REVIEW ARTICLE

Stroke in Young Women

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ABSTRACT: In women ages 15-45 years, an additional set of risk factors are important in the pathogenesis of ischemic stroke. Some of these pertain strictly to women, and relate to exogenous hormones and pregnancy. Various other conditions are more common in women, which include migraine with aura, selected vascular disorders and autoimmune conditions. These differences do have implications for management in both the primary and secondary prevention of stroke in this age group.

RÉSUMÉ: L'accident vasculaire cérébral chez les jeunes femmes. Chez les femmes de 15 à 45 ans, un ensemble additionnel de facteurs de risque sont importants dans la pathogenèse de l'accident vasculaire cérébral (AVC) ischémique. Certains sont propres aux femmes et reliés à la prise d'hormones et à la grossesse. Certains autres sont plus fréquents chez les femmes, dont la migraine avec aura, certaines maladies vasculaires et maladies auto-immunes. On doit tenir compte de ces facteurs de risque particuliers pour la prévention primaire et secondaire de l'AVC dans ce groupe d'âge.

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Compared with older adults, stroke in the young (15-45 years-of-age) is associated with an additional set of risk factors and aetiologies, some which are more prevalent in or unique to the female population. The goal of this review is to discuss common conditions that are related to stroke in young women, with an emphasis on exogenous hormone use, pregnancy, and migraine with aura.[1] The secondary goal is to summarize the risk factors and differential diagnosis of other causes of ischemic stroke more commonly found in young women, and to delineate other gender differences. Potential pathophysiologic mechanisms as well as possible management considerations for common situations are also discussed.

The aetiology of stroke in young women may be approached in the manner outlined in the Figure. Note that non-female predominant conventional and unconventional vascular risk factors remain important causes of stroke in young women.

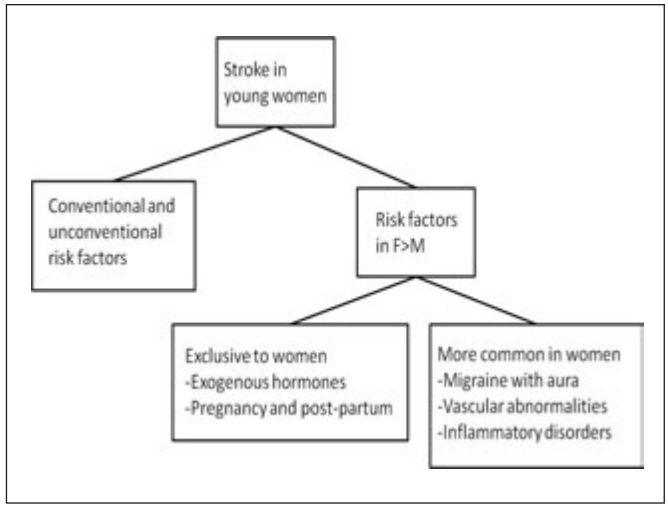

Figure: *Overview of broad categories of causes of stroke in young women.*

1. Stroke risks exclusive to women

Stroke risks exclusive to women pertain to hormonal mechanisms (usually exogenous hormones), or pregnancy and the post-partum period.

Hormonal mechanisms

The role of female sex hormones in stroke risk is well-described. Endogenous ovarian hormones are protective against vascular disease on account of their favourable effects on lipoprotein metabolism, fibrinolysis, vascular inflammation, vasodilation and neuroprotection[2]. Conversely, exogenous hormone use increases the risk of stroke. Exogenous hormones

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are typically used for oral contraception (OC) in women of reproductive age, or as hormone replacement therapy (HRT) in peri- or post-menopausal women.

Oral contraception increases stroke risk in young women, and this risk is proportional to the hormonal dose[3]. The dose of estrogen is most directly related to stroke risk, although progesterone-only formulations are also correlated with a slightly increased risk of stroke[3]. Third generation low-dose OC (which are currently most commonly prescribed), are associated with a two-fold increased risk of stroke[4]. However, the relationship between low-dose OC with stroke has been more difficult to prove in patients without other risk factors, and it is possible that in this context low-dose OC are not associated with an increased stroke risk[5].

Table 1: Factors which increase stroke risk in combination with oral contraception

Characteristics of OC agent:

- Higher hormonal dosage
- Estrogen has higher risk than progesterone

Classical risks:

- Hypertension
- Hyperlipidaemia
- Obesity
- Age (>35)
- Smoking (dose-responsive)[6]

Migraine with aura

Genetic prothrombotic conditions:[7,8]

- Factor V Leiden
- Prothrombin G20210A
- MTHFR C677T
- F13A1 Tyr204Phe

Antiphospholipid antibodies[9]

Factors related to OC that increase the risk of stroke are summarised in Table 1. Management implications include the preferred use of OC with lower hormonal dosage, and possible preference for progestin-only formulations[10]. Smoking cessation and management of hypertension, hyperlipidaemia and obesity should be considered in all patients, even if OCs are not to be used. Stroke risk is directly related to the degree of hypertension in patients using OC[11], so managing hypertension is theoretically important in decreasing the risk of ischemic stroke in these patients. Currently, it is not considered to be cost-effective to order genetic testing for thrombophilias in most patients starting OC[12], although this option may be appropriate in the context of a family or personal history of thrombosis. The use of OC in migraine with aura (MA) patients is discussed in the section on migraine and stroke, but the use of OC in MA patients is generally contraindicated[13]. In patients who have one or more factors that increase their risk of stroke while on OC, decisions should be made on a case by case basis and weigh the benefits and risks. It should also be noted that the combination of certain risks (OC, smoking and MA) create a synergistic risk increase[14].

In principle, it was expected that HRT would decrease stroke risk, given that stroke risk in women increases after menopause (likely related to the loss of the protective effect of endogenous hormones). However, stroke risk is increased in primary prevention studies with HRT[15], and there is no difference in risk in secondary prevention studies[16,17]. This relationship does not appear to be affected by the timing of HRT after menopause[18]. Therefore, there is no indication for the use of HRT in stroke prevention.

Other hormonal factors in stroke relate to endogenous hormones, and are as such not modifiable. Stroke risk is increased in women who had menarche at the extremes of adolescence, due to an unclear mechanism[19]. Early menopause is also associated with increased stroke risk, probably because these women have a more extended withdrawal of their endogenous hormones, which are protective against cardiovascular disease[20]. There is indirect evidence that polycystic ovarian syndrome may be associated with increased vascular risk, and this may be related to hormonal mechanisms (and/or via the relationship of polycystic ovarian syndrome with type 2 diabetes, dyslipidaemia, and elevated homocysteine and inflammatory markers)[21]. Body mass index is linearly related with stroke in young women (modified by age)[22], which could potentially be related to hormonal mechanisms.

Pregnancy and post-partum period

The third trimester of pregnancy and the post-partum period represent a period of elevated vascular disease risk for young women, which includes an elevated risk of ischemic stroke during delivery and post-partum[23]. Several mechanisms may interact to produce this effect in the post-partum period. Hormonal alterations evolve throughout pregnancy, with more abrupt changes occurring during delivery and post-partum. Haemodynamic changes occur during pregnancy due to a high-output state for the cardiac, renal and circulatory systems, followed by a rapid transition to a lower-flow state post-partum as a result of blood loss and the vasoconstrictive effect of oxytoxin during delivery. Pregnancy and the post-partum period also produce a prothrombotic state[24] to prevent excessive blood loss. There may be other local effects, such as vascular stasis due to the enlarged uterus, or trauma during delivery[24], that could produce thrombi causing stroke in those vulnerable to paradoxical embolism. Vasospasm may also occur due to some of the above hormonal or haemodynamic mechanisms, relating to pre-eclampsia and eclampsia, or from reversible cerebral vasoconstriction syndrome[25]. Other conditions particular to pregnancy, such as peripartum cardiomyopathy, disseminated intravascular coagulation, and amniotic fluid embolism can result in stroke[26]. Mechanical aspects of labour, such as repeated

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straining, may increase the likelihood of cervical artery dissection or alter the pressure gradient across intracardiac shunts and increase likelihood of stroke[24].

A number of factors associated with elevated stroke risk in the post-partum period have been identified and are listed in Table 2. Women having MA are at higher risk of vascular disorders including stroke, and in particular peripartum migraine carries a 15-fold increase in stroke risk in the peripartum period[27].

Table 2: Factors associated with elevated risk of stroke during delivery and post-partum[24,26,28]

Migraine (especially peripartum migraine)
Haematologic disorders
• Thrombophilia
• Sickle cell disease
• Thrombocytopaenia
• Blood transfusion
• Disseminated intravascular coagulation
Cardiac conditions
Hypertension
Systemic lupus erythematosis
Age >35 years
African-American race
Substance use
• Smoking
• Alcohol
• Other
Particulars of pregnancy
• Caesarian delivery
• Post-partum infection
• Multi-parity
• Multiple gestations
Pregnancy-specific disorders
• Pre-eclampsia
• Gestational diabetes
• Peripartum cardiomyopathy

In women with a prior history of stroke who become pregnant, guidelines for prophylactic therapy are based upon level C evidence and recommend the use of low molecular weight heparin, with later use of low-dose ASA in the second and third trimesters[29]. In practise, it appears the most commonly prescribed agent is ASA during the first trimester[30].

2. Stroke risks which are more common in women

Migraine with aura

Migraine with aura has been identified as an independent risk factor for ischemic stroke in young women.[31,32] The risk of cerebrovascular events is further increased with a migraine attack frequency of greater than 12 episodes per year.[33,34] The relationship between migraine and ischemic stroke appears to be independent of traditional cardiovascular risk factors, except for smoking and OC use.[34] Women with migraine have been found to have an increased frequency of deep white matter lesions on imaging, which may indicate the occurrence of silent sub-clinical infarcts.[35]

There are a number of theories regarding the patho-physiologic basis for the association between MA and ischemic stroke. While the mechanisms involved are likely multifactorial, the incidence of cerebrovascular events in migrainous patients is popularly hypothesized to be the result of a complex interaction between cortical spreading depression, vasospasm, endothelial dysfunction, hypercoagulability and oxidative stress.[36-38] This unfavourable vascular state may contribute to the increased susceptibility of migraine patients to ischemic stroke, especially in the presence of other procoagulant agents such as OC.[38]

The mechanism for stroke in migraine patients may also relate to intracardiac shunts.[39] The association of patent foramen ovale (PFO) with migraine is particularly strong. Case control studies have indicated that as many as 50% of MA cases occur in the context of a PFO,[32] and migraine patients have larger right-to-left shunts than controls.[40] Higher rates of ischemic stroke in migraine patients with PFO have been reported, with the underlying theory that such patients are predisposed to paradoxical cerebral emboli, particularly when coupled with the platelet hyper-aggregation seen during migraine attacks.[41] Interestingly, paradoxical emboli most frequently cause ischemic infarctions in the posterior circulation, and hypoperfusion of this area is characteristic of MA.[37] The precise relationship between PFO and MA remains speculative, and the risk of ischemic stroke is similarly controversial.[39] The PFO closure in migraine patients was not supported in a randomized, sham-controlled trial, and further trials are ongoing.[42]

The link between MA and endometriosis is also of interest. There is a higher incidence of MA among women with endometriosis,[43] which may be related to a number of factors. Common mechanisms for MA and endometriosis include central sensitization,[44] prostaglandin E2 signalling,[45,46] nitric oxide metabolism,[45] elevated matrix metalloproteinase activity[43] and potentially genetics.[47] Endometriosis is not itself a risk factor for stroke, although its association with MA should alert physicians to the theoretical possibility of higher stroke risk, given that endometriosis is often treated with procoagulant agents such as OC and tranexamic acid (TA). Tranexamic acid is a plasmin inhibitor which has not been demonstrated to independently increase risk of thrombotic complications such as deep venous thrombosis (DVT),[48] and has not been studied in detail for stroke. Tranexamic acid has been associated with stroke in case reports, although other risk factors were present.[49-52] It may therefore be prudent to avoid OC and prothrombotic agents in patients with endometriosis who have a concurrent history of MA and/or other stroke risk factors. Non-systemic therapies for endometriosis may be preferable in these situations.

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Other conditions more common in women which contribute to stroke risk

Table 3 demonstrates risk factors for ischemic stroke which are more common in young women. These may be categorized in two groups. Those which are exclusive to women relate to exogenous hormones or pregnancy, and have been discussed above. Those which are more common in women but also occur in men fall into several sub-categories, including idiopathic disorders (MA, above), vascular disorders (fibromuscular dysplasia, distal embolism from giant cerebral aneurysm, reversible cerebral vasoconstriction syndrome, and cardio-embolism from atrial myxoma), and autoimmune disorders. As mentioned above, MA is associated with PFO, which appears in a higher-than-expected proportion of patients with cryptogenic stroke. Migraine with aura is also potentially associated with internal carotid artery dissection,[53,54] a common cause of stroke in the young. As discussed above, endometriosis is not a stroke risk factor by itself, and therefore does not appear on the table, although it is associated with MA and prothrombotic agents may be used in its treatment.

Table 3: Risk factors and etiologies for stroke in young women

Stroke risks exclusive to women

Exogenous hormone use

- Oral contraceptive[1]
- Hormone replacement therapy[15]

Pregnancy and post-partum period[55,56]

- Eclampsia
- Amniotic fluid embolism
- Choriocarcinoma
- Sheehan syndrome

Stroke risks more common in women

Migraine with aura (itself associated with PFO)[32,34,40]

Vascular disorders

- Fibromuscular dysplasia[57]
- Reversible cerebral vasoconstriction syndrome[25]
- Giant cerebral aneurysm[58]
- Atrial myxoma[59]

Vasculitides and idiopathic inflammatory disorders

- Systemic lupus erythematosis and its complications[60]
    - o Neuropsychiatric lupus
    - o Antiphospholipid antibodies[9]
    - o Libman-Sacks endocarditis
- Takayasu arteritis[61]
- Primary central nervous system angiitis[62]
- Moyamoya disease[63]
- Susac syndrome[64]
- Sarcoidosis[65]
- Hashimoto encephalopathy[66]
- Thrombotic thrombocytopenic purpura[67]

Other considerations in stroke in young women

Age at menopause (before age 42 years associated with increased risk)[20]

Age at menarche (extremes associated with increased risk)[19]

Gestational diabetes is a predictor of stroke risk based upon development of type 2 diabetes[68]

Polycystic ovarian syndrome may elevate vascular risk[21]

Endometriosis associated with migraine with aura[43] and treated with OC and prothrombotics

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Autoimmune disorders are an uncommon cause of stroke, although antiphospholipid antibodies deserve special mention. Recent study has demonstrated that antiphospholipid antibodies may be a major risk factor for stroke in young women, and that this risk is increased substantially by OC use and/or smoking[9]. Of the remaining autoimmune disorders, lupus and Takayasu arteritis are those which are more likely to present with stroke[69]. Lupus can result in stroke via multiple mechanisms (antiphospholipid antibodies, or by Libman-Sacks endocarditis), and strokes in Takayasu arteritis are the result of large-vessel occlusions.

It should also be emphasized that other conventional and unconventional vascular risk factors are important in the pathogenesis of stroke in the young, irrespective of sex.[70] It should furthermore be noted that despite the multitude of risk factors which are exclusive or more common in women, ischemic stroke in the young has a higher incidence in men than women.[71]

Table 4: Other sex-related considerations in ischemic stroke in women compared with men

Clinical presentation more often nontraditional and involving altered consciousness[72]
Later age of presentation with first stroke[73]
Greater disability post-stroke[73]
Higher surgical risk for carotid endarterectomy[74]
ASA effective in primary stroke prevention[75]
Later age at presentation with AF[76,77]
AF more likely symptomatic and higher rate[76]
Less likely to receive warfarin for AF[76]
More likely to have maternal family history[78]

AF=atrial fibrillation; ASA=acetylsalicylic acid; PFO=patent foramen ovale

It is of interest that numerous sex differences exist with ischemic stroke, which are not restricted to patients of younger age, but remain relevant to younger patients (Table 4). Clinical presentation of stroke in women more likely involves nontraditional symptoms or alteration of consciousness.[72] Stroke tends to occur at an older age in women, produces greater disability, and is more likely to be related to atrial fibrillation.[73,77] Women with atrial fibrillation present at a later age, are more likely symptomatic, are less likely to receive treatment with anticoagulation, and have higher likelihood of major bleeding complications on warfarin.[76] For unknown reasons, acetylsalicylic acid is effective in the primary prevention of stroke in women,[79] although this is not the case for men.[75] Women derive less benefit from carotid endarterectomy than men due to higher operative risk,[74] which is of uncertain cause but may be related to the smaller calibre of womens' arteries.[80] Women with stroke are more likely to have a parental history of stroke than their male counterparts, on account of a significantly higher likelihood of maternal family history[78]. This may be related to genetic factors that are more strongly expressed or heritable in the female population, and this requires further study.

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