Chapter 1

Introduction, Pathogenesis, Diagnosis

Endometriosis is one of the most common gynecologic diseases in women during their reproductive ages. This condition is a major medical problem that creates difficulties in patient management.[1, 2] The American Society for Reproductive Medicine (ASRM) committee considers endometriosis to be a chronic medical illness that requires a long-term treatment throughout a woman's reproductive life.[3] The prevalence of this disease has been reported in many studies, and it varies depending on the study population. Estimated prevalences in the literature are:

- 3.7 percent of women undergoing tubal sterilization [4]
- 63-70 percent of teenagers undergoing laparoscopy for evaluation of chronic pelvic pain or dysmenorrhea[5, 6]
- 49 percent of adolescents with refractory chronic pelvic pain [6]

In a 10-year cohort study of 90,065 women, who contributed 726,205 person-years of observation, the overall incidence of endometriosis was 237 per 100,000 person–years in women with no past history of infertility. The incidence increased markedly and reached 1,380 per 100,000 person–years in those with a history of infertility. The incidence decreases with increasing age, peaks between 25 - 29 years of age, and becomes very low at ages above 44 years. [7]

The reproductive risk of endometriosis includes an early age at menarche (<10 years), a short cycle length during late adolescence (< 26 days), menstrual blood flow obstruction (mullerian anomalies), prolonged exposure to endogenous estrogen, and a first-degree family history of endometriosis. Among parous women, increased parity and long duration of lactation are associated with a decreased risk.[8, 9]

About one third of women with endometriosis show no signs or symptoms. Common presenting symptoms include lower abdominal pain, chronic pelvic pain, abnormal uterine bleeding, dyspareunia and dyschezia. These symptoms can be summarized into four major groups, as shown in Table 1-1.

There are a number of disorders, gynecologic and non–gynecologic conditions, which share symptoms similar to endometriosis, and should always be included in the differential diagnosis of endometriosis. Common gynecologic disorders that mimic endometriosis include

pelvic inflammatory disease, adenomyosis and ovarian cysts. Examples of non-gynecologic conditions with similar symptoms are irritable bowel syndrome, diverticulitis and musculoskeletal disorders.

Table 1-1 Common presenting symptoms of endometriosis

Pain	**Bladder and bowel symptoms**	**Bleeding**	**Others**
dysmenorrhea	dysuria	irregular period	ovarian mass/tumor
dyspareunia	dyschezia	prolong bleeding	subfertility
chronic pelvic pain	irritable bowel	spotting	fatigue
low back pain	bowel cramping	heavy menstrual bleeding	depression
muscle cramp	diarrhea		exhaustion and
leg pain	constipation		tiredness
	urgency		
	hematuria		

Patient's history and physical examination, including a pelvic examination, may be sufficient to raise a suspicion of endometriosis. Rectovaginal palpation should be included in a pelvic examination, as it may reveal hidden tender nodularity in the cul-de-sac. Imaging study, mostly transvaginal ultrasonography, is often used to support a diagnosis of endometriosis. Final confirmation of the disease, if needed, must include a visualization of the lesion together with a histological report. Clinicians should include the patient's quality of life as one of the main final objectives of treatment.

Pathogenesis

Many theories have been proposed to explain the pathogenesis of endometriosis, but none of them alone can describe the entire pathogenesis and manifestation of the disease. A combination of the following theories offers the most reasonable explanation of this multifaceted disease: [10-13]

Transplantation theory;

Sampson proposed that the formation of ectopic endometrial lesion was caused by retrograde menstruation. This theory is the most widely accepted model to explain the pathophysiological and clinical manifestations of endometriosis.

Coelomic metaplasia theory;

The coelomic metaplasia theory proposes that endometrial cells and tissue may arise from metaplasia of undifferentiated potential cells that line the peritoneal or coelomic cavity, following various hormonal, environmental, or infectious stimuli. The supporting evidence is based upon embryological studies revealing that pelvic organs, including the endometrium, are derived from cells lining the coelomic cavity. This theory can explain the presence of endometriois in the absence of menstruation.

Induction theory;

The induction theory of endometriosis is a combination of the transplantation and coelomic metaplasia theories. It implies that shed endometrium, which gains access to the peritoneal cavity by retrograde menstruation, releases specific agents that induce undifferentiated mesenchyme to develop into endometriosis.

Embryonic theory;

The embryonic cell-rests theory suggests that cells remaining from Mullerian duct migration during embryonic development could be induced by a specific stimulus, such as estrogen, to form endometriosis. This theory can explain the presence of endometriosis in the rectovaginal septum, as well as other locations along the migratory pathway of the Mullerian duct remnants. However, the theory is unproven and remains speculative, as it assumes that embryological cell rests remain dormant and survive to adulthood.

Lymphovascular metastasis theory [13];

This theory explains the presence of endometriosis in distant sites outside the pelvis, by assuming that endometrial cells can spread by lymphatic or hemotogenous route to ectopic sites, such as the lung, brain and extremities. This theory is supported by demonstration of endometrial tissues in the uterine vasculature. Furthermore, intravenous injection of endometrial tissue has been shown to result in pulmonary endometriosis in the rabbit. However, this method of spread is unlikely to be the primary mechanism as the incidence of distant endometriosis outside the pelvis is extremely rare.

Stem cell theory [13];

Endometrial stem cells in the basalis layer of the endometrium may gain access to the peritoneal cavity by retrograde menstruation, lymphatic or vascular dissemination and develop into endometriotic lesion. The enhanced proliferative capacity of the stem cells, as well as their ability to form multiple cell types, may give them a selective advantage in their establishment and progression.

In summary, these theories together can explain most cases of endometriosis, and they are supported by a number of researches. However, certain cases involving premenarchal girls, newborns and males, may demand other alternative explanations. It is possible that fundamental differences in immunological, genetic, environmental, biochemical or other factors may also contribute to the diseases.

Factors affecting the pathogenesis of endometriosis

Immunologic Factors [14, 15]

Although the retrograde menstruation theory can explain most cases of pelvic endometriosis, it is likely that other factors are also responsible for the variable development and progression of the disease. For example, retrograde menstruation is encountered in 75-90% of women, but only 1-10% of them are diagnosed with endometriosis. The immune response has been suggested as one of the factors that is involved in the attachment or clearance of refluxed endometrial tissue fragments. Defective cellular immunity, with decreased natural killer cell activity, may result in decreased cytotoxicity to ectopic endometrium. The immunologic factors may also contribute to the reduced progesterone responsiveness in the ectopic endometrium, and further promote the growth of endometriotic lesion.

Genetics Factors [16, 17]

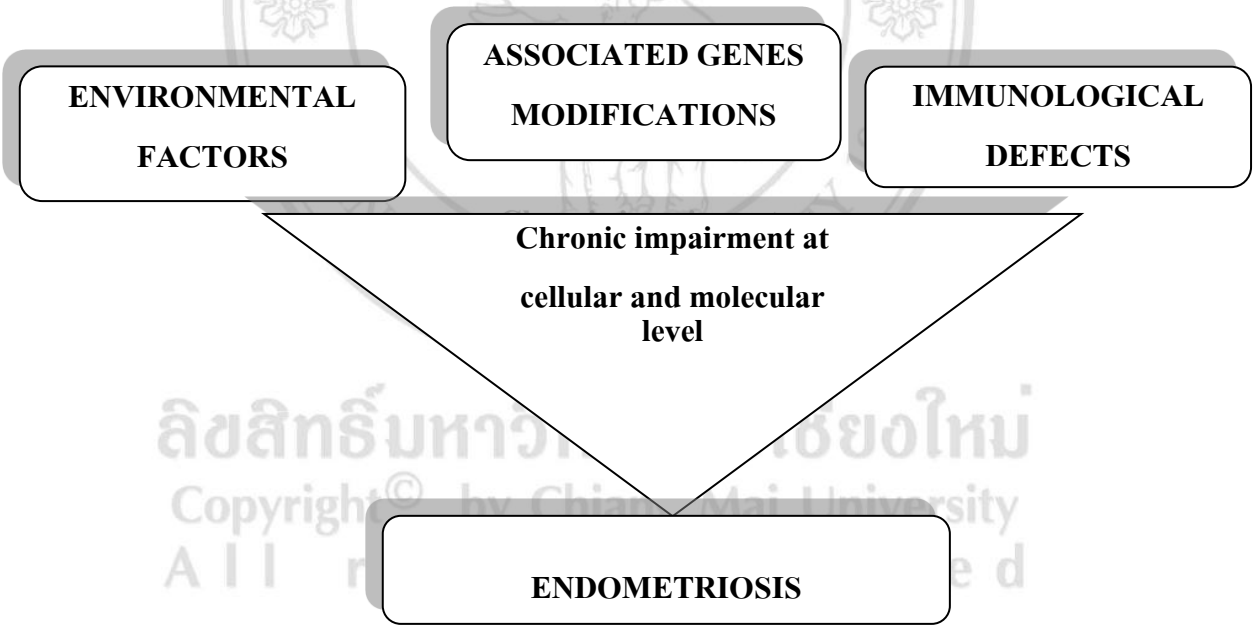
Genetic factors increase vulnerability to endometriosis. The risk of endometriosis is six times higher when the woman has a first-degree relative with a severe form of endometriosis. Concordance for endometriosis is greater in monozygotic than dizygotic twins. It is estimated that genetic factors contribute about 47-51% of heritability.

Environmental Factors

The link between endometriosis and environmental factors is still controversial. Dioxin and dioxin-like compounds (DLC), which are by-products of industrial processing, have been implicated in the pathogenesis of endometriosis. In a recent case–control study, women with a high plasma concentration of DLC were at a higher risk of having endometriosis than those with low plasma level.[18] However, the mechanism by which dioxin and DLC exert their effects is still uncertain and speculative.

The contributions of these intrinsic and extrinsic factors in the etiology of endometriosis can be summarized diagrammatically in Figure 1-1.

Figure 1-1 Complex interaction of internal and external factors in the pathogenesis of endometriosis

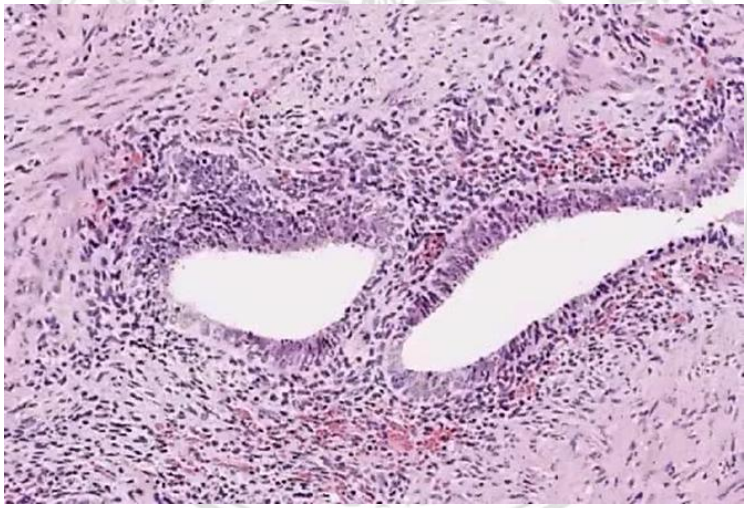


Diagnosis of endometriotic disease

Endometriosis is often diagnosed by laparoscopic visualization of the lesions in the pelvis. However, macroscopic appearance of the lesions can be deceptive, and histological confirmation of the presence of endometrial gland and mucosa is recommended (Figure 1-2).

Direct visualization of the lesion, together with a histological confirmation, is now considered to be the gold standard. The approach for retrieval of tissue for diagnosis can be accomplished by laparoscopy or direct biopsy in an open laparotomy. The common locations of disease in the pelvic cavity include the ovaries, cul-de-sac, broad ligament, uterosacral ligaments and rectovaginal septum. Uncommon sites of implantation are the bladder wall and ureter. In some circumstances, endometriotic disease is present outside the pelvic cavity, such as in the large and small bowel and at the lower part of the diaphragm.

Figure 1-2 Histological findings of endometrial mucosa and gland implanting outside the uterine cavity (high power in hematoxylin and eosin stain; Courtesy of the Department of Pathology, Faculty of Medicine, Thammasat University).



In clinical practice, endometriosis is categorized into three major groups:

1. Pelvic endometriosis
2. Endometrioma or ovarian endometriosis or endometriotic cyst
3. Deep infiltrating endometriosis (DIE)

Endometrioma is a subtype of endometriosis that accounts for 17 – 40 percent of all endometriotic lesions. It is a benign ovarian cyst, commonly named a chocolate cyst because of its content, which is a viscous tar black liquid similar to black chocolate. The endometrial shedding and bleeding at the site of implants from recurring menstrual cycles result in the accumulation of old blood and formation of chocolate cyst. Around 17 % of women with infertility have ovarian endometrioma, which often pose difficult and controversial

management issues when they plan to undergo assisted reproductive technology (ART) treatment.[1, 2]

Transvaginal sonogram (TVS) is a useful tool to differentiate endometrioma from other types of ovarian cysts. However, ultrasonographic appearances of ovarian endometrioma can be quite variable. The typical appearance is a unilocular homogeneous cyst, with a thick wall and low-level internal echo, as shown in Figure 1-3.

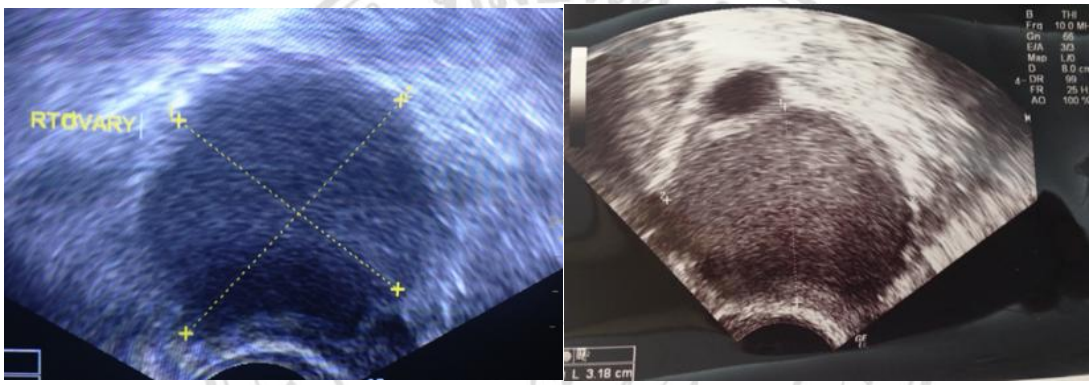


Figure 1-3 Transvaginal sonographic (TVS) imaging study shows an endometrioma of right ovary. The ground glass appearance with a homogenous, low–echo pattern is demonstrated.

Bilaterality of ovarian endometrioma is encountered in about 28% of cases. It is rare for patients to experience pain or dysmenorrhea, when the pathology consists of only ovarian endometrioma. When presented with pelvic pain, deep infiltrating endometriosis (DIE) should always be suspected and investigated. Transvaginal sonography (TVS) is also useful for the assessment of DIE in the rectum or rectovaginal septum. TVS combined with water-contrast in the rectum can aid in the diagnosis of rectovaginal endometriosis infiltrating the bowel.[19]

Doppler sonography for evaluating vascularity of the mass is also helpful. An ovarian endometrioma shows hypervascularity at the periphery, but scanty blood flow inside the ovarian mass itself. This is in contrast to moderate ovarian blood flow in normal ovarian tissue or enhanced flow in an ovarian tumor.[20]

There are reports of three dimension and B-mode ultrasonography, and magnetic resonance imaging (MRI) for differentiating ovarian endometrioma from other types of

ovarian cysts. Although MRI has a very high diagnostic accuracy, it is also very costly and not widely available. MRI should, therefore, be reserved for cases with uncertain or equivocal ultrasonographic findings, or in cases of rectovaginal and bladder endometriosis.[21]

Scope of the thesis

In this thesis, the focus was on the impact of conservative surgery for ovarian endometrioma on ovarian reserve, and the impact of conservative surgery on the recurrences of the disease. Specifically, we designed and carried out one case-control study, one randomized controlled trial, and one retrospective cohort study, as follow:

1. The first study entitled **"Anti-Mullerian hormone changes after laparoscopic ovarian cystectomy for endometrioma compared with the non-ovarian conditions"** was conducted to evaluate the impact of laparoscopic ovarian cystectomy for endometrioma on ovarian reserve, as measured by serum antimullerian hormone (AMH), and to compare the changes in AMH levels after laparoscopic ovarian cystectomy with those after other non-ovarian surgery. Many previous studies have demonstrated negative impacts of laparoscopic cystectomy, as measured by the serum AMH, on ovarian reserve in cases of ovarian endometrioma. However, most of these studies had no controls, and the results were still inconclusive. It is possible that any surgery alone or in combination with anesthetic use can decrease AMH level. In the design of this case-control study, we compared patients who underwent laparoscopic ovarian endometriotic cystectomy under anesthesia with a control group who underwent surgery for other non-ovarian condition under the same type of anesthesia.
2. The intra-operative methods of hemostasis have been questioned to contribute to the adverse effect of surgery on ovarian reserve. Most studies were non-randomized, and the available data were few, inconsistent, and limited to few months of follow-up after the surgery. The purpose of the second study entitled **"The impact of hemostasis methods, electrocoagulation versus suture, in laparoscopic endometriotic cystectomy on the ovarian reserve: a randomized controlled trial"** was to compare the effect of electrocautery versus suturing during laparoscopic endometriotic cystectomy on ovarian reserve. The changes in AMH levels before and after surgery were used to indicate changes in ovarian reserve.

3. The recurrence of endometriosis after a conservative surgery constitutes a major problem and creates difficulties for gynecologists in the management of their patients. The recurrence rates, as well as risk factors or determinants of recurrence, have been reported in many studies. However, the surgical approach, laparoscopy versus laparotomy, has been overlooked and not investigated. To fill this gap in knowledge, we designed and carried out a retrospective cohort study entitled **"Recurrence of endometrioma following conservative ovarian endometrioma cystectomy; laparoscopy versus laparotomy"**. In this study, we compared the time to recurrence of endometrioma after conservative surgery by either laparoscopy or laparotomy approach.

The detailed philosophical context of clinical epidemiology researches, including theoretical consideration, data collection, and statistical analyses, for each study that forms the basis of this thesis, is presented in Appendix A.

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