

We found a consistent association of fibroids with three indicators of low socioeconomic status during childhood (low household education, food insecurity, and poverty). These factors may influence development of fibroids through changes in methylation patterns in childhood that persist and affect gene expression as adults. Plausibility of this hypothesis is based on animal and human data on early-life neglect or abuse. Different methylation patterns within the hippocampus of adult rats were detected based on whether they received maternal care early in life (Weaver et al. 2004). In a small sample of adult men who committed suicide, methylation patterns in similar genes in the hippocampus varied based on whether they were abused during childhood (McGowan et al. 2009). Whether being exposed to low socioeconomic conditions during childhood can affect methylation patterns in genes relevant to fibroid pathogenesis needs further investigation.

We also found a strong association with fibroids for being born at least 1 month before mother's due date. A weak association with low birth weight was no longer present after excluding women who were born at least 1 month early. Because levels of estrogen and progesterone rise throughout pregnancy, one hypothesis is that women who are born early are deprived of the estrogen needed for full differentiation of their reproductive system (Trotter and Pohlandt 2000). Our analyses were limited by having only 60% of women who reported gestational age at birth. Missing data may be related to the true values of gestational age or other birth-related variables, but results were similar when we repeated the analyses assuming women missing gestational age data were not born ≥ 2 weeks early (data not shown).

Selection bias is a potential limitation for other exposures as well, given that the proportion of missing values was as high as 20%. There were slight differences in the proportion with fibroids based on whether exposures were missing, with generally more women reporting fibroids among those with missing responses. Based on the assumption that women with missing data for rare exposures (preeclampsia, pregnancy-related hypertension, soy formula, DES use, prepregnancy diabetes, and gestational diabetes) were likely to be unexposed, we repeated analyses in which we considered women with missing values for these factors as unexposed. However, changes in RR estimates were minimal (data not shown).

There is also the potential for misclassification of exposures given that women were reporting exposures during infancy and related to their mother's pregnancy. However, women were provided phone cards to encourage them to ask these questions directly of their mothers, and we excluded older women (> 59 years)

who would be less likely to have living mothers to ask about these exposures. In addition, response categories for many of the exposures included options of "definite" and "probable" that allowed for uncertainty in reporting. Associations with fibroids were generally consistent for definite and probable exposure, except associations with *in utero* DES exposure and maternal gestational diabetes, for which associations were much stronger with reporting probable exposure. Because none of these exposures is known to be related to fibroids, exposure misclassification would likely be nondifferential, which would generally result in RR estimates biased toward the null.

Our assessment of fibroid diagnoses was based exclusively on self-report. However, because fibroid incidence increases strongly with age, we only considered diagnoses by 35 years of age to reduce misclassification in the noncase group. Our estimated risk of 8% for early diagnosis of fibroids was similar to the risk of 11% for self-reported fibroids by 35 years of age in white women (35–49 years of age) from the NIEHS Uterine Fibroid Study (Baird DD, unpublished observations). We also reported a substantially greater proportion of women with early diagnosis of fibroids having hysterectomies compared with women without early diagnosis, which suggests that many of the women with fibroid diagnoses included in our case definition had fibroid-related morbidity. However, we do not have information on fibroid-related symptoms at time of diagnosis. We also excluded older women from our analyses because of possible secular differences in use of ultrasounds for fibroid diagnoses. Because studied factors may also be related to fibroids diagnosed later in life, including women with fibroids diagnosed after 35 years of age as noncases may have resulted in an underestimation of RRs. However, repeating our analyses after exclusion of women with later diagnoses of fibroids (> 35 years) from the noncase group did not affect RR estimates with early diagnosis of fibroids for four of our main findings (maternal prepregnancy diabetes, soy formula, low childhood socioeconomic status, and being born at least 1 month early (data not shown)).

Strengths of this study include a large sample size, which allowed us to examine associations with rare intrauterine and early-life exposures. We adjusted for factors that may affect recall of exposures, including participant's age and education. In addition, despite the potential for misclassification bias from self-reported exposure information and fibroid diagnoses, we observed expected associations between specific factors, including a positive association between early age at menarche and fibroids and an increased reporting of maternal preeclampsia among firstborn women and those from a multiple birth (data not shown).

Conclusions

Our study suggests that being fed with soy formula during infancy, having a mother with prepregnancy diabetes, being born at least 1 month early, and growing up with low socioeconomic conditions may increase the development of fibroids in early adulthood. This is the first study to explore these early-life and childhood factors in relation to the risk of fibroids. There are plausible biological mechanisms by which these factors could affect uterine physiology later in life and thus increase risk of fibroid development. Replication of findings in other populations including higher risk groups such as African Americans is needed.

CORRECTION

In Table 1, the values for body mass index were incorrect in the manuscript originally published online. They have been corrected here.

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