Current Status of Oral Contraceptive

by Dr. Wong Wai Ping
MBBS., FRCS(E)., MRCOG
Department of Obstetrics & Gynaecology,
Faculty of Medicine,
University of Malaya,
Kuala Lumpur,
WEST MALAYSIA.

and Associate Professor I. S. Puvan
MBBS., FRCS(Glas. & Edin.), MRCP(Edin)., MRCOG
Department of Obstetrics & Gynaecology,
Faculty of Medicine,
University of Malaya,
Kuala Lumpur,
WEST MALAYSIA.

WHEN ORAL CONTRACEPTIVE was first introduced in 1956, there was considerable sceptism about the potential for widespread usefulness of this new family planning innovation. Since then there has been a slow but steady increase in number of users so that by 1975, approximately 50 million women were on it. This increase was influenced to a great extent by numerous reports of the side effects of the oral contraceptive in medical journals and in mass media. The latter contributed in no small way to the adverse publicity on the taking of the Pill. Oral contraceptives have raised numerous problems in family planning but over the years, there have been great attempts to minimize them.

The original Pill was a "combined" type, consisting of oestrogens and progestogens given together over a period of 3 weeks out of every four. These initial tablets contained 10 mgm. of norethynodrel and up to 230 ugm. of mestranol. These were associated with a very high incidences of side effects including nausea, vomiting, headaches, weight gain, breakthrough bleeding, amenorrhoea, anxiety, changes in libido and other less common manifestations. In general, it was found that these side effects tended to last for a few cycles but because they determine the acceptability of the drug, much attention was paid to them. Some of these side effects were diminished by lowering the dose of oestrogens and progestogens in the combined pill. Sometimes, these side effects could be diminished by altering the type of oral contraceptive for a particular patient. Some workers developed theories covering the mixture of oestrogen and progestogens that is suitable for particular patients (Dickey and Dorr 1969). A variation of prescription of oral contraceptives was introduced using oestrogen alone for the first few weeks of a cycle to inhibit ovulation, followed by a week of oestrogen-progestogen combination (the serial or squential pills). This was considered more physiological with a closer simulation of the changes in endogenous hormones during a menstrual cycle. It was soon demonstrated that sequential contraception was similarly effective but though not quite to the same degree as the combined Pill. They however contain higher amounts of oestrogens over each cycle.

Major Side Effects:

By the late 1960's, it became evident that there were certain serious side effects associated with the oral contraceptives. By 1968, Vessey and Doll implicated the oral contraceptive as a causative factor of the increased incidence of venous thrombosis and thrombo-embolism among patients on the Pill. It seemed that the oestrogenic rather than the progestogenic component was responsible and the incidence of venous thrombosis was greater with oral contraceptives containing more than 50 ugm. of oestrogens (Inman et al 1970).

Steriod hormones have a marked influence on liver function (Kappas 1968). Large dose of steriod seem to induce cholestasis and hepatocellular damage but low dose seemed to have minimal effects. These changes in liver function seemed to be of no consequence to a healthy woman but they contribute to a case of not prescribing oral contraceptive to patients with recent hepatic dysfunction.

*Lecture given to Post-graduate Seminars in Seremban, Alor Star, Penang, and Ipoh.

Impared glucose tolerance were found by investigators as early as 1964 (Gershberg et al). Both combined and sequential pills could produce disturbances in carbohydrate metabolism and these side effects seemed to be related to the oestrogen dose (Spellacy 1969). These abnormal changes seemed to disappear with discontinuation of the oral contraceptive. Whether these changes are related to development of chemical diabetes is still unknown.

Lipid metabolism was shown to be disturbed by oral contraceptive (Wynn et al 1966 and Gershberg 1968). There seemed to be an increased mean serum levels of triglycerides, low density and very low density lipoproteins and a smaller increase in cholesterol in oral contraceptive users. These rise in triglycerides seem to be greater with increased oestrogen content in the Pill. The cholesterol rise seemed to be correlated with the progestogen content. These values seem to return to normal with discontinuation of the oral contraceptive though Wynn and Doar (1969) warned that the potential reversibility may not be maintained after prolonged usage of the Pill.

Minipills:

One development of oral contraception was the introduction of the "micro-dose" progestogen alone method. The thought was that minute doses of progestogens alone might provide contraception with no necessity for oestrogens. Studies were made on numerous progestogenic compounds and it became obvious that the progestogens achieved their effect by alteration of the cervical mucus so that sperms do not penetrate and of the endometrium so that implantation becomes impossible. The "micro-dose" pills were shown to provide effective contraception, although not in the same range as the combined oral contraceptive. One of these was chlormadinone acetate which was once withdrawn because they produce mammary lesions in beagle dogs, though relevance of this to human toxicity is debatable. There has been recent reports (Bonnar 1974, Hawkins 1974) that the minipill may not protect against ectopic pregnancy.

Once a Month Pill:

To solve the problem of regular taking of the Pill, the "once a month" pill was investigated. This pill is a combination of an long acting oestrogen, quinestrol, and a relatively shorter acting progestogen, quingestanol acetate. This has been proved effective and useful in substantial studies in Latin America (Rubio et al 1972). Unfortunately, there was a high incidence of breakthrough bleeding and cycle irregularity thereby limiting its acceptability. Efficiency was also not as good as combined pills.

Post-coital Contraception:

In the search for an effective antifertility agent, Morris and Van Wagener (1966) studied effects of oestrogens on inhibition of ovum implantation in rabbits and rhesus monkeys. They concluded that certain oestrogens given post-coitally prevented implantation of the ovum in primates. The present "morning after" pill consists of prescription of large doses of stilboesterol after coitus. The impression is that the method is effective (Haspels 1970, Kuchera 1971). There is, however, need for additional and more detail data, particularly about users' fertility and age. The majority of women in these studies were young college students, a number of them possibly still in the low fertility range. At present there is no positive evidence that the restricted post-coital use of diethyl stilboesterol carries a significant carcinogenic risk to either mother or foetus. However, a statistical association has been demonstrated between di-ethyl stilboesterol taken by women later in pregnancy to prevent spontaneous abortion and the appearance of adenocarcinoma of the vagina or cervix in their daughters at an early age. (Herbst et al 1971, Greenwald et al 1972). The possibility of teratogenic and other adverse effects on the foetus with very early administration of di-ethyl stilboesterol warrants further investigation. Until these investigations are complete, voluntary termination of pregnancy should be carefully considered when pregnancy occurs in spite of the use of di-ethyl stilboesterol.

Royal College of General Practitioners' Report:

Recently, there have been a number of large scale epidemiological studies on the effects of oral contraceptives. Among these was a long term prospective study launched in 1968 by the Royal College of General Practitioners' of Great Britain. It was a controlled investigation of the natural history of a large group of women (initially 46,000) half of whom had chosen the Pill as a contraceptive. The interim report (1974) sheds further light on the side effects of oral contraceptives. Deep vein-thrombosis of the leg was found to occur 5.6 times more often in Pill users than in controls, while no difference was reported between former users and controls (See Fig. 1). A related condition, superficial thrombosis of the leg occurred 48 percent more frequently among Pill users than among controls. The investigators found an apparent dose relationship of deep vein thrombosis to oestrogen with higher incidence rates for higher oestrogen doses (Fig. 2).

No apparent relationship to progestogen dosage or duration of Pill use was apparent. There was an increase incidence with increasing age and a possibly similar relationship to parity. The investi-

Fig. 1

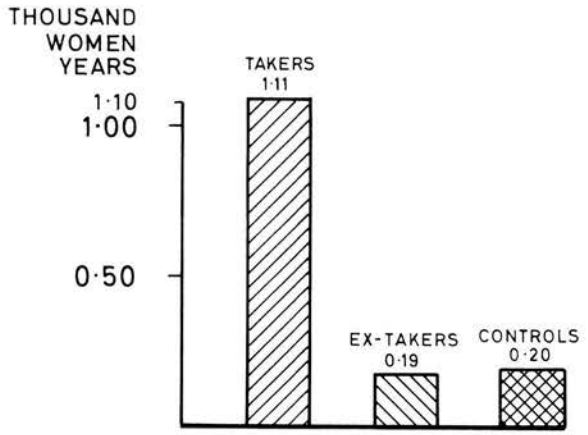

Fig. 1

Comparison of incidences of deep vein thrombosis in oral contraceptive users and non users (rate per 1,000 women per year)

Fig. 2

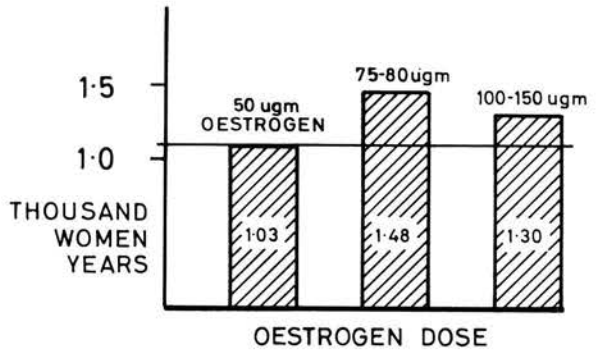

Fig. 2

Comparison of incidences of venous thrombosis in relation to oestrogen dose (ratio to low dose 50 ugm. oestrogen)

gations estimated that Pills with high oestrogen dosages were responsible for 112 cases of deep vein thrombosis per 100,000 women per year. This was much higher than 81 cases of deep vein thrombosis per 100,000 women per year seen with the oral contraceptive containing 50 ugm. of oestrogen per pill. This seems to confirm the findings of the Committee of Safety of Drugs in the United Kingdom (Inman et al 1970).

The study also showed that there is no correlation with cancers of the cervix and breast. In fact, it showed that Pill users of more than 2 years seems to be apparently protected from benign growths of the breasts. This slight reduction in breast disease in women using oral contraceptives raise the hope that use of this method by young women may eventually have some protective effect later against breast disease. (See Fig. 3)

Fig. 3

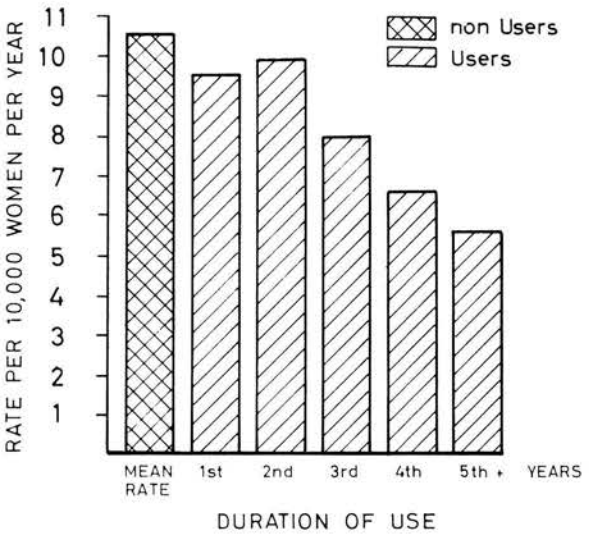

Fig. 3

Comparison of incidence of benign breast neoplasia in oral contraceptive users and non users by duration of use. (Rate per 1,000 women per year)

Hypertension seemed to be more commoner with increased duration of Pill usage so that by the fifth years, the incidence was 5 times that of the first year. These seemed to be a relationship between incidence of hypertension and progestogen dosage with the highest rates observed for women using pills with more than 3 mgm. of progestogens. Age definitely correlated with the development of hypertension in Pill users.

Pill users showed much higher incidence rates for coronary artery disease than controls but the numbers involved were too small for the difference to be statistically significant. This is because heart disease is extremely rare in young women. Pill users seemed to have more than 4 times the risk of developing cerebro-vascular disease of all forms than did non users.

A relationship was found between Pill use and these disease involving circulation in small blood vessels, namely, Raynaud's syndrome, chilbains and spontaneous bruising.

There seemed to be no increased incidence of psychosis among Pill users. There were more patients on Pills complaining of change in libido but it was thought that there were many reasons and opportunities to do so which were not related to the pharmacological action of the drug.

An increased incidence of gall bladder disease and gallstones among Pill users was also observed in this study. Although, the number of cases was not large enough for statistical differences, investigators felt that this was a definitive side effect of Pill. Also, a relationship to progestogen dosage was found, with increasing incidence of gall bladder disease accompanying increased progestogen dosage.

Urinary tract infectious were reported 20-50 percent more often in Pill users. The infection rate increased with increased oestrogen dosage. Increased sexual activity of pill users may be an important factor in this relationship.

Pill users had higher incidence rates for various vaginal infections, which are associated with sexual activity. Cervicitis seemed to be more common with increased progestogen dosage and with prolonged usage.

Post Pill Amenorrhoea and Infertility:

There are no satisfactory data on the prevalence of anovulatory menstrual cycles in healthy woman. Resumption of ovulation after discontinuation of oral contraceptives usually occur within 4 to 8 weeks. In a few women there is persistence of amenorrhoea and/or anovulation for 6 months or more. The estimated incidence is about 1 percent (Larson-Cohn 1969, Shearman 1971). It occurs with both the combined and sequential regime. It is commonly accompanied by galactorrhoea suggesting a hypothalamic effect. It seems to occur more commonly with women who have irregular menstrual cycles originally. There is no evidence that this is related to longer use of oral contraceptive. There is no scientific evidence that stopping the pill after 2 years will materially effect the incidence of anovulation.

Present studies undoubtedly indicate a delay of about 3 months in conception in women who have used the pills. In spite of the delay, it must be emphasised that almost 90 percent of previously pregnant cases conceived by the end of two years.

Biochemical Developments:

In the search for an effective, acceptable contraceptive with minimal metabolic effect, investigations of the biochemical effect of the Pill were instituted. It became apparent that ethinyl oestradiol seems to be more potent than a comparative dose of mestranol (3 methylether of ethinyl oestradiol). There is now sufficient evidence that mestranol is de-methylated to ethinyl oestradiol in the liver. This conversion seems to be interfered with by many progestogens as shown in vitro data (Kappus et al 1972), raising the question of invivo hepatic conversions of mestranol of various oral contraceptives. From this, it would seem prudent to avoid mestranol in favour of ethinyl oestradiol as the oestrogenic component of the pill.

Recent studies of the progesterone receptors seemed to show that a similar problem occurs with the progestogens. Nor-ethisterone acetate, ethynodiol di-acetate, norethynodiol and lynesterol all have to be metabolised in the liver to norethisterone before they can exert their biological effects.

These conversions could be affected by a number of exogenous and endogenous factors. Several drugs have already known to reduce contraceptive efficacy (Mumford 1974). Rifampicin, an anti-tuberculosis drug, is known to cause a high incidence of menstrual disorders in women on oral contraceptives and appears to affect the effectiveness of the pills (Reimers et al 1973). It is suggested that oestrogen breakdown is speeded up by Rifampicin. Other drugs that may interfer with the efficacy of oral contraceptive are ampicillin and barbiturates. These findings suggest interactions with other drugs may affect the efficacy of oral contraceptive adversely.

Low-dose Method:

It was natural that as some side effects of the Pill were dose related to the hormones in the Pill that attempts were made to reduce the dosages further. Other than a high incidence of breakthrough bleeding, good results were obtained from field trials of the low dose Pills (Woutersz 1974, Allen 1974, Brosens et al 1974, Moggia et al 1974, Wong & Puvan 1975). It also became obvious that the low-dose ethinyl oestradiol-norgesterol. combination seemed to have added advantages. Brigg (1974) showed that abnormal hepatic functions induced by oral contraception seemed to be less severe when the oral contraceptive used was the low dosage ethinyl-oestradiol norgesterol combination. Carbohydrate metabolism, as reflected by glucose tolerance, insulin secretion and blood pyruvate levels were little disturbed when low dose

ethinyl oestradiol-norgesterol was used as compared with other oral contraceptives (Wynn et al 1974). Serum lipid levels also seemed to be less disturbed (Wynn et al 1974). There is a great possibility that the minimal hepatic dysfunction and minimal disturbances of carbohydrate and fat metabolism could mean, in the long run, less side effects and that disturbances in weight and hypertension may not occur. If this was true, and field trials already suggest this may be so, then, we may be on the threshold of developing the ideal oral contraceptive.

Summary:

There have been considerable advance in oral contraception in recent years. Much of these have great relevance to a better prescription and management of patients on the Pills. The general impression is that with careful patient selection and careful medical supervision, oral contraceptive is and will continue to provide an excellent form of contraceptive with minimal side effects and metabolic disturbance.

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