

POLİKİSTİK OVER SENDROMUNDA GONADOTROPİN TEDAVİSİ

Doç.Dr. Özlem Moraloğlu Tekin
ZEKİ TAHER BURAK KADIN SAĞLIĞI EĞİTİM VE ARAŞTIRMA
HASTANESİ-ANKARA
UTD-2015 ANTALYA



POLİKİSTİK OVER SENDROMU

Stein & Leventhal, 1935



Üreme çağındaki kadınlarda en sık endokrin bozukluk %5-10
Prevelans ≈%20 (İnfertil kadınlar)

Heterojen bir sendrom!

Anovulasyon Sınıflaması (WHO)

Grup I: Hipogonadotropik-hipogonadizm (%10) –

↓ FSH, LH, E₂ – Prolaktin-normal

**Grup II: Normogonadotropik, normoestrojenik – PCOS (%80)-
Foliküler faz FSH-N/ Subnormal**

Grup III: Hipergonadotropik, hipogonadizm –
Ovaryan Yetmezlik (%10) – ↑ FSH ve LH ; ↓ E₂

Grup IV: Hiperprolaktinematik (%10)

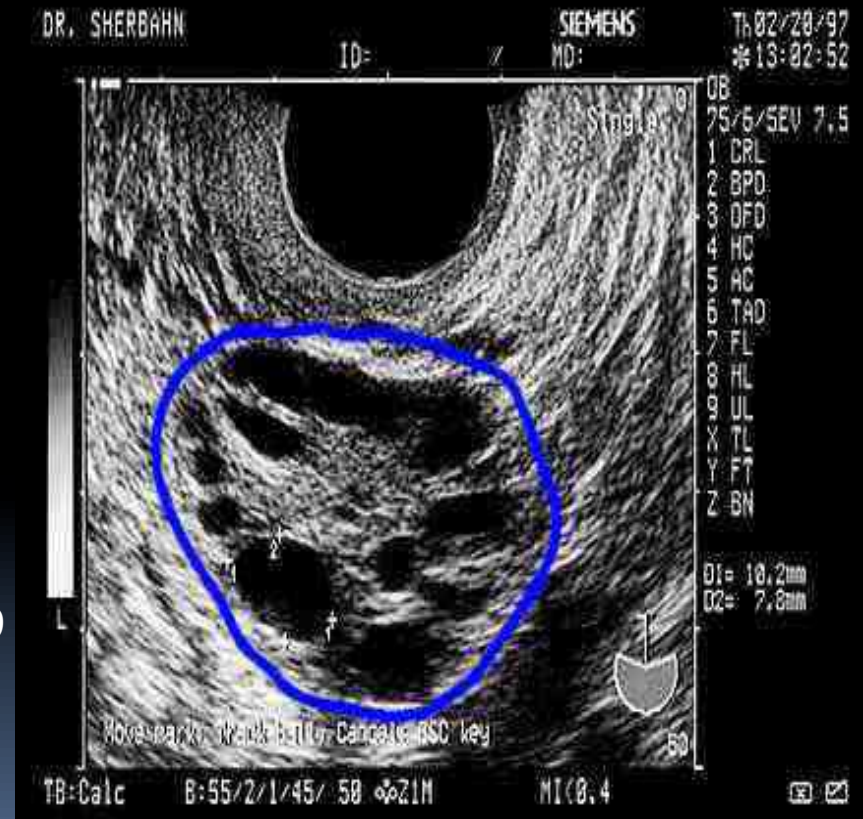
The Rotterdam ESHRE/ASRM Consensus Group Revised 2003 Diagnostic Criteria for PCOS

2 out of 3 criteria required

I) Oligo-ve/veya anovulasyon

II) Hyperandrojenizm (klinik ve/veya biyokimyasal)

III) Ultrasonografik olarak polikistik görünümde overler (PCO) >12 or more follicles measuring 2-9 mm diameter
- Diğer Hiperandrojenemi ety.nin ekarte edilmesi



Human Reproduction 2004; 19: 41-47. Fertility & Sterility, 2004; 81: 19-25.

Yeni tanı kriterleri PKOS tanımına yeni fenotipler eklemektedir

PCOS Phenotype	Oligo – or an ovulation	Biochemical hyperandrogenemia or clinical manifestation of hyperandrogenemia	Polycystic ovaries in transvaginal ultrasound
1- Severe PCOS	+	+	+
2- Oligo – or anovulation and hyperandrogenemia	+	+	-
3- ovulatory PCOS	-	+	+
4- MILD pcos	+	-	+

Robert J Norman, Lancet 2007; 370: 685–97

% 16-25 normal popülasyon



Bu fenotipik farklılıklar özellikle hastaların bireysel tedavi planlamasında önemli!...

PCOS İLE İLGİLİ VEYA BAĞLANTILI GENLER

Steroid metabolism and action	Insulin secretion and action/fuel metabolism	Gonadotropin action and regulation	Cardiovascular disease
CYP17 (17 α -hydroxylase/17,20-lyase)	Insulin	Follistatin*	Paraoxonase*
CYP11A (cholesterol side-chain cleavage enzyme)	Insulin receptor	LH β -subunit	PAI-1 (plasminogen activator inhibitor 1)
AR (androgen receptor)	Microsatellite D19S884 (located 1 cM from the insulin receptor gene)	FSH β -subunit*	IL6 (interleukin 6)
CYP21 (21-hydroxylase)*	IRS1 and IRS2 (insulin receptor substrates 1 and 2)	Dopamine D3 receptor*	IL6 receptor complex*
CYP19 (aromatase)*	CAPN10 (calpain-10)	FSH receptor*	Adiponectin
SHBG (sex hormone binding globulin)	PPARG (peroxisome proliferator activated receptor Γ)		EPHX (microsomal epoxide hydrolase)*
H6PD (hexose-6-phosphate dehydrogenase)*	Resistin*		Aldosterone synthase*
	IGF2 (insulin-like growth factor 2)*		Tumor necrosis factor receptor 2*
	PPP1R3* (glycogen-targeting subunit of protein phosphatase 1)		Matrix metalloproteinase-1*
	PC-1 (plasma cell membrane glycoprotein 1)*		Factor V*

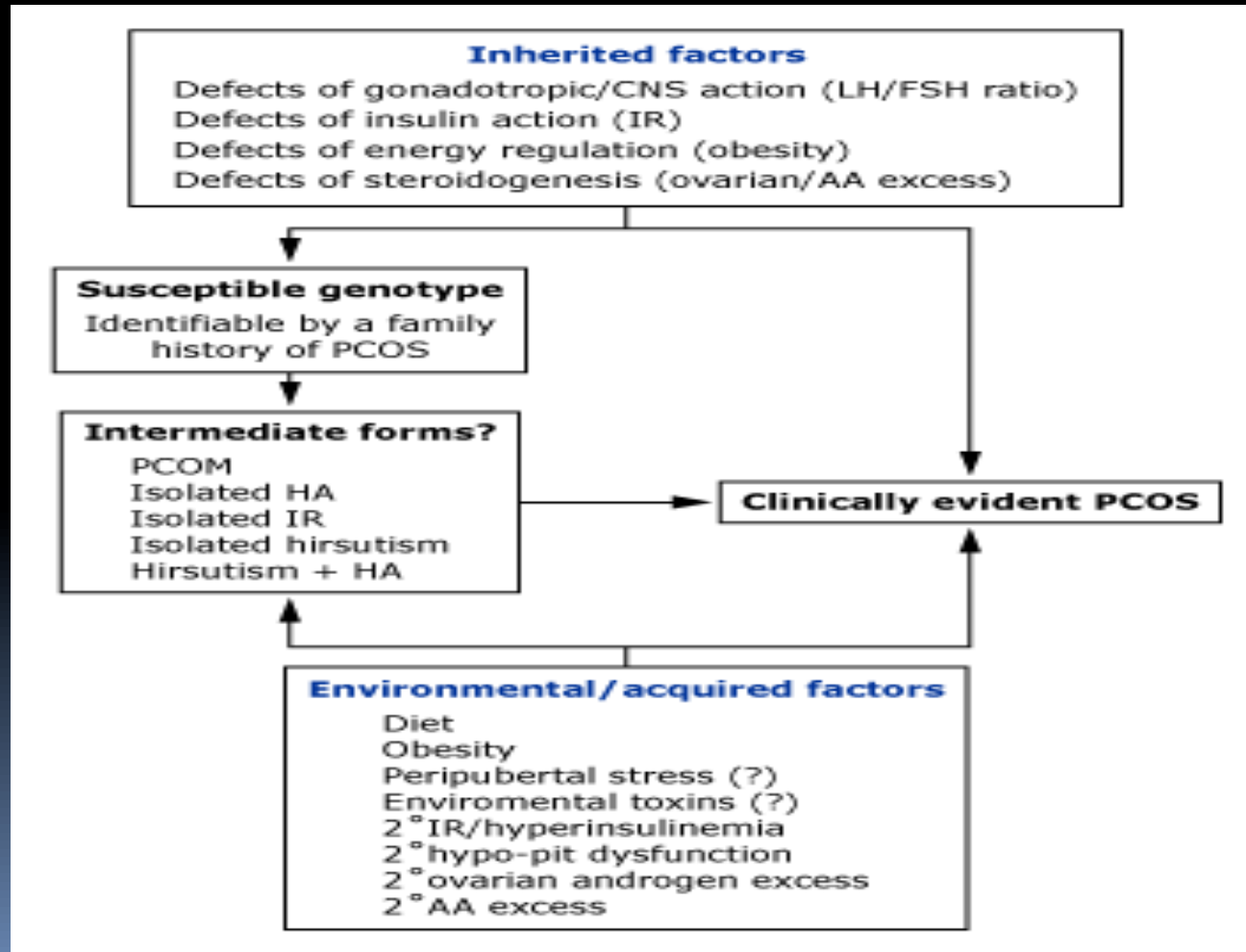
Goodarzi, MO, Azziz, R. Best Pract Res Clin Endocrinol Metab 2006

19. Kromozom üzerinde PCO'tan sorumlu bir dinükleotid markır bulunmuş Simoni M 2008

PCOS Patofizyolojisi ?

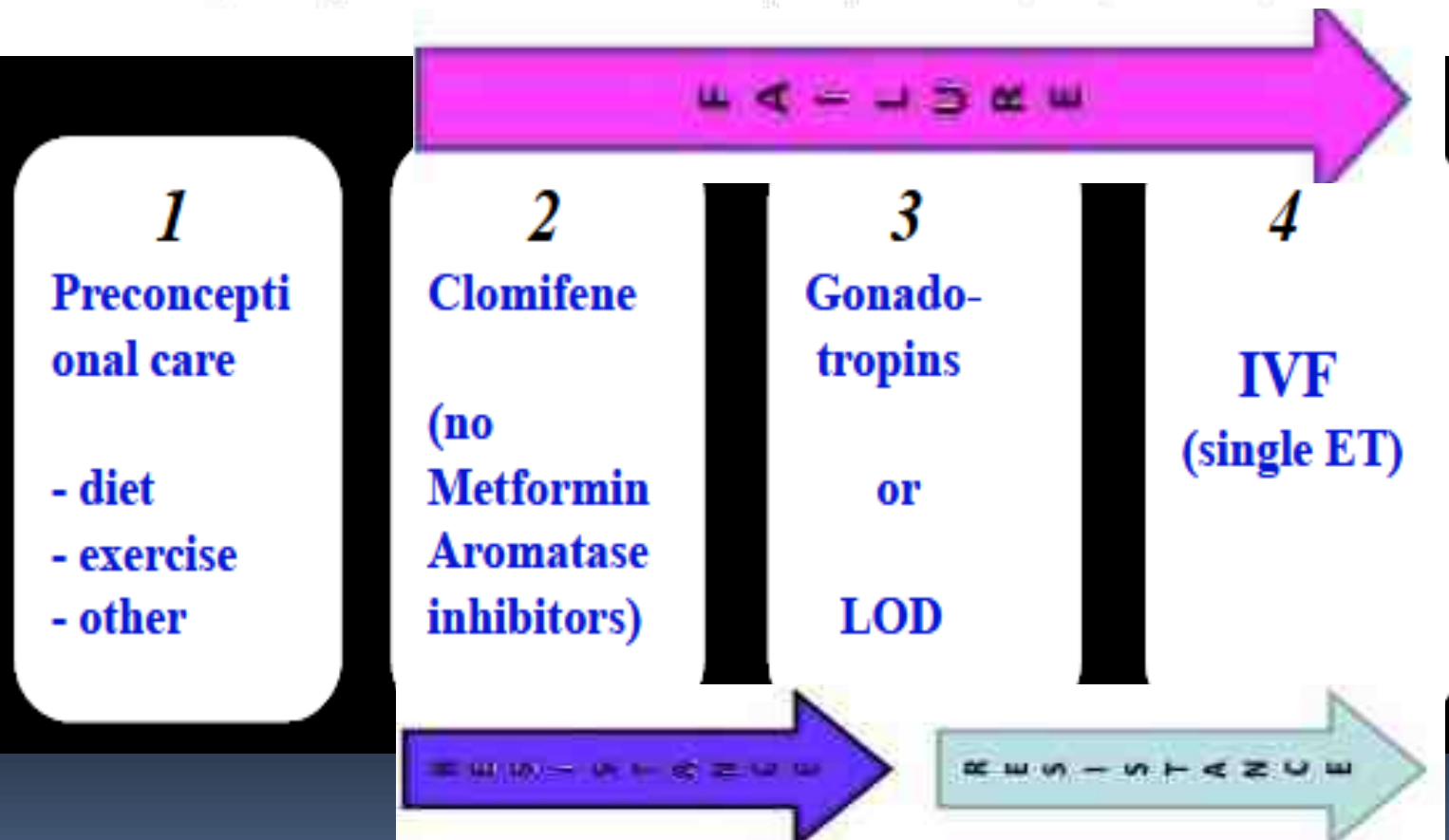
GENETİK, ÇEVRESEL VE KAZANILMIŞ FAKTÖRLERİN KOMPLEKS İLİŞKİSİ SÖZ KONUSU

İkiz ve aile çalışmalarında PCOS' un bir polijenik pattern ile genetik geçişli olduğu gösterilmiş



Consensus on infertility treatment related to polycystic ovary syndrome

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



Hastaya uygun tedavi modalitesi belirlenmeli!...

Anovulasyon mekanizmaları

LH /FSH ↑

GnRH pulse
frekansı ↑

- LH pulse frekansı ↑
- FSH pulse frekansı
değişmez

Hipofizer
GnRH
sensitivitesinde
artış

(Franks, 2005)

Hipotalamo–pituitar–over aks

Estrojen sekresyonuna rağmen LH surge olamaması

Pubertede maturasyon olmaması (Pozitif feedback bozuk)

Ektopik steroid hormon etkileşimleri

Anovulasyon Mekanizmaları

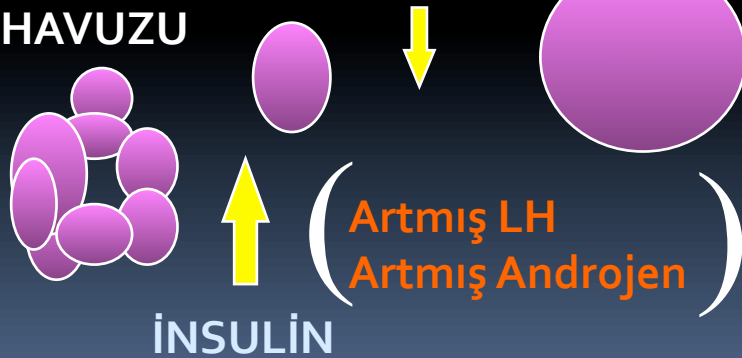
Normal follikülojeniz



Anormal follikülojeniz

1-GENİŞ FOLLİKÜL HAVUZU

LH a Erken Sensitivite



YETERSİZ LH SURGE



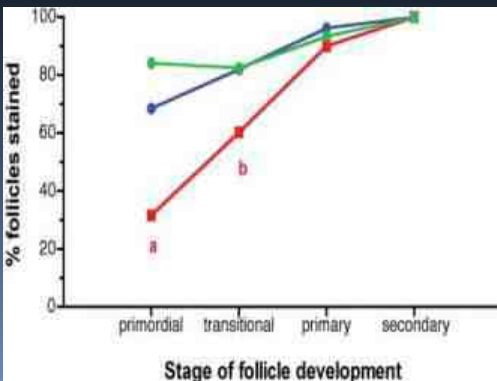
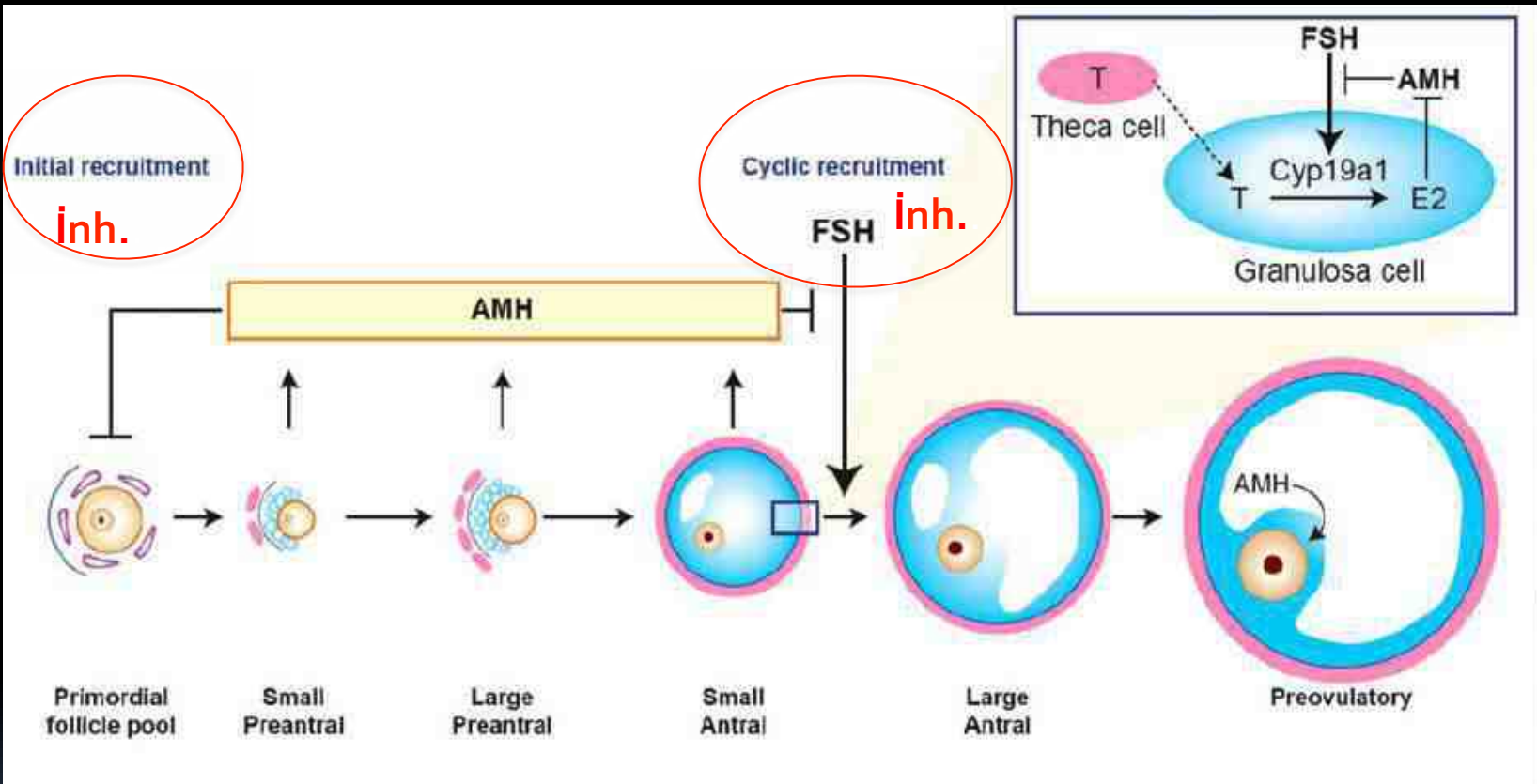
2-Rölatif FSH yetmezliği

- Artmış LH
- Artmış İnsülin
- Azalmış SHBG
- Artmış androjen
- Inhibin B, IGF₁, AMH'daki değişiklikler???

3-Follikül Gelişiminde Arrest

Franks S, 2005

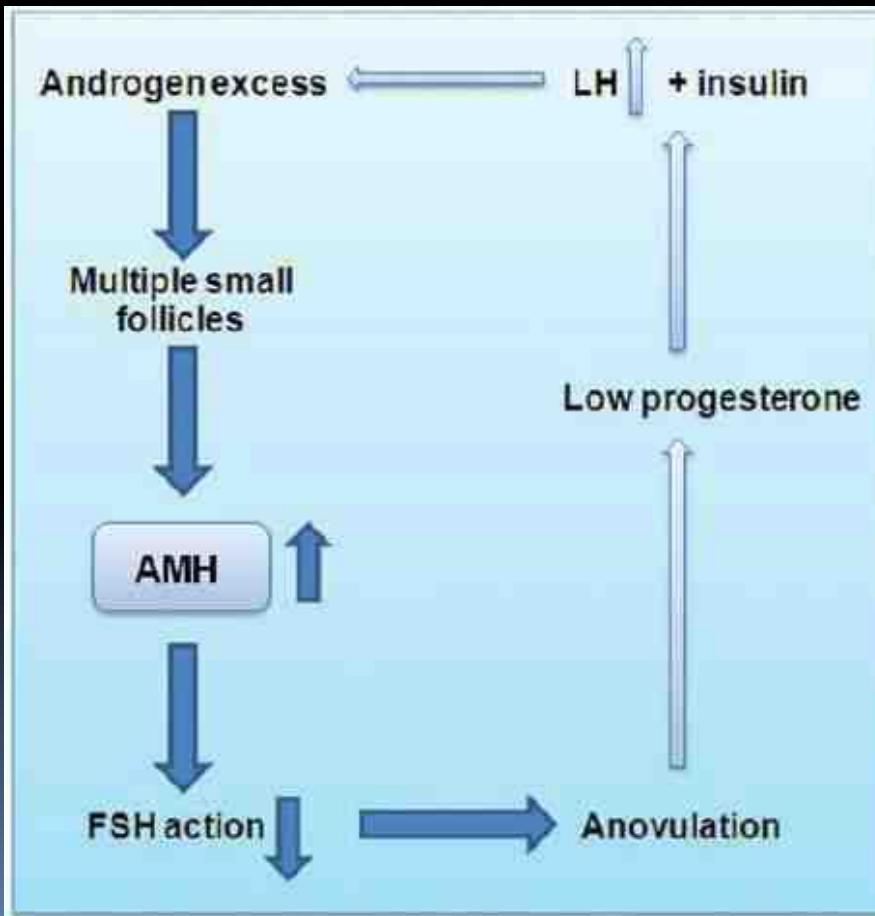
FSH'yı baskılayan ne???



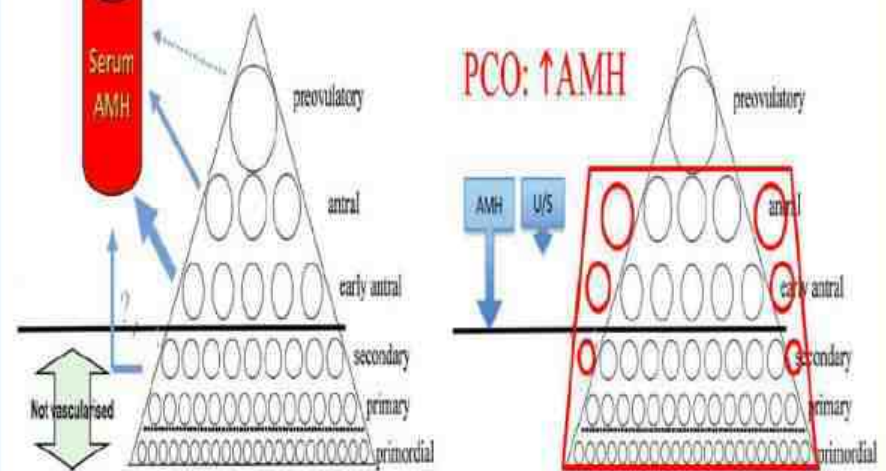
- normal overler
- PCOS ovülatuar
- PCOS anovülatuar

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

Roy Homburg and Giselle Crawford*



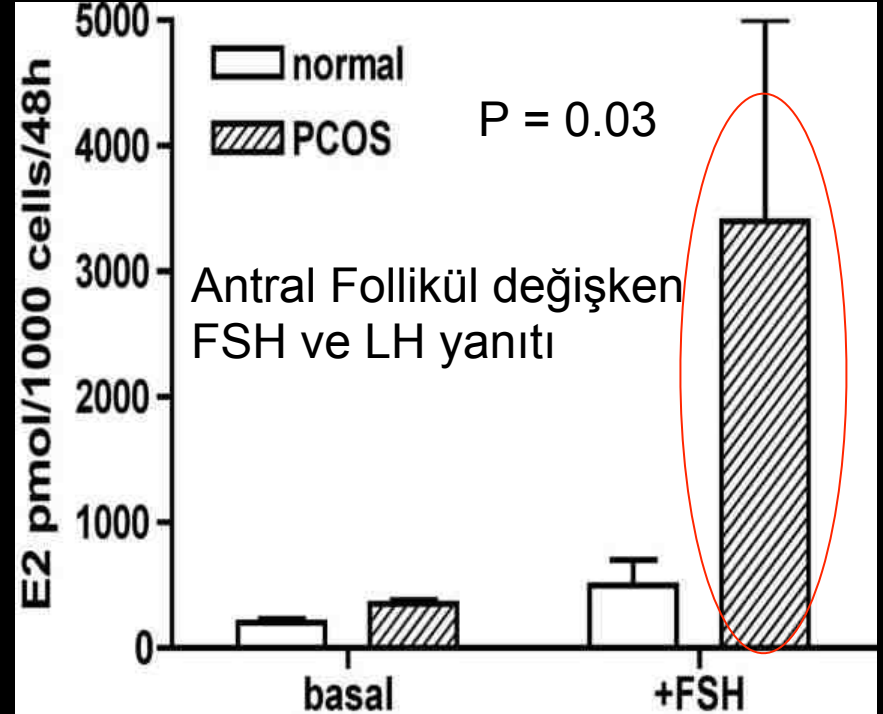
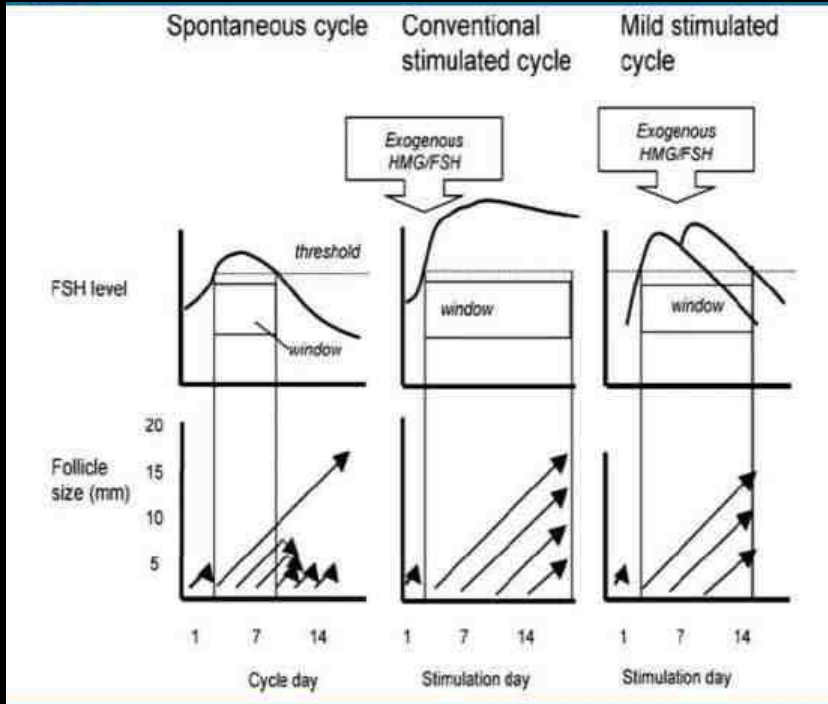
PROGNOSTİK MARKIR



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

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

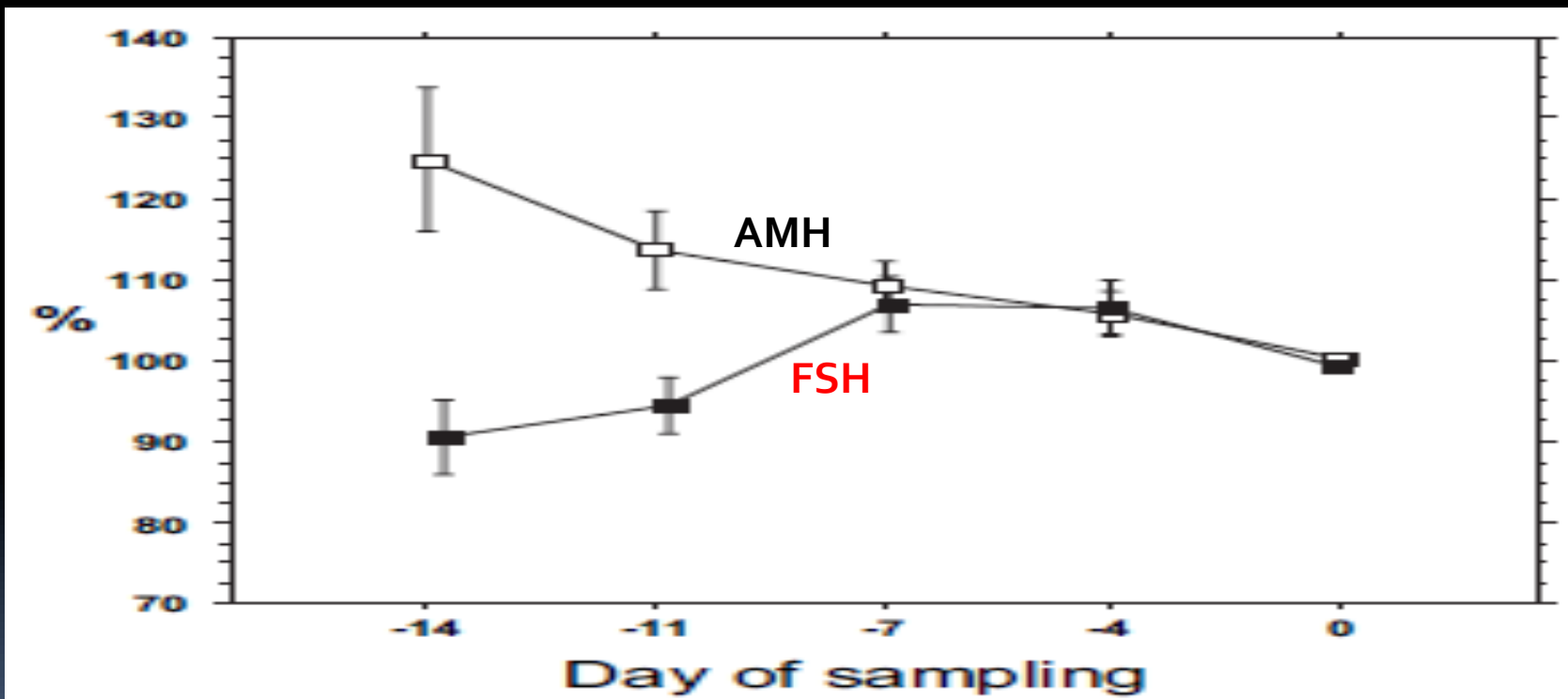
Anovulasyonda Tedavinin Mekanizması



Pencere döneminde düşük kalan FSH'nın Anti-östrojenlerle veya eksojen Gonadotropinlerle arttırılması ovulasyonu sağlar -PCOS'da eksojen Gn.lere artmış estradiol yanıtı mevcut

Changes in Serum Anti-Müllerian Hormone Level during Low-Dose Recombinant Follicular-Stimulating Hormone Therapy for Anovulation in Polycystic Ovary Syndrome

Sophie Catteau-Jonard, Pascal Pigny, Anne-Céline Reyss, Christine Decanter, Edouard Poncelet, and Didier Dewailly



Düşük doz Gonadotropin tedavisi ile AMH baskılanıyor

Burgers et al. 2010

PCOS' da Gonadotropinlerle Ovulasyon indüksiyonundaki Hedef

Monofoliküler gelişim ve ovulasyonu sağlamak

En ucuz tedavi ajanlarından başlamak,
lüzumsuz yüksek doz ajan kullanmamak

Düşük oranını minimum seviyede tutmak

Çoğul gebelikten kaçınmak

OHSS riskini minimumda tutmak

İyi monitarizasyon

İndüksiyon sonrası sağlıklı bir gebelik ve bebek elde edilmesi



Gonadotropinler- 50 yıldır kullanıyoruz!...

- 1958-İnsan pitüiter ekstrektı- Gamzel et.al.
- 1960-HMG- Menotropin
- 1980-Purifiye Urofollitropin- FSH-P
- 1990-Highly-purified Urofollitropin- FSH-HP
- 1994-Recombinant FSH-r-FSH (Follitropin alfa-Follitropin beta)

Preparation	Source of FSH	FSH activity (IU / ampoule)	LH activity (IU / ampoule)	Non-FSH urinary proteins
HMG	Urine	75	75	95%
Urinary FSH	Urine	75	<0.7	95%
Urinary FSH-high purity	Urine	75	<0.001	<1%
Recombinant FSH	Chinese hamster ovary	50, 75, 100, 150, 200	None	None

HMG = human menopausal gonadotrophin;

FSH = follicle stimulating hormone

PROBLEMLER

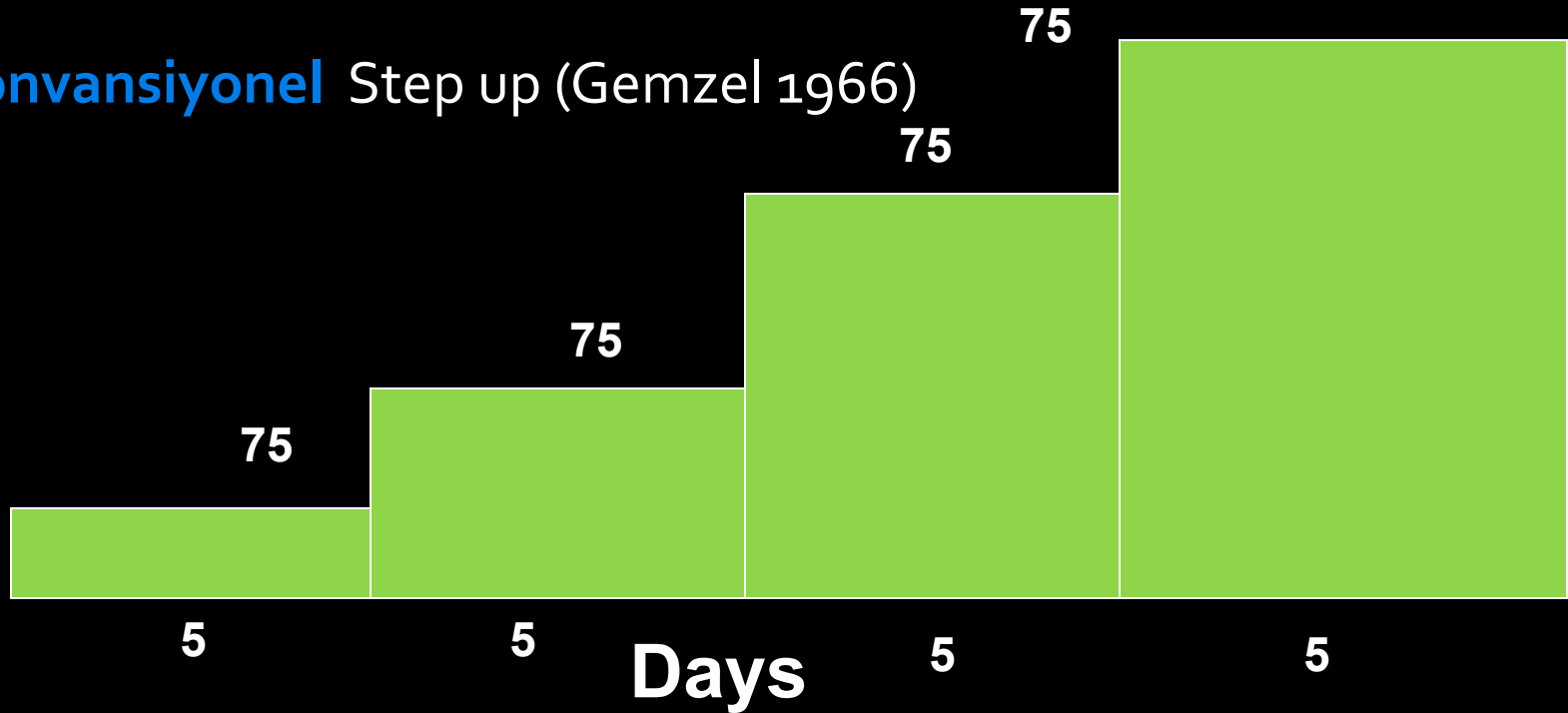
- Gnlk enjeksiyon
- Pahalı
- Doz ayarlaması ve monitorizasyon
- OHSS
- ođul gebelik
- Artmıř abortus oranı



- Hasta kliniđi iyice anlařılmalı
- Hastaya kliniđi ve tedavi iyice anlatılmalı
- Mmkn olan dozun en dřđ tercih edilmeli

Hangidoz/hangi protokol?

- **Konvansiyonel** Step up (Gemzel 1966)



- **Düşük Doz**
- Kronik düşük doz- (S Franks et al)
- Basamaklı azalan (Step-down) - (B Fauser et al)
- Ardışık (Sequential)- (Hugues et al)

Konvansiyonel Tedavi Sonuçları: 14 Series, 1966-1984, WHO I & II

Gebelik	46% (16-78)
Çoğul Gebelik	<u>34% (22-50)</u>
Abortus	23% (12-30)
Severe OHSS	4.6% (1.3-9.4)

Hamilton-Fairley & Franks, 1990

Table III. Comparison of gonadotrophin regimens (Hull, 1992)

Gonadotrophin regimen	Conventional	Low dose
No. of patients	111	243
Pregnancy rate per cycle (%)	23	11
Pregnancy rate per ovulatory cycle (%)	30	15
Miscarriage rate (%)	17	37
Ongoing pregnancy rate per cycle (%)	19	7
Multiple pregnancy rate (%)	23	9

WHO II-Düşük dozu (6 Çalışma-75 IU) konvansiyonel protokolle (6 Çalışma-150 IU) kıyaslayan **meta-analiz; Hull,1992**

Konvansiyel protokol ile gebelik oranı yüksek, düşük oranı daha az
AMA

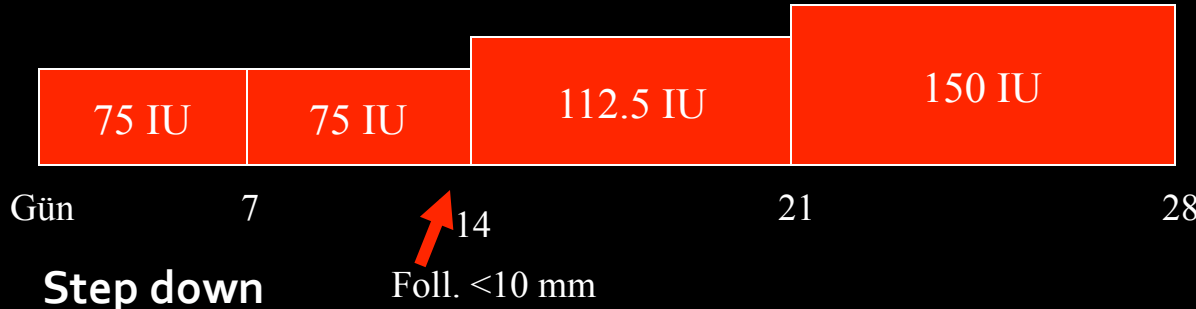
Çoğul gebelik ve OHSS (%1.1-14) oranı daha yüksek

Fauser,1997

Düşük Doz Protokolleri

hCG

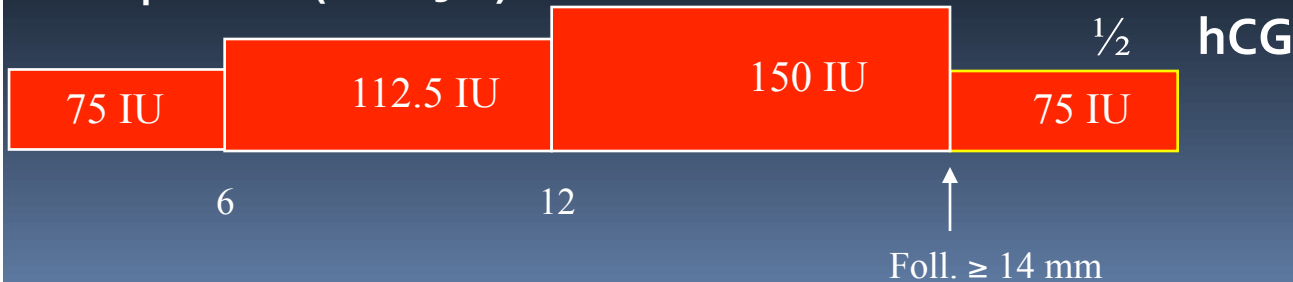
Kronik düşük doz step up



Step down



Sequential (ardışık)



Siklus İptali:

- ≥16 mm 2 folikül
- ≥16 mm 1 folikül ve ≥14 mm 2 folikül
- E2 seviyesi >1000 pg/ml

Low dose step-up protokol

Eşit dozda tekrarlanan FSH vücutta birikir, 4-7 günde FSH eşik değerine ulaşır

WHO grup II

hCG
5000-10000IU

FSH eşik

FSH doz

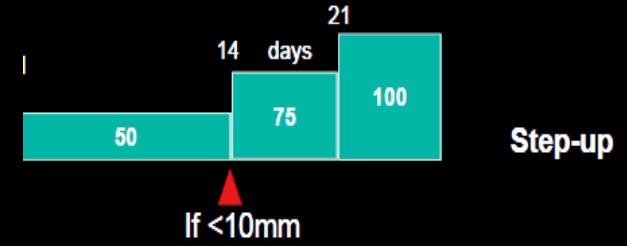
FSH Penceresi

FSH penceresi

Foliküler gelişim

FSH eşik değerini daha uzun sürede yakalayarak
multipl follikül gelişimini engellemektir

Low dose step-up protokol



Başlangıç dozu 37.5-75IU olup ilk doz artırımını 14. Günde %50(37.5IU) şeklindedir, maksimum 225IU'ye çıkılır

Avantajları;

Daha ekonomik, İlk siklusta hastayı tanıtır

OHSS (nadir fakat sıkıntılı)

Yüksek oranlarda monofoliküler gelişim olmasındır.

Dezavantajları;

Tedavi süresi uzun

Daha fazla gonadotropin gereksinimi

! Yaş, BMI ve LH tedavi başarısını azaltıyor

Düşük Doz Gonadotropinler ile tedavi sonuçları

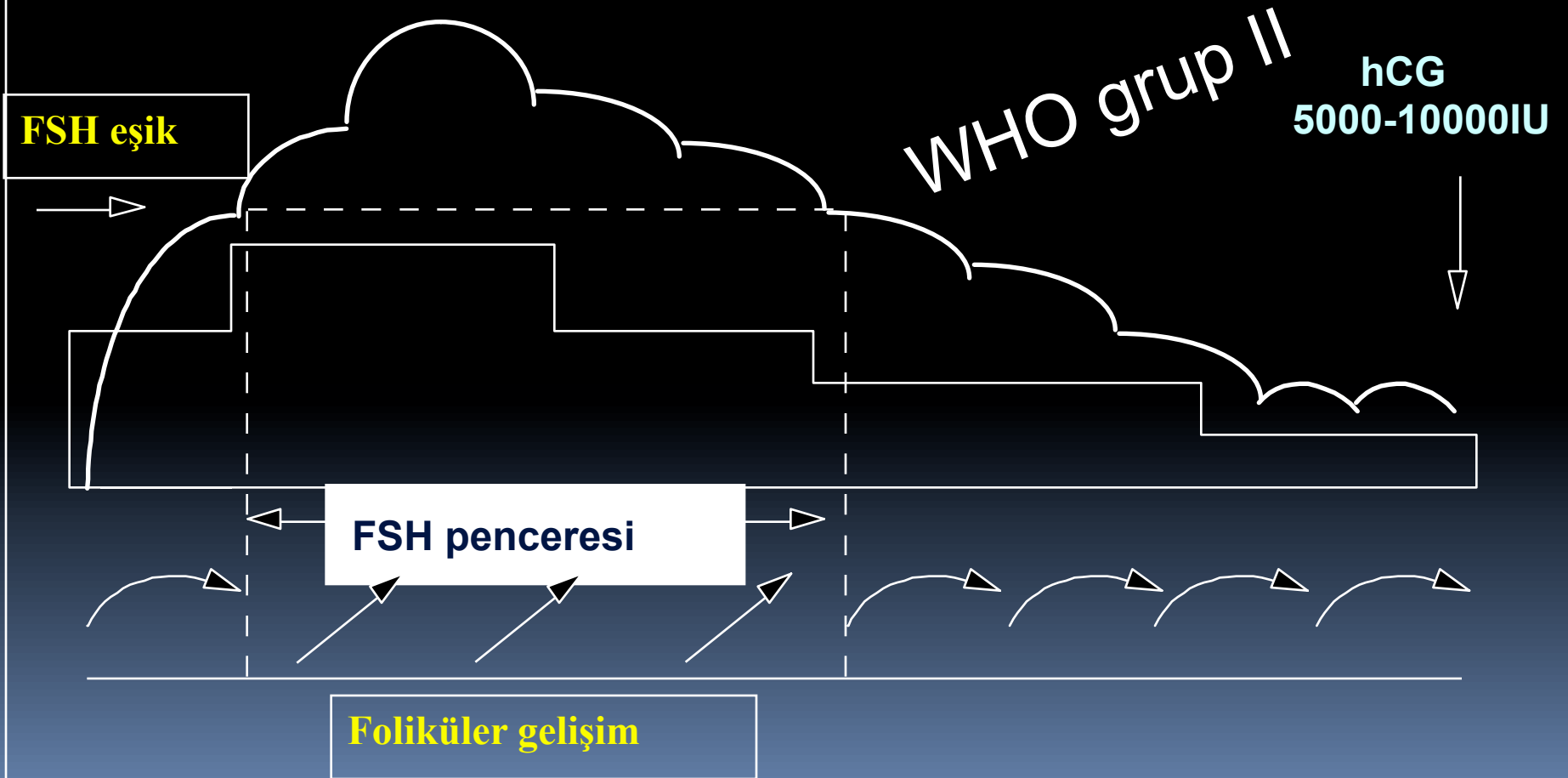
1040 hasta, 2472 siklus

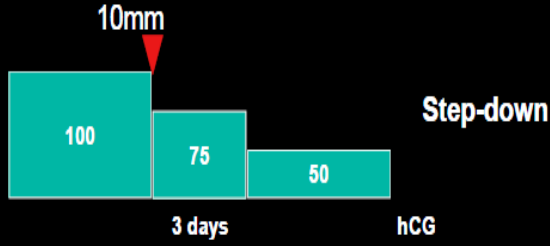
- Gebelik 411(% 40)
- Fekundite/siklus %23
- Monofoliküler gelişim %71
- OHSS %0.14
- Çoğul gebelik %5.1

Updated from Homburg & Howles, 1999

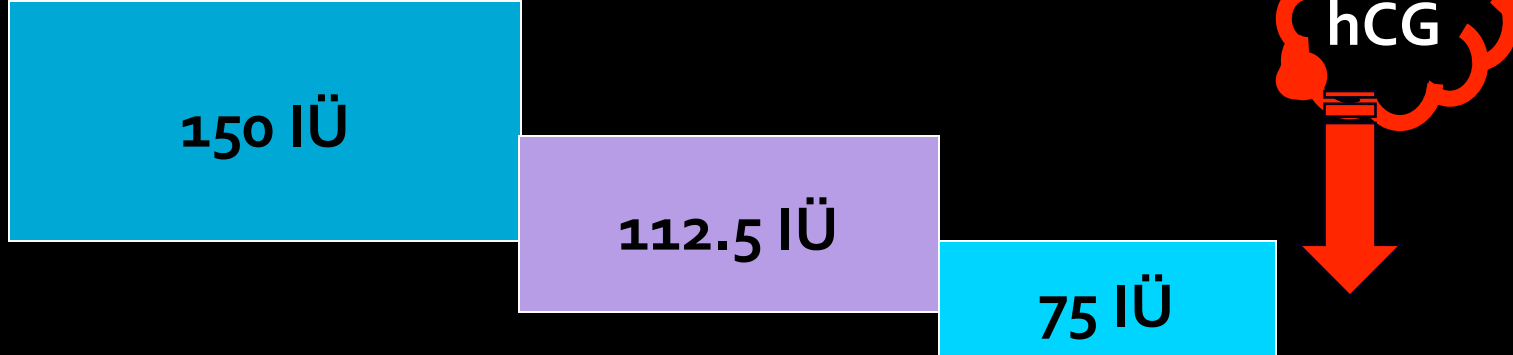
Low-dose step down

Fizyolojik FSH profiline daha uygundur, **FSH penceresi doz azaltılarak daraltılır**
Başlangıçtaki yüksek FSH seviyeleri multifoliküler gelişimi uyarır, dominant folikül seçildikten sonra yükselen estrojen FSH'yı düşürür, diğer foliküller atreziye uğrar.





Step-down



- 150 IÜ ile başlanır
- Folikül 10 mm olduğunda doz 37.5 IÜ azaltılır
- Doz her 3-5 günde bir düşürülür ----Siklus süresi daha kısa...
- Daha sık monitorizasyon ve tecrübe gerektirir
- FSH'daki bireysel farklılıklar nedeniyle başlangıç dozu yüksek ;
Multipl follikül gelişimi, OHSS ve Çoğul gebelik riski!

Step-up vs Step-down

Table III. Prospective randomized trials comparing the step-up with the step-down protocol in anovulatory patients with polycystic ovary syndrome

Study	Patients	Cycles	Mean days of treatment	Monofollicular development	Pregnancy rate/cycle (%)	Multiple pregnancy rate (%)	OHSS (%)	Miscarriage rate (%)
Van Santbrink and Fauser (1997)								
Step-up	19	19	18*	56 ^a	13†	0	33.3	0
Step-down	18	18	9*	88 ^a	31†	0	0	0
Balasch <i>et al.</i> (2001)								
Step-up	15	26	15.1	46 ^b	14.3	0	0	23
Step-down‡	14	26	15.7	54 ^b	7.4	0	0	0
Christin-Maitre <i>et al.</i> (2003)								
Step-up	44	85	15.2	68.2 ^c	18.7	11.7	12.5	2.25
Step-down	39	72	9.7	32 ^c	15.8	25	16.7	11
Van Santbrink and Fauser (2003)								
Step-up§	91	–	NR	70 ^d	15	0	0	1
Step-down¶	61	–	NR	50 ^d	16	0	0	1

Step-up'da monofolikül gelişimi daha fazla..

Klinik pratikte, step-up tercih edilen yöntemdir

- *Van Santbrink and Fauser, J Clin Endocrinol Metab 1997*
 - *Balasch et al., Human Reproduction 2001*
- *Christin-Maitre et al., Human Reproduction 2003*
- *Van Santbrink and Fauser, Human Reproduction 2003*

A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome

S.Christin-Maitre^{1,3} and J.N.Hugues² on behalf of the Recombinant FSH Study Group*

Table II. Clinical results of step-up and step-down administration of recombinant human FSH

	Step-up protocol (<i>n</i> = 85 cycles) 50IU	Step-down protocol (<i>n</i> = 72 cycles) 100 IU	<i>P</i>
Duration of treatment (days)	15.2 ± 7	9.7 ± 3.1	< 0.001
Total amount of rFSH (IU)	951 ± 586	967 ± 458	NS
Rate of monofollicular development (%)	68.2	32	< 0.0001
Rate of bifollicular development (%)	15.3	23.6	NS
Rate of multifollicular (>3) development (%)	4.7	36	< 0.0001
Estradiol plasma value at hCG (pg/ml)	454 ± 465	849 ± 1115	< 0.05
hCG administration (%)	84.6	61.8	0.001
Rate of hyperstimulation (%)	2.25	11	0.001
No response (%)	11.8	8.33	NS
Progesterone > 8ng/ml (%) in luteal phase	70.3	61.7	0.02
Pregnancy/cycle (%)	18.7	15.8	NS

- Low-dose step-up, step-down protokole göre monofoliküler gelişim ve ovulasyon sağlanmasında daha efektif bulunmuştur

Sequential step-up/step-down

- İlk siklusta step-up ile bulunan dozun 37.5IU yükseği ile ikinci siklusta step down protokolle başlanabilir ki buna da **ardışık step-up step-down protokolü** denir.
- Kümülatif ovulasyon oranı %82
- Devam eden gebelik oranı %58
- Tek canlı doğum oranı % 43
- Çoğul gebelik doğum oranı %5'dir

Sequential step-up and step-down dose regimen: an alternative method for ovulation induction with follicle-stimulating hormone in polycystic ovarian syndrome

Jean-Noël Hugues², Isabelle Cédric-Durnerin, Catherine Avril¹, Sylvie Bulwa, Florence Hervé and Michèle Uzan

	Group 1 Step-up 75IU	Group 2 Sequential 75 IU	P value
No of cycles (n)	35	34	
Luteal oestradiol (pg/ml)	657 ± 104	350 ± 77	<0.05
Luteal progesterone (ng/ml)	179 ± 21	171 ± 20	NS
Ovarian hyperstimulation syndrome (n)	0	0	NS
Pregnancies (n)	20	15	NS
Miscarriages (n) (%)	8 (40)	3 (15)	NS
Ongoing pregnancies (n)	12	12	NS

- RCT-75 IU Ufsh- Follikül çapı 14 mm. olunca doz yarıya düşülmüş ;
- hCG günü Estradiol daha düşük, 14-15mm follikül sayısı daha
 - Total FSH dozu daha düşük
 - Gebelik oranları aynı

Sequential low-dose step-up and step-down protocols with recombinant follicle-stimulating hormone in polycystic ovary syndrome: prospective comparison with step-down protocol

Luisa Casadei · Francesco Puca · Emanuela Emidi ·
Claudia Manicotti · Alessandra Madrigale ·
Emilio Piccione

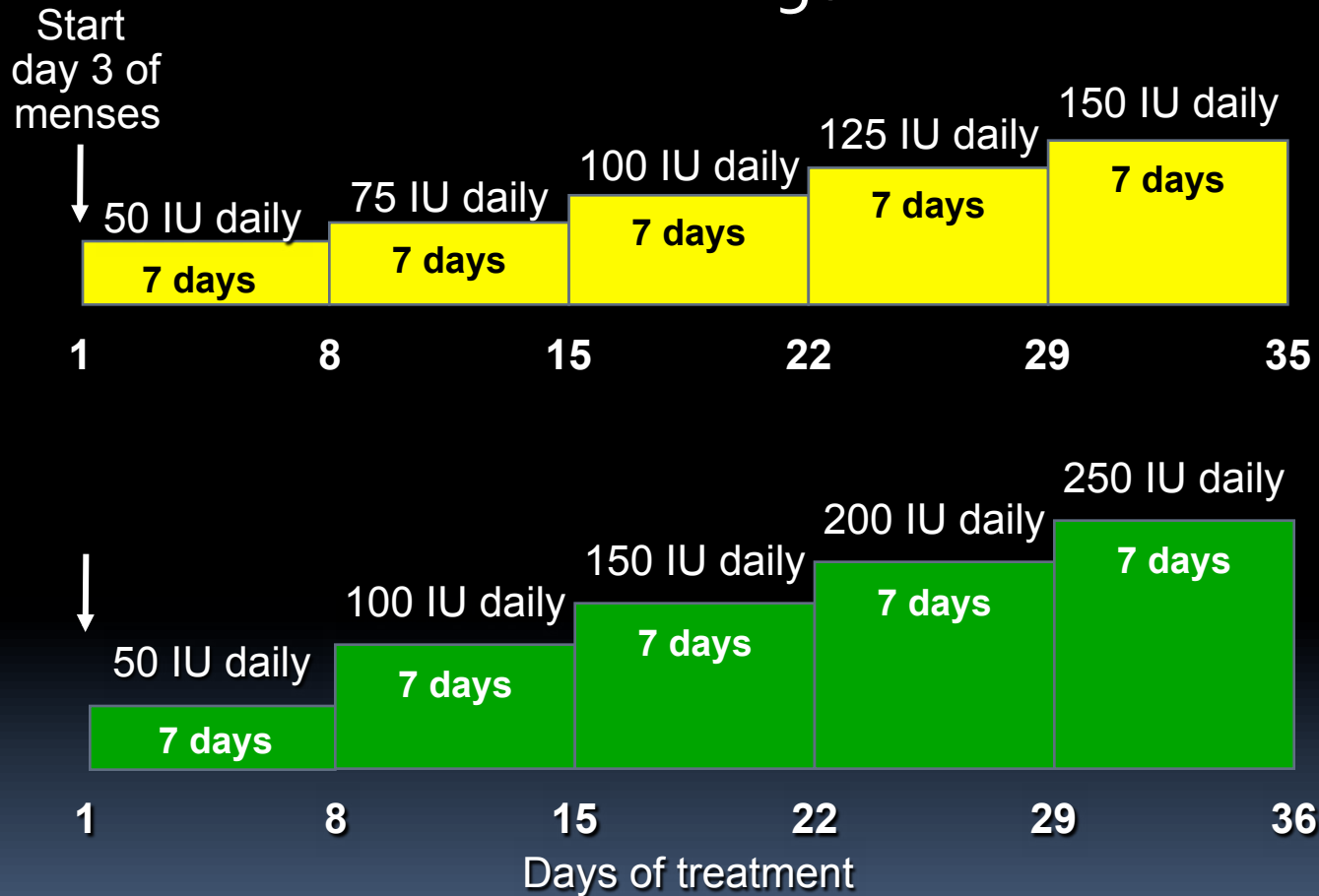
	37.5 IU group (A)	75 IU group (B)	Step down group (C)	P
Complete cycles	14	20	14	
No. of follicles >10 mm/complete cycle ^a	1.4 ± 0.7	1.8 ± 1	2.1 ± 1.3	N.S.
No. of follicles >10 mm/started cycle ^a	1 ± 0.9	1.8 ± 1	2.6 ± 2.2	0.005 A versus C
No. of follicles >10 < 16 mm/started cycle ^a	0	4.2 ± 1.87 (2-9)	6 ± 4 (1-16)	0.003 A versus B; <0.001 A versus C
No. of follicles >10 mm/started cycle ^b	1 ± 0.94 (0-3)	6.3 ± 2.45 (3-12)	8.6 ± 4.45 (2-17)	0.001 A versus B; <0.001 A versus C
Monofollicular cycles/complete cycle	10	11	7	N.S.
Monofollicular cycles/started cycle	10	11	9	N.S.
Bifollicular cycles/complete cycle	2	4	2	N.S.
Bifollicular cycles/started cycle	2	4	2	N.S.
Multifollicular cycles	2	5	8	N.S.
Cancelled cycles due to ovarian hyper-response	0	0	5	
Cancelled cycles due to no ovarian response	6	0	1	
OHSS	0	0	0	N.S.
Duration of treatment (days)/complete cycle ^a	16.6 ± 5.7 (10-29)	15.4 ± 4.6 (8-25)	13.2 ± 2.9 (10-20)	N.S.
Duration of treatment (days)/started cycle ^a	14.9 ± 5.4 (10-29)	15.4 ± 4.6 (8-25)	11.9 ± 3.1 (8-20)	N.S.
Total rFSH dose (IU)/complete cycle ^a	594.6 ± 473.8	1,082.9 ± 527.1	1,198.7 ± 462.1	0.02 A versus B; 0.007 A versus C
Total rFSH dose (IU)/started cycle ^a	716.2 ± 456	1,082.9 ± 527.1	1,146.6 ± 430.8	0.017 A versus C
Pregnancies/complete cycle	8	8	2	0.046 A versus C
Pregnancies/started cycle	8	8	2	N.S.
Abortion	0	1	0	
Twin pregnancies	0	2	0	

Doz Artışı?

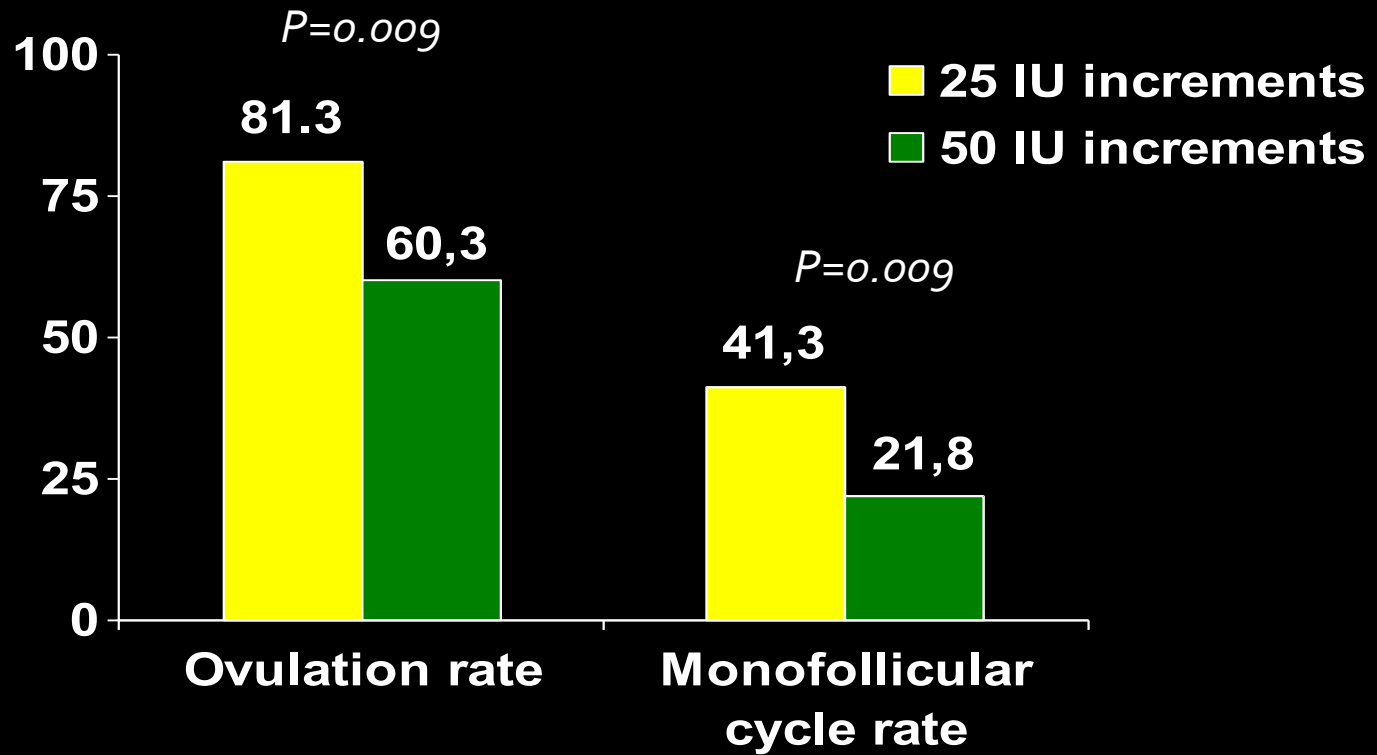
Leader et al, 2006

50 IU starting dose; increments of 25 or 50 IU

n=158



FSH increments: Only allowed when no follicle ≥ 12 mm
hCG: 1 follicle ≥ 18 mm
Cancellation: ≥ 3 follicles ≥ 15 mm



Higher cancellation rate with 50 IU increments

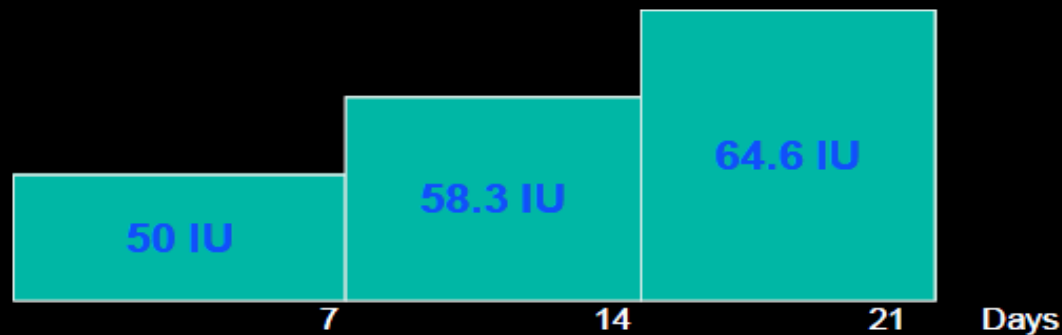
Duration and pregnancy rate - same

Leader et al, 2006

Chronic ultra-low dose follicle-stimulating hormone regimen for patients with polycystic ovary syndrome: one click, one follicle, one pregnancy

Orvieto and Homburg, Fertil Steril 2009

- Incremental dose rise of 8.3 IU each week



- N=25, PCOS, CC failures, 69 cycles

- FSH (rFSH-puregon) başlangıç dozu: $58,5 \pm 11,5$ IU 8range -50-100
20 kadına 50 IU, 2 kadına 75 IU, ayrıca birer kadına 58, 66 ve 100 IU verilmiş. [Yaş, BMI ve previous cevaba göre]
- Leading folikül ≥ 12 mm olana kadar, 7 günde bir 8,3 IU doz artışı

TABLE 1

The ovarian response and clinical outcomes in the present study using the chronic ultra-low-dose FSH step-up protocol for ovulation induction.

No. of patients	25
No. of cycles	69
Mean duration treatment (d)	10.8 ± 4.3 (range, 5–25)
Mean total dose of FSH (IU)	622 ± 286 (range, 208–1,641)
Mean threshold dose of FSH (IU)	56.4 ± 13.7 (range, 25–100)
Cycle cancellation rate due to	
Low ovarian response	0
Ovarian hyper-response	1
Mean serum E ₂ on day of hCG (pmol/L) administration	1,066 ± 567
Mean serum P on day of hCG (nmol/L) administration	1.9 ± 1.2
Ovulation rate (%)	98.5 (68/69 started cycles)
Monofollicular cycles (%), defined as	
One follicle only >16 mm	82.6% (57 of 69 started cycles)
One follicle only >14 mm	62.3% (43 of 69 started cycles)
Clinical pregnancies	20 (29% / started cycle)
No. of miscarriages	4 (20% of clinical pregnancies)
Ongoing pregnancies	16 (64% of subjects treated, 23.2% / started cycle)
Twin gestations	1 (5% of clinical pregnancies)
Ovarian hyperstimulation syndrome	0

Orvieto. Chronic ultra-low dose FSH regimen. Fertil Steril 2009.

- **Sonuç: Klinik gebelik %29
OHSS yok**

Başlangıç dozun süresi : 14 gün? 7 gün?

N=50, 107 cycles	14 days	7 days
FSH		
- Amps	22	17
- Days	17.4	13
1 follikül /cycle	74%	60%
E2 (pmol/L)	1659	2072
Gebelik	10 (40%)	14 (56%)
OHSS	0	0
Çoğul gebelik	0	2/14
Çalışma uzatıldığında; Çoğul gebelik	0/10	6/29

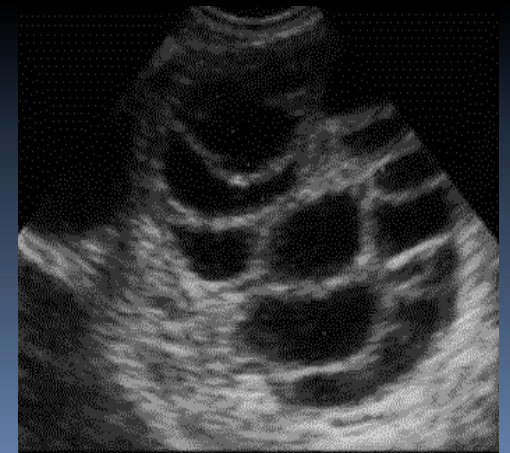
PKOS/Gonadotropin Protokolleri Monitorizasyon

- USG ile folliküler gelişim takibi zorunlu
- E2 takibi???
- hCG uygulaması iptali:
- 2 den fazla ≥ 16 mm follikül < 38 yaş
- 1 adet ≥ 16 mm ve 2 adet ≥ 14 mm folliküller
- E2 max > 1000 pg/mL
- Prematür luteinizasyon (LH > 10 IU/ml; Prog > 1.5 ng)
- Dominant follikül > 16 mm yoksa



Table II. Multiple birth rate related to the number of follicles > 15 mm on the day of hCG (From Serono International, 1995, with permission.)

No. of follicles on day of hCG	No. of cycles	Clinical pregnancies		Births		Multiple birth rate (%)
		<i>n</i>	Rate/cycle (%)	<i>n</i>	Twins	
1	277	47	17.1	39	2	5.1
2	77	20	26.0	17	2	11.7
3	32	11	34.4	10	2	20.0
> 3	19	5	26.3	4	2	50.0



OI-Monitorizasyon

USG OI' na folliküler yanıtın saptanmasında güvenli, etkin bir yöntemdir. Özellikle PCOS olgularındaki çoğul gebeliğin azaltılmasında E monitorizasyonuna tercih edilebilir

[Evidence level 2b]

USG' nin hCG zamanı fazla sayıda immatür follikül varlığını göstermesi OHSS gelişimini belirlemede çok değerlidir
[Evidence level 3]

OI sırasında yapılan **USG**, siklus kararlarının % 88' ini tek başına belirleyebilir

[Evidence level 3]

E monitorizasyonu USG bilgisine ek bir katkı sağlamaz

Hardiman et al., 1990
[Evidence level 2b]

PKOS: hangi gonadotropin?

Human menopausal gonadotropin-HMG

75 IU FSH+75 IU LH

(Humegon/Pergonal/Menogon/Merional)



Urinary highly purified-HMG

Menopur



Urinary purified FSH

(Metrodin)



Urinary highly purified FSH

(Metrodin HP/Fostimon)



Recombinant FSH/LH & hCG

(Puregon/Gonal F/Luveris/Ovitrelle)

Corifollitropin alfa-weekly long-acting(rFSH)

(Elonva)

u-FSH / rec-FSH

- RecFSH kullanımı daha kısa stimülasyon süresi ve daha düşük doz kullanım olanağı sunmakla birlikte uFSH'dan daha etkin olduğunu gösteren yeterli data bulunmamaktadır

Bayram, Cochrane, 2001

- Bazı çalışmalarda recFSH'nin in-vivo potensinin daha yüksek olduğu ileri sürülmüştür

Balash, J. Assist Reprod Genet, 1998

HP-hMG V rFSH

CC-rezistan WHO Grup II olgu (n=91 V n=93)
Düşük doz step-up protokol (75IU/gün-7 gün)
Ovulasyon oranı %83.5 V 84.9

Tek canlı doğum oranı %14.3 V 15.1

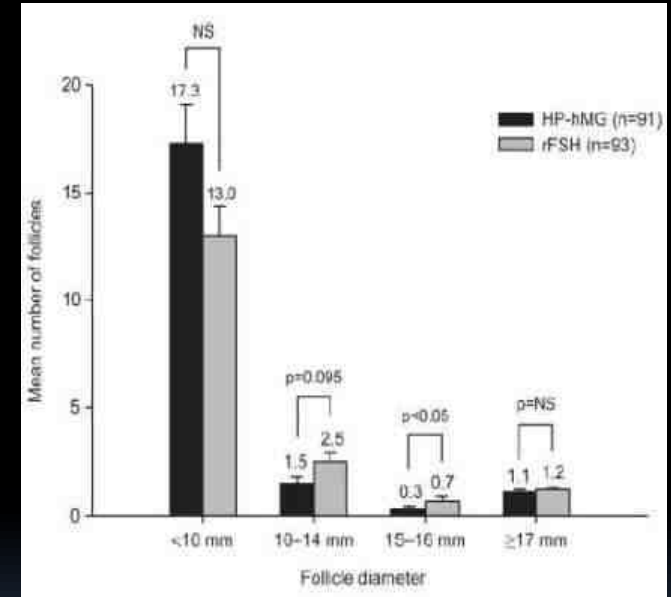
OHSS % 1.1 V 3.2

OHSS riski nedeniyle iptal % 2.2 V 9.8

Çoğul gebelik % 0 V 2.2

*HP-hMG grubunda (LH aktivitesi)
folliküler gelişimde daha az intermediate
follikül gelişimi*

1.0 V 1.9
(p < 0.009)



Platteau P,2006.

Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome (Review)

Weiss NS, Nahuis M, Bayram N, Mol BWJ, Van der Veen E, van Wely M

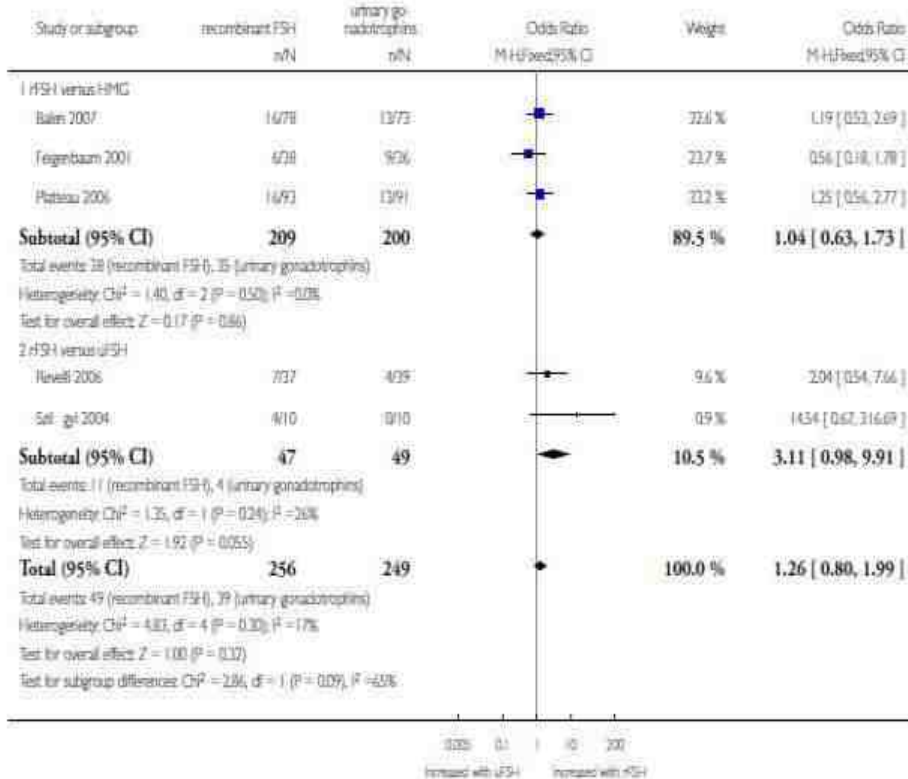
This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 9

Analysis 1.1. Comparison 1 recombinant FSH versus urinary-derived gonadotrophins, Outcome 1 Live birth rate per woman by urinary gonadotrophins.

Review: Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome

Comparison: 1 recombinant FSH versus urinary-derived gonadotrophins

Outcome: 1 Live birth rate per woman by urinary gonadotrophins



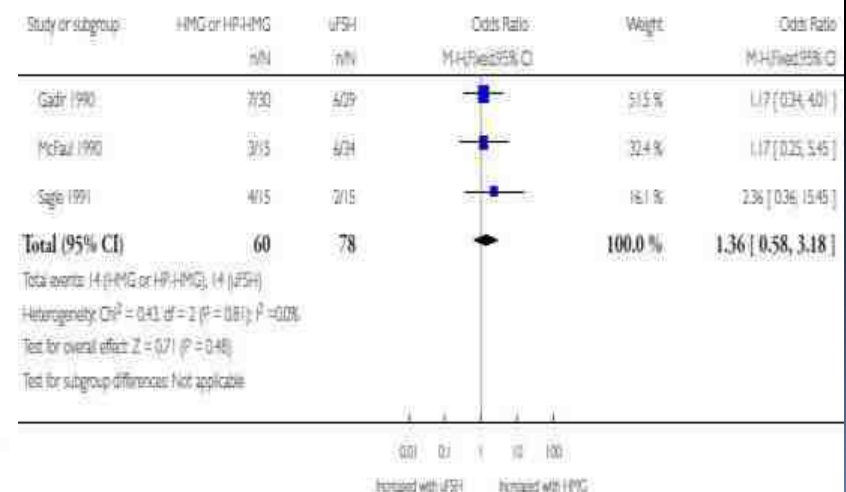
14 çalışma, 1756 hasta
7 çalışma, rFSH V FSH-HP
3 çalışma, rFSH V HMG
4 çalışma, FSH-P V HMG

Analysis 2.1. Comparison 2 HMG or HP-HMG versus uFSH, Outcome 1 Live birth rate per woman.

Review: Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome

Comparison: 2 HMG or HP-HMG versus uFSH

Outcome: 1 Live birth rate per woman

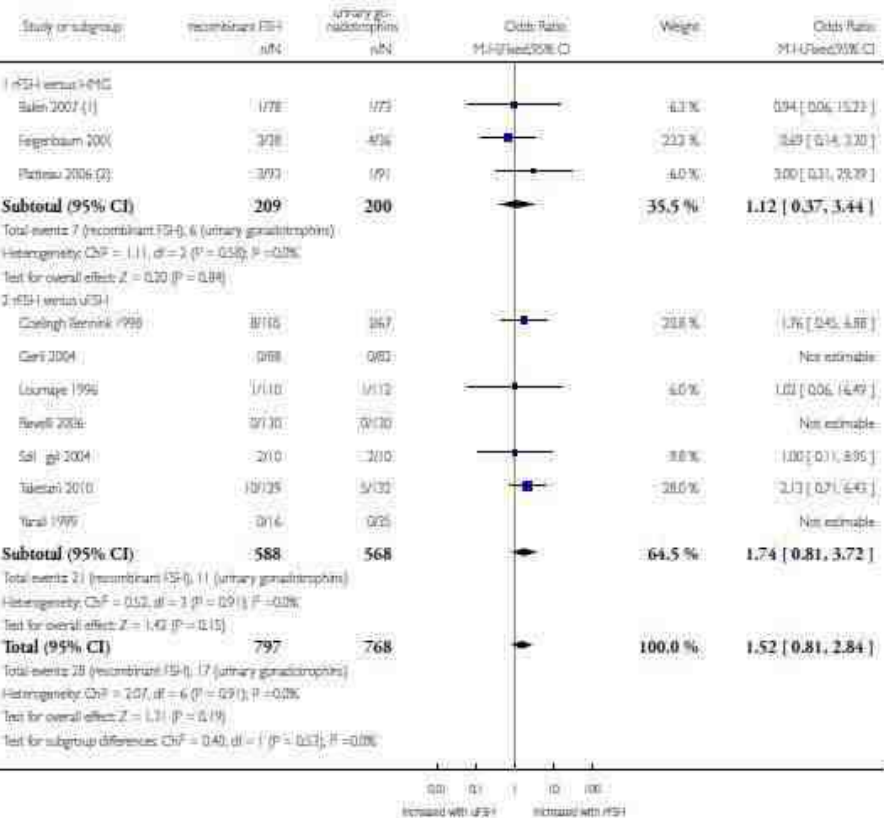


Analysis 1.3. Comparison 1 recombinant FSH versus urinary-derived gonadotrophins, Outcome 3 Incidence of OHSS per woman by urinary gonadotrophins.

Review: Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome

Comparison: 1 recombinant FSH versus urinary-derived gonadotrophins

Outcome: 3 Incidence of OHSS per woman by urinary gonadotrophins

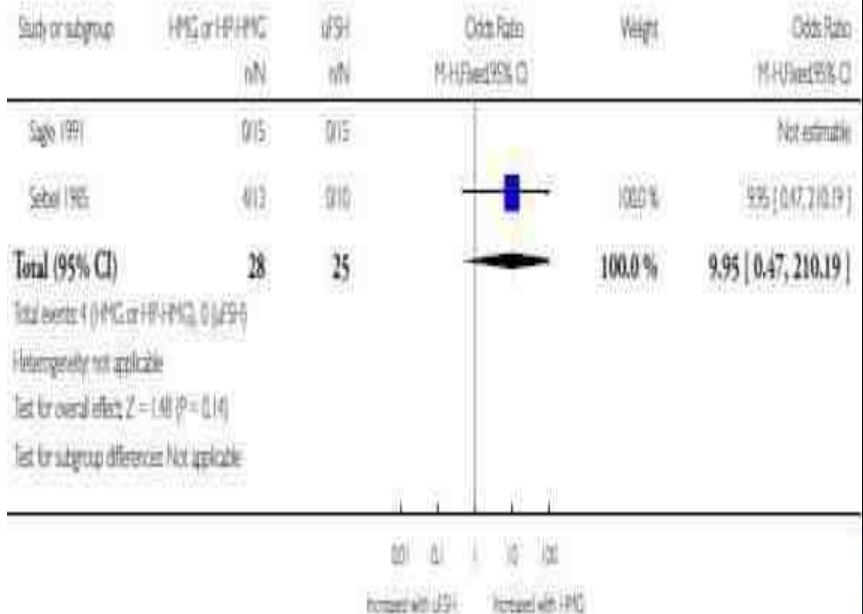


Analysis 2.2. Comparison 2 HMG or HP-HMG versus uFSH, Outcome 2 Incidence of OHSS per woman.

Review: Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome

Comparison: 2 HMG or HP-HMG versus uFSH

Outcome: 2 Incidence of OHSS per woman



Canlı doğum oranı HMG ve HP-HMG % 18 v uFSH ile % 9-37 fark yok (OR 1.36)
 rFSH % 13-26 v uFSH %16 fark yok (OR 1.26)
OHSS oranı rFSH ile üriner FSH fark yok (OR 1.52)
 HMG/HP-HMG ile FSH-P fark yok (OR 9.95)

Weiss et al, 2015

Cevabı Predikte Edebilir miyiz?

■ PCOS'da bireysel FSH eşik değerini etkileyen

- Klinik
- Endokrin
- Sonografik
- Genetik???

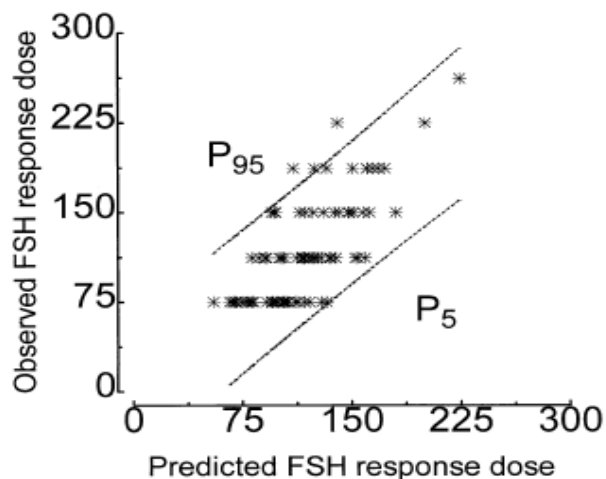
PCOS'da dominant folikül seçimindeki bozukluk ve FSH thresholddaki bireysel farklılıklar uygun FSH dozunun ayarlanmasını zorlaştıran en önemli nedenlerdir

Parametreler var mıdır??

PCOS'da "İndividual FSH threshold" öngörülebilir mi?

Prediction of the individual follicle-stimulating hormone threshold for gonadotropin induction of ovulation in normogonadotropic anovulatory infertility: an approach to increase safety and efficiency

Babak Imani, M.D.,^a Marinus J. C. Eijkemans, M.Sc.,^b Gerry H. Faessen, B.Sc.,^c Philippe Bouchard, M.D., Ph.D.,^d Linda C. Giudice, M.D., Ph.D.,^c and Bart C. J. M. Fauser, M.D., Ph.D.^a



Clinical

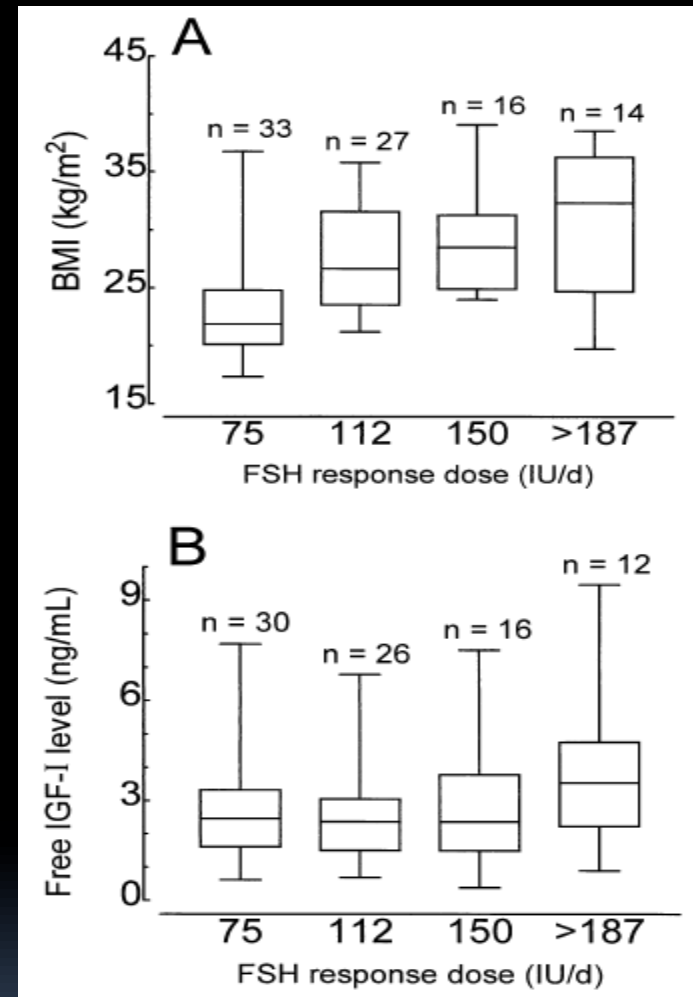
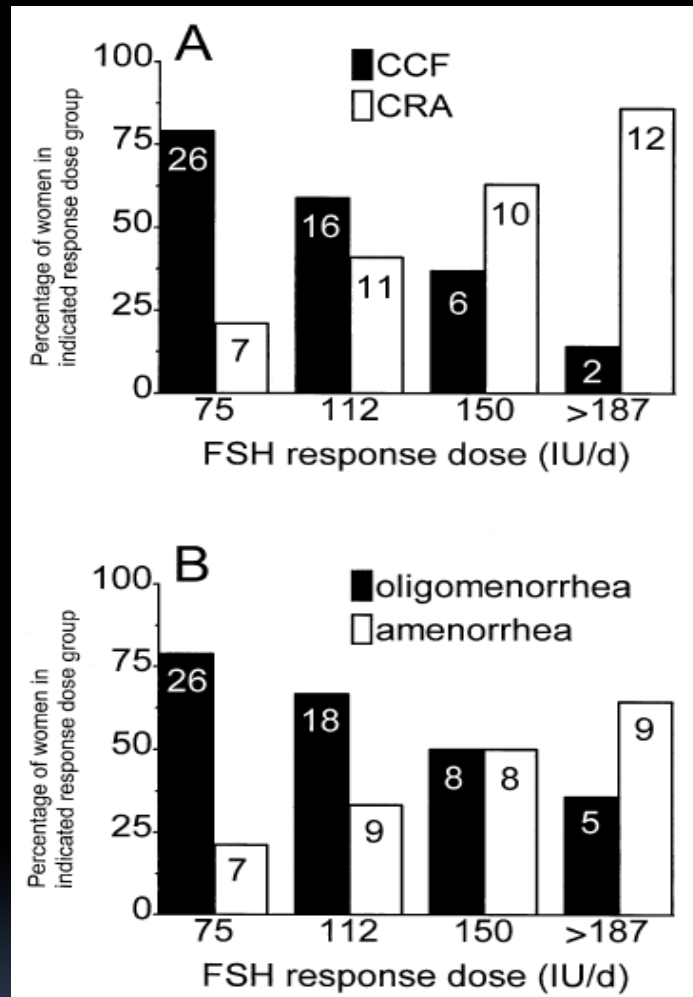
Amenorrhoea (n = 33)^d
Resistant to clomiphene citrate
BMI (kg/m²)

Endocrine

FSH (IU/L)
Free androgen index (T × 100/SHBG)
Insulin (mU/L)
Free IGF-I (ng/mL)
IGFBP-1 (ng/mL)
Leptin (ng/mL)

Ultrasonographic

mean ovarian volume (mL)



CRA ve Amenore varsa yüksek doz ile başlanmalı

Yüksek BMI ve yüksek f-IGF-I yüksek doz ile başlamayı gerektirir

PCOS'da "İndividual FSH threshold" öngörülebilir mi?

- BMI
- Serum leptin düzeyleri
- Siklus öyküsü
- CC'e yanıt

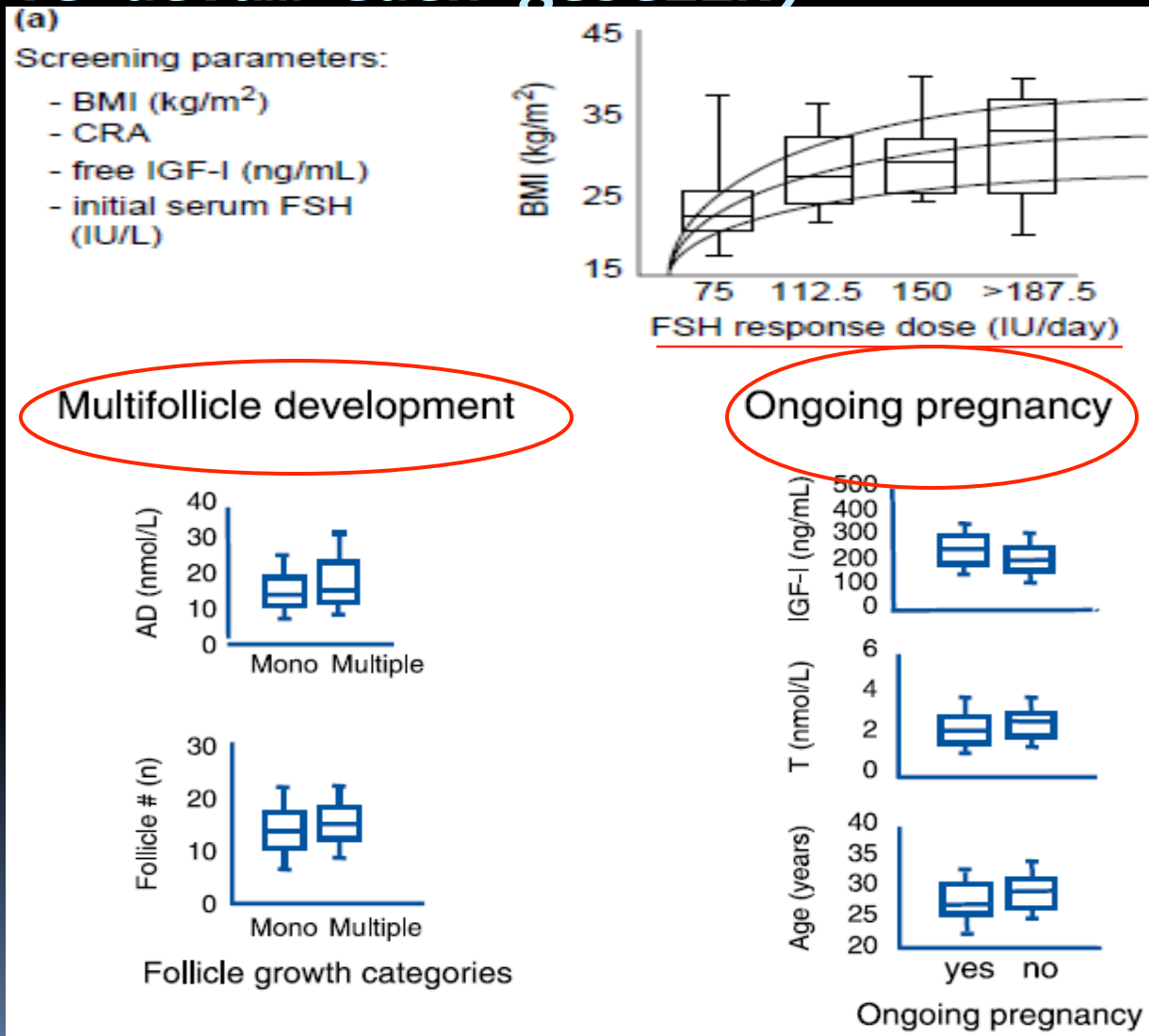
Imani et al.,
Fertil Steril 2002

- Free IGF-1 düzeyleri arttıkça FSH thresholdu artmaktadır.

$$\text{FSH response} = 4 \times \text{BMI} + 32 \times \text{CRA} + 7 \times \text{free IGF-1} + 6 \times \text{FSH-51}$$

CRA= Clomiphene resistant anovulasyon

FSH PREDİKTÖRLERİ (doz, monofoliküler gelişim ve devam eden gebelik)



WHO GRUPII'de Tedavi yanıtını predikte etmede bazal hasta özellikleri

	Clomiphene citrate		FSH			CC followed by FSH	IVF
	Ovulation	Pregnancy in ovulatory patients	FSH threshold	Pregnancy	Multifollicular growth	Clinical outcome ^b	Clinical outcome ^c
Age		Neg		Neg		Neg	Neg
Amenorrhea	Neg	Pos					
BMI	Neg		Pos			Neg	Neg
CC response			Pos		Pos		
Hyperandrogenism	Neg		Pos	Neg	Pos		
Insulin resistance	Neg					Neg	
References	[21,22]	[23,24]	[26]	[25]	[25]	[29,32]	[33]

Step down

^aPos/Neg, positive/negative correlation between patient characteristics and treatment outcome.

^bAmount of FSH administered, cancellation, ovulation, pregnancy, miscarriage rate.

^cAmount of FSH administered, cancellation.

Predictive markers for the FSH sensitivity of women with polycystic ovarian syndrome

A. Köninger^{1,*}, L. Sauter¹, P. Edimiris¹, S. Kasimir-Bauer¹,
R. Kimmig¹, T. Strowitzki², and B. Schmidt³

MAIN RESULTS AND THE ROLE OF CHANCE: An interquartile range (IQR) increase in AMH was associated with a 51.4% [95% confidence interval (CI): 24.7–79.0%; $P = 0.0003$] increase in the mean total FSH dosage per cycle (in IU) in a crude regression model, corresponding to a 7.2% increase in the mean total FSH dosage per cycle per ng/ml AMH. Adjustment for BMI augmented the effect of AMH, with a 58.3% (95% CI: 33.2–84.2%; $P = 1.8 \times 10^{-5}$) increase in FSH dosage per IQR AMH (corresponding to an 8.2% increase per ng/ml AMH) and a 46.2% (95% CI: 16.5–76.6%; $P = 0.003$) increase per IQR BMI (corresponding to a 3.7% increase per kg/m^2). AMH was the only independent variable for which the effect on FSH dosage was statistically significant in the crude regression model as well as after adjustment for other promising predictors. The association of BMI with FSH dosage was statistically significant while adjusted for AMH, but not in the crude model.

Table III Effect size estimators [percent change per interquartile range (IQR) of the respective variable], 95% confidence intervals (95% CI) and P -values of the multiple linear regression model adjusted for all promising predictors reporting the association with FSH dosage.

Variable	Estimated percent change per IQR	95% CI	P
Age (years)	-13.9	(-45.3 to 18.6)	0.39
BMI (kg/m^2)	46.6	(14.1 to 80.0)	0.006
AFC (n)	-6.3	(-36.3 to 25.6)	0.68
Total testosterone (nmol/l)	3.6	(-20.9 to 35.7)	0.79
AMH (ng/ml)	58.2	(22.7 to 95.5)	0.002

AFC, antral follicle count.

RESEARCH

Open Access

The influence of circulating anti-Müllerian hormone on ovarian responsiveness to ovulation induction with gonadotrophins in women with polycystic ovarian syndrome: a pilot study

Saad A Amer^{1*}, Ahmad Mahran^{1,2†}, Ayman Abdelmaged², Ahmad R El-Adawy², Moustafa K Eissa² and Robert W Shaw¹

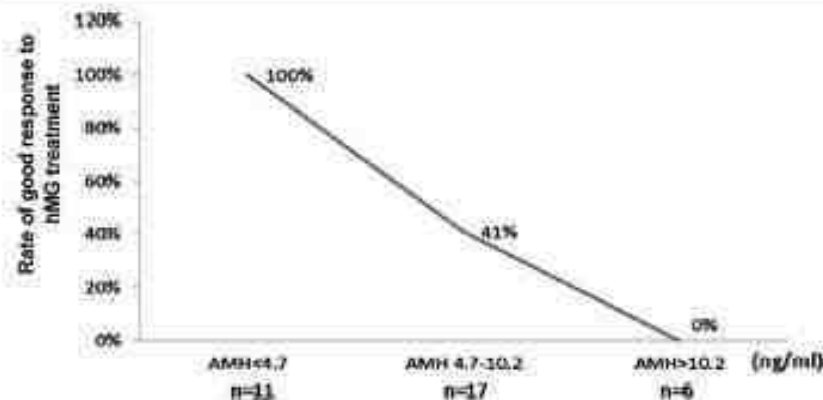


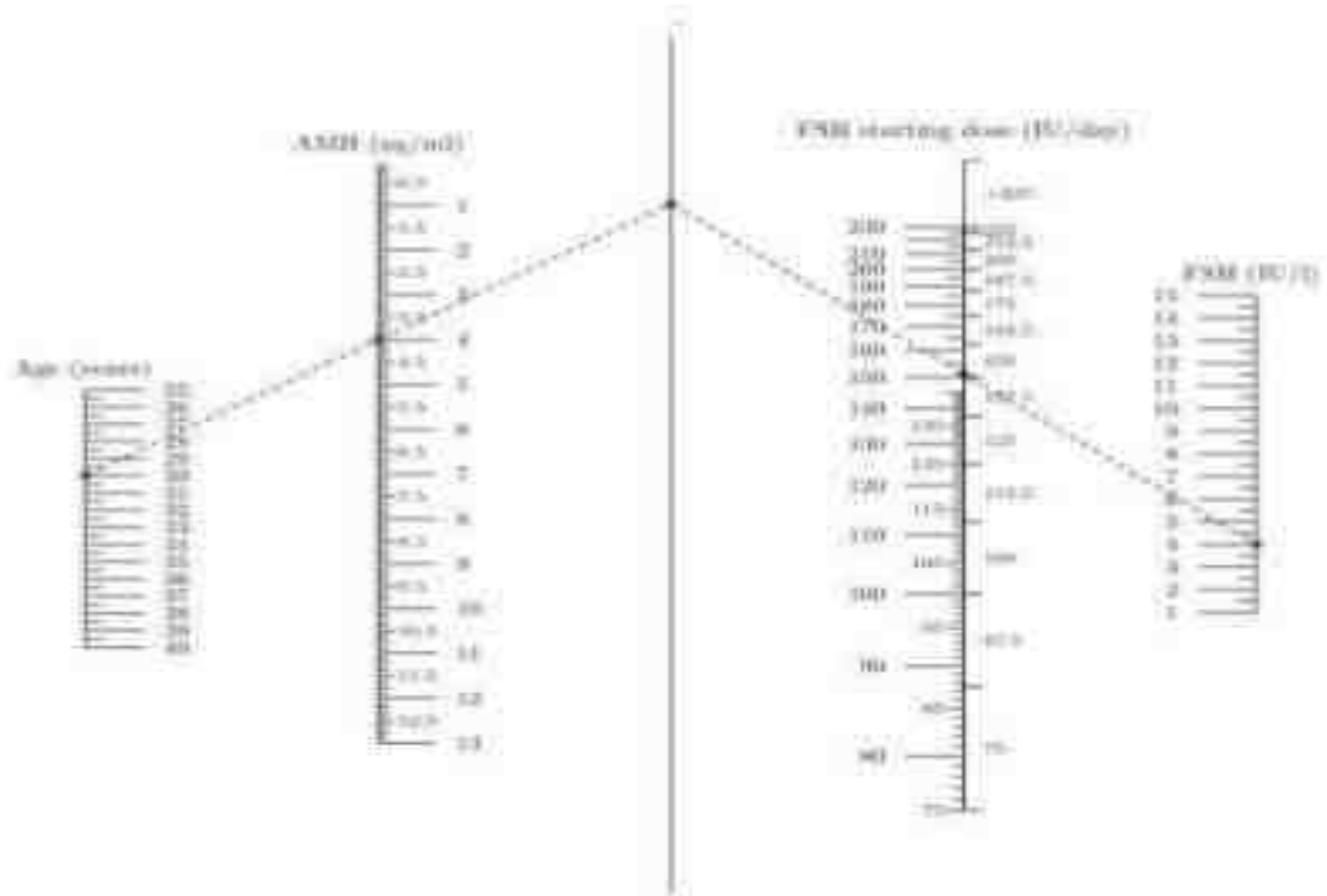
Figure 2 Good response rates in 34 cycles of hMG ovarian stimulation in PCOS women with different serum AMH levels.

Table 4 comparison of the total dose and duration of hMG in cycles with high (≥ 4.7 ng/ml) vs. low AMH (< 4.7 ng/ml)

FSH ovarian stimulation	All cycles (n = 34)	AMH ≥ 4.7 ng/ml (23 cycles)	AMH < 4.7 ng/ml (11 cycles)	P
Total dose (IU)	788 (225-1660)	1087 (450-1650)	525 (225-900)	$< .001$
Duration (days)	15 (6-30)	20 (12-30)	8 (6-14)	$< .001$

Data are presented as median (range) and Mann Whitney test was used for comparison.

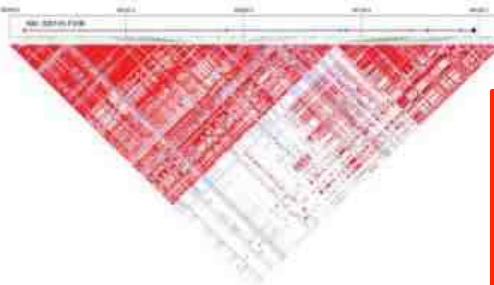
A Nomogram to decide the starting FSH dose in PCOS patients



FSH-Reseptör gen polimorfizmi?

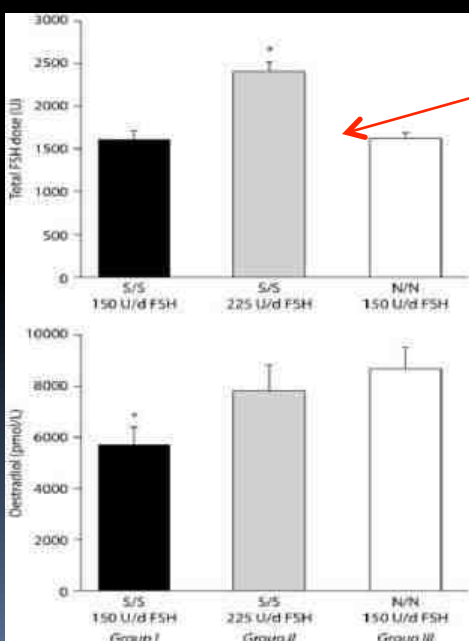
Polymorphisms and PCOS

Simoni et al 2008



Gene	Locus	Protein name	Protein function	Variant		Association with ovarian response		Phenotype (cases, controls)
				Name	dbSNP ID	Positive (cases, controls)	Negative (cases, controls)	
Sex hormones and hormone regulators								
<i>AMH</i>	19p13.3	Anti-Müllerian hormone	Hormone	p.149S	rs10407022			Caucasian women—E ₂ levels (53, 45) (Kewenaar <i>et al.</i> , 2007)
<i>AMHR2</i>	12q13	Anti-Müllerian hormone type II receptor	Hormone receptor	-482A/G	rs2002555			Caucasian women—E ₂ levels (53, 45) (Kewenaar <i>et al.</i> , 2007)
<i>ESR1</i>	6q25.1	Oestrogen receptor α	Hormone receptor	PvuII RFLP (-397T/C) (g.938T/C)	rs2234693	Spanish women (170) (Mao <i>et al.</i> , 2000; de Castro <i>et al.</i> , 2004)	Chinese women (200, 200) (Sundaraman <i>et al.</i> , 1999)	Caucasian women—follicule/oocyte ratio, pregnancy rate (100, 100) (Georgiou <i>et al.</i> , 1997)
<i>ESR2</i>	14q23.2	Oestrogen receptor β	Hormone receptor	AluI RFLP (1730A/G) (39A/G)	rs4986938	Spanish women (170) (Mao <i>et al.</i> , 2000; de Castro <i>et al.</i> , 2004)		Chinese women—serum oestradiol levels, follicule/oocyte ratio, pregnancy rate (200, 200) (Sundaraman <i>et al.</i> , 1999)
<i>FSHR</i>	2p21-p16	Follicle-stimulating hormone receptor	Hormone receptor	p.N680S (in complete LD with p.A307T, rs6165)	rs6166	German women (93) (Perez Mayorga <i>et al.</i> , 2000; Behre <i>et al.</i> , 2005)	Japanese women (58) (Sudo <i>et al.</i> , 2002)	German women—peak oestradiol level (93) (Behre <i>et al.</i> , 2005)
						Spanish women (102) (de Castro <i>et al.</i> , 2003; de Castro <i>et al.</i> , 2004)	Korean women (263) (Jun <i>et al.</i> , 2006)	German women—circulating FSH levels, number of follicles, luteal phase and menstrual cycle length (23) (Perez Mayorga <i>et al.</i> , 2000; Greb <i>et al.</i> , 2005)
							Greek women (125) (Louttridis <i>et al.</i> , 2006)	Japanese women (58)—basal FSH (Sudo <i>et al.</i> , 2002)
								Dutch women (148) (Laven <i>et al.</i> , 2003)
								Swedish women (68) (Falckner <i>et al.</i> , 2005)
								Korean women—basal FSH, pregnancy rate (263) (Jun <i>et al.</i> , 2006)
								Greek women (125)—FSH levels, follicule and oocyte number (Louttridis <i>et al.</i> , 2006)
								Dutch women—pregnancy rate (105) (Klinkert <i>et al.</i> , 2006)
Enzymes involved in metabolism and biosynthesis								
<i>CYP19A1</i>	15q21.1	Aromatase	Steroid biosynthesis	1672C/T	rs10846	Spanish women (170) (de Castro <i>et al.</i> , 2004)		
<i>BMP15</i>	Xp11.2	Bone morphogenic protein 15	Oocyte and follicular development	-673C/T	No dbSNP ID	Spanish women (307) (Moron <i>et al.</i> , 2006)		
						-9C/G	rs3810682	Spanish women (307) (Moron <i>et al.</i> , 2006)
						905G/A	rs3897937	Spanish women (307) (Moron <i>et al.</i> , 2006)
						308A/G (p.N1035)	rs41308602	Spanish women (307) (Moron <i>et al.</i> , 2006)
<i>MTHFR</i>	1p36.3	Methylenetetrahydrofolate reductase	Folate metabolism, linked to cardiovascular disease	677C/T (p.A222V)	rs1801133	German women (105) (Thaler <i>et al.</i> , 2006)		German women—E ₂ levels, oocyte number (105) (Thaler <i>et al.</i> , 2006)
						1298A/C (p.E429A)	rs1801131	North American women (223) (Rosen <i>et al.</i> , 2007)

Ser680Ser FSH-Reseptör Polimorfizmi



Behre et al. 2005
Overbeek 2009

7-İLK SEÇENEK OLABİLİR Mİ?

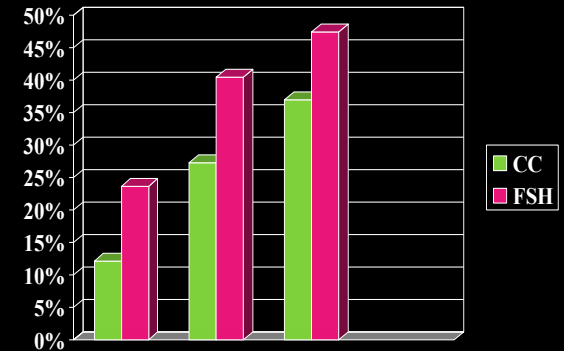
Human Reproduction, Vol.27, No.2 pp. 366–473, 2012
Advanced Access publication on November 29, 2011 doi:10.1093/humrep/dar401

human
reproduction

ORIGINAL ARTICLE *Infertility*

Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study

R. Homburg^{1,*}, M.L. Hendriks¹, T.E. König¹, R.A. Anderson²,
A.H. Balen³, M. Brincat⁴, T. Child⁵, M. Davies⁶, T. D'Hooghe⁷,
A. Martinez⁸, M. Rajkhowa⁹, R. Rueda-Saenz¹⁰, P. Hompes¹, and
C.B. Lambalk¹



After 3 cycles - CC 36.9%, FSH 47.4%
($P=0.03$)

BACKGROUND: Clomifene citrate (CC) is accepted as the first-line method for ovulation induction (OI) in patients with polycystic ovary syndrome (PCOS) associated with infertility owing to anovulation. Low-dose FSH has been reserved for women failing to conceive with CC. In this RCT, we tested the hypothesis that pregnancy rate (PR) and live birth rates (LBR) are higher after OI with low-dose FSH than with CC as first-line treatment.

METHODS: Infertile women (<40 years old) with PCOS-related anovulation, without prior OI treatment, attending 10 centres in Europe/South America were randomized to OI with either CC (50–150 mg/day for 5 days) or FSH (starting dose 50 IU) for up to three treatment cycles. The primary outcome was clinical PR.

RESULTS: Patients ($n = 302$) were randomized to OI with FSH ($n = 132$ women; 288 cycles) or CC ($n = 123$; 310 cycles). Per protocol analysis revealed that reproductive outcome was superior after OI with FSH than with CC with respect to PR per first cycle [30 versus 14.6%, respectively, 95% confidence interval (CI) 5.3–25.8, $P = 0.003$], PR per woman, (58 versus 44% of women, 95% CI 1.5–25.8, $P = 0.03$), LBR per woman (52 versus 39%, 95% CI 0.4–24.6, $P = 0.04$), cumulative PR (52.1 versus 41.2%, $P = 0.021$) and cumulative LBR (47.4 versus 36.9%, $P = 0.031$), within three cycles of OI.

CONCLUSIONS: Pregnancies and live births are achieved more effectively and faster after OI with low-dose FSH than with CC. This result has to be balanced by convenience and cost in favour of CC. FSH may be an appropriate first-line treatment for some women with PCOS and anovulatory infertility, particularly older patients.

ADJUVAN TEDAVİ?

GnRH-a / PCOS

- Ovulasyon oranlarında artış yok
- OHSS yüksek
- Gonadotropin dozu yüksek
- **Abortus az**

GnRH-a ovulasyon induksiyonunda önerilmemektedir

1.5.2.7 Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation. [2004]

Effectiveness of GnRH Antagonist in the Management of Subfertile Couples Undergoing Controlled Ovarian Stimulation and Intrauterine Insemination: A Meta-Analysis

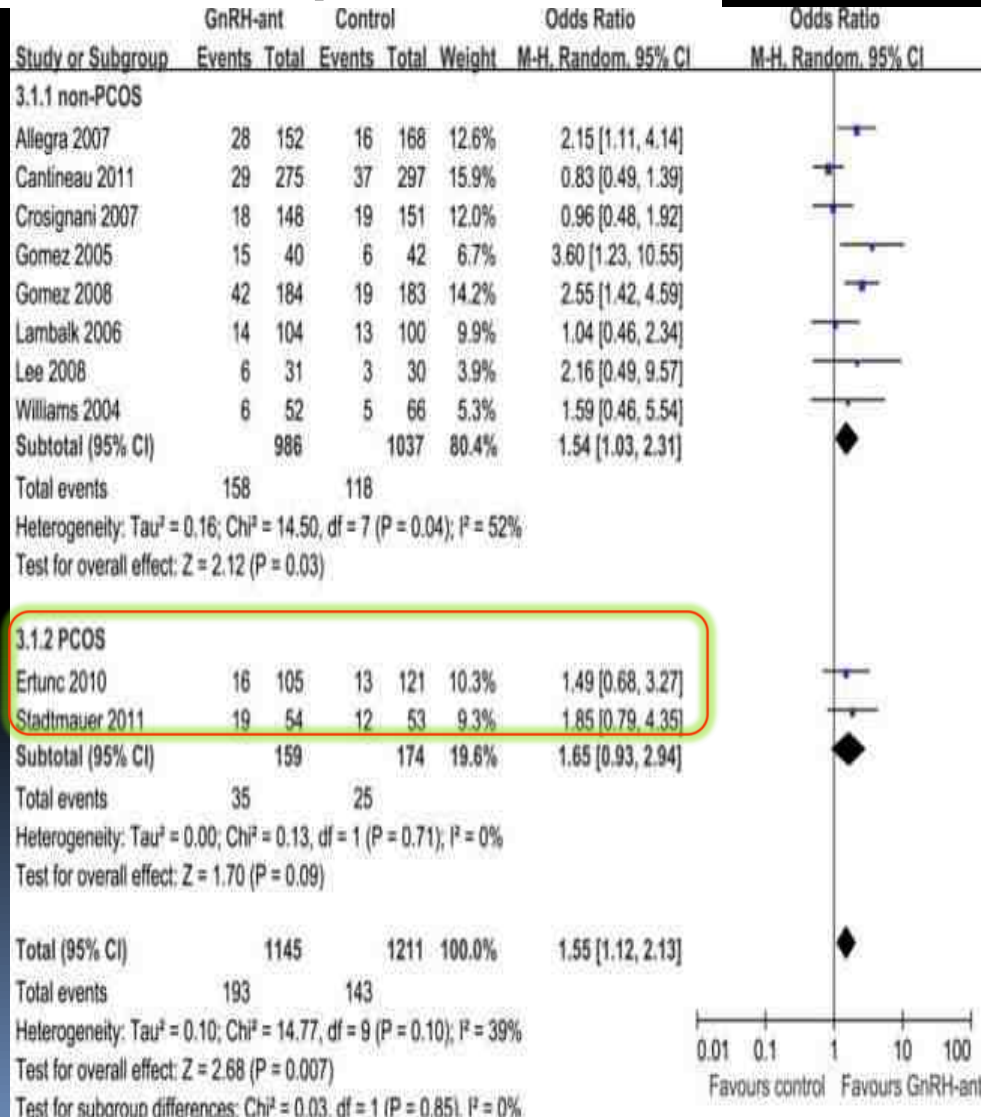
Shan Luo, Shangwei Li*, Song Jin, Ya Li, Yaoyao Zhang

2014

Conclusion:

This meta-analysis suggested that GnRH-ant can reduce the incidence of PL and increase the CPR when used in COS/IUI cycles, and it was especially useful for non-PCOS patients

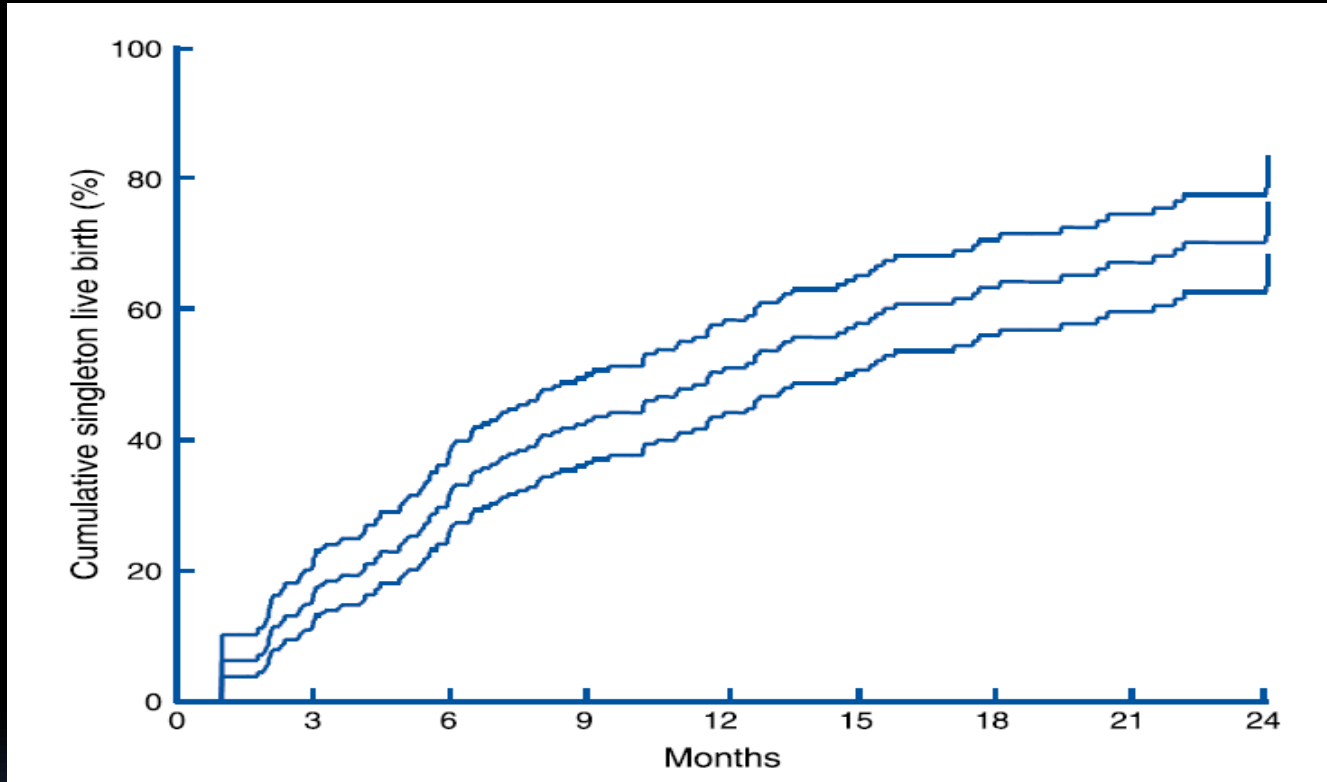
However, evidence to support its use in PCOS patients is still insufficient



PCOS'ta gn+GnRh Ant eklenmesi;
PL azaltır, hCG günü P düşürür

CPR, LBR VE DÜŞÜK ORANLARI -
FARK YOK
YETERLİ RCT YOK

SONUÇ - KONVANSİYONEL TEDAVİ (CC+FSH)



PCOS'ta ovulasyon indüksiyonunda konvansiyonel algoritme uyulursa (CC arkasından Gonadotropin) kümülatif tekil gebelik oranı 1.yıl %50, 2.yıl %71, gebe kalana kadar geçen süre **11.7** aydır.

MULTIVARIATE PREDICTION MODEL FOR PCOS

	Clomiphene citrate (CC)		Follicle-stimulating hormone (FSH)		Laparoscopic electrocautery of the ovaries (LEO)		
	Ovulation	Pregnancy (in ovulatory patients)	Pregnancy	Multifollicular growth	Ovulation	Ovulation	Pregnancy
Age		Neg ^a	Neg				
Amenorrhea	Neg	Pos					
BMI	Neg				Pos	Neg	
CC response (ovulation)				Pos	Neg		
Hyperandrogenism	Neg		Neg	Pos	Pos	Neg	Neg
Insulin resistance	Neg				Pos		
References	14,22	21,22	16	16	26	40	40

BU PREDİKTİF MULTIVARIATE MODELİN KULLANIMI İLE; BAZAL HASTA ÖZELLİKLERİNE GÖRE BAŞARI ŞANSI YÜKSEK TEDAVİ MODALİTESİNİ SEÇMEK VE BÖYLECE DAHA COST-EFEKTİF, DAHA GÜVENLİ VE DAHA AZ ZAMAN KAYBI İLE HASTAYI KENDİSİNE UYGUN TEDAVİYE YÖNLENDİRMEK MÜMKÜN OLACAKTIR.

GELECEK: GENETİK PREDİKSİYON; SNPs

- FSH-Reseptör gen polimorfizmi;
STK11— METFORMİNE KÖTÜ CEVAP
Ser680Ser- CC REZİSTANS- FSH HİPORESPONSİVE
- AMH RESEPTÖR TİP 2 – FSH SENSİVİTESİ

B. C. J. M. Fauser and M. J. C. Eijkemans

J Clin Endocrinol Metab, September 2009, 94(9):3183–3184

It should be a major challenge to consider many more genes in relation to ovarian response and pregnancy after stimulation, to design multivariate models combining clinical, endocrine, and genetic factors to reliably predict clinically relevant outcomes such as healthy (singleton) live birth. This approach may truly improve overall infertility treatment outcomes in PCOS, allowing identification of the most appropriate approach for a given woman, which may include assisted reproduction as the first-line treatment for some.

PCOS' TA GONADOTROPİNLER-ÖZET

- Tedavi başlangıcında hastanın bazal karakteristikleri iyi değerlendirilmeli ve tedavi planı buna göre yapılmalıdır
- Başlangıç dozu 37.5-50 IU/gündür
- 1. siklus için 14 günlük sabit doz ile aşırı uyarılma önlenir
- Doz artışları FSH dozunun %50'sini geçmemelidir
- Tedavi süresi 6 siklusu geçmemelidir
- Komplikasyonları (OHSS ve çoğul gebelik) azaltmak için sıkı monitorizasyon gerekir
- Tedavi öncesi hasta ile komplikasyonlar ve siklus iptali olasılığı hakkında konuşulmalıdır
- Günümüzde tüm çoğul gebelikleri ve OHSS'yi önlemek mümkün değildir
- OI'da Gonadotropinlere GnRH-a veya GnRH- ant. eklemekle OHSS ve Çoğul gebelik riski azalmaz iken maliyet artar ve gebelik oranları artırılmaz, rutin kullanımı önerilmez

SABRINIZ İÇİN TEŞEKKÜRLER

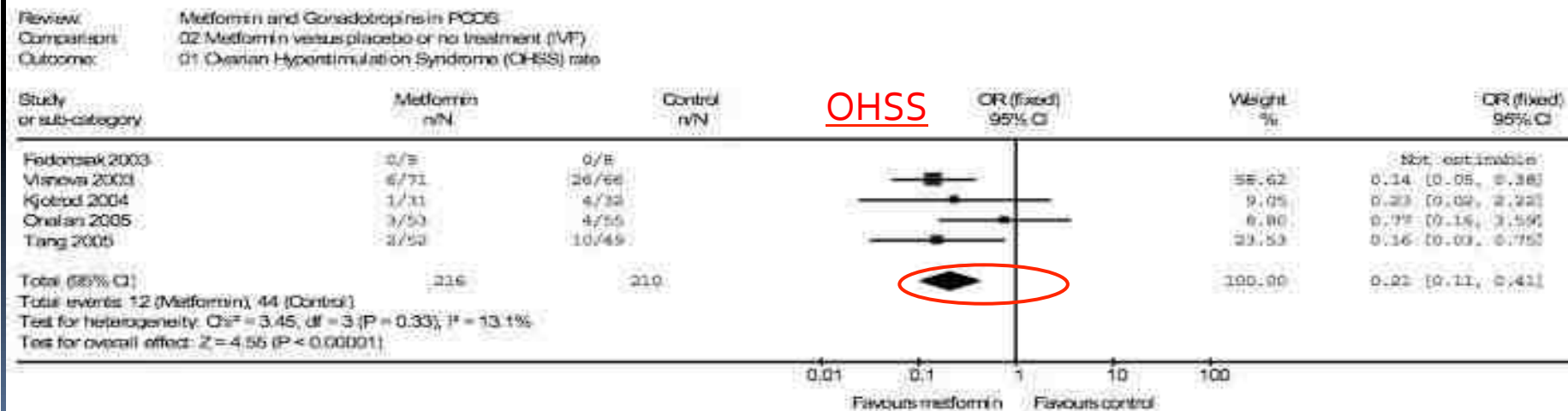
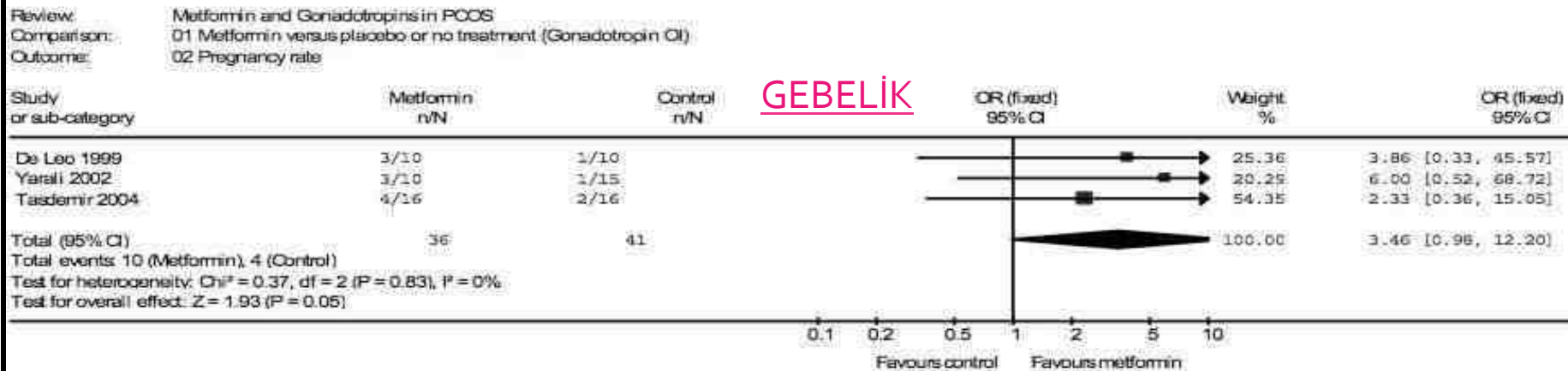


Metformin co-treatment

8 RCT Meta -analiz sonuçları

Metformin + gonadotropin / gonadotropin OI, IVF

Metformin ovulasyon oranında iyileşmeye neden olmaz Yaralı et al, 2002



Costello et al., 2006

REVIEW

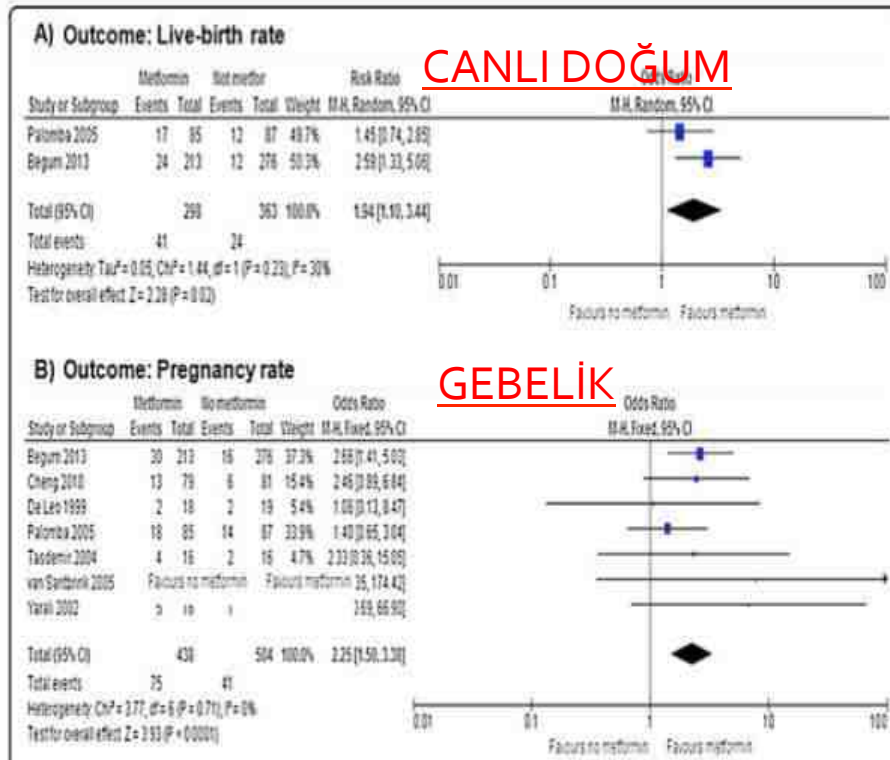
Open Access

Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials

Stefano Palomba^{1*}, Angela Falbo¹ and Giovanni B La Sala^{1,2}

Palomba et al. *Reproductive Biology and Endocrinology* 2014, **12**:3
http://www.rbej.com/content/12/1/3

Page 8 of 15



7 RCT Metformin +
gonadotropin / gonadotropin OI,
NO IVF

1500-1700mg/gün
MET(pretreatment)
+ FSH (50/75 IU) STEP-UP

SİKLUS İPTALİNDE %60 AZALMA
OHSS'de fark yok (p=0.14)

CANLI DOĞUM ve GEBELİK ORANLARI NDA 2 KAT ARTIŞ (p=0.02, p<0.0001)

IUI vs TI

Controlled ovarian hyperstimulation in women with polycystic ovarian syndrome with or without intrauterine insemination

(RETROSPEKTIF KOHORT)

Gynecological Endocrinology, 2012; 28(7): 502-504
© 2012 Informa UK, Ltd.

Table I. Characteristic of the patients in the groups of IUI and TIC.

Characteristics	TIC	IUI	P value
Total number of cycles	114	145	NS
Age years (mean ± SD)	30.6 ± 3.8	31.4 ± 3.9	NS
BMI (kg/M ²)	27.2 ± 6.1	25.0 ± 5.8	NS
Primary infertility	73/114 (64.1%)	103/145 (71.0%)	NS
Secondary infertility	41/114 (35.9%)	42/145 (29.0%)	NS
Basal FSH (IU/ml)	5.2 ± 1.7	4.9 ± 1.6	NS
Basal LH (IU/ml)	7.2 ± 5.9	6.6 ± 7.7	NS
Maximal endometrial thickness (mm)	7.9 ± 2.4	8.8 ± 2.2	NS
Total follicle ≥ 15 mm on day of hCG	1.5 ± 1.1	1.6 ± 1.0	NS

BMI, body mass index; FSH, follicle-stimulating hormone; LH, leuteinizing hormone; IUI, intrauterine insemination; TIC, timed intercourse.

Table II. Characteristics of partner's sperm during infertility evaluation.

Analysed parameters	TIC	IUI	P value
Concentration (million/ml)	90.0 ± 85.7	67.1 ± 100	NS
Motility (%)	38.4 ± 16.1	32.3 ± 17.9	NS
Normal morphology (%)	21.3 ± 0.8	17.2 ± 3.9	NS

IUI vs TI

Controlled ovarian hyperstimulation in women with polycystic ovarian syndrome with or without intrauterine insemination

Gynecological Endocrinology, 2012; 28(7): 502-504
© 2012 Informa UK, Ltd.

Table III. Total pregnancy rate and pregnancy rates according the type of the treatment.

Treatment types	TIC	IUI	P value
Clomiphene citrate	12/85 (14.1%)	4/53 (7.5%)	NS
Gonadotropins	7/18 (38.8%)	19/74 (25.7%)	NS
Aromatase inhibitors	1/11 (9.1)	1/18 (5.5%)	NS
Total pregnancy rate	20/114 (17.5%)	24/145 (16.6%)	NS
Total miscarriage rate	2/20 (10%)	4/24 (16.7%)	NS
Ectopic pregnancy rate	0/20 (0%)	2/24 (8.3%)	NS
Total live birth rate	18/114 (15.8%)	18/145 (12.4%)	NS

PCOS'ta KOH'a IUI eklemenin faydası yok

STUDY PROTOCOL

Open Access

The M-OVIN study: does switching treatment to FSH and / or IUI lead to higher pregnancy rates in a subset of women with world health organization type II anovulation not conceiving after six ovulatory cycles with clomiphene citrate – a randomised controlled trial

Marleen J Nahuis[†], Nienke S Weiss, Fulco van der Veen, Ben Willem J Mol, Peter G Hömpes, Jur Oosterhuis, Nils B Lambalk, Jesper MJ Smeenk, Carolien AM Koks, Ron JT van Golde, Joop SE Laven, Ben J Cohlen, Kathrin Fleischer, Angélique J Goverde, Marie H Gerards, Nicole F Klijn, Lizka CM Nekruš, Ilse AJ van Rooij,

There have been no randomised controlled trials that studied the effect of IUI in women undergoing ovulation-induction with CC or gonadotrophins for oligo- or anovulation.

- 1) CC plus intercourse
- 2) CC plus IUI
- 3) gonadotrophins plus intercourse
- 4) gonadotrophins plus IUI

Abstract

Background: Clomiphene citrate (CC) is first line treatment in women with World Health Organization (WHO) type II anovulation and polycystic ovary syndrome (PCOS). Whereas 60% to 85% of these women will ovulate on CC, only about one half will have conceived after six cycles. If women do not conceive, treatment can be continued with gonadotrophins or intra-uterine insemination (IUI). At present, it is unclear for how many cycles ovulation induction with CC should be repeated, and when to switch to ovulation induction with gonadotrophins and/or IUI.

Methods/Design: We started a multicenter randomised controlled trial in the Netherlands comparing six cycles of CC plus intercourse or six cycles of gonadotrophins plus intercourse or six cycles of CC plus IUI or six cycles of gonadotrophins plus IUI.

Women with WHO type II anovulation who ovulate but did not conceive after six ovulatory cycles of CC with a maximum of 150 mg daily for five days will be included.

Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome

Tso LO¹, Costello MF, Albuquerque LE, Andriolo RB, Macedo CR.

AUTHORS' CONCLUSIONS:

- This review found no conclusive evidence that metformin treatment before or during ART cycles improved live birth rates in women with PCOS
- However, the use of this insulin-sensitising agent **increased clinical pregnancy rates** and **decreased the risk of OHSS**

The role of inositol supplementation in patients with polycystic ovary syndrome, with insulin resistance, undergoing the low-dose gonadotropin ovulation induction regimen

TABLE 1

Comparison between ovulation induction cycles in patients with and without inositol co-treatment.

	Low dose step down Without inositol	With inositol	P value
Number of cycles	15	15	
Patient age (y)	31.6 ± 2.5	31.9 ± 2.6	ns
BMI (kg/m ²)	27.2 ± 1.4	27.3 ± 1.4	ns
HOMA	2.86 ± 0.26	2.88 ± 0.29	ns
Day 3 FSH (IU/L)	6.6 ± 1.4	6.4 ± 1.1	ns
Day 3 LH (IU/L)	8.9 ± 1.3	8.3 ± 1.1	ns
PRL (ng/mL)	16.7 ± 2.7	15.7 ± 3.2	ns
17-OHP (ng/mL)	0.98 ± 0.15	1.08 ± 0.16	ns
DHEAS (μg/dL)	122.6 ± 28.7	140.2 ± 32.1	ns
Ovulation induction			
Number of follicles >15 mm in diameter	3.5 ± 1.2	2.1 ± 0.5	<.001
Number of follicles >18 mm in diameter	2.0 ± 0.9	1.1 ± 0.5	<.003
Peak E ₂ levels on day of hCG administration (pg/mL)	955 ± 342	441 ± 91	<.001
Cancellation rate (%)	6/15 (40%)	0	<.002
Clinical PR (%)	2/15 (13.3%)	5/15 (33.3%)	ns

MYO-İNOSİTOL MET. DEN DAHA EFEKTİF Raffone E, 2010
 Inositol 3 gm/g 4 hafta önce başlıyor/ vit B8, intracellular second messenger
 Restores IR / Inofolic®