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Oral contraceptives and lipids

Role debatable in coronary disease but use lowest doses possible

Numerous studies have shown a correlation between serum lipid concentrations and the high risk of developing cardiovascular disease: the risk is higher with high serum concentrations of low density lipoprotein (LDL) cholesterol or apoprotein B and with low serum concentrations of high density lipoprotein (HDL) cholesterol or apoprotein A. Oral contraceptives change lipid metabolism, the magnitude of this depending on the dose and structure of the oestrogen and gestagen. Oestrogens generally tend to increase serum triglyceride and HDL cholesterol concentrations and decrease LDL cholesterol concentrations whereas gestagens tend to produce the opposite effects and thus may counteract the action of the oestrogen. The action of many of the older oral contraceptives in increasing serum LDL cholesterol concentration and decreasing serum HDL cholesterol concentration led to the suggestion that this may be one mechanism by which they increase the risk of cardiovascular disease.

Most oral contraceptives used in the United Kingdom contain 30-35 μg ethinyloestradiol so that any differences in their metabolic effects depend on the dose and type of gestagen. Their variable effects on lipid metabolism[1] have depended on how the investigation has been performed and may have been influenced by several factors: the age of the subjects, smoking, exercise, diet, alcohol intake, concomitant treatment with other drugs, serum concentration of lipids before the use of oral contraceptives, daily (and possibly seasonal) variations in serum lipid concentration, the state of the subject at the time of blood sampling, the procedure used for sampling, and whether the samples were stored before analysis and for how long. Many of these factors can be controlled in short term longitudinal studies, but this is more difficult in long term studies, and they have to be taken into account in analysing the results, particularly in cross sectional studies. In only a few studies have the results been satisfactorily analysed statistically. In laboratories specialising in lipid estimations, where the assays are well controlled, analytical accuracy should be high, but special care is needed when the serum LDL cholesterol concentrations are obtained by calculation rather than by direct estimation and when a precipitation method is used for HDL_2 cholesterol.

Because of these numerous sources of variability it is unwise to accept uncritically the results of any single study, no matter how eminent the laboratory or the investigator. For example, of published studies of oral contraceptives containing 30 μg ethinyloestradiol with 150 μg levonorgestrel, serum LDL cholesterol concentration was decreased in 12 and unchanged in 13.[2] Less information is available about oral contraceptives containing 0·5-1·0 mg norethisterone. The findings are more consistent for the triphasic oral contraceptive containing ethinyloestradiol and levonorgestrel, which produces no change in either serum LDL cholesterol or HDL cholesterol concentrations. The newer gestagens desogestrel and gestodene do not antagonise the increase in serum HDL cholesterol concentration induced by ethinyloestradiol as much as the older ones such as levonorgestrel and norethisterone. Thus for ethinyloestradiol combined with 150 μg desogestrel 15 studies report an increase in serum HDL cholesterol concentration and four no change, and nine show no change in serum LDL cholesterol concentration and two a decrease. As it is difficult to "grade" the quality of all of the published studies to obtain an acceptable, and probably correct, assessment of the findings, the doctor has to take a consensus view or use meta-analysis. Changes in lipid metabolism seem not to be progressive with continued use of oral contraceptives, and the lipids revert to their pretreatment concentrations after women have stopped taking the contraceptives.

The effects of oral contraceptives on the serum concentrations of apoproteins A and B are analogous to those on serum HDL and LDL cholesterol concentrations. Serum apoprotein concentrations may be a better discriminant for the risk of cardiovascular disease than those of lipoprotein cholesterol, and simple and accurate methods of estimation are now available. HDL cholesterol may be divided into various subfractions, of which HDL_2 seems to be more responsive to oestrogens and gestagens than HDL_3; moreover, HDL_2 concentration may correlate better with the risk of cardiovascular disease than total HDL cholesterol concentration, but much more evidence is required to substantiate this. Specific and accurate methods for measuring HDL_2 cholesterol concentration based on ultracentrifugation are costly and time consuming; simpler precipitation methods show great variability in results and are much less accurate. Moreover, the HDL_2 and HDL_3 subfractions are not homogeneous.

What are the clinical implications of these lipid changes? Whether women using oral contraceptives have an increased risk of developing cardiovascular disease is still controversial,[3] but, although the epidemiological evidence may be flawed,

the consensus view has indicated that the risk is slightly increased. Nevertheless, this view relates to the higher dose oral contraceptives and not to those currently used. There is no evidence that women who develop cardiovascular disease while using oral contraceptives are those whose metabolic responses are excessive. Nor is there any evidence suggesting a difference among different oral contraceptives in the incidence of cardiovascular disease. Some consider that oral contraceptives are not typical atherogenic risk factors at all[4]; occlusive coronary thrombosis may occur without appreciable atherogenic changes on angiography or histology of coronary vessels.

Metabolic changes occur in all women using oral contraceptives but few of them develop cardiovascular disease. Nevertheless, it is sensible to follow general therapeutic principles by using formulations containing the lowest doses consistent with efficacy and acceptability.

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Non-insulin dependent diabetes and ischaemic heart disease

Related, but how?

Non-insulin dependent diabetics are at greater risk from ischaemic heart disease than the general population.[1,2] This is not surprising: most metabolic abnormalities linked to vascular disease have been described in non-insulin dependent diabetics. These abnormalities include increased concentrations of glucose, insulin, and triglyceride and reduced concentrations of high density lipoprotein cholesterol.[1,2] Non-insulin dependent diabetics are more likely to have abnormalities of platelet function[3] and the coagulation system[4] and to be hypertensive and overweight.

These risk factors, however, do not completely explain the increased risk of vascular disease in diabetics. Nor is there evidence that conventional risk factors are relatively more important in diabetics than non-diabetics; for example, smoking, hypertension, and hypercholesterolaemia increase the risk of ischaemic heart disease by similar amounts in both groups.

Further complicating the story are epidemiological studies showing that the effect of diabetes as a "multiplier" of the risk of ischaemic heart disease varies according to geography and gender. Diabetic men in east Finland, for example, are more than twice as likely to have ischaemic heart disease as diabetic men in south west Finland.[5] Within the same population the excess risk of ischaemic heart disease due to diabetes seems higher in diabetic women than in diabetic men,[1,2] which could be explained by the greater clustering of coronary risk factors in female than male diabetics.[6]

Recent research into the association between non-insulin dependent diabetes and ischaemic heart disease has concentrated on the interactions among various metabolic abnormalities in diabetes. Insulin has been shown to act like a growth factor on the arterial wall, promoting the infiltration of smooth muscle cells into the intima and their replication there.[7,8] It may also affect the activity of low density lipoprotein receptors and the binding and degradation of low density lipoprotein in fibroblasts and other cells. Hyperinsulinaemia and insulin resistance are associated with hypertension and an atherogenic lipoprotein profile. Triglyceride rich lipoproteins are more atherogenic in diabetics than in non-diabetics. The formation of lipid peroxides is increased in diabetics[9,10]: oxidised low density lipoprotein accelerates the accumulation of cholesterol within endothelial macrophages. It may also promote atherogenesis by its cytotoxic properties[11] and its stimulation of monocyte chemotaxis.[12]

On the basis of the Whitehall study, which followed up more than 17 000 men for 15 years, Jarrett and Shipley have suggested that diabetes and ischaemic heart disease may not be causally linked at all but may share a common, possibly genetic, antecedent.[13,14] Their main evidence from the study was that the relative risk of death from ischaemic heart disease bore no relation to the duration of diabetes in both newly diagnosed and previously diagnosed diabetics.

Assessing the duration of diabetes retrospectively in a cross sectional survey may lead to bias for two reasons. The first is owing to sampling bias, which could also be called survival bias: subjects who have had diabetes for many years at the beginning of such a study are "survivors" and might have other characteristics protecting them from the increased risk that goes with increased duration of the disease. Possible protective characteristics, uncontrolled for in the analysis of the Whitehall study, relate to high density lipoprotein cholesterol concentration, coagulation factors, platelet function, dietary and physiological antioxidants, and relative weight. The second source of bias is that the duration of diabetes is dated from the diagnosis: a short history of diabetes may, however, have followed prolonged asymptomatic glucose intolerance. Short of following the glucose tolerance of a large birth cohort from adolescence onwards, circumventing this limitation is impossible.

Even if the findings of the Whitehall study are valid there are explanations for an association between non-insulin dependent diabetes and ischaemic heart disease other than a genetically linked predisposition. Both diseases could be linked, for example, through a third factor, such as obesity or low high density lipoprotein cholesterol concentration, neither of which the Whitehall study adjusted for.

Further epidemiological studies are needed before abandoning the concept that non-insulin dependent diabetes and ischaemic heart diseases are causally linked.

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