Progesterone and Progestogen

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- Besides the **progestogenic effect**, which is in **common for all progestins**,

- There is a **wide range** of **biological effects**,
- Which are **different** for the **various progestins** and

- **Have to be taken into account**,
- When **medical treatment is considered**.

Progestin side effects

- Bloating or water retention, weight gain and swelling (edema),
- Muscle, joint, or bone pain.

- Fatigue, headache, depression,
- Breast discomfort or enlargement, premenstrual syndrome (PMS)-like symptoms, drowsiness or insomnia,

- Acne and hirsutism,

- Lipid profile
- Hypertension & Diabetes

- Ovulation
- Spotting

- **Progestin Effects**:

- **Progestational effects** help:
- **Prevent ovulation** and
- **Lessen menstrual bleeding**.

- **Androgenic effects** :
- **Unwanted side effects** such as **acne** and **body hair growth**.

- Some of the **synthetic progestins** are **prodrugs**, which need to be metabolized to become active compounds.

- There is evidence from in vitro and animal research that:

- The **type of progestin**,
- **Formulation**,
- **Dose**, and
- **Route of delivery**

- Have a significant **impact on efficacy**

- **Progesterone** is a **steroid hormone** derived from **cholesterol**

- **Progesterone** is the **main progestogen** in the human **body**.

- **Progestogen**:
- Any **natural** or **synthetic** form of progesterone.

- **Progestin**:
- Specific for **synthetic** progestogens.

- Progestins are **functionally similar** but **structurally different** from **natural progesterone**.(up to date 2021)

- Classification

confusion.

- Based on time since market introduction:

1st

2nd

3rd

4th generation

- Based on structural derivation:

Estranes

Gonanes

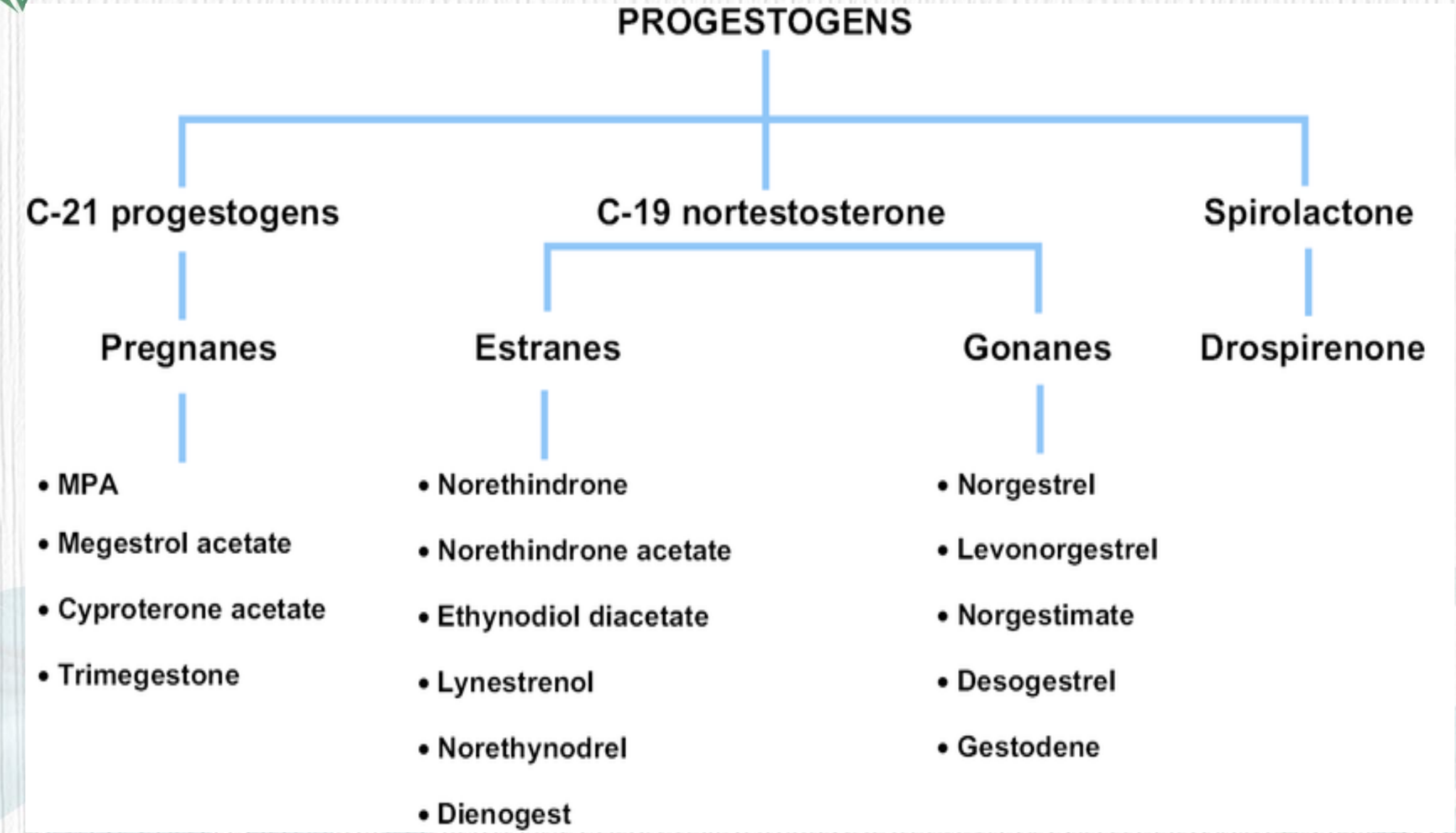
Pregnanes.

Progestin Generations

- Progestins are classified **as first to fourth** generation progestins based on when they **were first available**, but
- **Different generations** also have some **different characteristics**.
- **Keep in mind that newer isn't necessarily better.**
- **First generation**: Norethindrone, norethindrone acetate, and ethynodiol
- **Second generation**: Desogestrel and norgestrel
- **Third generation**: Norgestrel and norgestimate
- **Fourth generation**: Drospirenone

Classification of Synthetic Progestins

Classification by Structure	First	Second	Third
Estranes	Norethindrone	—	—
	Norethindrone acetate		
Gonanes	Norgestrel	Levonorgestrel	Desogestrel Norgestimate Gestodene
Pregnanes	Medroxyprogesterone acetate	—	—


PROGESTOGENS
C-21 progestogens
C-19 nortestosterone
Spirolactone
Pregnanes
Estranes
Gonanes
Drospirenone
• MPA
• Megestrol acetate
• Cyproterone acetate
• Trimegestone
• Norethindrone
• Norethindrone acetate
• Ethynodiol diacetate
• Lynestrenol
• Norethynodrel
• Dienogest
• Norgestrel
• Levonorgestrel
• Norgestimate
• Desogestrel
• Gestodene

Classification of progestogens:

Derived from progesterone	Derived from testosterone
Dydrogesterone	**Estranes**
Medrogesterone	Norethisterone
	Dienogest (non-ethyl)
17-OH Progesterone (Pregnanes)	
Medroxyprogesterone Ac	**Gonanes**
Cyproterone Ac	Levonorgestrel
Chlormadinone Ac	Desogestrel (Etonogestrel)
Megestrol Ac	Gestodene
	Norgestimate (Norelgestromin)
19-Norprogesterone	
Nestorone	
Nomegestrol Ac	
Trimegestone	
	Spironolactone
	Drospirenone

- **Natural progestin**,

- Different classes of **progestins**, such as:

- **Retroprogesterone** (i.e. **dydrogesterone**),

- **Progesterone derivatives** (i.e. medrogestone)
- 17-hydroxyprogesterone derivatives (i.e. chlormadinone acetate, **cyproterone acetate**, **medroxyprogesterone acetate**, **megestrol** acetate),
- 19-norprogesterone derivatives (i.e. nomegestrol, promegestone, trimegestone, nesterone),

- 19-nortestosterone derivatives norethisterone (NET), **lynestrenol**, **levonorgestrel**, desogestrel, gestodene, norgestimate, **dienogest**) and

- Spironolactone derivatives (i.e. **drospirenone**).

Table 1
Classification of progestins

Progestin	Example
Progesterone	Natural progesterone
Retroprogesterone	Dydrogesterone
Progesterone derivative	Medrogestone
17α-Hydroxyprogesterone derivatives (pregnanes)	Medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate
17α-Hydroxynorprogesterone derivatives (norpregnanes)	Gestonorone caproate, nomegestrol acetate,
19-Norprogesterone derivatives (norpregnanes)	Demegestone, promegestone, nesterone, trimegestone
19-Nortestosterone derivatives (estranes)	Norethisterone = norethindrone, norethisterone acetate, lynestrenol, ethinodiol acetate, norethinodrel
19-Nortestosterone derivatives (gonanes)	Norgestrel, levonorgestrel, desogestrel, etenogestrel, gestodene, norgestimate, dienogest.
Spirolactone derivative	Drospirenone

According to reference [5–8].

Classification of Progestogens

Progestogens

Progesterone

Progesterone

Retroprogesterone

Dydrogesterone

Spirolactone derivative

Drospirenone

Progesterone derivatives

17-OH-progesterone derivatives

Pregnane

- **Hydroxyprogesterone Caproate**
- Hydroxyprogesterone Heptanoate
- Gestonorone Caproate
- Chlormadinone Acetate
- Medrogestone
- **Medroxyprogesterone Acetate**
- **Cyproterone Acetate**

19-progesterone derivatives

Nor-Pregnane

- Nomegestrole Acetate
- Demegestone
- Promegestone
- Nestorone
- Trimegestone

Testosterone derivatives

19-nortestosterone derivatives

Estranes

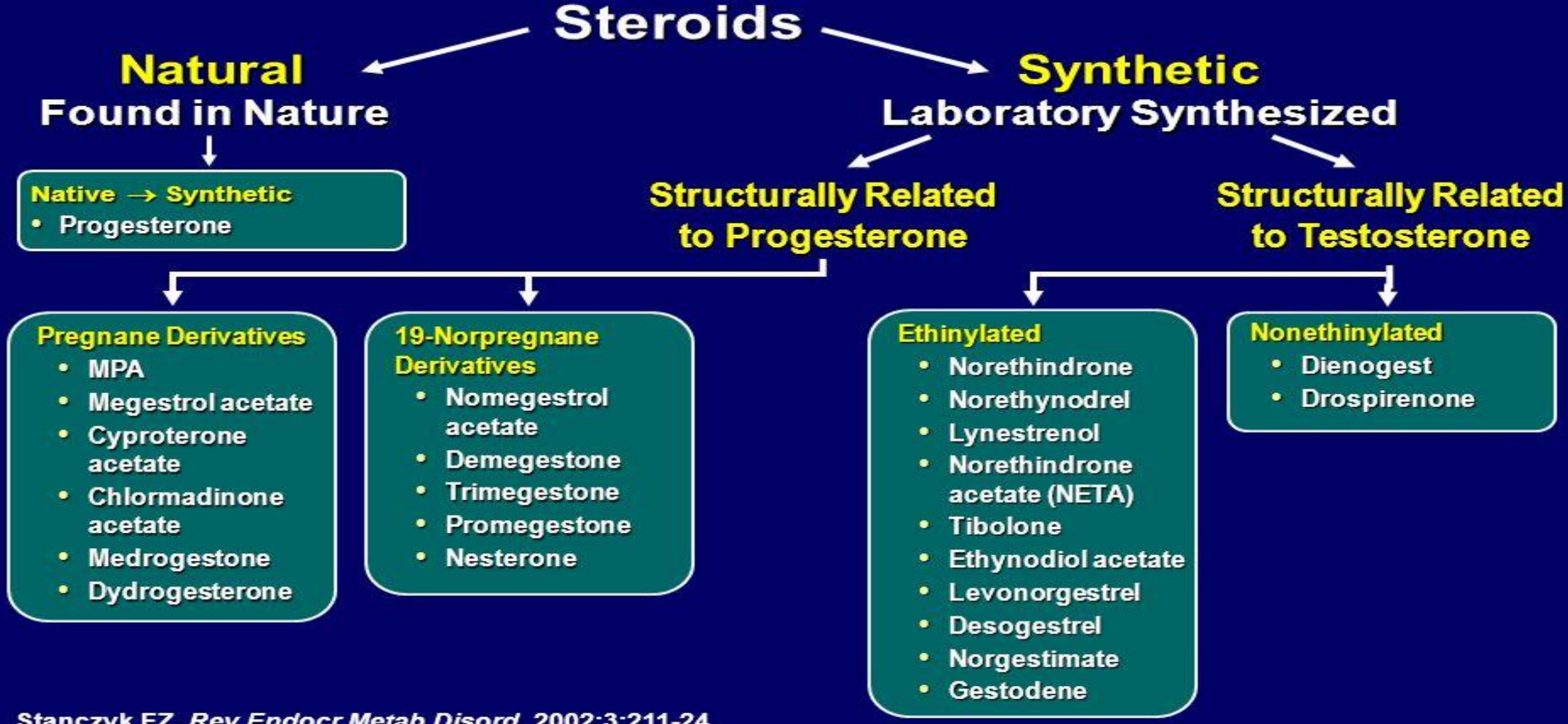
- **Lynestrenol**
- **Levonorgestrel**
- Norethisterone
- Norethisterone Acetate
- Ethinodiol Diacetate
- Norgestrienone
- **Dienogest**

Gonanes

- Norgestrel
- Desogestrel
- Gestodene
- Norgestimate

Adapted from: Druckmann R. Journal Für Menopause. 2002:1-5

Classification of Progestins



Stanczyk FZ. *Rev Endocr Metab Disord*. 2002;3:211-24.

Progestins and receptors

- **All progestins** bind to the **progesterone receptors** (PR)

- And **other steroid receptors**:

  - Estrogen receptor (ER)
  - Androgen receptor (AR)
  - Glucocorticoid receptor (GR)
  - Mineralocorticoid receptor (MR)

Differential Activity of Progesterone and Progestogens

Table 1
Relative binding affinities of progestogens to steroid receptors [1].

	Relative binding affinity [% of reference steroid]					
	Progesterone receptor	Androgen receptor	Estrogen receptor	Glucocorticoid receptor	Mineralocorticoid receptor	SHBG
Pregnanes						
Progesterone	50	0	0	10	100	0
Dydrogesterone	75	0	–	–	–	–
MPA	115	5	0	29	160	0
Norsteroids						
Norethisterone	75	15	0	0	0	16
Gestodene	90	85	0	27	290	40
Promegestone	100	0	0	5	53	0
Levonorgestrel	150	45	0	1	75	50
Androstanes						
Drospirenone	35	65	0	6	230	0
Reference steroid with 100% receptor binding affinity	Promegestone	Metribolone	Estradiol-17β	Dexamethasone	Aldosterone	Dihydro-testosterone

SHGB = sex hormone binding globulin; MPA: medroxyprogesterone acetate.

Table 2
Biological activities of natural progesterone and synthetic progestins

Progestin	Progesto-genic	Anti-gonado-tropic	Anti-estrogenic	Estro-genic	Andro-genic	Anti-andro-genic	Gluco-corticoid	Anti-mineralo-corticoid
Progesterone	+	+	+	−	−	±	+	+
Dydrogesterone	+	−	+	−	−	±	−	±
Medrogestone	+	+	+	−	−	±	−	−
17α-Hydroxy-derivatives								
Chlormadinone acetate	+	+	+	−	−	+	+	−
Cyproterone acetate	+	+	+	−	−	++	+	−
Megestrol acetate	+	+	+	−	±	+	+	−
Medroxy-progesterone-acetate	+	+	+	−	±	−	+	−
19-Nor-progesterone-derivatives								
Nomegestrol acetate	+	+	+	−	−	±	−	−
Promegestone	+	+	+	−	−	−	−	−
Trimegestone	+	+	+	−	−	±	−	±
Spirolactone-derivatives								
Drospirenone	+	+	+	−	−	+	−	+
19-Nortestosterone derivatives								
Norethisterone	+	+	+	+	+	−	−	−
Lynestrenol	+	+	+	+	+	−	−	−
Norethinodrel	±	+	±	+	±	−	−	−
Levonorgestrel	+	+	+	−	+	−	−	−
Norgestimate	+	+	+	−	+	−	−	−
3-Keto-desogestrel	+	+	+	−	+	−	−	−
Gestoden	+	+	+	−	+	−	+	+
Dienogest	+	+	±	±	−	+	−	−

Taken from reference [5,7,8,10–15]. (+) effective; (±) weakly effective; (−) not effective.

HORMONAL REPLACEMENT THERAPY

Biological activity of progestogens

Progestogen	Progestogenic effect	Androgenic effect	Estrogenic effect	Antiestrogenic effect
Progesteron	+	–		+
Dydrogesteron	+	–		+
Medroxyprogesteron acetate	++	–		+
Cyproterone acetate	++	–		+
Norethinodron	++	++	+	++
Levonorgestrel	+++	+++		++
Norgestimate	+++	+		++
Desogestrel	+++	+		++
Gestodene	+++	+		++

Androgenic progestins

- **Levonorgestrel** (implant, hormonal IUDs, pill, emergency contraception)
- **Norethindrone** (mini-pill)

- **Norethindrone acetate** (pill)
- **Norgestimate** (pill)

- **Desogestrel** (pill, mini-pill)
- **Etonogestrel** (**implant**, **vaginal ring**)

- **Norelgestromin** (patch)
- **Gestodene** (pill)

- **Medroxyprogesterone acetate** (weakly) (injection/shot)

- **<u>Anti-androgenic progestins</u>,**
- **Reduce the** effect of the endogenous **androgen** and
- **Decrease** the incidence of **acne** and **hirsutism, and lowering HDL.**

- Cyproterone acetate (pill)
- Drospirenone (pill)
- Dienogest (pill)

- **<u>Progestins with anti-mineralocorticoid activity</u>, Decrease bloating** or **water retention**

- Gestodene (pill)
- Drospirenone (pill)

– Different **synthetic progestogens** provide:

- Focused **progestational actions**
- **Diverse specificities**
- **Diverse side effects**

- Choice of progestogen will be balance of
- **Desired effects** and
- **Undesired** side-effects

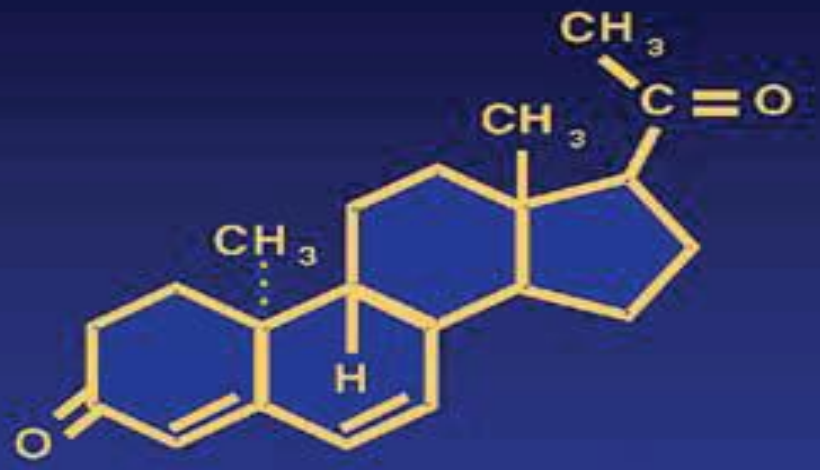
- Good **compliance** dependent on **minimising side-effects**

- There has been **interest** in synthesizing progestins that better **mimic the natural hormone**.

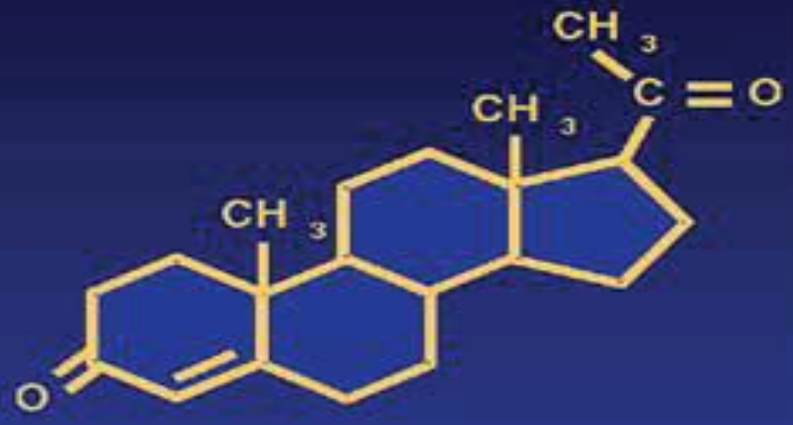
Differential Actions of Progesterone and Progestogens

Properties	Dydrogesterone	Progesterone	Progesterone derivatives	Testosterone & 19 nor-T derivatives
Block ovulation	– *	+	+	+
Estrogenic	–	±	–	+
Androgenic	–	–	+	+
Fetal masculinisation	–	–	+	+
Uterine relaxation	+	+	±	–
Adrenal atrophy	–	–	+	+
Thermogenicity	–	+	+	+
Blood clotting	–	–	+	+
Blood lipids	–	–	–	+

Dydrogesterone



Progesterone



Retroprogesterone

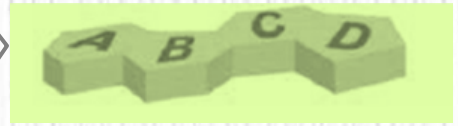
- It is a **stereoisomer** of the **natural progesterone**.
- This **configuration** is **ideal** for **interaction** with the **progesterone** receptor,
- The **configuration** is **not as ideal for binding** to **other steroid hormone receptors,**
- **Increased selectivity** for the **progesterone receptor**.
- Improved **oral activity** and **metabolic stability,** in **comparison** to **progesterone**

Molecular Properties: Structure

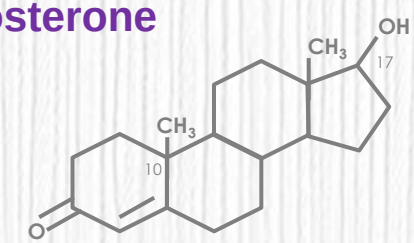
Dydrogesterone is a progesterone derivative[1]

Norethisterone is a testosterone analog[2]

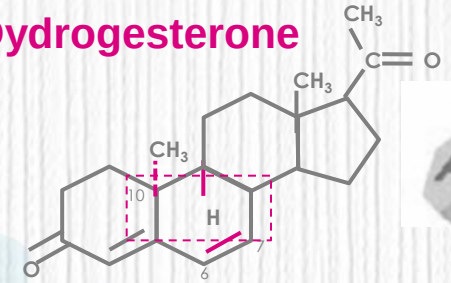
Progesterone



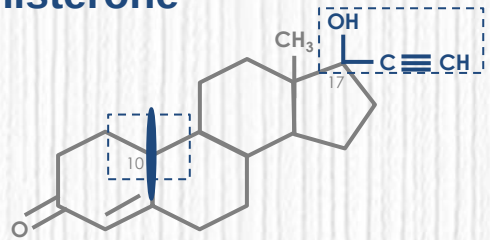
Testosterone



Dydrogesterone



Norethisterone



Differences in progestogen structure impact receptor selectivity and affinity, translating into different effects[1–3]

1. Kuhl *Climacteric* 2005; 2. Stanczyk *et al. Endocr Rev* 2013; 3. Kuhnz *et al. Contraception* 1997

Dydrogesterone

- Is a **synthetic** progestational hormone, (developed in the 1950s and introduced for **medical use** in **1961**)
- It is **structurally** and **pharmacologically similar** to **natural progesterone**

- Due to its **unique structure**, binds **almost exclusively** to the **progesterone receptor**
- Is a **highly selective progestogen**, and

- Does **not bind** importantly to the **androgen, estrogen**, or **glucocorticoid receptor.**
- **NO androgenic** or **antiandrogenic**, **estrogenic** or **antiestrogenic**, and **glucocorticoid** or **antiglucocorticoid** activity.

Dydrogesterone

- **Binds** to the **mineralocorticoid** receptor and **possesses antimineralocorticoid** activity **(weak)**.

- Is an **orally-active** progestogen, **good oral bioavailability**
- Is **completely metabolized**
- Its **major active metabolite; 20α-dihydrodydrogesterone (20α-DHD),** has **progestogenic** activity

- Is an **atypical progestogen** and **does not inhibit ovulation**
- **No increase in temperature**.

Dydrogesterone

- **The oral route of administration :**
- More **patient-friendly** regimen **;**
- Improve **compliance** to treatment**.**

- It has a **role as a progestin**.
- Produces a **complete secretory** endometrium in an estrogen-primed uterus
- **Protection for estrogen induced** increased risk for endometrium **hyperplasia** and/or **carcinogenesis**.

- It is **indicated** in **all cases** of **endogenous progesterone deficiency**

- **1: Barbosa et al. Oral dydrogesterone vs. vaginal progesterone capsules for luteal-phase support in women undergoing embryo transfer: a systematic review and meta-analysis. JBRA Assist Reprod. 2018 Apr-Jun; 22(2): 148–156.**

Receptor Binding of Progestogens[1,2]

Biological activity	Dydrogesterone	Progesterone	Norethisterone	MPA
Progestogenic	+	+	+	+
Blocking ovulation	–[a]	+	+	+
Thermogenicity	–	+	+	+
Anti-gonadotropic	–	+	+	+
Anti-estrogenic	+	+	+	+
Estrogenic	–	–	+	–
Androgenic	–	–	+	±
Anti-androgenic	±[b]	±	–	–
Glucocorticoid	–	+	–	+
Anti-mineralocorticoid	±	+	–	–

Dydrogesterone is selective for the progesterone receptor, reducing the likelihood of other receptor-related side effects[1–4]

[a]At normal dosage; [b]Dydrogesterone has less pronounced anti-androgenic effects than progesterone[4]

1. Schindler AE, et al. Maturitas 2008; 61(1–2):171–180. 2. Schindler AE. Maturitas 2009; 65(Suppl 1):S3–S11. 3. Dydrogesterone CCDS. 15 January 2016. 4. Rižner TL, et al. Steroids 2011; 76(6):607–615.

Dydrogesterone Affinity to Receptors

- Dydrogesterone is **selective** for the progesterone receptor,
- **Reducing** the likelihood of **other receptor-related side effects**[1–4]

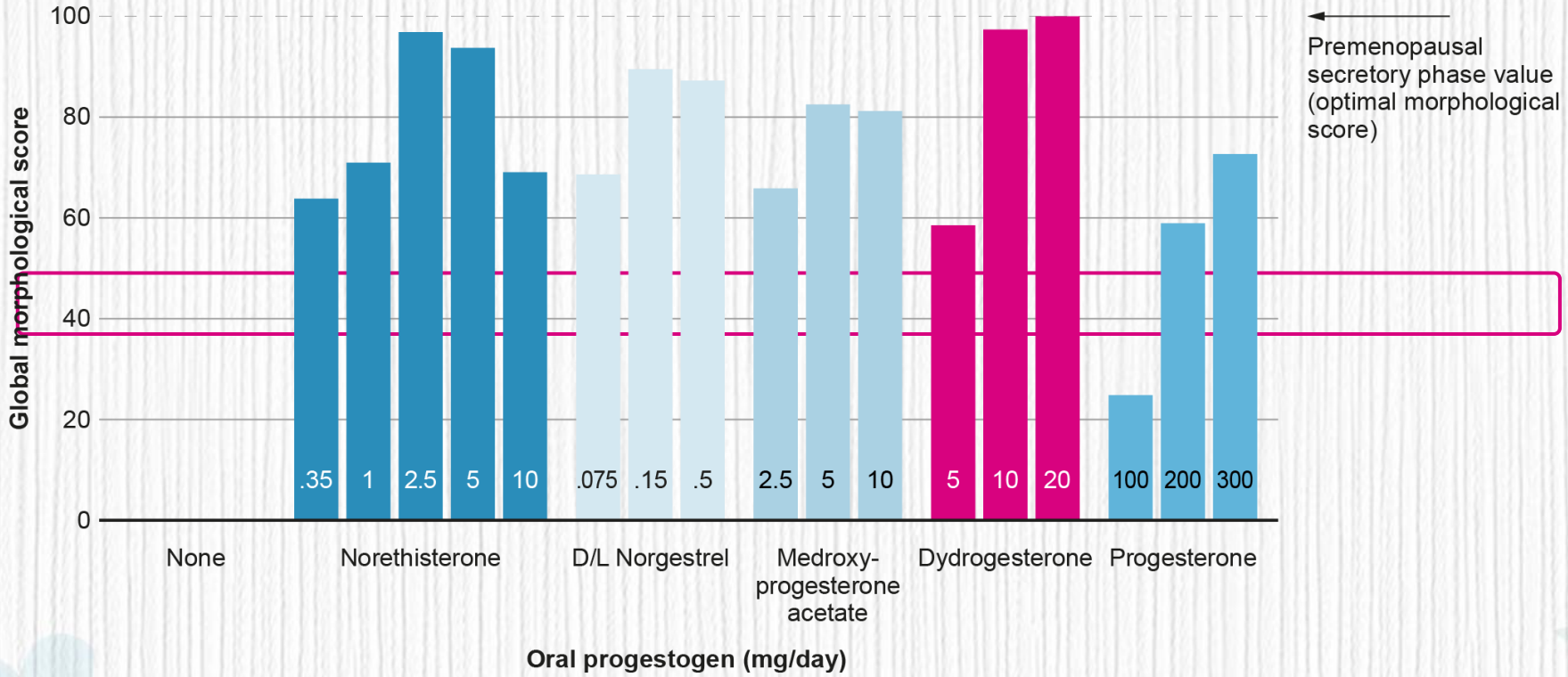
Relative binding affinities of progesterone and synthetic progestins to steroid receptors and serum binding proteins

Progestin	PR	AR	ER	GR	MR	SHBG	CBG
Progesterone	50	0	0	10	100	0	36
Dydrogesterone	75	0	–	–	–	–	–
Chlormadinone acetate	67	5	0	8	0	0	0
Cyproterone acetate	90	6	0	6	8	0	0
Medroxyprogesterone acetate	115	5	0	29	160	0	0
Megestrol acetate	65	5	0	30	0	0	0
Nomegestrol	125	6	0	6	0	0	0
Promegestone (R5020)	100	0	0	5	53	0	0
Drospirenone	35	65	0	6	230	0	0
Norethisterone	75	15	0	0	0	16	0
Levonorgestrel	150	45	0	1	75	50	0
Norgestimate	15	0	0	1	0	0	0
3-Keto-desogestrel	150	20	0	14	0	15	0
Gestodene	90	85	0	27	290	40	0
Dienogest	5	10	0	1	0	0	0

The reference steroids are listed. Taken from reference [8,10,13,15]. PR: progesterone receptor (promegestone = 100%). AR: androgen receptor (metribolone = 100%). ER: estrogen receptor (estradiol-17β = 100%). GR: glucocorticoid receptor (dexamethason = 100%). MR: mineralocorticoid receptor (aldosterone =100%). SHGB: sex hormone-binding globulin (dihydrotestosterone =100%). CBG: corticosteroid-binding globulin (cortisol=100%).

Schindler AE et al. Classification of Progestins. Maturitas 2003; 46SI:S7-S16

Molecular Properties: Transformation of the Endometrium



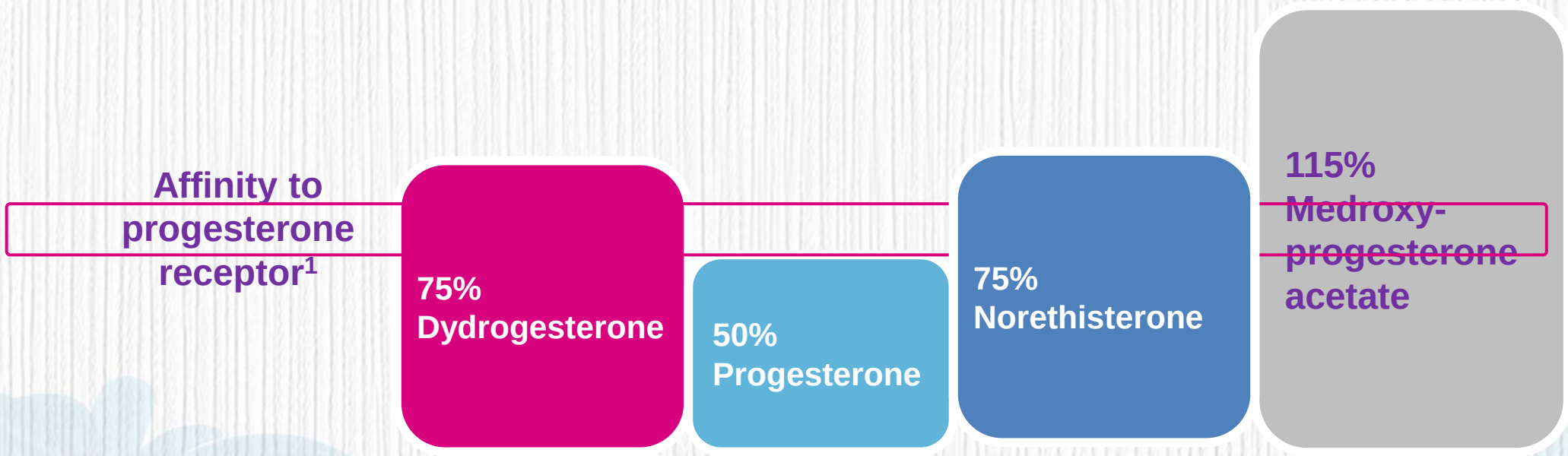
Dydrogesterone and norethisterone induce in-phase secretory transformation of the endometrium

[a]Postmenopausal women were treated with conjugated estrogens (every day) and an oral progestogen (for the last 6–12 days of the month); curettage was performed to obtain endometria after 6 days of progestogen treatment

Reprinted by permission from the American Society for Reproductive Medicine (*Fertility and Sterility*, 1986, 46, 1062–1066)

Progesterone Receptor Affinity

Dydrogesterone has ~1.5 times higher affinity to progesterone receptors than progesterone[1]



Dihydrodydrogesterone, the main **metabolite** of **dydrogesterone,** also has **progestogenic** activity[1–3]

1: Schindler AE, et al. Maturitas 2008; 61(1–2):171–180. 2: Schindler AE. Maturitas 2009; 65(Suppl 1): S3–S11. 3: drogesterone CCDS. 15 January 2016

Molecular Properties: Receptor Affinity

Progesterone receptor

75%

dydrogesterone and norethisterone

Dydrogesterone and norethisterone have equal affinity for the progesterone receptor

Androgen receptor

0% vs **15%**

dydrogesterone | norethisterone

Unlike dydrogesterone, norethisterone also has affinity for the androgen receptor

Dydrogesterone is highly selective for the progesterone receptor, whereas norethisterone also has affinity for the androgen receptor

Schindler *et al. Maturitas* 2008

Molecular Properties: Pharmacokinetics

Parameter	Dydrogesterone[1]	Norethisterone[2–4]
Absorption	Rapidly absorbed (T_{max} 0.5–2.5 h)	Rapidly absorbed (T_{max} 1.5±0.6 h)
Bioavailability	**28%**	**47–73%**
Main metabolites	**20α-dihydrodydrogesterone (progestogenic)**	**Ethinyl estradiol (estrogenic), 5α-dihydronorethisterone (androgenic)**
Elimination	Long stable effects ($t_{1/2}$ 5–7 h)	Long stable effects ($t_{1/2}$ 5–13 h)

Dydrogesterone and its metabolites are purely progestogenic[1]

Metabolites of norethisterone are androgenic and estrogenic[2–3]

1. Abbott Laboratories. Dydrogesterone CCDS. 2016; 2. Bayer. Primolut N® Product Information. 2013;
3. Kuhnz *et al. Contraception* 1997; 4. Kuhl *Climacteric* 2005

Dydrogesterone is the only one with no antigonadotrophic effects

Progestin	Progesto-genic	Anti-gonado-tropic
Progesterone	+	+
Dydrogesterone	+	–
Medrogestone	+	+
17α-Hydroxy-derivatives		
Chlormadinone acetate	+	+
Cyproterone acetate	+	+
Megestrol acetate	+	+
Medroxy-progesterone-acetate	+	+
19-Nor-progesterone-derivatives		
Nomegestrol acetate	+	+
Promegestone	+	+
Trimegestone	+	+
Spirolactone-derivatives		
Drospirenone	+	+
19-Nortestosterone derivatives		
Norethisterone	+	+
Lynestrenol	+	+
Norethinodrel	±	+
Levonorgestrel	+	+
Norgestimate	+	+
3-Keto-desogestrel	+	+
Gestoden	+	+
Dienogest	+	+

Taken from reference [5,7,8,10–15]. (+) effective; (±) weak

s of natural progesterone and synthetic progestins

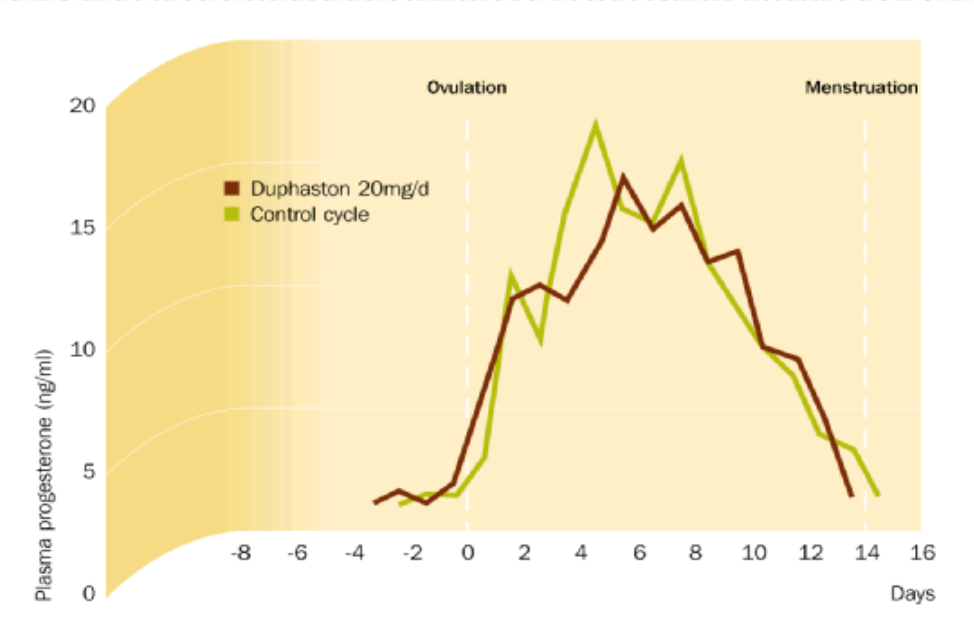
	Progesto-genic	Anti-gonado-tropic	Anti-estrogenic	Estro-genic	Andro-genic	Anti-andro-genic	Gluco-corticoid	Anti-mineralo-corticoid
	+	+	+	–	–	±	+	+
	+	–	+	–	–	±	–	±
	+	+	+	–	–	±	–	–
vatives								
etate	+	+	+	–	–	+	+	–
te	+	+	+	–	–	++	+	–
	+	+	+	–	±	+	+	–
rone-acetate	+	+	+	–	±	–	+	–
ne-derivatives								
te	+	+	+	–	–	±	–	–
	+	+	+	–	–	–	–	–
	+	+	+	–	–	±	–	±
atives								
	+	+	+	–	–	+	–	+
derivatives								
	+	+	+	+	+	–	–	–
	+	+	+	+	+	–	–	–
	±	+	±	+	±	–	–	–
	+	+	+	–	+	–	–	–
	+	+	+	–	+	–	–	–
	+	+	+	–	+	–	–	–
	+	+	+	–	+	–	+	+
	+	+	±	±	–	+	–	–

nce [5,7,8,10–15]. (+) effective; (±) weakly effective; (–) not effective.

Schindler AE et al. Classification of Progestins. Maturitas 2003; 46SI:S7-S16

Dydrogesterone does not Modify Plasma Levels of Endogenous Progesterone

- No significant depression in
- **Plasma Progesterone levels**
- In patients on Dydrogesterone



Balasch J et al. The effect of postovulatory administration of dehydrogesterone on plasma progesterone levels. Fertil Steril 1980; 34(1):21-23.

Table 4

Oral doses of progestogens (mg/day) required for endometrial transformation and inhibition of ovulation in women [1].

	Endometrial transformation		Inhibition of ovulation
	Sequential therapy	Continuous therapy	
Progesterone micronized	200–300	100	300
Dydrogesterone	10–20	5–10	>30
MPA	5–10	2.5	10
Medrogestone	10	/	10
Chlormadione acetate	10	/	1.5–2.0
Cyproterone acetate	1	/	1
Nomegestrol acetate	5	2.5	5
Promegestone	0.5	0.25	0.5
Trimegestone	0.25–0.5	/	0.5
Norethisterone	1	0.5	0.5

MPA: medroxyprogesterone acetate; /: no data available.

Table 3
Progestogenic effectivity on the level of the endometrium and antigonadotropic effects (dose for ovulation inhibition) of the different progestins

Progestin	Ovulation inhibition dose mg per day p.o.	Transformation dose mg per cycle	Transformation dose mg per day p.o.
Progesterone	300	4200	200–300
Dydrogesterone	>30	140	10–20
Medrogestone	10	60	10
Medroxyprogesterone acetate	10	80	5–10
Chlormadinone acetate	1.5–2.0	20–30	10
Cyproterone acetate	1	20	1.0
Norethisterone	0.5	100–150	/
Norethisterone acetate	0.5	30–60	/
Lynestrenol	2.0	70.0	/
Ethynodiol	2.0	15.0	/
Levonorgestrel	0.05	6.0	0.15
Desogestrel	0.06	2.0	0.15
Gestodene	0.03	3.0	/
Norgestimate	0.2	7.0	/
Dienogest	1.0	6.0	/
Drospirenone	2.0	50	/
Promegestone	0.5	10	0.5
Nomegestrol acetate	5.0	100	5.0
Trimegestone	0.5	/	0.25–0.5

Taken from reference [7,8,11–14]. / = no data available.

Dose to Inhibit Ovulation

Blocking of Ovulation Doses of Different Progrestogens

- **Dydrogesterone:** 30mg/day
- **MPA*:** 5mg/day
- **Norethinsterone:** 0.5mg/day

* Medroxy-progesterone

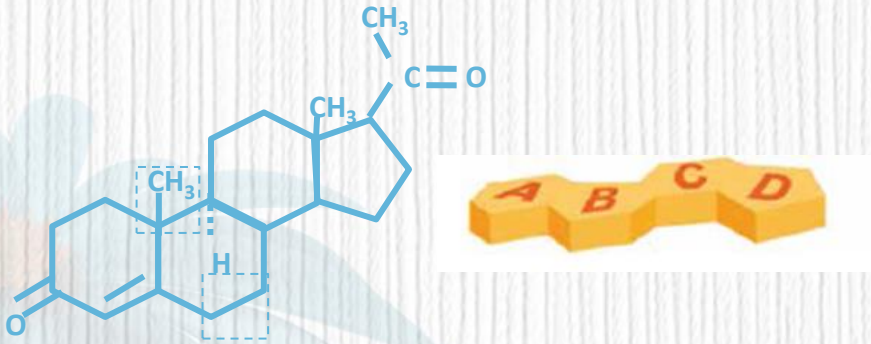
Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. Maturitas. 2008;61(1–2):171–180.

Dydrogesterone and Micronized Progesterone Are Synthesized from a Natural Source

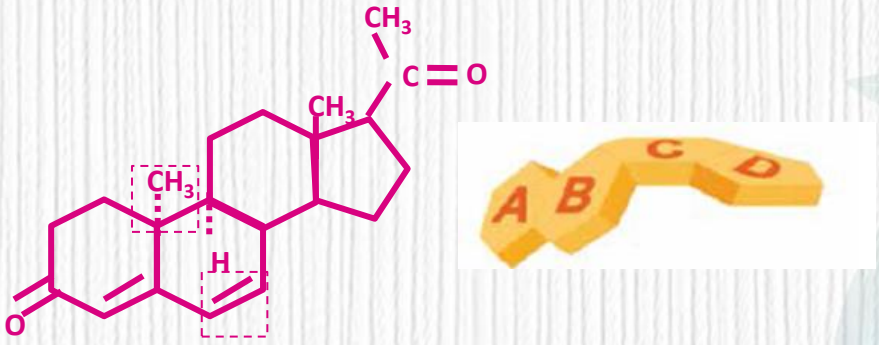
Dydrogesterone is a retroprogesterone, a stereoisomer of progesterone, with an additional double-bond between carbon 6 and 7[1]

- Dydrogesterone, shaped by light,[2] enhances the progestogenic effects[3]
  - No estrogenic, androgenic, or glucocorticoid effects[3]
  - Does not inhibit ovulation, at normal dosage[3]
  - Anti-androgenic potential of dydrogesterone is less pronounced in comparison to progesterone[4]

Progesterone



Dydrogesterone



1. Kuhl H. Climacteric 2005; 8 (Suppl 1): 3–63. 2. Fischer M. Agnew Chem Int Ed Engl 1978; 17: 16-26 3. Schindler AE. Maturitas 2009; 65S: S3–S11. 4. Rižner TL et al. Steroids. 2011;76(6):607–15

Pharmacokinetics Parameters of Progestogens

	Oral Micronized Progesterone (MCP/MCP SR)	Dydrogesterone
Metabolite	Metabolized mainly in liver to inactive metabolites - pregnanediols & pregnanolones	Active metabolite -"Dihydrodydrogesterone" - explains lack of estrogenic & androgenic effects of dydrogesterone
Bioavailability	5-10%	28%
Half-life	MCP - ~7 hrs MCP SR – 18 hrs	Dydrogesterone – 4-5 hrs and Dihydrodydrogesterone – 17 hrs
Peak Plasma Concentration	MCP/MCP SR - ~3 hrs	Rapidly absorbed with Tmax - 0.5 and 2.5 hrs
Use during Pregnancy	Administration of Oral MCP during 2nd & 3rd trimester of pregnancy may result in appearance of severe cholestasis or hepatitis **No** indication in TM / RM / LPD	Indication: - Threatened Miscarriage - Recurrent Miscarriage - Infertility due to LPD

Safety and Tolerability

Dydrogesterone	Norethisterone
• **Most commonly reported AEs (clinical trials):** Migraines/headache, nausea, menstrual disorders and breast pain/tenderness[1]	• **Most commonly reported AEs (clinical trials and post-marketing):** headache, nausea, uterine/vaginal bleeding and edema[6]
• No androgenic activity[1]	• Androgenic and estrogenic activity[6]
• **Minimal to neutral effects** on **lipid** metabolism, **glucose tolerance** or **blood coagulation**[2–5]	• **Impacts** lipid metabolism, **glucose metabolism** and **blood coagulation**[7,8]

Dydrogesterone has been used for more than 55 years, in an estimated 94 million patients, and benefits from a well-established safety profile; over 20 million pregnancies have been exposed to dydrogesterone *in utero*[9]

AE, adverse event

Not head-to-head comparison – for illustrative purposes only

1. Abbott Laboratories. Dydrogesterone CCDS. 2016; 2. Lacey *et al. Br J Clin Pract* 1983;
3. Godsland *et al. Clin Endocrinol (Oxf)* 2004; 4. Gelfand *et al. Menopause* 1997;
5. Seeger & Mueck *Gynecol Endocrinol* 2007; 6. Bayer. Primolut N® SPC. 2015; 7. Lehmann *et al. Contraception* 1993; 8. Fahmy *et al. Contraception* 1991; 9. Podzolkova *et al. Gynecol Endocrinol* 2016

Dydrogesterone

- Have **no side effects** on the **mother**.
- Has a **good safety** and **tolerability** profile , and **few side effects**.
- Has **no androgenic** effects on the **fetus**, and
- Does **not inhibit** the formation of **progesterone in the placenta.**

- Only Pelinescu-Onciul's reported **drowsiness**.
- Gelle and Schaeffer reported **nausea and vomiting**, but in only one patient, and
- Chang, reported nausea and vomiting in two patients.
- However, nausea and vomiting may be due to early pregnancy itself rather than the medication

Conclusions

- **Dydrogesterone**
- Very similar to progesterone, but is orally bioavailable[1]
- Highly selective for the progesterone receptor, and its metabolites are progestogenic[1]
- Does not inhibit endogenous progesterone secretion[2]
- Does not inhibit ovulation at recommended therapeutic dose[3]
- Effectively transforms estrogenized endometrium[4]
- Suitable for treatment of a variety of menstrual disorders[5]
- Recent studies have further demonstrated its effectiveness in regularizing menstrual cycles[6,7] and reducing menstrual bleeding[7,8] and pain[6,7]

1. Schindler AE, et al. Maturitas. 2008; 61(1–2):171-180. 2. Balasch J, et al. Fertil Steril 1980; 34(1): 21–23. 3. Kuhl H. Climacteric 2005; 8(Suppl 1): 3–63. 4. Karakus S, et al. Aust N Z J Obstet Gynaecol 2009; 49(6): 685–688. 5. Dydrogesterone CCDS. 15 January 2016. 6. Podzolkova N et al. Gynecol Endocrinol 2016 Mar;32(3):246–9. 7. Trivedi N et al. Gynecol Endocrinol 2016. 8. Tajjamal A and Zaman F. Gazzetta Medica Italiana 2015; 174(9):391–398

Thank You !

Questions?