Dysmenorrhea and Endometriosis in Young Women

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ABSTRACT

Dysmenorrhea is defined as symptoms associated with menstruation, such as abdominal pain, cramping and lumbago, that interfere with daily activity. Primary dysmenorrhea refers to menstrual pain without underlying pathology, whereas secondary dysmenorrhea is menstrual pain associated with underlying pathology. Endometriosis, one of the main causes of secondary dysmenorrhea, induces dysmenorrhea, pelvic pain and infertility, resulting in marked reduction of quality of life during reproductive age. This review article is a comprehensive overview of dysmenorrhea and endometriosis in young women.

Key words adolescent; infertility; laparoscopic surgery; oral contraceptive; prostaglandin

Dysmenorrhea is defined as pathological symptoms associated with menstruation, marked by abdominal cramping and pain during the menstrual period that interfere with daily activity. Associated general symptoms, such as nausea, vomiting, lumbago, diarrhea, and headache, are also common. Dysmennorhea is categorized into two types, primary and secondary. Primary dysmenorrhea refers to menstrual pain without underlying pathology, whereas secondary dysmenorrhea refers to painful menstruation associated with underlying pathology (Table 1).

One study, conducted with the support of the Japan Ministry of Health and Welfare, revealed that menstrual pain requiring pain medication occurs in 33% of menstruating Japanese women. In 6% of women, pain medications were ineffective and bedrest was needed. The study results suggest that 1/3 of women who menstruate may require medical intervention.[1] Ikeda et al., reporting the results of a questionnaire survey of menstrual pain among high school students, revealed that 90.8% of students experienced menstrual pain and that pain affected the daily activities of 51.8%. The incidence of menstrual pain increased in 3rd grade students (17–18 years old) compared with 1st and 2nd grade.[2]

The most common cause of secondary dysmenorrhea is endometriosis. Endometriosis is an estrogen-dependent inflammatory disease characterized by ectopic growth of endometrial stroma and glands affecting 5% to 15% of women of reproductive age.[3] The main clinical features are dysmennorhea, chronic pelvic pain and infertility. Endometriosis is a chronic and recurrent disease that adversely affects quality of life in reproductive age women.

Sampson's implantation theory, which describes intraperitoneal menstrual reflux leading to spillage of endometrial cells into the peritoneal cavity and the resulting development of endometrial lesions, is currently the prevailing explanation of the pathophysiology of endometriosis. Increased exposure to menstruation in terms of short menstrual cycles, prolonged flow and low parity are possible risk factors.[4] Therefore, retrograde menstruation observed in 90% of menstruating women is considered a key factor in the pathogenesis of endometriosis.

Incidence of endometriosis is believed to be increasing because of changes in women's lifestyle, such as the tendency to marry later and have fewer children. This life style change increases the number of times a woman menstruates and affects the incidence of endometriosis.

MECHANISM OF (PRIMARY) DYSMENORRHEA

The etiology of primary dysmenorrhea includes an excess or imbalance in the amount of prostaglandins (PGs) secretion from the endometrium during menstruation. Associated general symptoms, such as nausea, vomiting, lumbago, diarrhea and headache are the sequel of influx of PGs and its derivatives into systemic circulation. Synthesis of arachidonic acids and the pathway of cyclooxygenase are activated by a decline of progesterone concentrations in the late secretory phase. PG levels in the endometrium of the late secretory phase increase 3 times higher than those of the proliferative phase. A further increase in PG levels is observed during the menstrual phase. PGE2 and PGF2 alpha concentrations are higher in the menstrual fluid of women with dysmenorrhea than in women with painless periods.[5] Among PGs, PGF2a is considered the most potent causal factor of pain.

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Abbreviations: GnRH, gonadotropin-releasing hormone; LEP, low dose estrogen-progestin; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; OC, oral contraceptive; PG, prostaglandin

Table 1. Differential diagnosis of primary and secondary dysmenorrhea

	Primary dysmenorrhea	Secondary dysmenorrhea
Onset	Within 3 yr after menarche	More than 5 yr after menarche
Age	15–25 yr old	Over 30 yr old
Aging	Gradually improve	Become worse
Marriage	Improve	No change
Postpartum	Improve	No change
Findings of internal examination	Normal	Endometriosis, fibroma, etc.
Time	Menstruation	Menstruation or other time if worse
Duration	4–48 h	1–5 d

By preventing ovulation, oral contraceptives (OCs) suppress the progesterone-driven proliferation of the secretory endometrium, resulting in a decrease in prostaglandin synthesis and volume of menstrual fluid.[6] Consistent with Sampson's theory, reduced menstrual flow after taking OCs contributes to reduced retrograde menstruation, which then impede the development of endometriosis.

MECHANISM OF PAIN DUE TO ENDOMETRIOSIS

Concentrations of PGs are higher in the menstrual blood of women with endometriosis.[7] Bulletti et al. found that frequency, amplitude and basal pressure tone of uterine contractions in women with endometriosis were higher than in those without.[8] Thus, the severe dysmenorrhea of endometriosis patients may be the result of abnormal uterine contractions.

Endometriotic lesions and adhesions may also cause the deep pelvic pain associated with endometriosis. Action mechanisms of pain with endometriosis are outlined in Table 2. The pain of patients with endometriosis is thus due to both uterine contraction and endometriotic lesions.

ENDOMETRIOSIS IN YOUNG WOMEN

Retrospective studies report a diagnosis of endometriosis in 25% to 38% of adolescents with chronic pelvic pain.[9] Nonsteroidal anti-inflammatory drugs (NSAIDs) and oral OCs are prescribed for adolescent patients with chronic pelvic pain. If these agents are refractory, endometriosis has been diagnosed in 50% to 70% of these patients.[10] These results suggest that endometriosis should be part of the differential diagnosis of chronic pelvic or lower abdominal pain in premenarcheal and perimenarcheal girls.

While endometriosis usually occurs in women after menarche, a series of 5 premenarcheal girls (ages 8.5 to 13 years) were reported to have endometriosis.[11] The girls, who all had chronic pelvic pain and a negative gastrointestinal workup, were found to have peritoneal endometriotic lesions as classified by American Society of Reproductive Medicine. Laparoscopic resection or cautery of all visible lesions resulted in marked improvement of their pelvic pain.

Although Sampson's theory of retrograde menstruation and implantation is believed to explain most cases of endometriosis, this theory clearly cannot explain the cases of endometriosis in premenacheal girls who neither menstruate nor have retrograde reflux. A recent review by Brosens et al. suggested that endometriosis may develop by mechanisms other than retrograde menstruation and implantation, such as coelomic metaplasia, embryonic mullerian rests, or even the persistence of the forms of embryonic endometriosis recently described.[12, 13] They also proposed that the phenomenon of uterine bleeding in neonates and concomitant retrograde menstruation in the neonate might be a source of stem cells that develop into premenarcheal endometriosis.[12] Therefore, it is suggested that premenarcheal and possibly adolescent endometriosis develop by activation of resting stem cells shed at the time of neonatal retrograde uterine bleeding.

SYMPTOMS OF ENDOMETRIOSIS IN YOUNG WOMEN

Common symptoms in women with endometriosis include dysmenorrhea, lower abdominal pain and dyspareunia. Almost half of women with endometriosis also report their inability to become pregnant. The pain of endometriosis in adults is often cyclic while the presenting pelvic pain of adolescents can be either acyclic or cyclic. Bowel and bladder symptoms commonly occur in adolescents (Table 3). The Endometriosis Association's 1998 registry of 4,000 adult women with endometriosis reported that 2/3 of those responding to the survey experienced their first pelvic symptoms before 20 years of age, 21% before 15, and 17% between 15 to 19.[14]

Table 2. Mechanism of pain associated with endometriosis

A	**Pain due to endometriotic lesions**
1	Peritoneal lesions induce inflammatory reactions and secrete prostaglandins, cytokines, histamine and kinin that cause pain.
2	Deep infiltrating endometriosis destroys tissues and nerves.
3	Ruptured chocolate cysts may irritate peritoneum.
B	**Scar and fibrosis, secondary lesions**
1	Scar, fibrosis, traction, and adhesion may reduce mobility of organs. Pain may occur during movement or ovulation.
2	Adhesion of bowel may cause defecation pain or dyschezia.
3	Retroverted uterus due to adhesion, severe adhesion of ovaries to Douglas pouch, and induration of sacral ligament may cause dyschezia.

Table 3. Symptoms of endometriosis in young women

Symptoms	Frequency
Combination of cyclic and acyclic pain	62.5%
Acyclic pain	28.1%
Cyclic pain	9.4%
Intestinal pain	34.3%
Urinary symptoms	12.5%
Irregular menstruation	9.4%
Abnormal discharge	6.3%

Data source: Laufer et al., 1997.[10]

Table 4. Red peritoneal lesions in young patients with endometriosis

	Number	Age Mean [SD]	Patients with red lesions
Young patients	36	16.6 [1.4]	86%
LAVH	8	37.4 [3.4]	20%

LAVH, laparoscopically assisted vaginal hysterectomy.
Data source: Davis et al., 1993.[17]

DIAGNOSIS OF ENDOMETRIOSIS IN YOUNG WOMEN

Visual inspection by laparoscopy or laparotomy is the gold standard for diagnosing endometriosis. However, laparoscopy cannot always be performed in daily practice in Japan. Therefore, the term, "clinical endometriosis", is used when only patient history, clinical examination and ultrasound are available to support the diagnosis. Board certified gynecologists can correctly diagnose endometriosis in 80% of the patients without laparoscopy.

Differential diagnosis is challenging in adolescents because there can be coexisting diseases, including those of the gastrointestinal system and urinary tract, pelvic inflammatory disease, ovarian cysts, obstructive anomalies and pregnancy. The presenting symptoms can also vary, ranging from only dysmenorrhea, localized abdominal pain, dyspareunia, non-cyclic pain or combinations of these symptoms.

On examination, ovarian tumor and anomalies of the genital tract must be ruled out. We perform transabdominal ultrasound examination while the patient has a full bladder and rule out abnormalities in the uterus and ovaries. We then inspect the genital area and vagina and do a rectal examination if necessary. Magnetic resonance imaging (MRI) may also help to reveal an ovarian tumor or anomalies.

LAPAROSCOPIC FINDINGS IN ENDOMETRIOSIS IN YOUNG WOMEN

Endometriotic lesions consist of a variety of types, including peritoneal implants, ovarian chocolate cysts, adhesions, and deep infiltrated endometriosis. Ovarian endometrioma is a common disease lesion occurring in 17% to 44% of endometriosis patients.[15] However, the finding is rare among adolescents and young women. One review over a 15-year period reported no endometriomas among the ovarian masses found in 102 infants, children and adolescents.[16] Peritoneal endometriotic lesions are categorized into 3 subgroups: red, black and white. Davis et al. reported that red lesions are the predominant implant type in adolescent patients.[17] They examined 36 adolescent patients presenting with severe dysmenorrhea who were refractory to prior therapy. When compared with 46 women aged 31 to 46 years, significantly more red lesions were present in adolescents (Table 4).

Demco examined endometriotic lesions using patient-assisted pelvic laparoscopy to determine color and size and mapped these areas for pain.[18] Of the lesions that provoked a pain response, red, vascular lesions were the most painful. This finding suggests that red lesions, most frequently observed in young patients with endometriosis, may be the cause of their pain.

Although, no correlation has been found between severity of pain symptoms and stage of the disease or site of the endometriotic lesions, laparoscopic resection or cautery of the lesions improve symptoms in over 80% of patients.

Clear lesions are common in adolescent endometriosis but are often difficult to visualize and evaluate laparoscopically. Peritoneal defects or windows, which are also diagnostic of endometriosis, are reportedly very common in adolescents. Improved visualization and identification can often be obtained by increasing the laparoscopic magnification.[19]

CLINICAL MANAGEMENT OF ENDOMETRIOSIS IN YOUNG WOMEN

Treatment of endometriosis may be surgical or medical. Surgical treatment, especially laparoscopic surgery, is the most effective method to control pain. Careful history and examination is necessary to rule out pelvic tumor or inflammatory disease. Young women with dysmenorrhea should be treated initially with a combination of cyclic OCs and NSAIDs. In Japan, 2 cyclic OCs containing low dose estrogen-progestin (LEP) are covered by national insurance.[20] Side effects, such as nausea and atypical bleeding, usually occur during the first 3 months of therapy, and patients should be advised about this. If cyclic administration is not effective, the physician can recommend a continuous regimen of 3 to 4 months in which the patient takes the medication, disregarding any breakthrough bleeding. After laparoscopic surgery for ovarian cysts, a continuous LEP regimen is

more effective for pain and results in fewer recurring lesions after surgery for ovarian chocolate cysts.[21]

If pain persists with medical management, imaging, including ultrasound and MRI, may be ordered to evaluate endometriosis. Laparoscopy, the gold standard for diagnosis, and laparoscopic excision of the lesions are usually effective for patients with severe pain symptoms.

Gonadotropin-releasing hormone (GnRH) agonist therapy is widely used for adult patients, but it is not recommended as a first choice for young women because the drug causes significant reduction in bone mineral density. A new progestin, dienogest, has been available in Japan since 2008[22] and can be used for management of pain associated with endometriosis in young women. Dienogest has fewer side effects due to hypoestrogen and can be used for more than 1 year in adult patients. Data are not available for GnRH agonist and dienogest in an adolescent population. These agents may be introduced after establishing the diagnosis of endometriosis by laparoscopy.

In summary, LEP and laparoscopic surgery are treatments of choice for young patients with endometriosis. Endometriosis is a difficult disease to manage due to its chronic and recurrent nature. Long-term management, with special attention to preservation of ovarian function, is highly important in treating young women with endometriosis.

The author declares no conflict of interest.

REFERENCES

1 Taketani Y, Tsutsumi O, Terakawa N, Hoshiai H. (MHLW Grants System, Tokyo, Japan). [2000 General report for the prevention, diagnosis and treatment of endometriosis in the aspect of reproductive health] [Internet]. Tokyo: Ministry of Health, Labour and Welfare (Japan); [date unknown] - . [updated 2005 May 9; cited 2013 Jun 30]; [about 2 p.] Report No.: 200000351A. Japanese. Available from: http://mhlw-grants.niph.go.jp.

2 Ikeda T, Suzuki Y, Maeda T, Harada T. Analysis of dysmenorrhea-associated factors and relaxation methods in highschool students. Bosei Eisei. 2011;52:129-38. Japanese with English abstract.

3 Bulun SE. Endometriosis. N Engl J Med. 2009;360:268-79. PMID: 19144942.

4 Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am.1997;24:235-58. PMID: 9163765.

5 Rees MC. Heavy painful periods. Balliere's Clin Obstet Gynacol. 1989;3:341-56. PMID: 2692924.

6 Crosignani P, Olive D, Bergvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update. 2006;12:179-89. PMID: 16280355.

7 Karck U, Reister F, Schäfer W, Zahrandnik HP, Breckwoldt M. PGE2 and PGF2 alpha release by human peritoneal macrophages in endometriosis. Prostaglandins. 1996;51:49-60. PMID: 8900443.

8 Bulletti C, De Ziegler D, Polli V, Del ferro E, Palini S, Flamigni C. Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. Fertile Steril. 2002;77:1156-61. PMID: 12057721.

9 Kontoravdis A, Hassan E, Hassiakos D, Botsis D, Kontoravdis N, Creatsas G. Laparoscopic evaluation and management of chronic pelvic pain during adolescence. Clin Exp Obstet Gynecol. 1999;26:76-7. PMID: 10459441.

10 Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent women with chronic pelvic pain not responding to conventional therapy. J Pediatr Adolesc Gynecol. 1997:10:199-202. PMID: 9391902.

11 Marsh EE, Laufer MD. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. Fertile Steril. 2005;83:758-60. PMID: 15749511.

12 Brosens I, Puttemans P, Benagiano G. Endometriosis: a life cycle approach? Am J Obstet Gynecol. 2013;209:307-16. PMID: 23500453.

13 Signorile PG, Baldi F, Bussani R, D'Armiento M, De Falco M, Baldi A. Ectopic endometrium in human fetuses is a common event and sustains the theory of mullerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer. J Exp Clin Cancer Res. 2009;28:49. PMID: 19358700.

14 Ballweg ML. Big picture of endometriosis helps provide guidance on approach to teens: comparative historical data show endo starting younger, is more severe. J Pediatr Adolesc Gynecol. 2003;16:S21-6. PMID: 12742183.

15 Busacca M, Vignali M. Ovarian endometriosis: from pathogenesis to surgical treatment. Curr Opin Obstet Gynecol. 2003;15:321-6. PMID: 12858105.

16 Cass DL, Hawkins E, Brandt ML, Chintagumpala M, Bloss RS, Milewicz AL, et al. Surgery for ovarian masses in infants, children, and adolescents: 102 consecutive patients treated in a 15-year period. J Pediatr Surg. 2001:36:693-9. PMID: 11329568.

17 Davis GD, Thillet E, Lindemann J. Clinical characteristics of adolescent endometriosis. J Adolesc Health. 1993;14:362-8. PMID: 8399247.

18 Demco L. Mapping the source and character of pain due to endometriosis by patient-assisted laparoscopy. J Am Assoc Gynecol Laparosc. 1998;5:241-5. PMID: 9668144.

19 Laufer MR. Current approaches to optimizing the treatment of endometriosis in adolescents. Gynecol Obstete Invest. 2008;66 (Suppl 1):19-27. PMID: 18936548.

20 Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertile Steril. 2008:90:1583-8. PMID: 18164001.

21 Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frascà C, Elmakky A, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom recurrence after conservative surgery for endometriosis. Hum Reprod. 2009;24:2729-35. PMID: 19625310.

22 Harada T, Momoeda M, Taketani Y, Aso T, Fukunaga M, Hagino H, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis: a randomized, double-blind, multicenter, controlled trial. Fertile Steril. 2009:91:675-81. PMID: 18653184.