Published in final edited form as:

Curr Opin Obstet Gynecol. 2009 August ; 21(4): 301–305. doi:10.1097/GCO.0b013e32832e07d5.

Insulin Resistance in Women's Health: Why It Matters and How to Identify It

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Abstract

Purpose of Review—To examine the significance of insulin resistance in women's health and review methods for diagnosing it.

Recent Findings—Clinical phenotypes in conjunction with standard clinical biochemical assays, i.e. the metabolic syndrome, remain the key method to diagnose insulin resistance in clinical practice. Candidate alleles from type 2 diabetes offer little predictive value for cardiovascular events beyond traditional risk factors. Simple environmental factors such as irregular meal frequency appear to increase the risk of the metabolic syndrome and require greater scrutiny. Pregnancy complications, particularly gestational diabetes and preeclampsia in the mother and preterm birth in the fetus are events that suggest elevated risk for future cardiovascular morbidity in those affected.

Summary—Clinical phenotypes of insulin resistance identify women at risk for perinatal and reproductive complications.

Keywords

metabolic syndrome; diabetes; cardiovascular disease

Introduction

This article will examine key articles in the previous year that highlight the role of insulin resistance in Women's Health. The article will first discuss the recognition of insulin resistance and the relative role of clinical versus biochemical phenotypes with an emphasis on utilizing clinical phenotypes such as the metabolic syndrome. The article will then focus on insulin resistance throughout the life cycle of women from pregnancy to puberty to menopause and its response to treatment.

Recognizing insulin Resistance in Clinical Practice

Recognizing insulin resistance in clinical practice largely revolves around recognizing obesity and secondarily the metabolic syndrome. The quickest and simplest way to recognize obesity is to calculate a body mass index on every patient at every visit (kg/m²).

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This can be done with wheels, calculators, or nowadays most scales. Secondarily patients who are overweight (BMI > 25) should be screened for the metabolic syndrome. The metabolic syndrome is a constellation of signs and symptoms that identify women at risk for type 2 diabetes and most likely cardiovascular disease. These include two biometric factors: waist circumference (> 35 inches) and blood pressure (> 130/85), and three biochemical factors that are measured in fasting blood: glucose (> 100 mg/dL), HDL-C (< 50 mg/dL), and triglycerides (> 150 mg/dL). This has become synonymous with the clinical phenotype of insulin resistance.

Many have also recommended adding a 2h 75g oral glucose tolerance test to the definition of the metabolic syndrome. Most commonly attention has focused on the two hour value. However recent work has focused on the one hour level where the plasma glucose concentration is a strong predictor of future risk for type 2 diabetes (1). However, the metabolic syndrome designation and clinical utility does have its detractors. There is some concern how well the syndrome identifies individuals at risk for cardiac events (although the diabetes predictive value is high) (2*). Nonetheless previous work has shown that there are most likely gender differences in the predictive value of the metabolic syndrome and that women with centripetal obesity combined with high triglyceride levels are at particularly high risk for cardiovascular events.

The clinical measurement of insulin to diagnose insulin resistance has fallen to a certain extent by the wayside, except in rare cases of severe syndromes of insulin resistance with early and morbid onset (for example leprechaunism, lipodystrophy, etc.) or suspected insulin excess states such as insulinomas. Part of the difficulty in the routine measure of insulin levels is the great variability of insulin assays with no gold standard assay that has been universally accepted. This is somewhat analogous to the poor sensitivity of most androgen assays to elevated levels found in most female androgen excess disorders, most commonly PCOS. The debate over which clinical test to send to diagnose insulin resistance has ended and the loser is insulin. A study examining multiple insulin assays and the utility of HOMA-IR assessments (based on fasting glucose and insulin levels) found that insulin resistance ranged from 0.8 to 2.0 (P = 0.0007), from 1.9 to 3.2 (P = 0.842), and from 1.5 to 2.9 (P < 0.0001), respectively, i.e. a greater than twofold variation in HOMA (3). There is also variability in any test of insulin resistance in the same individual and abnormal tests may normalize from year to year (4).

Other Markers of Insulin Resistance

The search continues for another serum marker with good predictive ability to identify those at greatest risk for morbid events. The search has expanded as every organ is potentially a target for pathophysiologic changes due to insulin resistance, and additionally every organ has been recognized as an endocrine organ, i.e. it communicates with other tissues via endocrine signals. It was really the discovery of leptin and its role in appetite and energy homeostasis that fueled the discovery of other adipokines, and fat quickly overtook all the other endocrine organs as our “largest” endocrine gland. Now attention has focused on the bowel, and the world of incretins, and more recently bone, as we learn there are similar response pathways and myriad effects on these organ systems.

Adipokines continue to be a target of great interest. Of note there are adipokines with varying and opposing actions, for instance resistin is associated with increases in insulin resistance and adiponectin with decreases (i.e. a favorable hormone)(5). Pre-surgical HMW adiponectin concentration has been shown to independently predict losses of body weight and fat mass after bariatric surgery (6). Further the beneficial effects of wine have been linked to increases in adipocyte adiponectin production (7). Adiponectin, unlike leptin,

increases when obese children institute a lifestyle intervention (8). It, along with insulin levels, was found to be predictive of the development of gestational diabetes at 11 weeks (9). Nonetheless the value of adiponectin as an independent predictor of cardiac events continues to be questioned (10).

Bone has been found to secrete a hormone, osteocalcin which is associated with improved insulin sensitivity and may be mediated by this hormone, although the mechanisms have not been well delineated (10). Further iron metabolism appears to be affected by insulin resistance, best illustrated by the association of insulin resistance and diabetes with hemochromatosis. Increased ferritin levels do correlate with insulin resistance and are more common in individuals with the metabolic syndrome (11).

Perhaps the most important marker of insulin resistance is clinical pathology. There is continued focus on the association between insulin resistance and other syndromes and conditions. Sleep abnormalities including sleep disordered breathing, sleep apnea, and a short duration of sleep continue to be associated with insulin resistance (12), something that has been well documented in women with PCOS (13), but also appears more prevalent in children with risk factors (14).

Cause of Insulin Resistance

The major breakthrough in the identification of the genes involved in insulin resistance continues to be the exploration of candidates from the genome wide association studies that have been published over the last few years. Disappointingly, risk alleles had relatively poor predictive value in identifying individuals at risk for diabetes, at least when compared to traditional clinical risk factors (15**), although the value may improve with a longer period of follow-up (16**). Further they did not identify those individuals likely to develop diabetes who participated in the Diabetes Prevention Program (17*). Thus there is little current clinical role in using these candidate risk alleles in clinical medicine.

An interesting article explored the relationship between insulin resistance and dyslipidemia in individuals with mutation in an insulin receptor vs those with post receptor mutation. They found that individuals with the insulin receptor mutations had normal levels of HDL-C and low levels of triglycerides, and it was only the individuals with post receptor pathway mutations (for instance in AKT2) that had dyslipidemia (18). It is likely that a post receptor mechanism explains the selective tissue insulin sensitivity found in PCOS (19)

The search continues for environmental influences. Environmental disruptors continue to be explored as potential contributors to insulin resistance, but it is almost as these studies exist in a parallel universe, and never trickle over to the clinic. One study did find adverse effects on diabetes risk with increasing urinary bisphenol A levels (20). Air pollution has been associated with increased short term cardiovascular morbidity and reproductive impairment. Recently, exposure to diesel exhaust was shown to cause acute vasoconstriction, a possible mediator of increased event risk(21)

Perhaps the largest environmental contributor remains our sedentary lifestyle and our diet. TV time is a clear predictor of metabolic syndrome and the effect appears more pronounced in women. Compared to subjects who viewed TV < 14 hr/week, those who viewed TV > 20 hr/week had a 1.50-fold (95% confidence intervals (CI): 1.10, 2.03) risk for men and a 1.93-fold (95% CI: 1.37, 2.71) risk for women of having metabolic syndrome, after adjusting for physical activity and other covariates (22). Occupation also impacts risks preferentially in women. Among female subjects, the age-adjusted prevalence of metabolic syndrome was higher in blue-collar than in white-collar workers, but this difference was not evident among male workers (23). Eating meals irregularly contributes to insulin resistance and the risk of

the metabolic syndrome: eating regular meals decreases the risk of the metabolic syndrome by 60–70% (24*). Various dairy products may have differential associations with the metabolic syndrome. One group found a significant inverse association between intake of whole milk, yogurt, calcium, and magnesium and metabolic disorders. Odds ratios for one more daily serving of yogurt and 100 mg Mg for the metabolic syndrome were 0.40 (95% CI: 0.18, 0.89) and 0.83 (95% CI: 0.72, 0.96), respectively. The opposite was found for intakes of cheese, low-fat milk, and phosphorus (25).

The Life Span of Insulin Resistance in Women

The life span of insulin resistance goes back to conception, and there has been increasing scrutiny both of the intrauterine milieu and its effects on the fetus, and also on the dynamic state of pregnancy as a challenge test for future maternal morbidity. Beginning with the latter, it has long been known that one of the greatest risk factors for developing type 2 diabetes is a history of gestational diabetes, and further that there are ethnic differences with minorities disproportionately affected, and that the progression is more rapid than we thought. Glucose intolerance was recently identified as predictor of preterm labor in Chinese women undergoing IVF (26).

Similarly there has been increased documentation that hypertensive disorders during pregnancy identify women at risk for later morbidity. The most convincing data appeared from a Norwegian pregnancy registry in which pre-eclampsia is a marker for an increased risk of subsequent end stage renal disease, although the absolute risk was low (27**). Pre-existing insulin resistance and metabolic syndrome during pregnancy are associated with increased risk for pre-eclampsia (28) and eclampsia (29). This is also illustrated by the increased risks of gestational diabetes and pre-eclampsia among women with lipodystrophy (30). Icelandic women with a history of pre-eclampsia had higher CRP levels as postmenopausal women (31). One group studied modeling of risk factors associated with CVD and estimated a three fold greater risk in women with pre-eclampsia (32). There is familial predisposition as women with pre-eclampsia have parents with increased glucose levels, obesity, and signs of cardiovascular disease (33). Similarly children of women with PCOS show signs of hyperinsulinemia and metabolic dysfunction (34, 35).

The Barker Hypothesis suggests that limitations in intrauterine nutrition imprint insulin resistance into the fetus and shunt energy towards vital brain function and away from other organ systems (for example skeletal muscle) leading to smaller fetuses, and that further post birth nutritional excess leads to the excessive accumulation of body fat in these children and ultimately increased adult risks of developing diabetes and atherosclerosis. Supporting this hypothesis are interventions which improve outcomes. One multicenter study provided balanced protein-calorie supplementation (2.51 MJ, 20 g protein daily to pregnant women and preschool children aged under 6 years, which was found to increase height and the cardiovascular health of adolescents in a nutrient deprived environment in India (36). Most excess weight before puberty is gained before 5 years of age (37). This same study showed that weight at 5 years of age is not closely related to birth weight but instead closely predicts weight at 9 years of age. Preterm birth may add an additional risk factor beyond impaired intrauterine growth to diabetes and hypertension risk (38).

Pregnancy complications aside and considering the population of reproductive age women, a diagnosis of PCOS still identifies a reservoir of women more likely to have the metabolic syndrome (39). Obesity exacerbates the risk such that PCOS may not add as much cardiometabolic risk in adolescents (40) or normal weight women (41).

Menopause and its transition are associated with increased risks of developing insulin resistance and the metabolic syndrome. An important study from SWAN (Study of Women's

Health Across the Nation) showed that the odds of developing the metabolic syndrome per year were higher in perimenopause 1.45 (95% confidence interval, 1.35–1.56) than after menopause, 1.24 (95% confidence interval, 1.18–1.30) ($P < .001$) (42**). An increase in bioavailable testosterone or a decrease in sex hormone-binding globulin levels also increased the odds. The risk of developing metabolic syndrome also increases after surgical menopause (43). These studies highlight the importance of screening women earlier in the menopausal transition and immediately after surgical menopause for the metabolic syndrome given their increased cardiovascular risk.

SUMMARY

Insulin resistance still has manifold adverse effects on women's health from pregnancy to fetus to menopausal woman. Screening should revolve around recognition of the metabolic syndrome and its components, i.e. centripetal obesity, hypertension, hyperglycemia, and dyslipidemia. A variety of conditions including hypertensive and hyperglycemic disorders of pregnancy and PCOS should alert clinicians to institute tighter surveillance for diabetes and cardiovascular disease.

Acknowledgments

Funding/Support: This work was supported by NIH/NICHD grants U10 HD38992 (RL), U54 HD34449, and RO1 HD056510, a GCRC grant MO1RR10732 and construction grant C06 RR016499 to Pennsylvania State University.

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