Why is Parity Protective for Uterine Fibroids?

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Abstract: Uterine fibroids are benign tumors, the etiology of which is not understood. Symptoms can be debilitating, and the primary treatment is surgery, usually hysterectomy. Epidemiologic data show that pregnancy is associated with reduced risk of fibroids. We hypothesize that this association is attributable to a protective effect of postpartum involution of the uterus. After each pregnancy the uterus rapidly returns to prepregnancy size by dramatic remodeling of the tissue. We hypothesize that small fibroids are eliminated during this process. We present preliminary epidemiologic evidence that is consistent with this hypothesis. If the hypothesis is supported by more direct evidence, it may have broader implications, supporting the idea that tissue remodeling may be a general mechanism for limiting tumor development.
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Key words: uterine leiomyoma, pregnancy, involution, tissue remodeling, tumor regression.

Uterine leiomyomas, commonly known as fibroids, are the leading cause of hysterectomy in the United States.[1] Symptoms include pelvic pain, infertility, pregnancy complications and excessive uterine bleeding that can lead to anemia.[2–4] These tumors are of smooth muscle origin.[5] Multiple tumors in the same uterus are often found,[2] and each is clonally distinct.[6,7] Fibroids are dependent on ovarian hormones. They are diagnosed only after menarche,[8] and they decline after menopause.[9,10] Other etiologic factors are largely unknown.

Given the hormonal dependence of the tumors, one might expect that pregnancy with its high circulating estrogen and progesterone levels would promote tumor growth. However, the few studies that have followed fibroids during pregnancy report that most fibroids neither grow nor shrink during pregnancy.[11–15] Furthermore, nearly all epidemiologic studies of fibroids report an inverse association between parity and fibroids, suggestive of a protective effect.[9,16–24] This relation is not explained by infertility among women with fibroids.[18] The two studies that did not find an inverse association[25,26] have limitations that may have affected the parity results. In the first study,[25] colinearity between race and parity may have obscured an inverse association. In the second,[26] parity was substantially associated with reduced risk of fibroids in white but not black women. However, only eight black women were nulliparous. The few studies that report data on miscarriage or induced abortion show little or no evidence of a protective association for these pregnancies lost early.[19,20,22–26] Thus, the epidemiologic data suggest that pregnancy is protective, and the protective effect is likely to be linked to events that occur late in pregnancy, at delivery or during the postpartum process.

The reduced risk associated with parity might be attributable to a failure to account for breastfeeding, because breastfeeding suppresses ovarian hormones. Data on breastfeeding were not collected in most of the studies. However, the two studies that did examine breastfeeding do not support an association with fibroids. No relation was found in one,[21] and the inverse relation with fibroids in the other was uninterpretable because it was not adjusted for parity.[19]

The plausibility of a biological basis for a protective effect of parity is supported by an experimental study conducted in Eker rats.[27] These animals, used as an animal model for fibroids, are heterozygous for a mutation in the tumor suppressor gene, tuberous sclerosis-2, and show a background incidence of uterine leiomyoma of 65%. This high incidence is found at 16 months of age among rats that have never bred. In a study to test the effects of pregnancy, the percent of those with fibroids

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dropped to 10% among those allowed to breed throughout their lives. Furthermore, the pups were removed at birth so that breastfeeding could not explain the protective effect.[27] Mechanisms have not yet been explored in this animal model.

The Hypothesis

We hypothesize that the protective effect of pregnancy on fibroids involves the process of postpartum uterine involution. The uterus at term is a highly expanded, thin-walled, balloon-like structure. After involution it is restored to the size of a fist, with thick, muscular walls. Most of this change occurs during the first 2–3 weeks after delivery.[28–31]

The biological changes that occur during uterine involution are not well understood. Studies in rats show high levels of apoptosis during involution, but also high levels of proliferation.[32] The findings indicate that the involution process is not a simple shrinking of existing tissue, but rather a remodeling process. Uterine involution in rodents is marked by high activity of matrix metalloproteinases, a family of over 20 proteins that together can degrade any of the extracellular matrix components.[33] Recent work shows that these enzymes also play a role in generative processes.[32,34,35] Exposure to estrogen, progesterone and relaxin can inhibit the process in rodents.[36] However, little is known about factors that influence involution in humans.

Selective loss of early neoplastic lesions has been documented during apoptosis,[37–39] so we expect that early leiomyoma lesions would be eliminated with the apoptosis occurring during uterine involution. We also hypothesize that the extensive remodeling that occurs in the early puerperium may result in loss of even larger lesions, including fibroids that can be observed with ultrasound. A direct test of this hypothesis would involve longitudinal study of women through their pregnancies. Careful ultrasound examinations early in pregnancy would identify small fibroids, and reexamination after pregnancy would document whether loss of small fibroids occurs.

Cross-sectional ultrasound data on presence and size of fibroids could be used in a preliminary, indirect test of the hypothesis. If the primary protective effect of parity is to clear small fibroids, then the impact of a particular pregnancy should vary with maternal age and pregnancy history. A pregnancy that occurs while fibroids are small would be protective, whereas pregnancies occurring before fibroid development or after the tumors reach some critical size would not be protective. The timing of fibroid development is not known, but clinical data indicate that fibroids are rare in early reproductive years,[8,9] and the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study has demonstrated that large fibroids are relatively common by the time women reach their 40s.[40] Assuming this time course for uterine fibroid development, delivery at young ages would have little effect on fibroids because the lesions would not yet have developed. A first pregnancy late in life might also have little effect because some tumors could have grown too large to be eliminated by remodeling. Thus, we expect that the greatest protective effect of parity would occur for pregnancies during the mid-reproductive years. The protective effect of second and subsequent pregnancies would depend upon the time intervals between previous pregnancies. If the intervals were very short, they would provide little additional protection. Long intervals might also have little protective effect because the fibroids that develop after a previous pregnancy might have had time to grow beyond a size susceptible to remodeling.

Test of the Hypothesis

Data from the NIEHS Uterine Fibroid Study were analyzed as a preliminary test of the hypothesized age-dependent protective effects of parity. This study used abdominal and transvaginal ultrasound to screen randomly selected premenopausal study participants, 35–49 years of age, for fibroids, regardless of whether women had received a prior diagnosis.[40] The study successfully screened 87% of the 1245 premenopausal participants. The study was approved by the NIEHS Institutional Review Board, and participants gave informed consent. The characteristics of the participants have been described elsewhere.[40]

For our analysis we limited parous women to those with only one delivery because the predicted effects for subsequent pregnancies are difficult to model. Such effects depend on age at time of subsequent delivery, time since previous delivery and rate of fibroid growth for which we have no direct data. The analysis sample consisted of 410 nulliparous and 218 primiparous, premenopausal women for whom we have data on fibroid status. The mean age for women in this sample was 42; 44% were African American; the majority (68%) had a college education or more; 16% smoked; and median body mass index was 26. Thirty-seven percent of those with fibroids had been diagnosed before study screening.

Because the ultrasound screening that assessed fibroid size was done at one point in time, often years after the pregnancy, we cannot look directly for fewer small fibroids. Rather, we look for less fibroid development. Ordinal logistic regression was used to test for the effect on fibroid development associated with delivery at different ages. A four-level ordinal outcome variable was used to reflect the extent of fibroid development at the time of ultrasound screening (no detectable fibroids, N = 240; largest fibroid <2 cm in diameter, N = 98; 2–4 cm in diameter, N = 156; and 4+ cm in diameter, N = 134). Age at study participation, age of menarche, Af-

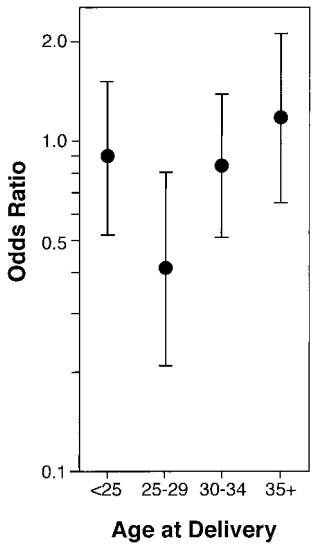

FIGURE 1. The relative odds of increased uterine fibroid development associated with age at delivery among 624 participants in the NIEHS Uterine Fibroid study. Fibroid development was modeled as a four-level ordinal variable (no detectable fibroids and largest fibroid <2 cm, 2–4 cm, and 4+ cm in diameter). The odds ratio is the relative odds of being in the next highest fibroid development category associated with each age at delivery interval. The reference category for each age of delivery interval is nulliparous women. The 95% confidence intervals are shown by the *vertical lines*.

rican-American ethnicity and infertility were included as covariates in the model. Smoking and BMI were examined and found not to be confounders. Age at delivery was modeled in four categories (<25, 25–29, 30–34, and 35+), and the reference group was nulliparous women. The results are shown in Figure 1. As hypothesized, delivery in mid-reproductive years appeared to be most protective for development of fibroids.

A previous analysis of data from the NIEHS Uterine Fibroid Study[41] evaluated the effects of delivery on fibroid development using a biologically based proportional hazards model that included multiparous as well as primiparous study participants. That model allowed fibroids to progress through different stages, with delivery-induced fibroid clearance occurring with probability dependent on the stage. The results of that analysis also suggested substantially increased protection during the mid-reproductive years when small detectable fibroids became more common, and leveling off as fibroids become larger in the late-reproductive years.[41]

Conclusions

The indirect tests of our hypothesis were consistent with loss of small fibroids during postpartum uterine involution. The relation needs to be replicated in other epidemiologic studies of uterine fibroids, but indirect tests are limited. We will attempt to study this issue more directly with an ultrasound study in which we will map fibroids early in pregnancy and again after pregnancy to look for disappearance of small tumors. If small fibroids disappear, it will document a process that results in natural regression of these tumors in premenopausal women. Understanding the biology of this process might lead to development of treatments that could be used by nonpregnant women to induce tumor regression.

Remodeling may also be protective of tumor development and growth in other organs. Remodeling that normally occurs during particular life stages or in response to normal life events may enhance selective elimination of transformed cells that occurs during apoptosis. Investigation of the possible role of tissue remodeling as an anticancer strategy for many organs in long-lived species might yield new insights for cancer prevention and treatment.[42]

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