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Preventing stroke and assessing risk in women

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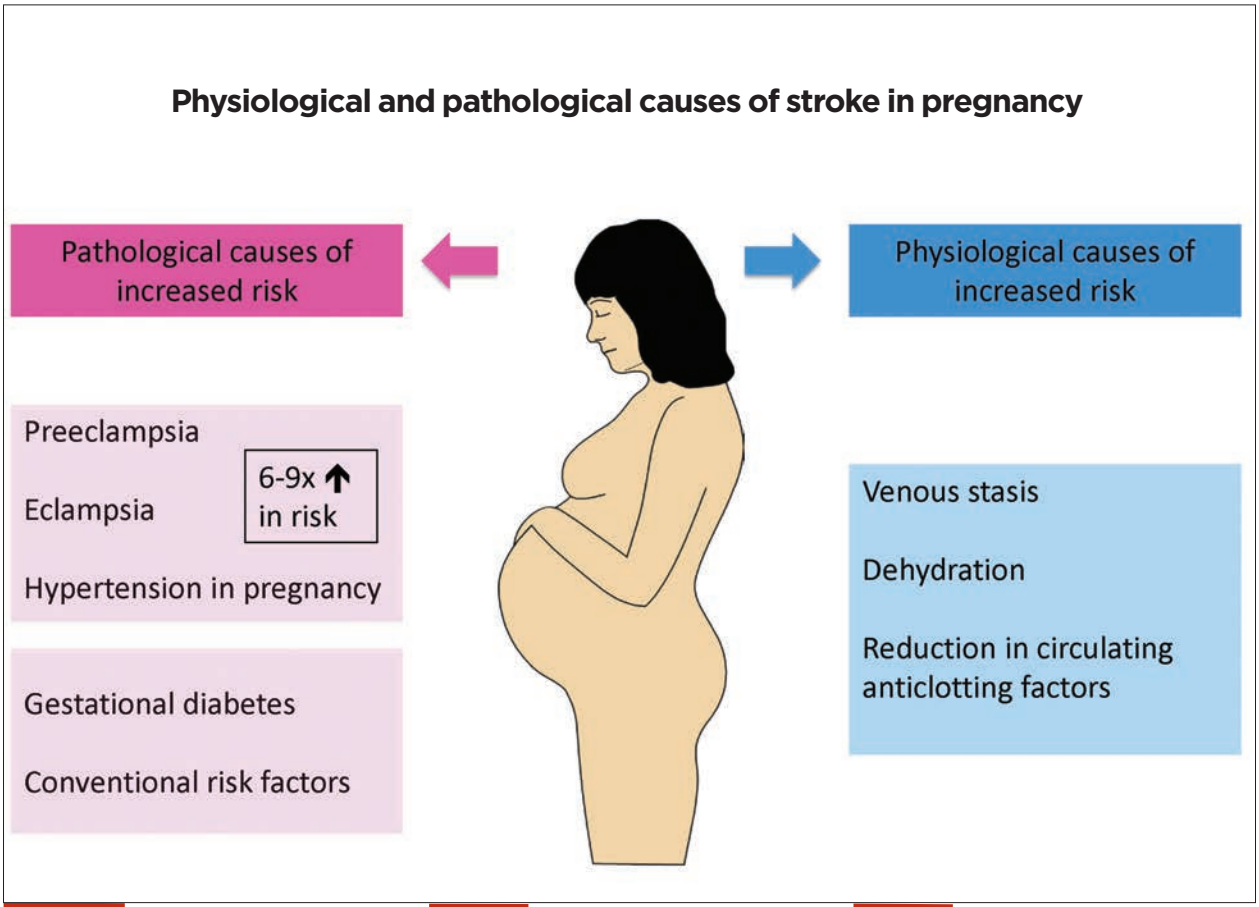

FIGURE 1
Physiological and pathological causes of stroke in pregnancy

What are the risk factors for stroke in women?

STROKE IS THE FOURTH LEADING CAUSE OF DEATH IN THE UK, AND THE SECOND GLOBALLY. Up to the age of 75 men have a 25% higher risk of suffering a stroke compared with women. However, the increased life expectancy of women ultimately results in a higher overall incidence of stroke. Indeed, over the age of 85 there is a dramatic reversal of risk between men and women. Twice as many women die from stroke compared with breast cancer.[1]

Hormonal factors, such as the decline in oestrogen and the relative increase in androgens in postmenopausal women, are believed to increase the risk and incidence of ischaemic stroke in this population. Additionally, increasing rates of non sex-specific risk factors in women, such as obesity and metabolic syndrome, also contribute to a greater number of women aged between 45 and 54 suffering ischaemic strokes compared with men in this age group.[2]

How do women present with stroke?

'The increased life expectancy of women ultimately results in a higher overall incidence of stroke'

How can outcomes be improved in women?

RISK FACTORS SPECIFIC TO WOMEN

Menopause

Ischaemic stroke is rare in premenopausal women but risk increases with advancing age and doubles in the ten years following the menopause. Data from the Framingham Heart Study demonstrate an incidence of 0.82 per 1,000 person-years in white women aged 45-54 with rates increasing two fold in those aged 55-64 years.[3]

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It has been hypothesised that this increased risk is a consequence of both hormonal changes during the perimenopause and an increase in cardiovascular risk. Oestrogen levels decline rapidly with a comparatively slower decrease in testosterone resulting in a relative increase in androgen levels.[4] The perimenopause is also associated with an increased prevalence of risk factors for atherosclerosis including obesity, increased total and LDL cholesterol and reduced HDL cholesterol, increased fasting glucose and raised blood pressure.[5]

'Twice as many women die from stroke compared with breast cancer'

Hormone replacement therapy

Contrary to expectation, the use of exogenous hormones is associated with an increased risk of stroke in postmenopausal women.[6,7] A randomised trial of 16,608 individuals which was part of the Women's Health Initiative, found that hormonal treatment of otherwise healthy postmenopausal women increased the risk of ischaemic stroke by 44%.[6] The association between hormone replacement therapy (HRT), ischaemic stroke and severity of stroke has also been confirmed by large meta-analyses.[8,9]

A medical records study of more than 50,000 women in the UK General Practice Research Database, who were under 55 when prescribed HRT, demonstrated an adjusted hazard ratio of 1.52 for stroke suggestive of an increased risk of stroke regardless of age or timing of hormone use.[10]

Table 1

CHA_2DS_2-VASc score for long-term stroke risk stratification in patients with atrial fibrillation

Risk factors	Score
Congestive heart failure/ LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior MI, PAD, aortic plaque)	1
Age 65-74 years	1
Sex **c**ategory (female gender)	1
Maximum	9

Pregnancy

Pregnancy is a unique risk factor for stroke in women. The risk is highest in the third trimester and peripartum period compared with non pregnant women.[11] In the UK, the maternal mortality rate from stroke is reported at 0.3/100,000 deliveries. However, the true rate is likely to be higher as the postpartum stroke rate is unaccounted for.[12] The rate is also likely to rise with increasing maternal age and medical comorbidities.[13]

Physiological adaptations to pregnancy, such as a reduction in circulating antithrombotic factors leading to a prothrombotic state combined with venous stasis and dehydration secondary to the sudden reduction in circulating blood volume post delivery, are thought to be the mechanisms leading to increased risk, see figure 1, p13.[14]

Hypertension in pregnancy, whether secondary to pre-existing disease, preeclampsia or eclampsia predisposes to a six- to nine-fold increase in risk of stroke compared with normotensive women.[15,16] Further evidence to suggest that hormonal factors influence long-term risk, is that women suffering from preeclampsia have a higher risk for at least one year after pregnancy (see table 3, opposite).[17]

Gestational diabetes is also associated with higher risk of stroke extending beyond childbearing years.[18] Other rarer pregnancy-specific causes of stroke include amniotic fluid embolus and postpartum cardiomyopathy.

Oral contraceptives

There is a small increase in the risk of stroke in younger women using oral contraceptives (1.4 to 2 fold) compared with non-pill users, which represents a lower risk than that associated with pregnancy.[16,19] The mechanism is likely to be an inflammatory or thrombotic process rather than secondary to atherosclerosis.[20] Although the overall risk is low, certain subgroups of women are at higher risk including older women, smokers, and women with hypertension or diabetes.

Migraine with aura

This phenomenon is more common in women than men and more than doubles the risk of ischaemic and haemorrhagic stroke. The absolute risk, however, is low and post-stroke prognosis remains favourable in these individuals. Studies have shown that risk further increases with smoking and oral contraceptive use and the American Heart Association/American Stroke Association (AHA/ASA) guidelines suggest strongly advising women who suffer from migraines with aura to stop smoking.[18]

Atrial fibrillation

Atrial fibrillation (AF) is an established independent risk factor for stroke in both sexes and associated with a four- to five-fold increase in risk.[18] However, while men have a higher incidence of AF in all age groups, women with AF exhibit a significantly higher stroke risk.[21,22] A large Swedish study of 100,802 patients with AF demonstrated a greater risk of ischaemic stroke in women than men (6.2% versus 4.2% per year).[23]

'Atrial fibrillation and hypertension are more potent risk factors for stroke in women'

Further, the combination of coronary artery disease with AF results in a five-fold increase in stroke risk in women, compared with only a two-fold increase in men.[24] This relative disparity remains in patients receiving anticoagulants. A study of 780 anticoagulated AF patients, 40 of whom suffered ischaemic events, demonstrated a relative risk ratio of 2.0 (95% CI: 1.3-3.1) in women versus men.[25] Women are also affected by more severe and disabling strokes than men on the same level of anticoagulation.[25] The increased risk in women is reflected by the CHA_2DS_2VASc scoring system where an extra point is accrued for female sex, see table 1, left.

SEX DIFFERENCES IN CLINICAL PRESENTATION

As in coronary artery disease, cerebrovascular disease in women can present with atypical symptoms when compared with men, see table 2 opposite.[26] A study of 461 patients demonstrated that women were 1.42 times more likely to report nonconventional symptoms.[26] Altered mental status (including unresponsiveness, confusion and behavioural change) is the most common nonconventional symptom, and is reported by 23% of women compared with 15% of men (P = 0.03).[26]

It is generally thought that failure to associate these sex-specific symptoms with stroke, either by the patient, GP receptionists or by physicians leads to delays in treatment and subsequent suboptimal recovery. Studies report differing findings as to whether sex-specific stroke symptoms lead to delays in treatment, and further large-scale studies are required to determine the clinical consequences of these sex differences.[26,27]

Table 2

Conventional and nonconventional symptoms of stroke reported by men and women

Conventional symptoms reported by both sexes
- Hemiparasthesia
- Hemiparesis
- Aphasia
- Dysarthria
- Visual disturbance excluding diplopia
- Diplopia
- Facial weakness
- Disco-ordination/ataxia
- Vertigo

Nonconventional symptoms more commonly reported by women
- Face or hemibody pain
- Lightheadedness
- Mental status change
- Headache
- Other neurological symptoms
- Non-neurological symptoms

SEX-SPECIFIC ASSESSMENT

AF and hypertension, although less common than in men, are more potent risk factors for stroke in women. However, there are no sex differences in current guidance for the assessment or monitoring of these risk factors. Given the disproportionate increase in stroke risk that multiple comorbidities represent in women, clinicians should consider more aggressive identification and management of additional risk factors when one risk factor is already identified.

SEX-DEPENDENT OUTCOMES

Sex discrepancies in management influence outcomes. Women experience longer waiting times in accident and emergency and are provided with less intensive therapy.[21,28] Gargano and colleagues found that women had 11% longer door-to-doctor times and 15% longer door-to-image times compared with men.[28] Statistics from the AHA demonstrate that 71.8% of men and 68% of women arriving at hospital within the first two hours of symptom onset received thrombolysis, with the percentage difference between men and women increasing at three hours.[29]

'Women are affected by more severe and disabling strokes than men on the same level of anticoagulation'

The Framingham Heart Study demonstrated that women were more disabled in various functional activities during the acute phase of stroke and at three to six months post stroke.[3] Studies have also assessed functional outcome using the Barthel index and discovered that fewer women overall were independent in activities of daily living than men.[21] These differences have been attributed to older age at presentation and lower pre-stroke physical function.[21]

Additionally, more women than men report depression after stroke, potentially impairing recovery and quality of life.

IMPROVEMENTS IN THE MANAGEMENT OF WOMEN

The AHA/ASA guidelines for the prevention of stroke in women provide recommendations for primary prevention including screening for AF in those over the age of 75, screening for hypertension before commencing the oral contraceptive pill and monitoring blood pressure during and after pregnancy, see table 3, below.[18]

There may be sex-related differences in the pharmacological efficacy of stroke prevention agents such as aspirin. The Women's Health Study investigated aspirin as a primary preventative agent in almost 40,000 women over the age of 45. No benefit was found for cardiovascular risk or haemorrhagic stroke, but ischaemic stroke risk was reduced by 24%.[30] Women over the age of 65 demonstrated greatest benefit »

Table 3

American Heart Association/American Stroke Association guidance for the prevention of stroke in women

Risk factor	Stroke risk	Recommendations[18]
Pregnancy	Increases risk of ischaemic stroke[11]	Hypertension in pregnancy should be treated safely
Preeclampsia	Doubles risk of stroke in later life[18]	Reduce risk of preeclampsia by use of low-dose aspirin from 2nd trimester
Oral contraception	Doubles risk especially with hypertension[18]	Screen blood pressure prior to commencing hormonal contraception
Hormone replacement therapy	Increases risk by 44%[6]	Should not be used to prevent stroke in postmenopausal women
Migraine with aura + smoking	Increases risk x2[18]	Strongly advise smoking cessation
Atrial fibrillation	Increases risk 4-5x[18]	Screen women >75 years for atrial fibrillation

key points

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Ischaemic stroke is rare in premenopausal women but risk increases with advancing age and doubles in the ten years following the menopause. Up to the age of 75 years men have a 25% higher risk of suffering a stroke compared with women. However, the increased life expectancy of women ultimately results in a higher overall incidence. Twice as many women die from stroke compared with breast cancer.

Women with cerebrovascular disease are more likely to present with atypical symptoms than men. Altered mental status (including unresponsiveness, confusion and behavioural change) is the most common nonconventional symptom, and is reported by 23% of women compared with 15% of men. Other nonconventional symptoms reported more commonly by women include face or hemibody pain, lightheadedness and headache.

Contrary to expectation, the use of exogenous hormones is associated with an increased risk of stroke in postmenopausal women. The Women's Health Initiative trial found that hormonal treatment of otherwise healthy postmenopausal women increased the risk of ischaemic stroke by 44%. The association between hormone replacement therapy, ischaemic stroke and severity of stroke has also been confirmed by large meta-analyses. There is a small increase in the risk of stroke in younger women using oral contraceptives (1.4 to 2 fold) compared with non-pill users, which represents a lower risk than that associated with pregnancy.

Pregnancy is a unique risk factor for stroke in women. The risk is highest in the third trimester and peripartum period. Physiological adaptations to pregnancy, such as reduction in circulating antithrombotic factors leading to a prothrombotic state, combined with venous stasis and dehydration secondary to the sudden reduction in circulating blood volume post delivery, are thought to be the mechanisms leading to increased risk. Women with hypertension in pregnancy, whether secondary to pre-existing disease, preeclampsia or eclampsia have a six- to nine-fold increased risk of stroke compared with normotensive women. Preeclampsia doubles the risk of stroke in later life. Gestational diabetes is also associated with higher risk of stroke extending beyond childbearing years.

Atrial fibrillation (AF) and hypertension, although less common than in men, are more potent risk factors for stroke in women. Compared with men with AF, women with AF are at increased risk of ischaemic stroke (6.2% versus 4.2% per year). This increased risk persists in anticoagulated patients with a relative risk ratio of 2.0.

from aspirin with a 30% reduction in ischaemic stroke, informing the AHA recommendation that women in this age group should be considered for treatment after bleeding risk has been assessed.[18] However, NICE does not recommend antiplatelet therapy for the primary prevention of cerebrovascular disease except in high-risk individuals and does not offer specific guidance for female patients.[31]

'Women had 11% longer door-to-doctor times and 15% longer door-to-image times compared with men'

Sex-specific stroke risk prediction scores have not yet been developed for women. However, risk scores which consider risk factors unique to women are likely to improve the reliability and accuracy of assessment, especially in younger women of reproductive age. Further studies on the long-term stroke risk of women with a history of preeclampsia and other pregnancy-related complications are also needed to predict risk in this cohort of women.

'Women report nonconventional symptoms more frequently than men which leads to delays in seeking medical attention and diagnosis'

CONCLUSION

Women report nonconventional symptoms more frequently than men which leads to delays in seeking medical attention, diagnosis, and accessing acute stroke services.

Public health interventions such as awareness campaigns highlighting symptoms that are unique to women may address this. Improvement in stroke awareness in women of childbearing age is required. Strategies should also focus on improving awareness in pregnant women in particular because of the multifactorial increase in stroke risk during pregnancy.

Increasing awareness of the specific risk factors and warning signs of stroke that are unique to women may help reduce the total burden of cerebrovascular disease.

While male sex has long been considered a risk factor for stroke, increasing life expectancy in females has now transferred the burden of mortality to women.[21] As the UK population continues to age this disparity will only increase.

The AHA/ASA advocates further development of stroke prediction models with the focus on risk profile development and prevention strategies specific to women.[18]

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Useful information

AHA/ASA Guidelines for the prevention of stroke in women
Stroke 2014;45(5):1545-88

Stroke Association
www.stroke.org.uk

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