

Ovarian reserve tests:
are we ready to move to objective criteria?

Professor Renato Fanchin, MD, PhD

La Murette ART Center
Paris-France
professeurfanchin@gmail.com

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Conflict of interests



Where I would like to lead you...

Advantages & limitations of AFC and AMH

Factors influencing the relationship between both markers

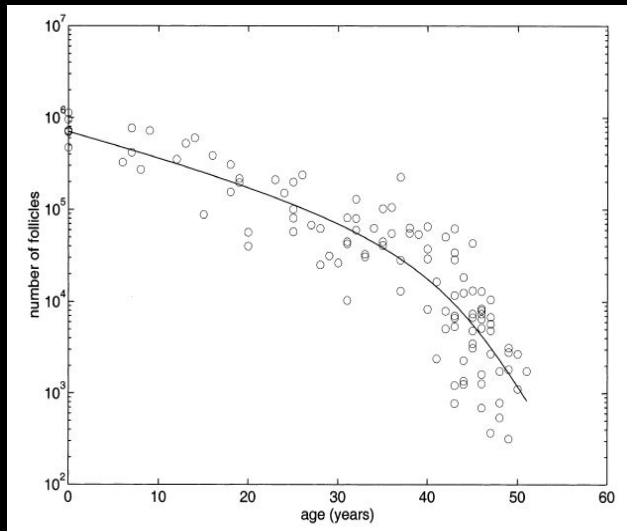
Factors influencing the predictability of both markers

Are they predictable of oocyte quality?

Conclusions

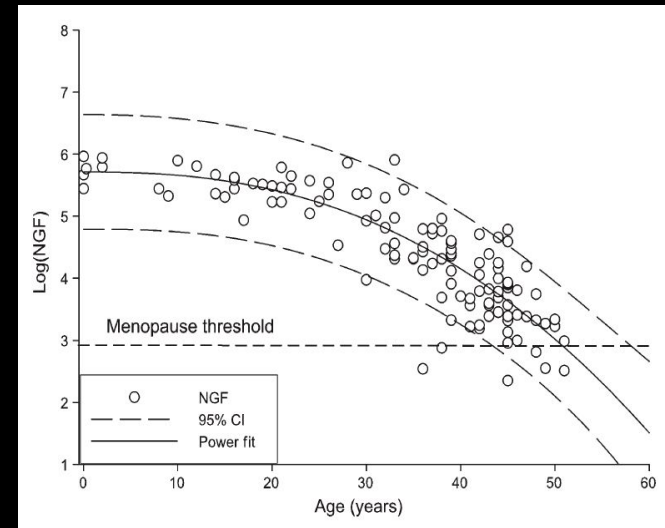
Ovarian aging

"Smoothed" model



Faddy & Gosden, Hum Reprod, 1996

"Power" model



Hansen et al, Hum Reprod, 2008

The decay of NG follicles with age is constant

What information should they provide?

Personalize information over age

Quantitative

Most of them...



Individualization of care

Qualitative

None of them?



Opportunity of care

Postulate: quantity & quality interrelated

Plethora of biomarkers available





Who's the best? Hum!

AMH x AFC: comparative features

AMH

AFC

Intracycle variability	+	++
Intercycle variability	+	++
Technique-dependence	+++	+++
Complexity	++	+
Practicality	+++	+
Cost	++	+

AMH x AFC: respective advantages

AMH

Activity of GCs

Not influenced by DF and CL

Little operator dependence

No ovarian access issues

AFC

Robust to ovarian asymmetry

Detects volume discrepancies

Immediate results

Id of co-factors

AMH: new assays

Pico AMH

- LoD: 0.001 ng/mL
- Manual ELISA
- Rec hAMH
- Detectability: 97%
(vs. 84% with Gen II)

Elecsys

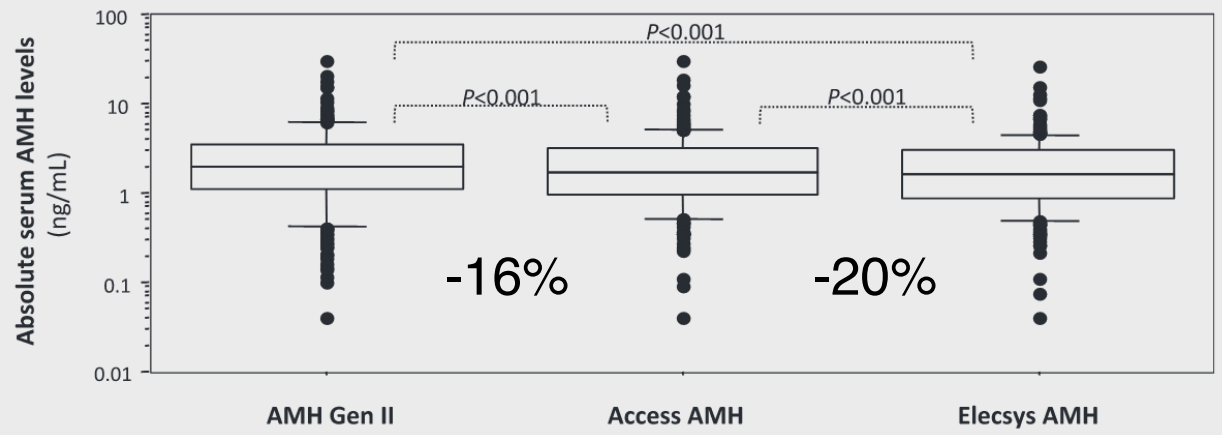
- LoD: 0.01 ng/mL
- **Automated** ELISA
- Rec hAMH
- Results within 18 min

Access

- LoD: 0.02 ng/mL
- **Automated** ELISA
- Rec bovine AMH
- Results within 40 min

New automated antimüllerian hormone assays are more reliable than the manual assay in patients with reduced antral follicle count

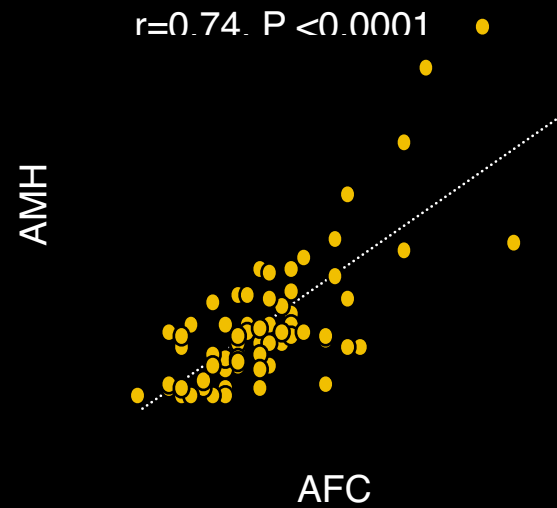
Teddy Tadros, M.D.,^{a,b} Bruno Tarasconi, M.D.,^{a,b,c} Jean Nassar, M.D.,^{a,b} Jean-Luc Benhaim, Pharm.D.,^d Joëlle Taieb, Pharm.D.,^e and Renato Fanchin, M.D., Ph.D.^{a,b}



AMH x AFC

AMH

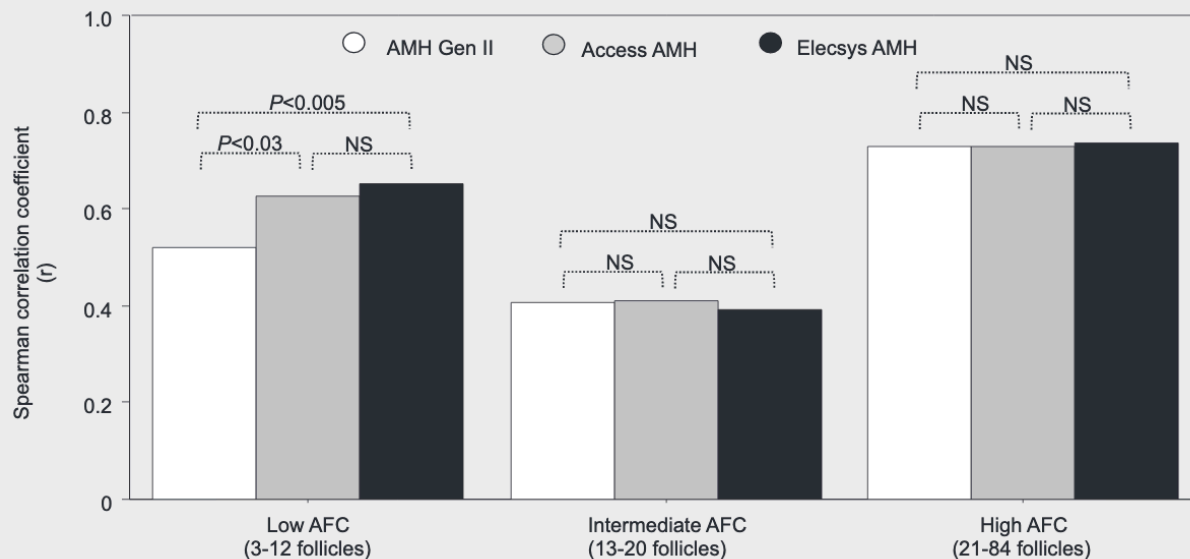
AFC



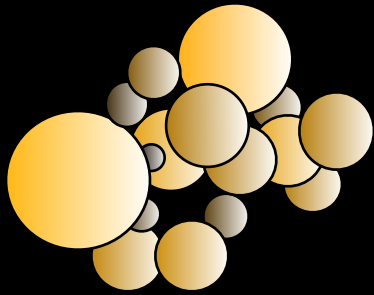
Remarkably strong relationship

New automated antimüllerian hormone assays are more reliable than the manual assay in patients with reduced antral follicle count

Teddy Tadros, M.D.,^{a,b} Bruno Tarasconi, M.D.,^{a,b,c} Jean Nassar, M.D.,^{a,b} Jean-Luc Benhaim, Pharm.D.,^d Joëlle Taieb, Pharm.D.,^e and Renato Fanchin, M.D., Ph.D.^{a,b}



AFC: methodological issues



1 mm

12 mm

Questions:

- Detectability of 1-2 mm follicles in all women?
- Similar responsiveness to FSH?
- Clinical soundness of counting small and large follicles?

AFC: methodological issues

Clinical considerations

Select patients with regular menstrual cycles with no coexisting pathologic condition that could technically affect the counting of follicles, such as ovarian endometriosis or previous ovarian surgery

Count follicles between days 2 and 4 of a spontaneous menstrual or oral contraceptive cycle to avoid the effect of intra-cycle variation

Include all antral follicles of 2–10 mm in diameter

Technical considerations

A limited number of personnel, appropriately trained in transvaginal sonography should perform AFCs in each unit

Real-time two-dimensional imaging is adequate

Use a transvaginal transducer

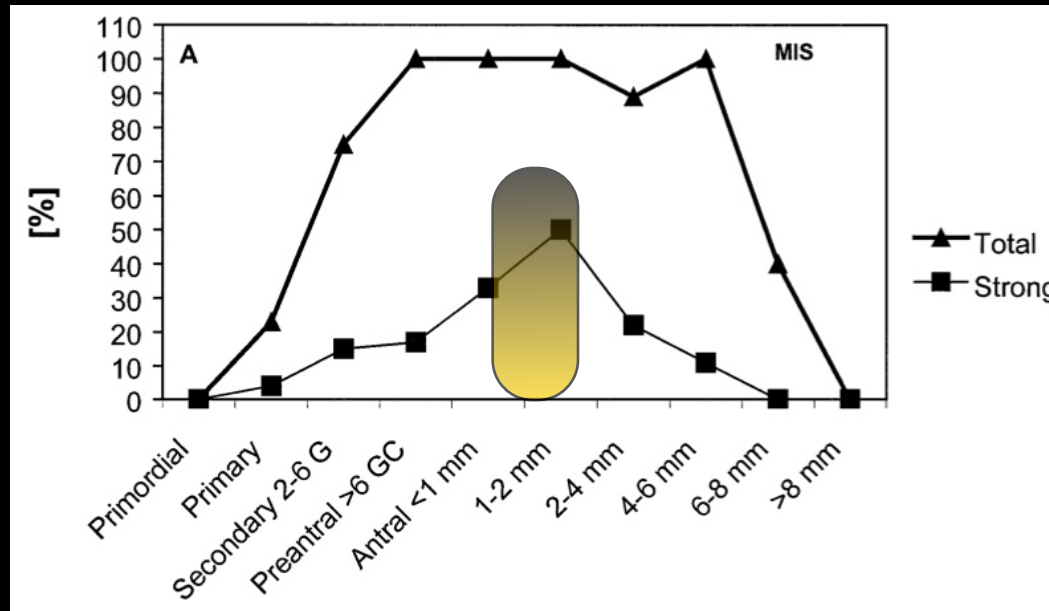
Use a probe with a minimum frequency of 7 MHz, which is maintained in an adequate condition and able to resolve a structure of 2 mm in diameter

Use a systematic process for counting antral follicles:

1. Identify the ovary
2. Explore the dimensions in two planes (perform a scout sweep)
3. Decide on the direction of the sweep to measure and count follicles
4. Measure the largest follicle in two dimensions
 - A. If the largest follicle is ≤ 10 mm in diameter:
 - i. Start to count from outer ovarian margin of the sweep to the opposite margin
 - ii. Consider every round or oval transonic structure within the ovarian margins to be a follicle
 - iii. Repeat the procedure with the contralateral ovary
 - iv. Combine the number of follicles in each ovary to obtain the AFC
 - B. If the largest follicle is > 10 mm in diameter:
 - i. Further ascertain the size range of the follicles by measuring each sequentially smaller follicle, in turn, until a follicle with a diameter of ≤ 10 mm is found
 - ii. Perform a total count (as described) regardless of follicle diameter
 - iii. Subtract the number of follicles of > 10 mm from the total follicle count

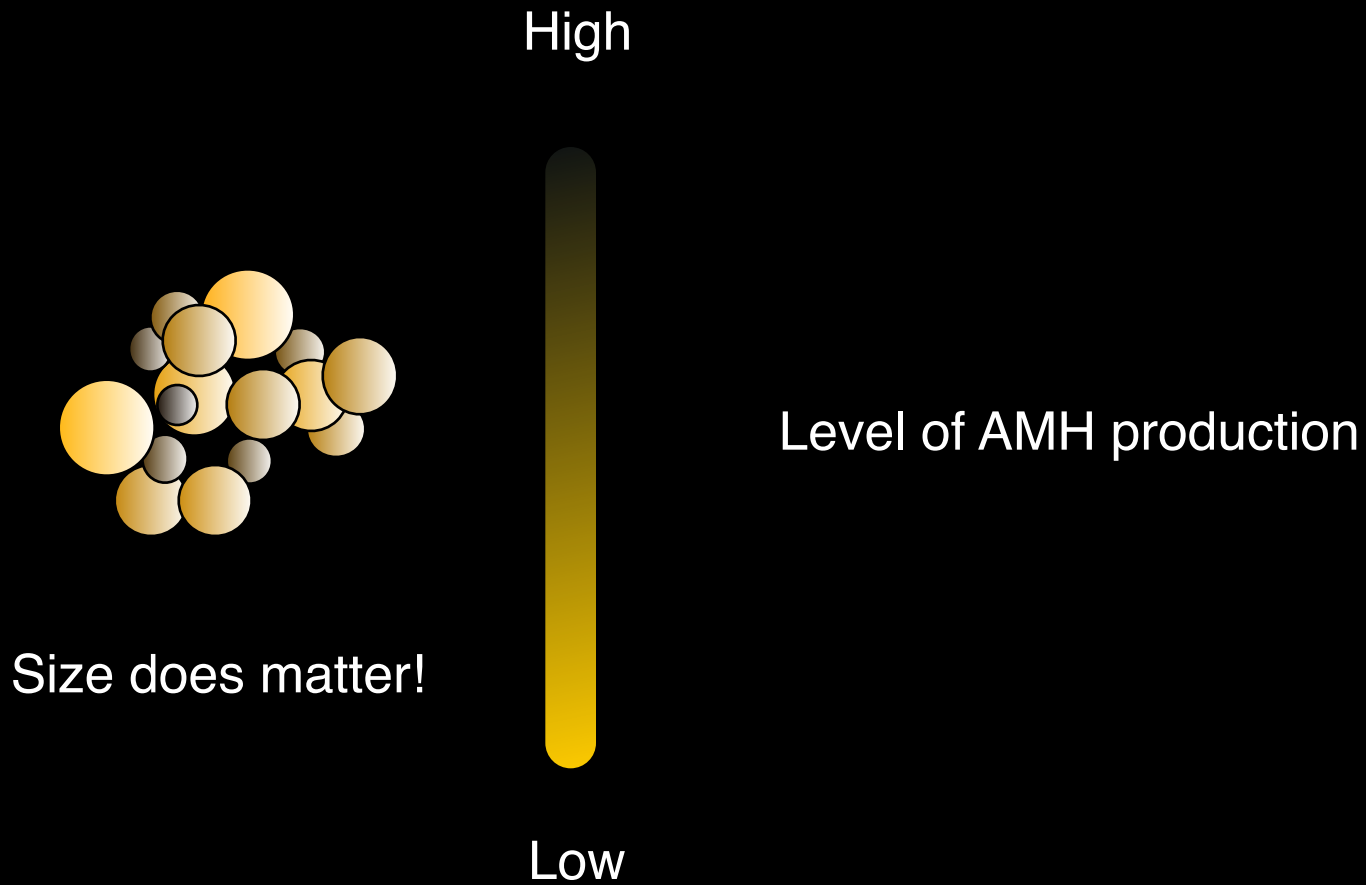
Relationship follicle size x AMH

Size does matter! For AMH, too...

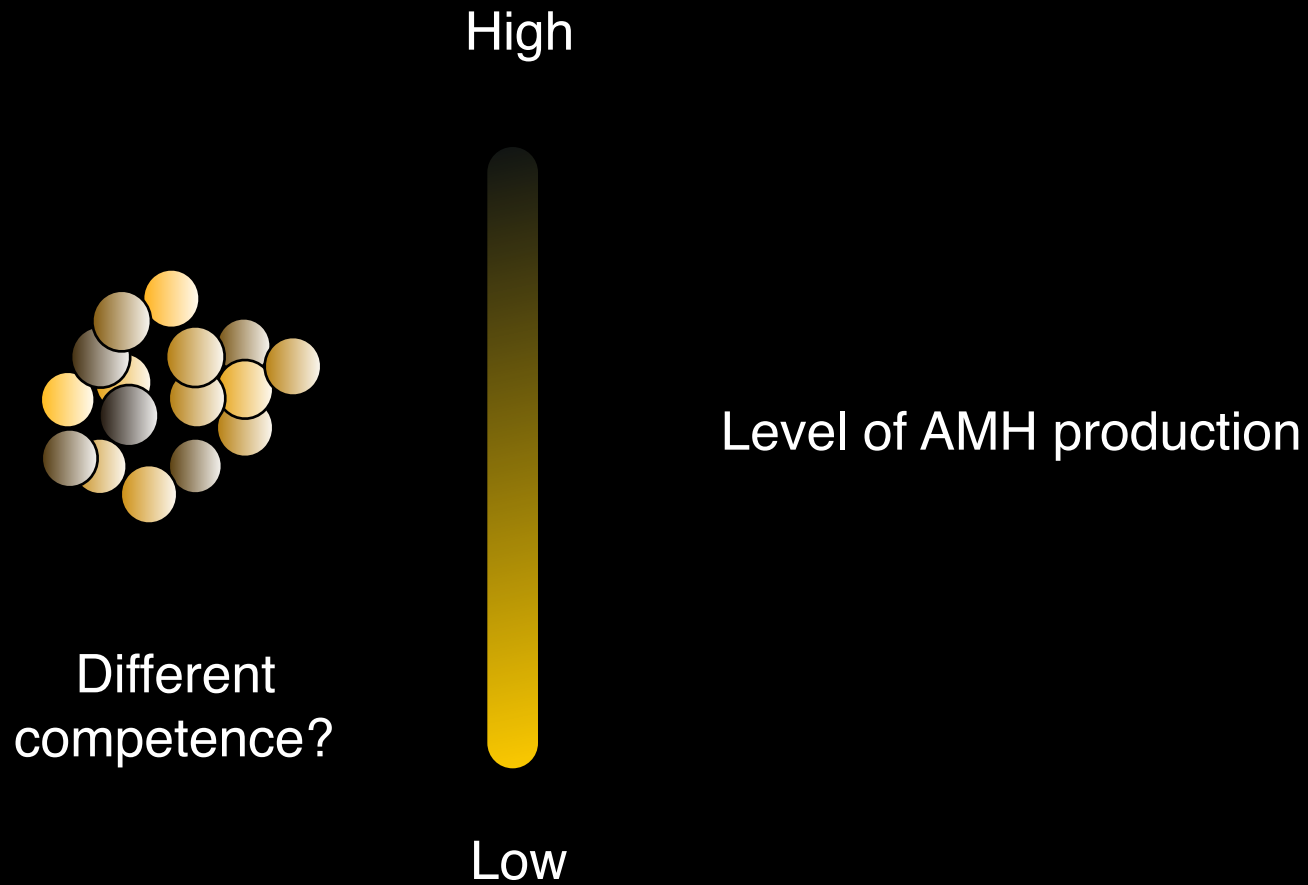


Differential AMH staining

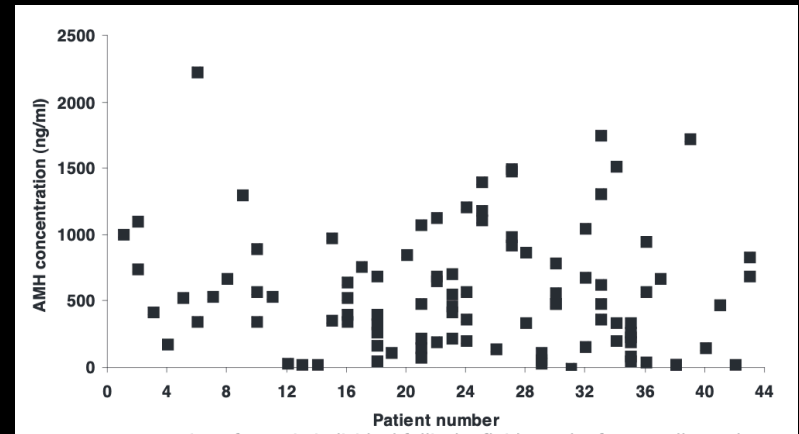
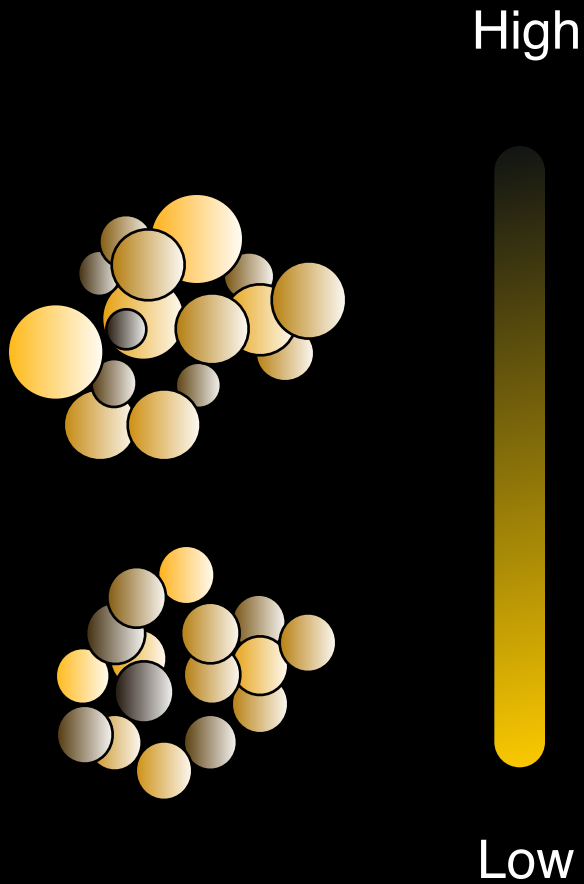
AMH-producing follicles



AMH-producing follicles

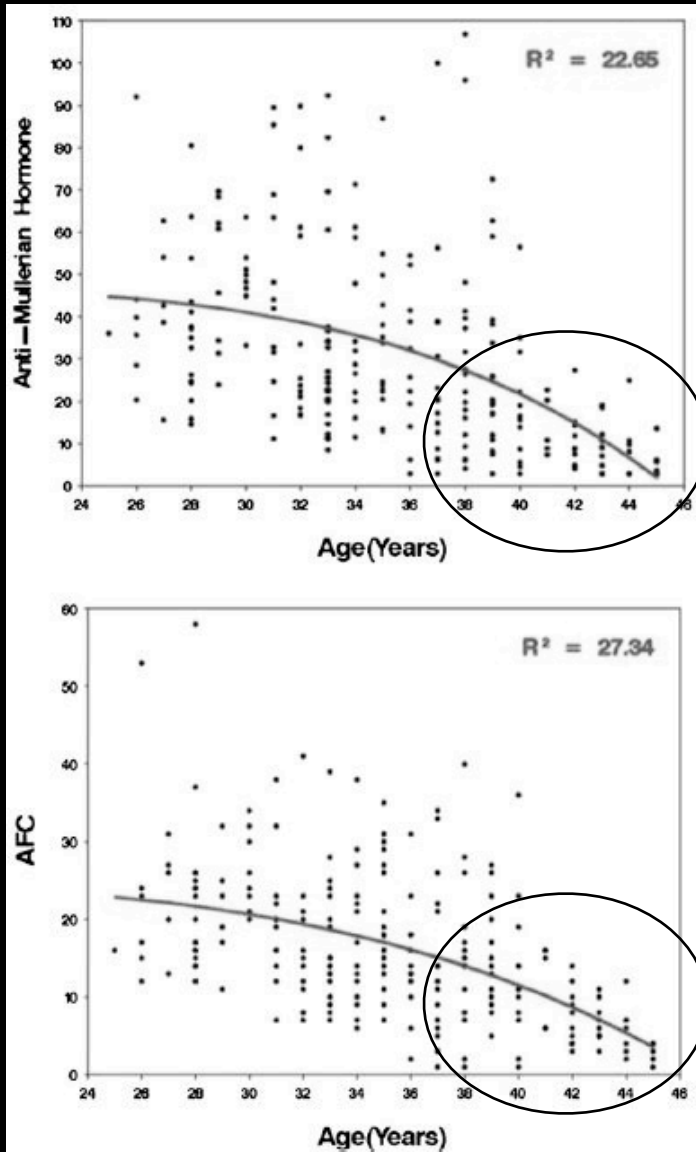


AMH-producing follicles



Differential AMH production

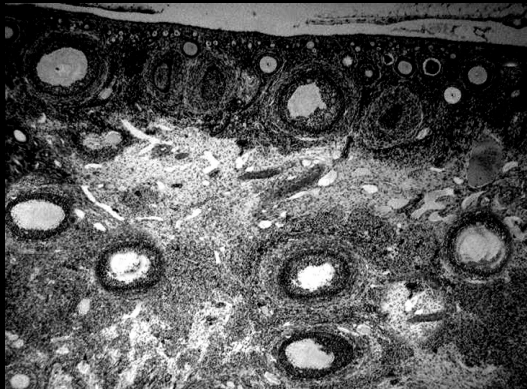
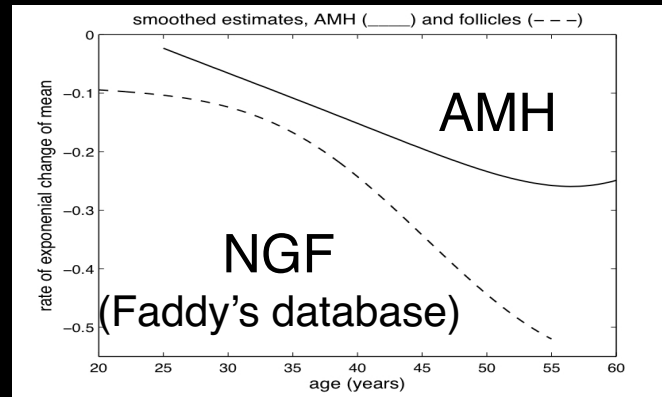
AMH x AFC & ovarian aging



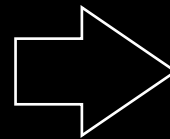
Different slopes >38 yo

AMH x AFC & ovarian aging

Rate of NGF and AMH change with age



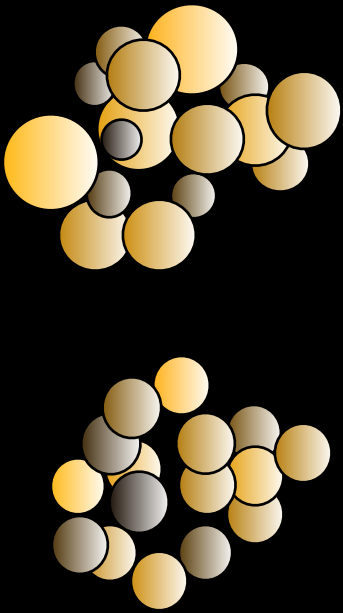
25 yo



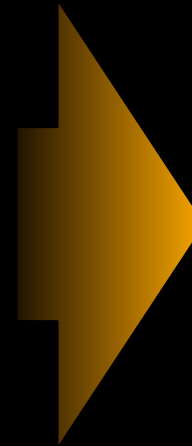
42 yo

Changes in the proportion between follicle classes with aging

AMH-producing follicles



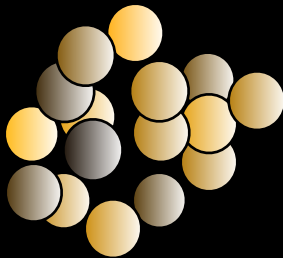
- AF number
- AF sizes
- AF “health”
- AF “environment”



Serum AMH levels

Complex equation!

AMH-producing follicles

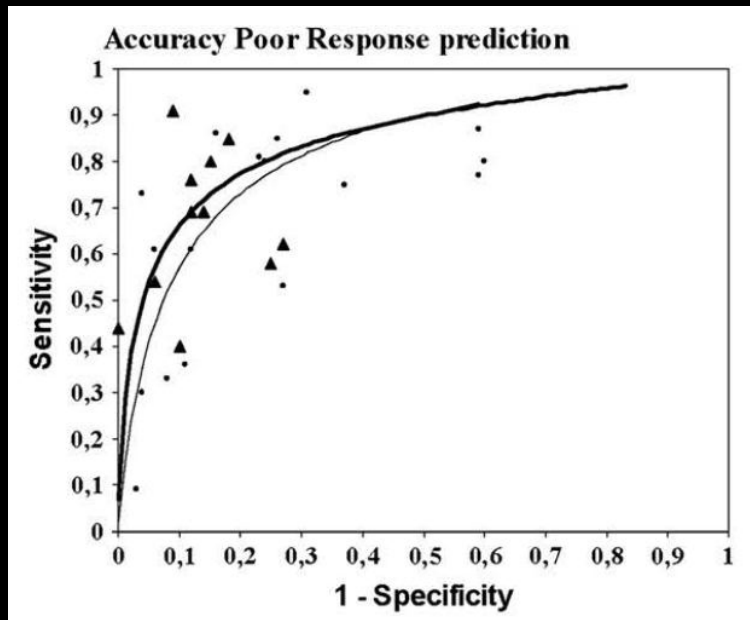


Influences on:

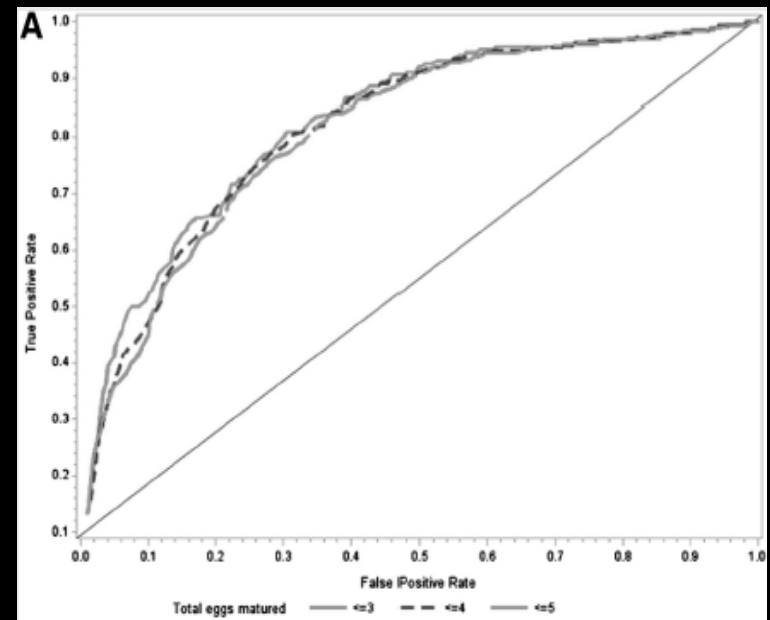
- AMH x AFC
- AMH x overall follicle status
- AMH x ovarian response
- AMH x ART outcome?

AFC & AMH
x
Ovarian response

Prediction of ovarian response



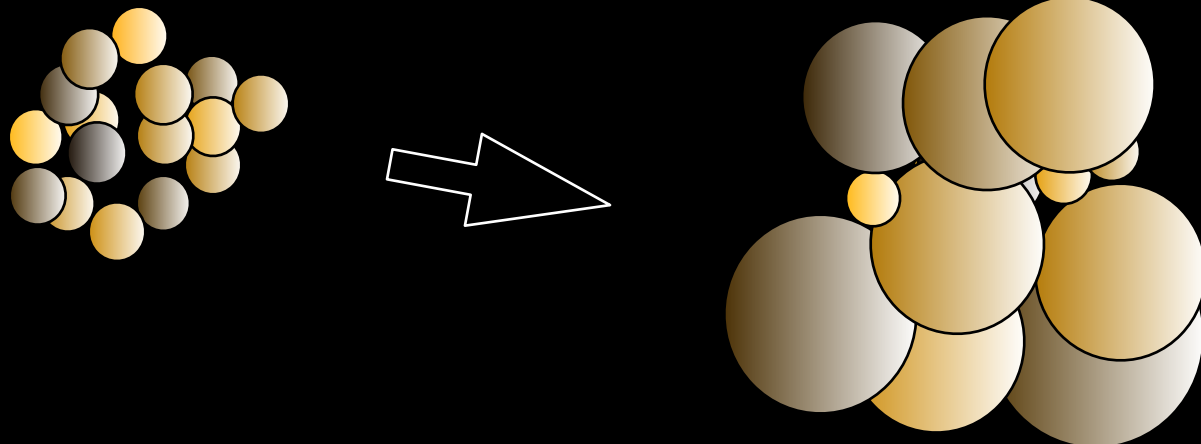
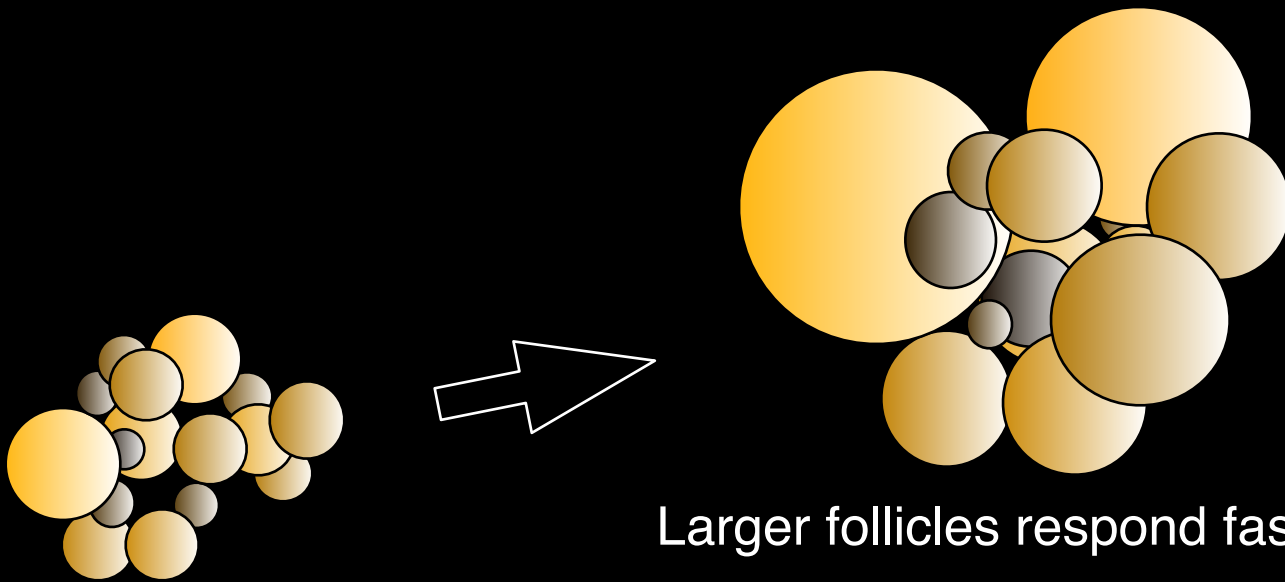
Poor response to COH



Oocytes retrieved

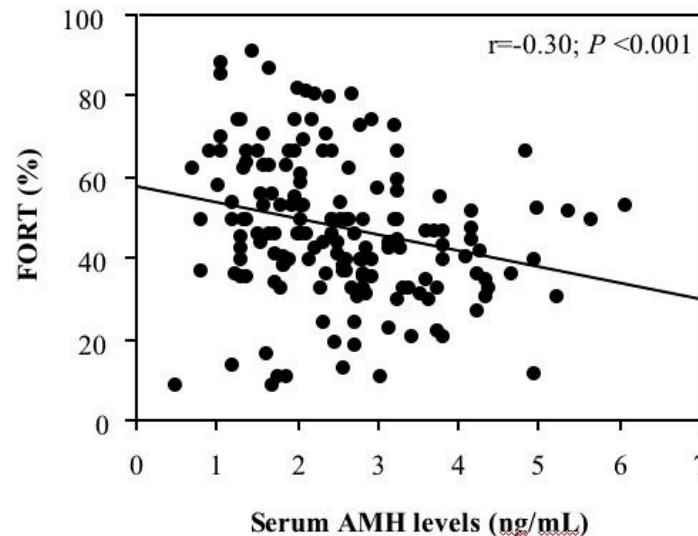
Remarkable predictability of AMH on ovarian response

AMH-producing follicles



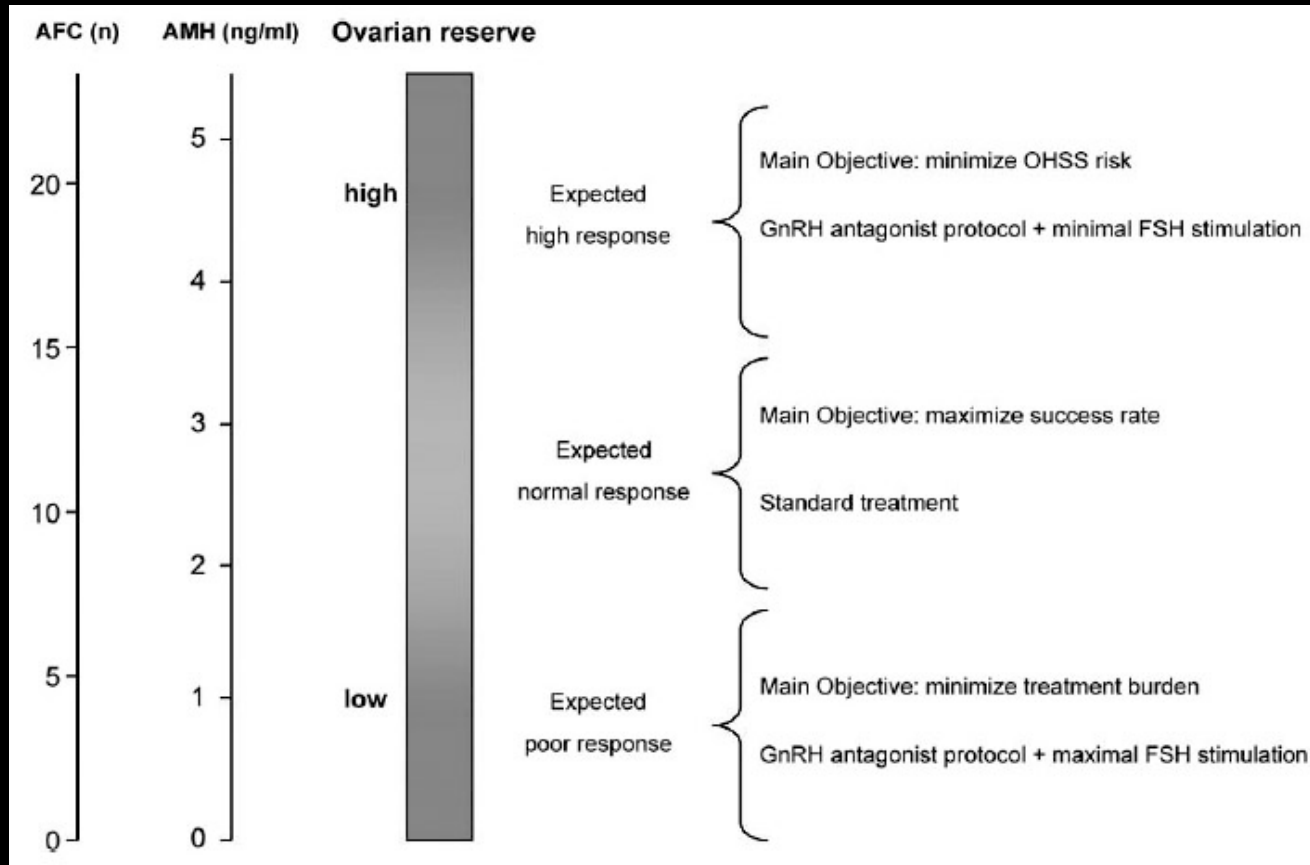
Serum anti-Müllerian hormone levels are negatively related to Follicular Output Rate (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation

V.K. Genro^{1,2,3,4}, M. Grynberg^{1,2,3}, J.B. Scheffer^{1,2,3}, I. Roux^{1,2,3}, R. Frydman^{1,2,3}, and R. Fanchin^{1,2,3,*}



Relationship between AMH and FORT

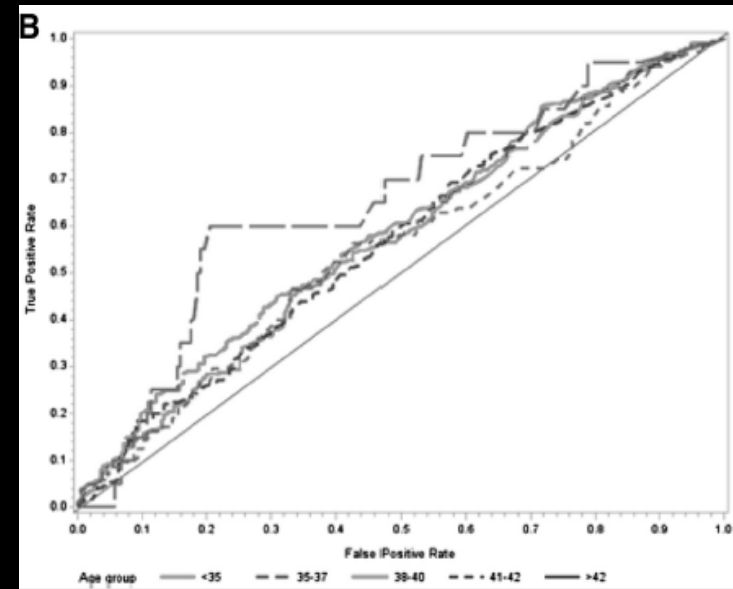
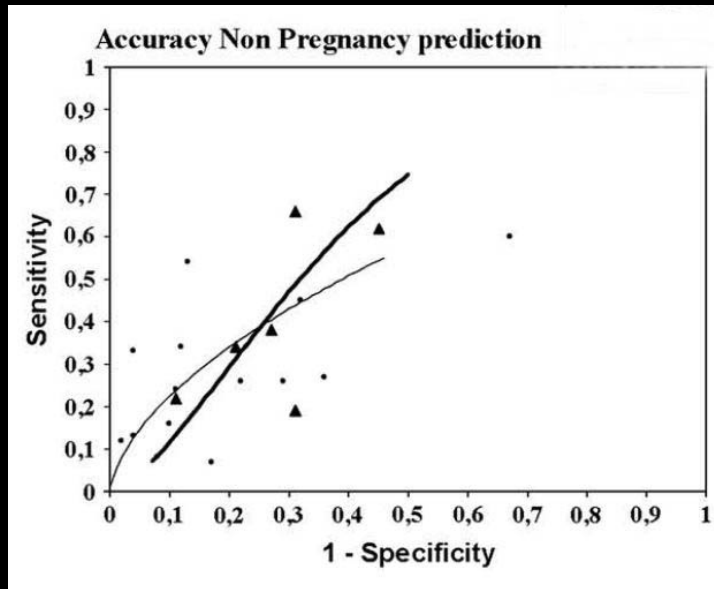
Prediction of ovarian response



Usefulness of AMH & AFC to adapt the type of COH protocol

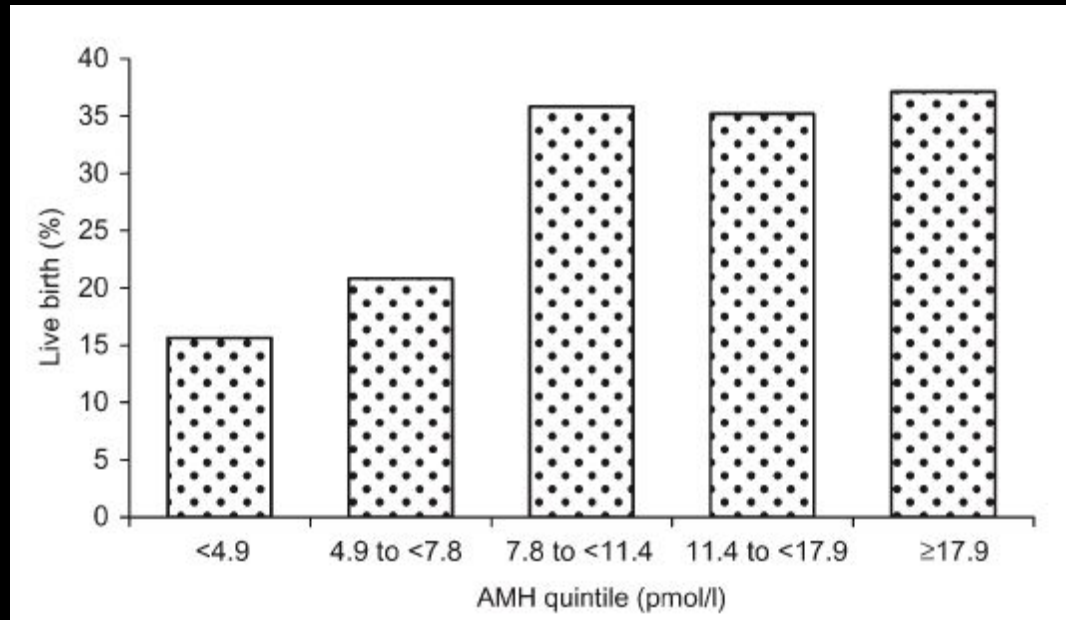
AFC & AMH
x
IVF-ET outcome

Prediction of pregnancy rate



Insufficient predictability of AMH and AFC on pregnancy rate

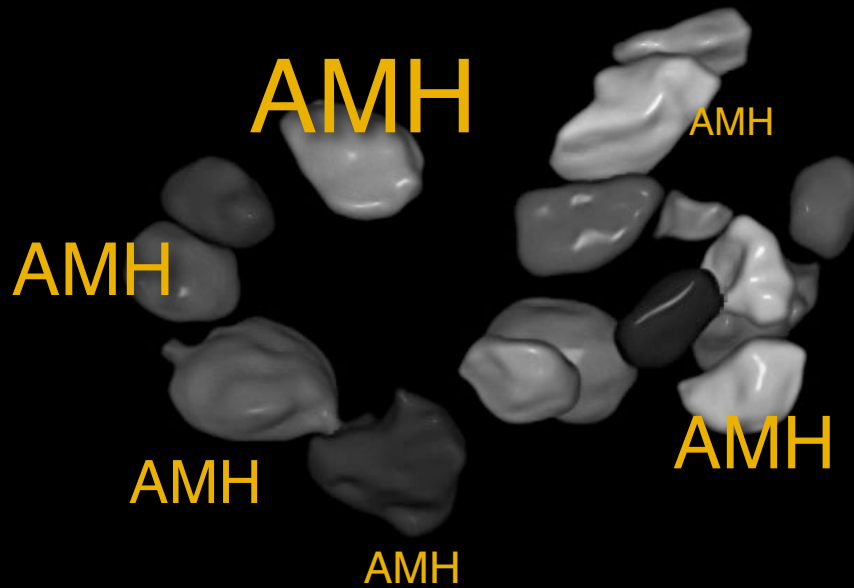
AMH predictive of birth rate?



AMH predictive of live birth rate

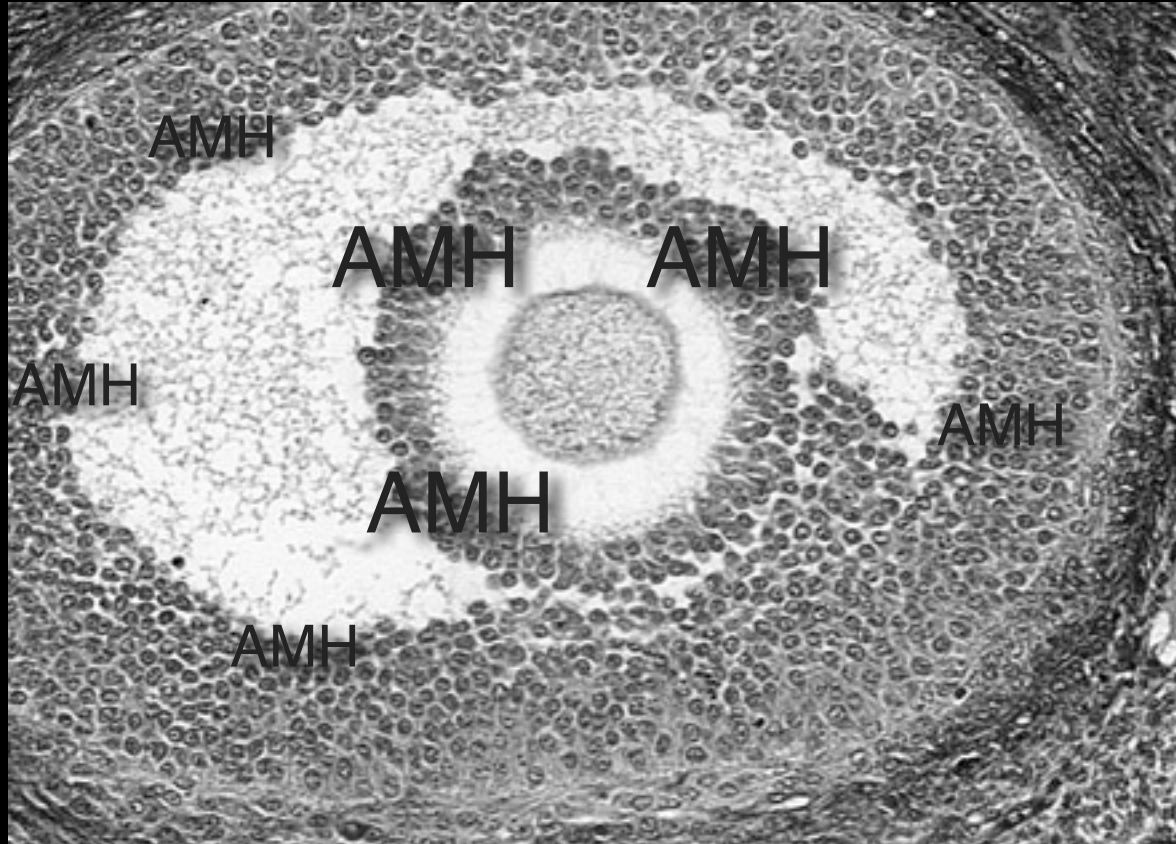
AMH: marker of oocyte quality?

Per-follicle AMH concentrations



Reflect of GC health?

Oocyte quality



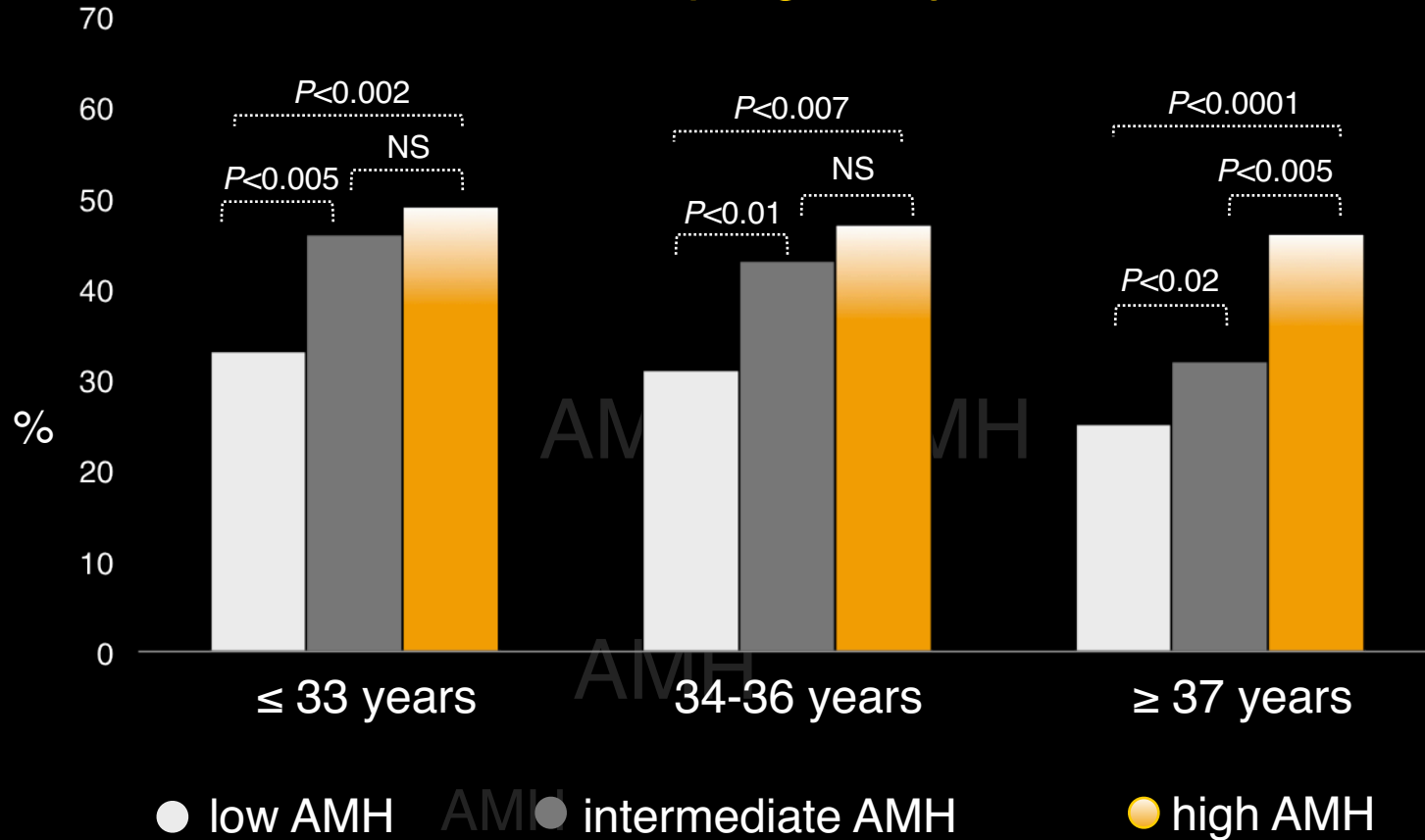
Bézard et al. J Reprod Fertil, 1987

Ueno et al. Endocrinology, 1989

Serum antimüllerian hormone levels are independently related to miscarriage rates after in vitro fertilization–embryo transfer

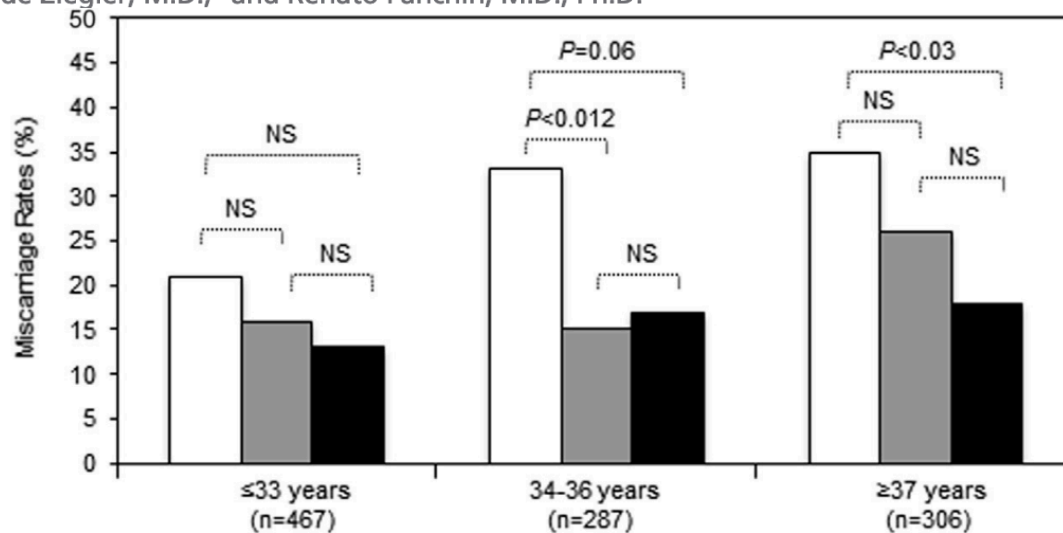
Bruno Tarasconi, M.D.,^{a,b} Teddy Tadros, M.D.,^a Jean-Marc Ayoubi, M.D., Ph.D.,^a Stephanie Belloc, Pharm.D.,^a Dominique de Ziegler, M.D.,^a and Renato Fanchin, M.D., Ph.D.^a

Clinical pregnancy rates



Serum antimüllerian hormone levels are independently related to miscarriage rates after in vitro fertilization–embryo transfer

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○ Low AMH (0.08-1.60 ng/mL; n=152) ● Intermediate AMH (1.61-5.60 ng/mL; n=651) ● High AMH (5.61-35.00 ng/mL; n=257)

Serum antimüllerian hormone levels are independently related to miscarriage rates after in vitro fertilization–embryo transfer

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Binary logistic regression analysis of the occurrence of a miscarriage according to age, serum AMH levels, and oocyte yield.

Variable	B	SE	Wald	df	P value	Exp(B)	95% CI for Exp(B)
Age	0.07	0.021	11.8	1	.001	1.07	1.03–1.12
AMH	−0.76	0.033	5.33	1	.021	0.93	0.87–0.99
No. oocytes	−0.008	0.016	0.28	1	.595	0.99	0.96–1.02

Multicollinearity diagnosis

Live birth

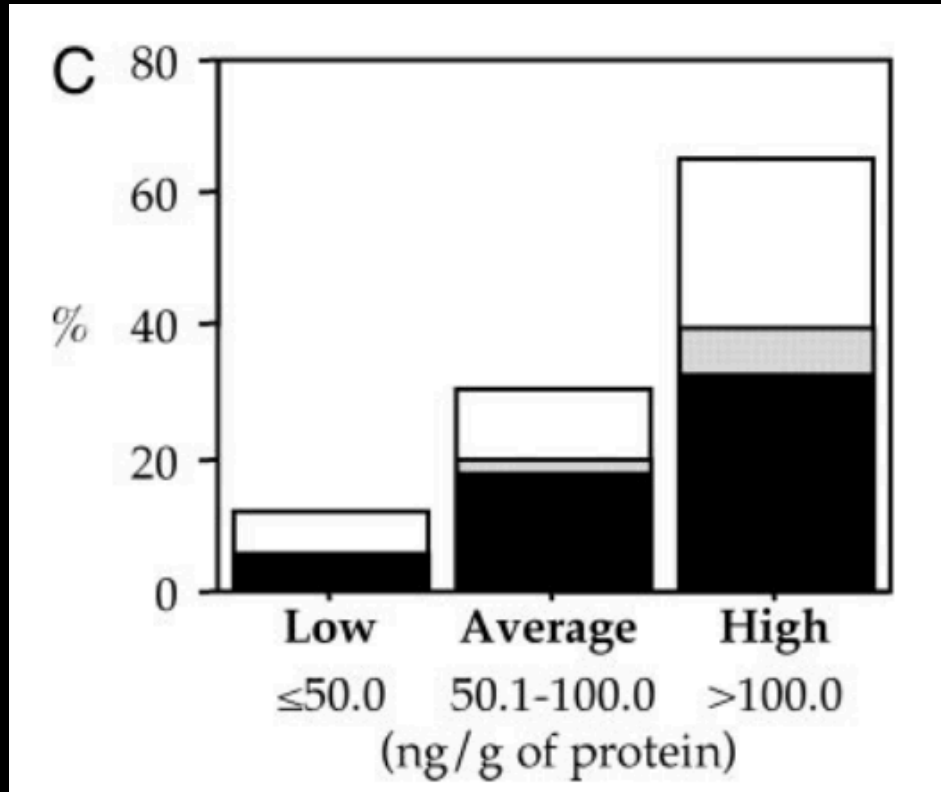
	VIF
Age	1,08
AMH	1,13
Nº Oocytes	1,12

Miscarriages

	VIF
Age	1,06
AMH	1,09
Nº Oocytes	1,09

➡ No multicollinearity

Follicular AMH x oocyte competence



FF AMH levels & oocyte/embryo fate

Conclusions

Biomarkers of the ovarian follicle status are serviceable for patient counselling and treatment adjustments

AMH and AFC should be used in combination as far as possible , for quality control and because they are complementary

Ideal biomarker of oocyte quality to be discovered