

PCOS: GONADOTROPİN İLE OVULASYON İNDÜKSİYONU

Prof.Dr. S. Temel CEYHAN

GATA Kadın Hastalıkları ve Doğum AD

Amaç

OI

GT
Protokol

Protokol
Farkları

Threshold

Hangi
GT

hCG

Sonuç

Non-Farmakolojik

Yaşam Tarzı Değişikliği

Diet

Egzersiz

Sigara'nın Bırakılması

Davranışsal Değişiklikler

**Farmakolojik -
Cerrahi**

1

Klomifen Sitrat

Gonadotropin

LOD

Bariatrik Cerrahi*

Aromataz İnhib. **

3

IVF

* Anovulatuvar ve $BMI \geq 35$;
en az 6 ay yoğun diet+ egzersize rağmen infertil

** CC rezistan

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Etkinlik, Avantaj, Dezavantaj

	Ovulation	Multiple pregnancies	Time to pregnancy	Ultrasound examinations	Side-effects	Patient compliance
Lifestyle interventions	↑					
Metformin	↑					
Clomiphene citrate	↑↑					
Letrozole	↑↑↑					
Gonadotrophins	↑↑↑					
Ovarian drilling	↑					

PCOS'ta OI ajanı olarak First Line Terapi: CC - FSH

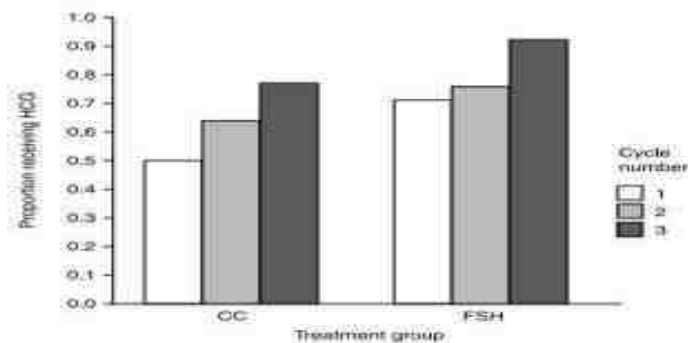


Figure 2. Proportion of cycles in which HCG was administered. (CC = clomiphene citrate; FSH = recombinant FSH.)

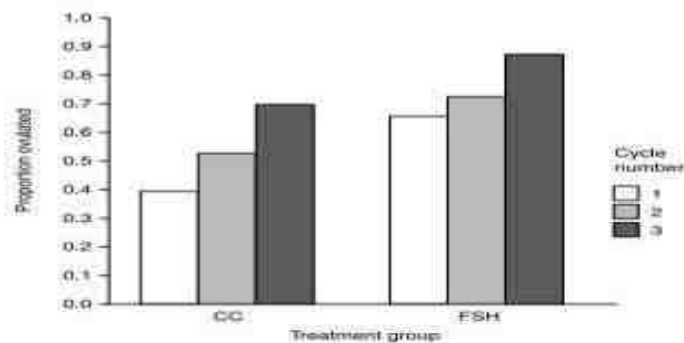


Figure 3. Proportion of cycles in which ovulation occurred. (CC = clomiphene citrate; FSH = recombinant FSH.)

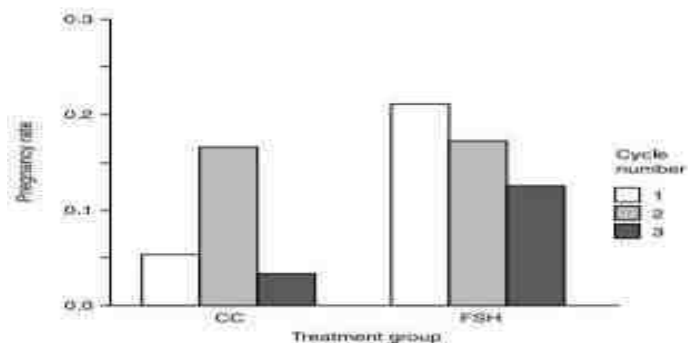


Figure 4. Pregnancy rate per cycle. (CC = clomiphene citrate; FSH = recombinant FSH.)

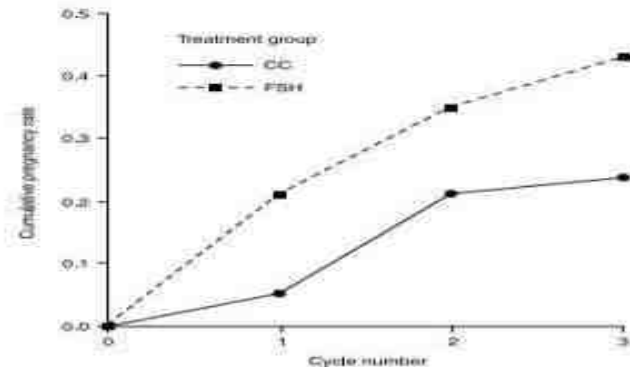
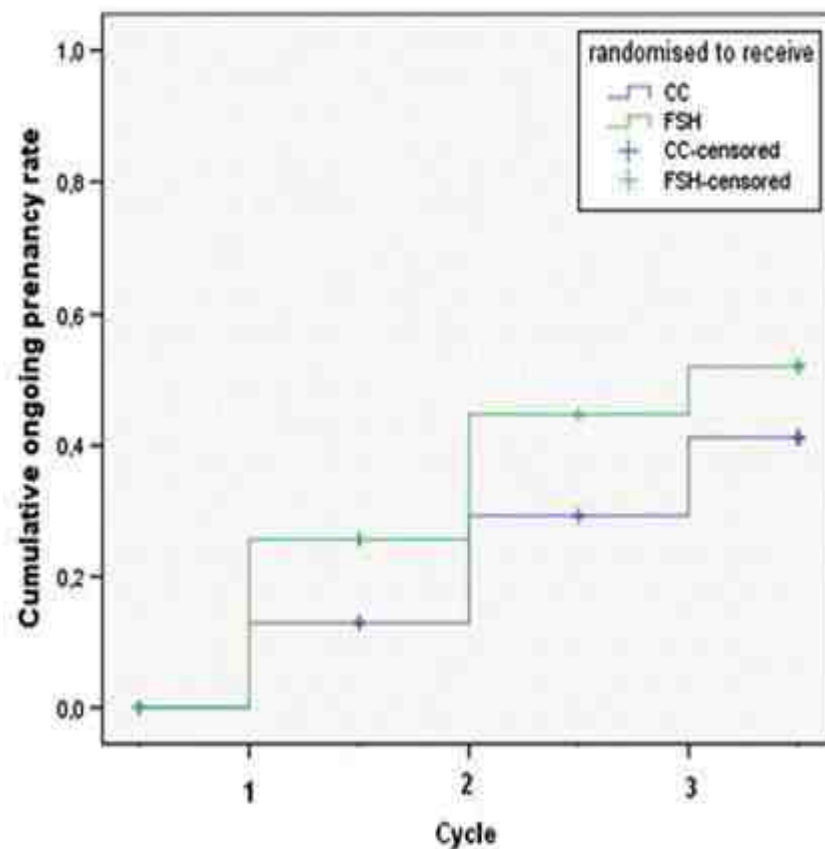
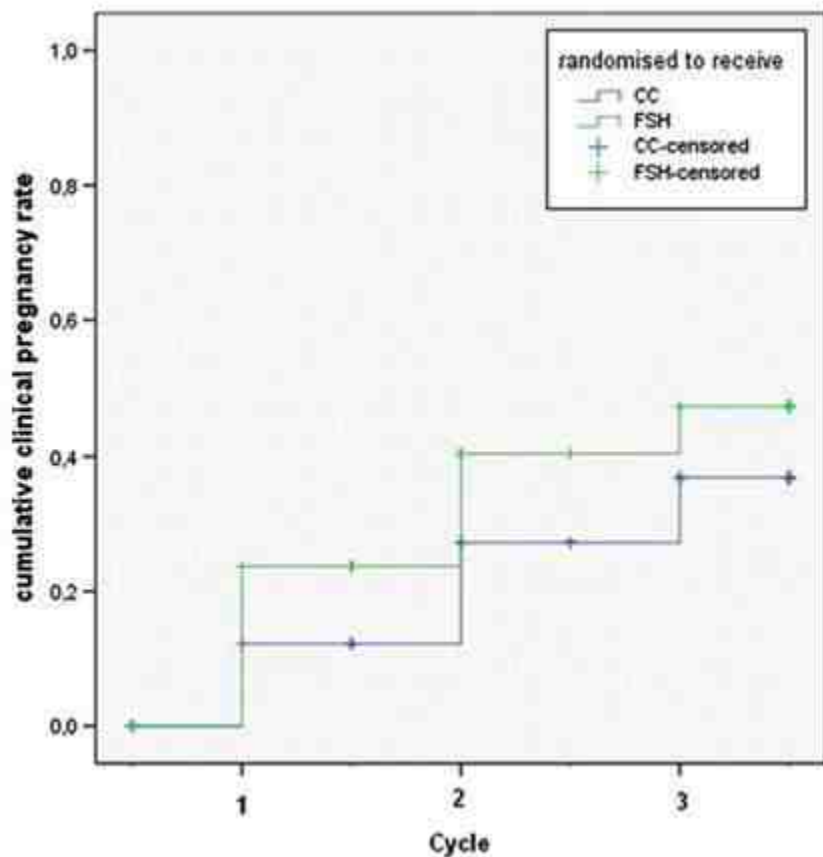


Figure 5. Cumulative pregnancy rate. (CC = clomiphene citrate; FSH = recombinant FSH.)

PCOS'ta OI ajanı olarak First Line Terapi: CC - FSH



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HANGİ PROTOKOLLER VAR

Konvansiyonel

Low-Dose Step Up

Step Down

Ardışık Step Up- Step Down

Bireyselleştirilmiş



PKOS lu Hastada Hangi Protokol Kullanılmalı

- Amaç
 - **Yetersiz** Stimülasyondan Kaçınma
 - **Aşırı** Stimülasyondan Kaçınma
 - **Cancel** oranını minimize etmek
 - **OHSS** riskini minimize etmek

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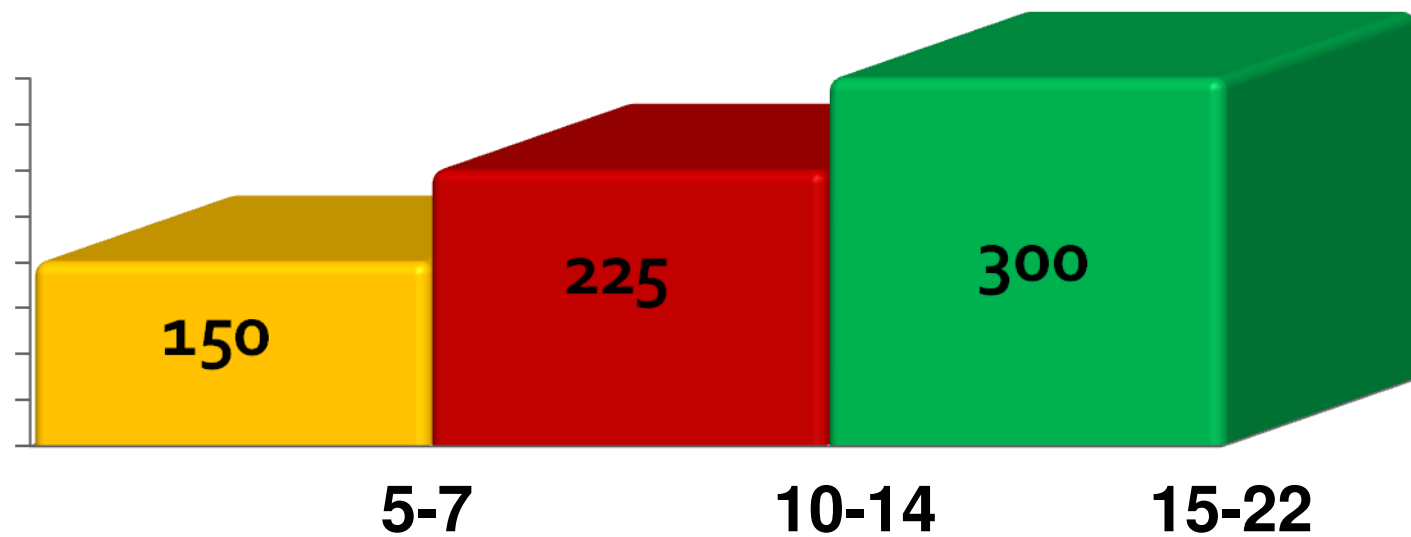
Threshold

Hangi
GT

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Sonuç

Konvansiyonel Protokol



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Konvansiyonel

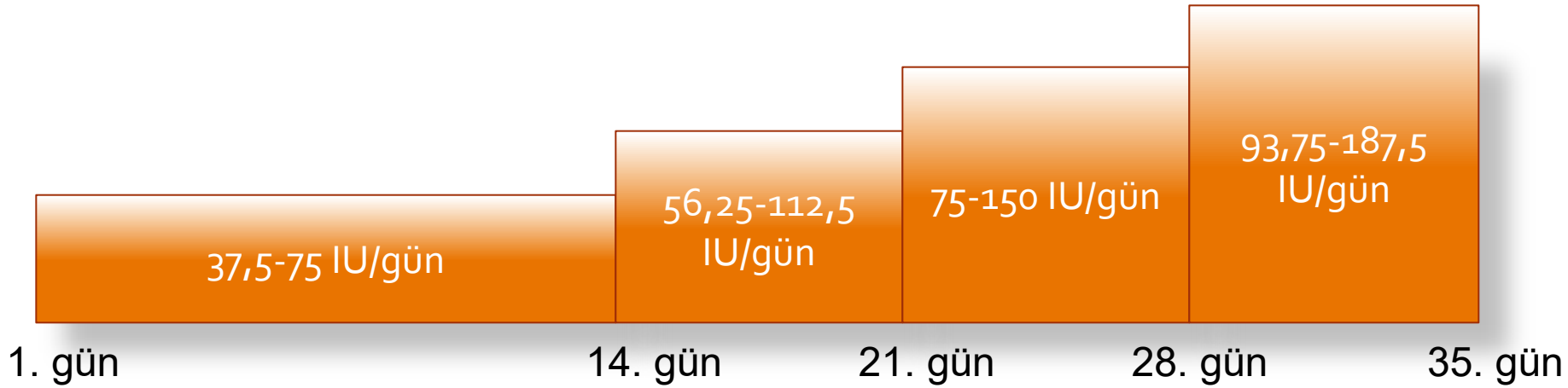
Low-Dose Step Up

Step Down

Ardışık Step Up- Step Down

Bireyselleştirilmiş

Low-Dose Step-up Protokolü



- Başlangıç Dozu: 37.5 – 50 IU Rec FSH (En yüksek doz: **225 IU/gün**)
- 7 Gün Sonra 10 Mm Üzeri follikül yoksa doz artırılır.
- Dominant follikül olana kadar doz artır.
- 35. günde hala yanıt yoksa **siklus iptal**.
- 18 mm üzeri follikül ve end eko: 7 mm üzeri (hCG)
- PCOS'ta optimal artış aralığı hakkında çalışma az.

- **1 follicle \geq 18 mm**
- **2-3 follicles \geq 16 mm**
- **E₂ >150 pg/ml/follicle > 16mm**

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Low-Dose Step Up

Step Down

Ardışık Step Up- Step Down

Bireyselleştirilmiş

Amaç

Oİ

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Protokol

Protokol
Farkları

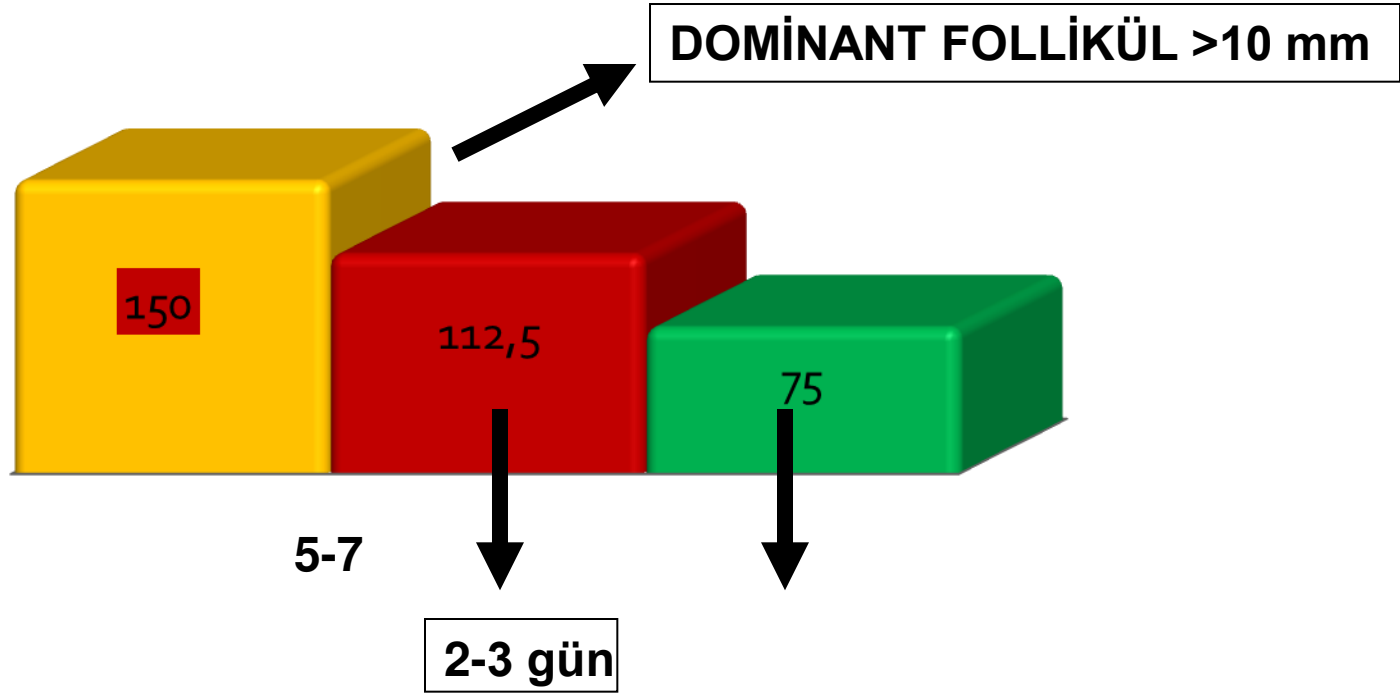
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Step-Down Protokolü



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Konvansiyonel

Low-Dose Step Up

Step Down

Ardışık Step Up- Step Down

Bireyselleştirilmiş

Amaç

OI

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Protokol

Protokol
Farkları

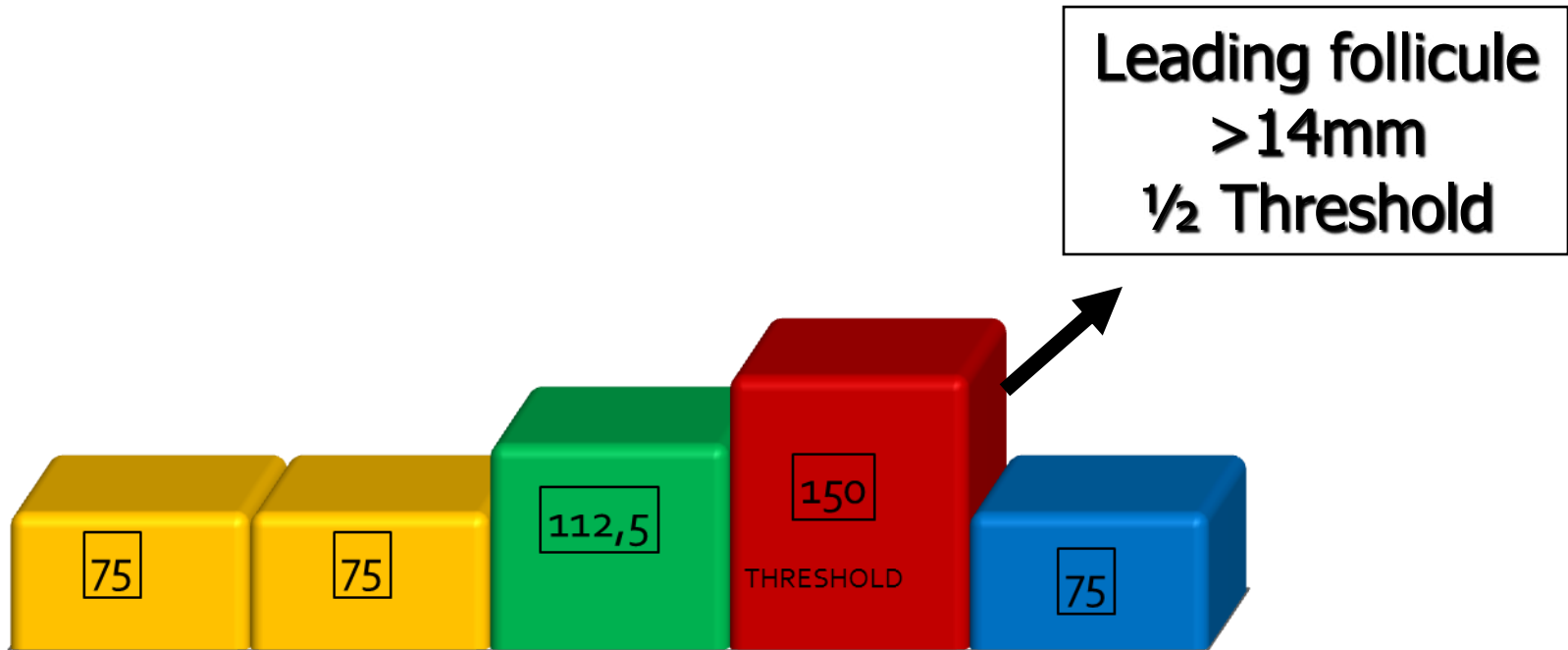
Threshold

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Low-Dose Sequential Step-Up & Step-Down Protokolü



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Low-Dose Step Up

Step Down

Ardışık Step Up- Step Down

Bireyselleştirilmiş

Amaç

Ol

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***PROTOKOLLER ARASINDA
FARK VARMI***



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Konvansiyonel Protokol

Ovulasyon

%70

Çoğul Gebelik

%36

OHSS

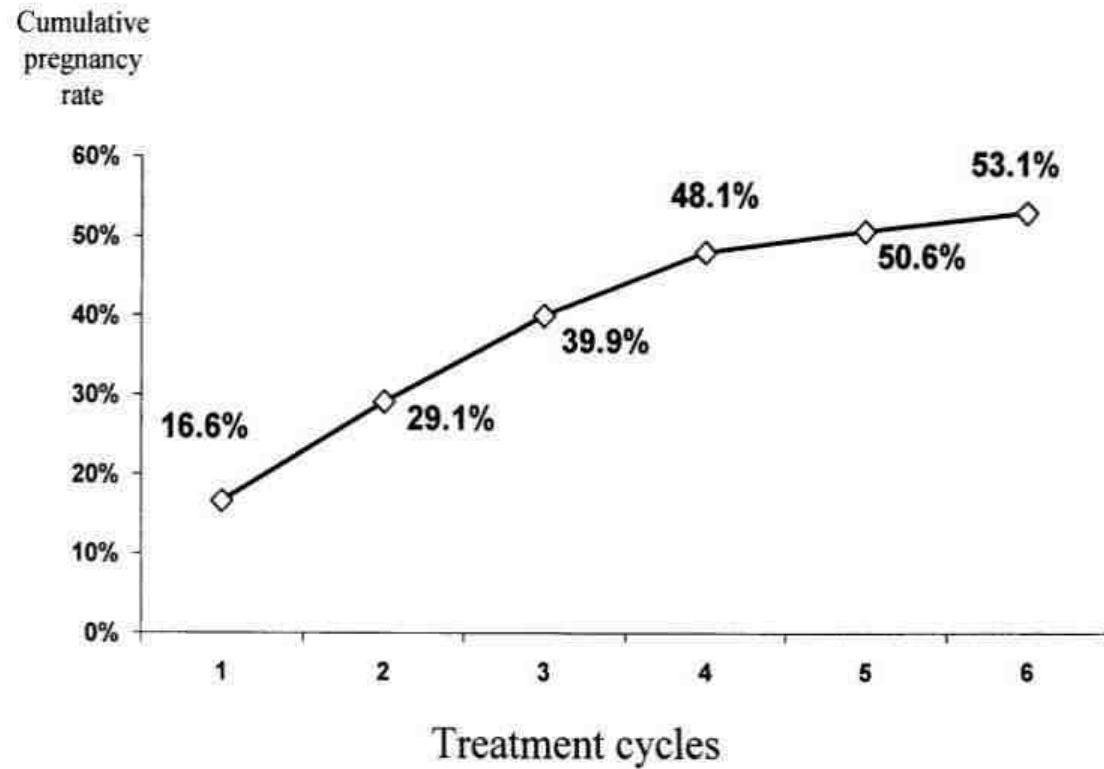
%14

Kümülatif Gebelik

%21-75

İSTEMİYORUZ !!!

Low Dose Step Up -Protokol



- **Monofoliküler gelişim:** %61.3
- **Cancel:** %13.5
 - Ovarian aşırı cevap
 - Spontan ovulasyon
- **Kümülatif ovulasyon oranı:** %84
- **Hafif-orta OHSS:** %6.8
- **İkiz:** %6

Low Dose Step Up vs Step Down

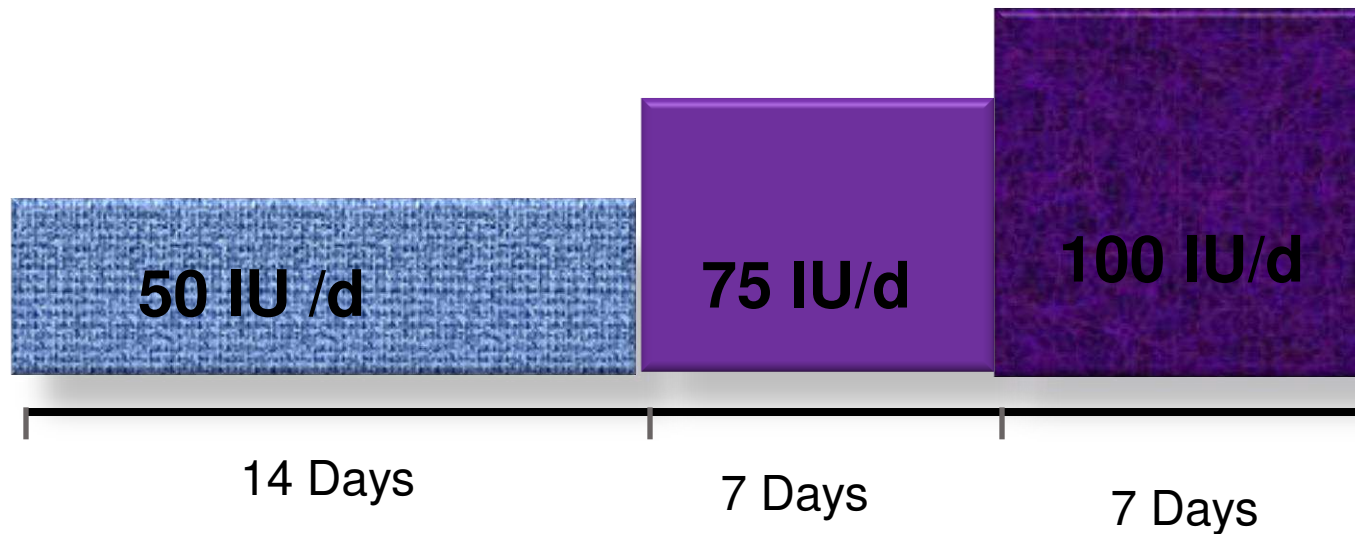
Human Reproduction Vol.18, No.8 pp.1626-1631, 2003

DOI: 10.1093/humrep/dpg336

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*

¹Reproductive Endocrine Unit, EA 1533, Hôpital Saint-Antoine, 75012 Paris and ²Reproductive Medicine Unit, Hôpital Jean Verdier, 93143 Bondy, France



Low Dose Step Up vs Step Down

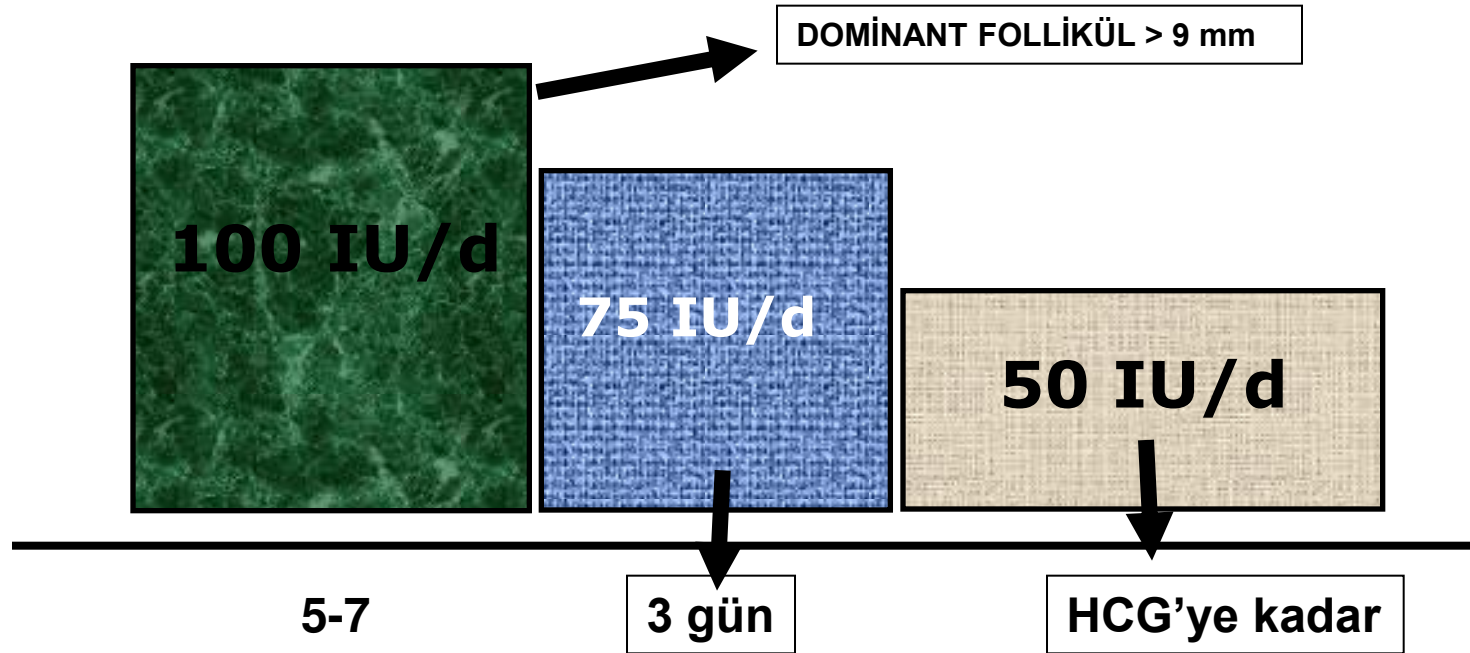
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Amaç	OI	GT Protokol	Protokol Farkları	Threshold	Hangi GT	hCG	Sonuç
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Low Dose Step Up vs Step Down

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

	Step-up protocol (n = 85 cycles)	Step-down protocol (n = 72 cycles)	P
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

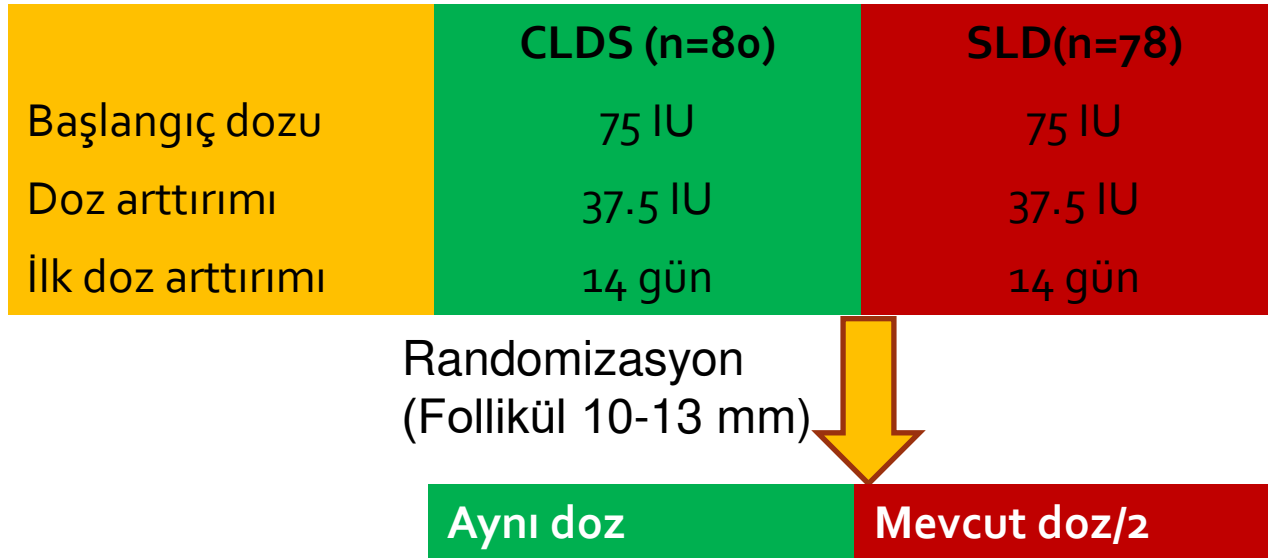
Kronik Low Dose Step Down vs Sequential

Human Reproduction Vol.21, No.11 pp. 2817-2822, 2008
Advance Access publication July 27, 2008

doi:10.1093/humrep/dn085

The use of a decremental dose regimen in patients treated with a chronic low-dose step-up protocol for WHO Group II anovulation: a prospective randomized multicentre study

J.N.Hugues^{1,3}, I.Cédric-Durnerin¹, C.M.Howles², On Behalf of the Recombinant FSH OI Study Group



Kronik Low Dose Step Down vs Sequential

Table II. Clinical results (mean \pm SD) of chronic low dose (CLD) and sequential (SQ) administration of recombinant human FSH (r-hFSH)

ITT	CLD protocol (n = 80)	SQ protocol (n = 78)	P
Parameters between randomization and hCG			
Duration of treatment (days)	4.6 \pm 3.5	5.6 \pm 4.4	0.14
Amount of r-hFSH (IU)	394 \pm 355	307 \pm 303	0.1
Parameters at the time of hCG administration			
Duration of treatment (days)	14.1 \pm 7.4	16.3 \pm 8.5	0.09
Total amount of r-hFSH (IU)	1174 \pm 818	1197 \pm 934	0.87
Number of follicles \geq 10 mm at hCG	2.9 \pm 2.3	2.7 \pm 2.4	0.94
Number of follicles between 10 and 13 mm at hCG	1.0 \pm 1.5	0.9 \pm 1.9	0.96
Number of follicles between 14 and 15 mm at hCG	0.4 \pm 0.7	0.5 \pm 0.8	0.59
Number of follicles \geq 16 mm at hCG	1.5 \pm 0.9	1.4 \pm 0.7	0.85
Rate of mono-follicular development (%) ^a	54 (42–65)	56 (45–68)	0.7
Rate of bi-follicular development (%) ^a	25 (16–36)	23 (14–34)	0.75
Rate of tri-follicular development (%) ^a	5 (1–12)	4 (1–11)	0.95
Estradiol plasma value at hCG (pg/ml)	441 \pm 360	425 \pm 480	0.82
Endometrium thickness (mm)	9.6 \pm 1.9	9.5 \pm 2.1	0.86
hCG administration (%)	100	100	NS
Patients with ovulation (%) (P4 > 10 ng/ml) ^a	54 (42–66)	45 (34–57)	0.25
Progesterone values in luteal phase (ng/ml)	21.8 \pm 24	23.7 \pm 24	0.74
Clinical pregnancy/cycle (%) ^a	17 (21) (13–32)	9 (12) (5–21)	0.12
Multiple pregnancy/clinical pregnancy (%)	2 (12)	1 (11)	NS
Mild and moderate OHSS (%)	2 (3)	3 (4)	NS
Miscarriages (%)	3 (4)	2 (3)	NS

14 gn rejimine uyulduęu takdirde



- ✓ Nonobese PCOS hastalarında 75 IU uygun doz.
- ✓ Doz ayarlama ancak %10 hastada gerekli oluyor.
- ✓ SQ rejime gerek yok çünkü OHSS çok az.

Düşük Doz Step-Up

- Başlangıç dozu ne olmalı?
 - 37.5 IU, **50 IU** veya 75 IU/gün ?
 - **75 IU kullanılırsa**
 - Siklusların %20'si iptal (multifoliküler gelişim nedeniyle)
 - 75 IU ile %72 monofoliküler
 - **52,5 IU** ile %84 monofoliküler
 - Ancak ovulasyon ve gebelik oranları benzer
 - **37,5 IU vs. 50 IU/gün?**
 - Benzer monofoliküler gelişim
 - **Doz azaldıkta OI süresi uzar.**

Düşük Doz Step-Up

- Monofoliküler gelişim için:
 - **14 günlük** başlangıç perioduna uymak önemli
- 75 IU başlangıçta **%50 artış ne zaman yapalım ?**
 - 14 gün vs 7 gün
 - **Kısa protokol ile:**
 - Daha az gonadotropin (17 vs. 22 ampul)
 - Daha kısa tedavi süresi (13 vs. 17,5 gün)
 - Ama Çoğul gebelik oranı yüksek (**%24 vs. %0**)

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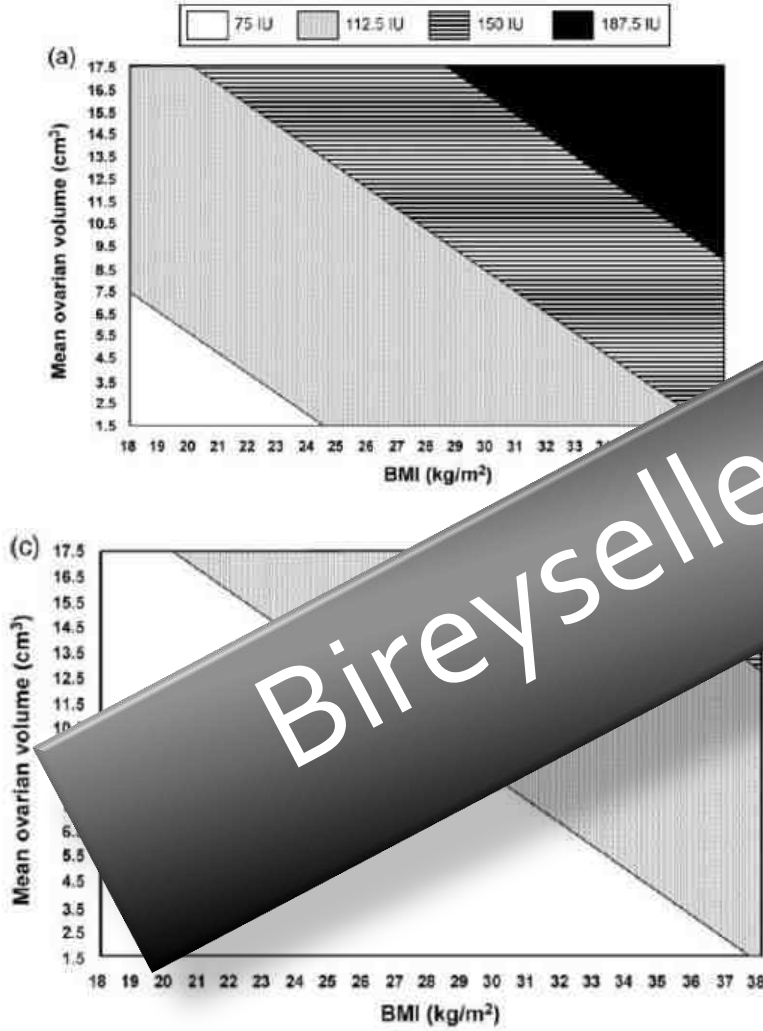
***THRESOLD DOZU
TAHMİN EDEBİLİR
MİYİM***



Predicting the FSH threshold dose in women with WHO Group II anovulatory infertility failing to ovulate or conceive on clomiphene citrate

Table II. Statistically significant predictors of FSH threshold dose (univariate and multivariate analysis).

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> -value ^a	OR (95% CI)	<i>P</i> -value ^a
Age (years)	0.91 (0.83–1.00)	0.040	—	—
BMI (kg/m ²)	1.10 (1.02–1.19)	0.010	1.17 (1.07–1.29)	<0.001
Failure to ovulate on clomiphene citrate: yes versus no	2.27 (1.14–4.52)	0.020	—	—
Menstrual cycle history		<0.001		<0.001
Amenorrhoea versus cycle length 21–35 days	8.33 (2.81–24.7)		11.88 (3.35–42.1)	
Oligomenorrhoea versus cycle length 21–35 days	3.48 (1.51–8.03)		2.57 (0.97–6.79)	
Mean ovarian volume (cm ³)	1.18 (1.06–1.31)	0.002	1.22 (1.08–1.37)	<0.001
Free androgen index (nmol/l)	1.25 (1.13–1.38)	<0.001	—	—
Total testosterone (nmol/l)	2.14 (1.14–4.03)	0.018	—	—
LH/FSH ratio (IU/l)	1.59 (1.03–2.45)	0.038	—	—



Bireyselleştirilmiş Doz

Hata payı 25 IU
%13 hastada yanlış doz
Model doğruluğu %60

Step-up protokolü yaparken, obez olgularda başlangıç dozu
en az 75 IU/gün

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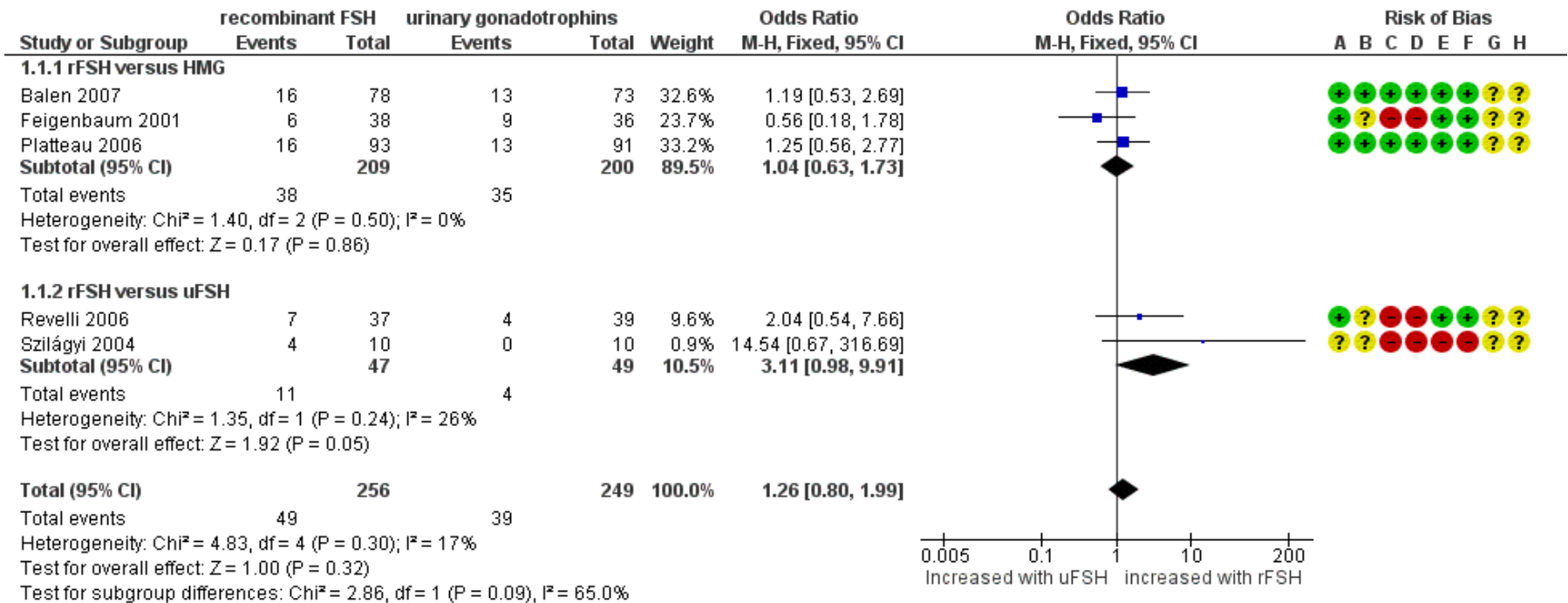
hCG

Sonuç

***HANGİ
GONADOTROPİN
DAHA İYİ ?***



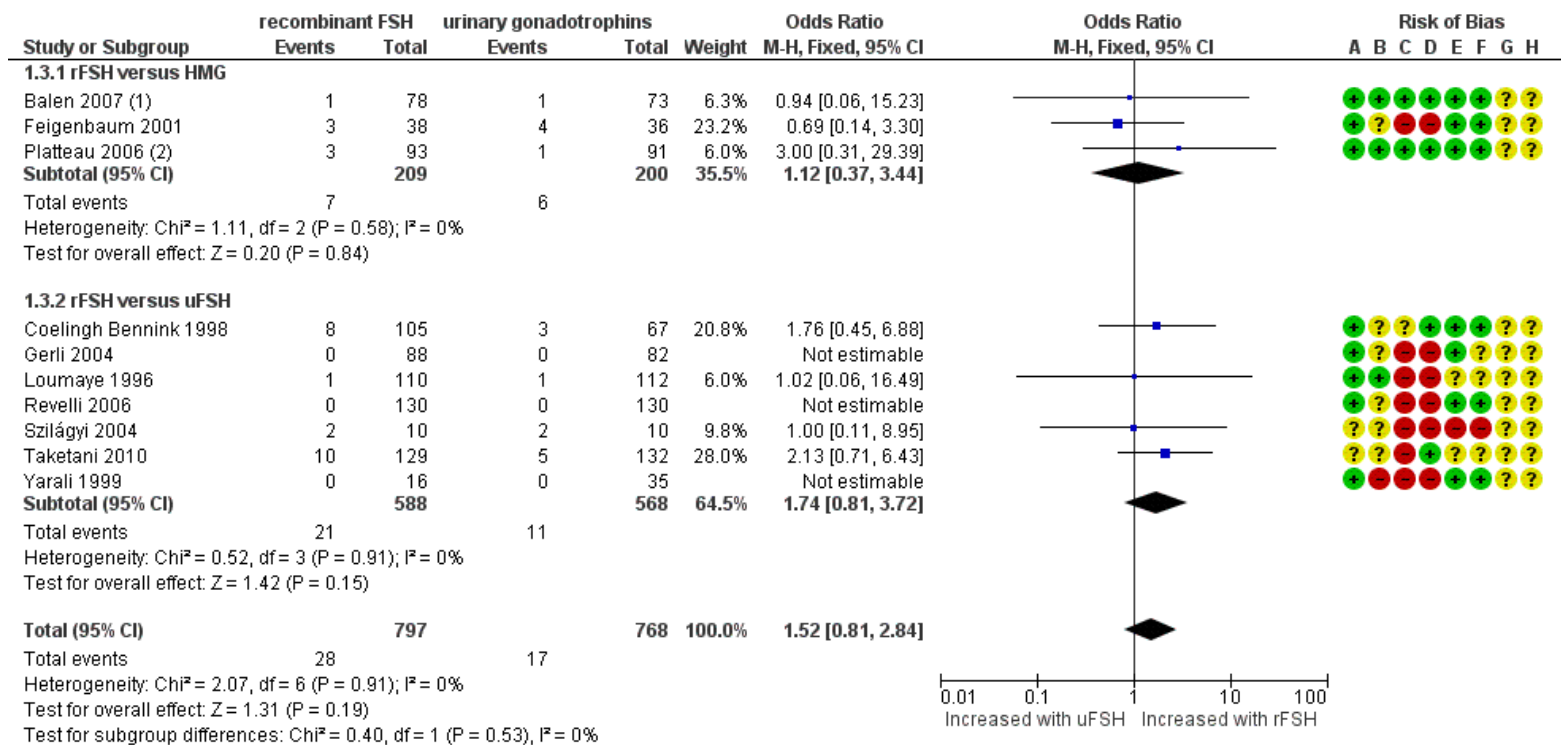
Rec FSH vs u FSH - Canlı Doğum



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias
- (H) Funding

Rec FSH vs uFSH-OHSS



Risk of bias legend

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Footnotes

- (1) OHSS was mild in both cases.
- (2) Grade of OHSS not mentioned

Takip

■ USG ve/veya E2

- 2-3 gün aralıkla

■ hCG:

- En öndeki follikül ≥ 18 mm (>17 mm)
- Dominant follikül başına E2 200 pg/mL
- ≥ 14 mm, >2 follikül \rightarrow İPTAL
- Selanik konsensusu \rightarrow Maksimal uyarı
 - ≥ 16 mm en çok 2 follikül
 - ≥ 16 mm 1 follikül + ≥ 14 mm 2 follikül

■ Serum P:

- Prematür LH yükselmesi?

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HCG YAPMALIMİYİM



Timed Intercourse vs IUI – hCG nin Etkisi

Reproductive Biology and Endocrinology

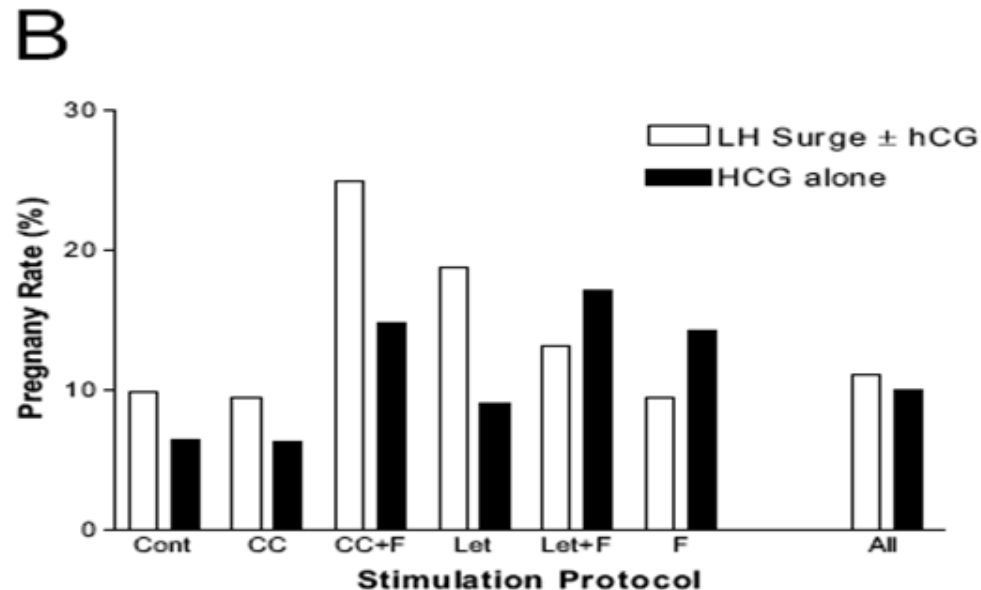


Research

Open Access

Human chorionic gonadotropin administration is associated with high pregnancy rates during ovarian stimulation and timed intercourse or intrauterine insemination

Mohamed F Mitwally^{1,2,3}, Sonya Abdel-Razeq² and Robert F Casper*¹



Etkinlik ve güvenlik açısından **yakın takip** gereklidir.

Tedavi öncesi hasta ile **kesin siklus iptal kriterleri** konusunda hemfikir olunmalıdır.

PCOS'ta gonadotropinlerle OI'da **GnRHa yeri yok.**



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