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Classification and pharmacology of progestins

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Abstract

Besides the natural progestin, progesterone, there are different classes of progestins, such as retroprogesterone (i.e. dydrogesterone), progesterone derivatives (i.e. medrogestone) 17α-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).

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

Keywords: Progesterone; Progestin; Classification; Biological effects; Pharmacology

1. Introduction

Recent prospective randomised studies on hormone replacement therapy (HRT), among others the HERS I and II as well as the WHI and MWS [1–5], have raised great concern regarding the role of progestins for the cardiovascular and venous system and breast cancer in the climacteric and postmenopausal woman. Neither secondary nor primary prevention of cardiovascular events seems to be accomplished and the rate of invasive breast cancer seems even to be raised. This could be related to the specific progestin used in HRT in these studies. Since there is a large body of data, partially conflicting, on the various progestins it appears mandatory to scrutinize the progestins in clinical use.

Basically all progestins do have only *one* effect in common, the progestogenic effect on the estrogen-primed endometrium of the rabbit, but there are large differences between progestins in the multitude of other biological effects elicited. In practice,

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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].

clinically used synthetic progestins have been selected on other effects, e.g. activity after oral administration and favourable bio-availability or inhibition of ovulation, but not on pregnancy maintaining capacity, a very important biological role for progesterone.

Besides natural progesterone, produced and secreted normally in the human female by the corpus luteum, the placenta and in small quantities by the adrenal cortex, there is a broad spectrum of steroids with progesterone-like actions, derived from different parent compounds. An overview is given in Table 1 and the formulations are shown in Figs. 1 and 2. Close to the natural progesterone we have retroprogesterone, followed by the pregnane-(17-hydroxyprogesterone, C-21) derivatives and the 19-norprogesterone-(19-norpregnane, C-20) derivatives. A clinically important group and the basis for the success of hormonal contraception are the 19-nortestosterone derivatives, subdivided in estranes (C-18) and gonanes (C-17). Recently, a spirolactone derivative has been developed for clinical use. Some of these compounds are prodrugs, they are metabolised to the active compounds by the liver, examples are promegestone converted to trimegestone, desogestrel to 3-keto-desogestrel and norgestimate to norgestrel [6–9].

2. Pharmacodynamics of progestins

With regard to the progestogenic activity, the time-course of the serum concentrations of the steroids after the application (pharmacokinetics) which is dependent upon absorption, metabolism in the gastro-intestinal tract and liver (first-pass effect), distribution and storage in fat and other tissues, binding to serum proteins, inactivation and conjugation, is of particular importance.

Depending on the route of administration, oral or parenteral (vaginal, intramuscular, transdermal), progestins can manifest different effects that are due to differences in metabolism. For progesterone this has been demonstrated experimentally [10]. Orally administered progesterone, even in micronised form, shows a wide variation of absorption and bioavailability in the individual person. After oral administration, synthetic progestins are in general rapidly absorbed and reach a maximum serum concentration within 2–5 h, they have a longer half-life than progesterone and display stable plasma levels on long-term use. Many of them are metabolised in the liver and are excreted via the urine [6,8,9,11].

2.1. Dydrogesterone

Dydrogesterone is a retroprogesterone, a stereoisomer of progesterone, with an additional double bond between carbon 6 and 7. The progesterone molecule is almost “flat”, the retroprogesterone molecule is bent by a change of the methyl group at carbon 10 from the β-position to the α-position and the hydrogen at C9 from the α to the β position. In addition, there is an additional double bond between C6 and C7 (see Fig. 3). Dydrogesterone appears to be a highly selective progestin which, due to its

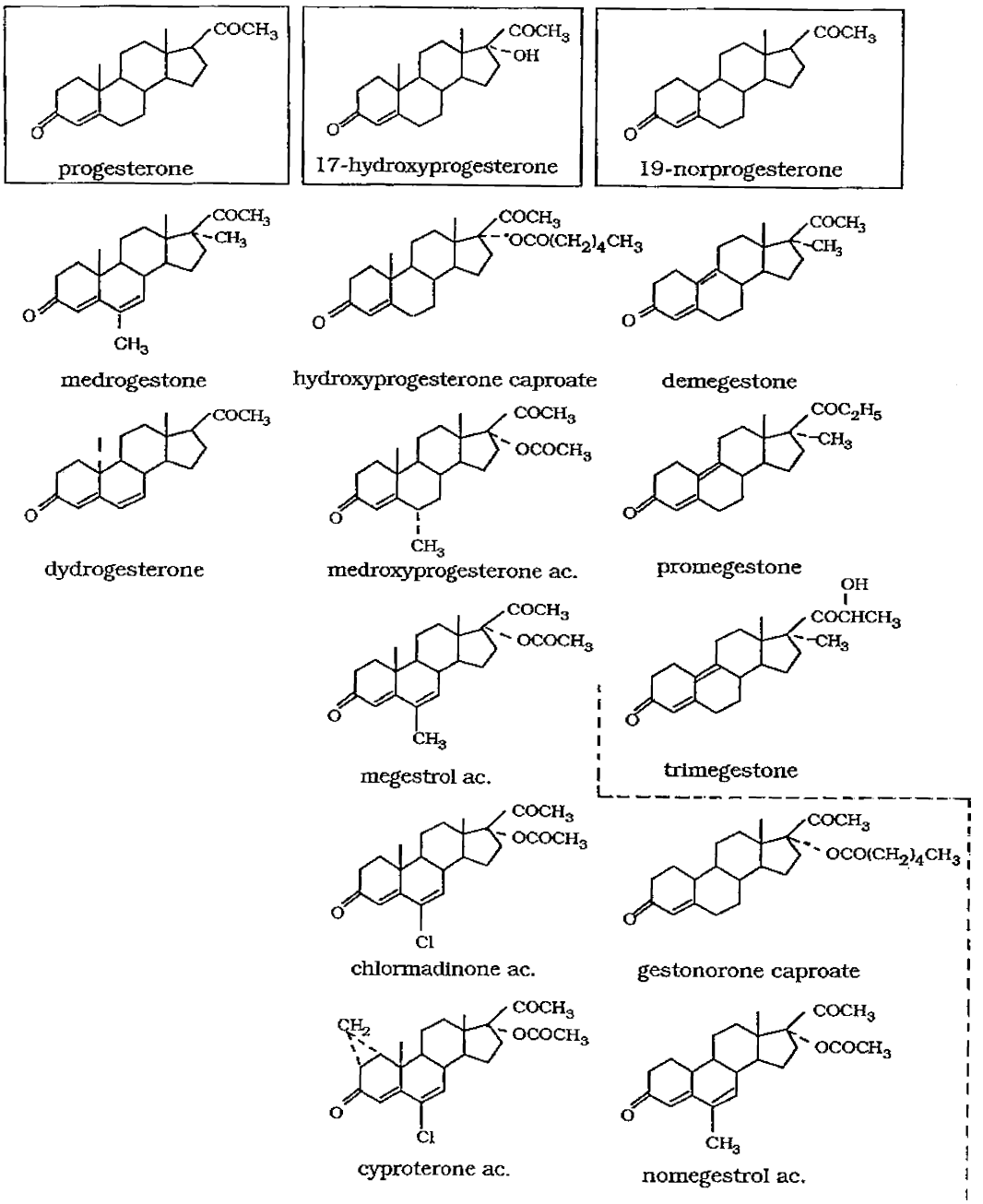


Fig. 1. Progesterone and progesterone derivatives (taken from reference [5]).

retrostructure, binds almost exclusively to the progesterone receptor. Though the binding affinity appears to be somewhat lower than that of progesterone, due to its better bioaviability and the progestogenic nature of the metabolites, the equivalence dose is 10–20 times lower, regarding endometrial proliferation. Dydrogesterone is metabolised by reduction at C20 to the 20α-hydroxy-derivative and by hydroxylation

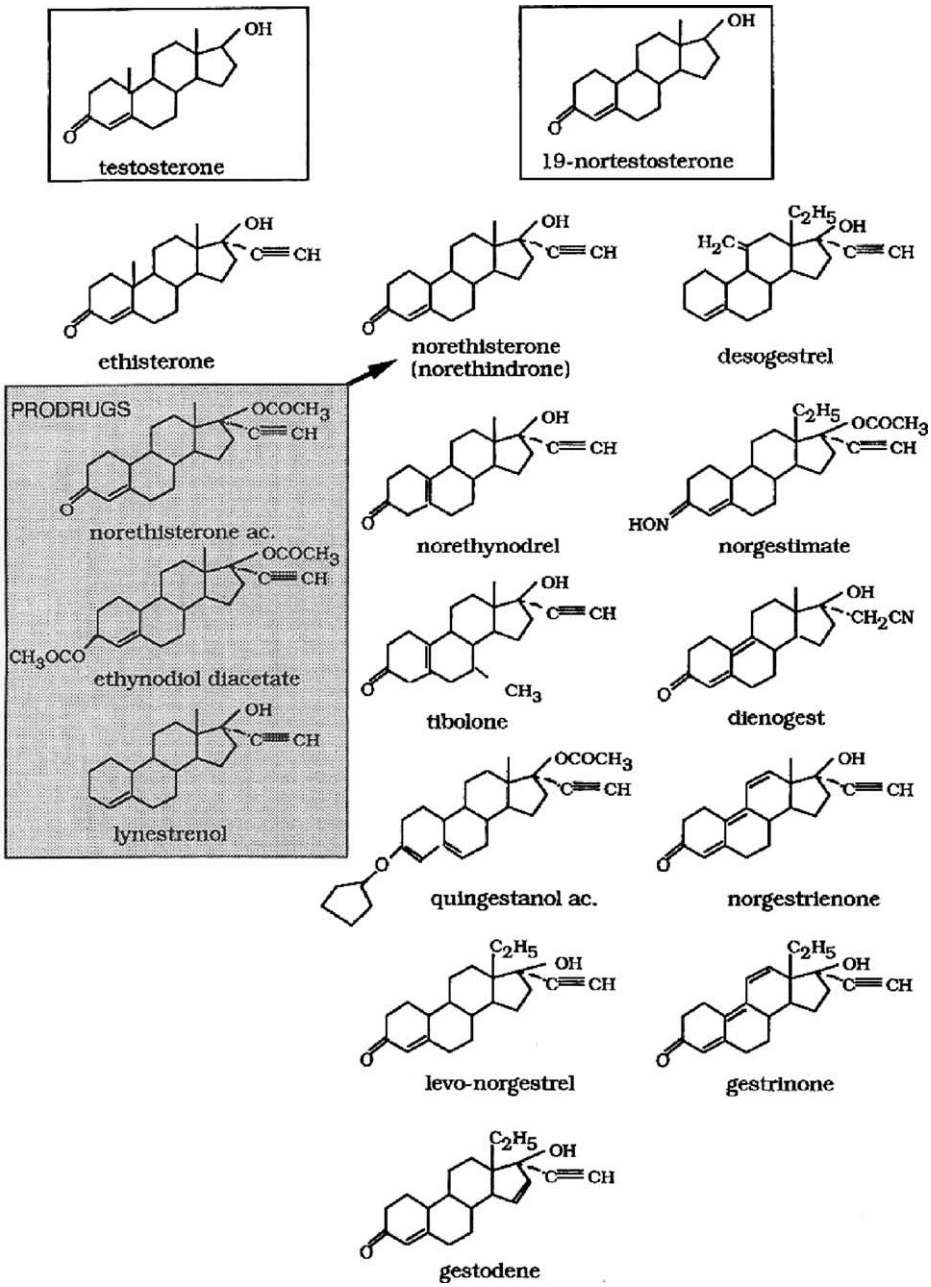


Fig. 2. Progestin structures (testosterone- and 19 nortestosterone derivatives (taken from reference [5]).

at the C21-methyl group and at the C16α-position. These three metabolites represent 70% of the urinary excretion after taking dydrogesterone. Metabolites maintain the retrosteroid structure and have a similar profile as dydrogesterone. Due to its selectivity, effects not mediated by the progesterone receptor are minimal or absent [6,8,9,11,12]. The effects of dydrogesterone are listed in Table 2.

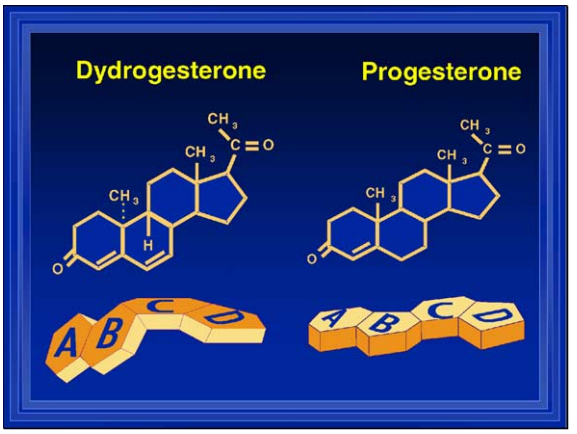


Fig. 3. Comparison of the structure differences of dydrogesterone with progesterone.

2.2. Medrogestone

Medrogestone is not a derivative of 17α-hydroxyprogesterone because it has a methyl group at the C17α- and the C6-positions and in addition, a double bond between C6 and C7 (see Fig. 1). After oral administration, absorption is rapid and the bioavailability is close to 100%; the peak plasma level is obtained at 1 h. The major proportion of medrogestone is bound to albumin. Inactivation of the molecule is accomplished by hydroxylation [6,8,11,14]. The biological effects tested are summarized in Table 2.

2.3. 17α-Hydroxyprogesterone derivatives

2.3.1. 17α-Hydroxyprogesterone and 17α-hydroxyprogesterone esters (see Fig. 1)

For the progestogenic activity the C17 position is of key importance. Progesterone looses its progestogenic activity with the introduction of the hydroxyl group of the position C17. While 17α-hydroxyprogesterone is hormonally inactive, its esterification on the one hand with acetate leads to weak progestogenic activity, while on the other hand esterification with caproate leads to a highly active progestin, which is clinically

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.

useful for intramuscular injection, and is found in the circulation as unmetabolised ester [6,8,9,11].

2.3.2. Medroxyprogesterone acetate (MPA) (see Fig. 1)

After oral intake medroxyprogesterone acetate does not undergo any first pass effect. The bioavailability is nearly 100%. MPA has no binding affinity to SHGB and CBG and in serum MPA is bound to albumin for 88%. The most important metabolic steps are hydroxylation reactions. The various biological effects are summarized in Table 2 [6,8,9,14,15].

2.3.3. Megestrol acetate (MA) (see Fig. 1)

Similar to MPA the bioavailability of MA is nearly 100%. MA is not bound to SHBG or CBG and the majority of circulating MA is bound to serum albumin. The most important metabolic pathways are hydroxylation reactions. The various biological effects of the compound are summarized in Table 2 [6,8,9,14,15].

2.3.4. Chlormadinone acetate (CMA) (see Fig. 1)

The chlorine atom at C6 characterizes the molecule. After oral administration CMA is rapidly absorbed and undergoes nearly no first pass metabolism. Therefore the bioavailability is nearly 100%. CMA accumulates in fat tissue. The elimination occurs slowly. After 7 days only 34% of the dose has been excreted. Inactivation occurs mainly through the reduction of the 3-keto-group whereby the double bound in ring A is preserved. The most important metabolite is the 3-hydroxy-CMA, which shows 70% of the anti-androgenic activity of CMA. Hydroxylation occurs at positions C2α, C3β and C15β. The majority of the metabolites are excreted renally, predominantly as glucoronides. The conjugates which are excreted with the bile, can be hydrolysed in the colon and reabsorbed. This enterohepatic circulation might be of clinical relevance with respect to the anti-androgenic properties of 3-hydroxy-CMA [6,8,9,14,15]. The various biological effects are summarized in Table 2.

2.3.5. Cyproterone acetate (CPA) (see Fig. 1)

The bioavailability is nearly 100%. Since there is no binding of CPA to SHBG and CBG in the serum, 93% of the compound is bound to serum albumin. It is stored in fat tissue and is excreted slowly. Therefore, daily intake of higher doses of CPA cause an accumulation resulting in a depot effect. Most important metabolic steps are hydroxylation reactions and de-acetylation. Also metabolites, such as 15β-hydroxy-CPA show anti-androgenic activity, similar to that of CPA, but the metabolite has only 10% of the progestogenic potency of CPA [6,8,9,14,15]. The biological effects of the compound are shown in Table 2.

2.4. 17α-Hydroxy 19-norprogesterone derivatives

2.4.1. Nomegestrol acetate (see Fig. 1)

Absorption is rapid after oral intake. The maximum concentration is reached after 2 h. Metabolism is essentially by glucoronide- and sulphate-conjugation with a considerable enterohepatic recirculation [8,9,11,12]. The biological effects are shown in Table 2.

2.5. 19-Norprogesterone derivatives

2.5.1. Promegestone (R5020) (see Fig. 1)

Promegestone is rapidly absorbed after oral intake and has a short half-life. The maximal concentration is reached 1–2 h after administration. Promegestone is bound only to a small extent to SHBG, the binding to CBG is weak and thus it is mainly bound to serum albumin. It is metabolised by hydroxylation [8,9,11,12]. The possible biological effects are shown in Table 2.

2.5.2. Trimegestone (see Fig. 1)

This is the most recent 19-norprogesterone derivative for clinical use. Trimegestone is an active metabolite of promegestone. It has a strong progestogenic effect. Further biological actions of the compound are summarised in Table 2 [8,9,11,12].

2.5.3. Nesterone

Nesterone, a 16-methylen-17α-acetoxyd-19-norpregnene-3,20-dione is only active, when administered parenterally because of its rapid hepatic metabolism. Nesterone has a low oral activity but is very potent parenterally. Besides the high binding affinity to the progesterone receptor, the binding to the androgen receptor is negligible. There is no binding to the estrogen receptor. It does not show glucocorticoid activity and there is no binding to SHBG. There is a rapid clearance [9,17,18].

2.6. 19-Nortestosterone derivatives

2.6.1. Norethisterone (NET) (see Fig. 1)

Norethisterone is also named norethindrone and is often used as norethisterone acetate (NETA). Both compounds are rapidly absorbed from the gastrointestinal tract. The bioavailability is about 64%, 36% are bound to SHBG, 61% to serum albumin and 3% are free in the circulation. The principal metabolite is 5-α-dihydro-norethisterone [8,9,16]. The biological activities of the compound are shown in Table 2.

2.6.2. Lynestrenol (see Fig. 2)

Lynestrenol is a prodrug and is converted in vivo to norethisterone. The conversion is rapid and almost total. The compound is metabolised by 3β-hydroxylation and dehydrogenation [8,9,12,16] The biological effects are listed in Table 2.

2.6.3. DL-Norgestrel

DL-Norgestrel is a racemic DL-mixture. Only the levorotatory form is biologically active [8,9,16].

2.6.4. Levonorgestrel (see Fig. 2)

It is rapidly absorbed when taken orally. The bioavailability is practically 100% and the peak-plasma-level is obtained between 1 and 3 h after administration. Levonorgestrel is bound to SHGB in 47.5%, 50% to serum albumin and 2.5% are unbound. Levonorgestrel causes a decrease of SHBG of 50% [8,9,16]. The biological effects are shown in Table 2.

2.6.5. Desogestrel (see Fig. 2)

Desogestrel is a prodrug, its activity is essentially based on transformation to 3-keto-desogestrel, the principal metabolite formed in vivo. Though the bioavailability is 76%, the peak plasma concentration after absorption is reached in 1.15 h. 32% are bound to SHBG, 66% to albumin and 2% remains free [8,9,16]. The biological effects are shown in Table 2.

2.6.6. Gestodene (see Fig. 2)

Gestodene is not a prodrug and is absorbed without modification so that its bioavaiability is almost 100% [8,9,16]. The biological effects are shown in Table 2.

2.6.7. Norgestimate (see Fig. 2)

Norgestimate is also a prodrug, which is rapidly absorbed and metabolised and converted to norgestrel. Unchanged norgestimate is not found in the urine. The absorption is rapid and the peak will be reached 1 h after intake [8,9,16]. The biological effects are listed in Table 2.

2.6.8. Dienogest (see Fig. 2)

This so called hybrid progestin has a unique pharmacological and pharmacodynamic profile combining the typical properties of the 19-nortestosterones with those of progesterone derivatives [10]. Dienogest is a 19-nortestosterone compound, which is not alkylated at C17. There is a cyanomethyl group at position 17α as well as a double bond between C9 and C10 in ring B of the molecule. The compound is rapidly absorbed after oral intake. The peak level is reached after 2 h. The bioavailability is about 90%. Ten percent of dienogest are free in the circulation and 90% bound to albumin. There is no binding to SHBG and CBG. Dienogest is metabolised by hydroxylation and aromatisation [8,9,16]. The biological effects are listed in Table 2.

2.7. Spirolactone derivatives

2.7.1. Drospirenone (see Fig. 2)

Drospirenone is rapidly absorbed after oral intake and the peak plasma level is reached in 1–2 h. The bioavailability is 76%, 95–97% of drospirenone are bound to serum albumen. Drospirenone does not bind to SHBG or CBG [15]. The biological activities are listed in Table 2.

3. Biological activities of the progestins

Because of the enormous variation in the chemical structures of steroids with progestational activity, it is very difficult to deduct various biological actions and activities from the chemical structure alone [10]. One of the essential requirements of any compound with such an activity is of course: being able to bind to the progesterone-receptor and thus some knowledge has been developed about the three dimensional structure required for a steroid to bind.

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.

Adding to the confusion is the fact that there appears to be several different forms of the progesterone receptors, usually called PR-A and PR-B, the difference being a sequence of amino-acids in the B-form that is not found in PR-A. Also biologically both forms have different specifications, interpreted by authors as: the PR-B is the "normal" receptor, the intermediate in the agonistic activity in several organs whereas the PR-B is capable of antagonising the effects stimulated by an activated PR-A [20]. Relatively little is known yet on the compostion of PR in different tissues during specific periods of development. Binding of the steroids to both forms is expected not to show differences as the steroid binding domain of both isoforms is identical.

All progestins have in common the so-called progestogenic effect i.e. the induction of a characteristic change in the estrogen-primed endometrium. The final progestogenic or progestational activity of any substance depends also on the route and timing of the administration. It varies widely and is often expressed by the difference in the dose required for the endometrial transformation in a woman, called the transformation dose (Table 3).

The transformation dose after oral application is also clinically dependent on whether the compound is used sequentially or in a continuous fashion (Table 4).

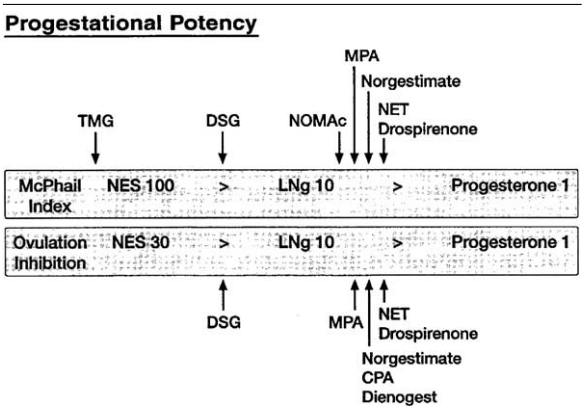
On the other hand progestins have been selected for clinical use on differences of the dose necessary for inhibition of ovulation. As shown in Table 3

Table 4
Progesterone dose (per oral) for transformation of the endometrium depending on sequential or continuous therapy

Progestin	Daily dose	
	Sequential	Continuous
Progesterone micronized	200–300	100
Dydrogesterone	10–20	5–10
Medrogestone	10	/
Chlormadinone acetate	10	/
Cyproterone acetate	1	/
Medroxyprogesterone acetate	5–10	2.5
Nomegestrol acetate	5	2.5
Promegestone	0.5	0.25
Trimegestone	0.25–0.5	/
Norethisterone	1	0.5

Taken from reference [7,10].

Table 5
Comparison of relative potencies of progesterone versus a synthetic progestin on standard bioassays



Taken from reference [17]. MyPhail index: testing the ability of the progestin to transform the endometrium, in rabbits. Ovulation inhibition was tested in rats. The order of potency is represented from left to right. The arrows indicate the order of potency of the progestins. TMG: trimegestone, DSG: desogestrel, NOMAc: nomegestrolacetate, MPA: medroxyprogesterone acetate, NET: norethisterone, CPA: cyproterone acetate.

progestogenic activity of the various progestins have been tested by standard bioassays using changes in the endometrium of estrogen-primed rabbits and also by the inhibition of ovulation in rats. This is summarised in Table 5 [18].

Biological effects at the cellular level are mediated by intracellular steroid receptors. The ability of any progestin to bind to the progesterone receptor varies between different compounds and by this, the biological effect of the progestin is influenced. This is also true in relation to binding to other intracellular steroid receptors. An overview of binding to various receptors is shown for the progestins and their metabolites in Tables 6 and 7. Very little knowledge is available on binding to the newest class of progesterone receptors, receptors located on the membrane of many different cells. For instance, it can be expected that some of the effects of progestins on the central nervous system are mediated by these membrane-receptors. There are also differences in binding to steroid binding proteins in the circulation (Table 6).

Recent in vitro studies with COS7 cells on the ERα and ERβ demonstrated some differences between progestins. The most significant upregulation of ERα-activity was found with norethisterone, norethin-

Table 6
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%).

Table 7
Relative binding affinities to steroid receptors of some progestin metabolites

Progestin	PR	AR	ER
Norethisterone	75	15	0
5α-Dihydro-norethisterone	25	27	0
Ethinodiol diacetate	1	0	0
Ethinodiol (3β-hydroxy-norethisterone)	1		18
Levonorgestrel	150	45	0
5α-Dihydro-levonorgestrel	50		
Norgestimate	15	0	0
Levonorgestrel-17β-acetate	135		0
Levonorgestrel-3-oxime (deacetylated norgestimate)	10	0	
Desogestrel	1	ß	ß
3-Keto-desogestrel	150	20	0
3β-Hydroxy-desogestrel	13	3	2
3-Keto-5α-dihydro-desogestrel	9	17	0
Dienogest	5	10	0
9α,10β-Dihydro-dienogest	26	13	
3,5α-Tetrahydro-dienogest	19	16	
Norethynodrel	6	0	2

Taken from reference [13]. PR: progesterone receptor (promegestone = 100%). AR: androgen receptor (metribolone = 100%). ER: estrogen receptor (estradiol-17β = 100%).

odrel and desogestrel. In contrast, ERβ was markedly activated only by norgestrel and to a lesser extent by norethisterone, norethinodrel and levonorgestrel. Gestodene failed to modify estrogen receptor activity. Since 19-nortestosterone derivatives, such as gestodene and desogestrel do not have any affinity for the estrogen receptor, it is supposed that the estrogen activity of norethisterone, norgestrel and levonorgestrel is at least in part a consequence of their metabolism into the 3(α,β) 5α-reduced derivatives by 5β-reductase activity in breast cancer cells [19].

4. Conclusions

Based on the available evidence from in vitro and in vivo experiments in animals amd humans, it is to be expected that the full spectrum of biological activities of different progestins must show considerable variations. However, relatively few studies have been conducted in women in which on a large scale systematic comparisons have been made between different progestins. In addition, very few of the progestins have been evaluated by long-term prospective, randomized double-blind trials. Evidence based on in vitro studies using cell lines is considered to be of value but extrapolation to the in vivo situation is very questionable and hardly can be used in arguments on effects in the human.

The available evidence for differences between progestins and related to specific fields of interest is reviewed in the following contributions.

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