Invited Commentary: Uterine Leiomyomata—We Know So Little but Could Learn So Much

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Uterine leiomyomata, commonly called fibroids, are the leading cause of hysterectomy in the United States (1), yet as of a decade ago, there had been virtually no US study of this condition. Earlier studies in Italy (2) and Britain (3) had included only surgical cases, a highly selected case sample since many women with fibroids do not elect to have surgery. Thus, it is not surprising that there are few clearly established risk factors for fibroids. The new report from the Black Women’s Health Study is an important contribution (4), complementing the previous reports from the Nurses’ Health Study (5–7), which included mostly White women.

The clearly established risk factors are age (increasing risk with increasing premenopausal age), menopause (risk decreases with menopause), and African-American ethnicity (higher risk compared with that of non-Hispanic Whites). There is still no adequate explanation for the higher risk among African Americans. The estimated cumulative incidence remained significantly higher for African Americans after controlling for parity and body mass index in an ultrasound screening study (8). The new report from the Black Women’s Health Study cohort focuses on age of menarche, pregnancy history, and hormonal contraceptive use.

Age of menarche

Given the new findings from the Black Women’s Health Study cohort, early menarche can now be added to the list of established risk factors. Menarche at or before the age of 11 years was associated with a 25 percent increase in risk compared with menarche at the ages of 12 and 13 years, the same magnitude of effect as reported for women in the Nurses’ Health Study (5–7). In both studies, the risk also continued to decrease as the age of menarche increased. The decreased risk is probably not just a function of fewer years of menstrual cycling. If that were the mechanism, one would expect to see factors that interrupt cycling, such as breast-feeding and each additional birth after the first, contributing to incremental decreases in risk. However, this pattern was not found.

So, why might early age of menarche be a risk factor for uterine fibroids? Perhaps early menarche and uterine fibroids share causal pathways. If that is the case, there are other hypotheses that would be ripe for exploration. Increased prepubertal weight is a strong risk factor for early menarche (9), and exercise can delay it (10). Perhaps childhood obesity or exercise is also related to fibroid development. Girls who have early menarche have been reported to move through the stages of puberty faster than girls with later menarche (11). This difference may reflect enhanced tissue sensitivity to hormones and/or suppressed feedback controls of steroid production. Are these biologic differences seen in women with fibroids? Low birth weight or small-for-gestational-age birth weight has been associated with early menarche (12, 13). Perhaps prenatal development could influence susceptibility to fibroids as well. Early exposure to diethylstilbestrol increases uterine fibroid incidence in experimentally treated mice (14), demonstrating the plausibility of prenatal factors in fibroid development. Understanding more about why early menarche is associated with increased risk of fibroids may provide critical information for prevention or the basis for designing a highly focused experimental study.

Parity

Parity appeared to protect against uterine fibroids in the Black Women’s Health Study cohort, findings very similar to those reported for the Nurses’ Health Study (6). Although a protective effect of parity has been found in other studies as well (15–21), this association remains difficult to interpret because of potential bias. In studies of surgically diagnosed fibroids (primarily hysterectomy cases), this relation can arise from selection bias: Women who have their desired children are more likely candidates for hysterectomy than are women who still want children.

There has also been concern about reverse causation: Fibroids may cause infertility before they are diagnosed. If fibroids are diagnosed at a later date in those infertile...
women, it will appear that nulliparous women are at high risk of fibroids and that parity is protective. This bias was examined in both of the prospective cohort studies and could not account for their findings; the parity effect remained after the exclusion of women with fertility problems (4, 6).

However, a new bias can arise in prospective cohort studies because parous women with fibroids may be selectively excluded from these studies. The cohort studies rely on clinical diagnosis to define women with fibroids. Both incidental diagnoses made during general medical care and diagnoses made while investigating a problem are accepted. Women with prior diagnoses are excluded at baseline. Unfortunately, since undiagnosed fibroids are common, only a subset of the women who have fibroids at baseline will be excluded by excluding women with a prior diagnosis. Nearly all women with a prior pregnancy will have had an ultrasound examination during that pregnancy. Fibroids found at that time will be diagnosed incidentally, and like other women who have already been diagnosed at baseline, these women will be excluded from analysis. That is, women included in the prospective study who have had a past pregnancy would have had a prior screening for fibroids, and only those without fibroids would be included in the analysis. Thus, pregnancy could appear protective and the most recent pregnancies will be most protective. Both the Nurses’ Health Study and the Black Women’s Health Study found more protection from recent pregnancies, with little protective effect seen after 10 years. Miscarriages and abortions usually occur before the standard ultrasound examination, so these would not be expected to appear protective. Consistent with this hypothesized bias, these pregnancies were not inversely associated with fibroids in the prospective studies.

Still, the observed association between parity and uterine fibroids is probably not due entirely to bias. Parity reduced fibroid development dramatically in the Eker rat model of fibroids (22). In addition, we found that parity was protective in the National Institute of Environmental Health Sciences’ Uterine Fibroid Study, a study in which participants were screened for fibroids with pelvic ultrasound and the size of fibroid was analyzed. The protective effect varied with the age at delivery, as predicted by a prior hypothesis (23, 24). We had hypothesized that the protective effect of parity was due to apoptosis in small fibroids during uterine remodeling after delivery. Unbiased evidence of a protective effect for parity awaits a prospective incidence study in which cases are identified by ultrasound screening (see below).

**Hormonal contraception**

Oral contraceptive use was generally not associated with fibroids in the Black Women’s Health Study cohort, and findings from other studies have been inconsistent. However, it is worrisome that both the Black Women’s Health Study cohort and the Nurses’ Health Study cohort found increased risk among women who began oral contraceptive use as teenagers (4, 6). This observation needs to be explored in greater depth. Early use of oral contraceptives also reflects early sexual activity and, thus, potential for higher risk of sexually transmitted diseases. The infection hypothesis for fibroid etiology was raised in 1999 (25) and has only begun to be explored (26).

The protective effect of the injectable contraceptive, depot medroxyprogesterone acetate, reported for the Black Women’s Health Study cohort was consistent with findings from a study in Thailand (17). A progestin-releasing intrauterine device has also been shown to reduce risk (27). Prior studies were based on surgical cases of fibroids, so this is an important confirmation and extension of the previous research. The injectable birth control is problematic for some women because of concerns with adverse side effects on bone (28) and acute side effects of bleeding (29). However, understanding the biologic basis of the protective effect, if one truly exists, may suggest other protective treatments.

**Future research strategies**

There is much to be learned from epidemiologic study of uterine fibroids. Currently, so little is known that almost any new report contributes to the field. However, study design matters. A study of actual incidence (rather than clinical diagnosis) would be very valuable. A prospective incidence study is possible because small fibroids can be detected noninvasively with ultrasound, and the condition is common enough so that sufficient numbers of cases would arise over a reasonable time interval within a relatively small cohort. Fibroid growth could also be monitored for many of the participants because treatment is not recommended if the tumors are asymptomatic. Screening a cohort of 1,000 women in their mid-to-late twenties with follow-up ultrasound examinations every 2 years would provide invaluable information.

There are also less intensive designs that help deal with potential bias associated with the selectivity of clinical diagnoses of fibroids. Undiagnosed fibroids become more common with increasing premenopausal age. Thus, if the cases are defined by clinical diagnosis, limiting the study to young women can limit bias. One of many helpful sensitivity analyses described in the new report from the Black Women’s Health Study was the reanalysis among women under the age of 35 years. In this group, the number of undiagnosed cases will be fewer than in the older women, so the findings are more likely to be valid. However, analyses may need to be limited to an even younger group. We estimated that the cumulative incidence of fibroids in Black women exceeded 60 percent by the age of 35 years (8). Of course, the drawback of focusing on young women is that differences between age groups cannot be assessed.

Another consequence of undiagnosed fibroids is that there is enormous heterogeneity in tumor size among newly detected cases. The diameter of the largest tumor at the time of ultrasound screening in the National Institute of Environmental Health Sciences’ Uterine Fibroid Study varied from less than 1 cm to more than 6 cm among women who had had no previous diagnosis (8). A possible design that would allow researchers to take fibroid size into account would be to ask women who have been diagnosed with fibroids about the size of their largest fibroid and then to use these data on size as the outcome measure. Examining this outcome among prevalent cases of fibroids (not just newly diagnosed
cases) for samples of relatively young women would be informative. We investigated the validity of self-report of fibroid size (unpublished data) and found that there was a reasonable correlation between the self-reported size and the size found at ultrasound.

Another aspect of study design that is critical in future fibroid research is creative exploration of diverse exposures, including those outside the hormone box. One approach to setting priorities for exposure assessment is to follow the leads of researchers studying other hormonally influenced tumors. Another is to take advantage of geographic and ethnic variation. An ultrasound screening study in Sweden found a much lower prevalence of fibroids in that population than in US Whites (30), and US Blacks have even higher prevalence figures. Studying factors that might plausibly account for such differences would be important. Finally, one of the most productive strategies may be to develop collaborative work with laboratory researchers so that exposures can be tested in animal models and biologic changes in human uterine tissue can be examined. Although prevention may be the ultimate goal, efforts to increase the range of tools for medical management could reduce morbidity and might eliminate most of the surgeries for fibroids occurring in the United States today.

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**REFERENCES**