

# Ενδομητρίωση



**National  
Endometriosis  
Awareness  
Month**

**One of the most famous sufferers  
of Endometriosis was Marilyn Monroe**

**The condition was so severe that it destroyed her marriages,  
her wish for children, her career and ultimately her life.**

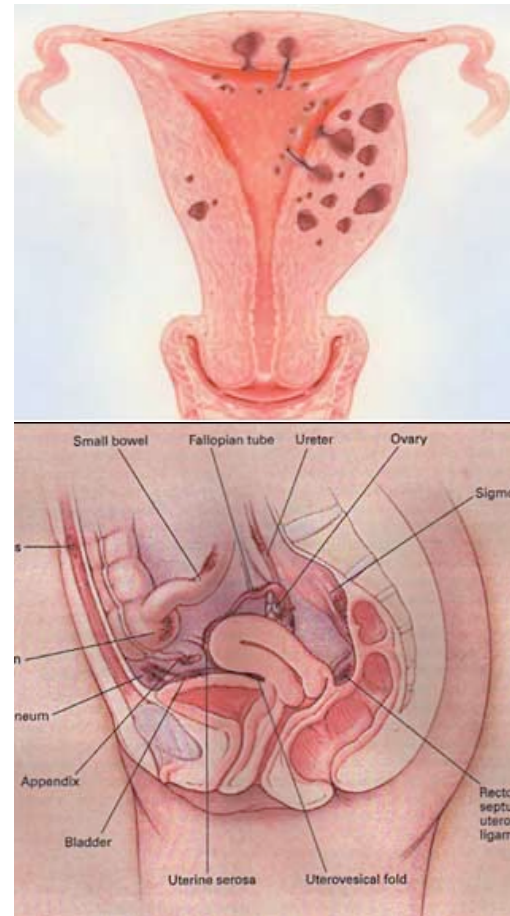
Before the days of effective medical therapies and conservative surgeries,  
treatment of Endometriosis consisted of progressively increasing use of  
strong analgesics, tranquilizers and hypnotics.  
**and ultimately - drug dependency.**

Endometriosis impacts the lives of some 176 million women world wide...  
**Please Help Us Put an END to Endo!**

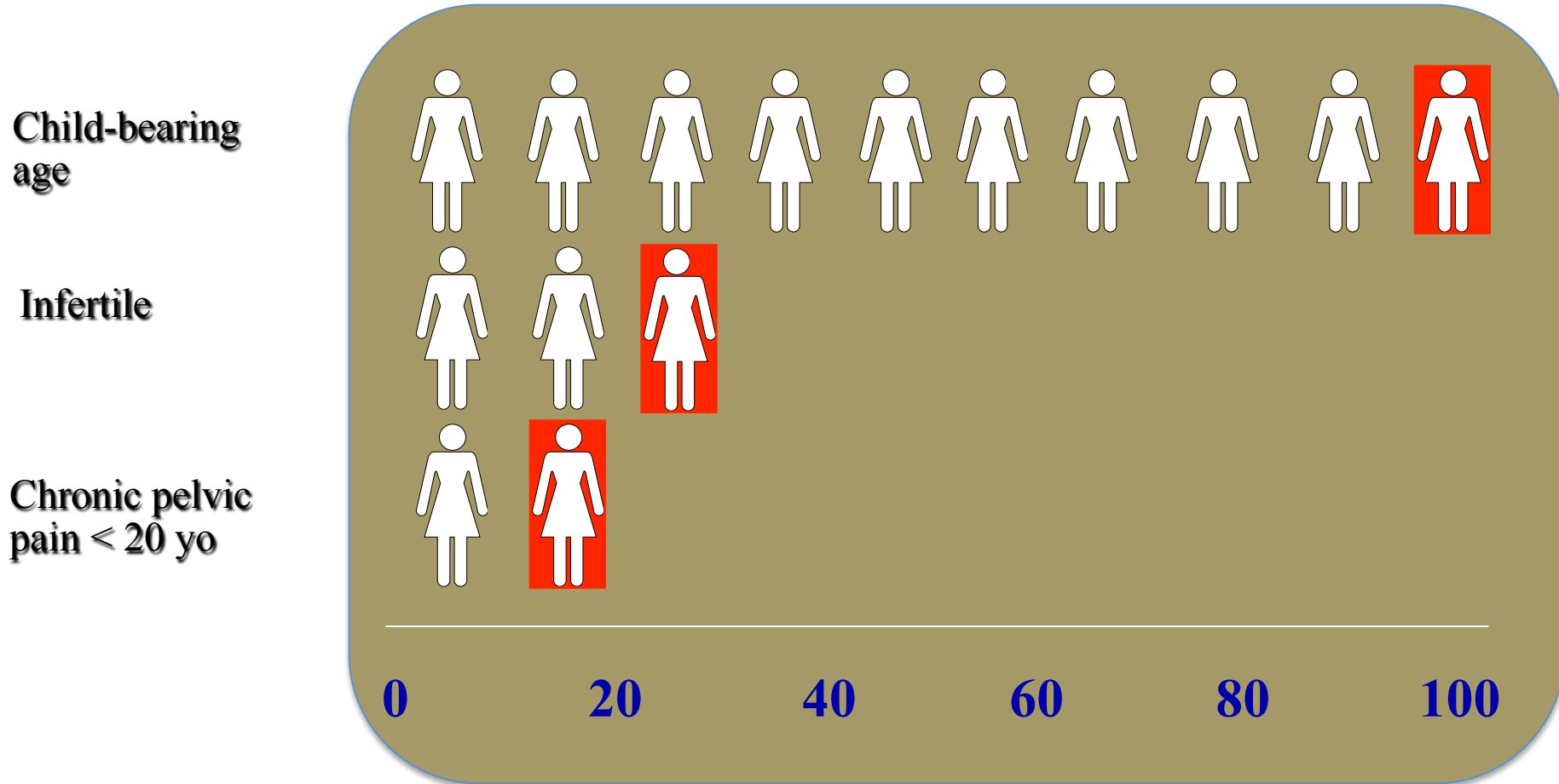
# Endometriosis

The presence of endometrial tissue outside the endometrial cavity.

- Endometriosis can affect any female, from [menarche](#) to [menopause](#).
- It is primarily a disease of the reproductive years.
- As an estrogen-dependent process, but can persist beyond menopause
  - in up to 10% of patients following hysterectomy.



# Prevalence



# Prevalence:

20-40% in infertile women  
(Mahmood et al 1991)

15-70% in women with chronic pelvic pain  
(Stanford et al 2005)

0.7-45% in asymptomatic women  
(Farguhar et al 2000)

6-18% in women undergoing sterilization  
(Matorras et al 1995)

# Economic Burden of Surgically Confirmed Endometriosis in Canada

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Robert Sambrook, MSc,<sup>1</sup> Mark Jeddi, MA,<sup>3</sup> Serge Bélisle, MD, MSc, FRCSC,<sup>4</sup>  
Robert L. Reid, MD, FRCSC<sup>5</sup>

**Results:** The estimated mean annual societal cost of endometriosis was \$5200 per patient (95% CI \$3700 to \$7100), with lost productivity and lost leisure time costs accounting for 78%. Extrapolating these figures yields an estimated total annual cost to Canadian society of \$1.8 billion (95% CI \$1.3 billion to \$2.4 billion) attributable to surgically confirmed endometriosis in Canada.

# The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres

**RESULTS:** Data analysis of 909 women demonstrated that the average annual total cost per woman was €9579 (95% confidence interval €8559–€10 599). Costs of productivity loss of €6298 per woman were double the health care costs of €3113 per woman. Health care costs were mainly due to surgery (29%), monitoring tests (19%) and hospitalization (18%) and physician visits (16%). Endometriosis-associated symptoms generated 0.809 quality-adjusted life years per woman. Decreased quality of life was the most important predictor of direct health care and total costs. Costs were greater with increasing severity of endometriosis, presence of pelvic pain, presence of infertility and a higher number of years since diagnosis.

# Endometriosis

- Risk factors:
  - Early menarche
  - Short cycles <27 days
  - Long duration of menses >7 days ( x2)
  - Family history
  - Nulliparity
- Recurrence rates: as high as 30-40% at 24-36 months following conservative surgery

(Porpora et al 2008, Vercellini et al 2008)

# Endometriosis

Generally regarded as a benign condition. It shows some of the characteristics of malignancy

Development of local and distal foci

Attachment and invasion of other tissues

Damage to other organs ( Garry et al 2001)

Recently endometriosis has been associated with increase risk of several malignancies ( vlahos et al.2010)



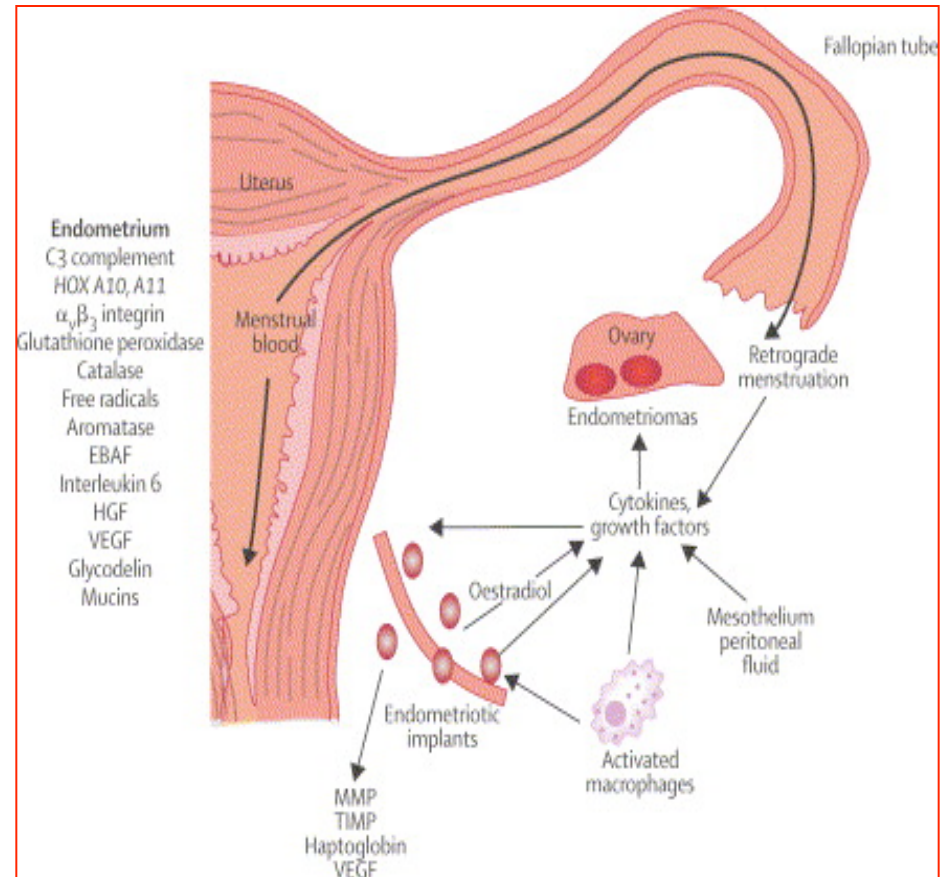
# Pathogenesis

Retrograde menstruation  
with transport of  
endometrial cells from the  
uterus

Metaplasia of coelomic epithelium

Hematogenous or lymphatic  
spread of endometrial cells

Altered host response, towards  
ectopic endometrial cells





Continuous war between the endometriotic offence and peritoneal defense.

- Endometriosis results from the failure of the defensive mechanisms or.....
- Overwhelming enemy power.

# Pathogenesis

## Endometriosis offence:

- Endometrial cells
- Adhesion molecules
- TMPs
- Growth factors
- TNF- $\alpha$ , IL-1,.....

## Peritoneal defense

- Peritoneal fluid
- Coelomic epithelium
- Macrophages
- T-cells
- Cytokines

# Pathogenesis

- Casualties

*(destruction of endometrial and epithelial cells)*

- Repairs

*(formation of fibrous tissue)*

- Collateral damage

*(destruction of adjacent healthy tissue)*

**Increased endometrial shedding  
with normal peritoneal response**



# Endometriosis



**Normal endometrial shedding  
with abnormal peritoneal response**

# What goes wrong?

- Defective immunosurveillance:
  - Suppressed NK cell activity
  - ICAM-1 (intracellular adhesion molecule-1)
  - Fas-Fas ligand interactions
- Increased number of macrophages and T-cells

# Dysregulation of Cytokines

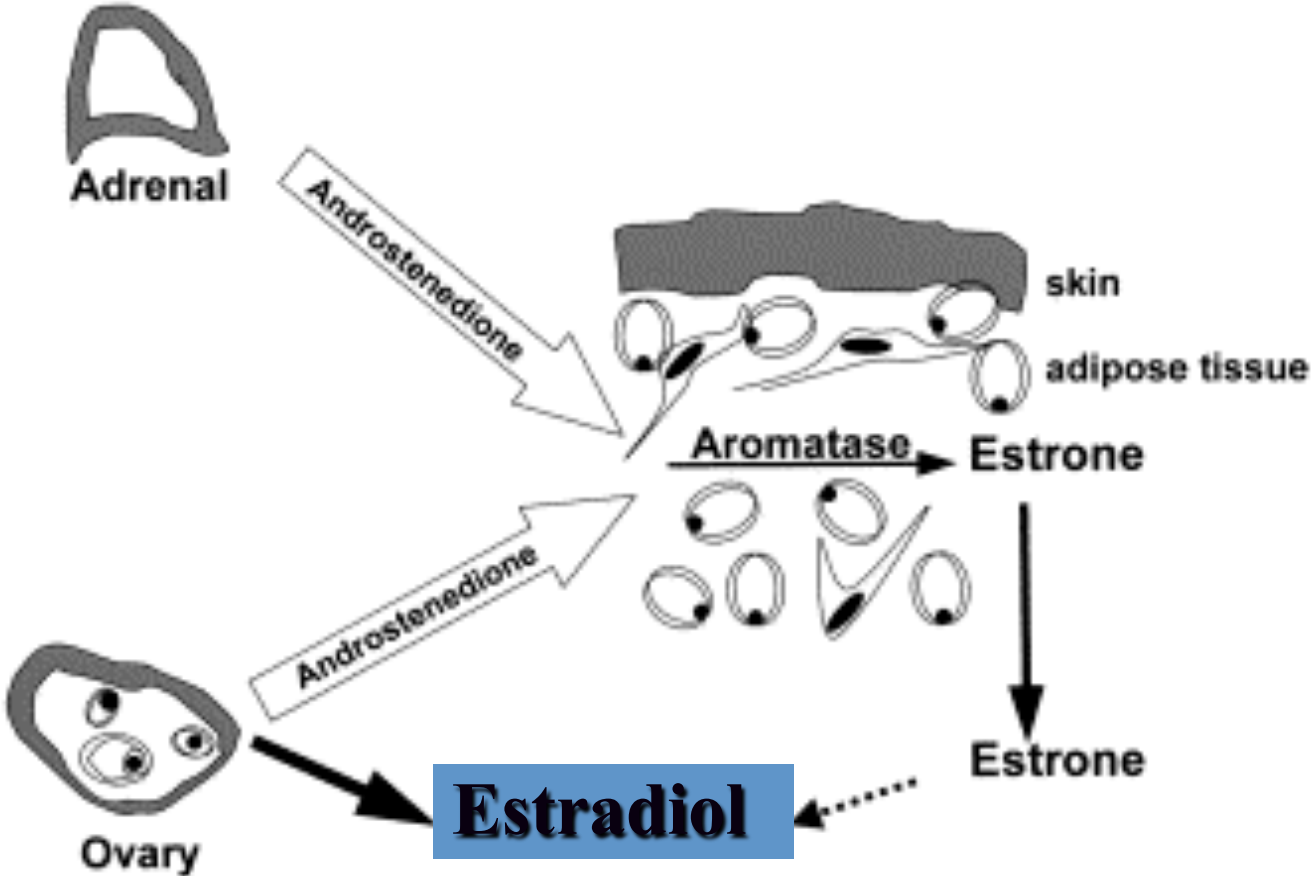
- IL-1
- IL-6
- VEGF
- TNF
- RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted)

# Pathogenesis

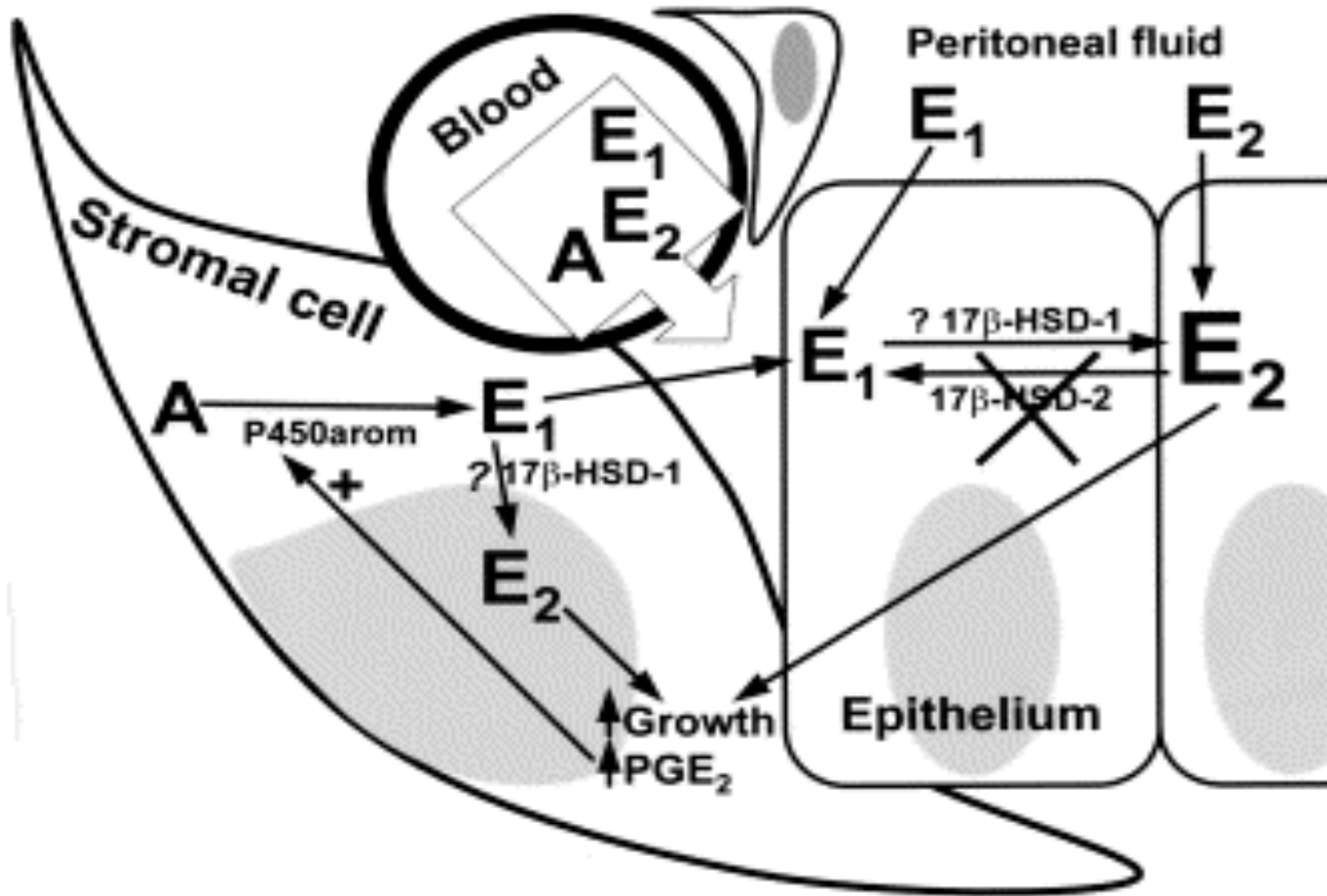
- Inefficient over-response of the immune system towards ectopic endometrial cells.
- Estrogen required for growth
  - Rarely occurs before menarche, usually regresses after menopause
  - Induces endometrial proliferation
  - Stimulates VEGF, RANTES



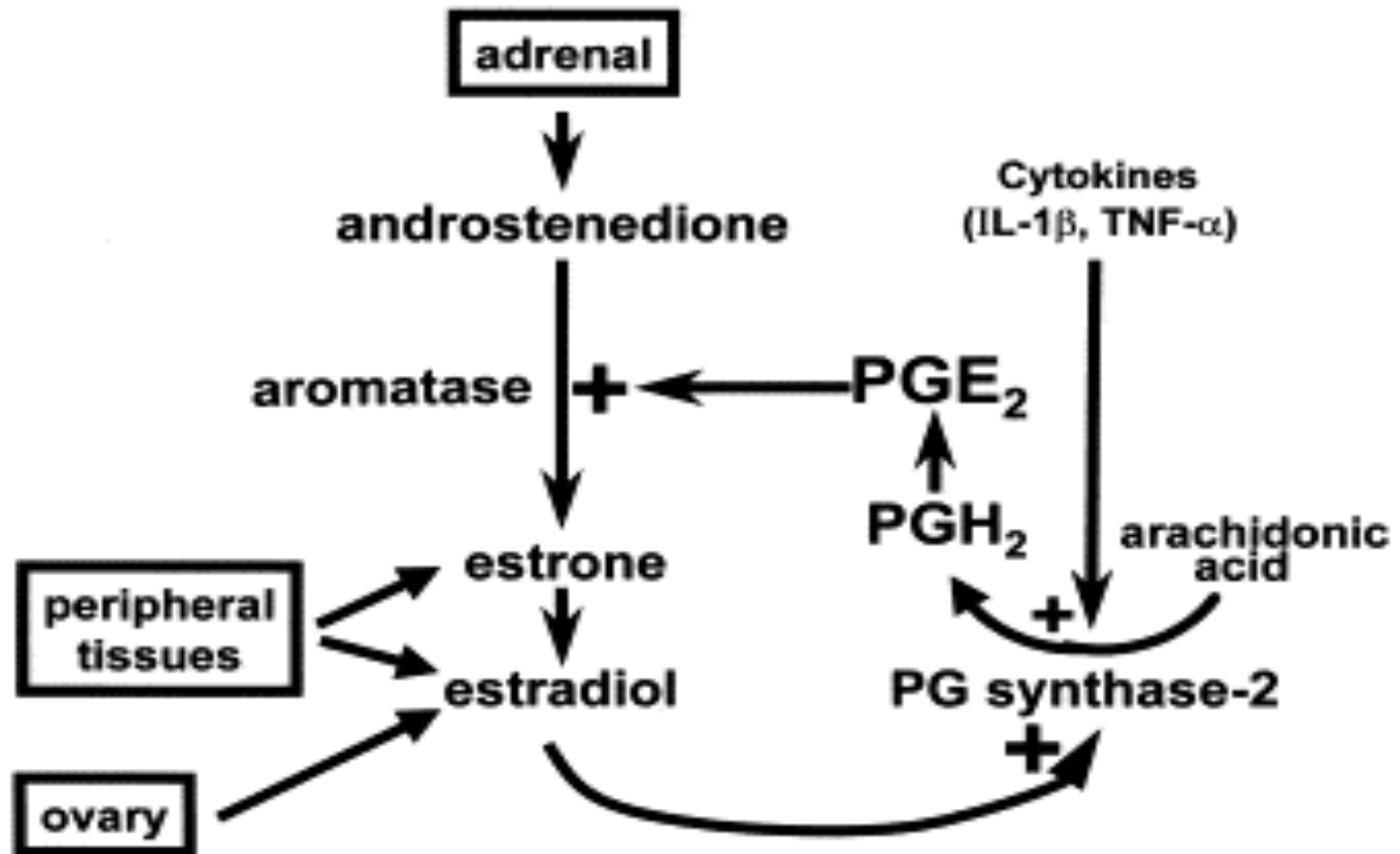
# Where is estrogen coming from?



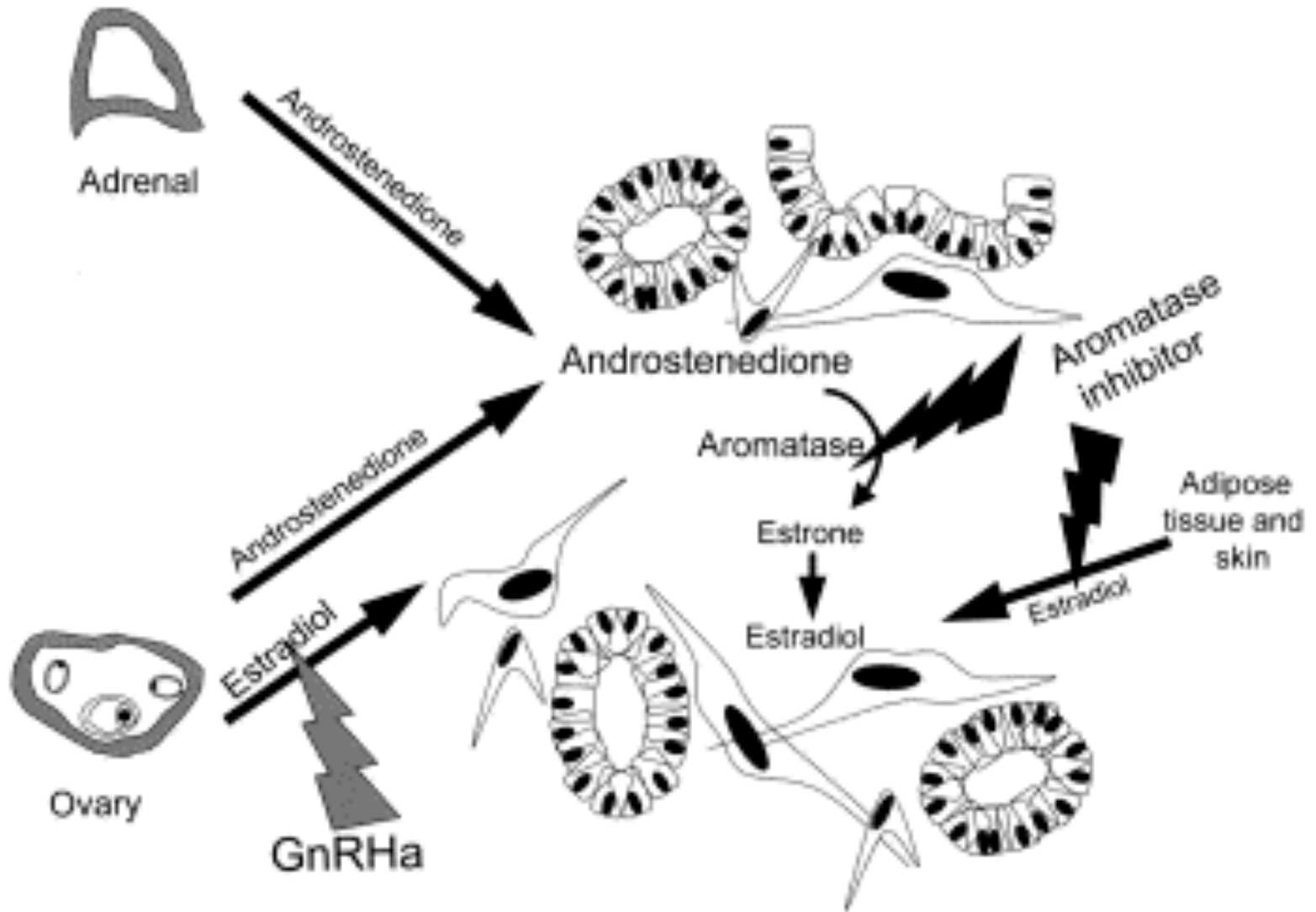
# Aromatase and 17 $\beta$ HSD activity in the pathogenesis of endometriosis.



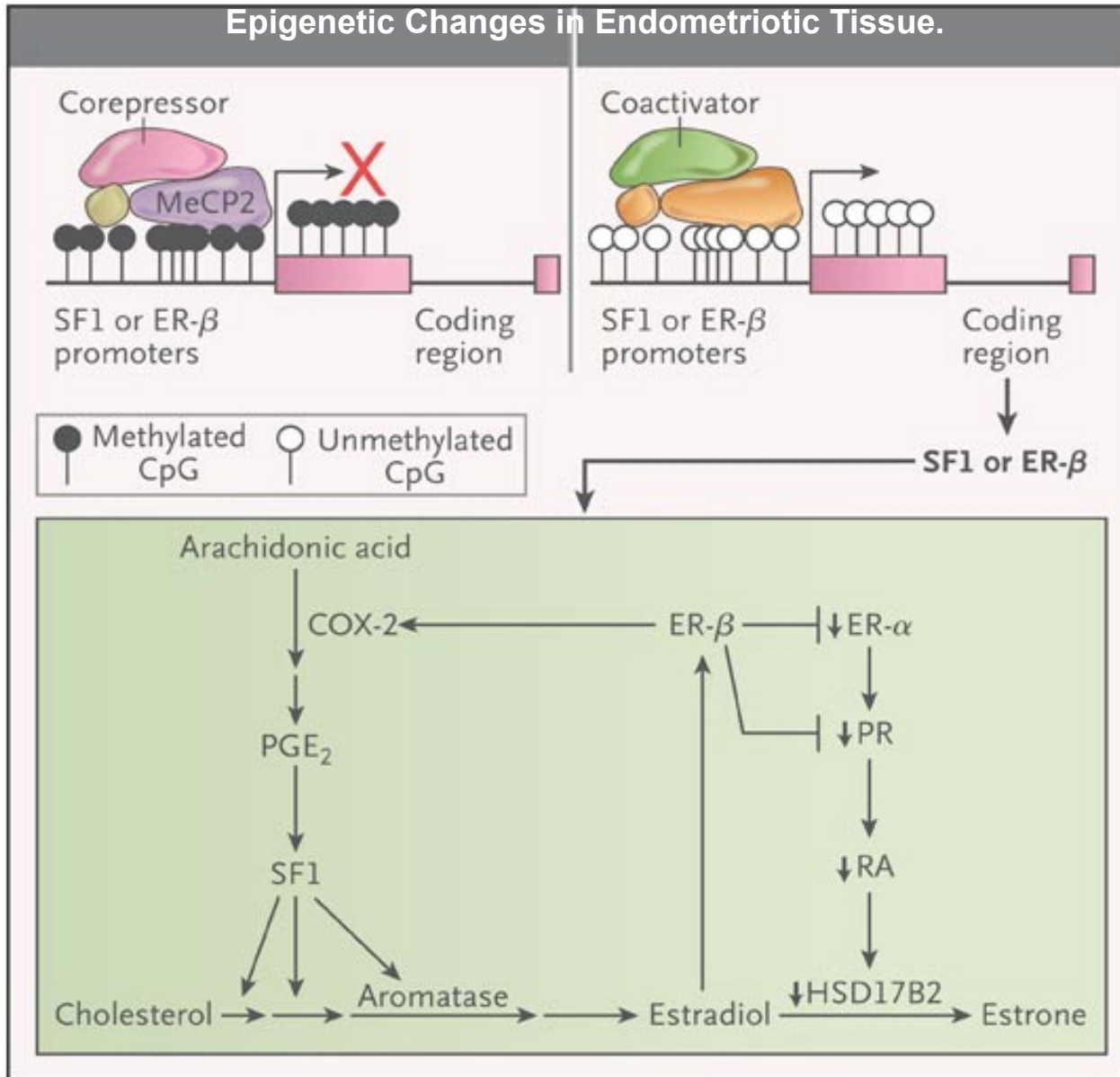
# Aromatase and PG activity in the pathogenesis of endometriosis.

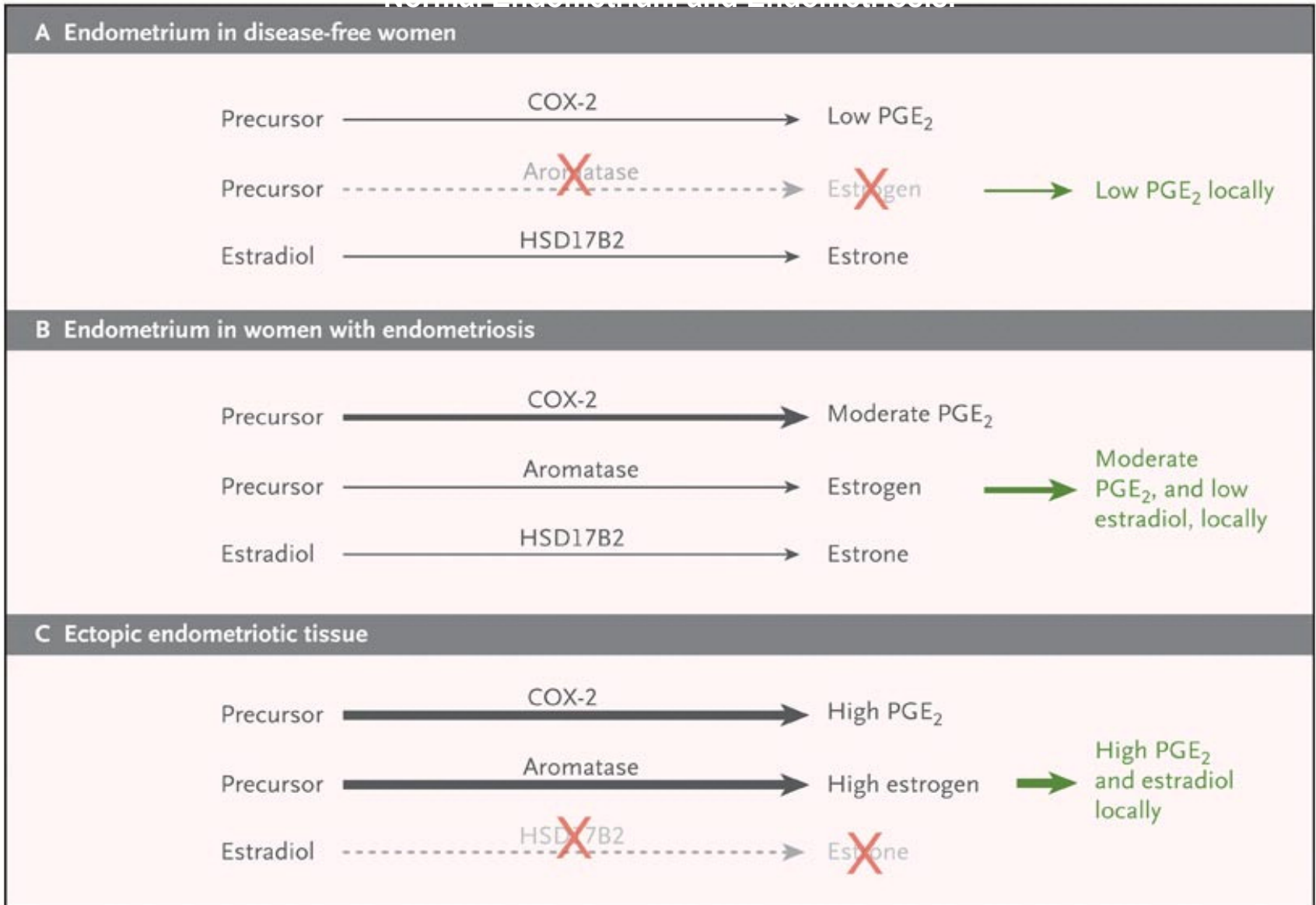


# Medical treatment of endometriosis

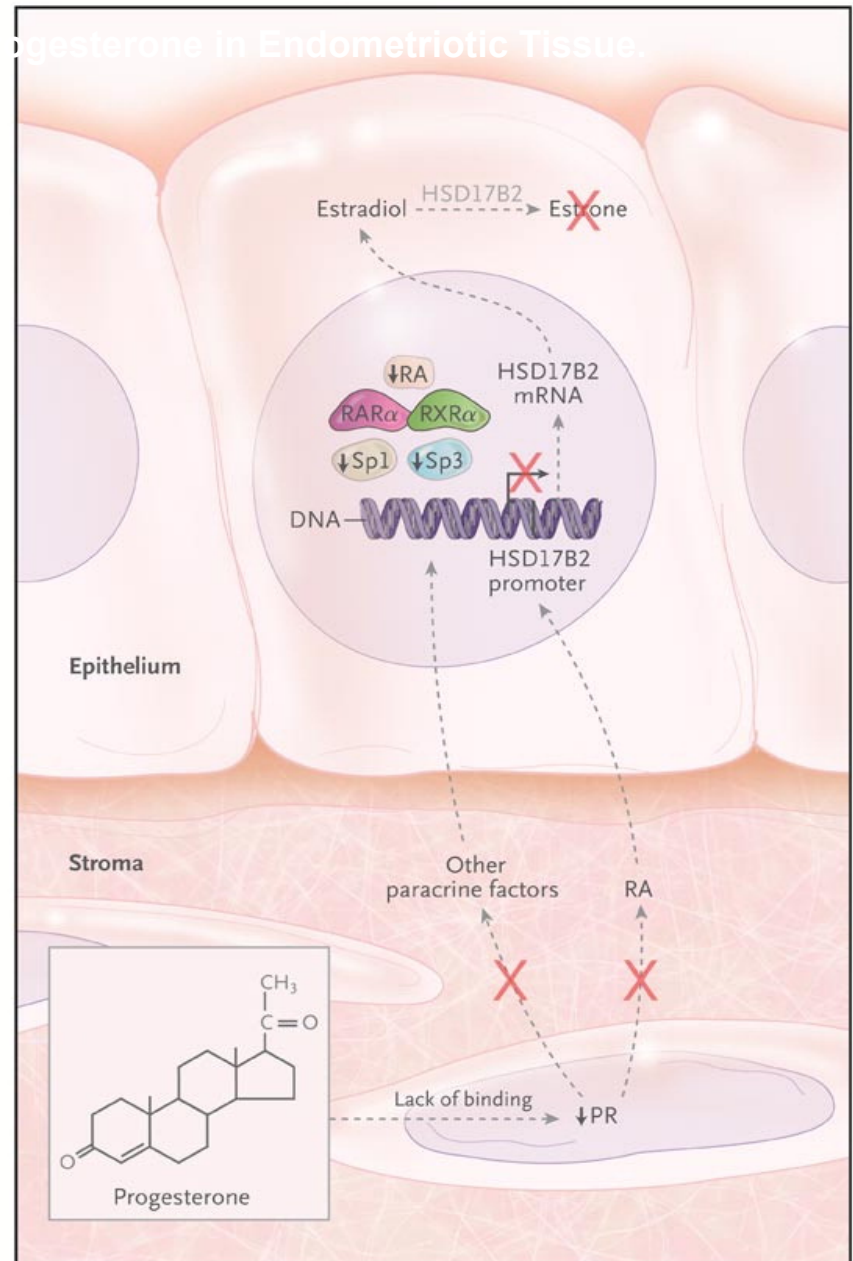


## Epigenetic Changes in Endometriotic Tissue.

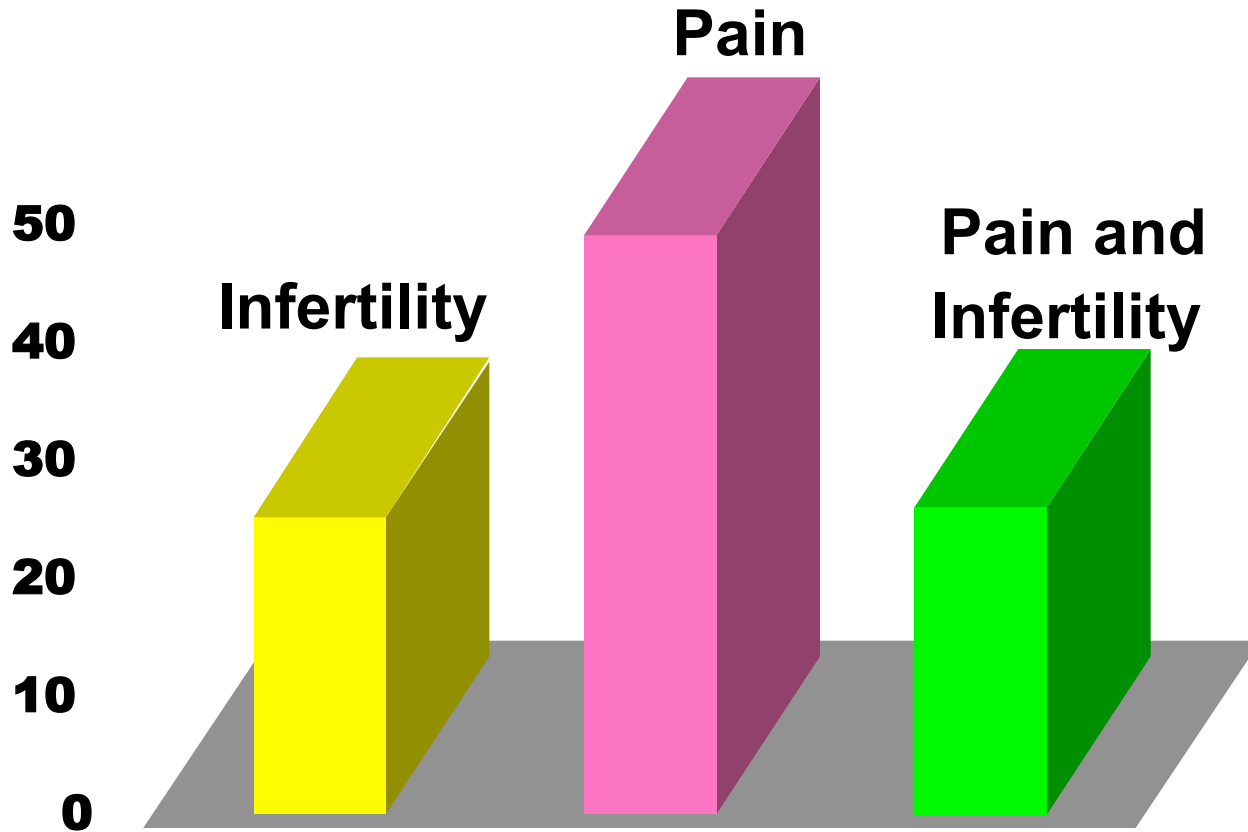




Disruption in the action of Progesterone in endometriosis.

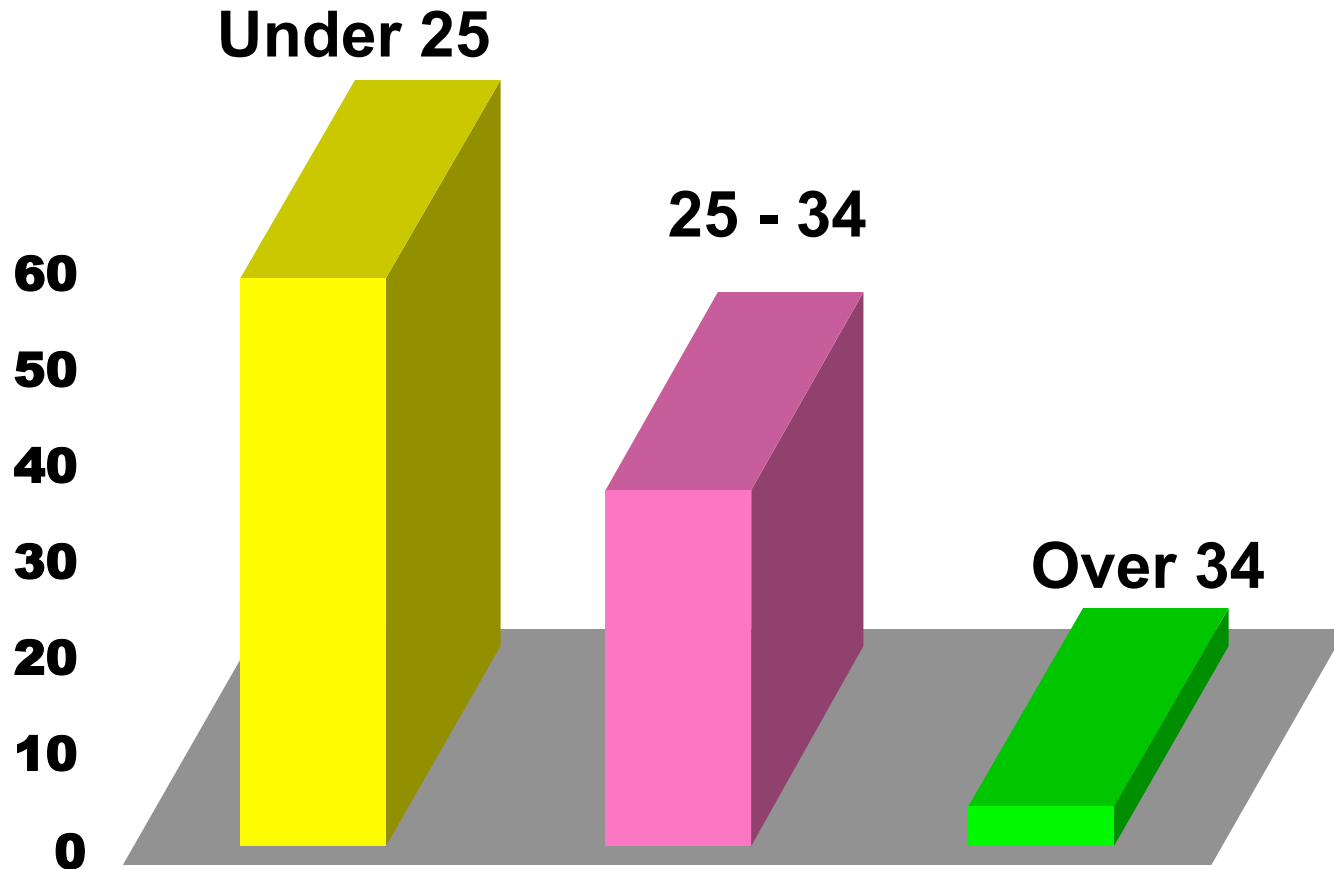


# Most Common Symptoms at Presentation

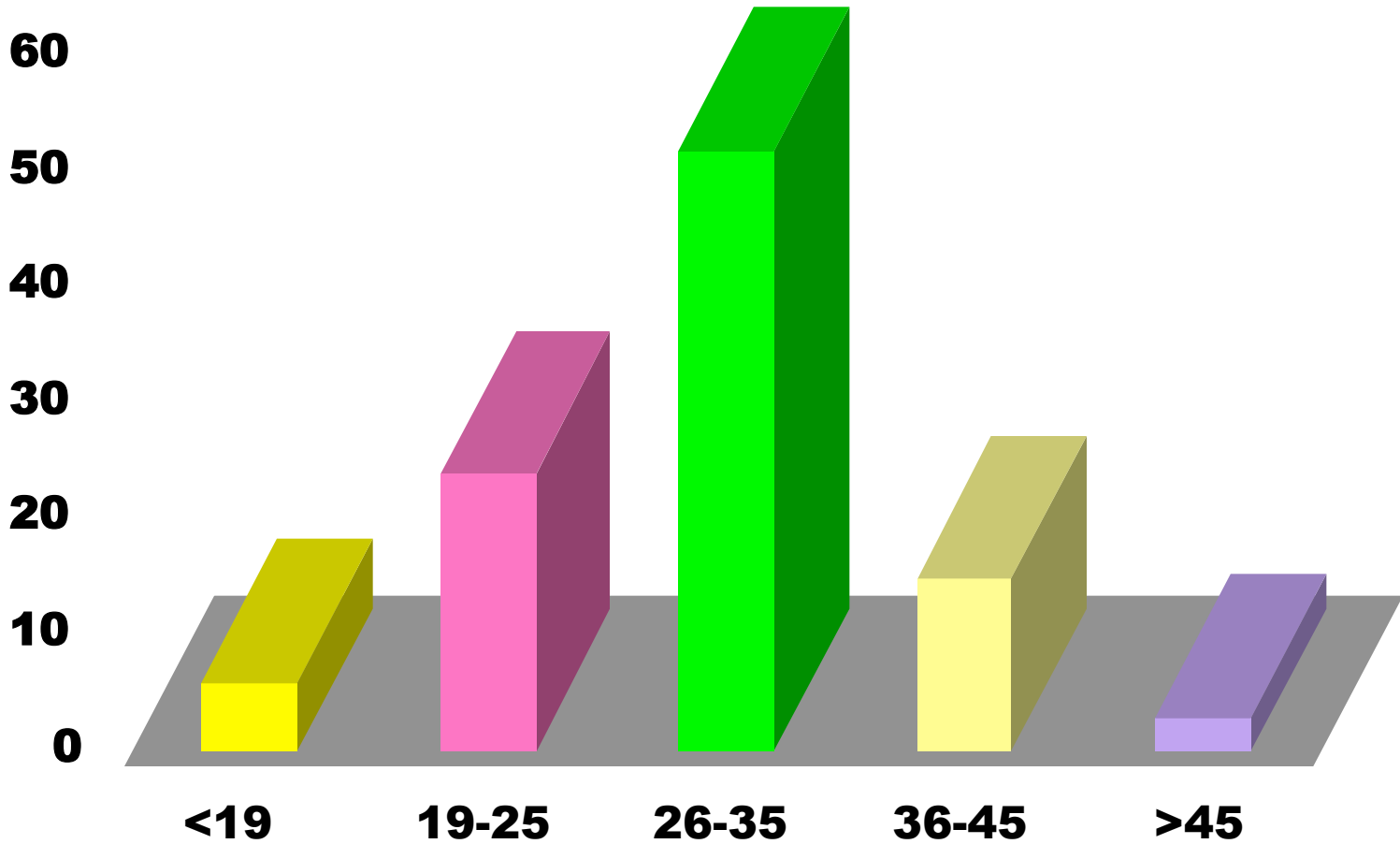




# Age at Presentation of Symptoms



# Age at Diagnosis



Adapted from Physicians Drug and Diagnosis Audit, 1993

# Proposed mechanisms for endometriosis related Pain

Adhesion formation that limits the motility of the viscera.

Secretion of inflammatory agents that stimulate nerve endings in the peritoneum

Nerve entrapment due to development of fibrosis

# Pain Treatment Choices

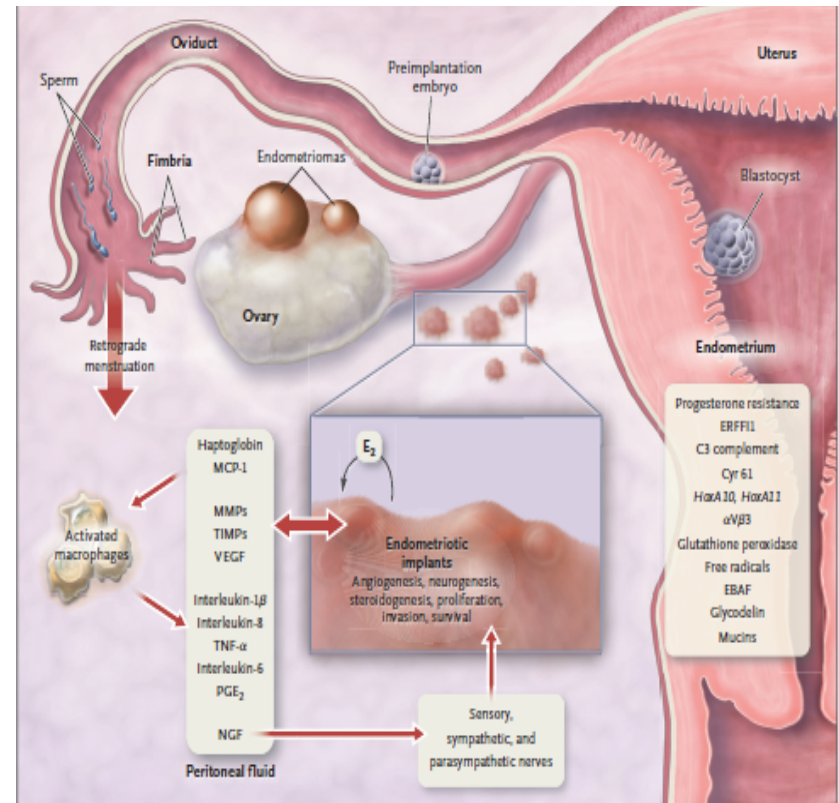
- Medical management
  - NSAIDs
  - OCPs
  - Progestins
  - GnRH-agonists/ antagonists
  - Aromatase inhibitors
  - Danazol
- Surgery
  - Conservative
  - Definitive
  - Radical

# Surgical treatment

- **Conservative Surgery:**
  - Tries to preserve ability to conceive
  - Excises endometriotic tissue
  - Aims to restore normal anatomy
  - Efficacy not clear in treating pain
- **Definite surgery:**
  - BSO with or without Hysterectomy remains the definitive treatment for endometriosis
- **Radical surgery:**
  - Debulking
  - Radical procedures consist of BSO with hysterectomy and with excision of all implants and adhesions ( may involve bowel resection, peritoneal stripping, ureterolysis, rectovaginal septum reconstruction )
  - May eliminate pain in up to 90% of patients

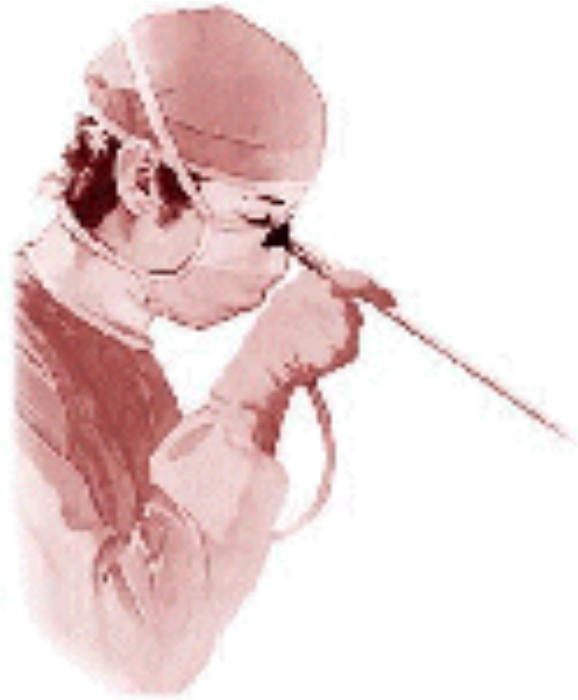
# Endometriosis and infertility (proposed mechanisms)

- ◆ Interference with ovum pick-up by the fimbriae,
- ◆ Defective tubal gamete-embryo transport
- ◆ Increased sperm destruction (phagocytosis)
- ◆ Ovulatory dysfunction
- ◆ Decreased fertilization
- ◆ Early implantation failure caused by hormonal or autoimmune phenomena

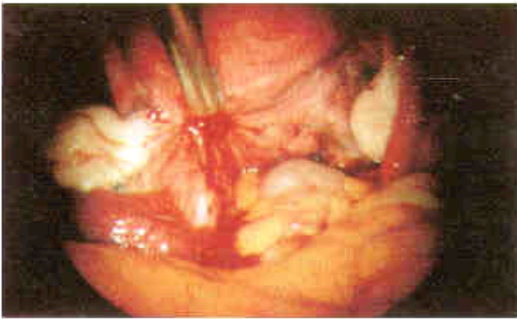


n engl j med 362;25 nejm.org june 24, 2010

# Diagnostic Tools



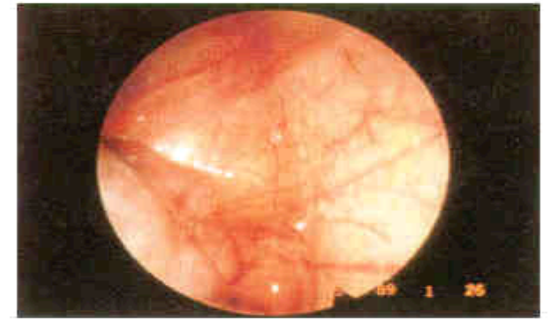
- History and Physical examination
- Imaging (Ultrasound , MRI)
- Serum markers are under investigation
  - CA-125
  - Anti-endometrial Abs
- Laparoscopy



**Red**



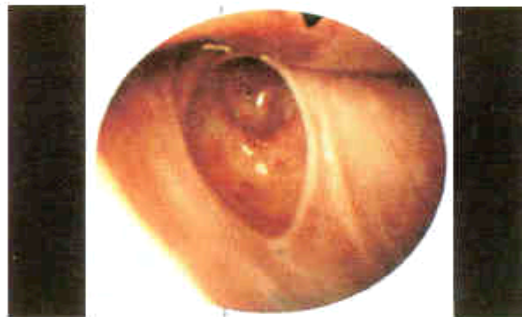
**Red-pink**



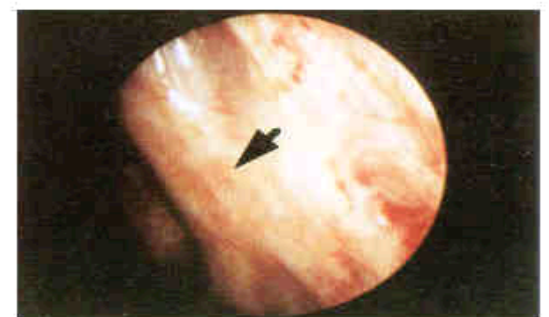
**Clear**



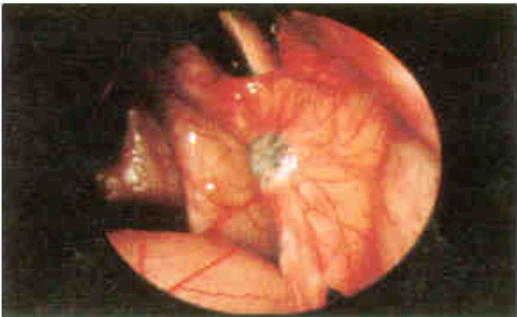
**White**



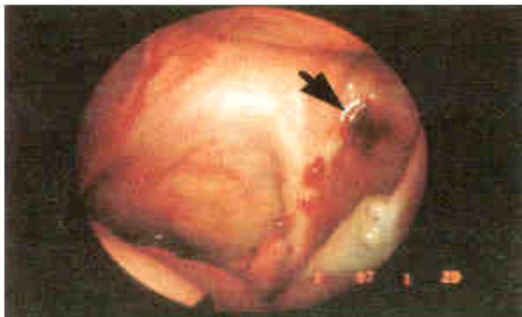
**Peritoneal defect**



**Yellow-Brown**



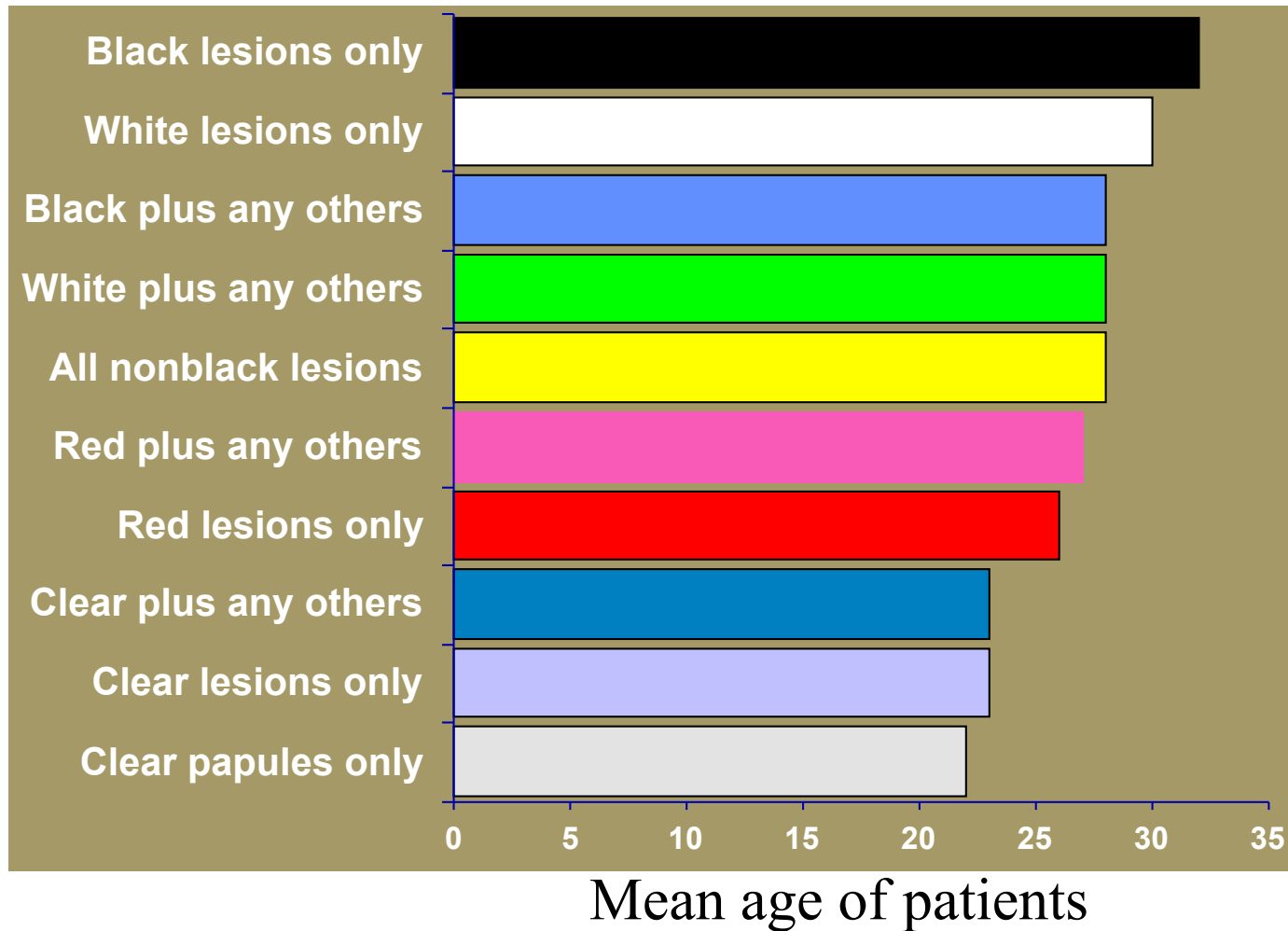
**Black**



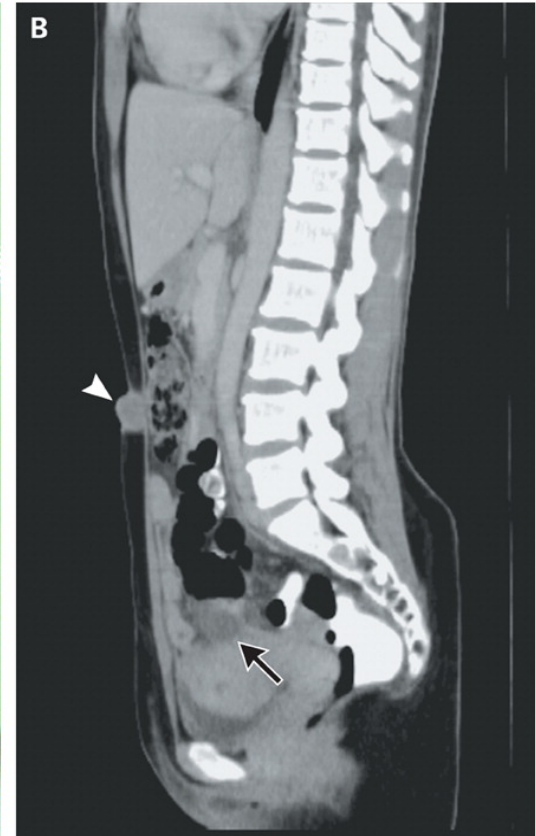
**Blue**



# Evolution of color appearance of endometriosis with age and mean age of patients with respective lesions



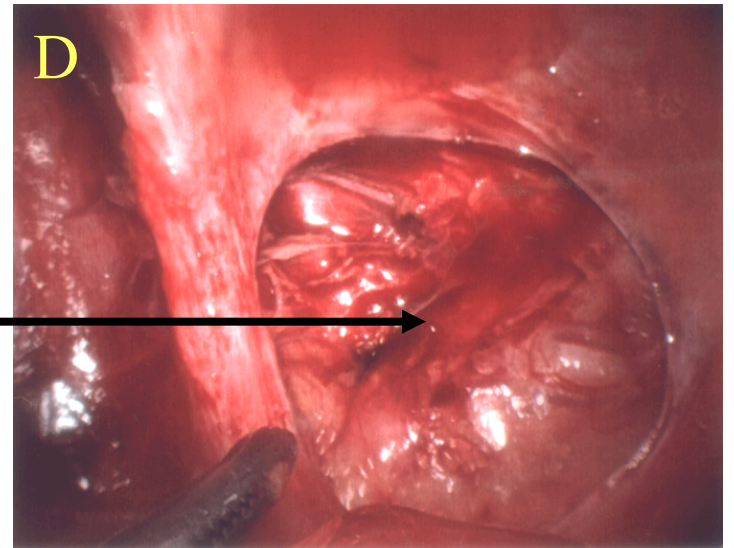
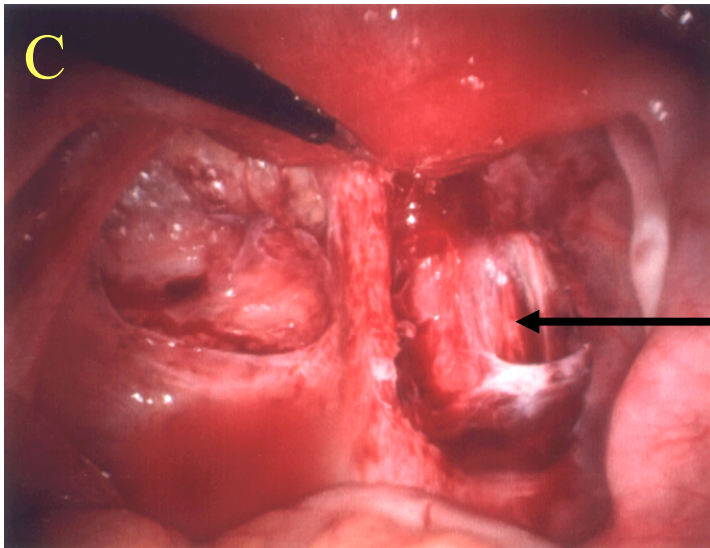
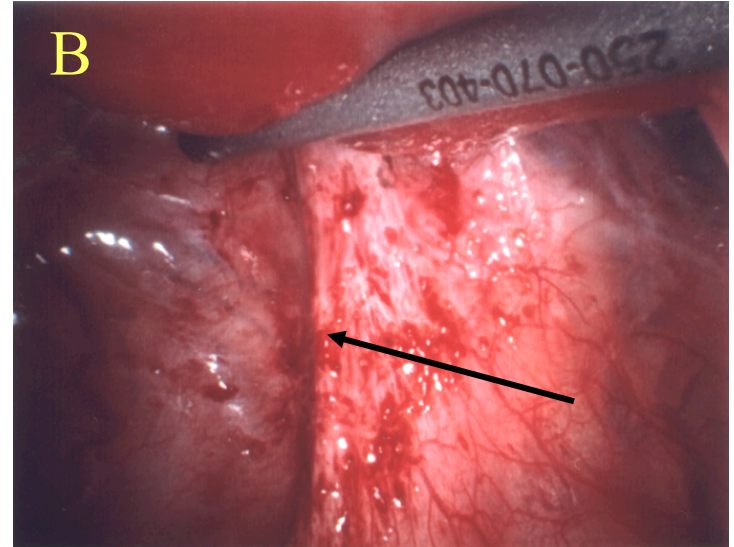
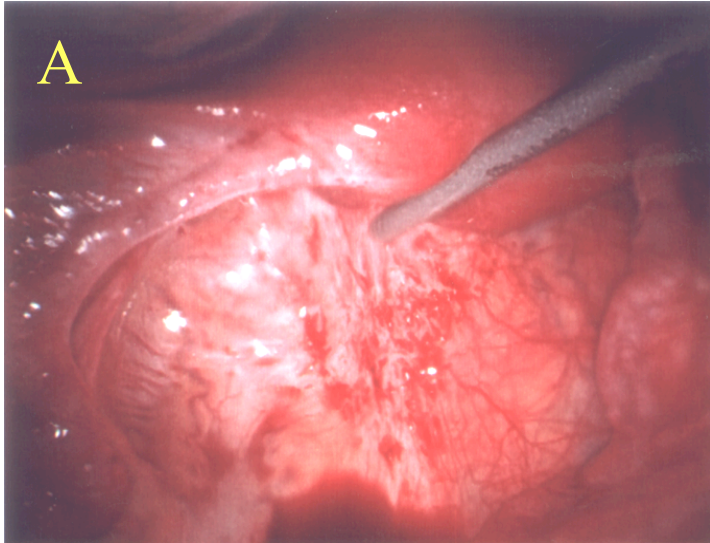
## Villar's Nodule — Umbilical Endometriosis

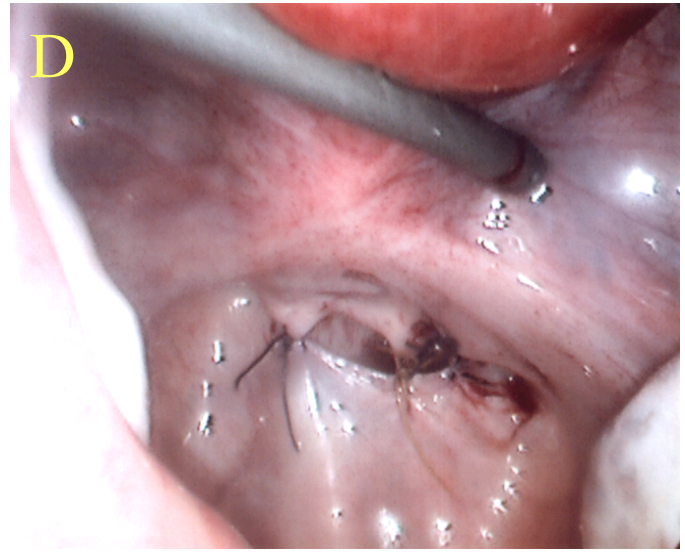
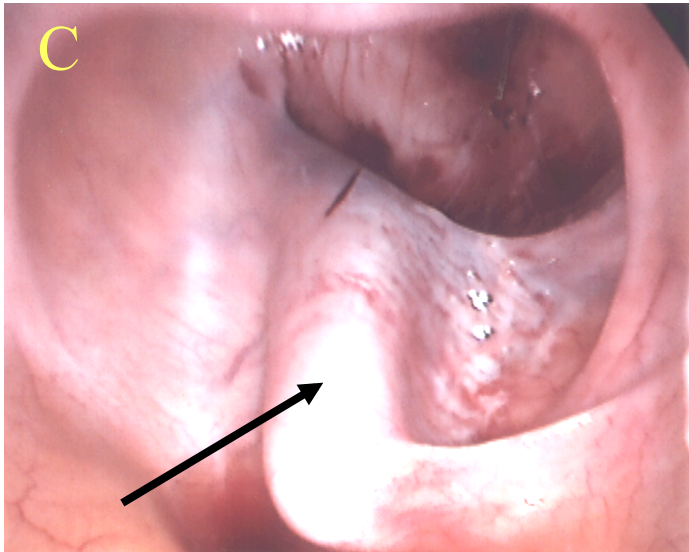
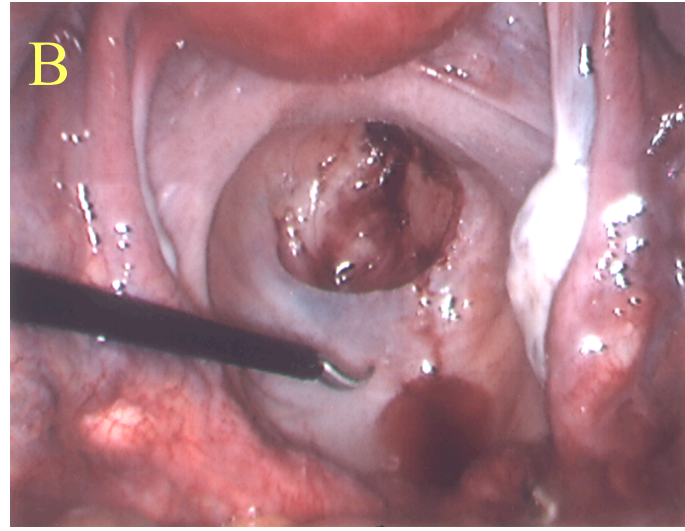
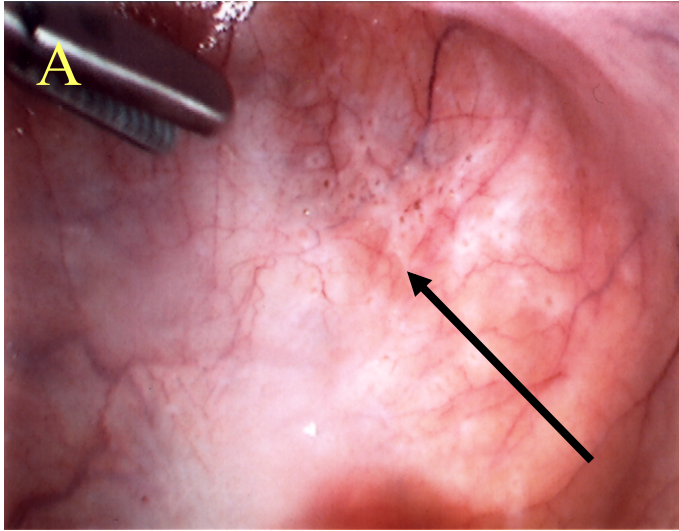


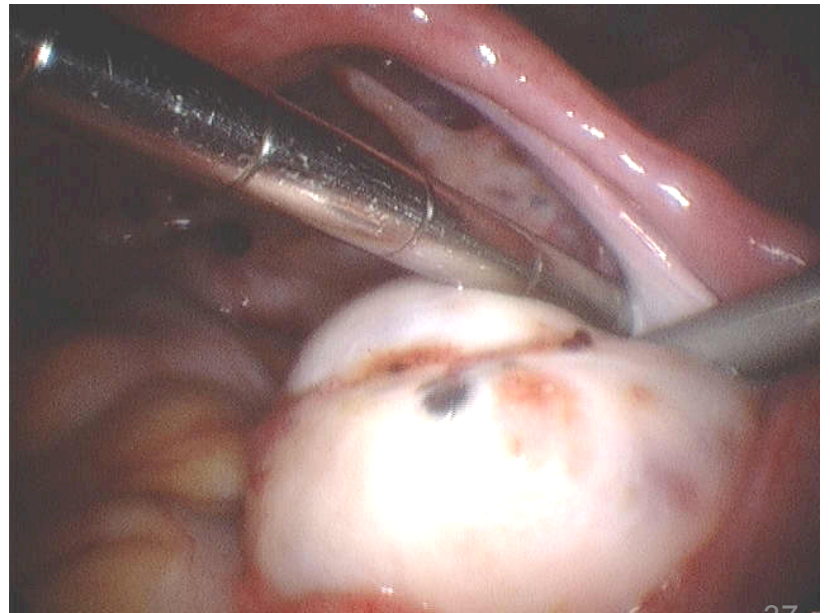
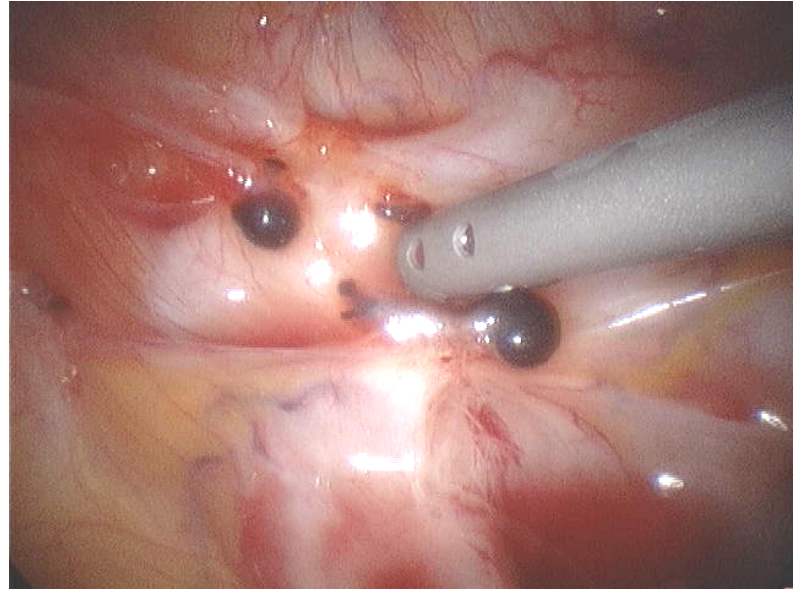
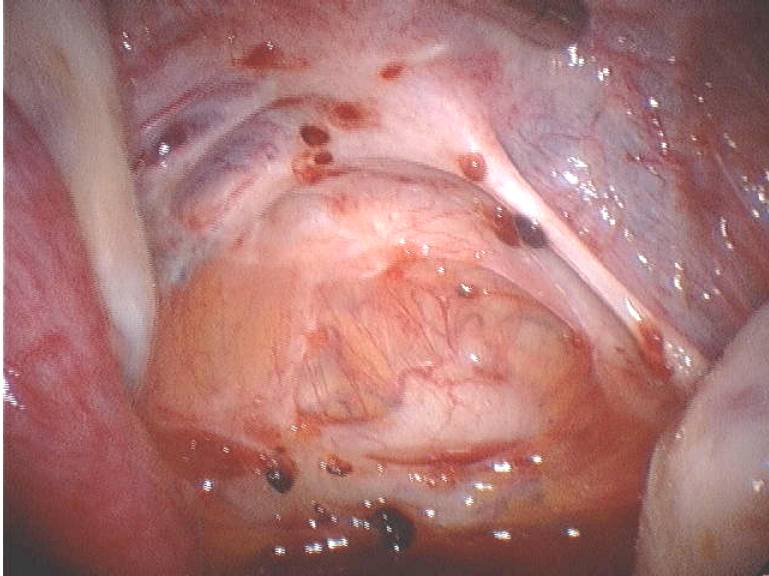
Weng C, Yang Y. N Engl J Med 2011;364:e45.

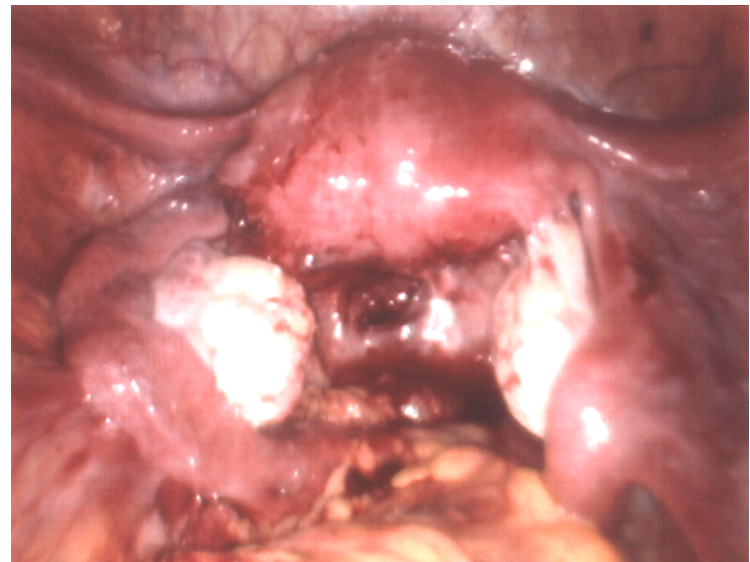
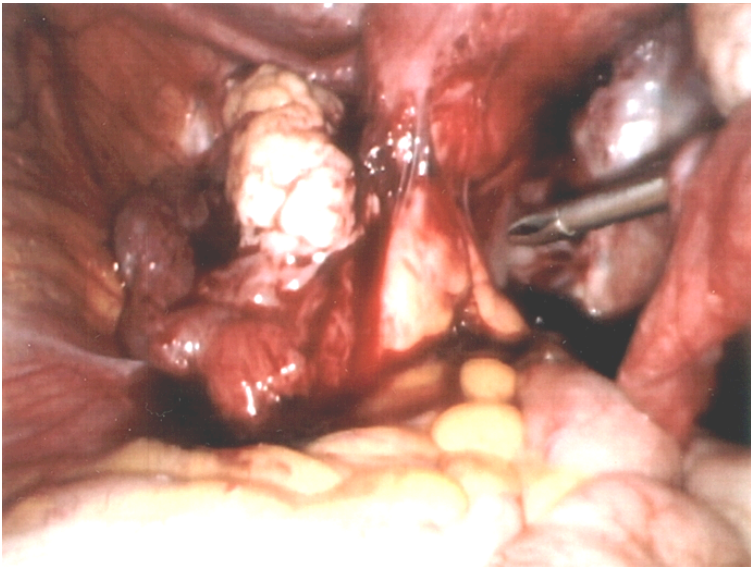
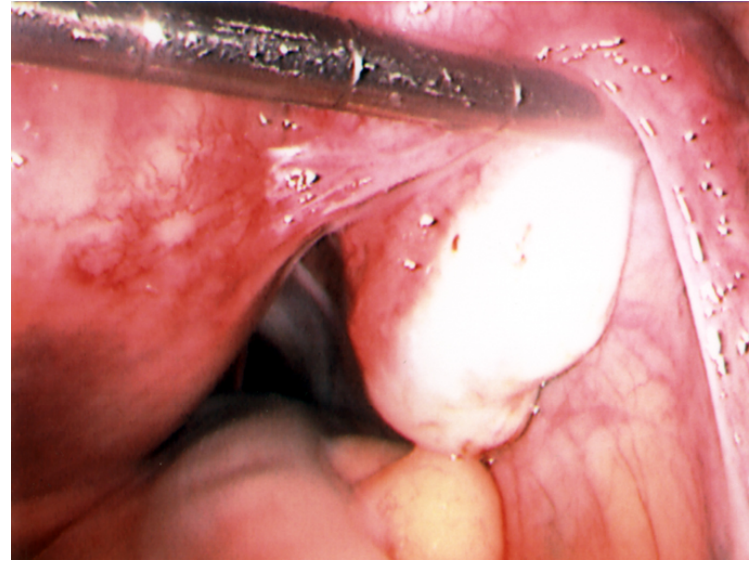
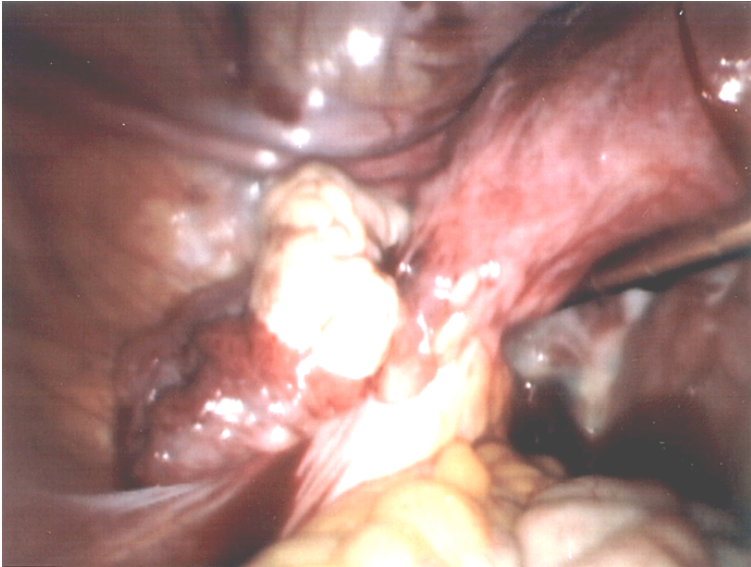


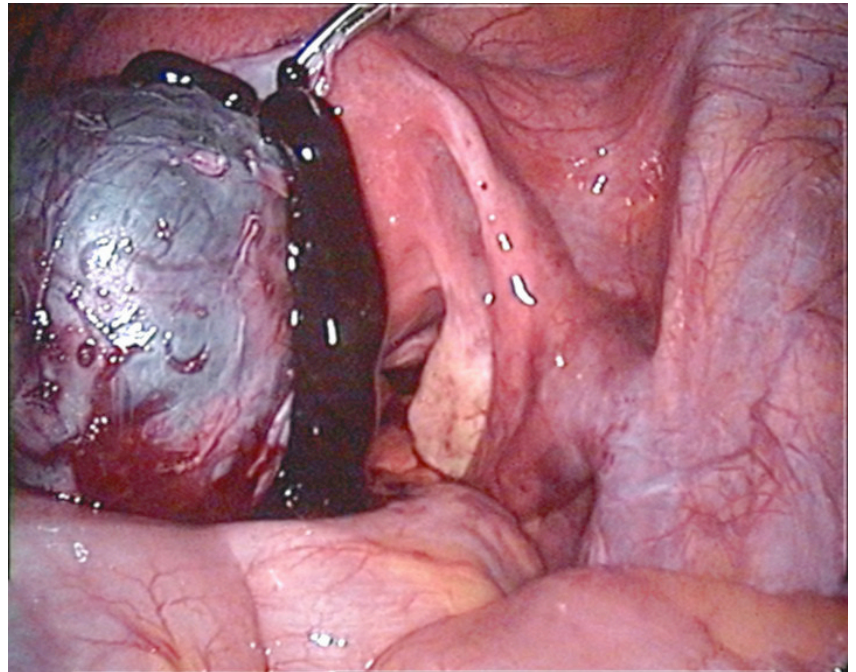
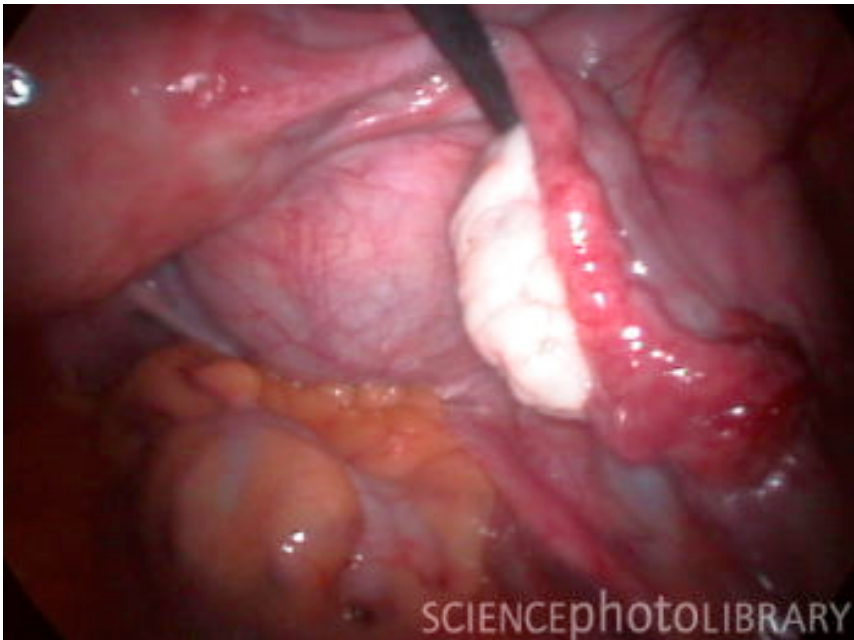
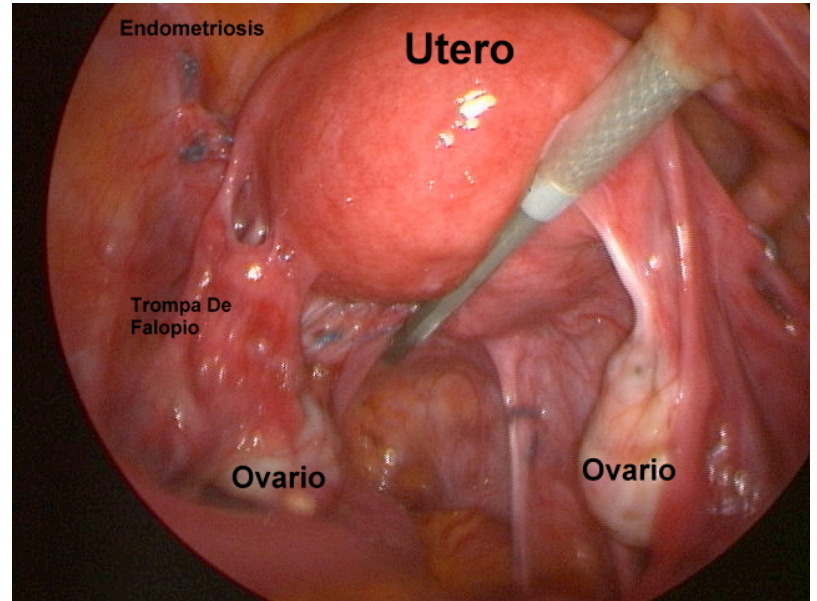
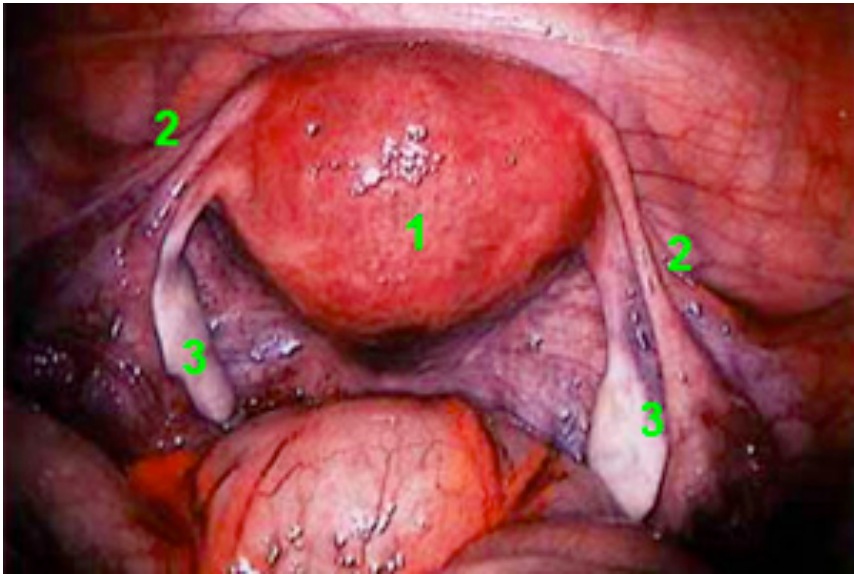
The NEW ENGLAND  
JOURNAL of MEDICINE

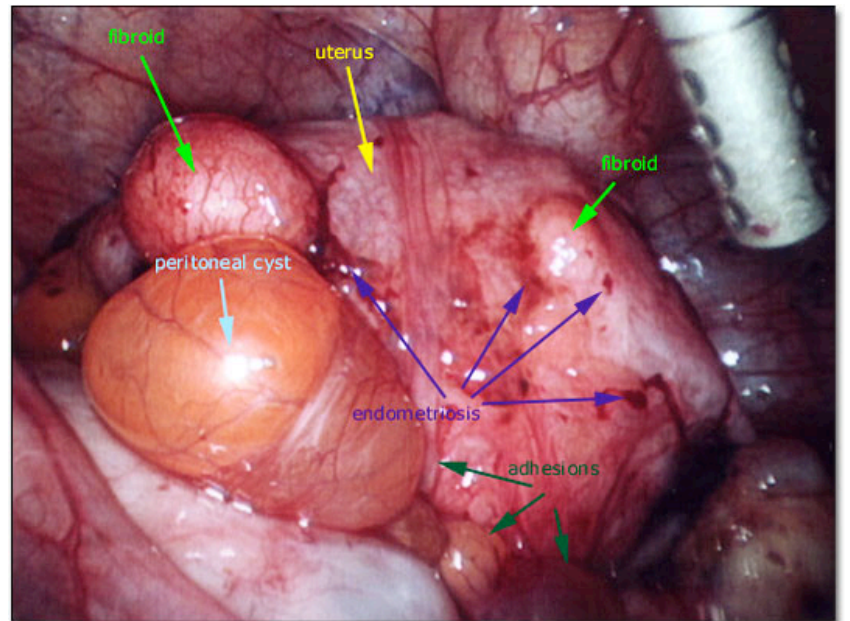
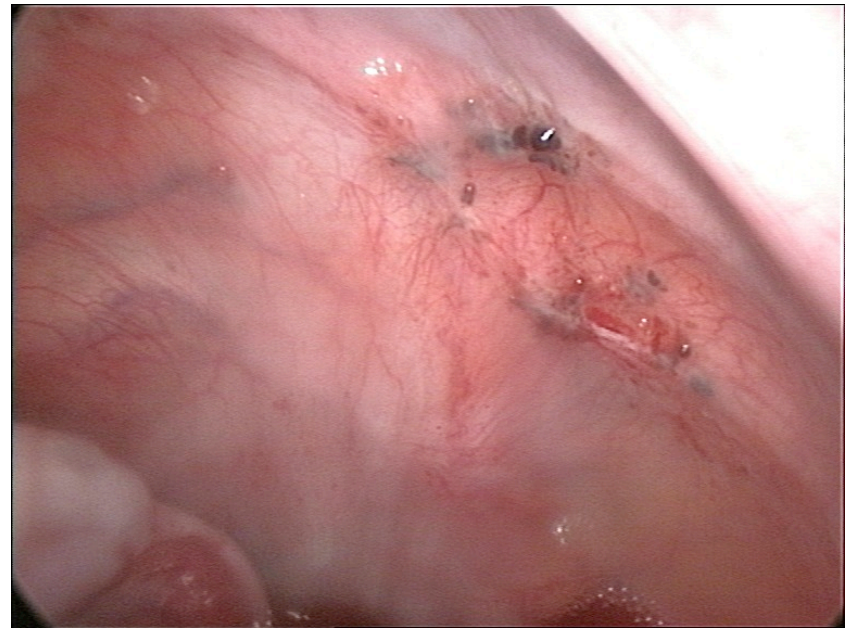
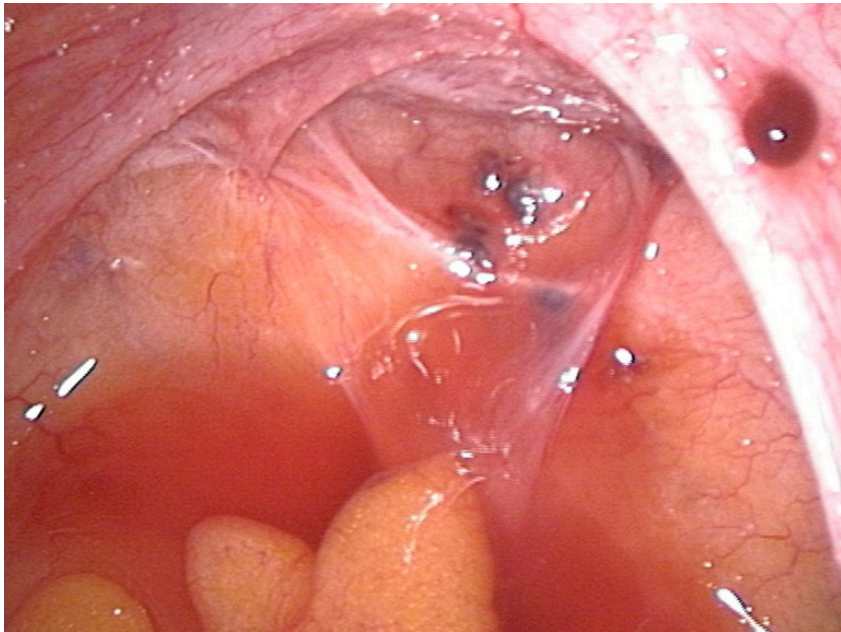






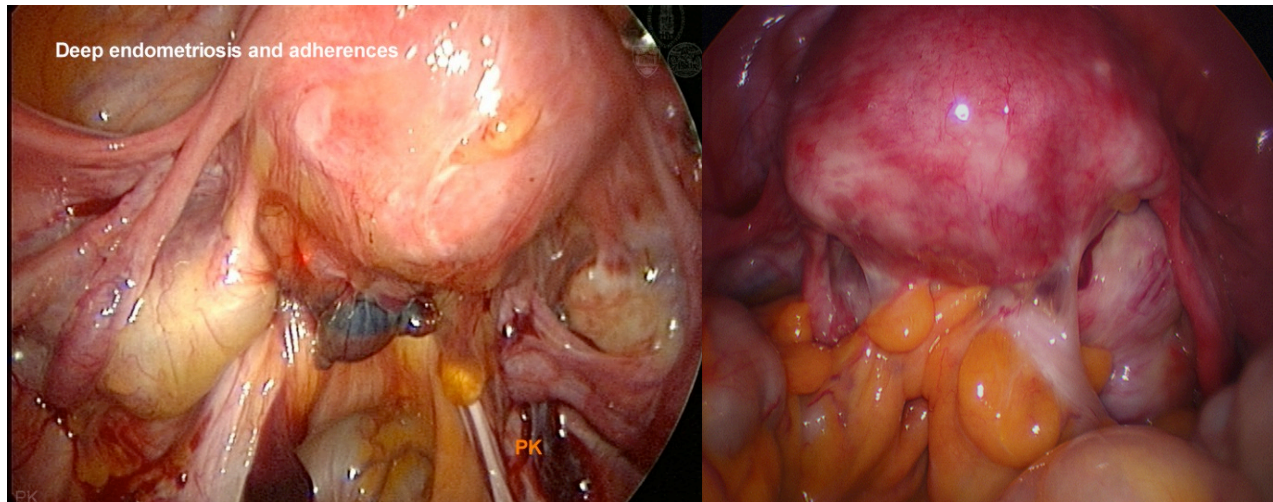
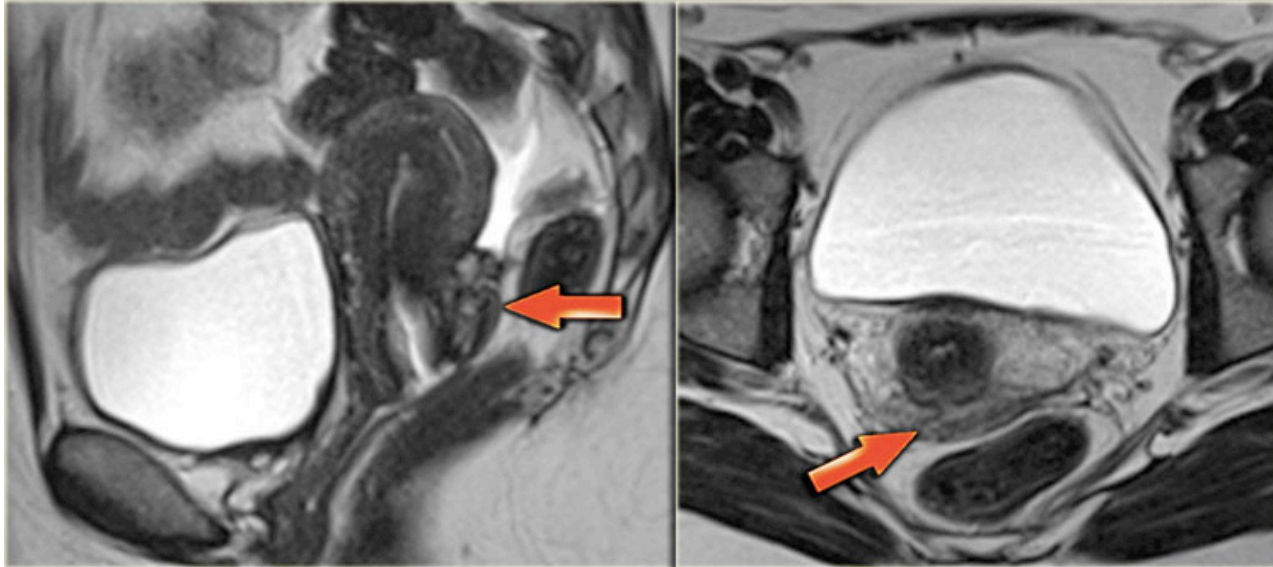


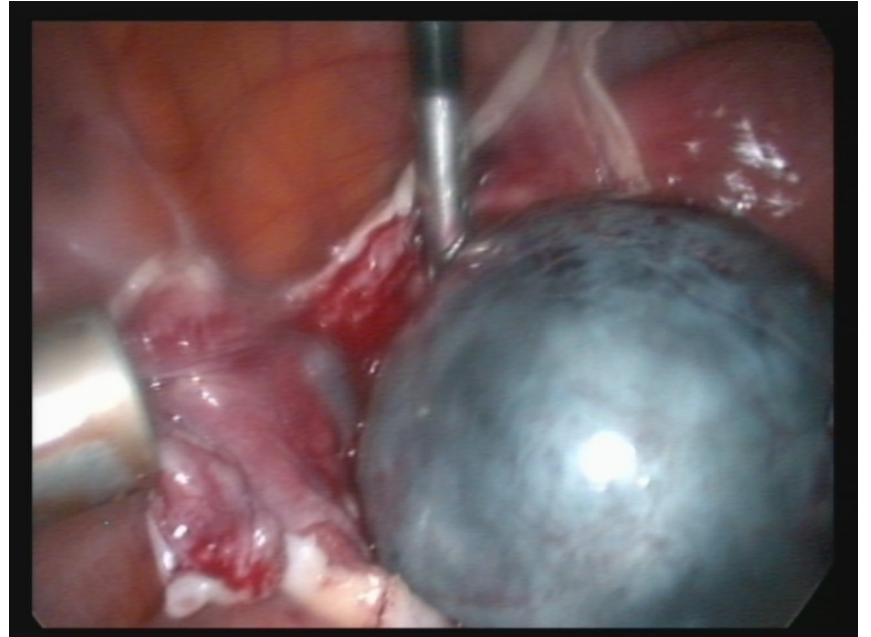






# Deep infiltrative endometriosis ( DIS)



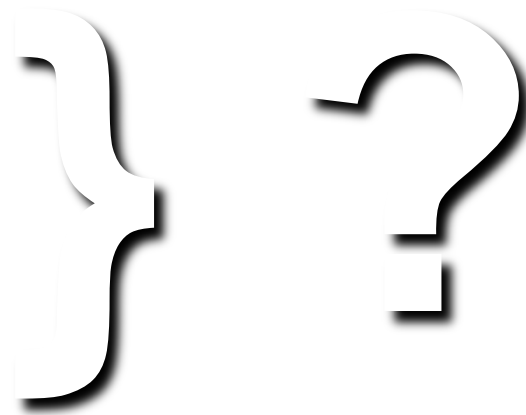


# When do we operate on endometriosis

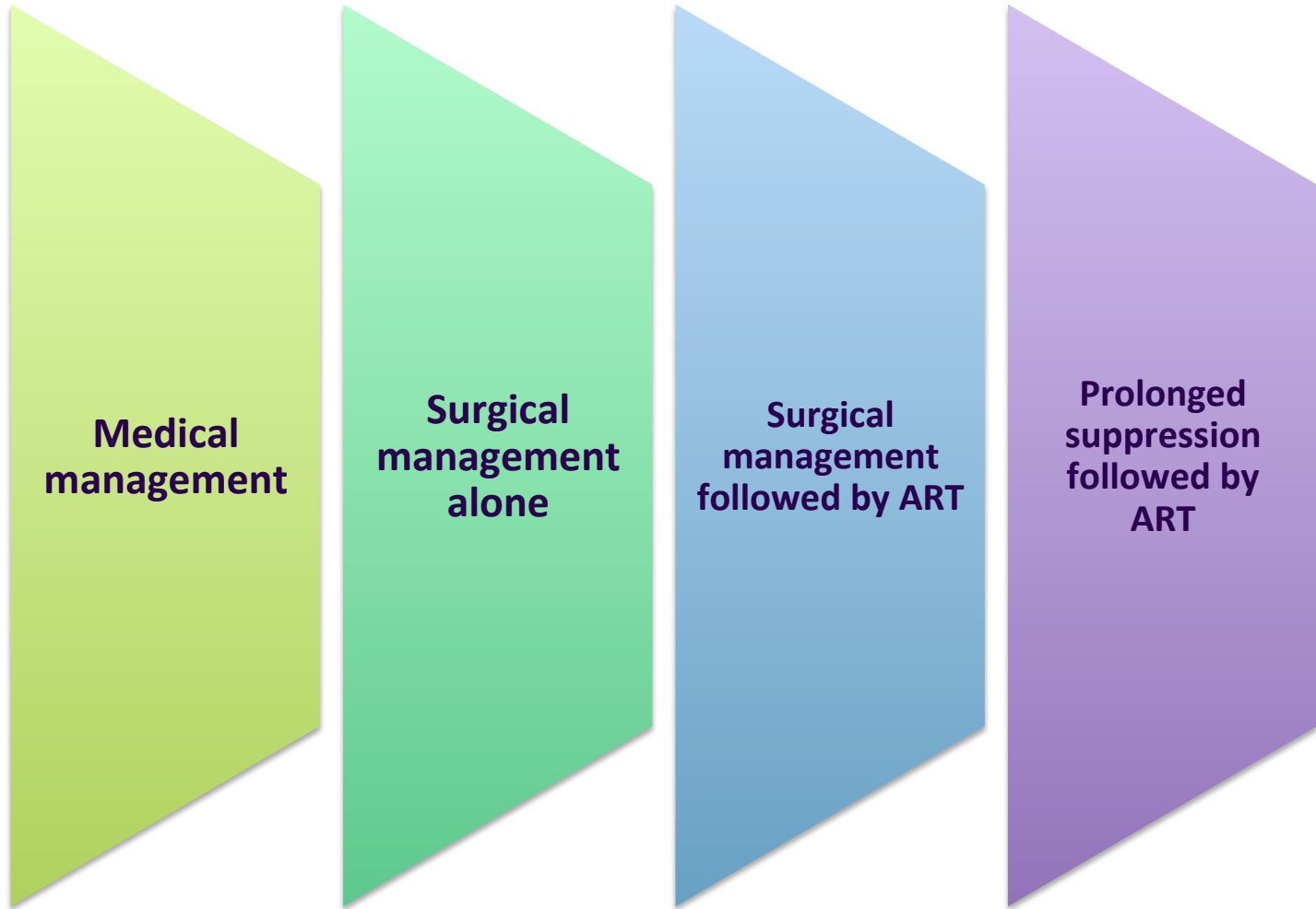
- To make the diagnosis?
- To restore fertility
- To treat pain?
- To exclude malignancy?

# Treatment Options for Infertility

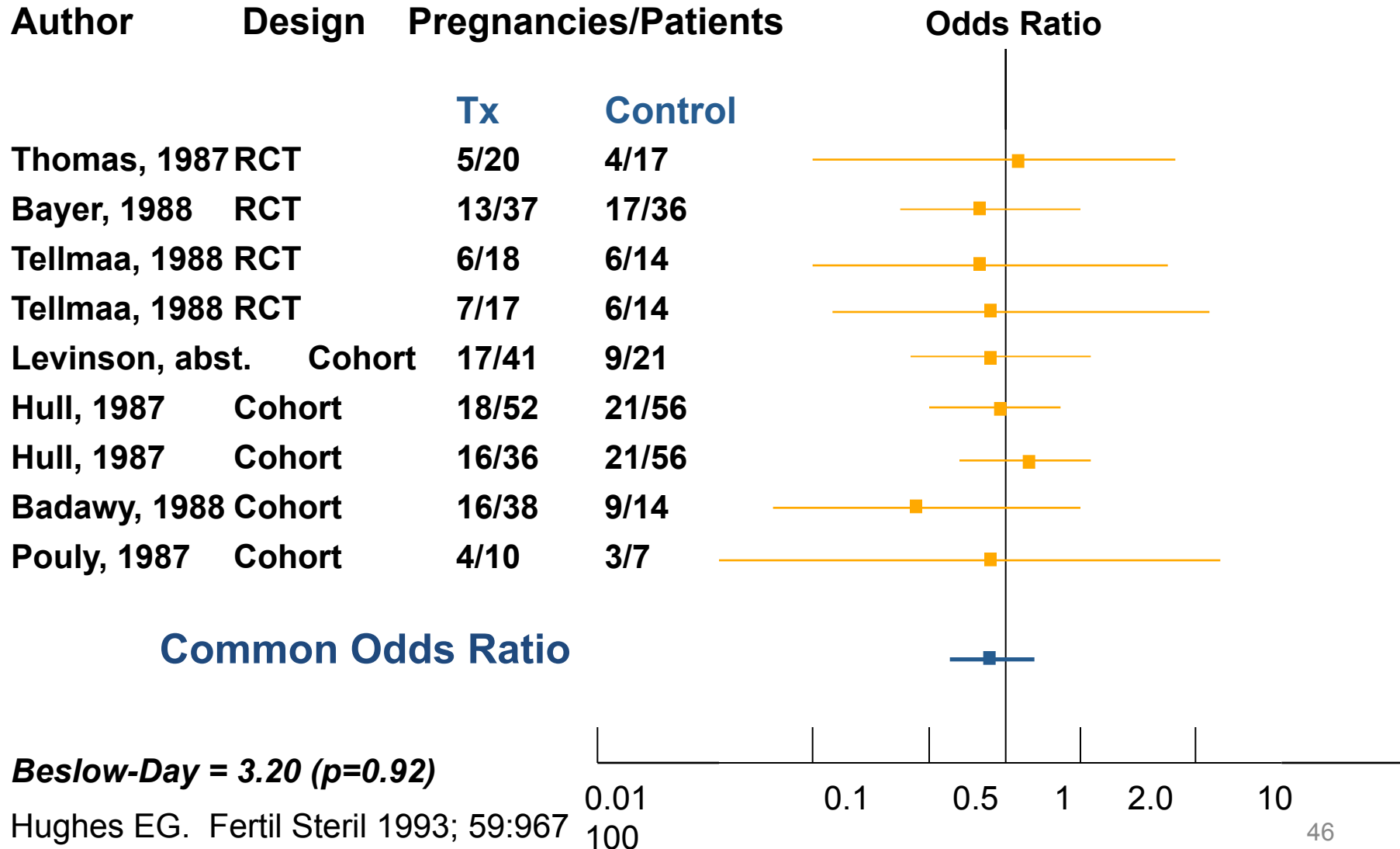
- Observation
- Medical management
  - OCPs
  - Progestins
  - GnRH-a
  - Danazol
- Surgery
  - Conservative
- *Assisted Reproduction*
- Aromatase inhibitors



# Endometriosis and Infertility



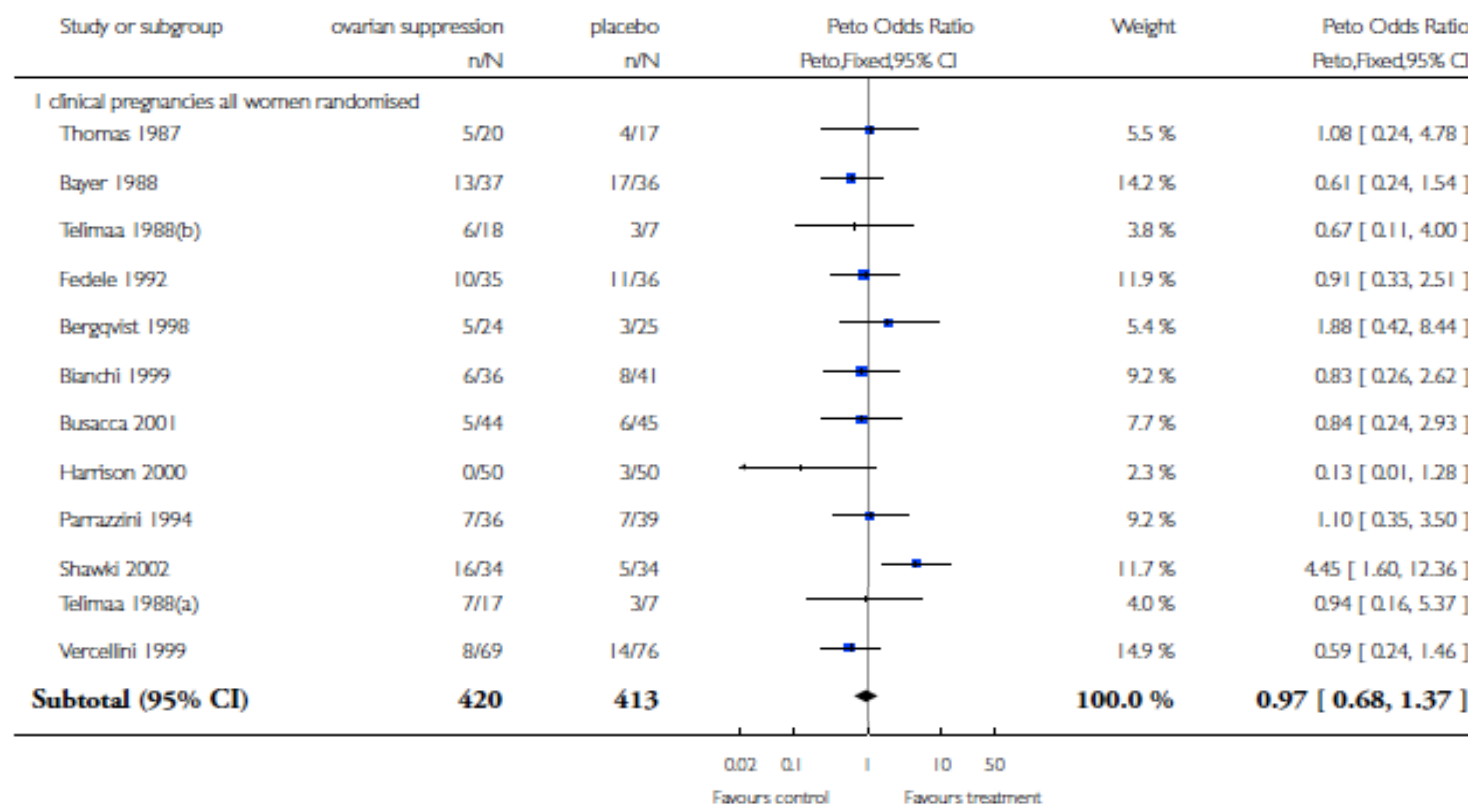
# Ovulation suppression vs. no treatment in the treatment of endometriosis-associated infertility



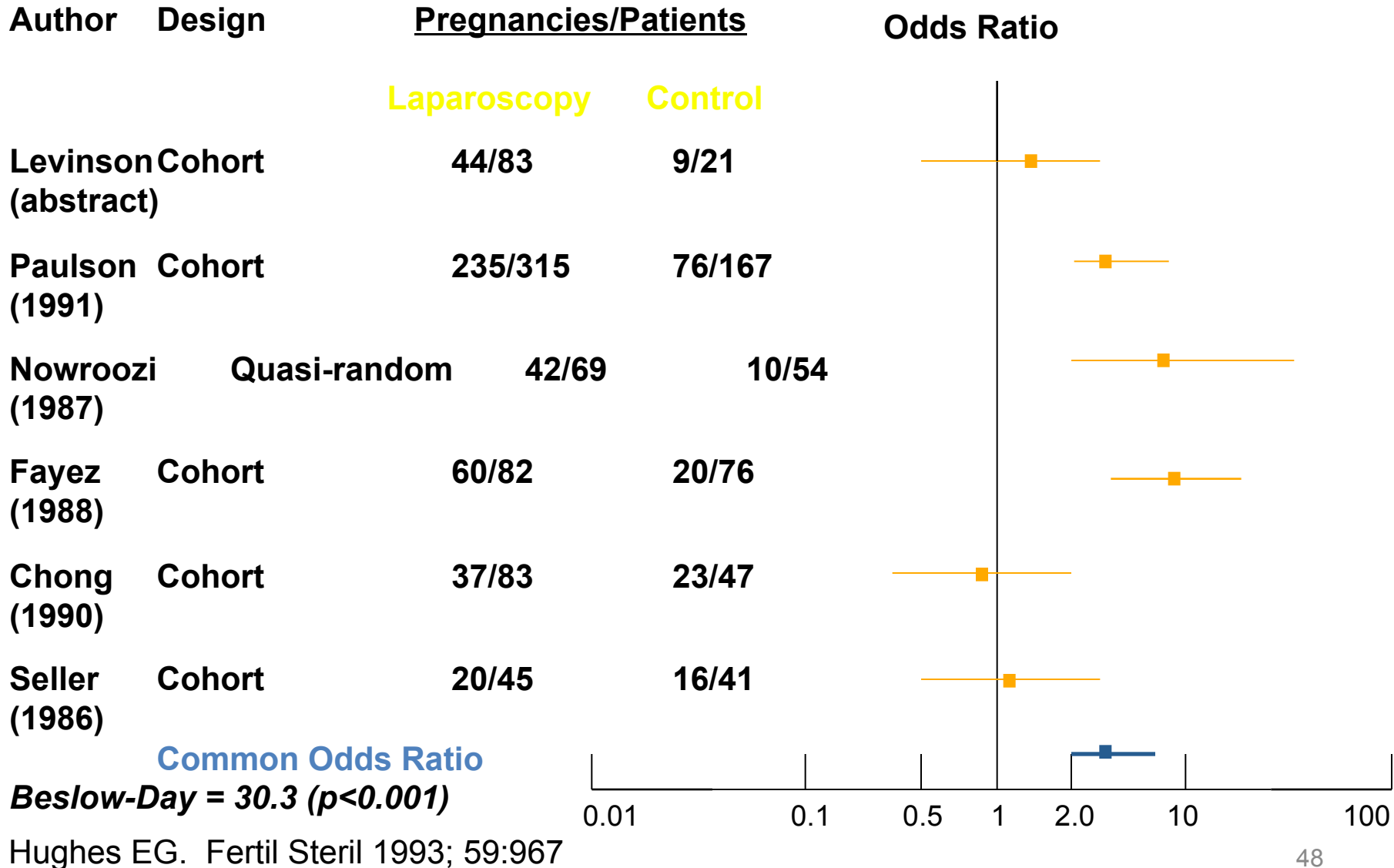
# Ovulation suppression for endometriosis for women with subfertility (Review)



Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P



# Laparoscopic surgery vs. no treatment or suppression





# Endometriosis and Infertility

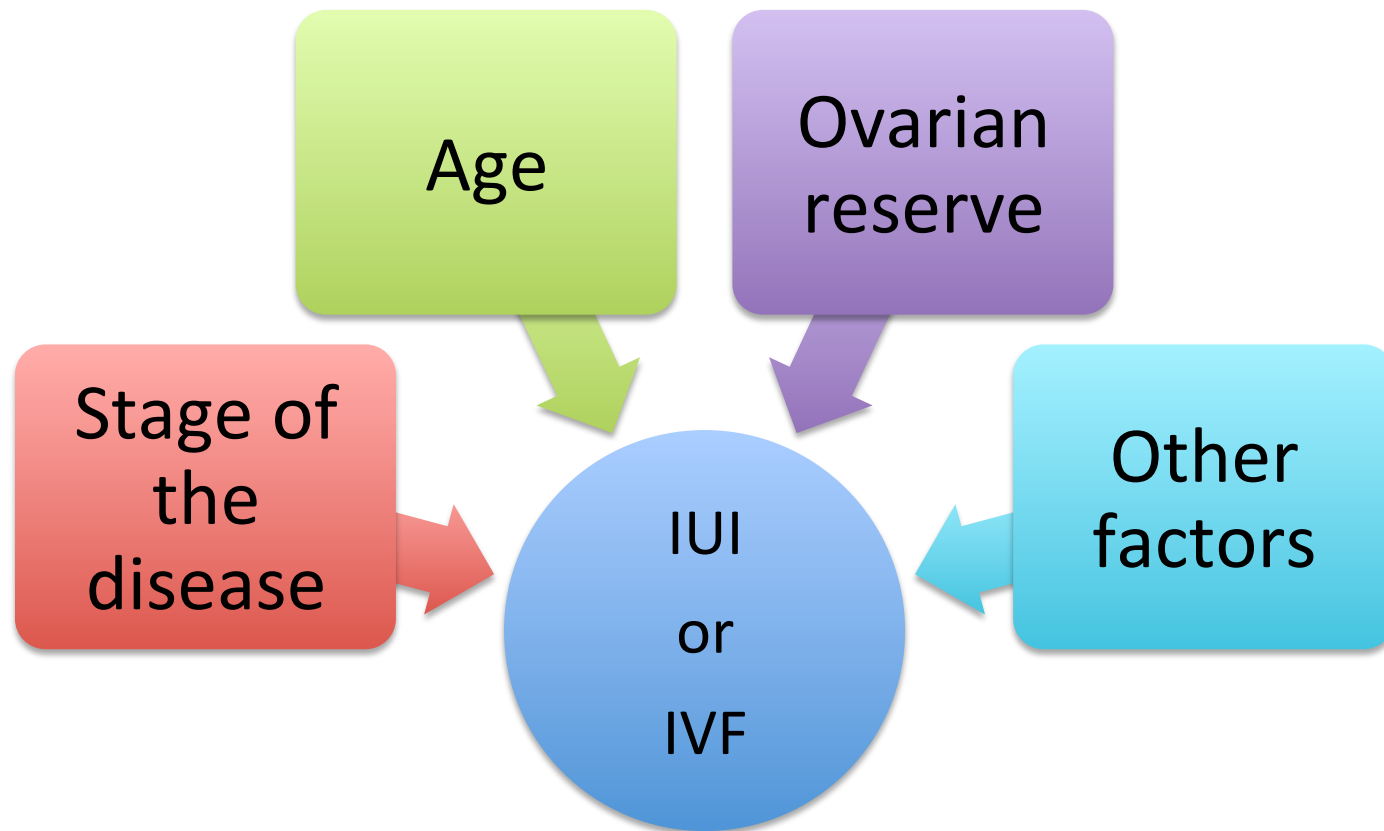
- Η χειρουργική έχει διαγνωστικό όπως επίσης και θεραπευτικό ρολό τόσο στην αντιμετώπιση του πόνου όσο και στην θεραπεία της υπογονιμότητας
- Η φαρμακευτική καταστολή της ωθητικής λειτουργίας δεν έχει κανένα ρόλο στην αντιμετώπιση της υπογονιμότητας.

The New England Journal of Medicine

the outcome measure.<sup>68-71</sup> In another eight trials danazol was compared with a second drug.<sup>19,38-40,44,48,72,73</sup> All were summarized recently in a meta-analysis (Fig. 2).<sup>74</sup> The results clearly indicate that none of these drugs are any better than any of the others and, more important, that none of them result in greater ferti-

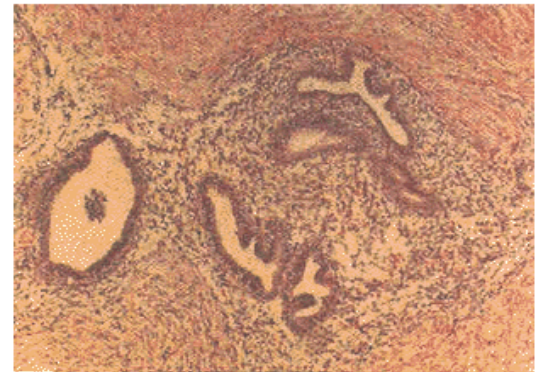
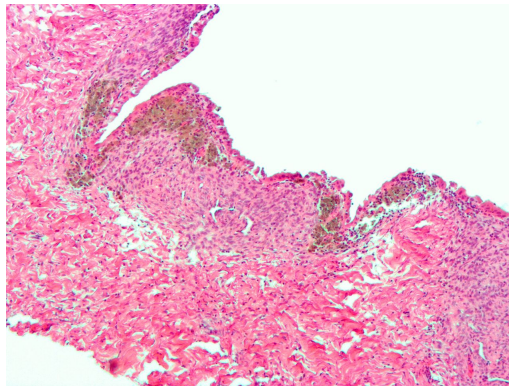
ity than placebo. Not only do these drugs not increase fertility, but they may also delay fertility, since women are unable to conceive while receiving treatment. Thus, there appears to be no role for drug therapy in the treatment of the infertility associated with endometriosis.

# Endometriosis infertility and Assisted reproduction

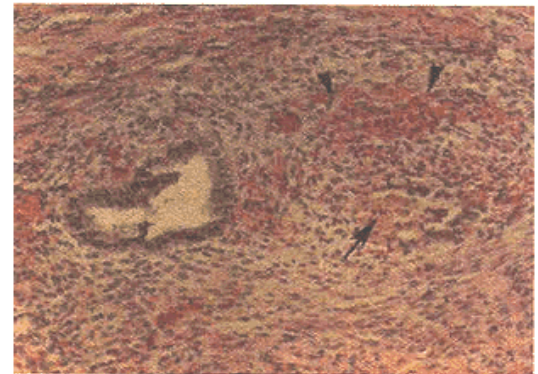


# Histology

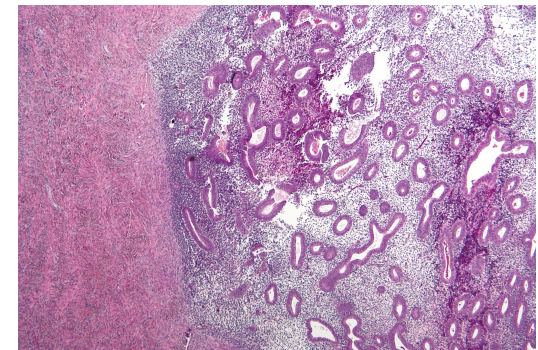
Endometrial glands and stroma, with or without associated inflammatory cells or hemosiderin-laden macrophages, is diagnostic of endometriosis.



A



B





## THE AMERICAN FERTILITY SOCIETY REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name \_\_\_\_\_ Date \_\_\_\_\_

Stage I (Minimal) - 1-5      Laparoscopy \_\_\_\_\_ Laparotomy \_\_\_\_\_ Photography \_\_\_\_\_

Stage II (Mild) - 6-15      Recommended Treatment \_\_\_\_\_

Stage III (Moderate) - 16-40

Stage IV (Severe) - >40

Total \_\_\_\_\_ Prognosis \_\_\_\_\_

PERTONEUM	ENDOMETRIOSIS	< 1cm	1-3cm	> 3cm
		Superficial	1	2
	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
Dense		4*	8*	16
L Filmy		1	2	4
Dense		4*	8*	16

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

Additional Endometriosis: \_\_\_\_\_

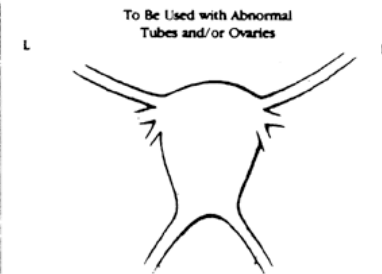
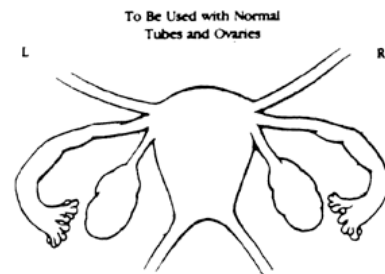
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Associated Pathology: \_\_\_\_\_

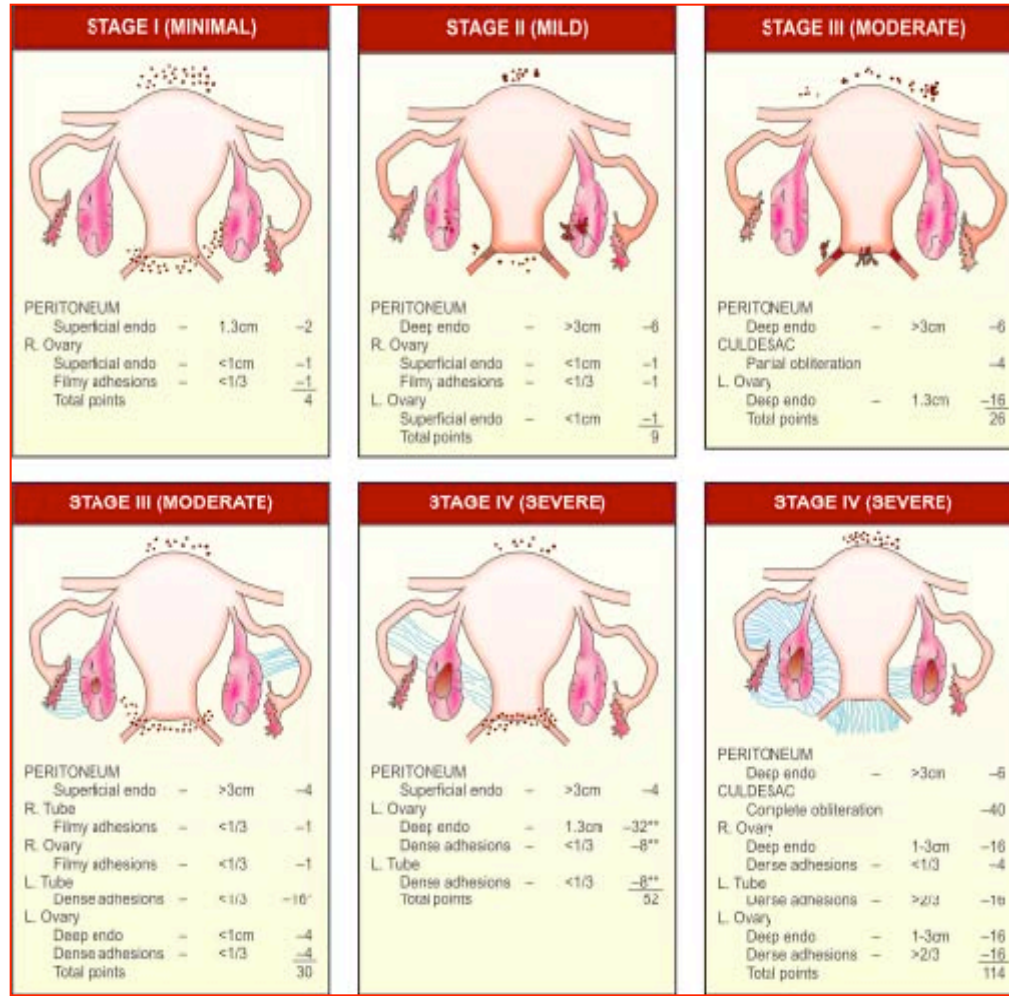
\_\_\_\_\_

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**A**

# Classification of Endometriosis



Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817-821.

# Classification of Endometriosis

- The rASRM score does not correlate well either with pain or with infertility
- Does not take into account deep infiltrative endometriosis (DIS).

# ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

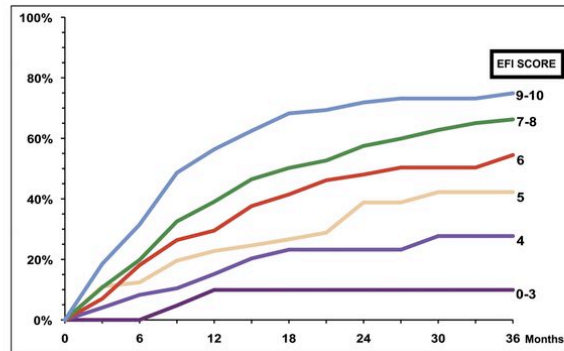
## LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right			
4	= Normal	Fallopian Tube	<input style="width: 30px; height: 20px;" type="text"/>	<input style="width: 30px; height: 20px;" type="text"/>			
3	= Mild Dysfunction	Fimbria	<input style="width: 30px; height: 20px;" type="text"/>	<input style="width: 30px; height: 20px;" type="text"/>			
2	= Moderate Dysfunction	Ovary	<input style="width: 30px; height: 20px;" type="text"/>	<input style="width: 30px; height: 20px;" type="text"/>			
1	= Severe Dysfunction						
0	= Absent or Nonfunctional						
To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.			Lowest Score	+	Lowest Score	=	<input style="width: 40px; height: 20px; border: 1px dashed black;" type="text"/>
			Left		Right		LF Score

## ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors				
Factor	Description	Points	Factor	Description	Points		
<u>Age</u>	If age is ≤ 35 years	2	<u>LF Score</u>	If LF Score = 7 to 8 (high score)	3		
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2		
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0		
<u>Years Infertile</u>	If years infertile is ≤ 3	2	<u>AFS Endometriosis Score</u>				
	If years infertile is > 3	0	If AFS Endometriosis Lesion Score is < 16	1			
<u>Prior Pregnancy</u>	If there is a history of a prior pregnancy	1	<u>AFS Total Score</u>				
	If there is no history of prior pregnancy	0	If AFS total score is < 71	1			
			If AFS total score is ≥ 71	0			
<b>Total Historical Factors</b>			<b>Total Surgical Factors</b>				
EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:			<input style="width: 60px; height: 25px;" type="text"/>	+	<input style="width: 60px; height: 25px;" type="text"/>	=	<input style="width: 60px; height: 25px; border: 1px solid black;" type="text"/>
			Historical		Surgical		EFI Score

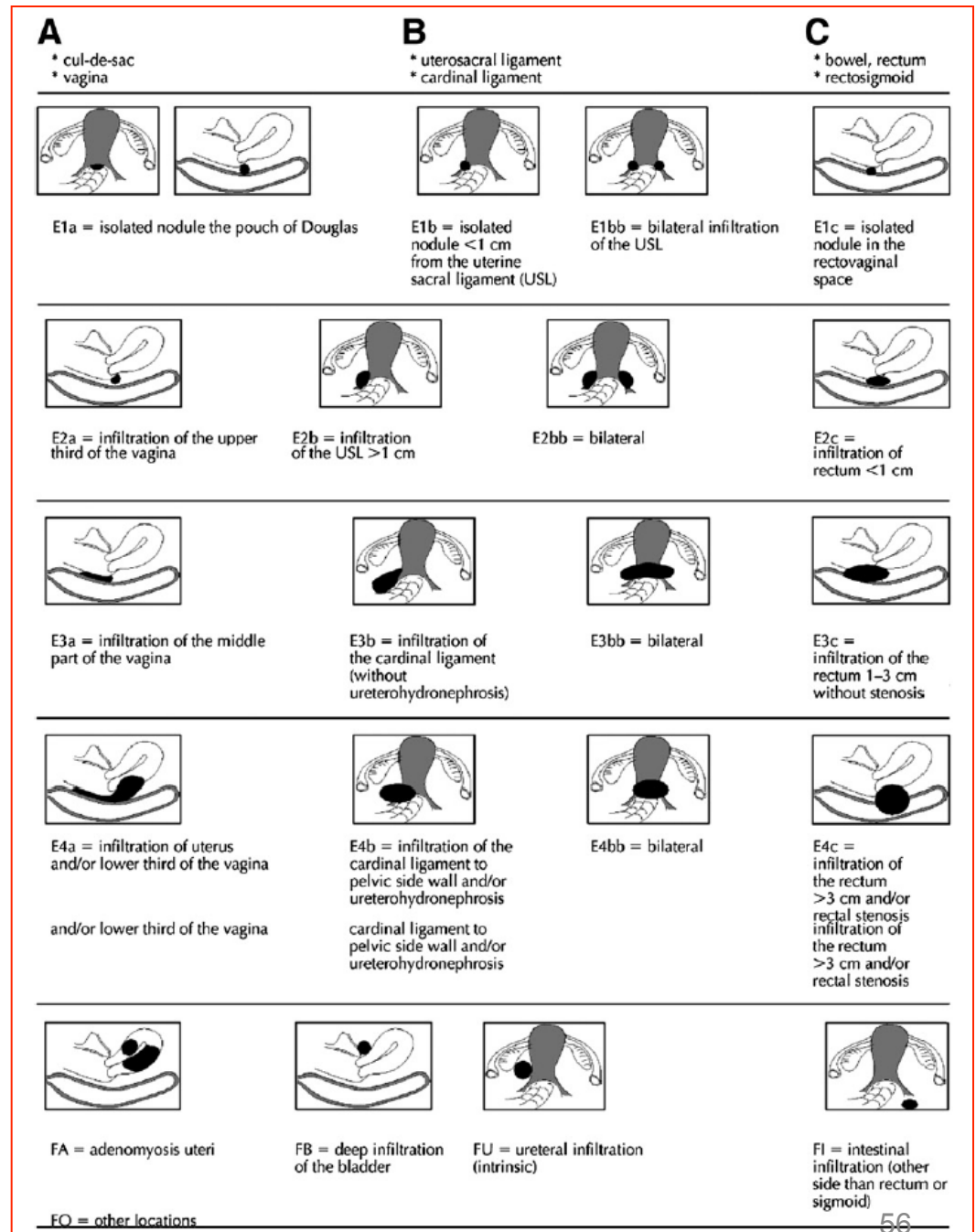
## ESTIMATED PERCENT PREGNANT BY EFI SCORE



# THE ENZIAN SCORE

The ENZIAN classification supplements the revised AFS score with regard to the description of deeply infiltrating endometriosis, retroperitoneal structures, and the involvement of other organs. The latter is easily classified by simple mention of the organs themselves, such as intestinal (FI), uterine (FA), intrinsic ureteral (FU), or bladder (FB) disease, or disease at other locations (FO). The prefix "F" stands for external disease.

Tuttles F, Keckstein J, Ulrich U, Possover M, Schewpe KW, Wustlich M, et al. ENZIAN Score. Eine Klassifikation der tiefen infiltrierenden Endometriose. Zentralbl Gynäkol 2005;127:275–81.





# Classification and scoring of endometriosis

The American Fertility Society and revised American Fertility Society endometriosis classification system has been helpful for documenting disease but is generally not clinically useful for predicting prognosis or management options for either pain or infertility.

The Endometriosis Fertility Index is a simple, robust, and validated clinical tool that predicts non-IVF pregnancy rates for patients following surgical staging of endometriosis.

The current ENZIAN staging system is not commonly used and the AAGL classification system is still being developed, but either or both may become clinically useful, especially for description, prognosis, and management of more severe endometriosis and pain.

# Endometriosis still an unresolved problem

Pathogenesis:  
unclear

Description of the  
extent of the  
disease: Poor

Medical  
management:  
Limited

Surgical  
management:  
Complex and risky

Risk of  
malignancy:  
Uncertain

# Endometriosis and Ovarian Cancer

- Endometriosis and ovarian cancer have common risk factors (infertility, early menarche, late menopause, short cycles)
- Tubal ligation is protective for endometrial and clear cell carcinoma but not for serous or mucinous.

# Endometriosis and Ovarian Cancer

## Patients with endometriosis

Histology	No.of patients	Total (%)	Atypical
Clear cell	43	30 (69.8)	25
Endometrioid	7	3 (42.9)	2
Serous	60	4 (8.0)	2
Mucinous	17	0 (0.0)	0
Total	127	37 (29.1)	29

Ogawa et.al. Gyn. Onc 77,298-304 (2000)

# Case #1

- 19 yo Poooo asymptomatic woman.
- On routine exam and sono she was found to have a 3.6 cm mass in the R . Ovary



# Case #2

- 39 yo Poooo with long hx of endometriosis and two prior laparoscopic surgeries is scheduled for IVF.
- Prior to stimulation she has a sono that shows a 3 cm endometrioma in the L. Ovary
- What would you do?

# Thank you



# Eye to the Future

- Non invasive methods to diagnose and quantify endometriosis.
- Identify genes and gene products (genomics/ proteomics) related to endometriosis.
- Design target-specific drugs.
- Develop treatment protocols.
- Identify patients at risk for cancer.



# Pain Treatment Choices

- Medical management
  - NSAIDs
  - OCPs
  - Progestins
  - GnRH-agonists/ antagonists
  - Danazol
- Surgery
  - Conservative
  - Definitive
  - Radical

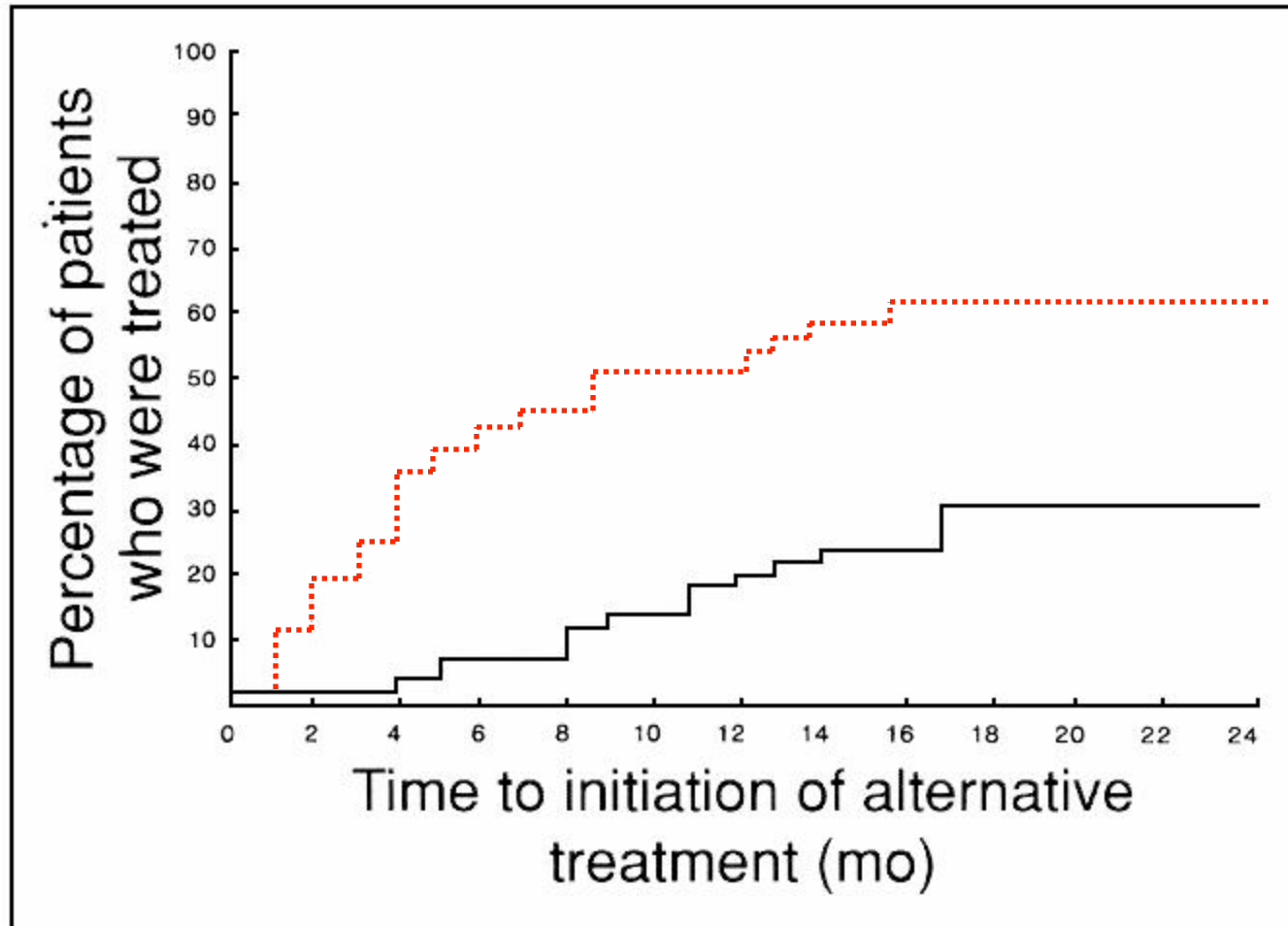
# Medical Therapy

- Progestins and oral contraceptives cause decidualization and shedding of endometrial tissue (Pseudopregnancy)
- GnRH analogs cause atrophy of the endometrial tissue by suppressing E2 production (Pseudomenopause)
- Aromatase inhibitors (Anastrozole, Letrozole)
- Rec. Human TNF Binding protein-1
- Immunomodulation (levamisole, loxoribine)

# Surgical treatment

- **Conservative Surgery:**
  - Tries to preserve ability to conceive
  - Excises endometriotic tissue
  - Aims to restore normal anatomy
  - Efficacy not clear in treating pain
- **Definite surgery:**
  - BSO with or without Hysterectomy remains the definitive treatment for endometriosis
- **Radical surgery:**
  - Debulking
  - Radical procedures consist of BSO with hysterectomy and with excision of all implants and adhesions ( **may involve bowel resection, peritoneal stripping, ureterolysis, rectovaginal septum reconstruction** )
  - May eliminate pain in up to 90% of patients

# GnRH-a treatment after reductive laparoscopic surgery for endometriosis





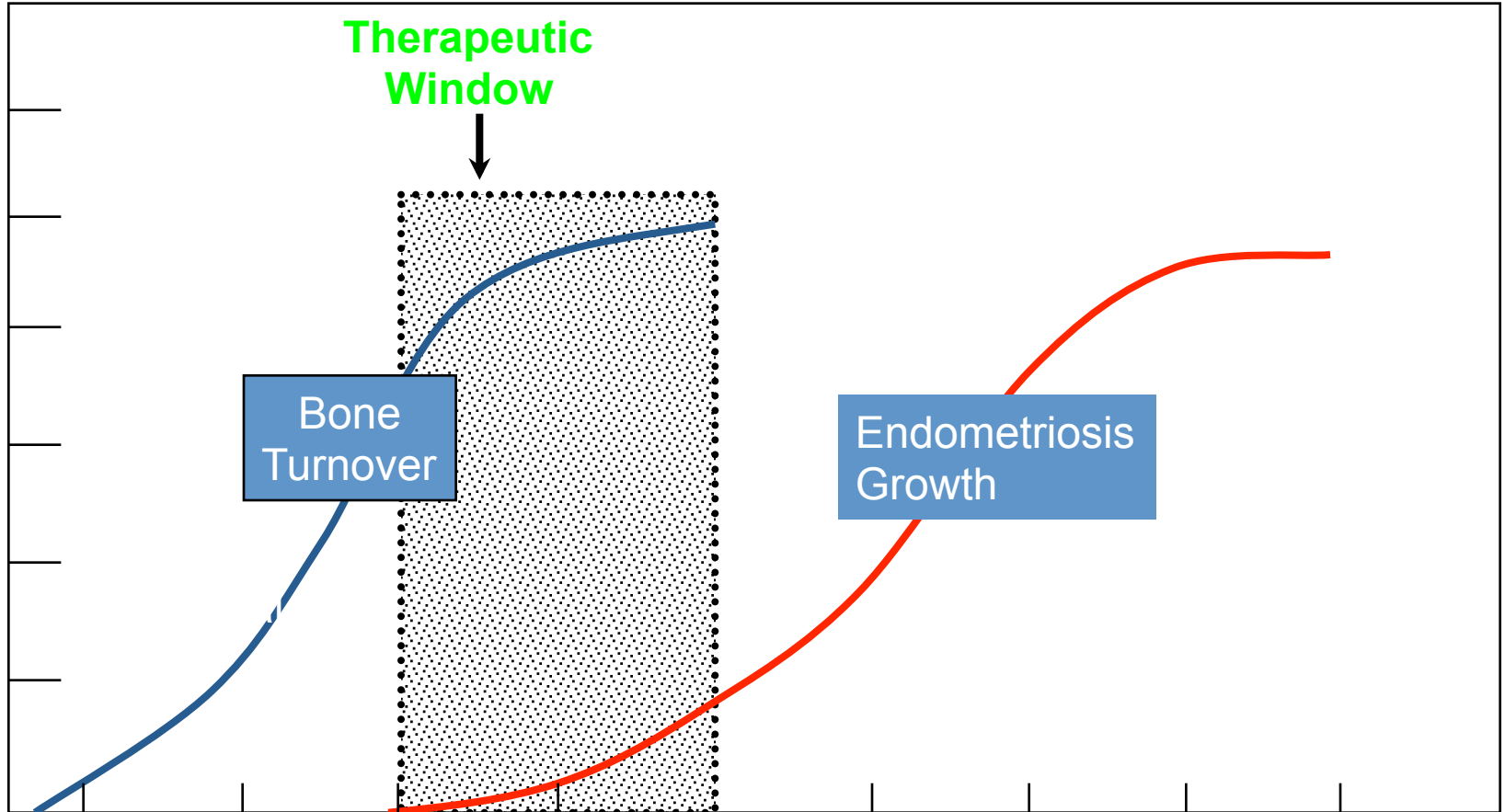
## Add-back therapy and GnRH-a in the treatment of patients with endometriosis

- Six months of therapy, ↓ vasomotor sx, ↓ BMD loss
  - 2.5 mg norethindrone or
  - 0.625 mg CEE / 2.5 mg MPA
- Twelve months of therapy, ↓ BMD loss
  - 5 mg norethindrone or
  - 0.625 mg CEE / 5mg norethindrone

# What about ERT in these patients?



- Potential to reactivate microscopic or residual endometriotic implants?
- Is there any value on delaying ERT after surgery?



Barbieri RL. Am J Obstet Gynecol 1992;166:740-5

# Ενδομητρίωση και Υπογονιμότητα

## *Evidence-Based Medicine:*

*(Επιστημονικά τεκμηριωμένη Άσκηση της Ιατρικής)*

*Συνδυάζει τα καλύτερα βιβλιογραφικά δεδομένα με την κλινική εμπειρία του Ιατρού για να προσφέρει την καλύτερη δυνατή λύση στα προβλήματα του συγκεκριμένου ασθενούς.*



# Ovulation suppression for endometriosis for women with subfertility (Review)

Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P



There is no evidence of benefit in the use of ovulation suppression in subfertile women with endometriosis who wish to conceive.

Cochrane Database Syst Rev. 2007 Jul 18;(3).

# Endometriosis and infertility: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine  
American Society for Reproductive Medicine, Birmingham, Alabama

- The benefit of laparoscopic treatment of minimal or mild endometriosis is insufficient to recommend laparoscopy solely to increase the likelihood of pregnancy.
- In younger women (under age 35 years) with stage I/II endometriosis-associated infertility, expectant management or SO/IUI can be considered as first-line therapy.
- For women 35 years of age or older, more aggressive treatment, such as SO/IUI or IVF may be considered.
- In women with stage III/IV endometriosis-associated infertility, conservative surgical therapy may be beneficial.
  - Surgical management of an endometrioma should include resection or ablation, rather than drainage, with resection preferred.
- For women with stage III/IV endometriosis who fail to conceive following conservative surgery or because of advancing reproductive age, IVF-ET is an effective alternative.

Fertil Steril 2012;98:591–8. 2012 by American Society for Reproductive Medicine.

# Endometriosis and IUI

- IUI is effective in women with minimal to mild endometriosis (patent fallopian tubes)
- Intrauterine insemination is less effective in women with endometriosis than those with unexplained infertility
- IUI combined with superovulation results in better pregnancy rates.
- CC or HMG have been used

Hughes et al 1997

Omland et al 1998

Tummon et al 1997

# Endometriosis and ovarian cancer

- Mutations in the genes that encode for metabolic and detoxification enzymes, such as **GALT** and **GSTM**, have been implicated in the pathogenesis of endometriosis and in the progression to carcinoma of the ovary.
- **PTEN**, a tumor suppressor gene commonly mutated in endometriosis, is found mutated in endometrioid carcinoma of the ovary, but not in other forms of ovarian cancer.
- Somatic mutations in the **PTEN** gene were identified in 20% of endometrioid carcinomas and 20.6% of solitary endometrioid ovarian cysts.

Swiersz LM. *Ann NY Acad Sci* 2002 Mar ;955:281-92

# Endometriosis and Ovarian Cancer

Histologic type	Number of patients	Presence of endometriosis
All types	79	22 <b>(28%)</b>
Endometrioid	23	9 <b>(39%)</b>
Clear Cell	□ 17	7 <b>(41%)</b>
Mixed	8	4 <b>(50%)</b>

La Cuesta et. al. Gyn Onc.60,238-244 (1996)

# Endometriosis and Ovarian Cancer



Borgfeldt C et al., Acta Obstet Gynecol Scand. 2004 Apr;83(4):395-400.

