CHAPTER IV
TYPES OF CONTRACEPTIVES

In 1956, rock, Garcia and Pincus first showed that fertility control in women can be achieved by suppressing ovulation with norethynodrel, a progestational agent. It was also found that by combining norethynodrel with mestranol an oestrogenic agent, efficacy can be improved and break through bleeding reduced. This heralded the birth of the first combined oral contraceptive pill. Enovial containing 10 mg norethynodrel & 0.15 mg mestranol.

Studies in Puerto Rico showed that it was an effective contraceptive, and in 1959 it was approved officially for use in the USA.

It was soon found that the side effects, including cardiovascular and metabolic changes, were too high owing to high doses of steroids present in the original pill. Since the 1960s attempts have been made to reduce the doses of both estrogen and progestogen in the pill with a view to reduce the side effectiveness. This had led to the development of low dose combined pills and phasic pills which contain different does of these steroids.

Oral contraceptives are broadly divided into two groups.

(A) Combined pills and (B) Progestogen only pills or minipills.

4.1 COMBINED PILLS

These are of two types: monophasic and multiphasic pills. Monophasic pills contain an oestrogen and a progestogen in the same amount in each pill. They are divided into subgroups.

Low dose pills containing ethinyl oestradiol (EE) of less than 0.05 mg in each pill and
High dose pills containing 0.05 mg of ethinyl oestradiol in each pill.

- High dose combined pills, such as were used earlier, have been completely abandoned for regular use due to their greater side effects and major complications. However, they are still being used for 1-3 cycles sometimes.

- At present low dose combined OCs contain less than 0.05 mg of oestrogen, down from 0.15 mg in the first OC and 0.05–0.1 mg in the OCs of the late 1960s and 1970s.

  Oestrogen doses of 0.03–0.05 mg ethinyl oestradiol (EE) are most commonly used nowadays. Some low doses have also been lowered substantially.

  Multiphasic pills: These phasic formulation employ low doses and variable amounts of oestrogen and progestogen in two (biphasic) or three (triphasic) periods within the menstrual cycle. The dose of progestogen is low at the beginning and higher at the end while the oestrogen remains either constant or rises slightly in mid-cycle. The total doses of steroids in a whole cycle are less in these pills. A biphasic pill containing a constant dose of 0.035 mg of EE combined with a low dose of progestogen for 10 days and a higher dose of progestogen for the following 11 days has been used. But biphasic pill have not become popular because of relatively higher failure rates.

  Triphasic pills have been available in most developed countries as well as in India since mid 1980s. A triphasic pill in India with the trade name of "Triquilar" provides 0.05 mg of l-norgestrel and 0.03 mg of EE per day for the first 6 days, 0.075 mg of l-norgestrel and 0.03 mg of EE per day for the first 5 days and 0.125 mg of l-norgestrel and 0.03 mg of EE per day during the last
10 days. This preparation supplies a monthly total dose of 0.68 mg of EE and 1.92 mg of 1-norgestrel supplied by "Ovral-L". While compared to "ovral" its EE content is reduced by 65% and 1-norgestrel amount is reduced by 36% although its efficacy is equal to the of "ovral" or ovral-L. Ovral (high dose pills) is no more used regularly for oral contraception. Another triphasic pill (ortho-Novum-777) has been extensively used in other countries although it has come to the Indian market only in July 1991 and is not easily available.

4.2 PROGESTOGEN ONLY PILLS OR MINIPILLS

These contain small amounts of one of the progestogens but no oestrogen. They are taken daily without interruption. These pills are much less used than the combined pills and have got different characteristics, although have a definite place among steroid contraceptive users.

4.3 PROPRIETARY NAMES & COMPOSITION:

Large number of commercial contraceptive preparations with hundreds of trade names are available in the world market, of which those which are available in India for general use of present are listed in table.

Mala-N is supplied free in India through F.W. clinics. Mala-D is sold at a subsidized rate (1/10 or 1/30 that of other preparation).

<table>
<thead>
<tr>
<th>Proprietary Names</th>
<th>Progestogen</th>
<th>Oestrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Combined Pills:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Low dose Pills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovral-L or Mala-D</td>
<td>1-NGL 0.15mg</td>
<td>EE 0.03 mg</td>
</tr>
<tr>
<td>Novelon</td>
<td>Desogestrel 0.15 mg</td>
<td>EE 0.03 mg</td>
</tr>
<tr>
<td>Femilon</td>
<td>Desogestrel 0.15 mg</td>
<td>EE 0.02 mg</td>
</tr>
<tr>
<td>Mala-N</td>
<td>dl-NGL 0.30 mg</td>
<td>EE 0.03 mg</td>
</tr>
<tr>
<td><strong>High dose Pills</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovral or Duolution</td>
<td>1-NGL 0.25 mg</td>
<td>EE 0.05 mg</td>
</tr>
</tbody>
</table>
B. Triphasic Pills:

<table>
<thead>
<tr>
<th></th>
<th>1-NGL 0.5 mg</th>
<th>EE 0.05 mg – 6 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triquilar</td>
<td>1-NGL 0.75 mg</td>
<td>EE 0.04 mg – 5 days</td>
</tr>
<tr>
<td></td>
<td>1-NGL 0.125 mg</td>
<td>EE 0.03 mg – 10 days</td>
</tr>
<tr>
<td>Ortho-Novum 777</td>
<td>NET 0.5 mg</td>
<td>EE 0.35 mg – 7 days</td>
</tr>
<tr>
<td></td>
<td>NET 0.76 mg</td>
<td>EE 0.35 mg – 7 days</td>
</tr>
<tr>
<td></td>
<td>NET 1.0 mg</td>
<td>EE 0.35 mg – 7 days</td>
</tr>
</tbody>
</table>

4.4 DETAILS OF OCP STUDIED

4.4.1 OVRAL

Ovral is a hormonal oral contraceptive (OCs) containing 0.25 mg of levonorgestrel (Fig. 4.3a) and 0.05 mg of ethinyl estradiol (Fig 4.3b). The hormonal components of ovral inhibit ovulation by suppressing gonadotropin release. Secondary mechanism which may contribute to the effectiveness of ovral as a contraceptive, including changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium.

![Fig.4.3a Levonorgestrel](image1)

![Fig. 4.3.b Ethinyl estradiol](image2)

4.4.1.1 PHARMACOKINETICS

Ethinyl estradiol and Levonorgestrel are rapidly and almost completely absorbed from the gastrointestinal tract. Ethinyl estradiol is subject to considerable first pass metabolism with a mean bioavailability of 40-50% Levonorgestrel does not undergo first pass metabolism and in therefore, completely bioavailable. Levonorgestrel is extensively plasma protein bound.
both to sex hormone binding globulin (SHBG) and albumin. Ethinyl estradiol, however, is bound in plasma only to albumin and enhances the binding capacity of SHBG. Following oral administration, peak plasma levels of each drug occur within 1 to 4 hours.

The elimination half life for ethinyl estradiol is approximately 25 hours. It is primarily metabolized by aromatic hydroxylatin but a wide variety of hydroxylated and methylated metabolites are formed and these are present both free and as conjugates with glucuronide and sulfate. Conjugated ethinyl estradiol is excreted in bile and subject to enterohepatic recirculation. About 40% of the drug is excreted in the urine and 60% is eliminated in the faces.

The elimination half life for levonorgestrel is approximately 24 hours. The drug is primarily metabolized by reduction or hydroxylation, followed by conjugation with sulfate and glucuronidation in the urine and 40% is eliminated in the faces.

4.4.1.2 THROMBOEMBOLIC DISORDERS

An increased risk to thromboembolic and thrombotic disease associated with the use of OCs is well established. A four to six fold increased risk of thromboembolic complications following surgery has been reported in users of OCs. If feasible, OCs should be discontinued at least 4 weeks before surgery associated with an increased risk of thromboembolism or prolonged immobilization.

4.4.1.3 MYOCARDIAL INFARCTION (MI) AND CORONARY ARTERY DISEASE (CAD)

An increased risk of MI associated with the use of OCs has been reported. Studies found that the greater the number of underlying risk factors
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Among other benefits that women obtain from Mala one protection against pelvic inflammation diseases, ectopic pregnancy, endometrial cancer, cancer of ovaries and benign breast diseases.

According to the present state of knowledge, an association between the use of Mala and an increased risk of venous and arterial thromboembolic diseases can not be ruled out. The relative risk of arterial thrombosis (eg. stroke, MI) appears to increase further when heavy smoking advancing age and the use of Mala coincide.

In rare cases benign and in even rarer cases malignant liver tumours leading in isolated cases to life threading extra-abdominal hemorrhage have been observed after the use of Mala.

Novelon is a combined OC preparation containing an active substances the ethinyl estradiol (0.03 mg) and the progestogen desogestrel (0.15 mg) (Fig. 4.6b). Clinical trials have revealed that Novelon containing ethinyl estradiol lack the unbalanced metabolic effects which are contained up be due to the progestogen activity of some progestogen ACs.

![Fig. 4.4a Ethinyl estradiol](image)

![Fig. 4.4b Norgestrel](image)

4.4.2.1 SIDE EFFECTS

In rare cases nausea, Vomiting headaches, gastric upsets, a feeding of tension in the breasts, changes in body weight and libido or depressive moods can occur. In predisposed women, long term use of the tablets can some times cause brownish patches on the face which are made worse by long exposure to the sun. Women who have this tendency would, therefore,
avoid spending time too long in the sun. Individual cases of poor tolerance of contact lenses have been reported.

4.4.2.2 CONTRA-INDICATIONS

Pregnancy, severe disturbance of liver function jaundice or persistent itching during a previous pregnancy. Dubin-Johnson syndrome, Rotor syndrome, previous or existing liver tumours, existing or previous thromboembolic process (e.g. stroke, MI), sicklecell anaemia, existing or treated cancer of the breast of the endometrium, severe diabetes with vascular changes, disturbance of lipometabolism, a history of pregnancy, otosclerosis during pregnancy.

4.4.3 NOVELON

Novelon is a combined OC preparation containing as active substances the estrogen ethinylestradiol (0.03mg) (Fig 5a) and the progestogen desogestrel (0.15 mg) (Fig. 4.5b). Clinical studies have revealed that OC preparations containing ethinyl estradiol and desogestrel lack undesirable metabolic effects which are considered to be due 70 the androgenic activity of some progestogens in OCs.

![Fig.4.5a Ethinyl estradiol](image1)

![4.5b Desogestrel](image2)

When taken according to the recommended dosage, Femilon suppresses the hypophyseal gonadal function and thereby, ovulation. In
addition, it includes a regular uterine bleeding which, with respect to amount
of flow and duration resembles a normal menstrual bleeding. Usually this
bleeding starts two or three days after the intake of the last tablet and is
painless. In clinical trials, Femilon, showed a very low pregnancy rate a good
cycle control, a low incidence of side effects and as a result, low dropouts' rate.

4.4.3.1 ADVERSE REACTIONS

The following adverse reactions have been associated with estrogen
and/or progestogen therapy.

➢ Genitourinary Tract: Intermenstrual bleeding, post medication
amenorrhoea, changes in cervical reaction, increasing size of uterine
fibromyomata, aggravation of endometriosis, certain vaginal infections.
  e.g. candidiasis.

➢ Gastro Intestinal Tract: Nausea, vomiting, cholelithiasis, choleslatic
jaundice.

➢ Cardiovascular system: Thrombosis, rise of blood pressure.

➢ Skin: Chloasma, crythema nodosum, rash.

➢ Breast: Tenderness, pain, enlargement, secretion.

➢ Eyes: Discomfort of the cornea if contact lenses are used.

➢ Central Nervous system (CNS): Headache, migraine, mood changes.

➢ Various: Fluid retention reduced glucose tolerance, change in body weight.

4.5 FEMILON

Femilon is a combined oral contraceptive (the combined pill). Each
tablet contains a small of two different female hormones. These are
desogestrel (a progestogen) (0.15 mg) and ethinylestradiol (an oestrogen) (0.02 mg). Because of the small amounts of hormones, Familon is considered a low dose oral contraceptive.

As all tablets in the pack combined in the same dose, it is considered a monophasic combined oral contraceptives.

4.5.1 POSSIBLE SIDE EFFECTS

The following side effects have been reported by users of the pill, although they need not be caused by the pill. These side effects may occur in the first few months that you are using the pill and usually lessen with time.

- breast tenderness, pain and secretion,
- headache,
- change in sexual drive,
- depressive moods,
- contact lens intolerance,
- nausea, vomiting and feeling sick,
- change in vaginal secretion