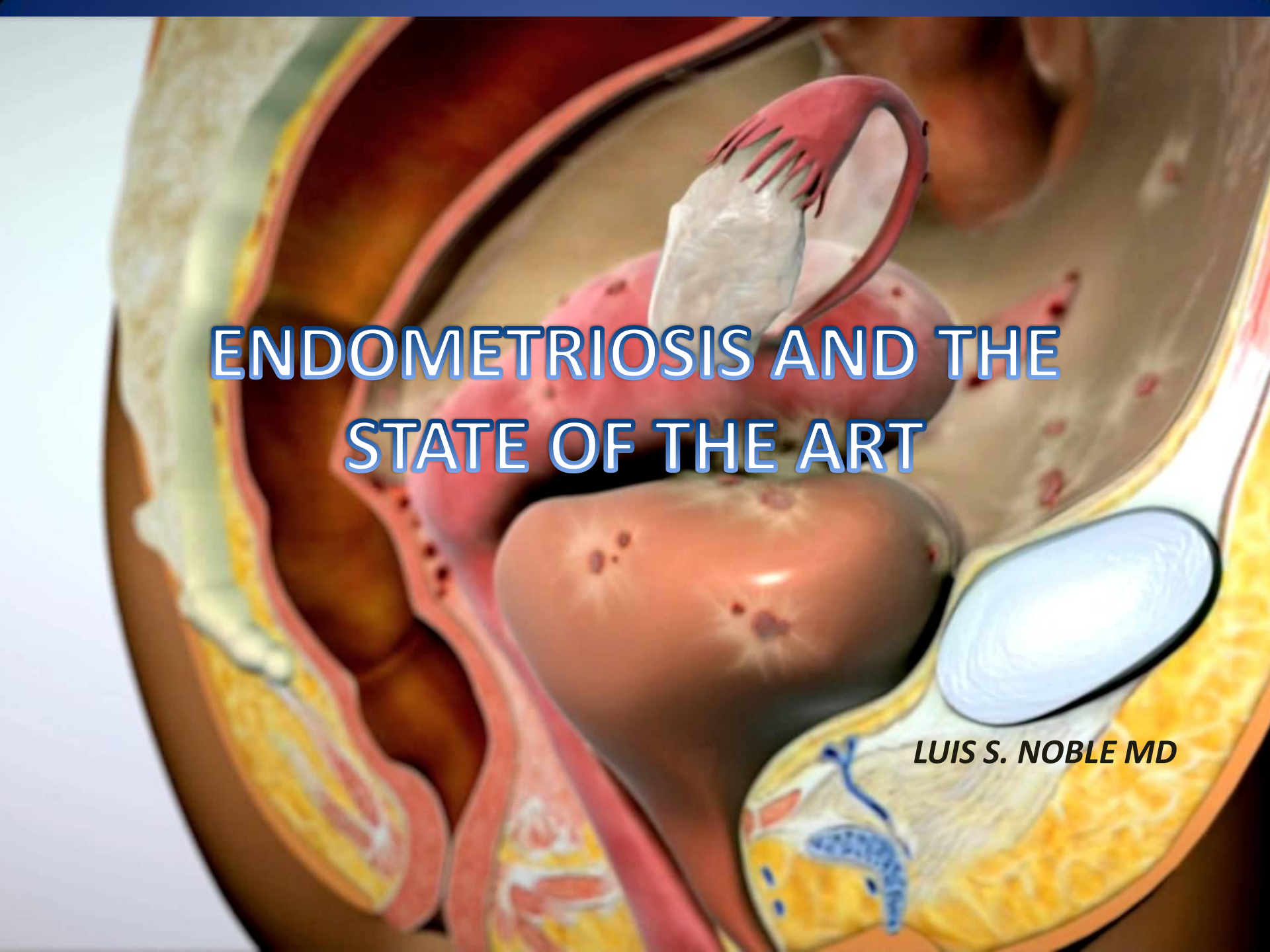
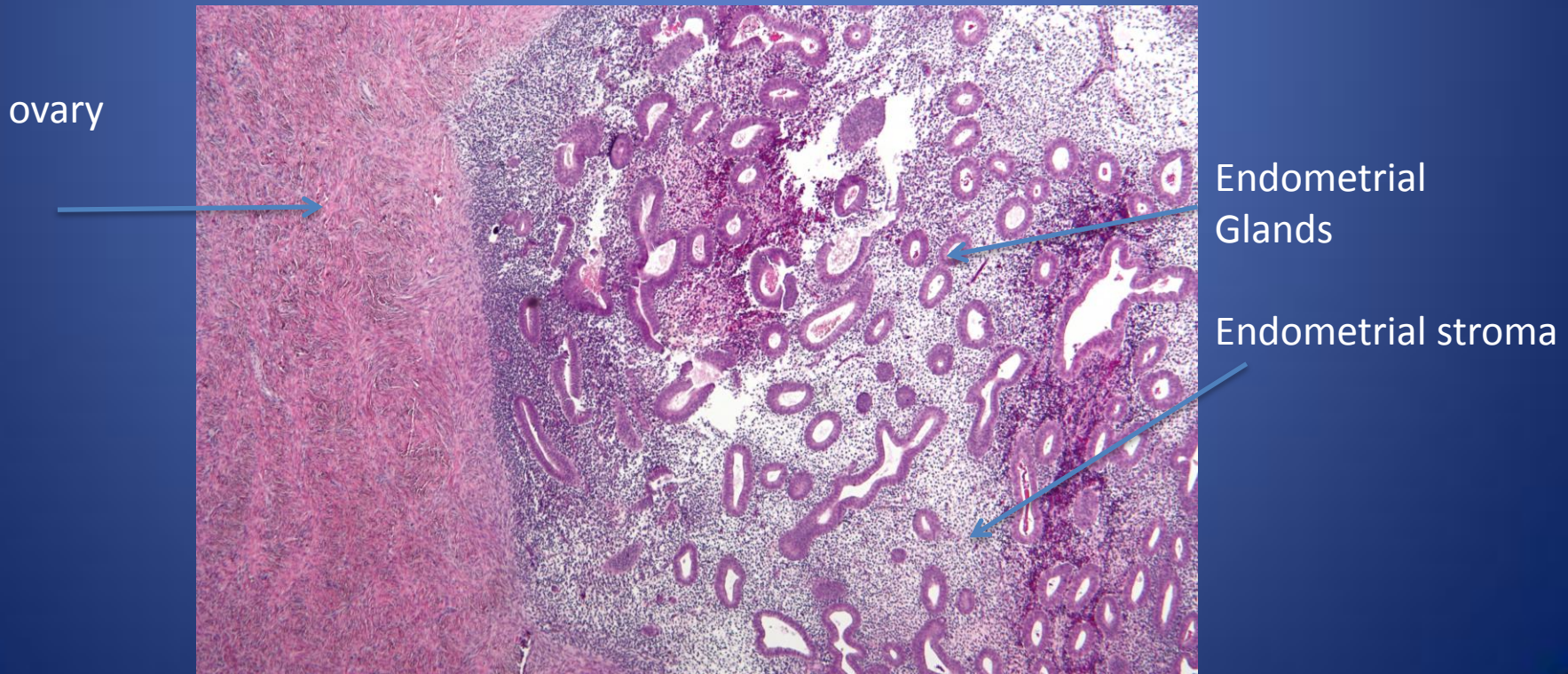

ENDOMETRIOSIS AND THE STATE OF THE ART
LUIS S. NOBLE MD

WHAT IS ENDOMETRIOSIS?

- The presence of endometrial tissue (glands and stroma) in an extrauterine location.



ENDOMETRIOSIS

- Affects 7-10% of reproductive age women
- Associated with:

-Pelvic pain, dysmenorrhea, dyspareunia.
-Infertility
-Ovarian cysts
-Pelvic adhesions
-Bowel dysfunction
-Bladder dysfunction
-Extra pelvic endometriosis

ETIOLOGY

- **RISKS FACTORS:**
- Family history of endometriosis
- Early age of menarche
- Short menstrual cycles (< 27 d)
- Long duration of menstrual flow (>7 d)
- Heavy bleeding during menses
- Inverse relationship to parity
- Delayed childbearing
- Defects in the uterus or fallopian tubes

ETIOLOGY

- Early in the 20th century (1927), Samson proposed his theory of retrograde menstruation through the fallopian tubes into the peritoneal cavity as a cause of endometriosis.
- Celomic metaplasia
- Vascular lymphatic spread
- Relatively recent research has suggested involvement of the immune system in the pathogenesis of endometriosis.
- Intriguing nonhuman primate studies have demonstrated a strong association between dioxin exposure and the development of endometriosis.

WHY?

- Retrograde menstruation is an almost universal event.
- Only 7-10% of all women get endometriosis
- Nearly 40% of infertile women have endometriosis
- ***Uninterrupted menstruation…***

Family history of endometriosis
Early age of menarche
Short menstrual cycles (< 27 d)
Long duration of menstrual flow (>7 d)
Heavy bleeding during menses
Inverse relationship to parity
Delayed childbearing
Defects in the uterus or fallopian tubes

- Regular predictable menses= Normal
- Regular predictable menses= Normal…but not natural from evolutionary standpoint?

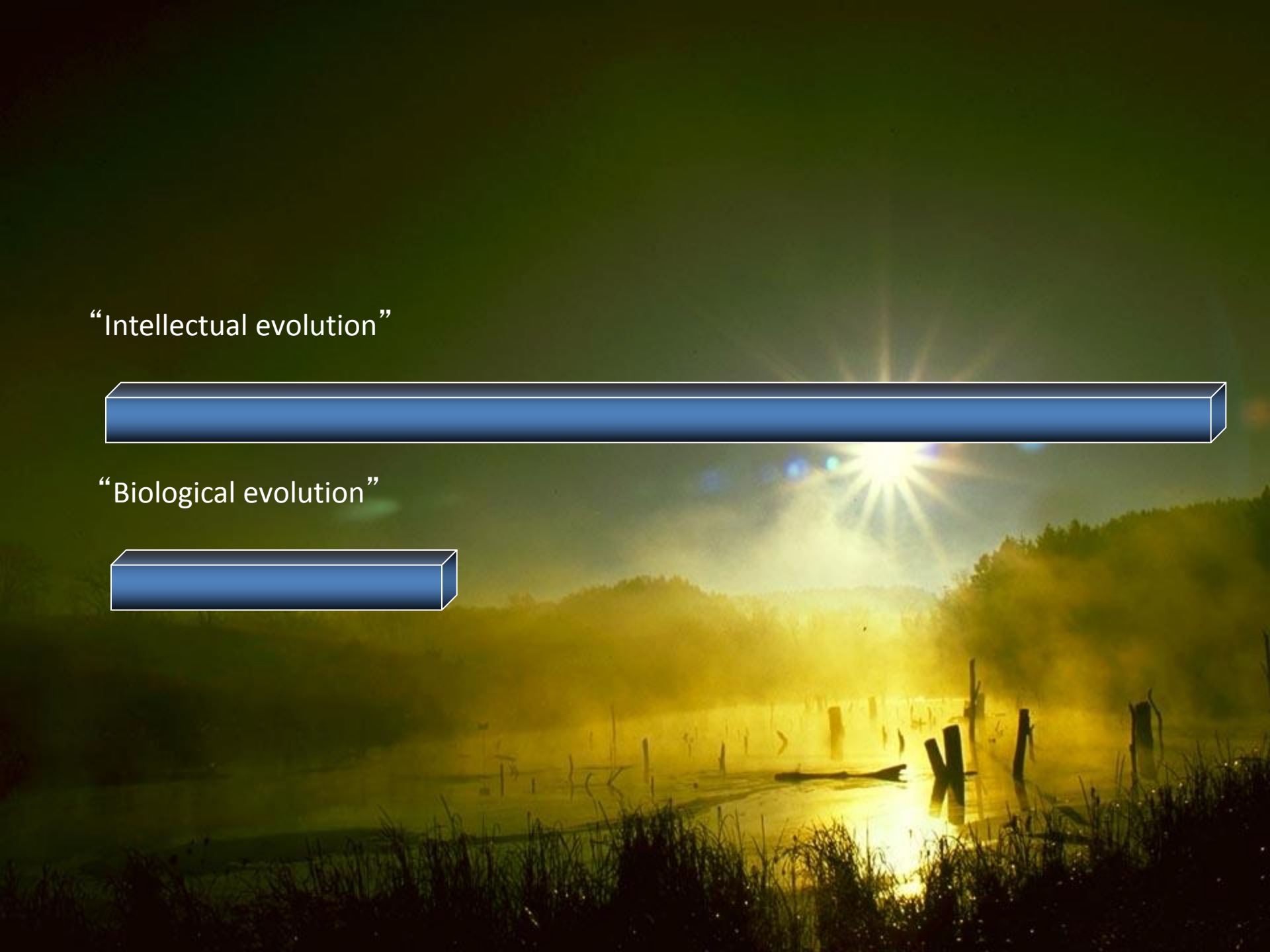
!Kung women

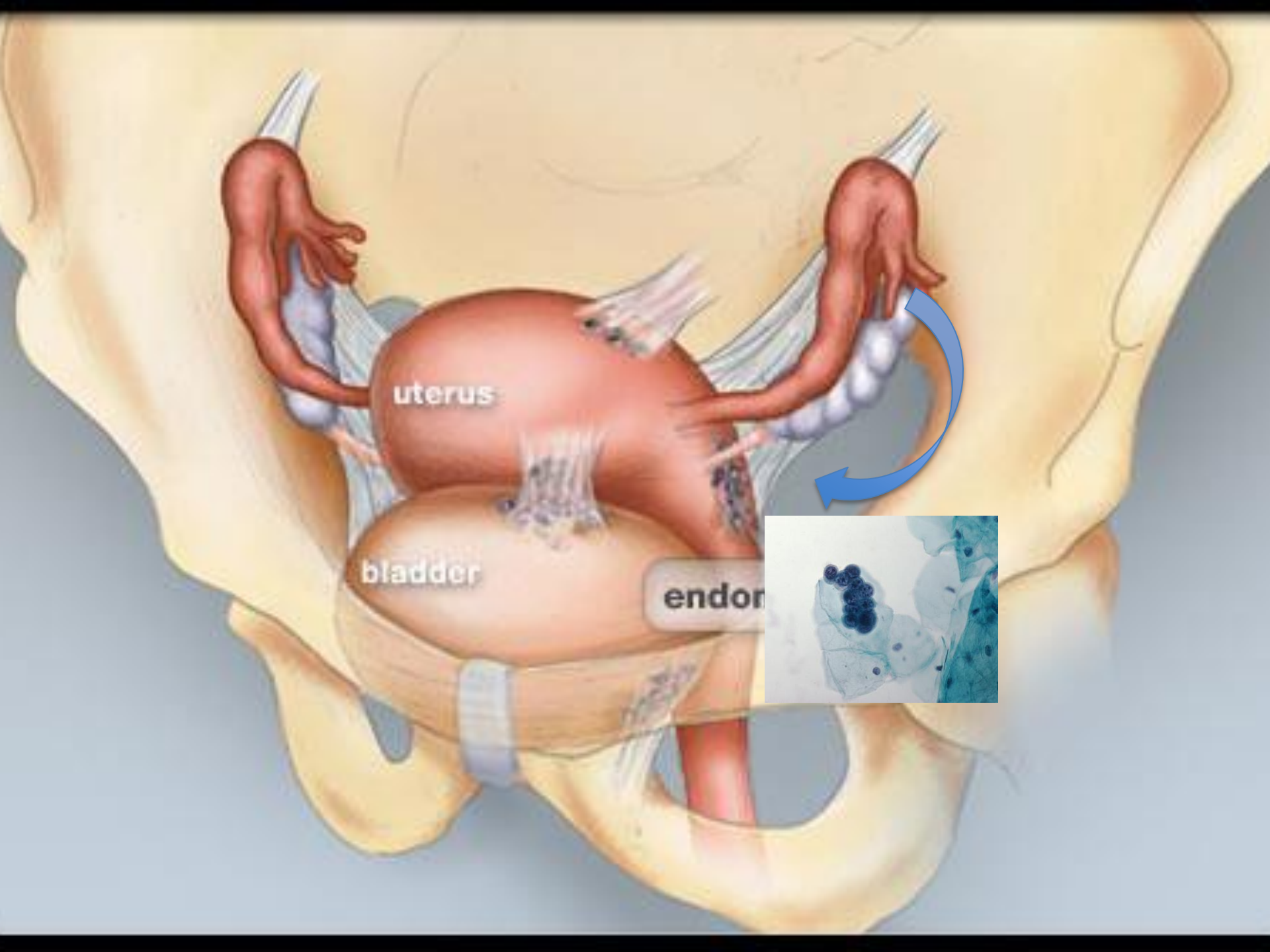
Average age of 1st pregnancy 15

15 years lactational amenorrhea

4 years of pregnancy

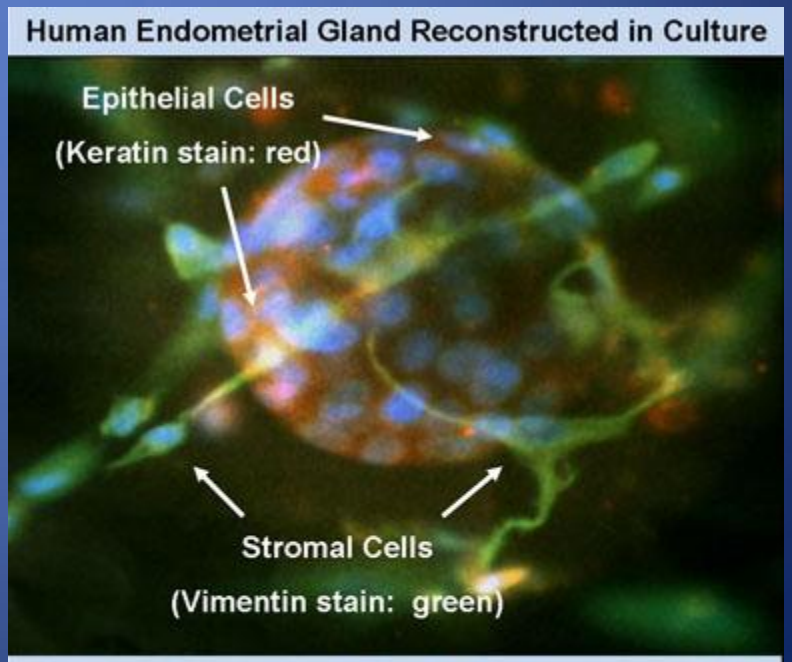
48 menstrual cycles


“Intellectual evolution”
“Biological evolution”

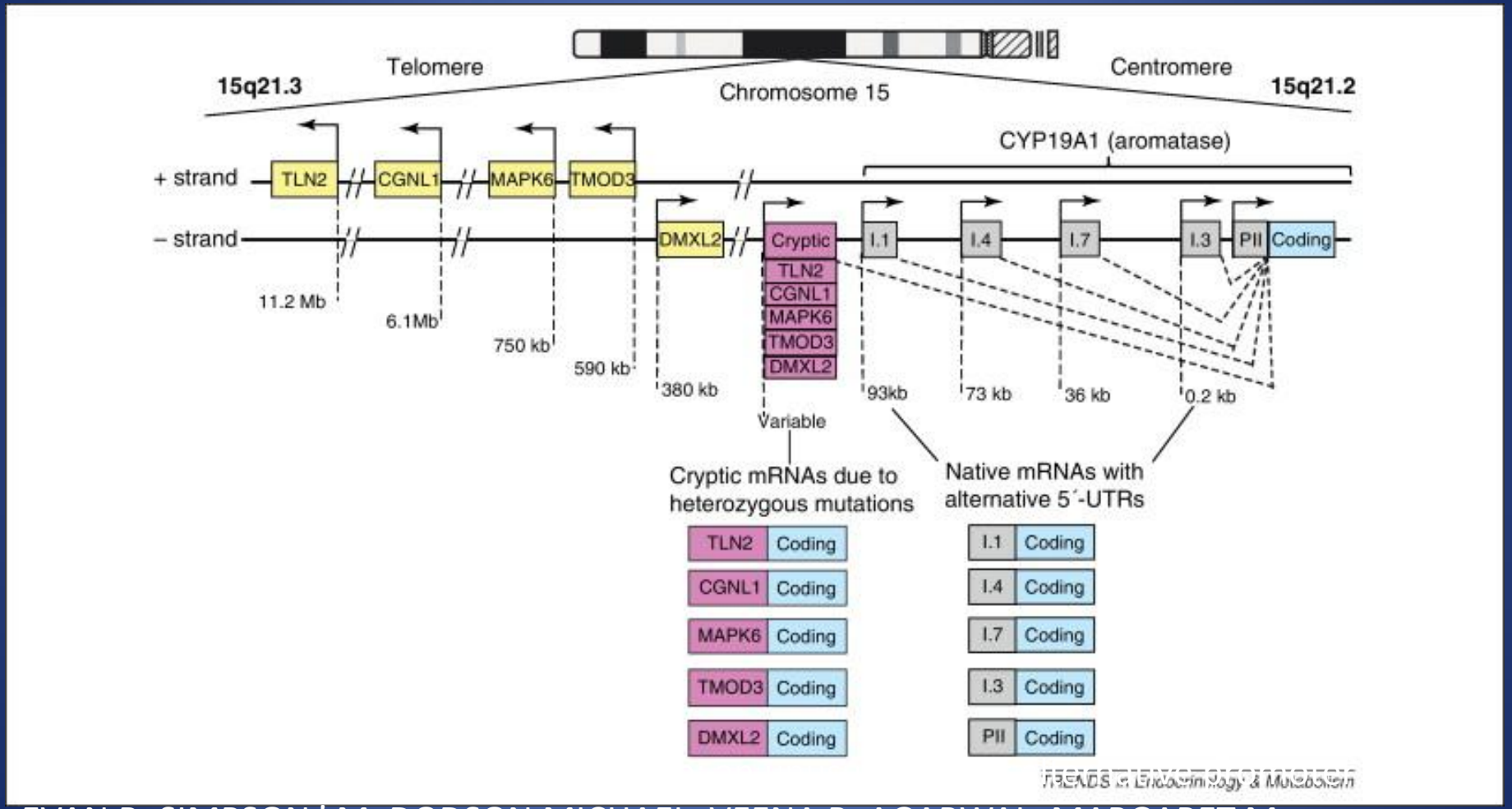

uterus
bladder
endor

Eutopic Endometrium

- Eutopic endometrium should have enhanced ability of proliferation, implantation and angiogenesis, and greater probability of escaping the unfavorable conditions of the ectopic environment.



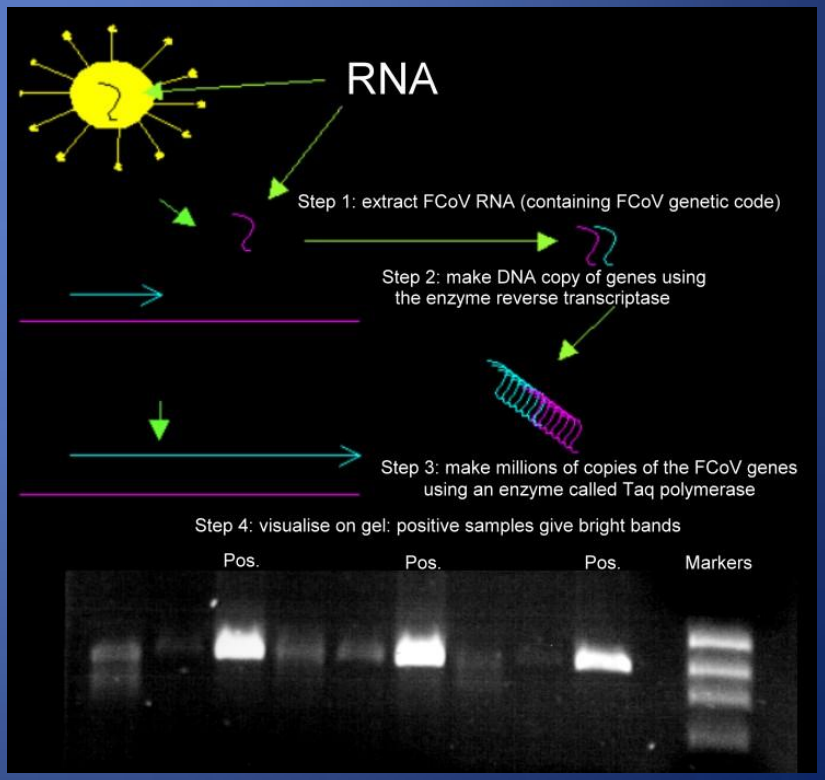
CYP 19



EVAN R. SIMPSON,' M. DODSON MICHAEL, VEENA R. AGARWAL, MARGARET M. HINSHELWOOD, SERDAR E. BULUN, AND YING ZHAO
The Cecil H. and Ida Green Center for Reproductive Biology Sciences, The University of Texas Southwestern Medical Center, Dallas, Texas, 75235-905 1, USA 1997

Endometriosis (super eutopic endometrial cells)?

- The Eutopic endometrium of women with endometriosis. Is it biochemically different?



CYP 19 GENE EXPRESSION

RT PCR for CYP 19 gene	RESULT
Peritoneum	Negative
Eutopic endometrium (no endometriosis)	Negative
Eutopic endometrium (endometriosis)	POSITIVE
Endometriotic implants	POSITIVE

- *Noble et al 1995 JCNM*

Molecular expression

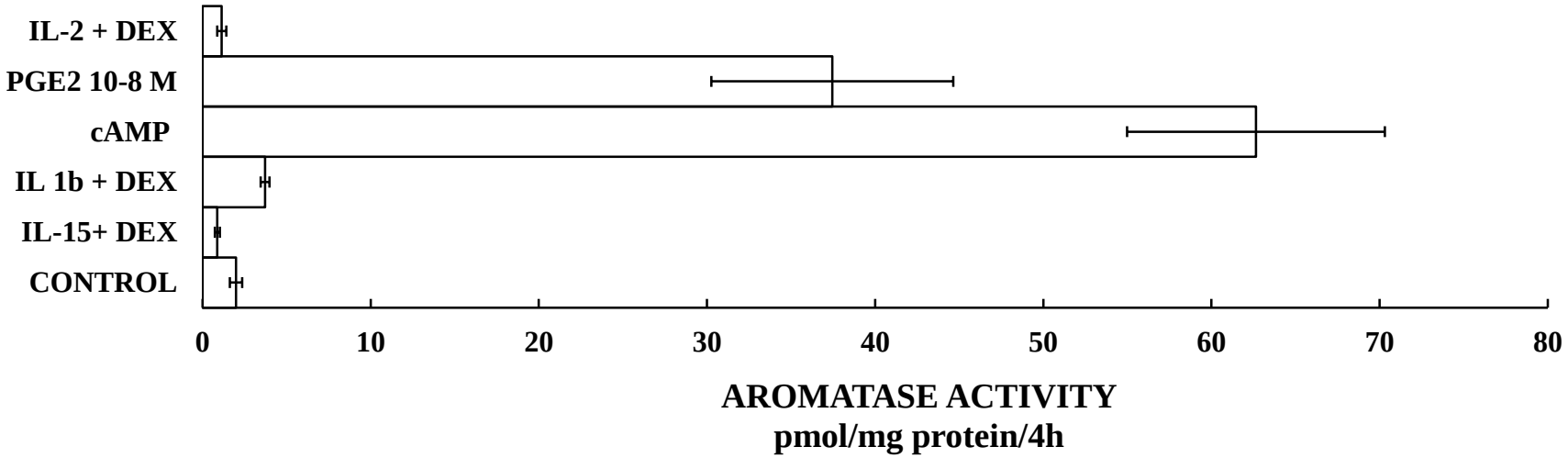
- Aromatase present in Endometrium of women with endometriosis. (*Noble et al 1995)*
- B-3 integrin expression is aberrant in endometrium of women with endometriosis

(*Lessey et al 1996*)

Molecular expression

Recent proteomic analysis revealed molecular dysregulation of more than 70 proteins in the proliferative phase of eutopic endometrium in stage IV and secretory phase of stage II, III and IV endometriosis. Using mass spectrometry, 48 proteins spots which were consistently differentially expressed from stage II to IV endometriosis were identified. *(Rai et al 2010)*

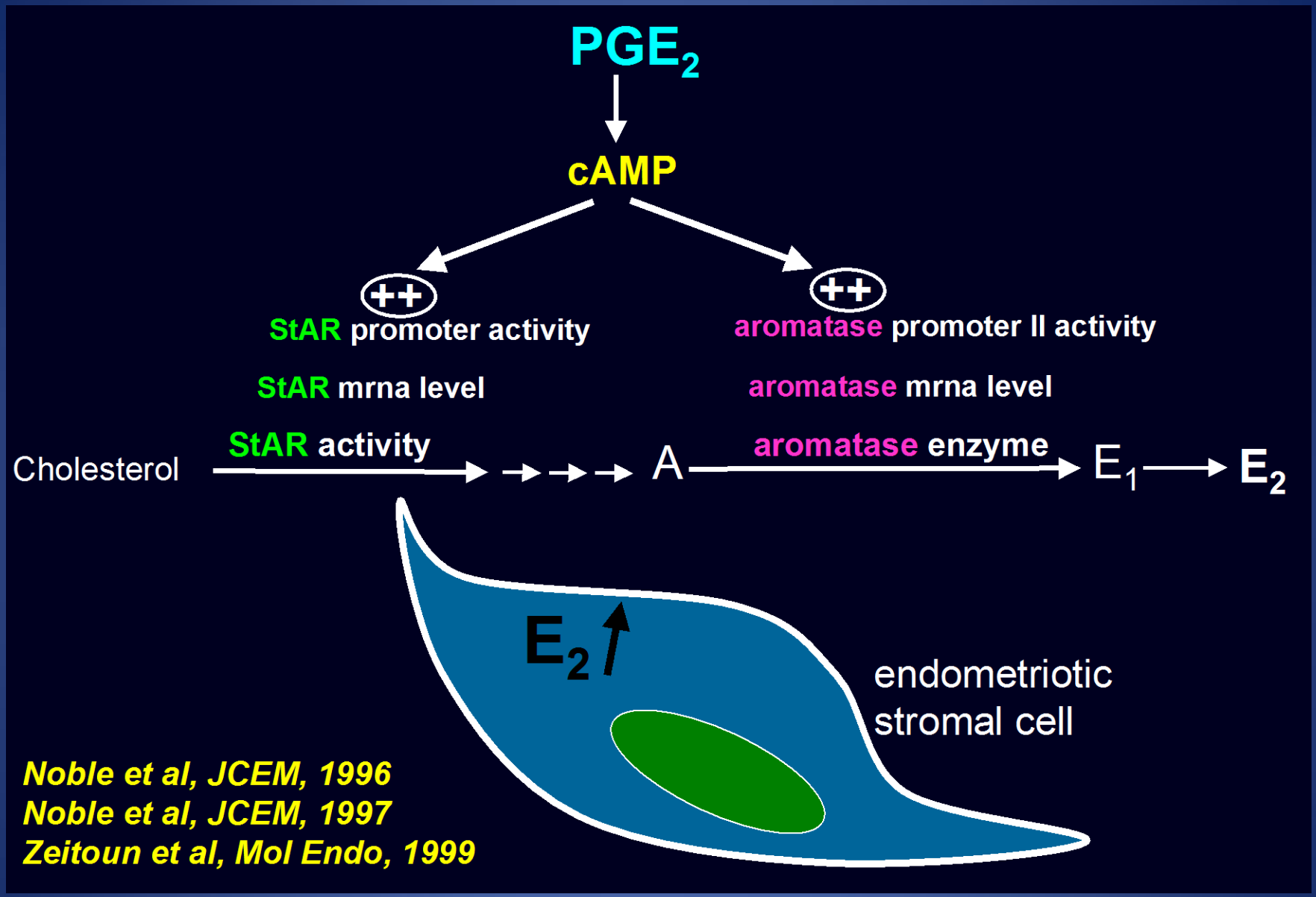
Aromatase expression



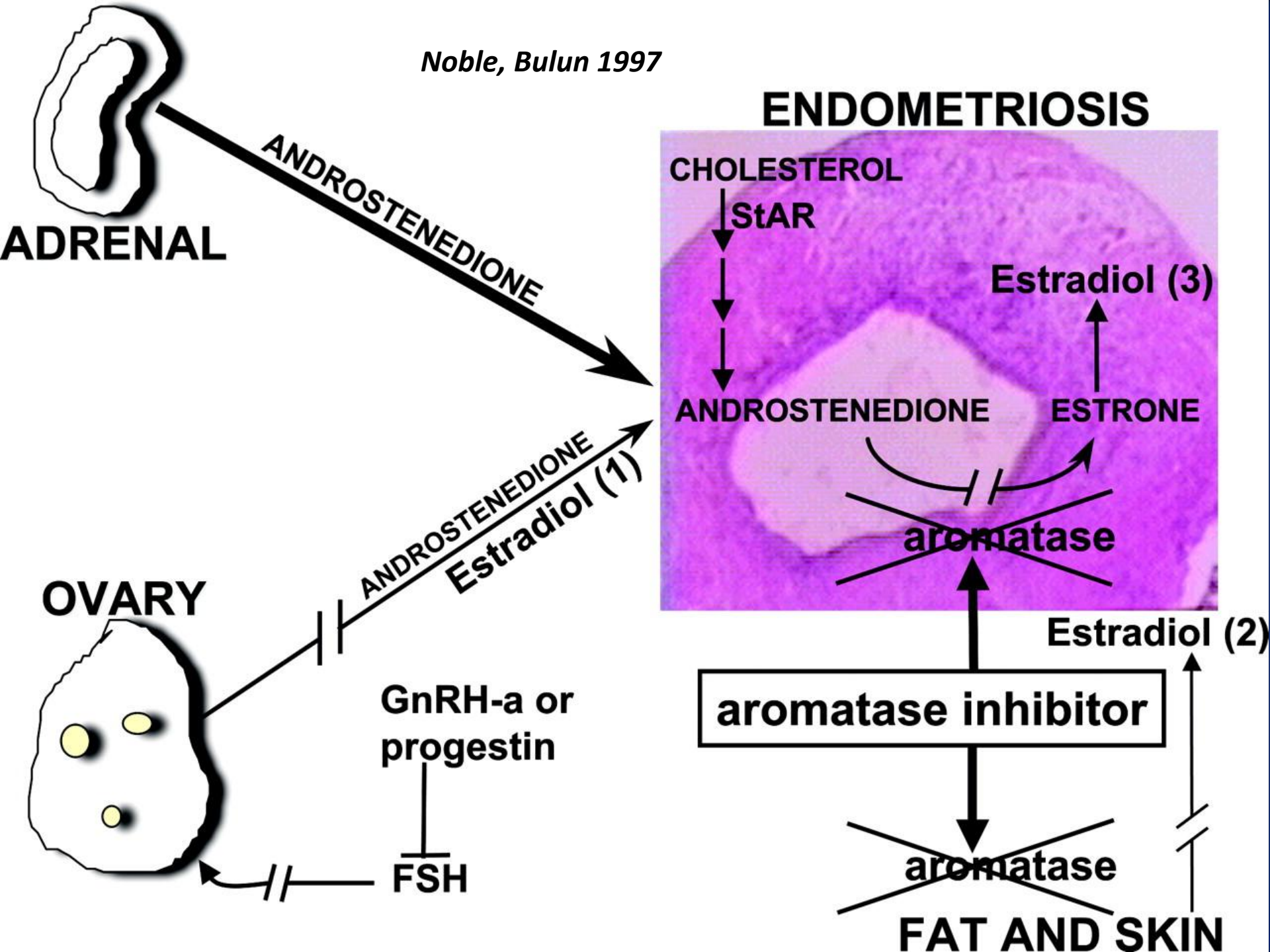
Noble, Bulun JCNM 1996

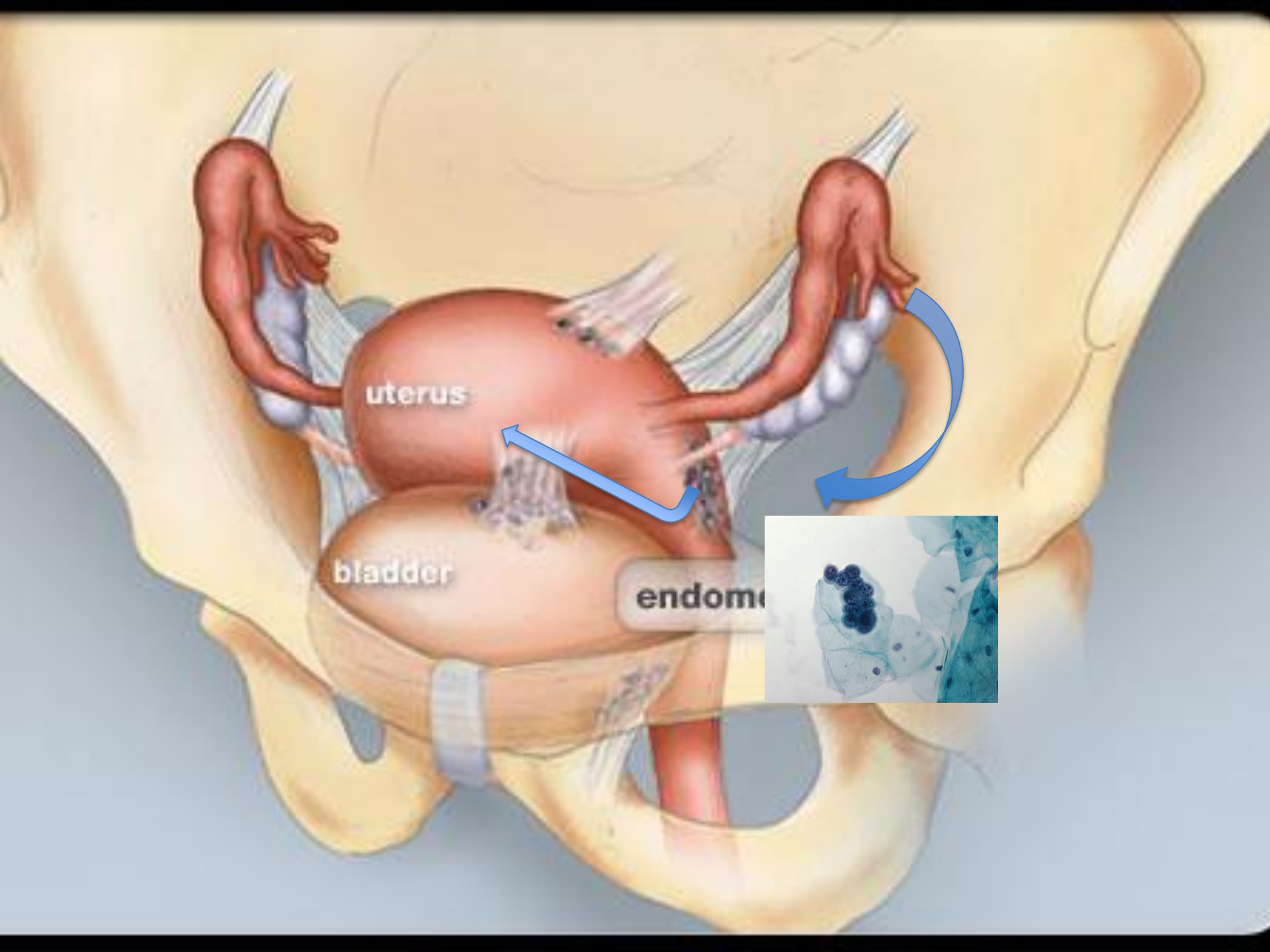
Inflammation and endometriosis

- Prostaglandins, such as PGE2 and PGF2α, are secreted in significantly higher levels from eutopic and ectopic endometrial cells in women with endometriosis (Dmowski et al., 1998; Gazvani & Templeton, 2002). Higher levels of PGE2 increase estrogen biosynthesis (Noble et al., 1997) by creating a positive feedback system favoring continuous estrogen production (Bulun et al., 1999; Bulun, Zeitoun, Takayama, & Sasano, 2000; Gazvani & Templeton; Noble et al.; Ulukus et al., 2006; Zeitoun & Bulun, 1999).

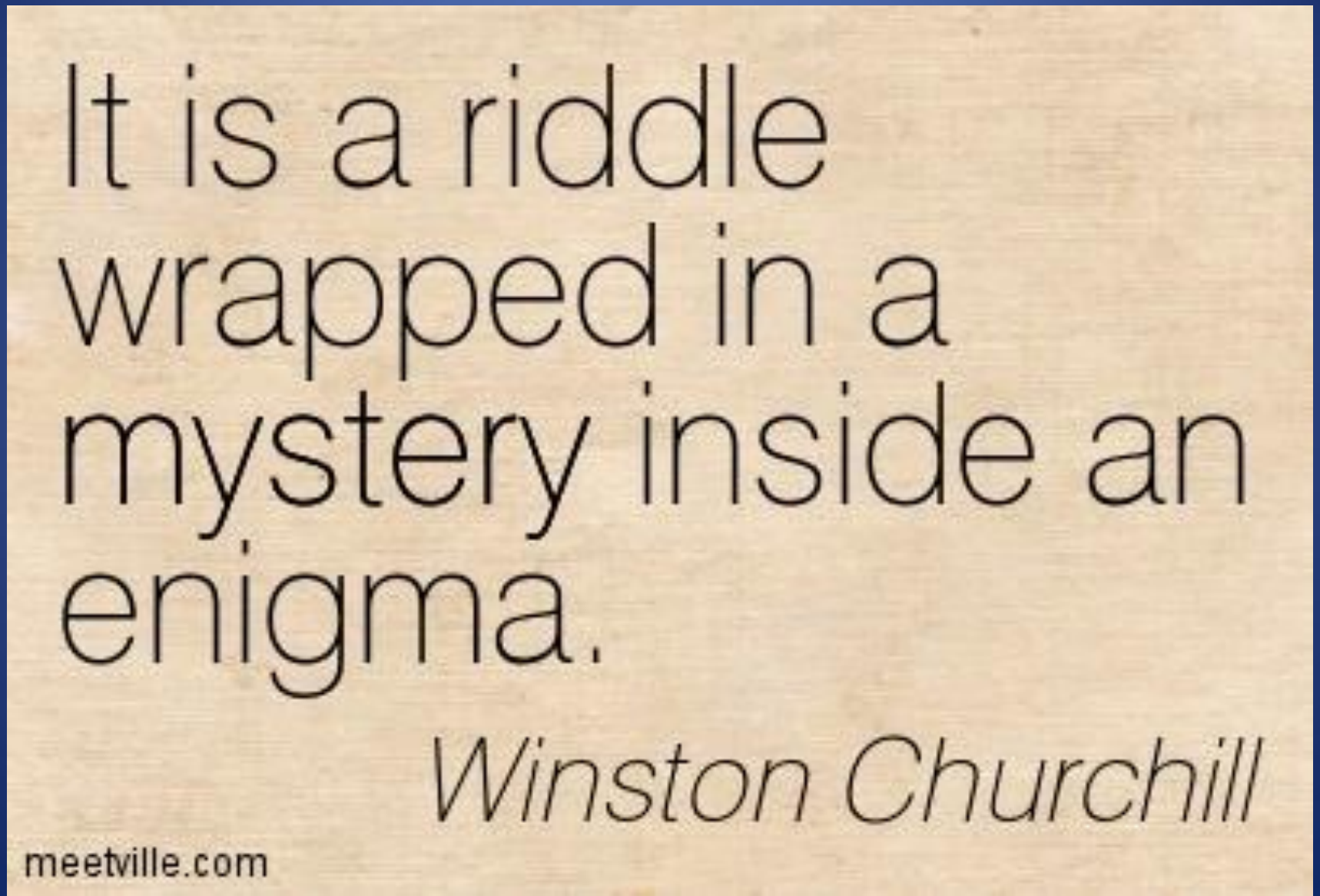

PGE2
cAMP
++
++
StAR promoter activity
aromatase promoter II activity
StAR mrna level
aromatase mrna level
StAR activity
aromatase enzyme
Cholesterol
A
E1
E2
E2
endometriotic
stromal cell
Noble et al, JCEM, 1996
Noble et al, JCEM, 1997
Zeitoun et al, Mol Endo, 1999

Noble, Bulun 1997




uterus
bladder
endome

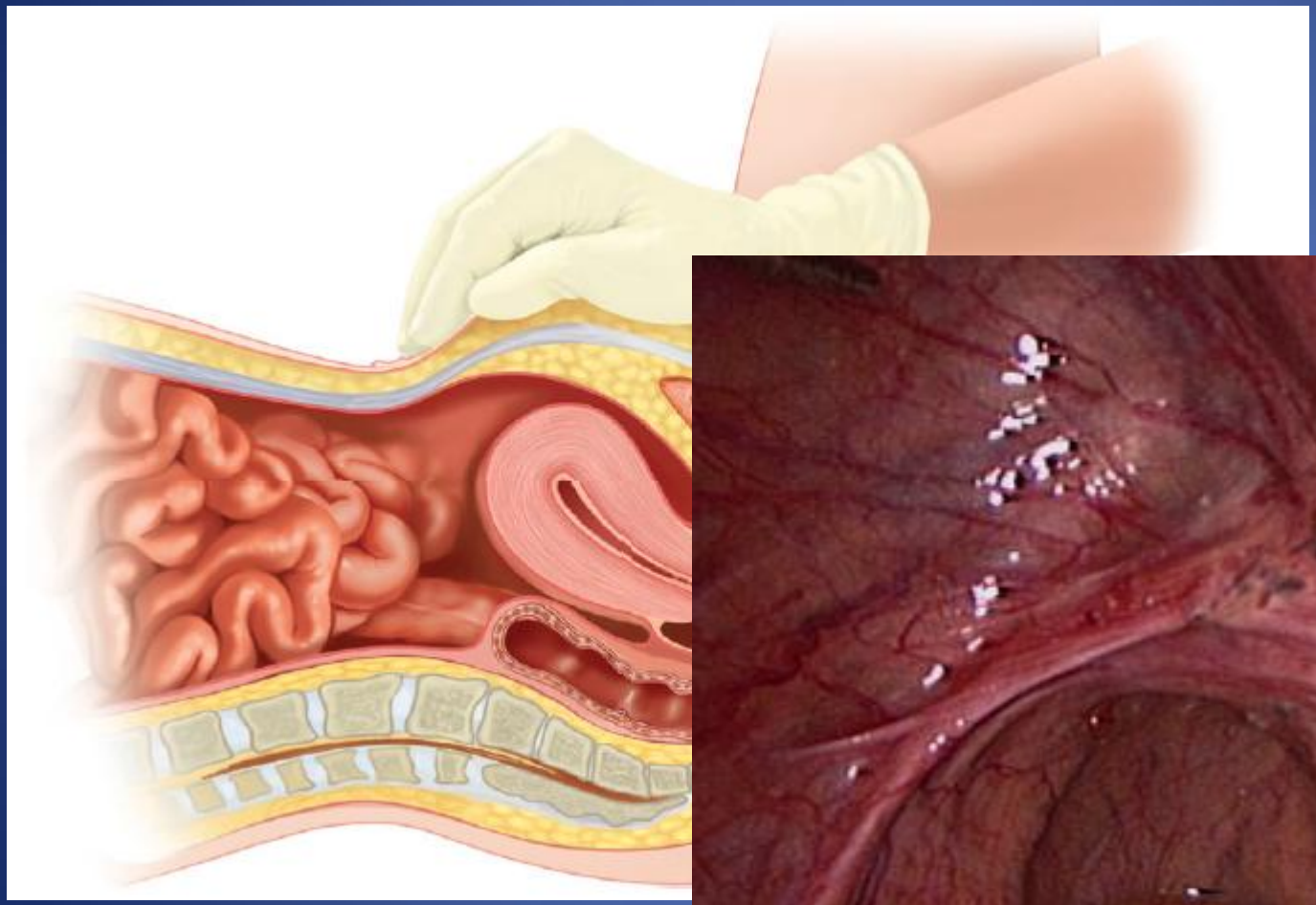
QUESTION REMAINS



Clinical Aspects

- **DIAGNOSIS:**
- Symptoms (pelvic pain, infertility, dysmenorrhea)
- Physical findings
- Imaging
- Laboratory testing

Uterosacral nodularity



Alogrithm in infertile couples

- History (dysmenorrhea, pelvic pain, dyspareunia
- Semen analysis
- HSG
- Endocrine evaluation (mid-luteal progesterone, ovarian reserve testing)
- Physical exam

Current data being analyzed for publication by

Dr. Park and Dr. Ramirez

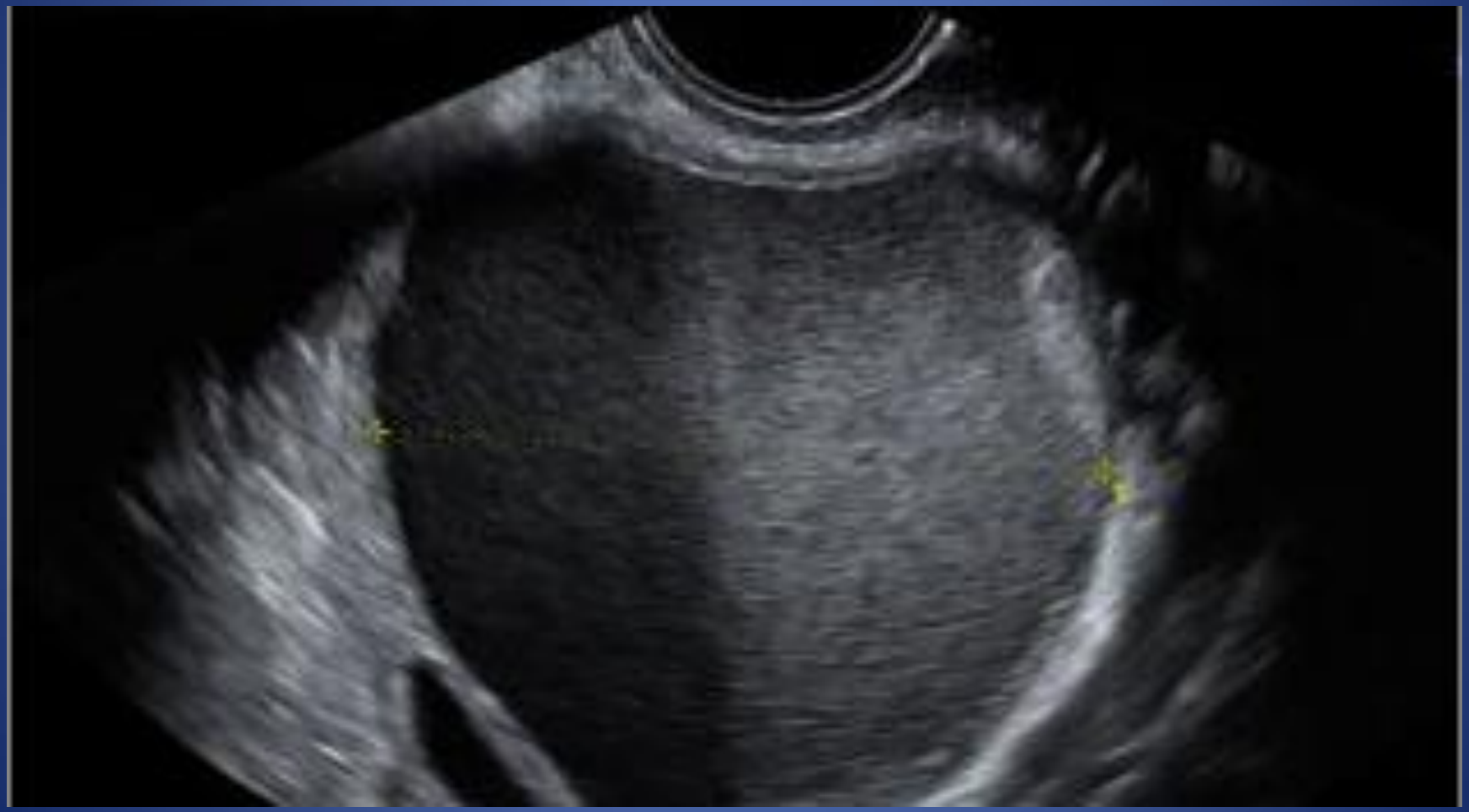
Chronic pelvic pain and endometriosis

- More complex history
- Look for signs of psychological suffering
- Not as clear cut as infertile couples
- 20-25% will have endometriosis
- Infertility couples (asymptomatic) up to 50% will have endometriosis.

Diagnosis

- Imaging: (Limited to advance stages) MRI can be used to detect up to 82 percent of endometriomas greater than or equal to 1 cm and 50 percent of hemorrhagic lesions less than or equal to 5 mm due to the small implant size and variable appearance (Brosens et al., 2004)..
- CA-125 testing unreliable
- beta-3 integrin, aromatase PCR or immunostaining with EMB promising
- Laparoscopy/Laparotomy

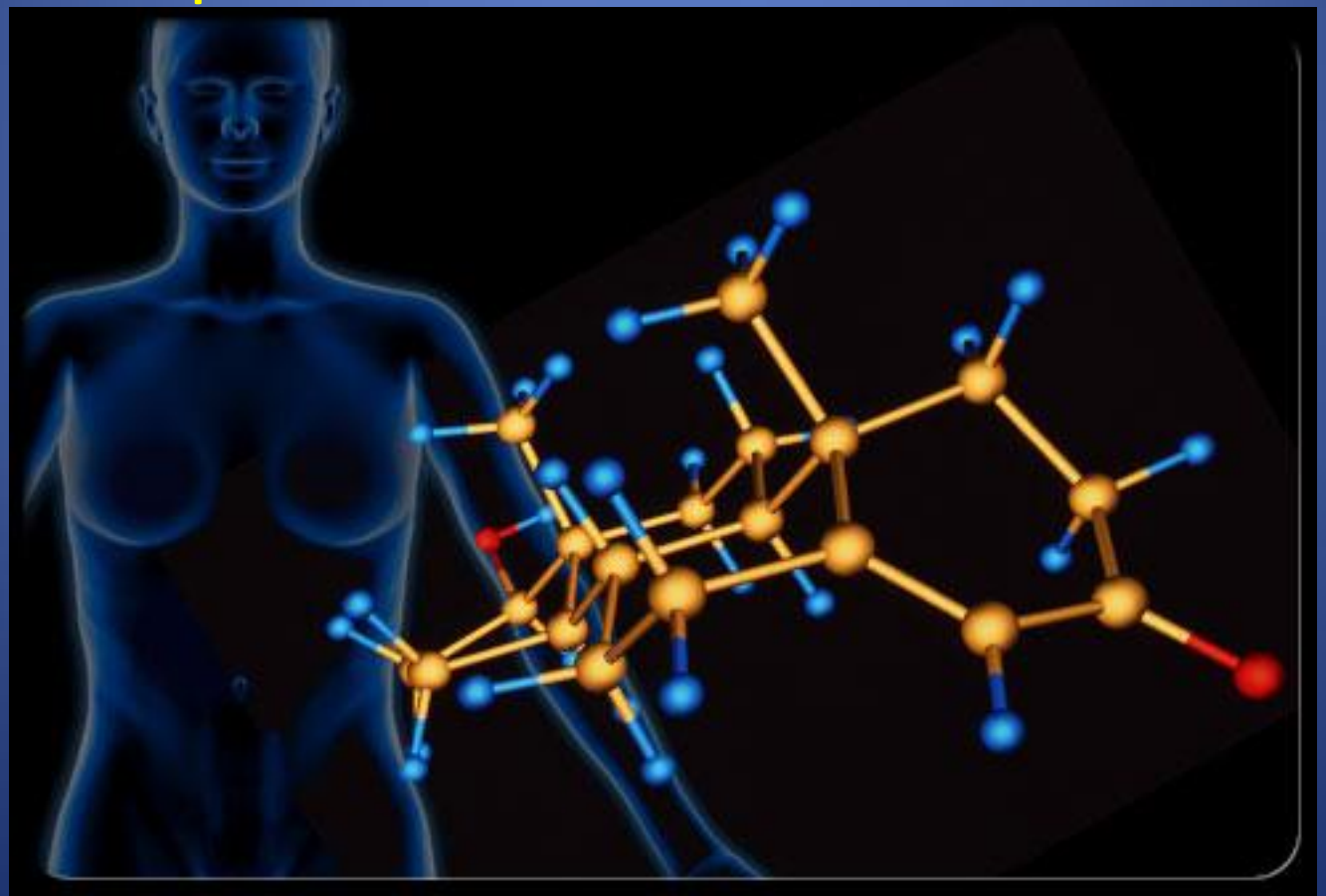
Ultrasound



SPLIT ROADS

MEDICAL MANAGEMENT OPTIONS

- Almost all medical management options are contraceptive:

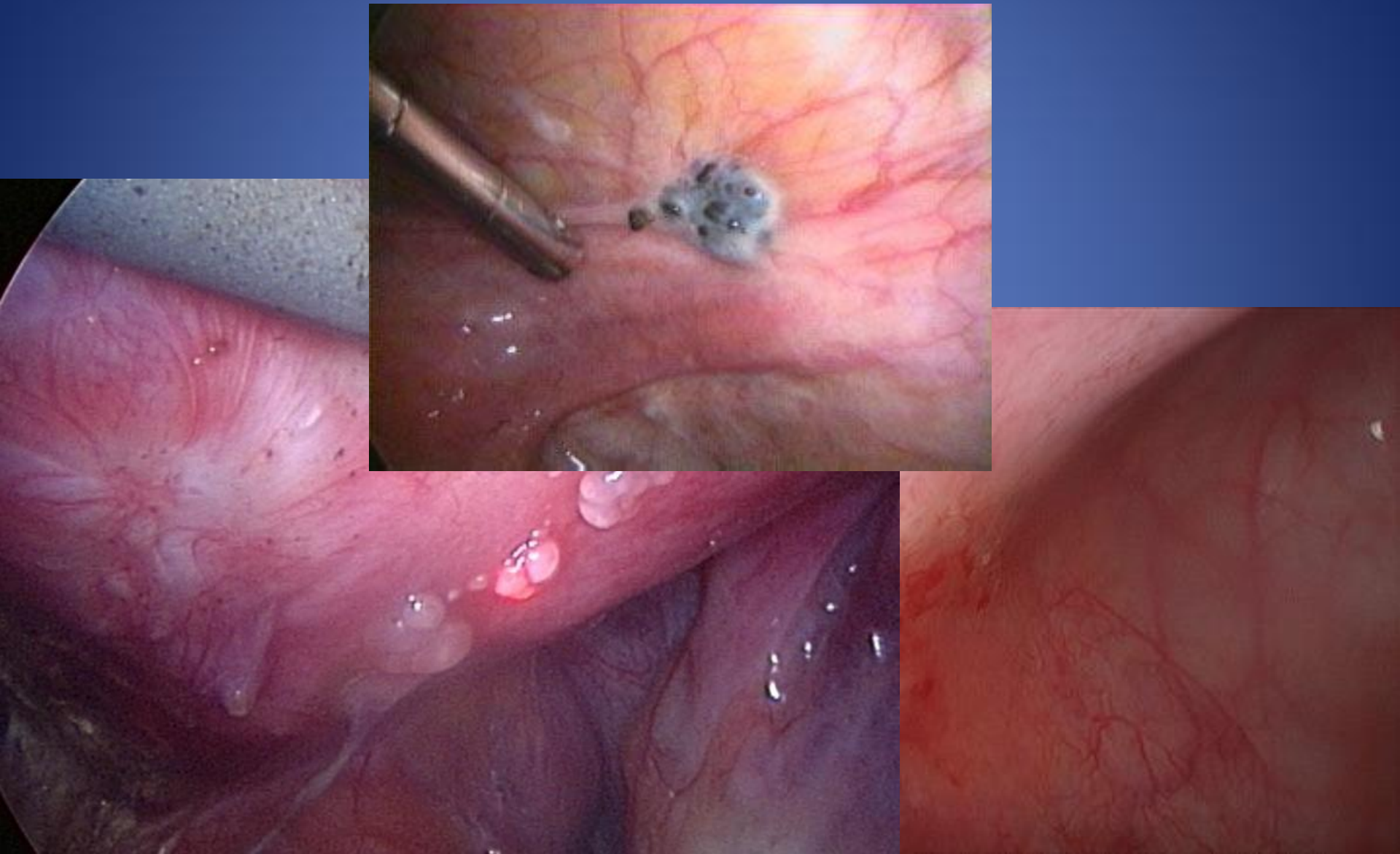


MEDICAL MANAGEMENT OPTIONS

- Danazol
- GnRh analogs + NSAIDS
- Continuous oral contraceptives +NSAIDS
- Progestins, oral, (IUD), injectable
- Aromatase inhibitors*: Anastrozole (Arimidex), Letrozole (Femara) in combination with progestin or GnRH analogs*
- Experimental: Inhibitors of VGEF

Laparoscopy

Endometriosis appearance



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patients' 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**	< $\frac{1}{3}$ Enclosure	$\frac{1}{3}$–$\frac{2}{3}$ Enclosure	> $\frac{2}{3}$ 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 closed, change the point assignment to 16.

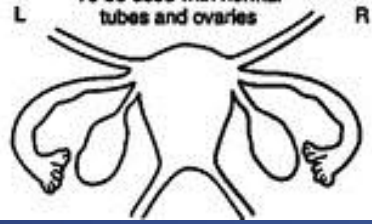
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should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

Denote appearance of of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles

Additional endometriosis: _____

Associated pathology: _____

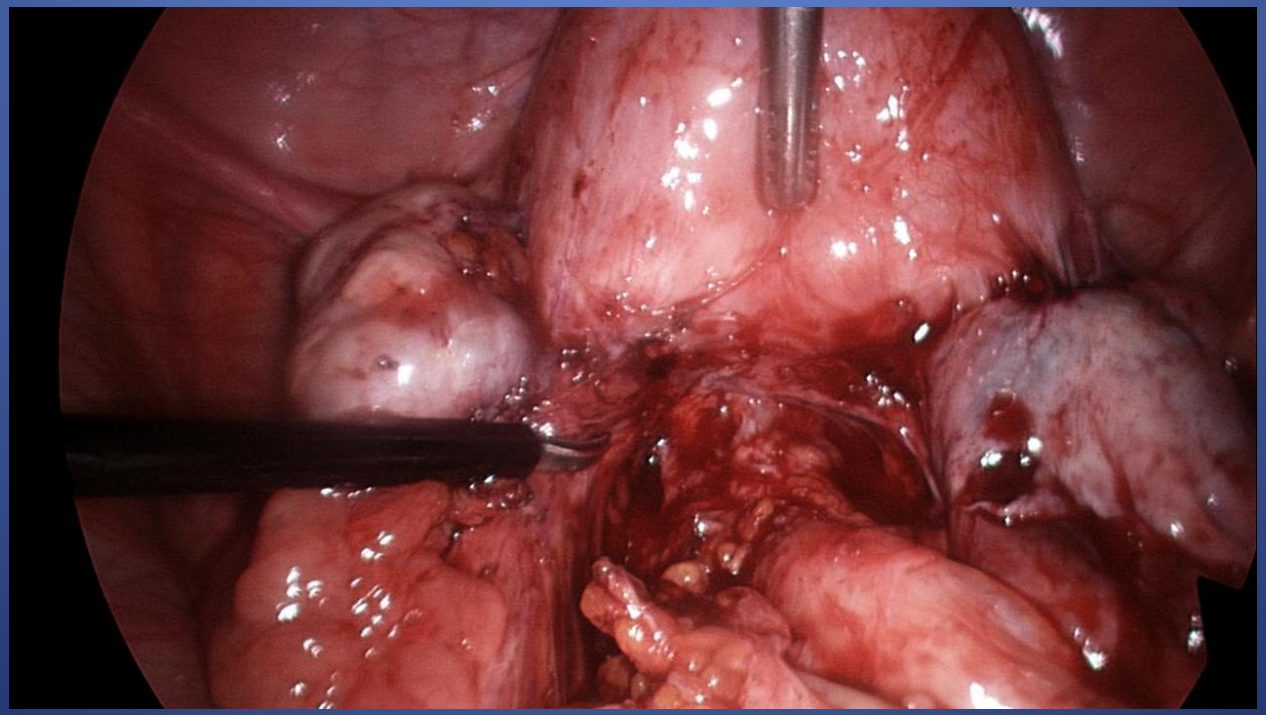
To be used with normal tubes and ovaries



To be used with abnormal tubes and/or ovaries

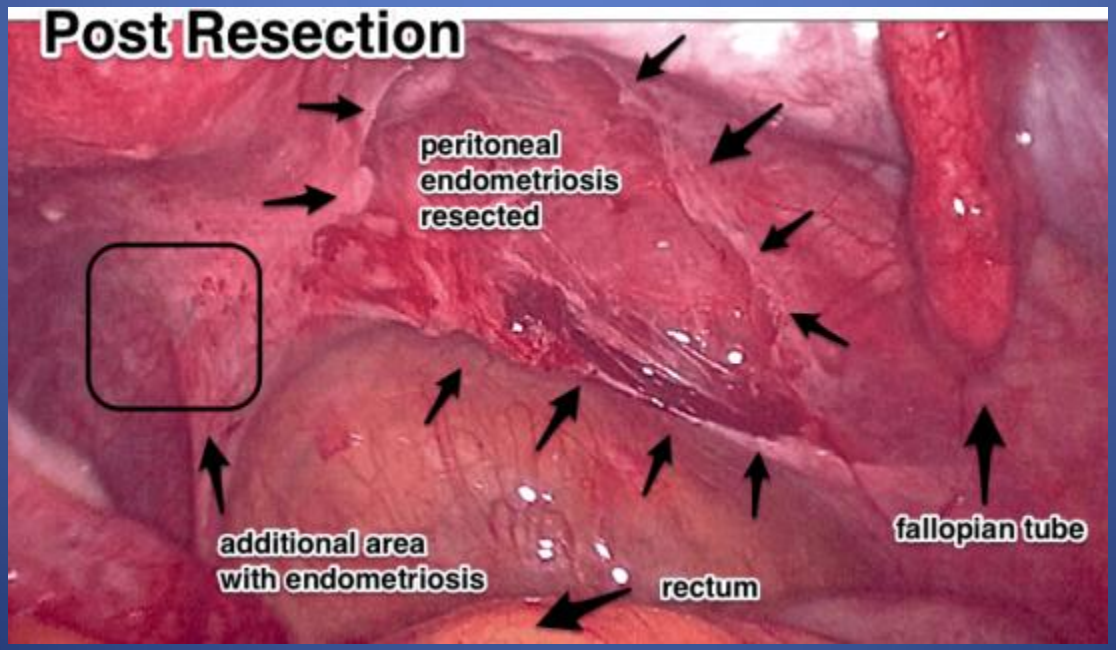
Staging

- Endometriosis staging has no relationship to severity of pelvic pain, however, is inversely correlated to fertility potential



Surgical management

- Resection superior than fulguration/vaporization
- For pain, presacral neurectomy or LUNA procedure.



Cytoreduction is the name of the game…

Resection vs Fulguration/ablation (vaporization)

1-**Fulguration versus resection of experimental endometrial peritoneal implants in the rat. (*Wilson et al)***

2- ***Winkel CA et al study*** **observed that** at 12 months, 96% of excision patients and 69% of vaporization patients were pain-free, falling to 69% and 23%, respectively, at 24 months.

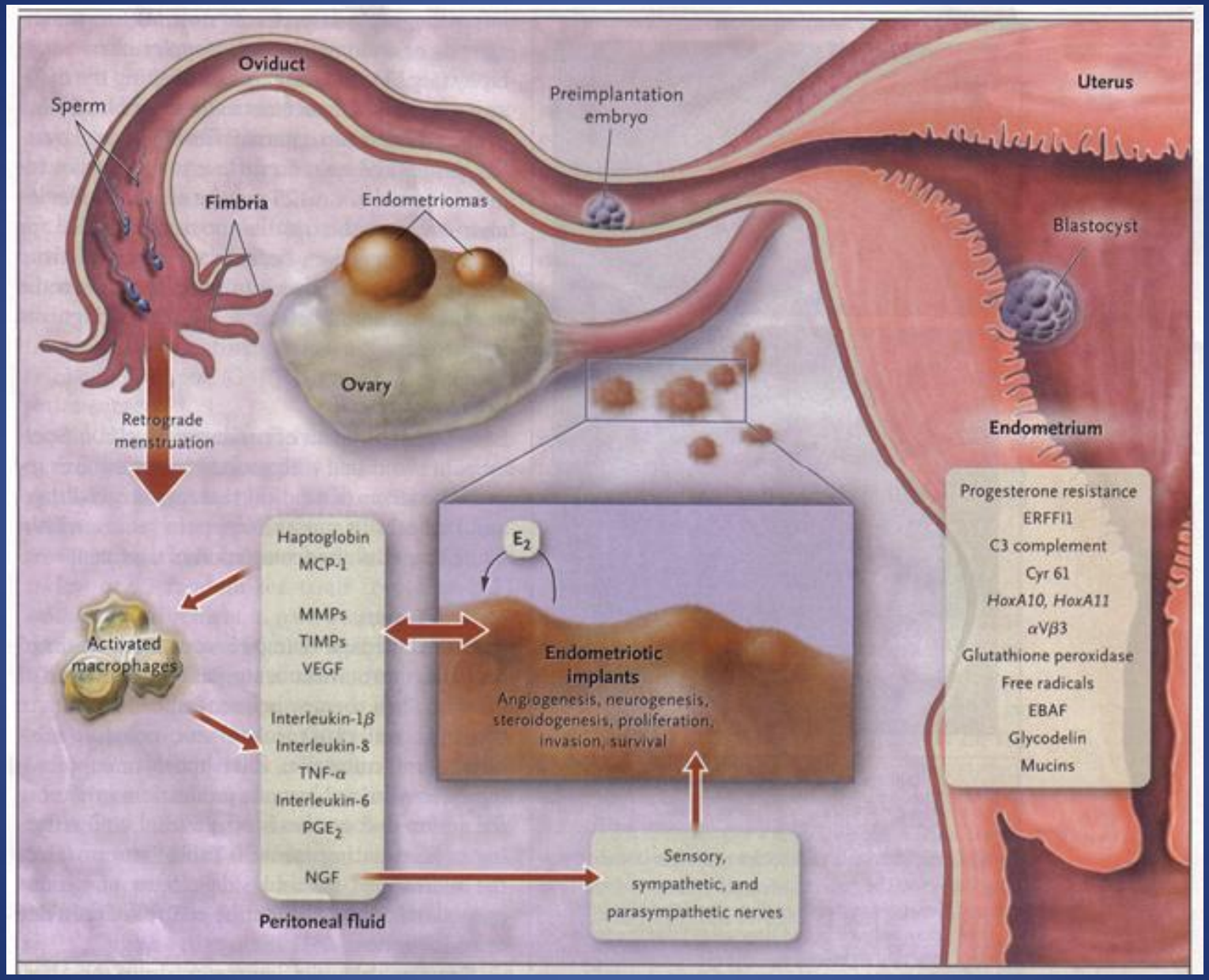
3. Findings from a study of 135 patients with a mean follow-up of 3.2 years revealed reductions in pain scores related to dysmenorrhea, no menstrual pelvic pain, and dyspareunia (Winkel CA et al).

Cytoreduction is the name of the game

- These studies suggest that converting from ablative to excisional therapy will refine diagnosis, reduce disease burden and morbidity, lengthen the time to recurrence, and improve outcomes overall.

Endometriosis and Infertility

- *Distorted Pelvic Anatomy*.
- *Altered Peritoneal Function*.
- *Hormonal and Ovulatory Abnormalities*.
- *Impaired Implantation* (challenged based on b-3 integrin research)
- *Oocyte and Embryo Quality*.
- *Abnormal Uterotubal Transport*.


Oviduct
Sperm
Preimplantation embryo
Uterus
Fimbria
Endometriomas
Blastocyst
Ovary
Retrograde menstruation
Endometrium
Progesterone resistance
ERFFI1
C3 complement
Cyr 61
HoxA10, HoxA11
αVβ3
Glutathione peroxidase
Free radicals
EBAF
Glycodelin
Mucins
E_2
Haptoglobin
MCP-1
MMPs
TIMPs
VEGF
Interleukin-1β
Interleukin-8
TNF-α
Interleukin-6
PGE_2
NGF
Activated macrophages
Endometriotic implants
Angiogenesis, neurogenesis, steroidogenesis, proliferation, invasion, survival
Peritoneal fluid
Sensory, sympathetic, and parasympathetic nerves

ABNROMAL PERITONEAL ENVIROMENT

- TABLE III.—*Possible negative effects of cytokine rich peritoneal fluid on gamete function and embryonic development.*
- *Spermatozoa*
- 1. Impairment of acrosome reaction
- 2. Impairment of sperm motility
- *Oocyte*
- 1. Impaired folliculogenesis
- 2. Impaired oocyte quality
- *Sperm-oocyte interaction impairment*
- *Impaired embryonic development*
- 1-2. Cell stage block
  2. Decreased blastulation

Peritoneal environment in endometriosis

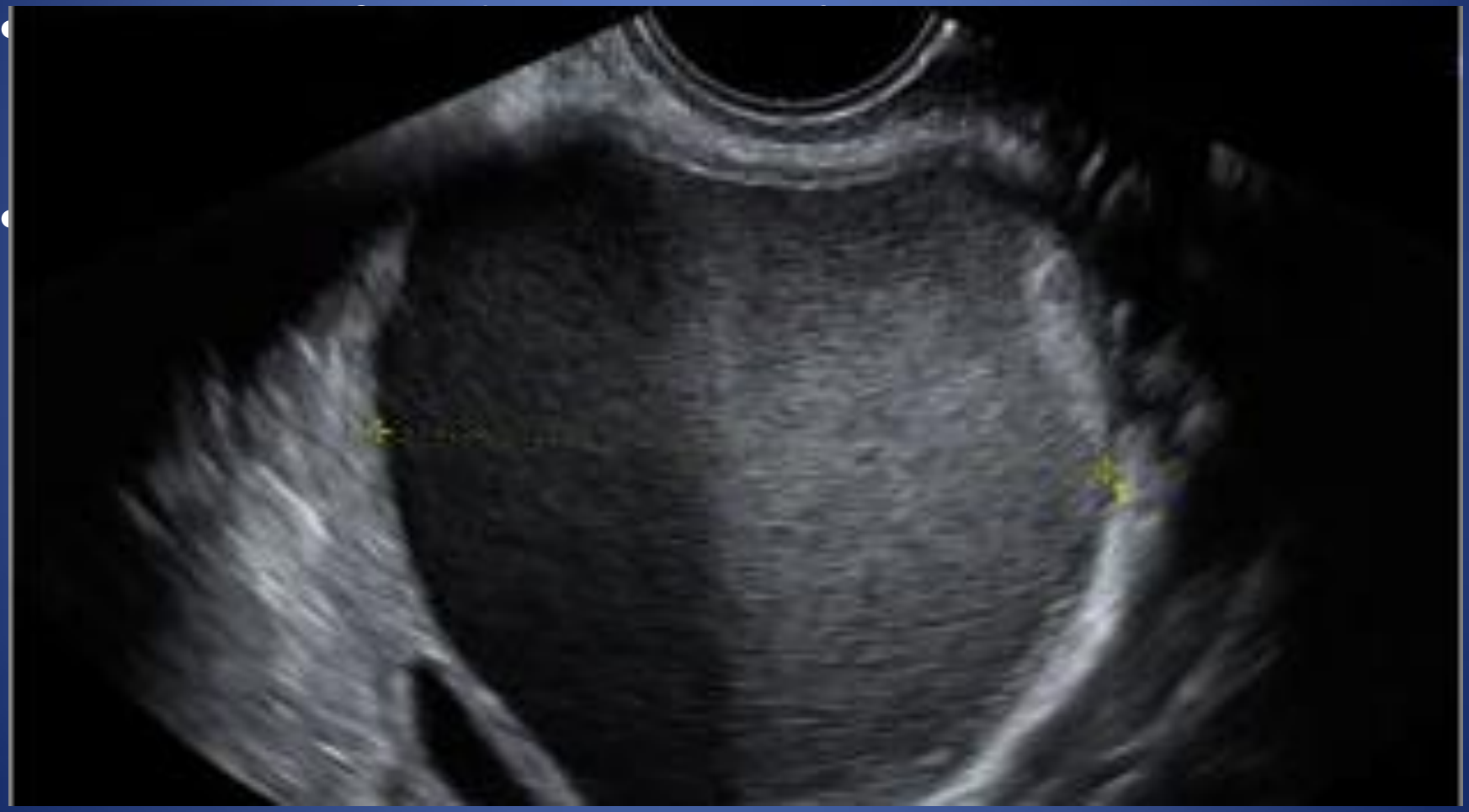
- Randomized clinical trials on the use of surgery for infertility or pain associated with endometriosis have shown a clear benefit. This clearly shows that the peritoneal environment is a critical part of the pathogenesis and treatment of the disease.

Infertility and Endometriosis
BYPASS OR EXCISE?

Bypass → ART

Excise → Laparoscopy

Laparoscopy/Endometriosis and Infertility



Endometriomas and surgery before ART

- Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case–control study☆

Juan A. Garcia-Velasco, M.D., Neal G. Mahutte, M.D., José Corona, M.D., Victor Zúñiga, M.D., Juan Gilés, M.D., Aydin Arici, M.D., Antonio Pellicer, M.D.

Received: February 11, 2003; Received in revised form: April 30, 2003; Accepted: April 30, 2003;

- Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas

Mauro Busacca, MD[a, b], Jennifer Riparini, MD[b, c], Edgardo Somigliana, MD[c], Giulia Oggioni, MD[a, b], Stefano Izzo, MD[b, c], Michele Vignali, MD, PhD[a, b], Massimo Candiani, MD[b, c]VALIDHTMLVALIDHTMLVALIDHTML

Received 19 November 2005, Revised 1 February 2006, Accepted 18 March 2006, Available online 8 May 2006

- Damage to ovarian reserve associated with laparoscopic excision of endometriomas: A quantitative rather than a qualitative injury

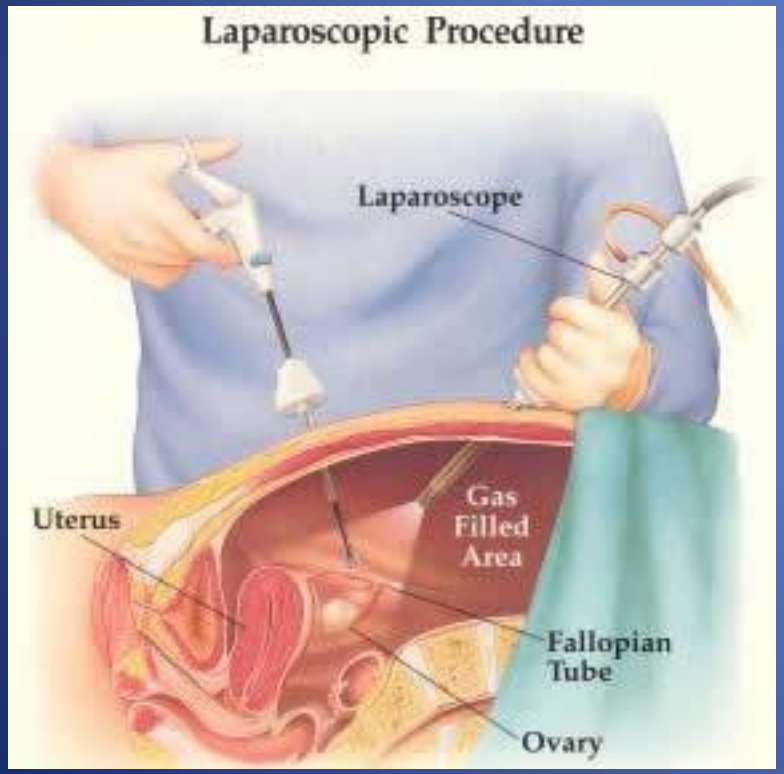
Guido Ragni, MD, Edgardo Somigliana, MD, Francesca Benedetti, MD, Alessio Paffoni, BS, Walter Vegetti, MD, Liliana Restelli, BS, Pier Giorgio Crosignani, MD

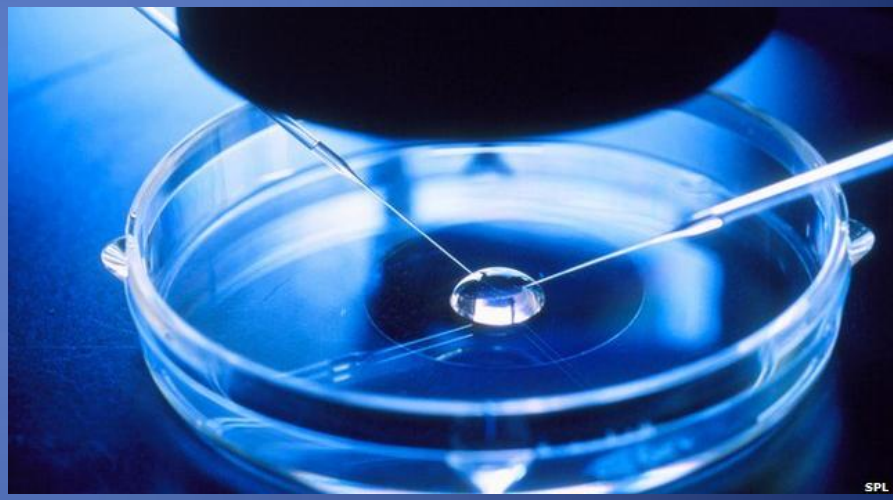
- Endometrioma Excision and Ovarian Reserve: A Dangerous Relation

Mauro Busacca, MD, Michele Vignali, Received 8 August 2008, Accepted 18 December 2008, Available online 3 March 2009

Endometriosis and ART

What should come first?





Endometriosis and ART

- Is the endometrium less receptive in endometriosis?
- Oocyte quality lower?
- Fertilization rates impacted?

Endometriosis and ART

Parameter	Endometroisis (*N*=78)	Tubal (*N*=100)	*P* value
Age	32.7±3.5	31.9±3.7	0.166
BMI	24.3±3.5	25.1±4.2	0.178
D2 FSH	6.9±2.1	6.3±1.9	0.652
D2 LH	5.3±2.4	5.02±2.4	0.442
AMH	2.9±1.4	2.7±1.5	0.382
AFC	11.1±5.1	10.9±3.8	0.722
Combined ovarian volume	11.8±5.8	10.3±4.3	0.043

SD=Standard deviation; BMI=Body mass index; FSH=Follicle-stimulating hormone; LH=Luteinizing hormone; AMH=Anti-müllerian hormone; AFC=Antral follicle count

Effect of endometriosis on implantation rates when compared to tubal factor in fresh non donor in vitro fertilization cycles
Neeta Singh, Kusum Lata, Moumita Naha, Neena Malhotra, Abhinash Tiwari, Perumal Vanamail Journal Human Reproductive Medicine 2014

Endometriosis and ART

	Endometroisis group (*N*=78)	Tubal group (*N*=100)	*P* value
Oocyte retrieved	6.2±3.6	7.9±5.5	0.016
M2 oocyte[a]	69.5	69.3	0.944
Fertilization rate[a]	64.8	70.2	0.044
Cleavage rate[a]	94.9	96.4	0.298
Grade 1 embryo[a]	49.6	50.4	0.767
No of embryo transfered	2.4±1.1	2.68±1.2	0.276
Clinical pregnancy	19 (19/78)[b]	34 (34/100)[c]	0.222

[a]percentage. [b]Embryo transfer not done in 12 cases. [c]Embryo transfer not done in 11 cases

Endometriosis and ART

- There is insufficient evidence to indicate that resection of endometriomas prior to IVF improves outcomes.
- IVF success rates in women with endometriosis appear to be diminished compared to women with tubal factor infertility; however, IVF likely maximizes cycle fecundity for those with endometriosis.
- Women with endometriosis have higher incidences of preterm delivery, pre-eclampsia, antepartum bleeding/placental complications, and cesarean section when compared to women without endometriosis.

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

Endometriosis treatment decision making

- Not so easy and clear cut
- Each patient should be individualized
- Decision making should encompass all potential avenues