Original Study

Fasting Glucose Changes in Adolescents with Polycystic Ovary Syndrome Compared with Obese Controls: A Retrospective Cohort Study

Asma Javed MBBS [1], Aida N. Lteif MD [1,*], Seema Kumar MD [1], Patricia S. Simmons MD [2], Alice Y. Chang MD, MSc [3]

[1] Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota
[2] Division of Pediatric and Adolescent Gynecology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota
[3] Division of Endocrinology, Department of Internal Medicine, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota

A B S T R A C T

Study Objective: To compare changes in fasting glucose among adolescents with polycystic ovary syndrome (PCOS) with those in obese adolescents without PCOS.
Design, Setting, and Participants: Retrospective cohort study of 310 adolescents with PCOS and 250 obese adolescents (age range 13 to 18 years) seen at Mayo Clinic, Rochester, MN, from 1996 to 2012.
Methods: Included for analysis were 98 adolescents with PCOS and 150 obese adolescents who had 2 or more fasting glucose measurements separated by at least 6 months. Adolescents with impaired fasting glucose (IFG) or diabetes were excluded. Multivariate models were used to assess predictors of change in fasting glucose.
Results: At diagnosis, adolescents with PCOS had lower body mass index (BMI) (kg/m^2) and older age than obese adolescents ($P < .001$). Adolescents with PCOS had shorter follow-up ($P = .02$). Baseline fasting glucose was not different between groups. Mean change in fasting glucose was 2.4 ± 9.4 mg/dL per year for PCOS and 2.2 ± 6.2 mg/dL per year for obese adolescents ($P = .83$). Significant predictors for change in fasting glucose were BMI and fasting glucose at diagnosis ($P < .01$). Within the PCOS cohort, BMI was a significant predictor for development of IFG ($P = .003$). Prevalence of hypertension increased in the PCOS cohort from baseline to follow-up ($P = .02$). PCOS and BMI were significantly associated with development of HTN in the entire cohort.
Conclusion: Adolescent girls with PCOS do not show a significant change in fasting glucose or an increased risk for the development of IFG compared with obese adolescents. BMI, not PCOS status, was the strongest predictor for changes in fasting glucose and development of IFG over time.
Key Words: Hypertension, Impaired fasting glucose, Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a condition of androgen excess, oligomenorrhea, and polycystic ovarian morphology (PCOM).[1,2] It affects 4% to 10% of adult women of reproductive age[3–5] and can be diagnosed as early as adolescence.[6] The appearance of PCOS symptoms in adolescence may predispose an individual to a more severe phenotype in terms of cardiovascular risk in adulthood. However, diagnosis in adolescence can be challenging due to the common symptoms of irregular menstrual cycles during the perimenarchal period.[7,8] The occurrence of PCOM may be even higher in asymptomatic adolescents (as many as one-third) than in asymptomatic adults, with a reported prevalence of 20% to 25%.[9,10] Earlier diagnosis identifying girls at higher risk for comorbidities in PCOS would be particularly clinically relevant as it could lead to earlier intervention and prevention strategies.

It is well established that PCOS is associated with insulin resistance independent of body weight.[11,12] Consequently, women with PCOS have a higher prevalence of type 2 diabetes and impaired glucose tolerance.[13,14] Adolescents with PCOS have a higher prevalence of glucose intolerance compared with healthy adolescent controls in cross-sectional studies.[12,15–17] Although it has been established that obese adolescents have a higher risk for developing impaired fasting glucose (IFG) over time,[18] it is not known whether PCOS by itself is associated with higher risk for the development of IFG compared with obese adolescents. Given the known interaction of obesity with PCOS, the debate about diagnostic criteria for PCOS in adolescence becomes even more clinically relevant if the risk for glucose intolerance is greater than that conferred by obesity. To determine whether adolescent girls with PCOS were at significantly greater risk for developing glucose intolerance, we sought to compare adolescents with PCOS with another group known to be at higher risk for glucose intolerance, in this case, obese adolescents.[18] Our primary objective was to compare changes in fasting glucose and development of IFG among adolescents diagnosed with PCOS between the ages of 13 and 18 years with obese adolescents without PCOS followed at a

The authors indicate no conflicts of interest.

* *Address correspondence to:* Aida N. Lteif, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Phone: +1 (507) 284-3300; fax: +1 (507) 284-0727
E-mail address: Lteif.aida@mayo.edu (A.N. Lteif).

1083-3188/$ - see front matter
http://dx.doi.org/10.1016/j.jpag.2015.01.001

single center over a time span of 15 years. As a secondary objective, we collected data on the rates of dyslipidemia and hypertension in both groups at baseline and follow-up.

Methods

This was a retrospective review of medical records of adolescent girls seen in the Department of Community Pediatric and Adolescent Medicine at Mayo Clinic, Rochester, MN. The Department of Community Pediatric and Adolescent Medicine provides preventive care and health screening to children and adolescents in Olmsted County, MN. The Division of Pediatric and Adolescent Gynecology primarily evaluates referrals for female reproductive health disorders including PCOS as well as medical examinations for contraception and reproductive health screening.

Participants

After receiving the approval of the Institutional Review Board at Mayo Clinic, Rochester, MN, adolescent girls aged 13 to 18 years with PCOS or those characterized with obesity were identified using coding and billing data. Identification of the cohorts was performed using the Mayo Clinic Life Sciences System (MCLSS), which is a complete clinical data repository containing patient demographics, diagnoses, hospital, laboratory, clinical notes, pathology, and billing data obtained from multiple clinical and hospital source systems within Mayo Clinic. Data in the MCLSS were accessed via the Data Discovery and Query Builder toolset, consisting of a web-based application that uses a unique text search engine and provides the capability to rapidly search for specific words and phrases within unstructured text documents such as clinical notes.[19] All girls seen within a 15-year period (January 1997 to December 2012) with the International *Classification of Diseases, Ninth Revision* (ICD-9) code for PCOS (256.4) or "PCOS" as a text word search term were identified. Girls characterized with obesity, but not PCOS, during a well-child visit in the Department of Community Pediatric and Adolescent Medicine were identified by searching charts for the ICD-9 code for obesity (278.0) or by a text word search for obesity.

Definitions

The PCOS status was determined by a single adolescent gynecologist using Rotterdam criteria requiring the presence of at least 2 of the 3 criteria of (i) clinical or biochemical evidence evidence of hyperandrogenism, (ii) oligo- or anovulation (defined as fewer than 9 periods per year), and (iii) PCOM.[20] During chart review, we identified girls who also met the National Institutes of Health (NIH) criteria for PCOS[21] requiring the presence of both oligoovulation and hyperandrogenism. Determination of PCOM was based on adult criteria of the presence of 12 or more 2- to 9-mm follicles in each ovary or ovarian volume greater than 10 mL as defined by Rotterdam criteria.[20] Subjects with untreated hypothyroidism, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome, pregnancy, androgen-secreting tumors, or a condition as the cause of hyperandrogenism were excluded.

Obesity was defined as a body mass index (BMI) at or greater than the 95th percentile on Centers for Disease Control and Prevention age- and sex-specific growth charts.[22]

Subjects with a hormonal or genetic diagnosis of obesity or who were pregnant were excluded. The definition of IFG was glucose between 100 and 125 mg/dl, hypertension (HTN) was defined as a systolic blood pressure (SBP) greater than120 mm Hg on 2 consecutive visits, hypertriglyceridemia as triglycerides of 150 mg/dL or greater, and low levels of high-density lipoprotein (HDL) as less than 50 mg/dL.[23,24]

Procedures and Measures

We used a standardized abstraction form for data collection. For each medical record, we identified the first visit in which the diagnosis of PCOS or obesity was identified (baseline visit) as well as the last follow-up visit with any Mayo Clinic provider. We collected information regarding age, PCOS diagnostic criteria, age at menarche, cardiovascular risk factors (hypertension, diabetes, family history of diabetes), BMI, and systolic and diastolic blood pressure at baseline and follow-up visits. Oral contraceptive pill (OCP) use was also recorded. The same information was retrieved for obese adolescents with the exception of PCOS diagnostic criteria. With regard to biochemical and ultrasound evaluations, fasting glucose was noted for the baseline and follow-up visits along with total cholesterol, triglycerides, HDL, and low-density lipoprotein. In addition, total testosterone measurements and ovarian ultrasound information such as ovarian volume and number of follicles, if available, were recorded for the PCOS cohort. All biochemical laboratory measures were obtained in the Mayo Clinic Laboratories using standard automated colorimetric enzymatic assays (Roche Diagnostics, Indianapolis, IN) with the exception of testosterone, which was measured using high-throughput liquid chromatography (Hamilton Robotics Inc, Reno, NV), and glucose, which was measured using a photometric rate reaction (Roche Diagnostics). Fasting glucose was obtained using a standard minimum 12 hours of fasting, which was verified on all samples. Samples obtained less than 12 hours since last meal were not reported as fasting.

Statistical Analyses

We compared the means of baseline characteristics between PCOS and obese adolescents; for variables not distributed normally, we used a *t* test and a Wilcoxon signed rank test to compare medians. Categorical variables were compared using χ^2 analysis. We used a χ^2 test to compare the proportion of girls meeting criteria for IFG both before subject selection and at follow-up visit for the 2 cohorts of PCOS and obese adolescents. Linear and logistic regression models were created in a stepwise fashion using JMP 9.0.1 (SAS Institute Inc, Cary, NC) to identify predictors of change in fasting glucose over time, change in SBP, and development of IFG. We used stepwise and clinical variables known to affect the outcomes.