TWO PROBLEMS IN ORAL CONTRACEPTION: ARTERIOSCLEROTIC CARDIOPATHY AND DRUG INTERACTIONS

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SUMMARY

The Authors examine two aspects of oral contraception: the risk of arteriosclerotic cardiopathy and the interaction with other drugs. The former is rather limited but increases significantly when other arteriosclerotic risk factors, first and foremost smoke, are present. The dose of both the estrogenic and the progestinic components also influences the risk.

The Authors examine the most recent information on the interference of some drugs with the contraceptive effectiveness of synthetic, especially low-dose, estroprogestinics, which is mediated by changes of the intestinal absorption or metabolic clearance rate.

Finally, they analyse the interference of contraceptive steroids with the kinetics of other drugs and, consequently, with the intensity of therapeutical and side effects.

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The original enthusiasm about the effectiveness of contraceptive steroids in controlling fertility has soon been replaced by a more cautions attitude owing to reports of side effects. Studies have been undertaken of the relationship of oral contraceptives with thromboembolism, metabolic troubles, genital neoplasias, endocrine disorders, etc. The conclusions drawn by many of these works are questionable, since they rely on occasional reports, laboratory tests on animals or brief retrospective studies.

This has triggered many debates, outside medical circles too, and press campaigns lacking the necessary scientific objectivity and critical review of information. Let us not forget that millions of women have already used contraceptive steroids under the most widely differing conditions of environment, living standards and patterns, nutritional habits, exposure to toxic drugs and substances. It is consequently extremely difficult correctly to assess the possible risks directly associated to the adoption of this contraceptive method.

This review takes into account two significant aspects of oral contraception: arteriosclerotic cardiopathy and interactions with other drugs.

Opinions still diverge on the role of contraceptive steroids in the etiology of myocardial infarction. The analysis of the statistical data on the causes of death from cardiovascular diseases in women in reproductive age can hardly lead to reliable conclusions since rheumatic cardiopathies, stress, and professional activity influence the picture to a significant extent. Moreover, rather few women in fertile age die, today, from cardiopathy.

Unlike the British studies, the World Health Organization's data and US statistics on death from cardiovascular diseases do not show higher prevalence for oral contraceptives users.

Probably, the data of different Countries cannot be compared owing to the

differing incidence of other cardiovascular morbidity and mortality risk factors, like hypertension, obesity, smoke, physical activity, genetic predisposition.

A recent study has once again examined the prevalence of myocardial infarction in relation to the use of estroprogestinic contraceptives. Rosenberg and Coll. ([9]), on the basis of answers to a questionary, found that 156 out of 121,944 women (1.2‰) had been hospitalized following myocardial infarction; 23 of them used oral contraceptives. The Authors concluded that the latter increase the risk of infarction by 1.8.

Shapiro and Coll. ([10]) studied 369 patients struk by infarction and an adequate control group. The overall 'relative frequence' in oral contraceptives users was 4 times, but it was 4.5 times in smokers and 39 times in non-smokers.

The smokers who did not use oral contraception showed a relative frequence of 7.8 times. Consequently, smoke appears to be a higher-risk factor than oral contraceptives. A combination of the two increases the risk dramatically.

Krueger and Coll. too, in a study ([5]) of women died from infarction, found a higher risk in oral contraceptive users and confirmed the danger entailed by smoke.

The risk of arteriosclerotic cardiopathy depends upon the dose of both the estrogenic and the progestinic components.

A research work by Meade and Coll. ([6]) highlights the importance of the dose of ethynylestradiol: the use of 30 instead of 50 micrograms per day significantly decreases the risk.

Similarly, a reduction of the progestinic dose lowers the incidence of damage to the arterial walls and, consequently, of ischemic cardiopathy. A reduction of noretisterone from 4 to 1 mg, or levonorgestrel from 0.25 to 0.15 mg decreases the importance of the changes induced in lipoprotein and cholesterol blood levels.

This recent information confirms the need for rigorous selection of women applying for steroidal contraception which is unadvisable in those who present other factors of arteriosclerotic risk, like smoke, obesity, hypertension, dislipemia or family predisposition.

In any case, the recent both estrogen and progesteron low-dose pills are less harmful.

While the side effects of oral contraceptives have been extensively examined in the literature, their interaction with other drugs has been rather neglected. Both estrogens and estroprogestinics, alone or combined, can interact with other drugs, although the relative importance of the two components in the various interactions that have been clinically reported is still unclear. No interactions have so far been reported with regard to what is known as 'minipill', exclusively progestinic, possibly owing to its limited use. There are two possible kinds of interaction: a drug interfering with the effectiveness of an oral contraceptive; an oral contraceptive interfering with the action of another drug. The recent introduction of low-dose estroprogestinic pills increases the likelihood of the former but decreases that of the latter.

Drugs influencing the effectiveness of estroprogestinic contraceptives

The study of the interactions of oral estroprogestinic contraceptives with other drugs stemmed from clinical observations and subsequently extended to experimental pharmacokinetic studies.

There are clinical reports of occasional cases of unexpected pregnancy or intramenstrual spotting. These facts have been ascribed to changes occurring in the pharmacokinetics of oral contraceptive owing to the influence of other drugs through mechanisms of reduction of the absorbtion, enzymatic induction or inhibition, changed bond with plasma proteins. No interference with the renal excretion has so far been reported.

Table 1. — *Interaction of drugs with the effectiveness of oral contraceptives.*

Reduction of the absorption because of enterohepatic recirculation:
– Ampicillin
– Chloramphenicol
– Neomycin
– Phenoxymethylpenicillin
– Lincomycin

A reduced absorbtion of oral contraceptives (table 1) can be observed in patients undergoing ampicillin or other antibiotic treatments (chloramphenicol, neomycin, phenoxymetylpenicillin). The destruction of the intestinal phlora causes a reduction of estroprogestinic contraceptives plasma levels since their enterohepatic circulation is interrupted. It is known that the intestinal phlora, by hydrolysing conjugated steroids, allows them to be re-absorbed, thus recovering the portion which would otherwise be excreted with the feces. The administration of a 500 mg dose of ampicillin twice a day significantly decreases ethynylestradiol plasma concentration in women using a combined pill containing 30 or 50 μg of this estrogen.

A recent experimental study on rats, by Back and Coll. ([1]) has shown that the progestinic component as well, noretisterone, is influenced by the administration of antibiotics. A four-day treatment with ampicillin or neomycin or an association of neomycin and lincomycin reduces mainly the aerobic but also the anaerobic intestinal phlora. The combination of the two antibiotics causes a sharp reduction of both. It takes at least 14 days from the end of the antibiotic treatment for the intestinal phlora to be restored. This treatment significantly lowers the bile concentration of labeled noretisterone, introduced in a conjugated form, in the duodenum or the caecum.

These research works proving the importance of antibiotic therapies in millions of pill users raise the question of whether many unespected pregnancies can be ascribed to this interaction rather than to the user's contraceptive negligence.

Interference due to enzymatic induction (table 2)

It is well known that pregnancy may occur in patients undergoing therapies with Rifampycin alone or in association with etambutole, despite the use of oral contraceptives. The same has been reported in epileptic patients undergoing cronic therapies with barbiturates and/or phenytoin.

This phenomenon originates from a drug-induced enzymatic induction which accelerates the metabolism of the steroids contained in oral contraceptive preparations.

The enzymatic induction of the drug elimination systems can be observed, though with remarkable individual differences, in usual oral contraceptives users. The administration of 100 mg/day phenobarbital for one month further increases the steroidal hepatic conjugation systems and, consequently, their velocities of elimination. From a clinical point, this results in the appearance of intermenstrual spotting or, sometimes, unexpected pregnancies. Long rifampicin or phenobarbital therapies lower the noretisterone plasma concentration. However, owing to the wide range of possible individual oral contraceptive metabolization velocities on-

Table 2. — *Interaction of drugs with the effectiveness of oral contraceptives.*

Drug-induced enzymatic induction:
– Rifampicin
– Phenytoin
– Barbiturates
– Tranquillizers
– Anti-histaminics
– Anti-phlogistics
– Analgesics

Table 3. — *Interaction of oral contraceptives with other drugs.*

Enzymatic competition:
– Imipramine
– Chloropromazine
– Exobarbital
Increase of hepato-toxicity:
– Troleandomycin
Enhancement:
– Corticosteroids
– Oral anti-coagulants
– Caffeine
– Chlordiazepoxide
Antagonism:
– Oral hypoglycemic drugs

ly in a small minority of women the levels are too low to ensure contraception, thus entailing pregnancy risks.

Other drugs too, like tranquillizers, anti-histaminics, anti-phlogistics or analgesics, may produce enzymatic induction at the level of the hepatic microsomes.

A reduction of both noretisterone and ethynylestradiol plasma levels has recently been demonstrated in a group of women treated with antitubercular chemotherapeutical substances and low-dose oral contraceptives. Some presented ovulation and irregular menstruations ([4]).

Isoniazid, however, does not produce this effect. A recent review of the literature found 25 cases of pregnancy in women using oral contraceptives associated with anticonvulsants (phenytoin, different barbiturates, associations of many of these drugs).

Interference of oral contraceptives with the activity of other drugs (table 3)

Doctors should know, in prescribing drugs, whether their patients use oral contraceptives, since these hormonal steroids may interfere with the expected therapeutical effect. A phenomenon of enzymatic competition may occur which slows down the elimination of the drug, thus exposing the patient to a 'relative overdose' despite the assumption of therapeutical doses. For instance, the ethynylestradiol contained in many combined pills inhibits the metabolism of other drugs like imipramine (a tricyclical antidepressive), chloropromazine (a phenothiazine), esobarbital (a barbiturate), ethylmorphine. Symptoms characteristic of an overdose of these drugs may sometimes appear.

It has recently been reported that the simultaneous administration of triacetiloleandomycin and oral contraceptives causees jaundice ([8]): 15 cases have so far been described. Jaundice appears after 3/9 days of antibiotic therapy; it originates from intrahepatic colostasis and disappears progressively in all cases when the therapy is interrupted. Probably, this antibiotic increases the hepatic toxicity of contraceptive steroids and should not be prescribed to pill users.

Oral contraceptives tend to enhance the effect of corticosteroids. They can increase its bioavailability thanks to a phenomenon of competition for carrier-proteins.

Vitamin K antagonists, oral anticoagulants, are less effective in oral contraceptive and oral hypoglycemizers users. It has been noted that the prothrombine time is higher when the patient uses both drugs than when she uses oral anticoagulants only. However, the results of De Teresa and Coll. ([3]) disagree with what has so far been accepted, since they found that contraceptive steroids enhance the anticoagulant effect.

A research study by Patwardhan and Coll. ([7]) shows that caffeine, contained in many drinks, is eliminated more slowly in oral contraceptive users owing to a mechanism of enzymatic competition with contraceptive steroids at the level of the hepatic oxygenase system linked to cytochrome P-450. These Authors advocate

a moderate use of caffeine-containing drinks for pill users.

The farmacokinetics of one of the most widely used tranquillizers, chlordiazepoxide, changes slightly in steroidal contraceptives users; with equal doses, a prolonged use tends to produce higher chlordiazepoxide plasma concentrations. However, the clinical importance of this phenomenon is still doubtful.

No drug has ever been studied more than oral contraceptives since the beginning of their commercialization. However, far from decreasing, the research on this subject seems increasing. This is probably due to the present tendency to go into social and environmental problems thouroughly which is absolutely necessary in the case of drugs used by millions of women. Many 'minor' aspects, like the interference of oral contraceptives with other drugs, are still awaiting confirmation by appropriate epidemiologic studies, planned according to adequate biostatistical techniques, since the reporting of individual cases or small series raises many doubts on the reliability of these data and may even result in unjustified alarmism.

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