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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Just Which Patients Are at Risk of Developing Uterine Fibroids?

By Robert W. Rebar, MD

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Dr. Rebar reports no financial relationships relevant to this field of study.

SYNOPSIS: Uterine fibroids occur commonly and are the most frequent reason for hysterectomy in the United States. Recognizing the risk factors for developing fibroids can help clinicians identify affected individuals and may lead to new approaches to treatment.

SOURCE: Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: A systematic review. *Br J Obstet Gynaecol* 2017;124:1501-1512.

This is the first systematic review reported exploring risk factors for uterine fibroids. The authors identified 60 registries and other observational studies with more than 1,000 patients and single-center studies with more than 100 patients published between January 1995 and April 2015 for inclusion in their analysis. The early date was selected because diagnostic techniques that might have affected the rate of fibroid diagnosis were developed in the mid-1990s. Because of the heterogeneity of the data, it was not possible to perform a meta-analysis. More than half of the studies (60%; 36 of 60) relied on self-report and may have been subject to recall bias. Selection bias was present in the vast majority of included studies, with populations randomly selected in only five studies. In 58% (35 of 60) of the studies, participants responded to a survey (and thus self-selected), and in 30% (18 of 60) of the studies, participants were gynecologic patients. Only pelvic examination was used to identify women with fibroids in 20% (12 of 60) of the studies, whereas ultrasonography, magnetic resonance imaging, or surgical pathology were used in 66% (40 of 60).

The range in the incidence of fibroids was wide, from 217 cases per 100,000 women-years in one study of California teachers to 3,745 cases per 100,000 women-years in the Black Women's Health Study. The prevalence of fibroids also varied widely across the studies, ranging

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from 4.5% to 68.6%. Black race was the only factor that consistently was associated with an increased risk of fibroids in cohort registry studies, ranging from two- to three-fold. In their analysis, the authors focused on and identified 11 risk factors for which the magnitude of the effect was approximately equal to or greater than the effect of race. Age, premenopausal status, hypertension, positive family history, time since last birth, and food additive and soybean milk consumption increased the risk for fibroids. However, use of oral contraceptives or injectable medroxyprogesterone acetate, smoking in women with low body mass index, and increasing parity decreased the risk of fibroids. The authors emphasized the need for high-quality prospective observational data to better understand the epidemiology of fibroids, with the intent of improving management.

■ COMMENTARY

Although uterine fibroids are a leading cause of morbidity in many women — resulting in heavy menstrual bleeding, anemia, fatigue, dysmenorrhea, abdominal pain, a sense of pelvic pressure, dyspareunia, reduced fertility, and bladder and bowel dysfunction — in other women, uterine fibroids are asymptomatic. We know astonishingly little about their epidemiology, let alone their pathogenesis.

An accompanying editorial by two clinicians from a leading group of investigators noted that the findings from this systematic review support the hypothesis that ethnic/genetic predisposition and ovarian hormone exposure are the principal determinants of fibroid development.[1] In fact, experimental evidence supports both postulates.

It long has been recognized that fibroids are generally monoclonal proliferations of benign smooth muscle.[2] Moreover, it now is clear that each monoclonal myoma may be associated with various chromosomal translocations, duplications, and deletions.[3] The majority of myomas contain nonrandom cytogenetic abnormalities, and most of the mutations are found in genes involved in cellular growth or are responsible for architectural transcription. Several genome-wide association studies (GWAS) have been conducted and indicated that particular ethnic groups may have loci associated with the development of fibroids. For example, a multi-stage GWAS study of uterine fibroids in African Americans identified a novel risk locus within CYTH4 that affects gene expression in the thyroid and potentially in fibroids.[4]

Endocrinologically, the estrogen receptor, the progesterone receptor, and the epidermal growth factor receptor appear to play important roles in the development of myomas.[5-7] In addition, aromatase p450 is overexpressed in leiomyomas, indicating that the local conversion of androgens to estrogens also may be important in potentiating the actions of estrogen with fibroids.[8]

The suggestion that these endocrine changes affect fibroid growth is supported by the evidence of which agents inhibit fibroid growth, at least temporarily. We know that medical treatment can alleviate pain and affect menstrual bleeding. Both gonadotropin-releasing hormone agonists and antagonists, which in the long term suppress ovarian steroid secretion, are known to reduce fibroid volume.[9] Selective progesterone receptor modulators (SPRMs), such as mifepristone and ulipristal acetate, have been shown to reduce fibroid size as well.[10] A recent Cochrane analysis concluded that short-term use of SPRMs resulted in improved quality of life, reduced menstrual bleeding, and higher rates of amenorrhea than seen with placebo.[11] Similarly, aromatase inhibitors also hold promise for short-term relief.[12] It remains to be determined whether medical congeners of any of these agents will be developed that can treat fibroids over the long term without resorting to any of the more invasive therapies, including myomectomy and hysterectomy, uterine artery and fibroid embolization, cryomyolysis, and magnetic resonance imaging-guided focused ultrasound therapy.

What is certain is that until more is known about the epidemiology, as well as the etiology and pathogenesis of uterine fibroids, our treatment measures will remain interventional rather than preventive. That is why studies such as the one reviewed are so important. ■

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ABSTRACT & COMMENTARY

The LNG IUS and Stress Reactivity: A Mechanism for Mood Effects or False Signal?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: Users of the levonorgestrel (LNG) intrauterine system showed an exaggerated response to stress compared to women using a combined LNG pill or those with natural cycles.

SOURCE: Aleknaviciute J, Tulen JHM, De Rijke YB, et al. The levonorgestrel-releasing intrauterine device potentiates stress reactivity. *Psychoneuroendocrinology* 2017;80:39-45.

Although side effects due to hormonal contraception receive little attention from clinicians in the United States, the topic remains front and center in the minds of European women and medical experts. Lacking from the debate on whether hormonal contraception causes an adverse effect on mood have been sound mechanistic arguments demonstrating how the effect might be mediated. Aleknaviciute et al conducted two experimental studies and one cross-sectional study in Rotterdam, Netherlands, to explore this question. For all three studies, they compared naturally cycling (NC) women to groups using the 20 µg/d levonorgestrel intrauterine system (LNG IUS) or a combined oral contraceptive (COC) containing ethinyl estradiol (30 µg) and levonorgestrel 150 µg. The authors recruited healthy, non-obese women (18 to 45 years old) through posted flyers and local internet advertisements, and financially compensated them for their participation. To be eligible, women in the hormonal contraceptive groups needed to report use of the method for at least four months, while those in the NC group could not have used a hormonal method for the same time interval. They further screened potential subjects using a clinician-administered Structured Clinical Interview for DSM-IV Axis I disorders, and excluded women with any Axis I psychiatric disorder (acute or in remission), current pregnancy or lactation, thyroid disorder, recent (within four months) medical illness, or use of any prescription medication other than hormonal contraceptives. They also excluded women with a prior diagnosis of endometriosis, polycystic ovary disease, or gynecologic infection, and those using hormonal contraceptives for treatment or prophylaxis of gynecological (e.g., heavy menstrual bleeding) or dermatological (e.g., acne) conditions. To reduce variability in assessment, the investigators tested subjects in the NC group during the luteal phase and those in the COC group during the active pill weeks. They tested women using the LNG IUS with a regular cycle during the luteal phase. The LNG IUS subjects with amenorrhea (proportion not described) were tested at an unknown time in the cycle.

In Study 1, the authors measured salivary cortisol at baseline and at defined intervals following the Trier Social Stress Test (TSST; LNG IUS, n = 15; COC, n = 15; NC, n = 25). The TSST involves a preparation period, free speech task, and verbal mental arithmetic task (each five minutes in duration), with continuous heart rate monitoring throughout the test. Compared to women with NC (10.85 ± 11.03 nmol/L) and those using COC (3.27 ± 2.83 nmol/L), users of the LNG IUS had an exaggerated salivary cortisol response to the TSST (24.95 ± 13.45 nmol/L; $P < 0.0001$). LNG IUS users also showed a significantly potentiated increase in heart rate during the test. To explore the possibility that the effect was due to the presence of an intrauterine device and unrelated to LNG, the investigators enrolled an additional 10 women using a copper IUD and performed the TSST. The results from this group were similar to the NC controls.

For Study 2, the team performed a low-dose (1 µg) adrenocorticotropic hormone stimulation test, and obtained salivary cortisol as well as serum total cortisol and serum cortisol-binding globulin (LNG IUS, n = 20; COC, n = 20; NC, n = 20). In this study, the COC group displayed a significantly higher total serum cortisol response in

comparison with the NC or LNG IUS groups. However, this effect disappeared after adjusting for corticosteroid-binding globulin (known to increase with COC use).

Study 3 evaluated "naturalistic cortisol exposure" in 95 women (LNG IUS, n = 33; COC, n = 33; NC, n = 29). For this experiment, the investigators removed approximately 150 hairs as close to the scalp as possible from the posterior vertex of the scalp. They then used the most proximal 3 cm of the sample to extract cortisol values for comparison; they found that LNG IUS users had significantly elevated levels of hair cortisol compared to the COC and NC groups. Taking these results together, the authors concluded that, compared to women using a COC containing LNG or those experiencing natural cycles, use of the LNG IUS induces a centrally mediated sensitization of both autonomic and hypothalamic-pituitary-adrenal axis responsivity, indicating an altered systemic physiological response to stress.

■ COMMENTARY

Does this study provide evidence of a mechanism to support a link between hormonal contraception and depression? As you recall, Skovlund et al used the Danish National Database to evaluate this question, and found generally weak associations (risk elevations under 2.0) for hormonal contraception use and incident diagnosis of and treatment for depression.[1] In my comments last year, I discussed the weaknesses of the Skovlund study, including the failure to capture baseline confounders, the weak associations, and the absence of a dose-response for progestin-only methods.[2]

More recently, Zethraeus et al published results of a double-blind, placebo-controlled randomized trial of 340 women in Sweden, and demonstrated a statistically significant decrease in general well-being among women receiving the active COC (30/150 EE/LNG) compared with placebo, but no effect on depressive symptoms or depressed mood.[3] In a second double-blind, randomized, controlled trial from Sweden also published this year, women who received active treatment with the non-androgenic progestin nomegestrol acetate in combination with estradiol reported significantly more mood side effects than women randomized to placebo.[4] However, the proportion of women in this study with clinically relevant mood worsening did not differ between the COC and placebo groups. Of greater importance, secondary analyses showed that women with previous adverse hormonal contraceptive experience reported significantly greater mood worsening in the intermenstrual phase in comparison with healthy women, suggesting that a susceptible phenotype may exist. Limitations of both of these studies included the short interval of study (3 to 4 months), as known COC-related treatment-emergent adverse systemic side effects (such as breakthrough bleeding, acne, breast tenderness) that tend to decrease over time may have influenced the outcomes. Older studies have demonstrated improvement in mood associated with continuous use of LNG COCs[5] and with a reduced hormone-free interval in a drospirenone COC.[6] These results align with the null effect on stress response of the LNG COC users in the Aleknaviciute study.

How might a progestin-only method that does not affect cyclicity, such as the LNG IUS, influence stress response and mood? And if progestins have a negative effect, why does the addition of an estrogen result in improvement? Some investigators hypothesize that progestin treatment decreases levels of the progesterone metabolite and potent $GABA_A$ receptor agonist allopregnanolone in the brain.[7,8] Although progestin-only methods that block ovulation, such as the implant, injection, or desogestrel pill, certainly prevent luteal levels of progesterone, most LNG IUS users ovulate after the initial months of use, so this mechanism does not explain the findings reported by Aleknaviciute.

We must consider several important limitations of the Aleknaviciute study before accepting that the LNG IUS results in an altered response to stress. First, self-selection of method results in considerable opportunity for bias. Although the authors attempted to screen out women using a hormonal method for a non-contraceptive benefit, important differences may have influenced choice. In particular, women with concerns regarding hormone effects on mood may have been more likely to use an LNG IUS. LNG IUS users reported much shorter durations of use of the method. This suggests that common but transient treatment-emergent side effects seen with initiation of a hormonal method (particularly the great increase in unscheduled bleeding seen with early use of the LNG IUS) might have influenced the results. Given the importance of contraception to women's lives, and proven efficacy benefit of long-acting reversible contraception methods, we must carefully evaluate any possible association for concern. A true prospective study that sorts out these effects would be a major contribution to the literature.

To respond to the Aleknaviciute and Skovlund studies, the European Society for Contraception (ESC) published a consensus expert statement on the effects of progestin-only contraceptives and mood,[9] raising many of the issues discussed in this commentary. This makes good reading for those who want more information on this issue. I am surprised that this controversy has not made headlines in the United States, given the widespread acceptance and push for greater use of long-acting reversible contraception methods. But perhaps we are distracted by other issues. The ESC recommends a patient-centered approach that emphasizes identifying women who may be at risk for adverse mood changes by taking a thorough history, discussing the possibility of adverse mood effects, and recommending a follow-up visit to discuss options in situations where troublesome adverse effects present. This sounds like good advice for clinical practice while the science settles. ■

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SPECIAL FEATURE

Management of Chronic Hypertension in Pregnancy

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

Chronic hypertension complicates about 5% of pregnancies and has been associated with higher rates of intrauterine growth restriction (IUGR), stillbirth, and, most importantly, superimposed preeclampsia. Through the years, I have heard repeatedly that the person who solves preeclampsia will win the Nobel Prize. Although the condition is far from being solved, there have been some major inroads made into its understanding through contemporary investigation.

Until recently, tools used to characterize cardiovascular changes in normal and abnormal pregnancies had been limited. Standard brachial blood pressure assessment has been the only method to evaluate the dynamics of a very complex system. It simply depicts the pressures during systole and diastole against which the heart is pumping, measured less than a foot from the heart.

Resistance in the cardiovascular system is dependent on peripheral blood vessel size, large vessel compliance, and the overall size of the circulatory bed. In pregnancy, by adding a dynamic placental circulation, the cardiovascular system becomes even more complicated. Today, cardiac output can be assessed noninvasively through standard transthoracic echocardiograms or sonography of the common carotid. Peripheral resistance can be quantified by impedance cardiography monitored over the radial artery. These sonographic windows now enable a better understanding of the physiologic variations in the cardiovascular system in normal and hypertensive pregnancies.

CARDIOVASCULAR FINDINGS IN NORMAL AND HYPERTENSIVE PREGNANCY

In normal pregnancies, cardiac output increases in the first trimester by about 20%. It then increases by another 20% over the next eight to 16 weeks, after which it generally is sustained until term.[1] Peripheral resistance trends downward in the middle trimester and then rises again toward term.[2]

In chronic hypertension, the cardiac output is higher than normal in the first trimester and consistently rises throughout pregnancy.[3] Peripheral resistance remains unchanged throughout most of pregnancy but trends downward toward term.[3]

In preeclampsia, cardiac output is elevated (even above those patients with chronic hypertension) in the first trimester and rises even further until the diagnosis is clear. At that time, interestingly, a crossover occurs in which the cardiac output drops as the peripheral resistance increases.[3]

STANDARD DEFINITIONS

Chronic hypertension is defined as a brachial blood pressure of > 140/90 mmHg, found at two separate sittings, preferably four hours apart — usually before 20 weeks of gestation.

Preeclampsia is diagnosed when brachial blood pressures exceed 140/90 mmHg, with the addition of proteinuria, defined as a single urine sample having a protein/creatinine ratio of 0.3, or if total protein exceeds 300 mg in a 24-hour specimen, occurring after 20 weeks of gestation.

COMPLICATIONS ASSOCIATED WITH CHRONIC HYPERTENSION

The risk of superimposed preeclampsia is about 21% in patients with chronic hypertension vs. 2.1% of the overall population.[4] Preeclampsia puts into play another mechanism, which involves a dysfunctional placental circulation and small vessel endothelial damage. The obvious threat of preeclampsia is eclampsia, and the best way to avoid this serious condition is to be prepared. Early

predictive methods can cue preemptive action to prevent or treat severe hypertension, to initiate seizure prophylaxis, and to employ a plan of timely delivery.

PREDICTION OF PREECLAMPSIA

First-trimester algorithms and scoring systems use combinations of patient historical factors, uterine artery waveforms, and placental biomarkers, such as pregnancy-associated plasma protein-A, placental growth factor, and angiogenic soluble fins-like tyrosine kinase-1. One algorithm yielded detection rates of about 40% for late-onset preeclampsia and 70% for early-onset disease.[5] In general, the more severe the preeclampsia, the better the predictive ability of all the methods. Also, many strategies have been designed for first trimester use, but the later in pregnancy they are applied, the better their predictive accuracy.

Baseline renal function tests will alert the clinician to the potential for preeclampsia. One recent study has shown that if patients with chronic hypertension had protein/creatinine ratios > 1.2 before 20 weeks, the odds ratio (OR) was 7.54 for severe preeclampsia prior to 34 weeks of gestation. If the ratio was below that cutoff, only 1.6% developed severe preeclampsia.[6]

The finding that 80% of chronic hypertension patients developing preeclampsia had an increase in cardiac output many weeks before the diagnosis was made could represent an additional early predictor for preeclampsia.[3]

PREVENTION OF PREECLAMPSIA

Low-dose aspirin. A large earlier study showed a weak effect (a 12% reduction) in preventing preeclampsia in general.[7] The latest trial has shown a stronger effect in avoiding preeclampsia (OR, 0.38), especially when it is severe enough to result in delivery before 34 weeks.[8] Evidence points to a greater benefit if it is initiated before 16 weeks.[9] There is little doubt that patients with risk factors for preeclampsia would benefit from low-dose aspirin, but there has been confusion regarding which dosage to use (81 mg vs. 150 mg), since no comparison studies have been conducted.

Low-dose aspirin and low-molecular-weight heparin. A recent meta-analysis of three studies showed a 50% drop in preeclampsia when patients at high risk were given a combination of the two above medications, compared with low-dose aspirin alone.[10] Pravastatin currently is being tested to prevent preeclampsia in high-risk patients and has passed a first step safety test in humans.[11]

Other attempted regimens. This includes calcium supplements and the antioxidants vitamin E and vitamin C, none of which has shown major benefit.

AVOIDANCE OF FETAL COMPLICATIONS IN CHRONIC HYPERTENSION

Stillbirth. Most studies have found a threefold incidence of stillbirth in patients with chronic hypertension vs. those without, and a recent study has shown that 68% occurred at less than 29 weeks of gestation and 93% were in IUGR fetuses.[4] In patients without chronic hypertension, the average time of stillbirth was 34 weeks of gestation, and most fetuses were appropriate for gestational age. This suggests a primary placental cause of the stillbirth in chronic hypertension.

Early detection of IUGR through ultrasound enables timely surveillance methods (nonstress tests, Dopplers, and kick counts) to be employed, which can be life-saving for those of salvageable gestational age.

There is some evidence that uterine artery analysis will identify most fetuses of chronic hypertensives who would be destined for stillbirth. A decrease in fetal activity (by fetal kick counts), coupled with abnormal second-trimester uterine artery waveforms, carries a five times greater risk of stillbirth.[12]

Intrauterine growth restriction. Most of the perinatal morbidity associated with chronic hypertension is linked to IUGR, which is doubled in these pregnancies. Birth weights below the fifth percentile occur in 10% of patients with chronic hypertension and in 22% of those with superimposed preeclampsia.[4] Since there is such a high predilection for IUGR, patients with chronic hypertension should have fetal growth assessments every four to six weeks through pregnancy.

TREATMENT OF CHRONIC HYPERTENSION

Patients with a previous history of chronic hypertension should be followed closely, even if their blood pressures are below 140/90 mmHg in the current pregnancy. Treatment should be instituted in patients with blood pressures between 140/90 mmHg and 160/110 mmHg (without proteinuria) with labetalol (200 to 400 mg every 12 hours up to 2,400 mg per day), methyldopa (250 mg every 8 to 12 hours, up to a total of 2 g per day), or nifedipine (10 mg every 8 hours or 30 to 60 mg extended release, not to exceed 1,200 mg per day).

Recent investigation has suggested that patients with chronic hypertension tend to be in a more hyper-dynamic state (increased heart rate and cardiac output) and, therefore, respond better to beta-blockers (labetalol), while those with preeclampsia, whose hypertension is linked more to increased peripheral resistance, appear to benefit more from a vasodilator, such as methyldopa or a calcium channel blocker (nifedipine).[13] Although angiotensin-converting enzyme inhibitors have been shown to affect maternal aortic compliance beneficially, they are rated as category D drugs because of possible teratogenicity after first trimester exposure and adverse effects on the fetal kidney with second and third trimester exposures.

Patients with severe hypertension with blood pressures exceeding 160/110 mmHg should be treated aggressively. This would involve intravenous (IV) administration of hydralazine or labetalol. If IV access is not established, oral nifedipine can be used in the interim.

Magnesium sulfate is still the primary agent to prevent and/or treat seizures. This should be given in an IV bolus of 4 to 6 g per 100 mL of fluid infused over 20 minutes followed by 2 g per hour through 24 hours postpartum.

The National Partnership for Maternal Safety has drafted guidance bundles[14] for treatment of hypertensive patients that now are being applied in many obstetrical care centers in the United States. A recent study of 23 hospitals involving 69,500 births in the United States showed an initial compliance rate with the guidelines of about 50%. However, by April 2016, 90% of these hospitals were complying and the incidence of eclampsia had decreased by 42% and severe maternal morbidity had dropped by 17%.[15] The authors believed that continued monitoring of compliance was essential to the success of this initiative.

The message is clear. With chronic hypertension, heightened vigilance will bear rewards in perinatal outcome. ■

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CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to AHCMedia.com and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on your mailing label, invoice, or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, a credit letter will be emailed to you instantly.
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CME/CE QUESTIONS

1. **In the Aleknaviciute study, an increased stress response was observed among which group of women?**
   a. Women in natural cycles who became pregnant during the study
   b. Women using an oral contraceptive containing EE/LNG
   c. Women using a copper IUD and women using an LNG IUS
   d. Women using the LNG IUS only
2. **Chronic hypertensives developing preeclampsia have a higher cardiac output as early as the end of the first trimester.**
   a. True
   b. False
3. **In addition to low-dose aspirin, what other oral medicines have been shown to prevent preeclampsia?**
   a. Vitamin C
   b. Vitamin E
   c. Standard adult dose of aspirin
   d. Calcium
   e. None of the above

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

[IN FUTURE ISSUES]

Trends in OB/GYN Malpractice Litigation