

American Diabetes Association 60th Scientific Sessions, 2000

Diabetes and pregnancy

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This is the first of seven reports on the American Diabetes Association (ADA) 60th Scientific Sessions held in San Antonio, TX, in June 2000. It covers topics related to diabetes and pregnancy.

Pregnancy, the Infant, and Dyslipidemia

Three symposia at the ADA meeting addressed questions related to gestational diabetes mellitus (GDM). At the first symposium, Lois Jovanovic, Santa Barbara, CA, discussed some of the alterations in metabolism seen during pregnancy. She noted the associations of obesity and ethnicity with diabetes, with Hispanic women of child-bearing age having a 5% prevalence of diabetes, exacerbated by the metabolic stresses of pregnancy. GDM, which may be defined as carbohydrate intolerance of variable severity first diagnosed during pregnancy, affects 135,000 women annually. In view of the risk of fetal malformation in women with unrecognized diabetes, which may be as high as 9%, early diagnosis is important.

During pregnancy, women with type 1 diabetes have an increase in insulin requirement from 0.7 to 1.0–1.5 U · kg⁻¹ · day⁻¹ from the first to the third trimester, which appears to be caused by human placental lactogen and progesterone of placental origin, as well as by increased maternal prolactin and cortisol secretion. Because maternal glucose crosses the placenta, the fetus responds to hyperglycemia, which causes macrosomia. Birth weights <3 or >4 kg are associated with adverse outcomes.

In a related study, Kirwan et al. (abstract 12) reported on an index of insulin sensitivity calculated as 10,000/square root of

(fasting glucose × fasting insulin) × (mean glucose × mean insulin during an oral glucose tolerance test [OGTT]) that was found to show excellent correlation with insulin sensitivity measured during a euglycemic-hyperinsulinemic clamp in nonpregnant individuals (1). This index correlated well with clamp insulin sensitivity before and during pregnancy in 15 women, suggesting a useful approach to this determination during pregnancy.

Bower et al. (abstract 1107) used nuclear magnetic resonance lipid subtype analysis to study women with GDM, finding patterns similar to those in type 2 diabetes: increased VLDL triglyceride and smaller HDL particle size than in women without diabetes. Dyslipidemia was less marked in African-American women. Kousta et al. (abstract 775) compared 420 women who had had GDM with 486 control subjects 2 years postpartum. Of the subjects, 28, 31, and 50% of European, South Asian, and Afro-Caribbean women had abnormal glucose tolerance, approximately half with diabetes. Obesity and insulin resistance were found in all groups, but dyslipidemia was less common among the Afro-Caribbean women.

Role of Diabetes Education

Carol J. Homko of Temple University discussed the role of the diabetes educator in the management of diabetes before, during, and after pregnancy. Many of these health care providers are “advanced practitioners” skilled in diabetes treatment but with limited prescription writing authority. Essential management principles in the preconception period include nutrition and exercise

counseling and insulin dose adjustment to achieve excellent glycemic control before pregnancy. Euglycemia is crucial during the first trimester, a period in which a decrease in insulin requirements is common. This decrease is worsened by the typical nausea and vomiting seen during this period, increasing the risk of starvation ketosis. Dietary counseling to adjust caloric intake and proportion of carbohydrate in the diet is critical. Insulin dose adjustment is also crucial.

Women are screened for GDM between 20 and 24 weeks of pregnancy, with levels >140 mg/dl 1 h after a 50-g load requiring a 3-h OGTT. In the postpartum period, insulin requirements decrease markedly, with little or no insulin required during the first 24 h. Homko suggested that glucose tolerance testing be performed several weeks postpartum in women with GDM to assess whether the diabetes has resolved, recognizing the 40–60% lifetime risk of development of diabetes in these women.

Labor and Delivery

Siri L. Kjos of the University of Southern California spoke about issues surrounding the timing of labor and method of delivery. Kjos suggested that an important factor in choosing vaginal or caesarian delivery is the mother's preference. Prior C-section, estimated fetal weight, maternal age, and other maternal medical conditions affect the decision. Most stillbirths in women with diabetes are caused by lethal congenital malformation, with obstetricians urgently initiating delivery upon any evidence of fetal distress.

Avoidance of macrosomia and consequent shoulder dystocia by glycemic control is another issue. One must bear in mind that the mother's prepregnancy weight and the degree of weight gain during pregnancy are strong risk factors for macrosomia, independent of glycemic control. Kjos pointed out that when GDM is not diagnosed, macrosomia rates increase, whereas when GDM is diagnosed and treated to achieve postprandial glucose levels <104 mg/dl, macrosomia rates are similar to those in nondiabetic populations (~10%). Thus, only 10–15% of infants of

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Abbreviations: IDM, infant of diabetic mother; IGT, impaired glucose tolerance; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

women with GDM would be expected to necessitate induction of labor for being large for gestational age. C-section rates are, however, similar among women with GDM with infants whose birth weight is either <4 or >4 kg.

Another consideration is whether the fetus has disproportionately great abdominal circumference, which might also increase the risk of difficulty with delivery. The risk of brachial plexus injury with shoulder dystocia is ~7% in infants whose birth weight exceeds 4 kg, but the risk is 14% for mothers with GDM, perhaps because these infants have greater degrees of abdominal obesity. An additional problem is that “we’re very poor at predicting which infants will be big.” Ultrasound identification of infants with birth weight >4 kg is often incorrect, although ultrasound is quite reliable for excluding large fetal size. Early third trimester ultrasound may be more accurate in identifying infants who will be large for gestational age.

A reasonable approach advocated by Kjos is to use this finding to begin maternal insulin treatment, which lowers fetal size, although more often it leads obstetricians to perform C-sections. She pointed out that vaginal delivery for women with GDM may be a complex undertaking, often requiring >24 h, with glucose testing and insulin dose adjustment every 2 h. Expectant management rather than induction of delivery often leads to C-section. Women who have diabetes predating pregnancy have C-section rates of 40–80%. “We probably do over-treat,” Kjos concluded, “but we all want a good outcome.”

In a related study, Jang et al. (abstract 1316) reported on serial ultrasound during weeks 30–40 of pregnancy in 20 women with GDM and 15 with normal glucose tolerance. The ultrasounds showed evidence of increased fetal triceps and thigh skinfold thickness in offspring whose birth weight was appropriate for gestational size, although to a lesser extent than in those large for gestational age. This suggests a role for ultrasound measurement of subcutaneous tissues in detection of fetuses at risk for increased adiposity.

Long-Term Outcome of GDM

Edmond A. Ryan of the University of Alberta, Edmonton, discussed the long-term outcome for women with GDM. The life expectancy of women in the U.S. is 79 years, and the average age of women with GDM is ~29 years, so these women have a 50-year

subsequent life expectancy. The risk of GDM during subsequent pregnancies is 30–70%, and the risk for type 2 diabetes ranges from ~5% during the subsequent 3–6 months to 47% at 5-year follow-up. Analysis of a number of reported studies suggests that at 15 years, ~40% of women previously diagnosed with GDM have diabetes.

Pregnancy is a state of insulin resistance, and this is worsened in women with GDM. Blood glucose levels tend to be lower during an OGTT in normal pregnancy because of increased insulin secretion, whereas there is evidence of decreased insulin secretion in women with GDM. In the postpartum state, both insulin resistance and a decrease in insulin secretion continue to be found, even without evidence of impaired glucose tolerance (IGT). Risk factors for subsequent development of diabetes are prepregnancy weight, insulin requirement during pregnancy, and glucose levels during OGTT. In some but not all studies, subsequent pregnancies have been shown to increase the risk of ultimately developing diabetes. The risk of diabetes increases two- to threefold with a 15-lb weight gain and sixfold with a 33-lb weight gain during adult life. Conversely, diet and exercise appear to decrease the risk of subsequent development of diabetes. It is likely that we can extrapolate these observations to women with GDM, although this has not yet been proven.

Targeted Screening for GDM

The complex topic of whether targeted or universal screening should be performed for GDM was debated at a second symposium. Anne Kenshole, Toronto, Canada, advocated targeted, or selective, screening. She noted that there is lack of consensus about the optimal means of diagnosing GDM and the glucose levels at which therapy is warranted. Crucial questions are whether screening decreases adverse events and whether it is cost-effective in terms of short-term outcomes for the infant as well as the mother.

The long-term health effect of controlling modest maternal hyperglycemia during pregnancy is unknown. Advocates of universal screening believe that the risks of GDM are substantial and can be reduced by intensive monitoring and treatment. Advocates of selective screening, however, believe that it is the risk factors for GDM that actually account for the morbidity attributed to GDM. Indeed, four meta-analyses carried out between 1989 and

1997 questioned whether universal screening is beneficial. Currently, the ADA recommends selective screening of pregnant women who are >25 years of age, are overweight, are members of an ethnic group with high GDM prevalence, have first-degree relatives with diabetes or have a personal history of GDM, or have a history of adverse obstetric outcome. Questions to be asked in assessing the validity of these guidelines are how many women will fill all these criteria, how many cases will be missed, and what will be the adverse effect of a missed case.

A number of studies in Australia and the U.S. show a doubling in GDM among at-risk ethnic groups. Similarly, family history of diabetes is found in 6–12% of women with GDM. Thus, the absence of family history and obesity in women of European descent does help to define a low-risk group. In the Nurses’ Health Study, assessment of 722 cases of GDM among 14,613 pregnancies between 1990 and 1994 showed that predictive factors were increasing age, BMI, weight gain, cigarette smoking, and non-European ethnicity (2). Women <30 years of age had 4.4% risk, whereas those >35 years of age had 6.5% risk. BMI <22 was associated with a 3.6% risk, whereas BMI >25 was associated with an 8.6% risk. Negative family history was associated with a 4.4% risk and positive family history with a 8.8% risk of GDM. As far as personal history of abnormal glycemia, in the U.S., a history of GDM gives a 50% risk of GDM in the next pregnancy. This risk is further increased by weight gain and family history. In Australia and Holland, the recurrence rates are similar at 30–35%.

History of poor obstetrical outcome has recently been added to the list of risk factors. Macrosomia is only questionably associated with GDM, and though it certainly can lead to adverse outcome, it is associated with multiple factors other than glycemia. The meta-analyses cited above showed that 80% of macrosomic infants are born to women with normal glucose tolerance, a figure that has been supported by subsequent studies. Maternal and paternal BMI, maternal height, race, age, parity, socioeconomic status, fetal sex, altitude above sea level (which shows an inverse association), and other factors are also determinants.

It should be noted that these “selective” guidelines only exclude 20% of women in Australia and 10% of women in the U.S. Approximately 3% of women with GDM would be missed. Because ~3% of the 4

million pregnancies per year in the U.S. are associated with GDM, 0.09% of the cases would be missed. Kenshole noted that screened women diagnosed as having GDM have an increased rate of C-section, and there is no evidence that adverse effects are seen in women whose diagnosis is missed. Looking at the potential for brachial plexus injury due to macrosomia, up to 50 C-sections are needed to prevent each brachial plexus injury and 500 C-sections to prevent each permanent injury, so there is very high cost to this treatment. Other adverse effects of screening include the high cost of glucose management and insulin treatment and the potential for psychological distress. Women who are found to have GDM have a greater degree of worry about their children's health and their own health and are more reluctant to conceive again.

Asked whether identification of women as being at risk for future diabetes is an additional benefit of screening, Kenshole replied that there is currently no evidence to this effect and that in some studies, women who are counseled after pregnancy about nutrition actually gain more weight than control subjects. She also noted that in well-run clinical laboratories, the coefficient of variation of glucose testing is 16%, a factor leading to difficulty in diagnosis. Studies in Canada have used more strict criteria for performing glucose tolerance tests and exclude up to 35% of women as being at low risk. Important ongoing studies will address the outcome of such approaches.

Universal Screening for GDM

Michael F. Greene, Boston, MA, took the opposing viewpoint that universal screening for GDM is warranted. He stated that "screening is already universal" if the use of risk factors is included as part of the screening process and that the question was rather whether to perform glucose tolerance screening. Cost-benefit analyses of universal rather than selective screening "are very difficult to unscramble" and depend on the makeup of sampled patients and the testing approach. Further, he suggested that the debate should not include "the medical-legal trump card" that failure to screen can place the obstetrician at risk of legal action when there is adverse pregnancy outcome. An important point that has been directed against universal screening is that it "leads to meddlesome interventions." Greene suggested one should address the question of how to care properly for patients with GDM rather than criticize those who make the diagnosis.

The risk criteria used by John O'Sullivan in his 1973 analysis of screening for GDM, which were based on birth weight >9 lb or having had adverse fetal outcomes, had a 44% prevalence in the studied population (3). Using positive family history, history of prior adverse pregnancy outcome, age >25 years, and positive family history as screening criteria, 77% of women would be screened and 97% of patients with GDM would be identified. Similarly, 78% of pregnant women are >25 years of age or obese or have a positive family history in a first- or second-degree relative, prior stillbirth, neonatal death, preterm delivery, or birth weight >9 lb; 56% of patients with GDM would have one of these risk factors, and 93% of patients with GDM would be detected.

Analysis of the Nurses' Health Study showed that maternal age, family history of a first-degree relative with GDM, and obesity were strong risk factors and that there were 2-, 1.6-, and 2.3-fold increases in risk among African-Americans, Hispanics, and Asians, respectively; Greene showed a similarly increased risk of GDM among Chinese patients despite low BMIs. A problem with using ethnicity as a risk factor is that it is often difficult for Americans to identify their ethnic group precisely. Further, a given ethnicity label (e.g., Hispanic) may actually indicate different populations in different geographic areas.

Studies from Toronto used a risk-scoring system based on age, BMI, and ethnicity. Patients with a low score comprised 35% of the group and had a <1% incidence of GDM. However, the probability of GDM depends on the a priori risk, and the time from the last meal to the start of the glucose challenge test affects the criteria that should be used for a positive test. In other populations, ~22% of young women were lean and could be excluded from screening, with tests identifying >90% of patients with GDM. Using these rules in other populations, only 10–11% of patients can be excluded to detect 96–97% of patients. This suggests that at-risk criteria "are so inclusive as to be trivial," whereas approaches that are less inclusive are so complex that they are impractical and let patients "fall between the cracks." Greene concluded that one should "simply screen everyone." Donald Coustan, Providence, RI, commented that unless one decides there is no benefit to GDM diagnosis, there may be some populations in which universal screening makes sense and other populations in which it does not and

that this may be the optimal way of deciding whether to do a selective or a universal screening program.

Fetal Outcomes

The third pregnancy-related symposium at the ADA meeting was titled "The Diabetic Intrauterine Environment: A Lifelong Legacy." William W. Hay, University of Colorado, discussed the effects of the diabetic intrauterine environment on growth and development, noting that "anything that could alter fetal growth" includes virtually all factors affecting the fetus. Infants of diabetic mothers (IDMs) may be unusually large (e.g., the infant of the suboptimally controlled mother with GDM) or small (e.g., the infant of the mother with longstanding diabetes). Hay pointed out that "the fetus is primarily a carbohydrate eater." Fat is stored, with human infants having among the highest percentage of body fat at birth of all mammals (~18%).

The regulation of fetal growth and metabolism by maternal and fetal insulin is complex. The insulin-deficient fetus has decreased growth, perhaps because of decreased glucose uptake. In sheep, glucose infusion into the fetus may modestly increase fetal fat. When insulin is also infused in variable amounts, maximal glucose uptake occurs at insulin and glucose levels approximately twice as high as normal, although it is not clear that this explains the large size of the classic IDM. In fact, high glucose oxidation rates could lead to fetal hypoxia, which would result in decreased fetal growth. It may be that pulsatile oversupply of glucose to the fetus leads to growth.

Factors other than glucose are also involved in the abnormalities of fetal growth. Maternal hyperinsulinemia may lower fetal as well as maternal levels of certain amino acids, particularly essential amino acids, potentially decreasing fetal growth. In contrast, fetal hyperinsulinemia may increase amino acid levels. This may be a mechanism of increased fetal growth and temporarily increased glucose transport, although glucose transport subsequently downregulates. Normal fetal metabolism involves active placental transport of amino acids into the fetal circulation, and the amino acid supply may be increased in the IDM. Amino acid infusion may have a chronic effect on fetal insulin secretion, although there is little acute effect.

An important question is whether the changes in fetal nutrition in the IDM lead to

“programming” of the fetus that persists after birth. In a relevant study reported at the ADA meeting, Boileau et al. (abstract 11) note that, paradoxically, the glycogen content is markedly increased in placenta of insulinopenic hyperglycemic streptozotocin-induced diabetic rats. They reported that placental glucose transport and glycogen synthesis are not stimulated by insulin, although both increase with exposure to higher glucose concentrations. The placenta does show insulin receptors, which undergo autophosphorylation upon insulin stimulation, leading to mitogen-activated protein kinase phosphorylation and increasing mitogenesis. This suggests that the placenta is a nonclassic insulin target. Under conditions of resistance to metabolic actions of insulin, hyperinsulinemia may therefore be anticipated to cause placental pathology, which may have bearing on the abnormalities of GDM.

Richard M. Cowett, Cleveland, OH, discussed the mixed-nutrient hypothesis, which posits that GDM involves lipids and amino acids as well as glucose. In relatively well-controlled GDM, there is not a direct correlation between mean glucose and birth weight, although with very poor control, the probability of macrosomia is increased. The birth weight ratio is also associated with plasma triglycerides during pregnancy, suggesting a mechanism of macrosomia as well as a role of this measurement in obstetric management.

Glucose homeostasis is in a transitional state in the neonatal period, adding to the complexity of neonatal management of the IDM. The risk of neonatal complications increases even when the mother's diabetes is well controlled. Treatment in the resuscitation room requires particularly knowledgeable care, watching for asphyxia, with a multiplicity of factors that can present as respiratory distress, including birth injury, congenital malformations, and hypoglycemia. Congenital malformations are mainly due to periconceptional hyperglycemia and include heart, neurological, and musculoskeletal diseases. Signs and symptoms of neonatal hypoglycemia may vary greatly, including an abnormal cry, tachypnea, and many other manifestations.

Rebecca A. Simmons spoke on long-term consequences of the diabetic intrauterine milieu on the offspring. “What we feed the IDM may have long-term implications,” she said, referring to a study of breast-feeding in Pima Indian women in which offspring of

women with normal glucose tolerance during pregnancy were followed (4). In each weight group of offspring, type 2 diabetes occurred less than half as frequently among those who were breast-fed as among those who were not breast-fed during infancy.

There are a number of developmental modulators of the differentiation of pancreatic ductal precursor cells into islet cells. After birth, there is a period of β -cell apoptosis followed by proliferation in rodents. β -Cell neogenesis occurs throughout life in this species, with control by a number of growth factors and transcription factors. Glucose and amino acids undoubtedly control these processes, although specific data is not available. In the IDM, β -cell hypertrophy causes hypoglycemia in the neonatal period. An animal model of neonatal growth retardation is associated with increased subsequent risks of insulin resistance, obesity, and development of hyperglycemia. Islets from these animals show increased insulin secretion and β -cell mass at 1 week, but a reduction in β -cell mass and in insulin secretion at 15 weeks, with corresponding changes in β -cell growth factors. Thus, Simmons suggested, “there are some aspects that we cannot modify [after birth] and we have to concentrate on modifying fetal development.” Fatty acids and reductive oxygen species can also affect these growth factors. Simons pointed out that breast milk fat was markedly increased in mothers who had had GDM, suggesting a relationship with different infant feeding patterns and subsequent diabetes development.

When maternal insulin is inadequate, multiple fuels are disturbed, with fetal insulin-sensitive sites such as adipose tissue particularly disturbed by consequent fetal hyperinsulinemia. Bernard L. Silverman of Northwestern University described results of long-term follow-up of the offspring of women with type 1 diabetes and gestational diabetes enrolled between 1978 and 1983. Measurements included HbA_{1c} , glucose, serial amniocentesis after week 30 for fetal insulin levels, and postpartum characterization of infant anthropometrics and metabolic levels as well as yearly glucose tolerance testing with insulin measurement at 0 and 2 h. Neonatal macrosomia was resolved by 1 year, with subsequent gradual development of increasing obesity, which was quite pronounced by adolescence and correlated with the mother's prepregnancy BMI. Similarly, hyperinsulinemia was seen in these children. Elevated amniotic fluid insulin was associated

with a 2.8-fold increase in risk of BMI >27 in adolescence. Similar data have been reported from studies of obesity in Pima Indian infants of mothers with GDM and pre-GDM.

In Silverman's study, although fasting glucose and insulin were similar among infants of mothers with GDM and control infants, 2-h glucose levels were higher than levels in the control population. Prepubertal children are highly insulin sensitive, but a physiological insulin resistance occurs during puberty. IGT was seen in 36% of the study group by 16 years of age, but in only 2.5% of the control population. Obesity and macrosomia did not fully account for the frequency of IGT. Increased amniotic fluid insulin was associated with a 4.8-fold greater risk of IGT. Systolic blood pressure was 118 mmHg in offspring of diabetic mothers but 110 mmHg in control subjects, which was not explained by the greater degree of obesity or by advanced pubertal stage. This correlated with free fatty acid levels during the second and third trimesters and with β -O-hydroxybutyrate levels during the third trimester. Thus, increased fetal insulin secretion may have the potential to cause diabetes.

Silverman noted the trend toward increased childhood obesity in the overall population, with a consequent increase in type 2 diabetes in adolescence. A first-degree relative has diabetes for 65% of these children, suggesting that individuals at increased risk can be identified. “The best way to break this cycle,” Silverman commented, “is to bring maternal fuels as close to normal as possible.”

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