

PKOS'da Hirsutizm tanı ve farmakolojik tedavisi

Yılmaz Şahin

Erciyes Üniversitesi Tıp Fakültesi

Kadın Hast. ve Doğum Anabilim Dalı

Üreme Endokrinolojisi ve İVF Ünitesi

Kayseri

83 PKOS hastanın

- %65 oligomenore
- %5 amenore
- %30 ömenore
- %100 hiperandrojenemi (fT>11.1 pmol/l)
- %92 hirsutizm
- %40 LH/FSH>2

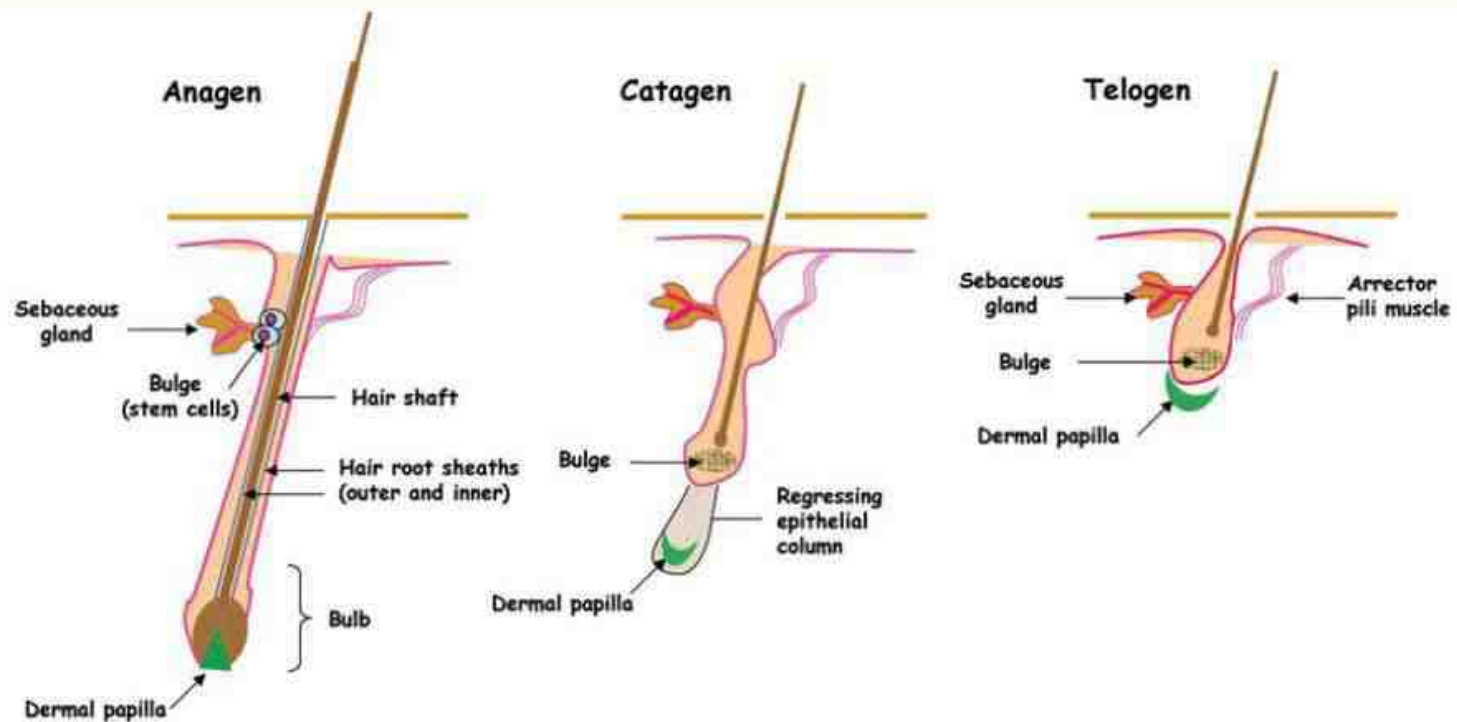


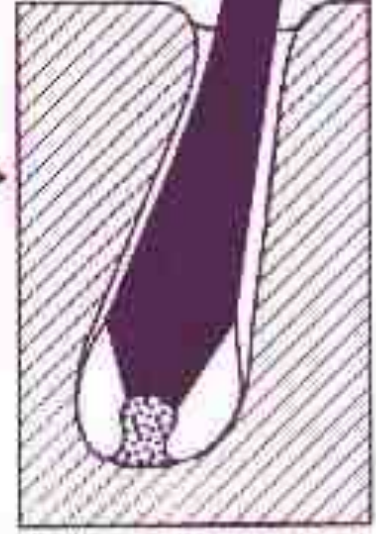
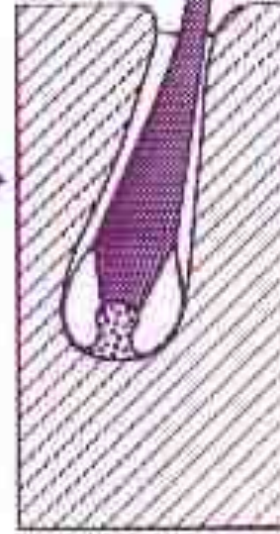
Figure 4 The hair follicle growth cycle. Hair follicles possess the ability, unique among mammalian tissues, to be partially regenerated in a process termed the hair follicle growth cycle. Hair follicles go through repeated cycles of development and growth (anagen), regression (catagen) and rest (telogen) to enable the replacement of hairs.

Yüz

vellus
follikül

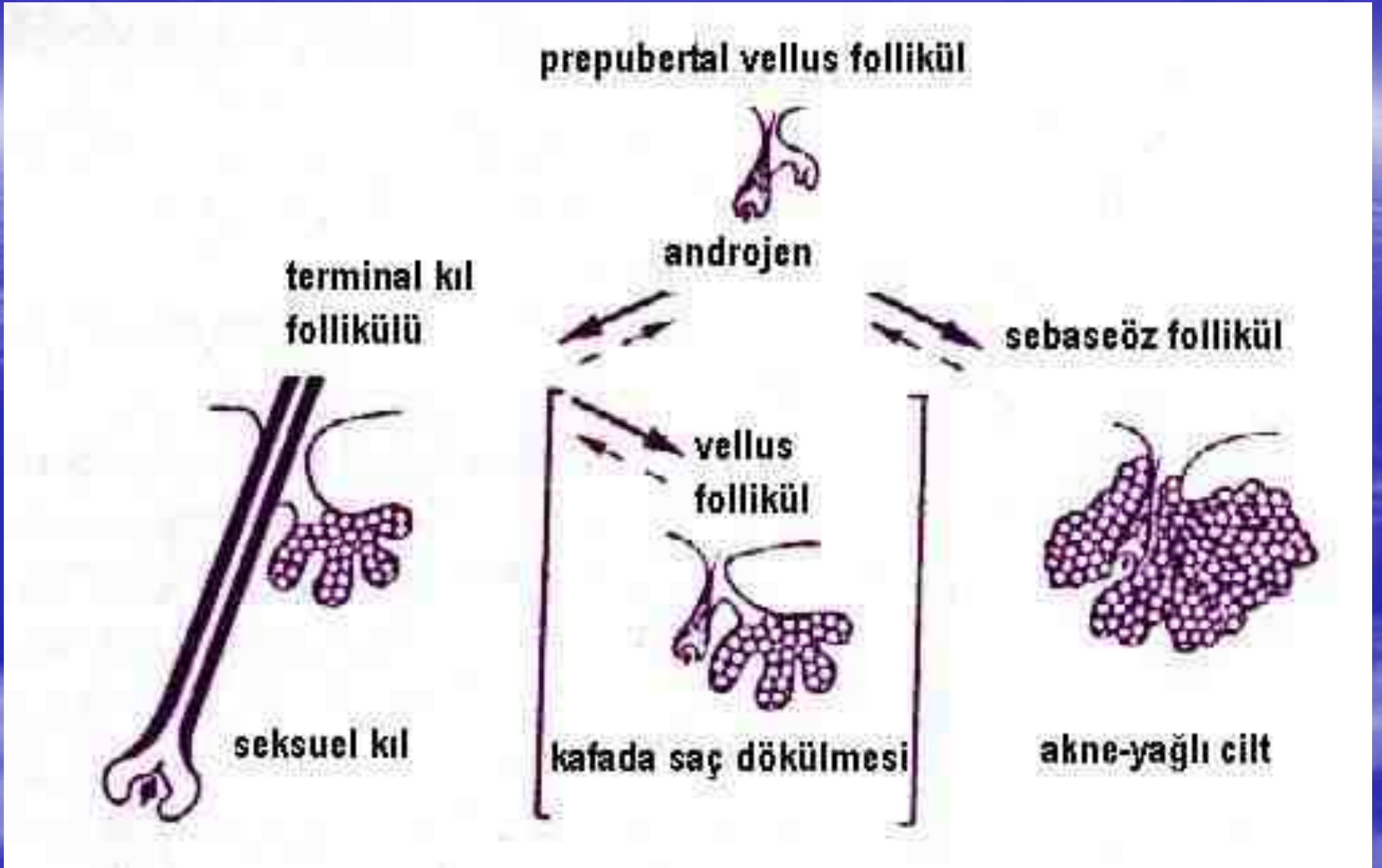
kısa, ince
pigmentsiz kıl

+
androjenler



uzun, kalın
pigmente
kıl

Şekil 1. Androjenlere hassas yüz gibi vücut bölgelerinde kıl folliküllerinin androjenlere cevabı.



Şekil 3. Pilosebaceöz ünitenin gelişmesinde androjenlerin rolü. Kalın çizgiler androjen etkisini, kesikli çizgiler ise antiandrojen etkisini göstermektedir.

Hirsutizm nedenleri

Polikistik over sendromu % 80

İdyopatik hirsutizm % 18

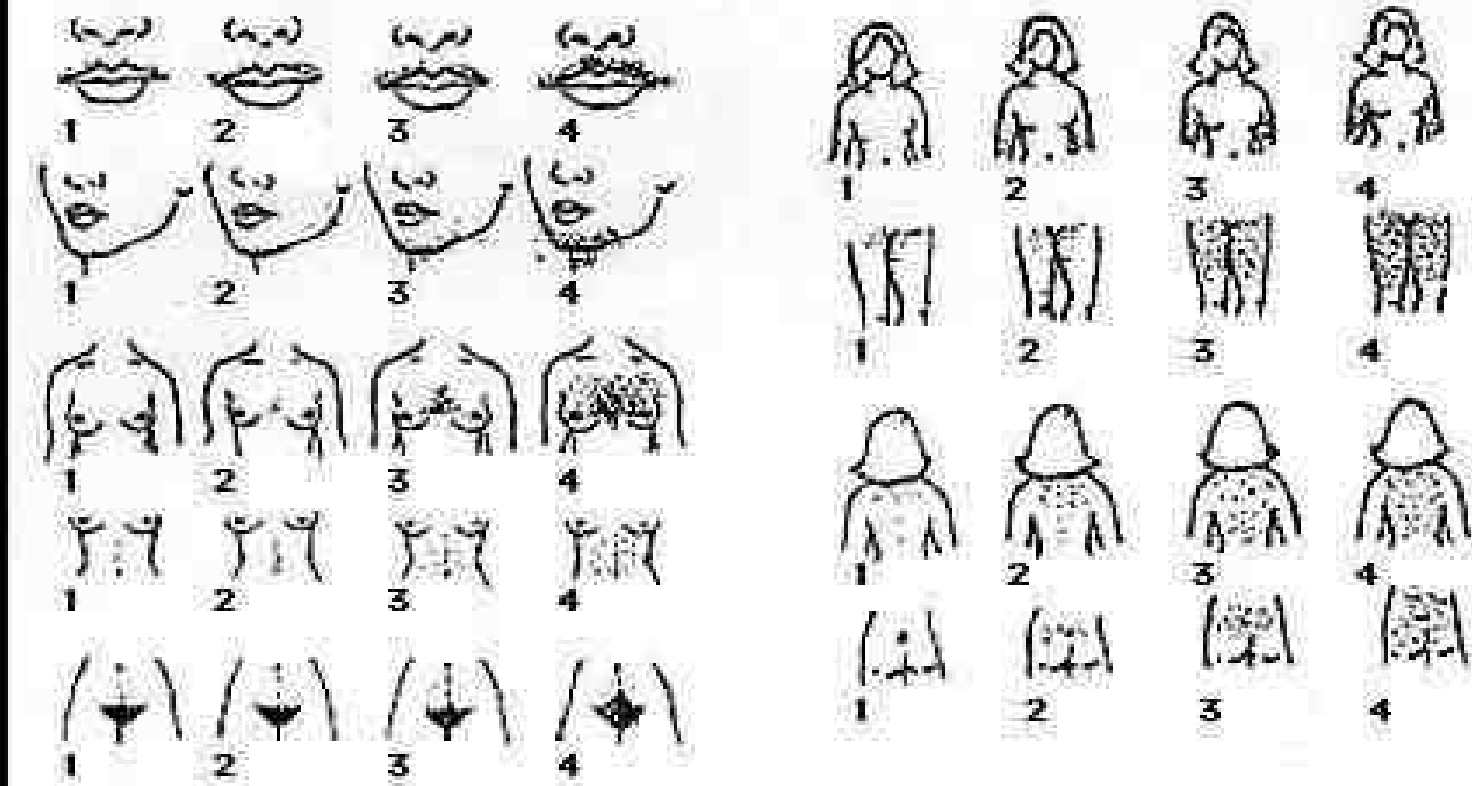
Kongenital adrenal hiperplazi < % 1

Androjen sekrete eden over tümörü < % 1

Cushing sendromu < % 1

Androjen sekrete eden adrenal tümör < % 1

Eksojen androjenik etkili ilaç alımı < % 1



Grading of severity of hirsutism in women Hirsutism scoring standards at different sites showing the spectrum from minimal hirsutism (grade 1) to frank virilization (grade 4). (Adapted from Hatch, R, Rosenfield, RS, Kim, MH, Tredway, D, Am J Obstet Gynecol 1981;140:815.)

Modifiye-FG skoru > 8 (2-10)

Total skor: 0-36

Hafif hirsutizm: 15' e kadar

Orta hirsutizm: 16 – 25

Şiddetli hirsutizm: 25 - 36

Skorlama

1. Subjektif

2. interobserver variation

**Hypertrikozis
+
Hirsutizm**

**Hipertrikozis
genellikle
herediterdir.**



2 15:44

**HA hipertrikozisi
artırabilir**

2 15:45

Hirsutizm, akne, yağlı cilt



Aynı hasta

Göğüs

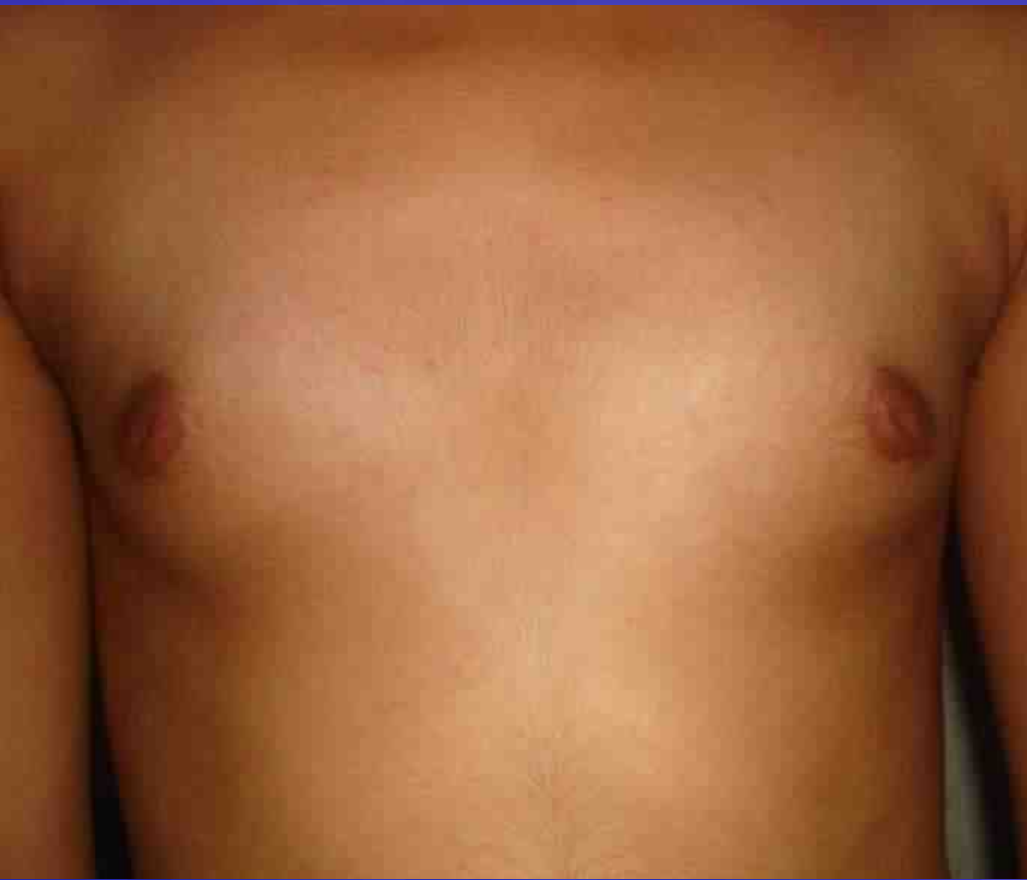
Bel



PKOS – hirsutizm

- ▶ İyi bir anamnez
- ▶ Fizik muayene
- ▶ Peripubertal başlangıç
- ▶ Yıllar içinde yavaş ilerleme
- ▶ Aile hikayesi sıktır





Simple virilizan KAH

Ovarian A-S tümör

59 y

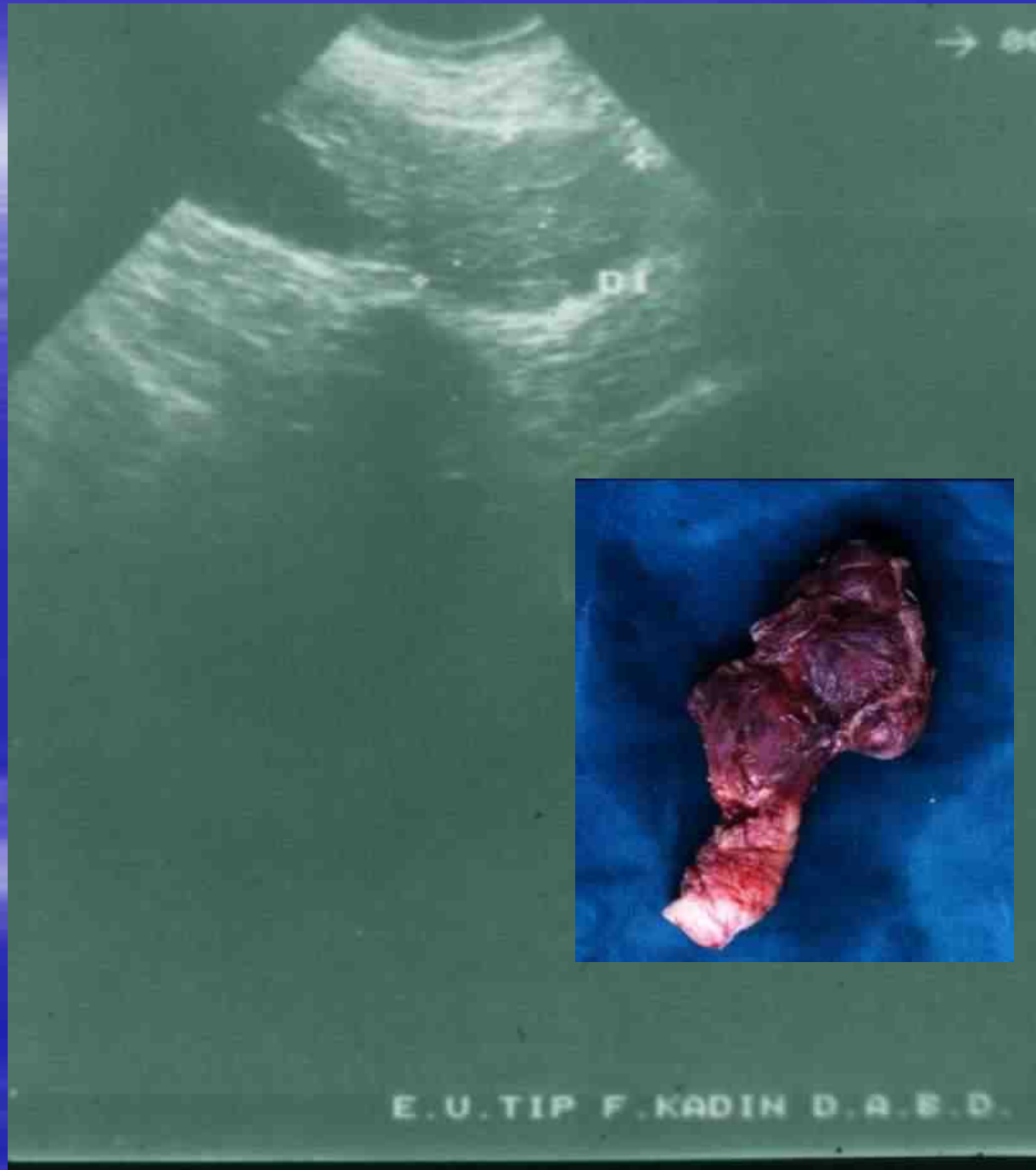
Hirsutizm, 1 yıl

Alopesi

Klitoromegali

Total T: 383 ng/dl

fT: 19 pg/ml



Genel prensipler

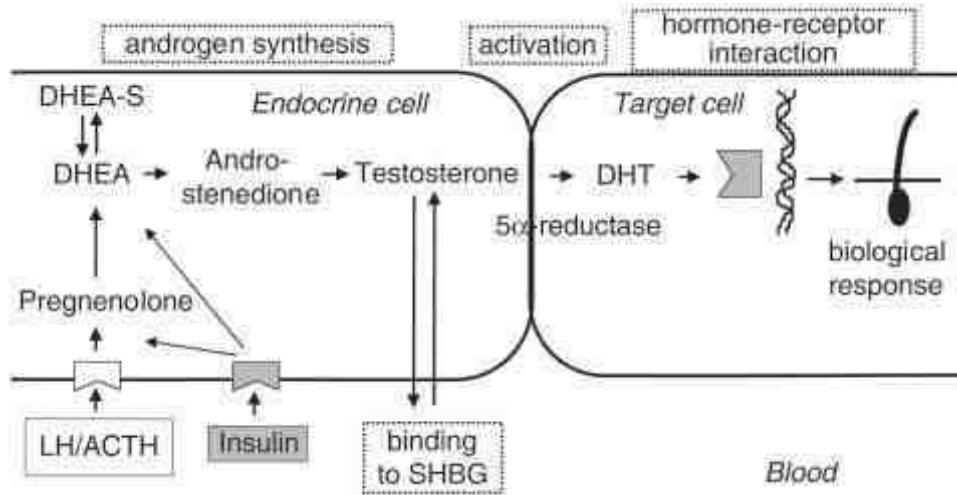
•5- α redüktaz aktivitesi kişilerde farklıdır

•A seviyeleri kıl-yagbezi unitesindeki A

konsantrasyonunu yansıtmayabilir. Chen and Zouboulis, 2009.

A etkisi A reseptör ekspresyonuna da bağlıdır.

A reseptör immünreaktivitesi farklı olabilir



Hirsutizm

- **Androjen seviyesi**
- **Lokal androjen konsantrasyonu**
- **Kıl folliküllerinin androjenlere duyarlılığı arasındaki etkileşimi yansıtır**

HİRSUTİZM - hekime başvuru nedeni

- ▶ Fasiyal hirsutizm
- ▶ Anksiyete, depresyon,
- ▶ Sosyal ilişkilerde bozulma

Hirsutizm tedavisi - Dual yaklaşım

▶ Hiperandrojeneminin farmakolojik tedavisi

Androjen sekresyonu ve/veya etkisini azaltmak

▶ Mevcut terminal kılların yok edilmesi

Tedavi

1-Genel prensipler

- ▶ Varsa altta yatan hastalığın tanı ve tedavisi
- ▶ Hastanın beklenti ve özellikleri dikkate alınmalı
- ▶ Tedaviyi bir uzman takip etmeli
- ▶ Obezite tedavisi

2-İlaç tedavisi

- ▶ Adrenal, ovaryan supresyon
- ▶ Anti-androgen tedavi

3-Kozmetik tedavi

4-Eğitim ve psikoterapi

5-Kombine tedaviler

Genel prensipler

Kıllar siklik büyür, klinik cevap için
6 - 9 ay tedavi gerekir

Tedavi hiçbir zaman küratif olmaz
Kronik tedavi gerekebilir.

Genel prensipler

Hafif hirsutizmde

Fasial hirsutizmde

Kozmetik tedavi daha etkilidir

Genel prensipler

Orta ve şiddetli hirsutizmde

Hirsutizm yaygınsa

Farmakolojik yaklaşım gerekir



Obezite
tedaviyi
negatif
etkiliyor

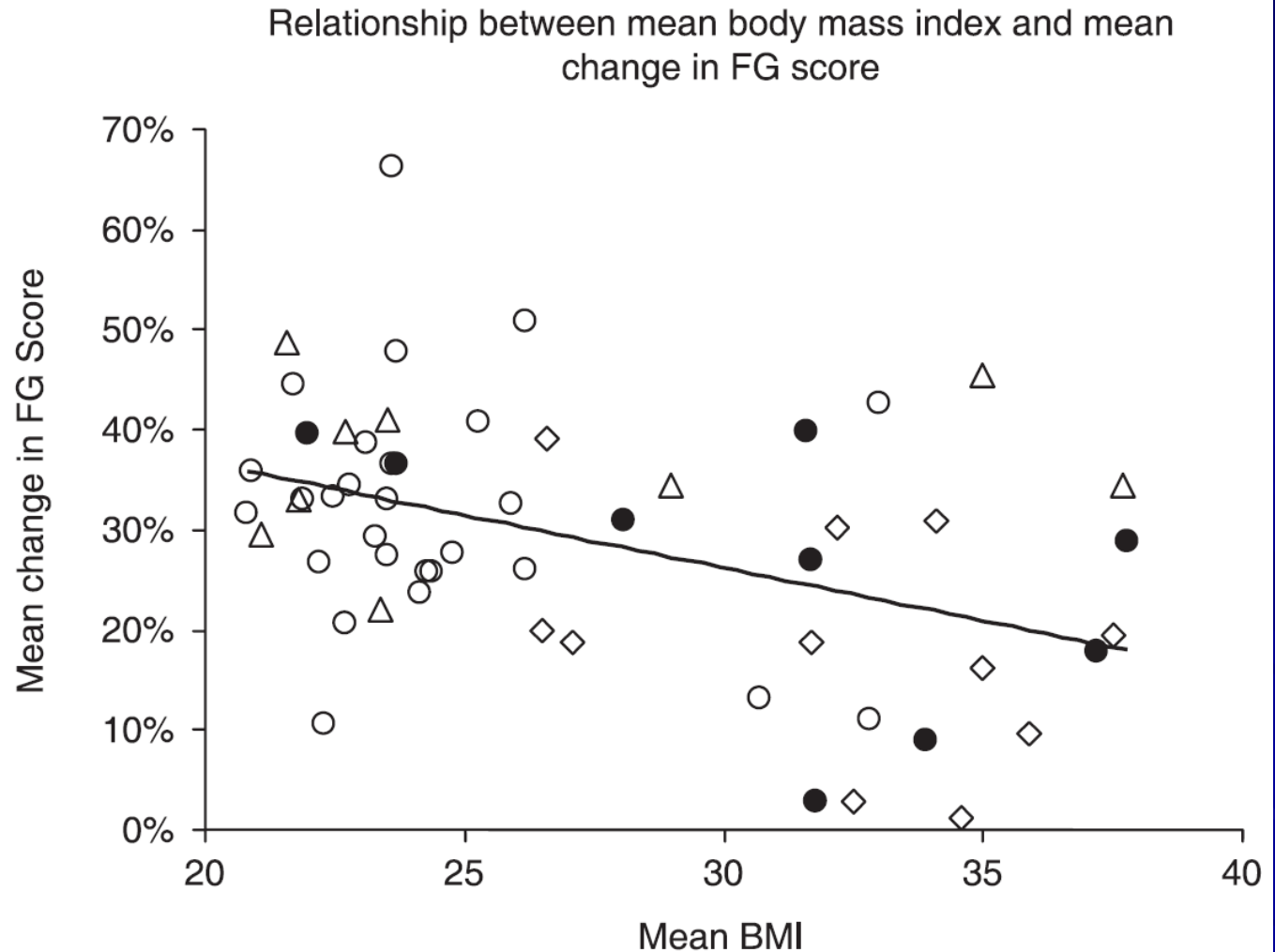


Fig. 2 Association between the mean percentage decrease in Ferriman–Gallwey (F–G) score after 6 months of treatment and mean body mass index (BMI) in 27 studies. Symbols represent different treatment groups: open circles, antiandrogens; diamonds, modulators of metabolism; closed circles, oral contraceptive pill; triangles, combination treatment.

Koulouri, 2008

Obezite tedavisi – Zayıflama

▶ Yaşam tarzı modifikasyonu

▶ Egzersiz

▶ Diyet

- * Açlık insülin seviyesini azaltır
- * SHBG yi artırıp androgenleri düşürür.

Giallauria, 2009

Farmakolojik tedavi

Yeni terminal kıl gelişimi baskılanır

Mevcut terminal kılların büyümesi yavaşlar (3-6 ay)

Mevcut kıllardan kurtulma sağlanamaz

Eş zamanlı olarak mekanik tedaviler gerekir

Table 1. Anti-androgen drugs, their new combinations, and insulin sensitizers used in the treatment of hirsutism.

Anti-androgen drugs and the new combinations

Anti-androgen drugs

- Spirolonolactone
- Cyproterone acetate
- Finasteride
- Flutamide

Anti-androgen combinations

- Cyproterone acetate and ethinyloestradiol plus spironolactone
- Cyproterone acetate and ethinyloestradiol plus finasteride
- Cyproterone acetate and ethinyloestradiol plus flutamide
- Spirolonolactone plus finasteride

Insulin sensitizers

- Metformin
 - Thiazolidinediones
-

İlaçlar

Etkili
Kost efektif
Güvenli

Anti-androgen tedavi

1. Gonadotropin supresyonu
2. SHBG sentezi stimülasyonu
3. 5- α redüktaz enzimi inhibisyonu
4. Androgen reseptörlerine bağlanma
5. Steroid biyosentezine etkiler

Kombine ilaç tedavileri

Antiandrojen ilaçlar

CPA

Spirolakton

Finasterid

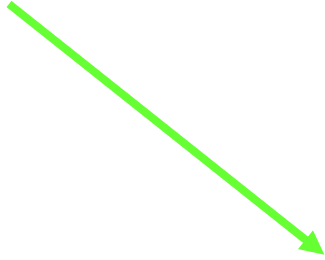
Flutamid

farklı etkilere sahiptir,

kombinasyonları daha etkili olabilir.

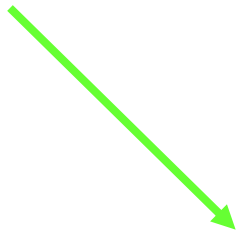
ORAL KONTRASEPTİFLER

ESTROGEN → **LH** ↓ → **ovaryan androgen** ↓



SHBG ↑ → **Free testosteron** ↓

Siklik progesteron + estrogen



Gebeliğin önlenmesi

**Oligomenoreyi düzeltir,
Endometrial hiperplaziyi önler**

ORAL KONTRASEPTİFLER

▶ **Potansiyel sinerjistik etki**

▶ **Kontrasepsiyon**

için antiandrojenler genellikle nonandrojenik (desogestrel, norgestimate, and gestodene) OK lerle kombine edilir.

▶ **Oligomenoreyi düzeltir,**

▶ **Endometrial hiperplaziyi önler**

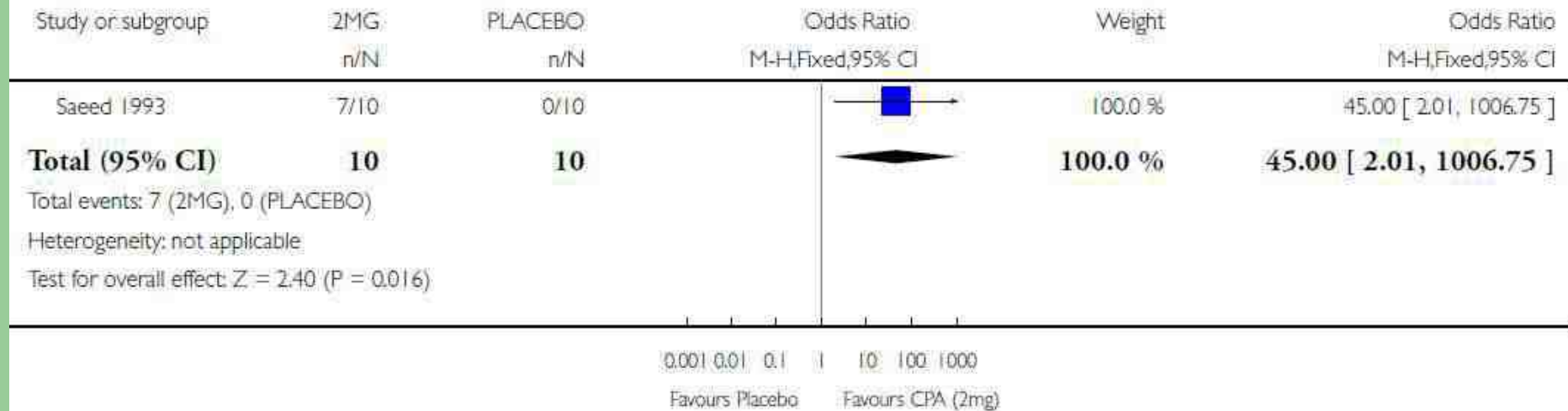
2 mg CPA vs Plasebo

Analysis 2.1. Comparison 2 CPA (2MG) + EE versus PLACEBO, Outcome 1 SUBJECTIVE IMPROVEMENT IN HAIR GROWTH.

Review: Cyproterone acetate for hirsutism

Comparison: 2 CPA (2MG) + EE versus PLACEBO

Outcome: 1 SUBJECTIVE IMPROVEMENT IN HAIR GROWTH



Cyproterone acetate for hirsutism (Review)

Cochrane review, 2009

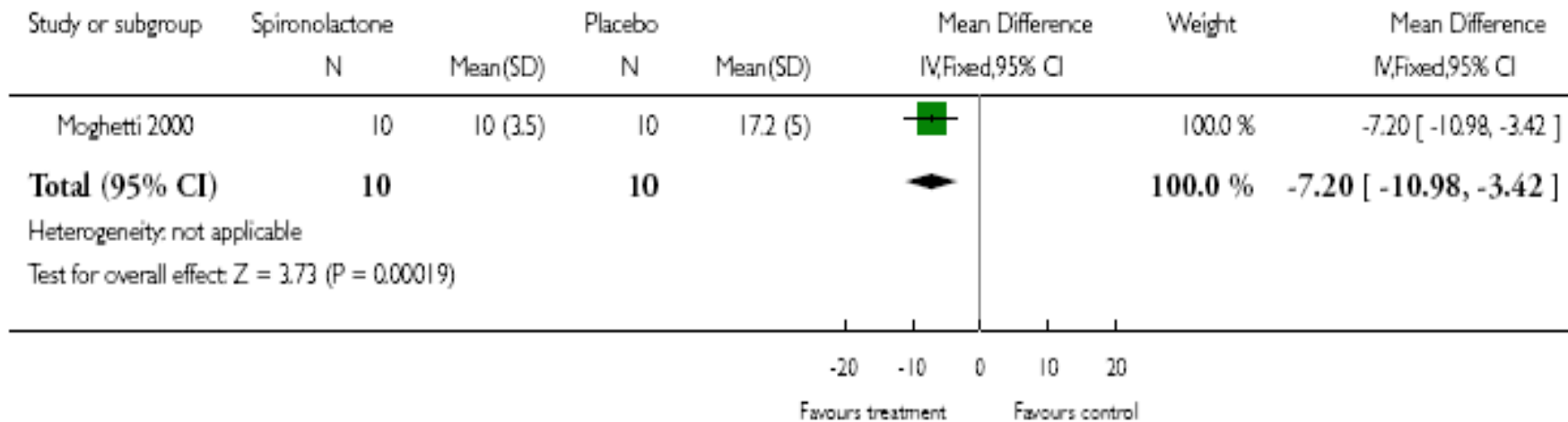
Spironolactone vs placebo

Analysis 1.2. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 2 Ferriman-Galwey score.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 2 Ferriman-Galwey score



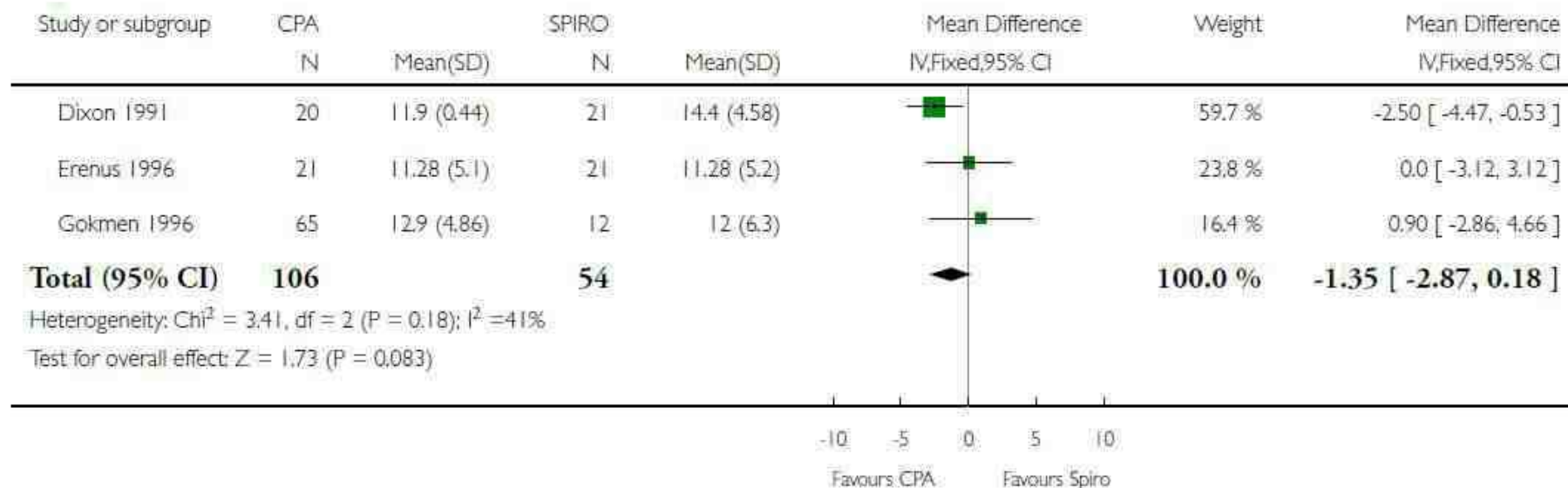
CPA vs Spironolactone

Analysis 5.3. Comparison 5 CPA versus SPIRONOLACTONE, Outcome 3 FERRIMAN GALLWEY AT 6 MONTHS.

Review: Cyproterone acetate for hirsutism

Comparison: 5 CPA versus SPIRONOLACTONE

Outcome: 3 FERRIMAN GALLWEY AT 6 MONTHS



Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society

**H.F. Escobar-Morreale^{1,*}, E. Carmina², D. Dewailly³, A. Gambineri⁴,
F. Kelestimur⁵, P. Moghetti⁶, M. Pugeat⁷, J. Qiao⁸, C.N. Wijeyaratne⁹,
S.F. Witchel¹⁰, and R.I. Norman¹¹**

Table IV Summary of RCTs comparing the efficacy of different antiandrogen drugs on hirsutism.

Author, year	Blinding	Months	Sample size	Disorders	Regimens compared*	Outcome	Efficacy on hirsutism
Belisle and Love (1986)	Double	12	158	Hirsutism (mFG > 14)	(1) Diane (2) Diane + CPA 100	mFG	Diane + CPA > Diane
McLellan et al. (1989)	Double	9	22	Hirsutism	(1) Spironolactone 100 (2) Placebo	Diameter Self-evaluation	No difference
Barth et al. (1991)	Double	12	38	Hirsutism	(1) Diane (2) Diane + CPA 20 (3) Diane + CPA 100	mFG Hair diameter Linear growth	No difference
Cusan et al. (1994)	Single	9	53	Hirsutism (mFG > 13)	(1) Flutamide 500 mg + OCP (2) Spironolactone 100 + OCP	mFG	Flutamide + OCP > Spironolactone + OCP
Giotta et al. (1995)	Single	9	18	PCOS Idiopathic hirsutism	(1) Finasteride 7.5 (2) Placebo	mFG	Finasteride > Placebo
Wang et al. (1995)	None	6	14	Hirsutism (mFG > 11)	(1) Spironolactone 100 (2) Finasteride 5	mFG Hair diameter Self-evaluation	No difference
Gingortou et al. (1996)	None	9	22	Idiopathic hirsutism	(1) CPA 100 (2) Flutamide 500	mFG	No difference
Erenus et al. (1997)	Single	9	40	Idiopathic hirsutism (mFG > 10)	(1) Spironolactone 100 (2) Finasteride 5	mFG	Spironolactone > Finasteride
Falsetti et al. (1997)	None	6	44	PCOS (mFG 11–24)	(1) Finasteride 5 (2) Flutamide 500	mFG Hair diameter	No difference
Muderris et al. (1997)	Single	12	65	Hirsutism	(1) Flutamide 250 (2) Flutamide 500	mFG	No difference
Kelestimur and Sahin (1998)	Single	12	50	Hirsutism (mFG > 8)	(1) Diane (2) Diane + Spironolactone 100	mFG	Diane + Spironolactone > Diane
Sahin et al. (1998)	Single	9	42	PCOS Idiopathic hirsutism	(1) Diane (2) Finasteride 5	mFG	Diane > Finasteride
Falsetti et al. (1999)	None	12	110	PCOS Idiopathic hirsutism (mFG 11–23)	(1) Finasteride 5 (2) Flutamide 500	mFG Hair diameter	Flutamide > Finasteride

Author, year	Blinding	Months	Sample size	Disorders	Regimens compared ^a	Outcome	Efficacy on hirsutism
Fruzzetti et al. (1999)	Single	12	45	Hirsutism	(1) Finasteride 5 (2) CPA 25 + EE 0.020 (3) Flutamide 500	mFG	No difference
Pazos et al. (1999)	None	9	33	Functional ovarian hyperandrogenism Idiopathic hirsutism	(1) GnRHa + OCP (2) CPA 100 + OCP (3) Flutamide 500 + OCP	mFG	Flutamide > (CPA = GnRHa)
Venturoli et al. (1999)	None	12	66	PCOS Idiopathic hirsutism NCCAH	(1) Flutamide 250 (2) Finasteride 5 (3) Ketoconazole 300 (4) 3) CPA 12.5 + EE 0.010-0.020	mFG Hair diameter Linear growth	(CPA = Flutamide) > Finasteride Ketoconazole 50% drop out rate
De Leo et al. (2000)	None	6	35	PCOS	(1) GnRHa (2) GnRHa + Diane (3) GnRHa + Flutamide 250	mFG	No difference
Moghetti et al. (2000a)	Double	6	40	Hirsutism	(1) Spironolactone 100 (2) Finasteride 5 (3) Flutamide 250 (4) Placebo	mFG Hair diameter Self-evaluation	(Spironolactone = Finasteride = Flutamide) > Placebo
Muderris et al. (2000)	Single	12	70	Hirsutism (mFG > 8)	(1) Flutamide 250 (2) Finasteride 5	mFG	Flutamide > Finasteride
Spritzer et al. (2000)	None	12	44	PCOS Idiopathic hirsutism (mFG 11-35)	(1) Spironolactone 200 (2) CPA 50 + EE 0.035	mFG	No difference
Tartagni et al. (2000)	Single	6	50	PCOS Idiopathic hirsutism	(1) Diane (2) Diane + Finasteride 5	mFG Self-evaluation	Diane + Finasteride > Diane
Sahin et al. (2001)	Single	12	40	Hirsutism	(1) Diane (2) Diane + Finasteride 5	mFG	Diane + Finasteride > Diane
Bayram et al. (2002)	None	12	46	PCOS Idiopathic hirsutism (mFG > 12)	(1) Finasteride 2.5 (2) Finasteride 5	mFG	No difference
Taner et al. (2002)	None	6	84	Hirsutism	(1) Flutamide 250 (2) Flutamide 250 + Diane	mFG	No difference

Unluhizarci et al. (2002)	Single	6	34	PCOS Idiopathic hirsutism	(1) Spironolactone 100 (2) Spironolactone 100 + Finasteride 5	mFG	Spironolactone + Finasteride > Spironolactone
Lakryc et al. (2003)	Double	6	24	PCOS Idiopathic hirsutism	(1) Finasteride 5 (2) Placebo	mFG Self-evaluation	Finasteride > Placebo
Beigi et al. (2004)	None	9	40	PCOS Idiopathic hirsutism	(1) Finasteride 5 (2) CPA 25 + EE 0.020	mFG	No difference
Ganie et al. (2004)	None	6	69	PCOS	(1) Spironolactone 50 (2) Metformin 1000	mFG	Spironolactone > Metformin
Kelestimur et al. (2004)	Single	12	65	PCOS Idiopathic hirsutism	(1) Spironolactone 100 (2) Spironolactone 100 + Finasteride 5	mFG	Spironolactone + Finasteride > Spironolactone
Tartagni et al. (2004)	Single	10	38	PCOS Idiopathic hirsutism (mFG > 10)	(1) Finasteride 2.5 once daily (2) Finasteride 2.5 every 3 days	mFG	No difference
Gambineri et al. (2006)	Single	12	76	PCOS	(1) Diet (2) Diet + Metformin 1700 (3) Flutamide 500 (4) Diet + Metformin 1700 + Flutamide 500	mFG	(Flutamide + Metformin + Diet) > (Flutamide + Diet)
Catalfà et al. (2007)	Double	12	119	PCOS Idiopathic hirsutism (mFG > 15)	(1) OCP (2) Flutamide 125 + OCP (3) Flutamide 250 + OCP (4) Flutamide 375 + OCP	mFG	Flutamide (125 = 250 = 375) + OCP > OCP

CPA, cyproterone acetate; Diane, cyproterone acetate 2 mg plus ethinylestradiol 35 µg; EE, ethinylestradiol; mFG, modified Ferriman–Gallwey score; GnRH-a, GnRH analog; OCP, oral contraceptive pill.

*Doses are mg per day unless stated otherwise.

Table V Summary of RCTs of interventions with insulin sensitizers for hirsutism.

Author, year	Blinding	Months	Sample size	Disorders	Regimens compared ^a	Outcome	Efficacy on hirsutism
Insulin sensitizers versus placebo							
Moggetti et al. (2000b)	Double	6	23	PCOS	(1) Metformin 1500 (2) Placebo	mFG	No difference
Pasquali et al. (2000)	Double	6	20	PCOS	(1) Diet + Metformin 1700 (2) Diet + Placebo	FG	Metformin > placebo
Azziz et al. (2001)	Double	11	410	PCOS	(1) Troglitazone 150, 300 and 600 (2) Placebo	mFG	Troglitazone 600 > placebo
Kelly and Gordon (2002)	Double	6	16	PCOS	(1) Metformin 1500 (2) Placebo	FG Hair growth Self-assessment	Metformin > placebo Metformin > placebo Metformin > placebo
Gambineri et al. (2004)	Single	6	20	PCOS	(1) Diet + Metformin 1700 (2) Diet + Placebo	FG	No difference
Hoeger et al. (2004)	Double	11	18	PCOS	(1) Metformin 1700 (2) Placebo	mFG	No difference
Maciel et al. (2004)	Double	6	34	PCOS	(1) Metformin 1500 (2) Placebo	FG	No difference
Onalan et al. (2005)	Double	6	139	PCOS	(1) Metformin 1700 (2) Placebo	FG	No difference
Gambineri et al. (2006)	Single	12	40	PCOS	(1) Diet + Metformin 1700 (2) Diet + Placebo	FG	No difference
Aroda et al. (2009)	Unclear	6	28	PCOS	(1) Pioglitazone 45 (2) Placebo	FG	Pioglitazone > placebo
Romualdi et al. (2010)	Double	6	28	PCOS	(1) Metformin 1000 (2) Placebo	FG	Metformin > placebo
Insulin sensitizers versus OCPs							
Morin-Papunen et al. (2000)	None	6	18	PCOS	(1) Metformin 1000 → 2000 (2) Diane	FG	Diane > Metformin
Harborne et al. (2003)	Unclear	12	52	PCOS	(1) Metformin 1500 (2) Diane	FG Hair diameter Self-assessment	Metformin > Diane No difference Metformin > Diane
Morin-Papunen et al. (2003)	None	6	20	PCOS	(1) Metformin 1000 → 2000 (2) Diane	FG	Diane > Metformin

Allen et al. (2005)	None	6	35	PCOS	(1) Metformin 1000 (2) Norgestimate 0.25 + EE 0.035	mFG	No difference
Lemay et al. (2006)	None	6	28	PCOS	(1) Rosiglitazone 4 (2) Diane	FG	Diane > Rosiglitazone
Luque-Ramirez et al. (2007)	None	6	34	PCOS	(1) Metformin 1700 (2) Diane	mFG	Diane > Metformin
Meyer et al. (2007)	None	6	110	PCOS	(1) Metformin 2000 (2) Diane (3) Levonorgestrel 0.100 + EE 0.020 + Spironolactone 100	FG	No difference
Hoeger et al. (2008)	Double	6	43	PCOS	(1) Metformin 1700 (2) Desogestrel 0.15 + EE 0.030 (3) Life-style modification (4) Placebo	FG	No difference
Metformin and thiazolidinediones							
Yilmaz et al. (2005)	Single	6	96	PCOS	(1) Metformin 1700 (2) Rosiglitazone 4	FG	Rosiglitazone > Metformin
Ortega-Gonzalez et al. (2005)	None	6	52	PCOS	(1) Metformin 2550 (2) Pioglitazone 30	FG	No difference
Dereli et al. (2005)	None	8	40	PCOS	(1) Rosiglitazone 2 (2) Rosiglitazone 4	mFG	Rosiglitazone 4 > Rosiglitazone 2
Metformin versus antiandrogens							
Ganie et al. (2004)	None	6	69	PCOS	(1) Spironolactone 50 (2) Metformin 1000	mFG	Spironolactone > Metformin
Gambineri et al. (2004)	Single	6	20	PCOS	(1) Metformin 1700 (2) Flutamide 500	FG	Flutamide > Metformin
Gambineri et al. (2006)	Single	12	76	PCOS	(1) Diet (2) Diet + Metformin 1700 (3) Diet + Flutamide 500 (4) Diet + Metformin 1700 + Flutamide 500	mFG	(Flutamide = Flutamide + Metformin) > (metformin + diet = diet)

*Doses are mg per day unless stated otherwise.

İnsülin hassaslaştırıcılar hirsutizm tedavisinde önerilmez

A consensus statement by AE-PCOS Society, 2011

İlaçların etkinliğinde kanıta dayalı bilgi yetersizdir

Çalışmaların çoğu çift kör değil

Tedavinin etkisi subjektif kriterle ölçülüyor

Hasta sayıları az

Tedavi süresi kısa kalıyor

Tedaviye cevapta bireysel farklılıklar var



Müderriş II, Bayram F, Sahin Y, Keleştimur F, Tutuş A, Ayata D.

The efficacy of 250 mg/day flutamide in the treatment of patients with hirsutism.

Fertil Steril, 1996

Müderriş I, Bayram F, Şahin Y, Keleştimur F.

A comparison between two doses of flutamide (250 mg/d and 500mg/d) in the treatment of hirsutism

Fertil Steril 1997

250 mg/d, 1 hastada 9.ayda AST: 107 U/L, ALT: 77 U/L (1-40)

J. Endocrinol. Invest. 32: 37-40, 2009

A comparison between finasteride, flutamide, and finasteride plus flutamide combination in the treatment of hirsutism

K. Unluhizarci, D. Ozel, F. Tanriverdi, Z. Karaca, and F. Kelestimur
Department of Endocrinology, Erciyes University Medical School, Kayseri, Turkey

Ciddi hepatotoksisite: görülmedi

Flutamide **vs** Flutamide + Diane

Flutamide 250 mg/d, n: 69, 6 ay

Benzer etkili

Hepatotoksisite: görülmedi

Taner C, Gynecol Obstet Invest , 2002

SHORT COMMUNICATION

Absence of hepatotoxicity after long-term, low-dose flutamide in hyperandrogenic girls and young women

Lourdes Ibáñez^{1,3}, Adriana Jaramillo¹, Angela Ferrer¹ and Francis de Zegher²

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BACKGROUND: Flutamide is a pure non-steroidal anti-androgen that may be hepatotoxic, when given in high-dose (750 mg/d). Low- to ultralow-doses (250–62.5 mg/day) have been recently explored in patients with Polycystic

190 PKOS hasta: 62.5-250 mg/gün flutamid

3 - 54 aya kadar takip

Hepatotoksisite (AST, ALT üst limit 3 katı) görülmedi

CLINICAL STUDY

Retrospective observational study on the effects and tolerability of flutamide in a large population of patients with various kinds of hirsutism over a 15-year period

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Abstract

Objective: The aim of the study was to evaluate the long-term effects and tolerability of flutamide (Flu) in hirsute women. To the best of our knowledge, this study represents the largest report, concerning the population studied and the duration of treatment, to evaluate Flu use in hirsutism treatment.

Design, patients and methods: Over a 15-year period spanning from January 1991 to January 2006, a total of 414 premenopausal women with hirsutism of different aetiopathogeneses received yearly reducing doses (250, 125 and 62.5 mg/day) of Flu alone or in combination with oral contraceptives for a period varying from at least 3 to 8 years and more. Clinical and endocrine evaluations were assessed half-yearly and yearly respectively in the first 3 years of the study, and yearly in the following years. Liver function evaluations were assessed quarterly.

414 hirsut hasta: 62.5-125-250 mg/gün flutamid, 3 – 8 yıl takip

Fatal liver complications with flutamide

Osculati A, Castiglioni C. Lancet, 2006

- ▶ 18 yaş, hafif akne, hirsutizm, KcFT bakmadan
- ▶ 375 mg/gün 1 ay + OK
- ▶ 250 mg/gün 3 ay
- ▶ Toksik hepatit, kc yetmezliği
- ▶ 3 kere Kc transplantasyonu: başarısız
- ▶ 2 ay sonra ex

Acute and fulminant hepatitis induced by flutamide: Case series report and review of the literature

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ABSTRACT

Flutamide is a non-steroidal anti-androgenic drug, commonly used in the treatment of advanced prostate cancer, acne and hirsutism. This drug may induce various degrees of liver injury, including acute liver failure (ALF), with further need for liver transplantation. Here, we present a report of 10 consecutive patients seen in a period of 14 years, with acute liver toxicity induced by flutamide (in most cases severe hepatotoxicity): 3 men and 7 women, with a mean age of 75 and 29 years old, respectively. All men received flutamide as treatment of advanced prostate carcinoma and they developed hepatotoxicity without ALF, and three months after withdrawal of the drug, they recovered completely. In contrast, in 7 young female with liver toxicity caused by flutamide as treatment of various hyperandrogenic conditions (acne and hirsutism), ALF was observed in 5 patients, all of them requiring urgent liver transplantation, with excellent outcome and survival in 4 of them. Based on the above, we believe that flutamide treatment should be preferentially avoided in young female patients with benign pathologies, or if it is used, patients should be warned of its potential severe complications. Also, serial liver tests should be closely monitored and, in case of elevations, the drug should be immediately withdrawn.

Table 2. Hepatotoxicity induced by flutamide in women (n = 7).

Indications for treatment	Age	Days of ingestion	Hepatic alterations (maximum)				Hepatitis	Outcome after withdrawal of flutamide
			Bill	AST	ALT	PT		
1. Hirsutism	44	90	4.2	390	605	90%	Acute	Good (1)
2. Hirsutism	27	60	27	1064	1803	10%	Fulminant	Good (2)
3. Hirsutism	32	60	25	1189	925	38%	Acute	Good (3)
4. Hirsutism	20	180	20	850	590	15%	Fulminant	Good (4)
5. Acne	22	180	25	1,576	1,116	14%	Fulminant	Good (5)
6. Acne	21	65	29	2,778	3,360	10%	Fulminant	Good (6)
7. Alopecia	38	90	44	2,130	1,430	24%	Fulminant	Died (7)

PT: Prothrombin time (%). Bill: Bilirubin (mg/dL). AST: Aspartate aminotransferase (IU/l). ALT: Alanine aminotransferase (IU/ml). (1) 1 month (2) 4 months post transplant. (3) 3 months. (4) 7 months post transplant. (5) 53 months post transplant. (6) 53 months post transplant. (7) Post operative period.

(1996 – 2010) Hirsutizm, akne, alopesi: flutamid 125-250 mg/gün

7 hastada hepatotoksisite (60 – 80 gün)

Hepatik değişiklikler: 5 gün – 10 ay

5 hastada akut karaciğer yetmezliği ile acil Kc transplantasyonu

4 hasta yaşıyor

1'i postop exitus

İdiosenkreatik , allerjik, genetik faktörler ?

Flutamid

Yan etki: Hepatotoksisite

Düşük dozla da olabilir Osculati, 2006, Garcia, 2001, Thole, 2004

Androgen Excess-PCOS Society hirsutizm tedavisinde flutamidi önermemektedir.

A consensus statement by AE-PCOS Society, 2011



Kombine tedaviler

Diane 35 + spironolactone F Keleştimur, Y Şahin. Fertil Steril, 1998

Diane 35 + finasteride Şahin Y, Dilber S, Keleştimur F. Fertil Steril, 2001

Spironolactone + finasteride Keleştimur F, Everest H, Unlühizarci K, Bayram F, Sahin Y. Eur J Endocrinol. 2004

Spironolactone 100 mg/gün + OC Erenus M, Yücelten D, Gürbüz O, Durmuşoğlu F, Pekin S. Fertil Steril, 1996

Sonuçlar

- ▶ **Farklı etkili antiandrojenlerin kombinasyonları daha etkili olabilir.**

Sonuçlar

**İnsülin hassaslaştırıcılar ve
Drospirenon içeren OK ler
sınırlı etkiye sahip veya yararsız.**

Bazı OK lerdeki dozda Drospirenon antiandrojenik değildir.

Bart, Fertil Steril, 2012. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ ASRM-Sponsored 3rd PCOS Consensus Workshop Group

Sonuçlar

Tedavi hiçbir zaman k ratif olmayacaktır

Kronik tedavi gerekebilir

Sonuçlar

Antiandrogenler teratojenik potansiyele sahiptir
(Erkek fötüsda ambiguous genitalia?)

**Antiandrogenler yeterli kontrasepsiyonla
kullanılmalı.**

OK

Sonuçlar

- ▶ Henüz hayat boyu kalıcı kıl eradikasyonu yapan hiçbir metod mevcut değildir.
- ▶ Tedavi öncesi hastaya bu gerçek söylenmeli hasta beklentisi: gerçekçi olmalı.

