TEKRARLAYAN ENDOMETRİOZİSLERDE YÖNETİM

Prof.Dr.Gürkan Uncu

Tekrarlayan Endometriozis

- Rekürrens endometriozisin gerçeğidir, komplet kür imkansızdır…. Neden?

1. İnsitu lezyonların gelişimi
2. Mikroskobik metastazların gelişimi
3. Yetersiz cerrahi

Rekürrensin tanımı

- Reoperation because of reappearance of symptoms
- Ultrasonography
- Second laparoscopy at the end of the second year
- Ultrasonographic evidence and the need for reoperation due to pains
- Presence of clinical and/or biopsy-proven endometriosis at laparoscopy or as the presence of an endometriotic cyst on ultrasound with cytological confirmation
- Recurrence of 1 symptom (urgency, frequency and pain at micturition) of moderate-to-severe intensity
- Clinical examination Ultrasonographic exam during the proliferative phase of the menstrual Cycle
- Evaluation of symptoms, pelvic examination, transvaginal ultrasonography and renal ultrasound
- Detection of cysts 2 cm by Ultrasonography
- Presence of endometrioma 2 cm as detected by ultrasonography
- Exacerbated symptoms 3 months after surgery plus at least one of: (i) reappearance of disappeared positive pelvic characteristics following surgery; (ii) ultrasonography and (iii) arise of serum CA125 following fall
- The presence of ovarian cysts more than 3 cm in diameter with a typical aspect detected by ultrasonography for two consecutive menstrual cycles
- Not clearly defined
- Either pain or ultrasonographic Evidence
- Pain: evaluated by visual analog scale (VAS)
- 'Symptom recurrence'
- Clinical exam, ultrasound, CA-125, second look laparoscopy based on clinical finding
- The sum of pain score (total pelvic symptom score) 7
- Four-point grading of dysmenorrhea,
- non-menstrual pain and deep
- dyspareunia, and the total score 5

Rekürrensin tanımı

- Rekürrensin tanımında odaklanılan nokta "Endometrioma" varlığı……

- Ultrasonografi ile endometrioma varlığı daha homojen, ağrı subjektif.

1 cm üzerinde endometrioma varsa

% 76 ağrı eşlik eder

% 24 asemptomatiktir…..

Exacoustos C, Zupi E, Amadio A, Amoroso C, Szabolcs B, Romanini ME, Arduini D. Recurrence of endometriomas after laparoscopic removal: sonographic and clinical follow-up and indication for second surgery. J Minim Invasive Gynecol 2006;13:281–288.

Rekürrens oranı

- Çok heterojen bir durum
  - Endometriozis tipi
  - Çalışma tipi
  - Çalışma yılı
  - AFS skoru
  - Denek sayısı vs.....

Rekürrens oranı

Human Reproduction Update, Vol.15, No.4 pp. 441–461, 2009
Advanced Access publication on March 11, 2009 doi:10.1093/humupd/dmp007

human reproduction update

Recurrence of endometriosis and its control

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23 çalışma

2 yıllık rekürrens % 19.1
5 yıllık rekürrens % 20.5 – 43.5

Rekürrens risk faktörleri

rAFS > 70

EA can be protective

rAFS stage, previous surgery

Younger age
Pregnancy is protective

Extent of surgical excision

Laterality of lesions

Bilateral cysts

rAFS score, older age

Previous medical treatment, size

Previous surgical history, bilateral pelvic involvement, involvement of left-side pelvic, high post-operation rAFS score, younger age painful nodule in the Doglas pouch, use of clomifene
Protective factors: number of pregnancies an post-operative progestin treatment

For recurrence of disease: rAFS score, younger age, previous use of medication
For dysmenorrhea: rAFS score

Ovarian preservation

rAFS stage, older age

Size of the cyst

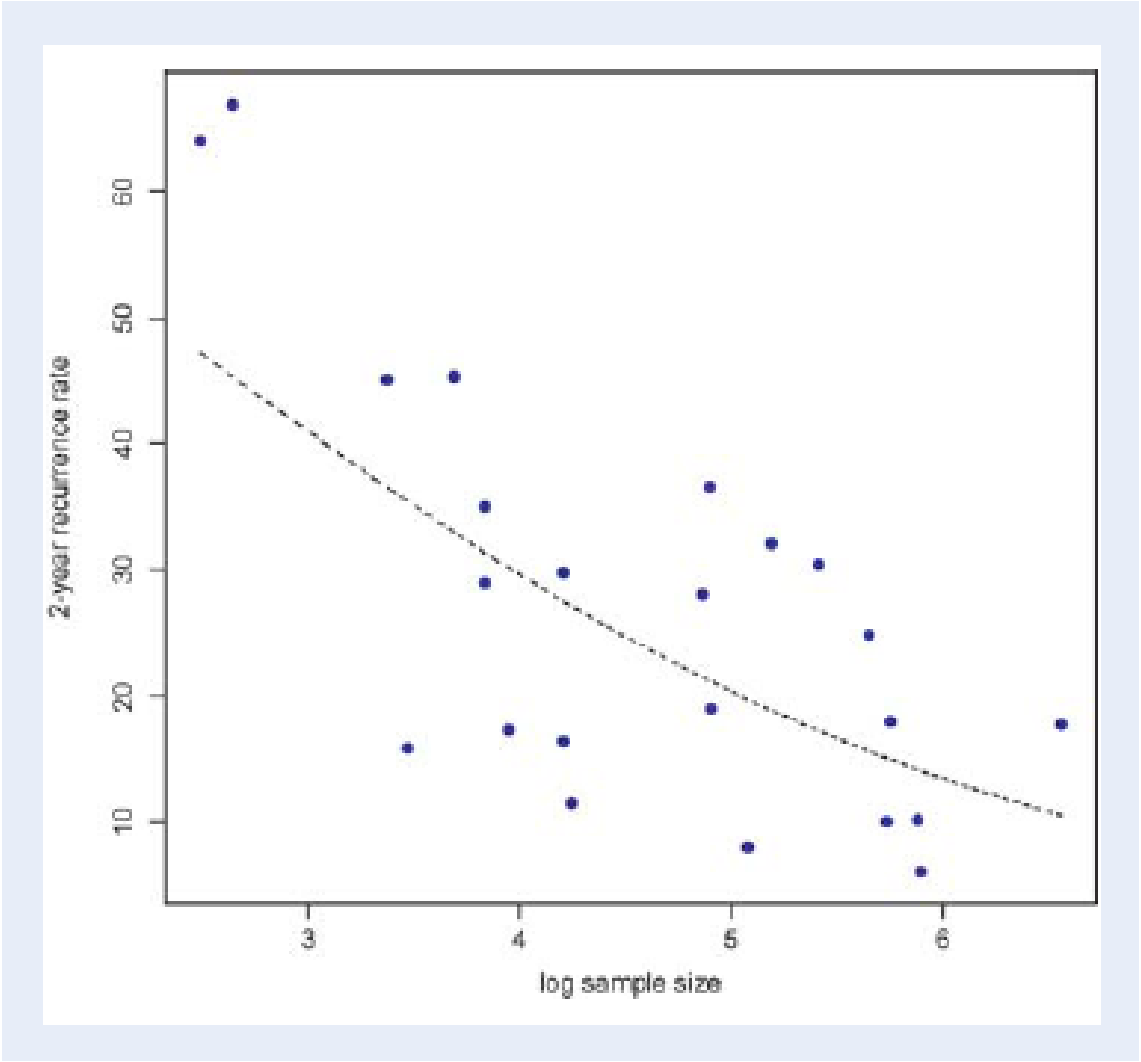
Younger age at surgery (for dysmenorrhea)
Post-operative medical treatment (for disease recurrence)

OC use is a protective factor

Younger age (for pain)
Obliteration of the Douglas pouch (for clinical signs)
Completeness of the first surgery (for reoperation)

rAFS stage

Rekürrens oranı



Tekrarlayan Endometriozis
Klinik

Tekrarlayan Endometriozis
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- Yaşam kalitesini bozan semptomlar

Tekrarlayan Endometriozis
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- Yaşam kalitesini bozan semptomlar
- İnfertilite

Tekrarlayan Endometriozis
Klinik

- Yaşam kalitesini bozan semptomlar
- İnfertilite
- Yaşam kalitesini bozan semptomlar ve infertilite birlikteliği

Tekrarlayan Endometriozis
Klinik

- Yaşam kalitesini bozan semptomlar
- İnfertilite
- Yaşam kalitesini bozan semptomlar ve infertilite birlikteliği
- Asemptomatik Endometrioma varlığı

Yaşam kalitesini bozan semptomlar varlığında;

Yaşam kalitesini bozan semptomlar varlığında;

- Yeniden cerrahi

Yaşam kalitesini bozan semptomlar varlığında;

- Yeniden cerrahi
- Medikal supresyon

Yaşam kalitesini bozan semptomlar varlığında;

- Yeniden cerrahi
- Medikal supresyon
- İzleme

Tekrarlayan cerrahi seçenekleri

- Endometrioma eksizyonu
- Pelvik denervasyon işlemleri
  - Presakral nörektomi (PSN)
  - Uterosakral ligament rezeksiyonu (LUNA)
- Definitif cerrahi

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Endometrima Eksizyonu

- Pain symptoms (42 women)
  - Stage IV in 14
  - Stage III in 25
  - Stage I in 3
- Follow-up of 42 months
- Dysmenorrhea and deep dyspareunia reappeared in eight women
- Non-cyclical pelvic pain in seven.
- **A third operation** was necessary in six **(14%)**
- The symptoms recurrence rate when repeat laparotomy was performed specifically **for pain is 25%**

Candiani GB, Fedele L, Vercellini P, Bianchi S, Di Nola G.
Repetitive conservativesurgery for recurrence of endometriosis.
Obstet Gynecol 1991;77:421-4.

Endometrima Eksizyonu

- 81 women re-operated, 60 months

	Laparotomy (n = 41)	Laparoscopy (n = 40)
Stage IV	14	11
Stage III	25	21
Stage II	0	2
Stage I	2	6
Dysmenorrhea	**22%** (7/32)	**29%** (10/35)
Deep dyspareunia	**30%** (7/23)	**25%** (4/16)
Pelvic pain	**35%** (9/26)	**32%** (7/22)

Busacca M, Fedele L, Bianchi S, et al. Surgical treatment of recurrent endometriosis: laparotomy versus laparoscopy. Hum Reprod 1998;13:2271–4.

Endometrima Eksizyonu

Laparoscopic excision (ovarian endometrioma - same ovary)

Primary (n = 305) Recurrent (n = 54)

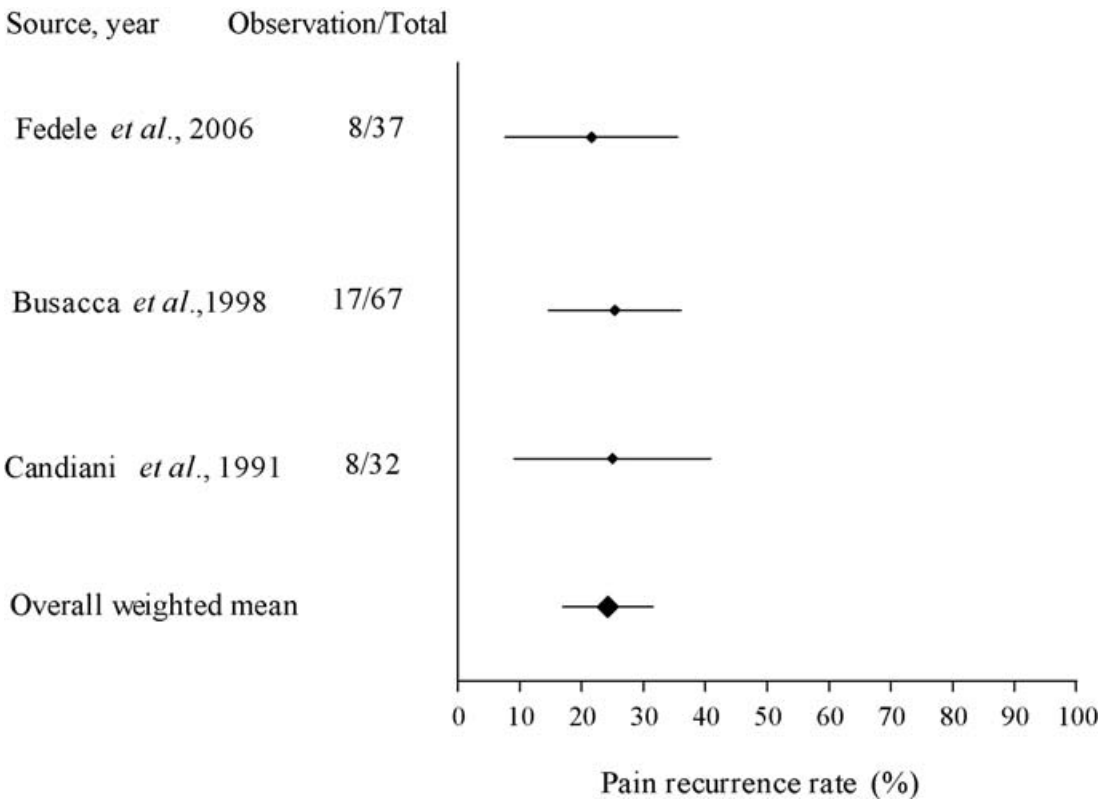
Pelvic pain (n = 37) Mean follow-up of 35 months.

Recurrence rate
(5-year cumulative pain)

- **After the first surgical procedure** **20 %**
- **After the second procedure** **17 %**

Fedele L, Bianchi S, Zanconato G, et al. Laparoscopic excision of recurrent endometriomas: long-term outcome and comparison with primary surgery. Fertil Steril 2006;85:694-9.

Endometrima Eksizyonu



The effect of repetitive laparoscopic surgery on pain is similar to that observed after first-line surgery.

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Presakral Nörektomi

Recurrence moderate or severe dysmenorrhea at 1-year

Conservative surgery plus PSN	Conservative
(n = 35)	(n = 36).
6/35 (17%)	**9/36 (25%)**

- In the PSN group, constipation developed or worsened in 13 patients and urinary urgency occurred in three patients.

Candiani GB, Fedele L, Vercellini P, Bianchi S, Di Nola G. Presacral neuroectomy for the treatment of pelvic pain associated with endometriosis: a controlled study. Am J Obstet Gynecol 1992;167:100–3.

Presakral Nörektomi

	Conservative surgery plus PSN (n:63)	Conservative (n:63)
Dysmenorrhea cure rate		
– 6-month follow-up	**87%**	**57%**
– 12-month follow-up	**60%**	**86%**
– 24-month follow-up	**83%**	**53%**

- At the end of the study period, the frequency and severity of deep dyspareunia and non-menstrual pain were also significantly lower in women from the PSN those in conservative.
- 11 women who underwent PSN referred long-term complaints such as de-novo constipation (n = 9, 15%) and urinary urgency (n = 3, 5%).

Zullo F, Palomba S, Zupi E, et al. Am J Obstet Gynecol 2003;189:5–10.
Zullo F, Palomba S, Zupi E, et al. J Am Assoc Gynecol Laparosc 2004;11:23–8.

Tekrarlayan cerrahi seçenekleri

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Uterosakral ligament rezeksiyonu (LUNA)

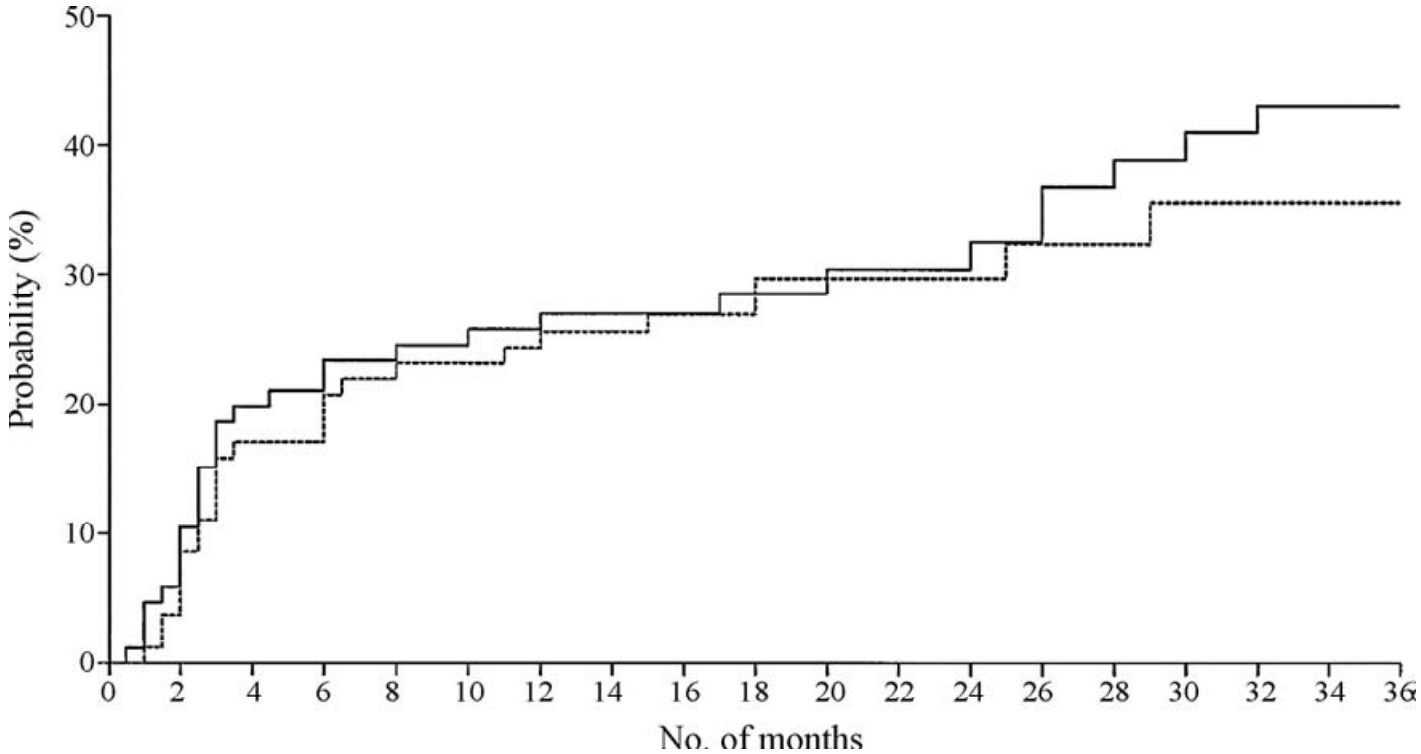
Recurrence moderate or severe dysmenorrhea

	Conservative surgery plus LUNA (n = 78)	Conservative (n = 78)
At first year	**29% (23 /78)**	**27% (21/78)**
At third year	**36% (21/ 59)**	**32% (18/57)**

- 68 of 90 **(75%)** patients in the LUNA group and 67 of 90 **(75%)** patients in the conservative surgery only group were satisfied at 1 year.

Vercellini P, Aimi G, Busacca M, Apolone G, Uglietti A, Crosignani PG. Laparoscopic uterosacral ligament resection for dysmenorrhea associated with endometriosis: results of a randomized, controlled trial. Fertil Steril 2003;80:310–9.

Uterosakral ligament rezeksiyonu (LUNA)



Cumulative 36-month probability recurrence of moderate or severe dysmenorrhea

Vercellini P, Aimi G, Busacca M, Apolone G, Uglietti A, Crosignani PG. Laparoscopic uterosacral ligament resection for dysmenorrhea associated with endometriosis: results of a randomized, controlled trial. Fertil Steril 2003;80:310–9.

Uterosakral ligament rezeksiyonu (LUNA)

- Cochrane meta-analysis
- The addition of LUNA to laparoscopic surgical treatment of endometriosis did not improve relief from secondary dysmenorrhea (OR 0.77; 95% C.I.,0.43–1.39), whereas PSN did (OR 3.14; 95% C.I., 1.59–6.21).

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Definitif cerrahi

- Tüm histerektomilerin yaklaşık % 10’ unda neden
  KRONİK PELVİK AĞRI

- Özellikle genç kadınlarda definitif cerrahi kararı almak çok zor..

- Çalışmaların ortak noktası, definitif cerrahinin yaşam kalitesi skalalarını yükselttiği yönünde AMA

- Özellikle genç hastalarda definitif cerrahi yapılacaksa bu çok ayrıntılı olaraka tartışılmalı..

Definitif cerrahi: Overler dursun mu?

- Hysterectomy for symptomatic endometriosis in 29 women

	Ovarian tissue was preserved	Both ovaries removed
	n: 29	n:109
Recurrent pain	18 (62%)	11 (10%)
Required reoperation	9 (31%)	4 (3.7%)

- Patients who underwent hysterectomy with ovarian conservation had 6.1 times greater risk of developing recurrent pain and 8.1 times greater risk of reoperation.

Namnoum AB, Hickman TN, Goodman SB, Gehlbach DL, Rock JA. Incidence of symptom recurrence after hysterectomy for endometriosis. Fertil Steril 1995;64:898-902.

Definitif cerrahi: Overler dursun mu?

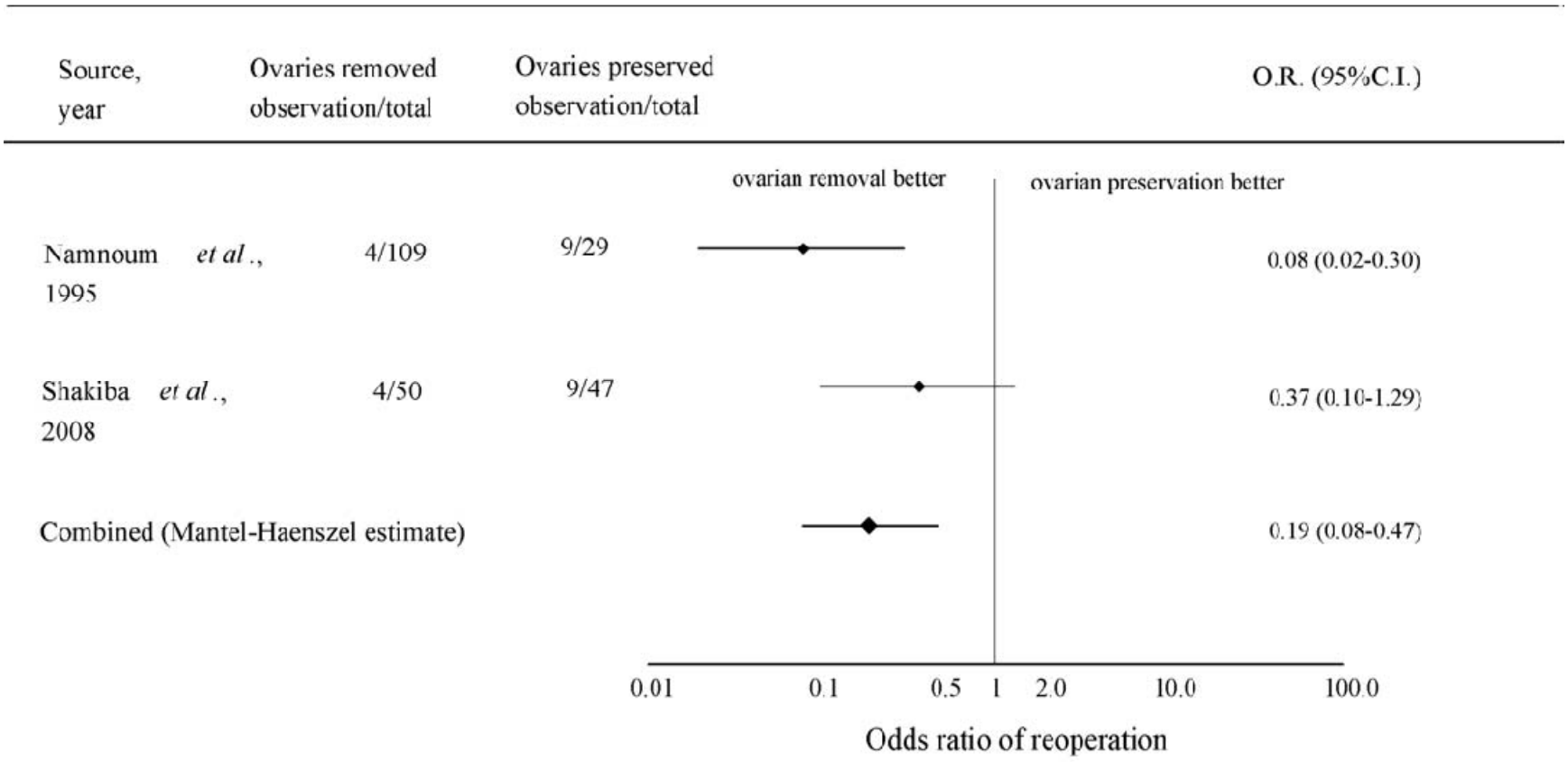
- Hysterectomy for symptomatic endometriosis in 29 women

	Ovarian tissue was preserved	Both ovaries removed
	n: 47	n:50
Required reoperation	9 (19.2%)	4 (8%)

- The reoperation rate associated with conservative surgery was 2.89 and 6.16 times higher in comparison to hysterectomy with or without ovarian preservation, respectively.

Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. Obstet Gynecol 2008;111:1285–92.

Definitif cerrahi



Tekrarlayan endometriozislerde medikal tedavi

- Tekrarlayan endometriomalarda medikal tedavinin başarısı ile ilgili veri yok…
- Endometrioma olmayan olgularda medikal tedavinin yeri ile ilgili de veri yok…
- Tek veri, primer cerrahi sonrası medikal tedavinin yeri ile ilgili….
- Bu verilere bakarak yorum yapılabilir.

Tekrarlayan endometriozislerde medikal tedavi

Human Reproduction, Vol.24, No.11 pp. 2729–2735, 2009
Advanced Access publication on July 22, 2009 doi:10.1093/humrep/dep259

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis

R. Seracchioli[1], M. Mabrouk, L. Manuzzi, C. Vicenzi, C. Frascà, A. Elmakky, and S. Venturoli

Tekrarlayan endometriozislerde medikal tedavi

Table I Design of the studies considered

Study	Outcome	Type of study	Number of patients	Medical Treatment
Muzii *et al.* (2000)	Anatomical and pain recurrence	RCT	35	None
			33	Cyclic OCP
Vercellini *et al.* (2003)	Pain recurrence	Prospective self controlled	50	Continuous OCP
Koga *et al.* (2006)	Anatomical recurrence	Retrospective	109	none
			15	OCP
Sesti *et al.* (2007)	Pain recurrence	RCT	110	placebo
			38/39	Continuous OCP/GnRH-analogues
			35	Dietary therapy
Vercellini *et al.* (2008a, b)	Anatomical recurrence	Cohort study	46	None
			231	Cyclic OCP
Seracchioli *et al.* (2008)	Anatomical recurrence	RCT	69	None
			75	Cyclic OCP
			73	Continuous OCP
Seracchioli *et al.* (2009)	Pain recurrence	RCT	87	None
			92	Cyclic OCP
			95	Continuous OCP

RCT: randomized controlled trial; OCP: oral contraceptive pills.

Tekrarlayan endometriozislerde medikal tedavi

Table II Surgical and medical interventions performed in the studies considered

Study	Surgical treatment	OCP Regimen	Type of pill	Time of medical treatment (months)	Follow-up (months)
Muzii *et al.* (2000)	LPS endometrioma excision	Cyclic	EE 0.030 mg, gestodene 0.075 mg	6	22
Vercellini *et al.* (2003)	LPS or LPT	Continuous	EE 0.020 mg, desogestrel 0.15 mg	24	24
Koga *et al.* (2006)	LPS endometrioma excision	Not specified	Not specified	9.5	24
Sesti *et al.* (2007)	LPS or LPT	Continuous	EE 0.030 mg, gestodene 0.075 mg	6	12
Vercellini *et al.* (2008a, b)	LPS endometrioma excision	Cyclic	EE 0.020 mg, desogestrel 0.15 mg	1–28	28
Seracchioli *et al.* (2008)	LPS endometrioma excision	Cyclic Continuous	EE 0.020 mg, gestodene 0.075 mg	24	24
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LPS: laparoscopy; LPT: laparotomy; EE: ethinilestradiol.

Tekrarlayan endometriozislerde medikal tedavi

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Tekrarlayan endometriozislerde medikal tedavi

Table III Results of the studies

Study	Outcome measured	Method of measurement	Definition of recurrence	Patients and treatment	Results	*P*-value
Muzii *et al.* (2000)	Endometrioma	TV US	Not specified	35 no therapy	Recurrence rate: oCP (2.9%) versus none (6.1%)	NS
	pain	VAS	VAS > 4	33 cyclic OCP	Recurrence rate: oCP (9.1%) versus none (17.1%)	NS
Vercellini *et al.* (2003)	Dysmenorrhoea	VAS, VRS	Not specified	50 continuous OCP	Reduction in mean VAS score of 45.95% after 2 years of continuous OCP therapy	<0.001
Koga *et al.* (2006)	Endometrioma	TV US	>2 cm diameter	109 no therapy 15 OCP	OCP do not influence endometrioma recurrence	NS
Sesti *et al.* (2007)	(a) Dysmenorrhoea	VAS	Not specified	110 placebo	(a) Lower VAS scores with OCP, GnRH-analogues and dietary therapy	<0.001
	(b) Dyspareunia			77 hormonal therapy	(b) Lower VAS scores with placebo	<0.001
	(c) CPP			35 dietary therapy	(c) Lower VAS scores with OCP, GnRH-analogues and dietary therapy	<0.001
Vercellini *et al.* (2008a, b)	Endometrioma	TV US	>2 cm diameter	46 no therapy 231 cyclic OCP	Recurrence rate: oCP (9%) versus none (56%)	<0.001
Seracchioli *et al.* (2008)	Endometrioma	TV US	>1.5 cm diameter	69 no therapy 75 cyclic OCP 73 continuous OCP	Recurrence rate: oCP continuous (8.2%) and cyclic OCP (14.7%) versus none (29%)	<0.005
Seracchioli *et al.* (2009)	(a) Dysmenorrhoea	VAS	VAS>4	87 no therapy	(a) Lower recurrence rate since 6 months (continuous OCP) or 18 months (cyclic OCP)	<0.001
	(b) Dyspareunia			92 cyclic OCP	(b) OCP do not influence recurrence	NS
	(c) CPP			95 continuous OCP	(c) OCP do not influence recurrence	NS

CPP: chronic pelvic pain; TV US: transvaginal ultrasonography; VAS: visual analogue scale; VRS: verbal rating scale; OCP: oral contraceptive pill, NS: non-significant.

Tekrarlayan endometriozislerde medikal tedavi

- GnRh Analogları
  - Tekrarlayan endometriomalarda başarısı?
  - Verisi yok
  - Kullanım mantığı var, kısa süreli baskılama ve OK ile devam etmek?

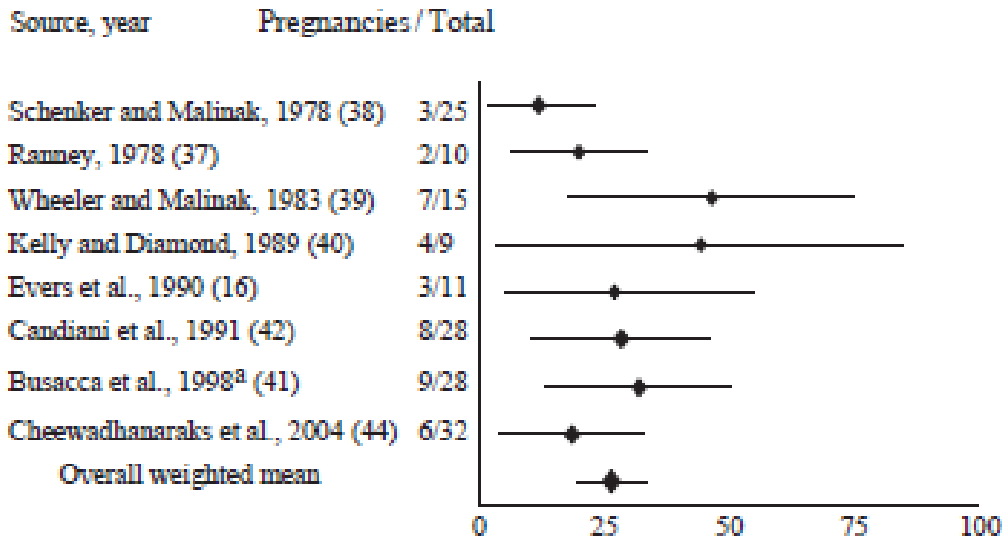
Tekrarlayan endometriozislerde medikal tedavi

- Aromataz İnhibitörleri
  - Tekrarlayan endometriomalarda başarısı?
  - Güçlü verileri yok
  - Olgu sunumları başarılı sonuç bildiriyor

Tekrarlayan Endometriozis ve İnfertilite

- Yeniden cerrahi
- Medikal tedavi
- Medikal Tedavi ve ART
- ART
  - KOH
  - KOH + IUI
  - IVF - ET

Tekrarlayan Endometriozis ve İnfertilite; Cerrahi

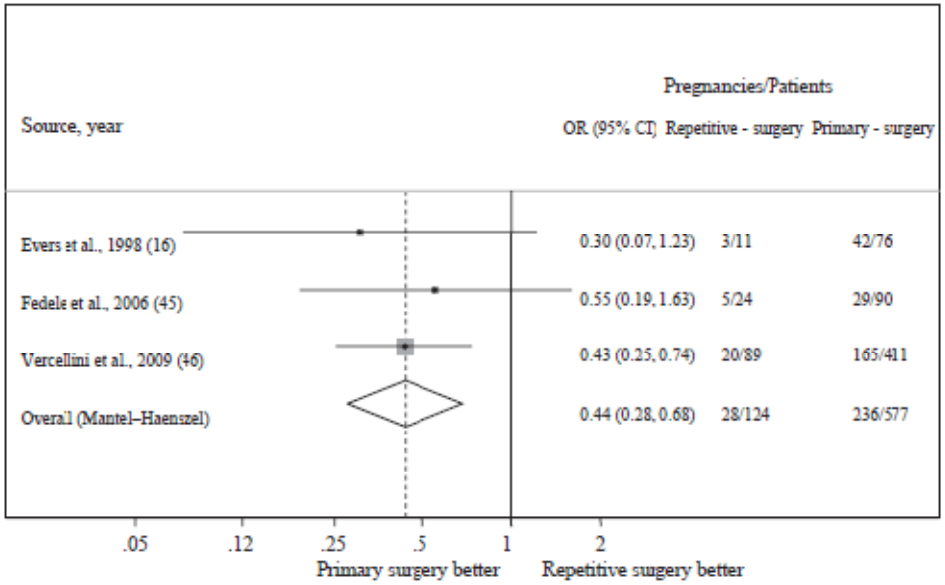


Laparotomi ile yapılan cerrehi sonrası spontan gebelik % 12 – 47 (%27)
Laparoskopi ile yapılan cerrahi sonrası spontan gebelik % 22 - 42 (%25)

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]

Tekrarlayan Endometriozis ve İnfertilite; 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

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Tekrarlayan Endometriozis ve İnfertilite; Medikal tedavi

- Tekrarlayan endometriozisde medikal supresyon yap ve sonra spontan gebelik bekle…..
- Böyle bir çalışma yok…..

Tekrarlayan Endometriozis ve İnfertilite; Cerrahi Öncesi Medikal Tedavi

- İnflamasyon azalabilir.
- Vaskülarizasyon azalabilir.
- İmplantlar küçülür.

} Kolay cerrahi

- Endometriozis mi fonksiyonel mi?

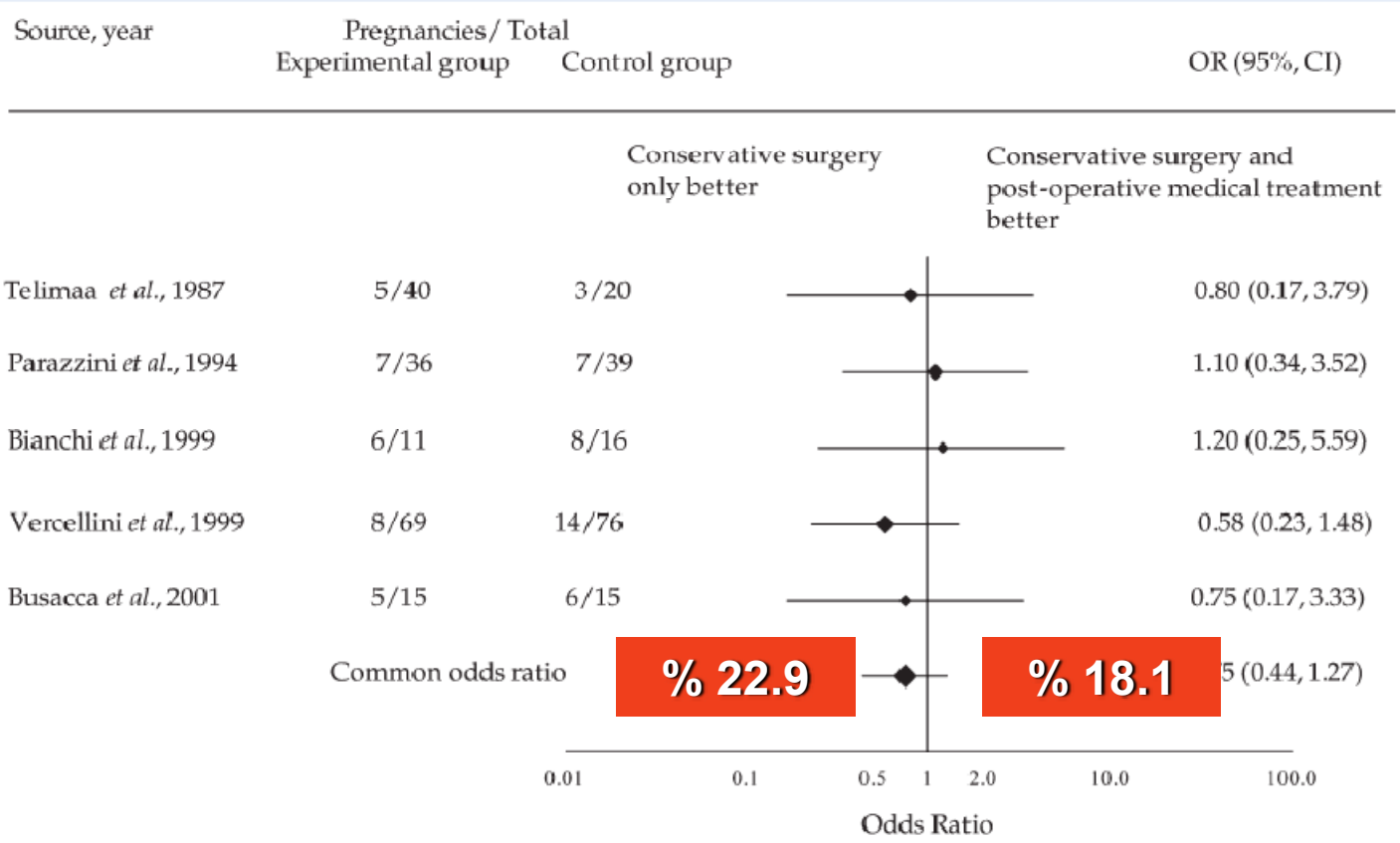
- Odaklar görünmez olup cerrahi yetersizliği artırabilir mi?

ÜREMEYE ETKİSİ YOK

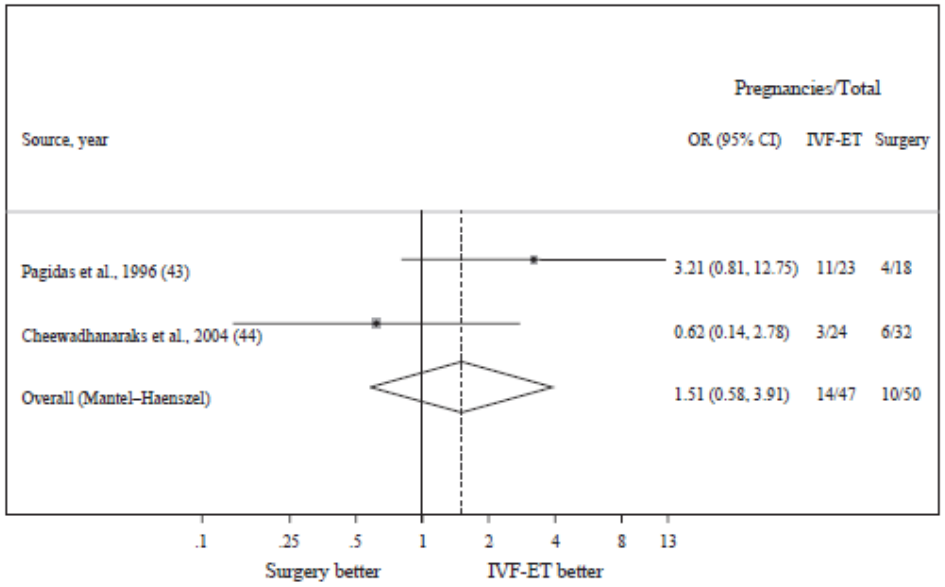
Yap C, Furness S, Farquhar C. Pre and post operative medical therapy for endometriosis. Cochrane Database Syst Rev 2004;3: CD003678.

Tekrarlayan Endometriozis ve İnfertilite; Cerrahi Sonrası Medikal Tedavi

» Rezidüel lezyonlar yok olabilir.
» Görülmeyen lezyonlar yok olabilir.



Tekrarlayan Endometriozis ve İnfertilite; IVF mi ? Yeniden Cerrahi mi?



ARALARINDA GEBELİK ORANLARI AÇISINDAN FARK YOK

AVANTAJ VE DEZAVANTAJLAR İYİ DEĞERLENDİRİLMELİ

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

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Kurumlar ne öneriyor?

Table II International guidelines on surgical treatment of endometriosis-associated infertility in asymptomatic women

Clinical condition	Recommendation		
	ESHRE 2005	ASRM 2006	RCOG 2006
Minimal-mild endometriosis (stage I–II disease)	Limited benefit: surgery recommended	Small benefit: surgery recommended	Demonstrated benefit: surgery recommended
Moderate–severe endometriosis (stage III-IV disease)	Possible but unproven benefit: surgery recommended	Possible benefit: surgery recommended	Possible benefit: recommendation uncertain
Post-operative adjuvant treatment	No benefit: not recommended	No benefit: not recommended	No benefit: not recommended
Surgery before IVF	Recommended if endometrioma ≥4 cm	Doubtful benefit: no recommendation	Recommended if endometrioma ≥4 cm
Recurrent endometriosis	No recommendation	Second-line surgery not recommended	No recommendation

Kurumlar ne öneriyor?

Table II International guidelines on surgical treatment of endometriosis-associated infertility in asymptomatic women

Clinical condition	Recommendation		
	ESHRE 2005	**ASRM 2006**	**RCOG 2006**
Tekrarlayan Endometriozis ve İnfertilite	Limited benefit: surgery recommended	Small benefit: surgery recommended	Demonstrated benefit: surgery recommended
	Possible but unproven benefit: surgery recommended	Possible benefit: surgery recommended	Possible benefit: recommendation uncertain
	No benefit: not recommended	No benefit: not recommended	No benefit: not recommended
	Recommended if endometrioma ≥4 cm	Doubtful benefit: no recommendation	Recommended if endometrioma ≥4 cm
	No recommendation	Second-line surgery not recommended	No recommendation

Kurumlar ne öneriyor

Table II International guidelines on surgical treatment of endometriosis-associated infertility in asymptomatic women

Clinical condition	Recommendation		
	ESHRE 2005	ASRM 2006	RCOG 2006
Tekrarlayan Endometriozis ve İnfertilite	**Önerim yok. Bildiğini yap**	Small benefit: surgery recommended Possible benefit: surgery recommended No benefit: not recommended Doubtful benefit: no recommendation Second-line surgery not recommended	**Önerim yok. Bildiğini yap**

Kurumlar ne öneriyor

Table II International guidelines on surgical treatment of endometriosis-associated infertility in asymptomatic women

Clinical condition	Recommendation		
	ESHRE 2005	ASRM 2006	RCOG 2006
Tekrarlayan Endometriozis ve İnfertilite	**CERRAHİ YAPMAKTAN SAKIN!** **IVF YAP**		

Tekrarlayan Endometriozis: Ne yapalım?

Sadece ağrı ve Endometrioma varsa;

- Yapılması gereken şey tekrar cerrahi ve sonrasında uzun süreli medikal supresyondur.
- Tekrarlayan endometriomalarda medikal supresyon yapılmasının verisi yoktur.
- Bu cerrahinin definitif cerrahi olması hasta ile ayrıntılı konuşularak karar verilecek bir durumdur.
- Konservatif cerrahiye LUNA eklenmesinin anlamı yoktur. PSN eklenmesi ağrıyı hafifletebilir fakat yeni sorunlara zemin hazırlar.

Tekrarlayan Endometriozis: Ne yapalım?

Sadece ağrı var ve Endometrioma yoksa;

- Medikal supresyon ilk seçenek olmalıdır.
  - OK
  - GnRh Analogları
  - Aromataz İnhibitörleri
- Medikal supresyon yapılamayan, medikal supresyonun başarısız olduğu ve yeniden tekrarlayan olgularda cerrahi seçeneği gündeme gelmelidir.
- Rektovajinal endometriozis varlığında cerrahi ve sonrasında medikal supresyon yapılmalıdır.

Tekrarlayan Endometriozis: Ne yapalım?

İnfertilite ve Endometrioma varsa;

- Yeniden yapılan cerrahi ve ART'nin başarı oranları aynıdır, birbirlerine üstünlükleri yoktur.

- Yeniden yapılacak cerrahinin zorluk – komplikasyon ve over rezervi üzerindeki negatif etkileri düşünüldüğünde, yapılması gereken şey olarak ART öne çıkmaktadır.

Tekrarlayan Endometriozis: Ne yapalım?

Asemptomatik endometrioma varsa;

- Malignensi lehine şiddetli bulgular olmadıkca izlenmeli, 4-5 cm üzerine çıkmadıkca ve semptom vermedikce dokunulmamalıdır.