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Reproductive characteristics and risk of uterine leiomyomata

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Abstract

Objective—To evaluate whether menstrual and reproductive characteristics may influence development of uterine leiomyoma since sex steroid hormones have been hypothesized to play a role in their development.

Design—A prospective cohort study (Nurses' Health Study II).

Setting—Participants were identfied from 14 states and followed for 14 years.

Study Population—A cohort of 116,609 female registered nurses ages 25 to 42 at baseline.

Interventions—We obtained data on uterine leiomyomata incidence and exposures through biennial questionnaires. We calculated hazard ratios and 95% confidence intervals adjusted for known and suspected risk factors.

Main Outcome Measures—Uterine leiomyomata confirmed by ultrasound or hysterectomy.

Results—During 1,163,439 person-years of follow-up, 9847 self-reported cases of hysterectomy or ultrasound confirmed uterine leiomyomata were reported. We observed a lower incidence of uterine leiomyomata with later age at menarche, longer menstrual cycles, parity, later age at first and last birth, shorter time since last birth, and breastfeeding.

Conclusions—Hormonal and anatomical changes associated with menstruation and pregnancy may influence uterine leiomyomata incidence.

Keywords

uterine leiomyoma; menstrual characteristics; parity; breastfeeding

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INTRODUCTION

Uterine leiomyomata, also known as fibroids, are benign tumors of the uterus and the leading cause of hysterectomy in the United States, accounting for $1.2 billion in hospital expenditures annually (1–3). Symptoms vary in severity and include pelvic pain, abnormal menstrual bleeding, and pregnancy complications (4).

The etiology of uterine leiomyomata is poorly understood. Increasing incidence of diagnosed uterine leiomyomata during reproductive years and decreased incidence with menopause, suggest the role of sex steroid hormones (5,6). Previous epidemiologic studies suggest a reduced risk of uterine leiomyomata with late age at menarche, parity, and late age at first birth as well as an increased risk of UL with time since last birth (7–14).

In 1998, Marshall and colleagues reported on the association between reproductive characteristics and risk of UL, including analyses of age at menarche, parity, age at first birth and year since last birth, based on 3006 UL cases and four years of follow-up (8). Here we have extended that analysis to include 9921 self-reported cases of ultrasound- or hysterectomy-confirmed UL and 14 years of follow-up. In addition, we have expanded the range of reproductive characteristics evaluated to include breastfeeding and menstrual cycle characteristics.

MATERIALS AND METHODS

In 1989, 116,609 female registered nurses ages 25 to 42 years responded to a baseline questionnaire about their medical histories and lifestyles. Women who reported cancer at enrollment (not including non-melanoma skin cancer) were excluded. Follow-up questionnaires have been sent biennially to update information on risk factors and medical events. Follow-up for this cohort exceeds 90%. This study was approved by the institutional review boards of Brigham and Women’s Hospital and Harvard School of Public Health (Boston, MA).

Exposure assessment

At baseline (1989) data was collected on age at menarche, number of years to regular menstrual cycles and usual menstrual cycle length and pattern during college. Current menstrual cycle length and pattern were assessed in 1993.

Parity history (defined as the total number of pregnancies lasting 6 months or more) including age at first pregnancy was collected at baseline and updated with each questionnaire cycle. Time since the last term birth was computed by subtracting the age of the participant at her most recently reported term birth from her current age. Data regarding lactation were first collected in 1993, including total months of breastfeeing for all births combined, and updated with more detailed data in 1997, including whether they had breastfed for at least one month, whether breastfeeding was supplemented by formula or something else, and when breastfeeding was stopped completely.

Outcome assessment

Incidence of uterine leiomyomata was first assessed in 1993 when the participants were asked if they had ever had uterine fibroids diagnosed by a physician. If a participant answered “yes”, she was asked when she was first diagnosed (before September 1989, September 1989 to May 1991, June 1991 to May 1993, after June 1993), whether the diagnosis was confirmed by pelvic exam, and whether the diagnosis was confirmed by ultrasound or hysterectomy. Women who reported an ultrasound- or hysterectomy-confirmed uterine fibroid between September 1989 and May 1991 were considered to be a

new case during that time period. Likewise, women who reported an ultrasound- or hysterectomy-confirmed uterine fibroid between June 1991 and May 1993 were considered to be new cases during that time period. For all subsequent questionnaires, women were asked if they had been diagnosed with fibroids before, during, or after the current two-year study period. During these follow-up intervals, a woman was considered a case only if she reported an ultrasound- or hysterectomy- confirmed UL during that time period.

Women who reported a new fibroid that had not been confirmed by pelvic exam only did not contribute person-time to that time period but were allowed to re-enter the analysis in the future if the fibroid was confirmed. The midpoint between the time of receipt of the questionnaire before diagnosis and the time of receipt of the questionnaire after diagnosis was assigned as the date of diagnosis. Marshall and colleagues validated self-reported diagnosis of UL in this cohort previously (15).

Statistical analysis

Women were excluded if they had a UL at baseline (n=5284), the date of fibroid diagnosis was unknown (n=900), had a hysterectomy (n=4900), were postmenopausal (n=482) or had history of cancer other than nonmelanoma skin cancer (n=692). Each participant contributed follow-up time, measured in months, from the return of the 1989 questionnaire until the first of the following events: report of a UL, death, hysterectomy, cancer diagnosis, menopause, the return of the 2003 questionnaire, or the last returned questionnaire (if lost to follow-up).

We used Cox proportional hazards regression models to estimate the association between reproductive characteristics and UL while controlling for known and suspected UL risk factors. Multivariate models adjusted for age in months, age at menarche (≤10, 11, 12, 13, 14–15, ≥16 years, missing), infertility (yes, no, missing), married (ever, never, missing), race (Caucasian, African American, Hispanic, Asian, Other), parity (nulliparous, 1, 2, 3, 4+ pregnancies lasting 6 or more months), age at first birth (≤ 24, 25–30, >30 years, missing), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, ≥16 years, missing), age at first oral contraceptive use (13–16, 17–20, 21–24, ≥25 years, missing), body mass index (<20, 20–21.9, 22–23.9, 24–24.9, 25–26.9, 27–29.9, ≥ 30 kg/m^2), diastolic blood pressure (<65, 65–74, 75–84, 85–89, ≥90 mm Hg), and antihypertensive medication (yes, no). Covariates were excluded from the model if they were colinear with the main exposure. In determining the final model, we adjusted for smoking (never, past, current) and observed no substantive changes in the results; therefore, smoking was excluded from our final model. Trend tests were performed using the midpoint of the intervals. In analyses stratified by fertility status, women who reported trying to become pregnant for more than one year without success were considered infertile, regardless of whether they reported other successful pregnancies.

RESULTS

After accounting for baseline exclusions, 104,350 women contributed 1,163,439 person-years of follow-up and we observed 9847 incident cases of UL confirmed by ultrasound or hysterectomy. Age at menarche was inversely associated with UL (p_{trend}<0.001) (Table 1). Time to regular menstrual cycling (Table 1) and menstrual pattern in high school (data not shown) were not associated with risk. However, cycle characteristics at later ages were associated with UL risk (Table 1). At ages 18–22, women with cycle lengths ≥ 40 days had a slightly decreased risk (covariate-adjusted RR=0.92, 95% CI=0.85–1.00) as did women with current (assessed in 1993) cycle lengths greater than 51 days (covariate-adjusted RR = 0.78, 95% CI=0.66–0.92). Interestingly, current cycle pattern had a U-shaped association with UL risk. Women in the “extremely regular (± 2 days)” and “always irregular” categories had a significantly reduced risk. Menstrual cycle associations were similar when restricted to hysterectomy-confirmed cases or when assessed by fertility status.

We also assessed all associations separately among women with a recent physical exam (breast or pelvic), as a proxy for access to medical care, and those without. We observed no differences in past menstrual characteristics by exam status, but we observed significant heterogeneity for current menstrual characteristics with stronger associations among women with no recent exam for current cycle length ($p_{heterogeneity}$ = 0.02). Among women with no recent exam, those with cycle length 51 days or longer had a significant reduction in risk (RR=0.34, 95% CI=0.16–0.72) while women with a recent exam had a non-significant reduction in risk (RR=0.87, 95% CI=0.74–1.04).

Overall, our data suggest no difference in UL incidence between women who reported ever or never using oral contraceptives (data not shown). However, further analyses are needed to determine whether duration, frequency, formulation, or timing of oral contraceptive use influences risk.

Parous women were less likely to develop UL (covariate-adjusted RR=0.69, 95%CI= 0.66–0.73) and the likelihood of UL among parous women decreased with each additional pregnancy (p_{trend}<0.001) (Table 2). Parous women with an older age at first birth, more recent last birth, and older age at last birth were less likely to report UL. Although these variables are correlated, they showed independent associations with UL risk as demonstrated in the multivariate models. Women whose last pregnancy was 16 or more years ago had more than two times the risk of UL compared to women pregnant within the last 1–3 years (RR=2.48, 95% CI= 2.13–2.87). Among parous women, both lifetime duration of breastfeeding (p_{trend}<0.001), and exclusive breastfeeding (p_{trend}=0.003) were inversely associated with UL risk.

Several of the reproductive associations changed when we restricted to hysterectomy-confirmed cases. The association between parity and UL lost its significance (covariate-adjusted RR = 0.91, 95% CI=0.82–1.01) but risk still decreased with increasing number of pregnancies (p_{trend}<0.001). Most other reproductive associations became stronger when we restricted to hysterectomy-confirmed cases. Women whose first birth was at 31 years of age or older had a nearly 40% reduction in risk of hysterectomy-confirmed UL (RR=0.62, 95% CI=0.53–0.74) and women who had their last birth at age 36 or older had a nearly 30% reduction in risk (RR=0.72, 95% CI=0.57–0.90). The association with time since last birth also strengthened with a nearly 4-fold increase in risk for women with 16 or more years since their last birth (RR=3.75, 95% CI=2.85–4.94) compared to women pregnant in the last 1–3 years. In addition, the magnitude of association between time since last birth was slightly stronger for fertile women (RR for ≥ 16 years since last birth = 3.93, 95% CI=3.48–4.44) compared to infertile women (RR=2.70, 95% CI=1.73–4.21) but the difference was not statistically significant ($p_{heterogeneity}$ = 0.11) and no other differences in reproductive characteristics were observed. Breastfeeding associations were slightly stronger for hysterectomy confirmed cases with a 27% reduction in risk for women who breastfed 37 months or more.

DISCUSSION

Generally, we observed the same associations between age at menarche, parity, age at first birth and time since last birth and UL as Marshall and colleagues (8), although we were able to evaluate finer categories due to our extended follow-up.

The inverse association in our data between age at menarche and UL risk is consistent with previous studies (7,8,11,12), although sometimes the association in previous studies did not reach significance (13). To our knowledge observations between current cycle pattern and UL risk have not been previously reported. We observed that women with the longest cycle

lengths or always irregular pattern were less likely to develop UL, perhaps due to less exposure to ovarian steroids. Conversely, women with extrememly regular cycles, who are unlikely to have anovulatory cycles, may have a reduction in risk due to regular progesterone exposure.

Consistent with earlier reports, parity was inversely associated with UL risk (8–10,14). Previously, the inverse association between parity and UL had been questioned since nulliparous women could be infertile (9,12). However, we observed an inverse association between parity and UL in both fertile and women who reported problems with fertility suggesting that parity is independently associated with UL.

We observed a trend in decreasing UL risk with longer duration of breastfeeding that was apparent across categories in the age-adjusted analysis but only evident after 19 months in the multivariate adjusted model. Investigators from the Black Women's Health Study also evaluated the association between breastfeeding and UL risk and observed no association across categories ranging from <1 month to ≥ 24 months (14). Although these data appear to be at odds, the confidence intervals overlap, and we have greater power to detect an association at the highest categories where the association is evident.

Though there are many potential influences on UL development [reviewed in (4,6,16)], endogenous hormones are hypothesized to be instrumental. UL incidence increases until menopause and GnRH agonists, which shut down gonadal hormone production, are an effective UL treatment (4). In addition, UL symptoms are often relieved with menopause but some women report that symptoms continue or develop with hormonal replacement therapy. Thus, our observations may be explained by extended exposure to endogenous estrogen and progesterone. For instance, decreasing risk with increasing age at menarche may be a reflection of decreased lifetime exposure to gonadal hormones. Similarly, breastfeeding, which induces amenorrhea and therefore periods of decreased estrogen/progesterone exposure, also reduced UL risk.

Though both estrogen and progesterone are elevated during pregnancy, progesterone, the predominant hormone, is required to establish and maintain the pregnancy (17) and may reduce UL risk. Baird and Dunson proposed that pregnancy is protective due to remodeling during uterine involution in the weeks following delivery (18). Alternatively, UL may develop in response to damage to myometrial cells during menstruation (19). Our observations regarding pregnancy, lactation, late age at menarche, and long menstrual cycle length would support this theory since all these exposures involve fewer menstrual cycles.

Our study is limited by the fact that many UL are asymptomatic and UL are identified in our study by self-report. Therefore, the UL identified by our study participants are likely to be symptomatic. Baird and colleagues have shown that 50% of women aged 35–49 with no previous history of UL will have a UL detected by ultrasound (18). Consequently, spurious associations may be observed between exposures that are associated with medical surveillance and UL. For instance, women receiving prenatal care may be more likely to have a UL detected. However, this would increase UL diagnoses among pregnant women and lead to a spurious positive association between parity and UL. Since we observed a decreased risk of UL with increasing number of pregnancies this type of bias is unlikely, although the true association could have been attenuated by an excess of UL diagnoses among pregnant women.

In addition, differences in multivariate and age-adjusted estimates suggest a role for confounding in these associations. Although we have adjusted for known and suspected UL risk factors, residual confounding could still account for some observed associations. Given the large number of statistical tests performed in this analysis, some associations could be

statistically significant by chance. However, all of the exposures evaluated were selected a priori, minimizing the likelihood of a chance finding.

With respect to public health significance, UL that come to clinical attention are the most relevant to study and understand since these are a source of considerable morbidity. Undetected UL are more likely to be asymptomatic (20); therefore, identification of factors involved in the initiation of UL development may not be as clinically important.

In our study, the proportion of new UL (9%) and new and existing UL combined (14%) is lower than the UL prevalence reported in other studies (21), likely due to the overwhelmingly Caucasian composition of our study population. Since UL are more common in African American women (15), the generalizability of our results are limited.

Our prospective analyses among premenopausal U.S. registered nurses suggest that late age at menarche, long menstrual cycles, parity, late age at first and last birth, short time since last birth, and breastfeeding reduce UL risk. The large sample size, prospective design, detailed assessment of menstrual and reproductive characteristics, and updated exposure and covariate information of the Nurses Health Study II allowed us to add to the limited knowledge of menstrual and reproductive characteristics and UL risk.

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Table 1

Menstrual characteristics and incidence of uterine leiomyomata, Nurses' Health Study II, 1989–2003

Menstrual Characteristic	Cases	Person-years	Age adjusted RR (95% CI)	Multivariate RR[a] (95% CI)	P trend[a]
Age at menarche, years[b]					
≤9	229	18757	1.42 (1.24, 1.62)	1.28 (1.12, 1.46)	<0.001
10	700	65225	1.21 (1.11, 1.31)	1.14 (1.05, 1.24)	
11	1829	187626	1.11 (1.05, 1.18)	1.07 (1.01, 1.13)	
12	3049	350398	1.00	1.00	
13	2518	322380	0.89 (0.85, 0.94)	0.92 (0.87, 0.97)	
14	900	123601	0.84 (0.78, 0.91)	0.88 (0.82, 0.95)	
15	342	52399	0.77 (0.69, 0.86)	0.82 (0.73, 0.92)	
≥16	243	39490	0.74 (0.65, 0.84)	0.77 (0.68, 0.88)	
Time to regularity, years					
< 1	4554	525351	1.00	1.00	0.57
1–2	2412	289632	0.98 (0.93, 1.03)	0.99 (0.94, 1.04)	
3–4	660	83761	0.95 (0.87, 1.03)	0.96 (0.89, 1.05)	
> 5	1228	136387	1.00 (0.94, 1.07)	1.03 (0.97, 1.10)	
never	935	121695	0.96 (0.89, 1.03)	0.96 (0.89, 1.03)	
Cycle length ages 18–22, days					
≤ 25	1109	130367	1.04 (0.98, 1.11)	0.99 (0.93, 1.06)	0.48
26–31	6527	764988	1.00	1.00	
32–39	1505	175296	0.99 (0.94, 1.05)	1.05 (0.99, 1.11)	
≥ 40 or irregular	686	89643	0.89 (0.83, 0.97)	0.92 (0.85, 1.00)	
Cycle pattern ages 18–22					
Very regular (+/−3 days)	4112	469636	1.06 (1.02, 1.11)	1.05 (1.01, 1.10)	0.26
Regular	3215	389223	1.00	1.00	
Usually irregular	1396	158981	1.08 (1.01, 1.15)	1.10 (1.03, 1.17)	
Always irregular	856	107653	0.96 (0.89, 1.03)	0.97 (0.90, 1.04)	
Current cycle length, days					
≤ 25	1085	104869	1.07 (1.00, 1.14)	1.02 (0.95, 1.09)	0.40
26–31	4226	455639	1.00	1.00	

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Menstrual Characteristic	Cases	Person-years	Age adjusted RR (95% CI)	Multivariate RR[a] (95% CI)	P trend[a]
32–50	658	74161	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)	
≥ 51 or irregular	147	21162	0.80 (0.68, 0.94)	0.78 (0.66, 0.92)	
Current cycle pattern					
Extremely regular (+/− 2 d)	1602	194072	0.91 (0.86, 0.97)	0.90 (0.84, 0.96)	<0.001
Very regular (+/− 4 d)	2335	244842	1.00	1.00	
Regular (+/− 7 d)	1650	161904	1.08 (1.01, 1.15)	1.06 (0.99, 1.13)	
Usually irregular	377	36595	1.12 (1.01, 1.25)	1.07 (0.96, 1.19)	
Always irregular	156	20504	0.86 (0.73, 1.02)	0.80 (0.68, 0.95)	

[a] Adjusted for body mass index, infertility, marital status, race, age at menarche, parity, age at first birth, time since last birth, age at first oral contraceptive use, antihypertensive medication use and diastolic blood pressure

[b] Age at menarche was not included as a covariate for this model since it is the main exposure of interest in this model

Table 2

Reproductive history and incidence of uterine leiomyomata, Nurses' Health Study II, 1989–2003

Reproductive characteristic	Cases	Person-years	Age adjusted RR (95% CI)	Multivariate RR (95% CI)	P trend
Parity					
Nulliparous	2587	244478	1.00	1.00[a]	
Parous	7002	841730	0.70 (0.68, 0.73)	0.69 (0.66, 0.73)	
Number of pregnancies lasting > 6 months (among parous women)					
1	1442	171776	1.00	1.00	<0.001[b]
2	3536	398410	0.96 (0.90, 1.02)	0.97 (0.90, 1.04)	
3	1570	201681	0.82 (0.76, 0.88)	0.88 (0.80, 0.96)	
≥ 4	454	69863	0.67 (0.60, 0.74)	0.78 (0.69, 0.89)	
Age at first birth, years (among parous women)					
≤ 25	3844	386148	1.00	1.00[c]	<0.001[c]
26–30	2533	360484	0.75 (0.71, 0.79)	0.86 (0.81, 0.91)	
≥ 31	805	145375	0.53 (0.49, 0.57)	0.71 (0.64, 0.79)	
Time since last birth, years (among parous women)					
< 1	83	28085	0.88 (0.70, 1.11)	0.89 (0.70, 1.13)[d]	<0.001[d]
1–3	598	173553	1.00	1.00	
4–5	523	99238	1.43 (1.27, 1.61)	1.33 (1.18, 1.50)	
6–7	603	93575	1.69 (1.50, 1.90)	1.51 (1.33, 1.70)	
8–9	702	88914	2.02 (1.79, 2.27)	1.71 (1.51, 1.93)	
10–12	1286	117929	2.68 (2.40, 2.99)	2.14 (1.89, 2.41)	
13–15	1137	91415	3.02 (2.69, 3.39)	2.24 (1.96, 2.56)	
≥ 16	1998	133214	3.75 (3.35, 4.22)	2.48 (2.13, 2.87)	
Age at last birth, years (among parous women)					
≤25	1321	101680	1.32 (1.23, 1.40)	1.09 (1.00, 1.18)[e]	0.02[e]
26–30	2975	325808	1.00	1.00	
31–35	2111	305885	0.69 (0.66, 0.73)	0.91 (0.84, 0.98)	
≥ 36	556	100673	0.46 (0.42, 0.50)	0.80 (0.70, 0.93)	
Total breastfeeding, months (among parous women)					

Reproductive characteristic	Cases	Person-years	Age adjusted RR (95% CI)	Multivariate RR (95% CI)	P trend
< 1	1470	137699	1.00	1.00[e]	<0.001[e]
1–3	453	49318	0.96 (0.87, 1.07)	1.03 (0.92, 1.14)	
4–6	656	77864	0.90 (0.82, 0.98)	0.97 (0.89, 1.07)	
7–12	1323	153569	0.89 (0.83, 0.96)	1.00 (0.92, 1.08)	
13–18	964	114225	0.85 (0.78, 0.92)	0.99 (0.91, 1.08)	
19–24	639	83375	0.75 (0.68, 0.82)	0.91 (0.83, 1.01)	
25–36	792	101123	0.75 (0.69, 0.82)	0.94 (0.86, 1.03)	
≥ 37	419	68487	0.57 (0.51, 0.63)	0.80 (0.71, 0.90)	
Exclusive breastfeeding, months (among parous women)					
< 1	2783	287392	1.00	1.00[e]	0.003[e]
1–3	737	80049	1.00 (0.92, 1.08)	1.05 (0.97, 1.14)	
4–6	816	96295	0.92 (0.85, 1.00)	1.02 (0.94, 1.10)	
7–12	1292	160233	0.84 (0.79, 0.90)	0.96 (0.90, 1.03)	
13–18	534	73153	0.74 (0.68, 0.81)	0.91 (0.82, 1.00)	
19–24	161	23494	0.68 (0.58, 0.80)	0.90 (0.76, 1.06)	
25–36	44	8046	0.54 (0.40, 0.72)	0.78 (0.57, 1.06)	
≥ 37	5	799	0.59 (0.25, 1.43)	0.92 (0.38, 2.23)	

[a] Adjusted for body mass index, infertility, marital status, race, age at menarche, age at first oral contraceptive use, antihypertensive medication use and diastolic blood pressure.

[b] Adjusted for age at first birth and time since last birth as well as all of the covariates listed in footnote a.

[c] Adjusted for parity and time since last birth as well as all of the covariates listed above.

[d] Adjusted for parity and age at first birth as well as all of the covariates listed in footnote a.

[e] Adjusted for parity, age at first birth, and time since last birth as well as all of the covariates listed in footnote a.