Stroke in Women
Recognizing Opportunities for Prevention

Shirin Jalini, MD, FRCPC


METALLICA

Disclosures

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Potential for conflict(s) of interest: None

Objectives

1) Review the stroke risk factors that are unique to women

1) Review the impact of conventional stroke risk factors on women

Stroke Risk Factors Unique to Women

Pregnancy

Endogenous Hormones

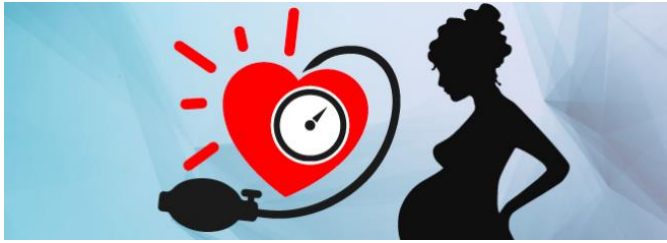
Exogenous Hormones

Pregnancy

- Affects ≈30 women for every 100,000 pregnancies
- Preeclampsia confers a 40-fold increase in risk of true ischemic stroke- single most important risk factor for both ischemic and ICH.
  - 24-48% of strokes in pregnancy are associated with eclampsia and preeclampsia. [1]
- Hallmarks of prevention:
  - Frequent antenatl blood pressure measurements
  - Screening for signs and symptoms of toxemia in the latter half of pregnancy

1 Stroke. 1995;26:930–936

Pregnancy: Preeclampsia



Control of Hypertension in Pregnancy (CHiPS Trial) [1]

– Safe to tightly control BP

– Supports use of aggressive utilization of antihypertensives for prevention of malignant hypertension

- ☑ Labetolol
- ☑ Methyldopa
- ☑ Nifedipine
- ☒ ACE Inhibitors/ARBs

Prevention of Preeclampsia in high risk patients

- ASA [2]
- Repletion of low calcium [3]

1 NEJM 2015: 372: 407-417
2 NEJM 2017; 377:613-622
3 Cochrane Database 2014: 6:CD001059

Long-Term Ramifications

- BP often normalizes after delivery
- But vascular risk does not return to baseline
  - Although it remains unclear if preeclampsia serves as a marker for future stroke or is within the causal pathway of arterial dysfunction, an 80% increased risk of stroke among those with history of preeclampisa persists later in life
- It may be decades before these women have formal cardiovascular risk factor screening and treatment, thereby accumulating atherosclerotic burden all the while.

Peripartum & Post Partum

- Stroke risk (both ischemic and ICH) is highest in the peripartum period remains high up to 6 weeks postpartum.
  - Normal stroke risk in women of child bearing age: 25/100,000 [1]
  - Increases 9-fold in peripartum period
  - Increases 3-fold in the postpartum period

- Risk of ANY thrombotic event remains high up to 12 weeks postpartum

1 J Am Heart Assoc. 2017: 6; e004601: 1-9

Pregnancy in Women with Prior Stroke

- Limited data from case series suggests an absolute risk of recurrent arterial ischemic stroke associated with pregnancy 0.7% (95%CI 0.04-4.4%)- area for future study. [1-3]

- Risk most likely depends on specific clinical circumstance

1 Neurology 2000; 55;269-274
2 Am J Obstet Gyncol 2004; 190:1331-1334
3 Arch Gynechol Obstet 2012: 286:599-604

Pregnancy in Women with Prior Stroke

- strokebestpractices.ca

Canadian stroke best practice consensus statement: Secondary stroke prevention during pregnancy

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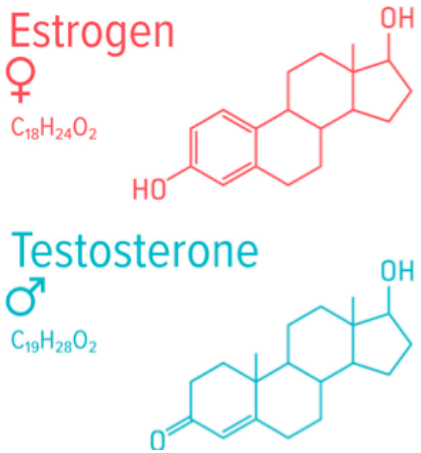
Endogenous Hormones:
Estrogen, Testosterone, DHEAS



- Data on relationship between endogenous hormones and risk of stroke is limited

- Estradiol
  - Meta-analysis of available studies have shown no relationship between estradiol levels and risk if ischemic stroke. [1]

- Testosterone
  - Although low testosterone has been associated with increased risk of stroke in men, no clear relationship has been shown to exist between testosterone and risk of stroke. [2]

- Dehydroepiandrosterone (DHEAS)
  - Endogenous adrenal hormone used for synthesis of estrogen and testosterone
  - Inversely related to both stroke incidence and severity [4-5]

1 J Clin Endocrinol Metab 2016:101:69-78
2 JAHA 2012; 1:e001388
3 Metabolism 2012; 61:84-91
4 J Clin Endocrinol Metab 2010; 95:4985-4992

Endogenous Hormones:
Age at Natural and Surgical Menopause

- Women of reproductive age are at a lower risk of CVD compared to men of similar age and lifestyle.
- But women who experience early menopause have increase cardiovascular risk [1]
- Nurses Health Study
  - bilateral oopherectomy before age 50 associated with increased risk of CVD mortality in women, especially if no hormone therapy is used. [2]
- Therefore, CVD incidence rising sharply after menopause suggests protective benefits of ovarian hormones.
- Reasons unclear. Perhaps due to increased rates of atherosclerosis due increase LDL and decreased HDL.

1 Menopause 2006; 13: 265-279 2 Onstet Gynecol. 2013; 121:709-716

Exogenous Hormones:
Hormone-Containing Birth Control

- Combined oral contraceptives are thrombogenic
- Second and third generation COCs continue to have a 60-80% increased risk of MI/Stroke in users compared to non-users.[1]
- Progestogen-only hormonal contraceptives have not been associated with increased risk of stroke (data is limited). [2]
- Nonoral methods of delivery of combined hormonal contraceptives including vaginal rings and patches seem to have the same risk as their oral counterparts [3]

1 J Clin Endocrinol Metab. 2005; 90: 3863-3870 2 Stroke 2009; 40: 1059-1062 3 NEJM 2012;366:2257-2266

Exogenous Hormones:
Hormone-Containing Birth Control and Migraine

- People with migraine are at increased risk of ischemic stroke.
  - Increased risk is **≈ 2-fold and only apparent in those who have migraine with aura** (not in those without aura). [1]
  - Also **≈ 2-fold increased risk in women compared to men**
- Women with migraine with aura + COCs have further increased risk (7.02 [95% CI, 1.51-32.68])
- Women with migraine with aura + COC + smoking have even higher risk (RR 10 [95% CI, 1.4-73.7]
- Women with migraine with aura should be adviced to control all modifiable risk factors and birth methods other than COCs should be considered.

1 BMJ 2009; 229: b3914

Exogenous Hormones:
Postmenopausal Hormone Therapy

- Women's Health Initiative [1-2]
  - RCT- women aged 50-79. Combined estrogen + progestrone vs estrogen alone vs placebo
  - Postmenopausal hormone therapy increased stroke risk
    - 31% [CI 2%-68%] estrogen + progesterone
    - 37% [CI 9-73%] estrogen alone
- Although subgroup analyses highlighted that stroke risk varies depending on woman's age, HRT is not recommended for stroke and other chronic disease prevention

1 JAMA 2003; 289:2673-2684 2 Circulation 2006; 113: 2425-2434

Exogenous Hormones:
Transgender Medicine

– **Transwomen**: assigned male, identify as female
  - Undergo treatment with estrogen, antiandrogens
  - Antiandrogens: usually spironlactone- does not seem to increase thrombotic risk
  - Estrogen: direct evidence of transwomen is scant. Most comes from small case control studies
  - Current Recommendation: Maintain a high index of suspicion for deep venous thrombosis/ PE/ CVST in transwomen on estrogen. Care provider should strongly encourage smoking cessation and maintain a close eye on cardiovascular risk profile. [1]

1 Stroke 2018; 49 (3) 518-523

Exogenous Hormones:
Transgender Medicine

– **Transmen**: assigned female, identify as male
  - Undergo treatment with testosterone
  - Testosterone does now seem to be associated with increased risk of thromboembolic complication
  - Majority of studies of transmen do not suggest an increased risk of cardiovascular morbidity with exogenous testosterone therapy. [1-3]

1 Clin Endocrinol 2013; 169: 471-478 2 Eur J Endocrinol. 2011; 164: 635-642 3Eur J Endocrinol 2014; 170:809-819

Exposure	Risk Association	Further Research Needed
Endogenous hormones		
Early age at menarche (<10 y)	↑	
Early age at menopause/BSO (<45 y)	↑	
Reproductive lifespan	?	Yes
Low DHEAS	↑	
Estradiol	?	Yes
Testosterone	→	
Exogenous hormones		
PMH: oral estrogens	↑	
PMH: transdermal estrogens	?	Yes
Combined oral contraceptives	↑	
Progestogen-only contraceptives	→	Yes
Transgender exogenous estrogens	↑	Yes
Transgender exogenous testosterones	→	Yes
Pregnancy-related exposures		
Pregnancy/peripartuition	↑	
Gestational diabetes mellitus	↑	
Hypertension in pregnancy/ preeclampsia	↑	Yes

Stroke 2018: 49: 518-523

Impact of Conventional Stroke Risk Factors on Women

Hypertension
Dyslipidemia
Atrial Fibrillation
Diabetes Mellitus

Table 1. Sex Differences in Risk Factor Prevalence, Associations, and Treatment Disparities, Women Compared With Men

Risk Factor	Prevalence	Association With IS	Treatment Disparity
Hypertension	Lower in women (vs men) in younger age groups, higher in older age groups	Similar in women (vs men) in younger age groups, higher in older age groups	In younger age groups, women more likely to have BP controlled; in older age groups, women less likely to have BP controlled
Dyslipidemia	Data conflict; either similar between sexes or lower in women	Lower in women	Women less likely to be on statins and have LDL controlled
Atrial fibrillation	Higher in women	Higher in women	Women less likely to be prescribed oral anticoagulants, less likely to have cardiac ablation, and receive lower doses of NOACs
Migraine	Higher in women	Higher in women	Unknown if migraine treatment reduces stroke risk
Diabetes mellitus	Similar women vs men	Higher in women	Data conflict on sex differences in meeting HbA1c goal
Cognitive impairment	Higher in women	Unknown whether there is a sex difference	Women less likely to be treated with antidementia drugs

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Conventional Stroke Risk Factors and Women

- These potentially modifiable risk factors account for 90% of the population attributable risk for stroke.

- Failure of stroke prevention in women most commonly occurs because women are systemically underscreened and undertreated in modifying these widely recognizable risk factors.

- Therefore it is in risk factor screening and treatment intensification where clinicians can best ameliorate the gender caps in stroke outcomes and prevention

Take away points

- Sex-specific risk factors exists at all ages and stages of life.
- Mediated by unique physiological stress of pregnancy, endogenous or exogenous hormones or traditional risk factors.
- Emphasis on aggressive treatment of obesity, hypertension, dyslipidemia, diabetes, smoking and AF in women

- Thank you!