Study of Environment Lifestyle and Fibroids (SELF): Advancing the Field of Fibroid Epidemiology

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IN THIS ISSUE OF THE *Journal of Women's Health*, Dr. Donna Baird and colleagues report on the methods, recruitment, and participant characteristics of the *Study of Environment Lifestyle and Fibroids (SELF)*,¹ a groundbreaking epidemiologic study of uterine leiomyoma (UL). UL are benign hormone-dependent neoplasms arising from smooth muscle cells of the myometrium and are clinically recognized in approximately 30% of reproductive-aged women.^{2–5} Although a large proportion of UL are asymptomatic,⁵ UL can cause severe reproductive morbidity such as menorrhagia, infertility, and pregnancy complications, and they remain the primary indication for hysterectomy in the United States (U.S.).^{3,4,6,7} The annual direct and indirect costs of UL in the U.S. are approximately \$34.4 billion, with \$9.4 billion attributed to health care costs.⁸ For reasons that remain poorly understood, black women have two to three times the UL incidence of white women, earlier disease onset, and greater symptomatology.^{5,6,9} Established risk factors do not explain the racial disparity.^{6,9,10}

Until recently, classification of UL in epidemiologic studies relied on self-reported diagnostic history, medical records, or hospital discharge databases.^{3,6,9,11–13} Most studies were restricted to cases with a clinical diagnosis or cases presenting for myomectomy or hysterectomy. Such cases generally represent the symptomatic end of the disease spectrum. Thus, epidemiologic studies based on such cases may identify risk factors operating late in the growth and development of the tumors, making it challenging to clarify the natural history of UL and options for early intervention.¹⁴

Ultrasound screening studies like SELF, in which all participants are screened for the presence of UL, represent a major advancement in UL research.^{5,15–20} This is because UL can go undiagnosed for years prior to symptom occurrence.⁵ The exclusion of subclinical asymptomatic UL cases from the non-case group decreases attenuation of associations by misclassification of UL status. Ultrasound is an ideal method for detecting UL in epidemiologic studies because it has high sensitivity and specificity relative to histologic evidence,^{21,22} and can detect tumors larger than 0.5 cm.¹⁵ It also is less invasive and less expensive than other types of diagnostic imaging (e.g., Magnetic Resonance Imaging).²³

Until the creation of SELF, ultrasound screening studies had been cross-sectional in design.^{5,15–20} Such studies provided valid data regarding UL prevalence, but they were

unable to identify the actual time of UL onset for undiagnosed subclinical UL. SELF is the first ultrasound study to follow UL-free women prospectively to detect the new onset of UL and their growth over time.

SELF overcomes several methodological limitations of previous studies. In this community-based prospective cohort study of 1,300 African American women aged 23–34 years at baseline, comprehensive questionnaire data are collected at baseline and participants are followed for 5 years. Every 20 months, blood and urine are collected, and transvaginal ultrasounds are performed by trained sonographers.¹⁹ Because SELF collects all covariate data before the occurrence of UL, reverse causation and differential reporting biases are minimized. The wealth of environmental, biomarker, and genetic data collected allows control for a wide range of potential confounders and the exploration of effect measure modification. SELF's focus on black women is a key strength, given black women are disproportionately higher risk for UL,^{5,6} have greater exposure to established or putative risk factors,^{24–29} and are traditionally underrepresented in clinical research. The focus on younger women is important because of the high prevalence of UL in reproductive-aged women. For instance, the NIEHS Uterine Fibroid Study reported that a large proportion of randomly-selected women aged 35–49 from a health plan without a previous UL diagnosis already had ultrasound evidence of UL.⁵ Enrollment of a younger age cohort ensures a smaller proportion of women will have UL at entry and that new tumor onset can be evaluated. Even in SELF, with a much younger age range (23–34 years), 22% of women without a previous UL diagnosis had ultrasound evidence of UL at baseline. This illustrates the importance of enrolling younger women into UL studies. SELF can also assess determinants of tumor characteristics (e.g., size, number, and location). For example, certain exposures are more strongly associated with tumor size³⁰ or number,³¹ than with incidence. Repeated measurement of biospecimens permits state-of-the-art analyses of highly variable, non-persistent endocrine-disrupting chemicals (e.g., phthalates and phenols).^{32,33} SELF also creates new opportunities to examine modifiable risk factors for UL symptom management once UL have already been diagnosed. There are limited data to guide women with symptomatic UL about non-invasive lifestyle or behavioral modifications that can effectively

manage or reduce symptoms. SELF is optimally designed to be able to answer these questions.

In summary, Dr. Baird's study advances the field in UL epidemiology in addressing the important limitations of previous studies. SELF has remarkable potential to identify determinants of the racial disparity in UL risk (*e.g.*, vitamin D deficiency, environmental toxicants) and to provide critical data on UL etiology and symptom management to the public, scientific community, and policy makers. With the establishment of SELF, the field of UL epidemiology takes an important step toward understanding the underlying causes of a significant public health problem for women.

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