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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.

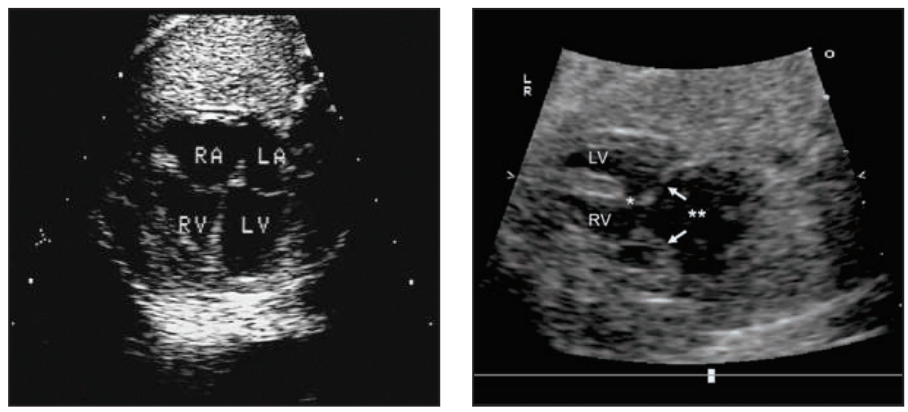
One epidemiologic study showed that women taking Paxil were two times more likely to have an infant with CHD, and 2.2 times more likely to have an infant with any congenital malformation, than were women taking other antidepressants.

► **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.

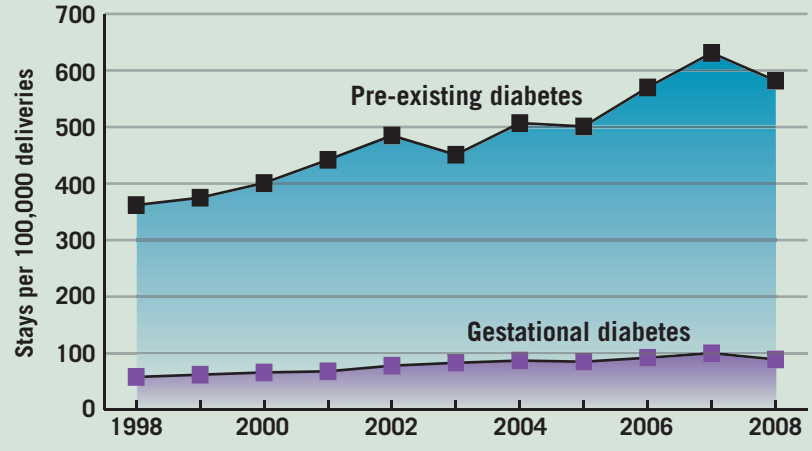
► **Monochorionic twins.** In a systemic literature review we conducted several years ago that included 40 fetuses with CHDs among 830 fetuses from monochorionic/diamniotic twin gestations, the rate of CHDs in these twin gestations was significantly higher than the prevalence rate of CHDs in the general 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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