



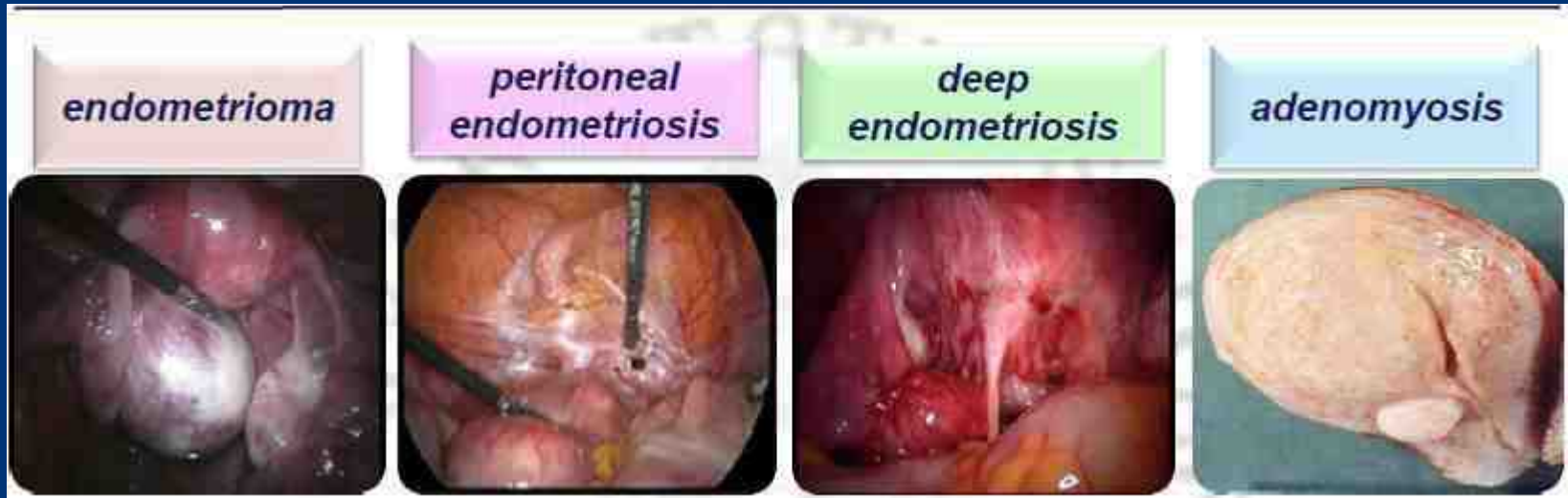
[www.endometriozis.org](http://www.endometriozis.org)  
[www.endometriozisderneği.com](http://www.endometriozisderneği.com)

# Endometriozisin yönetiminde Oral kontraseptiflerin yeri

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# Endometriozis Semptomlar

- Adenomyozis e bagli semptomlar
- İnfertilite
- Ekstragenital endometriozise bagli semptomlar

## Symptoms

### pain

- dysmenorrhea
- cyclic pelvic pain
- acyclic chronic pelvic pain
- dyspareunia
- cyclic dyschezia
- cyclic dysuria

## Expectant Management

## Pharmacologic treatment

## Surgery

### Advantages

Avoid premature interventions

- Delay progression of the disease
- Improvement in symptoms (80-90%)

- Diagnosis
- Preventing or delaying disease or symptom progression

### Disadvantages

Disease progression

- Side effects
- Cost
- Compliance
- Recurrence (50%)

- Trauma
- Infectious
- Ovarian reserve
- Adhesions
- Recurrence (50%)

# Medikal Tedavi endikasyonlari

- İlk secenek olarak
  - İnfertilite (IVF öncesi)
  - Ağrı
  - Derin Endometriozis
  - Ekstra-genital endometriozis
  - Adenomyozis
- Cerrahiden sonra rekürrensi önlemek için
- Cerrahi tedaviye uygun değil ise veya istemiyorsa
- Tanıdan emin olamama (Ampirik)
- İlk cerrahide yeterli eksizyon yapılmasına rağmen rekürrens gösteren durumlar.
- Cerrahi tedaviyle beraber medikal tedavi

# İDEAL MEDİKAL TEDAVİ NASIL OLMALI

Reduce pain

Block the growth

Prevent the recurrences

For long-term use

Low cost

Few side effects

Not affect fertility

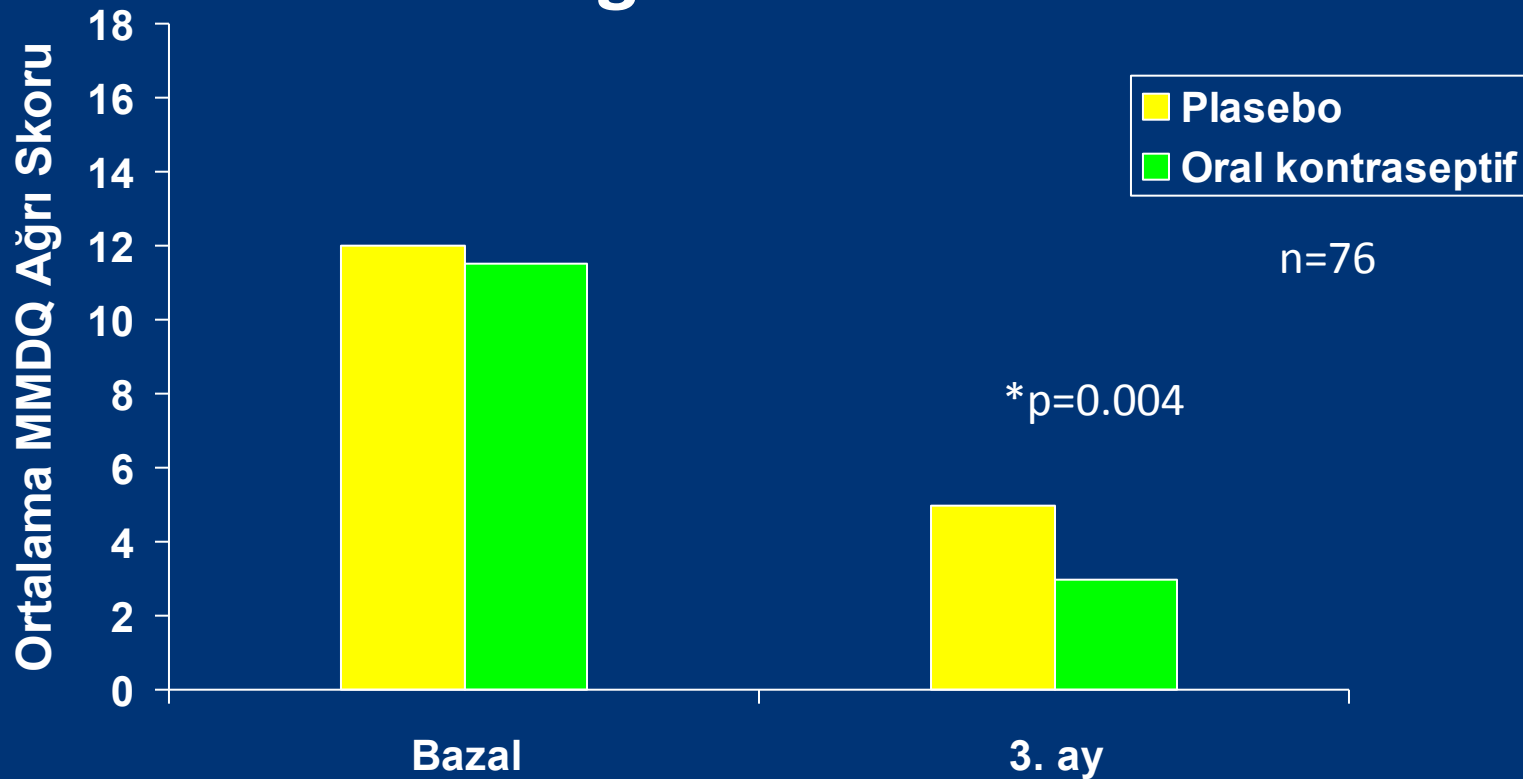
Medikal tedavi	Endikasyon	Tedavi tipi	Yan etki ve komplikasyonlar	Yorumlar
<b>NSAİİ'ler</b>	Dismenore	İlk basamak	Bulanti, kusma, Gİ iritasyon, sersemlik, baş ağrısı	Tedaviye menstrüasyon başlangıcında veya hemen önce başlayın; menstrüel kanamada biraz azalma
<b>Kombine oral kontraseptifler</b>				
Siklik	Dismenore	İlk basamak	Bulanti, kilo artışı, sıvı retansiyonu, depresyon, ara kanamalar, göğüslerde hassasiyet, baş ağrısı, menstrüel kanamada azalma	
Sürekli	Dismenore, non-siklik kronik pelvik ağrı	İkinci basamak	Bulanti, kilo artışı, sıvı retansiyonu, depresyon, ara kanamalar, göğüslerde hassasiyet, baş ağrısı, amenore	
<b>Progestinler</b>				
Medroksiprogesteron asetat	Dismenore, non-siklik kronik pelvik ağrı	İkinci basamak	Bulanti, kilo artışı, sıvı retansiyonu, depresyon, amenore, geç tekrar ovülasyon	
Levonorgestrel RiA	Dismenore, disparoni	İkinci veya üçüncü basamak	Şişkinlik, kilo artışı, baş ağrısı, göğüslerde hassasiyet	Özellikle semptomatik rektovajinal endometrioziste yararlı; 6-12 ay hipomenore veya amenore; 5 yıla kadar kullanılabilir; endometrioziste FDA onayı yok
<b>GnRH agonistleri</b>	Dismenore, disparoni	İkinci veya üçüncü basamak	Hipoöstrojenizm (vazomotor semptomlar, vajinal kuruluk, libido azalması, iritabilite, kemik mineral yoğunluğunda azalma)	Endometriozis ağrısında FDA onaylı; kemik mineral yoğunluğu kaybının engellenmesi için östrojen-progestin ekleme tedavisi yapılır
<b>Aromataz inhibitörleri</b>	Dismenore, non-siklik kronik pelvik ağrı	Üçüncü basamak	Hipoöstrojenizm, ovülasyon indüksiyonu	Ovülasyon indüklenebileceği için progestojenlerle, kombine oral kontraseptiflerle ve GnRH agonistleriyle kombine; endometriozis ağrısında FDA onayı yok
<b>Danazol</b>	Dismenore, non-siklik kronik pelvik ağrı	İkinci veya üçüncü basamak	Hipoandrojenik yan etkiler (akne, ödem, meme boyutunda küçülme)	Yan etkiler yaygın kullanımını sınırlandırır

Soru:

Primer dismenorenin tedavisinde OK  
lerin etkinliđi kanıtlanmıřtır

- Evet
- Hayır
- Yeri yoktur

# Oral contraceptives for dysmenorrhea in adolescent girls: a randomized trial.



MMDQ: Moos Mentruel Distress Questionnaire

KOK: 20µg EE+100 µg LNG

# Oral contraceptives for pain relief from dysmenorrhea: a review

Author	Date	Study size (no. of women)	Treatment length	Control measure	Drug 1	Drug 2	Drug 3	Dysmenorrhea outcome	Significance (yes/no)
<i>Hormonal contraception</i>									
Randomized controlled trials									
Davis et al. [80]	2005	76	3 months	Placebo	EE (0.02 mg)/ LNG (0.1 mg)	n/a	n/a	OC superior to placebo for reduction of pain severity	Yes
Winkler et al. [81]	2004	998	6 months	Comparison	EE (0.02 mg)/ DSG (0.15 mg)	EE (0.02 mg)/ LNG (0.1 mg)	n/a	Equal decrease in both groups	No statistics
Nonrandomized controlled trials									
Ahrendt et al. [82]	2007	406	3–4 months	None	DSG (0.075 mg)	n/a	n/a	Improvement in 93%	No statistics
Harel et al. [83]	2005	28	Up to 1 year	None	EE (0.075 mg)/ norelgestromin (6 mg)	n/a	n/a	39% decrease, 11% increase, 50% no change	No statistics
Kido et al. [84]	2007	41	3 months– 4 year	No-OC control group	EE (0.03–0.05 mg)/ LNG (0.03 and 0.04 mg), NES (0.035 mg) or NGS (0.05 mg)	n/a	n/a	Degree of experienced pain lower in the OC group, no severe menstrual pain in the OC group	Yes
Matsumoto et al. [85]	2007	110; 39 in the dysmenorrhea subgroup	3 months	None	Unspecified OCs	n/a	n/a	QoL scores significantly improved over all domains	Yes
Sabatini et al. [86]	2007	156	6 months	Comparison	EE (0.03 mg)/ CMA (2 mg)	EE (0.03 mg)/ DRSP (3 mg)	n/a	Progressive and significant reduction in mild and moderate dysmenorrhea in the EE/CMA group	Yes
Schramm and Heckes [87]	2007	16,781; 6169 in the dysmenorrhea subgroup	4 months	Comparison	EE (0.03 mg)/ CMA (2 mg)	Former contraception	n/a	61.1% complete resolution; 5.4% unchanged	No statistics

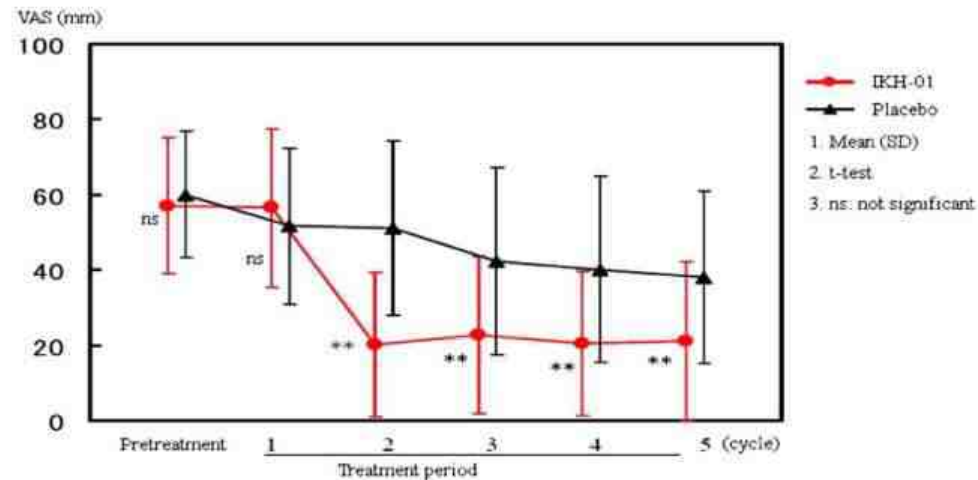
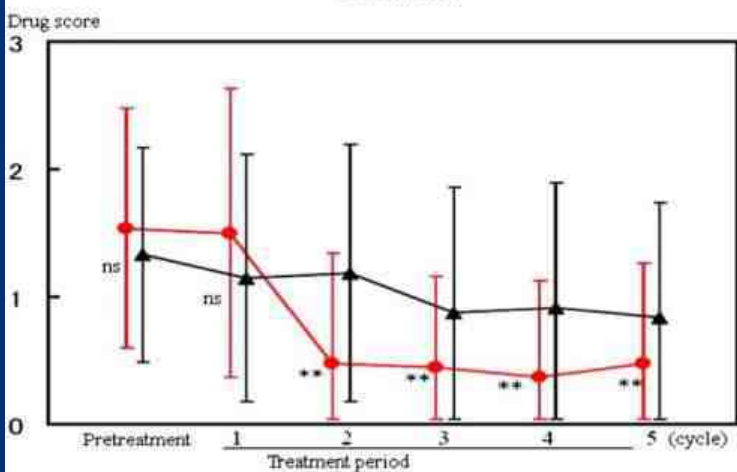
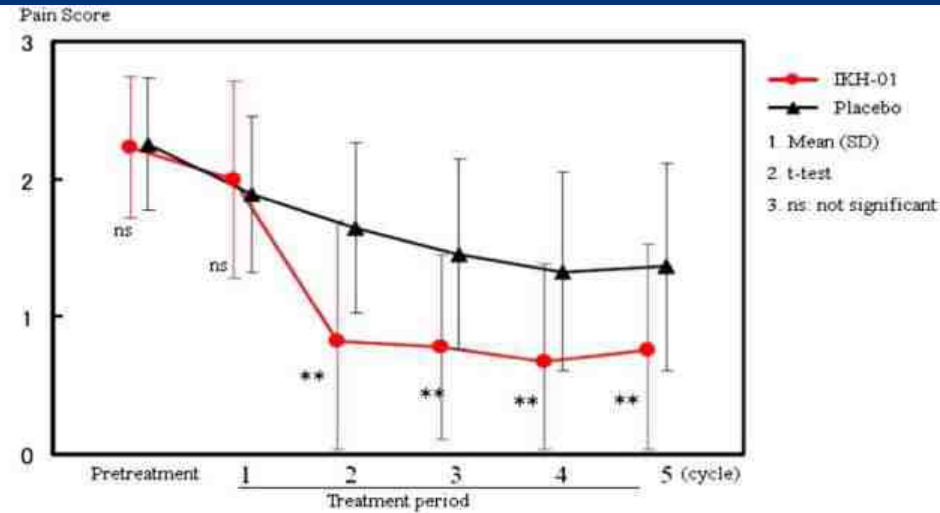
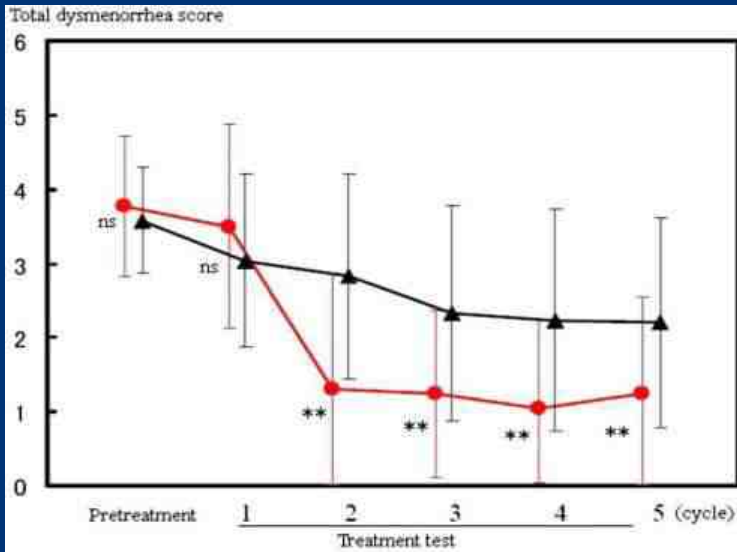
ACOG

## Noncontraceptive Uses of Hormonal Contraceptives ( Jan 2010)

Which hormonal contraceptives are beneficial for treatment of dysmenorrhea?

\*combined OC have been shown to reduce uterine PG production and relieve dysmenorrhea up to 70-80% of patients.

# Evaluation of a low-dose oral contraceptive pill for primary dysmenorrhea: a placebo-controlled, double-blind, randomized trial (N: 115)



Soru:

Endometriozisin medikal tedavisinde ilk tercihiniz hangisidir ?

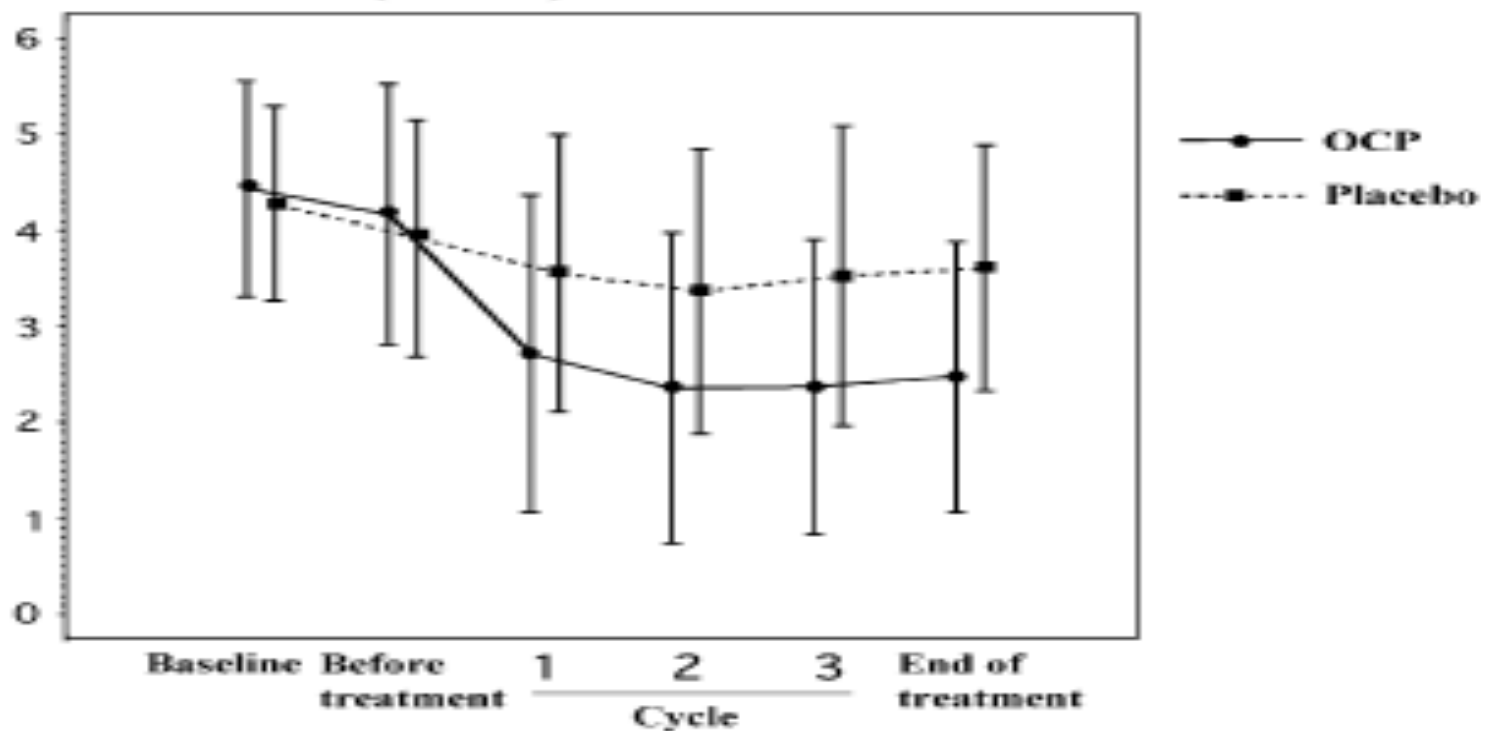
1. Aromataz İnhibitörleri
2. Dienogest
3. Danazol
4. OraL Kontraseptifler
5. GnRH Analogları
6. LNG (IUS)
7. Diğer progesteronlar
8. Endometriozis tedavisinde medikal tedaviye inanmam

Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial ( N: 100, 16 w)

**FIGURE 2**

Changes in mean dysmenorrhea score during the trial. OCP: oral contraceptive pill.

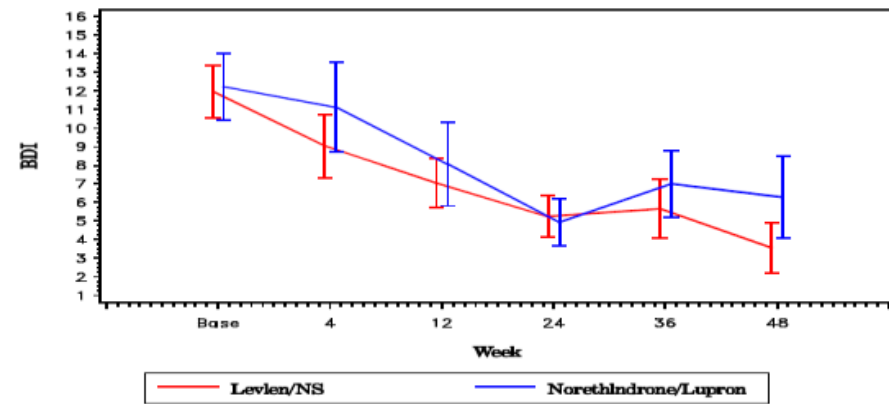
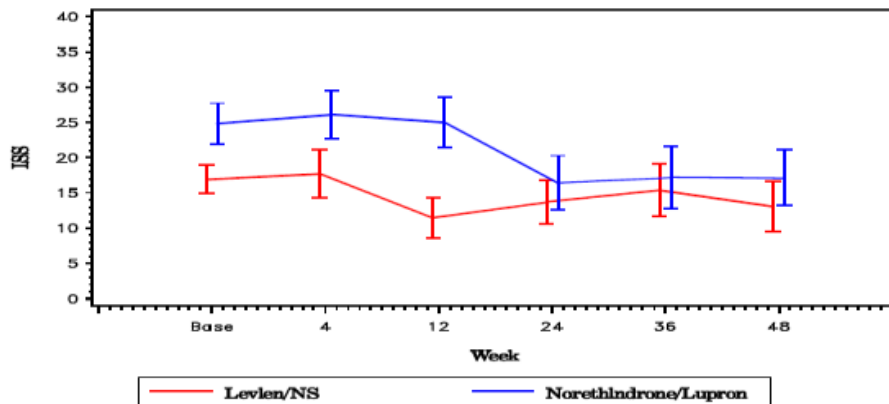
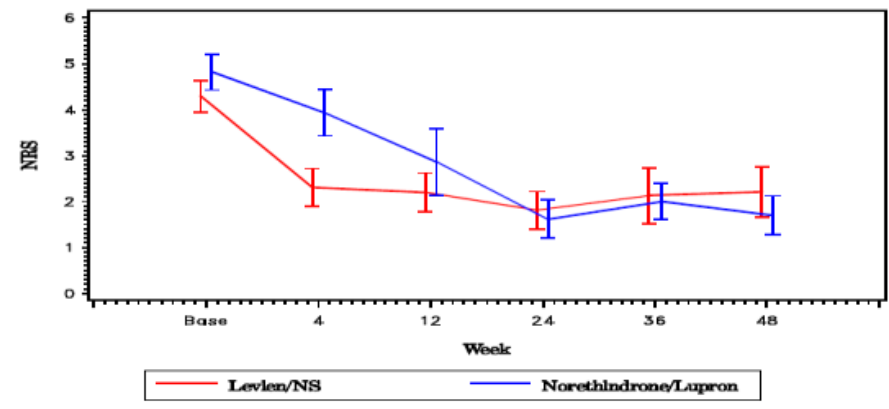
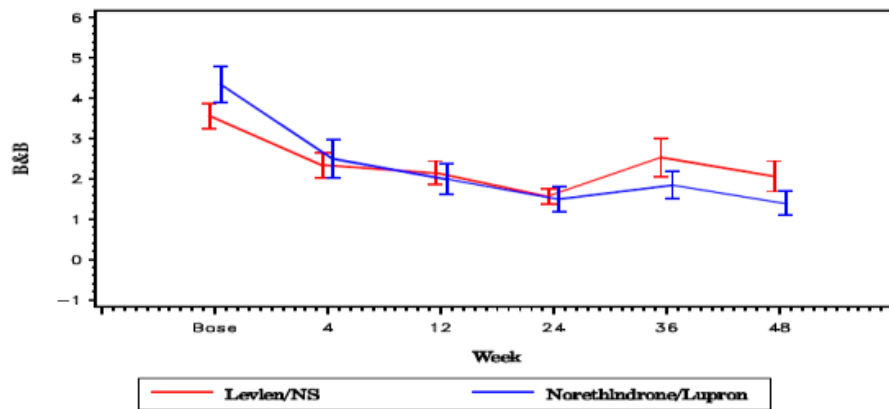
Total dysmenorrhea score (m + SD)



# Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain (n: 47, 48 w)

**FIGURE 1**

Comparison of trends between leuprolide and oral contraceptive groups in pain and quality-of-life assessments. Mean values with standard error bars are shown at each time of assessment.



# Oral contraceptives for pain associated with endometriosis

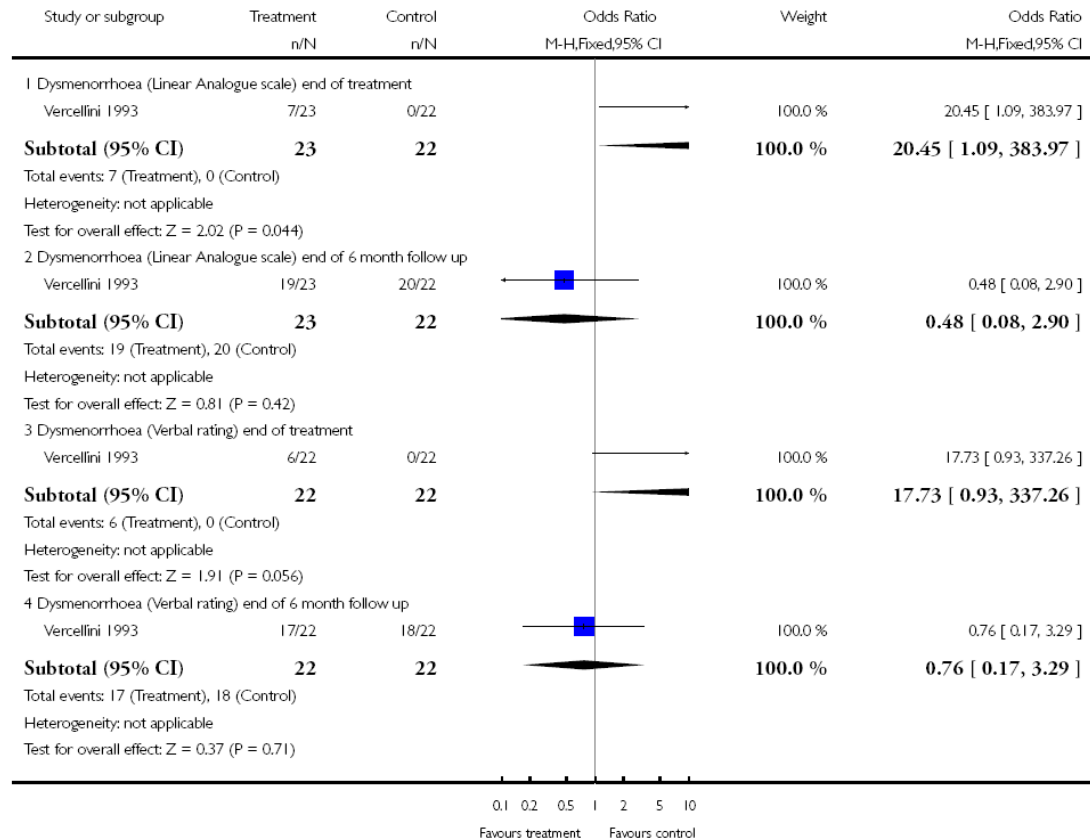
## Davis et al 2009

### Analysis 1.1. Comparison 1 OCP versus goserelin; reduction of pain to mild or zero, Outcome 1 Dysmenorrhoea.

Review: Oral contraceptives for pain associated with endometriosis

Comparison: 1 OCP versus goserelin; reduction of pain to mild or zero

Outcome: 1 Dysmenorrhoea



Dysmenorrhoea

# Oral contraceptives for pain associated with endometriosis

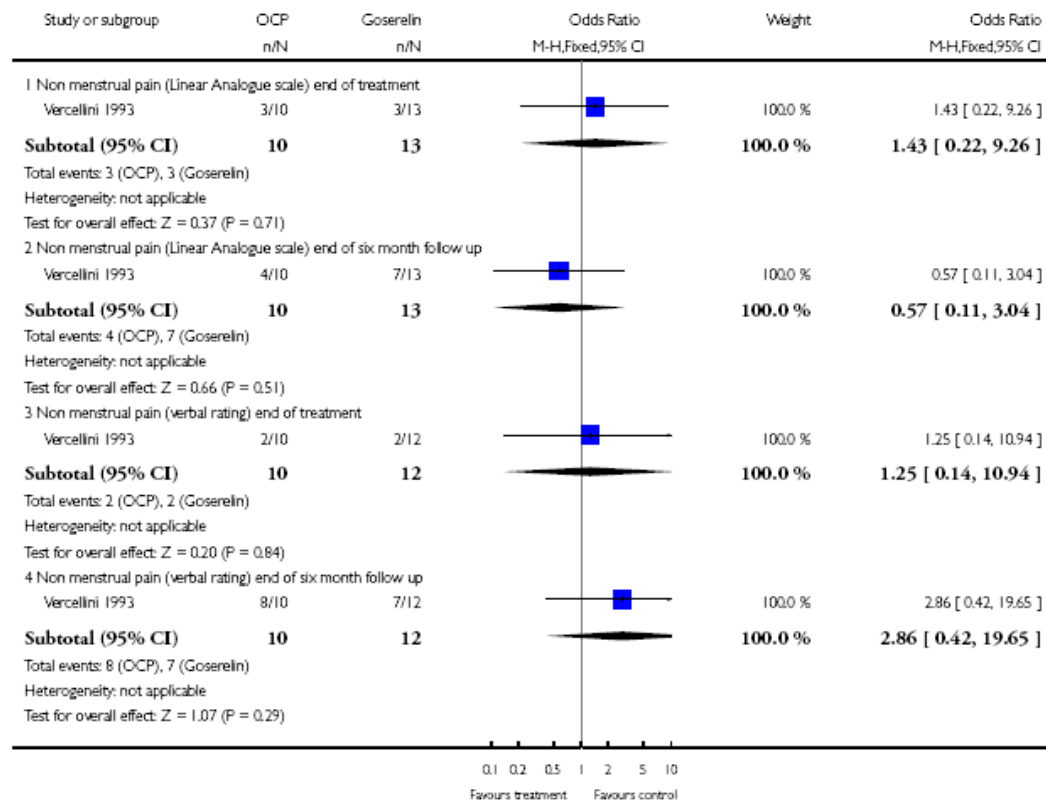
## Davis et al 2009

### Analysis 1.2. Comparison 1 OCP versus goserelin; reduction of pain to mild or zero, Outcome 2 Non menstrual pain.

Review: Oral contraceptives for pain associated with endometriosis

Comparison: 1 OCP versus goserelin; reduction of pain to mild or zero

Outcome: 2 Non menstrual pain



Non-menstrual pain

# Oral contraceptives for pain associated with endometriosis

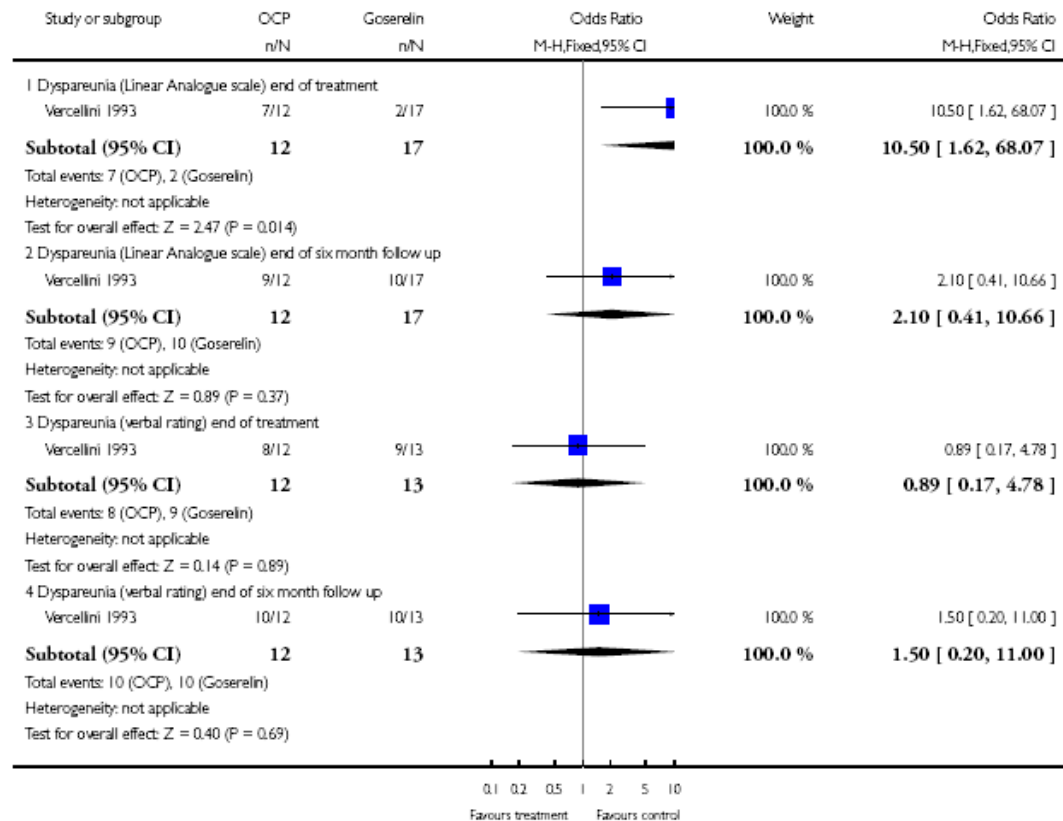
## Davis et al 2009

### Analysis 1.3. Comparison 1 OCP versus goserelin; reduction of pain to mild or zero, Outcome 3 Dyspareunia.

Review: Oral contraceptives for pain associated with endometriosis

Comparison: 1 OCP versus goserelin; reduction of pain to mild or zero

Outcome: 3 Dyspareunia



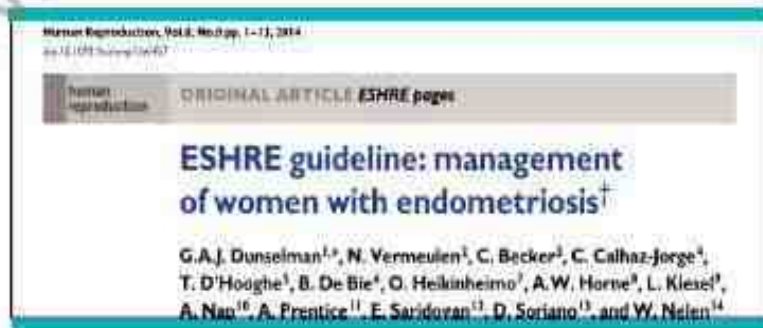
Dyspareunia

ACOG

## Noncontraceptive Uses of Hormonal Contraceptives ( Jan 2010)

Limited data suggest that COC can reduce the severity of dysmenorrhea in women with endometriosis. Continuous COC may offer additional benefit by elimination of menstruation and associated dysmenorrhea..

# Contemporary management of endometriosis



Based on:

- 2014 ESHRE Guidelines
- 2013 World Endometriosis Consensus
- 2010 SOGC Guidelines

ESHRE, European Society of Human Reproduction and Embryology; SOGC, Society of Obstetricians and Gynaecologists of Canada

ESHRE Guidelines 2014. Dunselman G *et al*. Human Reproduction 2014; 29(3):400–412.

WES Consensus. Johnson *et al*. Human Reprod 2013; 28(6):1552–68.

SOGC Clinical Practice Guideline. Endometriosis: Diagnosis and management. J Obstet Gynecol Can 2010.

TÜRKİYE  
ENDOMETRİOZİS  
TANI VE YÖNETİM  
KILAVUZU  
**2014**

ENDOMETRİOZİS &  
ADENOMYOZİS  
DERNEĞİ  
2009

[www.endometriozisdernegi.com](http://www.endometriozisdernegi.com)  
[www.endometriozis.org](http://www.endometriozis.org)

# On-label and off-label drug use in the treatment of endometriosis

2015

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## FDA onaylı "on-label" ilaçlar

Danazol (danasin)

GnRH-a (leuprolide acetate / goserelin acetate)

Progestinler (MPA / NETA) (depo provera / primolut-N)

## FDA onaysız "off-label" ilaçlar

(deneysel araştırmada değil klinik kullanımda ilaçlar)

Kombine OKS

NSAI ajanlar (naproksen)

Progestinler (dienogest) (visanne)

LNG-IUD (mirena)

Aromataz inhibitörleri (letrozole)

GnRH antagonistleri (cetorelix)

## Soru:

Hangisi OK ların endometriozis tedavisinde etkinliđi için yanlıřtır

- Ektopik endometrial dokularda atrofi
- Seks hormon düzeylerinde azalma
- Retrograd menstrüasyında azalma
- Apoptozisde artma
- Aromataz ekspresyonunu arttırma



# The use of Oral Contraceptives in Endometriosis

## Combined oral contraceptives (COCs)

- Widely used to reduce pain associated with endometriosis
- “An issue to consider when using COCs for the management of endometriosis pain is their estrogen component, which may result in stimulation of the disease”<sup>1</sup>
- Limited data available on efficacy and long-term safety profile in endometriosis patients
  - “Further research is needed to fully evaluate the role of oral contraceptive pills in managing symptoms associated with endometriosis”<sup>2</sup>
- Not approved for endometriosis

<sup>1</sup>Kappou, D, et al. Minerva Ginecol 2010;62:415–32;

<sup>2</sup>Davis LJ, et al. Cochrane Database Syst Rev 2007;CD001019

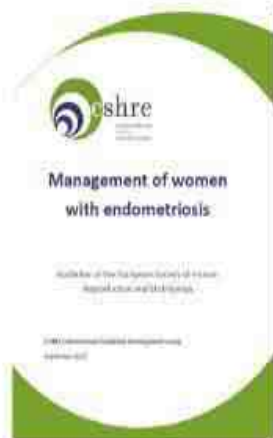
## Soru:

Hangi kılavuz endometriozisde ampirik tedaviyi desteklemez ?

- WES
- Turkiye
- ESHRE
- Kanada
- Hepsi destekler
- Hicbiri desteklemez

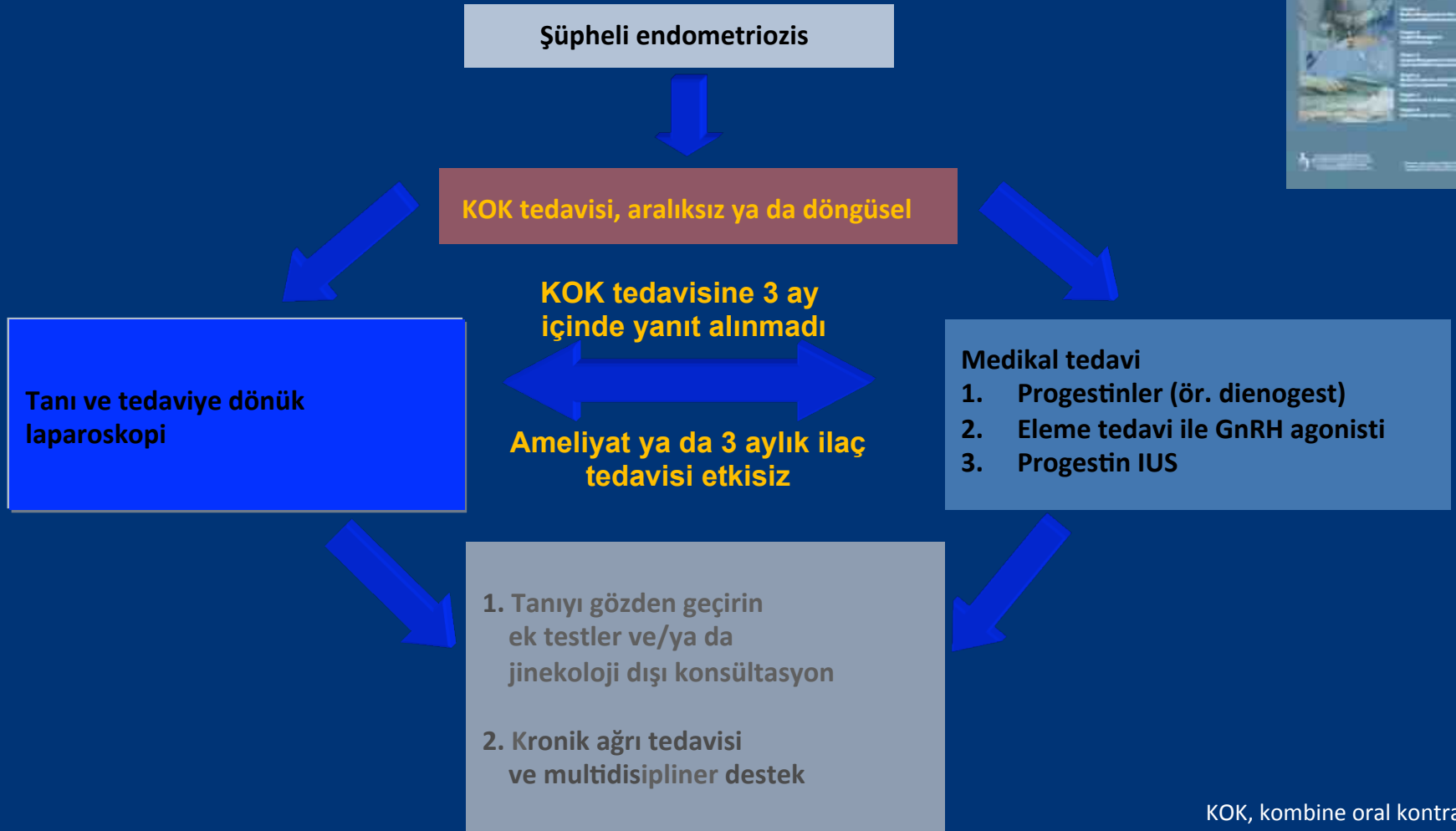
# COCs and pain management

- No COC is indicated for the treatment of endometriosis
- However, they are widely used off-label for the management of pain in endometriosis
- First-line, empirical medical treatment with COCs is supported by several endometriosis guidelines<sup>1-3</sup>



1. Dunselman G *et al.* Human Reproduction 2014; 29(3):400–412. 2. Leyland N *et al.* J Obstet Gynaecol Can 2010; 32 (7 suppl 2): s1–s32. 3. Johnson NP *et al.* Hum Reprod 2013; 28(6): 1552–1568.

# SOGC kılavuz algoritması: Endometriozis şüphesinde ağrı tedavisi



KOK, kombine oral kontraseptif IUS, intrauterine sistem

# WES international consensus on endometriosis

- Advocates early, proactive management of pelvic pain

“Management of pelvic pain should not be delayed in order to obtain surgical confirmation of endometriosis”

- Strongly supported by an extensive, international experienced and well-respected group of key opinion leaders, representatives of medical societies and patient groups



# Empirical treatment of pain

## Recommendation

The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens.

GPP

*Kılavuz hazırlama kurulu, endometriozise bağlı olduğu düşünülen pelvik ağrının yönetiminde ampirik medikal tedavi denenmesini kuvvetle tavsiye etmektedir.*

*Ampirik tedavide kombine oral kontraseptifler veya progestinler ilk seçenek olarak kuvvetle tavsiye edilmektedir.*

*Tedaviye başlamadan önce pelvik ağrıya yol açabilecek diğer hastalıkların ekarte edilmesi gerekmektedir.*

# ARE HORMONAL THERAPIES EFFECTIVE FOR PAINFUL SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS?

## Recommendations

Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), anti-progestagens (level A), or GnRH agonists (level A)] as one of the options, as it reduces endometriosis-associated pain (Vercellini, et al., 1993, Brown, et al., 2012, Brown, et al., 2010).

**A-B**

The GDG recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.

**GPP**

# *Hormonal contraceptives*

## Recommendations

Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Vercellini, et al., 1993).

**B**

Clinicians may consider the continuous use of a combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhea (Vercellini, et al., 2003).

**C**

Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce endometriosis-associated dysmenorrhea, dyspareunia and chronic pelvic pain (Vercellini, et al., 2010).

**C**

# ARE PREOPERATIVE HORMONAL THERAPIES EFFECTIVE FOR TREATMENT OF PAIN?

## Recommendation

Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis (Furness, et al., 2004).

A

# Treatment of pain associated with extragenital endometriosis

## Recommendations

Clinicians may consider surgical removal of symptomatic extragenital endometriosis, when possible, to relieve symptoms (Liang, et al., 1996, Marinis, et al., 2006, Nezhat, et al., 2011, Nissotakis, et al., 2010, Song, et al., 2011).

**D**

When surgical treatment is difficult or impossible, clinicians may consider medical treatment of extragenital endometriosis to relieve symptoms (Bergqvist, 1992, Joseph and Sahn, 1996, Jubanyik and Comite, 1997).

**D**

✓ Endometriozis nedeniyle opere  
olanlarda; endometriozis ilişkili  
dismenoreden korunmak için  
(disparoni, non-mens. pelvik ağrı değil)  
en az 18-24 ay LNG-IUD veya kombine  
hormonal kontraseptif önerilir. A

✓ Endometriozis tanısı almış infertil K'da ovarian fonksiyon supresyonu için hormonal tedavi, fertilitiyi iyileştirmedeğinden önerilmemektedir (Hughes et al.2007). A

✓ Endometriozisten primer korunmada O.K.'lerin yeri belirsiz.(Vercellini et al, 2011). C

# Endometriosis: Diagnosis and Management

- **Medical Management of Pain Associated With Endometriosis Recommendations**
- 1. Combined hormonal contraceptives, ideally administered continuously, should be considered as first-line agents. (I-A)
- 2. Administration of progestin alone—orally, intramuscularly, or subcutaneously—may also be considered as first-line therapy. (I-A)
- 3. A GnRH agonist with HT addback, or the LNG-IUS, should be considered a second-line therapeutic option. (I-A)
  - 4. A GnRH agonist should be combined with HT addback therapy from commencement of therapy and may be considered for longer-term use (> 6 months). (I-A)
- 5. While awaiting resolution of symptoms from the directed medical or surgical treatments for endometriosis, practitioners should use clinical judgement in prescribing analgesics ranging from NSAIDs to opioids. (III-A)

Endometriozis ile ilişkili dismenorenin azaltılmasında kombine oral kontraseptiflerin etkinliğini destekleyen orta kalite kanıt vardır.

Endometriozis ile ilişkili disparoni ve non-menstrüel pelvik ağrının azaltılmasında kombine oral kontraseptiflerin etkinliğini destekleyen düşük kalite kanıt vardır.

Endometriozis ile ilişkili dismenore, disparoni ve kronik pelvik ağrıyı azaltmak için vajinal kontraseptif halka veya transdermal bant (östrojen/progesteron) kullanımına dair düşük kalite kanıt vardır.

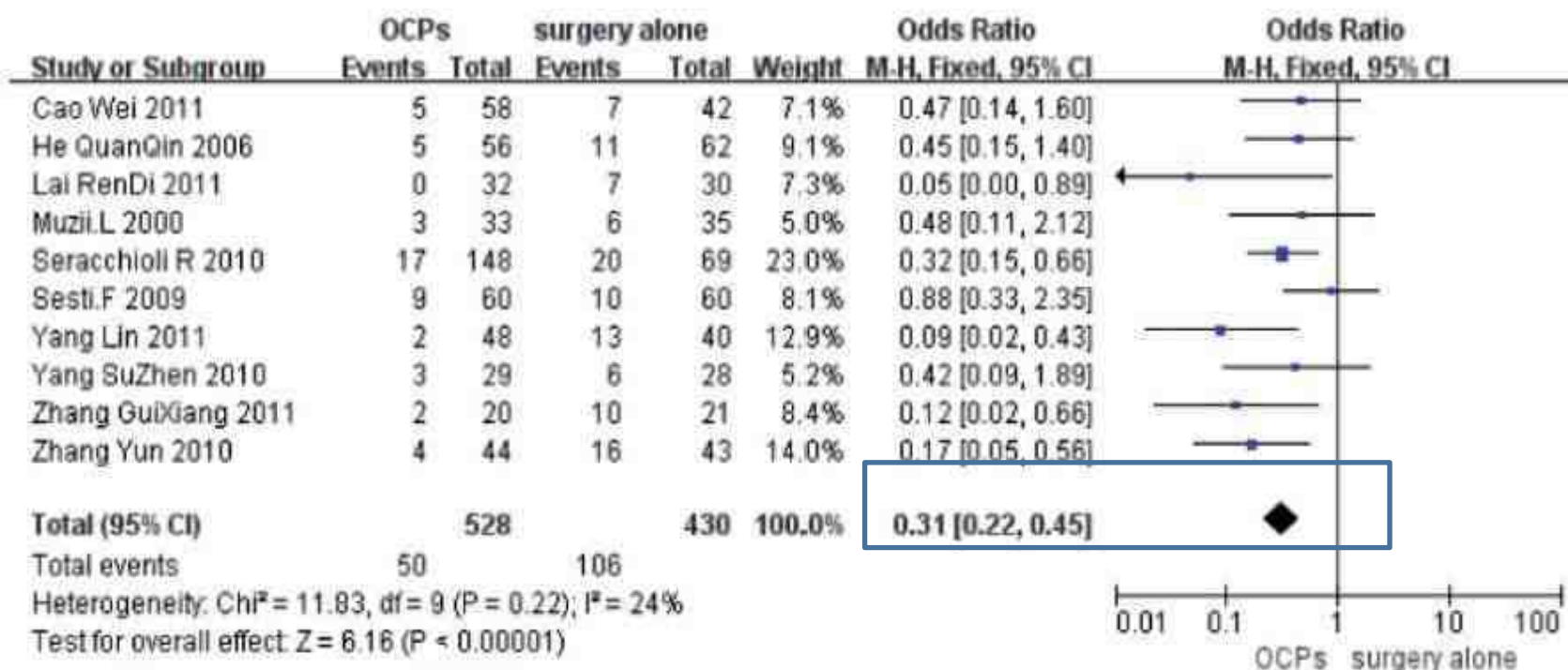
Kılavuz hazırlama kurulu, endometriozis ile ilişkili ağrının tedavisinde hormonal kontraseptiflerin kullanılması yönünde kuvvetli tavsiyede bulunmaktadır.

Endometrioma için kistektomi yapılmış, fertilité isteđi olmayan kadınlara postoperatif dönemde kombine oral kontraseptif verilmesinin rekürrens oranını azalttığına dair yüksek kalite kanıt vardır ve kullanılması kuvvetle tavsiye edilir.

Endometriozis için opere edilen kadınlarda en az 18 – 24 ay süreyle kombine oral kontraseptif, progestin veya levonorgestrel salınımlı intrauterin sistemin kullanılmasının postoperatif rekürrens ve semptomları azalttığına dair yüksek kalite kanıt vardır ve sekonder korunma amaçlı kuvvetle tavsiye edilmektedir.

## Oral contraceptive pills for endometriosis after conservative surgery: a systematic review and meta-analysis

Lixia Wu, Qianyu Wu & Lan Liu



**Recurrence rate of OCPs versus surgery alone**

# ENDOMETRİOMA SONRASI REKÜRRENS

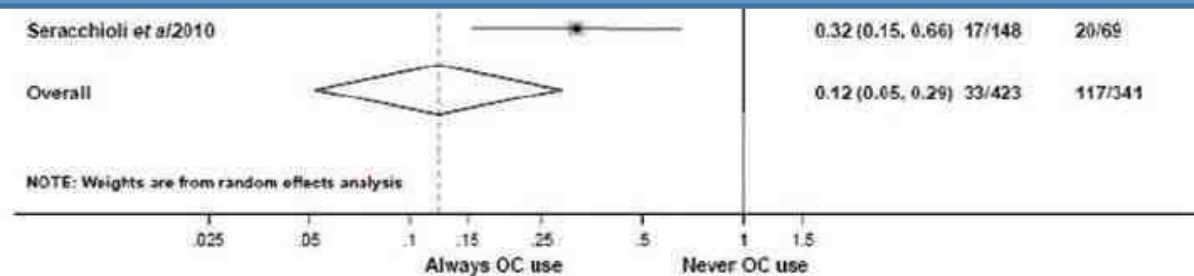
TEDAVİ	REKÜRRENS
YOK	%29
SİKLİK KOK	%15
SÜREKLİ	%8

AOGS REVIEW ARTICLE

2012

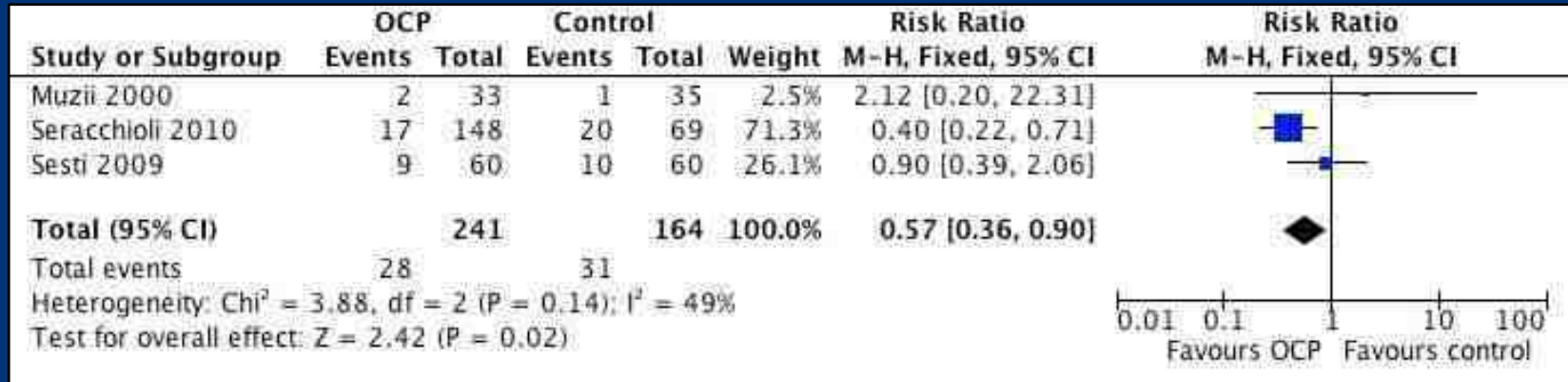
# Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic

A recurrent endometrioma was identified in 33 of 423 (8%) “always” OC users and in 117 of 341 (34%) women who underwent expectant management (pooled odds ratio 0.12; 95% confidence interval 0.05–0.29).



**Figure 2.** Results of studies comparing conservative surgery for ovarian endometriomas followed by postoperative long-term oral contraceptive (OC) use for the entire study period (“always OC users”) or expectant management (“never OC users”). Horizontal lines indicate 95% confidence intervals (CIs); boxes show the study-specific weight; rhombus represents combined effect size; and dashed line indicates the overall estimate. Breslow–Day test for heterogeneity:  $\chi^2_3 = 8.95$ ,  $p = 0.030$ .

# ENDOMETRIOMA SONRASI REKÜRRENS



After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe combined hormonal contraceptives for the secondary prevention of endometrioma (Vercellini *et al.*, 2010a, b).

A

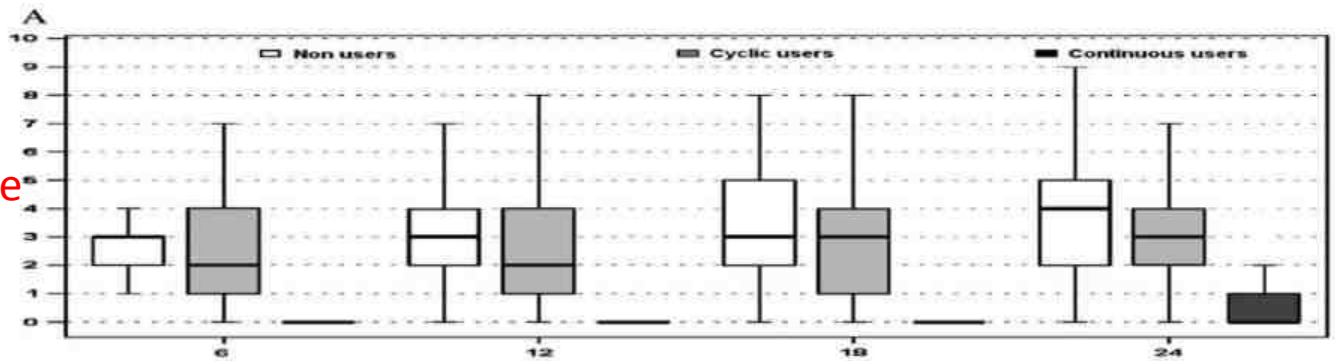
## Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial

- Prospective, randomized, controlled trial.
- Three hundred eleven women dysmenorrhea, dyspareunia, and chronic pelvic pain were assessed by a 10-point visual analogue scale (VAS) at 6, 12, 18, and 24 months postoperatively

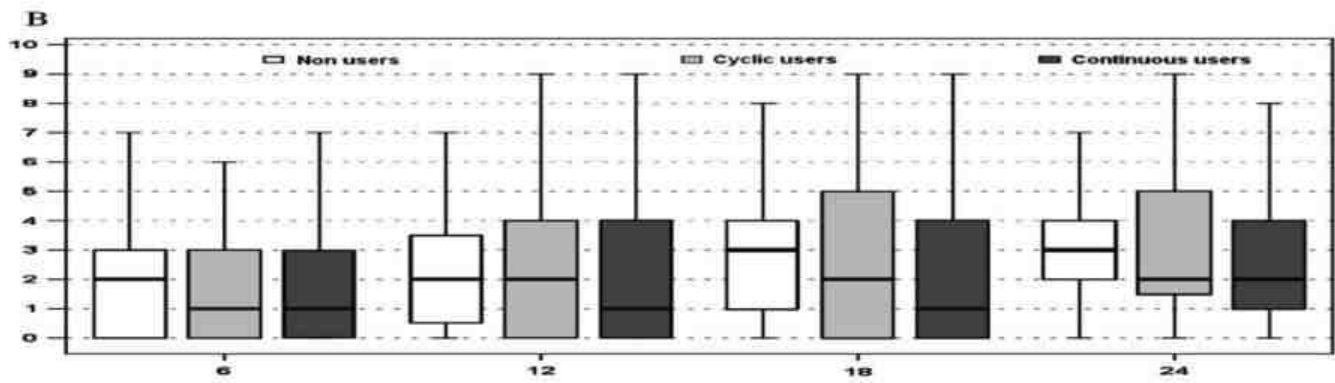
**FIGURE 4**

The visual analogue scale (VAS) score for the three types of pain at 6, 12, 18, and 24 months postoperatively. **(A)** Dysmenorrhea: VAS scores are lower in continuous users for the entire study period ( $P < .0005$ ) and in cyclic users versus nonusers from 12 months postoperatively. Nonusers show a significant worsening in pain intensity from 6–24 months. **(B)** Dyspareunia: no significant difference in VAS scores among the three groups. Cyclic and nonusers versus continuous users show a worsening of pain intensity from 6–24 months. **(C)** Chronic pelvic pain: no significant difference in VAS scores among the three groups. Nonusers versus continuous users show a worsening of pain intensity from 6–24 months.

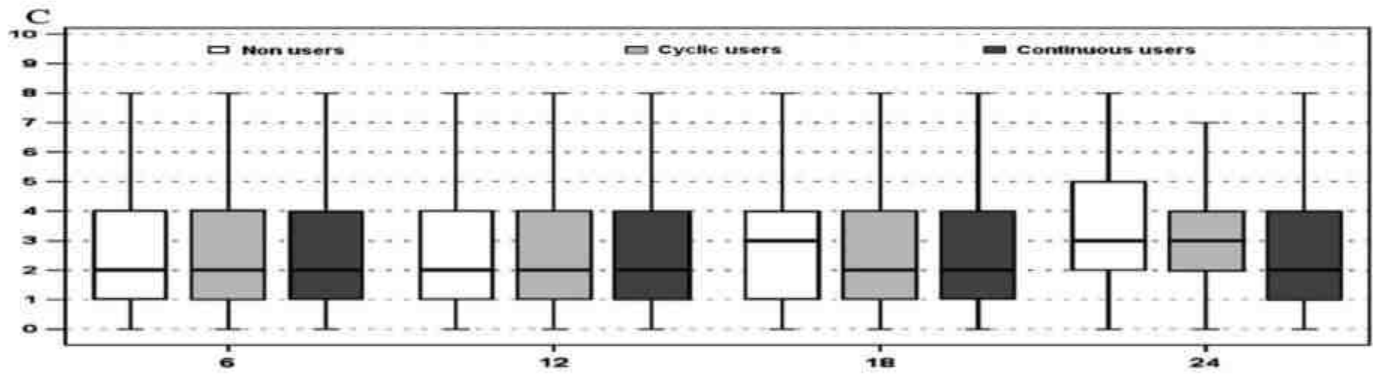
Dismenore



Disparoni

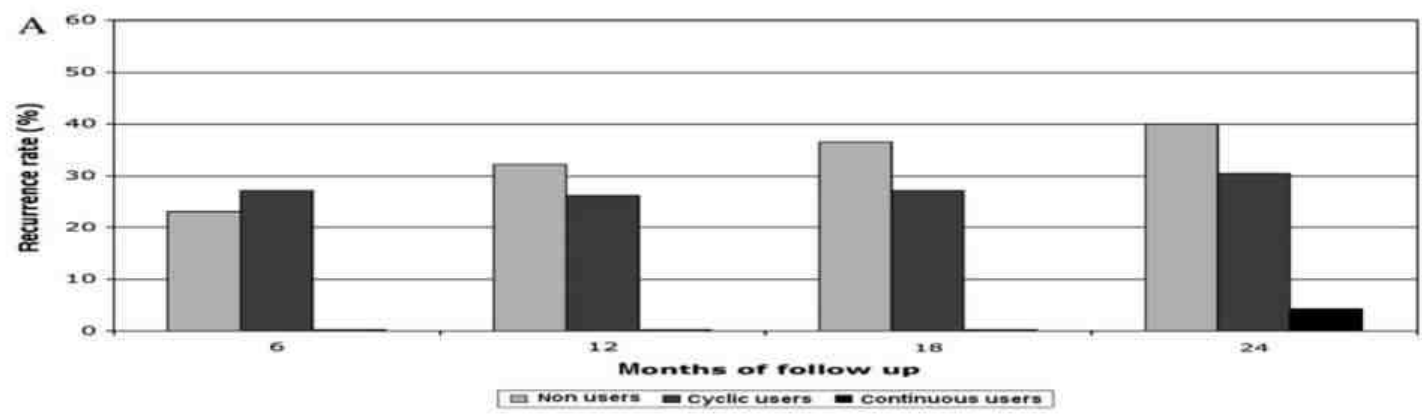


CPP

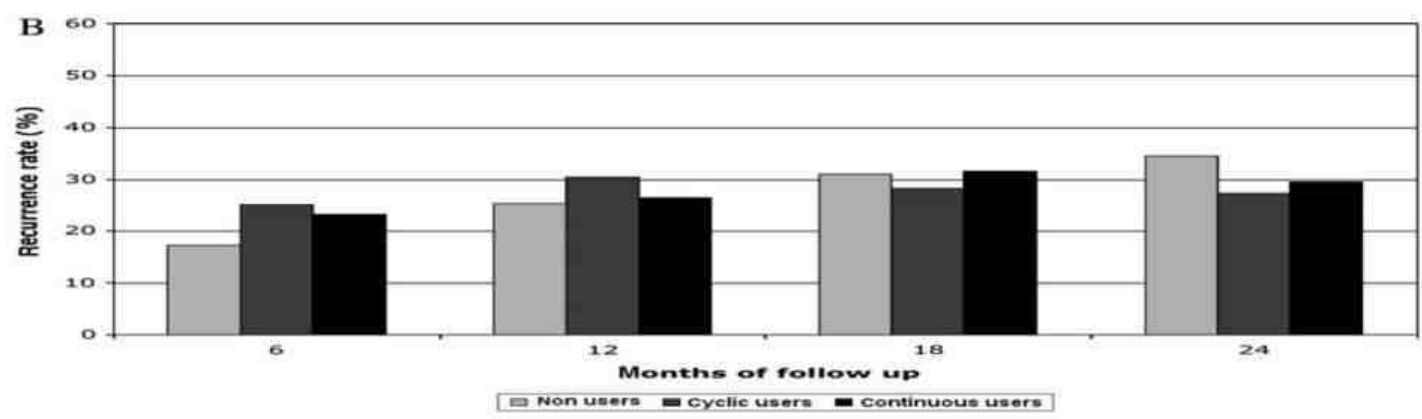


Recurrence rates for the three types of pain. **(A)** Dysmenorrhea recurrence rate: lower in continuous users for the entire study period ( $r < .0005$ ), reduced in cyclic users versus nonusers at 18 and 24 months ( $P = .01$ ,  $P = .009$  respectively). **(B)** Dyspareunia recurrence rate: no significant difference among the study groups. **(C)** Chronic pelvic pain recurrence rate: no significant difference among the study groups.

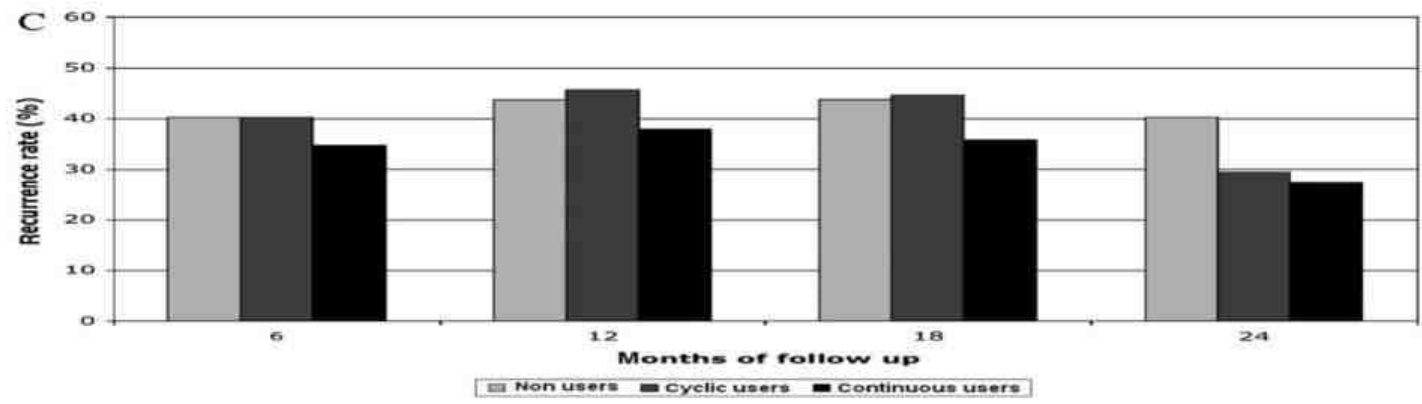
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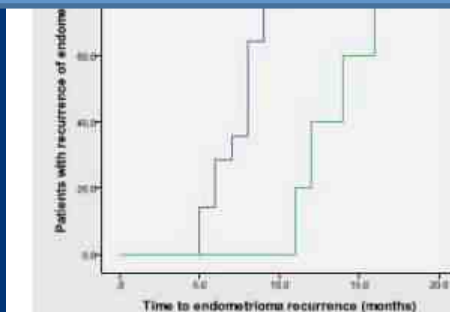
# Continuous versus cyclic use of oral contraceptives after surgery for symptomatic endometriosis: a prospective cohort study

Nikos Vlahos, M.D.,<sup>a</sup> Athanasios Vlachos, M.D.,<sup>b</sup> Olga Triantafyllidou, M.D.,<sup>a</sup> Nikolaos Vitoratos, M.D.,<sup>a</sup> and George Creatsas, M.D.<sup>a</sup>

2013

<sup>a</sup> 2nd Department of Obstetrics and Gynecology, Aretaieion Hospital, University of Athens, and <sup>b</sup> Lito Maternity Hospital, Athens, Greece

Continuous OC appears to be associated with a reduced recurrence rate for dysmenorrhea, nonmenstrual pelvic pain, and endometrioma but not for dyspareunia as compared with cyclic OC.



## Endometriosis-related symptoms after treatment with oral contraceptives (OC).

	Cyclic OC (%)	Continuous OC (%)	P value
No. of patients	167	85	
Duration of treatment (mo) ± SE	23 ± 2.9	21 ± 2.7	.34
Recurrence of symptoms			
Dysmenorrhea	35 (20.9)	8 (9.4)	.021 <sup>a</sup>
Dyspareunia	29 (17.3)	9 (10.5)	.193
Non-menstrual pelvic pain	40 (23.9)	8 (9.4)	.0062 <sup>a</sup>
Recurrence of endometrioma	14/84 (16.6)	5/54 (9.2)	.025 <sup>a</sup>
Abnormal uterine bleeding	21 (12.5)	20 (23.5)	.03 <sup>a</sup>
Discontinuation rates at	14 (8.3)	15 (12.9)	.037 <sup>a</sup>
12 mo from initial cohorts	14/197 (7.1)	15/96 (15.6)	.035 <sup>a</sup>

<sup>a</sup> Statistically significant differences between the two groups.

Vlahos. Oral contraceptives for endometriosis. *Fertil Steril* 2013.

## **Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review**

**Konstantinos A. Zorbas · Konstantinos P. Economopoulos · Nikos F. Vlahos**

Received: 16 October 2014 / Accepted: 27 January 2015  
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- Postoperative use of continuous oCP was associated with a reduction in the recurrence rate of dysmenorrhea, delay in the presentation of dysmenorrhea, reduction in nonspecific pelvic pain, and reduction in the recurrence rate for endometrioma.

Continuous versus Cyclic Oral Contraceptives after Laparoscopic Excision of Ovarian Endometriomas: A Systematic Review and Meta-Analysis

Ludovico Muzii, MD, Chiara Di Tucci, MD, Chiara Achilli, MD, Violante Di Donato, MD, Angela Musella, MD, Innocenza Palaia, MD, Pierluigi Benedetti Panici, MD



- Results: Three randomized clinical trials and one prospective controlled cohort study were included, for a total of **557 patients** with endometriosis, **343 patients** of which with ovarian endometriomas completing the assigned treatment and follow-up.
- *Lower recurrence rates for dysmenorrhea were obtained with a continuous schedule (RR 0.24; 95% CI 0.06 to 0.91; p=0.04).*
- Nonsignificant differences were present for chronic pelvic pain and dyspareunia.
- A continuous oral contraceptive schedule was associated with a non-significant reduction of cyst recurrence rates compared to a cyclic schedule (RR 0.54; 95% CI 0.28 to 1.05; p=0.07).
- Conclusions: A continuous oral contraceptive regimen, as opposed to a cyclic regimen, may be suggested after surgery for endometriomas because of lower dysmenorrhea recurrence rates. Due to the small number and small sample sizes of the included studies, further randomized clinical trials are needed to confirm the findings of the present systematic review.
- Also, outcomes related to patient satisfaction and quality of life should be addressed.

# Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis

2015

Kaori Koga, M.D., Ph.D., Masashi Takamura, M.D., Ph.D., Tomoyuki Fujii, M.D., Ph.D., and Yutaka Osuga, M.D., Ph.D.

Department of Obstetrics and Gynecology, University of Tokyo, Tokyo, Japan

TABLE 1

List of studies that reported the efficacy of postoperative medications administered for more than 6 months on pain recurrence.

Author	Reference	Year	Study design	Interventions	No. of patients	Follow-up period, mo	Outcome measured	Methods of measurement	Definition of recurrence	Results (recurrence rate)	P value
Vercellini et al.	22	2003	Cohort	Continuous OC	50	24	Dysmenorrhea	VAS, VRS	Not specified	mean VAS 75 → 31, mean VRS 2.4 → 0.7	NS
Vercellini et al.	25	2003	RCT	LNG-IUS/EM	20/20	12	(a) Dysmenorrhea	VAS	VAS ≥ 51	LNG-IUS (10%) vs EM (5 reduction)	< .05
Serachi										5 reduction	NS
										31% vs 61% (OC)	< .001
										8 (40%) vs 29% (OC)	NS
										34 (40%) vs 35% (OC)	NS
										34 (35%) vs 34% (OC)	NS
Wong et al.										34% (OC) vs 34% (OC)	< .05
										34% (OC) vs 34% (OC)	NS
										34% (OC) vs 34% (OC)	NS
Fahmy et al.										34% (OC) vs 34% (OC)	< .001
										34% (OC) vs 34% (OC)	< .05
										34% (OC) vs 34% (OC)	NS
Morelli et al.	21	2013	Cohort	LNG-IUS/OC	44/48	24	Pain	VAS	Not specified	LNG-IUS (VAS 29.0) vs OC (VAS 19.1)	< .05
Vlahos et al.	20	2013	Cohort	Cyclic OC/continuous OC	167/85	2 M/23	(a) Dysmenorrhea	Questionnaire <sup>a</sup>	Not specified	Cyclic OC (20.9%) vs continuous OC (9.4%)	< .05
					167/85	2 M/23	(b) Chronic pelvic pain	Questionnaire <sup>a</sup>	Not specified	Cyclic OC (23.9%) vs continuous OC (9.4%)	< .01
					167/85	2 M/23	(c) Dyspareunia	Questionnaire <sup>a</sup>	Not specified	Cyclic OC (17.3%) vs continuous OC (10.5%)	NS

Note: VAS = visual analog score; EM = expectant management; NA = not available; NS = not significant.  
<sup>a</sup> Dysmenorrhea plus chronic pelvic pain.  
<sup>b</sup> Self-administered questionnaire ([www.endometriosisfoundation.org/WEP/WEP-3/Questionnaire-English.pdf](http://www.endometriosisfoundation.org/WEP/WEP-3/Questionnaire-English.pdf)).

Most of these studies used oral contraceptives (OC), with either the cyclic or continuous regimen, while some used oral or intrauterine progestin. Continuous OC is more efficacious than cyclic OC, especially for dysmenorrhea

TABLE 2

List of studies that reported the efficacy of postoperative medications administered for more than 6 months on endometrioma recurrence.

Author	Reference	Year	Study design	Interventions (when no duration is indicated, the duration is not limited)	No. of patients	Follow-up period, months	Outcome measured	Methods of measurement	Definition of recurrence	Results (recurrence rate)	P value
Park et al.	40	2008	Cohort	GnRHα 6 months + OC (<24/24–48/48< months)	22/19/10	41 (19–94)	Endometrioma	TV US	>20 mm	OC <24 (4.5%)/24–48 (0%)/48< months (0%)	NA
Vercellotti et al.	30	2008	Cohort	OC (always)/OC (ever)/EM	102/129/46	38 (median)	Endometrioma	TV US	>20 mm	OC (always) (6%)/EM (49%)	<.001
Takamura et al.	31	2009	Cohort	OC for 24 months/EM	34/99	24	Endometrioma	TV US	>20 mm	OC (0.9%)/EM (43.5%)	<.001
Lee et al.	41	2010	Cohort	GnRHα 3 or 6 months + OC/GnRHα 3 or 6 months alone	175/187	35 (12–114)	Endometrioma	TV US	>20 mm	GnRHα + OC (7.4%)/GnRHα alone (28.9%)	<.001
Seraozioni et al.	24	2010	RCT	Cyclic OC/continuous OC/EM	75/73/69	24	Endometrioma	TV US	>15 mm	Cyclic OC (14.7%)/continuous OC (8.2%)/EM (2.9%)	<.005
Wong et al.	26	2010	RCT	LNG-IUS/MPA depot	15/15	36	Endometrioma	TV US	>30 mm	No recurrence were detected in both groups	NS
Monelli et al.	21	2013	Cohort	LNG-IUS/OC	44/48	24	Disease recurrence	CA125, TV US, pelvic exam	CA125 elevation and/or positive findings	LNG-IUS (20.5%)/OC (12.5%)	NS
Vlahos et al.	20	2013	Cohort	Cyclic OC/continuous OC at least 6 months	167/85	21/23	Endometrioma	TV US	Not specified	Cyclic OC (16.6%)/continuous OC (9.2%)	<.05
Cuchella et al.	34	2013	RCT	OC with desogestrel/OC with gestodene/OC with dienogest/EM	43/44/3/38	24	Endometrioma	TV US	Not specified	Desogestrel (26.5%)/Gestodene (31.8%)/Dienogest (0.5%)/EM (74.7%)	<.005 (all OC vs. EM)
Cho et al.	39	2014	Cohort	GnRHα 3 months followed by LNG-IUS/ followed by OC	42/57	17	Endometrioma	TV US	>20 mm	LNG-IUS (4.8%)/OC (10.5%)	NS
Ouchi et al.	32	2014	Cohort	OC (always)/OC (ever)/Dienogest/GnRHα 6 months/EM	25/97/16/110	38/3	Endometrioma	TV US	>20 mm	OC (always) (0%)/OC (ever) (56%)/Dienogest (3%)/GnRHα (2.5%)/EM (23%)	<.05 (OC always vs. OC ever)
Ota et al.	38	2015	Cohort	Dienogest/EM	15/14/17	60	Endometrioma	TV US	>20 mm	Dienogest (4%)/EM (69%)	<.0001

Note: TV US = transvaginal ultrasonography; EM = expectant management; NA = not available; NS = not significant.

Koga, Prevention of endometriotic recurrence. April 2015.

# Continuous low-dose oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic ultrasonography

STEFANO FERRARI<sup>1</sup>, PAOLA PERSICO<sup>1</sup>, FRANCESCA DI PUPPO<sup>2</sup>, PAOLA VIGANO<sup>1</sup>, IACOPO TANDOI<sup>2</sup>, ELISABETTA GARAVAGLIA<sup>1</sup>, PAOLO GIARDINA<sup>1</sup>, GIANNI MEZZI<sup>3</sup> & MASSIMO CANDIANI<sup>1,2</sup>

<sup>1</sup>Obstetrics and Gynecology Unit and <sup>3</sup>Department of Gastroenterology and Gastrointestinal Endoscopy, San Raffaele Scientific Institute, Milan, and <sup>2</sup>Università Vita-Salute San Raffaele, Milan, Italy 2012

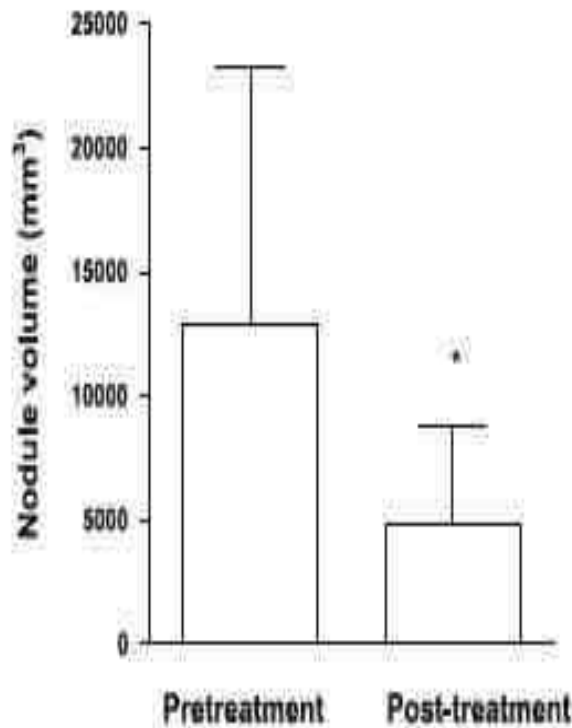


Figure 1. Changes in volume of the bowel nodules after 12 months of a low-dose oral contraceptive as measured by rectal endoscopic ultrasonography (n=26). \*p<0.01 vs. baseline conditions.

**Table 2.** Pain symptom score in patients with colorectal endometriosis (n=26) before and after 12 months of medical therapy according to visual analog scale (0–100).

Symptom	n	Basal	Post-treatment	p-Value
Dysmenorrhea	26	90.4±9.9	26.9±29.2	p<0.01
Dyspareunia	26	63.1±22.8	18.5±24.3	p<0.01
Painful defecation	26	57.7±28.2	13.1±17.6	p<0.01
Non-menstrual pain	26	65.0±27.3	18.5±19.1	p<0.01

•Lezyon çapında %26 azalma, lezyon volümünde %62 azalma

# Treatment of pain associated with deep endometriosis: alternatives and evidence

2015

Simone Ferrero, Ph.D.,<sup>a,b</sup> Franco Alessandri, M.D.,<sup>a</sup> Annalisa Racca, M.D.,<sup>a,b</sup> and Umberto Leone Roberti Maggiore, M.D.<sup>a,b</sup>

<sup>a</sup> Unit of Obstetrics and Gynecology, San Martino Hospital and National Institute for Cancer Research, University of Genoa; and <sup>b</sup> Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

**TABLE 1**

Level of evidence in the use of medical and surgical treatments for deep infiltrating endometriosis-associated pain.

Variable	Pros	Cons	Comments	Grade of recommendations for DIE treatment
Nonsteroidal anti-inflammatory drugs	Cost-effective Not contraceptive	No cytostatic effect	Only one randomized controlled trial has been published	No studies available
Progestogens	Generally cost-effective Effective in improving pain symptoms Available in different formulations (oral, intrauterine device, implant) Well tolerated	Contraceptive for women desiring to conceive	First-line therapy	A
Combined hormonal contraceptives	Cost-effective Effective in improving pain symptoms Available in different formulations (oral, vaginal, cutaneous) Well tolerated	Contraceptive for women desiring to conceive	First-line therapy	A
Gonadotropin releasing hormones agonists	Highly effective in improving pain symptoms Available in different formulations (intranasal, IM, SC)	Short-term use (6 mo) without add-back therapy Hypoeostrogenic AEs Expensive Contraceptive for women desiring to conceive	Second-line therapy	B
Danazol	Cost-effective Effective in improving pain symptoms	Androgenic AEs Need for barrier contraception	Low popularity due to their androgenic AEs	B
Aromatase inhibitors	Generally effective in improving pain symptoms in combination with hormonal contraceptives, progestogens, or GnRH agonists	Off-label High rates of hypoeostrogenic AEs Short-term use (6 mo)	To be used only in patients refractory to conventional therapies and in the setting of scientific research	B
Surgery	Highly effective in improving pain symptoms	Intraoperative complications Expensive	To be considered in patients refractory to hormonal treatment Second-third-line therapy	A

Note: A = (clinical) should be recommended; B = (clinical) is recommended/indicated; C = (clinical) is useful/effective; AE = adverse event; B = (clinical) can be recommended/indicated; DE = deep infiltrating endometriosis.

Ames. Deep endometriosis-associated pain management. April 2015.



## Review Article

## Medical treatment for adenomyosis and/or adenomyoma



Kuan-Hao Tsui <sup>a, b, 1</sup>, Wen-Ling Lee <sup>c, d, 1</sup>, Chih-Yao Chen <sup>a, e</sup>, Bor-Chin Sheu <sup>f</sup>,  
Ming-Shyen Yen <sup>a, e</sup>, Ting-Chang Chang <sup>g, \*\*</sup>, Peng-Hui Wang <sup>a, e, h, i, j, \*</sup>

Table 2

Summary of outcomes of women with adenomyosis and/or adenomyoma after medical treatment.

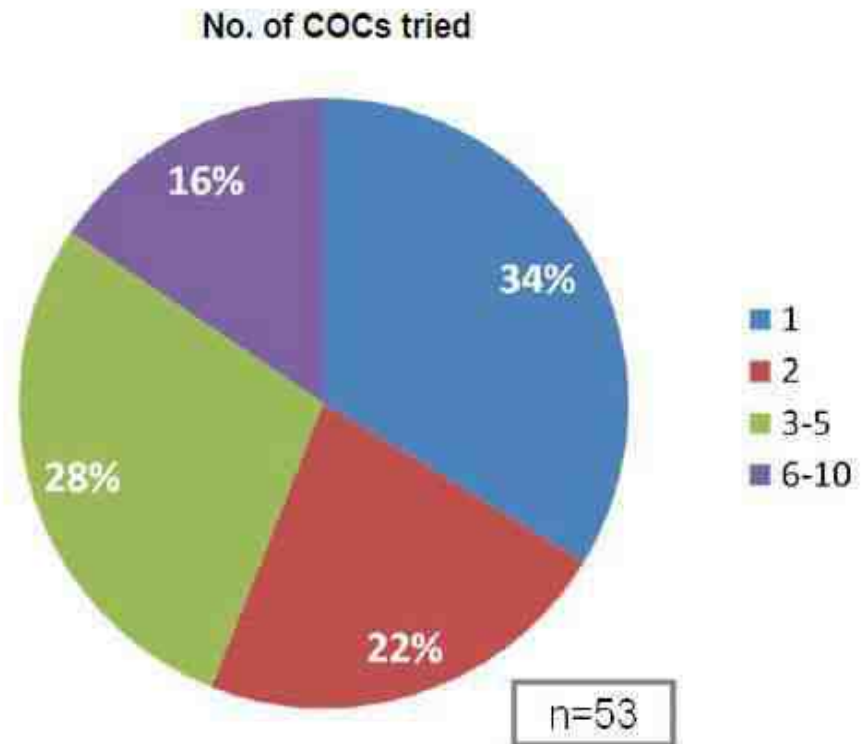
Drugs	Symptom control <sup>a</sup>	Adverse events
SERM	Unsatisfactory	Well-tolerated, hot flush, leg cramp, hypercoagulation status
SPRM	Good to excellent	Well-tolerated, headache, nausea, fatigue and dizziness
Progestins	Good to excellent	Irregular bleeding, nausea/vomiting, mood swings, hot flush, increased body weight
Gestrinone	Good	Seborrhea, hypertrichosis, and increased body weight, and the risk of metabolic syndrome, such as unfavorable effects on serum cholesterol lipoprotein distribution
AI	Unsatisfactory to fair	Frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy and mood instability, and a negative impact on bone health, also possible bad influence on cardiovascular health
OC	Good to excellent	Irregular bleeding, hypercoagulation status, nausea/vomiting, headache
Danazol	Good to excellent	Seborrhea, hypertrichosis and increased body weight, and the risk of metabolic syndrome, such as unfavorable effects on serum cholesterol lipoprotein distribution
LNG-IUS	Excellent	Irregular bleeding, abdominal pain
GnRH-a	Excellent	Frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy and mood instability, and a negative impact on bone health, also possible bad influence on cardiovascular health

AI = aromatase inhibitor; GnRH-a = gonadotropin-releasing hormone agonist; LNG-IUS = levonorgestrel-releasing intrauterine system; OC = oral contraceptives; SERM = selective estrogen receptor modulator; SPRM = selective progesterone receptor modulator.

<sup>a</sup> Symptom control: unsatisfactory (exacerbation or improvement <25%); fair (improvement 25–50%); good (improvement 50–75%); and excellent (improvement >75%).

# Current use of COCs in endometriosis\*†

- Two thirds of women with endometriosis have tried multiple COCs
- This may indicate:
  - A return of pain or,
  - A failure of pain resolution



\*COCs are not indicated for the treatment of endometriosis

Data on file†

†Data collected from 53 endometriosis patients in 2010, Canada

# Endometriozise baęlı aęrının medikal tedavisinde maliyet hesabı

Medikal Tedavi	Aylık maliyet (lira)
*Doęum kontrol hapi	30,43
*Gestagenler	
MPA 3 aylık IM	1,76
MPA 5 mg/gün po	12,27
NETA 5 mg/gün po	15,88
*GnRH analog	
Leuprolid	151,9
Goserelin	154,15
Depo triptorelin	192,58
Add-back NETA	10,18
*Danazol (600 mg/gün po)	116,77
*LNG-IUD	3,83
*NSAID	14,56
*Dienogest	90,02

# Endometrioziste ağrı tedavisine güncel yaklaşım

- **1. seçenek:**
  - Devamlı düşük doz monofazik OKS ve/veya
  - progestinler (oral)
- **2. seçenek:**
  - GnRH agonistleri + add-back
  - LNG-IUS (özellikle adenomyozis şüphesinde)
- **3.seçenek:**

Aromataz inhibitörleri,  
Düşük doz oral (100–200 mg/gün) veya intravaginal danazol
- **4.seçenek:**

Laparoskopik Cerrahi tedavi

# Endometriozis-Oral Kontraseptive

## Kanıtı Dayalı Tıp

- İnfertilite ----- yeri yok
- Pre operatif ----- yeri yok
- Ağrı-----Veri var A kalite
- Rekürrensi önlemek için ----- Veri var B kalite
- Postoperatif ----- Veri var B kalite
- IVF öncesi -----Tek çalışma
- Derin Endometriozis -----Veri var ama yeterli değil
- Ampirik -----veri var ama yeterli değil
- Ekstra-genital endometriozis ----- Veri yok
- Adenomyozis---- veri var ama yeterli değil

# Controversies in endometriosis and adenomyosis

Istanbul, Turkey  
26-28 February 2016

## European Society of Human Reproduction and Embryology



### ESHRE Campus Symposium



organised by **ESHRE**  
**Special Interest Group**  
**Endometriosis / Endometrium**  
In association with the Turkish  
Society of Endometriosis and  
Adenomyosis

### Course description

This course on endometriosis and adenomyosis provides an opportunity to discuss the most appropriate approach to its diagnosis and management. Lectures will also present current options for treatment of pain and infertility associated with endometriosis.

[Read more >](#)

### Programme



[View the programme](#)

### Venue



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Turkey

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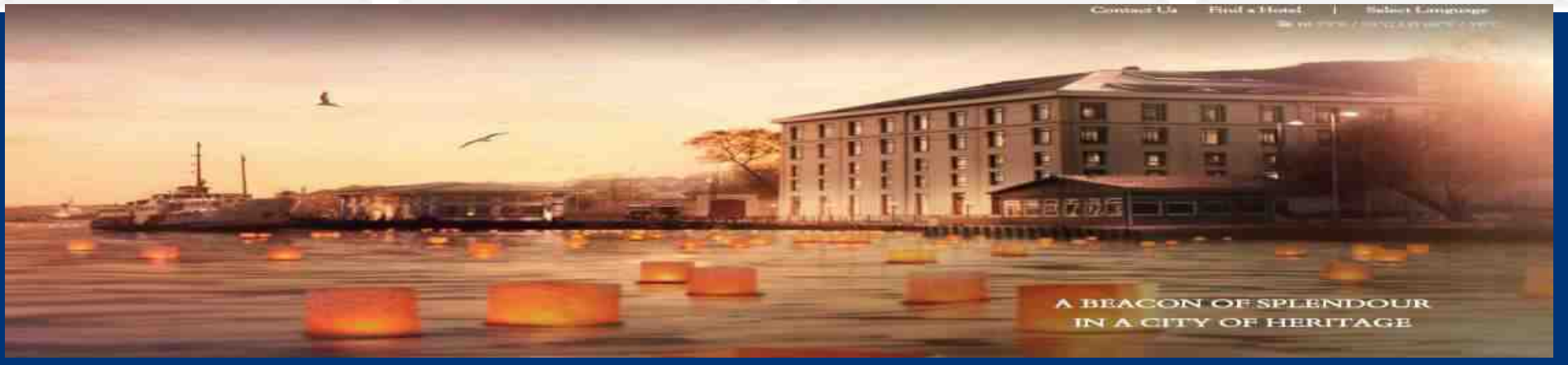


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