Toward a universal serum antimüllerian hormone threshold as a surrogate for polycystic ovarian morphology on ultrasound: the story is not over…

Although the serum antimüllerian hormone (AMH) assay has been proposed for approximately 20 years to replace or complement the results of transvaginal pelvic ultrasound (TVUS) in women with polycystic ovary syndrome (PCOS), no consensus threshold has been established to date (1). The reasons mainly are technical and methodologic. In the absence of an international standard, it is impossible to homogenize the results of studies using different assay techniques. In addition, the criteria for selecting patients and control cases vary from one series to another. Finally, the fact that an ultrasound appearance of polycystic ovaries (polycystic ovarian morphology, PCOM) is observed in 20% to 30% of the women included in the control groups because they are totally asymptomatic complicates interpretation of the data.

In this context, the use of serum AMH assay as a surrogate for PCOM is not recommended according to recent guidelines (2). Does the recent study by Dietz de Loos et al. (3) put an end to this long period of doubt and hesitation? One would be tempted to think so in view of the impressive size of the patient and control cohorts (unmatched to date), the careful use of relevant inclusion and exclusion criteria, the use of a semiautomated AMH assay technique that was identical for all participants and has been proven to be effective, and the rigor and richness of the statistical analysis, with elimination of the main potential biases, in particular age and body mass index (4).

However, and ironically, the investigators' proposal of a serum AMH threshold as equivalent for PCOM is based on an arbitrary and, therefore, subjective choice. They deliberately chose as a threshold the AMH value corresponding to "concordance"; that is, the one giving equal sensitivity and specificity, in this case 85% in their study. In this type of study based on the use of receiver-operator characteristic curves, concordance is not the gold standard, nor is the Younden index, used by many investigators. These "automatic" indexes are given as an indication,but the choice of the best compromise between sensitivity and specificity (knowing that favoring one is to the detriment of the other) must be adapted to the problematic of the disease studied. Thus, this choice must take into account medical, epidemiologic, economic, and even ethical aspects. Therefore, it is an expert choice that is not simply guided by statistical analysis. A consensus of international experts on the modalities of this choice with regard to the AMH assay as a replacement for PCOM is highly desirable.

Indeed, some may regret that the AMH threshold (3.23 ng/mL; i.e., 23 pMol/L) proposed by Dietz de Loos et al. (3) gives a specificity of 85%, which means a nonnegligible rate of false-positives in controls. It is easy to understand the investigators' concern not to use a higher threshold, which would result in a lower sensitivity, in particular in patients with phenotype D who are numerous in their series, with lower AMH levels than in those with phenotypes A and C and 25% of whom are below the threshold. These patients are responsible for almost all cases of discordance with ultrasound, which raises the question of the relevance of AMH measurement in this subpopulation of PCOS. This would be even truer with a higher threshold. We ourselves have seen this discordance in the D phenotype, to a lesser degree however, for reasons that remain to be determined (5).

Therefore, the use of a relatively low AMH threshold to "preserve" the diagnosis of the D phenotype seems questionable. In most cases, these patients (most of whom consult for infertility) will benefit from a TVUS anyway, which will allow recognition of PCOM. On the other hand, the generalization of this threshold risks leading to a nonnegligible number of false-positives in situations other than PCOS, in particular when TVUS is not possible or noncontributory. Knowing all that this diagnosis implies in terms of prognosis for fertility and for a certain number of long-term risks, it is to be feared that the medical, economic, and psychologic repercussions are totally unjustified.

Personally, I would, therefore, prefer an AMH threshold of 4 or even 4.5 ng/mL (28.5 and 32 pMol/L, respectively), which according to the investigators gives a specificity of 93% and a sensitivity of 70%. These figures apply to semiautomated techniques, which give lower values than the older "manual" techniques, as the investigators are quick to point out. When TVUS is not possible, such a threshold undeniably carries a risk of missing cases of PCOS with phenotypes C or D, which, therefore, would be considered to be either idiopathic hyperandrogenism or oligoanovulation, respectively. This does not have major consequences in the short term, as both entities are managed in the same way as true "mild" PCOS.

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https://doi.org/10.1016/j.fertnstert.2021.08.005

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