Use of Uterine Characteristics to Improve Fertility-Sparing Diagnosis of Adenomyosis

Amanda M. Ecker, MD,^{1,2} Dina Chamsy, MD,^{1,3} R. Marshall Austin, MD, PhD,⁴
Richard S. Guido, MD,¹ Ted T.M. Lee, MD,¹ Suketu M. Mansuria, MD,¹
Noah B. Rindos, MD,¹ and Nicole M. Donnellan, MD¹

Abstract

Objective: To describe patient demographics, determine accuracy of clinical diagnosis, and evaluate reliability of laparoscopic uterine characteristics in the diagnosis of adenomyosis.

Materials and Methods: Enrollment included 117 patients undergoing laparoscopic hysterectomy for benign indications. Intraoperatively, the attending surgeon predicted uterine weight; evaluated the presence of fibroids; and commented on the uterus' shape, color, and consistency while probing it with a blunt instrument. A prediction was also made about whether final pathology would reveal adenomyosis. Standardized video recordings were obtained at the start of the case. Each video was viewed retrospectively twice by three expert surgeons in a blinded fashion. Uterine characteristics were reported again with a prediction of whether or not there would be a pathologic diagnosis of adenomyosis. These data were used to calculate inter- and intrarater reliability of diagnosis.

Results: Women with adenomyosis were more likely to complain of midline pain as opposed to lateral or diffuse pain ($p=0.048$) with no difference in the timing of the pain ($p=0.404$), compared to patients without adenomyosis. Uterine tenderness on examination was not an accurate predictor of adenomyosis ($p=0.566$). Preoperative diagnosis of adenomyosis by clinicians was poor, with an accuracy rate of 51.7%. None of the intraoperative uterine characteristics were significant for predicting adenomyosis on final pathology, nor was any combination of the features ($p=0.546$). Retrospective video reviews failed to reveal any uterine characteristics that generated consistent inter- or intrarater reliability (Krippendorff's $\alpha < 0.7$) in making the diagnosis of adenomyosis.

Conclusions: Clinical and video diagnosis of adenomyosis have low accuracy with no uterine characteristics consistently or reliably predicting adenomyosis on final pathology. (J GYNECOL SURG 34:183)

Keywords: adenomyosis, dysmenorrhea, hysterectomy, menorrhagia, myometrial thickness, pelvic pain

Introduction

ADENOMYOSIS IS A PATHOLOGIC GYNECOLOGIC ENTITY, defined histologically by the benign invasion of endometrial glands and stroma into surrounding myometrium, resulting in hyperplastic myometrium.¹ Patients commonly present with menorrhagia, dysmenorrhea, and chronic pelvic pain, but the symptoms can vary widely.^{2,3} Despite a plethora of literature, there is little consensus regarding the underlying origin of adenomyosis and, to date, there is a lack of homogenous criteria

for diagnosis.⁴ Multiple hypotheses have been suggested to explain the pathophysiology of adenomyosis, including invagination of endometrium into myometrium, misplaced pluripotent Müllerian remnants, and hematologic spread of bone-marrow stem cells.⁵ The invagination hypothesis is the most popular, with the idea that weakened myometrium from prior surgical trauma or a flawed immune response may permit this invasion of endometrium into the myometrium.⁶

The “gold standard” for diagnosis of adenomyosis is the histologic identification of endometrial stroma and glands

¹Division of Minimally Invasive Gynecologic Surgery, Department of Obstetrics, Gynecology and Reproductive Sciences, Magee-Women's Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA.

²Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR.

³Department of Obstetrics and Gynecology, American University of Beirut, Beirut, Lebanon.

⁴Department of Pathology, Magee-Women's Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA.

within the myometrium.⁷ However, currently published literature uses varying depths of invasion into the myometrium to make the diagnosis. This contributes to the wide range in reported incidence of this disease, which can vary from 12% to 58% among hospitals and from 10% to 88% among pathologists.⁸ Moreover, the documented incidence of adenomyosis is likely highly inaccurate as these data are retrospectively derived from hysterectomy specimens.

Another challenge surrounding adenomyosis lies in generating a definitive preoperative diagnosis. Clinical presentation is regarded as a poor predictor of disease due to the lack of symptom specificity and physical examination findings.^{9–11} Both transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) have revealed variable accuracy with sensitivity and specificity values ranging from 52.9% to 89% and from 66.7% to 97.5% (TVUS) and 77.5%–89% and 75%–92.5% (MRI), respectively.^{12–16} Three-dimensional ultrasound (US) with the addition of Doppler flow may aid in differentiating leiomyoma from adenomyosis with reproducible accuracy.¹⁷ Hysteroscopy is not a reliable diagnostic tool for adenomyosis but will sometimes show hypervascularization, superficial irregularities, and cystic hemorrhagic lesions within the endometrium suggestive of the diagnosis.¹⁸

Previous studies have shown poor sensitivity and specificity of diagnosis with myometrial biopsy although one 2015 study showed improved results with a rate of 92.2%—guided myometrial biopsies being concordant with ultrasonographic diagnosis.¹⁹ In 2015, more unique testing strategies have been evaluated using biomarkers, and one study showed that patients with adenomyosis have higher mean levels of CA-125 than patients lacking adenomyosis shown on final pathology ($p < 0.001$).²⁰

Given the various limitations of the existing diagnostic techniques, the objective of this research was to develop a consistent set of visual features on laparoscopic evaluation of the uterus that could be used to create a validated scoring system for the diagnosis of adenomyosis. Magee-Women's Hospital of University of Pittsburgh Medical Center (UPMC) in Pittsburgh, PA, is a major tertiary referral center for management of gynecologic patients, with a minimally invasive gynecologic surgery division that performs more than 400 laparoscopic hysterectomies annually. Adenomyotic uteri have been anecdotally observed to have a “boggy” and hyperemic appearance, have a spongy consistency, and tend to be larger than nonpathologic uteri. Prior research studies have similarly described the appearance of uteri on both macroscopic evaluation and MRI.^{5,18} Women presenting for gynecologic care may not have completed childbearing; yet the gold standard for diagnosis of adenomyosis is by analysis of the hysterectomy specimen, which is in direct conflict with many patients' fertility goals. By creating a laparoscopic scoring system for diagnosis of adenomyosis, the goal was to provide an additional diagnostic tool to expedite appropriate diagnosis and treatment while preserving fertility.

Materials and Methods

Design

Patients undergoing hysterectomy for benign indications at Magee-Women's Hospital of UPMC between June 2013 and April 2015 were approached for inclusion in this study. Patients older than 18 years of age and without known

malignancy were eligible for inclusion whether they were having a total or supracervical hysterectomy and regardless of whether adnexal structures were removed or left intact. Exclusion criteria included uterine size >14 weeks, pregnancy, or performance of an emergent hysterectomy. (Fig. 1) Cases were also excluded from final analysis for the following reasons: surgery performed at another institution; dense abdominal adhesions obscuring uterine evaluation; demonstration of any instrument in the video recording that could identify the surgeon; or incompletely recorded video or pathology data. The first 3 patients were enrolled as a pilot group to evaluate feasibility, ensure that there was a unified agreement of the grading characteristics to meet the study objectives, and to confirm consistency of video grading among the expert surgeons. The data from the first 3 participants were not included in the statistical calculations or final study findings.

This study was approved by the University of Pittsburgh institutional review board (IRB # PRO12100369), and informed consent was obtained at enrollment. An effect size of 0.3 (moderate effect) was used as an estimate for the power analysis and 117 patients were enrolled to attain a power of 90%.

Procedures

The following parameters were abstracted from chart reviews: age; gravity/parity; race; body mass index (BMI); tobacco use; and prior gynecologic surgical history (including cesarean section, dilation and curettage, myomectomy, and endometrial ablation). Additionally, data were collected on presenting symptom(s), preoperative imaging, uterine size, presence or absence of uterine tenderness on examination, preoperative diagnosis/clinical impression, type of hysterectomy (total or supracervical), and if specimen morcellation was performed.

Intraoperatively, the attending surgeon performed an examination with the patient under anesthesia. Uterine fundal height and the presence of any palpable fibroids were recorded. After placement of the laparoscopic ports, uterine characteristics were observed and recorded. Through the use of a standardized questionnaire, the attending surgeon commented on uterine shape, color, and consistency, as well as the presence and size of any fibroids. Additionally, the surgeon was asked to push on the uterine serosa with a blunt probe at the anterior, posterior, and fundal aspects. The time for the myometrium to recover fully from the indentation and blanching due to the pressure was later recorded from the videos. Finally, the surgeon estimated which uterine wall was thicker (anterior, posterior, or neither), the final uterine weight in g, and a prediction of if the patient would have adenomyosis revealed on final pathology.

All specimens were examined by a single pathologist using a consistent evaluation technique. The uterus was cut in half and thicknesses of the anterior and posterior uterine walls were measured (unless morcellation was performed). Four different regions of both the anterior and posterior walls were prepared for histologic evaluation. The numbers of foci positive for adenomyosis in the eight samples were reported, as was the depth of those foci from the endomyometrial junction and from the uterine serosa. Final uterine weight and presence of any concomitant pathology were also reported.

FIG. 1. Enrollment diagram of patients undergoing hysterectomy for benign disease at Magee-Women's Hospital of University of Pittsburgh Medical Center between June 2013 and April 2015.

Finally, 3 expert surgeons (N.M.D., T.M.L., S.M.M.) reviewed the recorded videos retrospectively. Each video was de-identified, making the reviewers blinded to both the surgeon and patient. Based on the video reviews, the expert surgeons were required to provide their estimations of the uterine characteristics once again. Additionally, the surgeons were asked to predict whether a diagnosis of adenomyosis would be present on final pathology and how confident of their diagnoses they were on a Likert scale (rated 1–5).

Statistical methods

Descriptive statistics were reported for both cases and controls. Continuous variables were presented as medians and interquartile ranges (nonnormal distributed data). Categorical variables were presented as counts and percentages. For comparisons between cases and controls, the nonparametric Mann–Whitney–*U* test was used for all continuous variables due to small group sizes, and the χ^2 or Fisher's exact test (as appropriate) was used for categorical variables. The individual effect of each variable was evaluated with univariate analysis. The adjusted effect of the variables was then subsequently evaluated with a multivariate anal-

ysis. A *p*-value of <0.05 was considered significant for all analyses. Krippendorff's α values were calculated to demonstrate level of agreement among the video reviewers (interrater reliability) and intrarater reliability with multiple viewings of the same video. SPSS version 22 (Armonk, NY) was used for all statistical analyses.

Results

There was no difference in the baseline characteristics of the cases and controls other than gravidity, although there was a trend toward older age in patients with adenomyosis (median age: 42 versus 40; $p=0.06$; Table 1). History of cesarean section (or number of prior cesareans) was not significantly different in patients with adenomyosis ($p=0.79$). In a multivariate analysis, gravidity was the only independent predictor of adenomyosis ($p=0.008$) after controlling for all significant variables. Women with adenomyosis were no more likely to present with complaints of abnormal bleeding ($p=0.9$) or pelvic pain ($p=0.97$), but, in the patients who did present with pain, women with adenomyosis were more likely to complain of midline pain as opposed to lateral or diffuse pain ($p=0.048$), with no difference in the timing of

TABLE 1. PATIENTS' CHARACTERISTICS

Median (IQR)	Adenomyosis ^a	No adenomyosis	p-Value
Age	42 (13)	40 (9)	0.06
BMI	29 (8.9)	29.3 (11.4)	NS
Gravidity	2 (3)	2 (2)	0.009
Parity	2 (2)	1 (3)	0.06
# of prior cesareans	2 (1)	2 (2)	NS

N (%)	Adenomyosis ^a	No adenomyosis	p-Value
Non-Caucasian	8 (13.8)	7 (11.9)	NS
Tobacco use (ever)	14 (24.1)	17 (29.3)	NS
History of:			
Cesarean section	18 (31)	17 (28.8)	NS
D&C	12 (20.7)	6 (10.2)	NS
Endometrial ablation	12 (20.7)	8 (13.6)	NS

^aOn final pathology.

Bold values are statistically significant.

BMI, body mass index; NS, not significant; D&C, dilatation and curettage.

the pain ($p=0.35$; Table 2). Uterine tenderness on examination was not an accurate predictor of adenomyosis ($p=0.57$).

Cases and controls were equally as likely to have had US or MRI imaging preoperatively (Table 3). MRI was 100% sensitive and specific for diagnosis of adenomyosis, but only 8 patients in the cohort had MRI performed (4 with adenomyosis and 4 without). TVUS had a very poor sensitivity of 14.6%, with a specificity of 97.3%. Diagnostic suspicion for adenomyosis based on preoperative clinical examination was poor, with an accuracy rate of 51.7%.

TABLE 2. PRESENTING SYMPTOM(S)

N (%)	Adenomyosis ^a	No adenomyosis	p-Value
Abnormal bleeding	39 (67.2)	39 (66.1)	0.9
Type of abnormal bleeding:			0.82
Menorrhagia	25 (64.1)	26 (66.7)	—
Metrorrhagia	2 (5.1)	3 (7.7)	—
Menometrorrhagia	12 (30.8)	10 (25.6)	—
Pelvic pain	48 (82.8)	49 (83.1)	0.97
Pain location:			0.009
Midline	31 (66)	22 (45.8)	—
Lateral	5 (10.6)	18 (37.5)	—
Diffuse	11 (23.4)	8 (16.7)	—
Timing of pain:			0.35
Menstrual only	19 (40.4)	13 (26.5)	—
All month	8 (17)	11 (22.4)	—
All month, worse with menses	20 (42.6)	24 (49)	—
Intermittent	0 (0)	1 (2)	—

^aOn final pathology.

Bold values are statistically significant.

TABLE 3. PREOPERATIVE EXAMINATIONS

N (%)	Adenomyosis ^a	No adenomyosis	p-Value
Uterine tenderness on exam	43 (75.4)	41 (70.7)	0.57
US	41 (70.7)	36 (61)	0.27
Adenomyosis	6 (14.6)	1 (2.7)	—
No adenomyosis	35 (85.4)	36 (97.3)	—
MRI	4 (6.9)	4 (6.8)	1.0
Adenomyosis	4 (100)	0 (0)	—
No adenomyosis	0 (0)	4 (100)	—
Preoperative diagnosis			
Adenomyosis	42 (73.7)	41 (69.5)	0.62
Endometriosis	15 (26.3)	19 (32.2)	0.49
Fibroids	14 (24.6)	14 (23.7)	0.92

^aOn final pathology.

Bold values are statistically significant.

US, ultrasound; MRI, magnetic resonance imaging.

Intraoperatively, adenomyotic uteri were estimated to be larger (median: 122.5 g versus 100 g; $p=0.05$) but were no more likely to be morcellated (data not shown). Patients with adenomyosis on final pathology were more likely to be predicted intraoperatively to have adenomyosis (85.2% versus 68.4%; $p=0.037$; Table 4). However, none of the isolated laparoscopic uterine characteristics noted at the time of surgery were significant in predicting adenomyosis on final pathology, nor was any combination of the various

TABLE 4. INTRAOPERATIVE DETAILS

N (%)	Adenomyosis ^a	No adenomyosis	p-Value
Uterine size on EUA			0.23
Nonpalpable	6 (10.3)	8 (13.8)	—
Normal/small	16 (27.6)	22 (37.9)	—
8–10 weeks	27 (46.6)	15 (25.9)	—
10–12 weeks	2 (3.4)	2 (3.4)	—
12–14 weeks	7 (12.1)	11 (19)	—
Uterine characteristics			
Globular	34 (58.6)	31 (52.5)	0.51
Hyperemic	18 (31)	18 (30.5)	0.95
“Boggy”	50 (86.2)	45 (76.3)	0.17
“Lumpy”	22 (37.9)	25 (42.4)	0.62
Thicker uterine wall			0.17
Anterior	9 (15.5)	4 (6.9)	—
Posterior	29 (50)	38 (65.5)	—
Neither	20 (34.5)	16 (27.6)	—
Prediction of adenomyosis	46 (85.2)	39 (68.4)	0.037
Median (IQR):			
Estimated uterine weight (g)	122.5 (88)	100 (65)	0.05
Fundal tone (sec)	2 (1)	1 (2)	0.4
Posterior tone (sec)	3 (5)	3 (3)	0.66
Anterior tone (sec)	4 (5)	3 (5)	0.37

^aOn final pathology.

Bold values are statistically significant.

EUA, examination under anesthesia; sec, seconds.

TABLE 5. PATHOLOGY DATA

N (%)	Adenomyosis ^a	No adenomyosis	p-Value	Range
Location of adenomyosis				
Anterior	14 (25.9)	N/A	—	—
Posterior	16 (29.6)	N/A	—	—
Both	15 (27.8)	N/A	—	—
Unable to determine (morcellation)	9 (16.7)	N/A	—	—
Concomitant pathology				
Fibroids	25 (50)	29 (51.8)	0.85	—
Endometriosis	11 (22)	19 (33.9)	0.17	—
Subserosal endometriosis	6 (12)	5 (8.9)	0.61	—
Endometrial polyp	6 (12)	1 (1.8)	0.05	—
Endometritis/endocervicitis	27 (54)	41 (73.2)	0.039	—
Median (IQR) range				
Actual uterine weight (g)	138 (51)	117 (78)	0.12	—
<i>When adenomyosis present:</i>				
Maximal depth (mm)	6 (6)	N/A	—	1–20
Depth from serosa (mm)	13 (10)	N/A	—	0–23
<i>Total # of foci present:</i>				
# anterior foci	1 (2)	N/A	—	0–4
# posterior foci	1 (2)	N/A	—	0–5
<i>Uterine-wall thickness:</i>				
Anterior	23 (5)	20 (7)	0.013	—
Posterior	23 (7)	22 (7)	0.06	—

^aOn final pathology.

Bold values are statistically significant.

IQR, interquartile.

features ($p=0.48$). Clinical diagnosis of adenomyosis intraoperatively was minimally improved to 57.7%.

On final pathology, specimens with adenomyosis did not significantly weigh more than specimens without adenomyosis (138 g versus 117 g; $p=0.12$). In uteri with adenomyosis, there was a median of two foci of adenomyosis present with a range from 1 to 8 (8 total foci evaluated). There was no difference in the location of adenomyosis among the anterior, posterior, and bilateral uterine walls, but

the anterior wall was significantly thicker in patients with adenomyosis than in patients without adenomyosis (median: 23 mm versus 20 mm; $p=0.013$; Table 5). The median depth of invasion from the endomyometrial junction was 6 mm, and the median depth from the serosa was 13 mm. Patients with adenomyosis were more likely to have endometrial polyps ($p=0.05$) and less likely to have endometritis or endocervicitis ($p=0.039$) but there was no significant difference in the rates of concomitant fibroids and endometriosis (Table 5).

On retrospective video review, the only characteristics that had good intrarater reliability between the two separate video reviews were size estimation, “lumpy” shape and presence of fibroids. (Fig. 2). Presence of fibroids was the only characteristic that had good intrarater reliability (Krippendorff’s $\alpha \geq 0.8$) for more than 1 reviewer as well as acceptable interrater reliability. (Fig. 3).

Discussion

Adenomyosis remains a diagnosis shrouded in mystery. Increasing gravidity was the only significant risk factor for adenomyosis that was demonstrated in the current study. This was corroborated by prior studies.^{21,22} It was not possible to show any impact of uterine surgery (dilation and curettage, cesarean section, and/or endometrial ablation) on development of adenomyosis. With multiple previous studies having conflicting results, it remains unclear whether or not prior uterine surgery is a risk factor for adenomyosis.^{23–25}

Clinical diagnosis remains difficult, with uterine tenderness on physical examination having low sensitivity and accuracy of preoperative diagnosis, barely reaching 50% in this study. The results indicated that MRI was both 100% sensitive and specific for diagnosis of adenomyosis, but this

FIG. 2. Intrarater reliability on video diagnosis. Agreement on rating of uterine characteristics between the two video reviews for each expert reviewer. Line drawn at 0.8 to demonstrate good agreement (Krippendorff’s $\alpha \geq 0.8$).

FIG. 3. Interrater reliability on video diagnosis. Agreement on rating of uterine characteristics between the expert reviewers for the final video review. Line drawn at 0.8 to demonstrate good agreement (Krippendorff's $\alpha \geq 0.8$).

is a costly study that is not always readily available in small communities and might not affect the decision to perform a hysterectomy. Accuracy of TVUS was very poor in the current study—much lower than previously quoted rates. It is unclear why this was the case, particularly at this high-volume referral center, but TVUS is known to have certain limitations and is largely operator-dependent.

Conclusions

Unfortunately, the objective of creating a visual scoring system for diagnosis of adenomyosis was unable to be achieved due to a lack of laparoscopic uterine characteristics that were consistently reliable. Furthermore, the poor interrater reliability—even among experienced high-volume surgeons—demonstrated that these descriptive uterine characteristics are extremely subjective. In a larger scheme, this study should draw attention to the variation in descriptive characteristics used during surgery in general. Future research needs to be directed toward fertility-sparing diagnosis and treatment of adenomyosis for women who are not yet family-complete.

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Author Disclosure Statement

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Address correspondence to:

Amanda M. Ecker, MD

Department of Obstetrics and Gynecology

Oregon Health & Science University

3181 SW Sam Jackson Park Road

Portland, OR 97239

E-mail: eckera@ohsu.edu