www.endometriozisdernegi.com

Endometriozis:Ağrı Medikal Tedavi

Dr.Engin Oral

Cerrahpaşa Tıp Fak.

Kadın Hastalıkları ve Doğum A.B.D

Reprodüktif Endokrinoloji BilimDalı

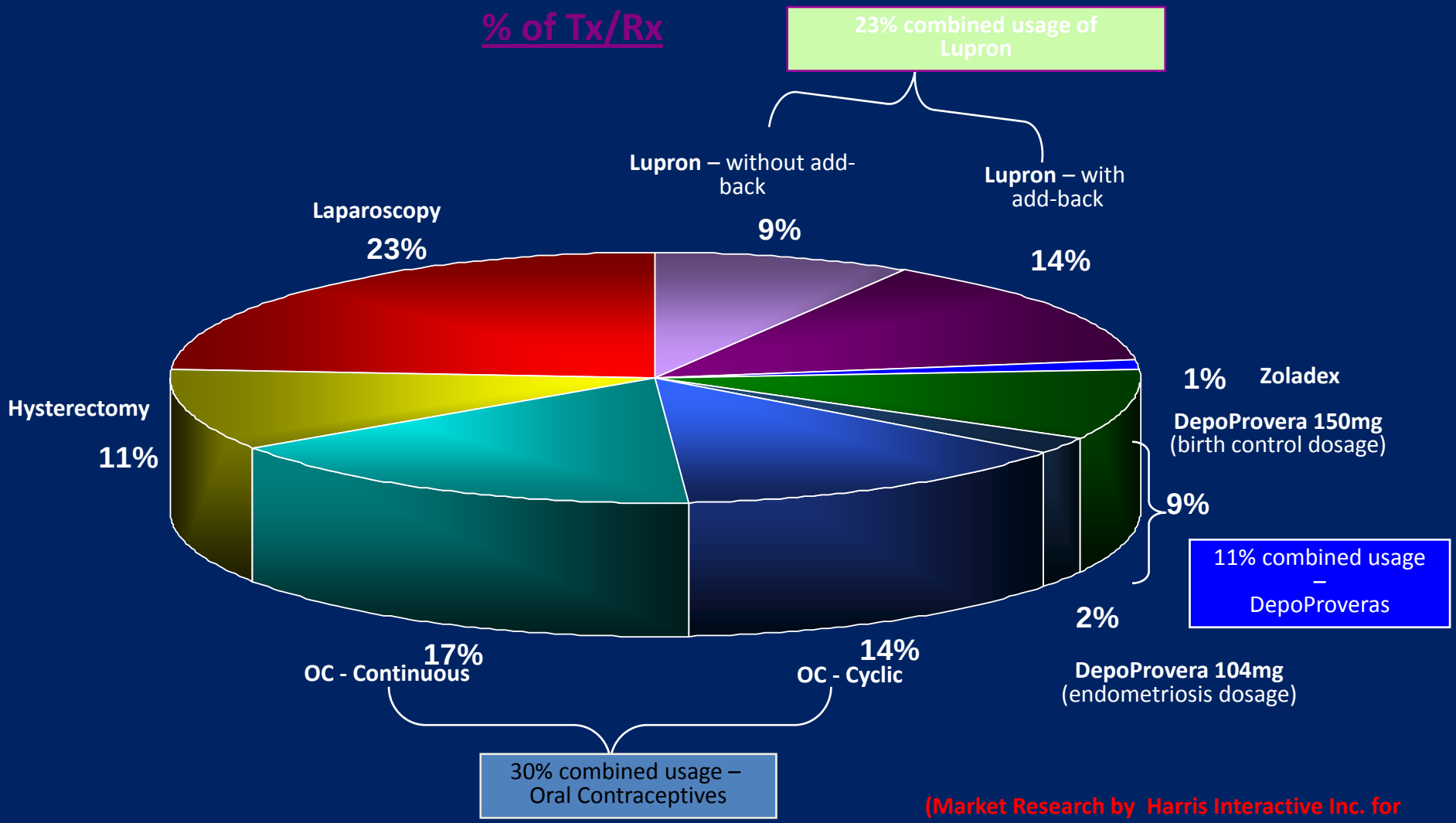
The Cost of Endometriosis

$22 billion in 2002 in the USA

DRUGS	DIAGNOSTICS	SURGERY	HEALTH CARE	OTHER
NSAIDs Progestagens c-OCP Danazol Gestrinone GnRH-a Add-back HRT Mirena coil Antibiotics Anti-depressants	Ultrasound scan Internal scan MRI Blood tests Swabs Barium enema Sigmoidoscopy Endoscopy Bone scans X-rays	Laparoscopy Laparotomy Hysteroscopy Hysterectomy Endometrial ablation Theatre costs	GP Gynaecologist Nurse Urologist Gastro-enterologist Anaesthetist Radiologist Theatre staff Haematologist Counsellor Physiotherapist Psychiatrist	ART A&E visits Hospitalisation Alternatives Transportation Child care Work absence ↓ productivity ↓ education ↓ activities

Endometriosis Overview

Endometriosis Treatment Usage in the US



(Market Research by Harris Interactive Inc. for TAP, 2006)

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]

2008

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 (	.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

Group 1 : evre 1-2 endom; group 2: evre 3-4 endom.

Table 3 Clinical endometriosis: a highly variable symptom complex[8] (endometriosis cases: $n = 529$; controls: $n = 208$)

Pain (92%); no pain (6–8%)
Extreme lethargy (97%)
Gastrointestinal symptoms (96%)
Urinary tract symptoms (44%)
Low resistance to infection (43%)
Low grade fever (42%)
Increased predisposition to autoimmune conditions
Genital tract bleeding:
– heavy menstrual bleeding (65%); premenstrual spotting (63%)

Markham R. Endometriosis symptoms in Australian women (PhD Thesis). The University of Sydney. 2002.

Soru

Derin endometriozisde dismenore-disparoni sıklığı nedir % ?

- 55-25
- 75-25
- 95-50
- 35-75
- 70-50

Deep Endometriosis: Symptoms

TABLE 1

Presenting symptoms of women in the study.

Symptoms	No. (N = 177)	%
Dysmenorrhea	166	93.8
Pelvic pain	145	81.9
Dyspareunia	85	48.0
Dyschezia	40	22.6
Menorrhagia	22	12.4
Infertility	17	9.6
Constipation	15	8.5
Bladder pain	14	7.9
Rectal bleeding	13	7.3
Other	4	2.3
Bladder bleeding	3	1.7

Pandis. Laparoscopic excision of endometriosis . Fertil Steril 2010

Pandis GK, 2010

Treatment Approach

- **'Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximising the use of medical treatment and avoiding repeated surgical procedures'**

Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2008.

Twenty-year history of endometriosis-associated pelvic pain: Too much surgery or not enough?

Table. Summary of surgical procedures

No.	*Date*	*Operation*	*Histologic diagnosis*
1	3/80	Laparotomy, left salpingo-oophorectomy	Hemorrhagic cyst
2	2/81	Laparoscopy, ablation of endometriosis along uterosacral ligaments and left broad ligament	NA
3	4/89	Laparoscopy/exploratory laparotomy, carbon dioxide laser vaporization of right endometrioma and enterolysis	Endometriosis
4	4/90	Laparoscopy with lysis of pelvic adhesions	NA
5	9/91	Laparoscopy with lysis of adhesions and carbon dioxide vaporization of endometriosis	Normal tissue
6	9/92	Laparoscopy with lysis of adhesions, right ovarian cystectomy, and cautery of right and left uterosacral ligaments	Endometriosis
7	3/93	Laparoscopy with carbon dioxide vaporization of endometriosis and lysis of adhesions	Chronic inflammation
8	12/95	Laparoscopic carbon dioxide laser vaporization of endometriosis, right salpingo-ovariolysis, and excision of ovarian adhesions	Endometriosis
9	2/97	Laparoscopy with right ovarian cystectomy, lysis of adhesions	Luteinized follicles
10	4/97	Total abdominal hysterectomy, left salpingectomy, and right salpingo-oophorectomy	Endometriosis, adenomyoma
11	11/00	Laparoscopy with lysis of adhesions, resection and ablation of endometriosis	Fibrous scar tissue

Ioannis M. Matalliotakis, 2003

End–point of medical treatment

- **Pain control**
- **Infertility**
- **Recurrence**

Blockade of hormonal pathways involved in ectopic endometrium growth and proliferation

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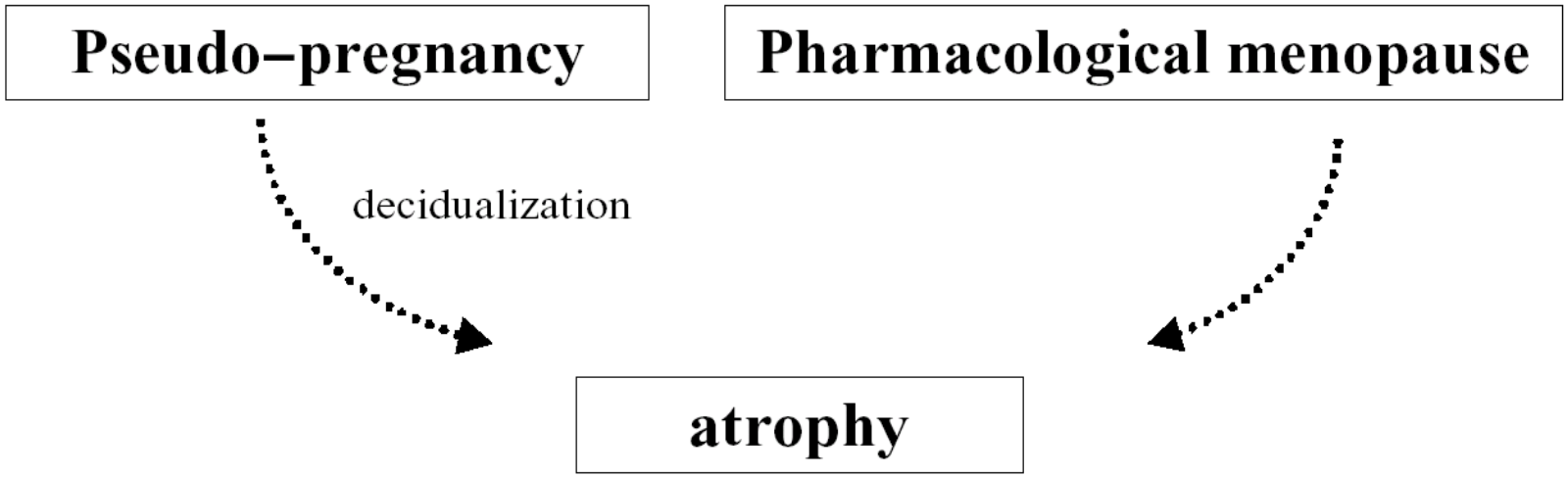
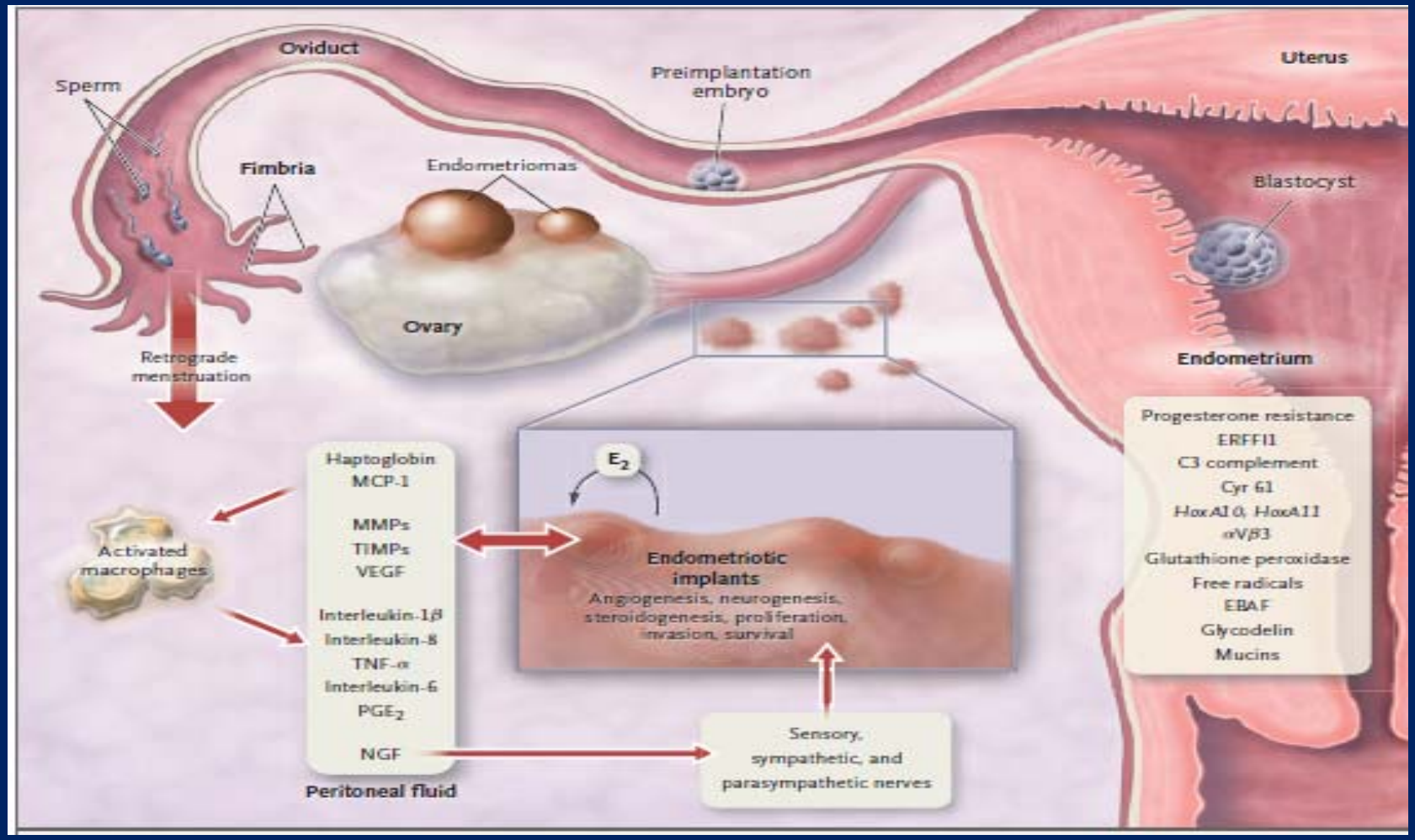


Ideal anti-endometriosis drug

1. Prevents the development of endometriosis
2. Cures existing endometriosis, also after cessation of treatment
3. No interference with menstrual cycle
4. No side effects
5. Safe for women who wish to become pregnant

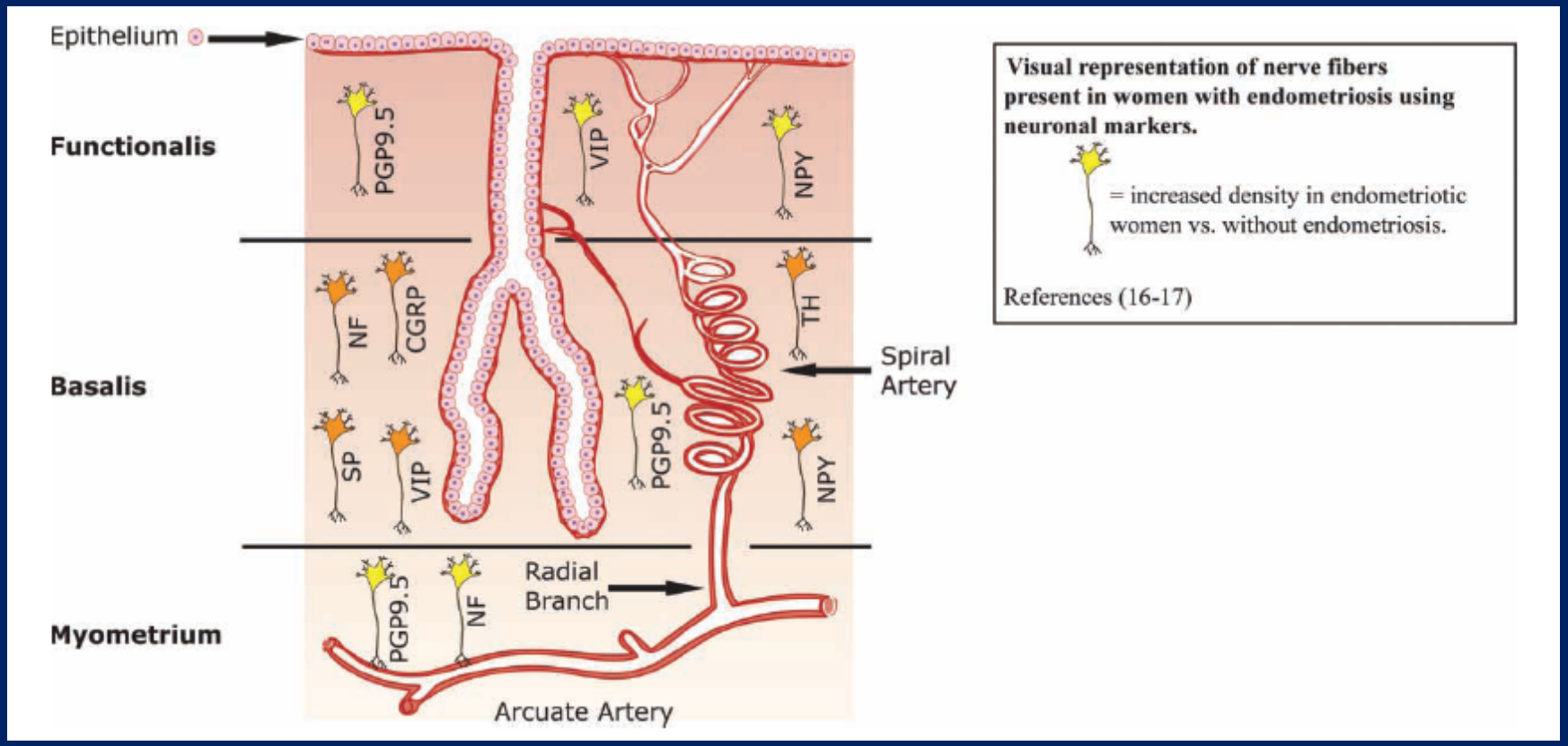
UCUZ OLMALI

Pathophysiology of Pain and Infertility Associated with Endometriosis.



Linda C. Giudice, 2010

Visual representation of nerve fibers present in the endometrium using neuronal markers.



MELISSA G. MEDINA, 2009

Effect of progestogens and combined oral contraceptives on nerve fibers in peritoneal endometriosis

- Biopsy samples from peritoneal endometriotic lesions in hormonally treated and untreated women with endometriosis. (N: 22 vs. N:40)
- The nerve fiber density (mean standard deviation/mm2) in peritoneal endometriotic lesions from hormone-treated women with endometriosis (10.6 2.2/mm2) was statistically significantly lower than in peritoneal endometriotic lesions from untreated women with endometriosis (16.3 10.0/mm2).
- Progestogens and combined oral contraceptives reduced nerve fiber density and nerve growth factor and nerve growth factor receptor p75 expression in peritoneal endometriotic lesions.

Natsuko Tokushige, 2009

Treatment	Indication	Type of Therapy	Side Effects and Complications	Comments
Medical therapy				
NSAIDs	Dysmenorrhea	First-line	Nausea, vomiting, gastrointestinal irritation, drowsiness, headache	Initiate treatment at beginning of or just before menses; somewhat decreased menstrual flow
Combined oral contraceptives				
Cyclic	Dysmenorrhea	First-line	Nausea, weight gain, fluid retention, depression, breakthrough bleeding, breast tenderness, headache, decreased menstrual flow	
Continuous	Dysmenorrhea, noncyclic chronic pelvic pain	Second-line	Nausea, weight gain, fluid retention, depression, breakthrough bleeding, breast tenderness, headache, amenorrhea	
Progestins				
Medroxyprogesterone acetate	Dysmenorrhea, noncyclic chronic pelvic pain	Second-line	Nausea, weight gain, fluid retention, breakthrough bleeding, depression, amenorrhea, delayed return of ovulation	
Levonorgestrel intrauterine system	Dysmenorrhea, dyspareunia	Second- or third-line	Bloating, weight gain, headache, breast tenderness	Especially beneficial for symptomatic rectovaginal endometriosis; hypomenorrhea or amenorrhea for 6–12 mo; can be used for up to 5 yr; not FDA-approved for endometriosis
GnRH agonists	Dysmenorrhea, dyspareunia	Second- or third-line	Hypoestrogenism (vasomotor symptoms, vaginal dryness, decreased libido, irritability, loss of bone mineral density)	FDA-approved for endometriosis pain; estrogen–progestin add-back therapy used to mitigate loss of bone mineral density
Aromatase inhibitors	Dysmenorrhea, noncyclic chronic pelvic pain	Third-line	Hypoestrogenism, induction of ovulation	Combined with progestagens, combined oral contraceptives, and GnRH agonists because ovulation may be induced; not FDA-approved for endometriosis pain
Danazol	Dysmenorrhea, noncyclic chronic pelvic pain	Second- or third-line	Hyperandrogenic side effects (acne, edema, decreased breast size)	Side effects limit widespread use

Linda C. Giudice, 2010

TABLE 2

Medical therapy for endometriosis.

Author	Agents	N	Rx time	F/u time	Results
Oral contraceptives					
Vercellini et al. (69)	1. OCs 2. GnRHa	57	6 mos.	1 yr.	Equal impact on dysmenorrhea, dyspareunia, and daily pain
progestogens					
Telimaa et al. (80)	1. danazol, 600 mg qd 2. MPA 100 mg po qd 3. placebo	59	6 mos.	1 yr.	Both relieved pain equally
Telimaa et al. (77)	1. danazol 600 mg qd 2. MPA, 100 mg. po qd 3. placebo	60	6 mos.	1 yr.	(Following surgery) both relieved pain equally
Overton et al. (78)	1. dydrogesterone, 40 mg. qd, luteal 2. dydrogesterone 60 mg. qd, luteal 3. placebo	62	6 mos.	1 yr.	60 mg dose marginally better than placebo (90% vs. 75%) at 1 yr.
Vercellini et al. (79)	1. OCs & danazol 50 mg qd 2. MPA 150 mg IM q 3 mos.	80	1 yr.	1 yr.	MPA better at 1 yr.
progestogen IUD					
Fedele et al. (55)	1. Lng- IUD	11	12 mos.		Improved pain and decrease in size of rectovaginal lesion
Vercellini et al. (54)	1. Lng- IUD 2. expectant	40	12 mos.		Lng-IUD better at 1 yr.
Lockhat et al. (56)	1. levonorgestrel IUD	29	6 mos.		Improved pain with Lng-IUD at 6 mos.
Antiprogestogens					
Fedele et al. (81)	1. gestrinone, 2.5 mg 2–3/wk. 2. danazol 600–800 mg qd	39	6 mos.	1 yr.	Both relieved pain equally
Hornstein et al. (83)	1. gestrinone, 2.5 mg. 2×/wk 2. gestrinone, 1.25 mg. 2×/wk	12	6 mos.	6 mos.	Both relieved pain equally
Bromham et al. (82)	1. gestrinone, 2.5 mg, 2/wk 2. danazol, 400 mg qd	269	6 mos.	6 mos.	Both relieved pain equally
GISG (72)	1. gestrinone, 2.5 mg 2/wk 2. leuprorelin, 3.75 mg q mo.	55	6 mos.	6 mos.	Gestrinone relieved pain better
GnRH Agonists					
Wheeler et al. (84)	1. leuprolide acetate 3.75 mg q mo 2. danazol 800 mg daily	270	6 mos.		Both relieved pain, decreased disease equally
Rock et al. (85)	1. goserelin acetate, 3.6 mg q mo 2. danazol 800 mg daily	315	6 mos.		Both relieved pain, decreased ASRM score and lesion size equally

ASRM Practice Committee. Treatment of pelvic pain and endometriosis. Fertil Steril 2008.

TABLE 2

Continued.

Author	Agents	N	Rx time	F/u time	Results
Hornstein et al. (63)	Leuprolide acetate 3.75 mg q mo with: 1. placebo 2. norethindrone acetate 5 mg daily 3. norethindrone acetate 5 mg + conjugated equine estrogens 0.625 mg daily 4. norethindrone acetate 5 mg + conjugated equine estrogens 1.25 mg daily	201	12 mos.		Leuprolide acetate + norethindrone or norethindrone + conjugated equine estrogen 0.625 mg suppresses pain equally while protecting against bone loss.
Parazzini et al. (86)	1. ethinyl estradiol 0.03 mg + gestroden 0.75 mg daily 2. tryptorelin 3.75 mg q mo for 4 months, then ethinyl estradiol 0.03 mg + gestroden 0.75 mg daily for 8 mo	112	12 mos.		Both relieved pelvic pain equally at 12 mos.

Note: F/u = follow-up; N = Number.

ASRM Practice Committee. Treatment of pelvic pain and endometriosis. Fertil Steril 2008.

Soru
Dismenorede NSAI icin hangisi doğrudur ?

- Plasebodan daha etkili değildir
- Parasetamol ile eşit ekinliğe sahiptir
- Farklı tiplerinde etkinlik aynıdir
- Yan etkileri plasebo ile aynıdır
- Tedavi de ilk seçilecek grupdur

NSAIDs

Marjoribanks et al 2010

- **COX-1 NSAIDs**
  - **Aceclofenac 100 mg/day**
  - **Aspirin 650 mg 4 hourly**
  - **Dexketoprofen 12.5-25 mg 6 hourly**
  - **Diclofenac upto 200 mg daily in divided doses**
  - **Etodolac 200-300 mg twice daily**
  - **Fenoprofen 100-200 mg 4 hourly**
  - **Fentiazac 100 twice daily**
  - **Ibuprofen 400 mg 3, 4 or 6 times daily**
  - **Indomethacin 25 mg tablets or 100 mg supp 3 times**
  - **Ketoprofen 25-50 mg 6 hourly**
  - **Lysine Clonixinate 125 mg six hourly**
  - **Meclofenamate sodium 100 mg eight hourly**
  - **Mefenamic acid 250 mg eight hourly**
  - **Naproxen/Naproxen sodium 250-275 mg four to eight hourly**
  - **Niflumic acid 250 mg three times daily**
  - **Nimesulide 50-100 mg twice daily**
  - **Piroxicam 20-40 mg daily**
  - **Tolfenamic acid 200 mg eight hourly**
- **COX-2 NSAIDs**
  - **Etoricoxib 120 daily**
  - **Meloxicam 7.5-15 mg daily**

NSAIDs

Marjoribanks et al 2010

- Pooled data:NSAIDs vs placebo
  - NSAIDs more effective in pain relief
  - NSAIDs cause more side effects (GI and neurological)
  - NSAIDs group less likely to require additional medication
  - NSAIDs group less interference with daily activities
  - NSAIDs group less absenteeism

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NSAIDs

Marjoribanks et al 2010

- NSAIDs vs NSAIDs
  - Diclofenac more effective than Meloxicam
  - Fenoprofen more effective than Aspirin
  - Naproxen more effective than Ketoprofen and Ibuprofen
  - Indomethacin more effective than Aspirin
  - No differences
    - Ibuprofen vs Nimesulide/Prixicam/ Lysine clonixinate
    - Mefenamic acid vs Meloxicam/Tolfenamic acid
    - Naproxen vs Diclofenac/Etoricoxib/Piroxicam/Flurbiprofen
  - No differences in side effect profiles/secondary outcome measures

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NSAIDs

Marjoribanks et al 2010

- NSAIDs vs Paracetamol
  - NSAIDs more effective than Paracetamol
  - No difference in side effect profile
  - No data on secondary outcome measures

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Human Reproduction Vol.20, No.10 pp. 2698–2704, 2005
doi:10.1093/humrep/dei135
Advance Access publication June 24, 2005.

ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy[1,10], Agneta Bergqvist[2], Charles Chapron[3], Thomas D'Hooghe[4], Gerard Dunselman[5], Robert Greb[6], Lone Hummelshoj[7], Andrew Prentice[8] and Ertan Saridogan[9] on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

PAIN – hormonal Tx

A	Suppression of ovarian function for 6 months reduces endometriosis-associated pain. The hormonal drugs investigated - COCs, Danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Moore et al, 2004; Prentice et al, 2004a; Prentice et al, 2004b; Selak et al, 2004; Farquar et al, 2004).	Evidence Level 1a

There are pilot data suggesting that the aromatase inhibitor, letrozole, may be effective, though there are concerns about bone density loss (Ailawadi et al, 2004).

Soru
Hangisinin FDA onayı yoktur ?

- NETA
- OK
- Depo-Provera
- GnRHa
- Danazol

FDA-onay

- NETA
- Depo-Provera
- GnRHa
- Danazol

Revised guidelines, 2007

Non-steroidal anti-inflammatory drugs

A	There is inconclusive evidence to show whether NSAIDs (specifically naproxen) are effective in managing pain caused by endometriosis (Allen et al., 2005).	Evidence Level 1a

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

NSAIDs for pain in women with endometriosis

Allen et al 2009

- Conclusion
  - Inconclusive evidence that NSAIDs are effective for pain in women with endometriosis
  - No evidence to suggest any NSAIDs more effective than others

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Revised guidelines, 2007

Hormonal treatment

A	Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone,medroxyprogesterone, acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Davis et al., 2007 ; Prentice et al., 1999; Prentice et al., 2000; Selak et al., 2007).	Evidence Level 1a

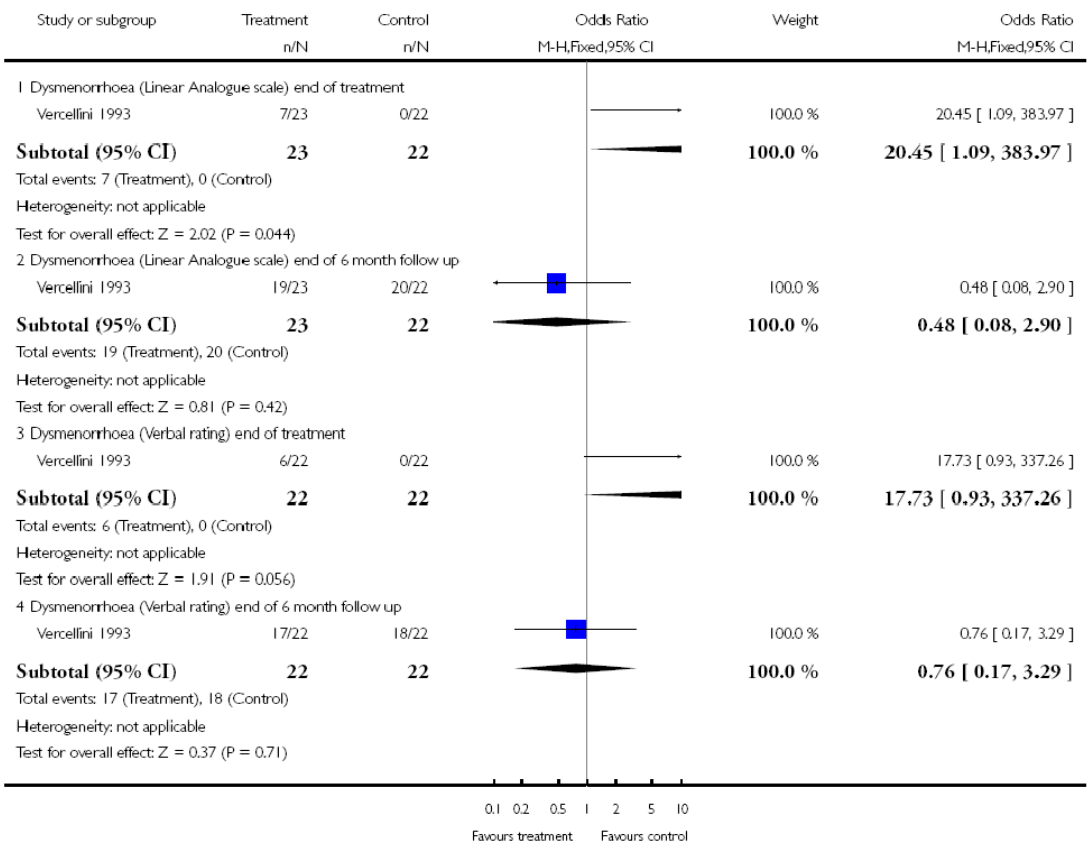
Oral contraceptives for pain associated with endometriosis Davis et al 2009

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

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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

Study or subgroup	OCP n/N	Goserelin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Non menstrual pain (Linear Analogue scale) end of treatment					
Vercellini 1993	3/10	3/13		100.0 %	1.43 [0.22, 9.26]
Subtotal (95% CI)	**10**	**13**		**100.0 %**	**1.43 [0.22, 9.26]**
Total events: 3 (OCP), 3 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
2 Non menstrual pain (Linear Analogue scale) end of six month follow up					
Vercellini 1993	4/10	7/13		100.0 %	0.57 [0.11, 3.04]
Subtotal (95% CI)	**10**	**13**		**100.0 %**	**0.57 [0.11, 3.04]**
Total events: 4 (OCP), 7 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
3 Non menstrual pain (verbal rating) end of treatment					
Vercellini 1993	2/10	2/12		100.0 %	1.25 [0.14, 10.94]
Subtotal (95% CI)	**10**	**12**		**100.0 %**	**1.25 [0.14, 10.94]**
Total events: 2 (OCP), 2 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
4 Non menstrual pain (verbal rating) end of six month follow up					
Vercellini 1993	8/10	7/12		100.0 %	2.86 [0.42, 19.65]
Subtotal (95% CI)	**10**	**12**		**100.0 %**	**2.86 [0.42, 19.65]**
Total events: 8 (OCP), 7 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.29)					

Non-menstrual pain

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Oral contraceptives for pain associated with endometriosis Davis et al 2009

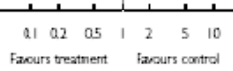
Analysis 1.3. Comparison 1 OCP versus goserelin; reduction of pain to mild or zero, Outcome 3 Dyspareunia.

Review: Oral contraceptives for pain associated with endometriosis

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

Outcome: 3 Dyspareunia

Study or subgroup	OCP n/N	Goserelin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Dyspareunia (Linear Analogue scale) end of treatment:					
Vercellini 1993	7/12	2/17		100.0 %	13.50 [1.62, 68.07]
Subtotal (95% CI)	**12**	**17**		**100.0 %**	**10.50 [1.62, 68.07]**
Total events: 7 (OCP), 2 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.47 (P = 0.014)					
2 Dyspareunia (Linear Analogue scale) end of six month follow up					
Vercellini 1993	9/12	10/17		100.0 %	2.10 [0.41, 10.66]
Subtotal (95% CI)	**12**	**17**		**100.0 %**	**2.10 [0.41, 10.66]**
Total events: 9 (OCP), 10 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.37)					
3 Dyspareunia (verbal rating) end of treatment					
Vercellini 1993	8/12	9/13		100.0 %	0.89 [0.17, 4.78]
Subtotal (95% CI)	**12**	**13**		**100.0 %**	**0.89 [0.17, 4.78]**
Total events: 8 (OCP), 9 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
4 Dyspareunia (verbal rating) end of six month follow up					
Vercellini 1993	10/12	10/13		100.0 %	1.50 [0.20, 11.00]
Subtotal (95% CI)	**12**	**13**		**100.0 %**	**1.50 [0.20, 11.00]**
Total events: 10 (OCP), 10 (Goserelin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					



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Dyspareunia

Oral contraceptives for pain associated with endometriosis
Davis et al 2009

- Conclusions
  - No significant differences in non-menstrual pain
  - Symptoms recurred in all patients six months after treatment
  - No difference in dyspareunia rates during or after treatment

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Postoperatif Dönemde Siklik veya Sürekli OKS kullanımı

- Prospektif randomize 24 aylık çalışma
- Siklik veya sürekli düşük dozlu monofazik OKS kullanımına karşın bekleme tedavisi
- Dismenore: Altıncı aylarda diğer gruplara göre sürekli OKS kullananlarda, 18 ay ilaç kullanmayanlara göre, siklik OKS kullananlarda nüks oranları ve VAS ölçeğinde anlamlı azalma
- Disparöni, kronik pelvis ağrısı: Gruplar arasında farklılıklar yoktu

Seraccholi ve ark., Fertil Steril 2010; 94: 464-71

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

- Conclusions – Progestagens
  - There is a paucity of data
  - Progestagens are effective for pain symptom associated with endometriosis
  - Progestagens are no more or less effective than other medical treatment options
  - Results should be interpreted with caution

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Dienogest: Overview of Pharmacodynamic Profile

Dienogest is a 19-nortestosterone derivative

- High specificity for progesterone receptor[1]
- Anti-androgenic properties
- No estrogenic, androgenic, mineralocorticoid or glucocorticoid activity[2,3]
- No affinity for sex hormone binding globulin/other hepatic binding globulins
  - no displacement of testosterone[3]
- Strong progestational effect on endometrium
- Relatively short plasma half-life of approximately 9–10 hours

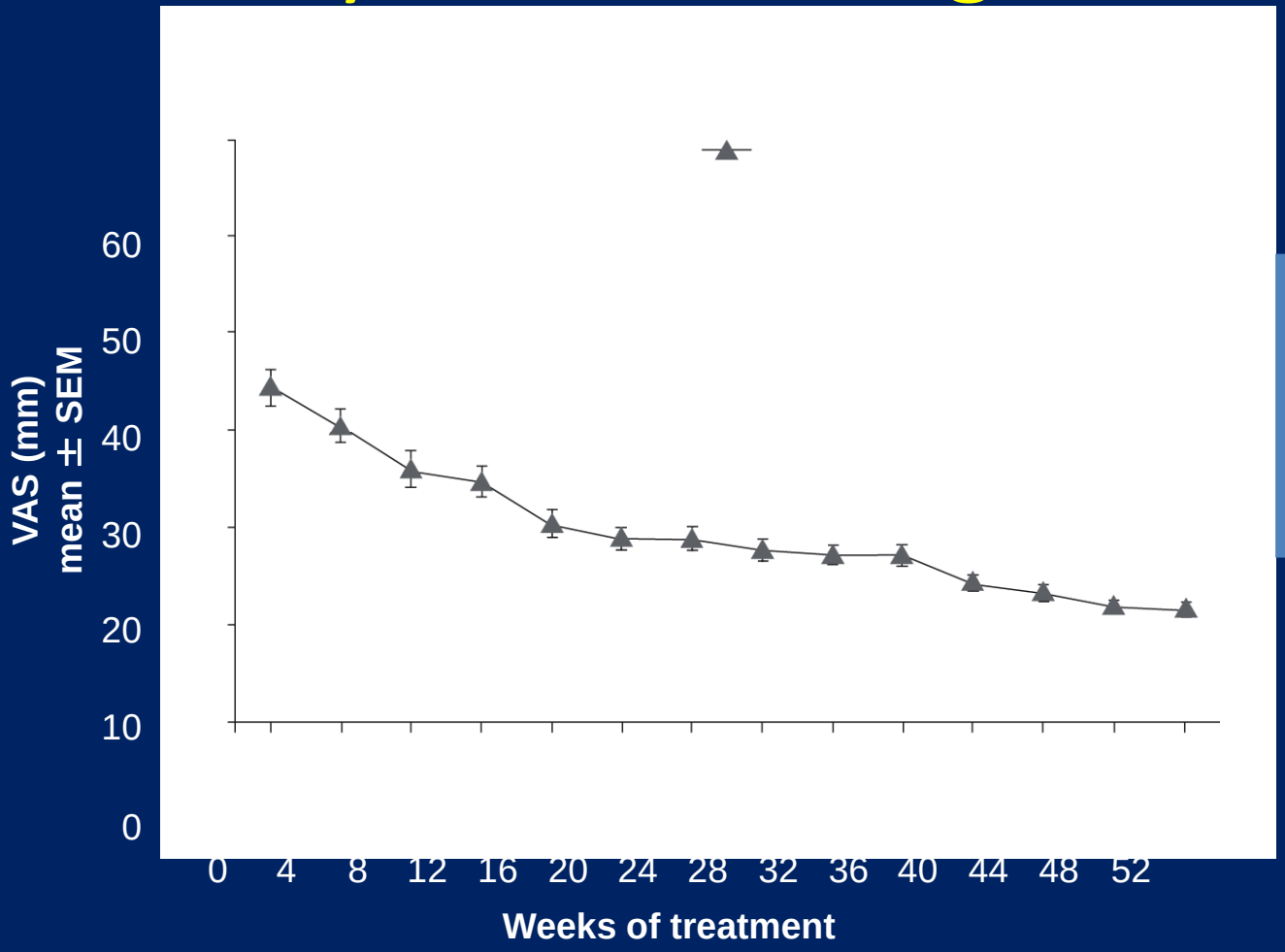
1. Sasagawa S *et al.* Steroids 2008;
2. Oettel M *et al.* Eur J Contracept Reprod Health Care 1999;
3. Krattenmacher R. Contraception 2000.

Key Studies

	Main efficacy end-points	Comparator/ Blinding	Treatment	Publication
Dose-range study	Lesion reduction: rAFS score	None/open	1, 2, 4 mg/day 24 weeks	Köhler *et al.* (2010)
Dienogest versus placebo	Pain relief: VAS	Placebo/ double-blind	2 mg/day 12 weeks	Strowitzki *et al.* (2010)
Dienogest versus leuprolide acetate	Pain relief: VAS	Leuprolide acetate/open	2 mg/day 24 weeks	Strowitzki *et al.* (2010)
Long-term extension study	Pain relief: VAS	None/open	2 mg/day 12 months + 6 month treatment-free follow up	Seitz *et al.* (2009)

Long-term Extension Study

Efficacy: Visual Analogue Scale Score



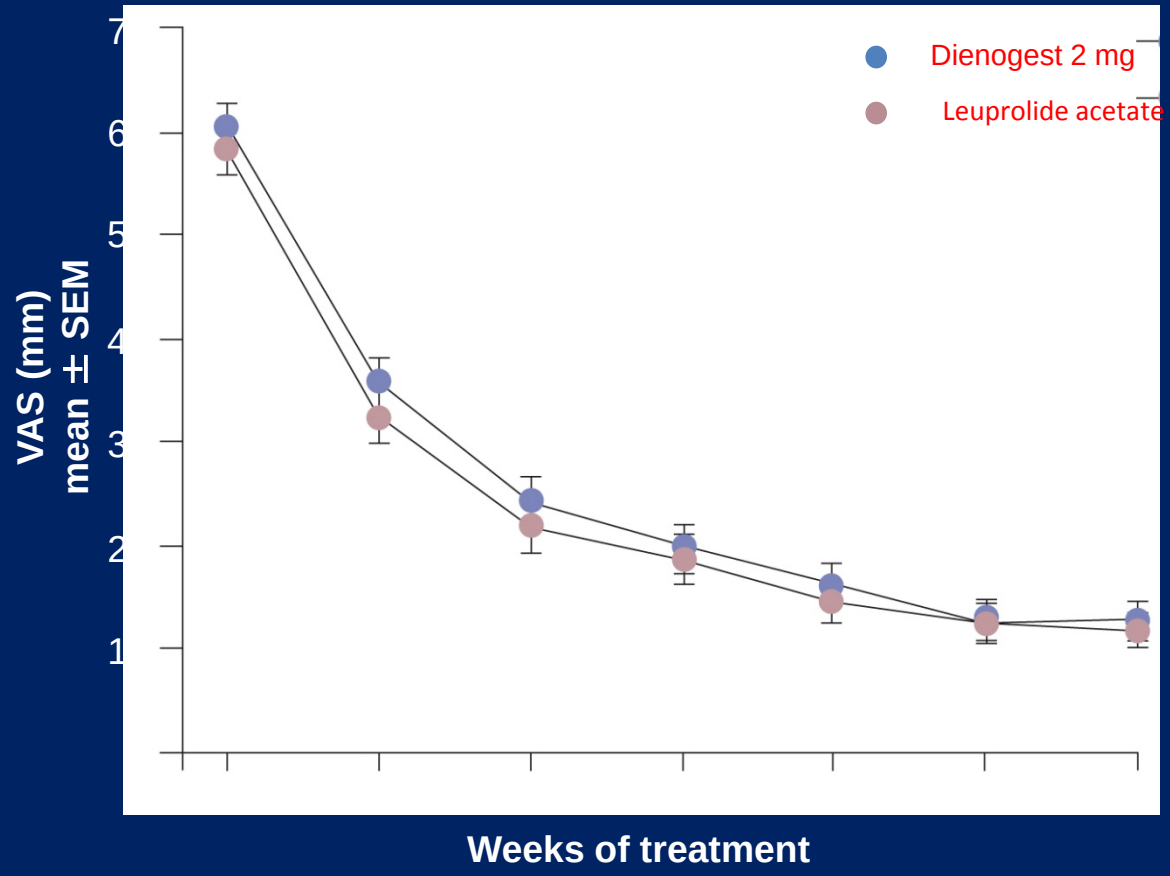
Mean VAS scores decreased progressively over the extended treatment period

EAPP, endometriosis-associated pelvic pain.

Seitz C et al. Fertil Steril 2009.

Dienogest 2 mg versus Leuprolide Acetate

Efficacy: Reduction of Pain



VAS, visual analogue scale.

Dienogest 2 mg showed similar efficacy to LA 3.75 mg IM

Non-inferior versus leuprolide acetate ($P<0.0001$)

Strowitzki T et al. Hum Reprod 2010.

Danazol for pain associated with endometriosis Selak et al 2010

- Bianchi et al 1999
  - 77 postsurgery women, Danazol 600 mg vs placebo, 3 months, AFS III-IV
- Kauppila et al 1988
  - 87 postsurgery women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months, AFS I-II
- Telimaa et al 1987a
  - 59 women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months, AFS I-II
- Telimaa et al 1987b
  - 60 women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months
- Telimaa et al 1990
  - 87 women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months, AFS I-II

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Danazol for pain associated with endometriosis Selak et al 2010

- Conclusions
  - Danazol is effective for symptoms and signs of endometriosis
  - Significant unpleasant side effects

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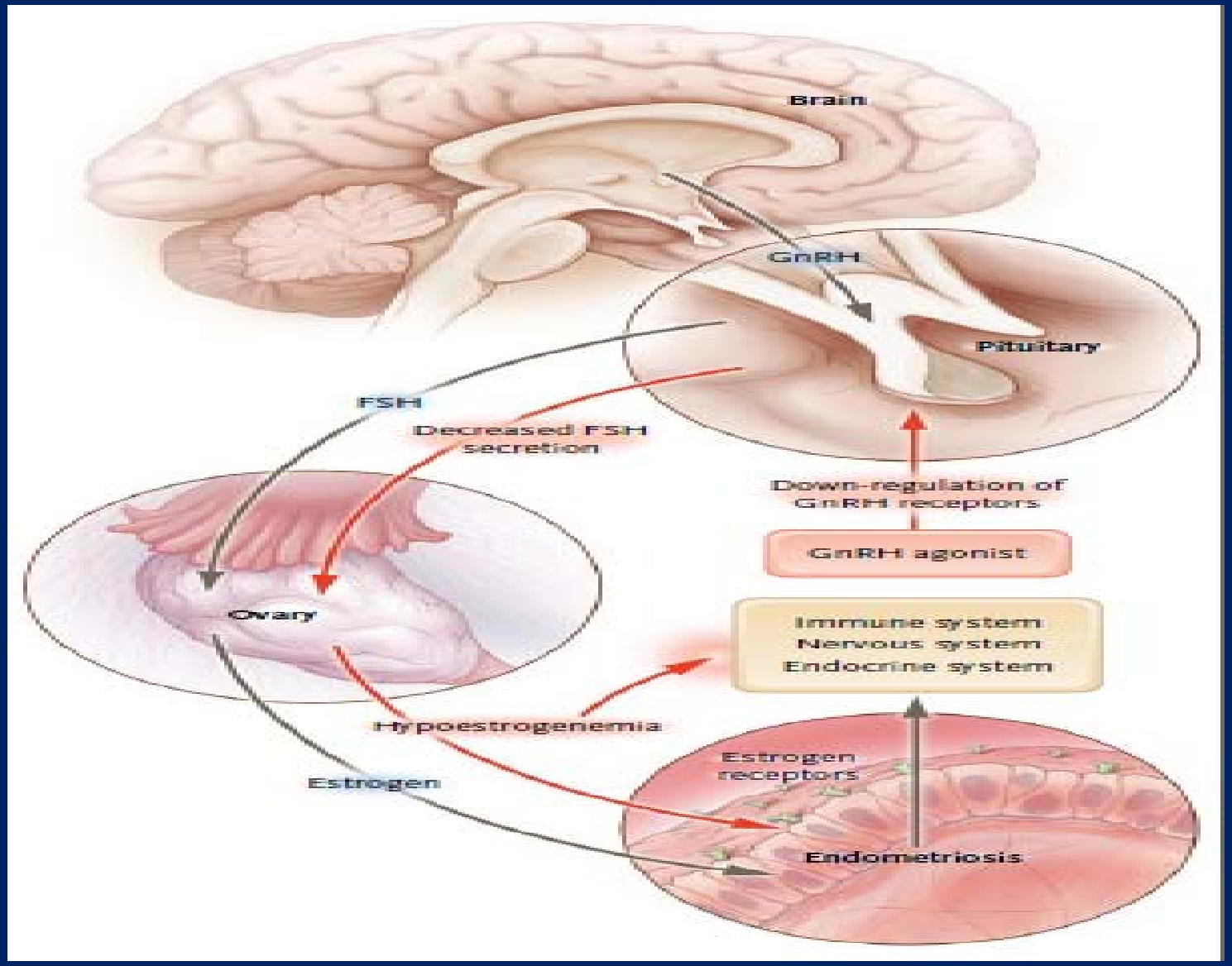
Danazol – side effects

- Due to hyperandrogenism and hypo-oestrogenemia
- Weight gain
- Fluid retention
- Fatigue
- Nausea
- Acne
- Hirsutism
- Oily skin
- Muscle cramps
- Reduced libido
- Reduced breast size
- Emotional disturbances
- Atrophic vaginitis
- Hot flushes
- Hepatocellular damage
- Irreversible deepening of voice

Endometriozis-GnRHa

- İnfertilite
- Pre operatif
- Ağrı
- Rekürrensi önlemek icin
- Postoperatif
- IVF öncesi
- Ampirik

. Effect of Gonadotropin-Releasing Hormone (GnRH) Agonists on Endometriosis



Endometriozis-MCP-1düzeyleri-Tedavi

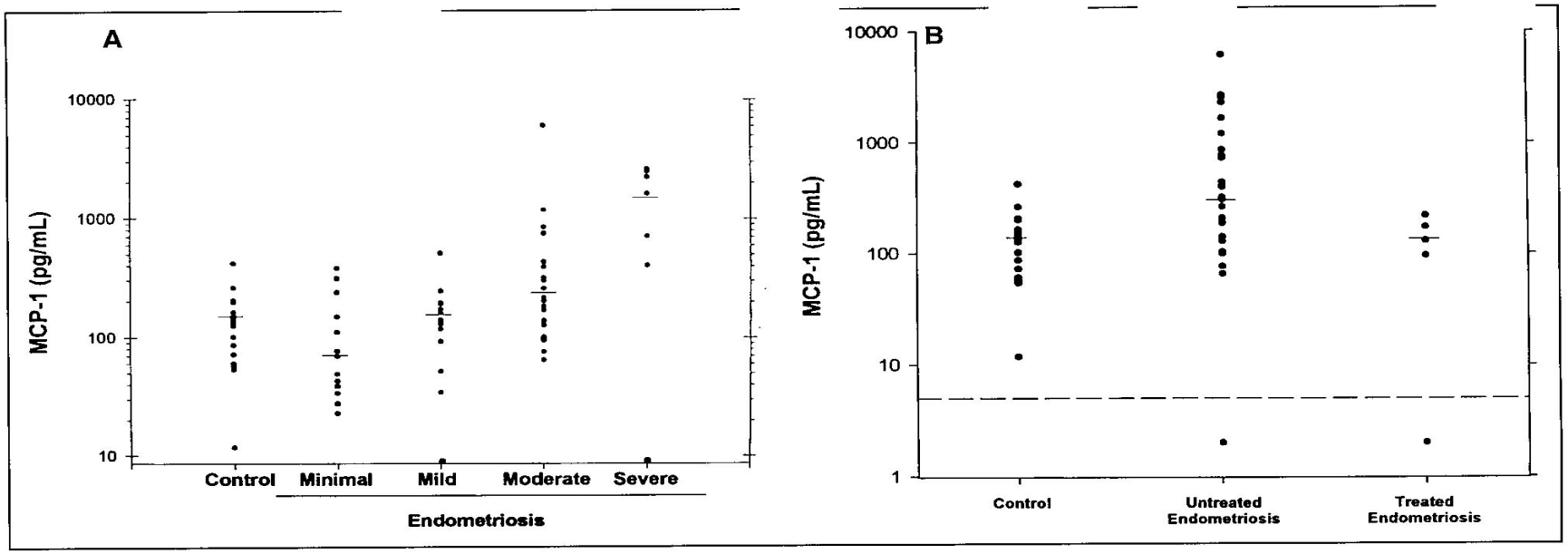


Figure 1 (**A**) Immunoreactive MCP-1 levels according to endometriosis stage: control (tubal ligation) (n = 18), minimal (n = 13), mild (n = 15), moderate (n = 24), and severe (n = 8) endometriosis. **Horizontal lines** represent medians. $P < 0.001$ overall; $P = 0.01$ for control versus moderate groups; $P = 0.03$ for control versus severe groups. (**B**) Concentration of MCP-1 in peritoneal fluid from women without endometriosis (n = 18), with untreated moderate or severe endometriosis (n = 26), and with medically (GnRH agonist) treated moderate or severe endometriosis (n = 5). *Horizontal lines* represent medians. *Dashed line* represents the lowest detection limit of the ELISA. $P = 0.03$ for treated versus untreated or control groups. MCP-1, monocyte chemotactic protein-1.

Arıcı A, Oral E, et al. Fertil Steril 1997

PAIN – duration of GnRH-a Tx

A	Treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief (Hornstein *et al.*, 1995).	Evidence Level 1b
A	Treatment for up to 2 years with combined estrogen progestagen 'add-back' appears to be effective and safe in terms of pain relief and bone density protection (Surrey and Hornstein, 2002). However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.	Evidence Level 1a

ESHRE 2005

Post-operative treatment

A	Treatment with danazol or a GnRH agonist for 6 months after surgery reduces endometriosis-associated pain and delays recurrence at 12 and 24 months compared with placebo and expectant management. However, post-operative treatment with a COC is not effective (Telimaa *et al.*, 1987; Parazzini *et al.*, 1994; Hornstein *et al.*, 1997; Bianchi *et al.*, 1999; Morgante *et al.*, 1999; Vercellini *et al.*, 1999b; Muzii *et al.*, 2000; Busacca *et al.*, 2001).	Evidence level 1b

Table 1. Adverse Effects of Treatment with Gonadotropin-Releasing Hormone Agonists.*

Common (in >60% of patients): hot flashes

Less common (in 20–60% of patients): headache, insomnia, memory disorder, substantial temporary loss of bone mineral density (if used for ≤6 mo)

Infrequent (2–19% of patients): substantial and persistent loss of bone mineral density, anxiety, dizziness, asthenia, depression, vaginal dryness, dyspareunia, weight change, arthralgias, myalgias, alopecia, peripheral edema, breast tenderness, irritability and fatigue, decreased skin elasticity, decreased libido, nausea, altered bowel function, irregular vaginal bleeding

Rare (<2% of patients): vaginal hemorrhage, allergic reaction

GnRHa: bone mineral density
Sagsveen et al 2009

- 30 trials, 2391 women included
- 15 trials, 910 women analysed

Nature of Comparison	n
With Danazol or Gestrinone	9
With GnRHa and progesterone only addback	4
With GnRHa and E+P addback	11
With GnRHa and high dose E+P addback	3
With GnRHa and calcium regulating agents	3
Three monthly with one monthly	1
With Placebo	1

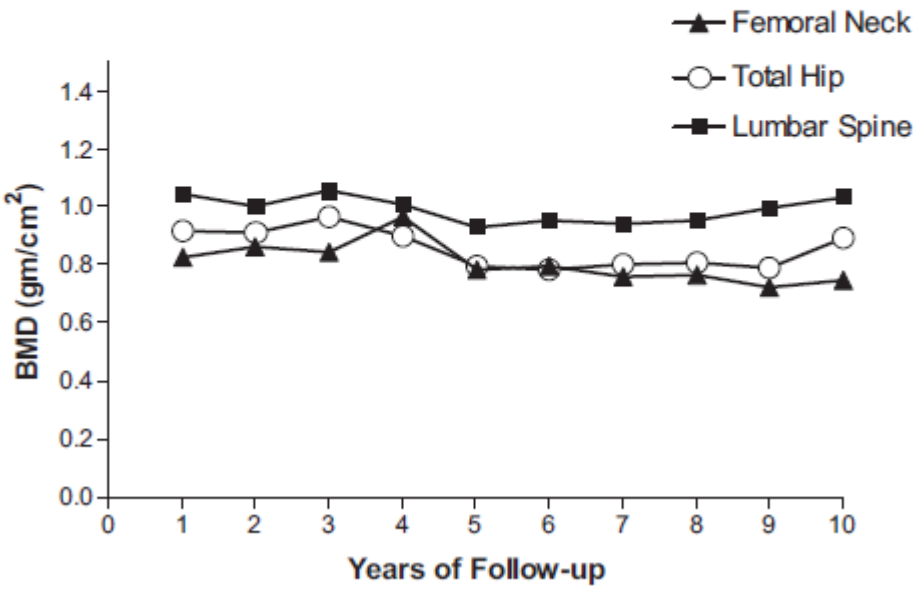
GnRHa: bone mineral density Sagsveen et al 2009

- Conclusions
  - Danazol/Gestrinone and E+P are effective against bone loss with GnRHa
  - Progesterone only addback is not protective against bone loss
  - Results do not allow conclusion on the effect of Calcium regulators

Treatment with leuprolide acetate and hormonal add-back for up to 10 years in stage IV endometriosis patients with chronic pelvic pain

FIGURE 1

Average BMD in the lumbar spine, femoral neck, and total hip measured by DEXA.



Mohamed A. Bedaiwy, 2006

Endometriosis Overview

Chronic Pelvic Pain Flow Chart (in the U.S.A.)

History, physical examination, labs, imaging

abnormal → Specific therapy

↓ Normal

Empiric NSAIDs, OCPs

response → Continue therapy

↓ No response

Empiric GnRH agonist + add back

response → Continue therapy to a maximum of 12 months

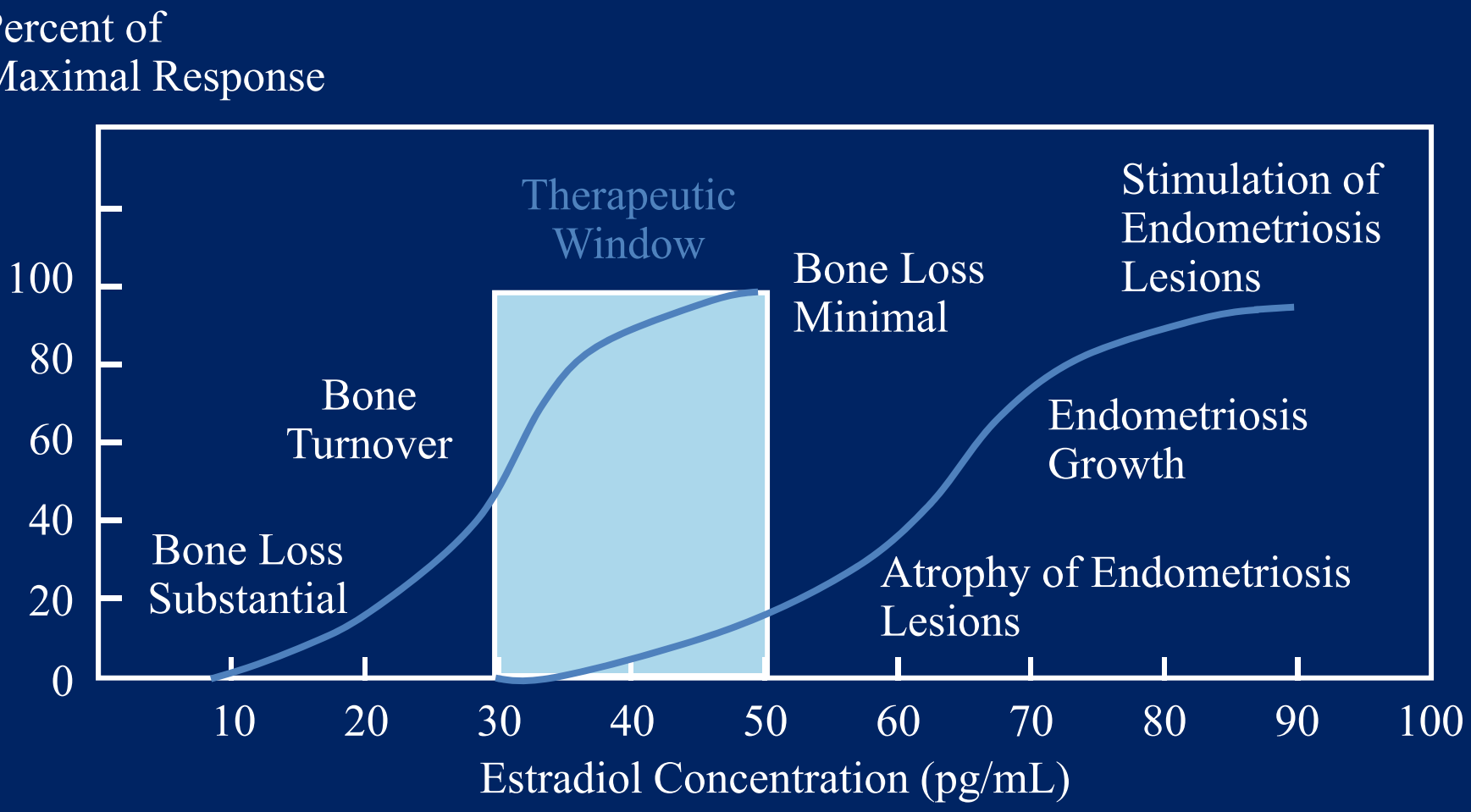
↓ No response

Laparoscopy, consultation, pain clinic

Source: Gambone et al. 2002. Fertil Steril 78:961,

Endometriosis Overview

The Estrogen Threshold Hypothesis



Barbieri (1992)

Pain-FDA approved labeling

- A second 6 mo course of GnRHa + progestin is appropriate for symptom recurrence after an initial treatment course (No interval between courses needed)
- Retreatment beyond 6 mo or with GnrHa alone cannot be recommended
- Normal bone density should be confirmed prior to treatment

Soru

Add-Back icin hangisi uygun değildir ?

NETA

Tibolone

E2+P

CEE + P

EE + P

Add-Back Therapy

- Estrogens ± Progestins (Do not use OCP)
- Progestins
- Progestins ± Bisphosphonate
- Tibolone
- GnRHa ≤ 3 mo
  - No need for Add-back
- GnRHa ≤ 6 mo
  - Add-back (Optional), Ca
- GnRHa > 6 mo or retreatment
  - Mandatory Add-back, Ca, BMD, Lipids ?

Gonadotropin-releasing hormone agonist and add-back therapy: what do the data show?

Table 1 GnRH agonist and add-back therapy: investigated regimens

Add-back	6 months	12 months
Medroxyprogesterone acetate (MPA)	+	–
Norethindrone acetate (NEt)	+	+
NEt + sodium etidronate	+	+
Medrogestrone	+	–
Ethinyl estradiol + desogestrel	+	–
17 β Estradiol + NEt	+	+
17 β Estradiol + MPA	+	–
Conjugated equine estrogens (CEE) + NEt	+	+
CEE + MPA	+	–
Promegestrone ± 17 β estradiol	+	+
Tibolone	+	+

Regardless of the regimen employed, it has been consistently demonstrated that effective add-back therapy should be initiated concomitantly with the GnRHa to minimize side effects.

However, for the woman who requires retreatment with a GnRHa or whose therapy is anticipated to extend beyond 6 months, add-back should be considered mandatory

Eric S. Surrey, 2010

GnRH Antagonistleri

- Klasik kompet. Inhibisyon var
- Düşük estrojenik ortam oluşturur
- Klasik GnRH agonistlerinde görülen

  -Flare-up etkisi yok

  -Desensitizasyon yok

– Batzer et al(2006): “Endometriozis odaklarında regresyon, ağrı hissinde azalma”

– Küpker et al(2002): “L/S ile tanı konmuş 15 olguda Cetrorelix 3mg/hf ,

8 hf sonunda %60 olgunun AFS skorlarında iyileşme”

(non-randomize,olgu sayısı az)

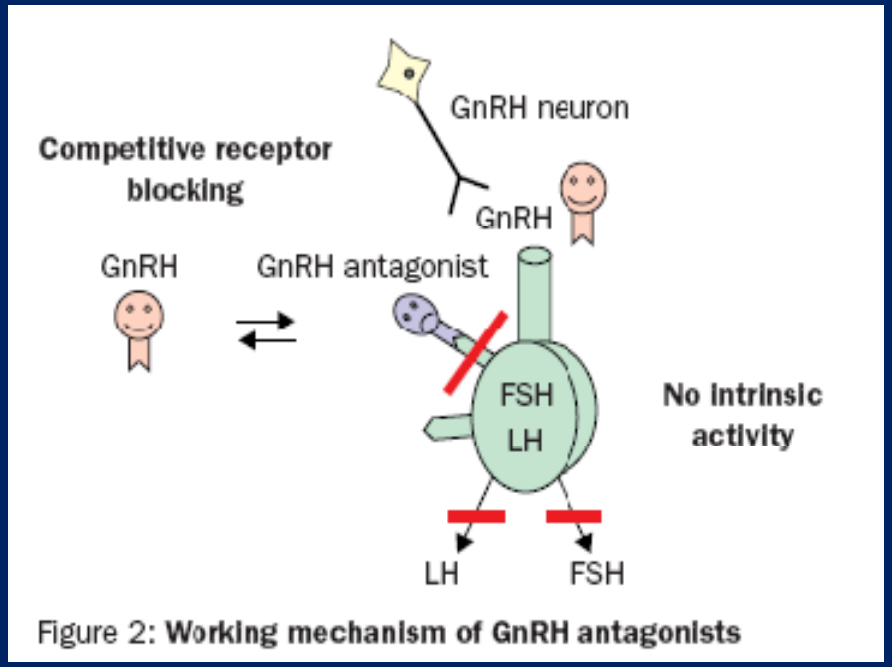
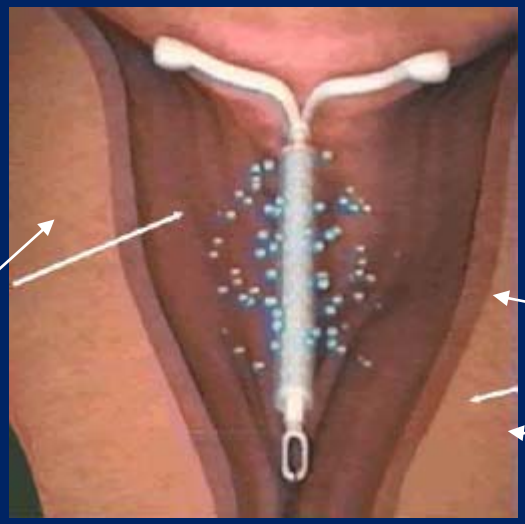


Figure 2: **Working mechanism of GnRH antagonists**

İntrauterin Sistemden (IUS) Lokal Levonorgestrel salımı



(Nillson ve ark., Contraception 1982)

LNG-RIA: Etki Mekanizması?

- Endometrial hücre proliferasyonunu azaltır, apoptotik aktiviteyi artırır, glandüler atrofiye neden olur
- Antienflamatuar ve Immunomodlatuar etkisi vardır
- Östrojen ve progesteron reseptörlerinde azalma
- Östrojenle indüklenen growth faktörlerin inhibisyonu
- Peritoneal sıvıda LNG artışı peritoneal implantlara lokal etki oluşturur
- Ektopik endometriumda hücre proliferasyonunda azalma, gland epitelinde ER-α ve PR-A ekspresyonunda azalma, Fas ekspresyonunda artma

Effects of the levonorgestrel-releasing intrauterine system on cell proliferation, Fas expression and steroid receptors in endometriosis lesions and normal endometrium. Gomes et al. Human Reproduction, Vol.00, No.0 pp. 1–10, 2009

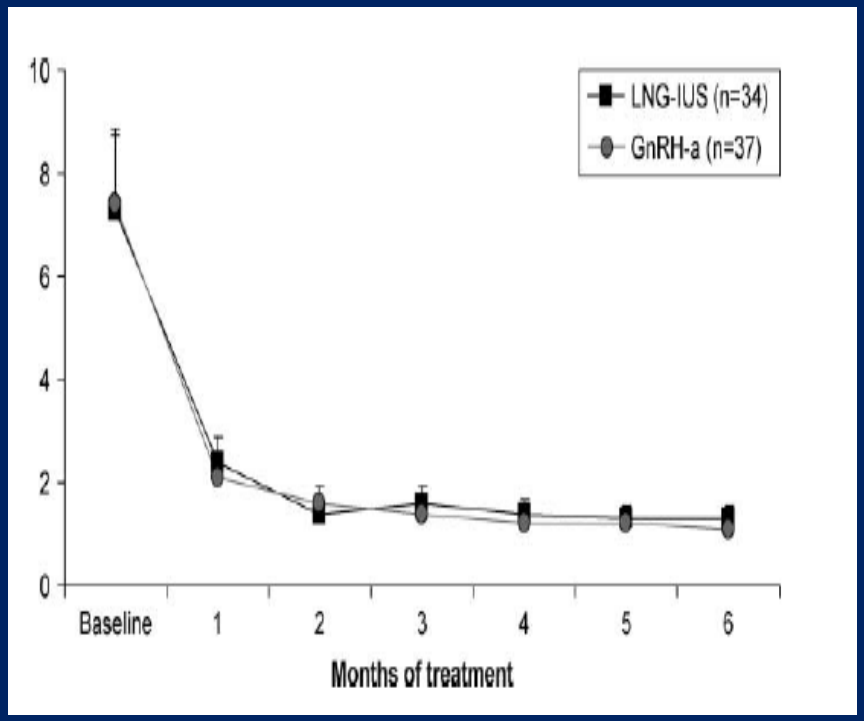
Serum and peritoneal fluid levels of levonorgestrel in women with endometriosis who were treated with an intrauterine contraceptive device containing levonorgestrel. Fertil Steril. Lockhat et al. 2005 Feb;83(2):398-404.

Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis

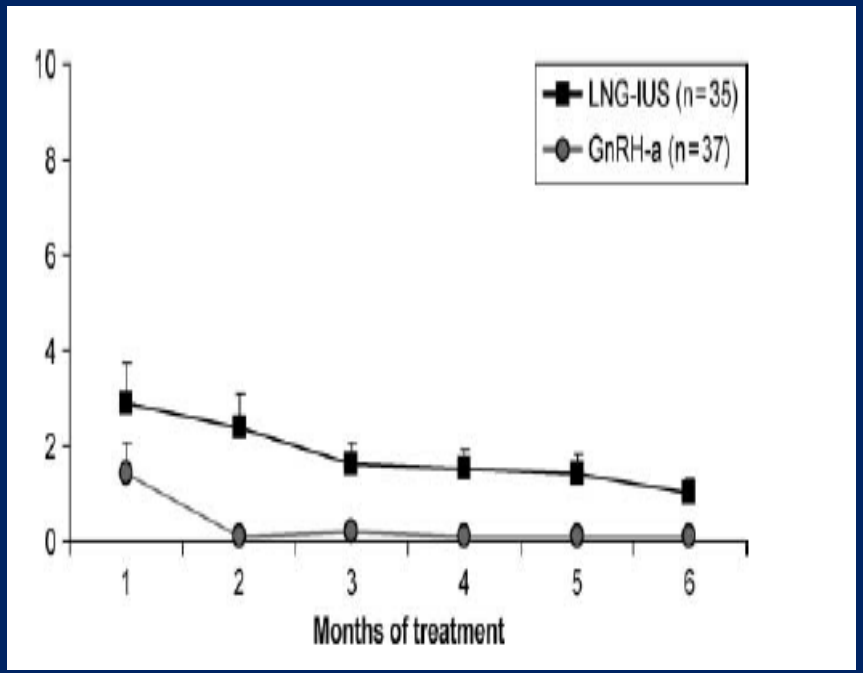
Evre III-IV daha iyi yanıt vermiştir

- **6. aylarda IUS ile % 78 , GnRH-a ile % 98'inde amenore**

visual analogue score pain scores



Changes in the bleeding scores



Carlos A.Petta, 2005

Adenomyozis Tedavisi

- Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging. Aristides M. *Contraception 76 (2007) 195–199*
- Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis. SiHyun Cho et al. *Am J Obstet Gynecol. 2008 Apr;198(4):373.e1-7.*
- The LNG-IUS study on adenomyosis: a 3-year follow-up study on the efficacy and side effects of the use of levonorgestrel intrauterine system forthe treatment of dysmenorrhea associated with adenomyosis. Sheng J. *Contraception 79 (2009) 189–193*

Adenomyozis

- Adenomyozise bağlı dismenoresi olan 94 olgu, LNG-IUS, 3 yıl takip
- Dismenore için VAS;

77.9 ± 14.7 (Bazal) ➔ vs 11.8 ± 17.9 (36.ay) p<0.001

- En belirgin iyileşme sistem yerleştirildikten sonraki ilk 3-6 ay içinde izlenmiş.
- 36. ay sonunda overall tatmin: %72.5

Sheng et al., Contraception, 79; 189-193, 2009

Revised guidelines, 2007

A	The levonorgestrel intra-uterine system (LNG IUS) reduces endometriosis associated pain.	Evidence Level 1a

A systematic review identified two RCTs and three prospective observational studies, all involving small numbers and a heterogeneous group of patients (Varma et al., 2005). Nevertheless, the evidence suggests that the LNG IUS reduces endometriosis associated pain (Petta et al., 2005; Vercellini et al., 1999a) with symptom control maintained over 3 years (Lockhat et al., 2004; Lockhat et al., 2005).

eshre
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LNG-IUS for symptomatic endometriosis following surgery Abou-Setta et al 2009

Analysis 1.1. Comparison 1 Postoperative use of LNG-IUD in women with endometriosis, Outcome 1 Painful symptoms.

Review: Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery

Comparison: 1 Postoperative use of LNG-IUD in women with endometriosis

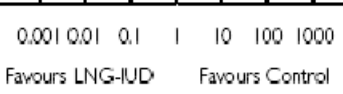
Outcome: 1 Painful symptoms

Study or subgroup	LNG-IUD n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Vercellini 2003	2/20	9/20		100.0 %	0.14 [0.02, 0.75]
Total (95% CI)	**20**	**20**		**100.0 %**	**0.14 [0.02, 0.75]**

Total events: 2 (LNG-IUD), 9 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.29 (P = 0.022)



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Deri altına Progestojen İmplantları (Etonogestrel)

- İmplantın etkisini değerlendiren az sayıda açık etiketli olgu serisi
- 21 Kadın: DMPA kullanan 20 kadınla karşılaştırılmış
    - Bir yılda VAS skorunda % 68 azalma

(Walch ve ark. 2009)

- 50 kadın: Üçüncü aylarda VAS skorunda 7,1 ± 2,1'den 0,8 ±1,7'ye düşüş
    - % 28 amenore
    - % 80'i memnun veya çok memnun

(Ponpuckdee ve ark. 2005)

Endometriyozise bağlı ağrının medikal tedavisinde maliyet hesabı

Medikal tedavi	**Aylık Maliyet(lira)**
*Doğum Kontrol Hapı	15.66
*Gestagenler	
MPA 3 aylık IM	1.66
MPA 5mg/gün po	11.61
NETA 5 mg/gün po	9.71
*GnRH analog	
leuprolid	177
Goserelin	186
Depo triptorelin	250.24
Add-back(NETA)	9.71
*Danazol (600mg/gün po)	110
*LNG-IUD	4.16
*NSAID	7.48

2011-Ocak

Endometrioziste ağrı tedavisine güncel yaklaşım

- 1. seçenek: devamlı düşük doz monofazik OKS ve gerektiğinde NSAID
- 2. seçenek: progestinler (önce oral, iyi tolere edilirse depo veya levonorgesterel)
- 3.seçenek:

  GnRH agonist + hemen hormon ekleme

- 4.seçenek: cerrahi tedavi, 1, 2, 3a sonrasında
- a Eğer diğer tedaviler tolere edilmezse Düşük doz oral (100–200 mg/gün) veya intravaginal danazol

Mahutte and Arici, 2003

İnfertilite problemi olmayan semptomatik endometriozis hastasında medikal tedavi alternatifleri

First-line treatments

Peritoneal disease and endometriotic cysts ≤3 cm

- Oestrogen–progestin combinations used cyclically or continuously* (oral, intravaginal or transdermic use)

Rectovaginal lesions

- Noretistherone acetate, 2.5 mg/day per os used continuously*

Second-line treatments

- Depot GnRH analogues plus add-back therapy (e.g. tibolone 2.5 mg/day per os)
- Alternative progestins (e.g. medroxyprogesterone acetate, desogestrel, cyproterone acetate)

Third-line treatments

- Low-dose danazol (e.g. 200 mg/day, oral or intravaginal use)
- Gestrinone, 2.5 mg twice weekly per os

Specific conditions

Parous women with dysmenorrhoea as main symptom

- Levonorgestrel-releasing intra-uterine device

Hysterectomized women with residual disease

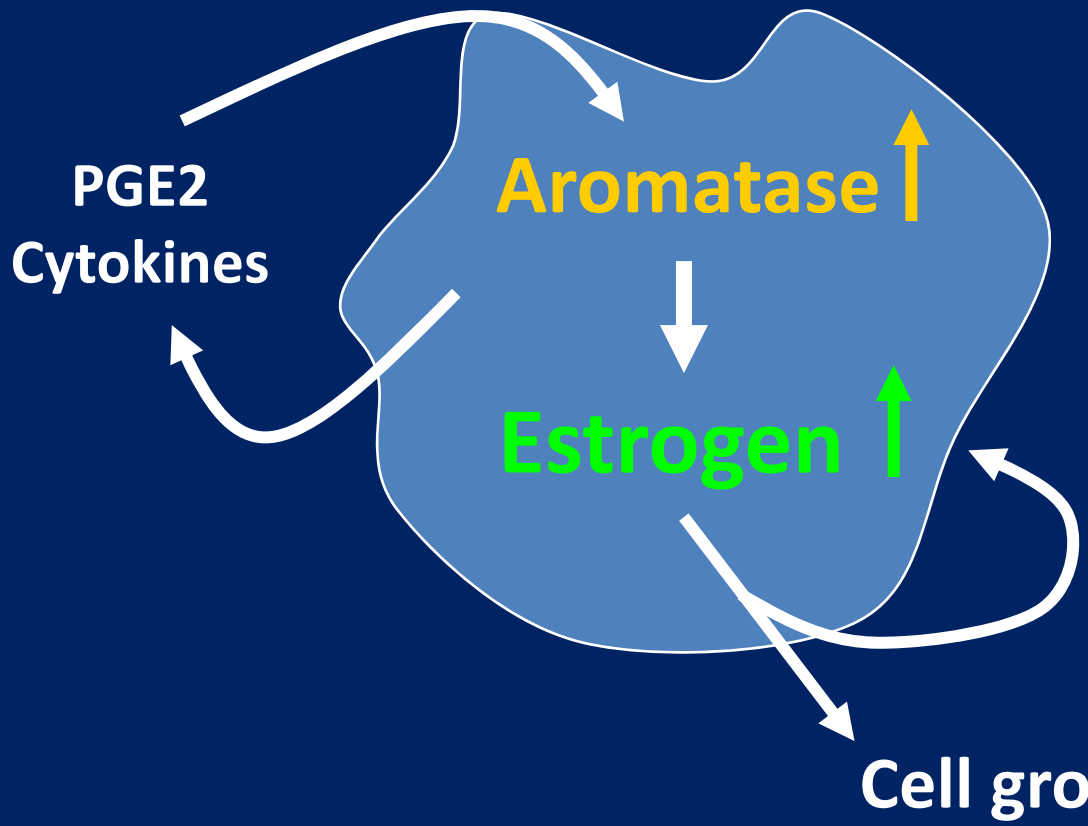
- Depot medroxyprogesterone acetate (150 mg intramuscularly every 3–6 months)

Paolo Vercellini, 2008

Aromatase In Endometriosis

- Aromatase is key for the biosynthesis of estrogen
- In patients aromatase expression is higher in endometriosis tissue than in normal endometrium
- In endometriosis tissue aromatase activity is stimulated by prostaglandin
- Estrogen synthesized by endometriotic tissue stimulates growth of lesions

Role of Estrogen in Endometriosis



Aromatase Inhibitors

- Letrozole
- Exemestane
- Anastrozole

Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis

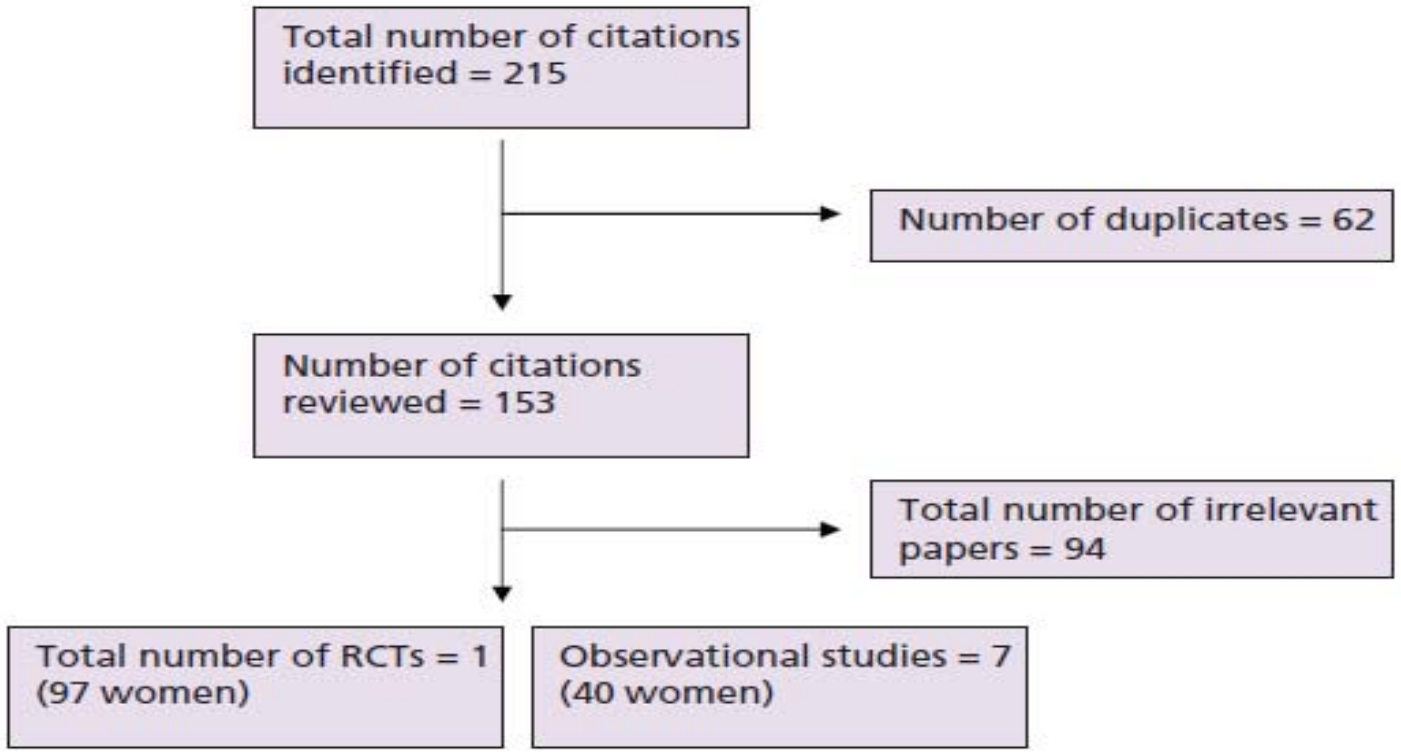


Figure 1. Study selection process for systematic review of aromatase inhibitors in endometriosis.

S Patwardhan, 2008

Table 1. Summary of study characteristics and interventions for endometriosis from individual studies included in systematic review of aromatase inhibitors

Study (year)	Study type	Menopausal status	Number of women	Mean age	Interventions	Treatment in months
Ailawadi *et al.*[19] (2004)	Nonrandomised	Premenopausal	10	29.9	2.5 mg letrozole + 2.5 mg norethindrone acetate + calcium and vitamin D supplement	6
Hefler *et al.*[20] (2005)	Nonrandomised	Premenopausal	10	31.2	0.25 mg anastrazole PV + calcium and vitamin D supplement	6
Razzi and Fava[15] (2004)	Case report	Premenopausal	1	20	2.5 mg letrozole + calcium and vitamin D supplement	3
Takayama *et al.*[16] (1998)	Case report	Postmenopausal	1	57	1 mg anastrazole + calcium supplement + 10 mg alendronate	9
Shippen and West[17] (2004)	Case report	Premenopausal	2	25	1 mg anastrazole + 200 mg prometrium + 12.5–30 mg rofecoxib + vitamin D supplement	6
Fatemi *et al.*[18] (2005)	Case Report	Postmenopausal	1	57	Letrozole	18
Amsterdam *et al.*[22] (2005)	Prospective nonrandomised	Premenopausal	15	23–46	1 mg anastrazole + 0.2 micrograms ethinyl E_2 + 0.1 mg levonorgestrel	6
Soysal *et al.*[21] (2004)	RCT	Premenopausal	97	31.3/32.4	3.6 mg goserelin ± 1 mg anastrazole vs 3.6 mg goserelin	6

Aromataz İnhibitörü (AI) Özet

1 RKÇ (postoperatif teori)

7 gözlemsel çalışma

AI'lerin küçük-orta dereceli etkisini (ağrı skorlarında 0,3 SS farklılık, α = 0,05 ve % 80 düzeyinde istatistiksel güçle) ortaya çıkartmak için her bir grupta 175 kadın (toplamda 350) deneğe gerek duyulacaktır

Semptomatik Endometriyozis
Letrozol + Noretisteron Asetat

- Günde 2,5 mg letrozol + 2,5 mg noretisteron asetat + 1000 mg kalsiyum + 880 IU D vitamini alan 41 kadınla günde 2,5 mg noretisteron asetat alan 41 kadın 6 aylık bir randomize olmayan açık etiketli çalışmada karşılaştırılmıştır

- Her iki grupta 3. aylara gelindiğinde ağrıda anlamlı azalma olmuştur ($p<.001$)

- 3. ve 6. aylarda ağrı ($p<.001$) ve disparöninin ($p= .002$) şiddet derecesi letrozol grubunda daha düşüktü

- Letrozolle yan etkiler (sıcak basmaları, duygudurum değişiklikleri, kas ağrıları, ara kanamaları) daha sık görülmüştür

Ferrero ve ark Hum Reprod 2009; 24:3022-41

Deep endometriosis: Medical treatment

Authors	N	Route	Products
Igarashi *et al., (1998)*	56	Vaginal ring	Danazol
Fedele *et al., (2000)*	15	IM	GnRH analogs
Fedele *et al., (2001)*	11	IUD	Levonorgestrel
Hefler *et al., (2005)*	10	Vaginal suppository	Anastrozole (IA)

Soru

Hangisi endometriozis tedavisinde denenmeyendir ?

- Cabergoline
- Atorvastatin
- Doksisiklin
- Rosiglitazone
- Rifampicin

Table I **Experimental drugs and proposed future therapeutic schemes for endometriosis (literature data 1987–2010).**

Anti-angiogenetic agents
Cabergoline
Endostatin
Sirolimus
Thalidomide
Vascular endothelial growth factor inhibitors
Antioxidants
N-acetylcysteine
Vitamin E succinate
Aromatase inhibitors
Anastrozole
Fadrozole
Formestane
Exemestane
Letrozole
Anastrozole plus oral contraceptive
Anastrozole plus GnRH analogue
Anastrozole plus progesterone, calcitriol and rofecoxib
Letrozole plus norethindrone acetate, calcium citrate and vitamin D
COX-2 inhibitor
Celecoxib
Indomethacin
Nimesulide
Rofecoxib
Valdecoxib
GnRH antagonists
Abarelix
Cetrorelix
Histone deacetylase inhibitors
Trichostatin A
Valproic acid
Valproic acid plus retinoic acid
Immunomodulators
Acetylcholine nicotine receptor analogue—Levamisole
Cytokines interleukin -12
Guanosine analogue—Loxoribine
Interferon-$\alpha_{2\beta}$
Rapamycin
Xantine analogue—Pentoxifylline
Mitogen-activated protein kinase inhibitors
FR167653
p38 inhibitor
Matrix metalloproteinases inhibitors
ONO-4817
Nuclear factor kappa B inhibitors
Caffeic acid phenethyl ester

Paolo Vercellini, 2010

Continued

Table I *Continued*

- Capsaicin
- SN-50

Perossisome proliferator-activated receptor-γ (Thiazolidinediones)

- Rosiglitazone
- Troglitazone

Progesterone antagonists

- Mifepristone (RU 486)
- Onapristone

Selective PR modulators

- Asoprisnil
- J-956 (asoprisnil ecamate)
- J-1042 (megestrone)

Selective estrogen receptor β agonists

- ERB-041

Selective estrogen receptor modulators

- Fulvestrant
- Raloxifene
- Tamoxifen

Statins

- Atorvastatin
- Lovostatin

TNF blockers

- Chimeric anti-TNF-α monoclonal immunoglobulin—Infliximab
- TNF-α receptor-immunoglobulin fusion protein—Etanercept

Paolo Vercellini, 2010

Anti-angiogenetic ajanlar

İmmunomodulatörler ve İnflamatuar cevabı azaltan ajanlar

TNF alfa-blokerleri

Matriks metalloproteinaz inhibitörleri

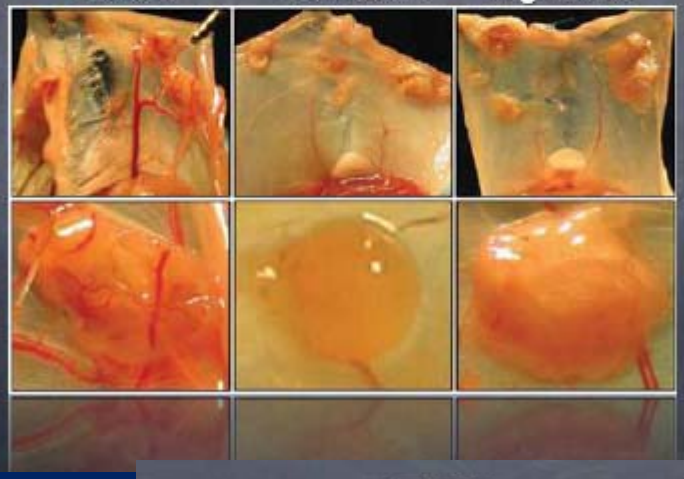
vasküler growth factor inhibitörleri

Antiangiogenic Agents 2/3

Novella-Maestre F, 2009

Cabergoline

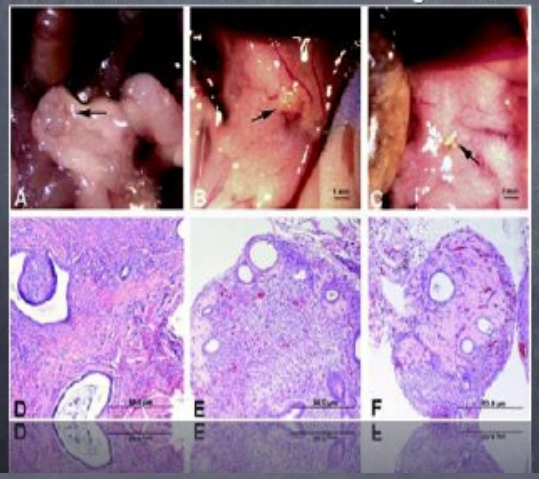
Control | Low dose | High dose

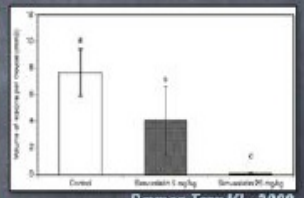


Antiangiogenic Agents 2/3

Simvastatin

Control | Low dose | High dose



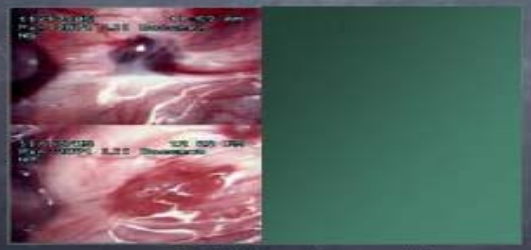


Brunner-Tran KL, 2009

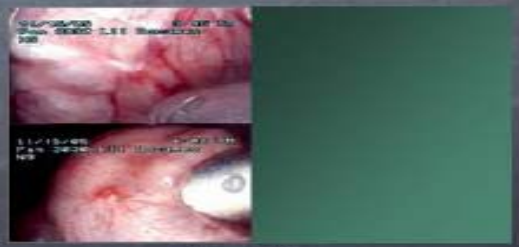
Effects of Rosiglitazone

Lebovic DI, 2007

Placebo



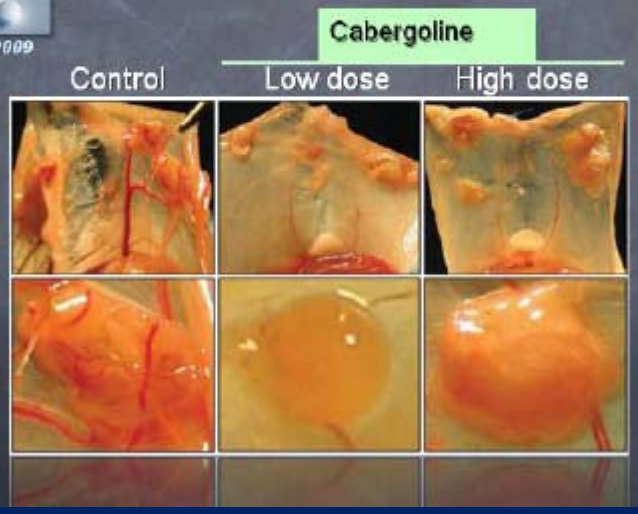
GnRH-antagonist



Rosiglitazone

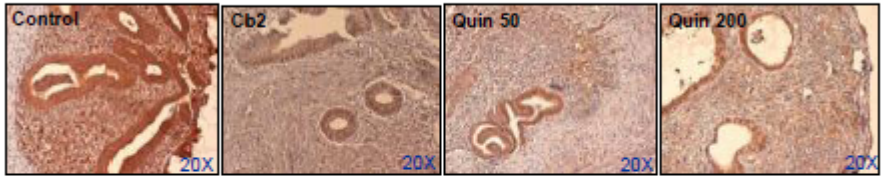
Antiangiogenic Agents 2/3

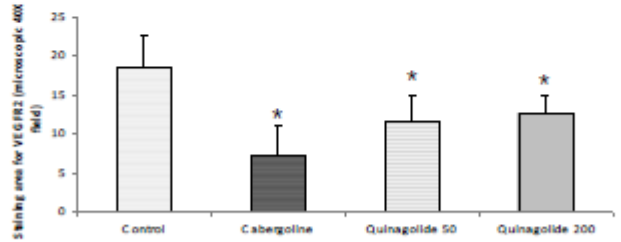
Novella-Maestre E, 2009



VASCULAR RESPONSE OF IMPLANTS

VEGFR-2 Expression





Both dopamine agonists decreased the expression of VEGFR2.
***Cabergoline p=0,009; Quinagolide 50 p=0,039; Quinagolide 200 p=0,046**

Prof. Antonio Pellicer

Progesteron antagonistleri ve SPRMs

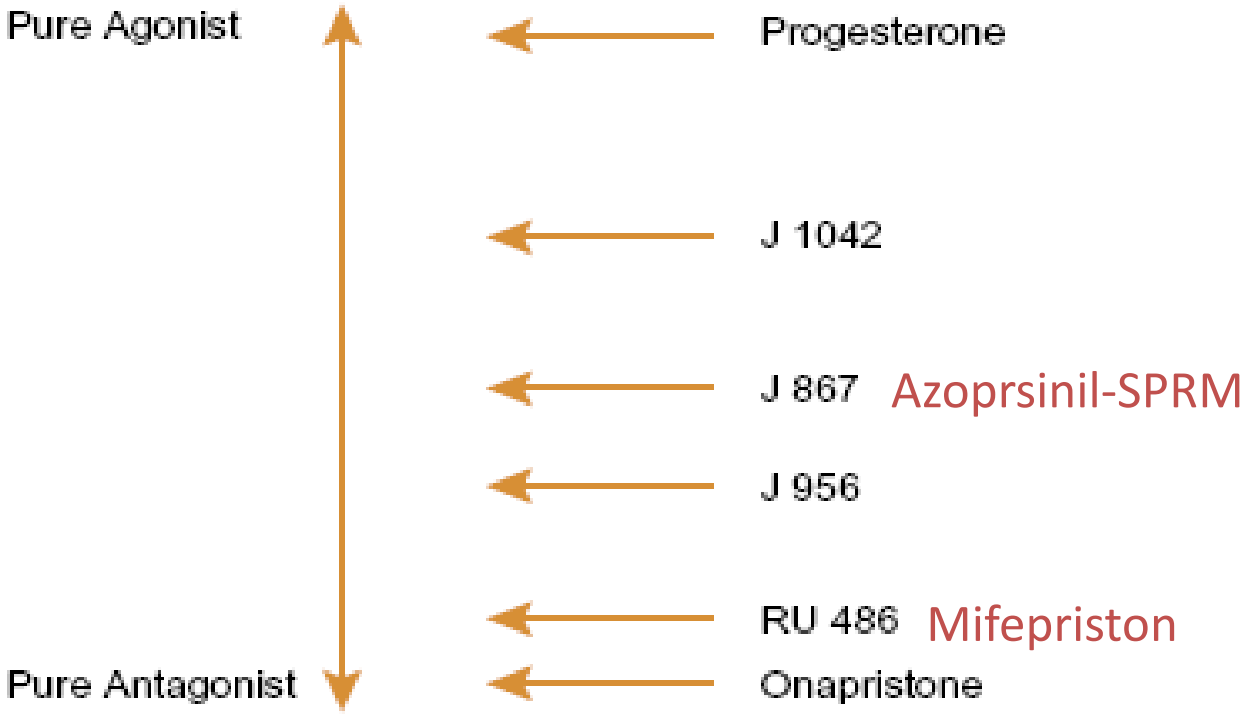


Figure 1. The relative agonist and antagonist activity of progesterone receptor modulators.

- Alternative interventions
  - biofeedback
  - stress management techniques
  - self-hyponosis
  - relaxation therapy
  - transcutaneous nerve stimulation (TNS)
  - trigger-point injections
  - spinal anesthesia
  - nerve blocks

Soru

hangisinin ağrı icin etkinliği kanıtlanmıştır ?

- B1
- B12
- Magnezyum
- E vit
- C vit

ESHRE guideline: Coping with disease

C	There is evidence from two systematic reviews suggesting that high frequency TENS, acupuncture, vitamin B1 and magnesium may help to relieve dysmenorrhoea (Proctor and Murphy 2002; Proctor et al, 2001). One RCT has shown that vitamin E may relieve primary dysmenorrhoea and reduce blood loss (Ziaei et al, 2005). Whether such treatments are effective for endometriosis associated dysmenorrhoea and heavy bleeding is unknown.	Evidence Level 4

Coping: acupuncture

A randomised controlled trial of 90 women with endometriosis

- Shu-Mu acupuncture (n=30)
- routine needling acupuncture (n=30)
- oral Danazol (n=30)

The total effective rate was similar in the three groups.
Shu-Mu point combination group was superior for:

- improvement of dysmenorrhoea and irregular menstruation
- decreased serum CA125

Sun and Chen, 2006

ESHRE guideline: Coping with disease

GPP	Many women with endometriosis report that nutritional and complementary therapies such as homeopathy, reflexology, Traditional Chinese Medicine, herbal treatments, etc, do improve pain symptoms. Whilst there is no evidence from RCTs in endometriosis to support these treatments, they should not be ruled out if the woman feels that they could be beneficial to her overall pain management and/or quality of life, or work in conjunction with more traditional therapies.

Coping: nutritional therapies (i)

Nutritional therapy/dietary modification has shown promising

effects on dysmenorrhoea in three small RCTs:

- supplementation with omega-3 fish oil combined with vitamin B12
- a diet high in vegetables and low in animal fats

Harel et al, 1996; Deutch et al, 2000; Barnard et al, 2000; Fjerbaek and Knudsen, 2007

http://guidelines.endometriosis.org

Coping: nutritional therapies (ii)

- Intake of fruit and green vegetables decreased the risk of endometriosis
- Ham, beef and other red meat increased the risk

Parazzini et al, 2004

Coping: nutritional therapies (iv)

A randomised controlled trial of 80 women with endometriosis demonstrated that two months of high-dose vitamin E and C therapy was associated with significant improvement in endometriosis pain and a reduction in inflammatory markers.

Santanam et al, 2003

Coping: exercise

Exercise releases endorphins, and can assist the body getting back into shape after surgery:

- walking
- swimming
- pilates
- yoga
- physiotherapy

http://guidelines.endometriosis.org

Complementary therapy

Proctor & Murphy 2009, Proctor et al 2009, Proctor et al 2010, Zhu et al 2010

- Treatment modalities shown to be effective
  - Vitamin B1
- Treatment modalities which may be helpful
  - Behavioural interventions
  - Magnesium
  - Fish oil
  - High frequency TENS
  - Topical heat
  - Tki-shakiyaku-san
  - Chinese herbal medicine
- Treatment modalities of unknown benefit
  - Vitamin B12
  - Acupuncture
- Treatment modality of no benefit
  - Vitamin E
  - Spinal manipulation

Endometriosis: Diagnosis and Management

- **Medical Management of Pain Associated With Endometriosis Recommendations**
- 1. Combined hormonal contraceptives, ideally administered continu ously, should be consi ered as first-line agents. (I-A)
- 2. Administration of progestin alone—orally, intramuscularly, or subcu taneously—may also be considered as first-line therapy. (I-A)
- 3. A GnRH agonist with HT addback, or the LNG-IUS, should be consid ered 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)