

MASTER CLASS

Diabetes-Related Birth Defects Are Preventable

Dr. E. Albert Reece, medical editor of Master Class, normally introduces our guest professor. This month, however, we are pleased to introduce Dr. Reece as our Master Class guest professor on diabetes-related birth defects.

Dr. Reece, who specializes in maternal-fetal medicine, is the vice chancellor and dean of the college of medicine at the University of Arkansas in Little Rock. He has studied various aspects of diabetes-related birth defects from causation to treatment strategies aimed at achieving euglycemia during early pregnancy and—better yet—before pregnancy.

This month, he will address the toll that poorly controlled maternal diabetes takes on the developing fetus and the responsibility of ob.gyns. to address the problem. He will tell us how ob.gyns. can reduce the rates of diabetes-related birth defects and, in the process, help to improve our infant mortality rate.

The World Health Organization judges the health of a country largely by its infant mortality rate. On this measure, the United States ranks 21st in the world. If we intend to improve the health of the nation, we must aggressively focus on reducing the two most significant contributors to infant mortality: prematurity and birth defects.

One of our efforts should focus on the fact that diabetes-related birth defects occur at a rate of 6%-10% among infants of diabetic mothers—a rate that is two to five times higher than the background rate of the general population.

These birth defects are often multiple and involve multiple organ systems, but

the anomalies that usually are the most serious, disabling, and that may even be associated with death, include those affecting the central nervous system (neural tube defects or spina bifida of various types) and the cardiovascular system.

Hyperglycemia: A Teratogen

The causation of these anomalies has been studied in my laboratory and by many other groups around the world. It is clear, based on scientific findings, that hyperglycemia is a teratogen and causes direct injury to early embryonic tissue in the same way that any other teratogen, such as thalidomide or radiation, inflicts injury on a developing tissue.

The injurious effect of hyperglycemia is mediated by the induction or the production of free radicals and—simultaneously—by reductions in the body's natural glutathione antioxidant defense capacity. This results in excess free radicals which relentlessly target various tissues in the midst of early organogenesis. (See chart.)

With this knowledge of the biology of birth defect causation, we now know that by avoiding hyperglycemia during early pregnancy (the first 8 weeks), we can reduce the incidence of birth defects among diabetic offspring to mirror the incidence found within the nondiabetic population. This has been shown in clinical trials throughout the world.

Preconception Programs and Therapies

It has also been shown that patients who enter controlled, preconception counseling programs, who achieve euglycemia prior to pregnancy, and who maintain that euglycemia through the first trimester will

benefit from an outcome rate similar to that of the nondiabetic population.

In some countries outside the United States, information on the avoidance of hyperglycemia during early fetal development appears to be better known or better incorporated into practice habits than it is here at home. Moreover, in certain countries in Europe, 50%-75% of diabetic women enter preconception programs prior to pregnancy, whereas only 10%-30% of women in the United States do so.

Admittedly, euglycemia is both difficult to achieve and difficult to maintain. We must not shy away from the responsibility, however. Although it is not a simple exercise, we must at least get to the first step of increasing the numbers of preconception programs and elevating their stature. In addition, we must encourage diabetic women to enter and follow through with these programs, so that efforts can be made to achieve euglycemia before early pregnancy.

We also must lower our threshold for diabetes screening among obese and overweight women who may be contemplating pregnancy. With the rise in obesity throughout North America, there has been a concomitant rise in the incidence of type 2 and gestational diabetes. Obese or overweight women may have undiagnosed diabetes that, if left unchecked and untreated, may well harm their infants.

Preconception programs will vary by institution and community. The programs should provide screening for a variety of possible medical disorders—such as thyroid, hematologic, and metabolic disorders—and should treat diagnosed conditions and achieve stability prior to pregnancy. Euglycemia should be achieved through a com-

bination of diet therapy, which typically is 35 calories per ideal of body weight, and the use of insulin therapy and/or oral hypoglycemic agents, such as glyburide.

Although patients in these programs will be nonpregnant, it nevertheless is preferable to use human insulin. Short-acting and intermediate-acting insulins should be used in combination, and in the mornings and afternoons as necessary and appropriate; these parameters should be adjusted accordingly to achieve euglycemia. Additional strategies may include the newer insulin analogues—lispro or aspart, in particular—as a substitute for regular insulin. Other insulin analogues are not well studied and should not be routinely used in pregnancy.

The Power of Supplements

Based on our laboratory work demonstrating that hyperglycemia depletes inherent and natural antioxidant defense mechanisms, we have also demonstrated that by supplementing diets with antioxidants and polyunsaturated fatty acids, we can reduce the incidence of birth defects in animals.

More recently, studies from the Centers for Disease Control and Prevention have confirmed our own laboratory's work showing that diabetic women taking multivitamins with folic acid are able to lower birth defect rates accordingly.

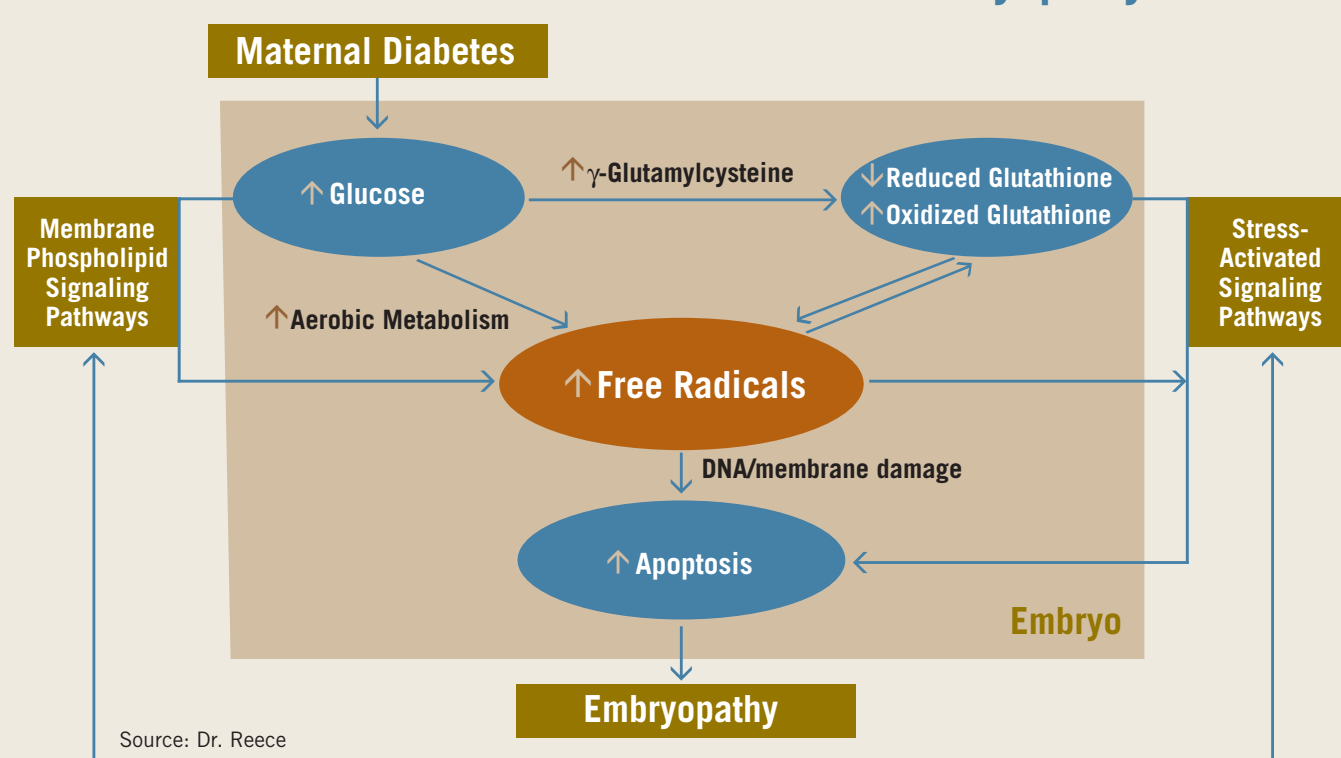
Although the specific amounts, the specific quantity, and the specific types of antioxidants and other substances are not known at this time—and although there is not a defined correlation regarding intake of multivitamins and specific outcome variables—we do know with certainty that the usage of multivitamins containing folic acid has been shown clinically to improve outcomes.

Given the public health problems of diabetes and obesity, obstetricians and primary care providers must encourage—and require to the extent possible—all diabetic patients to enter preconception care when they are contemplating pregnancies, and to undergo multivitamin therapy containing folic acid. It is, simply, a responsibility we hold. With such efforts, we can have a tremendous effect on pregnancy outcome and the reduction of birth defects. ■



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How Maternal Diabetes Results in Embryopathy



Diabetic Embryopathy

- ▶ The overall incidence of diabetic embryopathy is 6%-10%, which is five times higher than in nondiabetics.
- ▶ Diabetic embryopathy accounts for about 40% of deaths of infants of diabetic mothers.
- ▶ CNS and cardiovascular malformations are the most common and most serious effects.
- ▶ Neural tube defects are present in infants of diabetic mothers at a rate of 10-20 per 1,000 live births vs. 1-2 per 1,000 live births in the general population.

Source: Dr. Reece