ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Cardiovascular and metabolic profiles amongst different polycystic ovary syndrome phenotypes: who is really at risk?

Nadine M. P. Daan, M.D.,[a] Yvonne V. Louwers, M.D., Ph.D.,[d] Maria P. H. Koster, M.D., Ph.D.,[a] Marinus J. C. Eijkemans, Ph.D.,[a,b] Yolanda B. de Rijke, Ph.D.,[e] Eef W. G. Lentjes, Ph.D.,[c] Bart C. J. M. Fauser, M.D., Ph.D.,[a] and Joop S. E. Laven, M.D., Ph.D.[d]

[a] Woman and Baby Division, Department of Reproductive Medicine and Gynecology; [b] Julius Center for Health Sciences and Primary Care; and [c] Department of Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht; and [d] Division of Reproductive Medicine, Department of Obstetrics and Gynecology; and [e] Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, the Netherlands

Objective: To study the cardiometabolic profile characteristics and compare the prevalence of cardiovascular (CV) risk factors between women with different polycystic ovary syndrome (PCOS) phenotypes.
Design: A cross-sectional multicenter study analyzing 2,288 well phenotyped women with PCOS.
Setting: Specialized reproductive outpatient clinic of the Erasmus Medical Center Rotterdam and the University Medical Center Utrecht, the Netherlands.
Patient(s): Women of reproductive age (18–45 years) diagnosed with PCOS.
Intervention(s): Women suspected of oligo- or anovulation underwent a standardized screening consisting of a systematic medical and reproductive history taking, anthropometric measurements, and transvaginal ultrasonography followed by an extensive endocrinologic/metabolic evaluation.
Main Outcome Measure(s): Differences in cardiometabolic profile characteristics and CV risk factor prevalence between women with different PCOS phenotypes, i.e., obesity/overweight, hypertension, insulin resistance, dyslipidemia, and metabolic syndrome.
Result(s): Women with hyperandrogenic PCOS (n = 1,219; 53.3% of total) presented with a worse cardiometabolic profile and a higher prevalence of CV risk factors, such as obesity and overweight, insulin resistance, and metabolic syndrome, compared with women with nonhyperandrogenic PCOS. In women with nonhyperandrogenic PCOS overweight/obesity (28.5%) and dyslipidemia (low-density lipoprotein cholesterol $\geq$3.0 mmol/L; 52.2%) were highly prevalent.
Conclusion(s): Women with hyperandrogenic PCOS have a worse cardiometabolic profile and higher prevalence of CV risk factors compared with women with nonhyperandrogenic PCOS. However, all women with PCOS should be screened for the presence of CV risk factors, since the frequently found derangements at a young age imply an elevated risk for the development of CV disease later in life. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, cardiovascular risk

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/daann-cardiovascular-metabolic-pcos-phenotypes/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received April 25, 2014; revised July 3, 2014; accepted August 1, 2014.
N.M.P.D. has nothing to disclose. Y.V.L. has nothing to disclose. M.P.H.K. has nothing to disclose. M.J.C.E. has nothing to disclose. Y.B.d.R. has nothing to disclose. E.W.G.L. has nothing to disclose. B.C.J.M.F. has received fees and grant support from Andromed, Ardana, COGI, Euroscreen, Ferring, Genovum, Gedeon-Richter, Merck Serono, MSD, Organon, Ova-Science, Pantharei Bioscience, PregLem, Roche, Schering, Schering Plough, Serono, Uteron, Watson Laboratories, and Wyeth. J.S.E.L. has received unrestricted research grants from Ferring, Merck-Serono, Merck Sharpe & Dome, Organon, Shering Plough, and Serono.
Reprint requests: Nadine M. P. Daan, M.D., University Medical Center Utrecht, PB 85500, 3584 CX Utrecht, the Netherlands (E-mail: n.m.p.daan@umcutrecht.nl).

Fertility and Sterility® Vol. ■, No. ■, ■ 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.08.001

The polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. The prevalence of PCOS has been estimated to be 6%–10% depending on which diagnostic criteria are used (1). Ever since Stein and Leventhal first described a series of women with oligo- or amenorrhea and polycystic ovaries in 1935, there has been an ongoing debate regarding

the legitimacy of various criteria used to diagnose PCOS (2). In the absence of a universally accepted definition, the 1990 National Institute of Health (NIH) criteria were introduced, delineating PCOS as a syndrome of both chronic anovulation and clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies) (3).

During subsequent years the broad and heterogeneous clinical expression of PCOS gave rise to the perception that no single criterion should be mandatory for diagnosing PCOS, resulting in the 2003 Rotterdam diagnostic criteria. According to that consensus, PCOS should be diagnosed when at least two of the following criteria are present: ovulatory dysfunction (oligo- or amenorrhea), hyperandrogenism (either biochemical or clinical being hirsutism), and polycystic ovarian morphology (PCOM) (4). With the introduction of these broadened criteria, women with merely PCOM and normogonadotropic anovulation were added to the heterogeneous group of women with PCOS, resulting in a considerable increase in the prevalence of PCOS (5).

Over the years, evidence has accumulated that in women with PCOS, the presence of hyperandrogenism is associated with an increased prevalence of metabolic disturbances (6–10). Such an association has been established by numerous studies and meta-analyses comparing women with PCOS with non-PCOS control women. Therefore, in response to the introduction of the Rotterdam criteria, it has been postulated that PCOS should indeed be considered to be primarily a disorder of hyperandrogenemia (11). It may even be justified to distinguish the hyperandrogenic PCOS phenotype as a separate entity, given its profound metabolic implications, and assign this phenotype with a new name, because the current denomination is unsatisfying for both clinician and patients (12, 13).

It remains to be elucidated to what extent women presenting with ovarian dysfunction and polycystic ovarian morphology face similar long-term health risks compared with "classic" hyperandrogenic women with PCOS. At the most recent NIH Evidence-Based Methodology Workshop on PCOS in December 2012, an independent expert panel recommended maintaining the broad diagnostic Rotterdam criteria, along with the use of distinct phenotyping in future research related to PCOS. Furthermore, the panel underlined several future research priorities, one of which being the determination of the prevalence of cardiometabolic implications of the individual PCOS phenotypes, as was also stressed at the earlier European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine–endorsed third PCOS consensus meeting in Amsterdam (14, 15).

The aim of the present study was to create insight in the cardiometabolic profile and cardiovascular (CV) risk factor prevalence within a very large population of rigorously phenotyped PCOS women, distinguishing hyperandrogenic PCOS subphenotypes for comparison with nonhyperandrogenic PCOS and creating a clear insight in the cardiometabolic profile characteristics of what is usually considered to be the "mild" PCOS phenotype (PCOM and oligomenorrhea). By doing so we aimed to identify specific PCOS features on initial screening that are strongly associated with CV risk.

MATERIAL AND METHODS

Study Population

Women who were screened at the outpatient clinic of the Erasmus Medical Center Rotterdam or the University Medical Center Utrecht from January 1, 2004, to May 1, 2013, and diagnosed with PCOS according to the Rotterdam criteria, were eligible for inclusion in this study. The screening procedure was performed by trained professionals according to a standardized protocol that has been previously described in great detail (5, 6). The screening began with a thorough general medical/reproductive/family history taking, including self-reported ethnicity. Subsequently, anthropometric measurements were performed, including height, weight, body mass index (BMI), systolic and diastolic blood pressure (BP; measured twice in one visit), waist circumference measured midway between the arcus costae and anterior superior iliac spine, hip circumference measured at the level of the anterior superior iliac spine, and the measurement of hirsutism with the use of the Ferriman-Gallwey (FG) score. Furthermore, a systematic transvaginal ultrasonography was performed to assess double endometrial thickness, ovarian volume, and the total number of antral follicles measuring 2–10 mm. Finally, an extensive endocrinologic and metabolic profile was assessed.

PCOS was diagnosed according to the Rotterdam criteria; i.e., requiring the presence of at least two out of the three following criteria: ovulatory dysfunction, androgen excess, and PCOM (4). Ovulatory dysfunction was defined as oligomenorrhea (mean bleeding interval 35–182 days in last six menstrual bleeds) or amenorrhea (absence of menstrual bleeding for >182 days). We defined clinical and biochemical hyperandrogenism as an FG score >8, and/or a free androgen index (FAI: [(T/SHBG) × 100]) >4.5 (16). PCOM was defined as ≥12 follicles measuring 2–10 mm in diameter in at least one ovary, or increased ovarian volume (>10 cm^3) (17). In all women, basal levels of LH, FSH, and E_2 were assessed to rule out hypo- and hypergonadotropic hypogonadism. Furthermore, PRL and TSH were measured to screen for hyperprolactinemia and thyroid dysfunction.

Women who underwent the aforementioned standardized screening and were diagnosed with PCOS were classified into one of the four potential PCOS phenotypes:

1. Androgen excess + ovulatory dysfunction (AE + OD).
2. Androgen excess + polycystic ovarian morphology (AE + PCOM).
3. Ovulatory dysfunction + polycystic ovarian morphology (OD + PCOM).
4. Androgen excess + ovulatory dysfunction + polycystic ovarian morphology (AE + OD + PCOM).

Women had to be aged 18–45 years at the time of screening. Women were excluded if they were not fasting at the time of the blood withdrawal. Women also were excluded who could not be assigned to a specific PCOS phenotype.

Endocrine and Metabolic Assessment

Regarding cardiometabolic risk profile, we collected information on BMI, waist circumference, and systolic and diastolic