Chapter

# Novel Methods in the Diagnosis of PCOS: The Role of 3D Ultrasonographic Modalities

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## Abstract

Polycystic ovary syndrome (PCOS) is a common and complicated endocrine disorder, with its diagnosis based on clinical, laboratory and imaging criteria. The latter is usually assessed via two-dimensional ultrasound; however, the advent of three-dimensional ultrasound, along with three-dimensional power Doppler (3D-PD) could offer more accurate diagnoses and further our understanding of PCOS pathophysiology. Three-dimensional ultrasound (3D-US) has already been used successfully in many fields of gynecology. It offers improved image quality with stored data that can be processed either manually or automatically to assess many parameters useful in PCOS assessment, such as ovarian volume, number of follicles and vascular indices. The examination requires minimal time as data is assessed in post-processing, thus being more tolerable for the patient. 3D-US parameters are generally increased in PCOS patients when compared to controls and 2D measurements, with studies showing improved diagnostic performance, though that remains inconclusive. 3D transrectal ultrasound is more accurate in the diagnosis of virgin PCOS patients than the modalities currently available in that subgroup. Overall, though with some limitations, 3D-US is a promising diagnostic method in the assessment of PCOS which, regardless of diagnostic accuracy, can undoubtedly offer many practical advantages, more objective and reliable measurements, potentially improving PCOS diagnosis standardization.

**Keywords:** polycystic ovary syndrome (PCOS), 3D-transvaginal ultrasonography (3D-TVUS), 3D-power doppler angiography (3D-PDA), 3D-transrectal ultrasonography (3D-TRUS)

## 1. Introduction

Polycystic ovary syndrome (PCOS) is a complicated and heterogenous endocrine disorder affecting more than 10% of women worldwide and it is the most common endocrinopathy of women of reproductive age [1]. It is a syndrome with varied clinical manifestations and several degrees of severity. Some characteristics observed in PCOS patients include hyperandrogenemia, accompanied by acne and hirsutism, ovulatory dysfunction such as oligomenorrhea or amenorrhea, obesity, insulin resistance etc [1].

Diagnosis of PCOS was initially based on clinical characteristics alone, with three prevalent clinical features being agreed upon at the first international conference on PCOS [2, 3], namely:

- Chronic anovulation.
- Hyperandrogenism (evidently based on either clinical or laboratory findings).
- Absence of other endocrine disorders (i.e. adrenal hyperplasia, hyperprolactinemia, hyperthyroidism, hypothyroidism etc).

This definition and the diagnostic algorithm were lacking in several ways [3]. The associated clinical features necessary for diagnosis varied considerably in their clinical manifestation among patients, in particular menstrual instability, obesity and hirsutism and acne with the latter two being the manifestation of hyperandrogenism [4, 5]. Furthermore, no ultrasonographic evidence of PCOS was included in the diagnostic guidelines, although such evidence of PCOS was becoming more and more frequently included in the diagnostic workup of PCOS, with several centers, in fact, mandating it [6].

This led to a joint conference of the American Society for Reproductive Medicine and the European Society for Human Reproduction & Embryology in Rotterdam in 2003, where the previous diagnostic guidelines were revised [7]. The new Rotterdam criteria dictated that the diagnosis of PCOS must include at least two of the following:

- Chronic anovulation.
- Clinical or biochemical findings of hyperandrogenism.
- Clear PCOS findings on ultrasonographic scans.

With the revised criteria both hyperandrogenism and anovulation do not need to be present if ultrasound findings exist for the diagnosis of PCOS, thus including women that would elude diagnosis if the previous criteria were applied. The aforementioned ultrasound features necessary for PCOS diagnosis are the following [8]:

- Twelve or more follicles present.
- Follicle diameter 2–9 mm.
- Increased ovarian volume, more than 10 $cm^3$.
- Presence of the above features in at least one ovary.

The Rotterdam 2003 revised criteria constitute an important step in the standardization of diagnostic workup in PCOS, however, they do come with certain limitations. One of the most notable ones is the fact that ovarian volume measurements, collected based on data from 2D scans, mandate the use of a mathematical formula and therefore entail certain geometric assumptions and estimates [9]. A formula for a prolate ellipsoid (0.5 × length × width × thickness) is typically used, however, such calculations assume ovarian regularity, whereas PCOS ovaries have been repeatedly shown to be

more irregular than normal ones [10]. Another limitation of current diagnostic criteria is the lack of ovarian stromal volume and blood flow assessment. It has been shown that PCOS ovaries have increased stromal volume and blood flow [11, 12], two important parameters that could not only assist in the improvement of our understanding of the pathogenesis of the disease, but also serve as possible response predictors in the treatment of PCOS [13, 14]. However, neither of the two parameters are included in the 2003 guidelines, which could be partially attributed to the great degree of observer subjectivity in the description of stromal echogenicity, as well as to the technical difficulties in blood perfusion measurements using conventional Doppler ultrasound.

## 2. Three-dimensional ultrasound in gynecology

### 2.1 Technical aspects

Three-dimensional ultrasound (3D-US) as imaging technology was first developed in the 1980s and initially applied mostly in obstetrics for more accurate monitoring of fetal in utero development during pregnancy [15]. However, its success in that field led to research and trials for its potential application in gynecology as well.

Mirroring the application of two-dimensional ultrasound (2D-US), its more well-established and clinically applied counterpart, 3D-US is predominantly used transvaginally in the gynecological examination. The transducer is placed in close proximity to the target area and a complete 3D volume is acquired, which can be assessed either in real-time or digitally stored for later analysis. This option of data storage is particularly advantageous, as data acquisition via sweeping can be completed in seconds and thorough assessment at a later time significantly shortens the total examination time. This renders 3D-US a more tolerable and less time-consuming diagnostic modality overall.

The stored data can be displayed in several different ways, including display in three orthogonal planes, surface rendering, individual slice display (similar to conventional tomography) etc. This option for alternative displays can additionally provide detailed information about areas not previously accessible via conventional two-dimensional ultrasonographic display, namely, the coronal plane, which can significantly contribute to the diagnosis of uterine corner and adnexal pathology.

### 2.2 Application in benign gynecological disorders

3D-US over the years has been tested and applied in many benign gynecological disorders with varying levels of success, though on average, its performance is at least comparable to the conventional diagnostic methods and yielded results promising for its inclusion in the diagnostic work-up in clinical practice.

3D-US has been successfully applied in the diagnosis of congenital uterine abnormalities, with remarkable results, as studies have shown up to 100% sensitivity and specificity [16, 17]. Furthermore, research has proven the potential contribution of 3D-US to treatment optimization of uterine abnormalities as well, with 3D-US offering auxiliary visual guidance to the surgeon and improving the final surgical outcome [18]. Another application of 3D-US is in the evaluation of leiomyomas, offering the advantage of precise mapping of their location and clearer differentiation between intramural and submucosal variants when compared to the conventional method of assessment, namely 2D-US [19]. The 3D power Doppler modality is

beneficial in leiomyoma assessment as well, via the more precise evaluation of its vascularization. Therefore, more accurate selection and designation of patients as candidates for embolization treatment can be made [20]. The application of 3D-US in adenomyosis has been examined, with research showing encouraging results, as it facilitates superior visualization of the disrupted border between the endometrium and the basal endometrial layer [21, 22]. 3D-US has also been utilized in the assessment of intrauterine contraception device (IUD) malposition. It can clearly depict the device in its entirety and its position relative to the myometrium via the coronal view [23], whereas such images are far more challenging to obtain via conventional 2D-US. 3D-US also seems promising in pre-operational pelvic assessment in cases with deep pelvic endometriosis. Results are comparable to 2D-US and MRI in patients with intestinal loci of endometriosis and superior to the aforementioned imaging techniques in non-intestinal loci [24].

Apart from improving on currently available diagnostic techniques, 3D-US technology provides new, automated modalities as well. Such modalities mainly include being automated volume calculation, antral follicle counting and follicular growth monitoring, mainly utilized during IVF cycles. This technology has been shown to reduce overall cost, examination time and to deliver accurate and reproducible measurements as well [25–27].

### 2.3 Application in gynecological oncology

Regarding ovarian malignancies, 3D-US can accurately measure the volume of the mass, as well as visualize its internal structure, including wall irregularities, cystic elements, septae and so on [19], thus more accurately identifying suspicious masses [28]. In addition to 3D-US, 3D Doppler can offer precise information regarding mass vasculature, with increased mass perfusion and highly irregular vessel anatomy being indicative of possible malignancies [29]. In endometrial cancer, 3D-US can accurately measure endometrial volume, which is an important predictor of malignancy, as well as 3D Doppler vascular indices, however, more research is required to establish optimal cut-off values [30].

## 3. Three-dimensional ultrasound in PCOS

### 3.1 Technical aspects

As has been made evident so far, 3D-US has been successfully applied in the diagnostic work-up of many gynecological pathologies. Therefore, it was inevitable that similar research would be conducted on its application in PCOS assessment, particularly since the currently used technology does come with certain limitations as mentioned above.

Measurements and data acquisition methods vary between referral centers and studies, however, a similar procedure is followed. Measurements usually begin with a brief 2D-US assessment of the pelvis, followed by identification of the ovaries, with follicles larger than 10 mm and ovarian cysts being excluded. Subsequently, 3D mode is entered and the area of interest is defined. Subsequently, slow-sweeping at a 90° sweep angle or 30–45° angles is applied to ensure that the whole ovary is scanned [31, 32]. The resulting volumetric data is then stored for later evaluation. Compatible software, such as 4D view, allows for several calculations and measurements,

with techniques for ovarian volume, follicle count and ovarian stromal volume calculations.

Ovarian volume can be calculated by the rotational method, which in brief entails measurements at different rotational angles of the stored volume [31]. Follicle count can be facilitated by inversion mode, which entails setting a specific threshold that dictates which tissues are displayed. Therefore, it could be set to display liquid-filled, hypoechoic formations only, without the surrounding stroma, leading to easier and more accurate follicle counting. The same basic principle can be applied to display ovarian stromal volume or follicular volume and subsequently the voxels above or below the defined threshold can be automatically and accurately calculated to determine the OSV or the total follicular volume. This is known as semi-automatic measurement [31]. More recently, fully automated software such as Sono-AVC can automatically calculate the ovarian volume and follicle count, forgoing the traditional manual methods and providing more objective measurements with remarkable accuracy and reproducibility [32–34]. An example of automated follicle detection and the count is displayed in **Figures 1** and **2**.

## 3.2 3D-US parameters

### *3.2.1 Ovarian volume (OV)*

OV is an important ultrasonographic parameter that has been included in the Rotterdam criteria and is typically increased in polycystic ovaries and PCOS when compared to controls. The same observations are made when OV is measured via 3D-US, however, 3D measurements have been proven more reliable than 2D ones [35],

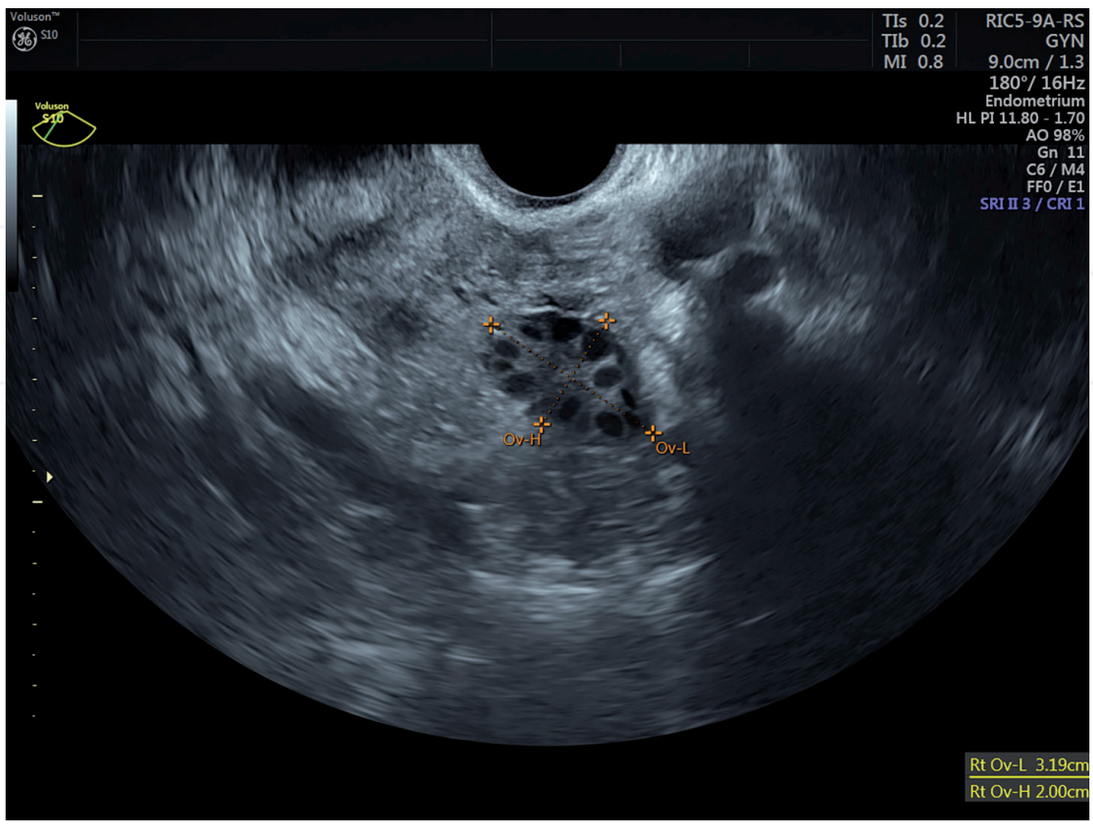


**Figure 1.**
*2D slice of a stored 3D volume of a PCOS ovary.*


**Figure 2.**
*Automatic follicle detection and count via post-processing software.*

| Study | PCOS group | | | | | Control group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Num | BMI | OV | OSV | AFC | Num | BMI | OV | OSV | AFC |
| Lam [31] | 40 | 27.35 | 12.56 | 10.79 | 16.3 | 42 | 24.1 | 5.66 | 4.69 | 5.5 |
| Pascual [36] | 38 | 23.3 | 13.21 | N/A | 22.5 | 45 | 21.3 | 6.65 | N/A | 7.4 |
| Lam [37] | 40 | 23.73 | 12.32 | 9.74 | 15 | 40 | 21.23 | 5.64 | 4.07 | 5.5 |
| Alcázar [38] | 42 | 23.5 | 11.2 | N/A | 22.5 | 38 | 23.1 | 5.6 | N/A | 7.4 |
| Battaglia [32] | 112 | 20.8 | 12.6 | 11 | 14.5 | 52 | 21.1 | 5.7 | 4.2 | 3.2 |
| Sujata [39] | 86 | 25.71 | 11.23 | 9.71 | 17 | 45 | 23.02 | 5.72 | 4.75 | 7 |

*Abbreviations: Num: number of participants in the group, BMI: body mass index, OV: ovarian volume ($cm^3$), OSV: ovarian stromal volume ($cm^3$), FC: follicle count, N/A: not assessed.*

**Table 1.**
*Comparison of three main ultrasonographic parameters assessed by 3D-US in PCOS patients and controls.*

as those necessitate certain mathematical assumptions. OV measurements in PCOS patients and healthy controls via 3D-US are presented in **Table 1**.

### *3.2.2 Follicle count (FC)*

FC is critical in the ultrasonographic diagnosis of PCOS and is included in the Rotterdam criteria. FC can be referred to as antral follicle count, or follicle number per ovary, or even total follicle count in different studies, but practically they are

the tertiary follicles adjacent to a fluid-filled cavity, or antrum and can be visualized accurately via ultrasound if they measure more than 2 mm in diameter [33]. Typically and in fact by definition, PCOS patients and patients with polycystic ovarian morphology have increased FC compared to controls. Follicle counting by 3D-US can be more easily conducted compared to conventional 2D-US, like inversion, the model can be applied and seamlessly differentiate between liquid-filled cystic components and the surrounding stroma [3, 31]. Additionally, automated counting software offers a diagnostic alternative to manual counting, which while not conclusively proven to possess superior diagnostic accuracy, is reportedly less time-consuming [36].

Regarding quantitative data, Allemand et al. found that with 3D-US and by application of the subtractive method, mean FC in PCOS patients was 29.8 ± 11.5 and in controls, 9.5 ± 3.1 and the optimal cut-off for PCOS prediction was 20 or more follicles, with 70% sensitivity, 100% specificity and 0.987 AUC resulting in no false-positive diagnoses [40]. Their proposed threshold is higher than what is included in the Rotterdam criteria [7], which can be partially attributed to the use of 3D-US, as it has been shown to measure larger FC than 2D [41]. On that basis, they propose a possible revision of said criteria to include greater thresholds when 3D-US is applied. FC measurements in PCOS patients and healthy controls via 3D-US are presented in **Table 1**.

*3.2.3 Ovarian stromal volume (OSV)*

OSV has been considered an important ultrasonographic parameter in PCOS patients and is measured in many studies. Such measurements were traditionally conducted manually and showed that there is a statistically significant increase of stromal volume in PCOS patients compared to controls [11], perhaps indicating that hypertrophy of the thecal cells of the ovarian stromal is the main androgen-producing factor in PCOS, as has been hypothesized [31]. 3D-US allows for the calculation of OSV, that being either manual via the activation of inversion mode or automatic via thresholding, with the latter being less time-consuming than the aforementioned manual methods.

OSV has not been included as a parameter in the Rotterdam criteria, possibly due to concerns of subjectivity during measurements. 3D ultrasonographic calculation of OSV may present an opportunity to re-evaluate that fact, as OSV could prove to be very useful in clinical practice [37]. OSV measurements in PCOS patients and healthy controls via 3D-US are presented in **Table 1**.

*3.2.4 Ovarian stromal volume to total ovarian volume ratio (OSV/OV)*

OSV/OV is a proposed diagnostic parameter for the assessment of PCOS patients, based on the increase of stromal volume that has been observed in many studies. Battaglia et al. calculated this parameter in their study and concluded that it was the most accurate predictor of both hyperandrogenemia and hirsutism, with an AUC of 0.915 and 0.891, respectively when compared to every other ultrasonographic parameter assessed, such as OV, FC, 2D and 3D Doppler indices [32]. They also showed that an OSV/OV ratio equal to or greater than 0.84 was the optimal cut-off for the prediction of the aforementioned PCOS manifestations, with a sensitivity of 92% and a specificity of 91%. In addition, this parameter was more accurate if based on 3D-US measurements rather than 2D-US, which can be attributed to the visualization of the stroma of the whole ovary in 3D, compared to measurements conducted on a single 2D slice [32, 42].

### *3.2.5 Total follicular volume (TFV)*

TFC is a parameter not used as regularly as the others in PCOS assessment, as its contribution is still in debate. Nardo et al. showed that it was in fact better correlated with PCOS laboratory findings compared to stromal volume and proposed that it was the increase of TFV that actually caused the increase in OV in PCOS patients rather than that of stromal volume [43]. This is in disagreement with several other studies showing that there is an increase in stromal volume and that it is an important predictor of PCOS, with TFV being lower in PCOS patients than in controls and being used mainly to calculate the OSV via subtraction from the total OV [32].

## 3.3 Comparison of 3D and 2D ultrasound

The comparative studies about 3D-US and 2D-US are not conclusive on one method's superiority over the other with regard to PCOS and polycystic ovarian morphology diagnosis.

On the one hand, some studies showed that the two methods showed no statistically significant difference between them as far as assessing the main ultrasonographic parameters, namely, FC and OV. Battaglia et al. found no significant difference between 3D and 2D-US parameters, however, they do acknowledge that 3D-US is a more appropriate method due to its reproducibility, it is requiring less mathematical assumptions, and its blood flow parameters assessed via 3D-Doppler [32]. As mentioned above, they also proposed the OSV/OV ratio as an important predictor, which was more accurate when based on 3D-US data. Similar conclusions were reached by Sujata et al. [39] as well as far as the comparison of 2D and 3D is concerned, with no significant difference between them is being made apparent.

Studies examining just the differences in FC between the two methods, outside of the PCOS setting also showed that 2D-US produced larger FCs. Deb et al. compared 2D estimations to 3D manual and automated estimations (via the SonoAVC software) of FC, with SonoAVC underestimating FC compared to the two other methods. However, 3D-US images were used for 2D estimates in that study, which might have led to the increase in FC that was observed. Moreover, a lower FC might be indicative of fewer double-counting incidents compared to manual measurements, thus in fact reflecting a more accurate FC. Regardless of FC, automated 3D-US FC was shown to possess greater inter-observer reproducibility than the other two methods [44]. In another comparative study by Deb et al. regarding 2D and 3D-US FC measurements in subfertile women, it was shown that 2D measurements of FC were significantly larger than 3D, but 3D FC semi-automated counting via SonoAVC was significantly faster, averaging approximately 130 s whereas manual counting via 2D-US lasted for an average of 324 s [45].

On the other hand, Nylander et al. concluded that 3D-US was more accurate as far as OV was concerned compared to 2D, as the 3D estimates were in closer agreement with MRI measurements. In their study, 2D measurements of ovarian volume were 14.9% smaller than 3D-US measurements and 11.6% smaller than MRI, which is in agreement with one previous study comparing 2D to MRI and other studies comparing it to volume measurements of anatomical specimens [46]. This observation is attributed to the assumption of a regular ovoid or ellipsoid shape of the ovary and the use of mathematical formulas in the calculation of OV in 2D-US, whereas 3D-US, MRI and anatomical measurements outline the ovary contours and thus result in more

precise measurements [46]. Regarding FC, the research team found that 2D estimates were 18% smaller than those of 3D-US and 16% smaller than those of MRI, suggesting that 3D-US more accurately counts antral follicles than 2D-US.

Overall, the currently available bibliography is still conflicted on which of the two methods provides the most accurate measurements of ultrasonographic parameters, however, what is undisputed is the speed and reproducibility of 3D-US measurements, which is superior to 2D.

## 4. Three-dimensional power Doppler

### 4.1 Technical aspects

Three-dimensional power Doppler (3D-PD) allows for vascularization and blood perfusion assessment via histogram analysis and has been shown to provide more data than frequency-based Doppler ultrasound, especially in low-velocity flow and when flow alterations take place [47, 48]. It has also been considered a means of objective assessment of vascularization and blood flow, contrary to 2D modalities which examine only specific blood vessels in a single slice and depend on the detection of the most representative image of the examined pathology [48]. With regard to ovarian pathologies, 3D-PD via scanning the organ in its entirety could offer very representative data of the vascularization and perfusion status of the whole ovary and perhaps applied in clinical practice.

The data acquisition procedure closely resembles 3D-US acquisition of 3D volume data, with the notable difference of specific Doppler settings being activated to capture relevant data. Afterward, the acquired information is stored digitally and via post-processing software, such as VOCAL or 4D-view, computer algorithms create a histogram of voxel data and calculate vascular indices. The indices most commonly assessed are the vascularization index (VI), the flow index (FI) and the vascularization and flow index (VFI), as described by Pairleitner et al. [48].

### 4.2 3D-PD parameters

#### *4.2.1 Vascularization index (VI)*

VI is the proportion of the scanned volume that emits a flow signal compared to the rest of the organ. In practicality it is the number of colored voxels (representing areas that flow was detected) and expressed as a percentage of the complete volume of the ovary, thus reflecting the blood vessel density in the scanned volume. It could be applied in the diagnosis of pathologies where vascularization either increases or decreases, without changes in the blood flow necessarily, as VI provides no information on the blood flow itself or its intensity [32, 48].

#### *4.2.2 Flow index (FI)*

FI is an average of the signal intensity of the blood flow detected in the scanned volume. In practicality, the software calculates the mean color value of all the colored vessels, representing the average intensity of the blood flow in the scanned volume, which could be used in pathologies where there are changes in blood flow but not in the anatomy of blood vessels or vascularization [32, 48].

### *4.2.3 Vascularization-flow index (VFI)*

Finally, VFI is the combination of the information provided by the other two indices, as practicality is the product of VI and FI. It could be applied to identify pathologies on the spectrum of low vascularization and decreased blood flow on the one extreme and increased vascularization and blood flow on the other [32, 48].

### *4.2.4 Mean grayness (MG)*

Mean grayness is not a vascular index, as it assesses the mean signal intensity of the gray voxels, meaning areas without detectable flow. It is a more objective representation of the tissue echogenicity which is traditionally assessed subjectively via 2D-US, as it is calculated by algorithm based on histogram data. Despite it not being a vascularity index, in most studies it is assessed along with the other three 3D-PD parameters, therefore, data on it will be presented along with the other three in this chapter as well [32].

## 4.3 Study results on 3D-PD parameters

There have been numerous studies conducted on PCOS patients that used 3D-PD and calculated mean values for both PCOS patients and controls. This data is summarized in **Table 2**. There is significant variation regarding the values acquired among the studies. This could be attributed to differences in study design and protocol (definition of PCOS, time of ultrasonographic data acquisition relative to menstrual cycle), the technology used (different devices, heterogenous settings) and disparities in demographical characteristics of the participants (age, BMI, clinical manifestations etc).

In general, there is still a lack of consensus on whether these parameters can be utilized in PCOS assessment, with many studies showing that some or all indices were significantly increased in PCOS patients, whereas others showed no statistical difference between the values at all. Data on the statistical significance of the differences of several parameters between the PCOS group and the control group are presented in **Table 3**.

| Study | PCOS group | | | | | Control group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | VI | FI | VFI | MG | N | VI | FI | VFI | MG |
| Järvelä [49] | 14 | 5.3 | 44 | 2.4 | 44.5 | 28 | 6.1 | 43.1 | 2.7 | 45.7 |
| Pan [12] | 25 | 3.99 | 50.26 | 2.1 | N/A | 54 | 1.44 | 44.44 | 0.8 | N/A |
| Lam [31] | 40 | 3.85 | 33.54 | 1.27 | 32.4 | 40 | 2.79 | 31.79 | 0.85 | 30.4 |
| Lam [37] | 40 | 2.56 | 30.19 | 0.82 | 22.4 | 40 | 2.41 | 29.36 | 0.73 | 23.3 |
| Mala [47] | 25 | 6.07 | 20.97 | 2.39 | N/A | 25 | 1.87 | 19.46 | 1.16 | N/A |
| Battaglia [32] | 112 | 4.2 | 35.5 | 2.3 | 30.9 | 52 | 1.7 | 27.1 | 0.8 | 18.6 |
| Sujata [39] | 86 | 10.7 | 16.84 | 1.79 | N/A | 45 | 10.0 | 16.35 | 2.17 | N/A |
| Garg [50] | 30 | 7.26 | 28.23 | 2.15 | N/A | 30 | 0.88 | 16.61 | 0.16 | N/A |

*N: number of participants, VI: vascularization index (%), FI: flow index (0–100), VFI: vascularization flow index (0–100), MG: mean grayness (0–100), N/A: not assessed.*

**Table 2.**
*3D-PD parameter values in PCOS patients and controls.*

| Study | BMI | Day | OV | FC | VI | FI | VFI | MG | OPI | ORI |
|---|---|---|---|---|---|---|---|---|---|---|
| Järvelä* [49] | N/A | 8–16 | ↑ | M/A | ND | ND | ND | ND | N/A | N/A |
| Pan [12] | ↑ | 2–3 | ↑ | N/A | ↑ | ↑ | ↑ | N/A | N/A | N/A |
| Lam [31] | ↑ | 3–5 | ↑ | ↑ | ↑ | ND | ↑ | ND | ND | ND |
| Lam [37] | ↑ | 3–5 | ↑ | ↑ | ND | ND | ND | ND | ND | ND |
| Mala [47] | ↑ | 2–5 | ↑ | ↑ | ↑ | ND | ↑ | N/A | ↑ | ↑ |
| Battaglia [32] | ND | 3–5 | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | N/A |
| Nylander [46] | ND | N/A | ↑ | ↑ | ND | ND | ND | N/A | N/A | N/A |
| Garg [50] | ↑ | 2 | ↑ | ↑ | ↑ | ↑ | ↑ | N/A | N/A | N/A |

*BMI: body mass index, Day: day of the menstrual cycle that 3D-PD measurements were taken (note: in cases with amenorrhea, the days are counted after withdrawal bleeding induced via progesterone administration for a week), OV: ovarian volume (cm3), FC: follicle count, VI: vascularization index (%), FI: flow index (0–100), VFI: vascularization flow index (0–100), MG: mean grayness (0–100), OPI: ovarian pulsatility index, ORI: ovarian resistance index, ↑: significant increase in PCOS group, ↓: significant decrease in PCOS group, ND: no significant difference between the two groups, N/A: not assessed.*2D-PD parameters (OPI, ORI) were measured on uterine arteries.*

**Table 3.**
*Several parameters of the PCOS group and their difference in comparison to control group measurements.*

From the assessed parameters, VI and VFI appear to be the more reliable of the four parameters, as they are significantly elevated in every study that 3D-PD parameters significantly differ between the PCOS and control groups. FI and MG are not shown to be as reliable relative to the other two, as they do not differ between the two groups in two studies, whereas VI and VFI are increased [31, 47]. No difference or effect on these results was noted based on differences in age, BMI or day of the cycle when the 3D-DP scan was performed.

Some of the included studies compared to the traditional way of ultrasonographic assessment of vascularity and blood flow, namely 2D-PD with the most frequently used parameters being pulsatility and resistance indices of the ovarian vessels to the 3D-PD parameters. Though data on this comparison is only available from four studies, it is inconclusive, as in three of the studies 2D-PD parameters are statistically different between the PCOS and control groups and in one, no statistically significant difference between the two is evident, with the 3D-PD parameters following the same trends in these studies as well. Lam et al. note that is based only on 2D-PD measurements, no difference between the PCOS patients and healthy participants would be noted, whereas that distinction was made apparent when 3D-PD was applied [31].

As far as cut-offs and reference values are concerned, from the studies that did find a significant difference, only Battaglia et al. attempted to create ROC curves and calculate optimal cut-off values, however, since the ROC curve was not statistically significant, no such values were obtained. More research is required, mainly to confirm the significance of 3D-PD measurements, as in half the studies no significant differences were noted and establish optimal cut-off values that could herald the application of 3D-PD in clinical practice as an objective means of vascularization and blood flow assessment in PCOS.

## 5. Three-dimensional transrectal ultrasound (3D-TRUS)

PCOS generally manifests during adolescence, in young and usually virgin women. In such patients, the so far described transvaginal ultrasonographic assessment with

its remarkable diagnostic accuracy is not recommended. Therefore, the transabdominal and transrectal approaches are considered viable alternatives, with the latter seeming more promising, as it is frequently difficult to obtain high-quality images via TA-US [51].

The advent of 3D-US technology marks a significant advance in that field, as 3D-TRUS could replace it in the cases that transvaginal cannot be applied, with hopefully similar results. Sun et al. attempted to evaluate 3D-TRUS' diagnostic accuracy in such a population, namely virgin PCOS patients. A total of 45 virgin patients with PCOS, aged 15–25 presenting with the classic PCOS clinical manifestations were enrolled in their study. In addition, 30 patients with only the ultrasonographic findings of polycystic ovarian morphology and no clinical symptoms, along with 25 healthy volunteers were enrolled as well. All patients received 2D-TAUS and 3D-TRUS and several 3D parameters were assessed.

The results were very encouraging, as 3D-TRUS allowed for improved detection of PCOS, in fact even surpassing transvaginal sonography's accuracy, with the most accurate parameter being the stromal area to total area ratio. Though very encouraging for 3D-US application in this specific subgroup of young patients, whose family planning can be severely impacted by PCOS, the results of this study should be verified by future studies on the subject, as the authors stress [51].

## 6. Limitations of 3D-US

As with every other diagnostic method, 3D-US is by all means not without some limitations which should be mentioned.

For 3D-US high-quality image acquisition, typically the probes used are larger than the corresponding 2D probes, although not by much. Thus, in theory, this could render the examination less tolerable by the patients, especially in transvaginal or transrectal ultrasounds. However, this in practice is balanced by the shorter examination time, as mentioned above and as 3D technology constantly evolves, it is very likely that such concerns about the transducer size will be eliminated [52].

Another consideration is data storage, as 3D-US stores data regarding the whole volume of the target and not just slice as its 2D counterpart. Therefore more space is required to store patient data, with said requirements likely to further increase, as technology improves and image quality improves exponentially. However, this is offset by the synchronous progress of digital media as well, with digital storage becoming more and more affordable and health centers using servers thus rendering physical storage media, such as DVDs and USBs obsolete [52].

3D-US remains a costly method to this day, with the latest equipment usually being unaffordable by most centers. Apart from the physical devices and peripheral attachments, the cost of software is also a major consideration, as the more advanced modalities that facilitate automatic follicle counting and volume measurement are an additional cost for potential buyers. However, as technology progresses, 3D-US equipment will undoubtedly become more and more affordable, particularly by centers and individuals specialized in PCOS and other fields where it can be applied.

Another easily overlooked limitation is the need for 3D-US operator additional training. Despite the many apparent similarities with the more established 2D-US, special training is required to obtain high-quality images as well as to process the acquired data after the examination. Many inexperienced operators face orientation problems during post-processing and viewing, as the improved space awareness combined with

an initial lack of correct orientation determination during the examination can lead to the false perception of the stored volume and false assumptions [52].

Finally, like every other imaging technique, 3D-US can produce artifacts, some that are similar to 2D and others limited to themselves due to the acquisition process, the rendering and the post-processing. It is more usual in 3D-US for motion artifacts to be produced, as the whole organ must be scanned and not every patient can stay still throughout the examination. Therefore, training on data acquisition and correct post-processing is required to reduce the number of artifacts that may be introduced to the images, as well as training on artifact recognition, as misinterpretation of them can lead to inaccurate diagnoses.

## 7. Conclusion

PCOS is a common endocrine disorder affecting many women worldwide, with varying clinical manifestations. Diagnosis is mainly based on 2D-US, however, the relative advent of 3D-US technology offers a promising alternative. 3D-US entails the acquisition of the complete 3D volume of the region of interest, along with vascularization data if Doppler mode is applied. This process is quick and thus more tolerable for the patients and provides vastly more information than 2D real-time assessment. The stored data can be evaluated at any time by many examiners and the measurements of OV, follicle count and VI, FI, VFI and MG, especially if automatically calculated are more objective and with significantly better inter-observer reproducibility of results.

Data on actual diagnostic performance in comparison to the currently available technology is still lacking and inconclusive, with some studies showing no difference and others indicating that 3D-US more accurately visualizes the underlying ovarian morphology and thus offers a more accurate diagnosis. The bibliography on 3D-PD ultrasound is more conflicted, as many studies did not manage to show statistically significant differences in PCOS patients' Doppler parameters in comparison with the control group. However, some studies actually did show a significant difference and in fact propose that 3D-PD offers a more objective and accurate assessment of the vascularization and blood flow of the ovary, as it visualizes the whole organ and its parameters are calculated based on histogram analysis and not the operator's observations, thus being more objective. 3D-TRUS is shown to be a very promising alternative to the traditional transvaginal approach in virgin patients, with remarkable results.

It is made apparent that more research is required to further assess the diagnostic accuracy and usefulness of 3D-US in PCOS assessment, especially as far as 3D-PD is concerned, as it shows much promise and could potentially lead to the inclusion of objective diagnostic criteria in the guidelines if sufficient evidence is found. In addition, new reference values and cut-offs need to be established, again especially in 3D-PD, as the current bibliography is still lacking in that regard.

## Conflict of interest

The authors have no conflict of interest to declare.

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