

AMH and ovarian function testing

Old and New Hormones: Updates on new discoveries of hormones and their receptors

Budapest, ESHRE Campus Course, 3-4 December 2009



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Reproductive Medicine
University Medical Center Utrecht

Take Homer

AMH is THE promise for
Ovarian Reserve testing



Agenda

- AMH physiology
- AMH as test for Ovarian Reserve
- AMH as diagnostic tool in PCOS



Physiology

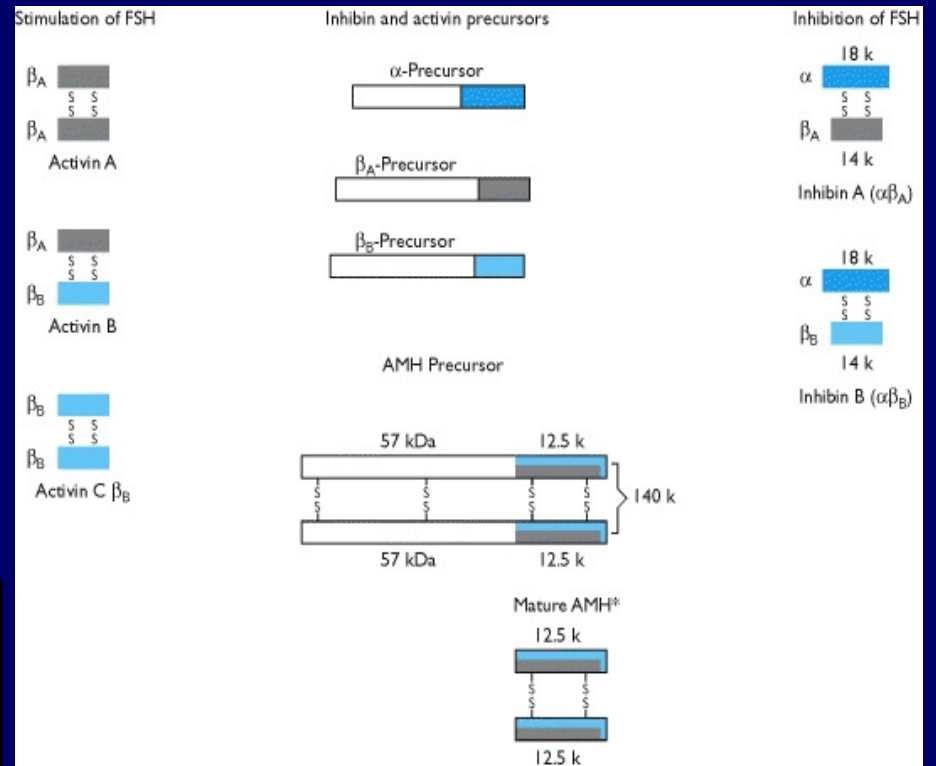
- What is AMH?
- Where is it produced?
- What does it do and how?
- Can we measure it?



AMH - dimeric glycoprotein

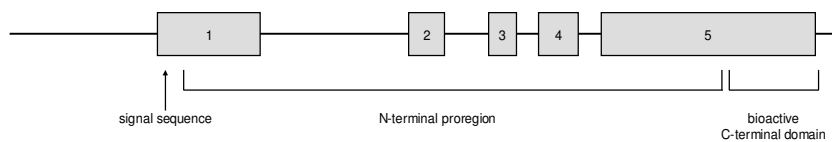
member of the transforming growth factor β (TGF- β) family of growth and differentiation factors

Inhibins and Activins



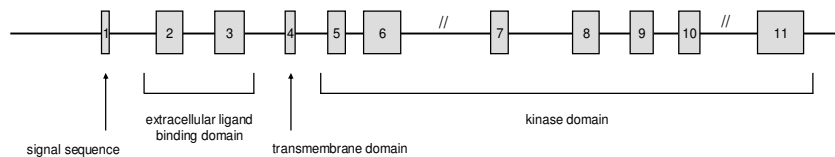
AMH

Chr. 19p13.3



AMHR2

Chr. 12q13

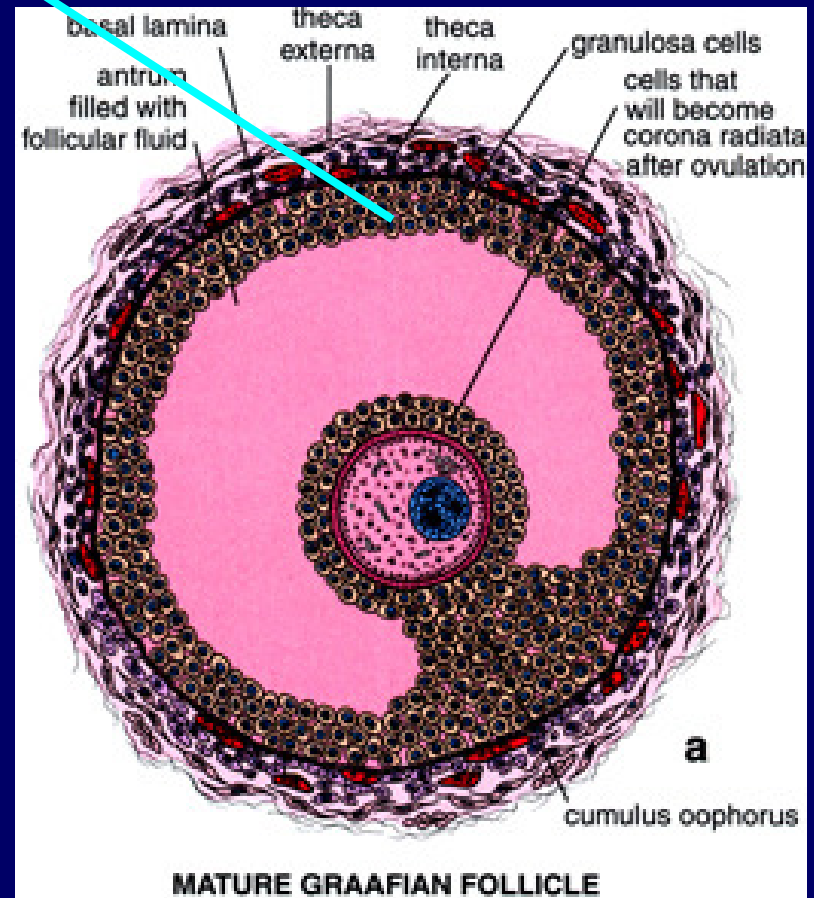
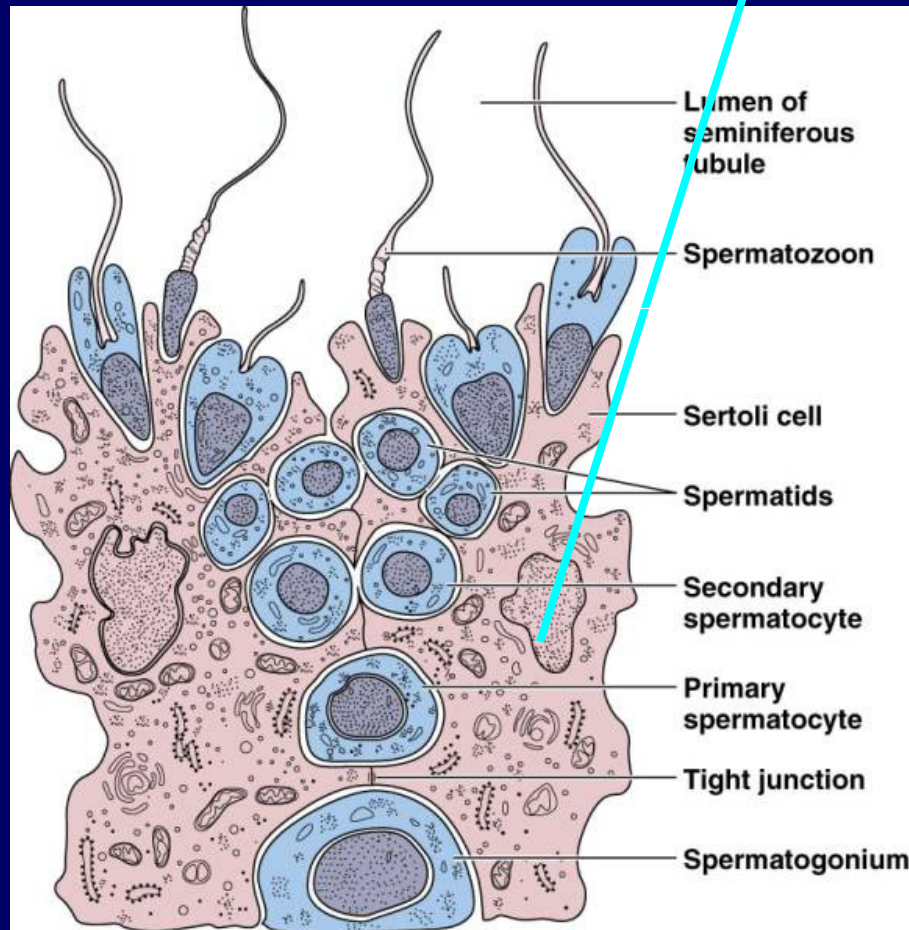


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Where is it produced?

AMH

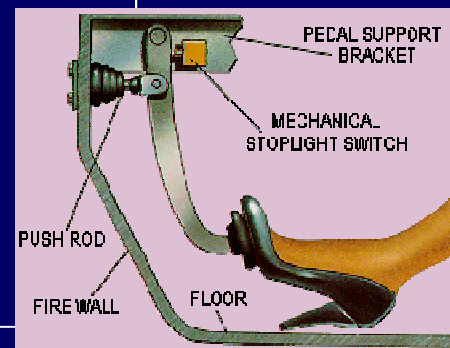
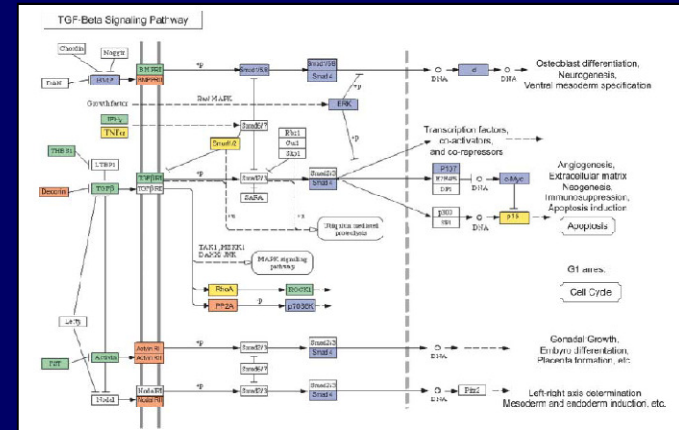
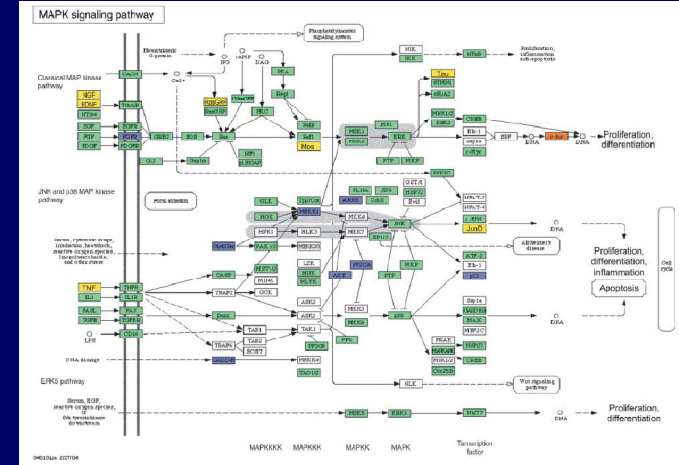


AMH effects through

receptors expressed in the gonads and in mesenchymal cells adjacent to the mullerian ducts

decrease the expression of stimulatory factors

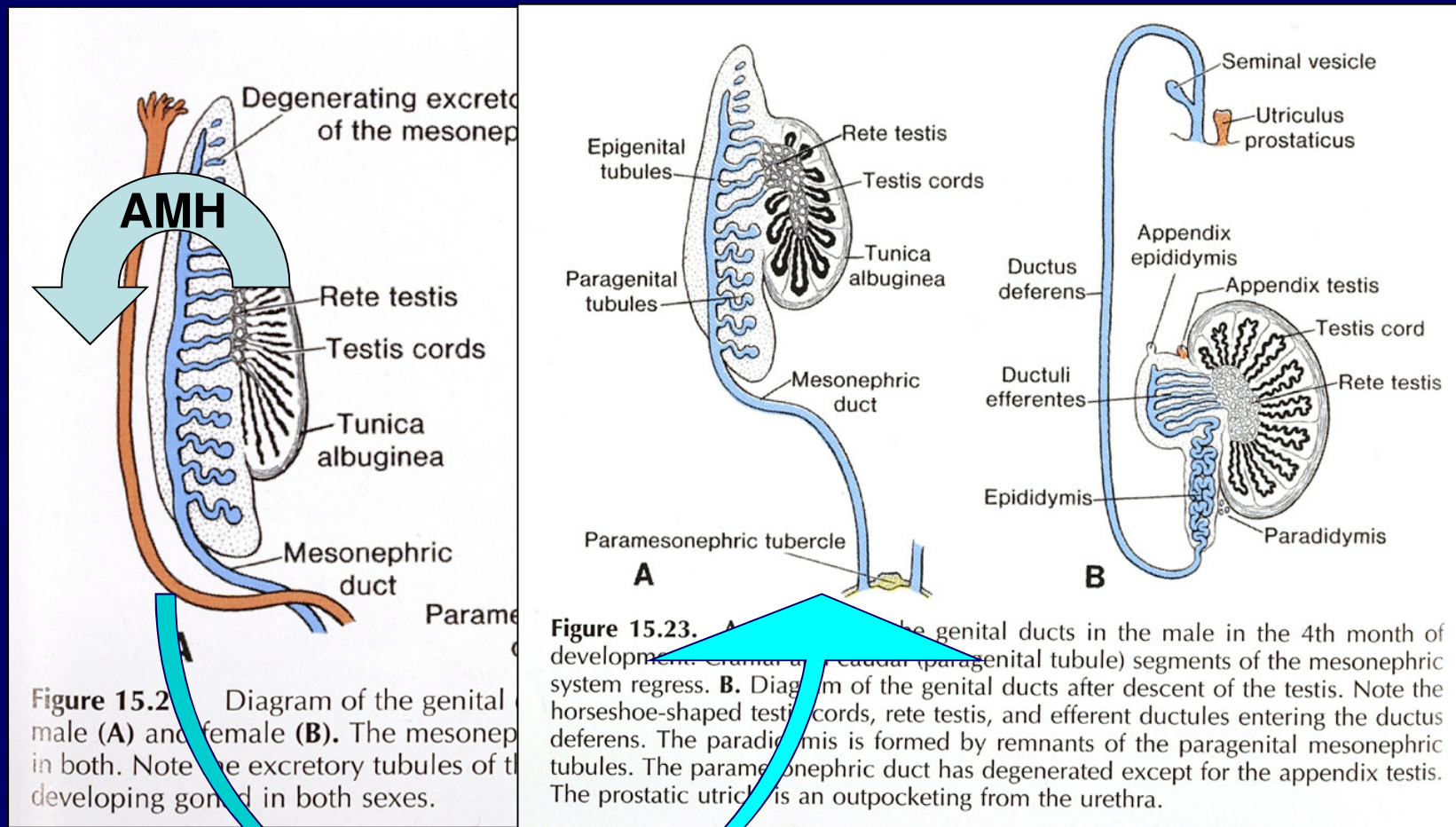
increase the expression of inhibitory factors



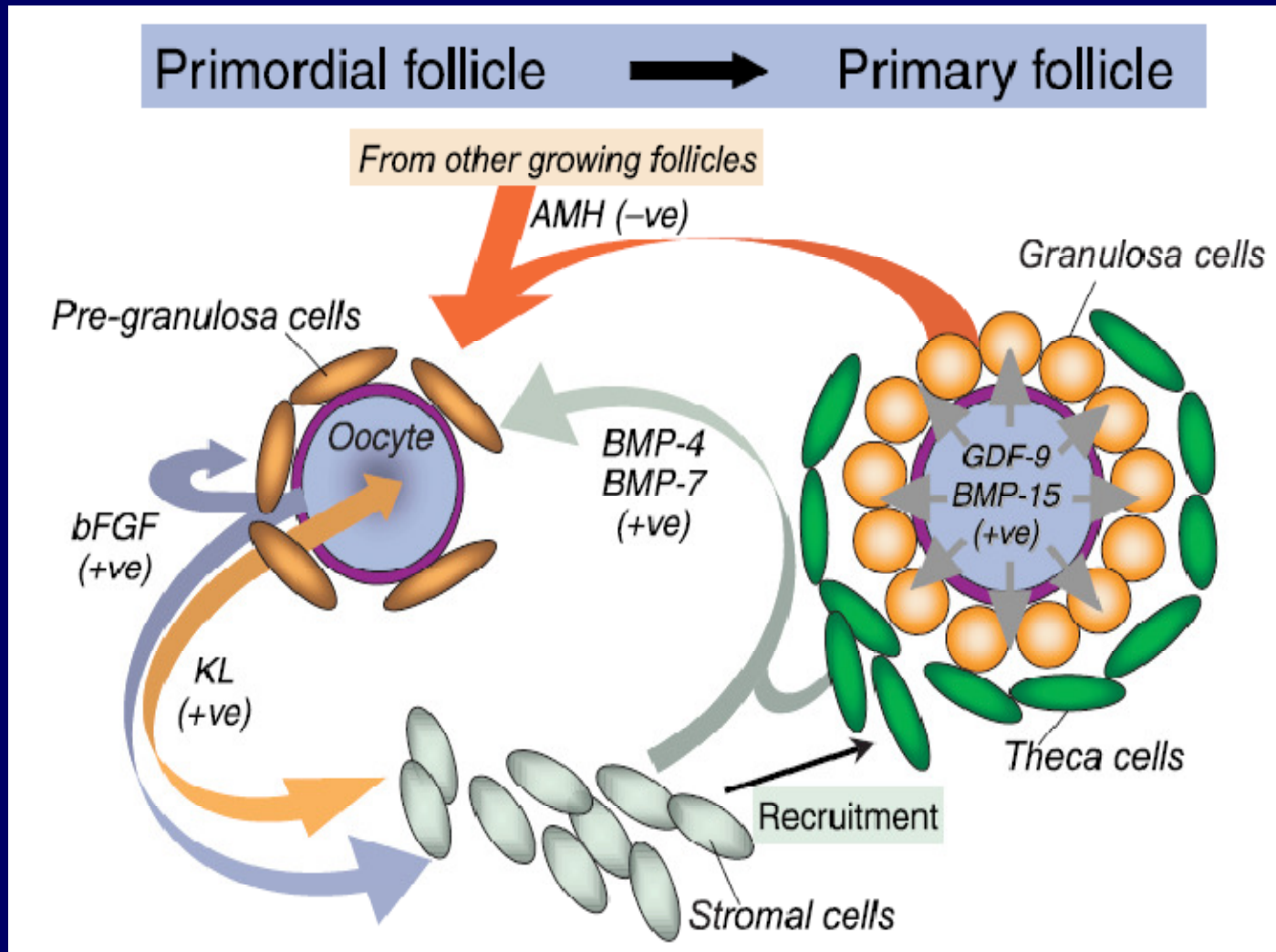
AMH – its role in gonadal differentiation

46 XY → SRY gene → Testis formation from primitive gonad

→ AMH secretion from Sertoli cells → Regression Mullerian ducts



AMH affects follicle recruitment



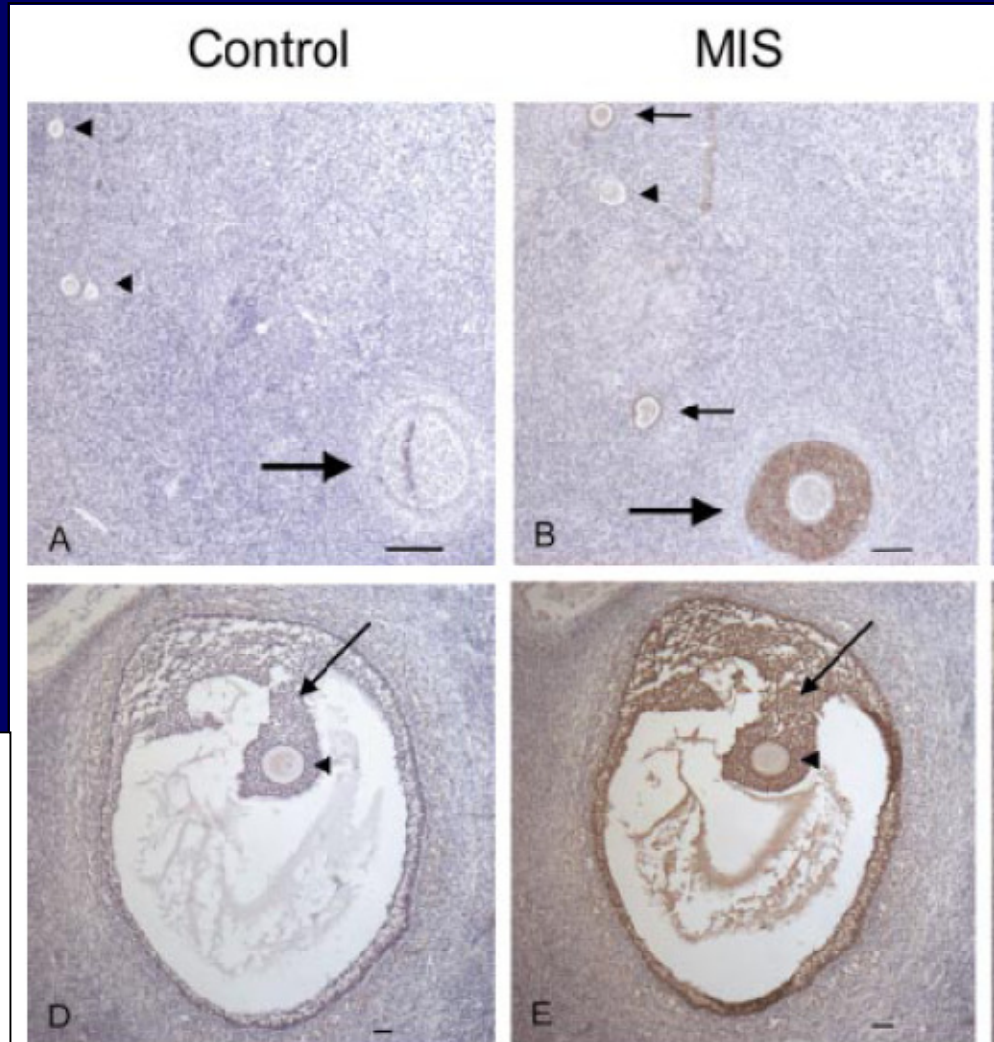
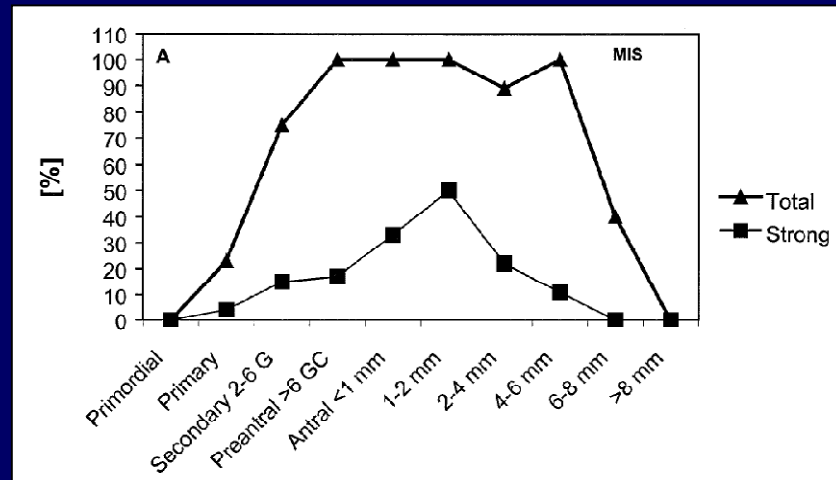
Knight, 2006

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Ovarian AMH expression

Granulosa cells of
Primary
Up to
Small antral follicles 6-8 mm

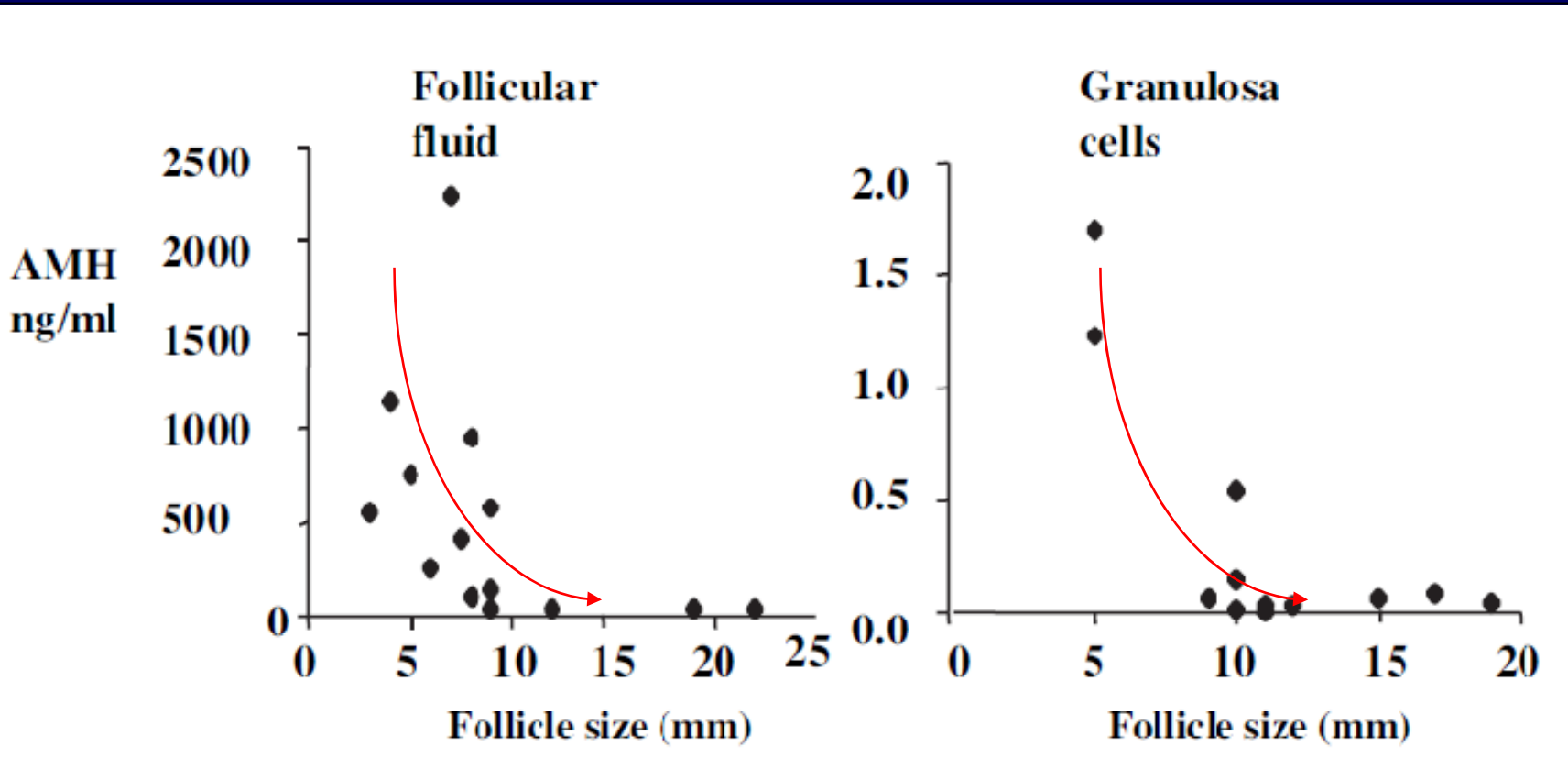


Weenen, 2006



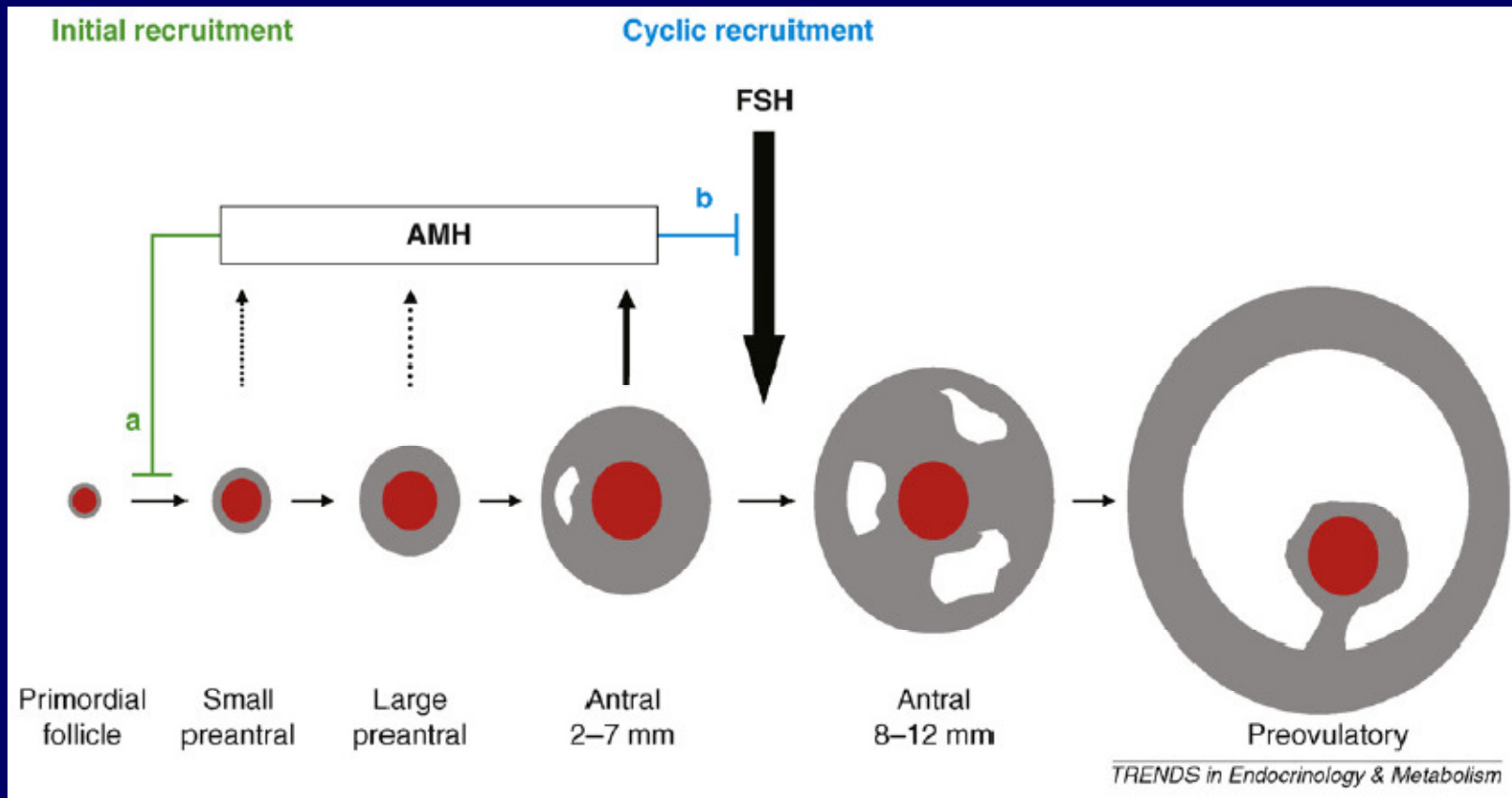
Levels of AMH in FF and from GC conditioned medium according to follicle diameter - Pellat, 2007

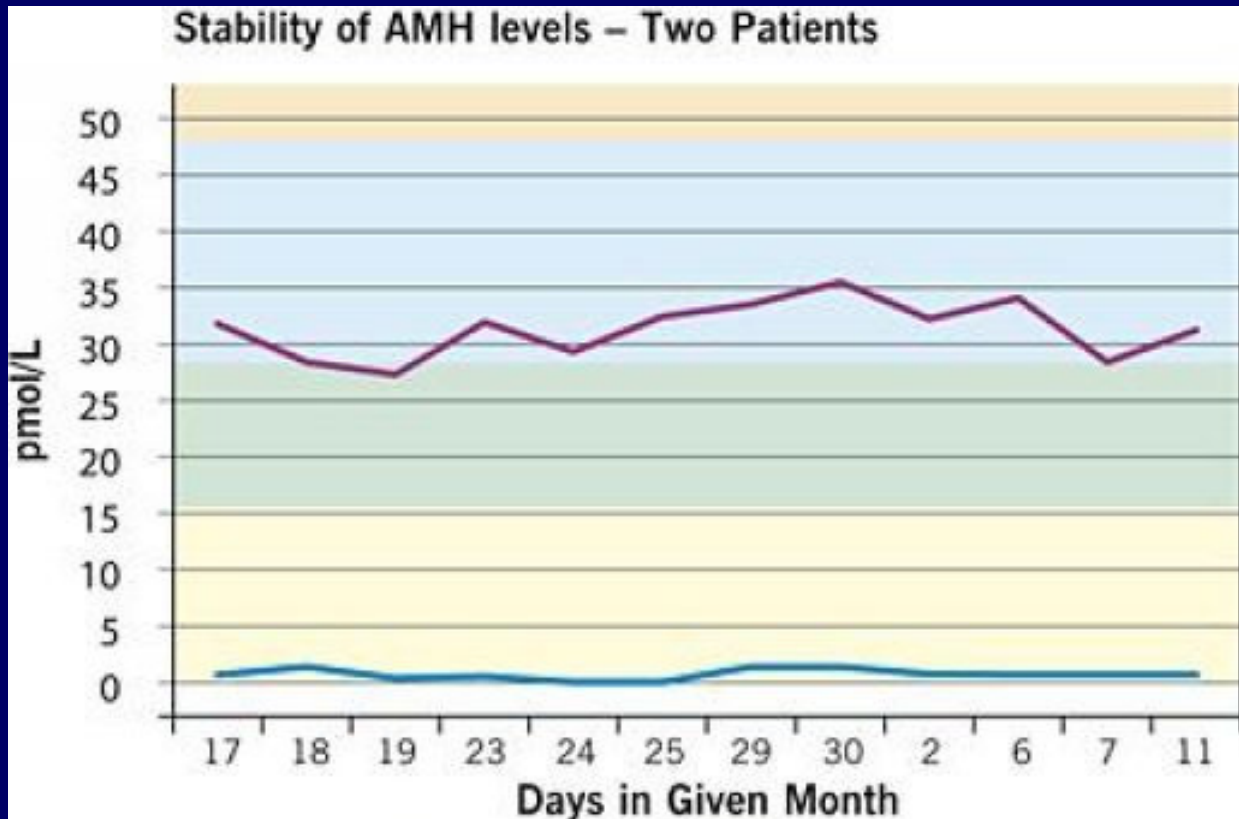
Larger follicles switch AMH off



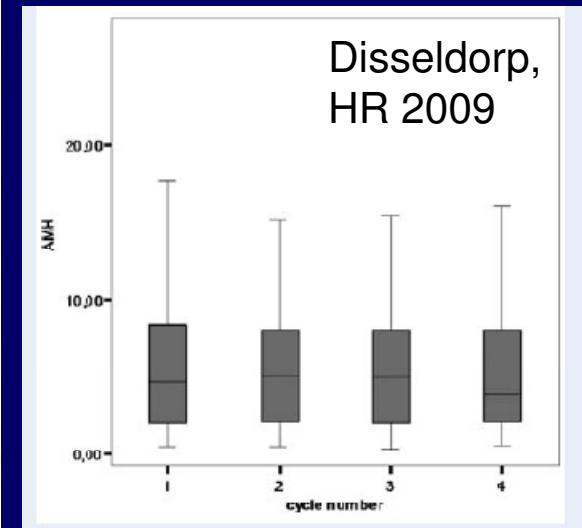
Summary - Ovarian AMH inhibits

1. Initial recruitment of primordial follicles into primary follicles
2. Sensitivity of antral follicles to FSH in cyclic recruitment





Can we measure it??



0021-972X/06/415.000
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(10):4057-4063
Copyright © 2006 by The Endocrine Society
doi: 10.1210/yc.2006-0331

Anti-Müllerian Hormone Levels in the Spontaneous Menstrual Cycle Do Not Show Substantial Fluctuation

Wouter J. K. Hehenkamp, Caspar W. N. Looman, Axel P. N. Themmen, Frank H. de Jong, E. R. te Velde, and Frank J. M. Broekmans

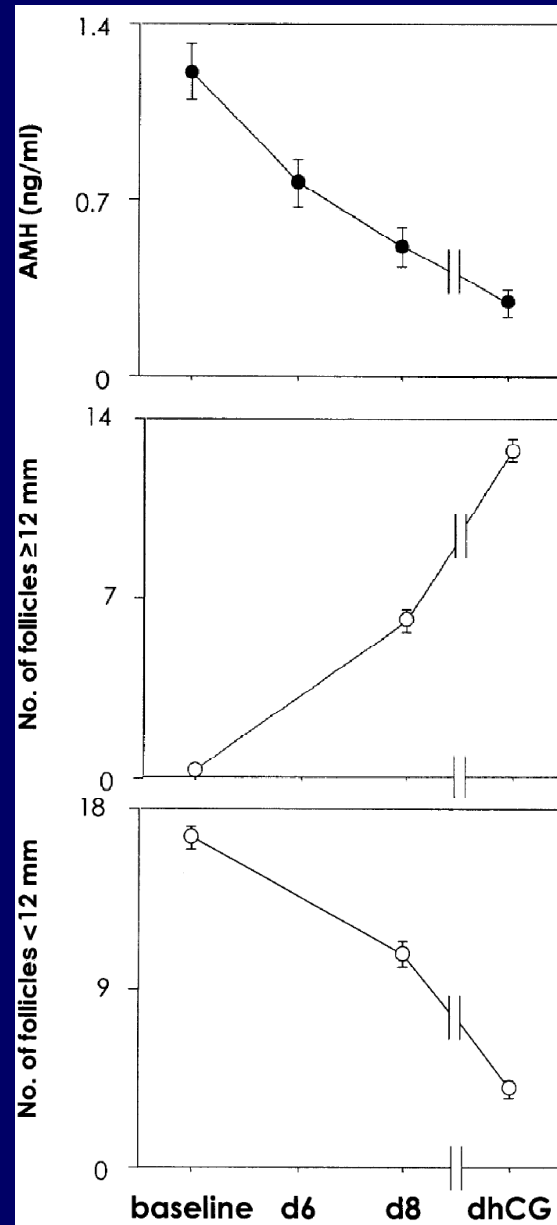


AMH is switched off when follicles grow into dominance

With FSH hyper stimulation:

Follicles 2-12 mm are more than halved in number, parallel to a more than 50% reduction in serum AMH.

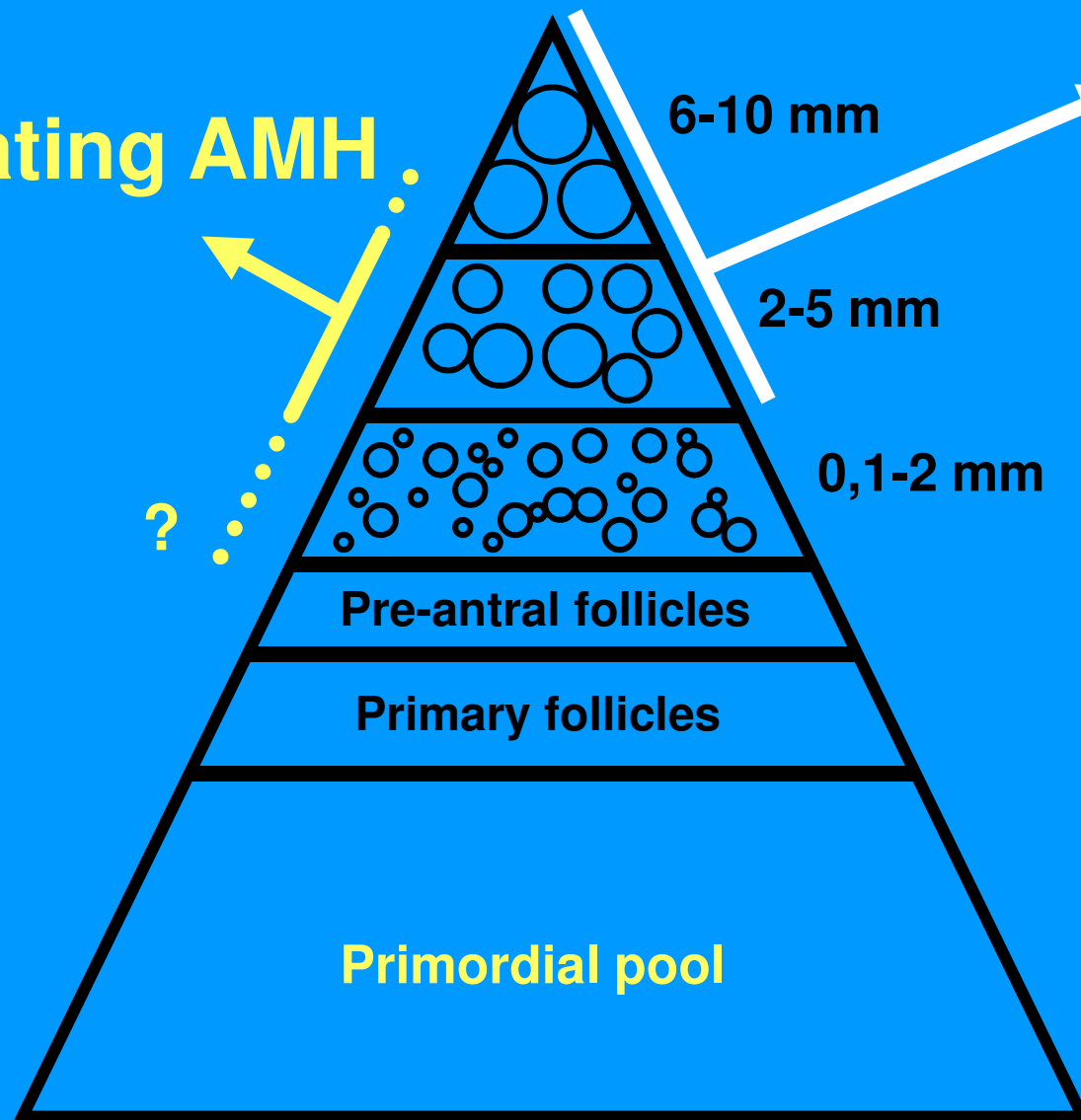
Fanchin, 2003



Which follicles contribute to serum levels??



Circulating AMH



Agenda

- AMH physiology
- AMH as test for Ovarian Reserve
- AMH as diagnostic tool in PCOS

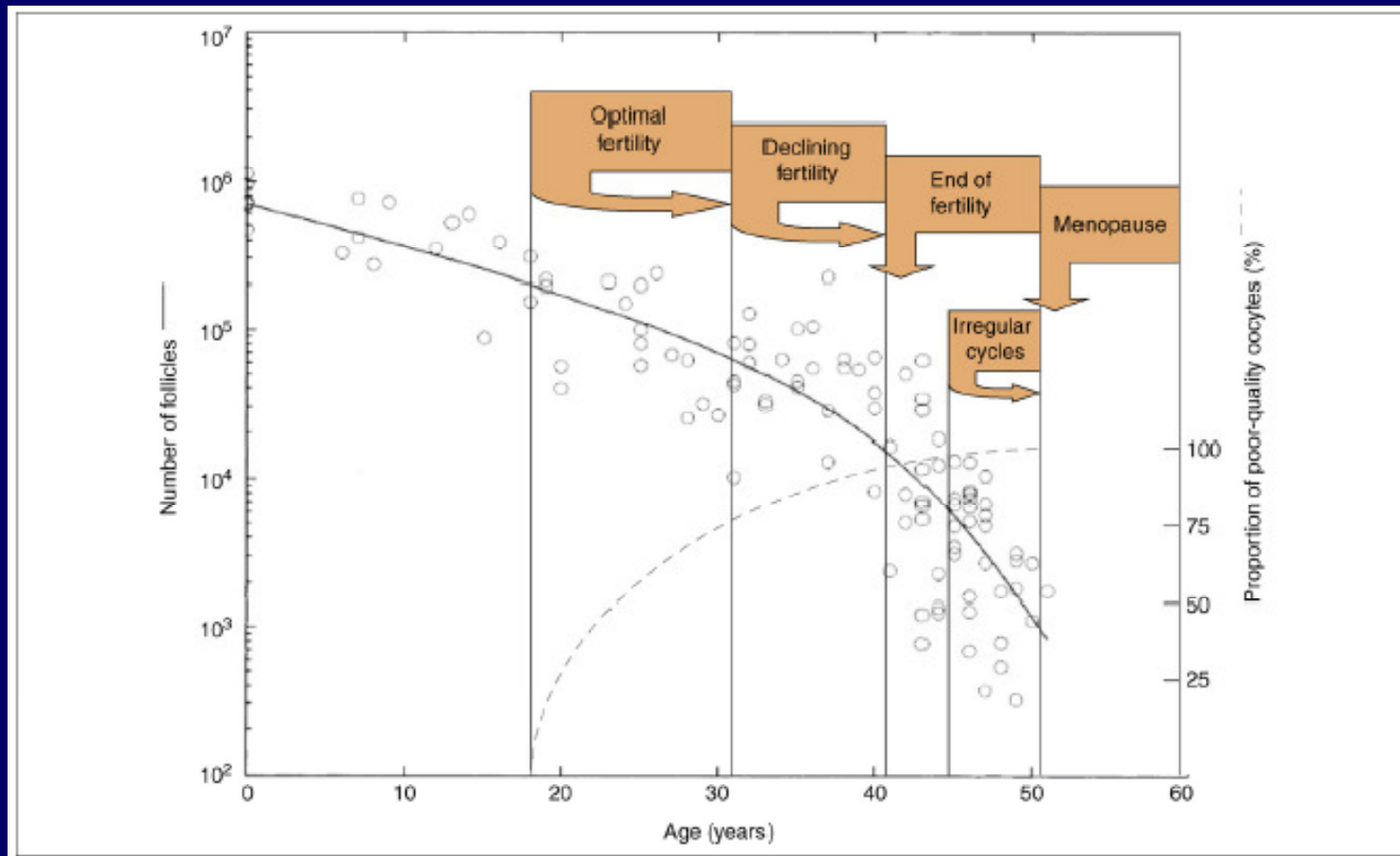


Testing Ovarian Reserve

- What is ovarian reserve?
- Is AMH a plausible marker for ovarian reserve??
- Has AMH proven to be a good marker for ovarian reserve
- And if so, what can we do with it?



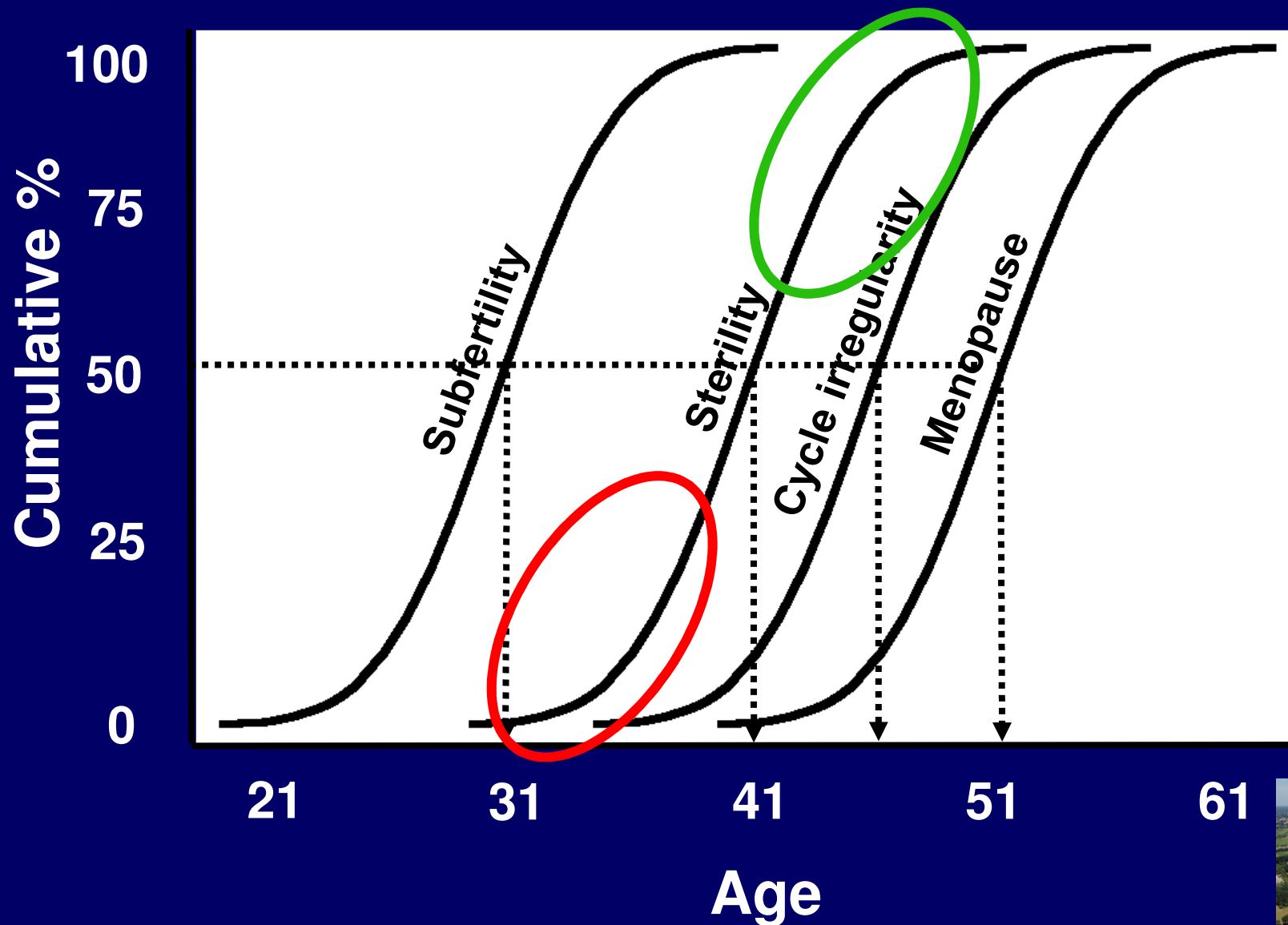
Ovarian Reserve = quantity and quality decline of the ovarian follicle/oocyte pool



Faddy, 1995, De Bruijn, 2003, O'Connor, 2001



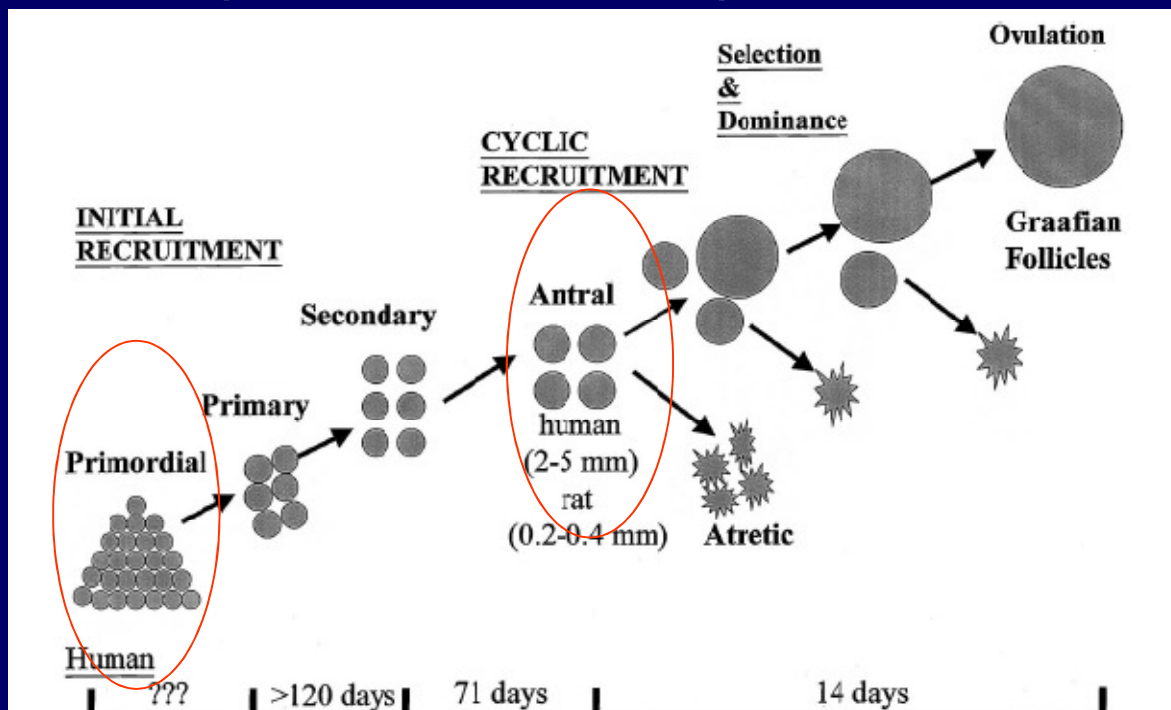
Variation in age at menopause and preceding reproductive events



Ovarian Reserve Tests

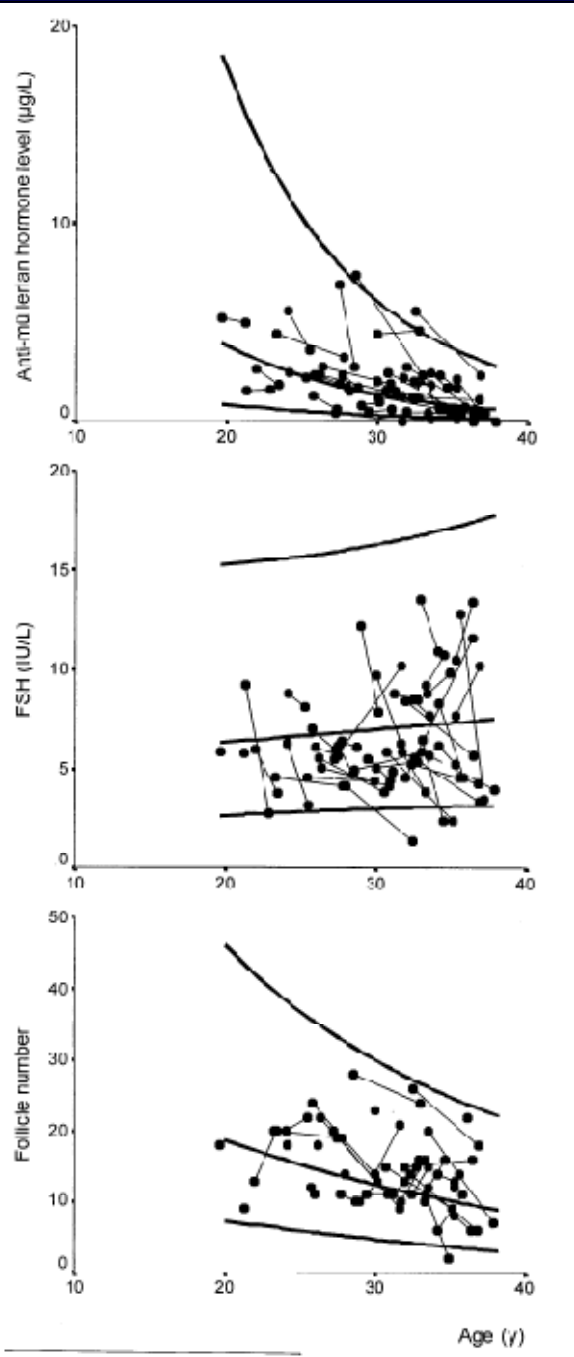
- Mark the size of the antral follicle cohort
- This cohort is proportionally related the primordial follicle pool

Quality?????



AMH levels decline with female age in follow up, as do AF numbers, but not FSH, over a mean range of 2.1 years

De Vet, 2002



Comparison of ovarian reserve tests over time in normal fertile women (T₁ value and T₂ value, mean time interval 4 years).

	T ₁	T ₂	P value ^a
AMH (µg/L)	1.2 (0.1–3.0)	0.5 (0.0–2.2)	<.001
AFC (n)	6 (2–16)	6 (0–16)	.56
FSH (IU/L)	7.8 (4.9–12.7)	8.7 (5.2–45.7)	<.001
Inhibin B (ng/L)	104 (14–160)	78 (8–139)	.002
E ₂ (pmol/L)	180 (98–353)	155 (87–292)	.36

Note: Values are median (10th–90th) percentiles. See text for abbreviations.

^a Wilcoxon signed rank test.

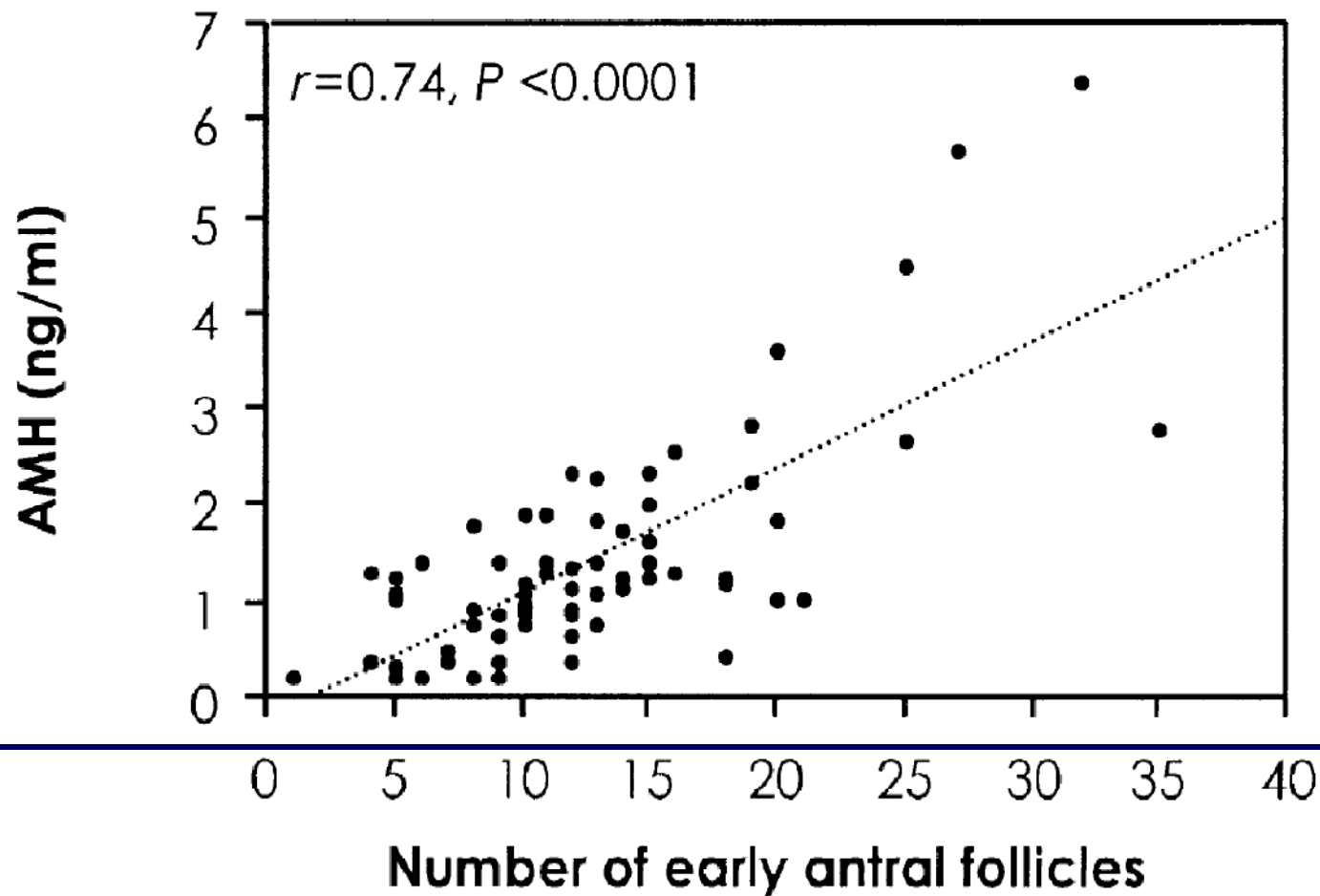
van Rooij. Serum AMH reflects female reproductive decline. Fertil Steril 2005.

....and 4 years
van Rooij, 2005



**AMH correlates well
with the number of 2-10
mm antral follicles**

Fanchin, 2003



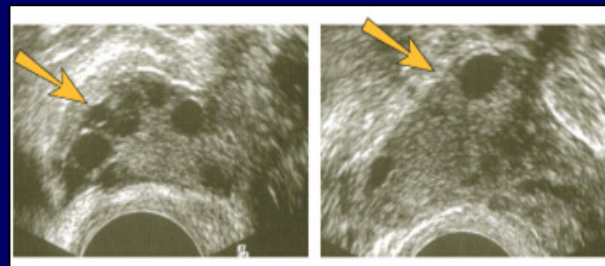
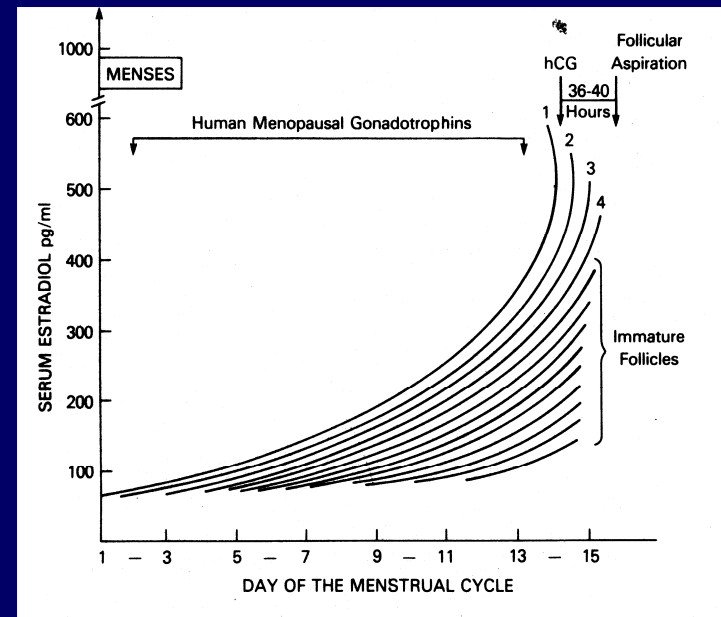
Has AMH proven to be a good marker for Ovarian Reserve for instance in IVF

=The number of follicles present in the “window of sensitivity”.

=Ovarian Response.

=Expressed by

female age
ovarian reserve
tests.

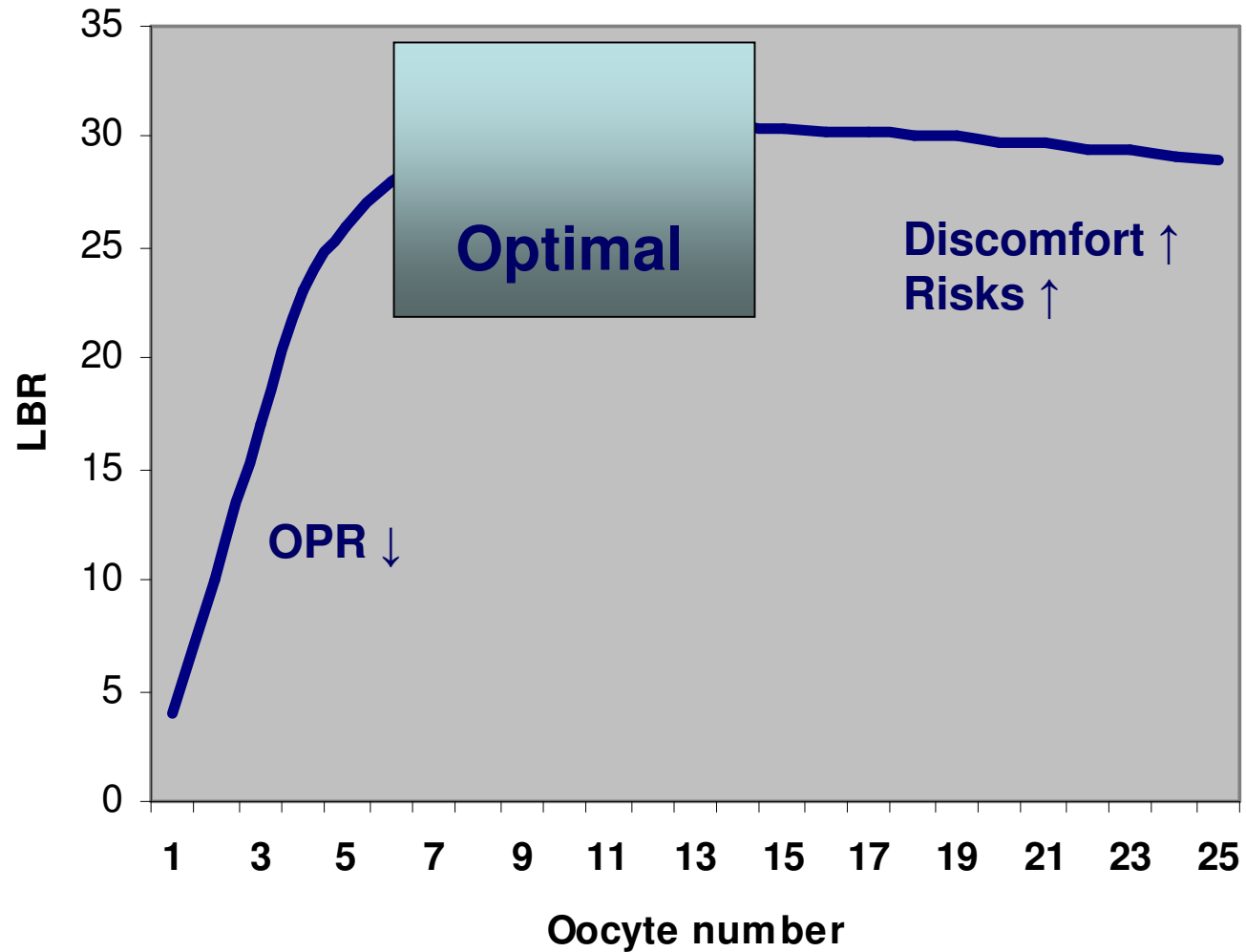


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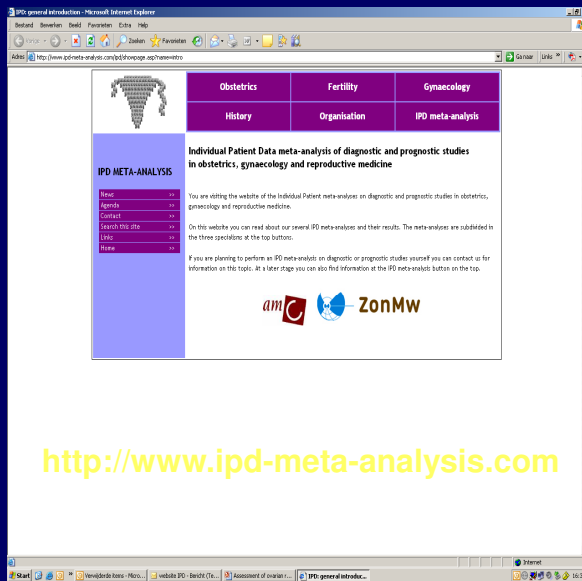
Balance...

Live birth rate and oocyte yield



Individual Patient Data Analysis: the IMPORT study

Added value to female age



<http://www.ipd-meta-analysis.com>

N= 2500

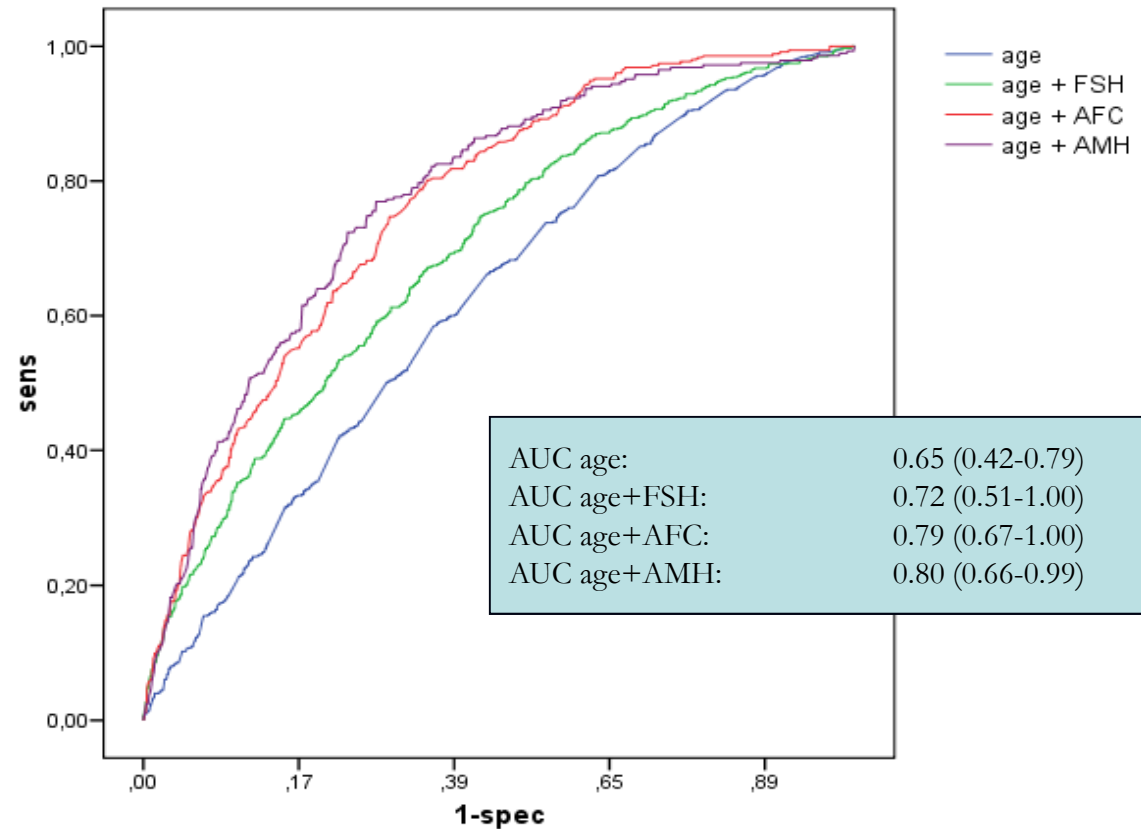
AUC-ROC = 0.80

IMPORT collaborators

- | | |
|-------------------|------------------------|
| • J. Kwee | • M. Erdem |
| • E. Ng | • M. McIlveen |
| • E. Caroppo | • B. Popovic-Todorovic |
| • R.A. Anderson | • I.K. Vladimirov |
| • E. Klinkert | • A. La Marca |
| • S. Nelson | • P.J.Q. vd Linden |
| • L.T. Merce | • T. Eldar-Geva |
| • L.F. Bancsi | • K. Jayaprakasan |
| • C. Tomás | • N. Fenning |
| • E.M. Greenblatt | • J.M.J. Smeenk |
| • S. Muttukrishna | • A.B. Copperman |
| • M. Ashrafi | • T. Ebner |



Poor response prediction

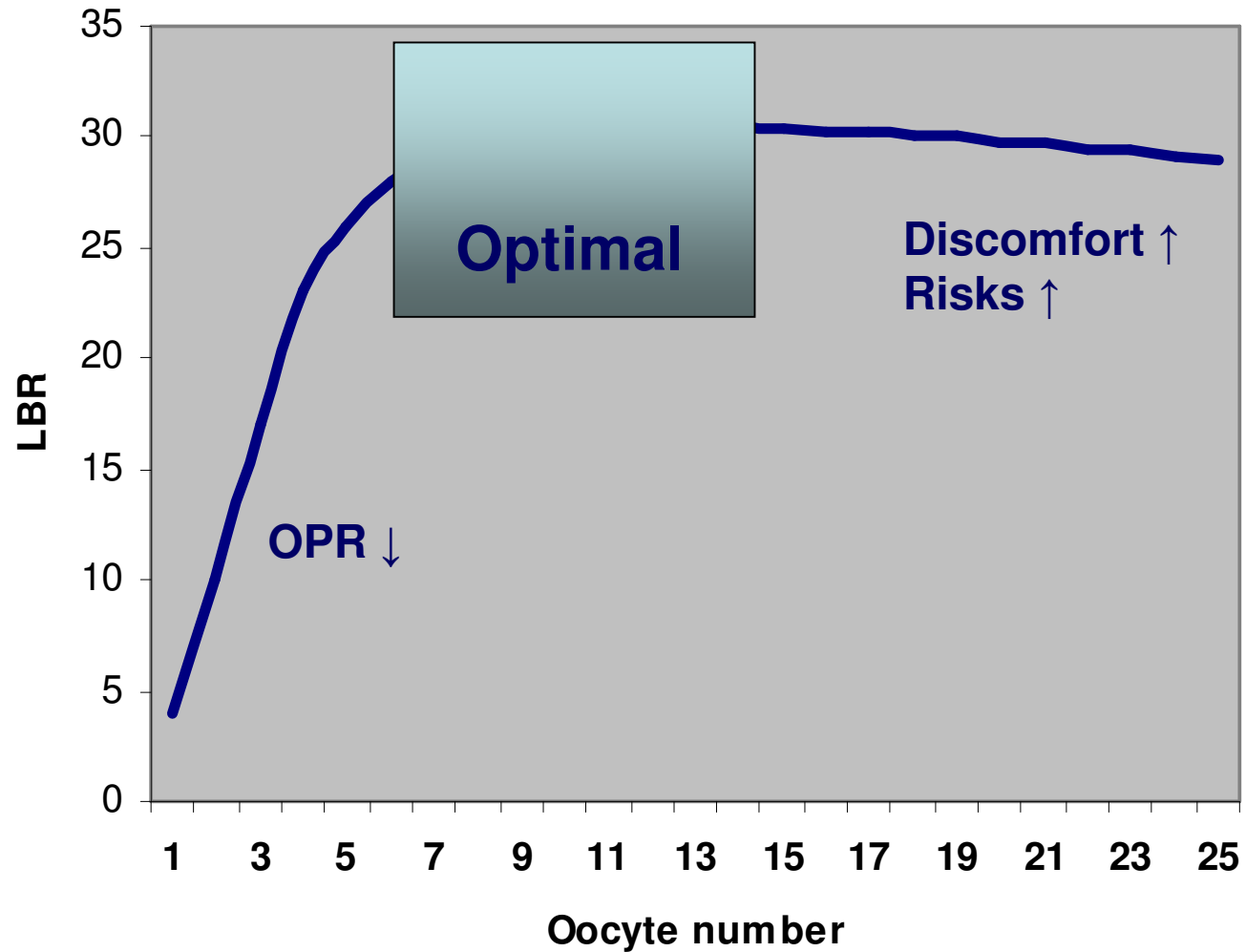


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Balance...

Live birth rate and oocyte yield

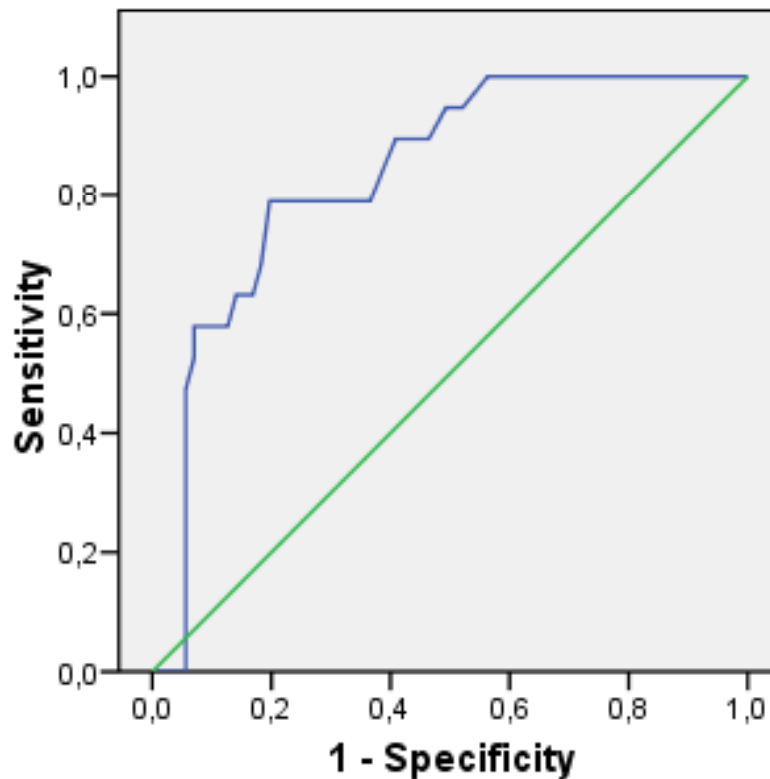


..ongoing literature **meta-analysis** on high response prediction from AMH...

Broer, Dolleman, Broekmans, Mol

AMH, 8 studies

ROC Curve



Diagonal segments are produced by ties.

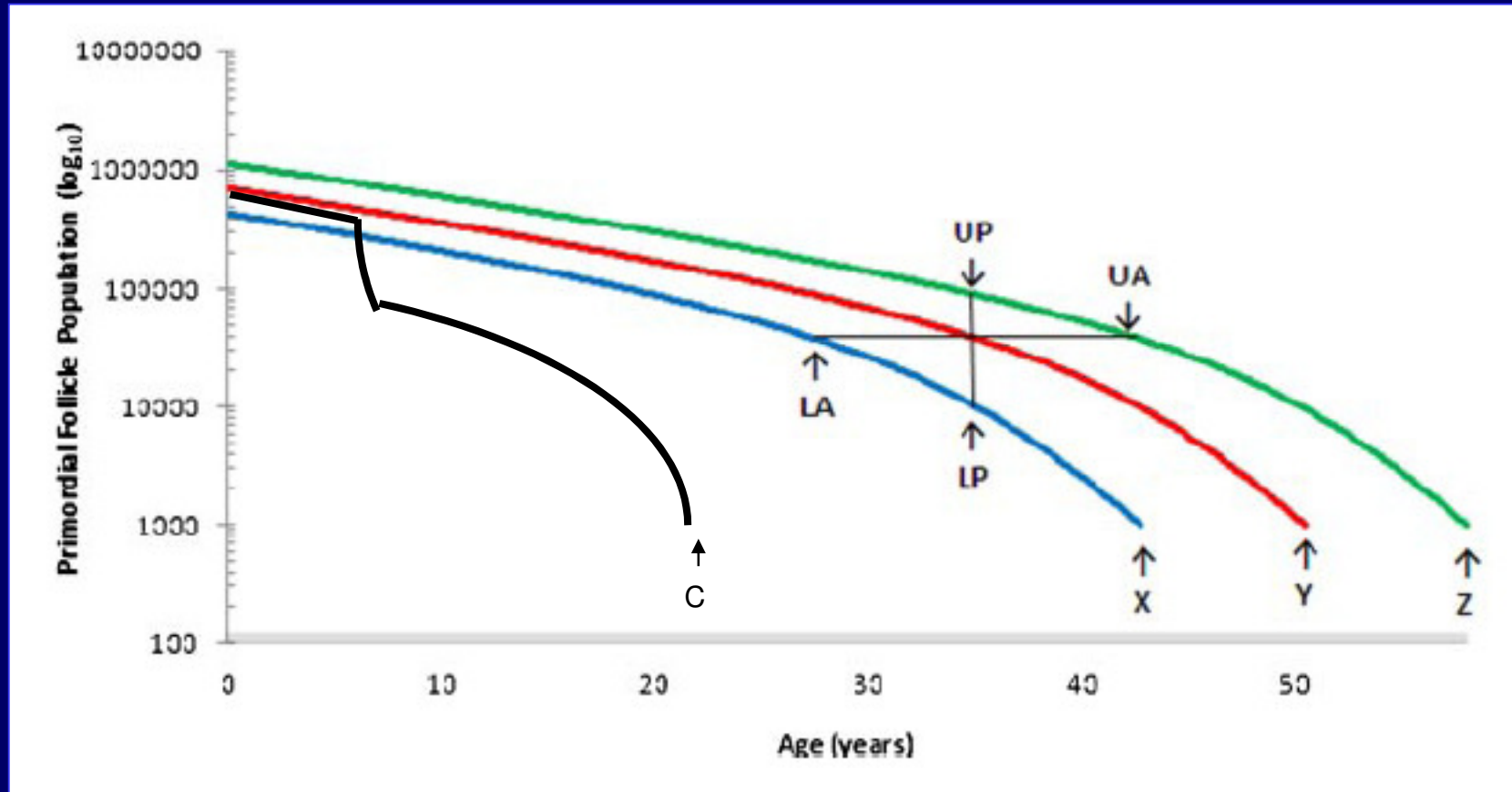
AMH as predictor of excessive response is *quite good*

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Effect of early-life iatrogenic ovarian damage on reproductive lifespan

Can we predict early menopause??

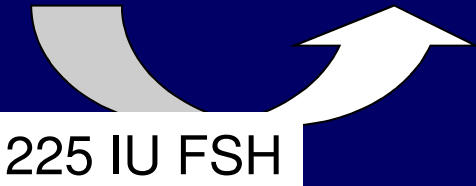
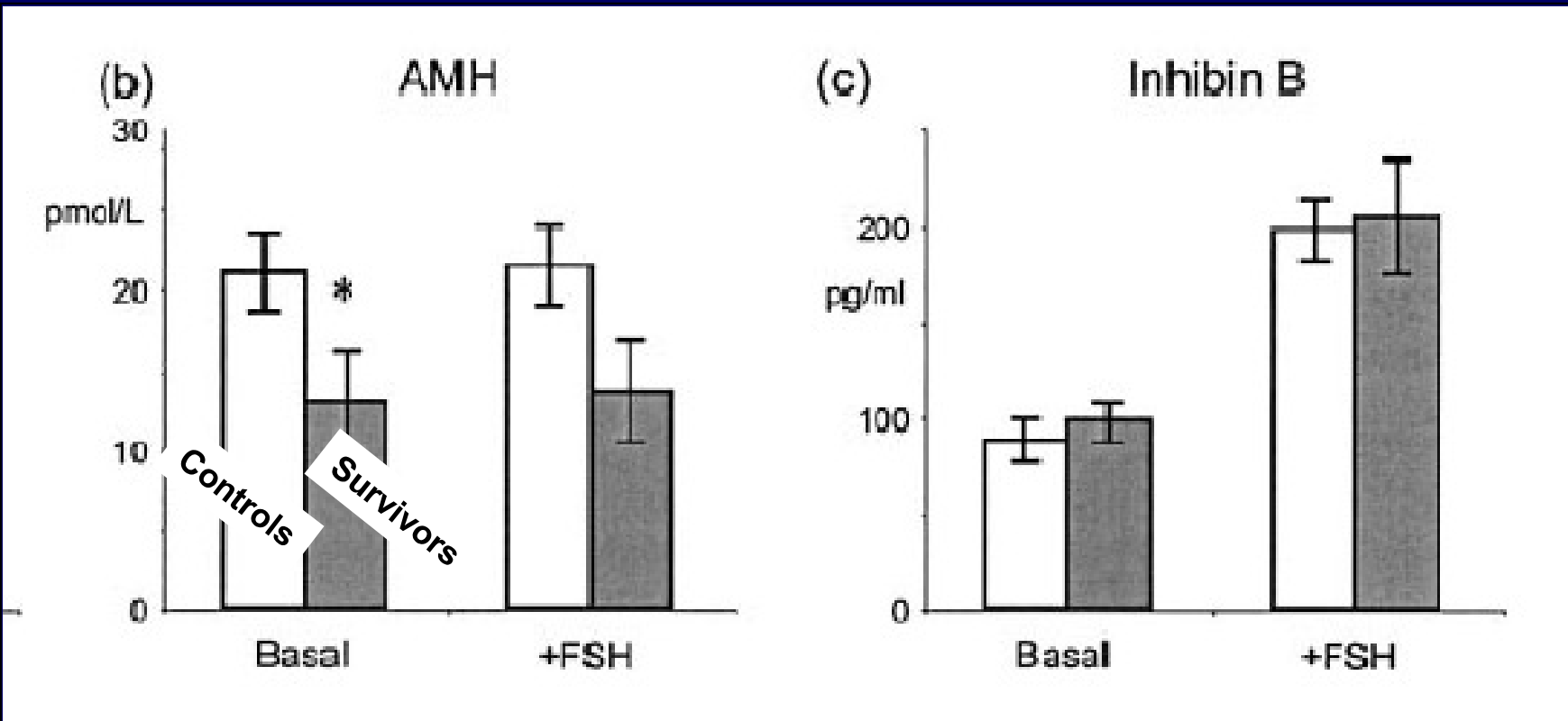


Johnston, Ped Blood Cancer 2009



Depletion of ovarian reserve in young women after treatment for cancer in childhood: detection by anti-Müllerian hormone, inhibin B and ovarian ultrasound

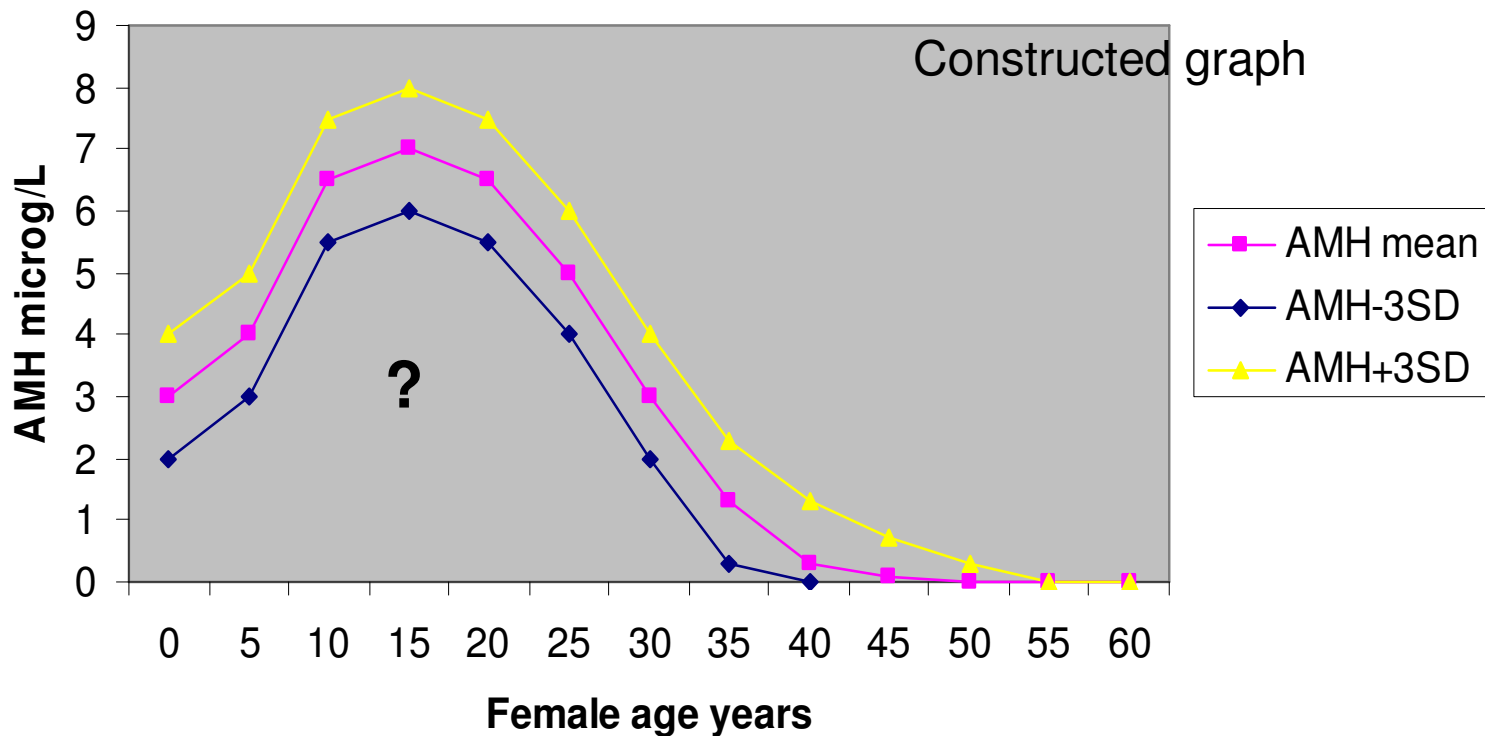
L.E.Bath^{1,3}, W.H.B.Wallace¹, M.P.Shaw¹, C.Fitzpatrick¹ and R.A.Anderson²



AMH serum levels and female age:

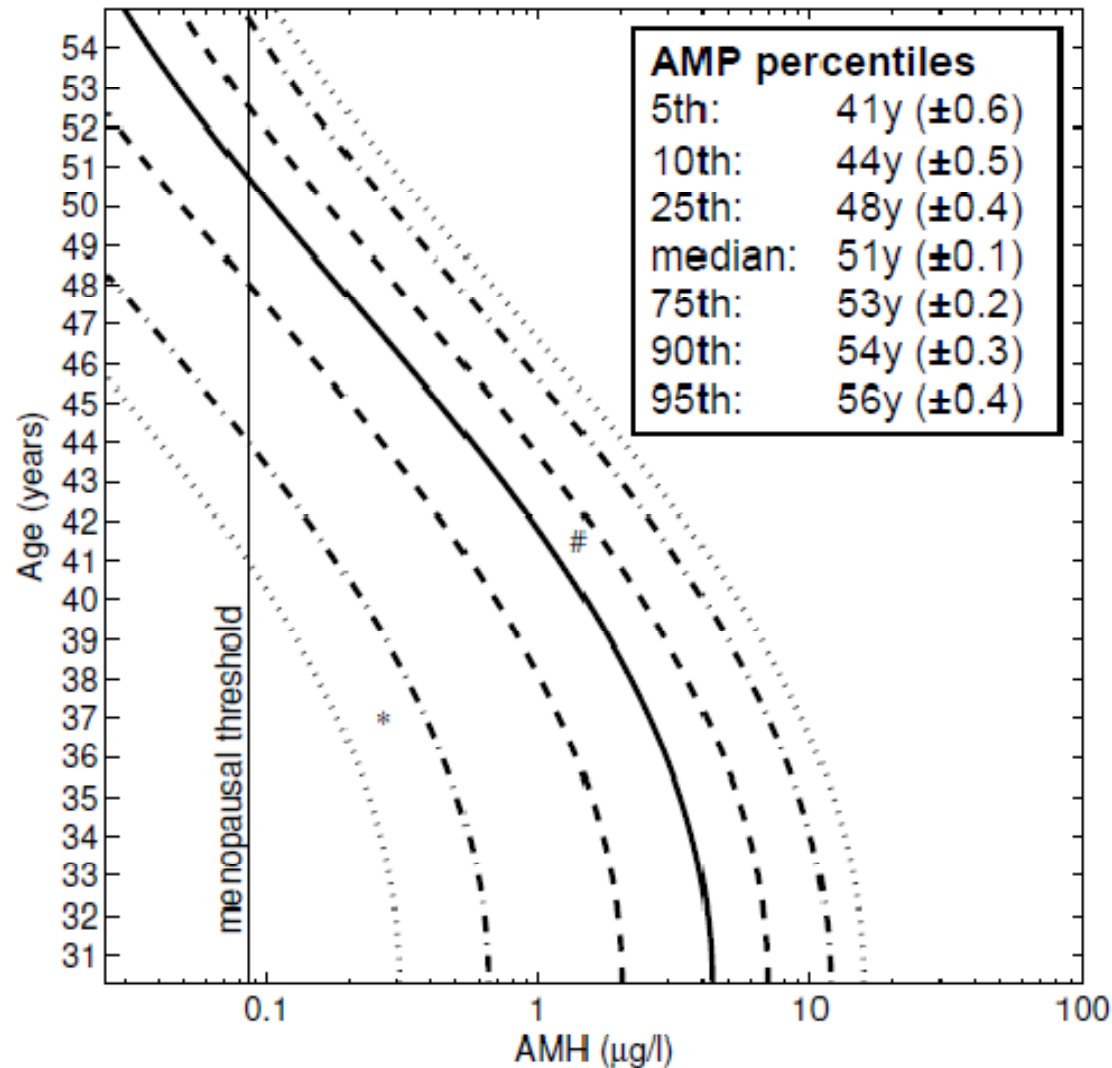
- not zero at birth and rise already before puberty (Lashen, pers comm)
- possible peak at puberty (Lashen)
- stable across twenties (Tremellen)
- gradual decline thereafter (van Rooij, de Vet, Sowers)

AMH by female age



AMH as predictor of reproductive lifespan?

Disseldorp, JCEM 2008



AMH as test for Ovarian Reserve

- **AMH can accurately predict response to hyperstimulation for IVF**
- **True value of OR testing in several clinical conditions remains to be elucidated**



Agenda

- AMH physiology
- AMH as test for Ovarian Reserve
- AMH as diagnostic tool in PCOS



PCO Syndrome

Rotterdam 2003 Consensus - ≥ 2 of 3 criteria

- **Oligo-Amenorrhea**
- **Hyperandrogenism**
(hirsutism / elevated FAI =
Testosteron/SHBGx100)
- **PCO ovaries at TVS**
(2-9 mm follicles >12
volume > 10 ml
1 or 2 ovaries)

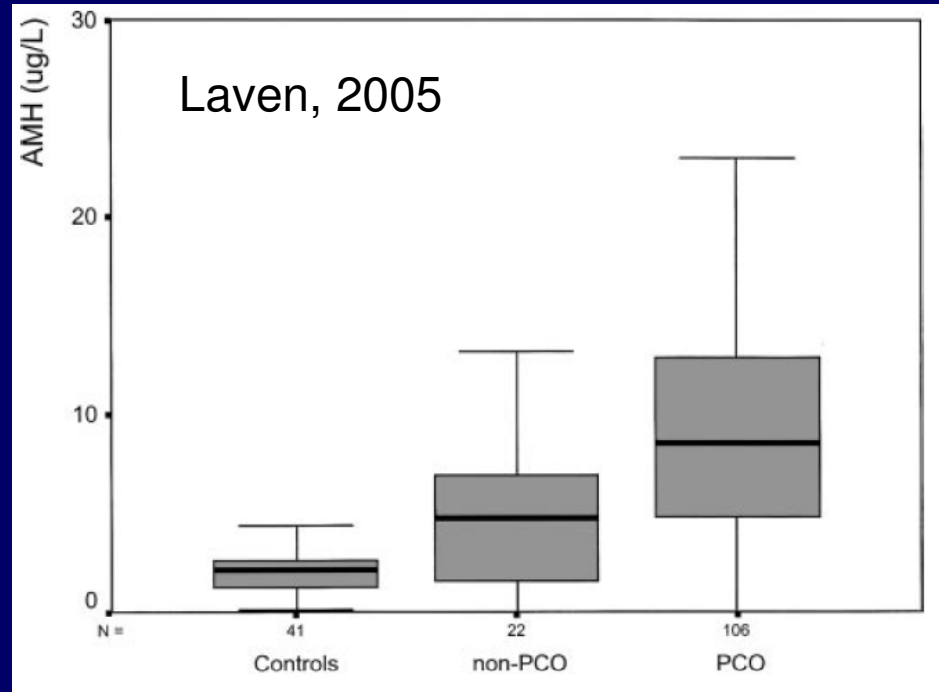


PCOS and AMH

- Can AMH be used in PCOS diagnosis??
- Is AMH useful as predictor of treatment outcome?



AMH levels in WHO II - PCOS are 2-3 times as high as in controls

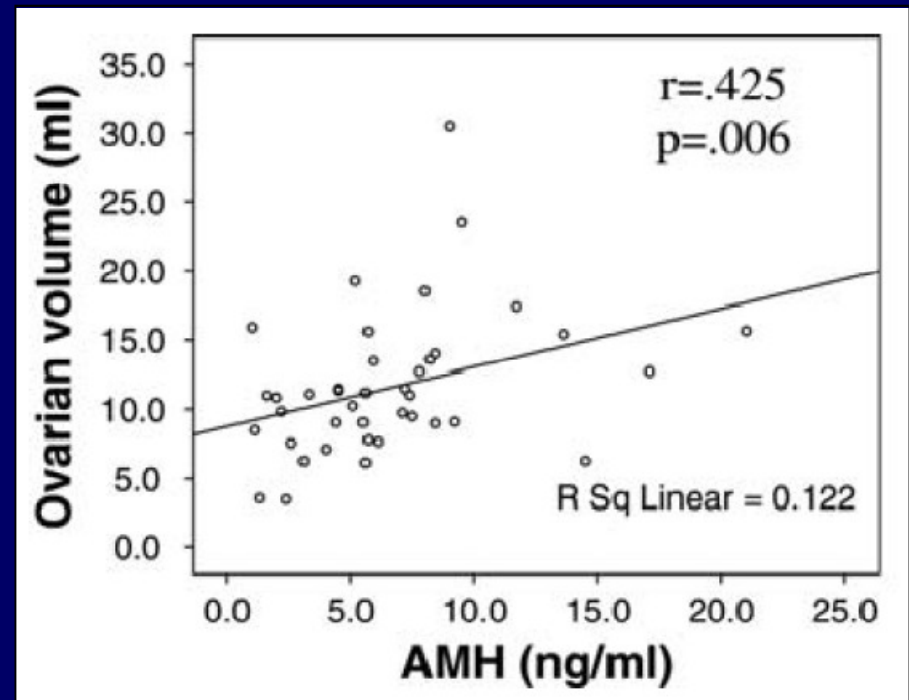
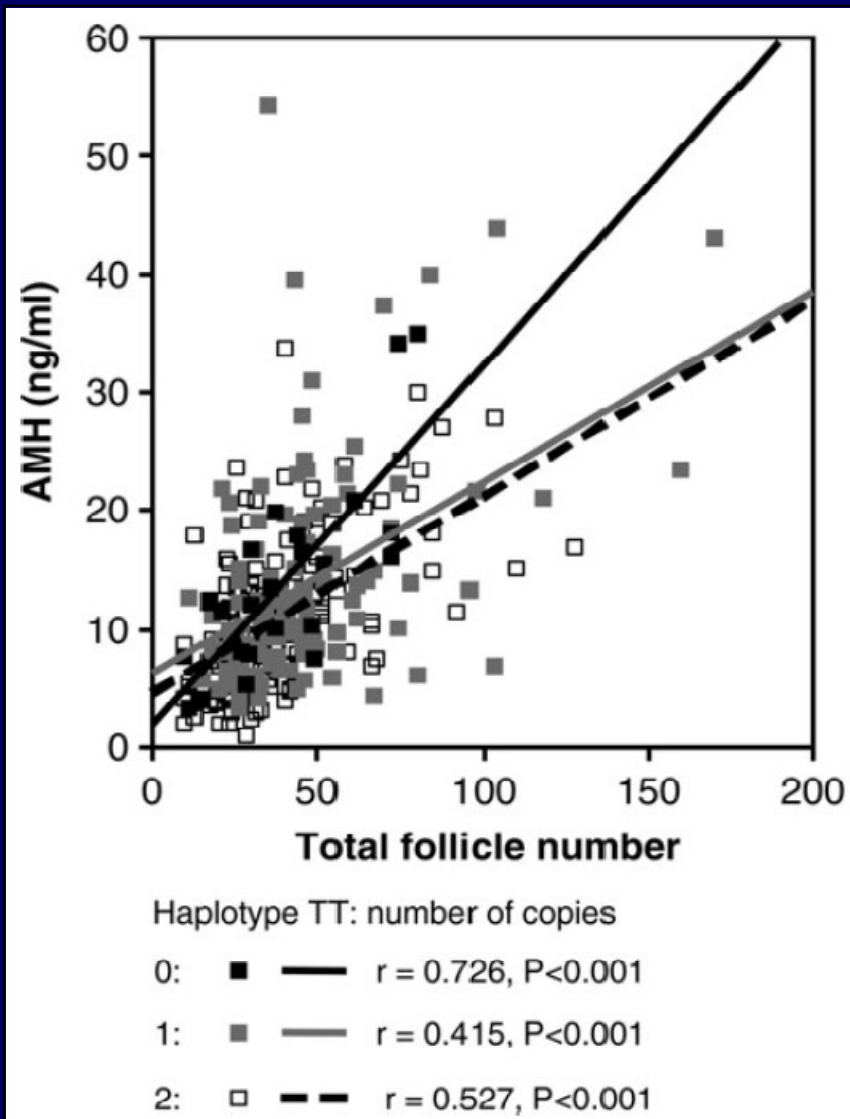


Author	Year	Number	AMH Controls	AMH PCOS
Cook	2002	47	2.4 ± 0.2 µg/l	5.3 ± 0.7 µg/l
Pigny	2003	104	2.9 ± 0.3 µg/l	6.6 ± 0.4 µg/l
Laven	2004	109	2.1 ± 0.6 µg/l	7.6 ± 1.8 µg/l
Piltonen	2005	170	2.4 ± 0.2 µg/l	8.1 ± 0.8 µg/l
Eldar-Geva	2005	52	1.6 ± 0.8 µg/l	5.1 ± 1.3 µg/l
La Marca	2006	34	3.5 ± 1.5 µg/l	7.4 ± 1.7 µg/l
Wachs	2007	27	2.1 ± 0.4 µg/l	7.2 ± 0.5 µg/l

Broekmans, 2008



In PCOS, AMH levels correlate with Ovarian volume and AFC

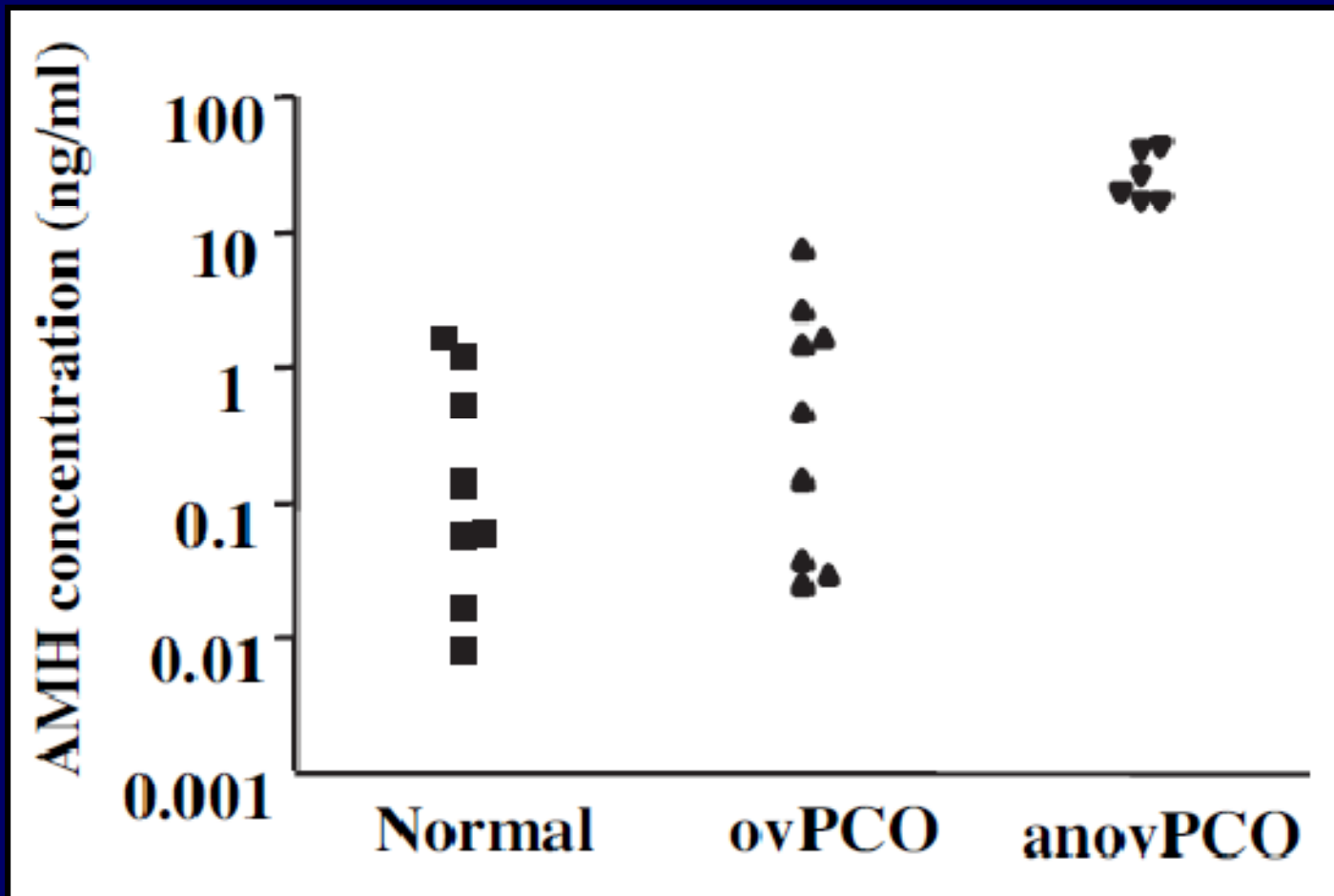


Chen, 2008

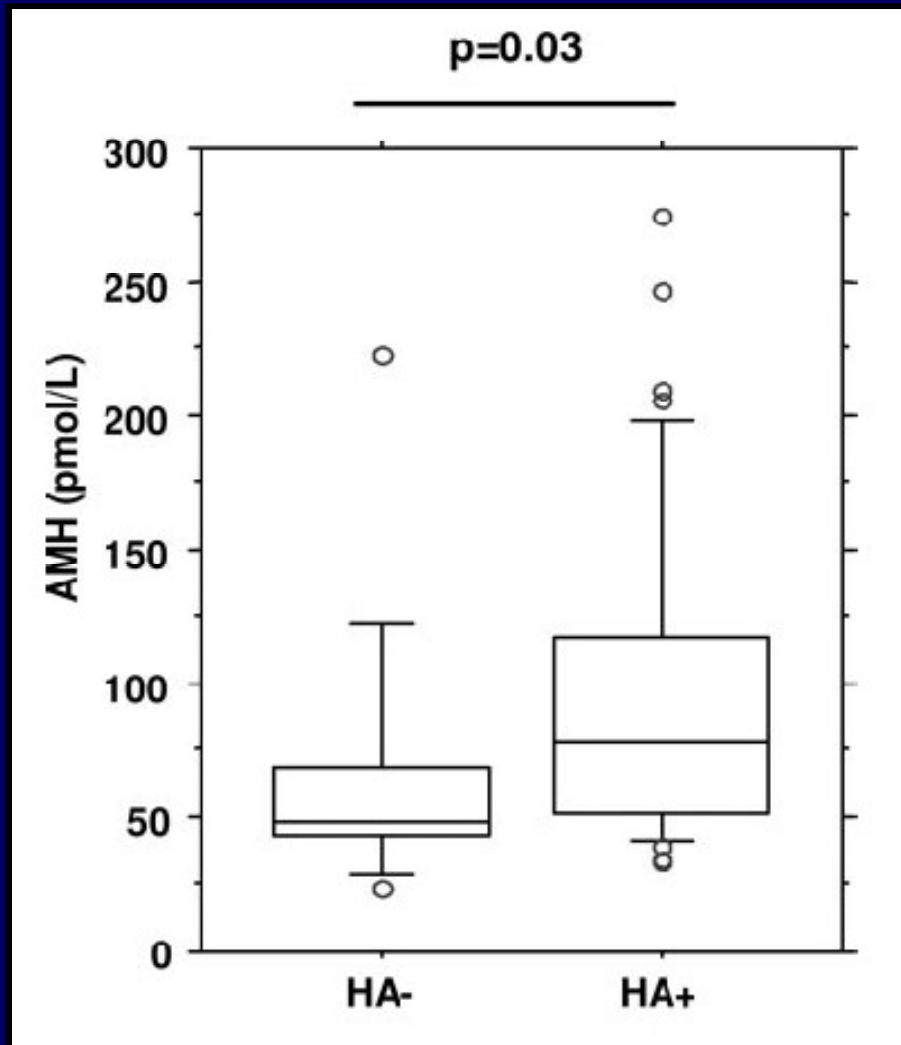
Kevenaar, 2009



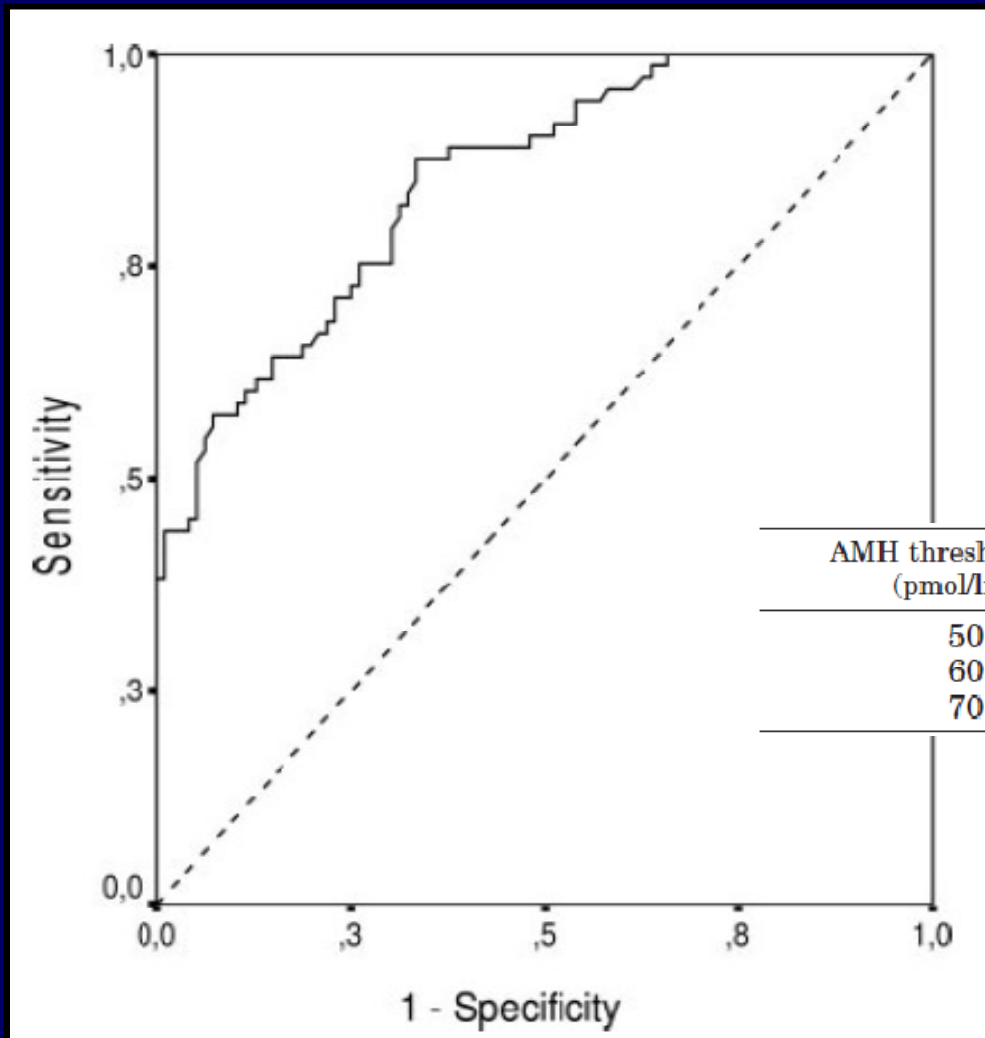
AMH in GC conditioned medium from unstimulated follicles is higher in PCOS cases, especially if anovulatory - Pellatt, 2007



AMH levels are higher in PCOS cases with hyperandrogenism - Pigny, 2006



AMH discriminates normal cycling women from PCOS classified according to the Rotterdam Criteria - Pigny, 2006



25% misclassifications
30% of PCOS missed
10% NEW PCOS

AMH threshold level (pmol/liter)	Sensitivity (%)	Specificity (%)
50	80	80
60	67	92
70	56	98



Can AMH be used in PCOS diagnosis??

- Very promising
- More studies on AMH as replacement of PCO morphology are awaited



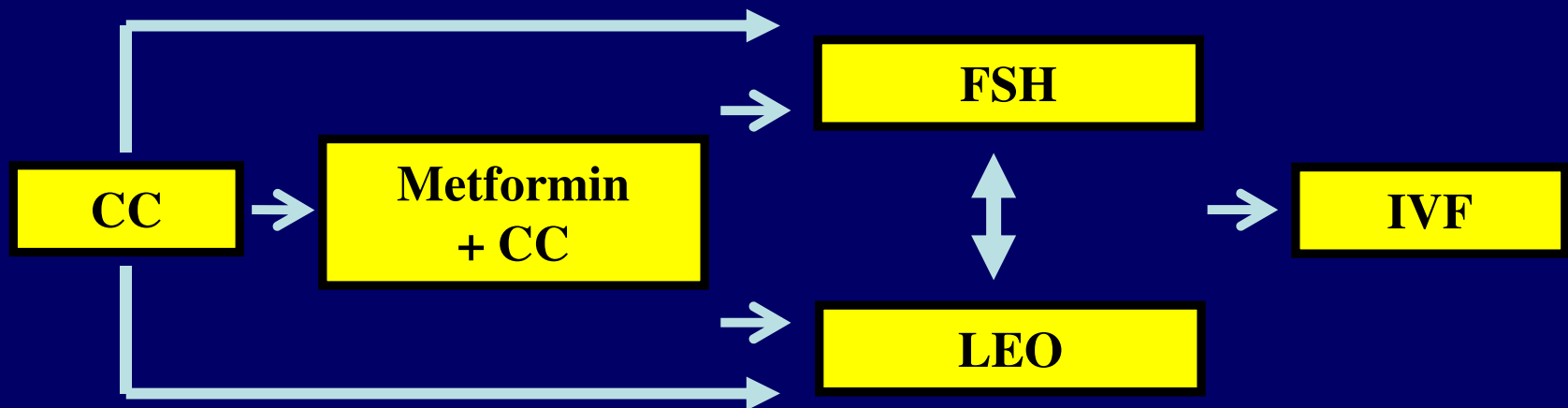
PCOS and AMH

Two questions

- Can AMH be used in PCOS diagnosis??
- Is AMH useful as predictor of treatment outcome?

Ovulation induction WHOII/PCOS

- *Treatment algorithm* -



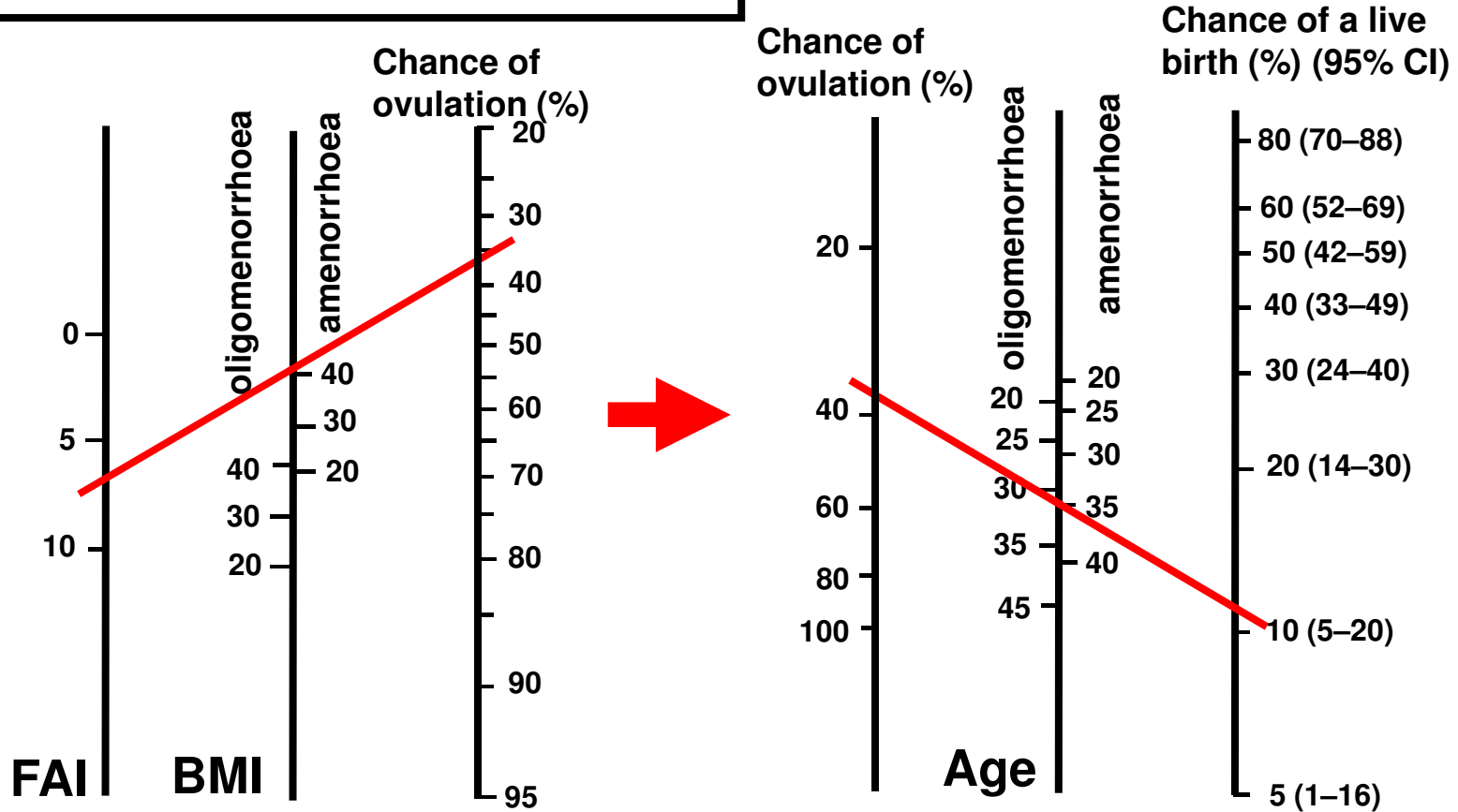
Weight Reduction/Caloric Restriction / Life Style changes



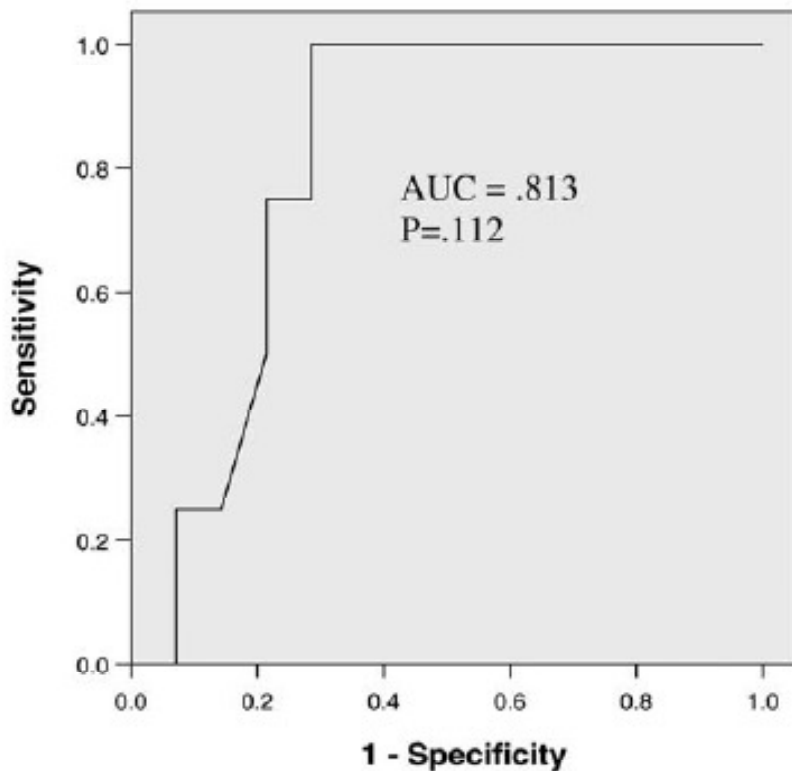
Required screening information:

- oligomenorrhoea or amenorrhoea
- BMI (kg/m²)
- FAI (T×100/SHBG)
- age (years)

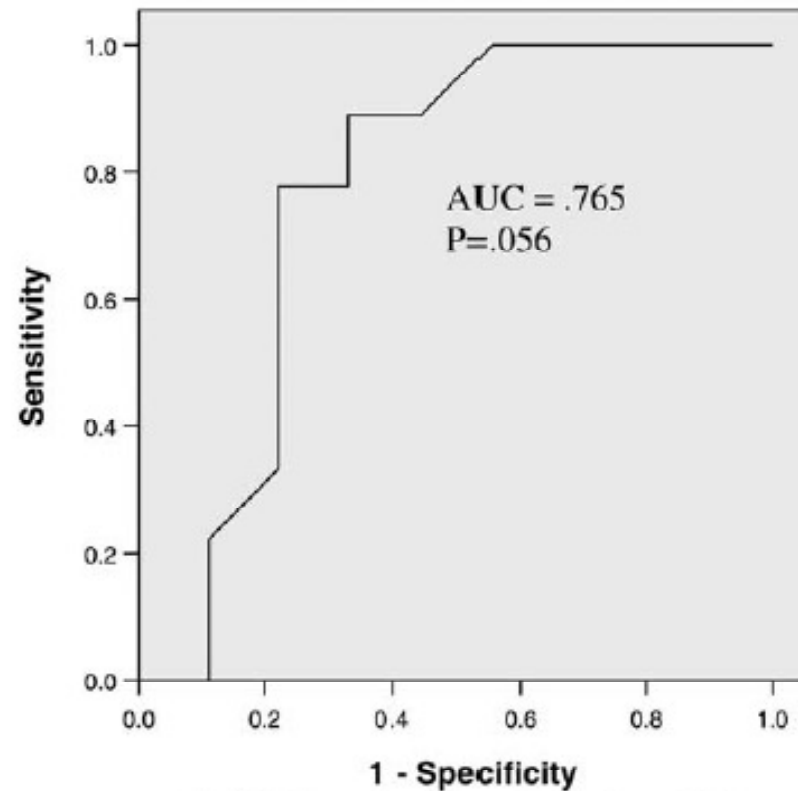
Nomogram: predicting live birth after clomiphene citrate



Prediction of treatment response from AMH levels in Clomiphene Citrate treatment - Amer, 2009



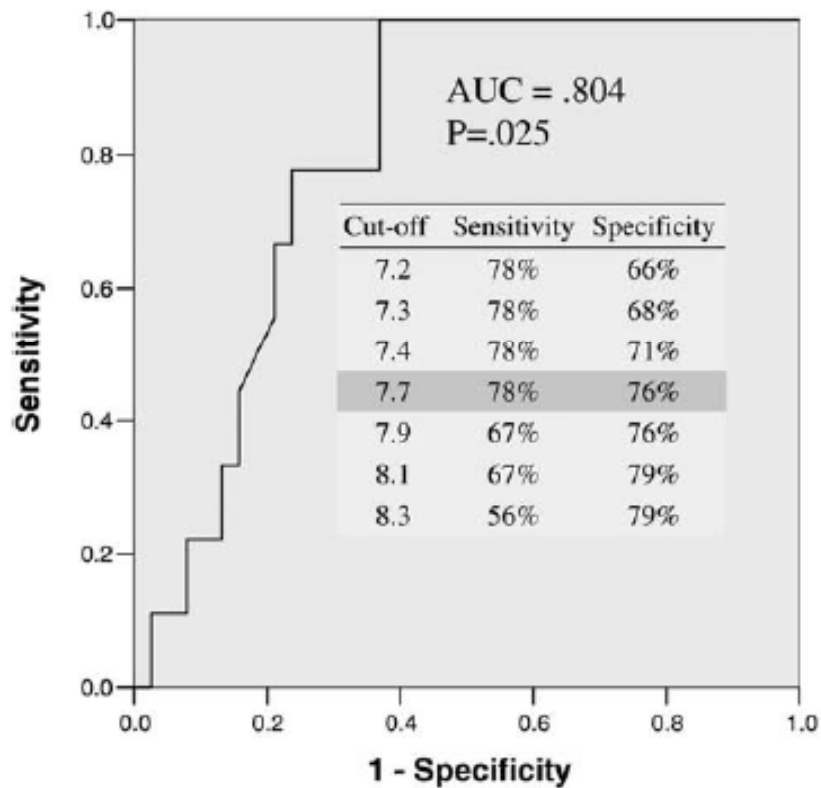
c) AMH and ovulation after CC



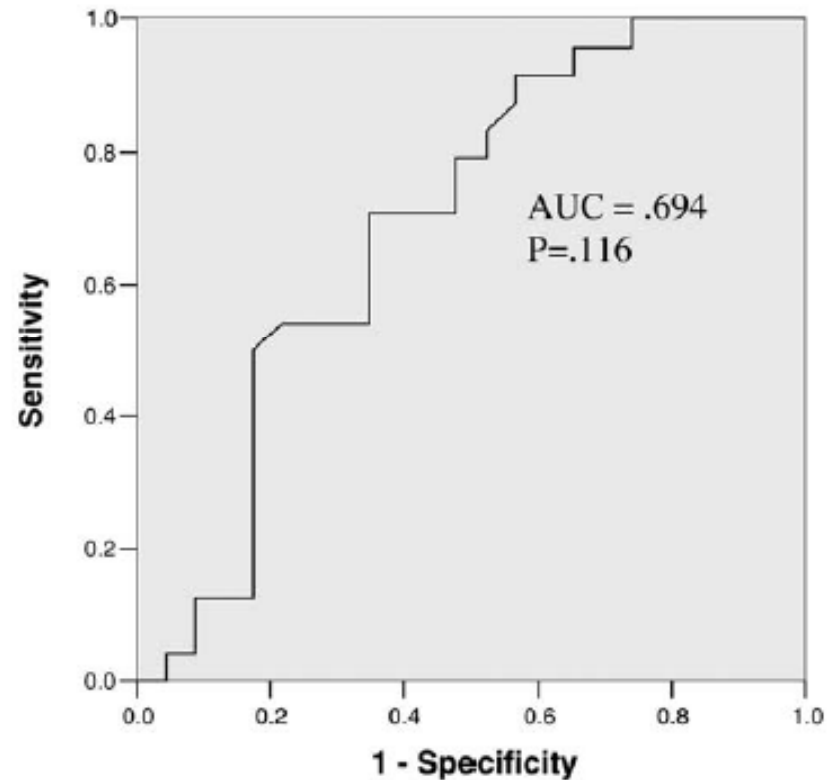
d) AMH and conception after CC



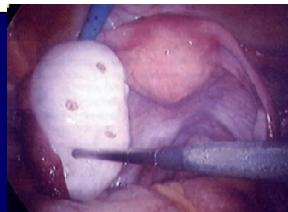
Prediction of treatment response from AMH levels in Laparoscopic Ovarian Electrocoagulation LEO - Amer, 2009



a) AMH and ovulation after LOD



b) AMH and conception after LOD

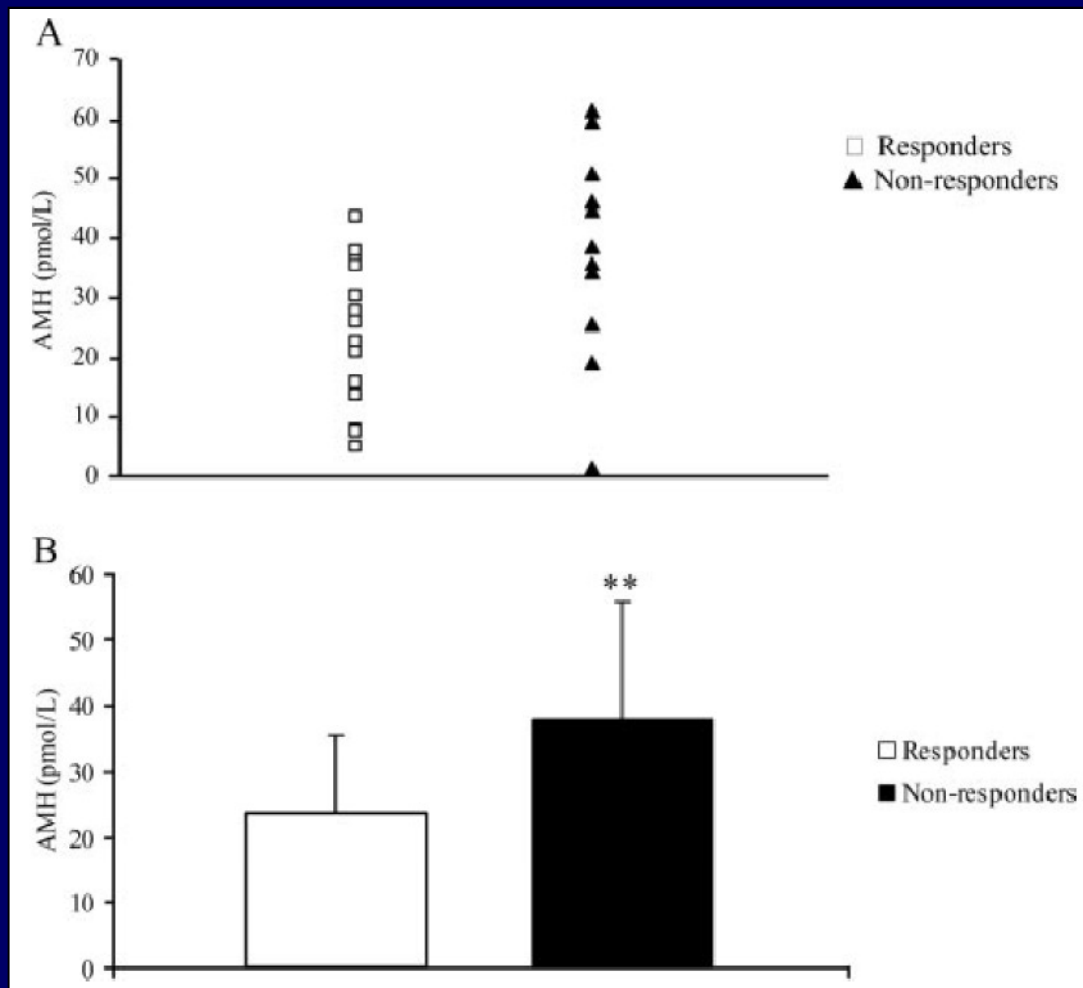


AMH levels decrease after Laparoscopic Ovarian Electrocoagulation LEO, especially in cases that become ovulatory - Amer, 2009

	AMH (ng/ml)	
	Pretreatment	Post-treatment*
LOD	6.1 (1.0–21.0), <i>n</i> = 29	4.6 (0.3–15.1), ^a <i>n</i> = 29
Clomiphene citrate	5.7 (1.3–9.5), <i>n</i> = 18	4.8 (2.7–9.2), <i>n</i> = 18

	Pre-LOD	Post-LOD (1 week)	P-value*
Responders	5.6 (1.0–21.0)	4.3 (0.3–15.1)	0.002
Non-responders	9.0 (6.1–17.1)**	10.4 (4.3–12.7)	0.465

Baseline AMH levels in PCOS with overweight according to restoration of menstrual cyclicity after Weight Reduction program - Moran, 2007



Is AMH useful as predictor of treatment outcome?

- AMH useful as outcome predictor
- Replace amenorrhoea status and BMI?
- Large validation studies needed!



AMH in Ovarian Function Testing

- Reflects antral follicle number
- Cycle independent
- Predicts Poor and High ovarian response in IVF stimulation
- Future Aid in PCOS diagnosis and treatment...

Thank You



am  *Center for reproductive medicine*



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