

ENDOMETRIOSIS

Carolyn Oleo

Women's Health Specialist

Kyabirwa Surgical Center

15/Dec/2023

Outline

- Definition
- Common location(s) of endometriotic implants
- Etiology
- Phenotypes of endometriosis
- Natural course of endometriosis
- Epidemiology
- Clinical presentation
- Diagnosis
- Management

Definition

- Endometriosis is a chronic estrogen-dependent condition that is characterized by the development and presence of endometrial glands and stroma (inner lining of the uterus) in anatomical positions and organs outside of the uterine cavity.

Common locations of endometriotic implants

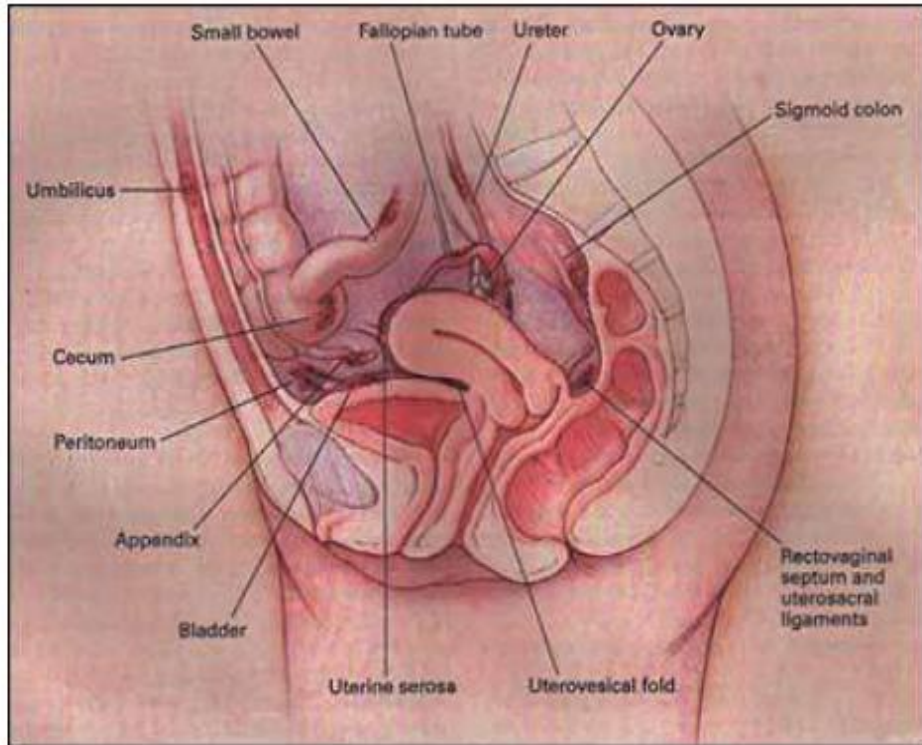


Figure 1

Common locations of endometriosis within the pelvis and abdomen. (Reprinted by permission from the New England Journal of Medicine 2001. Olive DL, Pritts EA. Treatment of Endometriosis. Vol. 345:267).

- Other sites / distant sites
 - Posterior broad ligaments
 - Pleura
 - Pericardium
 - CNS

Etiology of endometriosis

- Sampsons theory
 - Retrograde menstruation*
 - Factors that aid establishment of disease
 - Amount of endometrial debris, immunocompetency of the woman to clear the debris, molecular properties inherent in ectopic tissue
 - Molecular properties inherent in ectopic tissue
 - Must evade apoptosis, adhere to underlying peritoneum, degrade underlying extracellular matrix, generate a new vascular supply and evade immune surveillance.
- Chronic local inflammation
 - Increased levels of prostaglandins, chemokines, cytokines and TNF – enhance adhesion of endometriotic implants to peritoneal surfaces
 - Implantation aided by proteolytic membrane metalloproteinases
 - Angiogenesis and apoptosis are altered in favour of endometriotic implant
 - ROS – Perpetuate peritoneal damage and inflammation
- Estrogen
 - Increased levels of steroidogenic factor 1 (SF 1) – increases cyclo-oxygenase 2 (COX-2) activity – stimulates Prostaglandin E2 formation – upregulates aromatase activity.
 - Upregulation of estrogen receptors alpha and beta – lead to downregulation of progesterone receptors.

Etiology of endometriosis

- Meyers theory (Coelomic theory)
 - Parietal peritoneum epithelium differentiates into endometrial tissue.
 - Influenced by cytokines and growth factors of the endometrial stroma.**
- Halbans theory - Lymphatic and vascular metastasis
 - Endometriotic tissue can infiltrate the lymphatic and vascular system
 - This may facilitate transfer to distant organs
- Stem cell theory
 - Endometrial stem cells – responsible for the development and progression of the disease.
 - Endometrial progenitor cells identified in menstrual blood
 - Also identified as clonogenic cells in endometrial tissue
 - Aided by retrograde discarding of endometrial stem cells in the peritoneal cavity during neonate uterine bleeding or with menstruation.
- Mullerian remnant theory
 - Atypical migration or differentiation of mullerian remnants – imitate endometriotic tissue in the posterior pelvic floor***
- Epigenetic changes

Phenotypes of endometriosis

- Isolated superficial peritoneal endometriosis
 - Most common
 - Present in 80% of women suffering from this disease
 - Shallow lesions on the peritoneal surface
- Ovarian endometrioma
 - Cystic lesions stemming from the disease process of endometriosis.
 - Found on the ovaries
 - Frequency 17% to 44% of women with endometriosis
 - Bilateral in 50% of cases
 - Contain dark brown endometrial fluid (chocolate coloured)
- Deep infiltrating endometriosis
 - Endometrial tissue found > 5mm beneath the peritoneal surface.

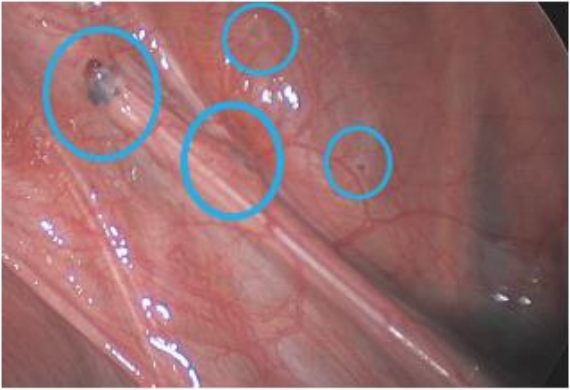
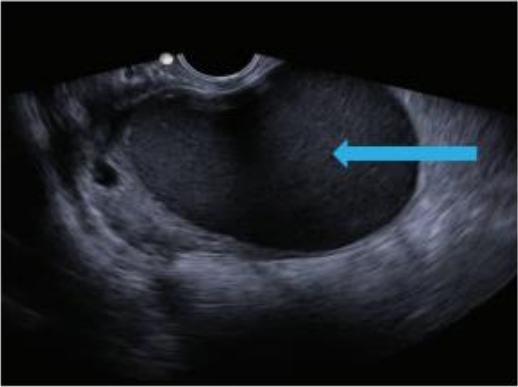
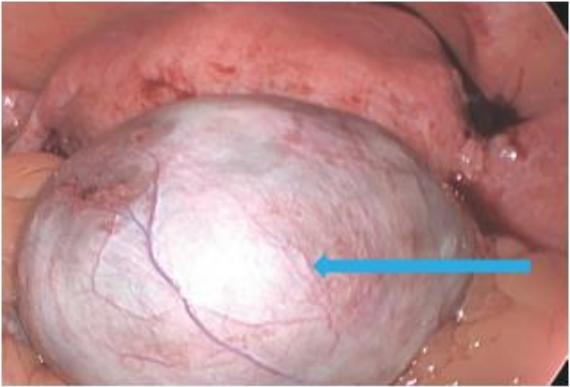


Endometriosis subtype	Transvaginal ultrasonography	Laparoscopy
Superficial peritoneal endometriosis	Not visible on imaging	
Ovarian endometrioma		
Deep endometriosis of sigmoid colon		

Figure 1: Imaging and laparoscopic appearance of endometriosis subtypes.

Natural course of endometriosis

- Difficult due to the need for repeat laparoscopy
- 2 prospective studies – repeat laparoscopy was done after 6-12 months in women who received placebo treatments
 - Lesions resolved spontaneously in a third of participants
 - Lesions worsened in nearly half of participants
 - Lesions remained unchanged in the remainder of participants

Epidemiology

- Demographics
 - Age at presentation 12 – 80yrs (average 28-years)
 - More common in Caucasians, than in African Americans and Asians
 - Taller women with a lower BMI more likely to suffer from the disease
 - Genetic factors – 51% of the risk
- Risk factors
 - Nulliparity, Early menarche, Frequent or prolonged menses
- Protective factors
 - Pregnancy, menopausal status, multiparity, periods of lactation, contraceptive use

Epidemiology continued

- Prevalence (worldwide)
 - Reproductive age women 2% - 50%
 - Women with infertility 20% - 50%
 - Chronic pelvic pain 71% - 80%
 - Menopausal women 2% - 4%
 - Men – rare (20 cases reported in literature)
- Prevalence Africa
 - Unknown
 - South African study - < 2%
 - Nigerian study – among women undergoing laparoscopy 48%
 - Nigerian study – Pathology specimens 0.9%

Clinical presentation

- Pain
 - Cyclic or chronic in nature
 - Dysmenorrhoea (Prevalence 80%)
 - Dyspareunia (Prevalence 30%)
 - Dysuria, dyschezia – associated with bladder or bowel involvement
 - Musculoskeletal – flanks, thighs, lower back
- Infertility
 - Mechanical obstruction b/w ovary and fallopian tubes
 - Reduced functional ovarian tissue after surgery
 - Altered folliculogenesis, decreased spermatozoal integrity, embryo fragmentation, impaired tubal function and decreased endometrial receptivity.
 - Altered cellular immunity and altered hormonal profile
- Other symptoms
 - Abnormal menstrual bleeding
 - Diarrhea, constipation,
 - Chronic fatigue

Impact of endometriosis on quality of life

- Negatively affects the quality of life
- Difficulties in managing the pain
- Hinders social, emotional and sexual wellbeing
- Affects efficacy and productivity at work
- Lower physical activity
- Those affected have higher stress levels
- Worse quality of sleep
- Depression, low self esteem

Physical exam findings

- Systematic vaginal and rectal exam should be performed since much of the dz – in the dependent parts of the pelvis
 - Palpable tender nodules – uterosacral ligaments, rectovaginal septum, cul-de-sac (just before menses)
 - Tenderness or induration in the vicinity of non-palpable lesions
 - Uterine or adnexal fixation or a tender adnexal mass

Table 1: Differential diagnosis of the most common symptoms of endometriosis

Differential diagnosis	Description
Dysmenorrhea	
Primary dysmenorrhea	Short-lasting (< 72 h), responsive to nonsteroidal anti-inflammatory drugs
Adenomyosis	Heavy menstrual bleeding, boggy tender uterus
Uterine fibroids	Heavy or intermenstrual bleeding, pressure symptoms, bulky uterus
Cervical stenosis	Decreased flow or amenorrhea, history of surgery on cervix
Obstructive lesions of the genital tract	Amenorrhea with cyclical pain, visible bulge at introitus
Deep dyspareunia	
Pelvic masses	Pelvic pressure, enlarged uterus or adnexae
Myofascial pain	Constant, worse with activity, tender pelvic floor muscles
Cervicitis	Abnormal discharge, postcoital spotting, localized tenderness to palpation, erythema of cervix
Painful bladder syndrome	Urinary symptoms (urgency, frequency, nocturia) with normal urinalysis, pain at bladder base on vaginal exam
Chronic pelvic pain	
Irritable bowel syndrome	Alteration of bowel habits with abdominal pain or bloating
Painful bladder syndrome	Urinary symptoms (urgency, frequency, nocturia) with normal urinalysis, pain at bladder base on vaginal exam
Myofascial pain	Constant, worse with activity, tender pelvic floor muscles
Pelvic inflammatory disease	Abnormal vaginal discharge, fever, irregular bleeding
Pelvic adhesions	Ovulatory pain, history of pelvic inflammatory disease or extensive abdominal surgeries
Neuropathy	Burning, searing pain in dermatomal distribution, localized allodynia
Pelvic venous disorders	Pelvic heaviness, worse with standing, better supine, postcoital ache

Diagnosis of endometriosis

- Transvaginal ultrasound scan
- Magnetic resonance imaging
- Laparoscopy
- Note: Ca 125 – not considered useful in establishing the diagnosis of endometriosis
- Diagnosis is delayed by 4-11years

#Enzian

(Classification of Endometriosis)

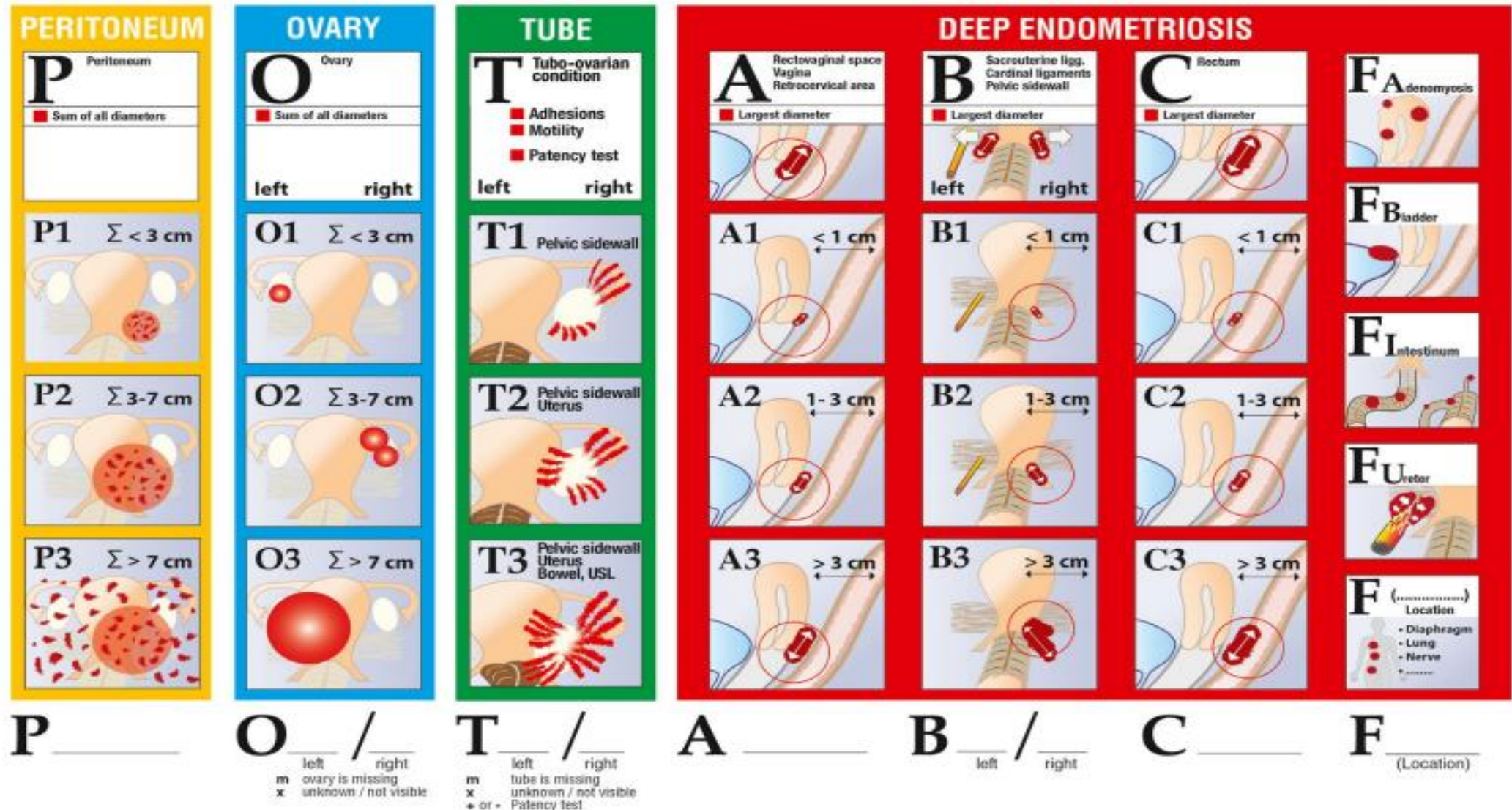


FIGURE 1 #Enzian classification: overview with potentially affected organs and compartments (<https://www.endometriose-sef.de/aktivitaeten/klassifikation-enzian/>)

Management of endometriosis

- Multi-disciplinary team
 - Endometriosis surgeon – Gynecologist
 - Colorectal surgeon
 - Urologist
 - Radiologist experienced in endometriosis
 - Physical therapist / pelvic floor specialist
 - Pain management doctor
 - Psychologist / psychiatrist
 - Nutritionist
 - Pathologist
 - Family/social support

Treatment of endometriosis

- Goals/indications of treatment
 - Pain reduction
 - Fertility treatment
 - Evaluation and or treatment of a pelvic mass
- Characteristics of treatments used for endometriosis
 - Safely used long term
 - May aim to cause amenorrhoea

Treatment of endometriosis associated Pain

- Types of drugs used for treatment of endometriosis
 - Hormonal treatment – oral contraceptives, progestins, danazol, gestrinone, medroxyprogesterone acetate, and GnRH agonists
 - Aromatase inhibitors
 - Non –steroidal inflammatory drugs
- Mechanism of action - suppress endometriotic lesion proliferation
 - Hypoestrogenic state – GnRH agonists
 - Hyperandrogenic state – danazol, gestrinone
 - Hyperprogestogenic state – oral contraceptives, medroxyprogesterone acetate

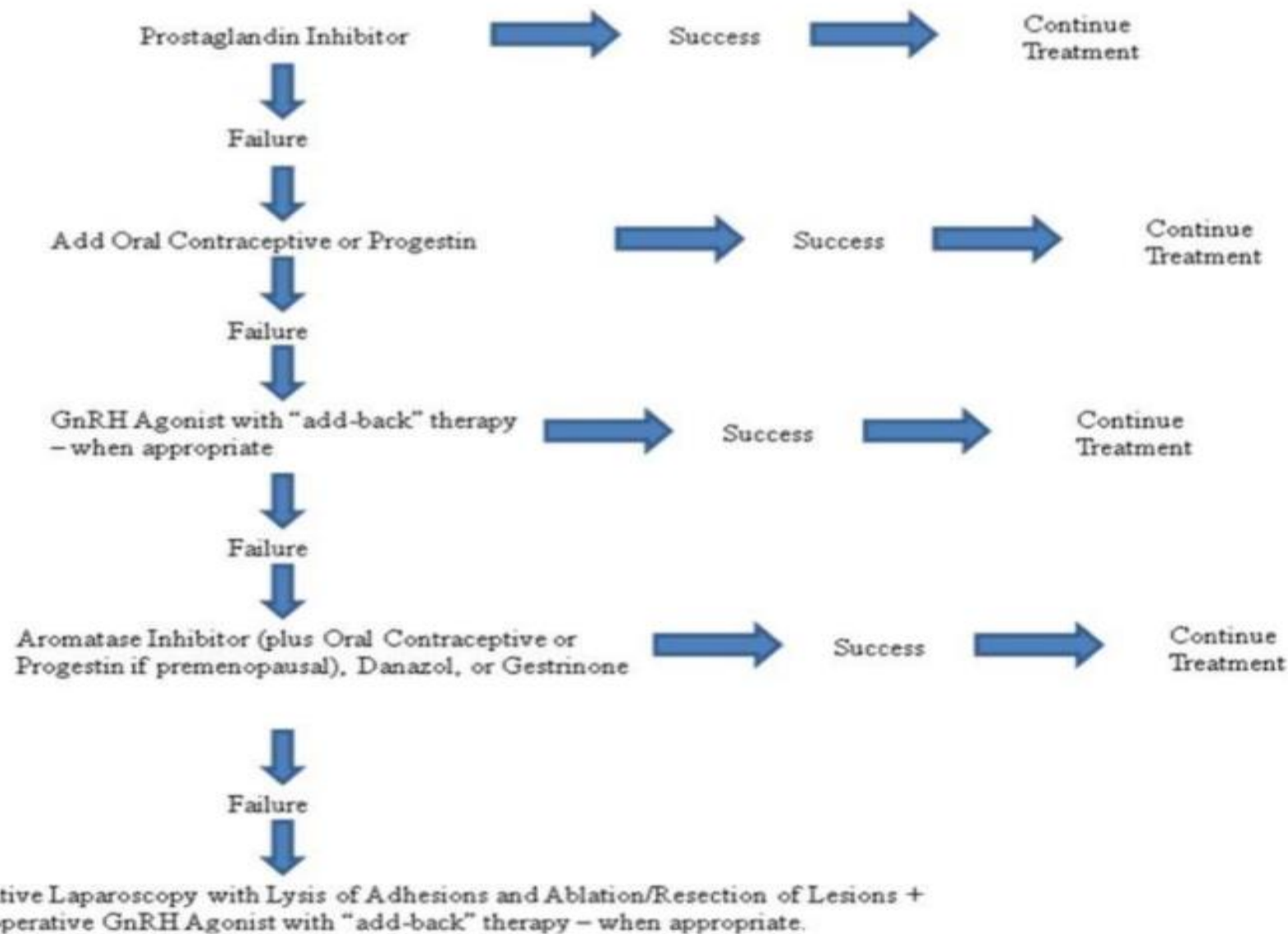


Figure 6 Treatment algorithm for pain associated with endometriosis

Table 2: Hormonal therapies for endometriosis			
Medication	Dosage	Adverse effects and special considerations	Relative cost
First-line therapies			
Combined hormonal contraceptives (continuous regimens)		<ul style="list-style-type: none"> Nausea, spotting, headache, mood changes, breast discomfort 	
Monophasic pill	1 oral tablet, daily; skip placebo pill		Low
Vaginal ring	1 ring, every 3 wk		Low
Transdermal patch	1 patch, weekly		Low
Progestins		<ul style="list-style-type: none"> Acne, spotting, mood changes, headache, weight gain, breast discomfort 	
Norethindrone	0.35 mg, 1–3 oral tablets, daily		Low
Norethindrone acetate	5 mg, 0.5–3 oral tablets, daily		Moderate
Dienogest	2 mg, oral, daily		Moderate
Medroxyprogesterone acetate	Depot: 150 mg, intramuscular, every 6–8 wk Oral: 10–20 mg/d		Low
Progestin subdermal implant	Etonorgestrel 68 mg, implant, every 3 yr		Low
Levonorgestrel intrauterine system	52 mg released over 5 yr or 19.5 mg released over 5 yr	<ul style="list-style-type: none"> Spotting, headaches, breast discomfort, functional ovarian cysts May need to be replaced sooner for pain control May not suppress ovulation pain reliably 	Low (amortized over 5 years)
Second-line therapies			
GnRH agonists		<ul style="list-style-type: none"> Hot flushes, headache, depression, decreased BMD and vaginal dryness Adverse effects minimized with add-back hormone replacement therapy 	
Leuprolide acetate	3.75 mg intramuscular, once monthly 11.25 mg intramuscular, every 3 mo		High
Nafarelin acetate	1 nasal spray (200 µg) 2 times/d		High
Goserelin acetate	3.6 mg intramuscular, every mo		High
Triptorelin	3.75 mg intramuscular, every mo		High
GnRH antagonists		<ul style="list-style-type: none"> Hot flushes, headache, depression, decreased BMD and vaginal dryness Adverse effects minimized with add-back hormone replacement therapy 	
Elagolix	150 mg, oral, daily 200 mg, oral, 2 times/d		High
Aromatase inhibitors		<ul style="list-style-type: none"> Hot flushes, decrease BMD and headaches Used in combination with other medication 	
Letrozole	2.5 mg, oral, daily		Moderate
Anastrozole	1 mg, oral, daily		Moderate
Note: BMD = bone mineral density, GnRH = gonadotropin-releasing hormone.			

Treatment of endometriosis associated Pain

- Indications for surgery
 - Lack of measurable pain relief with medical treatment
 - Severe pain over several months
 - Pain requiring systemic therapy, or admission to hospital
 - Pain requiring days off work or school
- Surgery
 - Laparoscopy preferred
 - Ablation
 - Resection
 - Presacral neurectomy

Treatment of endometriosis associated infertility

- In the absence of pain
 - Expectant management
 - Surgery (laparoscopy)
 - IVF

Prognosis after surgery

- Reoperation rates after initial surgery
 - 21% after 2yrs
 - 47% after 5yrs
 - 51% after 7yrs
 - Younger age was the highest predictor for reoperation

Tips for the general practitioner

- Suspecting endometriosis
 - Pain before or during menstruation
 - Poor response to NSAIDs or COCs
 - Days off school or work
 - Dyspareunia
- Initial investigations
 - Transvaginal ultrasound scan
- Refer patient with suspected endometriosis, if
 - Failed treatment of primary dysmenorrhea with NSAIDs or COCs.
 - Severe pain requiring systemic medication, days off work or school
 - Recurrence of symptoms in patients previously treated for endometriosis
 - Delayed fertility in association with endometriosis

Challenges on management of endometriosis in Africa

- Prevalence is underestimated
- Diagnostic delays among women with endometriosis symptoms
 - Lack of education about symptoms
 - Lack of trained specialists
 - Taboos on issues regarding menstruation
- Lack of development of suitable treatments – limited research in local populations
- Societal barriers

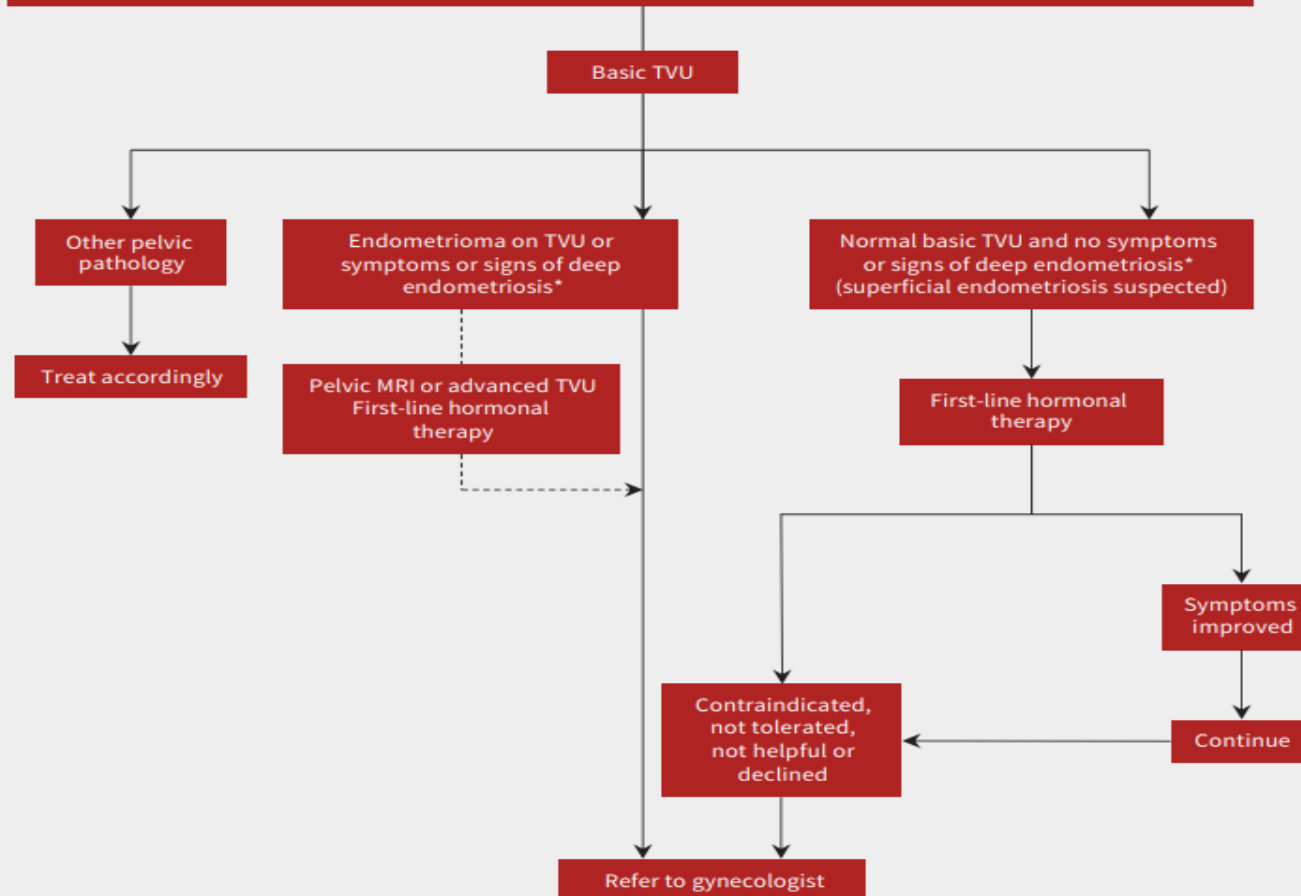


Figure 2: Diagnosis and first-line management of endometriosis. Note: BMI = body mass index, MRI = magnetic resonance imaging, SOB = shortness of breath, TVU = transvaginal ultrasonography. *Suspect deep endometriosis.



Fig 2 | Laparoscopy of an enlarged ovary containing an endometriotic cyst leaking “chocolate” fluid (arrow)
(reproduced with permission from Professor Peter Braude)