Cardiovascular Health: Cross-Generational Considerations

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Received date: August 18, 2015; Accepted date: September 23, 2015; Published date: September 30, 2015

Abstract

Cardiovascular disease (CVD) remains the number one cause of death for women in the United States. Although typically a time of low risk, the reproductive years of a woman’s lifetime offer an optimal time to address and prevent future cardiovascular disease by reducing risk factors such as dyslipidemia and early atherosclerosis. Although it is widely known that pregnancy is a state of increased insulin resistance, there are no current reference standards to define normal lipid parameters during pregnancy. Recent animal studies have suggested that dyslipidemia during pregnancy may potentially predispose or increase the inherent CVD risk for the offspring. Furthermore, women with uncontrolled diabetes, polycystic ovarian syndrome (PCOS) and specific metabolic disorders may all be at yet further increased lifetime risk of dyslipidemia, thereby affecting future health of the mother, her child and future generations. Despite the incomplete understanding of the pathophysiology relating these diseases with potential development of CVD, both in the mother and child, the importance of awareness and improvement in overall health remains paramount.

Keywords: Dyslipidemia; Hyperlipidemia; Pregnancy; Cardiovascular disease; Fetal development; Familial hyperlipidemia

Introduction

Cardiovascular disease (CVD) remains the number one cause of death for women in the United States. Although typically a time of low risk, the reproductive years of a woman’s lifetime offer an optimal time to address and prevent future cardiovascular disease by reducing risk factors such as dyslipidemia and early atherosclerosis. Dyslipidemia in pregnancy has historically been considered physiologic with little clinical relevance; recent evidence highlights the importance of preventing or optimizing maternal lipid health before and during pregnancy and the puerperium for the long-term benefit of both mother and the child. Historically it was assumed that maternal cholesterol does not cross the placental barrier; recent evidence suggests otherwise.

Understanding and promoting awareness of opportunities to reduce dyslipidemia before, during, and after pregnancy has major implications for reducing CVD risk for mother, child and for our entire population. Although it is widely known that pregnancy is a state of increased insulin resistance, there are no current reference standards to define normal lipid parameters during pregnancy. This commentary describes the basic understanding of the importance of cholesterol in fetal development as well as maternal management and treatment considerations during pregnancy and beyond.

Cholesterol and Fetal Development

Cholesterol metabolism is central to normal human development. Sources of fetal cholesterol come from endogenous production through synthesis within the yolk sac as well as from the placenta and from the maternal circulation. Specifically, cholesterol is central to the proper formation of cell membranes, membrane integrity, and the maintenance of cholesterol-rich domains important for membrane-associated signaling cascades. Cholesterol is the precursor to hormones such as sex steroids, vitamin D and bile acids. In order for exogenous cholesterol to be available for fetal use, the yoke sac and placenta must take up maternal cholesterol via receptor-mediated or receptor-independent transport processes, and thereafter transport the lipids across cellular barriers and/or secrete the maternally derived or newly synthesized cholesterol into fetal circulation [1,2]. Human and animal studies have shown that cholesterol may cross the placenta and concentrations are actually higher in the umbilical vein versus the arteries [2,3]. The importance of understanding these mechanisms has recently been revealed in small animal studies. In one study in particular, exposure of a fetus to elevated levels of cholesterol and oxidative by-products of cholesterol metabolism has been shown to result in programming of fetal arterial cells with a predisposition to atherosclerosis later in life [4]. Fatty streaks have been found in the aortas of six month-old fetuses of mothers who were hypercholesterolemic [5]. These findings suggest that unbridled dyslipidemia may potentially predispose or increase the inherent CVD risk for their offspring.

Detection, Management and Treatment of Dyslipidemia in Pregnancy

Pregnancy is a state of insulin resistance and is a cardiometabolic stress test. Lipid and lipoprotein profiles of pregnancy change in parallel. Significant increases in the average circulating values of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) are observed during gestation. In the first trimester, there is a noticeable decrease in levels for the first 6 weeks, and then they noticeably increase by the third month or the end of the first trimester. In the third trimester, levels peak near term. Values do not appear however normally to increase above 250 mg/dL on the average during the entire
Dyslipidemia during pregnancy should be treated principally by diet and exercise, although it is recommended that it be individualized between each patient and provider. Mediterranean diet and obstetrical recommendations for exercise apply unless there is a need for strict fat free diets because of marked hypertriglyceridemia. Care of pregnancies complicated by other comorbidities such as diabetes types 1 and II, which can be associated with hypertriglyceridemia, should focus first on glycemic control. Medications commonly used for treatment of pre-gestational or gestational diabetes in pregnancy are glyburide, metformin, and insulin to control blood glucose. A recent randomized trial however has failed to show benefit with Glyburide in gestational diabetic women on pregnancy related outcomes [9]. Attention needs to be focused on residual dyslipidemia in spite of glucose normalization to bring LDL cholesterol and non-HDL cholesterol to normal gestational age adjusted levels. Severe hypertriglyceridemia can be treated with omega 3 fatty acids, parenteral nutrition, plasmapheresis or even gemfibrozil in the mid to late trimesters (class C). With

<table>
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<th>Lipid Lowering Agent</th>
<th>Pregnancy Class</th>
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<tr>
<td>STATINS</td>
<td>X</td>
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<td>FIBRATES</td>
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<td>Ezetimibe</td>
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<tr>
<td>NIACIN</td>
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<td>Cholestyramine</td>
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<td>Colesvelam</td>
<td>B</td>
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<td>Mipomersen</td>
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Table 2: Provides the pregnancy classification of widely used lipid lowering agents.
medication intervention, lipids should be monitored every six weeks during pregnancy.

**Special Considerations**

Patients affected by heritable disorders of lipid metabolism such as familial hyperlipidemia (FH) require special attention, especially in the antenatal period and are best followed in tertiary care centers with experience in this particular patient population. In the pregnant patient with FH, a complete lipid profile assessment is recommended during each trimester. FH can be treated with lifestyle interventions and bile acid sequestrants with monitoring for potential increase in triglyceride levels. If further therapies are required for control, consideration can be given to mipomersen (pregnancy class B) and/or low-density lipoprotein (LDL) apheresis [10].

Another condition that affects a significant proportion of reproductive aged women, approximately 7-22%, is that of polycystic ovary syndrome (PCOS). Women with PCOS are at increased risk for complications of pregnancy, as well as diabetes mellitus, metabolic syndrome, and endometrial cancer [11,12]. Furthermore, irrespective of development of metabolic syndrome, women with PCOS are at greater risk for obstetric complications at baseline, and with obesity being the most common high-risk condition of pregnancy, these women need to be closely monitored throughout gestation. Regarding screening for dyslipidemia in this population, postpartum follow-up is strongly recommended.

**Conclusion**

Recent literature indicates that pregnancies affected by hypertensive disorders of pregnancy such as preeclampsia may have endothelial dysfunction that predisposes the mother to increased lifetime CVD risk [13]. This is further compounded by contributions of dyslipidemia, obesity, the presence of the metabolic syndrome or insulin resistance states prior to pregnancy. Despite lack of complete understanding of the pathophysiology relating these diseases with potential development of CVD, both in the mother and child, the importance of awareness and improvement in overall health remains paramount. The understanding of dyslipidemia and hypertensive diseases of pregnancy is constantly evolving. Advancing interest and maximizing research on this topic remains an important scientific, clinical and public health focus.

**References**