Neurologic diseases in women

Five new things

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Summary

This review highlights some of the new epidemiologic information concerning sex differences involving combined oral contraceptives and stroke, depression and selective serotonin reuptake inhibitors use during pregnancy, emerging knowledge of the teratogenicity and cognitive effects of anticonvulsants during pregnancy, demyelinating disorders in pregnancy, and the influence of timing of hormonal exposure on the risk of Alzheimer disease.

Women's neurology encompasses the spectrum of neurologic disease and its effect on women across their life cycle. This includes disorders that preferentially affect women as well as those that, because they involve women in their childbearing years, require special consideration.

Stroke and hormonal contraceptives

Women have unique stroke risk factors. These include hypercoagulable changes that occur related to pregnancy and autoimmune disorders, as well as effects of hormonal therapies.¹ Several important epidemiologic studies were published in 2012 looking at the risk of arterial thrombotic events with various combined hormonal contraceptives (CHCs). Data from a cohort of over 800,000 women taking CHCs (containing various amounts of ethinyl estradiol and a variety of progestins) were collected.² This information was used to compare risk of venous thrombotic events and arterial thrombotic events with CHCs. Three higher-dose CHCs—drospirenone-containing pills (drospirenone 3.0 mg, a fourth-generation progestin, and ethinyl estradiol, 0.03 mg), the norelgestromin-containing transdermal patch (6.0 mg norelgestromin, a third-generation progesterone, and ethinyl estradiol, 0.75 mg), and etonogestrol vaginal ring (11.7 mg etonogestrol, a third-generation progestin, and ethinyl estradiol, 2.7 mg)—were compared to low-dose CHCs (containing 0.02 mg of ethinyl estradiol). The study included subjects who were ages 10–55 years and new users of CHC. Women were excluded who had evidence of life-threatening disease or a study endpoint in the 6 months prior to entry. Analysis also excluded periods of pregnancy or abortion. There was an increased risk for stroke and myocardial infarction (MI) events only with the drospirenone-containing

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pills compared to the low-dose CHC (relative hazard ratio 2.01 with confidence interval [CI] 1.01–3.81). The age-adjusted specific incidence rate for women on drospirenone-containing pills hospitalized for acute thrombotic events was 4.7/100,000 for the women ages 35–44 and 22.4/100,000 for the 45–55 age range. No significant risks for the other preparations could be documented. This study demonstrated an increased risk for stroke and MI only with the drospirenone-containing pills, a CHC containing an intermediate amount of ethinyl estradiol, with the highest risk in the older cohort, ages 35–55 years.

Another trial published data on a 15-year prospective population-based study involving nonpregnant subjects taking hormonal contraception and their risk for MI and stroke. Subjects 15–49 years old, without any history of cancer or cardiovascular disease, were followed and their risk for either MI or stroke was stratified according to the type of CHC used.³ The study followed 1,626,158 women with 14,251,063 person-years of observation. A total of 3,311 thrombotic strokes and 1,725 MIs occurred. The overall risk for stroke and MI is small, 21.4/100,000 and 10.1/100,000 person-years. The absolute risk of thrombotic stroke and MI was increased compared to controls by 0.9–1.7 (95% CI) for CHCs containing ethinyl estradiol at a dose of 0.02 mg (low dose) and 1.4–2.2 (95% CI) when the ethinyl estradiol dose was 0.03–0.04 mg (intermediate dose). The study demonstrated that higher amounts of estrogen in the CHC were reflected in an increased risk for stroke and MI. The amount of progesterone had no influence on these endpoints.

These large population cohorts have clear limitations as not all potential confounders are available from registries/records. Nonetheless, when evaluating women with known risk factors for stroke—smoking, hyperlipidemia, family history, and older age—they should be carefully counseled on the risks of CHCs. How to put this information in a clinical context is illustrated in the following case.

A 36-year-old woman was sent to the clinic for neurologic follow-up after her stroke. She had no other medical history including no history of hypertension, diabetes, or migraine. She had presented 2 weeks earlier with acute onset vertical diplopia, gait instability, right facial weakness, and confusion. Her evaluation at that time revealed blood pressure 130/95 mm Hg, height 58 inches, weight 110 pounds, and NIH Stroke Scale score of 3, for right facial droop, right pronator drift, and right-sided ataxia. She reported no smoking, no illicit drug use, and occasional alcohol use. Her only medication at that time was TriNessa birth control pill (BCP) (a higher dose CHC). Aspirin and simvastatin were started after her stroke. There was no family history of stroke or clotting disorder. She denied any history of arthritis, spontaneous miscarriages, or clotting disorder. Brain MRI showed a left thalamic stroke (figure 1). The rest of her evaluation was unremarkable including brain and neck magnetic resonance angiogram, CT angiogram of neck and brain, hypercoagulable laboratories, normal lipid profile, transthoracic echo showed a tiny patent foramen ovale, normal 24-hour Holder monitor, as well as a normal 30-day event monitor. Her examination was normal. She requested advice on birth control and risk factor management.

Her only stroke risk factor was the CHC. She was advised to stop the TriNessa. From the data available, the higher dose estrogen in the CHC is the culprit. Safer contraceptive options would include either a nonhormonal method or a progestin-only contraceptive such as Depo-Provera, the Mirena intrauterine device, a progestin-only implant, or a progestin-only oral BCP.

Figure 1 Illustrative case: Diffusion-weighted imaging and apparent diffusion coefficient images of the acute left thalamic infarct

ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging.

Depression: Use of selective serotonin inhibitors during pregnancy

The risk of depression includes an increased risk of suicide, premature birth, low infant birth-weight, miscarriage, and developmental delay.⁴ Therefore, during pregnancy, it has generally been assumed that not treating depression far outweighs any risk of using selective serotonin reuptake inhibitors (SSRIs).⁵ Recent studies have begun to demonstrate the risk for major fetal malformation with SSRIs. Exposure in the first trimester to fluoxetine is associated with a 0.5% increase in absolute risk for ventricular septal defects (twofold increase as compared with nonexposed normal controls) and paroxetine a 0.2% increase in absolute risk for right ventricular outflow abnormalities (fourfold increase compared with nonexposed normal controls).⁶ A population-based prospective study was conducted to address the question of SSRI risk during pregnancy. All pregnant women who resided in Rotterdam and whose delivery date was between April 2002 and January 2006 were invited to participate. Data from 7,696 women were collected. The study looked at 3 groups of pregnant women: control nondepressed women, depressed women who did not use SSRIs during pregnancy, and depressed women who were treated with SSRIs during pregnancy. The use of SSRIs was obtained from self-reports and confirmed with prescription records. The study showed depressed women who used SSRIs during their pregnancy had less depressive symptomatology than depressed women who did not use SSRIs during their pregnancy. However, the risk of premature delivery, $p = 0.03$, and delayed head growth, $p = 0.003$, was almost twice that of healthy nondepressed peers. Information about important confounders including age, ethnicity, smoking, alcohol use, and socioeconomic status was obtained. Pregnant women with depression not using SSRIs were younger, less educated, and more likely to smoke and use alcohol as compared with controls. The group of pregnant depressed women on SSRIs were also less educated and more likely to smoke and use alcohol as compared to the control group.⁷

These studies provide some benchmarks to begin a meaningful comparison of the risks/benefits of treatment. Clinical judgment is needed to analyze this equation and decide whether there is a net benefit to treating depression during pregnancy. Those women with mild or moderate depression may be better served with counseling or psychotherapy rather than medication.

Anticonvulsants: Teratogenicity and cognitive effects

The results of a comparative safety of antiepileptic drugs (AEDs) during pregnancy were published in 2012.⁸ The study followed a population of pregnant women enrolled in the

Figure 2 Immune system and pregnancy

The current paradigm is that multiple sclerosis (MS) is an autoimmune disease that involves a predominantly T-cell-driven response against CNS myelin. MS is thought to be related to an upregulation of Th1 cells leading to a proinflammatory response. In pregnancy, there is an increase in Th2 cells, which decreases the inflammatory response. Neuromyelitis optica is believed to be a predominantly Th2-mediated disorder, which may reflect why pregnancy may exacerbate this condition.¹² IFN = interferons; IL = interleukins; LT = leukotrienes.

North American AED Pregnancy registry between 1997 and 2011. A total of 4,899 women were identified. Phone interviews were conducted to ascertain AED use and patient characteristics. Fetal malformations were confirmed by medical records. Women were considered exposed if they used any AED as monotherapy during the first 4 months of pregnancy. The risk of major malformations for first trimester exposure to valproate was 9.3% compared to 1.1% for the unexposed controls. The teratogenicity of valproate included neural tube defects, cardiac septal defects, hypospadias, cleft palate, and limb defects. Phenobarbital was associated with a higher risk of cardiovascular anomalies, 2.5% compared to 0.19% for the unexposed controls. In comparison, the risk of major malformations for first trimester exposure to lamotrigine was 2.0% and for levetiracetam was 2.4% (1.1% risk for unexposed controls). Moreover, epilepsy type and seizure frequency did not appear to affect malformation risk. Further trials are underway to define the risks of both fetal malformation and cognitive effects of anticonvulsants in this setting.

The clinical implications are clear, especially since many pregnancies are unplanned. Women with epilepsy in the childbearing years should be managed if possible with lamotrigine or levetiracetam.

Demyelinating disease and pregnancy

Pregnancy does not change the relapse rate for women with multiple sclerosis (MS). Relapse declines during pregnancy, increases in the first 3 months postpartum, and then returns to the prepregnancy rate.⁹ The association between prior pregnancy, number of offspring, and first clinical demyelinating event was explored.¹⁰ Increased number of parity, gravity, and offspring was found to be associated with decreased risk of a first clinical presentation of MS ($p = 0.001$). This association remained significant after adjustment for age, smoking, sun exposure, body mass index, exercise, and education. There was a 49% reduction in the risk of the initial demyelinating event with each subsequent birth ($p < 0.001$). The pathogenesis of this effect may be due to pregnancy's effect on modulation of the immune system.

Neuromyelitis optica (NMO) is a much rarer demyelinating disease, for which the effect of pregnancy is not well-established. A recent retrospective study by Bourre and colleagues¹¹

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provides preliminary evidence. They looked at 20 women with NMO who became pregnant. There were a total of 25 pregnancies in these women. The number of relapses the year prior to pregnancy was recorded, as well as the relapse rate during each trimester during pregnancy and the first year postpartum. Disability was evaluated using the Kurtzke Expanded Disability Status Scale (EDSS). The average relapse rate was 1.0 before pregnancy, rose to 1.2 in the third trimester, and 2.2 in the first year postpartum. This change was reflected by an increase in the women's EDSS score; mean EDSS went from 1.5 to 2.6. However, the study numbers were small and not statistically significant. Pregnancy may affect autoimmune disorders by estrogen's influence on the balance between TH1 and TH2 cytokines (figure 2).¹² During pregnancy, there is an increase in TH2 cytokines, leading to immune tolerance. The Th2-type cytokines include interleukins (IL) 4, 5, and 6, and also IL-10, which have more of an anti-inflammatory response. In this model, diseases like MS, which are TH1-mediated, would be improved, and disorders such as systemic lupus erythematosus and NMO, which are TH2-mediated, would be expected to worsen.

Female hormones and Alzheimer disease risk

The role of hormonal therapy and Alzheimer disease (AD) has been an area of controversy. Multiple observational trials support a neuroprotective role of estrogen.¹³ Estrogen acts at neuronal synapses to increase the concentration of neurotransmitters such as serotonin, dopamine, and norepinephrine, which play an important role in cognition and behavior. The number of receptors for these neurotransmitters, their release, and degradation are all affected by estrogen. In addition, estrogen possesses neurotrophic, neuroprotective, and vasodilatory properties.¹⁴ Observation trials were not substantiated by the Women's Health Initiative Memory study (WHIMS), a large randomized blinded trial that showed no protective effect for either conjugated estrogen alone or used with medroxyprogesterone as compared to placebo in postmenopausal women. Hormonal therapy was associated with a significant increased risk of dementia.¹⁵

In 2012, an additional 7 years of results from a prospective observational study of elderly women in Cache County, Utah, was published.¹⁶ The study followed 1,768 women 65 or older from 1995 to 2006. Detailed information about use of hormonal therapy and menopause was obtained. Hormonal therapy was classified as CHC or unopposed. These women were followed for development of AD. Women who initiated any kind of hormone therapy within 5 years of menopause had a 30% decrease in risk of developing AD, compared to women who had no hormonal therapy ($p < 0.05$). If hormone therapy was initiated beyond 5 years, no benefit was noted. Limitations to this observational study include an unequal distribution of potential confounders between groups, and women who used hormonal therapy were younger at menopause, better educated, and had fewer live births.

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- *Hormonal contraception and stroke—What are the risks?*
- *SSRIs during pregnancy—How safe are they?*
- *What are the risks of anticonvulsants during pregnancy and beyond?*
- *What's new in pregnancy and its effect on demyelinating disease?*
- *Estrogen and risk for Alzheimer disease—It is all in the timing of exposure?*

How does one make sense of these disparate results? These findings lend support to the idea that a critical window may exist for the beneficial effects of hormonal therapy. We know from the WHIMS trial that postmenopausal hormone therapy increased the risk of dementia compared to placebo. Whether hormonal therapy near menopause has a protective effect on the development of AD remains to be validated. Its use is not currently warranted given the known increased risk for myocardial infarction and stroke.

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