PCOS Hastalarında Ovulasyon İndüksiyonu

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Kadın Hst ve Doğum AD

PCOS

- Genellikle adölesan
- Düzensiz mensturasyon
- Hirsutizm
- Obesite
- İnfertilite
- Reprodüktif yaş grubunda %5-7
- Yaygın bir endokrinopatidir

Proposed diagnostic criteria for polycystic ovary syndrome

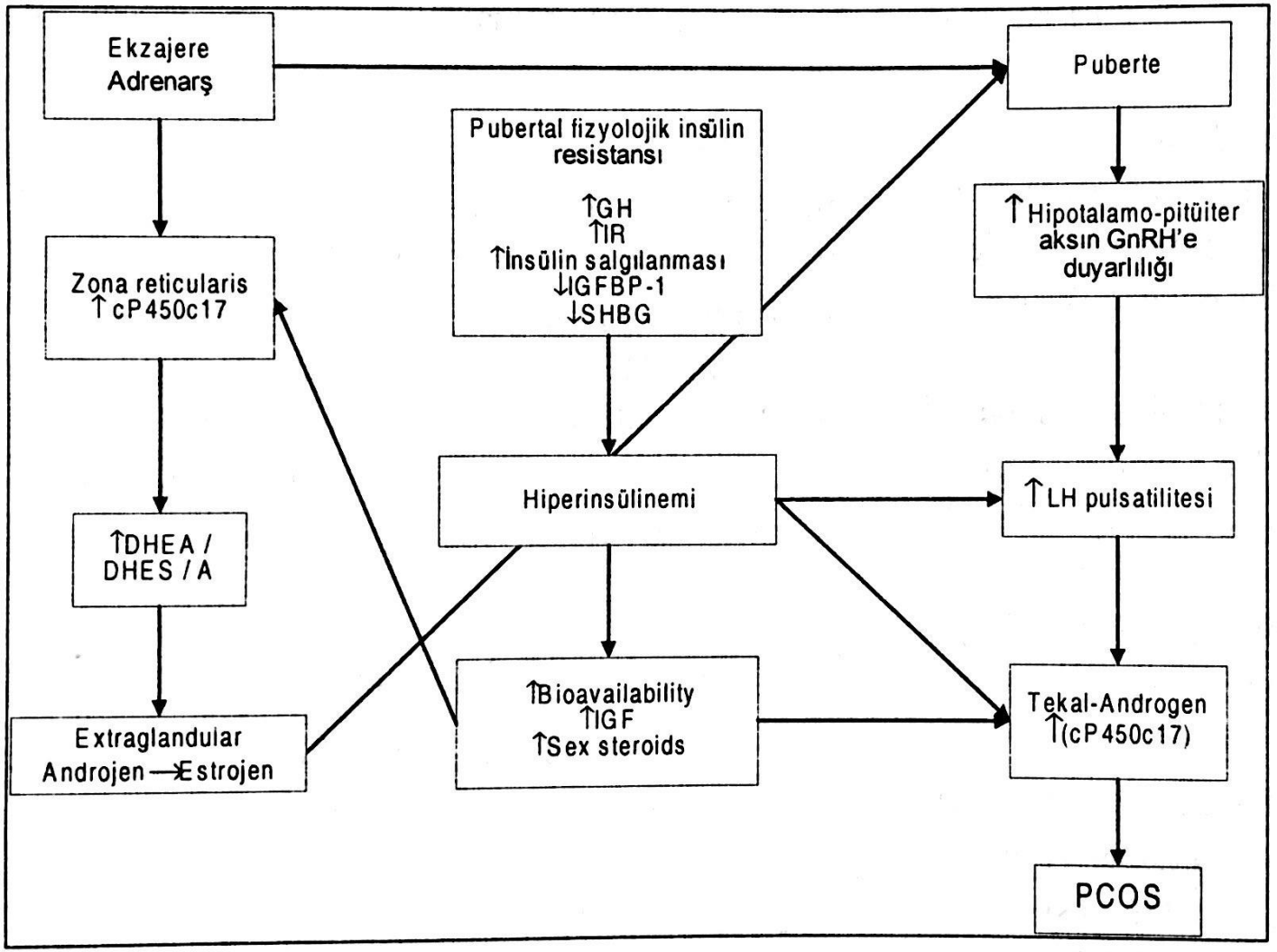
NIH consensus criteria 1990 [1] (all required)	Rotterdam criteria 2003* [2] (two out of three required)	AES definition 2008 [3] (all required)
Menstrual irregularity due to oligo- or anovulation	Oligo- or anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction – oligo/anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

PCOS: polycystic ovary syndrome; NIH: National Institutes of Health; AES: Androgen Excess Society; NCCAH: nonclassic congenital adrenal hyperplasia.
* Rotterdam criteria also require exclusion of other conditions that mimic PCOS. Criteria were developed at a 2003 consensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology [ESHRE]/American Society of Reproductive Medicine [ASRM] consensus workshop group).

References:

1. *Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In: Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc, Boston 1992. p.377.*
2. *Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19:41.*
3. *Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertil Steril 2009; 91:456.*

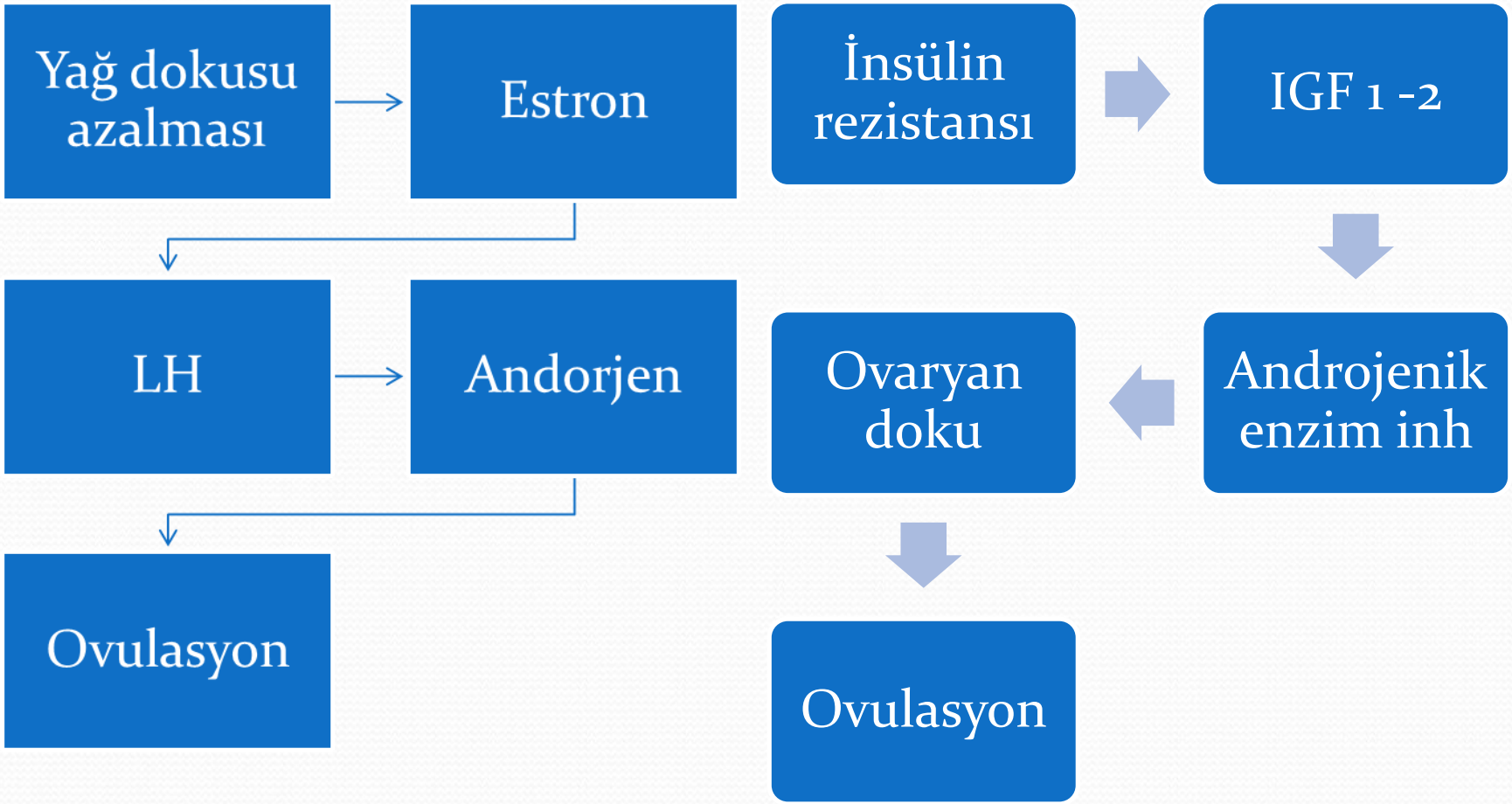
PCOS FİZYOPATOLOJİ



Multistep approach to treatment of anovulatory infertility associated with polycystic ovary syndrome

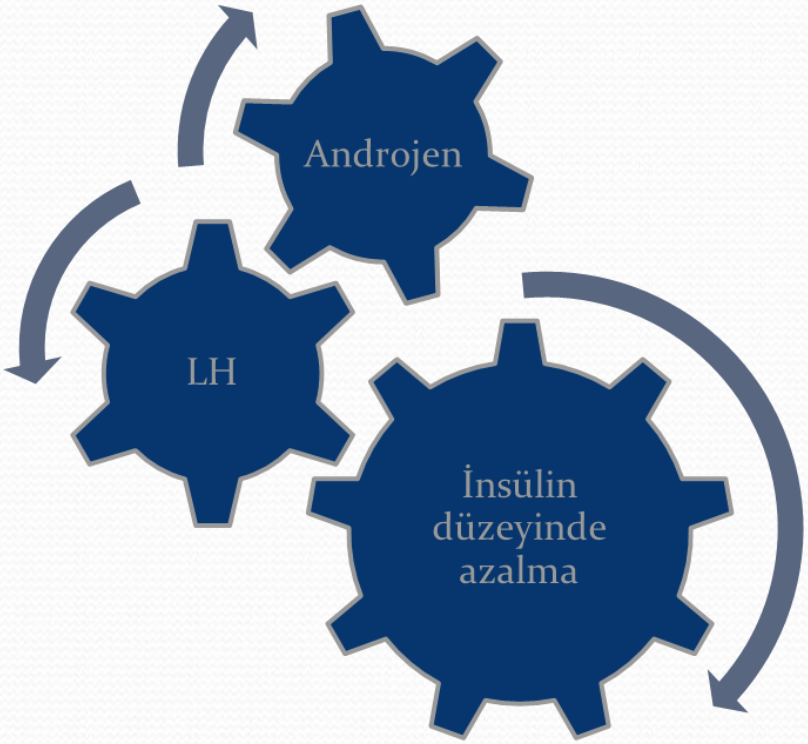
	Treatment	Cost	Multiple pregnancy risk
First line	Weight loss for high body mass index	Low	Not increased
First line	Clomiphene or letrozole with or without metformin	Low	Low
Second line	Follicle-stimulating hormone injections	High	High, includes high-order multiples
Second line	Ovarian drilling	High	Not increased
Third line	In vitro fertilization	Very high	High but reducible with single embryo transfer

KİLO KAYBI


Yağ dokusu azalması
Estron
İnsülin rezistansı
IGF 1 -2
LH
Andorjen
Androjenik enzim inh
Ovaryan doku
Ovulasyon
Ovulasyon

KİLO KAYBI


İnsülin rezistansı
SHBG
Androjen


Androjen
LH
İnsülin düzeyinde azalma

KİLO KAYBI SONUÇ

- Kilo kaybı için diyet egzersiz
- 10kg/m2 kilo kaybı: %78 ovulasyon %28 gebelik
- Hedef BMI: <27 kg/m2

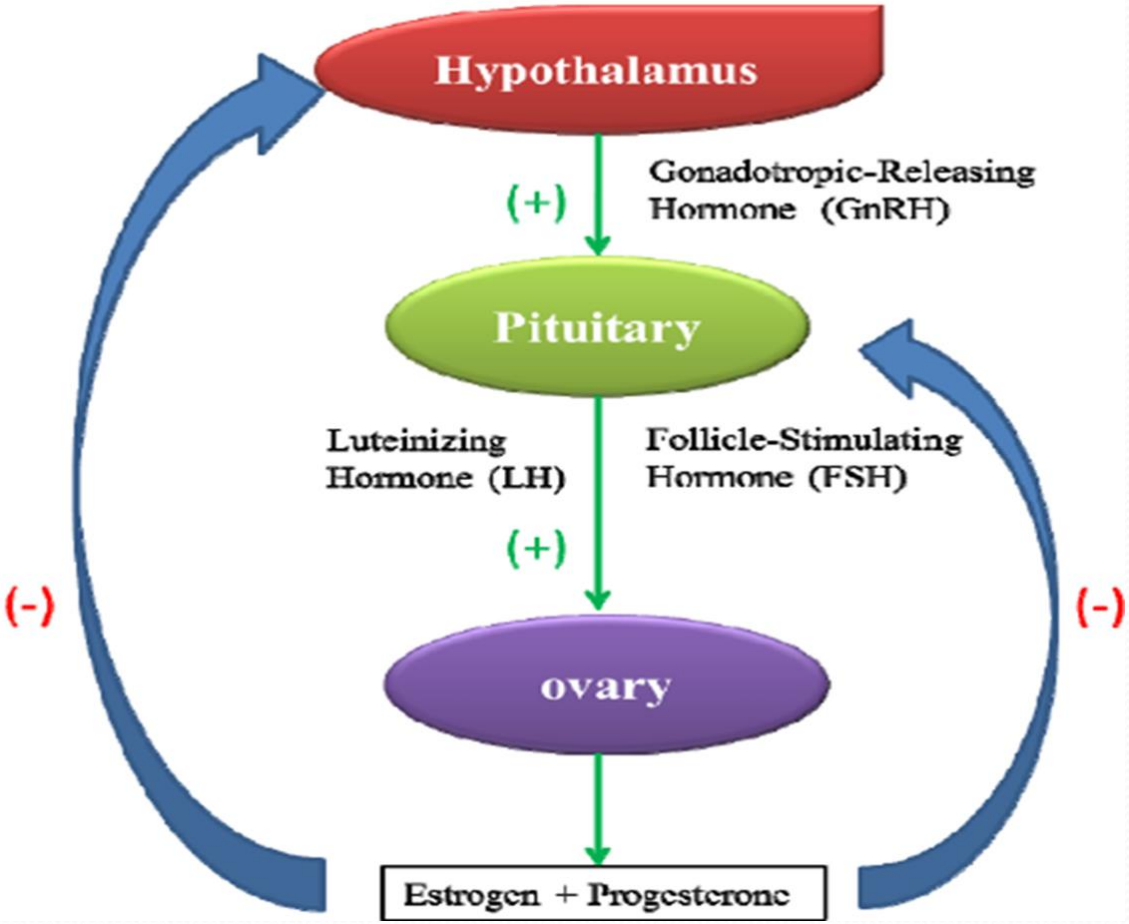
KLOMİFEN SİTRAT

- Non-steroidal, östrojene yapısal benzerliği olan SERM
- Östrojen reseptörlerini competetive inhibe eder
- Hedef dokuya bağlı olarak agonist veya antagonist
- Östrojenik etkisi sadece E2 seviyesi düşük olduğunda
- Etkin madde en-klomifen (%62)
- Hedef dokular hipotalamus-hipofiz-overler ve uterus

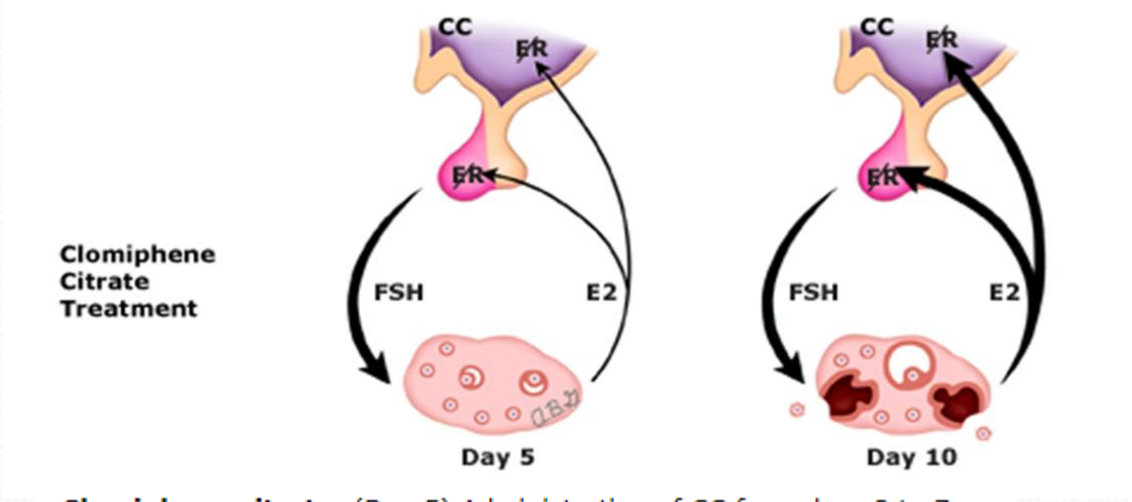
KLOMİFEN SİTRAT etki mekanizması

- Nükleer E2 reseptörüne uzun süre bağlanır ve reseptör yoğunluğunu azaltır
- Hipofizer seviyede gonadotropların GnRH'a duyarlılığını artırır
- Ovulatuar kadınlarda GnRH puls frekansını
- Anovulatuar kadınlarda GnRH puls amplitüdünü artırır
- Granüloza hücrelerinde FSH bağımlı LH reseptör yoğunluğunu arttırır

OVULASYON


Hypothalamus
(+)
Gonadotropic-Releasing Hormone (GnRH)
Pituitary
Luteinizing Hormone (LH)
Follicle-Stimulating Hormone (FSH)
(+)
(-)
(-)
ovary
Estrogen + Progesterone

KLOMİFEN SİTRAT ETKİ MEKANİZMASI



Clomiphene citrate: (Day 5) Administration of CC from days 3 to 7 results in ER depletion at the level of the pituitary and mediobasal hypothalamus. As a result, estrogen negative feedback centrally is interrupted and FSH secretion increases from the anterior pituitary leading to multiple follicular growth. (Day 10) By the late follicular phase, because of the long tissue retention of CC, there continues to be ER depletion centrally and increased E2 secretion from the ovary is not capable of normal negative feedback on FSH. The result is multiple dominant follicle growth and multiple ovulation.

KLOMİFEN SİTRAT KULLANIM ŞEKLİ

- Menstürel siklusun ilk 5 gününde başlanır
- Kontrol vajinal USG
- İlk tedavi siklusu 50mg ile başlanır
- 5 gün süre ile kullanılır
- Ovulasyon son dozdan 5- 12 gün sonra
- Ovulasyon sağlanmaz ise doz kademeli olarak doz 250 mg

KLOMİFEN SİTRAT KULLANIM ŞEKLİ

- Ancak 150 mg den sonra tedavi etkinliği azalır (FDA-ASRM >100 mg üstünü önermiyor)
- Ovulasyonun monitorizasyonu
- Ovulatuar sikluslarda gebelik oluşmamışsa aynı doz uygulanır
- Ovulasyon sağlandığında 4-6 siklus tedaviye devam edilebilir

KLOMİFEN SİTRAT KULLANIM ŞEKLİ

- M

Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000057. doi: 10.1002/14651858.CD000057.pub2.

Clomiphene citrate for unexplained subfertility in women.

Hughes E[1], Brown J, Collins JJ, Vanderkerchove P.

Author information

Abstract

BACKGROUND: The effectiveness of clomiphene citrate has been demonstrated in the treatment of subfertility associated with infrequent or irregular ovulation. The physiologic effects and clinical benefits in ovulatory women with unexplained subfertility are less clear. The drug is associated with an increased risk of multiple pregnancy and a suggestion of potentially increased ovarian cancer risks. In light of these concerns, defining the effectiveness of clomiphene citrate for ovulatory women with unexplained subfertility is extremely important.

OBJECTIVES: To determine the effectiveness of clomiphene citrate in improving pregnancy outcomes in women with unexplained subfertility, used in a dose range of 50 to 250 mg for up to 10 days. The primary outcome was live births.

SEARCH STRATEGY: We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register (June 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, Issue 2), MEDLINE (1966 to June 2009), EMBASE (1980 to June 2009) and reference lists of articles.

SELECTION CRITERIA: Only randomised controlled trials were included. Quasi-randomised designs were excluded.

DATA COLLECTION AND ANALYSIS: Fourteen potentially relevant trials were identified of which seven were included in this review. All trials were assessed for risk of bias using standardised Menstrual Disorders and Subfertility Group methodology.

MAIN RESULTS: Data relating to 1159 participants from seven trials were collated. There was no evidence that clomiphene citrate was more effective than no treatment or placebo for live birth (odds ratio (OR) 0.79, 95% CI 0.45 to 1.38; P = 0.41) or for clinical pregnancy per woman randomised both with intrauterine insemination (IUI) (OR 2.40, 95% CI 0.70 to 8.19; P = 0.16), without IUI (OR 1.03, 95% CI 0.64 to 1.66; P = 0.91) and without IUI but using human chorionic gonadotropin (hCG) (OR 1.66, 95% CI 0.56 to 4.80; P = 0.35). It should be noted that heterogeneity between studies ranged from 34% to 58% using the I(2) statistic.

AUTHORS' CONCLUSIONS: There is no evidence of clinical benefit of clomiphene citrate for unexplained fertility. When making this treatment choice, potential side effects should be discussed. These include the increased risk of multiple pregnancy and the concern that use for more that 12 cycles has been associated with a three-fold increase in risk of ovarian cancer.

KLOMİFEN SİTRAT KULLANIM ŞEKLİ

- Lüteal destek amacıyla progesteron ??

J Assist Reprod Genet. 2014 Jan;31(1):89-100. doi: 10.1007/s10815-013-0127-6. Epub 2013 Nov 6.

Efficacy of luteal phase support with vaginal progesterone in intrauterine insemination: a systematic review and meta-analysis.

Miralpeix E[1], González-Comadran M, Solà I, Manau D, Carreras R, Checa MA.

Author information

Abstract

PURPOSE: To evaluate the efficacy of luteal phase support with vaginal progesterone in women undergoing intrauterine insemination (IUI).

METHODS: Systematic review and meta-analysis. Randomized controlled trials (RCT) comparing supplementation of luteal phase with vaginal progesterone among women undergoing IUI versus a control group were included. The main outcome assessed was live birth rate.

RESULTS: Five RCT met the inclusion criteria. In all 1,271 patients were included (951 IUI cycles in the progesterone group, 935 in the control group). Women treated with vaginal progesterone achieved significantly higher live birth rate (risk ratio [RR] 1.94, 95 % confidence interval [CI] 1.36 to 2.77,), and clinical pregnancy rate (RR 1.41, 95 % CI 1.14 to 1.76) as compared with controls. In the subgroup analysis per stimulation protocol, this beneficial effect of receiving progesterone was only observed in the group stimulated with gonadotropins (RR 2.28, 95 % CI 1.49 to 3.51), compared to the group stimulated with clomiphene citrate (CC) (RR 1.30, 95 % CI 0.68 to 2.50). No differences were observed in the miscarriage and multiple pregnancy rates.

CONCLUSIONS: The supplementation of luteal phase with vaginal progesterone significantly increases live birth among women undergoing IUI when receiving gonadotropins for ovulation induction. Women receiving CC to induce ovulation do not seem to benefit from this treatment.

KLOMİFEN SİTRAT KULLANIM ŞEKLİ

- Klomifen sitrat tedavisine IUI eklenmesi ??

Acta Obstet Gynecol Scand. 2011 Apr;90(4):344-50. doi: 10.1111/j.1600-0412.2010.01063.x. Epub 2011 Feb 14.

Intrauterine insemination versus timed intercourse with clomiphene citrate in polycystic ovary syndrome: a randomized controlled trial.

Abu Hashim H[1], Ombar O, Abd Elaal I.

Author information

Abstract

OBJECTIVE: To compare the efficacy of intrauterine insemination vs. timed intercourse with clomiphene citrate as a first-line treatment for anovulatory infertility associated with polycystic ovary syndrome.

DESIGN: A randomized controlled trial following the CONSORT criteria.

SETTING: A university hospital and a private practice setting.

PATIENTS: 188 women (525 cycles) with polycystic ovary syndrome.

MAIN OUTCOME MEASURES: Women received three consecutive cycles of ovulation induction with clomiphene citrate and intrauterine insemination (n=93, 259 cycles) or three consecutive cycles of clomiphene citrate with timed intercourse (n=95, 266 cycles).

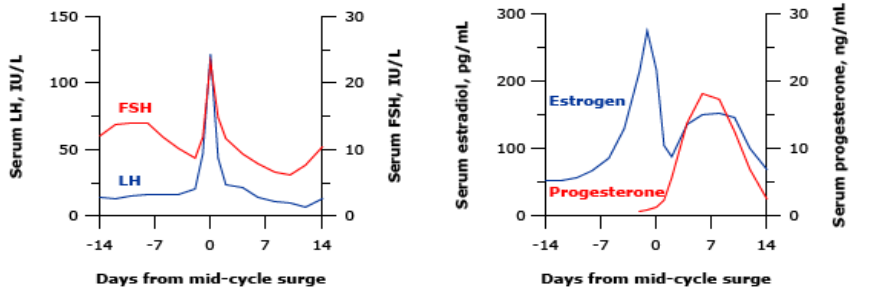
OUTCOME MEASURES: Clinical pregnancy rate per cycle, number of growing and mature follicles, serum estradiol, endometrial thickness at the hCG day, serum progesterone, ovulation, miscarriage and live birth rates.

RESULTS: There were no differences between the two groups regarding the clinical pregnancy rate per cycle or per woman (8.49 vs. 7.89% and 23.6 vs. 22.1%; p=0.26 and p=0.33, respectively). Two twin pregnancies occurred in each group. Miscarriage and live birth rates were comparable (18.1 vs. 19% and 19.35 vs. 17.89%; p=0.31 and p=0.33, respectively). No ectopic, higher-order pregnancies or cases of ovarian hyperstimulation syndrome occurred. No differences were found regarding the number of follicles, serum progesterone, ovulation rates, estradiol levels or endometrial thickness at the hCG day (7.7±0.4 vs. 7.5±0.6mm; p=0.54).

CONCLUSIONS: Ovulation induction with clomiphene citrate and timed intercourse is as effective as that with intrauterine insemination for achieving pregnancy in polycystic ovary syndrome and could represent the initial treatment option, being less invasive and less expensive than intrauterine insemination.

KLOMİFEN SİTRAT-HCG

Hormonal changes during normal menstrual cycle



Sequential changes in the serum concentrations of the hormones released from the pituitary (FSH and LH; left panel) and from the ovaries (estrogen and progesterone; right panel) during the normal menstrual cycle. By convention, the first day of menses is day 1 of the cycle (shown here as day -14). The cycle is then divided into two phases: the follicular phase is from the onset of menses until ovulation, and the luteal phase is from ovulation until the next menses. To convert serum estradiol values to pmol/L, multiply by 3.67, and to convert serum progesterone values to nmol/L, multiply by 3.18.

LH: luteinizing hormone; IU: international units; FSH: follicle-stimulating hormone.

- Etkisi ??
- Endojen LH piki saptanmayan ve IUI uygulanacak hastalarda

KLOMİFEN SİTRAT BAŞARI ORANLARI

- 3-6 siklus sonrasında %80 ovulasyon, %40 gebelik
- İnce endometrium
- Anormal lüteal faz endometrial morfoloji ??

- Servikal bezler (Mukus kalite ve miktarını bozar ?? >100 mg)
- Uterin kan akımı azalması
- Normal siklusa göre uterin volüm azalması
- Tubal motilite azalması

KLOMİFEN SİTRAT
YAN ETKİ

- Doz ile ilişkili değildir
- Sıcak basması
- Abdominal şişkinlik
- Meme hassasiyeti
- Bulantı kusma

KLOMİFEN SİTRAT
YAN ETKİ

- Mood değişikliği
- Görme bozuklukları (bulanık görme, skotom, çift görme)
- Baş ağrısı
- Çoğul gebelik
- OHSS

KLOMİFEN SİTRAT KANSER

- Artan ovulasyon ve hormonal seviyeye bağlı
- Over Ca
- Meme Ca
- İnfertilite ??
- Klomifen sitrat sonrası doğan çocuklarda kanser riskini arttırmadığı ifade ediliyor

Cochrane Database Syst Rev. 2013 Aug 13;(8):CD008215. doi: 10.1002/14651858.CD008215.pub2.

Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility.

Rizzuto I[1], Behrens RF, Smith LA.

Cancer Epidemiol Biomarkers Prev. 2017 Jun;26(6):953-962. doi: 10.1158/1055-9965.EPI-16-0809. Epub 2017 Jan 20.

Cancer Risk in Women Treated with Fertility Drugs According to Parity Status-A Registry-based Cohort Study.

Reigstad MM[1,2], Storeng R[3], Myklebust TÅ[2], Oldereid NB[4], Omland AK[4], Robsahm TE[2], Brinton LA[5], Vangen S[3], Furu K[6], Larsen IK[2].

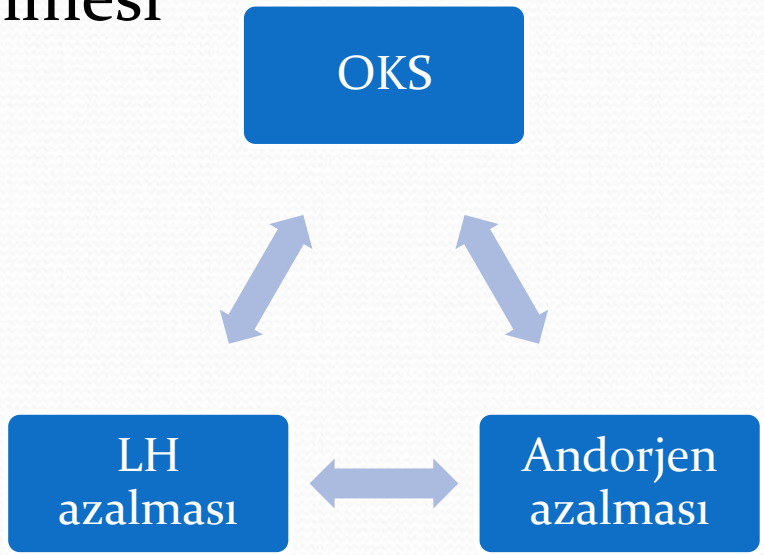
Author information

Abstract

Background: Long-term safety of assisted reproductive techniques (ART) is of interest as their use is increasing. Cancer risk is known to be affected by parity. This study examined the risk of cancer after fertility treatment, stratified by women's parity.**Methods:** Data were obtained from all women (*n* = 1,353,724) born in Norway between 1960 and 1996. Drug exposure data (2004-2014) were obtained from the Norwegian Prescription Database (drugs used in ART and clomiphene citrate). The Medical Birth Registry of Norway provided parity status. HRs were calculated for all site cancer, breast, cervical, endometrial, ovarian, colorectal, central nervous system, thyroid cancer, and malignant melanoma.**Results:** In 12,354,392 person-years of follow-up, 20,128 women were diagnosed with cancer. All-site cancer risk was 1.14 [95% confidence interval (95% CI), 1.03-1.26] and 1.10 (95% CI, 0.98-1.23) after clomiphene citrate and ART exposure, respectively. For ovarian cancer, a stronger association was observed for both exposures in nulliparous (HR, 2.49; 95% CI, 1.30-4.78; and HR, 1.62; 95% CI, 0.78-3.35) versus parous women (HR, 1.37; 95% CI, 0.64-2.96; and HR, 0.87; 95% CI, 0.33-2.27). Elevated risk of endometrial cancers was observed for clomiphene citrate exposure in nulliparous women (HR, 4.49; 95% CI, 2.66-7.60 vs. HR, 1.52; 95% CI, 0.67-3.42). Risk was elevated for breast cancer in parous women exposed to clomiphene citrate (HR, 1.26; 95% CI, 1.03-1.54) for thyroid cancer and among nulliparous women after ART treatment (HR, 2.19; 95% CI, 1.08-4.44).**Conclusions:** Clomiphene citrate appears associated with increased risk of ovarian and endometrial cancer. Elevations in risks of breast and thyroid cancer were less consistent across type of drug exposure and parity.**Impact:** Continued monitoring of fertility treatments is warranted. *Cancer Epidemiol Biomarkers Prev; 26(6); 953-62. ©2017 AACR.*

KLOMİFEN SİTRAT EK İLAÇ

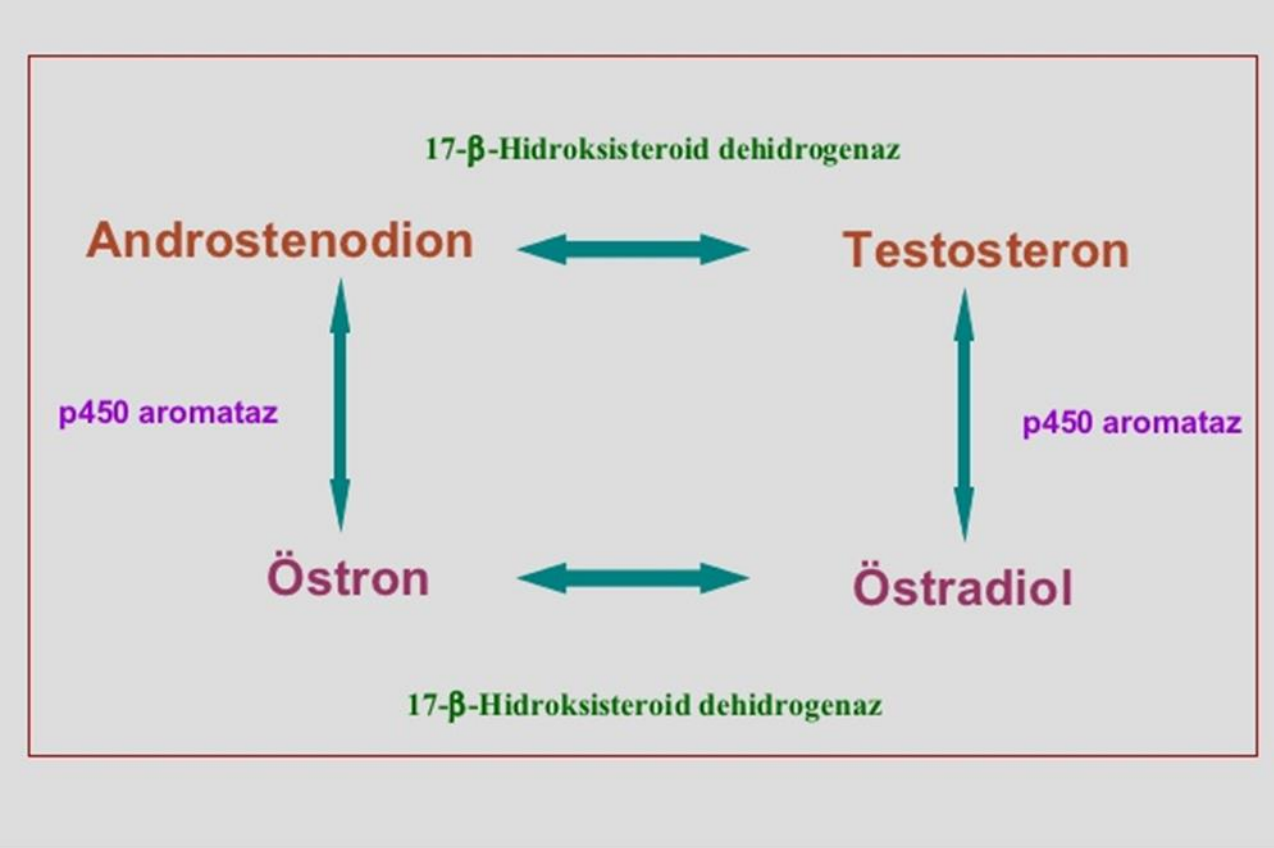
- Metformin eklenmesi (obez insülin direnci olan hastalarda)
- Dexametazon eklenmesi
- Tedavi öncesi 2 siklus OKS eklenmesi



KLOMİFEN SİTRAT Glukokortikoid

- DHEAS düzeyinin >200 µg/dl olduğu olgularda
- Sürekli yada foliküler fazda kullanılabilir (Gün: 5-14)
- Androjen süpresyonu
- Gelişen oosit üzerine pozitif etki
- FSH ile sinerjistik etki gösteren sitokin düzeyinde artış
- Prednisolon 5 mg/gün
- Dexametazon 0.5-2 mg/gün

AROMATAZ İNHİBİTÖRLERİ



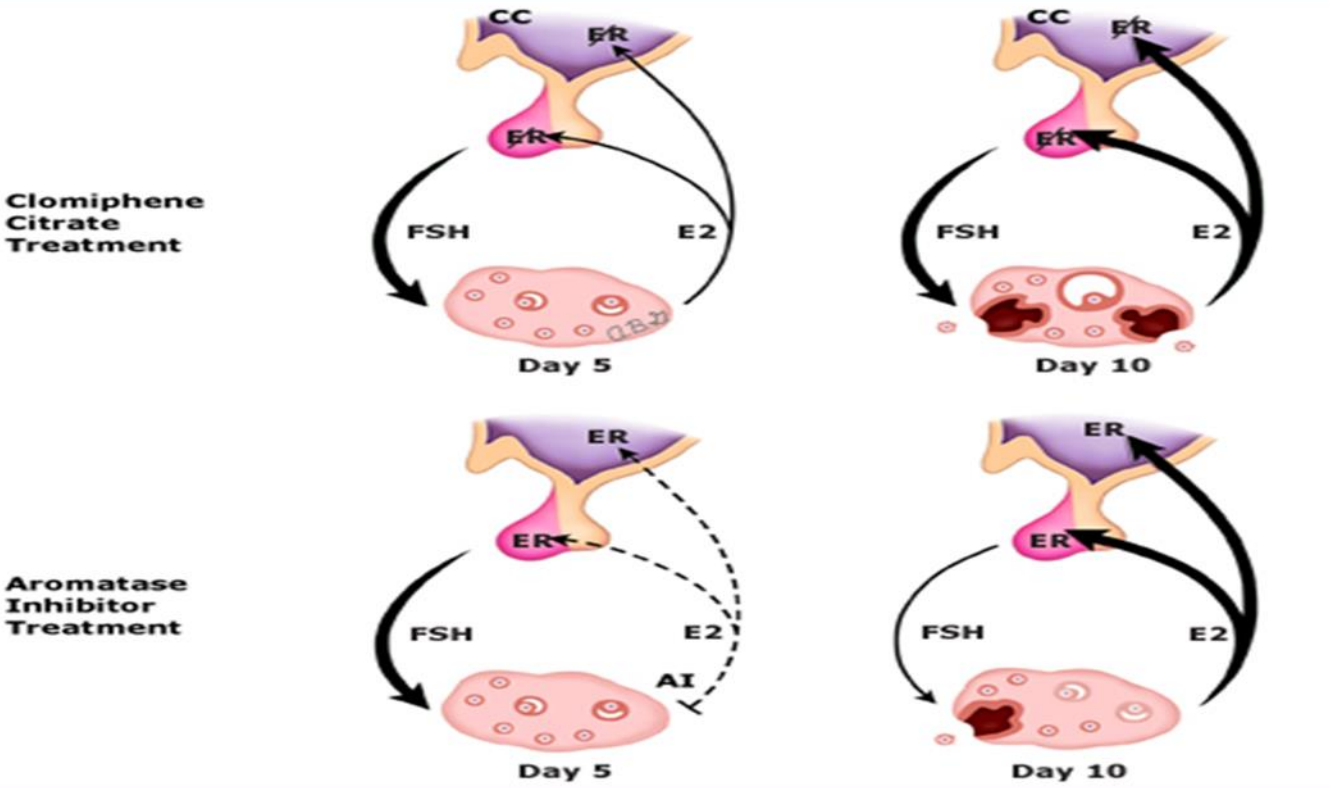
AROMATAZ İNHİBİTÖRLERİ

- İlk olarak postmenapozal meme kanseri tedavisinde
- Son yıllarda ovülasyon indüksiyonu amacıyla
- Ancak ovulasyon indüksiyonu için henüz onay almamıştır
- Günümüzde ovulasyon indüksiyonu için 3. kuşak aromataz inhibitörleri kullanılmaktadır.
- Steroid yapıda (Exemestan) non-steroid yapıda (Letrazol, Anastrazol)

AROMATAZ İNHİBİTÖRLERİ

- Letrazol, Anatrazol
- Triazol derivesi (antifungal)
- Aromatoz enzimini
- Reversible-Kompetetif
- Potent-Non-steroid
- 1-5 mg/ gün dozunda E2 üretimini %97-99 oranında inhibe eder ve östrojeni ölçülemeyecek düzeye düşürürler
- Yarı ömrü yaklaşık 45 saat (30-60 saat)

Aromatase inhibitor treatment



Aromatase inhibitor: (Day 5) Administration of an AI from 3 to 7 days results in suppression of ovarian E2 secretion and reduction in estrogen negative feedback at the pituitary and mediobasal hypothalamus. Increased FSH secretion from the anterior pituitary results in stimulation of multiple ovarian growth. (Day 10) Later in the follicular phase, the effect of the AI is reduced and E2 levels increase as a result of follicular growth. Because AIs do not affect ERs centrally, the increased E2 levels result in normal negative feedback on FSH secretion and follicles less than dominant follicle size undergo atresia, with resultant monofollicular ovulation in most cases.

AROMATAZ İNHİBİTÖRLERİ

- Genelde tek folikül gelişir
- Artan androjen düzeyine bağlı olarak folikülün FSH duyarlılığı artar
- Endometriumda E2 reseptör upregülasyonu
- Östrojen reseptörleri ile direk etkileşim olmadığından servikal mukus ve endometrium üzerinde anti östrojenik etkinliği yoktur

AROMATAZ İNHİBİTÖRLERİ kullanım şekli

- Menstürel siklusun 3-7. günleri arasında
- Letrazol 2.5-5-7.5 mg/gün
- Letrazol 20 mg tek doz
- Anastrazol 1-5-10-20-30 mg/gün
- Takip klomifen sitrat ile aynı

AROMATAZ İNHİBİTÖRLERİ
yan etki

- Sıcak basması
- Kemik ağrısı
- Sırt ağrısı
- Bulantı
- Bacaklarda kramp
- Yorgunluk
- Baş dönmesi

Klomifen sitrat aromataz inhibitör kıyaslaması

Multifoliküler gelişim	Monofoliküler gelişim
Çoğul gebelik (%7.4)	Çoğul gebelik (%3.4)
Servikal mukus (-) etki	Servikal mukus etki yok
Endometrium (-) etki	Endometrium (+) etki
Uzun yarılanma ömrü (2 hafta-teratojenite riski?)	Kısa yarılanma ömrü (48 saat-teratojenite riski az)
Daha fazla E2 üretimi	Daha az E2 üretimi (meme- endometrium kanserli)
BMI < 30 kg/m2	BMI >30 kg/m2

Klomifen sitrat aromataz inhibitör kıyaslaması

N Engl J Med. 2014 Jul 10;371(2):119-29. doi: 10.1056/NEJMoa1313517.

Letrozole versus clomiphene for infertility in the polycystic ovary syndrome.

Legro RS[1], Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; NICHD Reproductive Medicine Network.

⊕ Collaborators (57)

⊕ Author information

Erratum in
N Engl J Med. 2014 Oct 9;317(15):1465.

Cochrane Database Syst Rev. 2014 Feb 24;(2):CD010287. doi: 10.1002/14651858.CD010287.pub2.

Aromatase inhibitors for subfertile women with polycystic ovary syndrome.

Franik S[1], Kremer JA, Nelen WL, Farquhar C.

⊕ Author information

Abstract

BACKGROUND: Polycystic ovary syndrome (PCOS) is the most common cause of infrequent periods (oligomenorrhoea) and absence of periods (amenorrhoea). It affects about 4% to 8% of women worldwide and often leads to anovulatory subfertility. Aromatase inhibitors (AIs) are a novel class of drugs that were introduced for ovulation induction in 2001. Over the last ten years clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective as the first-line treatment clomiphene citrate (CC).

AUTHORS' CONCLUSIONS: Letrozole appears to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to clomiphene citrate. The quality of this evidence is low and findings should be regarded with some caution. There appears to be no difference in effectiveness between letrozole and laparoscopic ovarian drilling, though there were few relevant studies. OHSS was a very rare event, with no occurrences in most studies.

Klomifen sitrat aromataz inhibitör kıyaslaması

Reprod Biomed Online. 2011 Jul;23(1):91-6. doi: 10.1016/j.rbmo.2011.03.024. Epub 2011 Apr 3.

Fertil Steril. 2009 Sep;92(3):849-52. Epub 2007 Jun 19.

Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial.

Badawy A[1], Abdel Aal I, Abulatta M.

Author information

Abstract

OBJECTIVE: To compare the effects of letrozole (5 mg) and clomiphene citrate (100 mg) for ovulation induction in women with polycystic ovary syndrome (PCOS).

DESIGN: Prospective randomized trial.

SETTING: University teaching hospital and private practice setting.

PATIENT(S): The study comprised a total of 438 infertile women (1063 cycles) with PCOS.

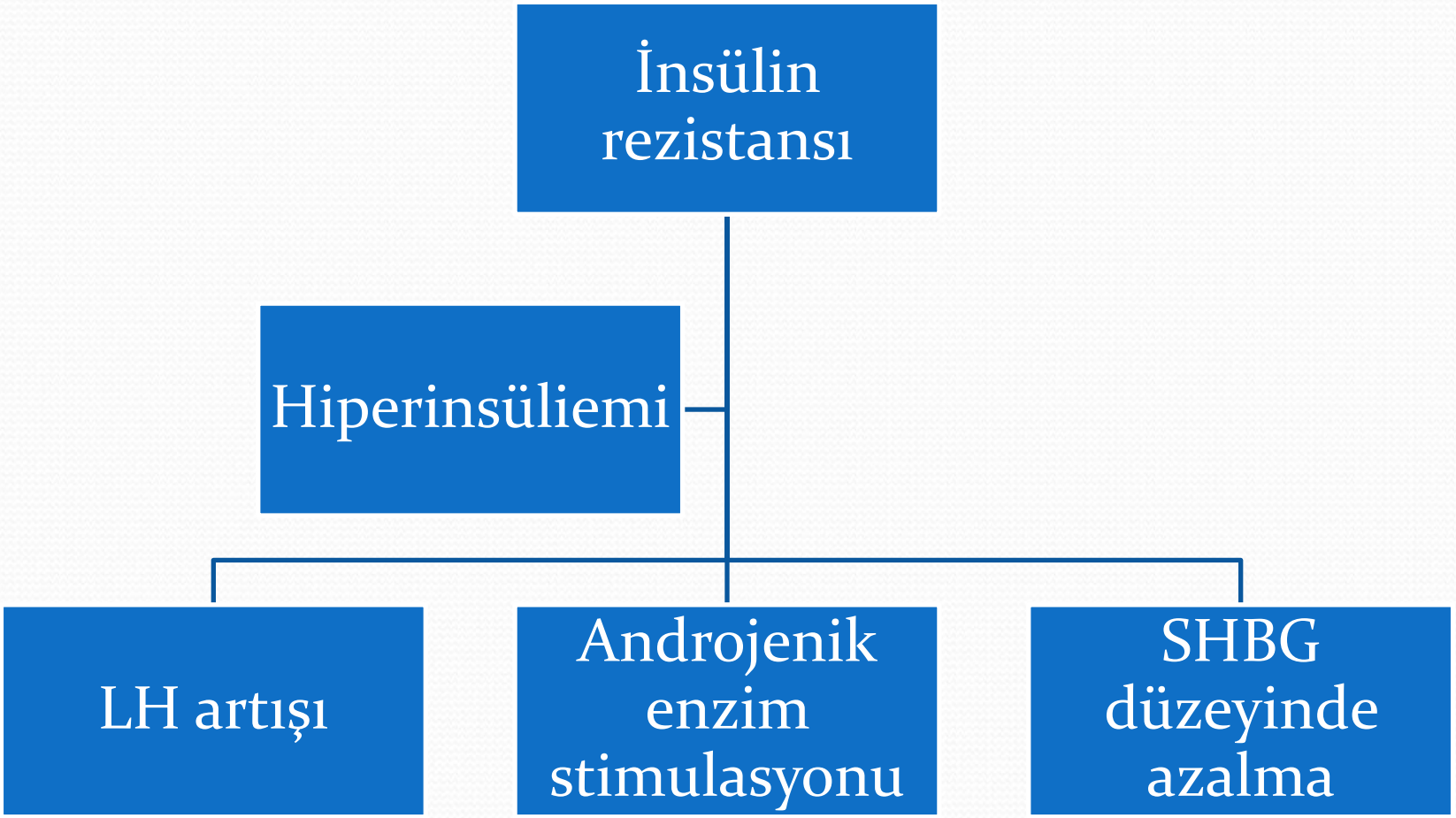
INTERVENTION(S): Patients were randomized to treatment with 5 mg of letrozole daily (218 patients, 545 cycles) or 100 mg of clomiphene citrate daily (220 patients, 518 cycles) for 5 days starting on day 3 of menses. Timed intercourse was advised 24 to 36 hours after hCG injection.

MAIN OUTCOME MEASURE(S): Number of follicles, serum estradiol, serum progesterone, endometrial thickness, and pregnancy and miscarriage rates.

RESULT(S): The mean age, parity, and duration of infertility in both groups were similar. The total number of follicles was statistically significantly greater in the clomiphene citrate group (6.8 +/- 0.3 versus 4.4 +/- 0.4). Endometrial thickness at the time of hCG administration was statistically significantly greater in the CC group (9.2 +/- 0.7 mm versus 8.1 +/- 0.2 mm). The duration to reach a dominant follicle was statistically significantly longer in the letrozole group (12.1 +/- 1.3 versus 8.8 +/- 2.9 days). Ovulation occurred in 365 out of 540 cycles (67.5%) in letrozole group and 371 out of 523 cycles (70.9%) without a statistically significant difference. Levels of serum estradiol and progesterone were statistically significantly higher in the clomiphene citrate group. The pregnancy rate per cycle was 15.1% in the letrozole group and 17.9% in the clomiphene citrate group without statistically difference between the groups.

CONCLUSION(S): The results of this study did not show any advantage to the use of letrozole over clomiphene citrate as a first-line treatment for induction of ovulation in women with PCOS.

Ovulasyon indüksiyonunda Metformin



Ovulasyon indüksiyonunda Metformin

- Serum androjen düzeyinde azalma (hirsutizde düzelme sağlamaz)
- Menstürel siklusun restorasyonu (%50)
- Ovulatuar sikluslar (?)
- Kilo kaybı (?)
- Ancak ovulasyon indüksiyonu için onay yok

Ovulasyon indüksiyonunda Metformin

- Sadece insülin rezistansı olan PCOS'lu hastalarda
- İnsülin rezistansını gösteren spesifik bir test yok
- Bazı klinisyenler bozulmuş GTT öneriyor
- Yükselmiş insülin düzeyi

Ovulasyon indüksiyonunda Metformin

- Günlük doz (500-2000 mg)
- Yan etkileri (GIS)
- Spontan abort (?)
- Gestasyonel DM (?)
- Kongenital anomali (?)

Ovulasyon indüksiyonunda Metformin

J Clin Endocrinol Metab. 2012 May;97(5):1492-500. doi: 10.1210/jc.2011-3061. Epub 2012 Mar 14.

Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial.

Morin-Papunen L[1], Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A, Tapanainen JS.

Author information

Abstract

BACKGROUND: The role of metformin in the treatment of infertility in women with polycystic ovary syndrome (PCOS) is still controversial. OBJECTIVE AND OUTCOMES: We investigated whether metformin decreases the early miscarriage rate and improves the pregnancy rates (PR) and live-birth rates (LBR) in PCOS.

METHODS: This was a multicenter, randomized (1:1), double-blind, placebo-controlled study. Three hundred twenty women with PCOS and anovulatory infertility were randomized to metformin (n = 160, Diformin; obese women, 1000 mg two times daily; nonobese subjects, 500 mg + 1000 mg daily) or identical doses of placebo (n = 160). After 3 months' treatment, another appropriate infertility treatment was combined if necessary. If pregnancy occurred, metformin/placebo was continued up to the 12th week.

RESULTS: Miscarriage rates were low and similar in the two groups (metformin 15.2% vs. placebo 17.9%, P = 0.8). Intent-to-treat analysis showed that metformin significantly improved PR and LBR (vs. placebo) in the whole study population (PR: 53.6 vs. 40.4%, P = 0.006; LBR: 41.9 vs. 28.8%, P = 0.014) and PR in obese women (49.0 vs. 31.4%, P = 0.04), and there was a similar trend in nonobese (PR: 58.6 vs. 47.6%, P = 0.09; LBR: 46.7 vs. 34.5%, P = 0.09) and in obese women with regard to LBR (35.7 vs. 21.9%, P = 0.07). Cox regression analysis showed that metformin plus standard infertility treatment increased the chance of pregnancy 1.6 times (hazard rate 1.6, 95% confidence interval 1.13-2.27).

CONCLUSION: Obese women especially seem to benefit from 3 months' pretreatment with metformin and its combination thereafter with routine ovulation induction in anovulatory infertility.

Ovulasyon indüksiyonunda Metformin

Cochrane Database Syst Rev. 2017 Nov 29;11:CD003053. doi: 10.1002/14651858.CD003053.pub6.

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

Morley LC[1], Tang T, Yasmin E, Norman RJ, Balen AH.

⊕ Author information

Abstract

BACKGROUND: Polycystic ovary syndrome (PCOS) is characterised by infrequent or absent ovulation, and high levels of androgens and insulin (hyperinsulinaemia). Hyperinsulinaemia occurs secondary to insulin resistance and is associated with increased risk of cardiovascular disease and diabetes mellitus. Insulin-sensitising agents such as metformin may be effective in treating PCOS-related anovulation.

OBJECTIVES: To evaluate the effectiveness and safety of insulin-sensitising drugs in improving reproductive and metabolic outcomes for women with PCOS undergoing ovulation induction.

AUTHORS' CONCLUSIONS: Our updated review suggests that metformin alone may be beneficial over placebo for live birth, although the evidence quality was low. When metformin was compared with clomiphene citrate, data for live birth were inconclusive, and our findings were limited by lack of evidence. Results differed by body mass index (BMI), emphasising the importance of stratifying results by BMI. An improvement in clinical pregnancy and ovulation suggests that clomiphene citrate remains preferable to metformin for ovulation induction in obese women with PCOS.An improved clinical pregnancy and ovulation rate with metformin and clomiphene citrate versus clomiphene citrate alone suggests that combined therapy may be useful although we do not know whether this translates into increased live births. Women taking metformin alone or with combined therapy should be advised that there is no evidence of increased miscarriages, but gastrointestinal side effects are more likely.

Ovulasyon indüksiyonunda Metformin

Fertil Steril. 2008 Mar;89(3):505-22. doi: 10.1016/j.fertnstert.2007.09.041. Epub 2008 Feb 20.

Consensus on infertility treatment related to polycystic ovary syndrome.

Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.

Collaborators (31)

Abstract

The treatment of infertile women with polycystic ovary syndrome (PCOS) is surrounded by many controversies. On the basis of the currently available evidence, a group of experts reached a consensus regarding the therapeutic challenges raised in these women. Before any intervention is initiated, preconceptional counseling should be provided emphasizing the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking, and alcohol consumption. The recommended first-line treatment for ovulation induction remains the anti-estrogen clomiphene citrate (CC). Recommended second-line intervention, should CC fail to result in pregnancy, is either exogenous gonadotropins or laparoscopic ovarian surgery (LOS). The use of exogenous gonadotropins is associated with increased chances for multiple pregnancy, and, therefore, intense monitoring of ovarian response is required. Laparoscopic ovarian surgery alone is usually effective in less than 50% of women, and additional ovulation induction medication is required under those circumstances. Overall, ovulation induction (representing the CC-gonadotropin paradigm) is reported to be highly effective with a cumulative singleton live-birth rate of 72%. Recommended third-line treatment is in vitro fertilization (IVF). More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS. Such approaches may result in deviation from the above mentioned first-line, second-line, or third-line ovulation strategies in well-defined subsets of patients. Metformin use in PCOS should be restricted to women with glucose intolerance. Based on recent data available in the literature, the routine use of this drug in ovulation induction is not recommended. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus.

PMID: 18243179 DOI: 10.1016/j.fertnstert.2007.09.041

[Indexed for MEDLINE]

Ovulasyon indüksiyonunda Metformin

Fertil Steril. 2017 Sep;108(3):426-441. doi: 10.1016/j.fertnstert.2017.06.026.

Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline.

Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org[1], Practice Committee of the American Society for Reproductive Medicine.

Collaborators (20)

Author information

Abstract

Metformin alone compared with placebo increases the ovulation rate in women with polycystic ovary syndrome (PCOS) but should not be used as first-line therapy for anovulation because oral ovulation induction agents such as clomiphene citrate or letrozole alone are much more effective in increasing ovulation, pregnancy, and live-birth rates in women with PCOS. There is fair evidence that metformin alone does not increase rates of miscarriage when stopped at the initiation of pregnancy and insufficient evidence that metformin in combination with other agents used to induce ovulation increases live-birth rates.

İlginiz ve sabrınızdan dolayı teşekkürler