Discussion

Stroke episodes result in the sudden appearance of signs and symptoms caused by the loss of focal or global brain functions that can last for more than 24 hours or lead to death due to neuronal injury. Stroke is a clinic emergency and one of the main causes of death in adults. Pregnancy causes physiological changes in circulatory dynamics, connective tissue integrity, immune responses, and blood coagulability; all these factors predispose the development of vascular

damages [14].

The prepartum/peripartum stroke rate is 18.3/100,000 pregnancies, whereas in the postpartum period this rate drops down to 14.7/100,000. The rate of death by a stroke depends on stroke type, severity, and intervention time (11). Reported death rates during pregnancy range from 2.75% to 20.4%; this number has not changed significantly in the last decades, despite the advances in treatments. Women in fertile age, with venous sinus thrombosis, do not have a high risk of undergoing stroke episodes during pregnancy. On the other hand, the ones who had previous stroke episodes seem to have a significantly higher risk of facing complications than pregnant women who did not have any previous stroke episodes [10]. A recent study conducted in the Netherlands by Alebeek et al. (2018), with 213 patients showed a recurrence rate of 0%. Adherence to treatment and adequate thromboprophylaxis after the episode could have led to such an outcome [15].

Both patients were young, in the meantime. One of them already had thrombophilia (case-1), whereas the other one was taken by surprise by the stroke episode during pregnancy - she did not have thrombophilia (case-2). Therefore, the recommendation is to perform

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a thrombophilia exam, even in young patients with no risk factors. However, since patient 2 was pregnant – a condition that can change the results of some exams –, we chose to examine her after the delivery in order to avoid any bias in the treatment [14,16]. A recent review of the panel of hereditary (protein S, protein C, factor V of Leiden, prothrombin mutation, anti-thrombin, homocysteine) and acquired (lupus anticoagulant, anticardiolipin and anti B2 glycoprotein) thrombophilia pointed towards C protein deficit in the patient.

Patient 1 had thrombophilia before pregnancy; therefore, stroke diagnosis did not happen during pregnancy. The current research identified PAI 4G/5G, the main fibrinolysis inhibitor. The insertion, or exclusion, of a nucleotide in the promoter region of the PAI-1 gene (-675 4G / 5G) seems to account for the change in the plasma synthesis of PAI-1. Homozygous individuals for 4G/4G deletion have high plasma levels of PAI-1; whereas individuals with 5G/5G have reduced levels of it and heterozygous individuals (4G/5G) have intermediate PAI-1 plasma levels [17]. The gene for PAI-1 is located in region q21.3-q22 of chromosome 7. There are many polymorphisms related to this gene, the most common one is the 4G/5G deletion/insertion polymorphism at -675 bp from the transcription start. A research conducted by Jood et al. (2005) [18] with 600 patients who had a stroke episode and 600 healthy individuals has reported that plasma levels of PAI-1 were associated with thrombotic events, but the presence of the 4G allele was not associated with stroke occurrence. On the other hand, data assessed by Wiklund et al. (2005) [19] suggested that the PAI-1 genotype influences stroke occurrence and that assessing the 4G/5G genotype would be more appropriate than simply assessing patients' plasma levels. Therefore, PAI-1 can assist stroke mechanisms in several ways, namely: by affecting the stroke risks, in acute tissue damage during brain ischemia, and even in responses to thrombolytic therapies; it may even determine major bleeding when the patient is in the 5G/5G20 group. Prophylaxis with enoxaparin (40 mg/day) was appropriate if taken into consideration the patient's clinical condition. Low molecular weight heparin was the anticoagulant used during pregnancy because it does not cross the placenta, is not

teratogenic, has a longer half-life, and can be used in a single daily dose [4,20]. Seferovic et al [21] showed that PAI-1 is a potential placental-insufficiency marker; they identified a close association between pathological hypoxia and angiogenesis in a subset of growth-restricted pregnancies in a research conducted in 2016. Therefore, the link between PAI-1 and vascular damage seems viable and accountable for several issues during pregnancy, such as preeclampsia, fetal growth restriction, and even intrauterine fetal death.

Patient 2 had a stroke episode during pregnancy; she reported intense cephalalgia and was refractory to usual medicines. Subsequently, the patient had a sensory loss and motor deficit. Cerebral Venous Thrombosis (TVC) is a brain disorder with venous origins, classified as acute (lasts less than 2 days), subacute (last from 2 days to 1 month), and chronic (lasts from 1 to 2 months) [11]. The patient presented the subacute clinical form of it, which is the most common one. TVC is different from the ischemic stroke because it occurs in venous regions and is more frequent in young women. The patient presented only pregnancy status as a risk factor; factors such as smoking, obesity, previous hypertension, diabetes mellitus, or hypercholesterolemia were ruled out. Thrombophilia examination was only performed after labor. Treatment consisted in low molecular weight heparin during the pregnancy (120mg/day); the patient reported good fetal development until the 35/36 week of pregnancy when she was hospitalized with severe preeclampsia. Thrombophilia was seen as a possibility because the patient had a stroke during pregnancy and preeclampsia at the end of pregnancy. The exams later confirmed that she had a protein C (PC) deficit. PC is a vitamin K dependent protein that acts in the coagulation cascade by inactivating activated cofactors V and VIII. This process results in natural inhibition of thrombin formation, and this outcome justifies the hypothesis that its deficiency may lead to a prothrombotic state [22].

Studies about thrombophilia are scarce and cannot detect plausible associations. However, data from these studies should be taken into account when patients are young and do not have any risk factors, but had a stroke episode or myocardial infarction [22]. Low

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molecular weight heparin was also the chosen anticoagulant, but the patient-2 dose was for real treatment, rather than for prophylactic purpose, as in the case of patient 1.

Progestogen was the adopted contraception method since combined hormonal therapy presents risks associated with thromboembolic events, mainly in patients with thrombophilia. Estrogen contributes to increase pro-coagulant factors in the coagulation cascade (factors VII, X, XII, and XIII) and to decrease the anticoagulant factors (protein S and antithrombin) [23-25].

The prognosis of pregnant women in the current research changed depending on the associated comorbidities, on the recurrence of the previous condition (19.5%), and on the degree of vascular involvement. Stroke accounts for high levels of morbidity and mortality; moreover, it can cause functional disabilities and death [26]. Therefore, the entire healthcare team must look forward to find early diagnosis and propaedeutic in case of stroke episodes in pregnant women. The adoption of preventive measures and early rehabilitation significantly improves the prognosis and reduces the negative impacts, as well as morbidity and mortality, associated with this disease. The association between stroke and pregnancy can be very aggressive when it comes to maternal mortality and disability; it can pose potential risks to the fetus, as well. Assessing the results from previous research about hereditary thrombophilia is a restricted task, given the small sample sizes; however, clinical cases of stroke episodes prior to or during pregnancy should be treated in separate. Only individual evaluations would allow adequate treatment for the accomplishment of a favorable outcome for both, mother and fetus.

Conflict of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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