REVIEW ARTICLE

Drugs 2003; 63 (5): 463-492
0012-6667/03/0005-0463/$33.00/0

Progestogens with Antiandrogenic Properties

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Abstract

Chlormadinone acetate, cyproterone acetate and dienogest are potent, orally active progestogens, which have antiandrogenic instead of partial androgenic activity. They act mainly by blocking androgen receptors in target organs, but also reduce the activity of skin 5α-reductase, the enzyme responsible for converting testosterone to the more potent androgen, 5α-dihydrotestosterone, in sebaceous glands and hair follicles. Chlormadinone acetate and cyproterone acetate also suppress gonadotropin secretion, thereby reducing ovarian and adrenal androgen production.

Combined oral contraceptives (COCs) containing antiandrogenic progestogens provide highly effective contraception (gross and adjusted Pearl indices: 0–0.7 and 0–0.3, respectively) with excellent cycle control. Furthermore, COCs containing 2mg of chlormadinone acetate or cyproterone acetate plus 30 or 35μg of ethinylestradiol produced improvement or resolution of seborrhoea in 80% of users, acne in 59–70%, hirsutism in 36% and androgen-related alopecia in up to 86%.

These COCs are generally well tolerated, the main adverse effects being nonspecific or as expected for a COC (headache, breast tenderness and nausea). They have no clinically relevant effects on metabolic or liver functions or on bodyweight. Effects on mood and libido are uncommon (<3.5% and <6% of women, respectively).

COCs containing antiandrogenic progestogens are likely to be particularly valuable in women with pre-existing androgen-related disorders who require contraception. They also increase the choice of products available for women with normal skin and hair who are concerned about the possibility of developing seborrhoea or acne with other COCs.

1. Introduction

Women produce androgens in their ovaries and adrenal glands during progesterone metabolism.[1,2] The active androgens, testosterone and 5α-dihydrotestosterone, may act locally; alternatively, both active androgens and their precursors may be transported to other sites. During transport, these hormones are highly bound to plasma proteins, especially sex hormone-binding globulin (SHBG). Only a small proportion (about 1–2% of the total testosterone concentration) remains unbound and is able to enter cells.[1,2]

Androgen precursors require further metabolism to become active. Major activation sites include the liver, skin and subcutaneous fat.[1,3] Such peripheral metabolism accounts for about 50% of the total testosterone level in women.[4] Furthermore, 5α-dihydrotestosterone is the active hormone in several androgen-responsive tissues and organs, including the skin.[1-3] Localised conversion of testosterone to 5α-dihydrotestosterone is catalysed by 5α-reductase,[5,6] which exists in two isoforms that differ in their kinetic characteristics and optimal pH values.[7] Both isoforms are expressed in the skin, although type 1 predominates.[3]

Activated androgens mainly exert their effects by acting at a specific androgen receptor. The structures of the receptor gene and protein have been elucidated[2,8,9] and are shown in figure 1. The androgen receptor belongs to the superfamily of *trans*-acting transcriptional factors, which also includes other sex steroid, glucocorticoid and mineralocorticoid receptors.[3] In its inactive state, the receptor is complexed to heat shock proteins 90 and 70 in the cytoplasm of target cells. When an active androgen attaches to its ligand-binding site, this complex dissociates and the androgen-bound receptor undergoes a conformational change and dimerisation. The dimer moves into the nucleus

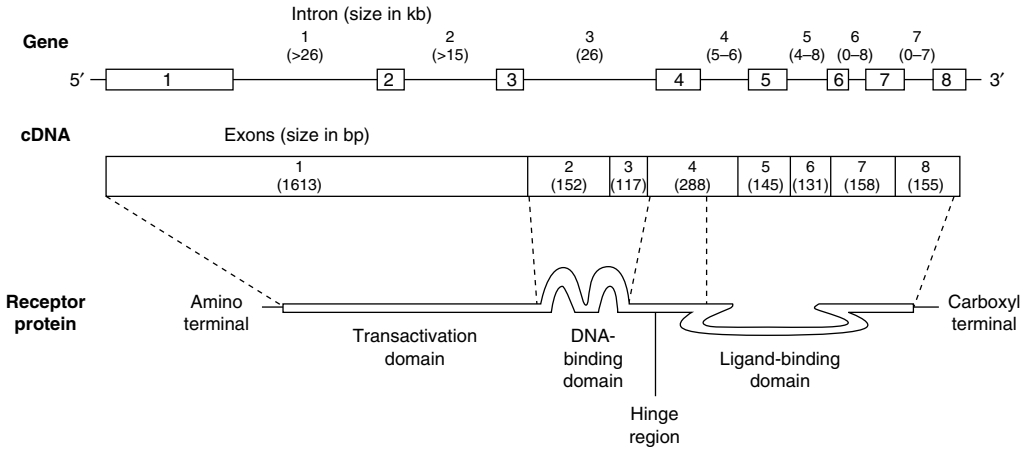

Fig. 1. The structures of the gene encoding the androgen receptor, its complementary DNA and the receptor protein (adapted from Montgomery et al. 2001).[8] The gene encoding the androgen receptor is located at position q11-12 on the long arm of the X chromosome. The gene encompasses 75–90kb of genomic DNA and consists of 8 exons (boxes) separated by 7 introns and preceded by a promoter region. In the complementary DNA, exon 1 encodes the DNA-transactivating domain of the receptor, exons 2 and 3 encode the DNA-binding domain, the 5′ end of exon 4 encodes the hinge region, and the 3′end of exon 4 plus exons 5–8 encode the ligand-binding domain. In the receptor protein, the ligand-binding domain in the carboxyl terminal region is responsible for androgen binding, coupling to heat shock proteins, receptor dimerisation and nuclear localisation signalling. Towards the centre are a hinge region (thought to control the conformational change in the receptor during transport into the nucleus) and a target DNA-binding domain featuring two 'zinc finger' motifs. The transactivation domain in the amino terminal region transcribes the target DNA and induces mRNA synthesis, thereby initiating the production of specific proteins.[2,9] **bp** = base pairs; **kb** = kilobases.

where it binds to specific sites on the target gene. DNA transcription by the transactivation domain then induces the synthesis of mRNAs and specific proteins (figure 2).[1,2,9]

Androgen receptors are present in many organs and tissues, including striated muscle, the cardiovascular and endocrine systems, liver and skin.[1,2] Androgens act on striated, myocardial and vascular smooth muscle to increase protein production, growth and glycogen content, and can alter glucose metabolism and cardiac contractility. They also have many effects on hepatic function, including changes in lipid and lipoprotein metabolism that result in a more atherogenic plasma profile.[2] Besides their receptor-mediated effects, androgens can suppress hepatic SHBG production (thereby increasing plasma levels of free active androgens) and stimulate their own aromatisation to estrone in fatty tissue. Estrone may then induce abnormal gonadotropin secretion by acting at estrogen receptors in the hypothalamus.[1,2] Elevated levels of 5α-dihydrotestosterone can also increase both androgen receptor and 5α-reductase levels in the skin, thus creating a cycle of enhanced androgen activity.[1]

Because of the wide ranging effects of androgens, hyperandrogenism in women is associated with various health risks such as dyslipidaemia, atherosclerosis, myocardial infarction, intravascular thrombosis and increased cardiovascular mortality, as well as disorders of glucose metabolism (insulin resistance, hyperinsulinaemia and type 2 diabetes mellitus).[1,2,10,11] In patients with particularly severe conditions (usually due to an androgen-producing tumour), there is also an increased risk of breast and endometrial dysplasia and cancer.[1] Furthermore, polycystic ovary syndrome, now thought to be a mixed endocrine-metabolic disorder with genetic and environmental triggers, is associated with ovarian and peripheral androgen overproduction, insulin resistance and obesity.[12,13] Women with this syndrome may experi-

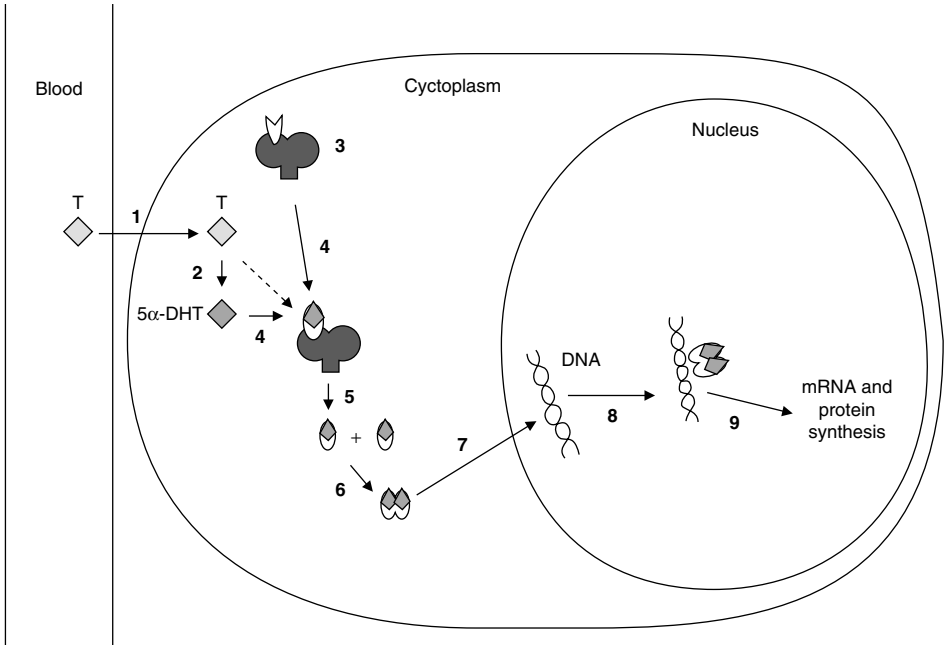

Fig. 2. The mechanism of androgen action via the androgen receptor. **1** = Diffusion of androgen into cell cytoplasm; **2** = 5α-reductase turns testosterone into its more active derivative 5α-dihydrotestosterone (5α-DHT); **3** = inactive androgen receptor is bound in cell to heat shock protein; **4** = binding of androgen receptor in receptor-heat shock protein complex; **5** = dissociation of receptor-heat shock protein complex; **6** = dimerisation of hormone-receptor-complex; **7** = nuclear translocation; **8** = hormone-receptor-complex binds to DNA; **9** = DNA transcription. **T** = testosterone.

ence hirsutism, acne and alopecia as well as a range of gynaecological disorders, encompassing increased risk of miscarriage, menstrual disturbances and anovulatory infertility.[1,14] Subsequent infertility treatment may result in ovarian hyperstimulation and an increased likelihood of multiple pregnancies.[14] Although not definitely proven, some studies also suggest a possible association between increased androgen levels and higher risks of pre-eclampsia, gestational diabetes and perinatal mortality during pregnancy.[11,15-17]

Raised levels of, or heightened sensitivity to, androgens can also produce acne and abnormal hair growth in women. The sebaceous glands, hair follicles and several types of skin cell contain androgen receptors and 5α-reductase (particularly type 1).[3] In the skin, 5α-dihydrotestosterone enhances follicular keratinisation, sebaceous gland growth and sebum secretion. Overstimulation of the glands results in seborrhoea, which in turn causes greasy skin and hair. Excess sebum may also plug the gland outlets to form comedones. Subsequent infection with *Propionibacterium acne*, which releases lipases and inflammatory mediators, produces the characteristic lesions of acne.[3,18] Seborrhoea and acne may be associated with elevated serum testosterone concentrations; however, most patients have normal levels. In these individuals, symptoms appear to be caused either by excessive local production of 5α-dihydrotestosterone due to skin 5α-reductase overactivity or by increased sensitivity to its effects.[19] 5α-dihydrotestosterone also promotes a male-type body and sexual hair distribution, and overproduction results in hirsutism.[1,2] Scalp hair responds differently, and increased 5α-dihydrotestosterone levels can lead to various forms of alopecia.[1]

The involvement of androgen receptors and 5α-reductase in these conditions indicates that their blockade would be a logical approach to treatment. Over the years, several agents that target these mechanisms have been used, with varying success rates (table I). Recently, an androgen receptor modulator, nilutamide, has become available for the treatment of metastatic prostate cancer;[20] a topical formulation of another such agent, RU-58841 (PSK-3841),[21-23] is currently in phase II trials for the treatment of androgen-dependent acne and alopecia. A more established option, which produces both androgen receptor antagonism and decreased skin 5α-reductase activity,[24] is a combination of an antiandrogenic progestogen with an estrogen. This combination has a major advantage over other agents in that it provides the contraceptive effect needed to safeguard against possible feminisation of a male fetus.[18,25,26] The original reverse sequential regimen, in which a high dose of cyproterone acetate is taken during the first ten days of a 21-day ethinylestradiol cycle,[18,26] was developed during the late 1960s and remains one of the most effective treatments for androgen-related skin and hair conditions (table II). Regimens with lower cyproterone acetate and ethinylestradiol doses have since been devised, particularly for the treatment of hirsutism (table II). However, as with other agents, improvements in hirsutism and androgenetic alopecia take longer to appear than in acne and seborrhoea, and are more variable and less pronounced. This lower responsiveness may reflect the natural length of the hair growth cycle, and the fact that these conditions may have multifactorial aetiologies involving genetic, metabolic, environmental and nutritional factors as well as androgen production.[12,13,25]

During the 1970s, a product containing cyproterone acetate 2mg and ethinylestradiol 50μg was developed as an acne treatment with integral oral contraceptive activity. It suppressed testosterone levels to a similar extent as the high-dose reverse sequential regimen, and was almost as effective in treating moderate/severe acne and seborrhoea. Although the lower cyproterone acetate dose made it less effective in hirsutism, worthwhile improvements were still obtained in individuals with a mild/moderate condition.[18,26] More variable results were observed in androgenetic alopecia.[18,25,26] Since then, a product containing cyproterone acetate 2mg and ethinylestradiol 35μg has been marketed,[18,26] and interest has been generated in the potential benefits of products designed as combined oral contraceptives (COCs) in androgen-related skin and hair conditions.

The clinical profile of a COC is determined by the dose of both its estrogen and progestogen components, and by the type of progestogen. Over the years, estrogen doses have been decreased to reduce the incidence of serious adverse effects;[29,30] consequently, the characteristics of the progestogen have become more apparent. Most progestogens used in oral contraceptives exhibit some androgenic activity, especially those based on 19-nortestosterone.[31,32] This is an obvious disadvantage for women with a pre-existing androgen-related condition; however, these progestogens may also provoke adverse effects such as greasy skin and hair or acne in previously unaffected women. In contrast, like cyproterone acetate, chlormadinone acetate and dienogest have antiandrogenic activity. There is long-standing experience with combined and progestogen-only oral contraceptives containing chlormadinone acetate in Germany and France; however, familiarity with this agent is limited in most other countries. A new chlormadinone acetate containing COC was launched in Germany in February 1999 and will soon be available in many other European countries. Dienogest is a relatively new progestogen that has recently become available in a COC in Germany.

This article reviews the pharmacological, pharmacodynamic, pharmacokinetic and clinical data on these antiandrogenic progestogens, their use in oral contraception and the clinical benefits of their antiandrogenic effects on skin and hair. Since dienogest has previously been reviewed in *Drugs*,[33] the

Table I. Non-progestogenic treatments available for acne, hirsutism and androgenetic alopecia in hyperandrogenic women

Agent	Condition	Dosage regimen	Improvement rates	Comments
Flutamide	Hirsutism[25]	High-dose:		Selective nonsteroidal antiandrogen with no progestogenic, estrogenic, corticosteroid or gonadotrophic activity. Strongly suppresses adrenal and ovarian androgens without affecting gonadotrophin secretion
		325–750 mg/d	Approx. 70% in 3–12mo	More rapid onset of effect than other treatments. Progressive effect on all hair assessment parameters
		250mg bid	40% after 8mo in PCOS	Adverse effects: most commonly skin dryness (75%) and greenish-blue tinge to urine; transaminase levels increased in <32% of patients; isolated reports of liver toxicity and fatal liver failure
		250mg bid + COC	Mean hirsutism score fell from 26–9 in 12mo; marked improvement in 19 of 20 women	Possible feminising effect on male fetus: adequate contraception mandatory
		500 mg/d	53 vs 58% for CPA 25mg/EE RS	Comparative studies indicate similar or slightly greater efficacy to CPA RS regimens
		250mg bid	46 vs 35% for CPA 100mg/EE RS	
	Hirsutism[25]	Low dose:		Doses chosen to maintain efficacy but minimise adverse effects and cost
		250 mg/d	Mean hirsutism scores fell from 17 to 5 in 6mo	
		125 mg/d	Mean hirsutism scores fell by 65%	
	Acne[25]	500 mg/d + COC	80% reduction in acne, seborrhoea and hair loss scores after 3mo	Several trials show complete resolution of acne with flutamide monotherapy
	Acne[27]	250 mg/d	59 vs 70% for CPA 2mg/EE 35μg and 77% for CPA 50mg/EE 25μg RS	All improvements significant vs baseline; no significant difference between treatments
	Androgenetic alopecia[25]	500 mg/d + COC	Cosmetically acceptable results in 6 of 7 women with diffuse alopecia	
Finasteride	Hirsutism[25]	5 mg/d	11–63% at 3–12mo	An azasteroid which competitively inhibits 5α-reductase, thus reducing androgenic effects by limiting 5α-dihydrotestosterone production Wide variations in efficacy. Slowest acting treatment but greater tolerability than other agents Possible feminising effect on male fetus: adequate contraception mandatory
		5 mg/d + COC	38–60%, vs 33–47% without COC	
		5 mg/d	20–45% vs 50–60% for CPA/EE combinations and 25–55% for flutamide	Comparative studies indicate less effective than CPA/EE or flutamide
		5 mg/d	11–15% vs 13–42% for spironolactone	Comparative studies indicate similarly or less effective than spironolactone
	Acne[27]	5 mg/d	36% vs 59% for flutamide, 70% for CPA 2mg/EE 35μg and 77% for CPA 50mg/EE 25μg RS	All improvements significant vs baseline but finasteride significantly less effective than other treatments

major focus will be on chlormadinone acetate and cyproterone acetate.

2. Development and Chemistry

Chlormadinone acetate and cyproterone acetate were originally developed from progesterone. Addition of a 17α-acetoxy group to progesterone prevented inactivation due to extensive first-pass metabolism after oral administration. Introduction of a chlorine atom and a double bond at position 6 of 17α-acetoxyprogesterone delayed further inactivation by inhibiting subsequent hydroxylation.[31] These modifications are shared by chlormadinone acetate and cyproterone acetate (figure 3).[31,32]

Dienogest is a hybrid progestogen which combines the features of progesterone and 19-nortestosterone-based progestogens such as norethisterone and levonorgestrel. It contains a 17α-cyanomethyl group instead of the 17α-ethinyl group typical of 19-nortestosterone derivatives (figure 3).[34]

3. Pharmacology and Pharmacodynamics

3.1 Progestogenic Activity

During *in vitro* receptor-binding affinity studies, chlormadinone acetate and cyproterone acetate exhibited high affinity for the progesterone receptor (about one-third higher than progesterone itself) [table III].[32] Dienogest was highly selective for this receptor, but its affinity compared with progesterone was <10%.[32,35,36]

In line with these findings, cyproterone acetate and chlormadinone acetate are highly potent progestogens in animals. Oral chlormadinone acetate is approximately 400 times as potent as 17α-acetoxyprogesterone, while cyproterone acetate is approximately 1200 times as potent.[18] In the McPhail assay, oral chlormadinone acetate induced dose-dependent endometrial proliferation in rabbits, being 2000 to 10 000 times as potent as oral progesterone and 10 times as potent as oral medroxyprogesterone acetate.[40]

Spironolactone	Hirsutism[25]	50–200 mg/d, titrated according to severity and tolerability. May be taken continuously or on days 4–22 of menstrual cycle	13–30% at 6mo; 42% at 9mo. Long-term treatment required	Aldosterone antagonist which also competes with androgens at the androgen receptor, and suppresses adrenal and gonadal androgen synthesis. Also inhibits 5α-reductase Now regarded as a second-line agent Adverse effects: initial diuretic effects may be troublesome; possible hyperkalaemia in renal insufficiency. Frequent menstrual disturbance at 100 mg/d, possibly related to weak progestogenic activity (may be alleviated by combination with a COC). Also produces breast enlargement, dizziness, mild hypotension, increased appetite, weight gain and transient nausea Possible feminising effect on male fetus: adequate contraception mandatory
		50mg bid + COC	30% vs 50% for flutamide 250mg bid + COC	Less effective than CPA/EE regimens and flutamide
		100 mg/d + COC	46% vs 52% for CPA 50mg/EE 35μg RS	
	Acne[25]	Start at 25–50 mg/d, titrate up to 100–200 mg/day, according to response and adverse effects	50% to almost 100%	Restricted prescribing in acne following association with breast cancer in rats Combination with a COC may be effective in resistant acne
	Androgenetic alopecia[25]	>150 mg/d		Variable results. Some small, open studies suggest benefit, others no response. Large trials suggest reduction in hair shedding but no promotion of hair regrowth

COC = combined oral contraceptive; **CPA** = cyproterone acetate; **bid** = twice a day; **EE** = ethinylestradiol; **PCOS** = polycysticìovary syndrome; **RS** = reverse sequential regimen.

Table II. Reverse sequential and continuous regimens containing cyproterone acetate (CPA) and ethinylestradiol (EE)

Regimen	Improvement rates in seborrhoea	Improvement rates in acne	Improvement rates in hirsutism	Improvement rates in androgenetic alopecia
Reverse sequential regimens				
EE 50 μg/d on d 5–26 of cycle, plus CPA 100 mg/day on d 5–14. Reduce CPA dose to 10–50 mg/d on d 5–14 for maintenance[18,26]	Almost 100% at 3–9mo	Almost 100% at 3–9mo	60–80% at 6–9mo	40–50% at 9–12mo
EE 35μg on d 1–21 of cycle, plus CPA 50 mg/d on d 1–10[25]			52% at 9mo	Vitamin B12 supplementation improves results: balding arrested, up to 30% show regrowth
CPA 100 mg/d on first 10 days of a COC cycle[25]			35%	
CPA 12.5 mg/d for first 10d of a biphasic or triphasic EE regimen (10–20 μg/d for 21d cycle)[25,28]			30–60% at 6–12mo	
Continuous treatment				
CPA 25 mg/d and EE 25 μg/d[25]			58% at 12mo	

COC = combined oral contraceptive.

Reviews of dienogest also report strong progestogenic activity in animals.[33,41]

3.2 Estrogenic and Antiestrogenic Activity

Antiandrogenic progestogens show no affinity for estrogen receptors *in vitro*,[35,36,38,42,43] suggesting absence of estrogenic effects at clinically relevant doses.

However, at subcutaneous or oral doses of 20–50μg, chlormadinone acetate exerted partial estrogenic (increased uterine weight) and strong antiestrogenic (antagonism of the uterotrophic effect of estrone) effects in immature female mice. The antiestrogenic effect was 10–20 times greater than that of progesterone or medroxyprogesterone acetate.[40]

Dienogest has also been reported to have slight estrogenic and antiestrogenic activity in animals.[33,41]

3.3 Antigonadotropic and Antiovulatory Effects

The progestogenic activity of chlormadinone acetate and cyproterone acetate produces some negative feedback on gonadotropin secretion, leading to inhibition of ovulation and reduced androgen biosynthesis.[18] For both progestogens, the dose required to prevent ovulation in 50% of rats (ED_{50}) was about 1 mg/day subcutaneously.[18] Similarly, chlormadinone acetate completely inhibited ovulation in rabbits with a threshold dose of 0.04mg subcutaneously, being 40 times as potent as progesterone and 8 times as potent as norethisterone.[44]

Testing in parabiotic pairs (a castrated male and an intact female) and immature male rats also indicated gonadotropic suppression by chlormadinone acetate. In the parabiotic pairs, ovarian weight in the female was reduced to a similar extent by chlormadinone acetate and progesterone. In the immature males, chlormadinone acetate was about three times as potent as progesterone and slightly more potent than medroxyprogesterone acetate in reducing seminal vesicle and prostate weight.[40]

Dienogest is reported to exert weak-to-moderate antigonadotropic effects in animals.[33,41]

3.4 Androgenic and Antiandrogenic Activity

Classically, the androgenic and antiandrogenic activities of progestogens are evaluated by *in vitro* receptor-binding affinity assays in animal tissues such as rat epididymis[39] and by their effects on androgen-dependent organs *in vivo*. More recently,

molecular biological assays of androgen receptor binding and activation, as well as skin 5α-reductase activity, have been developed. These allow more accurate prediction of agonistic and antagonistic effects.[24] All of these techniques have been applied to antiandrogenic progestogens.

3.5 *In Vitro* Receptor-Binding Assays in Animal Tissues

Antiandrogenic progestogens show relatively low affinity for the androgen receptor (3–21% of that of testosterone; table III). However, at high concentrations they compete effectively with androgens for receptors in target tissues to produce blockade.[18,32]

3.6 *In Vivo* Animal Models

The antiandrogenic actions of chlormadinone acetate and cyproterone acetate *in vivo* are summarised in table IV.

General antiandrogenic activity was investigated in male rats using the modified Hershberger assay. In this model, the weights of androgen-dependent organs are dramatically reduced by castration and restored by testosterone supplementation. Testosterone-induced weight gain in the prostate and seminal vesicles was dose-dependently inhibited by cyproterone acetate and was almost abolished at 1 mg/day.[18] Similarly, oral chlormadinone acetate 20 mg/kg decreased testosterone-induced weight gain in these organs by 50%.[37]

Cyproterone acetate also reduced prostate weight in intact rats, mice and dogs. Proliferative activity and secretion of prostatic marker substances were also inhibited in dogs.[18] Similarly, chlormadinone acetate produced macroscopic and ultrastructural signs of atrophy in rat accessory sex organs and inhibited their secretions.[46]

Besides its effects at androgen receptors, high doses of chlormadinone acetate may decrease androgen levels by suppressing biosynthesis and increasing hepatic metabolism. In rats, treatment with 20 or 100 mg/kg reduced testicular conversion of cholesterol to testosterone by 40–50% at 3–5 weeks. At 100 mg/kg, conversion of progesterone to testosterone was also inhibited. In the liver, testosterone hydroxylation was approximately halved, whereas metabolism by hepatic 5α-reductase was more than doubled.[47] Furthermore, chlormadinone acetate reduced the activity of enzyme systems involved in testicular and ovarian androgen biosynthesis in rats.[48,49]

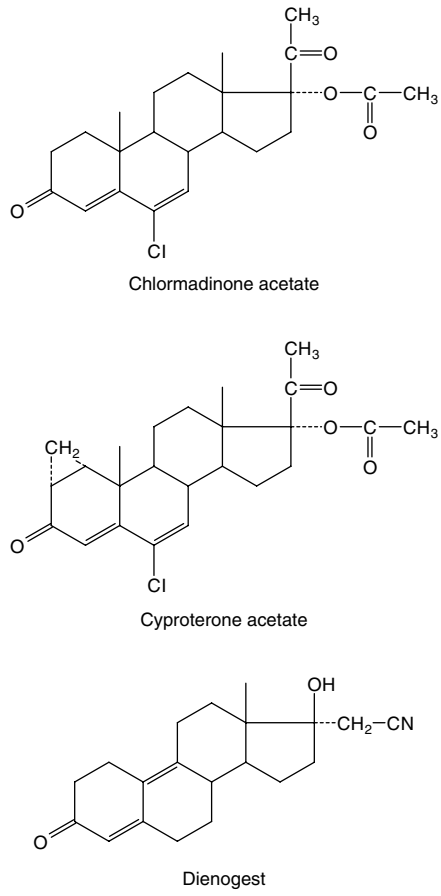

Fig. 3. Chemical structures of chlormadinone acetate, cyproterone acetate and dienogest.[32]

A further indication of general antiandrogenic activity was the feminisation of male rat fetuses by high doses of cyproterone acetate and chlormadinone acetate, instead of the virilisation of female rat fetuses observed with high doses of 19-nortestosterone derivatives.[18,43]

Table III. Binding affinities of chlormadinone acetate, cyproterone acetate and dienogest for steroid receptors[32,37-39]

Progestogen	Relative binding affinity (%)				
	progesterone receptor (promegeston = 100%)	estrogen receptor (estradiol = 100%)	androgen receptor (metribolone = 100%)	glucocorticoid receptor (dexamethasone = 100%)	mineralocorticoid receptor (aldosterone = 100%)
Progesterone	60	0	0	10	100
Chlormadinone acetate	87	0	3-10	8	0
Cyproterone acetate	90	0	6-21	6	8
Dienogest	5	0	10	1	0

Specific antiandrogenic effects on the skin were also investigated using various animal models. Modified Hershberger assays on the scent-marking glands of male mice (which have a similar structure and androgen response to human sebaceous glands) and on sebaceous glands in mouse dorsal skin showed that cyproterone acetate opposed testosterone-induced weight gain in a dose-dependent manner and provided histological evidence of inhibited sebocyte proliferation.[18,50] When administered to intact male mice, sebaceous gland volume and function were dramatically reduced.[50] Chlormadinone acetate had similar effects on the sebaceous glands of testosterone-supplemented female rats. At 2 mg/day, sebum production was decreased by about two-thirds and there was evidence of reduced mitotic activity in the glands.[51]

The antiandrogenic effects of dienogest in animals have been reviewed previously.[33,41] In a direct comparison, its antiandrogenic activity was similar to that of chlormadinone acetate and approximately one-third of that of cyproterone acetate.[52]

3.6.1 Effects at Other Steroid Receptors

Antiandrogenic progestogens show little or no affinity for other steroid receptors (table III) and have negligible or no glucocorticoid, mineralocorticoid or antimineralocorticoid effects at clinically relevant doses.[35,36,38,42,43]

4. Clinical Studies

4.1 Pharmacokinetics

4.1.1 Absorption and Plasma Profile

After single administration at the doses used in COCs, all three antiandrogenic progestogens undergo rapid and almost complete absorption from tablets, reaching peak plasma concentrations within 1–4 hours (table V).

During multiple dose administration, chlormadinone acetate exhibits linear, time-dependent pharmacokinetics with little accumulation in the plasma. Multiple dose administration has little impact on peak plasma concentrations, although the terminal elimination half-life ($t_{½\beta}$) is increased compared with single-dose administration (table V). Nevertheless, steady-state plasma concentrations are achieved within 8–15 days.[53] Linear, dose-related kinetics and minimal plasma accumulation have also been observed with multiple doses of dienogest. Steady-state plasma concentrations are achieved in about 6 days, and after 21 days, pharmacokinetic parameters are similar to those on day 1.[35,65]

4.1.2 Plasma Protein Binding and Effects on the Protein Binding of Other Hormones

Antiandrogenic progestogens are highly bound to plasma albumin. Chlormadinone acetate is over 96% bound,[53] whereas about 10% of a dose of dienogest remains unbound.[57]

Antiandrogenic progestogens have no affinity for SHBG or cortisol-binding globulin; therefore,

Table IV. Summary of the antiandrogenic effects of chlormadinone acetate (CMA), cyproterone acetate (CPA) and dienogest in intact animals

Animal model	Progestogen	Dose	Results
General antiandrogenic effects			
Modified Hershberger assay in castrated male rats	CPA	0.03–1 mg/animal/d SC	Dose-dependent inhibition of testosterone-induced weight gain in prostate and seminal vesicles. Almost total inhibition at 1 mg/animal/day[18]
	CMA	20 mg/kg PO	50% reduction in testosterone-induced weight gain in the prostate and seminal vesicles[37]
	Dienogest	2.5–62.5mg over 7d SC	Antiandrogenic activity approximately 40% of that of CPA, but greater than CMA[33,45]
Hershberger assay in castrated immature male rats	Dienogest	≤100 mg/kg/d PO, or 10 mg/d SC or 62.5mg over 7d SC	No significant increase in ventral prostate weight, indicating lack of androgenic activity[33]
Intact male animals	CPA	600 mg/wk (dogs)	Prostate weight reduced in rats, mice and dogs
			Proliferative activity and secretion of prostatic markers such as acid phosphatase and aminopeptidase also inhibited in dogs[18]
	CMA	15 mg/d SC for 15d	Involution of seminal vesicles, prostate and coagulation glands, and inhibition of their secretions. Intracellular changes including cell shrinkage, changes in nuclear morphology, loss of cytoplasm, reductions in organelles (especially Golgi areas and rough endoplasmic reticulum), and reduction in size and number of secretory granules[46]
Effects on androgen biosynthesis and hepatic metabolism	CMA	100 mg/kg for 1, 2, 3 and 5 wks	Both doses: testicular conversion of cholesterol to testosterone reduced by 40–50% at 4 wks
			100 mg/kg: conversion of progesterone to testosterone inhibited by 16% at 4 wks
		20 mg/kg for 4 and 6 wks	Rate of testosterone metabolism by hepatic 5α-reductase increased 2–3.5-fold; 2α, 6β and 16α hydroxylation reduced by 50%[47]
	CMA	5mg/animal/d SC for 15d	Reduced activity of 3β-hydroxysteroid dehydrogenase in castrated male rats[48]
	CMA	49 nmol/g tissue	Reduced ovarian steroid production due to inhibition of the 3β-hydroxysteroid dehydrogenase/δ-5-isomerase system[49]
Fetal studies	CPA	Mother received 10 mg/d SC on d 17–20 of gestation	Feminisation of male rat fetuses[18]
	CMA	'High dose'	Feminisation of male rat fetuses[18]
Antiandrogenic effects on the skin			
Modified Hershberger assay in castrated male mice	CPA	0.03–1 mg/animal/d	Dose-dependent opposition of testosterone-induced weight gain in scent-marking glands. Effects of testosterone almost abolished at 1mg/animal/day[18]
	CPA	1 mg/animal on alternate days for 4 wks	5-fold reduction in testosterone-induced weight gain in sebaceous glands compared with controls receiving testosterone only
			Histological evidence of inhibited sebocyte proliferation[50]
Intact male mice	CPA	1 mg/animal on alternate days for 4 wks	Sebaceous gland volume reduced to 19% of that in controls
			Reduction in sebaceous gland function[50]
Spayed female rats supplemented with testosterone 0.2 mg/day via implant	CMA	2 mg/d	Compared with controls receiving no CMA:
			after initial washing, testosterone-induced increase in sebum content of fur suppressed by 65%
			24% reduction in mitotic activity in sebaceous glands
			42% reduction in weight of scent-marking glands

PO = orally; **SC** = subcutaneously.

Table V. Pharmacokinetic parameters for chlormadinone acetate, cyproterone acetate and dienogest

Parameter	Chlormadinone acetate	Cyproterone acetate	Dienogest
C_{max} (μg/L):			
single dose	1.60 ± 0.46 [53]	7.2 ± 1.4[54]	0.054[35]
multiple dose	1.6–2[53]	NA	0.064[35]
Steady-state blood level (μg/L)	0.4–0.5[53]	NA	NA
t_{max} (h)	1.6 ± 0.4[53]	3.7 ± 0.8[54]a 1.8 ± 1.1[51]b	1–2[41]
Absolute bioavailability after oral administration (%)	100[38,55]	86[54]a 100[56]b	90[35]
Plasma protein binding (%):			
albumin	96.6–99.4a	NA	90[35,57]
SHBG	Nil[32]	Nil[32]	Nil[32]
Free in serum (%)	1–3	NA	10[35,36]
$t_{½}$ elimination (h):			
single dose	25.3 ± 9.8	NA	6.5–12[35]
multiple dose	36–39	30–40[32]	9[35]
Distribution	Fat, myometrium, cervix and fallopian tubes[58]	Biphasic distribution/redistribution between fat and plasma[54]	Limited
Vd (L)	NA	1300 ± 540[54]	40[35]
Metabolism	Extensive. 3α- and 3β-hydroxy metabolites possibly active[32]	Extensive. 15β-hydroxy metabolite active[54]	Yes, mainly to inactive 11β-hydroxy and aromatised metabolites[35,59]
Excretion (%)	Urine 45 ± 4 Faeces 41 ± 9 in 10d[61]	Urine 30.4 ± 7.3 Faeces 57.8 ± 6.9 in 10d[54]	Urine : faecal ratio 3.2 : 1[60]
Reabsorption	Yes (enterohepatic)[62-64]	NA	Yes (renal)[35,59,60]

a Based on gelatine capsules.

b Based on coated tablets.

C_{max} = peak plasma concentration; **NA** = not available; **SHBG** = sex hormone-binding globulin; **t_{max}** = time taken to reach C_{max}; **$t_{½}$** = elimination half-life; **Vd** = volume of distribution.

they do not displace androgens or cortisol from their carrier proteins.[32,35,36] Furthermore, although increased thyroxine-binding globulin and total thyroxine levels have been observed during chlormadinone acetate administration, free thyroxine and thyroid-stimulating hormone levels remained unchanged, indicating no alteration in thyroxine activity.[66]

In contrast, ethinylestradiol increases the hepatic synthesis of SHBG, leading to reduced free androgen levels through increased binding.[67,68] SHBG synthesis is decreased by progestogens with androgenic activity.[69] Importantly, unlike 19-nortestosterone derivatives (and to a lesser extent third-generation progestogens), chlormadinone acetate and cyproterone acetate do not antagonise the ethinylestradiol-induced increase in SHBG production.[70,71]

4.1.3 Distribution

Chlormadinone acetate and cyproterone acetate are highly lipophilic and are taken up by body fat.[54,58] Chlormadinone acetate is also stored in some reproductive tissues (table V).[58] This widespread distribution is reflected in the very large volume of distribution for cyproterone acetate (1300L).[54] In contrast, dienogest has a low volume of distribution (about 40L after a 1mg dose) indicating limited tissue uptake.[35]

Cyproterone acetate undergoes biphasic distribution, with half-lives of about 3 hours for the first

phase and 2 days for the second. These reflect initial rapid movement into fat and slower return into the plasma, with subsequent equilibration between plasma concentrations of the parent drug, metabolism and excretion.[54]

Storage in the body fat slows elimination, thus the biological half-lives of chlormadinone acetate and cyproterone acetate are long.[32,54] However, clinically relevant accumulation of chlormadinone acetate (which may be manifested by delayed withdrawal bleeding) is only apparent in some women taking high doses (≥10 mg/day) to treat androgen-related conditions.[32] Similarly, delayed withdrawal bleeding has been observed in obese women taking cyproterone acetate.[72]

4.1.4 Metabolism, Elimination and Reabsorption

All three antiandrogenic progestogens undergo extensive hepatic metabolism before excretion in the urine and faeces.

The main metabolites of chlormadinone acetate in human plasma are its 2α-, 3α- and 3β-hydroxy derivatives, although a wide variety of other reduced, hydroxylated and deacetylated metabolites are also formed.[32] There is some controversy over the activity of the 3α- and 3β-hydroxy metabolites. Animal studies have indicated them to be antiandrogenic,[37] while others suggest that this activity might result from back-transformation into chlormadinone acetate since an intact 3-keto group appears to be essential for androgen receptor binding.[32] Other chlormadinone acetate metabolites are inactive.[37,73]

Only about 5% of an oral dose of cyproterone acetate is excreted intact, the remainder being metabolised mostly to the active 15β-hydroxy derivative.[26,54]

Because of their extensive fat distribution, chlormadinone acetate and cyproterone acetate are excreted slowly, with $t_{½β}$ values of around 30–40 hours.[32] Faecal excretion predominates with cyproterone acetate, whereas chlormadinone acetate is excreted approximately equally in the urine and faeces (table V). In particular, glucuronide-conjugated forms of chlormadinone acetate and its 3β-hydroxy metabolite are excreted in bile, and undergo enterohepatic recirculation after hydrolytic cleavage of the glucuronide moiety.[62-64] Some investigators believe that this recycling, followed by back-transformation, may contribute towards antiandrogenic efficacy.[32]

Dienogest has a different elimination pattern. Because most of the dose remains in the blood, it is rapidly metabolised and has a short $t_{½β}$ compared with other progestogens (table V).[35] Excretion is principally via the urine[60] and some renal reabsorption may occur.[35,59,60]

4.2 Effects on the Human Female Reproductive Tract and Hormones

4.2.1 Endometrium

Progestogens have both progestogenic and antiestrogenic effects on the endometrium.

Classical progestogenic effects only become apparent after priming the endometrium with estrogen to induce proliferation and the development of progesterone receptors. Progestogens then dose-dependently promote conversion from a proliferative to a secretory state. In the Kaufmann assay, the total oral doses/cycle needed to achieve full secretory transformation were about 20mg for cyproterone acetate and 20–30mg for chlormadinone acetate, translating into daily doses of about 2mg.[32,74] There is conflicting evidence for the potency of dienogest in this assay; one study reported it to be almost four times more potent than chlormadinone acetate,[75] while another found it to be only one-third as potent.[76]

A further progestogenic function is to prevent endometrial breakdown, which helps in maintaining good cycle control with COCs. Progestogen withdrawal at the end of the pill-taking cycle allows endometrial shedding, inducing a regular bleeding pattern. With chlormadinone acetate, withdrawal bleeding normally occurs 2–5 days after the last dose.[32]

Administration of progestogens without estrogen from the early follicular phase of the cycle onwards allows their antiestrogenic action to suppress the usual cyclical endometrial changes,[77-80] producing an environment non-conducive to the

implantation of a fertilised ovum or to subsequent development of a normal placenta.[80,81] With chlormadinone acetate, the antiestrogenic effect on the endometrium emerges at doses lower than those needed to exert a progestogenic effect or inhibit ovulation (around 0.3–0.4 mg/day), is established at doses of 0.5–4 mg/day, and contributes to the efficacy of progestogen-only oral contraception.[77,78,82,83] Antiestrogenic effects are reflected by dose-related suppression of endometrial glandular secretion and tortuosity. In an assay based on these changes, chlormadinone acetate was one-third as potent as norethindrone, which has strong antiestrogenic activity in animals.[77] These characteristics were also marked in 28–37% of endometrial specimens taken during the latter half of the cycle from women receiving chlormadinone acetate 0.5 mg/day during contraceptive activity trials.[83-85] In specimens taken with less regard to timing, loss of correlation between the endometrial appearance and the phase of the cycle was often encountered. The changes observed included a prolonged post-secretory stage, premature secretion, general endometrial retardation and normal glands with reduced secretion.[79,80] In addition to these histological effects, chlormadinone acetate has been found to reduce the effects of estrogen by inhibiting estrogen receptor synthesis.[86,87]

4.2.2 Cervical Mucus

The antiestrogenic effects of progestogens also reduce the secretion, alter the composition and increase the viscosity of cervical mucus, thus hindering or preventing sperm penetration.[88] With chlormadinone acetate, these effects become maximal at 0.3–0.5 mg/day[58,89-91] and play a major role in its efficacy in both combined and low-dose progestogen-only oral contraceptives. Indeed, during studies with chlormadinone acetate 0.5 mg/day, 80–100% of cervical mucus samples showed characteristic changes and sperm penetration was impossible or poor in 67–85%.[78,81,83,91,92]

4.2.3 Fallopian Tubes

At 0.5 mg/day, chlormadinone acetate significantly decreases Fallopian tubular motility.[93] This may contribute to the efficacy of progestogen-only contraception by slowing ovum transport through the tubes.

4.2.4 Vaginal Epithelium

Progestogen-only contraception with chlormadinone acetate 0.5 mg/day has little effect on the vaginal epithelium apart from some clumping of the superficial cells. At 2 mg/day, however, the antiestrogenic actions of chlormadinone acetate induce considerable reductions in the karyopyknotic and acidophil indices. This effect is dose-dependently modulated by the estrogen component in COCs.[32]

4.2.5 Hypothalamic/Pituitary/Ovarian Axis, Follicular Maturation and Ovulation

When administered without estrogen, the daily doses required to ensure inhibition of ovulation are 1.5–2mg for chlormadinone acetate,[32,42,43] and 1mg for cyproterone acetate[18] and dienogest.[41,94]

The low daily dose of chlormadinone acetate used in progestogen-only contraception (0.5mg) inhibits ovulation in only 15–40% of women.[84,90,95] However, functioning of the corpus luteum is usually impaired even at doses as low as 0.3 mg/day, thus reducing endogenous progesterone levels and providing some contraceptive protection.[84,96,97]

At its ovulation-inhibiting dose, chlormadinone acetate moderately suppresses endogenous gonadotropin secretion, thus preventing follicular growth and maturation. It also prevents or disrupts the preovulatory luteinising hormone (LH) peak.[32,42,43] Dienogest appears to inhibit ovulation mainly by a peripheral effect, decreasing preovulatory ovarian estradiol secretion.[75,98] This prevents the normal positive feedback to the pituitary, resulting in delay or prevention of the follicle-stimulating hormone (FSH) and LH peaks.[99] However, dienogest has weak antigonadotropic activity even at 2 mg/day.[41,100] The balance between peripheral actions and central effects on gonadotropin secretion is reflected by the Kaufmann index, the ratio of the dose needed to prevent ovulation to that required for secretory transformation of the endometrium. This is 7 for chlormadinone acetate, 5 for cyproterone acetate,

16 for dienogest, 1 for 19-nortestosterone derivatives and 3 for third-generation progestogens.[101]

Estrogens act synergistically with progestogens, producing a negative feedback effect on FSH secretion that interferes with follicular development and maturation. Thus, when antiandrogenic progestogens are administered with ethinylestradiol in COCs, gonadotropin and ovarian hormone levels are profoundly suppressed throughout the cycle[102,103] and the follicles fail to either grow or rupture.[103] Similar findings have been made with cyproterone acetate- and dienogest-containing COCs in which ethinylestradiol has been wholly or partly replaced with natural estradiol.[104-106]

The effects of ethinylestradiol and progestogens on gonadotropin secretion have been exploited in a novel approach to contraception aimed at triggering a premature LH surge, thereby causing release of an immature oocyte or inhibiting further follicular maturation. A four-dose sequential regimen containing varying amounts of ethinylestradiol and chlormadinone acetate, started during the mid-follicular phase of the cycle, successfully induced an early LH surge. Estradiol was suppressed to below early follicular phase levels and progesterone concentrations remained low. However, unacceptable shortening of the menstrual cycle indicated a need for optimisation of the steroid doses.[107]

4.2.6 Contraceptive Efficacy

COCs containing antiandrogenic progestogens have shown very low failure rates during clinical trials and postmarketing surveillance studies (table VI). Standardising these rates using the following Pearl Index allows comparisons of practical efficacy across studies.

$$\frac{\text{Total number of pregnancies observed}}{\text{Total number of cycles of exposure}} \times 12 \times 100$$

Calculation after excluding pregnancies attributable to 'user failure' (missed pills or loss of efficacy caused by gastrointestinal upsets or drug interactions) gives the adjusted Pearl Index, a closer estimate of theoretical efficacy. COCs normally have a Pearl Index of 0.1–0.9,[116] with values below 0.5 indicating high efficacy.[117] Thus, combinations of ethinylestradiol plus chlormadinone acetate, cyproterone acetate or dienogest offer highly effective contraception (table VI), although it should be noted that cyproterone acetate/ethinylestradiol combinations are not licensed as oral contraceptives in many countries. Of particular interest are the results of postmarketing surveillance studies, which reflect COC usage under normal conditions by very large numbers of women. In such studies, very high efficacy was indicated by gross and adjusted Pearl Indices of 0.344 and 0.076, respectively, for chlormadinone acetate 2mg/ethinylestradiol 30μg,[108] and 0.14 and 0.09, respectively, for dienogest 2mg/ethinylestradiol 30μg.[114] Investigational formulations containing natural estradiol also appear promising (table VI), although there is as yet only limited experience with their use. In contrast, progestogen-only oral contraception with chlormadinone acetate 0.5 mg/day has far more variable results (table VI), reflecting the lack of reliable inhibition of ovulation.[84,90,95]

4.3 Clinical Benefits of Antiandrogenic Effects on Skin and Hair

Antiandrogenic progestogens and ethinylestradiol play complementary roles in reducing androgen activity. Antiandrogenic progestogens act mainly by blocking androgen receptors[2,18,32,45] but also reduce the activity of skin 5α-reductase, thus reducing 5α-dihydrotestosterone levels.[18,24,118,119] Ethinylestradiol increases SHBG levels (thereby reducing plasma free androgen levels)[67,68] and appears to have a direct effect on sebum production.[120] Ethinylestradiol, cyproterone acetate and chlormadinone acetate also suppress gonadotropin secretion, hence inhibiting androgen synthesis in the ovaries and adrenal glands.[18,121-123] Thus, combinations of these agents are a logical treatment choice for women with androgen-related skin and hair conditions, and for contraception in such women.

The high-dose reverse sequential cyproterone acetate/ethinylestradiol regimen was developed

Table VI. Contraceptive efficacy of products containing antiandrogenic progestogens. Pearl indices have been calculated where papers do not state values

Product	Number of women enrolled	Failure rate (pregnancies/cycles of exposure)		Pearl Index	
		overall	excluding user failure	gross[a]	adjusted[b]
CMA 2mg/EE 30μg[108]	21 820	36/125 634	8/125 634	0.344	0.076
CMA 2mg/EE 30μg[109]	1655	12/22 337	5/22 337	0.642	0.269
Biphasic CMA/EE 50μg:[110]					
study 1	719	2/11 464	1/11 464	0.21	0.1
study 2	3174	13/33 258	3/33 258	0.47	0.1
total	3893	15/44 722	4/44 722	0.40	0.1
CPA 2mg/EE 50μg[18]	1354	0/12 800	0/12 800	0	0
CPA 2mg/EE 35μg[111]	136	0/1361	0/1361	0	0
CPA 2mg/EE 50μg	33	0/396	0/396	0	0
CPA 2mg/EE 35μg[112]	40	0/480	0/480	0	0
Biphasic CPA/E2V[105]	288	1/2800	0/2800	0.43	0
DNG 2mg/EE 30μg[113]	2290	16/28 183	5/28 183	0.68	0.21
DNG 2mg/EE 30μg[114]	16 267	11/92 146	7/92 146	0.14	0.09
DNG 2mg/EE 10μg/E2V 1mg or DNG 2mg/EE 10μg/E2V 2mg[106]	135	0/400	0/400	0	0
CMA 0.5 mg/day[83]	945	14/8091	1/8091	2.08	0.15
CMA 0.5 mg/day[92]	40	0/189	0/189	0	0
CMA 0.5 mg/day[79]	46	4/406	3/406	11.82	8.87
CMA 0.5 mg/day[84]	124	5/1850	3/1850	3.24	1.95
CMA 0.5 mg/day[115]	194	3/2021	1/2021	1.78	0.59
CMA 0.5 mg/day[85]	200	6/1512	0/1512	4.76	0

a Calculated from overall pregnancy rate.

b Calculated after excluding user failure.

CMA = chlormadinone acetate; **CPA** = cyproterone acetate; **DNG** = dienogest; **EE** = ethinylestradiol; **E2V** = estradiol valerate.

empirically during the 1960s, and proved highly effective in treating seborrhoea and acne. Response rates for hirsutism and androgenetic alopecia were, however, less pronounced, more variable and took longer to emerge (see table II and section 1). This variability is also apparent in studies using the same or lower cyproterone acetate doses with smaller ethinylestradiol doses; indeed, improvement rates as low as 30% have been observed with these regimens (table II). The lower and slower response of hirsutism and alopecia to antiandrogen treatment may reflect the natural length of the hair growth cycle, and the fact that these conditions may have multifactorial aetiologies involving genetic, metabolic, environmental and nutritional factors as well as androgen production.[12,13,25]

A product containing cyproterone acetate 2mg and ethinylestradiol 50μg has been used to treat androgen-related disorders since the late 1970s, achieving resolution or improvement in 75–95% of women with moderate/severe seborrhoea and acne. Response rates in moderate hirsutism were about 50–70%, depending on the body site.[18] However, a direct comparison with the high-dose sequential regimen revealed that, although cyproterone acetate 2mg/ethinylestradiol 50μg produced improvement in 50% of patients with mild symptoms, the reverse sequential regimen was superior when all grades of hirsutism were considered, achieving improvement in 70% of patients at 1 year. This difference was thought to reflect the ability of the higher cyproterone acetate dose to compete more effectively with androgens at the androgen receptor.[26] As a result of these studies, cyproterone acetate 2mg/ethinylestradiol 50μg became the recommended treatment for seborrhoea, acne and mild hirsutism (to avoid adverse effects such as fatigue and decreased libido with high cyproterone

acetate doses), while the high-dose sequential regimen remained the standard initial therapy for women with more severe hirsutism.[26] Although cyproterone acetate 2mg/ethinylestradiol 50μg was found to be more effective than the high-dose sequential regimen in androgenetic alopecia during development,[18,26] later studies observed variable results.[25]

Subsequently, a product with a lower ethinylestradiol dose (35μg instead of 50μg) was developed. Direct comparisons have shown that this reduction did not impair contraceptive efficacy.[102] After 6–12 cycles, reductions in total and free testosterone and improvements in seborrhoea, acne, hirsutism and alopecia were similar with both estrogen dose-levels.[112] Similar and significant improvements in comedone, macule and papule counts were also seen by cycle 6 in women with moderate/severe facial acne; by cycle 12, two-thirds of participants had no or only a few scattered lesions.[112] Subsequent studies have generally confirmed these good responses to cyproterone acetate 2mg/ethinylestradiol 35μg.[111,124] However, a recent small study (n = 12 in each treatment group) recorded lower response rates to cyproterone acetate 2mg/ethinylestradiol 35μg (70%) and a reverse sequential regimen containing cyproterone acetate 50mg and ethinylestradiol 25μg (71%) in acne. Nevertheless, these responses were greater than that observed with flutamide (59%) and significantly superior to that obtained with finasteride (36%).[27]

Combined cyproterone acetate/ethinylestradiol products are now widely regarded as the benchmark for the treatment of acne. When used as the standard comparator for COCs containing the third-generation progestogen, desogestrel, cyproterone acetate 2mg/ethinylestradiol 35 or 50μg proved at least as effective in improving seborrhoea and acne, as well as in reducing plasma testosterone concentrations and increasing SHBG levels.[122,125,126] Furthermore, cyproterone acetate 2mg/ethinylestradiol 35μg was significantly more effective in treating acne than levonorgestrel 150μg/ethinylestradiol 30μg. After four cycles, the incidence of lesions decreased by 70% compared with 35%.[127]

Antiandrogenic progestogen-containing products that were originally designed as COCs have also been found useful in the treatment of androgen-related skin and hair conditions. With these preparations, the progestogen content is based on the dose required to inhibit ovulation; thus, potential progestogen dose-related effects cannot be assessed.

Chlormadinone acetate-containing COCs have proved similarly effective as cyproterone acetate/ethinylestradiol in women with androgen-related skin and hair conditions. A COC containing ethinylestradiol 50μg and biphasic chlormadinone acetate produced improvement or cure in 97–98% of women with mild/moderate or severe acne, and 94% of those with seborrhoea. Unusually high response rates were also observed for alopecia (88%) and hirsutism (74%).[110]

A monophasic COC containing chlormadinone acetate 2mg/ethinylestradiol 30μg has also achieved good results in acne. During a contraceptive activity trial,[109] 326 of the 1655 participants had pre-existing acne and took the preparation for at least 13 cycles. Of these, 209 (64%) showed a decrease in the number of lesions or a shift to a less severe form of acne, while facial lesions disappeared completely in 175 women (54%). Furthermore, a direct comparison with levonorgestrel 150 μg/ethinylestradiol 30μg showed chlormadinone acetate 2mg/ethinylestradiol 30μg to be superior in treating acne and to carry a lower risk of worsening the condition.[128] During this study, significantly more women taking chlormadinone acetate/ethinylestradiol experienced a 50% or greater reduction in papules/pustules per half of the face (59 vs 46%, $p = 0.02$). Chlormadinone acetate/ethinylestradiol also produced higher resolution rates and had a faster onset of action. By cycle 7, acne had disappeared completely in 10% of women taking chlormadinone acetate/ethinylestradiol compared with 5% of those taking levonorgestrel/ethinylestradiol; by cycle 12, corresponding rates were 17 and 4%, respectively.[128] Interestingly, the re-

sponse was particularly pronounced in women who had switched directly from another COC (about 40% of each treatment group) and therefore had an estrogenic influence already at work. Among this subgroup, response rates were significantly higher with chlormadinone acetate/ethinylestradiol than with levonorgestrel/ethinylestradiol (55 vs 33%, p = 0.014), indicating that a switch to an antiandrogenic progestogen is helpful to women whose acne persists on other COCs. Chlormadinone acetate/ethinylestradiol was also superior to levonorgestrel/ethinylestradiol in treating papular/pustular or comedonal acne at other body sites (table VII), while resolution rates for seborrhoea (80 vs 76%), alopecia (86 vs 91%) and hirsutism (36% each) were similar. The superiority of chlormadinone acetate/ethinylestradiol over levonorgestrel/ethinylestradiol for women with pre-existing acne was also reflected by lower deterioration rates. Over 12 cycles, worsening of papulopustular acne of the face occurred in 11% of the levonorgestrel/ethinylestradiol group but in none of the chlormadinone acetate/ethinylestradiol group. Worsening was also more common with levonorgestrel/ethinylestradiol than with chlormadinone acetate/ethinylestradiol for papulopustular acne of the chest (13.5 vs 0%) and back (6 vs 0%), and for comedonal acne of the face (9 vs 3%), chest (15 vs 3%) and back (11.5 vs 0%).

The antiandrogenic activity of dienogest 2mg/ethinylestradiol 30μg has recently been reviewed.[45] During a direct comparison against cyproterone acetate 2mg/ethinylestradiol 35μg in women with androgen-related conditions, there were no significant differences between the two products as assessed by reductions in androgen levels, increases in SHBG, and improvements in subjective and objective evaluations of acne. Furthermore, during a large postmarketing trial of the contraceptive efficacy and tolerability of dienogest 2mg/ethinylestradiol 30μg,[114] over two-thirds of the 16 087 evaluable participants spontaneously reported improvements in skin and hair condition.

Thus, COCs containing chlormadinone acetate or dienogest appear to be equally as effective as the established combination of cyproterone acetate and ethinylestradiol in treating pre-existing androgen-related skin and hair disorders. In this respect, chlormadinone acetate 2mg/ethinylestradiol 30μg has been shown to be superior to levonorgestrel 150μg/ethinylestradiol 30μg in treating acne (particularly in women whose symptoms have persisted during the use of other COCs) and to carry a lower risk of worsening the condition. This makes it a logical alternative for contraception in

Table VII. Outcome of acne treatment with chlormadinone acetate 2mg/ethinylestradiol 30μg (CMA/EE) and levonorgestrel 150μg/ethinylestradiol 30μg (LNG/EE)[128]

Condition	Agent	Treatment outcome (% of participants)		
		improved/cured	no change	worse
Papular/pustular acne on the face	CMA/EE	98.7[a]	1.3	0
	LNG/EE	87.1	1.4	11.4
Comedonal acne on the face	CMA/EE	88.9	8.3	2.8
	LNG/EE	77.3	13.6	9.1
Papular/pustular acne on the chest	CMA/EE	95.6	4.4	0
	LNG/EE	81.1	5.4	13.5
Comedonal acne on the chest	CMA/EE	91.9	5.4	2.7
	LNG/EE	73.1	11.5	15.4
Papular/pustular acne on the back	CMA/EE	97.7	2.3	0
	LNG/EE	87.9	6.0	6.1
Comedonal acne on the back	CMA/EE	97.3	2.7	0
	LNG/EE	76.9	11.6	11.5

a $p < 0.001$ vs LNG/EE.

women who experience acne while using COCs containing progestogens with androgenic activity. Furthermore, COCs containing antiandrogenic progestogens may provide a cosmetic improvement in skin or hair greasiness in women without frank androgen-related symptoms.

5. Safety Profile

Androgens have wide-ranging effects on the cardiovascular system, glucose and lipid metabolism, and liver function.[1,2] Progestogens with androgenic activity have been linked with a number of undesirable effects on these systems. These safety issues have also been taken into account with COCs containing antiandrogenic progestogens.

5.1 Cardiovascular System

Androgens increase the hepatic synthesis of low-density lipoprotein (LDL) and decrease the production of very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL), thus reducing the HDL/LDL ratio. This lipoprotein profile is linked with an increased risk of atherogenic cardiovascular disease,[129,130] and may explain the higher incidence of arteriosclerosis and myocardial infarction in men and in women with hyperandrogenic conditions.[2] Progestogens with partial androgenic activity have a similar unfavourable effect on the lipid and lipoprotein profile.[131-133]

Ethinylestradiol affects the hepatic metabolism of clotting and fibrinolytic factors, angiotensinogen, lipoproteins and lipids.[134] It has a beneficial influence on the lipid and lipoprotein profile, increasing HDL and reducing LDL (and hence improving the HDL/LDL ratio). However, its impact on the metabolism of the other listed factors is considered to be the main cause of hypertension, myocardial infarction, venous thromboembolism and strokes in COC users.[135-140] These effects are dose-related, and progressive reductions in the ethinylestradiol content of COCs have led to a decrease in their incidence.[29,30]

Studies of COCs containing cyproterone acetate, chlormadinone acetate or dienogest have found no clinically relevant changes in lipid and lipoprotein levels, although all noted increases in triglycerides (an estrogenic effect). Increases in HDL cholesterol, HDL subfractions 2 and 3, and the HDL structural proteins (apolipoproteins AI and AII), coupled with reduced or unchanged LDL, also usually resulted in an increased HDL/LDL ratio.[109,112,113,141] The overall picture is therefore of a beneficial, estrogen-dominated lipid and lipoprotein profile.

Myocardial infarctions in young users of COCs appear to have an arteriothrombotic rather than an atherogenic pathogenesis. Therefore, the activity of the coagulatory, anticoagulatory and fibrinolytic systems is of prime importance.[142] Studies of chlormadinone acetate 2mg/ethinylestradiol 30μg[143] and dienogest 2mg/ethinylestradiol 30μg[113,144] have shown that increased procoagulatory activity is balanced by enhanced fibrinolytic activity, with variable changes in anticoagulatory activity. These changes are unlikely to increase the thrombogenic risk unless a latent prethrombotic state or an endothelial abnormality is already present.

As regards venous thrombogenesis, a recent retrospective case-control study calculated that, after adjusting for body mass index, smoking and any history of androgen-related conditions and asthma, women taking cyproterone acetate-containing COCs were almost 4 times more likely to develop an idiopathic venous thromboembolism than those taking levonorgestrel-containing COCs (odds ratio 3.9; 95% CI 1.1–13.4). This risk was not affected by exposure duration.[145] Subsequent correspondence pointed out that use of high-dose cyproterone acetate (50 mg/day for 20 days per cycle) without estrogen produced a lower-than-expected incidence of venous thromboembolism in women with known predisposing factors, including systemic lupus erythematosus. The authors considered that the estrogen component was most probably responsible for the apparent increase in the risk of venous thromboembolism with

cyproterone acetate-containing COCs.[146] In contrast, only occasional thromboembolic events have been observed during published clinical trials of dienogest 2mg/ethinylestradiol 30μg.[113] Similarly, a global safety analysis of the chlormadinone acetate 2mg/ethinylestradiol 30μg clinical development programme, encompassing 24 205 cycles in 1855 women, identified venous thromboembolic events in five women. Four of these had predisposing factors.[53] Low incidence rates have also been reported in large postmarketing surveillance studies. With dienogest 2mg/ethinylestradiol 30μg, two cases of thrombosis in the leg and one suspected pulmonary embolism were observed during 92 146 treatment cycles in 16 087 women,[114] while with chlormadinone acetate 2mg/ethinylestradiol 30μg, one thrombosis in a superficial leg vein and one pulmonary embolism were encountered during 125 634 cycles in 21 820 women.[108] In the latter study, the overall incidence of venous thrombosis was 2.07 per 10 000 woman-years (95% CI 0.25–7.48), which is comparable to rates reported for second generation COCs in major epidemiological studies.[147-151]

No significant trends towards increased blood pressure or heart rate have been observed with COCs containing cyproterone acetate,[112] chlormadinone acetate[109] or dienogest.[113]

A new approach to reducing the cardiovascular risks of COCs is to replace ethinylestradiol with natural estradiol, thus avoiding stimulation of clotting factor and lipid metabolism by the ethinyl group. Cyproterone acetate- and dienogest-containing products in which ethinylestradiol is wholly or partially replaced by estradiol valerate are currently under development, and initial studies indicate no unfavourable effects on lipids, lipoproteins and blood pressure.[104-106]

5.2 Metabolic Effects

Cyproterone acetate, chlormadinone acetate and dienogest have very low affinity for glucocorticoid receptors. Consequently, chlormadinone acetate only shows glucocorticoid activity at doses much greater than those used in COCs.[32]

Studies of COCs containing antiandrogenic progestogens have revealed no clinically important effects on carbohydrate metabolism,[33,141,152,153] and have indicated that glucose intolerance is unlikely unless a predisposition is present.[113,154]

Cyproterone acetate, chlormadinone acetate and dienogest have no antimineralocorticoid activity.[32,35,36]

5.3 Effects on the Liver

5.3.1 Liver Function Tests

No clinically important alterations in liver function indicators have been observed with either dienogest 2 mg/day used as monotherapy for endometriosis,[155] or with COCs containing cyproterone acetate[112,125] or chlormadinone acetate.[109] In a postmarketing study of dienogest 2mg/ethinylestradiol 30μg, increased liver enzymes and hyperbilirubinaemia were reported in only two of the 16 000 participants.[114]

5.3.2 Potential for Liver Tumour Formation

During the early 1970s, concern was raised that COCs might be associated with the development of benign liver tumours.[156] Since then, other cases of focal nodular hyperplasia and hepatocellular adenoma, as well as a much smaller number of malignant hepatocellular carcinomas, have been reported with a range of COCs.[157,158] This concern was compounded by the finding that cyproterone acetate and its 3β-hydroxy metabolite were able to bind covalently to DNA to form stable adducts in rat liver cells. Adduct formation was also noted with chlormadinone acetate but at levels at least 20–50 times lower than after cyproterone acetate.[158] Furthermore, studies of 'unscheduled' DNA repairs showed that both cyproterone acetate and chlormadinone acetate increased the DNA repair rate in rat hepatocytes *in vitro* at concentrations of 1–5 μg/ml. The rate of adduct formation correlated with the unscheduled DNA repair rate for cyproterone acetate but not for chlormadinone acetate.[158]

Although adduct formation is one of the earliest steps in tumour initiation, tumour development does not automatically follow. For a tumour to be

fully initiated, a DNA lesion (such as incorporation of an adduct) must lead to the generation of a stable mutation that is expressed in future generations of cells.[157,158] This must then be followed by promotion, the selective proliferation (clonal expansion) of initiated cells as a result of activation of proto-oncogenes or repression of tumour suppressor genes,[159] before the tumour can progress. At the adduct stage, further tumour development depends on how easily the DNA damage can be repaired, and since DNA is constantly attacked by many endogenous and exogenous agents, all organisms have evolved efficient mechanisms that usually restore the original structure correctly.[158] Indeed, many known carcinogens often produce DNA adducts but these alone are not sufficient to result in further tumour development.[160,161] It also remains unclear whether adduct formation actually leads to the fixation of a mutation by incorrect DNA repairs, since adduct formation may occur at the same time as, as well as precede, mutation.[162] Furthermore, the adduct formation and DNA repair studies carried out in rodents showed a greater proportion of abnormalities in females than in males; this difference was not apparent during *in vitro* tests in human liver cells.[158] Thus, genotoxicity studies based on adduct formation and DNA repair studies in rodents are regarded only as a possible indicator of tumourigenicity in humans.

The drug development procedure also incorporates a battery of mutagenicity studies designed to detect gene mutations (the Ames test in bacteria and the hypoxanthine-guanine phosphoribosyl transferase test in mammalian cells), as well as chromosomal and genome mutations (chromosomal aberrations in mammalian cells and the micronucleus test in rodent bone marrow or human lymphocytes). Since these detect established mutations, they are a more realistic indicator of tumourigenicity than genotoxicity tests. None of these tests indicated that cyproterone acetate or chlormadinone acetate was mutagenic.[158,163]

Further tests of tumourigenicity include the development of putative pre-tumour states, such as the number of foci with an altered enzyme distribution (gamma-glutamyl transferase-positive and adenosine triphosphatase-negative) in the liver. In one such test, the initiation/promotion model, an increase in foci was found with cyproterone acetate 25 mg/kg/day or more given to female rats for 5 days. However, an alternative model, the Solt-Faber system, detected no such changes in male rats at 100 mg/kg.[158]

During long-term tumourigenicity studies, cyproterone acetate 2 mg/kg/day administered for 24 months produced a nonsignificant increase in nodular hyperplasia in female mice; similar results were obtained in rats but with a male preponderance. At a very high exposure level (50 mg/kg/day for 78 weeks), hepatomas were observed in rats, particularly in females.[158] Administration of 5–400 times the human therapeutic dose of chlormadinone acetate to mice and rats for up to 2 years produced a nonsignificant increase in benign liver tumours during a study conducted by the Committee on Safety of Medicines (CSM), UK.[163] During this study, benign tumours were observed in 1.3% of 75 females compared with 2.7–4.2% of those receiving other progestogens. No tumours were detected in male chlormadinone acetate-treated rodents, compared with 2.7–24.1% of those on other progestogens. Thus, the development of liver tumours in rodents is not a problem specific to these progestogens. In addition, treatment of dogs for up to 7 years and monkeys for up to 10 years with cyproterone acetate revealed no proliferative changes in the liver, suggesting that the results in rodents might be species-specific.[158]

The safety of cyproterone acetate in humans was assessed during a long-term retrospective surveillance study conducted by the German authorities in 1994.[164] This included 2506 patients treated at specialist centres, of whom 1135 were women being treated for hyperandrogenic conditions. The mean treatment duration in these women was 49.7 months and the mean dose was 18 mg/day. Overall, 17 000 patient years of exposure were assessed. Data from the German population-based cancer registry indicated an expected 1.5 cases of

malignant hepatocellular carcinoma for untreated people of the same age and gender mix as the study population, while case-control studies of risks in COC users indicated an expected six cases. In fact, no hepatocellular carcinomas were detected, although seven benign liver tumours (focal nodular hyperplasia, hepatocellular adenoma and haemangioma) were reported among women taking relatively low doses.

5.4 Prolactin Levels

COCs containing chlormadinone acetate or dienogest do not appear to increase serum prolactin levels.[113,165] In a further study, COC use did not worsen hyperprolactinaemia or promote the growth of pituitary microadenomas in 16 hyperprolactinaemic women, five of whom received cyproterone acetate/ethinylestradiol combinations.[166]

5.5 Drug Interactions

Several contraceptive steroids can inhibit cytochrome P450 (CYP)-dependent enzymes in the liver, thus slowing their own metabolism and that of other drugs. It has been suggested that this inhibitory effect is due to the presence of a 17α-ethinyl group[32,167-169] and that progestogens without this group (including chlormadinone acetate) do not inhibit the CYP system.[98] Dienogest, which contains a 17α-cyanomethyl instead of a 17α-ethinyl group,[34] produced no inhibition when used alone;[170,171] however, dienogest 2mg/ethinylestradiol 30μg inhibited dehydronifedipine formation by CYP3A4 to approximately the same extent as levonorgestrel 125 μg/ethinylestradiol 30μg.[172] Cyproterone acetate 2mg/ethinylestradiol 35μg did not significantly inhibit the CYP system as indicated by the urinary excretion ratio of 6β-hydroxycortisol to cortisol.[173]

6. Tolerability and Acceptability

6.1 Cycle Control

Good cycle control is a major factor determining the acceptability of COCs. Ideally, a COC should produce minimal breakthrough bleeding or spotting and, when used in the traditional cyclical manner, regular withdrawal bleeding so that pregnancy can be excluded. Many women also value the reduced blood loss and relief from menstrual complaints provided by COCs.

Several studies have shown that COCs containing antiandrogenic progestogens provide excellent cycle control. A comparison of cyproterone acetate 2mg plus ethinylestradiol 35 or 50μg showed equally good control with both products.[112] Average cycle length was 28 days and withdrawal bleeding lasted 5 days, with bleeding intensity lessening over time. Indeed, cycle regularity and blood loss were normalised in women who had previously had long cycles or heavy menstruation. Intracyclical bleeding was uncommon; spotting occurred in approximately 3% of cycles with both products, while breakthrough bleeding was noted in 0.4% of cycles in the low-dose group and 1% of cycles in the high-dose group. Furthermore, dysmenorrhoea improved in 83 and 64% of the low- and high-dose groups, respectively, by cycle 12. Similar findings were obtained with cyproterone acetate 2mg/ethinylestradiol 35μg over 12 cycles in 136 women.[111] The average cycle duration was 27 days, and withdrawal bleeding lasted 4 days. Amenorrhoea occurred in 1.5% of the 1361 cycles studied, while spotting became less frequent over time (figure 4). Cyproterone acetate 2mg/ethinylestradiol 35μg has also been found to cause less intracyclical bleeding than desogestrel 150μg/ethinylestradiol 30μg.[125]

Excellent cycle control has also been achieved with chlormadinone acetate 2mg/ethinylestradiol 30μg. In a study involving 1655 women, withdrawal bleeding was regular in 92% of the 22 337 cycles observed.[109] No withdrawal bleeding occurred in 2.4% of women per cycle.[53] Initially, lack of withdrawal bleeding was more common in starters (first-time oral contraceptive users or break from previous oral contraceptive >3 cycles; 16.1% of women) than in switchers (break from previous oral contraceptive <3 cycles; 11.9% of women). However, absence of withdrawal bleeding occurred most frequently during the first cycle; after-

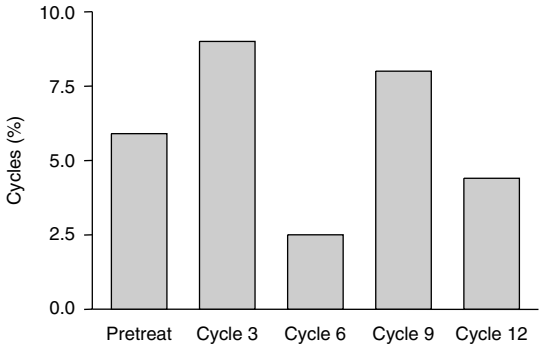

Fig. 4. Incidence of spotting during the use of cyproterone acetate 2mg/ethinylestradiol 35μg over 1361 cycles in 136 women.[111]

wards the proportion of women without withdrawal bleeding decreased, and the difference between starters and switchers disappeared.[109] The incidence of true secondary amenorrhoea (defined as three consecutive cycles without bleeding) was 0.9%.[53] Spotting and breakthrough bleeding were noted in 11.5% and 3.5% of cycles, respectively.[109] Again, the incidence was higher in earlier cycles and decreased with time.

A postmarketing surveillance study encompassing 125 634 cycles in 21 820 women using chlormadinone acetate 2mg/ethinylestradiol 30μg had similar findings. Seventy percent of participants experienced no bleeding problems, and the incidences of spotting and breakthrough bleeding fell from 19 and 4% of women, respectively, at cycle 1 to 1% and at cycle 6 to 0.4%. Amenorrhoea occurred in 4.3% of women overall, falling to 1.2% at cycle 6. Only 0.33% of participants experienced amenorrhoea lasting three or more consecutive cycles. The per-cycle incidences of spotting, breakthrough bleeding and amenorrhoea were 8, 2 and 1%, respectively.[108]

Dienogest 2mg/ethinylestradiol 30μg has also shown good cycle control. In one large trial (28 183 cycles in 2290 women), intracyclical bleeding arose in 21.5% of initial cycles but was considerably reduced by cycle 3. No differences were noted between starters and switchers. Amenorrhoea occurred in 3% of cycles overall.[113] During a postmarketing study in 16 267 women over 92 146 cycles, spotting occurred in 5% and breakthrough bleeding in 3.4% of initial cycles, while amenorrhoea occurred in 5.9% of women and 2% of cycles.[114] Again, the incidence of bleeding irregularities fell with time, as did the average duration of withdrawal bleeding.

6.2 Adverse Events

COCs containing antiandrogenic progestogens have generally been well tolerated during clinical studies. The most commonly reported adverse effects have been non-specific or as expected for COCs in general.

For cyproterone acetate 2mg/ethinylestradiol 35μg, the most frequently and consistently reported adverse effects in a series of relatively small studies were headache (11–13% of cycles), breast pain or tenderness (3–8% of cycles and 22% of women), nausea and vomiting (4% of cycles and 0.5% of women), nervousness (3–14% of cycles) and depression (1.3–4% of cycles).[18,111,112,125] A dose-level comparison found that adverse effects such as nausea and vomiting, oedema and chloasma were less frequent with the 35μg ethinylestradiol preparation than with the 50μg formulation.[18]

Qualitatively similar adverse effects were observed with chlormadinone acetate- and dienogest-containing COCs. The most commonly reported adverse effects during a large trial (n = 1655) of chlormadinone acetate 2mg/ethinylestradiol 30μg were headache (37% of women), nausea (23%), breast tenderness (22%) and vaginal discharge (19%).[109] A global analysis of adverse events for published and unpublished studies found the per-cycle incidence of these adverse effects to be 7.1, 2.0, 5.1 and 2.1%, respectively.[53] These and other adverse effects were most frequent during earlier cycles, then declined in incidence (figure 5).[109]

During a further postmarketing study involving 21 820 women and 125 634 cycles,[108] the most frequent adverse effects of chlormadinone acetate 2mg/ethinylestradiol 30μg were breast pain (3.6%

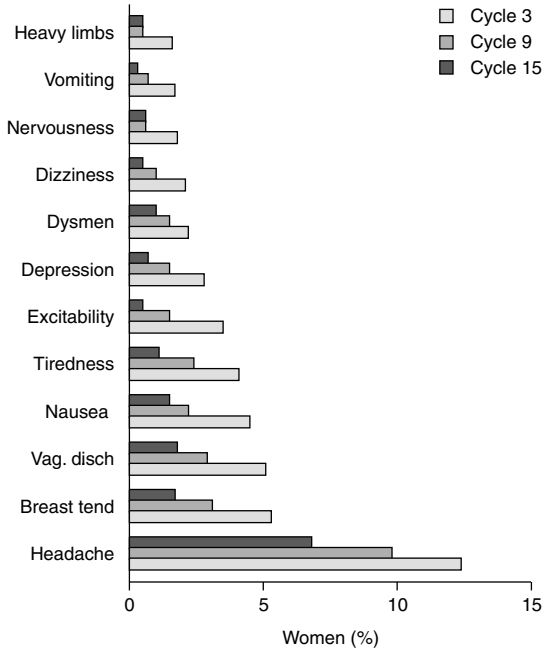

Fig. 5. Incidence of adverse effects over time in women using chlormadinone acetate 2mg/ethinylestradiol 30μg.[109] Adverse effects affecting >1% of women during cycle 3 are shown. **Breast tend** = breast tenderness; **Dysmen** = dysmenorrhoea; **Vag. disch** = vaginal discharge.

of women) and headache/migraine (2.6%). Again, incidence declined with continued use. Indeed, 85% of women with breast pain and 80% of those with headache/migraine before starting this COC found that their symptoms disappeared during use.

The most frequently and consistently reported adverse effects during large clinical and post-marketing studies of dienogest 2mg/ethinylestradiol 30μg were: headache (1% of women and 3–17% of cycles); breast pain (1.5% of women and 2–13% of cycles); nausea and vomiting (1% of women and 0.2–7% of cycles); and depression (0.3% of women and 0.5–4% of cycles). As with other COCs, incidence declined over time.[103,113,114]

6.2.1 Effects on Appetite and Bodyweight

Weight gain is a matter of considerable concern to oral contraceptive users and is a common reason for discontinuation. The incidence of weight gain among COC users has, however, been shown to be similar to that in placebo-treated women.[174] Accordingly, COCs containing antiandrogenic progestogens have generally produced only small, nonsignificant increases in mean weight or absolute weight changes of less than 2kg during trials.[108,109,112,113] Potential causes of weight gain such as oedema have also been rare, occurring in fewer than 1% of participants.[18,109] Furthermore, chlormadinone acetate 2mg/ethinylestradiol 30μg was reported to have no appreciable impact on appetite.[109] Although weight gains of over 2kg were reported in 6% of women taking cyproterone acetate 2mg/ethinylestradiol 50μg,[26] very large gains or losses (>10kg) were confined to only occasional individuals during trials of dienogest 2mg/ethinylestradiol 30μg.[113]

6.2.2 Mood Changes

Mood changes such as depression, nervousness and excitability are frequently considered to be associated with COC use, but again have been shown to occur at least as often in placebo-treated or untreated women.[174] Accordingly, during studies of COCs containing antiandrogenic progestogens, mood changes were reported in fewer than 3.5% of women during early cycles and incidence fell thereafter.[109,113]

6.2.3 Loss of Libido

Cyproterone acetate is a potent antiandrogen that can be used in high doses to treat sexual deviancy.[18] Consequently, there may be concern over its effects on libido even at the much lower doses used in COCs. Reduced libido has been reported in 0.7–6% of women receiving COC preparations.[26,125] Chlormadinone acetate and dienogest are less potent antiandrogens, and are therefore likely to have little impact on libido. Indeed, decreased libido has been reported in fewer than 5% of women receiving dienogest 2mg/ethinylestradiol 30μg,[33] while chlormadinone acetate 2mg/ethinylestradiol 30μg produced no reduction.[109]

7. Conclusions

Chlormadinone acetate, cyproterone acetate and dienogest are potent, orally active progestogens with antiandrogenic instead of partial androgenic activity. They act mainly by blocking androgen receptors but also suppress skin 5α-reductase activity, thus reducing conversion of testosterone to 5α-dihydrotestosterone in sebaceous glands and hair follicles. Chlormadinone acetate and cyproterone acetate also both inhibit gonadotropin secretion, thereby suppressing ovarian and adrenal androgen production.

COCs containing antiandrogenic progestogens provide highly effective contraception with excellent cycle control. They also lead to improvement or resolution of seborrhoea, acne, hirsutism and androgen-related alopecia in a high proportion of patients. These COCs are well tolerated and have no clinically relevant effects on metabolic or liver functions or on bodyweight.

COCs containing antiandrogenic progestogens are likely to be particularly valuable in women with pre-existing androgen-related disorders who require contraception. They also increase the choice of products available for women with normal skin and hair who are concerned about the possibility of developing unacceptable cosmetic changes, such as greasy hair, seborrhoea and acne, with other COCs.

Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review/study.

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