STROKE IN YOUNG WOMEN - HYPERCOAGULABLE STATES AND STROKE

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The objectives of this presentation are to:

1. Discuss the unique risk factors for stroke in young women
    a. Pregnancy, preeclampsia, and risk associated with stroke in future pregnancies
    b. Hormonal Contraception
2. Discuss Hypercoagulable States and Stroke
    a. Antiphospholipid antibodies
    b. Other thrombophilias

I. Stroke in Young Women

In young women of childbearing age, both pregnancy and oral contraceptive use are risk factors for stroke.

A. Stroke and Pregnancy

a. Stroke incidence during pregnancy is uncommon, but it is still higher (34 per 100,000 deliveries)[1] than the average incidence of non-pregnant women (21 per 100,000).[2] Alarmingly, there appears to be an increase in the incidence of peripartum stroke over the last 2 decades. Analysis of the Nationwide Inpatient Sample showed that rates of any stroke increased 47% from 1994-1995 to 2006-2007 in antenatal and 83% in post-partum hospitalizations.[3] This was true for each stroke subtype, including ischemic and hemorrhagic stroke, as well as cerebral venous sinus thrombosis. In 2006-7, 32% of antenatal and 53% of postpartum hospitalizations had concurrent hypertensive disorders or heart disease. Given the concurrent increases in stroke, hypertensive disorders and heart disease, the authors concluded that these risk factors most likely explained the trend in postpartum hospitalizations for stroke.[3]

b. Most analyses of pregnancy have shown that the highest risk of stroke is during the post-partum period. In an administrative analysis of California hospitals from 2005-2011, the rate of stroke hospitalization from delivery to 6 weeks post-partum was 14.8 per 100,000 deliveries.[4]

Risk Factors and Causes of Peripartum Stroke

c. Age and Race/ethnicity (Table 1)

Shown in Table 1, the stroke rate of pregnancies increases with age greater than 35 years, and is even higher with age greater than 40 years. In addition, African American women have a 50% increased risk of stroke compared with white women under age 35 years, but this risk increases 4.5-fold in African American women 35 years of age or older.

Table 1. Age and race related to stroke rates during pregnancy from the Nationwide Inpatient Sample.[1] Adapted from Obstet Gynecol 2005.

Variable	Stroke rate per 100,000 deliveries (95% CI)	OR (95% CI)	P value
Age 35-39 yrs vs age < 20 yrs (all races)	58.1 (51.4-64.8)	2.0 (1.4-2.7)	<.01
Age ≥ 40 yrs	90.5 (71.9-109.1)	3.1 (2.0-4.6)	<.01
African American (vs white)	52.5 (44.1-60.9)	1.5 (1.2-1.9)	<.01
White ≥ 35 yrs	59.9 (50.9-68.9)	2.2 (1.6-2.9)	<.01
African American < 35 yrs	42.6 (35.0-50.2)	1.5 (1.1-2.0)	<.01
African American ≥ 35 yrs	63.2 (25.2-101.2)	4.5 (2.9-6.8)	<.01

B. Pre-eclampsia/Eclampsia

Amongst the hypertensive disorders of pregnancy, preeclampsia/eclampsia is also a major cause of stroke, especially hemorrhagic stroke, during pregnancy. Preeclampsia is defined as new onset hypertension during pregnancy, with blood pressures of > 140/90 mm Hg and proteinuria (≥300 mg in 24 hours), which may occur early, before 37 weeks, or late, after 37 weeks gestation. Eclampsia is preeclampsia that progresses to seizures. Pregnancy-induced hypertension is defined as hypertension that occurs without other signs of preeclampsia, and generally resolves within 12 weeks post-partum. Preeclampsia and eclampsia are not limited to the antenatal or delivery setting, but can occur post-partum (see case 1). Women with severe post-partum headaches and/or hypertension may be seen in the adult Emergency Department settings, rather than the OB triage department, so it is very important to not miss this diagnosis, or the vasculopathies that may be associated with pregnancy-related complications, such as reversible cerebral vasoconstriction syndrome (RCVS)[5] or reversible posterior leukoencephalopathy syndrome (RPLS, also known as posterior reversible encephalopathy syndrome or PRES).[6] Although only a small percentage of women with preeclampsia will have cerebrovascular complications, it is a major cause of maternal mortality. In fact, a study of the Pregnancy Mortality Surveillance System showed that of women with complications from preeclampsia/eclampsia, the cause of death in nearly 40% of these women was a cerebrovascular event.[7]

In addition to the risk of major morbidity and mortality during pregnancy, hypertensive disorders of pregnancy (especially preeclampsia/eclampsia) increase the risk of stroke by about 2-fold up to 30 years after delivery.[8–10] In addition, there is about a 4-fold risk of hypertension later in life in these women compared to women with normal pregnancies.[8] Cardiovascular risks besides hypertension are increased, as well, and as a result, the Guideline recommends early cardiovascular risk factor screening and lifestyle changes in women with a history of hypertensive disorders during pregnancy.[8]

C. Risk of future pregnancies in women with a history of stroke

A common referral to neurologists is from an obstetrician/gynecologist or family medicine practitioner who is concerned about a woman with a history of stroke who now wishes to become pregnant. There is gathering evidence that the risk of a stroke occurring during pregnancy is reassuringly low. For example, a study from France showed that in 441 women followed for 5 years, the stroke recurrence risk was 1% within 1 yr and 2.3% in 5 yrs.[11] The women who suffered a stroke were more often not pregnant than pregnant, and those that occurred during pregnancy were in the post-partum time frame. In a more recent study of 102 women from Spain with either TIA, ischemic stroke, CVT, or ICH followed for median of 7.4 years, there were no recurrences of stroke during pregnancy.[12] Lastly, a U.S. of 23 women with a history of stroke followed over 35 pregnancies, there were again no cases of recurrent stroke.[13]

A recent consensus document was published that provided a multidisciplinary approach to the issues of: future pregnancies, type of delivery, labor induction, and secondary prevention during future pregnancy and lactation.[14] The most important point from this consensus is that for women with a history of stroke, future pregnancies are not contraindicated. For thromboprophylaxis recommendations, high risk conditions are those that would require anticoagulation, and low risk conditions as those that would require antiplatelet therapy outside pregnancy. The recommendations based on these risks, the stage of pregnancy, the method of delivery, and labor induction are shown in **Table 2** (see Caso, et al Stroke 2017 for the full set of recommendations). The teratogenic risks from the available antithrombotic therapies were also summarized in this consensus document (**Table 3**). The consensus panel concluded that further data would not be available via randomized controlled trials, and therefore recommended an international registry for women with strokes during childbearing years.[14]

Table 2. Recommendations from the multidisciplinary consensus panel. Adapted from Caso, et al. Stroke 2017.[14]

Questions	Recommendations	Grade	Level
Point 1: (a) Future pregnancies (b) Secondary prevention	• For women with a history of stroke, future pregnancies are not contraindicated based on available data.	2	B
	• Pregnant women with defined low-risk condition may be considered for treatment with UFH or LMWH throughout the first trimester, followed by low-dose aspirin for the remainder of pregnancy.	2	B
	• In pregnant women with defined low-risk conditions, no recommendations on other types of antiplatelets other than aspirin can be given.	2	C
	• In pregnant women with defined high-risk conditions, vitamin K antagonists should be avoided between the 6th and 12th week of gestation and close to term to avoid the delivery of an anticoagulated fetus. LMWH or UFH should be used either during these above periods alone and alternated with vitamin K antagonists that have the same target INR based on previous prescription or during the entire pregnancy.	2	B
	• High-risk condition women on NOAC treatment should be prescribed LMWH or UFH between the 6th and 12th week of gestation, while warfarin can be administered in the other periods. The vitamin K antagonist target INR needs to be based on the underlying pathology. Alternatively, UFH or LMWH may be prescribed throughout pregnancy.	2	C
Point 2: Methods of delivery	Natural birth may be preferred to caesarean section. Caesarean section should be performed based on obstetric indications and not on the previous history of stroke	2	C
Point 3: Labor induction	• When labor is pharmacologically induced, aspirin therapy may be continued	2	C
	• Therapeutic doses of UFH/LMWH should be discontinued 24 h prior to inducing labor and restarted within 24 h if no contraindications exist	2	C
	• Vitamin K antagonists may be restarted after 24 h after delivery without a loading dose	2	C

UFH = unfractionated heparin; LMWH = low molecular weight heparin.

Table 3. Associated teratogenic risks from antithrombotic therapies[14]

Antithrombotic Drugs	Placental Transfer	First Trimester	Second and Third Trimester
Low-dose aspirin (60-150 mg/day)	Yes	Contraindicated (risk of gastroschisis)	Not contraindicated
Other antiplatelets	No data	No data	No data
Warfarin	Yes	Contraindicated (teratogenic)	Not contraindicated Regular check of INR
UFH	No	Not contraindicated Risk of HIT	Not contraindicated Risk of HIT Regular check of APTT
LMWH	No	Not contraindicated	Not contraindicated
NOAC	Dabigatran: yes Rivaroxaban: Yes Apixaban: No data Edoxaban: No data	No data	No data

UFH = unfractionated heparin; APTT = activated partial thromboplastin time; LMWH = low molecular weight heparin; INR = internationalized normalized ratio; HIT = heparin induced thrombocytopenia; NOAC = New oral anticoagulants

To summarize stroke and pregnancy, the risk factors are still not entirely understood, but older age, African American race are clearly the most important non-modifiable risk factors. There are also other conditions that have been associated with an increased risk, such as migraines, heart disease, peripartum cardiomyopathy, and hypertensive disorders. The causes and mechanisms are generally

thought to be related to vasculopathies such as reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES), preeclampsia/eclampsia, severe hypertension (PRES), cardioembolic, and hypercoagulable states, such as antiphospholipid antibodies. Most women with a history of prior stroke can have a subsequent pregnancy free from stroke, but working with a high risk obstetrician (maternal fetal medicine specialist) and/or a hematologist is recommended.

D. Hormonal Contraception

Oral contraceptives are used by an estimated 10.7 million women between the ages of 15 and 44 years of age. The incidence of stroke in this population of women varies widely, from 3.4 per 100,000 in 15 to 19 year-olds, and increases steeply after age 35 to 64.4 per 100,000 in the age range of 45 to 49 year-olds.[2] Multiple meta-analyses have been published to estimate the cumulative odds of stroke with oral contraceptive use. The relationship varies by estrogen dose and by the generation of progesterone, but is generally considered to increase by 2-fold in OC users vs non-users.[15,16] A population-based analysis of pharmacy records and stroke incidence in Denmark reported that the risk of stroke was lowest with the low-dose estrogen-containing OC.[2] Although the relative risks with vaginal ring (RR 2.49, 95% CI 1.41-4.41) and transdermal patch (RR 3.15, 95% CI 0.79-12.60) were higher than the OC pills, the 95% confidence intervals were quite wide, suggesting significant variability due to less frequent use and smaller numbers of cases.[2] Another study of progesterone-only pills showed no increased risk for stroke.[17]

It is important to remember that women with stroke risk factors using OCs greatly increase the risk for stroke. Shown in the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study, women using OCs who also smoked cigarettes, had hypertension, hypercholesterolemia, obesity, or diabetes all had a significantly greater risk than women not using OCs.[18] Therefore the recommendation is to screen for high blood pressure prior to initiating OCs, acknowledge that OC use may be harmful in women with other stroke risk factors, and that aggressive therapy for risk factors in these women may be reasonable.[8] Women with migraines with aura who use OC pills and smoke cigarettes are also at an increased risk for stroke.[19]

II. Hypercoagulable States and Stroke

Thrombophilias are most commonly associated with venous thrombosis, but they have also been linked to the arterial cerebral circulation disorders, such as ischemic stroke. Approximately 5% of strokes are attributed to thrombophilias.[20] Defining a phenotype is complex in this population, in part because many of the stroke patients that have positive testing for a specific thrombophilia may also have one or more traditional stroke risk factors, such as tobacco smoking, hypertension, hyperlipidemia, or diabetes. Therefore, unique clinical characteristics of stroke patients with these disorders have not been clearly described.

Young patients with ischemic stroke are often the focus of thrombophilia investigations,[21] although there are no controlled studies that clearly identify the appropriate cut-off for age. Besides age, the phenotypic characteristics of patients with venous thrombotic manifestations of hereditary thrombophilias, and the syndromes associated with acquired thrombophilias, such as antiphospholipid syndrome, may be useful if applied to ischemic stroke patients, although the validity of this approach has not been tested prospectively.[20]

A comprehensive list of the disorders that have been associated with prothrombotic states are listed in Table 4. The focus of this presentation is the thrombophilias with the strongest evidence for an association with ischemic stroke, and would be commonly ordered in young adults. It is also important to consider the factors that may trigger ischemic stroke in an individual with a pre-existing prothrombotic state. These include: acute infection/inflammation, malignancy (particularly mucinous carcinomas), dehydration, hypoxia, trauma, excessive levels of coagulation proteins (e.g. Factor VIII) and tissue factor, activation of vascular endothelial cells or platelets by various stimuli, atherosclerotic plaque rupture, primary or secondary deficiencies of anticoagulant proteins, genetic predispositions, and reactions that promote conversion of Factor VII to FVIIa (initiate and sustain an enhanced procoagulant state). [22] Additional disorders related to cerebral arterial disease may also increase the risk of stroke in the setting of prothrombotic states. These include elevated lipoprotein(a), sickle cell disease, leukostasis caused by acute or chronic leukemia, hyperviscosity syndrome due to hypergammaglobulinemia, cryoglobulinemia, nephrotic syndrome, estrogen administration, pregnancy, postoperative state, prolonged immobilization, and cigarette smoking.

Table 4. Thrombophilias associated with venous thromboembolism

Inherited disorders for which there is strong evidence for predisposition to thrombosis

- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Factor V Leiden mutation
- Prothrombin 20210A mutation
- Elevated homocysteine

Acquired disorders for which there is strong evidence for predisposition to thrombosis

- Antiphospholipid syndrome
- Heparin-induced thrombocytopenia and thrombosis syndrome
- Myeloproliferative disorders
  - Myeloid metaplasia
  - Essential thrombocythemia
  - Polycythemia vera
- Malignancy
- Pregnancy/postpartum
- Trauma
- Surgery
- Therapy-related
  - Hormonal agents (oral contraceptives, hormone replacement, tamoxifen)
  - Chemotherapy/thalidomide
  - Heparin (heparin-induced thrombocytopenia)
- Paroxysmal nocturnal hemoglobinuria
- Inflammatory bowel disease
- Systemic lupus erythematosus
- Bechet's syndrome
- Obesity
- Tobacco use

Disorders for which there is some evidence for predisposition to thrombosis

- Elevated Factor VIII
- Elevated Factor XI
- Elevated Factor IX
- Elevated thrombin-activatable fibrinolysis inhibitor
- Plasminogen deficiency
- Factor XII deficiency
- Dysfibrinogenemia
- Plasminogen activator deficiency
- Heparin cofactor II deficiency
- Protein Z deficiency

A. Antiphospholipid antibodies and antiphospholipid syndrome

The most common acquired thrombophilia associated with stroke is the presence of antiphospholipid antibodies (i.e. anticardiolipin antibodies or aCL and lupus anticoagulant or LA). These antibodies have been associated with both arterial and venous vascular events, as well as recurrent pregnancy losses. Antiphospholipid syndrome (APS) may occur in isolation or in association with systemic lupus erythematosus (SLE), in which case the syndrome is secondary. Primary and secondary APS are indistinguishable with regard to the types of thromboses that occur. Specific criteria have been established for the diagnosis of antiphospholipid syndrome. This includes a history of thrombosis and laboratory evidence of antiphospholipid antibodies of moderate to high titer that are present on at least 2 occasions at least 6 weeks apart (Table 5, Sapporo criteria[23]). Other clinical features of APS include thrombocytopenia, hemolytic anemia, transverse myelopathy or myelitis, livedo reticularis, cardiac valve abnormalities, or chorea. [24]

Table 5. Revised Criteria for Diagnosis of Antiphospholipid Syndrome

Clinical criteria

Vascular thrombosis

- One or more clinical episodes or arterial, venous (except superficial), or small vessel thrombosis in any tissue or organ, confirmed by imaging, Doppler studies, or histopathology

Pregnancy morbidity

- One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation

OR

- One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia, or severe placental insufficiency

OR

- Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities, and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Anticardiolipin antibody of IgG or IgM isotype in blood. Present in medium or high titer (>40 GPL or MPL, or 99th percentile) on 2 or more occasions, at least 12 weeks apart.
2. Lupus anticoagulant (LA) present in plasma on 2 or more occasions 12 weeks or more apart
3. Anti-β2Glycoprotein-1 (Anti-β2-GP1) of IgG and/or IgM isotype in serum or plasma (in titer > 99th percentile), present on 2 or more occasions, at least 12 weeks apart

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Antiphospholipid antibodies can be detected in 30% to 50% of patients with systemic lupus erythematosus, in 4% to 18% of patients with venous thrombosis, and in 10% to 34% of patients with ischemic stroke. [25–28] The specificity of elevated anticardiolipin antibody titers to the etiology of ischemic stroke in unselected patients is controversial. For example, anticardiolipin antibody titers may be elevated in patients with multiple cerebrovascular risk factors,[29] with viral, bacterial, or parasitic infections, with lymphoproliferative disorders such as malignant lymphoma or paraproteinemias, or as a result of exposure to drugs such as phenothiazine, procainamide, phenytoin, quinidine, hydralazine. [30]

It is reasonable to evaluate the majority of young adults with strokes for aPLs. This is because the presence of APLs was independently associated with a 2.4-fold risk of recurrent thrombotic events in the Italian Project on Stroke in Young Adults (IPSYS), after adjustment, along with history of migraine with aura, family history of stroke, and medication discontinuation.[31]

If unclear whether to test for aPLs, other features that may increase the yield include: concomitant diagnosis of SLE, other features of APS, presence of thrombocytopenia, a prolonged aPTT or positive VDRL.[32] In addition to consideration of clinical features, ordering the most specific diagnostic tests will increase the yield of diagnosis of aPLs. Although the aCL ELISA lacks sensitivity, the assay is standardized, so this is a reasonable screening test. However, in accordance with the Sapporo criteria, the anti-β2GP1 IgG is the most specific for thrombosis, and will reduce the risk of a false positive diagnosis.

A recent International Consensus Panel performed a systematic review of antiphospholipid antibodies and risk for thrombosis.[33] The high risk serological features include lupus anticoagulant positivity, triple positivity (LA + ACL + anti-β2-GPI), or isolated persistently positive aCL at medium-high titers, and the low risk features include isolated, intermittently positive aCL or anti-β2-GPI at low-medium titers. This systematic review is an excellent resource, and also has recommendations for antithrombotic treatment based on the presence or absence of SLE, the low vs high risk serological testing results, and whether it is a venous or arterial event (see Table 6 in Ruiz-Irastorza, et al, Lupus 2011).[33]

Because of the lack of strong evidence for whether patients with stroke and protein C, S, or ATIII deficiencies, or FVL or prothrombin gene mutation require long term anticoagulation as written in the AHA Secondary Prevention Guidelines,[34] it has been suggested that testing young patients with their first thromboembolic event is not worthwhile.[35]

In this course, cerebral venous sinus thrombosis (CSVT) will not be covered. However, there is an excellent systematic review and meta-analysis of CSVT and thrombophilias that has been recently published.[36]

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