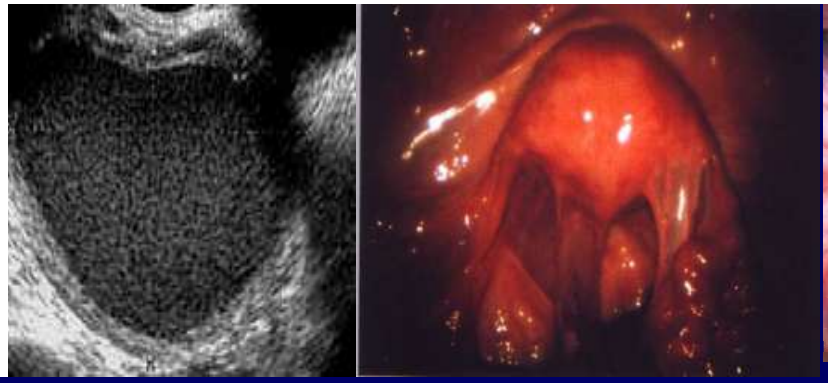


Endometriosis ve YÜT

Prof.Dr.Erol TAVMERGEN

E.Ü.T.F. Kadın Hastalıkları ve Doğum ABD

E.Ü.Aile Planlaması İnfertilite Uygulama ve Araştırma Merkezi

Bornova-İZMİR

Endometriosis fertiliteyi etkiler mi?

A. Evet
B. Hayır

Endometriosis fertiliteyi etkiler mi?

Evet

1. İnfertil olgularda daha sık rastlanır (Mahmoud and Templeton, 1991)
2. Gebelik oranları tedavi edilen olgularda daha yüksek (Marcoux et al, 1997)
3. Endometriosisli olgularda AID ile gebelik oranları daha düşük (Jansen, 1986)
4. YÜT uygulanan endometriosisli olgularda gebelik oranları daha düşük (Barnhart et al, 2002)

Pregnancy chances on an IVF/ICSI waiting list: a national prospective cohort study

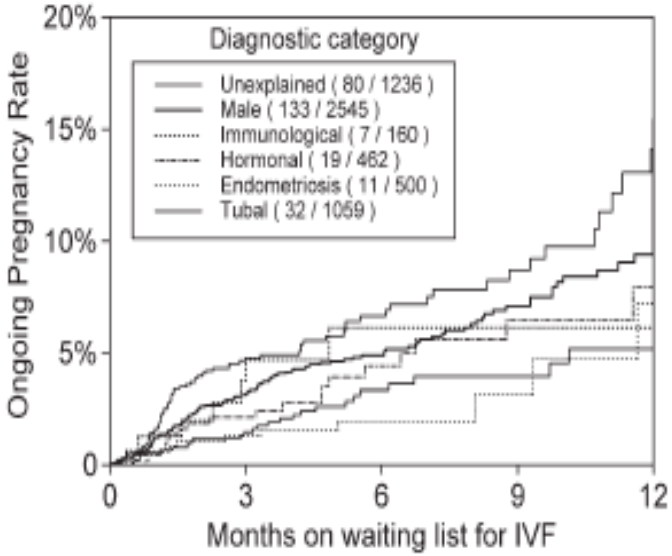


Figure 4: Cumulative chance of an ongoing treatment-free pregnancy, against time since registration on the waiting list for IVF or ICSI, separately for diagnostic categories.
Kaplan–Meier estimates, censoring for start of treatment and for termination of the active childwish.

Table II. HR for ongoing pregnancy without treatment of 5962 patients on the waiting list for IVF.

	HR	95% confidence interval lower–upper
Age (per year)	0.95	0.93–0.98
Duration of infertility (per year)	0.85	0.79–0.91
Indication		
Tubal pathology	1*	—
Endometriosis	0.73	0.37–1.46
Male	1.57	1.06–2.32
Hormonal	1.19	0.67–2.11
Unexplained	2.64	1.75–3.98
Immunological	1.69	0.75–3.84
Primary versus secondary infertility	0.71	0.56–0.90

Eijkemans et al., 2008

Endometriosisde spontan gebelik oranları

	STAGE OF DISEASE		
	MINIMAL/MILD	MODERATE	SEVERE/EXTENSIVE
Expectant	37.4%	22.3%	3.1%

Endometrioma

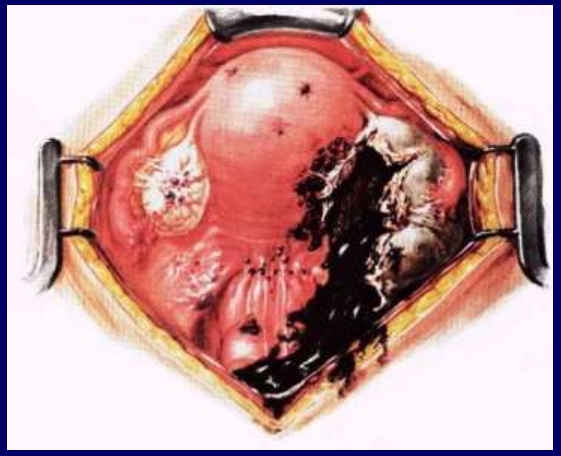
(GD Adamson Sem.Rep.Med.1997;15:263)

Endometriosise bağlı infertilite tedavisinde tahmini aylık fekundite oranları (%)

Adamson, ASRM Practice Guidelines Commitee 2004

Tedavi	Minimal/mild	Moderate	Severe
Ekspektan	3	3	0
Medikal	3	4	2
Cerrahi	5	5	3
IVF	19	16	12
GIFT	34	36	20

Endometriosis fertiliteyi neden etkiler?



1. Tubal adhezyonlar
2. Gamet interaksiyon bozuklukları
3. Peritoneal mikroçevrenin bozulması
4. Luteal faz defektleri
5. İmplantasyonun etkilenmesi

Endometriosisde olumsuzluklar Evre 1-2

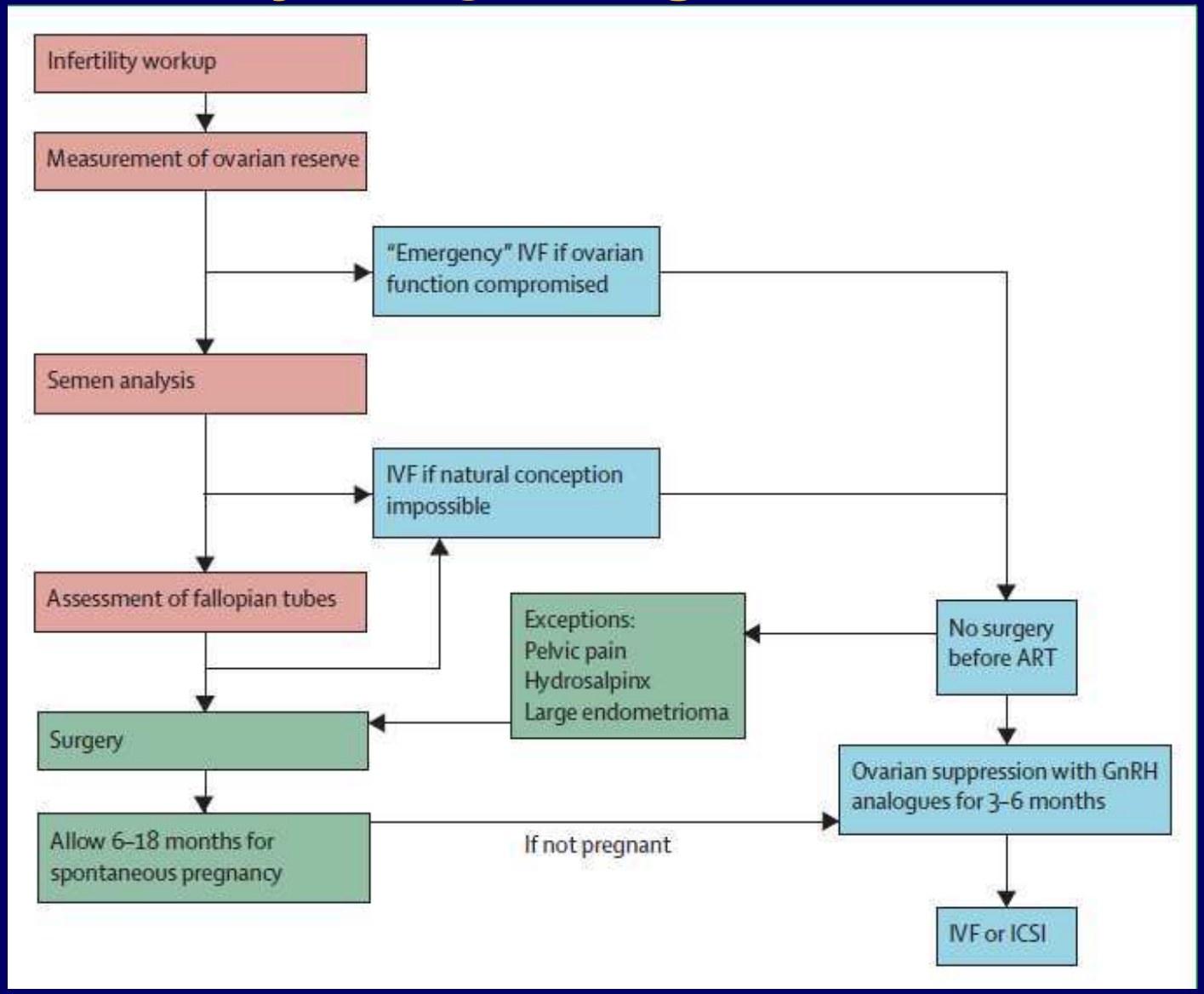
- Anormal follikulogenez
- Artmış oksidatif stress
- Bozulmuş immun fonksiyonlar
- Peritoneal ve folliküler mikro çevredeki hormonal değişiklikler
- Azalmış endometrial reseptabilite

Oosit kalitesinde azalma
Fertilizasyon sorunları
İmplantasyon sorunları

Endometriosis-YÜT Endikasyonları

- DOR
- Kadın yaşı>37
- İnfertilite süresi > 5 sene
- Başarısız KOH/IUI siklusları
- Tekrarlayan endometriosis
- Ciddi Adenomyosis
- Bilateral Tubal Faktör
- Erkek faktörü

Endometriosise bağlı infertilitede yaklaşım algoritması



Dominique de Ziegler, 2010

Endometriosis YÜT sonuçlarını etkiler mi?

- Evet
- Hayır

Endometriosisin IVF Sonuçlarına Etkileri

- **Çalışmaların bir kısmında olumsuz etkiler üzerinde durulurken bir kısmında da etkili olmadığı belirtilmektedir:**

- Evre arttıkça gebelik oranları ↓

- Elde edilen OCCC sayısının ↓

- Fertilizasyon oranlarının ↓

- Oosit ve embryo kalitesinin olumsuz etkilenmesi

- İmplantasyon oranlarının ↓ (Matson 1986 ; Simon 1994 ; Arıcı 1996 ; Cahill 1997)

- İmplantasyon oranları etkilenmez((Mills 1992 ; Inoue 1992 ; Dmowski 1995 ; Olivennes 1995 ; Tanbo 1995 ; Padigas 1996 ; Huang 1997 ; Hickman 2002 ; Suzuki 2005)

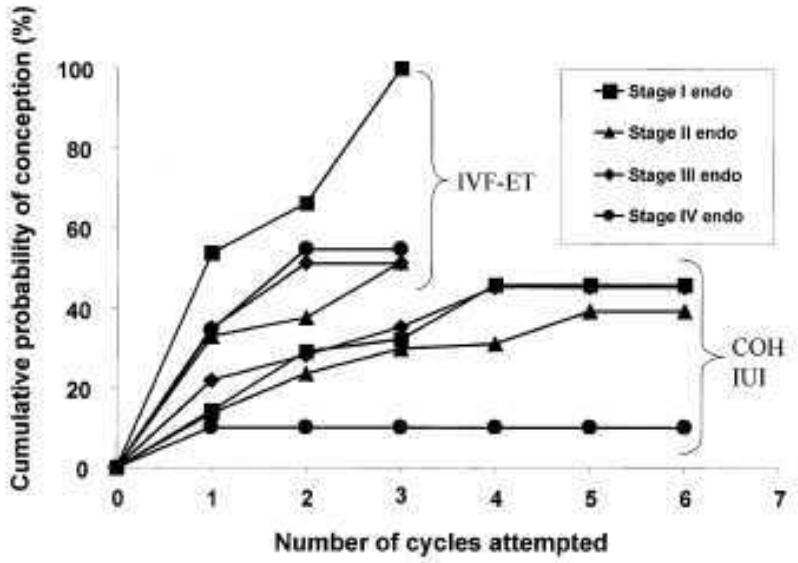
Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation–intrauterine insemination or in vitro fertilization–embryo transfer

W. Paul Dmowski, M.D., Ph.D., Michelle Pry, M.S.N., Jianchi Ding, Ph.D., and Nasir Rana, M.D., M.P.H.

Institute for the Study and Treatment of Endometriosis, Oak Brook, Illinois

FIGURE 2

Effect of COH-IUI or IVF-ET on fecundity according to the stage of endometriosis.



Dmowski. Fecundity with COH or IVF in endometriosis. Fertil Steril 2002.

Endometriosisin IVF Sonuçlarına Etkileri

- Endometriomalı olgularda anlamlı derecede yüksek gonadotropin dozu kullanılmakta
- Erken evre peritoneal endometrioziste daha uzun folliküler faz saptanmaktadır (Cahill)
- Aberan granulosa hücre sitokinleri oositlerin fertilizasyon kapasitelerini bozar (Mahutte NG, Arıcı A)
- Endometriozisli olgularda daha yüksek oranda apoptozis görülür (Toya)

Effect of endometriosis on in vitro fertilization

Kurt Barnhart, M.D., M.S.C.E.,[a,b] *Rebecca Dunsmoor-Su, M.D., M.S.C.E.,*[a] *and Christos Coutifaris, M.D., Ph.D.*[a]

Center for Reproductive Medicine and Surgery, University of Pennsylvania Medical Center and Health System; and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Objective: To investigate the IVF outcome for patients with endometriosis.

Design: Meta-analysis.

Setting: Academic research center.

Patient(s): A MEDLINE search and review of the literature were performed. Patients were classified by level of endometriosis, and controls were classified according to the indication for IVF.

Intervention(s): Bivariate analysis and multivariate logistic regression was used to estimate overall effect and control for confounding.

Main Outcome Measure(s): Pregnancy rates, fertilization rate, implantation rates, and numbers of oocytes retrieved.

Result(s): Twenty-two published studies were included in the overall analysis. The chance of achieving pregnancy was significantly lower for endometriosis patients (odds ratio, 0.56; 95% confidence interval, 0.44–0.70) when compared with tubal factor controls. Multivariate analysis also demonstrated a decrease in fertilization and implantation rates, and a significant decrease in the number of oocytes retrieved for endometriosis patients. Pregnancy rates for women with severe endometriosis were significantly lower than for women with mild disease (odds ratio, 0.60; 95% confidence interval, 0.42–0.87).

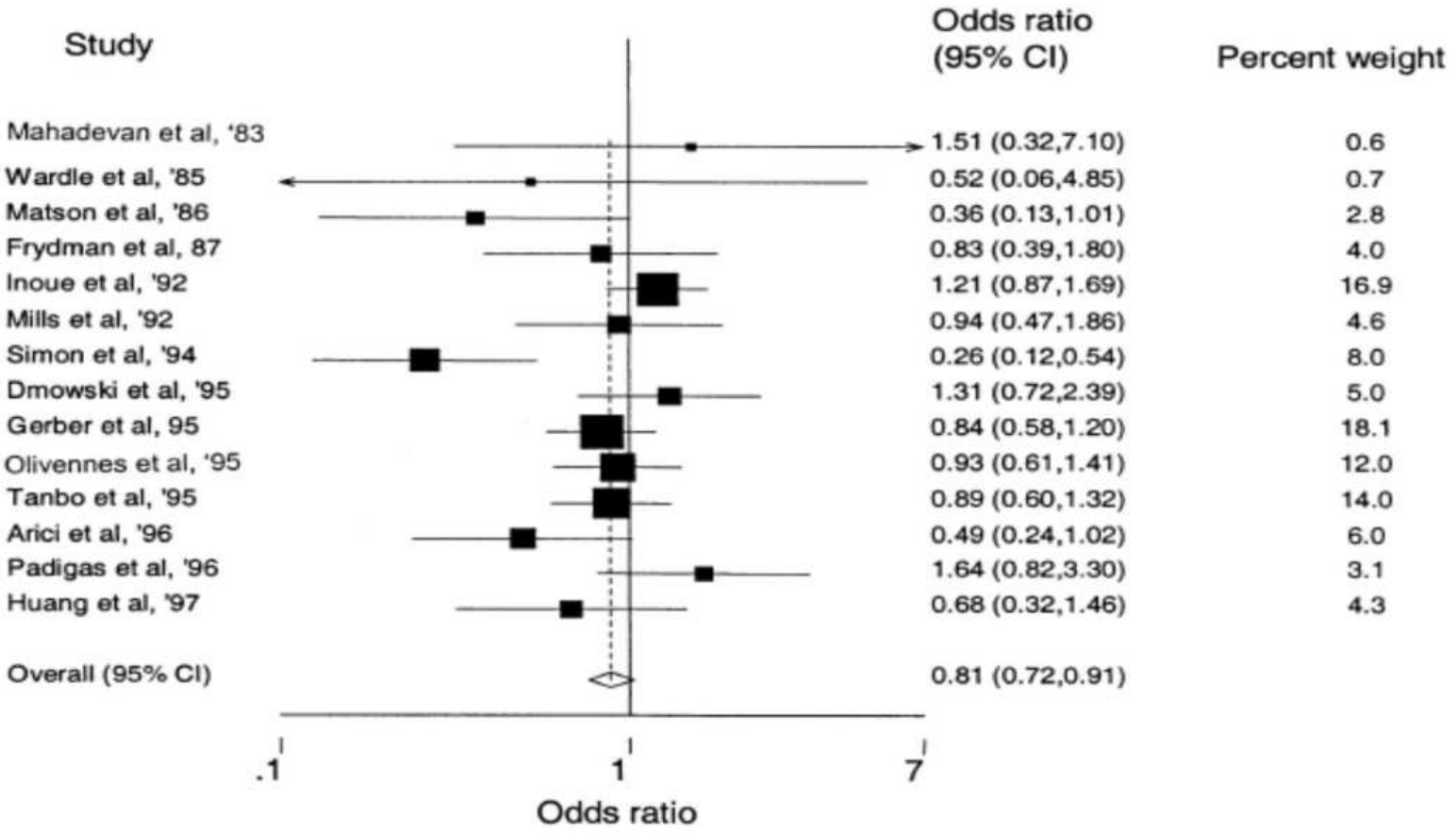
Conclusion(s): Patients with endometriosis-associated infertility undergoing IVF respond with significantly decreased levels of all markers of reproductive process, resulting in a pregnancy rate that is almost one half that of women with other indications for IVF. These data suggest that the effect of endometriosis is not exclusively on the receptivity of the endometrium but also on the development of the oocyte and embryo. (Fertil Steril® 2002;77:1148–55. ©2002 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, infertility, fertilization in vitro, meta-analysis

Barnhart K June 2002; Fertil Steril; 77:1148-1155

FIGURE 1

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



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

IVF Gebelik oranları Endometriozis/ Tubal faktör

	Endometriozis	Tubal faktör	Düzeltilmiş OR
Gebelik oranı	25.38	27.71	0.56 (0.44–0.70)
Fertilizasyon %	59.50	66.09	0.81 (0.79–0.83)
İmplantasyon %	12.72	18.08	0.86(0.85–0.88)

Barnhart. Fertil Steril 2002.

TABLE 3

Results of bivariate analysis and multiple logistic regression analyses comparing endometriosis patients with controls.

Outcome	Endometriosis	Control	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
All patients[b] (n = 2,909)				
Pregnancy rate	25.42	29.52	0.81 (0.72–0.91)	0.63 (0.51–0.77)
Fertilization rate	59.69	65.94	0.95 (0.94–0.95)	0.87 (0.85–0.88)
Implantation rate	12.72	18.08	0.86 (0.85–0.87)	0.86[c] (0.85–0.88)
Mean no. of oocytes	7.81	7.30	1.06 (1.04–1.08)	0.92 (0.85–0.99)
Peak E_2	3545.04	4399.93	N/A	N/A
Endometriosis only vs. tubal factor only[d] (n = 2,893)				
Pregnancy rate	25.38	27.71	0.88 (0.79–1.00)	0.56 (0.44–0.70)
Fertilization rate	59.50	66.09	0.95 (0.94–0.95)	0.81 (0.79–0.83)
Implantation rate	12.72	18.08	0.86 (0.85–0.88)	0.86[c] (0.85–0.88)
Mean no. of oocytes	7.79	7.30	1.06 (1.04–1.08)	0.82 (0.75–0.90)
Peak E_2	3545.04	4399.93	N/A	N/A
Stage I–II[e] (n = 2,602)				
Pregnancy rate	21.11	27.71	0.70 (0.56–0.87)	0.79 (0.60–1.03)
Fertilization rate	58.38	66.09	0.93 (0.92–0.94)	0.94 (0.93–0.96)
Implantation rate	11.31	18.08	0.80 (0.78–0.82)	0.88 (0.85–0.90)
Mean no. of oocytes	8.19	7.30	1.11 (1.06–1.14)	0.56 (0.49–0.65)
Peak E_2	5813.38	4399.93	N/A	N/A
Stage III–IV[f] (n = 2,575)				
Pregnancy rate	13.84	27.71	0.42 (0.31–0.57)	0.46 (0.28–0.74)
Fertilization rate	74.47	66.09	1.08 (1.06–1.10)	1.54 (1.39–1.70)
Implantation rate	10.23	18.08	0.75 (0.72–0.79)	not interpretable
Mean no. of oocytes	6.70	7.30	0.94 (0.91–0.98)	not interpretable
Peak E_2	1447.74	4399.93	N/A	N/A

Note: $P<.001$ comparing endometriosis with control group in every outcome category. N/A = not applicable.

[a] Adjusted for stimulation regime, publication date, and age except where noted.

[b] Includes endometriosis patients with other concurrent infertility factors; controls include all factors except endometriosis.

[c] Adjusted for publication date and age.

[d] Includes only endometriosis patients (all stages) with no other infertility factors, controls are tubal factor only.

[e] Compares stages I–II endometriosis patients with tubal factor controls.

[f] Compares stages III–IV endometriosis patients with tubal factor controls.

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

TABLE 4

Results of bivariate analysis and multiple logistic regression comparing endometriosis (Endo) patients with stage III–IV disease with patients with stage I–II disease.

Outcome	Endo III–IV	Endo I–II	*P*	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Pregnancy rate	13.84	21.12	<0.001	0.60 (.42–.87)	0.64 (.35–1.17)
Fertilization rate	74.47	58.38	<0.001	1.11 (1.09–1.13)	not interpretable
Implantation rate	10.23	11.31	0.003	0.93 (.89–.98)	0.21 (.15–.32)
Mean oocyte count	6.70	8.19	<0.001	0.83 (.78–.87)	0.31 (.24–.39)
Peak E_2	1447.74	5813.38	<0.001	N/A	N/A

Note: Total no. of observations: 669. N/A = not applicable.

[a] Adjusted for publication date and age.

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

Endometriosisin in vitro fertilizasyona etkileri

- IVF'te gebelik oranlarında % 54 azalma (Tubal faktör'e göre)
- İleri evre endometriosisde gebelik oranlarında % 36 azalma (Hafif endometriosise göre)

Barnhart K June 2002; Fertil Steril; 77:1148-1155

Endometriosis evre - ART

Table 2 Effect of Endometriosis Stage on In Vitro Fertilization/Intracytoplasmic Sperm Injection Outcomes[a]

	Endometriosis stage		Tubal factor
	I/II	III/IV	
Patients	31	67	87
Cycles	58	150	184
Age, y	32.6 ± 4.4	30.8 ± 4.8*	33.7 ± 4.3
Implantation rate (%)	28.3	13.7*	22.1

*$p < 0.05$.
[a]Modified from Kuivasaari et al.[16]

İleri evre endometriosiste bozulmuş granuloza hücre E ve P reseptör ekspresyonu

Azem F, Fertil Steirl, 1999
Kuivasaari, Hum Reprod, 2005

Endometriosis evresi YÜT sonuçlarını etkiler mi?

Table 2 Effect of Endometriosis Stage on In Vitro Fertilization/Intracytoplasmic Sperm Injection Outcomes[a]

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	I/II	III/IV	
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[a]Modified from Kuivasaari et al.[16]

Hum.Reprod. 2005 Nov;20(11):3130-5.

Endometriosis / ART

- Metaanaliz
  - Endometriosis vs. tubal faktör OR: 0.56
  - Şiddetli vs. hafif endometriosis OR: 0.60
- SART (canlı doğum/OPU)
  - Bütün infertilite tanıları %33.2
  - Endometriosis %39.1 !

SART Data, 2012
Barnhart, Fertil Steril, 2002

Endometriosis - ART

Table 1 Endometriosis and In Vitro Fertilization: 2010 SART Registry[a]

Age (y)	< 35	35–37	38–40	41–42
Live birth/cycle (%)				
Endometriosis	41.6	33.1	24.8	14.0
All diagnoses	41.7	31.9	22.1	12.5
Implantation rate (%)				
Endometriosis	36.7	26.4	18.0	11.3
All diagnoses	36.9	27.0	17.7	9.6

[a]Modified from 2010 Society for Assisted Reproductive Technology (SART) Clinic Summary Report.[1]

SART Data, 2012

Does endometriosis influence the reproductive outcome of women undergoing IVF/ICSI ?

Results from a meta-analysis and systematic review

Mukhri Hamdan[1,2,3] Nick Macklon[1,3] Ying Cheong[1,3]

[1] The department of Human And Developmental Health University of Southampton, UK
[2] Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[3] Complete Fertility Centre, Southampton, UK

Previous reviews

Barnhart et al 2002[4]	Harb et al 2013[5]
22 studies, 2377 cycles	27 studies, 8984 women
Clinical pregnancy rate (CPR) per cycle	CPR and Live Birth Rate (LBR) per woman
CPR ↓	CPR ↓ LBR →←
-Per-cycle rather than per woman data -Did not report LBR	-Included oocyte recipients -Limited to women with no prior surgery

[4] Barnhart K, Dunsmoor-Su R, and Coutifaris C. (2002) Effect of endometriosis on in vitro fertilization. Fertil Steril; 77 1148-55.
[5] Harb H, Gallos I, Chu J, Harb M, and Coomarasamy A. (2013) The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology.

The effect of endometriosis on *in vitro* fertilisation outcome: a systematic review and meta-analysis

2013

HM Harb,[a] ID Gallos,[a] J Chu,[a] M Harb,[b] A Coomarasamy[a]

[a] School of Clinical and Experimental Medicine, University of Birmingham, Birmingham Women's Hospital Foundation Trust, Birmingham, UK [b] Sandwell and West Birmingham Teaching Hospital, West Bromwich, UK

Correspondence: Prof A Coomarasamy, School of Clinical and Experimental Medicine, University of Birmingham, Academic Department, 3rd Floor, Birmingham Women's Hospital Foundation Trust, Metchley Park Road, Edgbaston, Birmingham B15 2TG, UK.
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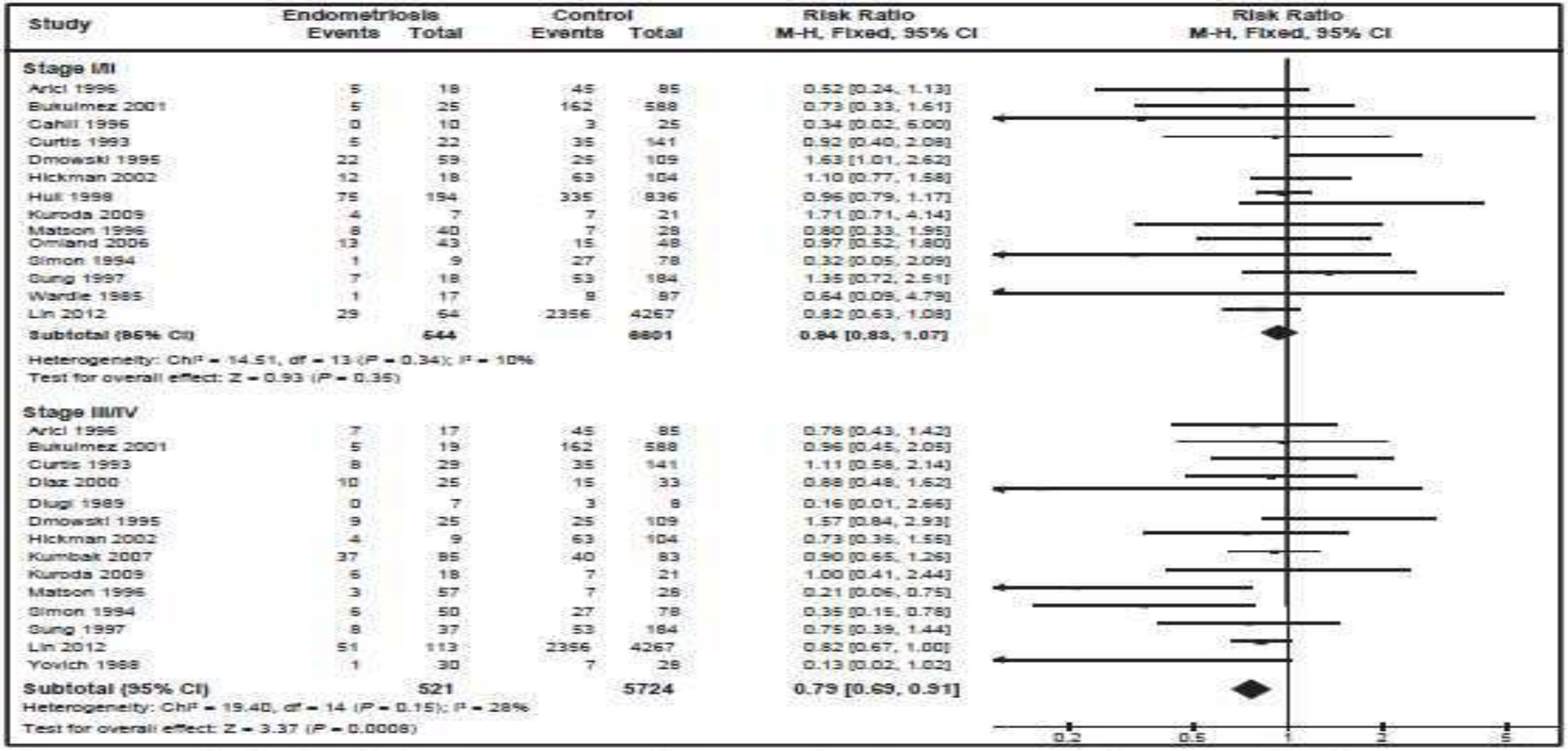


Figure 4. Forest plot of studies of endometriosis versus control in women undergoing IVF treatment for the outcome of clinical pregnancy.

ART: Endometriosis vs no endometriosis

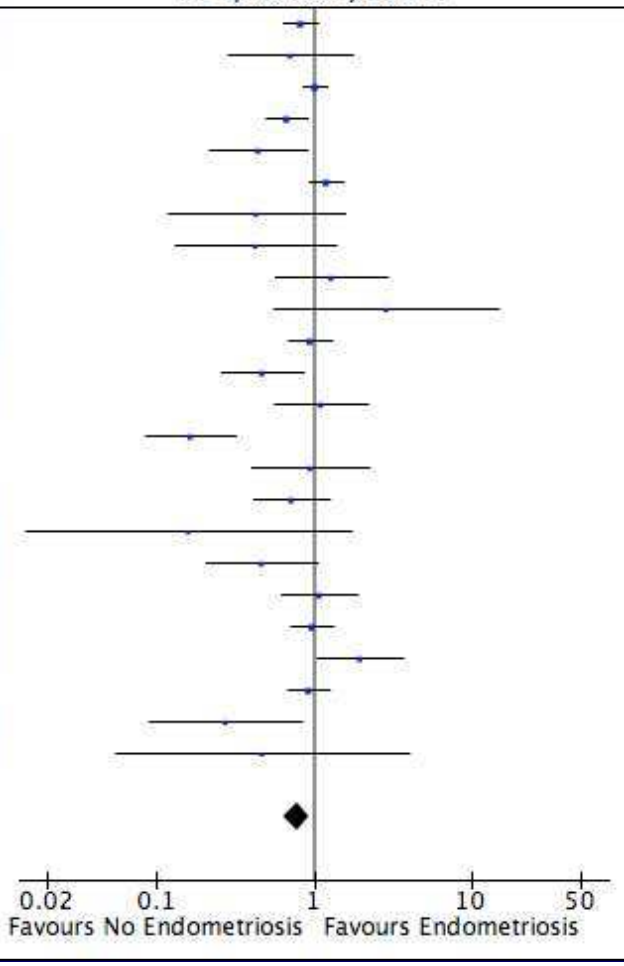
Klinik gebelik oranı

Endometriosisli olgularda ↓ KGO

Study or Subgroup	Endometriosis Events	Endometriosis Total	No Endometriosis Events	No Endometriosis Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Dong 2013	162	431	252	596	7.4%	0.82 [0.64, 1.06]	2013
Mekaru 2013	13	39	17	41	2.7%	0.71 [0.28, 1.75]	2013
Opoein 2012	376	1074	406	1171	8.0%	1.02 [0.85, 1.21]	2012
Lin 2012	80	177	2356	4267	7.0%	0.67 [0.49, 0.90]	2012
Coccia 2011	19	148	18	72	3.7%	0.44 [0.22, 0.91]	2011
Mohammed 2011	81	415	1158	6871	7.4%	1.20 [0.93, 1.54]	2011
Kim 2011	6	20	10	20	1.6%	0.43 [0.12, 1.57]	2011
Falconer 2009	5	34	11	38	1.9%	0.42 [0.13, 1.38]	2009
Nejad 2009	20	73	12	53	3.1%	1.29 [0.57, 2.94]	2009
Kuroda 2009	4	9	5	23	1.1%	2.88 [0.56, 14.94]	2009
Hull 2009	75	194	335	836	6.8%	0.94 [0.68, 1.30]	2009
Kuivasari 2005	50	98	60	87	4.4%	0.47 [0.26, 0.86]	2005
Loo 2005	27	85	21	71	3.9%	1.11 [0.56, 2.20]	2005
Aboulghar 2003	13	85	93	177	4.0%	0.16 [0.08, 0.32]	2003
Hickmann 2002	16	27	63	104	2.9%	0.95 [0.40, 2.24]	2002
Bukulmez 2001	17	78	250	895	4.8%	0.72 [0.41, 1.26]	2001
Pellicer 1998	1	12	4	11	0.5%	0.16 [0.01, 1.73]	1998
Arici 1996	12	35	45	85	3.1%	0.46 [0.20, 1.05]	1996
Olivennes 1995	48	90	57	111	4.8%	1.08 [0.62, 1.89]	1995
Tanbo 1995	74	331	158	690	6.9%	0.97 [0.71, 1.33]	1995
Dmowski 1995	31	84	25	109	4.2%	1.97 [1.05, 3.69]	1995
Inoue1992	131	309	165	372	7.0%	0.92 [0.68, 1.25]	1992
Matson 1986	8	96	7	28	2.0%	0.27 [0.09, 0.84]	1986
Wardle 1985	1	17	8	68	0.7%	0.47 [0.05, 4.03]	1985
Total (95% CI)		**3961**		**16796**	**100.0%**	**0.78 [0.65, 0.94]**	
Total events	1270		5536				

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 67.57$, df = 23 ($P < 0.00001$); $I^2 = 66\%$

Test for overall effect: Z = 2.62 (P = 0.009)



ART: Endometriosis vs no endometriosis

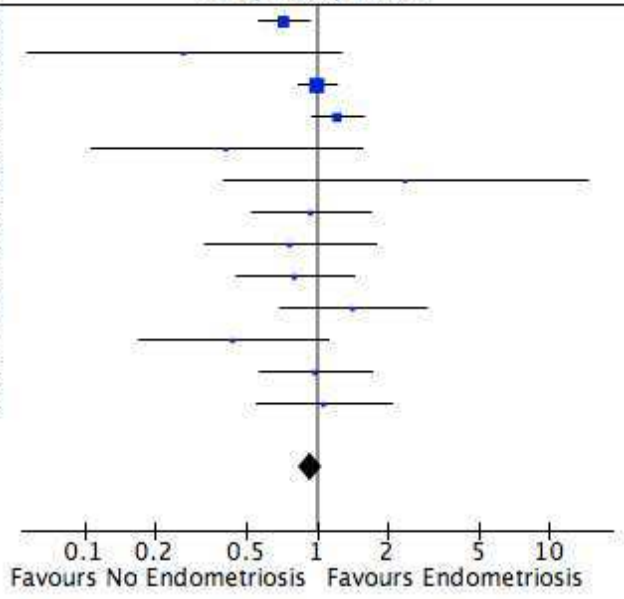
Canlı Doğum Oranı

Fark yok

Study or Subgroup	Endometriosis Events	Endometriosis Total	No Endometriosis Events	No Endometriosis Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Dong 2013	170	431	283	596	24.0%	0.72 [0.56, 0.93]	2013
Mekaru 2013	10	18	14	17	1.1%	0.27 [0.06, 1.27]	2013
Opoein 2012	272	1074	296	1171	35.3%	1.00 [0.83, 1.21]	2012
Mohammed 2011	77	415	1078	6871	16.7%	1.22 [0.95, 1.58]	2011
Kim 2011	5	20	9	20	1.1%	0.41 [0.11, 1.56]	2011
Kuroda 2009	3	7	5	21	0.2%	2.40 [0.40, 14.56]	2009
Kuivasari 2005	38	98	35	87	3.8%	0.94 [0.52, 1.70]	2005
Hickmann 2002	13	27	57	104	2.0%	0.77 [0.33, 1.79]	2002
Bukulmez 2001	15	78	205	895	4.4%	0.80 [0.45, 1.44]	2001
Bergendal 1998	18	48	29	98	2.0%	1.43 [0.69, 2.96]	1998
Arici 1996	7	35	31	85	2.4%	0.44 [0.17, 1.11]	1996
Olivennes 1995	41	90	51	111	4.2%	0.98 [0.56, 1.72]	1995
Mills 1992	15	67	42	198	2.8%	1.07 [0.55, 2.09]	1992
Total (95% CI)		**2408**		**10274**	**100.0%**	**0.94 [0.84, 1.06]**	
Total events	684		2135				

Heterogeneity: $Chi^2 = 18.40$, $df = 12$ ($P = 0.10$); $I^2 = 35\%$

Test for overall effect: $Z = 1.04$ ($P = 0.30$)



ART: Endometriosis vs no endometriosis

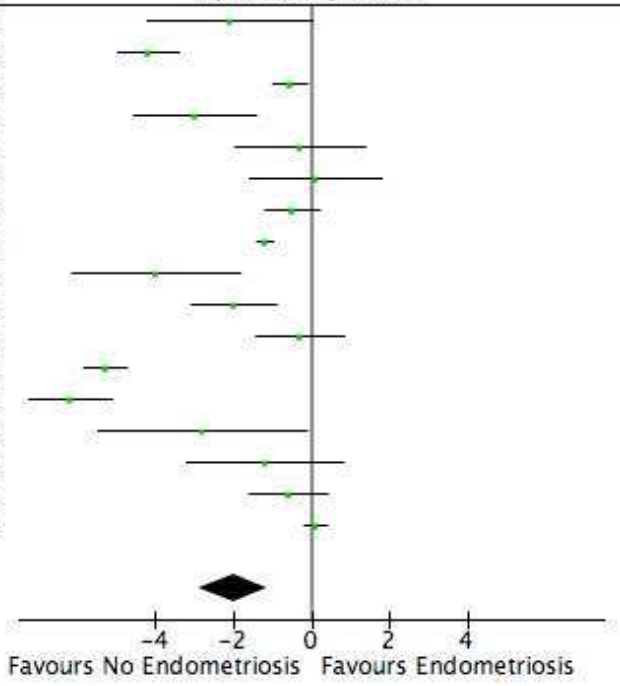
Ortalama elde edilen oocyt sayısı

Endometriosisli olgularda ortalama oocyt sayısı ↓

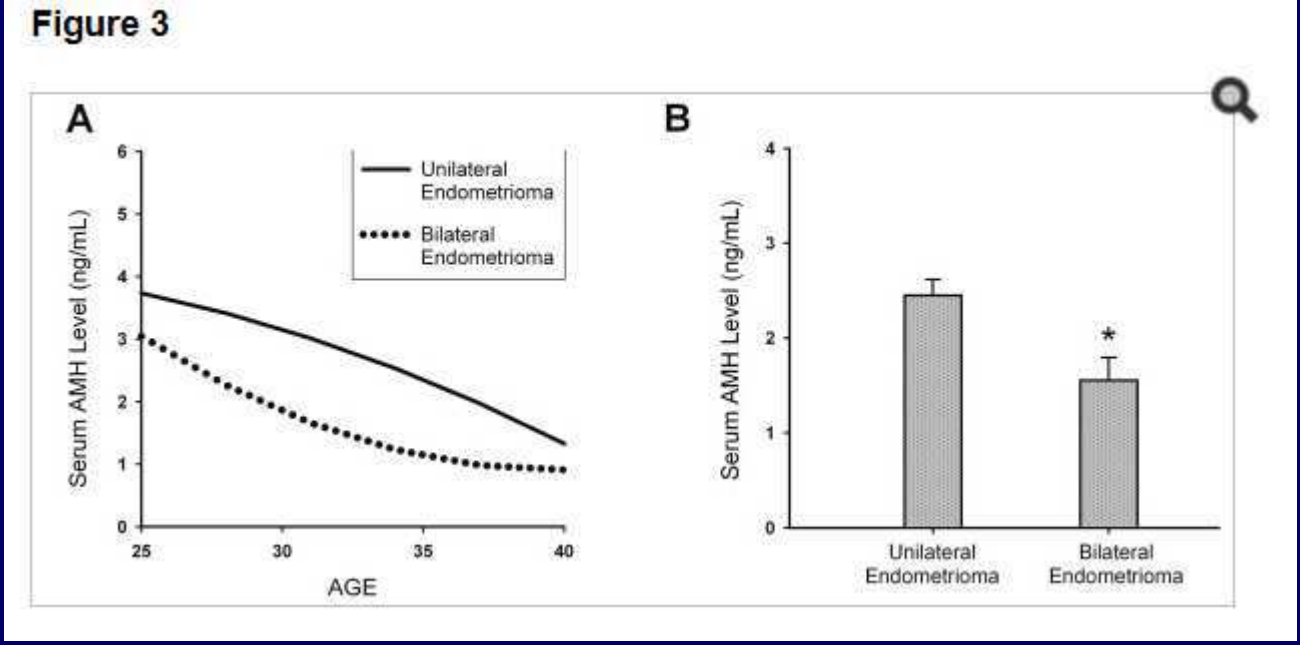
Study or Subgroup	Endometriosis Mean	SD	Total	No Endometriosis Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mekaru 2013	7.9	4.1	39	10	5.5	41	4.9%	-2.10 [-4.22, 0.02]	2013
Lin 2012	7.6	5.1	177	11.8	7.3	4267	6.5%	-4.20 [-4.98, -3.42]	2012
Opoein 2012	8.65	5.2	1074	9.2	5.6	1171	6.7%	-0.55 [-1.00, -0.10]	2012
Coccia 2011	7.8	5.4	164	10.8	6.1	80	5.6%	-3.00 [-4.57, -1.43]	2011
Kim 2011	9.2	2.6	20	9.5	2.8	20	5.5%	-0.30 [-1.97, 1.37]	2011
Nejad 2009	6.6	5.4	80	6.5	4.7	57	5.4%	0.10 [-1.60, 1.80]	2009
Kuroda 2009	1.3	1	15	1.8	1.3	27	6.5%	-0.50 [-1.20, 0.20]	2009
Al-Fadhli 2007	11.5	0.7	87	12.7	0.7	87	6.8%	-1.20 [-1.41, -0.99]	2007
Esinler 2006	7.1	4.4	23	11.1	6.1	99	4.8%	-4.00 [-6.16, -1.84]	2006
Loo 2005	5	3.7	127	7	4.4	95	6.2%	-2.00 [-3.09, -0.91]	2005
Kuivasari 2005	9	5.6	208	9.3	5.8	184	6.1%	-0.30 [-1.43, 0.83]	2005
Wu 2003	6	0.8	22	11.3	1.15	26	6.6%	-5.30 [-5.85, -4.75]	2003
Aboulghar 2003	4.5	3.2	85	10.7	5.6	177	6.2%	-6.20 [-7.27, -5.13]	2003
Hickmann 2002	11.9	6.2	31	14.7	8.3	108	4.2%	-2.80 [-5.49, -0.11]	2002
Marconi 2002	7.5	3.9	39	8.7	5.1	39	5.0%	-1.20 [-3.21, 0.81]	2002
Bukulmez 2001	8.7	4.3	78	9.3	5.2	895	6.2%	-0.60 [-1.61, 0.41]	2001
Medan-Vrtovec 2000	5	3.6	612	4.9	3.4	7339	6.7%	0.10 [-0.20, 0.40]	2000
Total (95% CI)			**2881**			**14712**	**100.0%**	**-1.98 [-2.87, -1.09]**	

Heterogeneity: $Tau^2 = 3.02$; $Chi^2 = 458.73$, df = 16 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: $Z = 4.37$ ($P < 0.0001$)



Unilateral/bilateral endometrioma varlığının AMH'ye etkisi



Ortalama serum AMH düzeyi bilateral endometriomalı olgularda unilateral endometriomalı olgulara nazaran istatistiksel olarak anlamlı daha düşük

	Unilateral	Bilateral
AMH (ng/mL)	2.45 ± 0.17	1.56 ± 0.24

Hwu et al, Reprod Biol Endocrinol, 2011

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

Francesca Raffi, Mostafa Metwally, and Saad Amer

University of Nottingham (F.R., S.A.), Royal Derby Hospital, Derby, DE22 3NE, United Kingdom; and Ninewells Assisted Conception Unit (M.M.), Dundee DD1 9SY, United Kingdom

Study or Subgroup	Mean [ng/ml]	SD [ng/ml]	Total	Mean [ng/ml]	SD [ng/ml]	Total	Weight	IV, Random, 95% CI [ng/ml]
Biacchiardi 2011	1.3	0.3	43	3	0.4	43	15.4%	-1.70 [-1.85, -1.55]
Ercan 2010	1.39	1.16	47	1.62	1.09	47	14.7%	-0.23 [-0.69, 0.23]
Ercan 2011	1.95	0.62	36	2.03	0.41	36	15.3%	-0.08 [-0.32, 0.16]
Hirokawa 2011	2.1	1.6	38	3.9	2.5	38	12.5%	-1.80 [-2.74, -0.86]
Hwu 2011	2.01	1.17	31	3.95	2.34	31	12.6%	-1.94 [-2.86, -1.02]
Kitajima 2011	3.024	2.48	19	4.27	3	19	8.4%	-1.25 [-3.00, 0.50]
Lee 2010	3.29	2.11	13	4.69	2.5	13	8.3%	-1.40 [-3.18, 0.38]
Tsolakidis 2009	2.9	0.63	10	3.9	1.26	10	12.8%	-1.00 [-1.87, -0.13]
Total (95% CI)			237			237	100.0%	-1.13 [-1.88, -0.37]

Heterogeneity: $Tau^2 = 0.95$; $Chi^2 = 146.47$, $df = 7$ ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: $Z = 2.93$ ($P = 0.003$)

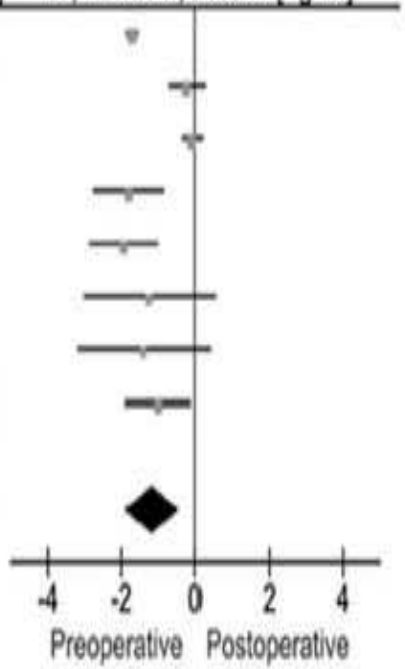


FIG. 2. Meta-analysis. Weighted mean difference in serum AMH after surgery for endometrioma: pooled results for all studies.

Endometrioma eksizyonunun ovarian rezerv testlerinden AMH de %40'a varan azalmaya neden olduğu gösterilmiştir

J Clin Endocrino Metab 97: 3146–3154, 2012

Effects of ovarian endometrioma on embryo quality

The proportions of good, fair, and poor embryos in 13 women with bilateral endometriomas were compared with those of 39 women without endometriomas and were found to be similar (47.2% vs. 41.1%, 28.3% vs. 32.8%, and 24.3% vs. 26.0%, respectively). Therefore, it appears that the presence of bilateral endometriomas during IVF treatment is not associated with reduced embryo quality. (Fertil Steril® 2011;95:2700–2. ©2011 by American Society for Reproductive Medicine.)

TABLE 1

Cycle outcome parameters.

Outcome	Bilateral endometriomas	Controls	*P* value
Oocytes collected	11.2 ± 1.6	12.3 ± 1.05	.57
Metaphase II oocytes	9.5 ± 1.7	13.2 ± 0.96	.07
Fertilization rate (%)	66 ± 0.09	73 ± 0.03	.83
Cleavage rate (%)	89.8 ± 7.9	98.4 ± 0.9	.40
No. of embryos transferred	2.75 ± 0.3	2.77 ± 0.2	.95
Good embryos transferred (%)	65.6 ± 6.8	74.5 ± 7.5	.34

Reinblatt. Correspondence. Fertil Steril 2011.

Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization

Fertility and Sterility® Vol. 83, No. 4, April 2005

Takahiro Suzuki, M.D., Shun-ichiro Izumi, M.D., Ph.D., Hidehiko Matsubayashi, M.D., Ph.D., Hideo Awaji, M.D., Kikuo Yoshikata, M.D., and Tsunehisa Makino, M.D., Ph.D.

Department of Obstetrics and Gynecology, Specialized Clinical Science, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, Japan

TABLE 1

IVF outcomes for the groups.

	endometrioma.	"endometriosis without endometrioma,"	tubal factor,"
Cycles	80	248	283
Age (y)	34.6 ± 3.3	34.7 ± 3.3	34.0 ± 8.8
BMI (kg/m^2)	22.3 ± 0.5	21.7 ± 0.9	22.1 ± 0.8
No. of oocytes retrieved	4.40 ± 2.99 (P = .0037 vs. group C)	4.48 ± 2.81 (P<.0001 vs. group C)	5.34 ± 2.99
Fertilization rate (%)	77.5 ± 28.1	78.8 ± 27.9	82.0 ± 21.9
Good quality rate[a] (%)	67.2 ± 32.5	63.0 ± 36.8	58.1 ± 35.1
Transferred embryos	2.20 ± 0.86 (P = .0001 vs. group C)	2.35 ± 0.83 (P = .0001 vs. group C)	2.67 ± 0.89
Implantation rate (%)	14.1	11.7	11.3
Pregnancy rate per ET (%)	25.3	22.3	23.9
Live birth rate per ET (%)	14.7	15.0	15.4

Note: Values are mean ± SD. IVF = in vitro fertilization; BMI = body mass index; ET = embryo transfer.

[a] Embryos were graded from 1 to 5 according to the classification of Veeks and defined as "good quality" when the embryo was 1 or 2 grade; 80 cycles had ovarian endometriomas that were aspirated and identified as "chocolate" cyst(s) at the time of oocyte retrieval (group A); 248 cycles did not have cysts at the time of oocyte retrieval, while endometriosis was diagnosed by laparoscopy or laparotomy before IVF (group B); 283 cycles had tubal factor without endometriosis, as diagnosed by previous laparoscopy (group C).

Suzuki. IVF outcomes with endometriomas. Fertil Steril 2005.

Endometriosis ve endometrioma elde edilen oocyt sayısını etkiler ancak embryo kalitesini ve gebelik sonuçlarını etkilemez

The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins

Edgardo Somigliana, M.D.,[a] *Mirco Infantino, M.D.,*[a,b] *Francesca Benedetti, M.D.,*[a,b] *Mariangela Arnoldi, M.D.,*[a,b] *Graziella Calanna, M.D.,*[a,b] *and Guido Ragni, M.D.*[a] N:66

TABLE 3

Number of codominant follicles according to the characteristics of the endometrioma(s) and the responsiveness to ovarian hyperstimulation.

	No. of cycles	Intact ovary	Ovary with endometrioma(s)	*P*
No. of cysts				
1	49	3.9 ± 2.0	3.2 ± 1.7	.08
2	7	5.1 ± 3.1	2.0 ± 1.5	.06
Diameter of the cysts[a]				
≤20 mm	31	3.7 ± 2.1	3.0 ± 1.4	.16
>20 mm	25	4.5 ± 2.2	3.2 ± 2.1	.03
Total IU of rFSH used				
≤2,700[b]	29	4.6 ± 2.1	3.1 ± 1.7	.01
>2,700[b]	27	3.4 ± 2.1	3.0 ± 1.8	.42
No. of oocytes retrieved				
≤5	27	3.6 ± 2.2	2.9 ± 1.8	.22
>5	29	4.5 ± 2.1	3.2 ± 1.7	.03

Kodominant follikül sayısı (>15 mm) sağlam overde 4.0 ± 2.2 iken endometriomalı overde 3.0 ± 1.7, idi(*P* = .01).

Bu fark %25'lik bir azalmaya karşılık gelmektedir. Endometrioma varlığı gonadotropa cevabı olumsuz etkiler.

Endometriosis'in YÜT öncesinde medikal tedavisi anlamlı mıdır?

- A. Evet
- B. Hayır

Endometriosisin YÜT öncesi tıbbi tedavisi

1. Kortikosteroidler (Kim et al, 1997) (RCT ancak az vakalı ve tekrarlanmamış)
2. Danazol (Tei et al, 1998) (RCT ancak az vakalı ve tekrarlanmamış)
3. GnRH agonistleri (Oehninger et al, 1989; Dicker et al, 1990; Dale et al, 1990; Nakamura et al, 1992; Curtis et al, 1993; Marcus et al, 1994; Chedid et al, 1995; Ruiz-Velasco and Allende, 1998)
4. Aromataz inhibitörleri (Lossl 2011)

YÜT öncesi Kortikosteroid (RCT)

	Corticosteroids (n = 54)	Controls (n = 57)	P value
CPR	42.6%	22.8%	<0.05
Miscarriage rate	21.7%	15.4%	NS
Multiple pregnancy rate	17.4%	15.4%	NS

Kim et al, J Obstet Gynaecol Res 23(5): 463-70, 1997

Tekrarlayan YÜT başarısızlıklarında YÜT öncesi Danazol (RCT)

	Danazol (400 mg/d for 12 wks)	Controls	P value
Number	41	41	
CPR	40%	19.5%	<0.05

Tei et al, J Reprod Med 43(6): 541-6, 1998

Potential role of aromatase inhibitors in the treatment of endometriosis

International Journal of Women's Health 2014:6 671–680

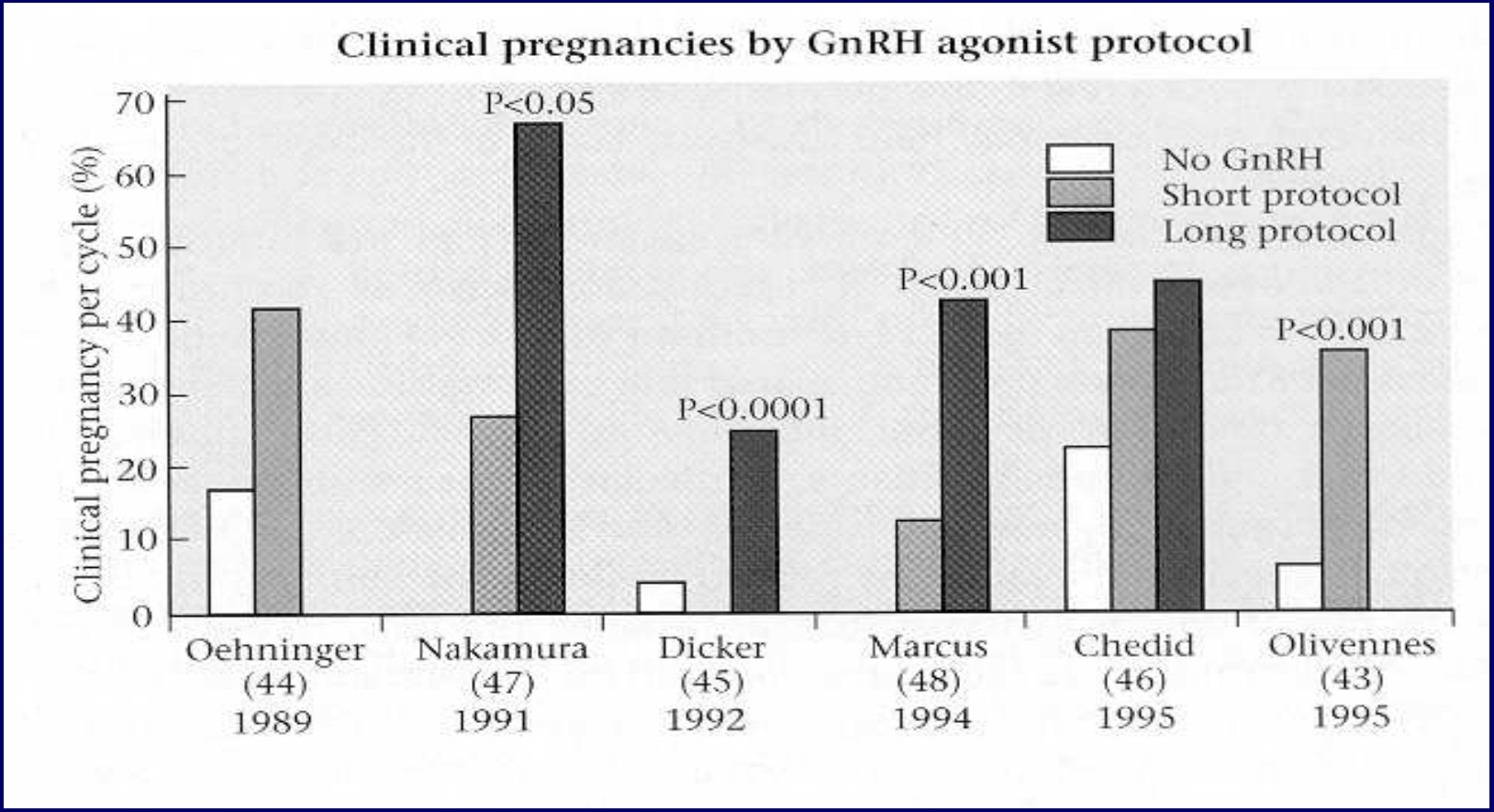
Table 2 Summary of recent studies evaluating the efficacy of aromatase inhibitors in treating endometriosis-associated infertility

Study	Design	Indication	Intervention	Outcome
Alborzi et al[33]	RCT (n=144)	Laparoscopic and histological diagnosis of endometriosis	Letrozole 2.5 mg/day versus triptorelin 3.75 mg IM every month versus no medication for 2 months after laparoscopic surgery, with a 12-month follow-up	No significant differences among the 3 groups with regard to the pregnancy rate (23.4% versus 27.5% and 28.1%, respectively) or the disease-recurrence rate
Abu Hashim et al[68]	RCT (n=136)	Minimal/mild endometriosis, no pregnancy 6–12 months after laparoscopy	Letrozole versus CC Combined with IUI	Letrozole is not more effective than CC, as clinical pregnancy rate per cycle and cumulative pregnancy rate after 4 cycles were comparable in both groups; total number of follicles and E_2 higher in CC group
Lossl et al[69]	Prospective pilot study (n=20)	Patients with endometriomas undergoing IVF/ICSI	Prolonged combined downregulation by anastrozole 1 mg and goserelin 3.6 mg prior to IVF	Significant reduction of endometriomal volume and serum CA125 by 29% and 61%, respectively; 25% clinical pregnancy rate and 15% live-birth rate

Abbreviations: RCT, randomized controlled trial; IM, intramuscularly; CC, clomiphene citrate; IUI, intrauterine insemination; E_2, estradiol; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

- **Endometriozisli olgularda YÜT de tercih edilecek ovulasyon indüksiyonu şeması hangisidir?**

COH Protokolü-Gebelik



Long-term use of gonadotropin-releasing hormone analogues before IVF in women with endometriosis

Erol Tavmergen[a,b], Murat Ulukus[b] and Ege Nazan Tavmergen Goker[a,b]

Curr Opin Obstet Gynecol 19:284–288. © 2007 Lippincott Williams & Wilkins.

Conclusion

In an effort to improve pregnancy and implantation rates in women with endometriosis being treated with IVF, the effect of long-term use of GnRH-a treatment prior to ARTs has been investigated by several nonrandomized and randomized clinical trials. The majority of the studies strongly indicate that prolonged pretreatment with GnRH-a in women with endometriosis clinically enhances pregnancy rates compared with those who did not receive such treatment. Rates of multiple pregnancy, ectopic pregnancy, fetal congenital abnormalities and complications, however, were not reported in any of these studies. The mechanism by which long-term pretreatment of GnRH-a clinically improves pregnancy rates in women with endometriosis is not completely understood. It is believed that GnRH-a suppresses the toxic factors that are found in the peritoneal fluid, which may be harmful to oocytes or embryos, or may restore endometrial receptivity. Therefore, we need further prospective randomized studies investigating the live birth rates and potential complications of such treatment. Furthermore, the mech-

GnRH Analogları ne kadar uzun süre verilmelidir?

Ovaryan Supresyon Süresi ve Dozu: Endometriozis IVF/ICSI

Variable	Group 1	Group 2	Group 3	*P* value
No. ET cycles	93	52	68	
No. of embryo transferred	2.43 ± 0.83	2.54 ± 0.75	2.33 ± 0.83	NS
CP rate, %	29.02 (27/93)	44.2 (23/52)	36.8 (25/68)	NS
Implantation rate, %	16.4	32.7 [a]	26.5	0.031
OP rate, %	25.8 (24/93)	40.4 (20/52)	33.8 (23/68)	NS

İmplantasyon oranları uzayan süre ile artar > 2ay.

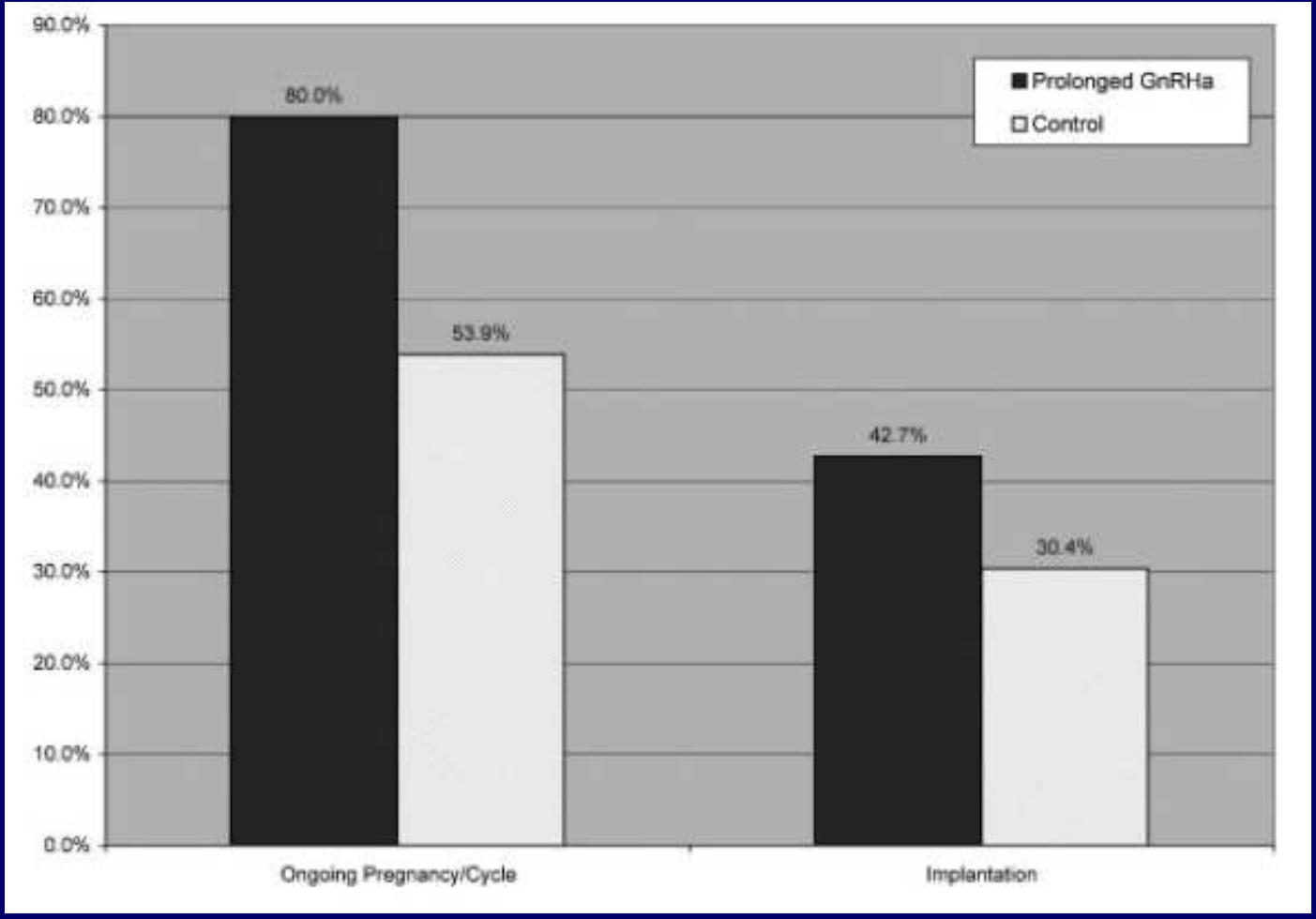
Caihong M, Int J Obstet Gynecol 2008

IVF öncesi GnRHa kullanımı (3-6 ay)

- İleri evre endometriosis
- Daha önce implantasyon başarısızlığı olan hastalar
- Ciddi ağrısı olan hastalar

Dicker D, Fertil Steril, 1992
Surrey, Fertil Steril, 2002

IVF öncesi GnRHa kullanımı (3-6 ay)



Surrey, Fertil Steril, 2002

EÜ Aile Planlaması İnfertilite Araştırma ve Uygulama Merkezi Sonuçları

- Grup 1: yüzeyel endometriozis.....L/S sırasında endokoagülasyon
- Grup 2: ovarian endometrioma.....L/S veya Laparotomi ile eksizyon
- Grup 3: ovarian endometrioma.....KOH öncesi aspirasyon
- Grup 4: tubal faktör

EÜ Aile Planlaması İnfertilite Araştırma ve Uygulama Merkezi Sonuçları

	Siklus	Ampul IU	Geliş follik	>15mm follik	oosit	M2	E2max	Fert. oranı	Klinik gebelik
Grup 1	29	2233+/-911	11,2+/-6,4	5,4+/-2,4	8,5+/-5,4	6,7+/-4,7	1669+/-758	%64	%31
Grup 2	38	2502+/-1017	9,2+/-7,3	4,6+/-2,5	6,6+/-3,7	5,8+/-3,2	1328+/-841	%66	%35
Grup 3	28	3351+/-1523	8,4+/-7,2	7,1+/-7,1	7,2+/-7,1	5,1+/-4,2	1554+/-1194	%70	%17
Grup 4	55	2944+/-1386	13,8+/-10,2	5,2+/-2,9	10,5+/-9,2	5,5+/-3,8	2216+/-2186	%84	%35

p=0,08 p=0,07 p=0,09 p=0,07

Endometriozisli Hastalarda IVF Öncesi Uzun Süreli GnRH-a

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

Sallam HN, Garcia-Velasco JA, Dias S, Arici A

THE COCHRANE COLLABORATION®

(3 RCT , 165 hasta ; 3-6 ay GnRH-a)

Sallam et al, Cochrane Database Syst Rev 25;(1):CD004635, 2010

Gonadotropin Dozları

Analysis 01.05. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 05 Dose of FSH or HMG (ampoules)

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

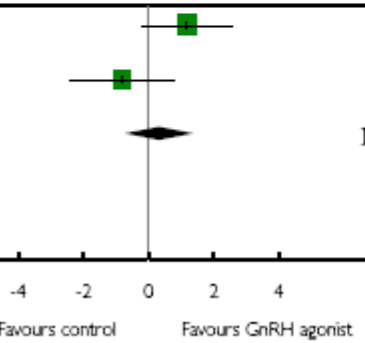
Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

Outcome: 05 Dose of FSH or HMG (ampoules)

Study	GnRH agonist N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Dicker 1992	35	41.80 (2.60)	32	40.60 (3.10)		56.9	1.20 [-0.18, 2.58]
Surrey 2002	25	42.40 (3.21)	26	43.20 (2.50)		43.1	-0.80 [-2.38, 0.78]
Total (95% CI)	**60**		**58**			**100.0**	**0.34 [-0.70, 1.38]**

Test for heterogeneity chi-square=3.49 df=1 p=0.06 I^2 =71.3%

Test for overall effect z=0.64 p=0.5



COH Süresi

Analysis 01.06. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 06 Duration of FSH administration (days)

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

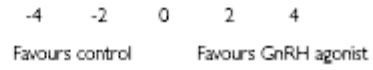
Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

Outcome: 06 Duration of FSH administration (days)

Study	GnRH agonist N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Surrey 2002	25	10.12 (2.15)	26	10.08 (1.07)		100.0	0.04 [-0.90, 0.98]
Total (95% CI)	**25**		**26**			**100.0**	**0.04 [-0.90, 0.98]**

Test for heterogeneity: not applicable

Test for overall effect z=0.08 p=0.9



Klinik Gebelik Oranları

Analysis 01.02. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 02 Clinical pregnancy rate per woman

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

Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

Outcome: 02 Clinical pregnancy rate per woman

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

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

Test for heterogeneity chi-square=0.83 df=2 p=0.66 I^2 =0.0%

Test for overall effect z=3.75 p=0.0002

0.01 0.1 1 10 100

Favours control Favours GnRH agonist

3-6 ay GnRHa klinik gebelik oranlarını 4 kat arttırır

Canlı Doğum Oranları

Analysis 01.01. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 01 Live birth rate per woman

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

Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

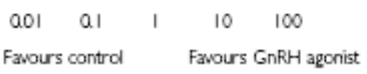
Outcome: 01 Live birth rate per woman

Study	GnRH agonist n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Dicker 1992	8/35	1/32		100.0	9.19 [1.08, 78.22]
Total (95% CI)	**35**	**32**		**100.0**	**9.19 [1.08, 78.22]**

Total events: 8 (GnRH agonist), 1 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=2.03 p=0.04



Abortus Oranları

Analysis 01.03. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 03 Miscarriage rate per clinically pregnant woman

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

Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

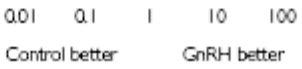
Outcome: 03 Miscarriage rate per clinically pregnant woman

Study	GnRH agonist n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Dicker 1992	4/12	1/2		100.0	0.50 [0.02, 10.25]
Total (95% CI)	**12**	**2**		**100.0**	**0.50 [0.02, 10.25]**

Total events: 4 (GnRH agonist), 1 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.45 p=0.7



Short/Long Protokol

Yeterli sayıda prospektif randomize çalışma yok

Tan et al (1994):

Endometriosisli olgularda short protokol ile long protokol kümülatif gebelik oranları long protokol lehine

%8.3-%50.3

GnRH Antagonistlerinin yeri ?

Pabuçcu 2007

Benschop 2010

Endometriozis grubunda long protokol ve antagonist karşılaştırması

GnRH agonist and antagonist protocols for stage I–II endometriosis and endometrioma in in vitro fertilization/ intracytoplasmic sperm injection cycles

Recai Pabuccu, M.D.,[a] *Gogsen Onalan, M.D.,*[b] *and Cemil Kaya, M.D.*[a]

	Endometriosis stage I–II			Resected endometrioma			Active endometrioma		
	Antagonist (n = 50)	Analogue (n = 48)	*P* value	Antagonist (n = 40)	Analogue (n = 41)	*P* value	Antagonist (n = 34)	Analogue (n = 33)	*P* value
E_2 level on hCG day (pg/mL)	2,452 ± 1,118	2,495 ± 997	NS	1,589.3 ± 1,201	1,844.2 ± 1,126	NS	1,512.2 ± 448	1,968.5 ± 1,211	.02
Total recombinant FSH ampules per cycle (n)	27.4 ± 8.8	28.6 ± 8.7	NS	29.9 ± 8.5	32.1 ± 9.3	NS	28.2 ± 8.7	30.3 ± 8.7	NS
>17 mm follicle number (n)	5.9 ± 1.7	5.4 ± 1.8	NS	3.6 ± 1.8	4.1 ± 1.5	NS	3.5 ± 0.9	5.1 ± 1.9	.0001
Retrieved oocyte (n)	12.1 ± 6.3	13.3 ± 5.9	NS	8.3 ± 4.5	10.4 ± 5.9	NS	6.7 ± 2.6	8.2 ± 5.5	.002
Metaphase II oocyte (n)	8.9 ± 4.4	9.6 ± 4.5	NS	4.3 ± 2.6	8.8 ± 4.6	.0001	4.9 ± 1.6	6.5 ± 4.2	.01
Fertilization rate (%)	73.7 ± 22.7	76.4 ± 18.9	NS	63.9 ± 21.1	71.2 ± 22.4	.001	73.5 ± 23.7	75.6 ± 15.4	NS
No of available embryos	6 ± 4.2	6.6 ± 4.8	NS	2.3 ± 0.8	5.4 ± 4	.001	2.9 ± 1	4.2 ± 2.6	.01
Number of transferred embryos	2.4 ± 0.6	2.3 ± 0.5	NS	2.1 ± 0.6	2.1 ± 0.7	NS	2.5 ± 0.6	2.4 ± 0.8	NS
Clinical pregnancy (%)	30 (15/50)	31.2 (15/48)	NS	27.5 (11/40)	39 (16/41)	NS	20.5 (7/34)	24.2 (8/33)	NS
Abortion rate (%)	4 (2/50)	2 (1/48)	NS	2.5 (1/40)	2.4 (1/41)	NS	2.9 (1/34)	3 (1/33)	NS
Implantation rate (%)	15.4	18.2	NS	15.9	22.6	NS	12.5	14.8	NS

Pabuccu. Fertil Steril 2007.

GnRH agonist and antagonist protocols for stage I–II endometriosis and endometrioma in in vitro fertilization/ intracytoplasmic sperm injection cycles

Recai Pabuccu, M.D.,[a] *Gogsen Onalan, M.D.,*[b] *and Cemil Kaya, M.D.*[a]

TABLE 3

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

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

Note: BMI = body mass index.

$P < .05$, statistically significant differences between GnRH analogue and antagonist groups.

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

Use of oral contraceptives in women with endometriosis before assisted reproduction treatment improves outcomes

In women with endometriosis, including those with endometriomas, 6 to 8 weeks of continuous use of oral contraception (OC) before assisted reproduction treatment (ART) maintains ART outcomes comparable with the outcomes of age-matched controls without endometriosis. In contrast, ART outcomes are markedly compromised in endometriosis patients who are not pretreated with OC. Ovarian responsiveness to stimulation was not altered by 6 to 8 weeks' use of pre-ART OC, including in poor responders with endometriomas. (Fertil Steril® 2010;94: 2796–9. ©2010 by American Society for Reproductive Medicine.)

	Group 1				Group 2			
		Endometriosis				Endometriosis		
	Controls	I–II	III–IV	OMA	Controls	I–II	III–IV	OMA
Clinical PR								
<37 y	42.0	55.0	39.6	40.9	39.7	29.7	23.8	12.0
>38 y	16.7	28.6	33.3	50.0	18.5	8.0	10.0	16.7
Total	35.0	48.1	37.9	41.4	32.5[a]	23.6	21.2	12.9[b]

E.Ü. YÜT-Endometriozis

Endometriozis vakası:119

36 vaka endometrioma

22 vaka opere endometrioma

48 vaka endometriozis

13 vaka rekürren endometriozis

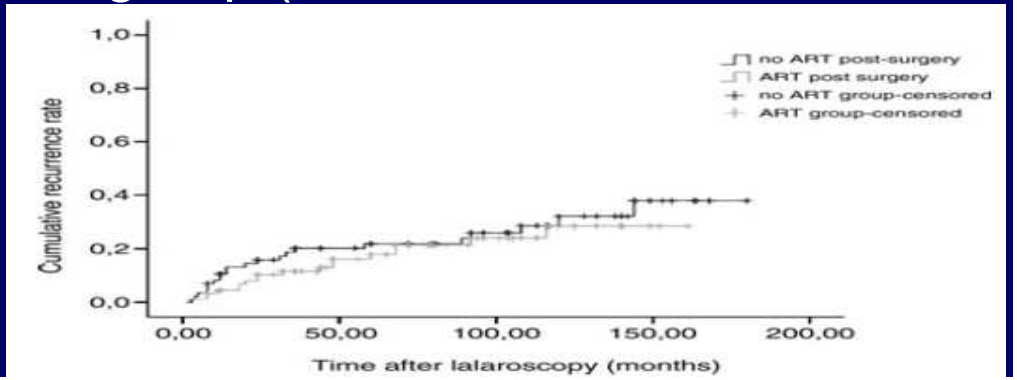
Kontrol grubu:128 idiopatik infertil

	Endometriozis grubu(n:119)	Kontrol grubu (n:128)	P değeri
Yaş	31,8±4,6	31,2±5,0	0,26
İnfertilite süresi	6,7±4,1	7,9±4,7	0,41
Basal FSH	7,9±3,7	6,6±3,2	0,03*
Basal E2	44,5±18,5	46,2±18,1	0,48
Uygulanan protokol	%16 long/%84 anta	%24long/%76anta	0,11
Toplam FSH dozu	2423±735	2258±676	0,06
İndüksiyon süresi	7,5±1,5	7,6±1,6	0,88
Max E2	1302±856	1481±851	0,10
OPU'da follikül sayısı	8,2±6,3	10,7±7,8	0,005*
MII oosit sayısı	6,7±5,2	8,3±5,8	0,02*
Fertilize olan oosit	2,3±2,4	2,0±1,7	0,66
Transfere giden hasta oranı	%89,9(107)	%92,9(119)	0,49
Transfer edilen embriyo sayısı	1,5±0,7	1,6±0,7	O,78
Gebelik oranı(transfer başına)	50/107(%46,7)	62/119%52,1)	0,5
Canlı doğum oranı	43/107(%40,1)	49/120(%40,8)	0,11

	Long prot grubu(n:119)	Antagonist grubu (n:100)	P değeri
Yaş	28,8±4,7	32,4±4,3	0,002*
İnfertilite süresi	6,0±3,4	6,8±4,2	0,44
Basal FSH	6,0±4,6	8,3±3,4	0,01*
Basal E2	36,2±15,8	45,9±18,7	0,04*
Toplam FSH dozu	2556±722	2398±738	0,39
İndüksiyon süresi	9,0±1,7	7,3±1,2	0,000*
Max E2	1691±958	1227±820	0,03*
Opuda follikül sayısı	10,2±5,9	7,8±6,3	0,12
MII oosit sayısı	7,8±4,3	6,5±5,4	0,30
Fertilize olan oosit	3,8±3,5	2,0±2,0	0,14
Transfere giden hasta oranı	18/19(%94,7)	89/100(%89)	0,68
Transfer edilen embriyo sayısı	1,6±0,7	1,5±0,7	0,88
Gebelik oranı(transfer başına)	9/18(%50)	41/89(%46,1)	0,48
Canlı doğum oranı	8/18(%44,4)	35/89(%39,3)	0,49

Does Controlled Ovarian Hyperstimulation in Women with a History of Endometriosis Influence Recurrence Rate?

- Retrospective cohort study of 592 patients submitted to laparoscopy for endometriosis, 177 with infertility-related endometriosis who underwent a periodic ultrasound follow-up after laparoscopy were selected.
- Women who started ART after laparoscopy (n90) were compared with the control group, who did not undergo ART (n87).
- Recurrence of endometriosis was defined as the presence of endometriotic lesions observed through TV-US.
- During a long-term TV-US follow-up (1–15 years), 40 (22.6%) recurrences were observed.
- Patients submitted to ART showed a cumulative recurrence rate similar to that of the control group (28.6% and 37.9% respectively, p0.471).

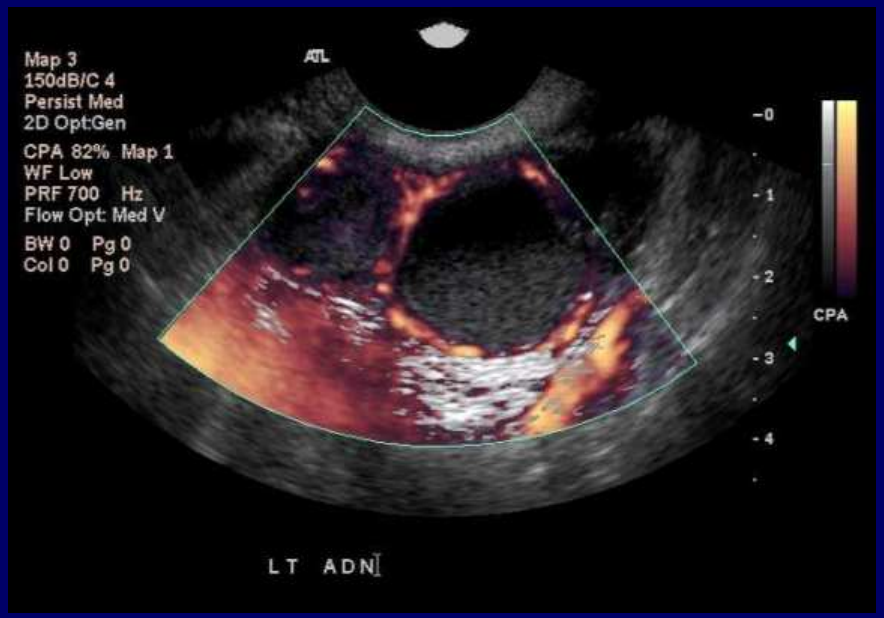


Maria Elisabetta Coccia, 2010

Endometriosisli Olgularda IVF'de Komplikasyon

Özellikle ovaryan endometriomalı olgularda over apsesi en korkulan komplikasyondur.

Endometriozisi olmayanlarda %0.2, endometriozisi olanlarda %2.3 görülür.



Evre I-II endometriosis
«ART öncesi cerrahi»

- **Orta kalitede veri mevcut- retrospektif kohort çalışma**
- **399 hasta ⇒ L/S eksizyon**
- **262 hasta ⇒ Tanısal L/S**
- **L/S eksizyon ile artmış gebelik, canlı doğum ve implantasyon oranları**

Opøien HK, Reprod Biomed Online, 2011

Endometrioma
«ART öncesi cerrahi, endometrioam >3cm»

- **Kistektomi ile artmış gebelik oranlarına dair veri yok**
- **Endometriosis ile ilişkili ağrıyı azaltmak ve foliküller ulaşımı kolaylaştırmak için L/S cerrahi önerilebilir**
- **Daha yüksek spontan gebelik oranları ve daha az rekürens riski nedeni ile cerrahi planlanır ise kistektomi, drenaj ve elektrokogulasyona tercih edilebilir**
- **Endometrioma cerrahisinde over rezervinin azalacağı mutlaka değerlendirilmeli**

Benschop, Cochrane Database Syst Rev 2010:CD008571.
Hart, Cochrane Database Syst Rev 2008

Derin Endometriosis
«ART öncesi cerrahi»

- **Yeteri veri yok**
- **Bu hastalarda şiddetli ağrı yakınması dikkate alınmalı**

Papaleo , Acta Obstet Gynecol Scand 2011
Bianchi PH, J Minim Invasive Gynecol 2009

ESHRE guideline: management of women with endometriosis†

Human Reproduction, Vol.29, No.3 pp. 400–412, 2014

Is MAR effective for infertility associated with endometriosis?

Intrauterine insemination. In a RCT, the live birth rate was found to be 5.6 times higher (95% confidence interval (CI) 1.18–17.4) in couples with minimal to mild endometriosis after controlled ovarian stimulation with gonadotrophins and IUIcompared with couples after expectant management (Tummon *et al.*, 1997). A longitudinal study showed a 5.1 times higher pregnancy rate (95% CI 1.1–22.5) in couples receiving Intrauterine insemination (IUI) after controlled ovarian stimulation with gonadotrophins compared with IUI alone. (Nulsen *et al.*, 1993).

ART. The influence of endometriosis on the success rate of IVF/ICSI is not unequivocal. The pregnancy rates after IVF/ICSI were reported to be lower in patients with Stage III and IV endometriosis as compared with those with tubal factor (Bamhart *et al.*, 2002). It has to be noted however, that some large databases show that endometriosis does not adversely affect pregnancy rates [e.g. the Society for Assisted Reproductive Technology (SART) and the Human Fertilisation and Embryology Authority (HFEA)]. GnRH antagonist protocol may be not inferior to GnRH agonist protocol in women with minimal to mild endometriosis and endometrioma (Pabuccu *et al.*, 2007).

Are medical therapies effective as an adjunct to treatment with ART for endometriosis-associated infertility?

In a Cochrane review on the effect of hormonal treatment prior to MAR, the authors conclude that down-regulation for 3–6 months with a GnRH agonist in women with endometriosis increases the odds of clinical pregnancy by >4-fold (Sallam *et al.*, 2006). Potential adverse effects of the intervention (miscarriage rates, multiple pregnancy rates or ectopic pregnancy rates) were not addressed in the included studies.

Should surgery be performed prior to treatment with ART to improve reproductive outcomes?

One retrospective cohort study compared reproductive outcomes in a group of women with minimal to mild endometriosis in whom all visible endometriosis was completely removed using laparoscopy prior to ART to women undergoing diagnostic laparoscopy only and found a significantly higher implantation rate, pregnancy rate and live birth rate in the treated group (Opoien *et al.*, 2011). However, this does not imply that a laparascopy should be performed prior to ART in all women with the only aim to diagnose and subsequently treat peritoneal endometriosis in order to improve the result of the ART treatment.

Several studies have evaluated the usefulness of cystectomy prior to ART to improve reproductive outcome in women with ovarian endometrioma, but there is limited consistency in the interpretation of the results (Donnez *et al.*, 2001; Hart *et al.*, 2008; Benschop *et al.*, 2010). Based on no difference in pregnancy rate, some authors advise cystectomy, whereas others advise caution with surgery because of the possible harmful effect on ovarian reserve.

For infertile women with deep endometriosis, we found no evidence to recommend performing surgical excision of deep nodular lesions prior to ART to improve reproductive outcomes (Bianchi *et al.*, 2009; Papaleo *et al.*, 2011). However, these women often suffer from pain, requesting surgical treatment.

Sonuç

Endometriosis:

- **IVF endometriosisin olumsuz etkilerini tam olarak engelleyemez ve düzeltemez**
- **Endokrin veya ovulatuar disfonksiyon ve OCCC'nin tuba tarafından yakalanamaması YÜT ile telafi edilebilir**
- **Endometriosise bağlı toksik etkiler embryoların dejenerasyonuna ve daha düşük implantasyon oranlarına yol açabilir**
- **Tekrarlayan IVF başarısızlıklarında endometriosis var ise cerrahi düşünülebilir**

Sonuç

- Endometriozis oosit sayısını ve fertilizasyon oranlarını azaltabilir
- Stage'in artması gebelik oranlarını azaltır

Sonuç

- IVF öncesi uzun süreli (3-6 ay) GnRH-a supresyonu gebelik oranlarını ⬆
- GnRH-a ile uzun protokol en iyi gebelik sonuçları elde edilir
- Endometriomaların çıkartılması tartışmalı
- IVF ilk tedavi seçeneği olabilir ?

Sonuç

- Endometriomalı hastalarda ART öncesi izlenecek, üzerinde konsensus sağlanmış bir tedavi protokolü yoktur. Optimum algoritmik yaklaşım her merkeze göre farklılık göstermektedir.
- ART öncesi tedavi protokolü hastanın özelliğine göre tercih edilmelidir.
- Endometrioziste seçilebilecek özel bir ovarian hiperstimülasyon protokolü bulunmamaktadır.Uygun ise GnRH agonistleri ile uzun down regülasyon protokolleri tercih edilmelidir.

Sonuç

Endometriosis ve infertilite tahmin edebildiğimizden çok daha bilinmeyeni olan bir klinik problem olarak karşımıza çıkmaktadır. Hastalığın immunolojik yönünü ve tedavi imkanlarına yönelik çalışmaların yapılması gereklidir.

Endometriosis - Sonuç:

- Bir IVF siklusu ile elde edilen gebelik oranı, 6 siklus COH-IUI siklusunun kümülatif gebelik oranından daha yüksektir (yaş ve hastalık evresinden bağımsız olarak),
- 3-4 siklus sonrası COH-IUI'ın etkinliği plato yapmaktadır,
- COH-IUI daha ziyade erken evre hastalıkta ve < 38 yaşta faydalıdır.

Endometriosis - Sonuç:

- IVF'in 'first line' tedavi olduğu durumlar:
  - > 38 yaş
  - Stage III-IV hastalık
  - İleri tubo-peritoneal faktör
  - Ağır androlojik faktör

YÜT uygulanan endometriosisli olgularda implantasyon ve gebelik oranlarını olumsuz etkilen faktörler

Oocyt kalitesinin bozulması (Hull et al, 1998; Norenstedt et al, 2001)

İmplantasyon yeteneği azalmış düşük kaliteli embryoların mevcudiyeti (Simon et al, 1994; Arici et al, 1996)

Oocyt kalitesini olumsuz etkileyen faktörler

- Folliküler sıvı progesteron düzeylerinin yüksek oluşu (Pellicer et al, 1998)
- Folliküler sıvı IL-6 düzeylerinin yüksek oluşu (Pellicer et al, 1998)
- Folliküler sıvı kortizol düzeylerinin düşük oluşu (Smith et al, 2002)
- Folliküler sıvı IGFBP-1 düzeylerinin düşük oluşu (Cunha-Filho et al, 2003)

Oocyt kalitesini olumsuz etkileyen faktörler

- Kültüre edilmiş granuloza hücrelerinde TNF-α nın artmış (Carlberg et al, 2000)

- Serum ve peritoneal sıvıdaki solubl Fas ligand düzeylerinin artması sonucunda granuloza hücrelerinin apopitosis oranında artış (Garcia-Velasco et al, 2002)

Endometriomalar YÜT öncesi tedavi edilmeli midir?

- A.Her zaman önce tıbbi
- B.Her zaman önce cerrahi
- C.Ön tedavi gerekmez
- D.Bazı durumlarda tedavi edilmelidir

Evre I-II Endometriosis
«ART - Endikasyonlar»

- Bozulmuş tubal faktör
- Erkek faktör varlığı
- Diğer tedavilerde başarısızlık
- GnRHa ile GnRHant benzer başarı oranlarına sahip

gkg, 1996

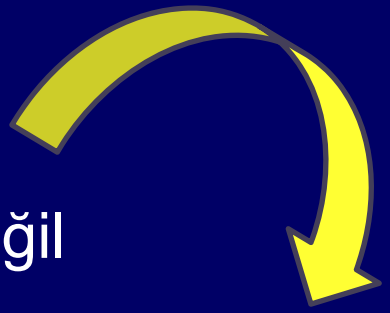
Evre I-II Endometriosis
«KOH riskleri»

- **KOH endometriosis progresyonuna neden olmaz**
- **Endometrioma varlığından OPU sırasında antibiyotik profaksisi ile abse formasyonu önlenebilir**

Benaglia, Fertil Steril, 2008
Benaglia, Hum Reprod, 2001

Endometriosis - ART
«Preoperatif Medikal Tedaviler»

- IVF öncesi 3-6 ay GnRHa kullanımı gebelik oranlarını arttırabilir
  - Çalışma sayısı az
  - Hasta sayısı az
  - Çalışmaların kalitesi iyi değil



- Oosit kalitesi
- Endometrial reseptivite

Sallam H, Cochrane Database Syst Rev 2006:CD004635

Endometriosis / daha öne opere olan hastalar

- IVF-ET daha akla yatkın bir seçenek

Kemmann, Int J Fertil Menopausal Stud 1993