NON-IVF HASTALARDA ORAL AJANLARLA OVULASYON İNDÜKSİYONU

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

İNFERTİLİTE

Fekundibilite: Genç, sağlıklı bir kadının bir reprodüktif siklusta gebe kalma olasılığı **%20-25**

(Diğer memelilere göre en düşük!...)

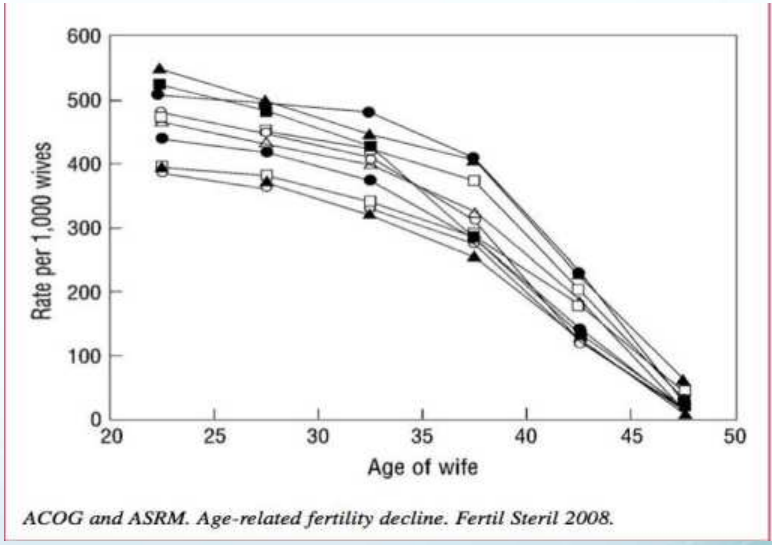
1 yıl korunmasız, düzenli cinsel ilişkiye rağmen gebe kalamamak…**İNFERTİLİTE**

<u>İnfertilite Araştırmalarına Ne zaman Başlamalı?</u>

<35 yaş**-1** yıl korunmasız, düzenli cinsel ilişkiye rağmen gebe kalamayanlar,

35-40 yaş-**6 ay** korunmasız, düzenli cinsel ilişkiye rağmen gebe kalamayanlar

>40 yaş veya **herhangi bir <u>bilinen risk faktörü</u>** olanlarda <u>hemen!</u>



ACOG and ASRM. Age-related fertility decline. Fertil Steril 2008.

Oligo-amennore hikayesi,
bilinen/şüpheli uterin,tubal hastalık
ileri evre endometriozis,
bilinen /şüpheli erkek faktörü

Düzenli Koitus

•Kayıt ve Eğitim

Ovulatuar Disfonksiyon

•Over rezervi

•Yaş faktörü

•PCOS

Erkek Faktörü

•Spermiogram

Utero-Tubal ve Peritoneal Faktörler

Tubal geçirgenlik ve Uterus kavitesinin değerlendirilmesi

İNFERTİLİTE NEDENİNE YÖNELİK ARAŞTIRMALAR SONUCUNDA;

- ERKEK FAKTÖRÜ-%35
- TUBAL VE PERİTONEAL FAKTÖRLER-%35
- OVULATUAR DİSFONKSİYON-%15
- AÇIKLANAMAYAN İNFERTİLİTE-%15
- DİĞER-%5

IVF DIŞI TEDAVİLERİ KULLANABİLECEĞİMİZ (NON-IVF) HASTALAR:

- OVULATUAR DİSFONKSİYON

- AÇIKLANAMAYAN İNFERTİLİTE

- SUBFERTİL ERKEK FAKTÖRÜ

- ERKEN EVRE ENDOMETRİOZİS

Tedavi Seçenekleri

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

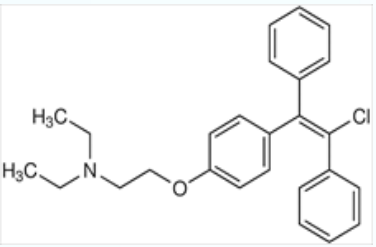
- OVULASYON İNDÜKSİYONU

Oral ajanlar
Gonadotropinler
Cerrahi ovulasyon indüksiyonu

- İNTRAUTERİN İNSEMİNASYON

Ovulasyon İndüksiyonunda Kullanılan Oral Ajanlar

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



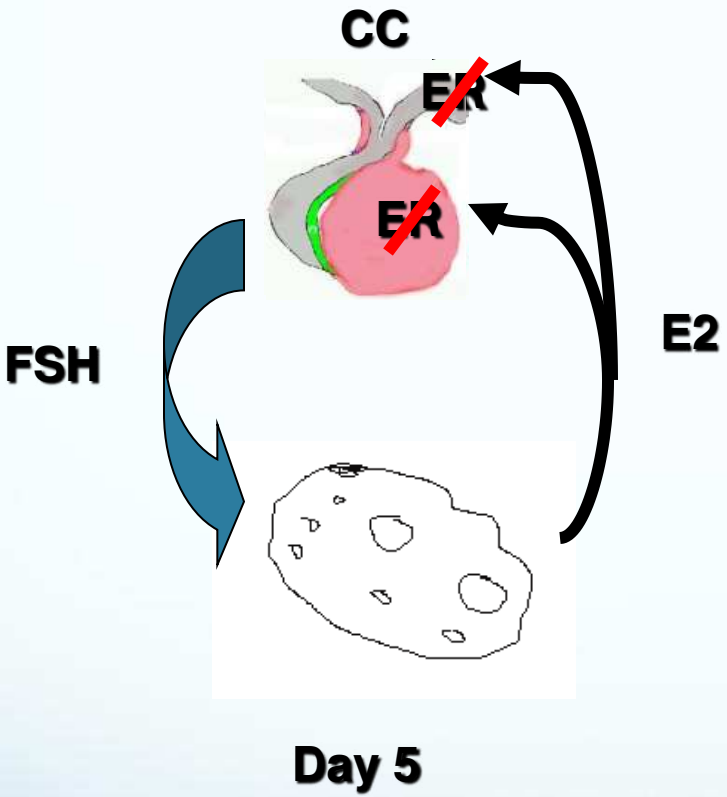
Klomifen Sitrat (CC)-SERM ANTİÖSTROJEN

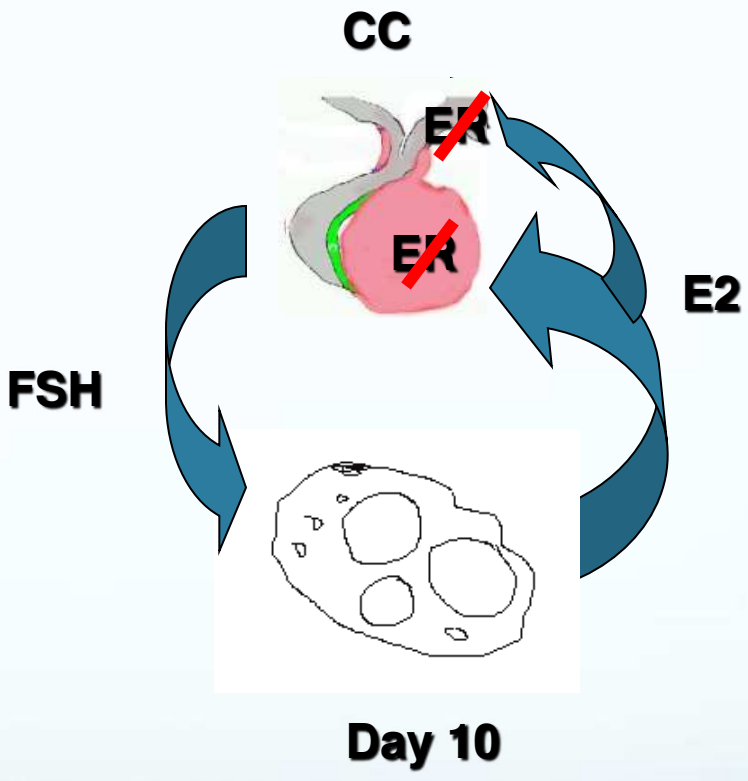
- Trifenyletilen derivesi

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





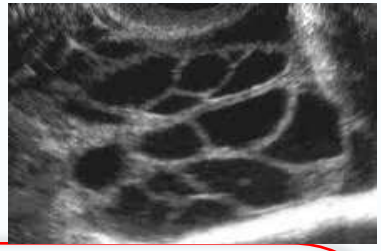
Casper & Mitwally

KULANIM ENDİKASYONLARI

- **WHO GRUP II ANOVULASYON**

Normogonadotropik,normoöstrojenik

%75-80'i PCOS



- 2003 Rotterdam Kıstasları (3 Kıstastan 2 tanesinin varlığı)
  - Oligo ve/veya anovulasyon
  - Ultrasonda PKO
  - Klinik veya Biokimyasal Hiperandrojenemi Bulguları
- Hiperandrojenizmin diğer bütün nedenleri dışlanmalıdır

- **AÇIKLANAMAYAN İNFERTİLİTE**
- Ovulatuar hastalarda, ampirik tedavide
- **C.C ile GnRh puls frekansı artar**

Cycle fecundity with clomiphene treatment

Group	Fecundity, percent
Anovulatory women who respond to treatment	15
Anovulatory women who respond to treatment and have no other infertility factors	22
Women with unexplained infertility	3.4 to 8.1

Anovulasyon mekanizmaları

LH /FSH ↑

GnRH pulse frekansı ↑

→

- LH pulse frekansı ↑
- FSH pulse frekansı değişmez

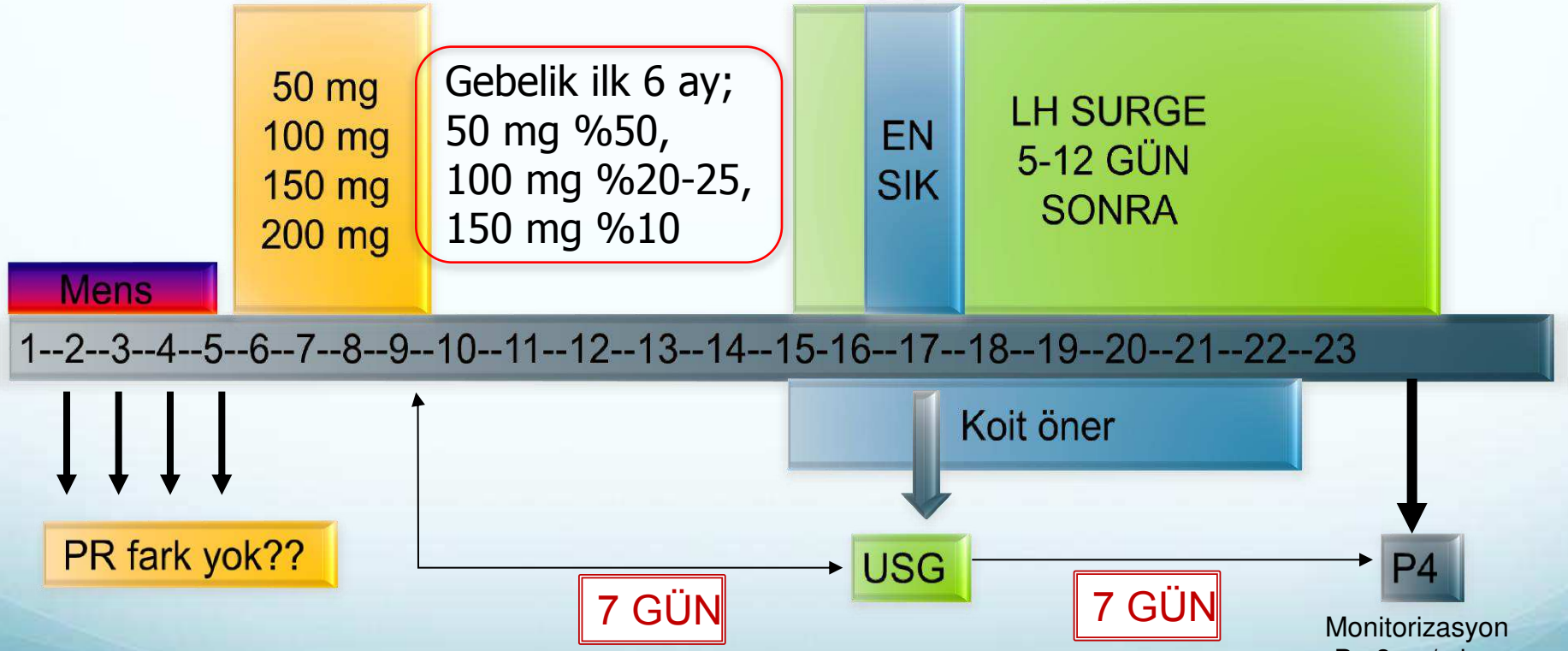
Hipofizer GnRH sensitivitesinde artış

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

(Franks, 2005)

CC-KULLANIMI;

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



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

FDA:Max.doz 100mg/gün
Son dozdan 5 gün sonra 1 hf. gün aşırı coit

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?*

- *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*

		Ovulation		Conception			Live Birth			
Menstrual Status Group	Cycles (n)	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	289	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

REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

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

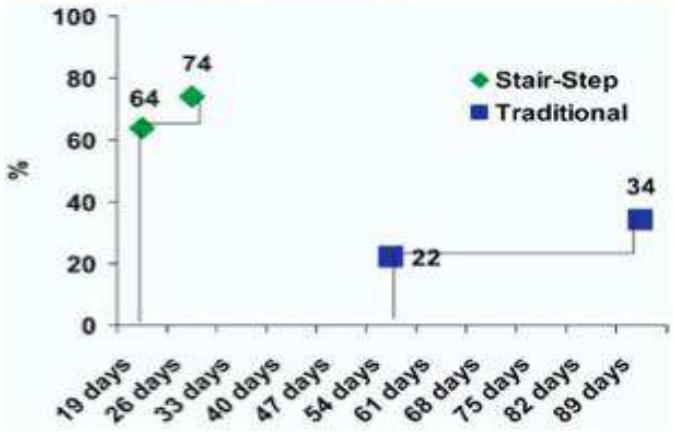
Bradley S. Hurst, MD; Jennifer M. Hickman, MD; Michelle L. Matthews, MD; Rebecca S. Usadi, MD; Paul B. Marshburn, MD

- 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



Bradley S. Am J Obstet Gynecol 2009;200:510.e1-510.e4.

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<7 mm

Homburg R. 2011ÜTD-ANTALYA

ovulasyon başarısız

- **FAI**
- **BMI**
- **LH**
- **İnsülin**

Ovulasyon+

Gebelik (-)

- **Anti-estrojenik etkiler**
  - **Servical mukus**
  - **Endometrium**
- **LH düzeyi** 

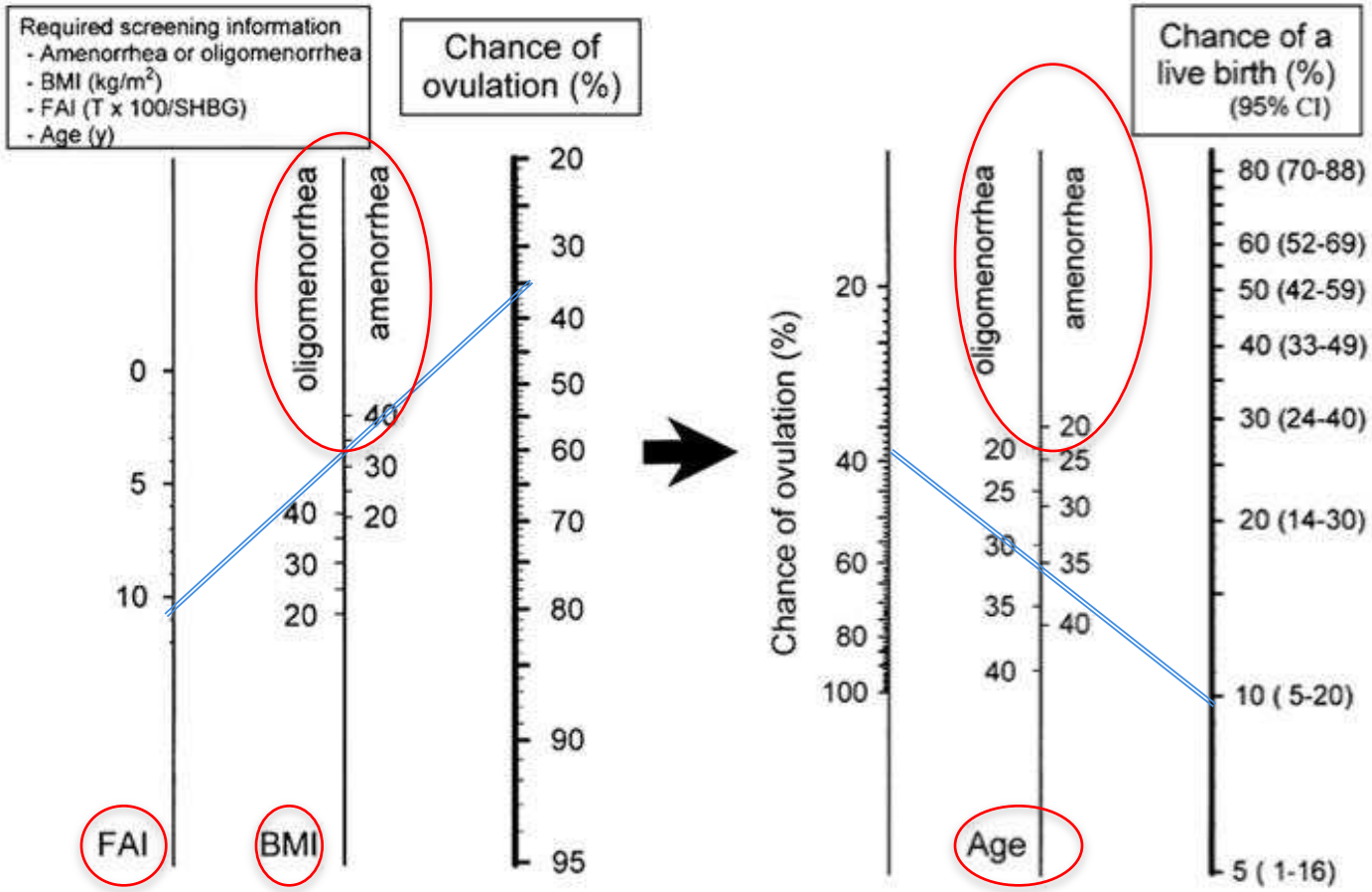
- Homburg R, 2011

Tedavi başarısızlığı ile artmış BMI arasında anlamlı ilişki vardır. BMI >27.2 kg/m2 Milsom SR,2002

GENETİK PREDİSPOZİSYON !... Overbeek 2007

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.

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 siklusa kadar öneriyor

Imani 2002

Messinis 2002

Homburg R 2005

Human Reproduction, Vol.29, No.11 pp. 2482–2486, 2014
Advanced Access publication on August 27, 2014 doi:10.1093/humrep/deu215

human reproduction ORIGINAL ARTICLE *Infertility*

How long should we continue clomiphene citrate in anovulatory women?

N.S. Weiss[1,2,3], S. Braam[1,4], T.E. König[2], M.L. Hendriks[2], C.J. Hamilton[4], J.M.J. Smeenk[5], C.A.M. Koks[6], E.M. Kaaijk[3], P.G.A. Hompes[2], C.B. Lambalk[2], F. van der Veen[1], B.W.J. Mol[1], 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%)

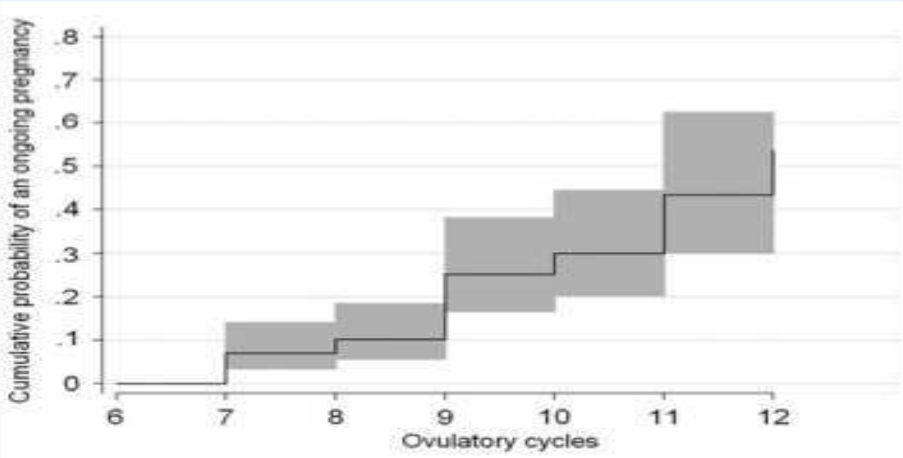


Figure 1 Cumulative probability of an ongoing pregnancy.

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

AÇIKLANAMAYAN İNFERTİLİTEDE AMPİRİK TEDAVİDE C.C.NİN ETKİNLİĞİ

Tedavi	Siklus Başına Klinik Gebelik Oranı (%) 1998[4]	Siklus Başına Klinik Gebelik Oranı (%) 2011
Tedavi uygulanmadan	%1,3-4,1	%1,3-4,1
KS	%5,6	%5,2[15]
IUI	%3,8	%4,76[15]
KS/IUI	%8,3	%9,5[3]
KOH	%7,7	%4,1[5]
KOH/IUI	%17,1	%8,7-11,4[3,5]
IVF	%20,7	%39,5[12]

AÇIKLANAMAYAN İNFERTİLİTEDE OVULASYON İNDÜKSİYONUNDA C.C KULLANALIM MI?

Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial

S Bhattacharya, professor of reproductive medicine,[1] K Harrild, medical statistician,[1] J Mollison, senior medical statistician,[2] S Wordsworth, senior research officer,[3] C Tay, consultant gynaecologist,[4] A Harrold, consultant gynaecologist,[5] D McQueen, consultant gynaecologist,[6] H Lyall, consultant gynaecologist,[7] L Johnston, research nurse,[1] J Burrage, research nurse,[6] S Grossett, research nurse,[5] H Walton, research nurse,[7] J Lynch, research nurse,[7] A Johnstone, research nurse,[4] S Kini, clinical research fellow,[4] A Raja, clinical research fellow,[4] A Templeton, professor of obstetrics and gynaecology[1]

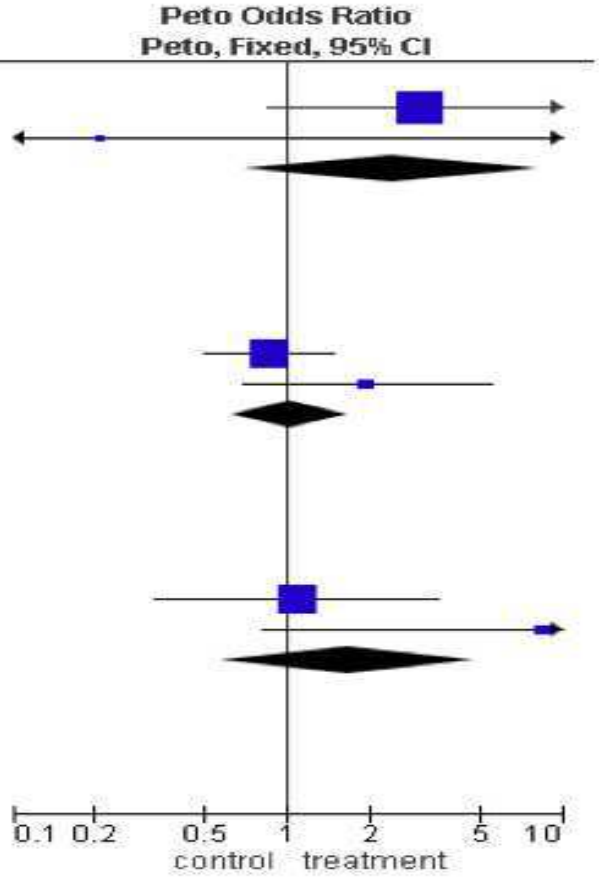
	No (%) in expectant management group	Clomifene citrate *v* expectant management			Intrauterine insemination *v* expectant management		
		No (%)	Crude	Adjusted†	No (%)	Crude	Adjusted†
All	32/193 (17)	26/192 (14)	—	—	43/191 (23)	—	—
Pure unexplained infertility:							
No	6/26 (23)	3/19 (16)	0.73	0.76	5/26 (19)	0.33	0.28
Yes	26/167 (16)	23/173 (13)			38/165 (23)		
Mild male infertility factor:							
No	30/184 (16)	23/181 (13)	0.61	0.53	41/177 (23)	0.39	0.25
Yes	2/9 (22)	3/11 (27)			2/14 (14)		
Mild endometriosis:							
No	28/176 (16)	26/183 (14)	—	—	40/178 (22)	0.62	0.68
Yes	4/17 (24)	0/9			3/13 (23)		
Mild male infertility factor and mild endometriosis:							
No	32/193 (17)	26/191 (14)	—	—	43/190 (23)	—	—
Yes	0/0	0/1			0/1		
Type of infertility:							
Primary	24/135 (18)	19/142 (13)	0.59	0.47	29/132 (22)	0.49	0.39
Secondary	8/58 (14)	7/50 (14)			14/59 (24)		

BMJ 2008;337:a716

Clomiphene citrate for unexplained subfertility in women (Review) 2010 The Cochrane Collaboration

Figure 4. Forest plot of comparison: 1 Clomiphene versus placebo or no treatment in unexplained subfertility, outcome: 1.2 Pregnancy per woman randomised.

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 With IUI						
Deaton 1990	8	23	4	28	91.0%	3.06 [0.84, 11.07]
Melis 1987	0	9	1	16	9.0%	0.21 [0.00, 12.44]
Subtotal (95% CI)		**32**		**44**	**100.0%**	**2.40 [0.70, 8.19]**
Total events	8		5			
Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² = 34%						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.2.2 Without IUI						
Battacharya 2008	29	192	33	193	78.5%	0.86 [0.50, 1.49]
Fisch 1989	12	37	7	36	21.5%	1.95 [0.69, 5.50]
Subtotal (95% CI)		**229**		**229**	**100.0%**	**1.03 [0.64, 1.66]**
Total events	41		40			
Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.2.3 Without IUI using hCG						
Fisch 1989	7	39	6	36	79.6%	1.09 [0.33, 3.59]
Harrison 1983	3	15	0	15	20.4%	8.57 [0.82, 89.45]
Subtotal (95% CI)		**54**		**51**	**100.0%**	**1.66 [0.58, 4.80]**
Total events	10		6			
Heterogeneity: Chi² = 2.36, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 1.98, df = 2 (P = 0.37), I² = 0%						



FASTT trial (fast track and standard treatment trial); cycle fecundity rate of 7.6 percent in women with unexplained infertility treated with clomiphene and IUI for three months. Reindollar RH, FERTİL STERİL 2010

AÇIKLANAMAYAN İNFERTİLİTEDE C.C KULLANIMI İÇİN ÖNERİLER

Use of clomiphene citrate in infertile women: a committee opinion 2013

The Practice Committee of the American Society for Reproductive Medicine

When used in combination with IUI, CC seems to be beneficial compared with expectant management

NICE 2013

1.8.1.1 Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**

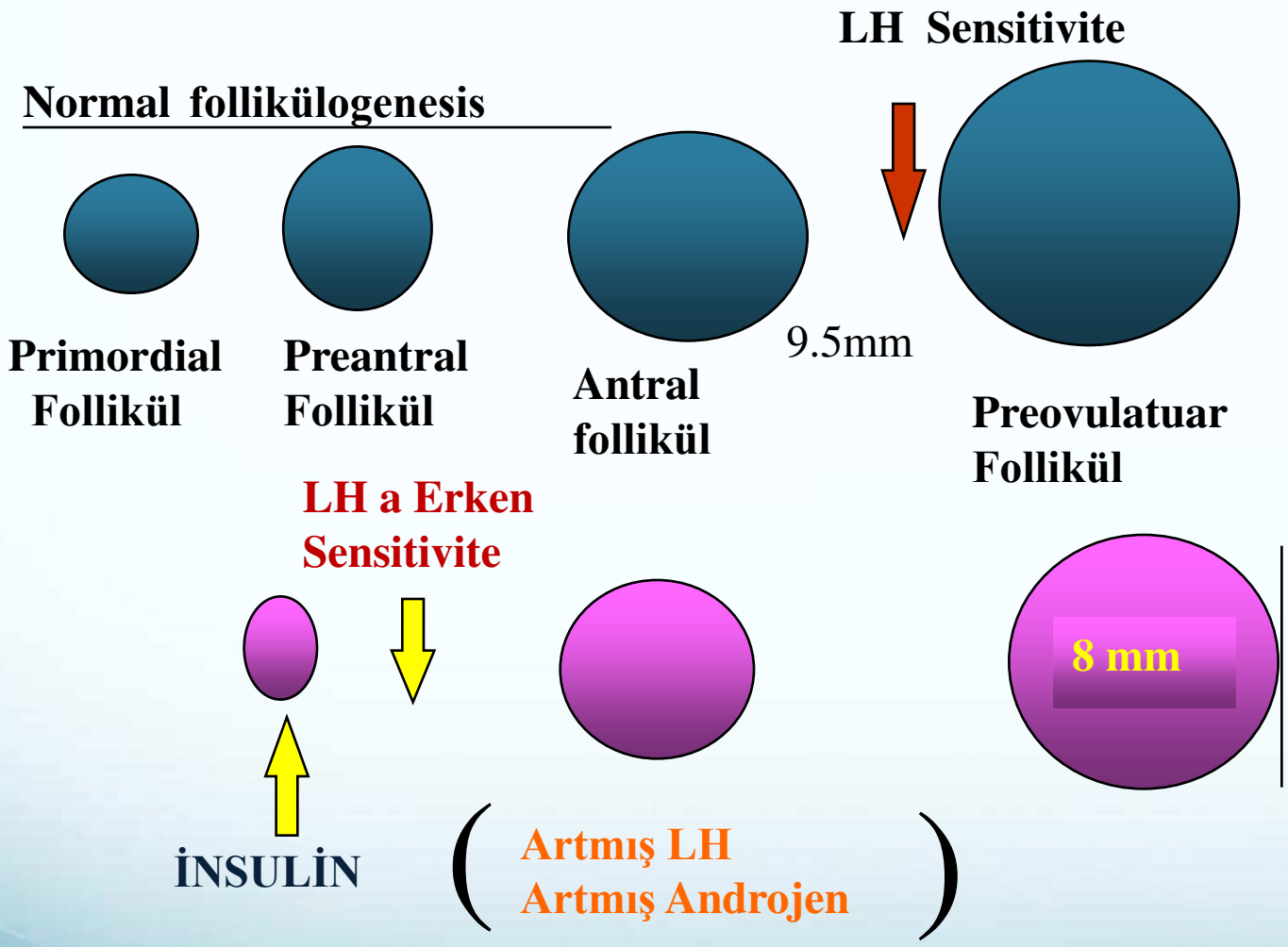
1.8.1.2 Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**

1.8.1.3 Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**

C.C REZİSTANS PCOS HASTALARINDA METFORMİN OVULASYON İNDÜKSİYONUNDA İLK TERCİH OLABİLİR Mİ?

- 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'i azaltır, periferal 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.

Anovulasyon Mekanizmaları



- *Rölatif FSH yetmezliği*
- *Artmış LH*
- *Artmış İnsülin*
- *Azalmış SHBG*
- *Artmış androjen*
- *İnhibin B, IGF, AMH'daki değişiklikler*

Follikül Gelişiminde Arrest

Franks S, 2005

PCOS/CC/ REZİSTANSINDA METFORMİN OVULASYONA NASIL ETKİ EDİYOR?

- İntrafolliküler steroidogenez üzerine etki ederek granüloza hüc.de IGF 1'i arttırıyor KOCAK M,2002
- Teka-interna hüc.de androjen sentezini inhibe ediyor ATTIA GR,2001

  Hepatik SHBG sentezini artırarak f-Testosteronu 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.

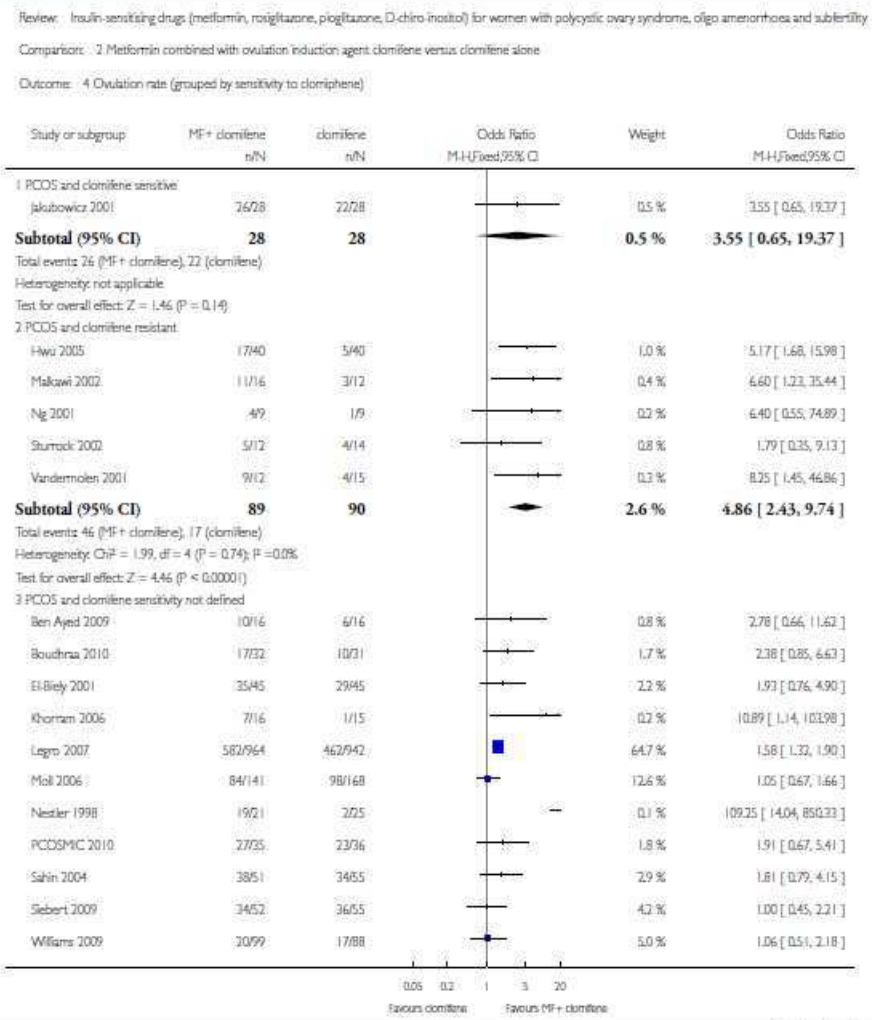
PKOS/CC Rezistansı'nda Metformin Kullanımı

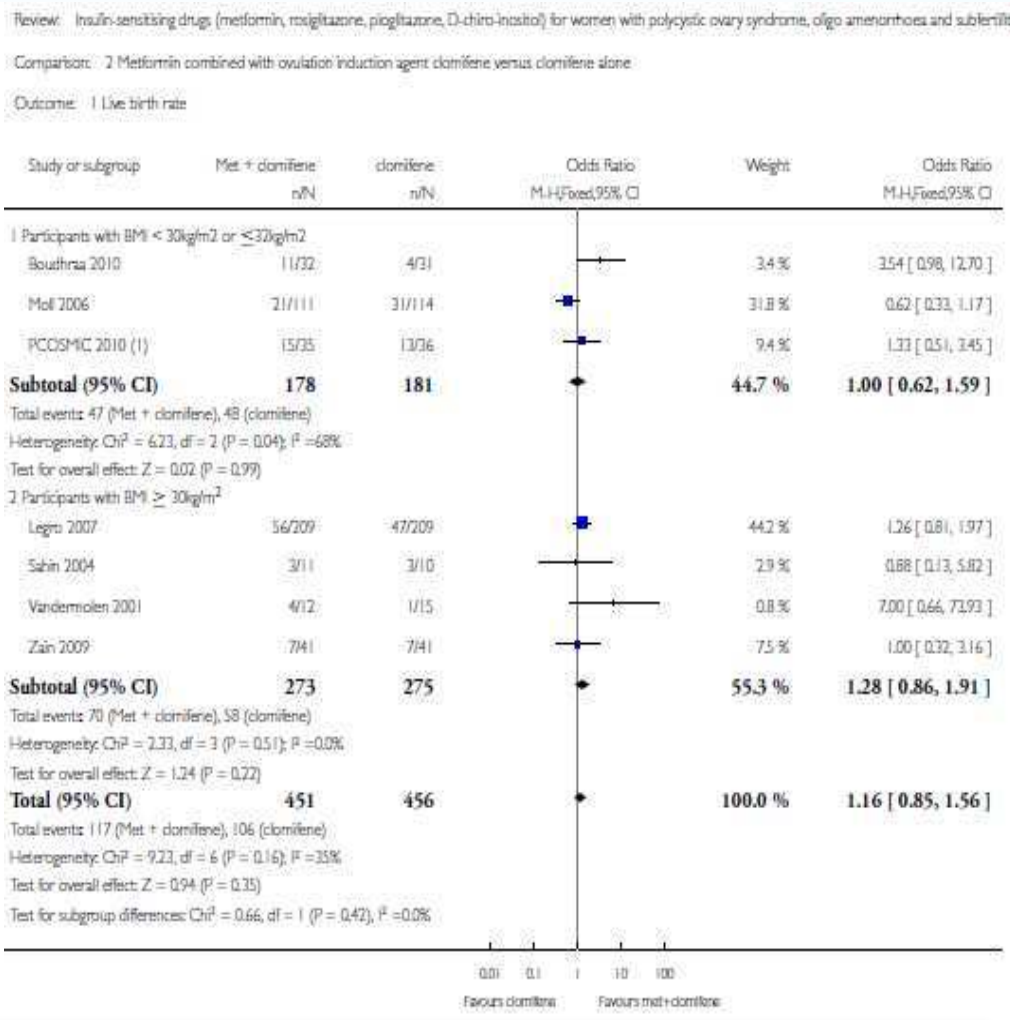
- Glukoz intoleransı saptanan hastalarla sınırlandırılmalıdır.
- Temel riski: KC , böbrek veya konjestif kalp yetmezliği olanlarda laktik asidoz.
- 1500 mg/gün, uygulamadan 6-8 hafta önce başlanması
- IR'nı gidermek için

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

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





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

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-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: 5 Ovulation rate (grouped by BMI)

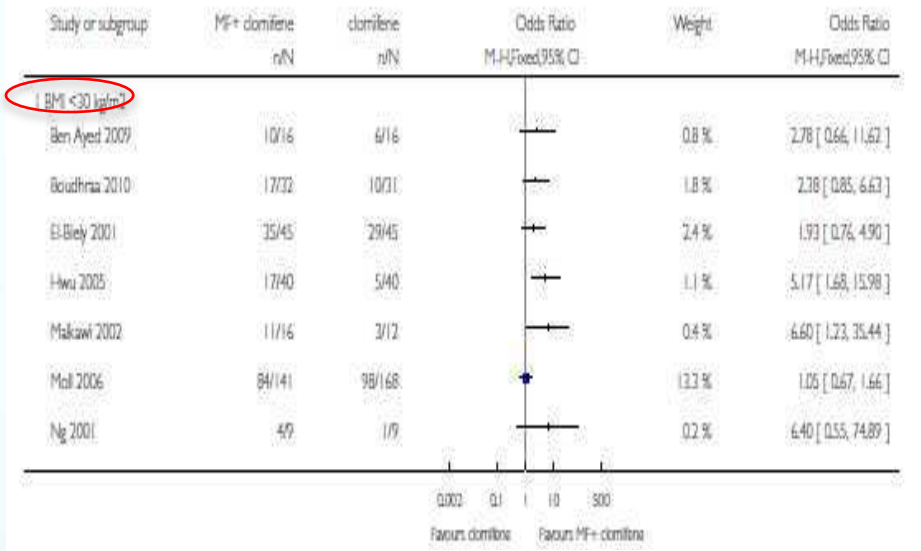


Figure 8. Forest plot of comparison: 3 Metformin versus clomiphene citrate, outcome: 3.1 Live birth: Participants with BMI ≤ 30kg/m2 or ≤32kg/m2.

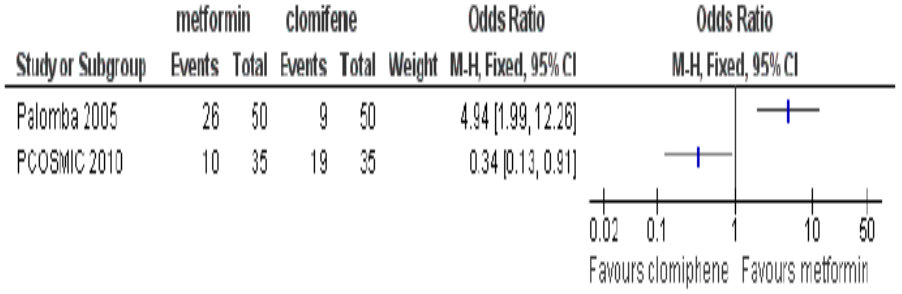
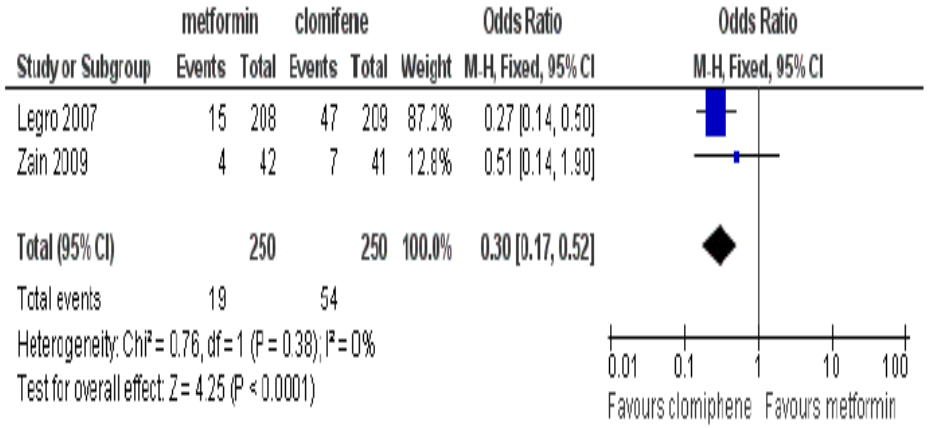
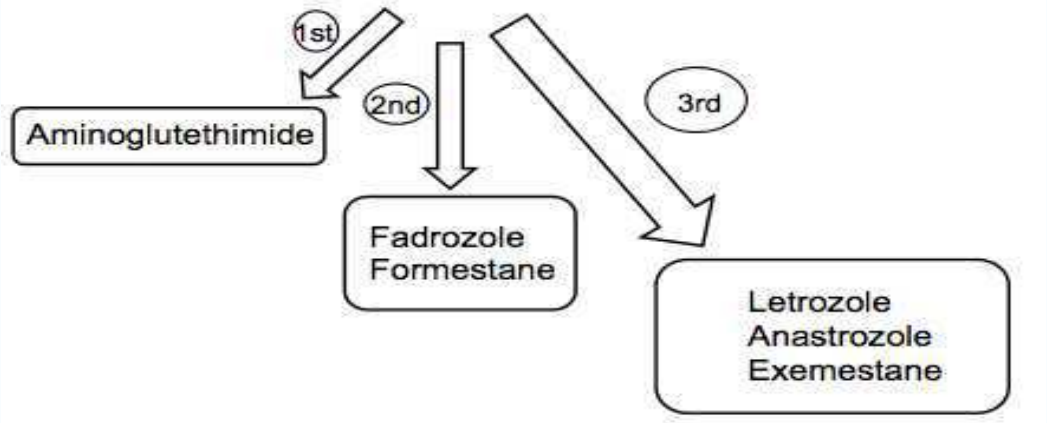


Figure 9. Forest plot of comparison: 3 Metformin versus clomiphene citrate, outcome: 3.2 Live birth: Participants with ≥BMI 30kg/m2.



BMI<30 kg/m^{2}olanlarda
MET+CC>CC>MET

Aromataz İnhibitörleri ovulasyon indüksiyonunda ilk tercih olabilir mi?



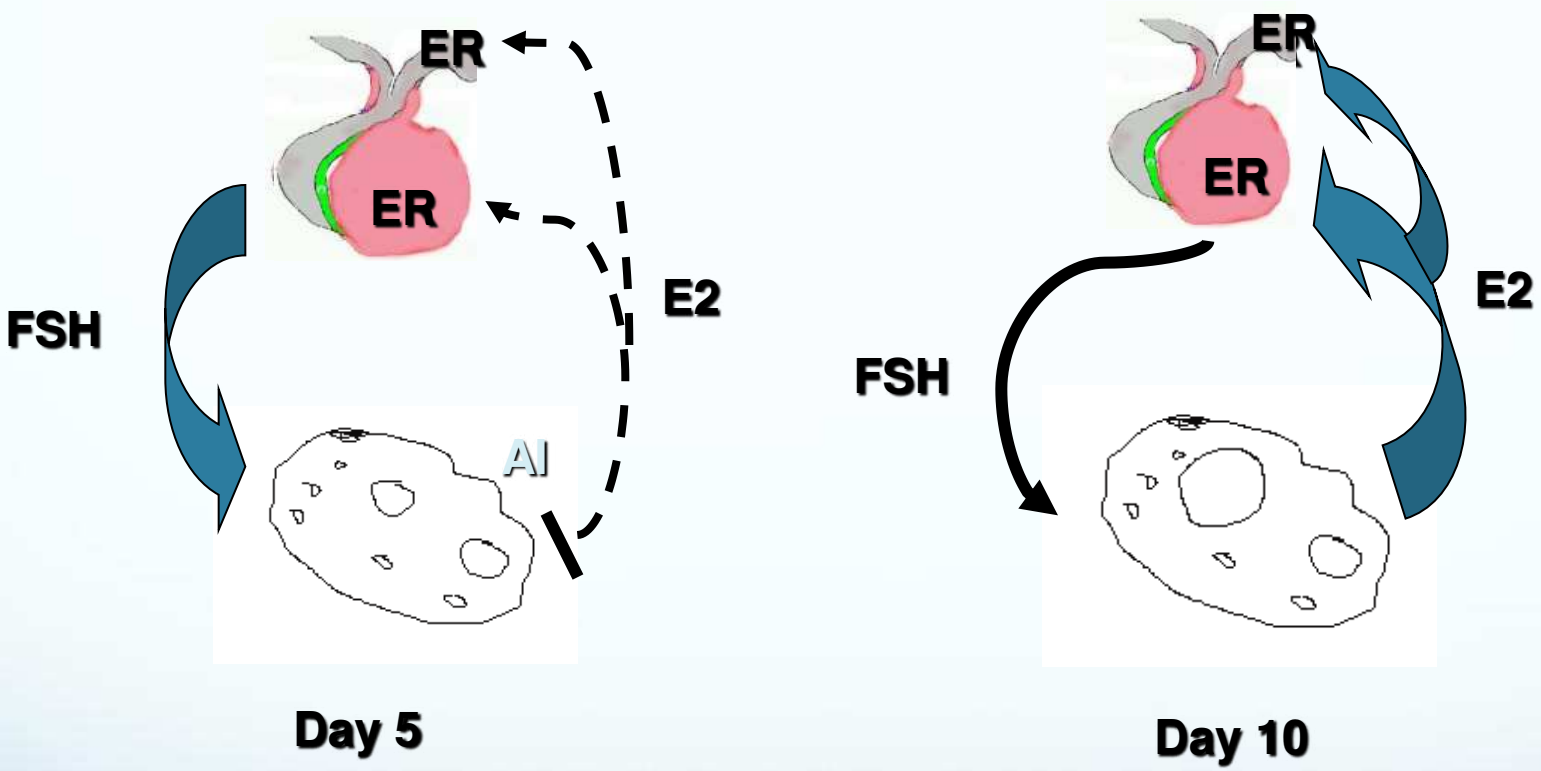
- Aromatazın inhibisyonu ile hipotalamo-pituiter aksın estrojen (-) feedback etkisinden yararlanılarak gonadotropin sekresyonunun artışı ve ovaryan folikül gelişiminin uyarılması gerçekleşir
- Siklusun 3-7.günleri arasında 2,5mg letrozole/gün verilen PCOS olgularında %75 ovulasyon ve %25 gebelik sağlanmıştır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

Mitwaly&Casper 2001

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

Aromatase Inhibitor Treatment



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

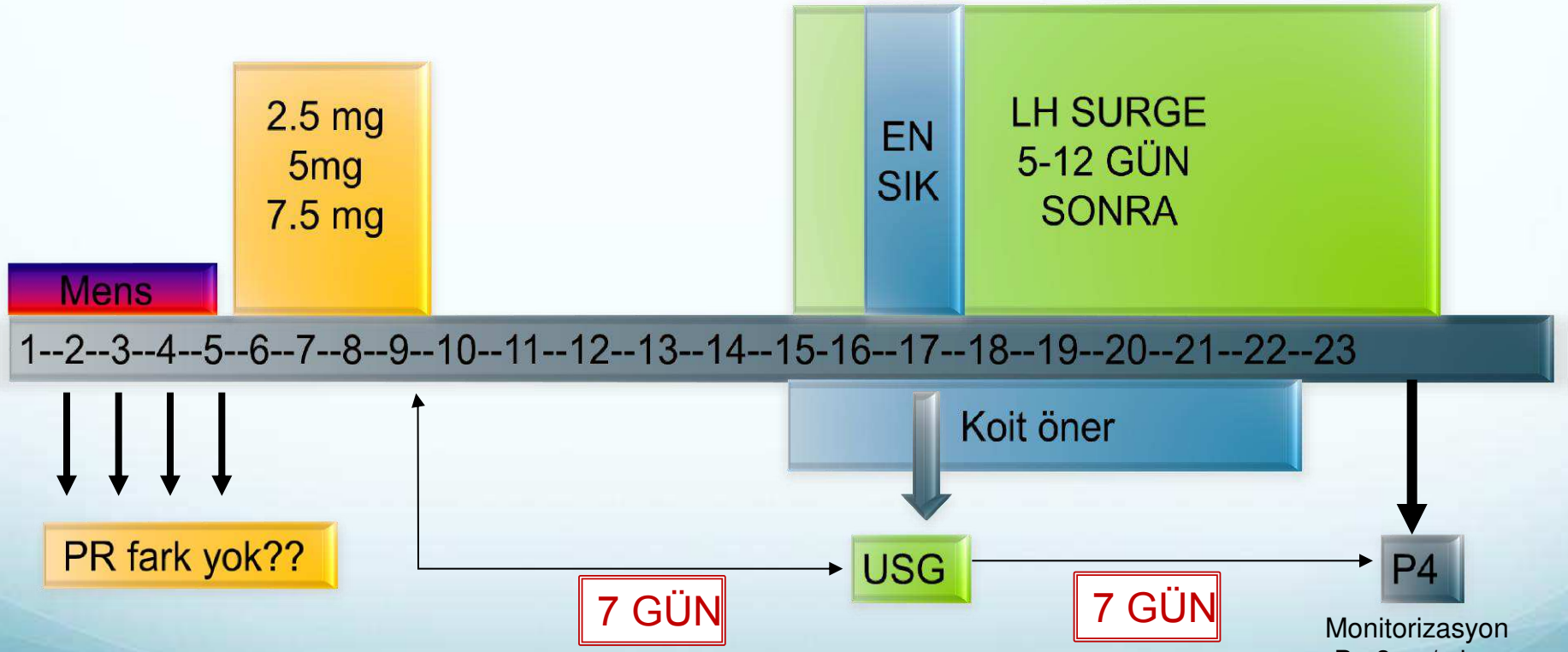
Weil S 1999

Casper & Mitwally

LETROZOL-KULLANIMI;

OFF-LABEL!!!

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



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

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 kardiak ve kemik malformasyonlarında artış???(n=150 yenidoğan)

Biljan MM 2005-ASRM

Letrozol ile C.C'ye göre daha az konjenital kardiak 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
Advance Access publication on May 15, 2008
doi:10.1093/humrep/den100

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

G.M. Tiboni[1,3], F. Marotta[1], C. Rossi[2] and F. Giampietro[1]

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
Fetuses with vertebral anomalies	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.

OPEN ACCESS Freely available online

PLOS | ONE

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

Sunita Sharma[1]*, Sanghamitra Ghosh[1], Soma Singh[1], Astha Chakravarty[1], Ashalatha Ganesh[2], Shweta Rajani[1], B. N. Chakravarty[1]

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.

Citation: Sharma S, Ghosh S, Singh S, Chakravarty A, Ganesh A, et al. (2014) Congenital Malformations among Babies Born Following Letrozole or Clomiphene for Infertility Treatment. PLoS ONE 9(10): e108219. doi:10.1371/journal.pone.0108219

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<0.226

TABLE 1

Patients' characteristics.

	Group A (letrozole group) (n = 123)	Group B (combined metformin–CC group) (n = 127)	*t*	χ^2	*P* value
No. of cycles	285	297			
Age (y)	28.3 ± 2.7	26.2 ± 2.2	2.66		.1
Parity					
Nulliparous	100 (81.3%)	106 (83.5%)		0.28	.83
Multiparous	23 (18.7%)	21 (16.5%)		0.87	.48
Clinical presentation					
Oligo/anovulation	90 (73.1%)	94 (74%)		0.03	.86
Hyperandrogenism	51 (41.5%)	60 (47.2%)		0.99	.32
Polycystic ovaries	88 (71.5%)	88 (69.2%)		0.26	.60
Height (cm)	166.3 ± 5.2	162.1 ± 5.1	2.95		.08
Weight (kg)	85.3 ± 6.4	88.1 ± 4.2	2.88		.09
BMI (kg/m^2)	29.1 ± 3.2	30.1 ± 2.3	2.05		.83
FSH (IU/mL)	4.6 ± 2.1	5.1 ± 2.2	3.88		.06
LH (IU/mL)	11.4 ± 2.8	11.8 ± 2.6	3.90		.06

TABLE 2

Outcome in letrozole and combined metformin–CC groups.

	Group A (letrozole group) (n = 123)	Group B (combined metformin–CC group) (n = 127)	*t*	χ^2	*P* value
Total no. of follicles	4.4 ± 0.4	6.8 ± 0.3	4.3		.042[a]
No. of follicles >14 mm	2.1 ± 0.3	3.7 ± 0.5	6.13		.008[a]
No. of follicles >18 mm	2.3 ± 0.1	3.1 ± 0.8	5.03		.003[a]
Pretreatment endometrial thickness	5.5 ± 0.5	5.3 ± 0.6	1.31		.22
Endometrial thickness at hCG (mm)	9.5 ± 0.2	9.1 ± 0.1	1.44		.53
Serum E_2 (pg/mL)	258 ± 62.2	386 ± 88.3	4.12		.022[a]
Serum P (ng/mL)	7.3 ± 0.9	11.4 ± 1.2	6.33		.024[a]
Duration of stimulation (d)	12.2 ± 1.3	8.1 ± 2.8	4.91		.036[a]
Ovulation/cycle	185/285 (64.9%)	207/297 (69.6%)		1.63	.82
Pregnancy/cycle	42/285 (14.7%)	43/297 (14.4%)		1.32	.53
Miscarriage/patient	4 (10.2%)	4 (9.5%)		1.73	.43

[a] Statistically significant difference: $P<.05$.

Abu Hashim. Letrozole or CC-metformin for CC resistance. Fertil Steril 2010.

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.

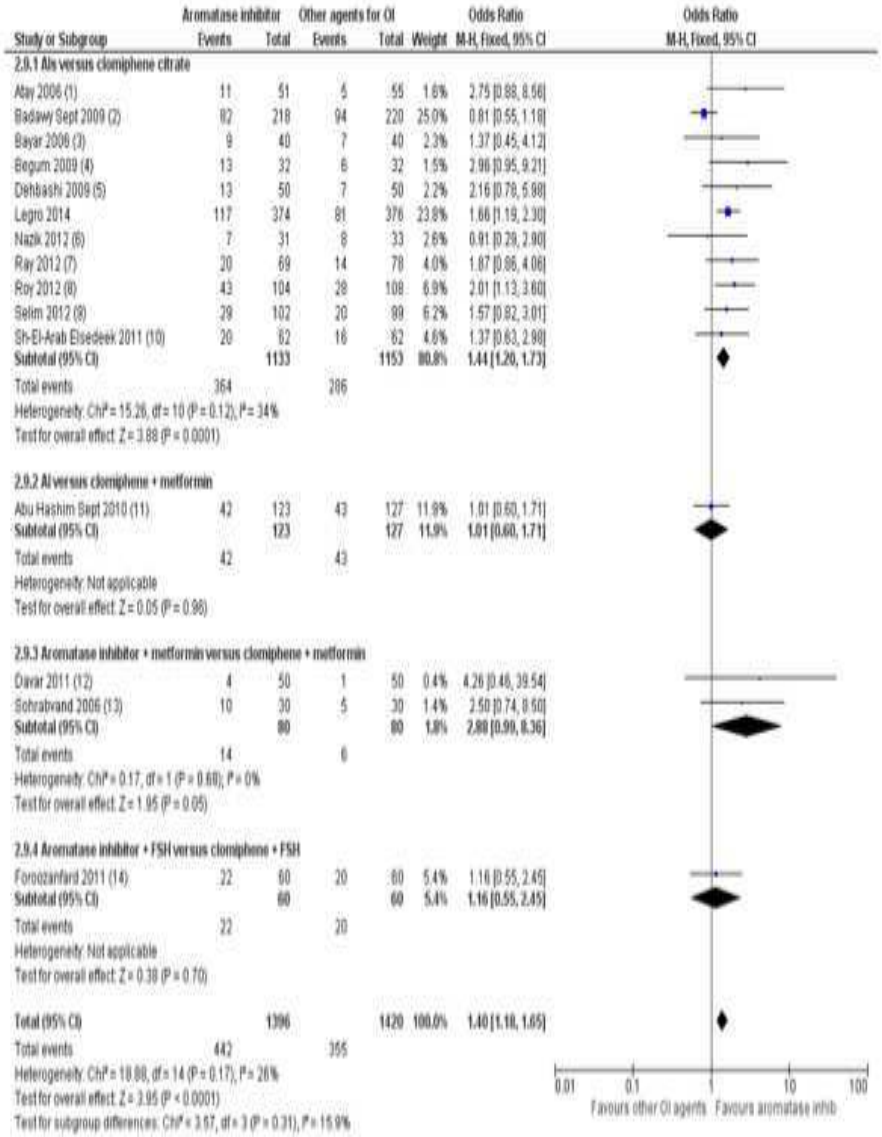
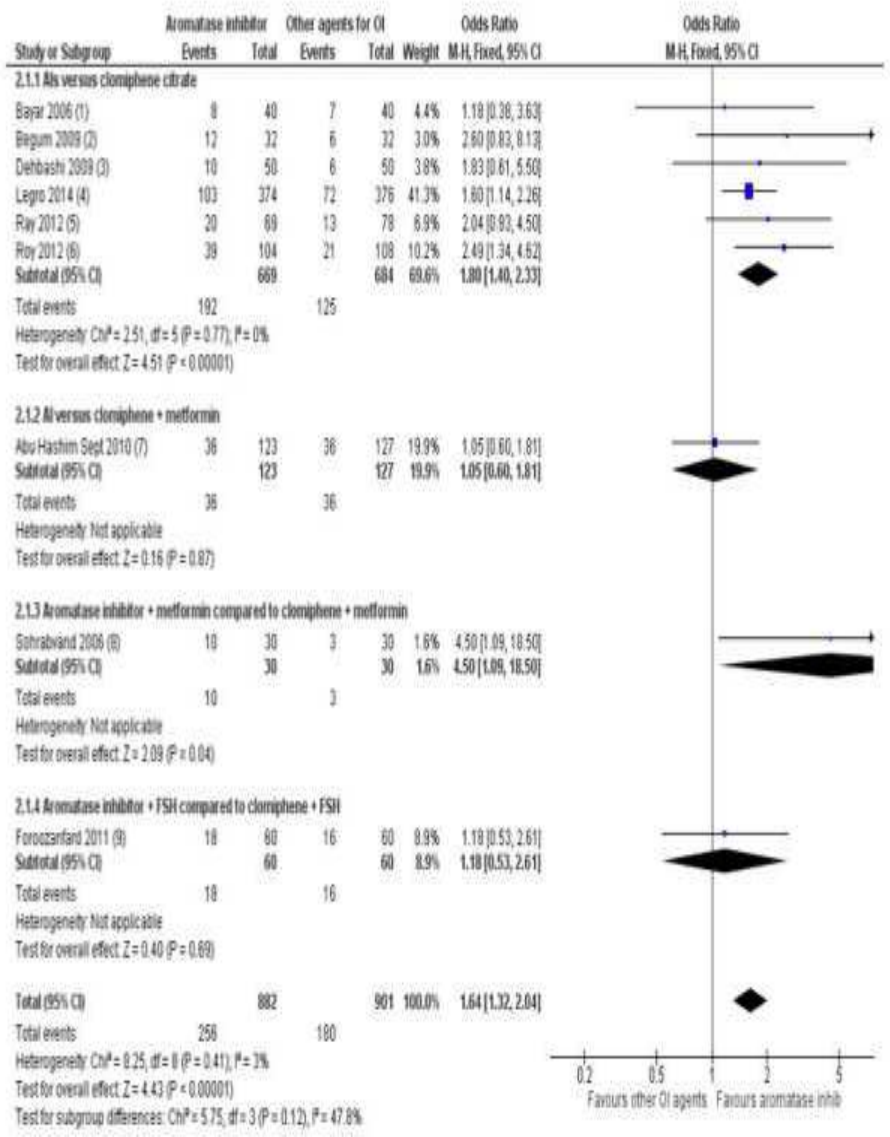


Figure 4. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.1 Live birth rate.



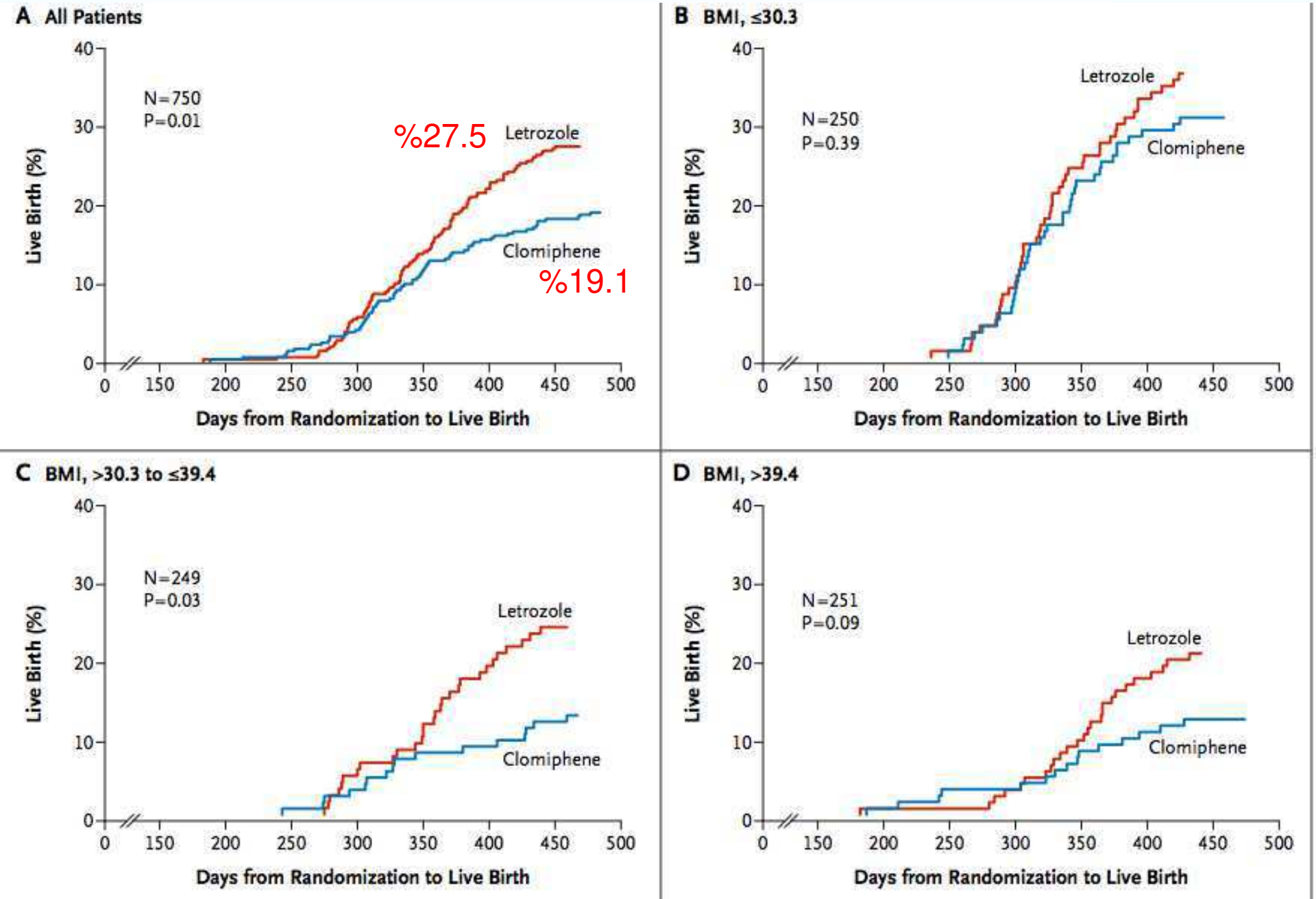
2014 YILINA DAMGAYI VURANLAR!!!!.

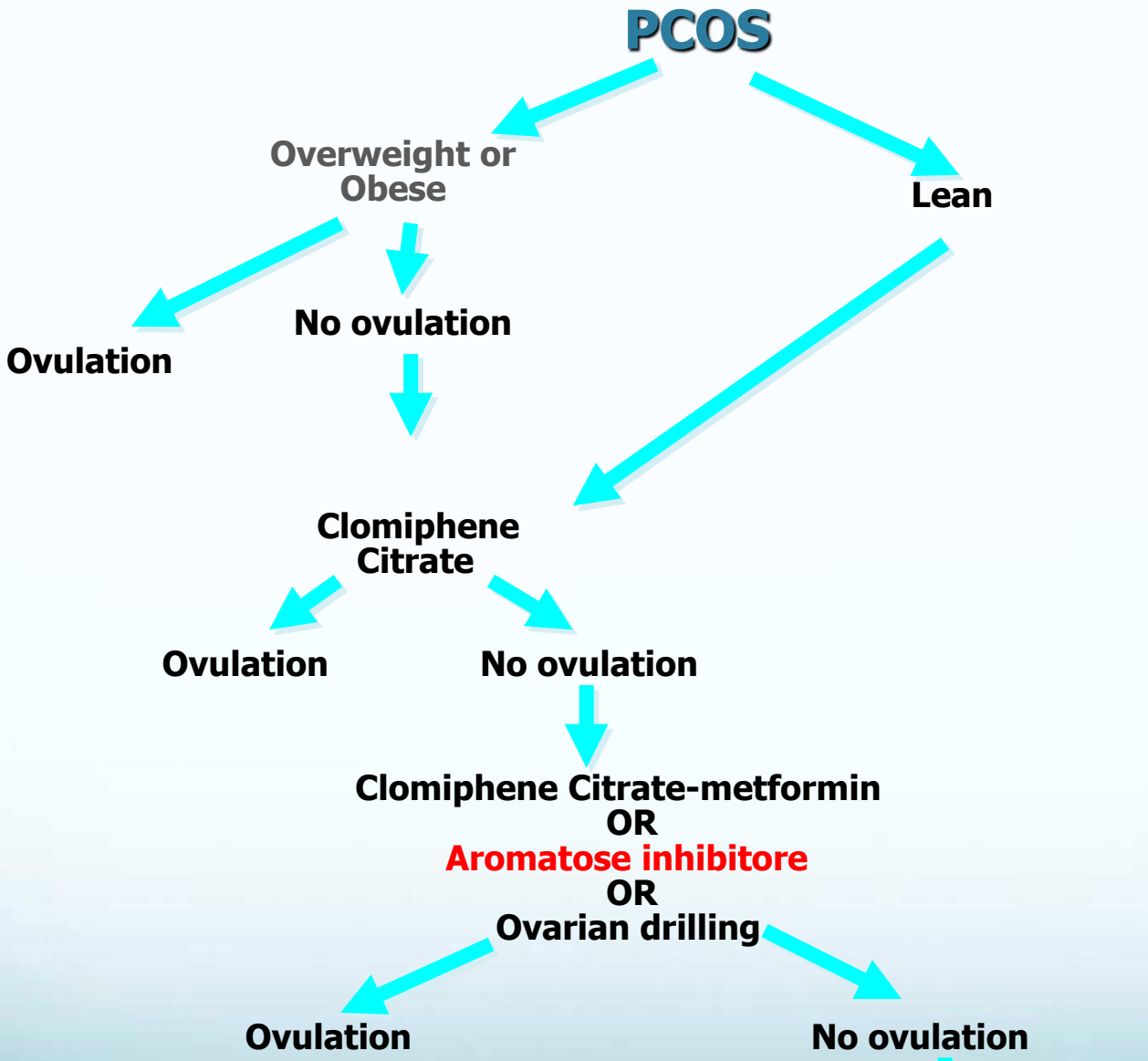
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network*


A All Patients
N=750
P=0.01
%27.5
Letrozole
Clomiphene
%19.1
Live Birth (%)
Days from Randomization to Live Birth
B BMI, ≤30.3
N=250
P=0.39
Letrozole
Clomiphene
Live Birth (%)
Days from Randomization to Live Birth
C BMI, >30.3 to ≤39.4
N=249
P=0.03
Letrozole
Clomiphene
Live Birth (%)
Days from Randomization to Live Birth
D BMI, >39.4
N=251
P=0.09
Letrozole
Clomiphene
Live Birth (%)
Days from Randomization to Live Birth



Guzick,David S.MD,PhD
Clinical Obstetric
Volume 50(1),March 2007,pp 225-267

AÇIKLANAMAYAN İNFERTİLTEDE LETROZOL

doi:10.1111/jog.12393 J. Obstet. Gynaecol. Res. Vol. 40, No. 5: 1205–1216, May 2014

Letrozole versus clomiphene citrate for unexplained infertility: A systematic review and meta-analysis

Aihai Liu[1], Chao Zheng[2], Junzhe Lang[3] and Wenbing Chen[1]

Departments of [1]Gynecology and [2]Endocrinology, The Second Affiliated Hospital of Wenzhou Medical University, and [3]Orthopedics Department, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Study or Subgroup		letrozole Events	Total	clomiphene citrate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Badawy 2009a	5 mg	76	205	74	207	25.4%	1.04 [0.80, 1.34]
Badawy 2009b	5 mg	36	269	77	420	22.3%	0.73 [0.51, 1.05]
Fouda 2011	2.5mg	40	106	24	105	20.5%	1.65 [1.08, 2.53]
Fozan 2004	7.5mg	13	74	11	80	12.9%	1.28 [0.61, 2.67]
Ibrahim 2012	2.5mg	30	130	14	131	16.3%	2.16 [1.20, 3.88]
Sammour 2001	2.5mg	4	25	1	24	2.6%	3.84 [0.46, 31.94]
Total (95% CI)			**809**		**967**	**100.0%**	**1.26 [0.89, 1.80]**
Total events		199		201			

Heterogeneity: Tau² = 0.11; Chi² = 15.03, df = 5 (P = 0.01); I² = 67%

Test for overall effect: Z = 1.29 (P = 0.20)

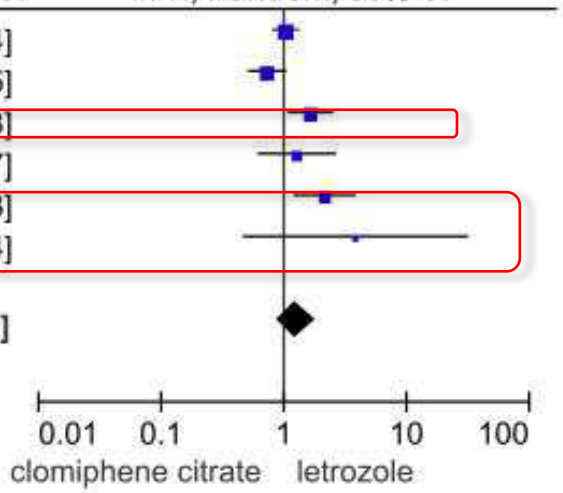


Figure 2 Clinical pregnancy rate for letrozole versus clomiphene in women with unexplained infertility. CI, confidence interval; M-H, Mantel–Haenszel.

Letrozol ile klinik gebelik oranı daha yüksek (R.R:1.26,p=0.01)

2.5 mg Let vs 100mg CC'ye göre daha yüksek klinik gebelik (RR=1.85,p=0.0004)

Systems Biology in Reproductive Medicine

http://informahealthcare.com/aan
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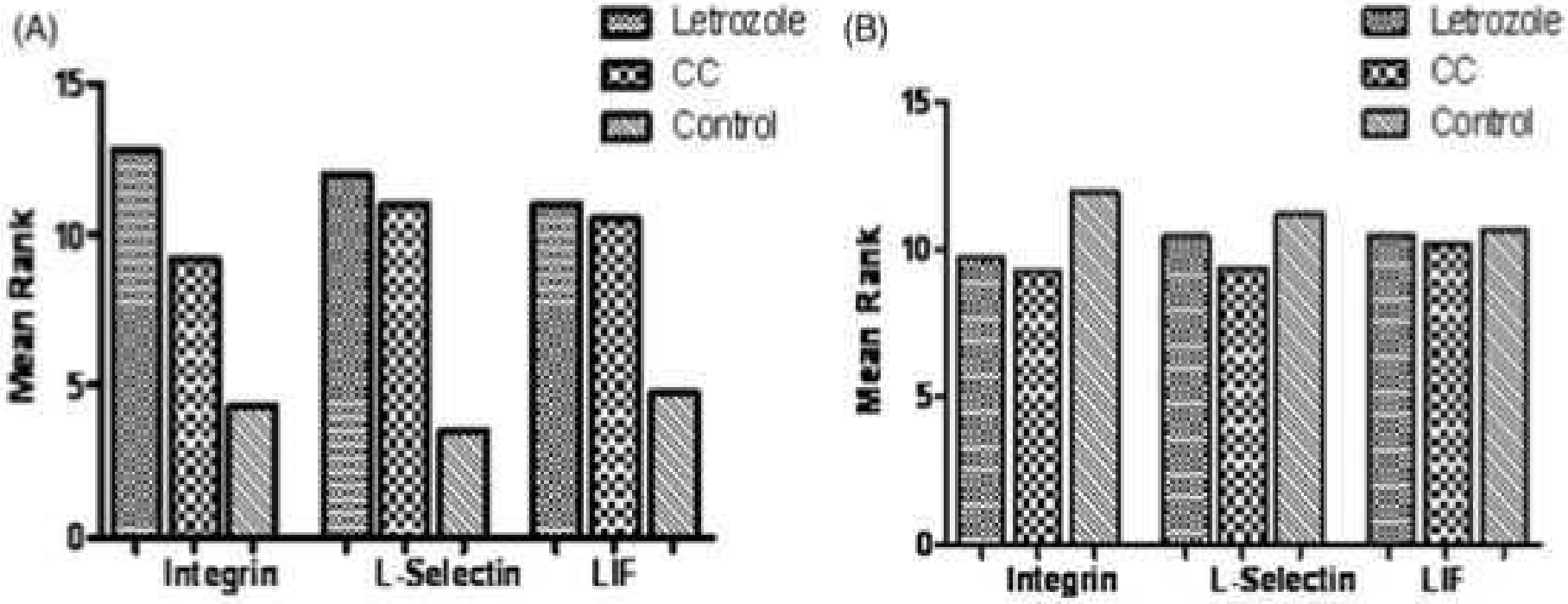
Syst Biol Reprod Med, 2014; 60(2): 105–111
 DOI: 10.3109/19396368.2013.862316

informa healthcare

RESEARCH ARTICLE

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

Ashalatha Ganesh[1]*, Nageshwar Chauhan[2], Soumen Das[3], Baidyanath Chakravarty[1], and Koel Chaudhury[4]



ERKEN EVRE ENDOMETRİOZİS'TE LETROZOL

Table 2 Summary of recent studies evaluating the efficacy of aromatase inhibitors in treating endometriosis-associated infertility

Study	Design	Indication	Intervention	Outcome
Alborzi et al[33]	RCT (n=144)	Laparoscopic and histological diagnosis of endometriosis	Letrozole 2.5 mg/day versus triptorelin 3.75 mg IM every month versus no medication for 2 months after laparoscopic surgery, with a 12-month follow-up	No significant differences among the 3 groups with regard to the pregnancy rate (23.4% versus 27.5% and 28.1%, respectively) or the disease-recurrence rate
Abu Hashim et al[68]	RCT (n=136)	Minimal/mild endometriosis, no pregnancy 6–12 months after laparoscopy	Letrozole versus CC Combined with IUI	Letrozole is not more effective than CC, as clinical pregnancy rate per cycle and cumulative pregnancy rate after 4 cycles were comparable in both groups; total number of follicles and E_2 higher in CC group
Lossl et al[69]	Prospective pilot study (n=20)	Patients with endometriomas undergoing IVF/ICSI	Prolonged combined downregulation by anastrozole 1 mg and goserelin 3.6 mg prior to IVF	Significant reduction of endometriomal volume and serum CA125 by 29% and 61%, respectively; 25% clinical pregnancy rate and 15% live-birth rate

Siklus başına gebelik oranı;Let:%15.9 vs C.C:%14.5
Kümülatif (4siklus) gebelik oranı;Let%64.7 vs C.C:%57.2 Abu Hashim et al.2012

EVE GÖTÜRÜLECEK MESAJLAR

- C.C, Anovulatuar ve BMI≤30 kg/m^2 olan hastalarda ovulasyon indüksiyonunda hala ilk seçenek…100 mg ile cevap alınamayanlarda Letrozol önerilebilir...
- Letrozol,C.C.rezistan ve BMI>30 kg/m^2 olan Anovulatuar hastalarda ovulasyon indüksiyonunda ilk seçenek olabilir!... Ama off-label kulanımı ile ilgili hastayı bilgilendirmek gerekli ve gebelik testi yapılarak başlanmalı…
- Metformin, sadece IR olan CC-rezistan ve BMI≤30 kg/m^2 olan hastalarda pretreatment olarak C.C.ile kombine kullanılabilinir…
- Açıklanamayan infertilitede oral ajanlar (C.C/LET) ile ovulasyon indüksiyonu yapılacaksa multi-folliküler gelişim hedeflenmeli ve IUI ile kombine edilmeli (3-4 siklus), hastanın **yaşı** ve **infertilite süresi** gözönüne alınarak tedavi planlanmalıdır…
- Erken evre endometriozis'de cerrahi sonrası Letrozol ile ovulasyon indüksiyonu +IUI ile ilgili RCT 'a ihtiyaç var…


HAPPY
LOVE
PEACE
FUN
NEW
YEAR
FAMILY
FUTURE
CHRISTMAS
WISHES
FRIENDSHIP
CHAMPAGNE
FORTUNE
HEALTH
2015
JOB
CHANGE
SUCCESS
FAIRNESS
FITNESS
HOLIDAY
X-MAS
FESTIVE
PARTNERSHIP
PARTY
PROSPERITY
FREEDOM
SATISFACTION
MIDNIGHT
CHANCE
GOOD
LUCK
2014
PROFIT
LIFE
BEST
WEALTH
2016
HAPPINESS
PROMOTION
ADVANCE
HOPE
MONEY