SUMMARY

Among women with polycystic ovary syndrome (PCOS), the prevalence of impaired glucose tolerance is estimated to be between 30 and 40%, whereas that of type 2 diabetes mellitus has been placed at 5–10%. These prevalences are among the highest known among women of reproductive age. The predisposition to glucose intolerance in PCOS may be influenced by antenatal events, including the rate of in utero growth and development as well as exposure to excess androgen concentrations from the maternal circulation. Once defects in insulin secretion develop in the setting of the characteristic insulin resistance of PCOS, glucose intolerance becomes evident. Provocative testing of pancreatic β-cell function may provide insights into the future risk for glucose intolerance among women with PCOS.

Key Words: Polycystic ovary syndrome; glucose tolerance; β-cell; insulin resistance.

1. INTRODUCTION

It is now well established that women with polycystic ovary syndrome (PCOS) are predisposed to develop a number of metabolic abnormalities, including impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM) (1,2). The prevalence of IGT has been estimated to be between 30 and 40%, whereas that of type 2 DM has been placed at 5–10% (1,2). Given that PCOS is thought to affect between 5 and 8% (5.7–9.1 million) of reproductive-aged women in the United States (3), it follows that at any given time an estimated 3 million women with PCOS will have IGT, whereas approximately 1 million women with PCOS will have type 2 DM. This chapter focuses on the origins of glucose intolerance in PCOS, with an emphasis on the role of the pancreatic β-cell in this process.

2. BACKGROUND

2.1. Antecedents to Glucose Intolerance in PCOS

Recent attention has focused on developmental origins of adult diseases, including both PCOS and type 2 DM. Evidence exists to support the hypothesis that low (4,5) birthweight and/or size for gestational age may lead to insulin resistance, obesity, and type 2 DM in later life. The mechanisms underlying these associations are unknown, but alterations in birthweight (reflecting in utero growth/nutritional status) have also been implicated in the pathogenesis of PCOS per se and its associated insulin resistance and glucose intolerance in some (6), but not all (7,8), studies.

Another developmental factor that has been proposed to influence the phenotypic expression of PCOS is in utero androgen exposure (see Chapter 23). In nonhuman primates, fetal exposure to high levels of androgen during early in utero development is associated with defects in insulin secretion.
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and action in adult life (9). Prenatally androgenized female rhesus monkeys exhibit glucoregulatory deficits similar to those seen in adult women with PCOS (10). Of interest, the timing of the androgen exposure appears to differentially affect glucose regulation: early androgen exposure has been associated with impaired pancreatic E-cell function, whereas exposure later in gestation appears to primarily alter insulin sensitivity. The extent to which these hormonal factors relate to the pathogenesis of PCOS in the human is not known.

It is now well documented that glucose intolerance in PCOS can occur as early as during the second decade of life (11–15). In one study, 27 adolescents with PCOS (mean age 16.7 ± 1.6 years; mean body mass index [BMI] 38.4 ± 8.8 kg/m²) had an oral glucose tolerance test (OGTT); 8 (30%) were found to have IGT, 1 (4%) had undiagnosed DM, and the remaining 18 (66%) had normal glucose tolerance (11). Studies by Arslanian et al. (13) have shown that metabolic precursors to type 2 DM (decreased first-phase insulin secretion, decreased glucose disposition index, and increased hepatic glucose production) are evident among obese adolescents with PCOS.

2.2. Relationship of Insulin Secretion to Insulin Action

Glucose intolerance typically develops when defects in insulin secretion are superimposed upon a background of insulin resistance (16). Despite the fact that women with PCOS are characteristically insulin resistant, not all develop abnormalities in glucose tolerance. It has become evident that insulin secretory defects play an important role in the propensity to develop DM in PCOS.

Insulin secretion is most appropriately expressed in relation to the magnitude of ambient insulin resistance. The product of these measures can be quantified (the so-called “disposition index”) and related as a percentile to the hyperbolic relationship for these measures (Fig. 1) established in normal subjects (17). We (18), as well as others (19), have found that a subset of subjects with PCOS has β-cell secretory dysfunction. In absolute terms, women with PCOS had normal first-phase insulin secretion compared to controls. In contrast, when first-phase insulin secretion was analyzed in

Fig. 1. Hyperbolic relationship between insulin secretion and insulin action in normoglycemic subjects studied with a frequently sampled intravenous glucose tolerance test reflecting the disposition index, based on data of Kahn et al. (17). As insulin sensitivity (S) declines, insulin secretion (acute insulin response to glucose [AIR glucose]) must increase to maintain normal glucose tolerance. Shown are mean percentiles for PCOS subjects previously reported (18) as well as mean summary data derived from the literature for women with a prior history of gestational diabetes mellitus (Former GDMs) and subjects with a first-degree relative with type 2 diabetes mellitus. (From ref. 31.)