ENDOMETRİOZİS İNFERTİLİTE

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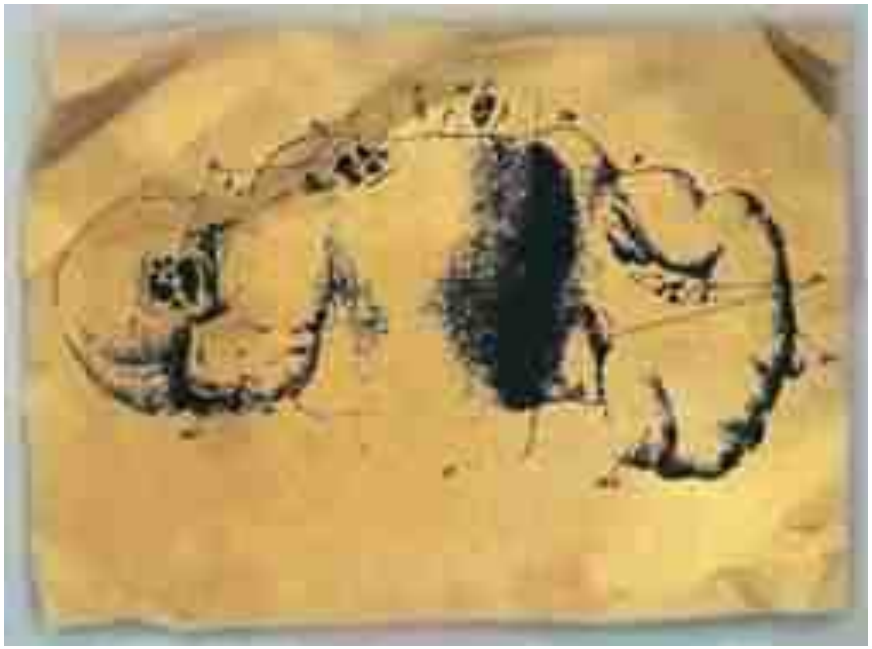
Endometriozis

- Endometrial dokunun uterus dışındaki varlığıdır.
  - Endometrial gland + Stroma ± İnflamasyon



Rokitansky
1860

Endometriozis özellikleri

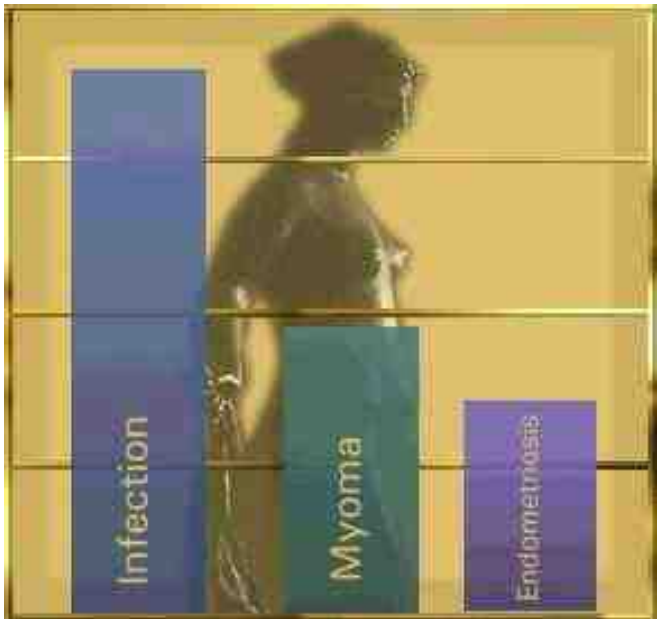
- Beningdir , ancak progresyon gösterir.
- Regresyon gösterebilir (%58)
- Rekürens yapma eğilimindedir.
- Lokal invaziv olabilir.
- Minimal lezyonlardan pelvik anatomiyi bozan varyasyonlar gösterebilir.

Sorular

- Endometriozis infertiliteye sebep olur mu?

Görülme Sıklığı

- Reprodüktif çağdaki kadınlarda % 7 – 10
- İnfertil kadınlarda 8 kat fazla %20 – 50
- Kronik pelvik ağrısı olanlarda %70 – 80
- Endometriozis varlığında İnfertilite %30 – 50



Endometriozis ve Doğurganlık

- Normal çiftlerde % 15-25
- Tedavi edilmemiş endometriozis hastalarında %2-10
  - Hastalığın evresi ile ilişkili

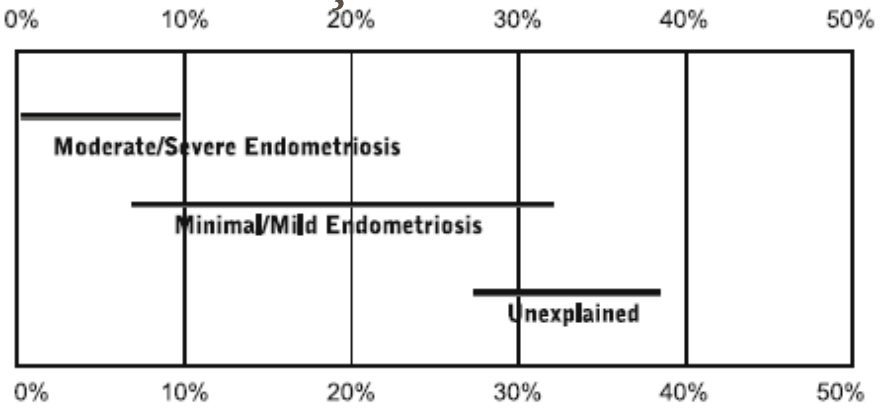


Fig. 1 The prognosis for live birth among untreated infertile couples. *Horizontal lines* indicate the cumulative live-births (± CI) recorded at 36 weeks of gestation for different groups of patients [14]

Differences in characteristics among 1,000 women with endometriosis based on extent of disease

Ninet Sinaii, Ph.D.,[a] *Katherine Plumb, B.A.,*[b] *Louise Cotton, R.N.,*[c] *Ann Lambert, Ph.D.,*[c] *Stephen Kennedy, M.D.,*[c] *Krina Zondervan, D.Phil.,*[d] *and Pamela Stratton, M.D.*[b]

Presenting symptoms for endometriosis diagnosis based on self-reported data from 940 women with surgically diagnosed endometriosis completing the OXEGENE study questionnaire.

Symptoms that led to diagnosis	Group I[a] (N = 423)	Group II[b] (N = 517)	Total (N = 940)	*P* value[c]
Dysmenorrhea	332 (78.5)	408 (78.9)	740 (78.7)	.95
Pelvic pain	302 (71.4)	350 (67.7)	652 (69.4)	.25
Dyspareunia	218 (51.5)	204 (39.5)	422 (44.9)	<.001
Bowel upset (e.g., constipation, diarrhea)	143 (33.8)	199 (38.5)	342 (36.4)	.29
Bowel pain	114 (27.0)	159 (30.8)	273 (29.0)	.23
Infertility	91 (21.5)	155 (30.0)	246 (26.2)	.004
Ovarian mass/tumor	31 (7.3)	152 (29.4)	183 (19.5)	<.001
Dysuria	48 (11.4)	45 (8.7)	93 (9.9)	.21
Other urinary problems	24 (5.7)	34 (96.6)	58 (6.2)	.67

Endometriosis-associated infertility

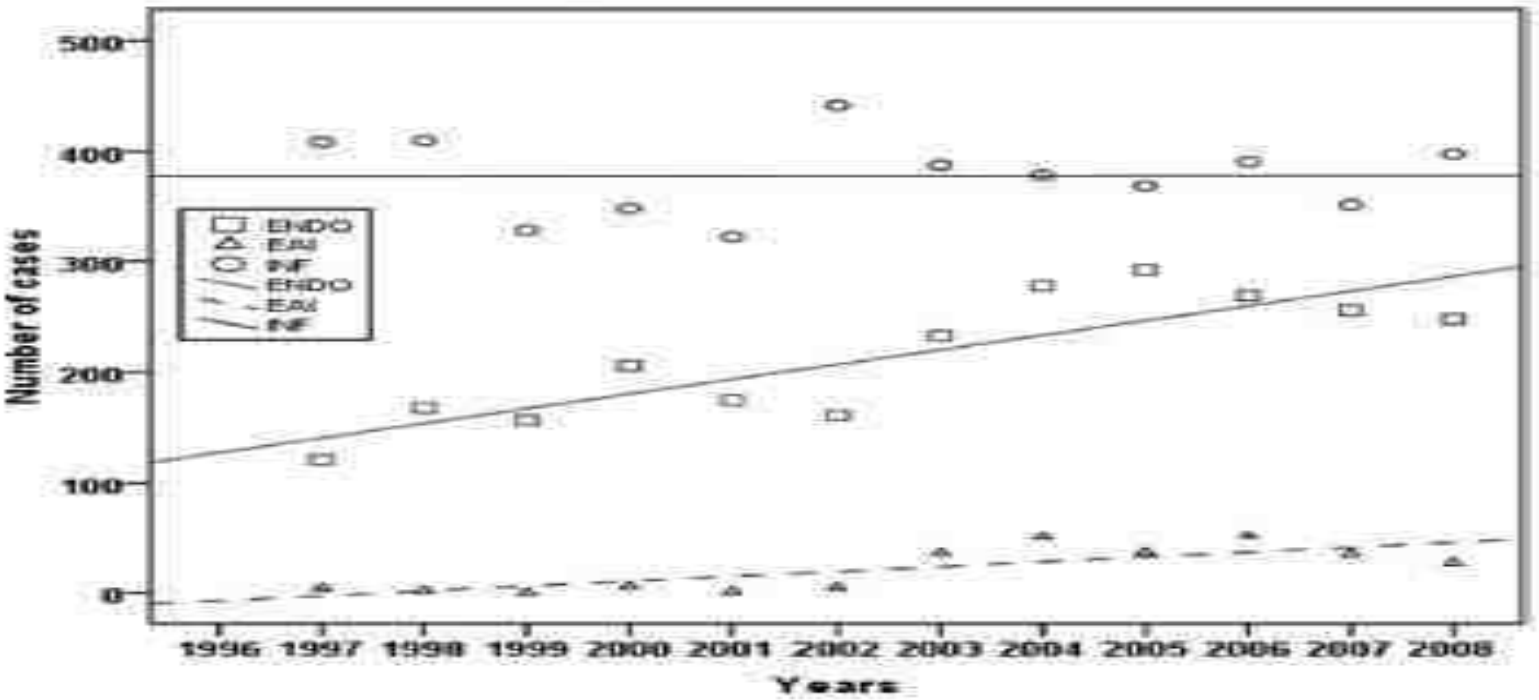


Figure 1. Annual variation of the number of newly diagnosed ENDO, EAI and INF cases between 1997 and 2008. Using simple linear regression analysis, there was a significative increase of ENDO ($r^2 = 0.717$, $p = 0.001$) and EAI ($r^2 = 0.601$, $p = 0.003$), while there was no increase of INF over years ($r^2 = 2813\ e{-}005$, $p = 0.987$).

KRYSTEL PARIS & AZIZ ARIS, 2010

Success in IUI: the role of etiology

- A total of 1,171 cycles among 532 infertile couples were retrospectively studied and the impact of different prognostic factors on pregnancy rate in five different etiology subgroups was analyzed.
- Results. The pregnancy rate/cycle was highest (19.2%) among women with anovulatory infertility and ***lowest (11.9%) in endometriosis*** based infertility.

Katja Ahinko-Hakamaa. Acta Obstet Gynecol Scand. 2007;86(7):855-60.

frontiers in SURGERY

REVIEW ARTICLE
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Endometriosis and infertility: how and when to treat?

Anis Fadhlaoui, Jean Bouquet de la Jolinière and Anis Feki*

Service de gynécologie obstétrique, HFR Fribourg – Hôpital Cantonal, Fribourg, Switzerland

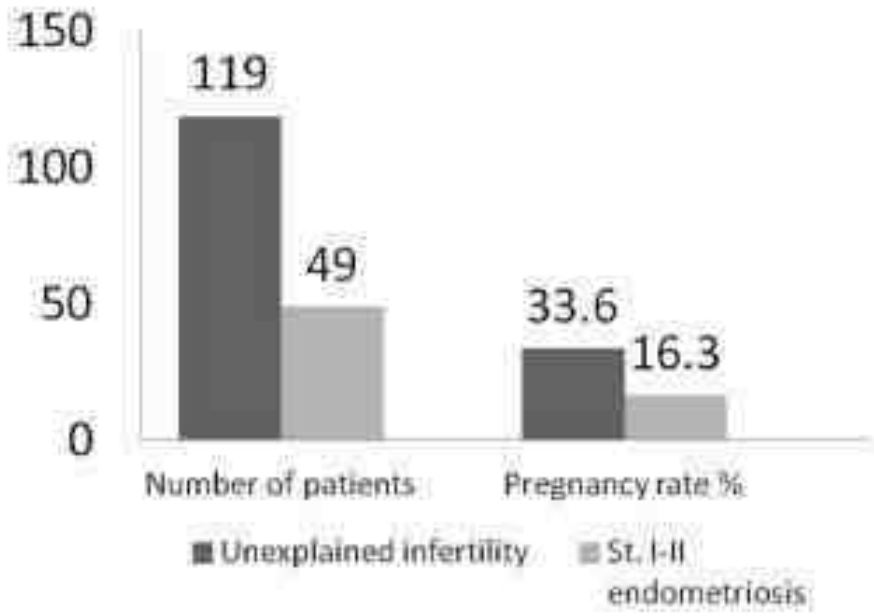


FIGURE 1 | Outcomes of COH–IUI in minimal or mild endometriosis (33).

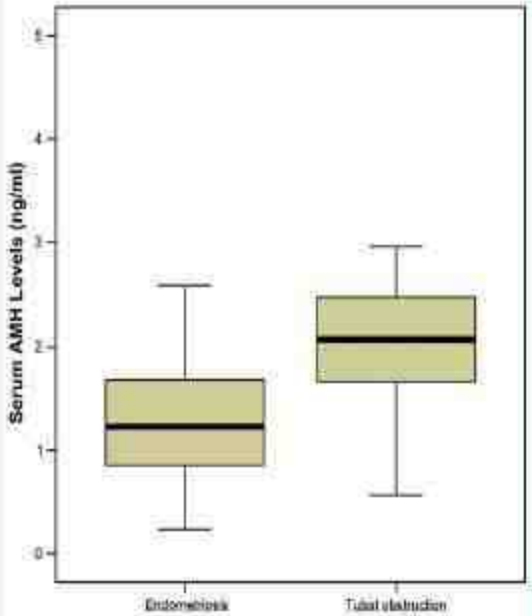
Endometriozis ve Doğurganlık

- Orta-şiddetli endometriozisi olan hastalara donor kadınlardan alınan oositlerle yapılan embriyo transferi: normal reseptivite ve gebelik oranları
- Endometriozisli hastalardan elde edilen oositlerden oluşan embriyolar: düşük implantasyon oranı ve kötü embriyo kalitesi *(Garrido, 2002)*

Decreased anti-Müllerian hormone and altered ovarian follicular cohort in infertile patients with mild/minimal endometriosis

FIGURE 1

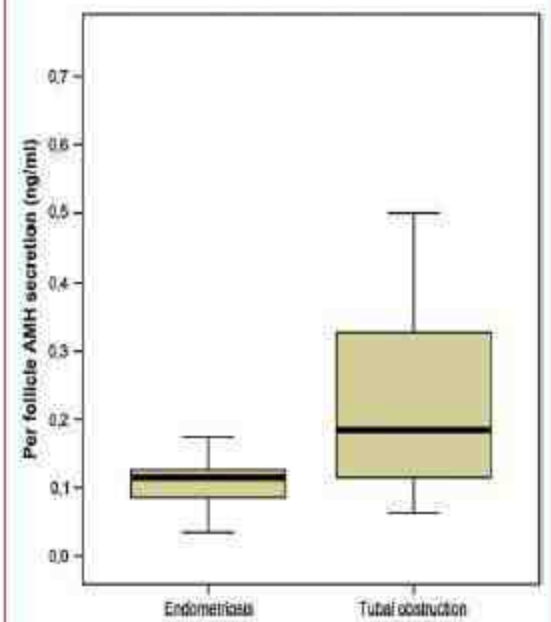
Serum anti-Müllerian hormone (AMH) (in nanograms per milliliter) comparison between infertile patients with minimal/mild endometriosis and infertile patients with tubal obstruction (without endometriosis). The box represents the interquartile range that contains the 50% of values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. A line across the box indicates the median. $P=.004$, Student's *t*-test.



Lemos. Follicular cohort, AMH, and endometriosis. Fertil Steril 2008.

FIGURE 2

Per follicle anti-Müllerian hormone (AMH) (in nanograms per milliliter) secretion comparison between infertile patients with minimal/mild endometriosis and infertile patients with tubal obstruction (without endometriosis). The box represents the interquartile range that contains the 50% of values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. A line across the box indicates the median. $P=.001$, Student's *t*-test.



Lemos. Follicular cohort, AMH, and endometriosis. Fertil Steril 2008.

NA Lemos, Fertil Steril. 2008 May;89(5):1064

Klinik prezantasyon

- Pelvik ağrı
- İnfertilite
- Dismenore
- Disparoni

Klinik prezantasyon

- Tipik olarak hastalar 30 lu yaşlarda, nullipar, infertil ve sekonder dismenoresi ve pelvik ağrısı olan kadınlardır.
- Hastalığın yaygınlığı ile semptomatoloji arasında korelasyon yoktur ve hastaların 1/3 ü asemptomatiktir.

Klinik prezantasyon

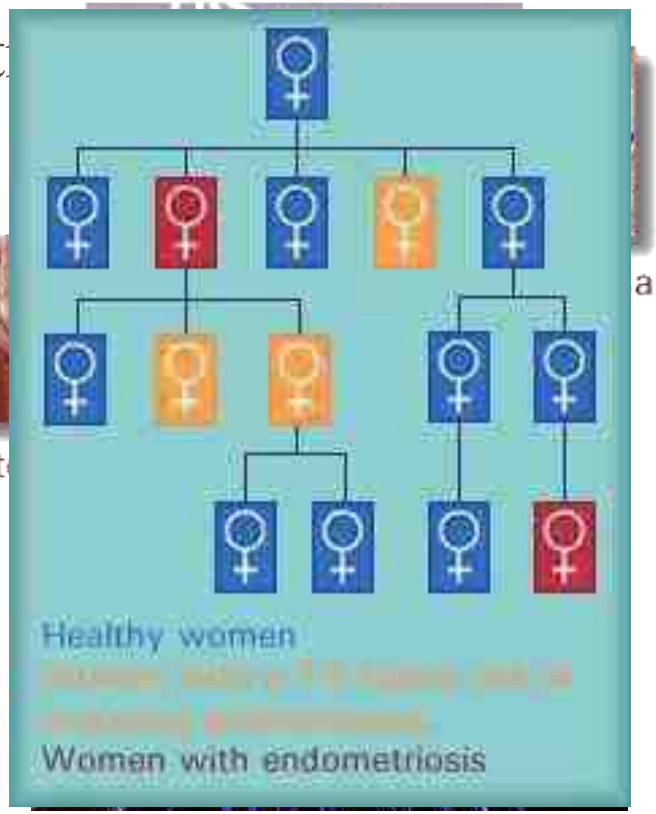
- Endometriozis infertil kadınlarda daha sık rastlandığından her infertil vakada endometriozis düşünülmelidir.

Sorular

- Endometriozis infertiliteye sebep olur mu?
  - Evet
- Endometriozis infertiliteye nasıl sebep olur?

Etyopatogenez

- Tam olarak bilinmemektedir.
- Farklı teoriler vardır :
  - Endometrial dokunun ektopik t
    - Retrograd menstrüasyon
    - Vasküler ve lenfatik diseminasy
    - Mekanik
  - Çölemik metaplazi
  - İmmün faktörler
  - Genetik faktörler

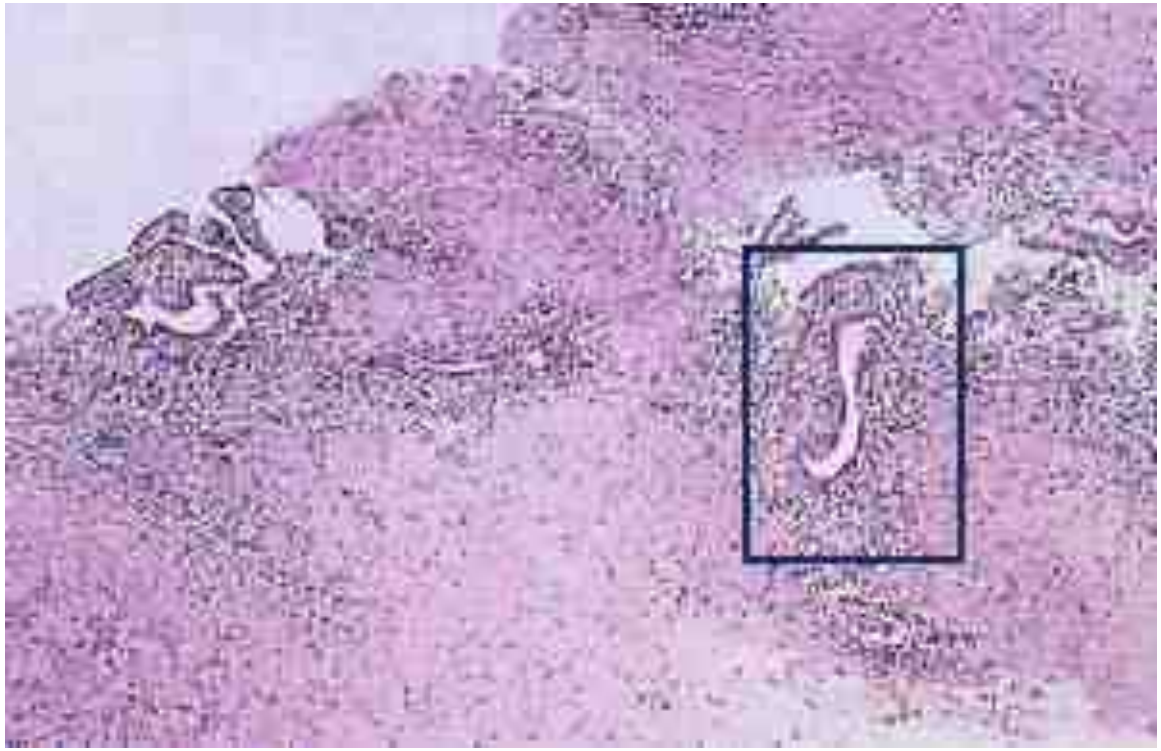


Erken inflamatuar reaksiyon

- Artmış vaskülarizasyon
- Hemorajik lezyonlar

Kronik inflamatuar reaksiyon

- Fibrozis



İnfiltrasyon

- Doku sınırı tanımaz
- Yayılım malign tm'e benzer

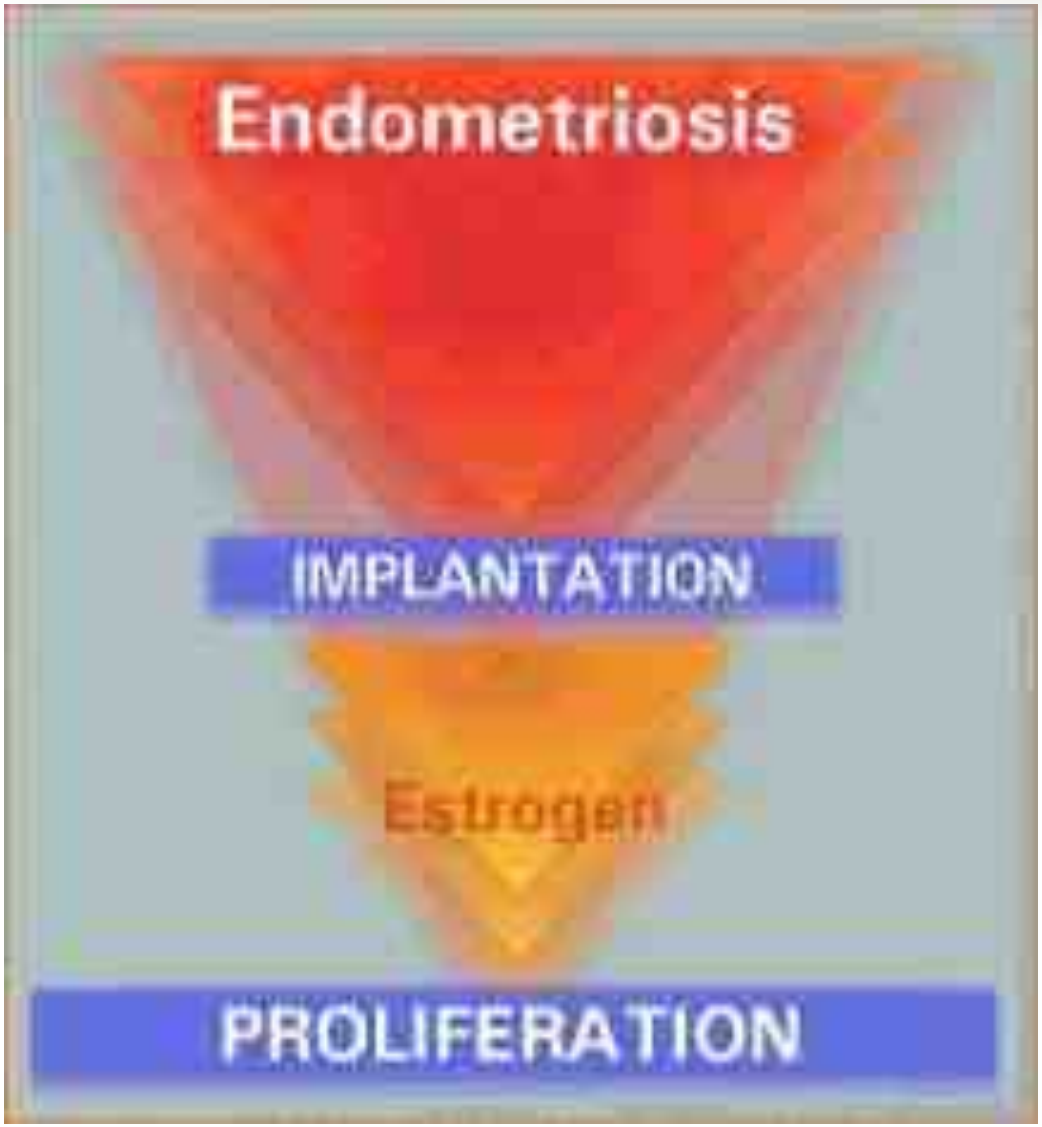

Endometriosis
IMPLANTATION
Estrogen
PROLIFERATION

TABLE 2. Proposed Mechanisms of Endometriosis on Fertility

Disruption	Point of Action	Proposed Mechanism
Oocyte production/ ovulation	Ovary/peritoneal fluid (PF)	Mechanical or inflammatory effects within the ovary of endometriomas
Gamete transport or oocyte pickup	Peritoneal fluid/fallopian tube function	Cytokine disturbances; expression difference in factors that regulate tubal function
Embryo toxicity	Inflammatory or toxic effects of the PF on gametes or embryos	Inflammation, hormonal disruption, LH concentrations, macrophage activation
Sperm quality or function	Peritoneal fluid or fallopian tube	Inflammatory or toxic effects of the PF or macrophages on sperm number or function
Disordered myometrial contractions	Uterus or fallopian tubes	Gamete transport or embryo placement
Pelvic distortion of anatomy	Uterus, tubes, ovaries, cervix	Mechanical disruptions preventing sperm, egg transport, fertilization, and embryo transport
Luteal phase defect	Endocrine	Ovulatory dysfunction, progesterone resistance
Endometrial receptivity	Endocrine, inflammatory cytokines	Progesterone resistance, aromatase expression, other causes?

Pelvik anatominin bozulması

- Overden oosit salınımı ve
- Oositin tubalar tarafından yakalanması ve taşınması olumsuz etkilenir

Schenken, 1984

Anormal uterotubal transport

- Fizyolojik uterotubal transport kapasitesinde azalma
  - Endometriozis %64 / Normal %32

Kissler 2005

Periton fonksiyonların bozulması

- Periton sıvısı artışı
- PG
- Proteazlar
- Sitokinler (IL-1, IL-6, TNFa, IL-8 ve VEGF) *Bedaiwy, 2002; Pizzo, 2002*
- Sistemik inflamasyon
  - Serum inflamasyon sitokinlerinde artış

Periton fonksiyonların bozulması

- Makrofajların proliferasyonu, aktivasyonu ve fagositotik fonksiyonlarının tam olmayışı *(Halme, 1983; Dmowski, 1998; Sharpe-Timms, 2002)*
- Proinflamasyon, büyüme ve anjiyogenetik faktörlerin sekresyonu *(Rana, 1996)*
- Natürel killer ve T lenfositlerde artış ve bunların disfonksiyonu *(Sukhikh, 2004; Oosterlynck, 1992)*

Hormonal ve hücresel fonksiyonlarda bozulma

- Endometriumda IgG, IgA ve lenfosit artışı
- Endometriuma karşı otoantikorlar
  - Endometrial reseptivite ve implantasyon bozulur *Lebovic, 2001*

Bozulmuş İmplantasyon

- İmplantasyon döneminde endometrial ***αvβ3 integrin*** (hücre adezyon molekülü) üretiminde azalma *(Lessey, 1994)*
- Endometrial ligand **L-selektin** (blastosist yüzeyindeki trofoblastları kaplayan protein) sentezi yapan enzimde azalma *(Genbacev, 2003)*

Bozulmuş İmplantasyon

- Endometriumda makrofaj *(Tokushige, 2007)* ve dentritik hücre *(Schulke, 2009)* artışı
- Sitokinlerde artış (IL-6, 8, 10, TGF ve TNFα)

Bozulmuş İmplantasyon

- Steroidogenik faktör-1, PG E2, CYP19A1 (aromataz kodlaması yapmaktadır) gen ekspresyonu ve Aromataz'ın aktivasyonu

  (Zeitoun, 1999 ve Noel, 2010)

- İn-situ estrojen üretimi *(Dassen, 2007)*
- Estrojen myometriumda peristaltik aktiviteyi bozmaktadır *(Leyendecker, 2009)*
- Estrojenin lokal olarak üretilmesi ile progesteron rezistansı oluşabilmektedir *(Burney, 2007)*

Endokrin ve Ovülasyon Anormallikleri

- LUF
- Luteal faz disfonksiyon
- Anormal foliküler büyüme
- Prematür ve multipl LH surge'leri *(Schenken, 1984)*
- Düşük E düzeyleri ile seyreden uzun foliküler faz ve lüteal dönemde LH bağımlı progesteron salınımında azalma *(Cahill, 1997 ve Cunha-Filho, 2003)*

Oosit ve Embriyo Kalitesi

- Folikül içindeki değişimler
  - Değişken progesteron ve sitokin seviyesi *(Pellicer, 1995)*
- Kötü oosit kalitesi ve embriyogenez
  - Daha yavaş embriyo gelişimi
- Azalmış endometrial reseptivite
  - Orta-şiddetli endometriozisli hastalara donor kadınlardan alınan oositlerle yapılan ET: normal reseptivite ve gebelik oranları
  - Endometriozisli hastadan elde edilen oositlerden oluşan embriyolar: düşük implantasyon oranı ve kötü embriyo kalitesi *(Garrido, 2002)*

Sperm ve oosit etkileşimi

- Peritoneal sıvıdaki TNF-α *(Faber, 2001),* IL-1 *(Sueldo, 1990),* Migrasyon inhibe edici faktör *(Carli, 2007)*
  - spermin zonaya bağlanma inhibisyonu
  - sperm kapasitasyonunda bozulma *(Carli, 2009)*
  - spermlerde DNA hasarı *(Mansour, 2009)*
- Oksidatif stres nedeniyle akrozom reaksiyonu ve sperm-oosit etkileşiminde bozulma *(Iborra, 2005 ve Baker, 2004)*

Pelvik ağrı - Disparoni

- Çiftlerin düzenli cinsel ilişkiye girmesini etkilemektedir

Sorular

- Endometriozis infertiliteye sebep olur mu?
  - Evet
- Endometriozis infertiliteye nasıl sebep olur?
  - ???
- Endometriozis tedavisi yapalım mı? Nasıl?

Tanı

- Kesin tanı için cerrahi girişim gereklidir
  - L/S
- Histolojik değerlendirme

Endometriozis heterojen bir hastalıktır

- Tipik ve atipik lezyonlar
- Lezyon boyutları değişkendir
  - 1mm peritoneal implant
  - >10 cm endometrioma
  - Douglas obliterasyonu

Klasifikasyon

- Yürürlükteki sınıflama ‘ ‘ AFS/ASRM ’ ’ sınıflama sisteminin revizyona uğramış şeklidir.
- Sistem hastalığın yaygınlığını yansıtır ancak ağrı veya infertilite ile korelasyonu yansıtmamaktadır.
- Bir puanlama sistemidir.
- Gebelik olasılığını öngörmede yetersiz

Endometriosis fertility index: the new, validated endometriosis staging system

2009

G. David Adamson, M.D. and David J. Pasta, M.S.

Descriptions of least function terms.

Structure	Dysfunction	Description
Tube	Mild	Slight injury to serosa of the fallopian tube
	Moderate	Moderate injury to serosa or muscularis of the fallopian tube; moderate limitation in mobility
	Severe	Fallopian tube fibrosis or mild/moderate salpingitis isthmica nodosa; severe limitation in mobility
	Nonfunctional	Complete tubal obstruction, extensive fibrosis or salpingitis isthmica nodosa
Fimbria	Mild	Slight injury to fimbria with minimal scarring
	Moderate	Moderate injury to fimbria, with moderate scarring, moderate loss of fimbrial architecture and minimal intrafimbrial fibrosis
	Severe	Severe injury to fimbria, with severe scarring, severe loss of fimbrial architecture and moderate intrafimbrial fibrosis
	Nonfunctional	Severe injury to fimbria, with extensive scarring, complete loss of fimbrial architecture, complete tubal occlusion or hydrosalpinx
Ovary	Mild	Normal or almost normal ovarian size; minimal or mild injury to ovarian serosa
	Moderate	Ovarian size reduced by one-third or more; moderate injury to ovarian surface
	Severe	Ovarian size reduced by two-thirds or more; severe injury to ovarian surface
	Nonfunctional	Ovary absent or completely encased in adhesions

To develop a clinical tool that predicts pregnancy rates (PRs) in patients with surgically documented endometriosis who attempt non-IVF conception.

FIGURE 1

Endometriosis fertility index surgery form.

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description
4	= Normal
3	= Mild Dysfunction
2	= Moderate Dysfunction
1	= Severe Dysfunction
0	= Absent or Nonfunctional

	Left	Right
Fallopian Tube		
Fimbria		
Ovary		

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	Left	+	Right	=	LF Score

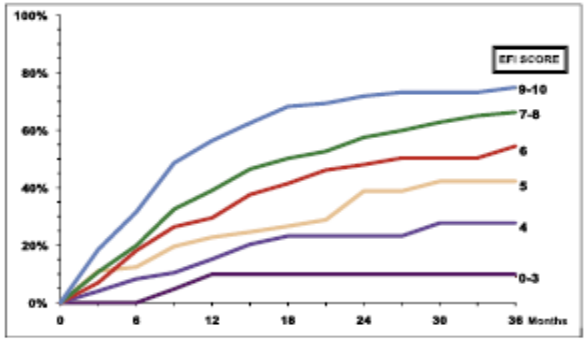
ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		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
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:

Historical	+	Surgical	=	EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE

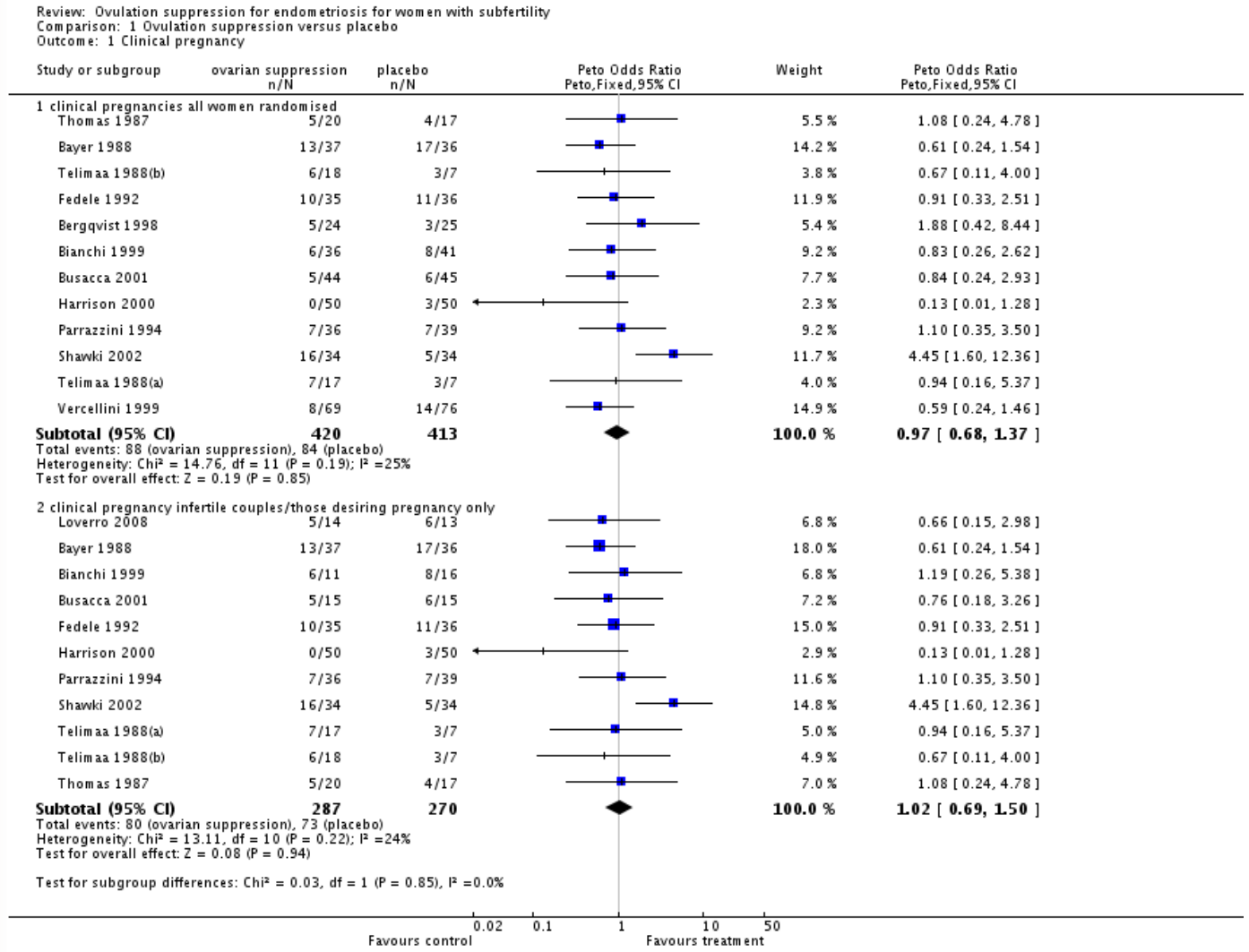


Adamson. Endometriosis fertility index. Fertil Steril 2009.

Tedavi

- Hastanın fertilite isteği,
- Yaşı,
- Semptomların derecesi,
- Lezyonların yeri,
- Hastalığın evresi,
- *Eşlik eden diğer durumlar göz önüne alınarak tedavi bireyselleştirilmelidir.*
- Optimal tedavi yoktur
- Hastalık kronikleşebilir

Endometriozis ve Medikal yaklaşım



Endometriozis ve Medikal yaklaşım

- Progesteron
- [illegible]
- G[illegible]nist
- [illegible]onist
- [illegible]azol
- *Aromataz inhibitörleri*

- Ağrı tedavisinde geçerli
- Hormonal baskılama infertilite tedavisinde etkisiz

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes, et al., 2007).	**A**

antagonistleri

Gözlem tedavisi

- Minimal ve hafif endometriozis
- İnfertilite süresinin kısa (< 4 yıl)
- Genç hastalarda uygulanabilir.

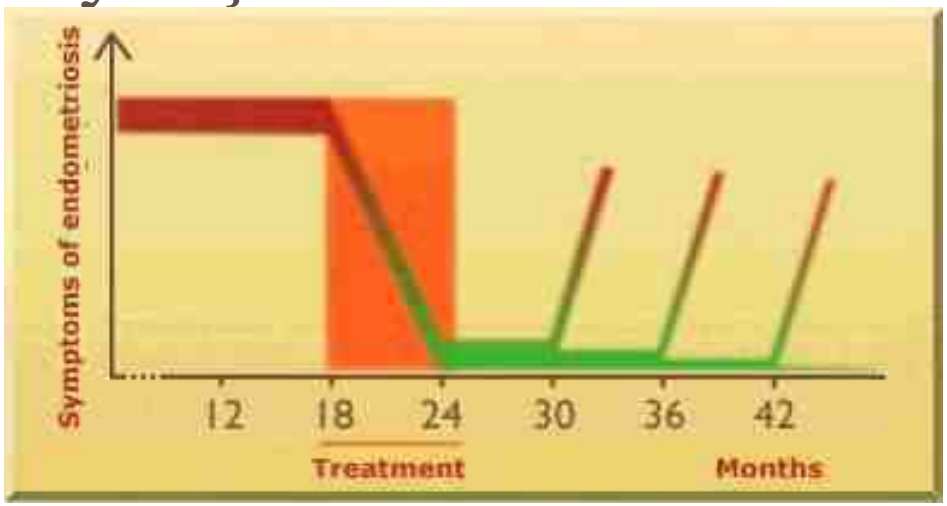
[Çeşitli çalışmalarda minimal ve hafif endometriozisin L / S tanısını takiben %30-72 ye varan gebelik oranları bildirilmiştir.]

- İleri evre endometrioziste gözlem tedavisi ile elde edilen gebelik sonuçları oldukça düşüktür.

Cerrahi tedavi

- Bütün endometriozis odaklarını ortadan kaldırmak
- Adezyonları açmak
- Reprodüktif fonksiyonu korumak
- Normal anatomiyi restore etmektir.

- Konservatif cerrahiyi takiben gebelik oranları hastalığın evresi ile ters orantılıdır.
  - Minimal endometrioziste % 75
  - Orta dereceli endometrioziste %50 – 60
  - Ciddi endometrioziste %30 – 40
- Rekürrens 3 yıl içinde > % 10
  5 yıl içinde > % 35



Surgery for endometriosis-associated infertility: a pragmatic approach

Paolo Vercellini[1,3,4], Edgardo Somigliana[2,3], Paola Viganò[3], Annalisa Abbiati[1,3], Giussy Barbara[1], and Pier Giorgio Crosignani[1]

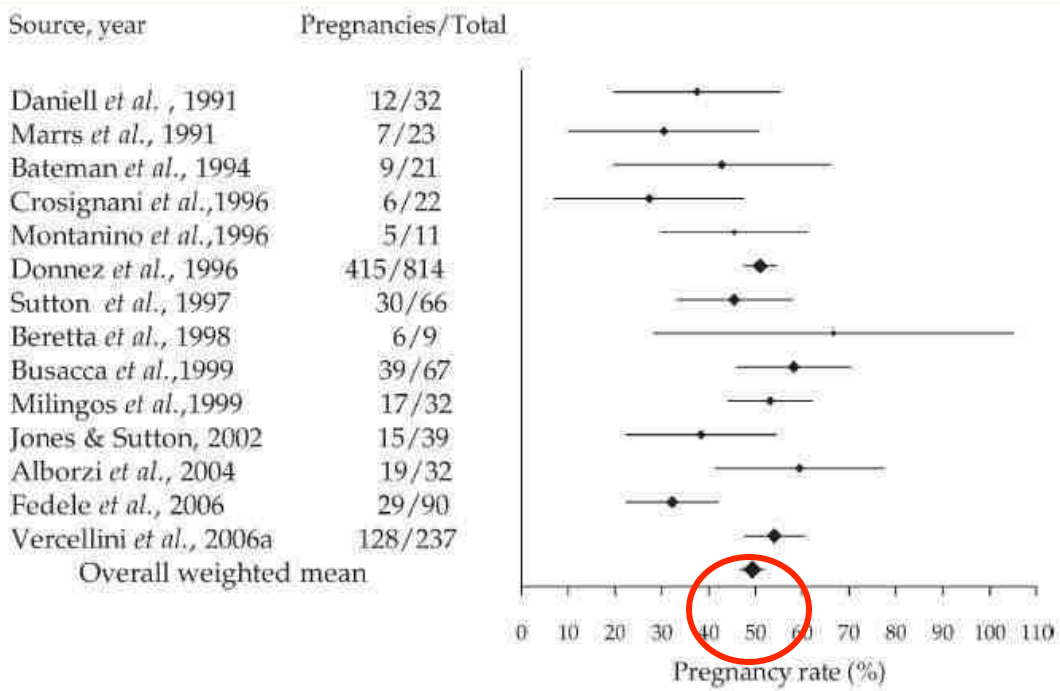


Figure 3 Pregnancy rates observed after laparoscopic excision of endometriomas.Diamonds represent percentage point estimates and horizontal lines represent 95% CIs. Modified from Jones and Sutton (2002), with permission.

Surgery for endometriosis-associated infertility: a pragmatic approach

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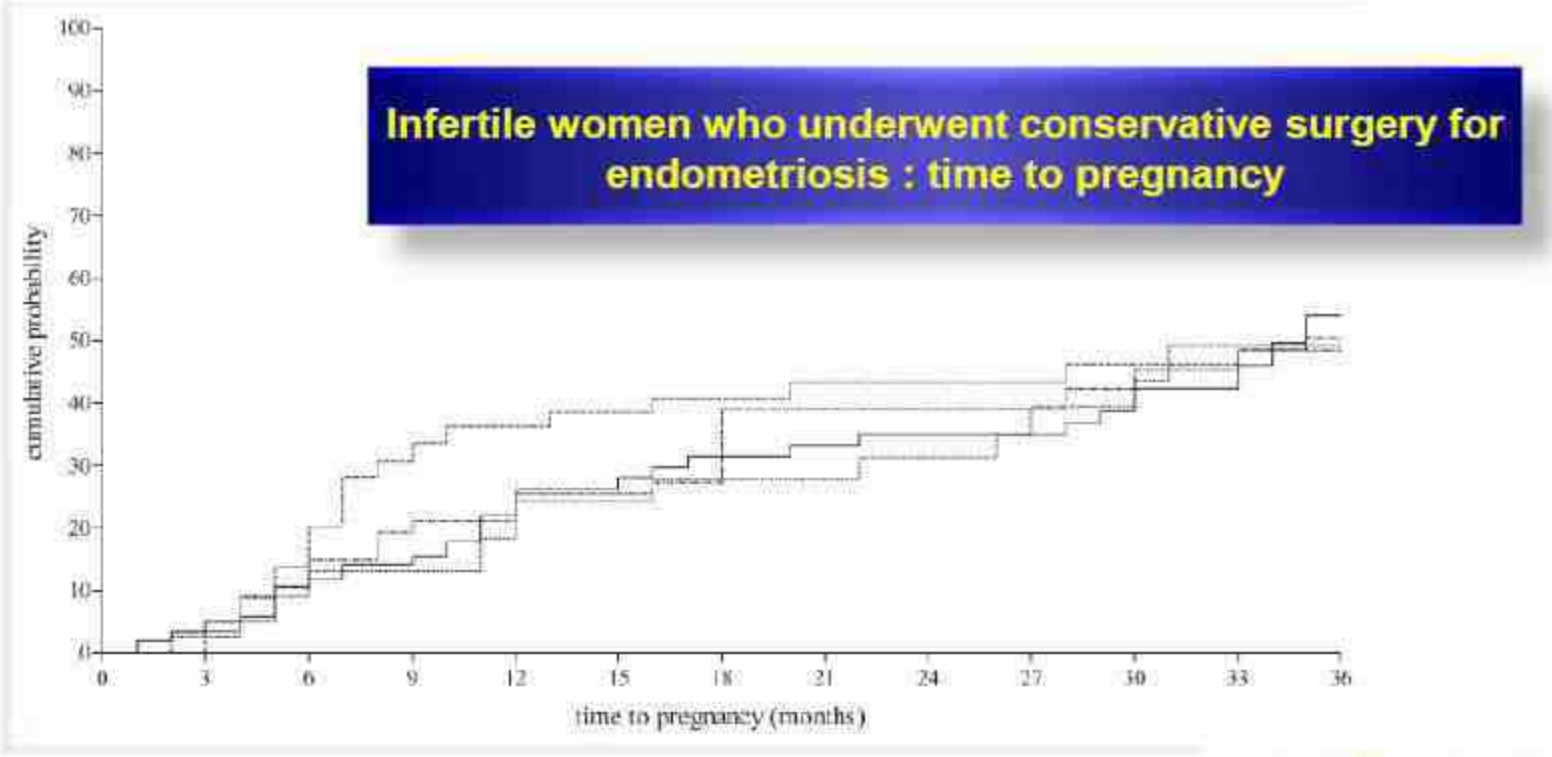
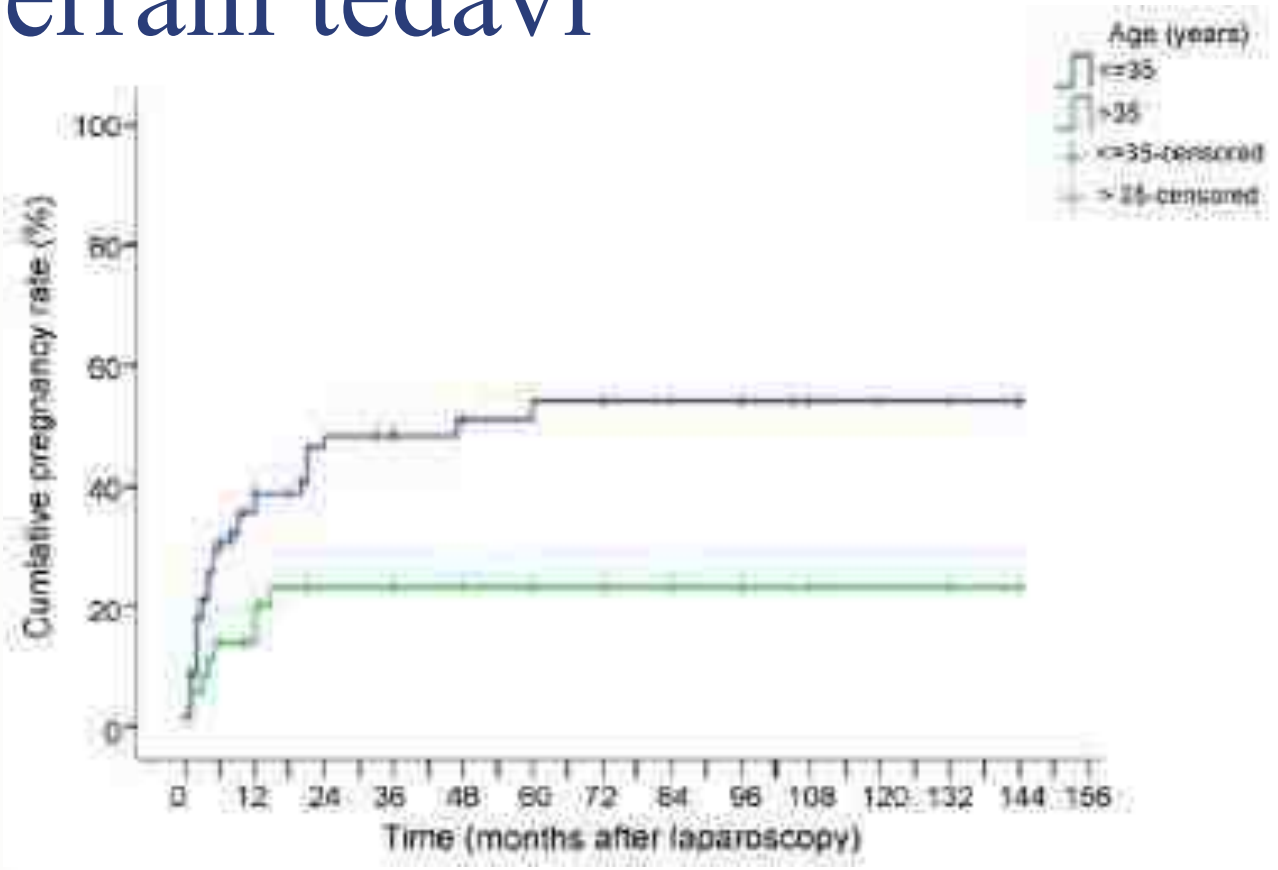


Hum reprod 2009

Cerrahi tedavi



Endometriosis and infertility Surgery and ART: An integrated approach for successful management
M. E. Coccia. European Journal of Obstetrics & Gynecology and Reproductive Biology 138 (2008) 54–59

Cerrahi tedavi

Analysis 1.1. Comparison 1 Laparoscopic surgery versus diagnostic laparoscopy, Outcome 1 ongoing pregnancy at 20 weeks or live birth.

Review: Laparoscopic surgery for subfertility associated with endometriosis

Comparison: 1 Laparoscopic surgery versus diagnostic laparoscopy

Outcome: 1 ongoing pregnancy at 20 weeks or live birth

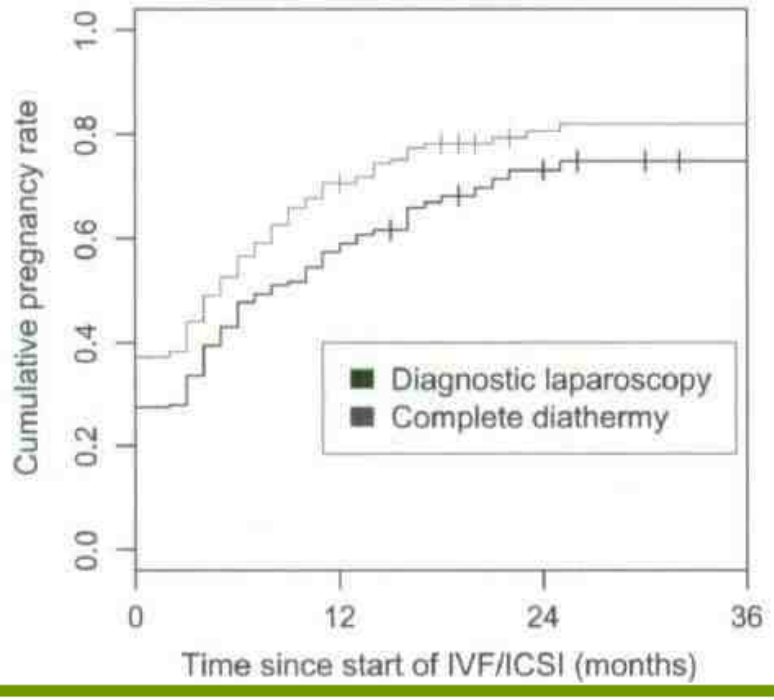
Study or subgroup	laparoscopic surgery n/N	control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Gruppo Italiano 1999	10/51	10/45		20.7 %	0.85 [0.32, 2.28]
Marcoux 1997	50/172	29/169		79.3 %	1.95 [1.18, 3.22]
Total (95% CI)	**223**	**214**		**100.0 %**	**1.64 [1.05, 2.57]**

Total events: 60 (laparoscopic surgery), 39 (control)

Heterogeneity: $Chi^2 = 2.14$, df = 1 ($P = 0.14$); $I^2 = 53\%$

Test for overall effect: $Z = 2.17$ ($P = 0.030$)

Cerrahi tedavi



Evre I-II Endometrioziste hormonal baskılama fertilite için etkin değildir, lezyonların ablasyon ve adezyolizisi diagnostik L/S'den üstündür

Evre III-IV Endometrioziste IVF öncesi cerrahi eksizyonun gebelik oranını artırdığına dair yeterli kanıt yoktur

In infertile women with AFS/ASRM stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat, et al., 1989, Vercellini, et al., 2006a).	**B**

Endometriosis and infertility

Carlo Bulletti · Maria Elisabetta Coccia · Silvia Battistoni · Andrea Borini

Table 5 Endometrioma: clinical variables to be considered when deciding whether to perform surgery or not in women selected for IVF [60]

Characteristics	Favours surgery	Favours expectant management
Previous interventions for endometriosis	None	≥1
Ovarian reserve [a]	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolateral disease	Bilateral disease
Sonographic feature of malignancy [b]	Present	Absent
Growth	Rapid growth	Stable

J Assist Reprod Genet (2010) 27:441–447

frontiers in SURGERY

REVIEW ARTICLE
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Endometriosis and infertility: how and when to treat?

Anis Fadhlaoui, Jean Bouquet de la Jolinière and Anis Feki*

Service de gynécologie obstétrique, HFR Fribourg – Hôpital Cantonal, Fribourg, Switzerland

Table 2 | Risk and benefits of observational and surgical management of endometriomas (19).

Observational	Surgery
BENEFITS	
Avoid surgery	Exclude malignancy
Low FSH doses	Relieve symptoms
Increased E2	Reduce the risk of cyst complications
Increased follicles	Facilitate transvaginal access to ovarian follicles
RISKS	
Pain	Ovarian failure because of destruction of normal tissue
No histological diagnosis	Reduced number of egg collected
Pelvic infection following oocyte retrieval	Risks of surgery

Medikal + Cerrahi tedavi

Analysis 3.3. Comparison 3 Post-surgical medical therapy vs placebo, Outcome 3 Pregnancy.

Review: Pre and post operative medical therapy for endometriosis surgery

Comparison: 3 Post-surgical medical therapy vs placebo

Outcome: 3 Pregnancy

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Parazzini 1994	7/36	7/39		82.9 %	1.08 [0.42, 2.79]
Telimsa 1987	2/18	1/8		17.1 %	0.89 [0.09, 8.44]
Total (95% CI)	**54**	**47**		**100.0 %**	**1.05 [0.44, 2.51]**

Total events: 9 (Treatment), 8 (Control)

Heterogeneity: $Chi^2 = 0.03$, df = 1 ($P = 0.87$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.11$ ($P = 0.91$)

Medikal + Cerrahi tedavi

In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.	GPP
In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness, et al., 2004).	A

Endometriozis IUI

Group	Unexplained	Endometriosis-associated infertility			
Treatment	Guzick et al. (1999)	Deaton at al. (1990)	Chaffkin et al. (1991)	Fedele et al. (1991)	Kemmann et al. (1993)
No treatment or intracervical insemination	0.02	0.033	-	0.045	0.028
IUI	0.05*	-	-	-	-
Clomiphene	-	-	-	-	0.066
Clomiphene/IUI	-	0.095*	-	-	-
Gonadotropins	0.04*	-	0.066	-	0.073*
Gonadotropins/IUI	0.09*	-	0.129*	0.15*	-
IVF	-	-	-	-	0.22

IUI, intrauterine insemination; IVF, in vitro fertilization. * P<0.05 for treatment vs. no treatment.

Endometriozis IUI

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates (Tummon, et al., 1997).	C
In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of intrauterine insemination alone, as it increases pregnancy rates (Nulsen, et al., 1993).	C
In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider performing intrauterine insemination with controlled ovarian stimulation within 6 months after surgical treatment, since pregnancy rates are similar to those achieved in unexplained infertility (Werbrouck, et al., 2006).	C

Endometriozis IVF

Group	Unexplained	Endometriosis-associated infertility			
Treatment	Guzick et al. (1999)	Deaton at al. (1990)	Chaffkin et al. (1991)	Fedele et al. (1991)	Kemmann et al. (1993)
No treatment or intracervical insemination	0.02	0.033	-	0.045	0.028
IUI	0.05*	-	-	-	-
Clomiphene	-	-	-	-	0.066
Clomiphene/IUI	-	0.095*	-	-	-
Gonadotropins	0.04*	-	0.066	-	0.073*
Gonadotropins/IUI	0.09*	-	0.129*	0.15*	-
IVF	-	-	-	-	0.22

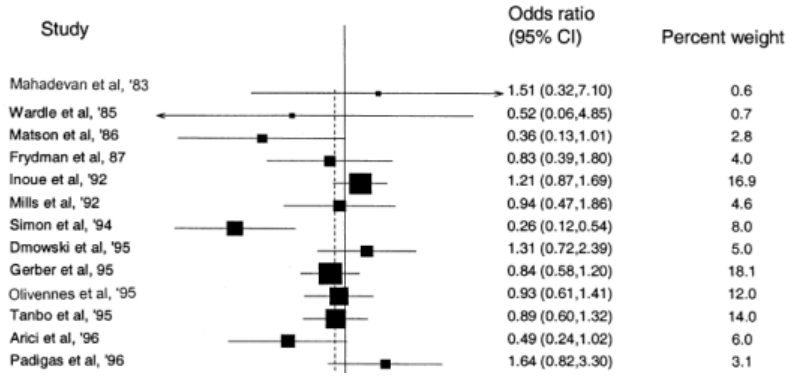
IUI, intrauterine insemination; IVF, in vitro fertilization. * P<0.05 for treatment vs. no treatment.

Endometriozis IVF

The GDG recommends the use of assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.	**GPP**

FIGURE 1

Unadjusted meta-analysis of odds of pregnancy in endometriosis patients vs. tubal factor controls.



HCG. In addition, the GDG noted that endometriosis does not adversely affect pregnancy rates in some large databases [e.g. the Society for Assisted Reproductive Technology (SART) and the Human Fertilisation and Embryology Authority (HFEA)].

Barnhart. IVF in endometriosis-associated infertility. Fertil Steril 2002.

Endometriozis IVF

Results of first attempt.

Type of treatment	ASRM I-II (n = 724)	ASRM III-IV (n = 350)	Tubal factor (n = 1171)
IVF	671 (92.7%)	332 (94.9%)	1119 (95.6%)
ICSI	53 (7.3%)	18 (5.1%)	52 (4.4%)[a]
Dose of FSH	1965 ± 930	2313 ± 1024[a]	2081 ± 1046
Cancellation rate	1.2% (9/724)	2.3% (8/350)	1.2% (14/1171)
No. of oocytes	9.3 ± 5.2	8.0 ± 5.3[a]	9.2 ± 5.6
Mature	90.3% (5082/5627)	91.3% (2050/2246)	90.4% (7619/8427)
Immature	8.5% (476/5627)	7.0% (158/2246)	7.2% (606/8427)
Others	1.2% (69/5627)	1.7% (38/2246)	2.4% (202/8427)
Sperm concentration	117 ± 89[b]	123 ± 77	135 ± 90
Sperm motility	54 ± 20[b]	57 ± 19	59 ± 20
Fertilization rate IVF	59.6%[b] (3643/6109)	62.9% (1626/2584)	63.5% (6447/10,145)
Implantation rate	[illegible] (294/1058)	[illegible] (133/533)	[illegible] (471/1895)
PR per started cycle	36.0% [illegible]61/724)	32.9% (115/350)	34.7% (406/1171)
PR per ET	[illegible] (261/662)	[illegible] (115/312)	[illegible] (406/1072)
Biochemical pregnancy (<6)	9.6% (25/261)	8.7% (10/115)	14.5% (59/406)
Miscarriage (6–12)	18.8% (49/261)	17.4% (20/115)	12.6 (51/406)
Birth/ongoing	[illegible] (187/261)	[illegible] (85/312)	[illegible] (296/406)
Birth/ongoing pregnancy per started cycle	25.8% [illegible]187/724)	24.3% [illegible]85/350)	25.3% [illegible]296/1171)

[a] P<.05
[b] P<.01

Opøien. Endometriosis and IVF/ICSI outcomes. Acta Stord 2012.

In vitro fertilization is a successful treatment in endometriosis-associated infertility
Hans Kristian Opøien. Fertility and Sterility® Vol. 97, No. 4, April 2012

Endometrioma IVF

Outcome of the first cycle in patients with ASRM stage III-IV without and with endometrioma.

	Without endometrioma	Endometrioma
No. of cycles	164	186
Dose of FSH (IU)	2152 ± 924	2446 ± 1124[a]
No. of oocytes	8.6 ± 5.3	7.6 ± 5.5
Fertilization rate	62.5% (866/1380)	61.6% (819/1329)
Implantation rate	36.9% (83/308)	20.9% (66/316)
PR	40.2% (66/164)	26.3% (49/186)[a]
Birth/ongoing PR	30.5% (50/164)	18.8% (35/186)[b]

[a] $P<.01$.
[b] $P<.05$.

Opøien. Endometriosis and IVF/ICSI outcomes. Fertil Steril 2012.

In vitro fertilization is a successful treatment in endometriosis-associated infertility
Hans Kristian Opøien. Fertility and Sterility® Vol. 97, No. 4, April 2012

Endometrioma IVF

TABLE 1

Number of antral follicles and retrieved oocytes from endometrioma-containing ovaries and from the contralateral ovaries.

	Ovary with endometrioma	Ovary with no endometrioma	*P* value	95% Confidence interval
No. of antral follicles	7.7 ± 1.0	8.5 ± 0.9	.3	−1.0 to 3.0
No. of retrieved oocytes	6.0 ± 0.4	6.1 ± 0.5	.8	−1.0 to 1.0
No. of retrieved oocytes when endometrioma size >25 mm	5.8 ± 1.4	6.6 ± 1.1	.5	−4.0 to 2.0

TABLE 2

Age, antral follicle count, total number of retrieved oocytes, total dose of gonadotropin used, days of stimulation, and E_2 levels on hCG day among women with unilateral ovarian endometrioma and those with no endometrioma.

	Endometrioma group	Control group	*P* value	95% Confidence interval
No. of patients	81	162		
Age (y)	35.2 ± 0.8	35.2 ± 0.4	.9	−2.0 to 2.0
Total dose of gonadotropin (IU)	3,847 ± 145	3,580 ± 190	.5	−22.0 to 41.0
Days of stimulation	11.1 ± 1.3	10.9 ± 1.9	.4	−1.0 to 3.0
E_2 levels on hCG day (pmol/mL)	6,201 ± 1,658	6,421 ± 1,842	.8	−230.0 to 413.0
Antral follicle count	15.0 ± 1.6	14.2 ± 1.4	.4	−1.0 to 2.0
No. of retrieved oocytes	11.9 ± 0.8	11.4 ± 0.5	.3	−1.0 to 3.0

Benny Almog, 2010

Endometrioma:
Surgical treatment and ovarian reserve

Different nature of ovarian cysts

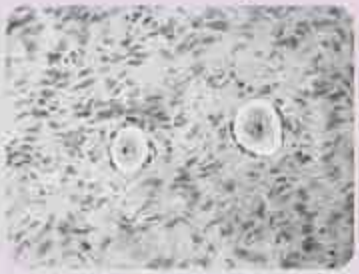
Well-defined ovarian capsule

- ✓ *dermoids*
- ✓ *serous cystadenomas*
- ✓ *mucinous cystadenomas*

→ **Ovarian tissue removed 6%**

Endometriomas
(margin of ovarian tissue)

Endometrioma cyst wall



Primordial follicles

→ **Ovarian tissue removed 54-69%**

Muzii L et al, J Am Assoc Gynecol Laparosc. 2004

A comparison of histopathologic findings of ovarian tissue inadvertently excised with endometrioma and other kinds of benign ovarian cyst in patients undergoing laparoscopy versus laparotomy

Saeed Alborzi, M.D.,[a] *Leila Foroughinia, M.D.,*[a] *Perikala Vijayananda Kumar, M.D.,*[b] *Nasrin Asadi, M.D.,*[a] *and Soroosh Alborzi, M.D.*[a]

TABLE 1

Comparison of the presence of ovarian tissue inadvertently excised in different ovarian cysts during laparotomy and laparoscopy.

Type of ovarian cyst	Laparoscopy (n = 150)	Laparotomy (n = 110)	*P* value
Endometrioma	49 (65%)	40 (80%)	.07
Nonendometrioma	24 (32%)	25 (41%)	.2

Alborzi. Cystectomy by laparoscopy and laparotomy. Fertil Steril 2009.

Endometrioma ve diğer over kistlerinin çevre dokusundaki histopatolojik değişiklikler

Tablo 1: Kist duvarındaki over dokusunda bulunan foliküler yapılar

	Endometrioma (n=50)	Non Endometrioma (n=50)	p
Yaş (yıl)	30.94 ± 6.18	32.14± 6.53	AD
Kist boyutu (cm)	4.42 ± 2.11	4.56 ± 2.21	AD
Folikül	1.5 ± 2.0	4.2 ± 3.0	<0.05
Primordial fol.	0.7 ± 1.0	1.7 ± 1.5	<0.05
Primer fol.	0.6 ± 1.0	1.8 ± 1.5	<0.05
Sekonder fol.	0.06 ± 0.2	0.4 ± 0.6	<0.05
Graf fol.	0.04± 0.2	0.1 ± 0.3	<0.05

Tablo 2: Kist duvarındaki over dokusunda bulunan foliküllerin karşılaştırılması

	Endometrioma (n=30)	Non Endometrioma (n=48)	p
Folikül	2.5 ± 2.0	4.4 ± 3.0	<0.05
Primordial fol.	1.3 ± 1.1	1.8 ± 1.5	AD
Primer fol.	1.0 ± 1.1	1.9 ± 1.5	<0.05
Sekonder fol.	0.1 ± 0.3	0.4 ± 0.6	<0.05
Graf fol.	0.07± 0.2	0.1 ± 0.3	AD

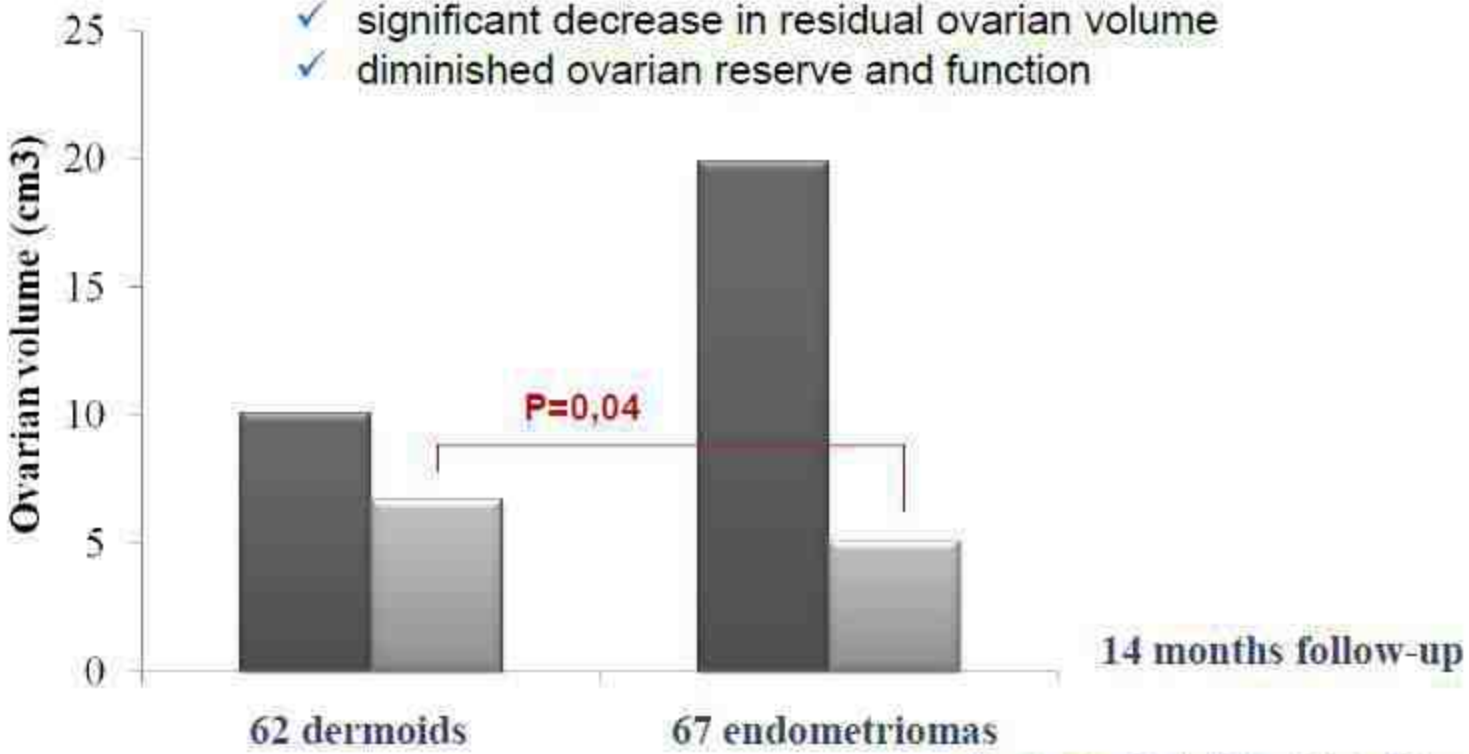
Tablo 3: Kist duvarındaki over dokusunda histopatolojik bulgular

	Endometrioma (n=50)	Non Endometrioma (n=50)	p
İnflamasyon	% 60	% 10	<0.05
Fibrozis	% 56	% 6	<0.05
Hemoraji	% 52	% 14	<0.05
Koter	% 50	% 14	<0.05

Endometrioma: Surgical treatment and ovarian reserve

Laparoscopic removal of endometriomas: sonographic evaluation of residual functioning ovarian tissue

- ✓ significant decrease in residual ovarian volume
- ✓ diminished ovarian reserve and function



Exacoustos C et al, Am J Obstet Gynecol. 2004

The Impact of Excision of Ovarian Endometrioma on Ovarian Reserve: A Systematic Review and Meta-Analysis

	Postoperative			Preoperative				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Hirokawa 2011	2.1	1.6	38	3.9	2.5	38	26.4%	-1.80 [-2.74, -0.86]
Hwu 2011	2.01	1.17	31	3.95	2.34	31	27.7%	-1.94 [-2.86, -1.02]
Kitajima 2011	3.024	2.48	19	4.27	3	19	7.7%	-1.25 [-3.00, 0.50]
Lee 2010	3.29	2.11	13	4.69	2.5	13	7.4%	-1.40 [-3.18, 0.38]
Tsolakidis 2009	2.9	0.63	10	3.9	1.26	10	30.8%	-1.00 [-1.87, -0.13]
Total (95% CI)			111			111	100.0%	-1.52 [-2.00, -1.04]

Heterogeneity: $Chi^2 = 2.61$, $df = 4$ ($P = 0.62$); $I^2 = 0\%$

Test for overall effect: $Z = 6.15$ ($P < 0.00001$)

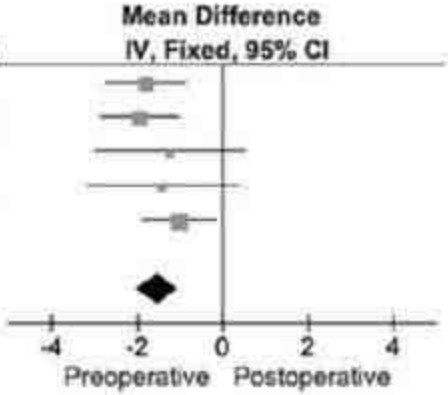


FIG. 3. Meta-analysis. Weighted mean difference in serum AMH after surgery for endometrioma: pooled results for studies with analysis of changes in AMH stratified by baseline AMH (≥3.1 ng/ml).

Ovarian cystectomy for endometriomas seems to cause significant damage to ovarian reserve with up to 40% fall in serum AMH concentration

Raffi F et al. J Clin Endocrinol Metab 2012

Effects of excision of ovarian endometrioma on the antral follicle count and collected oocytes for in vitro fertilization

Number of antral follicle count, dominant follicle, and collected oocytes in the operated ovaries and in the nonoperated ovaries among women with previous ovarian endometrioma.

	Operated side (n = 80)	Nonoperated side (n = 80)	*P* value	95% CI
Antral follicle count	4.5 ± 3.8	7.4 ± 5.2	0.003	1.0–5.0
No. of dominant follicles	4.7 ± 3.9	7.5 ± 4.7	<0.0001	1.5–4.2
No. of dominant follicles ≤ 2 (%)	24 (30%)	10 (12.5%)	0.02	5.1–29.8
No. of collected oocytes	4.3 ± 3.9	7.4 ± 4.8	<0.0001	1.7–4.4
No. of collected oocytes ≤ 2 (%)	32 (40%)	13 (16.2%)	0.008	10.3–37.2
No. of zero oocytes collected (percent)	15 (18.7%)	1 (1.2%)	0.0002	8.6–26.4

Almog B et al, Fertil Steril 2012

The effect of laparoscopic ovarian cystectomy versus coagulation in bilateral endometriomas on ovarian reserve as determined by antral follicle count and ovarian volume: a prospective randomized study

Presurgical and postsurgical basal follicle numbers.

Surgical technique	Basal follicle number		*P* value
	Presurgical	Postsurgical	
Cystectomy	5.58 ± 1.13	3.67 ± 1.26	.001
Cauterization	5.42 ± 0.77	4.75 ± 0.60	.02

Note: $P < .05$ was considered statistically significant. Data are expressed as mean ± standard deviation.

Var. Ovarian cystectomy vs. coagulation in bilateral endometriomas. Fertil Steril 2011.

Presurgical and postsurgical ovarian volumes.

Surgical technique	Ovarian volume		*P* value
	Presurgical	Postsurgical	
Cystectomy	13.03 ± 1.13	6.27 ± 1.95	.01
Cauterization	13.56 ± 1.5	9.87 ± 2.01	.01

Note: $P < .05$ was considered statistically significant. Data are expressed as mean ± standard deviation.

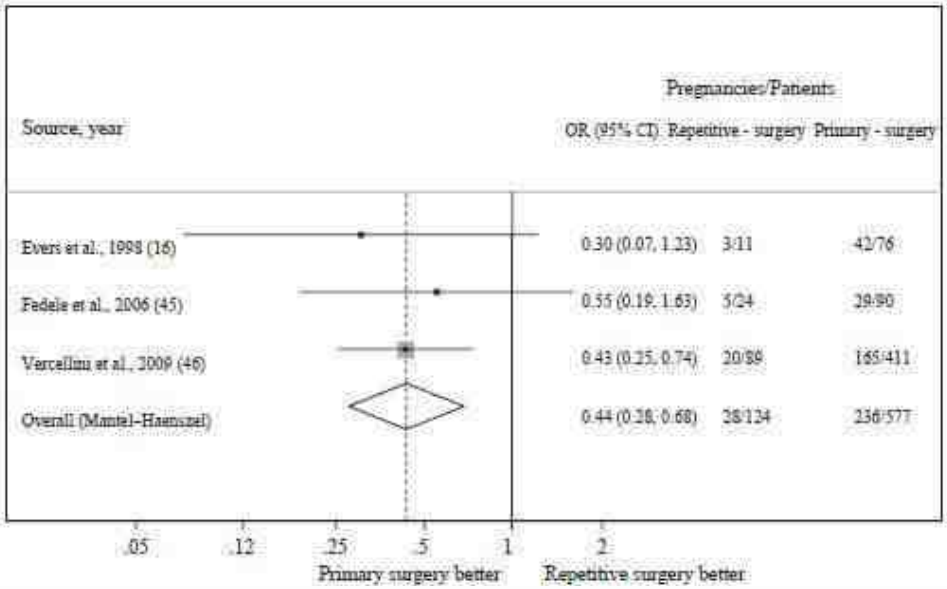
Var. Ovarian cystectomy vs. coagulation in bilateral endometriomas. Fertil Steril 2011.

Var T et al, Fertil Steril 2011

Endometriozis IVF

In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates. (Benschop, et al., 2010, Donnez, et al., 2001, Hart, et al., 2008).	A
In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles.	GPP
The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.	GPP

Tekrarlayan Endometriozis - Cerrahi



Primer cerrahi sonrası spontan gebelik 236/577 (% 41)

Sekonder cerrahi sonrası spontan gebelik 28/124 (% 23)

The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: A systematic review

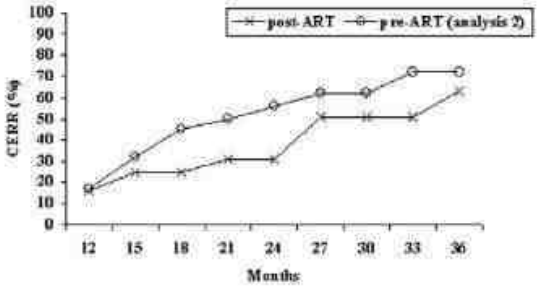
Paolo Vercellini [abc], Edgardo Somigliana [cd], Paola Viganò [c], Sara De Matteis [ef], Giussy Barbara [abc], Luigi Fedele [ab]

IVF Tekrarlayan Endometriozis

In infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI (Benaglia, et al., 2011, Benaglia, et al., 2010, Coccia, et al., 2010, D'Hooghe, et al., 2006).	C

FIGURE 4

Comparison of pre-ART and post-ART recurrence studies: CERR before (pre-ART) and after (post-ART) treatment with assisted reproductive technology. For information regarding analysis 2, see Figure 3.



D'Hooghe. Endometriosis recurrence after ovarian hyperstimulation. Fertil Steril 2006.

Endometriozis IVF GnRHa

Clinicians can prescribe GnRH agonists for a period of 3 to 6 months prior to treatment with assisted reproductive technologies to improve clinical pregnancy rates in infertile women with endometriosis (Sallam, et al., 2006).	**B**

Analysis 1.2. Comparison 1 GnRH agonist versus no agonist before IVF or ICSI, Outcome 2 Clinical pregnancy rate per woman.

Review: Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis

Comparison: 1 GnRH agonist versus no agonist before IVF or ICSI

Outcome: 2 Clinical pregnancy rate per woman

Study or subgroup	GnRH agonist n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dicker 1992	12/35	2/32		20.2 %	7.83 [1.59, 38.47]
Rickes 2002	21/28	9/19		39.4 %	3.33 [0.96, 11.54]
Surrey 2002	20/25	14/26		40.4 %	3.43 [0.99, 11.93]
Total (95% CI)	**88**	**77**		**100.0 %**	**4.28 [2.00, 9.15]**

Total events: 53 (GnRH agonist), 25 (Control)

Heterogeneity: $Chi^2 = 0.83$, $df = 2$ ($P = 0.66$); $I^2 = 0.0\%$

Test for overall effect: $Z = 3.75$ ($P = 0.00018$)

0.01 0.1 1 10 100

Favours control Favours GnRH agonist

Endometriozis IVF GnRHa / GnRHant

TABLE 3

Controlled ovarian hyperstimulation (COH) parameters and ICSI outcomes in the study groups.

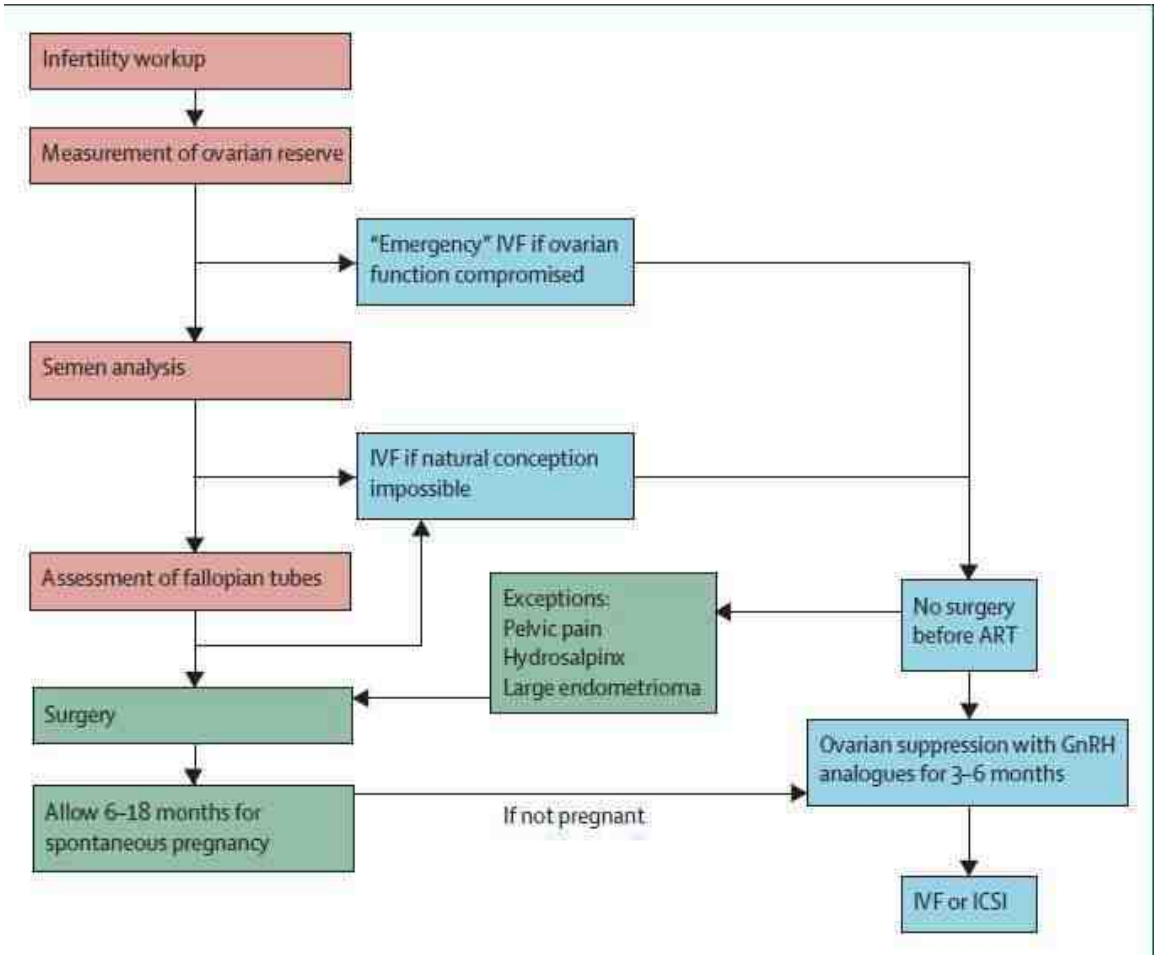
	Antagonist (n = 124)	Analogue (n = 122)	*P* value
Age (y)	31.2 ± 4.6	30.8 ± 3.6	NS
Duration of infertility (y)	7.4 ± 3.9	7.1 ± 3.8	NS
BMI (kg/m^2)	24.8 ± 4.1	24.2 ± 4.2	NS
Number of antral follicles	4.2 ± 1	4.2 ± 1.7	NS
Day 2 FSH (IU/mL)	7.1 ± 1.9	6.9 ± 1.7	NS
Day 2 E_2	50.8 ± 29	48.6 ± 26	NS
Duration of ovarian hyperstimulation (days)	10.1 ± 1.3	10.6 ± 1.5	NS
E_2 level on hCG day (pg/mL)	1,851.2 ± 922	2,102.5 ± 1,111	NS
Total recombinant FSH ampules per cycle (n)	28.5 ± 8.7	30.3 ± 8.9	NS
>17 mm follicle number (n)	4.3 ± 1.5	4.9 ± 1.7	NS
Retrieved oocyte (n)	9 ± 4.4	10.6 ± 5.8	NS
Metaphase II oocyte (n)	6 ± 2.9	8.3 ± 4.4	.005
Fertilization rate (%)	704 ± 22.5	74.4 ± 18.9	NS
No of available embryos	3.7 ± 2	5.4 ± 3.8	.003
Number of transferred embryos	2.3 ± 0.6	2.3 ± 0.6	NS
Clinical pregnancy (%)	26.6 (33/124)	31.9 (39/122)	NS
Abortion rate (%)	3.2 (4/124)	2.5 (3/122)	NS
Implantation rate (%)	14.6	18.5	NS

Note: BMI = body mass index.
$P < .05$, statistically significant differences between GnRH analogue and antagonist groups.

Pabuccu. GnRH protocols for endometriosis in ICSI. Fertil Steril 2007.

Pabuccu R, Onalan G and Kaya C. GnRH agonist and antagonist protocols for stage I-II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. *Fertil Steril* 2007; **88**:832–839.

Endometriozis Algoritma



Sorular

- Endometriozis infertiliteye sebep olur mu?
  - Evet
- Endometriozis infertiliteye nasıl sebep olur?
  - ???
- Endometriozis tedavisi yapalım mı? Nasıl?
  - ???

*“Endometriozis: tedavisiyle tartışmalı ve patogeneziyle bir **bilmecedir**…”*

J.Donnez et al Fertil Steril. 2012 98(3):509-10.

Sonuçlar

- Tedavi planlanırken yaş, infertilite süresi, pelvik ağrı, endometriozis evresi dikkate alınmalı
- Evre I-II Endometrioziste, sadece gebelik başarısını artırmak için yapılan L/S yararı, rutinde L/S önermek için yeterli değil
- Diğer nedenlerle yapılan L/S sırasında görülen lezyonlara ablasyon veya eksizyon uygulanmalı

Sonuçlar

- Evre I-II genç hastalarda (<35yaş) gözlem tedavisi veya SO+IUI düşünülebilir
- 35 yaş üstünde SO+IUI veya IVF öncelikle düşünülmeli
- Evre III-IV hastalarda konservatif cerrahi yararlı olabilir

Sonuçlar

- IVF öncesi endometrioma cerrahisinin sonuçları iyileştirdiğine dair yeterli kanıt yok
- Endometrioma cerrahisi yapılacaksa rezeksiyon tercih edilmeli
- Cerrahi sonrası gebe kalamayan veya yaşı ileri Evre III-IV hastalar için IVF etkin bir alternatifdir

33. Zeynep Kamil Jineko - Patoloji Kongresi

Bilimin Dostluğun Kadın Sağlının 33. YILI

7 – 8 Kasım 2015 **Wyndham Grand İstanbul Kalamış Marina Hotel**

Saygılarımla…

Dr. Tayfun KUTLU