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

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**Figure 1:** Representation of amounts of oestrogen and progestagen in monophasic, biphasic and triphasic PILLS throughout cycle.
Effective for 24-36 hours when taken orally. Mestranol is the C3 methyl ether of ethinylestradiol. In the body it is inactive until metabolized to ethinylestradiol. Weight for weight it is equipotent with its parent ethinylestradiol. 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, 17α-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 (17αethinyltestosterone). 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 progesterone 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 ethinylestradiol). Norgestrel does not affect endometrial development as much as the other progestagens and withdrawal 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 ethinylestradiol) 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.

**Figure 2:** Oestrogen Structures ethinyloestradiol R = H mestranol R = CH₃

**Figure 3:** Progestagen Structures

**Table 1:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norgestrel</td>
<td>O</td>
<td>C₂H₅</td>
<td>H</td>
<td>H₂</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>O</td>
<td>CH₃</td>
<td>H</td>
<td>H₂</td>
</tr>
<tr>
<td>Noristerone</td>
<td>O</td>
<td>CH₃</td>
<td>CH₃CO</td>
<td>H₂</td>
</tr>
<tr>
<td>Lynoestrenol acetate</td>
<td>H₂</td>
<td>CH₃</td>
<td>H</td>
<td>H₂</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
<td>OCH₂CO</td>
<td>CH₃</td>
<td>CH₃CO</td>
<td>H₂</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>H₂</td>
<td>C₂H₅</td>
<td>H</td>
<td>H₂</td>
</tr>
<tr>
<td>Gestodene</td>
<td>O</td>
<td>C₂H₅</td>
<td>H</td>
<td>H₂</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>NOH</td>
<td>C₂H₅</td>
<td>CH₃CO</td>
<td>H₂</td>
</tr>
</tbody>
</table>
TABLE 1: Classification of the Combined Oral Contraceptive Pills

<table>
<thead>
<tr>
<th>TYPE</th>
<th>OESTROGEN</th>
<th>PROGESTAGEN</th>
<th>PROPRIETARY NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EE: ethinyloestradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triphasic</td>
<td></td>
<td>Levonorgestrel</td>
<td></td>
</tr>
<tr>
<td>Biphasic</td>
<td>EE: 30/40/30 ug</td>
<td>50/75/125 ug</td>
<td>Logynon; Trinordiol</td>
</tr>
<tr>
<td></td>
<td>EE: 30 ug</td>
<td>75/150 ug</td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>EE: 30 ug</td>
<td>150 ug</td>
<td>Microgynon 30; Ovranette</td>
</tr>
<tr>
<td>Biphasic</td>
<td>EE: 30/40 ug</td>
<td>150/200 ug</td>
<td>Adépal</td>
</tr>
<tr>
<td>Monophasic</td>
<td>EE: 30 ug</td>
<td>250 ug</td>
<td>Euginon 30; Ovran 30</td>
</tr>
<tr>
<td>Biphasic</td>
<td>EE: 50 ug</td>
<td>50/125 ug</td>
<td>Binordiol; Sequilar</td>
</tr>
<tr>
<td>Monophasic</td>
<td>EE: 50 ug</td>
<td>125 ug</td>
<td>Microgynon 50</td>
</tr>
<tr>
<td>Monophasic</td>
<td>EE: 50 ug</td>
<td>250 ug</td>
<td>Neogynon</td>
</tr>
<tr>
<td>Monophasic</td>
<td>EE: 50 ug</td>
<td>500 ug</td>
<td>Euginon 50; Ovran 50</td>
</tr>
</tbody>
</table>

| 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      | Miniphas          |
| Monophasic| EE: 50 ug       | 1000 ug           | Minovar; 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        |

| Monophasic| EE: 35 ug       | 500 ug            | Triovin; 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           | Neocen 1/35; Norimen |
| Monophasic| EE: 50 ug       | 1000 ug           | Ortho-Novin 1/50 |

| Monophasic| EE: 50 ug       | 2500 ug           | Lyndiol; Minilyn |

| Monophasic| EE: 30 ug       | 2000 ug           | Conova 30       |
| Monophasic| EE: 50 ug       | 500 ug            | Demulen 50      |
| Monophasic| EE: 50 ug       | 1000 ug           | Ovranette 50    |

| Monophasic| EE: 35 ug       | 2000 ug           | Diane-35        |
| Monophasic| EE: 50 ug       | 2000 ug           | Diane           |
| Monophasic| EE: 30 ug       | 150 ug            | Marvelon        |

| Monophasic| EE: 30 ug       | 75 ug             | Gynera; Mirelet |

| Monophasic| 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 progestagens 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 progestosterone 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. ETHYNOBISOL 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 prostegastational 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 prostegastational 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 pharma-
cological 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
osages 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 or side effects
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 gynaecologi-
cal assessment is mandatory.

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
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
ethinodiol 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
cholesterol metabolism. The absence of
androgenic effects makes these pre-
parations 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.

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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