Identifying and Preventing Cardiac Risk Factors from Fetal Life

Lawrence M. Benedict1, Deeksha Sarma1, Achintya Moulick1,2, Randy Stevens1,2, Vicki Mahan*
1Drexel University College of Medicine, PA, USA
2Department of Pediatric Cardiothoracic Surgery, St. Christopher’s Hospital for Children, Philadelphia, PA, USA

Abstract

Cardiac risk factors in childhood are often overlooked in clinical practice, however cardiac risk factors can start before the child is even born. Maternal factors including diet, genetics, and smoking during gestation can all impact the long-term cardiac health of the offspring. Atherosclerosis starts as early as fetal life and can continue to develop in children with risks including high cholesterol. Current guidelines for screening of cholesterol in children, while improving in recent years, still allows years of damage to accumulate before identifying those at risk. Additionally, intervention for cholesterol and other known risks in children and adolescents are often avoided or started later than necessary for optimal cardiac health. Non-pharmacological approaches like diet and exercise for cholesterol and health management can be implemented very early in life, while many pharmacological options are approved for use in certain conditions as early as ages 8 to 10. Combating cardiac disease reaching endemic levels in the developed world will take an aggressive approach in management starting with identification early in life and utilizing the appropriate tools available, both medical and lifestyle.

Introduction

Cardiovascular Disease is the number one underlying cause of death worldwide1. Risk factors like diabetes, obesity, and dyslipidemia are endemic in the United States population. Obesity rates among children is as high as 16.9% in the United States2. One survey had found that an estimated 53% of the US population had some form of dyslipidemia including 27% with high LDL-C and 30% with high triglyceride levels3. In efforts to detect dyslipidemia during childhood, in 2011 the American Academy of Pediatrics has prescribed screening at ages 9-11 and 17-21 years of age proposing diet and exercise changes for initial treatment4. There is increasing evidence showing that atherosclerosis and other cardiac risk factors can begin in fetal and neonatal life5,6. It is becoming increasingly clear that there is a need for earlier diagnosis and intervention to ensure optimal cardiac health outcomes.

Risk Factors from the Mother

Maternal Genetics

Much concern has been placed on the maternal lipid level impact on the neonatal cholesterol and triglyceride levels. Evidence suggests that maternal cholesterol is transported to the placenta via ABCA1 and ABCG1 transporters7. These transporters have been found to be so important to fetal development that they are even
being investigated as a target for treatment of gestational Smith-Lemli-Opitz syndrome, a disorder of fetal synthesis of cholesterol. Maternal lipid profile is also known to have an important impact on the gestational size of the neonate.

Maternal ethnicity is known to have an important impact on maternal gestational cholesterol levels. Though hyperlipidemia can be as a result of dietary and other environmental factors, genetics typically plays a primary role in the phenotype of the individual. Dyslipidemias are classified using the Fredrickson classification, and can be monogenic or polygenic in nature. Fredrickson Type II or Familial hypercholesterolemia is the most common genetic dyslipidemia stemming from mutations in LDLR, APOB, PCSK9, and others. In fact, genetic disorders are known to vary by ethnicity. Familial hypercholesterolemia is believed to have a prevalence as high as 1:250 in the United States general population (higher than 1:500 previously reported) but 1:211 in African Americans and 1:414 in Mexican Americans. More broadly, other ethnicities show even larger extremes with a subset of French Canadians have prevalence of 1:154 and South African Jews have a rate as high as 1:67. As indicated above, maternal cholesterol is known to be transported across the placenta which may then impact the fetus.

A combined increase in cholesterol and triglyceride levels in pregnant mothers has been shown to be a predictor of preterm labor. Further, a low birth weight (which can be caused by premature birth as a result of preterm labor) can lead to complications during adult ages, including chronic diseases such as hypertension, type 2 diabetes mellitus, metabolic disease, and cardiovascular disease. More generally, preterm infants have significantly higher rates of being overweight and obese, and have had higher incidence of endocrine disorders.

More directly, maternal hypercholesterolemia enhances fatty streak formation in fetal arteries of some spontaneously aborted fetuses. While some fatty streak lesions in newborns regressed by as much as 64% during childhood, others progressed at an accelerated rate, particularly lesions in the aortic arch and abdominal aorta. In rabbits, increased maternal cholesterol via diet was sufficient to increase the fatty streak formation while cholesterol lowering treatment decreased this formation.

Further complicating the issue of maternal hyperlipidemia, control of cholesterol with statins and some other medications have been contraindicated during pregnancy due to teratogenicity. Reviews of pregnancies with statin exposures showed nervous system and limb developmental abnormalities in the offspring. One study showed promising results in improving glycemic control, reducing maternal cholesterol levels, and associated risks to the fetus, using phytosterols.

Diabetes mellitus in mother

A CDC study found that as many as 9.2% of pregnancies were affected by gestational diabetes mellitus. Additionally, all pregnancies impacted by diabetes, preexisting diabetes mellitus in pregnancy has increased from 10% to 21% of all diabetic pregnancies. Pregnancies in women with diabetes mellitus can result in an increased risk of certain morbidities affecting both mother and child. These include congenital malformations and morbidities, and obstetrical complications. One study found that, though women with diabetes mellitus type 1 may have planned their pregnancies and attempted to prepare well for their pregnancies, there were still morbidities that occurred disproportionate to the general population; complications included congenital malformations, macrosomia, preeclampsia, and hypoglycemia. In fact, children born to mothers with diabetes were found to have an increased rate of congenital malformations with a significant representation of cardiac malformations.

Another study showed that macrosomic children born to diabetic or obese mothers had a significantly higher risk of developing metabolic syndrome during their childhood. Increased rates of insulin resistance and presence of multiple components of metabolic syndrome were present in these patients by age 11, putting them at a further increased risk for developing cardiovascular disease and diabetes.

Maternal Smoking

Atherosclerotic lesions of coronary arteries can be seen in prenatal and infancy periods, and these lesions are highly associated with maternal cigarette smoking. Many of the lesions in the coronary vessels progress to juvenile atherosclerotic plaques with characteristic proliferation of the smooth muscle cells of the tunica media. The vessel wall thickening associated with these plaques decreased the lumen diameter by up to 30-40%.

Active maternal smoking during pregnancy has been associated with negative changes in birth weight. Decreased birth weight alone has been linked to additional risk for cardiovascular disease. Smoking also increased the perinatal death rate by nearly 20% in one epidemiology study. Active maternal smoking was linked with significant decrease in antioxidant capacity in the neonate whereas both active and passive maternal smoking was associated with worse total oxidant status and oxidative stress index. Unsurprisingly then, paternal smoking was also significantly linked to atherosclerotic lesions in the coronary vessels of neonates.

Maternal Drinking

Fetal alcohol exposure has long been associated
with Fetal Alcohol Syndrome after discovery of the syndrome in 1973 characterized by “craniofacial, limb, and cardiovascular defects associated with prenatal-onset growth deficiency and developmental delay.” Since that time there have been many different mechanisms by which the fetus may be impacted including multiple mechanisms involving alterations to the fetal lipid metabolism. In chickens, fetal exposure to alcohol caused reduced free cholesterol levels. In zebrafish, fetal exposure to alcohol also impacted signaling molecules utilizing cholesterol, including blocking covalent modification of Sonic Hedgehog by cholesterol; supplementation with cholesterol reversed this effect. In rats, fetal alcohol exposure was associated by cholesterol; supplementation with cholesterol reversed this effect. In rats, fetal alcohol exposure was associated with changes in the fatty acid and cholesterol composition in the brain which was found to persist into adulthood.

**Neonatal Factors**

The neonatal genetics play a very important role in their cholesterol levels. Neonates confirmed to have heterozygous familial hypercholesterolemia via DNA testing showed significant increases in cord cholesterol levels at birth and even greater difference by one year. Neonates with familial hypercholesterolemia were also found to have increased rate of synthesis of lanosterol, squalene, and other cholesterol precursors; interestingly, neonates born to mothers with familial hypercholesterolemia tended to have accelerated cholesterol synthesis at birth compared to those born to fathers with familial hypercholesterolemia. Even short-term elevations in cholesterol have resulted in fatty streaks in the aorta of the neonate. This fatty streak deposit can persist into adolescence resulting in a stiffened aorta.

In addition to cholesterol levels, triglycerides and HDL cholesterol play important roles in the development of atherosclerosis and cardiovascular disease. Children with increased triglyceride to HDL cholesterol ratio were found to have stiffened arterial walls. The CARITALY study of cardiovascular risk factors found that triglyceride to HDL cholesterol ratio had better discrimination of cardiometabolic risk factors in children and adolescents than using total non-HDL cholesterol.

**How to diagnose?**

The American Association of Pediatrics (AAP) currently recommends that all children between the ages of 9 and 11 be screened for dyslipidemia for the first time. Additionally, it recommends that the following groups of children be screened between the ages of 2 and 10: children whose parents or grandparents have a history of heart disease or atherosclerosis, children whose parents or grandparents have total blood cholesterol levels of over 240 mg/dL, or those whose family background is not known. This age range was selected for two reasons: this is around the time that the effects of atherosclerosis appear at a higher rate, and is also before the natural decline of LDL-C levels that is seen during puberty.

While not currently in professional guidelines for screening, DNA testing is available for familial hypercholesterolemia and other lipid abnormalities. Two such genetic tests for familial hypercholesterolemia using next generation sequencing include Progenika assessing six genes including LDLR, APOB, PCSK9, APOE, STAP1 and LDLRAP1, boasting 1600 variants of the disease identified and Invitae assessing LDLR, APOB, PCSK9, and LDLRAP1. The higher costs of genetic testing, compared to lipid methods, make it unclear if this is a cost effective method at this time.

There may be other limitations to DNA testing in familial hypercholesterolemia. The LOVD database has recorded over 1700 variants of the LDLR gene alone. In a UK based study, approximately 60% of patients diagnosed with FH were mutation-negative with genetic testing; this was despite 52% of mutation negative patients in the top 3 deciles for LDL-C gene scoring. This suggests more complicated polygenic causes for hypercholesterolemia limiting the efficiency of current DNA approaches. A cascade study involving relatives of known familial hypercholesterolemia patients found that approximately 50% of patients with familial hypercholesterolemia met clinical guidelines for lipid levels for diagnosis of the disorder; the genetic testing used in this group was found to have a sensitivity of 46.2% with a specificity of 88.0% compared to lipid methods.

Current diagnosis guidelines in the United States rely heavily on cholesterol levels and known family history. A study conducted testing the MEDPED criteria found that the lipid levels had 98% specificity, and 87% sensitivity in adults. Pediatric guidelines proposed by National Lipid Association Expert Panel on Familial Hypercholesterolemia indicate for further screening if LDL is greater than 160 mg/dl or non-HDL is over 190 mg/dl; approximately 80% specificity is achieved when LDL levels are greater than 190 mg/dl.

**What modifications can be used to treat?**

**Diet**

Lifestyle changes remain the first step in addressing elevated pediatric cholesterol levels, including a recommendation for referral to a dietician for initial management. Children fed a plant based, no added fat diet for 4 weeks showed decreased body mass index, decreased total and LDL cholesterol levels, decreased systolic blood pressure, and decreased C-reactive protein levels compared to their baseline. A study of children with hypercholesterolemia fed an enriched diet with plant sterols showed a decrease in LDL of 13% with no changes.
in other serum biochemical or hormonal markers\textsuperscript{49}. A diet with cereals enhanced with psyllium fiber was found to decrease cholesterol levels by 7\% in patients with hypercholesterolemia\textsuperscript{50}.

**Exercise**

An analysis of several studies comparing normal intensity aerobic, high intensity aerobic, and resistance training found positive effects on lipid profiles. Regular aerobic exercise elevated HDL cholesterol by 4.6\% and decreased triglycerides by 3.7\%; high intensity aerobic exercise additionally reduced LDL cholesterol by 12.8\%. Resistance training also was effective at reducing LDL cholesterol reducing levels by as much as 14.0\% under supervised training. The addition of resistance training to an aerobic exercise regimen could actually enhance the cholesterol control\textsuperscript{53}.

**Stress Management**

Stress management strategies including yoga, breathing exercises, meditation, and progressive muscle relaxation were shown to improve weight management and lower triglycerides. Total cholesterol/HDL ratio was decreased for males who adhered to a stress management routine. Diabetic patients that followed a stress management routine showed a decreased hemoglobin A1C\textsuperscript{52}.

**Medications**

Medical intervention should be started for patients ≥10 years of age with cholesterol ≥190 mg/dl where >6 months of lifestyle intervention has failed or ≥160 mg/dl with positive family history of cardiovascular disease or positive risk factors for development of cardiovascular disease, where >6 months of lifestyle intervention has failed. Statin use is generally regarded as the first line medication regimen for pediatric patients with substantially elevated non-HDL cholesterol levels after diet and exercise. A bile acid sequestrant is also recommended as possible therapy in this population, alone or in combination with statins\textsuperscript{47}.

**Statins:** Many of the statin drugs (HMG CoA Reductase Inhibitor) are FDA approved for use in children with heterozygous FH. Pravastatin (Pravachol) and rosuvastatin (Crestor) are approved for use in patients 8 years and older (post-menarcheal) while atorvastatin (Lipitor), fluvastatin (Crestor) are approved for use in patients 8 years and older while atorvastatin (Lipitor), fluvastatin (Crestor) are approved for use in patients 8 years and older (post-menarcheal) and simvastatin (Zocor) are approved for use in patients 8 years and older (post-menarcheal) while atorvastatin (Lipitor), fluvastatin (Crestor) are approved for use in patients 8 years and older (post-menarcheal) while atorvastatin (Lipitor). Fluvastatin (Crestor) is thought to bind to the LDL receptor encouraging its degradation. By inhibiting degradation, these drugs increase the number of LDL receptors available on the hepatocyte which decreases circulating levels of LDL cholesterol. These drugs are currently approved for use in adults with heterozygous familial hypercholesterolemia who are currently using diet and the maximally tolerated statin dose but still require additional decrease in cholesterol. Additionally, evolocumab is labeled for use in cases of homozygous familial hypercholesterolemia. The effect of these drugs on cardiovascular health have not yet been established\textsuperscript{66,67}. In trials evolocumab showed a 57\% decrease in LDL-C by 23-27\\%. No clinical adverse events or changes in hormones and sexual maturity were noted, however one study showed an increase in aspartate aminotransferase\textsuperscript{58-60}.

Similarly a two year, double blinded study found that pravastatin had a LDL-C lowering impact of 24.1\% for LDL-R, and a decrease in overall carotid intima change during the duration of the trial. No differences were noted between the control and test group for growth, enzyme, or hormone levels\textsuperscript{61}.

One major shortcoming to these statin studies are the relatively short durations, leaving long term impact unclear.

**Bile Sequestrants:** Colesevelam (Welchol) is approved for use from age 10 years (post-menarcheal)\textsuperscript{62}. A trial using Colesevelam on pediatric patients between 10 and 17 years old found decreases in LDL-C by 7\% at 1.875 g and 12\% at a dose of 3.75 g. Nasopharyngitis, upper respiratory tract infection, and headache were reported during the study\textsuperscript{63}. In conjunction with a low fat diet, low dose colestipol was found to decrease LDL-C by 19.5\% in a pediatric trial of ages 10-17. While patient growth was not impacted, serum levels of several vitamins including D and folate were reduced compared to control\textsuperscript{64}. Cholesterymine used by patients age 6-11 years found a reduction in LDL-C of 16.9\%. Similarly, while growth factors did not appear to be impacted, some serum vitamin levels including D and folate were found to be reduced compared to control\textsuperscript{65}.

**Cholesterol Absorption Inhibitor:** Ezetimibe (Zetia) has been evaluated for use in the pediatric population along with a statin regimen\textsuperscript{66}. Ezetimibe is a cholesterol absorption inhibitor which prevents uptake of dietary cholesterol. Guidelines suggest ezetimibe use can be considered as an add on therapy in familial hypercholesterolemia patients when cholesterol levels are not sufficiently reduced by statin therapy\textsuperscript{47}. In a study of familial hypercholesterolemia children and adolescents, cholesterol levels were decreased from 7.3 to 5.7 mmol/L with use of ezetimibe with no reported adverse effects\textsuperscript{67}.

**PCSK9 Inhibitors:** Alirocumab (Praluent) and Evolocumab (Repatha) are monoclonal antibodies against proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 is thought to bind to the LDL receptor encouraging its degradation. By inhibiting degradation, these drugs increase the number of LDL receptors available on the hepatocyte which decreases circulating levels of LDL cholesterol. These drugs are currently approved for use in adults with heterozygous familial hypercholesterolemia who are currently using diet and the maximally tolerated statin dose but still require additional decrease in cholesterol. Additionally, evolocumab is labeled for use in cases of homozygous familial hypercholesterolemia. The effect of these drugs on cardiovascular health have not yet been established\textsuperscript{66,67}. In trials evolocumab showed a 57\% decrease in LDL-C by 23-27\\%.
reduction in LDL cholesterol levels and alirocumab a 61% reduction\textsuperscript{60,71}. Safety and efficacy of these drugs in children are still being evaluated\textsuperscript{72,73}.

**What else can be done?**

**Neonatal Screening by Lipid Approach with Earlier Intervention**

While it is clear that the maternal cholesterol is transported, it is not clear if this transport results in altered lipid profiles in the neonate. After all, one would expect that if the maternal levels impact the neonatal levels that the results may not have utility in neonatal screening and diagnosis. In cases where maternal lipid levels were altered, there appeared to be no significant difference in the cholesterol or triglyceride levels of the neonate\textsuperscript{74,75}. In fact, fetal cholesterol levels in the first 6 months of gestation appear to correlate with maternal cholesterol levels, whereas older than 6 months there is no longer a correlation with maternal levels. Additionally, the fetal cholesterol levels were found to be inversely correlated with gestational age\textsuperscript{6}. It has even been shown that neonates with confirmed familial hypercholesterolemia via DNA testing had elevated cholesterol levels at birth\textsuperscript{35}.

It might seem strange to screen and diagnose at the neonatal stage when medications are labelled for 8-10 years of age, but even before medications become a factor, lifestyle interventions can be implemented. Encouraging a plant-based diet in children has been shown to help manage weight, decrease LDL cholesterol, and decrease blood pressure\textsuperscript{60}. Exercise has been shown to improve lipid profiles in children and adolescents\textsuperscript{51}. Stress management has been linked to improved weight management, lowered triglycerides, and increased control of diabetes\textsuperscript{52}.

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