HORMONAL CONTROL OF CONCEPTION

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Prologue

Prior to 1938 no form of oral hormonal contraception was possible as none of the then available hormones were active when given orally. The era of oral contraception commenced with the reports of Pincus et al (3). The contraceptive pills used today contain a synthetic oestrogen and a synthetic progestational agent. Oestrone and oestradiol were available prior to 1938 as esters but these were active only when injected. Impure injectables indicated then that they could prevent pregnancy.

The oestrogens used now and which are active orally are either mestranol which is 3 methyl ether of 17 ethinyl oestradiol or ethinyl oestradiol itself. These two synthetic oestrogens retain most of the biological properties of oestradiol.

Progesterone is primarily, a secretory hormone of the corpus luteum. The name is derived in part from progestin, first proposed in 1930 by Corner and Allen (1) for the active substance present in their extracts of the corpus luteum. Literally, the word 'progestin' indicates a hormone which supports or assists pregnancy. The relationship between progesterone and oral contraceptives is intimate but "the pill" is not a progesterone, but contains a progestational agent which has many of the biological properties of progesterone. The progestational agents in the pills are not naturally occurring hormones.

The most characteristic effect of progesterone is the induction of progestational change in the endometrium. The histological evidence of this change is quite variable from one species to another but in all species, the endometrial changes induced by progesterone are essential for the normal growth and implantation of the fertilized egg. An associated and equally important effect is exerted on the myometrium. This is generally manifested by myometrial quiescence and refractoriness to oxytocin. These functional alterations in the myometrium enable the uterus to adapt to the growing conceptus.

The biological effect of oestradiol on target organs is quite different from that of progesterone. Oestradiol is primarily a growth-promoting hormone. It induces growth of the
uterus, vagina, and breasts and brings these organs to sexual maturity. In the process, it brings about a subtle change which permits them to respond to progesterone. Without preliminary exposure to oestrogen, progesterone generally has no demonstrable effect.

Agents and their biological properties:

It is remarkable that the numerous progestogen—oestrogen combinations have similar basic effects despite the varied pharmacological properties of the individual ingredients. Table I shows the groups from which these compounds are derived. Common derivatives of progesterone which are active orally and have been used for contraceptive purposes are drugs like medroxy progesterone acetate, megesterol acetate and chlormadinone acetate.

Changes in the testosterone molecule give rise to compounds with properties comparable to progestogens (Table I).

### Table I: Synthetic components in contraceptive pills

<table>
<thead>
<tr>
<th>Natural steroid</th>
<th>Structural change</th>
<th>Group added</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol</td>
<td>None</td>
<td>3</td>
<td>Ethynil</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>6</td>
<td>Methyl</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>17a</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Progestrone</td>
<td>None</td>
<td>3</td>
<td>Ethynil</td>
</tr>
<tr>
<td></td>
<td>Methyl</td>
<td>6</td>
<td>Acetyl</td>
</tr>
<tr>
<td></td>
<td>Methyl</td>
<td>17a</td>
<td>Acetylene</td>
</tr>
<tr>
<td>Testosterone</td>
<td>None</td>
<td>3</td>
<td>Ethynil</td>
</tr>
<tr>
<td></td>
<td>Methyl</td>
<td>6</td>
<td>Chloro</td>
</tr>
<tr>
<td></td>
<td>Propynyl</td>
<td>17a</td>
<td>Methyl</td>
</tr>
<tr>
<td></td>
<td>Acetyl</td>
<td>17b</td>
<td>Acetyl</td>
</tr>
<tr>
<td></td>
<td>OH</td>
<td>17b</td>
<td>Acetyl</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>17b</td>
<td>Ethynil</td>
</tr>
</tbody>
</table>

Although it has been known since long that steroid hormones (oestrogen and progesterone) have contraceptive properties, it has taken almost two decades to put this knowledge into practice. These synthetic estrogens were not solubles in water, which made them difficult to administer orally. It was only when progesterone was obtained in a form called “Black Head” in Mexico that it was possible to develop an oral contraceptive pill. The potency and biological activity of these compounds are listed in Table II.

### Table II: Delay-of-menstrual

<table>
<thead>
<tr>
<th>Progestogen</th>
<th>Delay of menstrual test (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>30</td>
</tr>
<tr>
<td>Chlormadinone</td>
<td>4</td>
</tr>
<tr>
<td>Dimethisterone</td>
<td>10</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>7.5</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>1</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
<td>13.8</td>
</tr>
</tbody>
</table>

**I. Combined regimens:**

A. Containing various progestogens.
1. 20 or 21 day scheme (start on day 5).
2. 20 or 21 day scheme with ethinyl estradiol (3 mg).
3. “Lunar scheme” starting at day 1.
4. “Post ovulatory” day 16-25.
5. One-pill-a-month: on day 5, 10 or 20 mg. of a progestogen and oestrogen (3 cyclopentyl ethynyl estradiol).
6. One-pill-a-month: Starting on day 1 or 4 of cycle, 20 mg. of progestogen and 30 mg. of oestrogen.

B. Containing long-acting preparations.
1. Intramuscular each month.
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In the process, it led to progesterone. Without a pre-natal demonstrable effect.

Oestrogen combinations have similar properties of the individual ingredients, as are derived. Common derivatives used for contraceptive purposes are norethindrone and norethynodrel.

For contraceptive purposes are norethindrone and norethynodrel.

<table>
<thead>
<tr>
<th>Contraceptive pills</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>17b</td>
</tr>
<tr>
<td>Ethinyl</td>
<td>Ethinyl estradiol</td>
</tr>
<tr>
<td>Ethinyl</td>
<td>Norethindrone</td>
</tr>
<tr>
<td>Acetyl</td>
<td>Norethindrone acetate</td>
</tr>
<tr>
<td>Acetyl</td>
<td>Ethynodiol diacetate</td>
</tr>
<tr>
<td>Propynyl</td>
<td>Dimesthisterone</td>
</tr>
<tr>
<td>Ethinyl Acetyl</td>
<td>Lynestrenol</td>
</tr>
<tr>
<td>Ethinyl Acetyl</td>
<td>Norethynodrel</td>
</tr>
</tbody>
</table>

New knowledge into practice. These synthetic compounds had to be prepared because progesterone as such was not soluble in water, was short acting and was terribly expensive. Also it was only when progesterone was obtained in bulk and very cheap from a tuberous plant root called “Black Head” in Mexico and from other plant sterols that its wide use and its conversion into orally active compounds was thought of. Table II gives the comparative potency and biological activity of these compounds.

**Table II: Progestin potency**

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Delay-of-menses test (mg.)</th>
<th>Gonadotrophin suppression</th>
<th>Anabolic</th>
<th>Human foetal masculinization</th>
<th>Conversion to anti-oestrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chlormadinone</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>Unknown</td>
<td>0</td>
</tr>
<tr>
<td>Dimethisterone</td>
<td>—</td>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>7.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Norethynodrel</td>
<td>13.8</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**REGIMENS**

I. **Combined regimens**:

A. Containing various combinations of orally active oestrogens and progestogens.

1. 20 or 21 day scheme (starting day 5 of menstrual cycle).
2. 20 or 21 day scheme with placebos in the remaining 7 days.
3. “Lunar scheme” starting a 21 day schedule with each new moon.
4. “Post ovulatory” day 16-25: accompanied by fertile-period abstinence.
5. One-pill-a-month: on day 21 of cycle. A progestogen (Chlormadinone, retroprogesterone, 16-17 dimethyl-6-retroprogesterone, or the 18 homologue of norethisterone) together with a long acting oral oestrogen (3 cyclopentyl ether of ethiny1 oestradiol).
6. One-pill-a-month: Starting on day 1 or 2 of the cycle and every month subsequently. Long acting progestogen and oestrogen (Quingestanol acetate and Quinesterol).

B. Containing long acting progestogen + oestrogen combination for parenteral administration.

1. Intramuscular each month on day 7 or 8: dihydroxy-progesterone acetonaphenide and oestradiol enanthate.
II. Sequential regimens:

1. Classical sequential
   (i) Day 5 to 20 —oestrogen alone
   (ii) Day 21 to 25 —combined oestrogen and progestogen

2. Modified sequential
   (i) Day 5 to 16 —oestrogen alone
   (ii) Day 16 to 25 —combined oestrogen and progestogen

3. Step-up sequential
   (i) Day 1 to 5 —‘micro’ oestrogen dosage
   (ii) Day 5 to 16 —first oestrogen elevation
   (iii) Day 16 to 20 —second oestrogen elevation
   (iv) Day 20 to 25 —oestrogen and progestogen
   (v) Day 25 to 30 —‘micro’ oestrogen

III. Progestogen alone

1. ‘Micro’ doses continuous at 0.5 mg. daily.
2. One-pill-a-week: ‘Sunday Pill’ (Norgesterrinone).
3. Intramuscular Provera (Medroxy progesterone acetate) 150 mg every 3 months or 400 to 800 mg every 4 to 6 months.
4. Intramuscular injection every 3 months: Norethisterone enanthate 200 mg.
5. Intravaginal placement of silicone ring with medroxy progesterone acetate-inserted early in cycle and removed on day 27.
6. Subcutaneous silastic implant containing progestogen-continuous doses in micro quantities released for over a year.
7. Intracervical administration of progesterone by a slow releasing device (a silastic capsule containing progesterone attached to a Lippes loop).
8. Intracervical administration of progesterone by a slow releasing device (silastic capsule containing the steroid) placed in the cervical canal.

IV. Oestrogens administered post-coital.

MODE OF ACTION

Most of the oral combined/sequential preparations in use at present have their contraceptive action by preventing ovulation through the suppression of the hypothalamic-pituitary axis.

Both FSH and LH are suppressed. This is brought about by blocking the oestrogen receptor site in the hypothalamus and pituitary and subsequent reduction in gonadotrophin release and inhibition of ovulation.

There are some indications that the oestrogen factor reduces its sensitivity to gonadotrophin.

Rudel et al (2) brought to our attention the necessity to inhibit ovulation by inhibition of ovulation such as sperm transport etc. and that the cyclic pill thereby began.

Adverse changes in the endometrium and subsequently their occurrence are necessary to inhibit ovulation. With formulations as described this is not necessary. Pregnancy rate with sequential preparations is therefore, very insignificant.

Side Effects

Various side-effects have been reported including, fatigue, weight gain etc. Amenorrhoea and breakthrough bleeding are more frequent with sequential than with monophasic preparations. Some symptoms experienced have been related to progestogens. The selection of combinations for contraceptive is therefore, very important. Metabolic and other effects

1. Adrenal cortex
2. Thyroid
3. Hepatic effects
4. Integumental effects
5. Haematological changes
6. Cardiovascular effects
7. Central Nervous System including emotional
There are some indications that the contraceptives may directly act on the ovary and reduce its sensitivity to gonadotrophins.

Rudel et al (2) brought out the hypothesis that for the contraceptive action it was not necessary to inhibit ovulation. Search then went on for reproductive processes other than inhibition of ovulation such as fertilization, transport of fertilized ovum, implantation, sperm transport etc. and that is how the era of continuous low dose hormonal steroids began.

Adverse changes in the cervical mucus which hindered sperm survival, subtle changes in the development of endometrium to hinder implantation, rapid transport of fertilized ovum and subsequently their degeneration are some of the other ways by which these agents act. With formulations which are in a high enough dose to inhibit ovulation, if taken as prescribed i.e. combination regimens from day 5—25 etc. effectiveness is 100 per cent. Pregnancy rate with sequentials is a little higher as failure of ovulation has occurred in some cases.

Side Effects

Various side-effects have been reported which could be general such as nausea, vomiting, fatigue, weight gain etc. and others which pertain to menstrual periods such as scanty menses, amenorrhea and breakthrough bleeding.

Some symptoms experienced by these women are specific for oestrogen and others are related to progestogens. Therefore, depending on the symptoms complained, an appropriate selection of combinations can be made. History of a patient before giving the oral contraceptive is therefore, very important. History of excessive nausea and vomiting during pregnancy, unusual headache, visual complaints, tendency to gain weight etc. are important.

Metabolic and other effects:

1. ADRENAL CORTEX: Serum transcortin bound levels increase. No sign of hyperadreno-corticism.
2. THYROID: Slightly elevated PBI, normal thyroxin and I$^{131}$ uptake. Clinically normal, and BMR normal.
3. HEPATIC EFFECTS: Serum transaminase increases, BSP retention increases.
4. INTEGUMENTAL EFFECTS: Melanosis.
5. HEMATOLOGICAL CHANGES: Hb increases, MCHC increases, PCV increases, serum Fe increases, and Fe binding capacity increases.
6. CARDIOVASCULAR EFFECTS: Hypertension (renin, angiotensin, electrolyte and fluid balance increase and also sensitivity of smooth muscle).
7. CENTRAL NERVOUS SYSTEM INCLUDING EMOTIONAL: EEG changes variable, thermogenic action, depression, libido decrease.
8. **Carbohydrate Metabolism**: Related to type and dose of oestrogen, changes more with combined than sequential, increase in cortisol, increase in growth hormone, alteration in GI absorption, peripheral tissue utilization of glucose decreased.

9. **Lipid Metabolism**: Serum cholesterol increases, triglycerides increase and atherosclerosis.

10. **Blood Coagulation and Thrombophlebitis**: Definite oestrogen dependent relationship reported, i.e. state of hypercoagulability as a result of changes in level of various clotting factors, platelet function, physical state of vessels.

11. **Carcinogenic Effect**: Incidence of cervical cancer has not shown to be increased with the use of these contraceptives.

12. **Menstrual Disorders**: Combined preparations have better control. Associated with skipping of tablets and present in first few days. Sequential—less controlled withdrawal. Low-dose—greater variability.

13. **Subsequent Fertility**: Much needs to be done.

All these effects need to be studied and evaluated among women taking these preparations in our country. Available data on the effect of continuous low dose progesterone on these metabolic and other processes is not sufficient. Therefore, it is suggested that for the use of hormones as a contraceptive measure, the following be kept in mind:

1. proper selection of cases
2. good follow up
3. change of drug when indicated
4. picking up of complications soon enough

A total of 14 million women are using these drugs all over the world for the purpose of contraception. There is no reason why this should not increase with new lower dose schedules, long acting pills (one-pill-a-month) injectables containing long acting oestrogen and progestogens, subcutaneous implants for three years, hormone for slow release inside an intrauterine device. I am sure, research which is now in progress to find out the minimum dose and combination for our women, will lead to the development of a method which is simple, has maximum effectiveness, safety, least side-effects and therefore, a high acceptability index among our women.

**REFERENCES**

January 1972
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Estrogen, changes more with combined than  
alone increase in growth hormone, alteration in  
utilization of glucose decreased.

Triglycerides increase and atherosclerosis.

A relationship reported, i.e. state of hyper-  
changes in level of various clotting factors,  
state of vessels.

Has not been shown to be increased with the use of  
a better control. Associated with skipping of  
withdrawal.

Among women taking these pre-  
continuous low dose progesterone.

Therefore, is it suggested that for  
keeping be kept in mind:

Published all over the world for the purpose  
of not increase with new lower dose  
containing long acting oestrogen and  
hormone for slow release inside an  
progress to find out the minimum  
development of a method which is  
and therefore, a high acceptability

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ICMR LIST OF APPROVED ORAL CONTRACEPTIVES

1. Minovlar-28 Ethinyl oestradiol 0.05 mg.  
Norethisterone acetate 1 mg.

2. Norinyl-I (Norid) 21 plain tablets, each containing  
Mestranol 0.05 mg.  
Norethindrone 1 mg.

7 coloured tablets, each containing  
inert ingredients

3. Norlestrin Ethinyl oestradiol 50 mg.  
Norethisterone acetate 1 mg.

4. Ovral Ethinyl oestradiol 0.05 mg.  
Norgestrel 0.5 mg.

5. Eugynon Ethinyl oestradiol 0.05 mg.  
Norgestrel 0.5 mg.

6. Ovulen-50 Ethinyl oestradiol 0.05 mg.  
Ethynodiol diacetate 1 mg.

7. Lyndiol-E Ethinyl oestradiol B.P. 50 mg.  
Lynestrenol B.P. 2.5 mg.