Uterine leiomyoma and menstrual cycle characteristics in a population-based cohort study

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BACKGROUND: We examined the association of uterine leiomyoma with menstrual cycle characteristics in a population of non-care-seeking women. METHODS: This cross-sectional study uses data from the Seveso Women’s Health Study (SWHS), a population-based cohort in Italy. Participants included 341 premenopausal women, 30–60 years old, who had an intact uterus and were not pregnant, lactating, or using oral contraception or intrauterine devices. We examined the presence of any ultrasound-detected uterine leiomyoma in relation to self-reported menstrual cycle length, flow length and heaviness of flow. The association of leiomyoma number, volume, tissue layer location and axial position with menstrual cycle characteristics was also examined. RESULTS: Uterine leiomyomata were detected in 73 women (21.4%). After adjustment for covariates, the presence of a leiomyoma was not significantly related to menstrual cycle length, flow length or heaviness of flow [odds ratio (OR) for scanty flow = 1.9, 95% confidence interval (CI) 0.8–4.3; OR for heavy flow = 1.3, 95% CI 0.7–2.5: relative to moderate flow]. Number, volume, tissue layer location (subserosal or intramural) and axial position (anterior or posterior) of the leiomyoma were also not related to menstrual cycle characteristics. CONCLUSION: In this Italian population of women not seeking gynaecological care, menstrual characteristics are not related to leiomyoma.

Key words: epidemiology/leiomyoma/menstrual cycle/transvaginal ultrasound

Introduction

Uterine leiomyomata, commonly known as fibroids, are benign smooth muscle tumours of the uterus. Estimates of leiomyoma prevalence range from 3 to 20%, with African-American and older women having the highest prevalence (Graves, 1933; Borgfeldt and Andolf, 2000; Chen et al., 2001; Baird et al., 2003). Leiomyomata have been identified as one of the leading causes of hospitalization for gynaecological disorders and hysterectomy in the USA (Ve lebil et al., 1995; Lepine et al., 1997; Farquhar and Steiner, 2002) and elsewhere (Chryssikopoulos and Loghis, 1986; Luoto et al., 1994). Chronic pelvic pain or menorrhagia are the usual indicators for hysterectomy (Tre loar et al., 1999).

There are plausible biological reasons for an association between leiomyoma and menorrhagia and other menstrual cycle characteristics. Leiomyomata gradually increase the volume and surface area of the uterus; this increase expands the endometrium, thus requiring increased time or flow rate to shed during menses. Leiomyomata, especially submucosal ones, may distort the endometrium, causing ulceration or necrosis. The compression of nearby veins in the interior uterine layers can also cause congestion of blood flow in the endometrium, with increased releases (Koutsilieris, 1992; Lumsden and Wallace, 1998; Vollenhoven, 1998; Hickey and Fraser, 2000; Robboy et al., 2000).

Most studies of the relationship of leiomyoma to menorrhagia and other menstrual cycle characteristics have been based on care-seeking populations, including women undergoing myomectomy or hysterectomy (Buttram, 1986; Cramer et al., 1995; Sato et al., 2000; Faerstein et al., 2001) or tubal ligation (Chen et al., 2001), with mixed results. However, clinic-based studies may not be generalizable, because women who have menstrual irregularities may be more likely than asymptomatic women to seek treatment and to be referred for surgery, and women who seek sterilization are more likely to be fertile than other women.

To date, only one study has examined the association of leiomyoma and menstrual cycle changes in a non-care-seeking population. In a random sample of >900 health plan members, the presence of ultrasound-diagnosed leiomyomata was associated with ‘gushing-type’ bleeding (Wegienka et al., 2003). In a general population of non-care-seeking Italian women, we previously reported that dyspareunia and non-cyclic pelvic pain, but not dysmenorrhoea, increased in severity with the presence of uterine leiomyomata (Lippman et al., 2003). The purpose of the present
study was to examine in these women the relationship between leiomyoma presence, number, volume, location and position and menstrual cycle characteristics (cycle length, flow length and heaviness of flow). These women were recruited based on where they resided not on medical treatment or location of medical care.

Materials and methods

Study participants

The current investigation analysed a subgroup from the Seveso Women’s Health Study (SWHS), a population-based cohort of 981 women who resided near Seveso, Italy in 1976 at the time of a chemical plant explosion that released high levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin). The primary purpose of the SWHS was to study the reproductive health of the women 20 years after the explosion. Details of this study have been described previously (Eskenazi et al., 2000). The Institutional Review Boards at all participating institutions approved this study and all participants signed an informed consent.

All women 20–50 years old (n = 751) and those between 50 and 60 years old who were still menstruating (n = 14) were invited to undergo a pelvic examination and transvaginal ultrasound following an interview; 662 (87%) agreed to participate and were examined. Only women with an intact uterus who were currently menstruating were eligible for analysis, leading to the exclusion of women who had previous hysterectomy (n = 29), who had not menstruated in the previous year (n = 25), were using oral contraceptives (n = 119) or intra-uterine devices (IUDs) (n = 34), were pregnant (n = 1) or were lactating (n = 5), leaving 451 women (some women had more than one reason for exclusion). Preliminary analysis showed that none of the 110 women under 30 years of age had leiomyoma, so these younger women were excluded from further analysis. The final study sample therefore consisted of 341 currently menstruating women, who were 30 years or older.

Procedures

Study participants were interviewed by trained nurse-interviewers. In addition to being asked about their reproductive and life histories, participants were asked the following four questions about their menstrual cycle characteristics: (i) ‘In the past year, how long have your cycles been?’; (ii) ‘In the past year, were your cycles regular, i.e., was the number of days from the start of one period to the start of the next about the same, give or take 4 days?’; (iii) ‘In the past year, on average, how many days did your flow last?’, and (iv) ‘During the past year, how would you describe the heaviness of your menstrual flow: scanty, moderate or heavy?’ From the responses to these questions, we derived continuous variables for menstrual cycle and menstrual flow length in days, and a categorical variable for menstrual flow heaviness (scanty, moderate or heavy).

Following the interview, a transvaginal ultrasound was performed by a gynaecologist at the Mangiagalli Hospital of the University of Milan or at the Desio Hospital. The procedure used the Aloka colour Doppler 680 and SSD 2000, 5 MHz transvaginal probe for imaging, and 6 MHz pulsed Doppler system for blood flow analysis. Each ultrasound examination was videotaped and reviewed by a second gynaecologist for quality control.

Based on the ultrasound examination, the following leiomyoma variables were created for each woman: (i) presence of one or more leiomyoma; (ii) total number of leiomyomata; (iii) leiomyoma tissue layer location, i.e., any subserosal, any submucosal or any intramural leiomyoma (three separate indicators were created because multiple leiomyomata could be present and a single leiomyomata could span more than one location); (iv) leiomyoma axial position (four variables), i.e., presence of any leiomyoma in the fundus, isthmus, anterior or posterior; and (v) dimension, i.e. volume in cm$^3$ for each myoma using the formula for a prolate ellipse (West and Lumsden, 1989; Schwartz et al., 1998). For women with multiple leiomyomata, three summary volume measures were created: mean volume, maximum volume and total summed volume.

Statistical analysis

Because the analyses use cross-sectional data, the associations between leiomyoma and menstrual cycle characteristics could be modelled with either as the dependent variable. For the associations with continuous variables, cycle length and flow length, we designed these variables as ‘dependent’ and the leiomyoma characteristics as ‘independent’. For ease of interpretation for associations with the three-category variable, heaviness of flow, we designated the leiomyoma characteristics as the ‘dependent’ variable and heaviness of flow as the ‘independent’ variable. Bivariate associations were analysed with $\chi^2$, ANOVA and Fisher’s exact tests.

For multivariate analyses, we used least squares mean regression for cycle length and flow length, and logistic regression for heaviness of flow. Covariates considered included: age at interview, education, consumption of caffeinated beverage, cigarette smoking habits, alcohol consumption, history of IUD and oral contraceptive use, age at menarche, body mass index (BMI), gravity, parity and history of previous diagnosis of endometriosis, leiomyoma, ovarian problems or other reproductive problems (Samadi et al., 1996; Schwartz, 2001). Covariates that confounded the relationship between menstrual cycle characteristics and presence of fibroids, as determined by a 10% change in the parameter estimate, were kept in the model. All analyses employed model-free standard errors, which are valid even under departures from standard assumptions (Huber, 1967). Women who reported irregular cycles were excluded from analyses of cycle length. Analyses of leiomyoma volume, tissue location and axial position were restricted to the subset of women with leiomyomata. Data analysis was conducted using Stata Statistical Software, Release 8.1.

Results

Selected characteristics of the study sample are presented in Table I. In total, 73 women (21.4%) were diagnosed with at least one leiomyoma on transvaginal ultrasound. Women who were older, less educated, former smokers, former alcohol users or heavier coffee consumers were more likely to have leiomyomata (Fisher’s exact test, $P < 0.05$). Women who reported a shorter duration of oral contraceptive use (<1 year versus ≥1 year) or a longer time (>5 years versus ≤5 years) since last oral contraceptive use were more likely to have leiomyomata (Fisher’s exact test, $P < 0.01$).

Average cycle length was 27.9 ± 2.5 days among the 293 women with regular cycles, and 48 women (14.1%) reported cycles of irregular length in the previous year. Average past year menstrual flow length was 4.9 ± 1.5 days. A total of 43 women (12.6%) reported scanty flow, 198 (58.1%) reported moderate flow and 100 (29.3%) reported heavy flow. Former IUD users had longer menstrual flows ($P < 0.05$). Women who were older, parous and had a higher BMI were more likely to report heavy menstrual flow ($P < 0.10$).
Menstrual cycle characteristics and presence of leiomyoma

The relationship of menstrual cycle characteristics to leiomyoma is shown in Table II. In crude analysis, having a leiomyoma was not associated with menstrual cycle length \( (P = 0.40) \) or flow length \( (P = 0.90) \) and remained unrelated after adjusting for covariates (age, BMI, smoking, parity, duration of oral contraceptive use or past IUD use). In the crude analysis, having leiomyoma was associated with scanty menstrual flow [odds ratio (OR) \( = 2.4 \), 95% confidence interval (CI) \( 1.2–5.1 \)] and heavy menstrual flow (OR \( = 1.8 \), 95% CI \( 0.7–4.3 \)). Adjusting for TCDD exposure did not alter these results.

Menstrual cycle characteristics and leiomyoma number and volume

Among the 73 women with leiomyomata, the average number of leiomyomata per woman was 1.6 (SD = 0.9); 45 women (62%) had one leiomyoma and 28 (38%) had more

Table II. Crude and adjusted statistics for the presence of leiomyoma associated with menstrual flow heaviness, cycle length and flow length, SWHS, Italy, 1996–1998

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Leiomyoma</th>
<th>Crude statistic</th>
<th>Adjusted statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes ( (n = 73) )</td>
<td>No ( (n = 268) )</td>
<td></td>
</tr>
<tr>
<td>Heaviness of flow, ( n (%) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scanty</td>
<td>14 (19.2)</td>
<td>29 (10.8)</td>
<td>OR (95% CI) ( 2.4 (1.2–5.1) )</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 (45.2)</td>
<td>165 (61.6)</td>
<td>OR</td>
</tr>
<tr>
<td>Heavy</td>
<td>26 (35.6)</td>
<td>74 (27.6)</td>
<td>OR (95% CI) ( 1.8 (1.0–3.1) )</td>
</tr>
<tr>
<td>Cycle length (days), mean ( \pm SD )</td>
<td>27.7 ( \pm 2.6 )</td>
<td>28.0 ( \pm 2.5 )</td>
<td>t ( (P\text{-value}) = 0.78 (0.44) )</td>
</tr>
<tr>
<td>Flow length (days), mean ( \pm SD )</td>
<td>4.9 ( \pm 1.5 )</td>
<td>4.9 ( \pm 1.5 )</td>
<td>t ( (P\text{-value}) = 0.15 (0.88) )</td>
</tr>
</tbody>
</table>

\*Reference category.
\*Adjusted for age, age-squared, smoking, BMI and nulliparity.
\*Adjusted for age, age-squared, smoking, BMI, nulliparity and duration of oral contraceptive use.
\*Adjusted for age, age-squared, smoking, BMI and past IUD use.
than one. Cycle length, menstrual flow length or heaviness of menstrual flow did not vary by number of leiomyomata ($P > 0.20$, all comparisons) (data not shown).

The median of the mean volume per fibroid was 4.4 cm$^3$ (25th, 75th percentiles = 1.4, 10.2). The median of the summed volumes was 6.6 cm$^3$ (25th, 75th percentiles = 1.9, 19.3). None of the measures of leiomyoma volume (mean, maximum or summed) varied by menstrual characteristics including cycle length ($P > 0.6$, all comparisons), menstrual flow length ($P > 0.2$, all comparisons) or flow heaviness ($P > 0.6$, all comparisons) (data not shown).

### Table III. Menstrual cycle length, flow length and flow heaviness, by leiomyoma tissue layer location and axial position, SWHS, Italy, 1996–1998

<table>
<thead>
<tr>
<th>$n$</th>
<th>Menstrual cycle characteristic</th>
<th>Flow length (days)</th>
<th>Menstrual flow heaviness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle length (days)</td>
<td>Flow length (days)</td>
<td>Scanty $n$ (%)</td>
</tr>
<tr>
<td>All leiomyoma</td>
<td>73</td>
<td>27.7 ± 2.6</td>
<td>4.9 ± 1.9</td>
</tr>
<tr>
<td>Subserosal location</td>
<td>Any</td>
<td>32</td>
<td>27.5 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>41</td>
<td>27.8 ± 3.1</td>
</tr>
<tr>
<td>Intramural location</td>
<td>Any</td>
<td>34</td>
<td>26.6 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>39</td>
<td>27.7 ± 1.8</td>
</tr>
<tr>
<td>Anterior position</td>
<td>Any</td>
<td>23</td>
<td>28.1 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>50</td>
<td>27.4 ± 2.6</td>
</tr>
<tr>
<td>Posterior position</td>
<td>Any</td>
<td>22</td>
<td>26.9 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>51</td>
<td>28.0 ± 2.2</td>
</tr>
</tbody>
</table>

*Row percentage of total.

### Menstrual cycle characteristics and leiomyoma tissue layer location and axial position

A summary of menstrual cycle characteristics by leiomyoma tissue layer location (subserosal or intramural) and axial position (anterior or posterior) is presented in Table III. None of the menstrual characteristics varied by location or position in crude (shown in Table III) or age-adjusted analyses (data not shown). There were only a few leiomyoma cases in submucosal ($n = 3$) or pedunculated ($n = 3$) tissue layer locations and fundal ($n = 4$) or isthmal ($n = 5$) axial positions; therefore, no statistical analyses were performed with these locations or positions.

### Discussion

The present cross-sectional study examined the association of the occurrence and characteristics of uterine leiomyomata with menstrual cycle characteristics in a population of non-care-seeking women. The overall leiomyoma prevalence rate was 21.4% in premenopausal women who were not pregnant, lactating or using oral contraception or an IUD. This prevalence is similar to the 20% previously cited in the literature (Graves, 1933; Borgfeldt and Andolf, 2000), but is likely to be an underestimate because women who had previous leiomyomata treated by hysterectomy could not be examined and thus were excluded from the analysis. In fact, of the 29 women excluded from uterine ultrasonographic examination because they had a previous hysterectomy, 90% reported that the reason for having a hysterectomy was leiomyoma.

In our study, the presence, number and volume of leiomyomata were unrelated to menstrual cycle length, flow length and heaviness of flow. Our findings are consistent with previous studies (Cramer et al., 1995; Sato et al., 2000; Faerstein et al., 2001), but inconsistent with others (Clevenger-Hoef et al., 1999; Chen et al., 2001; Wegienka et al., 2003). Similarly, although some studies (Akkad et al., 1995; Clevenger-Hoef et al., 1999), but not all (Wegienka et al., 2003), have suggested that tissue layer location and the axial position of leiomyomata may play a role in severity of menstrual symptoms, we did not find an association between menstrual cycle characteristics and location (subserosal or intramural) or position (anterior or posterior) of leiomyomata.

Our findings probably differ from previous studies of care-seeking populations because women with menstrual irregularities are more likely to seek treatment. However, our results also differ somewhat from the only other population-based study of women sampled from a health maintenance organization. In that study, Wegienka et al. (2003) found that women with leiomyomata were more likely to report gushing-type bleeding (defined as an episode of bleeding which could not be controlled by pads or tampons) than women without leiomyomata. This definition may capture women with more problematic menstrual bleeding than we were able to in our study by asking about usual heaviness of menstrual flow over the past year with choices of scanty, moderate and heavy. Nevertheless, we found a significant crude association not only with heavy flow but also with scanty flow, which diminished after control of potential confounders. We note, however, that somewhat more women with leiomyomata reported using ‘maxi pads’ than women without leiomyoma ($P = 0.07$), lending some support to an association of leiomyoma and heavy flow.
Our study had several strengths. As a population-based cross-sectional study, the results are generalizable to the population of similar women, at least in Italy. The questionnaires were administered by highly trained nurse-interviewers, and the examinations were performed by experienced gynaecologist/ultrasonographers for research purposes. The participation rate in SWHS was high (81%). However, our study also had limitations. As noted elsewhere, if women with the most severe symptoms are more likely to be treated with hysterectomy, then we would have underestimated not only the overall prevalence of leiomyomata, but also the association between leiomyomata and heavy menstrual flow. However, of the 29 women excluded from ultrasonography because of prior hysterectomy, women who had hysterectomies because of leiomyomata were no more likely to report bleeding as an indication for surgery than women who had hysterectomies for reasons other than leiomyomata (26.9 versus 33.3%, $\chi^2 = 0.06, P = 0.8$).

Our study was limited to Caucasians, who may be at lower risk for leiomyoma (Kjerulf et al., 1996; Baird et al., 2003). Thus, we could not examine differences in menstrual characteristics associated with leiomyoma by race. It is possible that population differences may exist in the genetics (Kitawaki et al., 2001; Sato et al., 2002) and other biological aspects of leiomyoma which might affect menstrual characteristics (Roth et al., 2003).

In conclusion, based on this population-based study of non-care-seeking Caucasian women, we found little evidence that non-care-seeking Caucasian women, low length and heaviness of flow were related to number, volume, tissue layer location (subserosal or intramural) and axial position (anterior or posterior) of leiomyomata. The association of leiomyomata with menstrual cycle abnormalities has been based principally on previous studies of clinic-based populations, particularly of women seeking hysterectomy. Because asymptomatic women are under-represented in such populations, the association of leiomyoma with menstrual cycle disorders in the general population may previously have been overestimated.

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References


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