Pulmonary Hypertension Still High Risk in Pregnancy

BY MITCHEL L. ZOLER
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PHILADELPHIA — A Milwaukee cardiologist seems to have defied the textbook on what happens to women who develop pulmonary hypertension while pregnant.

The medical literature generally says that about half of these women will die during or soon after delivery if they carry the pregnancy close to term. But a series of 40 pregnant women with pulmonary hypertension who were seen or consulted on by Dr. Dianne L. Zwicke during 2000-2008 have all survived, and 39 of them delivered healthy infants, she reported at the annual meeting of the American College of Chest Physicians. The pregnancy of the 40th woman was electively terminated at 22 weeks.

Despite this perfect survival record so far, Dr. Zwicke is very cautious about the immediate implications of her series. "I have not encouraged any women with pulmonary hypertension to get pregnant. We don't have enough data to say that yet." In all except one instance, the 27 women who were directly treated by Dr. Zwicke and the 13 cases for which she provided ongoing consultation involved women who were diagnosed with pulmonary hypertension after they became pregnant.

There are not enough data to back encouraging women with pulmonary hypertension to get pregnant.

DR. ZWICKE

She also warns the women who choose to continue their pregnancy that they must be willing to do everything she instructs them to do, they must come in for every appointment, and they must understand what the medical literature says: that in the past many of these pregnancies have been fatal for the mothers.

The cases are generally first identified at 15-20 weeks' gestation. The first clue that something is wrong is when exercise-induced dyspnea or the woman's weight gain is disproportionate to the pregnancy, said Dr. Zwicke, a cardiologist in a group practice in Milwaukee. The patients that she has managed had an average age of 27 years (range 19-36 years). The most common cause of their pulmonary hypertension was idiopathic, in 50%, followed by congenital heart disease in 18%, mitral valve disease in 10%, and lupus in 10%. Their average pulmonary artery pressure was 59 mm Hg (range of 37-86 mm Hg), their average right ventricular ejection fraction was 30%-35% (range of 20%-45%), and their average right atrial pressure was 10 mm Hg (range 7-20 mm Hg).

Thirty-nine of the mothers were treated with intravenous prostaglandin infusions; one patient was primarily treated with a calcium channel blocker. Several other drugs were also used throughout pregnancy, but prostaglandin infusion is key. "There is never too much prostaglandin," she said. "The dosage must rise as soon as possible."

Thirty-four of the babies were delivered vaginally following induction. The remaining five live births were by cesarean section. No pregnant mother with pulmonary hypertension should expect a natural delivery, Dr. Zwicke said. One newborn required 2 days on a ventilator after delivery. All of the other 38 were ready to go home by the third day after delivery.

Following diagnosis, the most critical time during pregnancy is weeks 30-36, when hormonal and fluid shifts start to become dramatic. Prior to 30 weeks' gestation, women can be monitored every 4 weeks by ultrasound. Starting at week 30, ultrasound examination of the right heart must be done weekly. These exams should be done by the same echocardiographic technician to help ensure consistent images.

The key member of the delivery team is a cardiologist or pulmonologist, who is the person reading the weekly echocardiograms and deciding whether the patient's clinical state and right heart function has deteriorated so severely during the prior week that delivery must occur immediately. This happens when the patient can no longer do the exertional tasks that they could do the prior week, and when their right-side ejection fraction, right ventricular size, and right atrial size have all become very compromised.

During this key period of weeks 30-36, if "I can identify a reason why the patient is deteriorating and I can fix it, then we'll let the pregnancy continue." But if there is no obvious explanation for the deterioration and their status is worrisome or worsening, then delivery is immediately begun. Right heart status is more important than their pulmonary artery pressure, Dr. Zwicke said. If no crisis occurs, delivery is induced after 36 weeks' gestation.

Once delivery starts, the key to success is careful fluid control. Every milliliter that enters the women must eventually get taken out because of the high risk from excess fluid in these patients. "It's all about the right ventricle being able to handle the fluid," she said.

After delivery, the mother is taken to the ICU and closely monitored and treated so that she loses an average of 3 liters of fluid a day for 3 days. This is another critical time for the mother, especially the last several hours leading up to a full 72 hours elapsed following delivery. The normal redistribution of fluid within the mother that occurs at this time must be very tightly monitored.

The mother can usually be discharged on a low-dose diuretic 7 days after delivery and should be completely stable within 6-8 weeks. Dr. Zwicke has follow-up data on her 40 patients for a minimum of 2-3 months following delivery and during that period there were no complications. ■

Drugs, Pregnancy, and Lactation

Cigarette Smoking Cessation

The rate of cigarette smoking during pregnancy has declined to about 11%, but the prevalence is higher in younger (under 20 years) and older (over 35 years) women.

Smoking is a significant cause of embryonic, fetal, neonatal, infantile, and adolescent toxicity that includes growth restriction, a small increased risk for some birth defects, functional-neurobehavioral deficits, and death. In the 8th edition of "Drugs in Pregnancy and Lactation," smoking is cited as a major cause of premature birth, placental abruption, placenta previa, and premature rupture of the membranes (Philadelphia: Lippincott Williams & Wilkins, 2008). Because of the dose-effect relationship between smoking and these toxicities, pregnant women should try to stop, or at least reduce, smoking.

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The primary intervention strategy is nonpharmacologic: counseling, acupuncture, and hypnotherapy. A 2005 American College of Obstetricians and Gynecologists Committee Opinion detailed an intervention known as the 5 A's: Ask, Advise, Assess, Assist, and Arrange (Obstet. Gynecol. 2005;106:883-8), which also provided resources for smoking cessation. The few studies conducted with acupuncture and hypnotherapy have not clearly shown these therapies to be more effective than placebo; larger and better-designed studies are warranted (Clin. Obstet. Gynecol. 2008;51:419-35).

Pharmacologic therapy may be required if counseling is not successful. Such interventions include varenicline (Chantix); nicotine replacement therapy (NRT) with patches, gum, lozenges, inhalers, and nasal sprays); antidepressants, such as bupropion (Zyban, Wellbutrin); and nonspecific therapies.

The Food and Drug Administration approved varenicline for smoking cessation in 2006. Its mechanism is unique in that it prevents nicotine from binding to nicotinic acetylcholine receptors. Reproduction studies in animals are reassuring, but there are no human pregnancy data. Nevertheless, if a woman requires this therapy, the risk-to-benefit ratio appears to favor use of the drug.

The use of NRT in pregnancy is controversial. Nicotine is the primary chemical derived from smoking and it is a toxin, and since smoking is known to increase the risk of developmental toxicity, the same could occur with NRT. Although nicotine patches produce nicotine serum levels that are similar to smoking, they prevent exposure to other toxins, such as carbon monoxide, cyanide, dioxin, cadmium, thiosulfate, and the more than 3,000 other compounds identified in cigarette smoke. Removing the patch at night before going to sleep will reduce nicotine serum levels for part of the day. Nicotine gum, lozenges, inhaler, and nasal spray produce lower maternal nicotine serum levels but they may cause adverse effects such as poor taste and throat and nasal irritation and reduce compliance.

One study found a nonsignificant increase overall in birth defects in babies of women using NRT (Obstet. Gynecol. 2006;107:51-7). But there were significant increases in cleft lip and defects of the digestive tract and cardiovascular system. The data suggested an increased risk of defects but the authors could not prove or exclude causality.

Bupropion is approved by the FDA for smoking cessation and seems to be effective in reducing withdrawal, weight gain, and cravings. Adverse effects, such as insomnia, dry mouth, and an increased risk of seizures, can be problems, but the drug is more effective than NRT and does not expose the mother or the embryo-fetus to nicotine. The bupropion birth defect registry (now closed) collected data from 1997 to late 2007. It reviewed 1,005 prospective pregnancy outcomes and was able to exclude a major teratogenic effect. However, it was not designed to exclude an increase in the risk of specific defects.

Nonspecific therapies include the antihypertensive/central analgesic clonidine, narcotic antagonists naloxone and naltrexone, and melatonin. They've not been effective against smoking. Melatonin has not been studied in pregnancy or lactation and should be avoided.

Smoking decreases the duration of breastfeeding and exposes the nursing infant to nicotine and other toxins. If a mother can't stop smoking, she should at least not smoke around the infant or while nursing. The risks of using NRT during lactation are unclear because they have not been defined. Varenicline is probably excreted into milk and could cause adverse effects in the infant. Bupropion is excreted into milk and, in the case of one infant exposed via breast milk, no adverse effects were observed.

Counseling is the preferred treatment for smoking cessation. Bupropion would be my first choice for pharmacologic therapy, followed by varenicline, then NRT (avoid NRT in the first trimester.

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