ENDOMETRIOSIS

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Definition

Presence of endometrial glandular and stromal elements outside endometrial cavity and uterine musculature

Some define the ectopic tissue has to be functional too i.e difference between endometriosis & normal endometrium

Prevalence

An accurate prevalence is not determinable, because the definition requires a histological diagnosis.

Estimates are:

- 2-20% in women undergoing sterilization / laparotomy
- 5 - 10% female child bearing population
- 15-30% of women with pelvic pain undergoing laparoscopy
- 20 - 40% infertility patients
- 50%-80% adolescents undergoing laparoscopy for significant pelvic pain

average 10 years between symptoms and diagnosis endometriosis

Epidemiology

Socio-demographic factors.

Endometriosis increases with:

- age - peak incidence 40 - 44s
  also distribution of endometriosis varies:
  1) POD / uterosacral ligaments / broad ligaments decrease with age
  2) Ovarian involvement increases with age
- High social status (undergo more laparoscopies?)
- race Orientals > Caucasian > blacks (high prevalence in Japan)

Genetic

5% of 1st degree relatives have endometriosis; multi-factorial inheritance

Menstrual cycle

endometriosis increases with early menarche ≤ 11 ; cycle length < 27 days ; menses duration >7 days; un-interrupted regular cycles ie no intervening pregnancies conversely endometriosis decreases with increasing parity

Environmental

- smoking and exercise → reduced risk secondary to reduced estrogen
- ETOH / caffeine ↑ risk
- OCP inconsistent risk

Weight

↑ BMI → ↓ endometriosis (related to ↑ anovulatory cycles??)

Autoimmune diseases

↑ endometriosis in patients with rheumatoid arthritis ; SLE ; Hypothyroidism etc.

Ovarian cancer

↑ incidence of ovarian cancer (clear cell + endometrioid) in endometriosis :

- RR 2 endometriosis
- RR 3 endometriomas

Endometriosis and cancer share common traits eg local invasion, neoangiogenesis, resistance apoptosis etc

Risk factors:

- Menopause
- Endometriomas >9cm
- Unopposed estrogen

Incidence malignant transformation 1-2%

5% endometriosis occurs in P/M women:

- Unopposed HRT
- endogenous aromatase production in endometriosis lesions

Aetiology

Retrograde menstruation

75-90% all females have retrograde menstruation

↑incidence in congenital outflow obstruction

In adolescents with endometriosis, 10% congenital outflow obstruction

Metaplasia

Inductions agent (e.g. oestrogen) → metaplasia of coelomic tissue to endometrial tissue

Implies endometriosis can occur where no endometrium exists

Supported by:

- endometriosis in males
- extraperitoneal endometriosis
- prepubertal endometriosis

Theory has never been proven

Lymphatic / vascular dissemination

30% pelvic nodes are involved in endometriosis

Direct transplantation e.g. surgical scar

The immune system plays central role in endometriosis

Pathogenesis

Central to pathogenesis is overexpression Estrogen receptor beta in endometriotic cells

1) attachment and invasion of ectopic endometrial cells

mediated by:

- adhesion molecules
- ↑ matrix metalloproteinases (MMP) N.B progesterone ↓ MMP expression
- ↓ tissue inhibitor metalloproteinases (TIMP)
- other cytokines

2) survival and proliferation of ectopic endometrium

a) altered immune system

↓ CMI / NK → ↓ clearance of endometrial cells shed into pelvis

↑ B cell activation & antibody formation

↑macrophage activation → production of PG / cytokines

secretion of cytokines / growth factors leads to:

- pain
- toxicity to sperm / oocytes
- adhesion formation

b) abnormal hormonal environment

↑ aromatase activity → ↑ E2 production

↑ 17β hydroxysteroid dehydrogenase type 1 → ↑ E1 to E2

↓ 17β hydroxysteroid dehydrogenase type 2 → ↓ E2 to E1

all → ↑E2 environment

c) environmental factors

dioxin eg. Tetrchlorodibenzo-p-dioxin (TCDD) exposure → endometriosis in monkeys

Classification of endometriosis

Classification ideally :

1) reflects symptoms of pain and fertility
2) reflects prognosis with and without treatment
3) easily reproducible to allow communication between clinicians

parameters for pain different for fertility

rAFS scoring

problems with rAFS classification

1) correlates better for infertility than pain
2) does not account for morphological / functional activity of endometriosis eg.
   - Red lesion active growth
   - Black lesions less active
   - White lesion fibrotic
3) does not account for depth of lesions
4) large intra and inter observer variability

AFS Clasification of Endometriosis

Patient's Name _____ Date _____

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

Laparoscopy _____ Laparotomy _____ Photography _____

Recommended Treatment _____

Total _____

Prognosis _____

	ENDOMETRIOSIS	< 1cm	1–3cm	> 3cm
PERITONEUM	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 CULDESAC OBLITERATION	Partial	Complete
		4	40

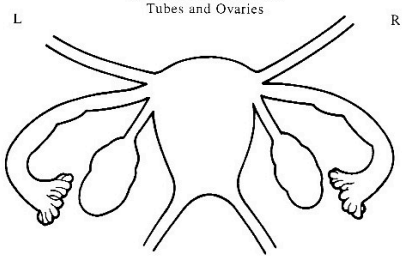
	ADHESIONS	< 1/3 Enclosure	1/3 – 2/3 Enclosure	> 2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

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

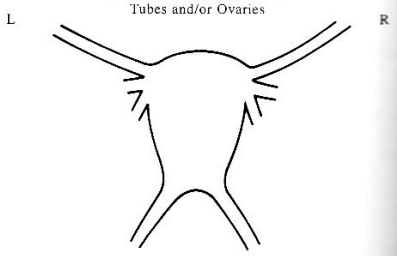
Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

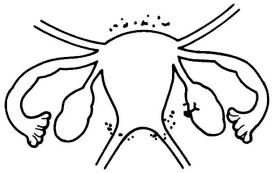


To Be Used with Abnormal Tubes and/or Ovaries



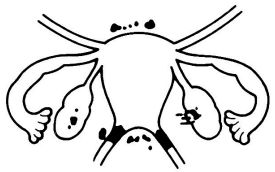
EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



PERITONEUM
Superficial Endo – 1-3cm - 2
R. OVARY
Superficial Endo – <1 cm - 1
Filmy Adhesions – <1/3 - 1
TOTAL POINTS 4

STAGE II (MILD)

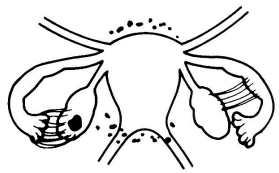


PERITONEUM
Deep Endo – >3cm - 6
R. OVARY
Superficial Endo – <1cm - 1
Filmy Adhesions – <1/3 - 1
L. OVARY
Superficial Endo – <1cm - 1
TOTAL POINTS 9

STAGE III (MODERATE)

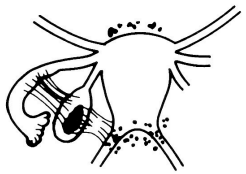
PERITONEUM
Deep Endo – >3cm - 6
CULDESAC
Partial Obliteration - 4
L. OVARY
Deep Endo – 1-3cm - 16
TOTAL POINTS 26

STAGE III (MODERATE)



PERITONEUM
Superficial Endo – >3cm - 4
R. TUBE
Filmy Adhesions – <1/3 - 1
R. OVARY
Filmy Adhesions – <1/3 - 1
L. TUBE
Dense Adhesions – <1/3 - 16 *
L. OVARY
Deep Endo – <1cm -4
Dense Adhesions – <1/3 - 4
TOTAL POINTS 30

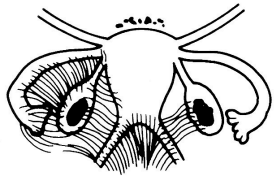
STAGE IV (SEVERE)



PERITONEUM
Superficial Endo – >3cm - 4
L. OVARY
Deep Endo – 1-3cm - 32 **
Dense Adhesions – <1-3 - 8 **
L. TUBE
Dense Adhesions – <1/3 - 8 **
TOTAL POINTS 52

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)



PERITONEUM
Deep Endo – >3cm - 6
CULDESAC
Complete Obliteration - 40
R. OVARY
Deep Endo – 1-3cm - 16
Dense Adhesions – <1/3 - 4
L. TUBE
Dense Adhesions – >2/3 - 16
L. OVARY
Deep Endo – 1-3 - 16
Dense Adhesions – >2/3 -16
TOTAL POINTS 114

Determination of the stage or degree of endometrial involvement is based on a weighted point sytem. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases.

To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size and location of endometrial implants, plaques, endometriomas and/or adhesions are noted. For example, five separate 0.5cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis or adhesions should be assigned the highest score only for peritoneum, ovary, tube or culdesac. For example, a 4cm superficial and a 2cm deep implant of the peritoneum should be given a score of 6 (not 8). A 4cm deep endometrioma of the ovary associated with more than 3cm of superficial disease should be scored 20 (not 24).

In those patients with only one adnexa, points applied to disease of the remaining tube and ovary should be multiplied by two. **Points assigned may be circled and totaled. Aggregation of points indicates stage of disease (minimal, mild, moderate, or severe).

The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin etc., should be documented under "additional endometriosis." Other pathology such as tubal occlusion, leiomyomata, urine anomaly, etc., should be documented under "associated pathology." All pathology should be depicted as specifically as possible on the sketch of pelvic organs and means of observation (laparoscopy or laparotomy) should be noted.

ENZIAN classification (DIE)

Complementary to rAFS
Anatomical Scoring for DIE
Surgical / histological staging (denoted by prefix ENZIAN) which can be provisionally based on clinical / US /MRI + diagnostic laparoscopy. (denoted by prefix C)

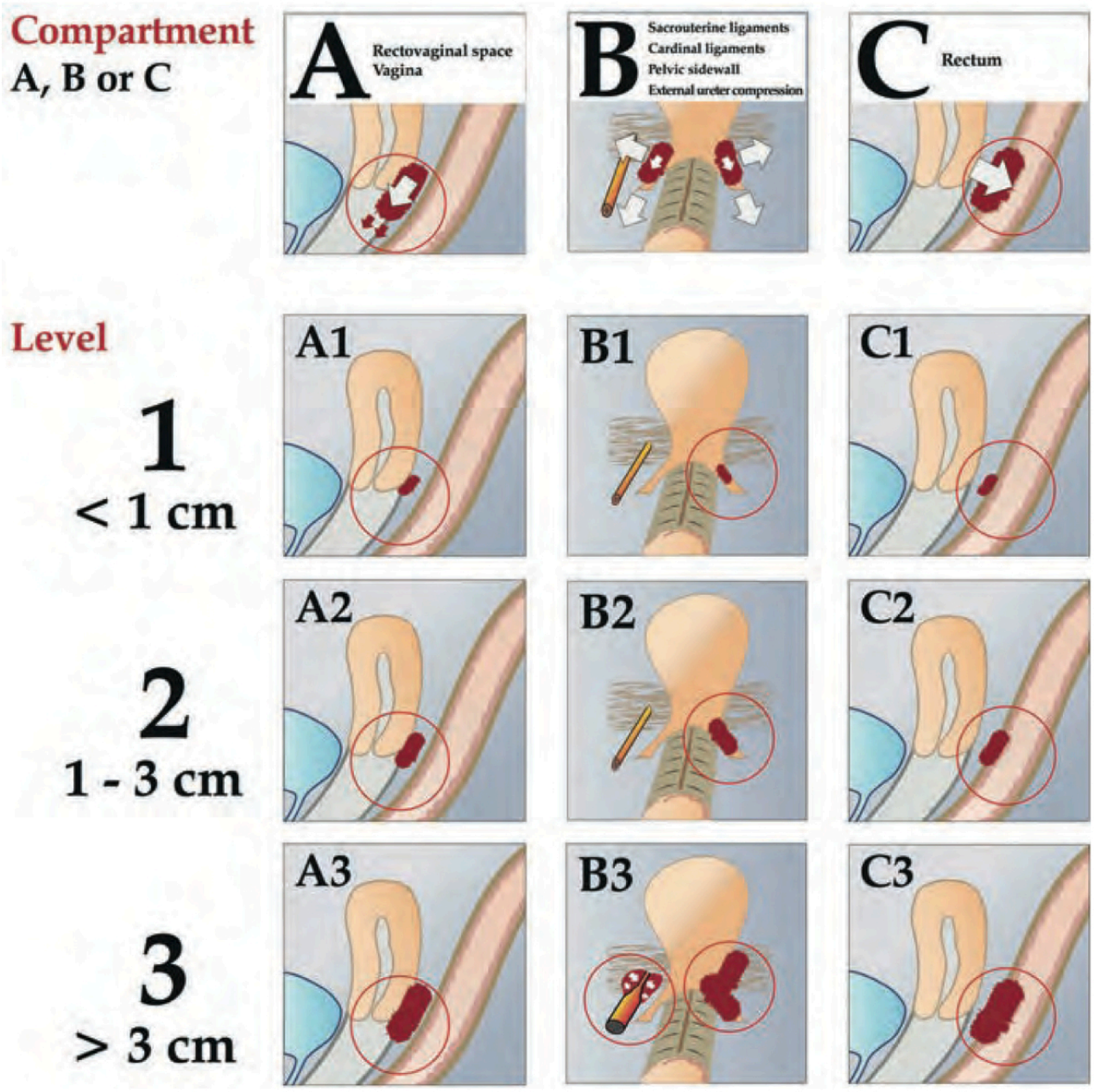


Fig. 1.53 ENZIAN Classification – Compartments A–C.[8]

A= rectovaginal space B=pelvic side wall including uterosacral ligaments C= rectum
1= <1 cm; 2=1-3cm; 3=>3cm lesions

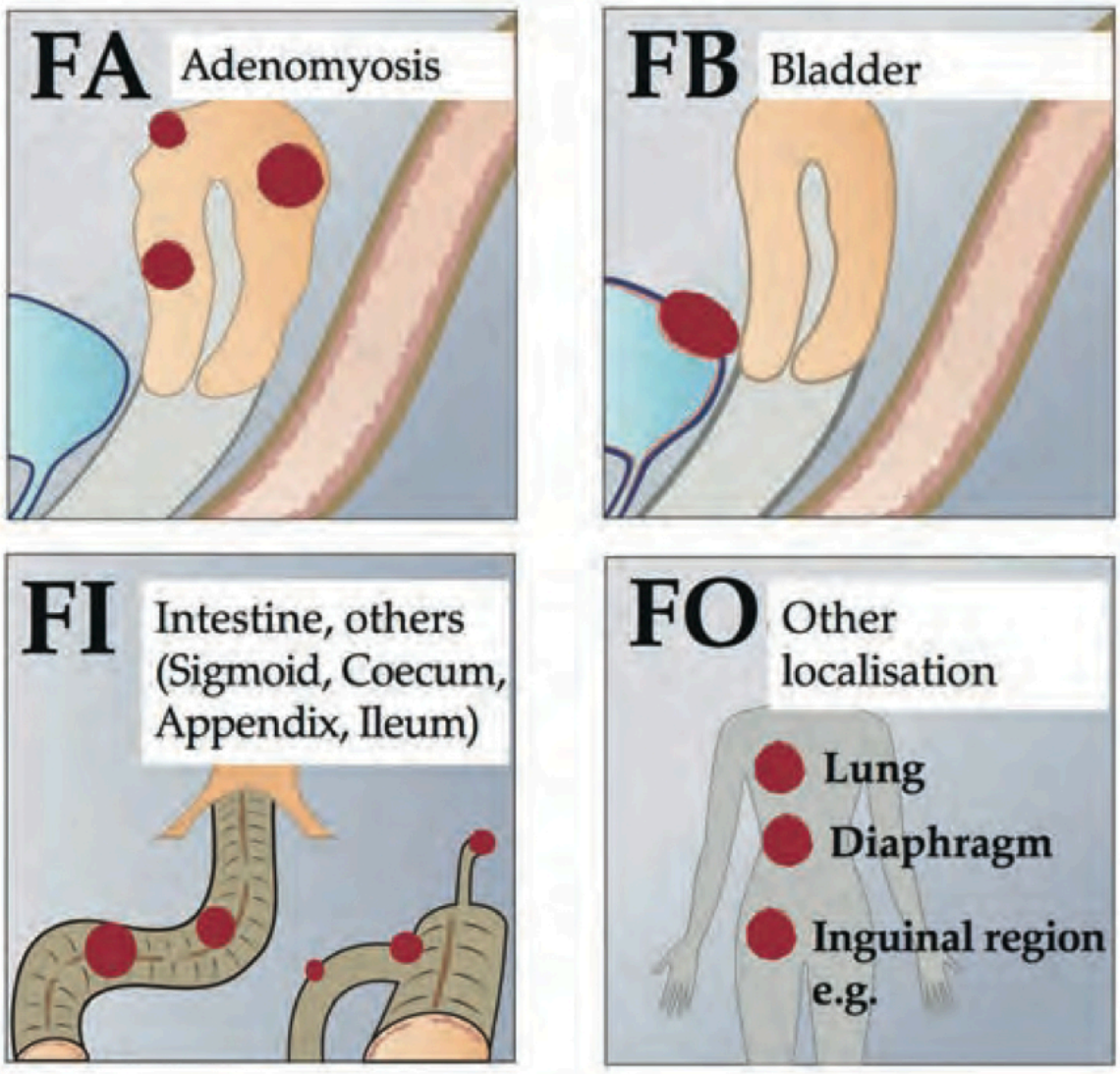


Fig. 1.57 The suffixes FA, FA, FI and FO are part of the ENZIAN classification scheme addressing the sites of endometriotic implants detected outside the lesser pelvis.[8]

F denotes other sites endometriosis.

Endometriosis Fertility Index (EFI)

Good prognostic indicator fecundity to guide future treatment options (Adamson 2010)

TABLE 1

Descriptions of least function terms.

Structure	Dysfunction	Description
Tube	Mild	Slight injury to serosa of the fallopian tube
	Moderate	Moderate injury to serosa or muscularis 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

Adamson. Endometriosis fertility index. Fertil Steril 2010.

Least Function score (LFS) is a surgical assessment after treatment of the least function of each side the tube / fimbriae / ovary. Accounts 30% EFI

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

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 LF score is obtained by doubling the lowest score on the side with the ovary.

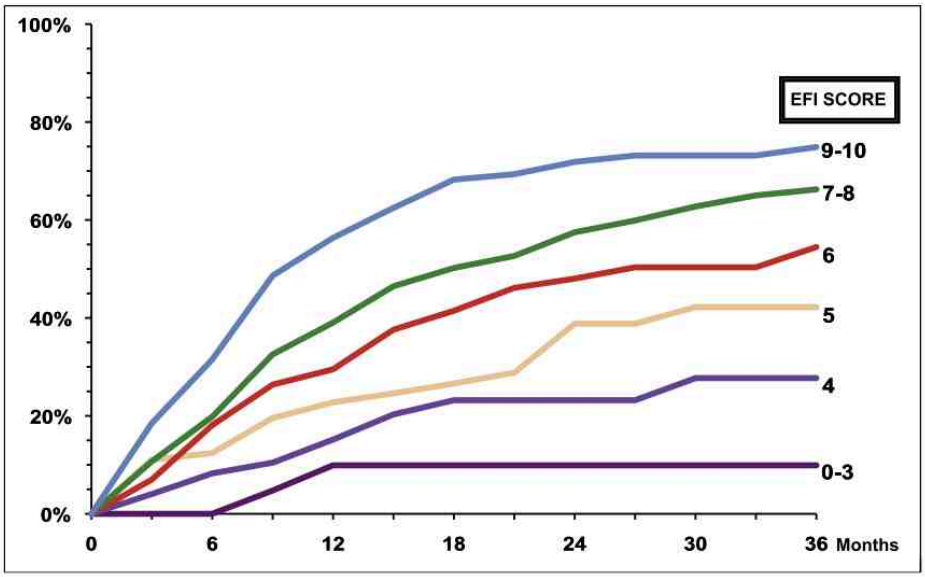
	Left		Right		
Fallopian Tube					
Fimbria					
Ovary					
Lowest Score		+		=	
	Left		Right		LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 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

ESTIMATED PERCENT PREGNANT BY EFI SCORE



Prognosis modified from Adamson 2010

EFI score	Years 1	2	3
0-3	<10%	<10%	<10%
4	10%	10%	30%
5-6	30%	40%	50%
7-8	35%	50%	60%
9-10	60%	70%	75%

Sites for Endometriosis

Genital Tract

Ovary > POD > UV peritoneum > posterior broad ligament > uterosacral ligaments > other sites

location	Implants		Adhesions	
	Number of patients	%	Number of patients	%
Anterior cul-de-sac	63	**34.6**	4	2.2
Posterior cul-de-sac	62	**34.0**	20	11.0
Right ovary	57	**31.3**	26	14.3
Left ovary	81	**44.0**	45	24.7
Right anterior broad ligament	2	1.1	2	1.1
Left anterior broad ligament	0	0	3	1.6
Right round ligament	1	0.5	2	1 .1
Left round ligament	1	0.5	2	1.1
Right fallopian tube	3	1.6	20	11,0
Left fallopian tube	8	4.3	28	15.4
Right posterior broad ligament	39	**21.4**	30	16.5
Left posterior broad ligament	46	**25.2**	50	27.5
Right uterosacral ligament	28	**15.3**	5	2.7
Left uterosacral ligament	38	**20.8**	8	4.4
Uterus	21	11.5	6	3.3
Sigmoid	7	3.8	22	12.1
Right ureter	3	1.6	0	0
Left ureter	2	1.1	3	1.6
Anterior bladder flap	1	0.5	1	0.5
Small bowel	1	0.5	4	2.2
Anterior abdominal wall	0	0	3	1.6
Omentum	0	0	4	2.2

Implants and adhesions by anatomic location. (from the American College of Obstetricians and Gynecologists, Obstetrics and Gynecology, 1986, 67: 335—338.)

Extra genital tract **(affects older population)**

Bowel (5-15%)

- commonly recto-sigmoid 85%
- small bowel 5%
- appendix / others 10%

most bowel endometriosis invasion through serosa/ muscularis only
10% cases invades mucosa therefore sigmoidoscopy rarely helpful.
When endometriosis >3cm and invades to submucosa, >40% circumference bowel is involved. Bowel resection is recommended
60% bowel lesions multifocal, indicating bowel resection.
Presentation

- Most asymptomatic
- Pain
- Dyschezia / tenesmus
- Haematochezia
- Diarrhoea / constipation
- Bowel obstruction rare (<1%)
  If there is bowel obstruction (small bowel > colon)
- Perforation (rare), occurs with pregnancy

Management depends on:

- Symptoms
- Fertility desires
- Extent and severity of endometriosis
- Complications eg. Obstruction

.
If significant symptoms are present, often surgery is required.
Aim of surgery:

- Relief symptoms esp pain
- Reduce recurrence
- Improve fertility (no RCTs)

High morbidity associated with surgery

Endometriosis is NOT cancer, therefore primary aim is minimize the amount of bowel resected but at the same time maximize symptom relief which may mean not clear margins / incomplete resection.

- Shaving bowel lesions
  - Superficial lesion on serosa
- Disc resection
  - <3cm diameter
  - <3 lesions
  - <30% circumference
  - invasion deeper than muscularis bowel wall

  Techniques:
  - endorectal resection with EES circular stapler

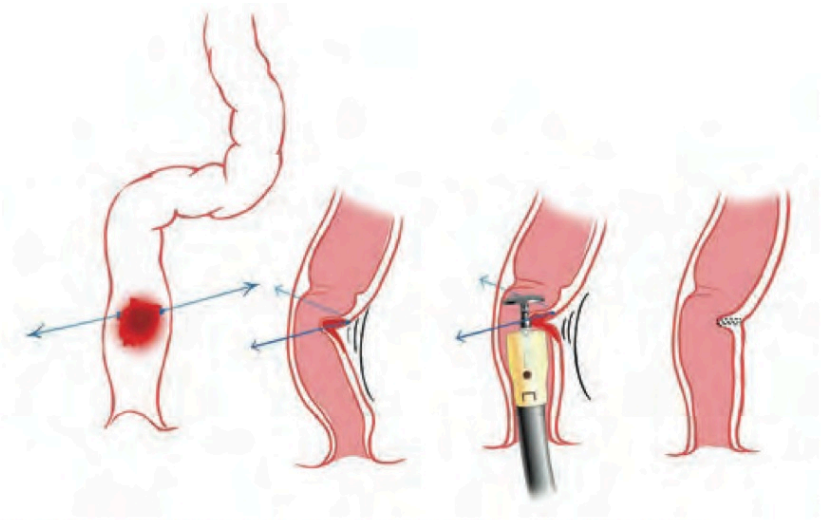
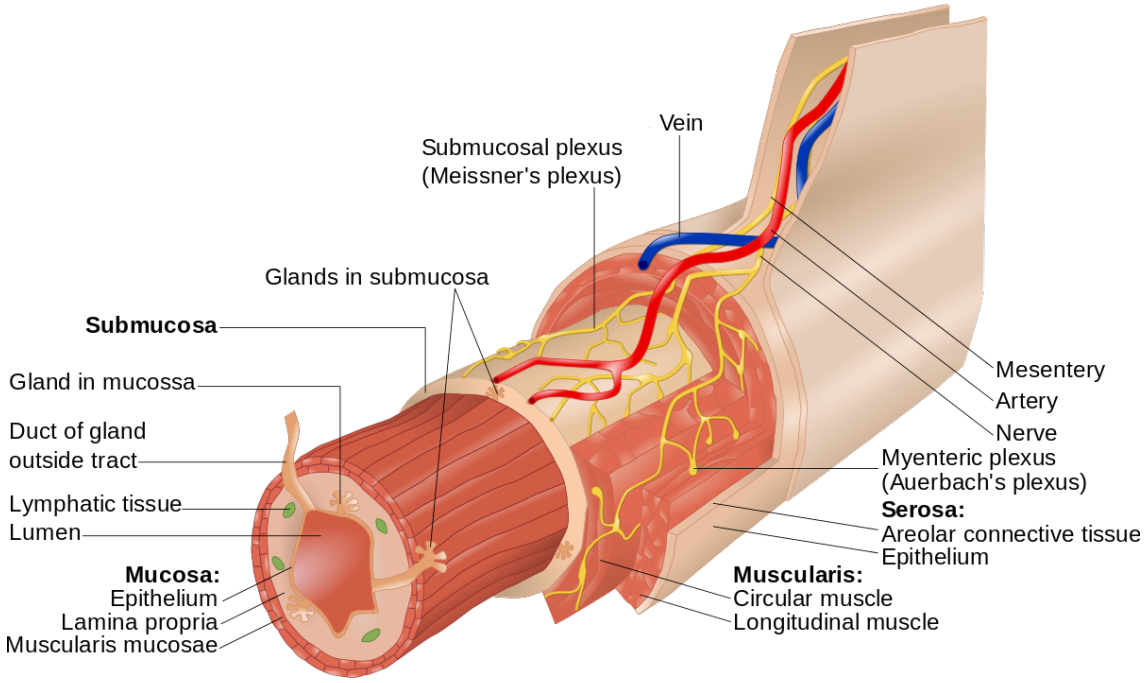


Fig. 6.18 Endolumenal wedge resection with a circular stapler.

- transrectal linear stapler
    - for higher lesion
- transanal pull through with linear stapler resection
    - for low lesions within 2 cm anus
- laparoscopic wedge resection with manual suture

- Anterior Bowel resection
    - >3cm size
    - >50% circumference bowel
    - multifocal lesions



layers of the bowel.

Urinary tract (1 - 4%)
increased incidence recently due to improved diagnosis
associate with RV nodules >30mm
sites:

- bladder 90% symptoms in 70%
- ureter 10% symptoms 10-15% often non specific
- renal / urethra rare

symptoms:

- dysuria / frequency
- pain suprapubic / flank
- haematuria

investigations:

- IVP
- US
- CT or MRI
- Cystoscopy and Laparoscopy

Management depends on:

- Renal function
- Location and extent of disease
- Symptoms
- Age and desire for fertility

a) medical
often hormonal therapy is required for longer periods compared to treatment for pelvic endometriosis.
b) surgical

- cystectomy
- ureterolysis (if external compression)
- ureteral resection with reanastomosis or reimplantation

Diaphragm
<1% endometriosis
R(95%) >L (4%) 3.5% bilateral
Typical presents with cyclic pain upper quadrant radiating to shoulder + arms
Treatment:

- medical
- ablation
- excision

Lungs
peritoneal / pleural (direct spread)
parenchymal (related to pelvic Sx & haematogenous spread)
R > L 9:1
Presentations
Catamenial and recurrent:

- pneumothorax 75%
- haemothorax 15%
- haemoptysis 5%
- lung nodule 5%

definitive diagnosis = regression of symptoms with endometriosis treatment
treatment:

- medical
- surgical excision at video assisted thoracoscopy (VATS)
- complications eg. Pneumothorax

Others:

- umbilicus
- scar tissue
- limbs
- nervous system etc

every organ has been documented except the spleen (sanctuary site ?)

Types of Endometriosis

- Superficial
- DIE >= 5mm beyond peritoneum
- Endometrioma

Presentations

Asymptomatic (discovered incidentally at laparoscopy)
These patients do not need to be treated unless symptomatic as cohort study over 15 years by Moen et al showed women with asymptomatic endometriosis have less pain than controls over time.

Symptoms

Pelvic pain
Including dysmenorrhoea / dyspareunia / dyschezia / pain on micturition
Pain is not proportional to volume of disease
Depends on:

- Site
- Activity
- Depth of invasion

Irregular bleeding
due to

- ovarian dysfunction
- antegrade loss of blood

Pelvic mass
need to exclude malignancy
Infertility

Diagnosis of endometriosis

Clinical

Up to 40% sensitivity for ovarian endometriomas

Imaging

Most imaging cannot detect peritoneal disease.

TV ultrasound

Accurate for endometriomas
SVG US
Negative sliding sign sensitivity 85% rectovaginal disease
Can also look DIE Uterosacrals / bladder + softmakers indicating adhesions

TR Ultrasound

Similar sensitivity TV US
Used virgins

MRI

Endometriomas / DIE sensitivity 95%

Biomarkers

Ca 125

Indicates active disease rather than extent/severity

Endometrial nerve fibres

PGP9.5

Increased in patient with uterine pain eg endometriosis / fibroids / adenomyosis

Laparoscopy (gold standard)

appearances maybe atypical

Important to stage endometriosis presurgery to assess the extent of surgery required especially in extra genital involvement.

Appearance of endometriosis

Correct visual identification of endometriosis depends on the experience of the surgeon, with identifying non-pigmented lesions

- Less experienced surgeons ID correctly 40%
- More experienced surgeons ID correctly 80%

appearance is quite diverse:

1) classical black lesions (burnt out disease in older patients)
2) red / polypoid lesions (most active lesions)
3) white endometriosis = scarring
4) peritoneal defects / clear lesions 80% associated with endometriosis
   28% endometriosis patients have defects
5) deeply infiltrating disease (Cullen's disease) → puckering / nodules

Differential diagnosis

- old sutures / residual carbon
- epithelial inclusions
- malignancy
- endosalpingiosis
- inflammatory lesions

Management of endometriosis

Endometrosis is a chronic disease requiring lifelong management with medical treatment for suppression and pain control and surgery when indicated.

treatment depends on:

1) **severity of symptoms**
2) extent of endometriosis and location
3) desire for fertility
4) age

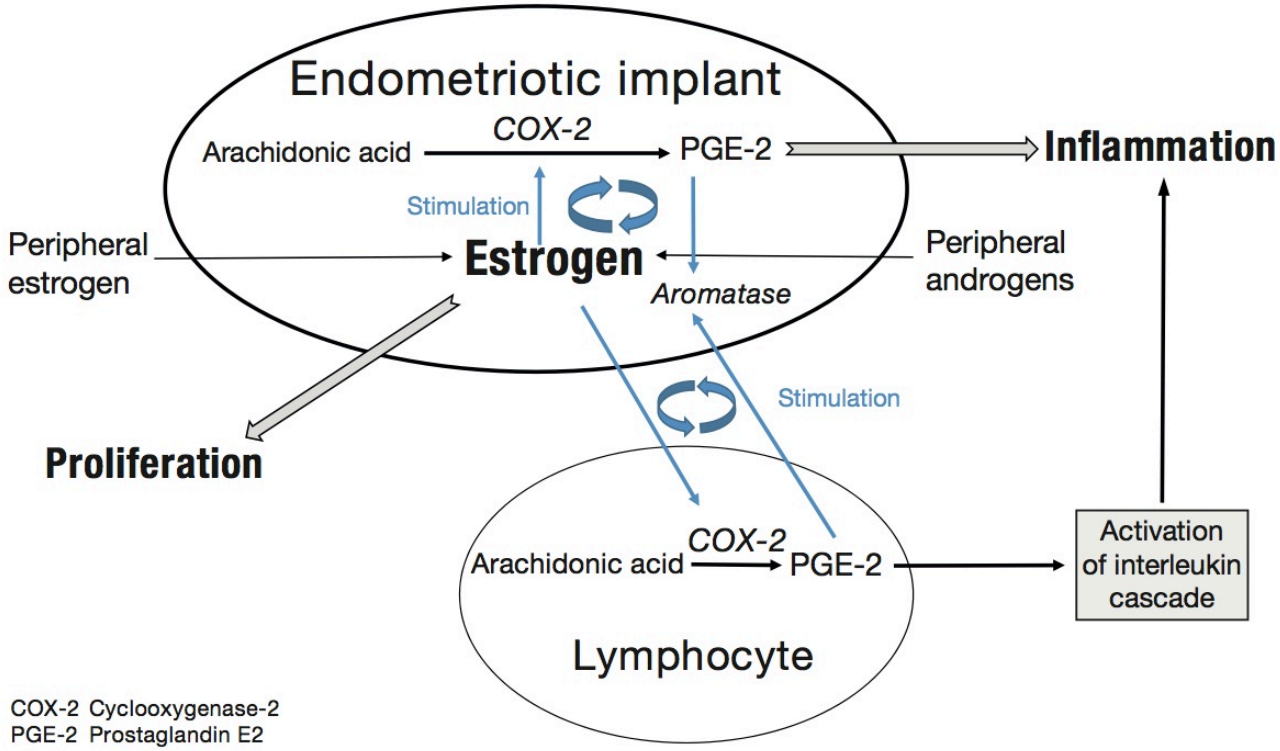
treatment options:

1) expectant
2) symptomatic
3) Hormonal suppression
4) Surgical
5) Combination

Treatment of pain

Pathophysiology of pain

1) inflammatory mediators eg. PGs
2) direct invasion and irritation of neural tissue (depth of invasion correlates with pain)
3) adhesions → mechanical disruption



Observation
applicable in absence of symptoms after routine laparoscopy, although long term suppression with OCP or progestins logical if one presumes endometriosis is a progressive disease.

NSAIDs
Effective for relieving pain
Used in combination with hormonal supression

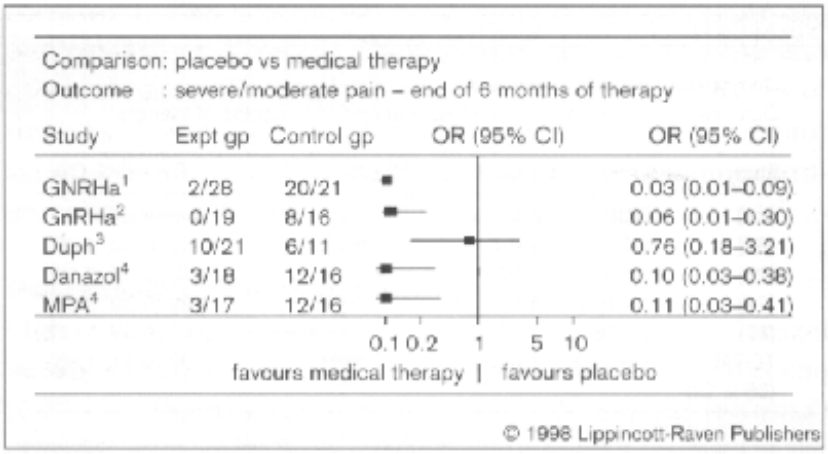
Medical therapy cannot treat infertility / endometrioma except dienogest may

Ovarian suppression

Aim pain therapy is to inhibit ovulation and produce amenorrhoea
Hormonal therapy is better than no treatment for pain (see table)
Overall medical suppression relieves pain 80-90% effective whilst on medications
No one regime is more effective than another, but SE profiles different

OCP
Continuous OCP → constant hormonal milieu which theoretically should treat endometriosis.
Major SE in 30% (BTB, bloating etc) → discontinuation
Monthly regimes may help mild symptoms
3 monthly regimes more effective than monthly, but less effective than GnRHa for dysmenorrhoea
theoretically high progestin content OCP or Dienogest

Figure 1. Randomized controlled trials of placebo medical therapy for the painful symptoms of endometriosis



OR, odds ratio; CI, confidence intervals.

GnRH analogues
Studies suggest no difference in outcome:

- Pain
- AFS scores

Between GnRHa and danazol, but different SE profile → ↑ compliance and less discontinuation rates
SE:

- Flushes
- Mood changes
- Osteoporosis (↓ BMD 3-5% over 6/12 reversible)

Starting in luteal phase is ideal → ↓ flare response and Amenorrhoea by 4weeks
If started in follicular phase → ↑ flare and Amenorrhoea by 8weeks
Success rate 50% after 6/12 but 10-20% recurrence per year
Menses return after 60-90days after depot
GnRH analogues + addback is effective for relief of pain, but higher oestrogen doses → ↑ pain.
Ideally use:

- Tibolone
- Kliovance
- Primolut etc No studies looking at addback therapy > 12/12

Progestins
Can be used long term >6/12
efficacy as effective as Danazol (100mg daily MPA)

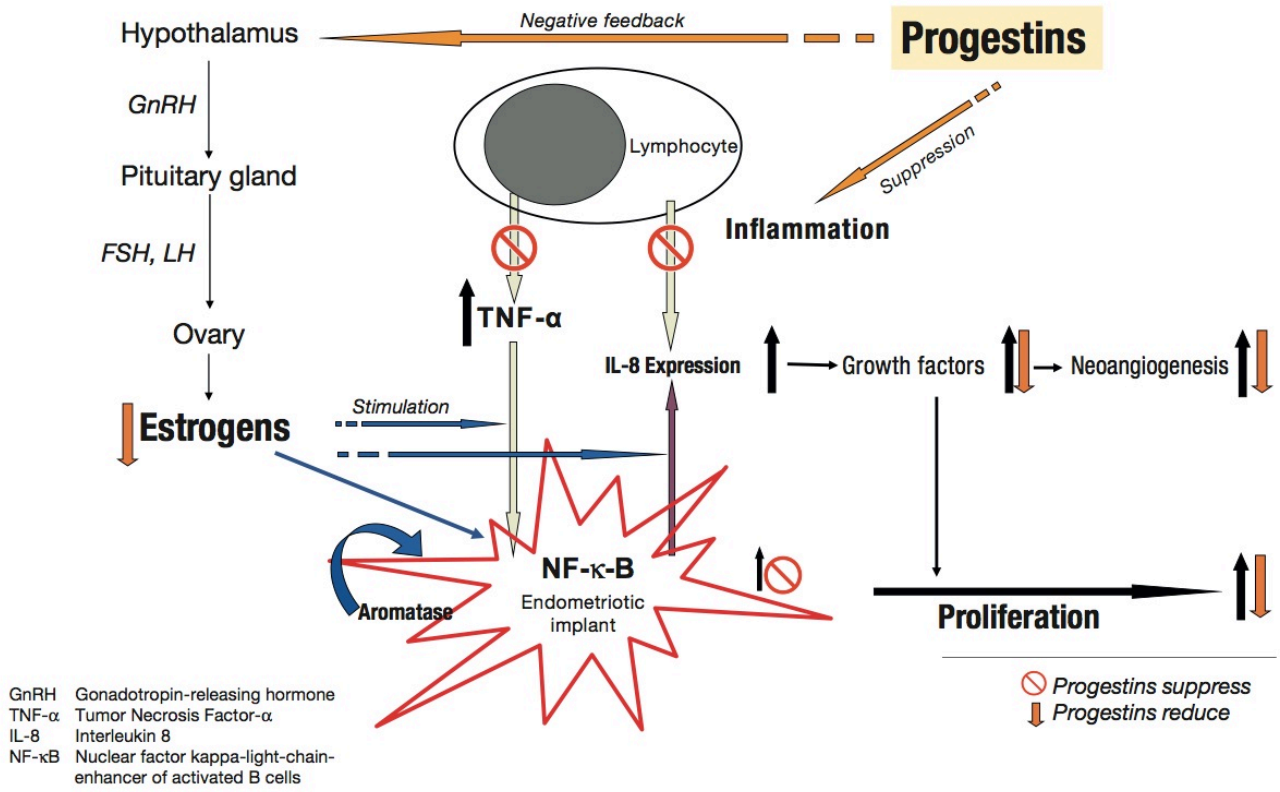
- Depot Provera 150mg IM q3months
- Provera PO 10mg tds – 100mg
- Primolut 5mg daily
- Duphaston 10-20mg daily (can conceive but less effective cf other progestogens)
  (luteal phase duphaston is no better than placebo)

Dienogest (Visanne)
19 nortesterone derivative synthetic progestin
mechanism of action at level endometrium:

- Progestational (antiproliferative)
- Anti gonadotropic (mildly anti oestrogenic)
- Reduction production aromatase / cyclooxygenase-2 / PGE2 in endometriotic cells (anti-inflammatory + anti angiogenic)

2mg daily used up to 5 years with cumulative efficacy
similar pain relief versus GnRHa
continued effect after cessation for up to 24 weeks

Mirena IUCD
Mirena similar efficacy to GnRHa and DMPA with less SE and better compliance
Ideal after surgery for continued suppression



GnRH antagonist (elagolix)
Oral antagonist
Doses 150mg daily and 200mg bd had significant reduction dysmenorrhea + non menstrual pain (vs placebo (approximately 50% / 75% / 20% reduction)
Higher dosage associated with hypoestrogenic SE
Duration 6 months

Antiprogesterone (RU 486)
50-100mg daily
suppresses ovulation
induces endometrial atrophy
pilot studies suggest

- Reduced pain
- Reduced endometriosis by 50%

Theoretical risk of endometrial hyperplasia

Danazol
600-800mg daily divide doses (lower doses are less effective)
Mechanism of actions:

- inhibits LH/FSH mid-cycle surge
- directly inhibits steroidogenesis enzymes
- binds to androgen / progesterone, but not estrogen receptor though
- ↑ androgen directly and displaces testosterone from SHBG
- immunological

Inhibits ovulation after 4-6 weeks ∴ 1st month use barrier contraception
Side effects (up to 80% will experience SE therefore compliance major issue)

(a) androgenic :acne / weight gain / hirsutism
(b) hypo-estrogenic: hot flushes /↓ libido / vaginal dryness / mood changes
(c) others : GIT changes / cramps / headache and dizziness

80% symptomatically improve, however after cessation 15-20% recurrence after 1st year then 5% pa thereafter up to 50% after 5 years ie Cumulative recurrence 50% after 5 years
60% improvement in AFS scoring after 6/12 compared with 20% without treatment
Can be given PV for rectovaginal endometriosis!
Recurrence related stage of endometriosis:

25% mild
50% moderate
60% severe disease

Gestrinone 2.5-5.0mg x 2 / week
Progesterone partial agonist with mild androgen profile
Similar efficacy to danazol with less SE
Mechanism of action

- inhibits mid-cycle FSH/LH
- anti- estrogen/ progesterone
- SHBG → ↑ testosterone

Aramotase inhibitors
Cause profound reduction in circulating oestrogen levels → enhanced hypoestrogenic environment.A AI with (NET / OCP or GnRHa) better than GnRHa alone
Need ovarian suppression as AI alone lead cyst formation / bone loss
Letrazole 2.5mg daily

Neuropathic pain treatments

Surgical treatment

Surgical treatment of endometriosis esp. complete excision results in pain relief but 20-25% patients requiring additional surgery at 5 years
NB Recurrent pain may not be associated with recurrent endometriosis

Conservative

Resection of implants with ureterolysis / shaving but conserving viscus.
Aims:

- removal / ablation of all visible endometriosis
- restoration of normal pelvic anatomy including ventral suspension
- symptom relief via LUNA, pre-sacral neurectomy etc

Endpoints

- symptom relief
- treatment of visible disease
- pregnancy

Surgery compared with medical therapy or observation:

- Hefni et al 1998 in RCT on laser laparoscopy (60% improvement) versus diagnostic laparoscopy (20%) criticism = the diagnosis of endometriosis
- J Abbot et al 2004. RCT laparoscopic excision of endometriosis versus placebo showed significant improvement in symptoms for all stages versus placebo.
  Placebo arm over 6/12:
  - 50% progression
  - 30% static
  - 20% improved

Excision vs ablation

Both are better than no treatment regarding pain relief.
Healy et al 2014 RCT with 5 years FU n= 178 excision vs ablation for genital endometriosis (included DIE) showed better pain relief with dyspareunia (VAS reduction 6 vs 3) + less medical therapy with excision 20% vs 31%, otherwise other pain symptoms NS
JMIG meta analysis 2017 of 3 trials showed excision better improvement at 12 months:

- dysmenorrhoea
- dyschezia
- chronic pelvic pain

Excision preferred over ablation as:

- deep implants can be treated esp infiltrating nodules
- vital structures identified
- histological confirmation

excisional surgery preferred for bladder / bowel / ureter endometriosis, as failure to excise → high recurrence symptoms

surgical excision with adjuvant medical treatment results in better

(1) symptom relief
(2) objective eradication of endometriosis

Adjuvant treatments

Pre-operative medical Rx can:

- relief pain
- reduce endometrial implants
- reduce endometrioma size

but there is no data

- improved pain vs surgery alone
- improved fertility
- disease recurrence

main indication is relief of symptoms prior to surgery (especially pain)

Post-operative medical Rx

Aim to suppress residual microscopic endometriosis with long term OCP/progestins /Mirena / GnRHa if pregnancy is not desired

- reduced pain
- reduced recurrent disease at 12 months

Vercillini et al 2003 mirena post op → reduced dysmenorrhoea / dyspareunia and ↑ patient satisfaction rates at 1 year.

most pregnancy naturally conceived will occur within 18/12 post-op

Hysterectomy with conservation of ovaries

HE results in good pain relief with 25% requiring additional surgery up to 7 years vs <10% if BSO also performed (RR0.25)

Key is to remove all endometrial implants with HE

BSO needs to be individualised depending:

- severity endometriosis
- completeness of surgery
- ovarian involvement
- age of patient

Suggest retention of ovaries

- if ovaries are normal
- all endometriosis is cleared / less severe disease
- younger patient e.g < 45 years???

BSO

Role of BSO needs to be individualized

BSO in premenopause without HRT:

- increased osteoporosis
- increased CVD
- increase mortality

25% require further surgery especially for residual ovary syndrome & recurrent endometriosis

Recurrence:

- 5% Stage I / II
- 40% Stage III / IV

conserving ovaries vs BSO :

- ↑ recurrent pain
- ↑ repeat surgery RR 4

May be role of adjuvant medical therapy if not all residual disease removed after surgery

Radical excision DIE
Resection of bladder / ureter / bowel with repair
See management extra genital endometriosis
Currently a move towards nerve sparing radical EO endometriosis to preserve bladder + bowel function.

LUNA
results in 50-85% pt improvement in pain scores short term although no RCT .
no evidence of long term pain relief better than placebo
Maybe role ?? in negative laparoscopy gp & severe dysmenorrhoea / central pain

Presacral neurectomy
Effective for treatment of midline pain / dysmenorrhoea
Technically challenging surgery operating around major vessels
Major SE constipation / urine retention

HRT with past endometriosis

Women with history of endometriosis especially with surgically induced menopause need to be counseled and HRT individualized
Concern HRT esp unopposed estrogen:

- recurrence endometriosis
- malignant transformation

Data is unclear, but likely:

- HRT does increase risk recurrence up to 2%
- Increased risk malignant transformation esp endometrioid adenocarcinoma most common (absolute risk uncertain)
- No data if delaying HRT beneficial, but wise if there is incomplete resection, to delay giving HRT
- Theoretically tibolone or continuous E + P better and lead to less recurrence vs Estrogen only or potential SERMS eg bazedoxifene
- Recurrence can occur without HRT

Other risk factors recurrence:

- Incomplete excision
- Hyperestrogenemia eg obesity
- Genetics

Case reports isoflavones and recurrent endometriosis + malignant transformation

Management of endometriomas

20-40% of patients with endometriosis have endometriomas
adversely affect AMH, IVF eggs retrieved, but PR not reduced compared with no endometrioma IVF
Pathogenesis:

- originate from invagination of endometriosis on the ovarian cortex from retrograde menstruation, associated with scarring of the ovary.
- Metaplasia

In symptomatic patients removal of cyst improves symptoms and natural fertility, but also stripping does reduce ovarian reserve:

- Removes normal primordial follicles with stripping (care needs to be taken with cystectomy minimize removing normal tissue with sharp dissection). NB Histology shows ovarian capsule contain damaged primordiol follicles.
- Thermal damage with bipolar (minimize this)
- Compromised blood supply from physical damage, inflammation and oedema.

Good RCT evidence excision/stripping better than drainage and ablation:

- ↓ recurrence
- ↑ pain relief
- ↑ pregnancy rates (in natural conception but not IVF)
- provides histology and excludes malignancy

endometrial glands penetrate up to 3mm into capsule and ablation results in variable depth penetration

Beretta et al 1998 RCT FU 26 months

	Stripping	Drainage ± ablation
Recurrence of severe pain	15% at 2 years	50-75%
Recurrence of endometrioma	5-10%	Up to 100%
Cumulative PR (natural)	66% at 2 years	25%

Postoperative hormonal suppression reduces recurrence endometriomas (8% vs 32% RR0.12)

Ablation may not reduce ovarian reserve as much as stripping especially with bilateral cysts and larger cysts (>5cm). Potentially use of laser or plasma jet may minimize thermal damage and preserve eggs, but to date careful stripping considered gold standard.

Techniques for haemostasis:

- bipolar. Should be minimized in view of thermal damage
- suturing. Don't strangulate tissues (theoretically better)
  some data shows suturing may less reduction ovarian reserve compared to bipolar, but not real differences in fertility outcome (lack of power in studies?)
- sealants eg floseal
  may be effective and reduce need to bipolar, but some concern of post op inflammation + SBO
- vasopressin
  may reduce the need for bipolar

Techniques for cystectomy to minimize ovarian damage:

- ID correct plane ? use of saline or vasopressin
- Accurate pin point bipolar with aqua wash out to ID exact bleeding points
- Careful suturing (not to strangulate) and judicious use sealants

Other factors to consider:
- Bilateral endometriomas have lower AMH and after greater loss of AMH after surgery
- Larger endometriomas lower AMH with greater loss of AMH after surgery (cut off ? 5-7cm?)
- After cystectomy AMH drops which may improve up to 1year, but often does not recover fully.

INFERTILITY

Prevalence of infertility 50% in women endometriosis vs 10% non endometriosis women
MFR 2-10% vs 15-20% in fertile couples

Mechanism of infertility in endometriosis:

Secretion of inflammatory factors leading to:
- Mechanical distortion from adhesions and scarring
- Peritoneal toxic factors

  Macrophages →
    - PG
    - Free radicals
    - Lymphokines/cytokines/angiogenic factors etc

  Which inhibits sperm /oocyte and embryo development and interaction
- Impaired oocyte release
- Reduced sperm / embryo transport
- Reduced endometrial receptivity with Progesterone resistance
- Auto-immunity leading↑ Ig cross react with ovarian tissue / gametes etc

Management of endometriosis in infertility patients depends on:

1) female age
2) severity of endometriosis
3) presence of adhesions and other infertility factors
4) symptoms

Treatment options:

1) expectant
2) surgery goals
    - resect all endometriosis
    - restore anatomy
    - prevent adhesions

1st surgery PR up to 40% vs 22% with repeat second surgery

3) Clomid / Letrazole + IUI
4) FSH + IUI

	MFR	15% versus 2-5% in controls
	twin pregnancy	20%
	≥ triplets	8%

5) IVF

Medical treatment does NOT enhance natural fertility in endometriosis

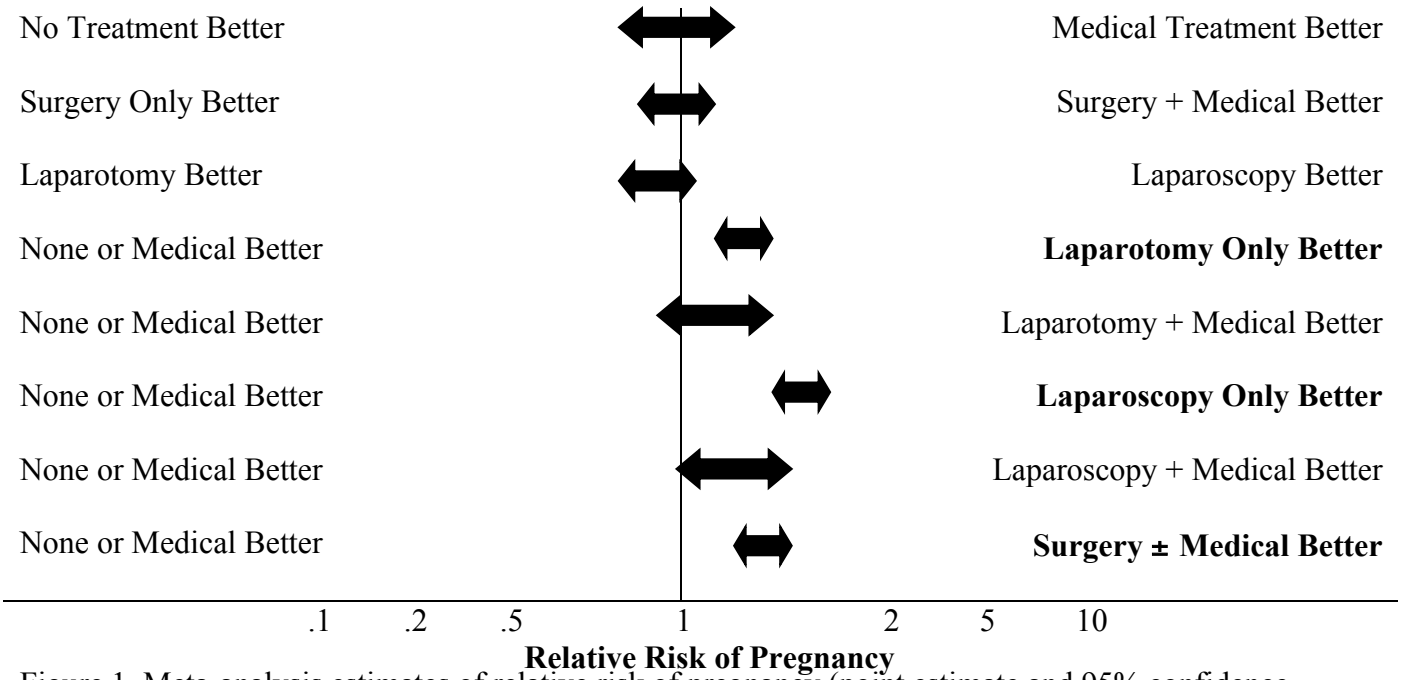
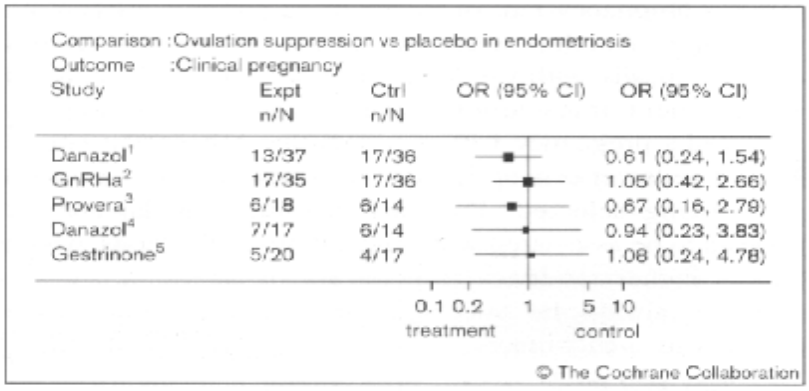


Figure 1. Meta-analysis estimates of relative risk of pregnancy (point estimate and 95% confidence interval) for different endometriosis treatment comparisons. *(From* Adamson GD, Pasta DJ: Surgical treatment of endometriosis-associated infertility: Meta-analysis compared with survival analysis. Am J Obstet Gynecol 171:1488, 1994)

Figure 7. Meta-analysis of ovulation suppression versus placebo for the treatment of infertility



Minimal / Mild endometriosis

Expectant

Up to 60% will conceive naturally after 24/12 with MFR 3-10%

Surgery

laparoscopic ablation / excision leads to improved fertility outcome with MFR 5% versus 2.5% (Marcoux 1997) NND 12

super-ovulation ± IUI

after surgery may further improve fecundity 15% per cycle (max 6 cycles)

IVF

Moderate / Severe endometriosis

Overall natural conception rate (MFR 1-3%)

Moderate	25%	without adhesions up to 50% may conceive
Severe	<5%	

each additional infertility factor reduces MFR by 50% e.g. infertility >12 months, age >35 etc

EFI post surgery is good predictor natural fertility after surgery

NO RCT comparing surgery vs expectant rx and PR

Surgery

MFR up to 5%

DIE bowel resection MFR 2.3% vs <1% of bowel disease left behind

most occur within 24/12

add superovulation + IUI

Repeat surgery does not improve fertility. Only role is if significant pain

Risks surgery need to be considered especially with bowel resection

IVF

Advanced age

Failed surgery after 6-12 months

Dense adhesions/ tubal blockage (EFI <5)

Other infertility factors present

Role of surgery for DIE prior to IVF needs to be individualized. Limited non randomized cohort studies indicating improved PR 41% with sx + IVF vs 24% IVF alone

Endometriosis and IVF

Endometriosis does affect IVF:

- Reduced ovarian response to Gntp, esp. with endometriomas
- Reduced oocyte quality
- Reduced fertilization rates esp. stage 3+4

Women undergoing IVF reduced PR vs tubal factor infertility (RR 0.56)

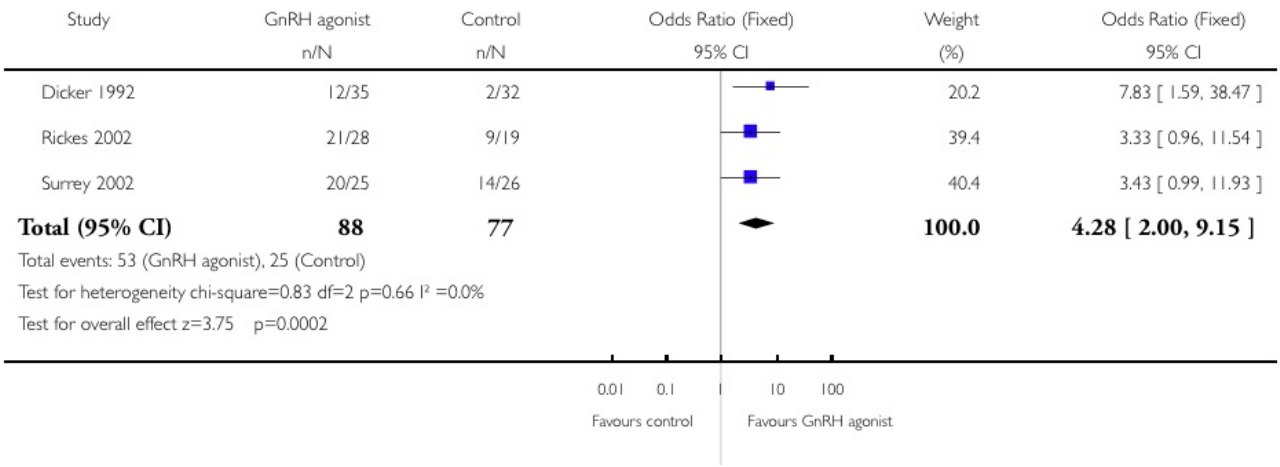
Good evidence pretreatment GnRHa 3 months → increased PR versus standard IVF (RR = 3.4) (Surrey et al 2002)

Analysis 01.02. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 02 Clinical pregnancy rate per woman

Review: Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis

Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

Outcome: 02 Clinical pregnancy rate per woman



NO RCT Surgery preIVF enhances PR, in contrast to natural fertilization.

Endometriomas and IVF

Cystectomy for endometriomas improves:

- natural PR
- pain symptoms
- cyst recurrence
- but do not affect IVF PR rates
- reduces ovarian reserve. This is a concern with low baseline ovarian reserve e.gAMH <10,bilateral endometriomas.

Larger endometriomas (>4cm?) →

- ↓ ovarian response
- ↓ oocyte per retrieval
- ↓ fertilization
- ↑ infection

patients need to be carefully counseled about mx options of endometriomas and IVF:

- cystectomy if pain, large size with good ovarian reserve
- drainage + GnRHa if large size and low AMH, bilateral
- move straight to IVF if small size

Effect of Endometriosis on Pregnancy

Endometriosis associated adverse pregnancy outcome.

Saraswat et al 2016 Cohort 14665 women (of which 5373 women with surgical diagnosed endometriosis were compared to those without endometriosis) over 30 years 1981-2010 found:

- increase MC RR 1.76
- increased EP RR 2.7
- placenta previa RR 2.24
- PPH RR 1.3
- PT birth RR 1.26

Table 2. Univariable and multivariable analysis for early pregnancy outcomes in women with and without endometriosis

Early pregnancy outcomes	Endometriosis *n* = 5375 (%)	No endometriosis *n* = 8280 (%)	Odds ratio (95% confidence interval)	*P*-value	Adjusted odds ratio* (95% confidence interval)	*P*-value
Miscarriage	662 (12.3)	450 (5.4)	2.44 (2.16, 2.77)	<0.001	1.76 (1.44, 2.15)	<0.001
Ectopic pregnancy	86 (1.6)	51 (0.6)	2.62 (1.85, 3.71)	<0.001	2.70 (1.09, 6.72)	0.03
Termination of pregnancy	395 (7.3)	1072 (12.9)	0.53 (0.47, 0.60)	<0.001	1.12 (0.74, 1.69)	0.59

*Adjusted for age, parity, socio-economic status and year of pregnancy.

Table 3. Univariable and multivariable analysis for pregnancy outcomes (>24 weeks' gestation) in women with and without endometriosis

Pregnancy outcomes (>24 weeks)	Endometriosis *n* = 4232 (%)	No endometriosis *n* = 6707 (%)	Odds ratio (95% confidence interval)	*P*-value	Adjusted odds ratio* (95% confidence interval)	*P*-value
Hypertensive disorders of pregnancy	350 (8.3)	452 (6.7)	1.25 (1.08, 1.44)	0.003	1.06 (0.91, 1.24)	0.57
Placenta praevia	72 (1.7)	54 (0.8)	2.13 (1.50, 3.04)	<0.001	2.24 (1.52, 3.31)	<0.001
Placental abruption	18 (0.4)	27 (0.4)	1.05 (0.59, 1.91)	0.85	0.91 (0.48, 1.74)	0.78
Unexplained APH	270 (6.4)	281 (4.2)	1.57 (1.33, 1.86)	<0.001	1.67 (1.39, 2.00)	<0.001
Postpartum haemorrhage	844 (19.9)	786 (11.7)	1.88 (1.69, 2.09)	<0.001	1.30 (1.61, 1.46)	<0.001
Mode of delivery						
Spontaneous	2108 (49.8)	4495 (67)	Reference		Reference	
Caesarean	1299 (30.7)	1281 (19.1)	2.16 (1.97, 2.38)	<0.001	1.40 (1.26, 1.55)	<0.001
Instrumental	822 (19.4)	928 (13.8)	1.89 (1.70, 2.10)	<0.001	1.21 (1.08, 1.36)	0.002
Preterm birth	321 (7.6)	388 (5.8)	1.33 (1.14, 1.55)	<0.001	1.26 (1.07, 1.49)	0.007
Low birthweight	285 (6.7)	409 (6.1)	1.11 (0.96, 1.30)	0.19	1.12 (0.94, 1.32)	0.21
Stillbirth	20 (0.5)	28 (0.4)	1.13 (0.64, 2.01)	0.67	0.89 (0.48, 1.66)	0.91
Neonatal death	3 (0.1%)	1 (0.01%)	4.75 (0.50, 45.75)	0.18	3.83 (0.36, 41.36)	0.27

*Adjusted for age, parity, socio-economic status and year of pregnancy.

from Saraswat el et 2016

Those pregnant with endometriosis were:

- Older
- More likely nulliparous
- Higher SES

Theorised Mechanism: defective remodeling of spiral arteries during placentation.

Endometriosis in Adolescents

Considered to be different and more aggressive than adult endometriosis
Pathogenesis relate to neonatal retrograde menstruation and implantation of "stem" cells that are activated with oestrogen leading to growth of highly angiogenic implants.
Principles of mx:

- Early diagnosis with laparoscopy (80% pts with CPP non responsive to conventional medical therapy have endometriosis). Often atypical appearance
- Surgery effective treatment for pain, reducing infertility and reducing disease progression.
- Minimise damage of the ovary with endometriomas
- Long term medical suppression until wanting fertility
- Consider ovarian cryopreservation in girls with significant endometriomas

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