The role of anti-Müllerian hormone (AMH) - Assessing Ovarian Reserve and more?

Siemens Healthineers Academy

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OVERVIEW

- Infertility
- Ovarian reserve
- Assessing ovarian function
- AMH
- Clinical utilities
- AMH assays

INFERTILITY

- Inability to conceive after 12 months of unprotected intercourse
- Prevalence: 10% to 15% of couples in West-Europe
- Etiology:
  - > 35% female factor
  - > 35% male factor
  - > 20% combination of both male and female factors
  - > 10% “unexplained infertility”

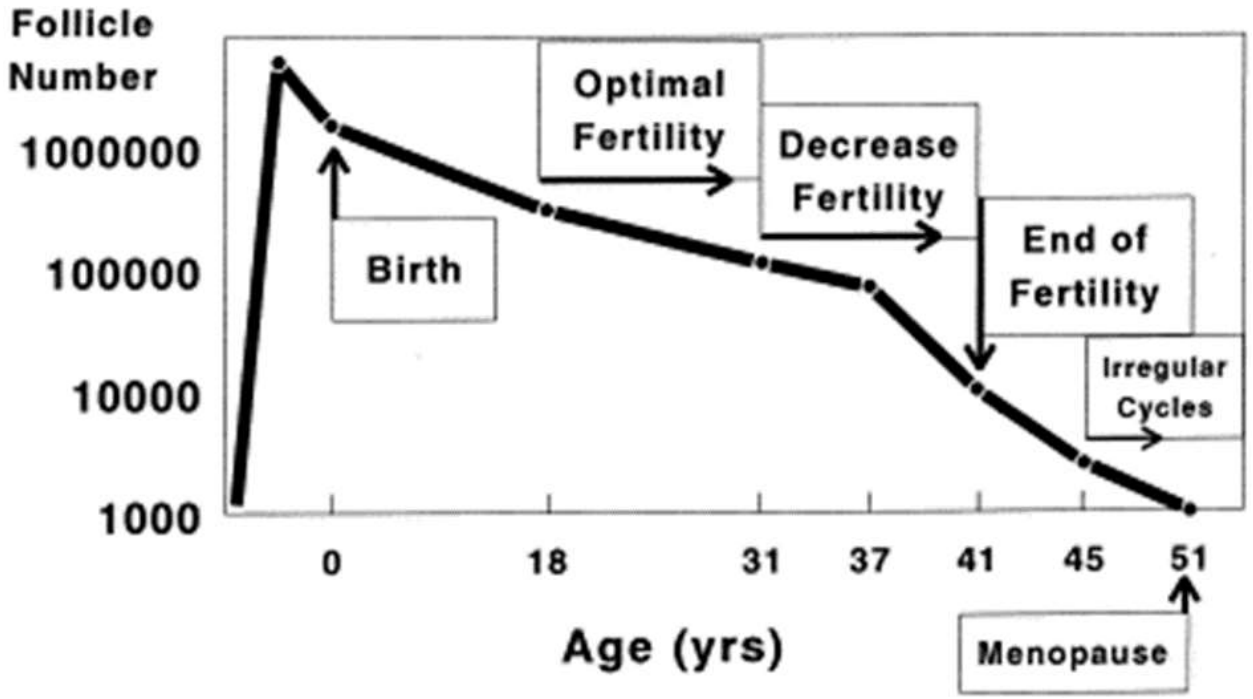
CAUSES OF INFERTILITY

- Non-adequate semen
- Hormonal abnormalities:
  - Hypergonadotropic hypogonadism: LH & FSH ↑; androgens ↓
  - Hypogonadotropic hypogonadism: LH & FSH ↓; androgens ↓
  - Hyperprolactinemia: prolactin ↑

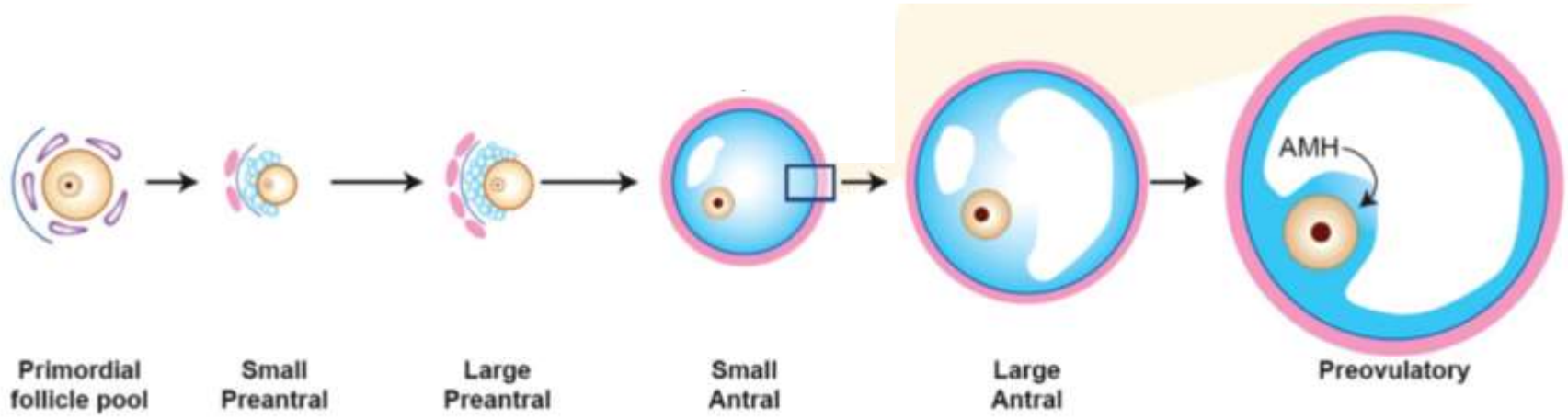
- Hypogonadotropic hypogonadism (WHO I, 10-30%): LH & FSH ↓; E2 ↓
- Normogonadotropic anovulation (WHO II, mainly PCOS: 70-85%): LH > FSH; SHBG ↓, androgens ↑
- Hypergonadotropic hypogonadism (WHO III, 5-10%): LH & FSH ↑; E2 ↓
- Hyperprolactinemia (5-10%): prolactin ↑

OVARIAN RESERVE

- Indicator of fertility
- Size of ovarian **primordial** follicle pool, reflected by the number of growing follicles
- Finite number of oocytes: declines with increasing age



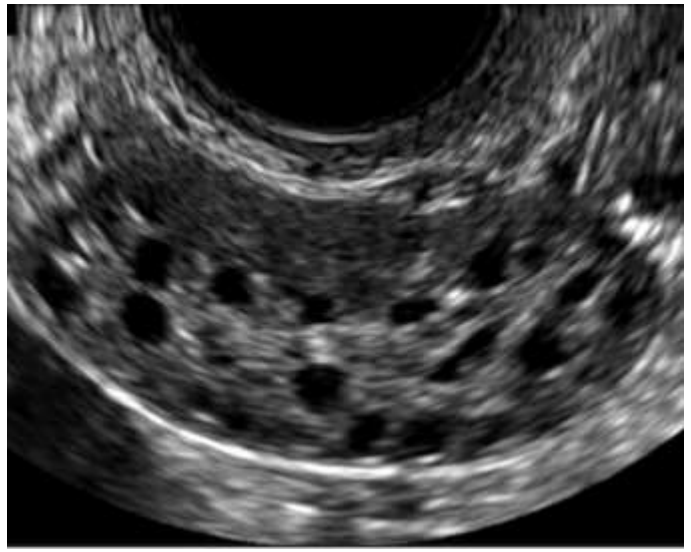
FOLLICULOGENESIS



ASSESSING OVARIAN FUNCTION

Direct measurement of ovarian function

- Antral follicle count = gold standard
  - By transvaginal ultrasonography during the early-follicular stage
  - Antral follicles of 2–10 mm counted in both ovaries
  - Sum of antral follicles = antral follicle count (AFC)



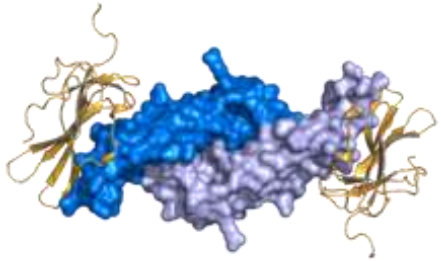
Total AFC	Ovarian Reserve	Interpretation
0–4	Very low	Very high risk of poor response to ovarian stimulation, decreased chance of pregnancy
5–8	Low	High risk of poor response to ovarian stimulation
9–19	Normal	Expected normal response to ovarian stimulation
≥20	High	High risk of excessive ovarian response and ovarian hyperstimulation syndrome

ASSESSING OVARIAN FUNCTION

Indirect measurement of ovarian function

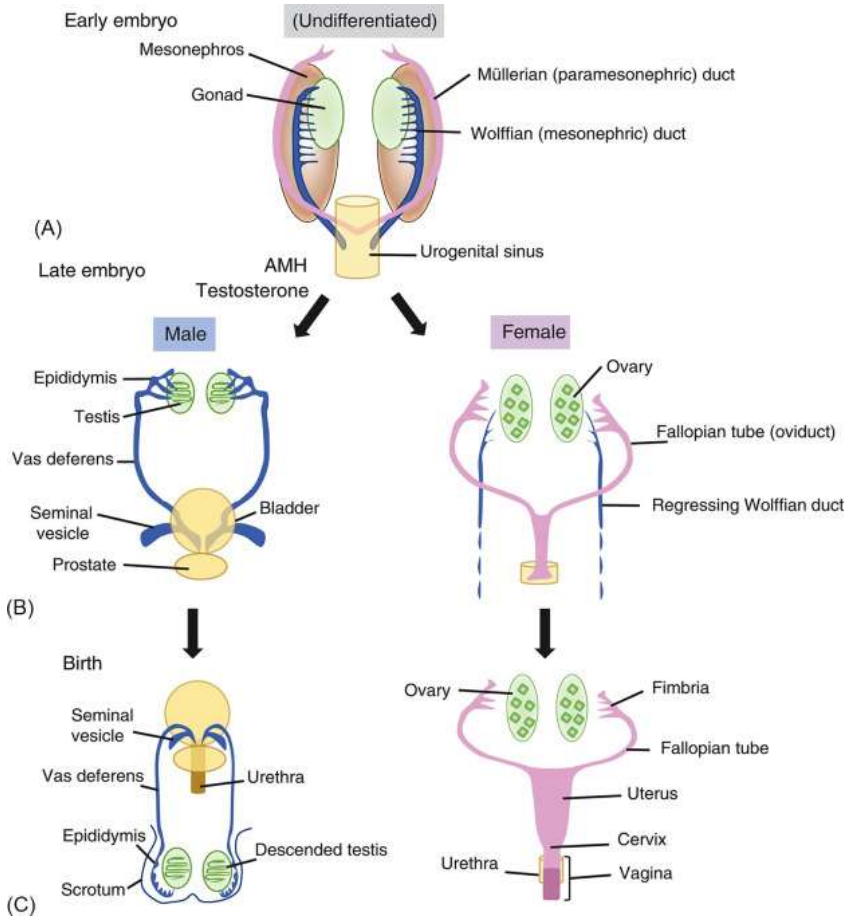
- **FSH** on day 3 of menstrual cycle <10 à 12 IU/L
- **Inhibin B**: secreted from granulosa cells of preantral and antral follicles
- **Anti-mullerian hormone (AMH)**

ANTI-MULLERIAN HORMONE



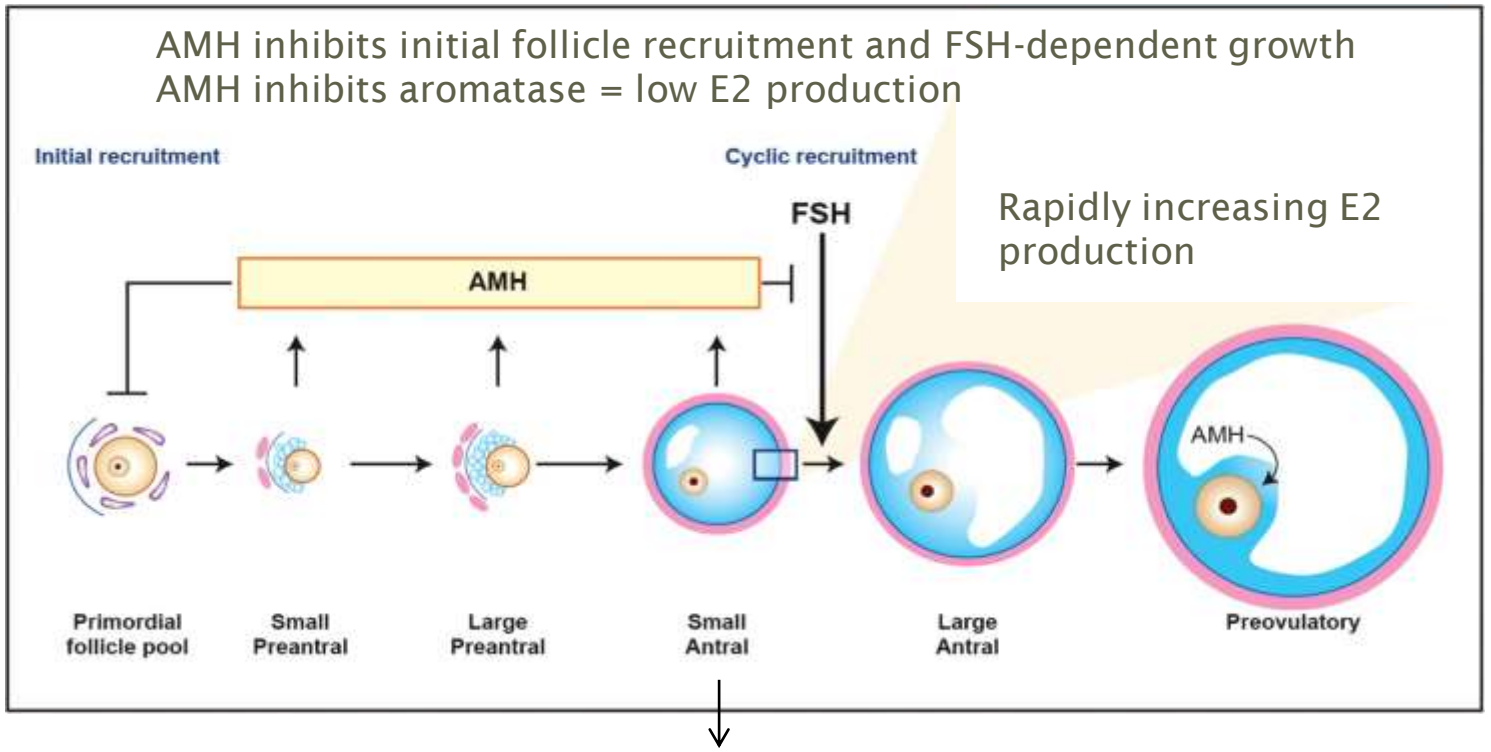
- Glycoprotein, 140 kDA homodimer
- TGF-β family of growth differentiation factors:
- Expressed almost exclusively in gonads:
  - → Men: Sertoli cells in testis
  - → Women: Granulosa cells of growing follicles in ovaria
- During early life role in sex differentiation:
  - Regression of Müllerian ducts in males

    = anti-Müllerian



FOLLICULOGENESIS

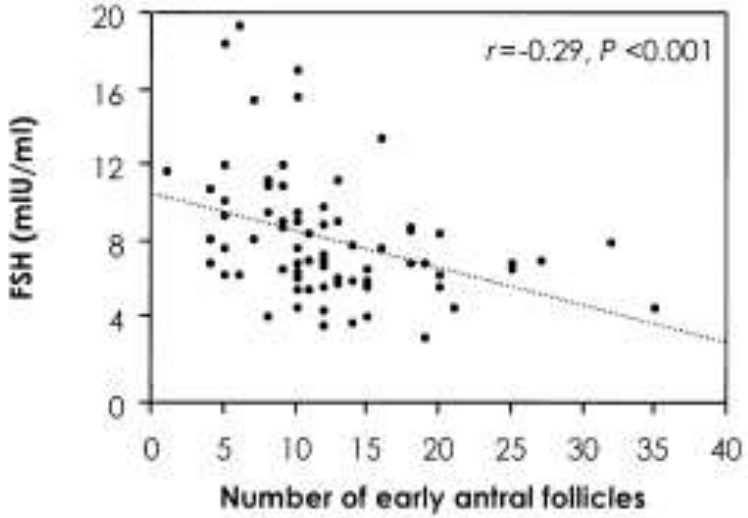
AMH inhibits initial follicle recruitment and FSH-dependent growth
AMH inhibits aromatase = low E2 production

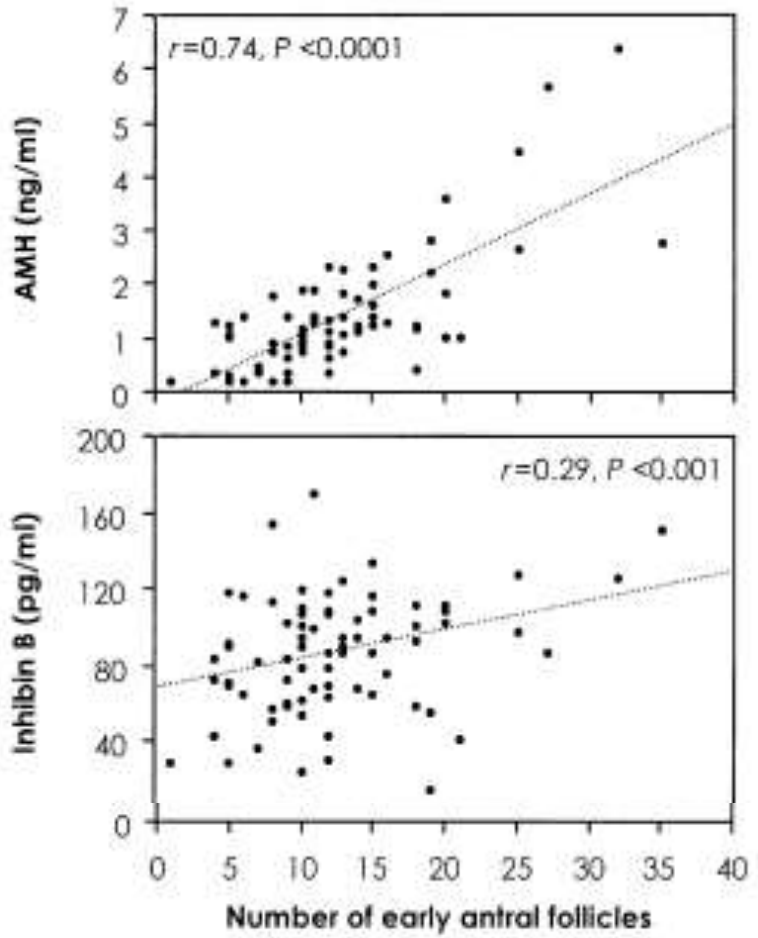


5-8 mm: greatest contribution to serum AMH

CORRELATION WITH ANTRAL FOLLICLE COUNT

Serum AMH is more strongly correlated to the antral follicle count than inhibin B or FSH





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Fanchin, Hum Reprod 2003 | 11

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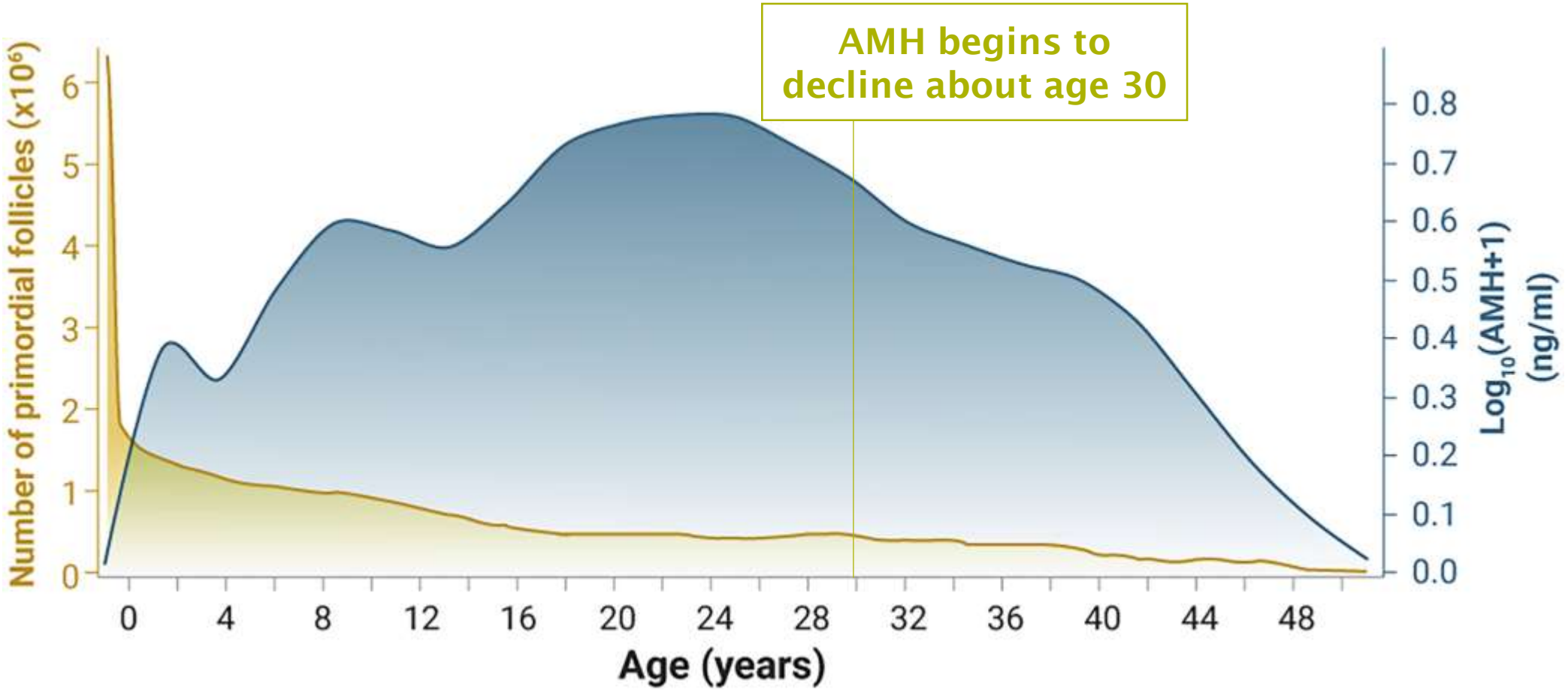
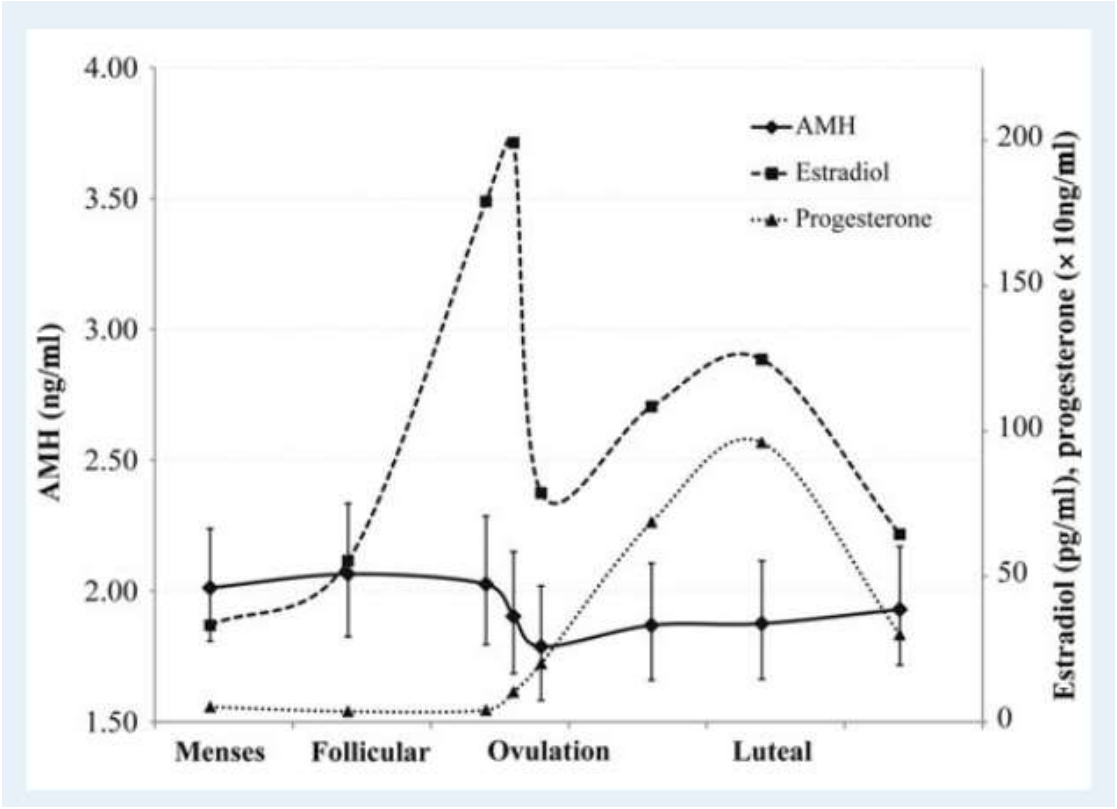
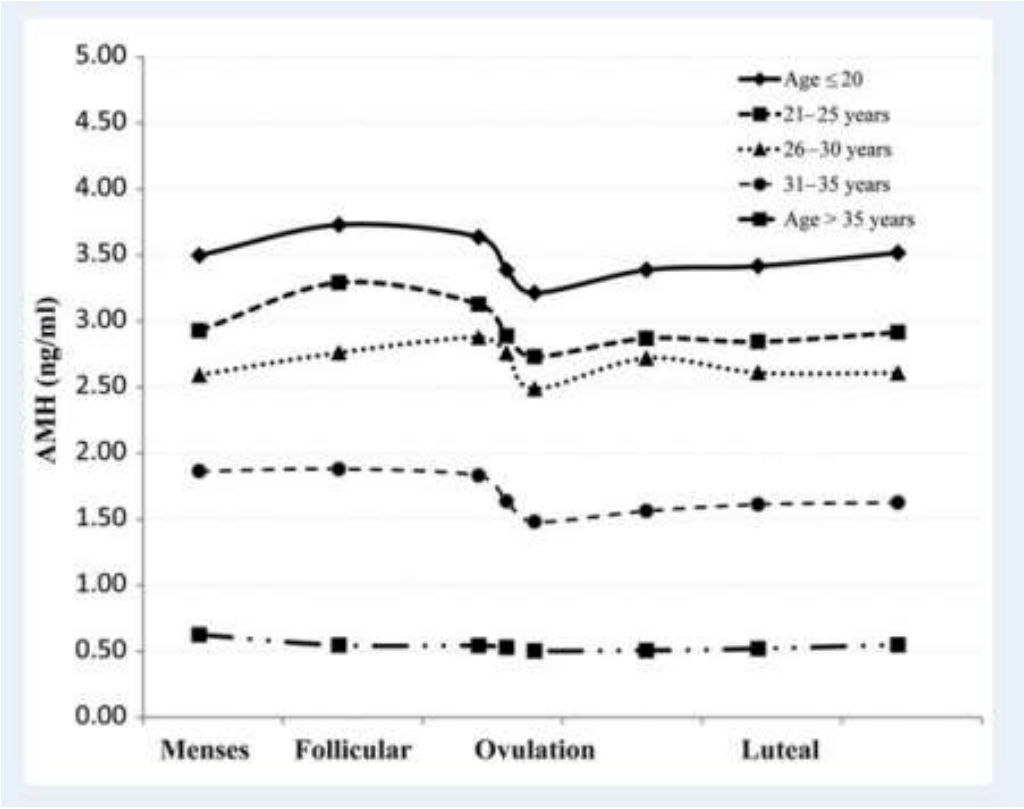
AMH IS A MARKER OF OVARIAN AGEING



Xu, et al. The Innovation 2. 2021

AMH HAS LOW INTRA-CYCLE VARIABILITY





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Kissell, K A et al. Human reproduction. 2014

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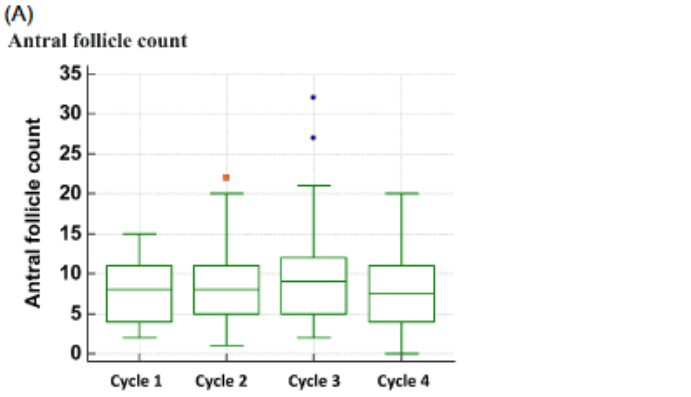
AMH HAS LOW INTER-CYCLE VARIABILITY

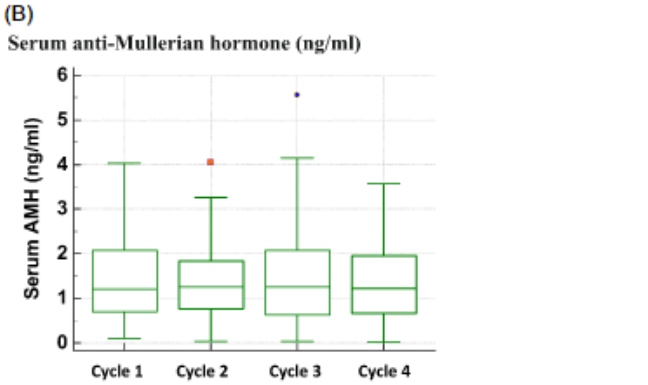
n=78

(A)



P<0.001 (Friedman's test)
Cycle 3 was significantly higher than Cycles 1, 2 and 4. (p<0.05, Conover post-hoc test)

(B)



No statistically significant difference among all four time points (p=0.608, Friedman's test)

TABLE 3 Receiver operating characteristic curve analyses of the predictive performance of antral follicle count and serum anti-Mullerian hormone on poor ovarian response (defined as AFC < = 5)

(a) Antral follicle count	
Time point	**Area under the curve (95% confidence interval)**
First cycle	0.742 (0.628–0.836)
Second cycle	0.728 (0.613–0.825)
Third cycle	0.657 (0.538–0.763)
Fourth cycle	0.743 (0.630–0.837)
(b) Serum anti-Mullerian hormone	
Time point	**Area under the curve (95% confidence interval)**
First cycle	0.731 (0.616–0.827)
Second cycle	0.730 (0.615–0.826)
Third cycle	0.751 (0.638–0.844)
Fourth cycle	0.780 (0.670–0.868)

No significant difference between 4 cycles for AMH and AFC in predicting poor ovarian response.

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CLINICAL UTILITY OF AMH

- Assess fertility
- Predict ovarian aging
- Predict ovarian response in ART
- Guide recombinant FSH dose during controlled ovarian stimulation
- Predicting and evaluating ovarian damage before and after chemotherapy

CLINICAL UTILITY OF AMH

- **Assess fertility**
- Predict ovarian aging
- Predict ovarian response in ART
- Guide recombinant FSH dose during controlled ovarian stimulation
- Predicting and evaluating ovarian damage before and after chemotherapy

CLINICAL UTILITY OF AMH

Assess fertility

Good agreement between AMH and AFC-based classifications of low, normal and responders:

Agreement table for antral follicle count (AFC) groups and new defined antimüllerian hormone (AMH) groups.

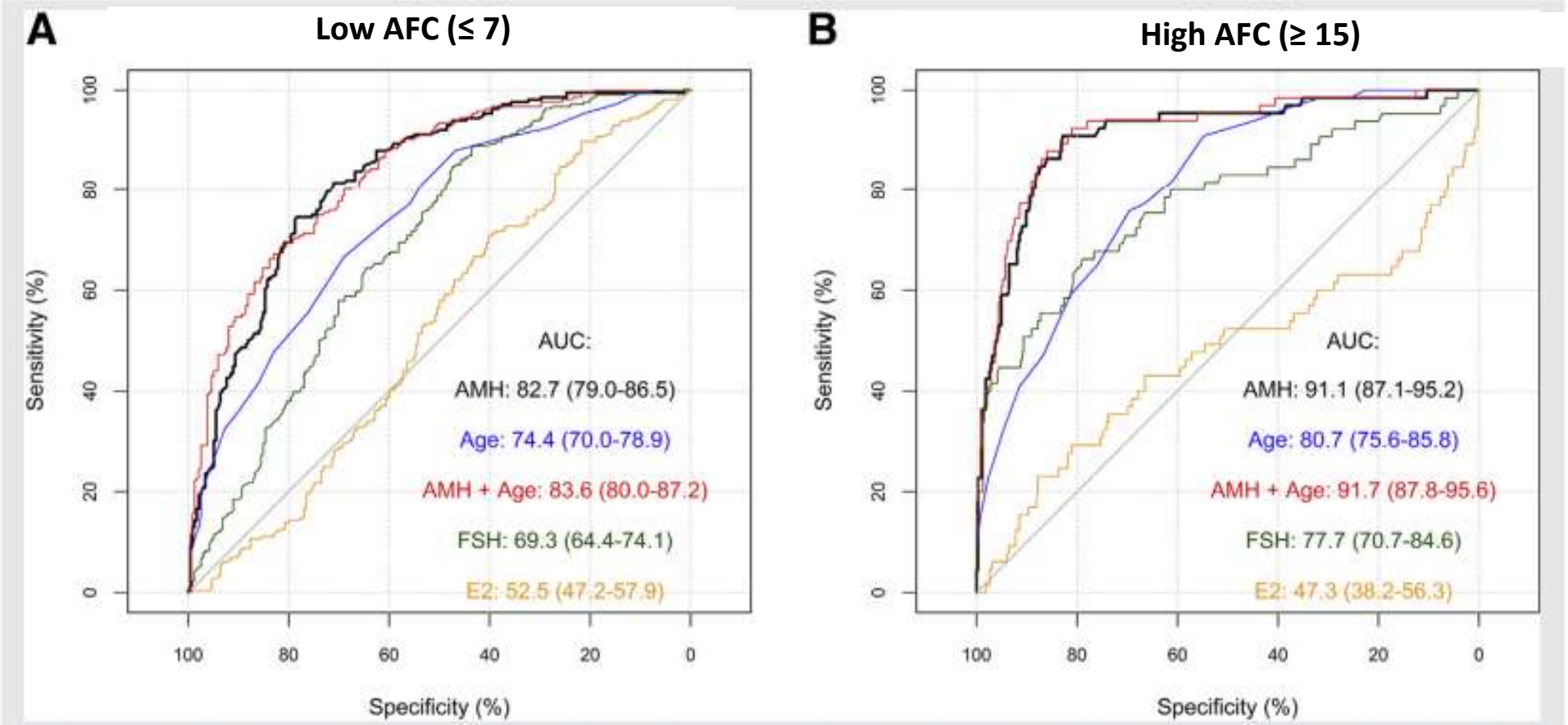
AMH group	AFC 0–7	AFC 8–15	AFC > 15	N
AMH ≤ 0.681	43 (63.2%)	22 (32.4%)	3 (4.4%)	68
0.681 < AMH ≤ 2.27	20 (12.0%)	95 (56.9%)	52 (31.1%)	167
AMH > 2.27	3 (1.4%)	52 (24.1%)	161 (74.5%)	216
N	66	169	216	451

Note: Percentages refer to AMH group numbers (AMH values in ng/mL).

Anderson. Automated AMH assay in ovarian assessment. Fertil Steril 2015.

CLINICAL UTILITY OF AMH

Assess fertility



ROC curves for classification of (**A**) low AFC and (**B**) high AFC, by AMH, FSH, E_2 and age. For low AFC, n = 66 patients with AFC ≤7 versus 385 subjects AFC >7. For high AFC, n = 216 subjects with AFC >15 versus 235 patients AFC ≤15.

Anderson. Automated AMH assay in ovarian assessment. Fertil Steril 2015.

CLINICAL UTILITY OF AMH

- Assess fertility
- **Predict ovarian aging**
- Predict ovarian response in ART
- Guide recombinant FSH dose during ovarian stimulation in ART
- Predicting and evaluating ovarian damage before and after chemotherapy

CLINICAL UTILITY OF AMH

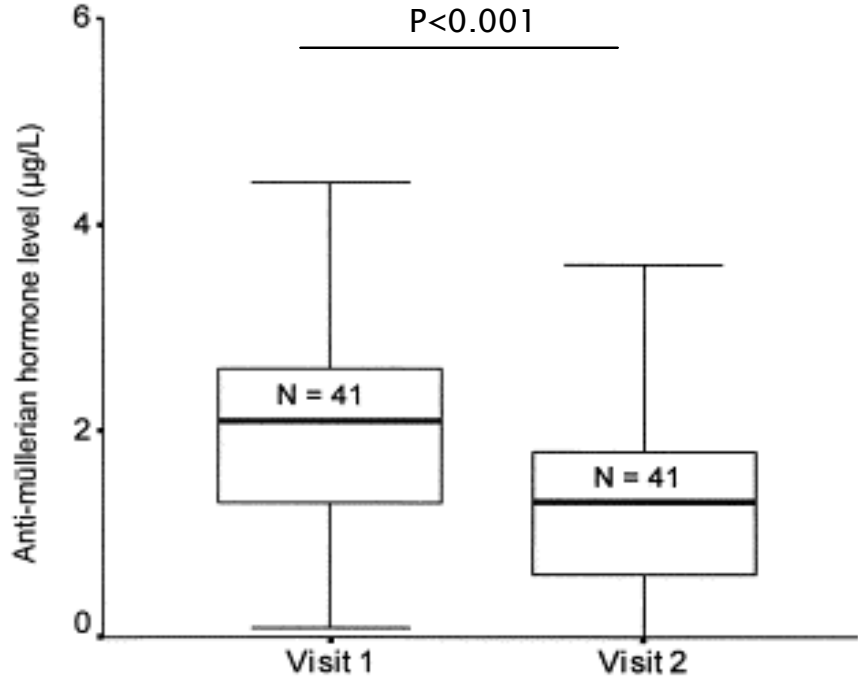
Predict ovarian aging

- Physiological menopause between 40-60 years (median age: 51)
- Decrease in fertility starts 10-13 years prior to menopause
- Only when follicle number fall below critical threshold of few thousand -> irregular menstrual pattern
- At menopause: <1000 follicles -> AMH = undetectable

CLINICAL UTILITY OF AMH

Predict ovarian aging

AMH is the earliest endocrine marker of ovarian aging



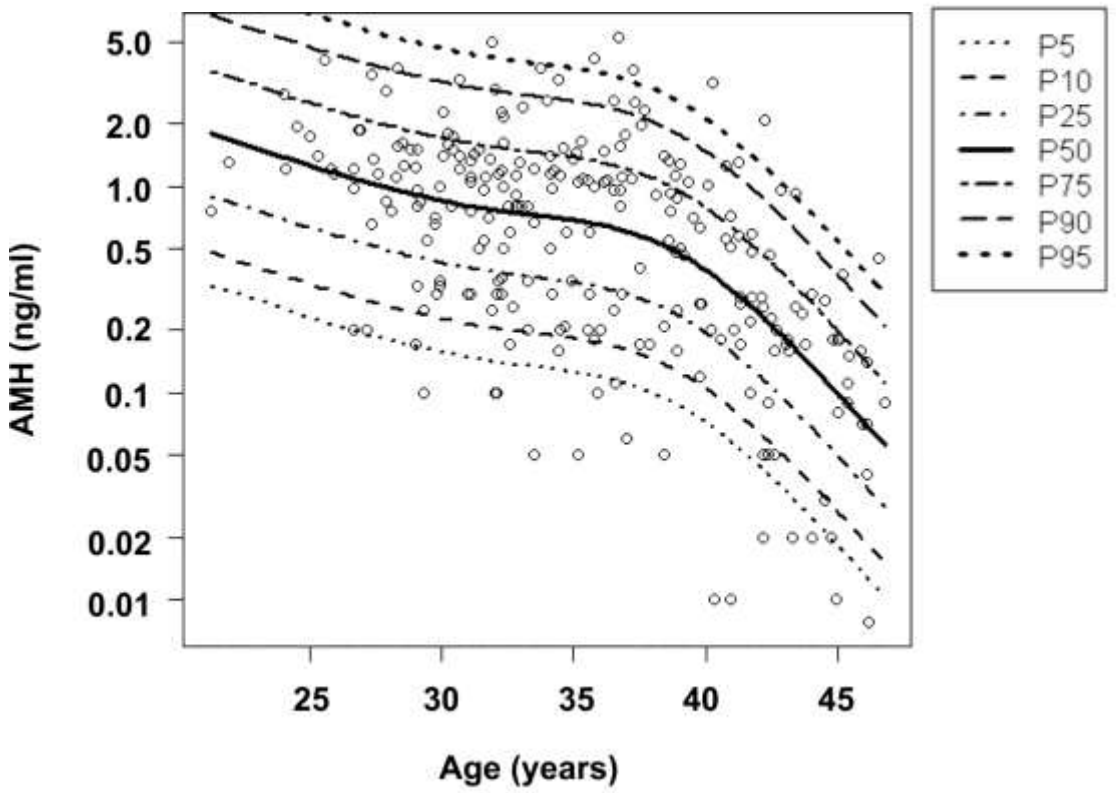
After 2.6 +/- 1.7 y

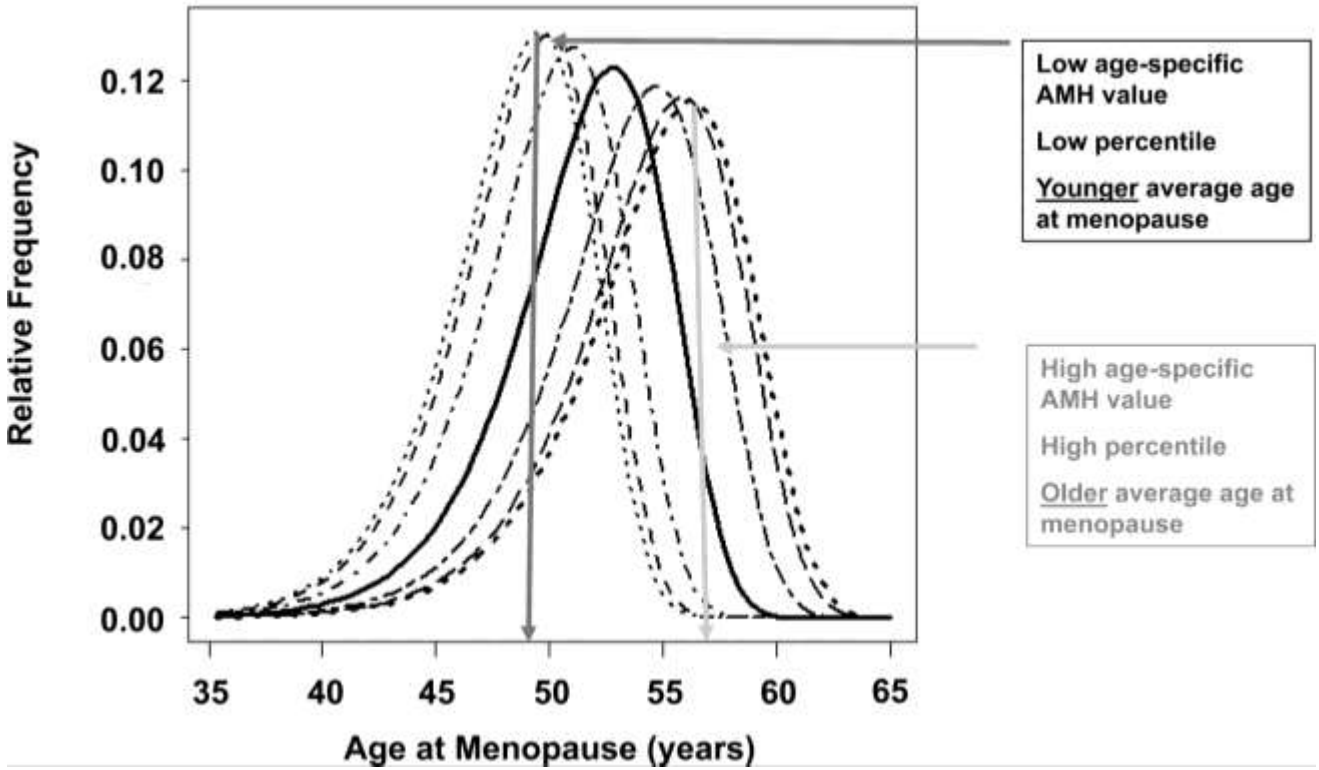
Serum FSH, inhibin B and Antral Follicle Count (AFC) did not change during this interval

CLINICAL UTILITY OF AMH

Predict ovarian aging

n= 257, AMH measured at entry of the study (average age 35y) and age at menopause assessed 11 years later





AMH has added value on top of clinical predictors (age, smoking, BMI, menstrual cycle characteristics) in models for menopause prediction

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CLINICAL UTILITY OF AMH

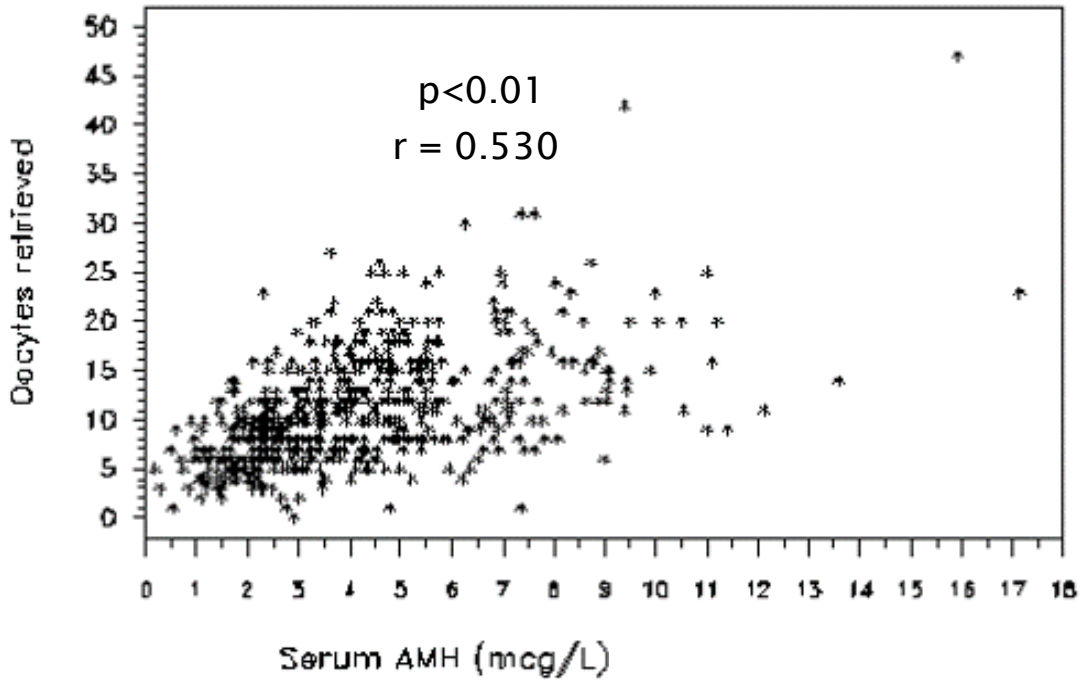
- Assess fertility
- Predict ovarian aging
- **Predict ovarian response and define individualised protocols during controlled ovarian stimulation (COS)**
- Predicting and evaluating ovarian damage before and after chemotherapy

CLINICAL UTILITY OF AMH

Predict ovarian response and define individualised protocols during COS

AMH correlated with the number of oocytes retrieved after ovarian stimulation

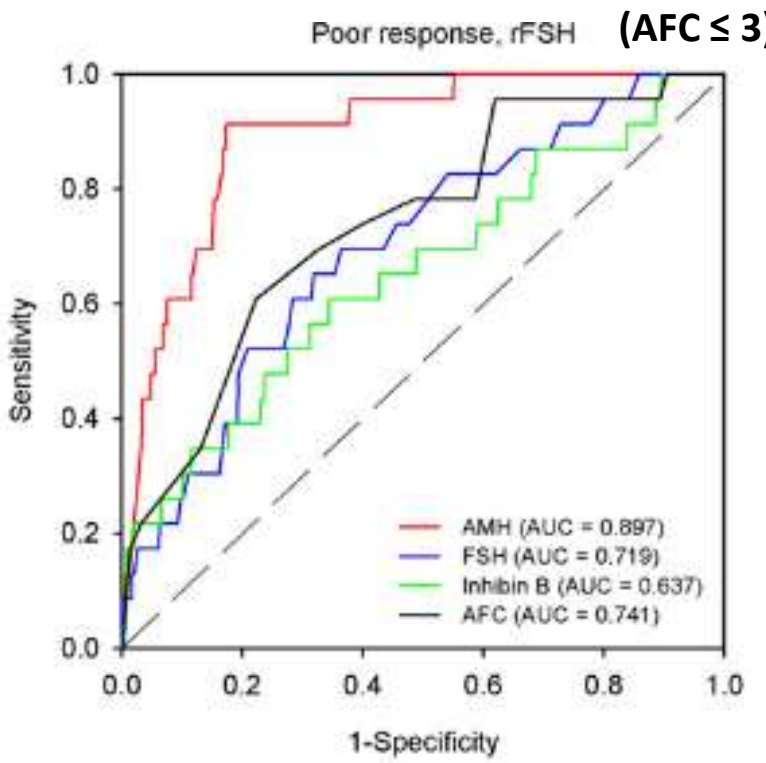
n = 731 infertile normo-ovulatory women

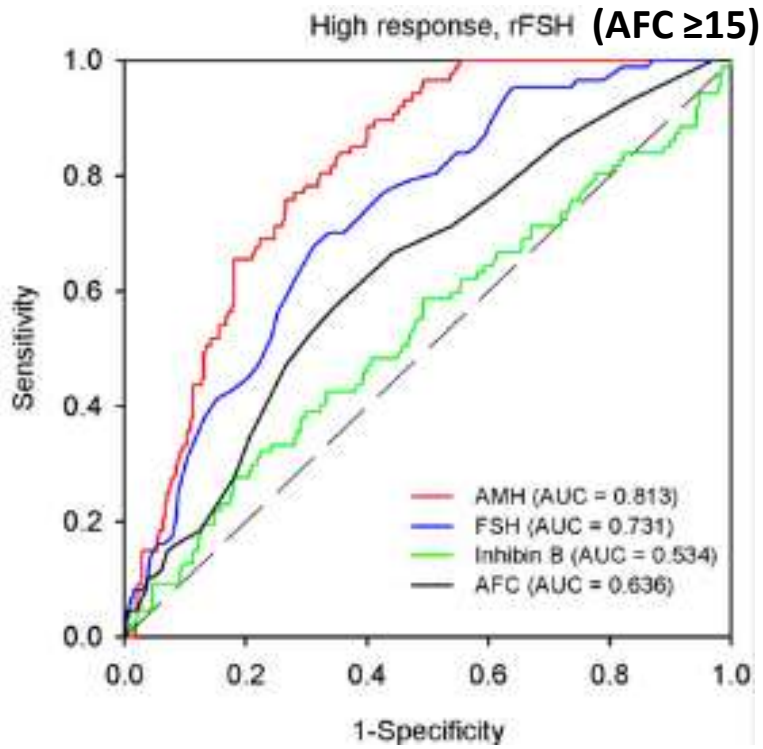


CLINICAL UTILITY OF AMH

Predict ovarian response and define individualised protocols during COS

During controlled ovarian stimulation (COS) several studies have shown AMH to be a stronger predictor of ovarian response than AFC, FSH and inhibin B





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Arce JC, et al. *Fertil Steril* 2013;
Iliodromiti S, et al. *Hum Reprod* 2015;
La Marca, A, et al. *Hum Reprod* 2007;
Islam Y, et al. *Mid East Fert Soc* 2016.

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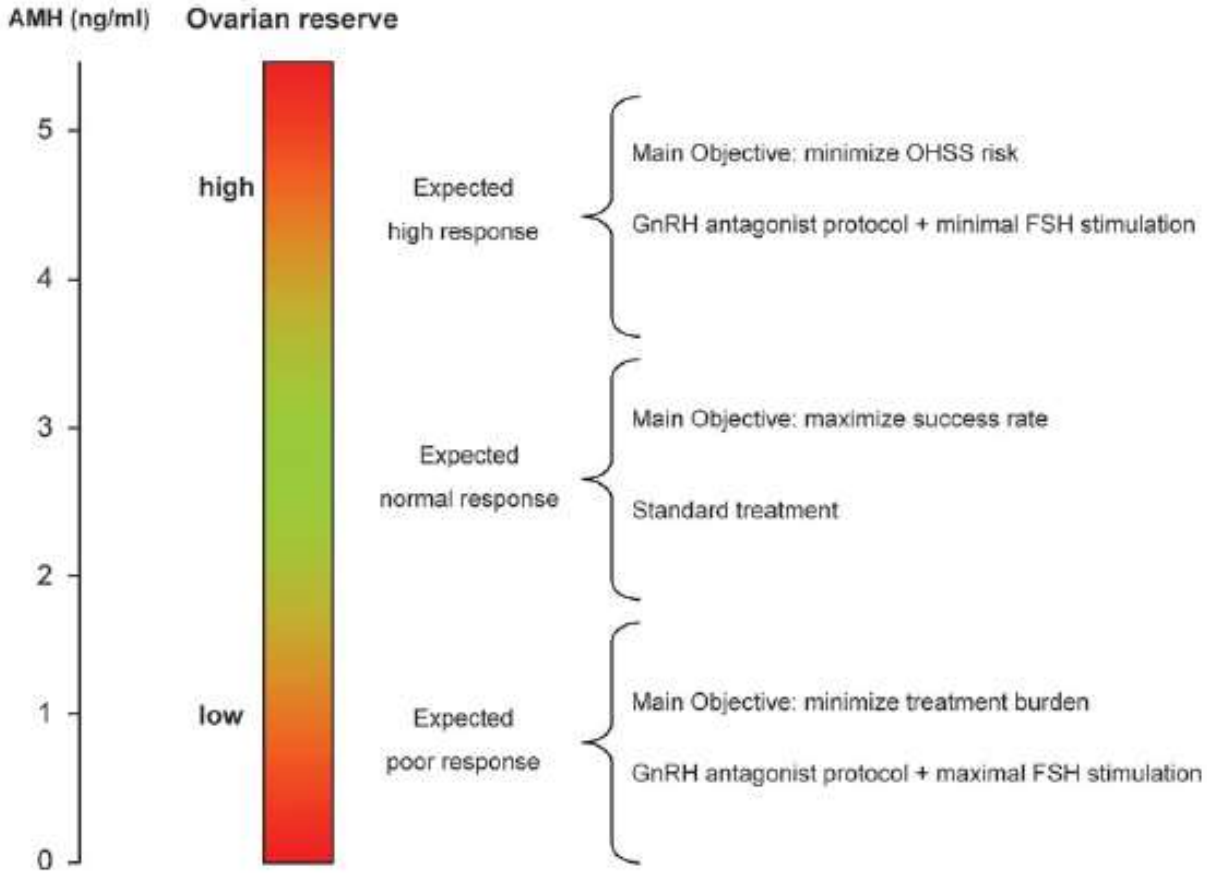
CLINICAL UTILITY OF AMH

Predict ovarian response and define individualised protocols during COS

AMH can be used to define indivualised protocols to (1) reduce risk of unexpected ovarian response and to (2) optimise the oocyte yield:



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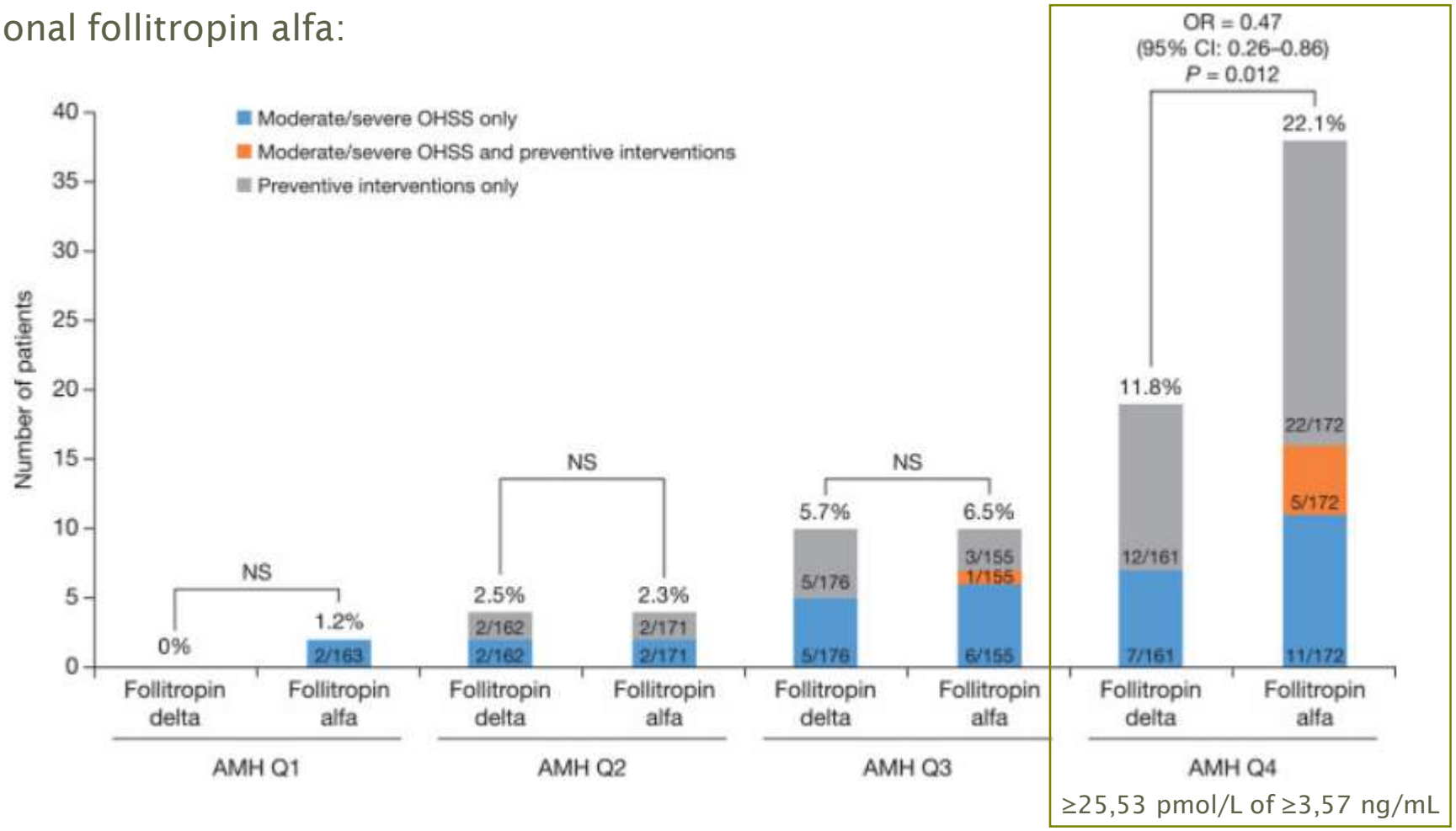
CLINICAL UTILITY OF AMH

Predict ovarian response and define individualised protocols during COS

Individualized dosing with follitropin delta as a preventive strategy for OHSS risk in comparison to conventional follitropin alfa:



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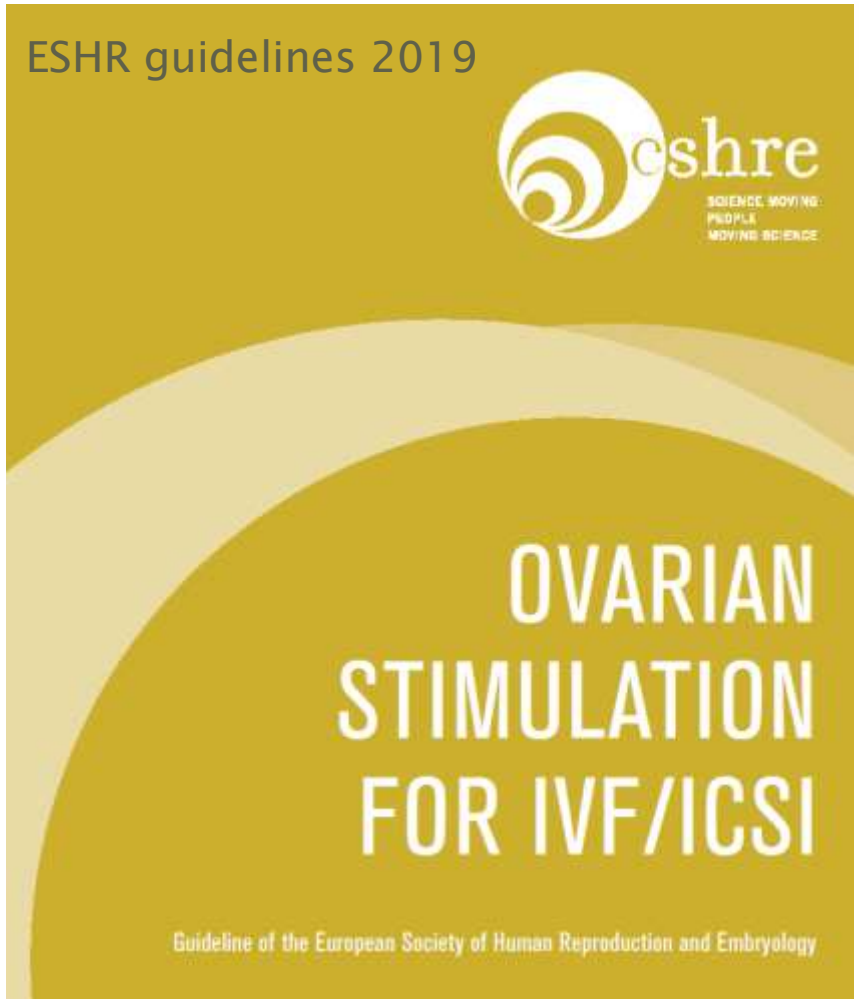
CLINICAL UTILITY OF AMH

Predict ovarian response and define individualised protocols during COS



List of all recommendations

Chapter	No.	Recommendation	Strength	Quality of evidence	Justification	Remarks
Pre-stimulation management						
1	1	For predicting high and poor response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests. *The clinical implications of these tests regarding change in management with the purpose of improving efficacy and safety have not been evaluated by the GDG.*	Strong	⊕OOO	AFC and AMH both have a high accuracy in the prediction of an ovarian response. Basal FSH and inhibin B do have some predictive value for ovarian response, however for an accurate prediction very high cut-off levels need to be used. Age also has some predictive value, however assessment of expected ovarian response by age alone is not sufficiently reliable. Basal oestradiol and BMI alone are not predictors of ovarian response.	

CLINICAL UTILITY OF AMH

Predict ovarian response and define individualised protocols during COS

Treatment individualization based on AMH:

- Reduced treatment burden
- Reduced cost
- Reduction in adverse effects (OHSS)
- Maintained (or higher) pregnancy rates and live birth rates

CLINICAL UTILITY OF AMH

- Assess fertility
- Predict ovarian aging
- Predict ovarian response and define individualised protocols during controlled ovarian stimulation (COS)
- **Predicting and evaluating ovarian damage before and after chemotherapy**

CLINICAL UTILITY OF AMH

Predicting and evaluating ovarian damage before and after chemotherapy

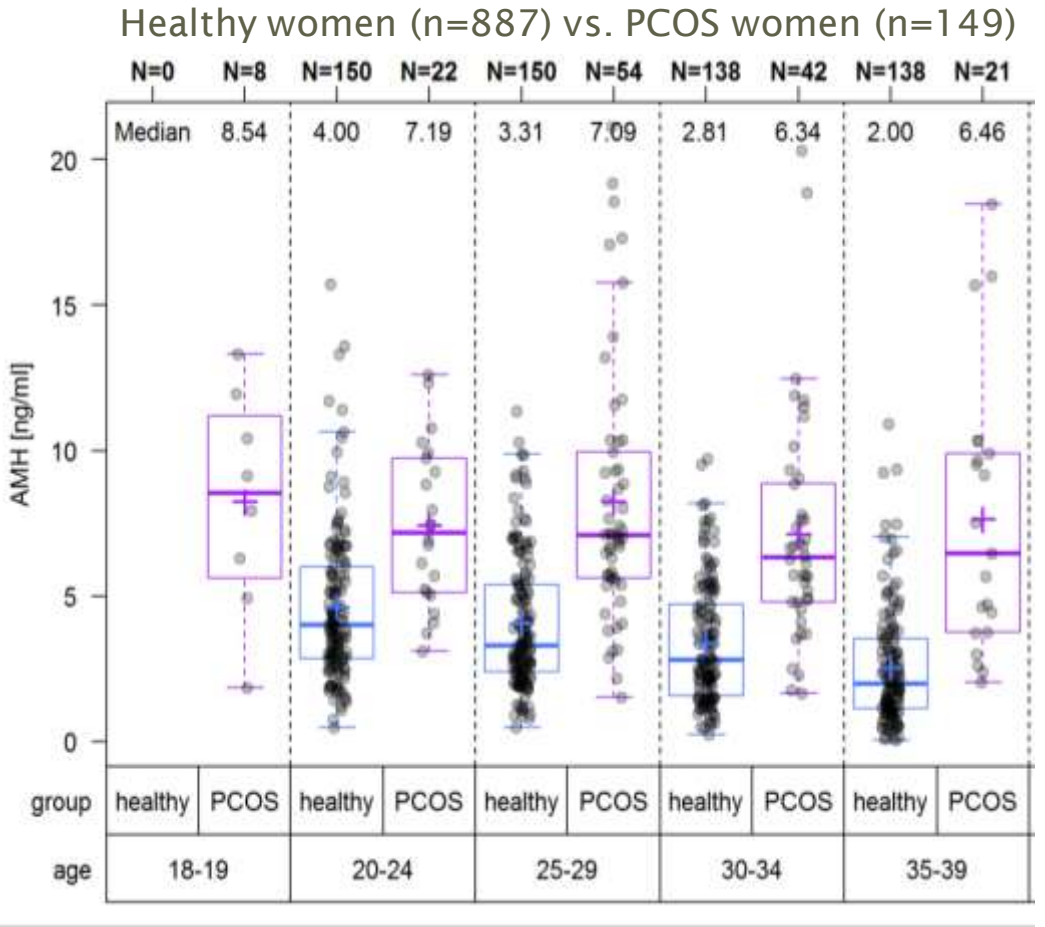
- Many chemotherapeutics used are gonadotoxic
- AMH falls markedly during chemotherapy with variable recovery thereafter depending on the degree of gonadotoxicity of the treatment administered
- Basal AMH level before start of chemotherapy can predict the risk of ovarian damage
  - > high pretreatment AMH levels were predictive of higher AMH levels during recovery of ovarian function after chemotherapy
  - > Role in fertility preservation
- AMH level after chemotherapy is the most sensitive marker of gonadotoxic damage

Anderson RA and Cameron DA, J Clin Endocrinol Metab 2011.
Van Beek RD, J Clin Endocrinol Metab 2007

OTHER CLINICAL UTILITIES OF AMH

- Helpful in diagnosis of Polycystic Ovarian Syndrome (PCOS)
- 2-4 fold higher levels in PCOS women than in healthy women
- AMH correlates with the degree of PCOS-phenotype as
  - > Intra-ovarian androgen excess leads to the accumulation of small antral follicles which contribute to AMH secretion
  - > Local AMH excess may play a role in anovulation by reducing the sensitivity of follicles to FSH
- ! Considerable overlap with healthy women:

  ESHRE guidelines 2018: AMH should not yet be used as an alternative for diagnosis of PCOS



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Dewailly, Front. Endocrinol, 2021; Anckaert E, Clin Biochem 2015

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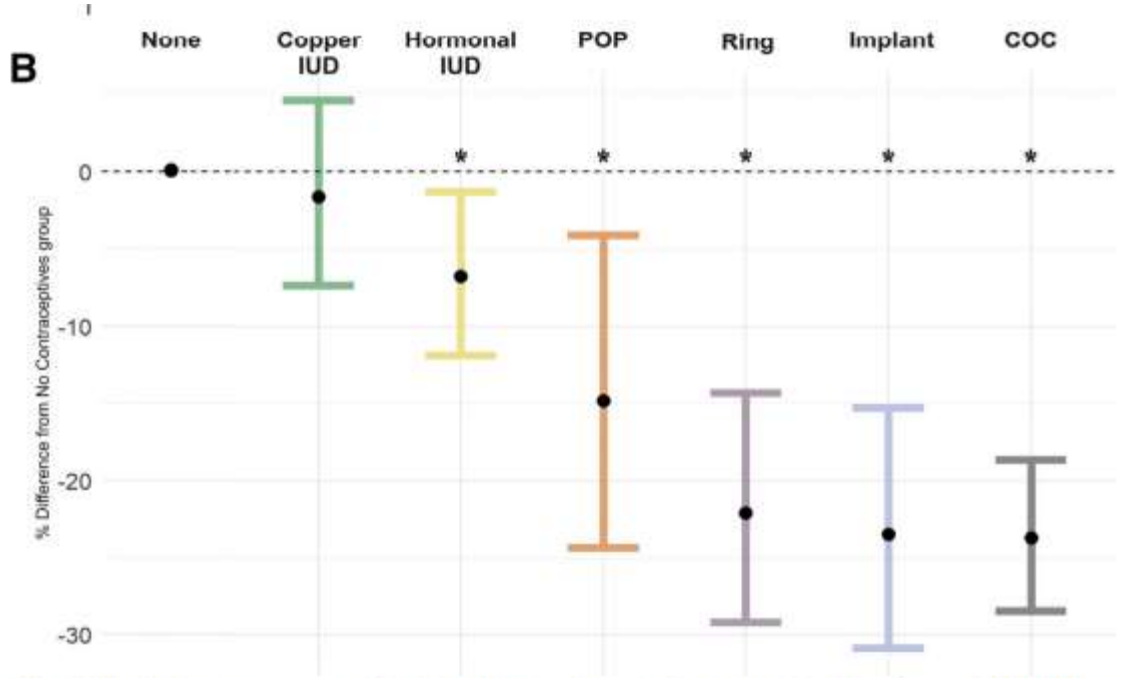
INFLUENCE OF HORMONAL CONTRACEPTIVES

- Used by majority of women of reproductive age
- Data from cross-sectional cohort (n=27125 females):
  - Highest decrease (-18 to -28%) of AMH with combined oral contraceptives
  - Reversible effect after discontinuation within 3-6 months



A, Individual values, means, and 95% confidence intervals for natural log transformed AMH values across contraceptive groups, adjusted for covariates. **B,** Percent difference estimates and 95% confidence intervals in AMH across contraceptive groups relative to women not on contraceptives. The *asterisks* represent significant differences from women not on contraceptives at $P<.05$. Combined oral contraceptives (COC); progestin-only pill (POP); None refers to participants who were not using contraceptives at the time of AMH measurement.

AMH, anti-Müllerian hormone.

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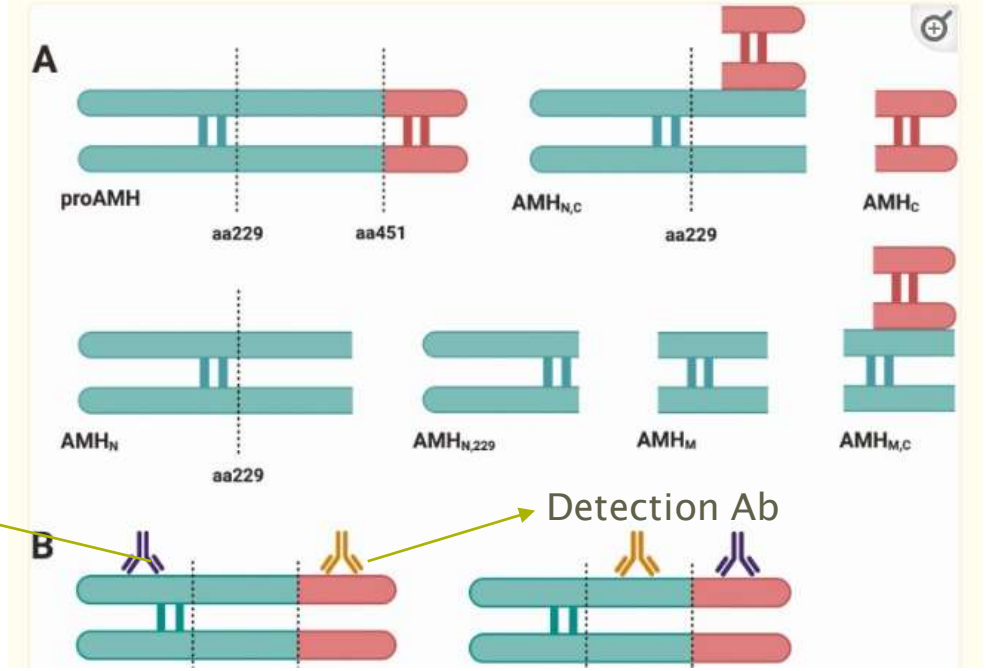
AMH ASSAYS

- First ELISA in 1990
- Early 2000's: 2 commercially available ELISA's
- Currently more than 21 different immunoassay platforms/methods available
- Assay variability due to different (monoclonal) antibodies and lack international AMH reference standard



KEY MESSAGES

- AMH is the **earliest** endocrine marker for ovarian aging/iatrogenic damage
- **Intra- and inter-cycle variability** of serum AMH is **low**
- AMH can be used to **assess fertility** and predict ovarian aging
- AMH is the **best predictor during COS**
- AMH prior to COH **allows treatment individualization** with reduced cost and treatment burden
- **Assay harmonization** is necesssary

MANY THANKS FOR YOUR ATTENTION

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