THE ATHEROGENIC INDEX IN USERS OF COMBINED ORAL CONTRACEPTIVES

THESIS

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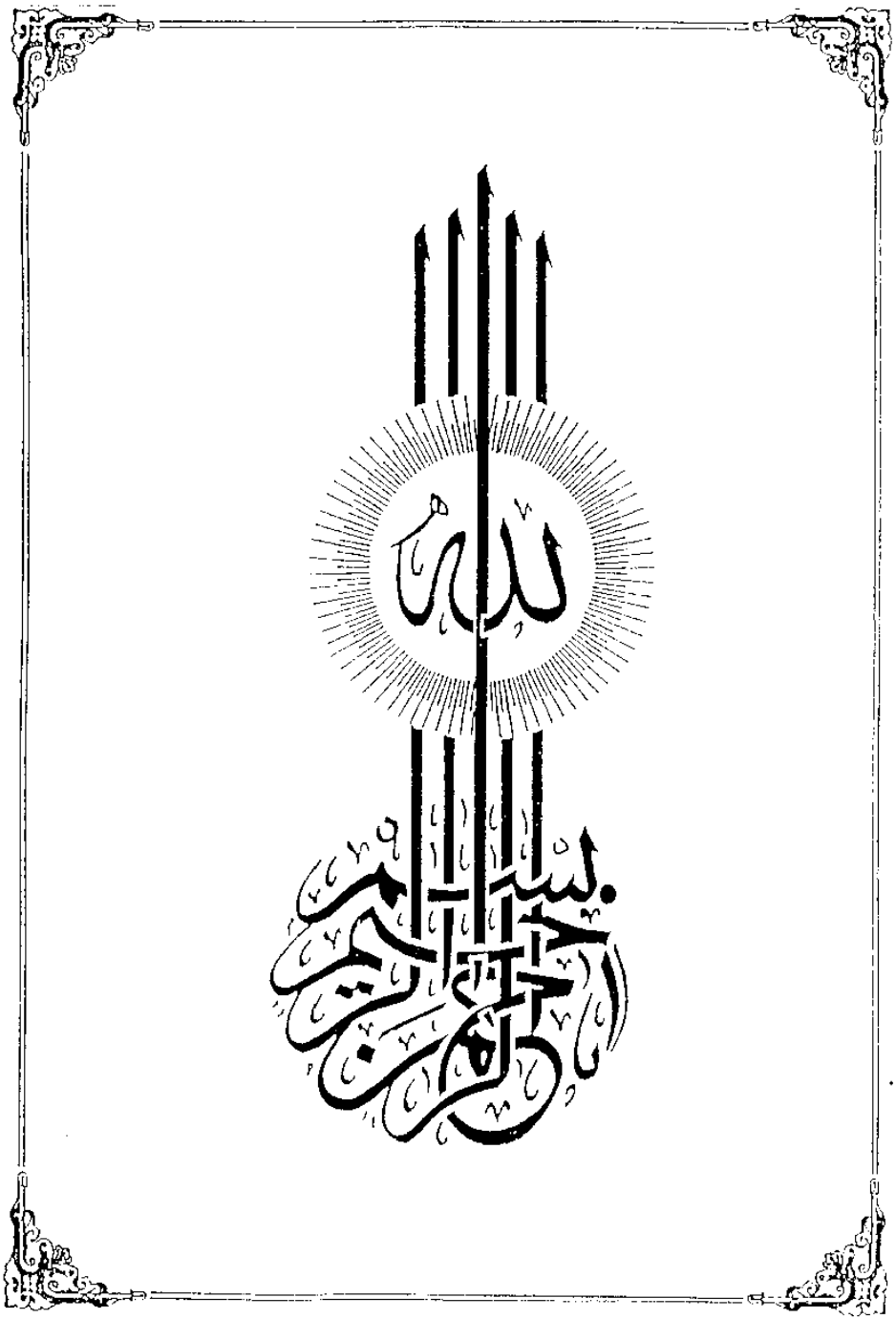

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INTRODUCTION

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Abnormal concentrations of plasma lipoproteins are associated with atherosclerosis which is a major cause of death in both developing and developed countries. Not only have abnormal concentrations of lipids and lipoproteins been shown to be major risk factors for cardiovascular disease (CVD) but also the evidence is now that altering lipid and lipoprotein levels by dietary and drug intervention can dramatically alter CVD. Age, male sex, tobacco smoking, hypertension and increased serum low density lipoprotein (LDL) cholesterol and decreased high density lipoprotein (HDL) cholesterol levels have been identified as major independent factors. Obesity, diabetes, a family history of premature CVD and a sedentary life style are also independent risk factors (Bachorik et al., 1991).

Pure water, sanitary environment and nutritious food have long been recognized as prerequisites of good health. Since the late sixties, medical studies have revealed another essential component of health strategies: family planning. Today no health program can be considered complete unless it can also offer family planning measures appropriate for all potential parents (Eckholm and Newland, 1977).

In 1980, the World Fertility Survey demonstrated that about half of all married women in the world currently want no more children, nevertheless only a small proportion use any form of contraception because the available methods simply don't meet the needs of many potential users (Zeidenstein, 1980 and Fathalla, 1983).

What is needed is a highly effective, reversible, and safe method that can be administered easily by nonphysicians in remote areas, that is totally independent of coital activity and that does not require specialized facilities or supplies. Combined oral contraceptive pills fill most of these requirements more closely than do other methods currently in use (Nancy, 1991).

During the past decades, epidemiological data have established a relationship between the use of oral contraceptives (OCs) and an increased risk of ischaemic heart disease. Changes in lipid and lipoprotein metabolism, which are associated with CVD, are due to the active components in most OCs: oestrogen and progestogens (Kjaer et al., 1993).

In general, the effects of oestrogens on lipid metabolism are considered favourable. By contrast, progestogens exert effects on lipid metabolism which are considered unfavourable due to their androgenic activity. The

changes depend upon both the type and dose of each of the steroids (Kjaer et al., 1993).

Although some oestrogens have a positive influence on lipid metabolism, they are responsible for major side effects such as thromboembolism. Accordingly, the dose of oestrogens has been reduced over the last decades. However, this reduction in oestrogen content has drawn attention to the negative influence of progestogens on lipid metabolism. Therefore, in recent years, much effort has been put into the development of the so-called third generation progestogens, i.e. progestogens with very low androgenic activity. Two such progestogens that are currently widely used are gestodene and desogestrel (Kjaer et al., 1993).

Recently, Godsland et al. (1993) and Gillian (1994) found that third generation progestogens (gestodene, desogestrel and norgestimate) increases serum HDL cholesterol levels and decreases LDL cholesterol levels and this is considered a favourable effect protecting against atherosclerosis and subsequently ischaemic heart disease. However Thorneycroft (1992) did not find any significant difference between the third generation progestin formulations and the older progestin oral contraceptives such as levonorgestrel and norethisterone.

So, at present, the advantage of the third generation progestogens over the old progestogens regarding their effect on the lipid profile and atherosclerosis is still debatable.

AIM OF THE WORK

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In view of the considerable controversy regarding the favourable effect of novel progestins on lipid profile, the first objective of the present work is an attempt to throw light upon this issue and compare the effect of different types of progestins with the same amount of ethinyl estradiol on circulating lipid and lipoprotein constituents.

The second objective in this study is to identify women using different types of combined oral contraceptive pills who have an abnormal lipid profile and may lie at risk of subsequent development of atherosclerosis to advise them to use an alternative method of family planning.

REVIEW OF LITERATURE

Plasma Lipids and Lipoproteins

Plasma lipids have been shown to play an etiologic role in the development of atherosclerosis, a direct link exists between lipid levels and cardiovascular risk. There is an increasing recognition that most acute cardiovascular episodes are the result of local thrombosis superimposed on pre existing plaque formation (Lobo, 1990).

Composition

Extraction of the plasma lipids with a suitable lipid solvent and subsequent separation show the presence of triacylglycerols, phospholipids, cholesterol and cholesteryl esters in addition to free fatty acids that account for less than 5% of the total plasma lipids. The latter fraction is metabolically the most active of the plasma lipids. There are also minute amounts of glycolipids, certain important hormones and vitamins of lipid nature.

Practically, all these lipids are transported in plasma and other body compartments in the form of lipoproteins, which are macromolecular complexes composed of a hydrophobic lipid core (triglycerides and cholesterol ester) and a hydrophilic phospholipid, free cholesterol and protein surface (Fig. 1). This arrangement allows the transport of

the water insoluble lipids in the aqueous medium of the plasma (Segal et al., 1984).

Pure fat is less dense than water, so as the proportion of lipid to protein in lipoproptein increases, the density decreases, and hence separation of the various lipoproteins in the plasma by ultracentrifugation into chylomicrons, very low density lipoproteins, intermediate density lipoproteins, low density lipoproteins, and high density lipoproteins (Mayes, 1991).

In addition to the use of techniques depending on their density, lipoproteins may be separated according to their electrophoretic properties into α, B and pre B lipoproteins and may be identified more accurately by means of immunoelectrophoresis (Fig. 2) (Mayes, 1991).

The protein moiety of lipoproteins is known as an apolipoprotein or apoprotein, constituting nearly 60% of some HDL and as little as 1% of chylomicrons. Some apolipoproteins are integral and cannot be removed, whereas others are free to transfer to other lipoproteins (Mayes, 1990).