Luteinizing Hormone in Premenopausal Women May Stimulate Uterine Leiomyomata Development

Donna D. Baird, PhD, James S. Kesner, PhD, and David B. Dunson, PhD

OBJECTIVE: *Human chorionic gonadotropin (hCG) has proliferative effects on uterine smooth muscle and leiomyoma tissue in vitro. We hypothesized that luteinizing hormone (LH) would have the same effect by activating the LH/hCG receptor, and it would follow that premenopausal women with higher basal LH levels would be more likely to have leiomyomata.*

METHODS: *Randomly selected women, aged 35 to 49 years, from a prepaid health plan were screened for leiomyomata with pelvic ultrasound. Urine samples collected during the first or last 5 days of the menstrual cycle were analyzed for LH by immunofluorometric assay, and concentrations were corrected for creatinine (n = 523). Logistic regression and Bayes analyses were used to evaluate the association of LH with presence and size of leiomyomata, adjusting for age, and other risk factors.*

RESULTS: *Women with higher LH were more likely to have leiomyomata (adjusted odds ratios for second and third tertiles were 1.7 and 2.0 compared with lower tertile; 95% confidence intervals, 1.0 to 2.7 and 1.2 to 3.4, respectively). The association was stronger for large leiomyomata. Bayes analyses designed to estimate LH effects on tumor onset separately from tumor growth showed significantly accelerated tumor onset but little evidence of effects on tumor growth. Age, an independent risk factor for leiomyomata, was not affected by inclusion of LH in the logistic models.*

CONCLUSIONS: *As hypothesized, women with higher LH were more likely to have leiomyomata, but this did not explain the age-related increase in leiomyomata during perimenopausal ages. Determining whether LH is causal or a marker for susceptibility will require further research. (J Soc Gynecol Investig 2006;13:130–5)*

KEY WORDS: Uterine leiomyoma, uterine fibroids, luteinizing hormone, perimenopause.

Uterine leiomyomata (fibroids) are benign smooth muscle tumors that develop in the majority of US women before menopause.[1] Although fibroids are often asymptomatic, some women develop pain, bleeding, and pregnancy complications.[2] Symptoms depend on the size and location of the fibroids.[2–4] Fibroids are the leading cause of hysterectomy in the United States.[5] These tumors apparently require a premenopausal hormonal milieu.[6] They increase in incidence through the premenopausal years, while few are first diagnosed after menopause.[7,8] The need for surgical treatment is especially high for women during their 40s.[7] It is not known why women in this age group seem to be particularly susceptible to fibroid development.

One possibility is that hormonal changes during perimenopause, particularly the rise in gonadotropins, may be important. There is growing evidence from laboratory studies for direct effects of luteinizing hormone (LH) on the uterus, independent of the ovary.[9,10] LH and human chorionic gonadotropin (hCG) bind to a common receptor that has been found in the myometrium,[11,12] and *in vitro* studies show that hCG has proliferative effects on uterine smooth muscle cells.[13] These laboratory findings led us to hypothesize that increased endogenous LH might stimulate fibroid development in premenopausal women. The hypothesis is limited to premenopausal women because, though circulating LH continues to increase after menopause, LH/hCG receptor induction appears to require a premenopausal steroidal milieu.[14] We tested this hypothesis by measuring LH concentrations in urine collected during menstrual cycle days excluding the LH-midcycle rise, as a marker of circulating LH throughout the menstrual cycle.[15,16] Participants were randomly selected women who were screened for fibroids with ultrasound.

From the Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina; Biomonitoring and Health Assessment Branch, Division of Applied Research and Technology, National Institutes of Occupational Safety and Health, Cincinnati, Ohio; and the Biostatistics Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina.

This study was funded as intramural research at the National Institute of Environmental Health Sciences with support from the Office of Research on Minority Health.

Michael Hill supervised the ultrasound screening examinations, and Joel Schectman administered the clinical aspects of the NIEHS Uterine Fibroid Study. Glenn Heartwell managed the study and Deborah Cousins provided programming support. Freya Kamel and William Schrader reviewed an earlier draft of the manuscript.

Address correspondence to Donna Baird, PhD, Epidemiology Branch, MD A3-05, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709. E-mail: baird@niehs.nih.gov

1071-5576/06/$32.00
doi:10.1016/j.jsgi.2005.12.001

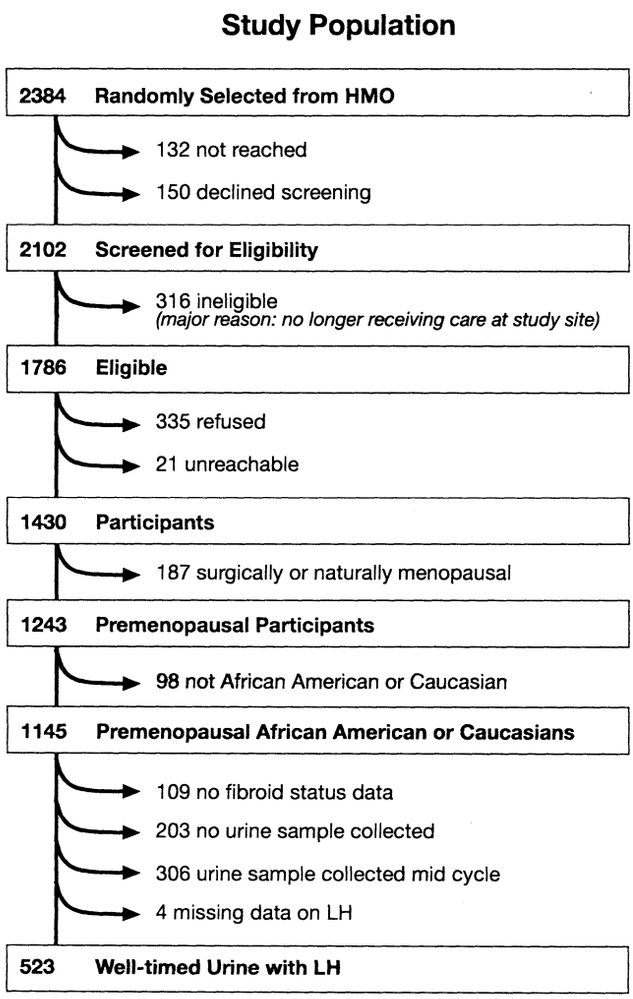

Figure 1. Flowchart showing the number of African American and Caucasian women in the NIEHS Uterine Fibroid Study for whom we have appropriately timed urinary LH measurements.

METHODS

The National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study was designed to estimate fibroid prevalence, and to identify risk factors for the condition. Detailed methods have been described.[1] Briefly, the computerized membership records of a prepaid health plan in Washington, DC, were used to randomly select 35- to 49-year-old women who received primary care at a single urban site. The age range was chosen because this is the age group most likely to be clinically treated for fibroids. Health plan members were screened for eligibility by telephone. Eligibility criteria were as follows: (1) confirmation of computerized information (age, sex, and membership site), and (2) ability to communicate in English. Eighty percent of eligible women participated (Figure 1). We limited this analysis to African American and Caucasian women because other racial/ethnic groups were poorly represented. Participants completed a telephone interview that assessed prior diagnosis of fibroids, reproductive status, and hormonal medication history. Participants were also asked to (1) visit the primary care clinic for an ultrasound examination, (2) complete self-administered questionnaires regarding medical history and diet, and (3) prospectively maintain a daily menstrual diary for 42 days. The research was approved by the NIEHS and the health plan human subject's review boards, and participants gave informed consent.

Fibroid status was determined for most participants by the ultrasound screening examination. Abdominal and transvaginal ultrasound was used because it is as effective as magnetic resonance imaging (MRI) for detecting fibroids[17] but less expensive. Participants who had recently undergone an ultrasound examination at the clinic for clinical purposes (21%) were not asked to repeat the examination for this study. For these women fibroid status data were abstracted from the clinic radiology report. The study ultrasound examinations were performed by sonographers that were certified by the American Registry of Diagnostic Medical Sonographers and were trained for this study to consistently collect and record data on fibroids of 0.5 cm diameter or larger. They were under the direct supervision of one radiologist with fellowship training in ultrasound, and each study was checked at its completion by this radiologist. The examinations were performed on ultrasound units ATL HDI 9 (ATL, Bothell, WA), Acuson 128 XP (Siemens, Issaquah, WA) and Diasonics DRF 400 (G.E., Milwaukee, WI) using transabdominal (3.5 to 5.0 mHz) and transvaginal (5.0 to 7.0 mHz) ultrasound probes. The abdominal portion of the examination evaluated fibroid change arising from the upper uterus that would not be readily seen with the transvaginal approach alone. Sonographers completed a data collection form designed for this study which included data on uterine size (length, width, anterior/posterior diameter), uterine contour (smooth or lobulated), heterogeneity of the echo pattern (none, diffuse, and/or focal), and number and size of focal fibroids. Any questionable sonograms were reviewed by a single radiologist. Those with diffuse heterogeneous pattern but no focal fibroids ($n = 62$) were categorized as having fibroids, but analyses were also repeated without these women, and results did not change. For participants who failed to complete their ultrasound screening examinations, we accepted self-report of a prior diagnosis. We did not rely on self-report of "no fibroids" because undiagnosed fibroids are common; about half of the undiagnosed women in our study were found to have fibroids at ultrasound screening.[1]

LH was measured in urine. Because LH rises markedly at time of ovulation, and timing of ovulation is quite variable among menstrual cycles,[18] we obtained samples from a randomly selected subset of participants that were timed to avoid the midcycle surge. The original protocol called for obtaining 500 well-timed urine samples to test the hypothesis in question. The first 638 participants were sent special urine collection kits and instructed to collect first morning urine samples on the second and third days of their menstrual cycles, and refrigerate the samples until sending them within a day by overnight courier in a cold-storage pack to the study management site in North Carolina. At the North Carolina site, a

pooled aliquot comprised of equal volumes from these two collected neat samples was prepared, with 7% glycerol added to prevent loss of hormone activity.[19] The remaining participants were instructed to bring a first morning urine specimen collected that day to their study clinic visit, which was scheduled during morning hours. Those who came to the clinic without the urine sample were asked to provide a spot urine sample at the clinic. Aliquots of these neat samples were also prepared with 7% glycerol and frozen within 24 hours at the clinic until mailed in batches with dry ice to North Carolina. Frozen aliquots were stored at −80C until assayed. We supplemented the early follicular phase urine samples sent from home with any processed at the clinic that had been collected on the first or last five days of the menstrual cycle. Well-timed urine samples were available for 523 women (Figure 1): 437 had 2-day pooled urine samples, 71 had single first morning urine samples, and 15 had single spot urine samples.

Urinary LH was assayed in duplicate using a noncompetitive, two-site time-resolved immunofluorometric assay.[20] Creatinine was measured spectrophotometrically.[21] Endocrine values were divided by creatinine concentrations to adjust for urine dilution.[22] Within- and between-assay percent coefficients of variation were 7.3% and 8.7% for LH and 2.2% and 4.2% for creatinine.

The relationship between endogenous LH and uterine fibroids was evaluated by logistic regression and Bayesian methods. For logistic regression, we examined LH levels both as a continuous variable (after log transformation) and categorized into approximate tertiles. We first estimated the relative odds of having any fibroids. As a measure of fibroid development we considered size of the largest fibroid in categories based on diameter of largest tumor (small, <2 cm; medium, ≥2 but <4 cm; large, ≥4 cm), and compared each category as a separate outcome to women without fibroids (categorical data modeling [CATMOD] procedure in SAS, SAS Institute, Cary, NC). We entered women with diffuse heterogeneous echopattern but no focal fibroids ($n = 62$) into the fibroid size categories on the basis of their uterine size. To do this we regressed log of uterine volume (using ellipsoid formula 0.52 × length × width × anterior/posterior diameter) against diameter of largest fibroid for those with focal fibroids and used the resultant formula to calculate an estimated fibroid size based on uterine volume for those with diffuse heterogeneous echogenic pattern.

Finally, to assess associations between LH and fibroid growth versus fibroid onset, we applied the Bayesian multistate modeling approach of Dunson and Baird.[23] This method is based on a flexible stochastic model that incorporates data on age at any prior diagnosis, age at study ultrasound, and size of largest fibroid (if any were found) to characterize onset and subsequent growth of fibroids. Fibroid onset is defined to occur when the tumors first grow large enough to be detectable by a sonogram. This onset time is unknown and tumors may remain latent for a number of years prior to clinical detection. During this preclinical detectable phase and even after clinical diagnosis, fibroids may continue to grow. The Dunson and Baird[23] method is used to assess whether LH is associated with *onset* (age-adjusted rates of initial onset of small fibroids) or *growth* (latency time-adjusted size of largest fibroid) based on survival analysis. The analysis is implemented using Markov chain Monte Carlo (MCMC), after choosing noninformative prior distributions. Hypothesis tests of ordered trends in tumor onset and growth across categories of LH are based on Bayes factors and posterior probabilities.

In both the logistic and Bayesian analyses, the association between LH and uterine fibroids was adjusted for other factors found to be related to fibroids. These were age (in years), ethnicity (black or white), age of menarche (<11, 11, 12, 13, 14, >14), body mass index (BMI; kg/m^2 categorized as <25, 25–29, 30–34, 35+), number of full-term pregnancies after age 24 (used because pregnancies at early ages were not associated with fibroid occurrence[24]), and exercise. Exercise was modeled as a four-level index based on reported hours per week of vigorous, moderate, and walking activities and estimated metabolic units used for each general type of activity; the inclusion of household chores in the index was important for African American women but not whites, and thus time doing chores was included for African Americans. For logistic analyses adjusted odds ratios (ORs) are presented with 95% confidence intervals. For the Bayesian analyses age-specific relative risks were averaged across ages, and overall relative risks are presented with estimates of 95% confidence intervals.

RESULTS

Participants in our analysis sample were very similar to the total group of premenopausal participants (Table 1). The majority of women (65%) had fibroids (75% of African Americans and 53% of Caucasians). Although many had only small tumors, large tumors were especially common in African American women, 23% of whom had large tumors, compared with 11% in Caucasians. The distribution of urinary LH is shown in Figure 2 (mean, 5.4; SE, 0.2). LH concentrations did not differ by cycle day ($P = .28$) or ethnic group ($P = .92$), and were weakly correlated with age ($r = .09$, $P = .05$).

Controlling for age, ethnicity, and other risk factors, a 1-unit (mIU/mg creatinine) increase in LH on a log scale was associated with an adjusted OR for fibroids of any size of 1.3 (1.0 to 1.6). The adjusted ORs for small, medium, and large fibroids were 1.1 (0.8 to 1.5), 1.2 (1.0 to 1.6), and 1.7 (1.2 to 2.4), respectively. The associations did not differ significantly by age, ethnicity, or BMI (all P values for interaction ≥.20). When LH was divided into approximate tertiles, the prevalence of fibroids was higher in the moderate and high LH groups relative to the low LH group, and the association with large fibroids was especially strong (Figure 3). The OR for large fibroids associated with the high LH group was 3.3 (1.6 to 6.8).

We had hypothesized that an association between LH and fibroids would explain at least some of the increase in fibroid development with age. Therefore, we compared the age association with and without LH in the logistic model. A 5-year increase in age was associated with an OR of 1.7 (1.3 to 2.1)

Table 1. Characteristics of NIEHS Uterine Fibroid Study Participants Analyzed for Urinary LH Compared With Characteristics for All Premenopausal African American and Caucasian Participants

Characteristic	Analysis sample (N = 523) N (%)	Total sample (N = 1,145) N (%)
Age (yr)		
35–39	187 (36)	420 (37)
40–44	194 (37)	397 (35)
45–49	142 (27)	328 (29)
Ethnicity		
African American	309 (59)	690 (60)
Caucasian	214 (41)	455 (40)
Fibroid status*		
None	179 (34)	362 (35)
Small	98 (19)	175 (17)
Medium	152 (29)	298 (29)
Large	94 (18)	201 (19)
Missing	0	109
Source of fibroid status data		
Ultrasound	508 (97)	982 (95)
Surgical report	4 (1)	14 (1)
Self-report	11 (2)	40 (4)
LH (mIU/mg creatinine)		
Low (0.0–3.0)	176 (34)	246 (29)
Medium (3.0–6.0)	187 (36)	270 (32)
High (6.0+)	160 (31)	331 (39)
Missing	0	298
Age of menarche (yr)		
<11	45 (9)	97 (9)
11	78 (15)	179 (16)
12	141 (27)	315 (28)
13	153 (29)	310 (27)
14	50 (10)	121 (11)
>14	55 (11)	118 (10)
Missing	1	5
No. of full-term pregnancies delivered after age 24		
0	296 (57)	636 (56)
1–2	132 (25)	283 (25)
3+	95 (18)	226 (20)
Index of physical activity		
Low	156 (30)	355 (31)
Medium	178 (34)	371 (33)
High	99 (19)	217 (19)
Very high	87 (17)	196 (17)
Missing	3	6
BMI		
<25	207 (40)	453 (40)
25–29.99	147 (28)	312 (27)
30–34.99	78 (15)	176 (15)
35+	91 (17)	202 (18)
Missing		2
Current smoker		
No	426 (81)	886 (77)
Yes	97 (19)	258 (23)
Missing		1
Length of menstrual cycle†		
<27 days	143 (29)	299 (29)
27–30 days	297 (61)	606 (58)
>30 days/irregular	48 (10)	136 (13)
Missing	35	104

* Fibroid status was categorized based on the diameter of largest fibroid (0–2 cm, small; ≥2–4 cm, medium; >4 cm, large). Sixty-two women had diffuse heterogeneous pattern but no focal fibroids, and these were entered into the fibroid size categories on the basis of their uterine volume (13 small, 42 medium, 7 large).

† Menstrual cycle length was set to missing if participant had been using hormonal contraception or other hormone treatment.

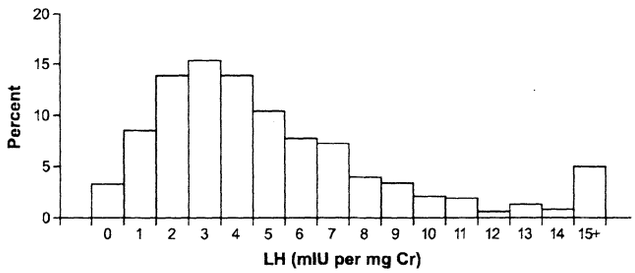

Figure 2. The distribution of urinary LH concentration (mIU per mg creatinine), rounded to the nearest whole number for 523 participants in the NIEHS Uterine Fibroid Study.

when LH was not in the model. When LH was added, the age estimate was unchanged, still 1.7.

The ORs for fibroid development in relation to LH remained essentially unchanged when we used slightly modified definitions of fibroid status (Figure 4, groups 2 through 4) and when we limited analyses to the sample of women who were selected to collect first morning urine for 2 days early in their cycle (Figure 4, group 5).

Women with polycystic ovary disease often have higher basal LH levels.[25] To determine whether this condition was driving the association we observed, we conducted several further analyses. First we excluded those with the highest LH levels (top 5%) and saw little change (Figure 4, group 6). Then we excluded the 36 women who either reported being diagnosed with polycystic ovary disease (n = 7) or were missing data for the question (n = 29), and the results showed only minor changes (Figure 4, group 7). We also considered whether menstrual cycle length as an indirect measure of hormonal status affected the association between LH and fibroids. Cycle length was not associated with fibroid status, and the inclusion of this variable resulted in only minor changes in the association between LH and fibroids (Figure 4, group 8).

We re-examined our primary results (Figure 3) using the

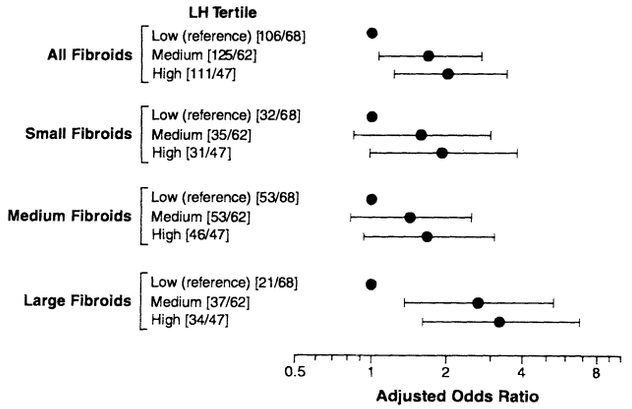

Figure 3. The adjusted ORs for fibroids (all sized fibroids, small, medium, and large fibroids) associated with increased urinary LH levels. The ORs are adjusted for age, ethnicity, BMI, age of menarche, number of full term pregnancies after age 24, and exercise. The horizontal lines show 95% confidence intervals. The numbers to the left show the number with and without fibroids in each of the LH categories. The total number with data on all covariates was 519.

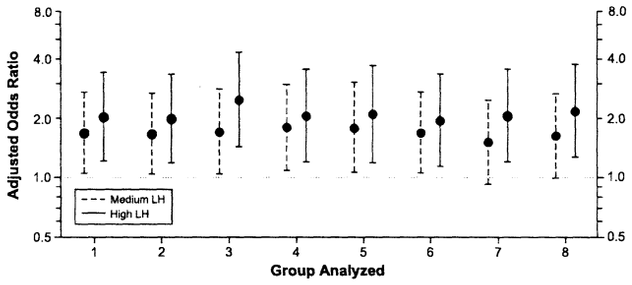

Figure 4. Results of sensitivity analyses to evaluate the stability of the LH findings. Group 1 (n = 519) is the total sample with complete data (four of the 523 participants with LH data were missing data for a covariate). Group 2 (n = 508) excludes women whose fibroid status is based only on self-report. Group 3 (n = 519) is the result of switching fibroid status for the 26 women who had reported having a previous diagnosis of fibroids, but no fibroids detected at ultrasound screening, from the "no fibroid" group to the "fibroid" group. Group 4 (n = 457) excludes women who were judged to have fibroids on the basis of a diffuse heterogeneous pattern at the ultrasound examination, but who did not have measurable focal fibroids. Group 5 (n = 437) includes only those women with pooled urine collected from 2 early follicular phase days of their menstrual cycles. Group 6 (n = 493) excludes women in the top 5% of urinary LH concentration. Group 7 (n = 483) excludes those who reported a previous diagnosis of polycystic ovary disease or were missing data for that question. Group 8 (n = 484) excludes women taking any medication that might affect their menstrual cycle length and controls for cycle length.

Bayesian multistate model. These results indicated that urinary LH concentration was not significantly associated with tumor growth, but was significantly associated with earlier tumor onset. When the age-specific Bayesian estimates of the risk of tumor onset were averaged across ages, the relative risk for moderate LH was 1.2 (1.0 to 1.4) and the relative risk for high LH was 1.3 (1.1 to 1.6).

DISCUSSION

We found that women with higher urinary basal LH levels were more likely to have fibroids than women with lower LH. This is consistent with the laboratory research that motivated the study. LH/hCG receptors have been found in myometrial and fibroid tissue,[26,27] and hCG has been shown to have proliferative effects on uterine smooth muscle cells.[13] Whether the myometrial LH receptor is identical to the ovarian receptor is still unclear.[28]

We measured LH in urine rather than serum because, in a large epidemiologic study, it is very difficult to time clinic visits to specific menstrual days so that the midcycle LH surge can be avoided. Instead we provided a random subset of women with urine collection kits that they could use at home on the early follicular days of their cycle. Though serum LH is the usual clinical measure, urinary LH is highly correlated with serum LH.[15] Indeed, because the urine provides a time-integrated measure of the pulsatile gonadotropins in the circulation, urinary measurements provide less variable endpoints than serum measurements.[29] A limitation of this study is the cross-sectional nature of the data, so cause and effect cannot be demonstrated. It is theoretically possible, though it seems implausible, that fibroids somehow stimulate basal LH secretion. A longitudinal study of fibroid development would provide stronger evidence of a causal association.

Because elevated basal LH is seen in polycystic ovary syndrome (PCOS),[25] and the hyperinsulinemia often associated with PCOS might increase risk of fibroids,[30] we investigated a possible role of PCOS in our findings. We conducted several sensitivity analyses to evaluate this question (Figure 4, groups 6 through 8), and none changed the association substantially. Furthermore, the levels of LH we found were normal for premenopausal women with no known fertility problems, as demonstrated by the similarity with women from the North Carolina Early Pregnancy Study.[31] Thus, we do not think the finding can be explained by PCOS.

The rate of surgery for fibroids, usually associated with large fibroids, increases rapidly in the late reproductive years,[7] suggesting that fibroids may grow more rapidly at this time. We had hypothesized that perimenopausal hormonal changes, particularly increases in LH, might explain some of this strong age dependency. However, we found that though women with higher LH were more likely to have fibroids, the LH association did not explain any of the increase in fibroid development with age. Furthermore, the Bayesian analysis suggested that LH is primarily associated with tumor onset, not tumor growth. Therefore, our findings do not appear to be due to fibroid growth stimulated by perimenopausal gonadotropin increase.

Although LH may have direct proliferative effects that could increase tumor onset, LH may also be associated with fibroids through other mechanisms. LH may increase angiogenesis,[32] and increased vessel development in microscopic lesions could increase the risk of tumors developing to a detectable size, since vascularity enhances growth.[33] In addition, it is possible that higher LH is a marker of a steroid hormone pattern that increases susceptibility to fibroids. Our uterine fibroid study enrolled women 35 to 49 years of age, the majority of whom already had developed a fibroid (although many had not been diagnosed before study ultrasound screening).[1] It would be of great interest to know if higher basal LH levels measured in younger women before they develop fibroids are predictive of subsequent fibroid development.

In summary, this study shows an association between higher LH levels and fibroids. Further research is needed to replicate these findings and evaluate the mechanisms. If higher LH directly increases fibroid development by increasing smooth muscle cell proliferation, reducing LH levels could help prevent fibroid development. If LH has little direct effect on leiomyoma development, measurement of LH might still provide a marker of susceptibility.

REFERENCES

1. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High incidence of uterine leiomyoma: Ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
2. Stewart EA. Uterine fibroids. Lancet 2001;357:293–8.

3. Buttram VC Jr, Reiter RC. Uterne leiomyomata: Etiology, symptomatology, and management. Fertil Steril 1981;36:433–45.
4. Wegienka G, Baird DD, Hirtz-Picciotto I, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003;101:431–7.
5. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. Obstet Gynecol 2002;99:229–34.
6. Schwartz SM, Marshall LM. Uterine leiomyomata. In: Goldman MB, Hatch MC, eds. Women and health, San Diego: Academic Press, 2000:240–52.
7. Ross RK, Pike M, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: Reduced risk associated with oral contraceptives. BMJ 1986;293:359–62.
8. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435–38.
9. Shemesh M. Actions of gonadotrophins on the uterus. Reproduction 2001;121:835–42.
10. Tesarik J, Hazout A, Mendoza C. Lutienizing hormone affects uterine receptivity independently of ovarian function. Reprod Biomed Online 2003;7:59–64.
11. Reshef E, Lei ZM, Rao CV, Pridham DD, Chegini N, Luborsky JL. The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and deciduas. J Clin Endocrinol Metab 1990;70:421–30.
12. Zuo J, Lei ZM, Rao CV. Human myometrial chorionic gonadotropin/luteinizing hormone receptors in preterm and term deliveries. J Clin Endocrinol Metab 1994;79:907–11.
13. Horiuchi A, Nikaido T, Yoshizawa T, et al. HCG promotes proliferation of uterine leiomyomal cells more strongly than that of myometrial smooth muscle cells in vitro. Mol Hum Reprod 2000;6:523–8.
14. Lei ZM, Reshef I, Rao V. The expression of human chorionic gonadotropin/luteinizing hormone receptors in human endometrial and myometrial blood vessels. J Clin Endocrinol Metab 1992;75:651–9.
15. Tanabe K, Susumu N, Hand K, Nishii K, Ishikawa I, Nozawa S. Prediction of the potentially fertile period by urinary hormone measurements using a new home-use monitor: Comparison with laboratory hormone analyses. Hum Reprod 2001;16:1619–24.
16. Lenton EA, Landgren BM. The normal menstrul cycle. In: Shearman RP, ed. Clinical reproductive endocrinology. Edinborough, UK: Churchill Livingstone, 1985:81–108.
17. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol 2002;186:409–15.
18. Baird DD, McConnaughey DR, Weinberg CR, et al. Application of a method of estimating day of ovulation using urinary estrogen and progesterone metabolites. Epidemiology 1995;6:547–50.
19. Kesner JS, Knecht EA, Krieg EF Jr. Stability of urinary biomarkers of female reproductive hormones stored under various conditions. Reprod Toxicol 1995;9:239–44.
20. Kesner JS, Knecht EA, Krieg EF Jr. Time-resolved immunofluorometric assays for urinary luteinizing hormone and follicle stimulating hormone. Anal Chim Acta 1994;285:13–22.
21. Jaffe M. Ueber den neiderschlag, welchen pikrinsäure im normalen harn erzeught und über eine neue reaction des kreatinins. Z Physiol Chem 1986;10:391–400.
22. Kesner JS, Knecht EA, Krieg EF Jr, Wilcox AJ, O'Connor JF. Detecting pre-ovulatory luteinizing hormone surges in urine. Hum Reprod 1998;13:15–21.
23. Dunson DB, Baird DD. Bayesian modeling of incidence and progression of disease from cross-sectional data. Biometrics 2002;58:813–22.
24. Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology 2003;14:247–50.
25. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
26. Ziecik AJ, Derecka-Reszka KA, Rzucidlo SJ. Extragonadal gonadotropin receptors, their distribution and function. J Physiol Pharmacol 1992;43 Suppl 1:33–49.
27. Kornyei JL, Lei ZM, Rao CV. Human myometrial smooth muscle cells are novel targets of direct regulation by human chorionic gonadotropin. Biol Reprod 1993;49:1149–57.
28. Stewart EA. Gonadotropins and the uterus: Is there a gonad-independent pathway? J Soc Gynecol Investig 2001;8:319–26.
29. Kesner JS, Knecht EA, Krieg EF Jr. Measuring endocrine profiles of women in field studies. Scand J Work Environ Health 1999;25 Suppl 1:17–9.
30. Faerstein E, Szklo M, Rosenshein NB. Risk factors for uterine leiomyoma: A practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. Am J Epidemiol 2001;153:11–9.
31. Baird DD, Weinberg CR, Zhou H, et al. Preimplantation urinary hormone profiles and the probability of conception in healthy women. Fertil Steril 1999;71:40–9.
32. Zygmunt M, Herr F, Keller-Schoenwetter S, et al. Characterization of human chorionic gonadotropin as a novel angiogenic factor. J Clin Endocrinol Metab 2002;87:5290–6.
33. Tsuda H, Kawabata M, Nakamoto O, Yamamoto K. Clinical predictors in the natural history of uterine leiomyoma: Preliminary study. Ultrasound Med 1998;17:17–20.