MEDIXY
CENTRE DE MÉDECINE DE LA REPRODUCTION

Endometriosis

Dr PD Didier Chardonnens

Training in Research in Reproductive Health
Geneva 2005

Endometriosis

1. Introduction
2. Genetics
3. Endocrinology
4. Immunology
5. Apoptosis
6. Implantation
7. Diagnosis
8. Medical treatment
9. Surgical treatment
10. Future

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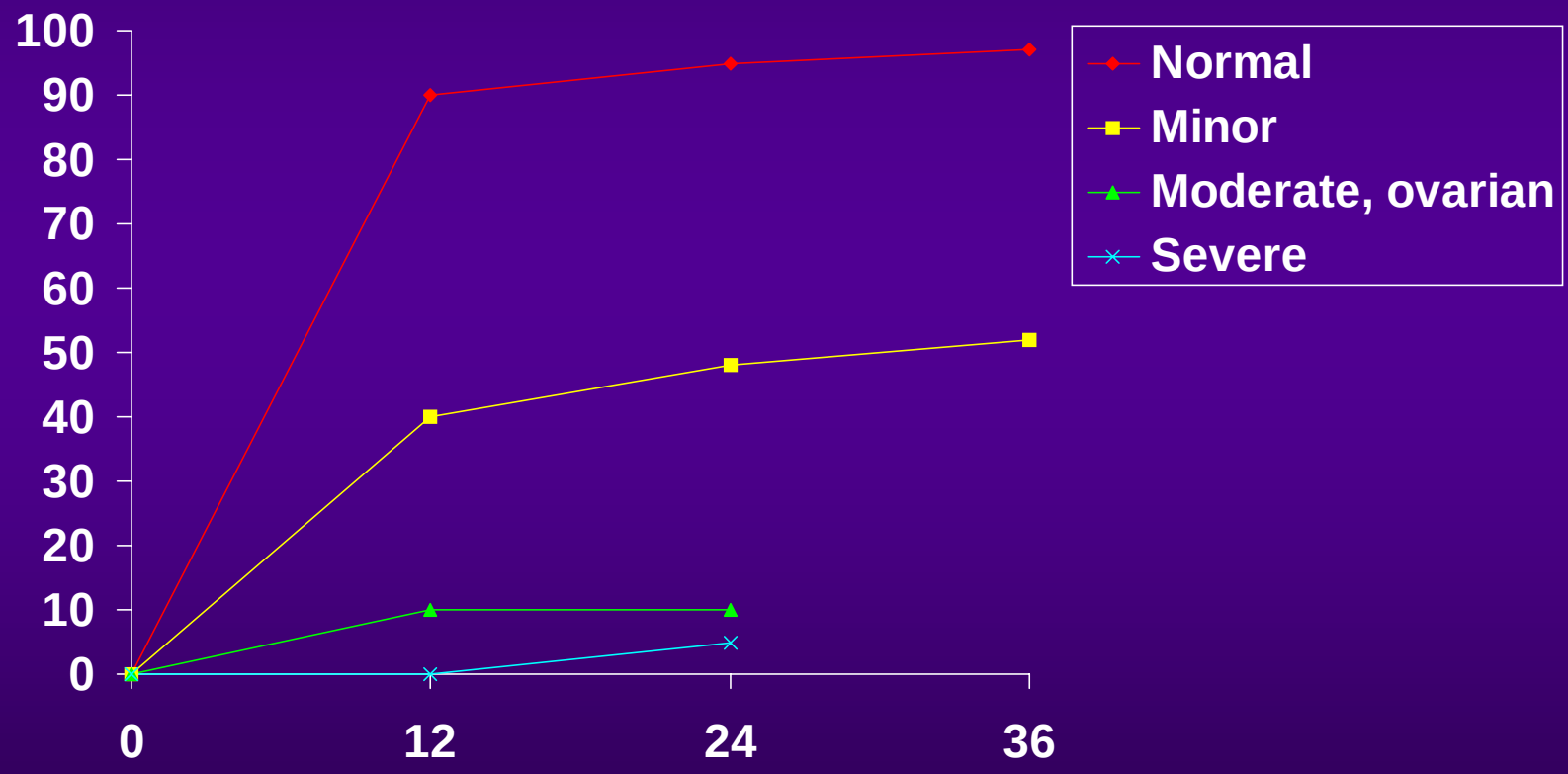
Epidemiology

S Missmer et al. Obst Gynecol Clin N Am 2003.

- 2-18 % of women of reproductive age
- 5 to 21 % of women with admission to the hospital because of chronic pelvic pain
- 5 to 50% of women suffering from infertility

Endometriosis and fertility



Epidemiologic findings

S Missmer et al. Obst Gynecol Clin N Am 2003.

- Menstrual history
  - Early Menarche
  - Short cycles
- Body habitus
  - Greater height
  - Lower BMI
- Lifestyle
  - Alcohol, caffeine
  - Dioxine

Epidemiologic findings

S Missmer et al. Obst Gynecol Clin N Am 2003.

- Immune disorders
  - Rheumatoid arthritis (2 vs 0.8%)
  - LED (0.8 vs 0.05%
  - Hypothyroidism (6.8 vs 1.5%)
  - Hyperthyroidism (1.5 vs 1.1%)
  - MS (0.6 vs 0.1%)
- Family clustering
- Caucasian women

Epidemiologic findings

S Missmer et al. Obst Gynecol Clin N Am 2003.

- Progressive disease in a significant proportion of women (30-60 %)
  - Deterioration approximately 50 %
  - Improvement approximately 30 %
  - No change in approximately 20 %

Etiology

- Retrograde menstruation
- Immune system tolerance
- Coelomic metaplasia

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Genetics

Kennedy et al Sem Reprod Med 2003

- Family clustering
  - 6 to 15 times increased prevalence in first degree relatives
- Concordance between monozygotic and dizygotic twins
- Future with positional cloning
  - Suggestive linkage has been reproted for at least one chromosomal locus (ENDOGENE study)

Genetics

Kennedy et al Sem Reprod Med 2003

- There are aberrant genes expression in the ectopic endometrium
  - Aromatase
  - Endometrial bleeding factor
  - 17 beta OH-steroid dehydrogenase
  - HOXA-10, HOXA-11
  - LIF
  - MMP 7 and 11
  - Progesterone receptors

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Paracrinology

Gurates et al Sem Reprod Med 2003

- Increased endometrial concentrations of E2
  - Aromatase overexpression
  - Decreased 17 beta OH-steroid dehydrogenase expression
  - Decreased progesterone B receptor expression

Paracrinology

Gurates et al Sem Reprod Med 2003

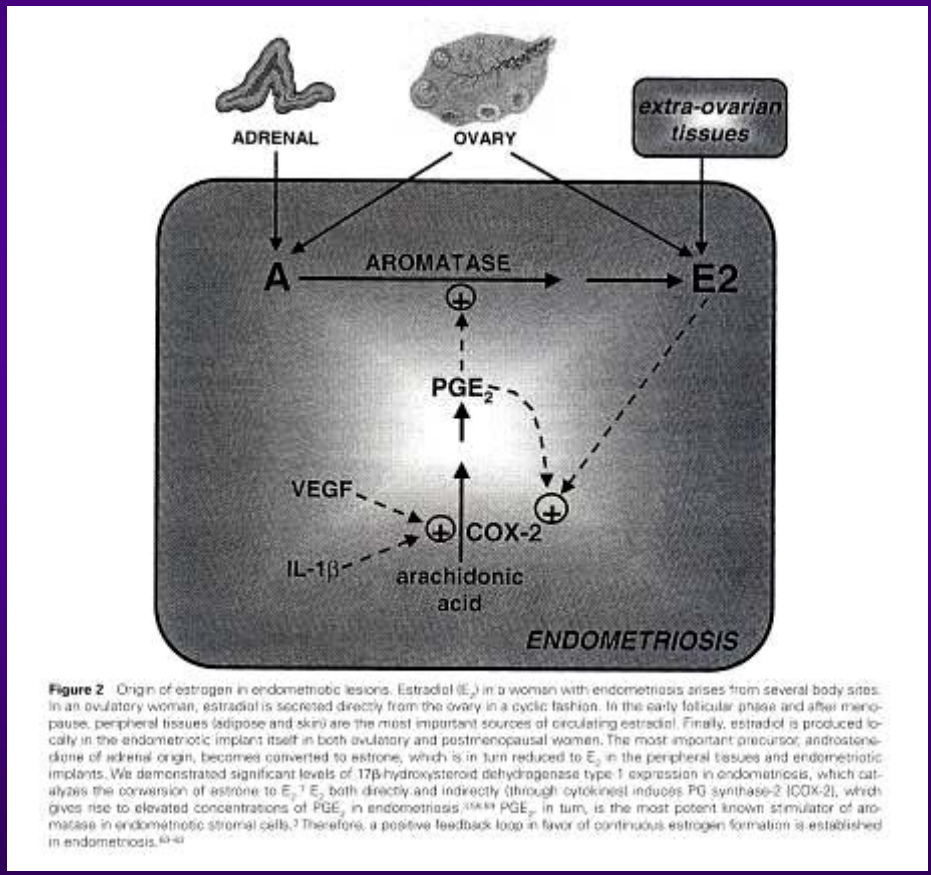

Figure 2 Origin of estrogen in endometriotic lesions. Estradiol (E_2) in a woman with endometriosis arises from several body sites. In an ovulatory woman, estradiol is secreted directly from the ovary in a cyclic fashion. In the early follicular phase and after menopause, peripheral tissues (adipose and skin) are the most important sources of circulating estradiol. Finally, estradiol is produced locally in the endometriotic implant itself in both ovulatory and postmenopausal women. The most important precursor, androstenedione of adrenal origin, becomes converted to estrone, which is in turn reduced to E_2 in the peripheral tissues and endometriotic implants. We demonstrated significant levels of 17β-hydroxysteroid dehydrogenase type 1 expression in endometriosis, which catalyzes the conversion of estrone to E_2.[1] E_2 both directly and indirectly (through cytokines) induces PG synthase-2 (COX-2), which gives rise to elevated concentrations of PGE_2 in endometriosis.[2,3,4,5] PGE_2, in turn, is the most potent known stimulator of aromatase in endometriotic stromal cells.[1] Therefore, a positive feedback loop in favor of continuous estrogen formation is established in endometriosis.[6–8]

Paracrinology

Gurates et al Sem Reprod Med 2003

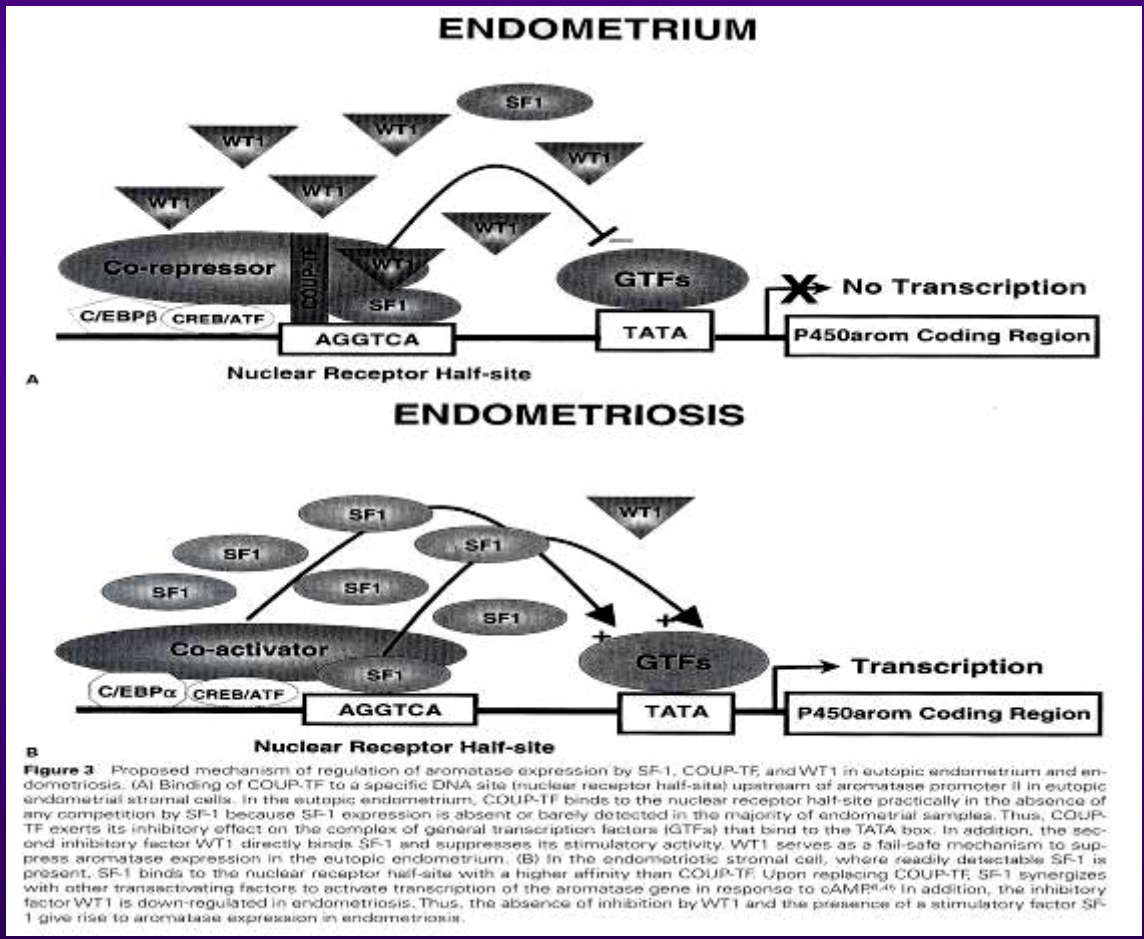

Figure 3 Proposed mechanism of regulation of aromatase expression by SF-1, COUP-TF, and WT1 in eutopic endometrium and endometriosis. (A) Binding of COUP-TF to a specific DNA site (nuclear receptor half-site) upstream of aromatase promoter II in eutopic endometrial stromal cells. In the eutopic endometrium, COUP-TF binds to the nuclear receptor half-site practically in the absence of any competition by SF-1 because SF-1 expression is absent or barely detected in the majority of endometrial samples. Thus, COUP-TF exerts its inhibitory effect on the complex of general transcription factors (GTFs) that bind to the TATA box. In addition, the second inhibitory factor WT1 directly binds SF-1 and suppresses its stimulatory activity. WT1 serves as a fail-safe mechanism to suppress aromatase expression in the eutopic endometrium. (B) In the endometriotic stromal cell, where readily detectable SF-1 is present, SF-1 binds to the nuclear receptor half-site with a higher affinity than COUP-TF. Upon replacing COUP-TF, SF-1 synergizes with other transactivating factors to activate transcription of the aromatase gene in response to cAMP[6,45] In addition, the inhibitory factor WT1 is down-regulated in endometriosis. Thus, the absence of inhibition by WT1 and the presence of a stimulatory factor SF-1 give rise to aromatase expression in endometriosis.

Paracrinology

Gurates et al Sem Reprod Med 2003

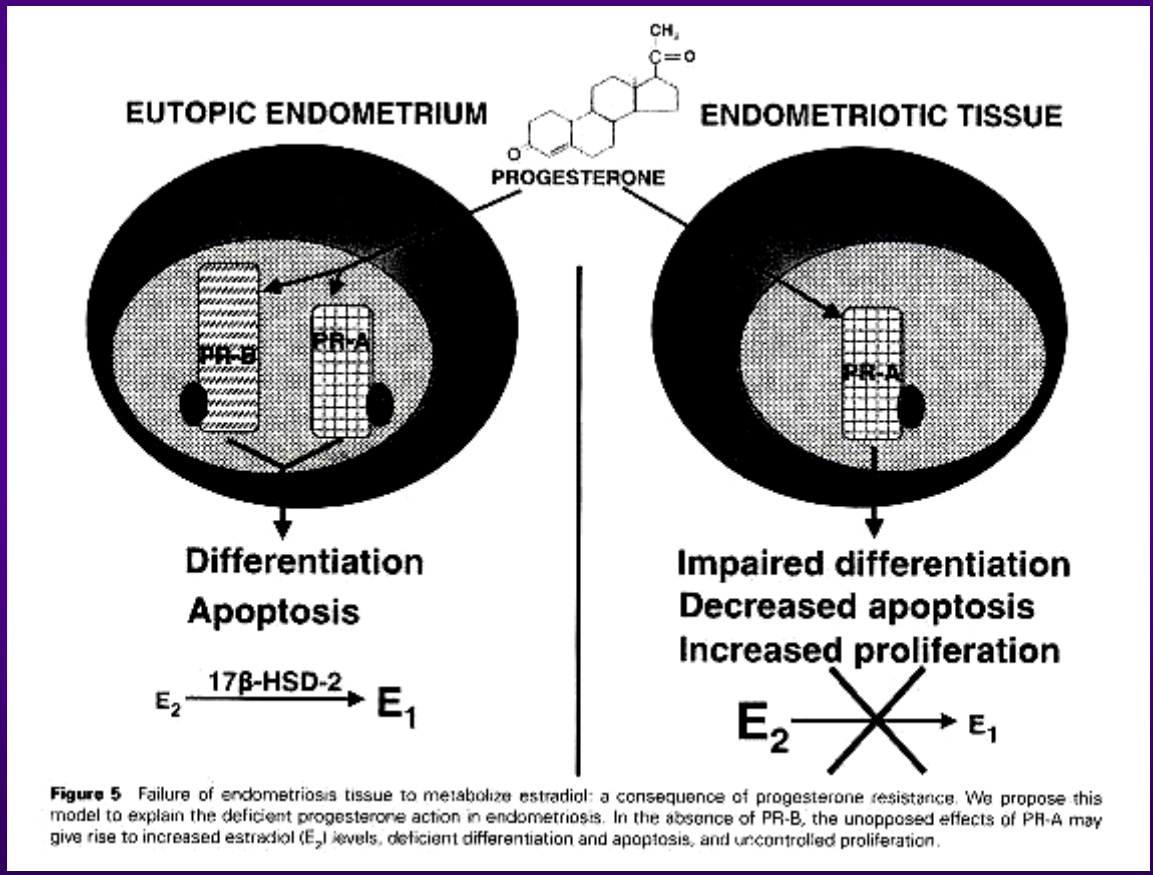

Figure 5 Failure of endometriosis tissue to metabolize estradiol: a consequence of progesterone resistance. We propose this model to explain the deficient progesterone action in endometriosis. In the absence of PR-B, the unopposed effects of PR-A may give rise to increased estradiol (E_2) levels, deficient differentiation and apoptosis, and uncontrolled proliferation.

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Cellular immune response

- Increased number of peritoneal macrophages with aberrant immune response
  - Increased release of growth promoting cytokines with impaired scavenger function
- Diminished cytotoxicity of NK cells
  - Increased Killer Inhibitor Receptors (KIR)

Cellular immune response

- Polyclonal activation of B lymphocytes with auto antibodies against a certain number of tissues
- Increase in cytokines
  - IL1 and IL1R
  - IL8
  - Monocytic Chemotactic protein (MRCP-1)
  - RANTES
  - TNF alpha
  - VEGF

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Apoptosis

Garcia-Velasco et al Sem Reprod Med 2003

- There is an increased apoptosis of activated T cells

Apoptosis

Garcia-Velasco et al Sem Reprod Med 2003

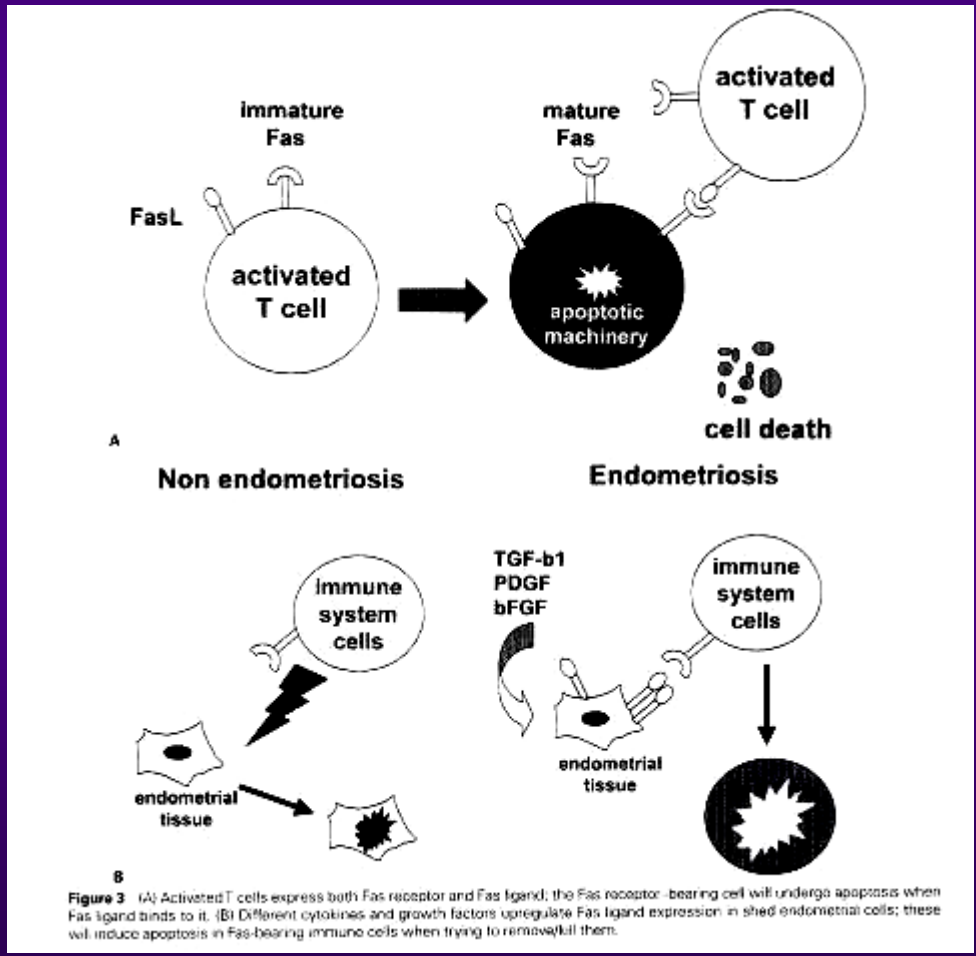

Figure 3 (A) Activated T cells express both Fas receptor and Fas ligand; the Fas receptor–bearing cell will undergo apoptosis when Fas ligand binds to it. (B) Different cytokines and growth factors upregulate Fas ligand expression in shed endometrial cells; these will induce apoptosis in Fas-bearing immune cells when trying to remove/kill them.

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MMPs and endometriosis

Osteen et al Sem Reprod Med 2003

- Relative insensitivity to progesterone leads to increased MMP3 and 7 in eutopic secretory endometrium of endometriotic women with diminished TIMP3 expression

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Non invasive diagnosis

- Clinical examination
- Ultrasound
- MRI
- Serum markers

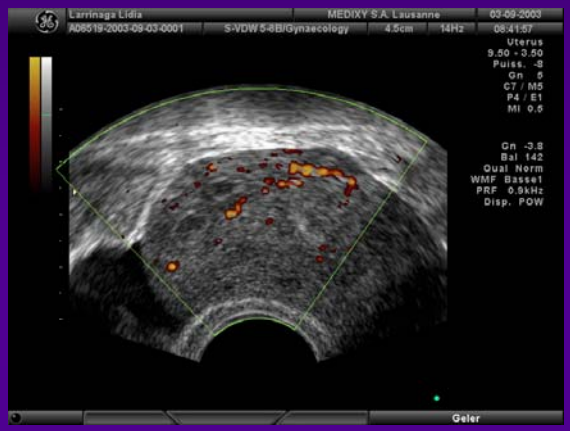
Clinical examination

Spaczinski et al.Semin Reprod Med 2003

Table 1 Reliability of Pelvic Examination in Diagnosis of Endometriosis

Reference (*n* = Number of Patients)	Finding/Location	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ripps et al, 1992[89] (*n* = 94)	Focal pelvic tenderness (overall)	79	32	65	50
	Uterosacral ligaments	56–58	72–80	54–62	60–64
	Cul-de-sac	37	97	87	70
	Adnexa	38–43	72–80	54–62	60–64
Koninckx et al, 1996[84] (*n* = 140 and **n* = 55)	Pelvic induration and/or nodularities	36			
	Pelvic induration and/or nodularities at menstruation (overall)*	79	92		
	Deep endometriosis*	77	76	88	
	Endometrioma*	78	70		
	Severe cul-de-sac*	92	77		
Eskenazi et al, 2001[90] (*n* = 90)	Pelvic induration and/or nodularities of uterosacral ligaments/cul-de-sac and/or fixed adnexal mass, fixed uterus and/or vaginal endometriotic lesion	76	74	67	81
Chapron et al, 2002[85] (*n* = 160)	Painful pelvic induration and/or nodularities (overall)	90			
	Bladder endometriosis	73			
	Uterosacral ligaments	83			
	Vaginal endometriosis	100			
	Intestinal endometriosis	94			

Ultrasound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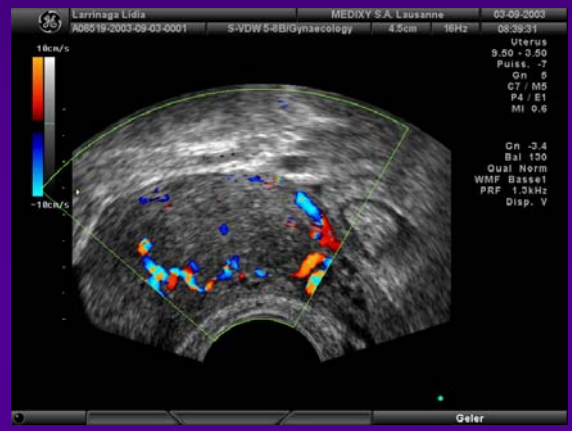
MEDIXY S.A. Lausanne
03-09-2003
Uterus
Geler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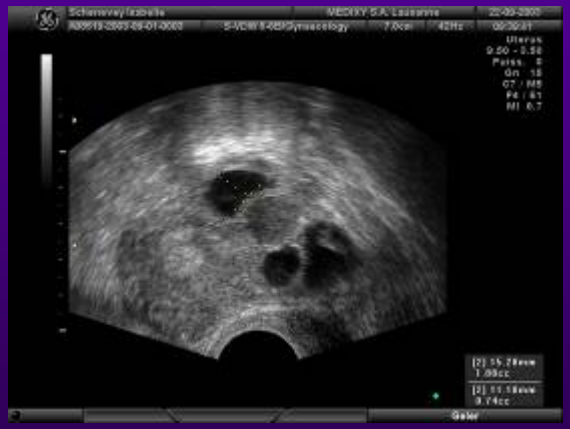
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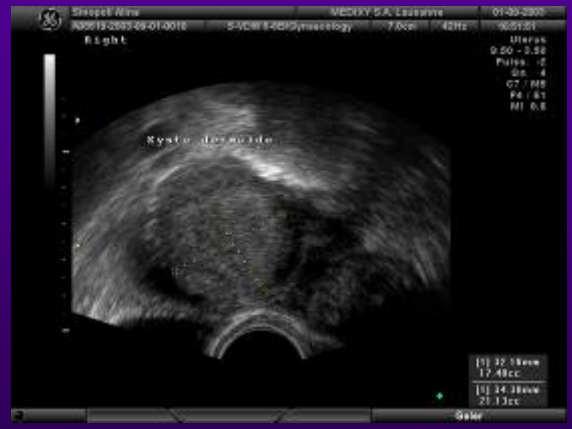
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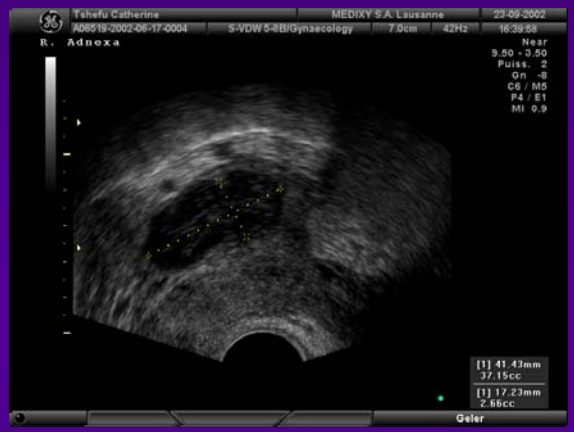
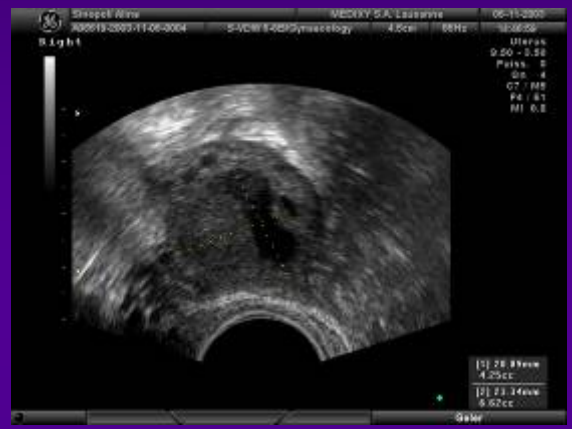
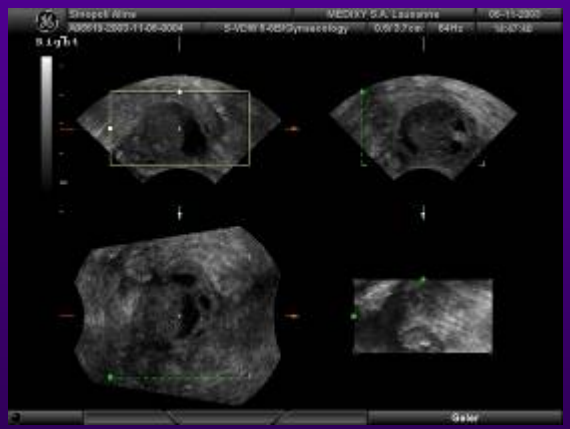
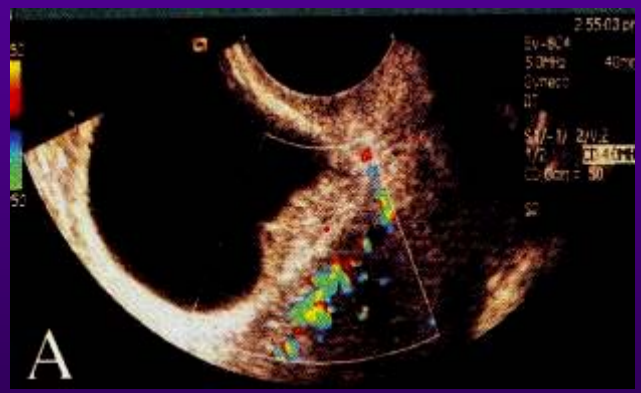
Ultrasound









Ultrasound and endometriosis

Spaczinski et al.Semin Reprod Med 2003

Table 3 Reliability of Transvaginal Ultrasound in Diagnosis of Endometriomas

Reference (*n* = Number of Patients)	Ultrasound Mode; Indication for Surgery	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
Mais et al, 1993[178] (*n* = 236)	B-mode; infertility, CPP, fibroids, adnexal mass	10	75	99	78	98	
Guerriero et al, 1996[179] (*n* = 118)	B-mode; adnexal mass	33	85	97	94	93	0.84
Alcazar et al, 1997[126] (*n* = 78)	B-mode	33	89	91	84	95	
	B-mode + color Doppler imaging (CDI); adnexal mass		76	89	82	82	
Guerriero et al, 1998[127] (*n* = 170)	B-mode	34	81	96	92	91	0.80
	Color Doppler energy (CDE); adnexal mass		90	97	95	95	0.88
Pascual et al, 2000[128] (*n* = 352)	Color Doppler imaging (CDI); adnexal mass	52	92	95	96	92	
Eskenazi et al, 2001[90] (*n* = 90)	B-mode; adnexal mass, fibroids, CPP, infertility	23	57	98	95	76	0.58

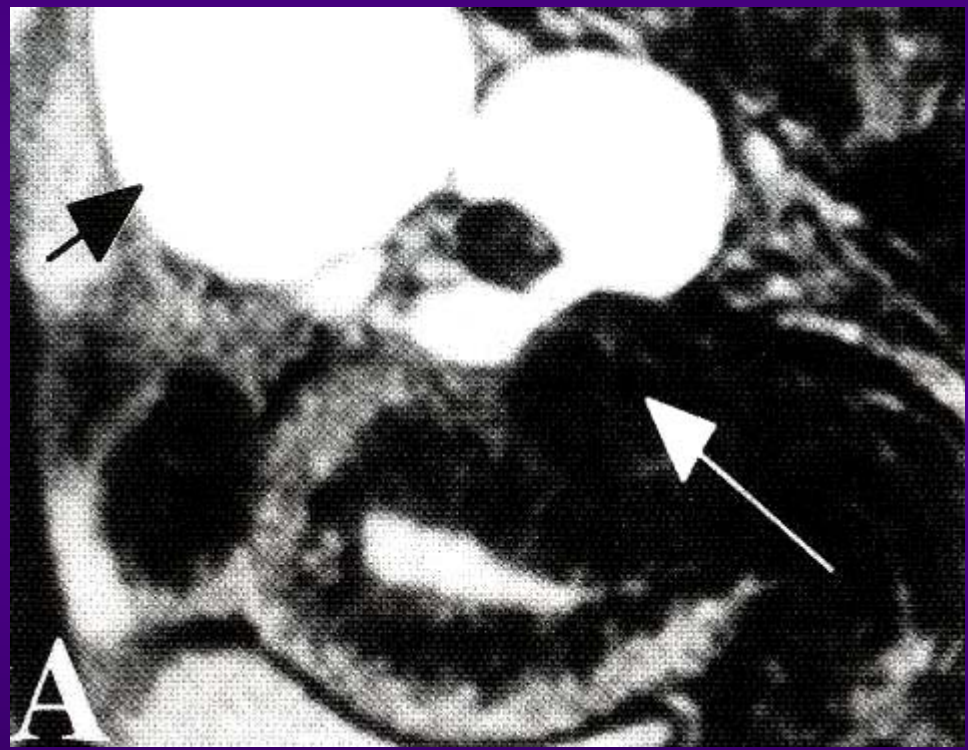
CA 125

Spaczinski et al.Semin Reprod Med 2003

Table 2 Reliability of CA-125 in Diagnosis of Endometriosis (Cutoff Level used 35 IU/mL Unless Stated Otherwise)

Reference (*n* = Number of Patients)	Assay; Timing of Sample Collection	Stage	Sensitivity (%)	Specificity (%)
Barbieri et al, 1986[91]	Standard assay; timing of	All	17	96
(*n* = 147)	sample collection unknown	III+IV	54	96
Patton et al, 1986[177]	Standard assay; timing of	All	14	93
(*n* = 113)	sample collection unknown	III+IV	18	93
Pittaway and Fayez, 1986[92]	Standard assay (cutoff level	All	17	93
(*n* = 414)	30 IU/mL); follicular phase	III+IV	42	93
Koninckx et al, 1992[94]	Standard assay; late luteal	All	13	96
(*n* = 259)	phase	III+IV	31	94
O'Shaughnessy et al, 1993[96]	Standard assay; menstrual	All	27	100
(*n* = 100)		III+IV	67	100
Hornstein et al, 1995[97]	Standard assay; early	All	16	92
(*n* = 123)	follicular phase	III+IV	40	92
	CA 125 II assay; early	All	23	94
	follicular phase	III+IV	60	94
Medl et al, 1997[114]	Standard assay; timing of	All	36	92
(*n* = 368)	sample collection unknown	III+IV	44	86
Chen et al, 1998[107]	CA 125 II assay;	All	61	88
(*n* = 157)	luteal phase	III+IV	87	88

MRI



MRI and endometriosis

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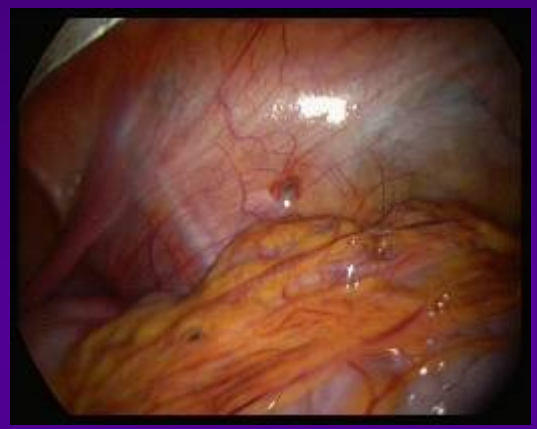
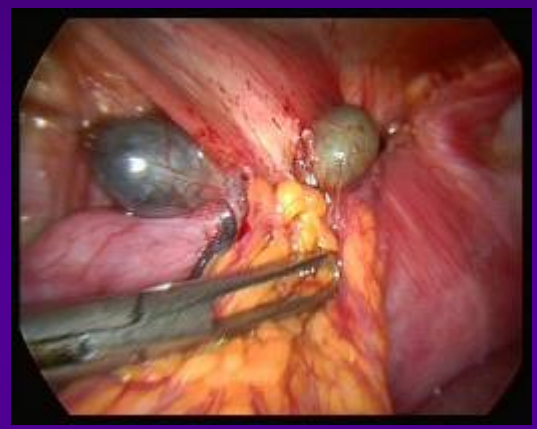
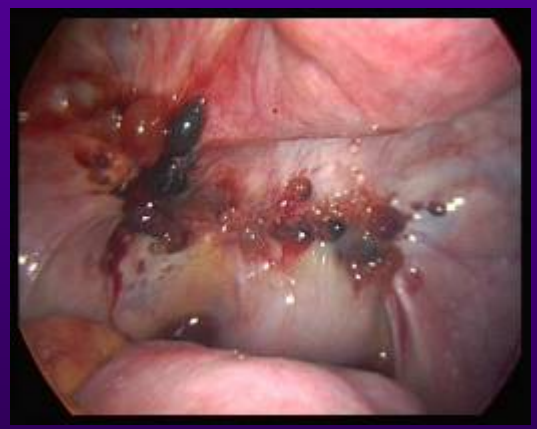
Table 4 Reliability of Magnetic Resonance Imaging in Diagnosis of Endometriosis

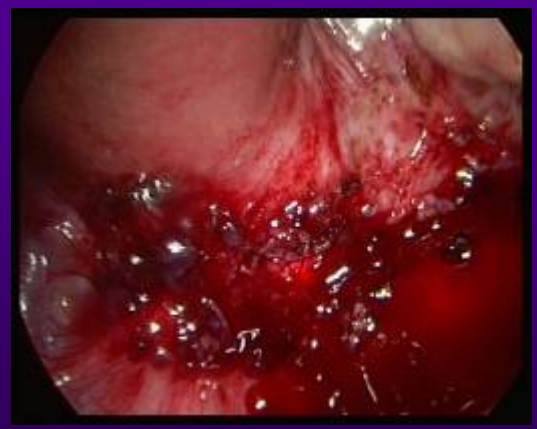
Reference	Assay	Lesion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Zawin et al, 1989[136]	T1- and T2-weighted imaging	All lesions	71	82	77	76
Arrive et al, 1989[135]	T1- and T2-weighted imaging	All lesions	64	60	—	—
		Implants	13	60		
		Adhesions	48	60		
		Endometrioma	88	60		
Togashi et al, 1991[141]	T1- and T2-weighted imaging	Endometrioma	90	98	94	97
Sugimura et al, 1993[142]	T1- and T2-weighted imaging	Endometrioma	82	91	90	84
		Implants	11	98	33	90
	T1/T2 and fat-suppressed imaging	Endometrioma	91	94	94	92
		Implants	47	97	64	94
Ha et al, 1994[137]	T1- and T2-weighted imaging	Implants	27	98	93	55
	Fat-suppressed imaging		61	87	83	67

Invasive diagnosis

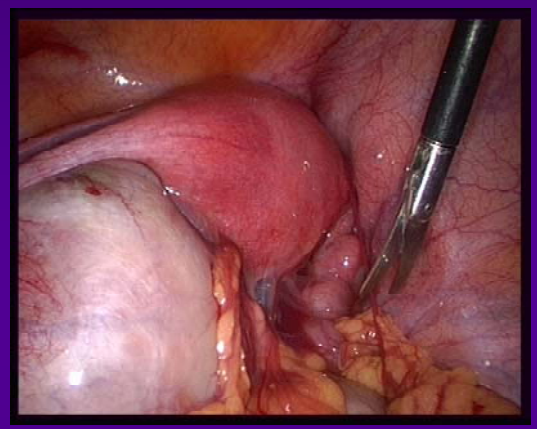


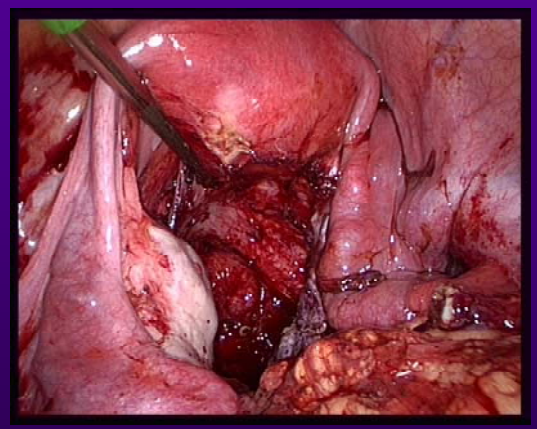


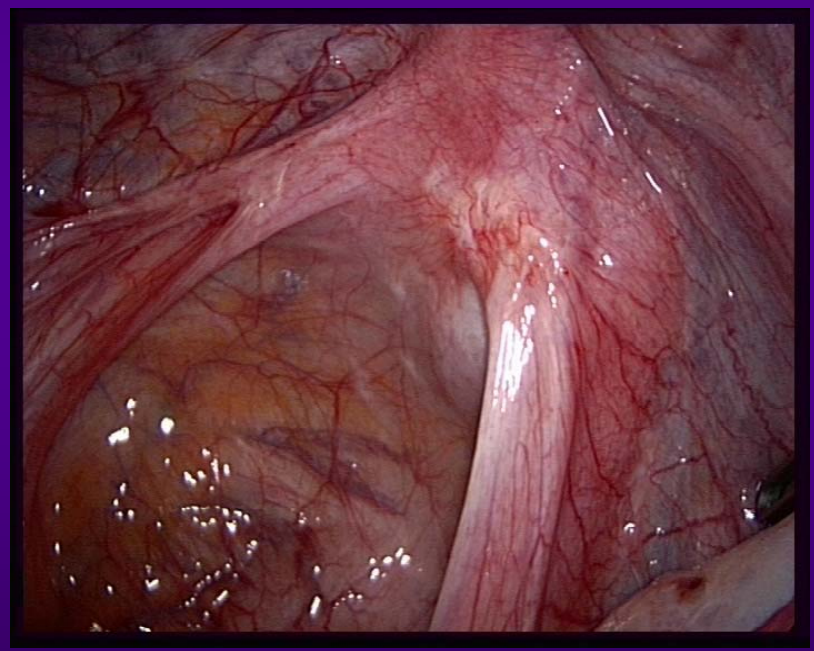




Invasive diagnosis







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 implants types as red (RB), red, red-pink, flamelike vesicular blebs, clear vesicles), white (W opacifications, peritoneal defects yellow-brown), or black (BB) black, hemosiderin deposits, blue). Denote percent of total described as R ___%, W ___% and B ___%. Total should equal 100%.

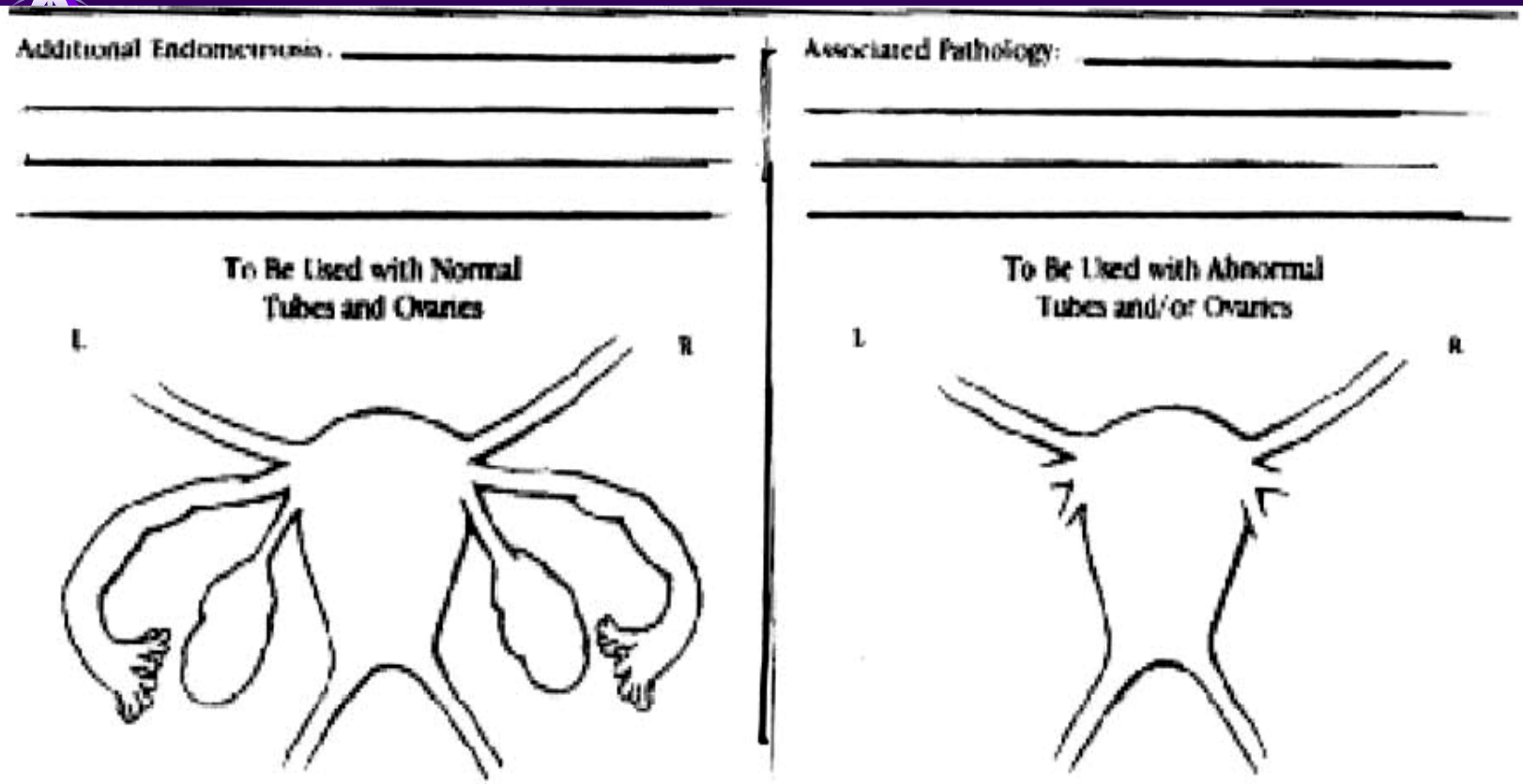


Fig. 2. The American Fertility Society revised classification of endometriosis. (*From* American Fertility Society. Revised classification of endometriosis. Fertil Steril 1985;43:351–2; with permission.)

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Pain treatment

Table 3
Placebo-controlled trials evaluating medical treatments of endometriosis-associated pain

Medication	Sample size[a]	Duration of therapy	Results
Danazol [4]	$n = 18$	6 mo	Significant reductions in pain scores
600 mg/d			Decrease in number and size of endometriotic lesions
Provera [4]	$n = 16$	6 mo	Significant reductions in pain scores
100 mg/d			Decrease in number and size of endometriotic lesions
GnRH agonists			
Lupron Depot [55]	$n = 32$	6 mo	90% complete relief of dysmenorrhea
• 3.75 mg intramuscularly every 28 d			Significant reductions in pelvic pain, tenderness, and nodularity
Triptorelin [56]	$n = 24$	6 mo	Significant reductions in pain scores
• 3.75 mg intramuscularly every 28 d			Decrease in number and size of endometriotic lesions

[a] Number of participants who received the active study medication.

Side effects

Box 2. Side effects of progestins

- Breakthrough bleeding (40% – 80%)
- Weight gain, fluid retention (40% – 50%)
- Acne (20%)
- Breast tenderness (10%)
- Headaches (10%)
- Mood changes (10%)
- Muscle cramps
- Adverse lipid changes (↑ LDL, ↓ HDL)

Estimates of prevalence are a composite from published clinical trials [34,36,48].

Side effects

Box 1. Side effects of danazol[a]

Androgenic
- Hot flashes (50%)
- Acne, oily skin (30% – 60%)
- Weight gain, fluid retention (30% – 50%)
- Muscle cramps (30%)
- Adverse lipid changes(↓HDL, ↑LDL)
- Decreased breast size (25%)
- Hirsutism (15%)
- Irreversible deepening of the voice (8%)

Breakthrough bleeding (40%)
Mood changes (20%)
Liver damage

[a] Estimates of prevalence are a composite from published clinical trials [4,34,38].

Side effects

Box 3. Side effects of GnRH agonists

- Hot flashes (80% – 90%)
- Sleep disturbances (60% – 90%)
- Vaginal dryness (30%)
- Joint pain (30%)
- Breakthrough bleeding (20% – 30%)
- Headaches (20% – 30%)
- Mood change (10%)
- Bone loss (↓ bone density 5% – 6%)
- Adverse lipid changes (↑ LDL, ↓ HDL)

Estimates of prevalence are a composite from published clinical trials [19,55,56,65].

Add back therapy

Box 4. Add-back regimens proven to preserve bone density for 1 year

- Norethindrone acetate 5 – 10 mg orally every day
- Premarin 0.625 – 1.25 mg + norethindrone acetate 5 mg orally every day
- Cyclic etidronate 400 mg + Os Cal 500 mg + norethindrone acetate 2.5 mg orally every day

Medical treatment strategy for endometriosis pain

Box 6. Suggested approach to endometriosis-associated pain

1st line: continuous low-dose monophasic oral contraceptive 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[a]

[a] May consider low-dose (100–200 mg every day) danazol if other therapies poorly tolerated.

Post operative medical treatment

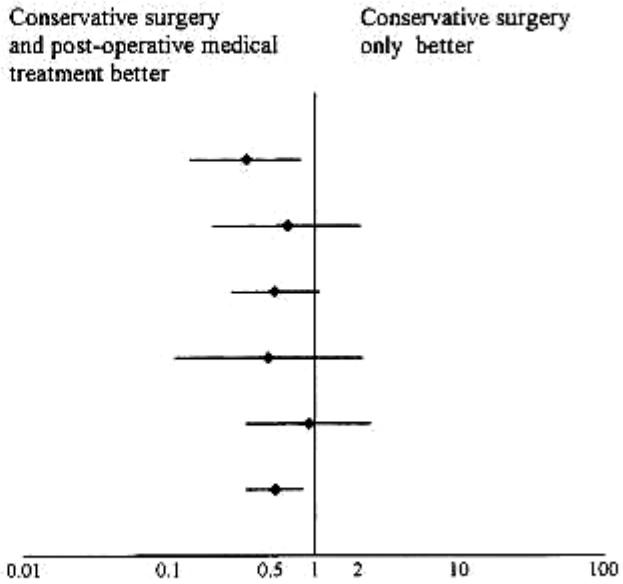
Box 5. Postoperative therapies proven to delay the recurrence of endometriosis if given for at least 6 months

- Medroxyprogesterone acetate 100 mg orally every day [34]
- Danazol 600 mg orally every day [34]
- Nafarelin 200 g intranasally twice daily [91]
- Goserelin 3.6 mg sc every month [95]

Post op medical treatment for pain RCT trials

Vercellini et al. Obstet Gynecol Clin N Am 2003

Trial Identifier	Pain Recurrences / Patients	
	Experimental	Control
Hornstein *et al.* (42)	15/49	25/44
Bianchi *et al.* (47)	7/31	9/29
Vercellini *et al.* (46)	19/81	27/74
Muzii *et al.* (43)	3/33	6/35
Busacca *et al.* (48)	10/44	11/45
Common odds ratio		



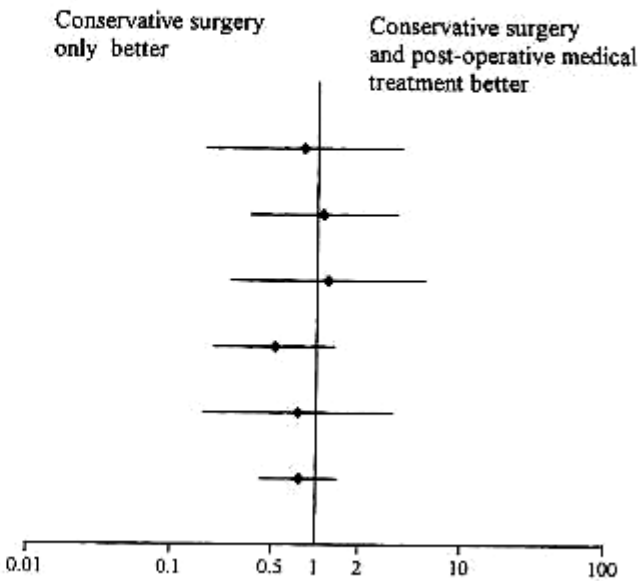
Breslow-Day = 2.12 (P = 0.71)

Post op medical treatment RCT trials for fertility

Vercellini et al. Obstet Gynecol Clin N Am 2003

Trial Identifier	Pregnancies / Patients	
	Experimental	Control
Telimaa *et al.* (45)	5/40*	3/20
Parazzini *et al.* (44)	7/36	7/39
Bianchi *et al.* (47)	6/11	8/16
Vercellini *et al.* (46)	8/76	14/76
Busacca *et al.* (48)	5/15	6/15
Common odds ratio		

Breslow-Day = 0.95 ($P = 0.91$)



Effect of medical treatment on IVF outcome

Surrey et al Fertil Steril 2002

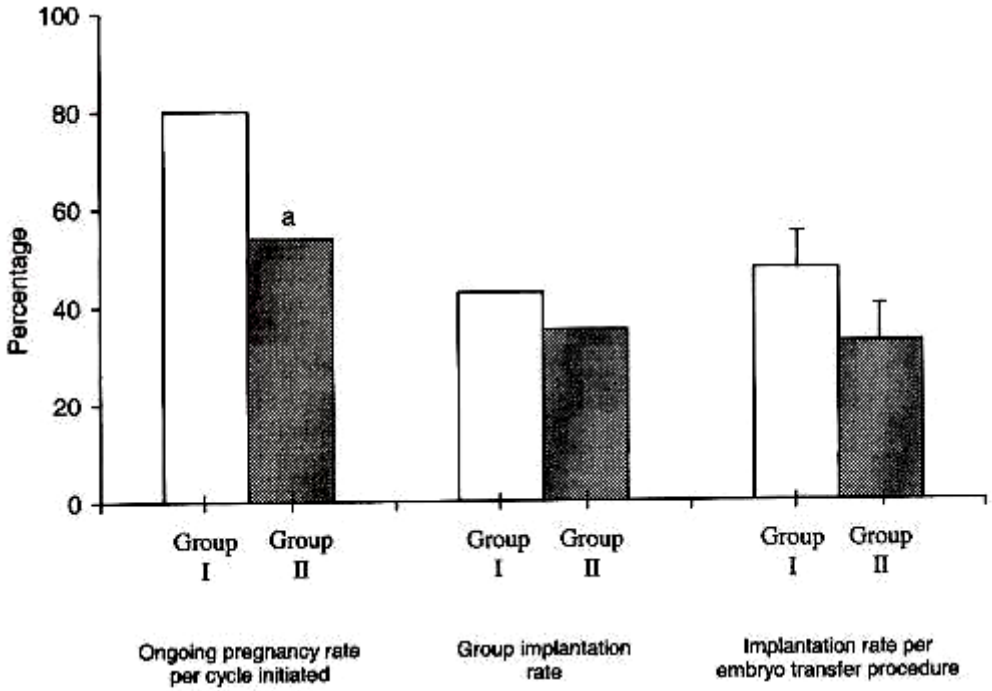


Fig. 3. IVF cycle outcomes for patients with endometriosis who were pretreated with a GnRH agonist for 3 months (group I) immediately before controlled ovarian hyperstimulation or undergoing standard controlled ovarian hyperstimulation (group II). $P<0.05$ versus group I (*a*). (*From* Surrey ES, Silverberg KM, Surrey MW, Schoolcraft WB. The effect of prolonged GnRH agonist therapy on in vitro fertilization-embryo transfer cycle outcome in endometriosis patients: a multicenter randomized trial. Fertil Steril 2002;78:699–704; reprinted with permission from the American Society for Reproductive Medicine.)

IUI and ovarian stimulation in endometriosis

Tummon et al Fertil Steril 1997

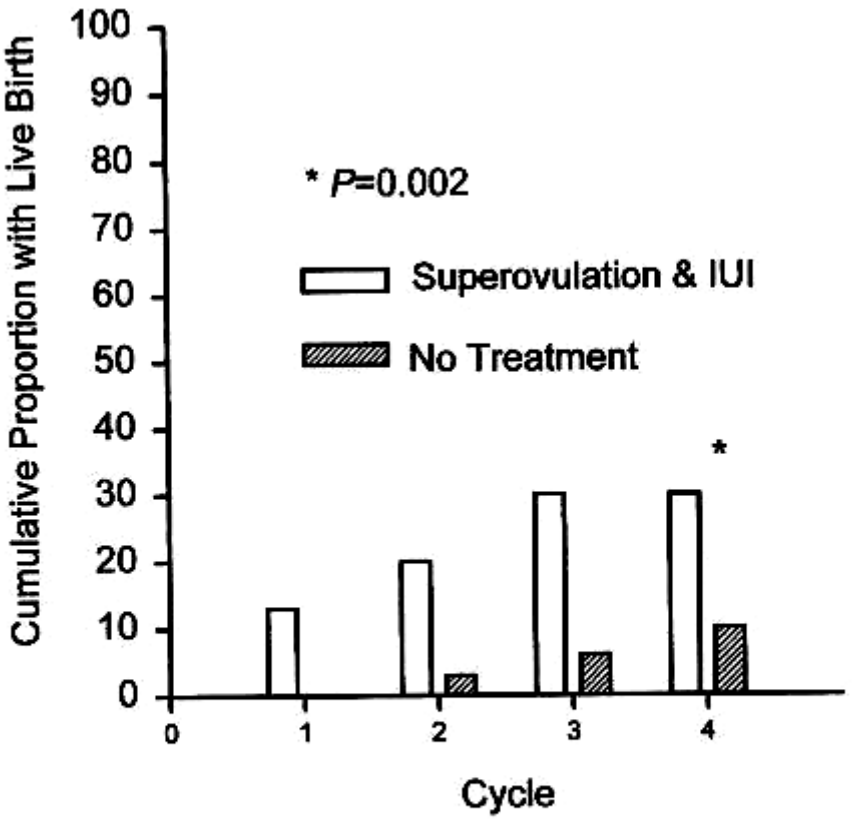
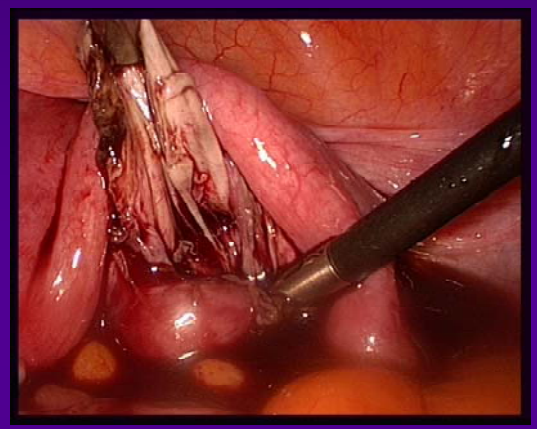


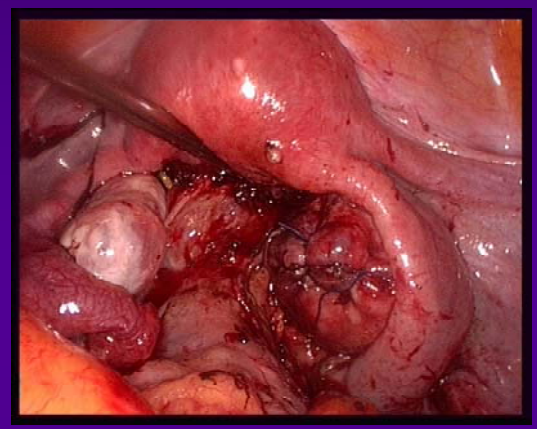
Fig. 2. Cumulative proportion of endometriosis patients with live births after undergoing superovulation and intrauterine insemination versus expectant management. (*From* Tummon IS, Asher LJ, Martin JSB, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril 1997;68:8–12; reprinted with permission from the American Society for Reproductive Medicine.)

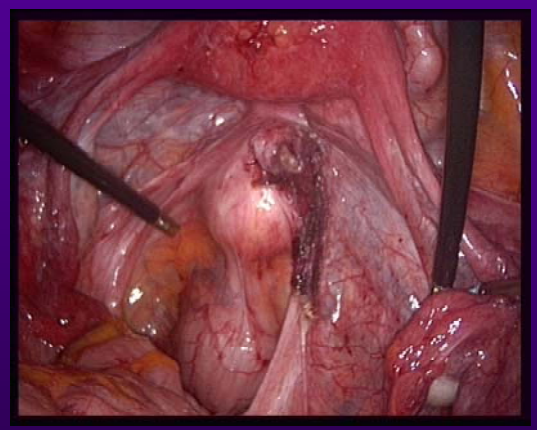
Endometriosis

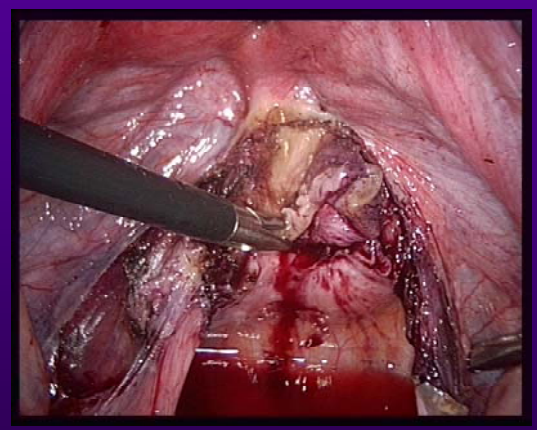
1. Introduction
2. Genetics
3. Endocrinology
4. Immunology
5. Apoptosis
6. Implantation
7. Diagnosis
8. Medical treatment
9. Surgical treatment
10. Future

Surgical treatment

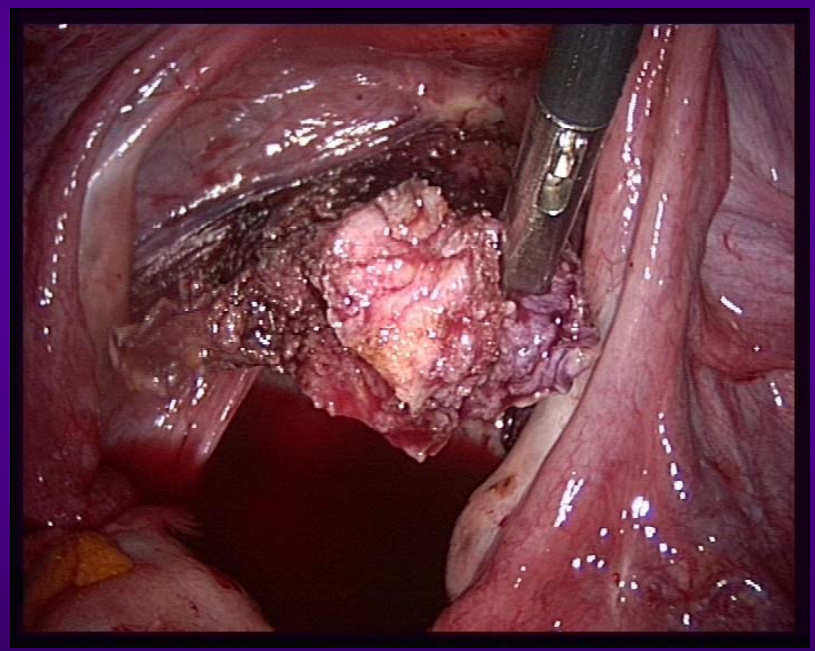


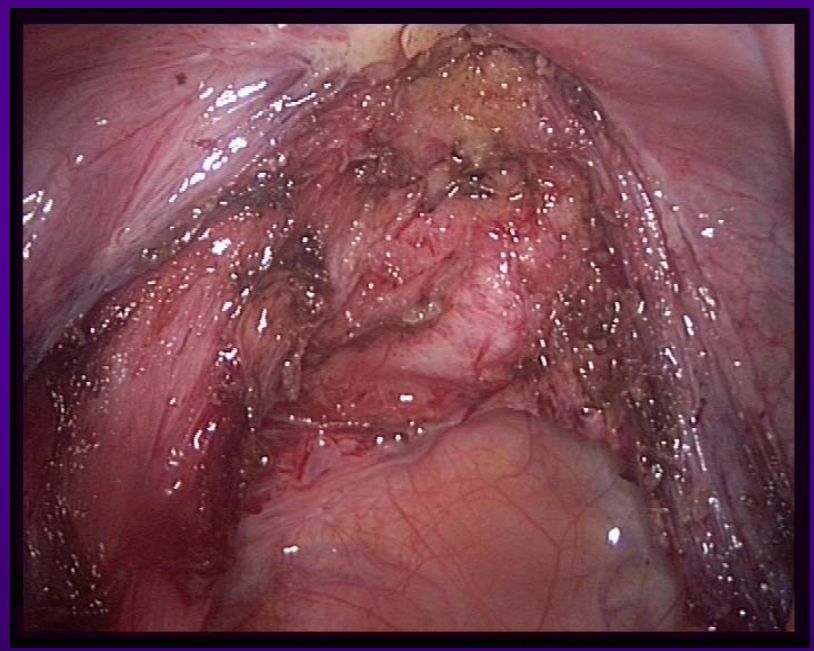




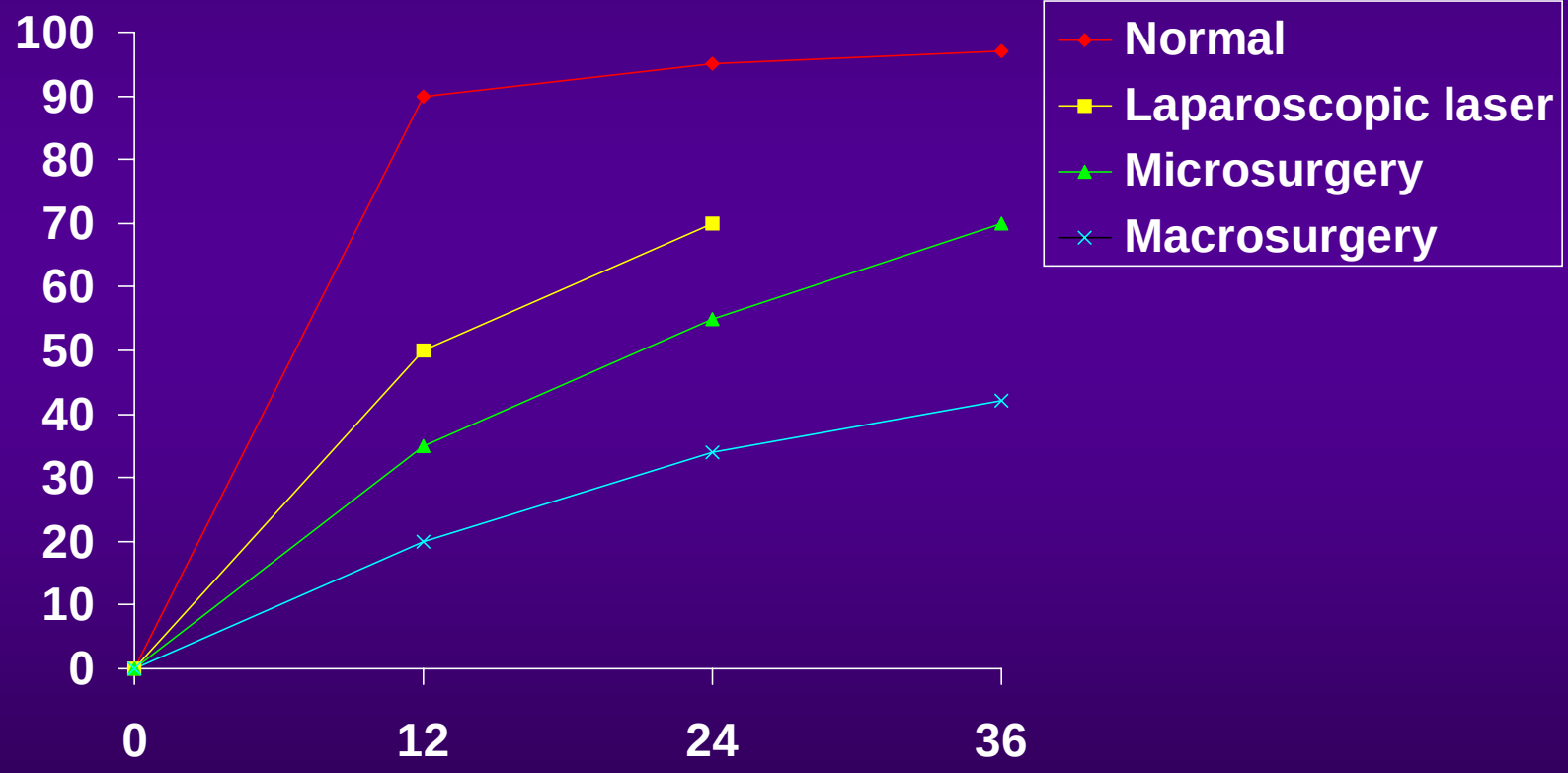


Surgical treatment



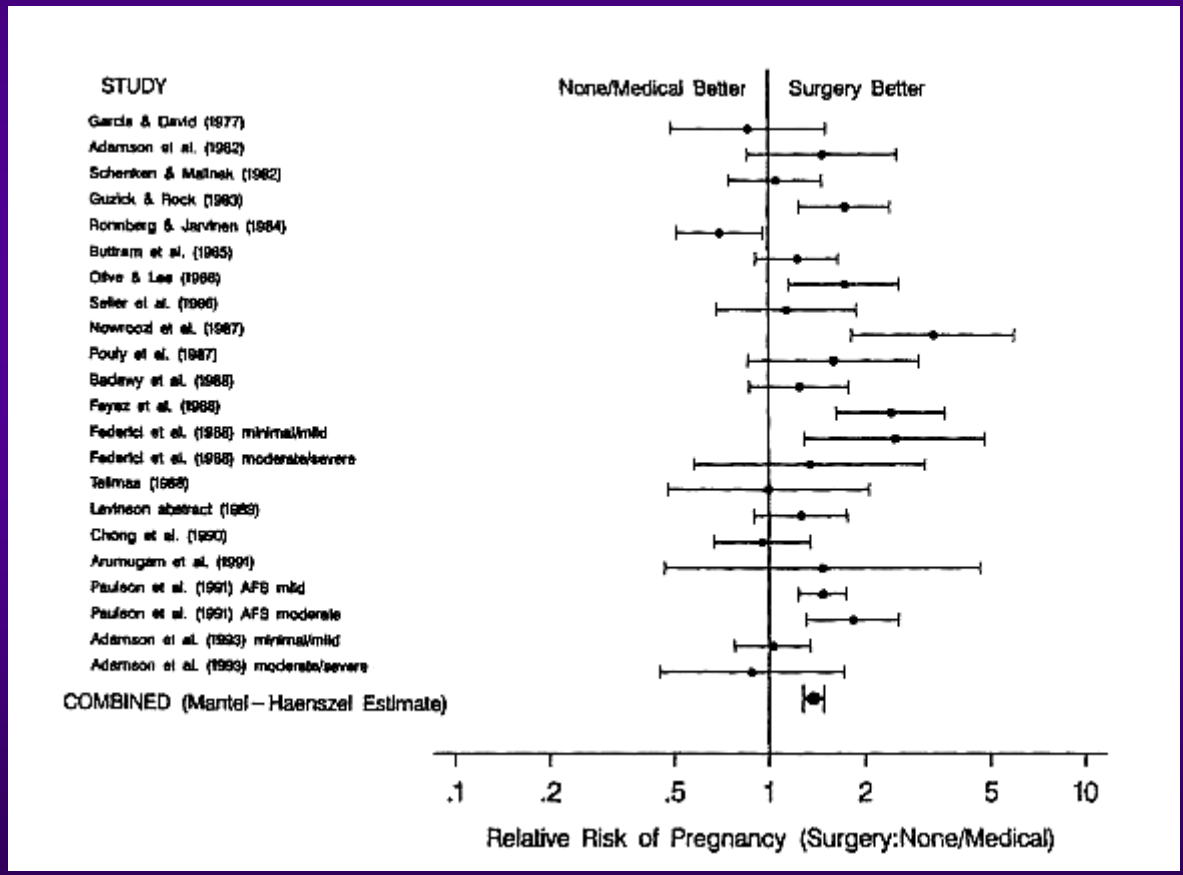


Endometriosis surgical treatment and infertility



Meta-analysis of surgical vs medical management of endometriosis related infertility

Adamson et al AM J Obstet Gynecol 1994



Endometriosis surgical treatment and pain

- Improves pain score in approximately 80 % of patients
- Recurrence rate
  - 5-20 % per year
  - 50 % after 5 years

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Lack of progress in endometriosis research

- Unknown length of time of disease at the time of diagnosis
- Lack of adequate study design
  - No proper control group easily available
- Endometriosis should be studied in multidisciplinary groups not only on a surgeon perspective
- Endometriosis natural occurrence
  - Humans
  - Non human primates (baboons, cynomolgus monkey, pigtailed macaques, rhesus monkey, de Brazza monkeys)

New medications

- Hormonal treatments
  - SERM
  - Aromatase inhibitors
    Takayama et al. Fertil Steril 1998
  - Progesterone antagonists
    Slayden et al. Hum Reprod 2001
  - Selective progesterone receptor modulators
    Chwalisz et al. Ann NY Acad Sci 2002
  - GnRH antagonists

New medications

- Non hormonal treatments
  - Selective blockade of TNF-α activity
    D'Antonio et al. J Reprod Immunol 2000
  - Interferon α
    Ingelmo et al. Fertil Steril 1999
  - Interleukin 12
    Somigliana et al. Hum Reprod 1999
  - Loxoribine, lovamizole
    Keenan et al. Fertil Steril 2000
  - Anti VEGF
    Taylor et al Ann NY Acad Sci 2002
  - Anti MMPs
    Bruner et al. JCI 1997

The rodent model

- Advantages
  - Low cost
- Disadvantages
  - No spontaneous endometriosis
    - Induced endometriotic lesions are different histologically and clinically in the rodent when compared to spontaneous endometriotic lesions in the primates or the humans
  - Lack of menstrual cycle

The baboon model

- Phylogenetically close to humans
- Reproductive anatomy and physiology are close to humans
- Continuous breeder with cycles throughout the year
- Proven accepted model in
  - cardiovascular and endoscopic surgery
  - endocrinology
  - teratology
  - toxicology
  - contraception
  - placental development

The baboon model

- Strong primates
  - Repetitive blood sampling
  - Complex surgical procedures
- Spontaneous presence of peritoneal fluid
- Direct access to uterine cavity without the need of hysterotomy
- Different stages of spontaneous endometriosis similar to humans

The baboon model

- Allows adequate observations for endometriosis
  - Etiology
  - Natural history
  - Infertility
  - Pain
  - Surgical treatments
  - Medical treatments
    - Prevention
    - Treatment