GYNECOLOGY

Depressive symptoms and risk of uterine leiomyomata

Lauren A. Wise, ScD; Se Li, PhD; Julie R. Palmer, ScD; Lynn Rosenberg, ScD

OBJECTIVE: Uterine leiomyomata (UL) are a major source of gynecologic morbidity and the primary indication for hysterectomy. Depression can cause dysregulation of the hypothalamic-pituitary-adrenal axis, which may affect the synthesis of reproductive hormones involved in UL pathogenesis. We assessed the association between depressive symptoms and UL among 15,963 premenopausal women.

STUDY DESIGN: Data were derived from the Black Women's Health Study, a prospective cohort study. In 1999 and 2005, the Center for Epidemiologic Studies Depression Scale (CES-D) was used to ascertain depressive symptoms. On biennial follow-up questionnaires from 1999 through 2011, women reported physician-diagnosed depression, antidepressant use, and UL diagnoses. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox regression.

RESULTS: There were 4722 incident UL cases diagnosed by ultrasound (n = 3793) or surgery (n = 929) during 131,262 person-years of follow-up. Relative to baseline CES-D scores <16, IRRs were 1.05 (95% CI, 0.98–1.13) for CES-D scores 16-24 and 1.16 (95% CI, 1.06–1.27) for CES-D scores ≥25 (*P*-trend = .001). IRRs for current and past physician-diagnosed depression relative to no depression were 1.15 (95% CI, 0.98–1.34) and 1.25 (95% CI, 1.13–1.39), respectively. Results persisted after further control for antidepressant use. IRRs for current and past use of antidepressants (any indication) relative to never use were 1.11 (95% CI, 0.97–1.28) and 1.32 (95% CI, 1.14–1.52), respectively.

CONCLUSION: In this cohort of black women, greater depressive symptoms were associated with UL, independent of antidepressant use, supporting the hypothesis that dysregulation of the hypothalamic-pituitary-adrenal axis increases UL risk.

Key words: African Americans, antidepressants, depressive symptoms, prospective studies, uterine neoplasms

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Uterine leiomyomata (UL) are clinically recognized in 30% of reproductive-aged women[1,2] and are a major contributor to gynecologic morbidity[3] and medical costs.[4] African American women are 2-3 times more likely to be diagnosed with UL than white women,[2] but established risk factors do not explain the racial disparity.[5] Sex steroid hormones are thought to influence UL pathogenesis.[6,7]

UL risk has been linked to greater exposure to psychosocial stress.[8] A cross-sectional study found a higher prevalence of UL among women reporting more major life events and greater "stress intensity."[9] In the Black Women's Health Study (BWHS), a prospective cohort study, perceived racism was positively associated with UL diagnoses.[10] In agreement with a previous cohort study of white women,[11] the BWHS documented a positive association between child sexual abuse and incident UL diagnoses.[12]

Major depressive disorder is the second leading cause of years of life lost due to premature mortality in the United States,[13] and the incidence in women is twice that of men.[14] Depression is more common in African Americans than in other ethnic groups in some[15-17] but not all[18-20] studies, and African Americans with depression are less likely to take antidepressant medications.[21,22] Studies limited only to those receiving medical treatment may miss an important segment of the African American population with depression.

A large body of clinical and basic research reports an association between dysregulation of hypothalamic-pituitary-adrenal (HPA) axis hormone dynamics and mood disorders such as depression.[23-25] HPA-axis abnormalities observed in depressed individuals include hypercortisolemia, as reflected by elevated levels of cortisol in plasma, cerebrospinal fluid, and 24-hour urine

From Slone Epidemiology Center, Boston University, Boston, MA.

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Corresponding author: Lauren A. Wise, ScD. lwise@bu.edu

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overall[26-28] and in response to psychological stress.[29] Lower levels of dehydroepiandrosterone sulfate (androgen precursor produced by adrenal gland) have also been reported among depressed patients.[30] Alterations in the HPA axis can cause dysregulation of the hypothalamic-pituitary-ovarian axis,[25] which may influence the synthesis of sex steroid hormones.[31-33] For instance, depressed women were found to have lower serum levels of estradiol but higher serum levels of progesterone compared with nondepressed women[25,34,35] and progesterone may have a stimulatory effect on UL.[7,36] Depressive symptoms can also deleteriously influence health-related behaviors, including sedentariness, alcohol consumption, and poor diet, all of which may increase UL risk.[37-40]

In a large cohort of African American women, we evaluated prospectively the association between depressive symptoms and UL risk, and the extent to which antidepressant use mediates this association.

Materials and Methods

Study population

The BWHS is an ongoing prospective cohort study of 59,000 African American women aged 21-69 years at baseline.[41] In 1995, subscribers of *Essence*—a magazine with a large African American female readership—were invited to enroll in a long-term health study by completing comprehensive self-administered baseline questionnaires. Biennial follow-up questionnaires update exposure and medical information; cohort retention was 80% through 2011. Participants reside in >17 states across the United States. The institutional review board of Boston University Medical Center approved the study protocol.

Assessment of depressive symptoms, diagnosed depression, and antidepressant use

The 1999 and 2005 follow-up questionnaires included the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), which was designed to assess depressive symptoms in community samples and population-based studies.[42] Respondents indicated the frequency of various feelings experienced during the previous week on a 4-point scale ranging from "rarely or none of the time" to "most or all of the time." The measure included items such as "I felt sad," "I felt lonely," "I felt depressed," and "I enjoyed life." Total scores ranged from 0-60, with higher scores indicating higher levels of depressive symptoms.

Women had the opportunity to report a clinical diagnosis of depression under an open-ended question about "other serious illness" in 1995, or under questions about "depression treated with medication" on biennial follow-up questionnaires from 1997 through 2009. Because African American women are less likely to take medication for depression than other populations,[21,22] we asked separately about "depression" and "depression treated with medication" in 2005 to capture clinically depressed women we may have missed in previous years. Year of first diagnosis was elicited on all questionnaires.

Users of antidepressant medications were defined as participants who reported using "medication for depression" in 1997; "antidepressants (Prozac, Zoloft, Elavil, etc.)" in 1999, 2001, 2003, or 2005; or antidepressants under "Please list all other medications or supplements that you currently take at least 3 days a week" (all years), regardless of the indication for use. The Slone Drug Dictionary was used to code medications.[43]

Assessment of UL

Incident cases were women who reported a first diagnosis of UL confirmed by ultrasound or surgery. Ultrasound has high sensitivity (99%) and specificity (91%) relative to histologic evidence.[44,45] On follow-up questionnaires, women reported whether they had been diagnosed with "uterine fibroids" in the previous 2-year interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by "pelvic exam" and/or by "ultrasound/hysterectomy" (1999 or 2001) or "ultrasound" and "surgery" (2003 or later). To maximize the specificity of UL classification, cases identified by pelvic exam only (N = 350) were treated as noncases.[46]

Assessment of covariates

On the 1995 and biennial follow-up questionnaires, we collected data on reproductive and contraceptive history, gynecologic surgeries, anthropometric factors, physical activity, smoking, alcohol consumption, geographic region of residence, socioeconomic correlates (education, marital status, occupation), medical conditions, and Pap smear frequency. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. We estimated total metabolic equivalents (METs) per week by summing the METs from moderate physical activity (hours/wk × 3.5) and vigorous exercise (hours/wk × 7.0).[47] In 2003, women reported their household income. In 2007, participants reported their recency of pelvic exam (never, <5, 5-9, ≥10 years ago) and pelvic ultrasound (never, <5, 5-9, ≥10 years ago). In 2005, participants completed the 10-item Carver coping scale,[48] with higher scores indicating higher coping skills.

Validation studies

Uterine leiomyomata

We mailed supplemental questionnaires to a random sample of 248 cases and requested permission to review their medical records. We corroborated the self-report in 122 (96%) of 126 women from whom we received medical records. Most cases (87%) reported that their condition came to clinical attention because they sought treatment for symptoms or a tumor was palpable during a routine pelvic exam. Details about the validation study may be found elsewhere.[49]

Depressive symptoms

The validity and reliability of the CES-D have been documented in several populations,[15,42,50-53] including the BWHS.[54,55] In the BWHS, factor analysis indicated that the 4-factor structure of the CES-D was supported,[54,55] and Cronbach alphas demonstrated high internal consistency of the CES-D responses.[55]

Restriction criteria

Of the 22,284 BWHS premenopausal participants at baseline who had never been diagnosed with UL, we excluded