

# Clinical Manifestations Of Adenomyosis Patients With Or Without Pain Symptoms

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Qian Chen\*  
Yun-Wei Li   
Shu Wang   
Qing-Bo Fan  
Hong-Hui Shi  
Jin-Hua Leng  
Da-Wei Sun  
Jing-He Lang  
Lan Zhu 

Department of Gynecology and  
Obstetrics, Peking Union Medical College  
Hospital, Chinese Academy of Medical  
Sciences and Peking Union Medical  
College, Beijing, People's Republic of  
China

\*These authors contributed equally to  
this work

**Purpose:** Our study aims to investigate the distribution of pain symptoms and the association between pain symptoms and clinical parameters in patients with adenomyosis.

**Patients and methods:** The clinical and pathological data of 291 patients diagnosed with adenomyosis in the Obstetrics and Gynecology Department of Peking Union Medical College Hospital from March 2012 to September 2015 were collected, and analyzed in regard to the pain symptoms.

**Results:** The median age at disease onset was 34 years. 71.8% of the patients had pain symptoms (pain group) and 28.2% had no pain symptoms (painless group). Patients with symptoms accompanied by dysmenorrhea accounted for 68%, among which 30.3% were mild, 36.9% were moderate, and 32.8% severe, while 56.1% presented with progressive pain. Through comparison, significant differences were identified between the pain and painless groups with regard to age at diagnosis ( $P=0.009$ ), age at onset of disease ( $P=0.008$ ), and level of pre-surgical CA125 ( $P<0.001$ ), as well as proportion of patients with rectal irritation ( $P=0.008$ ), elevated CA125 level ( $P<0.001$ ), thickened myometrial layer ( $P<0.001$ ) and concurrent endometriosis ( $P=0.001$ ). In the multivariable analysis, an elevated level of pre-surgical CA125 ( $P<0.001$ ) and thickened posterior myometrial layer ( $P=0.023$ ) were both independent risk factors for the morbidity of pain symptoms. Similar results except for the difference in rectal irritation were noticed when we made further comparison between the dysmenorrhea and non-dysmenorrhea groups in adenomyosis patients.

**Conclusion:** Our research analyzes the clinical features related to pain symptoms in patients with adenomyosis, which may provide clues for the possible presurgical diagnosis of adenomyosis, as well as references for pain management of adenomyosis.

**Keywords:** adenomyosis, pain symptoms, clinical features, risk factors

## Introduction

Uterine adenomyosis is a status of hyperplasia and hypertrophy of uterine myometrium due to the ectopic growth of the endometrial glands and stroma.<sup>1</sup> Though clinically common, it confuses us due to a lack of standard diagnostic criteria.<sup>2</sup> Adenomyosis can be diagnosed by surgical procedure, such as hysterectomy, which gives an access to a full myometrial assessment, or by myometrial biopsies.<sup>3</sup> Two common noninvasive imaging methods, transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI), are widely adopted in clinical work with high accuracy.<sup>4</sup>

Heterogeneous as it is in clinical features, adenomyosis may lead to various performances in different individuals, such as abnormal uterine bleeding (AUB), different forms of pain, nausea, difficulties with urination and so on. Among them,

Correspondence: Shu Wang; Qing-Bo Fan  
Department of Obstetrics and  
Gynecology, Peking Union Medical  
College Hospital, Chinese Academy of  
Medical Sciences and Peking Union  
Medical College, I ShuaiFuYuan,  
Wangfujing, DongCheng District, Beijing  
100730, People's Republic of China  
Tel +86-10-69156204  
Fax +86-10-69154875  
Email wangshu219@hotmail.com;  
qingbo\_f@sina.com

AUB and dysmenorrhea are the top two reasons for patients to see a doctor, which may exert burdensome impacts on their daily life. Several published literatures have shed light on the treatment of the pain caused by adenomyosis, especially dysmenorrhea.<sup>5–7</sup> Few studies have focused on the factors or clinical behaviors related to pain arising from adenomyosis. Our previous study identified that patients with adenomyosis received less accurate preoperative diagnosis, as the accuracy rate was only 36.4%.<sup>8</sup> Most patients with pain symptoms were not correctly diagnosed before surgery, resulting in inappropriate or inadequate treatment. We carried out this retrospective study with an intention to help understand the clinical features of patients with adenomyosis-related pain and improve the preoperative diagnosis rate of such patients, thus providing timely and effective treatment for them.

## Methods

From March 2012 to September 2015, 361 patients received surgery and were pathologically diagnosed with uterine adenomyosis in the Department of Obstetrics and Gynecology at Peking Union Medical College Hospital. We enrolled 291 of them who were in accordance with our inclusion and exclusion criteria described in our previously published article<sup>8</sup> (Figure 1). Relative clinical and pathological data were

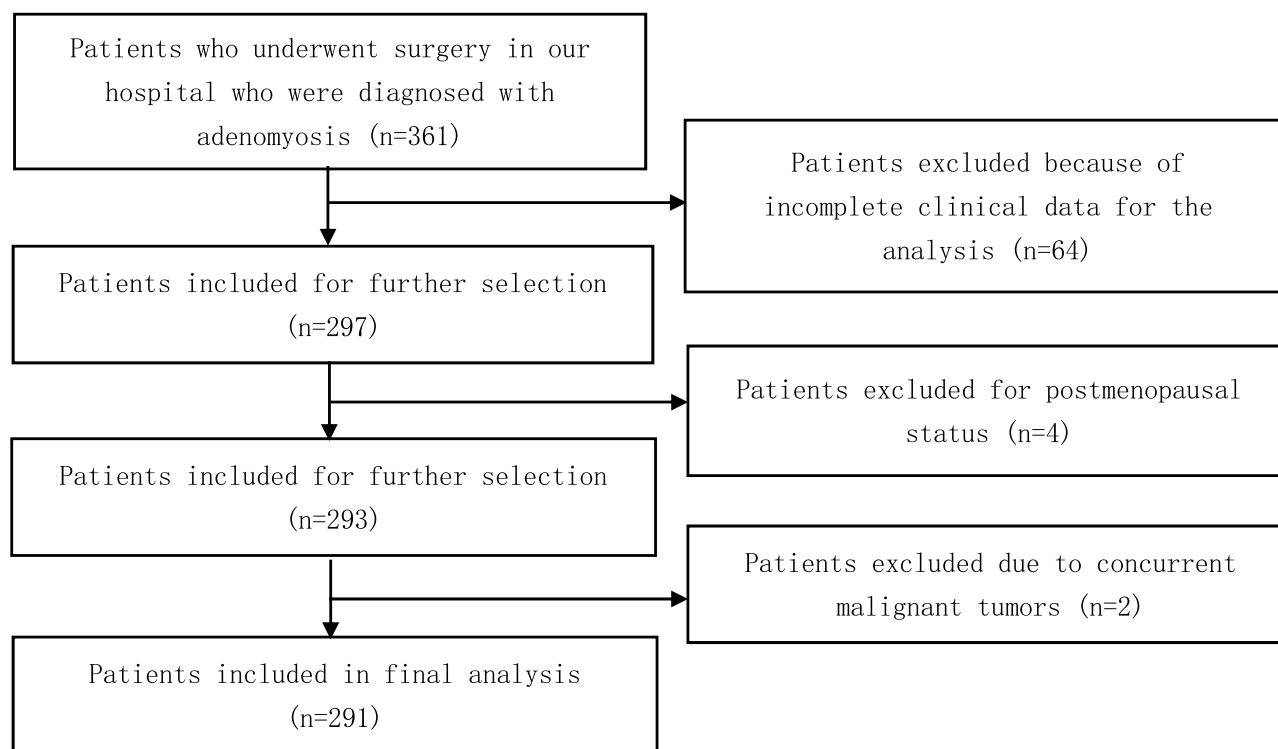
extracted for analysis, such as demographic characteristics, clinical manifestations, and pathological results.

The severity of pain symptom was evaluated with the method of 10-cm Visual Analog Scale (VAS) before the use of any relative drugs or surgery based on the self-assessment of patients.<sup>9</sup> The degree of pain was defined as mild if VAS was 1–3, moderate if 4–7, severe if 8–10, and none if 0. An elevated CA125 means the concentration of CA125 is above 35 U/mL.

We used IBM SPSS 23.0 software (IBM, USA) to statistically analyze the data. Continuous variables were analyzed with non-parametric *U*-test, and categorical variables with Chi-square test or Fisher's exact test. Multivariate analysis was conducted with Cox proportional hazards regression model. A *p*-value of <0.05 was considered significant.

## Results

Of the 291 included patients, 209 (71.8%) complained of pain symptom. A total of 198 (68.0%) patients presented dysmenorrhea, among which, 111 (56.1%) were progressively worsened. With regarding to the pain degree of the dysmenorrhea, mild cases accounted for 30.3%, moderate cases 36.9% and severe cases 32.8%. Totally, 70 (24.1%) patients' symptoms were accompanied by chronic pelvic pain, 24 (8.2%) with dyspareunia, and 7 (2.4%) with anorectal pain (Table 1).



**Figure 1** Flowchart for the patient selection progress.

**Table I** Pain Characteristics In Patients With Adenomyosis

| Variables                       | Number | Percentage |
|---------------------------------|--------|------------|
| Total number of patients        | 291    |            |
| Pain*                           |        |            |
| Yes                             | 209    | 71.8%      |
| No                              | 82     | 28.2%      |
| Dysmenorrhea                    |        |            |
| Yes                             | 198    | 68.0%      |
| No                              | 93     | 32.0%      |
| Degree of dysmenorrhea* (N=198) |        |            |
| Mild                            | 60     | 30.3%      |
| Moderate                        | 73     | 36.9%      |
| Severe                          | 65     | 32.8%      |
| Progressive worsening (N=198)   |        |            |
| Yes                             | 111    | 56.1%      |
| No                              | 87     | 43.9%      |
| CPP                             | 70     | 24.1%      |
| Dyspareunia                     | 24     | 8.2%       |
| Anorectal pain                  | 7      | 2.4%       |

**Note:** \*The degree of pain was defined as mild if VAS was 1–3, moderate if 4–7, severe if 8–10 and none if 0.

**Abbreviation:** CPP, chronic pelvic pain.

The overlapping of pain symptoms were shown in [Supplementary Table 1](#). The number of patients with pure dysmenorrhea, chronic pelvic pain, and dyspareunia were 131, 10, and 2, respectively. The remaining patients were with two or more kinds of pain symptoms.

## Comparison Between Pain And Painless Group

We divided all the patients into two groups in terms of the pain manifestation: pain group and painless group ([Table 2](#)). Patients in pain group were much younger than those in painless group when focusing on the age at diagnosis and onset of disease (median [Q1, Q3], 40.0 [34.0, 44.0] vs 42.0 [36.0, 46.0] years,  $P = 0.009$ ; 33.0 [28.0, 39.0] vs 36.0 [30.1, 42.0] years,  $P = 0.008$ , respectively). A higher level of pre-surgical CA125 was identified in patients of pain group (85.9 [43.0–176.7] vs 33.2 [16.3–58.5] U/mL,  $P < 0.001$ ). More patients in pain group presented rectal irritation (20.1% vs 7.3%,  $P = 0.008$ ), elevated CA125 (65.1% vs 29.3%,  $P < 0.001$ ), thicken myometrial layer (18.7% vs 2.4%,  $P < 0.001$ ) and concurrent endometriosis (45.0% vs 23.2%,  $P = 0.001$ ). Differences were not significant in the interval between onset and diagnosis, age of menarche, duration or interval of

menses, gravidity, parity, menorrhagia, bladder irritation, HGB level, GnRHa injection, CA199 level, volume of uterus, coexisting uterine fibroids and benign endometrial diseases.

In the multivariable analysis, an elevated level of pre-surgical CA125 ( $P < 0.001$ ) and thicken posterior myometrial layer ( $P = 0.023$ ) were both independent risk factors for the appearance of pain symptoms ([Table 3](#)).

## Comparison Between Dysmenorrhea And Non-Dysmenorrhea Group

Since 68% patients presented dysmenorrhea, we made a further analysis for adenomyosis patients with pure dysmenorrhea (131) (presented in [Supplementary Table 1](#)).

Patients in dysmenorrhea group were also much younger than those in non-dysmenorrhea group in terms of the age at diagnosis and onset of disease ( $P = 0.012$  and  $P = 0.012$ , respectively). A higher level of pre-surgical CA125 was identified in patients of dysmenorrhea group compared with the other one ( $P < 0.001$ ). More patients in dysmenorrhea group presented elevated CA125 ( $P < 0.001$ ), thicken myometrial layer ( $P < 0.001$ ) and concurrent endometriosis ( $P = 0.023$ ). ([Supplementary Table 2](#)). In the multivariable analysis, an elevated level of pre-surgical CA125 ( $P < 0.001$ ) and thicken posterior myometrial layer ( $P = 0.008$ ) were both independent risk factors for the appearance of dysmenorrhea ([Supplementary Table 3](#)).

## Discussion

In our study, we identified that most adenomyosis patients had symptoms accompanied by pain manifestation. Proportions of various forms of adenomyosis-related pain were also calculated, with dysmenorrhea ranking the first. Patients in pain group presented following characteristics compared to those without pain: younger onset age and younger diagnosed age, higher level of CA125, more likely to have concomitant rectal irritation, elevated CA125, thicken myometrial layer and endometriosis. We also identified that an elevated level of pre-surgical CA125 and thicken posterior myometrial layer were both independent risk factors for the morbidity of pain symptoms.

The pain manifestation was one of the main driving factors for adenomyosis patients to carry out relative physical examinations. In our research, adenomyosis-related pain included dysmenorrhea, chronic pelvic pain, dyspareunia, and anorectal pain, none of which were specific enough to be highly predictive for adenomyosis.<sup>10</sup> An

**Table 2** The Comparison Between Adenomyosis Patients With Or Without Pain Symptoms

|                                                                                    | <b>Pain Group % (No.)</b> | <b>Painless Group % (No.)</b> | <b>P</b> |
|------------------------------------------------------------------------------------|---------------------------|-------------------------------|----------|
| Number of patients                                                                 | 209                       | 82                            |          |
| <b>Age at diagnose</b><br>(Median [IQR], y)                                        | 40.0 (34.0–44.0)          | 42.0 (36.0–46.0)              | P=0.009* |
| <b>Age at onset of disease</b><br>(Median [IQR], y)                                | 33.0 (28.0–39.0)          | 36.0 (30.1–42.0)              | P=0.008* |
| <b>Interval between onset and diagnose</b><br>(Median [IQR], d)                    | 4.0 (2.0–8.0)             | 4.0 (2.0–7.0)                 | P=0.610  |
| <b>Age of menarche</b><br>(Median [IQR], y)                                        | 14.0 (9–19)               | 14.0 (13–15)                  | P=0.495  |
| <b>Duration of mense</b><br>(Median [IQR], d)                                      | 5.5 (4.5–6.5)             | 5.5 (4.5–6.5)                 | P=0.148  |
| <b>Interval of mense</b><br>(Median [IQR], y)                                      | 28.0 (26.5–29.0)          | 29.0 (26.9–29.0)              | P=0.355  |
| <b>Gravidity (n)</b><br>n=0<br>n≥1                                                 | 20.1% (38)<br>79.9% (151) | 25.4% (18)<br>74.6% (53)      | P=0.359  |
| <b>Parity (n)</b><br>n=0<br>n≥1                                                    | 30.0% (86)<br>70.0% (201) | 39.7% (31)<br>60.3% (47)      | P=0.101  |
| <b>Menorrhagia</b><br>Yes<br>No                                                    | 23.9% (50)<br>76.1% (159) | 25.6% (21)<br>74.4% (61)      | P=0.763  |
| <b>Rectal irritation</b><br>Yes<br>No                                              | 20.1% (42)<br>79.9% (167) | 7.3% (6)<br>92.7% (76)        | P=0.008* |
| <b>Bladder irritation</b><br>Yes<br>No                                             | 11.0% (23)<br>89.0% (186) | 6.1% (5)<br>93.9% (77)        | P=0.202  |
| <b>Pre-surgical HGB</b><br>[Median (IQR), g/L]                                     | 127 (114–135)             | 127 (109–137)                 | P=0.867  |
| <b>Pre-surgical GnRHa</b><br>Yes<br>No                                             | 23.0% (48)<br>77% (161)   | 17.1% (14)<br>82.9% (68)      | P=0.269  |
| <b>Pre-surgical Ca125 level</b><br>[Median (IQR), U/mL]                            | 85.9 (43.0–176.7)         | 33.2 (16.3–58.5)              | P<0.001* |
| <b>Pre-surgical Ca125 elevated</b><br>Yes<br>No                                    | 80.0% (136)<br>20.0% (34) | 47.1% (24)<br>52.9% (27)      | P<0.001* |
| <b>Pre-surgical Ca199 level</b><br>[Median (IQR), U/mL]<br>Parameter of ultrasound | 18.9 (10.6–42.3)          | 13.8 (6.8–27.4)               | P=0.512  |

(Continued)

**Table 2** (Continued).

|                                                             | Pain Group % (No.) | Painless Group % (No.) | P        |
|-------------------------------------------------------------|--------------------|------------------------|----------|
| <b>Volume of uterus</b><br>[Median (IQR), cm <sup>3</sup> ] | 129 (82–210)       | 117 (59–241)           | P=0.429  |
| <b>Thicken myometrial layer</b>                             |                    |                        |          |
| Yes                                                         | 18.7% (39)         | 2.4% (2)               | P<0.001* |
| No                                                          | 81.3% (170)        | 97.6% (80)             |          |
| <b>Decreased echogenicity in myometrial layer</b>           |                    |                        |          |
| Yes                                                         | 51.7% (108)        | 42.7% (35)             | P=0.167  |
| No                                                          | 48.3% (101)        | 57.3% (47)             |          |
| <b>Coexisting EM</b>                                        |                    |                        |          |
| Yes                                                         | 45.0% (94)         | 23.2% (19)             | P=0.001* |
| No                                                          | 55.0% (115)        | 76.8% (63)             |          |
| <b>Degree of coexisting EM (rAFS)</b>                       |                    |                        |          |
| None or Mild (Stage I+II)                                   | 84.2% (21)         | 86.6% (8)              | P=0.087  |
| Moderate and severe (Stage III+IV)                          | 15.8% (73)         | 13.4% (11)             |          |
| <b>Coexisting uterine fibroids</b>                          |                    |                        |          |
| Yes                                                         | 55.0% (115)        | 65.6% (54)             | P=0.092  |
| No                                                          | 45.0% (94)         | 34.1% (28)             |          |
| <b>Coexisting endometrial lesions</b>                       |                    |                        |          |
| Yes                                                         | 10.0% (21)         | 9.8% (8)               | P=0.940  |
| No                                                          | 90.0% (188)        | 90.2% (74)             |          |

**Note:** \*The difference reached statistical significance.

**Abbreviations:** EM, endometriosis; CPP, chronic pelvic pain; GnRHa, gonadotropin-releasing hormone agonist; HbG, hemoglobin; rAFS, staging system revised by American Fertility Society.

**Table 3** The Multivariate Analysis By Logistic Regression For Adenomyosis Patients With Pain Symptoms

| Variables                            | P value | OR (95% CI)         |
|--------------------------------------|---------|---------------------|
| Age at diagnosis                     | 0.992   | 1.001(0.897–1.116)  |
| Age of onset of disease              | 0.329   | 0.95(0.857–1.053)   |
| Rectal irritation                    | 0.351   | 1.721(0.55–5.383)   |
| Pre-surgical CA125 elevated          | <0.001* | 5.828(2.696–12.599) |
| Pre-surgical uterine volume          | 0.172   | 0.999(0.997–1.001)  |
| Anterior myometrial layer thickened  | 0.618   | 1.81(0.176–18.607)  |
| Posterior myometrial layer thickened | 0.023*  | 4.624(1.238–17.272) |
| Diffused myometrial layer thickened  | 0.999   | /                   |
| Coexisting endometriosis             | 0.763   | 1.13(0.509–2.509)   |

**Note:** \*The difference reached statistical significance.

American study analyzed the symptoms of adenomyosis in the form of interviews, which provided us with more detailed and straight findings. Totally 11 different types of pain were documented together with several representative quotes, and dysmenorrhea was complained the most, which echoes our study. Pelvic pain and dyspareunia were also mentioned at lower frequencies.<sup>11</sup>

In our further analysis for dysmenorrhea, it was interesting to notice that the analysis results were consistent with the above pain analysis except for the symptom of rectal irritation. The elevated level of pre-surgical CA125 and thicken posterior myometrial layer were also independent risk factors for the appearance of dysmenorrhea. These results further indicated the close relationship between dysmenorrhea and adenomyosis.

Though poorly understood, a widespread theory is that the pathogenesis of adenomyosis is the presence of endometrial basalis layer in the myometrium through invagination,

possibly because of the damage of the endometrial-myometrial border or the changes of the immune system.<sup>12,13</sup> The occurrence of dysmenorrhea may attribute to increased prostaglandin production in adenomyotic tissues, inflammation, nerve fiber density as well as upregulated oxytocin receptors, all of which still needs to be further verified.<sup>14–16</sup>

Patients in pain group were at younger ages when diagnosed and suffered the onset of disease. Curiously, the median intervals between onset and diagnosis of the pain and painless group were the same, both 4 days. Maybe other symptoms such as AUB or subfertility were the driven factors for patients in painless group to obtain the diagnosis.

TVUS, either 2D or 3D, was widely used to make a diagnosis of adenomyosis with a group of studies carried out to evaluate its accuracy.<sup>17,18</sup> It played important roles in evaluating the severity of adenomyosis and providing a reference for the treatment. J. Naftalin et al suggested a statistically significant association between the ultrasound features of adenomyosis and the severity of menstrual pain, in detail, the irregular endometrial–myometrial junction and asymmetrical myometrial thickening.<sup>19</sup> A higher possibility of posterior thicken myometrial layer was also seen in pain group, with no significant differences between pain and painless group in concurrent uterine fibroids ( $P=0.092$ ) or benign endometrial diseases ( $P=0.940$ ).

The elevation of CA125 was quite common in adenomyosis, but it was far from satisfied to be a predictive marker because of the limited specificity. Actually, there are no biomarkers in use with certain values in differentiating adenomyosis from other gynecological disease, and more investigations are needed to bring through the standstill.<sup>10</sup>

Substantial similarities can be found between adenomyosis and endometriosis in terms of clinical features and pathogenetic pathways.<sup>20</sup> 38.8% of the 291 adenomyosis patients were identified with concurrent endometriosis, as previously reported in our group.<sup>8</sup> We also noticed a significant difference between pain and painless group on rectal irritation. The theory that rectal irritation and EM are related with pain symptoms is mostly empirical, lacking of clinical research data to support. More patients were found with coexisting endometriosis in the pain group in this study, which made sense as dysmenorrhea was quite common among endometriosis patients. Our results were evidenced by real-world data, suggesting that we should pay attention to the presence of EM in patients with adenomyosis-related pain in clinical work.

For adenomyosis, no standard treatment guidelines are provided for clinical management and no drug is FDA approved. Nonsteroidal anti-inflammatory drugs (NSAIDs)

are a common option for alleviating the pain symptoms, especially dysmenorrhea, but we should pay attention to its potential adverse effects.<sup>21</sup> Other medical choices such as GnRHa, danazol, oral progestins, and aromatase inhibitors as well as surgical treatments are also applied in clinical work, but evidence from large randomized trials is needed to help select the best method.

## Conclusion

We summarized some characteristics related to pain manifestation and, more specifically, dysmenorrhea in patients with adenomyosis. The symptoms of pain together with obvious elevation of CA125 and rectal irritation as well as thicken myometrial layer under the TVUS may be regarded as clues for clinicians when dealing with adenomyosis. A clinical model constituted by these characters may improve the pre-operative diagnosis rate of adenomyosis, thus providing timely and effective treatment for the patients. Further investigations are required for better pain management in clinical work.

## Ethical Approval And Consent

Our study has been approved by Ethics Committee of Peking Union Medical College Hospital, Beijing, China, and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

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## Disclosure

The authors report no conflicts of interest in this work.

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