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OPINION

Has the name PCOS run its course?

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Since its discovery in 1935 polycystic ovary syndrome (PCOS) has suffered somewhat of an identity crisis. Initially named Stein–Leventhal syndrome after its two most prominent advocates [1], it subsequently adopted the name "polycystic ovary syndrome" partially due to the hormonal disturbances seen in these patients and the ultrasound morphology routinely observed through ultrasound, commonly termed "polycystic ovarian morphology" (PCOM).

This naming convention puts too much emphasis on PCOM, which is problematic as these so-called cysts are rather arrested follicles [2]. The use of PCOS is further misleading as "polycystic ovaries" are quite common, especially in adolescents, and can appear in patients who do not present with the other classical symptoms of the syndrome [3]. Furthermore, the use of the term PCOS paints the syndrome solely as a gynaecological condition, when the clinical picture is much more complex, with metabolic and hormonal alterations taking the driving seat.

Clinically PCOS has been diagnosed by the Rotterdam Criteria since 2003, and has been continuously updated, most notably in 2018 and 2023 with the International Clinical Guidelines of the European Society of Human Reproduction and Embryology [4, 5]. The Rotterdam criteria defines PCOS as a condition exhibiting at least two of the following: clinical and/or biochemical hyperandrogenism, oligo or amenorrhea, and PCOM, thus the combinations of these features resulted in four "phenotypes" of PCOS termed A, B, C, and D. A crucial part of PCOS not included in the 2023 international clinical guidelines, is the issue of insulin resistance. This is a matter of contention for many in the field, as insulin resistance is said to affect 65–95% of PCOS patients [6]. The hyperinsulinemia resulting from insulin resistance is known to contribute to localized hyperandrogenism. Specifically, acting as a helper gonadotrophin to increase LH-induced androgen synthesis in the membrane of ovarian theca cells [7].

To correctly consider the role of insulin resistance in PCOS, the Experts Group on Inositol in Basic and Clinical Research and on PCOS (EGOI-PCOS), proposed a new set of criteria which recommended the inclusion of insulin resistance [8]. This followed suit from other classifications such as AE-PCOS that sought to divide hyperandrogenic and non-hyperandrogenic PCOS. The EGOI-PCOS and other researchers in the field have argued that the metabolic abnormalities, such as hyperinsulinemia, metabolic syndrome, and obesity are not only a crucial part of the syndrome, but casual factors, or alternatively the antagonist in this scene, with the ovary being an innocent bystander caught in the crossfire [9]. With this being the case, a name which puts emphasis on ovarian factors appears misguided, thus the EGOI-PCOS proposed the term Endocrine Metabolic Syndrome (EMS), which much can be broken up in separate clinical subtypes, mirroring the PCOS phenotypes A, B, and C. Phenotype D, typically lacking the metabolic involvement, would remain PCOS according to the EGOI-PCOS criteria, with a different etiopathogenesis of ovarian origin. While the precise mechanism is still not understood, the leading theory from the group is that localized excessive IGF-1 levels lead to unchecked proliferation of ovarian follicles and a relative

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localized hyperestrogenism causing follicular arrest and ovarian function disturbances [10].

Nevertheless, this reclassification still includes the use "polycystic ovarian syndrome", when the appearance could be termed multi-follicular without the use of the term cysts which has been the font of much controversy in the past. Furthermore, the question must be asked if the term syndrome is still appropriate for these patients who, unlike prior PCOS classifications, do not display a heterogenic array of symptoms but rather these are clearly defined. In detail, these formally classified phenotype D patients present with disruption to the ovarian cycle, defined as oligo or amenorrhea, normal androgen levels, multi-follicular morphology containing arrested follicles, increased endometrial thickness and insulin resistance. Consequently, would the term disorder be more suitable?

Considering the above, we present the term **multi-follicular ovarian disorder (MFOD)** as a more suitable term for these ex-PCOS phenotype D patients. This new terminology allows for a more accurate description of the condition while shifting focus away from the poorly termed PCOM. The next result of this would be a distancing between the hyperandrogenic EMS patients and the normoandrogenic MFOD patients, clearly reflecting the different clinical needs of these sets of patients. Furthermore, should these normoandrogenic patients be set aside from the hyperandrogenic EMS, it is likely that this would encourage further research in this area, so that understanding of the pathogenesis would increase with time.

It is apparent that any name change must be carefully considered with all stakeholders: patients, researchers, physicians, and companies working in the field being adequately consulted. It is paramount that such name does not disrupt patients' access to care, in addition to allowing those with commercial or intellectual capital within this medical space time to adapt. Such consultations have occurred, previously with terms like "androgens", hormones, or imbalance being unacceptable to key stakeholders [11]. The term MFOD centres around the ovarian nature of the condition without these poorly tolerated terms and neither does it use misleading terminology like polycystic.

In conclusion, while the name PCOS has been in use now for many years, it is clearly time for a change. The current guidelines incorporate non hyperandrogenic patients for whom the available treatment options are not adequate, and by grouping them together with their hyperandrogenic counterparts we simply stimy future research into potentially tailored and more effective therapies. The new terms EMS and MFOD address this issue, and we hope that this piece encourages a critical assessment about the current nomenclature.

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Declarations

Conflict of interest S.H.M, G.P and V.U are employees of Lo.LI Pharma s.r.l

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