

Adolescent Endometriosis in China: A Retrospective Analysis of 63 Cases

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ABSTRACT

Study Objective: To investigate the clinical presentations, diagnosis, treatment modalities and prognosis of endometriosis in adolescents in China.

Design: Retrospective study.

Setting: Data were collected from records of the Peking Union Medical College Hospital from 1992–2010.

Participants: This study consisted of 63 patients ≤ 20 years old with surgically diagnosed endometriosis. Their clinical presentations, auxiliary examinations, surgical outcomes, and post-operative medical treatments were analyzed. The follow-up information of 35 cases was collected.

Results: Mean age at diagnosis was 18.41 ± 1.84 years with a much earlier disease onset in adolescents with genital tract malformations. Of the 35 patients with follow-up time that ranged from 12–98 months, nine in 15 patients who didn't proceed with medical treatment after operation had a recurrence (9/15), seven in 15 patients who took oral contraceptive pills (OCP) or progestin only pills had reoccurrence recurred (7/15), and none of the five patients received gonadotropin-releasing hormone agonist (GnRHa) therapy recurred (0/5). In this study, multiple sites lesions was defined as more than one site being involved of the following four sites: the left ovary, the right ovary, the rectovaginal pouch and the uterosacral ligament. Among the 15 cases without postoperative medical therapy, all five cases with multiple sites lesions had recurrence (5/5), while only four of the other 10 cases had relapse (4/10). The difference was of statistical significance (Fisher exact test, $P = 0.044$).

Conclusion: Multiple sites lesions found in operation was a risk factor of recurrence. GnRHa was effective to prevent the recurrence.

Key Words: Adolescent, Endometriosis, Congenital abnormalities

Introduction

Endometriosis in adolescents presents a particular challenge of differential diagnosis and choice of treatment. No epidemiological data are available on the incidence or prevalence although some data suggest that about two thirds of adult women with endometriosis report symptoms arising before 20 years of age.¹ The presentation of endometriosis in adolescents is variable, and it is often difficult to distinguish endometriosis from primary dysmenorrhea. Early diagnosis and interventions are essential in order to minimize the symptoms and hopefully prevent disease progression and preserve future fertility.² There are no specific published data for treatment of adolescents and long-term outcomes. In this study, we aimed to present our experience in diagnosis, management and follow-up of endometriosis in a Chinese adolescent population.

Materials and Methods

This study included 63 patients younger than 21 years of age who underwent surgery and had a pathologically confirmed diagnosis of endometriosis between 1992 and

2010 in Peking Union Medicine College Hospital. Clinical data of general characteristics (age at menarche, age at diagnosis, age at onset of the symptoms), clinical characteristics (symptoms, diagnosis and history of other relevant gynecological conditions, preoperative ultrasound findings), surgery findings, post operation management, and follow-up information were analyzed based on case files. The stage of disease was defined by the revised American Fertility Society (rAFS) classification system. Follow-up information was collected through telephone calls and clinical records review.

Analysis was undertaken using SPSS for Windows (18th ed, IBM). Measurement data was analyzed with the use of independent-sample *t* test. Enumeration data was analyzed using the Mantel-Haenszel procedure, and tested with the use of chi-square test or the Fisher exact test. $P < 0.05$ was considered significant.

Results

General Characteristics

Fifteen of the 63 cases had genital tract malformations, including two oblique vaginal septum syndromes, six atresia of lower part of vagina (one with didelphic uterus), one imperforate hymen with bicornuate uterus, one congenital atresia of the cervix, two atresia of upper part of the vagina with congenital atresia of the cervix, two didelphic uterus (one with absence of the right cervix, one with atresia of the

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right cervix), one rudimentary horn of the uterus. The average age of the total 63 cases was 18.41 ± 1.84 years (range 12–20, with median age of 19). The 15 cases with genital malformations were diagnosed at a mean age of 16.21 ± 2.12 years (range 12–20, with median age of 17 years), while for the other 48 cases was 19.04 ± 1.10 years (range 16–20, with median age of 19). The age of diagnosis is significantly younger in genital malformation group (*t* test, $P < 0.001$). The average interval between onset of symptoms and diagnosis was 11.51 months (range one day to seven years).

Presenting Symptoms

Pelvic pain, either cyclic (45/63) or chronic (13/63), was the most common reason for the hospital visit. Other symptoms included acute abdominal pain (19/63), gastrointestinal dysfunction (19/63), irregular menses (5/63), and dyspareunia (1/63).

Preoperative Auxiliary Examinations

Serum level of cancer antigen 125 (CA125) was tested in 43 cases, and elevated (> 35.0 kU/L) in 35 cases (81.40%), with a median value of 72.6 kU/L (range 6.6–884). All of the 63 cases were examined with ultrasonography before surgery and a pelvic mass was found in 55 cases (87.30%).

Surgical Procedure and Findings

All the patients underwent surgical treatment for pelvic mass(es) or malformations either by laparoscopy (48/63) or laparotomy (15/63). The visible lesions of endometriosis and endometriomas were removed with ovary preservation, the pelvic adhesions were eliminated. All the patients were debulked to stage I at most. In the 15 cases with genital tract malformations, deformity correction was also performed. Three patients with severe malformation of the uterus or continued obstruction of the cervix after previous surgery underwent hysterectomy, but the reproductive ability was preserved in the other 60 cases.

Of all the 63 cases, ovaries were involved in 55 cases (87.30%), rectovaginal pouch was involved in 18 cases (28.57%), and the uterosacral ligaments were involved in 20 cases (31.75%). Of all the 15 cases with anomalies, ovaries were involved in 14 cases (93.33%), while rectovaginal pouch or uterosacral ligaments were only involved in two cases (13.33%). However, of the 48 cases without anomalies, 26 had rectovaginal pouch or uterosacral ligaments involved (26/48). The difference is of statistical significance ($OR = 7.718$, $P = 0.005$). Other sites such as peritoneum, bladder, ureter and so on were also affected in some cases. According to the revised American Fertility Society classification system, endometriosis was found to be stage I in 7.94% (5/63), stage II in 3.17% (2/63), stage III in 52.38% (33/63), and stage IV in 36.51% (23/63).

Post-operative Therapy

Patients were suggested to take post-operative therapy according to the pre-operative symptoms. Thirty-one patients (31/63, 49%) including four with genital

malformation agreed to post-operative medical therapy, which included combined OCPs (20/31, 65%) progestins (2/31, 65%) continuously for six to nine months, or gonadotropin releasing hormone agonists (9/31, 29%) for three to six months.

Follow-up and Prognosis

Follow-up information was collected on 35 patients with a mean follow-up time of 46.31 months (range 12–98). Six of them had obstructive genital malformations. All the patients who underwent surgery achieved optimal lesion elimination and significant symptoms relief. We defined recurrence as that of new pelvic endometriosis and/or masses which was found by ultrasound or similar symptoms which recurred at least six months post-operatively. Sixteen of the 35 cases experienced recurrence of the disease (16/35, 45.71%) including three cases of genital abnormalities. Pelvic masses confirmed by ultrasonography recurred in nine cases, and pain symptoms requiring analgesics recurred in seven cases. The average recurrence time of the 16 cases was 33.44 months. Four people got pregnant after treatment.

Of the 35 patients, 15 didn't proceed with medical treatment post-operation (Group 1), 13 took OCPs (Group 2), two took progestins (Group 3), and five received GnRHa therapy (Group 4). Disease recurred in nine cases of group 1 (9/15, 60%), six cases of group 2 (6/13, 46%), one case of group 3 (1/2, 50%), and none of group 4 (0/5, 0%), respectively (Table 1). Only the difference of the recurrent rate between group 1 and group 4 was of statistical significance (Fisher exact test, $P = 0.038$). Therefore, compared with OCPs and progestin, GnRHa appeared to be more effective to prevent recurrence.

In our study, "Multiple sites lesions" was defined as ≥ 2 sites being involved of the following four sites: the left ovary, the right ovary, the rectovaginal pouch and the uterosacral ligament. Among the 15 cases without post-operative medical therapy, all the five cases with multiple sites lesions had relapse (5/5, 100%), while only four of the other 10 cases had relapse (4/10, 40%) (Table 2). The difference was of statistical significance (Fisher exact test, $P = 0.044$), which suggested multiple site lesions was a risk factor of endometriosis reoccurrence.

Of the 35 cases, multiple sites lesions were found in 19 cases. Of the 19 cases, 14 received post-operative medical therapy and six of them experienced recurrence (6/14, 43%), while the disease recurred in all the remaining five cases who took no treatment post-operatively (5/5, 100%) (Table 3). The difference was of statistical significance (Fisher exact test, $P = 0.045$), which suggested that post-operative treatment could reduce the recurrent rate.

Table 1
Patients with Follow-Up Information were Divided Into 4 Groups According to Different Post-operative Therapy. Recurrence Rate was Calculated

Groups	Without post-operative medical therapy	6–9 months continuously		GnRHa (3–6 doses)
		OCPs	Progestins	
Number	15	13	2	5
Recurrence	9	6	1	0
Ratio	9/15 (60%)	6/13 (46%) 7/15 (47%)	1/2 (50%)	0/5 (0%)

Table 2

Patients Without Post-operative Therapy were Divided into Two Groups According to Lesion Numbers. Recurrence Rate was Calculated

Without post-operative therapy	Single site involved	Multiple sites lesions
Case number	10	5
Recurrence	4	5
Ratio	4/10 (40%)	5/5 (100%)

There was concern that bias might be introduced into our analysis because six of the 35 cases had genital malformations, so these cases were excluded to minimize confounding in the further analysis. In the 29 cases without genital malformation, six of 10 cases that didn't take medical treatment after operation suffered from recurrence (6/10, 60%), six of 13 cases that took OCPs (6/13, 46%) and one of two cases that took progestins (1/2, 50%) recurred, while all the four cases received GnRHa therapies were free of disease at the time of follow up (0/4, 0%) (Table 4).

In the 29 cases without genital malformations, 10 cases received no post-operative medical therapy. Among the 10 cases, all the four cases with multiple sites lesions had relapse (4/4, 100%), while only two of the other six cases had relapse (2/6, 33%) (Table 5).

Of the 29 cases, multiple sites lesions were found in 18 cases. 14 cases took post-operative medical therapy and six of them experienced recurrence (6 /14, 43%), while the disease recurred in all the remaining four cases who didn't receive medication post-operatively (4/4, 100%) (Table 6).

Discussion

Endometriosis has been documented in adolescents. The youngest patient diagnosed with endometriosis was eight years old in literature,³ and 11 years old in China.⁴ Of the 63 patients in our study, the average age was 18.41 years. Thus, clinicians involved in the care of adolescents should be aware of endometriosis as a pathological etiology in girls who present with dysmenorrhea or chronic pelvic pain.

Malformations

Müllerian anomalies are unique characteristics of adolescent patients with endometriosis, especially those with outflow tract obstructions. It has reported that 11–40% of the adolescent patients had genital tract anomalies,⁵ which is consisted with our data 24% (15/63). On the other hand, Uğur et al⁶ reported a 58% incidence of endometriosis in females with genital obstructive malformations, which is much higher than that in females without genital obstructive malformations (18%). Therefore, gynecologists should keep in mind that there is

Table 3

Patients with "Multiple Sites Lesions" were Divided into Two Groups According to Post-operative Therapy. Recurrence Rate was Calculated

Multiple sites lesions	Without post-operative therapy	OCPs, Progestins or GnRHa
Case number	5	14
Recurrence	5	6
Ratio	5/5 (100%)	6 /14 (43%)

Table 4

Patients Without Genital Malformations were Divided into 4 Groups According to Different Post-operative Therapy. Recurrence Rate was Calculated

Groups	Without post-operative medical therapy	(6–9 months continuously)		GnRHa (3–6 doses)
		OCPs	Progestins	
Case number	10	13	2	4
Recurrence	6	6	1	0
Ratio	6/10 (60%)	6/13 (46%) 7/15 (47%)	1/2 (50%)	0/4 (0%)

possibility of malformations in adolescent patients with endometriosis.

Meanwhile, there are obvious differences in the manifestations between the adolescent patients with malformations and those without. Firstly, in our research, the mean age in the patients with genital tract anomalies is much younger than those without (16.21 vs 19.04). The reason of early onset of adolescents with obstructive genital malformations might be excessive retrograde menstruation in the abdomen. Secondly, we found that the lesion sites varied in these two groups. In obstructive genital malformations, ovaries were the first to be affected (14/15), while rectovaginal pouch or uterosacral ligaments were less likely to be involved (2/15) compared to genitally normal patients (26/48). This might be associated with the anatomical position of the ovaries—retrograde menstruation first arrives at ovaries when passing through fallopian tubes and enters the peritoneal cavity. This phenomenon supports the theory of retrograde menstruation and implantation from another side. Sanfilippo et al⁷ reported a series of patients with extensive endometriosis in association with genital tract obstruction. Once the outflow tract obstruction was corrected, the intra-abdominal endometriosis was reversed. Hence, for patients with genital tract obstruction, the best therapy appears to be to correct the obstruction as early as possible in order to relieve the retrograde menstruation.

R- AFS Stage

It has been reported that in western countries adolescent endometriosis patients mainly presented with the revised AFS classification staged I and II while seldom with stage III and IV.⁸ Among the 39 adolescent endometriosis cases reported in Korea by Bai et al,⁹ 44% were at stage II, 46% at stage III and stage IV. In our research, most patients were at an advanced stage (88.90%). The potential reasons for the high percentage of advanced stages of endometriosis in our country might be: (1) In China most adolescents with chronic pelvic pain fail to present until symptoms become severe enough to warrant a healthcare provider visit. They

Table 5

Patients Without Genital Malformations and Post-operative Therapy were Divided into Two Groups According to Lesion Numbers. Recurrence Rate was Calculated

Without post-operative therapy	Single site involved	Multiple sites lesions
Case number	6	4
Recurrence	2	4
Ratio	2/6 (33%)	4/4 (100%)

Table 6

Patients with “Multiple Sites Lesions” but Without Genital Malformations were Divided into Two Groups According to Post-operative Therapy. Recurrence rate was Calculated

Multiple sites lesions	No post-operative therapy	With post-operative therapy
Case number	4	14
Recurrence	4	6
Ratio	4/4 (100%)	6/14 (43%)

prefer Chinese herbal medicine to OCPs from the initial onset of dysmenorrhea; (2) Surgical evaluation and treatment has traditionally been accepted as an option only when pelvic masses have been found, which delay the diagnosis.

Diagnosis

There is often a delay in the diagnosis and treatment of endometriosis in adolescents. Ballweg¹⁰ reviewed 4000 endometriosis cases and concluded that it took 9.3 years on average from the onset of symptoms to actual diagnosis. The first 4.7 years were delayed by patients and another 4.6 years were due to doctors. Ventolini et al¹¹ reported a follow-up of 28 adolescent endometriosis cases for 8.6 years, and found an inverse relationship between stage of disease at diagnosis and fecundability. Thus, diagnosis and clinical management of endometriosis in the early stage of disease are of great importance.

In order to make the initial diagnosis, a thorough history and physical examination are paramount. Distinguishing endometriosis from primary dysmenorrhea can be difficult. However, patients with endometriosis often describe a more progressive and continuous pain than those with primary dysmenorrhea. Surveying for gastrointestinal and genitourinary symptoms, such as diarrhea, hematochezia, hematuria, and frequency may also be useful for diagnosis.⁵ The physical examination is somewhat special because in a non-sexually active bimanual examination is not appropriate, especially in China. Rectoabdominal examination can reveal pelvic floor trigger points and uterosacral nodularity.

Serum CA-125 level is neither specific nor sensitive in diagnosing endometriosis.¹² In our study it is not apparently associated with r-AFS stages. Pelvic ultrasonography and MRI can be used in detecting the Mullerian anomalies and pelvic masses. However, peritoneal endometriosis can't be diagnosed definitely by either pelvic ultrasonography or MRI. Laparoscopic examination is most effective in early and accurate diagnosis of endometriosis, but it is still unclear in choosing the optimal time for intervention.

Management

The current management of adolescent endometriosis is similar to that of the adult with endometriosis. The goals of management for adolescent patients with endometriosis are pain relief, prevention of disease progression, and fertility preservation. The American Congress of Obstetricians and Gynecologists published a stepwise treatment algorithm in 2005.¹ For an adolescent girl presenting with

severe dysmenorrhea, recommendations include initiation of treatment with nonsteroidal anti-inflammatory medications and OCPs. If symptoms of dysmenorrhea continue beyond three months despite these interventions, patients should be offered a diagnostic laparoscopy and surgical ablation and resection if endometriosis is found. The situation is quite different in China, OCPs are not fully accepted by common people in management of adolescent patients presenting with dysmenorrhea compared to Chinese herbal medicine. To prevent relapse, it is widely accepted in our country that patients especially with advanced stages should receive postoperative medical therapy for several months. The first line medicine recommended for patients under the age of 16 is continuous OCPs. For patients over 16 years, either continuous OCPs or GnRHa with add-back can be chosen.

Follow-up and Prognosis

There is little follow-up information with regard to adolescent endometriosis studies in the English literature. We can only deduce several points from this retrospective study.

Follow-up Time

It has been reported that in adult endometriosis patients recurrence was 36% in five years after the first operation, and onset of symptoms at a younger age was a risk factor for recurrence.¹³ In our study, the average time of recurrence was 33 months. So we suggest that the adolescent patients should be followed up for at least three years if long-term follow-up can't be achieved.

Risk Factors of Recurrence

To maximally eliminate the potential bias, we analyzed those patients without postoperative treatment. Neither age at diagnosis, dysmenorrhea, gastrointestinal symptoms, serum CA125 level before surgery, nor r-AFS stage had been found to be statistically significantly associated with recurrence of the disease. The only risk factor for recurrence was multiple sites lesions found at surgery.

Post-operative Medication

As endometriosis is generally perceived to be a chronic and progressive disease with high recurrence rate; the American Congress of Obstetricians and Gynecologists suggests that adolescent patients should receive post-operative medical therapy until they desire pregnancy.¹ Long-term medical therapy had been reported to be reliable to reduce the frequency and severity of recurrent endometriosis-related dysmenorrhea and anatomical relapse of endometriosis in adults.^{14,15} However, in our initial analysis the recurrence rate between patients with post-surgery medical therapy and those without post-surgery medication was of no statistical significant difference (OR = 2.175, $P = 0.140$). We had concern that bias might be introduced into our analysis because of difference in disease severity among the cases, we selected those patients with multiple sites lesions to be further analyzed. Then the difference was of statistical significance (Fisher exact test,

$P = 0.045$). Therefore, post-operative medical therapy may also be effective in preventing endometriosis recurrence in adolescent patients.

At this time, there is no consensus of which medication is best for adolescent endometriosis. Although none of the five patients who received GnRHa therapy suffered from recurrence, we are not sure GnRHa is the best choice of post-operative therapy because the number is so small and because of the side effects, such as bone density loss and growth restriction. It might be safe for older adolescent, over 16, as many authors suggested, due to the side effect of bone mineral density reduction, that this could be minimized by hormonal add-back therapy.¹⁶

We have attempted to eliminate confounding factors such as deletion of obstructive Müllerian anomaly patients in analysis, focusing on specific groups of patients. But our study is still far from satisfactory because this is a retrospective study with such a small number of cases. Based on this study we recognized several questions could be addressed in future research. When is the best time to do laparoscopy? Which medication is ideal after surgery? Should we pay much more attention to patients with multiple site lesions? At least our study indicates that pediatricians and gynecologists in China and maybe other traditional countries should lay stress on early diagnosis and patient education.

Conclusion

When an adolescent patient complains of dysmenorrhea or chronic pelvic pain, a gynecologist must take into mind the possibility of endometriosis. Early diagnosis by laparoscopy is of great importance. Multiple sites lesions found at surgery was a risk factor for recurrence.

Post-operative medical therapy was recommended as well as a long term follow-up. GnRHa was effective to prevent recurrence.

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