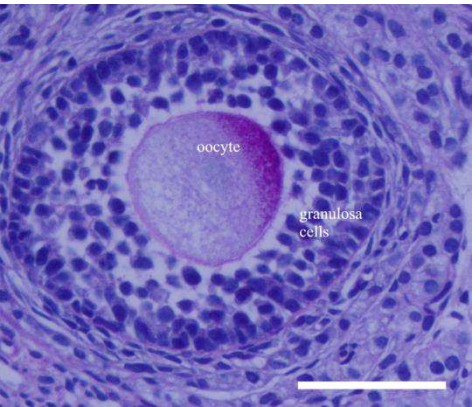
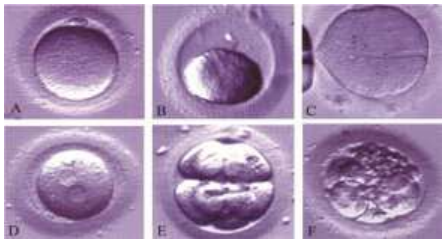
Kötü Ovaryan Yanıtlı Hastalarda KOH protokolleri

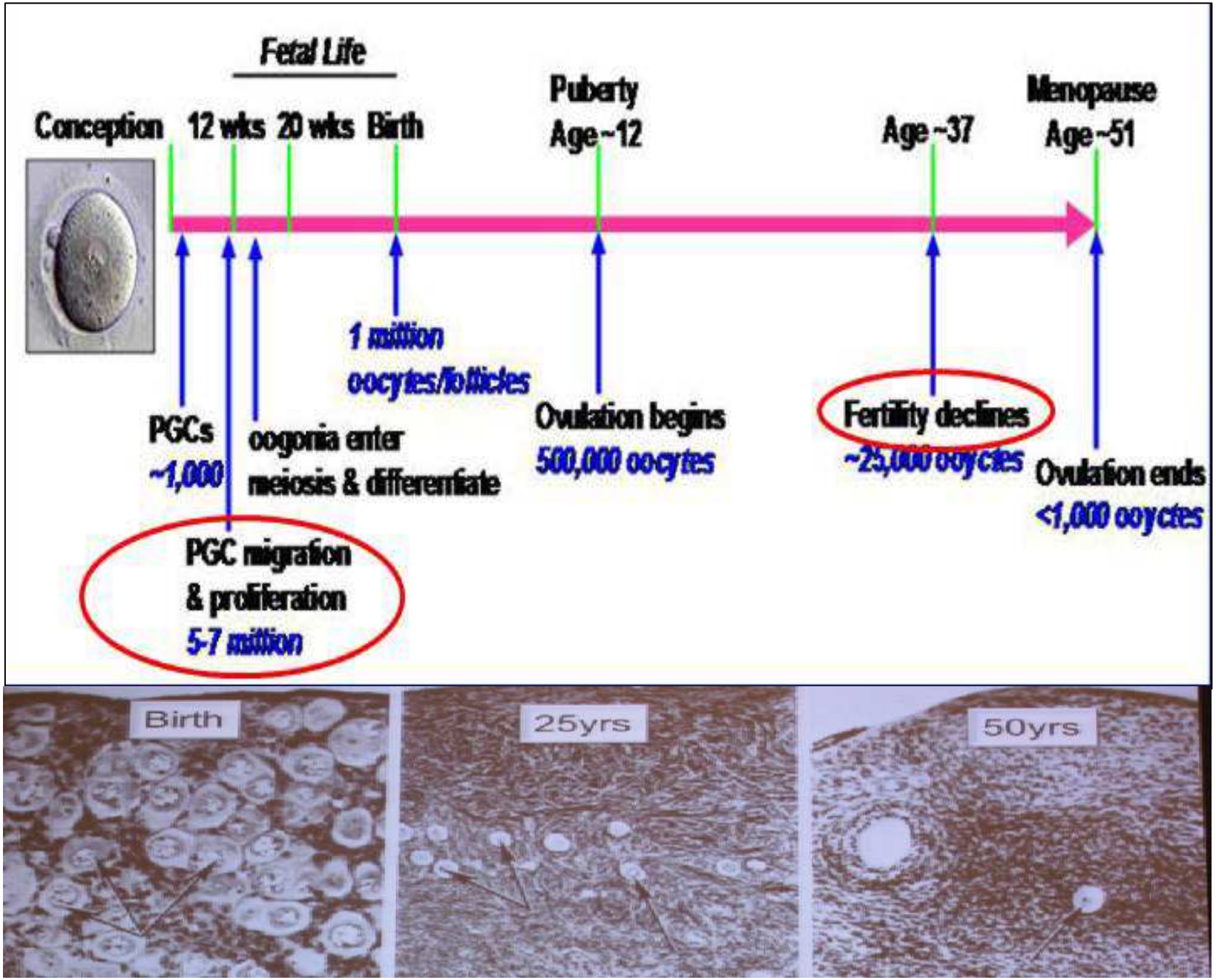
Doç.Dr.Berna Dilbaz



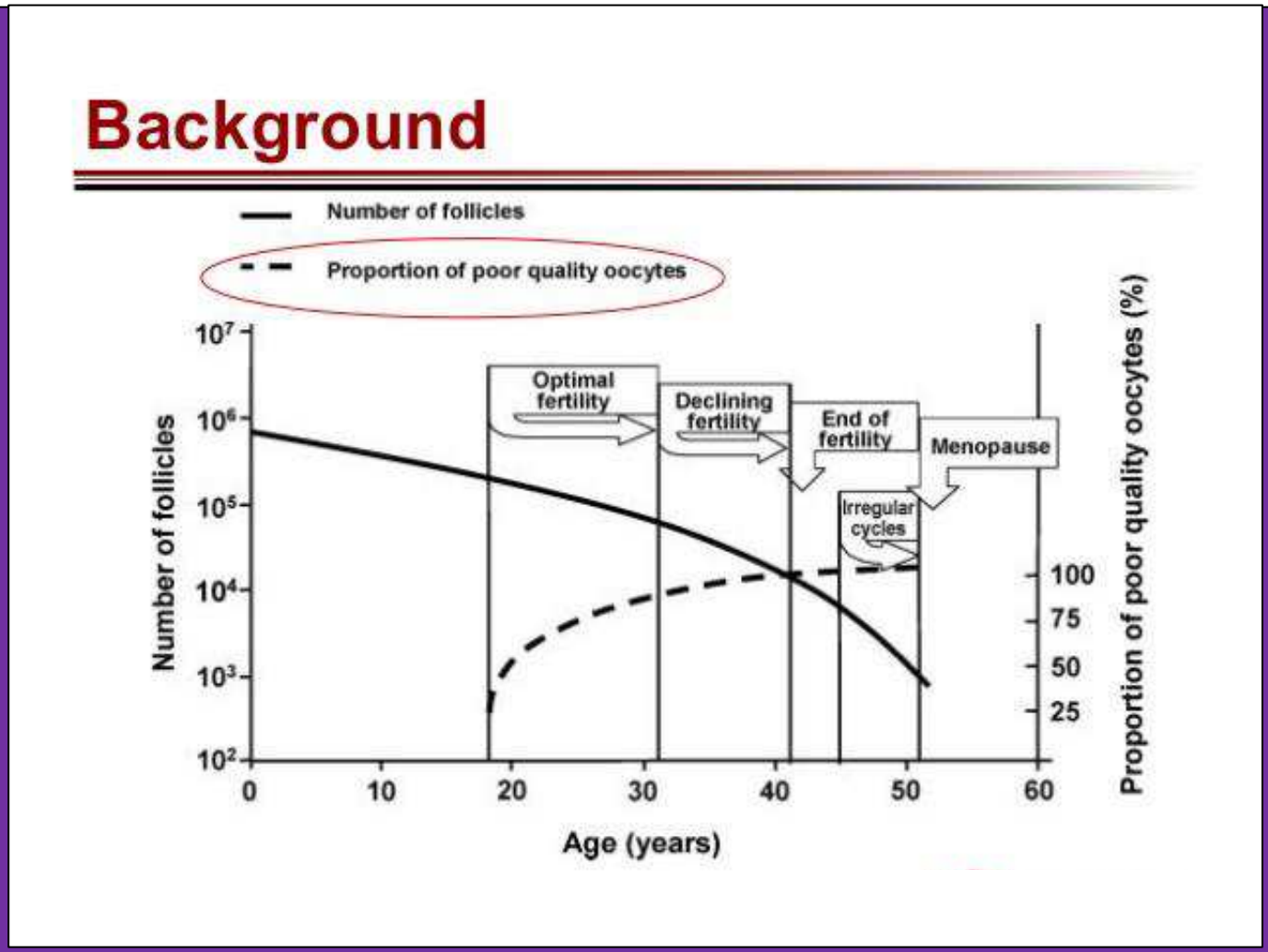


Konu başlıkları

- Kötü ovaryan yanıt tanımı
- Kötü ovaryan yanıt insidansı
- Kötü ovaryan yanıt etiyolojisi ve risk faktörleri
- Hastaların saptanması
- Kötü ovaryan yanıtta tedavi stratejisi
- Klasik KOH protokollerinin Kötü ovaryan yanıtta kullanım sonuçları
- Kötü ovaryan yanıtta öngörülen protokoller
- Sonuçlar


Fetal Life
Conception
12 wks
20 wks
Birth
Puberty
Age ~12
Age ~37
Menopause
Age ~51
1 million
oocytes/follicles
PGCs
~1,000
oogonia enter
meiosis & differentiate
Ovulation begins
500,000 oocytes
Fertility declines
~25,000 oocytes
Ovulation ends
<1,000 oocytes
PGC migration
& proliferation
5-7 million
Birth
25yrs
50yrs

Yaş ve oosit kalitesi



KÖTÜ OVARYAN YANITTA TANI KRİTERLERİ KESİNLEŞMEMİŞTİR: ASRM 2004

- Bazal FSH değeri >6.5-15 mıu/ml
- Peak E2 300-660 pg/ml
- AF sayısı <6
- Yaş > 38-40
- Gonadotropin dozu/gün>300 IU
- Matür oosit sayısı <3-6
- Toplanan oosit sayısı <3-5
- Matür follikül sayısı <2-5

Human Reproduction, Vol.26, No.7 pp. 1616–1624, 2011
Advanced Access publication on April 19, 2011 doi:10.1093/humrep/der092

human reproduction ESHRE PAGES

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria†

A.P. Ferraretti[1,*], A. La Marca[2], B.C.J.M. Fauser[3], B. Tarlatzis[4], G. Nargund[5], and L. Gianaroli[1] on behalf of the ESHRE working group on Poor Ovarian Response Definition‡

Aşağıdaki 3 kriterden en az ikisi olmalı

- 1- Yaş ≥ 40 veya POR için diğer risk faktörlerinin varlığı
- 2-Daha önce konvansiyonel stimulasyonla

  ≤ 3 oosit elde edilmesi
- 3-Anormal over rezerv testi varlığı

  (AFC<5-7 veya AMH < 0.5-1.1 ng/ml)

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- Yaştan bağımsız olarak bir hastanın maksimal stimulasyona rağmen 2 siklusta < 4 oosit üretmesi
- 40 yaş ve üstü bozuk over rezerv testi olan hasta stimulasyon yapılmadan da POR kabul edilir

Kötü Ovaryan Yanıt Görülme Sıklığı

- İlk tanımlayan Garcia periferik E2 yanıtı

  (*Human menopausal gonadotropin/human chorionic gonadotropin follicular maturation for oocyte aspiration: phase II, 1981., Fertil Steril Feb.* 1983 *ve Jones,Costa, Garcia Sept, Fertil)*

- İnfertil popülasyonda %9-24, %5-24

  (Ubaldi 2014, Loutradis 2008)

- Konvansiyonel IVF tedavisi görenlerin %10-15'de

  (Pellicer 1987, Tanbo1989)

- Oran giderek artıyor mu?

Kötü Ovaryan Yanıt Görülme Sıklığı

- Değişik etnik gruplarda farklı oranlarda

  (Mahmud 1995)
- Genital TBC bir etken olabilir mi?

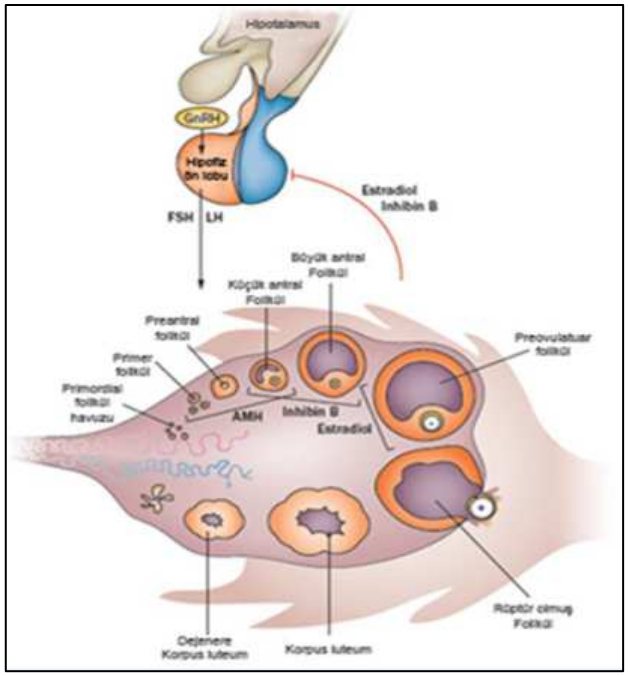
  (Malhotra, 2012)
- Genetik faktörler, risk faktörleri
- Farkı tanımlar olduğu için sıklığı bilinmiyor
- **Ortak bir terminoloji gerekli**

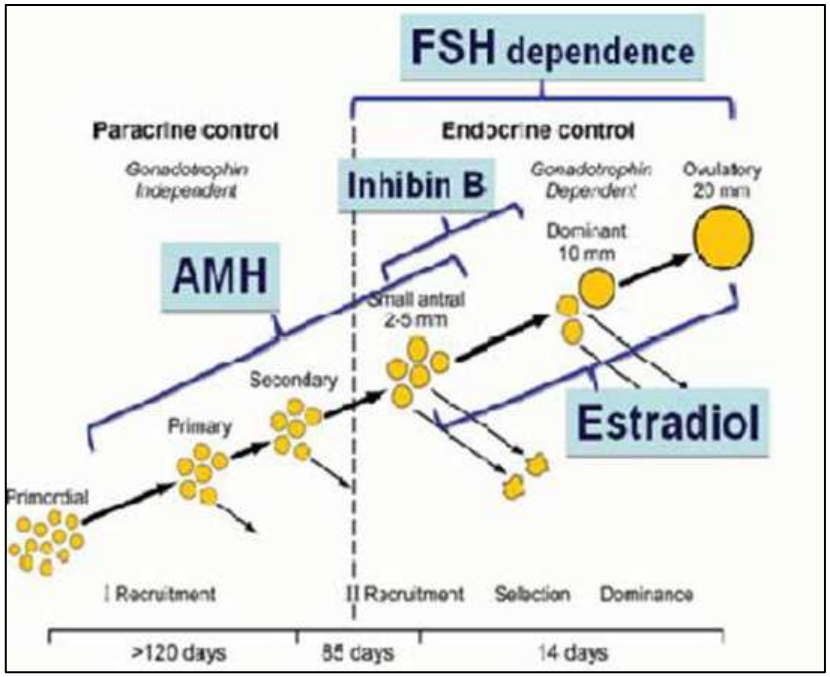
Kötü Ovaryan Yanıt Etiyolojisi:

- Recruitment için uygun follikül havuzu küçük

veya

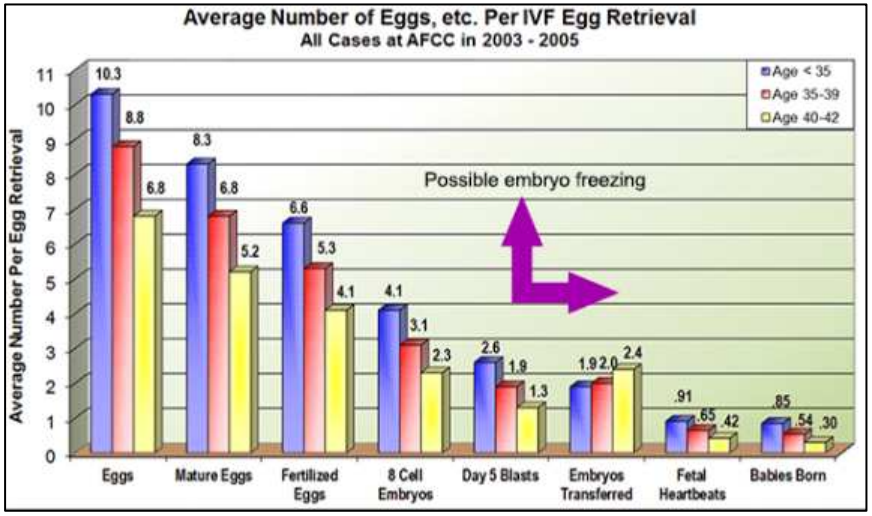
- Folliküllerin gonadotropin uyarısına duyarlılığı azalmış (*Broekmans 2007*)



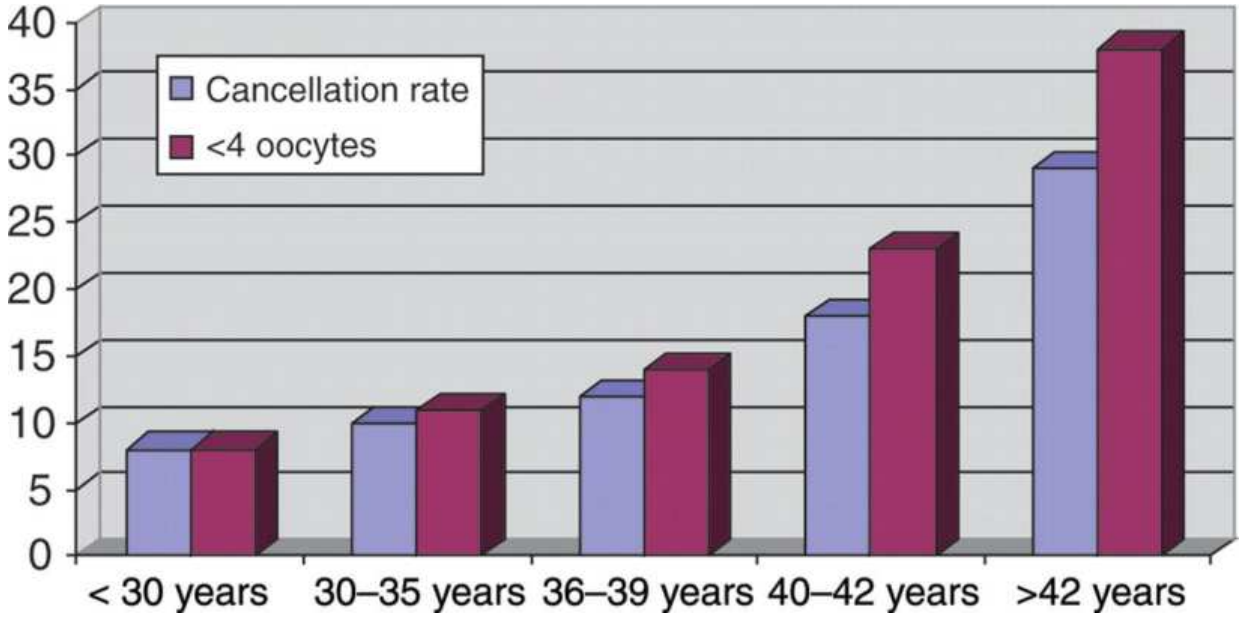


Kötü Ovaryan yanıt için risk faktöreri:

- >37 yaş
- Over cerrahisi (endometrioma)
- Genetik bozukluklar
- Kemoterapi
- Radyoterapi
- Oto immün bozukluklar
- Tek over
- Kronik sigara içimi
- BMI ⇑
- Yeni olarak: DM tip1, Beta-talasemi,uterin arter embolizasyonu



The relationship between age and POR (cycles cancelled because of absent or low ovarian response or pick-ups with ≤3 oocytes) in 3825 women entering the first cycle in the Bologna S.I.S.Me.R unit and in the Modena IVF university unit between January 2004 and December 2009.



Ferraretti A et al. Hum. Reprod. 2011;26:1616-1624

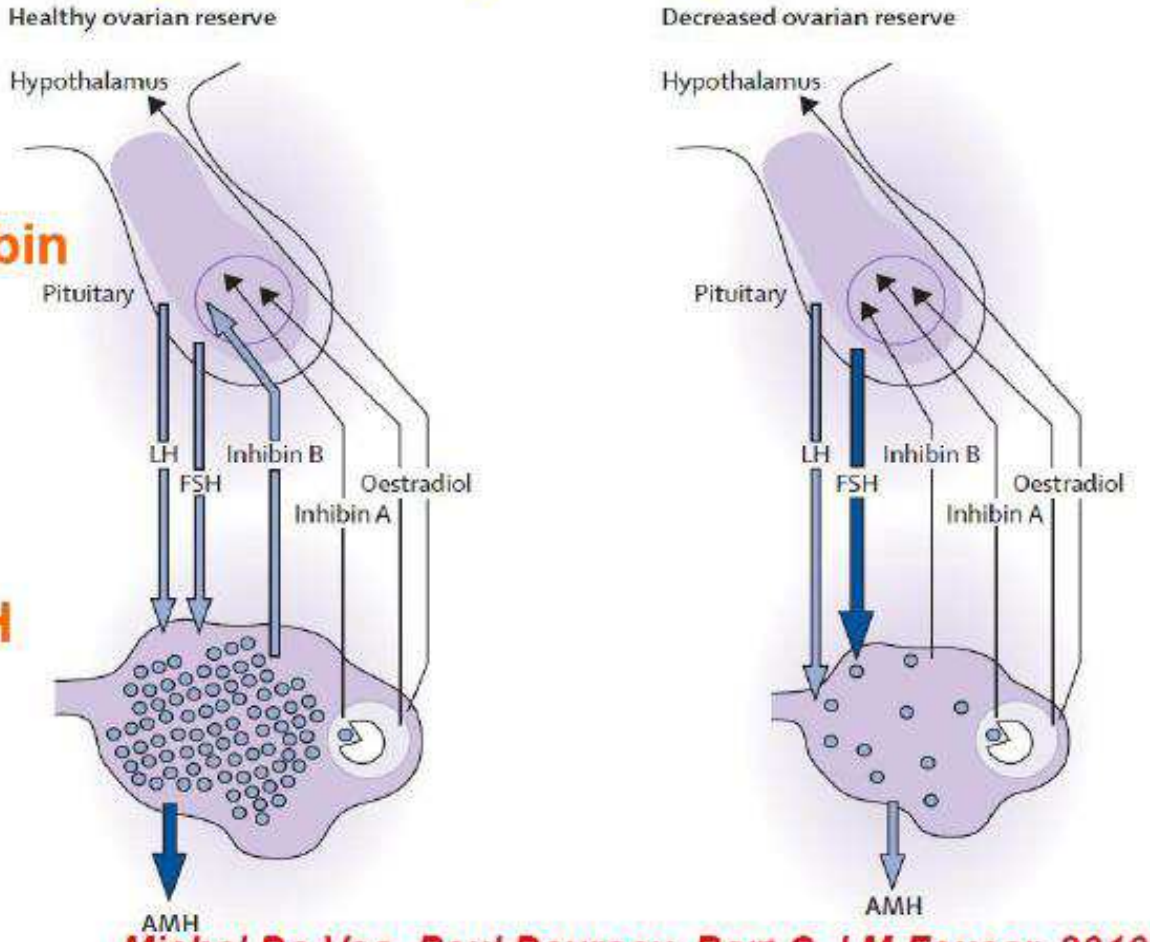
human reproduction

Düşük over rezervi dışı nedenlerle Kötü ovaryan yanıt olabilir mi ?

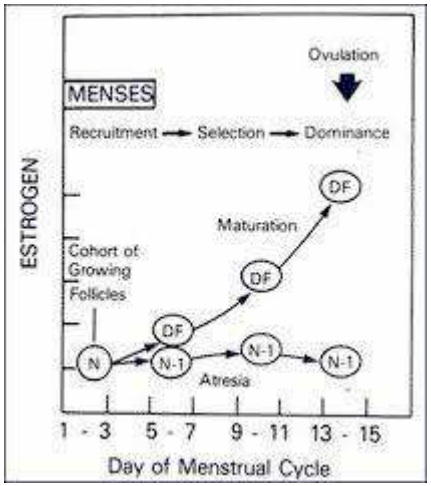
- ✓ Granüloza hücrelerinde FSH reseptör sayısında azalma
  (Zeleznik, 1981)
- ✓ FSH reseptör bağlanması sonrasında sinyal iletiminde bozukluk
  (Hernandez 1992)
- ✓ Folliküler sıvıda FSH reseptör bağlanma inhibitörü varlığı
  (Lee, 1993)
- ✓ Lokal damar ağındaki defekt sonucu gonadotropin dağılımının bozulması
  (Pellicer 1998)
- ✓ Gonadotropin surge'ni durduran GnSAF biyoaktivitesinde azalma
  (Martinze 2002)

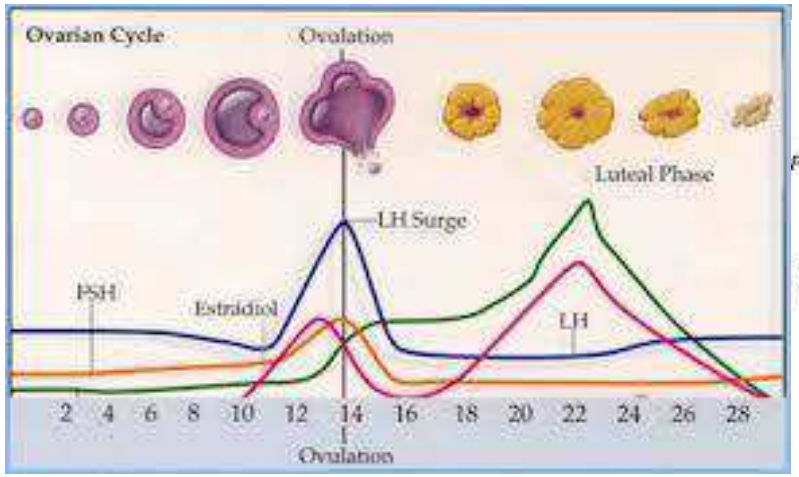
Healthy and decreased ovarian follicular reserve with increased age and changes in concentrations of ovarian and hypothalamopituitary hormones

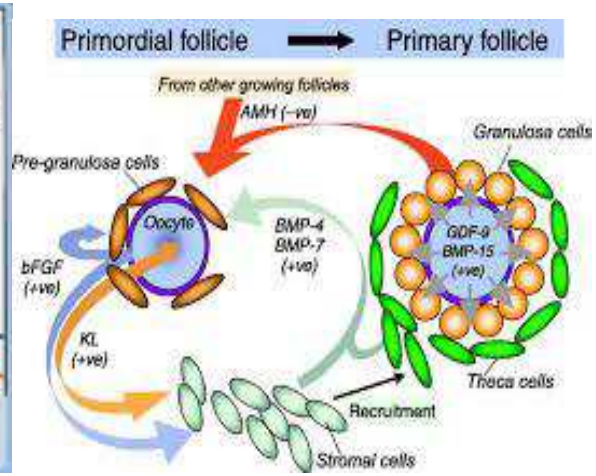
- Decreasing inhibin
- Rising FSH
- Erratic estradiol
- Decreasing Testosterone
- Decreasing AMH



Michel De Vos, Paul Devroey, Bart C J M Fauser, 2010







Over parakrin aktivitesi azalır

Hurwitz & Santaro 2004

Androjen sekresyon kapasitesi azalır

Piltonen 2003

LH reseptörü ve LH biyoaktivitesi azalır

Vinko 1996
Mtchiell 1995

Kötü Ovaryan Yanıtta YÜT Başarısı:

Kötü oosit kalitesi

Düşük fertilizas oranı

Düşük embriyo

Artmış erken gebelik kaybı

Oosit sayısı= Oosit kalitesi

Oosit sayısı ~ Oosit kalitesi

- Toplanan oosit sayısı ⇩
- Embriyo sayısı ⇩
- aşına gebelik
- Gebelik oranı ⇩
- Canlı doğum oranı ⇩

Westergaard 2000, Esposito 2001, Humaidan 2002)

Hastaların saptanması

- Day 3 FSH>15 mIU/ml, FSH/LH >3

  (Faber 1998)
- 3.gün bazal E2 > 75 – 85 pg/ml,
- Day 6 E2‘nin 75 pg/ml ‘nin altında olması

  (Kovacs 2002)
- 3. gün inhibin B < 45 pg/ml,
- Dinamik testler; EFORT, GAST, CCCT

Hastaların saptanması

- Anti Müllerian hormon seviyesinin düşüklüğü, (<0.5-1.1)
- Yaş ≥ 40,
- Daha önceki IVF/ICSI siklusunda POR öyküsü,
- Yüksek dozda gonadotropin kullanım ihtiyacı (> 44 ampul)

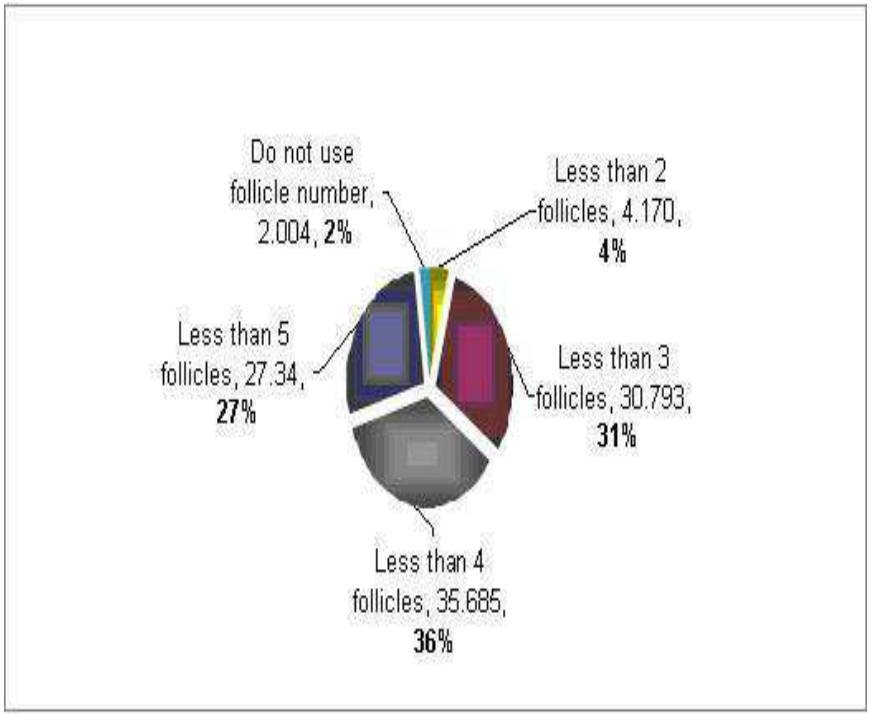
  (Faber 1998)
- Uzamış stimulasyon süresi
- IVF iptali HCG günü <3 follikül

  (Surrey1998, Pandian 2010)

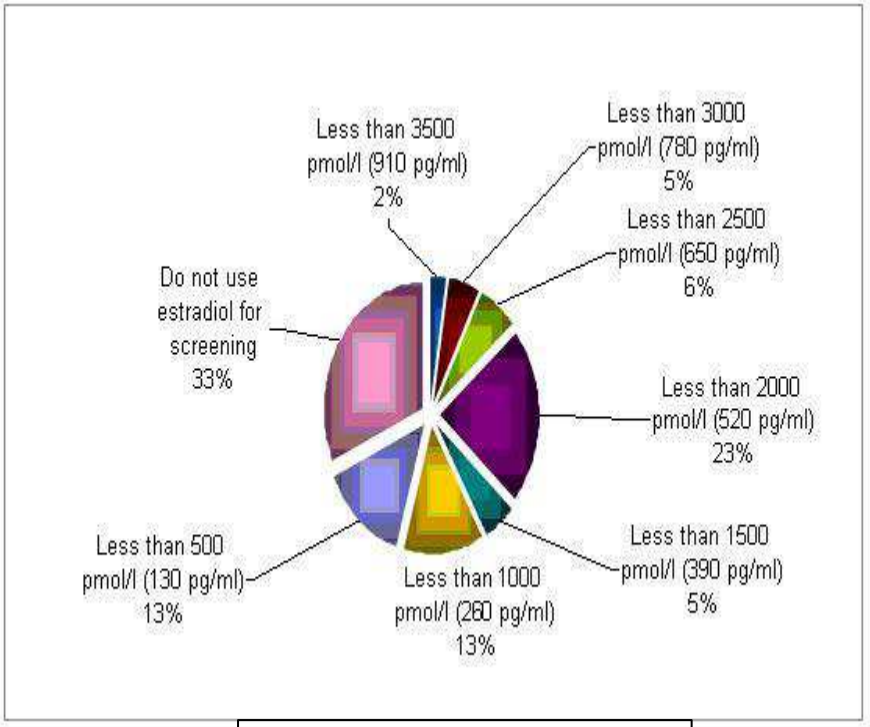
Poor responders: How to define, diagnose and treat?

Results of 124,700 IVF treatment cycles
(196 centres from 45 countries) IVF Worldwide

- Poor responder tanımı:



4,33,5 AFC

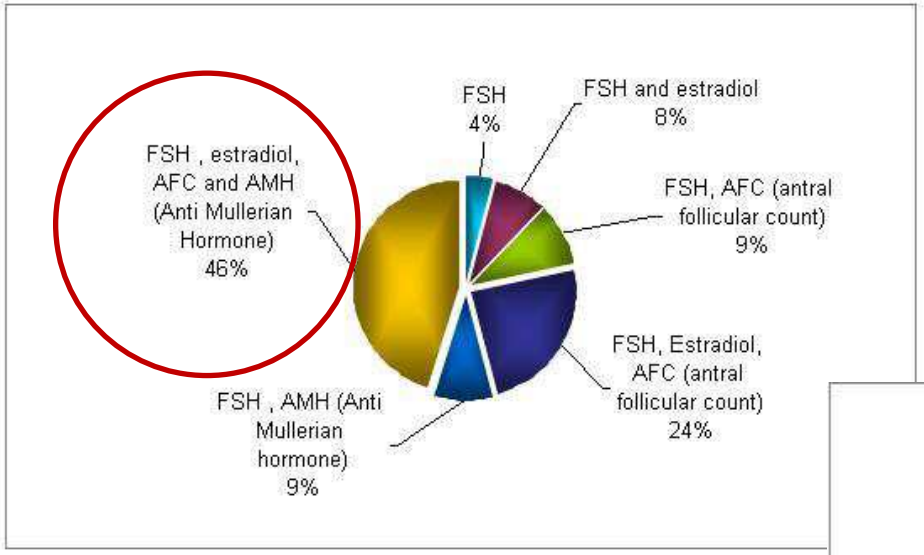


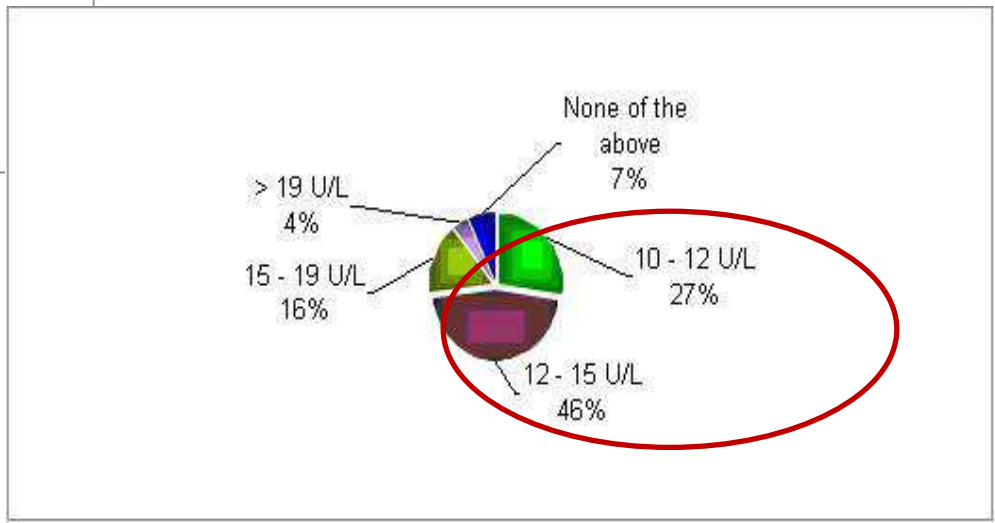
E2ye bakmıyor, 520pg/ml

Poor responders: How to define, diagnose and treat?

Results of 124,700 IVF treatment cycles (196 centres from 45 countries) IVF Worldwide

- Poor responder tarama testi ve FSH değeri :

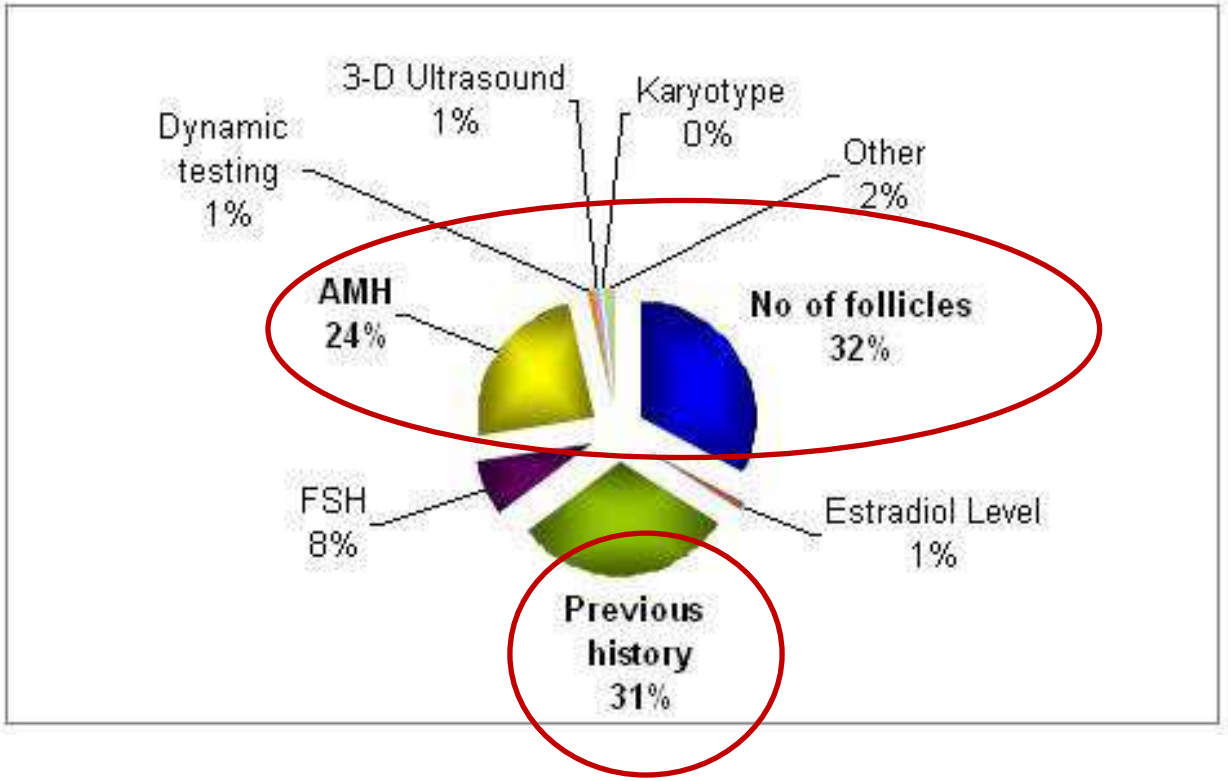




Poor responders: How to define, diagnose and treat?

Results of 124,700 IVF treatment cycles (196 centres from 45 countries)
IVF Worldwide

- Poor responder prediksiyonunda en önemli kriter:



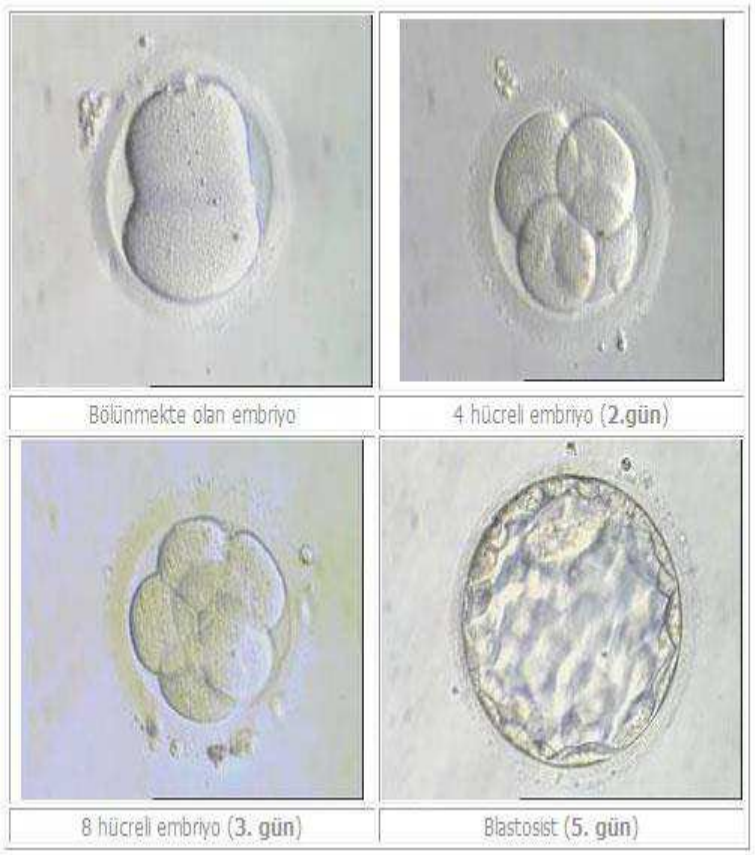
Kötü Ovaryan Yanıtlı hastalarda tedavi startejisi

Risk taşıyan hastayı belirle

Kişiye özel KOH tasarla

En iyi laboratuvar şartlarını sağla

İdeal embriyo transferini sağla



Kötü Ovaryan Yanıtlı hastalarda tedavi stratejisi

Risk taşıyan hastayı belirle

İleri yaş
Geçirilmiş over cerrahisi
Yüksek FSH
Daha önce kötü yanıt öyküsü

Tanınması kolay

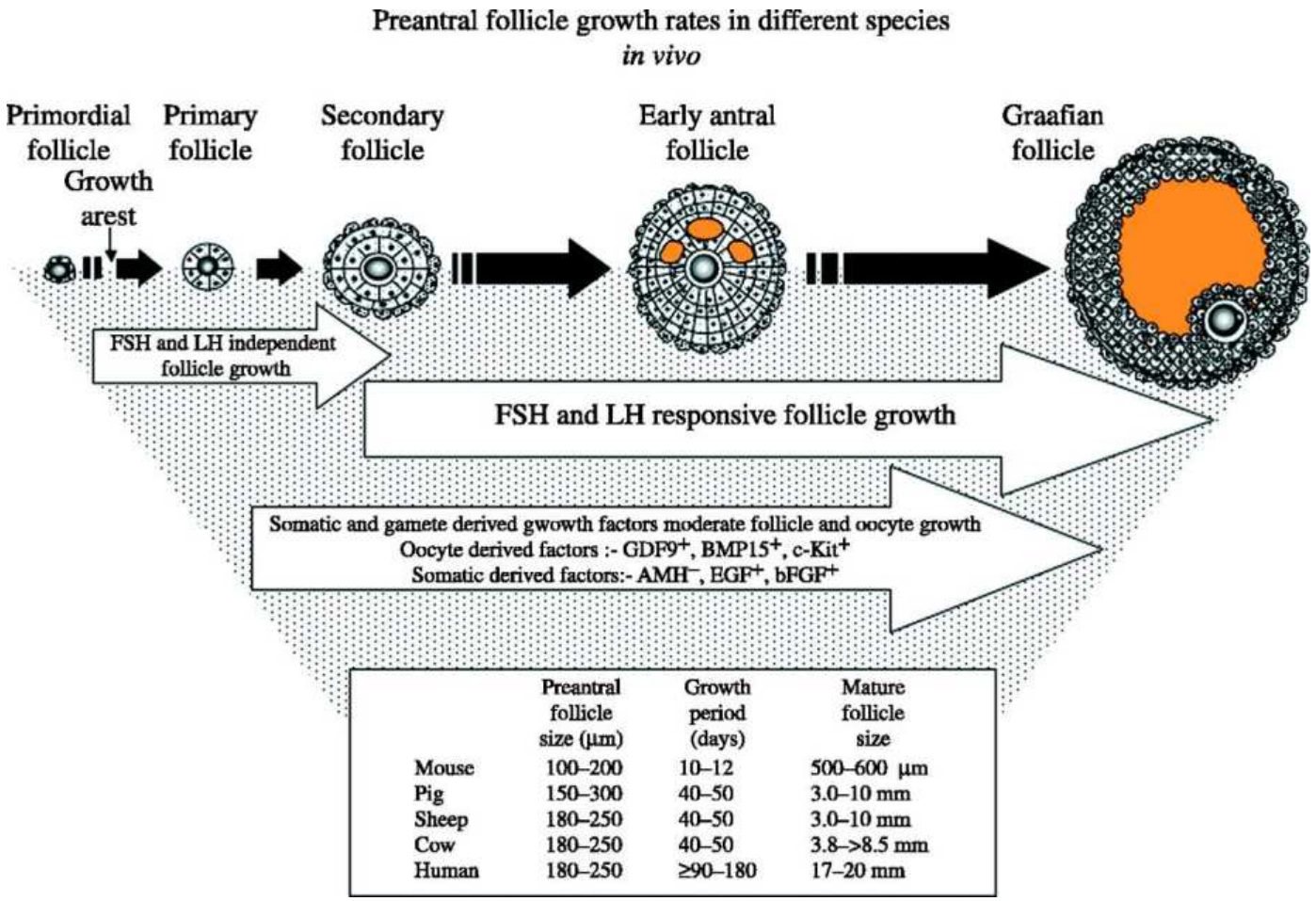
Biyomarkerlarla kötü yanıt öngörülen kadınlar

Kişiye özel KOH tasarla

En iyi laboratuvar şartlarını sağla

İdeal embriyo transferini sağla

Oosit gelişimi



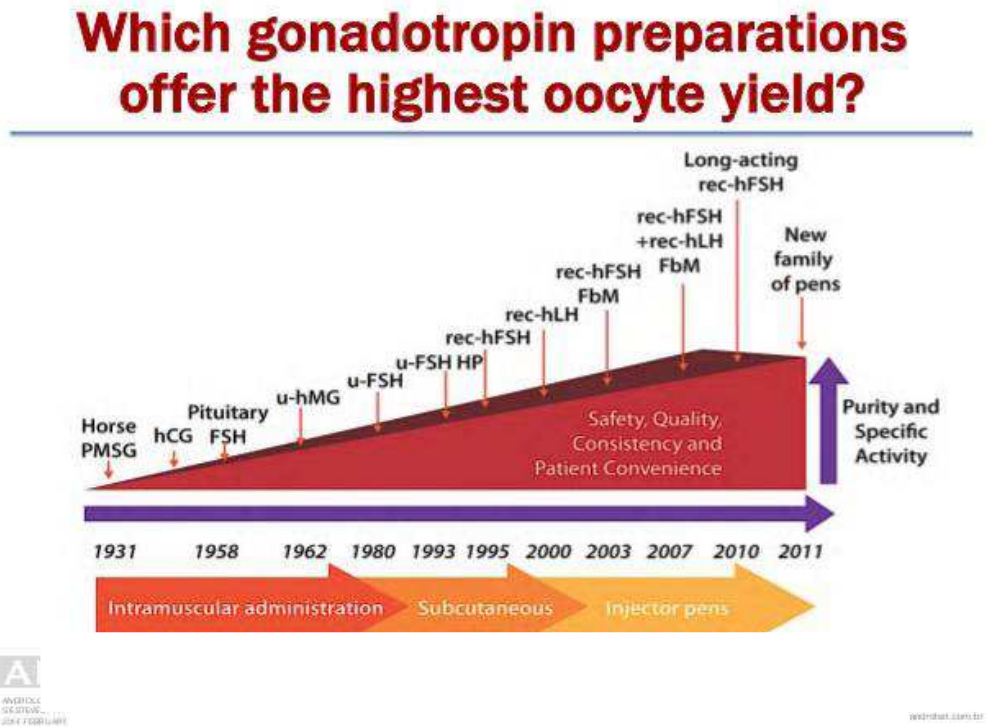
	Preantral follicle size (µm)	Growth period (days)	Mature follicle size
Mouse	100–200	10–12	500–600 µm
Pig	150–300	40–50	3.0–10 mm
Sheep	180–250	40–50	3.0–10 mm
Cow	180–250	40–50	3.8–>8.5 mm
Human	180–250	≥90–180	17–20 mm

Kötü Ovaryan Yanıtlı hastalarda kullanılacağı protokolün özellikleri nasıl olmalı?

- Yeterli ve kaliteli oosit elde etmeye yönelik
- Endometriyal reseptiviteyi olumsuz etrkilemeyen (yüksek doz steroidlerin olumsuz etkisi?)
- Hasta ve doktor tarafından uygulama kolaylığı
- Cost-effective
- İyi kalitede embriyo ve sağlıklı gebelik elde etmeye yönelik

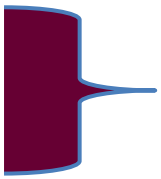
Kötü Ovaryan Yanıtlı hastalarda kullanılacağı protokolün özellikleri nasıl olmalı?

- Cost-effectif:
- Gonadotropin dozu
- Stimülasyon süresi
- Siklus iptal oranı
- Klinik gebelik oranı
- Canlı doğum oranı
- Hasta memnuniyeti ?????



Hangi protokoller başarılı olabilir?

- Yüksek doz gonadotropin
- rFSH kullanımı
- FSH'nın luteal fazda başlanması
- LH eklenmesi
- Uzun etkili FSH
- GnRH agonist ve luteal fazda GnRH agonisti
- GnRH agonist «STOP» protokol
- GnRH-agonist : «FLARE» protokol
- Mikrodoz GnRH agonist flare protokol
- Kısa protokol
- GnRH antagonist protokol
- Doğal siklus- modifiye doğal siklus
- Stimülasyon başlangıç safhasında düşük doz hCG
- Growth Hormon eklenmesi
- Androjen eklenmesi
- Letrazol eklenmesi



Adjuvan eklenmesi

Gonadotropin dozunu arttırmak faydalı mı?

Table 1. Gonadotrophins.

Intervention	Studies	Design of study	Conclusion
Increase dose	Centre for Clinical Effectiveness	Cochrane database	No advantage
	Klinkert et al., 2005	Randomised controlled trial	No benefit
	Lekamge et al., 2008	Retrospective study	No benefit

- Doz arttırımının faydası var

  (Crosignani, Hoffman 1989)
- Başlangıç dozu en az 300 IU olmalı
- Doz yükseltmek daha fazla oosit gelişime yol açıyor ama gebelik artmıyor (225 yerine 450 IU)

  (Land et al 1996)

Poor responderlarda YÜT sikluslarında Gonadotropin dozu arttırımı

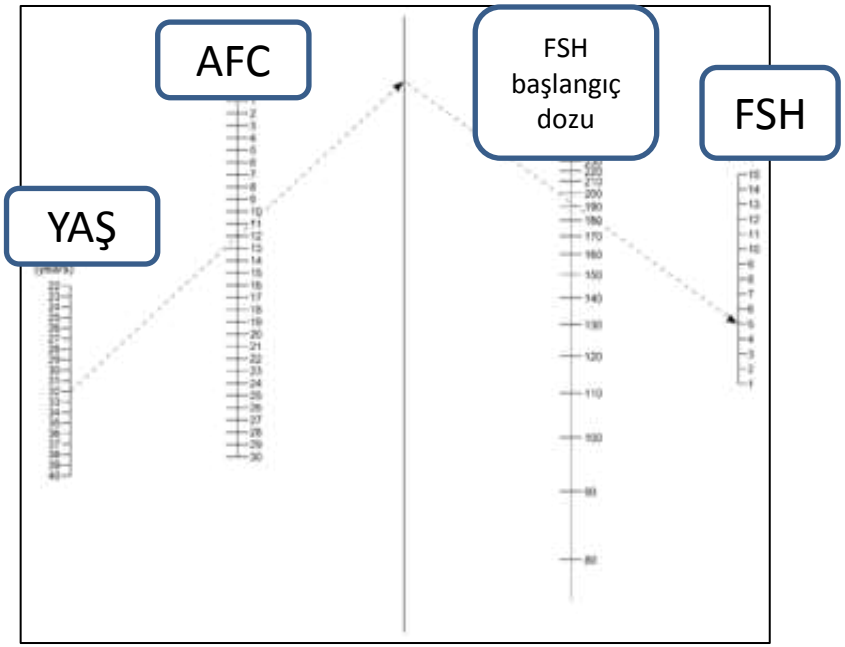
- Berkkanoğlu & Özgür (2010) mikrodoz flare-up protokolde 300 IU, 450IU, 600IU gonadotropin kullanımı arasında toplanan oosit, embriyo ve gebelik oranları arasında fark yok

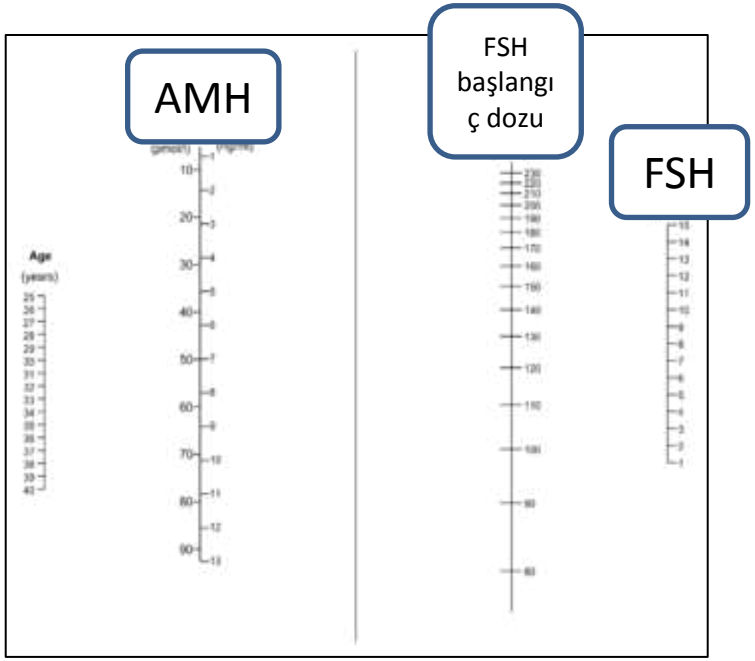
- Daha az gelişebilecek follikül var, doz artsa da ancak gelişebilecek bu folliküller recruitment havuzuna giriyor

Responder'larda FSH dozunun arttırılması başarıyı arttırıyor mu?

- Poor responder 91 hasta
- Microdoz flare-up protokol
- 375 IU/g vs 450 IU/G
- Metafaz 2 oosit ve implantasyon oranları benzer, klinik gebelik ve canlı doğum oranları 375 IU/G grubunda biraz daha yüksek ama istatistiksel olarak anlamlı değil

Dilbaz S ve ark, Gynecol Endocrinol 2011





"Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: From theory to practice". *Human Reproduction Update* La Marca, A.; Sunkara, S. K. (2013).

Poor responderlarda YÜT sikluslarında Gonadotropin dozu arttırımı

- Başlangıç dozunuz ve maksimum günlük doz nedir?

What should be the starting dose of gonadotropins (FSH alone or hMG) that you use?

Usual dose (150-225 IU)	11.4
300-375 IU daily	36.7
375-450 IU daily	27.9
450-600 IU daily	23.7
More than 600 IU a day	0.3

What is the maximum daily dose of gonadotropins (FSH alone or hMG) that you use?

600	93. 0
900	5.9
1200	1.0
1500	0.1

Several units reported that they do not use more than 450 IU/day

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Poor responderlarda r-FSH kullanımı

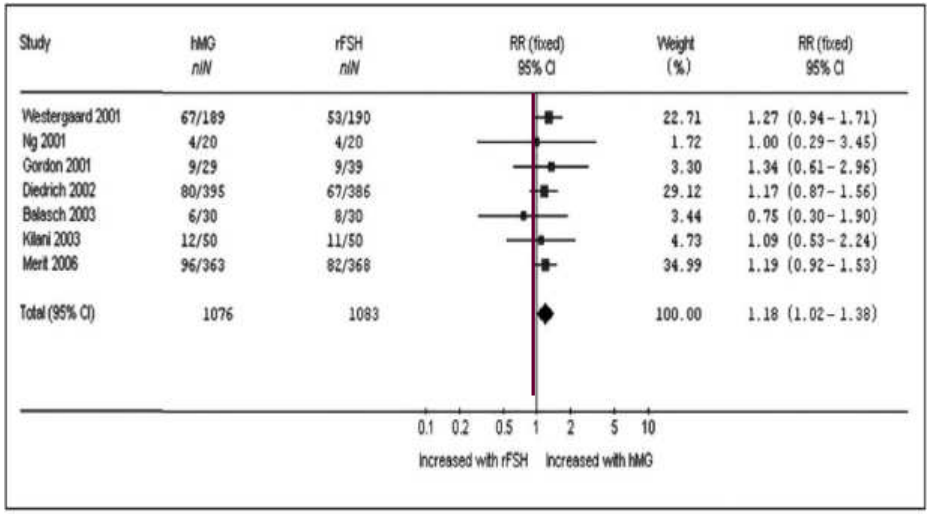
Yararlı

- LH oranının minimize edilmesi oosit/embriyo kalitesini arttırır özellikle genç hastalarda

  (Raga 1999, De Placido 2000, Out 1996)

Fark yok

- Genel anlamda önemli bir fark yok **(Cochrane 2011)**



Test for heterogeneity (Chi-square test): $P=0.97$.
Test for overall effect: $P=0.03$.

Hatta uzun down-regülasyonda HMG daha yüksek canlı doğum oranı

Coomarasamy,2008

Poor responderlarda bir önceki siklus luteal fazda FSH başlanması:

- Teorik bilgilere göre luteal fazda başlanması recruitment penceresinin daha erken açılması, daha fazla oosit gelişimini sağlar mı???
- Pratikte uygulamada erken OPU ama siklus iptali yüksek, toplanan oosit sayısında fark yok

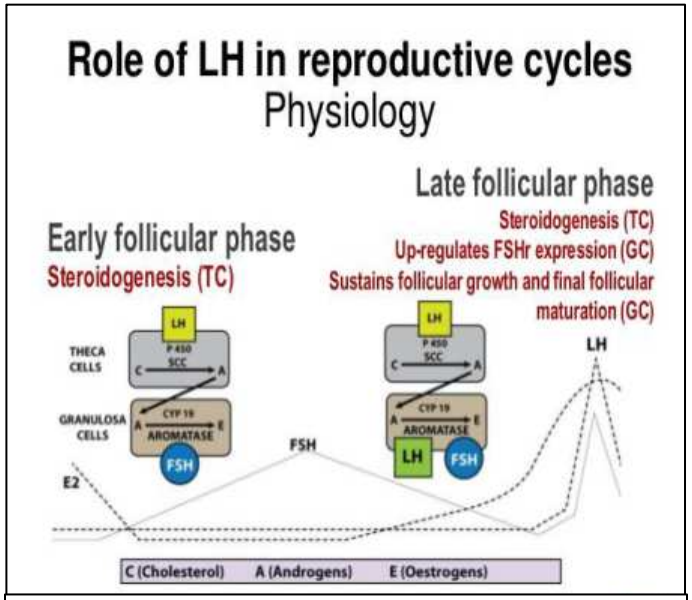
(Rombauts, 1998)

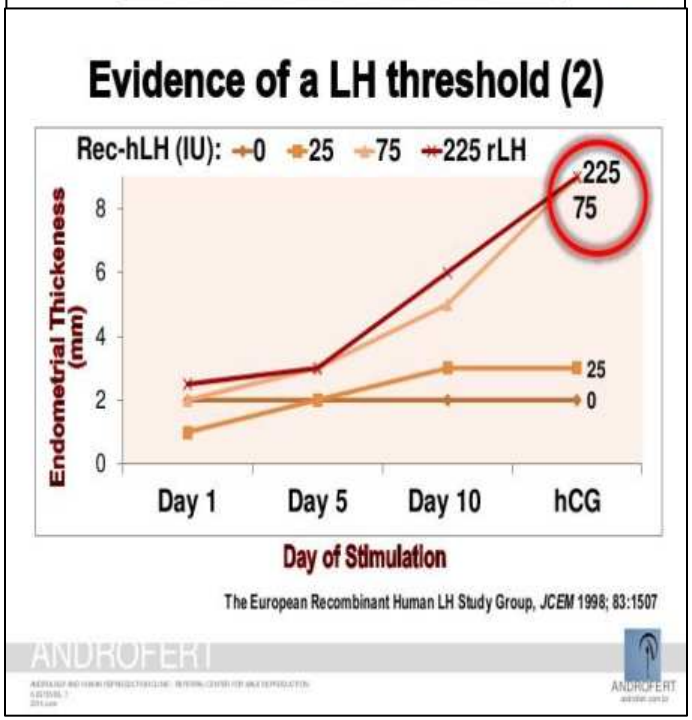
Luteal initiation of FSH	Eskandar et al., 2004	prospective comparative study	No difference
	Al-Inany et al., 2005	Meta-analysis	No difference
	Rombauts et al., 1998	Prospective, randomized, controlled study.	No benefit
	Kucuk et al., 2007	Prospective, randomized, controlled study.	More mature oocytes
	Kansal Kalra et al., 2008	Randomized controlled pilot trial	Similar outcomes

Dört protokolle ilgili çalışmaların karşılaştırılması:

Table 1. Gonadotrophins.

Intervention	Studies	Design of study	Conclusion
Increase dose	Centre for Clinical Effectiveness	Cochrane database	No advantage
	Klinkert et al., 2005	Randomised controlled trial	No benefit
	Lekamge et al., 2008	Retrospective study	No benefit
Recombinant FSH (rFSH) Vs purified urinary FSH (uFSH)	De Placido et al., 2000 Raga et al., 1999	Observational study prospective randomised study	Benefit with rFSH Benefit with rFSH
	Gordon et al., 2001	prospective randomised study	No difference
	Eskandar et al., 2004	prospective comparative study	No difference
	Al-Inany et al., 2005	Meta-analysis	No difference
Luteal initiation of FSH	Rombauts et al., 1998	Prospective, randomized, controlled study.	No benefit
	Kucuk et al., 2007	Prospective, randomized, controlled study.	More mature oocytes
	Kansal Kalra et al., 2008	Randomized controlled pilot trial	Similar outcomes





Yüksek LH	Erken lüteinizasyon Folliküler atrezi Oosit gelişiminde bozulma
Normal LH	Yeterli androjen, östrojen yapımı, Normal folliküler gelişim, Matür oosit
Düşük LH	**Yetersiz östrojen yapımı** **Oosit matürasyonunda , embriyo kalitesinde bozulma** **Yetersiz endometriyal proliferasyon**

(Drakakis, 2005)

Poor responder - LH eklenmesi

- Aromataz aktivitesi ve östrojen yapımı için periovulatuvar LH düzeyi için eşik değer bilinmiyor (<1.5 IU/l, 3IU/L) (Esposito 2001, Sullivan 1999)
- Mochtar ve ark. Poor-responderlarda r-LH eklenmesi gebelik oranlarını arttırır (OR: 1.85)(Cochrane Database, 2007)
- Bazal FSH level ≥10IU/L, hMG kullananlara göre FSH ‘ya r-hLH eklenenlerde gebelik oranı daha yüksek ama AFC <6 ise fark yok (Dahan 2014)

Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis

Lehert et al. BioMed Central

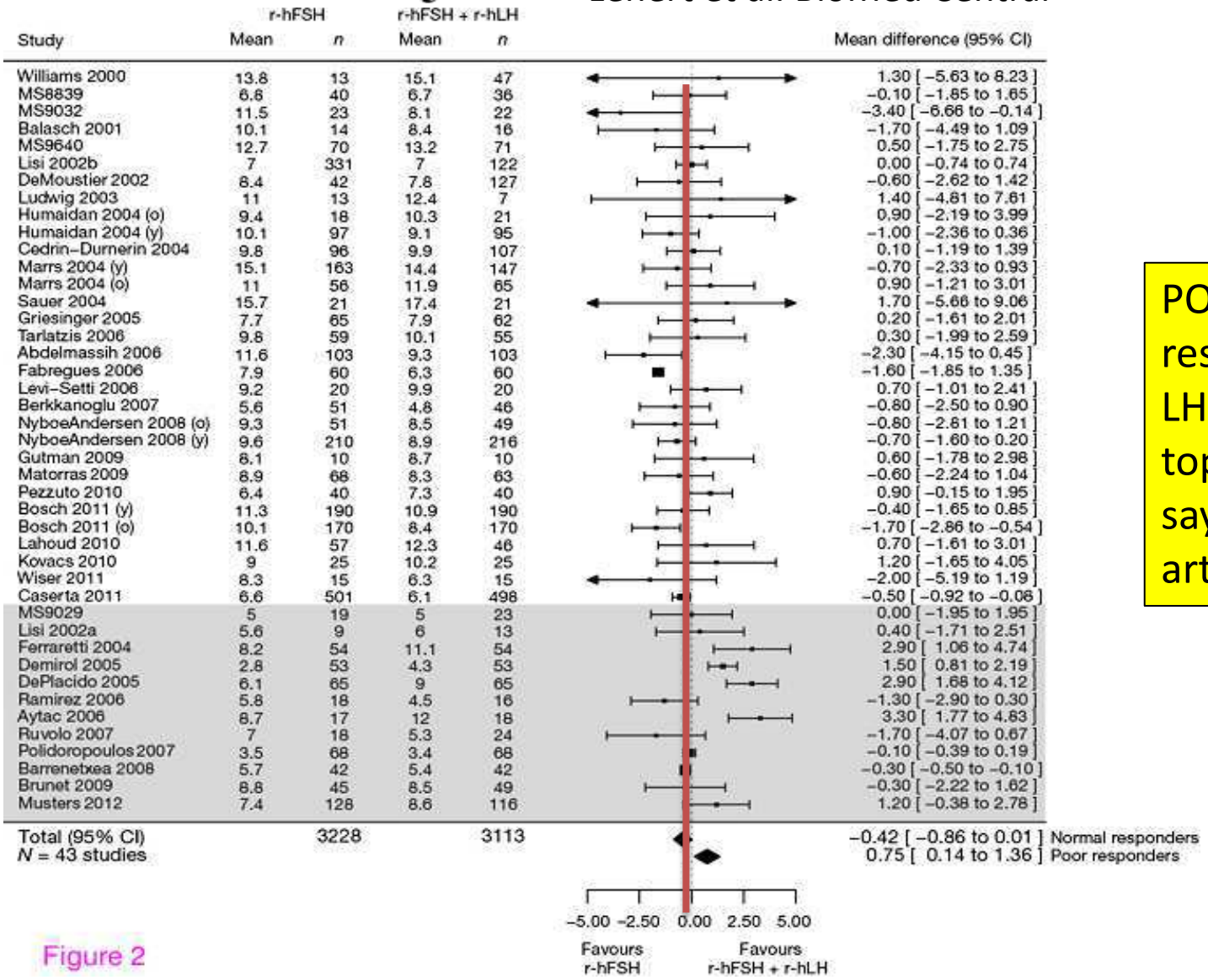


Figure 2

POOR responderlarda LH eklenmesi toplanan oosit sayısında 0.75 artış

Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis

Lehert et al. BioMed Centralo

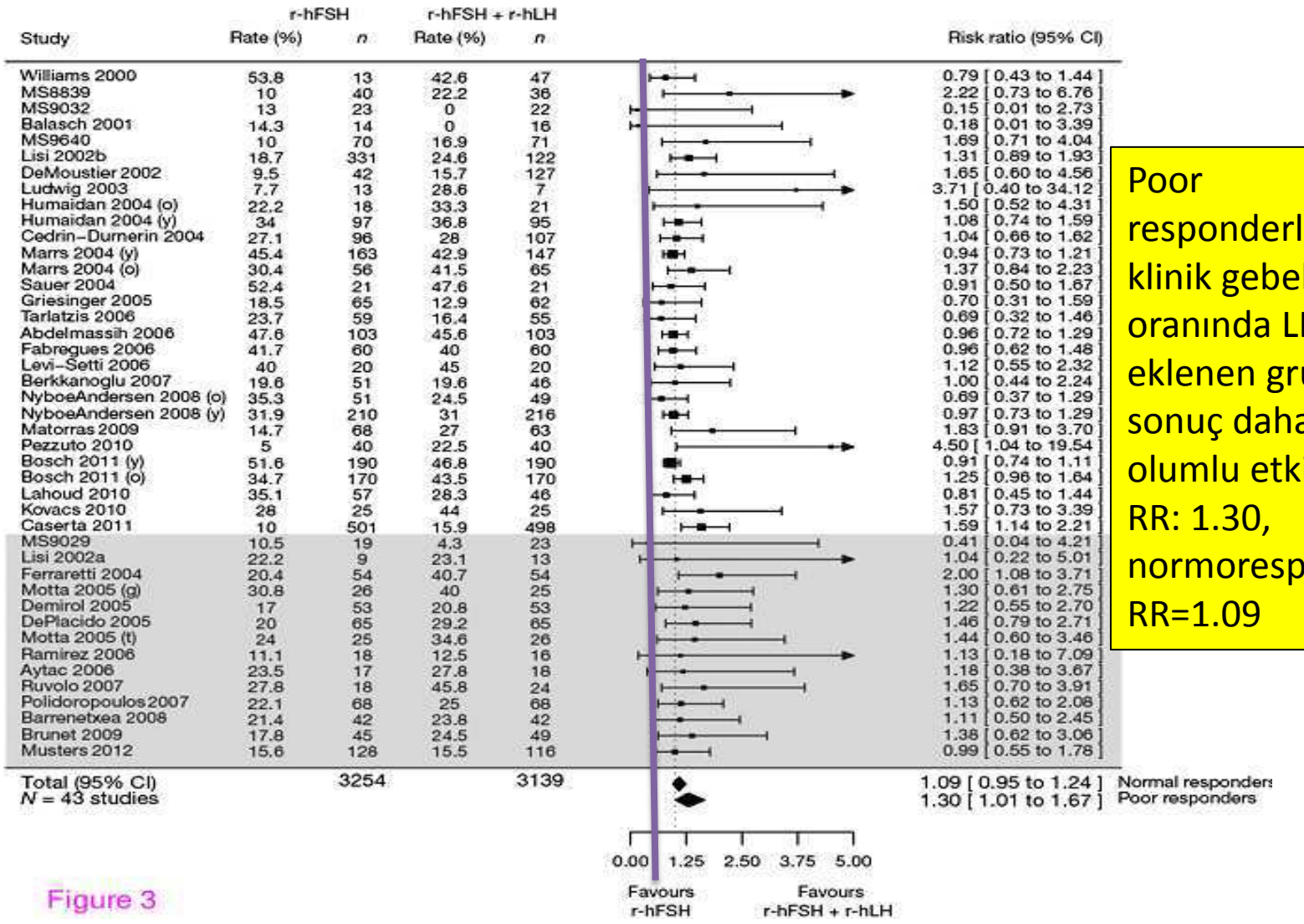


Figure 3

Poor responderlarda klinik gebelik oranında LH eklenen grupta sonuç daha olumlu etkilenmiş RR: 1.30, normoresponder RR=1.09

Corifollitropin alfa compared with follitropin beta in poor responders undergoing ICSI: a randomized controlled trial.
Kolibianakis, Venetis et al Hum Reprod. 2014

Dahil edilme kriterleri:

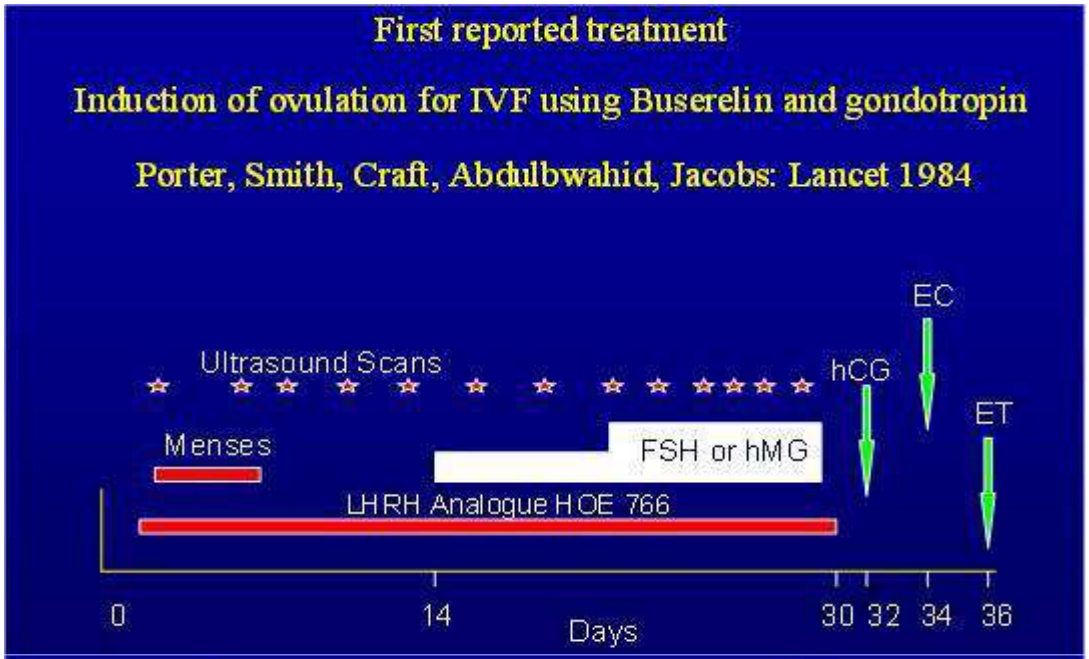
- Maksimum stimülasyona rağmen kötü ovaryan yanıt öyküsü (≤4 COCs)
- <45 yaş, spontan siklus, BMI: 18-32 kg/m2, FSH ≤20 IU/l

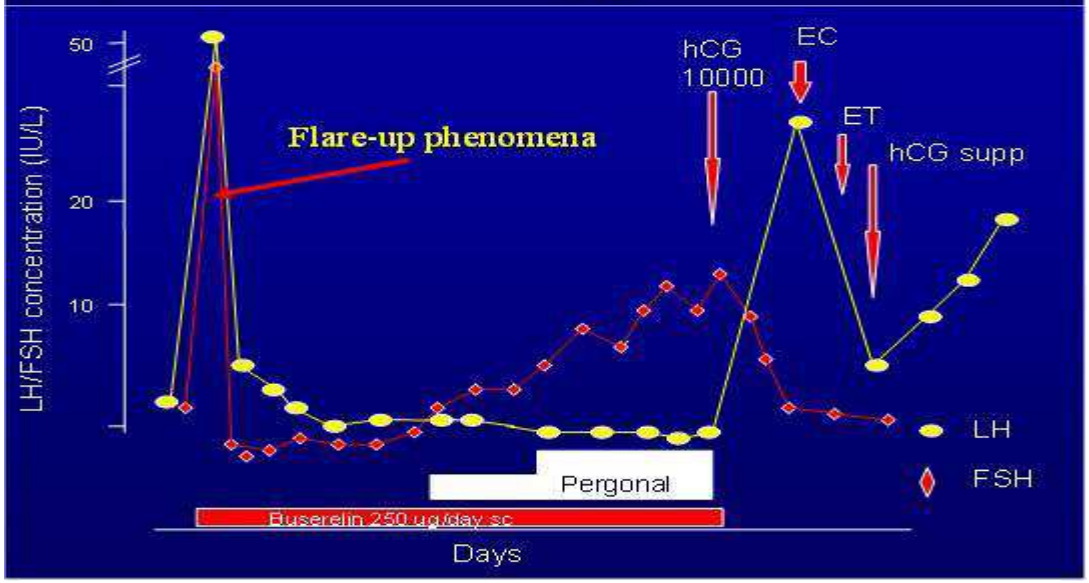
  - A grubu: s.c dose 150 µg corifollitropin alfa (n = 40) + D8-HCG günü 450 IU Follitropin beta
  - B grubu: Günlük 450 IU of follitropin beta (n = 39).

- Gerektiğinde erken luteinizasyonu önlemek için antagonist kullanılmış
- En az 2 adet 17 mm follikül oluşunca Trigger 250 µg r-hCG
- Toplanan COC sayısı farklı değil

  [Median 3 versus 2, 95% CI 2-4, 2-3, respectively, P = 0.26].
- Canlı doğum farklı değil (live birth per patient reaching oocyte retrieval: 7.9 versus 2.6%)

GNRH-agonist protokoller:



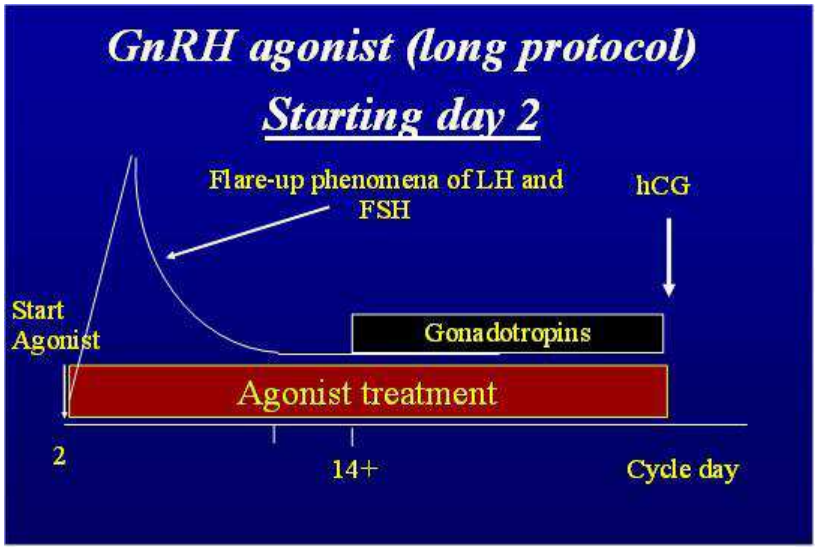


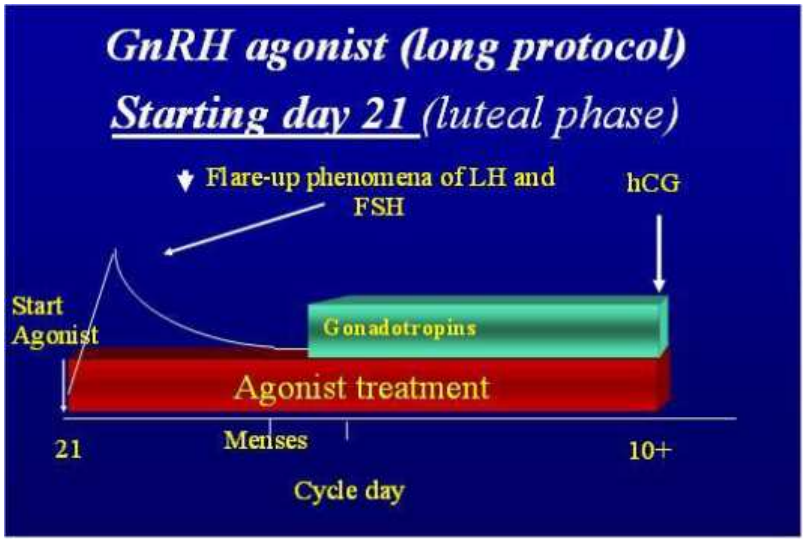
Amaç:

Normoresponderlarda daha az siklus iptali, daha fazla a preovulatuvar follikül, toplanan oosit sayısı, embriyo kalitesinde artış

Kötü ovaryan yanıtlı poor responderlarda aşırı over baskılanması folliküler cevabın azalması veya baskılanmasına yol açar
(Yoshimura 1992, Kowalik 1998)

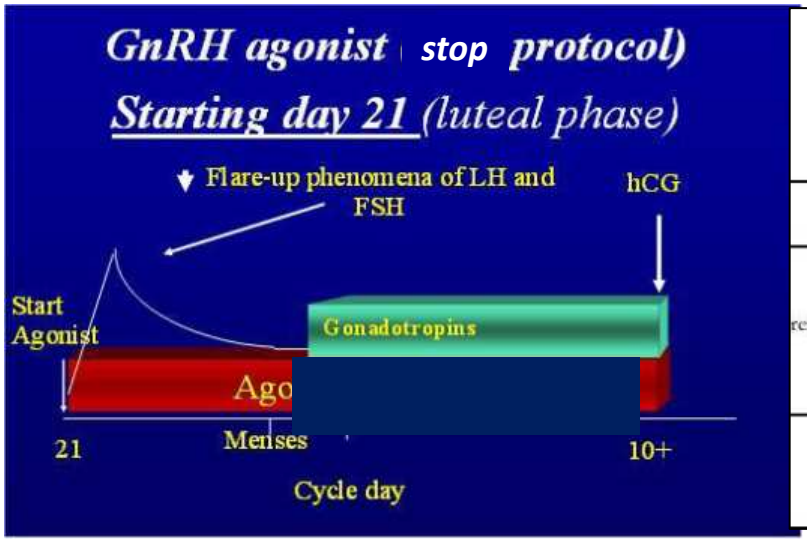
Poor responder: GnRH analog-long protokol olumsuz etkileri azaltmak için:





- ✓ GnRH kullanarak supresyon süresi kısaltılmalı (short, ultra-short, mini veya mikrodoz flareup) (Padilla, 1996)
- ✓ GnRH agonisti luteal fazda başlayıp tedavi siklusunda azaltmak veya kesmek (STOP protokol) (Lindheim, 1996)
- ✓ Erken lüteinizasyonu engellemek için geç folliküler fazda GnRH agonisti ile beraber antagonist kullanmak (Akman, 2000)

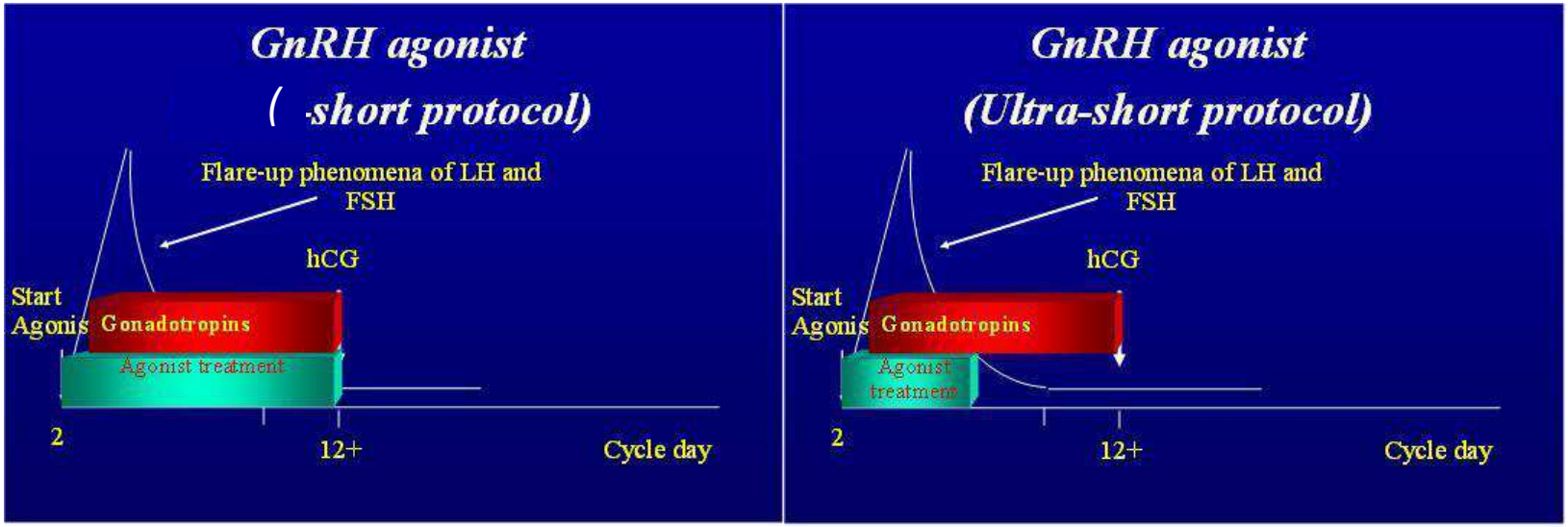
Poor responderlarda GnRH analog-long protokol olumsuz etkileri azaltmak için:



Modification of the Long GnRH agonist protocol	
▣ Dirnfeld et al.,1999	Garcia-Velasco et al., 2000
Definition of poor response: ≤ 4 mature oocytes retrieved in at least one previous IVF cycle and/or a previous low response to COH as evidenced by a peak E2 level of<2.000 pmol/L	Definition of poor response: <3 follicles ≥18mm in diameter in a previous IVF attempt and presence of basal FSH concentration <12 IU/L
Outcome : ongoing pregnancy rate	Outcome : pregnancy rate

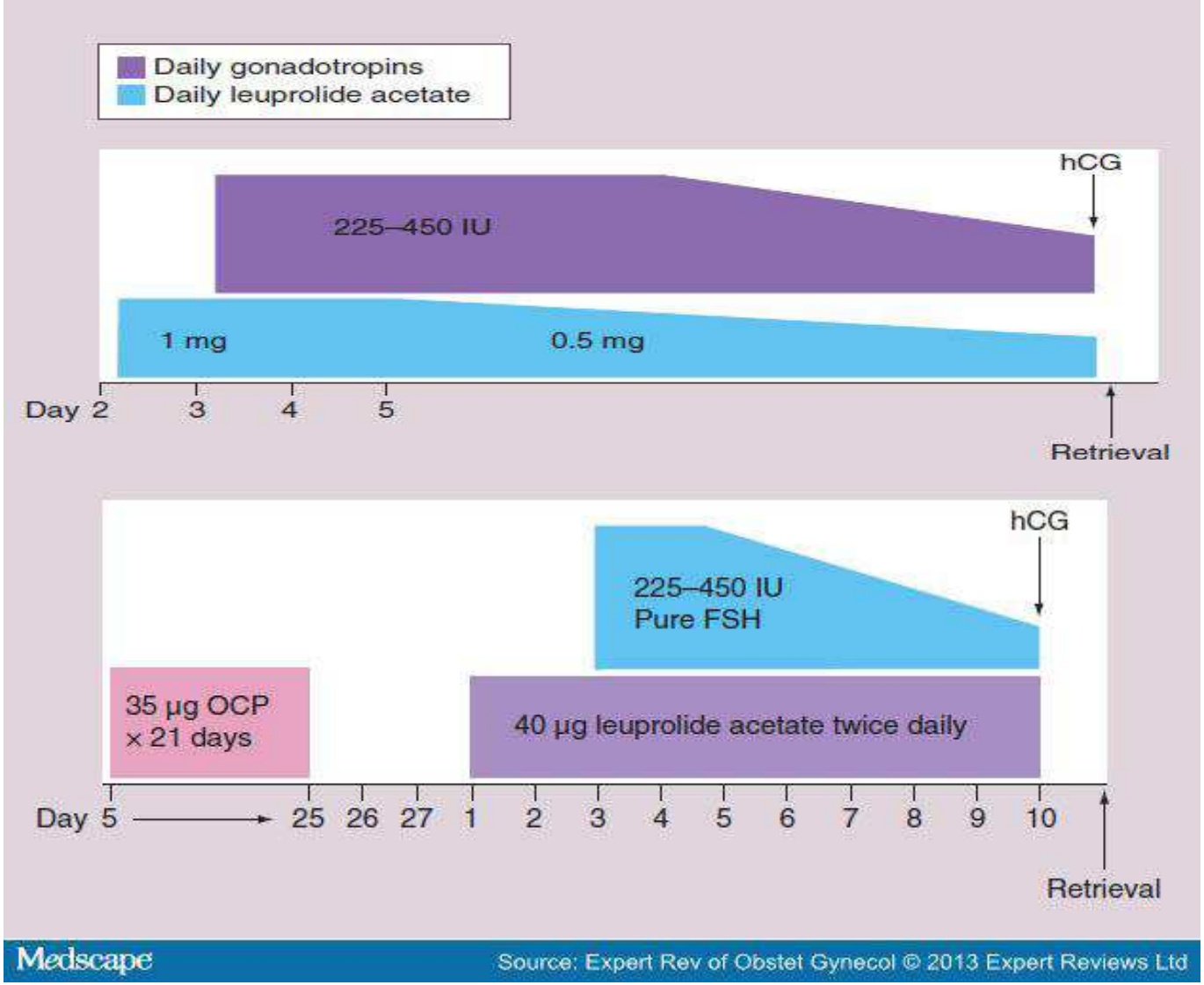
- GnRH analogu 21.gün-gonadotropin başlangıcı arasında, amaç GnRH süpresyonunu azaltmak
- Kullanılan gonadotropin dozunda azalma veya daha iyi klinik sonuçlarla ilgili yayınlar (Pinkas 2000, Schachter 2001)

Poor responder: short, ultrashort flare-up protokol



Amaç:

- GnRH agonistinin flare-up etkisinden faydalanmak
- Başarısız long-luteal GnRH protokol öyküsü, FSH<15 olanlarda siklus başına gebelik hafif yüksek ama canlı doğum oranı aynı (Karacan, 2001)
- Kyrou ve ark meta-analizinde (2009) long protokolle arasında indüksiyon süresi ve klinik gebelik oranları açısından fark yok



GnRH-analoglarının erken folliküler fazda düşük doz başlanması atrezik follikül sayısını (corpus luteum) arttırabilir, bu nedenle bir önceki siklus KOK verilir

GnRH agonist protokoller işe yarar mı?

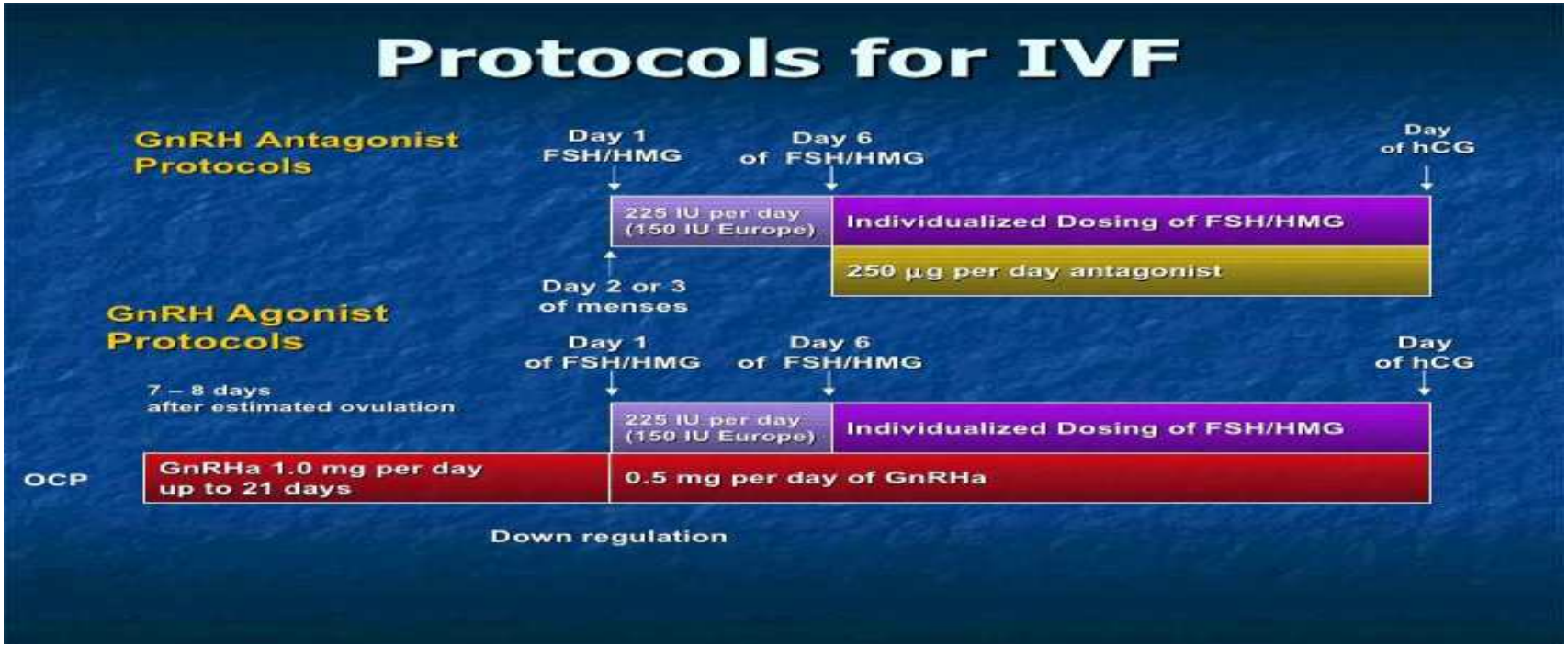
Table 2. Gonadotrophin releasing hormone agonists (GnRH agonists).

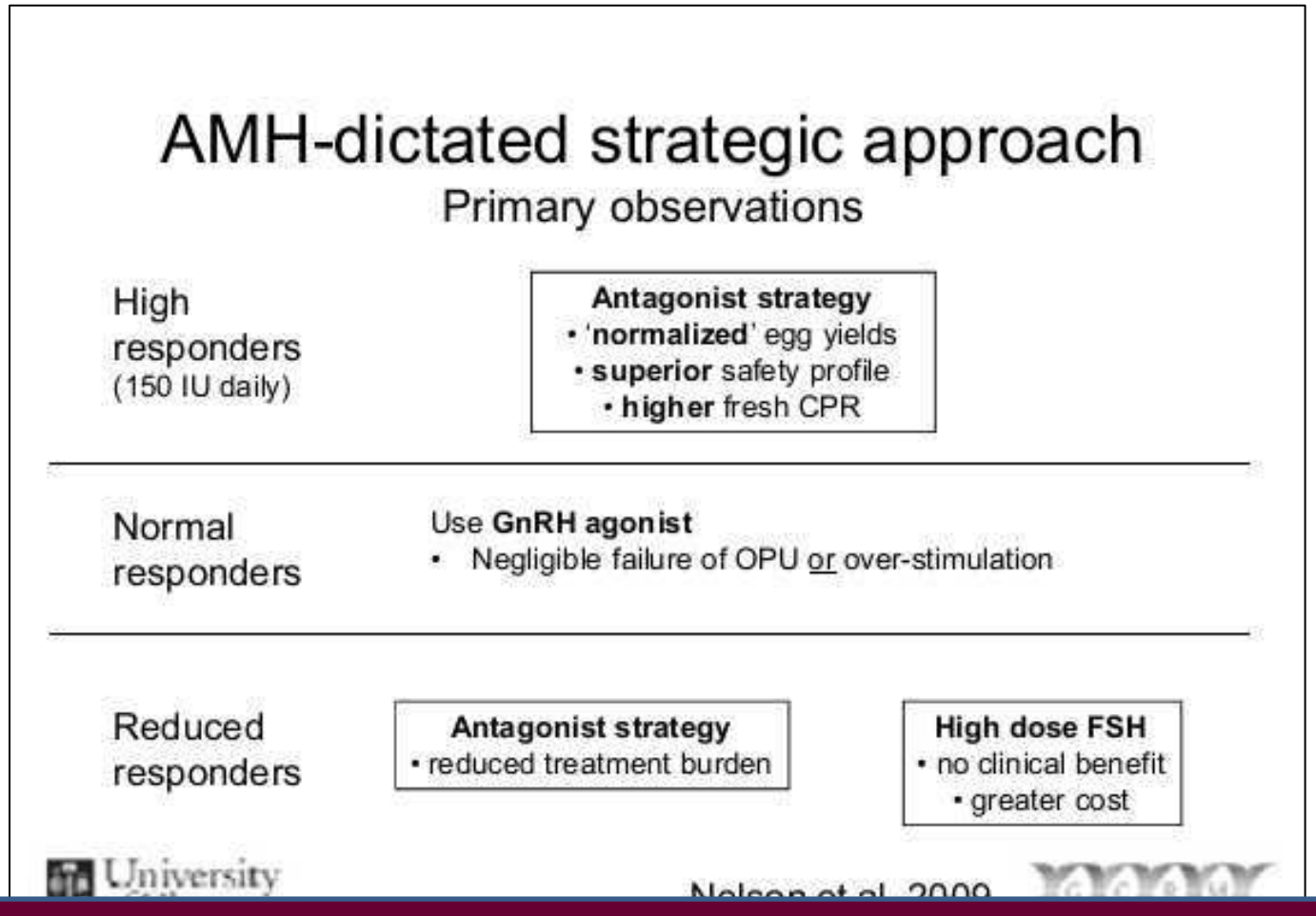
Intervention	Studies	Design of Study	Conclusion
GnRH agonist stop protocol	Garcia-Valesco et al., 2005	Prospective, randomized controlled trial	No difference compared with standard long protocol
	Dirnfeld et al., 1999	prospective, randomized controlled trial	
	Katayama et al., 1988	Small observational study	
	Toth et al., 1996	Retrospective study	Higher pregnancy rates
Flare-up GnRH agonist regime	Padilla et al., 1996	Prospective comparative study	
	Karande et al., 1990	Prospective clinical trial	
	Gindoff et al., 1990	Prospective comparative study	No improvement in either ovarian response or cycle outcome
	Anserini et al., 1997	Retrospective comparative study	
	Spandorfer et al., 2001	Retrospective analysis	
	Weissman et al., 2003	Randomised, prospective study.	Significantly less oocytes and lower pregnancy rates as compared to conventional long protocol
Microdose Flare	Surrey et al., 1998	Prospective, non-randomised trial	Improved cycle outcome
	Scott & Navot, 1994	Prospective analysis	
	Detti et al., 2005	retrospective cohort study	No difference compared with "stop" or "flare" protocols
Minidose	Feldberg et al., 1994	Retrospective analysis	Improved cycle outcome
	Olivennes et al., 1996	prospective analysis	

Microdose: LA 20-40-50 µgx2/G , Minidose: midluteal 0.1, devamı 0.05mg/G
Erken folliküler fazda (D2) 20-50 µg FSH, ve LH arttırıcı etkiye sahip

GnRH Antagonist protokoller poor responderlarda kullanımı

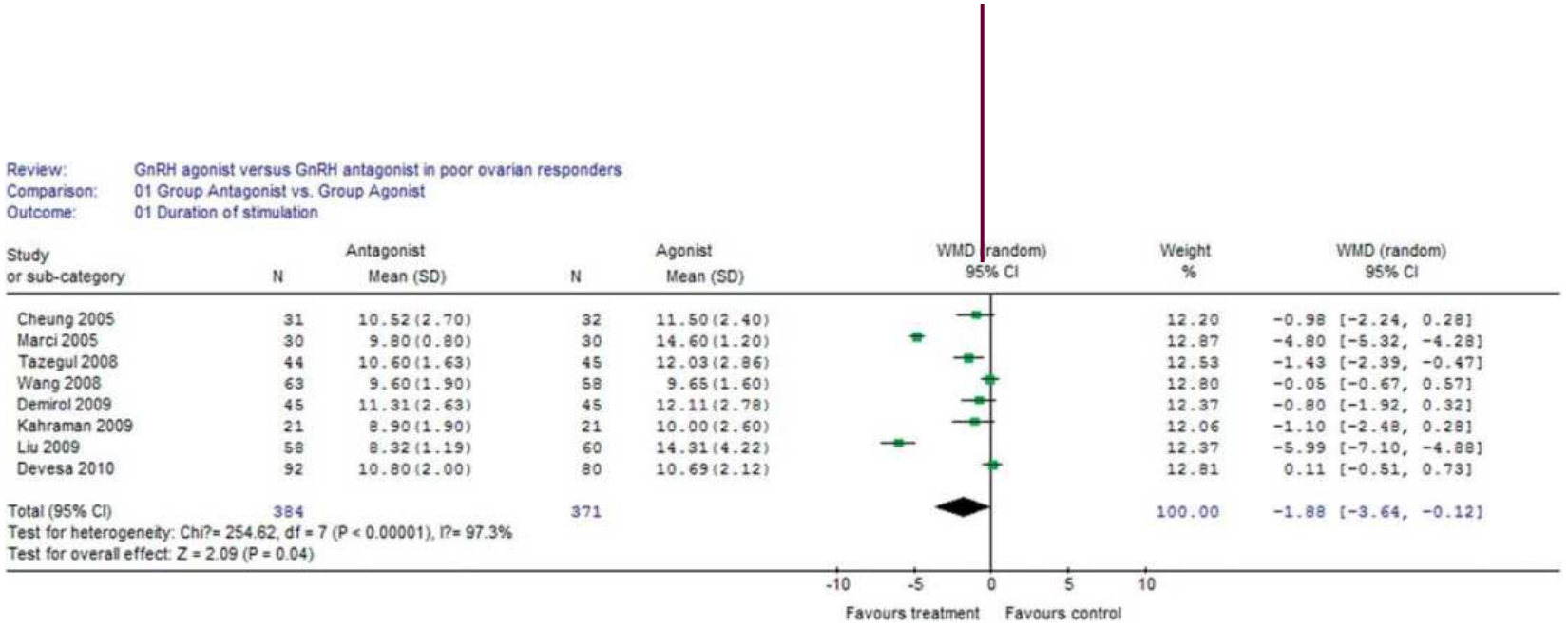
- Antagonistlerin avantajları: folliküler recruitment aşamasında uygulanmadığından endojen gonadotropin süpresyonu yapmaz





Antagonistlerin mid-luteal fazda eklenmesi erken luteinizasyonu engeller
Kullanılan gonadotropin dozu daha az, stimülasyon günü daha az
kompliyans iyi
AFC sayısında göre gonadotropin başlanır, sonradan antagonist eklenir
Corrifollitropin alfa ile birlikte kullanılabilir

Meta-analysis of GnRH-ant versus GnRH-a treatments in poor responders for the duration of stimulation.

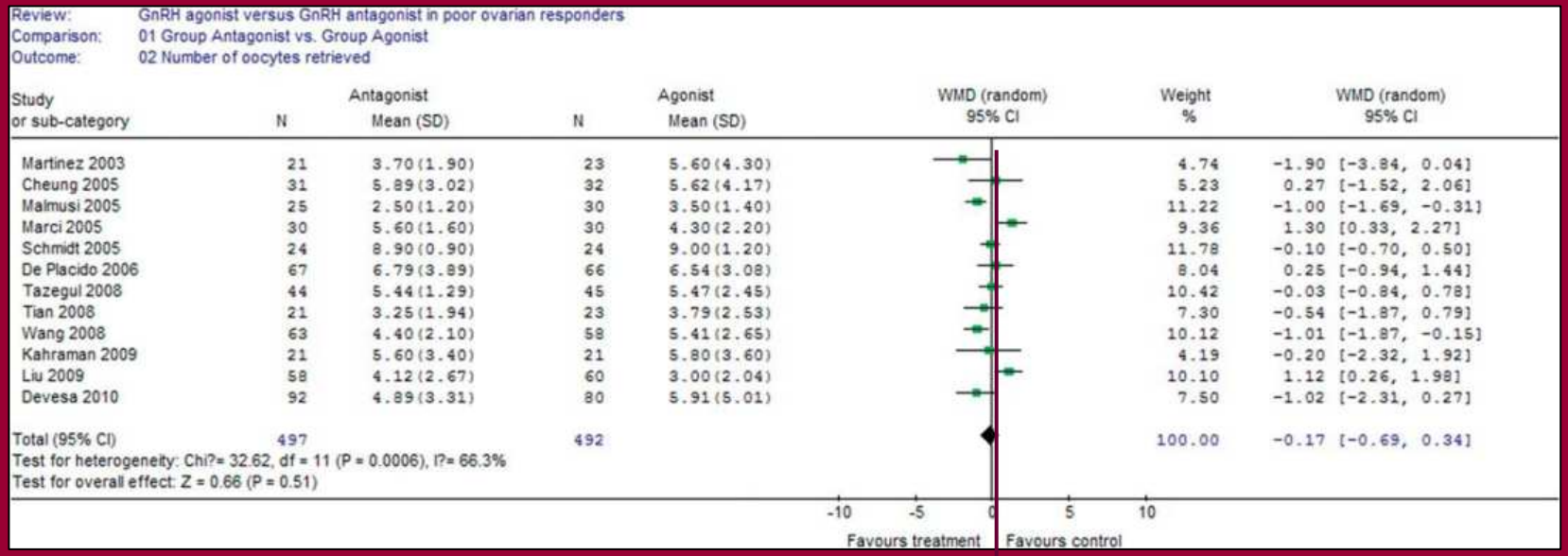


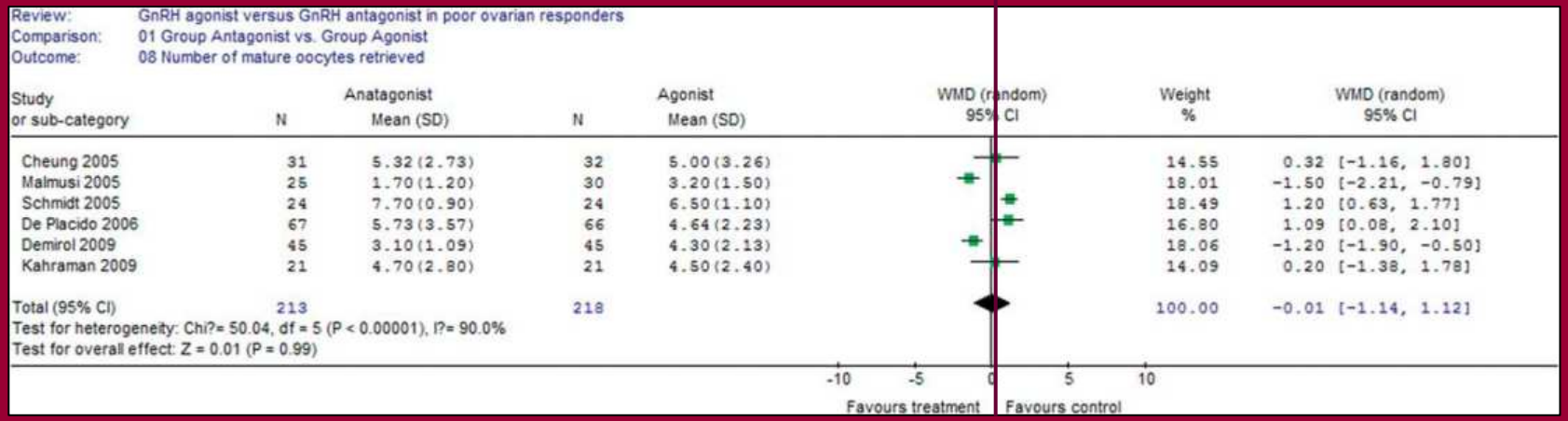
GnRH-antagonist protokollerde stimülasyon süresi daha kısa (P = 0.04; WMD: -1.88, 95% CI: -3.64, -0.12),

Pu D et al. Hum. Reprod. 2011;26:2742-2749

human reproduction

Meta-analysis of GnRH-ant versus GnRH-a treatments in poor responders for the number of oocytesand mature oocytes retrieved. Pu 2011

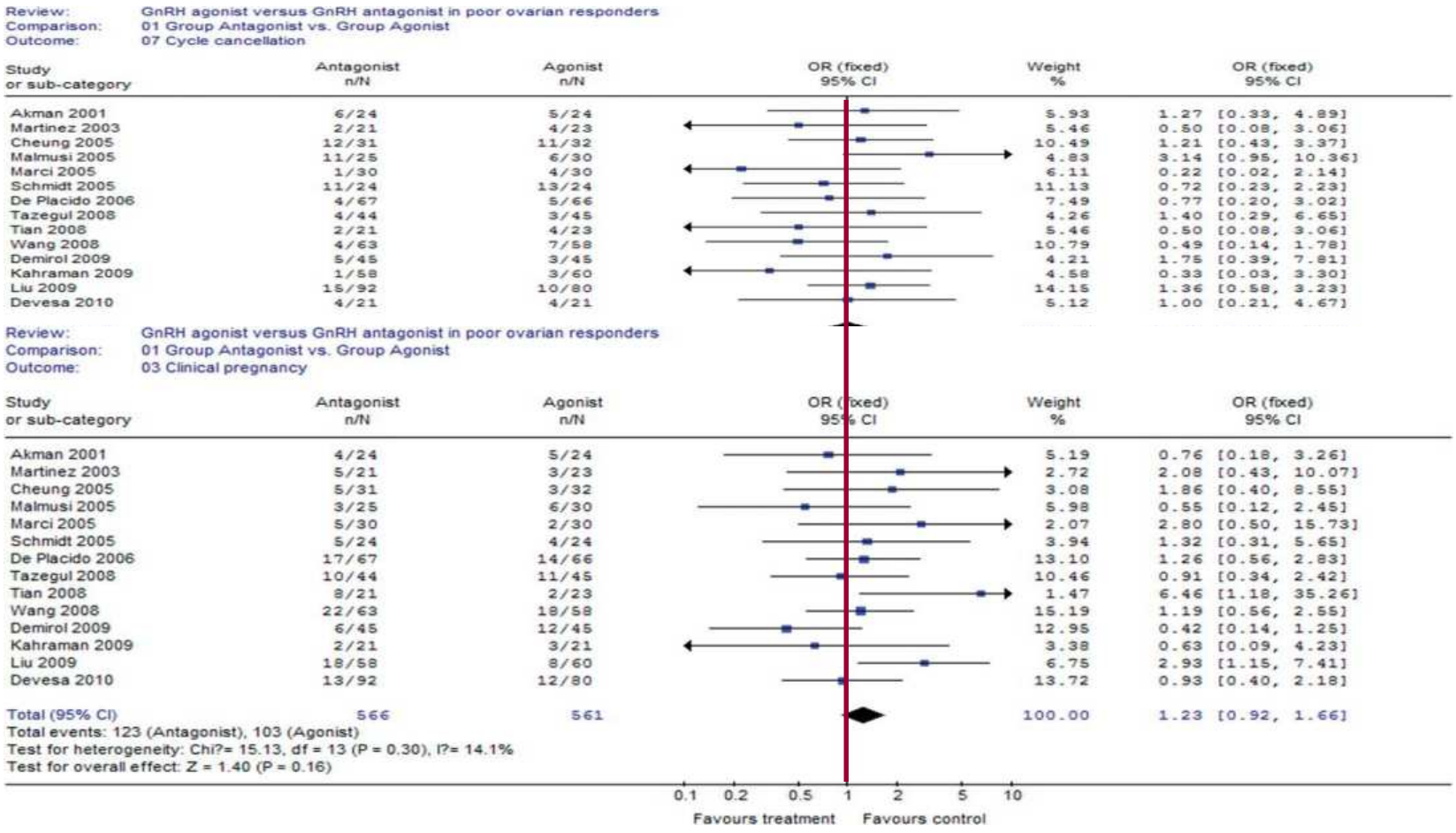




Pu D et al. Hum. Reprod. 2011;26:2742-2749

Toplanan oosit sayısı (P = 0.51; WMD: -0.17, 95% CI -0.69, 0.34) ve matür oosit sayısı açısından (P = 0.99; WMD: -0.01, 95% CI: -1.14, 1.12) fark yok

Meta-analysis of GnRH-ant versus GnRH-a treatments in poor responders for the CCR. OR = odds ratio. Pu 2011



Siklus iptal oranı (CCR, P = 0.67; OR: 1.01, 95% CI: 0.71-1.42) veya klinik gebelik oranı açısından fark yok (CPR, P = 0.16; OR: 1.23, 95% CI: 0.92, 1.66).

human reproduction

Antagonist protokoller poor responderlarda işe yarar mı?

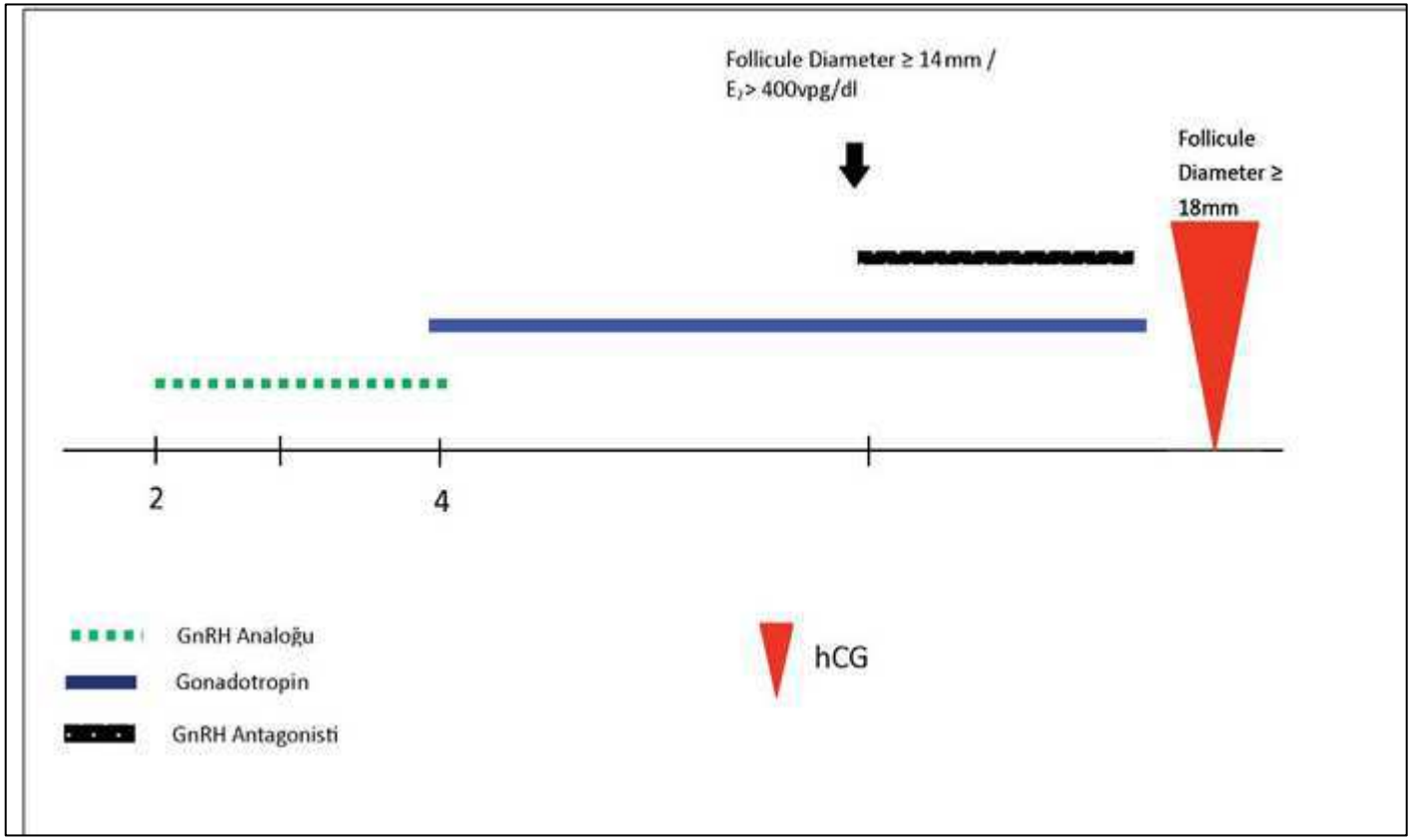
Table 3. GnRH antagonists.

Studies	Design of Study	Conclusion
Schmidt et al., 2005	Randomised prospective study	No difference compared to microdose flare
Akman et al., 2001	Prospective randomised trial (antagonist vs microdose flare)	No difference in pregnancy rates
Malmusi et al., 2005	Randomised prospective study (antagonist vs Agonist Flare protocol)	Less mature oocytes compared with flare protocol; pregnancy rates similar
Cheung et al., 2005	Prospective, randomised, controlled trial antagonists vs long agonist protocol	No difference compared to conventional long agonist protocol
Marci et al., 2005	Prospective randomised trial antagonists vs long agonist protocol	More number of oocytes, less gonadotrophin requirement but similar pregnancy rates compared to long agonist protocol
D'Amato et al., 2004	Prospective, controlled, clinical study. High dose rFSH + clomiphene citrate+antagonist vs long agonist protocol	Better cycle outcome as compared to long agonist protocol
Schoolcraft et al., 2008	Prospective controlled trial (antagonist+letrozole vs microdose flare protocol).	Higher ongoing pregnancy rates and better implantation rates with microdose flare
Nilsson et al., 2010	Pilot study (Luteal phase initiation of antagonists for luteolysis)	No beneficial effect of luteal phase administration of antagonists

Comparison of the ultrashort gonadotropin-releasing hormone agonist-antagonist protocol with microdose flare -up protocol in poor responders: a preliminary study

Zayıf over cevaplı hastalarda ultra kısa GnRH agonist/antagonist protokolünün mikrodoz flare up protokolü ile karşılaştırılması

Bülent Berker[1], Candan İltemir Duvan[2], Cemil Kaya[3], Ruşen Aytaç[1], Hakan Şatıroğlu[1]



Agonist-antagonist protokol

Comparison of the ultrashort gonadotropin-releasing hormone agonist-antagonist protocol with microdose flare -up protocol in poor responders: a preliminary study

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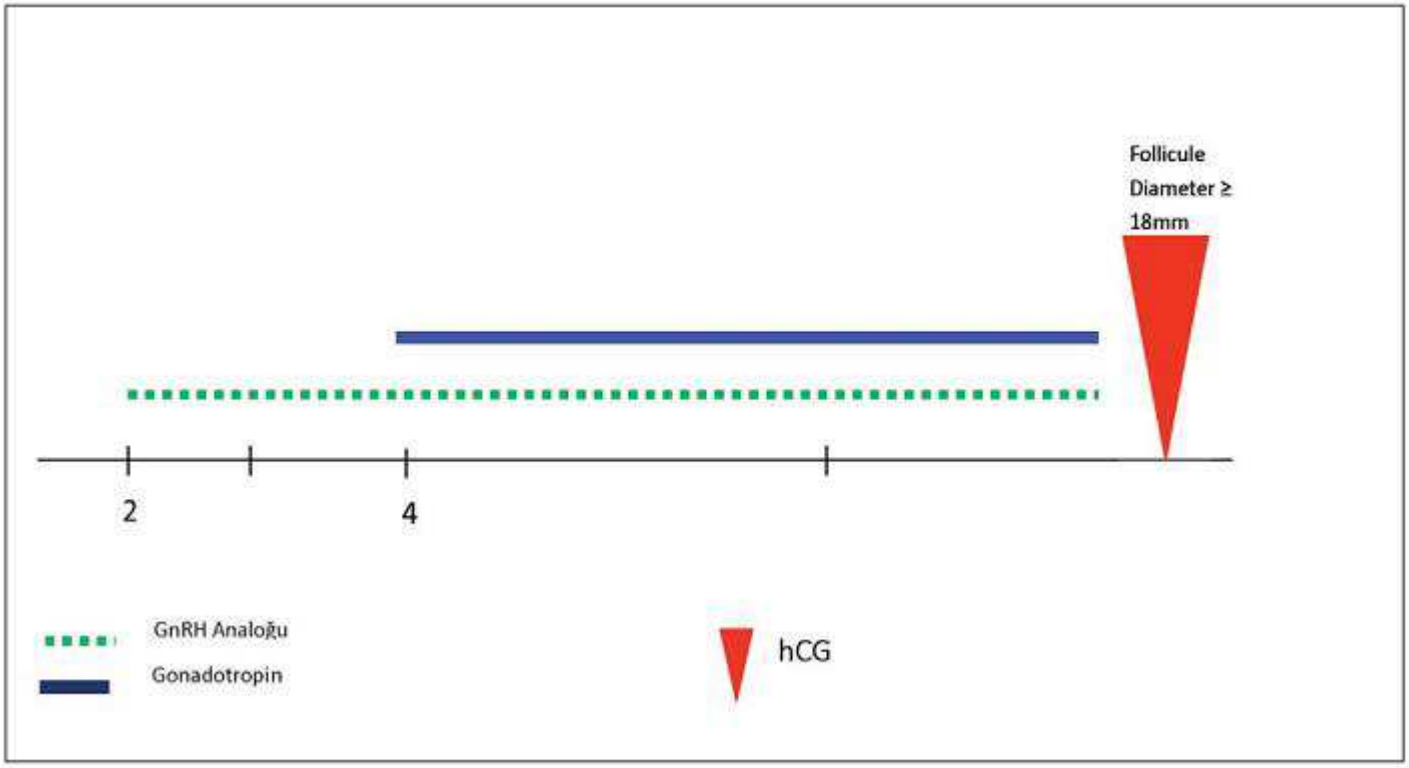


Mikrodoz GnRH analogu (40 µgx2 /G) microdoz flare-up

Table 2. The ovarian stimulation cycle characteristics in both groups

Parameter	Agonist-Antagonist	Microdose flare-up	p
Days of stimulation (n)	10.51±2.4	9.05±2.61	<0.05
Gonadotropin administrated (IU)	3365.93±1627.59	2327.02±929.46	<0.05
Canceled cycle (n)	2	2	NS
Peak estradiol (pg/ml) on hCG day	1370.86±718.64	2029.57±1365.78	NS
Endometrial thickness on hCG day (mm)	9.68±1.43	9.83±2.47	NS
Number of oocytes retrieved (n)	7.82±5.24	8.52±6.38	NS
Number of mature oocytes (n)	7.16±4.94	7.4±6	NS
Number of 2PN	3.54±3.39	4.17±4.2	NS

Parameter	Agonist-Antagonist	Microdose flare-up	p
Fertilization rate (%)	54	62	NS
Grade A embryo (%)	66	59	NS
Number of embryos transferred (n)	2.62±1.37	3.05±1.55	NS
Implantation rate (%)	7.6	8.6	NS
Clinical Pregnancy rate /cycle(%)	19.5 (8/41)	26.3 (10/38)	NS

*NS, Not significant. Statistical significance was defined as p<0.05. Groups were compared using Student's t or Mann Whitney U test, where appropriate

Berker ve ark, 2010: Fark Agonist-antagonist protokolde kullanılan gonadotropin dozu fazla

Poor responder: mikrodose-flare up protokol

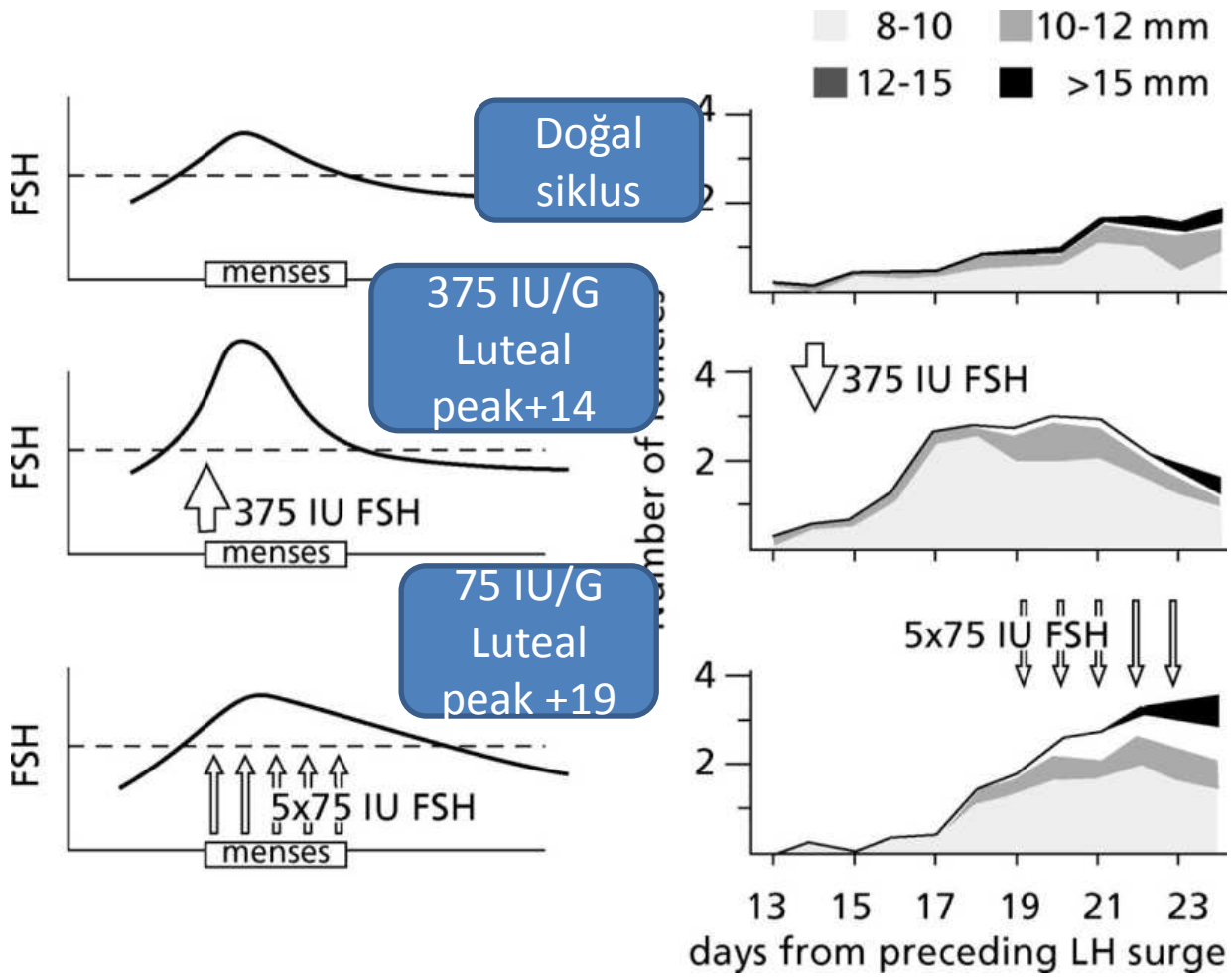
Comparison of microdose flare-up and antagonist multiple-dose protocols for poor-responder patients: a randomized study. Demirol A, Gurgan T. Fertil Steril. 2009

- Her grupta 45 hasta
- Mikrodoz- flare-up: gonadotropin kullanımı daha az, toplanan oosit sayısı fazla,
- İmplantasyon oranı yüksek (%22, %11),
- Fertilizasyon ve klinik gebelik oranları biraz daha yüksek

Microdose flare-up vs. flexible-multidose GnRH antagonist protocols for poor responder patients who underwent ICSI. Esinler I. Clin Exp Obstet Gynecol. 2014

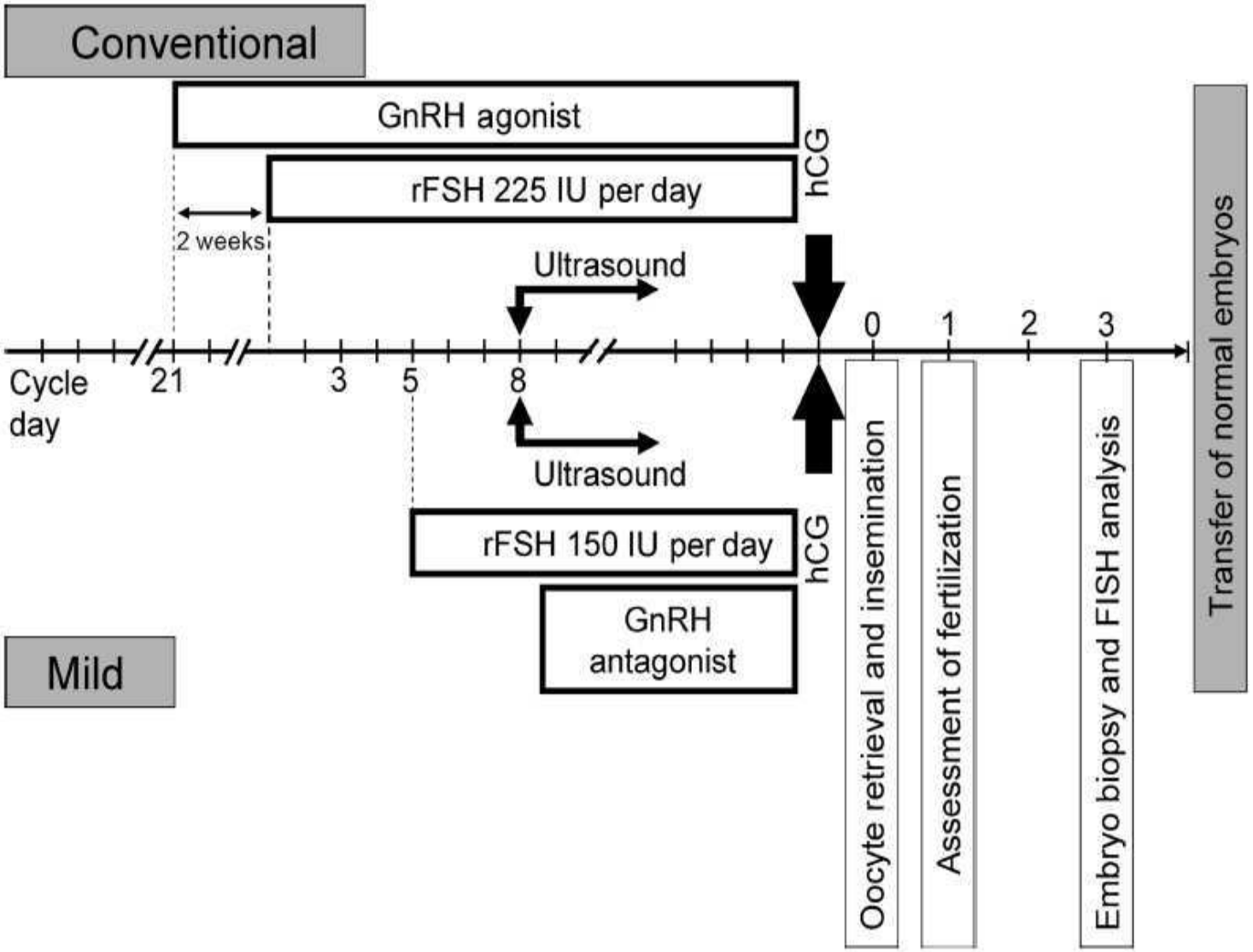
- 127 siklus
- Total gondotropin dozu ve stim. süresi mikrodozda daha fazla, toplanan oosit sayı ve kalitesi daha kötü
- İmplantasyon oranları (%8.6vs 12.2) ET/klinik gebelik oranları (%16.3 vs. 25.8) benzer

FSH window concept with mild intervention approaches, stressing the significance of the limited duration of FSH elevation above the threshold level rather than the height of the elevation of FSH for multiple dominant follicle selection.



Mild stimülasyon FSH penceresi konseptine dayanır:
Çok sayıda follikül gelişmesi için FSH yükselmesinin tepe noktasından çok FSH'nın eşik değer üzerinde kaldığı dönem önemlidir
Hem de fizyolojik olmayan E2 değerleri önlenmiş olur

Verberg M et al. Hum. Reprod. Update 2009;15:13-29


Conventional
GnRH agonist
rFSH 225 IU per day
hCG
2 weeks
Ultrasound
0
1
2
3
Cycle day
21
3
5
8
Ultrasound
rFSH 150 IU per day
hCG
GnRH antagonist
Mild
Oocyte retrieval and insemination
Assessment of fertilization
Embryo biopsy and FISH analysis
Transfer of normal embryos

Tanım	Hedef	Yöntem
Doğal siklus IVF	Tek oosit	İlaç yok
Modifiye Doğal siklus IVF	Tek oosit	hCG + antagonist ve/veya antagonist ve/veya Sabit düşük doz FSH/HMG (en fazla 150 IU) Luteal faz desteği (hCG or P)
Mild IVF	2-7 oosit	Sabit düşük doz FSH/HMG (en fazla 150 IU), antagonist, adjuvan
Klasik IVF	≥8 oosit	FSH/HMG standart dozlarda + agonist veya antagonist

"Mild" vs. "long" protocol for controlled ovarian hyperstimulation in patients with expected poor ovarian responsiveness undergoing in vitro fertilization (IVF): a large prospective randomized trial.

J Assist Reprod Genet. 2014

Revelli A1, Chiadò A, Dalmasso P, Stabile V, Evangelista F, Basso G, Benedetto C.

- "mild" protocol CC ve düşük doz gonadotropin
- vs GnRH-antagonist (CC/Gn/GnRH-ant protocol) "long" protocol" GnRH-agonist and yüksek doz Gn
- "mild" stimulation: kısa folliküler faz, kullanılan Gn miktarı daha az, E2 peak değeri daha düşük
- "long" protocol, ovaryan yanıtın azlığına bağlı siklus iptali daha az, daha fazla oosit , daha fazla matür oosit, daha fazla embriyo, daha kalın endometrium
- IVF SONUCU: Birbirine yakın implantasyon, klinik gebelik ve 12 haftada devam eden gebelik oranları

Kötü ovaryan yanıtlı hastalarda doğal siklus sonuçları:

Morgia *et al*. (2004)	Poor-responding patients (<4 follicles in a previous IVF attempt) with a regular menstrual cycle. ICSI was performed in all cycles	Natural cycle IVF with hCG when the leading follicle was ≥16 mm (59 patients, 114 cycles)	GnRH analog flare protocol with 0.05 mg buserelin twice daily from Day 1 and 600 IU purified FSH/day from Day 3 (70 patients, 101 cycles)	**Cycles resulting in embryo transfer 41.2 versus 68.3%. Ongoing pregnancy rate (per cycle) 6.1 versus 6.9% (NS)**

Natural-cycle in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles

Mauro Schimberni, M.D.,[a] *Francesco Morgia, B.S.,*[a] *Julio Colabianchi, M.D.,*[a] *Annalise Giallonardo, M.D.,*[a] *Claudio Piscitelli, M.D.,*[a] *Pierluigi Giannini, M.D.,*[a] *Monica Montigiani, B.S.,*[a] *and Marco Sbracia, M.D.*[b]

[a] Bioroma Centro di Riproduzione Assistita Casa di Cura "Paideia," and [b] Center for Endocrinology and Reproductive Medicine (CERM), Rome, Italy

TABLE 1

Data on poor responder women treated with natural-cycle IVF in all cases, stratified by women's age.

Parameters	All cases	≤35 years	36–39 years	≥40 years
No. of patients	294	60	69	165
No. of cycles	500	105	120	275
Cycles without oocytes	21.9%	19.1%	19.6%	24.0%
Cycles without embryos	21.0%	19.1%	23.5%	20.6%
Cycles with transfer	57.0%	61.8%	56.9%	55.4%
No. of embryos	285	65	68	152
Embryo A type	37.0%	43.1%	49.0%	30.7%
Embryo B type	51.9%	41.1%	41.5%	58.7%
Embryo C type	11.1%	15.7%	9.4%	10.6%
No. of embryos/transfer	1.0	1.0	1.0	1.0
Pregnancy/cycle	9.8%	18.1%	11.7%	5.8%
Pregnancy/transfer	17.1%	29.2%	20.6%	10.5%
Pregnancy/patient	16.7%	31.7%	20.3%	9.7%
Implantation rate	17.1%	29.2%	20.6%	10.5%
Abortion rate	16.3%	10.5%	14.3%	25.0%

Schimberni. IVF with natural cycle in poor responder women. Fertil Steril 2009.

YAŞ ÖNEMLİ

Natural-cycle in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles

Mauro Schimberni, M.D.,[a] *Francesco Morgia, B.S.,*[a] *Julio Colabianchi, M.D.,*[a] *Annalise Giallonardo, M.D.,*[a] *Claudio Piscitelli, M.D.,*[a] *Pierluigi Giannini, M.D.,*[a] *Monica Montigiani, B.S.,*[a] *and Marco Sbracia, M.D.*[b]

[a] Bioroma Centro di Riproduzione Assistita Casa di Cura "Paideia," and [b] Center for Endocrinology and Reproductive Medicine (CERM), Rome, Italy

TABLE 2

Data on poor responder patients treated with natural-cycle IVF stratified by first, second, third, fourth, or further cycle.

Parameters	Number of consecutive cycles				
	1	2	3	4	≥5
No. of cycles	294	103	50	39	14
Cycles with oocytes	77.9%	78.6%	78.0%	79.5%	64.3%
Cycles with transfer	57.5%	57.3%	58.0%	56.4%	42.9%
No. of embryos obtained	169	59	29	22	6
No. of embryos/transfer	1.0	1.0	1.0	1.0	1.0
Pregnancy/cycle	9.5%	9.7%	12.0%	10.2%	7.1%
Pregnancy/transfer	16.6%	16.9%	20.7%	18.2%	16.7%
Implantation rate	16.6%	16.9%	20.7%	18.2%	16.7%
Abortion rate	14.3%	20.0%	16.7%	25.0%	0

Schimberni. IVF with natural cycle in poor responder women. Fertil Steril 2009.

Modified Natural Cycle Using GnRH Antagonist Can Be an Optional Treatment in Poor Responders Undergoing IVF

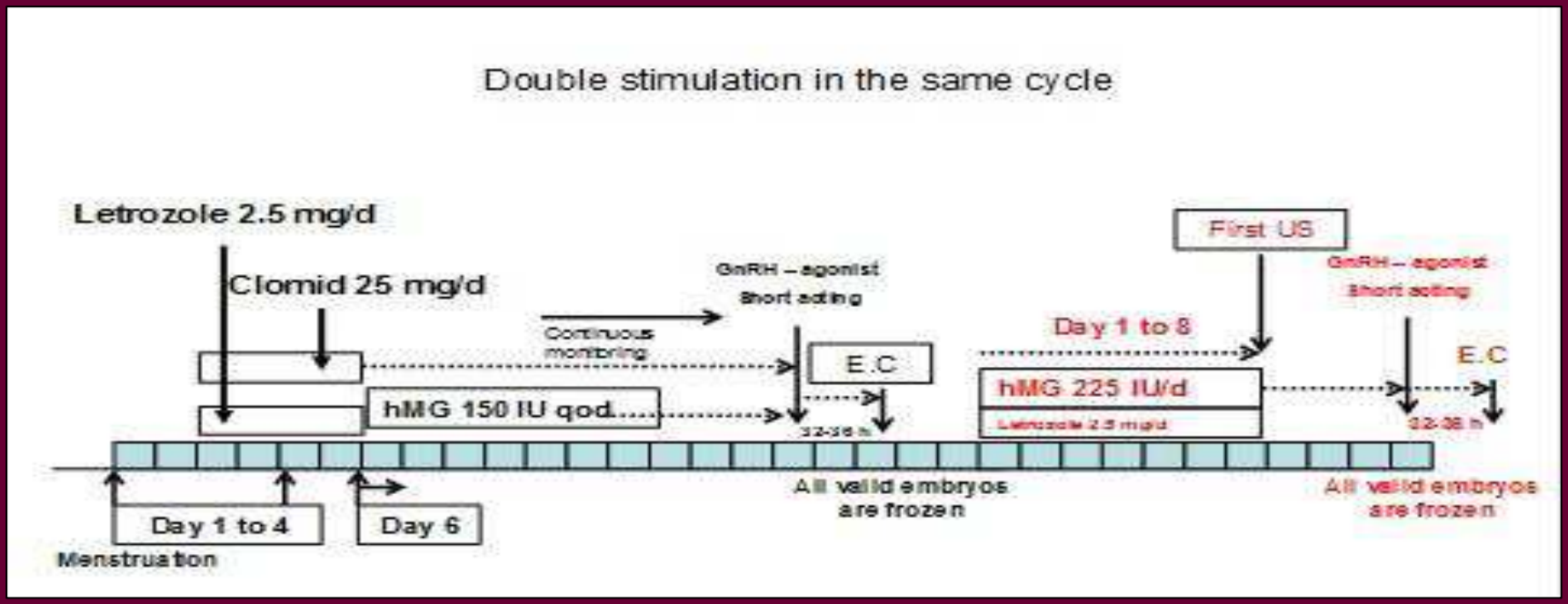
Shai E. Elizur,[1,2,3] Dilek Aslan,[1,2] Adrian Shulman,[1,2] Boaz Weisz,[1,2] David Bider,[1,2] and Jehoshua Dor[1,2]

Table I. Women's and Cycle Characteristics

	Modified natural (mean ± SD)	Antagonist (mean ± SD)	Long agonist (mean ± SD)	*P* value
No. of cycles	52	200	288	
Women's age (years)	39 ± 5.8	38.4 ± 4.7	38.1 ± 6	NS
FSH (day 3) (IU/L)	10.5 ± 5.8*	8.7 ± 4.3	7.8 ± 3.0	
E_2 (on HCG day) (pg/mL)	349.3 ± 223.4*	599.5 ± 345.5	770 ± 478.3	
No. of oocytes retrieved	1.4 ± 0.5*	2.3 ± 1.1	2.5 ± 1.1	
No. of canceled cycles (%)	17/52 (32.6)*	34/200 (17)	53/288 (18.4)	
Fertilization rate (%)	80	70.8	75.3	NS
No. of embryos transferred	1.1 ± 0.3*	1.8 ± 0.9	1.9 ± 0.9	
Implantation rate (%)	10	6.75	7.4	NS
Clinical pregnancy/cycle (%)	9.6	8.5	8.6	NS
Clinical pregnancy/transfer (%)	14.3	10.2	10.6	NS

Note. FSH – follicle-stimulating hormone; HCG – human chorionic gonadotrophin.
*$p < 0.05$ (modified natural vs. antagonist and long agonist protocol).

Modifiye doğal siklus: 13 mm follikül olunca Cetrorelix 0.25mg/G + 2-3 amp hMG
Antagonist: HMG veya rFSH 225Ü/G, 13mm follikül 0.25mg/G Cetrorelix
Long-agonist: Agonist 21. gün 4 süpresyon sağlanınca minimum 225 IU/G HMg veya rFSH



D2-6 Letrozole 2.5 mg/G ve Klomifen sitrat 25 mg/G

D- 6 Letrozole ve Klomifen STOP yerine HMG, 150 IU/d günaşırı

USG ve E-2 ile monitorizasyon GnRH agonisti ile triggering ve OPU- cryopreservation

OPU'dan 2-3 gün sonra Letrazol 2.5 mg ve HMG 225 IU /G7. gün USG, dominant follikül 14 mm olduğunda letrazol stop, HMG devam trigger GnRH agonsiti (Triptoreline 0.1mg) OPU ve kriyoprezervasyon.

Kuang et al

- **Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF).**
  Pandian Z, McTavish AR, Aucott L, Hamilton MP, Bhattacharya S.
  Cochrane Database Syst Rev 2010

- **Daha önceki IVF tedavisinde poor responder olarak değerlendirilen ve iki ayrı KOH protokolünü karşılaştıran çalışmalar dahil edilmiştir.**
- Konvansiyonel GnRH-a long protokolde, stop protokol ve GnRH antagonist protokole göre toplanan oosit sayısı daha az ve kullanılan total gonadotropin dozu daha yüksek
- GnRHa flare-up grubunda GnRHa long protokole göre siklus iptali daha yüksek
- Sadece bir çalışma canlı doğum oranlarını vermiş, abortus ve ektopik oranları verilmemiş
- SONUÇ:
- **Şu anda yayınlanmış verilerin ışığında poor responderlarda herhangi bir KOH protokolü veya adjuvan tedavinin üstünlüğünü gösteren yeterli kanıt yoktur.**

Siklus öncesi:

Androjen

Luteal FSH

Luteal östrojen

KOK

SİKLUS YÖNETİMİ: KOH PROTOKOLLERİ

Adjuvan kullanımı: GH,GH-RF,Aspirin, L-Arginin, Dexametazon

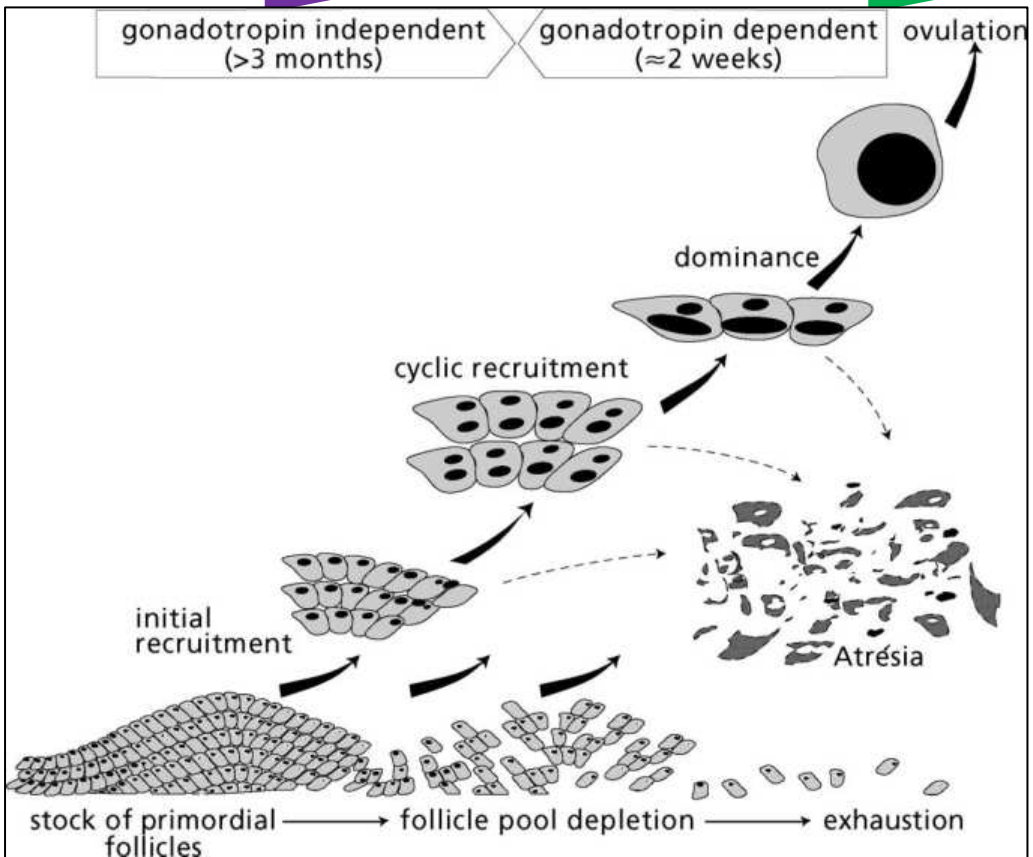
Siklus sonrası:

Luteal faz desteği

Östrojen supp.

ICSI

IVM vb....



Poor responder: en iyi protokol nedir?

- Etiyoloji bilinmiyor
- Tanım geniş bir spektrumu içeriyor
- Yayınlarda kullanılan kriterler farklı
  - Gonadotropin başlangıç dozları, rekombinan, üriner, doz artışları,
  - Araştırma sonuçları -main outcome- (oosit sayısıs, matür embriyo sayısı, klinik gebelik oranı, canlı doğum oranı vb..)

human reproduction update

The poor responder in IVF: is the prognosis always poor? A systematic review

J.F. Oudendijk[1], F. Yarde[1], M.J.C. Eijkemans[2], F.J.M. Broekmans[1], and S.L. Broer[1,*]

[1]Department of Reproductive Medicine and Gynaecology, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

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Table I Characteristics of the included studies.

Author	Year	Design	*n*	Definition poor response	Definition pregnancy	One or consecutive cycles	Predictive Factor studied	Compared with normal responders
Baka *et al.*	2006	RC	96c	≤3 oocytes or E2 level <500 pg/ml day of hCG injection or FSH < 20 IU/l	Clinical	One	Number of oocytes	No
Biljan *et al.*	2000	PC	828w	≤3 follicles US	Clinical	One	Age	Yes
Gaast, van der *et al.*	2006	RC	7422w	Not specified	Unclear	One	Number of oocytes	No
Galey-Fontaine *et al.*	2005	RC	163c	<5 follicles >14 mm + E2 <1000 pg/ml before HCG injection	Clinical	One	Age, FSH	No
Hanoch *et al.*	1998	RC	143c	E2 level <1000 pg/ml day of HCG injection	Clinical	One	Age	No
Hellberg *et al.*	2004	RC	1699w	<5 oocytes retrieved	Live birth	Consecutive	Number of oocytes	No
Hendriks *et al.*	2008	PC	222w	<4 oocytes or cancellation	Ongoing	Consecutive	ORT	Yes
Inge *et al.*	2005	RC	805c	≥1 oocyte and ≤5 oocytes	Live birth	One	Age	No
Klinkert *et al.*	2004	RC	225w	<4 oocytes or <3 follicles	Ongoing	Consecutive	ORT	No
Orvieto *et al.*	2009	RC	397w	<5 oocytes	Clinical	One	BMI	No
van Rooij *et al.*	2003	PC	93w	<4 oocytes	Ongoing	One	Age	No
Saldeen *et al.*	2007	RC	1706c	≤5 oocytes	Clinical	One	Age	Yes
Schimberni *et al.*	2009	RC	294w	previous cycle ≤1 follicle	Clinical	Consecutive		No
de Sutter *et al.*	2003	RC	9644c	≥1 oocyte and <5 oocytes	Ongoing	One	Age	Yes
Timeva *et al.*	2006	RC	1017c	≤5 oocytes	Clinical	One	Number of oocytes	Yes
Ulug *et al.*	2003	RC	209c	≤4 follicles >10 mm US	Clinical	One	Age, number of oocytes	No
Veleva *et al.*	2005	RC	45w	≤3 oocytes	Clinical	Consecutive	Poor response consistency	No
Yih *et al.*	2005	RC	4862c	≤4 oocytes	Clinical	One	Age	No
Zhen *et al.*	2008	RC	944c	<4 oocytes	Clinical	One	Age	Yes

n, number of women(w)/cycles(c). Study design: RC, retrospective cohort; PC, prospective cohort; US, ultrasound; E2, estradiol.

human reproduction update

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Submitted on April 1, 2011; resubmitted on July 18, 2011; accepted on August 3, 2011

Table II Comparison of pregnancy rate in poor responders to normal responders.

Author	n	Definition poor response	Definition of pregnancy	PR/cycle poor responders (%)	PR/cycle normal responders (%)	P-value	Age in poor responders	Age normal responders	P-value
Bijan et al.	805w	≤3 follicles US	Clinical	14.3	33.0%	Not stated	37.3[a] 41.4[b]	34.5[a] 42.3[b]	0.003[a] NS[b]
Hendriks et al.	222w	<4 oocytes + cancellation	Ongoing	7.6	25.9	0.001	39	35	0.01
Sahlaen et al.	1706c	≤5 oocytes	Clinical	9.0	32.6	<0.0005	35.9	33.7	<0.0001
Sunter, de et al.	9644c	≥1 oocyte and <5 oocytes	Clinical	17.5	35.3	<0.0001	Not stated	Not stated	
Tinneva et al.	1017c	≤5 oocytes	Clinical	12.1	29.5	<0.05	Not stated	Not stated	
Zhan et al.	944c	<4 oocytes	Clinical	14.8	36.7	<0.05	36.6	33.3	<0.05
Pooled estimate	14 338			14.8	34.5				

n, number of women(w)/cycles(c) included; PR, pregnancy rate. NS, non-significance.
[a]Group <40 years.
[b]Group ≥40 years.

human reproduction update

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CONCLUSIONS: Poor responders are not a homogeneous group of women with regards to pregnancy prospects. Female age and number of oocytes retrieved in particular will modulate the chances for pregnancy in current and subsequent cycles. Applying these criteria will allow the identification of couples with a reasonable prognosis and balanced decision-making on the management of poor responders.

Key words: poor responder / IVF / pregnancy rate / number of oocytes / systematic review

human reproduction update

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Table III Female age category and pregnancy rate per cycle started.

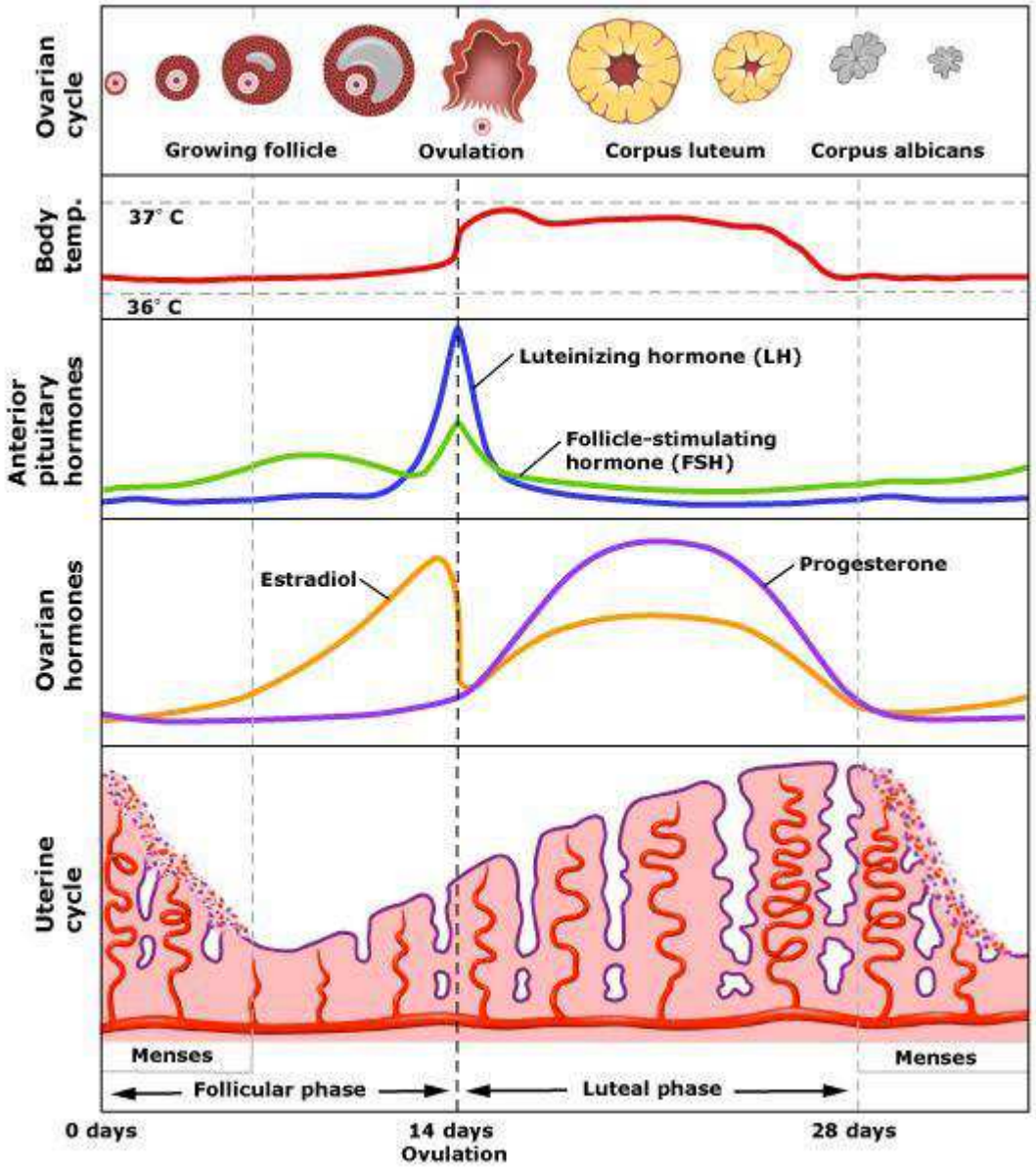
Article	n	Definition poor response	Female age 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 >46	P-value	Note
Zhen et al.	472c	<4 oocytes	18.5% / 2.8%	<0.001	
Rooij, van et al.	47w	<4 oocytes	13.0% / 4.0%	NS	
Biljan et al.	42w	≤3 oocytes US	27.8% / 4.2%	>0.05	
Saldeen et al.	290c	≤5 oocytes	14.0% / 3.0%	NS	PR per ovarium pick up
Inge et al.	173c	≥1 oocyte and ≤5 oocytes	27.1% / 12.7%	NS	DR per cycle
Sutter, de et al.	1280c	≥1 oocyte and ≤5 oocytes	23.0% / 12.0%	<0.0001	
Galey Fontaine et al.	163c	<5 foll. + E2 < 1000 pg/ml before HCG	14.6% / 4.9%	<0.04	PR per retrieval
Ulug et al.	209c	≤4 follicles >10 mm US	19.5% / 7.2% / 1.5%	<0.04	PR per embryo transfer
Hanoch et al.	143w	E2 level < 1000 pg/ml day of HCG injection	19.3% / 6.0% / 6.5%	0.004	
Yih et al.	525w	≤4 oocytes	35% / 21% / 17% / 11%	NS	PR per retrieval

n, number of women(w)/cycles(c) included; PR, pregnancy rate; DR, delivery rate; US, ultrasonographically; SD, standard deviation; NS, not stated; E2, estradiol.

Table V Poor responder and pregnancy rate in subsequent cycles.

Author	*n*	Cycles		PR per cycle (cumulative PR)		Definition pregnancy	Note
				Expected poor responder (EPR)	Unexpected poor responder (UPR)		
Hendriks *et al.*	79w	3	Cycle 1 Cycle 2 Cycle 3	8% 7% (11.5%) 0% (11.5%)	7% 11% (14.8%) 21% (25.9%)	Ongoing	(un)expected poor responder: 'tri-variable-model' [12 × FSH (IU/l)] – [14 × AFC (*n*)] – [1 × inhibin B (pg/ml)]
Klinkert *et al.*	225w	3	Cycle 1 Cycle 2 Cycle 3	11% 9% (19%) 0% (19%)	9% 22% (29%) 25% (47%)	Ongoing	EPR: ≥41 years FSH ≥ 15 IU/l UPR: <41 years and FSH < 15 IU/l
				Poor responder in cycle 1			
Schimberni *et al.*	294w	≥5	Cycle 2 Cycle 3 Cycle 4 Cycle 5	9.7% (12.9%) 12.0% (15.0%) 10.2% (16.3%) 7.1% (16.7%)		Clinical	Natural cycle IVF after cycle 1 Poor responder if in previous cycle ≤1 follicle
Hellberg *et al.*	1699w	2	Cycle 2	1–2 oocytes cycle 1 3–4 oocytes cycle 1	9.5% 16.5%	Live birth	Poor responder if <5 oocytes retrieved
Veleva *et al.*	45w	3	Cycle 2 a/o Cycle 3 Cycle 2 a/o Cycle 3	Poor response Normal response	10.1% (*n* = 43w) 16.7% (*n* = 2w)	Clinical	

n, number of women(w)/cycles(c) included; PR, pregnancy rate; AFC, antral follicle count.


Ovarian cycle
Growing follicle
Ovulation
Corpus luteum
Corpus albicans
Body temp.
37° C
36° C
Anterior pituitary hormones
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Ovarian hormones
Estradiol
Progesterone
Uterine cycle
Menses
Menses
Follicular phase
Luteal phase
0 days
14 days
Ovulation
28 days

KÖY'da DHEA-S

- DHEA supplementation for at least 3 months has been shown to be associated with spontaneous and treatment-induced pregnancies in women with very high FSH or very low anti-mullerian hormone (AMH) levels (Mamas and Mamas, 2009a; Gleicher and Barad, 2010). Benefits of DHEA supplementation have been reported since the beginning of this decade (Casson *et al*., 2000; Barad and Gleicher, 2005, 2006; Barad *et al*., 2007; Gleicher *et al*., 2009, 2010a,b; Sonmezer *et al*., 2009; Mamas and Mamas, 2009a,b, Wiser *et al*., 2010).

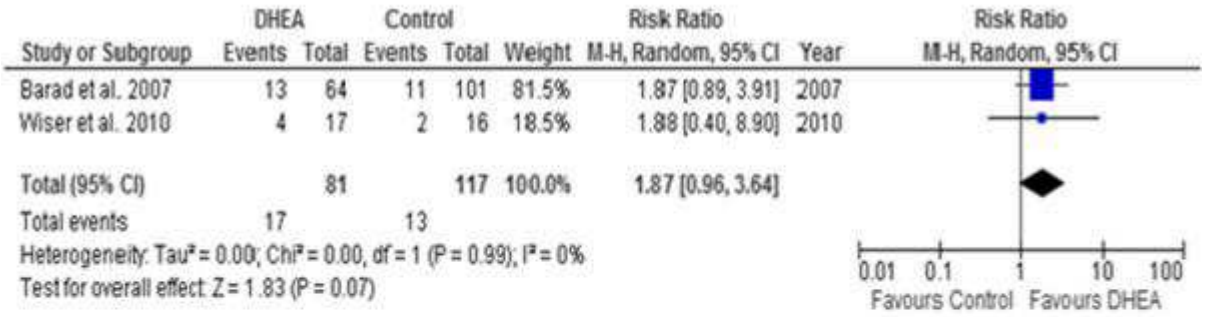
- The evidence on DHEA use in women to enhance the ovarian reserve is based on retrospective analyses (Gleicher *et al*., 2010b), prospective self-controlled studies (Casson *et al*., 2000; Barad and Gleicher, 2006; Sonmezer *et al*., 2009, Gleicher *et al*., 2010a), case reports/series (Barad and Gleicher, 2005; Mamas and Mamas, 2009b), case–control studies (Barad *et al*., 2007; Gleicher *et al*., 2009) and a single randomized controlled trial (Wiser *et al*., 2010).

Efficacy of dehydroepiandrosterone to improve ovarian response in women with diminished ovarian reserve: a meta-analysis.

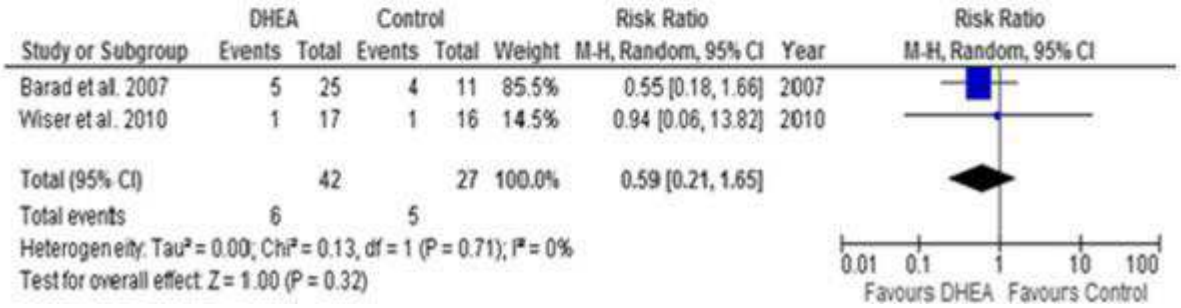
Narkwichean A[1], Maalouf W, Campbell BK, Jayaprakasan K.

Reprod Biol Endocrinol. 2013; 11: 44.

A: Clinical Pregnancy Rate



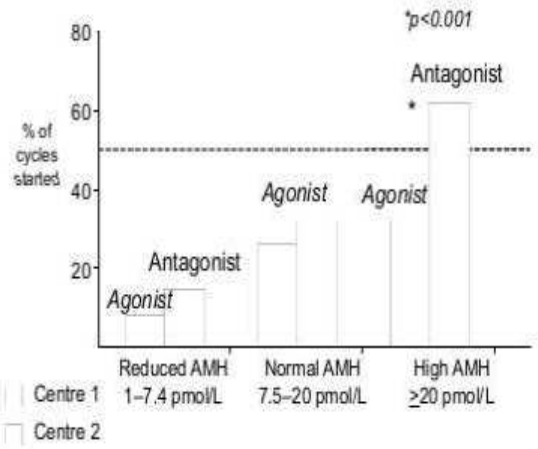
B: Miscarriage Rate



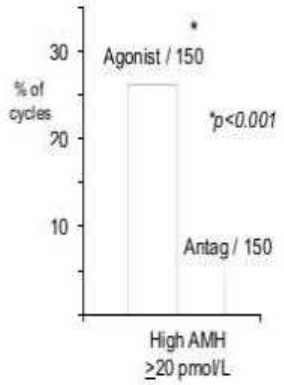
Issues of Ovarian Stimulation

AMH, pmol/L		TRADITIONAL LONG COURSE AGONIST CONTROL	MILD STIMULATION ANTAGONIST CONTROL
Gen II	High Response	Risk: ↑OHSS	↓OHSS SAFER ..*but* ↓egg yield. ***disadvantageous?***
20 – 15	Normal Response	'Normal' & *safe.* Maximal recruitment. *advantageous?*	
7.5 – 5.0	Reduced Response	Excess burden - few eggs	Reduced burden ? impact on egg yields
1.5 – 1.1			

Clinical pregnancy rates



Excess responses OHSS



University of Glasgow

Nelson et al, 2009

Antagonist protokollerde neden daha az oosit gelişiyor?