Diabetes Issues in Women and Children

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At the American Diabetes Postgraduate Course in New York, NY, on 12 January 2003, a number of important topics relating women’s health and diabetes were reviewed.

Polycystic ovary syndrome
Andrea Dunaif, Chicago, IL, discussed the polycystic ovary syndrome (PCOS), pointing out its frequency in the population and association with type 2 diabetes. PCOS is associated with a 40% decrease in insulin sensitivity (1) and with evidence of relative β-cell dysfunction (2). PCOS is a major risk factor for type 2 diabetes in adolescents (3) and in premenopausal women (4), with ~40% of individuals with PCOS developing impaired glucose tolerance (IGT) or type 2 diabetes, a rate similar to that seen among Pima Indians. Among women with oligomenorrhea (menses ≤6/year), 77% have PCOS and 33% (vs. 7.7% of control subjects) have glucose intolerance. Using menstrual cycle length ≥40 days as a proxy marker, the Nurses Health Study data showed a 2.18-fold increase in risk of diabetes among women with long cycles (5). The same dataset showed a menstrual cycle ≥40 days to be associated with a 1.53-fold increase in coronary heart disease (CHD) risk (6). Thus, the disease “has substantial health consequences” and represents an important target population for diabetes prevention. Dunaif humorously suggested that as PCOS represents an expression of the metabolic syndrome in women, it should be called “Syndrome XX.”

The mechanisms of insulin resistance may include specific genetic abnormalities. Postbinding abnormality in insulin signaling can be shown, with abnormal autophosphorylation of the insulin receptor and of insulin receptor substrate (IRS)-1. Tyrosine phosphorylation is decreased and serine phosphorylation increased at both of these receptors, leading to a decrease in the metabolic actions of insulin. Dunaif noted that cytochrome P450c17 is involved in ovarian androgen synthesis and activated by a serine kinase that may play a role in the abnormal insulin receptor and IRS-1 phosphorylation.

There is complex interplay of the gonadal steroid abnormalities of PCOS and insulin resistance, with partial suppression of androgen levels improving the insulin resistance (7), while thiazolidinedione (TZD) treatment decreases both androgen and insulin levels (8). With troglitazone, luteinizing hormone levels decrease, hirsutism can be demonstrated, and resumption of ovulation occurs in 60% of women. Other approaches to improving insulin sensitivity, such as weight reduction and metformin, have also been shown to decrease androgen levels and to restore ovulation. Dazoxide lowers insulin levels and decreases androgens while not improving insulin sensitivity or restoring ovulatory function, while central nervous system–specific insulin resistance can cause PCOS-like findings in animal models (9), suggesting this as a potential mechanism of the syndrome.

PCOS, like type 2 diabetes, has increased prevalence in families. Affected sisters show similar degrees of elevation of total and free testosterone levels (10). Among affected families, a bimodal distribution of testosterone and dehydroepiandrosterone (DHEA) concentrations can be shown, suggesting a genetic trait. Body weight is greater among PCOS sisters, and insulin levels are similarly elevated (11). Among brothers, DHEA levels are increased and there appears to be reduced insulin sensitivity and increased risk of diabetes, further suggesting a genetic component. Transmission disequilibrium testing and affected sibling pair analysis suggest an abnormal gene coding for a regulatory factor in the region of the insulin receptor (12). Individuals with this marker have evidence of insulin resistance, hypertension, and hyperglycemia. Among males, higher proinsulin and triglyceride levels are seen.

Osteoporosis in postmenopausal women with type 2 diabetes
Michael Kleerekoper, Detroit, MI, discussed osteoporosis in postmenopausal women with type 2 diabetes, asking whether it is the same disease as in non-diabetic postmenopausal women. Osteoporosis, he pointed out, is a systemic disease characterized by low bone mass and microarchitectural deterioration of the skeleton, leading to increased risk of fracture. At the population level, bone mineral density (BMD) predicts risk of fracture approximately three times more accurately than cholesterol does myocardial infarction. Although women with type 2 diabetes have a higher BMD, they have a higher incidence of fragility fracture than women matched for age and size (13). In a prospective study of 8,997 non-diabetic and 551 diabetic women not receiving insulin and 106 insulin-treated diabetic women >age 70, with mean diabetes duration 8 and 14 years in the latter groups, femoral and radius BMD were higher in both diabetic groups. Rates were 1.5- and 1.2-fold higher for hip and wrist fractures, respectively, in the diabetic compared with nondiabetic group, although only foot and ankle fractures, which are not usually considered osteoporosis related, occurred significantly more commonly. Plausible explanations for fracture at higher BMD in diabetes, a phenomenon also observed among individuals treated with steroids, include impaired vision and peripheral neuropathy leading to greater risk of falling. There is also evidence of a greater rate of bone loss among the diabetic women. Kleerekoper suggested that “For the diabetic who has had a fracture, ignore the bone density.

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That patient needs to be treated as though she has osteoporosis."

Determinants of fracture risk not described by BMD include bone microarchitecture and bone quality, and although there is no evidence of association of diabetes with osteomalacia, there may be abnormal bone turnover or remodeling. Type 1 collagen is the major protein of bone, with pyridinium cross-links between the COOH-terminal telopeptide and helical portion of individual molecules. Markers of these proteins can be measured, without consistent abnormality shown in diabetes. Osteocytes, as well as osteoclasts and osteoblasts, play a role in bone nutrition and in producing signals that initiate remodeling. Osteocytes and adipocytes derive from common mesenchymal bone marrow cells, with differentiation regulated by common factors, including insulin, growth hormone, IGF-1, transforming growth factor, and peroxisome proliferator-activated receptor-γ, the latter presumably explaining the effect of troglitazone on osteocytes (14).

Diabetes during pregnancy
Donald R. Coustan, Providence, RI, discussed the management of diabetes during pregnancy. Mortality rates during pregnancy for women with diabetes were 45% in 1909, 3% in 1933, 7% in 1939, and virtually nil in 1953. Perinatal mortality rates were 49% in 1909, 41% in 1933, 38% in 1939, and 26% in 1953, with current rates linearly related to mean maternal blood glucose (4, 15, and 24%) for mean glucose during the last trimester <100, between 100 and 150, and >150 mg/dL (15). The concept was advanced in the 1970s that maternal hyperglycemia causes fetal hyperglycemia, causing fetal hyperinsulinemia, which leads to diabetic retinopathy. (16). The mean glucose of normal women during the third trimester is 76 mg/dL, with maximal level <120 mg/dL 1 h after breakfast (17). The glycemic goals that have been suggested are fasting, 1-h, and 2-h glucose <100, 130–140, and 120 mg/dL, respectively. Comparing pre- and postprandial glucose monitoring, the Diabetes in Early Pregnancy study of pregnant women with type 1 diabetes suggested that 1-h postprandial levels better predict adverse fetal outcome than preprandial levels. (18). In a comparison of 33 women randomized to preprandial with 33 to 1-h postprandial monitoring, with respective goals of 60–105 and <140 mg/dL, the latter group had a greater fall in glycohemoglobin, with 12 vs. 42% large-for-gestational-age babies, 12 vs. 36% cesarean sections for cephalopelvic disproportion, and 3 vs. 21% neonatal hypoglycemia (19).

There are no data available for safety of the insulin analogs aspart and glargine. Lispro does not appear in cord blood (20), and although cases of worsening retinopathy were reported on initial use, this has not been substantiated. Oral hypoglycemic agents are now being reaccessed. There had been concern that sulfonylureas might stimulate fetal insulin production, which could worsen diabetic retinopathy, but glyburide crosses the placenta poorly, and argument has been made for its use. In a study of 404 women with gestational diabetes whose fasting glucose was between 95 and 140 mg/dL or 2-h postprandial glucose >120 mg/dL, similar glucose control was reported with insulin versus glyburide, although 4% of those treated with glyburide required insulin (21). Cesarean section, macrosomia, and neonatal hypoglycemia occurred at similar rates, and no glyburide was detected in neonatal cord blood despite measurable levels in maternal blood. The safety of glyburide in early pregnancy is unknown. Acarbose was shown in one study to decrease postprandial glucose in pregnant women. Metformin crosses the placenta, and although animal studies show no fetal risk, Coustan stated, “My tendency is to stop it as soon as I know the person is pregnant.” There are no data regarding TZD use in pregnancy.

Diabetic retinopathy may worsen with short-term good control and progress rapidly in pregnancy, with a study of 133 pregnant and 241 nonpregnant women suggesting that pregnancy and HbA1c independently predict retinopathy progression (22). In the Diabetes in Early Pregnancy study of 155 pregnant women with type 1 diabetes, 10% of those without retinopathy progressed, while worsening occurred in 55% of those with moderate-to-severe retinopathy, and the risk was proportional to both the baseline level of and the change in glycosylated hemoglobin. Brittle diabetes poses a dilemma for women who attempt to achieve excellent control, but there is some evidence that glycemic excursions tend to decrease during pregnancy, suggesting this to be less of a problem than had been thought.

Cesarean section is often performed in children with high estimated fetal weight to prevent shoulder dystocia. Calculation suggests that, using estimated fetal weight >4.5 kg as a cutoff, 3,695 nondiabetic women and 443 diabetic women would need the procedure at respective costs of $8.7 and $0.9 million to prevent one permanent brachial plexus injury (23). Congenital anomalies, including caudal regression, neural tube defects, and heart and renal anomalies, affect 7–10% of infants of diabetic mothers. All have occurred by 6 weeks after conception, so that preconception glycemic control is required. Of women whose HbA1c was <8.6% during the first trimester, 3% had congenital anomalies, while these occurred in 22% of women with higher HbA1c levels (24). Early versus late entry in a tight control study led to anomalies in 4.9 vs. 9% of women, while anomalies were seen in 2% of children of normal control subjects (25). Another study comparing women who attempted good control beginning before versus after conception showed 1.2 vs. 10.9% anomaly rates (26). Thus, good control before conception is crucial, with Coustan stressing the need for “adequate, effective contraception . . . because every conception should be planned in the diabetic woman.”

Hormone replacement therapy in women with diabetes
Elizabeth Barrett-Connor, La Jolla, CA, discussed the role of hormone replacement therapy (HRT) in women with diabetes. Observational studies suggest that women with diabetes are much less often prescribed HRT but that women with diabetes receiving HRT have better glucose control. They also suggest that women without HRT are protected from incident diabetes. With acute administration, HRT appears to improve glycemia and insulin sensitivity among women with diabetes (27). In general, clinical trials of HRT for women with diabetes have been small and of <6 months duration, limiting their applicability. 17-β estradiol (1 mg daily) decreased insulin levels in one study (28), and another trial of 199 women without diabetes showed that HRT decreased fasting insulin and HbA1c in women without diabetes. Trials of conjugated equine estrogen (CEE) (0.3–0.625 mg daily), involving 1,274 total women, showed no evidence of benefit (29). Part of the diffi-
Determinants of type 2 diabetes in utero

The annual Harold Rifkin memorial meeting of the American Diabetes Association was held 13 April 2003 in New York, NY. The topic was pediatric diabetes. Rebecca A. Simmons, Philadelphia, PA, discussed the aberrant intrauterine milieu as a risk factor for the development of type 2 diabetes in offspring. Potential relevant factors may include both a decrease in nutrient availability, causing growth retardation, and nutrient excess leading to overweight and diabetes. Risk factors for type 2 diabetes in childhood include genetic, dietary, and endocrine factors.

Uteroplacental insufficiency and malnutrition decrease the availability of nutrients and growth factors, leading to fetal growth retardation. The Dutch famine (between Oct 1944 and May 1945, a time when the country was under German occupation) led to an average daily calorie ration of 580–1,200 kcal/day. Individuals who were born after maternal famine showed fetal growth retardation, and those exposed to the famine who had low birth weight had increased diabetes risk during adult life. Adult obesity rates were highest for those exposed to starvation in utero during the first two trimesters and lowest for individuals exposed during the third trimester and first months of infancy (32). Both low birth weight and overweight at age 8 years are associated with greater degrees of insulin resistance (33).

In the Nurses’ Health Study, birth weight <5 lb was associated with almost a doubling of risk of diabetes, while high birth weight, controlling for maternal gestational diabetes, did not lead to an increase in risk (34). However, other studies have shown that both low and high birth weight are associated with development of type 2 diabetes, including a report of Pima Indians (35) and a study based on mass screening from 1992 to 1997 of children in Taiwan in which urine screening identified 495 children with diabetes, with birth weight <2.5 kg associated with 2.5-fold increase, while birth weight >4 kg was associated with a 1.6-fold increase in risk adjusted for age, sex, BMI, family history of diabetes, social class, and maternal gestational diabetes. Although obesity was more common among children with high birth weight, only 38% of those with low birth weight who developed diabetes were obese (36). In the Health Professionals Study, low birth weight was associated with increased diabetes risk, although not as convincingly as that seen for high birth weight (37). A number of studies have shown that those individuals whose mothers have type 2 diabetes have a higher risk than those whose fathers have diabetes. Among Pimas, the subsequent incidence of type 2 diabetes in offspring is higher among those whose mother had gestational diabetes during their pregnancy than among those whose mother subsequently developed diabetes (38).

Similarly, offspring of women with glucose intolerance diagnosed during pregnancy have a 25% prevalence of IGT at age 10–16 years (39).

Therefore, there is substantial evidence that the intrauterine environment plays a role in development of diabetes during either childhood or later in life. Simmons hypothesized that the intrauterine environment influences development of the fetus by modifying expression of pluripotent cells. Potential mechanisms include maternal nutrient deprivation, maternal steroids, and abnormalities of uterine circulation (40). In studies of nutrient deprivation, rats fed 5–8% protein during the latter third of gestation and during lactation develop glucose intolerance with decreased β-cell proliferation, islet size and vascularity, and insulin response to glucose. Prenatal glucocorticoid administration causes a 10% decrease in birth weight, glucose intolerance, and insulin resistance. Uterine artery ligation at the end of pregnancy retards somatic growth, but at 9–11 weeks, these rats show increased growth rate and by 19 weeks they have increased weight. Between 7 and 12 weeks they show increased insulin and triglyceride levels with increasing insulin resistance and glucose intolerance, and at 26 weeks diabetes is seen. β-Cell proliferation and total β-cell mass decrease over time, as opposed to the increase in normal rats.

β-Cell mass depends on the balance between neogenesis and proliferation versus apoptosis, with evidence that the former decrease and the latter increases in this model. Nestin, a marker of β-cell precursors, decreases at 1 week in the islet of the rat with intrauterine growth retardation. Pancreatic pluripotent stem cells produce pancreatic duodenum homeobox protein-1 (Pdx-1), a transcription factor involved in the regulation of the expression of multiple genes essential for the proper functioning of β-cells, with Pdx-1 mRNA levels showing progressive decrease from week 1 through 15. β-Cell apoptosis is not seen until ~15 weeks, when hyperglycemia is manifest. Mitochondrial function is important for insulin secretion and may be involved in these abnormalities, with electron microscopy showing disruption in mitochondrial architecture and evidence of decreased islet ATP production and multiple abnormalities in the Krebs cycle and electron transport chain at 5 weeks. This may lead to production of reactive oxygen species that may further impair insulin secretion and cell proliferation. Using the animals who had retarded growth at birth as a model of gestational diabetes, their offspring show increased fetal size, increased weight
Perspectives on the News

Type 2 diabetes in youth
Silva Arslanian, Pittsburgh, PA, discussed type 2 diabetes in youth, a problem now reported in many areas around the world: Japan, China, Libya, Bangladesh, Australia, and Europe, as well as in the U.S. The majority of studies in this field have been published within the past decade, with particular importance placed on minority populations; onset during mid-puberty, with most series reporting an excess among females; and common findings of obesity, acanthosis nigricans, positive family history, and ketoacidosis (although with lower degree of acidosis than in type 1 diabetes) often present at presentation or during intercurrent illness. It is often difficult, then, to distinguish type 2 diabetes among children from type 1 diabetes. The pathophysiology involves both insulin resistance and insulin deficiency (41). There is a continuum of decrease in insulin sensitivity with increasing body weight, particularly with central obesity (42). Evidence of retinopathy at diagnosis was reported in 33.6% of young individuals with type 2 diabetes in Japanese studies and microalbuminuria in 22% of Pima Indians. Arslanian reviewed the diagnostic approach proposed in a recent American Diabetes Association position statement for distinguishing type 1 from type 2 diabetes in young individuals, suggesting measurement of fasting C-peptide or insulin if the child is obese and autoantibodies for nonobese children as the initial approach (43). In Pima Indians and other populations, there appears to have been a progressive increase in type 2 diabetes among children over the past decade.

Type 2 diabetes is more common among African-American children, which has led to an increase in overall diabetes prevalence in this group (44). Comparing African-American and Caucasian children, the former show a greater degree of hyperinsulinemia correcting for BMI (45), with both first- and second-phase insulin response to hyperglycemic clamp increased (46) and insulin sensitivity decreased (47). The mid-pubertal onset of type 2 diabetes coincides with a period of decreased insulin sensitivity by ~30%, with evidence of compensatory increase in insulin secretion, perhaps caused by increased growth hormone levels (48). The increased prevalence among females may be related to PCOS, which is associated with IGT and diabetes (4). Comparing adolescent girls with similar degree of obesity, those with PCOS have decreased insulin sensitivity (49). Similarly, adolescents with a positive family history of type 2 diabetes have decreased insulin sensitivity (50), as do those with acanthosis (51).

Treatment of type 2 diabetes in adolescents includes family-centered lifestyle change in diet and activity, with insulin sensitizier administration being pathophysiologically reasonable; metformin is currently approved for this purpose (52), and TZDs are being studied. Management of ketoadidosis, establishment of glycemic goals, and treatment of hypertension and hyperlipidemia are additional important considerations. Noting the very high frequency of IGT and appreciable frequency of type 2 diabetes among obese adolescents (53), Arslanian pointed out that children who are overweight with any two risk factors, such as a family history of type 2 diabetes, high-risk ethnic group, hypertension, PCOS, or acanthosis, should be screened with fasting glucose measurement beginning at age 10 years or at the onset of puberty and repeating every 2 years. Whether glucose tolerance testing should be performed is not known.

Prevention of type 1 diabetes
Jay S. Skyler, Miami, FL, discussed the status of efforts to prevent type 1 diabetes in susceptible individuals. Elliot Joslin in 1916 noted that “the prophylactic and etiologic treatment of diabetes will surely play an important role in the future.” Skyler suggested a schema of genetic predisposition with environmental trigger leading to T-cell–mediated β-cell injury, causing development of humeral antibodies that are markers of the immune process, leading to a decline in β-cell mass with loss of first-phase insulin response to glucose and then to a deterioration in oral glucose tolerance and, after loss of >80% of β-cell mass, to diabetes development. Islets appear to affect only the minority of islets in the person developing type 1 diabetes, with many islets already having lost β-cells and without ongoing inflammatory infiltrate. There is a balance between susceptibility and protective genes between environmental triggers and environmental protective factors and between immune destruction and immune protection.

The IDDM1 locus on chromosome 6p21 accounts for more than half of the genetic predisposition, with DR4 and DQA1*0301 among the high-risk HLA types, whereas other types, including DR2 and DQA1*0102, are protective, appearing to be dominant over the susceptibility alleles so that they prevent development of type 1 diabetes, even with the presence of a susceptibility allele. Prolonged breast-feeding appears to protect against development of type 1 diabetes, although it may instead be that early exposure to cow’s milk is detrimental. Early exposure to certain infections such as pinworm may be protective. Immune susceptibility involves Th1, CD3, and CD8 T-cells, which have direct cytotoxicity and produce cytokotoxic cytokines, while regulatory Th2 and Th3 T-cells are protective and tend to decrease the destructive response. In theory, intervention could begin at the onset of diabetes to preserve the remaining 20% of β-cell mass, at pre-diabetes, at the time of loss of first-phase insulin response, at the time of development of isitis, or even before onset of immune response to the β-cell at a time of increased risk.

A number of intervention studies have been carried out at the time of onset of diabetes. There is evidence of response to treatment with azathioprine and steroids (54) or with cyclosporin (55,56), but after several years of immunosuppressive treatment the disease relapses (57), which is particularly problematic in view of the toxicity of these agents, with evidence of renal dysfunction in individuals who received such treatment. The DiaPeP277 fragment of heat shock protein has been shown to preserve β-cell function (58), and administration of a nonactivating humanized monoclonal antibody against CD3 showed benefit at 12 months (59), although with loss of β-cell function at 24 months.

Two intervention studies have been carried out at the pre-diabetes stage. The Diabetes Prevention type 1 (DPT-1) study
hypothesized that antigen-based treatment with insulin of nondiabetic relatives could delay development of type 1 diabetes. Two trials were carried out simultaneously, a parenteral insulin study of individuals with 5-year projected risk >50% because of loss of first-phase insulin response and an oral insulin study of individuals whose 5-year risk was 26–50% because of the presence of two or more positive antibodies. A total of 3,478 islet cell antibody–positive individuals were found (3.6% of the 103,351 relatives who underwent screening). BB rat and NOD mouse studies had shown effect of insulin administration, as had a protocol of closed-loop insulin for 2 weeks after diagnosis of type 1 diabetes (60) and a pilot trial of low-dose insulin to prevent diabetes in relatives of patients with type 1 diabetes (61). Despite the suggestive rationale, the 3.7-year study of annual 4-day continuous insulin plus subcutaneous ultralente insulin at a dosage of 0.125 units/kg twice daily did not show benefit in the in 339 individuals studied, with diabetes developing in 69 subjects in the intervention group and 70 subjects in the observation group (62). Skyler recalled Francis Bacon’s statement, “Truth is the daughter not of authority but of time.” (Francis Bacon, 1620, Novum Organum, London). A number of important observations were made in the study. The risk factors identified were age, with greatest risk for those 13–18, and lowest for those ≥18. Diabetes Care, Volume 26, Number 8, August 2003

Insulin pump treatment in children with type 1 diabetes

William V. Tamborlane, New Haven, CT, discussed “fulfilling the potential of pump treatment” in children with type 1 diabetes. Before 1980, type 1 diabetes was treated with one or two insulin injections daily, using urine tests, with aggressive therapy considered unsafe and of unknown benefits. HbA1c levels averaged 11–12%, and eye and renal complications were common. Early studies with continuous subcutaneous insulin infusion (CSII) showed marked amelioration of glycemia (64). Tamborlane noted that there is a dose-dependent time-action curve of subcutaneous regular insulin, with a peak at 3–5 rather than at 2 h and a duration of 8 rather than 4 h, leading to difficulty in controlling postprandial glycemic excursions. This is not seen with the rapid-acting insulin analogs, leading these to be preferred agents for CSII. Many pediatric endocrinologists have been reluctant to start CSII. In Tamborlane’s experience, 161 patients treated since 1997 with at least 12 months of data before and after pump initiation have shown a 0.6% decrease in HbA1c from 8.1 to 7.5% with sustained benefit and with severe hypoglycemia decreased from 37 to 24% per year. Among children <7 years of age at initiation of pump use, HbA1c decreased from 7.4 to 6.9% at 12 and 6.8% at 24 months, with a decrease in severe hypoglycemia from 79 to 39%. An important goal will be the performance of randomized clinical trials of efficacy and safety of CSII in children and adolescents. He cited a preliminary study in which HbA1c decreased from 8.3 to 7.7% at 8 weeks, with a subsequent increase to 8.1% at 16 weeks with glargine treatment, while decreasing from 8.1 to 7.0% at 8 weeks and remaining at 7.2% at 16 weeks in a small number of individuals treated with CSII. Using continuous glucose monitoring in 56 individuals, 75% of those treated with CSII, unexpected postprandial hyperglycemia and frequent and prolonged nocturnal hypoglycemia were detected, although the accuracy of these approaches for detecting hypoglycemia is uncertain. Implanted sensors are being developed, with feedback control of insulin delivery the ultimate goal in fulfilling the promise of pump technology to produce a closed-loop artificial pancreas.

References


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