Hirsutism and Hyperandrogenism

Medical options for women with Acne and Hirsutism

Dr. Gulrez Tyebkhan

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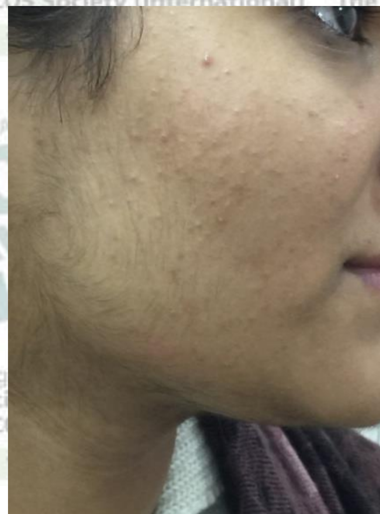
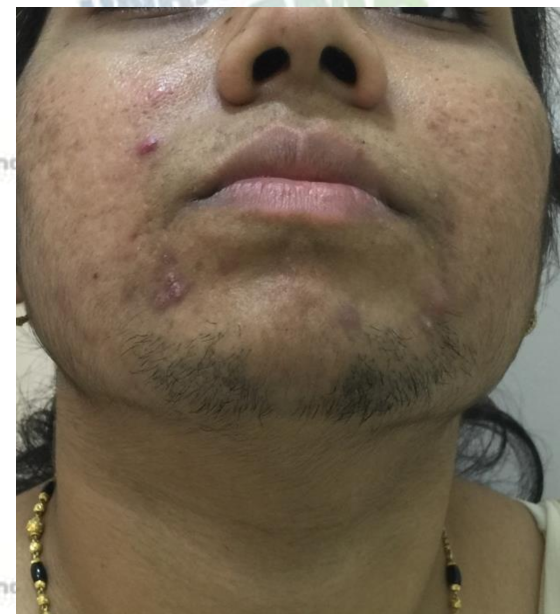
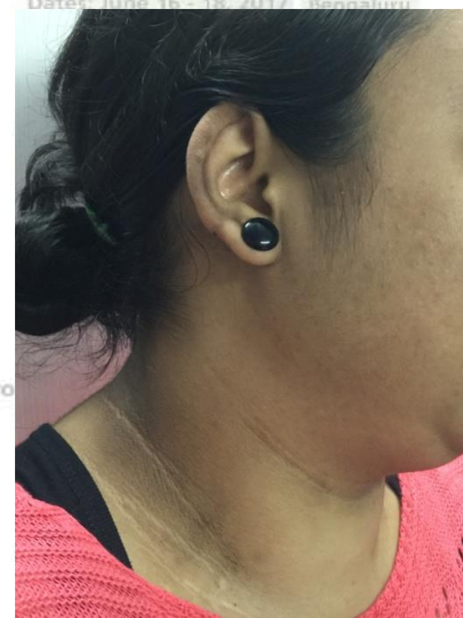
Skin : a mirror of PCOS

- **Hyperandrogenism**: **Clinical**
  - **Hirsutism**
  - **Acne**
  - Seborrhea
  - Female pattern Alopecia
- **Insulin resistance**
  - Acanthosis nigricans
  - Skin tags
- **Others**
  - Stretch marks
- considerable heterogeneity in clinical findings, and variation in same patient over time







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Hirsutism, Acne and Hyperandrogenemia: Association

Hirsutism and Acanthosis Nigricans are the most reliable cutaneous markers of PCOS.

Presence should raise clinical concern; warrants further diagnostic evaluation for metabolic comorbidities.

Acne and androgenic alopecia are prevalent but unreliable markers of biochemical hyperandrogenism.

ESHRE/ASRM-sponsored third PCOS consensus workshop group suggested that acne is not commonly associated with hyperandrogenemia, should not be regarded as evidence of hyperandrogenemia.

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Schmidt TH, Khanijow K, Cedars MI. Cutaneous Findings and Systemic Associations in Women With Polycystic Ovary Syndrome. JAMA Dermatol. 2016 Apr;152(4):391-8. Fauser BC[1], Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012 Jan;97(1):28-38.e25.

Peculiarities & Prevalence in Indian women

Indian women with PCOS have a **higher degree of hirsutism**, infertility, and **acne** compared to women of Caucasian ethnicity.

Prevalence studies of cutaneous manifestations in PCOS patients

- **Gowri et al (n=40)**
  - Hirsutism: 62.5%
  - Acne: 67.5%

  Presents at an early age
- **Ramanand et al (n=120**)
  - hirsutism : 44.16%
  - acne : 20%

Malik, et al.: A Consensus Evidence-based Good Clinical Practice Recommendations. Fertility Science and Research 2014; 1(1): Gowri B V, Chandravathi P L, Sindhu P S, Naidu K S. Correlation of skin changes with hormonal changes in polycystic ovarian syndrome: A cross-sectional study clinical study. Indian J Dermatol 2015;60:419. Sunita J. Ramanand SJ et al. **Clinical characteristics of polycystic ovary syndrome in Indian women.** Indian J Endocrinol Metab. 2013 Jan-Feb; 17(1): 138–145.

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Prevalence

Obese vs Lean

- Hirsutism (33.6 vs. 28%)
- Acne and oily skin (40.6 vs. 22.6%)

- significantly higher in **obese than lean PCOS women;**

Acne and hirsutism do not always appear concomitantly …

	Group A	Group B	*P*-value
	Obese n = 300 (%)	Lean n = 150 (%)	Odds ratio 95%CI
Mean age in years	29.1	28.4	
Clinical hyperandrogenism:			*P*–0.000 (OR–2.82, 1.86–4.25) (Power 100%)
Clinical hyperandrogenism present	223 (74.2)	76 (50.6)	
Hirsutism	101 (33.6)	42 (28)	
Acne & oilyskin	122 (40.6)	34 (22.6)	
Hirsutism, acne & oily skin	56 (18.6)	25 (16.6)	
Clinical hyperandrogenism absent	77 (25.8)	74 (49.4)	

OR = Odds ratio

Majumdar A, Singh TA. Comparison of clinical features and health manifestations in lean vs. obese Indian women with polycystic ovarian syndrome. J Hum Reprod Sci 2009;2:12-7

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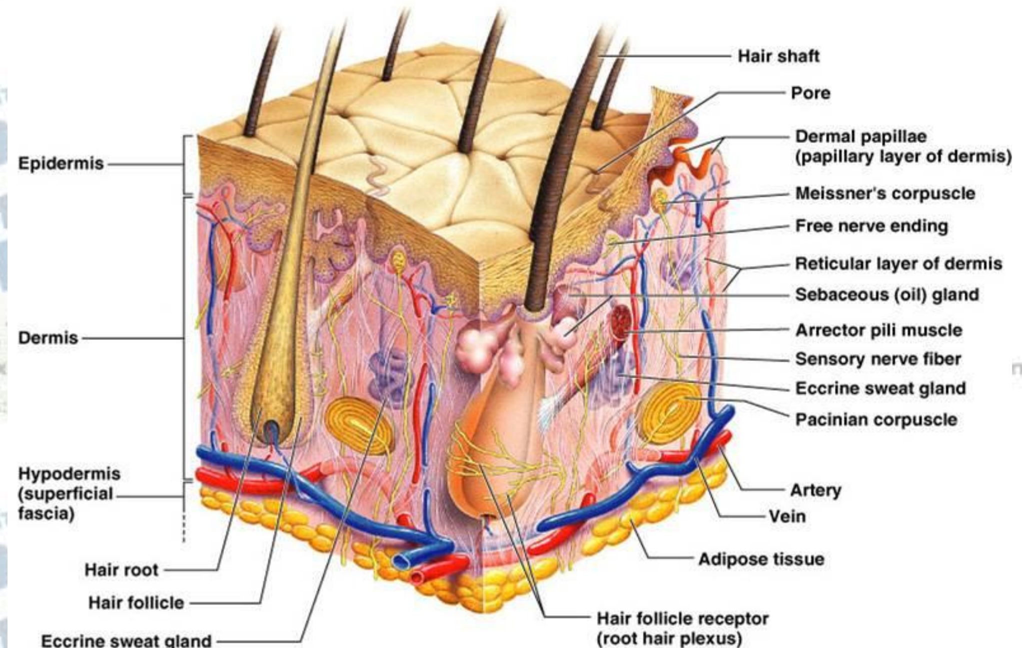
“DermatoEndocrinology”

- Skin is an endocrine organ per se
  - can synthesize diverse hormones;
  - expresses many hormone receptors
  - also the target of various hormones
- Hormones generated in skin can exert
  - systemic effects;
  - **“Intracrine action”** - very important for sex hormone effects on the skin.



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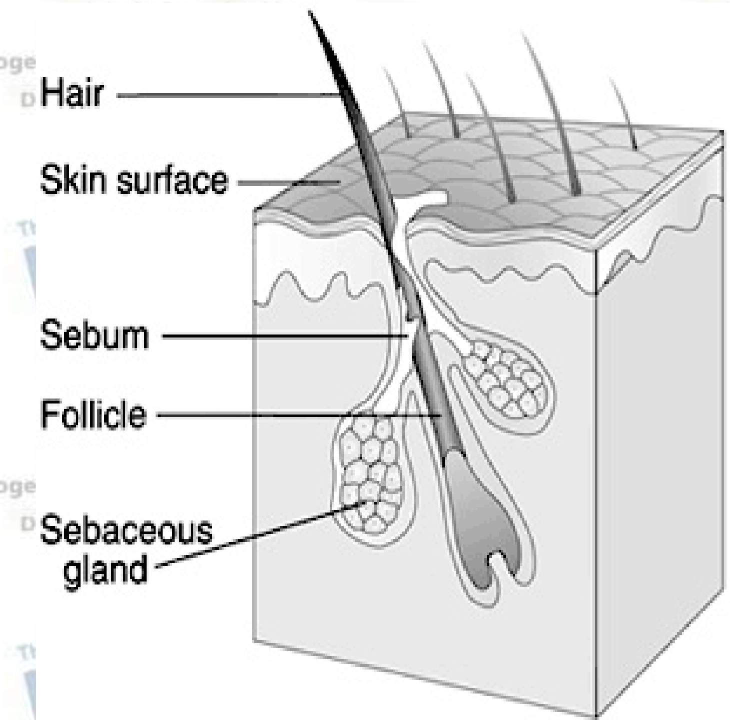
Pilosebaceous unit: single morphological source of origin



- Hair follicle and sebaceous gland (SG)
- Main factory for hormone production in skin

Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol. 2004;22(5):360-6. Zouboulis CC. [Acne vulgaris. The role of hormones]. Hautarzt. 2010 Feb;61(2):107-8, 110-4. http://www.skintherapyletter.com/2010/15.10/1.html

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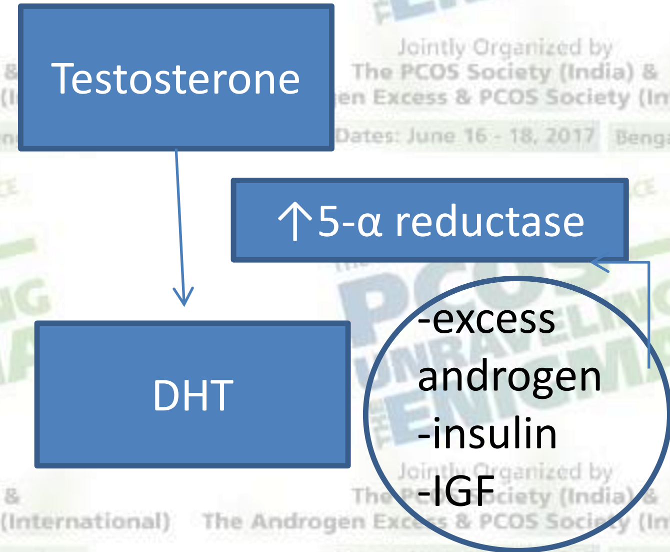
Acne and hirsutism do not always appear concomitantly…

- Hair follicle and SG may have different degrees of sensitivity to similar androgenic stimulation – qualitative variability.
- Acne and hirsutism may be the expression of the different metabolic fate of DHT itself.
- *5 alpha-reductase 2 inhibitors are most likely not promising candidates for acne therapy…*



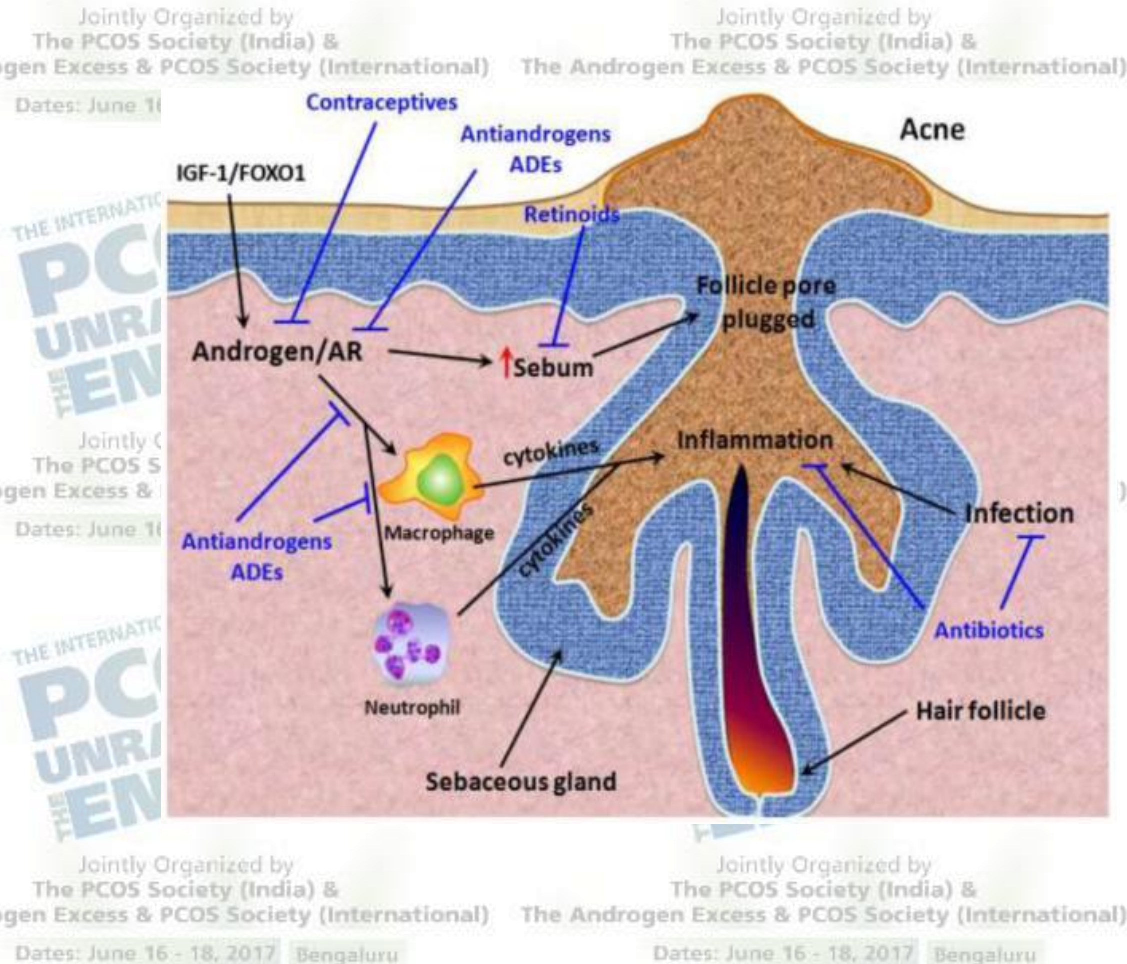
Type 1/3 in sebaceous gland (SG)
Type 2 in hair follicle

Local androgen bioactivity is regulated, in part, by 5-α-reductase, which converts free testosterone to the more potent DHT.

Toscano V et al. Mangiantini A.Two different pathogenetic mechanisms may play a role in acne and in hirsutism. Clin Endocrinol(Oxf). 1993 Nov;39(5):551-6 Joura EA et al..Serum 3 alpha-androstanediol-glucuronide is decreased in nonhirsute women with acne vulgaris. Fertil Steril. 1996 Dec;66(6):1033-5.

Androgenic stimulation, hyperinsulinemia and FOX 01 signaling in Acne and Hirsutism

- **Androgens** - promoting the anagen phase - change from vellus to terminal hair.
- **Androgen receptor (AR)**
  - **Hirsutism: activate** the dermal cells of the papilla
  - **Acne:** promotes
    - sebum production
    - Inflammation
- Insulin/IGF-1: in part determines AR activity.
- Nuclear transcription factor FoxO1 - suppresses androgen receptor



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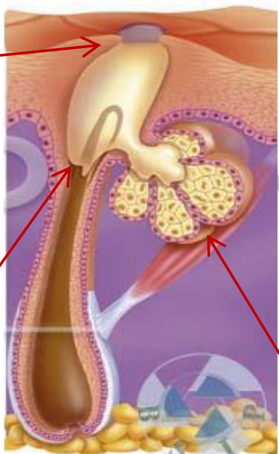
Lai JJ et al. The role of androgen and androgen receptor in skin-related disorders.Arch Dermatol Res.2012 Sep;304(7):499-510. Rotaru M et al. Study regarding the microscopic aspects of pilo-sebaceous units after antiandrogen treatment in hirsute women.Rom J Morphol Embryol.2015;56(1):63-9.

Pathogenesis of Acne: Multifactorial

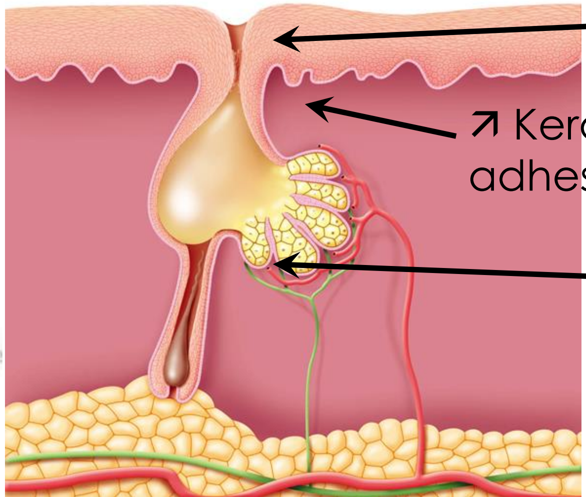
❷ Hyperkeratinisation

❸ Bacterial proliferation
❸ Inflammation



❶ Hyperseborrhea

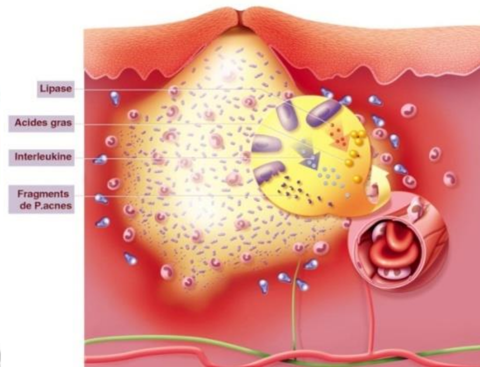
I. Pilo sebaceous canal obstruction



↗ Keratinocyte hyperproliferation, adhesion and differentiation

II. Sebum retention: sebaceous gland volume increases

IV. Inflammation



III. Concentration and activity of *Propionibacterium acnes*

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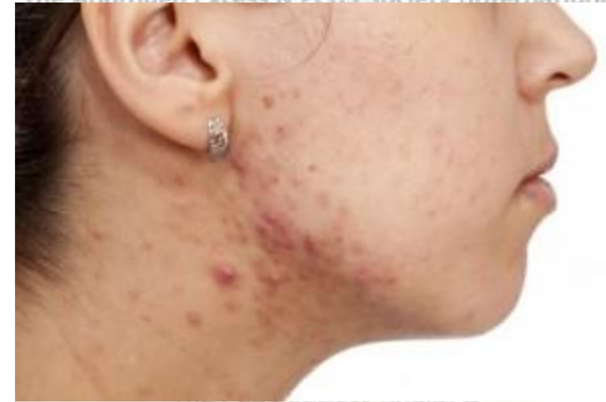
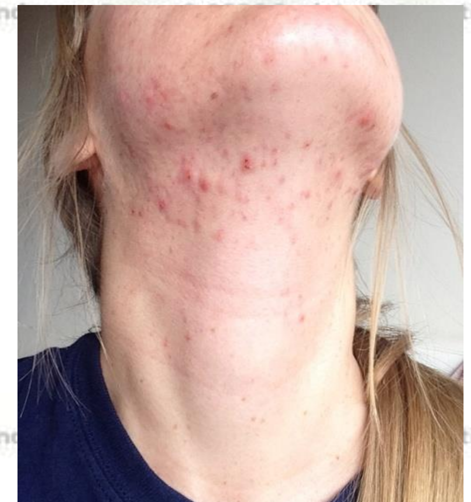
Acne: Presentations in PCOS

- Presentations:
  - Moderate to severe acne
  - Inflammatory lesions on lower face, neck (facial V area), chest, upper back
  - Acne beginning or persisting into adulthood (over the age of 25 years)
  - Flares severely with menstrual cycle
  - Refractory
    - Acne that has proven to be resistant to conventional therapy
    - Relapse shortly after isotretinoin therapy





Trivedi MK, Shinkai K, Murase JE. **A Review of hormone-based therapies to treat adult acne vulgaris in women.** Int J Womens Dermatol. 2017 Mar 30;3(1):44-52.

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Appendix Table 1: Grading of acne severity: Recommendation of Indian Acne Association

Grade	Criteria
Mild acne (Grade I) Predominance of comedones	Comedones < 30 Papules < 10 No scarring
Moderate acne (Grade II) Predominance of papules	Comedones any number Papules > 10 Nodules < 5 With or without scarring
Severe acne (Grade III) Many nodules	Comedones any number Papules any number Nodules/cysts > 5 With scarring

Source: Kubba R *et al.* 2009

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Standard Non hormonal therapy - Acne: Combination is key

- **Mild acne**: benzoyl peroxide is an effective first-line treatment. If results are unsatisfactory, topical tretinoin or adapalene should be added.
- **Moderate acne:** a regimen including
  - Topicals: benzoyl peroxide, antibiotics (clindamycin), and a retinoid (tretinoin, adapalene, or tazorotene).
  - Oral antibiotics (Azithromycin, Minocylcine, Doxycycline) may be tried for a predominance of inflammatory lesions not responding favorably to topical treatments.
- **Severe acne:** oral isotretinoin is the most effective therapy. In patients who are not candidates for oral isotretinoin, topical and oral treatments as mentioned above.

Whitney and Ditre. Clinical, Cosmetic and Investigational Dermatology 2011:4

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Oral Isotretinoin (13-cis-retinoic acid) : breakthrough against severe nodulocystic acne

- Single most effective drug in the treatment of acne.
- A new era in acne treatment - observation of Peck *et al*. in 1979 that it produced marked clearing in nodulocystic acne → Approval by the US FDA in 1982
- Mechanism: on all 4 pathogenic factors
- Standard regimen of 0.5–1.0 mg/kg/day for 16–32 weeks (total dose of 120-150mg/kg) causes many dose-dependent mucocutaneous and systemic adverse effects
- Routine monitoring of liver function tests, serum cholesterol, and triglycerides at baseline and again until response.
- Risks – metabolic side effects

Bodo C. Melnik. Isotretinoin and FoxO1 A scientific hypothesis. Dermato-Endocrinology 2011; 3:3, 141-165. Dhaked DR et al. A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris. Indian Dermatol Online J. 2016 ;7(5):378-385.

Low-dose oral isotretinoin treatment regimens in moderate to severe acne

- Low-dose isotretinon regimens are *better tolerated* and effective in inducing acne clearance
- To assess and compare efficacy and tolerability of two low-dose oral regimens (n=240)
  - 20 mg daily and
  - 20 mg alternate days for 24 weeks
- Both were well tolerated and effective
- In moderate acne - 20 mg alternate day regimen may be preferred.
- In severe acne - 20 mg daily regimen is a better choice for in terms of response.

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Dhaked DR et al. A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris. Indian Dermatol Online J. 2016 ;7(5):378-385.

Other topical/Oral agents

- Topical
  - Azelaic acid: only FDA-approved medication to treat acne during pregnancy is (category B)
  - Dapsone gel
  - Salicylic acid gels

- Oral
  - Antioxidants- kiwi seed extracts
  - Zinc

Whitney and Ditre. Clinical, Cosmetic and Investigational Dermatology 2011:4

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Adjuvant treatment and patient counseling : improves compliance

- Key: since long-term therapy; BP, R irritants
- Start with a medication with the most tolerable side effects and increase in strength as needed and tolerated by the patient.
- Explain need for multiple medications.
- Combine with moisturizers for oily skin.
- Use mild cleansers
- Advise on regular and long-term usage
- Maintenance therapy

Whitney and Ditre. Clinical, Cosmetic and Investigational Dermatology 2011:4

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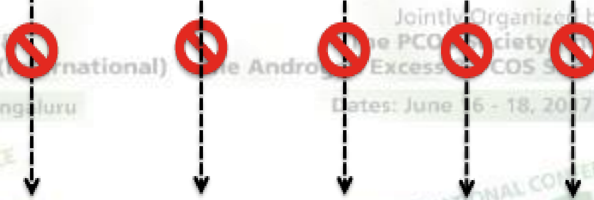
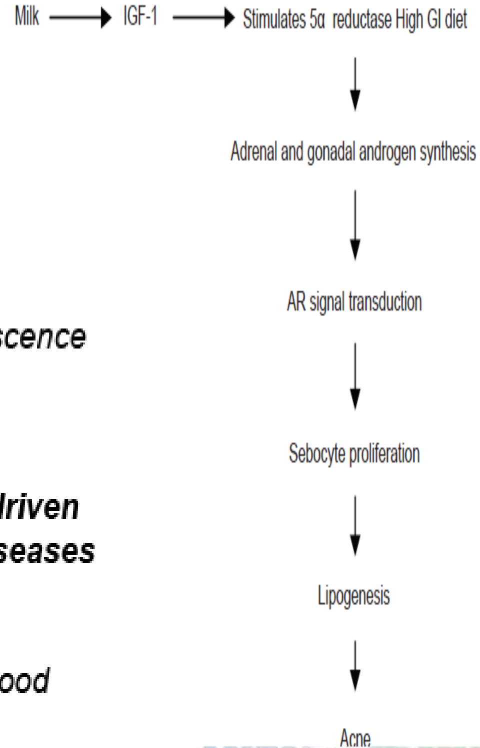
Diet and acne





Kumari R, Thappa DM. Role of insulin resistance and diet in acne. Indian J Dermatol Venereol Leprol 2013;79: 291-9.

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Anti-acnecity of Low glycemic index Diet

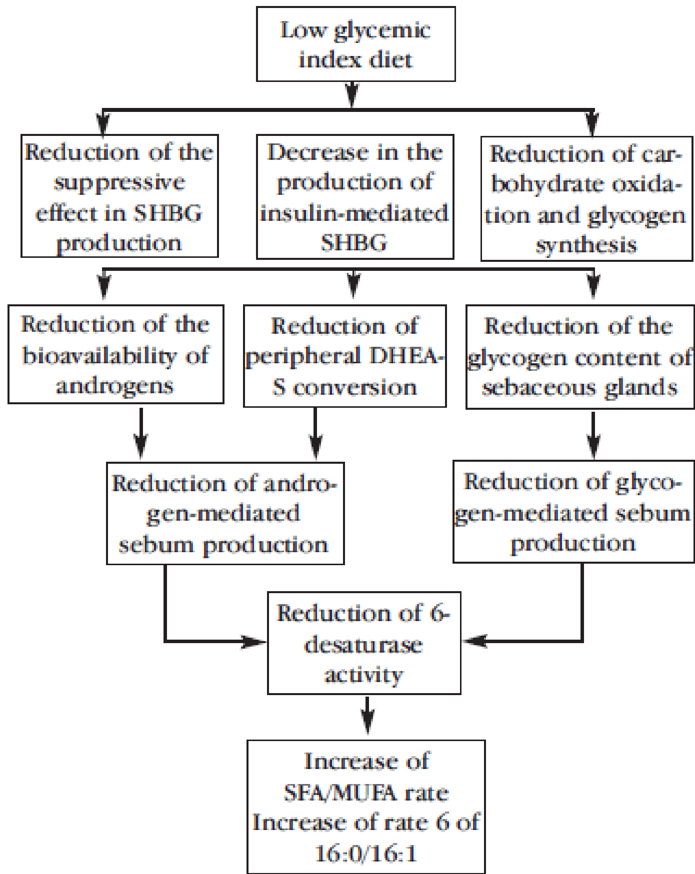


Figure 1: Anti-acgenicity of a low glycemic index diet

- Metformin, green tea, resvertrol decreases mTORC
- Isotretinoin, curcumin, BPO increases Fox O1
- Paleo diets
- MRC –KHS activity

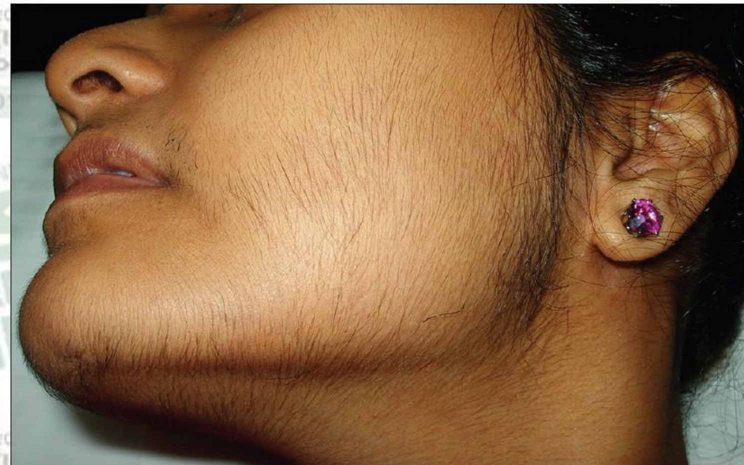
An Bras Dermatol. 2010;85(3):346-53. Melnik BC. FoxO1 - the key for the pathogenesis and therapy of acne? J Dtsch Dermatol Ges. 2010 Feb;8(2):105-14.

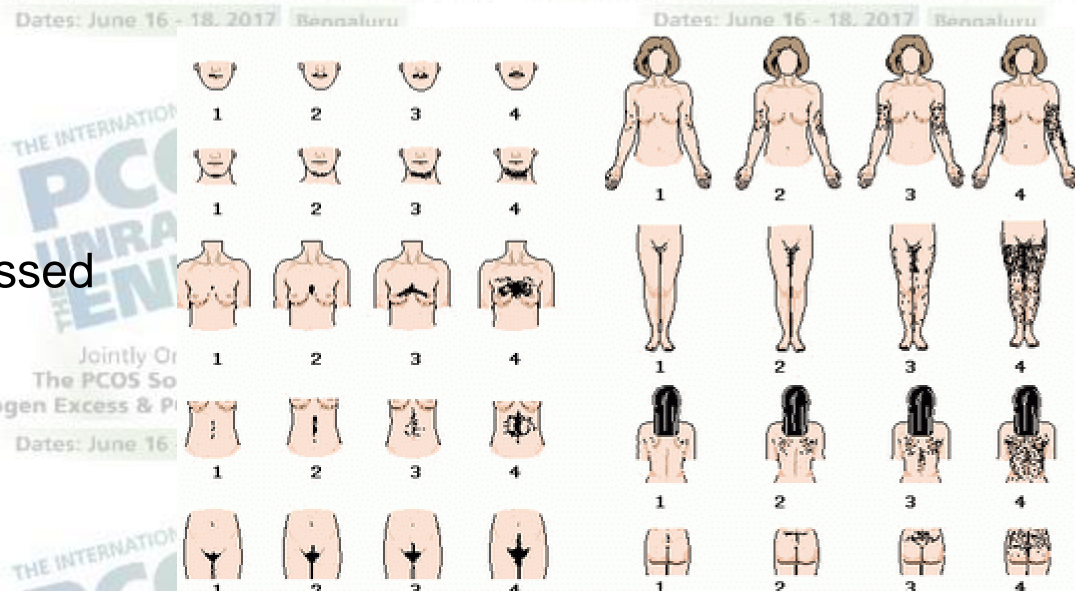
Hirsutism: Presentation and Assessment of severity

- Excessive terminal body hair in a male (androgen dependant) distribution
- early hirsutism
- hirsutism for > two years
- mFG score is used to grade
  - A score of 0 (none) to 4 (severe) in nine areas of the body is assigned with a maximum possible score of 36.

❑ < 4 – mild
❑ 4-7 - moderate
❑ ≥ 8 indicate severe

Cosmetic discomfort not assessed





Malik, et al.: A Consensus Evidence-based Good Clinical Practice Recommendations. Fertility Science and Research 2014; 1 (1):

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Standard Non hormonal therapy of hirsutism

- **Localized hirsutism** : Best treatment is **cosmetic** therapy.

- Cosmetic treatment including
  - short-term (shaving, chemical depilation, plucking, threading, waxing, and bleaching) and
  - long-term (electrolysis, laser therapy, and intense pulse light therapy)

- **Generalized hirsutism** may benefit from a combined medical and cosmetic approach.

http://www.racgp.org.au/afp/2012/october/polycystic-ovary-syndrome/
Lizneva D et al. Androgen excess: Investigations and management. Best Pract Res Clin Obstet Gynaecol.2016 Nov;37:98-118.

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Eflornithine: 13.9% cream - topical treatment to reduce the rate of growth

- Treatment of local facial hair may be augmented in the short term by topical eflornithine
- A total of 18 patients completed the study protocol of twice daily for 6 months.
  - 1 month after final IPL-treatment, eflornithine reduced hair regrowth by 14% (P = 0.007, n = 20 patients),
  - at 3 months by 9% (P = 0.107, n = 19) and
  - at 6 months by 17% (P = 0.048, n = 18) compared to no treatment.
- Limited success rate and overall patient's satisfaction, even with a long-term and high-frequency application
- Topical eflornithine provides a self-administered treatment with a potential to maintain IPL-induced hair reduction in hirsute patients.
- Side effects – Acne; Costly
- Integration of microneedling into topical eflornithine therapy represents a potentially viable approach to increase its ability to inhibit hair growth (animal study).

Vissing AC, Taudorf EH, Haak CS. Adjuvant eflornithine to maintain IPL-induced hair reduction in women with facial hirsutism: a randomized controlled trial. J Eur Acad Dermatol Venereol.2016;30(2):314-9.
Kumar A, Naguib YW, Shi YC. A method to improve the efficacy of topical eflornithine hydrochloride cream.Drug Deliv.2016 ;23(5):1495-501.

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HORMONAL THERAPY FOR ACNE AND HIRSUTISM

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Management of clinical hyperandrogenism

- Androgen suppression,
  - a hormonal combination contraceptive, COC

- Androgen blockade
  - Anti androgens:
    - Cyproterone acetate
    - Spironolactone
    - Flutamide
  - Inhibition of peripheral androgen conversion (5α-reductase type 2 inhibitors)
    - Finasteride
    - Dutasteride : 3 times more potent in inhibiting 5 alpha reductase 1 and 100 times more potent in inhibiting 5 alpha reductase 2

- Insulin sensitizing agents
  - Metformin

Lizneva D, Gavrilova-Jordan L, Walker W. Androgen excess: Investigations and management. Best Pract Res Clin Obstet Gynaecol.2016 Nov;37:98-118.

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Guideline Recommendations: Adults with PCOS

Guidelines for management of Hyperandrogensim

Hirsutism in Adults

- Low-dose CoCs with anti-androgen progestins **(Grade A, EL 2)**
  If there is no improvement with COCs or COCs are not tolerated, it is recommended to use spironolactone or finasteride (Grade A, EL 2)
- The ideal time to stop hormonal therapy for hyperandrogenism cannot be established with current evidence **(Grade A, EL 4)**
- Risk of Thromboembolism: Identifying susceptible patients and/ or pausing treatment for 3 months after 1 year of treatment **(Grade A, EL 4)**

Malik et al. Management of Polycystic Ovary Syndrome in India. Fertility Science & Research. Jan-Jun 2014; 1(1): 23-4

L.IN.WH.03.2015.0620

Guideline Recommendations: Adults with PCOS

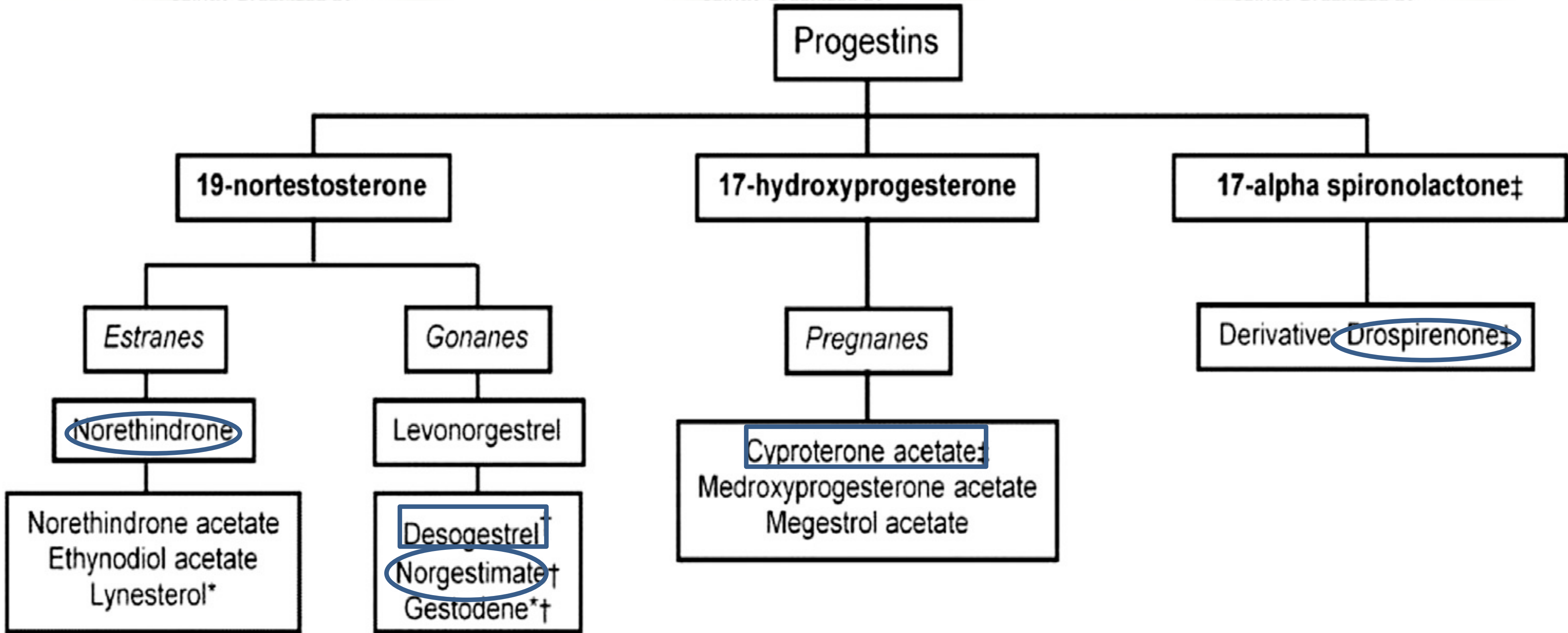
Guidelines for management of Hyperandrogensim

Acne in Adults

- Suggested to use topical medication along with pharmacological interventions based on clinical presentation of acne **(Grade A, EL 4)**
- Oral contraceptives (CPA, Drospirenone & Desogestrel) are suggested as first-line therapy for management of all acne lesions **(Grade A, EL 1)**
- Cyproterone acetate is more beneficial in Indian conditions
- Evaluation of hormonal status is a prerequisite before initiating hormone therapy. Hormone therapy with low-dose EE/CPA or high-dose CPA or spironolactone are specifically suggested

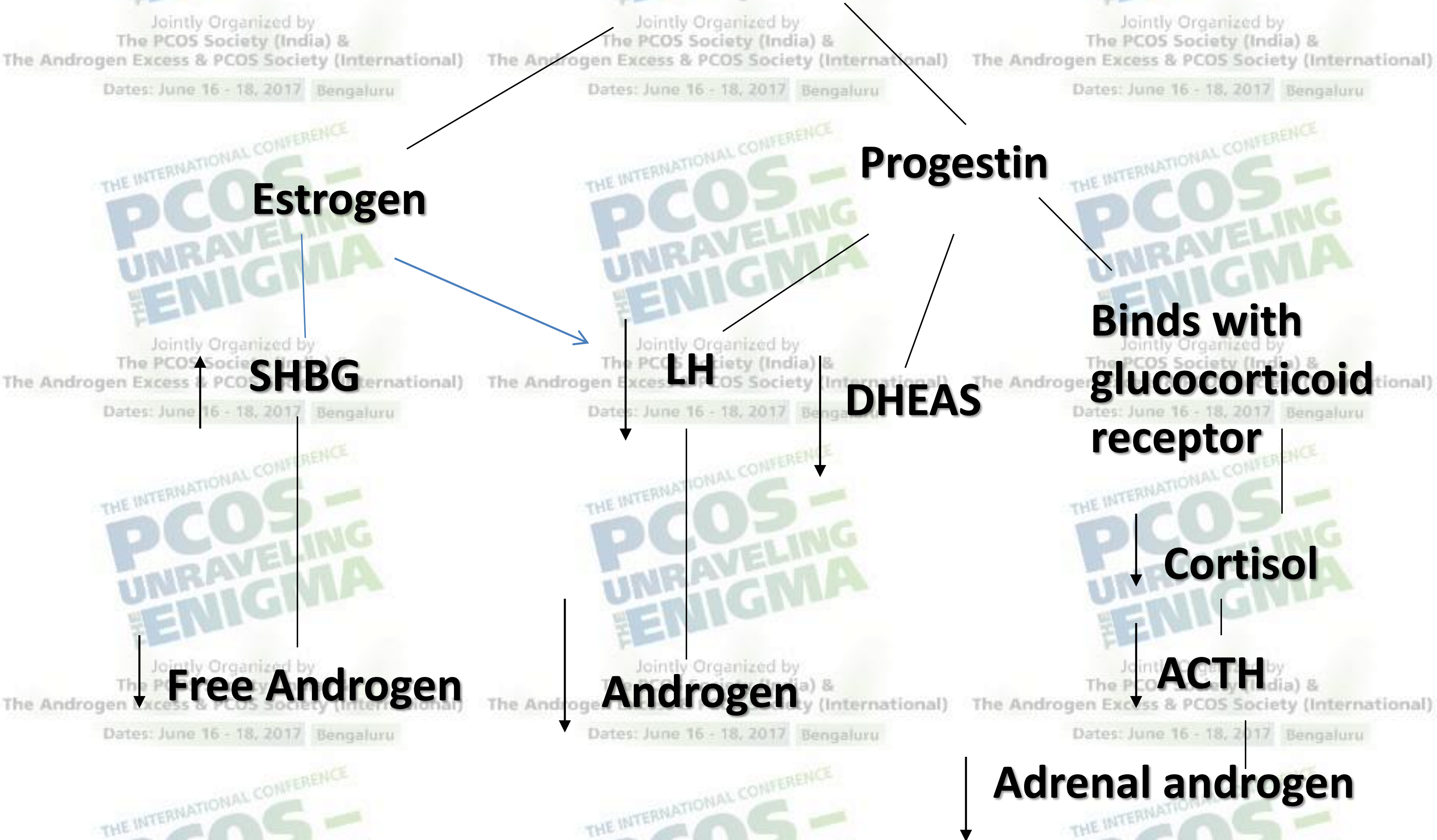
Malik et al. Management of Polycystic Ovary Syndrome in India. Fertility Science & Research. Jan-Jun 2014; 1(1): 23-4

Combined OC pills ((very) low dose ethinyl estradiol with progestins)



4 OCs are approved in the US for the management of acne (*JAMA Dermatol.* 2017;153(4):249-250.)

Role of OC pills- Mechanism of action



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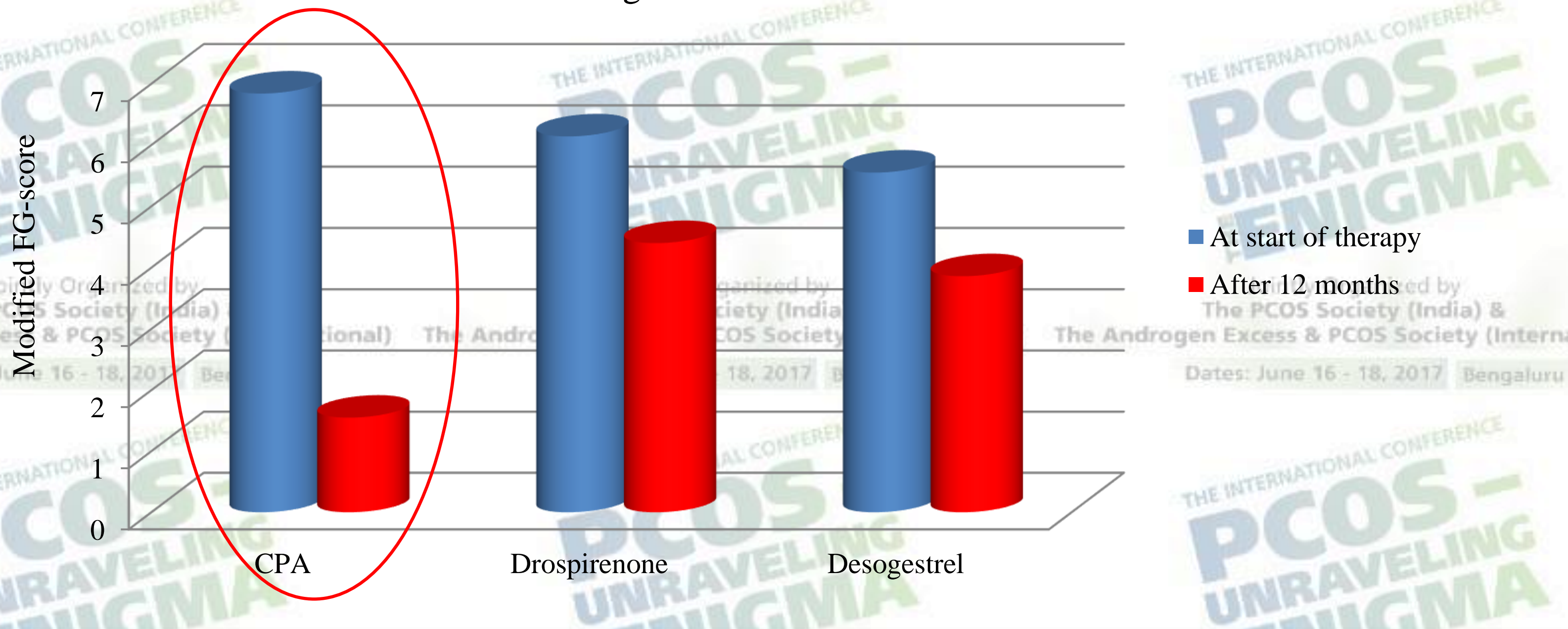
Current Indian Evidences

Bhattacharya et al



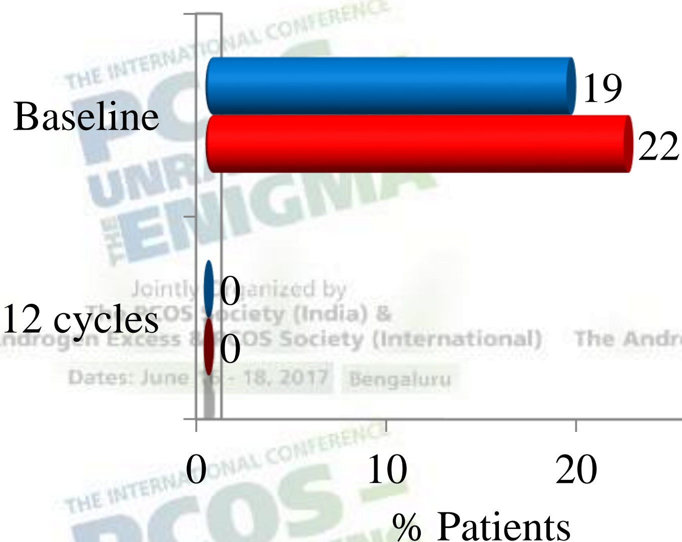
At the end of 12 months, CPA significantly decreased the modified Ferrimen Galeway as compared to Drospirenone ($p = 0.02$) & Desogestrel ($p = 0.003$)

Bhattacharya et al. Comparative study of therapeutic effects oral contraceptive pills containing desogestrel, cyproterone acetate and drospirenone in patients with polycystic ovary syndrome. Fertil Steril. 2012; 98 (4): 1053-59

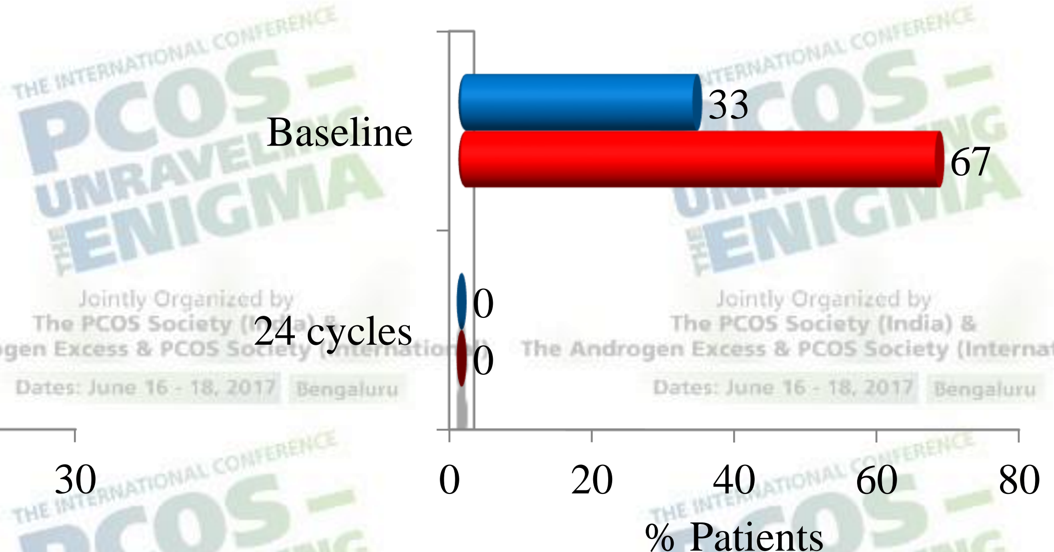
L.IN.WH.03.2015.0620

Acne Management

35mcg EE + 2mg CPA 12 cycles[1]



35mcg EE + 2mg CPA 48 cycles[2]



Cyproterone acetate causes 100% remission from severe and moderate acne – also reduces seborrhoea

1. Golland and Elstein Ann N Y Acad Sci. 1993 May 28;687:263-71
2. Falsetti et al. J Obstet gynaecol 1997; 17: 565-8.

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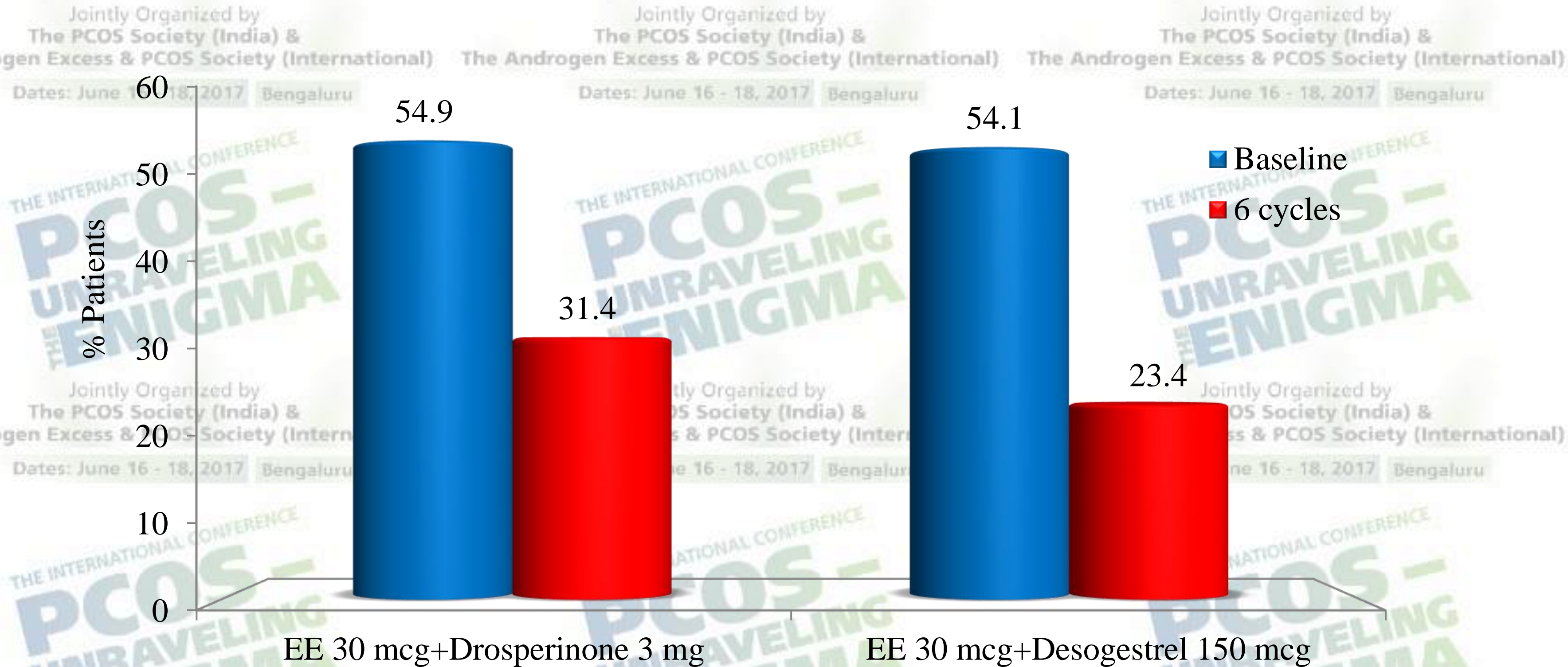
Acne Management- India



Reduction of acne with Drospirenone and Desogestrel,

1. Bhattacharya et al. J Turkish-German gynaecol Assoc 2011; 12: 144-7.
2. Bhattacharya et al. J Obstet Gynaecol Res. 2012;38(1):285-90

L.IN.WH.03.2015.0620

Response to hormonal Management of clinical hyperandrogenism

- Generally, acne responds to therapy relatively rapidly, in 2-3 months after starting
- whereas hirsutism is slower to respond, with improvements observed as early as 3 months, but routinely only after 6 or 8 months (9-12 months) of therapy because of the long duration of the hair growth cycle.

Lizneva D, Gavrilova-Jordan L, Walker W. Androgen excess: Investigations and management. Best Pract Res Clin Obstet Gynaecol.2016 Nov;37:98-118.

Ideal candidates for COC therapy

- Under 35 years of age and at least 14 years old, who have achieved menarche, who
- Do not smoke,
- Do not have migraine headaches, and
- Normotensive
- Indicated for acne only if the woman desires contraception
- Have no known contraindications to OC therapy

- **Examination**: breast examination, USG breast

- **Contraindications**: Diabetes mellitus with nephropathy • Retinopathy • Neuropathy • Vascular disease • Deep vein thrombosis (history or current) • Heart disease • Stroke • Pregnancy • Breast cancer (current)

Julie C. Harper. Update on Oral Contraceptive Therapy in Acne. PRACTICAL DERMATOLOGY 2012; http://practicaldermatology.com/2012/09/update-on-oral-contraceptive-therapy-in-acne/

To reduce impact on CHO and lipid metabolism

- A number of studies have also investigated the combination of metformin and COCs in women with PCOS and suggested that it may improve the insulin sensitivity.

- The addition of metformin to COCs may, therefore, have metabolic benefits in the treatment of women with PCOS.

Feng GM. Comparison of Drospirenone- with Cyproterone Acetate-Containing Oral Contraceptives, Combined with Metformin and Lifestyle Modifications in Women with Polycystic Ovary Syndrome and Metabolic Disorders: A Prospective Randomized Control Trial. Chin Med J 2016;129:883-90.

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Spironolactone

- specific antagonist of aldosterone, which completely binds to the aldosterone receptors in the distal tubular region of the kidney.
- Treatment of hirsutism (also useful in acne) is based on the following mechanisms :

1. Competitive inhibition of DHT at the intracellular receptor level.
2. Suppression of testoesterone biosynthesis by a decrease in the CYP enzymes.
3. Increase in androgen catabolism (with increased peripheral conversion of testosterone to estrone.
4. Inhibition of skin 5α-reductase activity.
5. Side effects: menstrual Irregularity – so helpful to use with OCPs

   Breast tenderness, dyspepsia,fatigue, to monitor for hyperkalemia, liver dysfunction and hypotension.

Need for contraception

Dose: 100-200mg in 2 divided doses for atleast a year

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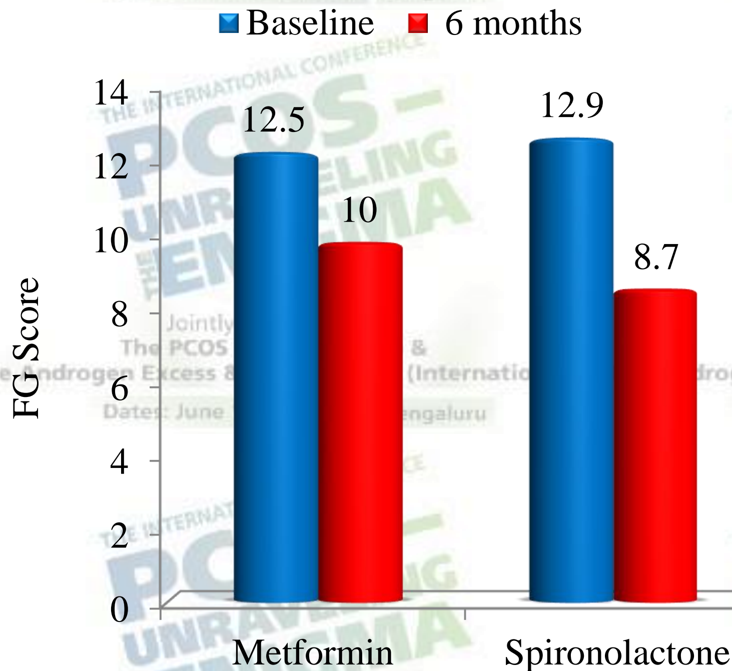
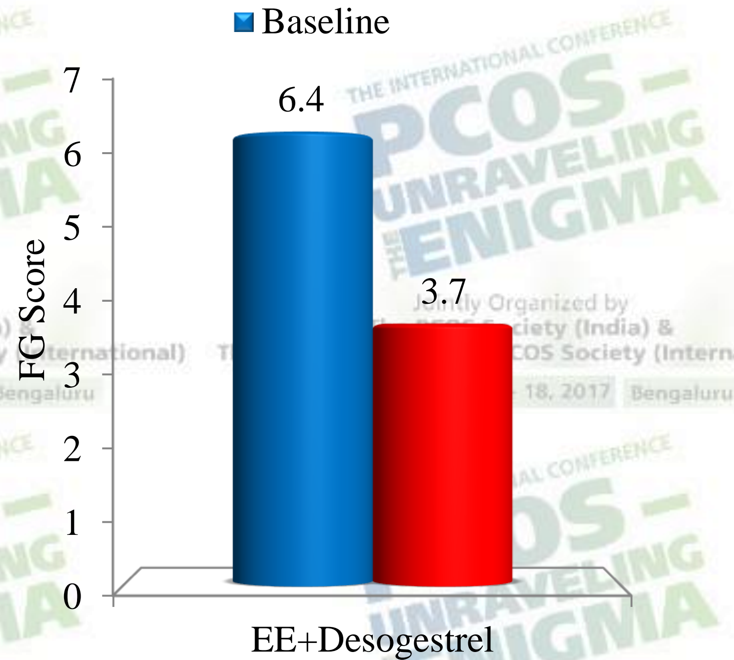
Hirsutism Management - India

- Metformin 500mg bid and Spironolactone 50mg od[1]



- Ethinyl estradiol 30mcg + Desogestrel 150mcg[2]



Spironolactone is better than metformin in improving hirsutism

1. Ganie et al. J Clin Endocrinol Metab. 2004;89(6):2756-62.
2. Bhattacharya et al. J Obstet Gynaecol Res. 2012;38(1):285-90

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Finasteride

- A 5-α-reductase type 2 inhibitor,
- commonly used for prostatic disorders and to treat hirsutism.
- Effectiveness for hirsutism is comparable to that of spironolactone.
- Efficacy for acne questionable and has not been well evaluated…

Chuan SS, Chang RJ Polycystic ovary syndrome and acne. Skin Therapy Lett.2010 Nov-Dec;15(10):1-4.

Flutamide

- non-steroidal androgen receptor antagonist indicated for the treatment of prostate cancer.
- Effective for treating hirsutism. may be used for mild to moderate acne.
- Low doses: 62.5 mg or 125 mg/day (may be used twice a day) - shown to be effective.
- Combination of OCPs and flutamide is likely more efficacious than flutamide alone.
- In hirsute women with acne who were treated with OCPs, the addition of flutamide was significantly more effective than spironolactone.
- The potential for hepatotoxicity limits its use. However, no cases of fatal hepatotoxicity have been reported with doses less than 500 mg /day. There have been reports of mild, transient liver impairment at doses ranging from 375-500 mg /day.
- Women should remain on OCPs for birth control purposes as feminization of a male fetus can occur while on this medication. Patients should be off the medication for 3 months before conception.

Chuan SS et al . Polycystic ovary syndrome and acne. Skin Therapy Lett. 2010 Nov-Dec;15(10):1-4.

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Insulin Sensitizing Agents: Current status

- Decrease androgen production by lowering hyperinsulinemia.
- Improve important metabolic and endocrine aberrations, not recommended when hirsutism is the sole indication for use.
- Efficacy of this approach to treat hirsutism – inconsistent (some, not all studies have shown benefit).
- Monotherapy with an insulin sensitizer does not significantly improve hirsutism
- At present, these agents are not recommended as acne therapy for women with PCOS.

Somani N, Turvy D. Hirsutism: an evidence-based treatment update.Am J Clin Dermatol. 2014 Jul;15(3):247-66.
Chuan SS, Chang RJ. Polycystic ovary syndrome and acne. Skin Therapy Lett. 2010 Nov-Dec;15(10):1-4.

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THANK YOU

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Metformin

- Antidiabetic biguanide drug that improves insulin resistance and decrease hyperinsulinemia in patients with PCOS.
- Metformin inhibits ovarian androgen production in PCOS patients via effects on steroidogenic acute regulatory protein and 17α-hydroxylase*.
- Ascertain that kidney and liver function are normal and that the patient does not have advanced congestive heart failure before starting metformin.
- Less effective in those who are significantly obese (BMI greater than 35 kg/m2),
- Metformin not a first line treatment of PCOS.

  Dose - 1.5 to 2.5 gm/day Start at 500mg once daily after dinner for 1 wk

  - ↑ to 500mg BD for a week. Finally 500mg TDS
- The extent to which these effects translate into improvement in hirsutism and acne remains to be determined.

*Wang QY, Song Y, Huang W, Xiao L, Wang QS, Feng GM. Comparison of Drospirenone- with Cyproterone Acetate-Containing Oral Contraceptives, Combined with Metformin and Lifestyle Modifications in Women with Polycystic Ovary Syndrome and Metabolic Disorders: A Prospective Randomized Control Trial. Chin Med J 2016;129:883-90.

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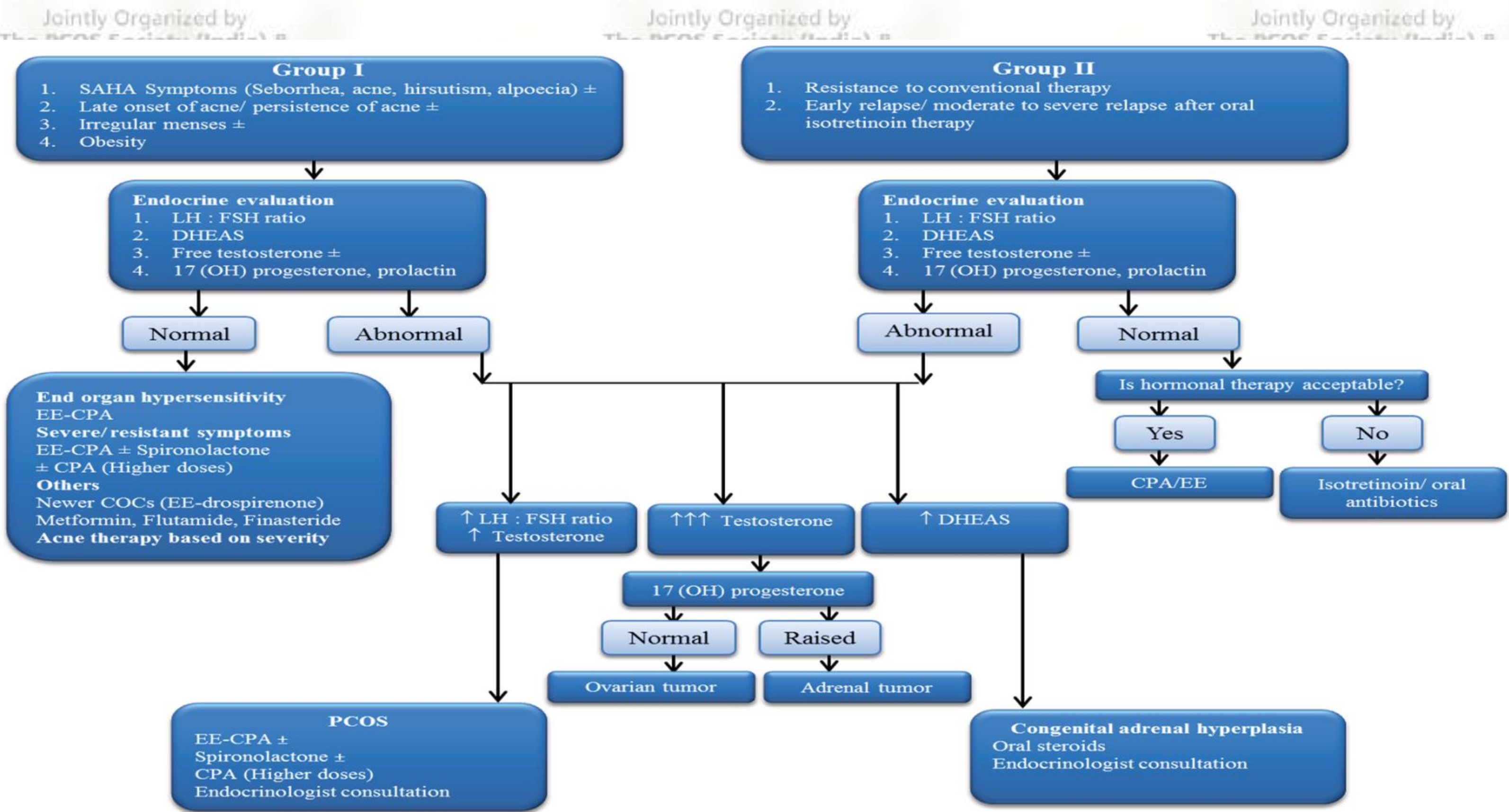
Hormonal management of acne: IAA consensus guideline



Abbreviations: OCP-oral contraceptive pills, CPA- cyproterone acetate, EE- ethinyl estradiol, DHEAS- dehydroepiandrosterone sulfate, LH- luteinizing hormone, FSH- follicle stimulating hormone, 17 (OH) progesterone- 17 hydroxyprogesterone, PCOD- polycystic-ovarian disease

Source: Adapted from Kubba R et al. [illegible]9

Recommendations in acne: IAA consensus guideline

- Hormone therapy is suggested as first-line therapy for androgenicacne in women with PCOS, SAHA syndrome, HAIRAN syndrome (hyperandrogenism, IR, AN), or cutaneous hyperandrogenism.
- Justifies hormonal therapy in refractory/difficult acne and in nodulocystic acne where isotretinoin is either contraindicated or inadequate.
- However, due to the multiple causes of acne vulgaris, evaluation of hormonal status is a prerequisite before initiating hormone therapy.
- Hormone therapy with low-dose EE/CPA or high-dose CPA or spironolactone are specifically suggested.
  - **Adults**: COCs (CPA, drospirenone, or desogestrel as progestin component) as first-line therapy (Grade A, EL 1). CPA has been shown to be more beneficial than other progestins in Indian conditions.
  - **Adolescents**: COCs (cyproterone acetate, drospirenone, or desogestrel as progestin component) based on the clinical presentation of acne.
- Use topical medication along with pharmacological interventions

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Acne: COCs

- In women with moderate to severe acne or acne refractory to treatment, placement on a combined oral contraceptive pill with or without spironolactone offers significant relief and reduction of acne lesions.
- More studies are needed to fully evaluate the potential benefit of spironolactone in improving acne.

Whitney and Ditre. Clinical, Cosmetic and Investigational Dermatology 2011:4

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Age important consideration

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- Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):56-66. doi: 10.1097/MED.0000000000000309.
- **Polycystic ovary syndrome in adolescent girls.**
- Baldauff NH[1], Witchel SF

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Acne: Outcomes with standard therapy

- In one prospective study of 200 women over the age of 25 years, approximately 80% of women failed multiple courses of systemic antibiotic medications and approximately 30% of patients relapsed after several therapeutic cycles of isotretinoin (Goulden et al., 1997)
- The high rates of treatment failure with traditional therapies along with more consciousness about antibiotic stewardship in dermatology patients, many of whom are on systemic antibiotic therapy for acne treatment, have motivated clinicians to reconsider the therapeutic targets of treatment in this population

Trivedi MK, Shinkai K, Murase JE. **A Review of hormone-based therapies to treat adult acne vulgaris in women.** Int J Womens Dermatol. 2017 Mar 30;3(1):44-52.

Hormonal management of hirsutism

- For mild hirsutism there is evidence of limited quality that OCPs are effective.
- Flutamide 250 mg twice daily and spironolactone 100 mg daily appeared to be effective and safe, in more severe cases albeit the evidence was low to very low quality.
- Finasteride 5 mg daily showed inconsistent results in different comparisons, therefore no firm conclusions can be made.
- Metformin is not associated with (direct) benefit
- Therefore, spironolactone and finasteride can be used as second-line treatment for the management of hirsutism in patients with PCOS.

van Zuuren EJ[1], Fedorowicz Z, Carter B. Interventions for hirsutism (excluding laser and photoepilation therapy alone). Cochrane Database Syst Rev. 2015 Apr 28;(4):CD010334.
van Zuuren EJ, Fedorowicz Z. **Interventions for Hirsutism.** JAMA. 2015 Nov 3;314(17):1863-4.

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Global acne grading system

Location	Factor
Forehead	2
Right cheek	2
Left cheek	2
Nose	1
Chin	1
Chest and upper back	3

Note: Each type of lesion is given a value depending on severity: no lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4. The score for each area (Local score) is calculated using the formula: Local score = Factor × Grade (0-4). The global score is the sum of local scores, and acne severity was graded using the global score. A score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very severe

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Drospirenone side effects vs norgestimate

- Today, drospirenone is considered to be most effective in managing androgen levels in women, but it does come with significant side-effects.
- VTE: First, while the statistical risk appears to be real, the absolute risk to our patients is still very low. The risk of VTE in a young woman who is not on an OCP is about three per 10,000 woman years. A young woman on an OCP has a higher risk of VTE, about six per 10,000 woman years. Keeping these baseline numbers in mind, a woman on a drospirenone-containing OCP has a risk of about 10 per 10,000 woman years
- the progestin norgestimate has been presented as a reasonable alternative to drospirenone in treating acne vulgaris for those with a higher risk of blood clots, although it is slightly less effective in the management of acne.

Lynn DD[1], Umari T[1], Dunnick CA[2], Dellavalle RP. **The epidemiology of acne vulgaris in late adolescence.** Adolesc Health Med Ther. 2016 Jan 19;7:13-25.
http://practicaldermatology.com/2012/09/update-on-oral-contraceptive-therapy-in-acne

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Adverse effects and risks

- Side effects associated with OCP use may include irregular bleeding, nausea, mood changes, and breast tenderness.
- ischemic stroke, which is 2.5 times more likely in women aged 20-24.[1]Data indicate that this risk is directly proportional with estrogen dose and that risk increases with age. In addition, hypertension (HTN), cigarette smoking, and migraine headaches substantially increase risk of stroke. Other potential risks include myocardial infarction; however, 80 percent of heart attacks among OCP users are attributable to cigarette smoking,
- breast cancer among OCP users, although this has not been fully substantiated
- Bone density: Diminished bone density represents a recent area of concern regarding OCP use.
- . Second, the risk of VTE during pregnancy is about 12 per 10,000 woman years and after delivery the risk increases to about 30 per 10,000 woman years.

http://practicaldermatology.com/2012/09/update-on-oral-contraceptive-therapy-in-acne/

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- Anecdotal instances of metformin improving outcomes with IPL for hirsuitism.
- The efficacy of this approach to treat hirsutism has been inconsistent, as some, but not all studies have shown benefit.

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Systemic antibiotics: mainstay for moderate-severe inflammatory acne

- Anti-inflammatory properties, effective against *P acnes.*
- Tetracycline group commonly prescribed. Doxycycline and minocycline - more lipophilic and hence more effective than tetracycline.
- Other antibiotics, including trimethoprim alone or in combination with sulfamethoxazole, and azithromycin, reportedly are helpful.
- Oral antibiotic use can lead to vaginal candidiasis; doxycycline can be associated with photosensitivity; and minocycline has been linked to pigment deposition of the skin, mucus membranes, and teeth.
- Systemic antibiotic use should be limited to the shortest possible duration; to minimize the development of bacterial resistance, reevaluation at 3-4 months

http://emedicine.medscape.com/article/1069804-guidelines

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Drospirenone side effects in perspective

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  - on an OCP has a higher risk, about 6 per 10,000 woman years.
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Lynn DD et al.The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther.2016 Jan 19;7:13-25.
http://practicaldermatology.com/2012/09/update-on-oral-contraceptive-therapy-in-acne

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