

# A short history of oral contraception

► In 1960, the first combined hormonal oral contraceptive, containing 150µg mestranol (a methylether of ethinyl-oestradiol (EE)) and 9.8mg norethynodrel (Enovid®) was approved by the US FDA. Pincus and his associates had developed 'the pill', but they, like other famous endocrine therapists, were standing on the shoulders of inventive chemists and biochemists.

It was Inhoffen and Hohlweg in 1938 who synthesised the extremely potent EE that largely escaped the hepatic metabolism of 17β-oestradiol, and Djerassi in 1954 who developed ethinylated derivatives of 19-nortestosterone (among them norethynodrel) as highly potent orally active progestogens. In 1921, Haberlandt and colleagues in Innsbruck had shown that transplantation of ovaries of pregnant rabbits into fertile female rabbits suppressed their ovulation and fertility. The effective hormone was progesterone, which was demonstrated in 1944.

Oestrogens alone also suppress ovulation at high dosage, but in the pill it is mainly the progestogen that inhibits ovulation, while the oestrogen serves to imitate regular menstrual bleedings. This is the basic premise of hormonal contraception, except for low-dose contraception using progestogens alone (the mini-pill). This seems to act mainly by changing the properties of uterine cervical mucus such that its penetration by spermatozoa is inhibited.

The effectiveness of the combined oral contraceptives in women who took the pill regularly was unrivalled by any other method. It changed sexual and social life and the demographic development of the modern world, though not always in a desirable direction.

When I spent a sabbatical year (1970-1971) at the MRC Blood Pressure Unit in Glasgow, the effect of oral contraceptives on blood pressure was an important topic of research. Several alarming cases of malignant hypertension in women taking the pill, some of them leading to irreversible renal failure or death, had focused interest on its non-reproductive side-effects. It was found that EE greatly stimulated the synthesis or inhibited the metabolism of a host of hepatic proteins, among them the renin substrate angiotensinogen, several clotting

factors, sex hormone-binding globulin, corticosteroid-binding globulin and thyroxine-binding globulin.

Activation of the renin-angiotensin system is the main cause of oral contraceptive-induced hypertension in susceptible women. An activation of the blood clotting cascade which is not completely compensated for by increased fibrinolysis seems to be the main mechanism for the three- to fourfold increase in the risk of thromboembolism in users.

The further evolution of oral contraceptives was mainly driven by the hope of minimising side-effects, while the extremely high contraceptive efficiency of the first oral contraceptive on the market could not be improved. Only one year after Enovid®, the first European oral contraceptive (Anovlar®) containing only 50µg EE and 4mg norethisterone acetate was available. Epidemiological studies seemed to indicate that lowering the dosage of EE (and possibly of the synthetic progestogens) would lead to better tolerability (e.g. reduced breast tenderness or weight gain) and to fewer non-reproductive complications. Today's conventional oral contraceptives contain between 20 and 35µg EE and microgram amounts of second or third generation derivatives of ethinylated 19-nortestosterone.

Other interesting developments have been the introduction of 17-hydroxyprogesterone derivatives with anti-androgenic properties for women with acne or hirsutism (e.g. cyproterone acetate), and of the progestagenic and anti-mineralocorticoid spironolactone derivative drospirenone for women with a tendency to fluid retention and an increase in blood pressure. Both are used in combination with low-dose EE.

However, these oral contraceptives still have a prothrombotic effect, although their EE content is low. The thromboembolic risk associated with the recently introduced transdermal combined contraceptive Evra® does not seem to be any better than modern oral contraceptives, since it also uses EE. This, unlike natural oestradiol, seems to affect hepatic protein synthesis independent of its route of application.

In postmenopausal hormone replacement therapy, the transdermal route of oestradiol application seems to be devoid of a prothrombotic risk. Development of a transdermal combined hormonal contraceptive with oestradiol instead of EE would provide a great next chapter in this endocrine story.

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spend on promoting endocrinology over the next few years. We expect that the results for 2005-2006, which will be finalised in August, will add to this. The uncertainty surrounding publishing income means that we mustn't go mad, and in particular we mustn't make plans to spend money we haven't earned yet (in case we don't), but we can certainly identify some additional services over the next few years.

The Society held a strategic review late last year, and the spring Council meeting approved outline plans resulting from this. So look out for a number of new grants and other funding opportunities aimed at

supporting scientists, clinicians and nurses in endocrinology. We are also looking at using some of the money, often in collaboration with other organisations, to help address some of the wider questions:

- ▷ can we encourage more good young scientists and doctors to opt for a career in endocrinology?
- ▷ can career structures for scientists be improved?
- ▷ can we encourage more schoolchildren to opt for a bioscience degree?
- ▷ can the negativity of parts of the public towards animal experimentation be countered?
- ▷ how can we increase awareness of endocrinology among the general public?

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