Ovarian antimüllerian hormone system: more complex than was thought

The antimüllerian hormone (AMH) in blood may present in different isoforms. In women it is secreted by ovarian granulosa cells as a pre-pro-protein and after the removal of the signaling sequence it turns to a proprotein called proAMH. It is believed that the proAMH cannot bind to the AMH specific receptor (AMH receptor type 2, AMHRII). A successive proteolytic cleavage of the proprpotein occurs and leads to the generation of the amino terminal (AMH_N) and carboxy –terminal dimer (AMH_C). These two peptides are nonconvalently associated ($AMH_{N,C}$) and the formation of a complex between the two increases solubility of the peptides, hence facilitating their diffusion to tissues and cells (1, 2). The AMHRII can be bound by both the AMH_C and $AMH_{N,C}$, while the ligand AMH_N is thought to be inactive but may have a role in increasing the activity of the ligand AMHc (2).

The most updated research suggests that circulating AMH is mainly represented by proAMH and $AMH_{N,C}$ with very low (if any) concentration of AMH_N or AMH_C. It is believed that the $AMH_{N,C}$ only dissociates in AMH_N and AMH_C at the binding sites where the hormone exerts its action. Some nonconclusive evidence suggests that the conversion of proAMH to $AMH_{N,C}$ may not to take place in the blood but only at ovarian level and if this will be the case the use of the ratio of circulating proAMH/$AMH_{N,C}$ could represent the rate of extracellular proprotein cleavage at ovarian level (1).

According to this hypothesis, the ovary is controlling the important step in the physiology of AMH, that is the conversion from an inactive to active isoform of the hormone itself. Considering the relevant role of AMH in controlling ovarian physiology, it may be very interesting to understand whether modification in this process of intraovarian activation of AMH could have consequences in ovarian activity itself. In fact, AMH has a central role in the paracrine control of ovarian steroidogenesis and folliculogenesis and this hormone has been largely involved as a key player in the pathophysiology of anovulation, polycystic ovarian syndrome (PCOS), reduced ovarian reserve and primary ovarian insufficiency, but very little is known regarding a possible direct role of abnormalities in the activation of proAMH at the ovarian level.

The activation of proAMH is thought to be dependent by proprotein convertase subtilisin/kexin-type-3 (PCSK3) and PCSK5 (3). The expression of these proteases is at least part controlled by hormones including luteinizing hormone (4), so the very frequent increase in mean luteinizing hormone levels in PCOS may lead to modification in the ovarian conversion rate of pro-AMH in active AMH.

Accordingly, while in ovarian follicular fluid from healthy women only 8% of AMH seems to be cleaved, it is as high as 24% in follicular fluid from PCOS patients. Hence the ovarian AMH cleaving path appears to be accentuated in PCOS (5).

Physiologically AMH impair the aromatazing capacity of granulosa cells in antral follicles. When follicles reach dimensions of 8-10 mm, the reduced AMH expression corresponds to the entrance of follicles at the stage of selection and dominance which is typically associated to increased estradiol production. Thus, AMH is clearly involved in the regulation of follicle growth initiation and the threshold for FSH sensitivity. That PCOS may be associated with an increase rate of the active AMH isoform, which may be responsible for a deeper inhibition of estradiol production by antral follicles, is in line with a central role of this hormone in the anovulation associated to PCOS.

In this issue, Wissing and colleagues (5) measured circulating levels of AMH isoforms with three different AMH ELISA assays in 88 PCOS women. The ratio between different AMH isoforms showed some relationship with metabolic parameters (such as lipids, body mass index, sex hormone binding globulin, and insulin resistance index). However, in contrast to previous articles (1, 2, 4, 5), the Wissing's study showed that the ratios of the AMH isoforms did not differ between PCOS and controls. Importantly it should be highlighted that the assays used were not the same in the different studies (1, 2, 5). Collectively the prediction of the PCOS condition was high for each AMH assay showing ROC-curves with an area under the curve between 90% and 92%.

All previously reported suggests that the recognition of different isoforms for AMH is undoubtedly interesting and increases the complexity of the AMH pathophysiology but at the same time we need to be cautious in advocating the clinical utility of using different assays with the objective of identifying and measuring different circulating isoforms of this hormone. For sure we need more research on sufficiently large samples of patients and with the specific objective of analyzing the ratio of the different isoforms either under physiologic conditions or in response to gonadal pathology.

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