

REVIEW

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Sex-specific risk factors for stroke in women: Focus on the 2024 AHA/ASA guideline

ABSTRACT

Women are less likely to have a stroke compared with men, but certain sex-specific risk factors can increase their risk for ischemic or hemorrhagic stroke later in life. The 2024 American Heart Association and American Stroke Association guideline for primary prevention of stroke emphasizes female-specific factors that increase risk for stroke, including adverse pregnancy outcomes, premature and early menopause, endometriosis, and certain hormone therapies (eg, combined hormonal contraceptives). This review explores these sex-specific risk enhancers and highlights the importance of a detailed gynecologic and obstetric history when assessing stroke risk in women.

KEY POINTS

Medical disorders and complications during pregnancy (eg, gestational diabetes mellitus and hypertensive disorders) can increase risk of stroke and cardiovascular disease later in life.

Early menopause (before age 45) and premature menopause (before age 40) are associated with increased stroke risk. Treatment with estrogen replacement therapy, when appropriate, may mitigate much of the excess risk.

Endometriosis is associated with an elevated risk of cardiovascular disease and stroke via inflammatory, biological, vascular, and hormonal mechanisms.

A detailed gynecologic and obstetric history in women is crucial for identifying and addressing stroke risk factors.

APPROXIMATELY 800,000 PEOPLE in the United States experience a stroke each year, and stroke remains the country's fifth leading cause of death.^{1,2} Most strokes are ischemic (87%), with intracerebral (10%) and subarachnoid (3%) hemorrhagic strokes accounting for the remainder.³ Just over half (51.8%) of strokes occur in women.³

Throughout most of the lifespan, men are more likely than women to have a stroke. After age adjustment, men have an approximately 30% higher stroke incidence than women, until about age 75 to 85 years, after which incidence is similar between women and men.⁴ This rise in women's risk for stroke later in life can be related to the presence of certain sex-specific risk factors.

The 2024 guideline for the primary prevention of stroke from the American Heart Association (AHA) and American Stroke Association (ASA)² emphasizes several female-specific factors as risk-enhancers, including adverse pregnancy-related outcomes, premature or early menopause, endometriosis, and certain hormone therapies. These factors largely exert their influence on ischemic stroke risk through mechanisms involving atherosclerosis and endothelial dysfunction.⁵

Identifying stroke risk factors early provides an opportunity for timely counseling, aggressive risk-factor modification, and individualized preventive strategies, including judicious use of hormone therapy when indicated. As such, the AHA/ASA guideline underscores

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the need to incorporate these factors into routine cardiovascular risk assessment. This review explores the sex-specific risk factors outlined in the AHA/ASA guideline² and highlights the importance of obtaining a detailed gynecologic and obstetric history when caring for women, especially when considering stroke risk.

■ ADVERSE PREGNANCY OUTCOMES

Medical disorders and complications during pregnancy can signal potential health issues later in life. Gestational diabetes mellitus and hypertensive disorders of pregnancy are common pregnancy complications that significantly affect both maternal and fetal health. Although these conditions are often viewed as temporary and typically resolve after childbirth, emerging evidence suggests that women who experience either of them are at higher risk for chronic metabolic conditions later in life, such as type 2 diabetes mellitus, hypertension, and cardiovascular disease, including ischemic stroke, as outlined below.⁶

Gestational diabetes mellitus

Once considered a temporary condition during pregnancy, gestational diabetes mellitus is now recognized for its long-term health impacts. Women diagnosed with gestational diabetes mellitus have a 10-fold higher lifetime risk of type 2 diabetes mellitus than women without gestational diabetes and have a significantly higher risk of chronic kidney disease and end-stage renal disease.⁷ These factors independently and cumulatively increase the risk of ischemic stroke; however, a history of gestational diabetes mellitus alone doubles the risk of future cardiovascular diseases, including ischemic stroke.⁸

Hypertensive disorders of pregnancy

Characterized by elevated blood pressure during pregnancy, these disorders include preexisting hypertension, gestational hypertension, preeclampsia, and eclampsia. Gestational hypertension is defined as new-onset hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) occurring after 20 weeks of gestation without proteinuria or other systemic findings. Blood pressure typically normalizes by 12 weeks post partum.⁹

Preeclampsia affects approximately 2% to 8% of pregnancies and is defined as new-onset hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) after 20 weeks of gestation, with proteinuria or signs of end-organ dysfunction.^{9,10} Eclampsia, a severe form of preeclampsia with

seizure and encephalopathy, can occur as a progression of preeclampsia, spontaneously, or post partum.¹⁰

Pathogenic mechanisms in hypertensive disorders of pregnancy include placental maladaptation, endothelial dysfunction, and dysregulation of the renin-angiotensin-aldosterone system.¹¹

Regarding maternal health later in life, hypertensive disorders of pregnancy are associated with increased risk of cardiovascular disease, chronic hypertension, both hemorrhagic and ischemic stroke, and renal disease.² Based on a meta-analysis, women with a history of preeclampsia have an 81% higher risk of stroke compared with those without preeclampsia.¹² Preeclampsia is now recognized as an independent cardiovascular risk factor.¹³

Women with a history of gestational diabetes mellitus and hypertensive disorders of pregnancy should be advised about their increased risk of future stroke. Other pregnancy-related risk factors that have been associated with an increased risk of stroke later in life include recurrent pregnancy loss, preterm birth, placental abruption, small-for-gestational-age infant, and stillbirth.^{2,12}

■ PREMATURE AND EARLY MENOPAUSE

Menopause is defined by 12 consecutive months without menstruation; for 90% of individuals, this will occur between age 46 and 56 years.² It is marked by the loss of follicular ovarian function and accompanied by a significant decline in ovarian estrogen production. Menopause that occurs before age 40 is considered *premature*, and menopause that occurs before age 45 is considered *early*. About 5% of women experience early menopause naturally, while many more will experience it either surgically (bilateral oophorectomy) or medically (chemotherapy, ovarian suppression, radiation therapy).²

The most recent AHA/ASA guidelines for lipid-lowering therapy and primary prevention of stroke recognize premature menopause and early menopause as risk-enhancing factors to consider during clinical risk assessment.^{2,14,15}

Mechanisms and evidence on stroke risk

Multiple cardiovascular risk factors begin accumulating around the menopause transition, and cardiovascular risk doubles in the first 10 years after menopause.¹⁶ Multifactorial mechanisms account for increased stroke risk during this time and are incompletely understood. The decline in estrogen leads to a relative androgen excess, which may contribute to the accelerated rate of risk-factor accumulation.^{2,16,17} Increases in visceral

adiposity, triglycerides, low-density lipoprotein, lipoprotein(a), blood glucose, and blood pressure, which peak in late peri- and early postmenopause, can lead to increased vascular disease and stroke risk.^{14,16,18,19} In premature menopause, however, stroke risk increases well before the resulting blood pressure and lipid changes, indicating a more complex mechanism than accumulation of risk factors alone.²

The data are clear that experiencing menopause before age 45 increases stroke risk, irrespective of the etiology.^{2,20–22} Results from multiple meta-analyses of observational data show that stroke risk rises by at least 20% to 30% in this population.^{20,22–24} Zhu et al²³ analyzed pooled data from multiple prospective studies and found incrementally increased risk with lower ages of menopause. Risk of stroke increased 57% in individuals with naturally occurring menopause at age 40 to 44, and 69% when menopause occurred at 35 to 39 years. Analyses of surgical menopause showed similarly increased risk for all types of stroke when oophorectomy was performed under age 48.^{24,25}

Importance of hormone therapy

In many of these studies, excess risk was primarily seen in people who did not use hormone therapy, with a significantly lower risk when hormone therapy was provided until at least age 45.^{21,23,26–28} Estrogen replacement therapy mitigates some, but not all, of the excess stroke risk posed by premature menopause,^{21,23,26,29,30} so early identification and treatment are essential. Guidelines for the treatment of premature menopause recognize that estrogen has beneficial cardiometabolic impacts and may improve cardiovascular and stroke risk.^{23,24} Guidelines and experts consistently recommend estrogen replacement therapy at physiologic, premenopausal levels (plus progestogens in women with an intact uterus) until the average age of menopause, unless a contraindication exists.^{21,29,30}

■ ENDOMETRIOSIS

Endometriosis is a chronic inflammatory gynecologic condition that affects about 11% of women of reproductive age; its prevalence is higher—30% to 40%—in women presenting with infertility.^{31,32} Diagnostic laparoscopy and tissue diagnosis may be needed in some symptomatic women suspected to have endometriosis, as imaging methods cannot reliably provide the diagnosis.^{31,32}

Evidence on stroke risk

Several large studies have conclusively and consistently demonstrated an elevated risk for cardiovascular

disease and stroke in women with laparoscopically proven endometriosis; in a prospective cohort study, a 34% increased risk of stroke was observed in this population.^{32,33} A 2023 systematic review and meta-analysis showed a significant association between endometriosis and stroke (odds ratio 1.28, 95% confidence interval 1.07–1.53; hazard ratio 1.20, 95% confidence interval 1.11–1.30).³⁴ Another meta-analysis yielded a stroke risk of 7% to 29% in women with endometriosis.³⁵

Multiple international studies also have consistently demonstrated this elevated risk. A nationwide Danish study of over 60,000 women with endometriosis and more than 240,000 matched controls reported a 15% increased risk of stroke.³⁶ Similarly, a United Kingdom–based study identified a 19% increased risk of stroke in women with endometriosis.³⁷ While the absolute risk of ischemic stroke was low in a Canadian retrospective population-based cohort study, the reported increases in risk for stroke were similar to those in other international studies.³⁸

Mechanisms

Several mechanisms have been proposed to explain the observed link between endometriosis and stroke, including inflammatory, biological, vascular, and hormonal factors.

Chronic systemic inflammation due to diffuse extrauterine endometrial lesions can lead to extravasation of activated macrophages and proinflammatory cytokines into the peritoneal fluid, which can contribute to endothelial dysfunction and hypercoagulability.³⁹ Elevated vascular adhesion protein-1 has also been implicated as a contributing factor.⁴⁰

Multiple hormonal factors may account for the increased risk of stroke with endometriosis. Analysis of data from the Nurses' Health Study II³³ found that hysterectomy and oophorectomy leading to earlier surgical menopause, thereby modifying the vascular risk, accounted for approximately 39% of the association between endometriosis and stroke, while hormone therapies used to treat endometriosis accounted for another 16%.^{33,41}

Coexisting factors in patients with endometriosis such as hypertension, cardiac arrhythmia, or other vascular dysfunction can increase stroke risk.^{36,37} Also, psychosocial factors such as adversity in early life have been linked to endometriosis and increased lifetime risk for stroke, underscoring the need for a holistic approach to risk assessment.⁴² Women with endometriosis face higher rates of adverse pregnancy outcomes, which can independently elevate stroke risk and risk for postpartum stroke.⁴³

Combined hormonal contraceptives are used along with nonsteroidal anti-inflammatory medications and gonadotropin-releasing hormone agonists and antagonists for treatment of symptomatic endometriosis. Use of combined hormonal contraceptives independently and synergistically increases the risk for myocardial infarction and ischemic stroke, with a dose-dependent effect when the estrogen dose is greater than 50 µg. A Cochrane review showed that patients who used combined hormonal contraceptives with ethinyl estradiol dosages greater than 30 µg had an increased vascular risk compared with nonusers, but progestin type did not seem to influence the risk.⁴⁴

The United States medical eligibility criteria recommend using combined hormonal contraceptives that contain less than 35 µg of ethinyl estradiol in women with multiple cardiovascular risk factors and recommend against using combined hormonal contraceptives in patients with a personal history of ischemic heart disease or stroke.⁴⁵ Most of the currently used combined hormonal contraceptives are formulated as low-dose preparations with less than 35 µg of ethinyl estradiol. In our practice, we tend to start most of our patients on combined hormonal contraceptives containing ethinyl estradiol 30 µg or less.

Unintended pregnancy itself increases adverse health outcomes in women with endometriosis. Therefore, clinicians should consider having shared decision-making discussions with these patients about nonhormonal or lower-risk hormonal options, such as progestin-only methods, for long-term endometriosis management and contraception purposes.⁴⁶ Of the progestin-only options, depot medroxyprogesterone acetate injection is associated with increased stroke risk, while progestin-only pills containing drospirenone, norgestrel, or norethindrone; etonogestrel insert; and levonorgestrel intrauterine devices are not associated with increased risk.^{45,47,48}

Risk assessment

Although the absolute stroke risk for any individual woman with endometriosis remains low, clinicians should incorporate cardiovascular risk assessment into the routine care of women with endometriosis, particularly in those with additional risk factors such as type 2 diabetes mellitus, hypertension, polycystic ovary syndrome, smoking, premature menopause, and prolonged hormone therapy use.^{33,46}

■ POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome is not recognized by the AHA/ASA guideline² as an independent sex-specific

risk factor for stroke; however, it is associated with an increased risk of stroke in women due to the metabolic disorders associated with it. Large cohort studies and meta-analyses consistently report elevated stroke risk in women with polycystic ovary syndrome. A 2024 meta-analysis of over 1 million women found 71% higher odds of stroke (odds ratio 1.71, 95% confidence interval 1.20–2.44).⁴⁹ Accordingly, the 2023 International Evidence-Based guideline⁴⁹ recommends assessing cardiovascular risk in women with polycystic ovary syndrome and counseling patients on the elevated risk of stroke.

■ PREVENTION AND COUNSELING

Obtaining a detailed gynecologic and obstetric history in women is crucial in identifying and addressing risk factors for stroke. Patients with any of these sex-specific risk factors should be informed that their condition can increase risk for stroke in the future. Strategies for primary prevention of stroke must rely heavily on comprehensive lifestyle modification, including a heart-healthy diet, regular physical activity, smoking cessation, and maintaining a healthy weight. Sex-specific risk factors for stroke along with mitigation strategies are summarized in **Table 1**.^{2,12,20,23,24,33–36,38,45,47,48}

Decisions about monitoring intervals and management should be based on the presence of risk factors and overall assessment of cardiovascular risk.^{2,29,30}

■ FUTURE RESEARCH

Further research is needed to disentangle the relative contributions of hormonal, inflammatory, and other mechanisms to the increased risk of stroke associated with reproductive health factors. Understanding these mechanisms will be crucial for developing targeted prevention strategies. Additionally, more work is needed to incorporate sex-specific risk factors into risk-prediction models as well as into clinician education about risk prediction and stratification.

■ TAKE-HOME MESSAGE

Sex-specific factors play a critical and often under-recognized role in shaping lifetime stroke risk in women. Adverse pregnancy outcomes, premature or early menopause, endometriosis, and polycystic ovary syndrome signal heightened risk long before traditional cardiovascular risk factors become apparent. Although further research is needed to clarify underlying mechanisms and refine risk stratification, integrating sex-specific risk factors into clinical prac-

TABLE 1
Sex-specific risk factors for stroke and recommendations for mitigating them

Risk factor	Risk for any stroke (95% confidence interval)	Recommendations to mitigate risk
Adverse pregnancy outcomes		
Hypertensive disorders of pregnancy	RR 1.74 (1.45–2.10) ²	Detailed obstetric history for all individuals
Gestational diabetes	RR 1.45 (1.29–1.63) ²	
Preterm birth	RR 1.65 (1.51–1.79) ²	Regular screening for hypertension, weight, smoking status, diabetes, and hyperlipidemia
Stillbirth	HR 1.38 (1.11–1.71) ²	
Placental abruption	RR 1.70 (1.19–2.42) ²	Comprehensive lifestyle modification ^a
Recurrent pregnancy loss	HR 1.42 (1.05–1.90) ²	
Small-for-gestational-age	HR 1.30 (1.0–1.70) ²	
Preeclampsia	RR 1.81 (1.29–2.55) ¹²	
Premature menopause		
	RR 1.25 (1.04–1.51) ²⁰	Estrogen replacement therapy until age of natural menopause
	HR 1.69 (1.37–2.08) ²³	
	HR 1.23 (1.12–1.36) ²⁴	
Early menopause		
	HR 1.57 (1.43–1.71) ²³	Lipid and diabetes screen at time of premature menopause diagnosis
		Annual screening for hypertension, weight, smoking status, and hyperlipidemia
		Comprehensive lifestyle modification ^a
Endometriosis		
	HR 1.34 (1.10–1.62) ³³	Avoid treatments that induce premature and early menopause when possible
	HR 1.20 (1.11–1.30) ³⁴	
	HR 1.17 (1.07–1.29) ³⁵	Consider combined hormonal contraceptive with ethinyl estradiol ≤ 30 µg or progestin-only option
	HR 1.18 (1.12–1.23) ^{36,b}	
	HR 1.13 (1.03–1.24) ^{38,b}	
		Regular screening for hypertension, weight, smoking status, and hyperlipidemia
		Comprehensive lifestyle modification ^a
Hormonal contraceptives		
Progestin-only contraceptives	Odds ratio 0.96 (0.70–1.31) ⁴⁷	Consider combined hormonal contraceptive with ethinyl estradiol ≤ 35 µg or progestin-only option or nonhormonal contraceptive in patients with elevated baseline risk for stroke ⁴⁵
Combined hormonal contraceptive with ethinyl estradiol ≥ 50 µg	No longer in use due to unacceptable risk ⁴⁸	Regular screening for hypertension, weight, smoking status, and hyperlipidemia
Combined hormonal contraceptive with ethinyl estradiol ≤ 20 µg, 30–40 µg	Incidence rate ratio 1.77 (1.62–1.93) ⁴⁸	
		Comprehensive lifestyle modification ^a

^aComprehensive lifestyle modification includes heart-healthy diet, regular physical activity, smoking cessation, and maintaining a healthy weight.

^bRisk refers specifically to ischemic stroke.

HR = hazard ratio; RR = relative risk

tice represents a critical step toward improving stroke prevention and long-term cardiovascular outcomes for women.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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