Anti Müllerian Hormone:
New roles for an established biomarker of ovarian reserve

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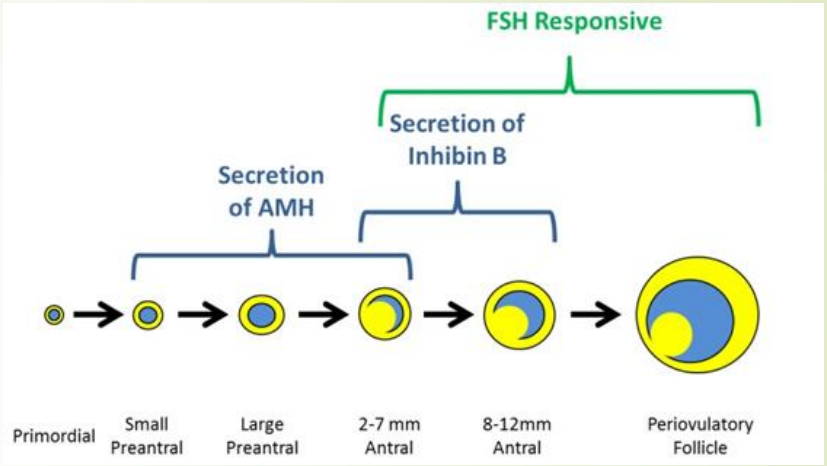
Introduction

- Anti Müllerian Hormone (AMH): an homodimeric glycoprotein that belongs to TGF-b superfamily
- In females, AMH is secreted by primary, secondary, pre-antral and small antral follicles (< 7 mm).
- The fact that its serum concentration is strongly correlated with the ultrasound marker antral follicle count (AFC), (r > 0,7),

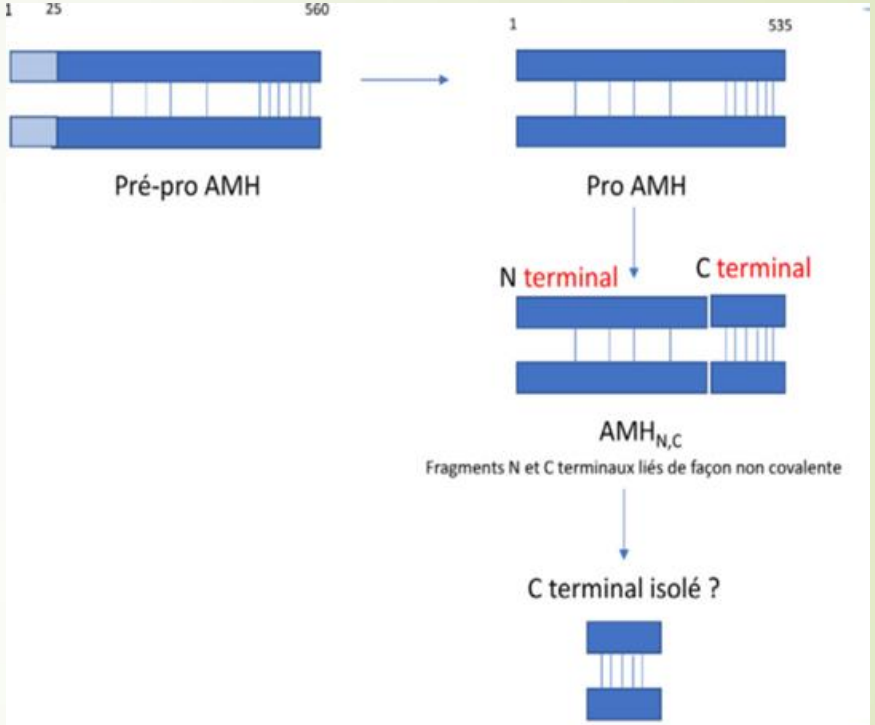
  makes AMH a reliable biomarker of ovarian function and ovarian reserve

  AMH has also the advantage of low variation within and between cycles.
- Recent studies suggested some other roles for AMH:
  - prediction of menopause onset,
  - ovarian response to stimulation in Assisted Reproduction Technologies (ART)
  - iatrogenic amenorrhea due to gonadotoxic cancer treatment
  - marker of Polycystic Ovary Syndrome (PCOS)



Measurement of AMH

- In serum, AMH is found in different forms:
  - an inactive non-cleaved form known as pro-AMH
  - a cleaved, biologically active form composed by N- and C-terminal fragments
  - Both Pro-AMH and active AMH are detected by immunometric assays.
- Until 2014, manual enzyme-immunoassays
  - mainly **Beckman**, **Immunotech**, and **Anshlab** assays
- After 2014, automated immunoassay have been developed
  - **Roche Elecsys** and **Beckman-Coulter Access**
- Automated immunoassays:
  - have improved the sensitivity and reproducibility
  - show 15% to 20% lower values compared to manual assays.

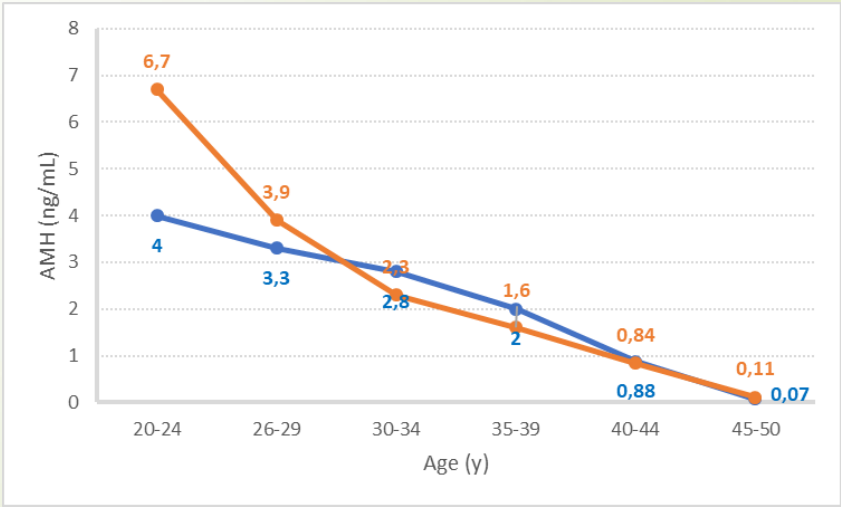


Peigne' M, Robin G, Catteau-Jonard S, Giacobini P, Dewailly D, Pigny P. [How to deal with the different serum AMH kits in France in 2017?] Gynecol Obstet Fertil Senol 2017;45(10):558–65

AMH and Age

- AMH concentrations strongly decline with woman's age
- Estimated decline rate:
  - **0,2 ng/mL per year**
  - **34% of total variation of AMH values is due to age**
- In normo-ovulatory women, a peak of AMH secretion is observed between 20-25 years, with AMH values decline thereafter until menopause
- In a study of 2016, measured AMH for normo-ovulating women with Elecsys assay and calculated age-specific medians (**blue**)
- We also measured AMH with Roche Cobas e411 and we found similar values (**orange**)

Age range	AMH (ng/mL)	AMH (Our study)
20-24	4,0	6,70
26-29	3,3	3,90
30-34	2,8	2,30
35-39	2,0	1,60
40-44	0,88	0,84
45-50	0,07	0,11
> 51		< 0,10



E. Anckaert et al., Multicenter analytical performance evaluation of a fully automated anti-Müllerian hormone assay and reference interval determination. Clin Biochem 49, 260-7 (2016)

AMH and menopause

- The age of menopause is important for all women
  - Especially: seeking fertility, individualized counseling, or oocyte preservation.
- No marker enough reliable exists to assess the onset of menopause.
  - Studies propose that AMH may be a more effective marker than **FSH**, **menstrual irregularities**, or **maternal age**
  - AMH levels decrease by **5.6% per year**, and become undetectable during the **3–5 years before the onset of menopause**.
- A meta-analysis (M. Depmann, 2018) showed that AMH associated to age, was more effective in the prediction of early menopause than age alone
- But, there is no consensus about a specific AMH threshold for menopause

M. Depmann et al., Does AMH relate to timing of menopause? Results of an Individual Patient Data meta-analysis. J Clin Endocrinol Metab, 103, 3593-3600 (2018).

AMH and Chemotherapy

- Treatments such as chemotherapy (CT), radiotherapy, ovarian surgery, are known to have detrimental effects on ovaries and female fertility in general.
- Recent studies have suggested that AMH could be used to predict ovarian follicle loss after CT treatment
- In a large prospective study of breast cancer patients (A. Dezellus, 2017),
  - mean AMH levels before CT: **4.19 ng/mL**
  - 4 months after CT AMH levels: **0.78 ng/mL (more than 80% loss)**
- Another study found that the group of patients who had before CT:
  - AMH levels above 0.7 ng/mL,
  - Age under 40 years,
  - BMI > 25 (overweight or obese)
- **Had the greater possibility to regain ovarian function after CT**

A. Dezellus et al., Prospective evaluation of serum anti-Müllerian hormone dynamics in 250 women of reproductive age treated with chemotherapy for breast cancer. Eur J Cancer 79, 72-80 (2017).

AMH and Fertility

- It remains unresolved whether low AMH levels are predictive of lower spontaneous fertility
- One prospective study on patients aged from 30 to 44 years:
  - found lower fertility rates in patients with AMH levels **under 0.7 ng/mL**.
- Conversely, another study showed that women with low AMH levels (< 0.7 ng/mL):
  - **did not have a significantly different predicted probability of conceiving** after 6 or 12 cycles
- AMH appears to be a weak independent predictor of qualitative outcomes in ART like implantation rate, pregnancy rate, or live birth
- Although different AMH values have been proposed (from 0,3 to 1 ng/mL), still no clear AMH threshold exists:
  - to conclude on a **low, normal or increased ovarian reserve**
  - To estimate **chances of a future pregnancy**.

AMH and Polycystic Ovary Syndrome

- Polycystic ovary Syndrome (PCOS) is the most common cause of chronic anovulation and hyperandrogenism in young women
- It is estimated that concerns about 5 to 10% of all women
- Definition of PCOS (Rotterdam criteria 2003): includes any 2 of the following 3 criteria:
  - Menstrual irregularities
  - Clinical or biochemical hyperandrogenism
  - Polycystic ovary morphology (PCOM)-Excess antral follicles
- It was hypothesized that AMH may play a role in the diagnosis of PCOS, given its strong correlation with AFC

AMH and Polycystic Ovary Syndrome (2)

- Firstly, studies have found that AMH is more elevated in anovulatory PCOS than in ovulatory, compared to normal cycles
  - Elevated AMH levels in PCOS is not explained only by the number of pre-antral follicles but also by the severity of symptoms
- Secondly: no AMH clear threshold exists to diagnose PCOS
  - In a metanalysis (Iliodromiti 2013) of ten studies, using a cutoff **4.7 ng/mL**, found SE: 82.8%, Sp: 79.4% for the diagnosis of PCOS
  - Other studies have proposed cutoffs: 4.2 ng/mL (30pM) or 5.6 ng/mL (40pM) or the combination of AMH with Testosterone or FAI
- American Association of Clinical Endocrinologists (2015) proposed that AMH might be an interesting alternative for the diagnosis of PCOS
- The new ESHRE guidelines (2018) do not recommend AMH as an alternative for the detection of PCOM, nor as a single test for the diagnosis of PCOS

Iliodromiti S, Kelsey TW, Anderson RA, Nelson SM. Can anti-Mullerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data. J Clin Endocrinol Metab 2013;98(8):3332–40.

Conclusion

- AMH have been proposed as a biomarker for almost all the procedures (normal or pathological) that ovary is involved
- It seem that it has a significant role:
  - In the prediction of menopause
  - Iatrogenic amenorrhea
  - Ovarian response to stimulation in ART
- Future studies will possibly strengthen its role in the above, and reveal new areas where AMH could be useful as a biomarker

Thank you