MATERNAL CONDITIONS AFFECTING THE FETAL HEART

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PRENAT CARDIO. 2013 SEP;3(3):5-11
DOI 10.12847/09131

Key words: *diabetes mellitus, seizures disorders, lupus erythematosus, maternal CHD, infectious diseases, rubella, coxsackie, cytomegalovirus, HIV, antidepressant therapy*

INTRODUCTION

When one considers the innumerable ways that maternal exposures, ingestions, and diseases can impact a developing fetus, the concept of a "low-risk pregnancy" seems impossible to fathom. The techniques of prenatal diagnosis - in particular ultrasound, echocardiography, and genetics - are ever evolving, as are their roles in understanding, diagnosing, and managing complicated pregnancies. This review articles presents some of the most common maternal conditions that have an impact on the developing fetal cardiovascular system and the challenges associated with the management of these conditions.

DIABETES MELLITUS

Pregestational Diabetes Mellitus (DM) affects 1% of all pregnancies[1] and the number of women hospitalized during pregnancy due to diabetes continues to increase anually[2]. Though perinatal mortality has decreased in recent years[3], major congenital anomalies are seen in 6-12% of pregnancies complicated by pregestational diabetes[4] and continue to be a leading cause of perinatal death[5]. Congenital heart defects (CHD) represent 50% of the anomalies. The most common CHDs seen in diabetic pregnancies include transposition of the great vessels, ventricular septal defect, single ventricle, hypoplastic left heart syndrome, coarctation of the aorta, persistent patent ductus arteriosus, and pulmonary stenosis[5,6].

Prenatal diagnosis of CHDs is accomplished with fetal ultrasonography and echocardiography between 18-22 weeks gestation, and sometimes even earlier. Most major cardiac anomalies can be detected at the mid-trimester using targeted ultrasound evaluation of fetal cardiac structures, including the great vessels. Fetal echo may be indicated in cases of suspected cardiac defects or when the fetal heart cannot be visualized by ultrasonography[7,8]. Though the sensitivity of fetal echo is 90-97% for identifying CHD[9,10], the use of routine fetal echo in women with a normal detailed anatomic survey is controversial[11]. Additional emerging evidence indicates that the myocardial performance index, or Tei index (TI), can be used as a prognostic indicator of heart failure. The Tei index is a Doppler-derived time interval index that reflects both left ventricular systolic and diastolic function. The diagnostic role of TI is still evolving and it may prove to be a useful tool in exploring fetal cardiac function in different clinical situations[12,13,14].

How to cite this article:
Hua M, Weiner S.
Maternal Conditions Affecting the Fetal Heart. Prenat Cardio. 2013 Sep;3(3):5-11

Hypertrophic cardiomyopathy occurs in 40% of infants born to diabetic mothers, and is usually transient and asymptomatic. However, up to 5% of affected infants will experience significant complications from impaired cardiac function, including congestive heart failure. The pathophysiology of fetal cardiomyopathy is unclear but does not appear to correlate with third-trimester HbA1c[15,16,17]. Russell et al have demonstrated impaired cardiac function in fetuses of diabetic mothers as early as the first trimester. Impaired diastolic function and global cardiac function may therefore precede the structural changes typically seen in the third trimester; fetuses of diabetic mothers show a thickened interventricular septum and right ventricular wall thickening. The authors hypothesize that the changes in cardiac structure develop to compensate for impaired diastolic filling seen in early pregnancy[17].

The management of pregestational diabetes in pregnancy involves stringent glucose monitoring and

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Submitted: 2013-08-15, accepted: 2013-08-30

treatment with insulin. The importance of good glycemic control during pregnancy is obvious, but appropriate metabolic control prior to conception is also desired in order to maximally reduce fetal risks. Guerin et al have demonstrated a linear relationship between HbA1c and the risk of congenital malformations[18]; however the relationship between severity of HbA1c and the severity of CHD has not been well studied[16]. Additionally, there are differing opinions as to whether normalization of HbA1c prior to conception produces a risk reduction equal to that of non-diabetic women[16,18]. Absolute amount of risk reduction aside, multiple studies have demonstrated that optimal glucose control prior to and during pregnancy reduces the rates of spontaneous miscarriage, congenital anomalies, and other adverse pregnancy outcomes[19,20].

SEIZURE DISORDERS

Seizure disorders, or epilepsy, affect 0.3% to 0.8% of all pregnancies[21,22]. Offspring of women with epilepsy have a two- to three- fold increased risk of congenital malformations, which most commonly manifest as congenital heart defects (CHD), cleft lip or palate, and neural tube defects[23]. While CHDs are the most common malformations seen, no pathognomonic CHD lesion is associated with fetuses born to mothers with epilepsy. The most prevalent include atrial septal defects, ventricular septal defects, tetralogy of fallot, coarctation of the aorta, patent ductus arteriosus, and pulmonary stenosis[24].

Available data currently suggests that the increased risk for birth defects is not a sequelae of epilepsy but rather due to the teratogenic effects of antiepileptic drugs (AEDs). Tomson and Bettino found that pooled data from 26 studies revealed a major congenital malformation rate of 6.1% in offspring of women with epilepsy who were treated with AEDs during pregnancy. This compares to a 2.8% malformation rate in offspring of women with untreated epilepsy, and 2.2% in the healthy control population[25]. It is also evident that the risk of AED-induced malformations is dose dependent and increased by multi-drug therapy, especially with the combination of carbamazepine, valproate, and phenobarbital[26,27]. The data regarding newer AEDs and congenital malformations suggests that there may have less of a teratogenic effect[28], but studies have been criticized for small sample sizes and confounding multi-drug regimens[25].

There are various drug-type specific proposed mechanisms for the pathogenesis of AED induced birth defects. The formation of toxic metabolites has been identified as the causative factor in carbamazepine related malformations[29]. Formation of free radicals and induced-oxidative stress may be responsible for the teratogenic potential of phenobarbital[30,31]. Altered folate metabolism as well as provoked DNA hypomethylation have been implicated in the pathway of valproic acid-induced malformations[32,33]. Regardless of the underlying mechanism, it is well known that teratogens work on susceptible genotypes, additionally interacting with environmental factors, to induce their damage on the fetus[34].

Though there is known risk associated with some AEDs, most women with epilepsy will require AED therapy throughout their entire pregnancy to control seizures. The prevailing wisdom holds that the lowest efficacious dosage of a single agent (if possible) is most desirable to minimize the risk of congenital malformations. Folate supplementation is recommended for all women of child-bearing age, though the necessity of higher doses for women with epilepsy is not clear[34,35]. Thorough ultrasound and fetal echocardiography evaluations are necessary and generally intiated between 16 to 20 weeks gestation in order to identify congenital malformations. Fetal surveillance with serial growth ultrasound examinations or non-stress testing may not be necessary, as risk for other adverse pregnancy outcomes - including fetal death, growth restriction, and preterm birth - does not appear to be increased in women with epilepsy[22].

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an auto-antibody mediated autoimmune disease that frequently affects women of child-bearing age[36]. Fertility rates of women with SLE are equal to those of the general population but SLE patients with antiphospholipid antibodies (APLS) are known to have an increased rate of spontaneous abortion and preterm birth[37]. Pregnancy in SLE patients with or without APLS is considered a high risk condition. Maternal and fetal prognoses are improved when SLE is quiescent at the time of conception and when renal disease is in remission for at least 6 months prior to conception[38].

Neonatal lupus (NL) occurs in 1-2 percent of babies born to mothers with autoimmune disease, most commonly SLE and Sjogren's syndrome[39,40]. NL consists of congenital heart block (CHB), rash (cutaneous lupus), leukopenia, anemia, and thrombocytopenia[41] and appears to be mediated by the transplacental passage of maternal autoantibodies to Ro/SSA and La/SSB. CHB is the most severe manifestation of NL; the mortality rate is at least 20% and the majority of affected infants require pacemaker placement within the first year of life[42].

The precise mechanism of tissue injury in CHB is unknown however it is hypothesized that anti-SSA/SSB antibodies bind to fetal cardiac tissue, leading to autoimmune injury of the antrioventricular (AV) node and its surrounding tissue[42]. Additionally, anti-SSA/SSB antibodies may interfere directly with calcium channel transport in the myocardial tissue, which would disrupt action potential propagation and conduction in the SA and AV nodes[43]. Still, maternal antibodies are not sufficient for CHB. Concordance has not been observed in monozygotic twins who have identical genotypes and exposures to the maternal circulation, implying that an intrinsic component of fetal development serves a crucial role in the pathogenesis of CHB[44].

In general, pregnancy is not contraindicated in SLE patients who have controlled, inactive disease. Screening of pregnant women with accepted risk factors (known autoimmune disease or previous child with NLS/CHB) is recommended[45]. Antibody detection is initially performed by ELISA techniques and if the mother is negative for both anti-Ro/SSA and anti-LA/SSB antibodies the risk of CHB is considered negligible[46]. Women who test positive for anti-SSA/SSB antibodies should undergo serial fetal echocardiography in order to detect signs of early myocarditis and heart block.

There are no formal guidelines for the frequency of testing to detect CHB but weekly fetal echo from 16-26 weeks and every other week until 34 weeks is a reasonable approach[46]. The highest risk period for the fetus is between 18-24 weeks gestation. New onset heart block rarely occurs after 30 weeks gestation[47]. The diagnosis of autoimmune associated congenital heart block is generally made by the detection of persistent bradycardia in the fetus without obvious anatomical abnormalities or evidence of infection. A spectrum of atrioventricular blocks though first-degree heart block (prolongation of the PR interval) is uncommon and does not appear to precede more advanced block in all cases. In actuality, advanced block and cardiomyopathy can occur within 7 days of a normal echocardiogram without intial first-degree block[47].

The basis for treatment of fetal CHB is to decrease synthesis and transplacental passage of antibodies, thereby preventing complete heart block. Corticosteroids, intravenous gammaglobulin, and plasmapheresis have been utilized. Published reports have varying rates of success with regard to controlling inflammatory processes (such as myocarditis or pericardial effusions) or reversing second-degree block, however all reports agree that complete heart block is irreversible[47,48,49]. When this occurs in the premature fetus, betamimetic therapy may be considered to increase the fetal heart rate and thereby cardiac output. Preventative therapy for women with anti-SSA/SSB antibodies is currently being studied, but success rates are variable and risk-benefit ratios have not been clearly outlined. Preventative treatment with glucocortecoids or IVIG are not generally recommended[50,51], however there is some evidence that preemptive treatment with hydroxychloroquine in pregnant women with a prior child affected by CHB may decrease the overall risk of CHB in the current pregnancy[52]. More prospective studies are needed in order to confirm these observations.

MATERNAL CHD

Advances in cardiac surgery and the management of congenital heart disease (CHD) have increased the number of patients with CHD in adulthood[53]. Demographics have shifted such that there are more adults with CHD now than children, and a significant proportion of the CHD population is comprised of reproductive-aged women. Additionally, the proportion of births to women with CHD increased 218% in a mere decade[54]. Despite improvements in quality of life and overall life expectancy however, CHD remains an important cause of maternal morbidity and mortality. It is also becoming increasingly clear that there are neonatal consequences of maternal CHD as well.

Normal alterations in pregnancy physiology lead to increased cardiac output (via increased stroke volume and heart rate) and decreased systemic vascular resistance[21]. In the presence of maternal heart disease, the circulatory changes of pregnancy may result in decompensation of the maternal-fetal unit[55]. Recent studies have demonstrated the link between maternal CHD and poor fetal growth, stillbirth, and prematurity[56,57,58]. Adverse maternal outcomes include arrhythmia, pulmonary edema, stroke, cardiac arrest, endocarditis, and death[59]. Large prospective studies have indicated that those with poor pre-pregnancy functional status and cyanotic heart disease have worse pregnancy outcomes and that the risk of cardiac events can be predicted using the Cardiac Disease in Pregnancy (CARPREG) risk score[59,60].

Pregnancy is generally not contraindicated in those with mild or moderate cardiac disease; however, care of the pregnant patient with CHD should include counseling on pregnancy termination when gestationally appropriate. Patients with CHD are ideally counseled in the preconception period[61]. A female with CHD who is approaching reproductive age should undergo a comprehensive cardiac and genetic work-up so that reliable counseling can be provided. Women should be given information about contraception and the potential risks associated with pregnancy[62]. Fetal surveillance should include echocardiography to evaluate cardiac malformations, generally beginning at 18-22 weeks gestation[63]. Though many congenital heart defects are sporadic events, there are reports that indicate an increased risk for fetal CHD if the mother is affected[59,63,64].

INFECTIOUS DISEASES

Rubella

Since the advent of the rubella vaccine, maternal rubella is now considered a rare infection in developed countries. However, in many developing countries, congenital rubella syndrome (CRS) continues to be a major cause of congenital heart defects[65]. Placental infection occurs with maternal viremia, resulting in focal areas of necrosis in the epithelium of chorionic villi and in the endothelial cells of its capillaries. The endothelial cells subsequently desquamate into the vessel lumen and act as infected endothelial cell emboli, causing fetal infection and damage to fetal organs[66]. A 50-80% fetal transmission rate is predicted when maternal infection occurs in the first trimester, and decreases significantly thereafter[67,68].

The most common clinical features of CRS include cataracts, rash, and deafness. The common cardiac defects include patent ductus arteriosus, peripheral pulmonary artery stenosis, ventricular septal defect, and myocarditis[69]. The prognosis of CHD due to rubella

is related to the presence of other anomalies; the majority of cases with severe multi-system involvement are lethal within the first year[67].

Due to the mass immunization programs in the United States, rubella is no longer considered endemic. Additionally, there has been a shift in demographics which has resulted in the majority of infections being found not among children, but among individuals of child-bearing age. This increases the probability of CRS development should a rubella outbreak occur[70]. If exposure to rubella is suspected in a non-immune obstetric patient, immediate laboratory diagnosis is recommended. Rubella infection may be diagnosed in the fetus via detection of viral DNA in the amniotic fluid, cord blood, or placental tissue[71]. At this time, there is no specific pharmacologic treatment for gestational rubella infection[72,73,74].

Coxsackie

The enteroviruses, specifically the Coxsackie group A and B (type 2, 3, 4, 5) viruses, are the most common pathogens associated with adult myocarditis and the subsequently developing dilated cardiomyopathy[75]; the association with cardiac defects resulting from congenital infection is not as strong. Determining the prevalence of maternal coxsackie infection and the risk of fetal transmission is difficult, since the disease is often asymptomatic or self-limiting in the mother and serologic confirmation is not standard. In general, transplacental transmission is rare and intrapartum transmission (via maternal secretions during delivery) or postnatal transmission through secretions is much more common. Fulminant neonatal infections are characterized by meningoencephalitis, hepatitis, and myocarditis. The extent of neonatal disease is related to the degree of maternal viremia, the mode of transmission, and the presence of specific receptors on fetal tissues[76]. Because of the ubiquitous nature of the enteroviruses and the variability of neonatal effects after maternal infection, viral screening is not recommended[77].

Cytomegalovirus

Cytomegalovirus (CMV) is the most common cause of viral intrauterine infection, with an incidence of 0.5%-2.5% worldwide. Transplacental transmission is common; 30% of affected mothers will transmit the infection to their fetus. The vast majority of infected fetuses are asymptomatic at birth but up to 10% may suffer from CMV induced "cytomegalic inclusion disease" characterized by intrauterine growth restriction, jaundice, hepatosplenomegaly, thrombocytopenia, and severe central nervous system damage[45]. Congenital heart disease is a rare complication of CMV infection, although nonspecific conditions such as fetal hydrops, growth restriction, cardiomegaly, and polyhydramnios have also been reported in association with intrauterine CMV infection[78]. Routine screening for CMV is not recommended, as there is no proven intervention if seroconversion is diagnosed[79], although trans-placental therapy with hyperimmune CMV gamma-globulin appears promising[80].

Prevention of CMV via behavioral modification has shown to decrease CMV conversion during pregnancy by 84%, and is the mainstay of pregnancy management[81].

HIV

HIV in pregnancy poses numerous challenges to the obstetrician, as women account for a growing proportion of those infected with HIV/AIDS worldwide. In the United States, 27% of all HIV/AIDS cases are among women, up from 7% in 1985[78]. The risk of viral transmission to the fetus is 12-25% and occurs both transplacentally and through perinatal exposure to maternal bodily fluids[82]. Antenatal treatment with anti-retroviral drugs has decreased the risk of perinatal transmission to less than 2%[78].

Children infected with HIV have been shown to have an increased incidence of left ventricular dysfunction and dilated cardiomyopathy, however it is unclear whether this is a direct result of viral effects or whether it is due to confounding effects, such as medications, inadequate nutrition, substance use, or increased susceptibility to other infectious diseases[83,84,85].

ANTIDEPRESSANT THERAPY

Nearly one third of all women are exposed to a psychotropic medication at some point during pregnancy, as nearly 500,000 pregnancies per year are affected by psychiatric illness[86]. It is generally accepted that maternal psychiatric illness in pregnancy should be treated, as inadequately treated disease is associated with maternal and neonatal morbidity. Decreased compliance with prenatal care, poor nutrition, use of tobacco, alcohol, and illicit substances, are all possible sequelae to poorly controlled psychiatric disorders[87]. However, the potential teratogenic risk of some psychotropic medications is a concern to both provider and patient. Misperceptions of the risks associated with various medication exposures in pregnancy can lead to unwarranted discontinuation of medication. This is of particular concern in the pregnant women being treated for depression. Walfisch and colleagues have demonstrated that depressed women are more likely to have an unrealistically high perception of the risk of having a baby with a birth defect after medication exposure, leading to more medication discontinuations and relapsing depression[88].

All psychotropic medications studied to date cross the placenta and are present in amniotic fluid. Therefore, maternal euthymic mood should be achieved using the lowest effective dose and the fewest number of medications that will give a therapeutic effect. Use of a single medication at a higher dose is preferred over the use of multiple medications[87]. Selective serotonin reuptake inhibitors (SSRIs) are large classes of drugs that are highly effective in the treatment of anxiety and depression and

have been well studied in pregnancy; overall, there is limited evidence of teratogenic effects related to their use in pregnancy. However, there is conflicting data on the risk of cardiac malformations – namely atrial and ventricular septal defects – associated with SSRI use[89,90,91]. Paroxetine use in pregnancy, in particular, has been implicated in cardiac malformations and the current recommendation is to avoid use in pregnancy. Exposure to paroxetine in early pregnancy may warrant evaluation with a fetal echocardiogram[87].

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Financing: The research was not financed from the external sources

Conflict of interest: The author declares no conflict of interest and did not receive any remuneration