The pressing need for standardization in epidemiologic studies of PCOS across the globe

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The pressing need for standardization in epidemiologic studies of PCOS across the globe

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ABSTRACT

The polycystic ovary syndrome (PCOS) is a common and important complex endocrine metabolic disorder affecting women mainly in the reproductive age. The prevalence of the disorder varies depending on the epidemiologic design and criterion used to study the disease. This variation in methodology and subsequent effect on epidemiologic estimate makes it difficult to compare prevalences and phenotypes across geographical areas and assess the effect of cultural and racial variations on PCOS phenotypes. Overall, there is an urgent need for a globally accepted standardized protocol for epidemiologic studies of PCOS, which will maximize the comparability of studies around the globe. To address this issue the Androgen Excess and PCOS Society, Inc. has designated an expert Task Force to draft recommendations to guide epidemiologic research worldwide. Once completed, the use of such recommendations will enable epidemiologists to the effects of geographical and cultural variations of PCOS prevalence and assist in determining the phenotype-genotype associations in the disorder. Further, it will assist in developing informed, and thus effective, public health policy. In essence, the need to standardize epidemiologic studies across the globe is pressing and urgent.

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine metabolic complex genetic trait affecting women and is most apparent in the reproductive age. The syndrome is characterized by chronic oligo-ovulation (OA), biochemical and/or clinical hyperandrogenism (HA) and polycystic ovarian morphology (PCOM). PCOS impacts negatively reproductive function (infertility, recurrent pregnancy loss, etc.) and predisposes to adverse obstetric outcomes, such as gestational diabetes mellitus, pre-eclampsia, fetal macrosomia, and perinatal morbidity and mortality. There is also a direct link between PCOS and endometria carcinoma, type-II diabetes mellitus (T2DM), and several other metabolic disorders and possibly cardiovascular disease in later years. Dyslipidemia is more common in women with PCOS, with patients demonstrating higher levels of low-density lipoprotein (LDL)-cholesterol and triglycerides, and lower levels of high-density lipoprotein (HDL)-cholesterol compared with women without the disorder.

While PCOS is most obvious clinically in reproductive age women, emerging evidence suggests that prepubertal girls and postmenopausal women may also have related symptoms. Postmenopausal women are at increased risk of T2DM and possibly cardio-metabolic complications though symptoms attributable to excess androgen may improve or even disappear. PCOS in children may manifest as premature pubarche while menstrual irregularity and clinical evidence of hyperandrogenemia may be the main signs and symptoms in the adolescent group.

PCOS prevalence is affected by variations in methodology and research design

Globally, the reported prevalence of PCOS varies from 5% to 20% in various studies, depending on which diagnostic criterion was used (or more precisely which phenotypes were included, see below), how the study population was identified, the methods used to define each feature of the criterion, how complete were the phenotypic assessments, and the recruitment process of the study population [1]. Of note, most if not all studies of PCOS prevalence are from North America, Europe, the Middle East, Southern Asia, and Australia; there is no significant data as of yet from South America, Russia (i.e. Northern Asia), the island countries of Oceania (Melanesia, Micronesia, and Polynesia) and Africa [2]. In fact, our group is working to address the paucity of data arising from the African continent. These variances in methodology create great degree of uncertainty around prevalence and phenotype of PCOS, hampering the comparability of studies; the interpretation of genetic analyses; the ability to detect the impact of race/ethnicity, environment, socioeconomics, and diet and nutrition, among other factors; the estimation of economic burden; and the development of informed and effective public health policy.

Where it has been studied so far, the prevalence of the disease has been fairly constant at 5–9% in most parts of the world when using the stricter 1990 NIH Criterion, which includes two of the PCOS phenotypes (Phenotype A: OA + HA + PCOM and...
Methodologic issues in defining each feature of the criterion

The methods used to define each feature of the criterion are critical in ensuring the complete detection of the disorder. How OA, HA and PCOM is defined will play a significant role in determining the prevalence of PCOS observed. For example, when Ovulation (OA + HA) was defined as the presence of at least 10 ovulatory cycles per year, the prevalence of PCOS among women aged 18 to 44 years was 11%. However, when the definition was changed to include women who had experienced at least 15 ovulatory cycles per year, the prevalence of PCOS increased to 15%. These findings highlight the importance of selecting an appropriate definition for each feature of the criterion to ensure accurate and consistent classification of PCOS patients.

To determine the appropriate definition for each feature, it is important to consider both the clinical and epidemiological aspects of PCOS. For example, the definition of OA should take into account factors such as age, body mass index, and the presence of other reproductive disorders. Similarly, the definition of HA should consider factors such as ethnicity, body mass index, and the presence of other medical conditions. Additionally, the definition of PCOM should consider factors such as the size and shape of the ovaries, the number of follicles, and the presence of associated conditions.

In conclusion, the methods used to define each feature of the criterion are critical in ensuring the complete detection of PCOS. Selecting appropriate definitions for OA, HA, and PCOM is important to ensure accurate and consistent classification of PCOS patients. Future research should focus on developing and validating standardized definitions for each feature to improve the accuracy and consistency of PCOS diagnosis.
ovarian morphology as has been used for determining ‘abnormal’ facial or body terminal hair growth or androgen levels in the circulation [6].

And not only do epidemiologic studies of PCOS suffer from the use of different criteria, different recruitment schemes, and even more variability in phenotyping, but the diagnostic scheme for PCOS itself advocates against a complete assessment of these subjects. ‘Healthy controls’ in a population are often diagnosed simply by the absence of a history of irregular menstruation and medical problems, and the absence of clinical signs of HA on physical exam. Alternatively, diagnosing a woman with PCOS requires many more tests. It requires that subjects undergo blood testing to exclude thyroid dysfunction and hyperprolactinemia, and 17-hydroxyprogesterone to exclude 21-hydroxylase deficient nonclassic adrenal hyperplasia. It may even require additional tests to exclude Cushing’s syndrome, congenital adrenal hyperplasia, or androgen-secreting neoplasms. As mentioned, full phenotyping may also require measurement of luteal progesterone levels and/or transvaginal ultrasonography. Hence, there is a much higher likelihood that subjects with PCOS will not be less willing to complete their evaluation, which may take multiple visits and invasive tests, than controls, yielding many more ‘incompletely assessed’ subjects with PCOS than controls (and consequently biasing against the PCOS diagnosis). For example, in a large population-based study of medically unselected women of reproductive age in Tehran, Iran, Tehrani et al reported that, more than a third of their cases would have been undiagnosed or misdiagnosed had they not assessed the participants for subclinical menstrual dysfunction or biochemical hyperandrogenism [7]. We have addressed this evaluation bias by including all subjects in our analysis, whether completely or incompletely evaluated, and assigning those women who were incompletely evaluated a ‘weight’ for the diagnosis of PCOS based on the results in similarly phenotyped individuals who were completely assessed [8].

Conclusions

Overall, these issues strongly indicate that epidemiologic studies of PCOS worldwide vary greatly in methodology and outcome, and comparisons can only be inferred. Overall, there is an urgent need for a globally accepted standardized protocol for epidemiologic studies of PCOS, which will maximize the comparability of studies around the globe. To address this issue the Androgen Excess & PCOS Society, Inc. has designated an expert Task Force to draft recommendations to guide epidemiologic research worldwide. Once completed, the use of such recommendations will enable epidemiologists to the effects of geographical and cultural variations of PCOS prevalence, and assist in determining the phenotype-genotype associations in the disorder. Further, it will assist in developing informed, and thus effective, public health policy. In essence, the need to standardize epidemiologic studies across the globe is pressing and urgent.

Disclosure statement

R. A. consults for Ansh Labs, Longitude Capital, Spruce Biosciences, and Medtronics. He serves on the advisory board of Martin PET Imaging. No potential conflicts of interest was reported for any of the remaining authors.

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