
In the name

Overview of treatment of Endometriosis

Dr N.Navli
Ob&gyn
Infertility fellowship

- Presence of endometrial tissue (glands & stroma) outside the uterus

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- It is a progressive debilitating disease affecting general physical, mental & social well being of women

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- Affects nearly 7 to10% of the women in reproductive age, 30% of those who are infertile or present with pain.

- The most frequent sites of implantation are pelvic viscera and the peritoneum

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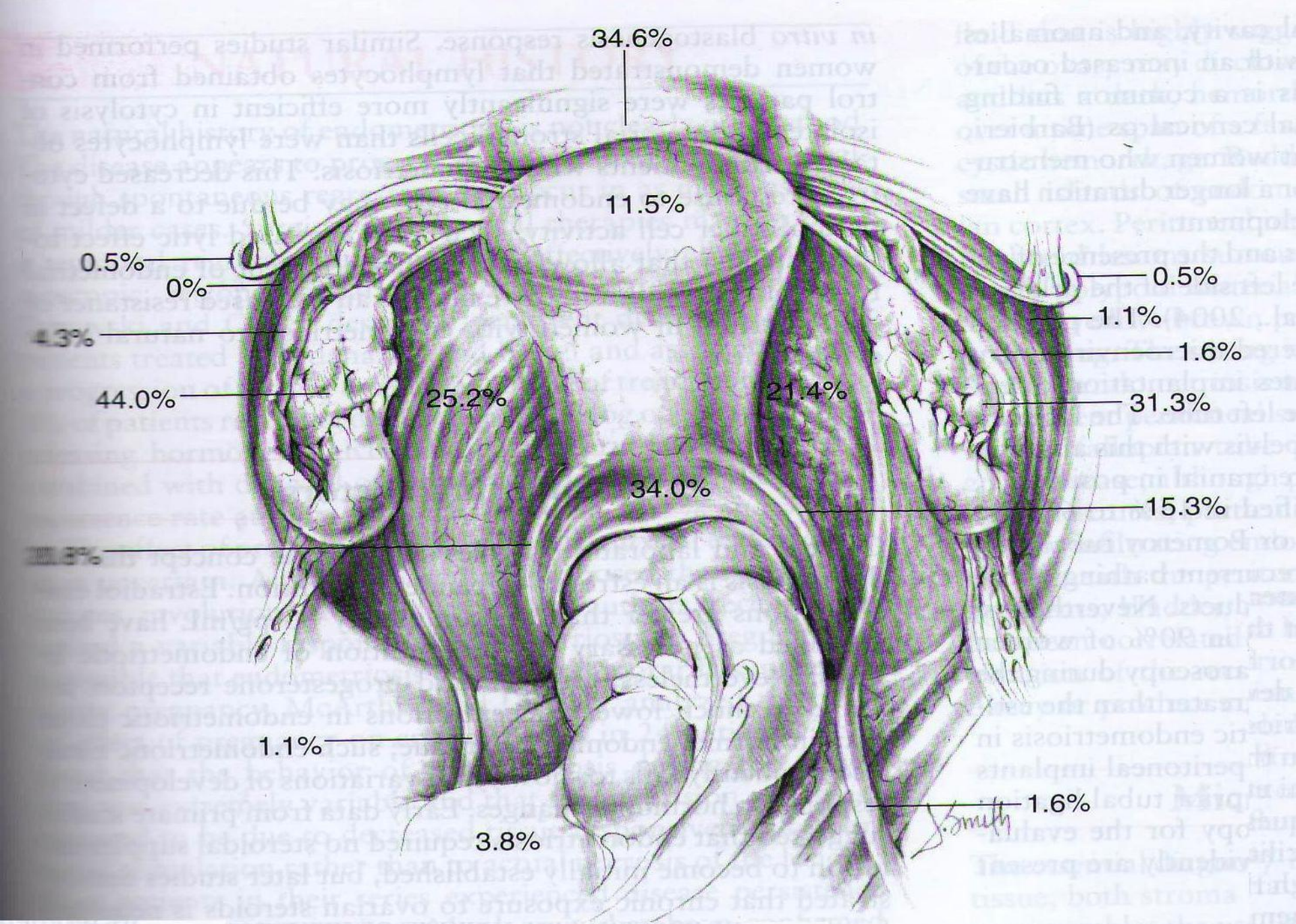
- Less commonly cervix, hernial sacs, the umbilicus, laparotomy or episiotomy scars may be involved


34.6%
11.5%
0.5%
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4.3%
44.0%
25.2%
34.0%
1.1%
3.8%
0.5%
1.1%
1.6%
21.4%
31.3%
15.3%
1.6%

Sites of endometriosis

- ***Pelvic***
  - Ovary
  - Cul de sac
  - Uterosacrals
  - Posterior surface of uterus
  - Posterior broad ligament
  - Rectovaginal septum
  - Tubes and round ligaments
- ***Extrapelvic sites***
  - Intestines (rectosigmoid, cecum, terminal ileum, proximal colon, appendix)
  - Lungs & thorax
  - Urinary tract
- ***Less common sites***
  - Cervix
  - Hernial sacs
  - Umblicus
  - Laparotomy/episiotomy sites
  - Tubal stumps after sterilization
- ***Rarest***
  - Extremities

Why Newer Concepts are required

- First described by Daniel Shroen in 1690 but still we are not very sure of its definitive cause
- Endometriosis is considered to be an enigmatic disease owing to
  - **Lack of specific symptoms,**
  - **Poorly understood pathogenesis**
  - **Limited effective therapeutic options**
- The last three decades have witnessed a significant volume of research related to endometriosis

- *Incidence is increasing b/c of changing life style, increased awareness and better diagnostic modalities*

Endometriotic lesions

Variable appearance

Peritoneum

Typical

Superficial

- Early red lesions
- Powder burn or gunshot
- Black, dark brown or bluish puckered lesions
- White plaques
- Adhesions –flimsy,vascular,dense

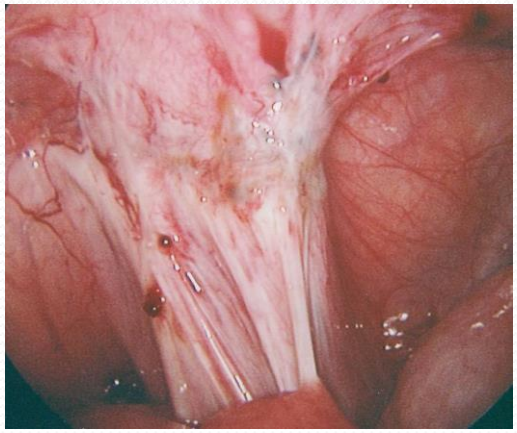
(DIE) Deeply Infiltrating Endometriosis , >5mm depth

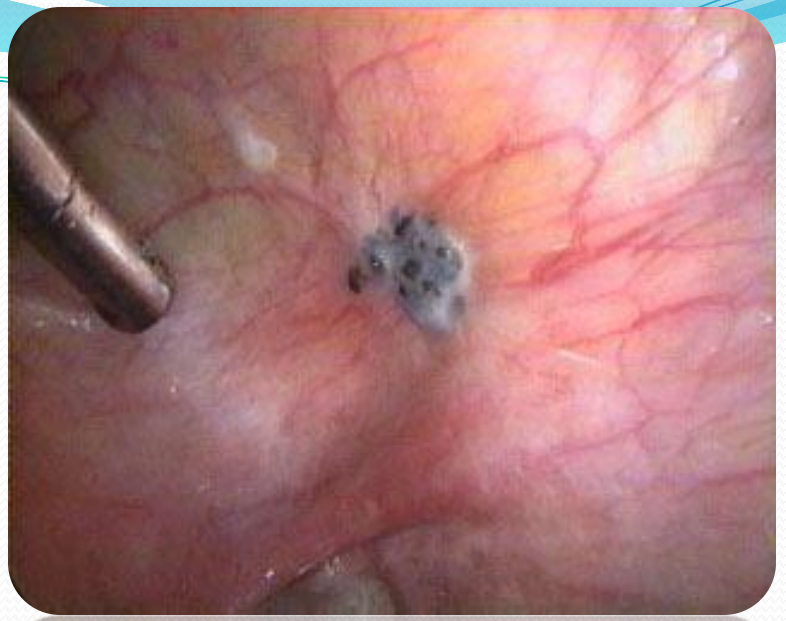
Atypical or subtle lesions

- Serous / clear vesicle
- Yellowish discoloration

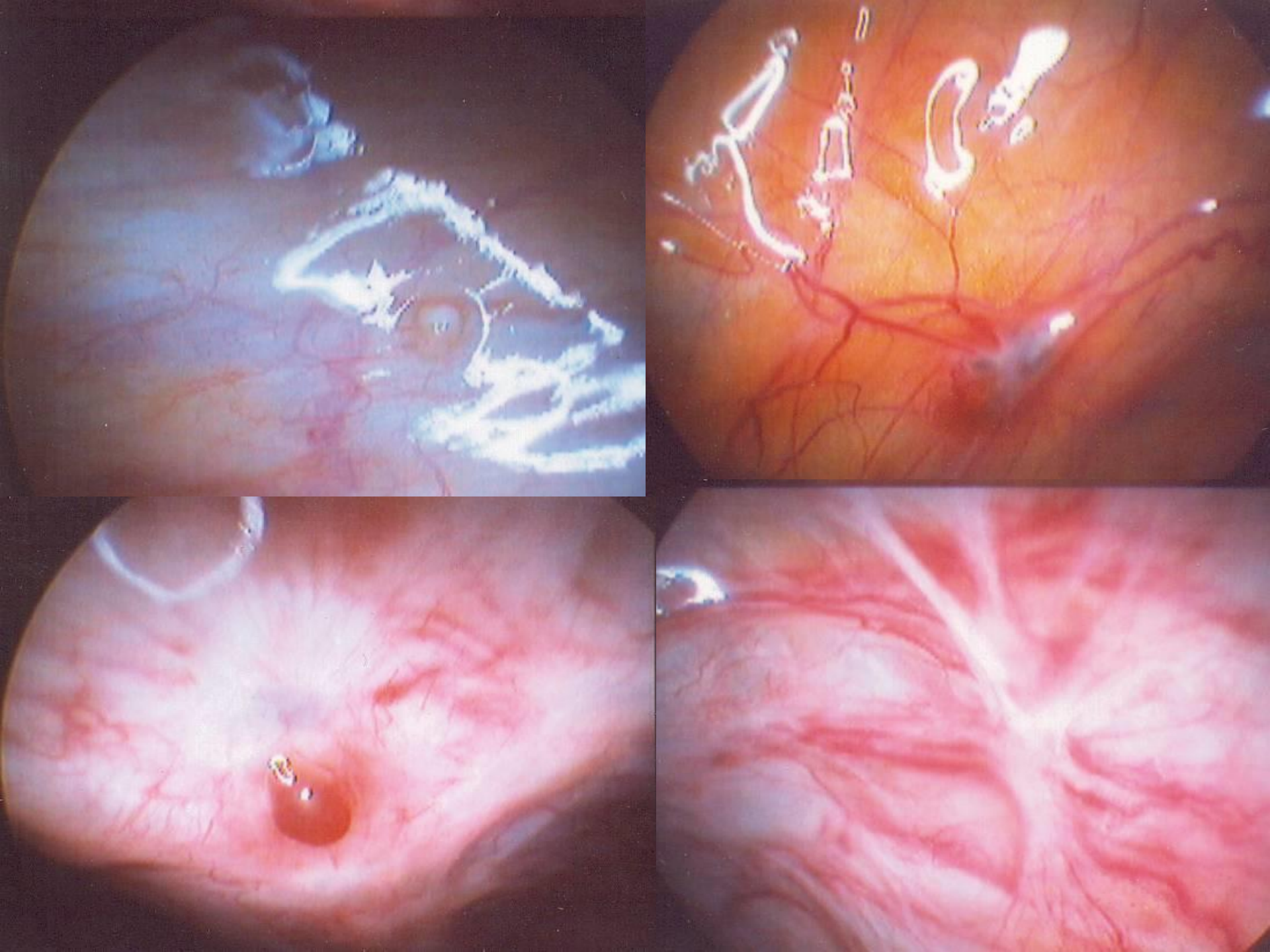
Ovaries

- Superficial
- Subovarian adhesions
- Endometriomas






Clear endometriosis

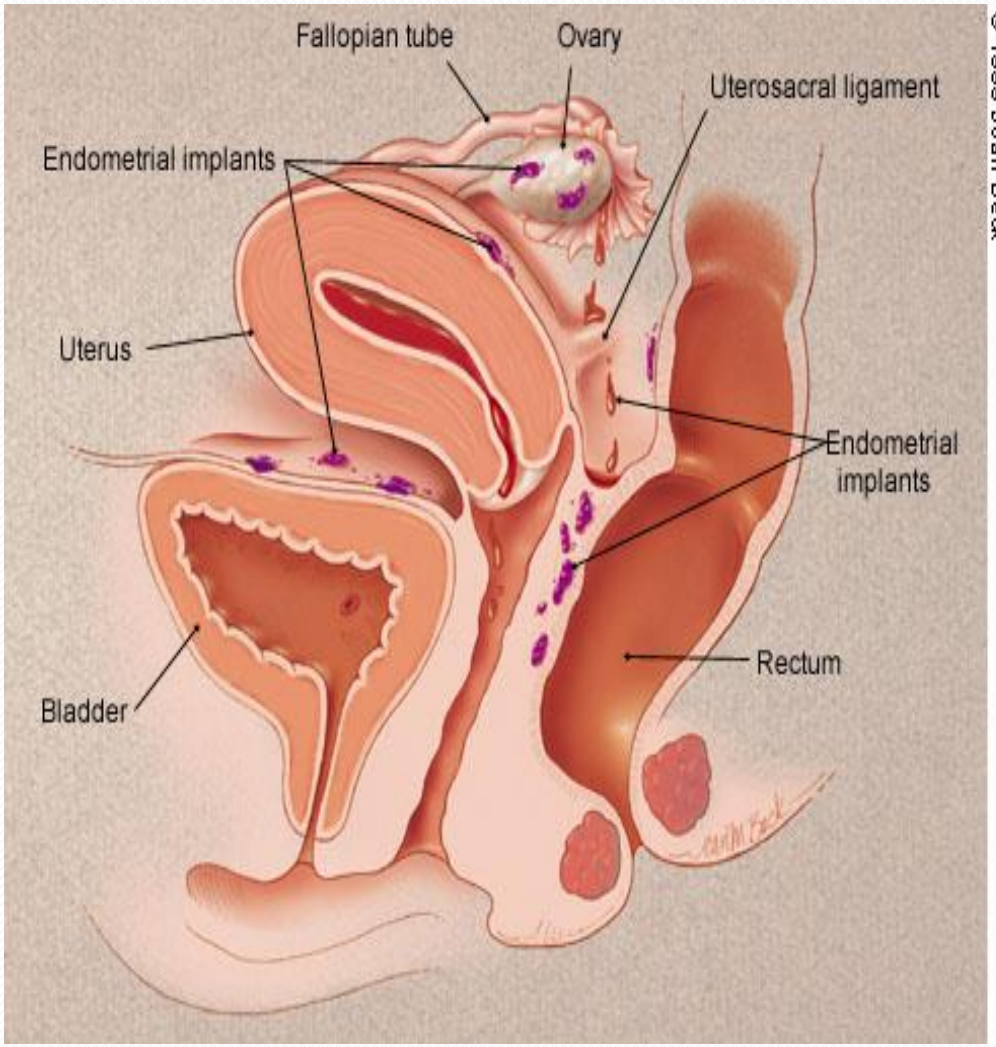


Why does it occur ?

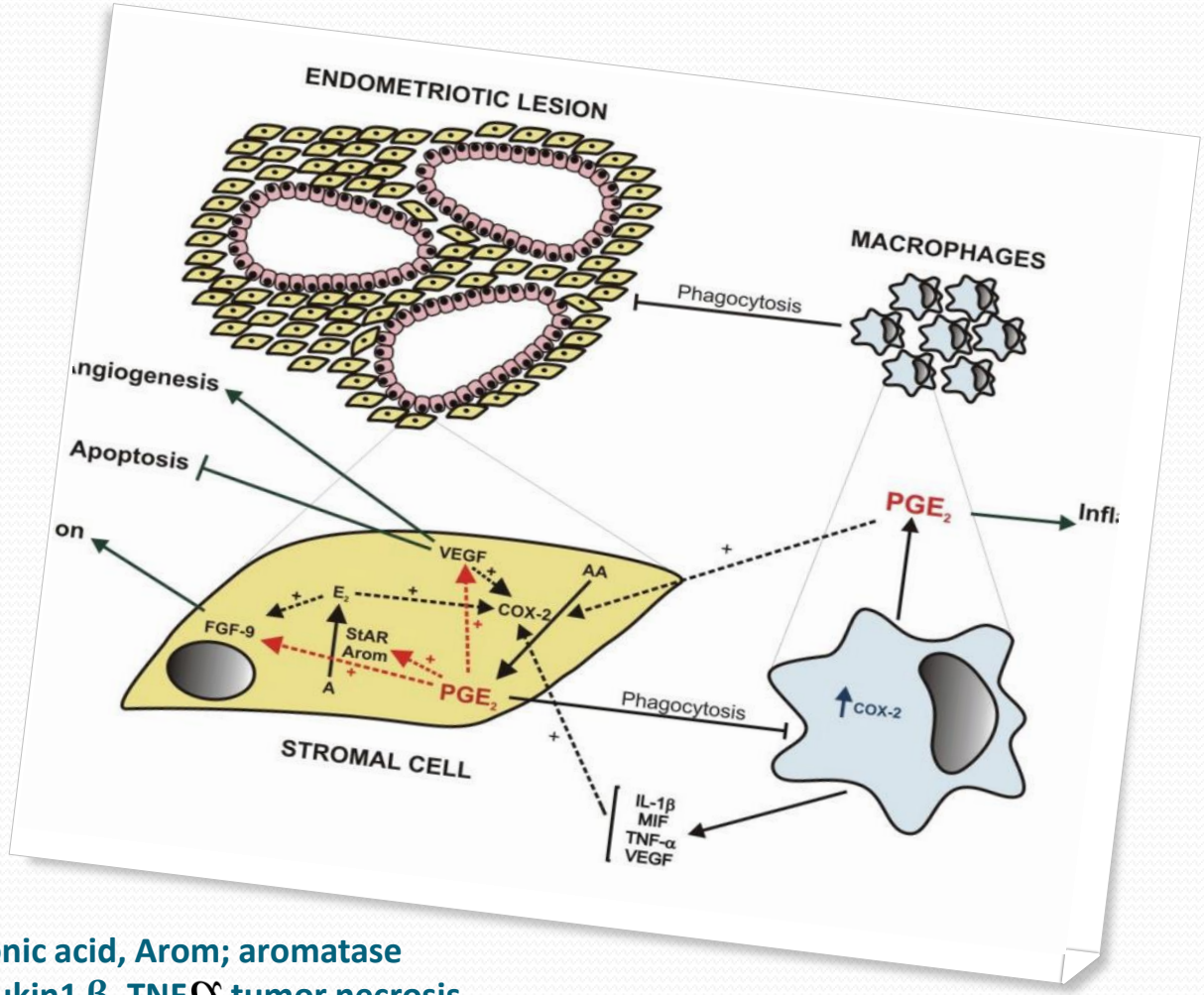
- Transplantation theory (Sampson)
- Coelomic metaplasia theory(Mayer and Ivanoff)
- Induction theory (Merril)
- Genetic factors
- Immunologic factors
- The cellular and molecular etiologic theories label endometriosis as **an inflammatory and estrogen dependent disorder**

Transplantation theory:

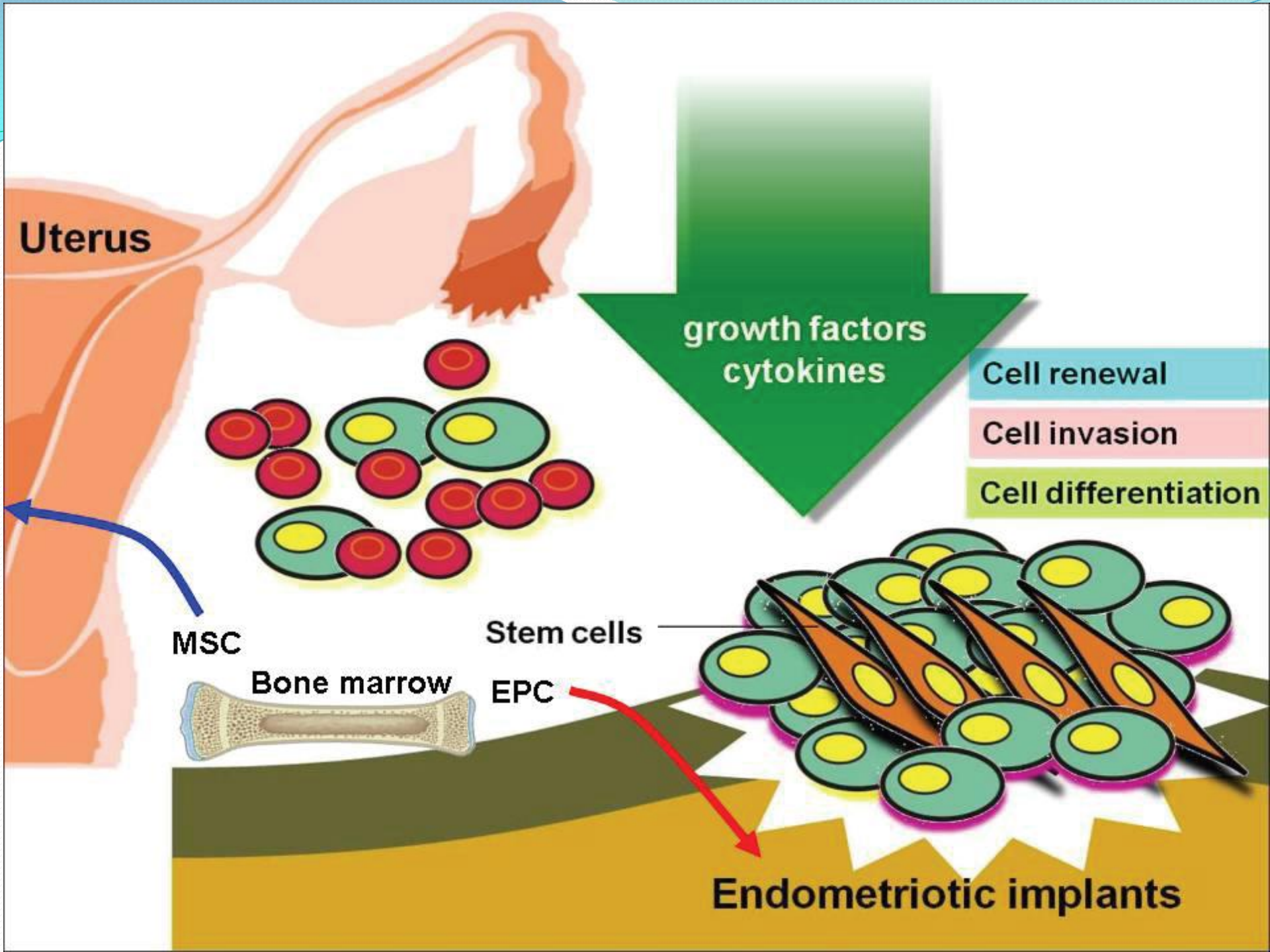
- Originally proposed by Sampson in 1920
- Based on assumption that endometriosis is caused by implantation of the endometrial cells by transtubal regurgitation during menstruation.
- Seen in 70-90% of women , more common in endometriosis

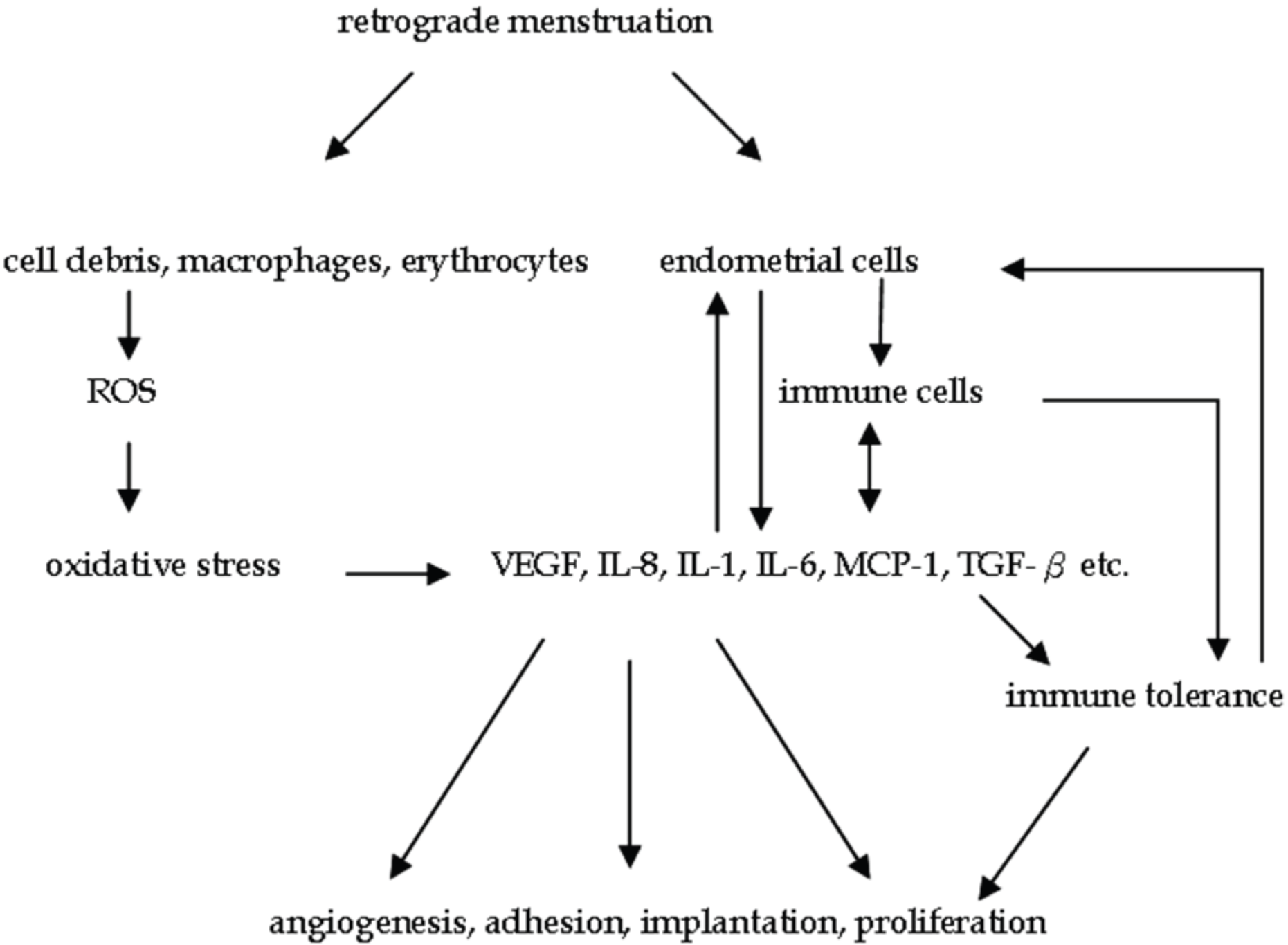


Peritoneal Environment in Endometriosis



A; androstendione, AA; arachidonic acid, Arom; aromatase P450,E2; estradiol, IL-I β interleukin1 β, TNF-α tumor necrosis factor α , VEGF; vascular endothelial growth factor


Uterus
growth factors
cytokines
Cell renewal
Cell invasion
Cell differentiation
MSC
Bone marrow
Stem cells
EPC
Endometriotic implants


retrograde menstruation
cell debris, macrophages, erythrocytes
endometrial cells
ROS
immune cells
oxidative stress
VEGF, IL-8, IL-1, IL-6, MCP-1, TGF- β etc.
immune tolerance
angiogenesis, adhesion, implantation, proliferation

Is It Inherited ?

- No Mendelian pattern of inheritance, multi factorial inheritance is suggested.
- **Risk of endometriosis is 7 times if first degree relative is affected.**
- 75% incidence in monozygotic twins.
- No mutations have been identified so far.
- Aneuploidy- chromosome 11,16,17, losses of 1p,22q,5p,6q,16,&18 have been demonstrated in endometriotic cells.

Grading of Endometriosis

Endometriosis	Deposits	< 1cm	1-3 cm	> 3cm
Peritoneal	Superficial	1	2	4
	Deep	2	4	8
Ovary	Right superficial	2	4	8
	Right deep	4	16	20
	Left superficial	2	4	8
	Left deep	4	16	20
Cul-de-sac obliteration	Partial	4	Complete	40
Adhesions	**Enclosure**	**<1/3**	**1/3-2/3**	**>2/3**
Ovary	Right filmsy	1	2	4
	Right dense	4	8	16
	Left filmsy	1	2	4
	Left dense	4	8	16
Tube	Right filmsy	1	2	4
	Right dense	4	8	16
	Left filmsy	1	2	4
	Left dense	4	8	16

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION 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
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	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

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

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

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

Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

To Be Used with Abnormal Tubes and/or Ovaries

Clinical Presentation

Severe dysmenorrhoea

Deep dyspareunia

Chronic pelvic pain

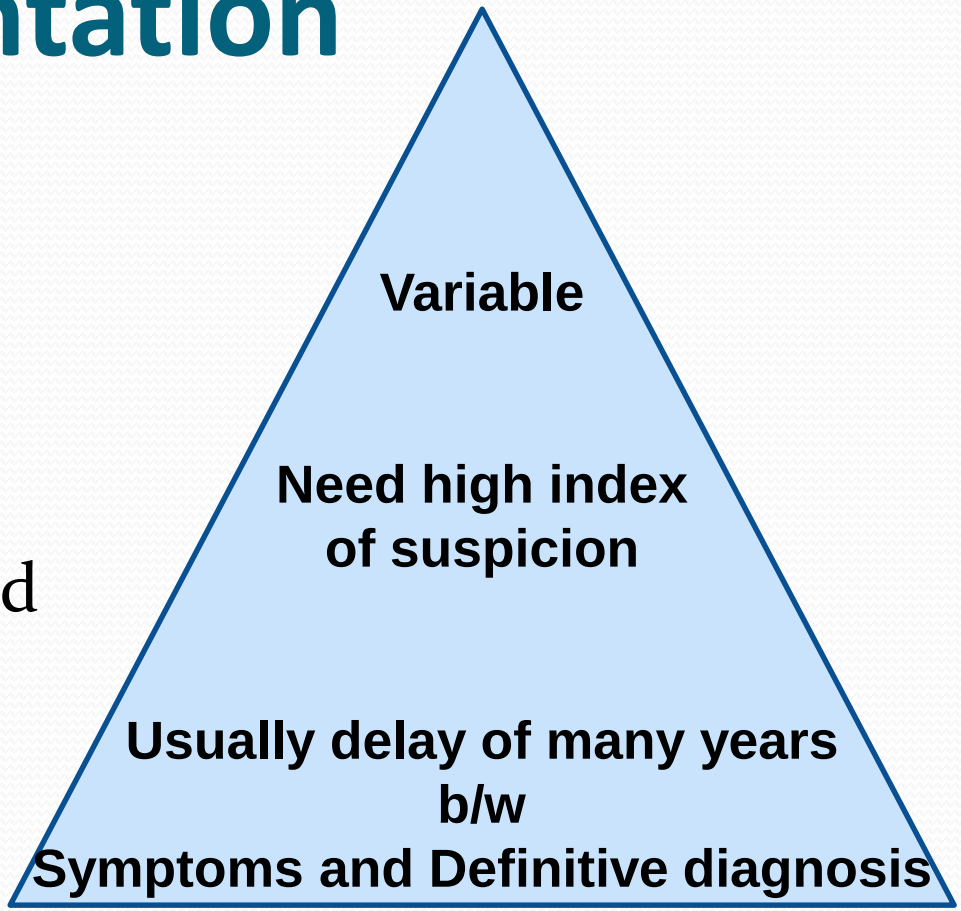
Ovulation pain

Perimenstural pain/bleed

Infertility

Chronic fatigue

Pain during defecation



Dysmenorrhea & pelvic pain-

- Often starts after years of pain free menses.
- Starts before the onset of periods and continues throughout menses
- Most studies failed to show correlation between degree of pain and severity of endometriosis.
- Causation of pain –
  - local peritoneal inflammation,
  - deep infiltration- proximity to nerve fibers,
  - adhesion formation and fibrotic thickening,
  - collection of shed menstrual blood in implants, resulting in painful traction with physiological movements.

Infertility

Possible mechanisms

- **Mechanical causes**
  - Altered tubo ovarian relationships
  - Altered tubal motility
  - Impaired oocyte pickup
- **Alterations in peritoneal fluid**
  - ↑Macrophages, PGs, Cytokines - affect sperm motility, sperm oocyte interaction, sperm phagocytosis, implantation failure
- **Alteration of systemic immune response**
  - ↑ antiendometrial antibodies –*(Gajbhiye et al 2008,Mathur et al 2000)*
  - ↑ cell mediated gametocyte injury

- **Hormonal factors-**
  - Defective folliculogenesis
  - Luteinized unruptured follicle (4-35%)
  - Luteal phase deficiency
  - Hyperprolactinemia and galactorrhea
  - Fertilization and implantation failure
- Monthly fecundity rate is lower in women with mild disease (5-11% vs 25%)
- No evidence that spontaneous abortion rates are higher in endometriosis.

Diagnosis

- Pelvic tenderness, a fixed retroverted uterus, tender utero-sacral ligaments or enlarged ovaries suggest endometriosis.
- Deeply infiltrating nodules on utero-sacral ligaments/POD or visible lesions on vagina or cervix give more certainty.
- The detection is improved if examined during menstruation. Acceptance may be an issue
- Rectovaginal examination is required if suspecting DIE.

Diagnosis

- For a definitive diagnosis of endometriosis visual inspection of the pelvis at laparoscopy is the gold standard investigation, unless disease is visible in the vagina or elsewhere.(RCOG recommendation level B)

- There is insufficient evidence to justify timing the laparoscopy at a specific time in the menstrual cycle but it should not be performed during or within 3 months of hormonal treatment so as to avoid under diagnosis .

Is Histological confirmation necessary ?

(RCOG Recommendations)

- Positive histology confirms the diagnosis of endometriosis
- Negative histology does not exclude it.
- Whether histology should be obtained if peritoneal disease alone is present is controversial. **Visual inspection is usually adequate but histological confirmation of at least one lesion is ideal.**
- In case of ovarian endometrioma (more than 3cm) and in deeply infiltrating disease histology should be obtained to identify endometriosis and to exclude rare instances of malignancy.

TVS in diagnosing Endometriosis

- Compared to laparoscopy, TVS has limited value in diagnosing peritoneal endometriosis
- But it is a useful tool both to make and exclude the diagnosis of ovarian endometrioma. (RCOG level A ,Recomendations.)

- TVS may have a role in the diagnosis of disease involving the bladder or rectum

- Sensitivity-83% & specificity-98% for endometrioma.

Classical appearance-

- homogenous, hypoechoic mass with low levels internal echoes with hyperechoic foci within wall.
  - 95% show internal echoes & hyperechoic lesions are due to cholesterol deposits.
  - Lesions- unilocular/ moltilocular with thick/thin septa

Differential diagnosis:

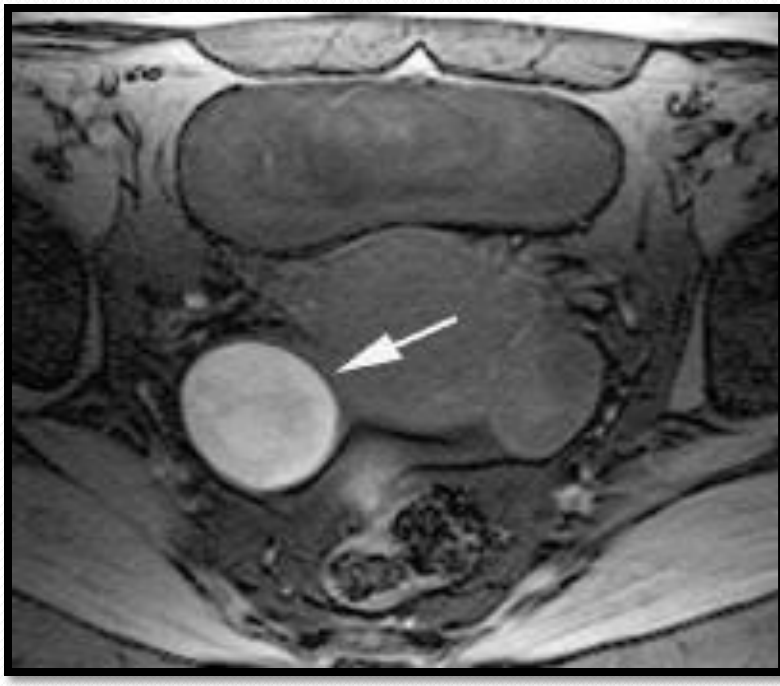
- Dermoid cyst- acoustic shadowing (calcium) & echogenic lesion (fat).
- Hemorrhagic cyst- high levels of internal echoes with thin walled cyst, resolves with time.
- Cystic neoplasm

Transrectal ultrasound:

- Better resolution, diagnostic accuracy, restricted field of visualization (Distal bowel can be imaged).
- Deposits- round hypoechoic, infilteration of bowel wall is seen as thickening of muscularis propria.
- Sensitivity-97%, specificity-89% for rectal lesions (better than MRI).

Role of Doppler

- Diagnostic accuracy is enhanced by doppler.
- **Pericystic flow** with RI more than 0.45, indicating low resistance waveform.
- ***MRI:***
- Advantage of imaging entire pelvis in multiple planes.
- Particularly useful in evaluating rectum & cul de sac.
- Appearance depends upon- iron content, proteins and products of blood degradation.



CA -125

- Low sensitivity (25-50%), not used as screening method.
- Helpful to predict recurrence.
- Levels in non menstrual phase-
  - Minimal/mild-14-31U/ml
  - Moderate/severe-13-95U/ml

- 80% of patients with pelvic pain & raised CA125 levels have endometriosis, while only 6% of those without endometriosis have raised CA125 levels. *(Pittaway et al 1989)*

- High levels of CA-125 have been reported in cases of large endometrioma/ ruptured endometriomas.

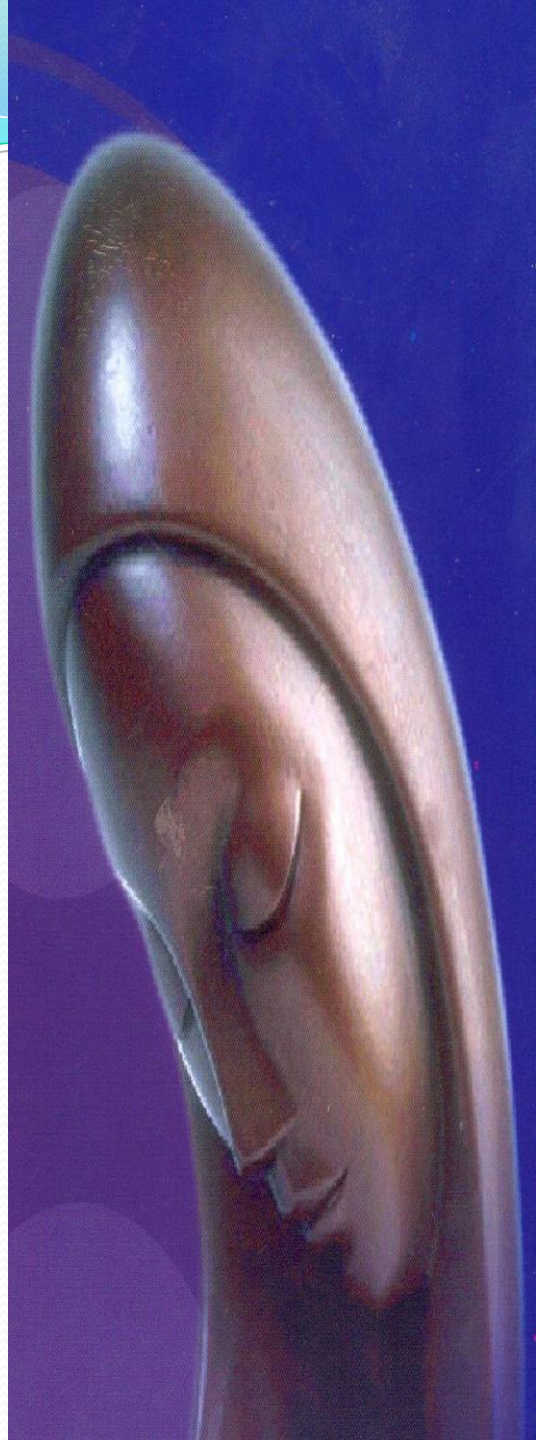
(Shiau et al 2008,Kahraman et al 2007,Ghaemmaghami et al 2007,Phuphong et al 2004)

Laparoscopy – gold standard

- Diagnose the **extent** and **severity** of disease.
- Should not be performed within 3 months of hormonal therapy to avoid under diagnosis.
- **Methodical approach required**. Thoroughly inspect the lateral sidewalls, all ovarian surfaces, both sides of broad ligament, bladder, bowel serosa and inferior aspects of the cul de sac.
- **Uterine manipulation** helps in visualizing POD and recto vaginal septum
- **Photography** and video recording of the findings should be done ideally.

Treatment Options

- **Medical Therapy**
  - NSAIDs and Cox2 inhibitors
  - COCs
  - Progestogens
  - Anti progestins
  - GnRH agonists and antagonists
  - Aromatase inhibitors
  - Selective Estrogen Receptor Modulators
  - Selective Progesteron Receptor Modulators
- **Surgical Treatment**
  - Conservative Surgery
  - Definitive Surgery



Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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

- Inconclusive evidence, if NSAIDs (specifically naproxen) are effective in managing end. associated pain.(level-A)

- Suppression of ovarian function for 6 mths reduces end. associated pain.(level-A)

- COCs, MPA, Danazol, Gestrinone and GnRH agonists are equally effective but their adverse effects and cost profiles differ and can be chosen accordingly (level-B)

- ACOG recommends 3 months trial of NSAID & cyclic OCP.
- If pain persists after 3 months then laparoscopy
- If patient > 18 yrs and wish to avoid surgery-empiric GnRHagonists
- If pain resolves then diagnosis of endometriosis is confirmed

- Any low dose OCP containing 30-35 mg of ethinyl estradiol used continuously (to achieve amenorrhea) can be effective in treatment of endometriosis. (Moghessi et al 1999)

- Cyclic OCP is used to provide prophylaxis against either the development or recurrence of endometriosis.

- Nuva ring can also be used.

Progesterones(cont)

Drug	Dose	
MPA	30mg	Daily , orally
Norethisterone acetate	2.5-5mg	Daily, orally
Megesterol	40mg	Daily , orally
Lynestrenol	10mg	Daily , orally
Dydrogesterone	20-30mg	Daily , orally

GnRH Agonist

- Causes pseudomenopause by down regulation of pitutary, very effective
- Indicated if patient is unable to have an acceptable degree of pain control with COCs. Not to be given if< 17 yrs (ESHRE 2005)
- Leuprolide 3.75mg/mth, Gosereline 3.6mg/mth
- Buserelin, Nafarelin,Triporelin

Add back therapy

- CEE .625 mg+ norethindrone , noreth. alone or tibolone 2.5 mg + 1200 mg of Calcium & Vitamin D daily

Goal of add back – effectively treat endometriosis associated pain while preventing vasomotor symptoms or bone loss.

- Treatment up to 2 yrs with COC add back appears to be effective and safe in terms of pain relief and bone density.

GnRH Antagonists

LNG Intra Uterine System

- LNG- IUS appears to reduce endometriosis associated pain **(RCOG level -A)**
- Insertion after laparoscopic surgery for endometriosis associated pain, significant reduction in the risk of recurrent moderate–severe dysmenorrhoea at 1 year follow-up.(level A)
- Causes significant reduction in pain, dysmenorrhea, dyspareunia and size of rectovaginal endometriosis (upto 3yrs).
- It also has minimal systemic effects, effective contraception & long term 5 years of benefit, as compared to 6 mths, typical of GnRHa treatment.

Dienogest ; highly selective PRM, as effective as GnRHa

- May prove better option,Now available…2mg continuously

- **Danazol** 400-800 mg/day, first drug approved for end. in US. Adverse side effects limit its use
- **Gestrinone** Causes cellular inactivation and degeneration of endometrial implants.
- 1.25- 2.5mg twice weekly for 24weeks.
- Amenorrhea occurs in 50-100% of cases.
- Equally effective, Seems to prove good alternative
- Side effects- androgenic but less intense than danazol.
- Pregnancy is contraindicated due to masculinization of fetus.
- **Mifepristone** 25-50mg/day,Seems promising

Aromatase inhibitors-

- *Aromatase is the key enzyme responsible for estrogen production in the ectopic endometrium, further stimulated by PGE2.*
- Inhibitors decrease local estrogen synthesis and inhibit the growth of endometriotic implants.
- Require add-back therapy to protect bones.
- letrozole ,2.5mg along with norethisterone 2.5mg/ calcium(1000mg)+vit D (800IU) for 6 months reduced pelvic pain scores and no significant change in BMD (Ailawadi et al 2004,Remorgida et al 2007)
- Preliminary data favours its (**letrazole, anastrazole**) potential future use .But RCTs are needed to confirm.

SERMs(Selective Estrogen Receptor Modulators)

- Non-steroidal anti-estrogens bind to ERs, can act as either estrogen agonists or antagonists, depending on the target tissue.
- Have estrogen antagonist activity on the endometrium but agonist activity on bone and circulating lipoproteins.
- Role yet to be studied in humans.
- **TZE-5323, raloxifene-** decrease volume of implants in dose dependent manner in animal studies.

Selective Progestrone Receptor Modulators SPERMs

- Can act as either agonists or antagonists of progestogenic activity, depending on the target tissue.
- Suppress endometrial proliferation selectively in the presence of an estrogenic environment, allowing the treatment of endometriotic implants without the side effects of systemic estrogen deprivation.
- Role yet to studied in humans.
- J867, J956, J912 and J1042 being studied.

Endometriosis and Fertility

Hormonal or antihormonal therapy has no beneficial effect

on fertility either alone or as an adjunct to surgery (RCOG recommendation)

only surgical ablation or excision of disease will restore fertility (RCOG recommendation)

Infertility and endometriosis

- Suppression of ovarian function to improve fertility in minimal–mild endometriosis is not effective and should not be offered for this indication alone. There is no evidence of its effectiveness in more severe disease. **(level A RCOG)**

- Postoperative hormonal treatment has no beneficial effect on pregnancy rates after surgery. **(level A RCOG)**

Infertility and endometriosis

- Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal–mild endometriosis is effective (**level A,RCOG**).

- The role of surgery in improving pregnancy rates for moderate-severe disease is uncertain.

- No randomised controlled trials or meta-analyses are available to answer the question.

Conservative Surgery

- An asymptomatic patient with incidental finding of Endometriosis does not require any treatment
- Excision or ablation reduces pain.
- Excision rather than drainage or fulguration provides better pain relief, reduced recurrence, and histological diagnosis
- Surgical excision with scissors, bipolar coagulation or laser
- Ovarian endometrioma < 4 cms – Aspirated, irrigated and interior wall vaporized to destroy mucosal lining

  >4cm cystectomy is recommended (level–A RCOG)

Infertility and endometriosis

- ***Laparoscopic ovarian cystectomy is recommended if an ovarian endometriomas ≥ 4 cm in diameter***
  - to confirm the diagnosis histologically
  - improve access to follicles
  - possibly improve ovarian response
  - prevent endometriosis progression
- The woman should be counseled regarding the risks of reduced ovarian function after surgery.

- IUI improves fertility in patients when combined with ovarian stimulation.
- Pregnancy rate is lower in than with unexplained fertility.
- Poor ovarian response and need for high dose of gonadotropin therapy for ovarian stimulation.
- **IVF** is appropriate treatment, especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.
- Treatment with a GnRH agonist for 3–6 months before IVF in women with endometriosis increases the rate of clinical pregnancy.(level A)

Recurrent endometriosis

- Spontaneous resolution occurs in about 20% of endometriosis stage I-II.
- **Residual disease-** persistence of symptoms or reappearance of symptoms within 3 months .
- **Recurrence** usually appears after 3 months .
- Incidence-6-30% in various studies.
- Depends on- age, stage of disease, prior treatment, completeness of surgery, extent of peritoneal disease.
- Usually presents as chronic pelvic pain , dysmenorrhea

Recurrent endometriosis

- Diagnosis- rising CA-125,TVS, MRI, laparoscopy.

Treatment-

- Pain killers
- Hormones- progesterones, OCPs, GnRH analogues
- **Conservative surgery-**
  - Indicated if medical therapy fails or contraindicated or intolerable side effects.
  - Cystectomy/ adhesiolysis may be an option after IVF fails..
- Postoperative hormone therapy delays recurrence but does not reduce the recurrence.
- **LNG IUCD-** reduces recurrences post surgery & role is being studied in recurrent disease.
- **Hysterectomy with bilateral salphigo oophorectomy**

Newer Treatments

- Angiogenesis Inhibitors
- Antioxidants-Vitamin C,Vitamin E
- Tumor Necrosis Factors-α inhibitors
- Matrix Metalloproteinase Inhibitors
- Immunomodulators
- Chinese methods
- Green Tea
- Stem Cells Therapy
- Gene therapy

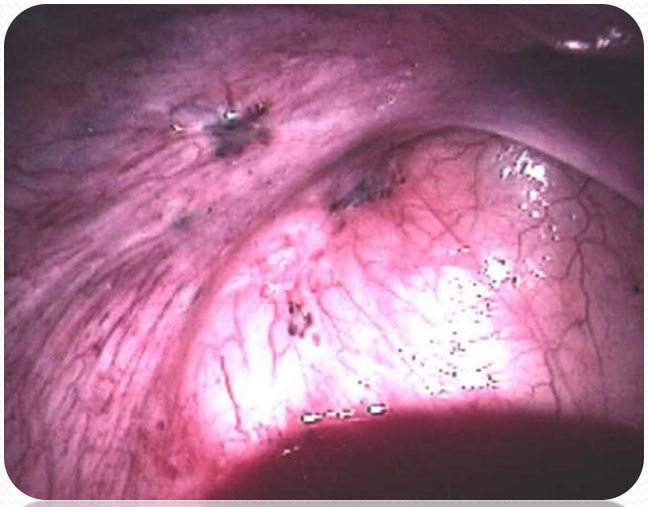
- **Pentoxiphylline** could change the immune cell function by inhibition of Cytokine and TNF-alpha secretion. (Cochrane review 2009)

- **VEGF- C** suggested to be an effective factor for significant reduction in endometriotic implants after Pentoxiphylline administration (Vlahos et al. 2010)

- Another immunomodulator **Etanercept (ETA)** has promising reductive effect equal to Letrazol in early investigation (Ceyhan et al. 2011)

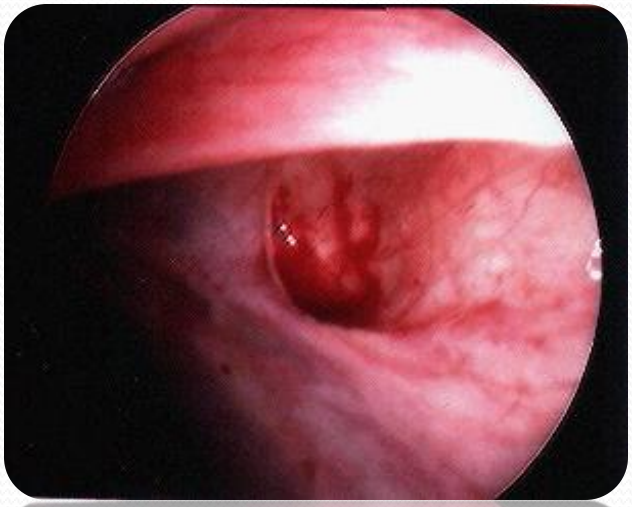
- According to Cochrane review Chinese herbal medicine has shown equal results as compared to Gestrinone

(Flower et al. 2009)



- Abdominal acupuncture showed significant effect in dysmenorrhoea relief and decreasing CA 125 levels

(Xiang et al. 2011)



Surgery for pain relief

- **Drug therapy may relieve inflammation and reduce pain in early superficial disease but corrective surgery +/- drug therapy is preferable (Padwick 1999)**
- **Rectovaginal, rectal and uterosacral lesions always need surgery**
- **Endometriomas always need surgery**
- **Abnormal Anatomy and adhesions always need surgery**

Role of surgery in pain

- Ablation of endometriotic lesions reduces endometriosis-associated pain, outcome is poorest in minimal endometriosis. **(level A,RCOG)**
- There is no evidence that laparoscopic uterine nerve ablation(LUNA) is necessary when ablating endometriotic lesions and **LUNA** by itself has no effect on dysmenorrhoea associated with endometriosis. **(level A,RCOG)**
- There is currently no evidence to recommend the use of LUNA to treat endometriosis although there is some evidence for the use of presacral neurectomy (PSN). **(Cochrane data 2005)**

- Postoperative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months and has no effect on disease recurrence. **(level A,RCOG)**

- LNG-IUS, inserted after laparoscopic surgery for endometriosis associated pain, significantly reduced the risk of recurrent moderate–severe dysmenorrhoea at 1 year follow-up. **(level A,RCOG)**

Deep Infiltrating Endometriosis

Classification	*Operative procedure*
A Anterior DIE	
A1: Bladder	***Laparoscopic partial cystectomy***
P: Posterior DIE	
P1: Uterosacral ligament	***Laparoscopic resection of USL***
P2: Vaginal	***Laparoscopically assisted vaginal resection of DIE infiltrating the posterior fornix***
P3: Intestinal	
P3a: Solely intestinal location	
- without vaginal infiltration (V-)	***Intestinal resection by laparoscopy or by laparotomy***
- with vaginal infiltration (V+)	***Laparoscopically assisted vaginal intestinal resection or exeresis by laparotomy.***
P3b: Multiple intestinal location	***Intestinal resection by laparotomy***

Definitive Surgery ? Ovarian conservation

- In DIE & severe cases hysterectomy and removal of all visible endometriotic tissue can be done. **BSO** may result in improved pain relief & reduced chances of future surgery .(RCOG guidelines)

- In cases with normal ovaries, hysterectomy with **ovarian conservation** and removal of endometriotic lesions should be considered.(ACOG guidelines 2010)

- TAH-**BSO is reserved** for women with debilitating symptoms ,who have completed childbearing & other therapies have failed. (ASRM &Canada OBG Society,2010)

Conclusions

Treatment must be individualized

- Multidisciplinary approach involving pain clinic & counseling should be considered

Endometriosis is an inflamatory and Oestrogen dependent condition

- Drugs targeting this are under trial.
- Laproscopy is the gold standard dignostic tool

Drug therapy should be selected considering efficacy, cost and adverse effects

- Treat early and agressively by surgical destruction or excision preferably by laparoscope


Thank you