Self-Reported Heavy Bleeding Associated With Uterine Leiomyomata

Ganesa Wegienka, PhD, Donna Day Baird, PhD, MPH, Irva Hertz-Picciotto, PhD, Siobán D. Harlow, PhD, John F. Steege, MD, Michael C. Hill, MD, Joel M. Schectman, MD, and Katherine E. Hartmann, MD, PhD

OBJECTIVE: To characterize the relationship between self-reported bleeding symptoms and uterine leiomyoma size and location.

METHODS: The leiomyoma status of a randomly selected sample of women aged 35–49 in the Washington, DC, area was determined using abdominal and transvaginal ultrasound to measure size and location of leiomyomata found at screening. Women were asked about symptoms of heavy bleeding (gushing-type bleeding, long menses, pad/tampon use) in a telephone interview. Using multivariable regression, we examined the relationships between leiomyoma characteristics and heavy bleeding symptoms among 910 premenopausal women.

RESULTS: Women with leiomyomata (n=596) more likely to report gushing-type bleeding than women without leiomyomata; risk increased with leiomyoma size. Adjusted relative risks with 95% confidence intervals (CI) for women in each leiomyoma size category compared with the reference category (women without leiomyomata) were as follows: adjusted relative risk of 1.4 (95% CI 1.1, 1.9) for diffuse only, adjusted relative risk of 1.4 (95% CI 1.1, 1.8) for small leiomyomata (less than 2 cm), adjusted relative risk of 1.6 (95% CI 1.3, 2.0) for medium leiomyomata (2–5 cm), and adjusted relative risk of 1.9 (95% CI 1.5, 2.5) for large leiomyomata (greater than 5 cm). Reported use of eight or more pads/tampons on the heaviest days of menstrual bleeding increased with leiomyoma size, with a nearly 2.5-fold risk for women with large leiomyomata compared with women without leiomyomata (adjusted relative risk of 2.4; 95% CI 1.8, 3.1). Nonsubmucosal leiomyomata were associated with essentially the same increase in heavy bleeding as submuscosal leiomyomata of similar size.

CONCLUSION: Small leiomyomata were associated with increased risk of heavy bleeding, and risk increased with size. Contrary to published articles, nonsubmucosal leiomyomata were associated with heavy bleeding to the same extent as submucosal leiomyomata. (Obstet Gynecol 2003;101:431–7. © 2003 by The American College of Obstetricians and Gynecologists.)

Reported prevalence of uterine leiomyomata among premenopausal women in the United States ranges from 20% to 77%.[1,2] The leading preoperative diagnosis for hysterectomy in the United States is uterine leiomyomata, accounting for more than a third of all hysterectomies.[3,4] Inpatient care costs associated with leiomyomata were estimated at $2 billion in 1997, and outpatient costs are likely to be substantial, although they have not yet been estimated.[5]

One of the most commonly reported symptoms of leiomyomata among premenopausal women is heavy menstrual bleeding,[1,5–8] which can have impacts that are personal (interference with social and sexual activities, time spent seeking treatment), financial (lost work, cost of pads/tampons and medical care), and medical (development of anemia). Several hypotheses have been offered for the underlying biologic mechanisms by which leiomyomata could cause excess bleeding, but none have been adequately studied.[1,7] Although location, size, and number of leiomyomata have been postulated to determine bleeding risk, the relationship between leiomyomata and self-reported bleeding has not been well char-

From the Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, North Carolina; Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina; Department of Epidemiology and Preventive Medicine, University of California, Davis, California; Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan; Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina; and Departments of Radiology and Health Care Sciences, George Washington University Medical Center, George Washington University, Washington, DC.

JMS is currently affiliated with the University of Virginia, Charlottesville, Virginia.

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acterized in a population-based study with ultrasound confirmation of leiomyoma status.

The purpose of this research was to compare self-reported symptoms of heavy bleeding for women with leiomyomata and women without leiomyomata, and to estimate the risk of heavy bleeding associated with increased leiomyoma size and with submucosal location. Leiomyoma status was assessed with ultrasound screening of randomly selected women aged 35–49. Specifically, the prevalence of gushing-type bleeding, length of menses (days of actual flow, excluding days of just spotting), and pad/tampon use on the heaviest days of bleeding were examined.

MATERIALS AND METHODS

The data for this analysis are from the National Institute of Environmental Health Sciences Uterine Fibroid Study, which was conducted from 1996 to 1999 in the Washington, DC, area as a collaboration with the George Washington University Medical Center. The study was designed to determine the prevalence of leiomyomata in black and white women.[9] The Institutional Review Boards of both the National Institute of Environmental Health Sciences and the George Washington University Medical Center approved the original study, and the University of North Carolina School of Public Health Institutional Review Board approved this analysis.

We obtained a random sample of 2384 health plan enrollment records from the George Washington University Health Plan (a health maintenance organization) for women who were aged 35–49 and had telephone numbers. Of those women, 129 (5%) were not reachable, 150 (6%) declined eligibility screening, and three were not contacted because of error. Of 2102 women screened, 316 (15%) were found to be ineligible, the majority of whom no longer obtained care at the Washington, DC, site. Of the 1786 eligible, 335 (19%) declined participation. Additionally, 17 (1%) who agreed to participate and four (0.2%) who were undecided about participation became unreachable before a telephone interview could be completed. Thus, 1430 (80% of the eligible) participated in the study; 1245 of these (87%) were premenopausal. Premenopausal women were those who had a menstrual period or were pregnant or breast-feeding during the previous 12 months.

Participants completed a telephone interview and recorded demographic data in a self-administered questionnaire. The telephone interview collected information about reproductive, menstrual, medical, and contraceptive histories, and about any previous leiomyoma diagnoses or treatments. We asked women who had not had a recent ultrasound examination to have study ultrasounds (details below) and asked all women to come in for a clinic visit. Weight was measured at the clinic visit. If a woman did not come in for a clinic visit, her weight reported at the interview was used to calculate body mass index as kg/m^2. Each participant gave informed consent.

If a woman had been previously diagnosed with leiomyomata and had an ultrasound in the prior 5 years or had not had a leiomyoma diagnosis and had an ultrasound in the prior 2 years, we obtained those sonogram records in lieu of a study sonogram. For this study, each woman underwent both a transabdominal and a transvaginal ultrasound. The transabdominal ultrasound allowed the evaluation of leiomyoma changes in the upper uterus that would have been difficult to detect with only a transvaginal ultrasound. Ultrasound examinations were performed by sonographers certified by the American Registry of Diagnostic Medical Sonographers, and were directly supervised by a radiologist with fellowship training in ultrasound; each study was reviewed by a radiologist at completion. The sonographers used ultrasound units ATL HDI 9 (Philips Medical Systems, Bothwell, WA), Acuson 128 XP (Siemens/Acuson, Mountain View, CA), and Diasonics DRF 400 (GE/Diasonics, Waukesha, WI) with transabdominal (3.5–5.0 mHz) and transvaginal (5.0–7.0 mHz) ultrasound probes. A data collection form was designed for the study and completed by the sonographers. The data collected included the following: diffuse heterogeneity of the echopattern (yes or no), focal leiomyomata (yes or no), the size and location of the two largest leiomyomata at least 2 cm in diameter, and the size of the three largest submucosal leiomyomata. A single radiologist (MCH) reviewed all questionable ultrasounds.

Of the 1245 participants, 152 failed to have the requested study ultrasound, and seven had an indeterminate leiomyoma status. Thirty-two of these reported a prior diagnosis of leiomyomata and were included in this analysis because of the high probability that they did actually have leiomyomata, but the remainder who had no prior diagnosis and no sonogram (study or otherwise) were dropped because their leiomyoma status could not be determined with certainty. An additional 208 women had conditions or were taking medications that could alter their menstrual periods (21 were pregnant or breast-feeding, 168 were taking oral contraceptives and/or other hormones, 16 had intrauterine devices, and three had recent myomectomies). The responses of the remaining 910 women served as the basis for this analysis.

The bleeding characteristics examined were: a) self-report of gushing-type bleeding during the last year (yes or no), b) reported pad/tampon use during a 24-hour

Table 1. Demographic Characteristics by Leiomyoma Status

	No focal leiomyomata (N = 314) (35%)		Any focal leiomyomata (N = 488) (54%)		Diffuse heterogeneous echopattern (N = 108) (12%)	
	n	%	*n*	%	*n*	%
Ethnicity						
White	154	49	134	27	32	30
Black	132	42	320	66	69	64
Other/unknown	28	9	34	7	7	6
Age at telephone interview (y)						
35–40	158	50	148	30	45	42
41–45	107	34	196	40	38	35
46–51	49	16	144	30	25	23
Highest level of education						
Less than college	110	38	232	53	50	50
College degree	84	29	89	21	28	28
Graduate degree	97	33	113	26	22	22
Never smoker	168	54	253	52	48	44
Ex-smoker	87	28	133	27	25	23
Current smoker	59	19	101	21	35	32

period on heaviest days of flow (categorized as one to seven or eight or more pads/tampons), and c) reported length of menses at last period, ie, days of real flow (excluding spotting) for the last period (categorized as 1–5 days or 6 days or more). All responses were taken from the telephone interview. Whether or not the woman had gushing-type bleeding was determined by her response to the following question: "(Again) thinking of the year before your most recent period, did you have any times when you had heavy, gushing-type bleeding that was too much for your pads or tampons even when changed frequently?" The response rates to each of the three bleeding questions were greater than 99% (responses to each question: n = 902 for gushing-type bleeding, n = 909 for bleeding length, n = 905 for pad/tampon use). The distribution of total pads/tampons on the heaviest days of bleeding was not normal and was not improved by a transformation. The 75th percentile, eight pads/tampons in a 24-hour day, was used as a measure of high pad/tampon usage.

The association of menstrual flow with age, reported ethnicity (categorized here as black, white, and other), education, total household income, marital status, parity at age 35, body mass index (kg/m^2), current cigarette smoking, current physical activity (including walking), and alcohol was also examined.

Using the GENMOD procedure in SAS 8.0 (SAS Institute Inc., Cary, NC), risk models were used to analyze the binary outcomes (gushing, bled 6 or more days, used eight or more pads/tampons). Scaled Poisson regression models were used to analyze continuous bleeding length.[10]

RESULTS

We had sonogram information from 878 of the 910 women; 564 had fibroids detected, and 314 had none detected. The remaining 32 women without sonogram information were classified as having fibroids because they reported having a prior diagnosis and no treatment and were likely to have fibroids. Of the 564 with fibroids detected at sonogram, 551 had complete detailed information on both fibroid size and location. Of those women with complete detailed fibroid information, 119 (22%) had at least one submucosal leiomyoma, 324 (59%) had only nonsubmucosal leiomyomata, and 108 (20%) had only a diffuse heterogeneous echopattern.

Compared with women without leiomyomata, women who had leiomyomata were more likely to be black, slightly older, and have less education (Table 1). Figures 1 and 2 show the distribution of days of flow and pad/tampon totals by leiomyoma status. For both outcomes, the distribution for women with leiomyomata is shifted to the right (ie, these women bled more and longer than those without leiomyomata). The most frequently reported length was 5 days for those with leiomyomata (median = 4), compared with 4 days for those without leiomyomata (median = 4). Similarly, the most frequently reported value for pad/tampon use was six per day for those with leiomyomata (median = 6), compared with four per day for those without leiomyomata (median = 5). Detailed information about size and location of leiomyomata and bleeding characteristics is given in Table 2. In nearly all categories, women with

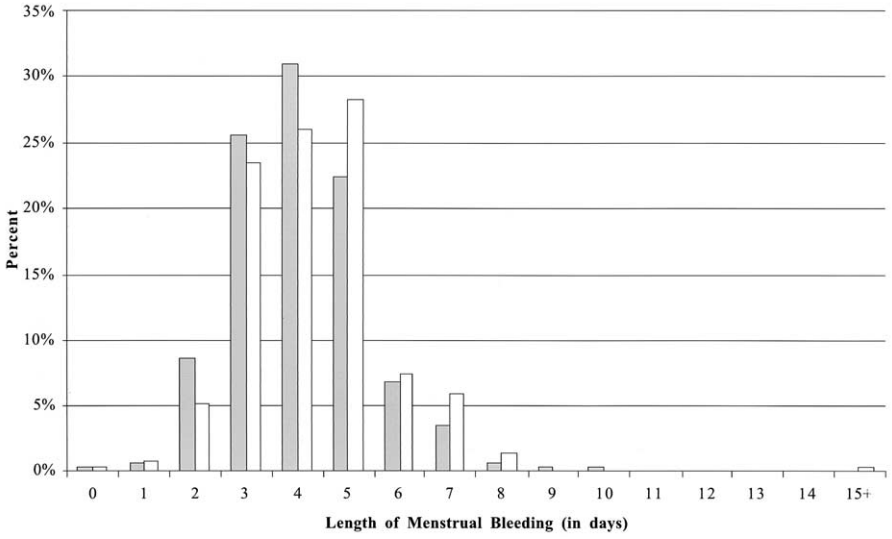

Figure 1. The distribution of the length of menstrual bleeding in days for women with and without uterine leiomyomata. The gray bars represent women without leiomyomata, and the white bars represent women with leiomyomata.

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leiomyomata had more bleeding than those with no leiomyomata.

Very high body mass index (40 kg/m^2 or greater) and parity were associated with increased menstrual bleeding as measured by gushing and an increased bleeding length (not shown). Being parous was also associated with an increased risk of reporting high pad/tampon use (not shown). Therefore, we adjusted leiomyoma status for these factors in the multiple regression models (Table 3).

Of those with leiomyomata, 46% reported gushing-type bleeding, compared with only 28% of women without leiomyomata. Multivariable analysis to assess the risk of gushing-type bleeding associated with the presence of leiomyomata showed an elevated risk for women with both small and large leiomyomata compared with women without leiomyomata; the risk was 40% higher (95% confidence interval 10, 80) for small (0–2 cm) leiomyomata, 60% higher (95% confidence interval 30, 100) for moderate-size leiomyomata (2–5 cm), and 90% higher (95% confidence interval 50, 150) for leiomyomata greater than 5 cm. Among women with leiomyomata, after adjusting for size of the largest leiomyoma, having a submucosal leiomyoma or multiple leiomyomata did not influence the risk of gushing-type bleeding (Table 3). The relationships between gushing-type bleeding and leiomyomata did not differ by ethnicity.

With respect to pad/tampon use, the overall mean was 7.1 ± 4.6 (range 0–48). For those with leiomyomata, the mean was 7.5 ± 4.9 (range 0–48); for those without leiomyomata, the mean was 6.1 ± 3.8 (range 1–40). In a multivariable model examining size of largest leiomyoma, the risk increased as the size of the largest leiomyoma increased, but after adjusting for leiomyoma size, having a submucosal leiomyoma or having multiple

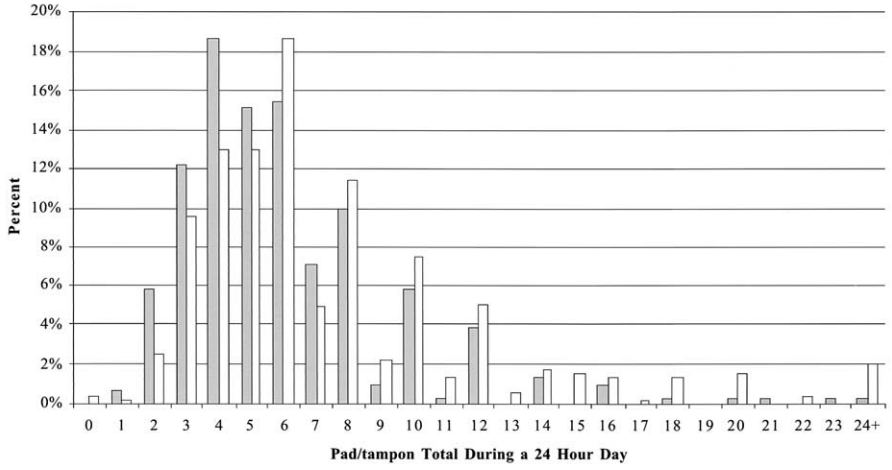

Figure 2. The distribution of pad/tampon use per day for women with and without uterine leiomyomata. The gray bars represent women without leiomyomata, and the white bars represent women with leiomyomata.

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Table 2. Characteristics of Bleeding by Leiomyoma Status*

	n	Gushing prevalence %	Length of menses		Pad/tampon total	
			Mean (SD)	Median	Mean (SD)	Median
All women						
No leiomyomata	314	28	4.1 (1.3)	4	6.1 (3.8)	5
Any leiomyomata	596	46	4.4 (1.6)	4	7.5 (4.9)	6
Largest ≤ 5 cm	486†	44	4.3 (1.6)	4	7.0 (4.2)	6
Largest > 5 cm	69†	56	4.5 (1.7)	4	10.7 (7.3)	8
Women with leiomyomata at a single location						
Diffuse only	108	41	4.3 (1.2)	4	7.4 (4.2)	6
Nonsubmucosal only						
Largest ≤ 5 cm	161	38	4.3 (1.6)	4	6.5 (3.9)	6
Largest > 5 cm	21	52	4.3 (1.7)	4	11.1 (4.8)	10
Submucosal only						
Largest ≤ 5 cm	25	48	4.4 (1.1)	4	6.0 (2.3)	6
Largest > 5 cm	4	67	4.5 (1.0)	5	6.3 (1.1)	10
Women with leiomyomata at multiple locations						
Nonsubmucosal and diffuse						
Largest ≤ 5 cm	124	50	4.2 (1.5)	4	7.4 (4.5)	6
Largest > 5 cm	18	61	4.8 (1.8)	4.5	12.8 (11.8)	8
Nonsubmucosal and submucosal						
Largest ≤ 5 cm	17	35	3.6 (1.7)	3	8.2 (7.8)	5
Largest > 5 cm	8	63	5.6 (2.7)	5	13.0 (5.2)	12
Submucsoal and diffuse						
Largest ≤ 5 cm	15	67	4.3 (1.1)	4	6.7 (3.7)	5
Largest > 5 cm	3	67	4.0 (0)	4	7.0 (3.0)	7
Nonsubmucosal, submucosal, and diffuse						
Largest ≤ 5 cm	35	49	4.9 (2.2)	5	7.2 (3.1)	6
Largest > 5 cm	12	50	3.9 (1.1)	4	6.7 (2.9)	6

SD = standard deviation.
* Forty-five women have incomplete leiomyoma information.
† Numbers do not sum to 596 because of missing size information.

leiomyomata was not associated with an increased risk of reporting high pad/tampon use (Table 3). The relationships between leiomyomata and high pad/tampon use did not differ by ethnicity.

The women without leiomyomata who responded to the bleeding length question (n = 313) had a mean bleeding length of 4.1 ± 1.3 days (range 0–10 days). The 595 women with leiomyomata and a response to the bleeding length question had a mean bleeding length of 4.4 ± 1.6 days (range 0–18 days). One woman who had leiomyomata and reported a bleeding length of 58 days for her last menstrual period was excluded from these analyses. Leiomyomata were not significantly associated with bleeding length in a scaled multivariable Poisson model, nor with bleeding 6 days or more as examined by a multivariable risk model.

DISCUSSION

Although bleeding is a commonly reported symptom of leiomyomata, after an exhaustive literature search using PubMed (1966 to April 2002; all languages; search terms: "fibroids," "leiomyoma," "leiomyomata," "abnormal utering bleeding," "heavy menstrual bleeding," "menorrhagia"), we were unable to locate any published studies that have systematically assessed the presence or absence of leiomyomata in a population-based sample and examined their menstrual bleeding characteristics. Women with leiomyomata from our cohort drawn from a health maintenance organization in Washington, DC, were more likely to report gushing-type bleeding and high pad/tampon use, compared with women without leiomyomata. Though more blacks than whites had leiomyomata, the associations between leiomyomata and menstrual bleeding did not differ by race. Also, the results did not differ even after excluding women who only had leiomyoma data from a prior ultrasound (and did not have an ultrasound specifically for the study).

Our results extend previous work that examined women undergoing hysterectomy. Carlson et al[11] found that women with a preoperative diagnosis of leiomyoma or abnormal bleeding were more likely to report heavier and longer bleeding, compared with those with some other preoperative diagnosis (pelvic pain, other). Some review articles have suggested that submucosal leiomy-

Table 3. Adjusted Relative Risks of Bleeding Outcomes Associated With Leiomyoma Characteristics

	Gushing		Used eight or more pads/tampons	
	RR	95% CI	RR	95% CI
Among all women*				
Noleiomyomata	1.0	Reference	1.0	Reference
Diffuse only	1.4	1.1, 1.9	1.5	1.1, 2.0
Largest < 2 cm	1.4	1.1, 1.8	0.9	0.6, 1.3
Largest 2–5 cm	1.6	1.3, 2.0	1.5	1.2, 2.0
Largest > 5 cm	1.9	1.5, 2.5	2.4	1.8, 3.1
Parous at age 35				
No	1.0	Reference	1.0	Reference
Yes	1.3	1.1, 1.6	1.4	1.2, 1.7
BMI > 40 kg/m^2				
No	1.0	Reference	1.0	Reference
Yes	1.4	1.1, 1.7	1.1	0.9, 1.5
Among women with leiomyomata†				
Has a single leiomyoma or diffuse only	1.0	Reference	1.0	Reference
Has multiple leiomyomata	1.0	0.8, 1.3	1.1	0.8, 1.4
Has leiomyomata, none are submucosal	1.0	Reference	1.0	Reference
Has at least one submucosal leiomyoma	1.1	0.9, 1.4	0.9	0.7, 1.1

RR = relative risk; CI = confidence interval; BMI = body mass index.

*Model includes leiomyoma category (no leiomyomata, diffuse only, largest < 2 cm, largest 2–5 cm, largest > 5 cm), having a large BMI, and being parous at age 35.

† Model includes leiomyoma category (no leiomyomata, diffuse only, largest < 2 cm, largest 2–5 cm, largest > 5 cm), having a large BMI, being parous at age 35, having a submucosal leiomyoma, and having multiple leiomyomata.

omata are the greatest source of leiomyoma-related symptoms[6] or heavy bleeding.[8] In contrast, we found that leiomyomata in any location, rather than just submucosal leiomyomata, were associated with increased risks of gushing or high pad/tampon use. This means nonsubmucosal leiomyomata were associated with essentially the same increase in heavy bleeding as submuscosal leiomyomata of similar size. Those associated risks increased further with an increase in the size of the largest leiomyoma.

Although leiomyomata can cause increased bleeding, exactly how they do so is not clear. Leiomyomata might affect the vascularization of the uterus, leading to increased vessel number or abnormal function.[1,7,8] Another common clinical hypothesis is that leiomyomata increase the surface area of the endometrium, thus increasing the volume of material expelled during menses. An increased surface area could be caused by a submucosal leiomyoma or a large leiomyoma. Our results do not support the conclusion that having a leiomyoma in a submucosal position further increases the risk of heavy bleeding. Perhaps leiomyomata impede the normal sequence of uterine contractions, and uterine contents are not expelled in an efficient manner. Previous work has found more expandable venules in the endometrium of uteri containing leiomyomata,[12] and it has been hypothesized that clotting is less efficient in these vessels.[7] Further studies of the impact of leiomyoma growth on uterine vascularity and menstrual contractility are needed.

These findings have implications for epidemiologic research on menstrual bleeding. Future studies need to incorporate leiomyoma status. Including leiomyoma status will be difficult because self-report is a poor proxy; more than half the women in this study who were found to have leiomyomata at ultrasound screening (57%) did not know they had them at the time of the telephone interview. As a result, imaging is necessary for research.

These data are from a single random sample from an urban health maintenance organization. Although this group of women was ethnically diverse (more than 50% were black), this sample may not be representative of all women. However, the associations between leiomyomata and bleeding did not vary by ethnicity, income, or age in our study, suggesting that results may be generalizable.

We used transvaginal and abdominal ultrasound for assessing leiomyoma status and to map size and location. Several publications have shown that ultrasound detection of submucosal leiomyomata is highly sensitive (100%,[13,14] 99%,[15] 90%[16]), and that it also has good specificity (98%,[16] 94%,[13] 87%[14]), positive predictive value (93%,[14] 90%,[16] 81%[13]), and negative predictive value (100%,[13,14] 98%[16]). Three[13,14,16] of these publications used surgical specimens to determine the "true" disease status, whereas the fourth[15] study used hysteroscopic results. It has also been reported to be as efficient as magnetic resonance imaging in leiomyoma detection, and essentially as good for assessing leiomyoma characteristics (size and location) if uteri have less than five

leiomyomata.[17] In our study, only two women had five or more leiomyomata of more than 2 cm. Our rates of submucosal leiomyomata (22% of those with leiomyomata) are similar to those found by Kjerulff et al[18] in their study that used routine pathology examinations of uteri removed at hysterectomy to record leiomyoma details (21% of white women and 32% of black women), supporting the validity of our assessment of leiomyoma location.

We classified women with a diffusely heterogeneous echopattern as a separate group, though they are likely to have several small leiomyomata. They could also include women with adenomyosis. However, adenomyosis tends to have a heterogeneous echopattern clustered around the endometrial cavity and may contain small cysts. The overall shape of the uterus tends to be globular with adenomyosis, but lobulated with leiomyomata. The study sonographers were trained by our radiologist (MCH) to note these different characteristics.

These data provide further evidence that leiomyomata cause heavy menstrual bleeding. This study shows that even small leiomyomata are associated with an increase in risk of heavy menstrual bleeding, and the associated risk of heavy bleeding increases further with leiomyoma size. The data do not support previous reports that submucosal leiomyomata are the most important factor causing heavy menstrual bleeding. Until more definitive studies assess longitudinal symptom change in relation to leiomyoma development, we should consider even small, nonsubmucosal leiomyomata to be potentially symptomatic. This provides further impetus for developing nonsurgical treatment strategies for this common condition.

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Address reprint requests to: Ganesa Wegienka, PhD, National Institute of Environmental Health Sciences, Mail Drop A3-05, P.O. Box 12233, Research Triangle Park, NC 27709; E-mail: wegienka@niehs.nih.gov.

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