Strong and Secure a New Option in Oral Contraception

Fatih DURMUŞOĞLU,M.D

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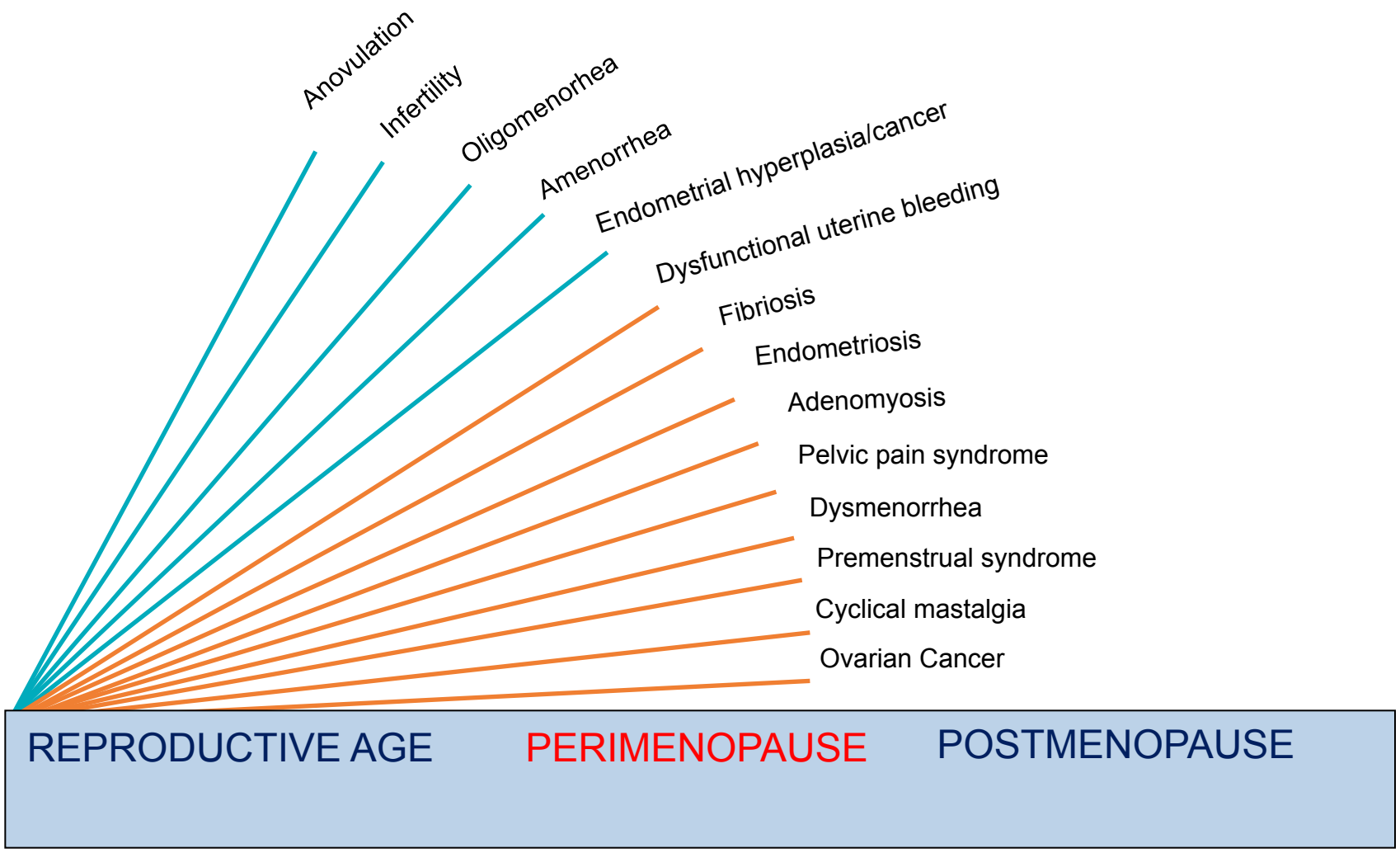
Hormonal Contraception

Paul D. Blumenthal, MD, MPH, and Alison Edelman, MD, MPH

In terms of cost-effectiveness, prevention of unplanned pregnancies through contraceptive use has repeatedly been shown to be a highly cost-effective use of health care dollars. Every dollar spent on family planning services has been estimated to save state and federal governments $3.80 in Medicaid and Title X funds for prenatal and neonatal care.[1]

(Obstet Gynecol 2008;112:670–84)

Wide range of OC usage in Reproductive Medicine



Search for an Estradiol-based OC

WHO 1980

World Health Organization Task Force on Oral Contraception:
A randomized, double-blind study of two combined oral contraceptives containing the same progestogen, but different estrogens

- 925 women, 1-year duration
  - 3 mg NETA plus 50 µg EE
  - 3 mg NETA plus 4 mg estradiol plus 2 mg estriol
- Contraceptive efficacy: No difference
- Incidence of various menstrual irregularities: Significantly higher with the 'natural' estrogen preparation (approx 50% versus 20%)

Conclusions:

'The high incidence of menstrual problems associated with the combination of "natural" estrogens and norethisterone acetate make it much less suitable for general use in family planning programmes than combinations containing synthetic estrogens.'

Contraception 1980; 21 (5): 445–59

Pharmacokinetics Ethinylestradiol (EE)

Absorption:	rapidly and completely. first-pass metabolism 50% (20-60%)
Distribution:	highly bound to serum albumin (98.5 %),but induces an increase of SHBG
Metabolism:	wide variety of hydroxylated and methylated metabolites, free metabolites and glucuronides and sulfates.
Elimination:	half-life of excretion wide variations, mostly about 1 day; frequently dependent on co-medication
Steady-state	reached during the second half of a treatment cycle. Serum levels accumulate by a factor 2.0 to 2.5.

Cycle Control with E_2-Based OCs

- E_2-based OCs provide effective contraception[1–8]
- However, simple monophasic/biphasic regimens associated with poor cycle control[1,4–8]
  - E_2 has lower bioavailability than EE[9,10]
    - Rapidly metabolized to E_1
    - Less sustained biologic activity[11]
  - Endometrial E_2 receptor expression reduced in presence of progestogens[12]
- New regimens with new progestogens needed to improve cycle control

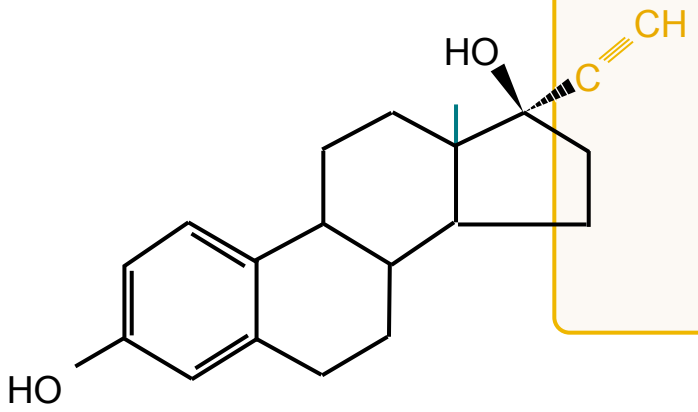
[1]Astedt *et al*. Br J Obstet Gynaecol 1979;86:732–6; [2]Csemiczky *et al*. Contraception 1996;54:333–8; [3]Hirvonen *et al*. Maturitas 1995;21:27–32; [4]Kivinen & Saure. Eur J Contracept Reprod Health Care 1996;1:183; [5]Koetsawang *et al*.1980;21:445–59; [6]Schubert & Cullberg. Acta Obstet Gynecol Scand 1987;66:543–7; [7]Serup *et al*. Lancet 1979;2: 471–2; [8]Wenzl *et al*. Fertil Steril 1993;60: 616–9; [9]Düsterberg *et al*. Maturitas 1982;4:315–24; [10]Kuhnz *et al*. Handbook of Experimental Pharmacology 1999:261–322; [11]Hoffmann *et al*. Exp Toxicol Pathol 1998;50:458–64; [12]Zhu *et al*. Hum Reprod 1999;14:970–5

Biologic Effects of EE

Biologic effect	EE
FSH suppression	20 mcg EE[1–3]
Endometrial stimulation	20 mcg EE[3]
Vaginal surface cell maturation	20 mcg EE[3]
Hepatic protein synthesis	20 mcg EE[1,4–6]

FSH: follicle-stimulating hormone. [1]Mashchak *et al*. *Am J Obstet Gynecol*. 1982;144:511-8. [2]Endrikat *et al. Contraception*. 2008;78:218-25. [3]Data on file; clinical study report B709, 2000; [4]Lindberg *et al*. *Thromb Haemost*. 1989;61:65-9. [5]Wiegratz *et al*. *Contraception*. 2004;70:97-106. [6]Helgason. *Acta Obstet Gynecol Scand*. 1982;107(Supp l.):1-29

Estradiol vs. Ethinyl Estradiol



Change in:
Reactivity
Pharmacokinetics
Metabolism
Receptoraffinity
hepatic activity

ESTRADIOL:
Hormone Replacement Therapy

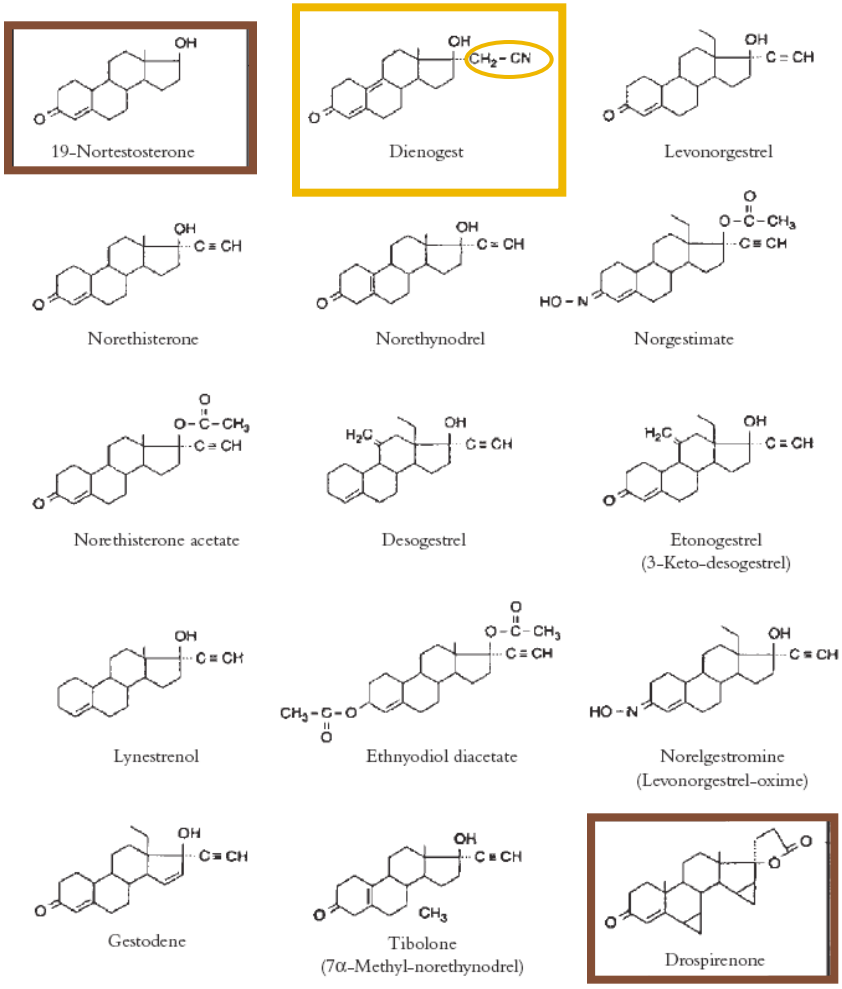
Strong effects on endometrium, breast and CNS
mild effects in liver proteins

ETHINYL ESTRADIOL:
Contraception

Main reason for use:
to ensure cyclic stability in combination with a progestin

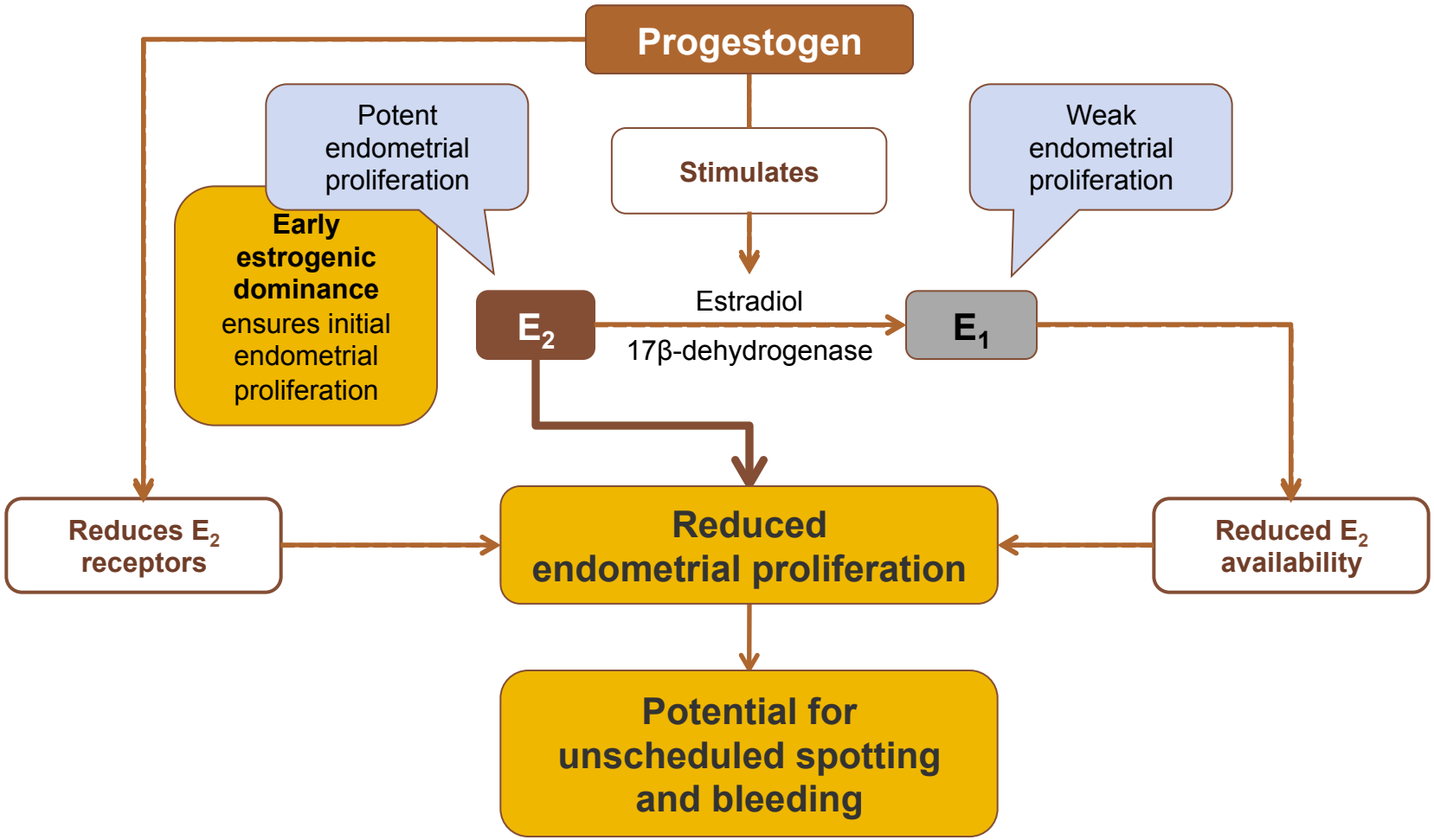
Chemical Structure of Progestins

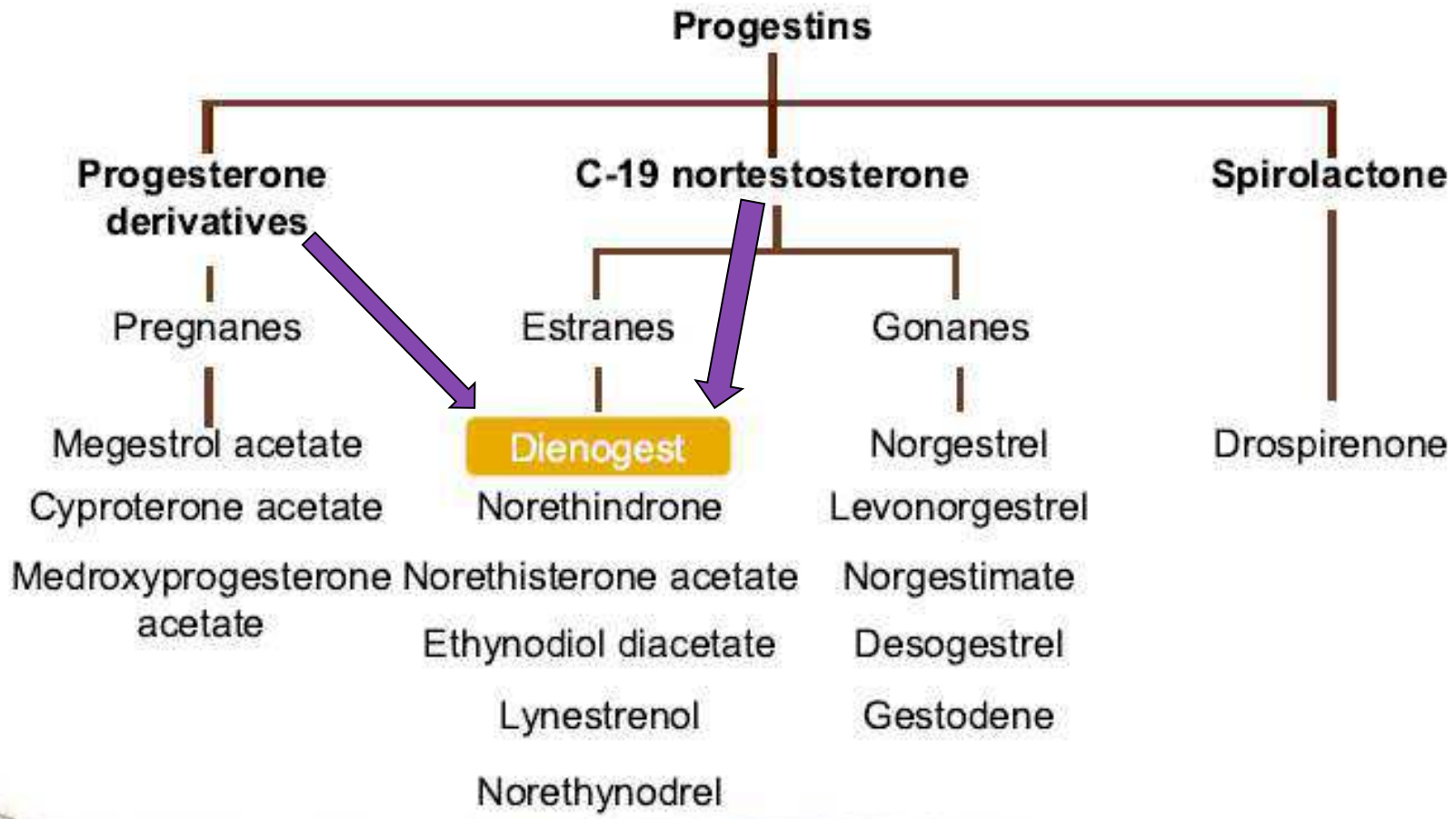
Structural formula of 19-Nortestosterone derivates and of the spirolactone derivate drosperinone



Kuhl H. Climacteric 2005; 8 (S1)

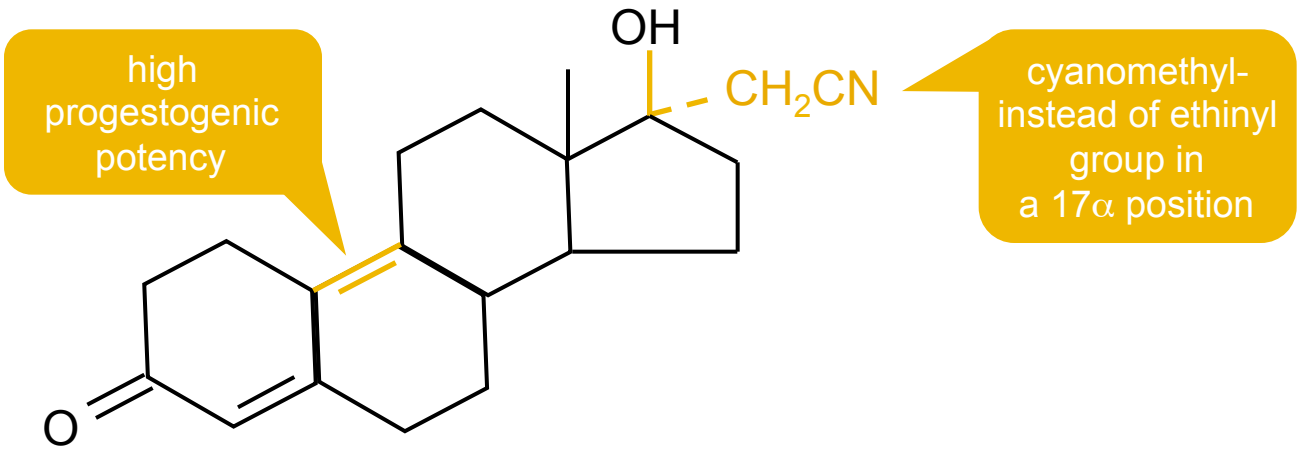
Progesterone effect on Endometrium





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

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

Pharmacokinetics of Dienogest

Absorption:	rapidly and almost completely **90% bioavailability**
Distribution:	10% free Dienogest, 90% binding to albumin, **no binding to SHBG and CBG**
Metabolism:	hydroxylation and conjugation, mostly inactive metabolites. **Unchanged DNG dominant** due to very quick excretion of metabolites.
Elimination:	plasma half-life approx.11 hours
Steady state	reached after 3 days, not influenced by SHBG levels. **No relevant accumulation.**

Specific Properties of DNG

- DNG is a 19-nortestosterone derivative that has no ethinyl-group but possesses additional proporties characteristic for the progesterone derivatives

Similarities to 19-nortestosterone derivatives	Similarities to progesterone derivatives	Specific properties of DNG
• Short plasma half-life (11h)	• Relatively low inhibition of gonadotropin secretion	• No interaction with specific transport proteins (SHBG, CBG)
• **Strong progestational effect on the endometrium**	• Doses in milligram range	
• High oral bioavailability (more than 90%)	• Anti-androgenic activity (40% of cyproterone acetate [CPA])	• High concentration of unbound substance in serum: 10% unbound, 90% bound to albumin

Pharmacologic Properties of DNG

			Plasma binding (%)	
		Elimination half-life (h)	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

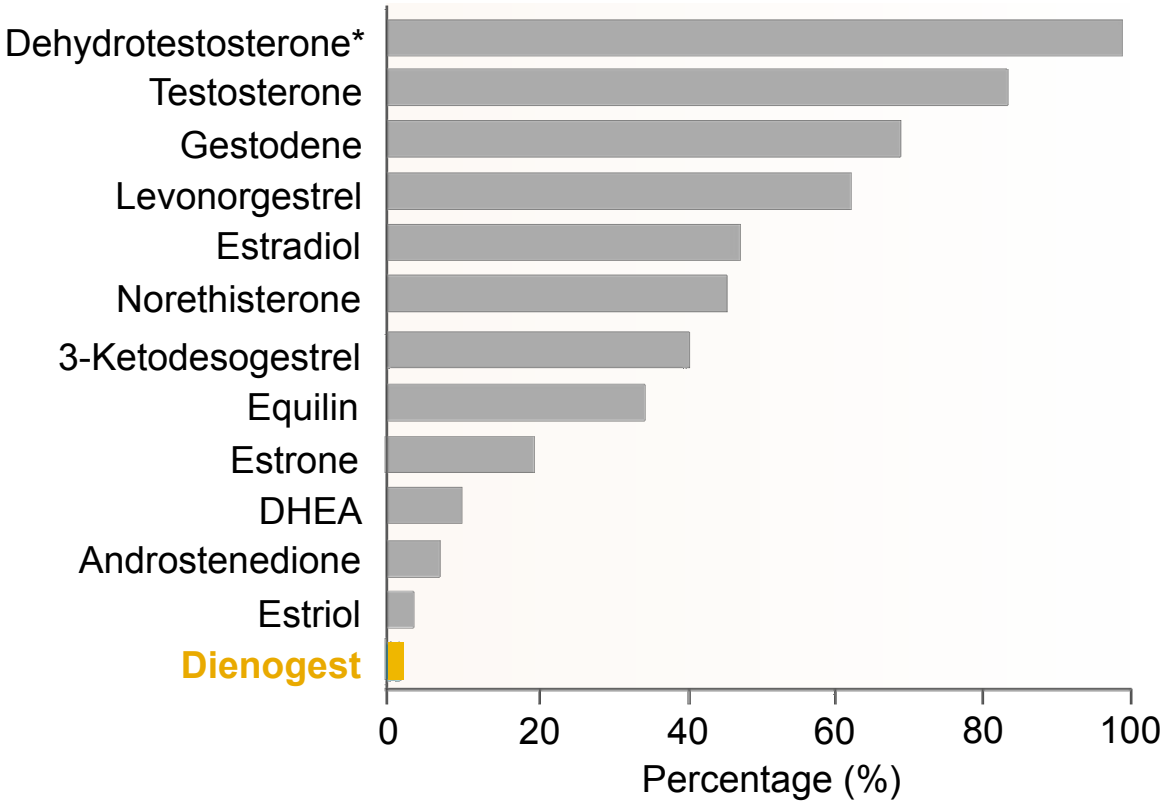
[a]Half-life varies depending on formulation and route of administration. [1]Oettel *et al*. Eur J Contracept Reprod Health Care 1999;4(Suppl. 1):2–13; Qlaira® SPC, 2008

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

Dienogest: Relative Affinity for SHBG

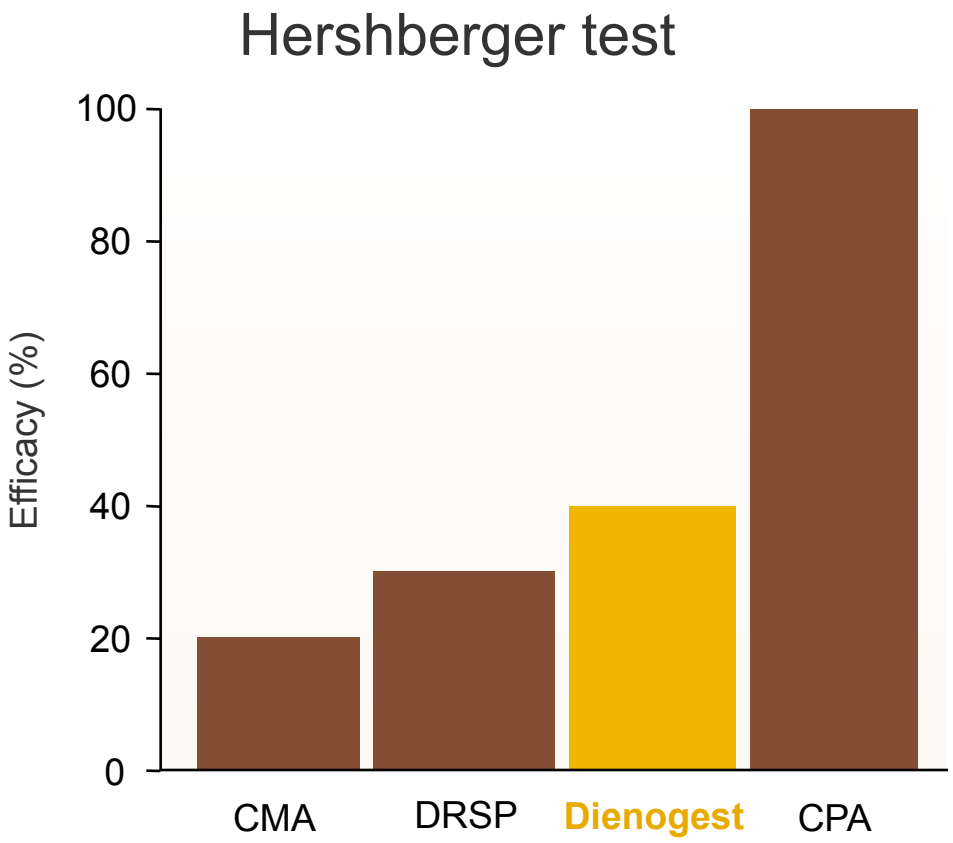


Unlike other progestins, dienogest has minimal interaction with SHBG

SHBG, sex hormone binding globulin; *Dehydrotestosterone = 100% DHEA, dehydroepiandrosterone

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

Dienogest: Relative Anti-androgenic Effect



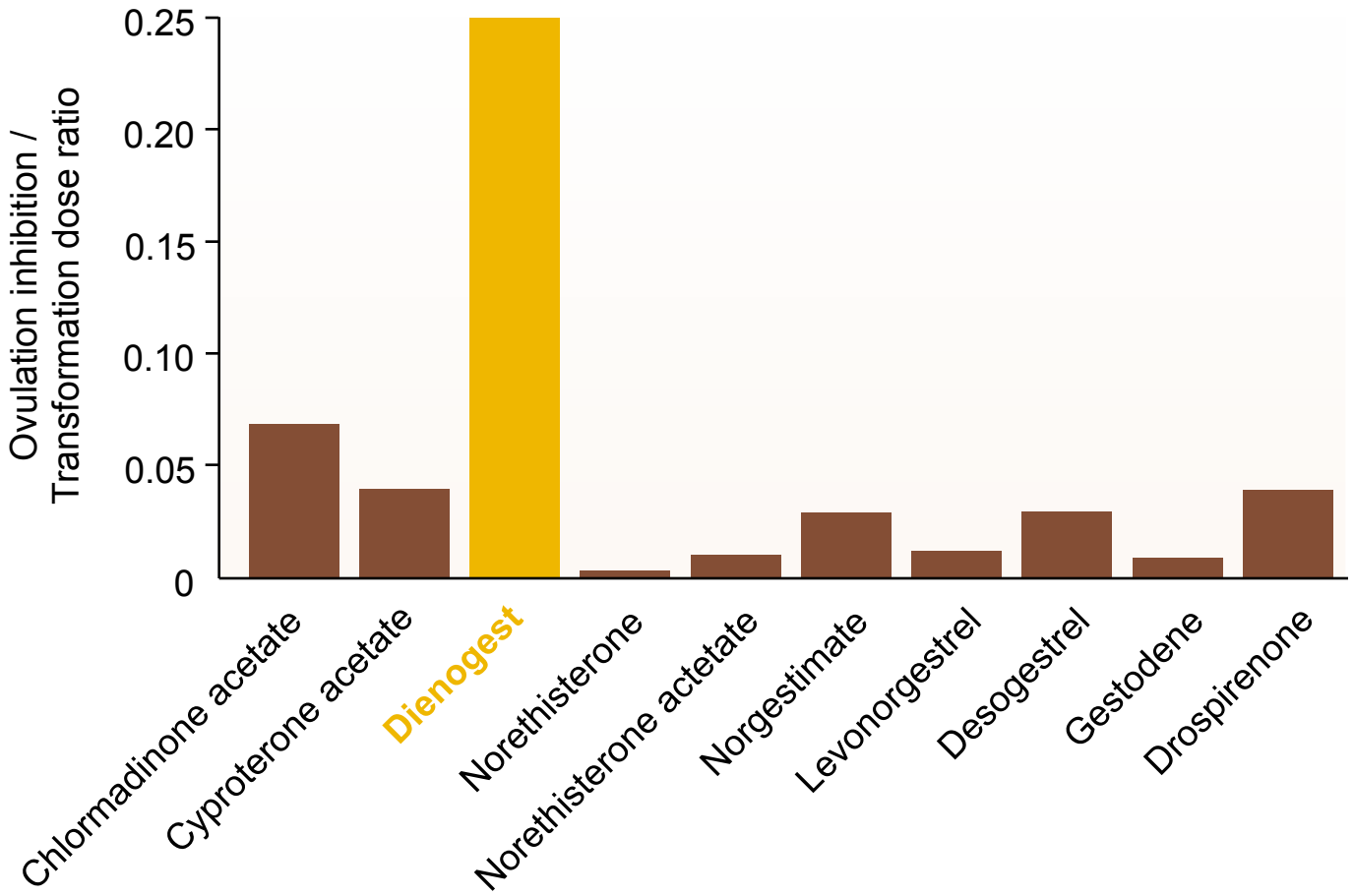
Dienogest has approximately one-third of the anti-androgenic activity of cyproterone acetate

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

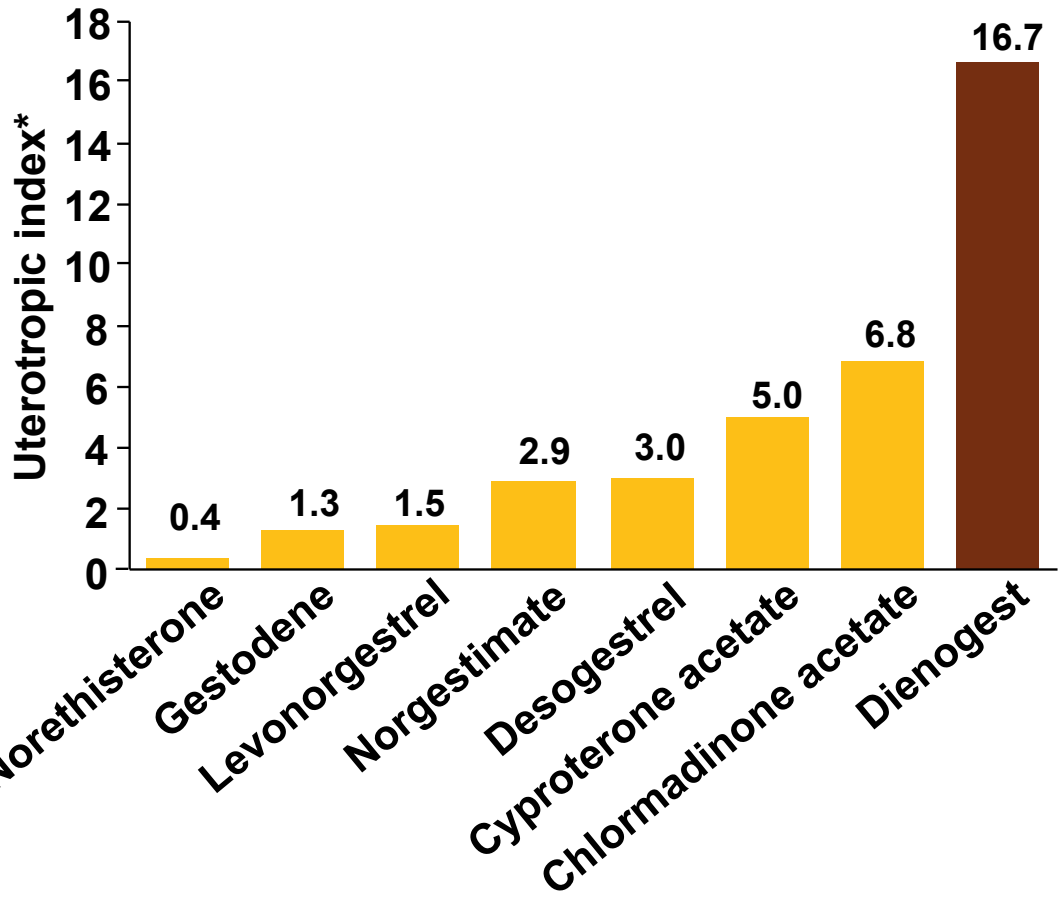
"Progestogenic Potency" of Progestins

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

"Progestogenic Potency" & Endometrium



*Ovulation inhibition dose (mg/day)/transformation dose (mg/cycle) x 100.

[1]Oettel M, et al. Eur J Contracept Reprod Health Care 1999;4(Suppl. 1): 2–13; [2]Kuhl H. Drugs 1996;51(2):188–215.

Effects on Ovarian Function and Gonadotropin Secretion

- Reliable ovulation inhibition,
  while maintaining FSH levels:
  these only were suppressed with addition of EE
  - Strong peripheral (ovarian) effects
    (Schleussner *et al*. 1995)
- Apoptosis of granulosa cells of dominant follicle, while maintaining FSH levels (monkeys)
  (Sasagawa *et al*. 2008)

Dienogest: Genital Effects

A progestin with pronounced endometrial focus

- Protection of endometrium and cycle stability achieved with 2-3 mg DNG
- Anti-estrogenic effects on cervical mucus, supporting contraceptive efficacy
- No relevant anti-estrogenic effect on vaginal epithelium
- Anti-proliferative effects on endometriosis tissue

Dienogest: Extragenital Effects

Many Studies !

- No clinically relevant effects have been observed in various clinical studies with with up to 20 mg/day DNG over 24 weeks

  (DNG monosubstance, endometriosis indication, data on file A04431)

  - lipid metabolism
  - glucose metabolism
  - liver enzymes
  - hemostatic parameters
  - adrenal and thyroid gland metabolism

  etc.

Pharmacology of Dienogest: Summary

- Result of special chemical structure:
  pharmacological spectrum combines advantages of the 19-nor-progestogens and of the progesterone derivatives

- 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).

- DNG has no 17-alpha ethinylgroup:
  minimal impact on liver and lipid- and carbohydrate metabolism.
  no interference with E_2-induced SHBG-Production which enhances the anti-androgenic effects of E_2val/DNG-combinations

Clinical Properties of DNG

1. Effective ovulation inhibition at 2 mg/day[1]
   - Additional local ovarian effects likely contribute to inhibition[2,3]
2. Effective cycle control
   - Pronounced endometrial effect[1,2,4]
   - Excellent bleeding profile in OC and HT products[4,5]
3. Progestogenic effects on cervical mucus[6]
   - Additional contraceptive protection

[1]Foster and Wilde. *Drugs Today* 1998;56:825-35, 834-5; [2]Sasagawa *et al*. J Endocrinol Invest 2008;31:636–41; [3]Schleussner. In: Teichmann A (editor). Dienogest. Präklinik und Klinik eines neuen Gestagens. New York: Walter de Gruyter, 1995:171-9; [4]von Schoultz B. Climacteric 2003;6(Suppl 2):24–32. [5]Zimmermann *et al*. Eur J Contracept Reprod Health Care 1999;4:155–64. [6]Ulstein M, Myklebust RU. Acta Obstet Gynecol Scand Suppl. 1982;105:45-9

Potential area of Dienogenest in Reproductive Medicine

- Strong and reliable hormonal contraception
- Hyperandrogenism
- Intermenstrual bleeding (IMB)
- Pelvic pain /Endometriosis

THANK YOU FOR YOUR PATIENCE & ATTENTION

Be in good health and peace