Macrovascular complications in pregnancy and diabetes

Rakesh Kumar Sahay, Venu Madhavi Pydi

Abstract

This review discusses macrovascular conditions which may occur during pregnancy complicated by diabetes. It describes the effect of dyslipidaemia and hypertension on foeto-maternal outcomes and explores the pathogenesis of these states.

Keywords: Cholesterol, diabetes, hypertension, myocardial infarction, preeclampsia.

Introduction

Diabetes in pregnancy poses serious problems for both mother and foetus and has long term health implications for the child. Rates of adverse outcomes in pregnancies complicated by preexisting diabetes (type 1 and type 2) and gestational diabetes mellitus (GDM) have improved, but still there is excess maternal and foetal morbidity compared with normal pregnancy.[1]

Other than glucose, multiple maternal metabolic, hormonal, and inflammatory factors are associated with maternal and foetal outcomes. These include maternal amino acids, glycerol, ketones, and lipids which are altered in pregnancies complicated by pre pregnancy diabetes and GDM.[2] In this review, we discuss lipids and various macrovascular complications like hypertension and myocardial infarction complicating diabetic pregnancy.

Lipid Metabolism in Pregnancy

The effect of diabetic pregnancy on fuel metabolism can be described as reduced facilitated anabolism and hyper accelerated starvation. Maternal metabolism is designed to provide adequate nutrition for foetal growth, in the form of glucose, ketones, lipids, and other fuels.

Maternal metabolism becomes more catabolic to support the acceleration of foetal growth[2] in the third trimester. Maternal insulin resistance increases in third trimester; this combined with lipolysis in peripheral adipose tissue results in increased maternal lipoprotein concentrations and elevated lipoprotein triglyceride content. TG content predominantly increases in late gestation by about two to four times but precipitously falls to pre-pregnancy levels following delivery.[3] Hence normal pregnancy is marked by an increases in lipid concentration as gestation progresses. However these elevations are non atherogenic.

Very low density lipoprotein (VLDL), high density lipoprotein (HDL) and low density lipoprotein (LDL) content also increase in pregnancy. VLDL levels are increased due to high estrogen levels and also due to decreased lipoprotein lipase activity. Elevation in LDL in mid and late gestation occurs due to enhanced conversion of VLDL with increase in proportion of smaller dense LDL particles. Because of reduced hepatic lipase activity, there is reduced conversion of HDL2 to HDL3. It is HDL2 that is responsible for elevated HDL in pregnancy with peak levels during second trimester.

Free fatty acids, fatty acids and cholesterol are important for foetal growth and development which are provided via maternal lipoproteins. However maternal lipoproteins cannot cross placenta directly. They are transported to the foetus via specific lipoprotein receptors, lipases, and fatty acid binding transport proteins on the placenta.[4] In mouse placenta it has been demonstrated that there is direct uptake of chylomicron remnant particles.[5] This may even occur in human pregnancy.

Maternal Lipids in Diabetic Pregnancy

Diabetes is associated with altered lipoprotein metabolism with a tendency towards hypertriglyceridaemia. Hence, when both pregnancy and diabetes are associated this results in an exaggerated response. Plasma triglycerides (TG) are elevated more compared to total cholesterol in diabetic pregnancy. However the changes also depend on the type of diabetes and lipoprotein fractions considered. Maternal obesity is associated with an increase in maternal lipid levels.

Lipoprotein a [Lp(a)] levels tend to increase throughout pregnancy similar to other lipid fractions. However the levels normalize within six months post-partum.[6] Preeclamptic women tend to have increased levels of Lp(a), which is more commonly associated in pregnant women with preexisting diabetes.[7]

Lipid profiles in pregnant women with uncomplicated preexisting type 1 diabetes are similar to healthy counterparts.[1] However when associated with other risk factors like maternal obesity, poor glycaemic control,

Department of Endocrinology, Osmania Medical College, Hyderabad, India.
Correspondence: Rakesh Kumar Sahay. Email: sahayrk@gmail.com

preexisting metabolic syndrome, hypertension, pre-eclampsia and underlying renal disease there are more exaggerated elevations in TG levels in first trimester and lower HDL levels when compared to healthy counterparts.[8]

TC, HDL-C, LDL-C and TG increase throughout gestation but the increase is not as significant as in those women without preexisting metabolic syndrome.[8] Women with normoglycaemia with type 1 diabetes (mean HbA1c= 6.1%) had lipoprotein levels comparable to women with uncomplicated pregnancy, but those with poor control (mean HbA1c = 8.3%) at the time of delivery had higher triglycerides and VLDL and lower HDL3 levels without significant changes in LDL fractions.[9]

Women with type 1 diabetes with nephropathy showed a greater elevation in total cholesterol and LDL-C throughout gestation without much effect on TG levels. Women with type 1 diabetes who go on to develop preeclampsia later in pregnancy have higher LDL-C and cholesterol than women with type 1 diabetes who do not develop preeclampsia.

Women with preexisting type 2 diabetes have higher TG and lower HDL-C levels during the first trimester than in women with type 1 diabetes or GDM,[10] without any significant change in Lp(a) levels and LDL fractions when compared to normal gestation.[11] However data regarding lipid alterations in type 2 diabetes is scarce.

Maternal TG levels have been found to be increased throughout gestation in GDM.[12] Maternal cholesterol either increases or remains unchanged throughout gestation.[12] LDL-C concentrations were found to be reduced, though small dense LDL levels were noted to be increased.[13]

Fetomaternal Outcomes and Dyslipidaemia

Maternal Outcomes

In various observational studies it has been found that both high and low maternal cholesterol have been associated with pre-eclampsia,[14] pre-term birth, GDM,[15] and larger for gestational age(LGA) infants. Elevated TG and low levels of HDL-C are associated with adverse pregnancy outcomes in a non-diabetic pregnancy. Diabetic pregnancy is associated with higher levels of TG when compared to normal pregnancy, hence they are at higher risk of complications and adverse outcome. Strict glycaemic control however will help in reducing adverse outcomes. Type 1 diabetic women with LDL-C elevation in early pregnancy later tend to develop pre-eclampsia. There are no studies examining the relationship between lipids and preeclampsia in women with type 2 diabetes. In GDM there was no association found between lipid profiles and pre-eclampsia.[16]

Fetal Outcomes

Even with good glycaemic control, women with pre gestational diabetes and GDM have increased frequency of LGA than women with uncomplicated pregnancy.[17] Usually these infants have increased fat mass.[18] This trend has been associated with elevated maternal glucose levels and also maternal lipids. Elevated maternal TG and low HDL-C in the third trimester is associated with increased risk of LGA infants in women with preexisting diabetes. In GDM, maternal triglyceride levels measured post-oral glucose tolerance testing correlate with birth weight to the same extent as 1- and 2-h glucose measures.[19]

Hypertension in Diabetic Pregnancy

Pre-gestational diabetes is often associated with hypertensive disease of pregnancy. Women with pre-gestational diabetes have been shown to have a significantly higher risk of having a pregnancy complicated by hypertensive disease when compared to women with normal carbohydrate metabolism.

There is a spectrum of hypertensive disorders that can occur in pregnancy which includes:

- Chronic hypertension - Elevations in blood pressure precede conception.
- Gestational hypertension - Elevated blood pressure without proteinuria occurring during pregnancy.
- Preeclampsia - new-onset gestational hypertension and proteinuria
- Eclampsia - preeclampsia associated with neurologic defects.

Pre-eclampsia occurs three to four times more frequently in women with pre gestational diabetes than with non-diabetic women. Associated diabetic nephropathy also contributes to hypertension in women with preexisting diabetes. In a Swedish study it was observed that 18.7 % of pregnant women with type 1 diabetes who did not have overt nephropathy developed hypertension which is far higher than the 5 % prevalence of hypertension in non-diabetic women.[20]

Dyslipidaemia, Diabetes and Pre Eclampsia

Several studies have identified pro-atherogenic patterns in lipid concentrations that precede clinical manifestations of preeclampsia. Preeclamptic women tend to have increased levels of Lp (a). These gestations

are also marked by higher levels of TG, lower levels of HDL-C, and greater fractionation of small dense atherogenic LDL particles. Elevated LDL fractions with lower HDL-C levels appear to be more pronounced in women with gestational hypertension and diabetes, and preeclampsia. Women with type 1 diabetes who go on to develop preeclampsia later in pregnancy have higher LDL-C and cholesterol than women with type 1 diabetes who do not develop preeclampsia.[21]

Furthermore, women who have higher concentrations of small dense LDL fractions during pregnancy tend to have increased risk of cardiovascular disease later in life. Dyslipidaemia, especially during mid-gestation, is associated with mild preeclampsia. Women with severe preeclampsia tend to have low LDL-C levels with less atherogenic profiles suggesting a different pathologic mechanism between mild and severe disease. Dyslipidaemia is implicated in endothelial dysfunction, and hence, potentially in the pathogenesis of preeclampsia.

Pregnancy Related Changes in Cardiovascular Physiology

Pregnancy causes profound cardiovascular changes that result in increasing stresses throughout the pregnancy especially for patients with preexisting heart disease. These changes lead to greater myocardial oxygen consumption because of the increase in cardiac output, left ventricular size, and increased oxygen consumption during physical exercise. In patients with coronary artery disease this increase may lead to inadequate oxygen supply to the myocardium. The fall in systemic vascular resistance that occurs in early pregnancy may shunt blood away from coronary arteries, which have been narrowed by atherosclerosis.

Whether pregnancy effects coronary artery blood flow or results in coronary artery vasodilatation is unknown. During labour additional demands are placed on the heart in as much as cardiac output can rise to an additional 50 percent above baseline values. With each contraction there is a 300 to 500 ml auto transfusion of blood into the central circulation with transient effects on stroke volume, cardiac output, arterial pressure, and heart rate. Immediately after delivery even greater fluxes to the cardiovascular system can occur. If only local anaesthesia is utilized, the cardiac output can peak at 80 percent above pre labor values. Finally, acute blood loss at delivery may cause hypotension with resultant decrease in coronary artery perfusion.

Myocardial Infarction in Diabetic Pregnancy

Coronary heart disease and myocardial infarction are uncommon complications during pregnancy. Preexisting diabetes, metabolic syndrome, obesity, pre-eclampsia further increase the risk of acute coronary events complicating pregnancy. Symptomatic coronary artery disease in women with pregestational diabetes mellitus is most commonly seen in those with long standing disease, nephropathy and hypertension.

Women with type 1 diabetes have a much greater risk of serious coronary heart disease, but few cases of myocardial infarctions occurring during pregnancy have been reported. Women with type 1 diabetes have an increased risk of coronary artery disease and seem to lose the protective effect of estrogen that limits the incidence of coronary artery disease in women without diabetes. The experience at the Joslin Clinic has suggested that, in patients with type 1 diabetes, arterial age equals chronologic age plus the number of years of diabetes. Thus, the risk of a 30 year old women with type 1 diabetes for 20 years might approximate that of a 50 year old individual.[22]

The reported maternal mortality in diabetic women with myocardial infarctions during pregnancy seems to be higher than in the nondiabetic patient, but comparisons are difficult given the small number of patients. Of the 10 patients reported, maternal mortality was 50 percent and foetal loss 60 percent. The amount of cardiac function remaining after infarction appears to be a major determinant of pregnancy outcome.[23]

Conclusion

The present article highlights the importance of assessing cardiovascular risk factors such as dyslipidaemia and hypertension in patients with diabetes during pregnancy, since the presence of these factors indicate a higher risk for pre-eclampsia, adverse maternal and foetal outcomes rarely, acute coronary events. Timely intervention and therapeutic measures may prevent the maternal and foetal complications.

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