Chapter 2

Pathology and Staging of Endometriosis & Endometrioma

The appearance of pelvic endometriosis varies depending on the duration of the disease, locations of the implants and degree of inflammatory response. A particular lesion may look different during the menstrual cycle due to cyclical hormonal changes. The term endometriosis is distinct from adenomyosis or endometriosis interna, which is defined as the generalized infiltration of endometrial gland and stroma within the myometrium. Present evidences suggest that both conditions have a different pathogenesis, clinical manifestation, epidemiological pattern and etiology.[1, 2]

Gross pathology[3, 4]

Gross visualization of macroscopic lesions can be sub-divided by clinicopathological characteristics into 3 groups, as follows:

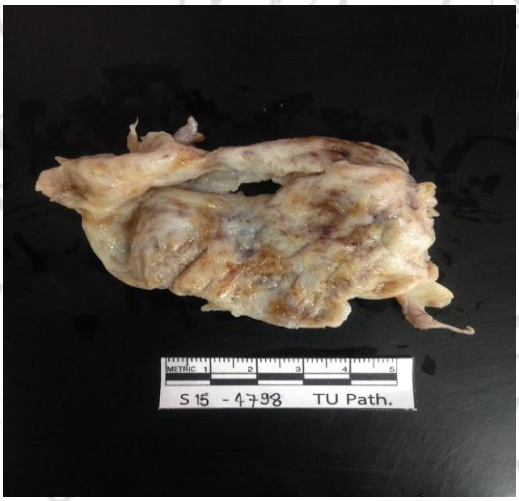
1. Peritoneal endometriosis, an ectopic endometrium in the pelvic cavity, usually occurs in hormonally responsive tissues. These lesions can be seen as superficial plaques across the peritoneum, powder-burn or flame red lesions. In some circumstances, they can also take on fibrotic appearances.
2. Ovarian endometrioma is a pseudo-cyst, which contains degenerated dark-brown blood products that looks like chocolate in color. The inner wall of the cyst is lined by functional ectopic endometrium that produces cyclical hemorrhage into the cyst. Endometrioma usually coexists with adhesions and rectovaginal nodules.
3. Deep infiltrating endometriosis consists of an infiltration of ectopic endometrium deep into the uterosacral ligaments or recto-sigmoid area, causing the formation of fibromuscular nodules. This type of lesion responds poorly to hormonal stimulation.

The main pathological mechanism is cyclical bleeding from functional ectopic endometrium, followed by an inflammatory response with an increase in macrophages and leukocytes to phagocytose hemolyzed blood and cell debris. In early stages, the lesions appear as petechiae, or flame-like lesions. In chronic cases, the lesions evolve into fibrous formation and become white scar tissue or plaques. The lesion varies in size from few millimeters to a full centimeter, and is usually surrounded by fibrotic tissues.

Other implants may appear as clear, non-pigmented, brownish, dark red polyps or hemorrhagic nodules. Typical late-stage lesions are white and scarred because of the formation of fibrotic tissue. In many circumstances, small and faint lesions can be overlooked during surgery even by experienced gynecologists.

Endometriotic cysts are typically confined within the ovarian tissue, while superficial implants are scattered on the lateral and inferior cortical surfaces of the ovaries. Accumulation of hemorrhagic debris, after repeated cyclical bleeding into the cyst, slowly increases the size of endometrioma. When intra-cystic pressure is high, the cyst has a tendency to perforate, causing leakage of its content. As endometiotic content is very irritating to surrounding tissues, it stimulates inflammatory process that results in dense adhesion formation with adjacent organs. During surgery, lysis of adhesion to free the cyst from surrounding tissues is often prone to cause rupture and leakage of endometriotic fluid.

Figure 2-1 Gross pathology of ovarian endometrioma, showing white fibrotic cyst wall with scattered area of brownish pigmentation (Courtesy of the Department of Pathology, Faculty of Medicine, Thammasat University).



Microscopic Pathology

Histopathological finding of both endometrial stroma and gland outside the uterus signifies the final confirmation of endometriosis. However, most pathological sections do not show this ideal, typical histology. The endometriotic cyst wall is usually fibrotic and variable in thickness. It is lined by simple cuboidal epithelium, with interspersed area of hemorrhage that extends into adjacent tissues. In practice, some suggest that at least two of the following

four cardinal findings must be present to justify a histological diagnosis of endometriois: endometrial glands, stroma, fibrosis, and hemorrhage as evidenced by the presence of hemosiderin-laden macrophages or pseudoxanthoma cells.

Mechanism of pain from endometriosis[5]

There are multiple mechanisms for pain production in endometriosis. Peritoneal lesions may induce inflammatory reactions, and the release of pro-inflammatory cytokines, histamines, kinins, and prostaglandins that cause uterine contraction and pelvic pain. Endometriotic tissues also secrete nerve growth factor (NGF), which induces invasion of nociceptors and increases the number of nerve terminals in the lesions, causing the perception of pain. Bleeding from endometriotic implants may directly or indirectly irritate peritoneum and lead to pain. Direct invasion of infiltrating endometriosis into pelvic floor nerves may also contribute to pain. Estrogen may increase pain associated with pelvic endometriosis by directly stimulating its growth. The central nervous system can also be sensitized by peripheral nerve fibers that signal through the spinal cord. The increased signaling alters neural modulation of inhibitory and excitatory pain pathways throughout the central nervous system, resulting in a state of generalized hyperalgesia.

Mechanism of infertility[1, 6]

The mechanisms of endometriosis-associated infertility are multiple and complex. They include distortion of pelvic anatomy, impaired folliculogenesis, poor oocyte quality, decreased implantation and immunological dysfunction. In moderate-to-severe stages of the disease, adhesion caused by endometriosis can impair tubo–ovarian motility, and interfere ovum pickup function of the fimbria. In a retrospective study, fewer numbers of oocytes were retrieved during in-vitro fertilization treatments in patients with endometriosis.[7] The presence of ovarian endometriosis is associated with a poor response to gonadotropins.[8, 9] Endometrial defects have been postulated on the basis of a decreased expression of several biomarkers of implantation. Impartment of fertility may also be related to the enhanced immune response that decreases sperm motility and function.

Classifications

There are many proposed systems for staging the severity of endometriosis. Most classifications are based upon visualization of anatomic lesions, size and degree of the peritoneal lesions. The well-known and widely accepted system was first introduced by the American Society for Reproductive Medicine (ASRM) in 1979, which was then revised in 1996 (rASRM).[10] The rASRM system designates a point score directly to the size, depth, degree of adhesion and location of implants. The score is higher if the lesion is considered to be a deep implant or if the adhesion is dense. It should be noted that if cul-de-sac is involved and completely obliterated, the total score would indicate a severe (stage 4) disease, regardless of other lesions.

REVISED AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE CLASSIFICATION OF ENDOMETRIOSIS

PERITONEUM	**ENDOMETRIOSIS**	< 1 cm	1-3 cm	>3 cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	**R** Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CUL-DE-SAC OBLITERATION	Partial		Complete
		4		40
OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	**R** Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Total score

Stage I (Minimal) : 1-5

Stage II (Mild) : 6-15

Stage III (Moderate) : 16-40

Stage IV (Severe) : > 40

Figure 2-2 The revised ASRM classification Scoring for endometriosis (adapted from Hoeger KM[10])

The rASRM staging for endometriosis does not correlate well with pain symptoms. It also correlates poorly with infertility, except for advanced stages of the disease.[11, 12]

The scores are summed and used to classify endometriosis into four levels of severity. A score of 1–5 points indicates minimal disease (level 1 or stage I), a score of 6-15 indicates mild disease (level 2 or stage II), a score of 16–40 indicates moderate disease (level 3 or stage III), and a score more than 40 is indicative of severe endometriosis (level 4 or stage IV).

Minimal endometriosis is characterized by the presence of small, isolated, superficial peritoneal lesions, with no or minimal adhesion. Mild disease consists of similar but larger superficial implants, usually <3 cm in diameter, scattering on the peritoneum or board ligaments. Some lesions may be on ovarian surface on either side. There are often some filmy adhesions of the tubes and ovaries as well.

Multiple areas of both superficial and deep implants, with tubo-ovarian adhesion, are present in moderate and severe endometriosis. In stage 3 diseases, small to medium-sized ovarian endometrioma, with a size of 3 – 5 cm, is usually present. For stage 4 diseases, an endometrioma larger than 4-5 cm is commonly seen. In many circumstances, dense adhesions involving both tubes and ovaries are present, with complete or partial obliteration of the posterior cul-de-sac.

Ovarian endometriosis of 3 cm or larger is considered to be a deep lesion, and carries a score of 20 points. It, thus, indicates at least a stage III disease. If the posterior cul-de-sac is completely obliterated, the score will increase to 40 points, and the most severe stage is diagnosed. Currently, the revised American Society for Reproductive Medicine (rASRM) scoring system is the most widely accepted classification for endometriosis because it is simple and easy to understand.

The rASRM classification for endometriosis is inadequate to predict the recurrence potential of endometriosis or the chance for pregnancy after surgery. In a retrospective study of 739 women with endometriosis, Vercellini *et al.*[11] found no association between endometriosis stage, or lesion type or lesion site, and postoperative pregnancy rate, using Cox's proportional hazards regression analysis.

In 2005, the Enzian classification was proposed to complement the rASRM classification.[13, 14] It took the presence of retroperitoneal and rectovaginal lesions into consideration, which was neglected by the rASRM classification. This system was revised and simplified for clinical use in 2011. However, the revised Enzian classification still receives low level of acceptance. In this system retroperitoneal implants are subdivided into the following three compartments:

- Compartment A: rectovaginal septum and vagina
- Compartment B: uterosacral ligament to pelvic wall
- Compartment C: rectum and sigmoid part of the colon

Severity of the disease is weighted in the same way for each compartment, as follows:

- Grade 1: invasion <1 cm
- Grade 2: invasion 1–3 cm
- Grade 3: invasion >3 cm

The letter "F" stands for the lesion and other abbreviations are used as follows:

FA = adenomyosis

FB = involvement of the bladder

FU = intrinsic involvement of the ureter

FI = bowel disease cranial to the rectosigmoid junction

FO ("other") = other locations, such as abdominal wall endometriosis

The nomenclature is very similar to the TNM classification of malignant tumors. For example, the description of a 0.5 cm lesion in the rectum, with a 2 cm mass on the uterosacral ligament and an adenomyotic uterus, will be: A0 B2 C1 FA. When more than one lesion is present in any compartment, only the largest one is scored, and distant locations are only described when present.

The most important advantage of the Enzian classification is the accuracy in the description of the location and extent of retroperitoneal involvement, as contrast to the rASRM classification. It leads to a suspicion of rectal wall or cul-de-sac involvement, which is the site highly vulnerable to injury or perforation during an operation. The preoperative counseling and bowel preparation can then be anticipated, and other necessary steps can be undertaken to minimize the risk of surgery. The symptoms of pain and dysmenorrhea are

strongly related to the ENZIAN scores, and the classification also correlates with rASRM staging.[13]

There are some disadvantages of the Enzian classification. At this moment, its international acceptance is minimal. The classification is utilized almost exclusively in German-speaking countries. Very few studies have been published using this classification in international journals. The Enzian classification is more complicated than the rASRM scoring, and it is very difficult for patients to understand. Currently, there is insufficient information to conclude that the Enzian classification is correlated with subfertility.

Another classification system is the Endometriosis Fertility Index (EFI). It was proposed by Adamson and Pasta in 2010.[15] The main purpose of this new staging system is to predict fecundity or the likelihood of a pregnancy after surgical treatment of endometriosis. In the current rASRM scoring system, there is no direct correlation between the stages of endometriosis and the chance of achieving a pregnancy, except in advanced stages of the disease where the tendency is toward a reduced fecundity.[16] This is not surprising as the rASRM scoring is dependent on the size of an endometrioma, which is not a major risk factor for decreased fertility.[17]

EFI includes both historical and surgical indices that relate to the probability of achieving a pregnancy. These variables are patient's age, duration of infertility, gravidity, total rASRM score and the "least function (LF) score". The "LF" score is the functional capability of the tubes, fimbria and ovaries bilaterally to perform their individual reproductive functions, as determined by the surgeon after surgery. The functional score is arbitrarily set as 0 when absent or nonfunctional; 1, 2, and 3 when there is severe, moderate, and mild dysfunction, respectively; and 4 when the function is normal. For example, "LF" score for normal ovaries will be 4, and 3 if there is minimal or mild injury to ovarian serosa. If the ovarian size is reduced by one-third or there is moderate injury to ovarian surface, the "LF" score will be 2. With further reduction in ovarian size by two-thirds or more, or there is severe injury to ovarian surface, the score will be reduced to 1. In case of ovarian absent or complete encasement of both ovaries in adhesion, a score of 0 is assigned.

The comparison of advantages and disadvantages of the three main classifications systems for endometriosis is summarized in Table 2-1.

Table 2 -1 Advantages and disadvantages of 3 main classification systems for endometriosis

	rASRM	Enzian	EFI
Advantages	» Simple to use » Most well known » Widely accepted » Easy for patients to understand	» Include retroperitoneal lesions » Could be used for preoperative preparation	» Include essential clinical factors » Mainly to predict the probability of a pregnancy
Disadvantages	» Not include retroperitoneal lesions » Poor correlation between disease stages and pain » Poor correlation between disease stages and fertility » Not contribute any data on morphological appearance of endometriosis	» Difficult to use » Low level of international acceptance	» Complexity of scores » Insufficiency data for validation

rASRM, the revised American Society for Reproductive Medicine ; EFI, Endometriosis Fertility Index

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