MASTER CLASS

Diagnosing Birth Defects

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Birth defects continue to account for the majority of infant deaths, and their biologic basis continues to present a mixed picture, with the majority of causes still unknown. Cardiac defects – the most common type of birth defect – result in varying types of morbidity, but remain the most severe and disabling of all birth defects. As our guest author points out below, cardiovascular defects are the single largest contributor to birth defect–attributable infant mortality.

What is clear is the fact that when birth defects are identified prenatally, decisions can be made regarding the timing and route of delivery and even the facility where delivery occurs. We know that such decision making can be highly influential on the ultimate outcome of the infant.

Fortunately, there has been improvement in recent years in diagnostic technology that enables more prenatal diagnosis of congenital heart disease, and certain conditions that in the past went unknown or undiagnosed are now being identified early so that specialists can intervene in a timely manner.

While certain pregnancies are clearly at higher risk – those involving mothers who have pregestational diabetes, for instance, or mothers with exposure to particular toxins – there are other scenarios and factors that increase risk of which we should be aware.

It's a tricky evaluative process, for, as our guest author points out, most infants born with congenital heart disease do not have defined risk factors. At the least, however, we can be aware of the familial, maternal, and fetal factors that are known to increase risk and then ensure that all at-risk pregnancies are properly evaluated – often with fetal echocardiography – to determine if a cardiac defect is present and, if so, to plan the delivery-related issues of timing, mode, and facility.

In light of the importance of this subject and the role that ultrasound scanning, genetic counseling, and early decision making and planning can play in the ultimate outcome of the fetus, we decided to do a Master Class on congenital heart defects. We have invited Dr. Joshua A. Copel, professor of obstetrics, gynecology, and reproductive services, and of pediatrics, and vice chair of obstetrics at Yale University, New Haven, Conn., to serve as our guest professor.

Dr. Copel has written and lectured extensively on fetal arrhythmias, fetal cardiac anomalies and congenital heart disease, and sonographic monitoring and fetal echocardiography. Here he discusses what we should know about both familial contributions to congenital heart disease and various noninherited risk factors. ■

DR. REECE, *who specializes in maternal-fetal medicine, is vice president for medical affairs at the University of Maryland, Baltimore, as well as the John Z. and Akiko K. Bowers Distinguished Professor and dean of its school of medicine. He said he had no conflicts of interest relevant to this column. He is a member of the* OB.GYN. NEWS *editorial advisory board and is the medical editor of this column.*

Congenital Heart Disease Risk Assessment

While infant deaths associated with congenital heart defects have declined substantially over the past 2 decades, congenital heart disease remains the most common fatal congenital anomaly in the first year after birth.

Prematurity is the most significant cause of death in the first week of life, but after that point, birth defects take over as the leading cause of infant mortality (and overall, birth defects are the leading cause of infant mortality). Cardiovascular defects, in turn, are the single largest contributor to infant mortality attributable to birth defects – severe congenital heart disease (CHD) affects approximately 0.5% of all neonates and is responsible for one-third of deaths between birth and 1 year of life.

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Prenatal diagnosis of CHD is important because early detection can improve the planning of services and provision of coordinated multidisciplinary care. While most fetal therapy for CHD is investigational and still evolving, studies from all over the world have shown that if a baby is known to have a heart problem and is delivered at a facility that provides definitive care, the baby will likely fare better.

Unfortunately, most infants born with CHD do not have defined risk factors. As obstetricians we must always be alert to the possibility that, even without a clear risk factor, there could be a cardiovascular problem.

It is important to know, on the other hand, who is at increased risk and should be evaluated further, and who is not at increased risk. We know now that certain infants whom we haven't traditionally thought of as being at risk for CHD are indeed at higher risk. Our knowledge of familial contributions to CHD has grown, for instance, giving obstetricians the responsibility to be alert for potential familial genetic patterns so that the proper counseling can be provided.

There are also noninherited risk factors that can be identified and potentially modified. It is unclear what proportion of CHD can be prevented, but at the least, obstetricians should be aware of such risk factors so they can provide guidance to parents and future parents that could reduce the risk of their children having a major cardiovascular malformation, and so they can ensure proper surveillance in any pregnancy.

Familial Risks

Over the past 15 years or so, our understanding of inherited causes of congenital heart defects has increased significantly, and while there is much more to learn, it is now appreciated that genetics plays a greater role in CHD than previously estimated.

Molecular genetics studies in families with multiple affected individuals have even led to the identification of specific genetic abnormalities for several forms of CHD, such as the single gene mutation sometimes seen in tetralogy of Fallot; others are related to mutations in more than one gene.

While most chromosome defects are not inherited, some anomalies or syndromes with cardiac phenotypes – for instance, those involving microdeletions or gonadal mosaicism – can be inherited and play a small but increasingly appreciated role in CHD. The William-Beuren syndrome and the 22q11.2 deletion syndrome, for instance, are microdeletion syndromes that show autosomal dominant inheritance.

Overall, parents of a child with CHD that is not associated with a typical chromosomal aberration have a 2%-3% chance of having another child with CHD; it is estimated that half of affected siblings will be diagnosed with the same lesion, the other half with a different lesion.

Classic Mendelian transmission is occasionally responsible for inherited CHD in families, but recurrence risk is significant only when the family history of CHD involves first- or second-degree relatives.

Fetal echocardiography is definitely warranted when the mother or father – or a sibling – of the fetus has CHD, as well as when CHD has affected a parent's own mother, father, sister, or brother.

Once you get further out in the family history, to cousins and other third-degree and more distant relatives, the risk is not high enough to warrant a more detailed fetal examination. This is important for counseling; parents who are worried about a history of CHD in third-degree relatives should be reassured.

Among the changes in patterns of referral for fetal echocardiography that we detected at Yale-New Haven Hospital from 1985 to 2003 was an 18% increase in referrals for a family history of CHD, including family history in more distant relatives.

This increase was not accompanied by any change in the percentage of structural cardiovascular heart defects consequently detected (J. Ultrasound Med. 2006;25:197-202).

As an increasing number of patients with major congenital cardiac defects have been surviving to adulthood and parenthood, numerous investigators have attempted to identify specific recurrence risks.

One study done in the United Kingdom, for instance, identified 727 adults with surgically modified major heart defects and their 393 live offspring. Of these infants, 16 were born with cardiac malformations, representing a total recurrence risk of 4.1%. Recurrence risk in offspring ranged from 3.1% for tetralogy of Fallot to 7.8% for atrioventricular septal defect (Lancet 1998;351:311-6).

CHD occurred more often in offspring of affected mothers (5.7%) than affected fathers (2.2%). Compared with offspring, sibling risk was significantly lower: 2.1% overall.

A much larger and more recent study done in Denmark again showed strong familial clustering in first-degree relatives for CHDs, particularly for recurrences of the same heart defect. (Very few families experience a second heart defect, the study found.)

The study – a national cohort study of more than 1.7 million people born during a 29-year period – also is one of the largest studies, if not *the* largest study, to document a decreasing risk as family history gets more distant.

The relative risks of any CHD in singletons were 3.21 for a family history of any CHD in first-degree relatives, 1.78 for a family history involving second-degree relatives, and 1.10 for a family history in third-degree relatives (Circulation 2009;120:295-301).

Only with a history of affected first- and second-degree relatives was there a statistically greater chance of having an affected fetus.

In twins, the relative risks of any CHD were 12.5 for same-sex twins and 6.93 for twins of both sexes, the Danish investigators noted.

And in looking at the contribution of CHD family history to the total number of CHD cases in the population, they found that 2.2% of heart defect cases in the population were attributed to CHD family history in first-degree relatives.

Another notable finding from other studies is that women with cyanotic heart disease have a higher risk of having a baby with CHD than do women with noncyanotic heart disease.

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Maternal Risks

Just as we've learned much about inherited causes of congenital heart disease over the past 15 years, there is a growing body of epidemiologic literature on potential fetal exposures – from maternal illnesses to maternal drug exposures – that can alter the risk of CHD.

The risk factors for CHD maternal teratogen exposure are numerous. They include lithium, alcohol, isotretinoin, and various anticonvulsant drugs, and many are well-appreciated by ob.gyns.

Other factors for which risk has been well determined, and can be better appreciated, include:

► **High vitamin A intake.** Findings are not completely consistent, but we have enough data now to suggest that women who take extra-large doses of vitamin A may actually be putting their fetuses at risk of birth defects.

One study worth noting found that among more than 22,000 pregnant women, those who took more than 10,000 IU of vitamin A from supplements were 4.8 times more likely to have babies with birth defects associated with cranial-neural-crest tissue than were women who consumed 5,000 IU or less per day (N. Engl. J. Med. 1995;333:1369-73).

Typical prenatal vitamins have 5,000 IU in each dose. This is one reason that women with twin pregnancies can take extra folic acid, but should not double up on their prenatal multivitamins.

► **Folate antagonists.** Common drugs such as trimethoprim, triamterene, sulfasalazine, phenytoin, phenobarbital, primidone, carbamazepine, and cholestyramine may increase the risk not only of neural-tube defects, but of cardiovascular defects as well, in addition to oral clefts and urinary tract defects.

Fortunately, studies such as one published in 2000 involving thousands of infants show that the folic acid component of prenatal multivitamin supplements can reduce the risks of these defects, just as it reduces the risk of neural-tube defects (N. Engl. J. Med. 2000;343:1608-14).

► **Paxil (paroxetine).** This is the only antidepressant that has been shown in some studies to increase the risk of CHD. Its manufacturer, GlaxoSmithKline, changed the label's pregnancy precaution in 2005 from a Pregnancy Category C to Category D. If a patient becomes pregnant while taking the drug, she should be advised of potential harm to the fetus.

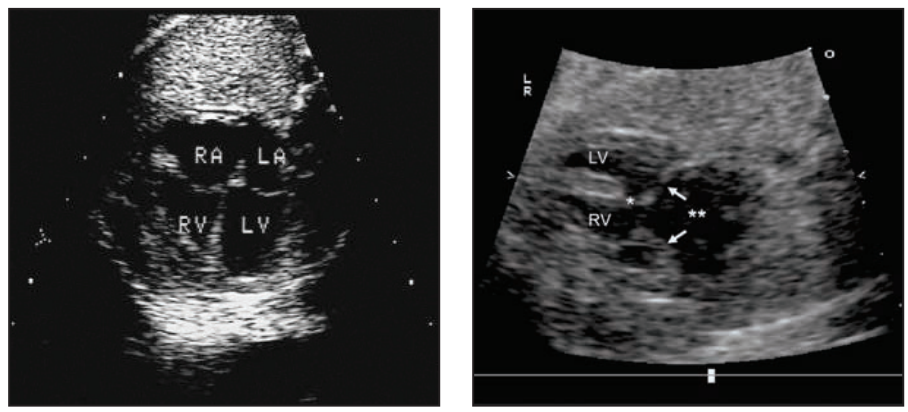
One epidemiologic study showed that women taking Paxil were two times more likely to have an infant with CHD, and 2.2 times more likely to have an infant with any congenital malformation, than were women taking other antidepressants.

► **Diabetes.** The risk of fetal anomalies with maternal diabetes and elevated hemoglobin A_{1c} in early pregnancy has been known for some time.

In a study published in 1981, for instance, the risk of CHD and other fetal anomalies rose from 5% to 22% as maternal HbA_{1c} rose from a range of 7%-8.5% to greater than 8.5% (N. Engl. J. Med. 1981;304:1331-4).

We've also known for some time that differences in CHD may exist even with good metabolic control. Studies have documented mild cardiac hypertrophy involving the interventricular septum and the ventricular free walls, for instance, in diabetic mothers with good metabolic control (J. Pediatr. 1991;118:103-7 and Am J. Obstet. Gynecol. 1991;164:837-43). Such growth affects cardiac diastolic function.

With the epidemic of obesity and the increasing prevalence of early type 2 diabetes and glucose intolerance among women of childbearing age, however, this is an increasingly important risk factor to appreciate and counsel about.



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A two-dimensional four-chamber view of a normal fetal heart (left). Fetal image of a complete atrioventricular septal defect with large atrial (**) and ventricular (*) septal defects (right).

The most important message, we've learned, is that there's no such thing as perfect control – that good metabolic control will not necessarily protect diabetic mothers from the higher risk of CHD.

Just as detection and appropriate management of diabetes before and during pregnancy are of utmost importance, so is fetal echocardiography for every pregnant woman who has pregestational diabetes – even diabetes that is well controlled.

Indeed, the same review of all fetal echocardiography performed between 1985 and 2003 at Yale-New Haven Hospital that showed an increase in referrals for family history also showed a 9% increase in the proportion of studies done for pregestational diabetes as the indication. The increase was most striking when it came to women who had recently been diagnosed, compared with long-standing diabetes – a finding that likely reflects the increase in obesity.

► **Phenylketonuria.** Fortunately, strict dietary control before conception and during pregnancy can reduce the increased risk of heart defects faced by women with this disorder. We need to remember that aspartame (NutraSweet) can cause phenylalanine levels to increase in women with PKU, but not in normal women. Women without PKU can be reassured that there is no evidence linking aspartame with birth defects.

Fetal Risks

Among the fetal risk factors important to consider are:

► **Extracardiac anomalies.** The identification of any extracardiac anomaly should raise our level of suspicion for other anomalies, including congenital heart defects. If we see one anomaly – anywhere in the fetus – there often are really two. And if we see two anomalies, there frequently are really three.

► **Nonimmune hydrops.** All fetuses found to have NIH should be evaluated with fetal echocardiography. Structural heart disease in fetuses with NIH is usually indicative of a poor prognosis for survival, but when rhythm disturbances/arrhythmias are detected in association with NIH, there is sometimes an option for prenatal treatment.

► **Fetal arrhythmias.** An irregular heartbeat is usually not a problem, but tachycardia and especially bradycardia are associated with an increased risk of CHD. There may be structural heart defects in as many as half of fetuses with fixed bradycardia (i.e., baseline heart rate less than 100). In general, it is best that all arrhythmias are examined; it is just too hard to tell them apart by auscultation alone.

► **Nuchal translucency.** Numerous studies have shown that elevated first-trimester nuchal translucency (NT) increases the risk of major congenital heart defects in chromosomally normal fetuses, and that risk increases with increasing NT measurement.

In a large prospective multicenter study conducted by the National Institute of Child Health and Human Development, for instance, investigators identified 21 cases of major congenital heart defects in 8,167 chromosomally normal pregnancies. They reported that the incidence of CHD per 1,000 pregnancies rose from 1.9 with an NT measurement of less than 2.0 mm, to 4.8 with an NT measurement of 2.0-2.4 mm, to 6.0 with an NT measurement of 2.5-3.4 mm, to 23 of every 1,000 pregnancies with an NT measurement of 3.5 mm or greater (Am. J. Obstet. Gynecol. 2005;192:1357-61).

If the NT is greater than 3.5 mm, measured by a qualified sonographer or sonologist at 11-14 weeks as part of an aneuploidy risk assessment scan, the patient should be referred for fetal echocardiography.

► **In vitro fertilization.** We recently investigated the prevalence of congenital heart defects among IVF pregnancies at our referral program at Yale, and found that children conceived through IVF were 3-12 times as likely to have CHD as was the general population (J. Ultrasound Med. 2010;29:917-22).

Similar data have come from Australia and Europe, with reported odds ratios for IVF versus natural conception of 3-4. I tell patients, therefore, that it's not just one place or one study suggesting risk. Indeed, it's a meaningful risk factor.

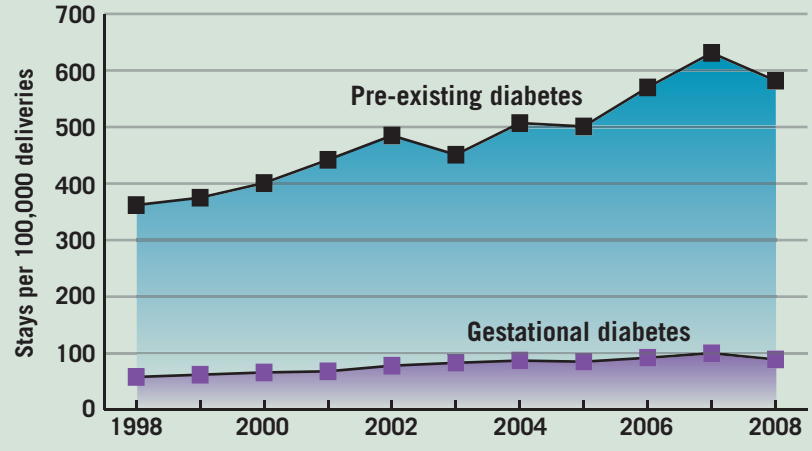
► **Monochorionic twins.** In a systemic literature review we conducted several years ago that included 40 fetuses with CHDs among 830 fetuses from monochorionic/diamniotic twin gestations, the rate of CHDs in these twin gestations was significantly higher than the prevalence rate of CHDs in the general population (J. Ultrasound Med. 2007;26:1491-8).

Congenital heart defects were almost three times as likely to complicate the monochorionic/diamniotic twin gestations affected by twin-to-twin transfusion syndrome (TTTS), compared with those without TTTS, but an increase occurred regardless of the presence of TTTS. Ventricular septal defects were among the most frequent heart defects. Fetal echocardiography may be considered for all monochorionic/diamniotic twin gestations.

Dr. Copel disclosed that he has received research support from Philips Healthcare and Siemens Healthcare. Both companies manufacture echocardiography and other ultrasound systems. ■

DATA WATCH

Diabetes-Related Hospital Stays in Pregnancy on the Rise



Note: Based on data from the Nationwide Inpatient Sample.
Source: Agency for Healthcare Research and Quality

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