ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Ovarian morphology assessed by magnetic resonance imaging in women with and without polycystic ovary syndrome and associations with antimüllerian hormone, free testosterone, and glucose disposal rate

Henrik Leonhardt, Ph.D., M.D.,[a] Mikael Hellström, Ph.D., M.D.,[a] Berit Gull, Ph.D., M.D.,[b] Anna-Karin Lind, Ph.D., M.D.,[b] Lars Nilsson, Ph.D., M.D.,[b] Per Olof Janson, Ph.D., M.D.,[b] and Elisabet Stener-Victorin, Ph.D.[c,d]

[a] Department of Radiology and [b] Department of Obstetrics and Gynecology, Institute of Clinical Science, and [c] Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and [d] Department of Obstetrics and Gynecology, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China

Objective: To characterize ovarian morphology and perfusion by magnetic resonance imaging (MRI) in women with and without polycystic ovary syndrome (PCOS) and to investigate associations with antimüllerian hormone (AMH), free T, and glucose disposal rate (GDR).
Design: Explorative cross-sectional study.
Setting: University hospital.
Patient(s): Fifty-eight women with PCOS and 31 controls from the general population.
Intervention(s): None.
Main Outcome Measure(s): Antral follicle count (AFC), ovarian/stromal volume, perfusion, AMH, free T, and GDR.
Result(s): Antral follicles of 1–3 and 4–6 mm, but not 7–9 mm, were more numerous, and total AFC (1–9 mm) was higher in women with PCOS. Ovarian volume was larger in women with PCOS. AMH and free T were higher and GDR was lower in women with PCOS. All values were more deranged in classic compared with nonclassic PCOS. There was a positive correlation between AMH and AFC, 1–3 mm ($r = 0.81$), and between AMH and total AFC ($r = 0.87$). In receiver operating characteristic analyses, the area under the curve was 0.89 for total AFC, 0.86 for AMH, and 0.90 for free T. PCOS was independently associated with AFC and free T but not with AMH or GDR when adjusted for age and body mass index.
Conclusion(s): Counting antral follicles down to 1 mm in size by MRI yielded higher AFCs than previously reported. AFC, AMH, and free T discriminated with high accuracy between women with PCOS and controls, but AMH was not independently associated with PCOS.
Clinical Trial Registration Number: NCT00484705. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: PCOS, magnetic resonance imaging, antral follicle count, AMH, testosterone

Discuss: You can discuss this article with its authors and other ASRM members at http://fertstertforum.com/ovarian-morphology-magnetic-resonance-polycystic-ovary-syndrome/

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 November 11, 2013; revised February 10, 2014; accepted February 12, 2014.
H.L. has nothing to disclose. M.H. has nothing to disclose. B.G. has nothing to disclose. A.-K.L. has nothing to disclose. L.N. has nothing to disclose. P.O.J. has nothing to disclose. E.S.-V. has nothing to disclose.
This study was financed by grants from the Swedish Medical Research Council (project no. K2012-55X-15276-08-3), Jane and Dan Olsson Foundations, Novo Nordisk Foundation, Hjalmar Svensson Foundation, Adlerbert Research Foundation, Göteborg Medical Society, Fred G. and Emma E. Kanold Foundation, Hildur Wingquist Foundation, Kristina Stenborgs Foundation, Swedish Society of Radiology, Swedish federal government under the LUA/ALF agreement (ALFGBG-136481 and ALFGBG-138301), and Regional Research and Development agreement (VGFOUREG-5171, VGFOUREG-11296, and VGFOUREG-7861).
Reprint requests: Elisabet Stener-Victorin, Ph.D., Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Box 434, SE-405 30 Gothenburg, Sweden (E-mail: elisabet.stener-victorin@neuro.gu.se).

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

http://dx.doi.org/10.1016/j.fertnstert.2014.02.022

Polycystic ovary syndrome (PCOS), the most common endocrine-metabolic disease in women of reproductive age, is associated with chronic oligomenorrhea/anovulation, hyperandrogenism, obesity, and insulin resistance (1, 2). For diagnosis, the 2003 Rotterdam criteria require at least two of the following: oligomenorrhea or anovulation, clinical or biochemical signs of hyperandrogenism, and at least one polycystic ovary defined as the presence of $\geq$12 antral follicles 2–9 mm in diameter or ovarian volume >10 mL at ultrasound (3). This consensus definition has been disputed, and another expert group has argued that the antral follicle count (AFC) cannot replace hyperandrogenism in the definition of PCOS (4). Recently, principal component analysis showed that polycystic ovarian morphology itself is a sign of hyperandrogenism (5), as is a high serum level of antimüllerian hormone (AMH) (5), a peptide produced predominantly by the granulosa cells of small follicles. In patients with PCOS, AMH correlates strongly with the number of follicles (6, 7). Therefore, a simplified classification for the diagnosis of PCOS has been proposed that is based on the presence of both oligomenorrhea/anovulation and hyperandrogenism; if one criterion is absent, AFC or AMH could be used as a surrogate for oligomenorrhea/anovulation or hyperandrogenism (5).

Although characteristic ovarian morphologic features may be found in PCOS, polycystic ovarian (PCO) morphology is a common finding in women, and the number of follicles observed and the size of the ovary may overlap in women with and without PCOS (8, 9). The proportion of overlap depends on the imaging technique and the cutoff values used for AFC and ovarian volume (5). It is possible that the use of a higher threshold for AFC, or solely counting follicles 2–5 mm in size, might be more specific for PCOS (6, 10–12). Because of technological developments, the threshold value of 12 follicles may no longer be appropriate. A threshold of >19 follicles has been proposed, but a serum AMH >35 pmol/L (or 5 ng/mL) was a more sensitive and specific criterion (9). In a recent Canadian study, using a programmable grid system with the sonographic viewing window of recorded cine-loops, an AFC threshold of 26 follicles (1–9 mm) had the highest diagnostic accuracy when discriminating between PCOS (having both hyperandrogenism and oligo-/amenorrhea) and controls (13).

Other morphologic criteria for PCOS have been discussed, including stromal echogenicity (reviewed in 14), stromal blood flow (14–20), stromal volume (18, 21, 22), and the ratio of ovarian stromal area to total ovarian area (S/A ratio) (21, 22). However, assessing these variables in a standardized manner during ultrasound is inherently subjective and difficult and yields conflicting results (14). Therefore, these criteria were not included in the Rotterdam criteria. It has been suggested that ovarian volume is a good surrogate for stromal volume in clinical practice (14).

The antral follicles have been described to be predominantly peripherally arranged in women with PCOS but may also be scattered throughout an increased amount of stroma (23, 24).

Transvaginal ultrasound (TVUS) is the preferred method for clinical detection of PCO morphology. However, magnetic resonance imaging (MRI) is a useful noninvasive alternative method, for instance, in adolescent or very obese women (8, 25, 26). Although it is less available and more costly than TVUS, MRI allows standardized and more precise measurements of ovarian morphology (27). Thus, MRI may be considered a preferable choice of imaging modality in research on PCOS. With advances in ultrasound and MRI since the 2003 Rotterdam criteria were declared, follicles as small as 1 mm in diameter can be identified. Whether it is meaningful to count follicles smaller than 2 mm is an open question. We hypothesized that the use of MRI for detailed analysis of ovarian morphology, including the smallest follicles, would provide a more accurate characterization of the PCO.

We have previously reported that women with PCOS have elevated levels of sex steroid precursors, estrogens, androgens, and glucuronidated androgen metabolites as measured by mass spectrometry (28). In combination, circulating levels of estrone and free T discriminated with high sensitivity and specificity between women with and without PCOS (28). Obesity and insulin resistance may also contribute to the large pool of antral follicles and to larger ovarian volume in women with PCOS (29). AMH levels are negatively affected by increasing obesity (29, 30). However, the relationship between the hormonal imbalance, the morphologic appearance of the ovaries, and the definition of PCOS as determined with MRI remains unclear.

We recently also reported that it is possible to count antral follicles down to 1 mm in size using MRI and to do precise three-dimensional (3D) volume estimations of ovaries independent of nonellipsoid ovarian shape measurement errors (27). Further, it is possible to assess measurements of signal intensity of ovarian stroma before, during, and after administration of a contrast agent to reflect dynamic perfusion of this tissue. Thus, the main objective of the present study was to characterize ovarian morphology (AFCs in different size intervals down to 1 mm, total ovarian and stromal volumes, the S/A ratio, stromal signal intensity) and perfusion by MRI in women with PCOS compared with healthy women according to TVUS. A secondary aim was to explore any associations between ovarian characteristics and biochemical variables with potential predictive capacities with adjustment for age and body mass index (BMI), that is, AMH, free T, and glucose disposal rate (GDR), the latter reflecting insulin resistance, which is known to be deranged in PCOS.

SUBJECTS AND METHODS

Study Population and Study Design

This prospectively designed cross-sectional study was conducted from November 2005 to September 2008 at the Sahlgrenska Academy/University Hospital. The study was performed in accordance with the Declaration of Helsinki, and it was approved by the Ethical Review Board in the Västra Götaland region. All participants gave oral and written consent. Potential participants were recruited by advertising in the local community. They underwent a gynecologic examination, including TVUS to investigate ovarian morphology. The inclusion criteria for women with PCOS were PCO