ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Metabolic syndrome, hypertension, and hyperlipidemia in mothers, fathers, sisters, and brothers of women with polycystic ovary syndrome: a systematic review and meta-analysis

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Objective: To provide an evidence-based assessment of metabolic syndrome, hypertension, and hyperlipidemia in first-degree relatives of women with polycystic ovary syndrome (PCOS).
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Mothers, fathers, sisters, and brothers of women with and without PCOS.
Intervention(s): An electronic-based search with the use of PubMed from 1960 to June 2015 and cross-checked references of relevant articles.
Main Outcome Measure(s): Metabolic syndrome, hypertension and dyslipidemia, and surrogate markers, including systolic blood pressure (BP), diastolic BP, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.
Result(s): Fourteen of 3,346 studies were included in the meta-analysis. Prevalence of the following was significantly increased in relatives of women with PCOS: metabolic syndrome (risk ratio [RR] 1.78 [95% confidence interval 1.37, 2.30] in mothers, 1.43 [1.12, 1.81] in fathers, and 1.50 [1.12, 2.00] in sisters), hypertension (RR 1.93 [1.58, 2.35] in fathers, 2.92 [1.92, 4.45] in sisters), and dyslipidemia (RR 3.86 [2.54, 5.85] in brothers and 1.29 [1.11, 1.50] in fathers). Moreover, systolic BP (mothers, sisters, and brothers), total cholesterol (mothers and sisters), low-density lipoprotein cholesterol (sisters), and triglycerides (mothers and sisters) were significantly higher in first-degree relatives of PCOS probands than in controls.
Conclusion(s): Our results show evidence of clustering for metabolic syndrome, hypertension, and dyslipidemia in mothers, fathers, sisters, and brothers of women with PCOS.
Systematic Review Registration Number: PROSPERO 2016 CRD42016048557. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Dyslipidemia, first-degree relatives, hypertension, metabolic syndrome, polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age. Depending on the diagnostic criteria used, PCOS affects between 4% and 19% of reproductive-aged women (1–6). The etiology of PCOS remains largely unknown, but the syndrome is now considered as a complex disorder with both genetic and environmental influences (7). Polycystic ovary syndrome is a heterogeneous endocrine disorder and associated with both reproductive (hyperandrogenism, oligo/amenorrhea, infertility, increased pregnancy complications) and metabolic abnormalities (dyslipidemia, metabolic syndrome [MetS], and coronary heart disease) (8–12).

Several studies on metabolic disturbances in women with first-degree relatives with PCOS have been published. Moreover, the prevalence of MetS, hypertension, dyslipidemia, and additional metabolic parameters, including blood pressure (BP) and lipid profiles, was investigated in family members of women with PCOS. However, individual studies focused on different abnormalities, and the majority is limited, with relatively small sample sizes preventing definitive conclusions. The present systematic review and meta-analysis aims to provide a comprehensive overview of the prevalence of MetS, hypertension, dyslipidemia, and other relevant surrogate abnormalities in first-degree relatives of women with PCOS.

MATERIALS AND METHODS

Search Strategy

PubMed (from 1960 to June 2015) was searched using the following MeSH terms and keywords: polycystic ovary syndrome, family, parent, mother, father, sibling, hypertension, dyslipidemias, metabolic syndrome, blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

Two independent authors (B.Y. and B.O.Y.) who were not blinded to the authors or source of publication reviewed reference lists from the primary search. Studies that were not published in English or did not include a control group were excluded. Reference lists of included studies were manually screened to identify other relevant publications.

Any disagreement was resolved by consensus after discussion between the two authors.

Inclusion Criteria

Studies comparing the prevalence of MetS, hypertension, and dyslipidemia and systolic BP, diastolic BP, total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides between mothers, fathers, sisters, and brothers of women with PCOS (referred to subsequently as "PCOS mothers," "PCOS fathers," etc.) and their controls were included. One of the following diagnostic criteria specified by the National Institutes of Health (4), the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (5), and/or the Androgen Excess Society (6) was required for diagnosis of PCOS in probands. Controls were reproductive-aged women without PCOS.

Data Extraction

Study characteristics (author, publication date, study design, and period), study population (sample size, age, body mass index [BMI], study location, and ethnicity), selection criteria for first-degree relatives of PCOS probands and their controls, criteria used for PCOS, MetS, hypertension, and dyslipidemia diagnosis, and other parameters regarding systolic BP, diastolic BP, Total-C, LDL-C, HDL-C, and triglycerides were extracted from all included studies. When duplicate publications or secondary publications with overlapping patient populations were detected, the authors were contacted to collect non-overlapping data for inclusion in the meta-analysis. Two reviewers (B.Y. and B.O.Y.) extracted the data from all articles, with an inter-reviewer agreement of approximately 0.93. Any disagreement was resolved by consensus.

Metabolic syndrome was diagnosed according to the authors of the articles, the National Cholesterol Education Program Adult Treatment Panel III guidelines (2001), or American Heart Association criteria (13). Controls were defined as age-comparable sex-matched individuals without a history of prior type 2 diabetes mellitus or impaired glucose tolerance and not taking any antihyperglycemic, antihypertensive medications or any medications for dyslipidemia.

Some of the studies by Dunaif, Legro, and colleagues (14–17) used data from the National Health and Nutrition Examination Survey (NHANES) for control data. In the original articles, control subjects were of comparable age and BMI. Because it was unclear which control subjects were used for individual studies, and the NHANES data used were not available, the age range was selected as reported in each of the articles. For the PCOS sisters, comparable age for control women was defined as age between 18 and 47 years (14). For the PCOS mothers, comparable age for control women was defined as age >40 years (17).

For the PCOS brothers, comparable age for control men was defined as age between 16 and 48 years (18, 19). For PCOS fathers, comparable age was defined as age >40 years (16).

Outcome Measures

The primary endpoint was the risk ratio (RR) of MetS, hypertension, and dyslipidemia, and secondary endpoints involved systolic BP, diastolic BP, Total-C, LDL-C, HDL-C, and triglycerides in first-degree relatives compared with controls.

Risk of Bias Assessments

Each original study was assessed by two authors (B.Y. and P.V.) using the National Heart, Lung, 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. Results were expressed as RR with 95% confidence intervals (CIs). Continuous data from each of the eligible studies