Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis

Daria Lizneva, M.D., Ph.D.,[a,b,c] Richard Kirubakaran, Ph.D.,[d] Kateryna Mykhalchenko, M.D.,[e] Larisa Suturina, M.D., Ph.D.,[c] Chernukha Galina, M.D., Ph.D.,[f] Michael P. Diamond, M.D.,[a] and Ricardo Azziz, M.D., M.P.H.[a,g]

[a] Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, Georgia; [b] Medical Company IDK, Samara, Russian Federation; [c] Department of Reproductive Health Protection, Scientific Center of Family Health and Human Reproduction, Irkutsk, Russian Federation; [d] South Asian Cochrane Network and Centre, Professor B.V. Moses and ICMR Advanced Centre for Research and Training in Evidence Informed Health Care, Christian Medical College, Vellore, India; [e] Maimonides Medical Center, Department of Obstetrics and Gynecology, Maimonides Medical Center, Brooklyn, New York; [f] Department of Gynecological Endocrinology, Scientific Center for Obstetrics, Gynecology and Perinatology, Moscow, Russian Federation; and [g] Department of Medicine, Medical College of Georgia, Augusta University, Augusta, Georgia

Objective: To compare the prevalence of polycystic ovary syndrome (PCOS) phenotypes and obesity among patients detected in referral versus unselected populations.

Design: Systematic review and meta-analysis.

Setting: Not applicable.

Patient(s): Thirteen thousand seven hundred ninety-six reproductive-age patients with PCOS, as defined by the extended 2003 Rotterdam criteria.

Intervention(s): Review of PUBMED, EMBASE, and Cochrane Library, 2003–2016. Only observational studies were included. Data were extracted using a web-based, piloted form and combined for meta-analysis.

Main Outcome Measure(s): PCOS phenotypes were classified as follows: phenotype A, clinical and/or biochemical hyperandrogenism (HA) + oligo-/anovulation (OA) + polycystic ovarian morphology (PCOM); phenotype B, HA+OA; phenotype C, HA+PCOM; and phenotype D, OA+PCOM.

Result(s): Forty-one eligible studies, reporting on 43 populations, were identified. Pooled estimates of detected PCOS phenotype prevalence were consequently documented in referral versus unselected populations, as [1] phenotype A, 50% (95% confidence interval [CI], 46%–54%) versus 19% (95% CI, 13%–27%); [2] phenotype B, 13% (95% CI, 11%–17%) versus 25% (95% CI, 15%–37%); [3] phenotype C, 14% (95% CI, 12%–16%) versus 34% (95% CI, 25–46%); and [4] phenotype D, 17% (95% CI, 13%–22%) versus 19% (95% CI, 14%–25%). Differences between referral and unselected populations were statistically significant for phenotypes A, B, and C. Referral PCOS subjects had a greater mean body mass index (BMI) than local controls, a difference that was not apparent in unselected PCOS.

Conclusion(s): The prevalence of more complete phenotypes in PCOS and mean BMI were higher in subjects identified in referral versus unselected populations, suggesting the presence of significant referral bias. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, phenotypes, prevalence, epidemiology, meta-analysis, referral bias

Discuss: You can discuss this article with its authors and with other ASRM members at

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Reprint requests: Ricardo Azziz, M.D., M.P.H., Department of Obstetrics and Gynecology, Augusta University, 1120 15th Street, CB–2209, Augusta, Georgia 30912 (E-mail: razziz@augusta.edu).

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Polycystic ovary syndrome (PCOS) is a highly prevalent metabolic-hyperandrogenic-ovulatory disorder that affects 4.8%–19.9% of women (1–3), depending on criteria, and is associated with a high frequency of metabolic dysfunction (4), ovulatory infertility (5), preterm birth, perinatal mortality (6), and endometrial cancer (7). Recent genetic studies (8–10) and historical evidence suggest the persistence of this disorder across millennia, despite its potential reproductive disadvantages, which represent an evolutionary paradox (11). The presentation of PCOS can be categorized into discrete phenotypes, depending on the features used in the diagnostic criteria: [1] phenotype A, clinical and/or biochemical hyperandrogenism (HA) and oligo-/anovulation (OA) and polycystic ovarian morphology at ultrasound (PCOM); [2] phenotype B, HA with OA only; [3] phenotype C, HA with PCOM only; and [4] phenotype D, OA with PCOM only (12). However, we should note that our understanding of PCOS phenotypes and their distribution is primarily based on studies of patients diagnosed in the clinical setting.

We previously reported on evidence of referral bias in PCOS (13), in a study using of two prospective cohorts: [1] patients with PCOS referred for outpatient medical assessment (referral setting) and [2] women with PCOS identified through the screening of a population undergoing a mandatory preemployment physical at the same institution (unselected setting). This study used National Institutes of Health (NIH) 1990 criteria (14) in the diagnosis of PCOS. We observed that patients with PCOS diagnosed in the referral setting had a greater mean body mass index (BMI), greater prevalence of obesity, and higher serum androgens and a hirsutism score than women with PCOS detected in the medically unselected population (13). In addition, phenotypic distribution demonstrated a higher prevalence of the more complete phenotype in referral compared with unselected PCOS (13).

Our observation that PCOS phenotype differs if patients are studied in the clinical (i.e., referred or biased) environment versus in epidemiologic studies of medically unbiased (i.e., unselected) populations may have a significant impact on our understanding of PCOS phenotype as a whole and on our understanding of the evolutionary development and persistence of PCOS. As PCOS appears to represent an evolutionary paradox (11, 15), much of our understanding of the evolutionary origins of this pervasive disorder will arise from its presentation in the general population.

As our original study was performed in a well-defined population located in the southeastern region of the United States using NIH 1990 diagnostic criteria for PCOS (14), we now aim to expand our analysis to include other populations worldwide, using systematic review and meta-analysis. We also focused on those studies that used the Rotterdam 2003 criteria (16, 17) to ensure the inclusion of the greatest variation in phenotypes.

MATERIALS AND METHODS

This study was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (18). Official institutional review board approval was not required because data sets were extracted from previously published studies. The protocol for the current study was specified in advance and made available on the Center for Reviews and Dissemination website (registration no. CRD42015015710); extracted data are available on the Systematic Review Data Repository (http://srdr.ahrq.gov/projects/445).

Outcomes and Study Eligibility Criteria

The primary outcome of interest was the prevalence of PCOS phenotypes. Phenotypes A–D were classified by extended Rotterdam criteria as described above (12). All eligible studies reported the prevalence of these four PCOS phenotypes, or at a minimum provided sufficient data to calculate the individual phenotype prevalence. Secondary outcomes of interest included mean difference in BMI compared with healthy subjects without PCOS reported within the publication (i.e., "local" controls).

We used the following criteria for study inclusion, based on type of publication, study design, population characteristics, and outcome measures:

- Types of publications: we included only full-text reports and did not consider abstracts.
- Study design: we included only observational studies (case-control, cohort, cross-sectional). To study secondary outcomes, we considered case-control studies, where controls were not BMI matched.
- Types of population: we included reproductive-age patients with PCOS (approximate limits 18–49 years), defined by Rotterdam 2003 criteria. This review was limited to include only those studies in which investigators or clinicians actually saw the patients. To avoid overlapping data, we considered the most recent or those that included more complete methods used to define PCOS phenotypes from centers that reported progressively larger cohorts over time. Studies were excluded if they reported on referral populations with less than 100 total PCOS subjects, if the number of patients in each phenotypic group was predetermined a priori, or if PCOS symptoms were associated with any iatrogenic cause (i.e., valproate exposure). We included studies that enrolled 100 or more subjects in the referral population for two reasons: [1] to include studies from investigators experienced with the disorder, that is, if the author(s) of the report could not garner even 100 subjects in a consecutive clinical study, the likelihood that they would be experts in the field of PCOS would be low; and [2] to decrease intercenter variance by including only reports with a significant number of subjects.

Alternatively, to estimate the prevalence of PCOS phenotypes in unselected settings, we reviewed all published studies on PCOS prevalence and identified those reporting the distribution of PCOS phenotypes. The restriction in number of PCOS subjects did not apply to PCOS detected unselected populations, as the number of PCOS subjects detected in these populations is the variable of interest, by definition. We intentionally framed our study selection criteria to primarily