Published in final edited form as:

Fertil Steril. 2009 January ; 91(1): 201–206. doi:10.1016/j.fertnstert.2007.11.025.

Adenomyosis a variant not a disease? Evidence from Hysterectomized Menopausal Women in the SWAN Study

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Abstract

Objective—Our study evaluates the symptoms commonly attributed to adenomyosis in women undergoing the menopausal transition. We hypothesized that adenomyosis is more commonly seen in women with fibroids, pelvic pain, abnormal uterine bleeding, and in the presence of endometriosis.

Design—Retrospective cohort

Setting—multi-site community based study

Patients—SWAN study enrollees who had hysterectomies

Interventions—None

Main Outcome Measurements—Relationship of Adenomyosis to other entities

Results—Adenomyosis was found in 48% of 137 patients. Frequencies of presenting symptoms were similar in those with and without evidence of adenomyosis. The same prevalence of fibroids, 37 % versus 43% ($p=0.39$), endometriosis, 3% versus 5% ($p=0.41$), abnormal bleeding, 27% versus 33% ($p=0.72$), or chronic pelvic pain in the presence of fibroids 12% versus 17%, ($p=0.58$), was seen in the presence or absence of adenomyosis.

Conclusions—Adenomyosis is a common diagnosis seen in hysterectomized specimens from women undergoing the perimenopausal transition. Adenomyosis is equally common in women who also have fibroids, endometriosis, pelvic pain, or abnormal uterine bleeding, and those women that do not. Therefore, adenomyosis is an incidental finding, not the source of the symptomatology. It appears not to be a “disease” per se, but a normal variant.

Keywords

Adenomyosis; Endometriosis; Fibroids; Pelvic Pain

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Capsule: Adenomyosis is not a disease, but a normal variant not related to endometriosis, pelvic pain, fibroids, or abnormal uterine bleeding.

INTRODUCTION

Adenomyosis, a common non-malignant condition of the uterus, is characterized by the presence of endometrial glands and stroma ectopically placed in the myometrium. Adenomyosis induces hyperplasia and hypertrophy of the myometrium, thus enlarging the uterus. The literature suggests that it may be related to chronic pelvic pain and abnormal uterine bleeding, (1,2,3) although adenomyosis is often asymptomatic (4–7). The diagnosis of adenomyosis has usually been made pathologically, after hysterectomy, most commonly by microscopic criteria, although preoperative diagnosis by magnetic resonance imaging is becoming more common and a variety of medical and surgical treatments are now being recommended (8–10). The diagnosis of adenomyosis is used as an indication for hysterectomy.

The general incidence of adenomyosis has not been accurately determined. In hysterectomy specimens the incidence of adenomyosis reported in the literature varies, ranging from a high of 61.5% to a low of 8.8% (2,5,11–15). Hyperestrogenemia, a cause of endometrial hyperplasia and fibroid growth, has been associated with adenomyosis, (5,11) as has prior pregnancy (2, 3,13,15,16). Adenomyosis has also been related to the presence of endometriosis (2,17–19).

The major symptoms of adenomyosis are thought to be abnormal uterine bleeding (1,3–5,9) chronic pelvic pain, and dysmenorrhea (1–3,20–22). When present, these symptoms lead to a presumptive preoperative diagnosis of adenomyosis, and are often used as an indication for hysterectomy. While some have suggested that adenomyosis is associated with these symptoms (1–5,20–22) and more commonly coexists with fibroids (2) and endometriosis (2,17–19) others have concluded the opposite view (3,11–16). It is apparent that these issues need further clarification. The purpose of this study is to determine the incidence of adenomyosis in hysterectomy specimens as well as to examine the association of adenomyosis with uterine fibroids, endometriosis, abnormal uterine bleeding and chronic pelvic pain.

MATERIALS AND METHODS

The Study of Women's Health Across the Nation (SWAN) is a multi-ethnic, multi-site community based study of 3302 women being followed through the menopausal transition. Women were pre- and early peri-menopausal at baseline and have provided up to 10 years of annual data as part of an 11 year study. The design of the study has been previously described (23). Briefly, a screening survey was conducted between November 1995 and December 1997 to assess eligibility for enrollment and to collect demographic, reproductive, health and lifestyle data. From the 16,065 women who completed this initial screener, approximately 450 eligible women were recruited for continued follow up at each of seven clinical sites. In addition to Caucasian women, each site recruited women from one specified minority group (African Americans in Pittsburgh, PA, Boston, MA, Detroit area, MI, and Chicago, IL; Japanese in Los Angeles, CA; Chinese in the San Francisco East Bay region, CA; and Hispanic women in Newark, NJ). To be eligible for the longitudinal cohort, women had to be aged 42–52 years; have an intact uterus; have had at least one menstrual period and not have used reproductive hormones in the previous 3 months; and have self-identified with one of the site's designated race/ethnic groups. The Institutional Review Boards at all participating sites approved the study protocol.

Of the 3302 cohort women, 200 never completed a follow up visit. From the remaining 3102 women, 239 incident hysterectomy cases were reported over nine years (8%). Of the 186 participants that provided consent to have medical records requested, 166 medical records were obtained, and 137 of these records contained information on histological pathology. 71 of these records had no evidence of adenomyosis, while 66 did. Of the 73 participants whose hysterectomy was not verified via medical records, 20 consented but medical records were

unobtainable, 19 refused consent, and 34 were never approached regarding consent (e.g. lost to follow up before protocol implemented, participant not approached for medical record release, or unable to contact participant). There was some differential ability to obtain consent and medical records across sites, likely influenced by differences in site populations (e.g. HMO versus not), geographic area they represented (contained versus widespread area) and the temporary closing of one site (Newark). The SWAN retention rate at the end of the ninth follow-up examination was 69% for all sites and greater than 75% for five of the seven.

SWAN participants at all seven sites were assessed with a common protocol. Baseline and annual assessments included interviewer-administered and self-administered questionnaires about health, lifestyle and psychosocial factors, plus anthropometric measurements. All study forms and materials were available in English, Cantonese, Japanese, and Spanish and bilingual staff was used, as appropriate.

Age, race/ethnicity, education ($\leq$ high school degree, some college/vocational training, college degree or more), difficulty paying for basics (as an indicator of socioeconomic status: very hard, somewhat hard, not hard at all) and parity (number of all prior pregnancies: miscarriages, stillbirths, tubal pregnancies, abortions and live births) were obtained at the baseline examination; incident pregnancies were determined annually. Current smoking status, exogenous hormone use, and menopausal status were assessed annually. Body mass index (BMI; kg/m^2) was calculated from measurements of weight and height, which were obtained annually with a calibrated scale and stadiometer. For 11 of the 14 participants for whom BMI at the visit the hysterectomy was reported was not available, BMI was imputed from the two closest visits.

Beginning at the first annual follow up visit, each participant was asked if, since her previous study visit, she had had “a hysterectomy (an operation to remove the uterus or womb).” Women who reported an incident hysterectomy were then asked to consent to have their medical records requested. The timing of requests for consent of medical record release and requests to the health care providers varied, because the abstraction protocol was not steadily implemented across visits or across sites. Physicians and medical institutions were requested to provide all information from the medical record pertinent to the hysterectomy, including pre and post-operative notes. A single reviewer (GW) completed an abstraction form from these medical records. Included on the abstraction form were lists of presenting symptoms, pre-operative diagnosis, histologic findings, uterine weight, record of uterine and ovary removal, and any surgical complications. Presenting symptoms were available on 130 participants and included abnormal bleeding and chronic pain. Evidence of fibroids and endometriosis were verified via histologic findings. Adenomyosis was coded as present (i.e. described in the medical record) versus not (i.e. no mention of adenomyosis in the histological notes). Because chart review was dependent on what had been recorded, additional information regarding the severity of disease, including depth of penetration, degree of spread, and configuration of lesion, could not be consistently evaluated.

Standard chi-square/ Fisher’s exact and student t-test/ Wilcoxon tests were used as appropriate to compare general characteristics of women with and without evidence of adenomyosis and to examine associations between adenomyosis and fibroids, endometriosis, abnormal bleeding and chronic pain. Multivariable logistic regression models, with evidence of fibroids, endometriosis, abnormal bleeding, or chronic pain as independent variable, were used to assess whether these conditions were associated with adenomyosis independently of other factors. Covariates considered for the multivariable models were determined *a priori* based on the literature and included smoking status (current versus not), socioeconomic status (either difficulty paying for basics, or education) and parity (ever/never pregnant) at baseline, menopausal status at the study visit prior to the participant’s hysterectomy, age at time of

hysterectomy, and BMI at the visit the hysterectomy was reported. Study site and race/ethnicity were included in each model to account for the multi-site nature of the study. In the model evaluating chronic pain, evidence of fibroids was also included as a covariate. Model fit was evaluated via the Hosmer & Lemeshow goodness-of-fit statistic (24).

Additional testing was done to compare the sample of women with histologic data to those for whom medical records were not obtained, did not include histologic data, or were not consented. Sensitivity analyses were conducted to examine if missing data influenced primary hypotheses. Findings were consistent with results that are reported below regarding associations with adenomyosis. All analyses were computed using SAS (Version 9.1, SAS Institute, Inc. Cary, NC).

RESULTS

In our study, the incidence of adenomyosis was 48% (n=66); and in only one instance was it the only diagnosis. The demographics of the patients with histologic data are presented in Table 1. It is clear that there are no significant differences between the women with or without adenomyosis in terms of their race, education, difficulty paying for basics, smoking, age, BMI, or uterine weight. Women with adenomyosis were more likely to have been pregnant than women without adenomyosis (95% versus 85%, respectively, $p=.03$), but the higher number of total prior pregnancies in women with adenomyosis was not statistically significant.

The presenting diagnoses of women having hysterectomies are shown in Table 2. There is no significant difference in the presenting diagnoses for women with or without adenomyosis. Therefore despite a women's presenting symptom, or indication for hysterectomy, she is equally likely to have or not to have adenomyosis.

The associations of some other gynecological conditions with adenomyosis are presented in Table 3. The percentage of women with adenomyosis and fibroids is similar to the percentage of women without adenomyosis but with fibroids. There is also no association between presence of abnormal bleeding or endometriosis and the presence or absence of adenomyosis.

In the presence of fibroids and adenomyosis, chronic pelvic pain was present in 12% of patients, and absent in 33%; In the presence of fibroids, but without adenomyosis, chronic pelvic pain was present in 17% of patients and absent in 38% ($p = 0.58$). When fibroids were absent, but adenomyosis was present, chronic pelvic pain was present in 11% and absent in 42%; In patients without fibroids or adenomyosis, chronic pelvic pain was present in 4% of patients, and absent in 42% ($p = 0.60$). This demonstrates that adenomyosis is not a determinant of chronic pelvic pain in patients with and without fibroids.

Multivariable logistic regression models were conducted to see if the lack of association between adenomyosis and fibroids, endometriosis, abnormal bleeding or chronic pain might be due to other characteristics of the women. However, after controlling for race, study site, age, BMI, smoking, difficulty paying for basics, and parity no associations were found. Additionally, the only covariate that significantly predicted adenomyosis in these four models was parity (odds ratio ranged from 5.0 [CI: 1.2, 20.9] for endometriosis to 8.0 [CI: 1.5, 42.9] for chronic pain).

Examinations of missing data showed that women who were never approached for or refused consent were more likely to be Hispanic and from the Newark site, which was to be expected, given the temporary stoppage of data collection at this study site. Also consistent with the characteristics of this site, these women were more likely to report having a hard time paying for basics ($p=0.006$). When comparing those with and without histologic data (137 versus 102), the latter group was more likely to be post menopausal and less likely to have indeterminate

menopausal status. The availability of data varied by site ranging from a high of 97% of participants consenting and medical records being obtained to a low of 17%.

DISCUSSION

Our data, generated in a national, community based sample of hysterectomies, demonstrates that adenomyosis is a common finding present in almost half of hysterectomy specimens of middle-aged women. In our study the incidence of adenomyosis is 48% based on diagnosis made by the pathologist who reviewed the specimen. In only one instance was adenomyosis the only diagnosis. This study tested four hypotheses derived from the literature. These are:

1. Adenomyosis is associated with the presence of fibroids.
2. Adenomyosis is more common in the presence of endometriosis.
3. Adenomyosis is associated with abnormal uterine bleeding.
4. Symptoms of chronic pain are more likely in uteri with fibroids if adenomyosis is present.

The data generated in this study did not provide evidence in support of these hypotheses. Our study concludes that presenting symptoms are equivalent in type and frequency in women with and without adenomyosis. Adenomyosis is no more likely to be observed in the presence of fibroids, endometriosis, abnormal uterine bleeding, or chronic pelvic pain in the presence of fibroids than in specimens without these conditions, in contradiction to previous reports in the literature (2,3,5,17–20,25). Therefore, in patients with confirmed adenomyosis, there are clearly other causes that are responsible for the presenting symptoms, and adenomyosis is not the underlying cause of the symptoms.

Adenomyosis is found commonly in hysterectomy specimens of women with concurrent fibroids. The reported incidence of concurrent fibroids has ranged from 19%–57% (2,5,6,13, 14,25,26). Many authors have concluded that this high prevalence reflects an association between adenomyosis and fibroids (22). However, the majority of these studies did not examine the incidence of fibroids in the control specimens, women without adenomyosis. Two previous authors, Shaikh et al (13) and Vercellini et al. (15), concluded that fibroids are equally common in the specimens with and without adenomyosis. In our study the same prevalence of adenomyosis was observed in the presence and absence of fibroids, suggesting no association.

The literature has also suggested that adenomyosis is associated with, if not a variant of, endometriosis, and that the two entities are usually found concomitantly (2,17–19). However, in our study only 11/137 cases of endometriosis were noted, (4/66) in women with adenomyosis, and (7/71) in women without adenomyosis. The preoperative diagnosis of endometriosis based on prior observations was made 4 times, twice in patients with adenomyosis and twice without adenomyosis. Three prior controlled studies reported prevalence of endometriosis between 5–10% in specimens with adenomyosis and 7–8% without adenomyosis (13,15,16). These differences were not statistically significant. Taken together with our results, these findings suggest that adenomyosis is not more common in the presence of endometriosis and that the two are separate entities.

Few cases of obvious endometriosis were noted in our study. A review of operative reports and pathology reports of all specimens that were removed was done in order to evaluate if endometriosis was identified at the time of surgery. In the absence of a prior diagnosis, histological evidence of endometriosis at the time of surgery or on the gross specimen, or mention of visualization by the surgeon in the operative report, endometriosis was not diagnosed. A search of multiple sections to find the disease was not done in any case. However

if endometriosis was missed, it is likely to be trivial and not significant as well as unlikely to be clinically observed or important.

Chronic pelvic pain and abnormal uterine bleeding are symptoms thought to be suggestive of and attributable to the presence of adenomyosis. In our study the prevalence of adenomyosis was observed equally in the presence and absence of abnormal uterine bleeding. The data also demonstrate that in women with or without fibroids, the presence of chronic pain is not associated with the presence of adenomyosis. Bergholt et al. (11) and Kilkku et al. (12) also found no association between chronic pelvic pain, dysmenorrhea, dyspareunia and adenomyosis. Symptoms of heavy/abnormal bleeding are thought to be positively associated with the depth of penetration of adenomyosis into the myometrium (6). We were not able to assess the depth of penetration in our chart review, so there is the possibility that associations with vaginal bleeding may be masked in our study. Further, because not all participants in our study have yet completed the transition to postmenopausal status, our results may be biased toward what happens early in the transition. In particular, our data suggested that there might be a higher association between abnormal bleeding and adenomyosis later in the transition. However, our sample size was too small to sufficiently test this.

The major advantage of this study is that it is based on a large community based population, decreasing bias. It is also a controlled study, in that it enables comparisons to hysterectomies in which adenomyosis was not found. A potential weakness of the study is its relatively small number of incident hysterectomy cases and available histologic data. It is not likely that this would produce a type-2 error, however, since the p-values were not close to significance. Another potential weakness is the fact that multiple pathologists evaluated the histology sections. This however is a “real world” observation; the way adenomyosis is usually diagnosed. It would be inappropriate to have a section by section search for adenomyosis since it is not clear that this is at all clinically meaningful. One may question what criteria were used to make the pathological diagnosis of adenomyosis. Since different authors use different criteria, and there is no universally accepted way to diagnosis adenomyosis (2,8,11,27), it is probable that pathologists in the community did in fact use varying criteria to make the diagnosis. Other gynecological pathologies, such as fibroids or cervical cancer, have clear diagnostic criterion and no one questions whether the disease is present or absent. However, the fact that the definition of adenomyosis remains ambiguous helps solidify our argument that adenomyosis is not a disease, but an incidental finding. Since adenomyosis was noted to be the only diagnosis in only one case, it is unlikely that the diagnosis was being used to validate the procedure.

This current study provides little insight into the etiology of adenomyosis. It is present and absent in fairly equal proportions in the hysterectomy population based upon presenting diagnoses and symptoms. It was rarely diagnosed correctly, preoperatively only twice, and it has no special symptom complex of its own. The symptoms that have been classically attributed to adenomyosis most likely have other underlying etiologies since the frequencies of the symptoms are seen in the presence and absence of adenomyosis are equal. Adenomyosis appears to be a benign and incidental finding in most uteri, unrelated to symptomatology. Precluding the relatively rare cases in which large adenomyoma are present, which could be a different than adenomyosis altogether, or a uterus is dramatically increased in size by the presence of large amounts of adenomyosis alone, conditions which were not present in any of the hysterectomies in the study, adenomyosis appears to be not a “disease” per se, but a normal and minimally significant variant.

Acknowledgements

Clinical Centers: University of Michigan, Ann Arbor - MaryFran Sowers, PI; Massachusetts General Hospital, Boston, MA - Robert Neer, PI 1994 – 1999; Joel Finkelstein, PI 1999-present; Rush University, Rush University Medical Center, Chicago, IL - Lynda Powell, PI; University of California, Davis/Kaiser - Ellen Gold, PI; University of California, Los Angeles - Gail Greendale, PI; University of Medicine and Dentistry - New Jersey Medical School, Newark - Gerson Weiss, PI 1994 – 2004; Nanette Santoro, PI 2004 – present; and the University of Pittsburgh, Pittsburgh, PA - Karen Matthews, PI.

Funding Support: The National Institutes of Health, DHHS, through the National Institute on Aging, the National Institute of Nursing Research and the NIH Office of Research on Women's Health (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495).

NIH Program Office: National Institute on Aging, Bethesda, MD - Marcia Ory 1994 – 2001; Sherry Sherman 1994 – present; National Institute of Nursing Research, Bethesda, MD – Program Officers.

Central Laboratory: University of Michigan, Ann Arbor - Daniel McConnell; (Central Ligand Assay Satellite Services).

Coordinating Center: New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001; University of Pittsburgh, Pittsburgh, PA – Kim Sutton-Tyrrell, PI 2001 – present.

Steering Committee: Chris Gallagher

Chair Susan Johnson, Chair

We thank the study staff at each site and all the women who participated in SWAN.

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Table 1
Comparison of Participants with and without Adenomyosis

Participant Characteristics	Adenomyosis	No Adenomyosis	P-value
N	66	71	
Race, N (%)			0.47
African American	24 (36)	27 (38)	
Caucasian	31 (47)	35 (49)	
Chinese	1 (2)	4 (6)	
Hispanic	2 (3)	1 (1)	
Japanese	8 (12)	4 (6)	
Education at baseline, N (%)			0.34
High school or less	18 (27)	12 (17)	
Some college / technical school	24 (36)	27 (39)	
College degree / post graduate degree	24 (36)	31 (44)	
Paying for basics at baseline, N (%)			0.65
Very hard	4 (6)	2 (3)	
Somewhat hard	19 (29)	22 (31)	
Not hard at all	43 (65)	46 (66)	
Smoker at baseline, N (%)	11 (17)	14 (20)	0.65
Parity (i.e. ever pregnant), N (%)	63 (95)	60 (85)	0.03
Number of prior pregnancies, Mean $\pm$ SD	3.5 $\pm$ 2.3	2.9 $\pm$ 2.1	0.07
BMI at visit nearest hysterectomy, Mean $\pm$ SD	30.1 $\pm$ 8.0	37.5 $\pm$ 7.7	0.63
Age at time of hysterectomy (years), Mean $\pm$ SD	49.5 $\pm$ 3.4	49.0 $\pm$ 3.4	0.40
Uterine weight, Median [IQR]	240 [134, 436]	293 [150, 720]	0.10

Table 2Presentation, N (%) ^a

Symptom	Adenomyosis	No Adenomyosis	P-value
Prolapse	6 (10)	7 (10)	1.00
Problems with vaginal bleeding	35 (58)	43 (61)	0.72
Fibroids	34 (57)	46 (66)	0.29
Acute pelvic pain	3 (5)	3 (4)	0.85
Chronic pelvic pain	15 (25)	19 (27)	0.78
Known cancer / suspicious mass	2 (3)	3 (4)	1.00
Stress urinary incontinence	5 (8)	6 (9)	0.96
Other	13 (22)	11 (16)	0.38

^a Columns do not add to 100% because more than one presentation may be present.

Table 3Associations with Adenomyosis, N (%) ^a

Adenomyosis		No Adenomyosis		P-value
Fibroids present	Fibroids absent	Fibroids present	Fibroids absent	0.39
51 (37)	15 (11)	59 (43)	12 (9)	
Endometriosis present	Endometriosis absent	Endometriosis present	Endometriosis absent	0.41
4 (3)	62 (45)	7 (5)	64 (47)	
Abnormal bleeding present	Abnormal bleeding absent	Abnormal bleeding present	Abnormal bleeding absent	0.72
35 (27)	25 (19)	43 (33)	27 (21)	

^aNumber of participants equals 137 across each of the first two rows and 130 across the final row; Each row totals to 100%.