Clinical Focus on

Endometriosis

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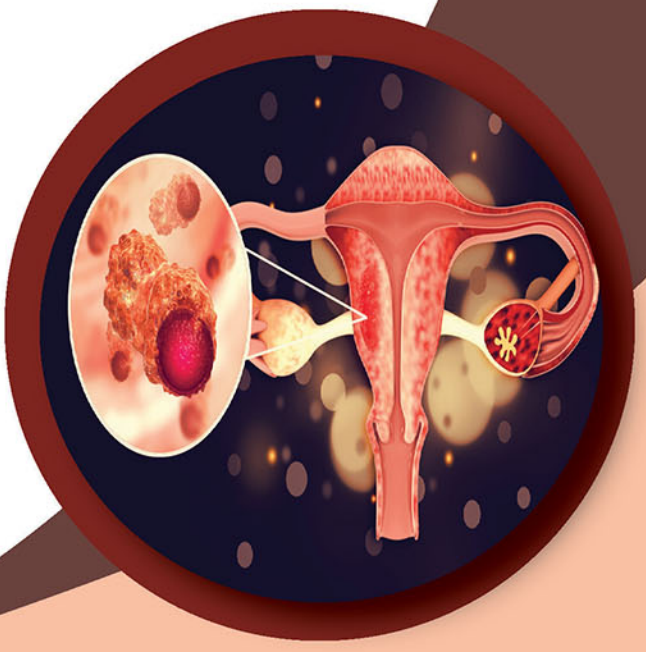

Foreword
Nandita Palshetkar

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CHAPTER 2

Newer Thoughts on Etiopathology, Staging, and Guidelines

Panchampreet Kaur, Jaideep Malhotra, Neharika Malhotra

INTRODUCTION

Endometriosis is an inflammatory disease of chronic nature and involves the presence of endometrium-like tissue outside the uterus.[1,2] It presents most commonly as ovarian endometriotic cysts followed by extraovarian deposits in pouch of Douglas, peritoneum, bladder and rarely pleural and stomach deposits. The International Working Group of American Association of Gynecologic Laparoscopists (AAGL), European Society for Gynaecological Endoscopy (ESGE), European Society of Human Reproduction and Embryology (ESHRE), and World Endometriosis Society (WES), et al. have defined endometriosis as a disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process.[3] It generally affects 2–10% of women of reproductive age.[4]

ETIOPATHOGENESIS

Various theories which have been proposed that explain the origin and development of endometriosis are described hereunder.

Sampson's Theory of Retrograde Menstruation

This is the most common explanation theory which still holds its importance. It has been postulated that during menses, endometrial cells grow retrograde into the peritoneal cavity through the fallopian tubes and thereby get implanted there.[5] This theory is somewhat supported by the fact that incidence of endometriosis is increased in girls having obstructive müllerian anomalies. On the flip side, it has also been reported that not all who have retrograde menstruation will definitely have evidence of endometriosis.[6]

Premenarchal Endometriosis

There have been isolated reports of endometriosis in premenarchal girls which puts a jolt at the retrograde theory of menstruation as these girls present with endometriosis even before the menstruation starts.[7] The possible explanation supporting this includes the presence of müllerian embryonic rests and also neonatal uterine bleeding due to withdrawal of maternal hormones.

Microembolization

Spread of endometrial tissue in microemboli form through the venous or the lymphatics to distant organs like lungs is also a proposed theory. These microemboli are thought to affect both the hemithoraces equally although right side hemithorax has been seen to be involved in >80% of the patients.[8]

Coelomic Metaplasia

It has been proposed that pluripotent cells transform to differentiated endometrium and this theory has been supported by literature which reports a case of endometriosis in a young woman with Mayer-Rokitansky-Küster-Hauser syndrome.[9]

Genetics: Recently, genetic studies have identified genomic regions and abnormalities in cancer driver genes (*PIK3CA, KRAS, ARID1A*) associated with endometriosis.[10-12]

The gross endometriotic lesions have been categorically divided as superficial, deep, and ovarian.

Superficial peritoneal: These lesions or deposits can present superficially as peritoneal deposits. On histopathology, presence of endometrial glands and/or stroma is diagnostic of same. Occasionally, hormonal and metaplastic changes may mask the glandular component.

Deep endometriosis: Deep endometriosis is defined as presence of endometriotic deposits or tissue extending beneath the peritoneum. It is defined as lesion involving > 5 mm of depth into the peritoneum.[13] It is generally found in the ureter, bladder, rectosigmoid colon, rectum, rectovaginal septum and other pelvic tissues such as parametrium and vagina.

Ovarian endometriosis: It may present in the form of ovarian cysts of varying sizes. Endometriotic cyst can be confused with hemorrhagic cyst/corpus luteal cyst. Symptomatology of the patient and a repeat follow-up scan in postmenstrual phase can distinguish between the two. The physiology revolves around cyclical bleeding in the ectopic endometrial tissue at ovarian site resulting in a hemorrhagic collection over a period of time surrounded by ovarian parenchyma.[14]

The pain associated with endometriosis is usually due to inflammation and pain mediators in addition to some neurologic dysfunction. Endometriosis is associated with subfertility which may be the result of pelvic adhesions and anatomic distortion due to endometriotic cysts. The chemical milieu involving secretion of prostanoids, cytokines, and growth factors which are found in endometriosis might be antagonistic to gamete formation, sperm mobility, and fertilization process.

STAGING SYSTEMS AND GUIDELINES

Various classification systems have been reviewed. Classifying endometriosis helps overcoming the interobserver bias and corroborates the clinical and surgical findings thereby improving the treatment approach. This is helpful for research purposes as well. The standard systems which are usually considered include the revised American Society for Reproductive Medicine (rASRM) classification, Enzian classification, endometriosis fertility index (EFI), and AAGL classification. The WES has given guidance to use rASRM classification, Enzian classification (in case of deep infiltrating endometriosis) and EFI classification (in cases of desired future fertility) for a comprehensive approach and further treatment.

The American Society for Reproductive Medicine Revised Classification[15]

The rASRM classification has been depicted in **Table 1** and comprises following stages.

Stage 1 (Minimal)

Score 1–5: Superficial peritoneal and ovarian implants and filmy adhesions in one or both ovaries.

TABLE 1: American Society for Reproductive Medicine (ASRM) revised classification of endometriosis.[15]

Patient's name_____ Date_____

Stage I (Minimal) — 1–5
Stage II (Mild) — 6–15
Stage III (Moderate) — 16–40
Stage IV (Severe) — >40
Total_____

Laparoscopy_____Laparotomy_____Photography_____
Recommended treatment_____
_____
Prognosis_____
_____

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.
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B), black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Stage 2 (Mild)

Score 6–15: Few superficial and a few deep implants in the peritoneum and ovaries, filmy adhesions, and small chocolate cysts in the ovaries.

Stage 3 (Moderate)

Score 16–40: Deep peritoneal implants, ovarian cysts, dense tubal adhesions and/or partial posterior cul-de-sac obliteration.

Stage 4 (Severe)

Score >40: Many deep peritoneal implants, large chocolate cysts, many dense adhesions, and complete cul-de-sac obliteration.

The rASRM score does not consider the deep infiltrating endometriosis involving the retroperitoneal structures and there is a weak correlation between the extent of endometriosis and pain, sterility, and surgical complexity. So, newer classifications were made. Adamson and Pasta described the EFI classification in 2010 which considered the clinical and the surgical factors **(Tables 2 to 4)**.[16]

The Enzian classification was developed in 2005 in Austria[17] due to paucity of description on deeply infiltrating endometriosis in the previous classifications. The same was revised in 2011 for better comprehension.

Revised Enzian Classification

They have divided structures into various compartments. Retroperitoneal structures are categorized into the following three compartments: Compartment A includes vaginal and rectovaginal septum (RVS), compartment B has uterosacral ligament up to pelvic wall and compartment C for rectum and sigmoid colon. Severity is graded from grades 1 to 3 which are defined as invasion < 1 cm, 1–3 cm, and > 3 cm, respectively. If there are several foci, then the largest focus in each compartment is evaluated.

Deep invasion of endometriosis beyond the lesser pelvis in distant sites can be described separately and is labeled as prefix "F" which stands for "far" or "foreign," [FA = adenomyosis, FB = involvement of the bladder, FU = intrinsic involvement of the ureter,

TABLE 2: Terminology used in endometriosis fertility index (EFI) classification.[16]

Structure	*Dysfunction*	*Description*
Tube	Mild	Slight injury to tubal serosa
	Moderate	Moderate injury to serosa or muscularis layer of the fallopian tube, moderate limitation in mobility
	Severe	Fallopian tube fibrosis or mild/moderate salpingitis isthmica nodosa; severe limitation in mobility
	Nonfunctional	Complete tubal obstruction, extensive fibrosis or salpingitis isthmica nodosa
Fimbria	Mild	Slight injury to fimbria with minimal scarring
	Moderate	Moderate injury to fimbria, with moderate scarring, moderate loss of fimbrial architecture and minimal intrafimbrial fibrosis
	Severe	Severe injury to fimbria, with severe scarring, severe loss of fimbrial architecture and moderate intrafimbrial fibrosis
	Nonfunctional	Severe injury to fimbria, with extensive scarring, complete loss of fimbrial architecture, complete tubal occlusion or hydrosalpinx
Ovary	Mild	Normal or almost normal ovarian size; minimal or mild injury to ovarian serosa
	Moderate	Ovarian size reduced by one-third or more; moderate injury to ovarian surface
	Severe	Ovarian size reduced by two-thirds or more; severe injury to ovarian surface
	Nonfunctional	Ovary absent or completely encased in adhesions

TABLE 3: Endometriosis fertility index classification.[16]

Historical factors			***Surgical factors***		
Factor	*Description*	*Points*	*Factor*	*Description*	*Points*
Age			LF score		
	If age is ≤35 years	2		If LF score = 7–8 (high score)	3
	If age is 36–39 years	1		If LF score = 4–6 (moderate score)	2
	If age is ≥40 years	0		If LF score = 1–3 (low score)	0
Years infertile			AFS endometriosis score		
	If years infertile is ≤3	2		If AFS endometriosis lesion score is < 16	1
	If years infertile is > 3	0		If AFS endometriosis lesion score is ≥16	0
Prior pregnancy			AFS total score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥71	0
Total historical factors			**Total surgical factors**		

EFI = Total historical factors + Total surgical factors

[ ] + [ ] = [ ]

Historical Surgical **EFI score**

TABLE 4: Least function (LF) score at conclusion of surgery.[16]

Score		*Description*
4	=	Normal
3	=	Mild dysfunction
2	=	Moderate dysfunction
1	=	Severe dysfunction
0	=	Absent or nonfunctional

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the score is obtained by doubling the lowest score on the side with the ovary.

	Left	*Right*
Fallopian tube	[ ]	[ ]
Fimbria	[ ]	[ ]
Ovary	[ ]	[ ]
Lowest Score	[ ] +	[ ] = [ ]
	Left	Right **LF score**

FI = bowel disease cranial to the rectosigmoid junction and FO (other) = other locations, such as abdominal wall endometriosis].

The new #Enzian classification focuses on the classification of superficial, ovarian, deep, and extragenital endometriosis, and pelvic adhesions. The #Enzian classification is based on the known Enzian classification for deep endometriosis using three compartments including far locations as described above. In addition, it covers peritoneal involvement (P), ovary (O), intestines (sigmoid colon, small bowel; FI); adhesions, involving the tuboovarian complex (T) and tubal patency. Individual compartments or organ involvement are identified with the initial capital letters, respectively, [P (peritoneum), O (ovary), T (tubo-ovarian unit), A (RVS, vaginal), B (uterosacral), C (rectum, sigmoid colon), F (far)] and are arranged in this order. **(Fig. 1)** The extent of disease is represented by the numbers 1, 2, and 3 in each of the compartments. The severity of disease in paired organs (such as ovaries, tubes,

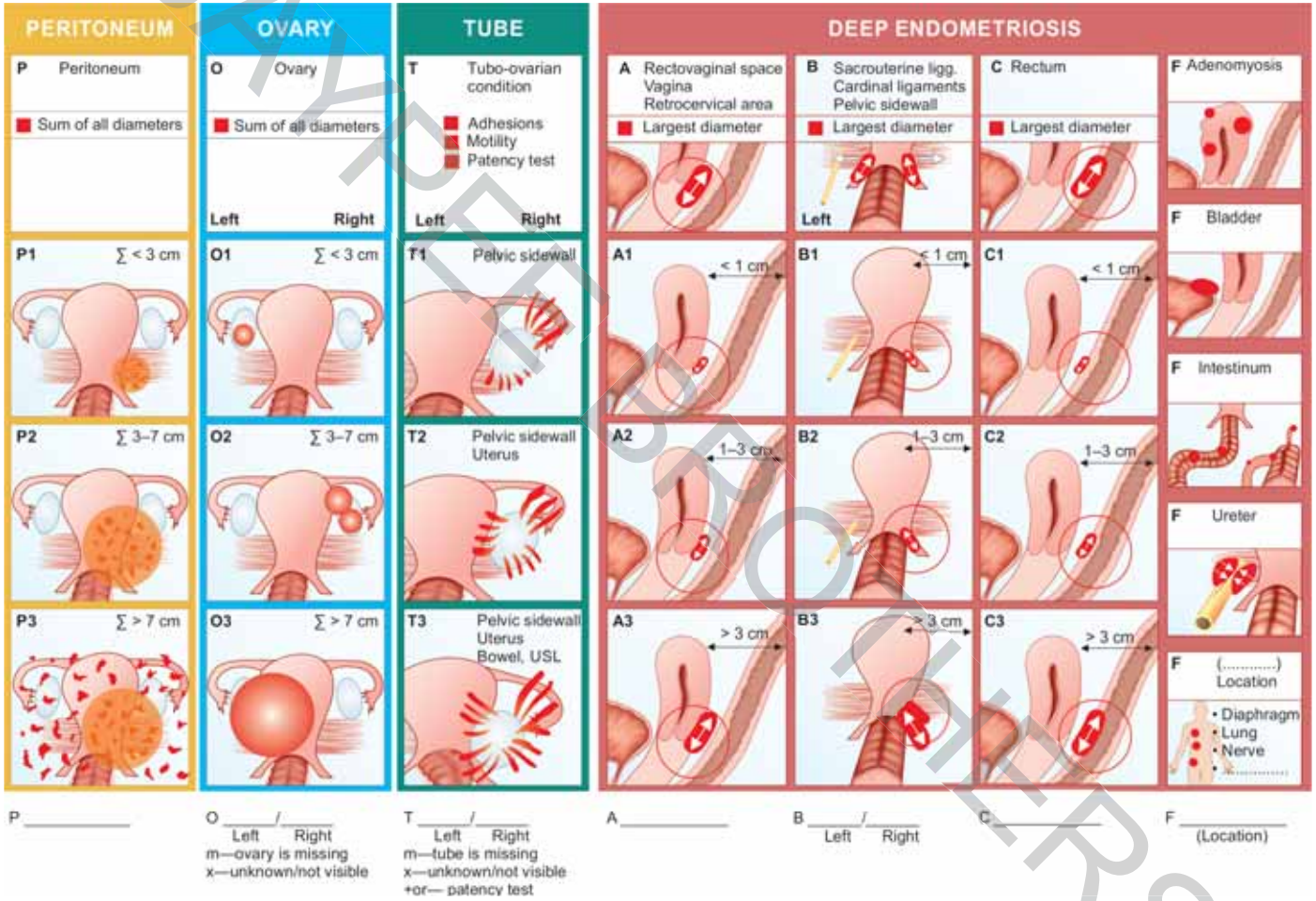

Fig. 1: The #Enzian classification of endometriosis.

uterosacral ligaments, parametrium, ureters) is denoted separately as left/right. Missing or invisible ovary or tube are described with respective suffix (m, missing; x, unknown).[18]

The #Enzian classification has an added advantage to previous listed classifications as location and extent of disease and involvement of retroperitoneal structures including deep infiltrating disease can be described with precision and this classification can be used as a supplement to the rASRM score. This can also provide a relative idea about anticipated operating time. The main disadvantage is the lack of international acceptance. Although the use has been simplified, but still rASRM has a better score in regard to user compatibility.

AAGL Classification

Mauricio S Abrao et al. conducted a multicenter study which included a total of 1,224 patients all of whom were undergoing surgery for endometriosis. The main objective of the study was to decipher a classification which could give a better insight into surgical complexity in relation to patient symptomatology. The AAGL classification gave scores based upon the extent of the disease and finally staging was done from I to IV depending upon the score **(Fig. 2)**. The said classification was compared with ASRM staging system and it was concluded that the former classification allowed for better

Superficial	Score
<3 cm	2
≥3 cm	4
Vagina (muscularis)	**Score**
<3 cm	5
≥3 cm	8
Left ovary	**Score**
Superficial	2
<3 cm	5
≥3 cm	7
Left ureter	**Score**
Extrinsic	6
Intrinsic	8
Hydroureter	9
Left fallopian tube	**Score**
Slight serosal involvement/damage	2
Moderate immobility	4
Severe immobility	6
Complete obstruction	7
Cul-de-sac obliteration	**Score**
Partial	6
Complete	9
Rectum/Sigmoid colon	**Score**
<3 cm	7
≥3 cm	9
Rectovaginal septum	**Score**
Present	8

AAGL endometriosis stage	Total score
Stage 1	≤8
Stage 2	9–15
Stage 3	16–15
Stage 4	>21

Retrocervical	Score
<3 cm	5
≥3 cm	8
Bladder detrusor	**Score**
<3 cm	5
≥3 cm	7
Right ovary	**Score**
Superficial	2
<3 cm	5
≥3 cm	7
Right ureter	**Score**
Extrinsic	6
Intrinsic	8
Hydroureter	9
Right fallopian tube	**Score**
Slight serosal involvement/damage	2
Moderate immobility	4
Severe immobility	6
Complete obstruction	7
Small bowel cecum	**Score**
<3 cm	6
≥3 cm	8
Appendix	**Score**
Present	5

Fig. 2: The American Association of Gynecologic Laparoscopists (AAGL) classification on endometriosis.[19]

discrimination in intraoperative surgical complexity.[19]

The AAGL 2021 Endometriosis Classification score has the potential to improve clarity in communication within medical records and in clinical research.

CONCLUSION

There have been almost 22 published classifications on endometriosis between 1973 and 2021. There is still no international consensus on which specific classification to be used. Classifications have been evolving over the years depending upon the parameters which are studied ranging from symptomatology to its impact on quality of life and infertility to the extent of disease and surgical complexity. To summarize, the #ENZIAN classification system holds its importance for surgical description of deep infiltrating endometriosis. Likewise, EFI classification focused on extent of disease and its impact on fertility. Likewise, the AAGL classification focuses on intraoperative complexity. sASRM scoring still holds importance for the basics that have been taken into account and the ease with which it can be comprehended which improves the communication between the gynecologist and the patient.

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Foreword by


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Clinical Focus on Endometriosis is a clinician's guide to the very prevalent condition in women today. We have tried to bring out all the issues of Endometriosis and their management in a simplified way.

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