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## **Anti Müllerian Hormone: more than a biomarker of female reproductive function**

Mathilde Victoria<sup>1</sup>, Julie Labrosse<sup>1</sup>, Fabien Krief<sup>1</sup>, Isabelle Cédric-Durnerin<sup>1</sup>, Marjorie Comtet<sup>1,2</sup>,  
Michaël Grynberg<sup>3,4,\*</sup>.

<sup>1</sup> Department of Reproductive Medicine and Fertility Preservation, Hôpital Jean Verdier, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance Publique - Hôpitaux de Paris, Bondy 93143, France

<sup>2</sup> University Paris XIII, 93000 Bobigny, France

<sup>3</sup> Department of Reproductive Medicine and Fertility Preservation, Hôpital Antoine Béclère, Hôpitaux Universitaires Paris Sud, Assistance Publique - Hôpitaux de Paris, Clamart 92140, France

<sup>3</sup> Université Paris-Sud, Université Paris Saclay, Le Kremlin Bicêtre 94276, France

<sup>4</sup> Inserm U1133 Université Paris Diderot, Paris 75013, France

\* Correspondance to: Prof. Michaël Grynberg, <sup>1</sup>Department of Reproductive Medicine and Fertility Preservation, Hôpital Antoine Béclère, 157, rue de la Porte de Trivaux, 92140 Clamart, France.  
Phone: +33145374053 ; Fax: +33145374980 ; Email: michael.grynberg@aphp.fr

# **Anti Müllerian Hormone: more than a biomarker of female reproductive function**

*Mathilde Victoria<sup>1</sup>, Julie Labrosse<sup>1</sup>, Fabien Krief<sup>1</sup>, Isabelle Cédrin-Durnerin<sup>1</sup>, Marjorie Comtet<sup>1,2</sup>, Michaël Grynberg<sup>3,4,5</sup>*

**1.** Department of Reproductive Medicine and Fertility Preservation, Hôpital Jean Verdier, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance Publique - Hôpitaux de Paris, Bondy 93143, France

**2.** University Paris XIII, 93000 Bobigny, France

**3.** Department of Reproductive Medicine and Fertility Preservation, Hôpital Antoine Bécclère, Hôpitaux Universitaires Paris Sud, Assistance Publique - Hôpitaux de Paris, Clamart 92140, France

**4.** Université Paris-Sud, Université Paris Saclay, Le Kremlin Bicêtre 94276, France

**5.** Inserm U1133 Université Paris Diderot, Paris 75013, France

- **Corresponding author:**

**Pr. Michael Grynberg**

Department of Reproductive Medicine and Fertility Preservation

Hôpital Antoine Bécclère, 157 rue de la Porte de Trivaux, 92140 Clamart, France

Telephone: +33145374053

Fax: +33145374980

michael.grynberg@aphp.fr

## **Abstract**

Anti-Müllerian hormone (AMH), known for its role during sexual differentiation, is a dimeric glycoprotein that belongs to the transforming growth factor- $\beta$  (TGF- $\beta$ ) family. AMH has recently been identified as a reliable marker of ovarian reserve that can help predict early ovarian follicle loss and menopause onset. AMH levels also reflect the effects of damaging gynecologic surgeries or gonadotoxic treatments such as chemotherapy on ovarian reserve. Furthermore, AMH participates in the diagnosis of certain diseases such as granulosa cell tumors or Polycystic Ovary Syndrome (PCOS). Currently used to establish patient profiles and predict ovarian response to stimulation, its role in ART techniques is crucial. Nevertheless, AMH appears to be a weak independent predictor of qualitative outcomes such as implantation, pregnancy, and live birth. As the reliability and reproducibility of AMH dosage have raised many doubts due to different existing standards and thresholds, an international consensus is still expected to improve AMH measurement and interpretation.

**Short title:** AMH in female

**Keywords:** Anti-Müllerian Hormone; AMH; ovarian reserve; menopause onset

## 1 **Introduction**

2 Anti-Müllerian Hormone (AMH), a homodimeric glycoprotein belonging to the transforming  
3 growth factor  $\beta$  (TGF- $\beta$ ) superfamily, has first been described in the 1940s by Alfred Jost for  
4 its role in male sexual differentiation (1, 2). It is today also known for its determining role in  
5 ovarian function (3, 4). Encoded on chromosome 19, (19p13.2-13.3), its molecular weight is  
6 of 140 kDa and its signaling pathway is mediated through two serine/threonine kinase  
7 transmembrane receptors (5, 6). AMH binds to AMH type II receptor, which provokes the  
8 phosphorylation of AMH type I receptor and consequent downstream signaling through the  
9 activation of Smad proteins. After translocation to the nucleus, phosphorylated Smad proteins  
10 activate or inhibit the transcription of specific genes (7).

11

## 12 **Biological roles of AMH**

13 In males, the SRY gene expressed on chromosome Y is responsible of testicular  
14 differentiation. Müllerian ducts regress under the influence of AMH (produced by Sertoli cells  
15 from the end of the 7th week of gestation), and Wolffian ducts are maintained under the  
16 influence of testosterone (produced by Leydig cells). Virilization of the external genitalia is  
17 then induced by the transformation of testosterone into dihydrotestosterone (DHT).

18

19 In females, Müllerian ducts persist and develop into what will become the tubes, the uterus  
20 and the upper part of the vagina. AMH secretion by ovarian granulosa cells starts around 36  
21 weeks of gestation, reaches a peak around 25 years of age, and continues until menopause (8).  
22 AMH is mostly secreted by primary, secondary, pre-antral and small antral follicles (< 4mm)  
23 (9). No AMH secretion is observed in FSH-dependent nor atretic follicles (10, 11).

24 Most studies concerning the role of AMH in ovaries were performed in mouse model. Faster  
25 rates of primordial follicular recruitment were observed in absence of AMH, resulting in a

26 depleted ovarian reserve at a younger age (12). In humans, an *in vitro* analysis of ovarian  
27 cortical tissue suggested that AMH was also involved in the inhibition of follicular  
28 recruitment (13). AMH may also protect growing follicles from premature maturation by  
29 opposing the effects of FSH (14).

30

31 In an analysis of 42 women undergoing oophorectomy for benign gynecologic reasons,  
32 Hansen *et al.* reported a correlation between AMH levels and the number of primordial  
33 follicles present in ovarian tissue (15). Antral follicle count (AFC - defined as the number of  
34 follicles of 2 to 10 mm on both ovaries estimated by ultrasound) and AMH are currently  
35 considered as the most reliable biomarkers for the assessment of ovarian reserve, which is  
36 consistent with the idea that AMH is mainly produced by small follicles (10). Dewaily *et al.*  
37 suggested that Body Mass Index (BMI), menstrual cycle length, as well as FSH, LH and  
38 testosterone levels could explain discordant values of AMH and AFC observed in a same  
39 patient (16).

40

#### 41 **Measurement of AMH levels**

42 A challenge in the interpretation of AMH dosage relies in the different standards and  
43 thresholds that exist. Serum AMH is found in different forms: an inactive non-cleaved form  
44 known as pro-AMH and a cleaved, biologically active form called AMH(N,C). AMH(N,C) is  
45 composed of N-terminal and C-terminal non-covalently associated fragments that can bind to  
46 AMH receptors (AMH RII) (17). Pro-AMH and AMH(N,C) are detected by an immunometric  
47 method in which a capture antibody and a detecting antibody bind to the N-terminal or C-  
48 terminal portions of AMH. The existence of an isolated C-terminal form (AMHC) in serum is  
49 currently being debated.

50 Despite a large number of publications over the last 10 years, the reliability and  
51 reproducibility of AMH measurement have raised many doubts, mainly due to the operator-  
52 dependent manual dosing technique that uses different antibodies and thresholds: Elisa assays  
53 (mainly Beckman Gen II and EIA/AMH Immunotech) and two Anshlab assays:  
54 (Ultrasensitive (Al-105i) and Pico-AMH). Since 2014, automated dosing techniques have  
55 been developed to overcome these limitations and improve the sensitivity and reproducibility  
56 of AMH measurements. Elecsys AMH (Roche Diagnostics International) and Access AMH  
57 (Beckman Coulter) kits have shown superiority over manual assays, with 15% to 20% lower  
58 values, but have the disadvantage of using different thresholds (18). In 2017, Peigné *et al.*  
59 (17) compared different AMH kits available in France: three manual (AMH Gen II,  
60 Ultrasensible Al - 105i, AL-124i or « pico-AMH) and two automated ones (Elecsys AMH,  
61 AMH Access Dxi). The two automated methods were four times more accurate, faster (18-40  
62 min vs. 4-6h for manual), ten times more sensitive than Elisa assays, required less serum for  
63 analysis (50 mL) and reduced 5 inter-laboratory variations (18,19). Differences between kits  
64 were mostly observed for low AMH values. Values obtained with Access Dxi were equal or  
65 lower to that of Gen II, and Elecsys Roche values were 12 to 28% lower. No difference was  
66 observed between the two automated assays.

67

68 A recent study reported that median values of AMH were of 2.69 ng/mL (Access) and  
69 2.34ng/mL (Roche) between 18 and 35 years old (20). Anckaert *et al.* (21) suggested median  
70 age-specific values of AMH for normo-ovulating women with Elecsys assays: 4 / 3.31 / 2.81 /  
71 2 / 0.882 and 0.071 ng/mL for age ranges respectively : 20-24 / 25-29 / 30-34 / 35-39 / 40-44  
72 and 45-50 years old. International standards are expected in order to measure AMH levels  
73 accurately, as precise measurement of low AMH levels is notably important for post  
74 chemotherapy evaluation of ovarian recovery (22).

75 **Serum AMH variations**

76 Nomograms on AMH levels in normo-ovulatory women from birth to menopause have been  
77 developed (23, 24). The first full description of AMH production up to menopause in healthy  
78 women was lead by Kelsey *et al.* in 2011, showing that 34% of AMH variation was due to  
79 age. A peak of secretion of AMH is observed during neonatal life, before puberty, and around  
80 24.5 years of age. AMH then declines until menopause. Variations of AMH levels during the  
81 first months of life can be explained by an activation of the hypothalamic-pituitary-gonadal  
82 axis during neonatal period that induces a transient increase of gonadotropins that stimulates  
83 hormone production (25). Moreover, since AMH inhibits FSH-dependent follicle recruitment  
84 and FSH-dependent follicular growth, the production of AMH may limit inappropriate  
85 activation of follicular growth related to high rates of neonatal FSH. Between ages 8 to 24,  
86 plasma AMH concentrations remain relatively stable (26). Small fluctuations during the  
87 pubertal transition have been reported, but appear to be minimal (27). After a peak between  
88 16 and 25 years old, AMH declines until menopause, reflecting the progressive depletion of  
89 ovarian reserve (23, 27, 28).

90 AMH levels do not considerably vary within and between cycles, contrarily to other hormonal  
91 markers of ovarian follicular status (FSH, estradiol, Inhibin B) (29, 30). Contradictory results  
92 were observed concerning the influence of hormonal contraception (HC) on serum AMH  
93 levels, some observing lower AMH levels in women using HC, while others did not find a  
94 significant difference (31). Kucera *et al.* observed no negative impact of HC on AMH serum  
95 levels in women examined one year after termination of HC used during at least ten years  
96 (32).

97 **Prediction of the age of menopause onset**

98 Mean age of menopause is estimated around 51 years old (33). Individualized counseling,  
99 early treatment or oocyte preservation can be options for patients concerned by early  
100 menopause. However, so far, no marker exists to assess the onset of menopause. AMH may  
101 be a more effective marker than FSH, menstrual irregularity, or maternal age (34, 35). AMH  
102 serum levels decline with age; starting from 21 years of age and onwards, AMH levels  
103 decrease from 5.6% per year, and become undetectable during the 3 to 5 years before  
104 menopause onset (36, 37). Consequently to Broer *et al.* (38), Depmann *et al.* (20) showed in a  
105 prospective study that AMH significantly predicted menopause in a model next to age.  
106 However, coherently to other studies, AMH appeared to be less effective to predict extreme  
107 menopausal ages (34, 39, 40).

108 A recent prospective study lead on 327 women concerned by early menopause showed that  
109 every AMH decrease of 0.10 ng/mL was associated to a 14% higher risk  
110 of early menopause (95% CI [1.10-1.18];  $p < 0.001$ ) (41). After adjusting on demographic,  
111 behavioral, and reproductive factors, the calculated odds ratios for early menopause  
112 associated with AMH levels of 1.5, 1.0 and 0.5 ng/ml were 2.6, 7.5 and 23, respectively,  
113 compared to an AMH level of 2.0 ng/ml ( $p < 0.001$ ). Furthermore, a meta-analysis (42) lead  
114 on 2596 patients (of which 1077 menopausal women) showed that AMH associated to age  
115 was more effective in the prediction of early menopause than age alone (Hazard Ratio: 1.01  
116 and 95% CI [0.97-1.04] for age alone vs. Hazard Ratio: 0.33 and 95% CI [0.24-0.45] for age  
117 + AMH). Nevertheless, a precise AMH threshold remains to be defined and other variables  
118 such as maternal age of menopause, genetics, and lifestyle factors (smoking, BMI, use of  
119 alcohol, parity) have to be considered.

120 **Prediction of the risk of iatrogenic amenorrhea**

121 Treatments such as chemotherapy (CT), radiotherapy, ovarian surgery or artery embolization  
122 are known to have detrimental effects on female fertility. The ovarian toxicity of CT relies in  
123 increased apoptotic processes, cortical fibrosis and blood vessel injury and varies with age,  
124 treatment and dosage (43, 44). Alkylating agents are identified to be the most ovariotoxic  
125 existent agents, but no clear threshold yet exists for a safe alkylating agent dose (44).  
126 Ovariotoxicity of other chemotherapy agents remains debated and poorly documented. A  
127 systemic review by Silva *et al.* showed that exposure to taxanes was negatively associated  
128 with menses recovery (45).

129

130 Recent studies have suggested that AMH could be used to predict ovarian follicle loss for CT  
131 patients. A study including 59 women treated with chemotherapy for early breast cancer  
132 demonstrated that long-term ovarian function after treatment could be predicted by  
133 pretreatment serum AMH concentrations and that this marker was the only significant  
134 predictor of menses after 4-5 years compared to age, Inhibin B and FSH (46). AMH also  
135 enables to follow the evolution of ovarian reserve during chemotherapy. Anderson *et al.*  
136 reported a 55% decrease of AMH levels after one CT cycle and that baseline AMH levels  
137 were significantly correlated with AMH levels after the first CT cycle, as they remained  
138 higher in patients with higher baseline serum AMH levels (46). In 2017, Dezellus *et al.*  
139 analyzed a large prospective multicentric cohort of 249 breast cancer patients (47). Mean  
140 basal AMH levels were of 4.19ng/mL (median 2.95ng/mL). Four months after CT  
141 completion, AMH levels were of  $0.78 \pm 1.40$ ng/mL. Women with post-chemotherapy  
142 amenorrhea were significantly older and had lower basal AMH levels than women that  
143 recovered menses (47). Moreover, a prognostic score to estimate the time to recovery of  
144 ovarian function following chemotherapy was developed based on 109 breast cancer patients,

145 considering age, AMH and BMI (48). Patients with AMH levels above 0.7 ng/mL before  
146 chemotherapy, under 40 years old, and overweight or obese (BMI > 25) were more likely to  
147 regain ovarian function.

148

149 Radiation therapy is also recognized as highly ovario-toxic even at low doses, associated to  
150 extremely low or undetectable AMH dosages in post-treatment patients (49). Furthermore, the  
151 damage of gynecological surgeries on ovarian function (endometriomas, cysts, etc.) can be  
152 evaluated by comparing pre- and post-operative AMH levels (50). Endometrioma surgery is  
153 associated with a significant decrease in AMH levels, corresponding to an important removal  
154 of ovarian tissue (51-54), and is correlated with the bilaterality and severity of endometriomas  
155 (55). It is therefore crucial to consider these consequences before operating patients with  
156 endometriosis that have a pregnancy desire.

157

### 158 **AMH and fertility**

159 It remains unclear whether low AMH levels are predictive of lower spontaneous fertility (56).  
160 Adjusted on age, a prospective study lead on patients aged from 30 to 44 years old found  
161 lower fertility rates in patients with AMH levels under 0.7 ng/mL (57). Conversely, by  
162 measuring biomarkers of ovarian reserve (AMH, FSH and Inhibin B) in 750 women aged  
163 from 30 to 44 years old without a history of infertility, Steiner *et al.* (58) showed that women  
164 with low AMH levels (<0.7ng/mL) did not have a significantly different predicted probability  
165 of conceiving compared to other women, after 6 cycles (65% vs. 62%, respectively), nor after  
166 12 cycles (84% vs. 75%). Similarly, a study of 87 women found no correlation between  
167 baseline AMH levels and time required to conceive naturally (52). Pregnancies were reported  
168 even in women with undetectable AMH levels, particularly for young patients (59).

169 A study comparing three groups of patients according to AMH levels (low: < 1.3ng/mL  
170 (9.5pmol/L), intermediate: 1.3-4.6ng/mL (9.5-33pmol/L), and high: > 4.6ng/mL (33pmol/L))  
171 observed significantly increased pregnancy rates and reduced time to pregnancy for women  
172 with high AMH levels, compared to women with intermediate and low AMH levels (60).  
173 However, highest pregnancy rates (84.1%) were seen in regular cycling women with high  
174 AMH and spontaneous pregnancies were observed in patients with AMH levels down to  
175 0.2ng/mL (1.2pmol/L) (60). Conversely, fecundability in young healthy patients (19 to 35  
176 years old) seems to be reduced when associated to high AMH levels ( > 5.5 ng/mL) (39  
177 pmol/L) compared to AMH levels under 2ng/mL (14pmol /L), which could be explained by  
178 polycystic ovary syndrome patients (61).

179

180 AMH appears to be a weak independent predictor of qualitative outcomes of ART such as  
181 implantation, pregnancy, and live birth. In a meta-analysis by Iliodromiti *et al.* comprising  
182 6.356 women, the predictive accuracy of AMH on live birth in women undergoing IVF was  
183 poor (62). In a meta-analysis of 5.373 women undergoing IVF, Tal *et al.* (63) found that the  
184 area under ROC curve (AUC) for AMH in prediction of clinical pregnancy was of 0.63 (95%  
185 CI [0.618–0.650]).

186

187 Although an AMH threshold of 1 ng/mL (7.1 pmol/L) is usually taken, no clear AMH level  
188 threshold exists to conclude on a low, normal or increased ovarian reserve, nor on the chances  
189 of a future pregnancy (64). As other factors most likely affect pregnancy chances, clinicians  
190 should not only rely on the dosage of AMH, but on the patient's whole clinical context. The  
191 poor predictive power of AMH for live births should thus be kept in mind when counseling  
192 infertility patients regarding ART outcomes, and low or even undetectable AMH values  
193 should not be used as a sole factor in excluding patients from undergoing ART. Moreover,

194 clinicians should consider the psychological impact of AMH routine testing for women  
195 potentially that might lead to unjustified anxiety.

196

197 **Prediction of ovarian response to stimulation: Individualized Controlled Ovarian**  
198 **Stimulation (iCOS)**

199 Serum AMH values help identify patient profiles and predict response to ovarian stimulation  
200 (65). Thus, AMH associated to antral follicular count may be the best predictive marker of  
201 hyper- or hypo-response (66). Since 2013, dosing AMH before IVF is recommended by  
202 ESHRE (European Society of Human Reproduction and Embryology) and NICE (National  
203 Institute of Excellence for Health and Care) to individualize strategies for ovarian stimulation.  
204 The NICE consensus sets the threshold of 0.75ng/mL (5.4 pmol/L) for a predictive low  
205 response to stimulation and that of 3.5 ng/mL (25 pmol/L) for a strong response (67). More  
206 recently, the POSEIDON group has defined several factors, including AMH, as tools to help  
207 treatment decisions. Defined with the manual dosing technique (17), the AMH threshold  
208 associated to low response was 1.2 ng/mL (8.6 pmol/L) (68, 69). Recent data suggest that the  
209 individualization of ovarian stimulation, based on specific measurement of parameters  
210 specific to each patient, improves results while reducing treatment cost (70). Thus, AMH is a  
211 key tool to determine the initial stimulation dose to be administered, enabling individualized  
212 counseling and strategy adjustments.

213

214 **AMH: a diagnostic tool**

215 **Granulosa Cell Tumors**

216 Granulosa cell tumors (GCT), the most common type of tumor of the "sex cord-stromal  
217 tumors" family, are rare tumors of variable malignancy. Although signs of clinical  
218 hyperestrogenesis or the presence of a unilateral, adnexal mass (either cystic, multilocular, or

219 both solid and cystic) in MRI can lead to its diagnosis, its preoperative diagnosis remains  
220 difficult to establish. Conventional ovarian tumor markers (CA125, CA19-9 and ACE) are  
221 generally elevated. By aromatizing androgens, the tumor secretes both estrogen, inhibin B,  
222 and AMH. Studies suggested AMH as a robust marker of tumor recurrence, progression and  
223 treatment efficacy in adult type GCTs, more sensitive than serum inhibin levels and more  
224 specific than estradiol levels (71-73). Chang *et al.* observed a significant correlation between  
225 aggregate tumor mass and serum AMH levels, in pathological specimens and when  
226 determined non-invasively by abdominal CT or MRI (74). Walter *et al.* showed that elevated  
227 AMH concentrations in female dogs were indicative of granulosa cell tumors (75). However,  
228 negative testing does not rule out the existence of small GCTs, and differentiating granulosa  
229 cell tumors from luteinized follicular cysts may be difficult. In a meta-analysis published in  
230 2009 evaluating the performance of Inhibin B and AMH in the diagnosis and monitoring of  
231 GCT, authors reported that the sensitivity of Inhibin varied from 89 to 100 % and that of  
232 AMH from 76 to 91%, both with high specificity (91-100%) (76).

233

### 234 **Polycystic ovary syndrome (PCOS)**

235 Concerning 5 to 10 % of women, Polycystic Ovary Syndrome (PCOS) is the most common  
236 cause of chronic anovulation and hyperandrogenism in young women. Since 2003, PCOS is  
237 defined by the Rotterdam classification (2003), requiring at least 2 out of the 3 following  
238 characteristics: (i) cycle disorder, (ii) clinical or biological hyperandrogenism, (iii) antral  
239 follicular excess on ultrasound with  $\geq 12$  follicles from 2 to 9 mm per ovary and/or ovarian  
240 volume  $\geq 10$  mL. Due to the capacity of ultrasonographic technology to detect smaller  
241 follicles, the cut off is now of 19 to 25 follicles (77, 78). This threshold is nonetheless still  
242 dependent on the operator and ultrasound equipment, and might continue to increase (79).

243

244 Since a solid correlation exists between AMH and AFC, AMH may play a role in the  
245 diagnosis of PCOS. Its use is yet not recognized in clinical practice. In vitro, AMH production  
246 by granulosa cells was found to be 4-fold higher in normo ovulatory PCOS and 75-fold higher  
247 in anovulatory PCOS compared to normal ovaries, suggesting that AMH in PCOS women is  
248 not only explained by the increase of pre-antral and small antral follicles (80). The role of  
249 androgens has been evoked, since a positive correlation between serum androgen and number  
250 of follicles has been reported. The overproduction of androgens could be an intrinsic defect of  
251 theca cells in PCOS patient (81, 82). Serum AMH levels could therefore be correlated to the  
252 severity of PCOS symptoms (hyperandrogenism or severity of ovulation disorders).

253

254 AMH may be used as an item in the Rotterdam classification. However, no AMH threshold  
255 exists to define PCOS. With the enzyme immunoassay AMH-EIA by Beckman Coulter  
256 Immunotech, Dewailly *et al.* (83) found that serum AMH levels were a more reliable marker  
257 of polycystic ovarian morphology (PCOM) than follicle number, and suggested an AMH  
258 threshold of 5 ng/mL (35pmol/L) to be included in the current diagnostic classifications of  
259 PCOS. In 2013, a systematic review and meta-analysis have leaned the capacity of AMH to  
260 diagnose PCOS (84). Ten studies were included and a summary ROC curve was constructed.  
261 Using a cutoff level of 4.7ng/mL, AMH had a 82.8% sensitivity and a 79.4% specificity for  
262 PCOS diagnosis, with an AUC of 0.87. Pigny *et al.* (85) recently compared threshold values  
263 according to five types of assays (tested manual assays: Gen II, EIA AMH / MIS Immunotech  
264 and Ultrasensitive Anshlab, and automatic assays: Access Dxi and Elecsys Cobas). AMH  
265 thresholds of 5.6 ng/mL (40 pmol/L) for manual tests and 4.2ng/mL (30pmol/L) for  
266 automated tests were defined. Despite the absence of consensus on an AMH threshold for  
267 PCOS diagnosis (85), serum AMH assays might be an interesting alternative, and are  
268 recommended by the American Association of Clinical Endocrinologists (86). The new

269 ESHRE guidelines published in 2018 do not recommend the use of serum AMH levels as an  
270 alternative for the detection of PCOM, nor as a single test for the diagnosis of PCOS (87).  
271 However, it is mentioned that with improved standardization of assays and established cut off  
272 thresholds validated in large scale populations of different ages and ethnicities, AMH assays  
273 would be a reliable diagnosis tool for PCOM.

274

### 275 **Unresponsiveness of antral follicles to FSH**

276 Savage syndrome or unresponsiveness of antral follicles to FSH is very rare syndrome  
277 characterized by the association of primary amenorrhea, gonadotropin levels at menopausal  
278 range, and normal antral follicle count. This condition is frequently misdiagnosed and  
279 confused with ovarian failure. A normal AMH assay according to age, indicating the presence  
280 of antral follicles, could help establish its diagnosis. Although these patients are poor  
281 responders to ovarian stimulation, they may be candidates for oocyte in vitro maturation  
282 (IVM) rather than initially being oriented towards oocyte donation. The first case report on  
283 IVM in a 29-year-old Savage Syndrome patient has been published in 2013. The patient had  
284 high gonadotrophin levels, normal serum AMH levels (between 4,36 and 4,50 ng/mL) and an  
285 AFC between 18 and 23 (88). Fifteen immature oocytes were obtained, 12 of which reached  
286 metaphase II, leading to seven embryos and three transfers. A pregnancy was obtained and the  
287 patient delivered a healthy baby at term.

288

### 289 **Perspectives**

290 Research on AMH opens new perspectives, especially in therapeutics. Devoid of any toxicity,  
291 AMH may be a potential natural anti-cancer agent to treat tumors expressing the AMH  
292 receptor. Furthermore, the administration of recombinant AMH during treatment could reduce  
293 follicular loss induced by chemotherapy.

294 **Conclusion**

295 As a reliable marker of ovarian reserve, AMH plays an increasing role in the prediction of  
296 menopause onset, iatrogenic amenorrhea, and ovarian response to stimulation in ART  
297 techniques, thus facilitating individualized counseling of patients. Since no clear AMH level  
298 threshold exists to conclude on a low, normal or increased ovarian reserve, an international  
299 consensus on AMH measurement is expected.

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