Endometriozis Fertilite

Bildiklerimiz - bilmediklerimiz

ENDOMETRİOZİS & ADENOMYOZİS DERNEĞİ 2009

ENDOMETRİOZİS SEMPOZYUMU 2011

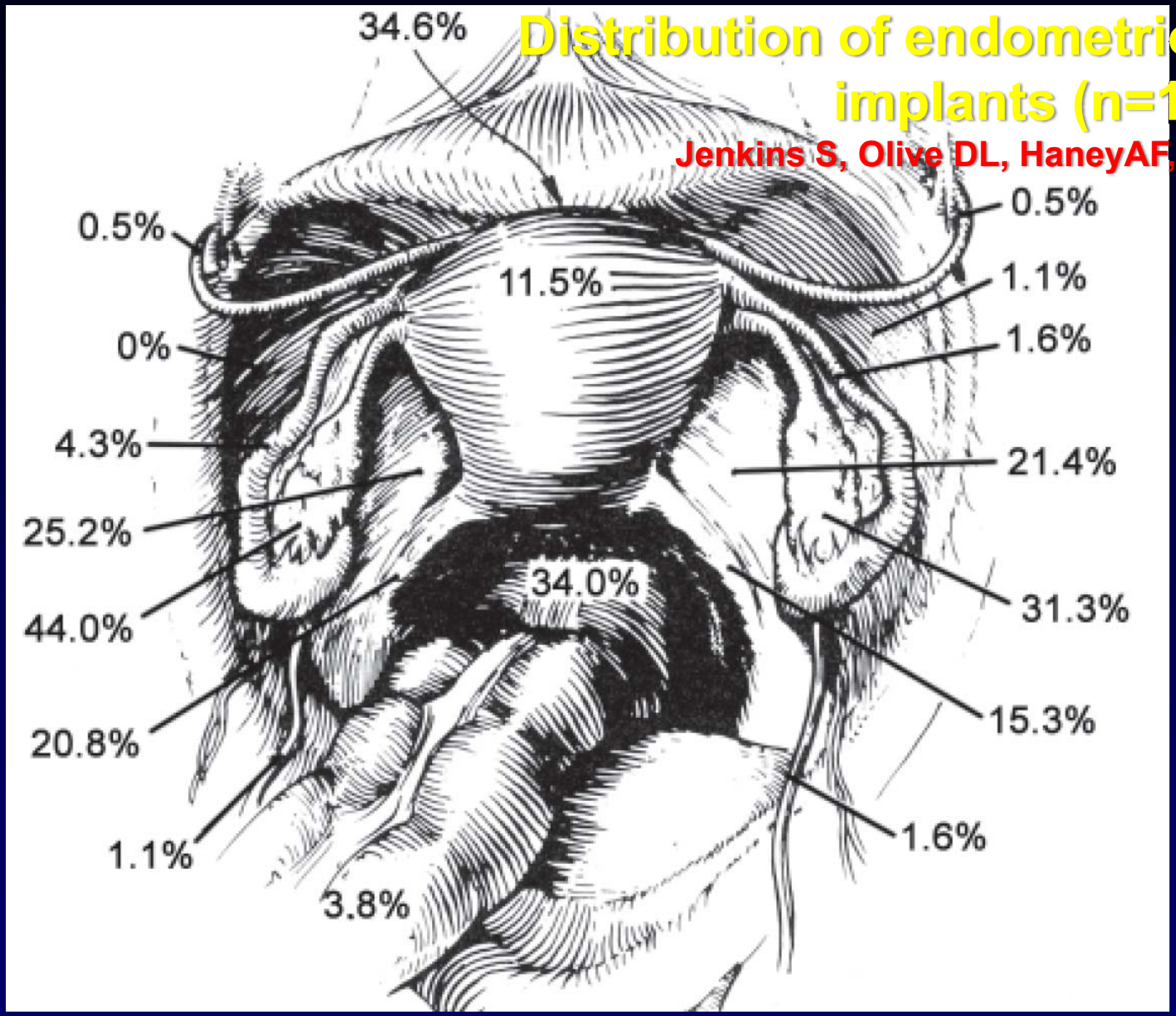
Tarih : 23 Ocak 2011 Pazar
Saat : 09.00-17.00
Yer : Ankara Swiss Otel

Levent M. ŞENTÜRK, *Prof. Dr.*

Istanbul Üniversitesi Cerrahpaşa Tıp Fakültesi
Kadın Hastalıkları ve Doğum Anabilim Dalı,
Reprodüktif Endokrinoloji Bilim Dalı, ÜYTE Bölümü

Distribution of endometriotic implants (n=182)

Jenkins S, Olive DL, HaneyAF, 1986



Prevalence of endometriosis among previously fertile patients undergoing sterilization, 1976-1987

Reference	*N*	*N (%) w/Endo*	*Min/Mild*	*Mod/Severe*	*Histological confirmation*
Hasson, 1976	296	4(1.5)	—	—	No
Drake and Grunert, 1980	43	2(5)	—	—	No
Strathy, et al, 1982	200	4(2)	4	0	No
Liu and Hitchcock, 1986	74	32(43)	32	0	No
Moen, 1987	108	19(18)	15	4	No
Subtotal, 1976-1987	721	61(8)	51/54(93%)	4/55(7%)	

Prevalence of endometriosis among previously fertile patients undergoing sterilization, 1988-2000

Reference	*N*	*N (%) w/Endo*	*Min/Mild*	*Mod/Severe*	*Histological Confirmation*
Kirshon et al, 1989	566	42(7.5)	28	4	No
Wheeler 1989	3060	49(1.6)	—	—	No
Trimbos et al, 1990	200	5(2.5)	1	4	No
Moen and Muus, 1991	107	24(22)	23	1	Yes
Mahmood and Templeton, 1991	598	37(6)	30	7	No
Rawson, 1991	8	4(50)	—	—	No
Sangi-Haghpeykar and Poindexter, 1995	3384	126(3.7)	121	5	No
Balasch et al, 1996	30	13(43)	13	—	No
Subtotal 1988-2000	7953	300(4)	216/239 (91%)	21/239 (9%)	
Total	8674	361(4)	267/292 (91%)	25/292 (9%)	

Prevalence of endometriosis among infertile patients, 1970-1987

Reference	*Total N*	*N (%) with endometriosis*
Peterson and Behrman, 1970	204	70 (33)
Duignan et al, 1972	675	52 (8)
Liston et al, 1972	312	25 (8)
Pent, 1972	22	1 (5)
Goldenberg and Magendatz, 1976	112	29 (26)
Hasson, 1976	66	15 (23)
Cohen, 1976	1380	320 (23)
Musich and Behrman, 1982	182	63 (35)
Strathy et al, 1982	100	19 (19)
Nordenskjold and Ahlgren, 1983	433	69 (16)
Chang et al, 1987	2053	44 (2)
Subtotal, 1970-1987	5539	707 (13)

Prevalence of endometriosis among infertile patients, 1988-2000

Reference	*Total N*	*N (%) with endometriosis*
Mahmood and Templeton, 1989	490	101
Koninckx et al, 1991	416	283 (68)
Mahmood and Templeton, 1991	654	133 (21)
Gruppo Italiano, 1996	660	195 (30)
Balasch et al, 1996	52	26 (50)
Corson et al, 2000	100	43 (43)
Subtotal	2372	781 (33)
Total	7911	1068 (13.5)

Prevalence of endometriosis according to stage of disease in infertile and fertile women

Fertility Status	*Number*	*Endometriosis*	*Minimal-Mild*	*Mod-Severe*
Previously fertile	7953	300 (4%)	216 (91%)	21 (9)
Infertile	2372	781 (33%)	463 (58%)	215 (32%)
P value	P < 0.0001		P < 0.0001	

Cycle fecundity rate and implantation rate - IUI
minimal-mild endometriosis
vs. unexplained infertility

Rate	*Reference*	*Minimal-Mild Endometriosis*	*Unexplained Infertility*	*P Value*
Cycle fecundity rate	Omland et al, 1998	8/49 (16%)	40/119 (34%)	<0.05
	Nuojua-Huttunen et al, 1999	9/138 (6%)	63/413 (15%)	0.05
Implantation rate	Omland et al, 1998	9/49 (18%)	52/119 (44%)	<0.05

Cycle fecundity rate and cum. preg. rate – donor insemination minimal-mild endometriosis *vs.* unexplained infertility

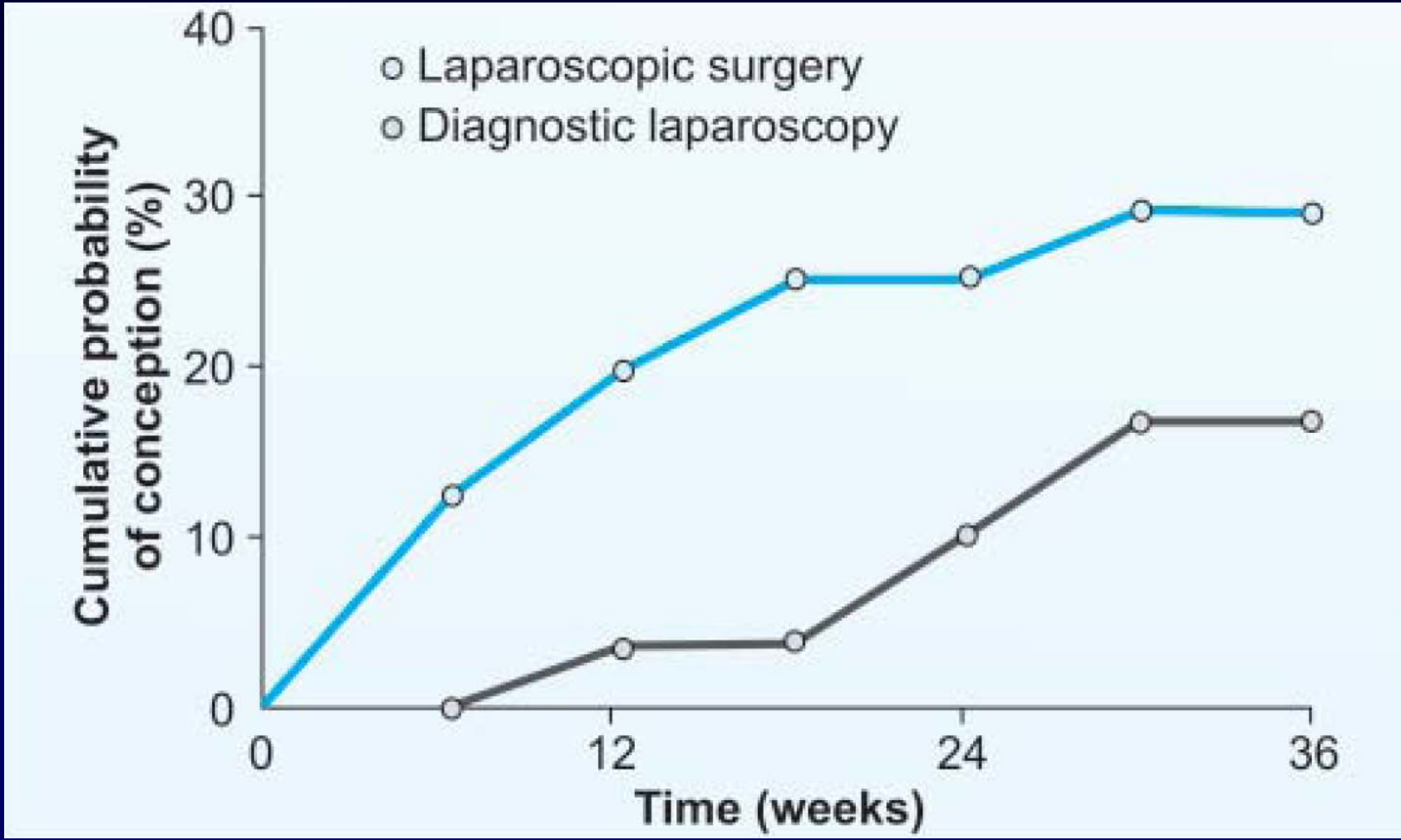
Rate	*Reference*	*Minimal-Mild endometriosis*	*Unexplained Infertility*	*P Value*
Cycle fecundity rate	Hammond et al, 1986 Toma et al, 1992	9/218 (4%) 5/86	38/196 (20%) 29/212 14% (95%CI, 8-20%)	< 0.05
	Jansen et al, 1986	2/56 (4%)	12% (46/380)	< 0.05
Cumulative Pregnancy rate after 6 cycles	Hammond et al, 1986 Toma et al, 1992	20% 38%	55% 80%	

Summary of combined Mantel-Haenszel meta-analysis estimates of endometriosis treatment

Adamson and Pasta (1994)

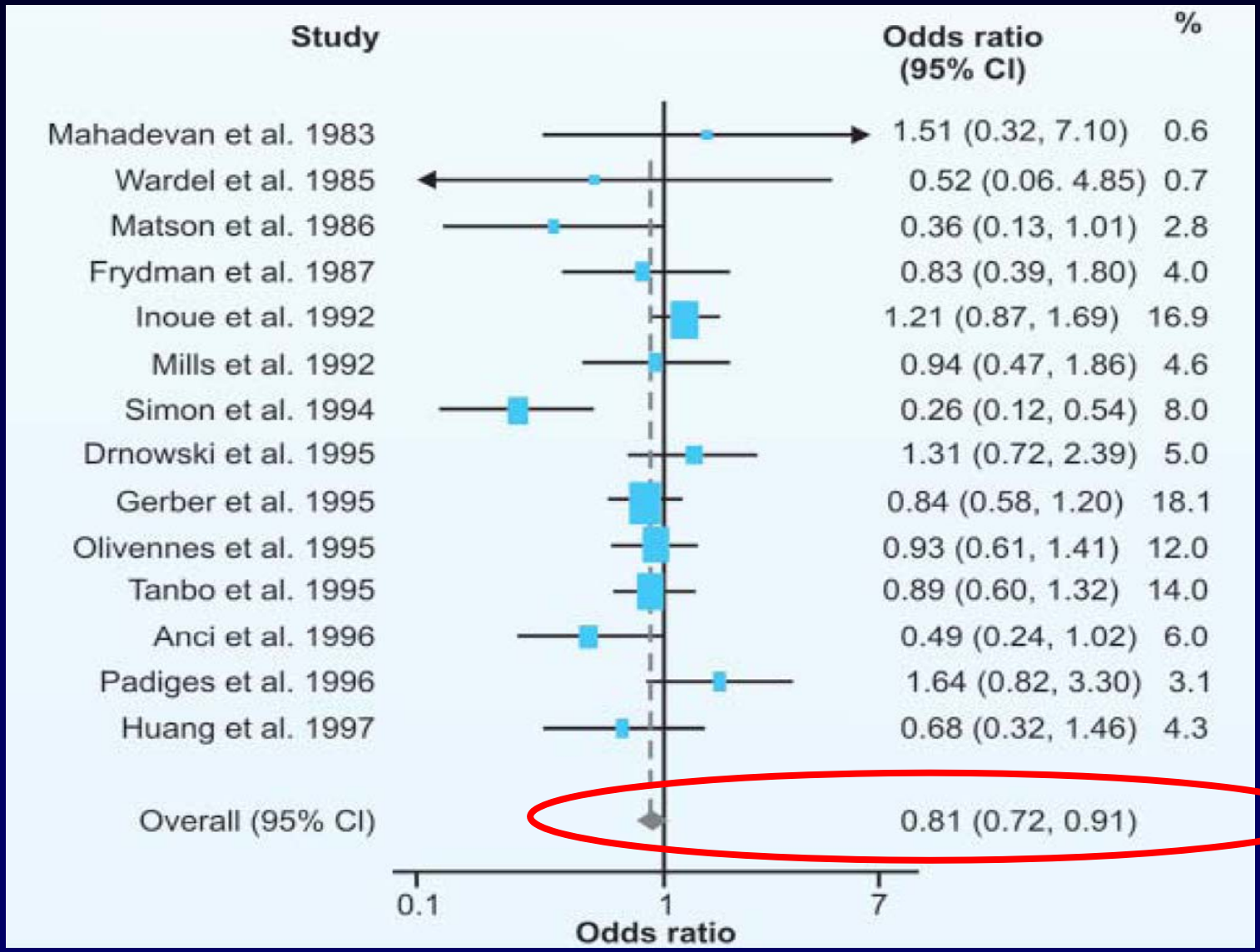
Cumulative probability of a pregnancy carried beyond 20 weeks in the 36 weeks after laparoscopy in women with endometriosis

Marcoux S, Maheux R, Berube S (1997) [ENDOCAN]



Unadjusted meta-analysis of the odds of pregnancy: endometriosis *vs.* tubal factor

Barnhart, *et al* (2002)



Outcome of IVF

endometriosis *vs* tubal factor

Simon et al, Hum Reprod 1994;9(4):725-729

Diagnosis	*Tubal factor*	*Endometriosis*		
		Total	*I and II*	*III and IV*
No. of cycles	96	96	14	82
No. of patients	78	59	9	50
Age (years)	32.2 ± 0.4*	31.9± 0.3	32.1±0.9	31.9± 0.3
#oocytes fertilized (%)	12.1± 0.7	9.6 ± 0.7	9.6±1.0	9.6± 0.7
Type 1 (%)	61.8	55.7	55.4	57.1
# oocytes fertilized (%)	57.7 ± 2.9	43.5 ± 3.4	55.6±8.9	54.1±3.7
# transfer cycles	91	79	12	67
# embryos transferred/cycle	3.6 ± 0.1	3.5 ± 0.2	3.6 ± 0.4	3.4 ± 0.2
# type I transferred	3.0 ± 0.3[a]	2.2 ± 0.2	2.3 ± 0.6	2.2 ± 0.3
# pregnancies/cycle (%)	34/96 (34.4)[b]	12/96 (12.5)	2/14(14.2)	10/82(12.1)
# pregnancies/transfer (%)	34/91 (37.3)[c]	12/79 (15.1)	2/12(16.6)	10/67(14.9)
Implantation rate (%)	44/329 (13.4)[d]	16/275 (5.8)	3/43(6.9)	13/232(5.6)

* Values are mean ± SEM. [a] p<0.001, [b] p<0.0004, [c] p<0.002, [d] p<0.003

Outcome of oocyte donation according to the recipient's cause of infertility

Simon et al, Hum Reprod 1994;9(4):725-729

Diagnosis	*Premature ovarian failure*	*Low response*	*Endometriosis*
# patients	54	77	10
Age (years)	34.7±0.7[b]	37.2±0.5[a]	30.0±0.8[b]
# transfer cycles	71	96	11
# oocytes donated/cycle	7.8±0.3	7.7±0.3	7.6±0.6
# embryos transferred/cycle	3.8±0.2	4.1±0.2	3.6±0.4
# pregnancies	35	51	8
# sacs	51	68	10
PR/transfer (%)	49.3	53.2	72.7
PR/patient (%)	64.8	66.2	80.0
Implantation rate (%)	19.2	17.0	25.0

[a] *vs* [b] $p<0.05$

Impact of stage III–IV endometriosis on recipients of sibling oocytes: matched case-control study Diaz et al, F&S 2000; 74: 31

	Study group		
	Endometriosis (III–IV)	Control	*P* value
No. of patients	25	33	
No. of cycles	25	33	
Age[a]	35.0 ± 3.4	38.5 ± 4.9	0.004
No. of oocytes donated[a]	7.8 ± 1.6	7.7 ± 1.9	NS
No. of embryos transferred[a]	4.0 ± 0.7	4.1 ± 1.2	NS
No. of good quality embryos transferred[a]	3.6 ± 0.2	3.7 ± 0.1	NS
Implantation (%)	15/101 (14.8)	22/137 (16.0)	NS
No. of pregnancies (%)	10 (40.0)	15 (45.5)	NS
Miscarriage (%)	3 (30.0)	4 (26.0)	NS
Live birth (%)	7 (28.0)	9 (27.2)	NS

Note: NS = not significant. [a] Values are mean ± SD.

Outcome of oocyte donation according to the donor's cause of infertility

Simon et al, Hum Reprod 1994;9(4):725-729

Oocyte donor Characteristics	*No. of cycles*	*Pregnancy rate/transfer*	*Implantation rate*
Fertile	34	15 (44.0)	23/142 (16.2)
Polycystic ovaries	58	35 (6-.3)	55/233 (23.6)
Idiopathic infertility	20	9 (45.0)	9/80 (11.2)
Tubal infertility	27	15 (55.5)	18/96 (18.7)
Male infertility	28	17 (60.7)	21/110 (19.1)
Endometriosis	11	3 (27.3)	3/43 (7.0)[a]

[a] $p<0.05$

SART 2006 verilerine göre hangisinde gebelik başarısı en düşüktür?

a. Tubal Faktör

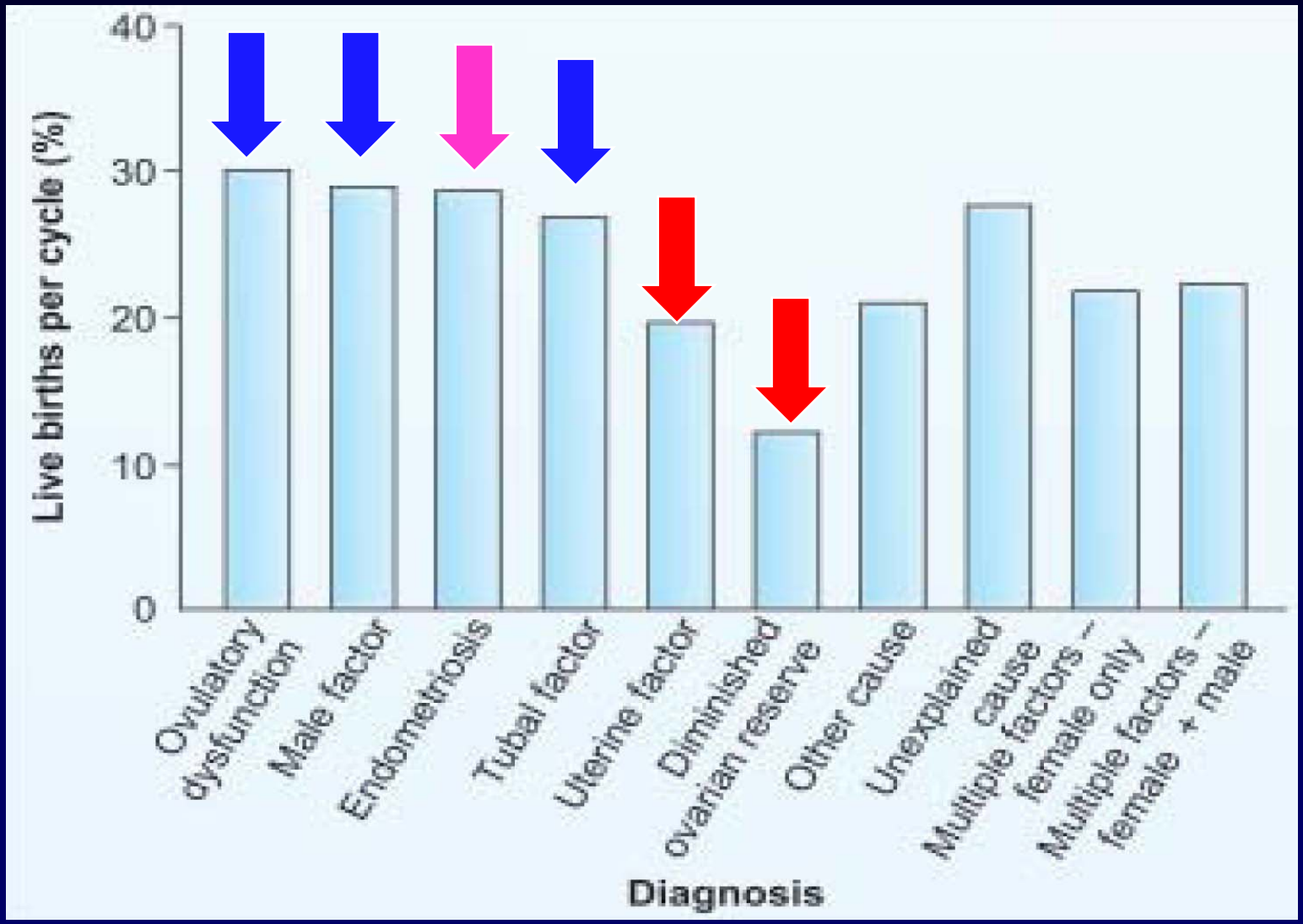
b. Uterus faktörü

c. Erkek faktörü

d. Endometriozis

e. Ovulatuar faktör

Live birth rates in ART cycles: endometriosis *vs* other diagnoses fresh non-donor eggs or embryos (SART, 2006)



Pelvic factors and infertility in patients with moderate-to-severe endometriosis

- Adhesions with distortion of pelvic architecture interfering with the release of the oocytes and the tubal pick-up of these oocytes
- Fimbrial distortion or even occlusion can occur
- Hydrosalpinx can occur if the distal end of the tube is damaged
- Tubal narrowing and constriction
- Proximal tubal obstruction

Possible mechanisms of infertility in patients with mild-to-moderate endometriosis

Changes in peritoneal fluid

- Increase in volume
- Reduced sperm motility and binding
- Presence of interleukins and tumor necrosis factor
- Increased prostaglandin levels
- Increased number of macrophages

Eutopic endometrium abnormalities

Myometrial and peristalsis abnormalities

Possible mechanisms of infertility in patients with mild-to-moderate endometriosis

Follicular environment and embryo quality

- Increased progesterone and interleukin-6
- Decreased vascular endothelial growth factor

Ovulation disorders

- Anovulation
- Hyperprolactinemia
- Abnormal follicular genesis
- Premature follicular rupture
- Luteinized unruptured follicles
- Luteal phase defect

Possible mechanisms of infertility in patients with mild-to-moderate endometriosis

Pelvic pain

Immunological abnormalities

- T-lymphocytes
- Antigen-specific B-lymphocyte activation
- Non-specific B-lymphocyte activation
- Anti-endometrial antibodies

Spontaneous abortion

Implantation disorders

Role of altered immunologic factors in endometriosis-associated infertility

Gupta, *et al.*, 2008

Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility
Follicular fluid studies			
VEGF	Decreased	Decreases follicle health and vascularisation	Decreased embryo quality and implantation rates
IL-6	Increased	Decreases aromatase activity within follicles	Decreased intrafollicular E_2 levels, leading to decreased fertility and fertilizing capacity

Role of altered immunologic factors in endometriosis-associated infertility

Gupta, *et al.*, 2008

Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility
Peritoneal fluid studies			
RANTES	Increased	Attracts monocytes and memory T-cells to inflamed areas	Increased inflammation, cytotoxic effects on healthy cells, and OS produced, leading to decreased fertility
IL-10	Increased	Prevents p27 down regulation in developing granulosa cells	G_0 arrest of granulosa cell cycle, resulting in low-quality oocytes
VEGF	Increased	Induces the formation of angiogenesis promoting fibrin matrix in the peritoneal cavity	Increased adhesion of free endometrial tissue within the peritoneal cavity
TNF-α	Increased	Causes increased prostaglandin production by endometrial epithelial cells	Increased adhesion of free endometrial tissue within the peritoneal cavity, and increased inflammation, leading to subfertility

Role of altered immunologic factors in endometriosis-associated infertility

Gupta, *et al.*, 2008

Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility
TNF-α	Increased	Decreases the effect of TIMP	Increase effects of MMP, leading to increased endometriotic tissue invasiveness
PAPP-A	Increased	Increases follicular androstenedione syntheses	Increased conversion of androstenedione to E_2 by endometriotic tissue, leading to increased tissue proliferation
Cathepsin D	Increased	Initiates harmful proteolytic events	Degradation of basement membrane and extracellular matrix components

Role of altered immunologic factors in endometriosis-associated infertility

Gupta, *et al.*, 2008

Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility
Altered immune factors in peritoneal fluid and their adverse effects on spermatozoa			
IL-6	Increased	Induces the release of gp130 by sperm	Decreased sperm motility
TNF-α	Increased	Initiates a Caspase cascade	Sperm apoptosis and a/ oligospermia
TNF-α	Increased	Induces ROS production from spermatozoa	Sperm plasma membrane lipid peroxidation and abnormal sperm function

ROS: reactive oxygen species; OS: oxidative stress; MMP: matrix metallo- proteinases; TNF-a: tumor necrosis factor-alpha; PAPP-A: pregnancy-associated plasma protein; VEGF: vascular endothelial growth factor; TIMP: tissue inhibitors of MMP.

Endometriozis – Infertilite
Folikül ve folikülogenez

- Uzun foliküler faz
- Yavaş ve yetersiz gelişen foliküller

- → kötü oosit kalitesi
- → fertilizasyon oranı ↓
- → kötü embriyolar
- → Implantasyon oranı ↓

Garrido N, 2003; Pellicer A, 2000; Trinder J, 2002; Cahill DJ, 1997

Endometriozis – Infertilite

Granuloza hücre fonksiyonu

- Granuloza hücre kinetiğinde değişiklikler (S fazı ve apopitotik granuloza h ↑)

Saito H, 2002; Toya M, 2000

- Endometriozis derecesi ↑≈ Granuloza h. apopitozis ↑ ⇒ oosit ve embriyo kalitesi ↓, fertilizasyon ve gebelik ↓

Nakahara K, 1997; Sifer C, 2002

- Endometriozise bağlı granuloza h. Oksidatif stres (OS) ↑. OS nedeni olan ROS başlıca eritrosit, apopitotik endometrioma hücreleri ve aktive makrofajlar tarafından üretilir

Saito H, 2002; Gupta S, 2006; Ota H, 2001

Endometriozis – Infertilite
Granuloza hücre fonksiyonu

- OS: mayotik ağı bozarak oosit dejenerasyon ve apopitozu ↑

Agarwal A, 2006

- OS: Plazma membran lipid peroksidasyonu ⇒ membran geçirgenliği ↑, enzim inaktivasyonu, DNA yapısal hasarı ⇒ hücre ölümü

Bedaiwy MA, 2002

- OS: Embriyoda fragmantasyon ↑

Agarwal A, 2006

Endometriozis – Infertilite

Folikül sıvısı: immunolojik degisiklikler

- B lenfosit, *Natural Killer*, monosit-makrofaj ↑

  Lachapelle MH, 1996

- IL-6, IL-1β, IL-8, IL-10, TNF-α ↑ ⇒ hücre siklus boz.

  Saito H, 2002

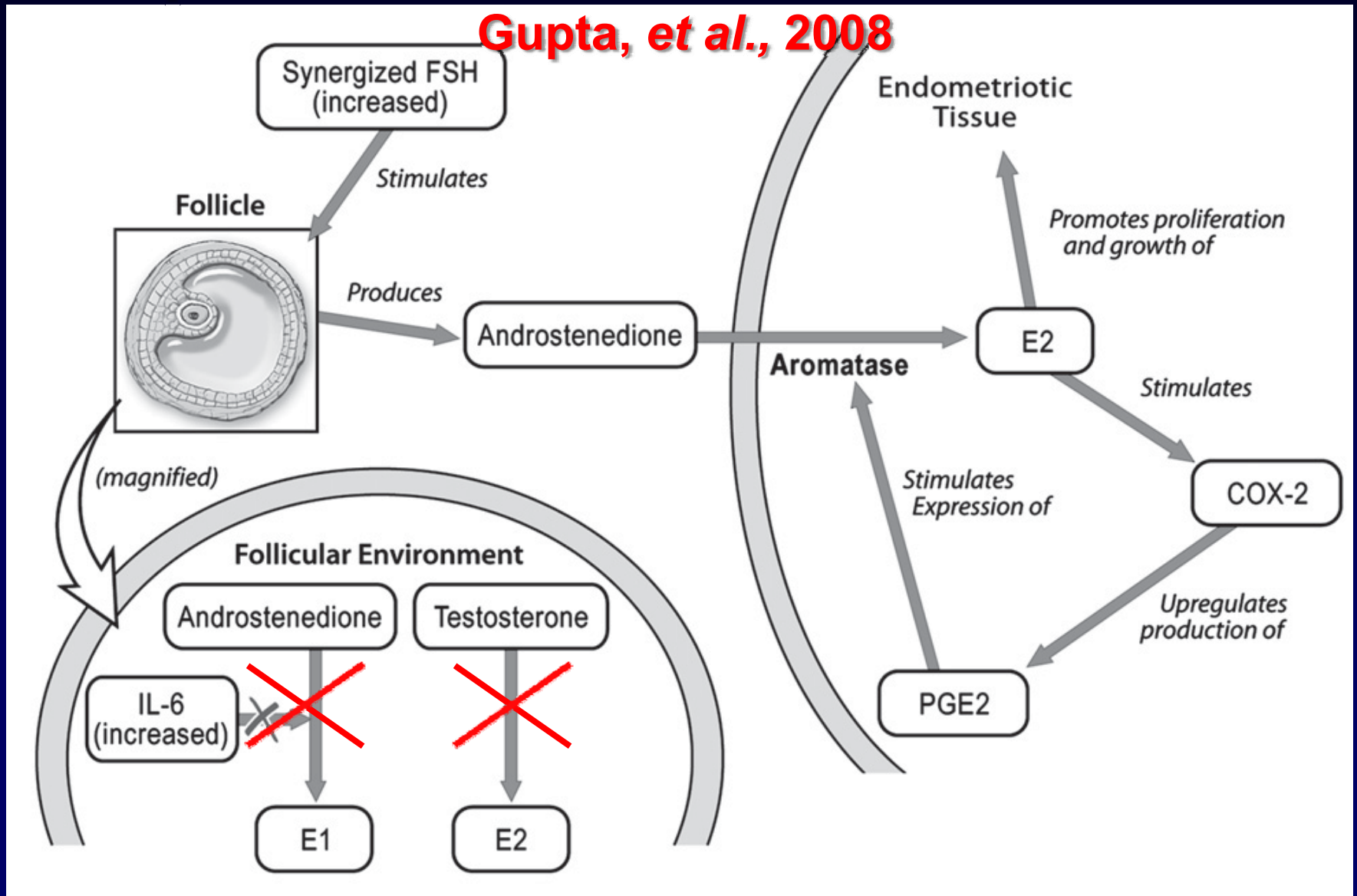
- VEGF (fol. Vask) ↓ ⇒ embriyo kalitesi ve implantasyon ↓

  Pellicer A, 2000; Pellicer A, 1998; Garrido N, 2000; Wunder DM, 2006; Lucena E, 1999

- IL-6 ↑ ⇒ fol. içi aromataz akt. ↓ (androstenedion →E1 ve testosteron → E2 ↓↓↓). → fol. içi östrojen ↓

  Yoshida S, 2004; Ulukus M, 2006

Role of COX-2 and aromatase in a persistent endometriotic state



Endometriozis – Infertilite

Periton sıvısı: immunolojik degisiklikler

- Humoral ve hücresel immunite degsiklikleri…

Lebovic DI, 2001

- Aktive makrofaj, T lenfosit, NK ↑
- NK hücre sitotoksisitesi ↓

Lebovic DI, 2001; Oosterlynck DJ, 1993

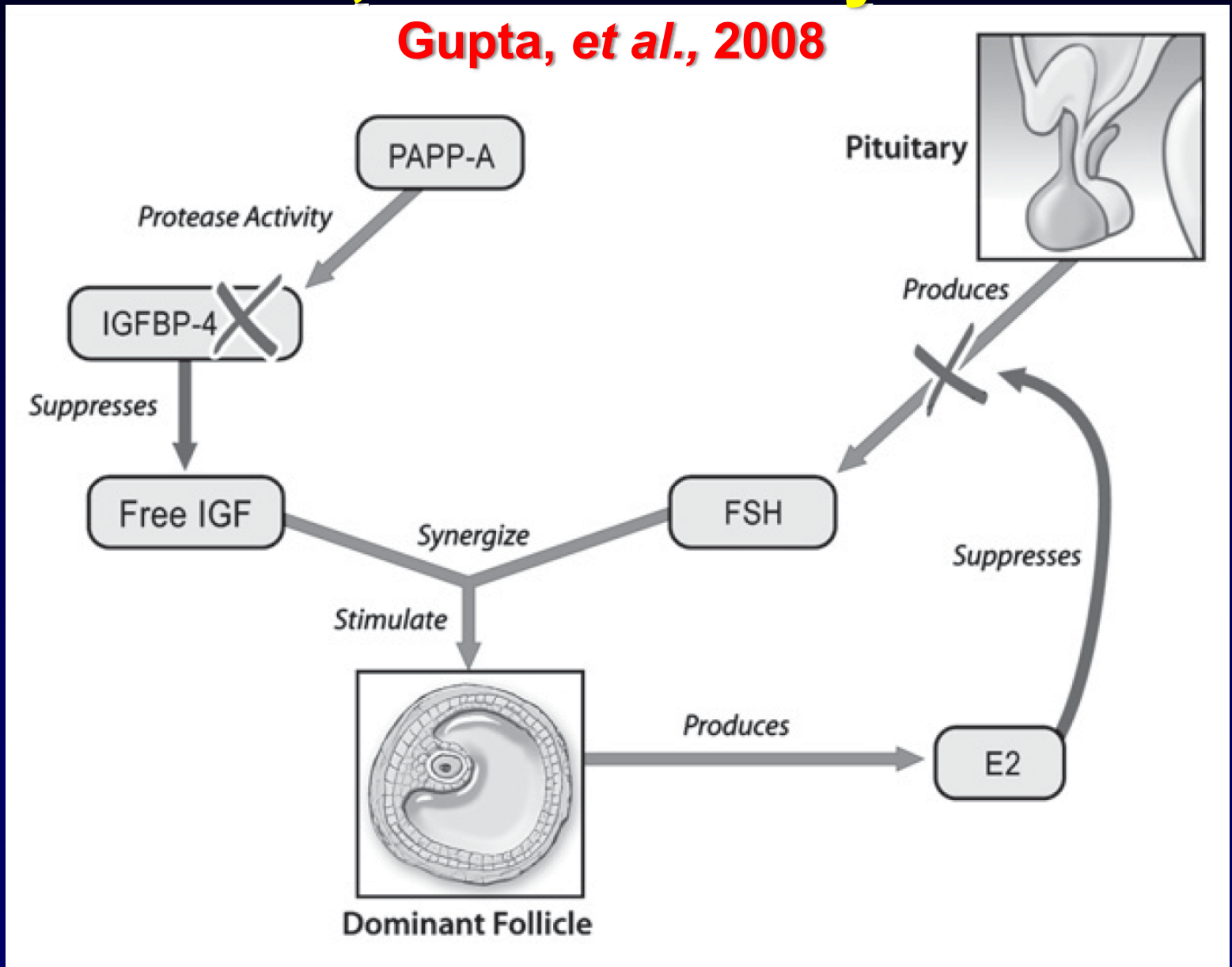
- E2 ↑ ⇒ COX2 akt. ↑

Attar E, 2006; Noble LS, 1997

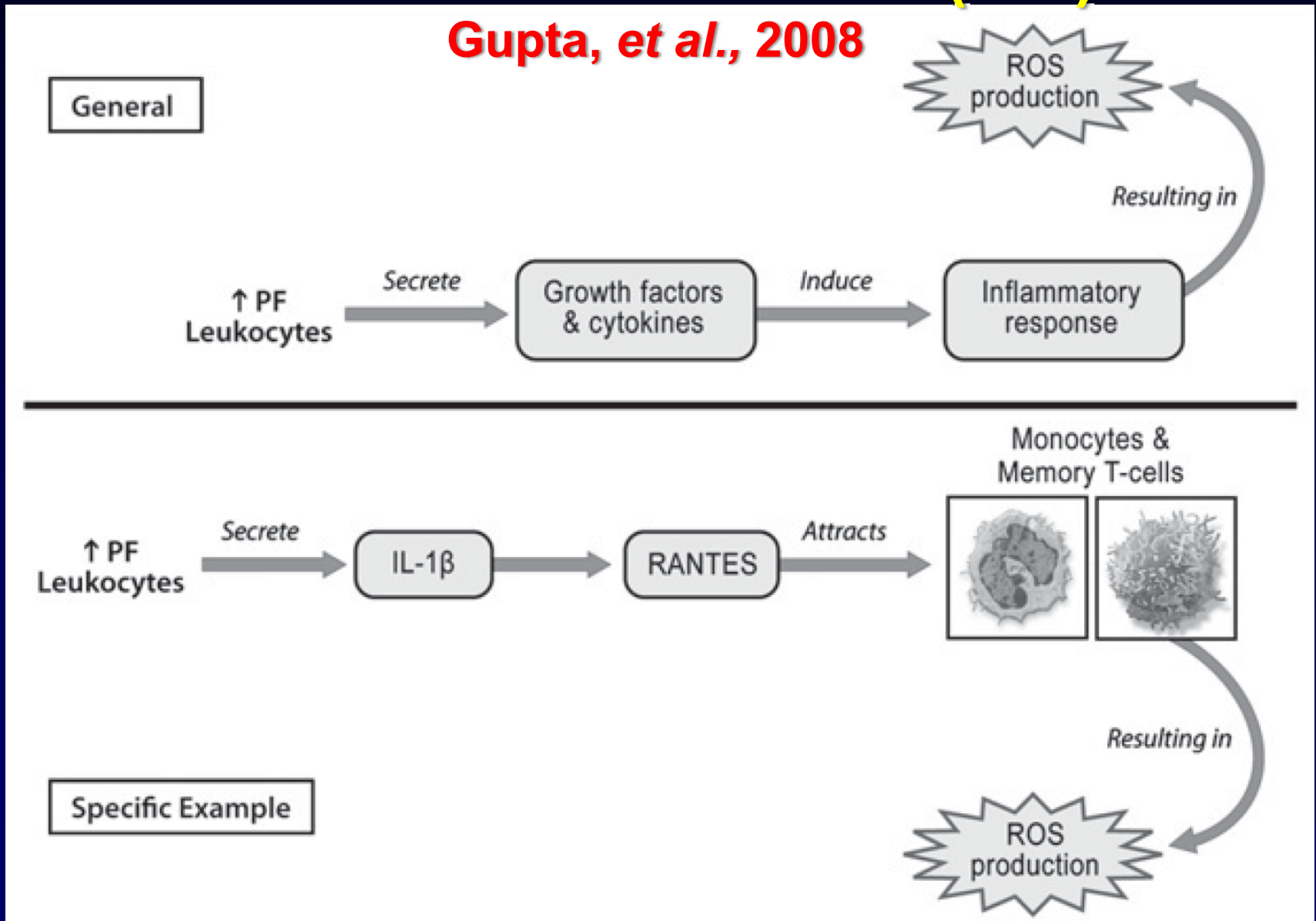
- PAPP-A ↑ ⇒ IGFBP-4 ↓ ⇒ serbest IGF ↑ FSH ve LH ile sinerji ↓ ⇒ endometriozis gelişimi artar

Fortune JE, 2004; Arici A, 2003

Endometriosis, peritoneal biologic window, and role of cytokines



Endometriosis, peritoneal environment, and oxidative stress (OS)



Endometriozis – Infertilite

Periton sıvısı ve oksidatif stres (OS)

- Makrofaj sayı ve aktivite ↑ ⇒ sitokin ve NO ↑

Dong M, 2001

- ↓ NO: over fonksiyonları ve implantasyonda olumlu etkili. Ancak endometriozisde peritondaki makrofajlarda NO ve NOS (nitrik oksid sentetaz) ↑

Khorram O, 2002

- ↑ NO: tuba fonkisyonları ve sperm motilitesine olumsuz etkili. Embriyolara toksik ve implantasyonu bozuyor . ART gamet hücrelerini bu şekilde toksik etkilerden (NOS ve ROS) uzaklaştırarak gebeliği ↑ OLABILIR ???

Osborn BH, 2002

Endometriozis – Infertilite

Periton sıvısı (PS) ve oksidatif stres (OS)

- Endometriozis olgularında PS toplam antioksidan kapasitesi ↓

Szczepanska M, 2003

- ↑ ROS ⇒ adhezyon oluşumunu ↑

Alpay Z, 2006

- OS: genom ve mitokondride DNA hasarını ↑ ⇒ fertiliteyi ↓.
- Endometriozis şiddetiyle ve inkübasyon süresi ile orantılı olarak endometriozisli PS ⇒ Sperm, oosit ve embriyoda DNA hasarı ve fragmantasyonunu ↑ ⇒ fertilizasyon ve implantasyon ↓, abortus ↑

Aitken RJ, 2001; Guerin P, 2001; Mansour G, 2007

Endometriozis – Infertilite

Sperm fonksiyonları

- **Endometriozisde PS'da aktive makrofajlarda ROS yapımı ↑ ⇒**
  - Sperm DNA fragmantasyonu ↑
  - Lipid peroksidasyonu ⇒ membran bütünlüğü ↓, enzim inaktivasyonu
  - Akrozom reaksiyonu ve sperm-oosit füzyonunun bozulması

Van Langendonckt A, 2002; Baker MA, 2004

- **TNF-α ↑ ⇒**
  - sperm apopitozis ↑
  - Spermde ROS ↑ ⇒ lipid peroksidasyonu ↑ ⇒ sperm fertilizasyon kapasitesini ↓

Said TM, 2005

Endometriozis – Infertilite

Sperm fonksiyonları

- Endometriozis olgularında tuba ampulla epiteli spermi daha sıkı bağlayarak, içinde serbestçe hareket etmesini ↓ ⇒ fertilizasyon şansını ↓

  Reeve L, 2005

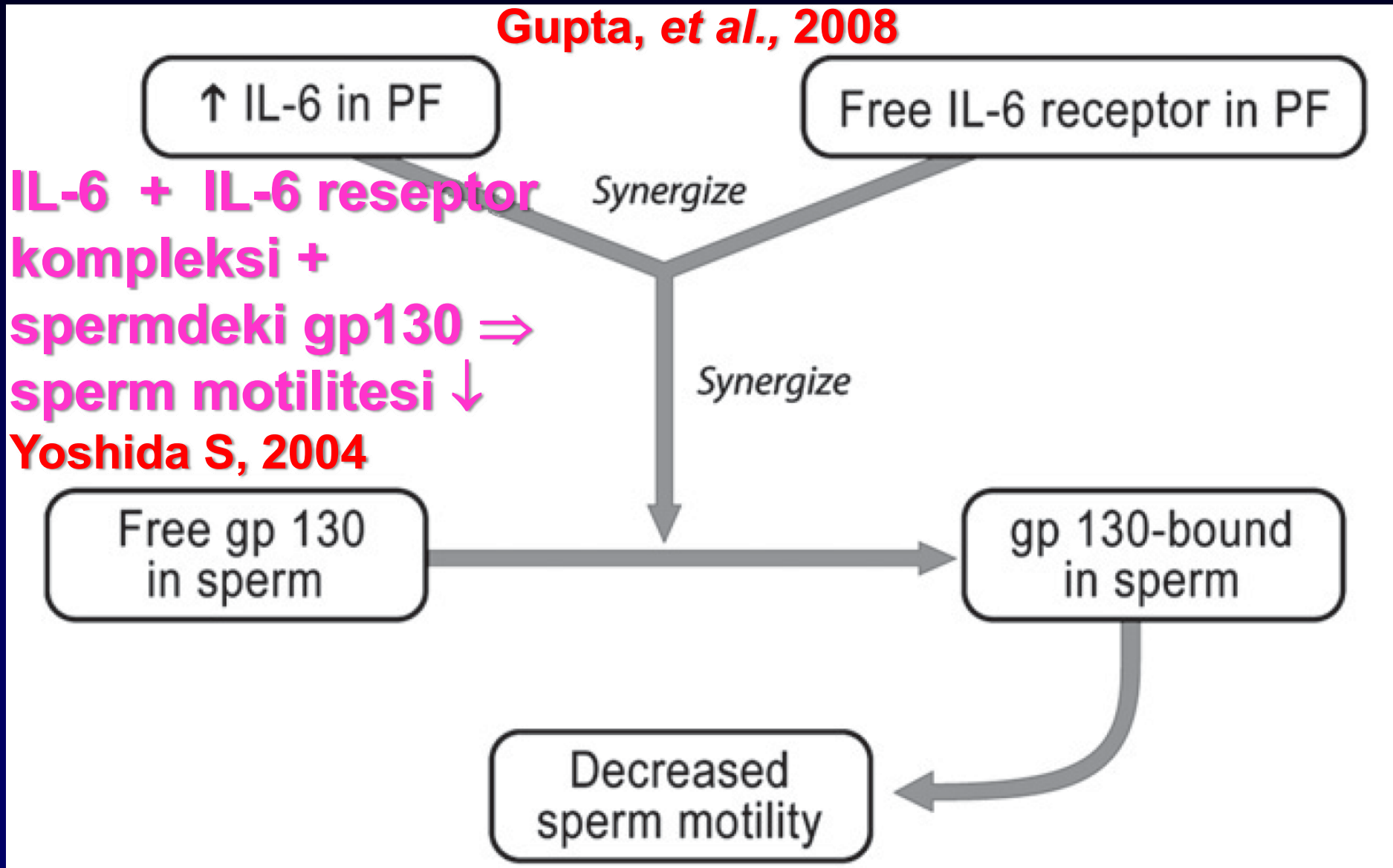
- PS da IL-1, IL-6 ↑ ⇒ uterus içi sperm motilitesi ↓

- IL-6 + IL-6 reseptor kompleksi + spermdeki gp130 ⇒ sperm motilitesi ↓

  Yoshida S, 2004

Endometriosis: impact on sperm function

Gupta, *et al.*, 2008



IL-6 + IL-6 reseptor kompleksi + spermdeki gp130 ⇒ sperm motilitesi ↓

Yoshida S, 2004

Endometriozis – Infertilite

Fertilizasyon

- **Endometriozis fertilizasyonu ↓ (IVF)**

  Azem F, 1999; Hull MG, 1998; Pal L, 1998; Simon C, 1994; Harlow CR, 1996

- **Endometriozis fertilizasyonu etkilemez (IVF)**

  Matson PL, 1986; Mahmood TA, 1991

- **Endometriozisli hastaların PS, sperm- zona pellusida bağlanmasını ↓**

  Coddington CC, 1992; Faber BM, 2001

- **Fertilizasyon ↓ ???**
  - Oosit kalitesi düşük (donorlerde fertilizasyon daha iyi)
  - Düşük kaliteli oositlerde mikrotübüllerde sorun
  - Endometriozis fol sıvısı sperm-zona pellusida bağlanmasını ↓

  Pellicer A, 1995; Brizek CL, 1995; Qiao J, 1998

Endometriozis – Infertilite
Implantasyon

- Endometriyum reseptivitesi ↓
- Endometriyozisde, implantasyon penceresinde αvβ3 integrin ekspresyonu ↓

  Lessey BA, 1994; Lessey BA, 1994; Creus M, 1998
- Çeşitli genlerin ekspresyonunda bozukluk

  Kao LC, 2003
- Zona'da olası problem ??? Ancak, AHA bu durumu <u>düzeltemedi!!!</u>

  Ciray HN, 2005

Endometriozis
Gebelik Kaybı

	Spontan Abortus %
Minimal –hafif	32.4
Orta-Ağır	33.3

OR: 1.05 [0.71-1/56]

Matorras R, 1998; Sinaii N, 2008

Endometriozis

Gebelik Kaybı (%)

	L/S Cerrahi	Diag L/S
ENDOCAN	20.6	21.6

Marcoux S, 1997

Italyan Ç	L/S önce	5.8	6.7
	L/S sonra	16.7	23.1

Gruppo Italiano per lo Studio Endometriosi, 1999

- Endometriozisde spontan abortus artmaz !!!
- L/S cerrahi ile de abortus oranı daha da düşmez !!!

Endometriozis
Gebelik Kaybı

- Endometriozisde spontan abortus artmaz !!!
- Endometriozisle tekrarlayan gebelik kaybı arasında ilişki yoktur!!!
- Endometriozis -
  başarısız ART ya da
  tekrarlayan ART başarısızlığı arasında olası ilişki??? (Kötü folikül ⇒kötü oosit ⇒ kötü embriyo ⇒ implantasyon sorunu ⇒ canlı doğum ↓ (?)

DONÖR oosit verilecek olan , endometriozisli alıcılarda, tubal faktör olgularına kıyasla ART gebelik başarısı…

a. Belirgin olarak daha düşüktür

b. Belirgin olarak daha yüksektir

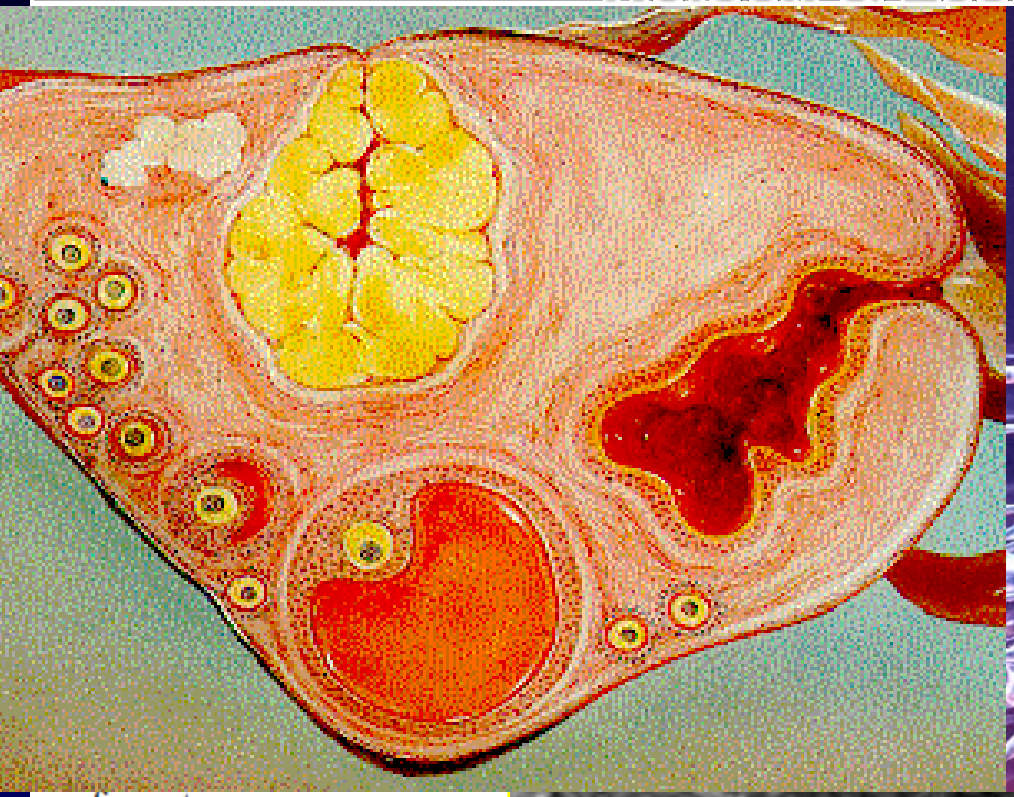
c. Anlamlı fark yoktur

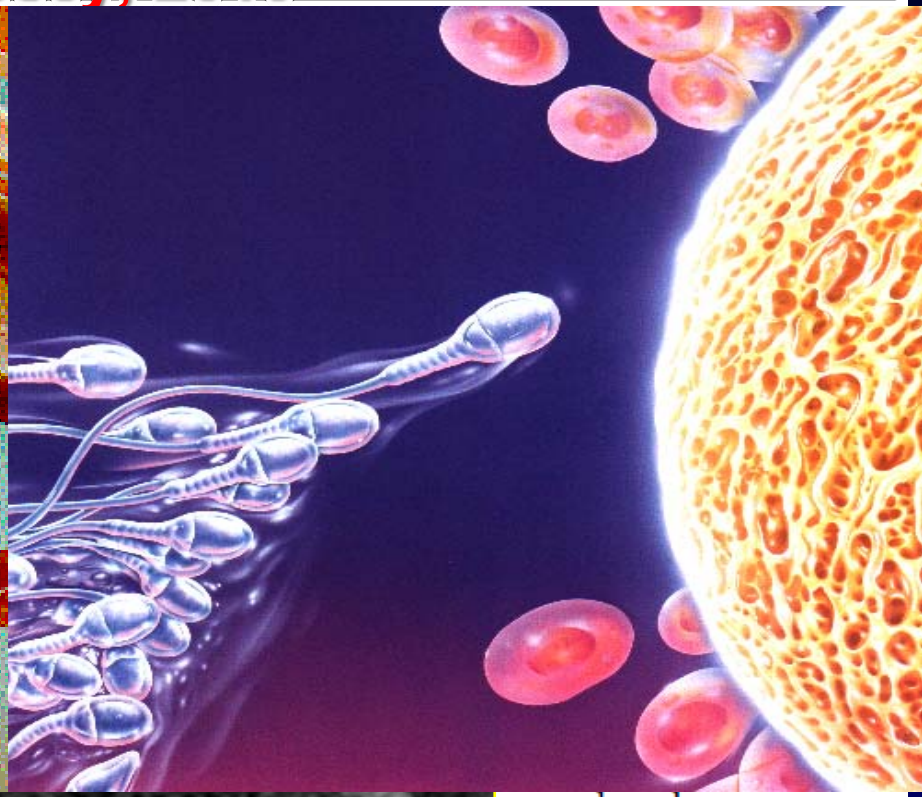
Hangisi yanlıştır?

a. Endometriozisde spontan abortus artmaz
b. Endometriozisle tekrarlayan gebelik kaybı arasında belirgin ilişki yoktur
c. Endometriozis olgularında periton sıvısında antioksidan kapasitesi azalmıştır
d. Endometriozisli kadınlarda sperm fonksiyonları etkilenmez
e. Endometriozis olgularında oosit kalitesi düşer

Proposed Mechanisms of Endometriosis on Fertility

Holoch & Lessey, 2010





of anatomy

Luteal phase defect

Endometrial receptivity

n, and embryo

, progesterone

e, aromatase

ses?

Endometriozis Fertilite

Bildiklerimiz - bilmediklerimiz

Teşekkürler...

ENDOMETRİOZİS SEMPOZYUMU 2011

ADENOMYOZİS DERNEĞİ 2009

Tarih : 23 Ocak 2011 Pazar
Saat : 09.00-17.00
Yer : Ankara Swiss Otel

Levent M. ŞENTÜRK, *Prof. Dr.*

Istanbul Üniversitesi Cerrahpaşa Tıp Fakültesi
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Reprodüktif Endokrinoloji Bilim Dalı, ÜYTE Bölümü