Which morphological investigations and how to interpret them to make the diagnosis of PCOS?

Quelles investigations morphologiques et comment les interpréter pour poser le diagnostic d’OPK ?

D. Dewailly, S. Catteau-Jonard, E. Poncelet

Department of Endocrine Gynaecology and Reproductive Medicine, hôpital Jeanne-de-Flandre, CHRU de Lille, avenue Eugène-Avinée, 59037 Lille, France

Department of Radiology, hôpital Jeanne-de-Flandre, CHRU de Lille, avenue Eugène-Avinée, 59037 Lille, France

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Presented by J. Bertherat

Résumé
Le besoin d’une imagerie calibrée des ovaires polykystiques (OPK) est plus fort que jamais depuis la conférence de consensus qui s’est tenue à Rotterdam du 1er au 3 mai 2003. Cependant, imager les ovaires polykystiques n’est pas une procédure facile et requiert un certain savoir-faire technique et médical. L’échographie en deux dimensions reste l’examen standard d’imagerie des OPK et la définition des OPK dans le consensus actuel retenue à la conférence de consensus ASRM/ESHRE repose sur cette technique: 12 ou davantage de follicules mesurant 2 à 9 mm de diamètre et/ou un volume ovarien augmenté au-delà de 10 cm³. Cependant, ces seuils nécessitent d’être revus avec les nouveaux appareils possédant une meilleure résolution spatiale et avec l’apparition de l’échographie 3-D. Les études en doppler et en imagerie par résonance magnétique (IRM) sont rarement utiles au diagnostic mais peuvent être intéressantes en recherche clinique.

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Mots clés : Ovaires polykystiques ; Échographie ; Follicule ; Stroma ; Diagnostic ; Doppler ; IRM

Abstract
The need for a calibrated imaging of polycystic ovaries (PCO) is now stronger than ever since the consensus conference held in Rotterdam in 2003. However, imaging PCO is not an easy procedure and it requires a thorough technical and medical background. The two-dimensional (2-D) ultrasonography (U/S) remains the standard for imaging PCO and the current consensus definition of PCO determined at the joint ASRM/ESHRE consensus meeting on PCOS rests on this technique: either 12 or more follicles measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 cm³). However, these thresholds need being revisited with the use of the new machines that have better spatial resolution and with the advent of the 3-D U/S. Doppler study and magnetic resonance imaging (MRI) are seldom useful for diagnosis but may be interesting for clinical research.

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Keywords: Polycystic ovary; Ultrasonography; Follicle; Stroma; Diagnosis; Doppler; MRI

1. Introduction
The need for a calibrated imaging of polycystic ovaries (PCO) is now stronger than ever since the consensus conference held in Rotterdam in 2003. Indeed, the subjective criteria that were proposed 20 years ago and still used until recently by the vast majority of authors are now replaced by a stringent definition using objective criteria [1,2].

Imaging PCO is not an easy procedure. It requires a thorough technical and medical background. The goal of this review is to provide the reader with the main issues ensuring a well-controlled imaging for the diagnosis of PCO.
two-dimensional (2-D) ultrasonography (U/S) will be first and extensively addressed since it remains the standard for imaging PCO. Other techniques such as three-dimensional (3-D) U/S, Doppler and magnetic resonance imaging (MRI) will be then more briefly described.

2. Two-dimensional ultrasonography

2.1. Technical aspects and recommendations

Women with regular cycles should undergo investigation at the start of the follicular phase (days 3 to 5 of the cycle). Women presenting oligoamenorrhea may be investigated either at any time, or between 3 and 5 days after progestin-induced withdrawal bleeding. The transabdominal route should always be the first step of pelvic sonographic examination, followed by the transvaginal route, excepted in virgin or refusing patients. Of course, a full bladder is required for visualization of the ovaries. However, one should be cautious that an over-filled bladder can compress the ovaries, yielding a falsely increased length. The main advantage of this route is that it offers a panoramic view of the pelvic cavity. Therefore, it allows excluding associated uterine or ovarian abnormalities with an abdominal development. Indeed, lesions with cranial growth could be missed by the transvaginal approach exclusively.

With the transvaginal route, high frequency probes (> 6 MHz) with a better spatial resolution but a less examination depth can be used because the ovaries are close to the vagina and/or the uterus and because the presence of fatty tissue is usually less disturbing (except when very abundant). With this technique, not only the size and the shape of ovaries are visualizable but also their internal structure, namely follicles and stroma. It is now possible to get pictures that have a definition close to anatomical cuts. However, the evaluation of the ovarian size via the transvaginal approach is difficult. To be the most accurate, it requires choosing meticulously the picture where the ovary appears the longest and the widest. This picture must then be frozen. Two means can be proposed for calculating the ovarian area: either fitting an ellipse to the ovary whom the area is given by the machine, or outlining by hand the ovary with automatic calculation of the outlined area. This last technique is given by the machine, or outlining by hand the ovary with automatic calculation of the outlined area. This last technique, not only the size and the shape of ovaries are visualizable but also their internal structure, namely follicles and stroma. It is now possible to get pictures that have a definition close to anatomical cuts. However, the evaluation of the ovarian size via the transvaginal approach is difficult.

The consensual volume threshold to discriminate a normal ovary from a PCO is 10 cm³ [1]. It has been empirically retained by the expert panel for the Rotterdam consensus, as being the best compromise between the studies that were available at that time [6,7]. However, none of them had used an appropriate statistical appraisal of sensitivity and specificity of the volume threshold. This prompted us to recently revisit this issue through a prospective study including 154 women with PCOS compared to 57 women with normal ovaries [8]. The Receiver Operating Characteristic (ROC) curves indicated that a threshold at 10 cm³ yielded a good specificity (98.2%) but a weak sensitivity (39%). Setting the threshold at 7 cm³ offered the best compromise between specificity (94.7%) and sensitivity (68.8%) [8]. Then, in our opinion, the threshold at 10 cm³ should be lowered in order to increase the sensitivity of the ovarian volume for the definition of PCO.

2.2. The consensual definition of polycystic ovaries

According to the literature review dealing with all available imaging systems and to the discussion at the joint ASRM/ESHRE consensus meeting on PCOS held in Rotterdam, May 1st–3rd, 2003, the current consensus definition of PCO is the following: “either 12 or more follicles measuring 2 to 9 mm in diameter and/or increased ovarian volume (> 10 cm³)”.

The priority was given to the ovarian volume and to the follicle number because both have the advantage to be physical entities that can be measured in real time conditions and because both are still considered as the key and consistent features of PCO.

2.2.1. The increased ovarian volume

Many studies have reported an increased mean ovarian volume in series of patients with PCOS [4,6,7,16,17]. However, the upper normal limit of the ovarian volume suffers from some variability in the literature (from 8 to 15.6 cm³). Such variability may be explained by:

- the small number of controls in some studies;
- and/or differences in inclusion or exclusion criteria for control women;
- and/or operator-dependent technical reasons: it is difficult indeed to obtain strictly longitudinal ovarian cuts, which is an absolute condition for accurate measures of the ovarian axis (length, width, thickness).

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2.2.2. The increased follicle number

The polyfollicular pattern (i.e., excessive number of small echoless regions less than 10 mm in diameter) is strongly suggestive, since it is in perfect reminiscence with the label of the syndrome (i.e., “polycystic”). It is now broadly accepted that most of these cysts are in fact healthy oocyte-containing follicles and are not atretic.

The consensus definition for a PCO is one that contains 12 or more follicles of 2 to 9 mm diameter. Again, the expert panel for the Rotterdam consensus considered this threshold as being the best compromise between the most complete
2.3. Other criteria and other definitions

2.3.1. External morphological signs of polycystic ovaries

At its beginning in the 1970s, the weak resolution of U/S abdominal probes allowed to detect exclusively the external morphological ovarian features that were used as the first criteria defining PCO:

- the length, whom the upper limit is 4 cm, is the simplest criterion, but this uni-dimensional approach may lead false positive results when a full bladder compresses the ovary (with the transabdominal route) or false negative results when the ovaries are spheric, with a relatively short length;
- because of the increased ovarian size and the normal uterine width, the uterine width/ovarian length (U/O) ratio is decreased (< 1) in PCO;
- PCO often display a spherical shape in contrast to normal ovaries which are ellipsoid. This morphological change can be evaluated by the sphericity index (ovarian width/ovarian length), which is higher than 0.7 in PCO.

These parameters are less used nowadays because of their weak sensitivity [15].

2.3.2. The ovarian area

It is less used than the volume and was not retained in the consensus definition but, in our recent study revisiting the ovarian volume [8], the diagnostic value of the ovarian area (assessed by the ROC curves) was slightly better than the ovarian volume (sensitivity: 77.6%, specificity: 94.7% for a threshold at 5 cm² per ovary). We also observed that the measured ovarian area (by outlining by hand the ovary or by fitting an ellipse to the ovary) was more informative than the calculated ovarian area (by using the formula for an ellipse: length × width × π/4). Indeed, ovaries are not strictly ellipsoid and this can explain that the diagnostic value of the former was better than the latter. We previously reported that the sum of both ovaries area was less than 11 cm² in a large group of normal women [16,17], but a threshold at 10 cm² seems to offer the best compromise between sensitivity and specificity. Beyond this threshold, the diagnosis of PCO can be suggested.

2.3.3. The increased stroma

Stromal hypertrophy is characterized by an increased component of the ovarian central part, which seems to be rather hyperechoic (Fig. 1). In our [16,17] and in others' opinion [18], the stromal hypertrophy is highly specific of PCO. However, in the absence of a precise quantification, the stromal hypertrophy is a subjective sign.

For standardizing the assessment of stromal hypertrophy, we designed a computerized quantification of ovarian stroma, allowing selective calculation of the stromal area by subtraction of the cyst area from the total ovarian area on a longitudinal ovarian cut [16,17]. By this means, we were able to set the upper normal limit of the stromal area (i.e., 95th percentile of a large control group of 48 normal women) at 380 mm² per ovary. However, providing a precise outlining of the ovarian shape on a strictly longitudinal cut of the ovaries, the diagnostic value of the total ovarian equaled the one of stromal area since both were highly correlated.

Fulghesu et al. [19] proposed the ovarian stroma/total area ratio as a good criterion for the diagnosis of PCOS. The ovarian stromal area was evaluated by outlining with the caliper the peripheral profile of the stroma, identified by a central area slightly hyperechoic with respect to the other ovarian area. Although highly specific, this parameter is not easy to register in routine practice and its superiority over the FNPO has not been established.

The estimation of stromal hyperechoicnecity is also highly subjective, mainly because it depends on the settings of the ultrasound machine. Buckett et al. [20] found no difference in the stromal echogenicity between women with PCOS and women with normal ovaries. The conclusion is that the subjective impression of increased stromal echogenicity is due both to increased stromal volume alongside reduced echogenicity of the multiple follicles.

In summary, ovarian volume or area correlates well with ovarian function and are both more easily and reliably measured in routine practice than ovarian stroma. Thus, in order to define the polycystic ovary, neither qualitative nor quantitative assessment of the ovarian stroma is required.
2.3.4. Follicle distribution

In PCO, the follicle distribution is predominantly peripheral, with typically an echoless peripheral array, as initially described by Adams et al. [4] (Figs. 1 and 2). For some authors [21], younger patients display more often this peripheral distribution while a more generalized pattern, with small cysts in the central part of the ovary, is noticed in older women. At the Rotterdam meeting, this subjective criterion was judged to be too inconstant and subjective to be retained for the consensus definition of PCO [1].

3. Other techniques for imaging polycystic ovaries

3.1. Three-dimensional ultrasound

The 3-D U/S has been initially proposed to avoid the difficulties and pitfalls in outlining or measuring the ovarian shape [22,23,24]. From the stored data, the scanned ovarian volume is displayed on the screen in three adjustable orthogonal planes, allowing the three dimensions and subsequently, the volume to be more accurately evaluated. Nardo et al. [25] found good correlations between 2-D and 3-D ultrasound measurements of ovarian volume and PCO morphology. However, in this prospective study, total ovarian volume, ovarian stromal volume, follicular volume and follicle number did not correlate with testosterone concentration.

The superiority of 3-D over 2-D ultrasound to determine accurately the FNPO is not evident, but the literature is still scarce about this issue. To our knowledge, there is so far no study comparing both techniques in the same groups of patients and controls. Our preliminary results indicate no significant difference (unpublished data). In a study including small numbers of patients and controls [26], the threshold of FNPO discriminating between PCO and normal ovaries was set at 20 with 3-D U/S, hence clearly higher than the “Rotterdam” threshold. Whether this is due to the 3-D technique specifically or to the higher resolution of those new machines impacting both on 2-D and 3-D data has still to be investigated.

So far, the main interest of 3-D U/S resides essentially in the possibility to re-analyse the data on the saved volumic acquisitions. This is helpful in case of discordance between U/S and clinical/biological data. Some softwares allow counting automatically the follicles on the volumic acquisitions (Fig. 2) but for the moment, they are not reliable enough for follicles smaller than 10 mm.

3.2. Doppler ultrasonography

The assessment of uterine arteries will not be addressed in this chapter exclusively devoted to PCO imaging. Color (or power) Doppler allows detection of the vascularization network within the ovarian stroma. Power Doppler is more sensitive to the slow flows and shows more vascular signals within the ovaries, but it does not discriminate between arteries and veins. The combination of 3-D and power Doppler ultrasound (“3-D power Doppler angiography”) allows examining more closely the vascularity of PCO [27].

However, the study of the ovarian vascularization with both the 2-D and 3-D techniques is still highly subjective. The blood flow is more frequently visualized in PCOS (88%) than in normal patients (50%) in early follicular phase and seems to be increased [28]. In the study by Zaidi et al. [29], no significant difference in Pulsatility Index values was found between the normal and PCOS groups, while the ovarian flow, as reflected by the peak systolic velocity, was increased in the former. With the 3-D ultrasound technique, Ng et al. [30] did not find an increased
ovarian stromal vascularization in a Chinese population with PCOS.

Some data indicate that Doppler blood flow may have some value in predicting the risk for ovarian hyperstimulation during gonadotropin therapy [31]. Increased stromal blood flow has also been suggested as a more relevant predictor of ovarian response to hormonal stimulation than parameters such as ovarian or stromal volume [32].

To summarize, the increased stroma component in PCO seems to be accompanied by an increased peak systolic velocity and a decreased PI at the ovarian Doppler study. However, in all studies, values in patients with PCO overlapped widely the ones of the normal patients. No data support so far any diagnostic usefulness of Doppler in PCO.

3.3. Magnetic resonance imaging

Data about MRI for PCO are still scarce in the literature (33–36 and reviewed in 37). This technique allows a multiplanar approach of the pelvic cavity, which helps to localize the ovaries. Imaging quality is improved by the use of pelvic dedicated phased-array coil receiver. The most useful planes are the transversal and coronal views. The T2-weighted sequence suits the best to the ovarian morphology. With this sequence, the follicular fluid displays an hypersignal (white) and the solid component (stroma) a low signal (black). T1-weighted sequences offer less information, but the gadolinium injection allows studying the stromal vascularization. The fat saturation technique increases the contrast obtained after the medium uptake by the vascularized areas.

The external signs of PCO (see above) are easy to analyze on MRI transversal sections. In addition, the T2-weighted sequence displays the excessive number of follicles, but their detection and numbering is less easy than with U/S, because of the poor spatial resolution of MRI, unless high magnetic fields are used (1 to 1.5 Tesla). As with U/S, the stromal hypertrophy remains a subjective observation, although obvious in many cases. After gadolinium injection, there is a high uptake by the stroma, suggesting that it is highly vascularized in PCO.

In most cases in practice, MRI does not afford more informations than U/S for imaging PCO [34,36]. It is only helpful in difficult situations such as a severe hyperandrogenism, when U/S is not possible or not contributive (virgin or obese patients, respectively). Its main role is to exclude a virilizing ovarian tumor which should be suspected when the ovarian volume is not symmetrical and/or when there is a circumscribed signal abnormality, either before or after gadolinium injection. PCO associated with an ovarian tumor might be a pitfall.

4. Conclusions

The U/S study of PCO has now left its era of artistic haidness. It must be viewed as a diagnostic tool which requires the same quality controls as hormonal assays. This supposes that its results are expressed as quantitative variables rather than purely descriptive data. Lastly, it can be used by the clinician only if the ultrasonographer is sufficiently trained and reproducible in his/her results. By its sensitivity (providing that sufficient specificity is guaranteed), U/S has widened the clinical spec-
trum of PCOS and this has led to a reduction in the numbers of cases diagnosed with “idiopathic hirsutism” and “idiopathic anovulation”.

The establishment of an international consensus definition for PCO was essential. However, one should keep in mind that the endovaginal U/S is an improving technique and becomes more and more accurate with time. Therefore, the thresholds of the currently used criteria are prone to change and new criteria defining PCO will probably appear in the future. Sooner or later, some new consensus shall probably be needed...

Conflicts of interest statement
None.

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