# the problematic pill

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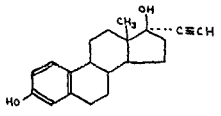
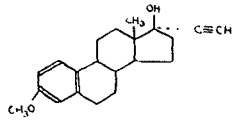
The first oestrogen containing oral contraceptive was introduced in 1957 as a clinical trial involving a few hundred Puerto Rican women; it was first sold on the open market in 1960, and it is now taken by over 14 million women throughout the world.

There are two types of oestrogen containing oral contraceptive, a combined preparation in which both oestrogen and progestogen are present in all 20 to 22 tablets, or a sequential preparation in which all the tablets contain an oestrogen, but only the last 5 to 7 contain a progestogen. Recently a pill containing a progestogen *alone* has been introduced, but as it is not very effective as a contraceptive its use is limited, and there has been as yet little research work carried out on its metabolic effects. Only the first two types, that is those containing an oestrogen, will be considered.

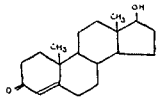
Two *oestrogens* are used at the present time in oral contraceptives. These are *ethynyl oestradiol* and its 3 methyl ether, namely *mestranol*. The chemical formulae of these compounds are shown:



ethinyl oestradiol



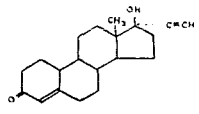
mestranol



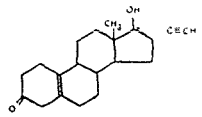
testosterone

The *progestogens* are divided into two groups, the derivatives of 19nor testosterone and those of progesterone.

Removal of the methyl group from the carbon 19 of testosterone reduces its androgenic properties considerably. Substitution of an ethynyl group at the 17 position produces *17 a ethynyl 19 nortestosterone, or norethindrone, or norethisterone.*

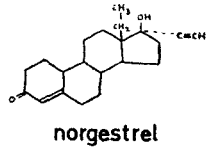


norethindrone/norethisterone

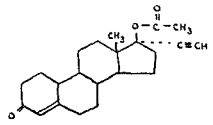


norethynodrel

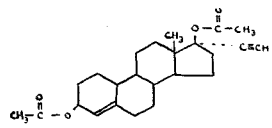
A shift in the double bond from the 4-5 to the 5-10 position produces *norethynodrel,* which in addition to being a progestogen also has some oestrogenic activity. The addition of a methyl group at the 18 position of norethisterone produces *norgestrel,* while acetylation at the 17 position produces *norethisterone acetate.* Finally reduction of the 3 ketone group with acetylation at positions 3 and 17 produces *ethynodiol acetate.*



norgestrel

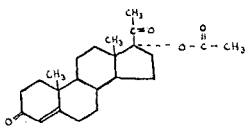


norethindrone acetate

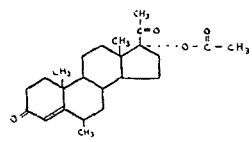


ethynodiol acetate

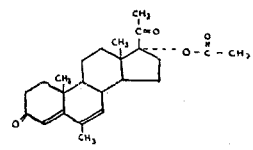
Progesterone itself is inactive when given orally, as is *17a hydroxy progesterone,* but esterification produces an orally active compound with progestational properties. The addition of substituents at position 6 further increases its effectiveness. A methyl group at this position produces *medroxyprogesterone acetate,* while the addition of a double bond between position 6 and 7 produces *megesterol acetate.*



17acetoxy progesterone



medroxy progesterone acetate



megestrol acetate

The progestational agents are metabolised to some extent to oestrogens, and hence they all have a varying degree of oestrogenicity, norethynodrel having moderate oestrogenic properties, while norethisterone and medroxyprogesterone acetate have minimal oestrogenic properties.

The principal mode of action of the pill is inhibition of ovulation by the elimination of the FSH and LH peaks of the menstrual cycle. Both the oestrogen and progestogen are responsible for this occurence. In addition the inhibition of the gonadotrophins by these synthetic steroids leads to a marked reduction in endogenous ovarian steroid production. Finally the progestogen is thought to exert some contraceptive effect by its direct action on the endometrium, causing atrophy of the glands, and also by making the cervical mucus more tenacious, and hence more difficult for sperm penetration.

Having given a brief synopsis of the structure and mode of action of these preparations I should now like to turn to their metabolic effects and the subsequent clinical problems.

Minor side effects such as breast fullness vaginal discharge and nausea are attributable to the oestrogen component, while apathy, pelvic discomfort, diminished libido and depression are attributable to the progestogen. Nausea during the first few cycles can occur in up to 40% of patients but its frequency diminishes rapidly thereafter. Depression and diminished libido are associated with high endometrial monoamine oxidase activity (Grant and Pryse-Davies, 1968) Another factor that may be responsible for depression is altered trytophan metabolism, leading to a functional deficiency of pyridoxine, which is a coenzyme in the production of 5 hydroxytryptamine. It has therefore been suggested that pyridoxine should be given prophylactically to all women with a history of depression who are taking oral contraceptives, or even that depression is a contraindication to taking these preparations.

Secondary amenorrhoea can follow cessation of the pill, probably being due to a failure of the gonadotrophin release factors to revert to their normal levels. Five per cent of patients who had been taking the combined pill for more than 2 years had a menstrual delay of 70 to 390 days. (Goldzieher, 1970)

The side effect that has recieved the greatest publicity is thromboembolism, with its occasional fatal culmination. Vessey, Doll and Inman in a series of papers during the last two years, and summarised by Doll and Vessey (1970) have concluded that there is a six-fold increase in deep venous thrombosis and pulmonary emboli with an eight-fold increase in mortality from these causes among women on oral contraceptives, together with a six-fold increase in the incidence of, and mortality from, cerebral thrombosis. Opinion in the U.S.A. is slightly sceptical of this work in that the studies were small, retrospective, and involved only hospital admissions. However one of the chief critics in quoting different figures refers to thrombophlebitis and not to deep venous thrombosis, so a comparison becomes less valid. (Drill and Calhoun, 1968) The incidence of coronary thrombosis has also been thought to be raised by oral contraceptives to the extent of being related to the dose of oestrogen used (Inmam et al; 1970) but other aetiological factors such as hyperlipidaemia and smoking have not been adequately excluded. (Oliver, 1970)

The statistical evidence at present is equivocal but nevertheless suggests that the oral contraceptive has some aetiological role in causing thrombosis. The results of large prospective studies currently being carried out will be necessary before this can be conclusively shown.

What then are the effects of oral contraceptives on the blood clotting mechanism? Plasma factors VII and X are raised after 3 months (Poller et al 1968) while factors VIII and IX do not appear to rise. (Poller and Thomson 1966; Hakim et al 1970) Platelet aggregation is increased when the platelets are exposed to ADP but not when exposed to noradrenaline, this being similar to the pattern observed in patients with atherosclerosis. (Bolton et. al 1968). Platelet aggregation was not increased in men who were given a natural oestrogen preparation—namely *Premarin* (Hampton, 1971). None of these changes occur with a progesterone alone hence suggesting that the oestrogen component is responsible for them.

The fibrinolytic system is also affected by oral contraceptives. Fibrinogen levels do not seem to be raised but fibrinolytic activity seems to be increased, because raised plasminogen levels have been found and the euglobulin lysis time is shortened in women taking oral contraceptives. (Brakman et al. 1970) Cryofibrinogen, which is an intermediate product in the partial breakdown of fibrinogen and fibrin, is increased. (Pindyck et al. 1970) Thus it is possible that the dynamic equilibrium between coagulation and fibrinolysis is maintained, but at an increased rate. However the pill by its action on the liver can raise the levels of a2 macroglobulin and of serum triglycerides, both these states diminishing fibrinolytic activity. (Barton et. al; 1970) In addition to raised serum triglycerides there is a rise in serum cholesterol levels, and there is some evidence that both these rises are dependent on the dose of oestrogen. Finally there is an increase in low density lipoproteins which may be caused by diminished lipoprotein lipase activity. It is this factor that may cause an alteration in platelet aggregation.

From this evidence one can postulate that the synthetic oestrogen in the pill, by inhibiting endogenous ovarian oestrogen production and by altering lipid metabolism, reduces the pre-menopausal woman's natural immunity to atherosclerosis and its complications, while substituting a state of hypercoagulability which is kept in check by increased fibrinolysis. A slight diminution in the latter may then be the cause of the thromboembolic complications.

The clinical significance of this is that no woman should undergo elective surgery while taking oral contraceptives. These should not be prescribed for anyone with a history of thromboembolism, nor for anyone with an increased tendency to clot formation, such as those with rheumatic heart disease.

Another aspect of altered metabolism which appears to be related to the amount of oestrogen used, is cortisol metabolism. Mestranol was found to increase unbound, protein bound and total cortisol levels. (Burke, 1970) The increased tissue exposure to unbound cortisol is small and probably not signficant, but it is this fraction of plasma cortisol that is responsible for hypothalamic control, and consequently any alteration of this level raises the question of long term interference, at the hypothalamic level, of cortisol homeostasis. Cortisol bound to a globulin may have access to hepatic cells, induce enzyme changes, and thereby be responsible for the altered production of proteins from the liver. This is perhaps one of the most fundamental physiological alterations that the oral contraceptives cause.

Carbohydrate metabolism is also altered by oral contraceptives, probably by the oestrogen component, and maybe secondary to increased cortisol levels. Mean fasting plasma glucose levels appear to be unchanged, but

both intravenous and oral glucose tolerance deteriorates. (Wynn and Doar, 1970) However 90% of cases rapidly return to normal on cessation of therapy. There is doubt about mean fasting plasma insulin levels, some authors showing a rise while others found them unchanged. There is no doubt, however that mean plasma insulin levels after both oral and intravenous glucose administration are higher during oral contraceptive therapy than those before therapy started.

There is evidence that as many as 77% of women taking oral contracptives for more than 8 years will develop abnormal glucose tolerance (Spellacy et. al; 1968) A family history of diabetes, previous large babies, or diminished carbohydrate tolerance during a previous pregnancy predispose to these changes, and certainly diabetes or a history of abnormal carbohydrate metabolism during pregnancy are absolute contraindications.

Liver function is altered as we have already seen, to the extent of producing increased amounts of certain proteins. In addition there is some impairment of transfer of substances from the liver to the bile, as manifested by up to a 12% retention of bromsulphthalein (Kleiner et. al; 1965) while 2% of patients have raised alkaline phosphatase levels due to alterations in the hepatic excretory mechanism. (Schaffner. 1966) A cholestatic jaundice occurs in some patients, preceeded by anorexia, nausea and pruritus, the serum bilirubin being in the range of 3 to 10mg.%. Microscopy of the liver at this stage shows dilatation of the bile canaliculi, with bile stasis. Histories of pruritus or jaundice in pregnancy are therefore contraindications to oestrogen containing oral contraceptives. A history of jaundice unrelated to pregnancy, or of infective hepatitis, is not a contraindication provided liver function is normal.

Finally there seems to be a slight rise in blood pressure among women on oral contraceptives. The mechanism involved is as yet unknown, but there is a rise in plasma renin substrate, which may in turn be caused by the oestrogenic stimulus to its hepatic production. Patients who are already hypertensive should not take oestrogen containing oral contraceptives, lest their hypertension is worsened.

Note: This paper was read at the Annual Clinical Meeting of the Association of Surgeons and Physicians of Malta, Nov. 1970.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From the evidence described it is obvious that the oestrogen containing oral contraceptives have a fundamental and diversified effect on the patient's physiology. What the outcome of this in terms of iatrogenic disease will be only time and long term prospective studies will tell. However it is important to put the risk at the present time in perspective, first to deaths related to other contraceptives, and secondly to deaths from other causes.

Table I illustrates the relative risks of various contraceptive methods, with the death rate associated with their failure.

TABLE I

| METHOD | Pregnancies per 1 million users | Deaths per 1 Million users caused by Pregnancy | Method | Total |
|---|---|---|---|---|
| Oral contraception | 20,000 | 5 | 21 | 26 |
| Intrauterine device | 40,000 | 10 | 20 | 30 |
| Condoms and diaphragms | 150,000 | 33 | 0 | 33 |
| Spermicides, coitus interruptus, etc. | 250,000 | 56 | 0 | 56 |
| Sterilisation, male and female | 1,000 | 0 | 15 | 15 |
| Unprotected intercourse | 800,000 | 223 | 0 | 223 |

Table II compares the risks of death from thromboembolism due to oral contraceptives with the risks of death from other causes and in the group more susceptible to thromboembolism i.e. 35-44, the risk is comparable to that of dying in a car accident and much less than the risks associated with pregnancy, delivery and the puerperium.

TABLE II

| Death per 100,000 Women from | AGE 20-34 | 35-44 |
|---|---|---|
| Thromboemoblism in oral contraceptive users | 1.5 | 3.9 |
| Cancer | 13.7 | 70.1 |
| All risks of prenancy delivery and puerperium | 22.8 | 57.6 |
| Motor Accidents | 4.9 | 3.9 |


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