

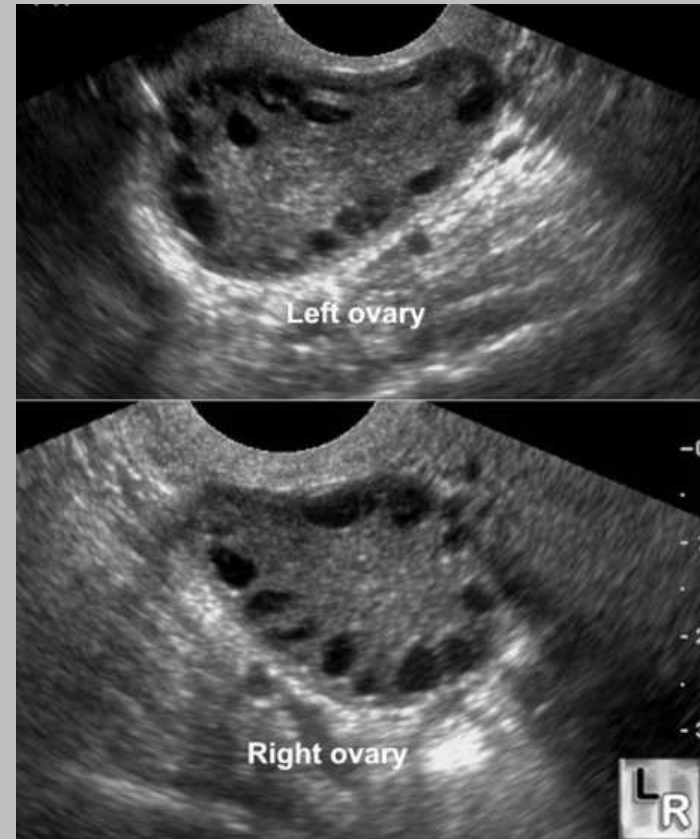
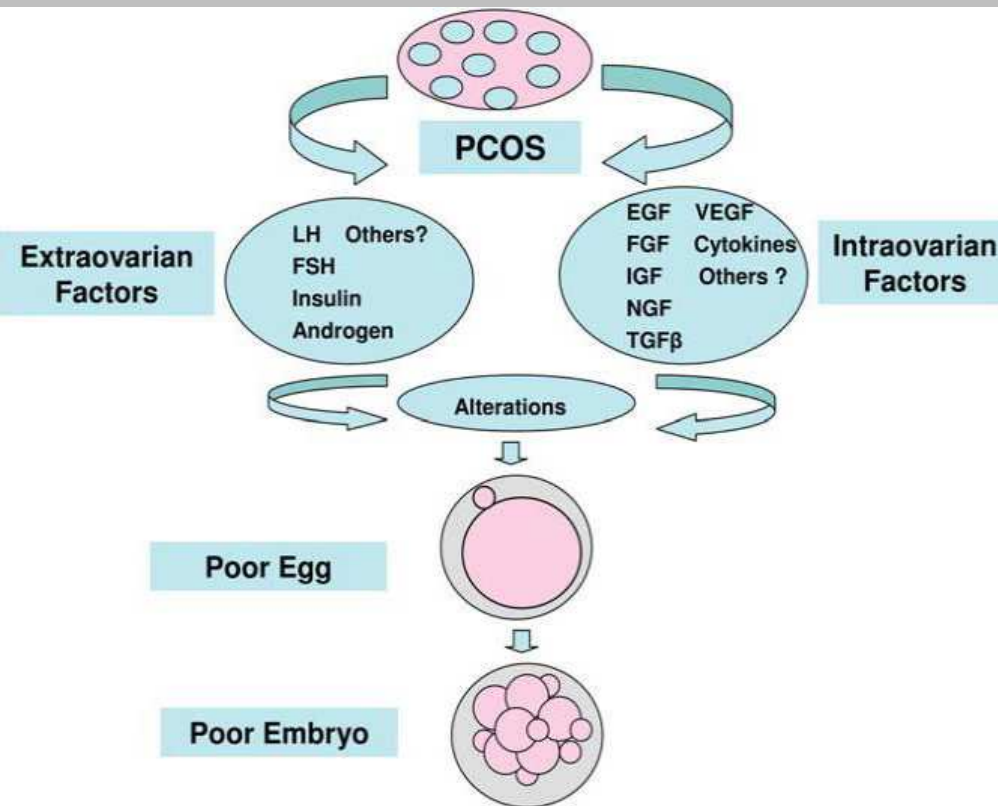
PCOS'da KOH ve GnRH Agonist Trigger'da Güncel Durum

Üreme Tıbbı ve Cerrahisi Derneği
İnfertilite Tedavisinde Güncel
Yaklaşımlar 21 Aralık 2014 İSTANBUL

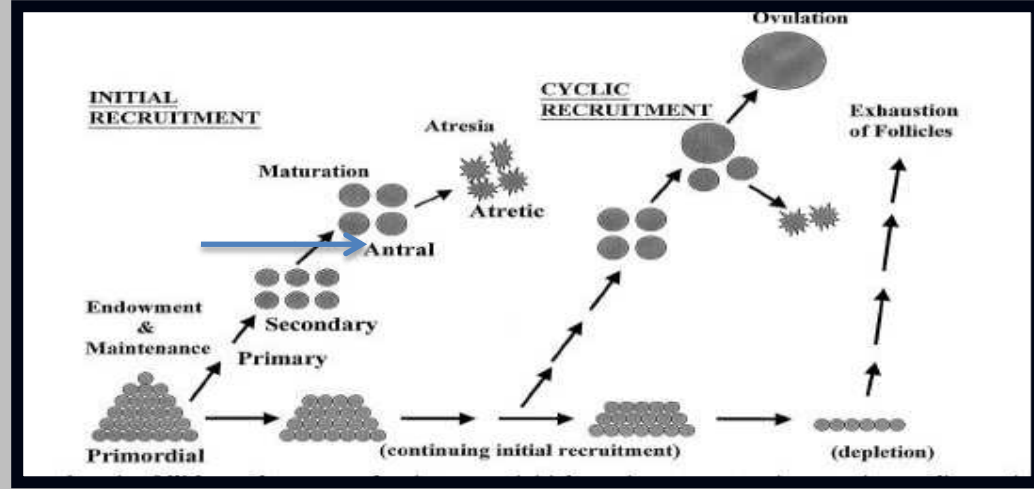
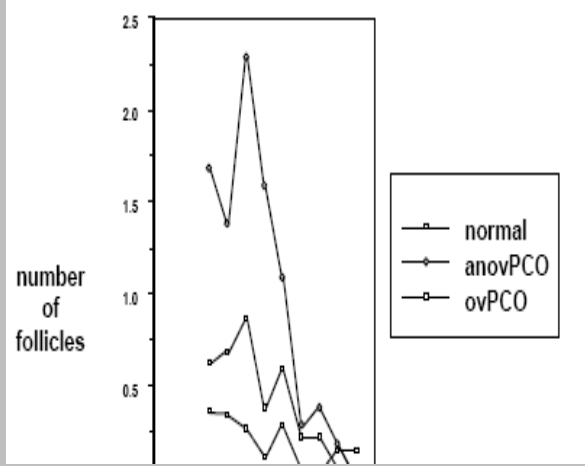
Prof. Dr. Recai PABUÇCU

*Ufuk Üniversitesi Tıp Fakültesi
Kadın Hastalıkları ve Doğum Anabilim Dalı*

PCOS Farklıdır..



PCOS Farklıdır..



Normal overe göre preantral folikül sayısı x6 kat fazladır

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

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.Eijkemans³, E.G.Hughes⁴, J.S.E.Laven², N.S.Macklon¹
and B.C.J.M.Fauser¹

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

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

A.P. Yates^{1,*}, O. Rustamov², S.A. Roberts³, H.V. Thornton⁴, A. Smith¹, and Update Advance Access published online first 12 June 2014
Hum Reprod, Vol.0, No.0 pp. 1–16, 2014

Human
reproduction
update

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

Didier Dewailly^{1,*}, Claus Yding Andersen², Adam Balen³, Frank Broekmans⁴, Nafi Dilaver⁵, Renato Fanchin⁶, Georg Griesinger⁷, Tom W. Kelsey⁸, Antonio La Marca⁹, Cornelius Lambalk¹⁰, Helen Mason⁵, Scott M. Nelson¹¹, Jenny A. Visser¹², W. Hamish Wallace¹³, and Richard A. Anderson¹⁴

¹Department of Endocrine Gynaecology and Reproductive Medicine, Hôpital Jeanne de Flandre, Centre Hospitalier de Lille, Université Lille 2, Lille, France ²Laboratory of Reproductive Biology, Children and Reproduction, University Hospital of Copenhagen, University of Copenhagen, Copenhagen, Denmark ³The Leeds Centre for Reproductive Medicine, Leeds Teaching Hospitals, Leeds LS14 6UH, UK ⁴Department of Reproductive Medicine and Gynecology, University Medical Centre Utrecht, Utrecht 3584 CX, The Netherlands ⁵St. George's, University of London, London SW17 0RE, UK ⁶Department of Obstetrics Gynecology and Reproductive Medicine, Hospital A. Béclère, University of Paris Sud, F-92141 Clamart, France ⁷Department of Reproductive Medicine and Gynecologic Endocrinology, University Clinic of Schleswig-Luebeck, Germany ⁸School of Computer Science, University of St Andrews, St Andrews KY16 9SX, UK ⁹Mother-Infant Department, University of Modena and Reggio Emilia, 41100 Modena, Italy ¹⁰Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, VU University Medical Center, Amsterdam, The Netherlands ¹¹Muirhead Chair in Obstetrics & Gynaecology, University of Glasgow, Glasgow G11 6NT, UK ¹²Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands ¹³Department of Obstetrics and Gynaecology, University of Edinburgh, 17 Millerfield Place, Edinburgh EH9 1LF ¹⁴MRC Centre for Reproductive Health, Edinburgh, UK

Article

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

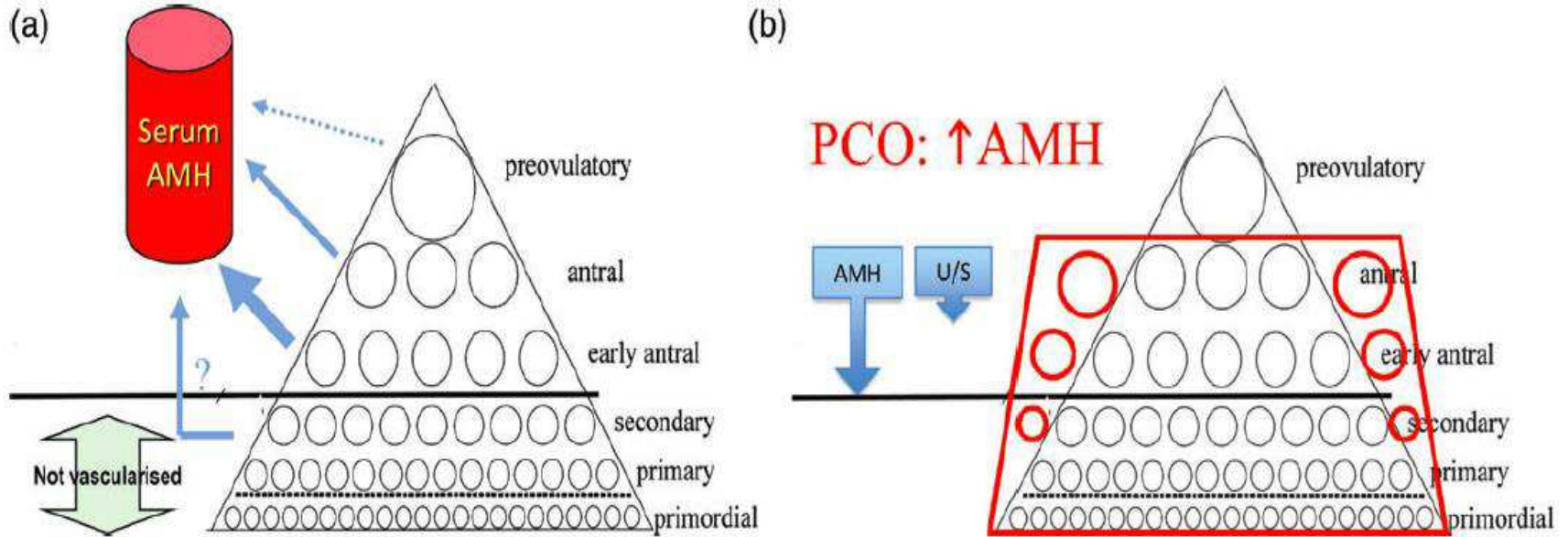


Dr Recai Pabuccu obtained his medical degree in 1975 from Istanbul University Faculty of Medicine, Turkey. After he completed his obstetrics and gynaecology residency, he worked as a clinical fellow in Reproductive Endocrinology and Infertility at the University of British Columbia, Canada. He has published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



PCOS-AMH
Yeni Ufuklar..

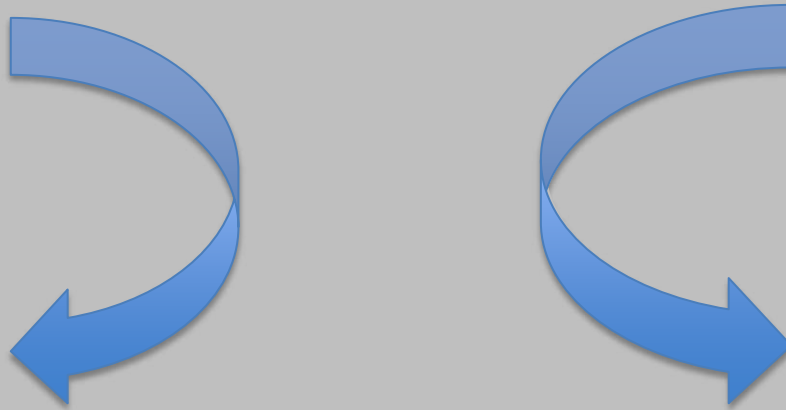
PCOS-AMH



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

Granuloza hücre AMH üretimi

(Sağlıklı Overlere kıyasla)



Anovulatuvar PCOS
olguları x75 kat
fazla

Ovulatuvar
PCOS olguları
x20 kat fazla

Yüksek AMH Ne Yapar?

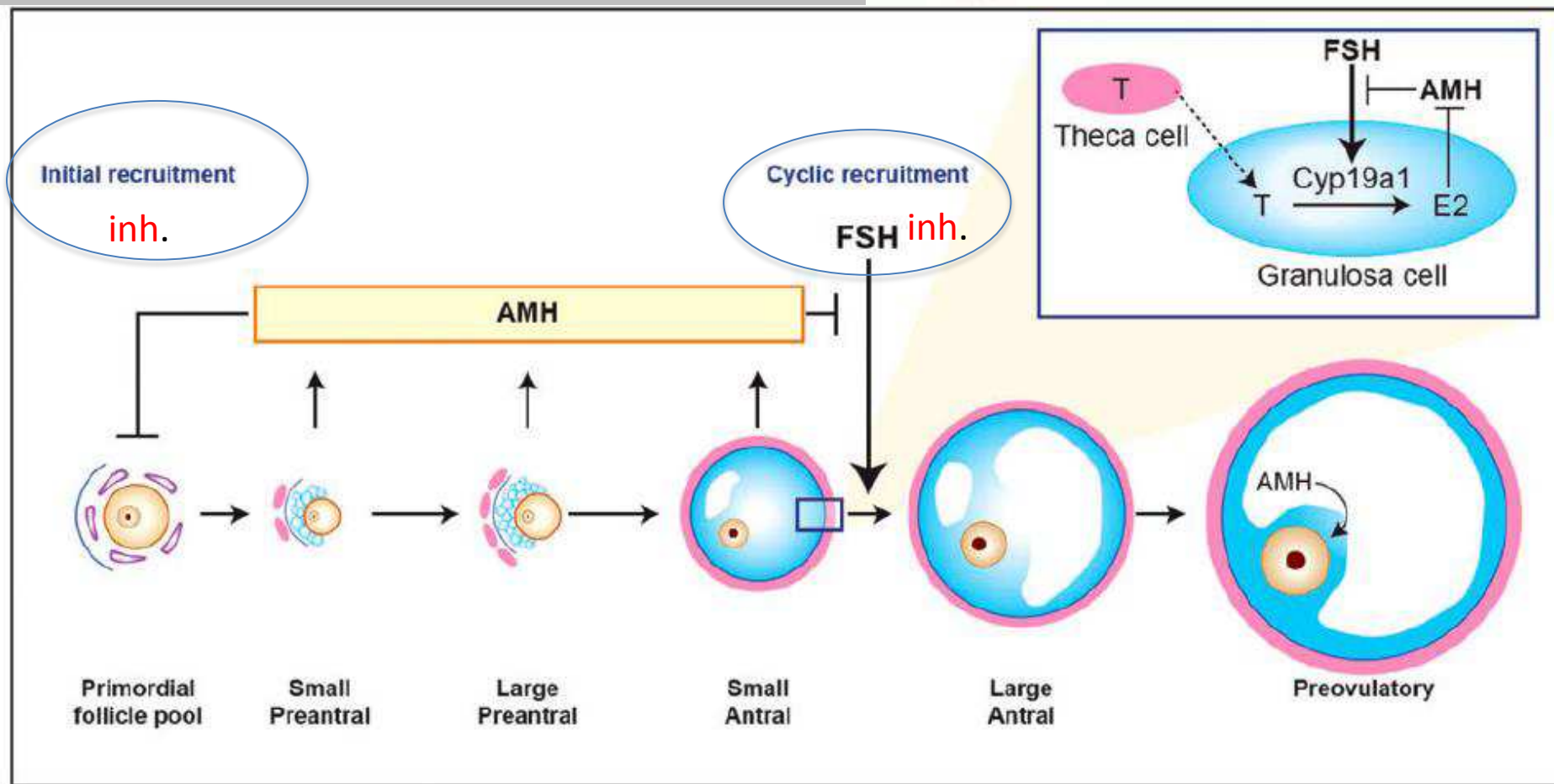


Anti-Müllerian hormone reduces follicle sensitivity to follicle-stimulating hormone in human granulosa cells

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

AMH Ne Yapar?

Important



PCOS-Ne zaman IVF?

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/LOD



- 3.basamak: **COH-IVF**

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

PCOS-COH

• Aşırı cevap-OHSS

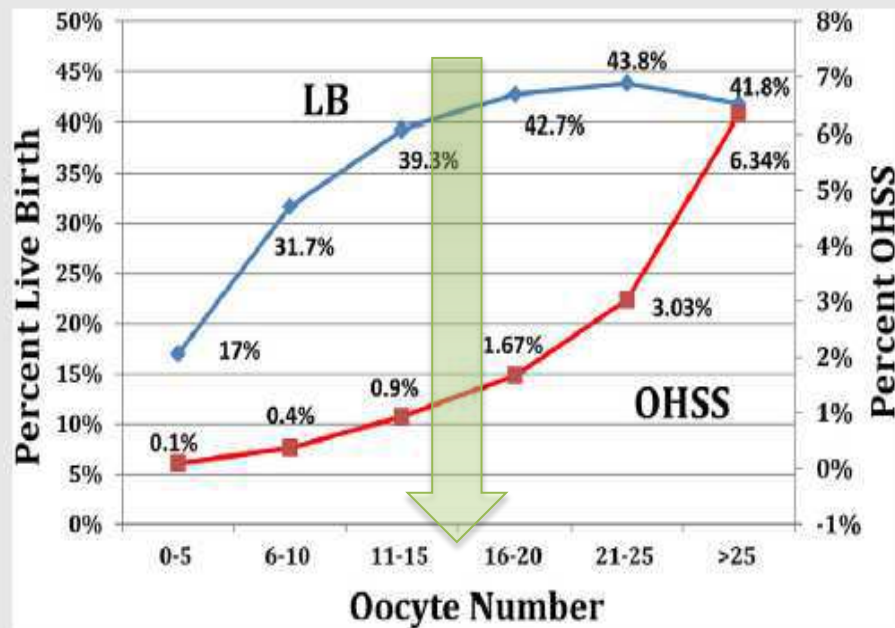
- Düşük fertilizasyon oranları
- Fazla sayıda immatür oosit
- Düşük klivaj oranları
- Düşük implantasyon oranları
- Yüksek abortus oranları

Heijnen, Human reproduction update 2006

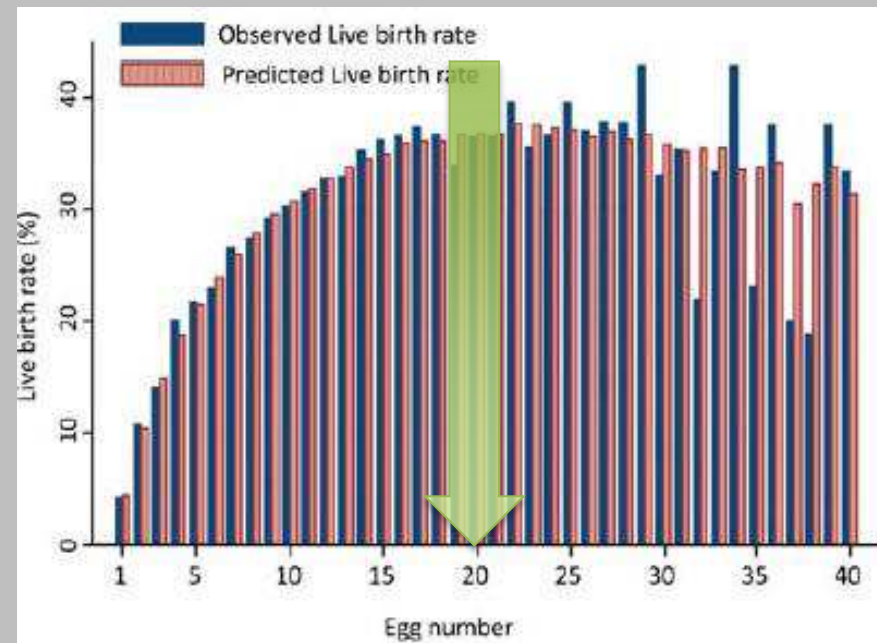


Yüksek Yanıt Sorunları..

Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles



Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles



PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

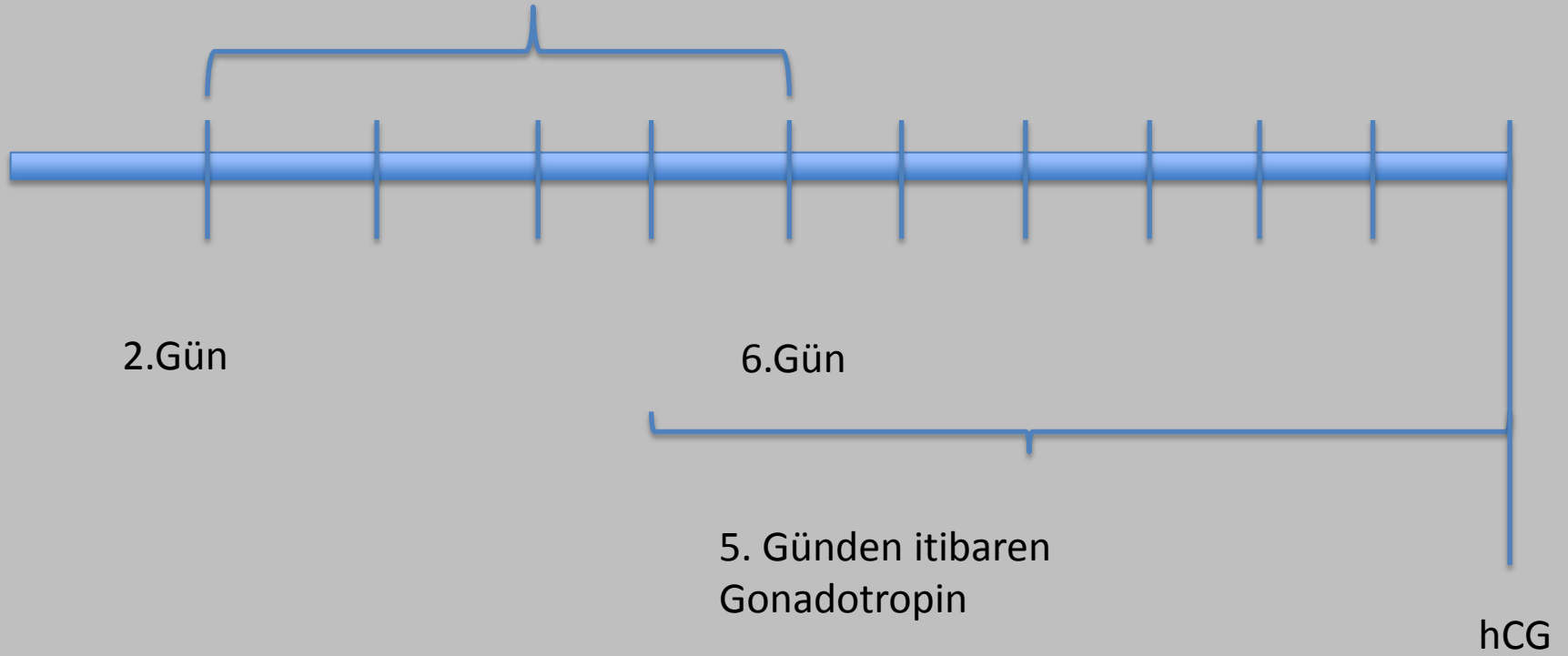
Modifiye Protokoller

- 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

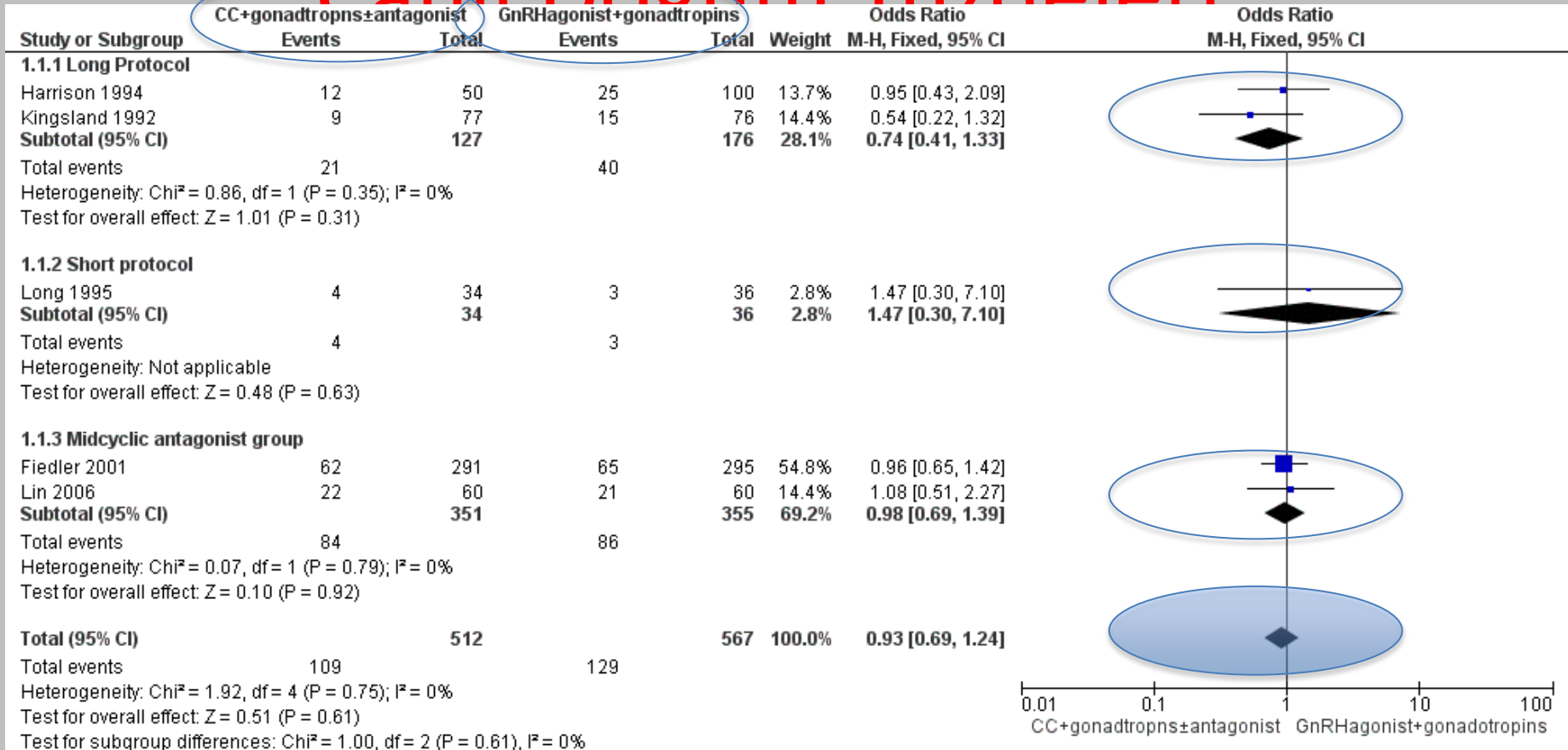
Clomiphene 50 mg 2x1



Minimal-Mild Stimulasyon

Sonuçlar

Canlı Doğum Yüzdeleri

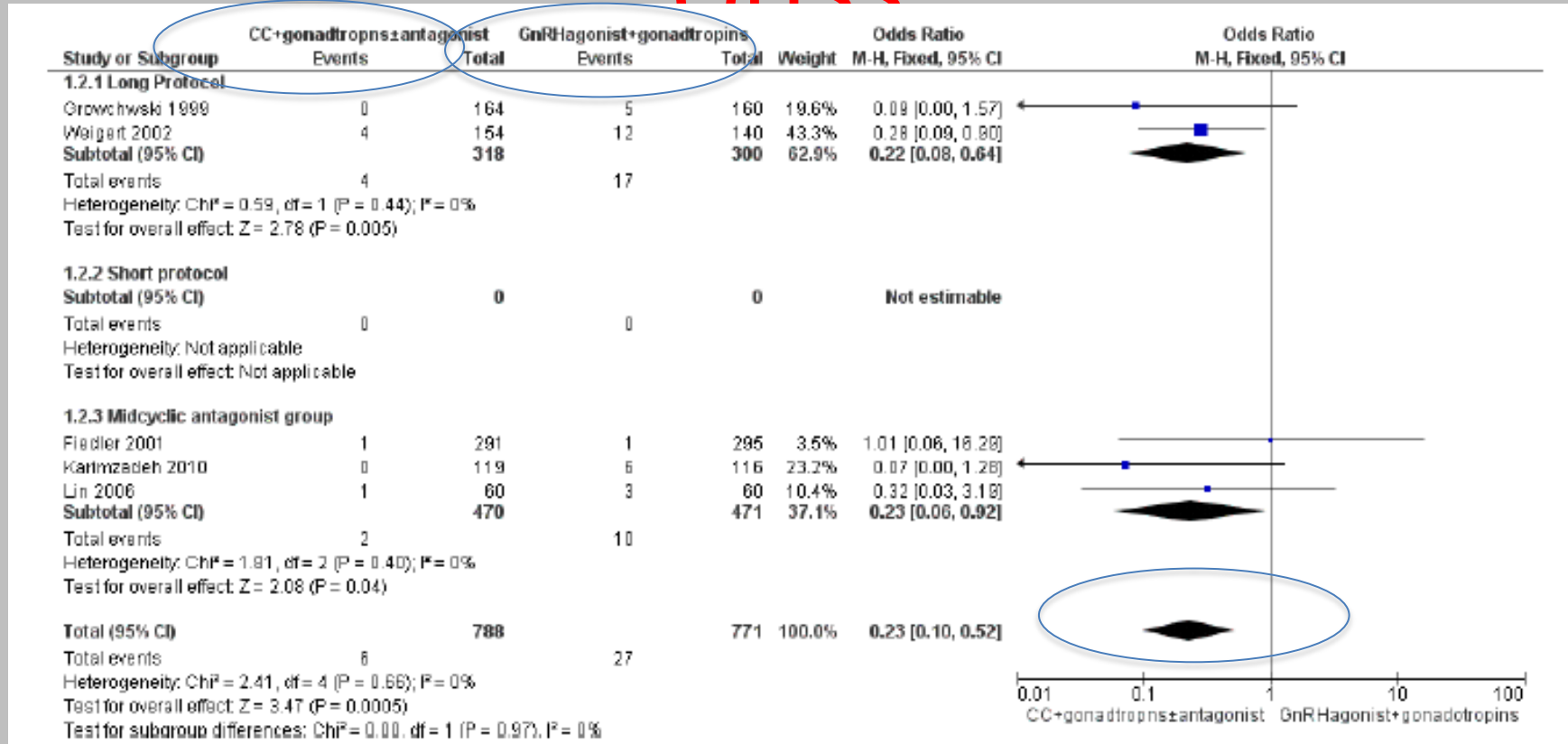


Canlı doğum oranları benzer

Minimal-Mild Stimulasyon

Sonuçlar

OHSS



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

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

Modifiye Protokoller

- GnRH antagonist sikluslarda GnRH agonist ile ovulasyon tetikleme
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PCOS-COH

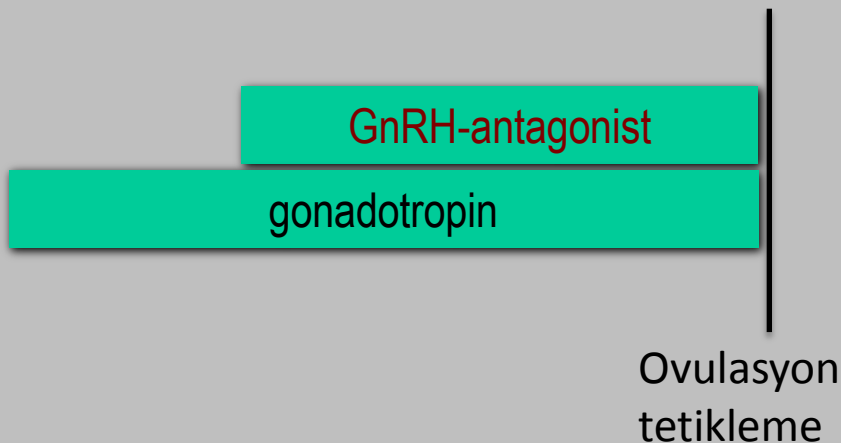
Agonist vs Antagonist

GnRH-ANTAGONİST:

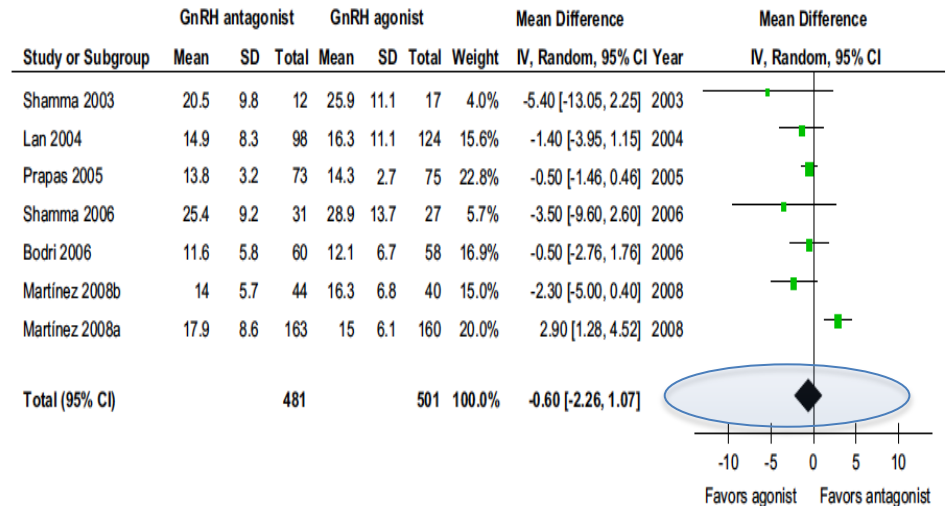
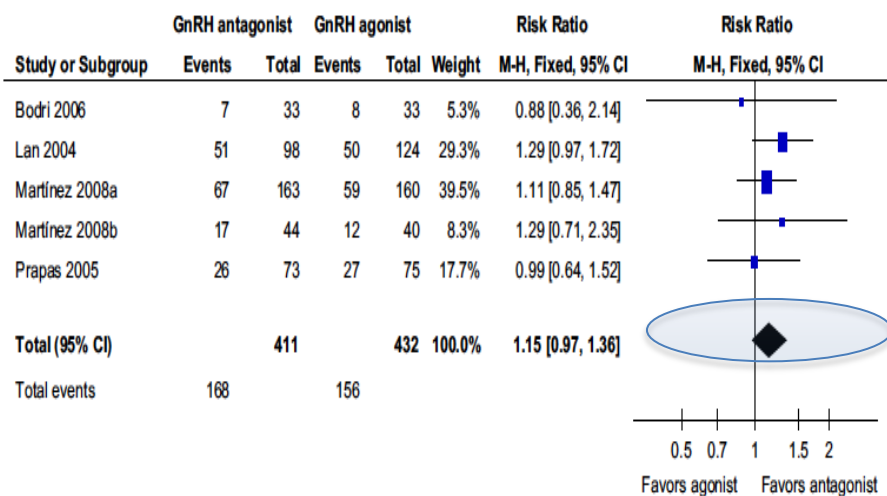
- Flare up etki yok
- Daha kısa sürede cevap
- Daha az gonadotropin dozu
- Fizyolojik siklusa benzer
- OHSS riskinde azalma



Özellikle
PCOS
grubunda
avantajlı ??



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



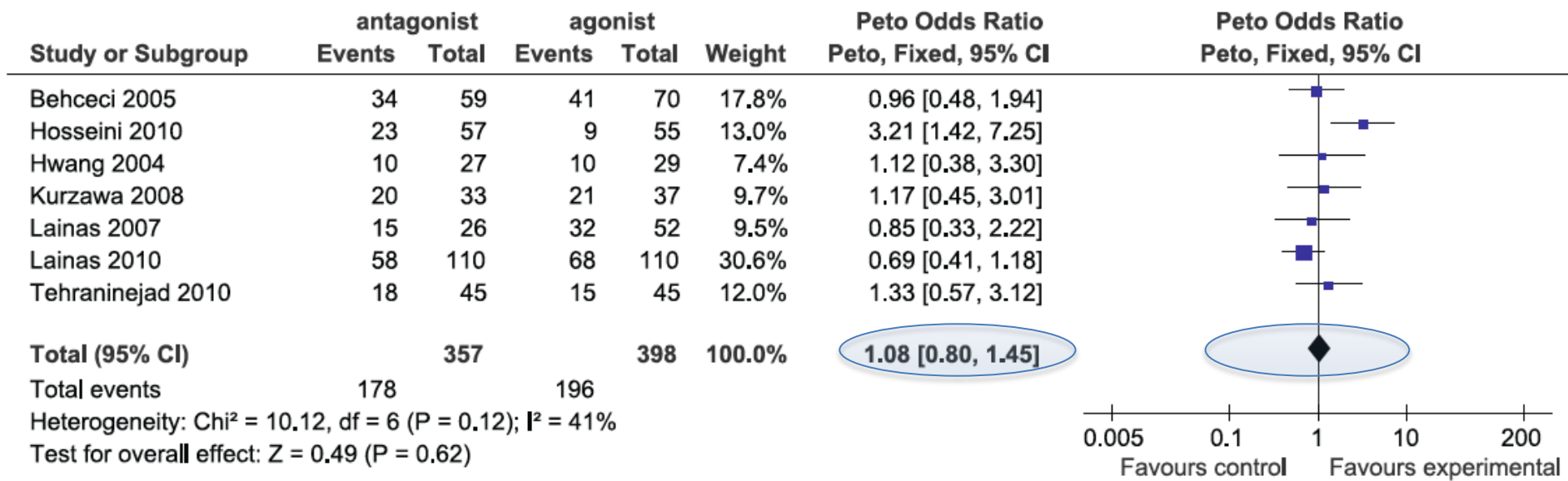
Donör sikluslarında, OPR ve toplanan oosit sayısı için gruplar arasında fark YOK

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

ÖZET: PCOS grubunda Agonist vs Antagonist

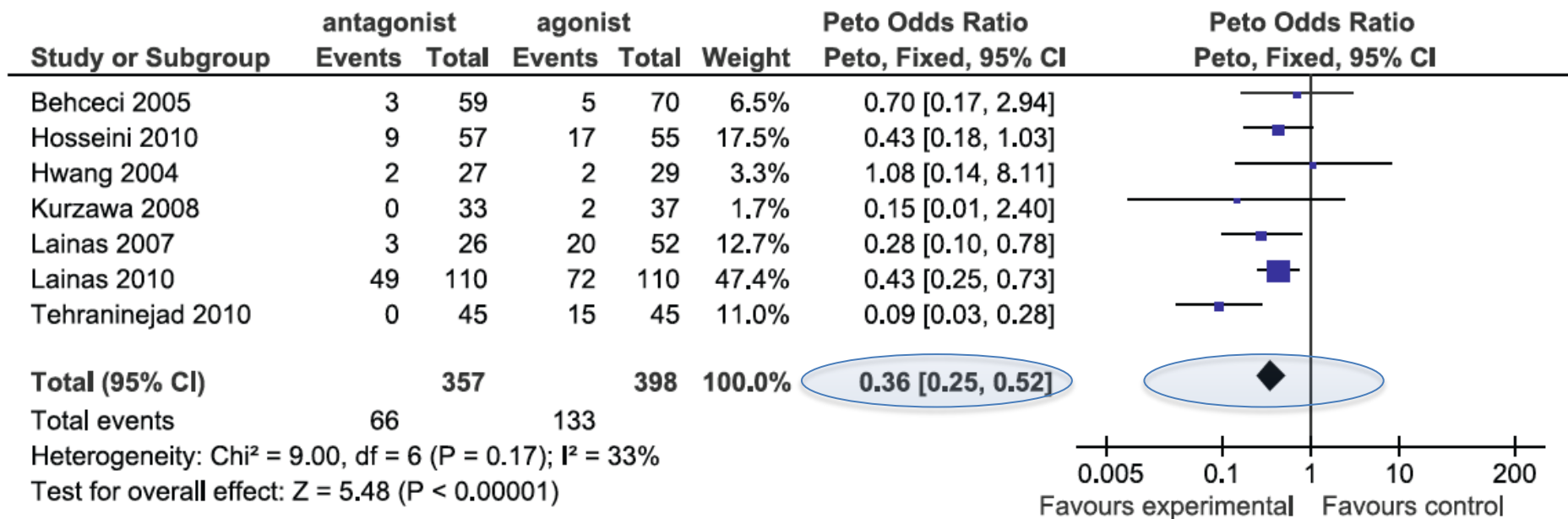
7 çalışma, 755 hasta

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



GnRH antagonist sikluslarda, agonist ile benzer klinik gebelik oranları (OR:1,08)

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



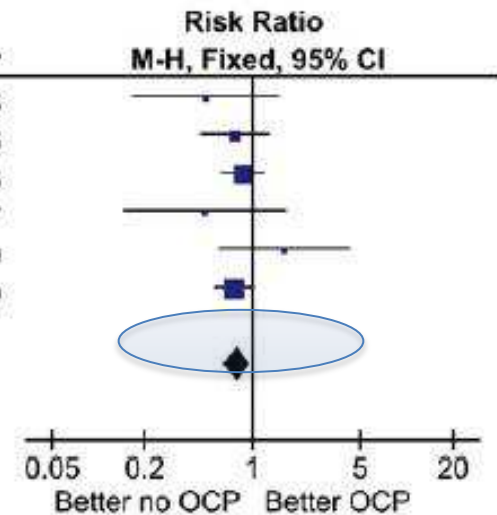
GnRH antagonist siklularda, agonist siklularda göre anlamlı az OHSS oranları (OR:1,08)

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		no OCP		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI		
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)								



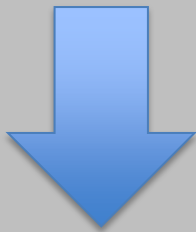
- Antagonist siklularda, OKS eklenmesi ile OPR anlamlı olarak daha az
- Siklus süresi ve kullanılan gonadotropin dozu daha fazla

Griesinger et al 2010

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

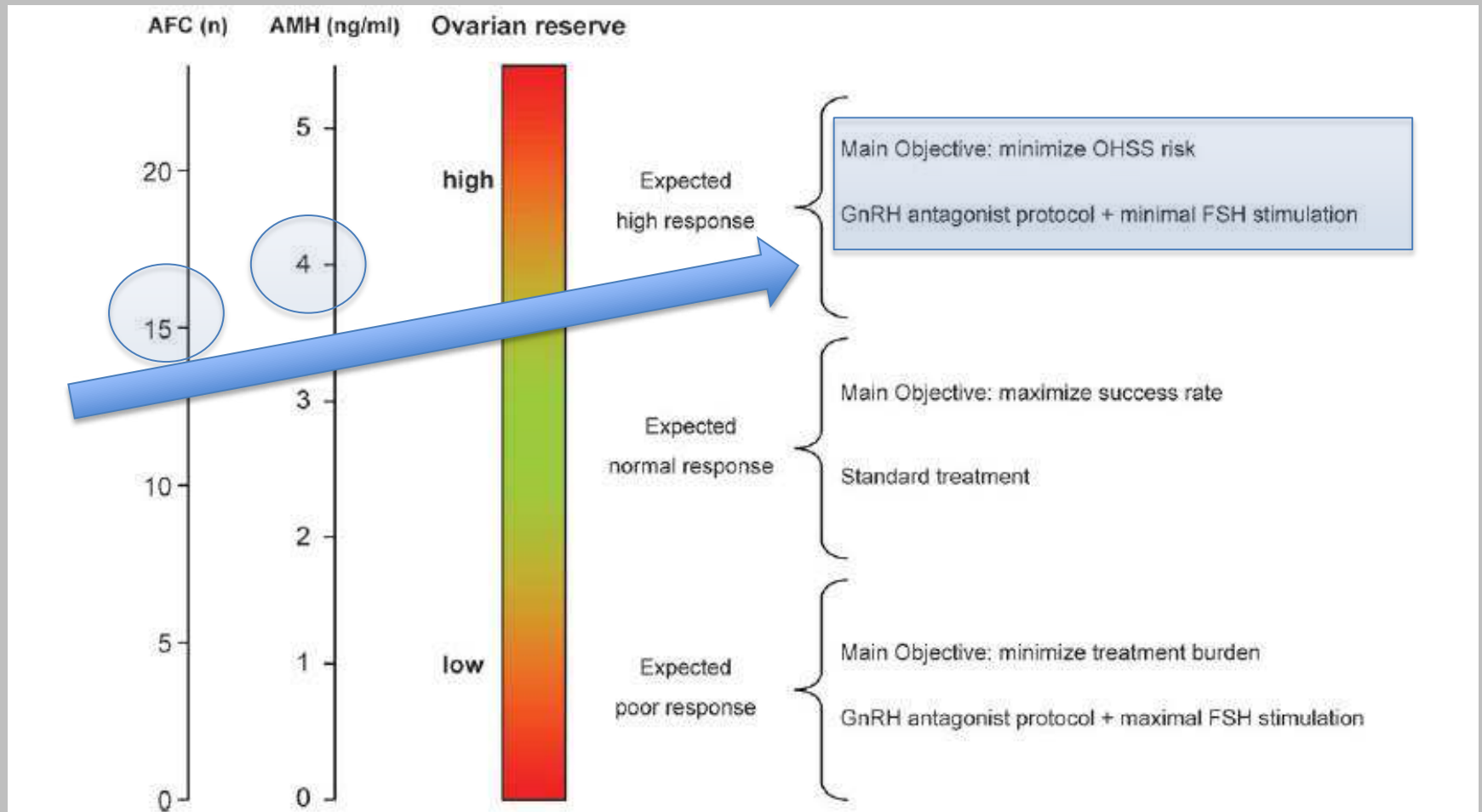


Başlangıç Dozu???

PCOS Modifikasyonları

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

PCOS-Yüksek Yanıt



AMH Based Models...

Anti-Müllerian hormone-based approach to controlled ovarian stimulation for assisted conception

Nelson 2009

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

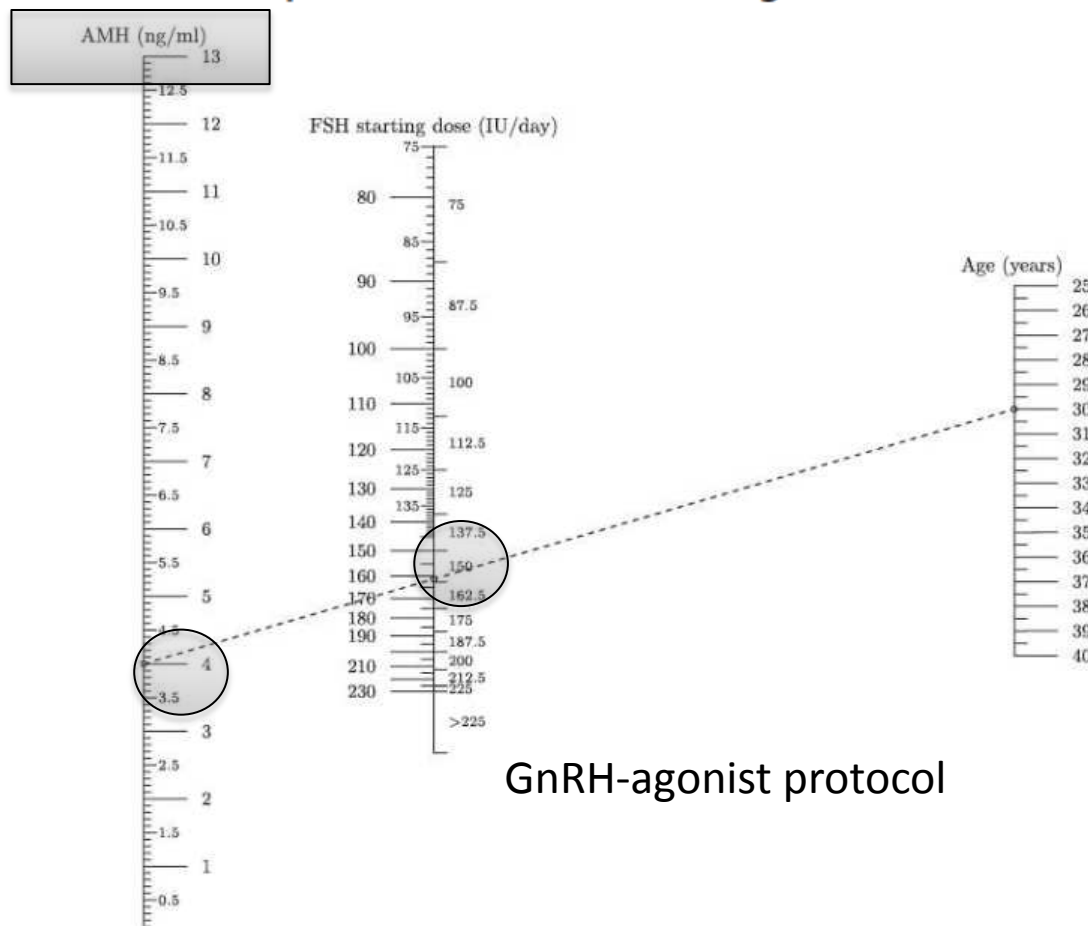
Yates 2011

Antimüllerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients

Arce 2013

Development of a nomogram based on markers of ovarian reserve for the individualisation of the follicle-stimulating hormone starting dose in *in vitro* fertilisation cycles

A La Marca,^a E Papaleo,^b V Grisendi,^a C Argento,^a S Giulini,^a A Volpe^a



AMH is significant contributor of ovarian sensitivity (number of oocytes retrieved per unit of starting dose of FSH)

PCOS-COH

COH Protokolleri

- Minimal-mild stimulasyon
- GnRH agonist
- GnRH antagonist

PCOS Modifikasyonları

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

Tehlike: OHSS

- 31 yaşında hasta.....ciddi ARDS....ex
Fineschi et al., 2006
- 28 yaş Japon hasta....şiddetli OHSS...akut
akciğer yetmezliği....ex Semba et al., 2000
- 21 yaşındaserebral infarkt....Komplet
persistan hemipleji Hwang et al., 1998
-

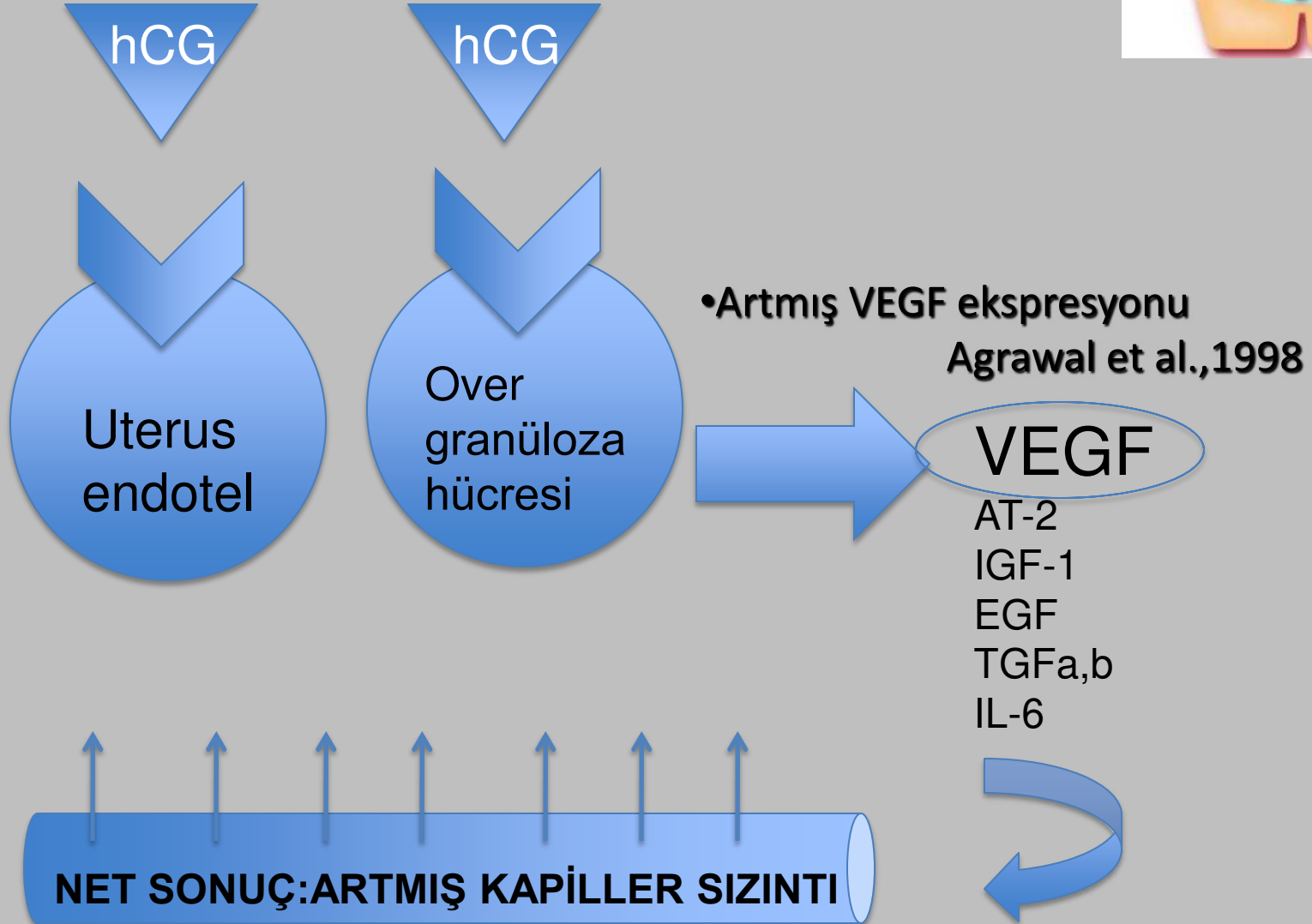
Ovulasyon Tetiklemede hCG

- 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

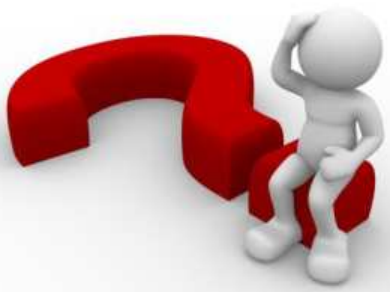


OHSS'yi
predikte
edebilir miyiz?

OHSS
öngördüğümüz
popülasyonda
elimizdeki
silahlar neler?

OHSS Prediksyonu için Özet

Risk Faktörleri	Cut-off
<i>Kişiye bağlı (Primer)</i>	
Yüksek AMH	3.36 ng/mL
Genç yaş	<33 yaş
Önceki OHSS öyküsü	hospitalizasyon
PCO benzeri overler	>24 antral follikül
<i>Over Cevabına Bağlı (Sekonder)</i>	
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	-



OHSS Prediksyonu

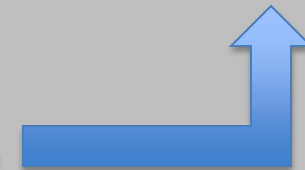
- OHSS'yi net olarak tahmin etmek güç
- Siklus başında ve geç folliküler dönemde elimizdekiler ile önlem almak durumundayız..

Preventing ovarian hyperstimulation syndrome: guidance for the clinician

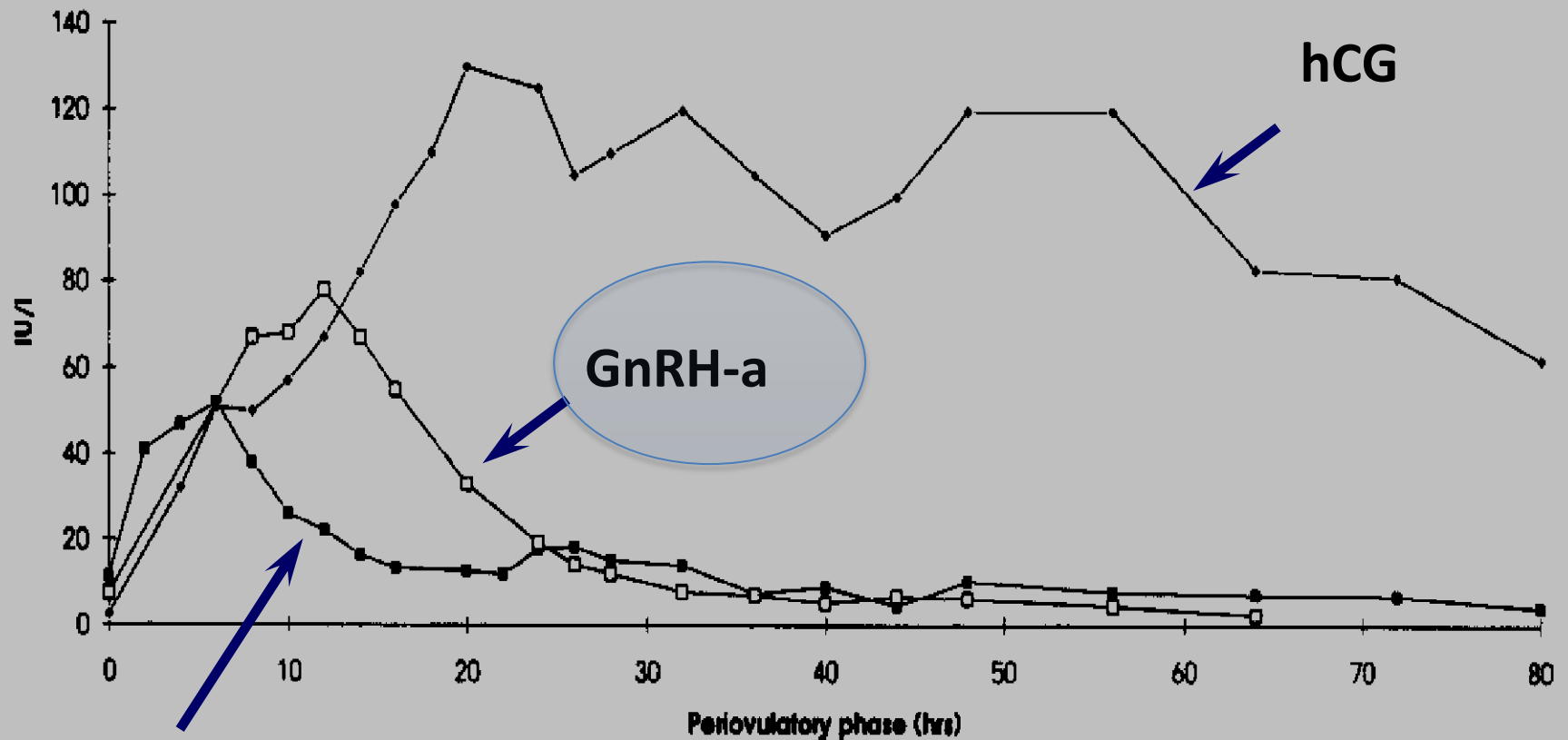
Peter Humaidan, M.D.,^a Jens Quartarolo, M.D.,^b and Evangelos G. Papanikolaou, Ph.D.^c

- 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



LH Surge Patternleri



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 Bredkjær², L.Bungum¹, M.Bungum¹, M.L.Grøndahl², L.Westergaard³ and C.Yding Andersen⁴

	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



- İlk çalışma: Normo-responder hastalarda:
- gebelik oranı **düşük**, abortus oranı **yüksek**..
- Sorun nerede????

GnRH-a İlk Çalışmalar

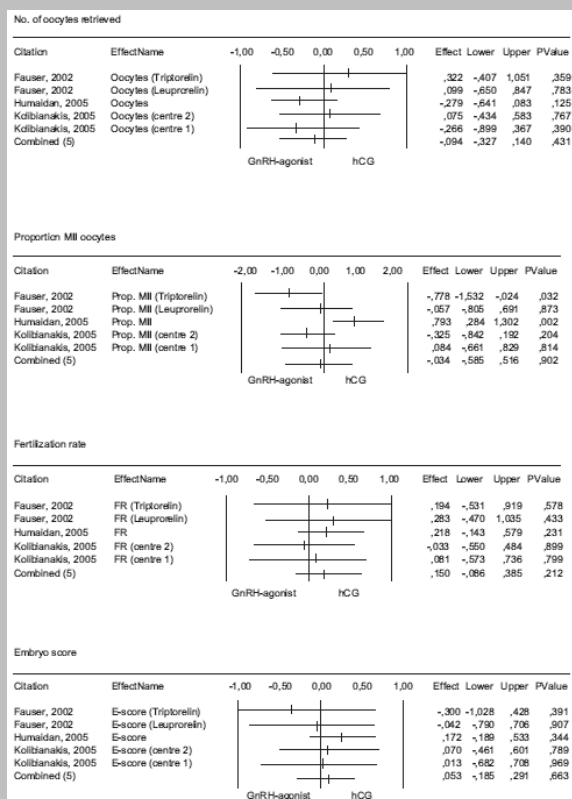
Reference	N	Positive hCG (%)	Ongoing PR (%)	Luteal Support
Humaidan et al ¹⁶	55	29	6	90 mg vaginal P and 4 mg oral E ₂ /day, <i>until the day of the pregnancy test</i>
Kolibianakis et al ¹⁷	50	18	4	Center 1: 600 mg micronized vaginal P and 4 mg oral E ₂ /day until 7 weeks Center 2: vaginal + IM P until 7 weeks
Fauser et al ¹¹	17	NA	18 (triptorelin)	IM P 50 mg for at least 2 weeks
	15		20 (leuprolide)	
Babayof et al ¹⁵	15	33	6.6	IM P 50 mg, oral E ₂ 4 mg only if E ₂ levels <200 pmol/L
Engmann et al ⁴	30	63.3	53.3	IM P 50 mg and 0.3 mg E ₂ patches every other day until 10 weeks and dose adjusted according to serum P and E ₂ levels

hCG, human chorionic gonadotropin; PR, pregnancy rate; P, progesterone; E₂, estradiol; IM, intramuscular; NA, not applicable.

Düşük gebelik oranları...

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.Diedrich¹, P.Devroey² and E.M.Kolibianakis²



0.2 triptorelin/0.5 mg buserelin vs. 10.0000 hCG arasında fark YOK..

Luteal faz: vajinal or i.m. P + oral E2

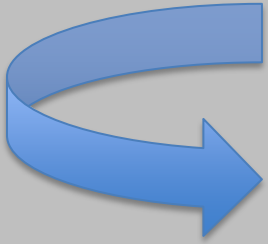
- oosit sayısı
- MII oosit sayısı
- fertilizasyon oranı
- embryo kalitesi



ANCAK;

- devam eden gebelik oranları belirgin DÜŞÜK

Sorun: Luteal Faz Desteği?



Çözüm:

- LH, E2 ve P düzeyini yüksek tutmak...

NASIL?

```
graph TD; A[NASIL?] --> B[Tek bolus hCG]; A --> C[Tekrarlayan hCG dozları]; A --> D[Rekombinant LH]; A --> E[Yoğun estrogen-progesteron];
```

Tek bolus hCG

**Humaidan 2006, 2009,
2010**

**Tekrarlayan hCG
dozları**

Castillo 2010

Rekombinant LH

Papanikolau 12

**Yoğun estrogen-
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 GnRH α vs. hCG-group.

Variable	GnRH α	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. Polyzos³, B. Alsbjerg¹, K. Erb⁴, A.L. Mikkelsen⁵, H.O. Elbaek⁶, E.G. Papanikolaou⁷, and C.Y. Andersen⁸

- PCOS grubu infertil populasyon/Short-antagonist COH
- 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

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Yüksek risk	>14 follicles		RR 95% CI P-value	≤14 follicles düşük risk		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

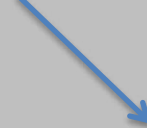
Cycles triggered with GnRH agonist: exploring low-dose HCG for luteal support

- Normoresponder 192 infertil hastanın retrospektif analizi
- Antagonist protokol-agonist trigger
- Standart 600 mg P desteğine ilave olarak; OPU sonrası 1.-3.-7.günler ek hCG

1.grup: **1000 IU**

2.grup: **500 IU**

3.grup: **250 IU**



Pregnancy rate (%)	24/44 (54.5)	59/115 (51.3)	16/33 (48.5)	NS	99/192 (51.6)
Clinical pregnancy (%)	21/44 (47.7)	49/115 (42.6)	13/33 (39.4)	NS	83/192 (43.2)
Moderate OHSS	4 (9.1)	3 (2.6)	1 (3.0)		
Severe OHSS	2 (4.5)	4 (3.5)	1 (3.0)		

A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study

Rec-LH Luteal Destek

- Normo-responder infertil hastalar, prospektif çalışma

1

2

- GnRH-a trigger-standart P
- OPU gününden itibaren gūnaşırı 300IU rec-LH luteal destek

- Rec-hCG trigger-standart P

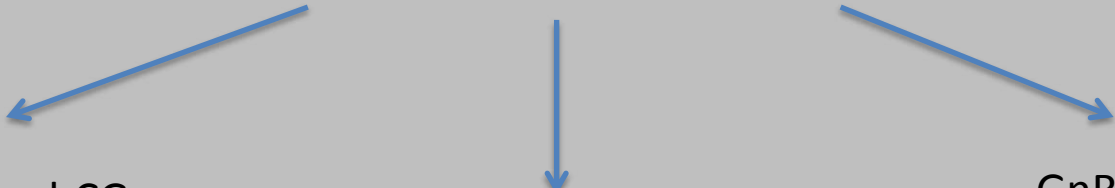
Gruplar arasında gebelik ve OHSS farkı YOK..

	1	2	
OHSS occurrence	0	0	n.a.
Pregnancy outcome			
Positive hCG test (per protocol analysis)	40.0% (6/15)	31.3% (5/16)	.7
Early pregnancy loss	33.3% (2/6)	20.0% (1/5)	n.a
Clinical PR (per protocol analysis)	26.7% (4/15)	25.0% (4/16)	.9
Implantation rate (per protocol analysis)	26.7% (4/15)	31.2% (5/16) ^b	.9
Delivery rate (per intension to treat analysis)	23.5% (4/17)	22.2% (4/18) ^c	.9

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

'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

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?

Peak oestradiol concentration^b
(pg/ml)
No. oocytes retrieved
Fertilization rate (%)
Number of embryos transferred
Clinical pregnancy rate (%)
Implantation rate (%)

1.grup

2944 ± 657

16.3 ± 8.1^c

56 ± 20

1.7 ± 0.5

14.9

13.1

2.grup

3174 ± 910

22.3 ± 9.1^d

56 ± 19

2.4 ± 0.7

15.8

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

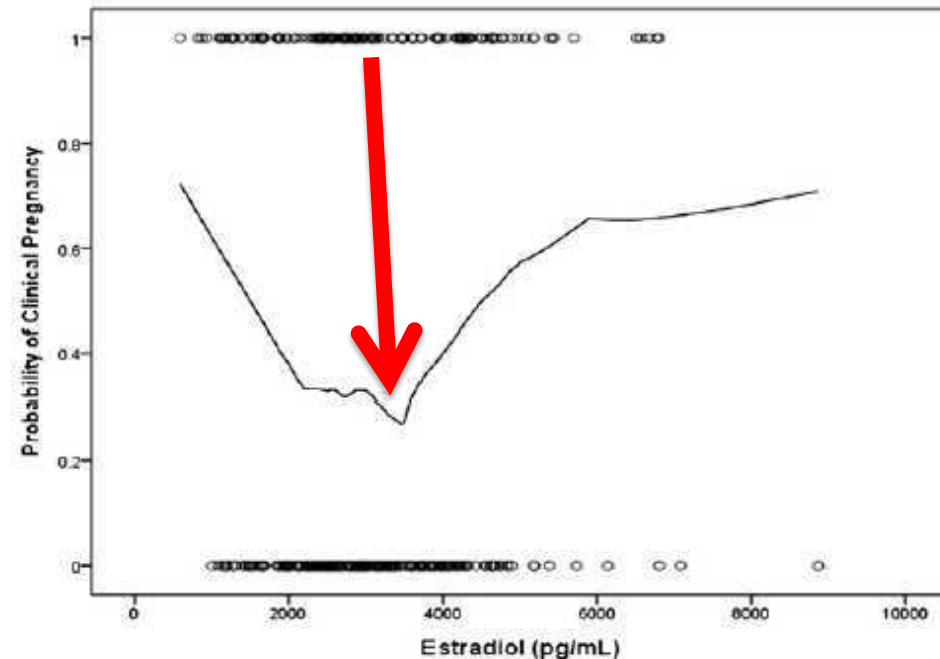


Factors that predict the probability of a successful clinical outcome after induction of oocyte maturation with a gonadotropin-releasing hormone agonist

- 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 ≥ 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

TABLE 2**Characteristics of ovarian stimulation.**

Variable	Group 1: E ₂ < 4,000 pg/mL	Group 2: E ₂ ≥ 4,000 pg/mL	P value
Outcome of ovarian stimulation			
Days of stimulation	9.9 ± 1.5	10.0 ± 1.2	.62
Total gonadotropins (IU)	1,816 ± 724	1,712 ± 759	.09
Patients using hMG (n [%])	41/246 (16.7)	17/69 (24.6)	.13
Oocytes retrieved	25.3 ± 11.9	28.2 ± 9.3	.09
Mature oocytes retrieved	19.1 ± 9.8	19.1 ± 8.7	.99
Fertilization rate (%)	71.4 ± 17.5	71.2 ± 16.2	.93
Patients with embryos available to freeze (n [%])	167/247 (67.6)	48/69 (69.6)	.76
Number embryos frozen	3.1 ± 3.9	4.1 ± 4.5	.11
Endocrine profile			
E ₂ day of trigger (pg/mL)	2,612 ± 776	4,908 ± 921	<.01
E ₂ day of trigger per egg retrieved (pg/mL)	125 ± 71	196 ± 85	<.01
LH day of trigger (IU/L)	2.0 ± 1.8	3.5 ± 2.5	<.01
LH day after trigger (IU/L)	55.3 ± 33.9	69.2 ± 39.9	<.01
E ₂ day of ET (pg/mL)	535 ± 230	844 ± 437	<.01
P day of ET (ng/mL)	26.1 ± 14.6	27.3 ± 14.7	.53
Midluteal E ₂ (pg/mL)	261 ± 188	392 ± 571	<.01
Midluteal P (ng/mL)	31.7 ± 20.6	36.5 ± 30.5	.14

Note: E₂ = estradiol; ET = embryo transfer; FSH = follicle-stimulating hormone; hMG = human menopausal gonadotropin; LH = luteinizing hormone; P = progesterone.

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

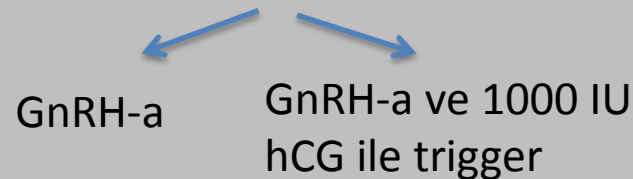
- OHSS için yüksek riskli hastaların retrospektif analizi
- GnRH-a (short-antagonist) vs Coasting (LLP) karşılaştırması
- Gruplarda E2 >4000 pg/L
- **2 grupta da sonuçlar benzer, yüksek E2'li olgularda agonist trigger coasting kadar etkin**

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

Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders

‘Dual Trigger’ Konsepti

- Yüksek riskli hasta grubunda (**peak E2<4000 pg/mL**)
- 2 farklı tekniğin karşılaştırılması, Retrospektif analiz

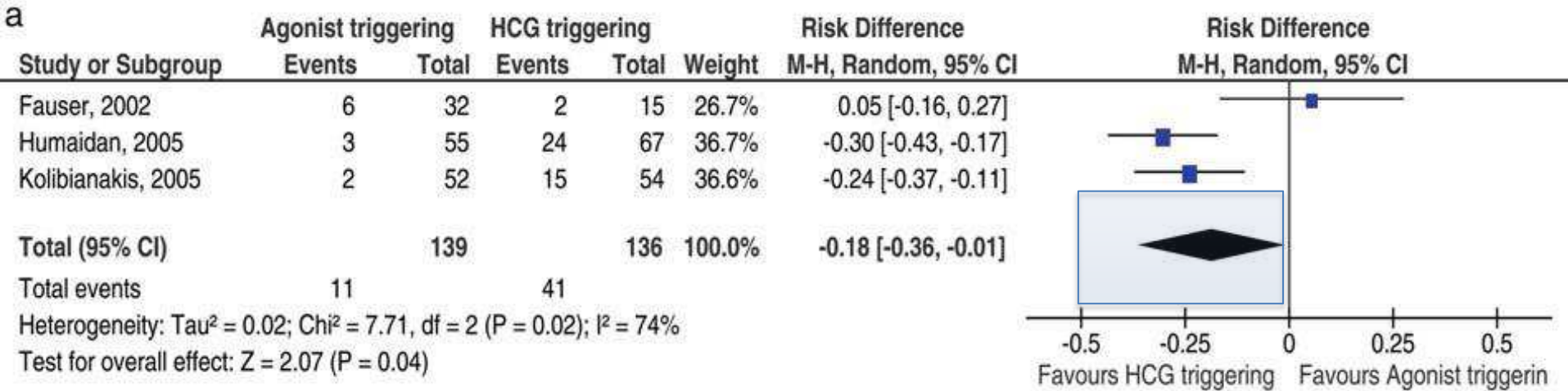


Outcome of IVF cycle.

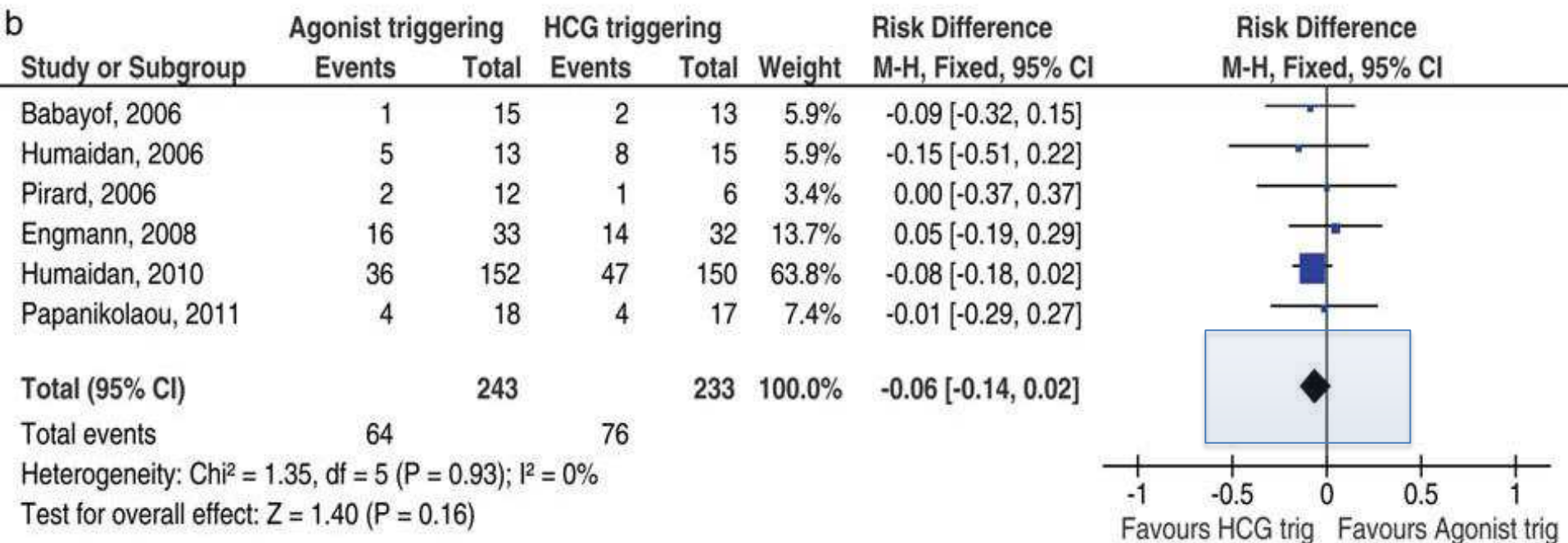
Variable	GnRHa alone	Dual trigger	P value
Biochemical miscarriage rate (%)	14/43 (32.6)	4/26 (15.4)	NS
Clinical miscarriage rate (%)	6/43 (14.0)	3/26 (11.5)	NS
Implantation rate (%)	27/122 (22.1)	26/62 (41.9)	<.01
Clinical pregnancy rate (%)	25/68 (36.8)	20/34 (58.8)	.03
Live birth rate (%)	21/68 (30.9)	18/34 (52.9)	.03
OHSS rate (%)	0/68 (0)	1/34 (2.9)	NS

Dual trigger, OHSS'yi artırmadan gebelik oranlarını iyileştiriyor..

Griffin et al., 2011

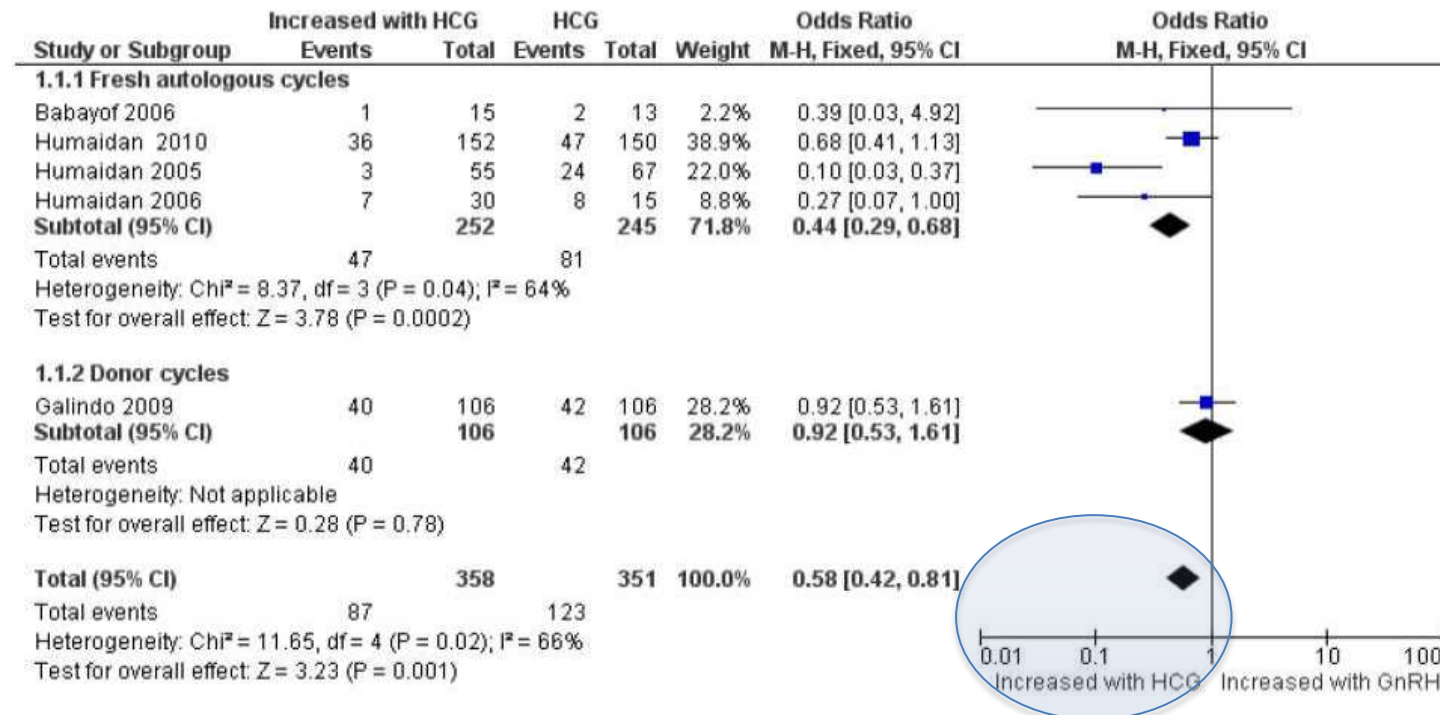


Standart luteal destek ile *devam eden gebelik* oranları **DÜŞÜK..**



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

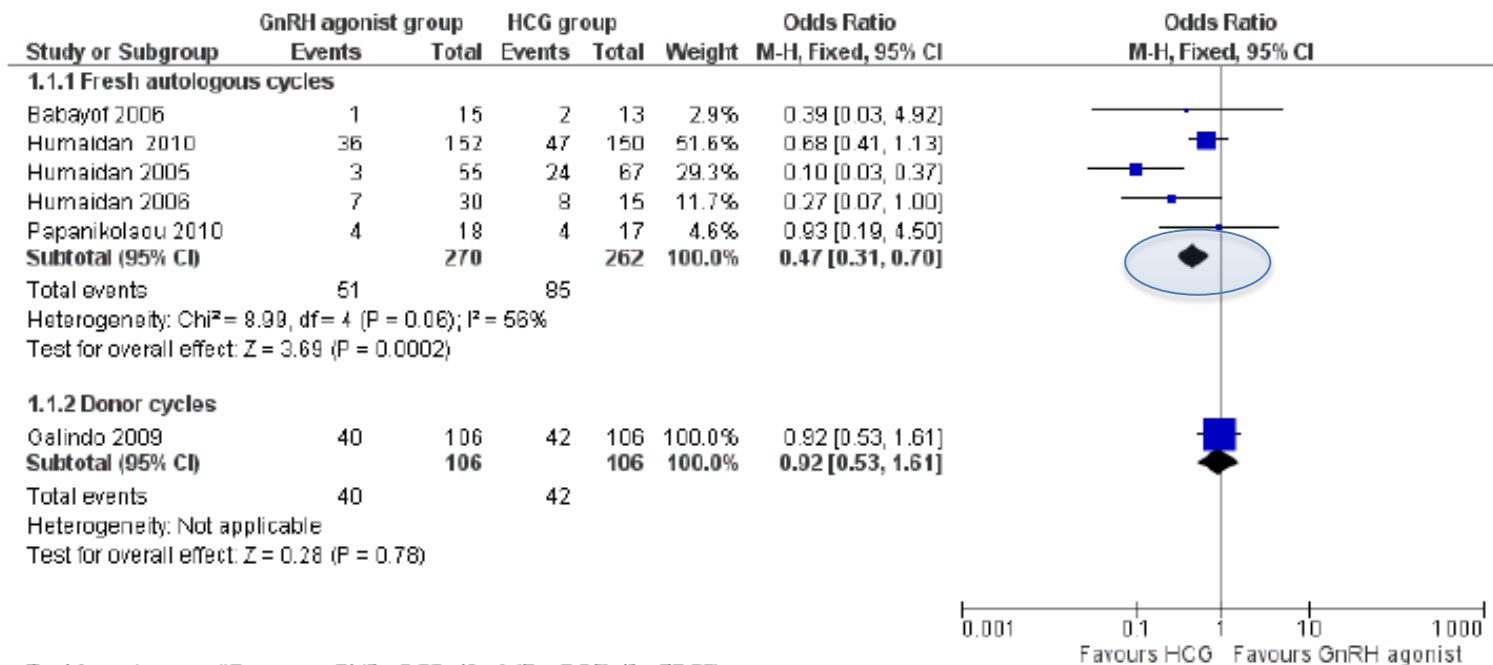
Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles (Review)



- Canlı doğum oranları düşük
- Rutin önerilmemeli, sadece OHSS için yüksek riskli grupta düşünülebilir

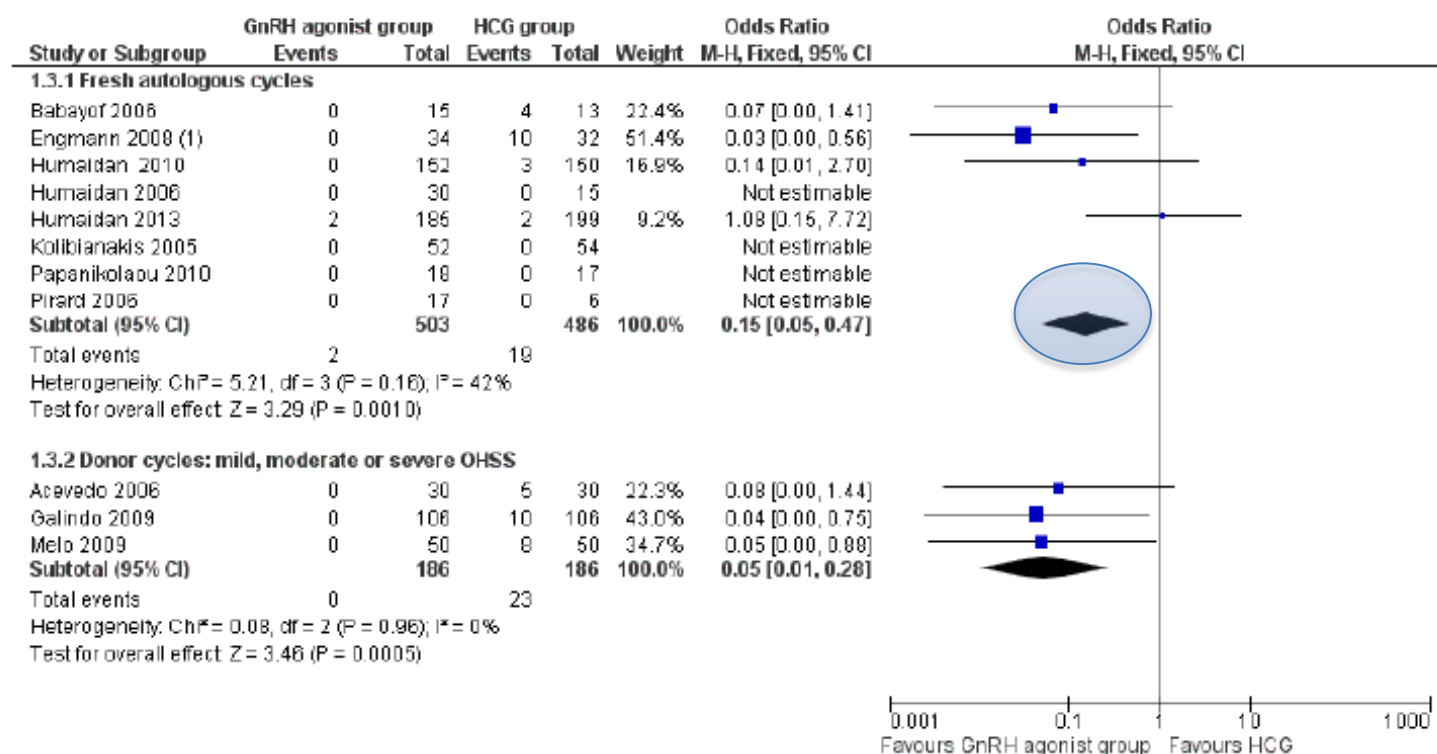
Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology (Review)

Figure 4. GnRH agonist versus HCG for oocyte maturation triggering, outcome: I. Live birth rate per women randomly assigned.



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

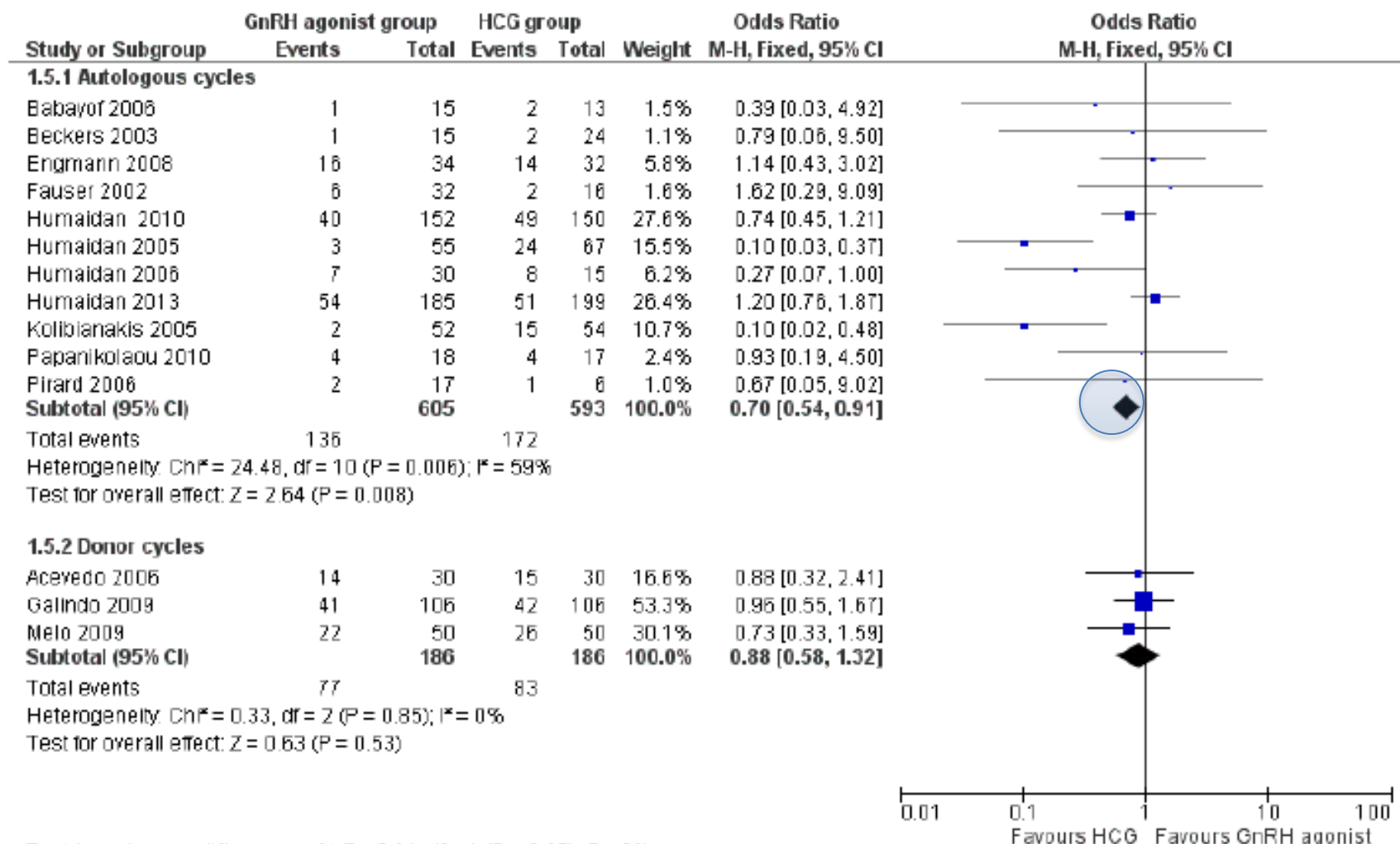
Figure 5. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.2 OHSS incidence per women randomly assigned.



Footnotes

(1) A sensitivity analysis without Engman 2008 (as has high number of events) results in pooled OR (95% CI) 0.28 [0.08, 1.02]

Figure 6. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.3 Ongoing pregnancy rate per women randomly assigned.



Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%

GnRH-a ile Diğer Sorunlar..

- **Empty follicle sendrom**
- Şiddetli OHSS riski???

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

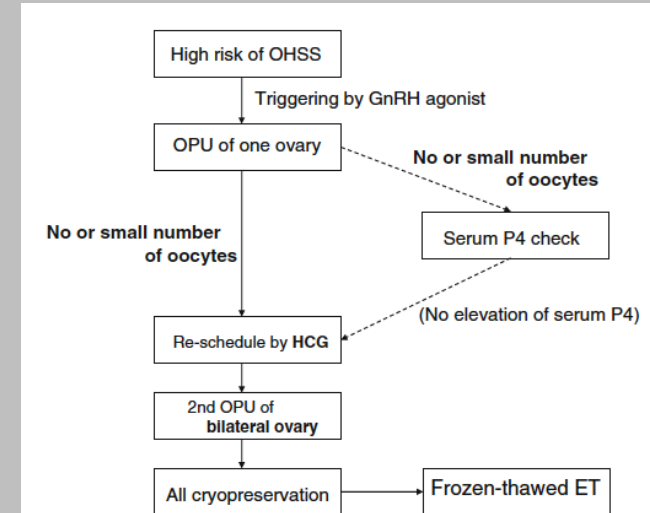


Fig. 1 Flow chart depicting management of the failure of GnRH-triggered oocyte maturation

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 <i>n</i> =2034	Patients <i>n</i> =1433	<i>p</i> 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..

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

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

N.E. Kummer¹, R.S. Feinn², D.W. Griffin¹, J.C. Nulsen¹, C.A. Benadiva¹, 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 description
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 (cetorelix 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

GnRH-a ile Diğer Sorunlar..

- Empty follicle sendrom
- **Şiddetli OHSS riski???**

Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG

Ayşe Seyhan^{1,2,†}, Baris Ata^{1,2,3,†}, Mehtap Polat⁴, Weon-Young Son², Hakan Yarali⁴, and Michael H. Dahan^{1,2,*}

- Retrospektif kohort çalışma, 6/23 şiddetli OHSS

Table III Patient and COS cycle characteristics of severe early OHSS cases.

	Age in years	BMI in kg/m ²	PCOS	Gonadotrophin starting dosage (IU/day)	Co-treatment	Number of follicles ≥ 12 mm	Peak E2 in pg/ml	Number of oocytes collected (metaphase 2 oocytes)	Number of transferred
Case 1 (McGill)	27	31.2	Yes	225	Metformin Cabergoline	11	5589	65 (41)	Freeze all
Case 2 (McGill)	30	29.1	No	200	Cabergoline	15	2563	49 (32)	Freeze all
Case 3 (McGill)	33	22.0	No	100	Cabergoline	34	3011	33 (18)	Freeze all
Case 4 (Anatolia)	31	32.6	Yes	175	Coasting	25	8364	26 (23)	2
Case 5 (Anatolia)	30	31.0	Yes	150	Coasting	24	6814	23 (14)	2

Seyhan et al
2013

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

- GnRH-a trigger takiben 2 şiddetli OHSS olgusu
- **1.vaka:** 29 yaşında, D3 FSH:4.6, AFC: 25'den fazla follikül
- 150 IU rec-FSH ile COH, final E2: 4300pg, USG: 25'den fazla oosit (15-16 mm), toplanan 30 oosit
- **2.vaka:** 27 yaşında, 187.5 rec-FSH ile COH, final E2: 3578pg, toplanan 30 oosit
- FSH-VEGF reseptör mutasyonu???

Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a “freeze-all” strategy: a prospective multicentric study

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- Toplam 51 OHSS için yüksek risk olgusu, short-antagonist protokol
- GnRH-a trigger
- Toplam 4 OHSS olgusu

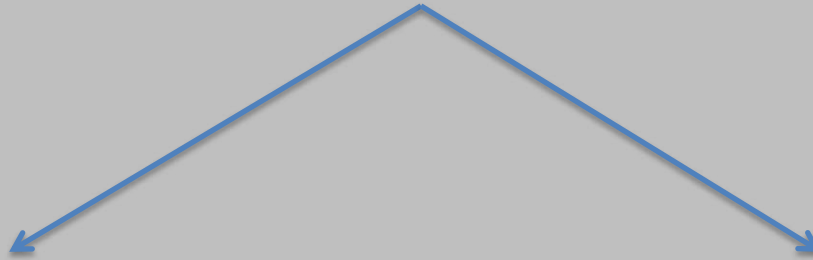
Three cases of OHSS II (3/51, 5.9%, 95% CI 2.0%–15.9%) and one early-onset case of OHSS III (1/51, 2%, 95% CI 0.3%–10.3%) occurred.

Sonuçlar-1

- Short antagonist
- AMH ve AFC tabanlı olarak 112,5-150 IU
gonadotropin başlangıç dozu

Sonuçlar-2

- Geç folliküler fazda 12 mm'lik follikül sayısı >15



Maksimal E2
<4000 pg ise:
DUAL TRIGGER
(GnRH-a+1000 IU
hCG)

Maksimal E2
>4000 pg ise:
Tek GnRH-a

Sonuçlar-3

- GnRH-a ile tetiklemeden 12 saat sonra:

LH >15 IU/l ve P > 3,5 ng/mL

ise EMPTY FOLLICLE
SYNDROME'dan
şüphelenmiyoruz..

Sonuçlar-4

- Geç folliküler fazda >12 mm folliküll sayısı >20 ise **FREEZE-ALL**
- NE KADAR PRATİK????
- NE KADAR BAŞARILI????

Sonuçlar-5

- OPU günü 1500 IU hCG desteği standart gibi oldu..
 - Tekrarlayan düşük hCG dozları OHSS ipuçlarına göre verilebilir ET günü ??? (LH düzeyleri?)
 - OPU ve ET sonrası (dönemler??) E2, P ve LH ölçümü ile kişiselleştirilmiş luteal destek konsepti
- GÜNDEMDEDİR...

- OHSS'si AZ
- hCG'si >100

GÜNLER

- ve MUTLU YILLAR DİLERİM..