Diabetes mellitus and insulin resistance in mothers, fathers, sisters, and brothers of women with polycystic ovary syndrome: a systematic review and meta-analysis

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Objective(s): To analyze whether first-degree relatives (FDR) of patients with polysystic ovary syndrome (PCOS) have an increased risk of insulin resistance and glucose intolerance.
Design: Systematic review and meta-analysis.
Setting: None.
Patient(s): Parents and siblings of women with and without PCOS.
Intervention(s): Search of PubMed database from 1960 to September 2017 with cross-checking of references of relevant articles in English.
Main Outcome Measure(s): Prevalence of type 2 diabetes mellitus (T2DM) and impaired glucose tolerance, and levels of fasting insulin, 2-hour insulin levels, and homeostatic model assessment insulin resistance (HOMA IR).
Result(s): Our search retrieved 4,796 articles of which 19 were included. The prevalence of T2DM was significantly increased in mothers and fathers of PCOS probands (rate ratio [RR] 2.43; 95% confidence interval [CI], 1.58–3.75, and RR 2.27; 95% CI, 1.25–4.12). Moreover, the fasting insulin (in mothers, fathers, and sisters) and HOMA IR (in mothers, fathers, and sisters) levels were statistically significantly higher in parents and siblings of PCOS patients. The sisters (RR 1.34; 95% CI, 0.59–3.03) and brothers (RR 1.51; 95% CI, 0.63–3.62) had a higher prevalence of T2DM than the control subjects, but the difference was not statistically significant.
Conclusion(s): Our meta-analysis provides quantitative evidence demonstrating clustering of T2DM and insulin resistance in the parents and siblings of PCOS probands.
Systematic Review Registration Number: PROSPERO 2016 CRD42016048551. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Diabetes mellitus, first-degree relatives, insulin resistance, meta-analysis, polycystic ovary syndrome, systematic review

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Polycystic ovary syndrome (PCOS) affects between 4% and 19% of reproductive-age women (1–3), depending on the diagnostic criteria used for definition of the syndrome (4–6). The condition is associated with both reproductive (hyperandrogenism, oligo/amenorrhea, infertility, increased pregnancy complications) and metabolic (insulin resistance, prediabetes, and type 2 diabetes mellitus [T2DM]) disturbances (4,7–12). The etiology of PCOS is unknown, but there is strong evidence that complex interactions among genetic, ethnic, environmental, and lifestyle factors contribute to the complex pathophysiology of this heterogeneous syndrome (8, 13).

Polycystic ovary syndrome is a highly heritable disease (14), with a

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concordance of 80% among twins and an increased prevalence of reproductive abnormalities in first-degree relatives (FDRs). In addition to the high heritability of the reproductive features of PCOS, many studies demonstrated an increased prevalence of metabolic abnormalities in FDRs. Norman et al. (15) reported that increased insulin levels were common (69%) among the FDRs of five probands with PCOS. Insulin resistance was confirmed by subsequent studies in the FDRs of PCOS patients (16–25). Moreover, most of the family studies of PCOS have shown that impaired glucose tolerance (IGT) and T2DM are more common in the FDRs of PCOS patients than in controls (17–20), although others reported no increase in the prevalence of T2DM in PCOS families (25, 26). Therefore, we performed a systematic review and meta-analysis to determine the prevalence of T2DM, IGT, and insulin resistance in the FDRs of PCOS patients.

MATERIALS AND METHODS

Search Strategy

The following medical subject headings, key words, and their combinations were used to search PubMed database from 1960 to September 2017: polycystic ovary syndrome, family, parents, mothers, fathers, sibling, diabetes mellitus, glucose intolerance, insulin resistance, first-degree relatives, mothers, fathers, sisters, brothers, impaired glucose tolerance, and fasting insulin. Two investigators (B.Y. and B.O.Y.), who were not blinded to the names of the authors or source of the publications, independently screened the results of the primary search. Full text articles were obtained for the studies fulfilling the inclusion criteria. Any disagreement between the investigators (B.Y. and B.O.Y.) was resolved by discussion and consensus. All articles published before September 2017 were considered for eligibility. The reference lists of the relevant studies were also hand searched to identify any relevant publications that had been missed in the electronic search. The investigators were contacted for additional data where required. Due to the substantial number of overlapping patients, data from the 11 studies by Dunaif and Legro (16,21–24,27–32) were combined for analysis as a single study.

Selection Criteria

We included articles if [1] they compared the prevalence of T2DM and/or IGT, the fasting and 2-hour insulin levels, and/or homeostatic model assessment insulin resistance (HOMA IR) between parents and siblings of women with PCOS with controls; [2] the PCOS in the probands was diagnosed by criteria specified by the National Institutes of Health (6), the European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine (ESHRE/ASRM, 2004) and/or the Androgen Excess and PCOS Society (4, 5); [3] they were published in English; and [4] they were published in full text formate. Controls were defined as age-comparable, sex-matched individuals without a history of prior T2DM or IGT who were not taking any antihyperglycemic medications.

Data Extraction

From all included studies, we extracted the general study characteristics (authors, publication date, study design, and period), the study population (sample size, age, body mass index [BMI], study location, and ethnicities), the selection procedures for FDRs of PCOS probands and their controls, the criteria used for diagnosis of PCOS, IGT, and T2DM, and the other parameters regarding fasting insulin, 2-hour insulin during oral glucose tolerance test (OGTT), and/or HOMA IR (where appropriate). If duplicate publications existed or secondary publications with overlapping patient populations were detected, we selected the appropriate data for inclusion after contacting the investigators. Two reviewers (B.Y. and B.O.Y.) extracted the data from all articles with an inter-reviewer agreement of 0.91. Any disagreement was resolved by consensus.

We calculated HOMA-IR as Insulin (μU/mL) $\times$ Glucose (mg/dL)/405 (33). We defined IGT and T2DM by physician diagnosis or by OGTT measures according to the World Health Organization (WHO) (34) and American Diabetes Association (ADA) (35) criteria.

Outcomes of Interest

The primary end points of this study were the rate ratio (RR) of prevalence of T2DM and IGT. The secondary end points were fasting insulin, 2-hour insulin levels, and HOMA IR.

Risk of Bias Assessments

Each original study was assessed by two authors (B.Y. and P.V.) using the National Heart, Long, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross Sectional Studies. Disagreements were resolved by consulting a third author (B.A.).

Statistical Analysis

Dichotomous data from each of the eligible studies were combined for meta-analysis using the Mantel/Haenszel model. The results were expressed as rate ratio (RR) with 95% confidence intervals (CI). Continuous data from each of the eligible studies were combined for meta-analysis using the inverse variance method. The results were expressed with standardized mean difference (SMD) and 95% CI. Study-to-study variation was assessed by using the chi-square statistic. The hypothesis tested was that the studies are all drawn from the same population—that is, from a population with the same effect size. A two-tailed $P<.05$ was required to statistically significant. A fixed effects model was used when there was no statistically significant heterogeneity between individual study results; otherwise, a random effects model was applied. All results were combined for meta-analysis with Revman Software (version 5.2, the Nordic Cochrane Centre; Cochrane Collaboration 2012).

RESULTS

Characteristics of Included and Excluded Studies

Our systematic retrieval process yielded 4,796 studies, as shown in Figure 1. We excluded 4,734 studies based on their