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Childhood Abuse and Fibroids

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There is growing evidence that adults who have experienced childhood abuse are more likely to have health problems than those without these experiences. Sequelae can be behavioral (e.g., substance abuse), mental-health-related (e.g., depression), as well as physical-health-related (e.g., cardiovascular disease).¹⁻⁴ The public health consequences are sobering given the numbers exposed. Even with probable under-reporting, prevalence estimates from the U.S. and Europe exceed 25%.^{2, 5} Adverse sequelae may be mitigated by social support and healthy coping.⁶ In this issue Boynton-Jarrett et al.⁷ add uterine leiomyoma (fibroids) to the list of possible adverse outcomes associated with childhood abuse. They also find a tendency for an emotionally-supportive relationship to mitigate these effects.

As Boynton-Jarrett and colleagues⁷ point out, fibroids are a major public-health issue. Fibroids have been the leading indication for hysterectomy in the U.S. for decades.^{8,9} Costs for both inpatient and outpatient medical management of fibroid-associated symptoms are high.^{10,11} The direct morbidity burdens fall on symptomatic women.

Though still in its early stages, epidemiologic research on fibroids has made major advances in the last two decades. This is due largely to a shift from study of surgical cases (which include only small, non-representative subsamples of all women with fibroids) to studies that screen women with ultrasound, or studies such as the Nurses' Health Study and the Black Women's Health Study that prospectively identify incident cases based on self-reported clinical diagnoses.

Newer studies still have limitations. The primary limitation of the large prospective cohort studies is misclassification of case status. Many women with fibroids are not clinically diagnosed. This occurs even if diagnoses are reported accurately and the diagnostic tools for detection of disease are valid—as has been demonstrated for ultrasound diagnosis of fibroids.¹² Ultrasound screening in premenopausal women aged 35-49 years who had never been diagnosed with fibroids revealed fibroids in 51%.¹³ Nearly all diagnosed women are a

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mix of those who sought care for symptoms and those discovered to have fibroids during a routine examination. The former are more likely to have severe disease; the latter are more likely to have mild disease. However, undiagnosed cases cannot be assumed to have more mild disease, because even women with severe disease may tolerate the symptoms. In one study that screened for fibroids, diagnosed and undiagnosed cases were equally likely to have symptoms of bleeding, after adjustment for fibroid size.¹⁴

How might such outcome misclassification affect the association reported by Boynton-Jarrett et al.⁷? Several studies have linked history of abuse with chronic pelvic pain¹⁵ and increased health-care utilization.¹⁶ Women with a history of abuse may be more likely to have ultrasound examinations and thus increased fibroid diagnoses, even if the history of abuse had no real etiologic relationship with fibroid development. Control for recent pelvic exam would not control for differential referral for ultrasound.

Another concern is potential selection bias from the standard prospective—cohort analysis strategy of excluding women with previously-diagnosed fibroids at baseline.

Women with early onset will tend to be over-represented in the excluded group. It would have been interesting to see results from an analysis of the prevalent cases at the beginning of follow-up, or to see whether the association in the prospective analysis was stronger for diagnoses by age 35 (early onset). The latter analytic strategy has been used in other investigations of risk factors for fibroids using prospective cohort data.¹⁷

Boynton-Jarrett and colleagues⁷ are the first to report increased risk of fibroids for women who experience early-life abuse, but other reports^{18, 19} have suggested a possible association between stress and fibroid development, and these bolster the plausibility of the findings reported in this issue. A recent cross-sectional study¹⁸ found a positive association between fibroid prevalence and the number of major life events, as well as “stress intensity.” In the Black Women's Health Study, perceived racial discrimination, (a chronic stressor) was positively associated with fibroid risk. The association was weaker among women with higher coping skills,¹⁹ suggesting that social and emotional support may buffer the impact of stress on fibroid risk. This is similar to the effect of an emotionally-supportive relationship in childhood found by Boynton-Jarrett et al.

New research on epigenetic changes shows that early-life exposures can have long-term functional affects.²⁰ Ongoing stress could also be important. The hormones estrogen and progesterone are mediators of fibroid development.^{21, 22} In the classic fight/flight response, stress can down-regulate the hypothalamic/pituitary support of ovarian steroids, but stress can also up-regulate adrenal progesterone.^{23, 24} Stress-related increases in progesterone have been demonstrated in Cebus monkeys²⁵ and in an experimental study of postmenopausal women.²⁴ Granulosa-cell tissue-culture studies suggest that there may also be situations in which ovarian steroid secretion is increased rather than decreased.²⁶ Moreover, various growth factors, cytokines, and matrix metalloproteinases involved in fibroid growth can be upregulated by stress hormones.^{23, 24} Stress can also lead to adverse health-related behaviors, such as physical inactivity, heavy alcohol consumption, and poor eating habits, and these may increase fibroid development.²⁷

Though not yet available, non-invasive medical treatments for fibroids are under development. When they become available, they are likely to be most effective early in the disease process. Identifying high-risk groups for systematic ultrasound screening will be important. Future fibroid research must provide this guidance. The two large cohort studies that have provided much new knowledge of fibroid epidemiology (the Nurses' Health Study and the Black Women's Health Study) will be aging out of fibroid research in the next decade. Their youngest participants are now 46 and 36, respectively. Many participants are already postmenopausal, a time when fibroids tend to shrink. Perhaps the mothers in the large pregnancy cohorts in the U.S. and Europe could be tapped for fibroid research. As women's children are followed, the health of the mothers could also be followed. Outcome data collection in large prospective-cohort studies can easily include clinical diagnosis (yes/no) and type of diagnosis (ultrasound, surgery, or pelvic exam), as well as a question about the circumstances of diagnosis (seeking help for symptoms vs. findings at routine health exam), as is currently being done in the Black Women's Health Study. Finally, it is time for a prospective study that recruits young women before they begin to develop fibroids. Periodic ultrasound screening during follow-up can then identify cases closer to the time of true disease onset. Data from these future studies will shed further light on the relationship of childhood abuse and uterine fibroid development, and the mechanisms by which such an association might arise.

Biographies

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