The burden of uterine fibroids: a search for primary and secondary prevention

Uterine leiomyomas, or uterine fibroids, are not only common, they also impose a tremendous burden on women who experience the symptoms related to fibroids. Pain, heavy bleeding, and fatigue are common symptoms and affect multiple domains of personal well-being and work productivity (1). Based on screening studies, the cumulative incidence of fibroids by the age of 50 years is nearly 70% among white women and exceeds 80% among black women (2). Not all women with fibroids, however, come to medical attention. Many fibroids are asymptomatic and remain undiagnosed unless identified as an incidental finding. Women may also have symptoms consistent with fibroids and remain undiagnosed because of health insurance status, barriers to health care access, or perception of symptoms as "normal." Many existing treatment options for the symptoms of fibroids can limit a woman's future reproduction. The higher cumulative incidence among black women is due, in part, to an earlier age of fibroid development (2). The earlier onset of disease in black women results in a high burden of symptomatic disease during the reproductive ages. Despite the high burden of disease and the ramifications of existing treatment options, research into modifiable risk factors for fibroids has historically been limited.

The natural history of fibroids offers multiple points of possible intervention. After initial development, fibroids vary in their rate of growth and the degree and speed at which they become symptomatic and require treatment. Although reducing the initiation of tumors might be the ideal (primary prevention), limiting the growth of small fibroids and avoiding symptoms (secondary prevention) would reduce the burden of disease immensely.

The high prevalence of undiagnosed fibroids creates challenges for studying this outcome in human populations. Cross-sectional, retrospective, and case-control studies that rely on self-reported or clinically diagnosed fibroids capture only prevalent, mostly symptomatic, fibroids. Many of the women with no clinical diagnosis of fibroids (control or disease-free groups) will in fact have fibroids evident on ultrasound. Case-control and cross-sectional studies can rarely establish whether the exposure of interest was present before fibroid development. Nor can these studies distinguish between exposures that influence initiation or growth and exposures that influence symptoms and clinical diagnosis. Given the frequent delay between symptom onset and diagnosis (1), numerous behavioral and environmental exposures may have changed by the time a diagnosis is made. Prospective studies with regular exposure assessment and frequent imaging are expensive but they are essential to identify modifiable risk factors for both initiation and growth of these tumors.

Given the limited number of identified modifiable risk factors, the study in this issue by Zota et al. (3) is an example of research that can move the field forward by identifying plausible modifiable exposures that warrant further investigation in larger cohorts. Phthalates are a ubiquitous exposure that are potentially modifiable through behavior modification or industry elimination from common products. Zota et al. note interesting differences in measured phthalate exposure by race/ethnicity, highlighting the plausibility that exposure to phthalates can be modified. With the use of a small clinical sample that only included cases, Zota et al. find an association between concentrations of specific high-molecular-weight phthalates and antiandrogenic phthalates and total uterine size. This finding suggests that phthalates may be associated with fibroid growth or number, both of which are integrated in the measure of uterine volume.

The Zota et al. study is not without limitations, most of which are acknowledged. As a case-only analysis, this study could not detect associations with fibroid initiation, only differences in fibroid burden among women seeking surgical treatment. If phthalates are associated with fibroid growth or the severity of symptoms, this would offer a point of intervention to delay progression for women with small fibroids or few symptoms. Despite the finding concerning uterine volume, the study did not see an association with fibroid size. The lack of an association with fibroid size may be due to the use of a single measure of the largest recorded fibroid dimension. This single measure will misclassify women with a high burden of disease due to multiple small or medium-size fibroids. On the other hand, women with larger uterine volume may be more likely to have comorbid adenomyosis, a condition which may prompt surgical intervention to treat symptoms even with smaller fibroids (4). This study could not rule out the possibility that the observed association is a result of adenomyosis or other hormone-dependent comorbid condition.

Despite these limitations, the study presents a persuasive observation that warrants further exploration in a larger cohort with prospective growth data and repeated sampling of phthalates. High-molecular-weight and antiandrogenic phthalates are found in a broad range of consumer and personal care products. These products contain a wide assortment of other compounds, resulting in individual exposure to complex chemical mixtures. Future work should consider mixture models (5) that accommodate the presence of multiple correlated biomarkers from similar compounds (e.g., phthalates) and from diverse compounds with potential endocrine-disrupting activity (phthalates, bisphenol A, and parabens which may be present in personal care products).

Fibroids result in a high burden of disease, and research has been slow to identify potential prevention and intervention options to improve or avoid symptoms while preserving the full range of reproductive options. Fibroids may be difficult to study, but rigorous and innovative research has the potential to mitigate the significant burden of this disease.

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