RATIONAL PRESCRIBING OF ORAL CONTRACEPTIVES

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Oral contraceptives are amongst the most popular drugs, at present about 60 million women are using this highly effective form of contraception. Following the classic demonstrations by Pinchus and Rock (1958) interest has centred on progesterone-oestrogen combinations as oral contraceptives. The first oral contraceptives to be introduced contained high doses of oestrogen and progesterone. Since then there has been a gradual, but significant reduction in both components, leading to a decrease in adverse effects. A large number of oral contraceptive pill formulations are available with an even greater number of proprietary preparations (Kestelman, 1981). Further preparations are being developed (Eyong, 1987).

Many women appear to be suited by any pill formulation they are offered, but some find only one formulation acceptable. Unfortunately there are no simple rules for identifying which formulation is suitable for a particular patient, and if the first choice of oral contraceptive formulation proves unsuitable, the second choice must be better and based on the knowledge of the composition of available varieties and the relationship to each other.

Types of Oral Combined Contraceptives

The most widely used oral contraceptive type continues to be a fixed combined daily dose of a progestagen plus an oestrogen — MONOPHASIC PILLS. These pills are usually started on day 5 of the menstrual cycle and taken for 20-22 days depending on the individual product. These are followed by a 6-8 day treatment-free or placebo interval during which a withdrawal bleed occurs.

A second type of oral contraceptive consists of tablets containing variable amounts of progestagen and oestrogen during the 21 day pill cycle — SEQUENTIAL PILLS. This group of oral contraceptives were developed with a view of producing cycles more closely resembling the natural ones. The incidence of vaginal spotting and bleeding and the incidence of amenorrhoea associated with the use of low-dose monophasic combined pills is thus decreased, while maintaining reduced overall doses of steroids in each cycle. BIPHASIC PILLS provide in succession two oestrogen-progestagen combinations in increasing doses, while the TRIPHASIC PILLS provide a continuous dose of oestrogen combined with a progressively increasing dose of progestagen from week to week. The advantages of lowered steroid dosages in sequential pills is exemplified by the formulations represented in Figure 1.

Pharmacological Considerations

The molecular structures of steroidal contraceptives are related to those of oestrogen and progesterone, but are modified to render them effective in low dosage by mouth. The contraceptive combined pill formulations are made up of a combination of an oestrogen and a progestagen.

OESTROGEN: A great number of chemical substances have oestrogenic activity, including steroidal oestrogens, non-steroidal synthetic oestrogens like stilboestrol, and many phenols. Only two synthetic oestrogens have so far been used in commercial oral contraceptive products: Ethinyloestradiol and mestranol (Figure 2) Ethinyloestradiol is a structurally more stable derivative of oestradiol, resisting hydroxylation and conjugation thus giving a more prolonged action, being

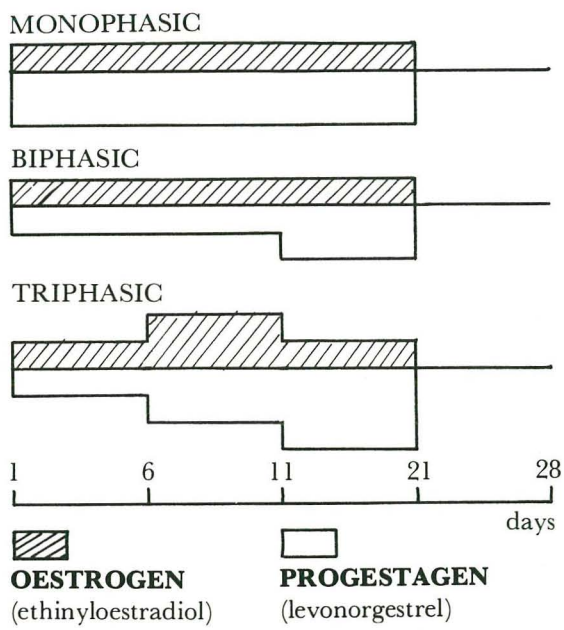


Figure 1: Representation of amounts of oestrogen and progestagen in monophasic, biphasic and triphasic Pills throughout cycle.

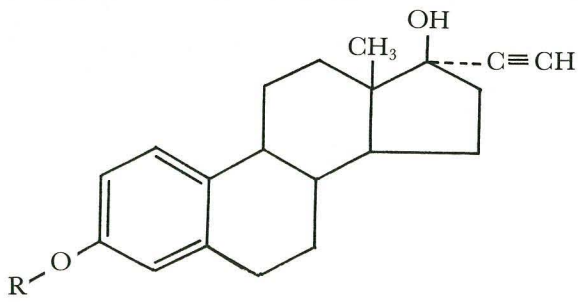


Figure 2: Oestrogen Structures ethinyloestradiol R = H mestranol R = CH_3

effective for 24-36 hours when taken orally. Mestranol is the C3 methyl ether of ethinyloestradiol. In the body it is inactive until metabolized to ethinyloestradiol. Weight for weight it is equipotent with its parent ethinyloestradiol. Only two preparations containing mestranol Norinyl-1 and OrthoNovin 1/50 are presently marketed.

Both oestrogens resemble natural oestrogens in their actions on the reproductive tract and hypothalamus, affecting Luteinizing Hormone production. They also alter lipid metabolism and blood coagulation in a manner similar to the changes found in pregnancy.

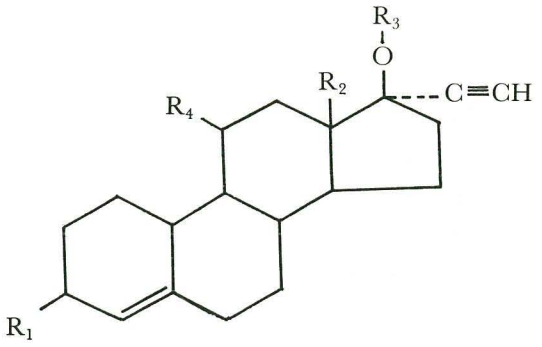
PROGESTAGENS: In contrast to the oestrogens, there is a very large range of progestagens which have been used for oral contraceptives. The synthetic progesterone-like substances are structurally related to four parent compounds: testosterone, 19-nortestosterone, 17*a*-hydroxyprogesterone and progesterone itself. All progestagens, except cyproterone acetate, currently used in combined oral contraceptives are derivatives of 19-norethisterone which is itself derived from the androgen, ethisterone (17*a*ethinyltestosterone). Taken orally, these progestagens remain active for 24-36 hours. They resemble progesterone in their action, inducing secretory changes in the oestrogen-primed endometrium, producing viscous cervical mucus, affecting Luteinizing Hormone production and inhibiting ovulation. In contrast they will not maintain pregnancy in oophorectomized animals, do not increase basal body temperature and are not metabolized to pregnanediol. Because of their relationship to testosterone, these progestagens have some androgenic effects occasionally aggravating acne and coarsening existing body hair. The next generation progestagens, desogestrel, gestodene and norgestimate show a higher ratio of binding to progresterone receptor sites than androgen sites giving less undesired androgenic effects especially on lipid metabolism. Cyproterone acetate is an anti-androgen with marked progestational action.

The progestagen present in a particular preparation determines the properties of that preparation. Current pill formulations are made up of nine different progestagens (Figure 3).

1. NORGESTREL has a very powerful antifertility action making it possible to reliably use low oestrogen dosages (30 ug ethinyloestradiol). Norgestrel does not affect endometrial development as much as the other progestagens and withrawal bleeding will not be reduced as dramatically.

It is thus not the treatment of choice in patients with menorrhagia from dysfunctional uterine bleeding. Common preparations are listed in Table 1.

2. NORETHISTERONE ACETATE has marked effects on endometrial development resulting in regression of the secretory changes in the endometrial glands and relative atrophy of the glands. The stroma appears oedematous but of relatively low vascularity. These changes in the endometrium often result in very light, or even failure of, withdrawal bleeding. This makes this group of preparations very effective at controlling menorrhagia of dysfunctional uterine bleeding, or in the management of endometriosis. These preparations however require a high dose of oestrogen (50 ug ethinyloestradiol) to effect reliable contraception, though one preparation of this group contains less oestrogen than any other combined pill. While this is useful when side-effects occur with higher doses of oestrogen, it is not as reliable for contraception, and may be associated with troublesome early spotting and breakthrough bleeding. Common preparations are listed in Table 1.



Compound	R1	R2	R3	R4
Norgestrel	O	C_2H_5	H	H_2
Norethisterone	O	CH_3	H	H_2
Norethisterone acetate	O	CH_3	CH_3CO	H_2
Lynoestrenol	H_2	CH_3	H	H_2
Ethynodiol diacetate	OCH_3CO	CH_3	CH_3CO	H_2
Desogestrel	H_2	C_2H_5	H	CH_2
Gestodene	O	C_2H_5	H	H_2
Norgestimate	NOH	C_2H_5	CH_3CO	H_2

Figure 3: Progestagen Structures

TABLE 1:
Classification of the Combined Oral Contraceptive Pills

TYPE	*OESTROGEN* *EE: ethinyloestradiol* *M: mestranol*	*PROGESTAGEN*	*PROPRIETARY NAME* *(eg)*
		Levonorgestrel	
Triphasic	EE: 30/40/30 ug	50/75/125 ug	Logynon; Trinordiol
Biphasic	EE: 30 ug	75/150 ug	
Monophasic	EE: 30 ug	150 ug	Microgynon 30; Ovranette
Biphasic	EE: 30/40 ug	150/200 ug	Adépal
Monophasic	EE: 30 ug	250 ug	Eugynon 30; Ovran 30
Biphasic	EE: 50 ug	50/125 ug	Binordiol; Sequilar
Monophasic	EE: 50 ug	125 ug	Microgynon 50
Monophasic	EE: 50 ug	250 ug	Neogynon
Monophasic	EE: 50 ug	500 ug	Eugynon 50; Ovran 50
		Norethisterone acetate	
Monophasic	EE: 20 ug	1000 ug	Loestrin 20; Nogest
Monophasic	EE: 30 ug	1500 ug	Loestrin 30
Biphasic	EE: 30/40 ug	1000/2000 ug	Miniphase
Monophasic	EE: 50 ug	1000 ug	Minovlar; Orlest 21
Monophasic	EE: 50 ug	2500 ug	Norlestrin; Orlest 2.5
Monophasic	EE: 50 ug	3000 ug	Gynovlar 21
Monophasic	EE: 50 ug	4000 ug	Anovlar 21
		Norethisterone	
Monophasic	EE: 35 ug	500 ug	Ovysmen; Brevinor
Triphasic	EE: 35 ug	500/750/1000 ug	TriNovum
Triphasic	EE: 35 ug	500/1000/500 ug	Synphase
Biphasic	EE: 35 ug	500/1000 ug	BiNovum
Monophasic	EE: 35 ug	1000 ug	Neocon 1/35; Norimen
Monophasic	M: 50 ug	1000 ug	Ortho-Novin 1/50
		Lynoestrenol	
Monophasic	EE: 50 ug	2500 ug	Lyndiol; Minilyn
		Ethynodiol diacetate	
Monophasic	EE: 30 ug	2000 ug	Conova 30
Monophasic	EE: 50 ug	500 ug	Demulen 50
Monophasic	EE: 50 ug	1000 ug	Ovulen 50
		Cyproterone acetate	
Monophasic	EE: 35 ug	2000 ug	Diane-35
Monophasic	EE: 50 ug	2000 ug	Diane
		Desogestrel	
Monophasic	EE: 30 ug	150 ug	Marvelon
		Gestodene	
Monophasic	EE: 30 ug	75 ug	Gynera; Mirulet
		Norgestmate	
Triphasic	EE: 35 ug	180/215/280 ug	
Monophasic	EE: 35 ug	250 ug	Cilest

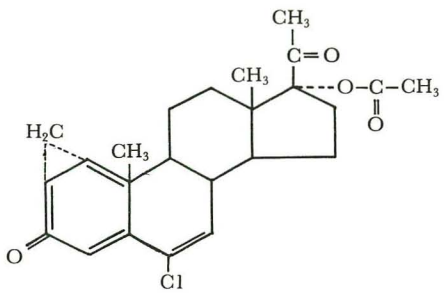


Figure 4: Anti-Androgen: cyproterone acetate

3. NORETHISTERONE is similar in its effects on the endometrium to norethisterone acetate. It is the only progestagen which is marketed in oral contraceptives employing mestranol. By incorporating ethinyloestradiol it became possible to reduce the oestrogen content to 35 ug while maintaining reliability. The preparations are listed in Table 1.

4. LYNOESTRENOL has more oestrogenic activity than the other progestagesn in common use. It is thus useful in managing androgenic problems such as acne and dysfunctional uterine bleeding caused by an atrophic endometrium. It is also a good alternative if the patient suffers progesterone dominant side-effects with lower progestagen dosages, particularly if norgestrel preparations were used. Only one formulation is currently available (Table 1) containing 50 ug of oestrogen.

5. ETHYNODIOL DIACETATE preparations are well-tried pills, but are available only in high oestrogen dosage formulations (Table 1).

6. CYPROTERONE ACETATE (Figure 4) blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. Besides its main anti-androgenic effect, cyproterone acetate has a marked progestational effect reaching, on subcutaneous injection, to about 100 times the effectiveness of progesterone, effecting not only the endometrium but also giving rise to an anti-gonadotrophin effect. Combined with ethinyloestradiol, it results in a reliable contraceptive useful for women who suffer from features of androgenization such as acne and hirsutism.

7. DESOGESTREL is one of the new generation progestagens. It has clear progestational activity and strong anti-oestrogenic activity. It has minimal androgenic and anabolic properties. Only one preparation is presently marketed combined with 30 ug of oestrogen.

8. GESTODENE has been shown to have very potent progestagenic effects with no oestrogenic activity. There appears to be no androgenic activity at clinical doses. Only one formulation combined with 30 ug oestrogen is presently marketed.

9. NORGESTIMATE is a lower-potency progestagen which exhibits virtually no androgenic response or oestrogenic activity. A triphasic preparation is in the late stages of development combined with 35 ug of oestrogen.

Selection of oral Contraceptives

The large variety of oral contraceptive formulations on the market makes it difficult to identify the right formulation for a particular patient. Based on acceptable pharmacological principles, the lowest effective dose of a compound should always be used, though the very lowest dose may not prove to be the eventual choice in a particular patient.

The triphasic pills are especially designed to provide sufficient steroids to maintain inhibition of ovulation while reducing substantially the dosages and hence the risks of side-effects of the steroid constituents. The phasic pills are probably the best first choice in oral contraceptive therapy today. When side effects such as acne, mastalgia, pre-menstrual tension or inadequate cycle control occurs, it may become necessary to change to the higher dose monophasic formulations.

In patients with normal menstruation, it may be best to start with a preparation containing norgestrel. The lowest dose formulation available is started and this is increased if spotting persists during the following three pill cycles. Breakthrough bleeding is not uncommon in the first two cycles, but if it persists or occurs when the patient is well established, a preparation with a higher progestagen content should be prescribed. Breakthrough bleeding may also occur in some patients on very low doses of oestrogen and in these cases an increase in oestrogen content may rectify the situation. If breakthrough bleeding still persists full gynaecological assessment is mandatory.

In patients where cycle control remains unacceptable with preparations containing norgestrel or in patients who have a previous history of dysfunctional uterine bleeding causing menorrhagia, a preparation containing norethisterone or norethisterone acetate should be prescribed. Low dose preparations are started, increasing the dose only if cycle control or side effects persist. It has been said that nausea, leucorrhoea premenstrual tension and relatively heavier uterine bleeding are probably associated with higher than usual levels of circulating oestrogens, while weight gain, premenstrual breast discomfort and scantier periods are more likely to be evidence of a stronger progestational effect.

In patients who have markedly dominant progestagen side-effects with low doses or in those with dysfunctional uterine bleeding from an atrophic endometrium, preparations containing ethynodiol diacetate may be useful. In patients with marked androgenic features such as acne and hirsutism, cyproterone acetate preparations may play a role.

The role of the new generation progestagens has not been fully elucidated, but clinical and pharmacological data indicate that these progestagens have very little effect on lipid and carbohydrate metabolism. The absence of androgenic effects makes these preparations useful in women susceptible to androgenic symptoms like acne and hirsutism.

It has been recommended (IPPF, 1987) that no more than four combined formulations be available in family planning programmes within the following ranges:

a) 30-50 ug oestrogen with the lower dose to be given first, and

b) 150 ug levonorgestrel or 1 mg norethisterone or its equivalent related compound.

TABLE 2:
Contra-Indications of Oral Conctraceptive use

ABSOLUTE CONTRA-INDICATIONS

* Hormone dependent tumours: malignancy of breast or genital tract
* Venous thromboembolism or predisposing conditions
* Cerebrovascular accident
* Undiagnosed vaginal bleeding
* Focal migraine
* Familiar hyperlipidaemia

RELATIVE CONTRA-INDICATIONS

* Patient's age over 40 years
* Smoking more than 20 cigarettes/day
* Mild hypertension or a history of hypertension during pregnancy
* Epilepsy
* Diabetes mellitus or impaired glucose tolerance
* History of bouts of depression
* Recent history of oligomenorrhoea/ammenorrhoea
* Gallbladder or liver disease (including a past history of idiopathic cholestatic disease of pregnancy)
* Uterine fibroids
* Sickle-cell anaemia

Contra-Indications to Oral Contraception

There are a number of situations where oral contraceptive use is absolutely contra-indicated (Table 2). There are also other situations where medical assessment of risk and benefits should be made before a woman is put on oral contraceptives (Table 2). In women who are otherwise well, oral contraceptive use may be continued for many years and there is no justification for the periodic withdrawal of the use of oral contraceptives.

References

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sized moving parts.

Fujimasa is confidently predicting that by the end of next year he will have a prototype micro-robot capable of travelling around in the body and communicating its whereabouts. Later, but still within the foreseeable future, he expects to be able to add simple sensors for doing reconnaissance jobs around our innards. Thereafter it will be on-board micro-lasers to zap our clots and beam up our tumours. Utterly incredible, but it doesn't half give you a creepy feeling....