

# Clinical Manifestations of Adenomyosis Patients with or without Coexisting Endometriosis

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To the Editor: Uterine adenomyosis (AM) is caused by the ectopic growth of endometrial glands and stroma in the myometrium of the uterus, accompanied by hyperplasia and hypertrophy of the surrounding smooth muscle cells, leading to a diffuse enlargement of the uterus. Although AM is a common benign gynecological disease, it may cause severe dysmenorrhea, menorrhagia, enlarged uterus, and infertility, which have negative impacts on patients' health and quality of life. Thus far, there is a lack of high-quality data to give clinicians a comprehensive understanding of AM with regard to its clinical manifestations and pathological characteristics. This report presented clinical and pathological features of AM with or without coexisting endometriosis (EM) to assist clinicians and patients to make early diagnosis and intervention for such a disease in the future. We hoped that the above features would improve patients' fertility and their quality of life.

The patients received surgical treatments and with pathologically diagnosed uterine AM between March 2012 and September 2015 at the Department of Obstetrics and Gynecology, Peking Union Medical College Hospital (PUMCH) were included retrospectively. The inclusion criteria: Patients who (1) were surgically treated at the Department of Obstetrics and Gynecology of PUMCH, (2) were histopathologically diagnosed with AM after surgical procedures, (3) had fully registered clinical and pathological data, and (4) were premenopausal. Patients were excluded if they (1) were given surgical treatment at other hospitals after diagnosed with AM in PUMCH according to pathological specimen, (2) were postmenopausal or pregnant, or (3) had concurrent pelvic infection or genital tract malformation or malignant tumors.

The following data of those eligible patients were retrospectively collected from their medical records: (1) demographic characteristics, (2) symptoms presented, (3) the details of preoperation investigations and surgical procedures, (4) pathological reports, and (5) adjuvant treatments. According to the pathological findings, the patient pool was categorized into two groups: (1) EM group: patients diagnosed with concurrent EM and (2) non-EM group: patients had no pathological evidence of EM.

IBM SPSS 23.0 software (IBM, USA) was used for statistical analysis. Continuous and categorical variables were analyzed using Mann-Whitney *U*-test and *t*-test/Fisher's exact test, respectively. Receiver operating characteristic (ROC) curve was plotted to demonstrate the optimal cutoff values for stratifying and grouping continuous variables. Logistic regression models were used for multivariate analysis, in which the variables included were those found to be statistically significant in the univariate analysis. Cox proportional hazards models were used in multivariate analysis to calculate adjusted group hazard ratios, and their 95% confidence intervals were utilized to assess the relative risk of death or relapse for each variable of interest while adjusted for other covariates. All statistical tests were two-sided and differences were considered statistically significant at a value of  $P < 0.05$ .

A total of 291 patients diagnosed with AM and met the inclusion criteria were included, among whom 113 patients were allocated in the EM group and 178 in the non-EM group according to the enrollment criteria. The median age of all the patients at diagnosis was 40.0 years, while the median age of onset was 34.0 years. At the time of diagnosis, 56 (21.5%) of the patients were nulligravida, 117 (41.3%) were nulliparous, and 51 (17.5%) were with the complaint of infertility. A total of 176 (60.5%) patients had normal menstruation cycle, and 115 (39.5%) patients had abnormal menstruation cycle. Of all the identified patients, abnormal conditions of menstruation included prolonged menstrual bleeding (12.4%), shortened cycle (4.1%), prolonged cycle (4.1%), irregular cycle (4.8%), and menorrhagia (24.4%). The most common presenting symptom was dysmenorrhea in 198 (68%) patients, chronic pelvic pain in 70 (24.1%), dyspareunia in 24 (8.2%),

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and anorectal pain in seven (2.4%) patients, whereas 27 (9.3%) patients were asymptomatic. Of the 198 cases with dysmenorrhea, mild, moderate, and severe pain was seen in 60 (30.3%), 73 (36.9%), and 65 (32.8%) cases, respectively, while 111 (56.1%) were with gradually increased symptoms. Other symptoms of AM included rectum irritation and bladder irritation, which were seen in 48 (16.5%) and 28 (9.6%) patients, respectively.

Preoperative CA-125 levels were determined in 221 patients, of whom elevated CA-125 levels (>35 U/ml) were found in 160 (72.4%) patients, while the median CA-125 level was 65.9 U/ml (range, 7.3–1227.0 U/ml). Likewise, elevated CA-199 levels (>34 U/ml) were seen in 23/88 (26.1%) patients, while its median level was 18.0 U/ml (range, 0.6–1200.0 U/ml). A total of 167 patients received ultrasound scan before surgeries for the measurements of uterine size, abnormal echo, and blood flow. The median and mean volumes of the uterus were 122 cm<sup>3</sup> and 185 cm<sup>3</sup>, respectively. Thickened myometrial layer of the uterine was seen in 41 (24.6%) of the patients, of which 33 (80.5%) were in the posterior wall, five (12.2%) were in the anterior wall, and three (7.3%) were diffuse enlargement, respectively. Heterogeneous echo of the myometrium was seen in 143 (85.6%) patients. Peripheral blood flow around the lesion was seen in 40 (24.0%) cases, while sparse and abundant blood flow inside the lesion was seen in 68 (40.7%) and 14 (8.4%) cases, respectively. In addition, 106/291 (36.4%) patients were diagnosed with AM before operation. A total of 113/291 (38.8%) cases were seen with coexisting EM, of which 77 (68.1%) were seen with ovarian EM, 56 (49.6%) with peritoneal EM, and two (1.8%) with deep infiltrating endometriosis (DIE). Of all the cases coexisting with EM, 84 (74.4%) cases were diagnosed with moderate-to-severe EM (Stage III–IV). Besides, 169/291 (58.1%) patients were diagnosed with combined uterine fibroids.

Among the 106 (36.4%) patients who were diagnosed with AM before their surgical procedures, 38 (35.5%) patients received preoperative GnRHa therapy, of which 14 (13.2%) received 1–3 injections, 17 (16%) received 4–6 injections, and seven (6.6%) received more than 6 injections, respectively. Of all the patients, 208 (71.5%) patients underwent surgical resection of focal AM, while 83 (28.5%) received hysterectomy (with or without adnexectomy).

Patients coexisting with EM were older both at diagnosis and onset of disease compared with women in the non-EM group (median [Q1, Q3], 38.0 [34.0, 43.0] vs. 41.0 [35.8, 46.0] years,  $P = 0.001$ ; 38.0 [34.0, 43.0] vs. 35.0 [29.8, 41.0] years,  $P = 0.004$ , respectively). Compared with patients in the non-EM group, patients in EM group had an earlier median age of menarche (13.0 vs. 14.0 years,  $P = 0.004$ ) and a higher rate of menorrhagia (78.8% vs. 61.2%,  $P = 0.002$ ). Patients in the EM group had a higher rate of moderate-to-severe degree of dysmenorrhea (60.0% vs. 39.3%,  $P = 0.001$ ) and a higher rate of progressively worse dysmenorrhea (47.8% vs. 32.0%,  $P = 0.007$ ). More patients in EM group had the complaint of rectal irritation (24.8% vs. 11.2%,  $P = 0.002$ ) and elevated presurgical level of CA-125 (80.9% vs. 66.1%,  $P = 0.014$ ). However, patients in EM group had a smaller median volume of the uterus before surgery compared with the non-EM group (median [Q1, Q3], 106 [64, 183] vs. 138 [82, 264] cm<sup>3</sup>,  $P = 0.026$ ). No significant difference was seen in the number of pregnancies, presurgery CA-199 level between the two groups.

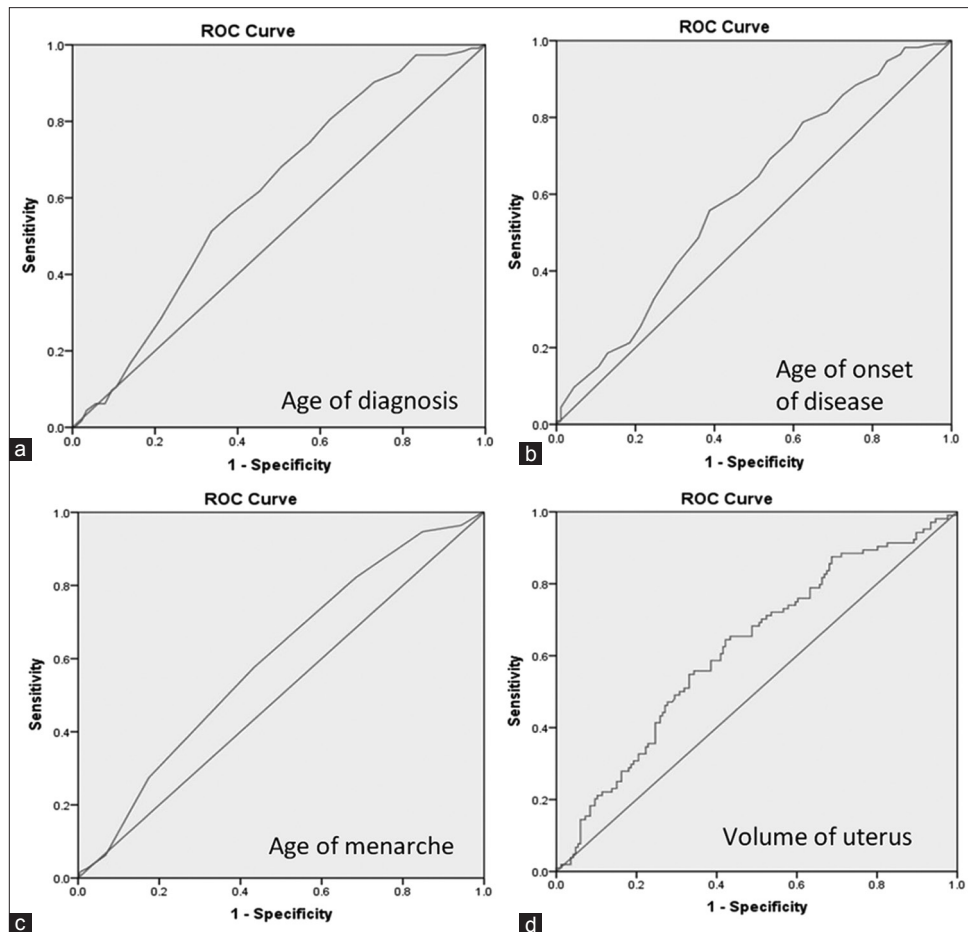
ROC curve was plotted to stratify the continuous variables. As a result, the optimal cutoff value was defined as 43.5 years for age at diagnosis, 33.5 years for age at onset of disease, 13.5 years for age of menarche, and 252.3 cm<sup>3</sup> for presurgery volume of the uterus [Figure 1]. In multivariable analysis by logistic regression, patients in the EM group were more likely to have an earlier age of menarche ( $P = 0.036$ ), a higher possibility of symptoms of rectal irritation ( $P = 0.038$ ), smaller presurgical volume of the uterus ( $P = 0.028$ ), and elevated presurgical level of CA-125 ( $P = 0.014$ ).

Previous studies generally believed that patients with AM were more likely to see doctors at the age of 40 years due to symptoms such as dysmenorrhea and menorrhagia. The mean age of patients at diagnosis in the study is comparable to previous studies. A recent study has shown a growing number of young patients, and infertility has become one of the chief complaints.<sup>[1]</sup> Among the 291 patients in our report, 51 (17.5%) were with the complaint of infertility at the time of diagnosis.

AM is a gynecologic disease with heterogeneity that patients with AM could show a variety of clinical manifestations. Literature indicated that the most common presenting symptoms of AM were heavy menstrual bleeding and dysmenorrhea while a relatively small percentage of patients could also be asymptomatic.<sup>[2]</sup> According to our results, abdominal pain is the main manifestation that 72.5% of the patients experienced it and 68.0% had dysmenorrhea of different severity (over 2/3 were moderate to severe and over 1/2 were progressive). In this study, 60.5% of the patients showed a normal menstruation cycle, while 12.4% had prolonged menstrual bleeding, and 24.4% had menorrhagia, which suggested that adequate attention should be paid to the patients with normal menstruation cycle. In addition, fertility problems are of great importance which requires special attention during the diagnosis and treatment of AM. All patients in the study were women of child-bearing age, among whom 21.5% were nulligravida, 41.3% were nulliparous, and 17.5% were with the complaint of infertility. One published meta-analysis showed that the rate of pregnancy in patients with AM was reduced by 28% than women without, while the rate of miscarriage for the former was also increased to some extent.<sup>[3]</sup> Therefore, the effects of AM on fertility and its corresponding treatments, along with its mechanism, fertility preservation, and AM-associated infertility would become the key challenges in the future research.

Regarding the diagnostic laboratory examinations, a number of studies have reported that elevated serum level of CA-125 is most relevant to AM. This study showed that 72.4% of patients were with elevated serum CA-125 while the remaining patients with a normal level, indicating that CA-125 is an important marker of AM. In addition, previous studies have shown that only 3–26% of AM patients can be diagnosed on the basis of clinical presentations before operation. Weiss *et al.*<sup>[3]</sup> found that most of the patients with AM are diagnosed by incidental pathology findings after hysterectomy, rather than receiving hysterectomy because of the clinical diagnosis of AM. In this report, only 36.4% of the patients were diagnosed with AM before surgery, which is comparable to the previous studies.<sup>[4]</sup> Till now, there are still no standard diagnostic imaging criteria, and a better preoperative diagnostic model of AM is expected.

In our report, 38.8% of the AM patients were combined with EM, 68.1% of which were with ovarian EM. Only two cases were found to have DIE. However, considering that DIE is a pathological diagnosis and some patients with DIE may not undergo surgical



**Figure 1:** (a) ROC curve for age of diagnosis; (b) ROC curve for age of disease onset; (c) ROC curve for age of menarche; (d) ROC curve for volume of uterus. ROC: Receiver operating characteristic.

resection, the above data may have underestimated the proportion of AM patients coexisting with DIE. It is noticeable that 74.4% of the patients with combined EM were classified as moderate and severe EM (Stage III–IV). Naphthalung and Cheewadhanaraks<sup>[5]</sup> presented their results that the prevalence of EM in patients with AM was 40.4% while 22.7% of patients with leiomyomas. Previous studies have reported that 34.6–79% of patients with EM could be combined with AM, whereas the incidence of coexisting EM in patients with AM was significantly higher (39.9%). The posterior wall of the uterus was thicker in the latter group of patients too. Moreover, compared to the patients with mild-to-moderate EM (Stage I–III), patients with severe EM (Stage IV) were with a higher proportion of coexisting AM (42.8% vs. 29.4%). These results suggested that patients with severe degree EM and coexisting AM should be carefully examined and the issue of postoperative adjuvant treatment should be considered thoroughly and comprehensively.

Furthermore, we compared the clinical features between the EM group and non-EM group, in which the diagnosis of concurrent EM was pathologically proved. As results, compared with the non-EM group, the patients in the EM group were younger at the time of diagnosis and onset of AM, and their age of menarche was earlier as well. In this study, the patients with concomitant EM were with a higher rate of menorrhagia (78.8% vs. 61.2%), moderate-to-severe and gradually aggravated dysmenorrhea (60.2% vs. 39.3%; 47.8% vs. 32.0%), and the symptoms of rectal irritation (24.8% vs. 11.2%), compared with

patients without coexisting EM. Moreover, the EM group had a higher level of CA-125 value and smaller volume of the uterus before surgery. Logistic regression analysis showed that age of menarche, symptoms of rectal irritation, volume of the uterus, and CA-125 level were significantly associated with the status of coexisting EM in patients with AM. Due to the related data from previous literature were rare, we hope that prospective study with large scale of samples could be performed in future.

Our report proposes some presurgical clinical manifestations which can be part of the basis for establishing the clinical diagnostic model for predicting coexisting EM in patients with AM in the future. It should be pointed out that, due to its retrospective nature, the main limitations of this report were recall bias and selection bias. However, the diagnosis is usually made after primary surgery, so it is difficult to recruit patients in a prospective study. Further prospective study is required to develop a predictive model which might be helpful for the decision of clinical strategy management for AM.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their

consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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