



PCOS'TA ORAL AJANLARLA OVULASYON İNDÜKSİYONU

DOÇ.DR.ÖZLEM MORALOĞLU TEKİN
ZEKAI TAHİR BURAK KADIN SAĞLIĞI EĞİTİM VE
ARAŞTIRMA HASTANESİ-ANKARA



POLİKİSTİK OVER SENDROMU

Stein & Leventhal, 1935

Üreme çağındaki kadınlarda en sık endokrin bozukluk
%5-10

Prevelans ≈%20 (infertil kadınlar)



Heterojen bir sendrom!

Anovulasyon Sınıflaması (WHO)

Grup I: Hipogonadotropik-hipogonadizm (%10) –

↓ FSH, LH, E2 –Prolaktin-normal

**Grup II: Normogonadotropik, normoestrojenik –PCOS
(%80)- Folliküler 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



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

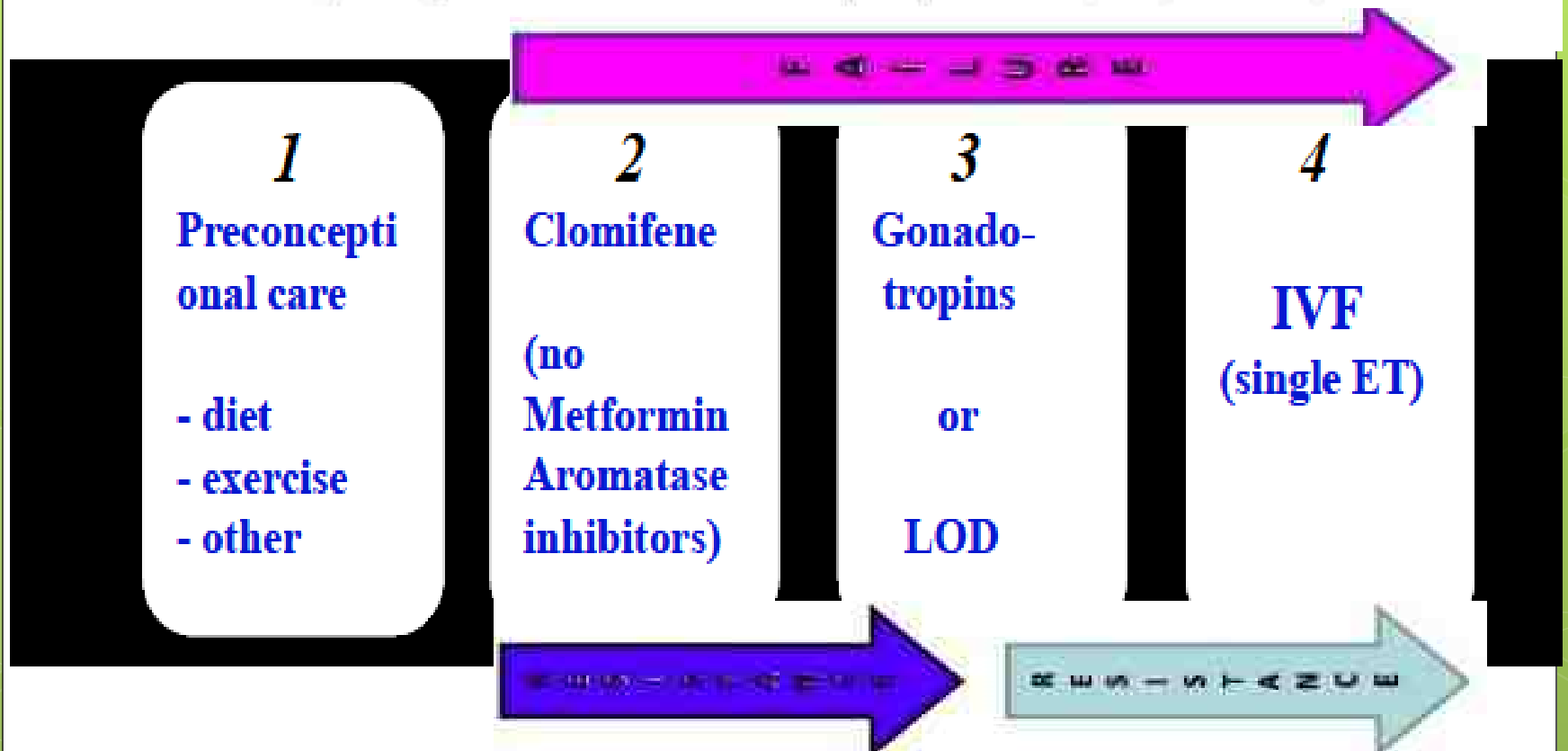
% 16-25 normal popülasyon



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

Consensus on infertility treatment related to polycystic ovary syndrome

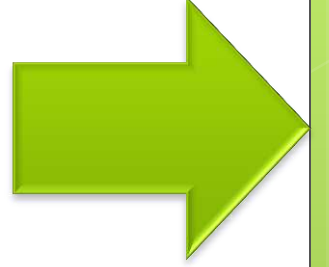
The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2-3, 2007, Thessaloniki, Greece:*



Hastaya uygun tedavi modalitesi belirlenmeli!...

Tedavi Seçenekleri

Uzmanın tecrübesi,
Hastanın hormonal durumu,
Semptomların şiddeti (siklus uzunluğu, **BMI**, **FAI**, İnsülin direnci)
Hastanın **yaşı** ve **infertilite süresi**



- OVULASYON İNDÜKSİYONU

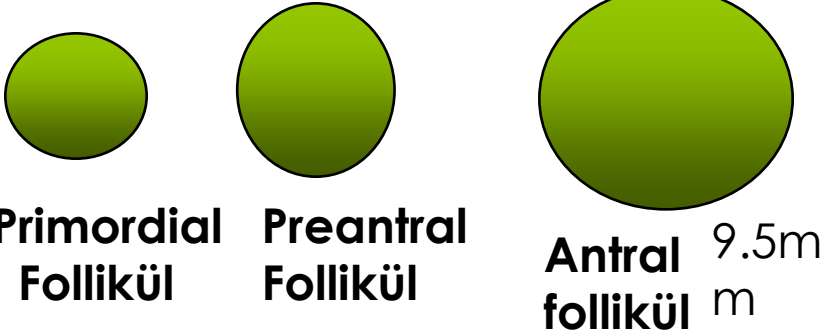
Oral ajanlar
Gonadotropinler
Cerrahi ovulasyon indüksiyonu

- İNTRAUTERİN İNSEMİNASYON

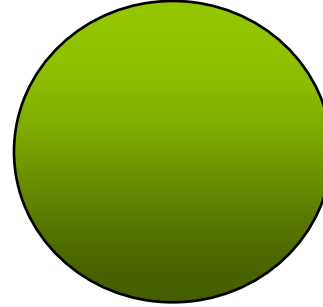


Anovulasyon Mekanizmaları

Normal follikülogenez



LH Sensitivite

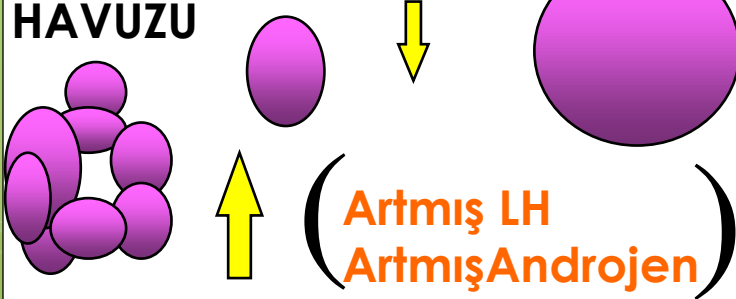


Preovulatuvar Follikül

Anormal follikülogenez

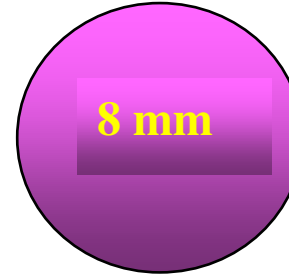
1-GENİŞ FOLLİKÜL HAVUZU

LH a Erken Sensitivite



İNSULİN

YETERSİZ LH SURGE



8 mm

2-Rölatif FSH yetmezliği

- Artmış LH
- Artmış İnsülin
- Azalmış SHBG
- Artmış androjen
- İnhibin B, IGF, AMH'daki değişiklikler???

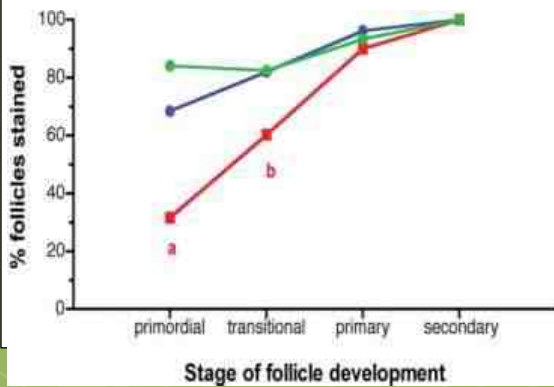
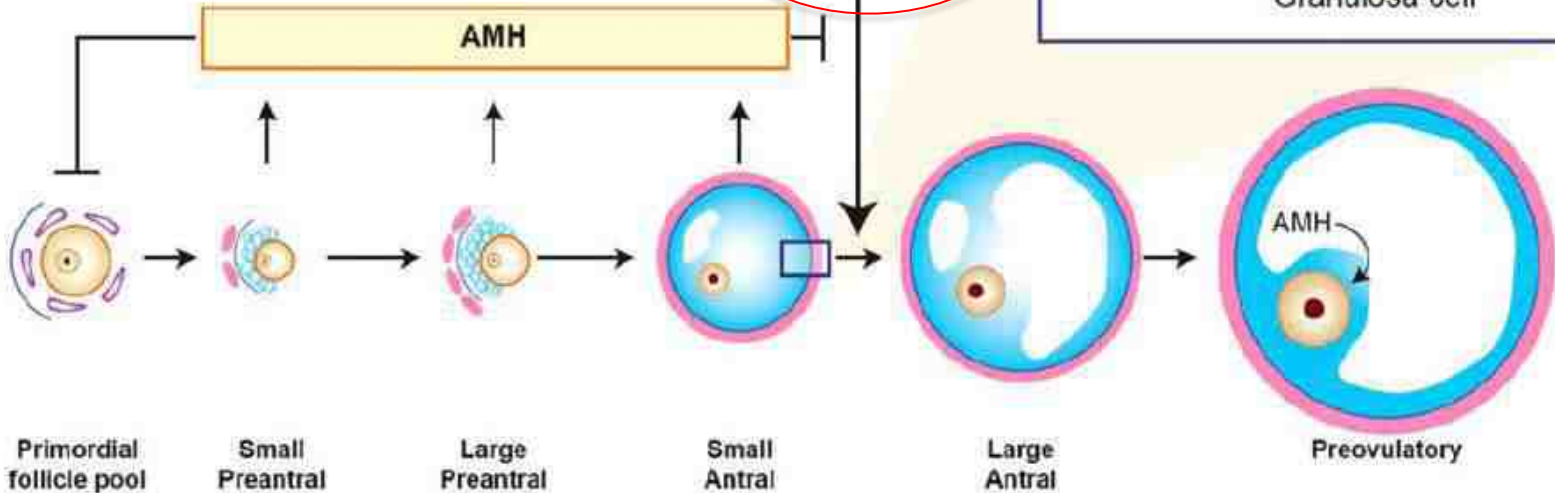
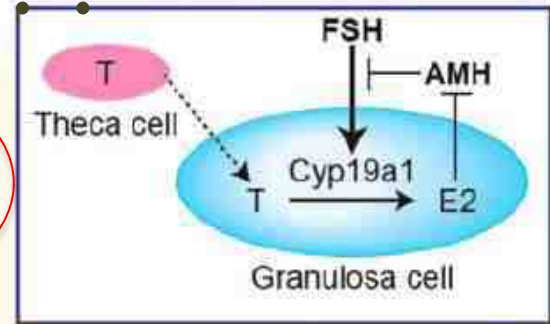
3-Folikül Gelişiminde Arrest

Franks S, 2005

FSH'yi baskılayan ne???

Initial recruitment
inh..

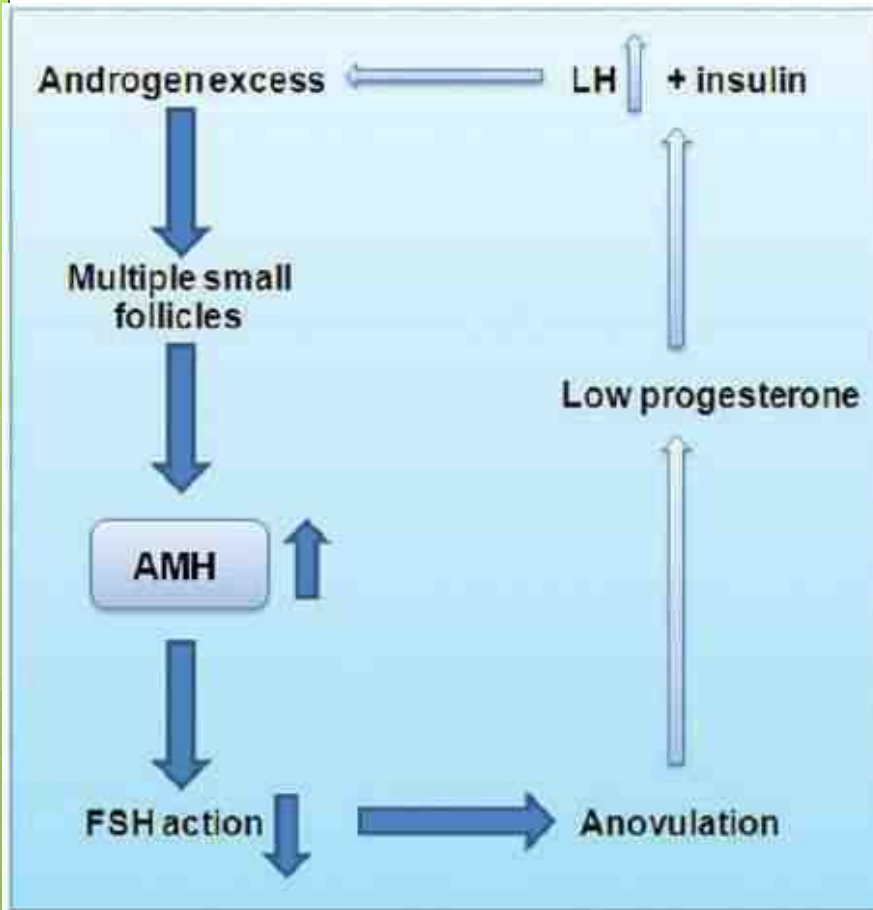
Cyclic recruitment
FSH inh..



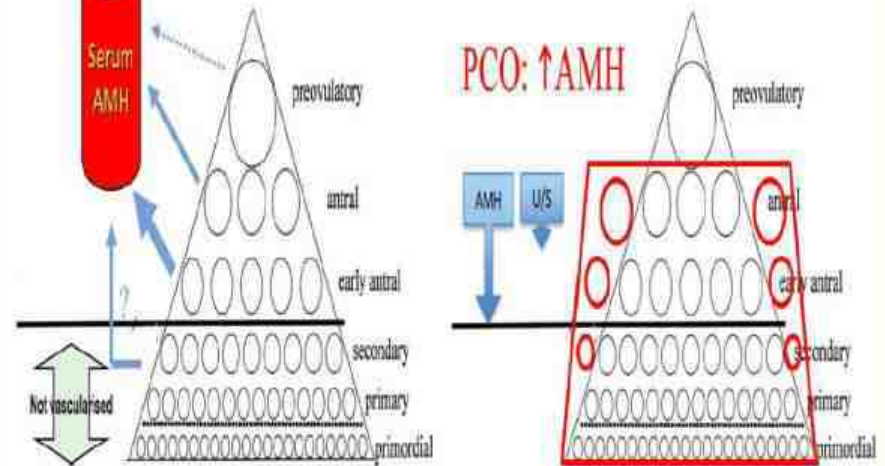
■ normal overler
■ PCOS ovülatuar
■ PCOS anovülatuar

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

Roy Homburg and Giselle Crawford*



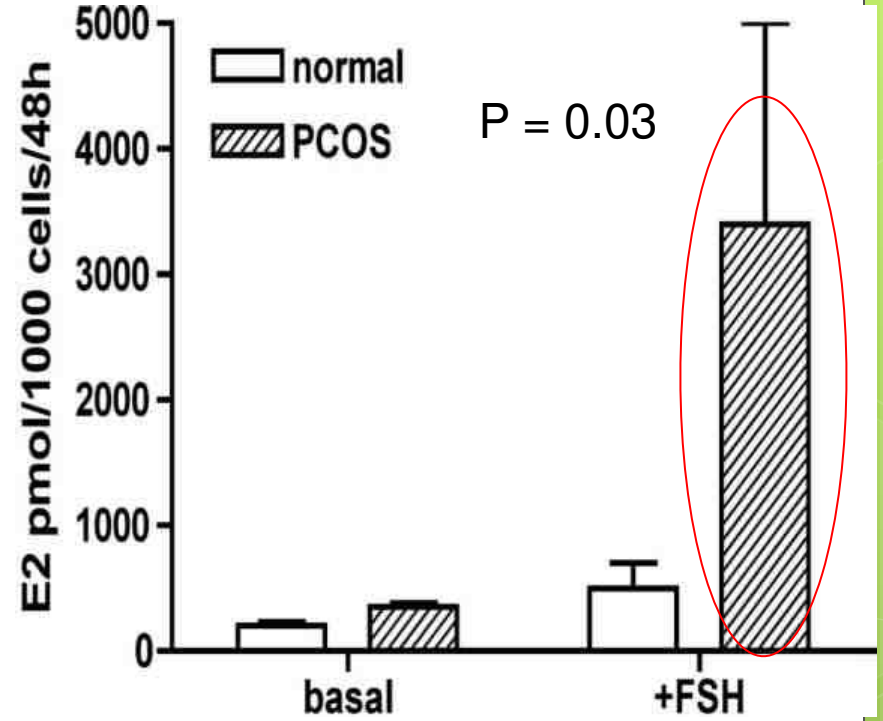
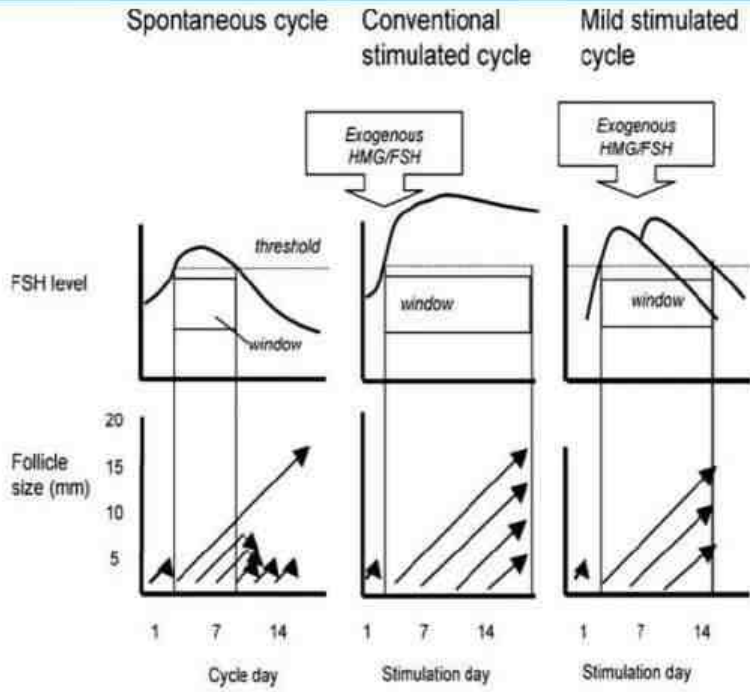
PROGNOSTİK MARKIR



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

Ovulasyon İndüksiyonunda Kullanılan Oral Ajanlar

- Anti estrojenik etkili ajanlar: Klomifen sitrat
Aromataz inhibitörleri
- İnsülin hassaslaştırıcılar Metformin
Thiazolidinedionlar
(tiaglitazon, roziglitazon, pioglitazon)
- Glukokortikoidler
- Dopamin agonistleri (Bromokriptin)

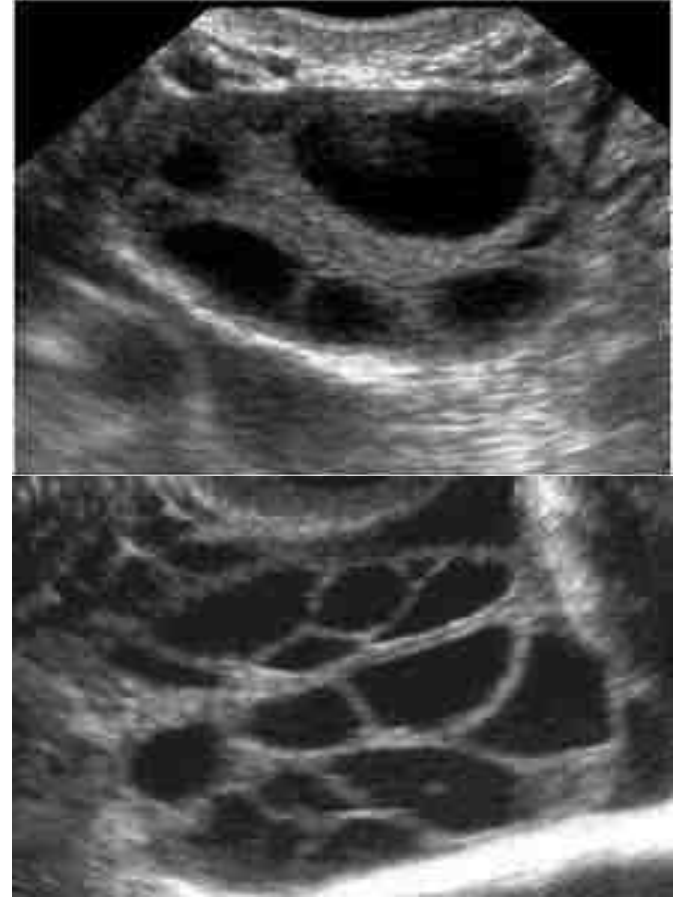
PCOS'lu hastalarda Ovulasyon indüksiyonundaki hedef

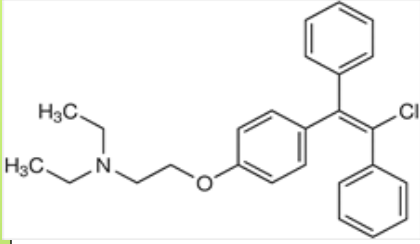
- Yeterli sayıda folliküler maturasyon sağlamak
- En ucuz tedavi ajanlarından başlamak, lüzumsuz yüksek doz ajan kullanmamak
- Düşük oranını minimum seviyede tutmak
- Çoğul gebelikten kaçınmak
- OHSS riskini minimumda tutmak
- İyi monitorizasyon
- İndüksiyon sonrası sağlıklı bir gebelik ve bebek elde edilmesi



Ol sonuçlarının deęerlendirilmesi

- Ovulasyon oranı ?
- Gebelik oranı ?
- Canlı doğum oranı?
- Düşük oranı ?
- Çoęul gebelik oranı ?
- Gebelik elde edene kadar geçen süre?





Klomifen Sitrat (CC)-SERM ANTIÖSTROJEN



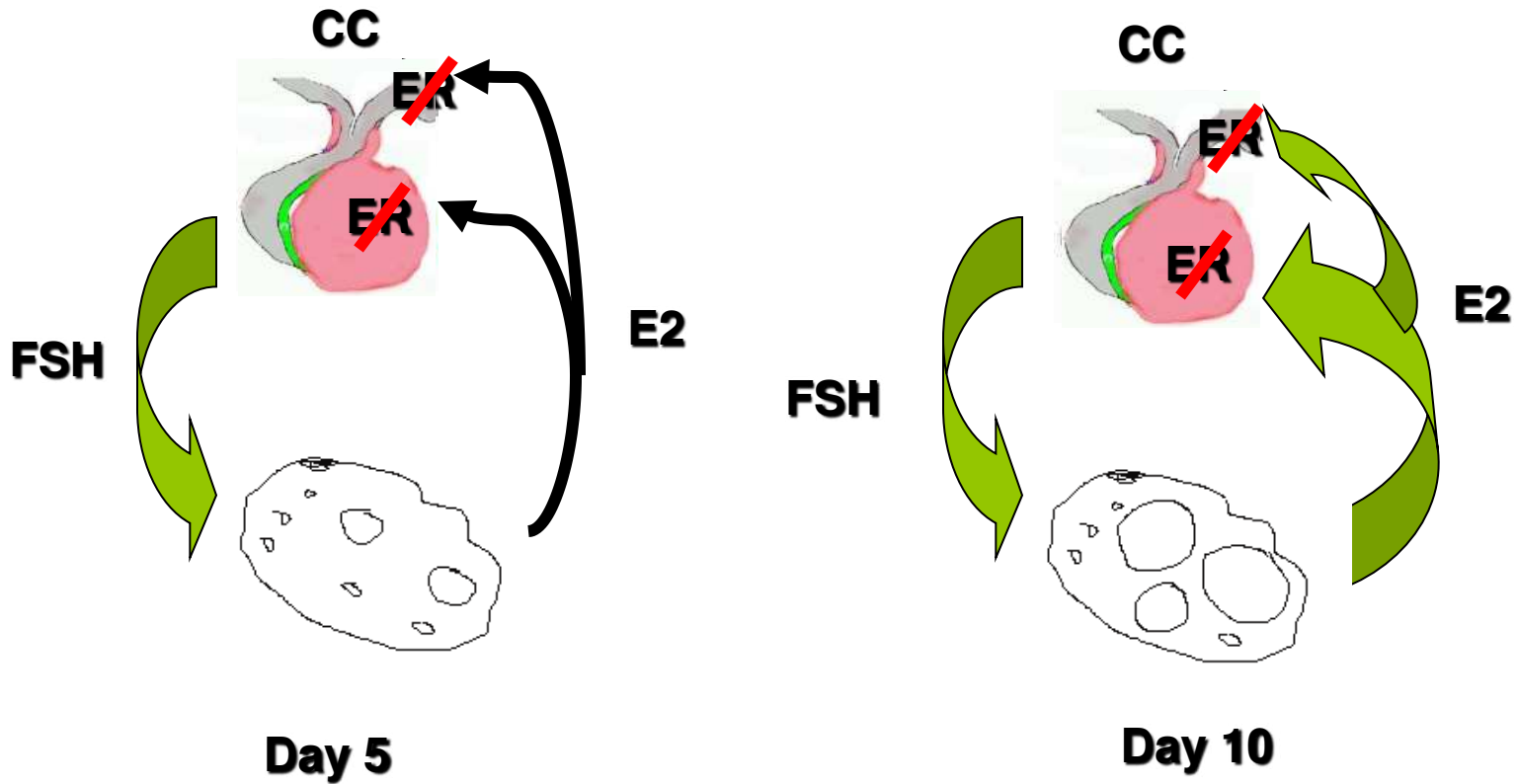
- Trifenyletilen derivesi

En-klomifen

Zu-klomifen

- Kompetitif östrojen(E) antagonisti (çok düşük E düzeylerinde agonistik etki)
- Oral alımı takiben karaciğerde metabolize olup feçesle atılır.
- Eliminasyonu :%85'i 6 günde, feçeste 6 hafta varlığı tespit edilmiş—zu-klomifenin birikici etkisi

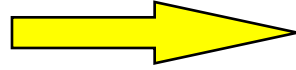
Clomiphene Citrate Treatment



Anovulasyon mekanizmaları

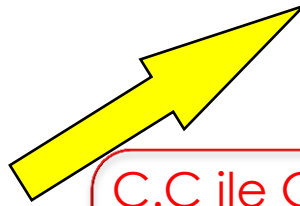
LH /FSH ↑

GnRH pulse
frekansı ↑



- LH pulse frekansı ↑
- FSH pulse frekansı değişmez

Hipofizer
GnRH
sensitivitesinde
artış

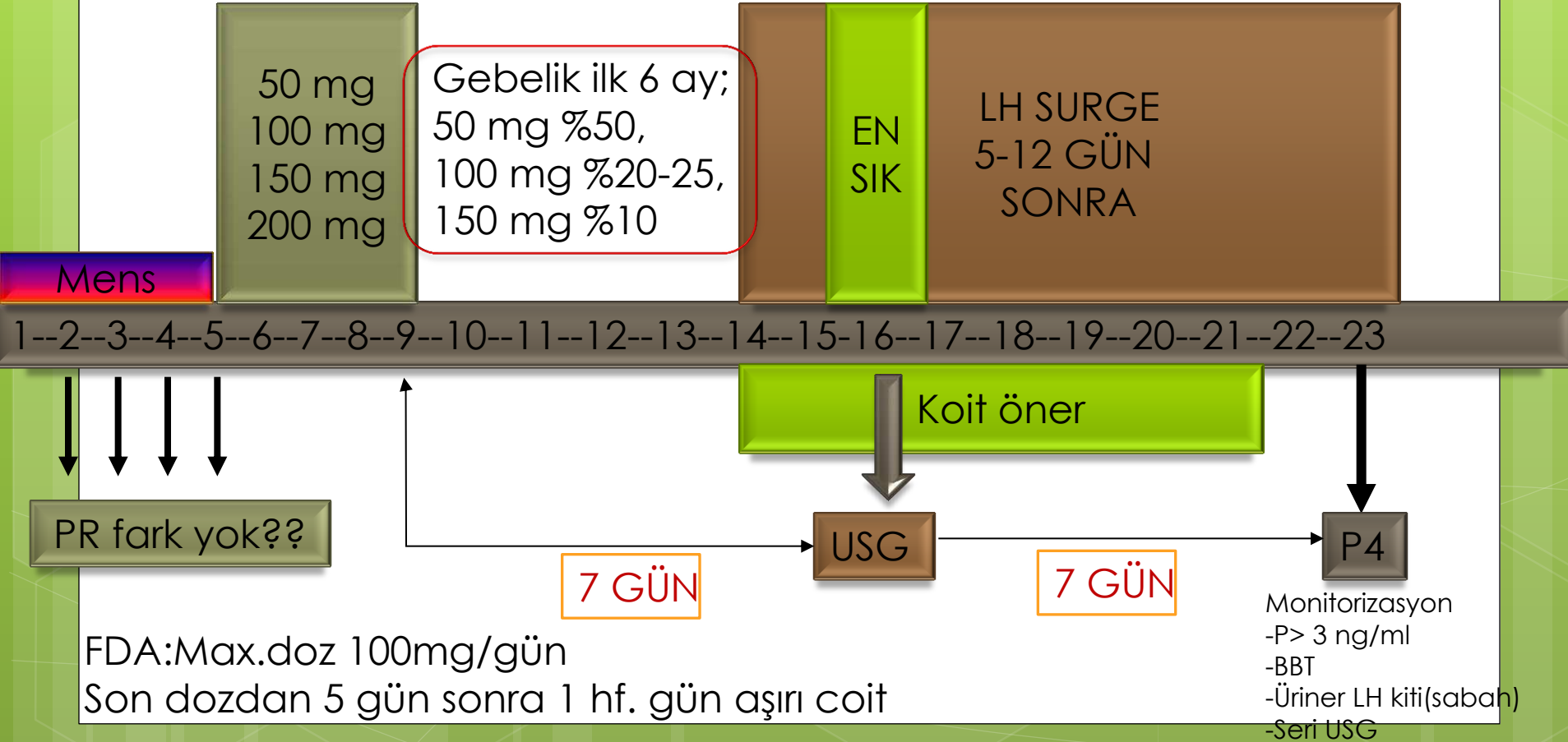


C.C ile GnRh puls amplitüdünü artar,
puls frekansını etkilemez

(Franks, 2005)

CC-KULLANIMI;

CC-5 GÜN-50+50mg,Ovulasyon, 4-6 siklus <12 siklus



C.C' NİN LİMİTASYONLARI

- CC ile %70-80 hastada ovulasyon sağlanır
- Ancak gebelik oranları %30-40'tır
- Endometrium üzerine östrojen antagonistik etki, azalmış kan akımı -azalmış embryo implantasyonu
- Artmış çoğul gebelik oranı-(%6.9-9 ikiz, %0.3-0.5 üçüz)
- Artmış yan etki sıklığı nedeniyle kullanımının kısıtlanması-**vazomotor semptomlar, baş ağrısı, mood değişikliği, visüel değişiklikler, ohss, ovaryan kist**
- Uzun yarılanma ömrü nedeniyle ve zu-clomifen metabolitinin birikici etkisi- olası fetal teratojenik etki!(Tulandi et al.Fertil & Steril.2006, CDC 2011)

C.C TEDAVİSİNDE TARTIŞMALI KONULAR

- *Tedaviye başlangıcı,spontan siklus mu, progesteron çekilme kanaması ile mi?*
- *Cevap alamazsak tedaviyi uzatabilir miyiz?*
- *Mid-siklus hCG verilmeli mi?*
- *CC ultrasound ile monitorize edilmeli mi?*
- *CC cevabı predikte edilebilir mi?*
- *C.C - Ne zaman keselim?*
- *C.C- Hala ilk seçenek mi?*

Endometrial Shedding Effect on Conception and Live Birth in Women With Polycystic Ovary Syndrome

Table 1. Pregnancy Outcomes in the Pregnancy in Polycystic Ovary Syndrome Trial as a Function of the Menstrual Status of the Preceding Cycle*

Menstrual Status Group	Cycles (n)	Ovulation		Conception			Live Birth			
		n	Ovulation per Cycle	n	Conception per Cycle	Conception per Ovulation	n	Live Birth per Cycle	Live Birth per Ovulation	Live Birth per Conception
Spontaneous menses	1,185	853	72.0	39	3.3	4.5	26	2.2	3.0	66.7
Anovulatory with progestin withdrawal	551	166	30.1	11	2.0	6.6	9	1.6	5.4	81.8
Anovulatory without progestin withdrawal	1,073	269	26.9	81	7.5	27.7	57	5.3	19.7	70.4
Total	2,809	1,308	46.6	131	4.7	9.9	92	3.3	7.0	70.1
P			<.001		<.001	<.001		<.001	<.001	NS

NS, not significant.

Data are % unless otherwise specified.

* Spontaneous menses, anovulation with progestin induced withdrawal bleed, and anovulation without progestin induced withdrawal bleed.

CC/Plasebo, Metformin/Plasebo, CC+Metformin/Plasebo

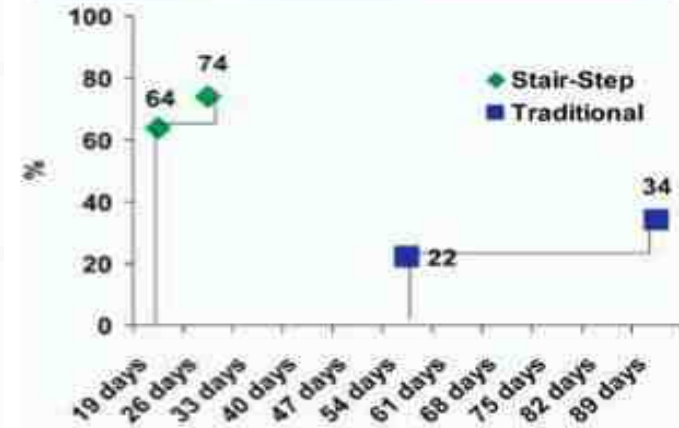
Diamond MP, Obstet Gynecol 2012

Novel clomiphene “stair-step” protocol reduces time to ovulation in women with polycystic ovarian syndrome

Bradley S. Hurst, MD; Jennifer M. Hickman, MD; Michelle L. Matthews, MD; Rebecca S. Usadi, MD; Paul B. Marshburn, MD

- 50 mg/gün başlangıç dozu ile 5 günlük Klasik CC uygulaması (D5-9)
- D14 TVUSG: yanıt (>10 mm foll) saptanmazsa
Hemen 100 mg/gün doz ile tekrar 5 günlük bir CC kürü başla (D14-18)
- D21 TVUSG: yanıt (>10 mm foll) saptanmazsa
Hemen 150 mg/gün doz ile tekrar 5 günlük bir CC kürü başla (D21-25)
- D28 TVUSG: Yanıt yoksa: CC rezistansı.

FIGURE
Time to ovulation
with both protocols



Ovulasyon oranı daha yüksek (%64vs%22) klinik gebelik oranı aynı (%13vs%15)



CC sikluslarında hCG mi verelim, üriner LH kiti mi kullanalım?

Agarwal & Buyalos, 1995 konsepsiyon oranlarında fark yok

Deaton et al, 1997

fark yok

Vlahos et al, 2005

hCG **faydalı olabilir**

Kosmas et al, 2007 (Meta-analiz)

Anovulatuarsa-hCG

AMA anlamlı fark yok

Ovulatuarsa -LH

Brown et al, 2009 (Cochrain review)

fark yok

hCG yapılacaksa dominant follikül **23-28mm** en yüksek gebelik

Palatnik A. Fertil Steril 2012

C.C+ IUI yapılacaksa, hCG ve LH kiti kombine gebelik oranları yüksek

Mitwally&Casper ,2004



Ultrason ile monitorize edelim mi?

	With U/S + hCG	No U/S or hCG
n	105	150
Cumulative pregnancy rate	48%	34.7%
Deliveries	35.6%	26.7%
Multiple pregnancies	0	1

Konig, Homburg et al, ESHRE, 2009

Fertility

Assessment and treatment for people with fertility problems

Issued: February 2013

NICE clinical guideline 156
guidance.nice.org.uk/cg156

- 1.5.2.3 For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. [2013]

ASRM 2013-COMMITTEE OPINION:

Nevertheless, regular contact with the patient should be maintained to review response to treatment and to ensure that any additional evaluation or alternative treatment that may be required is not delayed.

C.C İLE TEDAVİYE-NE KADAR DEVAM EDİLMELİ?

- **CC Başarısızlığı (CCF):** 6 siklus maksimum dozla ovulasyona rağmen gebelik elde edilememesi
- **CC Direnci (CCR):** Maksimum doza rağmen (150mg/gün) 2-3 siklus ovülasyonun olmaması (%15-40)

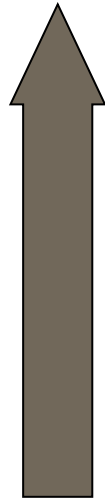
- 150 mg/gün ovulasyon (-)
- 6 ovulatuar siklus rağmen gebelik yok
- Ovulasyon + ama endometrial kalınlık < 7mm ise



Homburg R. 2011 ÜTD-ANTALYA

ovulasyon başarısız

- FAI
- BMI
- LH
- İnsülin



Ovulasyon+

Gebelik (-)

- Anti-estrojenik etkiler
 - Servikal mukus
 - Endometrium
- ↑ LH düzeyi

- Homburg R, 2011

Tedavi başarısızlığı ile artmış BMI arasında anlamlı ilişki vardır. BMI >27.2 kg/m²

Milsom SR,2002

GENETİK PREDISPOZİSYON !...

Overbeek 2007

DİRENÇLİ VAKALAR???



Obesite

Over seviyesinde FSH'a yanıtta lokal intra-ovaryan otokrin ve parakrin faktörler

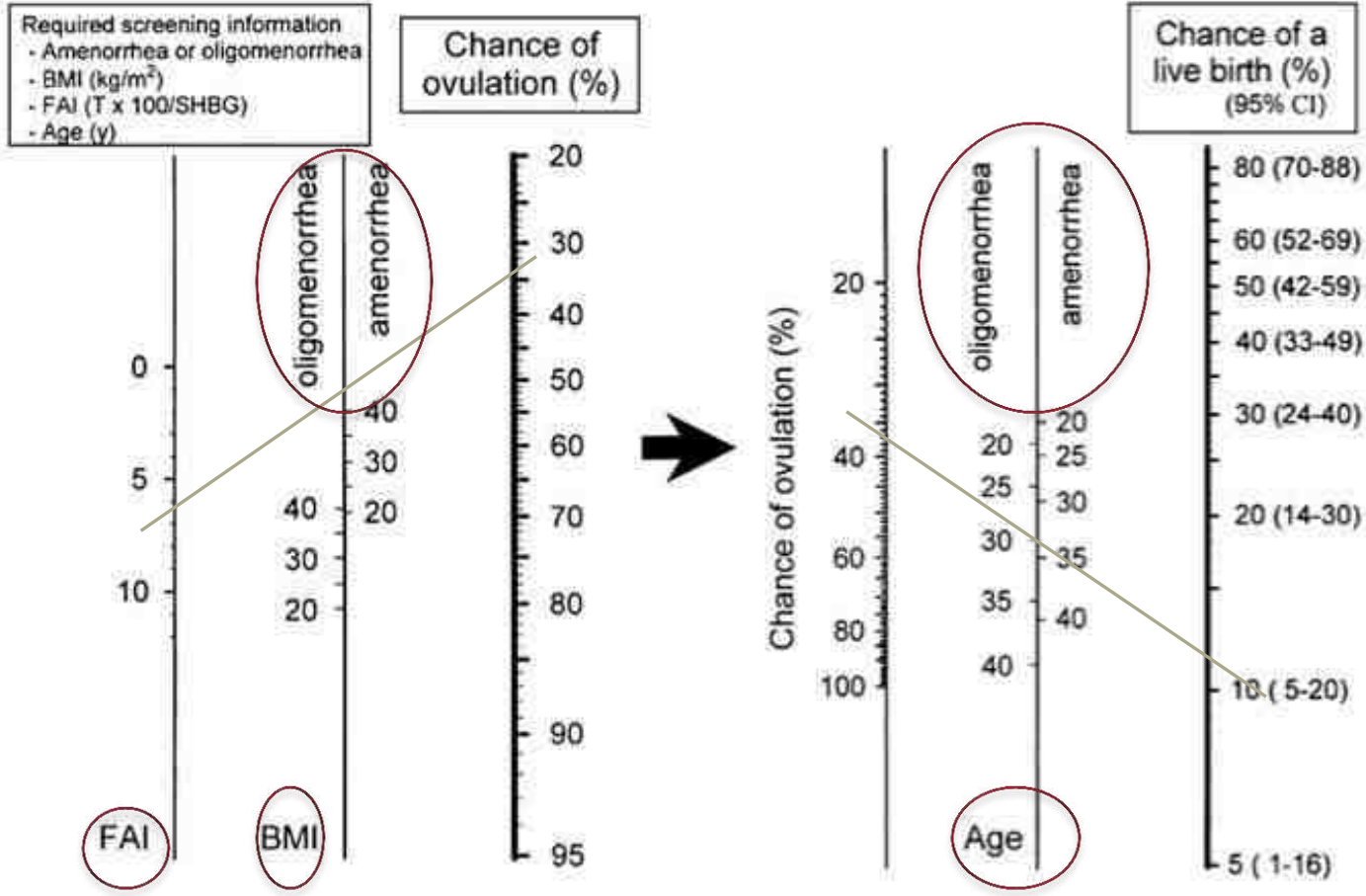
FSH reseptör ekspresyonu veya reseptörlerdeki polimorfizmin rol oynadığı düşünülmektedir

Yüksek AMH düzeyleri?...

PREDİKTE EDEBİLİR MİYİZ?

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91-7. Used with permission.)



Tarlatzis. Consensus on infertility treatment related to PCOS. Fertil Steril 2008.

Serum Leptin ve açlık kan insülin/ glukoz oranı . Imani 2000
 Bu nomogram C.C ye cevapsızların %80'nini predikte edebilir Ghobadi et al 2007

Clomiphene citrate resistance in relation to follicle-stimulating hormone receptor Ser680Ser-polymorphism in polycystic ovary syndrome

A. Overbeek^{1,4}, E.A.M. Kuijper¹, M.L. Hendriks¹, M.A. Blankenstein², I.J.G. Ketel¹, J.W.R. Twisk³, P.G.A. Hompes¹, R. Homburg¹, and C.B. Lambalk¹

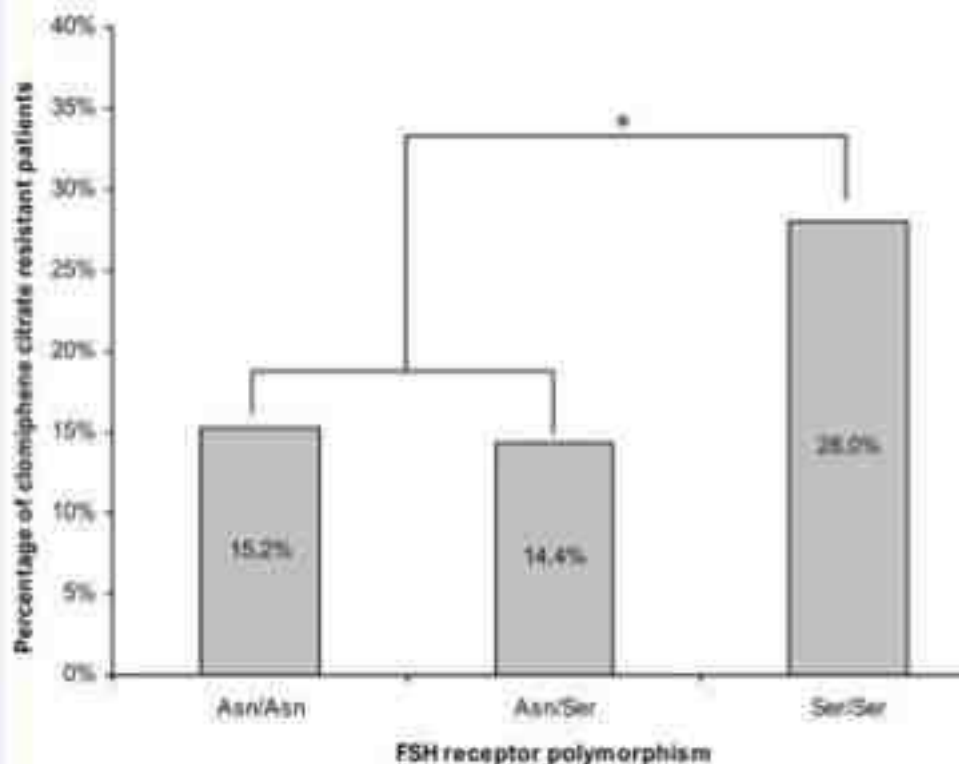


Table III Logistic regression model

Model	OR	P-value	95% CI
Model 1	0.44	0.04*	0.205–0.965
Dependent variable: ovulation			
Predictive variable: FSHR			
Model 2	0.26	0.03*	0.085–0.845
Dependent variable: ovulation			
Predictive variables: FSHR			
Independent variables: FSH, BMI, age, amenorrhea, mean ovarian volume and hyperandrogenism			

*P < 0.05.

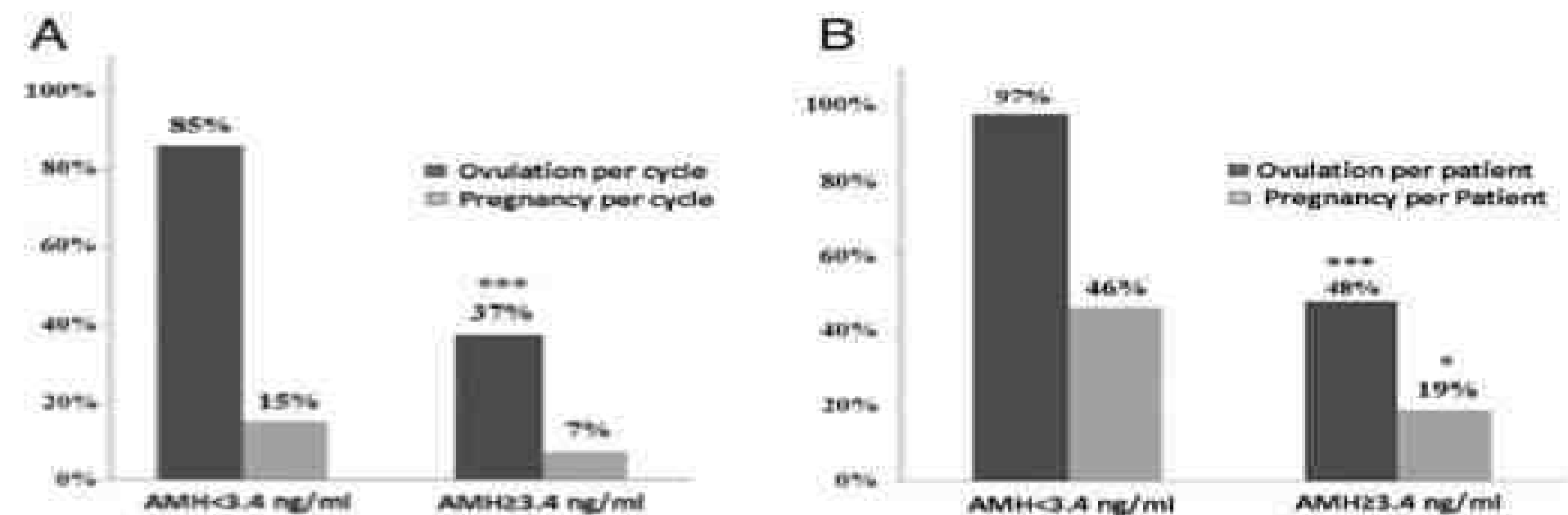
Table II Characteristics of clomiphene responders and non-responders

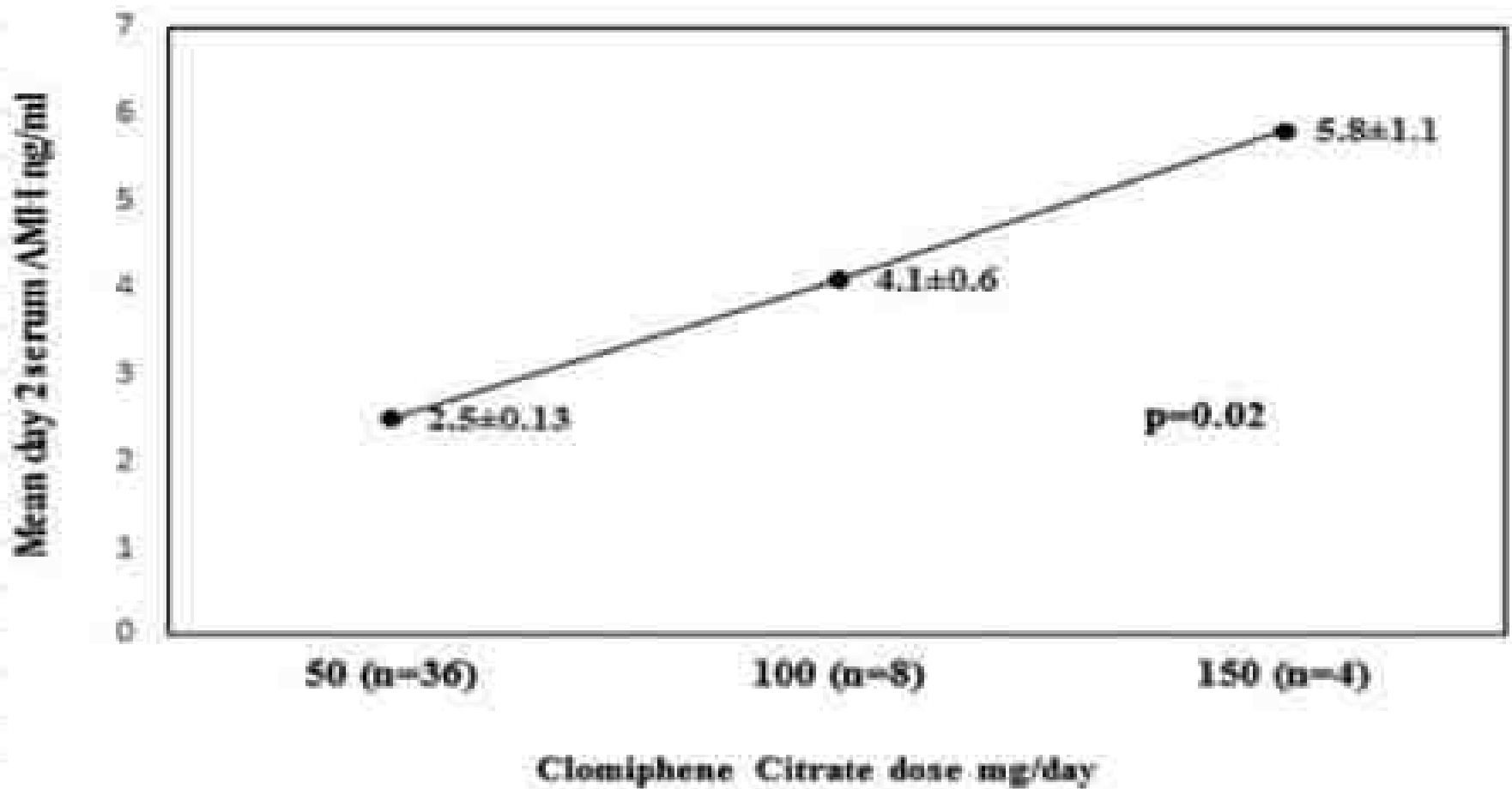
	Ovulatory (n = 158)	Clomiphene resistant (n = 35)	P-value
Age (year)	29.1 ± 4.2	27.0 ± 4.6	0.009*
Range	19–40	20–36	
Body mass index (kg/m ²)	23.6	26.3	0.039**
Range	14.5–47.4	17.6–41.6	
Testosterone (nmol/l)	1.82 ± 1.1	2.08 ± 1.1	0.222
Range	0.5–8.2	0.5–5.9	
Androstenedione (nmol/l)	8.88 ± 3.5	9.77 ± 3.6	0.208
Range	3.1–23.0	3.7–17.9	
Luteinizing hormone (IU/l)	11.0 ± 5.6	11.0 ± 4.5	0.981
Range	2.1–30.0	1.9–26.0	
Follicle-stimulating hormone (IU/l)	5.85 ± 1.4	5.05 ± 1.6	0.003*
Range	1.8–10.0	2.5–10.0	
Estradiol (pmol/l)	150.6 ± 67.6	151.4 ± 68.7	0.952
Range	47–499	43–376	
Dehydroepiandrosterone (μmol/l)	5.14 ± 2.3	5.87 ± 2.9	0.142
Range	1.4–12.0	0.6–16.0	
Mean ovarian volume (ml)	11.2 ± 5.5	12.0 ± 4.0	0.551
Range	3.3–32.4	5.6–18.5	
Amenorrhea (n)	33 (20.9%)	6 (17.1%)	0.618
Polycystic ovaries on ultrasound (n)	142 (89.9%)	32 (91.4%)	0.832
Clinical hyperandrogenism (n)	51 (32.3%)	8 (22.9%)	0.274
Biochemical hyperandrogenism (n)	74 (49.7%)	18 (54.5%)	0.612

The Predictive Value of Circulating Anti-Müllerian Hormone in Women With Polycystic Ovarian Syndrome Receiving Clomiphene Citrate: A Prospective Observational Study

YENİ BİR PREDİKTİF MARKIR...AMH

Ahmad Mahran, Ayman Abdelmeged, Ahmad Reda El-Adawy, Moustafa K. Eissa, Robert W. Shaw, and Saad A. Amer





Yüksek AMH düzeyi olanlara daha yüksek başlangıç dozu gerekir
Çok yüksek AMH düzeyi olan PCOS'lu hastalarda C.C ted
atlanarak direk Gonadotropin ile başlanabilir

NE KADAR DEVAM EDELİM?

- 6 siklus tedavi sonrasında ovulasyon oranı yüksek olmasına rağmen gebelik oranları % 50-60 oranlarında seyreder
- 6-9 siklus arasındaki tedavilerde kümülatif gebelik oranı %70-75
- NICE 2004** 6 siklus sonrası kümülatif gebelik oranı artmaya devam ettiği için 12 sıklusa kadar öneriyor

Imani 2002

Messinis 2002

Homburg R 2005

How long should we continue clomiphene citrate in anovulatory women?

N.S. Weiss^{1,2,3}, S. Braam^{1,4}, T.E. König², M.L. Hendriks², C.J. Hamilton⁴, J.M.J. Smeenk⁵, C.A.M. Koks⁶, E.M. Kaaijk³, P.G.A. Hompes², C.B. Lambalk², F. van der Veen¹, B.W.J. Mol¹, and M. van Wely^{1,*}

Table I Baseline characteristics.

	114 women recruited
Age years (mean ± SD)	30.4 ± 4.8
BMI kg/m ² (mean ± SD)	25.0 ± 5.4
Primary subfertile n (%)	76 (67)
Duration of subfertility years (mean ± SD)	1.4 ± 0.9
LH IU/l (mean ± SD)	8.8 ± 5.0
FSH IU/l (mean ± SD)	5.8 ± 1.7
Total motile sperm count × 10 ⁶ (median, min–max)	63 (3–557)

Table II Ongoing pregnancies per cycle.

Cycle number	Women	Ongoing pregnancies per cycle
7	114	8 (7%)
8	94	3 (3%)
9	80	12 (15%)
10	62	3 (5%)
11	45	6 (13%)
12	29	3 (10%)

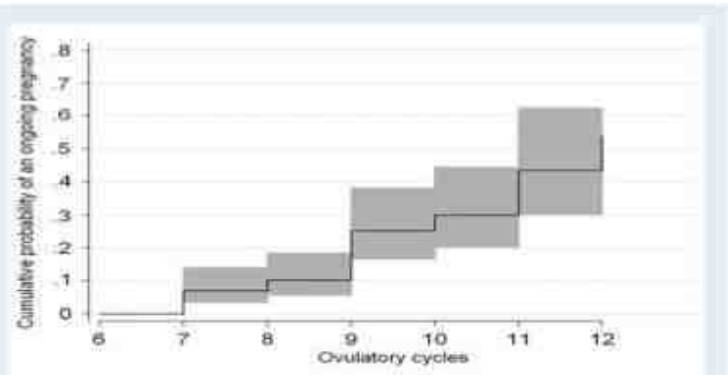


Figure 1 Cumulative probability of an ongoing pregnancy.

NICE 2013

1.5.2 WHO Group II ovulation disorders

1.5.2.4 For women who are taking clomifene citrate, do not continue treatment for longer than 6 months. [new 2013]

Use of clomiphene citrate in infertile women: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

2013

Failure to conceive after 3 to 4 successful CC-induced ovulation cycles is indication for further evaluation to exclude other contributing causes of infertility, particularly in women >35 years of age

C.C REZİSTANS PCOS HASTALARINDA METFORMİN OVULASYON İNDÜKSİYONUNDA İLK TERCİH OLABİLİRMİ?

- PCOS'lu hastaların %50-70'inde **IR** (İnsülin rezistansı) mevcut
- Hiperinsülinemi PCOS 'daki Hiperandrojenemiye katkıda bulunmakta
Legro 2004
- Metformin, sentetik bir biguanid, Tip 2 Diabet tedavisinde kullanılıyor
- Primer Klinik etki; Hepatik glucose üretimini inhibe eder, intestinal glukoz uptake'ı azaltır, periferel dokularda insulin sensitivitesini arttırır Grundy SM 2002
- İnsülin düzeylerini düşürür, glukoz düzeyini etkilemez
- Hedef doz; 1500–2550 mg/gün (500 veya 850 mg 3x1) Harbone LR. 2005
- Bulantı, kusma GI rahatsızlık gibi önemli yan etkileri görülebilir. Lord JM,2003.

PCOS/CC/ REZİSTANSINDA METFORMİN OVULASYONA NASIL ETKİ EDİYOR?

- İntrafolliküler steroidogenez üzerine etki ederek granüloza hüç.de IGF 1'i arttırıyor

KOCAK M,2002

- Teka-interna hüç.de androjen sentezini inhibe ediyor

ATTIA

GR,2001

Hepatik SHBG sentezini artırarak fTestosteronu azaltır

- Adrenal steroidogenezi azaltır

la MARCA A,1999

- Hipotalamo-hipofizer aksa etki ederek serum LH ve PRL düzeylerini azaltır

BİLLA E,2009

TABLE 2

Randomized trial from the National Institutes of Health Reproductive Medicine Network.

	CC	Metformin	Combination
N	209	208	209
Ovulation	49 ^a	29	60 ^b
Conception	20 ^a	12	38 ^a
Pregnancy	24 ^a	9	31 ^a
Live birth	23 ^a	7	27 ^a
Multiple	6	0	3

Source: Legro et al., N Engl J Med 2007;356:551–66.
Used with permission.

^a $P < .001$.

^b $P < .001$ (combination vs. clomiphene citrate [CC]).

Tarlatzis. Consensus on infertility treatment related to PCOS. Fertil Steril 2008.

CC Rezistansında Metformin?

Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008)
Consensus on infertility treatment related to polycystic ovary syndrome.
Fertil Steril 89:505–522.

- Sadece glukoz intoleransı olanlarda kullanım ile sınırlanmalı
- Ovulasyon indüksiyonu basamakları arasında yeri yok
- CC dirençli vakalarda GN veya LOD basamaklarına geçilmeli

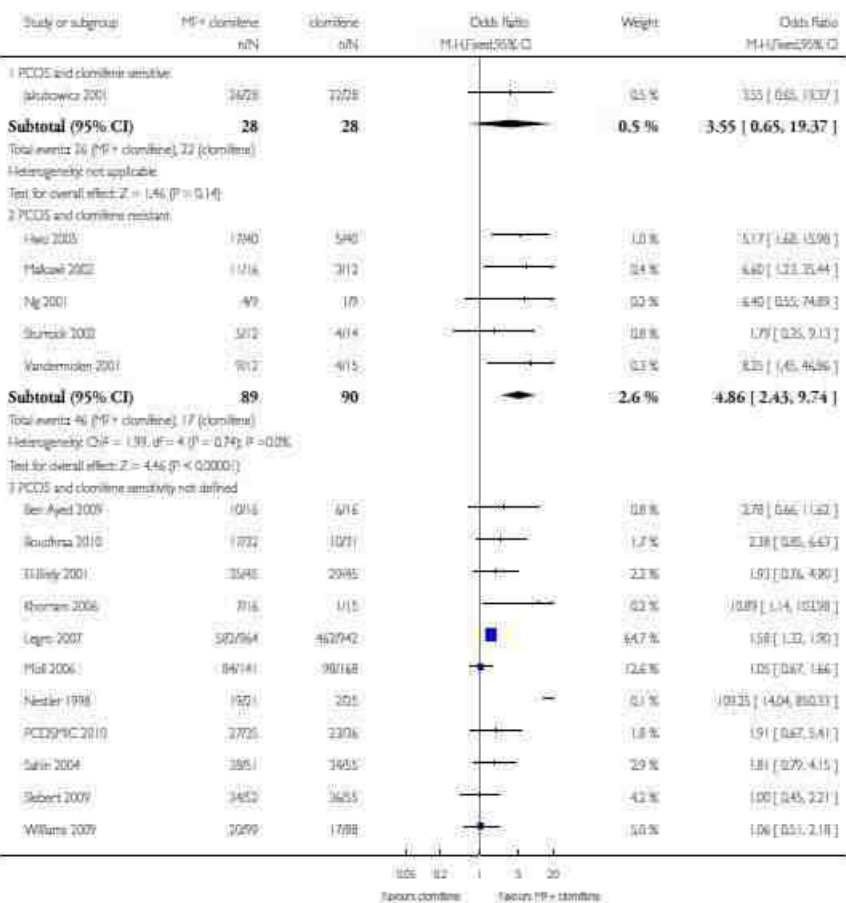
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility

Tang et al. Cochrane Library 2012

Review: Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility

Comparison: 2 Metformin combined with ovulation induction agent, clomifene versus clomifene alone

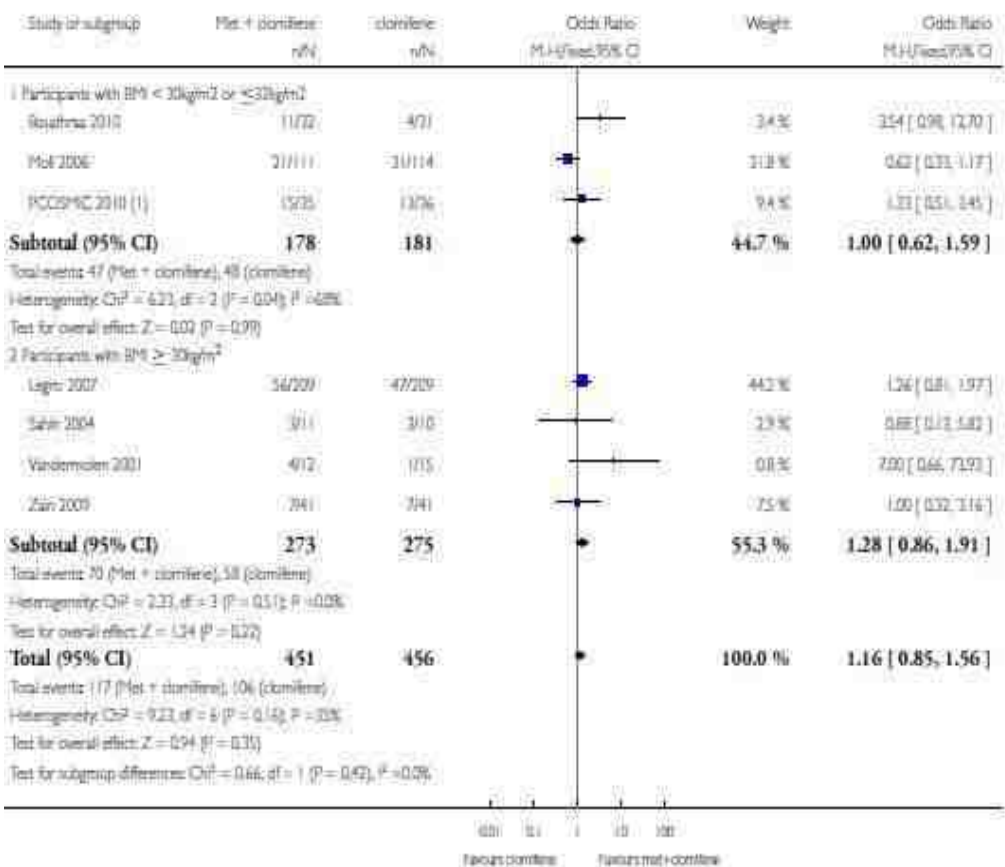
Outcome: 4 Ovarian rate (grouped by sensitivity to clomifene)



Review: Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility

Comparison: 2 Metformin combined with ovulation induction agent, clomifene versus clomifene alone

Outcome: 1 Live birth rate



CC REZİSTAN PCOS'LULARDA CC+METFORMİN KOMBİNE TED. SADECE CC' YE GÖRE OVULASYON VE KLİNİK GEBELİK ORANLARINA İYİ ETKİLİ AMA CANLI DOĞUM ORANLARINI ARTIRMİYOR.

Analysis 2.5. Comparison 2 Metformin combined with ovulation induction agent clomifene versus clomifene alone, Outcome 5 Ovulation rate (grouped by BMI).

Review: Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-choletholol) for women with polycystic ovary syndrome, oligo-amenorrhoea and subfertility

Comparison: 2 Metformin combined with ovulation induction agent clomifene versus clomifene alone

Outcome: 5 Ovulation rate (grouped by BMI)

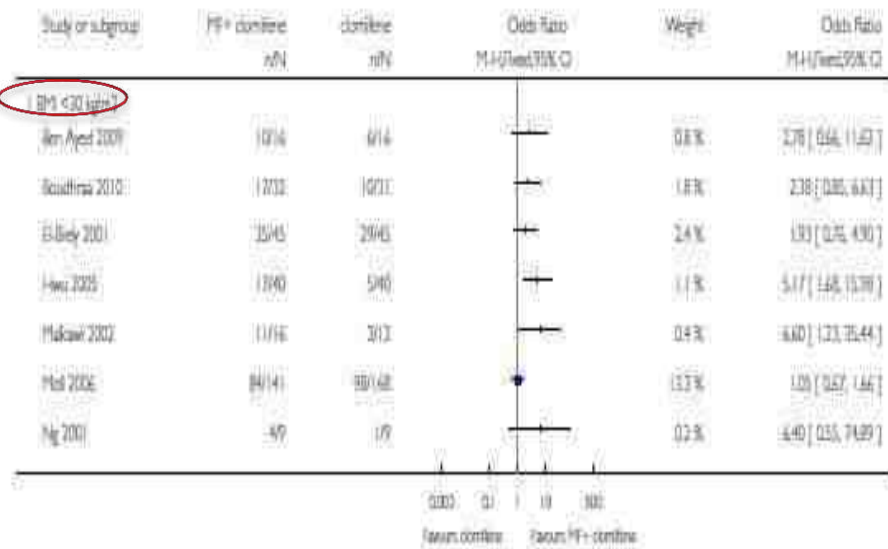


Figure 8. Forest plot of comparison: 3 Metformin versus clomiphene citrate, outcome: 3.1 Live birth:

Participants with BMI < 30kg/m² or < 32kg/m²

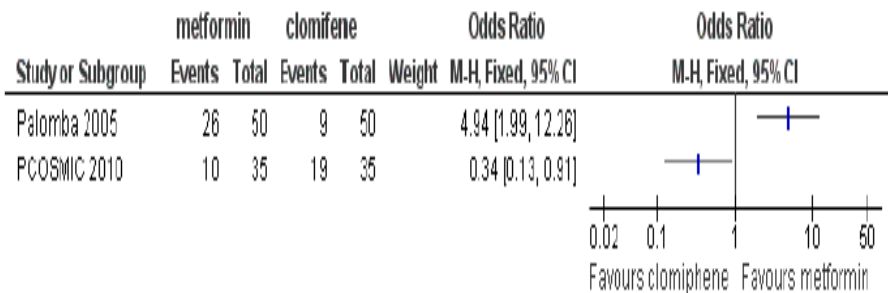
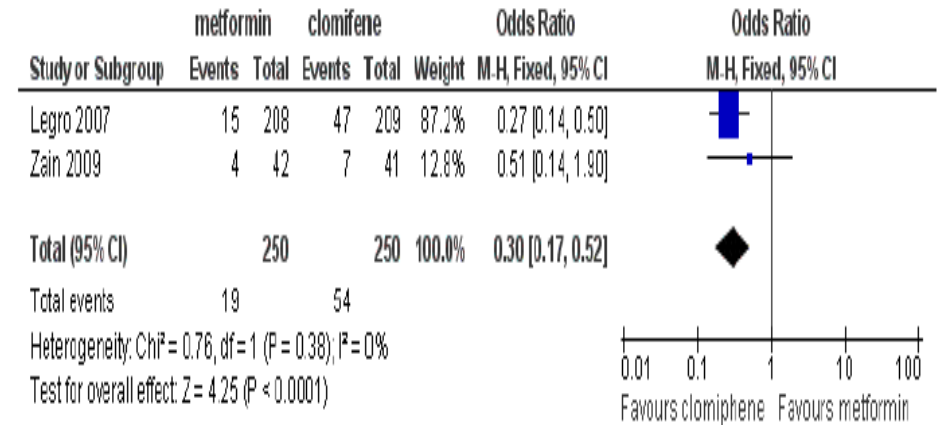


Figure 9. Forest plot of comparison: 3 Metformin versus clomiphene citrate, outcome: 3.2 Live birth:
Participants with BMI > 30kg/m²

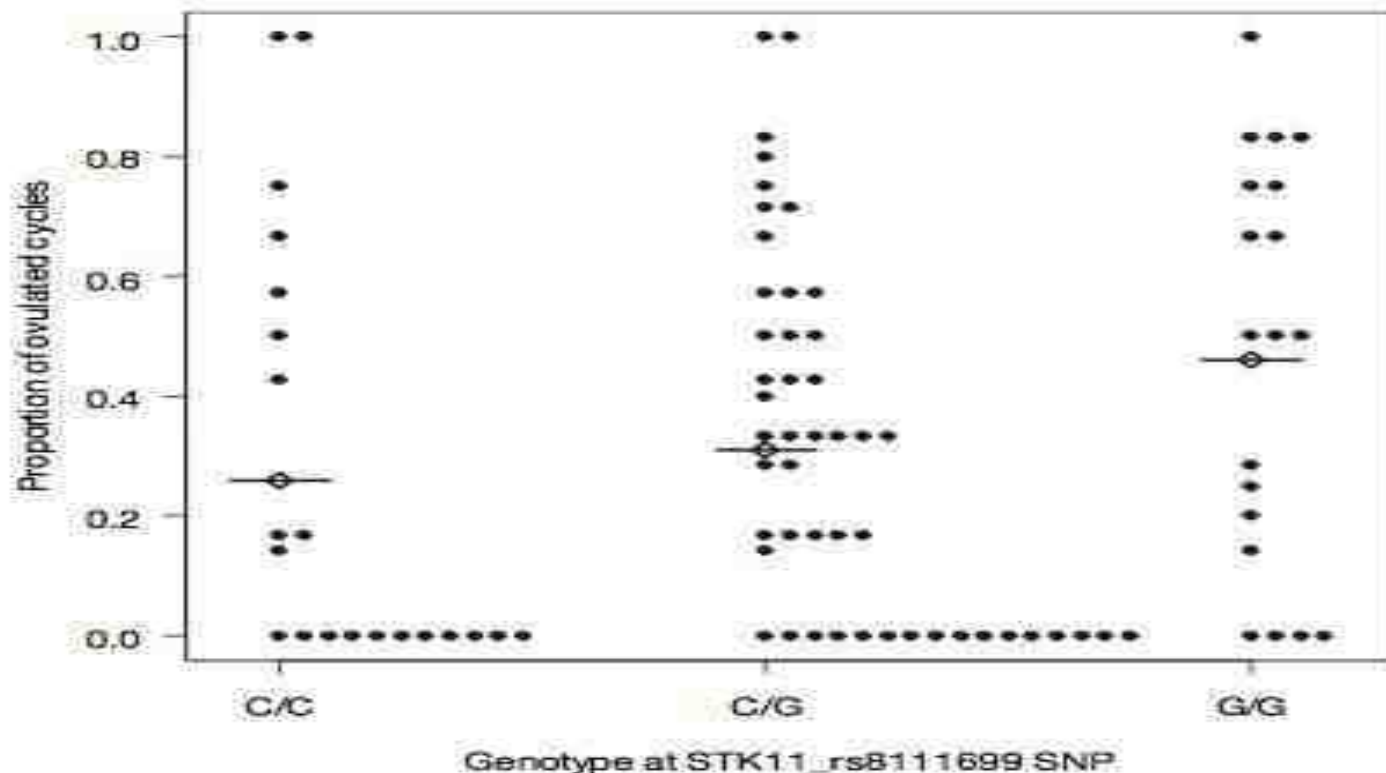


BMI < 30 kg/m² olanlarda
MET+CC > CC > MET

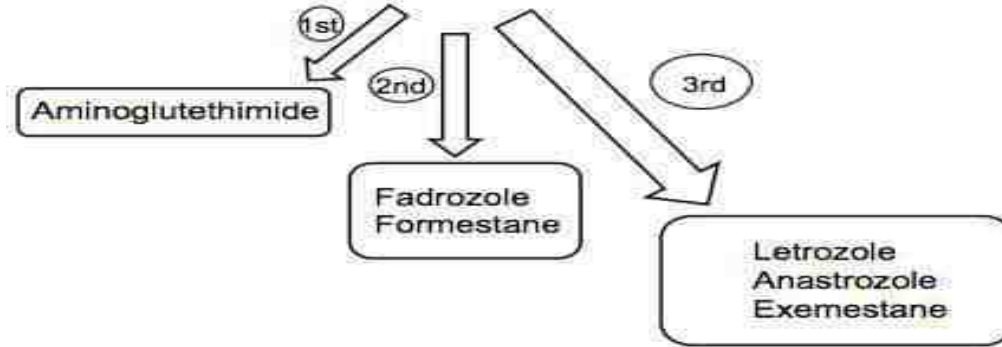
Ovulatory Response to Treatment of Polycystic Ovary Syndrome Is Associated with a Polymorphism in the *STK11* Gene

Richard S. Legro, Hussein X. Barnhart, William D. Schlaff, Bruce R. Carr, Michael P. Diamond, Sandra A. Carson, Michael P. Steinkampf, Christos Coutifaris, Peter G. McGovern, Nicholas A. Cataldo, Gabrielle G. Bosman, John E. Nestler, Lloyd C. Giudice, Kathryn G. Ewerts, Richard S. Spermin, Phyllis C. Leppert, and Earl R. Myers for the Reproductive Medicine Network*

J Clin Endocrinol Metab, March 2008, 93(3):792–800



Aromataz İnhibitörleri ovulasyon indüksiyonunda ilk tercih olabilir mi?



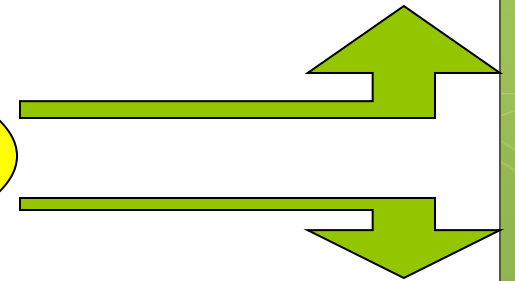
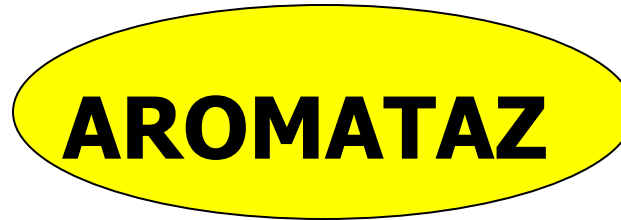
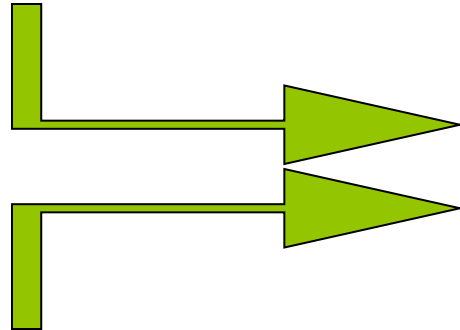
- Aromatazın inhibisyonu ile hipotalamo-pituitar aksın estrojen (-) feedback etkisinden yararlanılarak gonadotropin sekresyonunun artışı ve ovaryan folikül gelişiminin uyarılması gerçekleşir
- Siklusun 3-7.günleri arasında 2,5mg letrozole/gün verilen PCOS olgularında %75 ovulasyon ve %25 gebelik sağlanmıştır
- Endometrial kalınlık 10mm'nin üzerinde
- Folikül sayısı da CC'ye göre daha fazladır

Aromataz inhibitörleri- Etki mekanizması

- Aromataz enzimi, sitokrom p450 enzim kompleksine ait 19 karbonlu androjenlerin 18 karbonlu östrojenlere dönüşümü sırasında birbirini izleyen üç hidroksilasyon basamağını katalizleyen bir enzimdir.
- Aromataz inhibitörleri, testesteronun estradiole ve androstenedionun estrona çevrilmesini inhibe ederler

Androstenedion

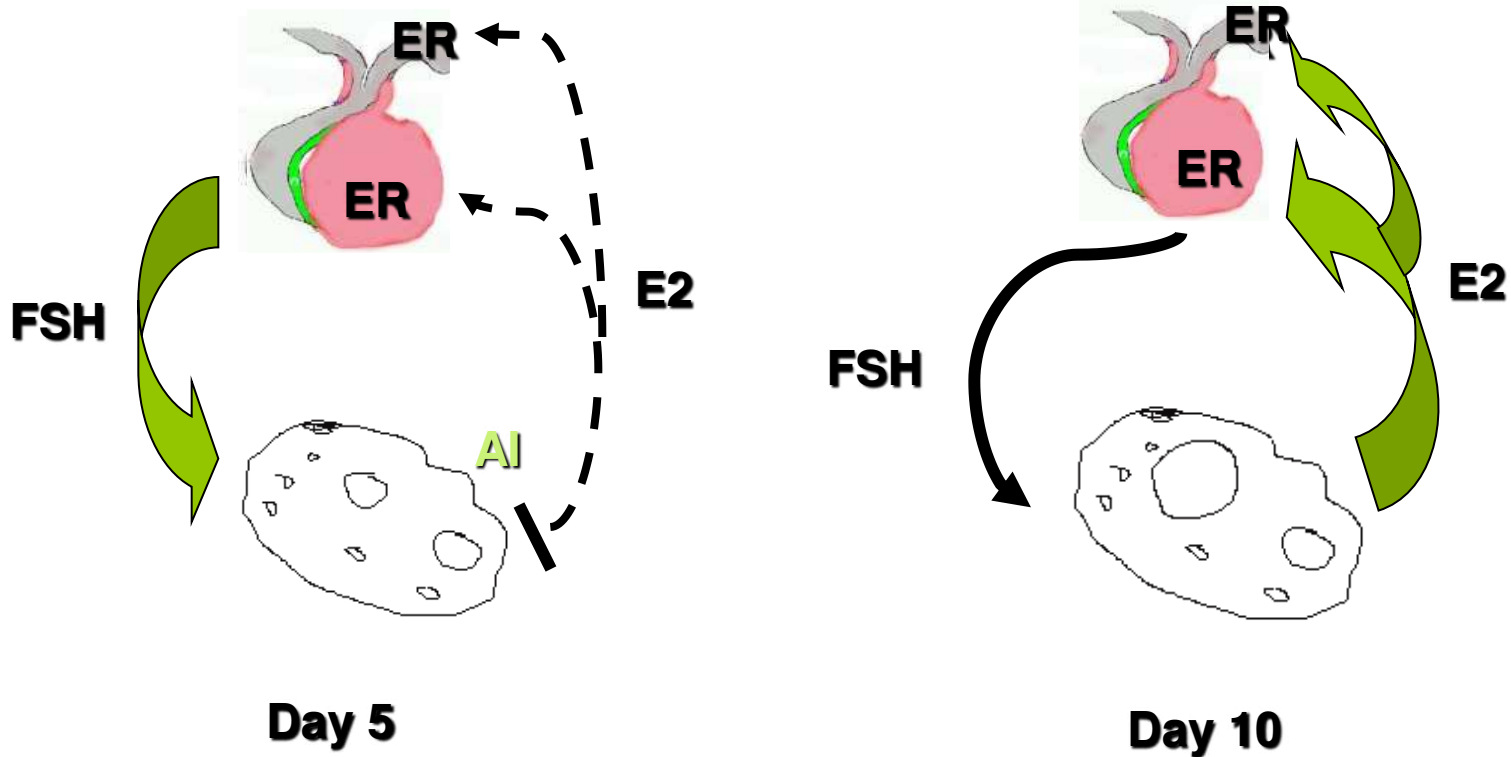
Estron



Testosteron

Estradiol

Aromatase Inhibitor Treatment



Lokal olarak intraovaryan androjenlerin artımı FSH reseptor gen ekspresyonunu artırdığı için FSH'a olan yanıt da artmaktadır

Weil S 1999

Casper & Mitwally

Aromatase inhibitors

Generation	Steroidal (type 1)	Nonsteroidal (type 2)
First (nonselective)	-	Aminoglutethimide
Second (selective)	Formestane	Fadrozole
Third (superselective)	Exemestane (Aromasin)	Anastrozole (Arimidex)
		Letrozole (Femara)

LETROZOL-KULLANIMI;

OFF-LABEL!!!

LET-5 GÜN-2.5+2.5mg,
3. günde tek doz olarak 20 mg Mitwally MF,Casper RF 2005

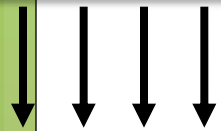
2.5 mg
5mg
7.5 mg

Mens

EN
SİK

LH SURGE
5-12 GÜN
SONRA

1--2--3--4--5--6--7--8--9--10--11--12--13--14--15--16--17--18--19--20--21--22--23



PR fark yok??

Koit öner

USG

7 GÜN

7 GÜN

P4

Monitorizasyon
-P> 3 ng/ml
-BBT
-Üriner LH kiti(sabah)
-Seri USG

FDA:Max.doz 7.5mg/gün
Son dozdan 5 gün sonra 1 hf. gün aşırı coit

Doz

2.5 – 5 mg / gün 3-7. günler- 5 gün veya 10 gün

7.5 mg ile endometrium üzerine C.C.ye benzer etki

Al Fozan H 2004

10 gün 2.5 mg / 5 gün 5mg'a göre daha başarılı

Badawy2009

3. günde tek doz olarak 20 mg

Mitwally MF,Casper RF 2005

Letrozolün

C.C'ye göre Teorik Avantajları:

- Estrogen reseptörlerini bloke etmez, negative feedback mekanizma devam etmez-multiple folliküler gelişme daha az
- Çoğul gebelik ve OHSS riski daha az
- Endometrium yada servikal mukusa antiöstrojenik etkisi yok
- O.İ sırasında oluşan suprafizyolojik östrojen düzeylerini azaltarak implantasyona olumlu etki, endometrial reseptiviteye olumlu etki...
- Letrozolün yan etkileri daha az (**vazomotor semptomlar, G.İ.rahatsızlık, bacak krampları**)—kısa kullanım sürelerinde CC'ye göre daha iyi tolere edildiği gösterilmiş
- Yarılanma ömrü (45-48 saat) daha kısa ve son dozdan 10-12 gün sonra vücuttan tamamen temizlenir (Casper&Mitwally MFM-2006)—İmplantasyona kadar elimine olacağı düşünülmekte-Fetal toksisite riski az

C.C VE LETROZOL İÇİN FETAL GÜVENİRLİLİK-- X GRUBU--

Letrozol ile konjenital kardiyak ve kemik malformasyonlarında artış???(n=150 yenidoğan)

Biljan MM 2005-ASRM

Letrozol ile C.C'ye göre daha az konjenital kardiyak anomali! (n=911)

Tulandi T 2006

C.C ve Letrozol ile konjenital anomalilerde artış yok, C.C grubunda LBW insidansı yüksek!

Forman R 2007

C.C ile nöral tüp defektleri ve hipospadias riskinde hafif bir artış!

Elizur SE 2008

HAYVANLAR ÜZERİNDE TERATOJEN ETKİ!...

Human Reproduction Vol.23, No.8 pp. 1719–1723, 2008

doi:10.1093/humrep/den100

Advance Access publication on May 15, 2008

Effects of the aromatase inhibitor letrozole on *in utero* development in rats

G.M. Tiboni^{1,3}, F. Marotta¹, C. Rossi² and F. Giampietro¹

Table II. Types and frequencies of vertebral morphological anomalies observed in Sprague–Dawley rat fetuses exposed to letrozole.*

Dose (mg/kg)	0	0.01	0.02	0.04
<u>Fetuses with vertebral anomalies</u>	6/98 (6.1%)	19/59 (32.2%) [†]	17/58 (29.3%) [†]	27/64 (42.2%) [†]
Type of vertebral anomaly [‡]				
Thoracic vertebrae				
Bipartite centrum	2/98 (2.0%)	1/59 (1.7%)	1/58 (1.7%)	4/64 (6.2%)
Bipartite ossification of centrum	1/98 (1.0%)	2/59 (3.4%)	5/58 (8.6%)	0/64 (0.0%)
Dumbbell ossification of centrum	2/98 (2.0%)	15/59 (25.4%)	12/58 (20.7%)	25/64 (39.1%)
Lumbar vertebrae				
Dumbbell ossification of centrum	1/98 (1.0%)	1/59 (1.7%)	3/58 (5.2%)	2/64 (3.1%)

*Rats received letrozole (or vehicle) in drinking water during gestation days 6–16. [†]A single fetus may be represented more than once in listing individual morphologic abnormalities. [‡]Statistically significant ($P < 0.05$, χ^2 test) versus control group.

Congenital Malformations among Babies Born Following Letrozole or Clomiphene for Infertility Treatment

Sunita Sharma^{1*}, Sanghamitra Ghosh¹, Soma Singh¹, Astha Chakravarty¹, Ashalatha Ganesh², Shweta Rajani¹, B. N. Chakravarty¹

¹ Institute of Reproductive Medicine, Kolkata, West Bengal, India, ² School of Medical Science and Technology, Indian Institute of Technology, Kharagpur, India

Abstract

Context: Clomiphene citrate (CC) is the first line drug for ovulation induction but because of its peripheral antiestrogenic effect, letrozole was introduced as the 2nd line drug. It lacks the peripheral antiestrogenic effect and is associated with similar or even higher pregnancy rates. Since letrozole is a drug for breast cancer, its use for the purpose of ovulation induction became controversial in the light of studies indicating an increased incidence of congenital malformations.

Aims: To evaluate and compare the incidence of congenital malformations among offsprings of infertile couples who conceived naturally or with clomiphene citrate or letrozole treatment.

Settings and Design: A retrospective cohort study done at a tertiary infertility centre.

Methods and Material: A total of 623 children born to infertile women who conceived naturally or following clomiphene citrate or letrozole treatment were included in this study. Subjects were sorted out from medical files of both mother and newborn and follow up study was done based on the information provided by parents through telephonic conversations. Babies with suspected anomaly were called and examined by specialists for the presence of major and minor congenital malformations. Other outcomes like multiple pregnancy rate and birth weight were also studied.

Results: Overall, congenital malformations, chromosomal abnormalities were found in 5 out of 171 (2.9%) babies in natural conception group and 5 out of 201 babies in the letrozole group (2.5%) and in 10 of 251 babies in the CC group (3.9%).

Conclusions: There was no significant difference in the overall rate of congenital malformations among children born to mothers who conceived naturally or after letrozole or CC treatment.

Key Messages: Congenital malformations have been found to be comparable following natural conception, letrozole and clomiphene citrate. Thus, the undue fear against letrozole may be uncalled for.

Table 4. Comparison of Congenital Malformations between Different Groups.

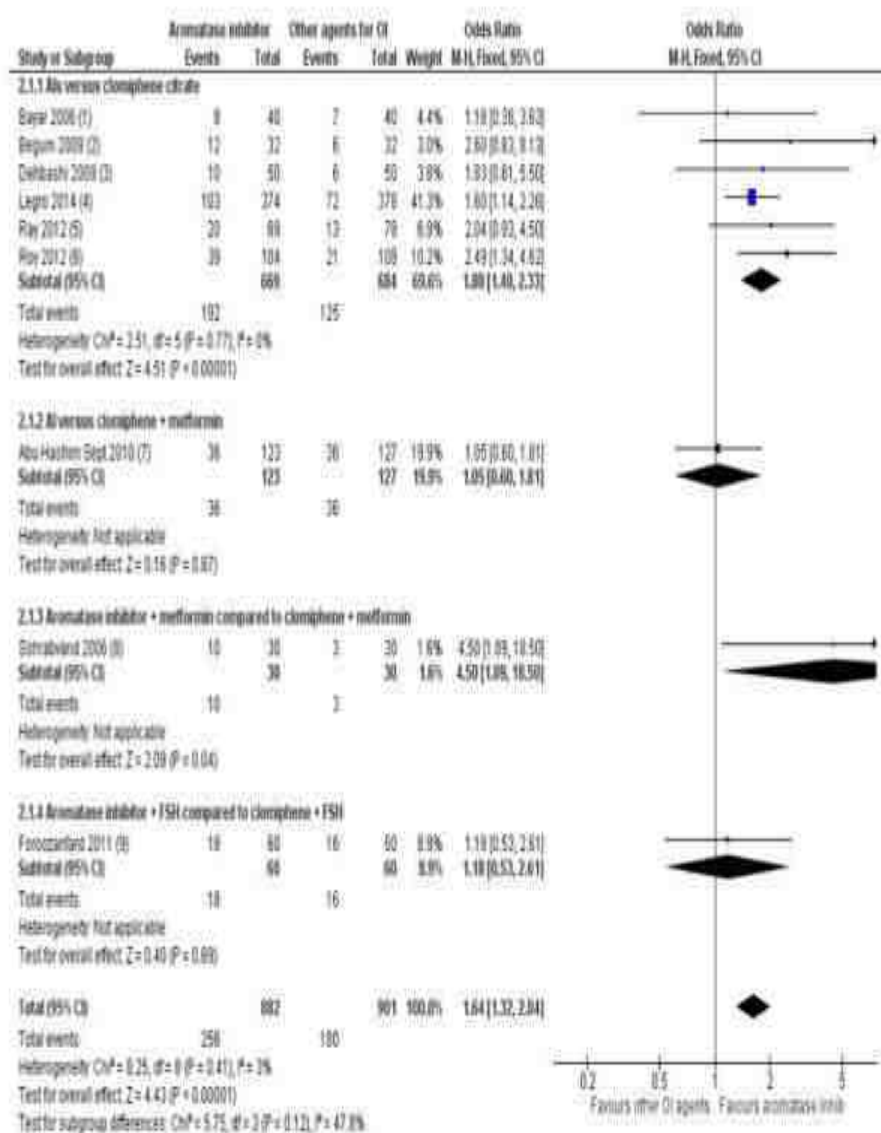
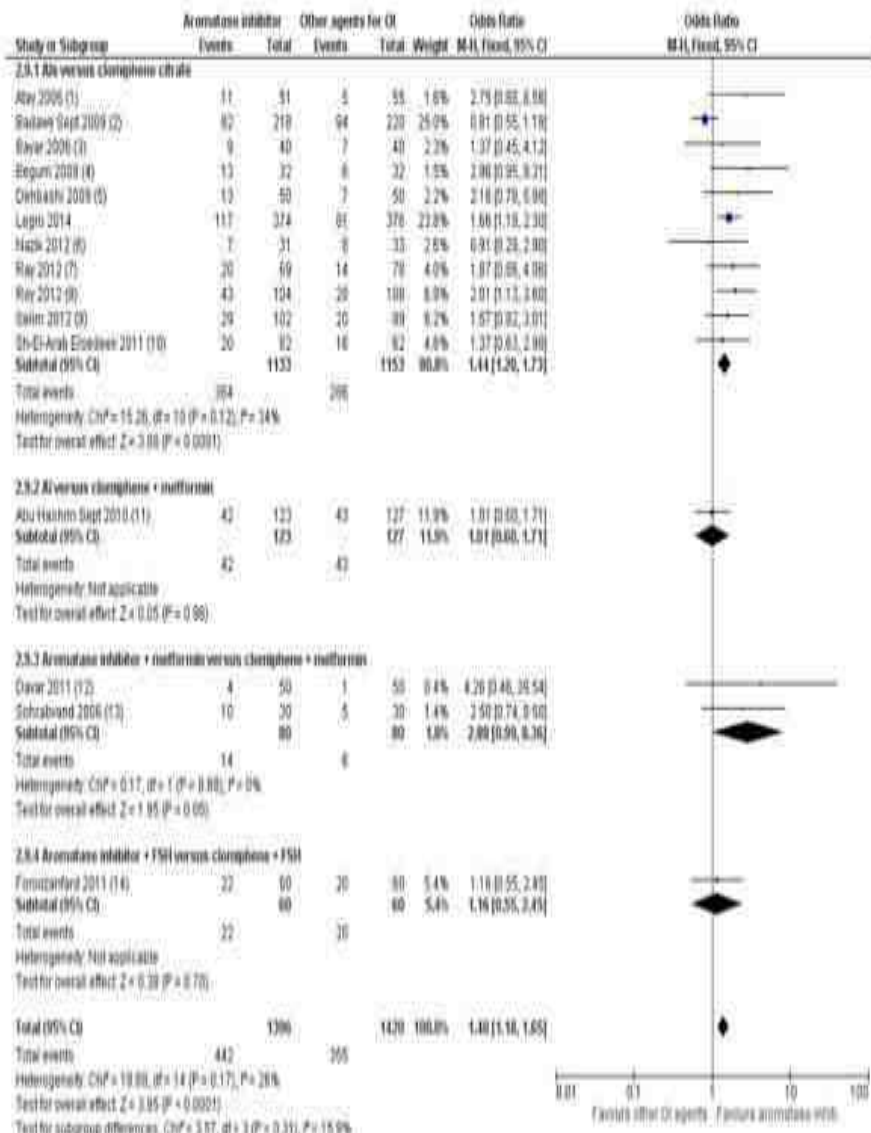
	Overall Congenital malformation OR [†] (95% CI [†])	Structural Malformations OR (95% CI)	Chromosomal Anomalies OR (95% CI)
Letrozole vs Natural conception	1.181 (0.336-4.150)	1.181 (0.336-4.150)	
CC vs Natural conception	0.726 (0.244-2.163)	0.915 (0.294-2.846)	0.291 (0.014-6.103)
CC vs Letrozole	0.614 (0.207-1.829)	0.775 (0.249-2.407)	0.248 (0.018-5.191)
Chi-square (Yate's corrected)	P<0.648	P<0.907	P<0.236

Aromatase inhibitors for subfertile women with polycystic ovary syndrome (Review)

Franik S, Kremer JAM, Nelen WLDM, Farquhar C

2014 - The Cochrane Collaboration

Figure 6. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.8 Clinical pregnancy rate. Figure 4. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.1 Live birth rate.



2014 YILINA DAMGAYI VURANLAR!!!!.

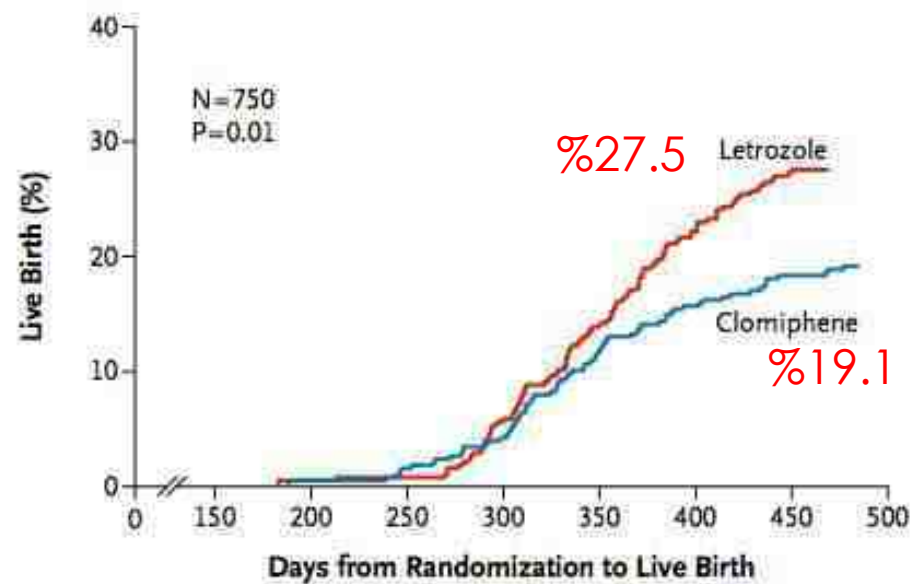
THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM

ORIGINAL ARTICLE

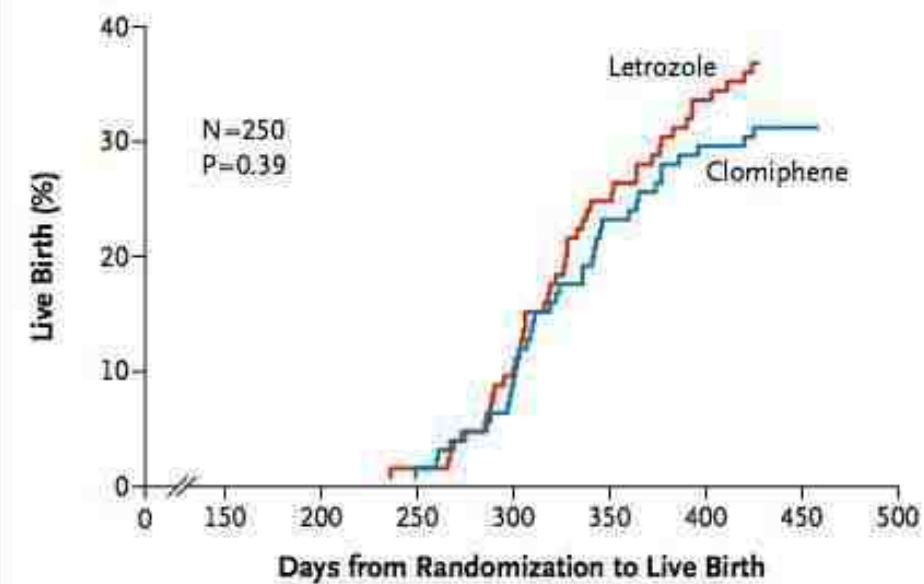
Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brucke, M.D., Ph.D., Michael F. Diamond, M.D.,
Christos Diamantakis, M.D., Ph.D., William D. Schaff, M.D., Peter Carson, M.D.,
Cecily M. Chouhan, M.D., Hao Huang, M.D., M.P.H., Gregsheng Yan, Ph.D.,
Ruben Ayres, M.D., Daniel J. Harloweider, Ph.D., Kurt T. Barnhart, M.D.,
G. Wright Barss, M.D., Rebecca Dawalt, M.D., Scott Luzzi, M.D., Valerie Baker, M.D.,
J.C. Fraxell, M.D., Stephen A. Krawitz, Ph.D., Peter Snyder, M.D., Dora OH, M.D.,
Narada Samojlik, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D.,
for the NICHD Reproductive Medicine Network

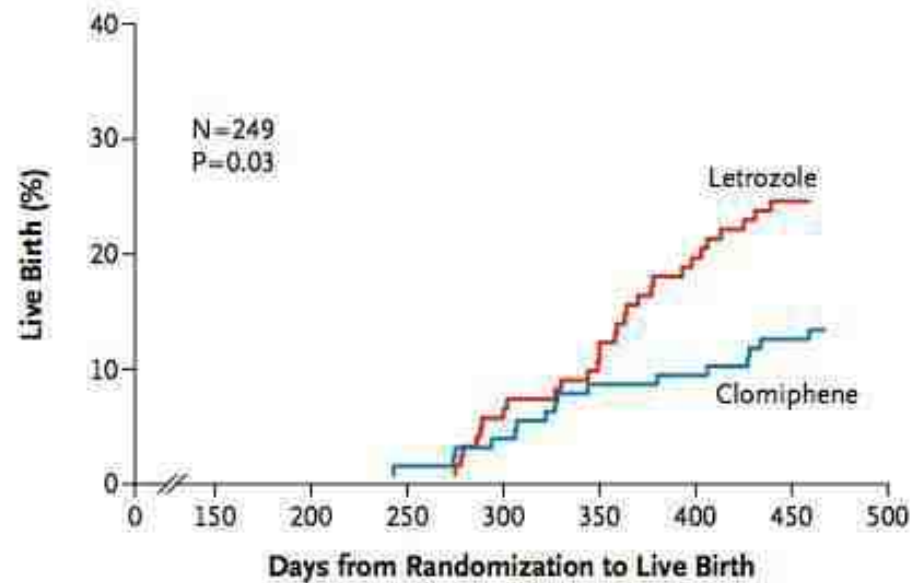
A. All Patients



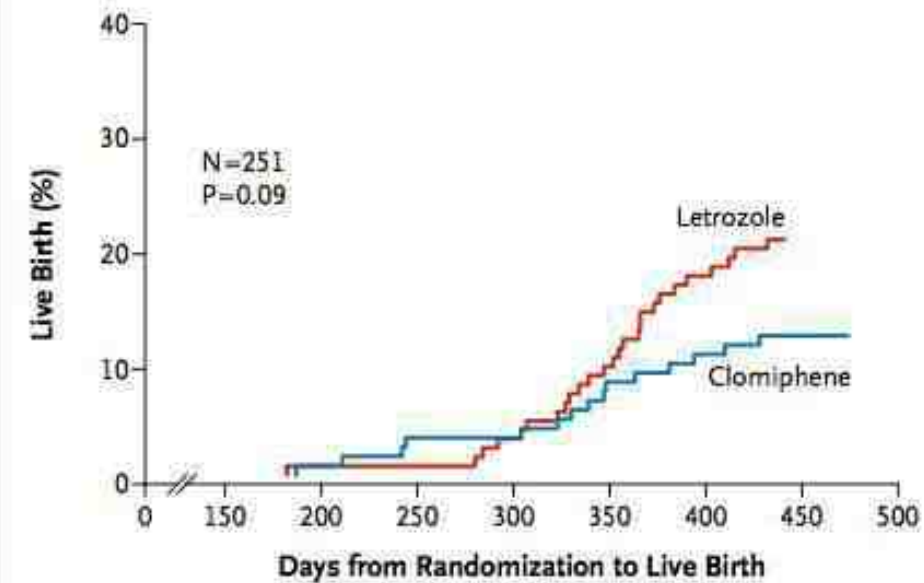
B. BMI, ≤ 30.3



C. BMI, >30.3 to ≤ 39.4



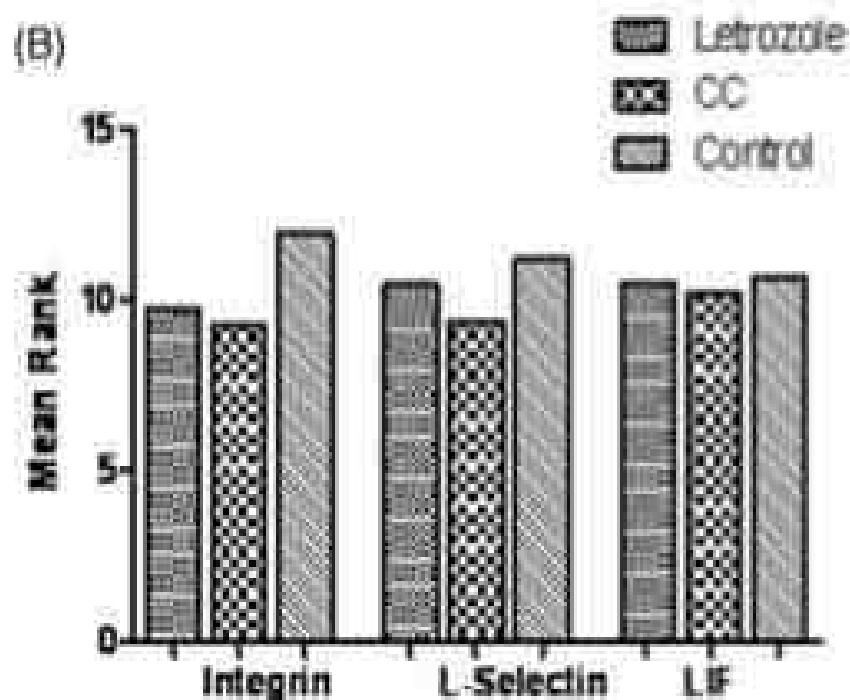
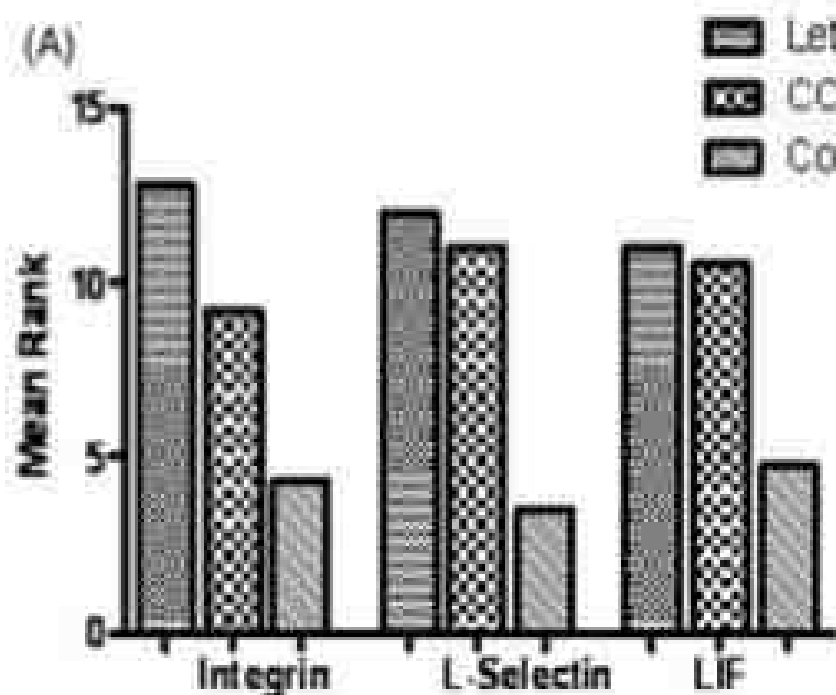
D. BMI, >39.4



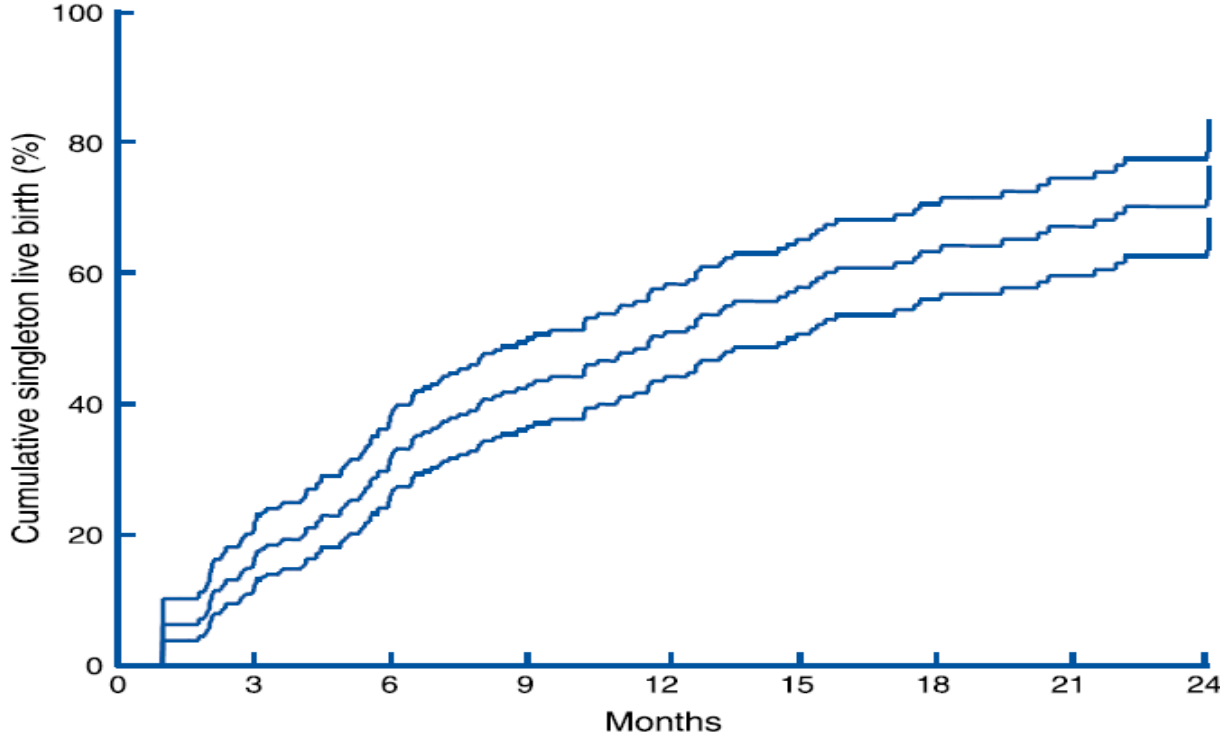
RESEARCH ARTICLE

Endometrial receptivity markers in infertile women stimulated with letrozole compared with clomiphene citrate and natural cycles

Ashalatha Ganesh^{1*}, Nageshwar Chauhan², Soumen Das³, Baldyanath Chakravarty¹, and Koel Chaudhury⁴



SONUÇ-KONVANSİYONEL TEDAVİ(CC+FSH)

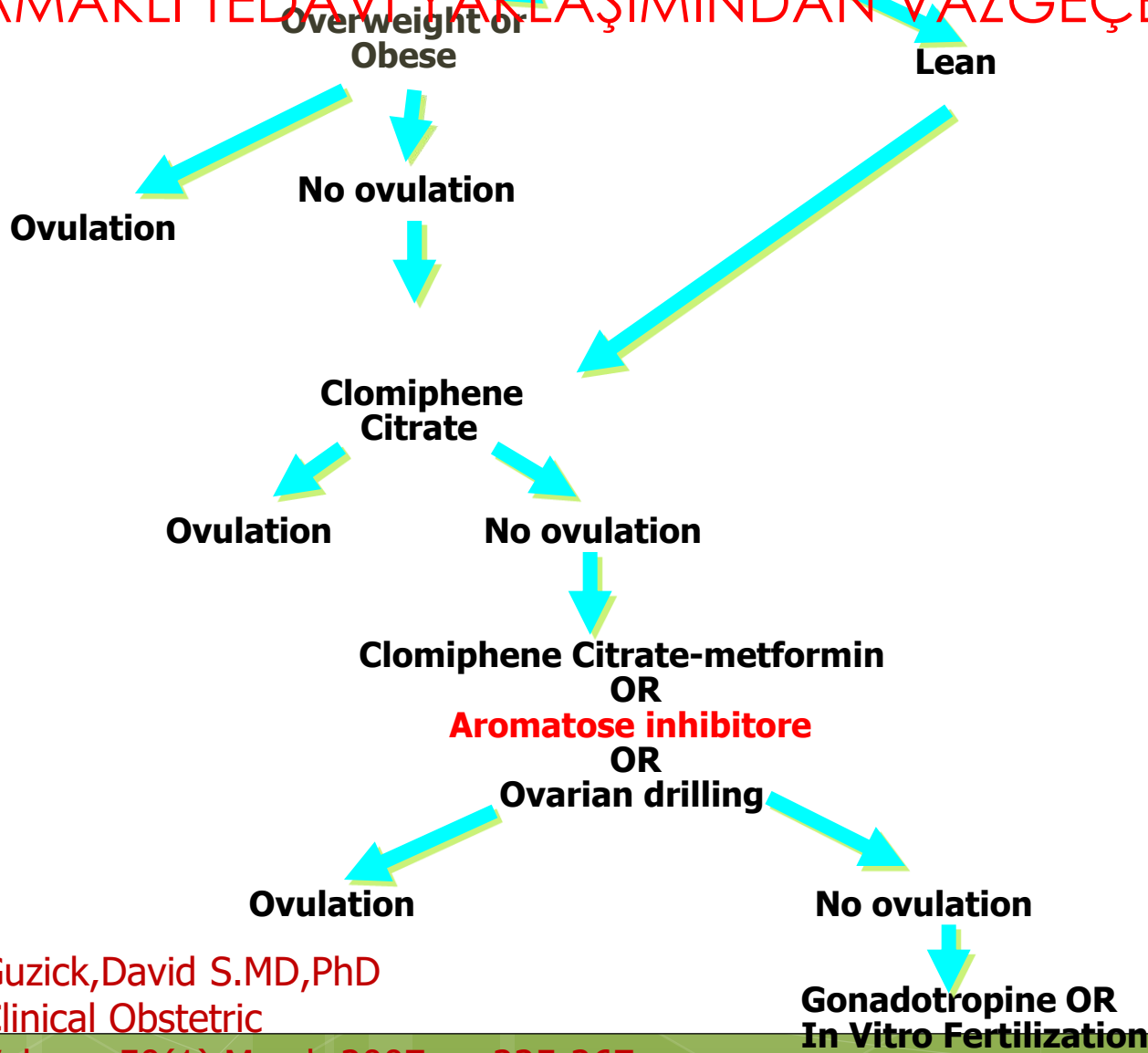


PCOS'ta ovulasyon indüksiyonunda konvansiyonel algoritme uyulursa (CC arkasından Gonadotropin) kümülatif tekil gebelik oranı 1.yıl **%50**, 2.yıl **%71**, gebe kalana kadar geçen süre **11.7** aydır.

Eijkemans et al.2003

PCOS

BASAMAKLI TEDAVI YAKLAŞIMINDAN VAZGEÇEBİLİR MİYİZ?



Guzick, David S. MD, PhD
Clinical Obstetric

Volume 50(1), March 2007, pp 225-267

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
AMH							
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 MULTİVARIATE 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. Santbrink&Fausser 2006

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.



EVE GÖTÜRÜLECEK MESAJLAR

- **C.C**, Anovulatuar ve $BMI \leq 30$ kg/m² olan hastalarda ovulasyon indüksiyonunda hala ilk seçenek...Hasta bazal özelliklerine göre prediksyon başarıyı arttırabilir...
- **Letrozol**,C.C.rezistan ve $BMI > 30$ kg/m² olan Anovulatuar hastalarda ovulasyon indüksiyonunda **ilk seçenek olabilir!**...
- Ama off-label kullanımını ile ilgili hastayı bilgilendirmek gerekli ve gebelik testi yapılarak başlanmalı...
- **Metformin**, sadece IR olan CC-rezistan ve $BMI \leq 30$ kg/m² olan hastalarda pretreatment olarak C.C.ile kombine kullanılabilir...
- Fizyopatoloji ile ilgili yeni bilgiler sayesinde basamaklı yaklaşım yerine hastaya uygun tedavi seçimi mümkün...
- Farmakogenetikteki gelişmeler O.İ. Ajanlarının seçiminde yeni bir yaklaşım ve artan başarı oranlarına sebep olabilir...

END RESULT IS TRULY A NATURES GIFT

