In Brief

This article evaluates the clinical relevance of ultrasonography during pregnancy complicated by diabetes for fetal surveillance, assessment of diabetes impact, guidance of diabetes treatment, and obstetric management. Although ultrasound has improved, its effect on reduction of perinatal morbidity and mortality remains to be proven, and its use to detect large-for-gestational-age fetuses is unreliable. Clinical decisions based on birth weight prediction by sonography are often in error. Measurement of the insulin-sensitive fetal fat layer and fetal abdominal circumference may better reflect the impact of diabetes on the fetus.

Ultrasound Surveillance in Pregnancy Complicated by Diabetes

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The number of large babies is growing, as is the number of obese children. The prevalence of type 2 diabetes is increasing, while the age of onset is decreasing. There is also an increased prevalence of gestational diabetes mellitus (GDM) among women without any history of diabetes. And these women are at increased risk for developing type 2 diabetes after childbirth. Diabetes has been implicated as a main contributor to morbidity and mortality and to rising health care costs, in large part because of the development of late complications of the disease.

Diabetes is a problem that spans the generations. There are genetic factors that pass from generation to generation, but there is also an environmental component—the metabolic environment that pregnant women create for their fetuses in utero—that also contributes to the development of subsequent diabetes in their children.

The Role of Obstetricians

Obstetricians are the gateway between two generations—mothers and infants. With their key position of access to this sensitive group, they have the first opportunity to detect and break the chain of "inheritance," the passing on of the potential to develop diabetes from one generation to another.

The diagnosis of diabetes can be challenging for obstetricians. Pregnancy weight gain is traditionally regarded as a healthy sign for both women and their developing fetuses, and in its initial stages, diabetes may be considered benign. The visible

signs of diabetes developing during pregnancy (i.e., maternal obesity, glucosuria, and fetal macrosomia) occur inconsistently and vary in onset. The obvious signs of the late complications of diabetes can appear after years of latency. Identifying the condition before it becomes a disease requires obstetricians to actively look for it and to make recommendations to pregnant women to change lifestyle behaviors to create a healthier environment for both mothers and fetuses. Pregnancy makes women's underlying diabetes status more visible and can be thought of as a preview of what may become a woman's "diabetes career." At the same time, pregnancy provides an opportunity to prevent the development of diabetes in apparently healthy women who would not otherwise seek health care or receive medical attention.

The Ecological System of the Maternal-Fetal Metabolic Unit
A pregnancy complicated by preexisting type 1 or type 2 diabetes or by GDM (diabetes with onset or first recognition during pregnancy) requires interdisciplinary care for women and their fetuses/infants by the endocrinologist, obstetrician, and finally pediatrician to avoid immediate and long-term harm to both women and children. Many studies have documented the relationship of maternal hyperglycemia on the degree of damage to women and their fetuses (i.e., maternal vessel disease, fetal malformation, obstetric and pediatric complications related to fetal macrosomia, and long-term health risks). The challenge of avoiding these complications lies in the unique ecology of the joint maternal-fetal metabolism, the maternal-fetal interchange circuit of the placenta.

The placenta is designed to share and capture resources on the fetal side. However, this allows free transfer of excessive maternal glucose to the fetus, with subsequent stimulation of the fetal pancreas. This triggers fetal hyperinsulinemia, which precipitates short-term complications (i.e., macrosomia and neonatal hypoglycemia) and long-term consequences (i.e., later development of diabetes in the child.)[1] Once fetal hyperinsulinemia has been induced, it is difficult to assess whether maternal glucose levels reflect the real situation, or whether the fetus is using the excess maternal glucose and artificially lowering maternal blood glucose readings.

Therefore, the goal of treatment is to achieve normoglycemia to reduce the risks of adverse outcomes.

Assessment of Fetal Metabolic Status
Amniocentesis provides direct information about fetal insulin levels because fetal urinary excretion of fetal insulin into the amniotic fluid reflects the degree of fetal hyperinsulinemia. However, amniocentesis is rarely performed and only used routinely to assess lung maturity of the fetus in cases where a preterm delivery is necessary because of increased maternal or fetal risk. Amniocentesis is an invasive approach reserved for experienced obstetricians to minimize the complications of infection, premature rupture of the membranes, or fetal injury. Therefore, fetal hyperinsulinemia is not possible to monitor in utero.

Ultrasonography is a noninvasive, readily available method to assess and monitor the fetus and is also a helpful guide for instituting early therapeutic management for pregnancies complicated by diabetes. Although ultrasonography is an obstetric tool that has been widely used to assess the fetus, the benefit of altering management of pregnant women with diabetes based on sonographic results has not been evaluated by large, randomized, controlled studies.

Sonographic Estimation of Fetal Development and Growth
Classically, ultrasonography has been used to support the clinical estimation of fetal size accomplished by palpation or fundal height measurement. Clinically estimated growth that does not correspond to the date of the pregnancy (after excluding date errors by using the first trimester sonogram for date corrections) can be either small for gestational age (SGA) or large for gestational age (LGA) and should raise concern and prompt a referral for sonography.

SGA Fetuses
In pregnancies complicated by diabetes, and particularly those involving vascular disease, impairment of placental perfusion will typically lead to asymmetric or disproportional growth retardation of the fetus such that the head will be normal-sized but the fetal body will be small. In this clinical setting, SGA fetuses are not uncommon.[2,3] Asymmetrical or disproportional growth retardation typically starts at the beginning of the third

trimester. The sonographic estimation of fetal size in this situation is superior to clinical estimation by palpation or fundal height measurement.[4] The tendency of women to develop hypertension during these pregnancies appears to be a result of the maternal response to improve placental perfusion.

An SGA fetus with symmetric growth delay, in which the head and body are equally small, raises the concern for genetic abnormalities or congenital malformations, as seen in pregnancy with severe preexistent diabetes. Severe compromise, such as impaired perfusion and/or poor placental development, leads to symmetrical or proportional growth delay that usually has an earlier onset and can be observed by the beginning of the second trimester. Amniocentesis for genetic typing should also be considered in these cases.

Biweekly sonographic and Doppler studies of the uterine and umbilical vessels should be used for follow-up of SGA fetuses. Doppler studies can assess any progressive loss of the diastolic component of the umbilical artery wave curve (discussed in more detail below), which demonstrates the progressive impairment of placental-fetal perfusion. Doppler also enables monitoring of changes when fetuses lose the ability to compensate for impaired placental blood supply. If Doppler results indicate that a fetus is beginning to decompensate by centralizing its circulation to supply only the vital organs (by enhancing its own diastolic flow to brain, kidney, and heart), delivery should be planned regardless of the fetal age.[2]

Conclusion. Ultrasonography is helpful for monitoring an SGA fetus with asymmetrical growth; however, when growth of an SGA fetus is symmetrical, Doppler studies of the uterine and umbilical vasculature must be done to assess and monitor potential impairment of placental blood supply.

LGA Fetuses
Sonographic estimation of LGA infants seems to be as predictive as clinical estimation.[5,6] The sensitivity of either method is low (45–65%) for screening purposes and depends on the specialization and experience of the physician.[5,7–9] In addition, the error of estimation increases with increased birth weight and the presence of maternal diabetes such that the weight of large infants will be either underestimated or overestimated as a result

of the increased fetal fat mass.[7,10–12] When compared with sonographic evaluation at the extremes of fetal weight (upper and lower 10th percentiles), physicians' clinical estimates of fetal weight are no more accurate than the mothers' estimates of fetal weight.[13]

To solve this dilemma, various factors have been considered, including which specific parameters to measure and which calculations to use.[8,14] The calculation of birth weight that includes the measurement of fetal abdominal circumference seems to have the best predictive value, particularly in LGA infants.[15–18] This parameter is found to be decreased in SGA or increased in LGA fetuses relative to the head of the fetus and reflects the nutritional state of the fetus.

Conclusion. Currently, the advantage of ultrasonography compared to clinical evaluation to estimate birth weight in LGA fetuses remains inconclusive.

Fetal Body Composition

Considering the uncertainties of weight prediction, it is reasonable to ask whether birth weight is the appropriate parameter to identify fetuses that are receiving an excessive supply of nutrients that will result in mechanical and metabolic problems at the time of birth. Because a large proportion of these affected newborns will have a normal weight (< 4,000 g or < 90th percentile), the focus has shifted to evaluating the fat layer, which is the insulin-sensitive tissue located in the subcutaneous layer of the skin in fetuses and infants.

In newborns, various studies have used anthropometric measurements obtained with the caliper meter to measure skinfold thickness in millimeters and correlate the results with birth weight and the presence of maternal diabetes.[19–21] However, a more precise method is to measure the electrical conductivity of the tissue to calculate the percentage of body fat.[22] Many studies have used these findings and applied them to measurements obtained during fetal sonography.[23–26] Results of these studies indicate that fetal fat, and in particular the truncal fat layer, has a stronger correlation with maternal glycemic control than does estimation of birth weight.[19]

Conclusion. Ultrasound-assessed increased fetal body fat, and particularly the truncal fat layer, is a sign of a hyperinsulinemic fetus.

Fetal Macrosomia, Obstetrical Management, and Birth Planning

Despite the inaccuracy and poor prediction of fetal weight and the lack of practical alternative parameters, obstetricians still feel compelled to use ultrasound to guide obstetrical management of pregnancies complicated by diabetes, and especially to plan the time and mode of delivery to avoid a potential adverse outcome for pregnant women and infants. Poor maternal glycemic control can result in maternal complications, such as high-degree perineal tears during delivery of a macrosomic infant and caesarean section resulting from failure of labor to progress. Fetal or neonatal complications can be significant and include sudden intrauterine death, shoulder dystocia resulting in brachial plexus injuries, intrauterine hypoxemia, and neonatal hypoglycemia.[2,27,28]

A fetus supplied with excessive nutrients can also develop asymmetrical growth. When body measurements of the fetus, especially the shoulders and the abdomen, exceed the head measurement, the risk of shoulder dystocia increases not only in LGA fetuses but also in normal-weight fetuses.[29] Shoulder dystocia can occur not only during a vaginal delivery with cephalic presentation but also during caesarean section.[28] Therefore, it is understandable that even though the recommendations for caesarean section are based on weight prediction and have resulted in a higher caesarean section rate, they have not been found to reduce the incidence of shoulder dystocia or brachial plexus injuries.[29]

Conclusion. Given the potential for catastrophic events, such as sudden intrauterine death and brachial plexus injury, and the lack of adequate methods for detecting fetuses at risk in pregnant women with diabetes, many obstetricians opt for recommended practices even if there is no evidence that the practice will reduce the likelihood of such events.

Doppler Sonography

Doppler sonography evaluates the blood flow to the uterus measured at the uterine arteries and between the placenta and the fetus measured at the umbilical artery and at different vessels within the fetus. Of particular interest is the analysis of the wave curve that in pregnancy is characterized by a large diastolic component primarily in the uterine vessels followed by the umbilical artery. This reflects maximal dilatation of the arteries and veins of the uterine side and the placental bed to ensure sufficient perfusion. In the smaller vessels within the fetus, a higher pressure is present. Hence, the diastolic flow is normally reduced.

The umbilical artery reflects the fetal-placental blood flow system, which in any case of compromised perfusion either on the placental or the fetal side would show a decrease in the diastolic component. The worst scenario is a diastolic zero flow, in which there is no deoxygenated blood moving from the fetus to the placenta for exchange or a reverse flow back to the fetus. The decrease in the diastolic component is usually expressed by an increased resistance index, pulsatility index, and systolic-diastolic ratio. The higher these values, the lower the diastolic component, and hence the greater the compromise to the fetal-placental perfusion system resulting in fetal growth retardation.

Disease conditions with impaired perfusion, such as pregnancy complicated by diabetes with vascular disease, hypertension, or preeclampsia, can result in SGA fetuses. Doppler is a good surveillance tool to judge and predict the turning point at which the decreased perfusion–adapted fetus decompensates and delivery is necessary.[2,30] In contrast, for LGA fetuses, with which the placenta is usually large as well, there is an increased blood flow present, and the wave curve is normal, such that the usual perfusion indexes fail to predict placental insufficiency.[31]

Doppler umbilical and uterine artery velocimetry have demonstrated statistically significant differences in third-trimester systolic-diastolic ratios, the number of stillbirths, and neonatal morbidity when well-controlled and poorly controlled pregnancies complicated by diabetes are compared.[32] The worst case scenario is an abrupt collapse of circulation resulting in sudden intrauterine death of the fetus. Unfortunately, there is no surveillance means that can predict such a situation.

Conclusion. Doppler studies are particularly good in the surveillance of SGA fetuses of any etiology but are of no benefit for observation of LGA fetuses.

Fetal Surveillance

Major malformations, intrauterine death, and perinatal mortality and

morbidity are of significant concern to obstetricians who care for women with pregnancies complicated by diabetes. In addition, perinatal losses are associated with poor maternal glycemic control. With an increased awareness of the adverse effect of suboptimal glycemic control and improved management and surveillance protocols, fetal losses resulting from maternal diabetes have decreased since 1990.[27]

The heterogeneity and variable severity of disease within the group of pregnant women with diabetes require different management and surveillance protocols. For instance, a pregnant woman with well-controlled diabetes and no signs of end-organ damage has approximately the same risk of having an adverse fetal outcome as that found in the general pregnant population.

Tests for fetal assessment include non-stress fetal heart rate monitoring, contraction stress testing, sonographic biophysical profile including amniotic fluid measurement, Doppler studies, and maternal assessment of fetal activity. Of these fetal assessment tests, the amniotic fluid measurement has the best predictive value regarding perinatal morbidity. A measured amniotic fluid < 2 cm is considered to be significantly reduced and should prompt delivery.

Because of the limitations in the predictive power of most of the fetal monitoring methods and the lack of randomized, controlled trials to support fetal monitoring methods, there is no agreement on the best way to monitor fetal health in diabetic pregnancies.[33] However, protocols for fetal antepartum monitoring can be reassuring that aggressive treatment with diet, insulin therapy, and exercise are successful in controlling maternal hyperglycemia. Therefore, most well-controlled pregnancies will be able to reach term, thus ensuring fetal maturation and the potential for normal delivery.[30]

Conclusion. During pregnancy complicated by diabetes, the results of fetal surveillance testing will correlate with the degree of maternal glycemic control.

Ultrasound-Guided Therapeutic Management of Maternal Glycemic Control

Review of the use of sonography to guide maternal glycemic control raises the question "What are normal blood glucose levels for nondiabetic pregnant women?"

Usually, normal control subjects are recruited among women who may have had risk factors for diabetes but had normal results when tested with either a glucose challenge screening test (50-g challenge) or a full glucose tolerance test (75-g challenge). According to American Diabetes Association criteria, normal results for the 50-g test are a 1-hour glucose value < 140 mg/dl. Normal results for the 75-g test are fasting 95 mg/dl, 1-hour 180 mg/dl, and 2-hour 155 mg/dl. Two values exceeding these glucose thresholds are considered positive for diabetes.

One study[34] eliminated diabetes risk factors, such as pregestational BMI > 25 kg/m^2, hypertension, and history of GDM, in a normal control group of 51 pregnant women with a negative screening test who monitored blood glucose concentration 15 times per day every 2 weeks from 28 to 38 weeks of gestation. The mean fasting glucose level was 56 mg/dl, and the peak postprandial glucose response occurred at 1 hour and never exceeded 105 mg/dl. In this group of women, mean hemoglobin A_{1c} (reflecting the previous 6 weeks of glucose metabolism) was 4.5% and equated to a mean blood glucose concentration of 90 mg/dl. These results suggest that the current thresholds for diagnostic testing and institution of therapy during pregnancy are set too high for the diagnosis and therapy of GDM. The diagnostic and treatment thresholds should be similar to levels in normal pregnancy to decrease the incidence of fetal macrosomia among women with diabetes.[32]

Glucose control and the therapeutic management of diabetes during pregnancy must be reconsidered. Fetal monitoring by ultrasonography should be included to identify signs of macrosomia, such as an increased abdominal circumference or truncal subcutaneous fat tissue > 5 mm wide. When apparent maternal glycemic control does not require insulin treatment, sonographic signs of fetal macrosomia will help to identify those women with GDM who require more aggressive early treatment for the prevention of macrosomia. Diabetic women whose fetuses do not show signs of macrosomia may require less aggressive treatment.[24,35–37]

Conclusion. From an obstetrician's point of view and in view of the difficulties in predicting LGA fetuses, if a large fetus or thick fat layer is present, it must be assumed that the pathologi-

cal mechanism of fetal hyperinsulinism has already taken place. The best prevention of LGA babies consists of timely identification and rigorous tight maternal metabolic control.

Recommendations

1. Maintaining glycemic levels as near as possible to the glucose levels achieved during normal pregnancy remains the goal for prevention of adverse pregnancy outcomes. Ultrasound is a useful surveillance tool during pregnancy complicated by diabetes.
2. The recommendation for the use of ultrasonography is no different for women with diabetes than the general recommendation for normal pregnancies.
3. Between 8 and 12 weeks' gestation, every pregnant woman should have an early sonogram for the correct estimation of gestational age.
4. At 20–24 weeks' gestation, every pregnant woman should have a sonogram for detailed fetal organ check.
5. From 28 weeks' gestation on, growth estimation should be conducted using biparietal diameter, abdominal circumference, and femur length parameters to detect SGA fetuses, particularly in pregnancies complicated by micro- or macrovascular disease resulting from diabetes, or to detect LGA fetuses in other groups of diabetic pregnant women. Abdominal circumference is the parameter best correlated with the nutritional state of the fetus.
6. If growth retardation is evident, Doppler studies should be conducted biweekly or more frequently if pathological wave curves are present. Doppler studies are not useful for LGA fetuses.
7. If an LGA fetus is suspected, soft tissue markers should be evaluated to detect the impact of fetal hyperinsulinism stimulated by excessive maternal hyperglycemia. Abdominal circumference is still the most sensitive parameter for excessive fetal growth. Additional measurements should include frontal truncal skin fat layer (best obtained by the abdominal circumference measurement), skin thickness above the scapula, and amniotic fluid index. An amniotic fluid measurement > 18 cm suggests hydramnios; < 6 cm may indicate inadequate placental supply.

Summary

Ultrasound surveillance can be a useful tool to supplement clinical evaluation of fetuses in pregnancies complicated by diabetes. Amniocentesis and Doppler studies may be required when ultrasonography identifies symmetrical or asymmetrical small growth of the fetus that is inconsistent with gestational age. Ultrasonography for the detection of LGA fetuses is not reliable for prediction of birth weight. Measurement of the fetal fat layer or fetal abdominal circumference correlates with development of fetal hyperinsulinemia and risk for macrosomia. Fetal ultrasonography may also be useful for determining early therapeutic intervention for control of maternal glycemia during mild GDM.

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