

Treatment of hyperlipidaemia in pre-menopausal women

Dr Vincent Maher

Are pre-menopausal women at risk?

Thankfully, heart disease does not raise its ugly head too often in those under 40 years of age. The incidence of myocardial infarctions before 40 years of age is 5% in men and less than 0.5% in women. There are, of course, certain situations where the likelihood of ischaemic heart is greater in pre-menopausal women. These include women who have a very strong family history of premature heart disease, long-term poorly-controlled diabetes and those with genetic forms of severe hyperlipidaemia. Rarely, women with arteritis due to lupus or other inflammatory conditions are at risk.

When does vascular disease begin in women?

There are those who would argue that the earliest features of vascular disease already exist *in utero* and that maternal eating and smoking habits during pregnancy are influencing factors. Post mortem studies in infants and in individuals who died at all ages have highlighted that the earliest visible features of vascular abnormalities, namely sub-intimal foam cells, are present from infancy. The extent and severity of foam cell deposition and early plaque formation increase with age. These changes have been shown to correlate with post-mortem blood cholesterol measurements, emphasising the importance of blood cholesterol levels and the development of these changes.

When these studies compared females with males, they showed that on average, the vascular changes in females lagged behind males by about 10 years. The composition of plaques also differed, in that early plaques with their greater cellularity were more prevalent in females.

Serial angiographic studies have chronicled the changes that occur with time on coronary angiograms. These studies have shown the natural progression of coronary vascular disease with time and how this process can be accelerated depending on the severity and number of cardiovascular risk factors present.

Evaluating risk in young women

Population studies such as the Framingham study have indicated that in women, as in men, the greater the number of major cardiovascular risk factors present the greater the cardiovascular risk. There is an incremental difference in heart disease mortality between women and men. However, this difference is lost if one includes diabetes as

a risk factor. It is in this regard that the protection normally afforded to women in the pre-menopausal years is lost if they have diabetes.

Hyperlipidaemia in a young pre-menopausal woman must therefore be considered in light of the number and type of concomitant risk factors and the presence or absence of proven vascular disease. The type and severity of the hyperlipidaemia must also be taken into account as outlined below.

Lipid disorders

Lipid denotes cholesterol, triglyceride and phospholipids. Cholesterol is a major component of our cell membranes and is also used to synthesize certain hormones. Triglyceride is used for insulation and as an energy source. Phospholipids are an intrinsic component of our cell membranes and provide substrate for the synthesis of prostaglandins. These molecules can be manufactured in our bodies or assimilated from our diets. As these fat particles are immiscible in water, they are bound *in vivo* to proteins called apoproteins. The complexes of cholesterol, phospholipid, triglyceride and apoproteins are called lipoproteins. These can be separated into different classes based on their density. These include very-low density, low density and high density lipoproteins, VLDL, LDL and HDL, respectively.

Under normal circumstances, dietary fat particles are digested, absorbed and assimilated in the liver into VLDL. The VLDL secreted by the liver undergoes hydrolysis in the blood stream to release triglycerides for energy purposes and to form LDL particles for delivery of cholesterol and phospholipids to cells via an LDL receptor on the cell surface. In contrast, HDL formed in the liver and as a by-product of VLDL hydrolysis is responsible for the removal of cholesterol from cells for excretion via the biliary tree.

Due to certain genetic defects in the protein structure of cell receptors, apoproteins or the enzymes responsible for hydrolysis of lipoproteins, an accumulation of abnormal lipoproteins may ensue in the blood stream. The defects in the LDL receptor which lead to very high LDL cholesterol levels in the disorder familial hypercholesterolaemia may be familial. Over-synthesis of certain apoproteins, such as apoprotein B-100, may also occur and this results in high concentrations of LDL cholesterol in some individuals and a raised VLDL concentration in others. Deficiency of apoprotein A-1 results

in very low levels of the protective HDL.

If lipoprotein trafficking is considered to be like trains on the DART service and enzyme or receptor defects as obstructions on the track, it can be seen how congestion can develop. To compound matters, there may be days where there is an increased number of individuals wishing to use the trains. This increased number represents over-production of triglyceride or cholesterol particles due to obesity, alcohol, diet, drugs and inactivity.

It is thus understandable that one can have a mixture of factors, some genetic, some environmental that produce congestion (hyperlipidaemia).

When we examine a lipid profile, we get a silhouette of what is going on beneath. We get total cholesterol levels, total triglyceride levels, LDL cholesterol levels and HDL cholesterol levels. These represent non-specific levels of lipid particles at one point in time in our blood stream. However, despite this snap shot, these measurements provide us with an indicator of the type of particles that are in excess in our blood stream. Very high LDL cholesterol levels are associated with an accumulation of this particle alone, as mentioned above. Raised LDL and triglyceride levels tell us that there may be an accumulation of both VLDL and LDL, or that there is an excess quantity of the more atherogenic intermediate density lipoprotein particles

(IDL). Further testing, such as lipid electrophoresis and specific apoproteins measurements, are needed to determine the underlying lipid profile and its atherogenic risk.

Women are as prone as men to develop these lipid derangements. They differ in that they usually have significantly higher HDL cholesterol levels than men during the pre-menopausal years.

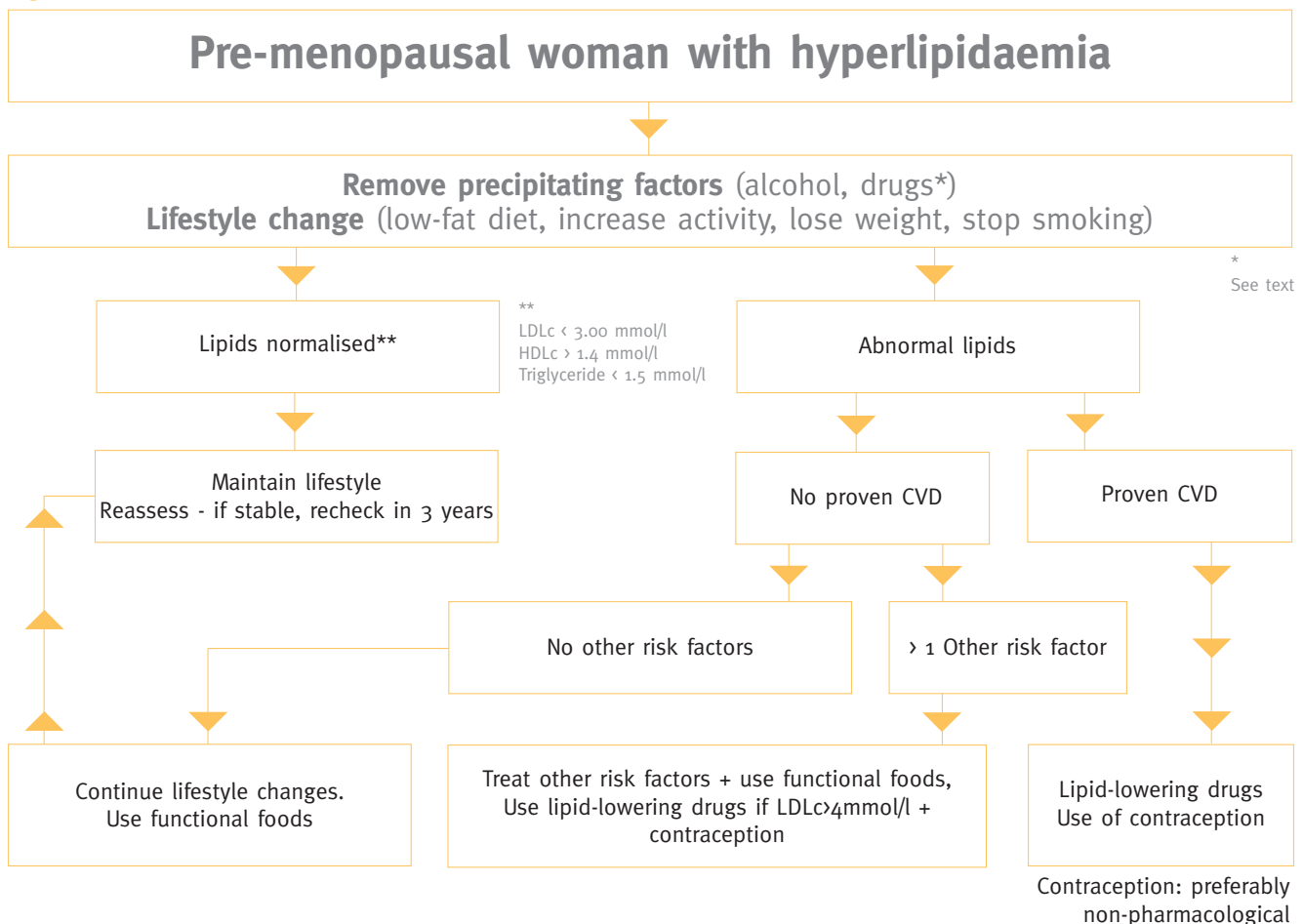
Despite the multiplicity of lipid or lipoprotein derangements, the main contributor to vascular disease is LDL particles. The size of these particles also influences disease as small dense particles found when individuals have diabetes, modest rises in triglyceride and low HDL cholesterol levels are more atherogenic than larger LDL particles. Lowering LDL particle numbers reflected by lowering LDL cholesterol levels is associated with a profound reduction in cardiovascular disease and its complications.

There are certain issues that are unique to pre-menopausal women compared to others, including contraceptive medications and pregnancy.

Impact of oral contraceptives on lipid levels

Use of oral contraceptive medication is associated with certain changes in the lipoprotein profile. These are mainly due to an increase in both VLDL and LDL. However, in some

Figure 1.



Functional foods = Benecol or Flora Proactiv

individuals, oral contraceptives are associated with the development of severe hypertriglyceridaemia and acute pancreatitis. The mechanism may be due to an oestrogen effect in reducing lipolysis or increasing VLDL synthesis. When the progestogenic component of the contraceptive pill is either norethisterone or levonorgestrel, it causes a reduction in the protective HDL cholesterol. This does not occur when the progestogenic component is desogestrel.

Effect of pregnancy on lipid levels

During pregnancy, there are slight rises in both VLDL and LDL cholesterol and these revert to normal post partum. This is due to the oestrogen effect. There are some instances where pregnancy induces severe hypertriglyceridaemia.

Treatment of hyperlipidaemia in women of childbearing age

When considering how to manage lipid disorders in young women, it is important to appreciate the natural history of atherosclerosis, the consequences of lipid derangements and the potential factors that have contributed to the hyperlipidaemia. Figure 1 represents an algorithm that the author uses when faced with this problem.

In all instances, it is imperative that lifestyle changes such as a low fat, high fruit and vegetable diet, weight reduction, smoking cessation and regular physical activity are recommended. These measures alone can normalise many lipid disorders without further need for intervention. Naturally, one should remove factors that aggravate hyperlipidaemia, such as alcohol and drugs like thiazide diuretics, beta blockers such as atenolol or metoprolol, isotretinoin and oral contraceptives if there is severe hypertriglyceridaemia. Following these interventions, one should repeat the lipid profile in a 2-3 month period and if it is normalised, to continue these lifestyle changes and review again in 2-3 years.

However, if the lipid profile is not normalised with these interventions, further options need to be considered. Firstly, you should ensure that the lifestyle recommendations and drug changes have been implemented and can be maintained. Dietary modification provides additional benefits beyond simply reducing cholesterol numbers. It should be a key and permanent component of all lipid management.

In patients in whom the lipid reduction has not reached ideal levels, it should be considered whether or not they have proven cardiovascular disease. In patients with proven vascular disease, it is imperative to initiate lipid-lowering drug treatment to supplement the lifestyle changes. The target for LDL cholesterol reduction, in the author's opinion, should be <2mmol/l in this population. The reason for this aggressive target is that these young females have developed vascular disease at a young age, despite the normal protection in the pre-menopausal years. This should set off alarm bells of a very aggressive atherosclerotic disease process. Since the use of statins is not recommended during pregnancy, it is important to advise these young women to practice contraception, preferably without using pharmacological agents, which

can aggravate hyperlipidaemia.

In women who have hyperlipidaemia, despite lifestyle changes and who do not have proven vascular disease, one should consider their additional cardiac risk factors when planning lipid management. In those without other risk factors, the author recommends that they continue with lifestyle changes and use one of the functional foods available, such as Benecol or Flora Proactiv. These plant sterols act by blocking cholesterol absorption and can reduce LDL cholesterol levels by 10 to 14%. The target LDL level in such patients should be <3mmol/l.

In those with other risk factors, the strategy would be to remove the additional risk factors, to promote lifestyle changes and use functional foods and to consider lipid-lowering drugs when LDL cholesterol levels exceed 4mmol/l. As with those who have proven disease, contraception should be considered when using lipid-lowering medications. The target LDL cholesterol should be <2.6mmol/l in this group.

Lipid management in women planning a pregnancy

Many women in this age group are planning a pregnancy and the dilemma arises as how best to manage lipid derangements in this population. In the overall scheme of things, the planning phase plus pregnancy may not exceed one year. A brief rise in lipid levels during this year should not have a major impact on vascular disease progression. Consequently, provided that all lifestyle measures are being practiced, there should not be too much concern in allowing hyperlipidaemia during pregnancy. The caveat being to exclude severe hypertriglyceridaemia, which may arise in some individuals and produce pancreatitis.

It is also noteworthy that there have been a number of reports of women who became pregnant while taking statins with no consequences to the baby.

Breastfeeding mothers

Use of lipid-lowering treatment during breastfeeding has not been studied in detail. Some of the statins have been shown to appear in breast milk and are therefore contraindicated during this period. There is no information available on fibrates. Resins such as cholestyramine and colestipol are not absorbed and thus would be a reasonable choice here. However, with prolonged use there is a reduction in the uptake of fat-soluble vitamins, which could affect mother and infant. It may be reasonable to use these resins on alternative days to allow fat-soluble vitamin absorption, but there is no scientific proof for this.

Summary

Pre-menopausal women are at a very low risk of cardiovascular disease. Lifestyle measures and drug alterations are usually sufficient to correct hyperlipidaemia. In those with proven cardiovascular disease or at high risk of same, lipid-lowering medication may be used, provided that care is taken to use contraception.

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