Second World Congress on the Insulin Resistance Syndrome

Mediators, pediatric insulin resistance, the polycystic ovary syndrome, and malignancy

ZACHARY T. BLOOMGARDEN, MD

This is the second in a series of articles on the Second World Congress on the Insulin Resistance Syndrome, Universal City, California, 18–20 November 2004.

Jacqueline Dekker (Amsterdam, the Netherlands) presented data from the Hoorn Study on the predictive power of insulin resistance syndrome diagnosis, pointing out that the public health role of identifying a person as having insulin resistance syndrome includes the ability to characterize populations to better understand the pathogenesis of adverse outcome, to allow comparison of characteristics of individuals in differing populations, and to serve a communications function in increasing risk awareness, particularly allowing identification of high-risk groups for cardiovascular disease (CVD), cancer, and diabetes. An important question is whether the existing definitions allow optimal diagnosis of high-risk groups. Comparing the Adult Treatment Panel (ATP-III) and American College of Endocrinology (ACE) definitions (1), she noted that the ACE definition starts with high-risk individuals, including non-Caucasian ethnicity, cigarette use, obesity, CVD, hypertension, polycystic ovarian syndrome (PCOS), nonalcoholic fatty liver disease, acanthosis nigricans, history of gestational diabetes, and diabetes. An important question is whether the existing definitions allow optimal diagnosis of high-risk groups. Comparing the Adult Treatment Panel (ATP-III) and American College of Endocrinology (ACE) definitions (1), she noted that the ACE definition starts with high-risk individuals, including non-Caucasian ethnicity, cigarette use, obesity, CVD, hypertension, polycystic ovarian syndrome (PCOS), nonalcoholic fatty liver disease, acanthosis nigricans, history of gestational diabetes, and impaired glucose tolerance (IGT), and family history of type 2 diabetes, hyperpertension, or CVD.

The Hoorn Study included 2,484 individuals aged 50–75 in 1989–1990, with follow-up examination in 1996–1998, and population registry ascertainment of morbidity and mortality. Of 2,162 without diabetes at baseline, there were 429 deaths, 145 with malignancy and 168 with CVD. Insulin resistance syndrome components for men and women included hypertension in 68 and 66%, abdominal obesity in 16 and 40%, impaired fasting glucose in 14 and 9%, IGT in 21 and 18%, high triglycerides in 35 and 29%, and low HDL cholesterol in 28 and 35%, respectively. Twenty-one and 29% of men and women, respectively, satisfied the ATP-III definition and 46 and 42% the ACE definition of insulin resistance syndrome. Despite the greater number satisfying the ACE definition, both criteria predicted adverse outcome. CVD mortality increased 1.8- and 1.2-fold among ATP-III-positive men and women and 1.5- and 1.8-fold among ACE-positive men and women, respectively. For malignancy, risk was increased 1.2- and 1.6-fold for those satisfying the ATP-III definition and 0.9 and 1.2-fold for those satisfying the ACE definition. All-cause mortality was increased 1.5-fold in both sexes with ATP-III-defined insulin resistance syndrome, whereas it was not significantly increased in men or women satisfying the ACE definition. Both the ATP-III and ACE predicted diabetes. Men satisfying the ACE criteria were 6.9-fold more likely to develop diabetes, and men meeting the ATP-III criteria were 2.9-fold more likely to develop diabetes. Both definitions predicted an approximate sixfold increase in diabetes risk among women. Dekker noted that the number of risk factors is the best predictor of adverse outcome and that other risk factors, such as C-reactive protein (CRP), also provide relevant information. Although the insulin resistance syndrome definitions have identified a large (25–50%) subset of the population as being positive, the use of these definitions has clearly raised awareness and allowed identification of population characteristics, allocation of funds for health care, and development of CVD prevention strategies.

Causes and mediators of insulin resistance

Patrick Vallance (London, U.K.) discussed asymmetric dimethylarginine (ADMA) as a link between metabolism and atherosclerosis. The endothelium is an important source of nitric oxide (NO), derived from arginine and molecular oxygen by the action of endothelial NO synthase with NO inducing vasodilatation and inhibiting processes including platelet aggregation and adhesion, white cell adhesion, and vascular smooth muscle cell growth. A number of disease states with increased arteriosclerosis, including hypertension, diabetes, hypercholesterolemia, smoking, and renal failure, are associated with diminished NO-mediated vasodilatation and presumably with a decrease in its other effects, and there is evidence that exogenous arginine may be beneficial in hypercholesterolemia and renal failure. Animal models not expressing endothelial NO synthase show accelerated arteriosclerosis, and the NO synthase inhibitor NO-G-monomethyl-L-arginine has been used in elucidating effects of NO. ADMA is an endogenous equivalent of NO-G-monomethyl-L-arginine, blocking NO synthesis and leading to vasoconstriction and hypertension in animals and humans. In healthy individuals, blood

© 2005 by the American Diabetes Association.

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Diabetes Center, Mount Sinai School of Medicine, New York, New York.

Abbreviations: ACE, American College of Endocrinology; ADMA, asymmetric dimethylarginine; ATP, Adult Treatment Panel; CRP, C-reactive protein; CVD, cardiovascular disease; DDAH, dimethylarginine dimethylaminohydrolase; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; FFA, free fatty acid; iCAM, intercellular adhesion molecule; IGF-BP, IGF-binding protein; IGT, impaired glucose tolerance; IL, interleukin; PCOS, polycystic ovarian syndrome; PKC, protein kinase C; vCAM, vascular cell adhesion molecule; WHR, waist-to-hip ratio.
pressure increases by 5–7 mmHg with ADMA administration in association with increased systemic vascular resistance (2). ADMA is excreted in large amounts by the kidney, hence accumulating in renal failure, with levels predicting death and CVD. It has the potential to affect the cardiovascular, nervous, immune, and gastrointestinal systems, and ADMA levels are increased in vitro by high glucose levels (3). Its levels also are increased among individuals with elevated cholesterol, elevated homocysteine, diabetes, hypertension, heart failure, and atherosclerosis—settings not necessarily associated with renal insufficiency—while levels decrease following treatment with rosiglitazone (4) and metformin (5), suggesting a relationship to insulin resistance. Vallance did note that metformin is likely associated with renal insufficiency—ADMA is excreted in large amounts by the kidney, hence accumulating in renal failure, ADMA is relatively constant, with clearance of $\sim 250 \frac{\text{mol}}{\text{mol} \cdot \text{day}^{-1}}$ by DDAH compared with $\sim 50 \frac{\text{mol}}{\text{mol} \cdot \text{day}^{-1}}$ by renal excretion. Animals with heterozygous loss of a DDAH-1 gene show reduced DDAH activity in both liver and kidney, with plasma ADMA levels increased two- to threefold, reduced aortic response to acetylcholine, and exaggerated response to exogenous NO. Similarly, incubation of blood vessels with a DDAH inhibitor leads to ADMA accumulation within endothelial cells, with consequent increased vasoconstriction, suggesting that the pathway is not dependent on extracellular ADMA levels. A human DDAH-1 mutation has been described with decreased enzyme activity, associated with insulin resistance and increased CVD risk, suggesting a naturally occurring human disease that may model the effect of a number of disease states on NO. Peroxisome proliferator-activated receptor $\gamma$ activation promotes DDAH transcription (6), suggesting a mechanism for the effect of thiazolidinediones in decreasing ADMA levels. Also of note is that fat is a major source of ADMA and expresses high levels of DDAH, potentially linking the adipocyte to endothelial dysfunction. Adipocytes, therefore, may have autocrine effects on NO synthase, as well as paracrine effects on the local microvasculature, and may be source of circulating ADMA.

Guenther Boden (Philadelphia, PA) discussed free fatty acids (FFAs) as linking obesity, insulin resistance, endothelial dysfunction, and atherosclerosis. He noted that obesity is associated with insulin resistance, that fat feeding produces insulin resistance, and that weight loss reduces insulin resistance, and he suggested that all are mediated by altered release of adipokines from the expanded fat mass, which interfere with insulin action on skeletal muscle. Potential compounds include tumor necrosis factor $\alpha$, leptin, resistin, adiponectin, and FFAs. Boden showed that FFAs cause insulin resistance. Levels are elevated in obesity and cause insulin resistance in muscles, liver, endothelial cells, and adipose tissue itself. During a euglycemic-hyperinsulinemic clamp, healthy men and women given infusions of triglyceride plus heparin to prevent the decline in FFAs otherwise occurring with insulin have 40% reduction in insulin action with a time delay of $\sim 3$ h (7). Conversely, lowering of FFAs improves insulin sensitivity to a lesser degree in lean individuals, to normal levels in obese individuals without diabetes, and to approximately half of normal levels in obese individuals with diabetes (8). Insulin prevents hepatic glucose production, but with an increase in FFAs the decrease in hepatic glucose production is blunted, largely due to ongoing glycolysis, again with a 2- to 3-h time lag from the increase in FFA levels to the hepatic effect (9). Insulin increases limb blood flow, an effect that appears to be mediated by NO and that also can be reduced by decreasing FFAs (10). It appears that FFAs also potentiate glucose-stimulated insulin secretion (11), an effect that may to some extent balance their effect in decreasing insulin action, although at the expense of causing hyperinsulinemia. Boden noted that individuals who have both parents with type 2 diabetes fail to show the FFA-related increase in insulin secretion.

The mechanism of the effect of fatty acids on insulin action may be due to their interference with carbohydrate oxidation (12), to their causing a defect in glucose transport (this appears after 2–4 h, compatible with the time course observed in Boden’s studies) (13), or to their producing a defect in insulin signaling associated with a decrease in phosphatidylinositol 3-kinase (14). Insulin sensitivity decreases in a number of tissues as intracellular lipid levels rise, with a dose-dependent increase in intramyocellular triglycerides occurring as extracellular FFA concentrations rise (15). Boden hypothesized that FFA elevations increase intracellular long-chain acetyl CoA, producing diacylglycerol, which activates the serine/threonine kinase protein kinase C (PKC), leading to serine phosphorylation of insulin receptor substrate 1, interfering with its tyrosine phosphorylation and blocking insulin action. Muscle PKC bioactivity can be shown to increase after a 6- to 7-h delay with lipid infusion (16). In liver, diacylglycerol and PKC show a similar pattern of increase following FFA exposure, and Boden noted that similar findings are reported in endothelial cells exposed to palmitate, with PKC also activating NAD(P)H oxidase in endothelial cells, interfering with NO synthesis. Activation of the nuclear factor $\kappa$B pathway, the prototypical pathway of inflammation, by phosphorylation and subsequent ubiquination of the inhibitor of $\kappa$B results in free nuclear factor $\kappa$B being taken up by nucleus, activating synthesis of proinflammatory factors. Boden noted that inhibitor of $\kappa$B decreases after $\sim 6$ h of increase in FFA levels, suggesting a link between FFA-mediated metabolic insulin resistance and inflammation.

Peter Reaven (Phoenix, AZ) discussed the relationships between the insulin resistance syndrome, obesity, and inflammation in causing the development of atherosclerotic vascular disease. Atherosclerosis is a chronic inflammatory process and has been recognized to involve influx of modified lipoproteins that stimulate endothelial cells to produce factors such as adhesion molecules. These enhance monocyte binding via integrin binding to intercellular adhesion molecule (iCAM) and vascular cell adhesion molecule (vCAM). In turn, proinflammatory factors are generated, including locally produced CRP, which causes release of further inflammatory cytokines such as IL-1 and -6. These have both local actions and distant effects, the latter including the hepatic synthesis of CRP and serum amyloid A. CRP has been shown to be a risk factor for CVD in many epidemiologic studies and may have direct atherosclerotic effects, including activation of complement, stimulation of cytokine secretion, and increasing ICAM and vCAM levels. In the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection
myocardial infarction without known diabetes, 25% are found to have diabetes and an additional 40% have IGT (23), while 80% of patients with diabetes die from vascular disease. Thrombosis and inflammation “are actually the same process,” Grant stated, noting that elevations in CRP predate and predict both the development of type 2 diabetes and CVD and that an animal model with overexpression of CRP shows atheromatous lesions containing CRP on immunostaining (24). Another component of the inflammatory state is the activated monocyte/macrophage, which initiates thrombosis by release of tissue factor.

Discussions prothrombotic aspects of the insulin resistance syndrome, Grant distinguished two fibrin structures, one looser and more readily lysed and the other denser; the latter form is found in healthy relatives of patients with premature coronary disease, showing decreased permeability and more densely packed fibers. There is a strong negative relationship between fibrin permeability and HbA1c, suggesting that glycation may influence the prothrombotic phenotype. Similarly, adding glucose in vitro and presumably in vivo decreases permeation and increases fiber density. Fibrinogen isolated from individuals with diabetes shows weaker binding to plasminogen and tissue plasminogen activator, potentially contributing to the slowing of fibrin lysis occurring in diabetes. Furthermore, the surface of the fibrin clot is a site of generation of plasmin that mediates fibrinolysis and acts as the counterbalancing enzyme to thrombin. Plasmin generation occurs less rapidly in diabetic patients, and as HbA1c increases, there is greater α-2 anti-plasmin binding, additionally inhibiting clot lysis. Plasmin acts by clearing lysine residues, which Grant described as being "the absolute cores of clot formation," so that glycation, which occurs at lysine residues, may well interfere with this process. Plasminogen activator inhibitor 1 is a rapidly acting inhibitor of plasmin that is related to atherosclerosis and is strongly associated with insulin resistance. Thus, in diabetes, fibrin formation is increased with smaller pore size, fibrin fiber thickness is increased, fibrinolysis is reduced, and platelet aggregation is increased, all of which contribute to the prothrombotic state.

Insulin resistance in children

Alan Sinaiko (Minneapolis, MN) discussed the insulin resistance syndrome in childhood at a symposium cosponsored by the American Academy of Pediatrics. Insulin sensitivity decreases during puberty (25) in association with an increase in lean body mass in both sexes and with body fat decreasing in boys while increasing in girls. There is strong correlation between BMI at 7 and 24 years of age (26), and the insulin resistance syndrome factors (such as BMI, triglycerides, HDL cholesterol, fasting insulin) cluster according to blood pressure at age 13 years, leading Sinaiko to suggest that the concept of the insulin resistance syndrome is applicable to children. Comparing children based on weight group and insulin sensitivity, those who are heavier have higher blood pressure, triglycerides, fasting insulin, and lower HDL cholesterol.

Those who are both heavier and more insulin resistant have particularly high triglyceride levels. In his population, 3, 5, and 8% of children at ages 13, 15, and 19 years, respectively, had insulin resistance syndrome. At age 13, this population was comprised mostly of girls, but by age 19, more boys than girls had the syndrome. Waist, triglycerides, and HDL cholesterol were the defining characteristics of most of the children with insulin resistance syndrome, although abnormal fasting glucose became a factor at age 19.

Dennis M. Styne (Davis, CA) discussed the epidemiology and consequences of childhood obesity. BMI is not a good measure of adiposity in childhood, and weight divided by height3 would actually be more accurate at <14 years of age. Styne reviewed the Centers for Disease Control terminology, which differs somewhat from that applied to adults, with “overweight” children defined as those with BMI >95th percentile and “risk of overweight” used to describe those with BMI in the 85th–95th percentile. In 1975, 1990, and 2000, 5, 10, and 11% of children in the U.S., respectively, were “overweight” according to this criterion, with a particular increase in obesity in minority groups (27). Native-American children had a higher prevalence of being overweight than of being at “risk of overweight” (28). Older children’s weight is
strongly predictive of their adult weight, while for younger children the parents’ weight is most strongly predictive of the children’s eventual adult weight (29). Extrapolation from these data suggest that ~30% of adult obesity begins in childhood. Furthermore, childhood-onset obesity may have worse consequence than adult onset. The cost of hospitalizations for obese children has tripled over the past 2 decades. A 57-year follow-up of 7-year-old children showed a doubling of all-cause and ischemic heart disease mortality with BMI >75th percentile (30). Effects of obesity in childhood include sleep apnea, pseudotumor cerebri, orthopedic conditions such as Blount’s disease, a growth disorder of the tibia, and slipped capital femoral epiphysis, dyslipidemia, cholelithiasis, hepatic steatosis, ovarian hyperandrogenism, glucose intolerance, and type 2 diabetes. Furthermore, obese children are ostracized with systematized “weight prejudice,” and quality of life assessment suggests that obese children feel as bad as children with malignancy.

Causes of childhood obesity are uncertain. There is surprisingly little direct evidence that diet is related, perhaps because small differences lead to long-term weight gain. Similarly, there is no clear relationship between low activity levels and obesity, although there is certainly evidence that girls have decreasing physical activity with age, somewhat more among African Americans than among Caucasians, and that the amount of time spent watching television is proportional to weight (31). Other potential factors include macrosomia, starvation early in pregnancy (associated with catch-up growth in early childhood and subsequent overweight), socioeconomic status, parental education, school influences on child care, and the “built environment,” with economically disadvantaged areas having fewer facilities for children’s activity and higher prevalence of obesity. Psychiatric medications may be important causes of weight gain among children, who may show extraordinary weight gain over a brief period of time with these agents. Treatment with behavior modification to increase activity and decrease food intake or with orlistat are of modest benefit.

Silva Arslanian (Pittsburgh, PA) discussed contrasts between African-American and Caucasian children in insulin sensitivity and secretion, noting that over the past decade there has been a reversal of the previous pattern, in which Caucasians were more likely to develop new-onset diabetes than African Americans. This was associated with a greater prevalence of obesity and acanthosis nigricans and a lower prevalence of islet antibodies in African-American children, suggesting the increasing importance of type 2 diabetes. African-American children have lower insulin sensitivity, perhaps related to lower adiponectin levels, as well as decreased insulin clearance, which appears to correlate with lower levels of carbohydrate intake (32). Lipolysis rates are lower in African-American prepubertal children, suggesting a decreased ability to mobilize fat (33). Interestingly, obese Caucasian children appear to have higher visceral fat mass and greater degrees of dyslipidemia, suggesting that they may have lower diabetes risk but a more atherogenic risk profile (34). Insulin sensitivity decreases by ~30% during puberty, with Arslanian noting that there is a lesser degree of compensatory increase in insulin secretion in African-American than Caucasian adolescents.

Sonia Caprio (New Haven, CT) discussed obesity and the insulin resistance syndrome in children and adolescents. In her obesity clinic study, 24% of children had IGT and an additional 4% of adolescents had previously unrecognized diabetes (35). In a study of ~500 children, defining the insulin resistance syndrome by BMI >97th percentile, triglycerides >95th percentile, HDL cholesterol <5th percentile, systolic and/or diastolic blood pressure >95th percentile, and IGT (three or more abnormalities), the insulin resistance syndrome was seen in 30–45% of moderately obese and 40–60% of severely obese children; the lowest prevalence was seen in African-American children and the highest in Hispanic children (36). The prevalence of all insulin resistance syndrome components increases with the degree of obesity, and IL-6 and CRP increase and adiponectin decreases with greater degrees of obesity and of insulin resistance. In a study of 71 obese children with normal glucose tolerance, most remained normal, while of 31 with IGT, 10 developed diabetes over 2 years, in association with greater weight gain and abnormal tissue partitioning of lipid in skeletal muscle and visceral fat. Comparing children with impaired and normal glucose tolerance matched for BMI, total body fat, and leptin, those with IGT had lower nonoxidative glucose disposal and increased intramyocellular lipid and greater visceral with lower abdominal subcutaneous fat (37).

**PCOS**

At a symposium cosponsored by the Androgen Excess Society, John Nestler (Richmond, VA) reminded the audience that PCOS is a clinical syndrome of chronic anovulation and hyperandrogenism affecting 6–10% of women of childbearing age, probably the most common endocrinopathy of young women, and the leading endocrine cause of infertility. The PCOS is strongly associated with insulin resistance, which may be exacerbated by coexistence of obesity, a typical finding among individuals with the syndrome. Insulin resistance and hyperinsulinemia stimulate ovarian androgen production, increase the likelihood of diabetes and CVD and lead to hypertension, low HDL cholesterol, increased triglycerides, and increased plasminogen activator inhibitor 1, endothelin-1, and CRP, with 22, 45, and 50% prevalence of insulin resistance syndrome among women with PCOS at <20, 20–29, and 30–39 years, respectively, which is not explained solely by their degree of obesity. In his clinical population of women with PCOS, 9, 22, 26, 30, 11, and 2% had none, one, two, three, four, and all five of the ATP-III insulin resistance syndrome factors (elevated blood pressure, waist circumference, glucose, and triglycerides and low HDL cholesterol), respectively.

Richard S. Legro (Hershey, PA) discussed the endeavor to identify PCOS susceptibility genes. Case series suggest autosomal-dominant inheritance, but it has become apparent that, as with diabetes itself, PCOS is a complex disorder that presumably is caused by a large number of different genetic abnormalities. By transmission/disequilibrium testing, it is possible to identify preferentially transmitted alleles. Affected sibpair analysis makes no assumptions about the mode of inheritance and involves determining the proportion of alleles shared in affected sibpairs at genetic markers. As the male phenotype has not been fully characterized, only affected sisters are being used for this analysis. In a study of sisters divided into three groups (PCOS, hyperandrogenism but normal menstrual cycles,
and unaffected), hyperandrogenemia showed bimodal distribution consistent with a monogenic trait controlled by two alleles at an autosomal locus (38). Hyperandrogenemia tracks with hyperinsulinemia and with elevated total and LDL cholesterol (39). Brothers also are hyperandrogenemic, with elevated dehydroepiandrosterone (DHEA), and are insulin resistant (40). Despite study of a number of candidate genes related to insulin action, steroid biosynthesis, and other potential determinants, no genetic marker has been identified.

Silva A. Arslanian (Pittsburgh, PA) discussed PCOS among adolescents who presented with hirsutism, acne, alopecia, and/or irregular menses, suggesting that PCOS usually develops during puberty rather than at the later time of presentation for infertility. Testosterone, androstenedione, and DHEA levels are usually increased, LH may be increased, and typically there is an increased level of insulin and decreased sex hormone–binding globulin and IGF-binding protein (IGFBP)-1. Arslanian discussed the case of a girl who had presented with normal glucose levels but with severe hyperinsulinemia and elevated testosterone and who subsequently developed diabetes, with lower insulin levels and a marked decrease in testosterone level, leading to the conclusion that rather than androgen excess being primary, it is caused by insulin resistance and hyperinsulinemia. In a study of girls with a short duration of PCOS, insulin levels were almost twice as high and the IGFBP-1 level was half that in control girls (41). There was insulin resistance in both skeletal muscle and liver, with a marked decrease in both oxidative and nonoxidative glucose disposal and with compensatory hyperinsulinemia. IGT is found in 31% of adults with PCOS (42), and Arslanian reported a similar frequency of IGT in adolescents with the syndrome (43). Girls with IGT have insulin sensitivity similar to those with normal glucose tolerance, higher hepatic glucose production, and an ~50% decrease in first-phase insulin secretion, suggesting the pre-diabetic state. Girls with PCOS and IGT fail to show the normal nocturnal fall in systolic blood pressure, suggesting an early stage in the development of vascular abnormality. In a study of 14 adolescents with PCOS and IGT treated with 850 mg metformin twice daily, there was a modest decrease in total and subcutaneous adipose tissue without a decrease in visceral adipose tissue. Glucose tolerance became normal in eight of the girls with treatment, with a decrease in insulin secretion and an increase in insulin sensitivity. The previous hyperresponsiveness of A2, 17-OH-progesterone, and 17-OH pregnenolone to ACTH improved. In a clinical study of adolescents with PCOS treated with metformin, menstrual regularity improved (45).

Premature pubarche may be an early marker of future PCOS. Forty-five percent of these girls develop functional ovarian hyperandrogenism compared with 3% of control subjects. Girls with a history of premature pubarche are at increased risk of anovulation, and DHEA sulfate (DHEAS) and androstenedione at the time of diagnosis of premature pubarche correlate positively with the 17-OH progesterone response to gonadotropin-releasing hormone. In a study of girls with premature adrenarche, comparing those with low and high insulin sensitivity, the former had higher 17-OH pregnenolone and a greater degree of obesity. The highest DHEAS levels are seen at the time of the largest BMI increases. Marked weight gain may therefore be causally involved. Administration of metformin appears to prevent the increase in DHEAS that otherwise occurs, with a decrease in IL-6 and an increase in adiponectin also occurring, further suggesting a benefit of insulin sensitizer treatment (46). Administration of metformin to girls with premature pubarche was associated with a decrease in testosterone and LDL cholesterol and an increase in HDL cholesterol (47). Stopping treatment led to an increase in testosterone and IL-6 and a decrease in adiponectin, suggesting a benefit of such an approach begun shortly after time of puberty, perhaps with the potential for prevention of progression to PCOS.

Arslanian brought up the interesting concept that PCOS may be programmed in utero, with an association between lower birth weight and increased adrenal androgen levels. Comparing twin pairs, one small and one normal for gestational age, the small one tends to have higher DHEAS; the problem with these children appears to be excessively rapid catch-up growth (48).

Legro discussed the emerging relationship between CVD and PCOS, noting that PCOS may be a distinct disorder of insulin sensitivity rather than merely a subset of the insulin resistance syndrome, so that although “there’s no doubt that these women develop CVD... the question is, do they develop it early?” Clearly, diabetes, obesity, dyslipidemia, and physical inactivity are present in women with PCOS, who have endothelial dysfunction, systolic and diastolic cardiac dysfunction, increased oxidative stress, and altered inflammatory markers. Sleep apnea and sleep-disordered breathing are seen in 10 and 15% of women with PCOS, with excessive daytime sleepiness in ~80 vs. 30% of controls (49). There is, Largo noted, no good data about increased CVD event rates (50), with carotid intimamedia thickness (IMT), coronary artery calcification (51), and echocardiographic abnormalities used as surrogate evidence of CVD, although what is needed are outcome studies. Many studies have based the diagnosis of PCOS on a single abnormality, such as the reported association between positive coronary angiography and hirsutism (52), or the report from the Nurses Health Study of a 50% increase in risk of coronary heart disease, a 5-fold increase in risk of diabetes, and a 24-fold increase in risk of hypertension among women with “very irregular” menses (53). There are important studies in which the diagnosis of PCOS was more firmly established, such as a 30-year follow-up of women who had had ovarian wedge resection showing a 3.6-fold increase in diabetes-related mortality (54) and a 10-year follow-up showing an age- and BMI-corrected increase in serum insulin, triglycerides, LDL cholesterol, systolic blood pressure, and waist-to-hip ratio (WHR) and a decrease in total HDL and HDL2 cholesterol among women with PCOS (55). In another study comparing women with both hirsutism and oligomenorrhea with control subjects, increased BMI, WHR, CRP, and triglycerides and decreased HDL cholesterol were again noted (56). Interestingly, there is evidence that PCOS tends to resolve as women reach the age of menopause, with menses becoming more regular and androgen levels tending to fall, with there also being evidence that at ~43 years of age, LDL cholesterol levels among control subjects are similar to those in women with PCOS, so that the lifetime CVD risk in PCOS women may not be increased (57), leading Legro to conclude that “the
Perspectives on the News

judy is still out" on CVD risk among these women (58).

David A Ehrmann (Chicago, IL) discussed PCOS as a precursor to type 2 diabetes, noting its association with dyslipidemia, a hypercoagulable state, hypertension, endothelial dysfunction, and obstructive sleep apnea, all of which suggest diabetes risk. Insulin resistance, β-cell dysfunction, and type 2 diabetes have been reported in this population since the 1920s, when questions were first raised as to whether this represented a special form of diabetes and whether the association with diabetes provides information about the pathogenesis of the other abnormalities of the syndrome. For 2 decades, PCOS has been known to be associated with hyperinsulinemia during oral glucose tolerance testing (59), with Dunaif first noting its association with insulin resistance to a degree exceeding that expected from the accompanying obesity (60). Analyzing five separate studies of 905 women with PCOS, 20–35% had IGT and 2–10% diabetes, with a higher prevalence of glycemic abnormality in U.S. studies, suggesting that of the 6–9 million women in the U.S. with PCOS, up to 1 million may have diabetes. The pathogenesis of diabetes involves β-cell dysfunction, whether acquired or caused by genetic factors, allowing progression of individuals with insulin resistance from normal to IGT to diabetes, with Ehrmann describing his studies comparing women with PCOS with or without a first-degree relative with type 2 diabetes, showing the former to have lower first- and second-phase insulin secretion and markedly decreased acute insulin response to glucose. Also, administration of glucose in an oscillatory fashion failed to cause entrainment of the insulin response (61), suggesting that abnormal β-cell function is a major component of the abnormal glucose tolerance in women with PCOS. In a study using the frequently sampled intravenous glucose tolerance test, insulin sensitivity is not as strongly heritable as the acute insulin response to glucose (62).

Addressing the question of screening for diabetes among women with PCOS, Ehrmann noted that the fasting insulin and insulin-to-glucose ratio are “probably . . . not that useful” and instead suggested performing an oral glucose tolerance test with 2-h glucose. He also noted the importance of recognition of obesity and of ascertaining whether there is a family history of type 2 diabetes.

Robert Norman (Woodville, Australia) discussed the roles of diet, exercise, and lifestyle modification in women with PCOS, reminding the audience that despite this being one of the earliest approaches to be shown effective, the approach is relatively poorly followed, particularly with “metformin flowing all over the place.” Clearly, obesity impacts adversely on female reproduction, with lifestyle intervention effective for fertility in PCOS and exercise important in attaining and sustaining weight loss. His patients, who usually wish fertility rather than being concerned about long-term risk, have obesity with central adiposity. Obesity before pregnancy increases the length of time to pregnancy, the frequency of menstrual disorders, and the rate of miscarriage. Obesity in pregnancy increases gestational diabetes and is associated with congenital abnormality, hypertension, and requirement for instrumental and operative delivery. Obesity after pregnancy increases risk of diabetes, hypertension, endometrial cancer, and CVD. BMI is an important negative lifestyle factor, along with cigarettes and alcohol, associated with reduced fertility (63). In the Nurses Health Study, infertility increases above a BMI of 26 kg/m² to an extent not explained on the basis of menstrual irregularity alone (64). A BMI >30 kg/m² is associated with an increased miscarriage rate (65). Comparing women with WHR <0.8 or >0.8 who had artificial insemination, fat distribution rather than BMI is the strongest determinant of difficulty in attaining fertility (66). Based on these data, his program began to change their emphasis in assisting women with weight loss, and discussing “waist” rather than “weight” and “fitness” rather than “fatness.” Gradual weight loss, sensible eating, exercise for overweight women, and social and psychological support using group therapy approaches were emphasized. In his initial study of 18 women with such an approach, 12 ovulated (67), with a larger subsequent study of 120 women approached to participate in the program. Of 87 consenting subjects, 20 dropped out, with 90% of those remaining in the study resuming ovulation, 78% becoming pregnant, and 67% having a live baby (68). A subsequent randomized controlled trial of 84 women meeting weekly, compared with 87 control subjects, showed a 6-month weight loss of 4.7 vs. 1.3 kg, with 61 vs. 21% becoming pregnant by 18 months. No difference has been found in this setting between a high-carbohydrate diet and a (modestly) high-protein diet (69), and his group is currently performing a randomized controlled trial of a low–glucemic index diet. Certainly, he stated, there is a role for metformin with or without clomiphene in these women, citing a meta-analysis showing benefit in menstrual regularity and ovulation (70), but a better approach is that of caloric restriction followed by metformin, with the latter improving the response of weight, waist circumference, visceral fat, and testosterone (71). However, a comparison of weight loss without metformin to metformin without weight loss suggests superiority of the former approach (72). When asking, “Why does our advice fail?”, Norman suggested that physicians need to exercise and diet themselves, that we need to treat patients for infertility with lifestyle rather than “high-tech” approaches, that all overweight women should be encouraged in lifestyle modification, and that weight loss itself should not be considered as important as reducing waist circumference and improving insulin sensitivity.

Maria J. Iuorno (Richmond, VA) further discussed the use of insulin sensitizers in PCOS, noting the importance of hyperinsulinemia itself, with a study of diazoxide administration for 10 days to women with PCOS decreasing testosterone levels in association with the decrease in insulin levels, despite causing hyperglycemia (73). She suggested that weight loss is difficult for women to maintain and is unlikely to be effective for the 20% of women with PCOS who are lean, leading to greater use of metformin and consideration of the use of TZDs. More than 30 studies of metformin have suggested a decrease in androgen levels and improved ovulation, with long-term beneficial effects. There are fewer studies of TZD treatment, but those that have been performed have shown decreased glucose and insulin levels during oral glucose tolerance testing, improvement in ovulation and testosterone, and some reduction in hirsutism with troglitazone (74–76), rosiglitazone (77), and pioglitazone (78). In a study (79) of women (BMI 24 kg/m²) treated for 6 months with 850 mg metformin twice daily, 4 mg rosiglitazone
twice daily, both, or neither, ovulatory improvement was more likely and the oral glucose tolerance test showed greater improvement with metformin. Testosterone decreased similarly with both approaches, and there was no evidence of synergistic benefit. A study (80) comparing metformin with laparoscopic ovarian drilling in clomiphene-resistant women with PCOS showed similar ovulation rates of 55 vs. 53% but pregnancy in 19 vs. 13%, with live birth rates of 82 vs. 65% of those pregnancies, suggesting greater benefit of metformin. There may be a role of hyperinsulinemia in causing first-trimester pregnancy loss, as two recent studies have suggested that metformin reduced early pregnancy loss in women with PCOS from 42 to 9% (81) and from 62 to 26% (82), showing particular benefit in women who had a prior history of early pregnancy loss. U尔orno pointed out that metformin is a category B drug; therefore, it is not contraindicated during pregnancy, although it cannot be stated to be completely safe. She suggested that it be continued for at least the first 12 weeks of pregnancy in women who have a history of early pregnancy loss but otherwise recommended discontinuing metformin once pregnancy has begun.

Insulin resistance and malignancy

Rowan Chlebowski (Los Angeles, CA) discussed modifiers of insulin action and breast cancer risk. Breast cancer risk factors include age, family history, and glycememia. Breast cancer is associated with lifestyle factors including physical activity, with ~2 h/week of brisk walking associated with 18% lower risk (83), as well as with cigarette smoking and with dietary calories, fat, fruits, vegetables, and alcohol. Obesity has been associated with breast cancer risk in a number of large epidemiological studies (84). In the Iowa Women’s Health Study of 21,707 women, those with intentional weight loss exceeding 20 lb had a reduction in breast cancer risk (85). Women with a higher serum estradiol concentration have greater breast cancer risk. Chlebowski reviewed results of studies with raloxifene showing breast cancer risk to be reduced only among women in the highest estradiol quartile. The association of breast cancer risk with BMI appears to be reduced by adjustment for free estradiol, suggesting that estrogens, perhaps produced by adipose tissue, may mediate the effect of obesity (86). There is also a modest relationship between dietary fat and breast cancer, with caloric restriction associated with lower breast cancer rates, as suggested by reduced breast cancer in women who had been hospitalized for anorexia nervosa (87).

Among women who already have breast cancer, overweight and obese patients have poorer survival and greater likelihood of recurrence. Among women treated with tamoxifen, Chlebowski stated, obese women had a 58% greater recurrence rate in the contralateral breast and a 31% greater total mortality than nonobese female subjects. Another study showed an association of recurrence and mortality with BMI >30 kg/m² in pre/perimenopausal but not postmenopausal women. In the Nurses’ Health Study, walking >9 h/week was associated with an ~50% reduction in breast cancer death. The data are contradictory, however, as while postmenopausal obesity is associated with increased risk of cancer, particularly among women not using hormone replacement, obese premenopausal women may have decreased breast cancer risk. Planned trials will study the effects of weight loss on breast cancer development and among women with existing breast cancer.

George Blackburn (Boston, MA) discussed the interrelationship among obesity, the insulin resistance syndrome, and cancer, reviewing the concept that excess adiposity may increase FFAs and cytokines, causing insulin resistance and hyperinsulinemia and potentially decreasing apoptosis and causing proliferation of some cell types. A hyperinsulinemia-related decrease in IGFBP-1 and -2 leading to increasing IGF-1 bioavailability may further promote these processes. Blackburn cited population-attributable risks from obesity of 11% for colon cancer, 9% for breast cancer, 39% for endometrial cancer, 25% for hypernephroma, and 37% for esophageal cancer. Obesity is associated with an ~50% increase in colon cancer (88), as is increased waist circumference in women, and weight gain from age 18 years is related to distal colon cancer risk, with individuals who have a weight gain >20 lb having a 56% greater risk. We are “on the road,” Blackburn concluded, “to adding cancer [to the insulin resistance syn-

References


Bloomgarden


34. Weiss R, Dufour S, Taksali SE, Tambor-
46. Ibanez L, Valls C, Barbetta G, Allen K, Ripe F, Sa- 
voye M, Dziura J, Sherwin R, Shulman GI, 
Caprio S: Prediabetes in obese youth: a 
syndrome of impaired glucose tolerance, 
tolerant insulin, and altered 
myocellular and abdominal fat partition-

38. Legro RS, Driscoll D, Strauss JF 3rd, Fox J, 
Dunaif A: Evidence for a genetic basis for 
hyperandrogenemia in polycystic ovary 
syndrome. Proc Natl Acad Sci U S A 95: 
14956–14960, 1998

39. Legro RS, Bentley-Lewis R, Driscoll D, 
Wang SC, Dunaif A: Insulin resistance in 
sisters of women with polycystic ovary 
syndrome: association with hyperandro-
genemia rather than menstrual irregular-
ity. J Clin Endocrinol Metab 87:2128– 
2133, 2002

40. Legro RS, Kunselman AR, Demers L, 
Wang SC, Bentley-Lewis R, Dunaif A: El-
vated dehydroepiandosterone sulfate 
levels as the reproductive phenotype in 
the brothers of women with polycystic 
ovary syndrome. J Clin Endocrinol Metab 
87:2134–2138, 2002

41. Lewy VD, Danadian K, Witchel SF, Arsla-
nian S: Early metabolic abnormalities in 
adolescent girls with polycystic ovarian 

42. Legro RS, Kunselman AR, Dodson WC, 
Dunaif A: Prevalence and predictors of 
risk for type 2 diabetes mellitus and im-
paired glucose tolerance in polycystic 
oviduct syndrome: a prospective, con-
trolled study in 254 affected women. 
J Clin Endocrinol Metab 84:165–169, 1999

43. Arslanian SA, Lewy VD, Danadian K: Glu-
cose intolerance in obese adolescents with 
polycystic ovary syndrome: roles of insu-
in resistance and beta-cell dysfunction 
and risk of cardiovascular disease. J Clin 
Endocrinol Metab 86:66–71, 2001

44. Arslanian SA, Lewy V, Danadian K, Saad 
R: Metformin therapy in obese adoles-
cents with polycystic ovary syndrome and 
impaired glucose tolerance: amelioration 
of exaggerated adrenal response to 
adrenocorticotropin with reduction of 
insulinemia/insulin resistance. J Clin 
Endocrinol Metab 87:1555–1559, 2002

45. Ibanez L, Valls C, Ferrer A, Marcos MV, 
Rodriguez-Hierro F, de Zegher F: Sensiti-
zation to insulin induces ovulation in 
nonobese adolescents with anovulatory 
hyperandrogenism. J Clin Endocrinol Metab 
86:3595–3598, 2001

46. Ibanez L, Valls C, Marcos MV, Ong K, 
Dunger DB, De Zegher F: Insulin sensitiz-
ation for girls with precocious pubarche 
and with risk for polycystic ovary syn-
drome: effects of prepubertal initiation 
and postpubertal discontinuation of met-
formin treatment. J Clin Endocrinol Metab 
89:4331–4337, 2004

47. Ibanez L, Ferrer A, Ong K, Amin R, 
Dunger D, de Zegher F: Insulin sensitiza-
tion early after menarche prevents pro-
gression from precocious pubarche to 
polycystic ovary syndrome. J Pediatr 
144:23–29, 2004

48. Francois I, de Zegher F: Adrenarche and fe-

49. Vgontzas AN, Legro RS, Bixler EO, 
Grayev A, Kales A, Chrousos GP: Polycys-
tic ovary syndrome is associated with ob-
structive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin 
Endocrinol Metab 86:517–520, 2001

50. Legro RS: Polycystic ovary syndrome and 
cardiovascular disease: a premature asso-

51. Christian RC, Dumesic DA, Behenbeck 
T, Oberg AL, Sheedy PF 2nd, Fitzpatrick 
LA: Prevalence and predictors of coronary 
artery calcification in women with poly-

52. Wild RA, Grubb B, Hartz A, Van Nort JJ, 
Bachman W, Bartholomew M: Clinical 
signs of androgen excess as risk factors 
for coronary artery disease. Fertil Steril 

53. Solomon CG, Hu FB, Dunaif A, Rich-Ed-
wards JE, Stampler MJ, Willett WC, 
Speizer FE, Manson JE: Menstrual cycle 
irregularity and risk for future cardiovas-
cular disease. J Clin Endocrinol Metab 

54. Pierpoint T, McKenige PM, Isaacs AJ, 
Wild SH, Jacobs HS: Mortality of women 
with polycystic ovary syndrome at long-
term follow-up. J Clin Epidemiol 51:381– 
386, 1998

55. Talbott EO, Guzzick DS, Sutton-Tyrrell K, 
McHugh-Pem P, Zborowski JV, Rens-
berg KE, Kaiser LL: Evidence for associa-
tion between polycystic ovary syndrome 
and premature carotid atherosclerosis in 
middle-aged women. Arterioscler Thromb 
Vasc Biol 20:2414–2421, 2000

56. Taponen S, Martikainen H, Jarvelin MR, 
Sovio U, Laitinen J, Pouta A, Hartikainen 
A, McCarthy MI, Frank S, Paludanius M, 
Ruokonen A, the Northern Finland Birth 
Cohort 1966 Study: Metabolic cardio-
vascular disease risk factors in women 
with self-reported symptoms of oligomen-
orrhea and/or hirsutism: the Northern 
Finland Birth Cohort 1966 Study. J Clin 
Endocrinol Metab 89:2114–2118, 2004

57. Talbott ET, Clerici A, Berga SL, Kuller L, 
Guzzick D, Detre K, Daniels T, Engberg 
RA: Adverse lipid and coronary heart dis-
ease risk profiles in young women with 
polycystic ovary syndrome: results of a 
case-control study. J Clin Epidemiol 51: 
415–422, 1998

58. Guzzick DS: Cardiovascular risk in PCOS. 
J Clin Endocrinol Metab 89:3694–3695, 
2004

59. Chang RJ, Nakamura RM, Judd HL, 
Kaplan SA: Insulin resistance in nonobese 
patients with polycystic ovarian disease. 
J Clin Endocrinol Metab 57:356–359, 1983

60. Dunaif A, Segal KR, Futterweit W, Do-
bransky A: Prolonged peripheral insulin 
resistance, independent of obesity, in 
polycystic ovary syndrome. Diabetes 
38:1165–1174, 1989

61. Ehrmann DA, Sturis J, Byrne MM, Karri-
sion T, Rosenfield RL, Polonsky KS: Insu-
lin secretory defects in polycystic ovary 
syndrome: relationship to insulin sensi-
tivity and family history of non-insulin-
dependent diabetes mellitus. J Clin Invest 
96:520–527, 1995

62. Colilla S, Cox NJ, Ehrmann DA: Herita-
bility of insulin secretion and insulin ac-
tion in women with polycystic ovary 
syndrome and their first degree relatives. 
J Clin Endocrinol Metab 86:2027–2031, 
2001

63. Hassan MA, Killick SR: Negative lifestyle 
is associated with a significant reduction 
in fecundity. Fertil Steril 81:384–392, 
2004

64. Rich-Edwards JW, Goldman MB, Willett 
WC, Hunter DJ, Stampfer MJ, Colditz GA, 
Manson JE: Adolescent body mass index 
and infertility caused by ovulatory disor-
der. Am J Obstet Gynecol 171:171–177, 
1994

65. Wang JX, Davies MJ, Norman RJ: Polycys-
tic ovarian syndrome and the risk of spau-
taneous abortion following assisted reproduc-
tive technology treatment. Hum Reprod 
16:2606–2609, 2001

66. Zaalstra BM, Seidell JC, Van Noord PA, te 
Veld ER, Habbema JD, Vrieswijk B, Kar-
baart J: Fat and female fecundity: prospec-
tive study of effect of body fat distribution 
on conception rates. BMJ 306:484–487, 
1993

67. Clark AM, Ledger W, Galletly C, Tomlin-
son L, Blaney F, Wang X, Norman RJ: 
Weight loss results in significant improve-
mnt in pregnancy and ovulation rates in 
avenogyl abdominal obese women. Hum 
Reprod 10:2705–2712, 1995

68. Clark AM, Thornley B, Tomlinson L, Gal-
letley C, Norman RJ: Weight loss in obese 
infertile women results in improvement 
in reproductive outcome for all forms of 
reproductive technology treatment. Hum 

69. Moran LJ, Noakes M, Clifton PM, Tomlin-
son L, Galletley C, Norman RJ: Dietary 
composition in restoring reproductive 
and metabolic physiology in overweight 
women with polycystic ovary syndrome. 
J Clin Endocrinol Metab 88:812–819, 2003

70. Lord JM, Flight IH, Norman RJ: Met-
formin in polycystic ovary syndrome: sys-
tematic review and meta-analysis. BMJ 

71. Pasquali R, Gambineri A, Biscotti D, Vi-


77. Brettenhaller N, De Geyter C, Huber PR, Keller U: Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunc-

tion in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 89:

78.8385–3840, 2004


82. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L: Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 17:

83. 2858–2864, 2002


84. 2858–2864, 2002


85. vad K, Clavel-Chapelon F, Nagel G, Boe-

86. ing H, Trichopoulos D, Economou G, Bellos G, Palli D, Tumino R, Pancio S, Sac-

87. erdote C, Krogh V, Peeters PH, Bueno-de-


89. creto G, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Nerishi K, Land CE, Cauley JA, Keller LH, Cum-

90. mings SR, Helzlsouer KJ, Alberg AJ, Bush TL, Comstock GW, Gordon GB, Miller SR, Longcope C, the Endogenous Hor-

91. mones Breast Cancer Collaborative Group: Body mass index, serum sex hor-

92. mones, and breast cancer risk in post-


94. 2003;95:1218–1226

95. Michels KB, Ekholm A: Caloric restriction and incidence of breast cancer. *JAMA* 291:

96. 1226–1230, 2004

97. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA: Leisure-time physical activity, body size, and colon cancer in women: Nurses’ Health Study Research Group. *J Natl Can-

98. cer Inst* 89:498–505, 1997


100. pendent signaling and inhibits human tu-


102. 8921, 2003