The epidemiology of uterine fibroids: Where do we go from here?

Uterine leiomyoma, commonly called uterine fibroids, are nonmalignant tumors composed of smooth muscle cells and fibroblasts. Fibroids are the most common pelvic tumors in women of reproductive age, affecting 1 in 4 adult women. Fibroids are the primary cause of hysterectomies in the United States and are a leading cause of hospitalizations for gynecologic conditions unrelated to pregnancy. Fibroid symptoms and consequences include infertility, pelvic pain, heavy or prolonged bleeding, anemia, and adverse pregnancy outcomes—resulting in significant impacts on quality of life. Individual and societal costs of fibroids include lost work and healthcare costs: surgery, hospital admissions, outpatient visits, and medications. Black women suffer disproportionately from fibroids, with fibroid prevalence 2–3 times that seen in White women.

In this issue of *Fertility and Sterility*, Bernardi et al. (1) use cross-sectional data from the Study of Environment, Lifestyle, and Fibroids (SELF) to examine the association between fibroids and the anti-Müllerian hormone (AMH) levels. Multiple fibroid characteristics (i.e., number, size, type, and position) were examined, and no significant associations were observed between fibroids and the AMH levels. The mean AMH concentrations decreased with the increasing number of fibroids, but this trend did not reach statistical significance despite the largest sample to date to examine this association (n = 362 fibroid cases). While this analysis provides some reassurance that fibroids in younger women do not have a strong influence on ovarian reserves as measured with AMH, it also highlights methodological challenges that impact fibroid research.

The SELF is the most rigorously designed epidemiologic study to date focused on fibroids. The use of repeated ultrasound screenings to identify new-onset fibroid cases, combined with excluding women diagnosed with fibroids before study enrollment and focusing on recruitment of younger participants (aged 23–34 years at baseline), makes the SELF an ideal study for examining the natural history of fibroids and their sequelae. In addition, the SELF was confined to self-identified Black women, the population group among whom fibroids are a major cause of morbidity.

A challenge inherent in all studies in this field is the difficulty in defining fibroids. Without serial ultrasounds, the exact onset of this condition cannot be determined at present. A US-based cross-sectional study demonstrated that 43%–59% of premenopausal women aged 35–49 years have undiagnosed fibroids (2). The SELF addressed this challenge by identifying fibroid cases early in development and ensuring a fibroid-free comparison group. This resulted in many of the fibroids identified being asymptomatic. For instance, only 10.8% of participants with fibroids compared with 11.6% of those without fibroids reported abnormal menstrual bleeding, which would be expected to occur more commonly in women with fibroids (1). Thus, while this study was well designed to answer the question of whether newly diagnosed fibroids in early reproductive years impact the AMH levels, the extension of its results to women with symptomatic fibroids or later in their reproductive years is unknown. Future analyses in the SELF may consider using blood samples collected during follow-up visits to examine changes in the AMH concentrations over time among women who had newly diagnosed fibroids.

Other epidemiologic approaches to studying fibroids have also had some success. Two large prospective cohorts that have contributed extensively to fibroid knowledge are the Black Women's Health Study (BWHS) (3), comprised of Black women, and the Nurses' Health Study II (NHSII), comprised primarily of White women (4). These studies have the benefit of decades of follow-up, with over 6,000 self-reported, clinically diagnosed fibroids in each cohort, but they are limited by the misclassification of fibroid case status because some women will have undiagnosed fibroids. The presence of undiagnosed fibroids usually leads to bias toward the null (i.e., reduces the probability of observing associations rather than generating false-positive associations). Nonetheless, the results from cohorts that do not identify undiagnosed fibroids can provide critical information about clinically relevant fibroids, which contribute the most to the individual and societal costs of fibroids. Consistent with this, in the BWHS and NHSII validation studies, most women who reported a diagnosis of fibroids reported substantial clinical symptoms (e.g., menorrhagia, heavy bleeding, and pelvic pain). However, despite multiple assessments of a variety of potential risk factors, these studies have not elucidated reasons for the racial disparity in incidence.

Examining the etiology and consequences of fibroids across varying study designs (e.g., ultrasound studies that follow fibroid-free women [SELF] and prospective cohorts with self-report ultrasound-/hysterectomy-confirmed fibroids [BWHS/NHSII]) is critical to advancing our understanding of fibroid incidence, growth/regression, and sequelae. Some risk factors may more strongly impact fibroid size and/or number, whereas others may impact age at fibroid onset. Conversely, some factors may have impacts across the fibroid continuum. For example, despite the BWHS identifying fibroids at an older age of onset than the SELF and using different fibroid identification methods, the BWHS and SELF found very similar associations between dietary intake of marine fatty acids and fibroid development (3, 5).

Looking forward, in regard to existing prospective cohorts with their wealth of fibroid cases, analytic methods to correct for unmeasured fibroids and assess their influence on observed associations are critical. In addition, lessons can be learned from another debilitating gynecologic condition, endometriosis, where data collection tools have been harmonized for use in studies across the globe through the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project. Support for this type of collaborative effort in the fibroid research

community would allow for collecting and harmonizing data on the full range of fibroid heterogeneity, a necessary step to advancing the field of fibroid epidemiology. None of this is possible without research funding. Fibroid research has been underfunded for decades, despite the extensive morbidity caused by this condition. Part of the explanation may be that mixed disease study sections tend to place more importance on studying diseases that result in death, thus penalizing fibroid research with poorer scores for certain review criteria (e.g., significance). This may be exacerbated by the methodological complexities inherent in the population-based studies of fibroids that are not always understood by nonepidemiologists. Given the high population prevalence, medical and economic burdens, and absence of known modifiable risk factors, prioritizing research on fibroids has the potential to dramatically impact and improve the lives of women, especially Black women who experience a disproportionate burden of fibroid sequelae.

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