Endometriosis & Adenomyosis

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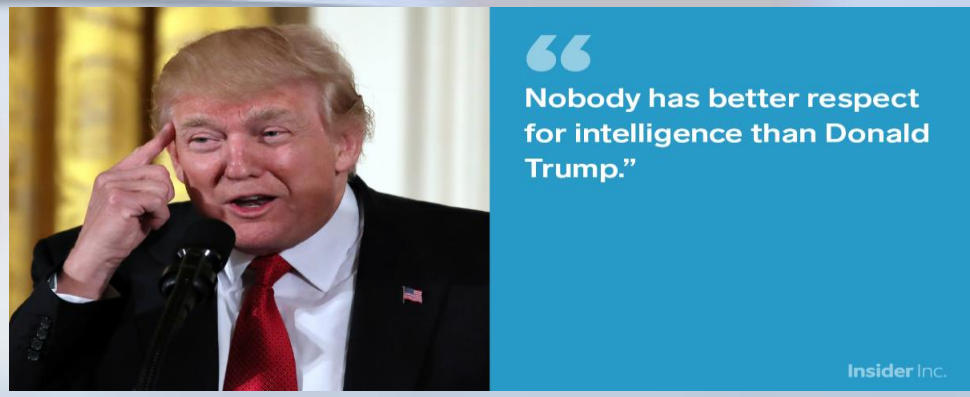
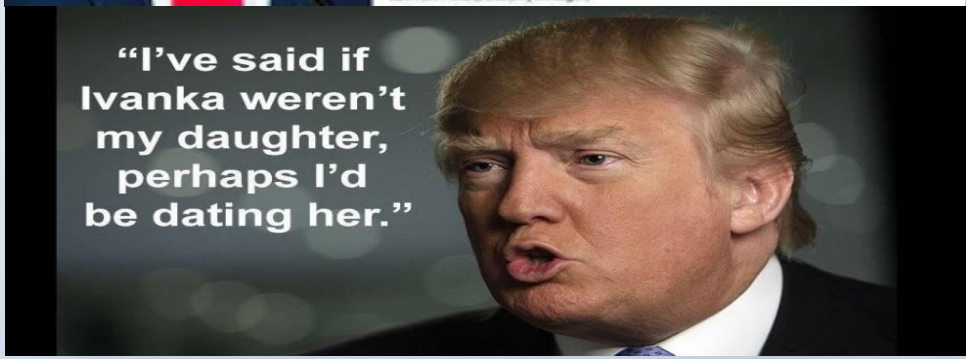
Endometriosis

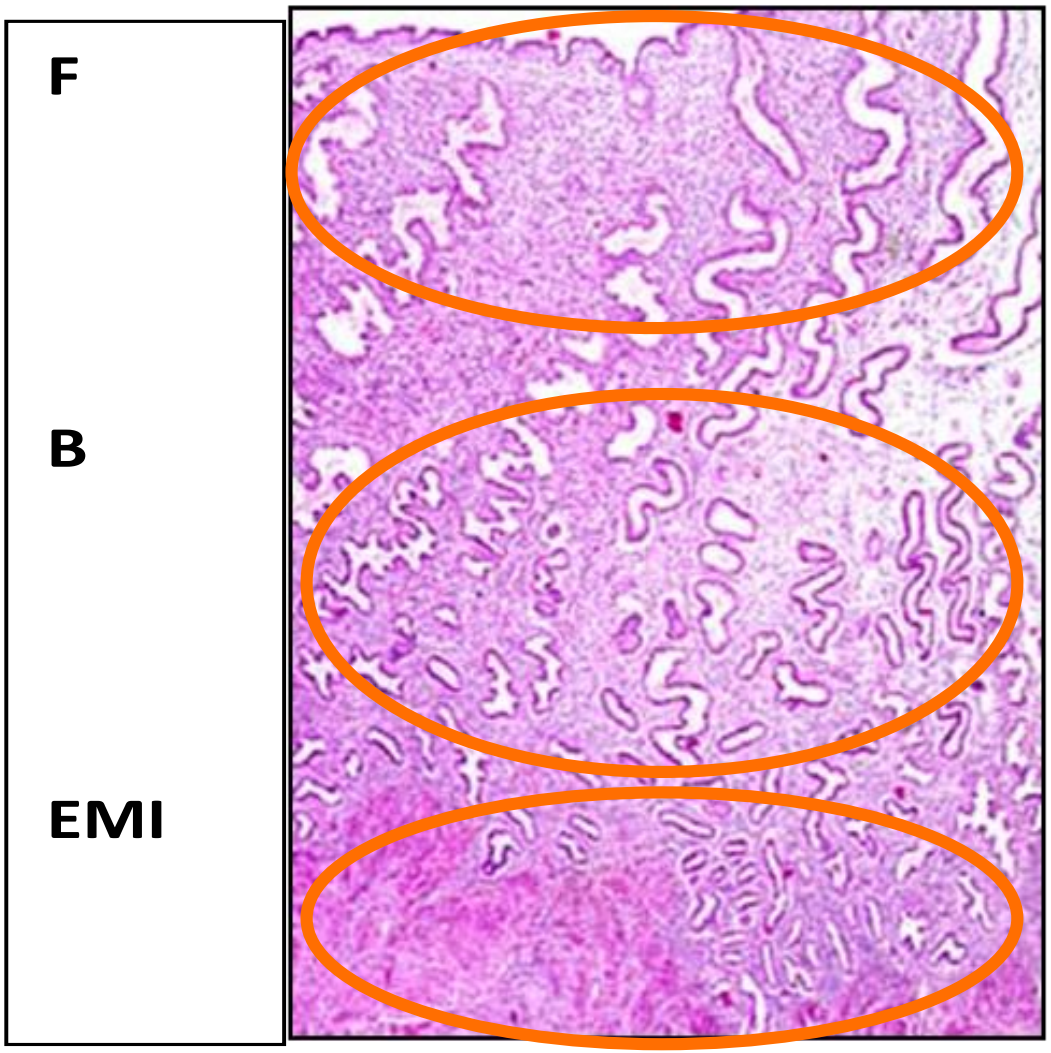
- Enigmatic
- Unpredictable
- Makes people sick





Endometriosis

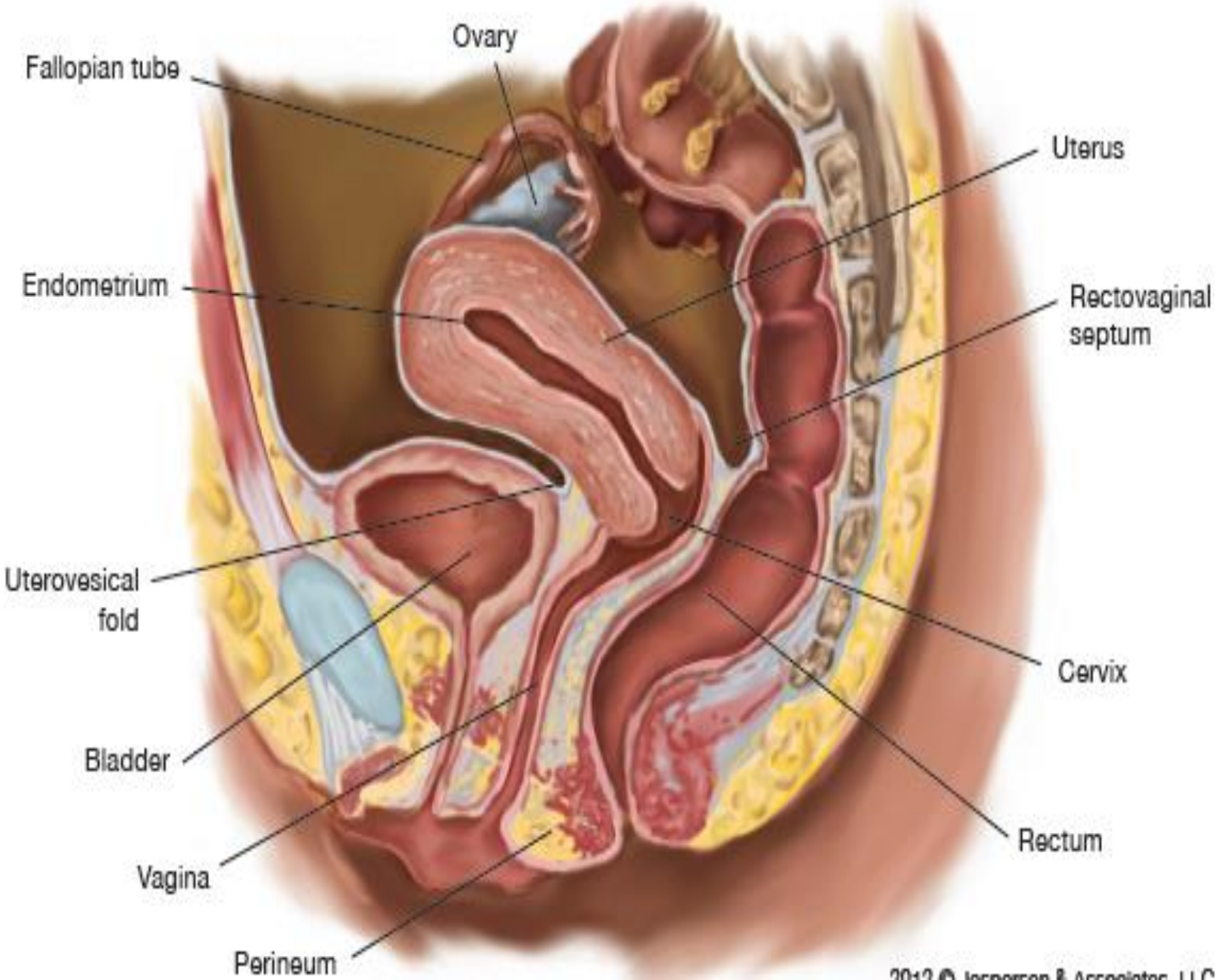
The normal endometrium

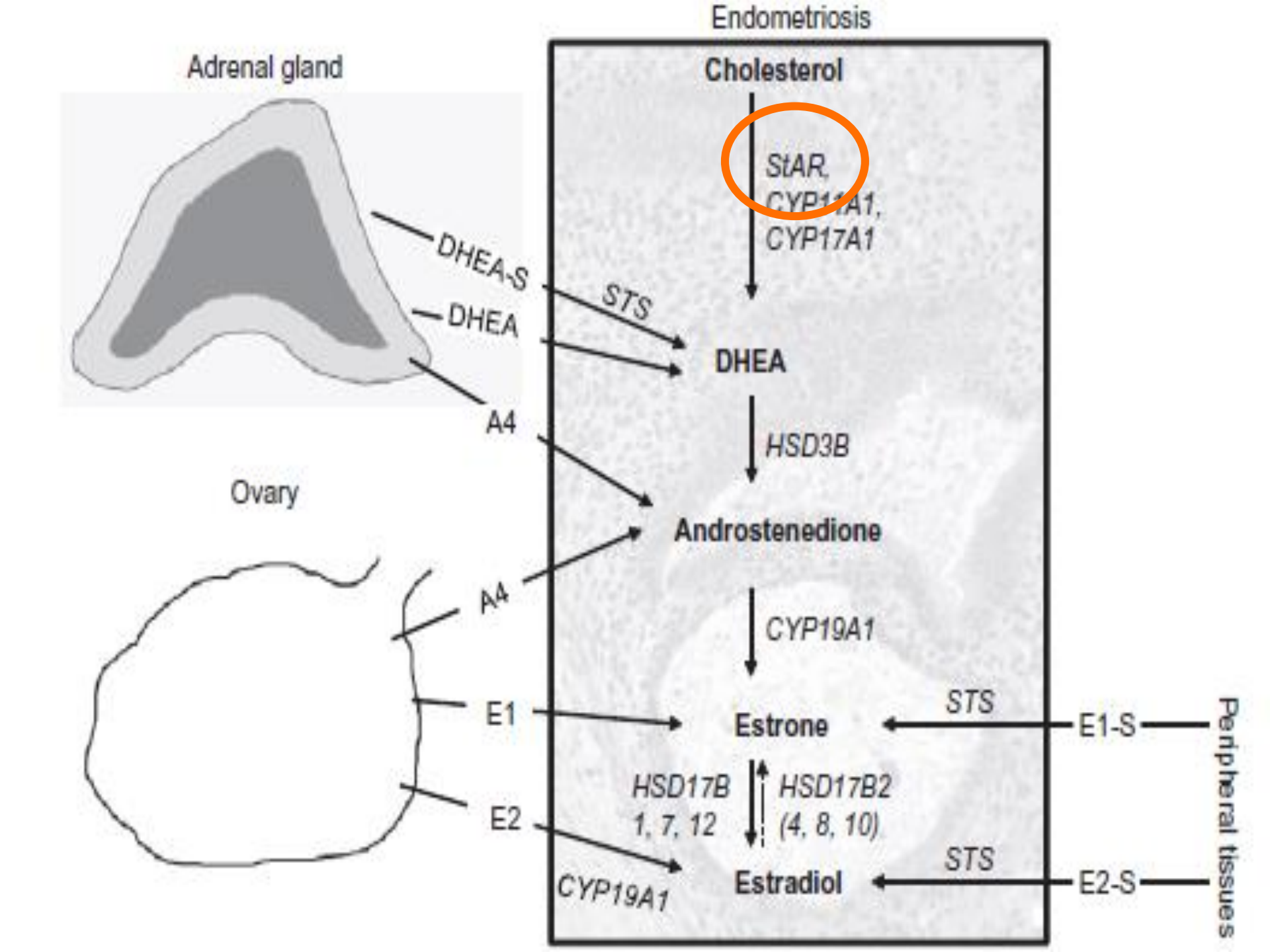


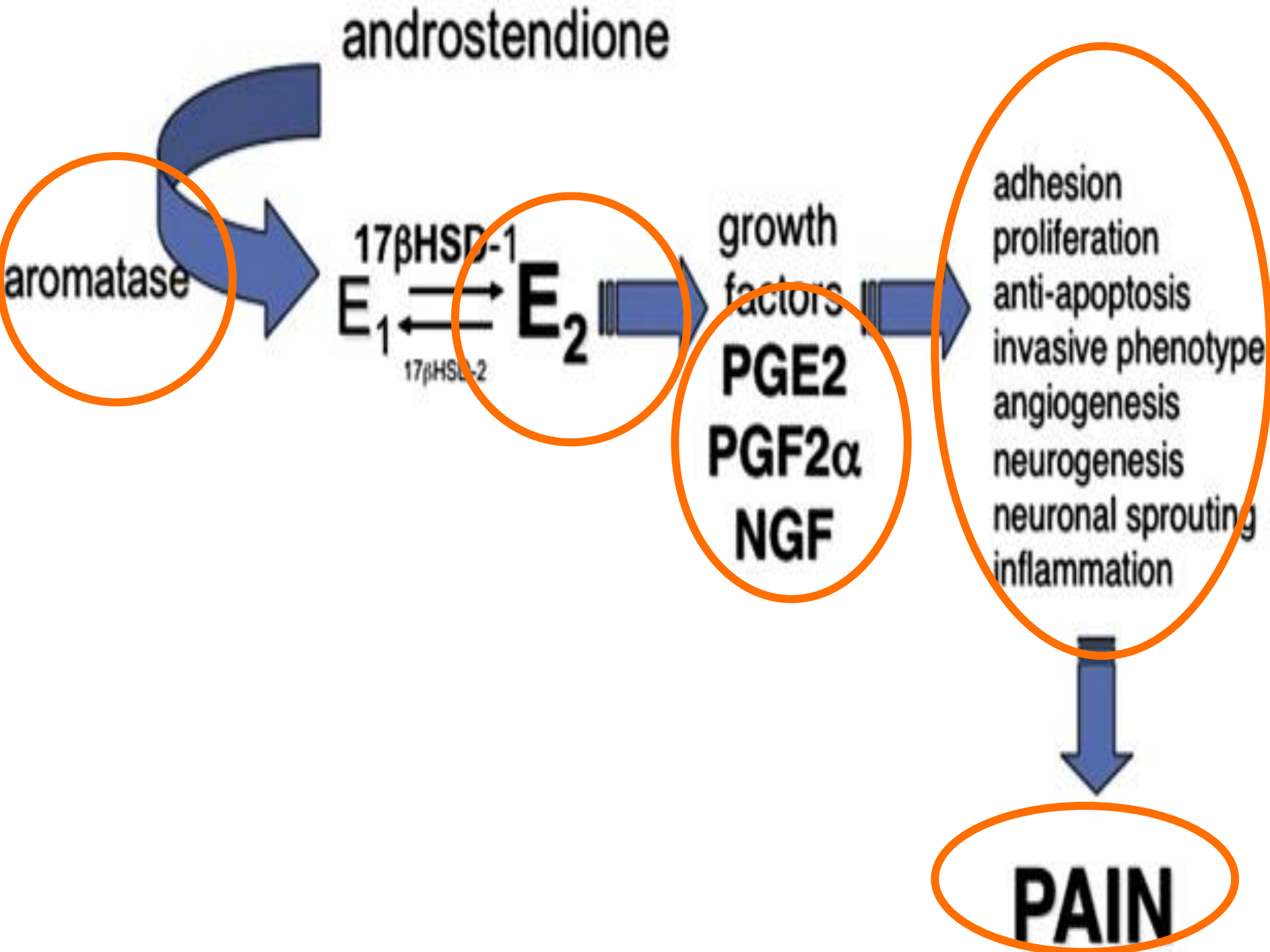
Functional layer

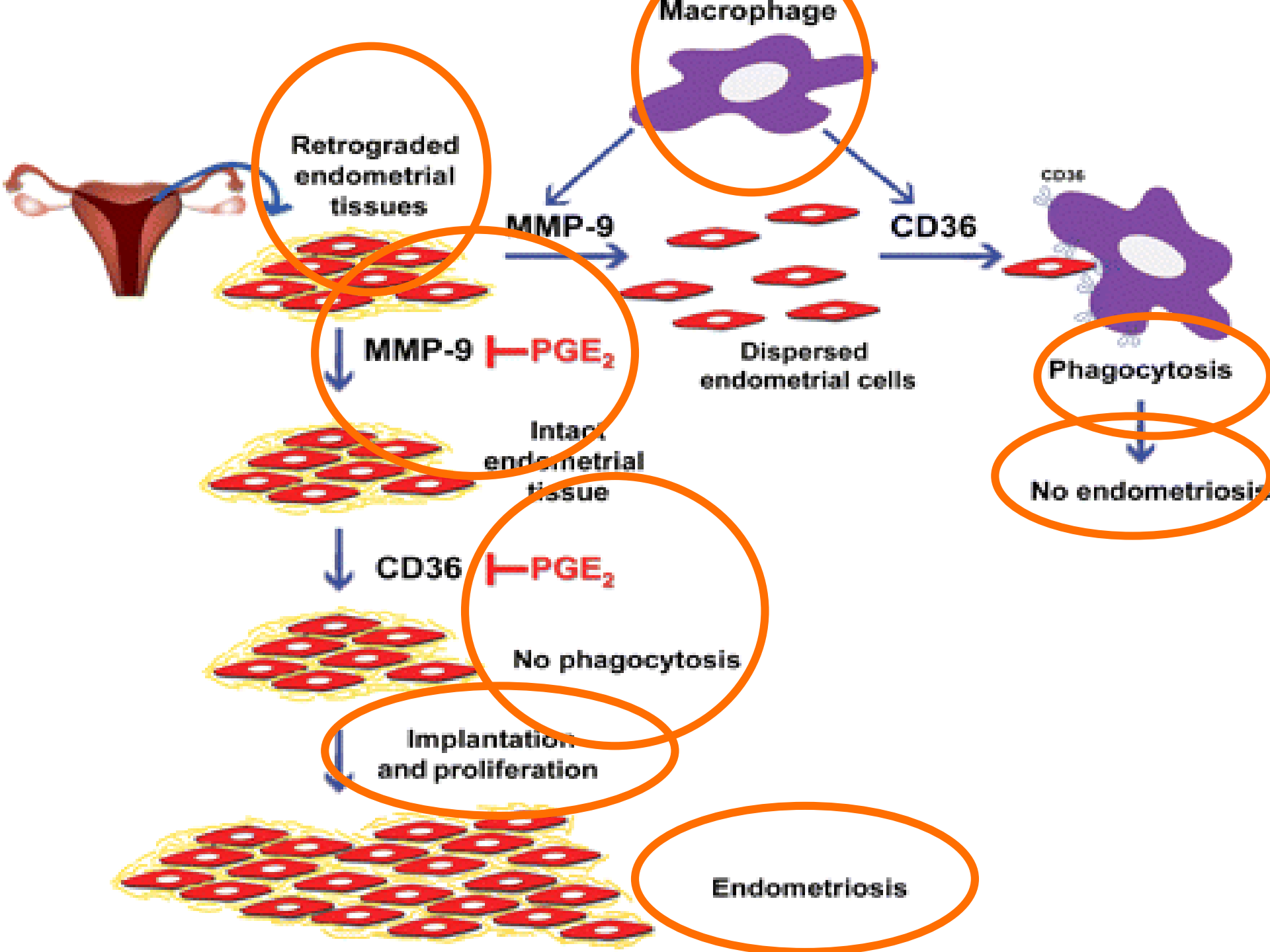
Basal layer

Endometrial myometrial interface


Fallopian tube
Ovary
Uterus
Endometrium
Rectovaginal septum
Uterovesical fold
Cervix
Bladder
Rectum
Vagina
Perineum

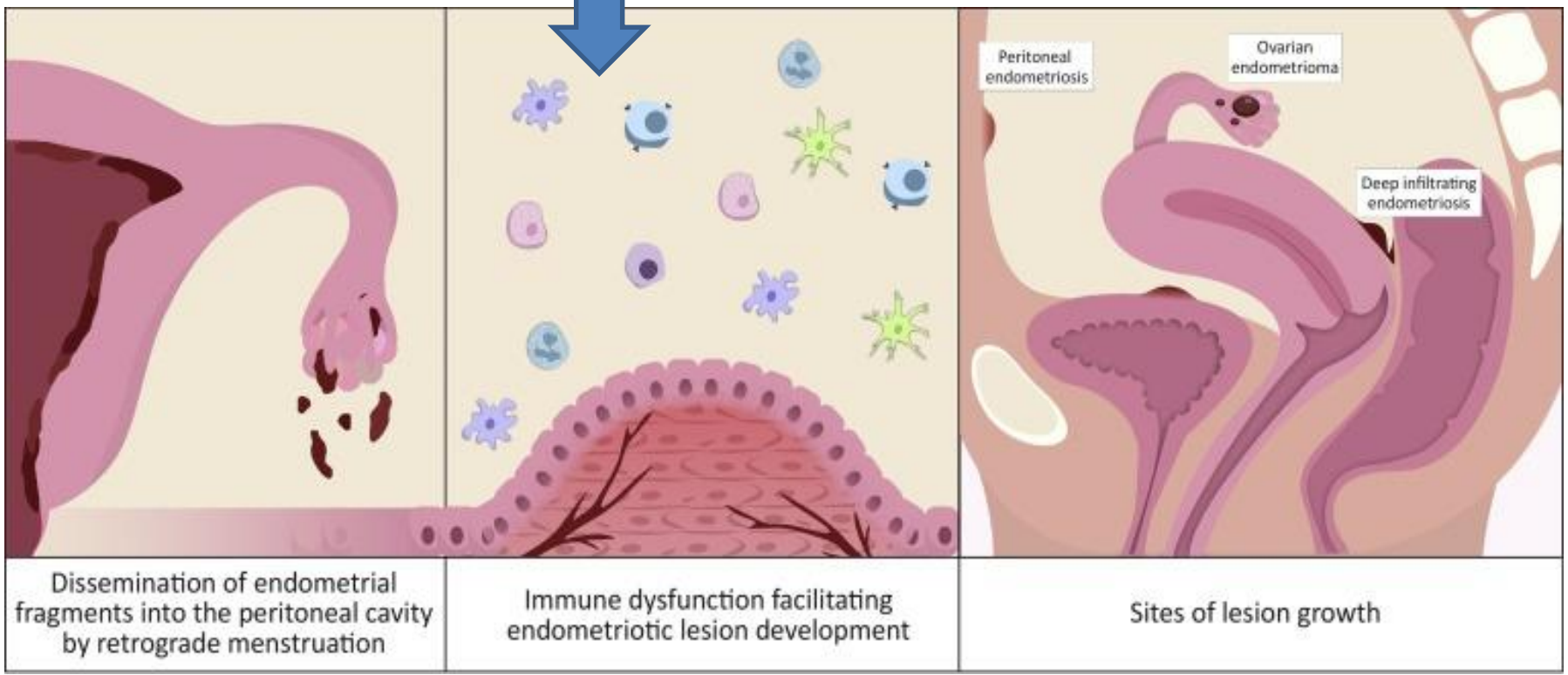

Endometriosis
Adrenal gland
Cholesterol
StAR,
CYP17A1
DHEA-S
DHEA
STS
DHEA
A4
HSD3B
Ovary
Androstenedione
A4
CYP19A1
E1
STS
Estrone
E1-S
HSD17B
1, 7, 12
HSD17B2
(4, 8, 10)
E2
STS
CYP19A1
Estradiol
E2-S
Peripheral tissues


androstendione
aromatase
17βHSD-1
E1
E2
17βHSD-2
growth
factors
PGE2
PGF2α
NGF
adhesion
proliferation
anti-apoptosis
invasive phenotype
angiogenesis
neurogenesis
neuronal sprouting
inflammation
PAIN


Macrophage
Retrograded endometrial tissues
MMP-9
CD36
CD36
MMP-9
PGE2
Dispersed endometrial cells
Phagocytosis
No endometriosis
Intact endometrial tissue
CD36
PGE2
No phagocytosis
Implantation and proliferation
Endometriosis

Sites for common endometriosis ectopic lesions

- Cell populations of the innate immune system that are predominantly implicated in endometriosis pathophysiology include neutrophils , macrophages, natural killer (NK) cells , and dendritic cells (DCs)



Endometriosis

- Endometriosis is a common problem of women of reproductive age, which may result in pelvic pain, infertility and menstrual dysfunction.
- Caucasians appear to be more likely to suffer from endometriosis than African Americans or Asians.
- Among Arabs: 2.5% in Jordan and 1.5% in UAE (Al-Jefout 2016,2018)
- Generally only seen in women of reproductive age –around 10%
- < 5% postmenopausal
- Found in 50% if complaint of pelvic pain
- Found in 30% of women with infertility
- The most common place to find implants is in the peritoneal cavity (involving the ovary, cul-de-sac, uterosacral, broad and round ligaments, fallopian tubes, colon, and appendix), but endometriosis lesions have occasionally been found in the pleural cavity, liver, kidney, gluteal muscles, bladder, abdominal scars, and even in men

Risk and protective factors

- Risk factors for this disease include:
  - nulliparity,
  - early menarche,
  - and frequent or prolonged menses.
- Protective factors include:
  - pregnancy,
  - menopausal status,
  - multiparity,
  - and periods of lactation

Distinctiveness of Adolescent Endometriosis

Time of diagnosis	8-10 years after the onset of symptoms
Risk factors specific for Adolescent Variant	Positive family history
	Early Menarche
	Short menstrual cycle length
	Lean body size
	Neonatal Uterine Bleeding
	Low Birth Weight
	Obstructive type Műllerian anomalies
Lifestyle	Intense physical activities
	Passive smoking
Recurrence	Higher as affected by the age of the patient at time of manifestation of the disease
Presentation during Laparoscopy	atypical, reddish, clear/polypoid or even vesicular lesions (common)
Infertility	Difficult to apply this parameter at this age
Progression	Not fully proven- Potentially higher

Theories

- Classically, three theories exist to explain the etiology of endometriosis;
  - Sampson's theory: women shed endometrial debris through their fallopian tubes into the peritoneum during menstruation
  - Meyer's theory: metaplasia of the coelomic epithelium is the origin of endometriosis
  - Halban's theory: distant lesions are established by the hematogenous or lymphogenous spread of viable endometrial cells.
  - Genetic Factors
  - Immune Factors
  - Environmental factors; Dioxin
  - Combination of the Above

Types of endometriosis

Peritoneal endometriosis

Superficial
Most common.
Associated with hemosiderin deposits.

Deep endometriosis

The presence of endometriotic lesions penetrating more than 5 mm under the peritoneal surface. Its exact incidence is unknown as it is not always symptomatic, but it has been estimated to affect 20–35% of women with endometriosis

Ovarian endometriosis

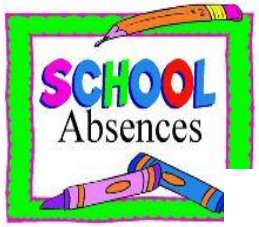
1- Superficial Haemorrhagic lesions
2-Haemorrhagic Cysts (**endometriomas**)
3- DI Ovarian Endometriosis
Usually indicates Deep endometriosis

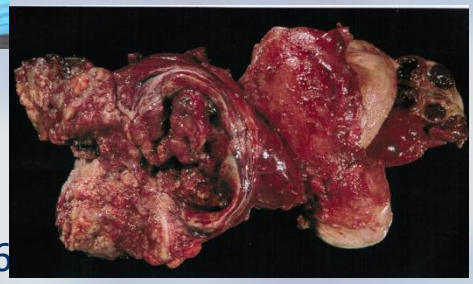
Clinical presentations

- Pain: dysmenorrhea (3 days before menses), deep dyspareunia (may indicate deep endometriosis), dyschezia, and dysuria (less common may indicate bowel and bladder endometriosis).
- Infertility (30–50%): due to anatomic distortion due to adhesions and blocked tubes, inflammation and a locally altered hormonal profile.
- Bloating
- Heavy menstrual bleeding (10–20%)
- Premenstrual spotting lasting 1–2 days (common)
- Cold intolerance: week evidence (Al-Jefout, 2018)

Via Dolorosa
"Path of Pain"

Menarche	Adolescence	Young adults life (18-21)	Adult life (21-35)	Adult life (35-50)	Menopause Premature POF!!
Dysmenorrhea 2-3 GPs- Medical treatment	1-2 Gynecologists First diagnostic laparoscopy	Endometrioma, Second Laparoscopy cystectomy	Recurrence +/- infertility Third laparoscopy IVF	Recurrence of pain Fourth surgery Long term medical Rx	TAH





Endometriosis still an enigmatic disease

Fifty percent of women with endometriosis may be asymptomatic.

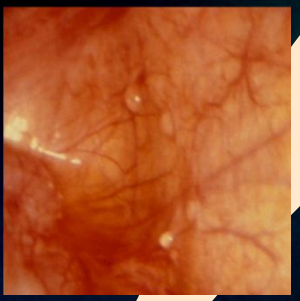
No clear relationship exists between the stage of the disease and a woman's symptoms.

The three endometriosis phenotypes has three different origins.

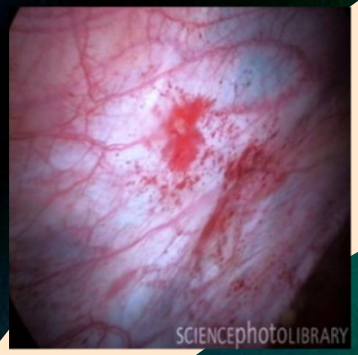
Progressiveness?? What is the case with symptomatic ???

Is endometriosis a progressive or non-progressive disease????

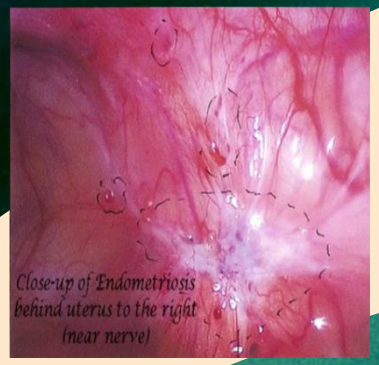
Main age 21 years

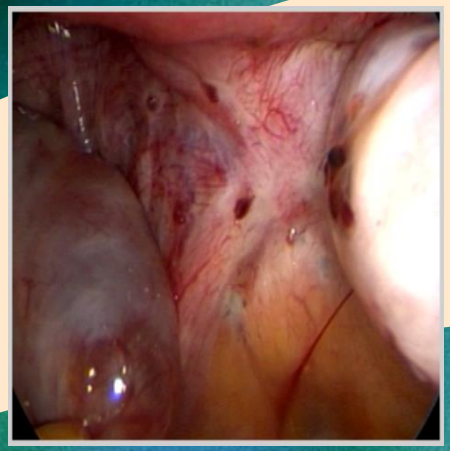


Main age 26 years



Main age 28 years





Main age 32 years

Endometriosis as a progressive disease
Disease will progress in 23–64% of women without therapy and in approximately 20% of women with therapy .
(Kauppila, 1993; Farquhar /Sutton, 1998, Redwine, 1987).

Natural course of endometriosis between first- and second-look laparoscopy in untreated patients. Data from published randomized controlled trials.

Source, year	Number of patients	Regression	No change	Progression
Thomas and Cooke, 1987	17	9	0	8
Telimaa *et al.*, 1987	12	1	8	3
Mahmood and Templeton, 1990	11	3	1	7
Overton *et al.*, 1994	15	8	3	4
Sutton *et al.*, 1994	24	7	10	7
Harrison and Barry-Kinsella, 2000	43	27	12	4
Abbott *et al.*, 2004	18	4	6	8
Total	140	**59 (42%)**	**40 (29%)**	**41 (29%)**

J.L.H. Evers, *Hum Reprod* 2013;**28**:2023.

Negatively influencing general physical, social and mental wellbeing during their most productive years.

(Kennedy S, 2005)

Endometriosis

More than 40% had tried three or more different medicines and had three or more surgical procedures

(Sinaii N, 2007)

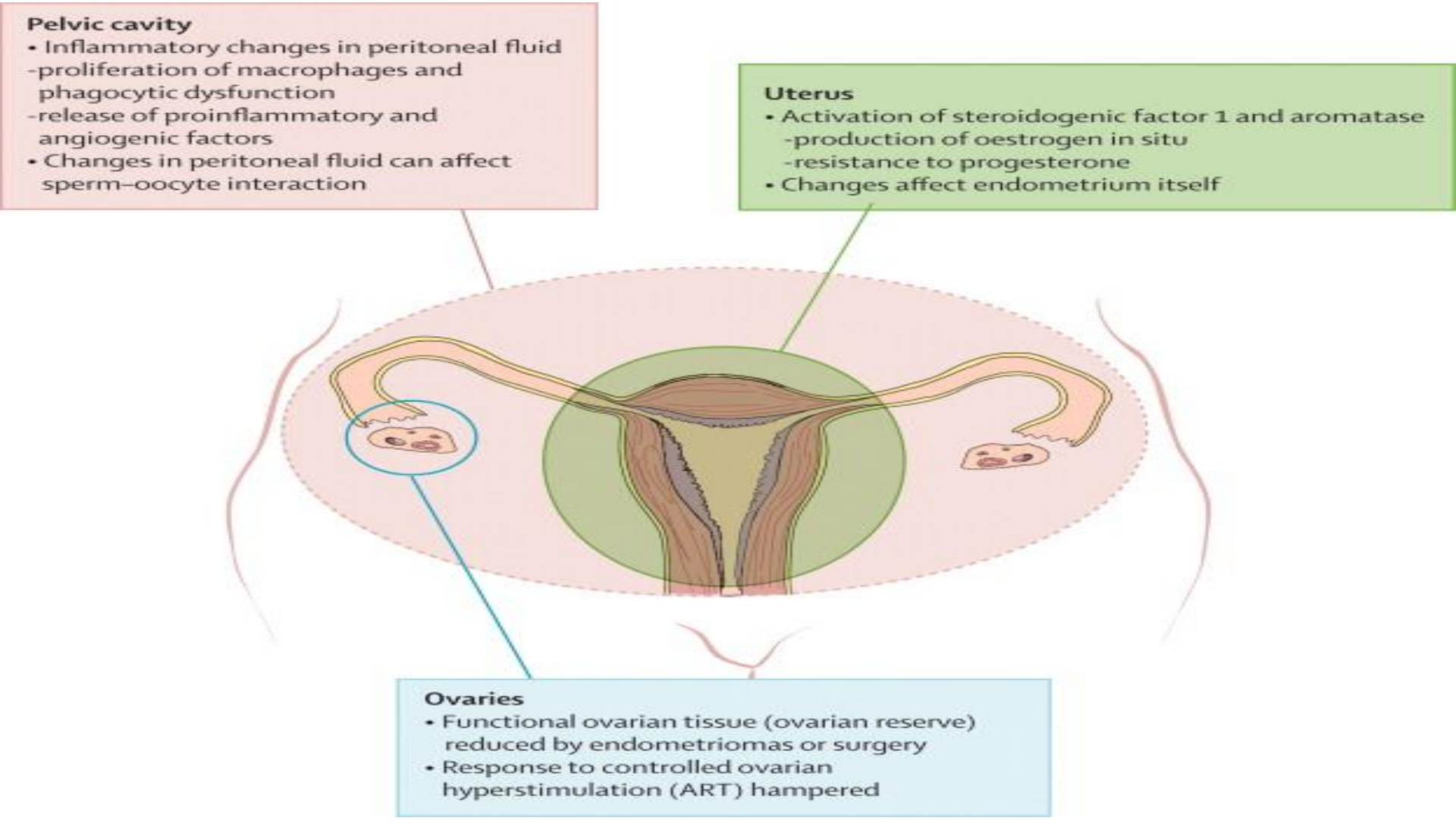
6-58% of infertile women have endometriosis
30-50% of women with endometriosis are infertile
(twice the rate of the general population)

Up to 22% of women have no symptoms
30-50% of women with this disease have had miscarriages

Between 1965-1984 ~2 million US women between ages 25-54 diagnosed received a hysterectomy

8 fold increase in first degree relatives

Mechanisms by which endometriosis could affect fertility



Prevalence Of endometrioma

Approximately one third of women with endometriosis have ovarian endometrioma
(Vercellini P, 2008; Jenkins S, 1986)

Ovarian endometriomas account for 35% of benign ovarian cysts and are associated with organic type pain, such as chronic pelvic pain and dyspareunia and it is frequently associated with adhesions
(G.B. Melis, 1994, Vercellini P, 1994)

Endometriomas are more frequently located in the left hemipelvis and left ovary. (H Al-Fozan, 2003)

It is estimated that 20–40% of women who undergo reproductive technology (ART) have endometriosis

Cancer risk in endometriosis

- Endometriosis has been associated with an increased risk of several cancers, most notably endometrioid and clear cell ovarian cancer, breast cancer, non-Hodgkin's lymphoma, and melanoma

  (A. Kokcu, 2011)

- Ovarian cancer develops in 1–5% of cases with ovarian endometriosis and in a lower percentage of cases with endometriosis outside the ovary.
- Ovarian endometrioid adenocarcinoma and clear cell carcinoma (10–20% and <5%, respectively) are the commonest types

  (C.M. Nagle, 2008)

- Cervical cancer incidence appears reduced in women with endometriosis, while no significant differences have been reported for the incidence of endometrial cancer (A. Kokcu, 2011)

Association of OEM with ovarian CA

Epidemiological studies suggest that OEM is associated with ovarian cancer (0.7%).
(E. Somigliana, 2006)

There is one extra ovarian cancer for every 10.000 women with endometriosis and this woman is likely to be close to menopause, with a large endometrioma in excess of 9 cm diameter.

Vercellini puts it like this:

'...in the worst scenario, the lifetime probability of developingovarian cancer increases from 1/100 to 2/100. In other words, a woman with untreated endometriosis has a 98 per cent probability, instead of 99 per cent, of not developing an ovarian malignancy'.

Endometriosis is an endometrial disease

(Al-Jefout et al, 2009)

The eutopic endometrium

Increasing evidence suggests that endometriosis is a disease originating from abnormalities of endometrial function and structure

Multiple molecular abnormalities

Neurogenesis and angiogenesis

Pain mechanisms

Irritation or direct nerve invasion of the eutopic and ectopic endometria

Neuropathic pains

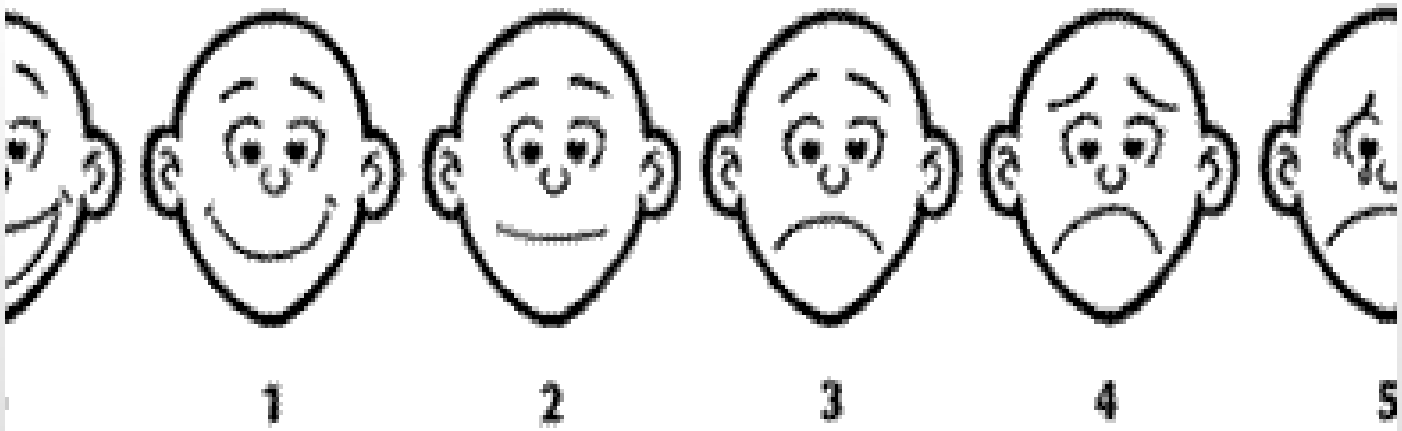
CNS sensitization and possible effect of growth factors, cytokines, prostaglandins, and histamines

How to measure pain in endometriosis patients???

- The Biberoglu & Behrman Score (B&B),
- The Visual Analog Scale (VAS),
- The Numerical Rating Scale (NRS)

VISUAL ANALOG SCALE

HAPPY FACE - SAD FACE SCALE



Endometriosis diagnosis

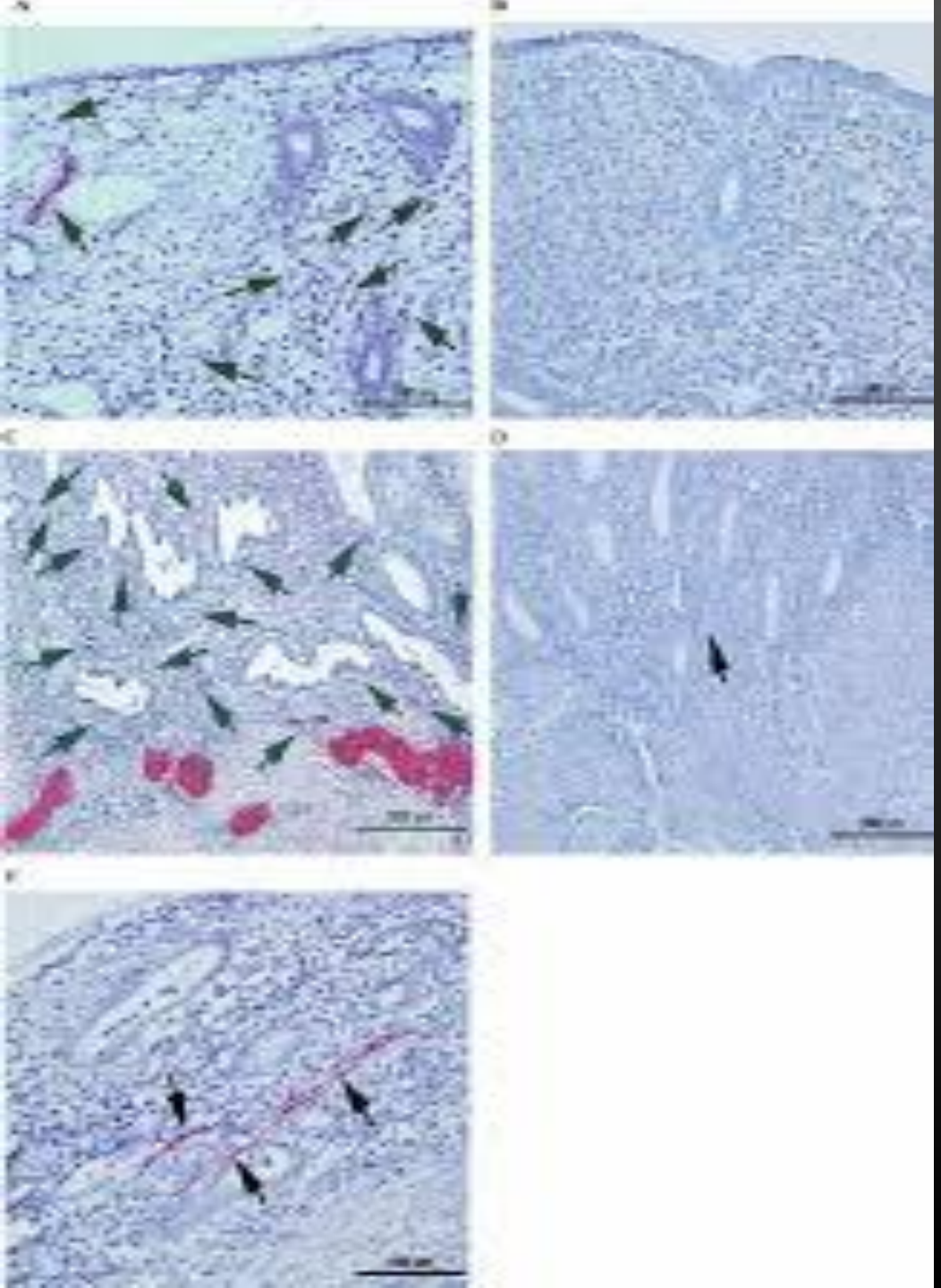
- Laparoscopy still the Gold standard
- Imaging: TVU, MRI, Ct scan
- Markers: ca 125

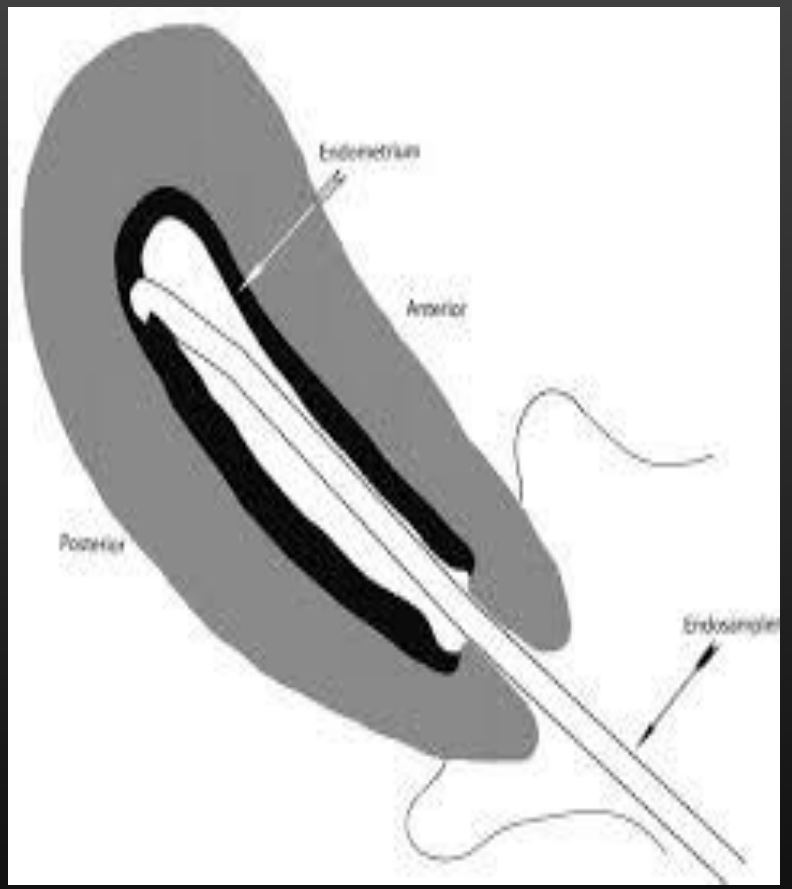
Endometriosis diagnosis

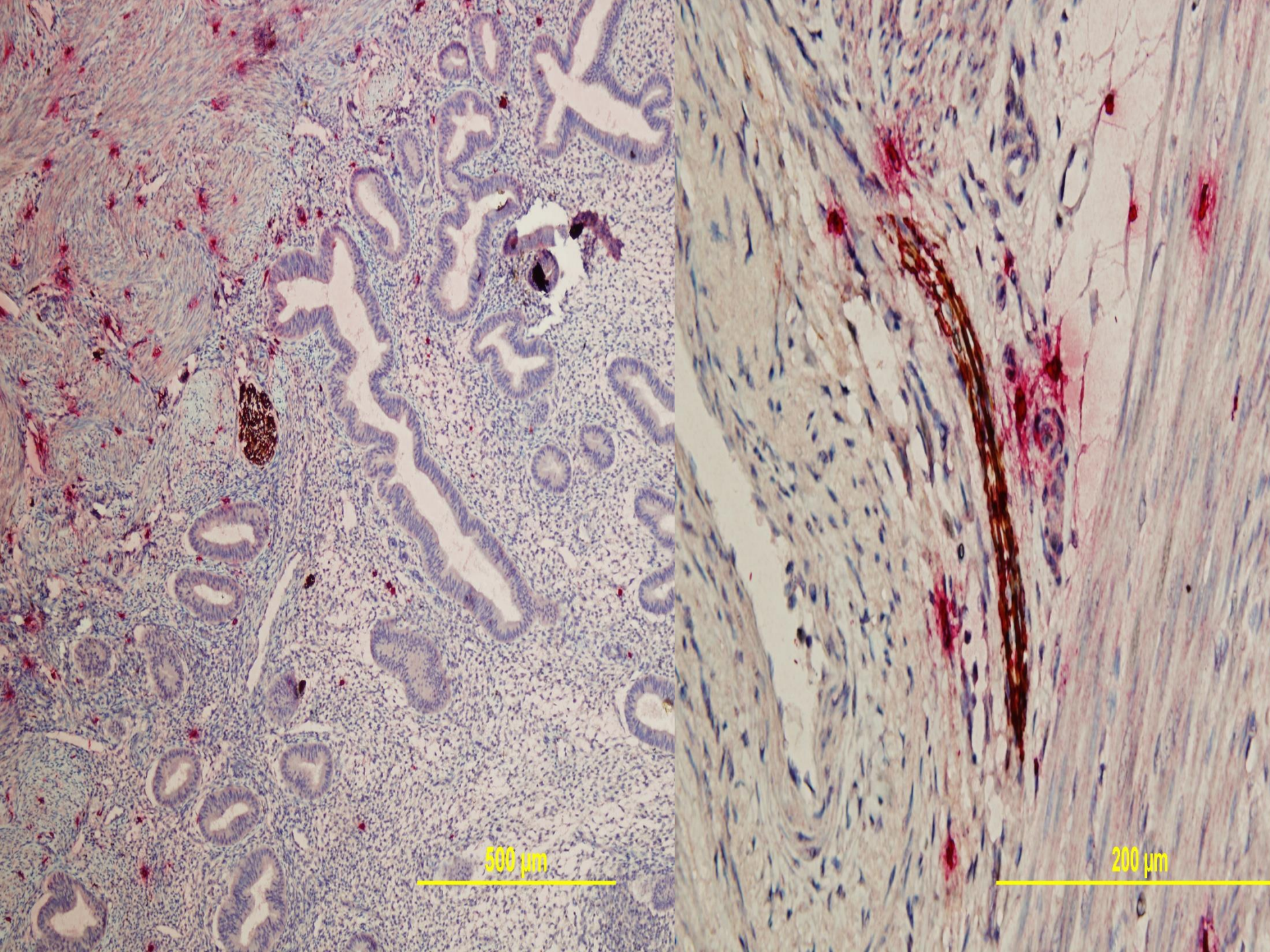
No sufficiently and packed by evidence perfect way

Delay in diagnosis is up to 7 years

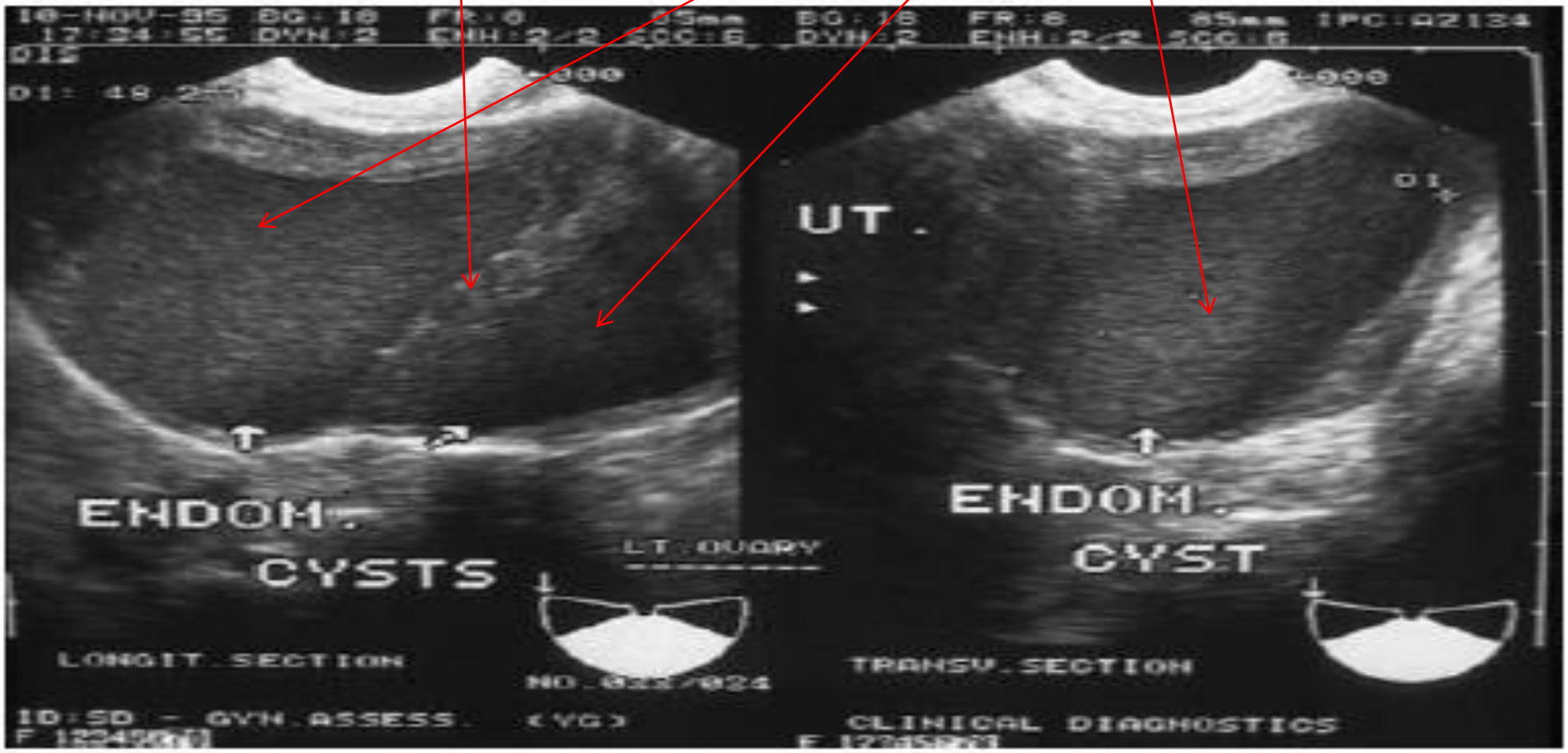
Pay attention to history




Endometrium
Anterior
Posterior


500 µm
200 µm

U/S scan showing endometrioma with septa



Laparoscopy for diagnosis (ESHRE Guidelines April, 2013)

- The GDG recommends to perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy truly proves the presence of disease.

  GPP

- A negative diagnostic laparoscopy in women with symptoms and signs of the disease is highly accurate for the exclusion of the diagnosis of endometriosis.

  A

- The GDG recommends that clinicians confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis although negative histology does not exclude it

  GPP

Diagnosis (ESHRE Guidelines April, 2013)

- In women with symptoms and signs of rectal endometriosis, transvaginal sonography is useful for identifying or ruling out rectal endometriosis

  (Hudelist, 2011). A
- Clinicians are recommended not to use immunological biomarkers in plasma, urine or serum, including CA-125, to diagnose endometriosis A

  (Mol et al., 1998; May et al., 2010).

Taking good history

The history

Family history of Endometriosis:
8 fold increase

Early menarche
Menarche that occurs before age 11 years is associated with the development of endometriosis

Long menstrual cycle
Prolonged, heavy cycles are associated with the development of endometriosis

Short menstrual cycle
Cycle lengths less than 27 days are associated with the development of endometriosis

Menstrual pains affecting QoL

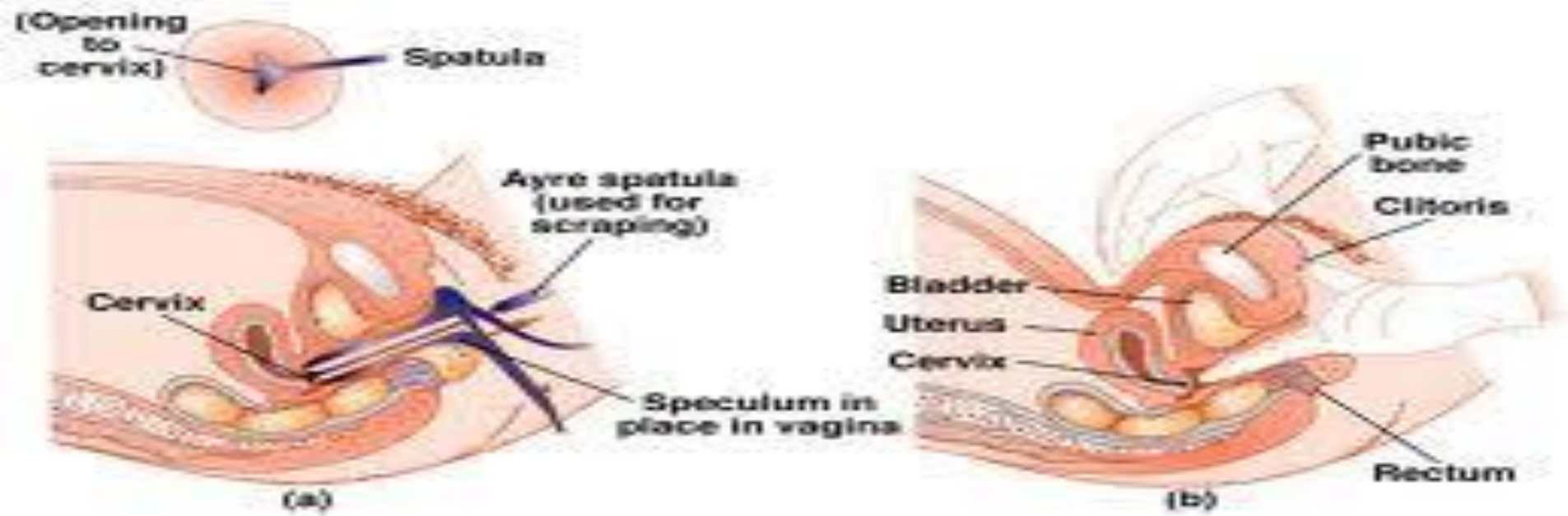
Please pay attention

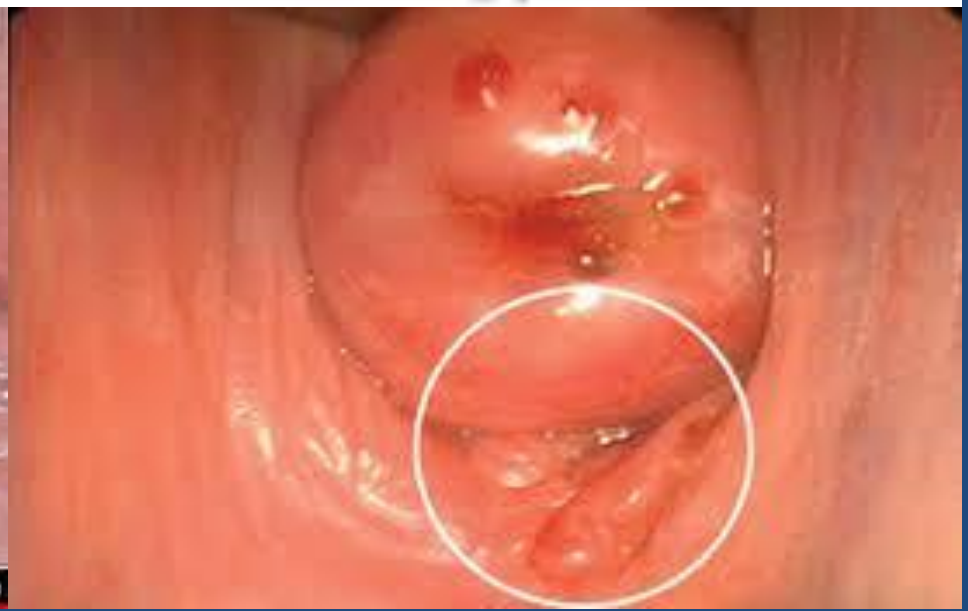
The cyclical usage of pain killers especially the injectable one.

Physical examination findings

- The physical examination is typically unrevealing.
- The findings are variable and of limited precision in either localization or diagnosis of endometriosis.
- Because much disease is found in the dependent areas of the pelvis, it is critical to perform a systematic rectovaginal examination.
- However, tender nodules may be palpable along the uterosacral ligaments, rectovaginal septum, or within the cul-de-sac, especially if the examination is performed just before menses.
- The clinician may also appreciate uterine or adnexal fixation or a tender adnexal mass (endometrioma).

Speculum and Bimanual Pelvic Exam

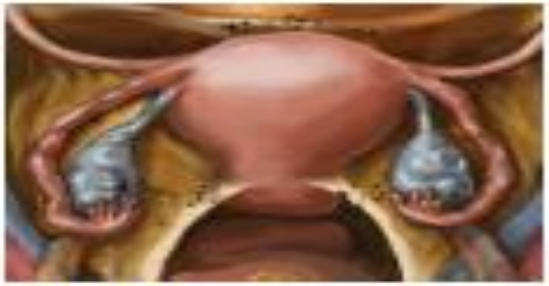




AFS staging

- Stage I (Minimal) Findings restricted to only superficial lesions and possibly a few filmy adhesions
- Stage II (Mild) In addition, some deep lesions are present in the cul-de-sac
- Stage III (Moderate) As above, plus presence of endometriomas on the ovary and more adhesions
- Stage IV (Severe) As above, plus large endometriomas, extensive adhesions

STAGE I (MINIMAL)

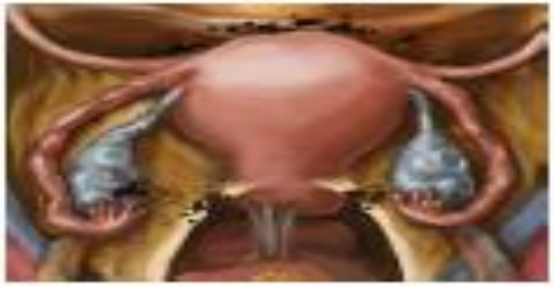


PERITONEUM	
Superficial Endo — 1–3cm	-2
L. OVARY	
Superficial Endo — <1cm	-1
Filmy Adhesions — <1/3	-1
TOTAL POINTS	4

STAGE II (MILD)

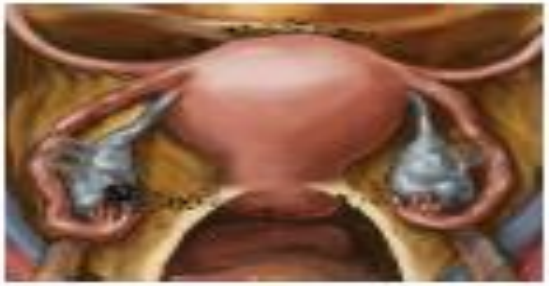
PERITONEUM	
Deep Endo — >3cm	-6
L. OVARY	
Superficial Endo — <1cm	-1
Filmy Adhesions — <1/3	-1
R. OVARY	
Superficial Endo — <1cm	-1
TOTAL POINTS	9

STAGE III (MODERATE)



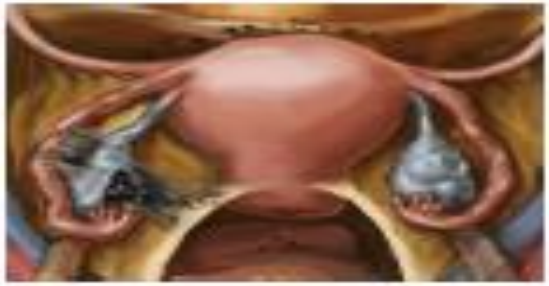
PERITONEUM	
Deep Endo — >3cm	-6
CULDESAC	
Partial Obliteration	-4
L. OVARY	
Deep Endo — 1–3cm	-16
TOTAL POINTS	26

STAGE III (MODERATE)



PERITONEUM	
Superficial Endo — >3cm	-3
L. TUBE	
Dense Adhesions — <1/3	-16*
L. OVARY	
Deep Endo — <1cm	-4
Dense Adhesions — <1/3	-4
R. TUBE	
Filmy Adhesions — <1/3	-1
R. OVARY	
Filmy Adhesions — <1/3	-1
TOTAL POINTS	29

STAGE IV (SEVERE)

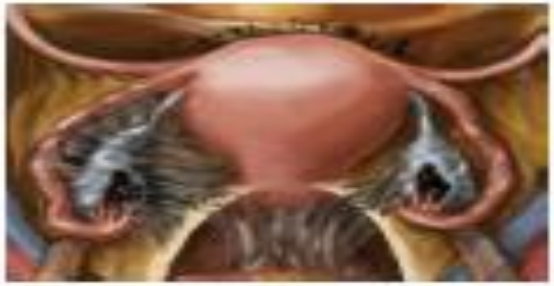


PERITONEUM	
Superficial Endo — >3cm	-3
L. OVARY	
Deep Endo — 1–3cm	-32**
Dense Adhesions — <1/3	-8**
L. TUBE	
Dense Adhesions — <1/3	-8**
TOTAL POINTS	51

*Point assignment changed to 16

**Point assignment doubled

STAGE IV (SEVERE)

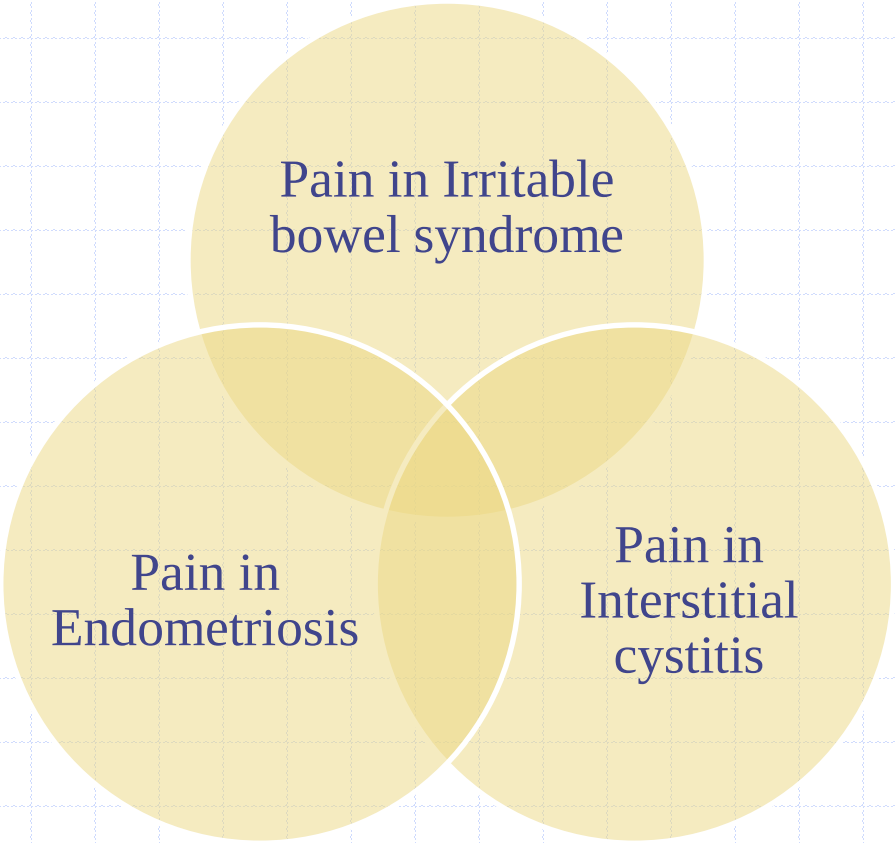


PERITONEUM	
Deep Endo — >3cm	-6
CULDESAC	
Complete Obliteration	-40
R. OVARY	
Deep Endo — 1–3cm	-16
Dense Adhesions — >1/3cm	-4
L. TUBE	
Dense Adhesions — >2/3cm	-16
L. OVARY	
Deep Endo — 1–3cm	-16
Dense Adhesions — >2/3cm	-16
TOTAL POINTS	114

The differential diagnosis of endometriosis

- Includes:
  - Adenomyosis
  - pelvic inflammatory disease,
  - tubo-ovarian abscess,
  - ectopic pregnancy,
  - irritable bowel syndrome,
  - interstitial cystitis, adenomyosis,
  - pelvic adhesions,
  - uterine fibroids,
  - Chronic and acute endometritis,
  - ovarian neoplasms

Confusion with other diseases (Al-Jefout, 2010)



CA-125 in endometriosis diagnosis

Not useful and should not be used

May be useful in cases for follow up

If higher than 200 IU you may need to exclude Ovarian tumors

Aims of treatment

The primary focus of investigation and treatment of endometriosis should be resolution of the presenting symptoms.

Maintain/restore fertility

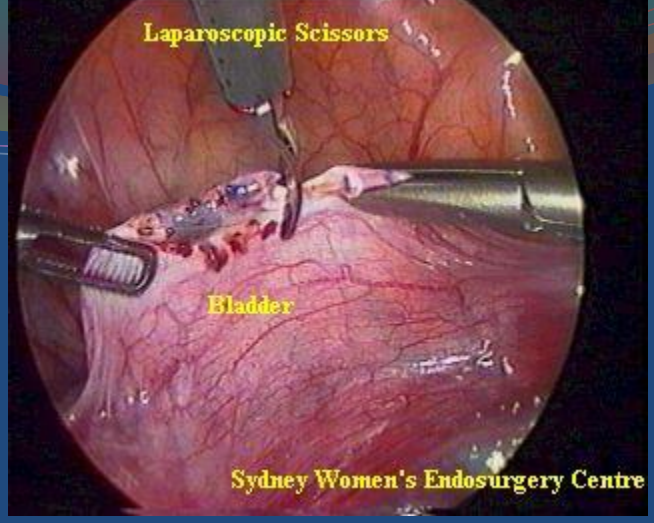
Improve quality of life

Avoid recurrence

Dealing with endometriosis

- Surgical
- Medical
- Combination of both

Surgical treatment

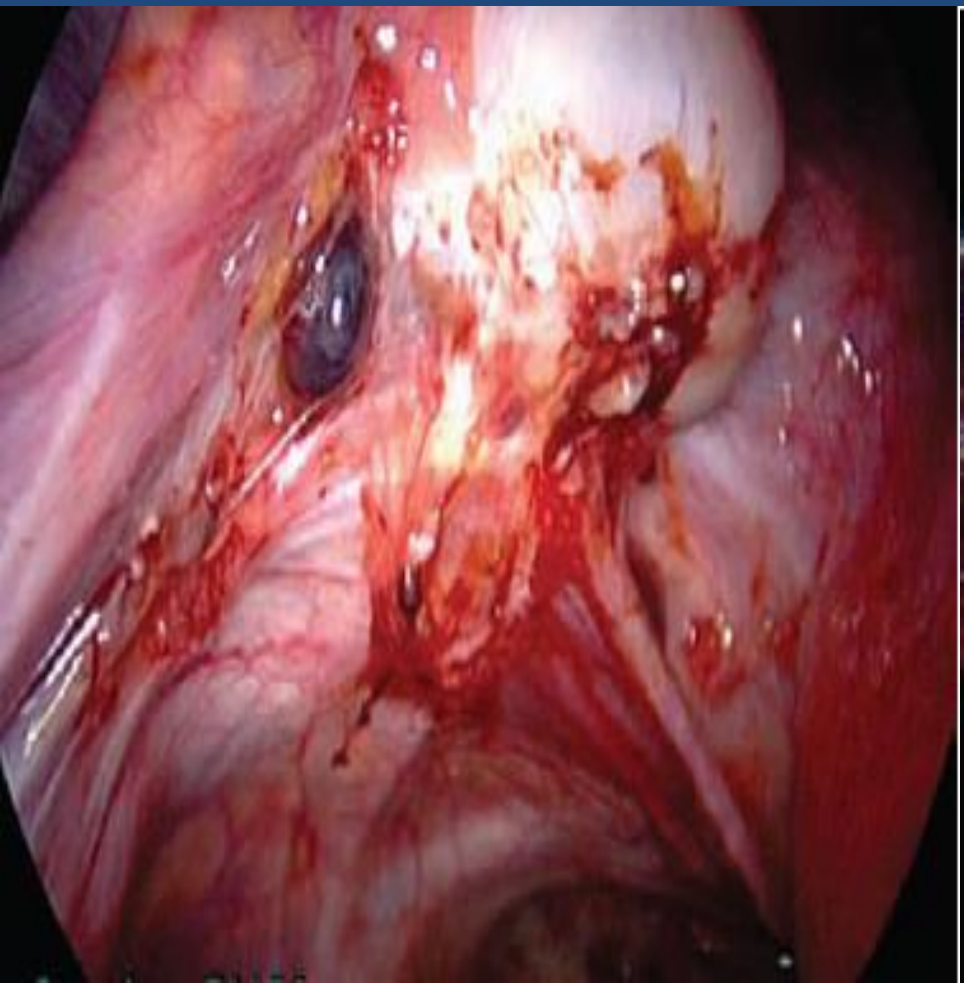


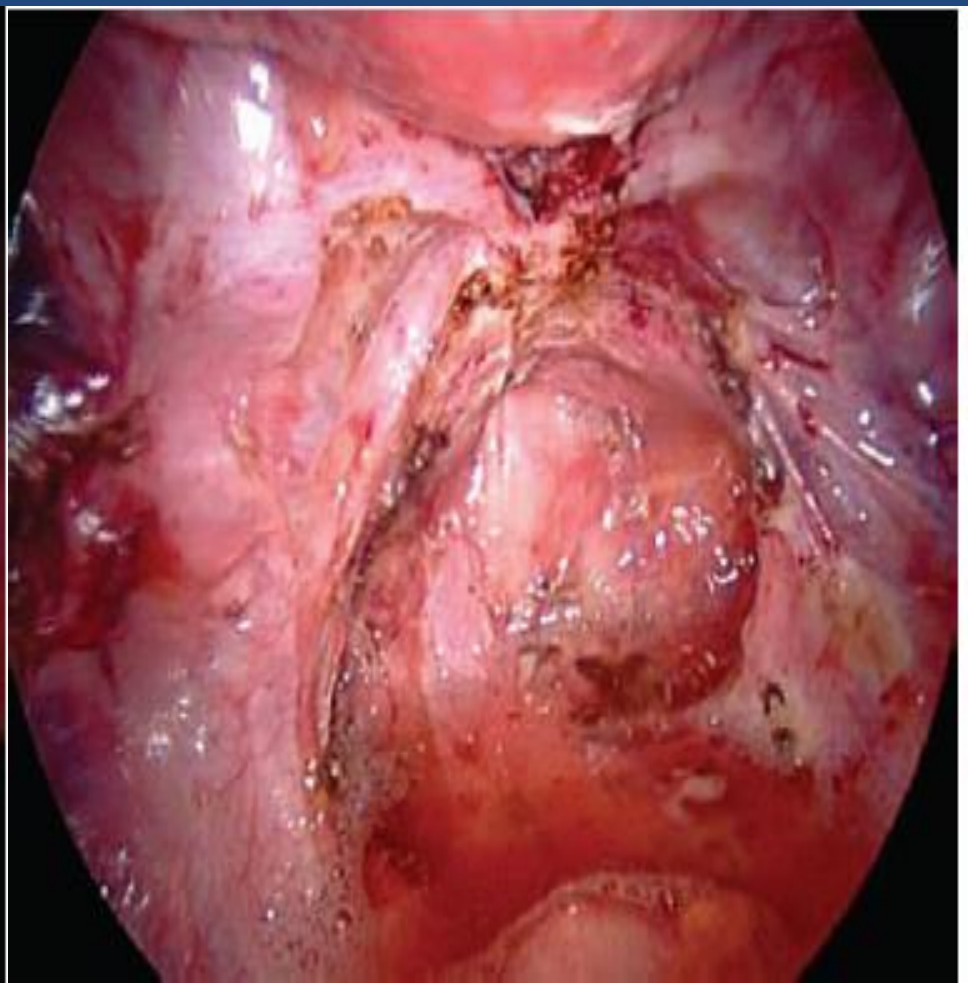
- Very attractive yet challenging!
- Depends on many factors- most importantly- the operator skills and the extent of the disease.
- Rapid improvement of symptoms for short terms

(Fritzer N, 2012)

- Not without risks:
  - Injury to bowel ureter **etc…rare yet when occur associated with high morbidity.**
  - Incomplete excision----- **very common**
  - Ovarian reserve depletion in cases of **improper** endometrioma removal

Complete removal of endometriosis in Pouch of Douglas





Medical Vs Surgical treatment

(Al-Jefout et al, 2010)

Medical treatment does not improve fertility (Hughes E, 2009, Cochrane review)

Long-term or repeated courses of medical therapy are required to control these symptoms

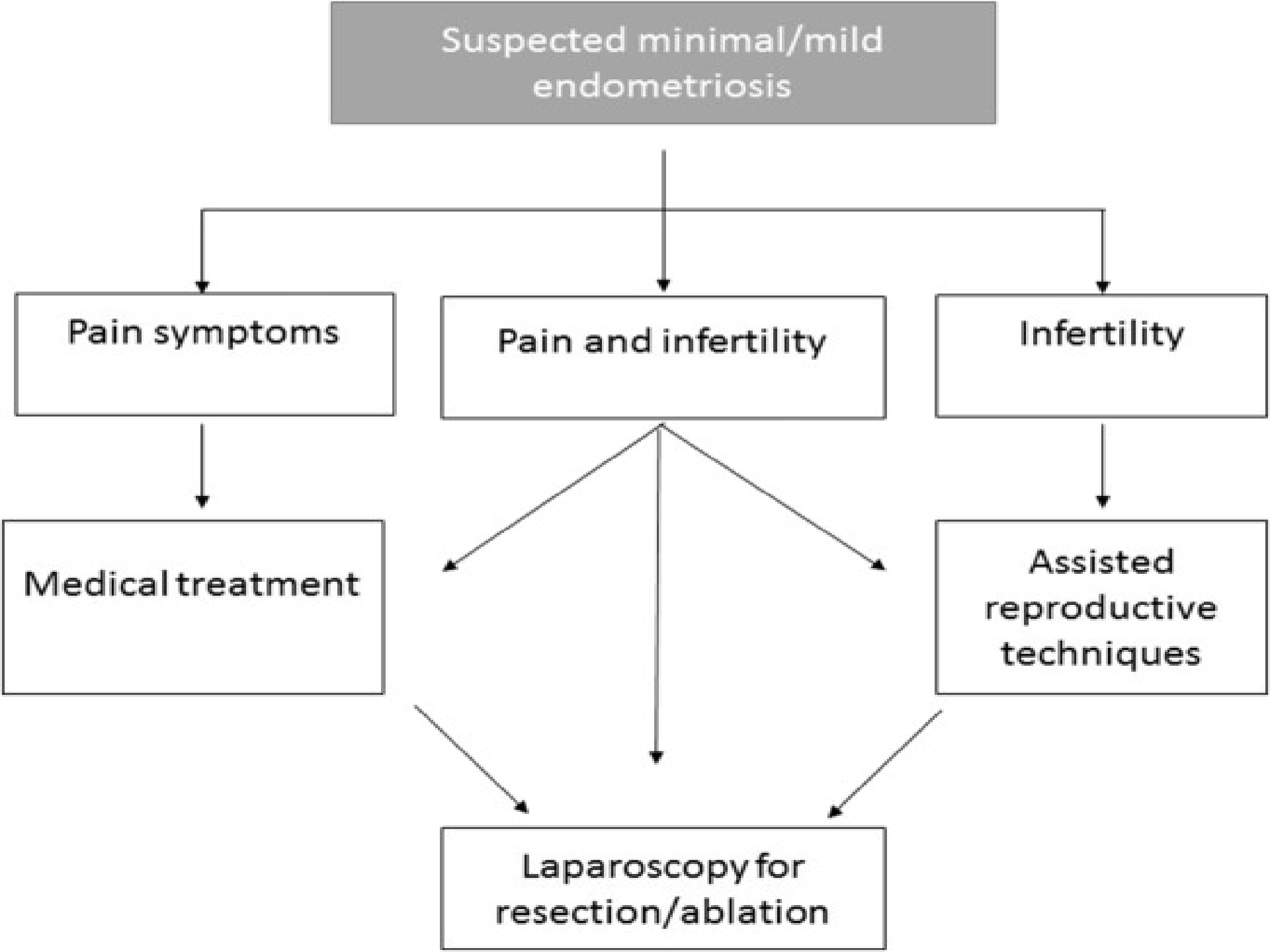
Previous medical treatment for endometriosis prior laparoscopy is a risk factor for recurrence. (Koga K, 2013)

Medical Vs Surgical treatment

Laparoscopic excision of DIE lesions significantly improves general health & QOL.

(Mabrouk M, 2011)

However, surgery is an invasive therapeutic option that is far from ideal, because 20% of cases do not respond (Abbott *et al*., 2004, Milingos *et al*., 2003).

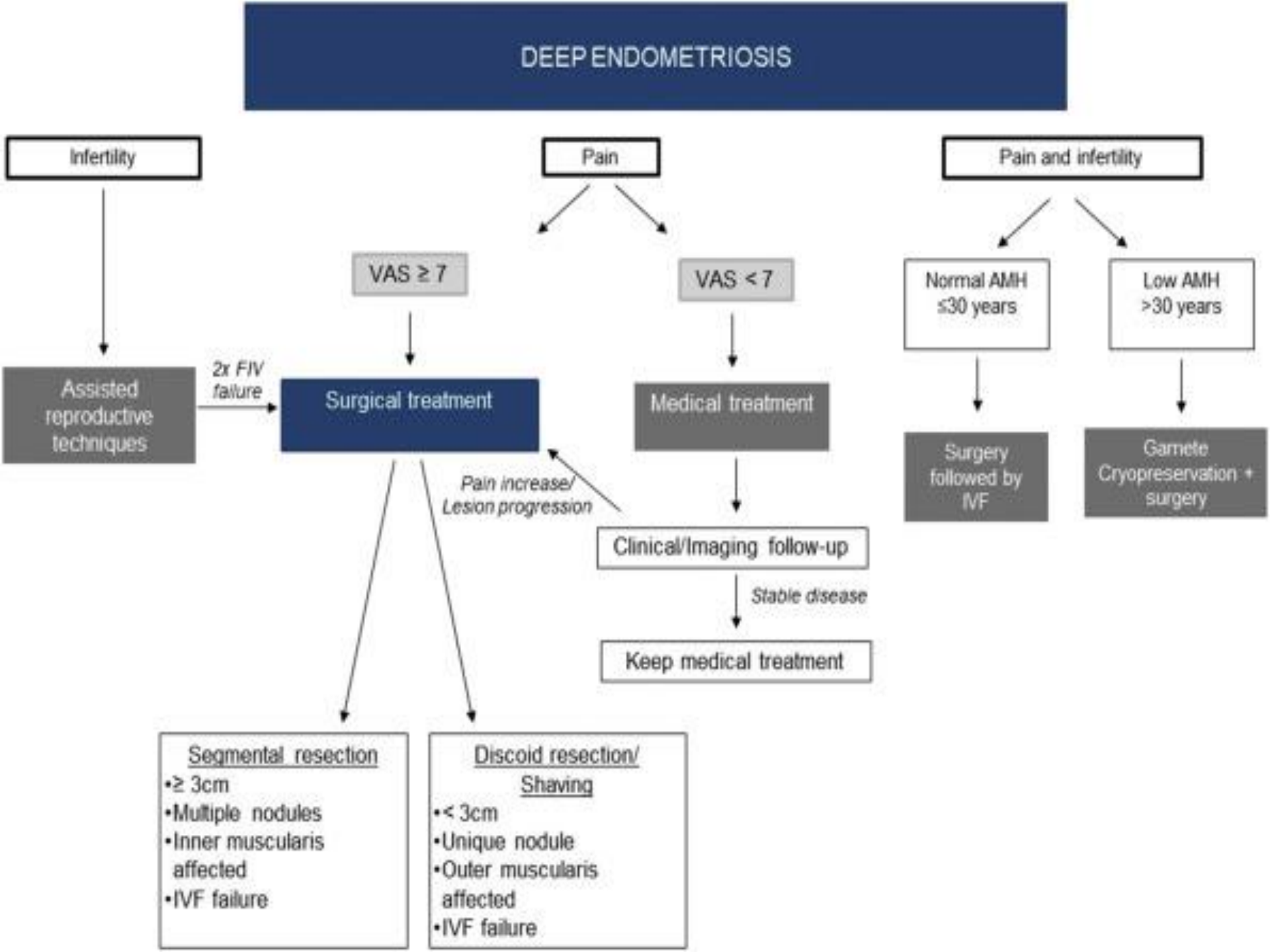

Suspected minimal/mild endometriosis
Pain symptoms
Pain and infertility
Infertility
Medical treatment
Assisted reproductive techniques
Laparoscopy for resection/ablation

Recurrence of endometriosis after surgery

Guo (2009) calculated that the disease relapse rate is higher than 20% at 2 years and 40–50% at 5 years.

In particular, data are accumulating on the post-operative endometrioma recurrence rates, which reportedly vary between 30 and 50% after 2–5-year follow-up

(Kikuchi et al., 2006; Koga et al.,2006; Vercellini et al., 2008b).


DEEP ENDOMETRIOSIS
Infertility
Pain
Pain and infertility
VAS ≥ 7
VAS < 7
Normal AMH ≤30 years
Low AMH >30 years
Assisted reproductive techniques
2x FIV failure
Surgical treatment
Medical treatment
Surgery followed by IVF
Gamete Cryopreservation + surgery
Pain increase/ Lesion progression
Clinical/Imaging follow-up
Stable disease
Keep medical treatment
Segmental resection
•≥ 3cm
•Multiple nodules
•Inner muscularis affected
•IVF failure
Discoid resection/ Shaving
•< 3cm
•Unique nodule
•Outer muscularis affected
•IVF failure

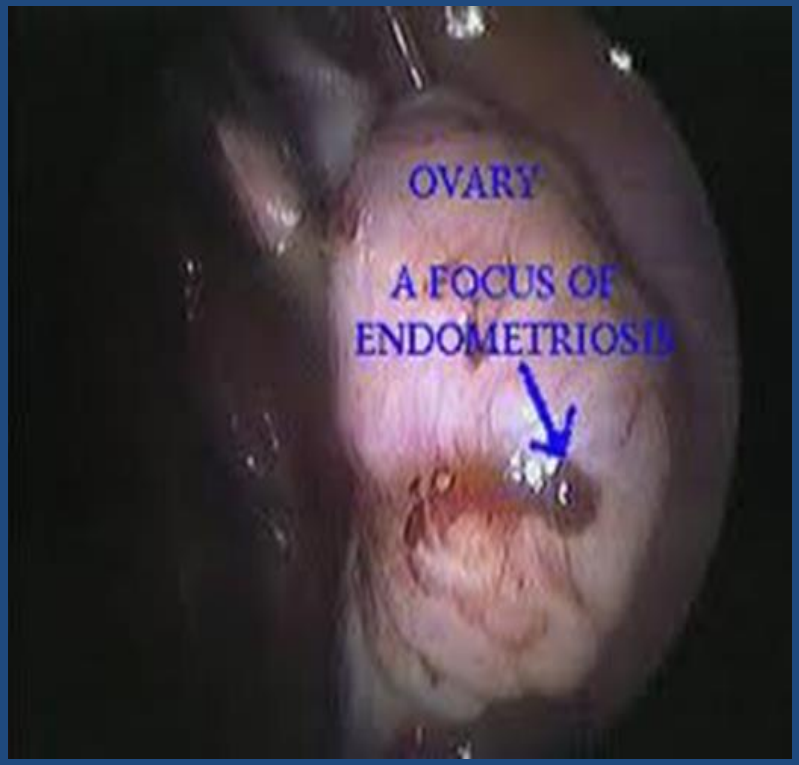
Treatment strategies in infertility related endometriosis

Medical treatment before surgery does not appear to improve fecundity and therefore will only delay attempts at conception.

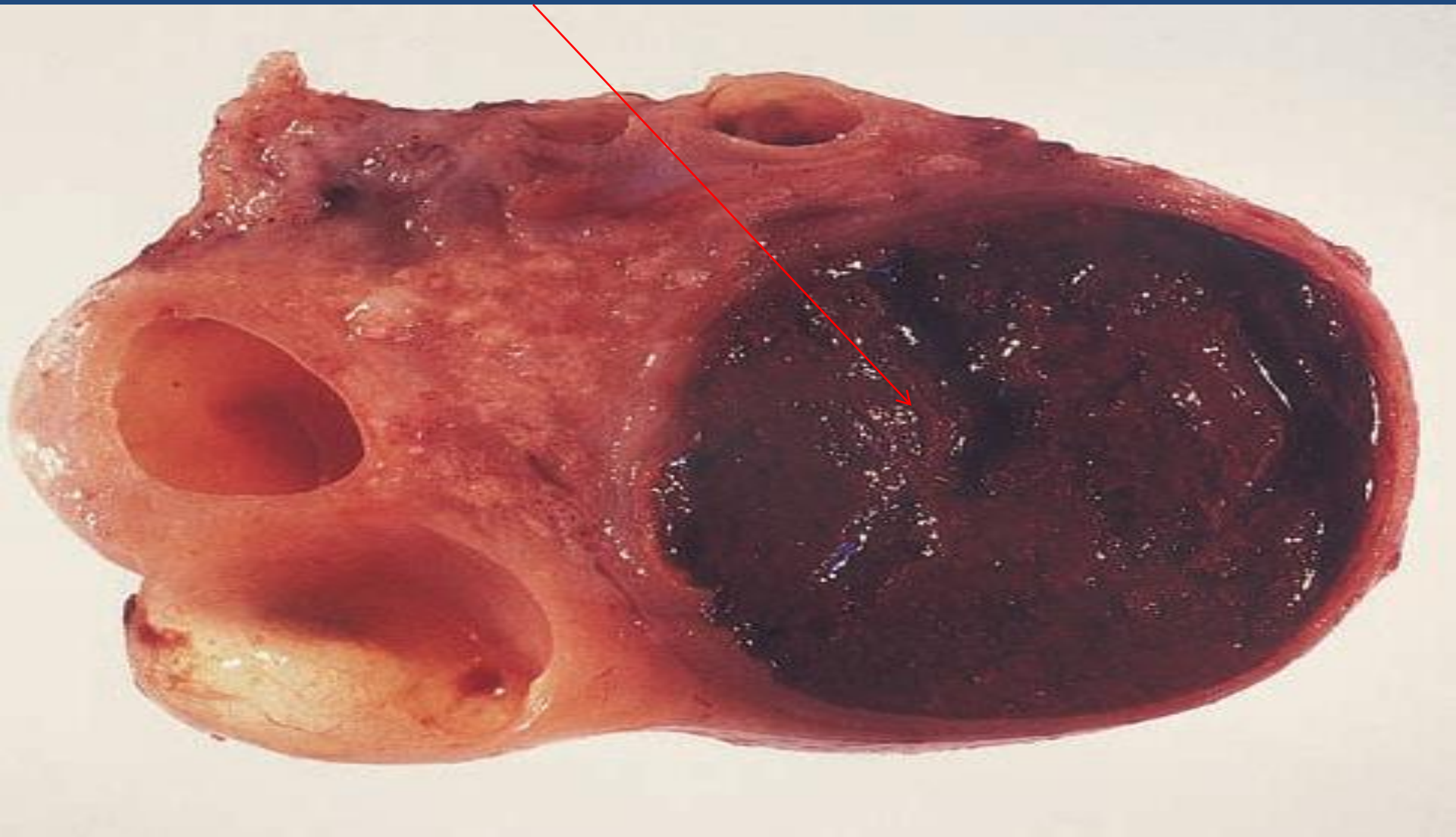
Surgical treatment should be reserved for symptomatic women or for women in whom reproductive anatomy is distorted but amenable to repair.

It is not recommended to perform a laparoscopy in subfertile women to look for asymptomatic endometriosis.

Ovarian endometriosis



Ovarian endometrioma



Surgery for endometriomas

Many studies support the evidence that surgical removal of endometriomas is deleterious to ovarian reserve and function.

(Jacobson TZ, 2010)

Surgery for removal of small endometriomas does not offer any additional benefits in terms of fertility outcomes.

Proceeding directly to COH in asymptomatic women with ovarian endometrioma < 4 cm might reduce the time to pregnancy, diminish patient costs, and avoid the potential complications of surgery.

Surgery for endometriomas

The singer not the song

asymptomatic patients with endometrioma > 4 cm might be advised to surgical treatment.

Cystectomy should be avoided in women with an already reduced ovarian reserve.

A Cochrane review found that excisional surgery provides better outcomes than ablative treatment.

(R.J. Hart, M. 2008)

Removal of the endometrioma was associated with a significant increase of spontaneous pregnancy in subfertile women (odds ratio: 5.21), with a reduction in the recurrence of endometrioma and pain symptoms

Removal Vs ablation of endometrioma

Study	Surgical approach	Results
Benaglia et al.(2010)	Endometrioma surgery	Ovarian damage
Horikawa et al.(2008)	Laparoscopic cystectomy	Reduces frequency of ovulation
Iwase et al. (2010)	Laparoscopic cystectomy	Postoperative decrease of serum AMH level
Var et al. (2011)	Coagulation/cystectomy	Decrease in AFC/ovarian volume
Loo et al. (2005)	Ovarian cystectomy for endometriomas	Fewer oocytes harvested during IVF

Endometriosis and Diminished Ovarian Reserve

	Controls	Endometriosis stage III-IV	
D3 FSH (age-matched) *N=75, 75*	9.7	12.6 $P < 0.03$	*Hock DL, 2001*
D1-4 AMH (age-matched) *N=306, 153*	3.6	2.4 $P < 0.001$	*Shebl O, 2009*

OEM and ovarian reserve

- OEM have a detrimental impact on follicle reserve in younger patients.
- Further, laparoscopic cystectomy for endometriomas may accelerate the rate of oocyte loss associated with aging

(K Masako, 2012)

- Endometrioma did not reduce the number of retrieved oocytes in a COH cycle for IVF treatment. However it should be noted that the ovarian response is affected by:
  - the size of endometrioma,
  - bilaterality,
  - previous surgeries,
  - recurrence,
  - the patient's age

(Kiran H, 2012)

Post-surgical Ovarian Failure

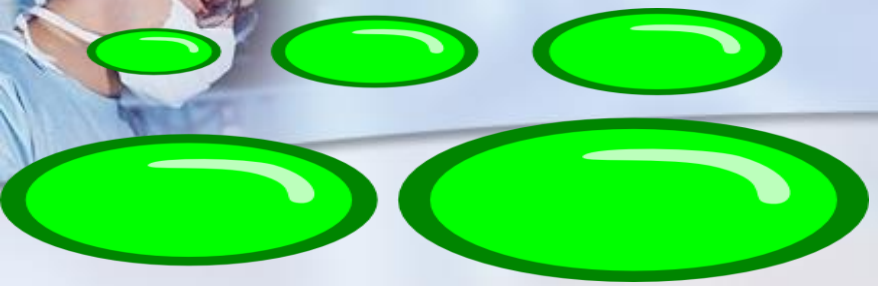
Occurs in **2.4%** of women who undergo cyst excision.

Possible causes:

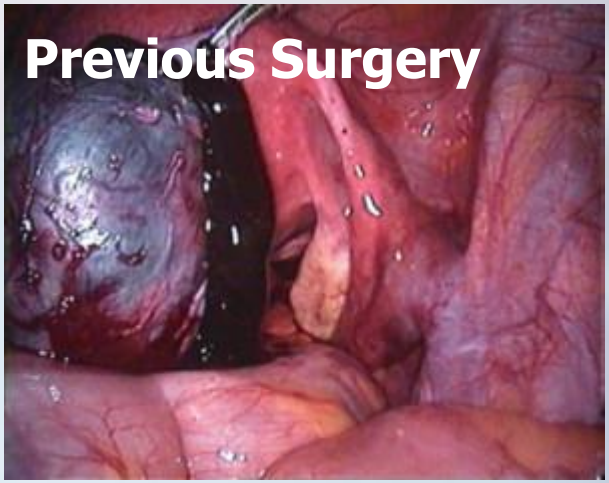
1. Irreversible trauma to ovarian vascularization
2. Excessive removal of ovarian tissue
3. Autoimmune reaction caused by severe, local inflammatory process

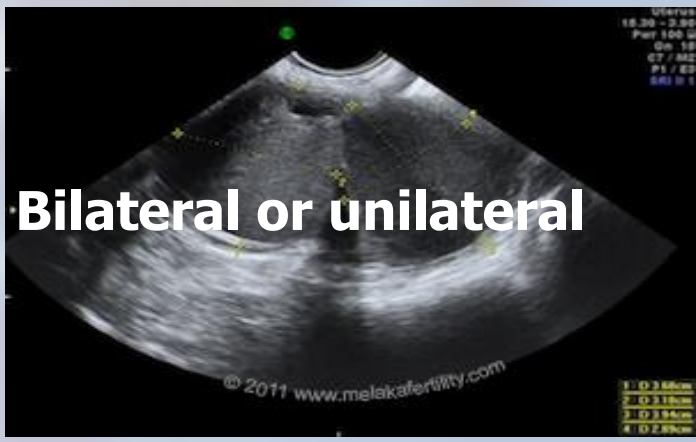
Factors influencing direction in Management of OMA

Size

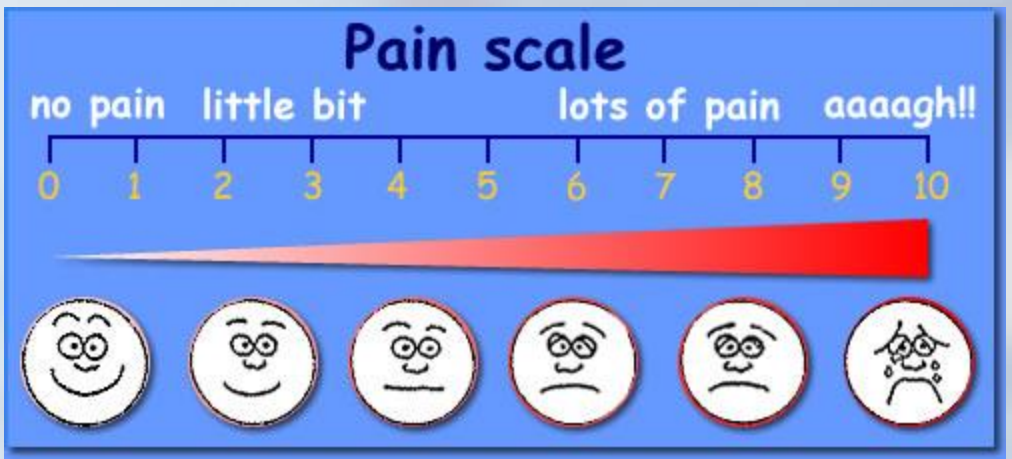


Age





Fertility desire



Endometrioma Surgery

More Radical
Many
Iinterventions

- Impaired ovarian reserve

Less Radical

- Recurrence

What are the guidelines world wide???????

Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Green-top Guideline No. 24
October 2006
(Minor revisions October 2008)

Visual inspection is usually adequate but histological confirmation of at least one lesion is ideal. In cases of ovarian endometrioma (greater than 3 cm in diameter) and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy. ✓

A guideline for the management of suspected ovarian malignancy should be followed in cases of ovarian endometrioma. ✓

Laparoscopic cystectomy for ovarian endometriomas is better than drainage and coagulation. **A**

The recurrence of endometriomas and symptoms are reduced by excisional surgery more so than drainage and ablation. Subsequent spontaneous pregnancy rates in women who were previously subfertile are also improved with this treatment.[58]

Evidence level Ia

Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Green-top Guideline No. 24

October 2006

(Minor revisions October 2008)

Laparoscopic ovarian cystectomy is recommended for endometriomas ≥ 4 cm in diameter. ✓

There are no randomised controlled trials comparing laparoscopic excision with no treatment before IVF. However, laparoscopic ovarian cystectomy is recommended if an ovarian endometriomas ≥ 4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles, and possibly improve ovarian response and prevent endometriosis progression. The woman should be counselled regarding the risks of reduced ovarian function after surgery[61,65] and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

ASRM guidelines for endometrioma 2012

- Cystectomy for endometrioma improves clinical preganacy rate better than aspiration or coagulation.
- Asymptomatic endometriosis has no effect on IVF outcome.
- Surgery should be done on endometrioma >4cm.

2. For women with endometriomas, excision rather than drainage or fulguration provides better pain relief, a reduced recurrence rate, and a histopathological diagnosis. (I)

3. Laparoscopic excision of ovarian endometriomas more than 3 cm in diameter may improve fertility. (II)

4. Ovarian endometriomas greater than 3 cm in diameter in women with pelvic pain should be excised if possible. (I-A)

5. In patients not seeking pregnancy, therapy with CHCs (cyclic or continuous) should be considered after surgical management of ovarian endometriomas. (I-A)

2. Excision or sampling of suspected endometriosis lesions and endometriomas helps confirm the diagnosis and exclude underlying malignancy. (II-2)

C N G O F

Collège National des Gynécologues et Obstétriciens Français

When an endometrioma is discovered in a patient presenting with pain due to endometriosis, it is recommended to search and treat other sites of endometriosis at the same time (grade B).

Endometriomas and IVF

Endometriomas have no impact on the final result of IVF (NP3). If an endometrioma is discovered during stimulation for IVF, this should not lead to interruption of the cycle (grade B). For endometriomas measuring less than 6 cm, neither repeat surgery nor drainage of the endometriomas is recommended prior to IVF (grade C).

C N O F
Collège National des Gynécologues et Obstétriciens Français

Laparoscopy is the most appropriate approach for treating ovarian endometriomas and superficial peritoneal endometriosis (grade B).

Laparoscopic cystectomy is superior to drainage followed by destruction of the cyst wall by bipolar coagulation for endometriomas measuring at least 3 cm in diameter, regardless of the indication for surgery (infertility, pain or adnexal mass) [NP1]. Cystectomy should be performed whenever technically feasible (grade A).

Use of preoperative medical treatment with Gn-RH analogs in order to render surgery for endometriomas easier is not recommended (grade C).

ESHRE Guidelines 2005

GPP	Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles and possibly improve ovarian response. The woman should be counselled regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

Summary Recommendations ASRM/ESHRE

- Asymptomatic women with endometriosis, surgical treatment guidelines:

Clinical condition	Recommendation
Stage I-II	Limited benefit: • Surgery recommended
Stage III-IV	Possible but unproven benefit: • Surgery recommended
Post-op adjuvant treatment	No benefit: • Not recommended
Surgery before IVF	Doubtful benefit: • Perhaps for endometrioma ≥4 cm
Recurrent endometriosis	• Not recommended

Vercellini P, 2009

PRACTICE POINTS

- Laparoscopy should be considered in patients with suspected superficial endometriosis and pain symptoms, who do not respond to, decline, or have contraindications to medical therapy.
- For superficial endometriosis-associated infertility, surgical resection may improve fertility outcomes; however, there is limited evidence to support laparoscopy procedure before all assisted reproductive techniques.
- Surgery for ovarian endometriosis can have a significant effect on ovarian reserve; therefore, critical factors should be considered when deciding the surgical treatment.
- Ovarian cystectomy should be performed instead of drainage and coagulation, as the former reduces endometriosis-associated pain and has a lower recurrence rate of the endometriotic cyst, as well as a higher subsequent pregnancy rate.
- There are no specific guidelines regarding when to indicate surgery and the type of procedure to be performed for deep endometriosis.

Medical approaches

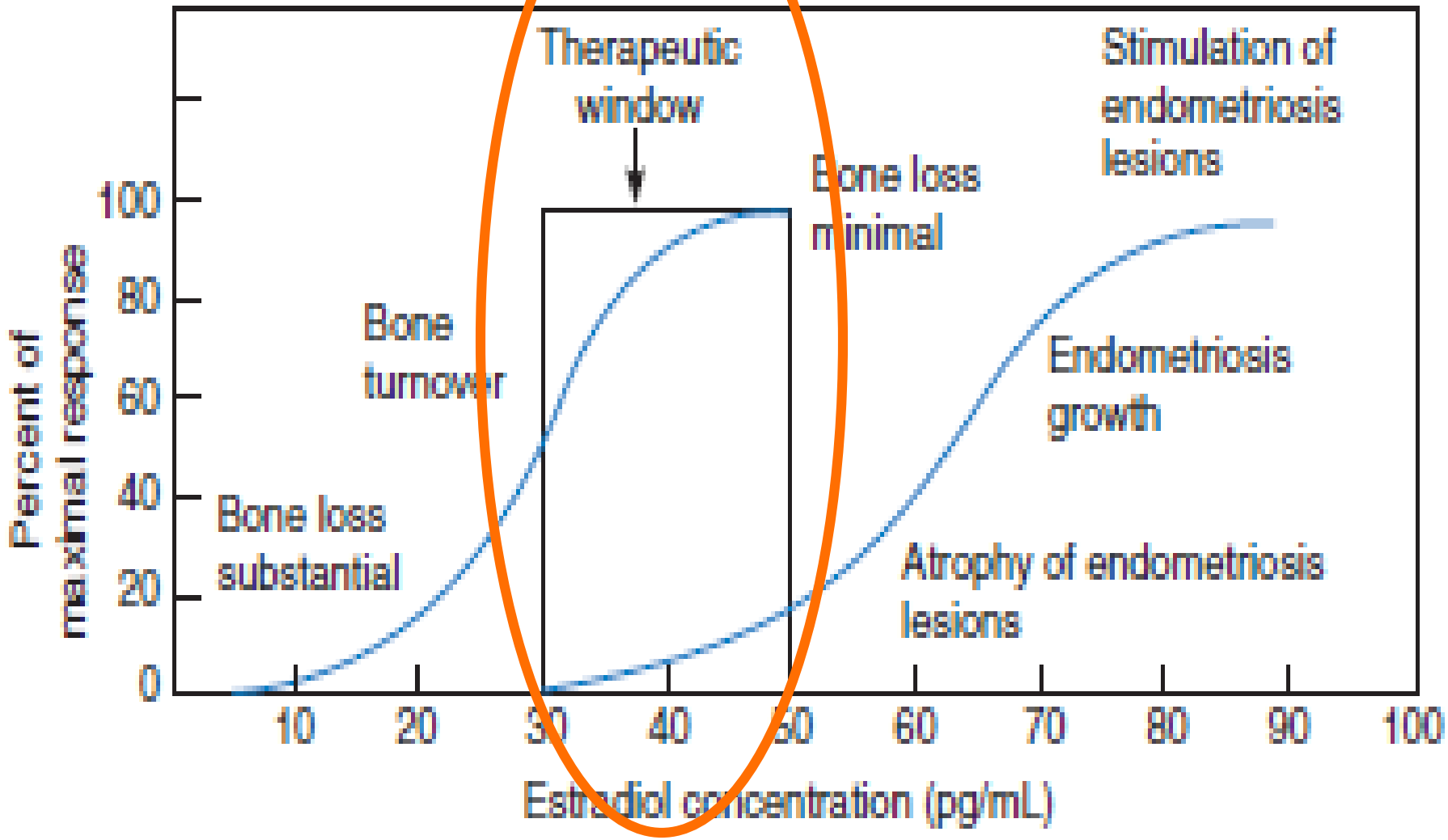
Analgesics.

Suppression of ovulation/estrogen production.

Direct action on endometrial deposits.

Modulation of the immune system

The optimal medical treatment



Empirical treatment of pain symptoms without a definitive diagnosis

The empirical treatment of pain symptoms suggestive of endometriosis can be utilized without a definitive diagnosis, using a hormonal agent

(Giudice LC. Clinical. N Engl J Med, 2010; Kennedy S, et al. ESHRE, 2005; RCOG Guidelines)

Treatment	Mode of action	Side-effects
Progestogens	Decidualization followed by atrophy	Breakthrough bleeding, weight gain, bloating, acne, mood changes
Combined oral contraceptive pill	Suppression of ovulation Hypo-oestrogenic state	Weight gain, headache, nausea, breast enlargement, depression, risk of thromboembolism
Androgenic agents danazol	Suppression of hypothalamic–pituitary axis	Weight gain, acne, oily skin, muscle cramps, hot flushes, depression, hirsutes, skin rash, deepening of the voice
Androgenic agents gestrinone	Suppression of hypothalamic–pituitary axis	As for danazol but fewer side-effects
Gonadotropin releasing hormone agonists	Pituitary gonadotroph, desensitisation via downregulation of gonadotropin releasing hormone receptors	Hot flushes, headache, vaginal dryness, reduced libido

NSAIDs for pain therapy in endometriosis

There is inconclusive evidence to show whether or not NSAIDs (naproxen) are effective in managing pain caused by endometriosis.

There is no evidence on whether any individual NSAID is more effective than another.

(RCOG Guideline No. 24 4 of 14)(Claire Allen1, Cochrane review, 2010)

Oral contraceptives Progestogens-OCPs

By suppressing ovarian activity, they may also reduce prostaglandin production secondary to endogenous estrogens and therefore decrease the inflammatory status

Better tolerability and lower metabolic impact than GnRH agonists and danazol.

Cyclic and continuous OCPs are considered the first-line chronic treatment for endometriosis.

Oral Contraceptives (OCPs)

The results of many studies have consistently confirmed that progestins and OCs are effective in relieving pain, generally well-tolerated, and not inferior to danazol, GnRH agonists and aromatase inhibitors

(Vercellini et al., 1993, 1996; Prentice et al., 2000, 2004; Cosson et al., 2002; Petta et al., 2005; Schlaff et al., 2006; Crosignani et al., 2006b; Davis et al., 2007; Selak et al., 2007; Harada et al., 2009; Ferrero et al., 2009b; Strowitzki et al., 2010a).

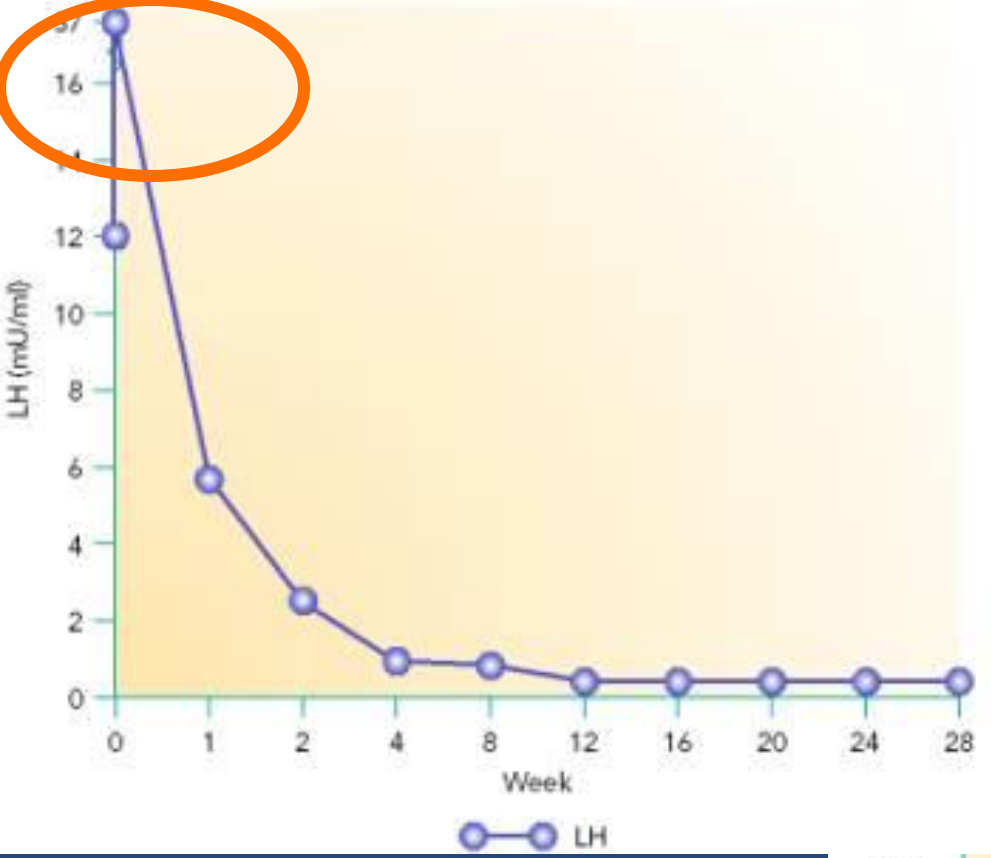
Continues Vs Cyclical

- For women in whom cyclic OCPs did not provide adequate relief, switching to continuous OCP use resulted in 50% decrease in visual analog scale dysmenorrhea scores and a significant improvement in overall satisfaction.

(Vercellini P, 2003)

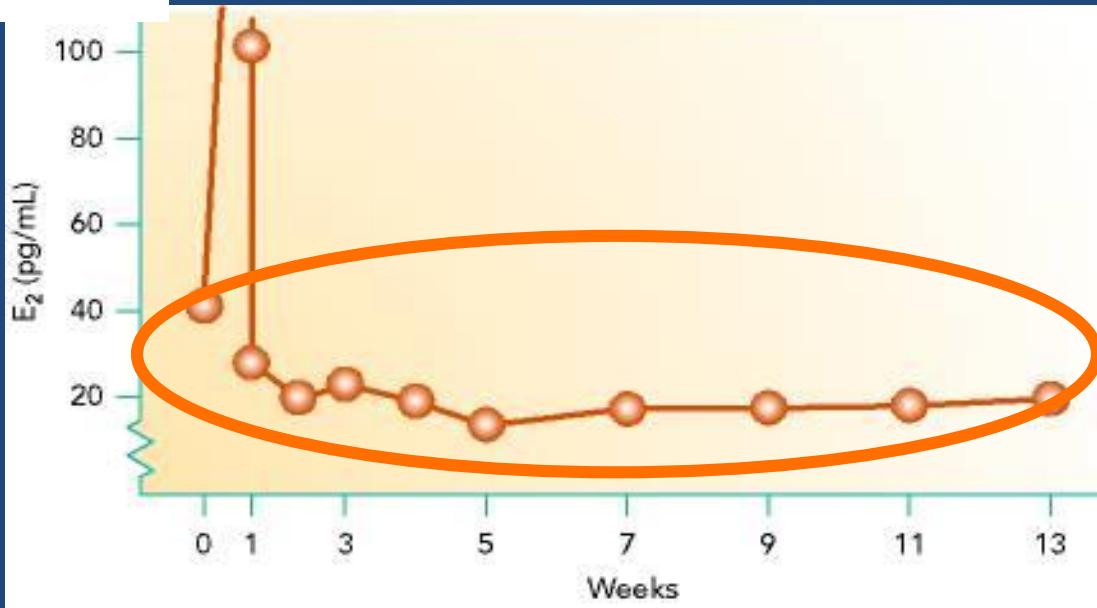
Gonadotropin-releasing hormone agonists (GnRh-a)

- They induce a reversible hypo-estrogenic state by down regulation of GnRH receptors and desensitation of pituitary.
- Agonist/analogs are 50–100 times more potent than GnRH.
- Acute administration of GnRHas, produces a marked increase of FSH and LH and subsequently of estradiol.
- Very effective for short term treatments.
- Yet, lots of side effects.



The ‘flare-up’

Downregulation



The most appropriate add-back regimen has not been ascertained definitively.

a low-dose continuous oestrogen and interrupted progestin should be considered initially.

Possibility to extend the duration of treatment for several months has been emphasized recently

(Bedaiwy M & Casper R., 2006)

Add-back therapy GnRh agonist

However, Cochrane review: there is little or no difference in the effectiveness of GnRH agonists and add-back treatment in comparison with other medical treatments for endometriosis

(Prentice A, 2007)

Mirena – levonorgestrel Intrauterine system (LNG-IUS)

- 46mg LNG released at rate of 20µg/24 hours
- reduces to 15 µg/24 hours after 5 years
- serum levels of LNG are 4 - 13% of pill users (Vercellini et al, 200

The levonorgestrel-releasing intrauterine System (LNG-IUS)

- The LNG-IUS is a real option for endometriosis pelvic pain treatment

  (Lockhat et al. 2005; Petta et al.2005).

- Leads to:
  - Glandular atrophy,
  - Pseudodecidualization of the stroma and vasodilatation,
  - An increase in apoptosis and a reduction in Bcl-2 protein, an inhibitor of apoptosis in the endometrial stroma,
  - Thinning of the vessel walls associated with a reduction in vascular density

Levonorgestrel -IUS

- In a cohort of 20 women with known endometriosis who had previously undergone conservative surgical treatment and had recurrent dysmenorrhoea, demonstrated that the LNG-IUS was associated with symptomatic relief in~70% of cases after 12 months therapy.

(Vercellini et al. 1999)

- A significant symptom improvement as well as radiological evidence of lesion regression in 11 women with recto-vaginal endometriosis.

(Fedele et al. 2001)

Combined therapy for severe cases- Mirena and Implanon

- Levonorgestrel intrauterine system combined simultaneously with an etonogestrel subdermal implant for refractory endometriosis-associated pelvic pain: An effective new therapy.
- One case report and follow up study on 50 patients

(Al-Jefout et al, 2009; Cecilia H. M. Ng, Ian S. Fraser, Moamar I. Al-Jefout and Anthony J. Marren, 2012)

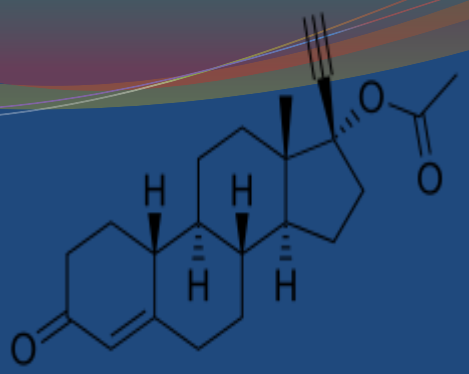
Norethisterone acetate (NETA):

- Dysmenorrhoea regressed in 92% subjects and chronic pelvic pain in 89%.
- At the end of treatment, 94% women had few or no symptoms.
- Low-dose oral NETA is probably the best choice for rectovaginal lesions

- Breakthrough bleeding 58% patients

(Vercellini et al., 2005, 2009; Remorgida et al., 2007; Ferrero et al., 2009, 2010).

Norethisterone acetate (NETA)



- NETA is known since 1957
- Upon oral ingestion, it is rapidly converted into norethisterone by esterases during intestinal and first-pass hepatic metabolism.
- Hence, as a prodrug of norethisterone, NETA has essentially the same effects, acting as a potent progestogen with additional weak androgenic and estrogenic activity

Clinical trials in norethisterone acetate (NETA)

- In deep rectovaginal endometriosis, the guidelines recommend complete excision, but it is also possible to treat with progestins symptomatically.
- This was shown in a prospective randomized controlled trial using NETA versus a combination of estrogen and cyproterone acetate (CPA).
- **Dyschezia, pelvic pain, deep dyspareunia and dysmenorrhea were reduced significantly with both treatment regimens.**
- The effects of norethisterone acetate in symptomatic pain relief were confirmed in a comparative study using NETA alone versus NETA combined with an aromatase inhibitor.
- More recently a study on patients with **rectovaginal endometriosis** (RVE) has shown **almost 70%** of 61 patients were **satisfied** with using up to 5 mg/day **for five years**.
- A study treating unilateral endometrioma showed **a 37% reduction** in volume after six months, however the sample size was only 6.

- (Special Interest Group for Endometriosis and Endometrium. ESHRE Guideline for the Diagnosis and Management of Endometriosis, 2005; Vercellini P, 2005; Ferrero S, 2009; Morotti M, 2017; Taniguchi F, 2017).

Clinical trials in norethisterone acetate (NETA)

- NETA in early studies, unlike OCPs, completely eliminated pelvic pain and dysmenorrhea in women with endometriosis and decreased implant size on second-look laparoscopy or decreased endometrioma size on ultrasound.
- **Dienogest and NETA** appear to be **equally effective** in alleviating pain and decreasing lesion size in endometriosis.
- Although NETA is less expensive, dienogest is slightly better tolerated because of fewer side effects

(Moghissi KS, 1976; Muneyyirci-Delale O, 1997; Vercellini P, 2016)

Continuous norethisterone acetate (NET-A), 5 mg vs cyclical combined oral contraceptive pill (COC) consisting of drospirenone 3 mg/ethinyl estradiol 20 µg pills in treating dysmenorrhea in young adult women. Al-Jefout et al 2018

- This prospective, open-label, nonrandomized study included 38 Jordanian patients: 20 patients in group N and 18 patients in group P.
- Main Outcome Measures: Pain scores, adverse effects, analgesic use, school absence, and cost.
- Results: **Both drugs were similar in suppressing dysmenorrhea at the 3-month follow-up visit**; VAS score mean (±SD) in group N and P were 1.30 ± 1.22 and 1.28 ± 0.83 (P = .22), respectively, and after 6 months, with mean VAS scores (±SD) of 1.30 ± 1.22 and 1.28 ± 0.83, respectively (P = .95). **The cost of the treatment in the N group was much less than in the P group.** Participants in the N group were less likely to use pain killers: 20% and 44% in the N and P groups, respectively (P = .006) in the first month and only 5% and 17% (P = .019) in the N and P groups, respectively, at the 3-month follow-up, and none of them used any analgesics at the 6-month follow-up.
- **Conclusion**
- **A continuous NET-A regimen is a well tolerated, effective, and inexpensive option for dysmenorrhea treatment and was as good as COC.**

Journal of Pediatric and Adolescent Gynecology
Volume 29, Issue 2, April 2016, Pages 143-147

Original Study

Continuous Norethisterone Acetate versus Cyclical Drospirenone 3 mg/Ethinyl Estradiol 20 μg for the Management of Primary Dysmenorrhea in Young Adult Women

Moamar Al-Jefout MD, PhD [1], Nedal Nawaiseh MD, PhD [2]

Journal of Obstetrics and Gynaecology Canada
Volume 39, Issue 7, July 2017, Pages 585-595

SOGC Clinical Practice Guideline

No. 345-Primary Dysmenorrhea Consensus Guideline

Margaret Burnett MD (Principal Author), Madeleine Lemyre MD (Principal Author)

Dysmenorrhea and Endometriosis in the Adolescent

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 760

Committee on Adolescent Health Care

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care in collaboration with committee members Geri D. Hewitt, MD and Karen R. Gerancher, MD.

Dienogest
Visanne®)

Is a hybrid between progesterone and 19-nortestosterone derivatives.

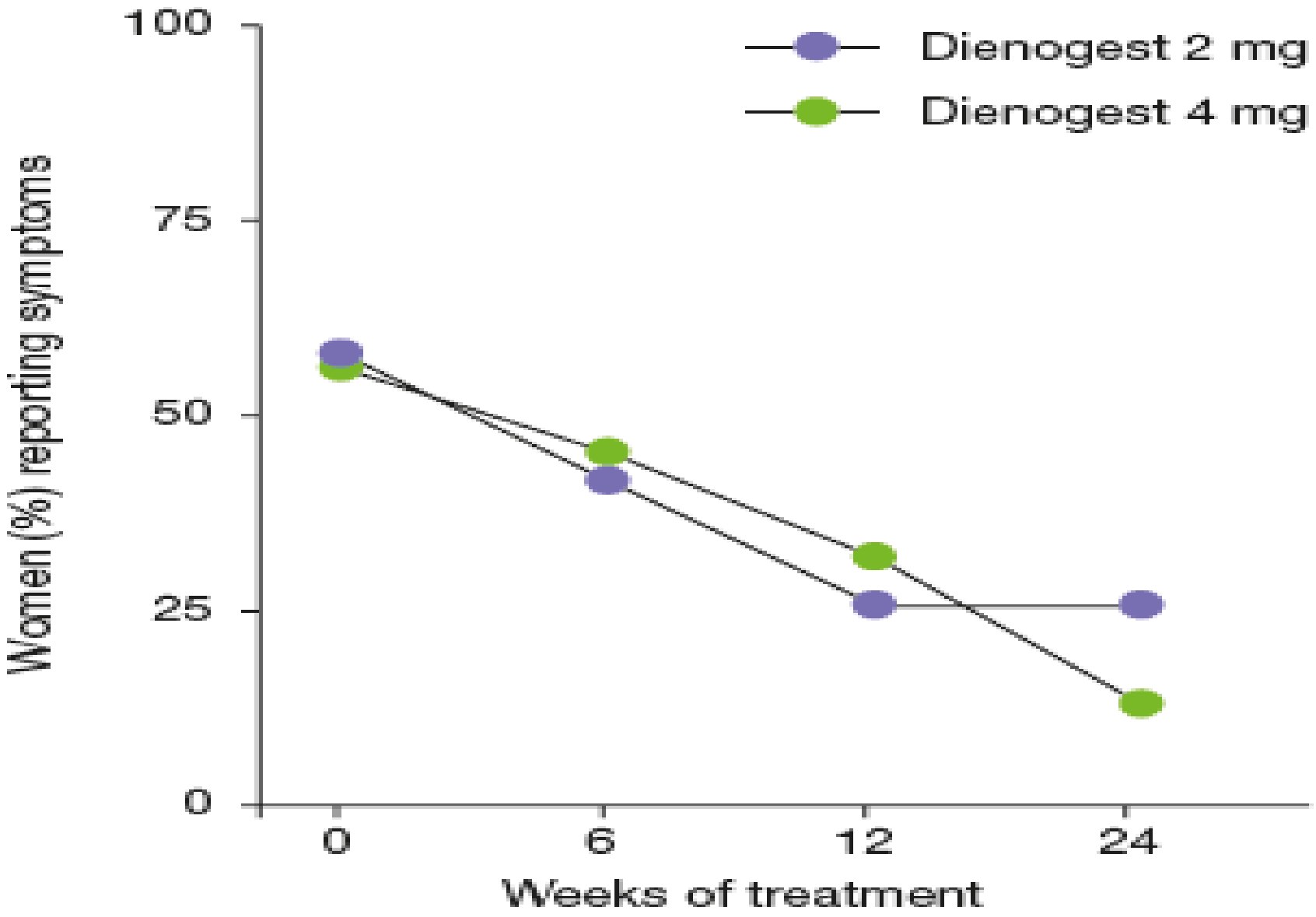
Received approval as a monotherapy for the treatment of endometriosis in Europe, Canada, Japan, Australia, and Singapore.

Dienogest 2 mg/day inhibits ovulation and produces hypo- estrogenic and hyperprogestational endocrine environment. (*C Seitz1,2008)*

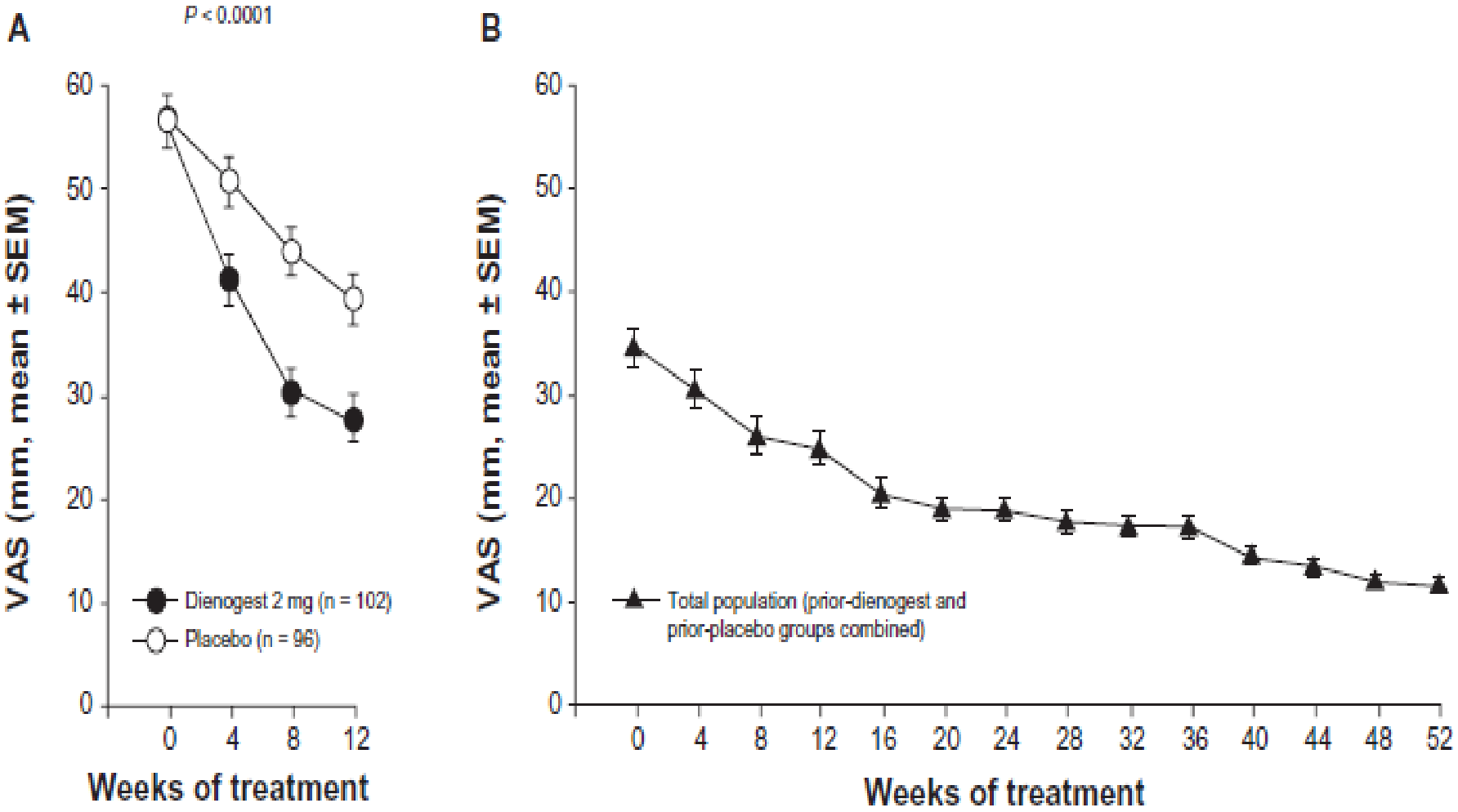
Moreover, it has also shown inhibitory activity on various components of the inflammatory response, as well as inhibiting angiogenesis.

D

Diffuse pelvic pain



Change in visual analog scale (VAS) score during the placebo-controlled (A) and the extension (B) studies. (Adolf E Schindler, 2011)



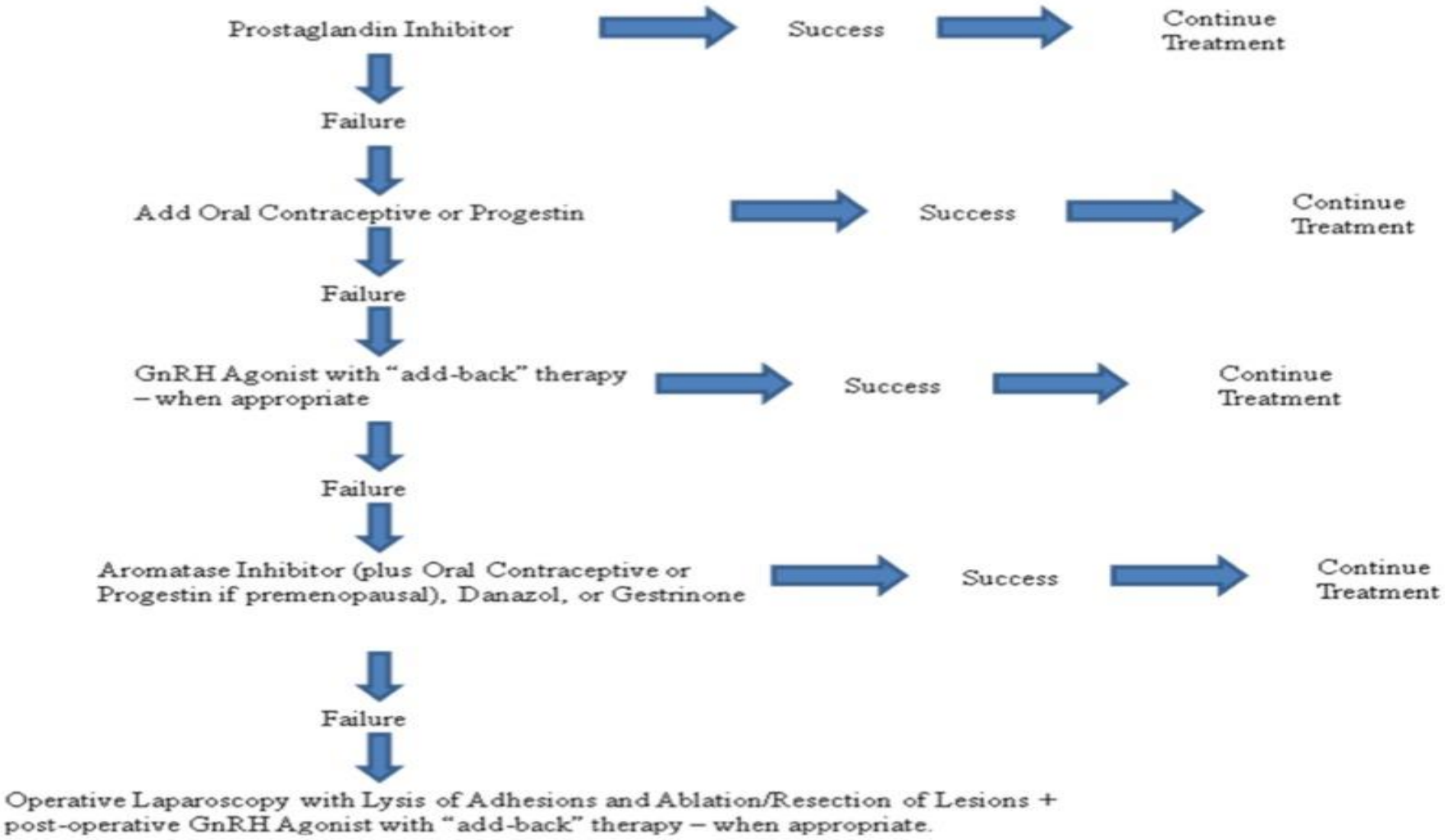
Elagolix (ORILISSA™):

- a promising oral GnRH antagonist for endometriosis-associated pain
- Highly effective
- Very expensive
- 200 mg twice a day and 150 mg once daily

Therapy Choices for Endometriosis

Class	Drug	Dosage
Androgen	Danazol	100 mg/d per vagina
GnRH agonist	Leuprolide	1 mg SC a day
	Leuprolide depot	3.75 mg IM monthly (11.75 mg IM q 3 mos)
	Buserelin	400 mcg intranasal TID
	Goserelin	3.6 mg SC monthly (10.8 mg/IM q 3 mos)
	Nafarelin	200 mcg/d bid intranasal BID
GnRH antagonist	Cetrotide	3 mg SC q week
Progestins	NETAc or Gestrinone	2.5-5 mg a day
	MPA	30 mg a day po for 6 months, followed by 100 mg IM q 2 weeks x 2 mos, then 200 mg IM monthly x 4 mos
	Depo-provera SC104	104 mg/0.65 mL SC every 3 mos
	Levonorgestrel-releasing-IUD	1 x 5 years
	Etonogestrel-releasing implant	1 x 3 years
Oral contraceptive	Monophasic estrogen/progestin	Low ethinyl estradiol dose or the NuvaRing continuously
Aromatase inhibitors	Femara (Vit D, Ca^{2+}, NET-Acetate)	Femara™ 2.5 mg PO a day NET-Ac 2.5 mg a day Vit D (800 IU qd) + Ca^{2+} (1.25 gm qd)

Plan of treatment



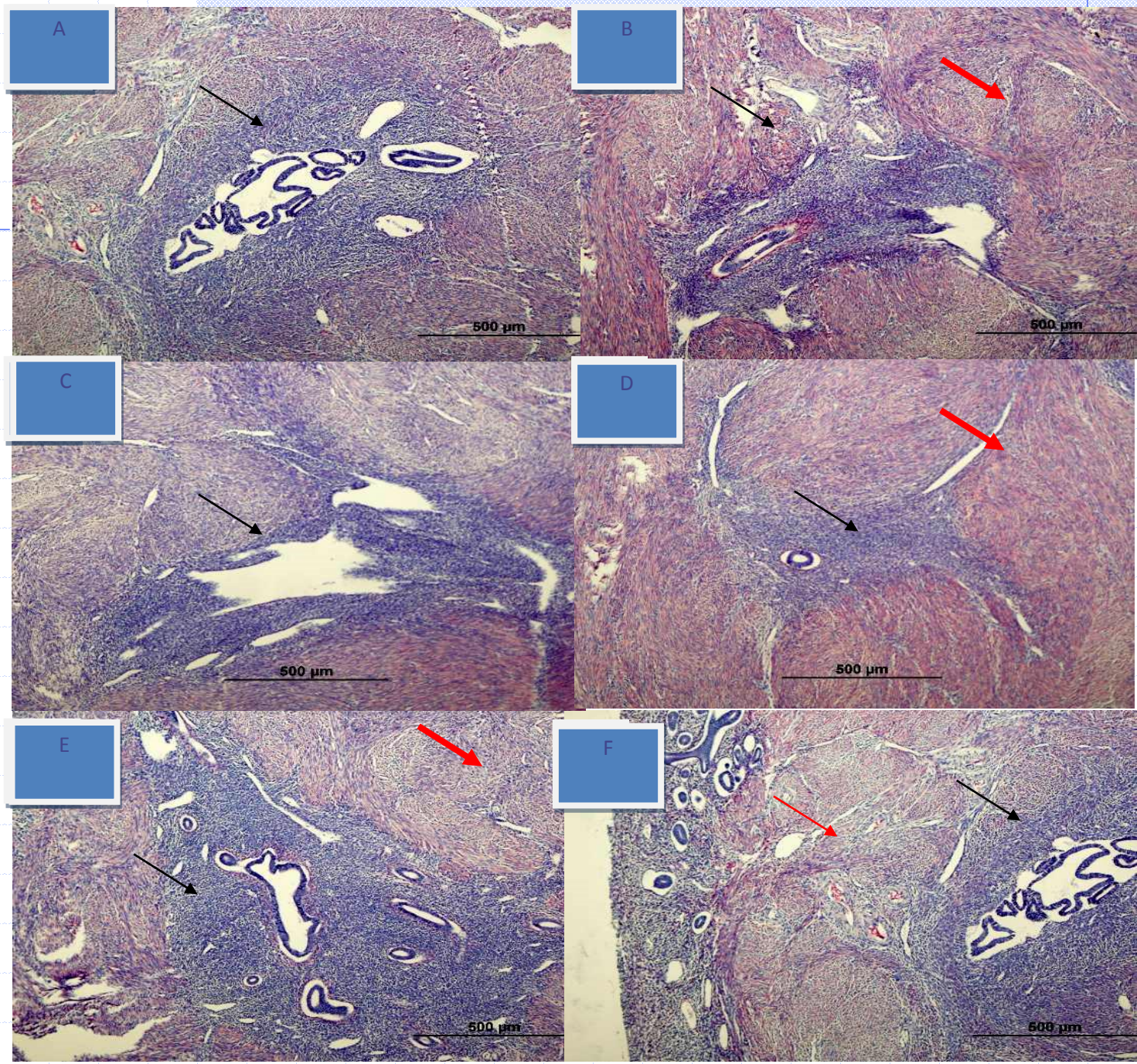
Adenomyosis

Adenomyosis

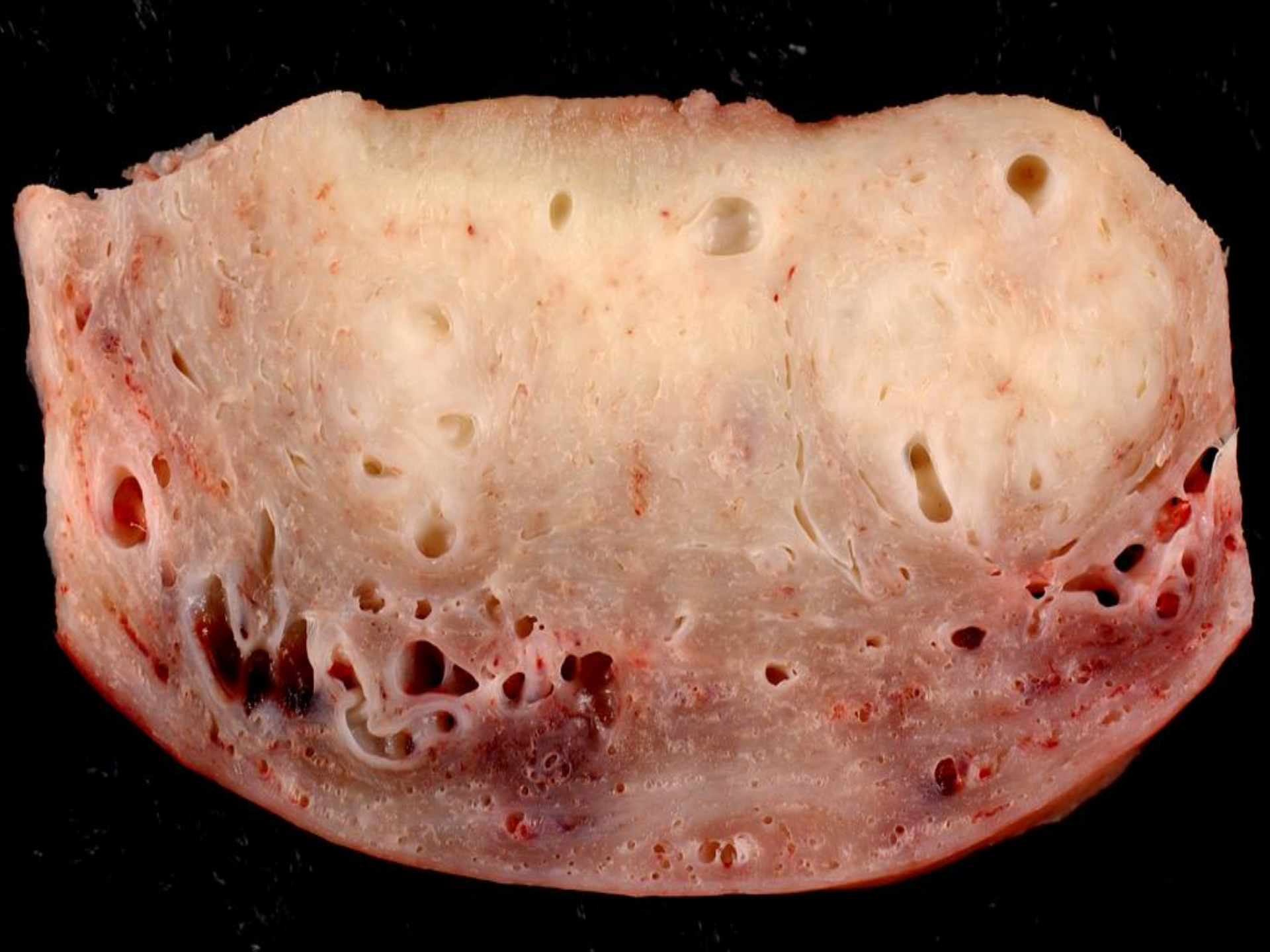
‘the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium

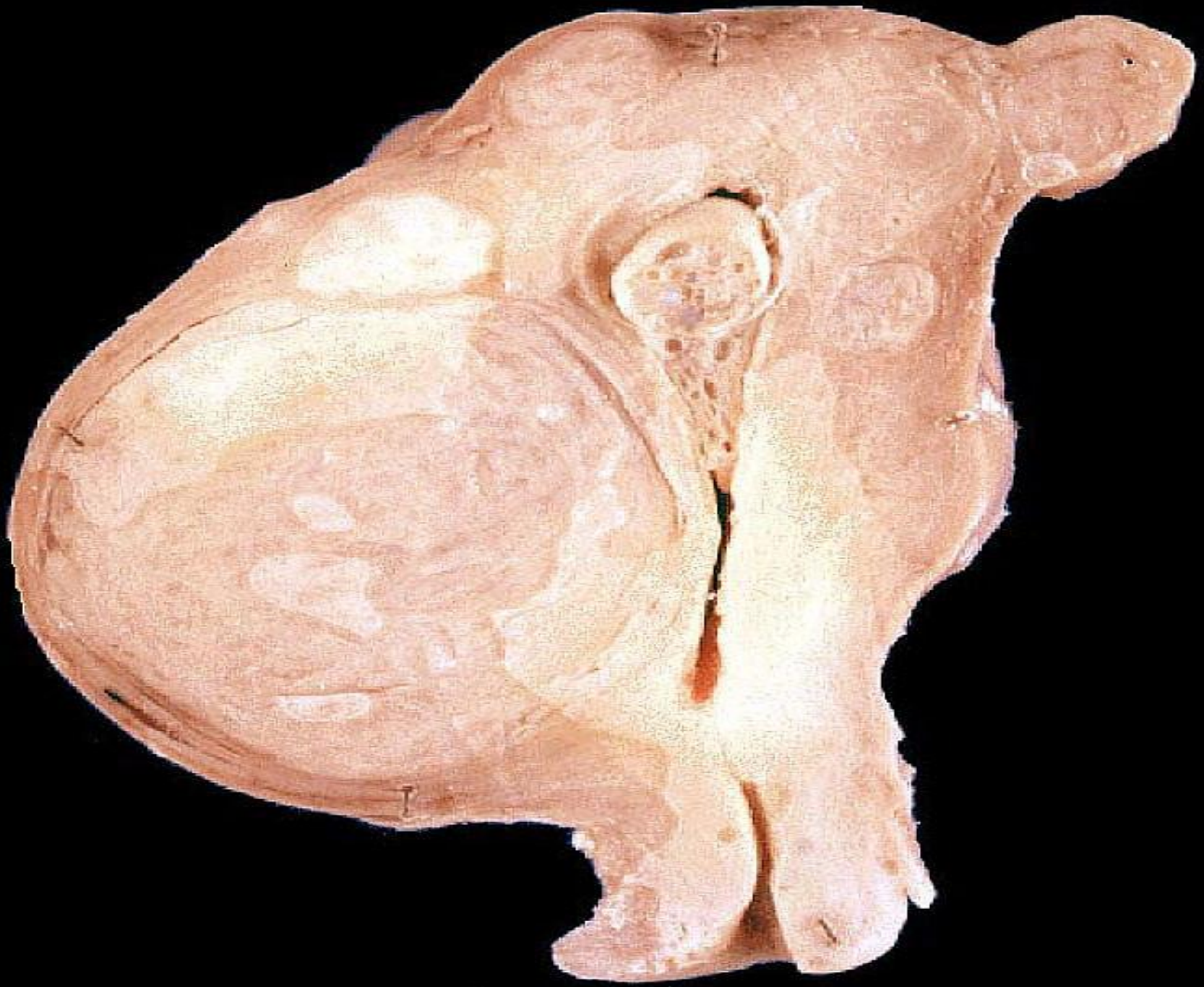
Background

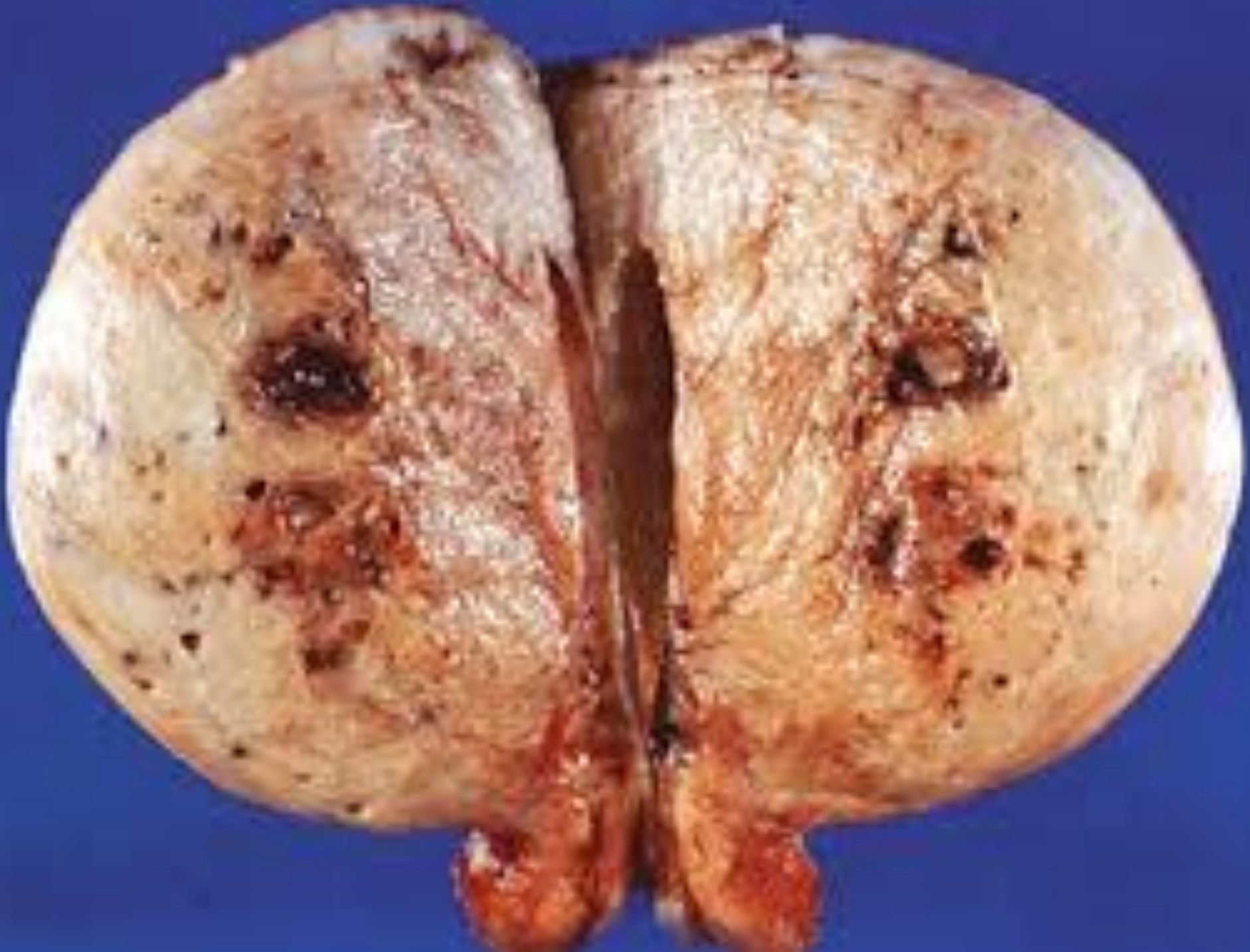
- ’The prevalence of adenomyosis reported in the literature ranges from 5 to 70%.
- Adenomyosis is most prevalent in women of late reproductive age between 35 and 50 years.
- Nearly all cases (90%) of adenomyosis occur in multiparous women, and it has been suggested that patients with adenomyosis have a high incidence of early miscarriage.



Al-Jefout et al, 2011







Mechanism of pain

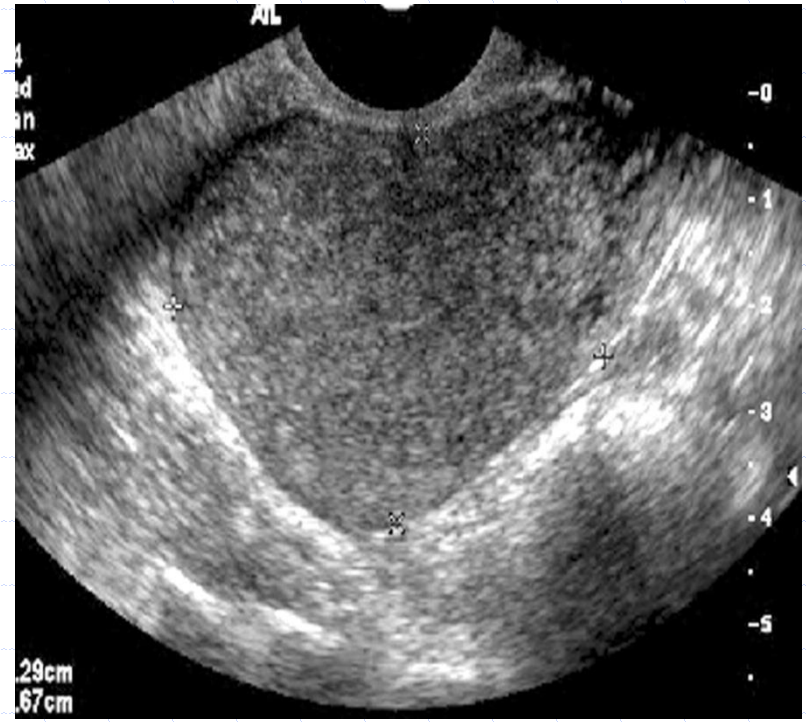
The gland tissue grows during the menstrual cycle and then at menses tries to slough, the old tissue and blood cannot escape

This ***trapping*** of the blood and tissue causes uterine pain in the form of monthly menstrual cramps.

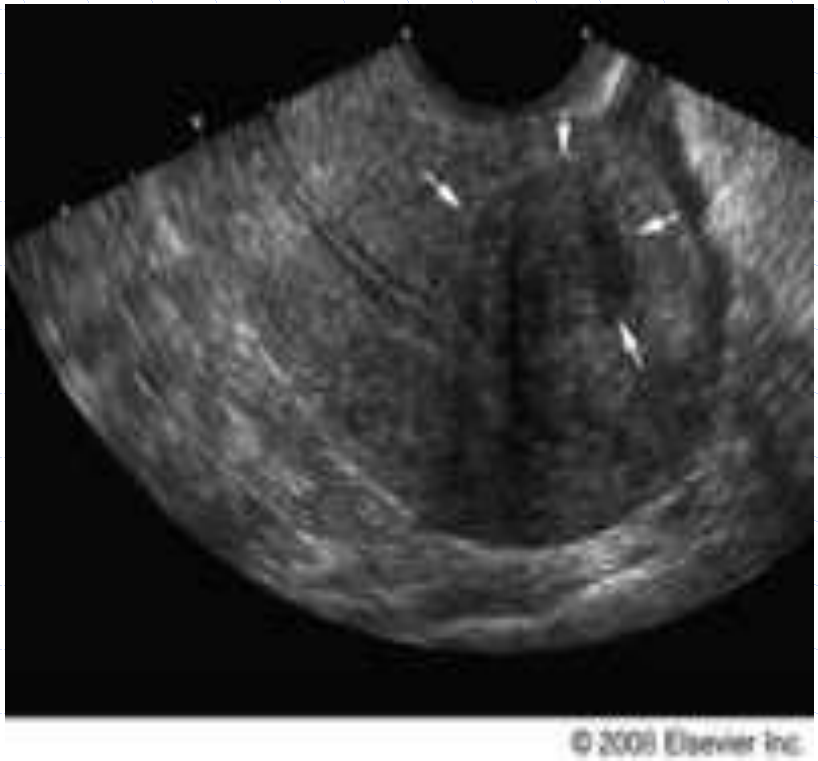
It also produces abnormal uterine bleeding.

Adenomyosis types

- There are two forms of adenomyosis:
  - Diffuse
  - Focal
- While diffuse adenomyosis determines varying degrees of diffuse uterine enlargement,
- focal adenomyosis (also known as adenomyoma) presents as a localized mass difficult to differentiate from leiomyoma.



diffuse adenomyosis



Focal adenomyosis

Clinical picture

- About 35% of adenomyotic cases are asymptomatic.
- Dysmenorrhoea 30%
- Menorrhagia 50%
- Metrorrhagia 30%,
- Deep dyspareunia
- Subfertility

Signs

- The uterus is typically diffusely enlarged, although usually less than 14 cm in size, and is often soft and tender, particularly at the time of menses.
- Mobility of the uterus is not restricted, and there is no associated adnexal pathology

Adenomyosis as an oestrogen dependent disease

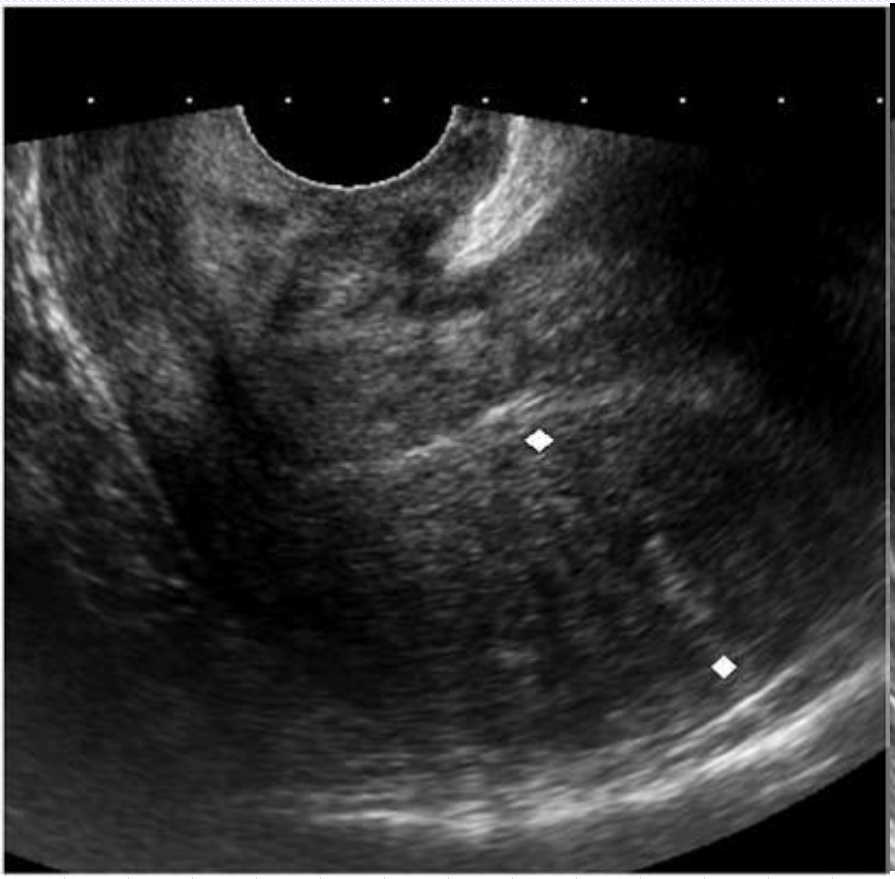
- Breast cancer, endometrial cancer, endometriosis, adenomyosis and leiomyomas are diseases that develop in an oestrogen-dependent fashion.
- These tumours commonly contain oestrogen receptors (ER), progesterone receptors (PR) and androgen receptors.

Diagnosis

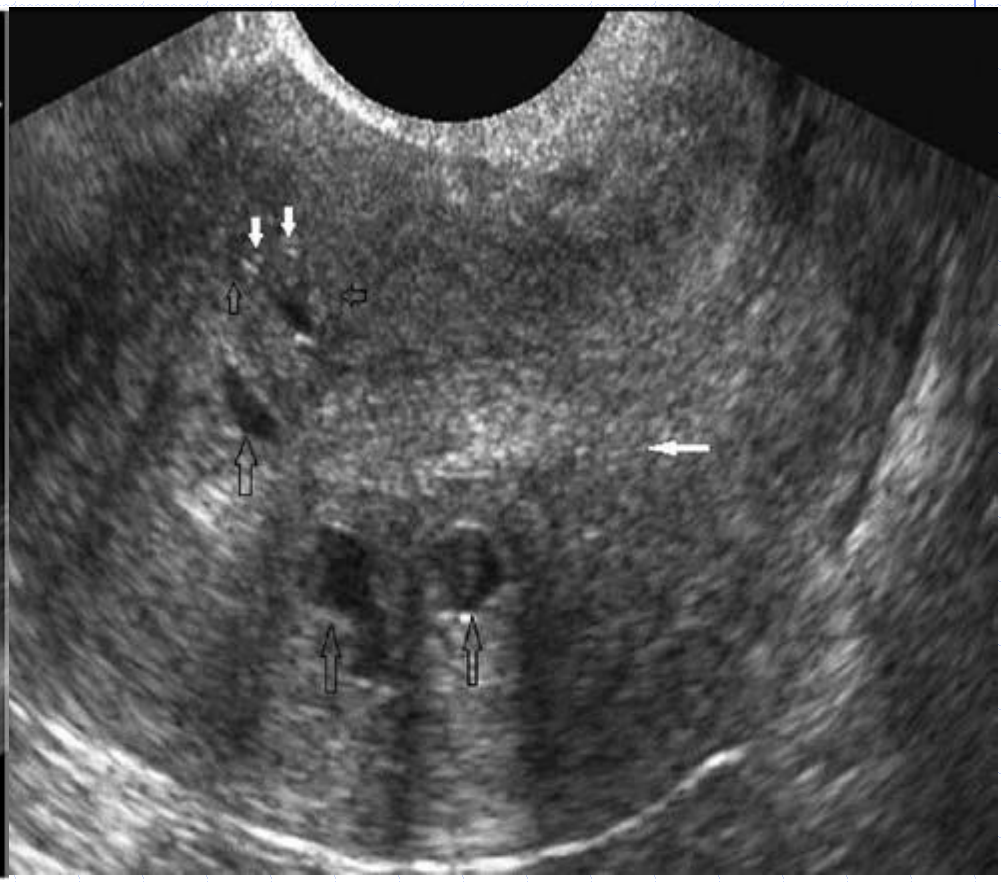
- Adenomyosis has traditionally been diagnosed by the pathologist in hysterectomy specimens or with invasive techniques such as percutaneous or laparoscopic uterine biopsies.
- However, the recent development of high-quality non-invasive techniques e e.g. transvaginal sonography (TVS) and magnetic resonance imaging (MRI) has renewed interest in diagnosing adenomyosis with sufficient sensitivity, specificity and predictive value prior to any treatment.
- Hysteroscopy is also helpful.
- Hysterosalpingogram can aid also in diagnosis

TVUS

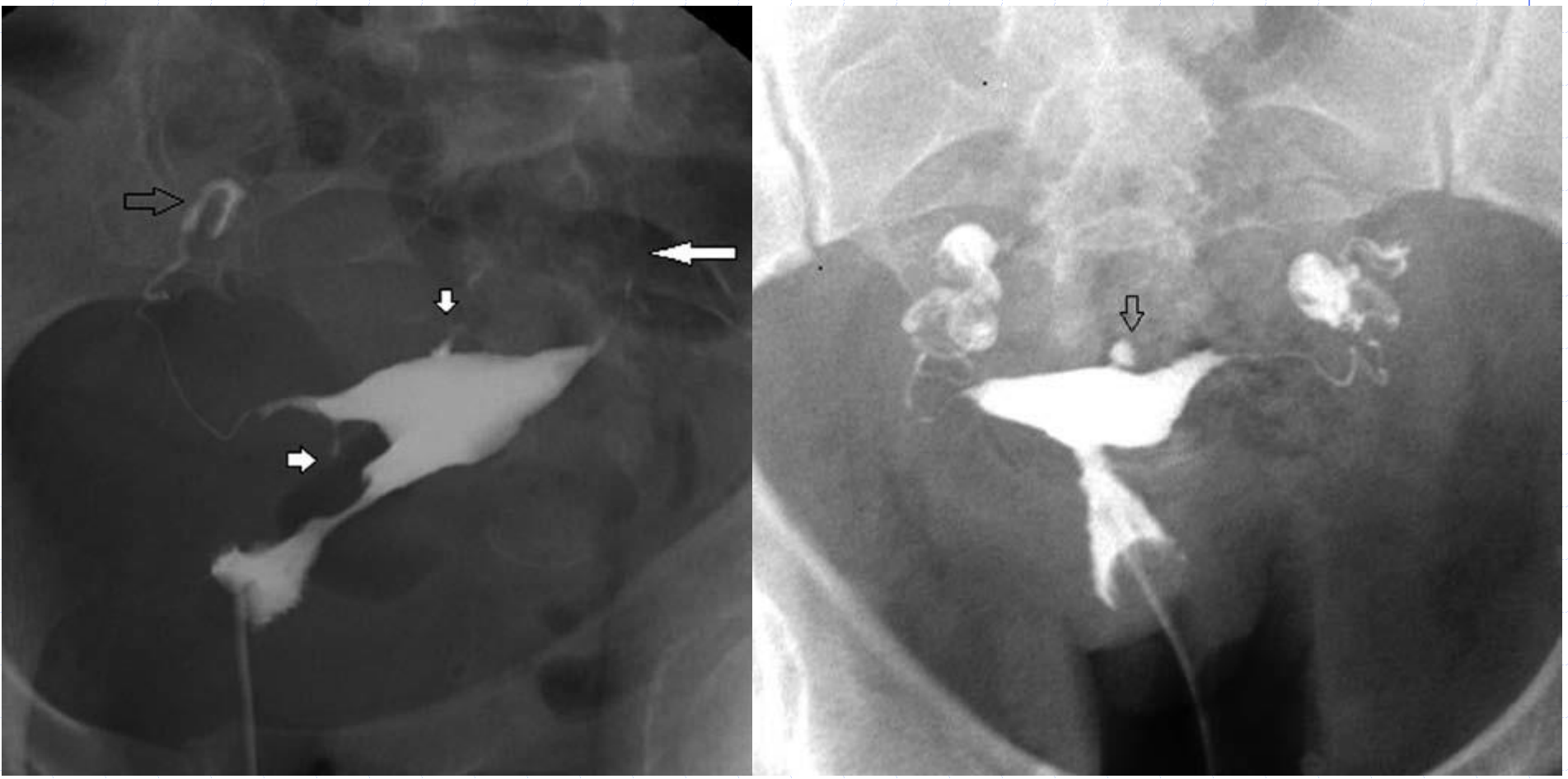
- increased myometrial echogenicity or linear hyperechoic bands extending deep into the myometrium, which indicates the presence of islets of ectopic endometrial tissue;
- hypoechoic areas in the myometrium compatible with hyperplasia of the muscle tissue surrounding the ectopic tissue;
- anechoic areas due to glandular dilatation or myometrial cysts;
- poor definition of the junctional zone;
- enlargement of the uterus



an asymmetric, ill-defined thickening of the myometrium in the posterior uterine wall (pseudowidening, callipers); on the oblique HSG



Diffuse adenomyosis. B-mode transvaginal ultrasound. Sagittal view of the uterus shows poor definition of the endomyometrial unction (big white arrow);



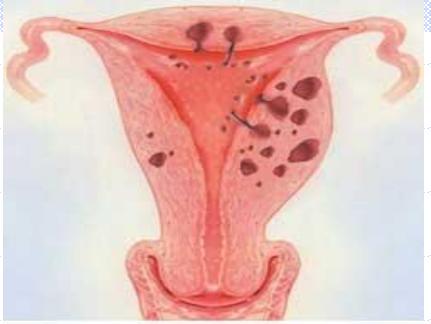
Cystic adenomyosis. Hysterosalpingography. Anteroposterior pojection demonstrates a pseudodiverticulum of the uterine fundus, caused by adenomyosis (arrow).

Pelvic Magnetic Resonance Imaging (MRI)

- Is the radiological investigation of choice for the diagnosis of adenomyosis, with a sensitivity and specificity approaching 90%

  ([Reinhold et al., 1998, Tamai et al., 2006]),
- Patients identified as having a thickened junctional zone ≥12 mm were considered to have sufficient MRI evidence of adenomyosis,
- Two prospective MRI studies have confirmed a link between failure of successful implantation of good quality embryos during IVF treatment and adenomyosis.
- [Kissler et al., 2006, Maubon et al., 2010])

Hormonal treatment



Adenomyosis. Note thickened wall of uterus which can be mistaken for fibroids.

Mirena for Adenomyosis

- A substantial reduction in menstrual blood loss and associated pain in women with adenomyosis .
- Fedele et al. first demonstrated that 23 out of 25 women with significant adenomyosis, diagnosed by transvaginal ultrasound, obtained dramatic reduction in menstrual blood loss following LNG IUS insertion.
- Even the grossly enlarged adenomyotic uterus may sometimes respond well.
- Possible use of two IUS for large utrii.?

(L. Fedele, S. *Fertil Steril*, 1997, A.M. Bragheto, *Contraception*, 2007, S. Cho, *Am J Obstet Gynecol*, 2008, Y.F. Fong *Contraception*, 1999)

GnRH agonists

- Are highly effective in the reduction of uterine volume and alleviation of symptoms associated with adenomyosis, although their use for long periods of time is impracticable due to hypo-oestrogenic side-effects.
- This therapy may therefore be indicated for women with diffuse adenomyosis seeking a pregnancy

Uterine artery embolization (UAE)

- All publications available from 1999 through 2010 are included in this report.
- Long-term data are available from 511 affected women from 15 studies. Improvements were reported by 387 patients (75.7%).
- The median follow-up was 26.9 months.
- UAE as treatment for adenomyosis shows significant clinical and symptomatic improvements on a short- and long-term basis.

(Lei Yu, 2011)

Surgical treatment

The ultimate treatment still TAH

Clinical cases discussion in endometriosis

A/Prof Moamar Al-Jefout MD PhD

CM&HS/UAEU

- Please suggest a treatment plan for the following cases

Case history #1

- A 20-year-old nulliparous married female presents with a history of progressively worsening menstrual pain and heavy prolonged periods that is now affecting her QoL.
- She misses 2 to 3 days of work each month. She finds no relief from ibuprofen. Her marriage is being affected by associated stress and pain during intercourse.
- On vaginal examination, her pelvic musculature is moderately tender. Her uterus is of normal size and minimally tender and not mobile. Rectovaginal examination reveals uterosacral nodularity and exquisite tenderness.
- She is also known case of VW disease.
- She is not planning for pregnancy for the coming 4 years.

Case history #2

- A 32-year-old P2 female presents with a history of progressively worsening menstrual pain that is now causing her distress for most of the month. She misses 2 to 3 days of work each month. She finds no relief from ibuprofen. Her marriage is being affected by associated stress and pain during intercourse. On vaginal examination, her pelvic musculature is moderately tender. Her uterus is of normal size and minimally tender and not mobile. Rectovaginal examination reveals uterosacral nodularity and exquisite tenderness.
- She is also know case of Sickle cell Anemia disease.
- She is not planning for pregnancy for the coming 2 years.

Case history #3

- A 39-year-old female presents to you as she and her husband have been trying to conceive for the past 2 years and have been unsuccessful.
- She has no complaints except for some mild lower abdominal bloating. Her past medical and surgical history is unremarkable. Her sister has recently been diagnosed with endometriosis.
- On examination, she is thin and in no distress.
- Pelvic examination reveals normal not tender mobile uterus and 6-8 cm bilateral adnexal mass.
- U/S scan reveals 8 cm bilateral adnexal masses resembling endometriomata

Case history # 4

- A 39-year-old female presents to you as she and her husband have been trying to conceive for the past 2 years and have been unsuccessful.
- She has no complaints except for some mild lower abdominal bloating. Her past medical and surgical history is unremarkable. Her sister has recently been diagnosed with endometriosis.
- On examination, she is thin and in no distress.
- Pelvic examination reveals normal not tender mobile uterus
- U/S scan reveals 3 cm unilateral adnexal mass resembling endometrioma

Case history # 5

- A 17 -year-old Virgo intacto female presents with a history of progressively worsening menstrual pain that is now causing her distress for most of the month. She misses 2 to 3 days of school each month. She finds no relief from ibuprofen.

Case history # 6

- Grand multipara 39 year-old. C/O heavy prolonged periods with dysmenorrhea and deep dyspareunia (VAS 6-8/10) for the last 6 months.
- Her Hb-9.5 gm/L
- She is not pregnant. O/E- 14 weeks enlarged tender and mobile uterus with no adnexal masses

Cases for Tomorrow

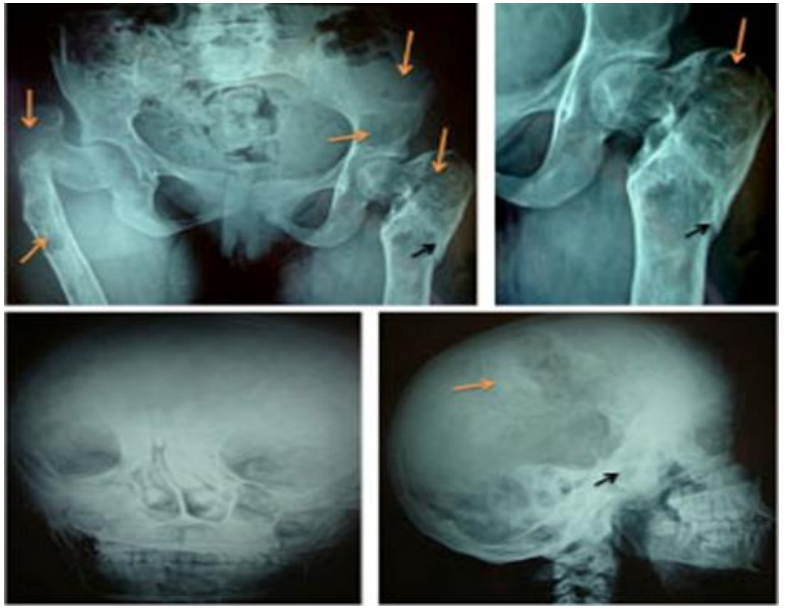
Case # I

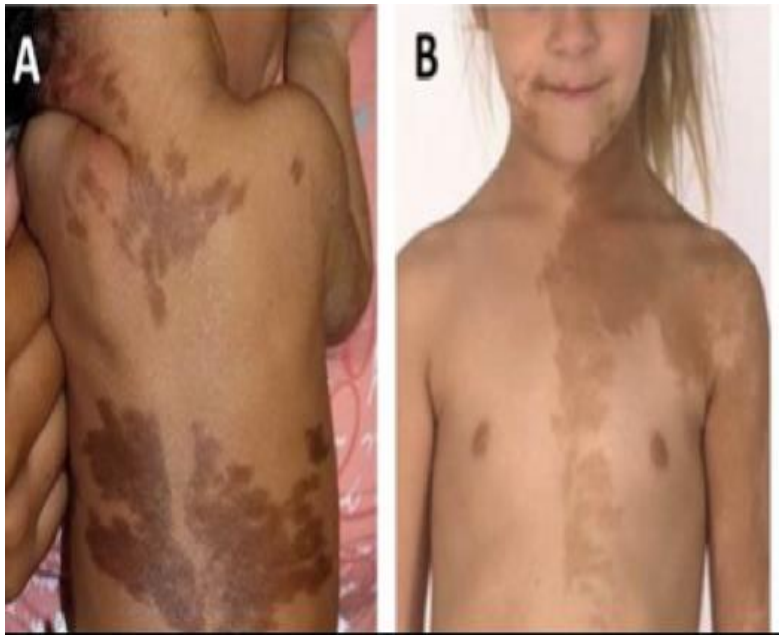
- A 27-year-old multiparous female, presents complaining of having no periods for the last 6 months. She denies any pelvic pains, weight loss or excessive exercise. On examination, she is 168 cm in tall and weighs 64 kg. Her blood pressure is 110/60 mm Hg. Her thyroid gland is normal. She underwent a D&C few months ago due to septic miscarriage after which her periods become less and less and eventually stopped. She also mentioned that her last vaginal delivery was complicated by severe postpartum hemorrhage and uterine curettage. However, she breast fed her son for three months.

How can you label this case? What is the most likely diagnosis and what are your differential diagnoses? What is your next diagnostic step? What is your therapeutic plan for this patient?

Case # II

An 8-year-old female presents to gyn clinic complaining of having early occurring periods. On examination, she is 130 cm in tall and weighs 31 kg. Her blood pressure is 110/60 mm Hg. Physical examination revealed pathology shown in figure 1: A &B. Her mother mentioned multiple visits to Emergency rooms due to bone pains & fractures after ordinary activities and showed recent report she had figure 2.






Thank You!