Endometriosis

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2018

Background

- 6-10% of women of reproductive age:
  - Asymptomatic - 2 to 50%
  - Dysmenorrhea – 50 - 60%
  - Subfertility - up to 50%
- Functional endometrial glands and stroma in sites outside the uterine cavity
- Diagnosis may be delayed by up to 8 years

Pathogenesis

- Retrograde menstruation
- Implantation on peritoneal surfaces
- Inflammatory response
- Angiogenesis, adhesions, fibrosis, scarring, neuronel infiltration
- Anatomic distortion
- Pain and infertility

Risk factors

- Obstruction of menstrual outflow (mullerian anomalies)
- DES exposure
- Prolonged exposure to endogenous estrogen (early menarche, late menopause, or obesity)
- Short menstrual cycles
- Low birth weight
- Exposure to endocrine-disrupting chemicals
- Genetic component
- Consumption of red meat and trans fat

Protective factors

- Eating fruits, green vegetables, and Omega 3
- Prolonged lactation
- Multiple pregnancies

Associations

- Autoimmune diseases: IBD, MS, Fibromyalgia
- Ovarian endometrioid and clear cell cancers
- Other cancers: non-Hodgkin lymphoma and melanoma

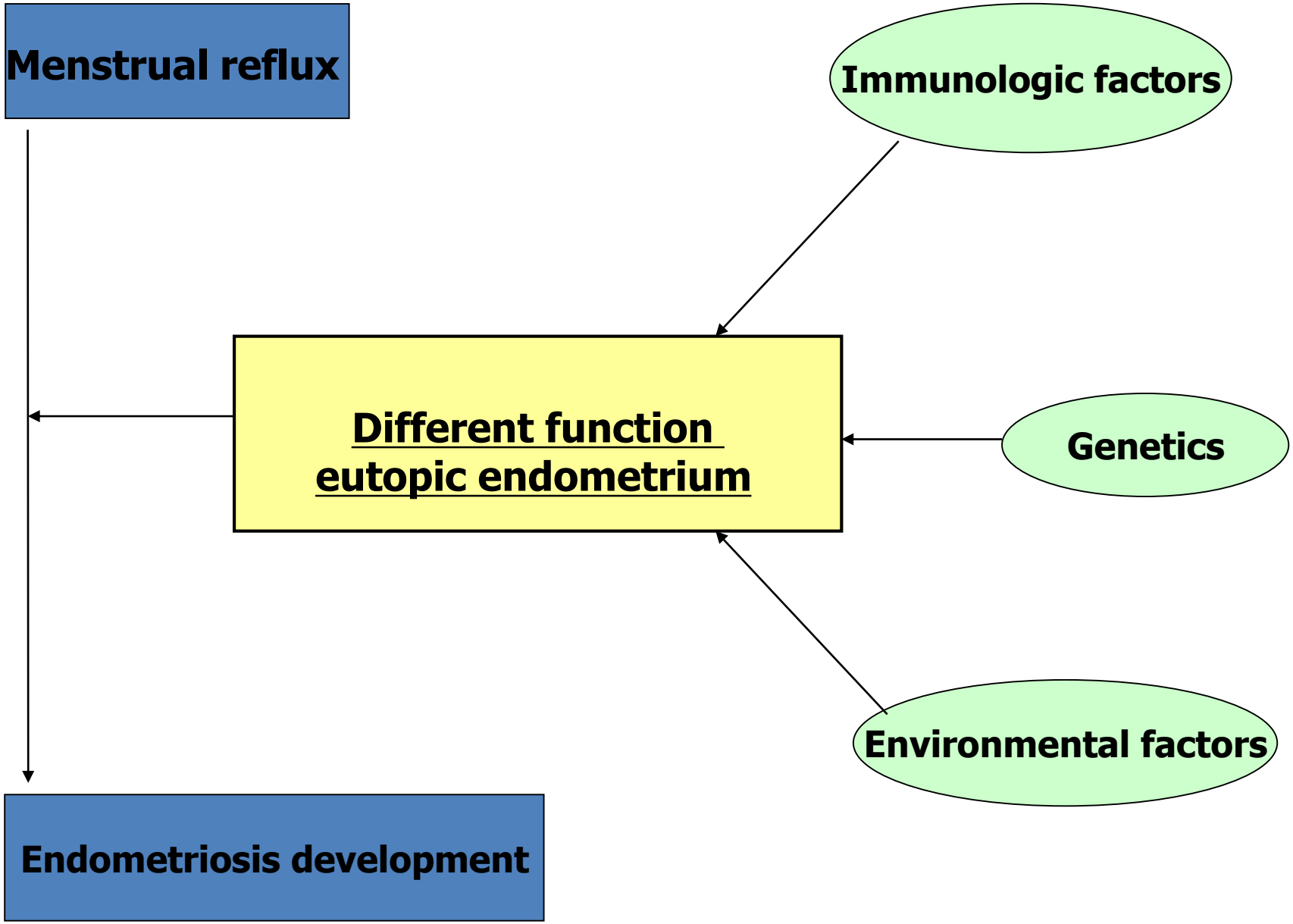
Genetics

- Genetic predisposition:
  - low progesterone levels may be genetic
  - 10-fold increased incidence in women with an affected first-degree relative
  - Familial clustering in animal model – Rhesus monkeys
- Series of multiple hits within target genes
- Individual genomic changes:
  - Changes in chromosome 10 at region 10q26
  - Changes in the 7p15.2 region

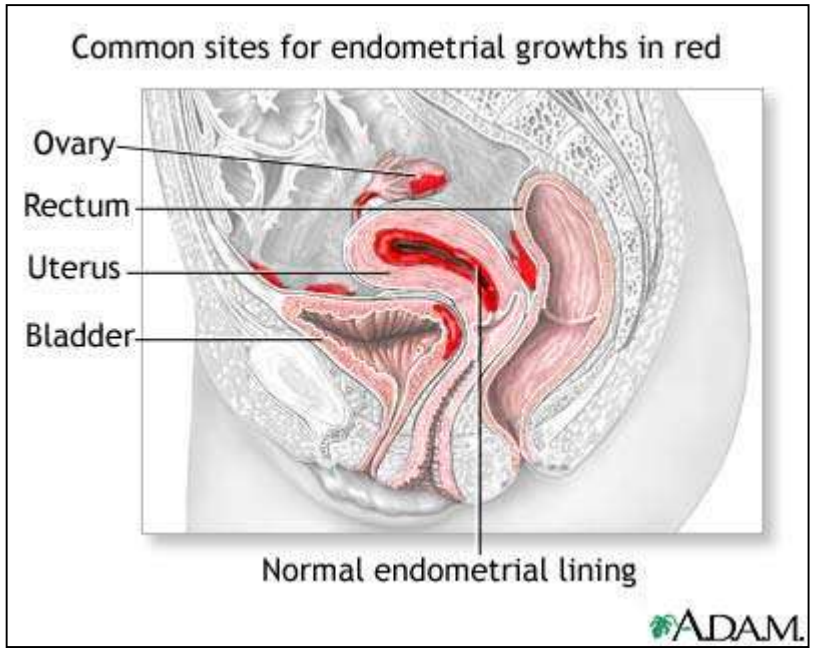
Environmental factors

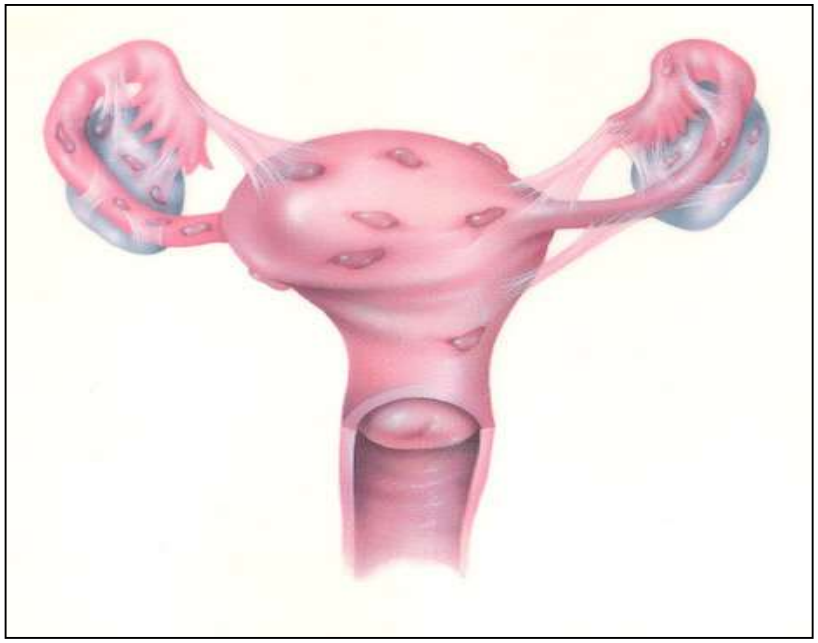
- Plastics and cooking with certain types of plastic containers with microwave ovens
- Dioxin exposure - 79% of monkeys developed endometriosis after receiving doses of dioxin
- Pesticides and hormones in our food cause a hormone imbalance
- The risk of endometriosis has been reported to be reduced in smokers (decreased estrogens)

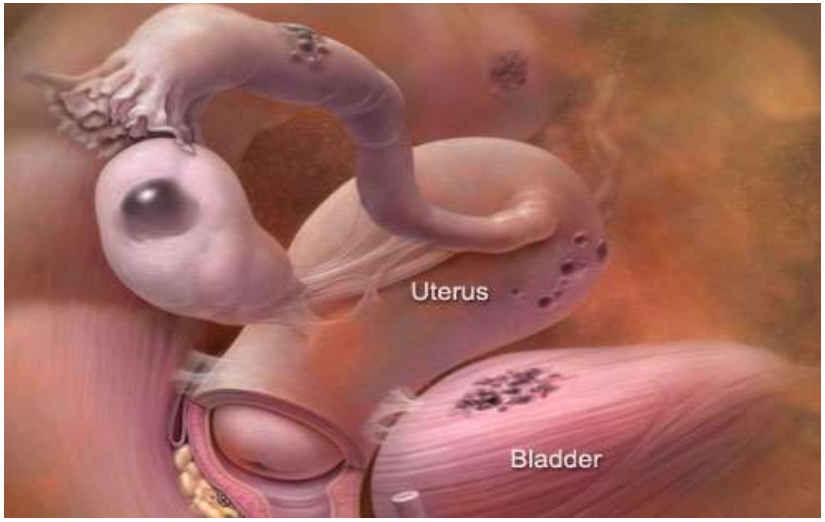
Etiology

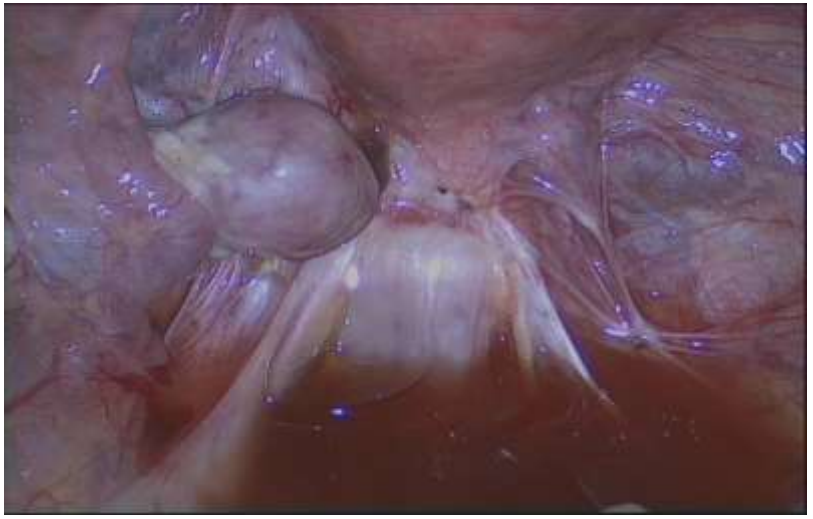

Menstrual reflux
Immunologic factors
Different function
eutopic endometrium
Genetics
Environmental factors
Endometriosis development

Disease locations









Etiology

- Peritoneal endometriosis
- Ovarian endometriosis
- Deep endometriosis

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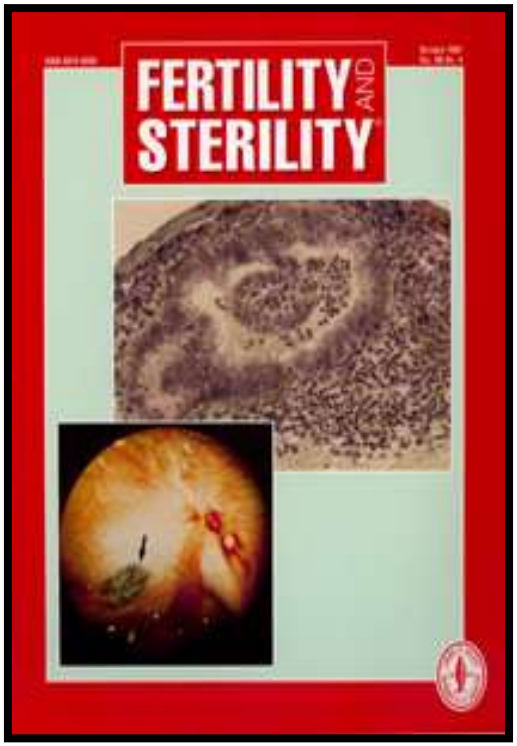


3 DIFFERENT ENTITIES

Diagnosis

- History
- Symptoms
- Clinical findings
- Ca 125
- Imaging
- Laparoscopy

Symptoms

- Chronic pelvic pain ≥ 6 months
- Dysmenorrhea – 50-90%
- Dyspareunia
- Deep pelvic pain
- Lower abdominal pain
- Pain: intermittently throughout the menstrual cycle, or continuous. Dull, throbbing, or sharp, exacerbated by physical activity
- Dysfunctional Uterine Bleeding
- Urinary symptoms (IC)
- Gastrointestinal Symptoms (IBS, IBD)
- Infertility

Assessment of Pain in Endometriosis

- Linear scales
  - Verbal Rating Scale (VRS)
  - Numerical Rating Scale (NRS)
  - A visual analog scale (VAS)
- Multidimensional Verbal Rating Scales
  - A clinician devised four point scale: Biberoglu and Behrman

    Am J Obstet Gynecol 1981;139:645-54

Findings

- Pelvic mass
- Immobile pelvic organs
- Rectovaginal/rectosigmoid/intestinal nodules
- Adnexal pain
- Local tenderness
- Uterosacral ligament nodularities
- Adenomyosis
- Urinary/flank pain

Ca 125

- Biomarker
- Source – epithelium of female reproductive tract, respiratory tract, ocular surface
- Endometrium and irritated peritoneum
- Limited specificity and sensitivity, especially in premenopause
- Elevated in: endometriosis, pregnancy, ovulation, menstruation, inflammatory conditions, PID, cirrhosis, diabetes, and various epithelial cancers

Treatment - Pain management

- Repeated courses of medical therapy, surgical therapy, or both
- Pain recurs 6-12 months after completion of treatment

Empirical medical therapy

- Minimizes inflammation
- Interrupts or suppresses cyclic ovarian hormone production
- Inhibits the action and synthesis of estradiol
- Reduces or eliminates menses

Empirical medical therapy

- NSAIDS
- OCT – first line - 20-25% failure rate
- Progestins - Medroxyprogesterone acetate
- Levonorgestrel IUD (Mirena) or PO (induces endometrial atrophy and associated amenorrhea)
- GnRH agonists (hypoestrogenic state, endometrial atrophy, and amenorrhea, requires addback therapy due to bone loss over 6 mo Rx)
- Aromatase inhibitors
- Danazol – severe androgenic effects

Complementary therapies

- Acupuncture
  - Cochrane - evidence of effectiveness without side effects
- TENS – short term management
- Traditional Chinese Medicine – TCM
- Vitamins B1, B6, E
- Magnesium
- Topical heat - no evidence
- Spinal manipulations – no evidence
- Behavioral interventions

Disease progression

- 17 to 29% of lesions resolve spontaneously
- 24 to 64% progress
- 9 to 59% are stable over a 12-month period

- Major cause of disability and compromised quality of life in women and teenage girls

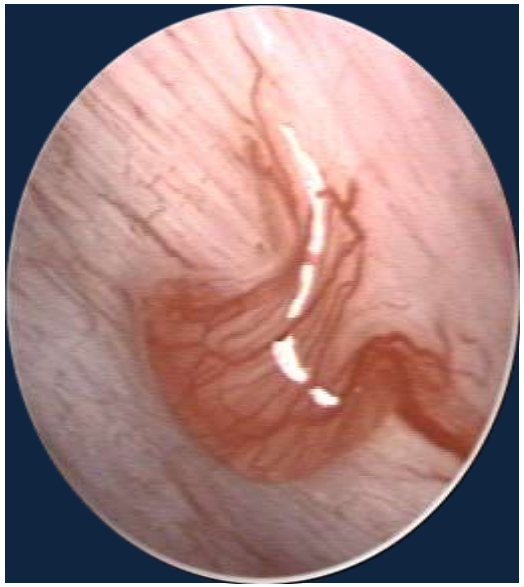
Surgical therapy

- Excision, fulguration, or laser ablation of endometriotic implants on the peritoneum, excision or drainage or ablation of endometriomas, resection of rectovaginal nodules, lysis of adhesions, and interruption of nerve pathways
- RCT's - 6 months, laparoscopic ablation of endometriotic implants is 65% effective in reducing pain, as compared with a 22% rate of pain reduction associated with diagnostic laparoscopy alone

Surgical therapy

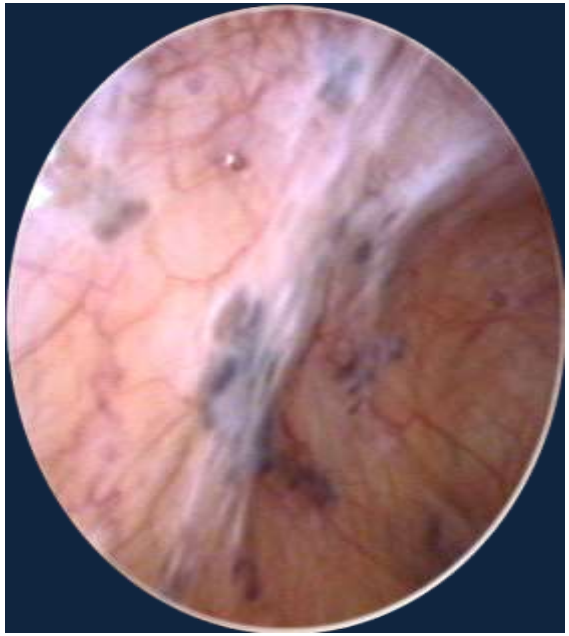
- Recurrence of pain requiring therapy - 30 to 60% within 6 to 12 mos
- Interruption of nerve pathways: Presacral neurectomy (removal of the nerve bundle within the boundaries of the interiliac triangle)
- TAH BSO - pain relief in 80 to 90% but recurs in 10% of the women within 1 to 2 years after surgery
- Postoperative HRT – combined (estrogen alone may stimulate growth of microscopic disease)

Diagnosis - surgical findings

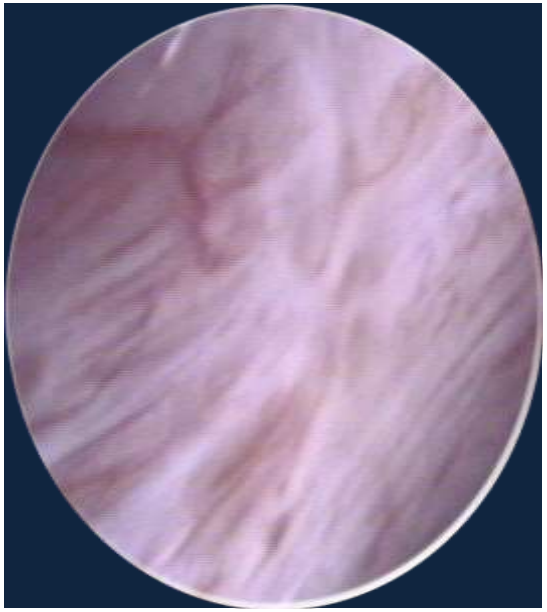


Red

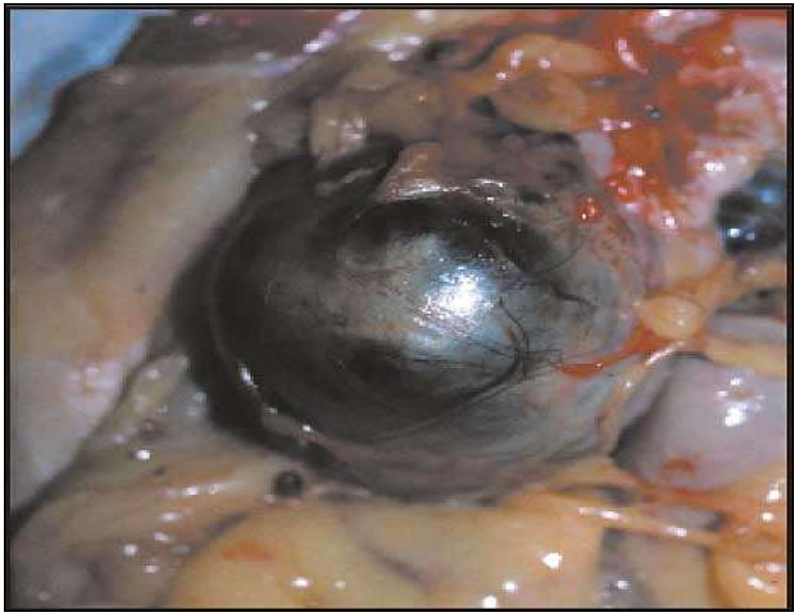
Black

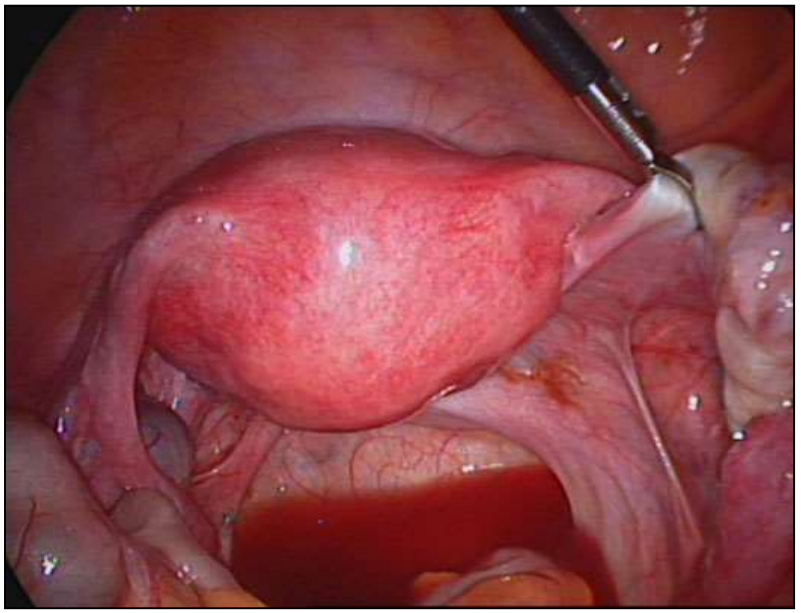


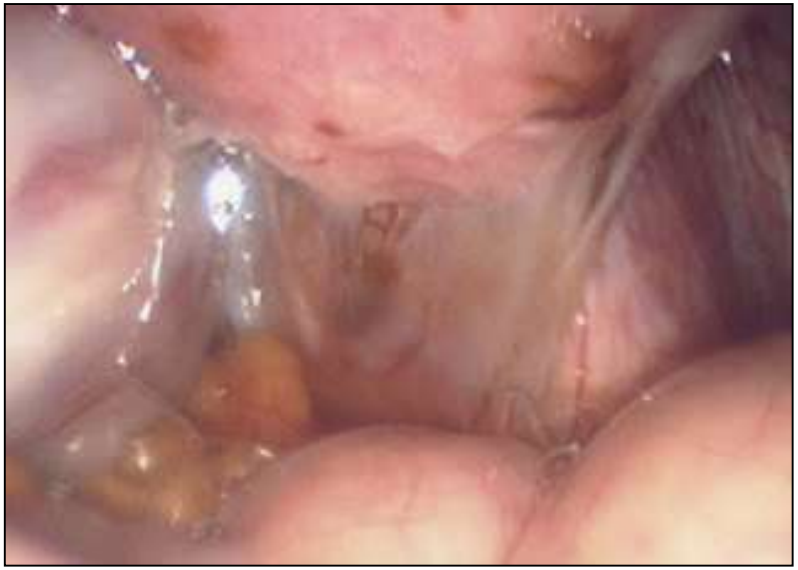
White

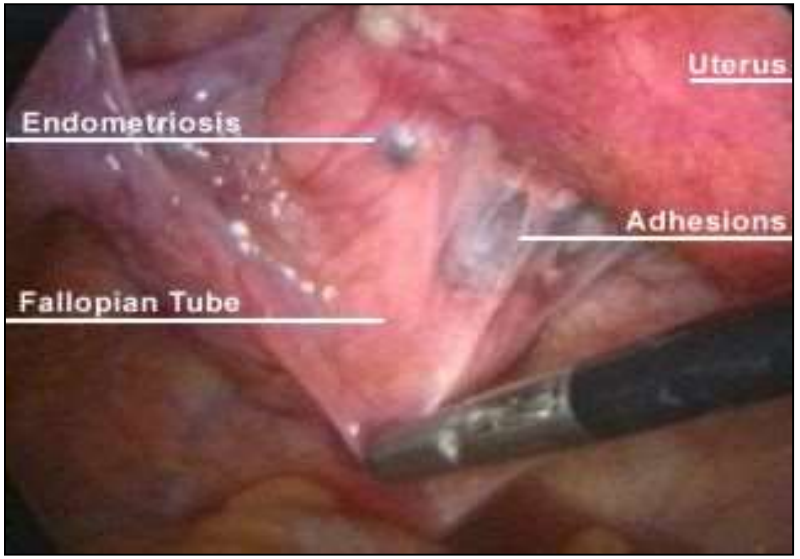


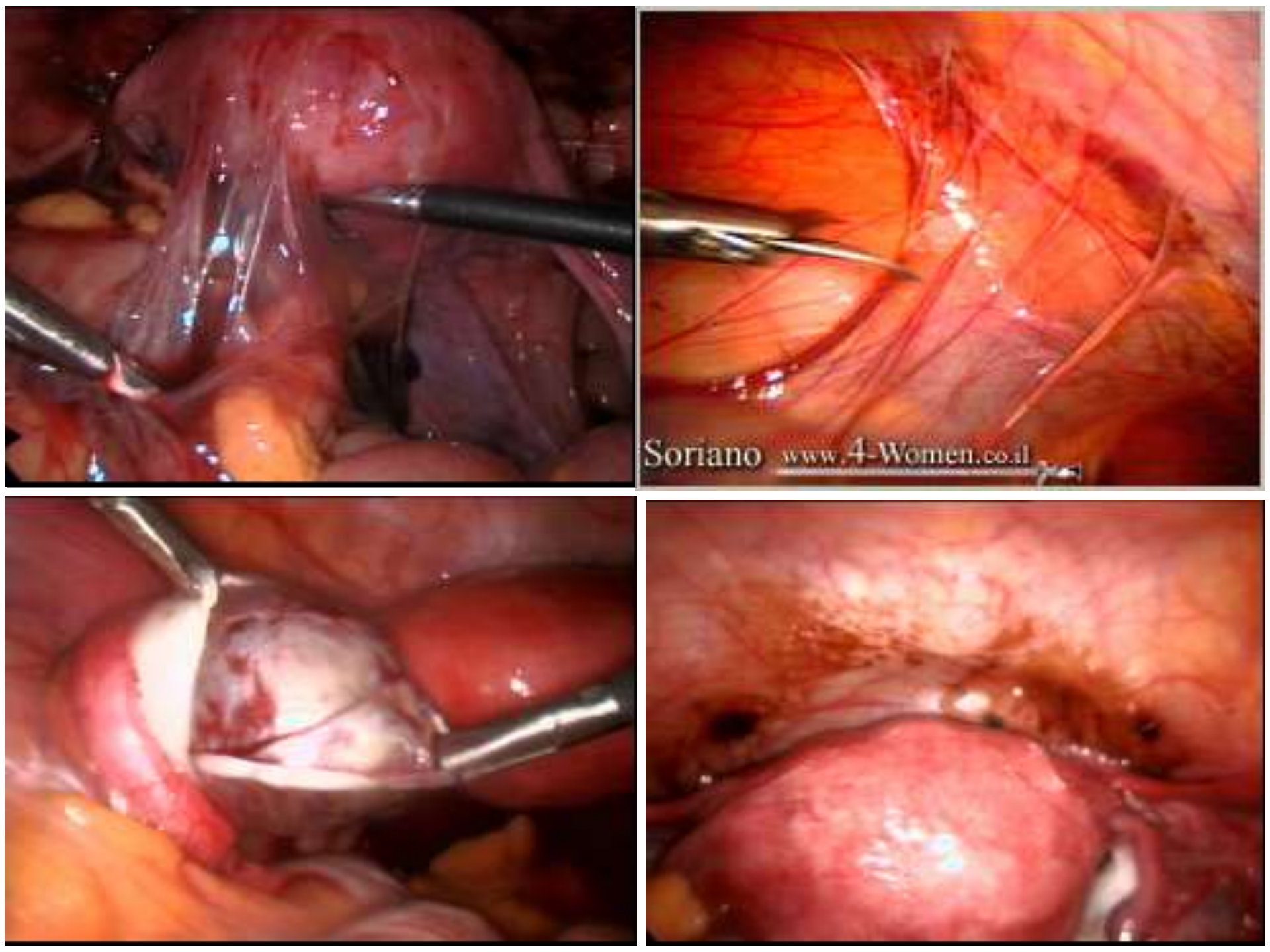
Diagnosis - surgical findings



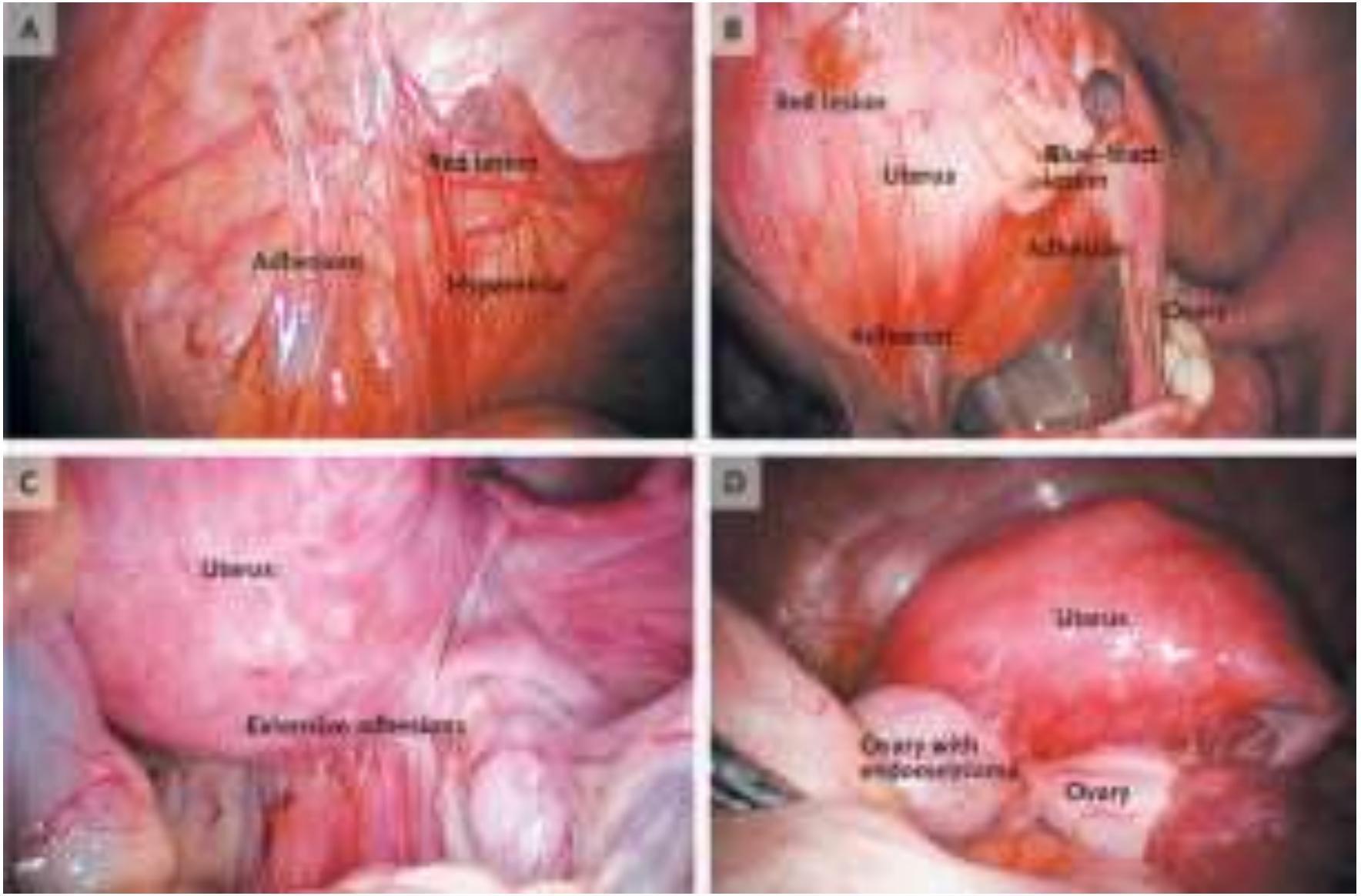




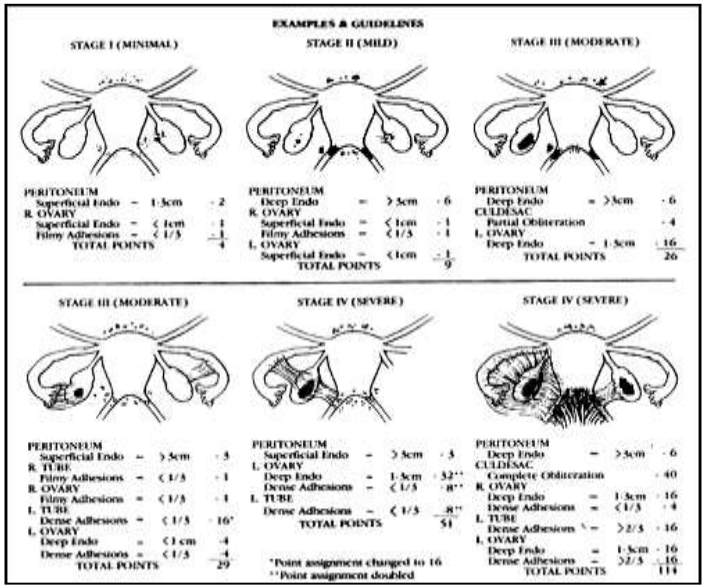



Soriano
www.4-Women.co.il

Diagnosis - surgical findings



Staging (AFS, revised ASRM)



EXAMPLES & GUIDELINES

STAGE I (MINIMAL)

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

STAGE II (MILD)

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

STAGE III (MODERATE)

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

STAGE III (MODERATE)

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

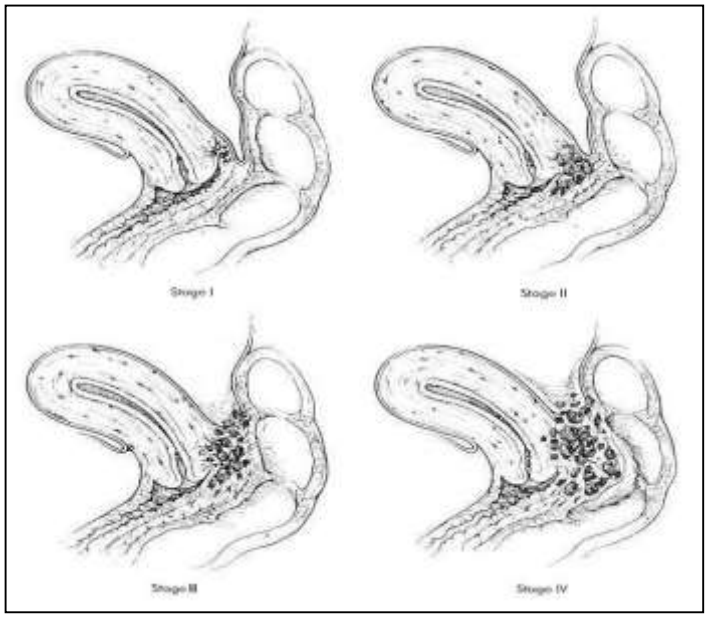
STAGE IV (SEVERE)

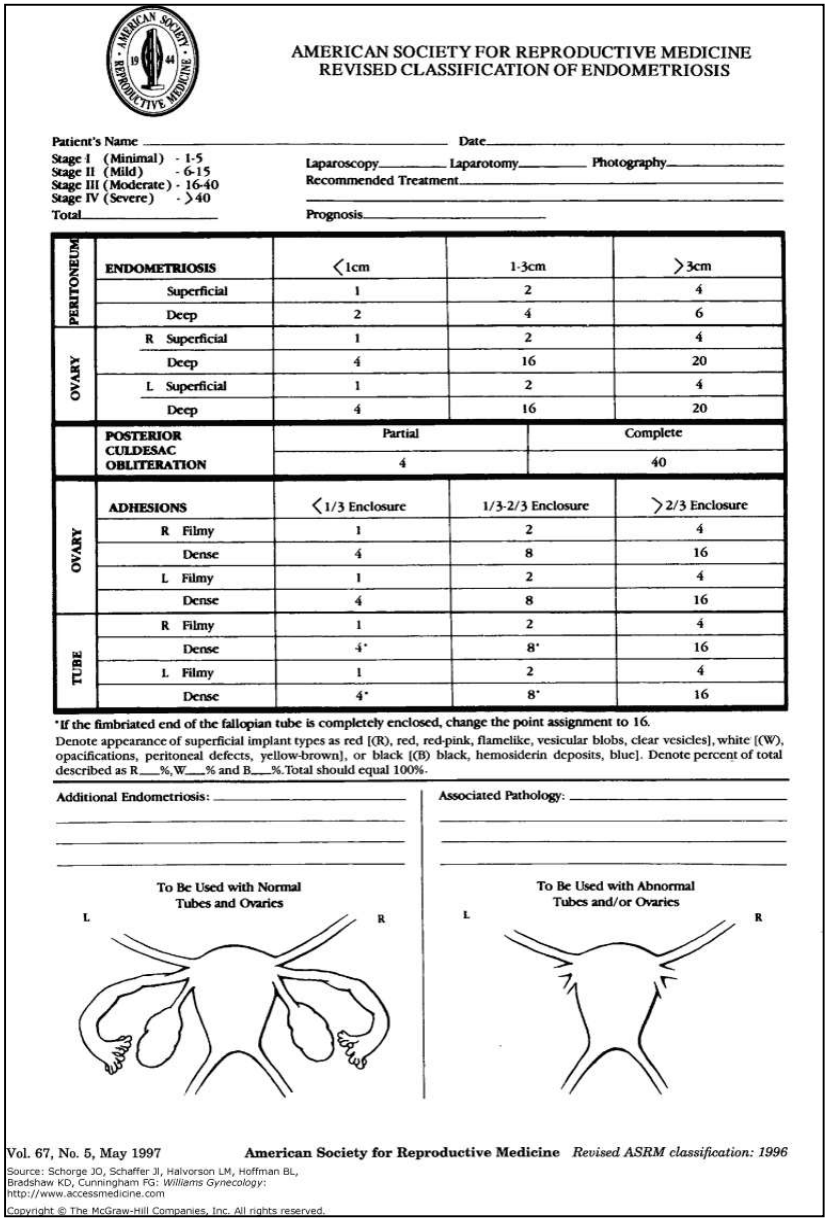
PERITONEUM
Superficial Endo – > 3cm · 3
L. OVARY
Deep Endo – 1-3cm · 32**
Dense Adhesions – < 1/3 · 8**
L. TUBE
Dense Adhesions – < 1/3 · 8**
TOTAL POINTS 51

*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 – < 1/3 · 4
L. TUBE
Dense Adhesions – > 2/3 · 16
L. OVARY
Deep Endo – 1-3cm · 16
Dense Adhesions – > 2/3 · 16
TOTAL POINTS 114





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 _____

	ENDOMETRIOSIS	< 1cm	1-3cm	> 3cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

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

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

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

L R

To Be Used with Abnormal Tubes and/or Ovaries

L R

Vol. 67, No. 5, May 1997 **American Society for Reproductive Medicine** *Revised ASRM classification: 1996*

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pain-Surgery vs. Medical

- Initial surgery superior with more severe disease
- No difference
  - Stage I-II endometriosis
  - Chronic Pelvic Pain
  - Previous surgery

Suggested approach to endometriosis-associated pain

- 1st line: continuous low-dose OCP with NSAIDs as needed
- 2nd line: progestins (start with oral dosing, consider switching to levonorgestrel intrauterine device or depo if well tolerated)
- 3rd line: GnRH agonist with immediate add-back therapy
- 4th line: repeat surgery, followed by 1, 2, or 3
- May consider low-dose (100–200 mg every day) danazol if other therapies poorly tolerated.

Mahutte and Arici, 2003

Experimental Treatments

- RU486 (mifepristone) and SPRMs
- GnRH antagonists
- TNF-α Inhibitors
- Angiogenesis Inhibitors
- MMP Inhibitors
- Immunomodulators
- Estrogen Receptor-β Agonists
- Aromatase Inhibitors

Management of infertility

- Gonadotropin therapy and intrauterine insemination
- In vitro fertilization (IVF)
- Cumulative pregnancy rates 4 cycles:
  - Intracervical insemination - 10%
  - Intrauterine insemination - 18%
  - Gonadotropin + intracervical insemination - 19%
  - Gonadotropin + intrauterine insemination - 33%
- Surgical:
  - Ablation of endometriotic lesions with lysis of adhesions
  - Excision of endometriomas ≥ 3 cm compared with drainage and ablation - significantly higher pregnancy rates
  - Ovarian surgery may diminish ovarian reserve in women with advanced disease

Management of infertility

- אנדומטריוזיס דרגה 1-2 – קונטרוברסיאלי האם גורם לאי פריון. טיפול כירורגי או תרופתי לא משפר פריון

- אנדומטריוזיס דרגה בינונית / חמורה :

1. אופציה ניתוחית – שיקום מבנה אנטומי. מאפשר ניסיון פריון ספונטני או עם טיפול פריון הגברת ביוץ.
2. אופציה טיפולית – הפניה לטיפול IVF ברובם דיכוי שחלתי ממושך לפני עם גלולות או GnRH.

Treatment of endometriosis

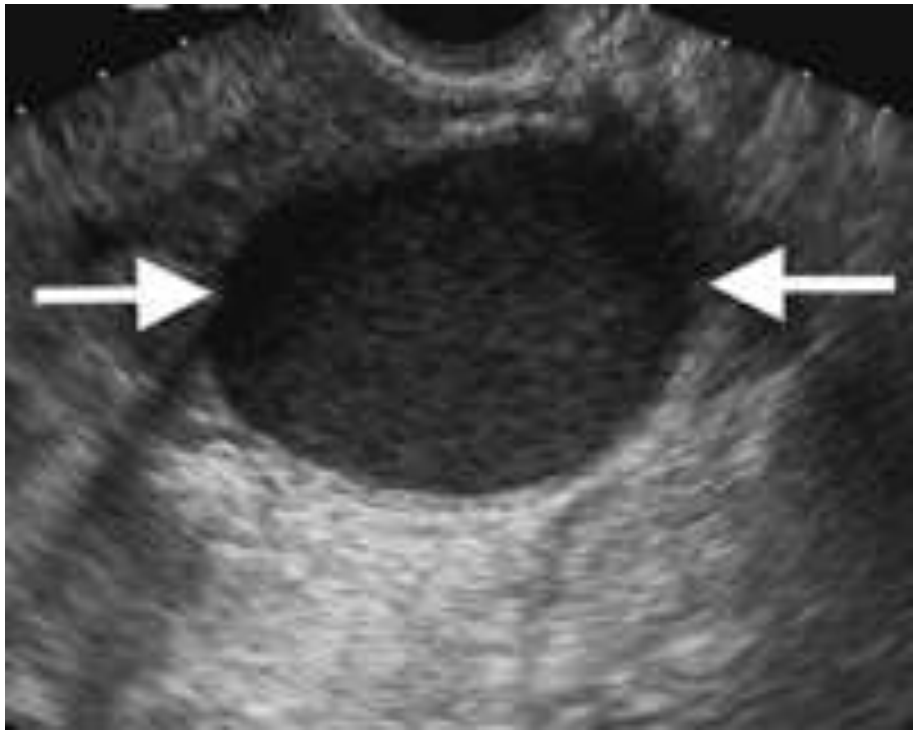
- גינקולוגיה
- אורולוגיה
- גסטרואנטרולוגיה
- כירורגיה כללית
- כאב
- עו"ס
- תזונה
- פסיכולוגיה
- סקסולוגיה

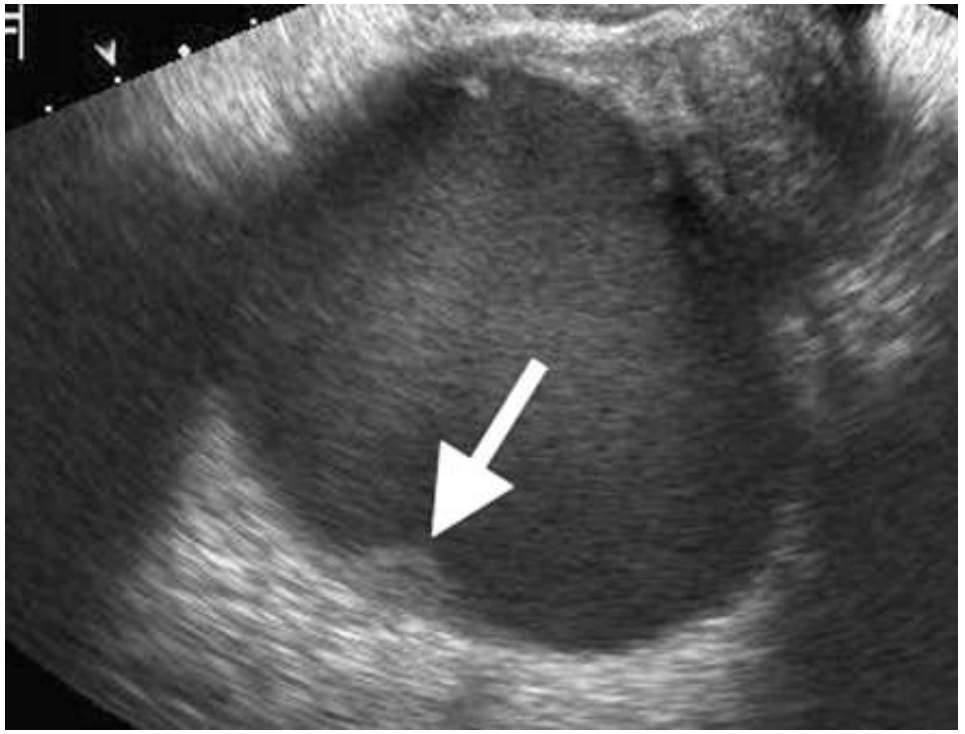
Imaging and endometriosis

- Transvaginal ultrasonography
- Magnetic Resonance Imaging
- Rectal endoscopic ultrasound
- Helicoidal CT scan
- Rectosigmoidoscopy
- Barium enema (double contrast)

- Principles:
  - Make the most accurate pre operative diagnosis:
    - Keep number of additional investigations to minimum
    - Place emphasis on least costly, least invasive if comparably efficient (Chapron 2004)

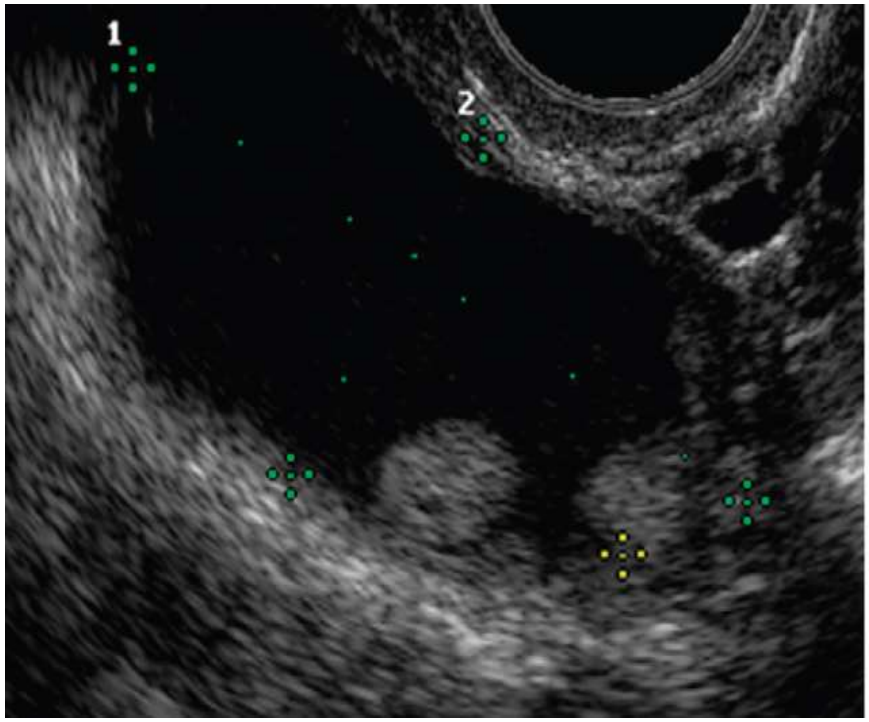
Typical endometriomas

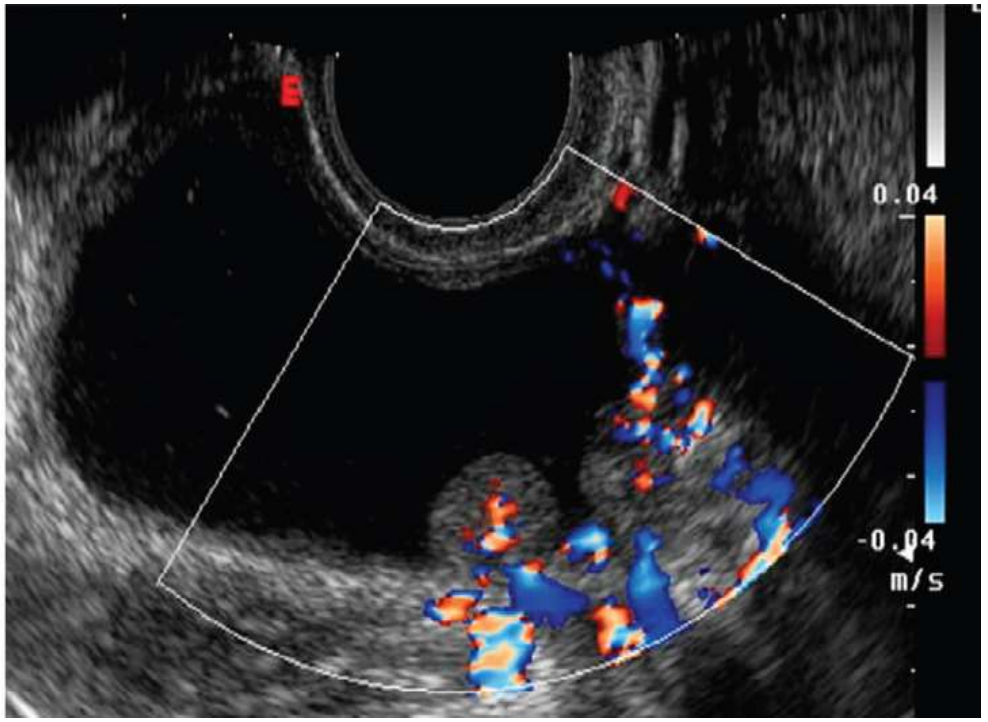




- Wall nodularity – 20%
- Hyperechoic wall foci result from cholesterol crystals break-up from chronic hemorrhage - 30% (old cysts)

Endometriomas in pregnancy





Endometriomas and malignancy

- Subjective impression – misclassification of malignancies as endometriomas in 0.2-0.9%
- Characteristics differ in pre-menopausal and post-menopausal women
- Postmenopausal with ground glass – high malignancy risk
- Precursors of endometrioid BOT which may progress to low-grade invasive carcinoma
- Associated clear-cell BOT

Testa 2011, Van Holsbeke 2010, Lalwani 2010

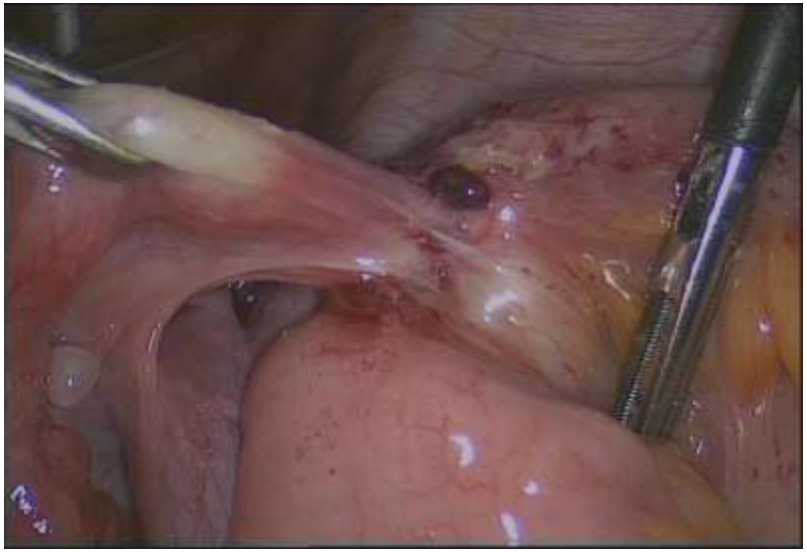
Superficial endometriosis

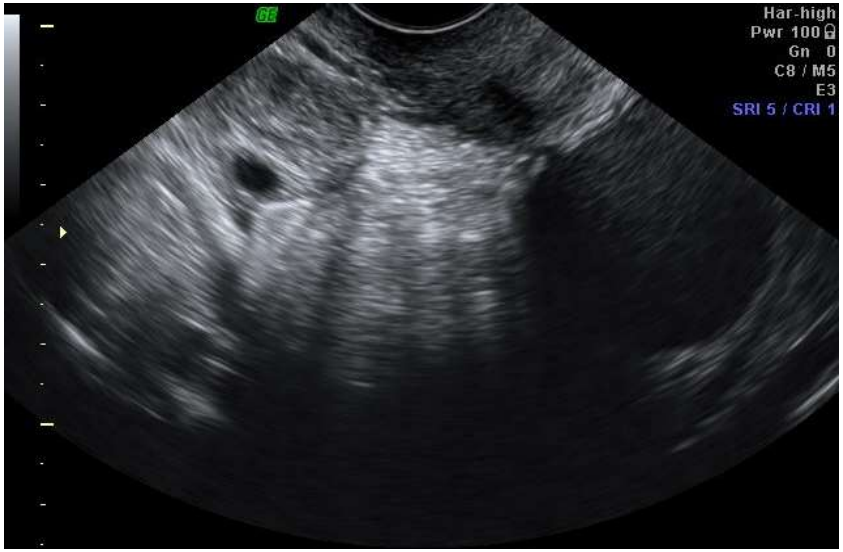
- Up to 15% of normal asymptomatic healthy women
- Not visible by imaging?
- Almost 100% of patients with endometriomas have superficial disease elsewhere
- But in the absence of endometrioma?

Diagnosis of adhesions to ovaries

- Fixation to the uterus of at least one ovary on US: (Guerriero, 2009)
  - Sensitivity 89%, specificity 90%, LR+ 8.92, LR-0.12
  - 96% probability of adhesions (27% when absent)

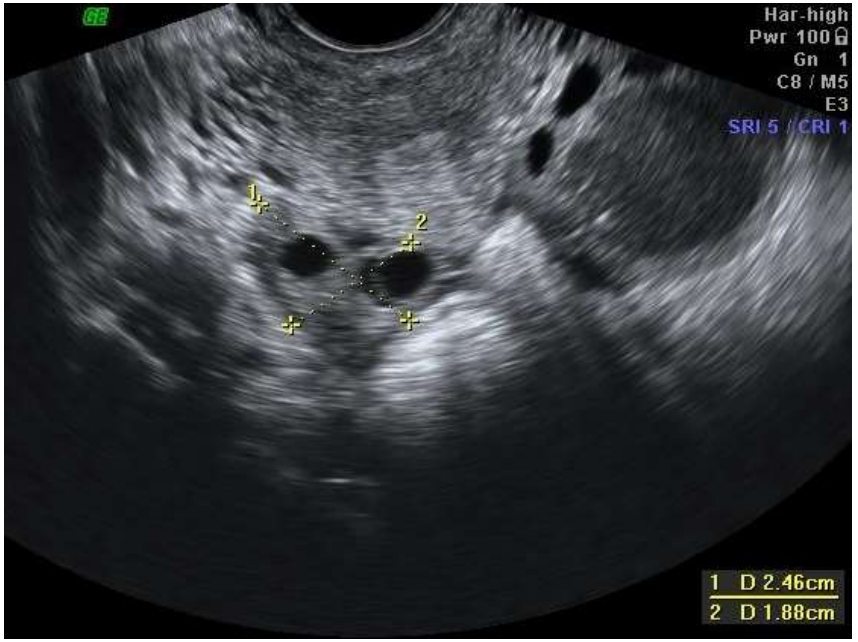
Adhesions small bowel to adnexa and uterus

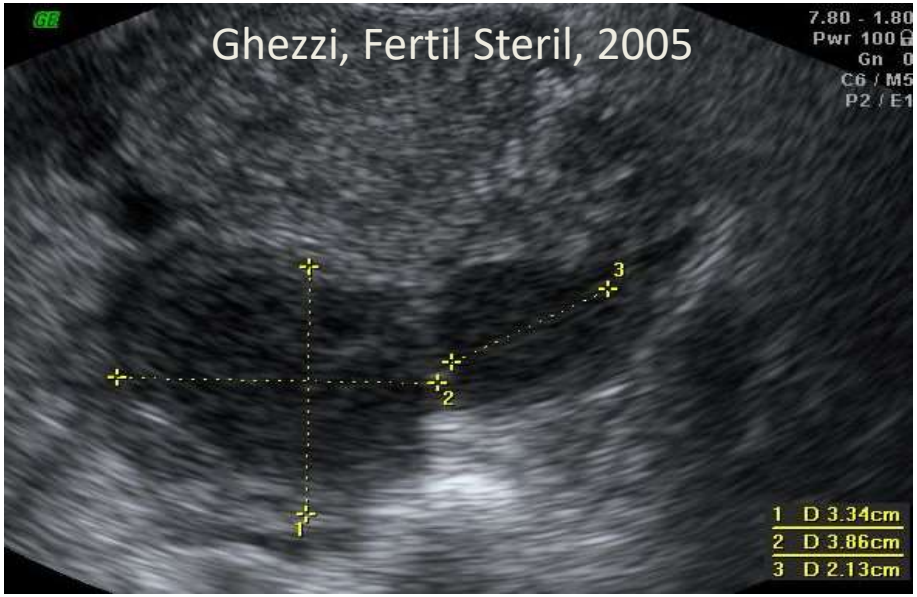


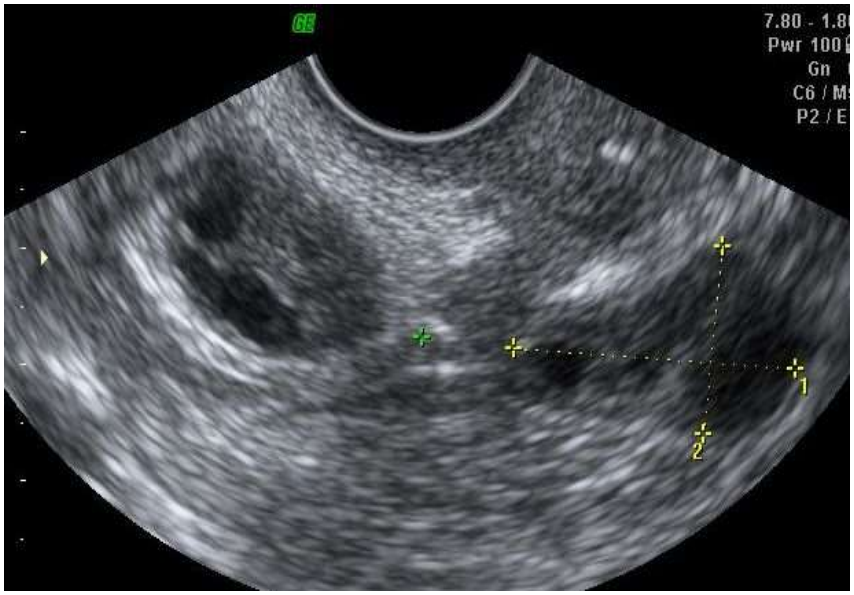


Kissing ovaries and deep endometriosis

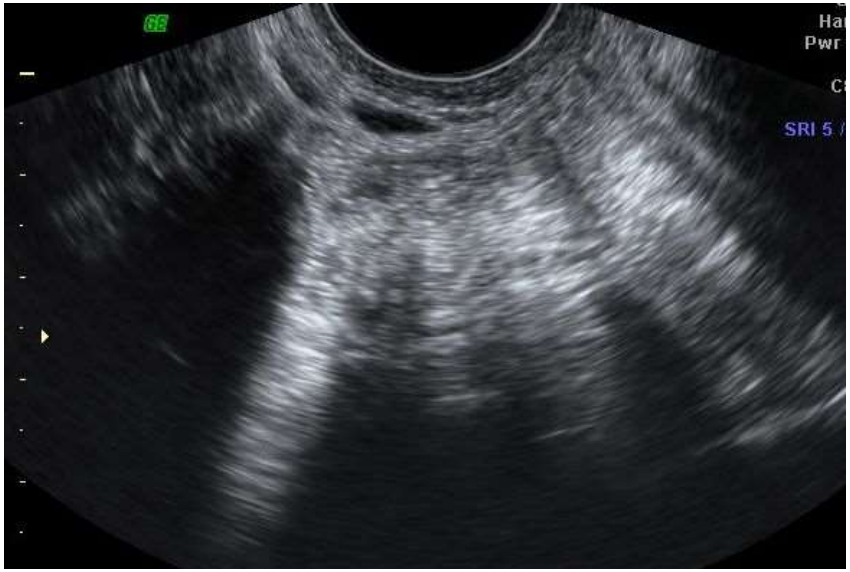
Criteria	Kissing ovaries	Non kissing ovaries
Bowel involvement	18.5	2.5
Fallopian tube obstruction	80	8.6
AFS score	74	35
Operating time	115 min	50 min

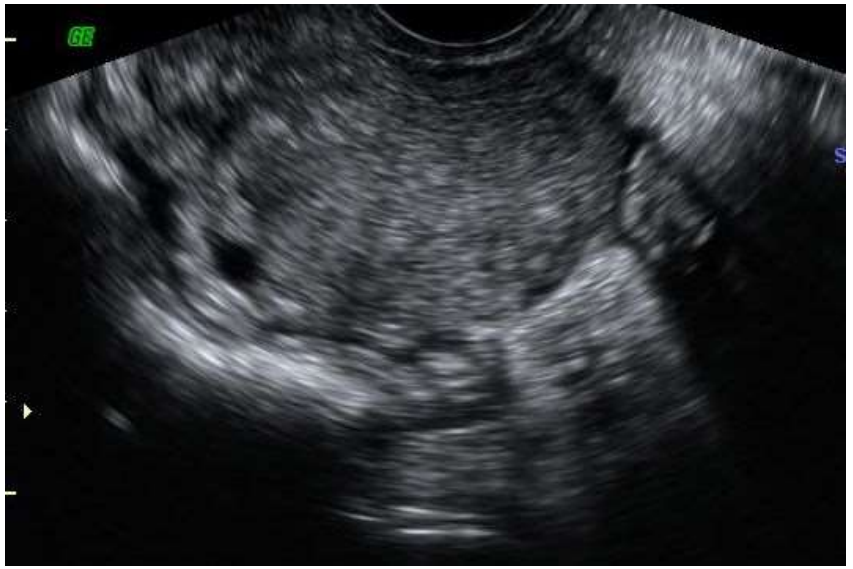


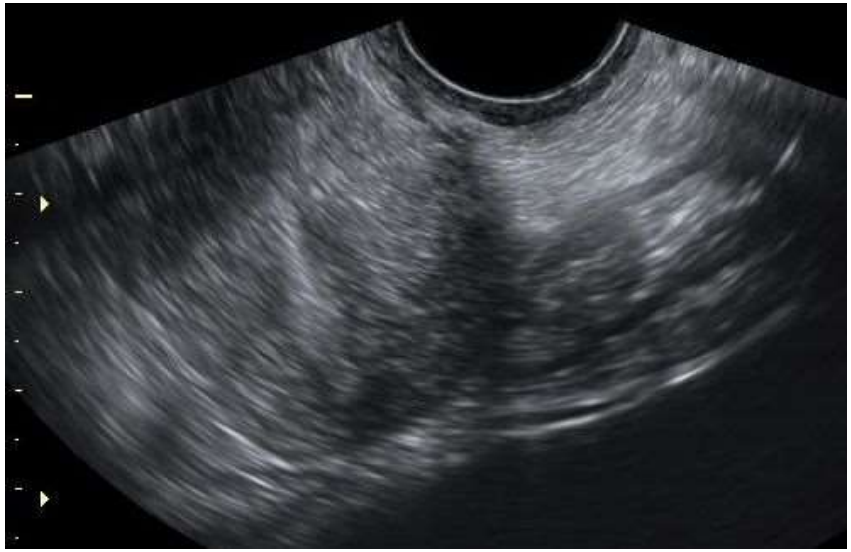




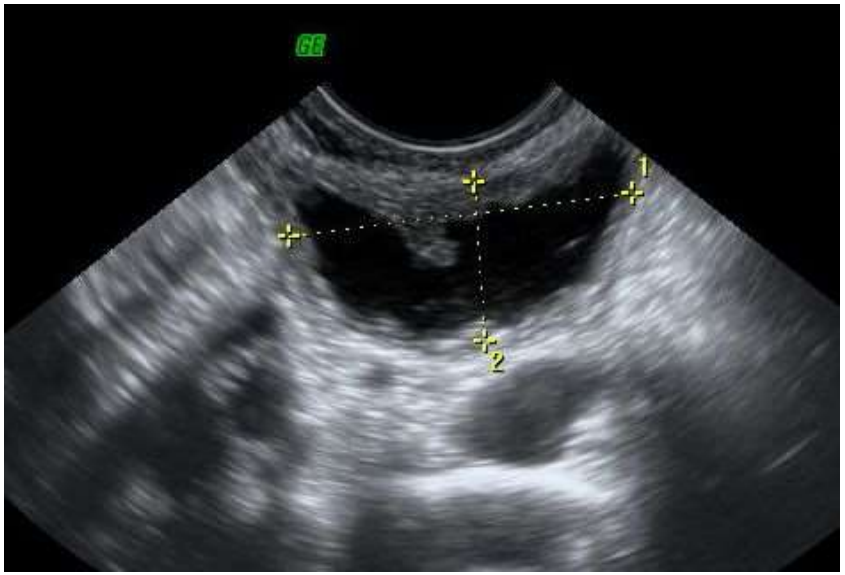
Intestinal adhesions

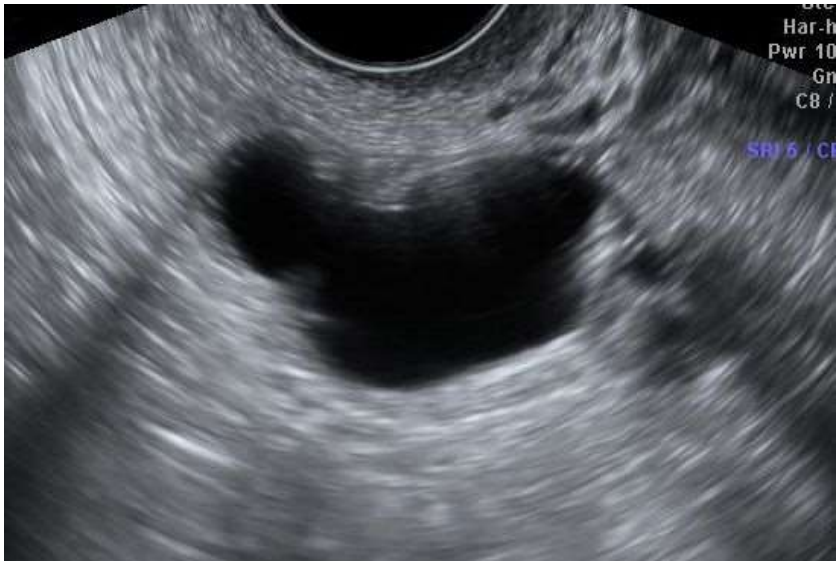


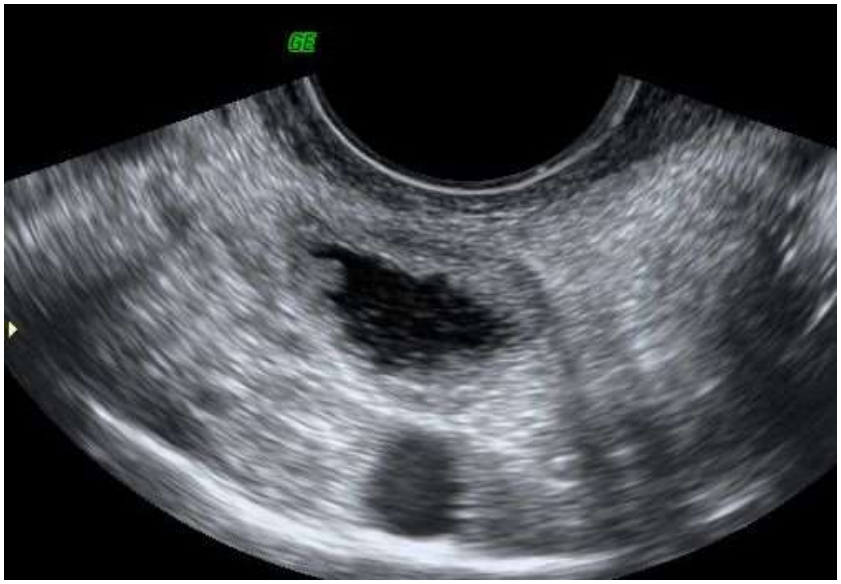


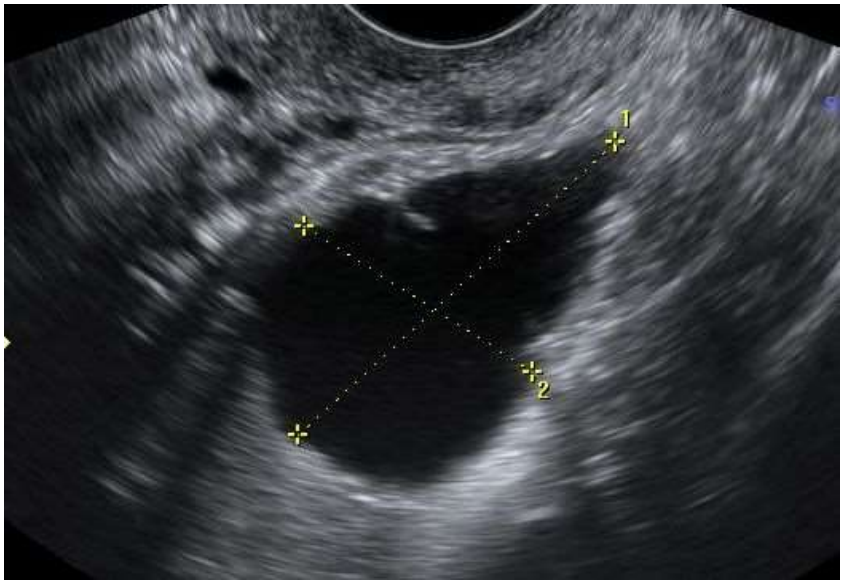


Tubal disease

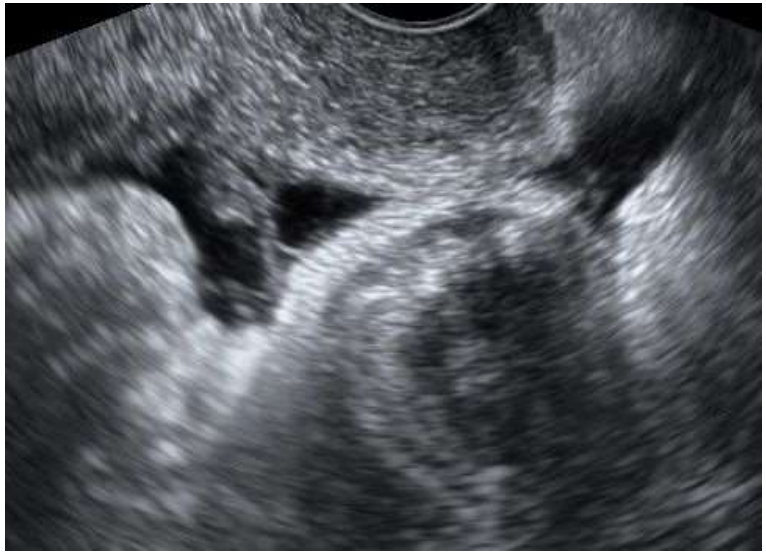


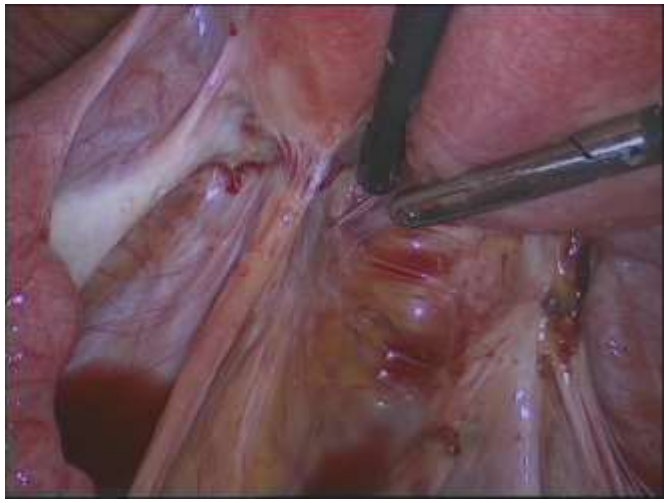




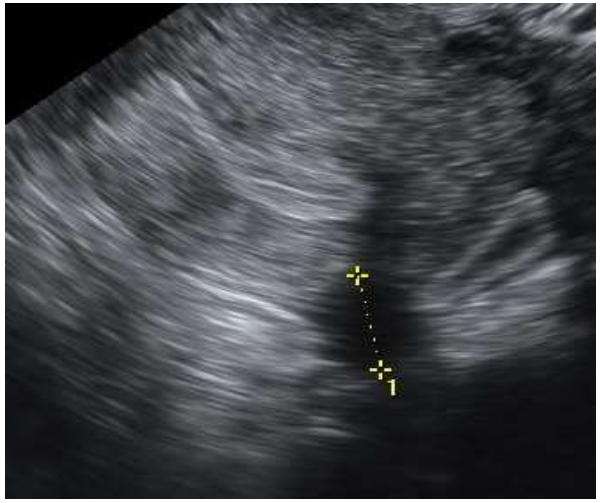


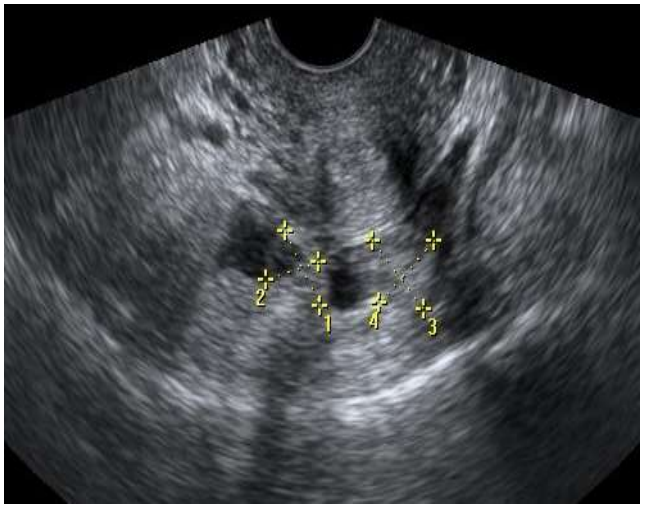
Sacrouterine involvement

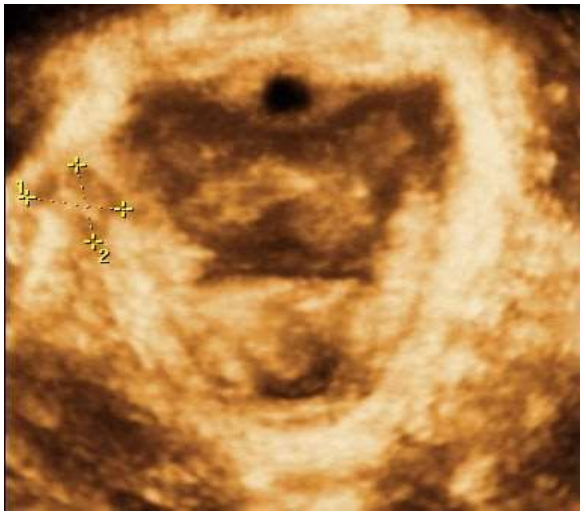




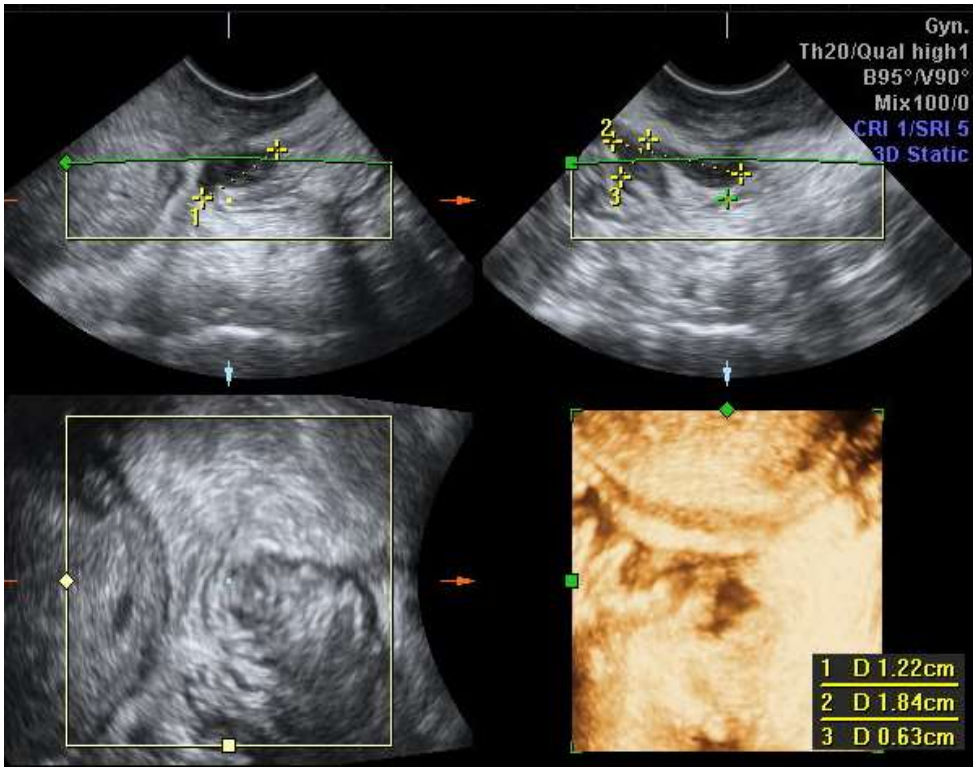
Involvement of the recto-vaginal space with both uterosacral ligaments involved and the normal anatomy of both ureters disturbed

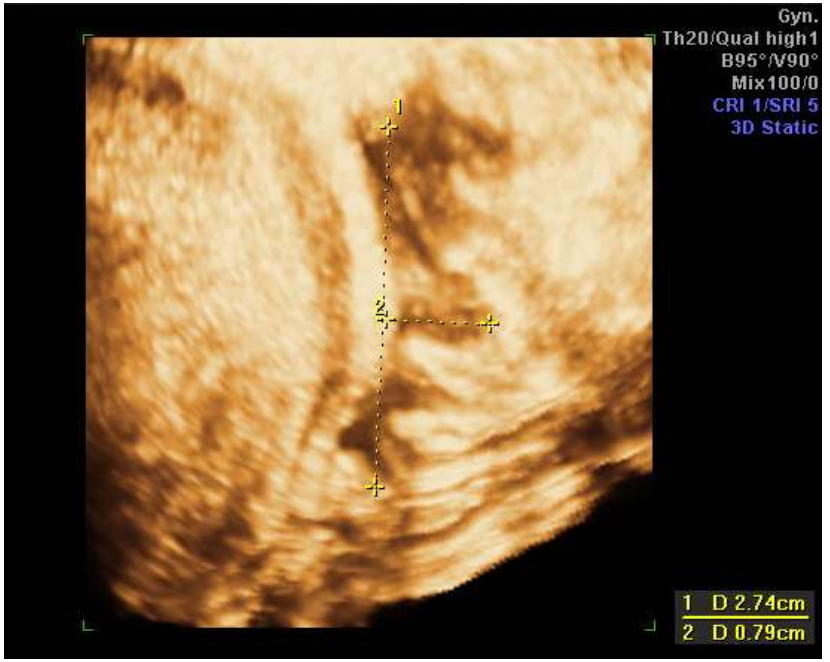






Rectosigmoid nodules

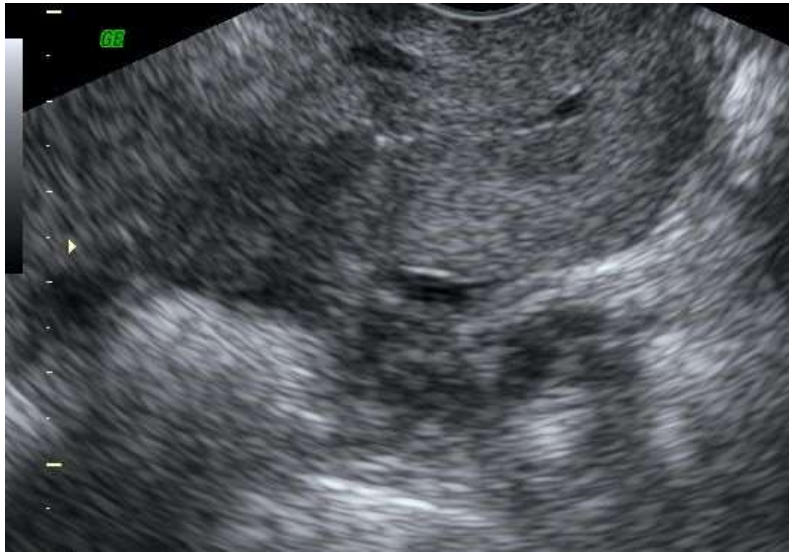


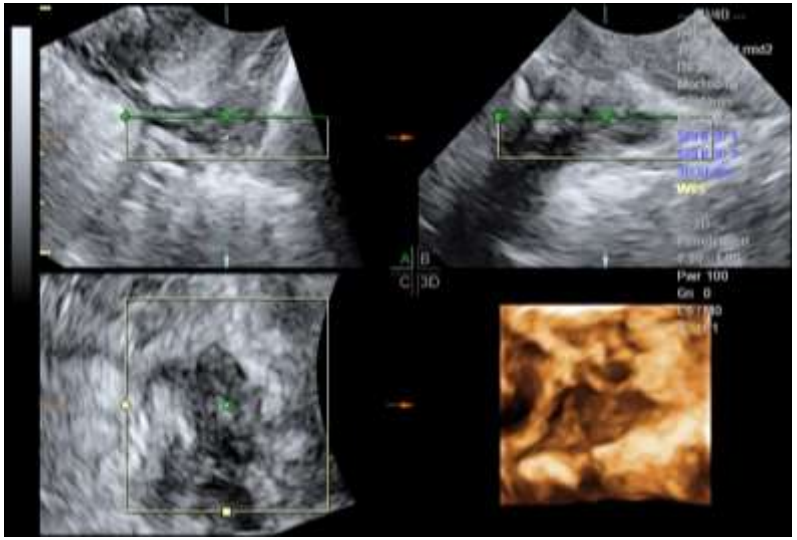


Indian headdress sign

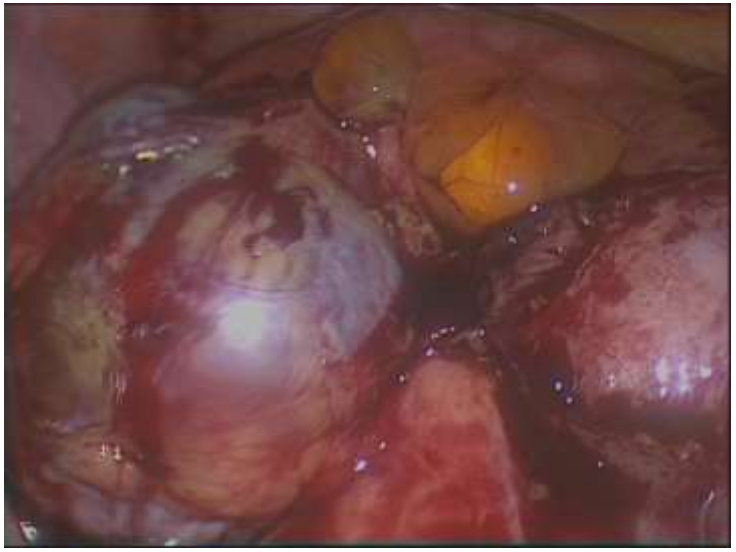
Rectosigmoid nodules

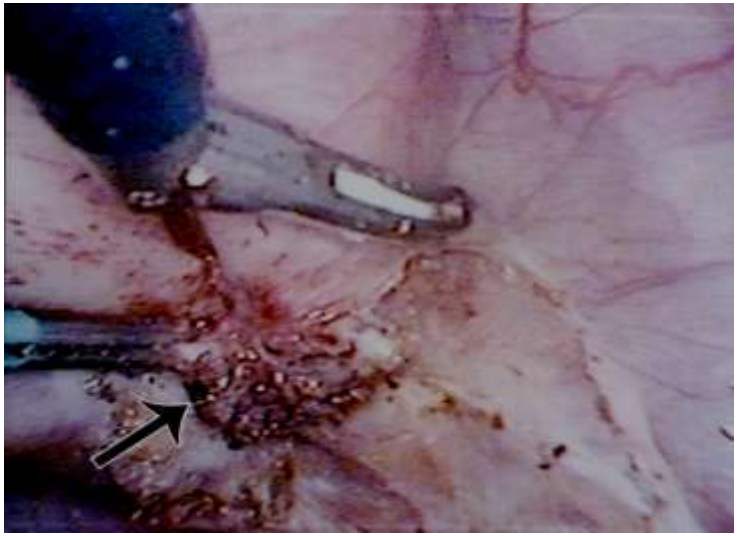
US diagnosis



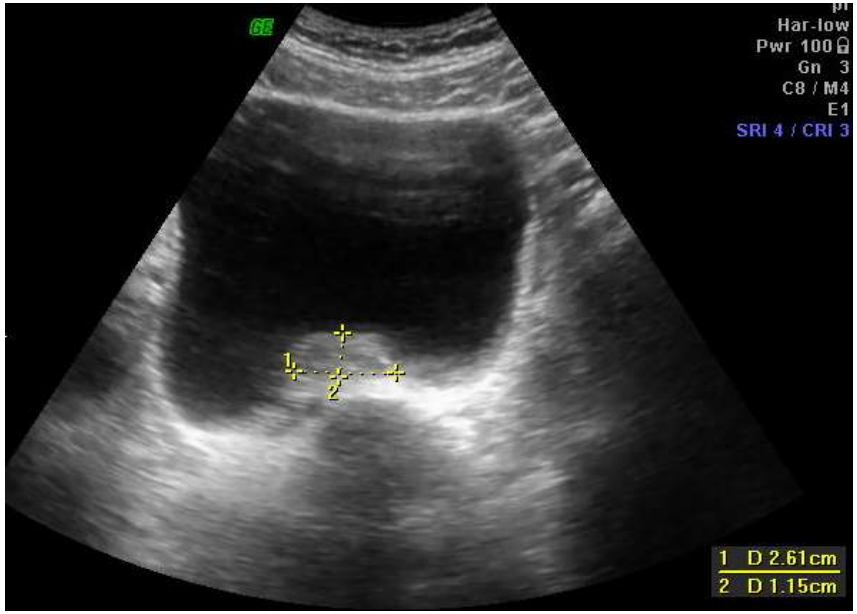


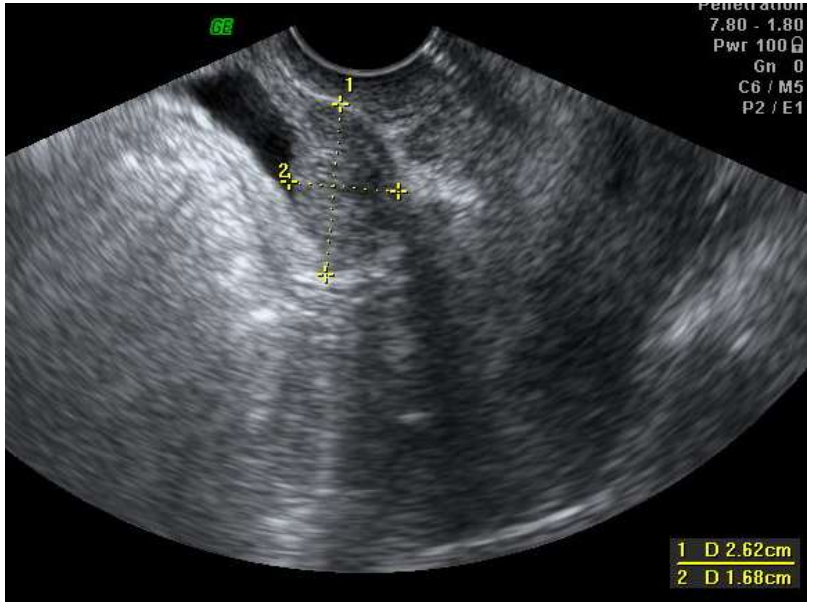
Surgical diagnosis

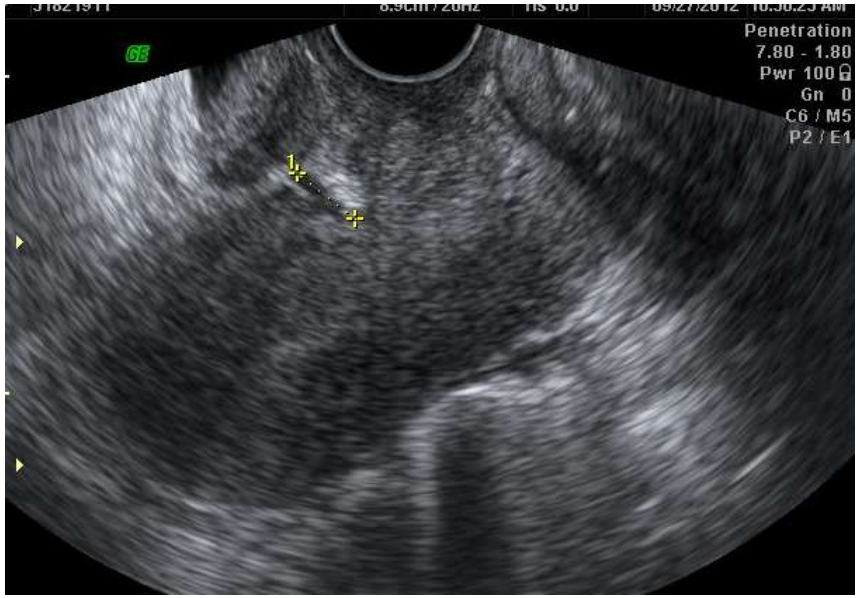


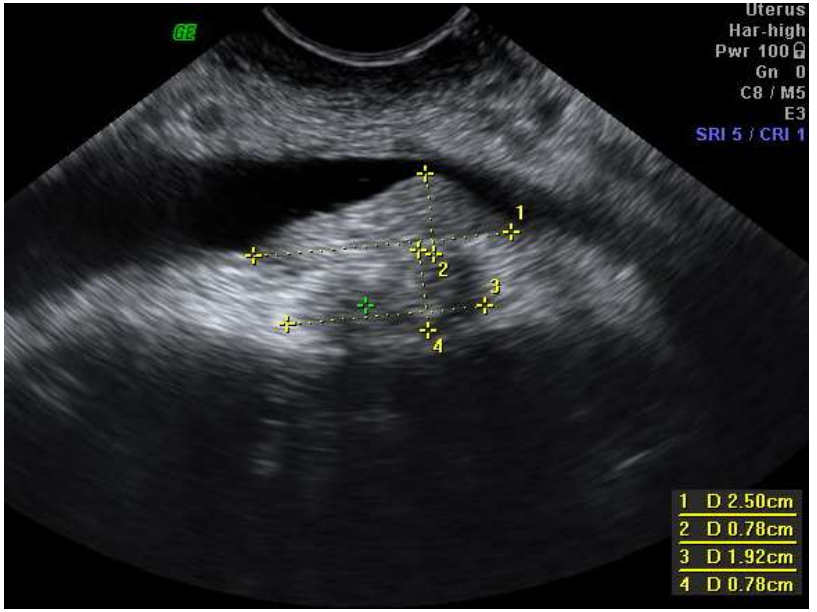


Anterior compartment involvement

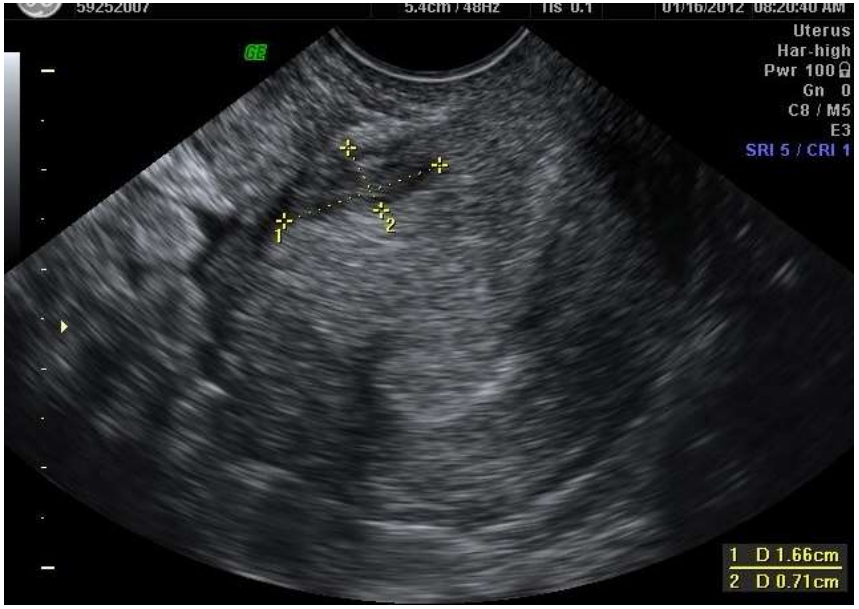




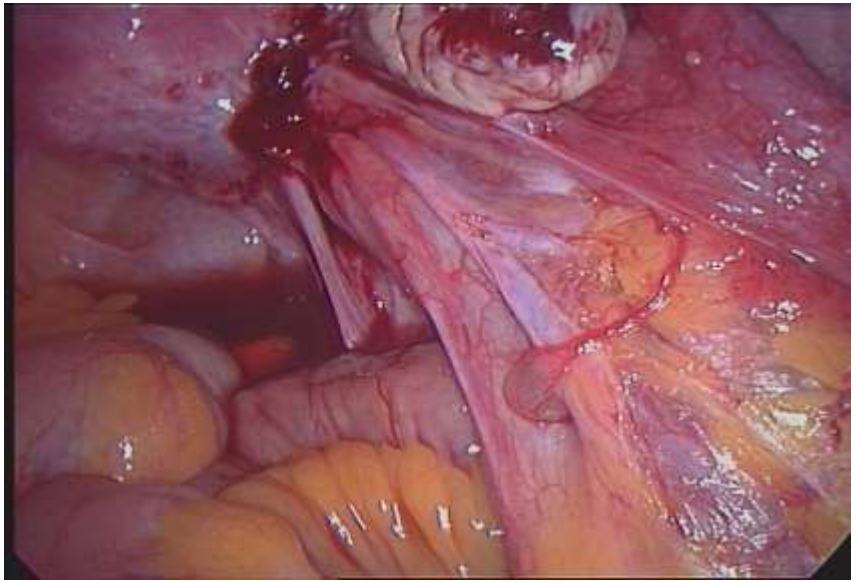


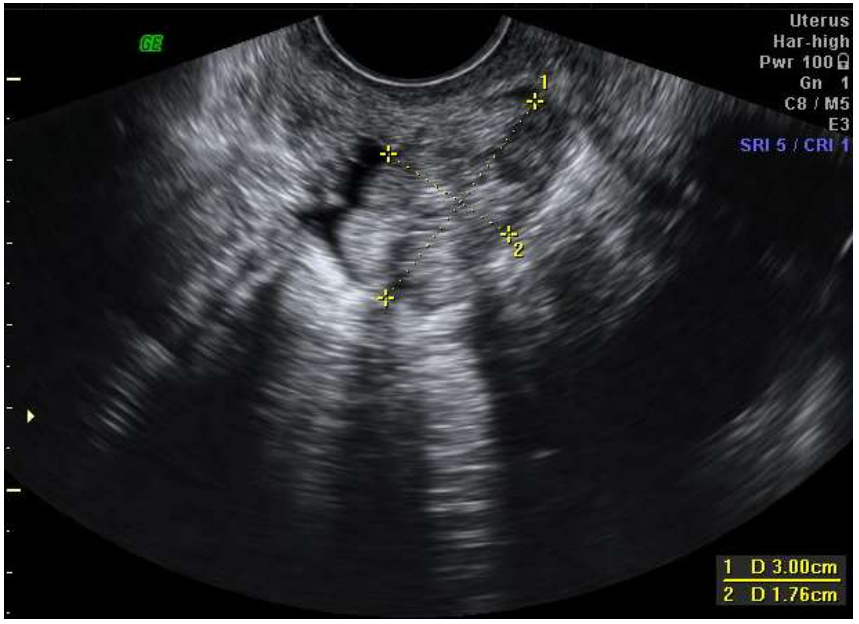


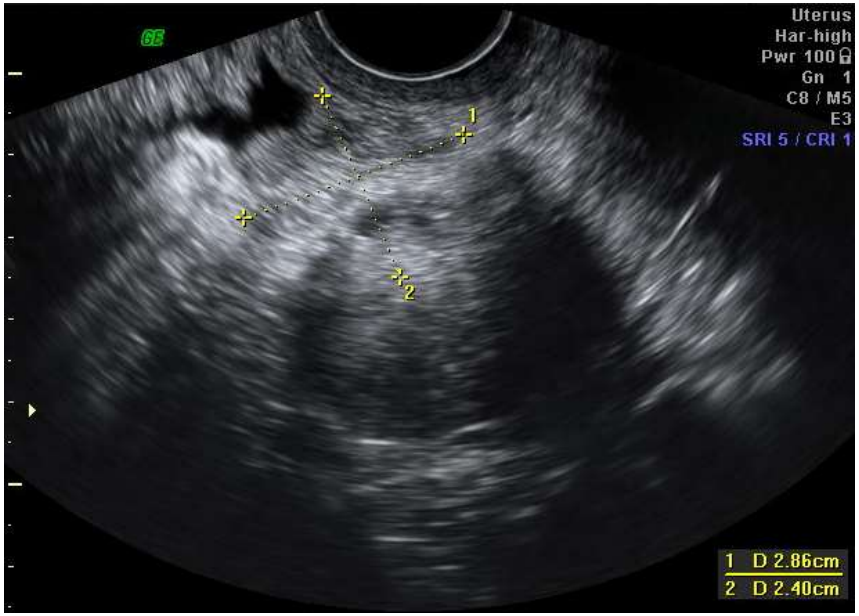
Anterior compartment involvement



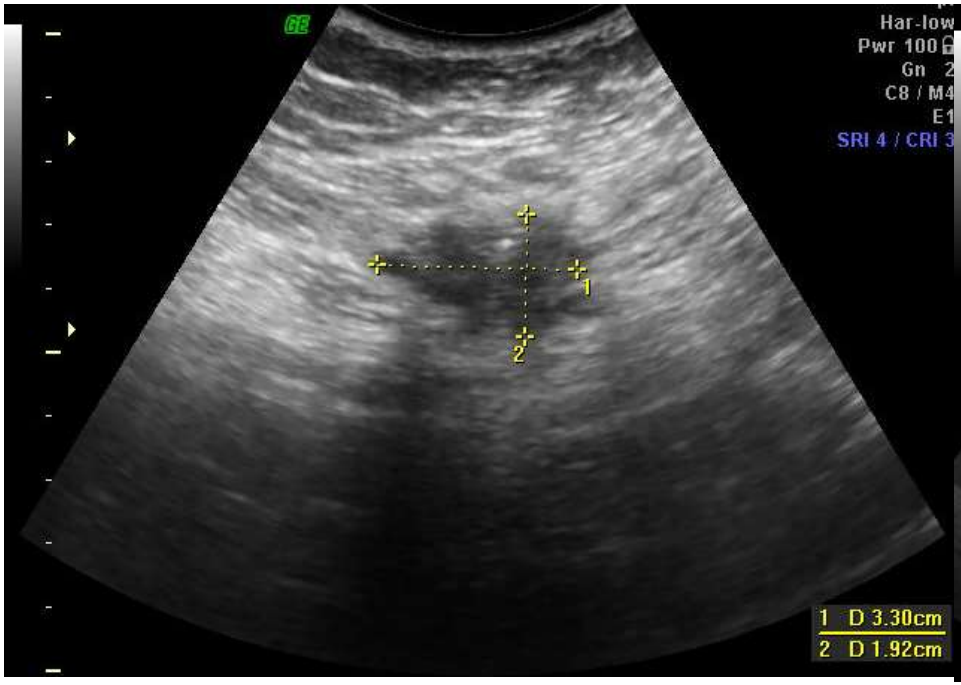
Bladder plica nodule

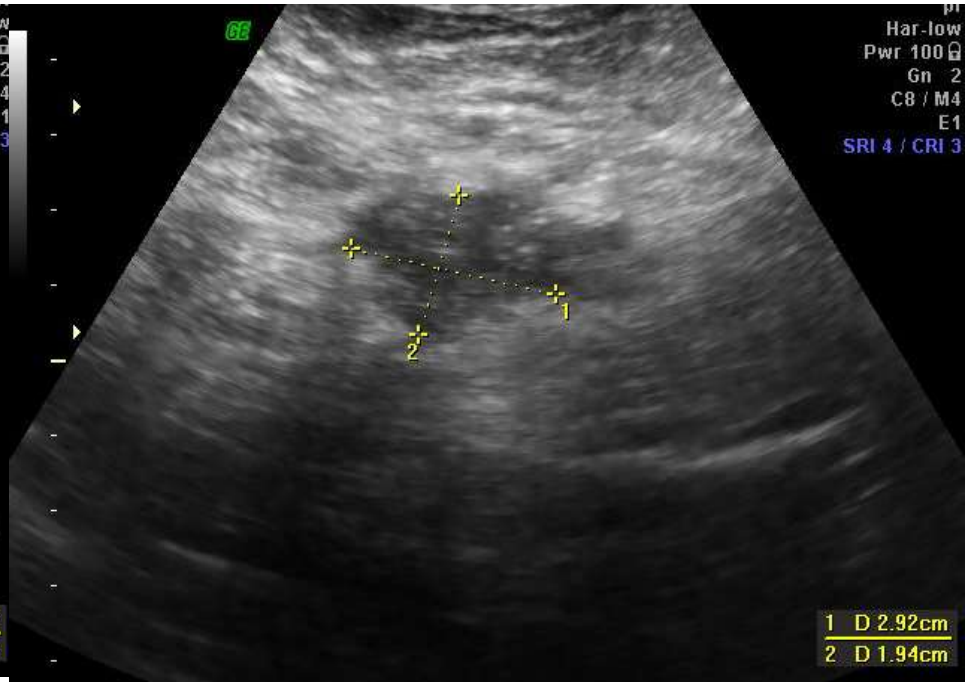






Abdominal wall endometriosis





Adenomyosis

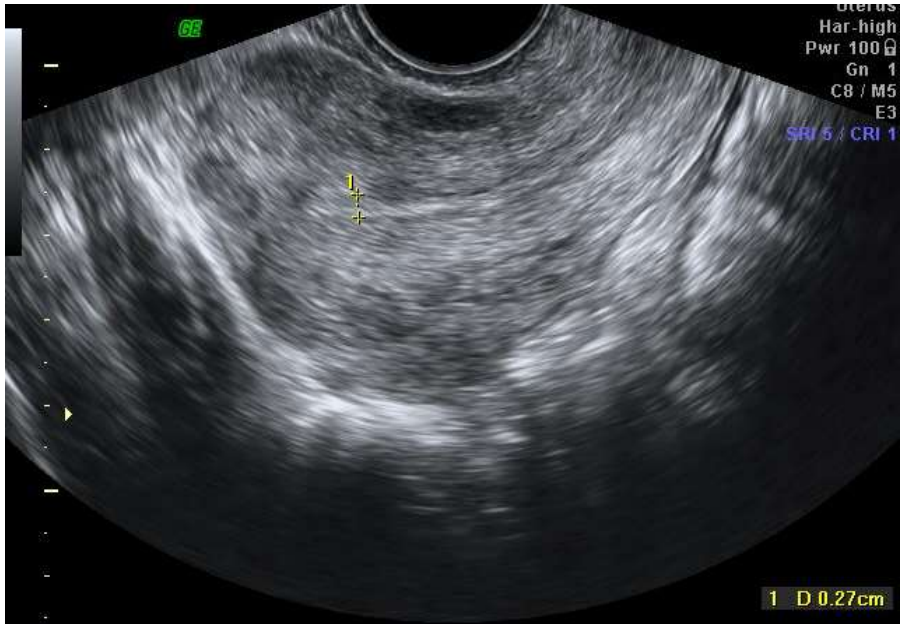
Clinical manifestations

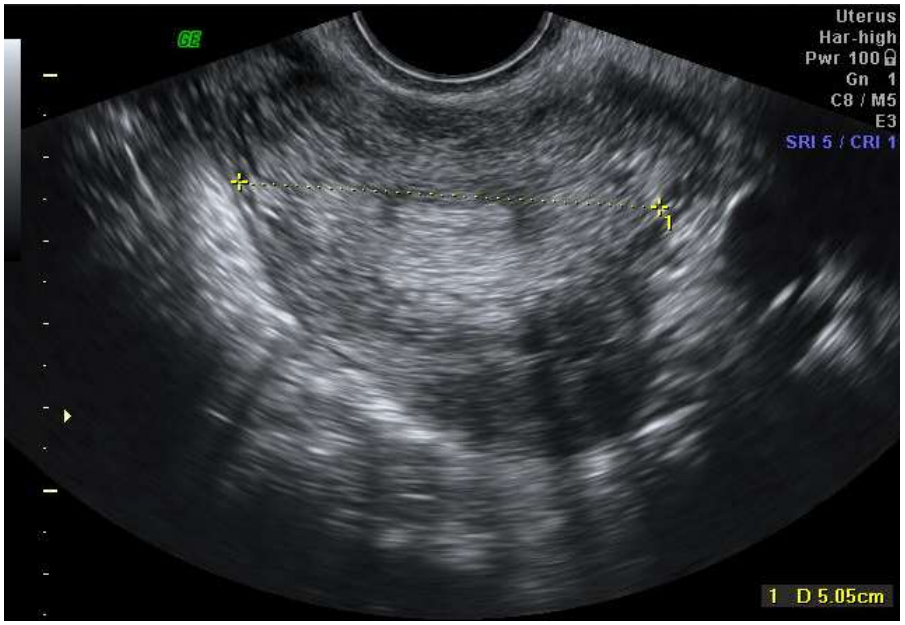
- Heavy menstrual bleeding
- Dysmenorrhea – 25% of women
- Chronic pelvic pain
- Symptoms develop between 40 - 50 years
- Menorrhagia may be related to the increased endometrial surface of the enlarged uterus
- Pain may be due to bleeding and swelling of endometrial islands confined by myometrium
- Approximately 1/3 of women are asymptomatic

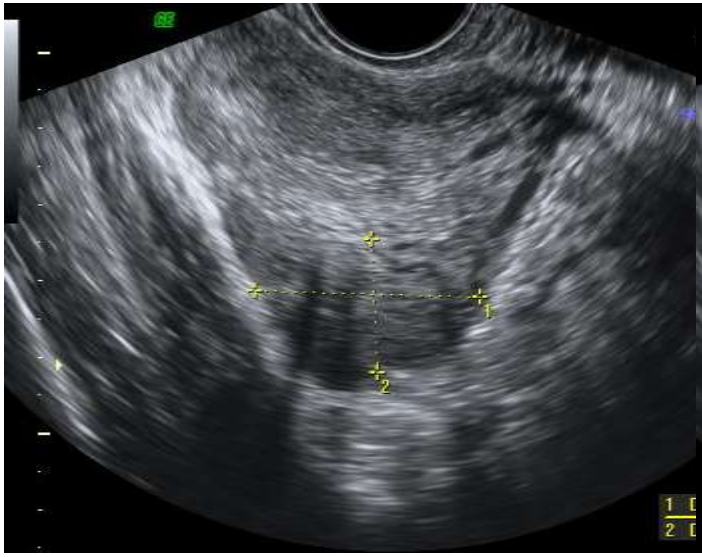
Risk factors

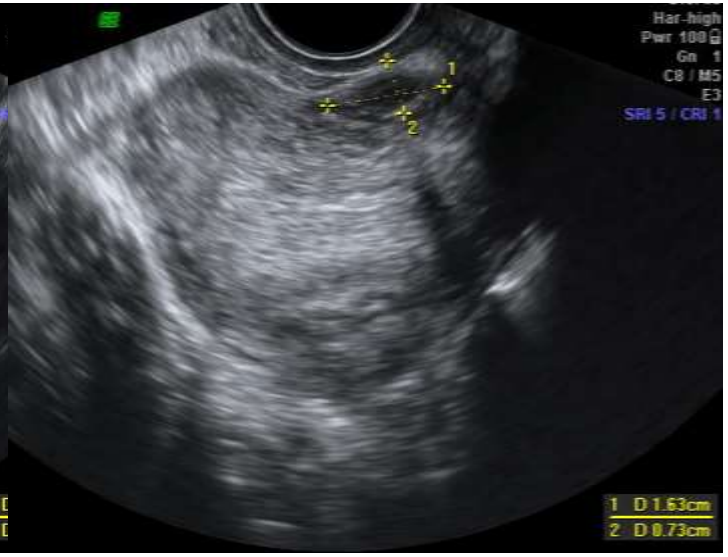
- Advanced age but not only
- Multiparity
- Early menarche
- Obesity
- Previous uterine surgery or intervention
- More common than previously thought

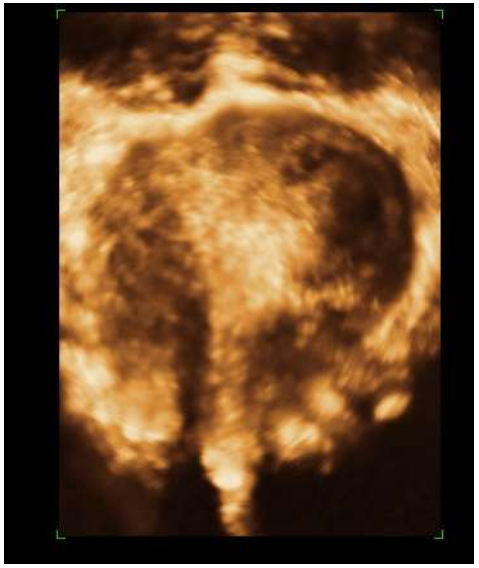
Adenomyosis



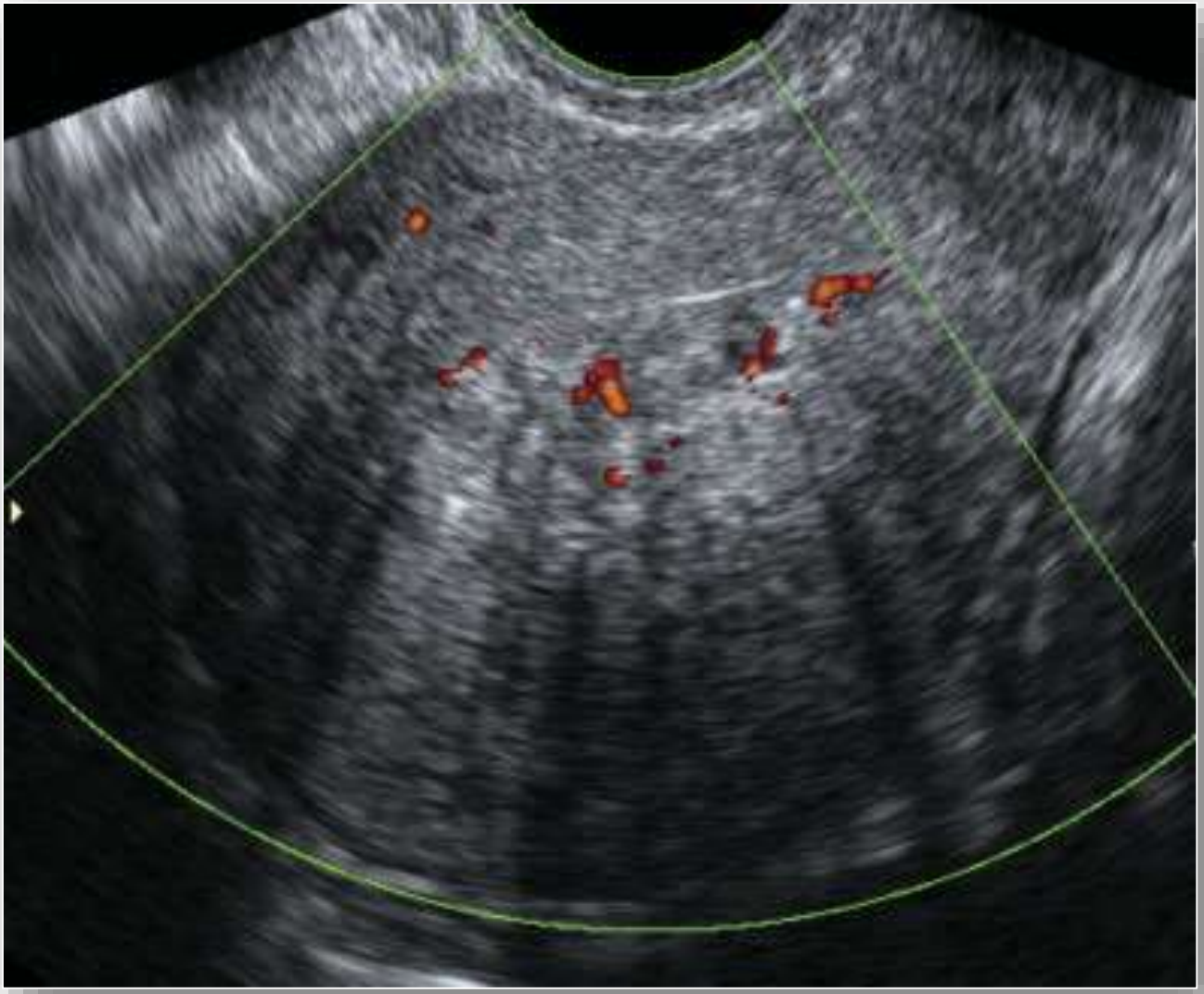




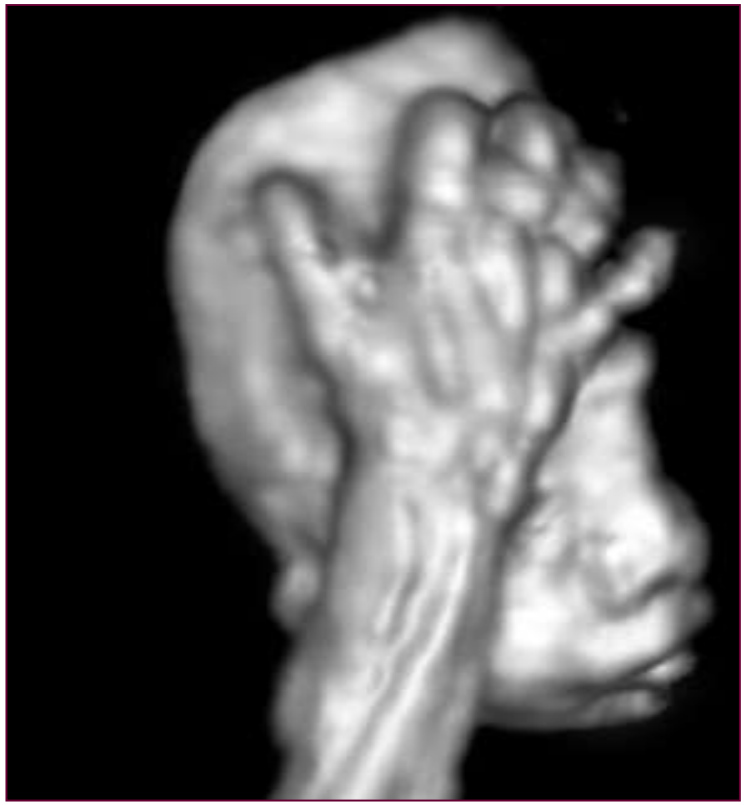




Few diffuse vessels



Thank you



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