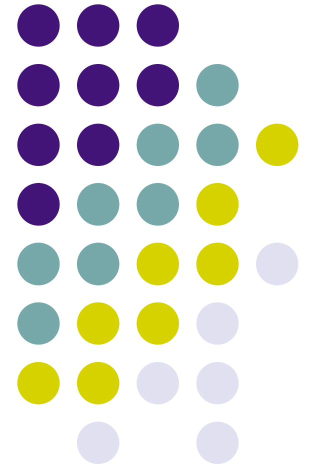
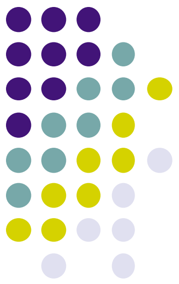
Oral contraceptions in the treatment of Hyperandrogenism



Fatih Durmuşoğlu,M.D



KISS

Keep **I**t **S**imple and **S**hort

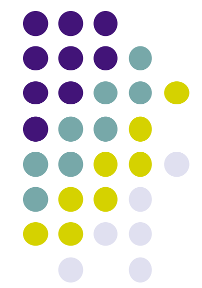
LH

ACTH

SHBG

Androgen Excess

ß - cell dysfunction



Adrenal

25%

50%

90%

100%

50%

Testosterone

Androstenedione

DHEA

25%

50%

10%

Ovary

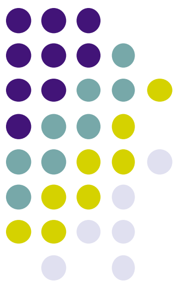
DHEAS

Source of androgens in women

Pucci and Petraglia. Gynecol Endocrinol 1997.

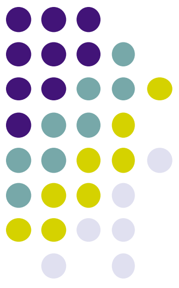
YŞ

The goal of treatment



- Suppression of hyperandrogenism at the source
- Decrease the bioavailability of Androgens
- Resume normal menstrual regularity
- Clearing the peripheric signs of HA on target tissues
- İf possible continue hormonal contraception throughout the treatment.For avoiding recurrences and side effects of other medications

PCOS



- Sixty-five to 85% of all women with androgen excess are diagnosed as having PCOS
- PCOS affects approximately 5% of reproductive-aged women
- The findings in PCOS are variable, with 40% to 60% of patients obese, 60% to 90% hirsute, 50% to 90% oligoamenorrheic, and 55% to 75% infertile.
- The high ovarian,androgen, or estrogen production disrupts the hypothalamic-pituitary-gonadotropic axis, resulting in an elevated LH/FSH ratio in up to 60% .
- High androgen levels inhibit follicular development

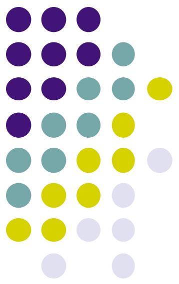
Polycystic Ovary Syndrome

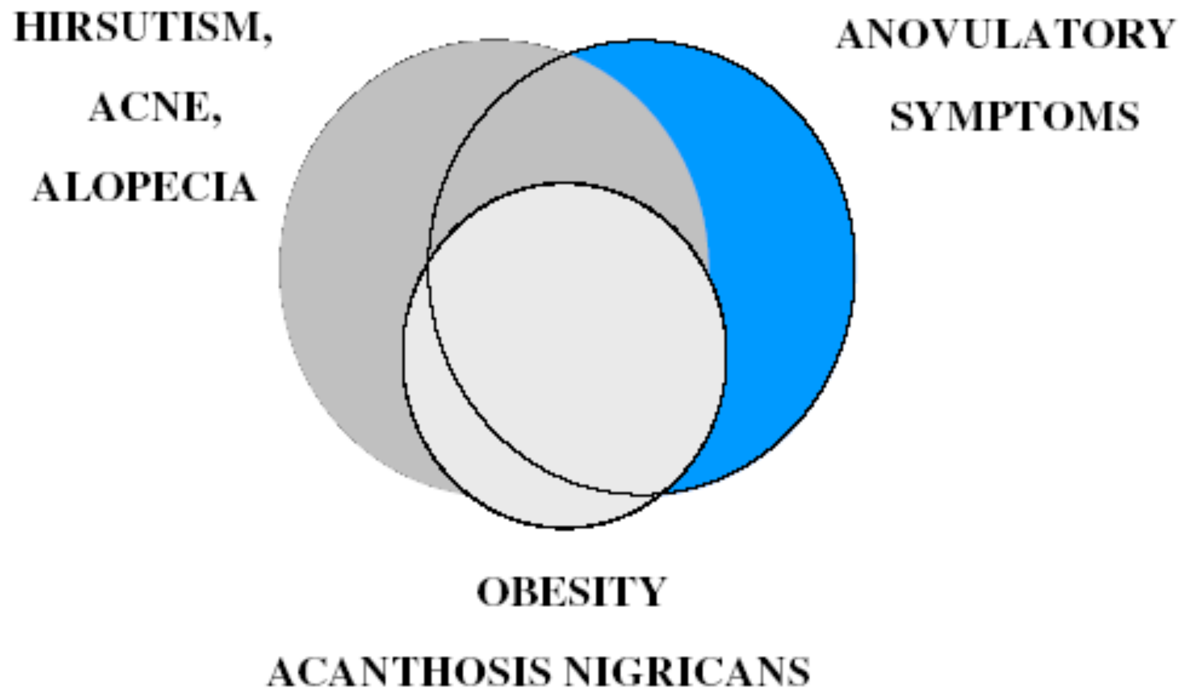
Anovulation → Oligo/Amenorrhea, Infertility, Endometrial Ca

Hyperandrogenemia → Hirsutism, Acne, Alopecia

Metabolic Derangements → Glucose Intolerance/DM, Dyslipidemia, Endothelial Dysfunction, Procoagulant State

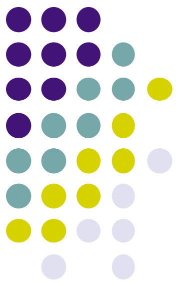
Clinical manifestations of PCOS





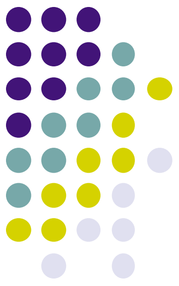
Endocrinol Metab Clin N Am 2005

Androgen Excess -I-

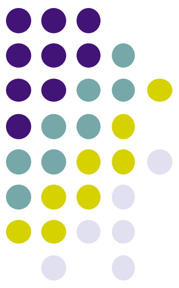


- Hirsutism is a common complaint,
- it may be the earliest sign of a potentially serious underlying disorder, such as an androgen-producing neoplasm.
- Higher androgen levels can produce frank virilization, characterized by male pattern
- Alopecia, clitoromegaly, deepening of the voice, and increased muscle mass.

Androgen Excess-II-

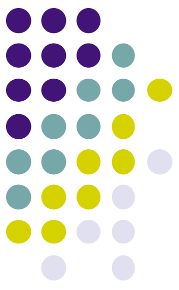


- Elevated androgens can be associated with lipoprotein abnormalities.
- Hirsutism is often seen with other risk factors for cardiovascular disease
- Anovulation is commonly associated with hyperandrogenism can lead to infertility and oligo or amenorrhea
- Endometrial hyperplasia , atypia and carcinoma may be seen in uncontrolled patient population.



Differential diagnosis

- Hyperandrogenic-Insulin Resistant – Acanthosis Nigricans (HAIRAN) syndrome
- Hyperthecosis
- Non-classic Adrenal Hyperplasia
- Cushing syndrome
- Iatrogenic causes
- Idipathic hirsutism
- tumors

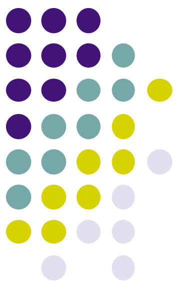


Evaluation

- Weight , waist/hip ratio and assesment of clinical signs of hyperandrogenism and insulin resistance
- FSH , TSH , PRL , Estradiol ,
- Nonclassic adrenal hyperplasia (NCAH) screening ; basal 17-hydroxyprogesterone level in the follicular phase of the cycle .If more than >2 ng/dL than ACTH stim test should be performed

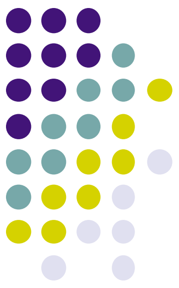
LegroRS,Dunaif A. Jclin Endoc Metab 1998:83

Evaluation-II-



- Free testosterone may be elevated when total T is normal.
- DHEAS levels > 7000 ng/dL are indicative of adrenal tumor.
- In obese adolescents the LH/FSH ratio is usually supressed(endogenous E2) , but in lean subjects LH/FSH may be elevated.
- The fasting glucose/insulin ratio in obese adult <4.5 correlates with insulin resistance and in adolescents a ratio <7 is consistent with insulin resistance
- Screening for diabetes mellitus ; 2 hour 75 g glucose tolerance test is shown to be more sensitive than fasting glucose

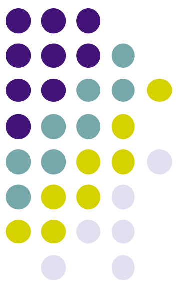
Legro RS. J Pediatr Endoc Metab 2002:15



Hormonal treatment

- Oral contraceptives
- Antiandrogens inhibitors (Spironolactone is an aldosterone antagonist and a mild diuretic useful in the treatment of hirsutism, although it is currently not approved by the FDA for this use)
- 5 alpha reductase inhibitors) its significant teratogenic potential
  - precludes its use in any women who may be at risk for pregnancy.
- Long acting GnRH Analogs
- Corticoid Suppression Dexamethasone (0.5 or 0.25 mg nightly, or 0.5 mg every other night) (24), prednisone (5 to 10 mg/day), or hydrocortisone (15 mg/day) is useful in
  - patients with NCAH.
- İnsulin - Sensitizing Agents
- Ketocanozole (adrenocortical suppression rarely used with caution!)

Hormonal treatment of HA

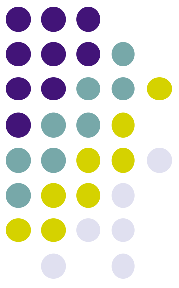


- The most popular treatment for hirsutism is estrogen-progestin preparations, which suppress circulating LH and FSH leading to a decrease in ovarian androgen production.

- In addition, the estrogen in the birth control pill increases SHBG, decreasing free testosterone levels.

- Patients with clinical conditions contraindicating such preparations are not candidates for this treatment.

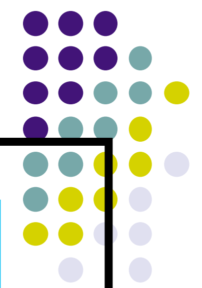
Why using OC pills in the treatment ?



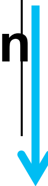
1. Resuming menstrual cycle as supposed to be, very important for compliance

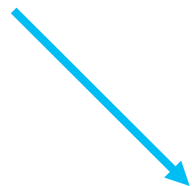
2. Estrogen and progesterone unique effects on HA

3. Reducing the side effects of other antiandrogens and teratogenic drugs



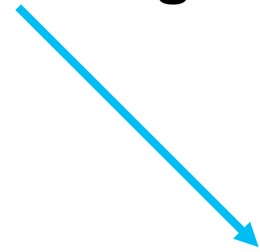
ESTROGEN → Pituitary suppression → ovarianandrogen





SHBG ↑ → Free testosterone ↓

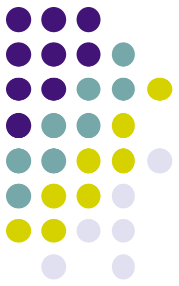
cyclic progesteron + estrogen

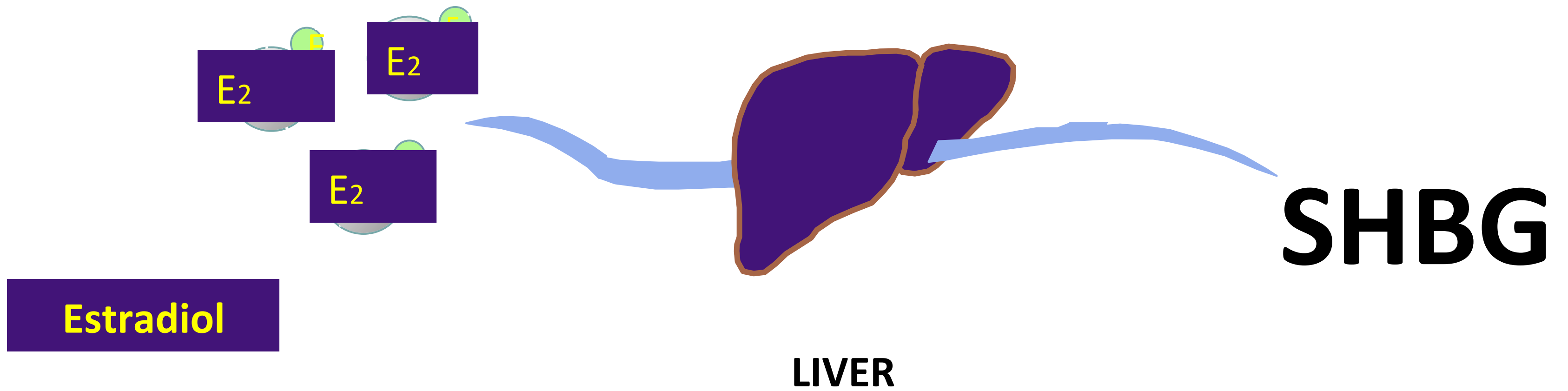


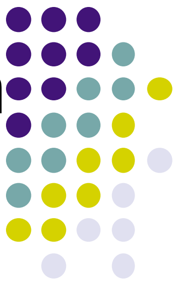
Prevention of pregnancy

Treats oligomenorrhea

Estradiol(E2)







PROGESTERONE → LH ↓ → ↓ovarian androgen

?

SHBG → Free testosterone ↓

(specially no binding to SHBG)

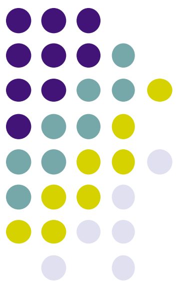
Cyclic EE+ P4

Contraception

Regulating menstrual cycle

Preventing Endometrial hyperplasia

Combination oral contraceptives



- Regulate menstruation
- Prevent endometrial hyperplasia
- Suppressing both FSH and LH
- Increasing SHBG
- After menarche , COC does not interfere with growth or development
- COC should be continued until the end of pubertal period which is 5 years after the menarch

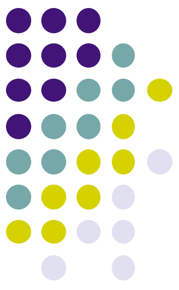
BurkmanRT. Am J Med 1995:98

Treatment for women with polycystic ovary syndrome.

Complaint	Treatment options
Infertility	Metformin; clomiphene; letrozole; gonadotropins; ovarian cautery
Skin manifestations	Oral contraceptive + antiandrogen (spironolactone, flutamide, finestride); GnRH agonists
Dysfunctional bleeding	cyclic progestogen; oral contraceptives
Weight/metabolic concerns	Diet/lifestyle management; metformin

Lobo. Choice of treatment for women with PCOS. Fertil Steril 2006.

Which progestin is proper for HA patient



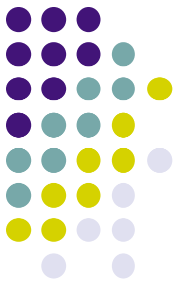
- Highly selective progestogen: pronounced endometrial focus and antiandrogenic properties

- Estrogenic, antiestrogenic, androgenic properties negligible. no upregulation of the glucocorticoid-receptor activity.

- No relevant extragenital anti-estrogenic properties, thus maintaining beneficial estrogenic effects (e.g. in liver, vascular system, CNS etc).

- Minimal impact on liver and lipid- and carbohydrate metabolism. no interference with E_2-induced SHBG-Production which enhances the anti-androgenic effects of E2 + P4-combinations

Classification of Synthetic Progestogens



Progestogens

- **Progesterone derivatives**
  - Pregnanes
    - Megestrol acetate
    - Cyproterone acetate
    - Medroxyprogesterone acetate
- **C-19 nortestosterone**
  - Estranes
    - Dienogest
    - Norethindrone
    - Norethisterone acetate
    - Ethynodiol diacetate
    - Lynestrenol
    - Norethynodrel
  - Gonanes
    - Norgestrel
    - Levonorgestrel
    - Norgestimate
    - Desogestrel
    - Gestodene
- **Spirolactone**
  - Drospirenone

Schindler *et al*. Maturitas 2008;61:171–80; Sitruk-Ware R. Maturitas 2004;47:277–83

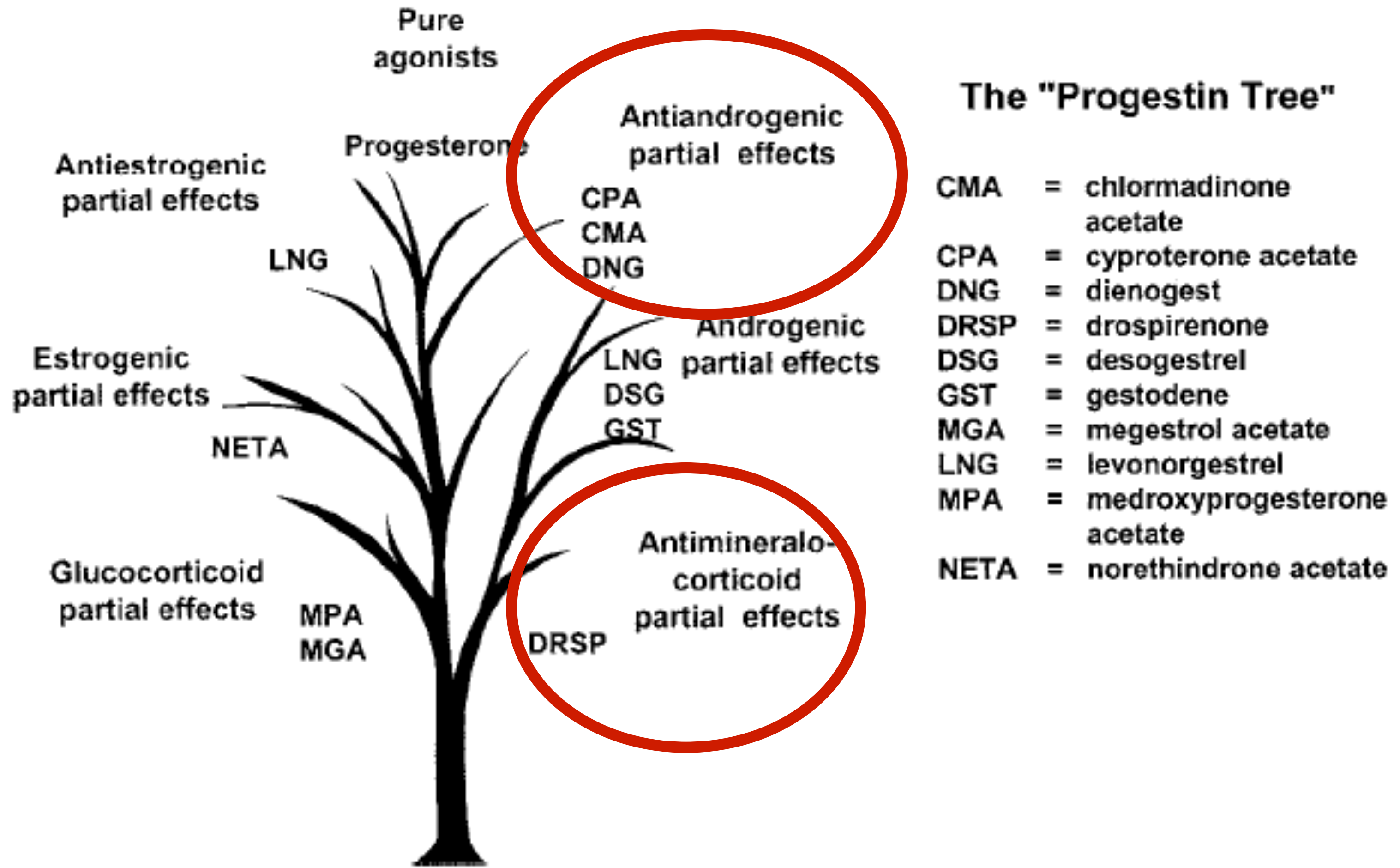
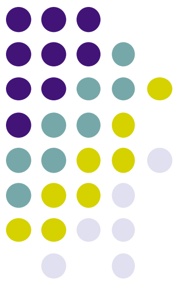
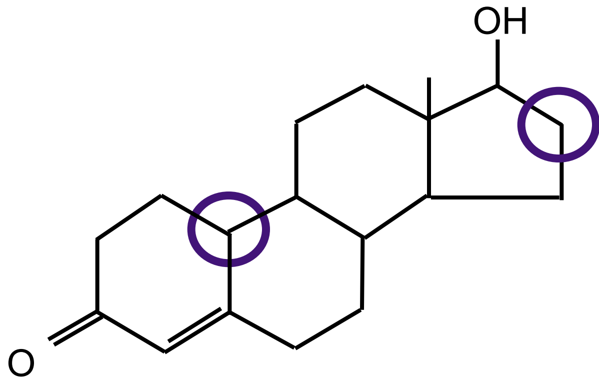


FIGURE 1. The "progestin tree."

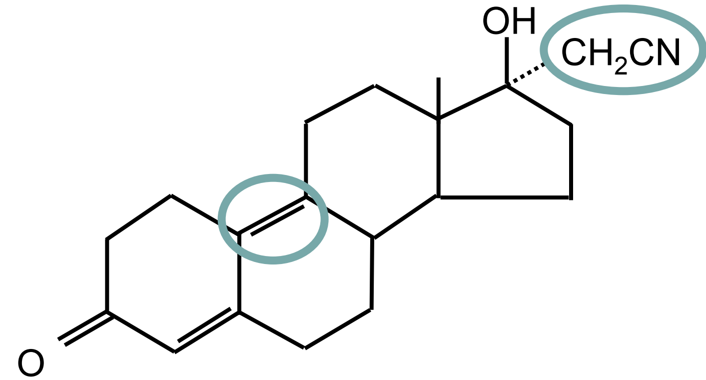


Chemical Structure of Progestins

The chemical structures of 19-Nortestosterone and Dienogest



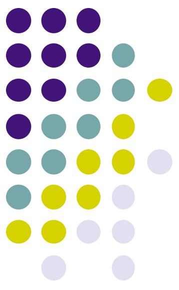
19-Nortestosterone



Dienogest

Kuhl H. Climacteric 2005; 8 (S1)

Pharmacologic Properties of Progestins

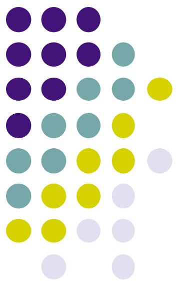


		Progestogenic	Anti-androgenic	Androgenic	Anti-mineralocorticoid
Nortestosterone derivatives	Levonorgestrel	++	–	+	–
	Gestodene	++	–	+	+
	Norgestimate	++	–	+	–
	Desogestrel	++	–	+	–
	Dienogest	**++**	**++**	**–**	**–**
Progesterone and derivatives	Cyproterone acetate	++	++	–	–
	Drospirenone	++	++	–	++
	Progesterone	++	+	–	++

++, Activity; +, Negligible activity at therapeutic dosages; –, No activity

Krattenmacher. Contraception 2000;62:29–38

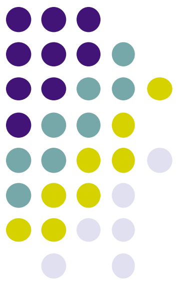
Pharmacologic Properties of Antiandrogenic Progestins



		Elimination half-life (h)	Plasma binding (%)	
			Albumin	Sex hormone binding globulin
Nortestosterone derivatives	Norethisterone	7.6	61.0	35.5
	Levonorgestrel	14.8	50.0	47.5
	Gestodene	11.2	24.1	75.3
	3-keto-Desogestrel	11.2	63.5	32.0
	Dienogest[1]	**11**	**90**	**0**
Progesterone and derivatives	Cyproterone acetate	43.9	96	0
	Drospirenone	30	95	0
	Progesterone	25–50[a]	54	0

[a]Half-life varies depending on formulation and route of administration. [1]Oettel *et al*. Eur J Contracept Reprod Health Care 1999;4(Suppl. 1):2–13; Qlaira® SPC, 2008

Antiandrogenic effect



T

drsp

SHBG

DNG

T

SHBG

T

DNG drsp

DNG

drsp DNG

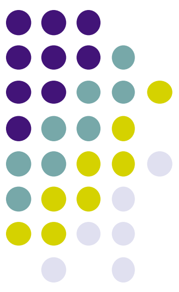
DNG drsp

drsp

DNG:dienogest SHGB:steroid binding globulin

drsp: drospirenon

Muhn P et al. Contraception 1995; 51: 99–110.

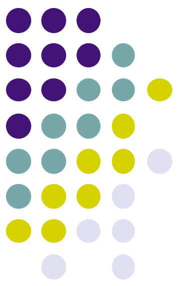


Evaluation of effects of an oral contraceptive containing ethinylestradiol combined with drospirenone on adrenal steroidogenesis in hyperandrogenic women with polycystic ovary syndrome

Vincenzo De Leo, M.D.,[a] *Giuseppe Morgante, M.D.,*[a] *Paola Piomboni, Ph.D.,*[a] *Maria Concetta Musacchio, M.D.,*[a] *Felice Petraglia, M.D.,*[a] *and Antonio Cianci, M.D.*[b]

[a] Department of Pediatrics, Obstetrics and Reproductive Medicine, Section of Obstetrics and Gynecology, University of Siena, Siena, and [b] University of Catania, Catania, Italy

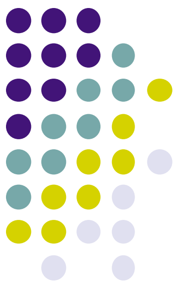
Pharmacokinetics of Progestins: Elimination half-lifes and Binding to Serum Proteins



	NET	LNG	KDG	GSD	DNG
Elimination half-life (h)	7.6	14.8	11.2	11.2	11.0
Plasma binding (%)					
Albumin	61.0	50.0	63.5	24.1	90.0
SHBG	35.5	47.5	32.0	75.3	0
free, unbound	3.5	2.5	4.5	0.6	10.0

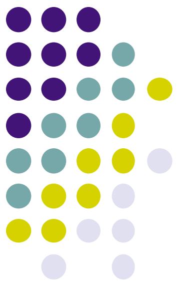
NET, norethisterone; LNG, levonorgestrel; KDG, 3-keto-desogestrel;
GSD, gestodene; DNG, dienogest; SHBG, sex hormone binding globulin

"Progestogenic Potency" of Progestins

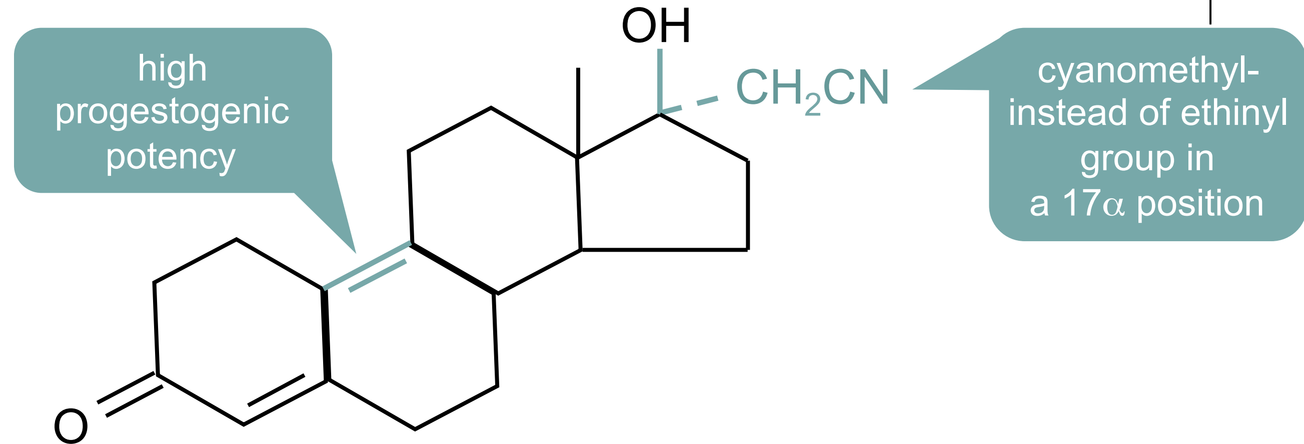


Assessed by ratio of ovulation inhibition dose (daily) and transforming dose (per cycle) (mg)

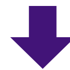
Oettel M *et al*. Gynecol Endocrinol 2001;15 (S4):68-90



DNG: Chemical Structure of a Unique Progestin



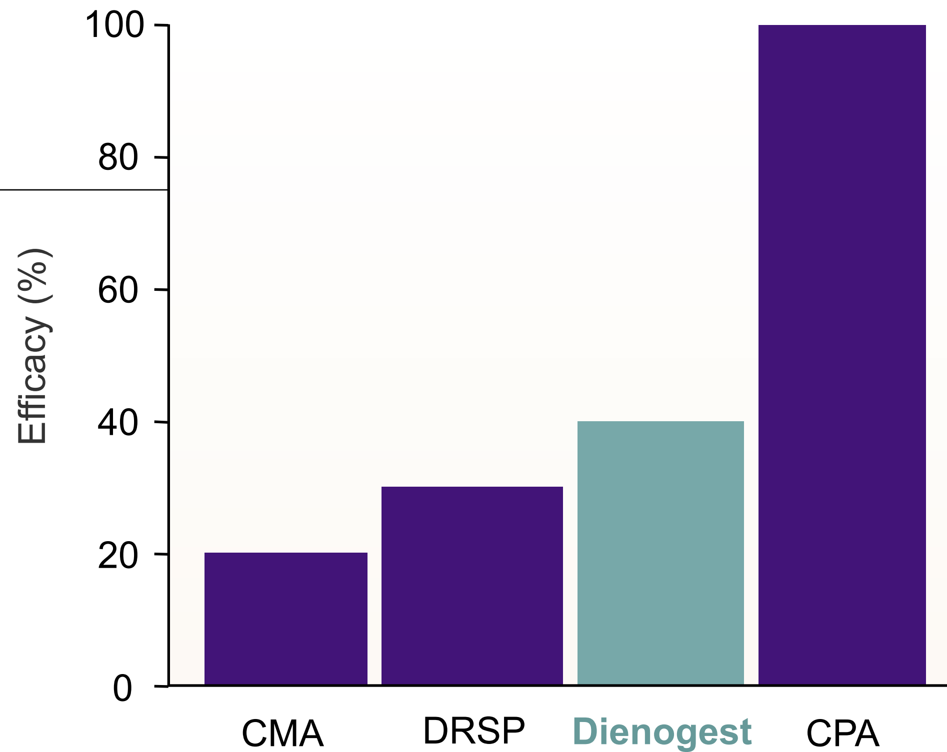
Dienogest - a 19-norgestagen. However:

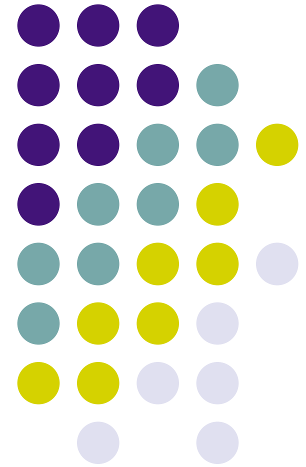


This special chemical structure leads to a unique beneficial efficiency spectrum

Dienogest – is the only progestin that combines both the benefits of 19-norgestagens and progesterone derivatives

Relative Anti-androgenic Effect

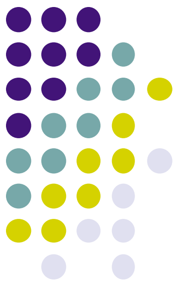




CMA, chlormadinone acetate;
CPA, cyproterone acetate;
DRSP, drospirenone

Oettel M *et al.* Drugs Today 1995; Oettel M *et al.* Eur J Contracept Reprod Health Care 1999

DURATION OF TREATMENT



- Hirsutism tx may take six or eight months before a difference is noted.
- Improvement will be slow and terminal hairs already present generally do not disappear.
- The removal of these already androgenized hair follicles will require electrolysis once hormonal therapy has exerted its full suppressive effect.
- Hormonal suppression should continue indefinitely. However, the dose of spironolactone used can be gradually decreased and eventually eliminated.
- Patients on glucocorticoid suppression should be switched to every other day therapy before stopping the Tx

THANK YOU FOR YOUR PATIENCE & ATTENTION

Be in good health and peace