PKOS, IVF & GnRH Analog Trigger

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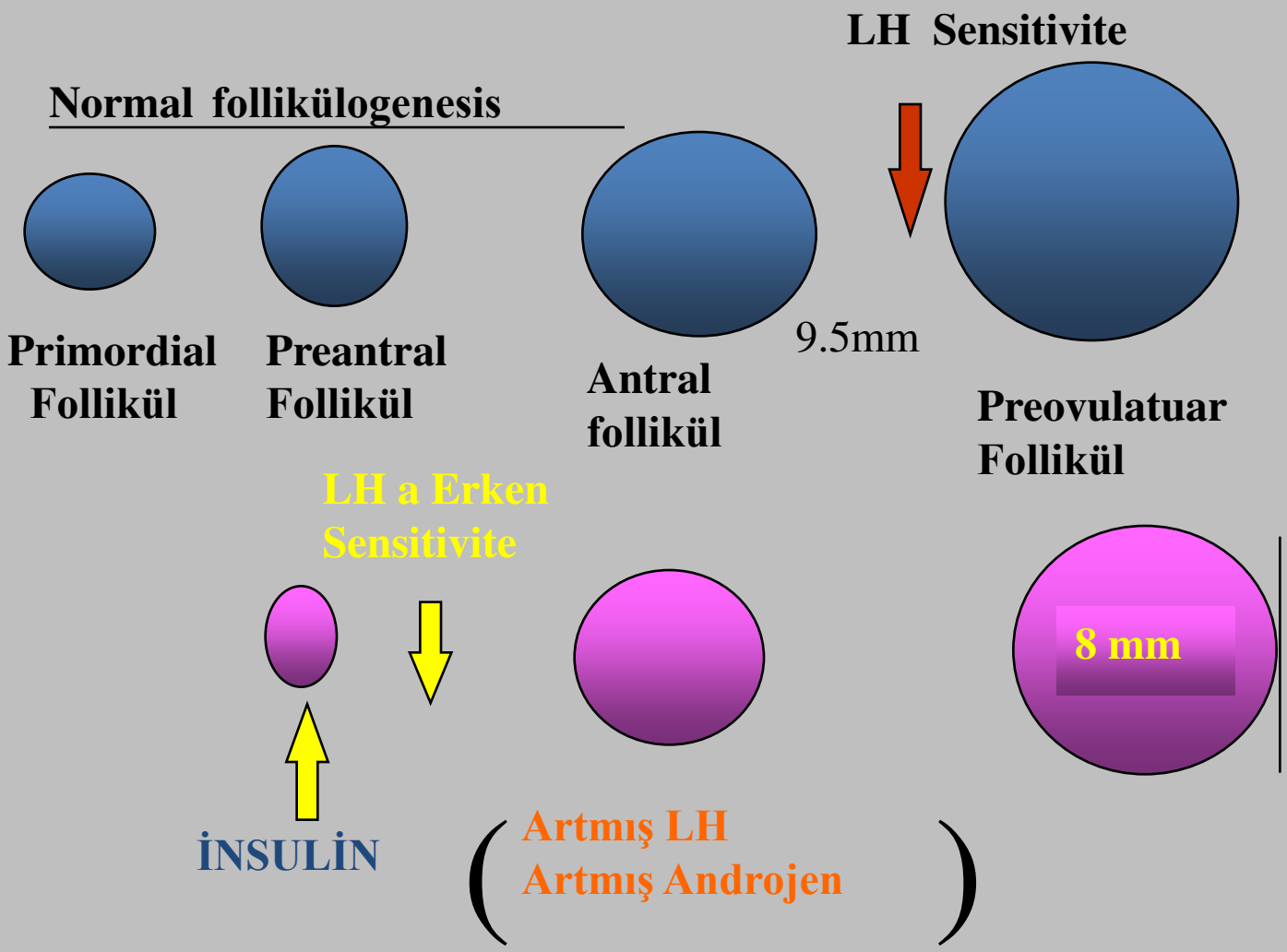
Kadın Hastalıkları ve Doğum Anabilim Dalı

Anovulasyon Mekanizmaları



- ***Rölatif FSH yetmezliği***
- ***Artmış LH***
- ***Artmış İnsülin***
- ***Artmış androjen***
- ***İnhibin B, IGF, AMH'daki değişiklikler***

Follikül Gelişiminde Arrest

Franks S, 2005

Anovulasyon mekanizmaları

LH /FSH ↑

GnRH pulse frekansı ↑

→

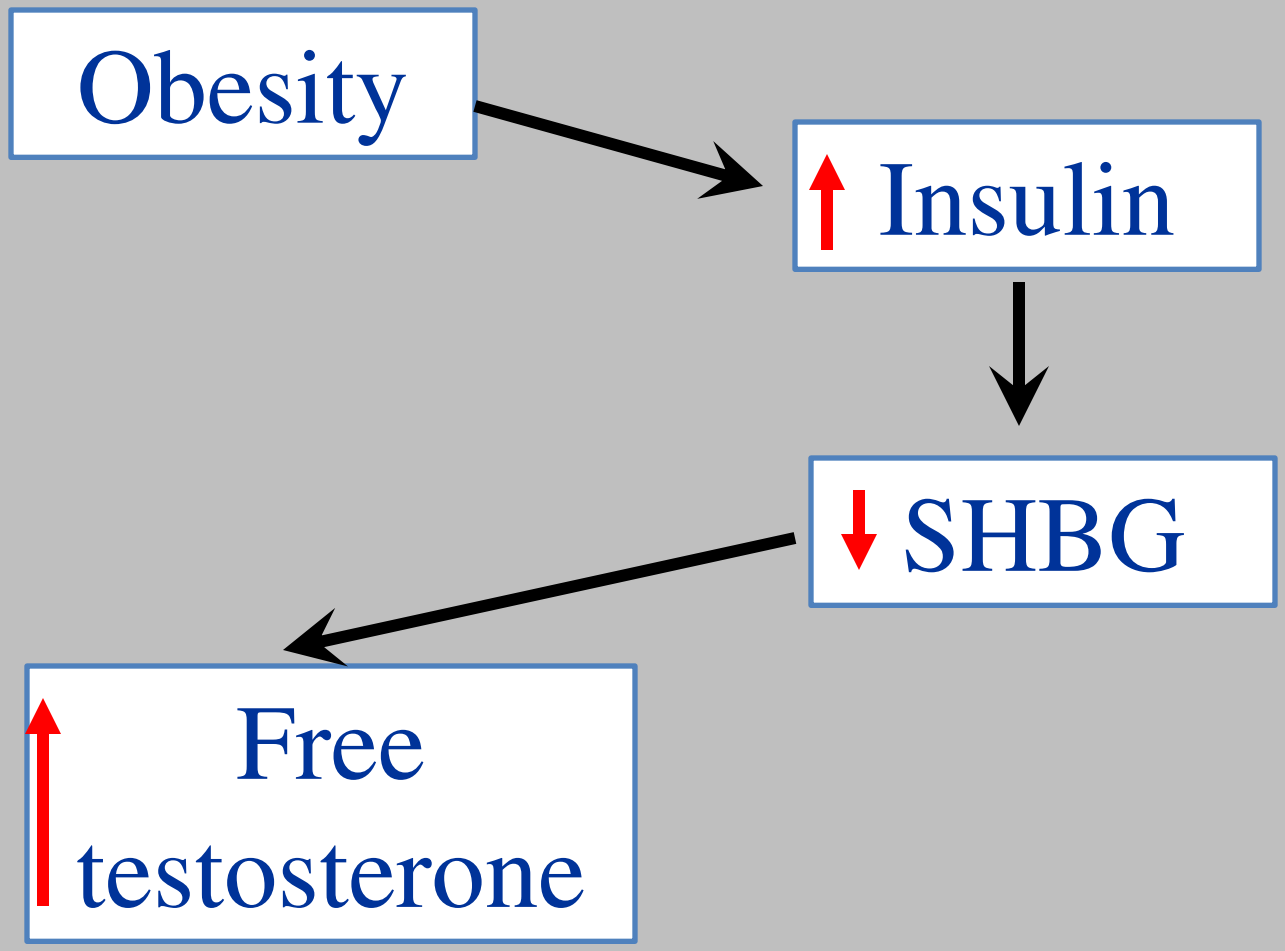
- LH pulse frekansı ↑
- FSH pulse frekansı değişmez

Hipofizer GnRH sensitivitesinde artış

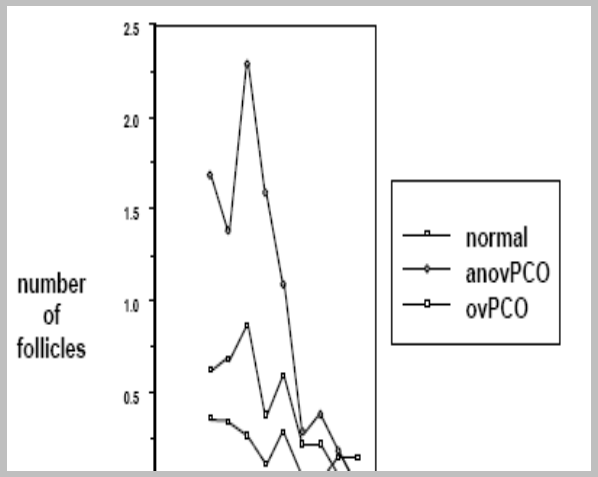
↗

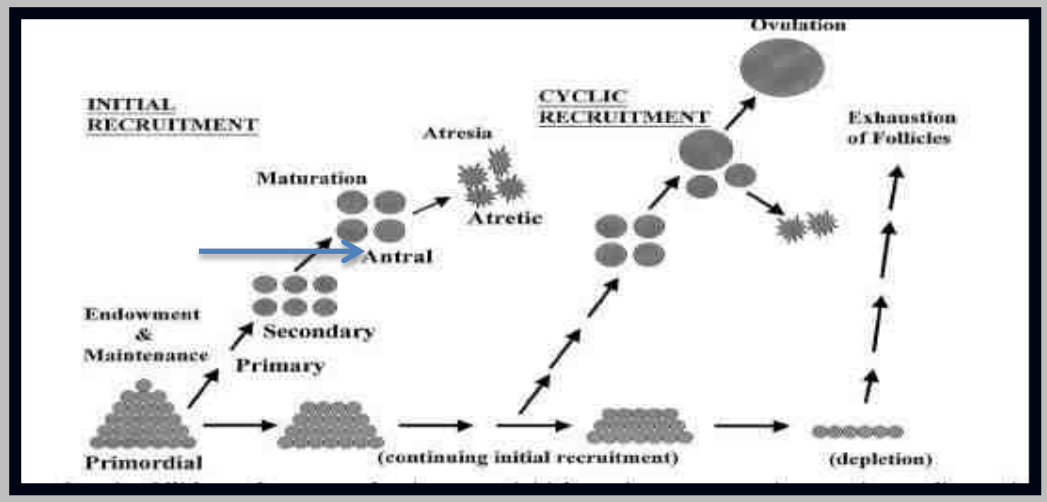
(Franks, 2005)

Obezite



PCOS Farklıdır..





Normal overe göre preantral folikül sayısı x6 kat fazladır

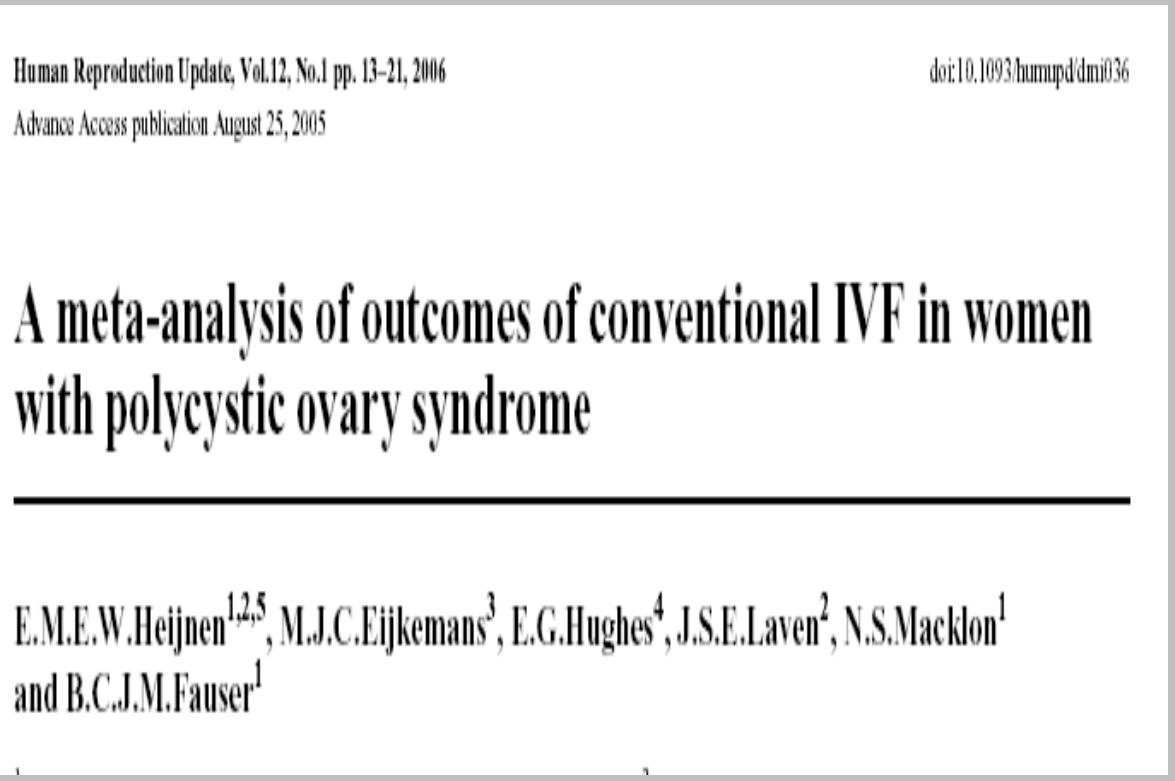
Folliküler gelişimde arrest olmuş geniş folikül havuzu, ekzojen gonadotropine cevap verme yetisindedir

Webber et al 2003

PCOS: Neden Farklı?

- Artmış Gonadotropin Sekresyonu
  - Yüksek LH düzeyleri
  - Artmış LH reseptör cevabı
  - LH βsubunit Genetik varyantları
- İnsülin Rezistansı (%50-70)
  - Artmış Teka hücre cevabı
- Obezite (yaklaşık %60)
- Artmış Androjen Üretimi
- Hiperprolaktinemi
- Tiroid gland anomalileri ?

PCOS Farklıdır
Fertilite Sonuçları Kötüdür



Human Reproduction Update, Vol.12, No.1 pp. 13–21, 2006 doi:10.1093/humupd/dmi036
Advance Access publication August 25, 2005

A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome

E.M.E.W.Heijnen[1,2,5], M.J.C.Eijkemans[3], E.G.Hughes[4], J.S.E.Laven[2], N.S.Macklon[1] and B.C.J.M.Fauser[1]

- Siklus iptal oranları fazla
- Stimulasyon süresi uzun
- Oosit sayısı fazla
- Fertilizasyon düşük
- Klinik gebelik oranları benzer
- Canlı doğum oranları benzer
- OHSS — data yeterli bulunmamış

Heijnen, **Human reproduction update** 2006

doi:10.1093/humrep/der182

ORIGINAL ARTICLE *Infertility*

Anti-Müllerian hormone-tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF

A.P. Yates[1,*], O. Rustamov[2], S.A. Roberts[3], H.Y.
[illegible], A. Smith[1], and Update Advance Access publi

Vol.0, No.0 pp. 1–16, 2014

reproduction update

The physiology and clinical utility of anti-Müllerian hormone in women

Didier Dewailly[1,*], Claus Yding Andersen[2], Adam Balen[3], Frank Broekmans[4], Nafi Dilaver[5], Renato Fanchin[6], Georg Griesinger[7], Tom W. Kelsey[8], Antonio La Marca[9], Cornelius Lambalk[10], Helen Mason[5], Scott M. Nelson[11], Jenny A. Visser[12], W. Hamish Wallace[13], and Richard A. Anderson[14]

[1]Department of Endocrine Gynaecology and Reproductive Medicine, Hôpital Jeanne de Flandre, Centre Hospitalier de Lille, Université Lille 2, Lille, France [2]Laboratory of Reproductive Biology, Children and Reproduction, University Hospital of Copenhagen, University of Copenhagen, Copenhagen, Denmark [3]The Leeds Centre for Reproductive Medicine, Leeds Teaching Hospitals, Leeds LS14 6UH, UK [4]Department of Reproductive Medicine and Gynecology, University Medical Centre Utrecht, Utrecht 3584 CX, The Netherlands [5]St. George's, University of London, London SW17 0RE, UK [6]Department of Obstetrics Gynecology and Reproductive Medicine, Hospital A. Béclère, University P Sud, F-92141 Clamart, France [7]Department of Reproductive Medicine and Gynecologic Endocrinology, University Clinic of Schlesw Luebeck, Germany [8]School of Computer Science, University of St Andrews, St Andrews KY16 9SX, UK [9]Mother-Infant Dep University of Modena and Reggio Emilia, 41100 Modena, Italy [10]Division of Reproductive Medicine, Departement of Obs Gynaecology, VU University Medical Center, Amsterdam, The Netherlands [11]Muirhead Chair in Obstetrics & Glasgow G11 6NT, UK [12]Department of Internal Medicine, Erasmus MC, Rotterdam, The Children, 17 Millerfield Place, Edinburgh EH9 1LF [14]MRC Centre for

Reproductive BioMedicine Online; www.rbmonline.com/Ar

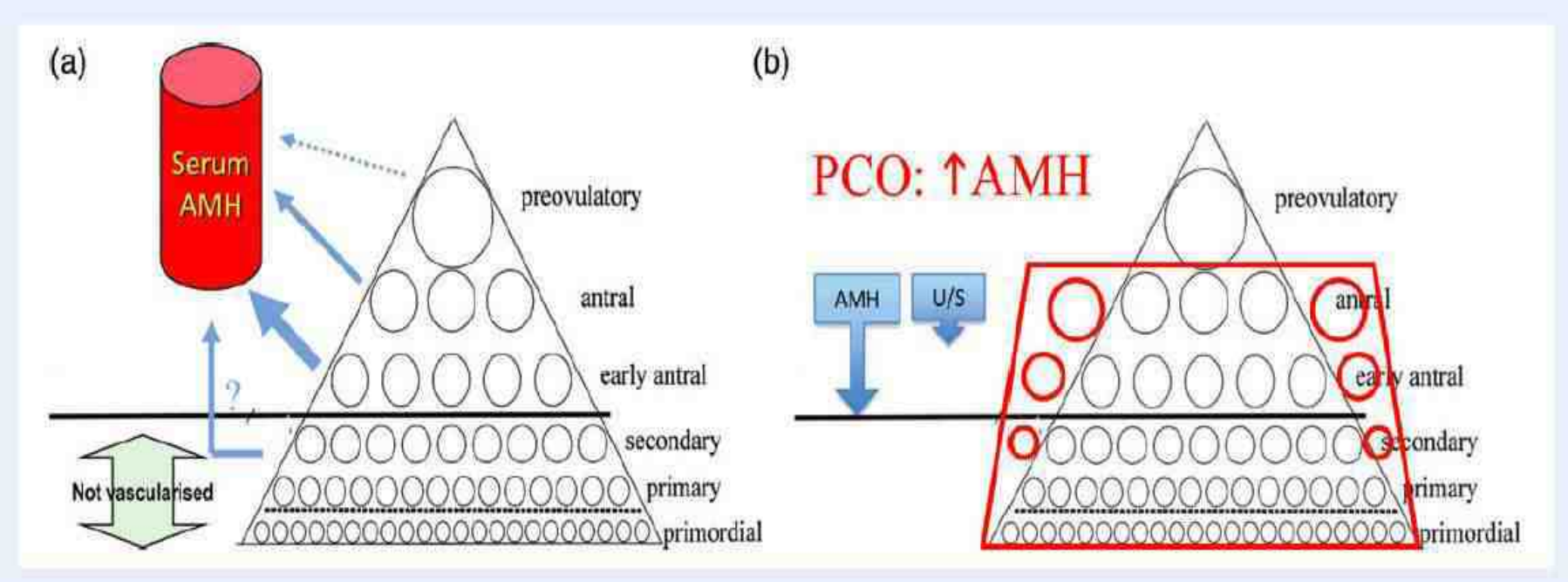
PCOS-AMH
Yeni Ufuklar..

Article

Follicular-fluid anti-Mullerian hormone concentrations are predictive of assisted reproduction outcome in PCOS patients

Dr Recai Pabuccu obtained his medical degree in 1975 from Istanbul University Faculty of Medicine, Turkey. After he completed his obstetrics and gynaecology residency, he worked as a clinical fellow in Reproductive Endocrinology and Infertility at the University of British Colombia, Canada. He has published more than forty articles in the field of assist reproductive technologies and reproductive surgery. Professor Pabuccu is Director Department of Obstetrics and Gynecology, Ufuk University, Faculty of Medicine

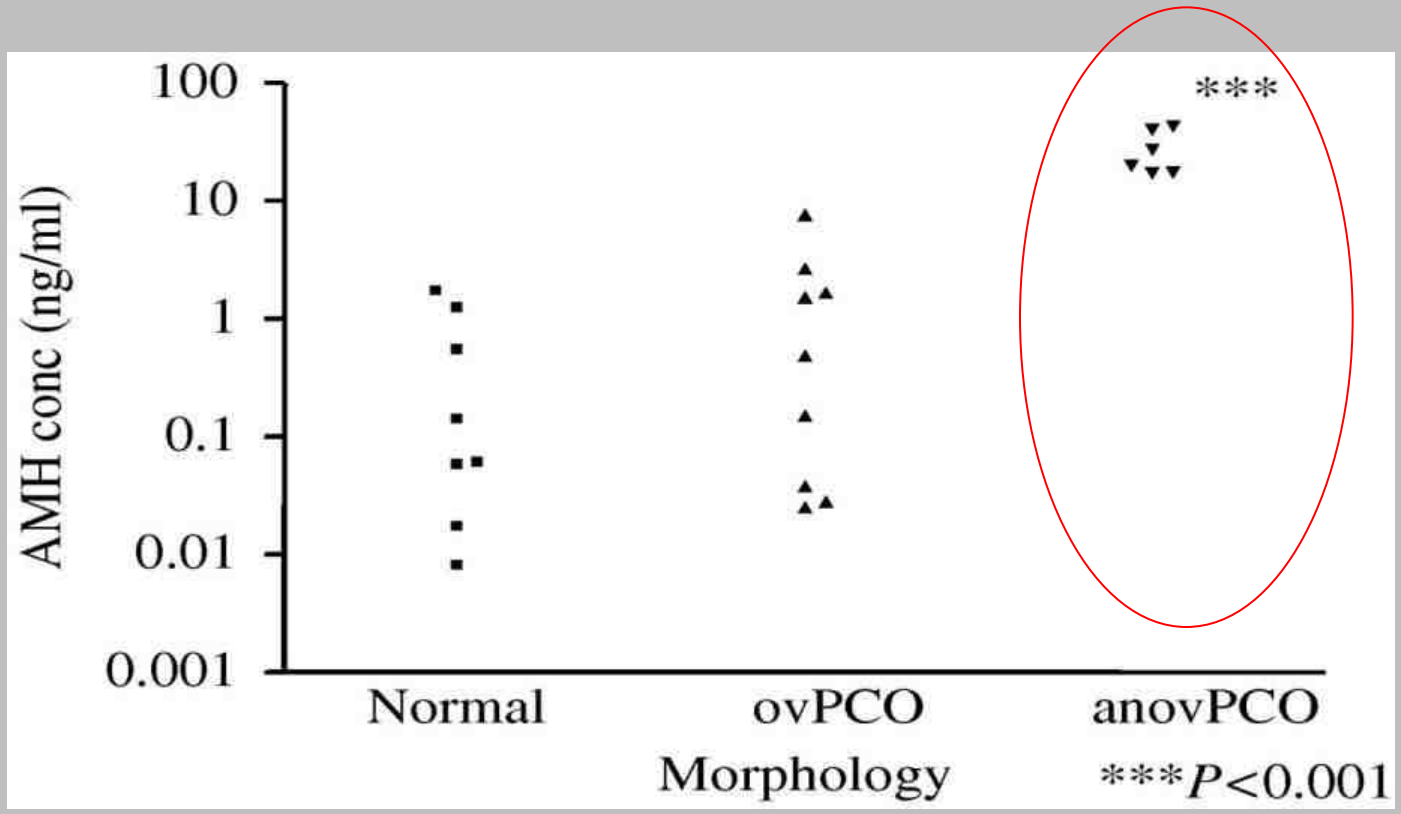
PCOS-AMH



Dolaşımdaki AMH miktarı, normal gruba göre 2-4 kat daha FAZLADIR…

Pigny et al., 2003; Laven et al., 2004; Park et al., 2010; Lie Fong et al., 2011

AMH Konsantrasyonu: PCOS



Anovulatuar PCOS olguları x75 kat fazla

Reproduction. 2010 May;139(5):825-833

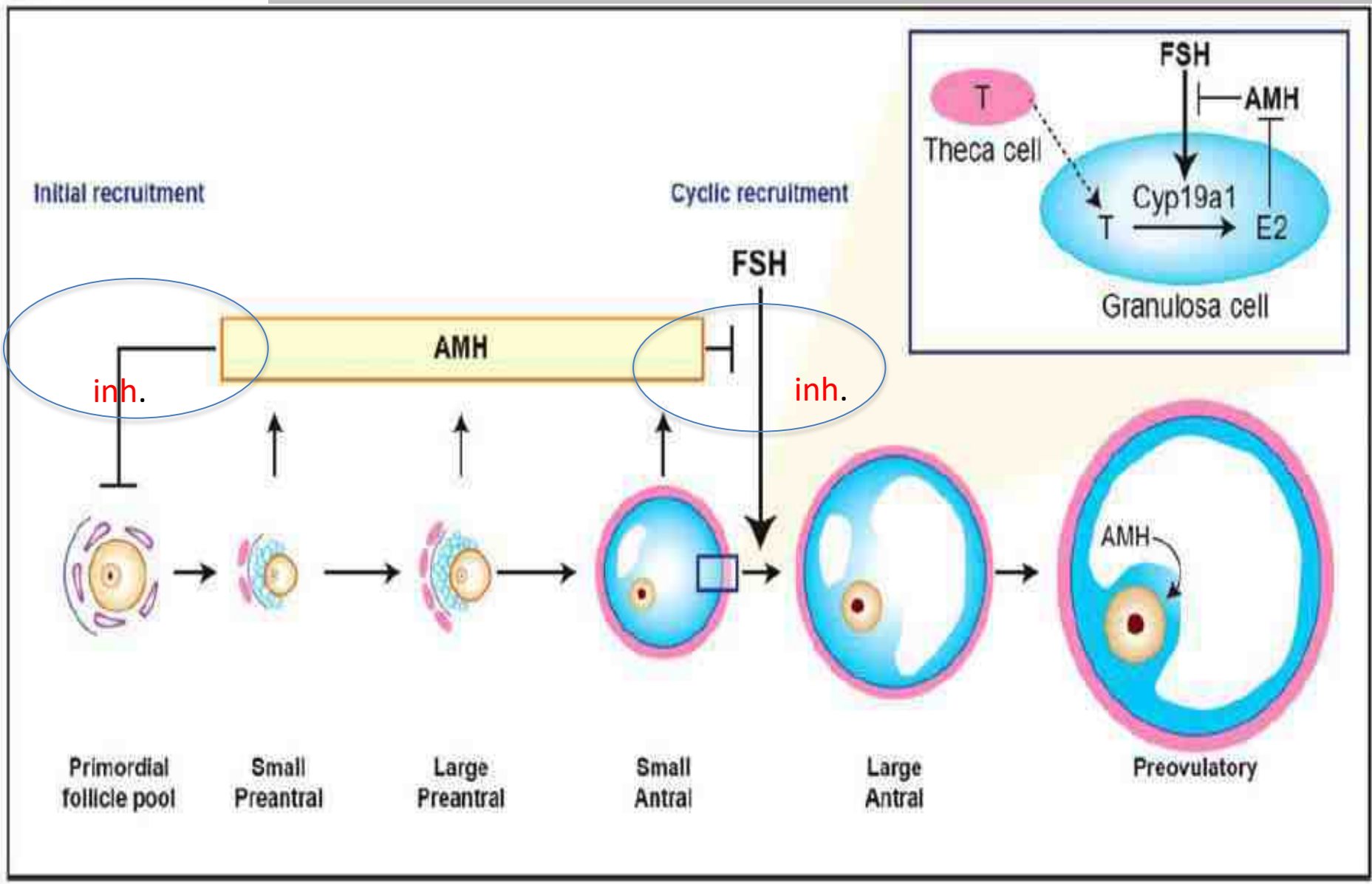
The role of AMH in anovulation associated with PCOS: a hypothesis

Anti-Müllerian hormone reduces follicle sensitivity to follicle-stimulating hormone in human granulosa cells

- Granüloza hücrelerindeki FSH-LH bağımlı aromataz ekspresyonunu azaltır
- Sonuçta; estradiol üretiminde belirgin azalma meydana gelir
- Anovulasyon sürecine ve İNFERTİLİTEYE katkıda bulunur

Pellat et al; Fertil Steril 2011;96:1246–1251 e1241.
Homburg et al 2014

Important


FSH
T
AMH
Theca cell
Cyp19a1
T
E2
Granulosa cell
Initial recruitment
Cyclic recruitment
FSH
AMH
inh.
inh.
AMH
Primordial follicle pool
Small Preantral
Large Preantral
Small Antral
Large Antral
Preovulatory

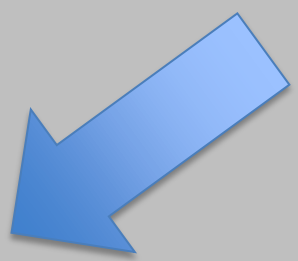
Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

- 1.basamak: **klomifen**
- 2.basamak: **gonadotropin veya LOD**

3.basamak: **COH-IVF**

PCOS



Ovulasyon indüksyonu

- Yaşam tarzı
- Oral ajanlar
- Gonadotropinler
- LOD

COH/IVF

PCOS

Ovulasyon indüksyonu

- Yaşam tarzı
- Oral ajanlar
- Gonadotropinler
- LOD

COH/IVF

- Başarısız OI
- Tubal patoloji varlığı
- Evre 3-4 endometriozis
- Preimplantasyon Genetik Tanı Gerekliliği
- İleri erkek faktörü infertilitesi
- İleri kadın yaşı (>39)

PCOS-COH/IVF

- **Aşırı cevap-OHSS**

- **Düşük fertilizasyon oranları**
- **Fazla sayıda immatür oosit**
- **Düşük klivaj oranları**
- **Düşük implantasyon oranları**
- **Yüksek abortus oranları**

Heijnen, **Human reproduction update** 2006

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

Modifiye Protokoller

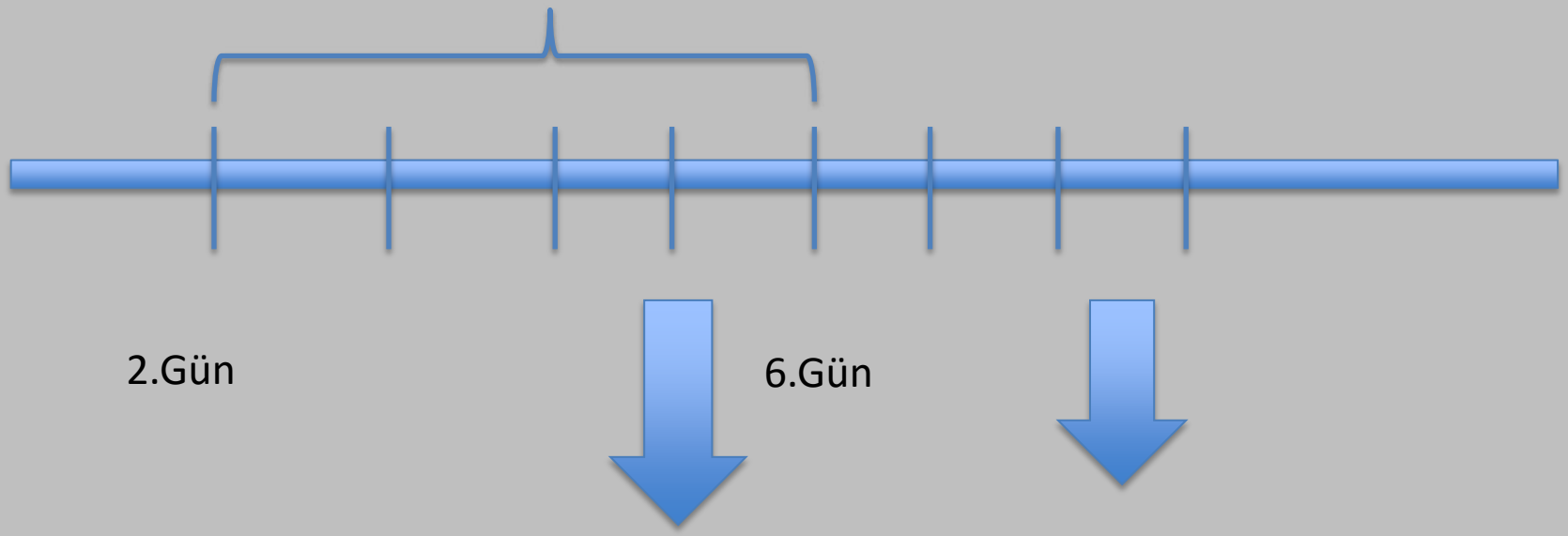
- GnRH antagonist sikluslarda GnRH agonist ile ovulasyon tetikleme
- Metformin kullanımı
- IVM
- Embryo freezing

Minimal-Mild Stimulasyon

- AMAÇ: düşük doz FSH, hMG ile oral ajanların GnRH antagonisti ile birlikte kullanımı ile 2-7 oosit elde etmek (ISMAAR Consensus)
- Düşük doz FSH/hMG (siklusun 5.gününden sonra)+GnRH-antagonist
- Klomifen sitrat tedavisini takiben düşük doz FSH (150 IU)+GnRH-antagonist
- Letrozole+düşük doz FSH+GnRH-antagonist

De Jong et al 2000; Williams SC et al 2002

Clomiphene 50 mg 2x1



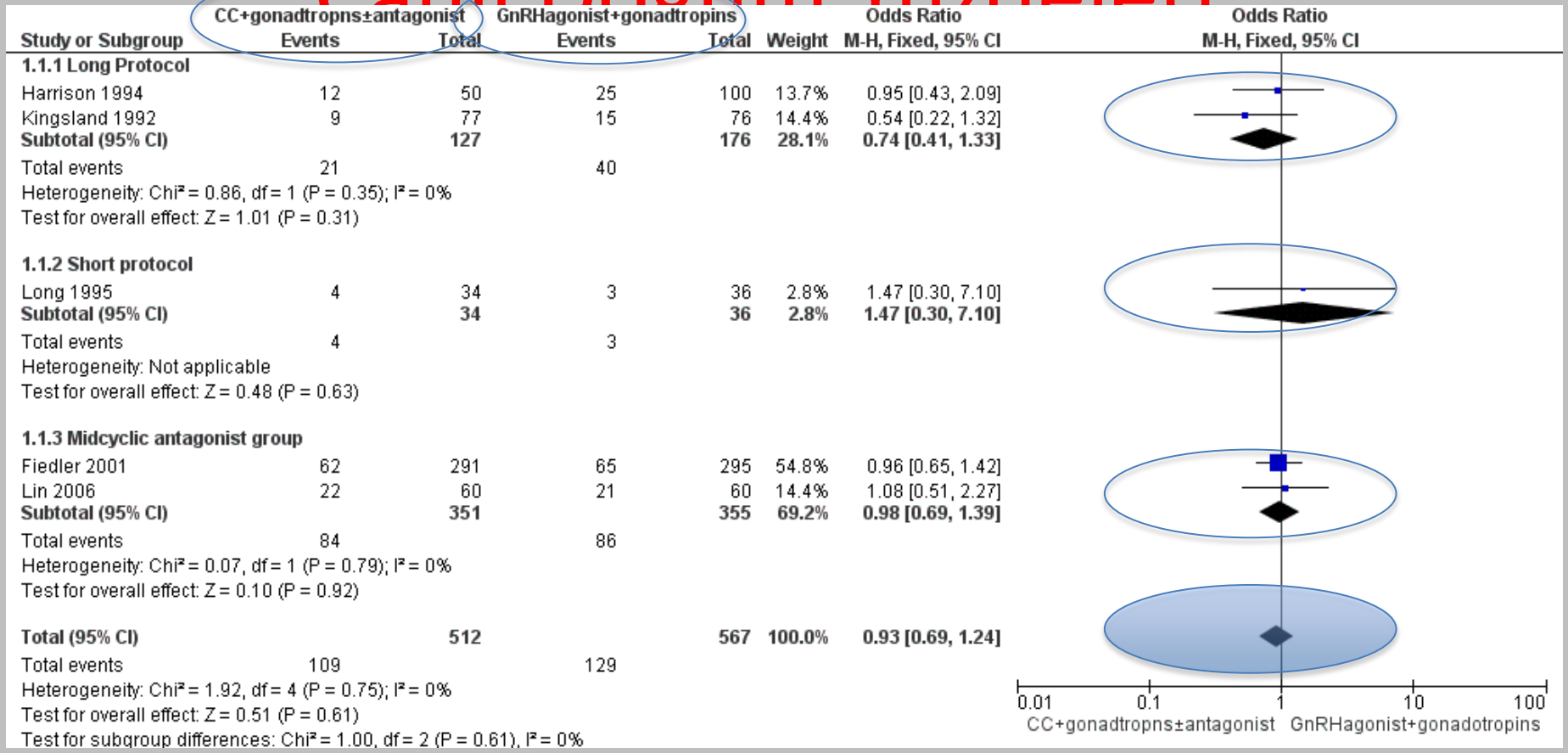
5. Gün 187,5-225 IU gonadotropin

7 veya 8. gün kontrol

Centrum Klinik Protokolü

Minimal-Mild Stimulasyon Sonuçlar

Canlı Doğum Yüzdeleri

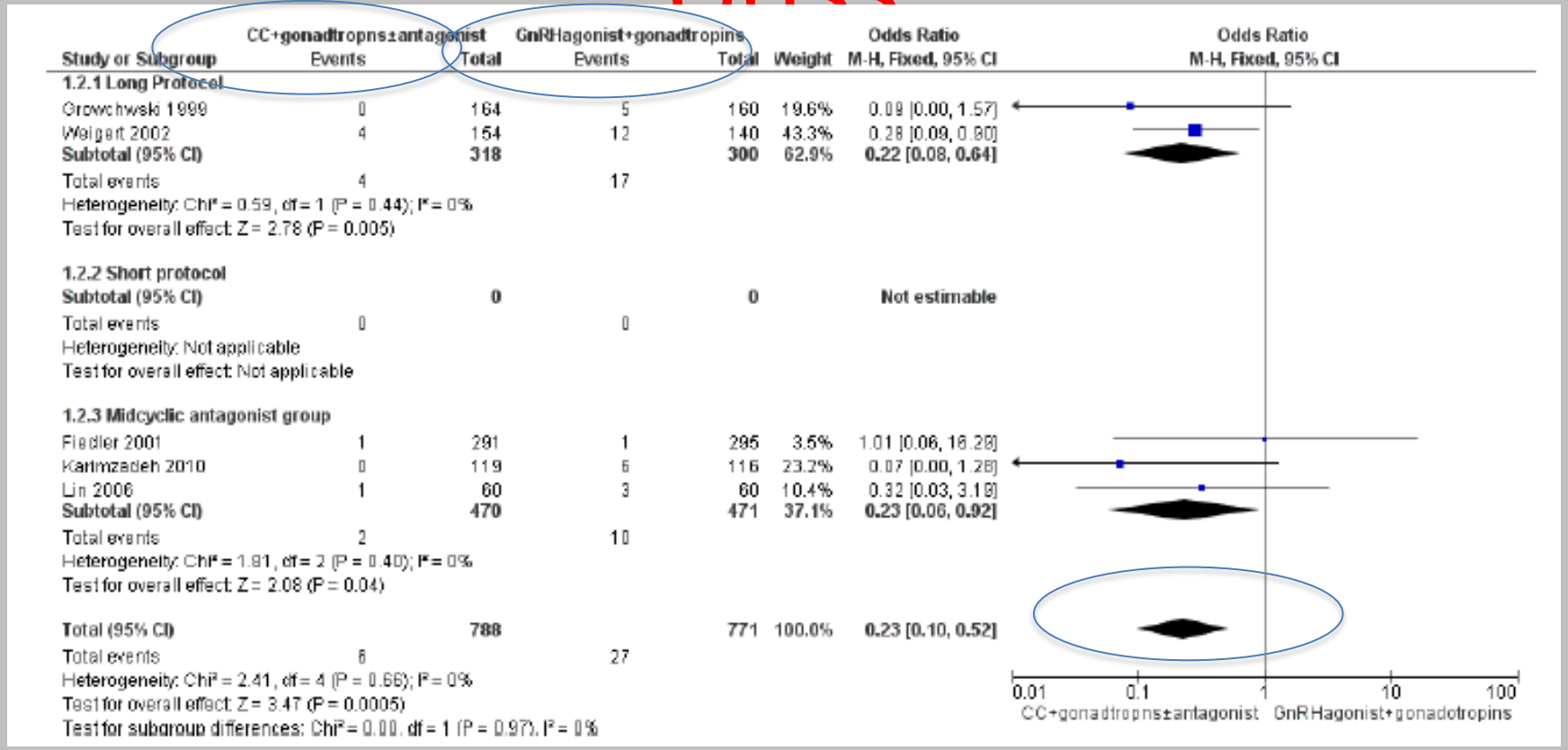


Study or Subgroup	CC+gonadtropns±antagonist Events	Total	GnRHagonist+gonadtropins Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Long Protocol						
Harrison 1994	12	50	25	100	13.7%	0.95 [0.43, 2.09]
Kingsland 1992	9	77	15	76	14.4%	0.54 [0.22, 1.32]
Subtotal (95% CI)		**127**		**176**	**28.1%**	**0.74 [0.41, 1.33]**
Total events	21		40			
Heterogeneity: Chi² = 0.86, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.1.2 Short protocol						
Long 1995	4	34	3	36	2.8%	1.47 [0.30, 7.10]
Subtotal (95% CI)		**34**		**36**	**2.8%**	**1.47 [0.30, 7.10]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.1.3 Midcyclic antagonist group						
Fiedler 2001	62	291	65	295	54.8%	0.96 [0.65, 1.42]
Lin 2006	22	60	21	60	14.4%	1.08 [0.51, 2.27]
Subtotal (95% CI)		**351**		**355**	**69.2%**	**0.98 [0.69, 1.39]**
Total events	84		86			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**512**		**567**	**100.0%**	**0.93 [0.69, 1.24]**
Total events	109		129			
Heterogeneity: Chi² = 1.92, df = 4 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 1.00, df = 2 (P = 0.61), I² = 0%						

Canlı doğum oranları benzer

Gibreel et al 2012 Cochrane Database

Minimal-Mild Stimulasyon Sonuçlar OHSS



Mild stimulasyon ile OHSS anlamlı daha az (OR: 0,23)

Gibreel et al 2012 Cochrane Database

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

Modifiye Protokoller

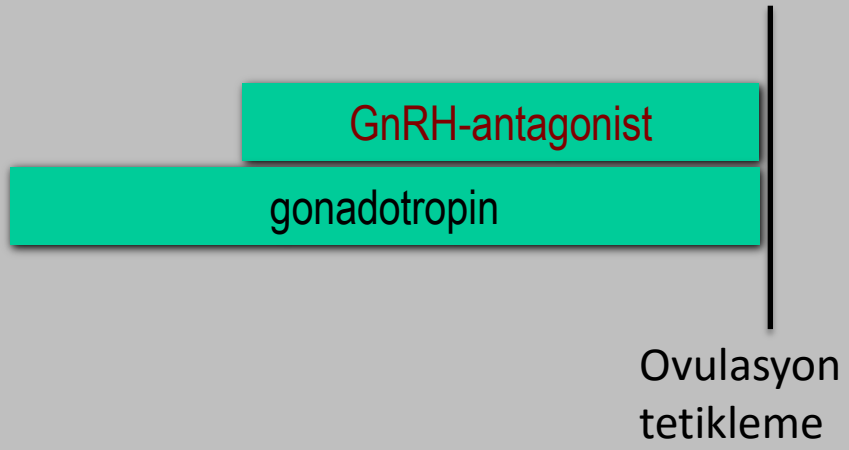
- GnRH antagonist sikluslarda GnRH agonist ile ovulasyon tetikleme
- Metformin kullanımı
- IVM
- Embryo freezing

PCOS-COH
Agonist vs Antagonist

GnRH-ANTAGONİST:

- Flare up etki yok
- Daha kısa sürede cevap
- Daha az gonadotropin dozu
- Fizyolojik siklusa benzer
- OHSS riskinde azalma

Özellikle PCOS grubunda avantajlı



Orvieto, Homburg et al 2008

Agonist vs Antagonist

- Gebelik oranları benzer
- OHSS oranları, antagonist siluslarda belirgin olarak daha az

Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT)

	Agonist group (n = 110)	Antagonist group (n = 110)	Difference % (95% CI)	P (Fisher's exact test)
Biochemical pregnancy, % (n)	68.2 (75)	62.7 (69)	5.5 (−7.0 to +17.9)	0.479
Clinical pregnancy, % (n)	61.8 (68)	52.7 (58)	9.1 (−3.9 to +22.0)	0.220
Ongoing pregnancy, % (n)	50.9 (56)	47.3 (52)	3.6 (−9.6 to +16.8%)	0.686

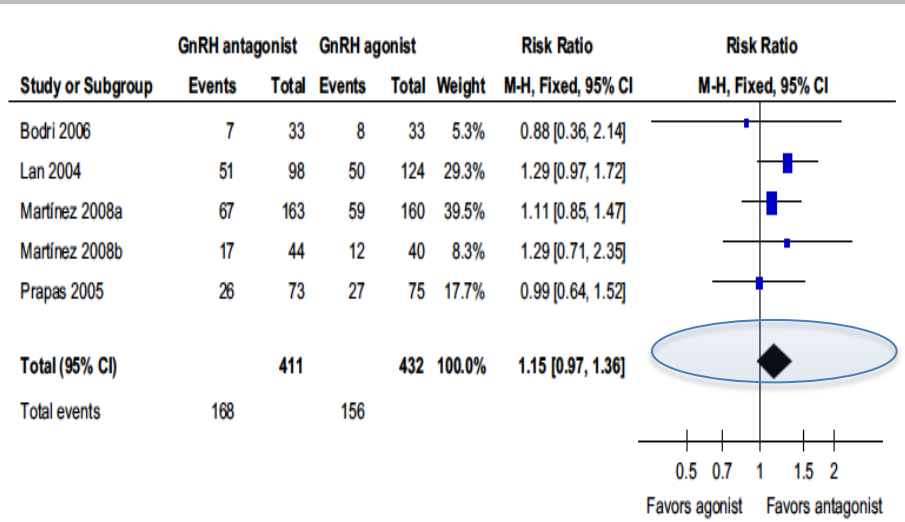
OHSS % (n)	Agonist group (n = 110)	Antagonist group (n = 110)	Difference (95% CI)	P-value (chi-square)
I	34.5 (38)	55.5 (61)	−21.0 (−33.8 to −8.1)	**0.006**
II	60.0 (66)	40.0 (44)	20.0 (+7.1 to +32.9)	
III	5.5 (6)	4.5 (5)	1.0 (−9.2 to +11.2)	

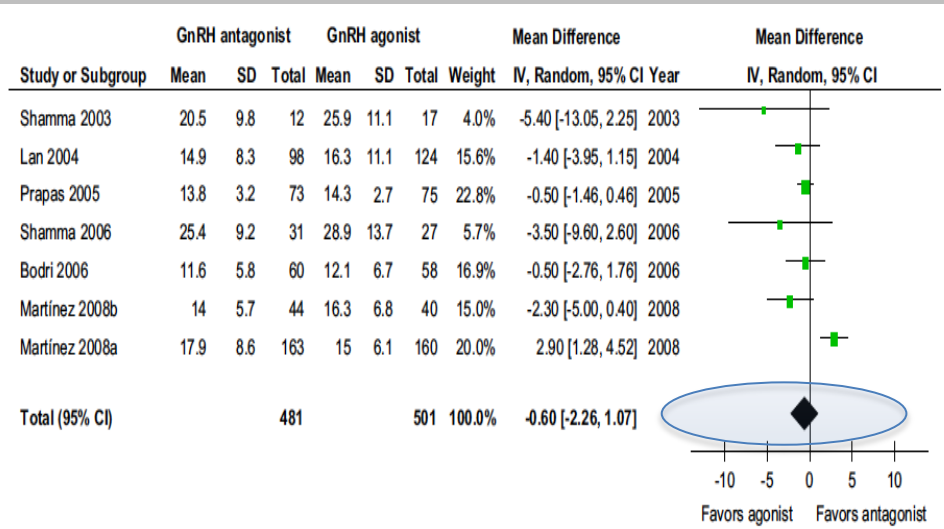
Antagonist sikluslarda; OPR benzer

Grade2 OHSS, kullanılan gonadotropin ve siklus süresi daha az..

Human Reproduction, Vol.25, No.3 pp. 683–689, 2010

Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyperstimulation in oocyte donors: a systematic review and meta-analysis





Donör sikluslarında, OPR ve toplanan oosit sayısı için gruplar arasında fark YOK

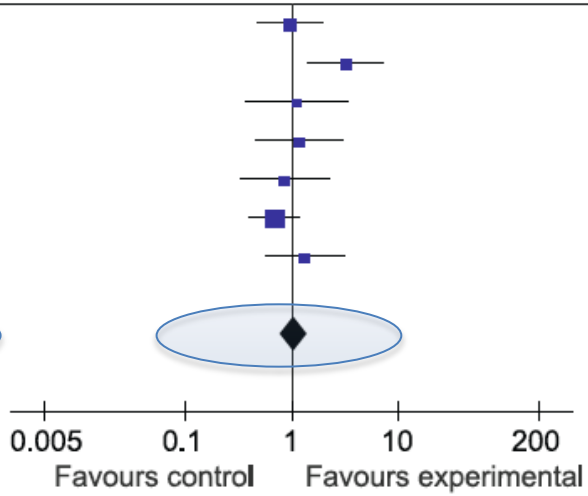
Bodri. GnRH analogues in oocyte donor cycles. Fertil Steril 2011.

ÖZET: PCOS grubunda Agonist vs Antagonist
7 çalışma, 755 hasta

Effectiveness of GnRH antagonist in the treatment of patients with polycystic ovary syndrome undergoing IVF: a systematic review and meta analysis

Study or Subgroup	antagonist Events	Total	agonist Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Behceci 2005	34	59	41	70	17.8%	0.96 [0.48, 1.94]
Hosseini 2010	23	57	9	55	13.0%	3.21 [1.42, 7.25]
Hwang 2004	10	27	10	29	7.4%	1.12 [0.38, 3.30]
Kurzawa 2008	20	33	21	37	9.7%	1.17 [0.45, 3.01]
Lainas 2007	15	26	32	52	9.5%	0.85 [0.33, 2.22]
Lainas 2010	58	110	68	110	30.6%	0.69 [0.41, 1.18]
Tehraninejad 2010	18	45	15	45	12.0%	1.33 [0.57, 3.12]
Total (95% CI)		**357**		**398**	**100.0%**	**1.08 [0.80, 1.45]**
Total events	178		196			

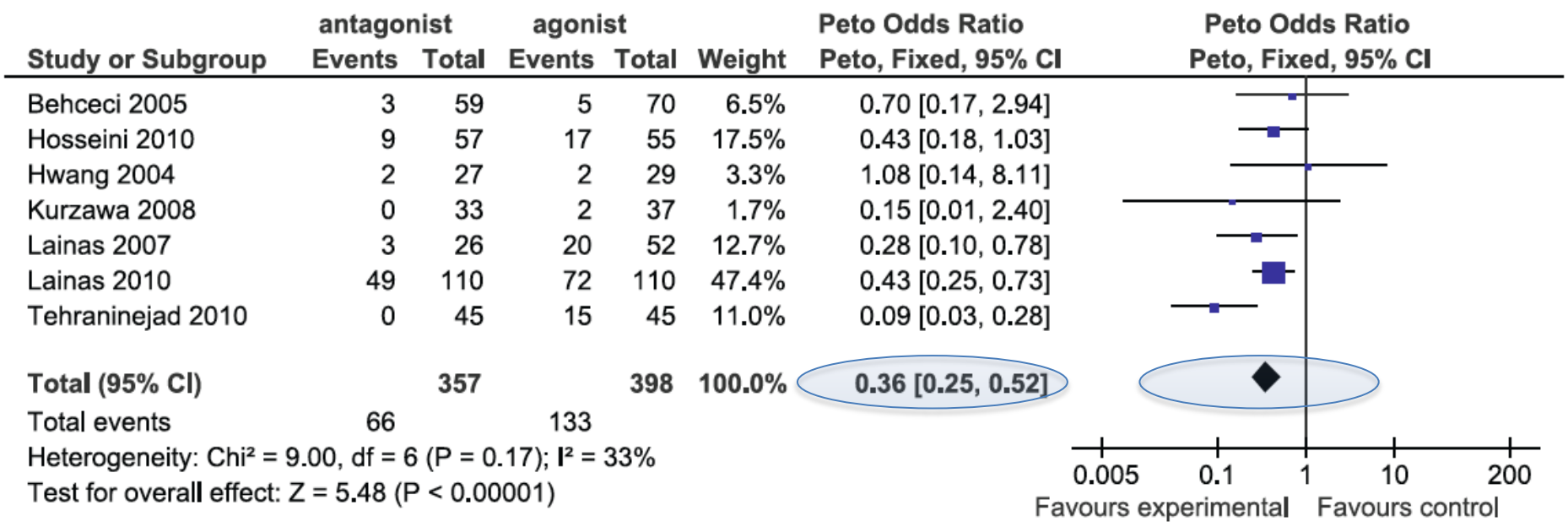
Heterogeneity: $Chi^2 = 10.12$, df = 6 (P = 0.12); $I^2 = 41\%$
Test for overall effect: Z = 0.49 (P = 0.62)



Klinik gebelik oranları protokoller arasında benzer (OR:1,08)

Xiao et al 2013

Effectiveness of GnRH antagonist in the treatment of patients with polycystic ovary syndrome undergoing IVF: a systematic review and meta analysis



Study or Subgroup	antagonist Events	Total	agonist Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Behceci 2005	3	59	5	70	6.5%	0.70 [0.17, 2.94]
Hosseini 2010	9	57	17	55	17.5%	0.43 [0.18, 1.03]
Hwang 2004	2	27	2	29	3.3%	1.08 [0.14, 8.11]
Kurzawa 2008	0	33	2	37	1.7%	0.15 [0.01, 2.40]
Lainas 2007	3	26	20	52	12.7%	0.28 [0.10, 0.78]
Lainas 2010	49	110	72	110	47.4%	0.43 [0.25, 0.73]
Tehraninejad 2010	0	45	15	45	11.0%	0.09 [0.03, 0.28]
Total (95% CI)		**357**		**398**	**100.0%**	**0.36 [0.25, 0.52]**
Total events	66		133			

Heterogeneity: Chi² = 9.00, df = 6 (P = 0.17); I² = 33%

Test for overall effect: Z = 5.48 (P < 0.00001)

OHSS, antagonist ile belirgin DAHA AZ (OR:0,36)

Xiao et al 2013

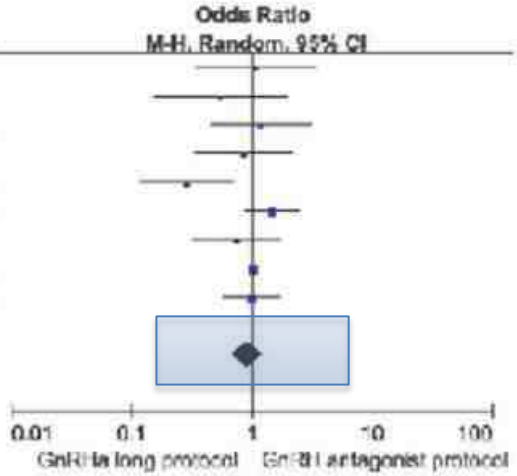
Is a GnRH Antagonist Protocol Better in PCOS Patients? A Meta-Analysis of RCTs

Haiyan Lin, Yu Li, Lin Li, Wenjun Wang, Dongzi Yang, Qingxue Zhang*

A

Study or Subgroup	GnRHa long protocol Events	Total	GnRH antagonist protocol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Jiann-Loung Hwang,2004	10	24	10	25	5.8%	1.07 [0.34, 3.35]	2004
Mahnaz Ashrafi,2005	6	22	9	22	4.8%	0.54 [0.15, 1.92]	2005
Trifon G,2007	32	52	15	26	7.8%	1.17 [0.45, 3.06]	2007
Rafal Kurzawa,2008	21	37	20	33	7.8%	0.85 [0.33, 2.22]	2008
Marzieh Aghe,2010	9	55	23	57	8.8%	0.29 [0.12, 0.70]	2010
Trifon G,2010	68	110	58	110	16.0%	1.45 [0.85, 2.48]	2010
Ensieh ,2010	15	45	18	45	9.2%	0.75 [0.32, 1.77]	2010
Bulent,2012	65	140	60	131	20.6%	1.03 [0.64, 1.65]	2012
Chung-Hoon Kim,2012	40	103	41	105	17.2%	0.99 [0.57, 1.73]	2012
Total (95% CI)		588		554	100.0%	0.91 [0.68, 1.23]	
Total events	266		254				

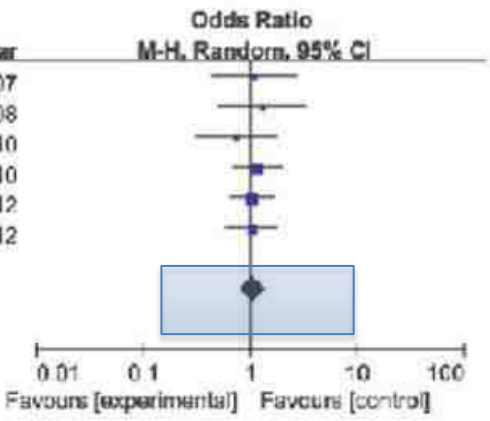
Heterogeneity: Tau² = 0.05; Chi² = 10.72, df = 8 (P = 0.22); P = 25%
Test for overall effect: Z = 0.60 (P = 0.55)



B

Study or Subgroup	GnRHa long protocol Events	Total	GnRH antagonist protocol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Trifon G,2007	25	52	12	26	7.9%	1.08 [0.42, 2.78]	2007
Rafal Kurzawa,2008	18	37	14	33	7.9%	1.20 [0.50, 3.31]	2008
Ensieh ,2010	13	45	16	45	8.9%	0.74 [0.30, 1.79]	2010
Trifon G,2010	56	110	52	110	25.1%	1.15 [0.68, 1.96]	2010
Bulent,2012	51	140	47	131	28.5%	1.02 [0.62, 1.68]	2012
Chung-Hoon Kim,2012	36	103	36	105	21.6%	1.03 [0.58, 1.82]	2012
Total (95% CI)		487		450	100.0%	1.05 [0.81, 1.37]	
Total events	199		177				

Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 5 (P = 0.97); P = 0%
Test for overall effect: Z = 0.36 (P = 0.72)



9 RCT, 588 LLP vs 568 GnRH-antagonist, CPR ve OPR benzer..

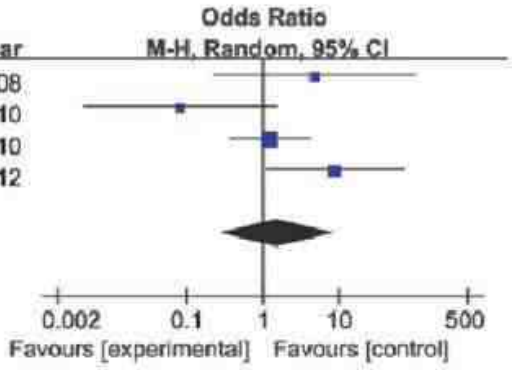
Lin 2014

Is a GnRH Antagonist Protocol Better in PCOS Patients? A Meta-Analysis of RCTs

Haiyan Lin, Yu Li, Lin Li, Wenjun Wang, Dongzi Yang, Qingxue Zhang*

Study or Subgroup	GnRHa long protocol Events	Total	GnRH antagonist protocol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rafal Kurzawa,2008	2	37	0	33	18.1%	4.72 [0.22, 101.93]	2008
Ensieh ,2010	0	45	5	45	19.2%	0.08 [0.00, 1.51]	2010
Trifon G.2010	6	110	5	110	36.2%	1.21 [0.36, 4.09]	2010
Chung-Hoon Kim,2012	8	103	1	105	26.5%	8.76 [1.08, 71.33]	2012
Total (95% CI)		**295**		**293**	**100.0%**	**1.56 [0.29, 8.51]**	
Total events	16		11				

Heterogeneity: Tau² = 1.69; Chi² = 7.22, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 0.51 (P = 0.61)



- Antagonist protokoller ile OHSS için fark anlamlı olmasa da, prevalans oldukça AZ
- Şiddetli OHSS için karşılaştırma yapılmış, çalışmalar arasında OHSS tanımı için oldukça farklılık var

Lin 2014

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

OKS etkinliği?

PCOS Modifikasyonları

- GnRH agonist ile ovulasyon tetikleme
- Metformin
- IVM
- Embryo freezing

Oral contraceptive pretreatment significantly reduces ongoing pregnancy likelihood in gonadotropin-releasing hormone antagonist cycles: an updated meta-analysis

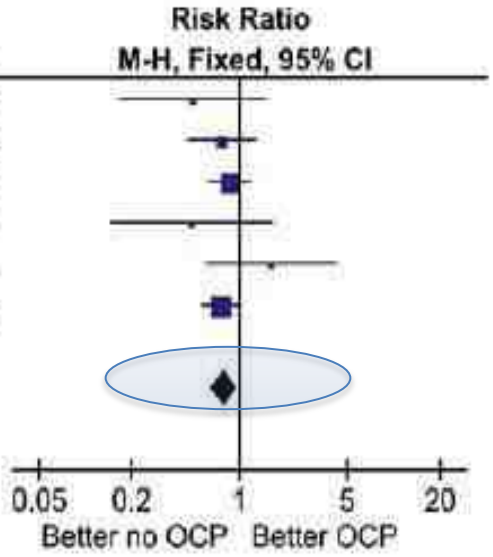
PCOS-Antagonist Sikluslarda OKS etkinliği Meta-analiz

A

Study or Subgroup	OCP Events	OCP Total	no OCP Events	no OCP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Huirne	4	32	8	32	4.5%	0.50 [0.17, 1.50]	2006
Rombauts	20	117	26	117	14.7%	0.77 [0.46, 1.30]	2006
Kolibianakis	51	250	60	254	33.7%	0.86 [0.62, 1.20]	2006
Cedrin	3	21	7	24	3.7%	0.49 [0.14, 1.66]	2007
Kim	8	27	5	27	2.8%	1.60 [0.60, 4.27]	2009
Tavmergen	55	223	71	219	40.5%	0.76 [0.56, 1.03]	2009
Total (95% CI)		**670**		**673**	**100.0%**	**0.80 [0.66, 0.97]**	
Total events	141		177				

Heterogeneity: $Chi^2 = 3.58$, $df = 5$ ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 2.28$ ($P = 0.02$)



- Antagonist sikluslarda, OKS eklenmesi ile OPR anlamlı olarak daha az
- Siklus süresi ve kullanılan gonadotropin dozu daha fazla

Griesinger et al 2010

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

PCOS Modifikasyonları

- GnRH agonist ile ovulasyon tetikleme
- Metformin
- IVM
- Embryo freezing

PCOS-Agonist Trigger

- Ovulasyonun doğal fizyolojisine uygun FSH, LH, E2 ve P4 düzeyleri
- OHSS insidansında azalma
- Luteal faz desteği??

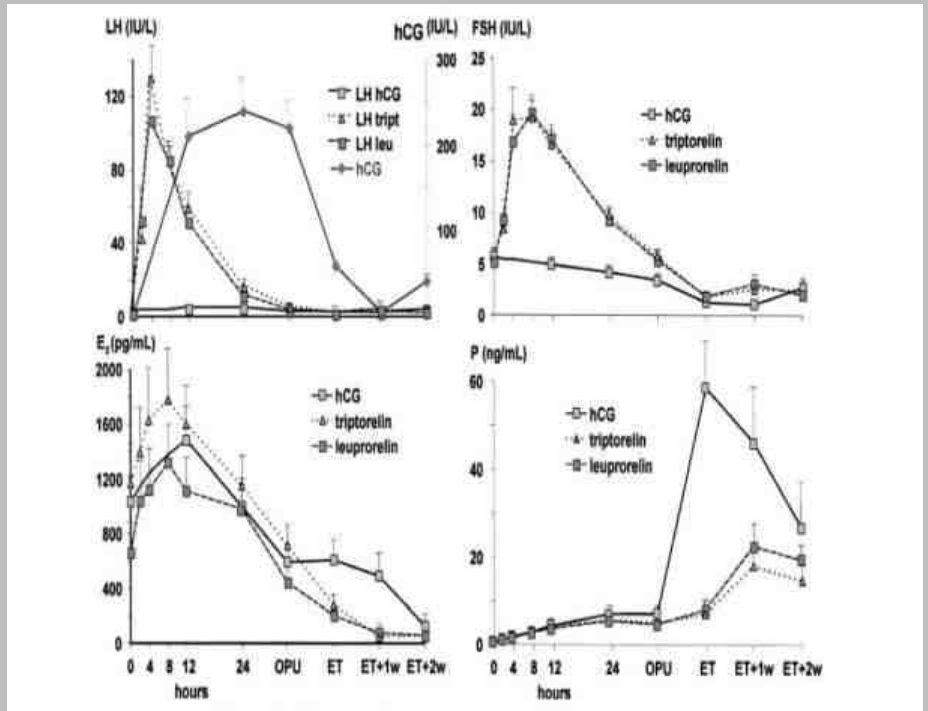


FIG. 3. Serum concentrations of LH (hCG), FSH, E2, and P (mean ± SEM) during triggering of final stages of oocyte maturation (0, 4, 8, 12, and 24 h) with two GnRH agonist (triptorelin and leuprorelin) or hCG after ovarian hyperstimulation for IVF and during the subsequent luteal phase [day of oocyte pick-up (OPU), embryo transfer (ET), and 1 and 2 wk after ET].

Ovulasyon Tetiklemede hCG

- Midsiklus LH surge mekanizmasını tetikler
- LH/hCG reseptörüne bağlanarak yapar
- LH yarı ömrü **60 dk** iken, hCG yarı ömrü **6 güne** kadar uzundur

Yüksek risk grubunda OHSS riskini tetikler…

Mekanizma

hCG

hCG

Uterus endotel

Over granüloza hücresi

•Artmış VEGF ekspresyonu

Agrawal et al.,1998

VEGF

AT-2
IGF-1
EGF
TGFa,b
IL-6

NET SONUÇ:ARTMIŞ KAPİLLER SIZINTI

OHSS‘yi predikte edebilir miyiz?

OHSS öngördüğümüz popülasyonda elimizdeki silahlar neler?

OHSS Prediksyonu için Özet

Risk Faktörleri	Cut-off
Kişiye bağlı (Primer)	
Yüksek AMH	3.36 ng/mL
Genç yaş	<33 yaş
Önceki OHSS öyküsü	hospitalizasyon
PCO benzeri overler	>24 antral follikül
Over Cevabına Bağlı (Sekonder)	
Fazla follikül	>13 follikül >11mm
Fazla follikül ve yüksek E2	E2 >5000 ve/veya >18 follikül
Toplanan oosit sayısı	>11-15
VEGF	-
İnhibin-b	-
Luteal destek için hCH	-

Fiedler et al 2012

Preventing ovarian hyperstimulation syndrome: guidance for the clinician

Peter Humaidan, M.D.,[a] *Jens Quartarolo, M.D.,*[b] *and Evangelos G. Papanikolaou, Ph.D.*[c]

-Gonadotropine maruziyeti azaltmak

-GnRH antagonist protokol tercihi

-Luteal faz desteği için hCG'den kaçınmak

-İn-vitro matürasyon

- Sekonder önleme

-Coasting

-hCG dozunu düşürmek

-Kriyoprezervasyon

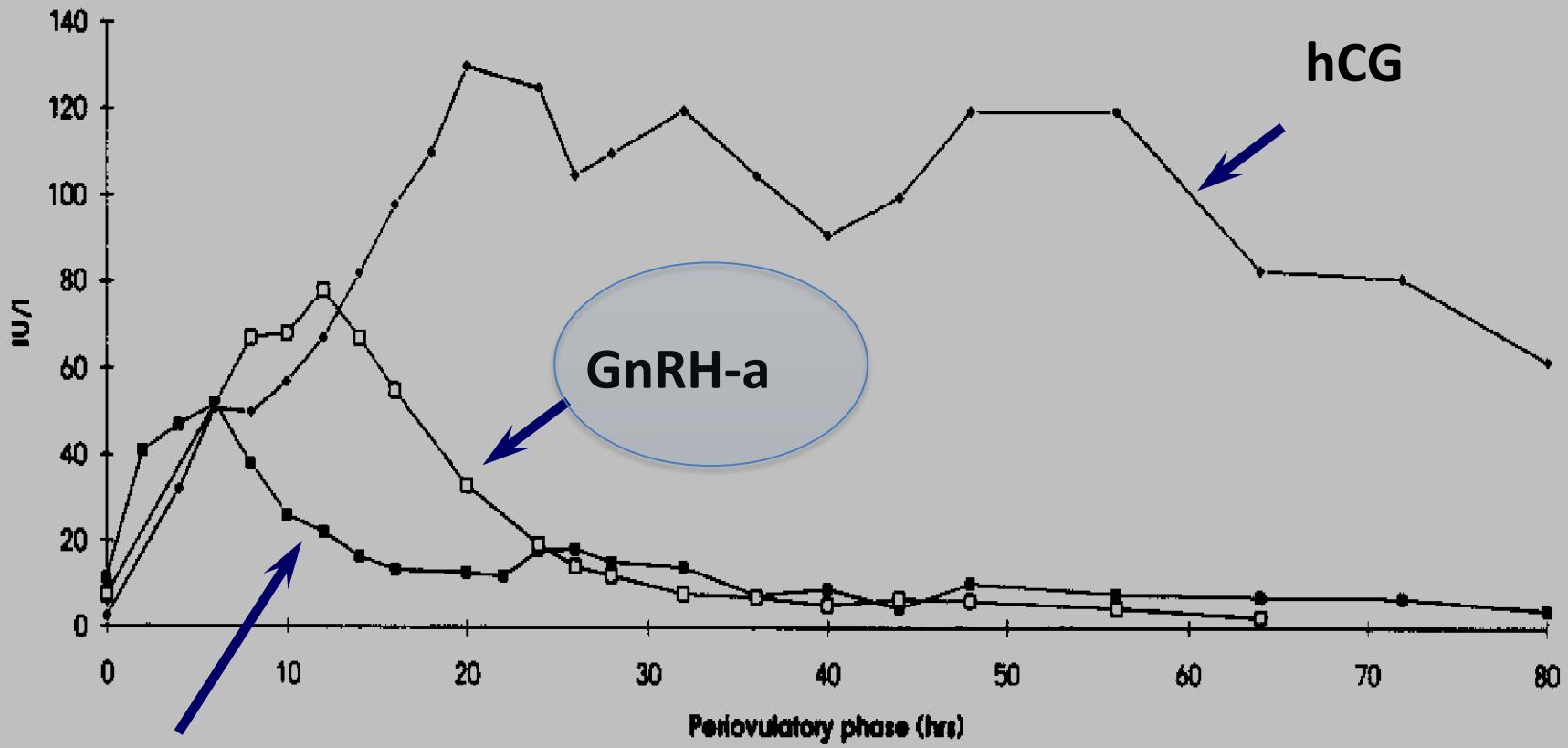
-Siklus iptali

-Ovulasyon tetikleme için alternatif ajanlar

GnRH-agonisti

Humaidan et. al. Fertil Steril 2010

LH Surge Paternleri



Spontan surge

Periovulatory phase (hrs)

GnRH-a Çalışmalar

GnRHa Type	Reference	Study Design	Dose	Study Population
Leuprolide	Engmann et al[14]	Retrospective	1 mg	High risk
	Engmann et al[4]	RCT	1 mg	High risk
	Shapiro et al[36]	Retrospective	4 mg	High risk
	Castillo et al[40]	Retrospective	1.5 mg	High risk
	Fauser et al[11]	RCT	0.5 mg	Low risk
Triptorelin	Itskovitz et al[1]	Retrospective	0.2 mg	High risk
	Fauser et al[11]	RCT	0.2 mg	Low risk
	Beckers et al[12]	RCT	0.2 mg	Low risk
	Babayof et al[15]	RCT	0.2 mg	High risk
	Kolibianakis et al[17]	RCT	0.2 mg	Low risk
Buserelin	Humaidan et al[16]	RCT	0.5 mg	Low risk

GnRHa, gonadotropin-releasing hormone agonist; RCT, randomized controlled trial.

GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study

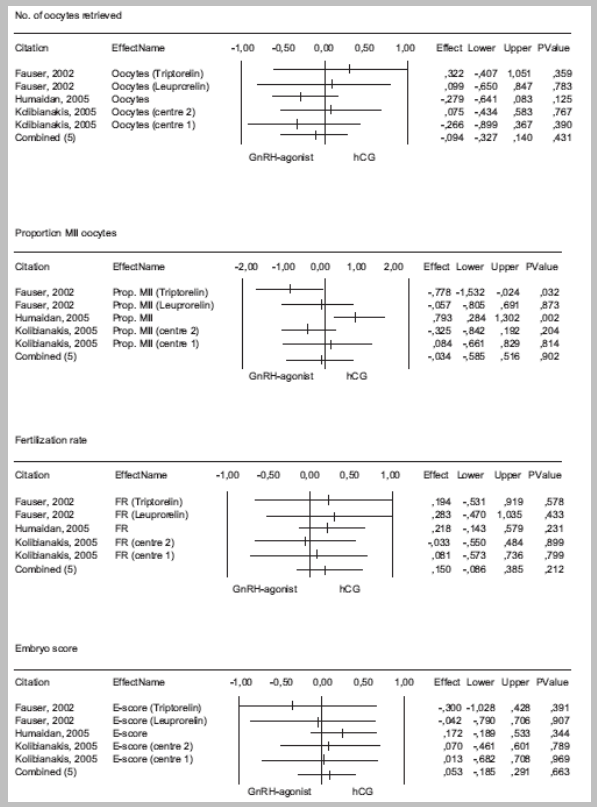
P.Humaidan[1,5], H.Ejdrup Bredkjær[2], L.Bungum[1], M.Bungum[1], M.L.Grøndahl[2], L.Westergaard[3] and C.Yding Andersen[4]

	Buserelin	hCG	P^a
Patients (*n*)	55	67	
Rate of embryo transfer (ET) [*n* (%)]	48 (87)	57 (85)	NS
No. of embryos transferred [mean (range)]	1.71 (1–2)	1.64 (1–2)	NS
Positive hCG per ET [*n* (%)]	14 (29)	25 (44)	>0.10[a]
Clinical pregnancy [*n* (% per cycle)]	3 (6)	24 (36)	0.002[a]
Implantation rate (*n*)	3/89	33/97	<0.001[b]
Early pregnancy loss [*n* (%)]	11 (79)	1 (4)	0.005[a]

Gebelik düşük, abortus yüksek..

GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis

G.Griesinger[1,3], K.Diedrich[1], P.Devroey[2] and E.M.Kolibianakis[2]



0.2 triptorelin/0.5 mg buserelin vs. 10.0000 hCG arasında fark YOK..
Luteal faz: vajinal or i.m. P + oral E2

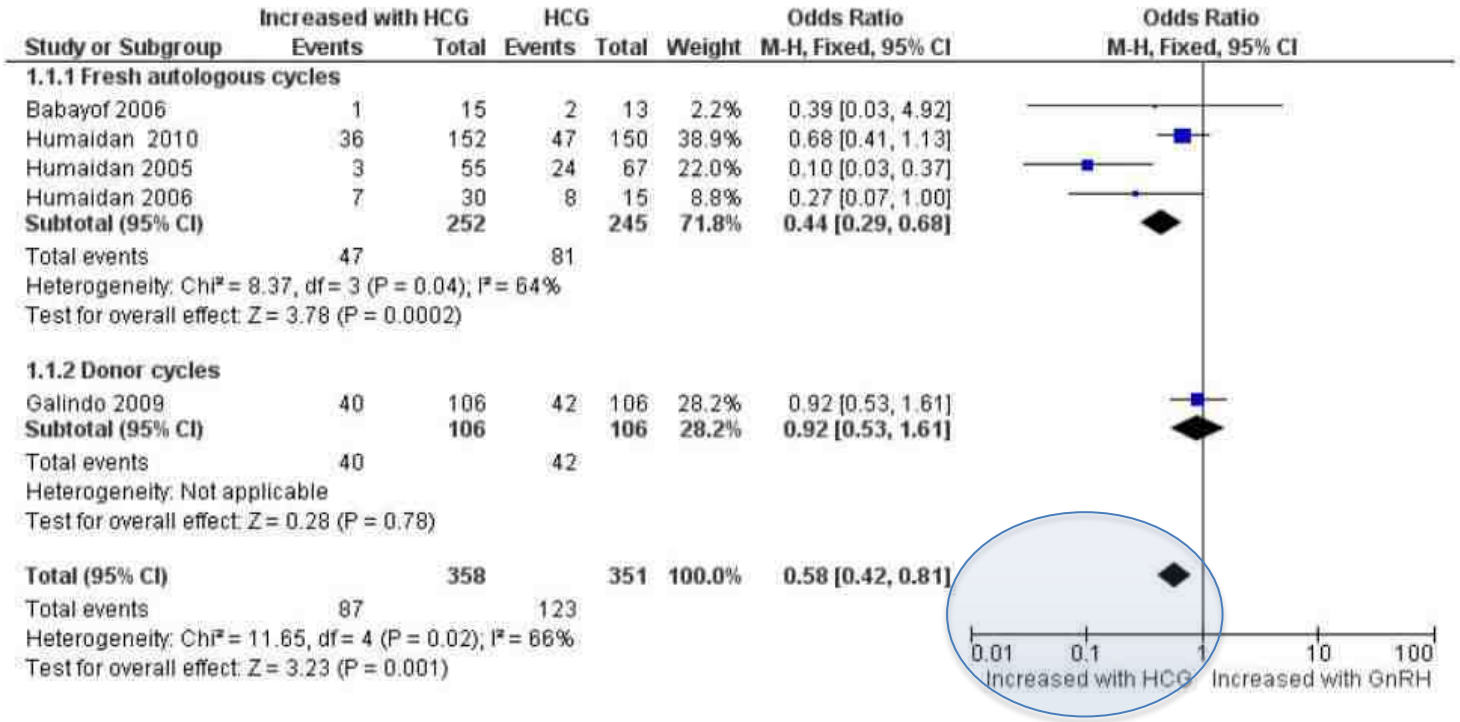
- oosit sayısı
- MII oosit sayısı
- fertilizasyon oranı
- embryo kalitesi

ANCAK;

- devam eden gebelik oranları belirgin DÜŞÜK

Hum Reprod Update 2006

Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles (Review)

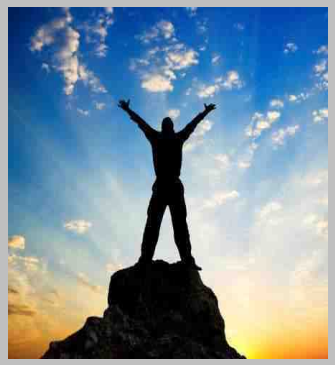


- **Youssef et al, ilk meta analiz:**
- GnRH-a trigger ile canlı doğum oranları ANLAMLI olarak AZ

Yousseff et al 2010

Agonist trigger: what is the best approach? Agonist trigger and low dose hCG

Peter Humaidan, M.D., D.M.Sc.



1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study

Peter Humaidan, M.D.,[a] *Helle Ejdrup Bredkjær, M.D., Ph.D.,*[b] *Lars Grabow Westergaard, M.D., D.M.Sc.,*[c] *and Claus Yding Andersen, D.M.Sc.*[d]

Pregnancy outcome in GnRHa vs. hCG-group.

Variable	GnRHa	hCG	OR (95% CI)	*P* Value
Patients, n	152	150		
Rate of transfer, n (%)	130/152 (86)	138/150 (92)	0.5 (0.4–0.7)	.054
Embryos transferred, median (range)	2 (1–2)	2 (1–2)		
Positive hCG per ET, n (%)	63/130 (48)	66/138 (48)	1.0 (0.9–1.2)	.36
Clinical pregnancy per patient, n (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	.29
Ongoing pregnancy per patient, n (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	.16
Early pregnancy loss, n (% of positive hCG)	13/63 (21)	11/66 (17)	1.3 (0.7–1.9)	.36

GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients

P. Humaidan[1,2,*], N.P. Polyzos[3], B. Alsbjerg[1], K. Erb[4], A.L. Mikkelsen[5], H.O. Elbaek[6], E.G. Papanikolaou[7], and C.Y. Andersen[8]

- 18-40 yaş, PCOS olguları dahil, Antagonist protokol
- 150-200 IU rec-FSH+Fiks 5.gün antagonist
- Ovulasyon tetikleme günü:

11mm'den büyük follikül sayısı >14 ise
YÜKSEK RİSK GRUBU

- A grubu agonist trigger+1500 IU hCG LPS (tek doz)
- B grubu hCG trigger

11mm'den büyük follikül sayısı <14 ise
DÜŞÜK RİSK GRUBU

- A grubu agonist trigger+1500 IU hCG LPS+5.gün ek 1500 IU hCG (2 doz)
- B grubu hCG trigger

Humaidan et al 2013, Hum Reprod

GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients

P. Humaidan[1,2,*], N.P. Polyzos[3], B. Alsbjerg[1], K. Erb[4], A.L. Mikkelsen[5], H.O. Elbaek[6], E.G. Papanikolaou[7], and C.Y. Andersen[8]

Yüksek risk

düşük risk

	>14 follicles		RR 95% CI P-value	≤14 follicles		RR 95% CI P-value
	Group A: GnRHa trigger + 1.500 hCG	Group B: hCG trigger		Group C: GnRHa trigger + 1.500 hCG × 2	Group D: hCG trigger	
Patients, *n*	60	58		125	141	
Rate of transfer, *n* (%)	52/60 (86.7)	57/58 (98.3)	0.88 [0.79–0.97] 0.02	110/125 (88.0)	116/141 (82.3)	1.06 [0.96–1.18] 0.18
Embryos transferred, mean (SD)	1.19 (0.40)	1.19 (0.40)	0.99	1.27 (0.45)	1.25 (0.43)	0.98
Positive hCG per embryo transfer, *n* (%)	25/52 (48.1)	21/57 (36.8)	1.30 [0.83–2.03] 0.23	47/110 (42.7)	41/116 (35.3)	1.20 [0.87–1.67] 0.25
Clinical pregnancy per patient, *n* (%)	21/60 (35.0)	17/58 (29.3)	1.19 [0.70–2.02] 0.51	43/125 (34.4)	40/141 (28.4)	1.21 [0.84–1.73] 0.28
Ongoing pregnancy per patient, *n* (%)	17/60 (28.3)	15/58 (25.9)	1.09 [0.60–1.98] 0.76	37/125 (29.6)	36/141 (25.5)	1.15 [0.78–1.71] 0.45
Implantation rate, *n* (%)	22/62 (35.5)	20/68 (29.4)	1.20 [0.73–1.98] 0.46	49/138 (35.5)	43/145 (29.7)	1.19 [0.85–1.67] 0.29
Early pregnancy loss, *n* (% of positive hCG)	4/25 (16.0)	4/21 (19.0)	0.84 [0.23–2.95] 0.78	4/47 (8.5)	1/41 (2.4)	3.48 [0.40–29.98] 0.25
OHSS rate, *n* (%)	0/60 (0)	2/58 (3.4)	0.24	2/125 (1.6)	0/141 (0)	0.22

- Agonist trigger ve 1500 IU hCG ile devam eden gebelikler daha fazla
- Erken gebelik kayıpları daha az
- Agonist grubunda OHSS yok..

Humaidan et al 2013, Hum Reprod

Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin

'Dual Trigger' Konsepti

- Yüksek riskli hasta grubunda (trigger öncesi >20 follikül ve E2>2500 pg/mL)
- 3 farklı tekniğin karşılaştırılması, Retrospektif analiz

GnRH-a ve hCG ile trigger ve standart luteal destek

GnRH-a ve standart luteal destek

GnRH-a ve fazla luteal destek

Shapiro et al., 2011

‘Dual Trigger’ Konsepti-Sonuçlar

	GnRH-a ve hCG ile trigger ve standart luteal destek	GnRH-a ve standart luteal destek	GnRH-a ve fazla luteal destek	
Oocytes retrieved	20.4 ± 6.2[a]	27.1 ± 11.2	25.4 ± 10.3	<.001
Bipronuclear oocytes	13.7 ± 4.8[a]	18.7 ± 9.0	16.8 ± 8.1	<.001
Blastocysts formed	5.3 ± 3.3[a]	8.1 ± 6.5	6.4 ± 3.7	<.001
Blastocysts transferred (mean)	1.9 ± 0.3	2.0 ± 0.4	1.9 ± 0.3	.098
Blastocysts transferred (total)	340	180	45	
Fetal hearts	166	37	17	
Implantation rate (%)	48.8[a]	20.6	37.8[a]	<.001
Pregnancies, n (%)	137 (75.3)[a]	55 (60.4)	15 (62.5)	.031
Ongoing pregnancies, n (%)	105 (57.7)[a]	23 (25.3)	12 (50.0)[a]	<.001
Early pregnancy losses, n (%)	32 (23.4)[a]	32 (58.2)	3 (20.0)[a]	<.001
OHSS, n (%)	1 (0.55)	0	0	.723

- Dual trigger ile devam eden gebelikler daha fazla
- Erken gebelik kayıpları daha az
- OHSS sadece 1 tane: dual trigger kolda (650 IU hCG)

Shapiro et al., 2011

The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study

Etkin Luteal Destek

- PCOS veya önceki high-response öyküsü
- Prospektif çalışma, 59 infertil olgu

Antagonist protokol-agonist trigger

- Trigger'dan 12 saat sonra serum E2 ve P4
- 50mg/gün P ve 3 adet 0.1 mg E2 patch
- E2 200pg/mL ve P4 20ng/mL olacak şekilde ek dozlar

Long luteal protokol

- Sadece 50 mg/gün im P4

Engmann et al., 2008

The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study

Etkin Luteal Destek

	Study group	Control group	Odds ratio (95% CI)	*P* value
Primary end points				
OHSS (intention to treat)				
Total n, (%)	0/33 (0)	10/32 (31.3)	0 (0–0.26)[a]	<.01
Moderate/severe, n (%)	0/33 (0)	5/32 (15.6)	0 (0-0.74)[a]	.02
OHSS (per protocol)				
Total, n (%)	0/30 (0)	10/29 (34.5)	0 (0–0.26)[a]	<.01
Moderate/Severe, n (%)	0/30 (0)	5/29 (17.2)	0 (0–0.73)[a]	.02
Secondary end point (per protocol)				
Implantation rate, n (%)	22/61 (36)	20/64 (31)	1.18 (0.52–2.65)	.69
Other end points (per protocol)				
Positive pregnancy, n (%)	19/30 (63.3)	18/29 (62.1)	1.06 (0.37–3.0)	.92
Clinical pregnancy rate, n (%)	17/30 (56.7)	15/29 (51.7)	1.22 (0.4–3.4)	.45
Ongoing pregnancy rate, n (%)	16/30 (53.3)	14/29 (48.3)	1.22 (0.4–3.4)	.45

Yoğun luteal destek ile YÜKSEK gebelik oranları…

Intensive luteal-phase support with oestradiol and progesterone after GnRH-agonist triggering: does it help?

	1.grup	2.grup
Peak oestradiol concentration[b] (pg/ml)	2944 ± 657	3174 ± 910
No. oocytes retrieved	16.3 ± 8.1[c]	22.3 ± 9.1[d]
Fertilization rate (%)	56 ± 20	56 ± 19
Number of embryos transferred	1.7 ± 0.5	2.4 ± 0.7
Clinical pregnancy rate (%)	14.9	15.8
Implantation rate (%)	13.1	7.8

- Yoğun Luteal destek alan ve almayan gruplarda düşük gebelik oranları…
- E2 <4000 pg/mL

Orvieto et al 2008

Intensive luteal phase support after GnRH agonist trigger: it does help

- Orvieto'nun çalışmasında grupların yoğun desteği net değil
- Grupların hepsinde E2 <4000 pg/mL
- E2 <4000 pg/mL olgularda GnRH-a etkinliği düşük

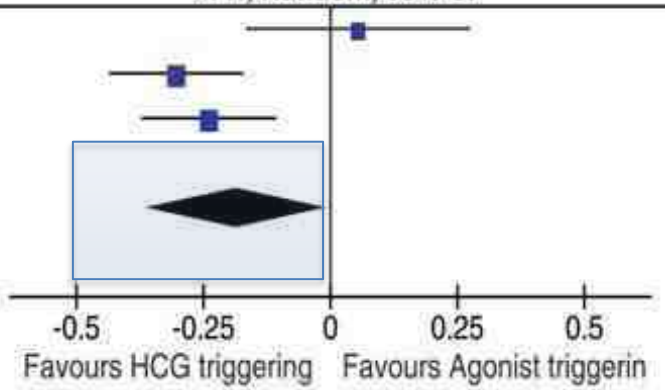
Engmann et al 2012

a

Study or Subgroup	Agonist triggering Events	Total	HCG triggering Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Fauser, 2002	6	32	2	15	26.7%	0.05 [-0.16, 0.27]
Humaidan, 2005	3	55	24	67	36.7%	-0.30 [-0.43, -0.17]
Kolibianakis, 2005	2	52	15	54	36.6%	-0.24 [-0.37, -0.11]
Total (95% CI)		139		136	100.0%	**-0.18 [-0.36, -0.01]**
Total events	11		41			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.71$, df = 2 (P = 0.02); $I^2 = 74\%$

Test for overall effect: Z = 2.07 (P = 0.04)



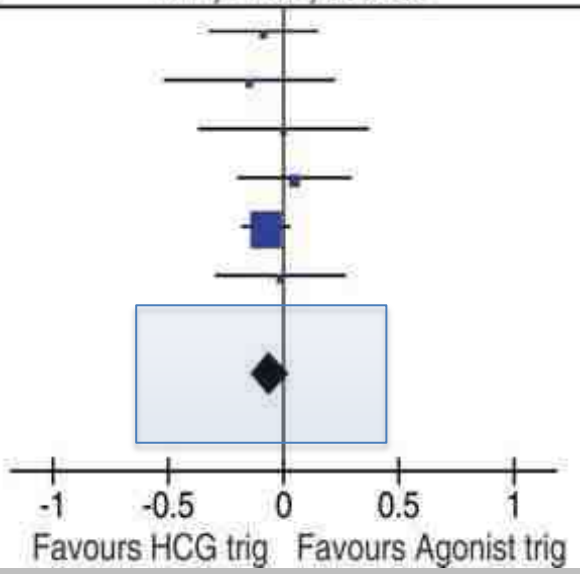
Standart luteal destek ile ***devam eden gebelik*** oranları ***DÜŞÜK..***

b

Study or Subgroup	Agonist triggering Events	Total	HCG triggering Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Babayof, 2006	1	15	2	13	5.9%	-0.09 [-0.32, 0.15]
Humaidan, 2006	5	13	8	15	5.9%	-0.15 [-0.51, 0.22]
Pirard, 2006	2	12	1	6	3.4%	0.00 [-0.37, 0.37]
Engmann, 2008	16	33	14	32	13.7%	0.05 [-0.19, 0.29]
Humaidan, 2010	36	152	47	150	63.8%	-0.08 [-0.18, 0.02]
Papanikolaou, 2011	4	18	4	17	7.4%	-0.01 [-0.29, 0.27]
Total (95% CI)		243		233	100.0%	**-0.06 [-0.14, 0.02]**
Total events	64		76			

Heterogeneity: $Chi^2 = 1.35$, df = 5 (P = 0.93); $I^2 = 0\%$

Test for overall effect: Z = 1.40 (P = 0.16)



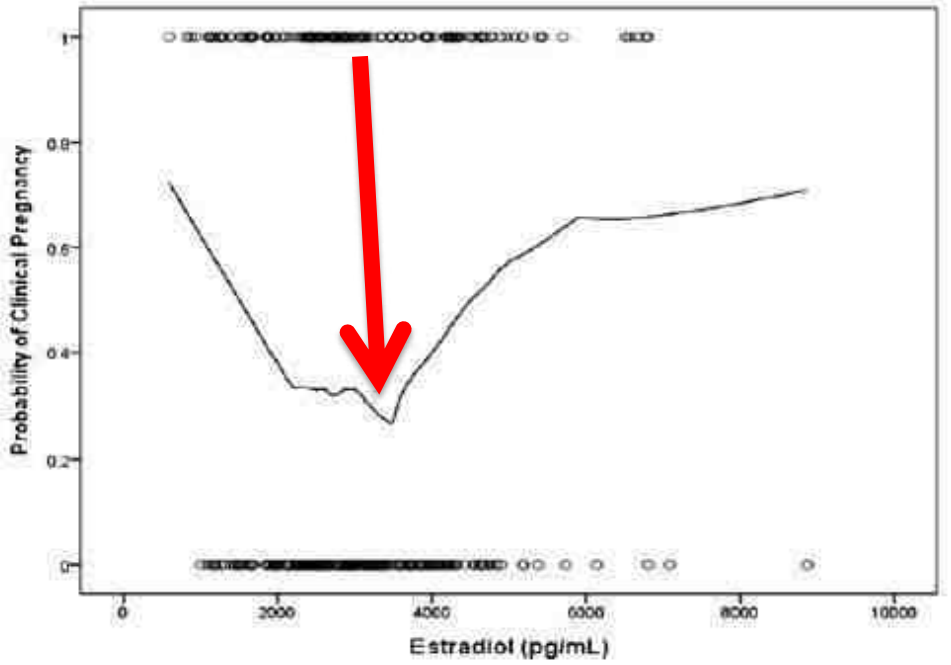
Modifiye luteal destek ile ***canlı doğum*** oranları hCG'ye ***BENZER..***

	Avantaj	dezvantaj	Luteal faz desteği
Oosit donör	• OHSS önlenir • Iyi kalitede oosit • Erken dönemde mens • Luteal over volümünde azalma	• yok	• Gerek yok
High-responder	• OHSS önlenir • Iyi kalitede oosit • Erken dönemde mens • Luteal over volümünde azalma	• ***DÜŞÜK GEBELİK ORANI..?***	• im P ve E2 patch • 1500 hCG OPU günü • Tekrarlayan hCG dozları • Tekrarlayan LH dozları • GnRH-a
Normo-responder	• OHSS önlenir • Daha fazla M2 oosit • Iyi oosit kalitesi	• Luteal destek halen tartışmalı	• im P ve E2 patch • 1500 hCG OPU günü • Tekrarlayan hCG dozları • Tekrarlayan LH dozları
Fertilite korunması amaçlı (kemoterapi öncesi oosit freezing)	• OHSS önlenir • Daha fazla M2 oosit • Iyi oosit kalitesi • Düşük luteal faz estradiol düzeyi	• yok	• Gerek yok

Factors that predict the probability of a successful clinical outcome after induction of oocyte maturation with a gonadotropin-releasing hormone agonist

- OHSS için yüksek riskli grubun retrospektif analizi
- Antagonist protokol-agonist trigger-modifiye luteal destek
- Gebelik oranları ve OHSS prediksyonu için parametreler incelenmiş
- Trigger günü LH ve E2 düzeyi en anlamlı parametreler
- ***E2 >4000 pg/L grubunda sonuçlar daha iyi***
  - Kummer et al 2011

LOESS curve showing probability of pregnancy by peak estradiol level.



Variable	Group 1: E_2 <4,000 pg/mL	Group 2: $E_2 \geq$4,000 pg/mL	*P* value
Biochemical miscarriage rate n (%)	35/144 (24.3)	6/45 (13.3)	.85
Clinical miscarriage rate n (%)	19/144 (13.2)	6/45 (13.3)	.57
Implantation rate n (%)	120/475 (25.3)	52/143 (34.4)	.03
Clinical pregnancy rate per cycle n (%)	94/247 (38.1)	37/69 (53.6)	.02
Ongoing pregnancy rate per cycle n (%)	82/247 (33.2)	31/69 (44.9)	.07

Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting

- OHSS için yüksek riskli hastaların retrospektif analizi
- GnRH-a (short-antagonist) vs Coasting (LLP) karşılaştırması
- Gruplarda E2 >4000 pg/L
- ***2 grupta da sonuçlar benzer, yüksek E2'li olgularda agonist trigger coasting kadar etkin***

Fertilization rate (%)	669/921 (72.6)	186/281 (66.2)	.04
Implantation rate (%)	44/140 (31.4)	12/53 (22.6)	NS (.23)
Clinical pregnancy rate (%)	32/61 (52.5)	9/33 (27.2)	.02
Ongoing pregnancy rate (%)	30/61 (49.2)	8/33 (24.2)	.02
Patients with surplus cryopreserved embryos (%)	40/60 (66.7)	9/23 (39.1)	.02
No. of cryopreserved embryos	4.4 ± 4.5	2.0 ± 3.5	.02
OHSS (%)	0	0	NS

Di Luigi et al 2010

Agonist Trigger Sonuç

- Agonist trigger olgularında bolus 1500 IU hCG, erken başlangıçlı OHSS'yi önlüyor..
- Reprodüktif sonucu da iyileştiriyor mu?

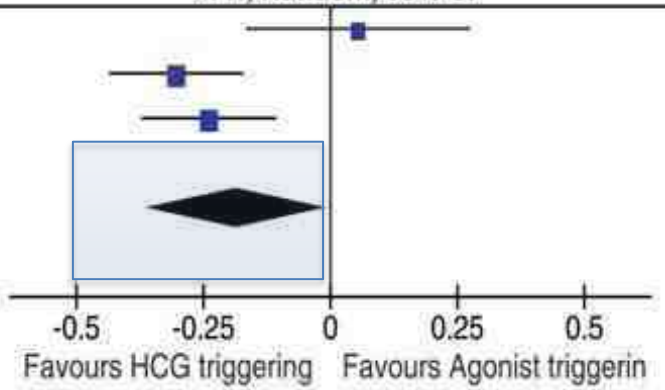
Humaidan, Reprod Biomed Online, 2009
Shapiro, Fertil Steril,2011
Radesic, Human Reprod, 2011
Humaidan, Fertil Steril, 2012

a

Study or Subgroup	Agonist triggering Events	Total	HCG triggering Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Fauser, 2002	6	32	2	15	26.7%	0.05 [-0.16, 0.27]
Humaidan, 2005	3	55	24	67	36.7%	-0.30 [-0.43, -0.17]
Kolibianakis, 2005	2	52	15	54	36.6%	-0.24 [-0.37, -0.11]
Total (95% CI)		139		136	100.0%	**-0.18 [-0.36, -0.01]**
Total events	11		41			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.71$, df = 2 (P = 0.02); $I^2 = 74\%$

Test for overall effect: Z = 2.07 (P = 0.04)



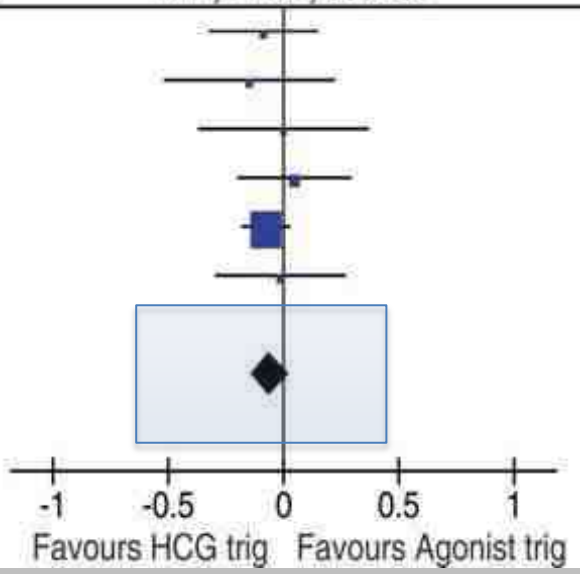
Standart luteal destek ile ***devam eden gebelik*** oranları ***DÜŞÜK..***

b

Study or Subgroup	Agonist triggering Events	Total	HCG triggering Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Babayof, 2006	1	15	2	13	5.9%	-0.09 [-0.32, 0.15]
Humaidan, 2006	5	13	8	15	5.9%	-0.15 [-0.51, 0.22]
Pirard, 2006	2	12	1	6	3.4%	0.00 [-0.37, 0.37]
Engmann, 2008	16	33	14	32	13.7%	0.05 [-0.19, 0.29]
Humaidan, 2010	36	152	47	150	63.8%	-0.08 [-0.18, 0.02]
Papanikolaou, 2011	4	18	4	17	7.4%	-0.01 [-0.29, 0.27]
Total (95% CI)		243		233	100.0%	**-0.06 [-0.14, 0.02]**
Total events	64		76			

Heterogeneity: $Chi^2 = 1.35$, df = 5 (P = 0.93); $I^2 = 0\%$

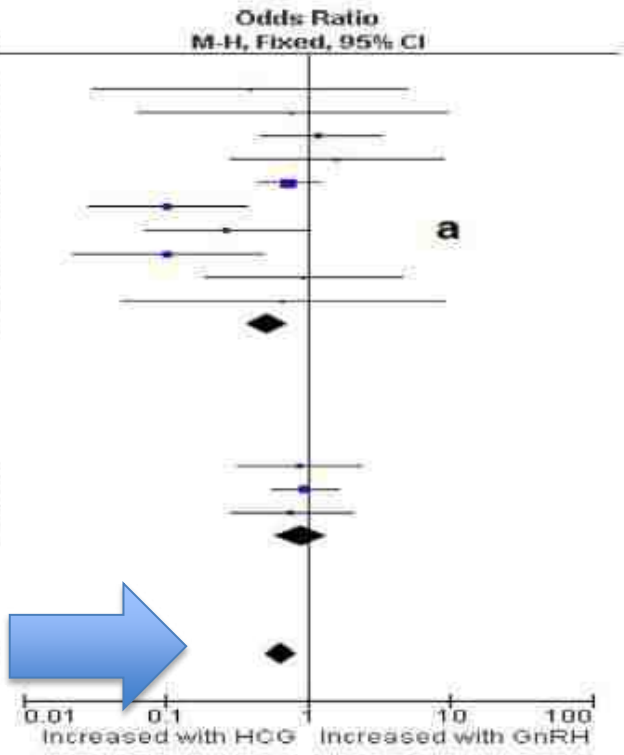
Test for overall effect: Z = 1.40 (P = 0.16)



Modifiye luteal destek (bolus hCG veya E+P) ile ***canlı doğum*** oranları hCG'ye ***BENZER..***

GnRH agonist for final oocyte maturation in GnRH antagonist co-treated IVF/ICSI treatment cycles: Systematic review and meta-analysis

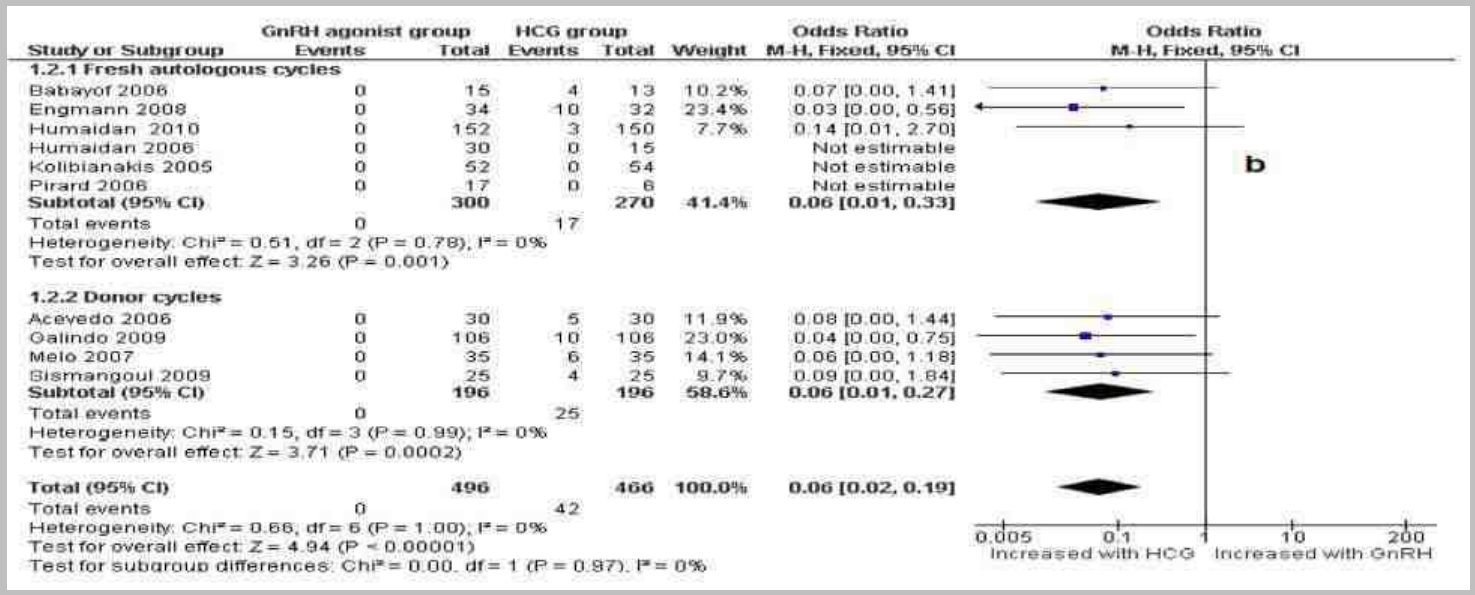
Study or Subgroup	GnRH agonist group Events	Total	HCG group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Fresh autologous cycles						
Babayof 2006	1	15	2	13	1.4%	0.39 [0.03, 4.92]
Beckers 2003	1	15	2	24	1.0%	0.79 [0.06, 9.50]
Engmann 2008	16	33	14	32	5.3%	1.21 [0.46, 3.21]
Fauser 2002	6	32	2	16	1.6%	1.62 [0.29, 9.09]
Humaidan 2010	40	152	49	150	28.1%	0.74 [0.45, 1.21]
Humaidan 2005	3	55	24	67	14.7%	0.10 [0.03, 0.37]
Humaidan 2006	7	30	8	15	5.9%	0.27 [0.07, 1.00]
Kolibianakis 2005	2	52	15	54	10.2%	0.10 [0.02, 0.48]
Papanikolaou 2010	4	18	4	17	2.3%	0.93 [0.19, 4.50]
Pirard 2006	2	17	1	6	0.9%	0.87 [0.05, 9.02]
Subtotal (95% CI)		**419**		**394**	**69.4%**	**0.52 [0.38, 0.73]**
Total events	82		121			
Heterogeneity: Chi² = 18.53, df = 9 (P = 0.03); I² = 51%						
Test for overall effect: Z = 3.79 (P = 0.0002)						
1.3.2 Donor cycles						
Acevedo 2006	14	30	15	30	5.7%	0.88 [0.32, 2.41]
Galindo 2009	41	106	42	106	18.5%	0.96 [0.55, 1.67]
Melo 2007	22	35	24	35	6.4%	0.78 [0.29, 2.09]
Subtotal (95% CI)		**171**		**171**	**30.6%**	**0.91 [0.59, 1.40]**
Total events	77		81			
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**590**		**565**	**100.0%**	**0.64 [0.49, 0.83]**
Total events	159		202			
Heterogeneity: Chi² = 21.05, df = 12 (P = 0.05); I² = 43%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Test for subgroup differences: Chi² = 3.82, df = 1 (P = 0.05), I² = 73.8%						



Devam eden gebelik oranları hCG ile daha FAZLA

Youssef et al 2015

GnRH agonist for final oocyte maturation in GnRH antagonist co-treated IVF/ICSI treatment cycles: Systematic review and meta-analysis



GnRH-a ile OHSS belirgin olarak AZ

Youssef et al 2015

Conclusions

The evidence suggests that GnRH agonists as a final oocyte maturation trigger in fresh autologous cycles should not be used routinely due to its association with a significantly lower live birth rate, lower ongoing pregnancy rate and higher rate of early miscarriage. The only indication for GnRH agonist use as oocyte maturation trigger is in women who donate oocytes to recipients or in women who wish to freeze their eggs for later use in the context of fertility preservation.

Sonuçlar

Fresh siklus GnRH-a trigger sonrasında

OPU günü 1500 IU hCG

Humaidan

Seri serum E ve P ölçümü ile steroid desteği

Engmann

Tekrarlayan düşük doz recLH veya hCG

Andersen

- Erken OHSS
- Boş follikül sendromu

DİKKAT

J Assist Reprod Genet (2013) 30:581–585
DOI 10.1007/s10815-013-9966-4

ASSISTED REPRODUCTION TECHNOLOGIES

Failure of GnRH agonist-triggered oocyte maturation: its cause and management

- 29-40 yaş arası 8 infertil olgu
- Unexplained-PCOS-male factor
- Short-antagonist protokol
- Toplam 600 mcg nazal buserelin ile trigger
- Tümünde oosit yok, tekrar hCG ile trigger ve 34 saat sonra her olguda 8-35 oosit
- 8 olgunun 7 tanesinde gebelik var
- NEDEN: şiddetli-geçici hipotalamo-hipofizer down-regülasyon??

Asada et al 2013

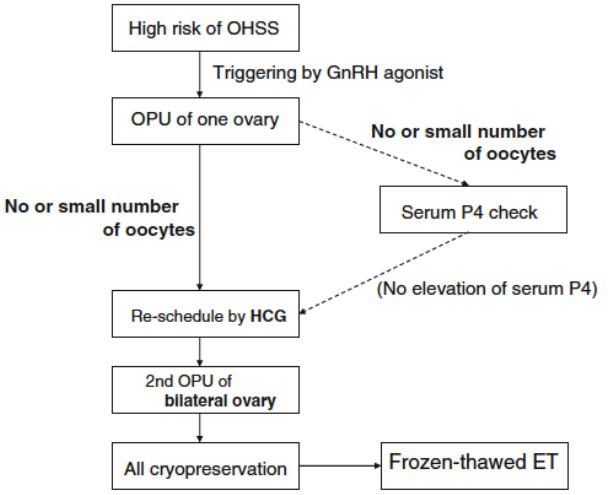


Fig. 1 Flow chart depicting management of the failure of GnRHa-triggered oocyte maturation

J Assist Reprod Genet (2012) 29:249–253
DOI 10.1007/s10815-011-9704-8

ASSISTED REPRODUCTION TECHNOLOGIES

Empty follicle syndrome after GnRHa triggering versus hCG triggering in COS

Juan C. Castillo · Juan Garcia-Velasco · Peter Humaidan

- 2034 donasyon ve 1433 IVF siklusunun retrospektif analizi

	Donors n=2034	Patients n=1433	p value
Age (years)	25.1±3.8	31.9±2.3	0.01
Peak serum E2 levels (pg/mL)	1892±1200	1702±1050	0.01
MII	9.8±4.3	7.2±4.6	0.01
% EFS (n)	3.5 (73)	3.1 (45)	n.s.

- Hipo-hipo düzeyi kadar olmayan borderline düşük FSH-LH rezervli olgular
- GnRH veya LH reseptör polimorfizmi
- Poor-responder'da fazla..

Castillo et al 2012

IVF Worldwide Survey

- IVF Worldwide. Survey on vitrification, GnRH trigger and differed embryo, 2013
- 123 IVF Merkezi
- 108.300 ART olgusu
- GnRH-a kullanım sıklığı: %5-36

Katılımcıların %11'i boş follikül durumu bildirdi

Human Reproduction, Vol.28, No.1 pp. 152–159, 2013
Advanced Access publication on October 17, 2012 doi:10.1093/humrep/des361

human reproduction

ORIGINAL ARTICLE *Infertility*

Predicting successful induction of oocyte maturation after gonadotropin-releasing hormone agonist (GnRHa) trigger

N.E. Kummer[1], R.S. Feinn[2], D.W. Griffin[1], J.C. Nulsen[1], C.A. Benadiva[1], and L.L. Engmann[1,*]

Table II Factors predicting oocyte yield using multiple linear regression analysis for 'total number of oocytes' and 'number of mature oocytes' as well as generalized linear model with logit link for 'proportion of mature oocytes'.

Independent variable	Total number of Oocytes		Number of mature oocytes		Proportion of mature Oocytes	
	Standard coefficient β	*P*-value	Standard coefficient β	*P*-value	Odds ratio	*P*-value
Age	−0.391	<0.001	−0.142	0.001	1.00	0.784
BMI	0.011	0.783	−0.039	0.377	0.99	0.018
Peak E_2	0.200	<0.001	0.151	0.001	1.00	0.667
Post-trigger LH	0.198	<0.001	0.168	<0.001	1.00	0.461
Post-trigger Progesterone	0.500	<0.001	0.484	<0.001	1.00	0.848
LH rise	0.090	0.025	0.091	0.039	1.00	0.517

GnRH-a sonrası 8-12. saat LH <15 IU/l, P <3,5 ng/mL ise oosit verimi kötü…

ANCAK....

Human Reproduction, Vol.27, No.5 pp. 1357–1367, 2012
Advanced Access publication on February 21, 2012 doi:10.1093/humrep/des037

human reproduction

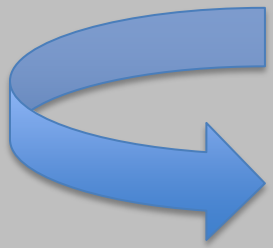
CASE REPORT *Infertility*

Empty follicle syndrome: successful treatment in a recurrent case and review of the literature

Date	Gonadotrophin	Dose Amp/ units per day	Total	GnRH analog	Protocol	Ovulation triggering	Estradiol levels (pg/ ml)	Follicle no.	Progesterone levels at hCG day (ng/ml)	Oocyte no.	Oocyte descriptio
1/2005	hMG	3	21	None	Gonadotrophin only	r-hCG*2	569	18	<0.5	0	
3/2005	hMG	4	36	GnRH agonist (0.1 mg/day)	LD	r-hCG*2		15		0	
7/2005	hMG	4	36	GnRH antagonist (cetrorelix acetate)	Antagonist, flexible	r-hCG	2027	12	8	0	
9/2005	hMG	4	36	GnRH agonist (3.75 mg)	LD	r-hCG	1810	30	<0.5	3	M1*1 M2*2[a]
3/2006	rFSH	300	2400	GnRH antagonist (Ganirelix)	Antagonist, flexible	r-hCG	2224	16	0.94	0	
7/2008	hMG	4	32	GnRH agonist (0.1 mg/day)	LD	r-hCG	934	13	<0.5	1	M1*1[a]
9/2008	HP-hMG	4	40	GnRH agonist (0.1 mg/day)	LD	hCG	4030	14	1.23	4	M1*2[a] GV*1 Atretic*1
2/2011	hMG	4	32	GnRH antagonist (Ganirelix)	Antagonist, flexible	GnRH agonist (0.1 mg) + r-hCG	1841	10	0.91	18	M2*16[b] M1*1

Fruchter et al 2012

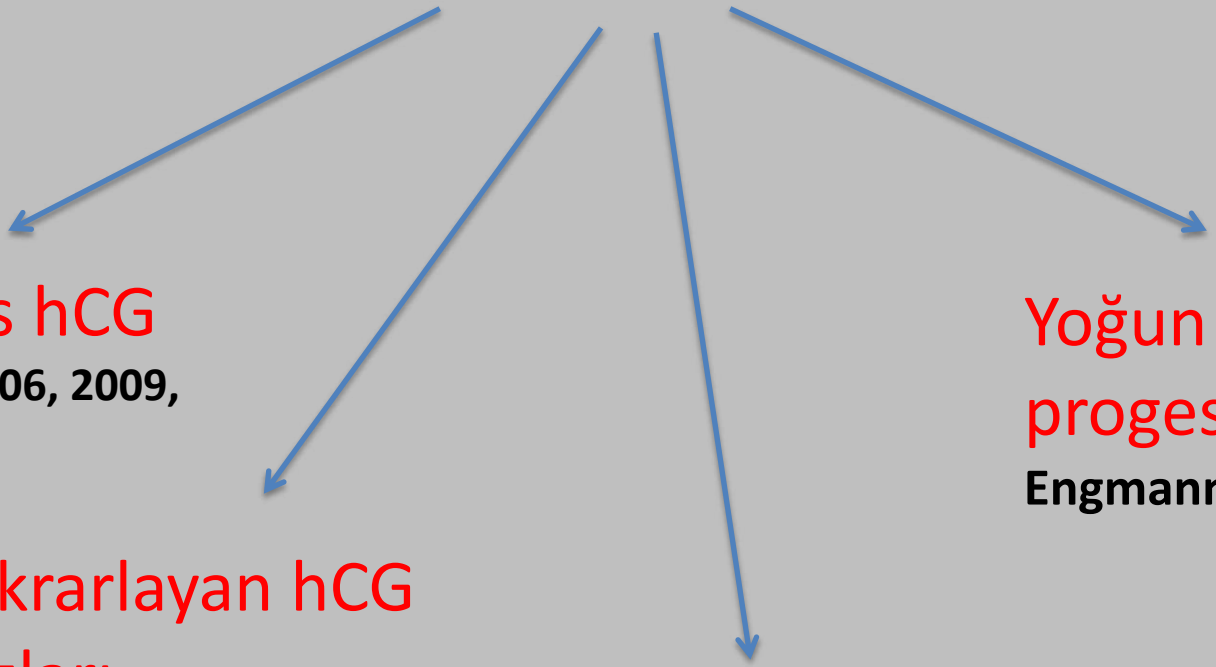
Sorun: Luteal Faz Desteği?



Çözüm:

- LH, E2 ve P düzeyini yüksek tutmak…

NASIL?



Tek bolus hCG

Humaidan 2006, 2009, 2010

Tekrarlayan hCG dozları

Castillo 2010

Rekombinant LH

Papanikolau 12

Yoğun estrojen-progesteron

Engmann08

Agonist trigger: what is the best approach? Agonist trigger and low dose hCG

Peter Humaidan, M.D., D.M.Sc.

1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study

Peter Humaidan, M.D.,[a] *Helle Ejdrup Bredkjær, M.D., Ph.D.,*[b] *Lars Grabow Westergaard, M.D., D.M.Sc.,*[c] *and Claus Yding Andersen, D.M.Sc.*[d]

Pregnancy outcome in GnRHa vs. hCG-group.

Variable	GnRHa	hCG	OR (95% CI)	*P* Value
Patients, n	152	150		
Rate of transfer, n (%)	130/152 (86)	138/150 (92)	0.5 (0.4–0.7)	.054
Embryos transferred, median (range)	2 (1–2)	2 (1–2)		
Positive hCG per ET, n (%)	63/130 (48)	66/138 (48)	1.0 (0.9–1.2)	.36
Clinical pregnancy per patient, n (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	.29
Ongoing pregnancy per patient, n (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	.16
Early pregnancy loss, n (% of positive hCG)	13/63 (21)	11/66 (17)	1.3 (0.7–1.9)	.36

REVIEW

GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis

Lawrence Engmann [a,*], Claudio Benadiva [a], Peter Humaidan [b]

Table 2 Luteal phase support protocols after gonadotrophin releasing hormone agonist trigger.

Protocol	*Indication*
Intensive luteal support	Peak serum oestradiol ≥4000 pg/ml
Dual trigger with GnRHa and HCG 1000 IU	Peak serum oestradiol <4000 pg/ml
GnRHa trigger and HCG 1500 IU 35 h later	<25 follicles
Freeze all oocytes or embryos	≥25 follicles

GnRHa, gonadotrophin releasing hormone agonist.

Engmann 2016, RBM, in press

The updated Cochrane review 2014 on GnRH agonist trigger: repeating the same errors

Shahar Kol [a,*], Peter Humaidan [b], Birgit Alsbjerg [b], Lawrence Engmann [c], Claudio Benadiva [c], Juan A Garcia-Velasco [d], Human Fatemi [e], Claus Yding Andersen [f]

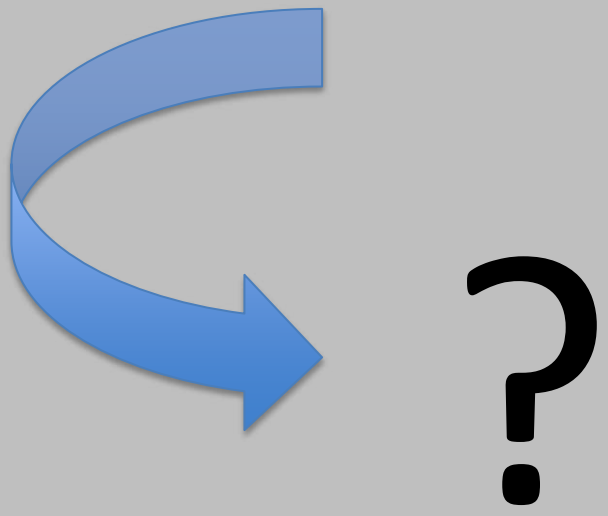
VS

Conclusions

The evidence suggests that GnRH agonists as a final oocyte maturation trigger in fresh autologous cycles should not be used routinely due to its association with a significantly lower live birth rate, lower ongoing pregnancy rate and higher rate of early miscarriage. The only indication for GnRH agonist use as oocyte maturation trigger is in women who donate oocytes to recipients or in women who wish to freeze their eggs for later use in the context of fertility preservation.

An OHSS-Free Clinic by segmentation of IVF treatment

Paul Devroey*, Nikolaos P. Polyzos, and Christophe Blockeel



Freeze-All Politikası-
Segmentasyon:

GnRH-antagonist siklusu
GnRH-a trigger
Freeze-all
Takip eden sikluslarda thaw ET

Human Reproduction vol.14 no.6 pp.1457–1460, 1999

Elective cryopreservation of all pronucleate embryos in women at risk of ovarian hyperstimulation syndrome: efficiency and safety

- 125 olgunun prospektif analizi
- OHSS için riskli olgular (E2 >1500 pg, OPU> 15 oosit
- A grubu: fresh B grubu: pronükleus Freeze-All

	Group A	Group B
No. of patients	67	58
No. of transfer cycles	74	79
No. of embryo per transfer cycle[a]	3.2 ± 1.0	3.1 ± 0.8
Clinical pregnancies	31	28
Pregnancy rate per patient (%)	46.3	48.3
Pregnancy rate per transfer cycle (%)	41.3	35.4
Implantation rate (%)	19.3	15
Live birth rate per patient (%)	38.8	39.6

A grubu: 4 OHSS
B grubu: 0 OHSS

Ferrareti et al 1999

Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective, observational proof-of-concept study

G.Griesinger[1], S.von Otte, A.Schroer, A.K.Ludwig, K.Diedrich, S.Al-Hasani and A.Schultze-Mosgau

Therefore, we decided to prospectively study the efficacy and safety of the following new protocol in OHSS risk patients: (i) triggering of final oocyte maturation with GnRH agonist instead of hCG in a GnRH-antagonist protocol, (ii) elective cryopreservation by vitrification of all two pronucleate (2 PN) oocytes and (iii) transfer of embryos in subsequent frozen–thawed ET cycle(s) (FT-ETs).

- hCG günü >20 follikül, E2 >4000 pg, önceki OHSS öyküsü: GnRH-a trigger, PN freeze-all
- **OHSS yok**

Griesinger et al 2007

Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol

- GnRH-a trigger sonrası, hCG verilmeden 2 OHSS vakası
- FSH, GnRH veya LH reseptör polimorfizmi?
- Her 2 olguda da toplanan oosit sayısı 30…

Fatemi et al 2014

PCOS-Sonuçlar

- KOH için antagonist protokoller (OK olmadan) agonist protokoller kadar gebelik vermekte
- OHSS oranları, kullanılan gonadotropin dozları antagonist protokoller ile daha AZ
- Antagonist protokollerde, GnRH-a ile ovulasyon tetikleme devam eden gebelikler ve abortuslar için tartışılıyor
- Donasyon ve freeze-all için GnHR-a ideal
- Luteal faz desteği optimize edilmeli

Özet

- GnRH-a trigger sikluslarında ‘high-responder’ tanımı farklılıklar gösteriyor
- Trigger kriterleri konusunda görüş birliği yok
- Trigger günü >20 matür follikül var ise, **E2’den bağımsız** GnRH-a trigger
- Eğer >25 follikül var ise GnRH-a trigger ve freeze-all
- Luteal destek için çalışmalara ihtiyaç var **(steroid olmadan-tekrarlayan düşük hCG dozları)**