The new International Federation of Gynecology and Obstetrics (FIGO) ovulatory disorder classification: PRO and CON

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Disclaimer: Authors for "fertile battles" are chosen to represent the full breadth of opinions. Individual authors, even within one side of the debate, do not necessarily agree with all viewpoints expressed.

PRO: For the new international federation of gynecology and obstetrics ovulatory disorder classification: *If it ain't broke, don't fix it?*

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CON: Against the modified classification of women presenting with ovulatory disorders proposed by figo—*Will it really change the future care of those patients*?

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A.H.B. reports that he was a coauthor of the FIGO Committee on Menstrual Disorders and Related Health Impacts system for classification of causes of ovulatory disorders. M.G.M. was a coauthor of the FIGO Committee on Menstrual Disorders and Related Health Impacts' system for classification of causes of ovulatory disorders; Consultant to AbbVie Inc, American Regent, Daiichi Sankyo, Myovant Sciences, and Pharmacosmos. H.C.O. has nothing to disclose. B.L. has nothing to disclose. B.C.J.M.F. has nothing to disclose.

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PRO: For the new international federation of gynecology and obstetrics ovulatory disorder classification: *If it ain't broke, don't fix it? (continued)*

The new classification of disorders of ovulation has stirred up a healthy debate about the need for change and brings to mind the phrase from which the title of this article derives "*I know it's an ugly-looking antenna, but it gets the job done, and if it ain't broke, don't fix it*" (1). The human condition, however, is about striving to improve what we have and enhance the utility of any available tools. To quote Henry Ford "*We do not make changes for the sake of making them, but we never fail to make a change when once it is demonstrated that the new way is better than the old way.*" Indeed it was this philosophy that 20 years ago led our esteemed opponent to co-convene the *European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine* consensus workshop, in which one of us (A.H.B.) was privileged to participate, and gave us a new definition for polycystic ovary syndrome (PCOS) (2). Moreover, we have all witnessed the stormy debate that has rumbled, sometimes explosively, since then, with even some consensus group members arguing against its own conclusions. The *European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine* definition of PCOS replaced an earlier *National Institutes of Health* consensus from 1990 that arose from a symposium but was never published in a peer-reviewed journal. Similarly, the *World Health Organization* (WHO) first presented a classification of ovulation disorders as a monograph (3), which also did not appear in a peer-reviewed journal.

The early iterations of the WHO classification contained between 1 and 7 groups, distinguished by estrogen activity, the presence or absence of hyperprolactinemia, and whether there was a pituitary tumor (4). This has been modified over time in various reviews and book chapters by single investigators, not by consensus or peer review. Indeed its pathway to the current incarnation is somewhat opaque and peppered by mis-citations. For example, the *United Kingdom Guidelines* on the investigation and management of infertility, first published in 2004 and updated in 2013 (5), in discussing the diagnosis of anovulation makes reference to the *WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple* (6), yet there is no mention of a classification of ovulatory disorders therein. The *National Institute for Health and Care Excellence* classification (5) describes the 3 groups that most investigators currently refer to, namely: group I, comprising women with low serum gonadotropin and estradiol concentrations and thereby encompassing hypogonadotropic hypogonadism, pituitary insufficiency, and hyperprolactinemia; group II is perhaps less well defined and often labeled "gonadotropin disorder" or "hypothalamic/pituitary dysfunction," with normal serum estradiol levels and therefore predominantly includes those with PCOS; and group III comprises those with high serum gonadotropin

CON: Against the modified classification of women presenting with ovulatory disorders proposed by figo—*Will it really change the future care of those patients? (continued)*

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The FIGO relies on opinions and consensus in the midst of a digital transformation, potentially allowing for a more accurate annotation and clearer classification of health conditions in an automated and replicable capacity? We believe that at the present time, a data-first, patient-centric approach to diagnostics, which uses electronic health records, imaging, biobanks, and multiomic datasets, represents the only robust way toward an unbiased assessment of the ovulatory disorders.

Indeed, the term *ovulatory disorders* is not well defined, and it is surprising to realize that the fundamentals of a classification originally put forward some 50 years ago by Insler and Lunenfeld (18,19), and subsequently adopted by the WHO (3), is still used today (20). Although various investigators have proposed some minor modifications over the years, serious attempts aiming to either validate or update the WHO classification based on solid scientific evidence are nonexisting.

The WHO classification may not be particularly science-based but instead is focused on the biological insights and newly available treatment options at the time. Clinical practice experience over many decades has proven this classification to represent a useful tool as a starting point for diagnosis and treatment in every day patient care. There should be compelling arguments and robust scientific evidence to replace such a system with a more complex classification, as currently proposed by FIGO.

We can easily agree on the many shortcomings of the current classification, as outlined at length in the recently published FIGO proposal (9). How to accurately diagnose the absence of ovulation in the first place. Moreover, how to take variations in cyclicity over time in oligo/anovulatory women into consideration, along with difficulty including hyperprolactinemia, prolactin assays only became available in the 1970s (21), into the system, and so on.

The Delphi method, originally developed in the 1950 by the RAND organization, aimed to *forecast the effect of technology on warfare* (Delphi method | RAND) (22). More recently, this structured communication technique—using various rounds of consultation based on questionnaires of expert panels—has been applied more widely in business, prediction markets, science and health care. Acknowledging the fact that even today little relevant scientific information considering *ovarian dysfunction* is available, we remain un-

PRO: For the new international federation of gynecology and obstetrics ovulatory disorder classification: *If it ain't broke, don't fix it? (continued)*

and low estradiol concentrations, namely, women with premature ovarian insufficiency (POI).

Those of us working in clinical practice see daily that hormone levels do not obey clear rules, so a classification based purely on their measurement is flawed. For example, underweight women with hypothalamic amenorrhea may have suppressed serum concentrations of luteinizing hormone (LH), whereas follicle-stimulating hormone (FSH) levels are often in the normal range (7). Additionally, those with PCOS often have serum FSH and LH levels in the normal range (8). Furthermore, ovulatory disorders comprise a spectrum of manifestations ranging from intermittent episodes of cyclical ovarian activity to chronic ovulatory failure and amenorrhea—and these states may fluctuate in an individual over time.

Over the last 50 years, since the first iterations of the WHO classifications, our understanding of the pathophysiology of ovulatory disorders has developed with advancements in assay technology, imaging techniques, and genomics. Hence, the *International Federation of Gynecology and Obstetrics* (FIGO) undertook a Delphi process whereby the international community of stakeholders in ovulatory disorders, including consumer organizations, designed a new system that has revised the WHO classification to meet better the needs of investigators, clinicians, and medical educators (9).

The FIGO consensus now provides a practical classification and a logical framework for making a precise diagnosis for any woman who presents with features of an ovulatory disorder. We now have 3 clear groups based on the anatomical origin: Hypothalamic, Pituitary, and Ovarian, and a fourth group comprises those with PCOS - resulting in a new acronym HyPO-P. Within the first 3 groups, we have subdivided causes into genetic, autoimmune, iatrogenic, neoplastic, functional, inflammatory/infectious, trauma and vascular, physiological, idiopathic, and endocrine, giving us the mnemonic "GAIN FIT PIE." Although we appreciate that acronyms may seem contrived and even irritating to some, they serve as an aide memoire for students and those less familiar with the broad complexities of reproductive endocrinology.

So why separate PCOS into a category of its own? First, the ovarian category comprises those within the spectrum of ovarian insufficiency, with elevated serum gonadotropins and hypo-estrogenism. Second, we feel that this should be self-evident as the pathophysiology of PCOS is multifaceted and encompasses disturbances of the hypothalamic-pituitary-ovarian axis, androgen production, and insulin metabolism, which in turn may each vary significantly depending on ethnicity and genetic as well as environmental influences (10, 11). Indeed, PCOS is such a complex and heterogeneous condition that it deserves special recognition,

CON: Against the modified classification of women presenting with ovulatory disorders proposed by figo—*Will it really change the future care of those patients? (continued)*

convinced whether the applied Delphi method represents the most suitable tool to come to an updated classification.

Moreover, the outcome of such a Delphi exercise very much depends on the questions asked during the first round, the expertise of expert panels involved, and the availability of sufficiently robust scientific evidence to answer such questions. As stated repeatedly in the FIGO document, the focus of these questionnaires has been clinicians, educators, and researchers. How about involving women suffering from cycle abnormalities themselves? Should those individuals not be the starting point for any exercise in the current era dominated by the principle of creating *value* for patients (23)? Unfortunately, representatives of patients were only involved later in the process. The lack of patient perspectives and data-informed decisions in the proposed FIGO classification somewhat undermines the power of the conclusions made.

If we go through the list of 42 questions prioritized for the first FIGO Delphi round, only a single query was dedicated to PCOS, by far the most common condition associated with ovarian dysfunction. Why was PCOS largely ignored in this first round? Moreover, a surprising number of 4 questions were dedicated to rather trivial and poorly defined conditions, such as *luteal out of phase cycle* and *luteinized unruptured follicle*. Finally, 4 questions concerning hormone assays (gonadotropins, steroids, and AMH) related to accessibility only.

Even more important, the currently available more robust scientific evidence pertinent to the classification of ovulatory disorders seems to be largely ignored, for unknown reasons. There is no mention of vital issues, like:

- The impact of the significantly improved quality of hormone assays over time and its potential implications for classification.
- The validity of currently used hormone threshold levels for diagnosis, like for instance a FSH concentration of 25 or 40 IU/L, at single or repeated assessments, and at what time interval should they be assessed for POI diagnosis (24).
- The arbitrary cut-off of 40 years for POI diagnosis.
- Whether free or total steroid serum levels should be assessed, and by either immunoassays or liquid chromatography (25), especially relevant for PCOS diagnosis.
- Moreover, above all the distinct role of AMH—a novel marker tightly associated with early follicle development—in the diagnosis of a variety of clinical conditions involving ovarian dysfunction, including PCOS (26), POI (27), or the extent of recovery of ovarian function after gonadotoxic treatment (28) is not discussed.

This true innovation in reproductive endocrinology has certainly shed important new light on the classification of ovulatory disorders.

PRO: For the new international federation of gynecology and obstetrics ovulatory disorder classification: *If it ain't broke, don't fix it? (continued)*

particularly as it accounts for approximately 90% of those with ovulatory disorders. This circumstance demands extensive guidance devoted to the diagnosis and management of PCOS at different life stages, not only of the impact on ovulation but also its numerous other manifestations whether hyperandrogenism, metabolic, or on long-term health (10). Every other cause of ovulatory disorder is more simply and clearly defined with respect to symptoms and pathophysiology and, therefore, easily sits within the HyPO–GAIN-FIT-PIE algorithm (review Balen et al, Human Reproduction Update, unpublished data).

The features of PCOS include menstrual cycle disturbances, signs of androgen excess, and abnormalities of biochemical profiles, including elevated serum concentrations of LH, testosterone (T), androstenedione, and antimüllerian hormone (AMH). Hyperinsulinemia and metabolic disturbances are associated features, particularly in the 40% to 50% of women with PCOS who are overweight. Presentation of the syndrome is so varied that one, all, or any combination of the aforementioned features may be present in association with/or without an ultrasound picture of the polycystic ovaries. There is considerable heterogeneity of symptoms and signs among women with PCOS, and, for an individual, these often change over time. Young women may, for example, be particularly troubled by the oversecretion of ovarian androgens, manifesting in acne and hirsutism, or by the effects of irregular and heavy menstrual periods. Then, when fertility is desired, PCOS is the commonest cause of anovulatory infertility, and there are significant challenges in providing effective and safe ovulation induction therapy (12). Although, paradoxically, women with PCOS may take longer to conceive, they end up with family sizes similar to those of the general population, their menstrual cycles tend to become more regular toward the end of their reproductive years, and their ovaries fertile for longer. For older women with PCOS, there are significant associations with metabolic problems, diabetes, and cardiovascular disease, although these do not always translate to high mortality.

Several interlinking factors affect the expression of PCOS: weight gain is associated with worsening symptoms, whereas weight loss may ameliorate symptomatology and the endocrine and metabolic profile. Overall, PCOS can be considered "a condition of our time," and as the epidemic of obesity and metabolic disease risk spreads, research that explores how this condition affects the health and well-being of future generations is becoming increasingly relevant. Although the manifestations of PCOS are well characterized, the pathophysiology of ovarian dysfunction originates in several ways. Ovarian dysfunction is evidenced by numerous immature egg-containing follicles (the eponymous "cysts") that fail to grow and ovulate in a coordinated fashion because of the hypersecretion of LH and insulin promoting the overproduction of androgens together with excess ovarian AMH

CON: Against the modified classification of women presenting with ovulatory disorders proposed by figo—*Will it really change the future care of those patients? (continued)*

Nobody would object to using etiology or anatomy as the guiding principle of any medical classification, but we question whether sufficiently robust diagnostic tools have been developed to do so. For instance, the primary hypothalamic or ovarian origin of PCOS is still debated, and a distinct overlap between these 2 options may occur. Consequently, what purpose does it serve to propose a new FIGO category - separate from hypothalamic or ovarian forms of ovulatory disorders—for the notoriously heterogeneous condition PCOS? It remains enigmatic on which data the proposed new FIGO classification is based, and how future patient care might benefit from such a complex and overlapping classification system.

In addition, the potential importance of co-morbidity, both short- and long-term, for the proposed modified diagnostic classification has not been addressed. For instance, women with PCOS might present at a relatively young age with irregular bleeding, hirsutism, infertility, and signs of (cardio) metabolic dysfunction (29). This clearly affects the preferred diagnostic tools as well as follow-up strategies and management of potential long-term general health risks. Such an approach would certainly also apply to other conditions of ovulatory disorders, like POI.

Current health care developments encompass a shift in attention from group diagnosis to individual prognosis, i.e., away from developing strategies for all patients toward interventions based on the complaint, context, and the desired outcome of a given individual (30). Available digital tools pave the way for a more personalized medicine-based approach. Such a patient-tailored strategy would take into account individual symptoms, biometrics, endocrinology, patient-led monitoring of cycle variability, and lifestyle factors.

The construction of (multivariate) prediction models, informed by prospective, cohort, follow-up studies of well-phenotyped patients, and carefully defined study endpoints, has developed into serious science (31). Such novel approaches have already revolutionized patient-tailored health care, especially in cardiovascular and cancer care. In more recent years, infertility care is slowly catching up: such developments include the assessment of pregnancy chances without medical intervention in a given couple with subfertility (32), identifying patient characteristics involved in ovulation induction success rates in women with PCOS (33), and even identifying predictors for pregnancy complications in such patients (34). Could this shift in our thinking along with newly generated knowledge not be included in a modified classification of ovulatory disorders?

High levels of data and technology literacy in the general public allow for patient-led, app-based, symptom and hormone monitoring through self-governed inquiry and diagnostic testing (35). This provides a unique opportunity for in-person clinical trials which moves away from one-time

PRO: For the new international federation of gynecology and obstetrics ovulatory disorder classification: *If it ain't broke, don't fix it? (continued)*

production that disrupts follicle recruitment. To understand the pathophysiology of PCOS, one has to consider both the nature of the dysfunction within the ovary and the external influences that prevail to modify ovarian behavior. These environmental influences may start as early as embryogenesis and certainly occur during fetal development and throughout life. The scene is set in utero through the combination of maternal endocrine milieu and placental function influencing fetal hypothalamic function, gonadal development, and fat deposition. Some of these elements may be further affected by epigenetic factors and the interaction of maternal and in utero environments.

The pathogenesis of polycystic ovaries and the associated syndrome is still being elucidated. Still, the heterogeneity of the presentation of PCOS suggests that there are multiple routes to the development of the condition. Furthermore, there are numerous phenotypes and quite significant ethnic variations. Historically, the genetic propensity to gain weight easily in some populations may have preserved fertility in times of famine (the "thrifty genotype"), as underweight women do not have the nutrition to sustain a healthy pregnancy. So the gene(s) that lead to PCOS may have previously conferred an evolutionary advantage. There have been numerous attempts to elucidate the genes that may be involved, with the latest genome-wide association studies identifying several potential loci of interest, but still no firm conclusions (13, 14). Recent data that DNA methylation and other epigenetic changes play a role in the development of PCOS (15) and the recent evidence that sperm methylation is affected by male obesity (16) and that this can influence the methylation status of genes for the offspring (17), also combine to provide an intriguing hypothesis about the possible paternal influences on the development of PCOS.

It is, therefore, clear that PCOS cannot be shoe-horned into the "Hy," "P," or "O" categories of the new FIGO classification, and so to quote Hippocrates, we can use the HyPO-P classification to "*understand the antecedents, know the present and foretell the future …… in order to mediate these things and have two special objectives in view with regard to disease, namely to do good and to do no harm.*" We, therefore, believe that the new HyPO-P classification of disorders of anovulation provides a clear and logical framework with which to better serve our patients for the future.

CON: Against the modified classification of women presenting with ovulatory disorders proposed by figo—*Will it really change the future care of those patients? (continued)*

snapshot analysis of health in a single appointment and moves toward the assessment of health as a continuous state.

Indeed, there is stark mention of the role of genetics in ovulatory disorders. The last 2 decades have seen incredible progress in genetic sequencing, allowing for high-resolution biological data that can be obtained using routine laboratory practice. Although the cost of such assays was previously prohibitive, the current price enables far greater interrogation into these conditions and the subtle differences between them. The complexity of molecular genetics, however, results in a lack of consideration for large or small-scale genomic studies leading to concrete associations with these conditions. There is room for systematically reviewing and meta analyzing these associations in the light of nuclear and mitochondrial genomic data in women with PCOS (36).

Individually, each of the omics has shown promise in different research and clinical settings. For instance, the clinical integration of genetic markers of malignant tumors resulting in an increase in approvals of companion diagnostic devices by the *US Food and Drug Administration* (FDA) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools). Comprehensive genomic profiling to identify molecular markers in liquid biopsy samples from

TABLE 1

Recommendations for improving the diagnostic criteria for ovulatory dysfunction.

- Take a more practical (public health) approach and focus predominantly on the most common conditions.
- Include a more patient-centered approach and the transition from diagnosis to prognosis toward individualized care.
- Discuss the role of genomics, heritability and the impact of lifestyle on the occurrence and prevalence of ovulatory disorders.
- Assess whether the profile of women suffering from ovarian dysfunction may have changed during the 50 year period (for instance, in relation to over- or underweight, exercise, environmental factors) since the introduction of the classification.
- Include discussion regarding possible implications of improved reproductive hormone assays, and relevant threshold values.
- Include the role of antimüllerian hormone in the classification system, especially focusing on polycystic ovary syndrome or primary ovarian insufficiency diagnosis and handling, and ovarian reserve testing.
- Assess the quality of hormone assays in blood, urine or saliva.
- Discuss the role of androgen assays in the classification, and management of women with ovulatory dysfunction.
- Include proper definitions of normal cyclicity, oligomenorrhea and amenorrhea.
- Use large data sets generated by current e-health tools, biobanks, digital clinical trials, genomics.
- Any recommendation should be backed up by proper scientific evidence and should be referenced.
- Relevant knowledge gaps should be identified.

Balen. New FIGO ovulatory disorders classification. Fertil Steril 2023.

PRO: For the new international federation of gynecology and obstetrics ovulatory disorder classification: *If it ain't broke, don't fix it? (continued)*

CON: Against the modified classification of women presenting with ovulatory disorders proposed by figo—*Will it really change the future care of those patients? (continued)*

blood and urine are becoming a widely used tool for precision diagnostics in oncology (37).

Combining data across multiple modalities including genomic, metabolomic, ultrasonography imaging, clinical records, wearable sensors, and more, whereas allowing consideration for social and environmental determinants, could pave the future of precision health and accurate diagnostics (35, 38) (Table 1). Irrespective of the use of such multimodal AI models, a data-led approach from any modality would be far more reliable in the formation of concrete consensus for a myriad of conditions relating to ovulatory dysfunctions.

The wealth and availability of open genetic databases has enabled the characterization of the genetic architecture of complex conditions and traits (39), including the precise mechanisms which can predict ovarian aging, menopause timing, and breast cancer susceptibility (40, 41). Although the successful integration of these very distinct types of data remains challenging, combined global datasets could radically expand our understanding of women's health conditions including infertility (42) and pave the way for precise and personalized characterization in turn leading to preventive and therapeutic strategies.

Conclusion

Based on the many arguments outlined above, we fail to see how patients might benefit from the proposed complex *anatomical* FIGO classification of ovulatory disorders. Why not start with the relevant complaints of women and propose a path to follow? Such an approach would represent modern thinking in health care research at large, identify jointly with women what is the primary complaint and the desired endpoint, and how to achieve this outcome in an efficient and cost-effective manner. Current thinking may require a shift in our thinking from diagnosis to prognosis, incorporating big data, e-health tools concerning individual symptoms, biometrics, improved hormone assays (including AMH), and patient-led monitoring of cycle variability and lifestyle factors.

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