Predicting fertility: ovarian reserve testing

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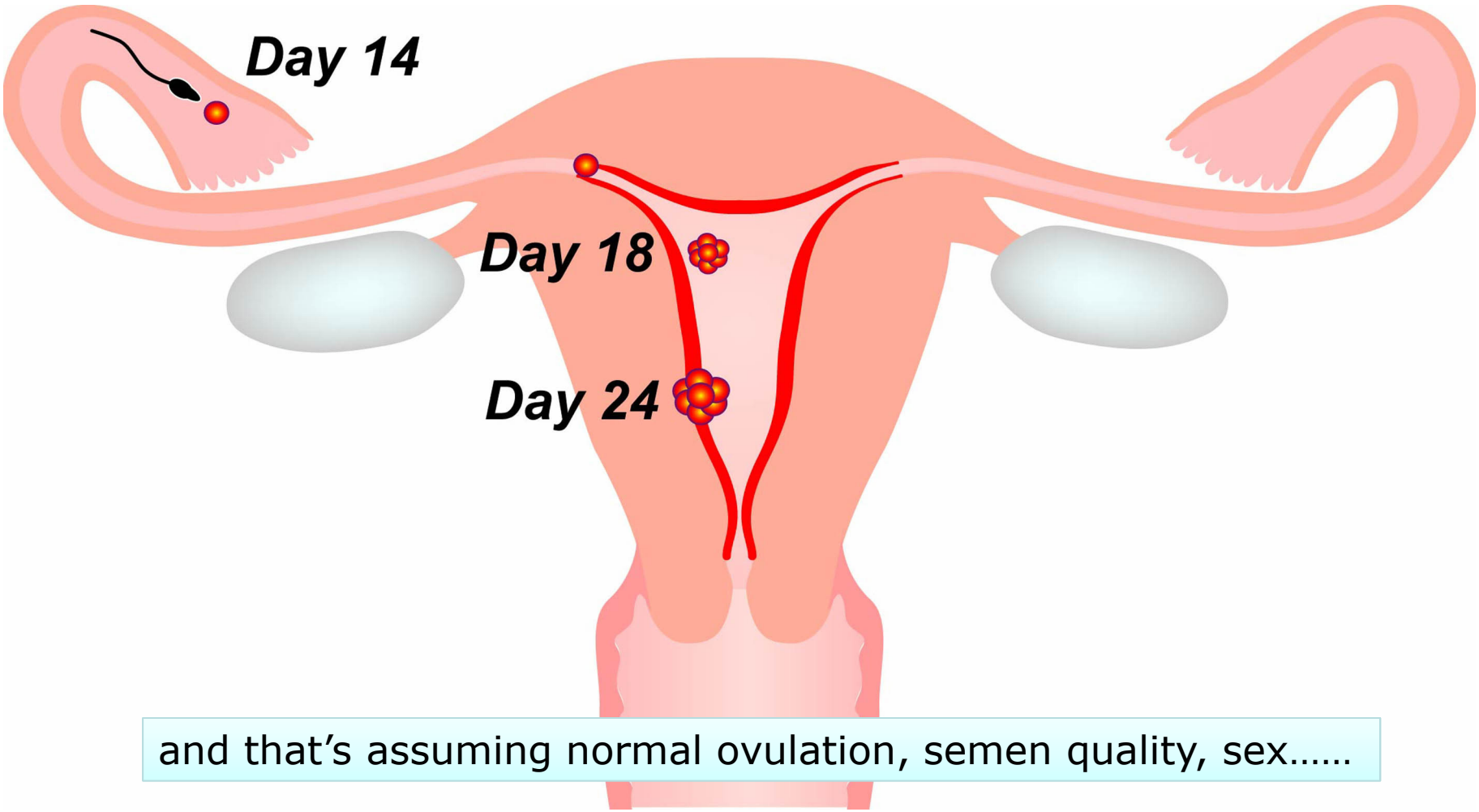
Key infertility questions

- What's wrong with me/us?
- Can you put it right, Doc?
  ie will I get pregnant?

Summary

- What is the ovarian reserve?
- How does it relate to fertility?
- How can you measure it?
- What does it tell you?
- Can it predict fertility?

Essentials of fertility: post-ovulatory



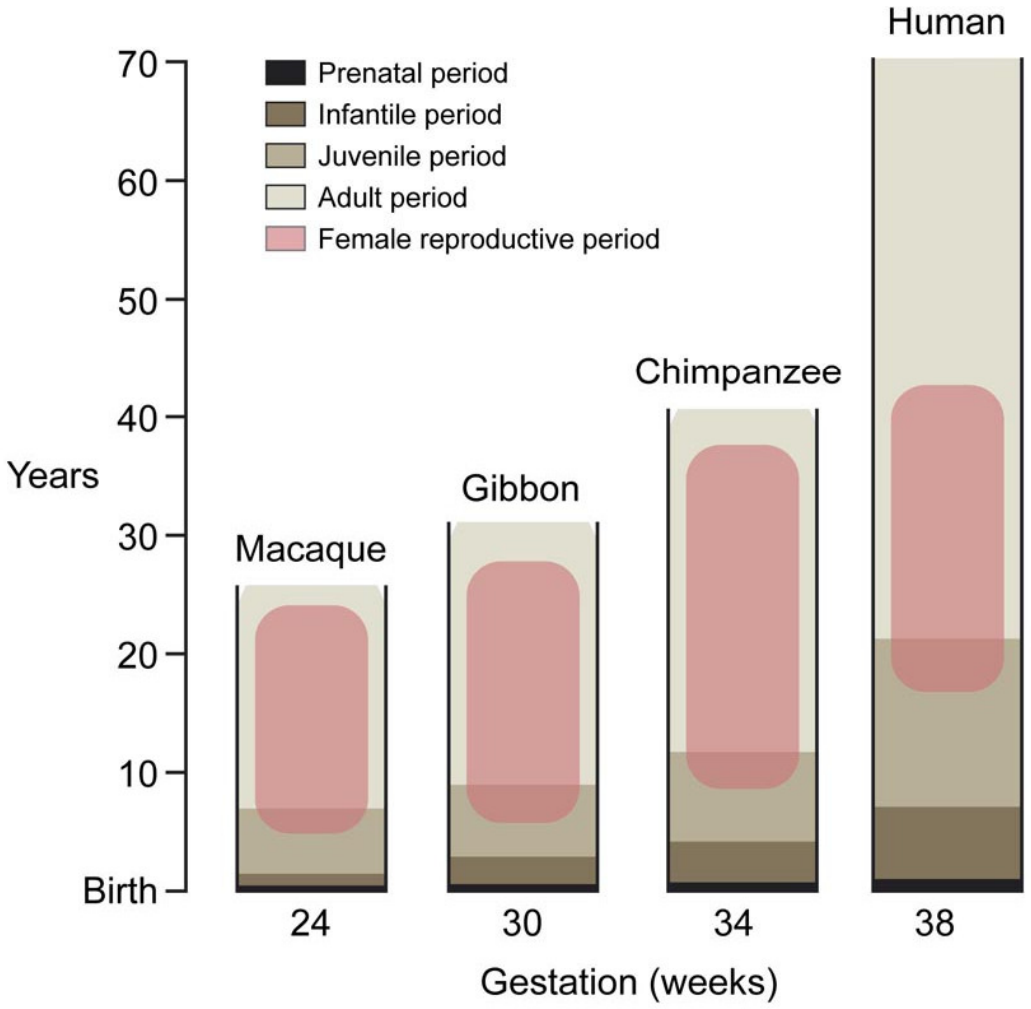
and that's assuming normal ovulation, semen quality, sex……

The ovarian reserve: what is it?

- The number of
  - oocytes within the ovaries
  - growing follicles
  - small antral follicles
  - follicles that can be stimulated by FSH
  - oocytes that can be recovered after FSH

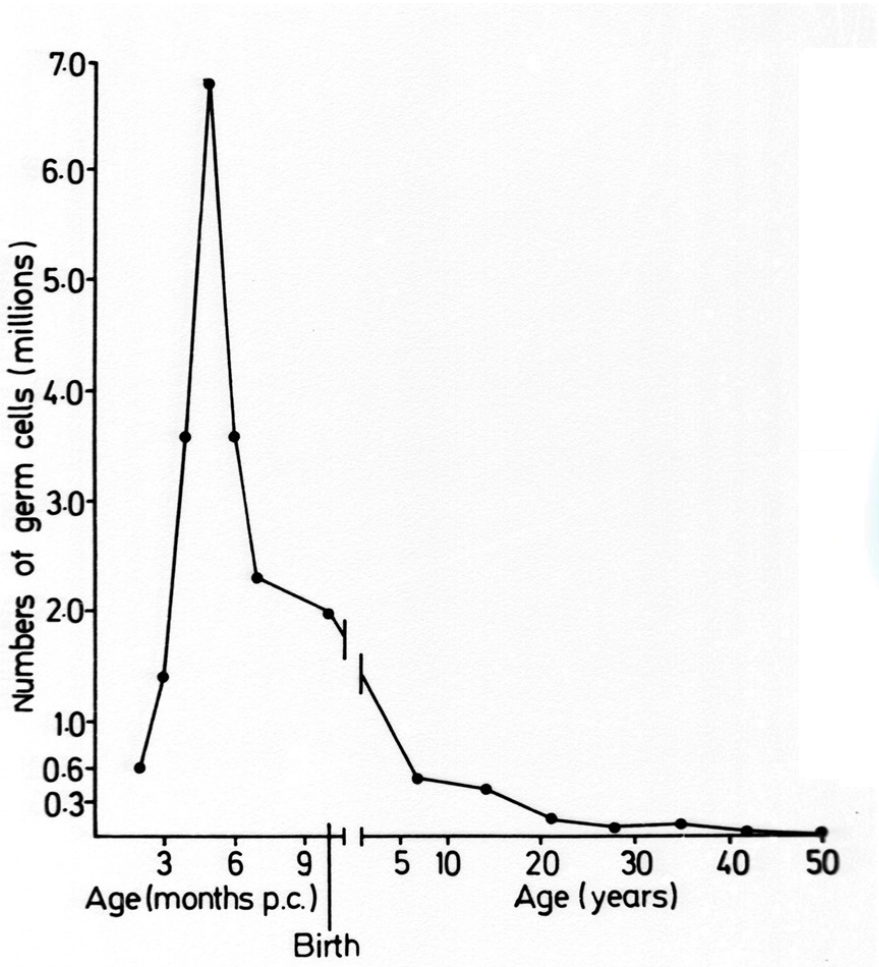
- What are we trying to predict?
  - natural fertility now
  - IVF outcome
  - Duration of fertility/age of menopause

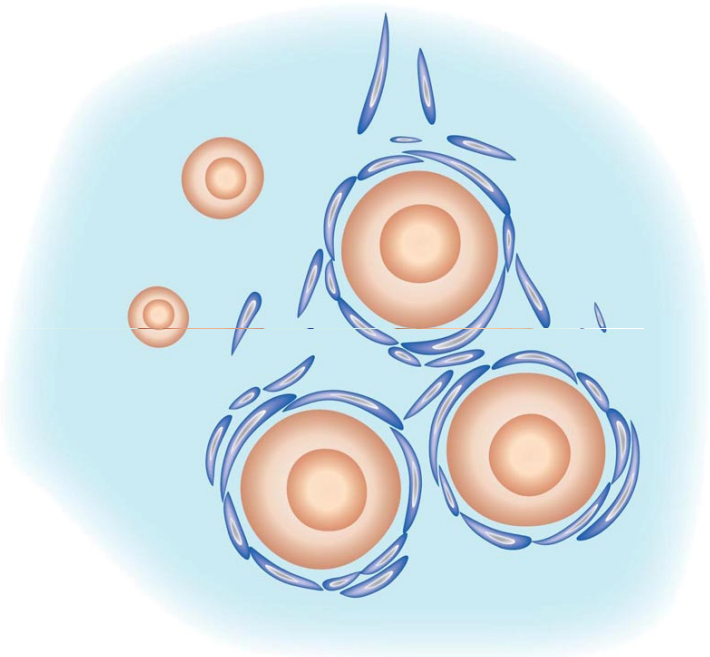
Humans have a limited reproductive lifespan



Modified from A. H. Schultz (1969) The Life of Primates (20), 149

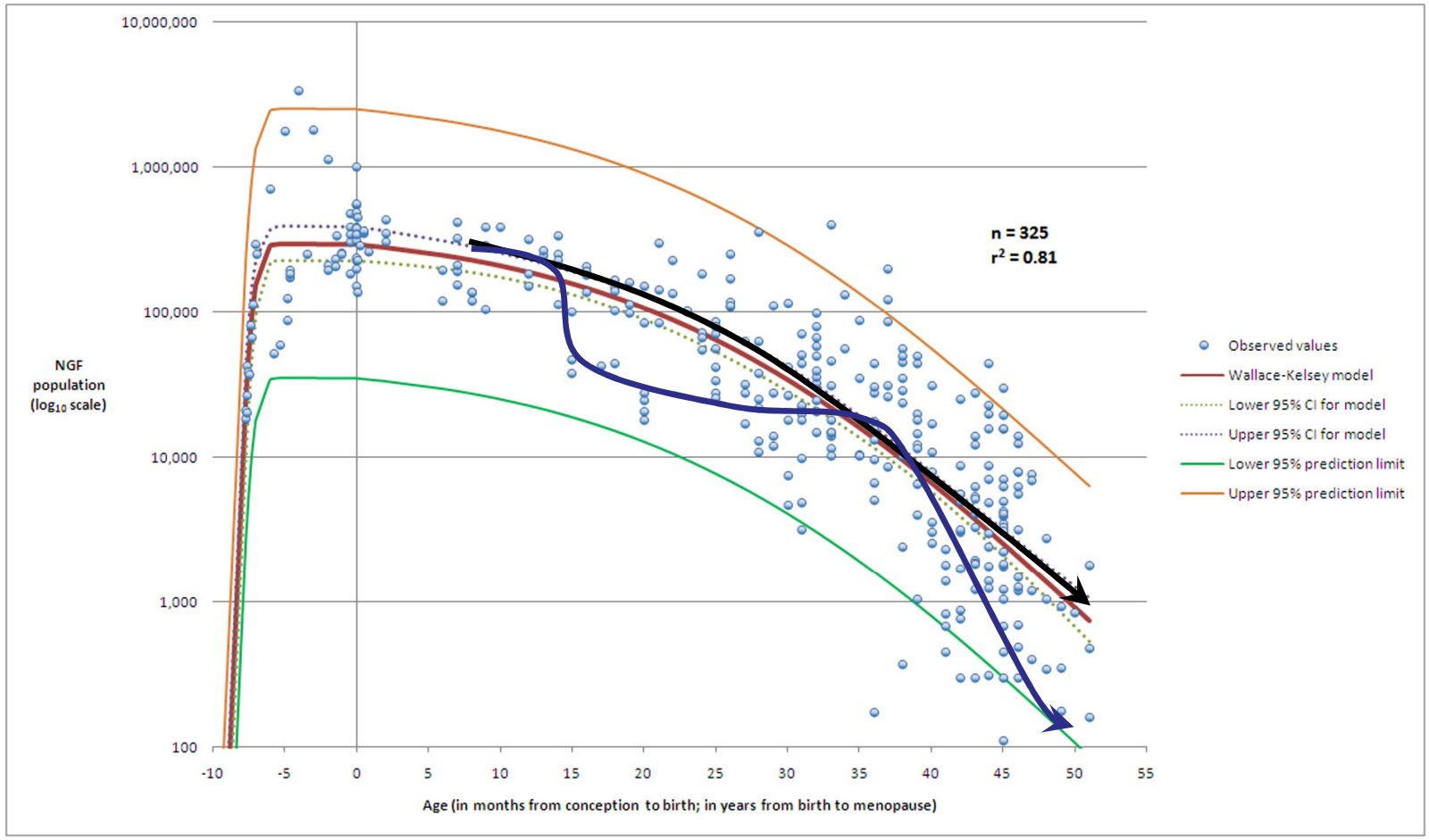
The ovarian follicular complement





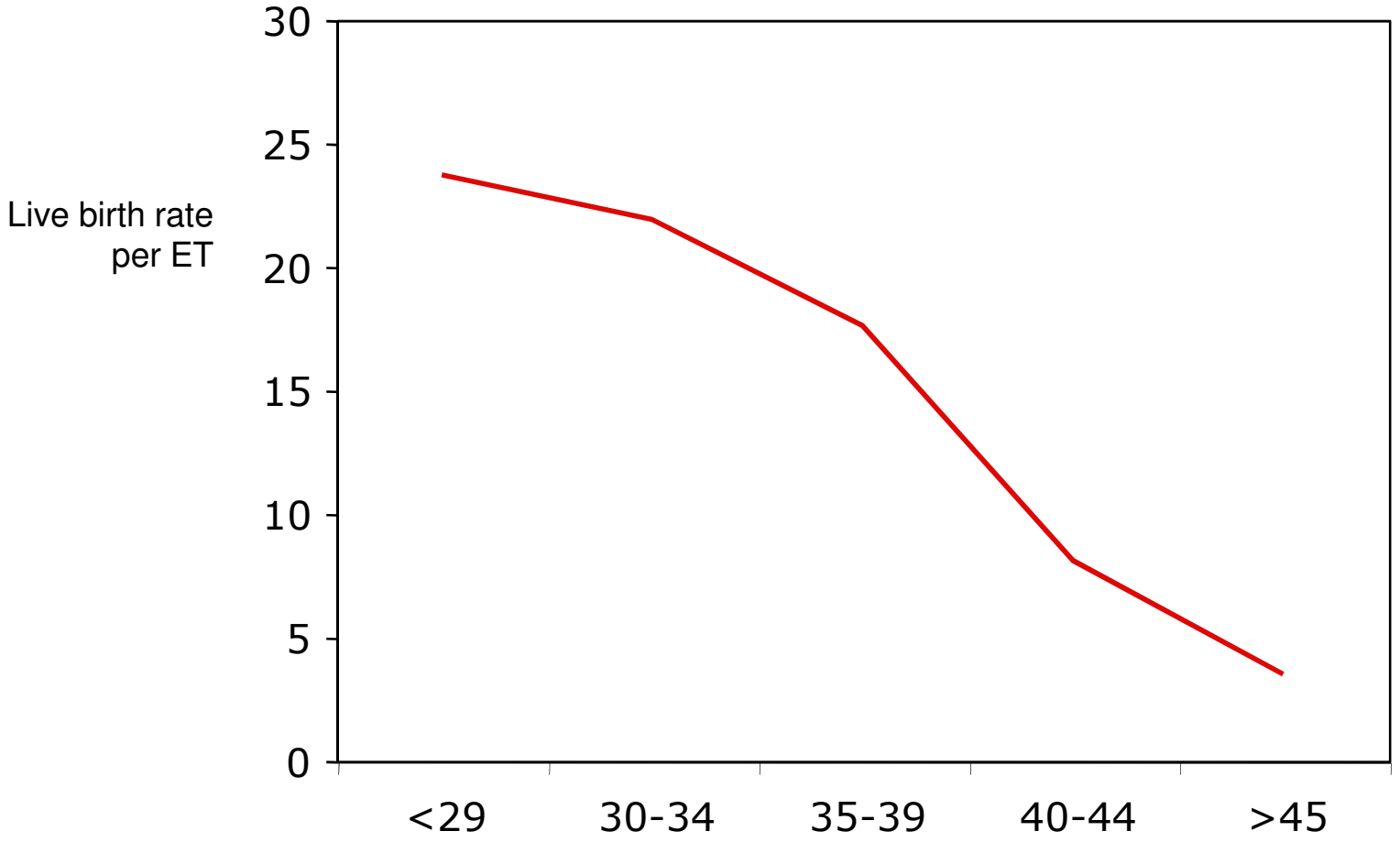
Data from Block 1952; Baker 1963

Current model of follicular depletion



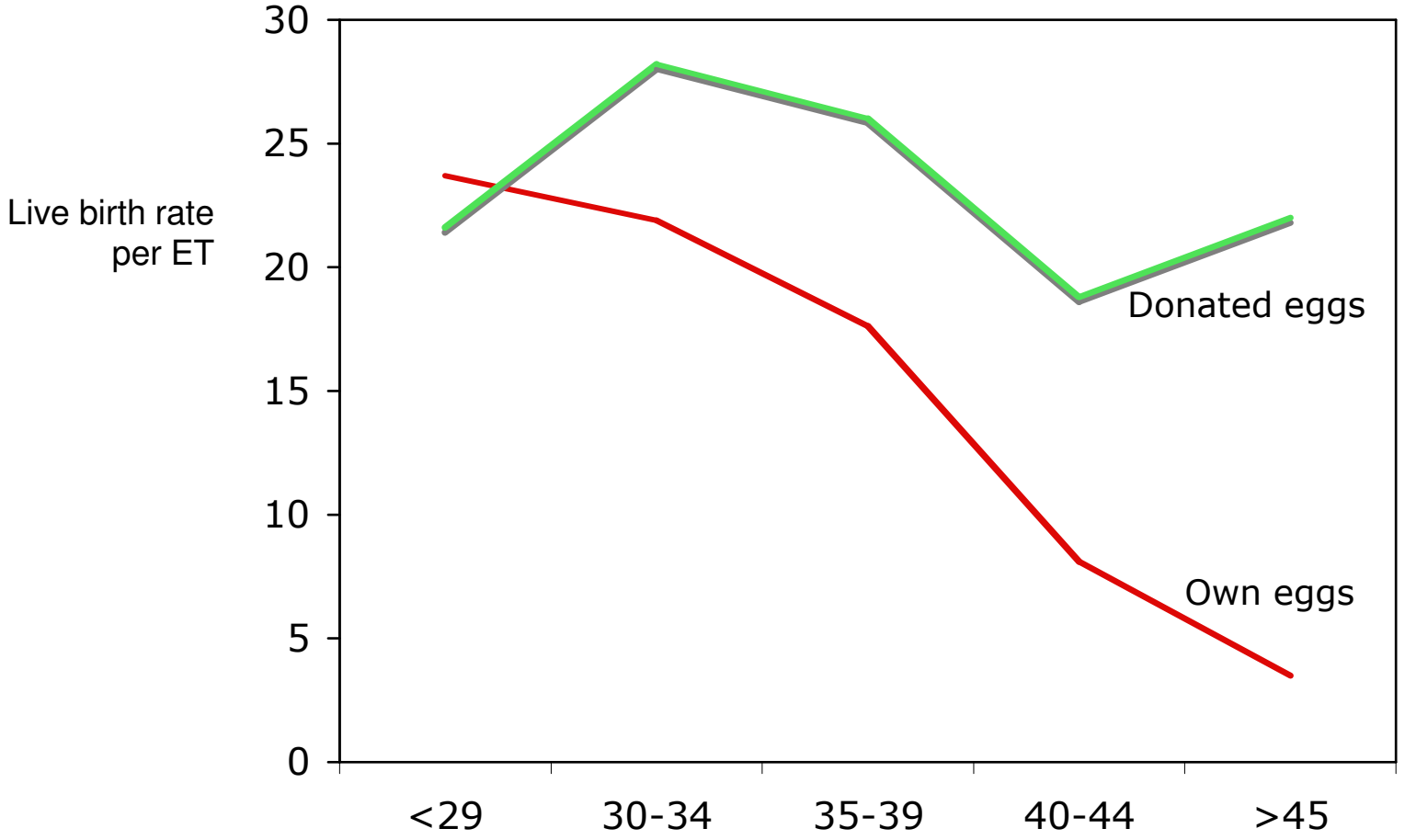
Wallace and Kelsey 2010 PLoS One 5; e8772

Age and reproductive success



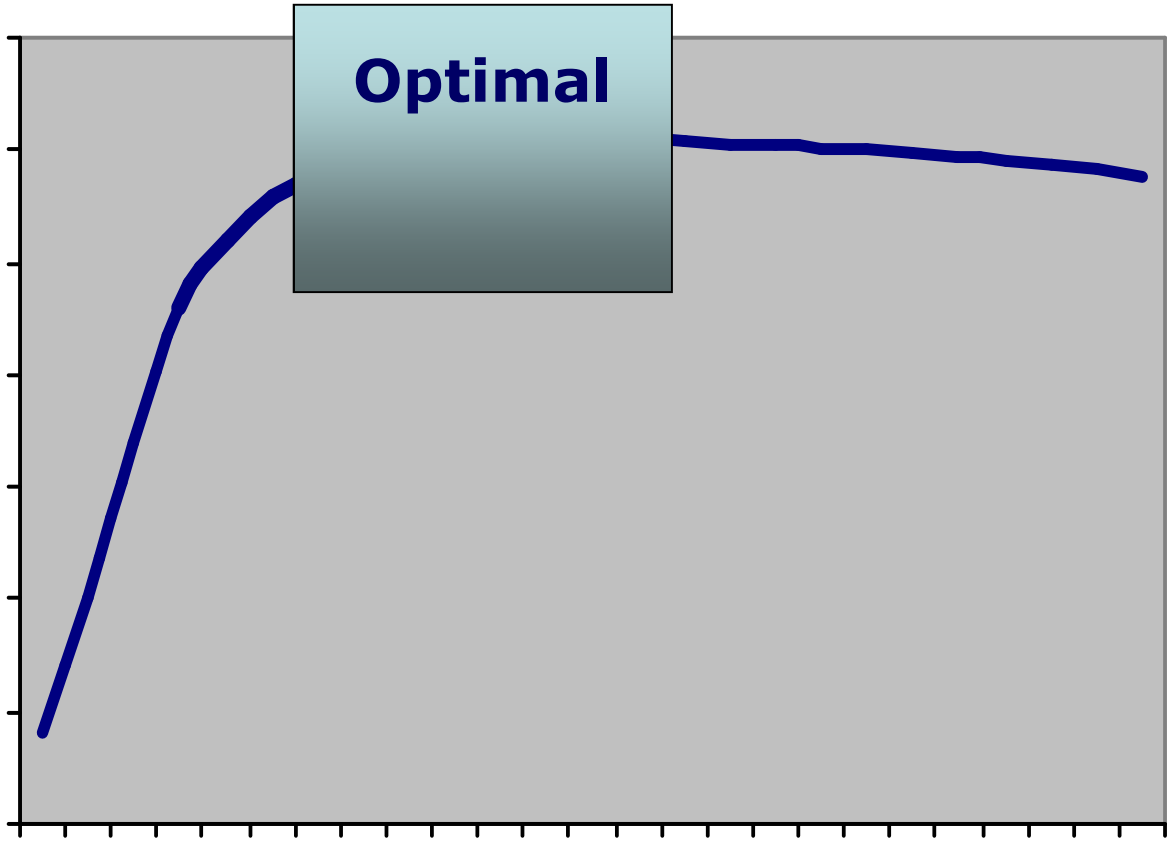
Templeton et al 1996 Lancet 384; 1402

Age and reproductive success



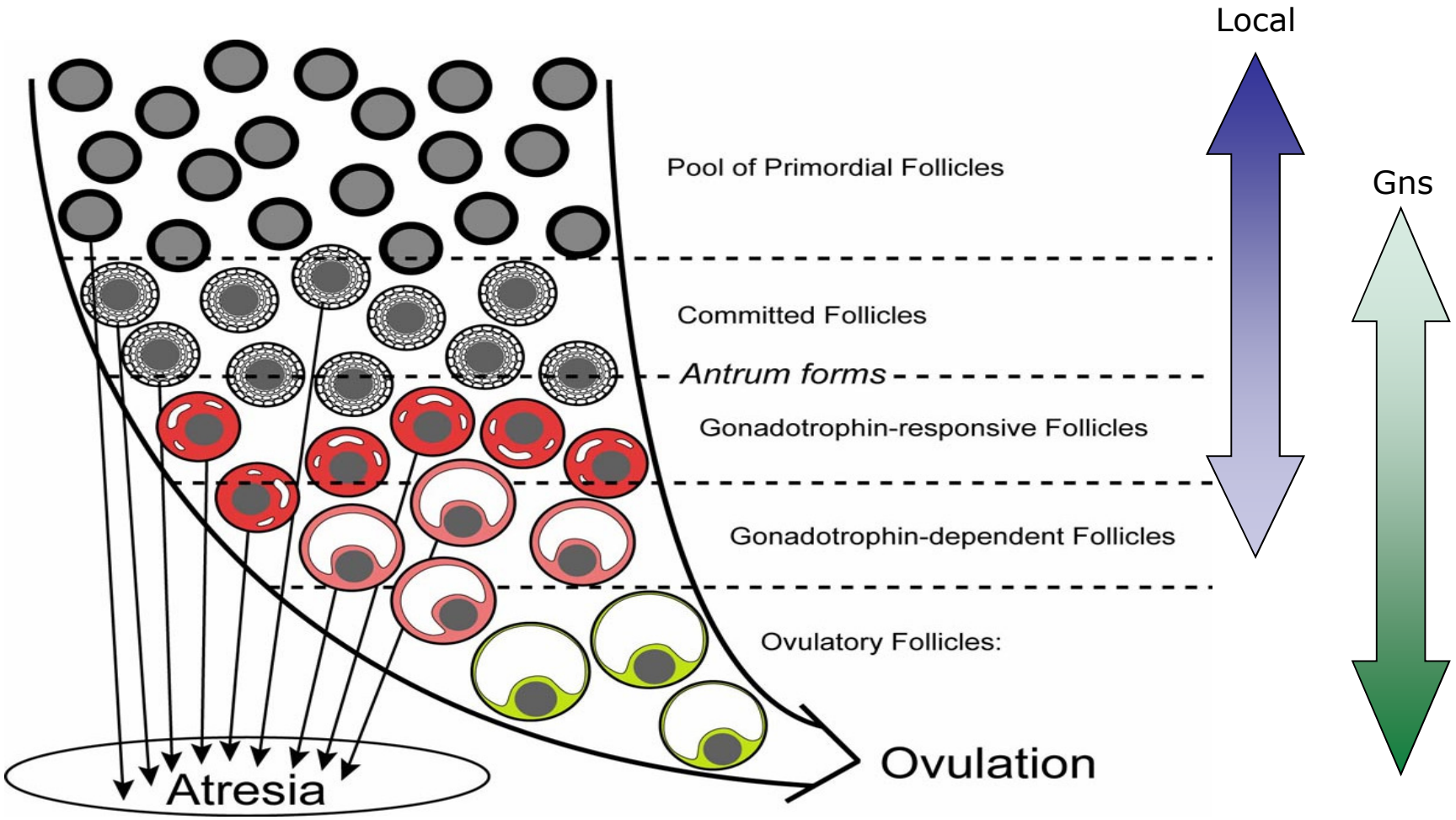
Templeton et al 1996 Lancet 384; 1402

The role of ovarian response prediction: improving balance



Van der Gaast et al, RBM Online, 2006

Progressive follicle selection



Scaramuzzi R et al 1993 Reprod Fertil Develop 5: 459-478

Prediction of 'ovarian reserve'

- Age: cheap and hard to beat!
- Biophysical: Antral follicle count and ovarian volume
- Biochemical: basal and stimulated

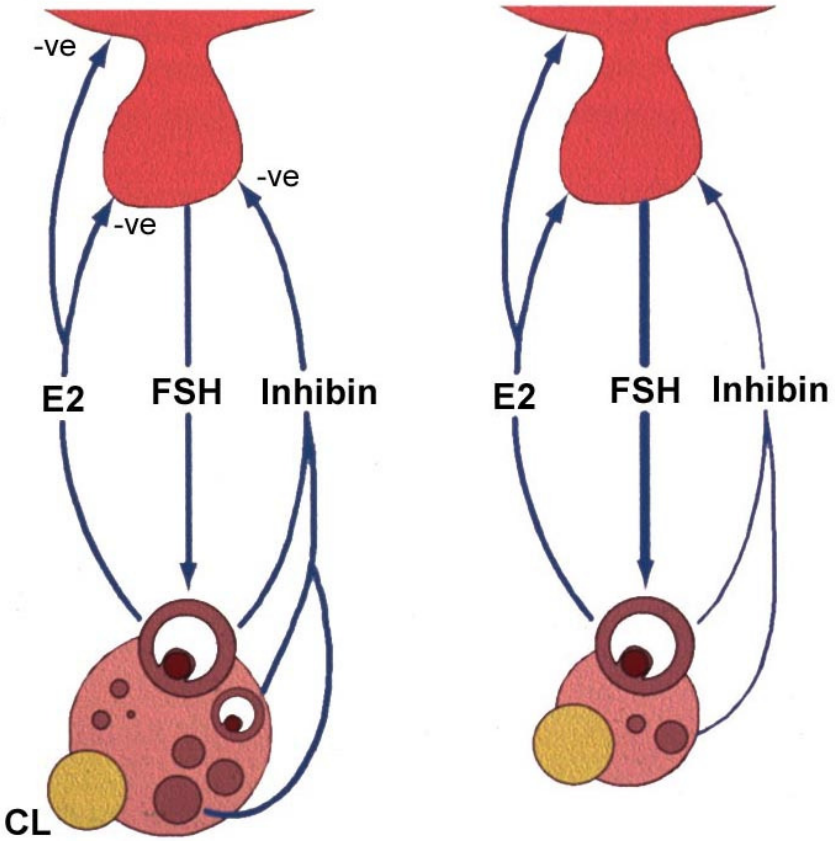
Predictive tests: basic biology

- Age: a surrogate, but includes ‘quality’.
- FSH: indirect, reflects growing follicles

- Stimulation tests (CC, EFORT) largely superceded
- AFC: relatively large, committed follicles
- AMH: mass of granulosa cells, also relatively large follicles
- (AFC and AMH are essentially measuring the same thing)

Where is there a mention of oocyte quality?

Assessment of ovarian age



Younger

Older

Age: a surrogate, but includes 'quality'.

FSH: indirect, reflects feedback

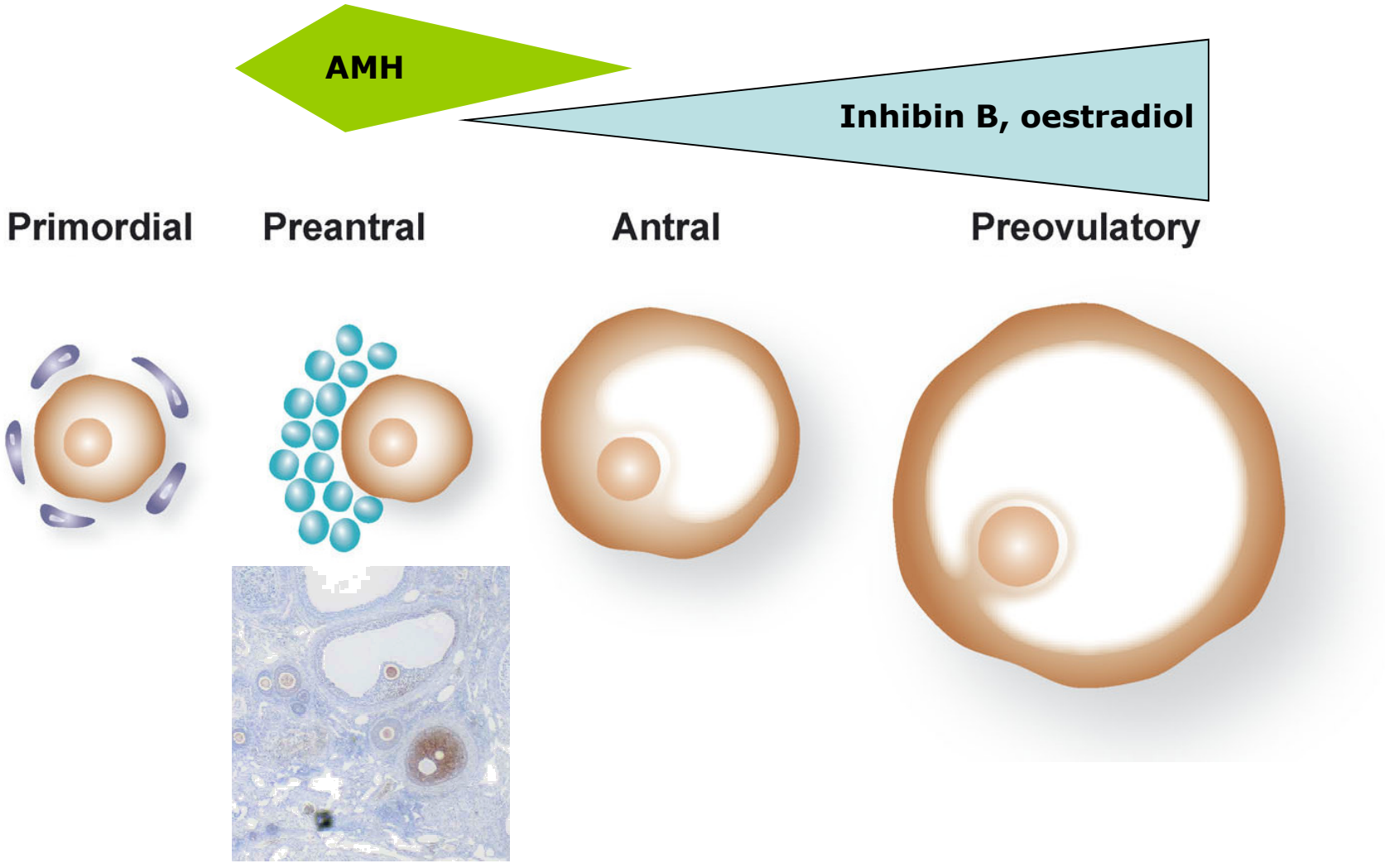
Stimulation tests (CC, EFFORT)

AFC: relatively large, committed follicles

AMH: mass of granulosa cells, also relatively large follicles

(AFC and AMH are essentially measuring the same thing)

The growing follicle produces changing hormones

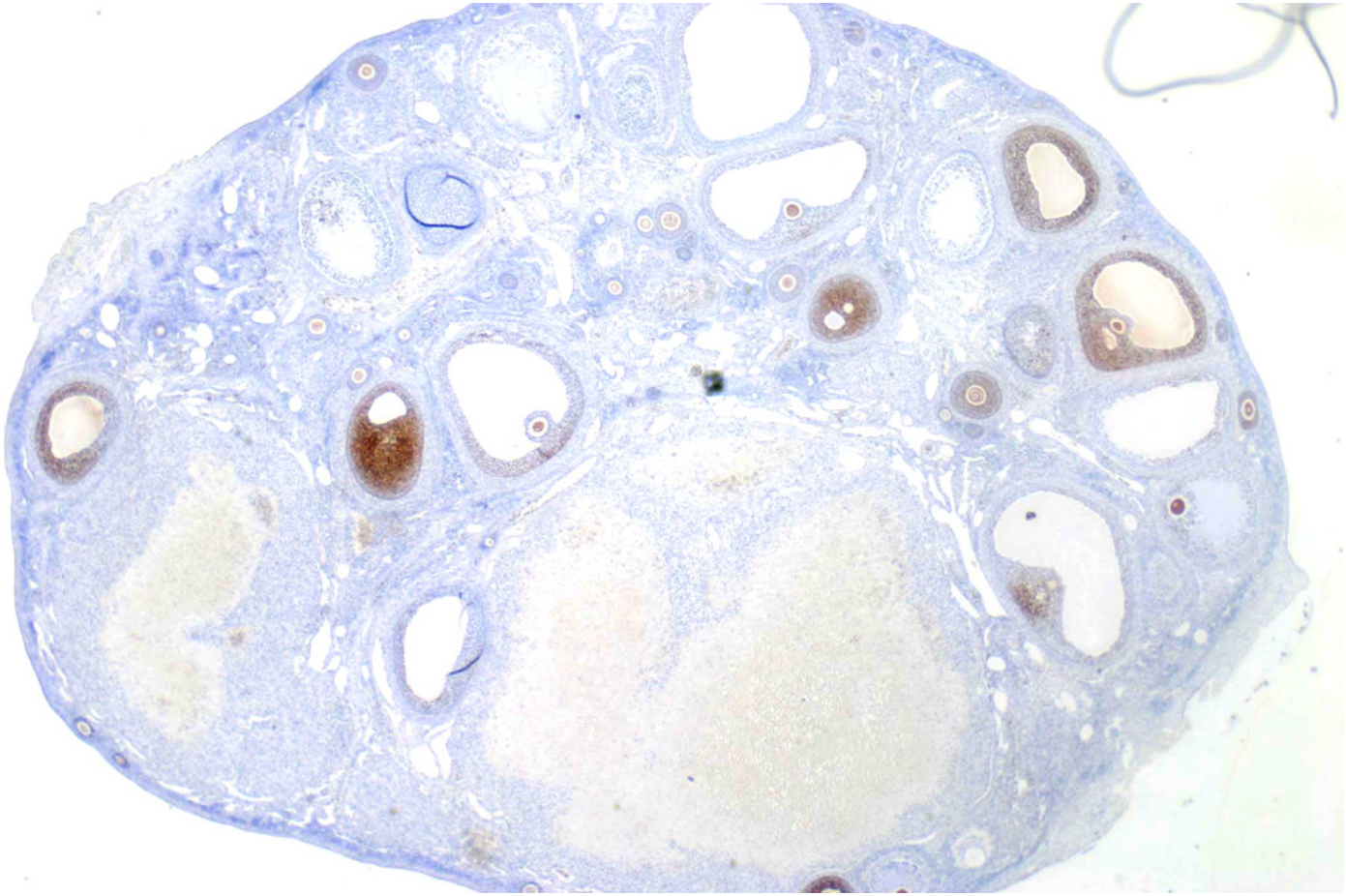


Age, FSH and inhibin B

	Oocytes recovered	After downreg.
Age	-0.2 (ns)	
FSH	-0.51 (<0.001)	
Inhibin B	0.24 (ns)	0.65 (<0.001)
stim Inhibin B	0.44 (0.002)	0.69 (<0.001)
AFC	0.42 (0.004)	0.44 (0.002)

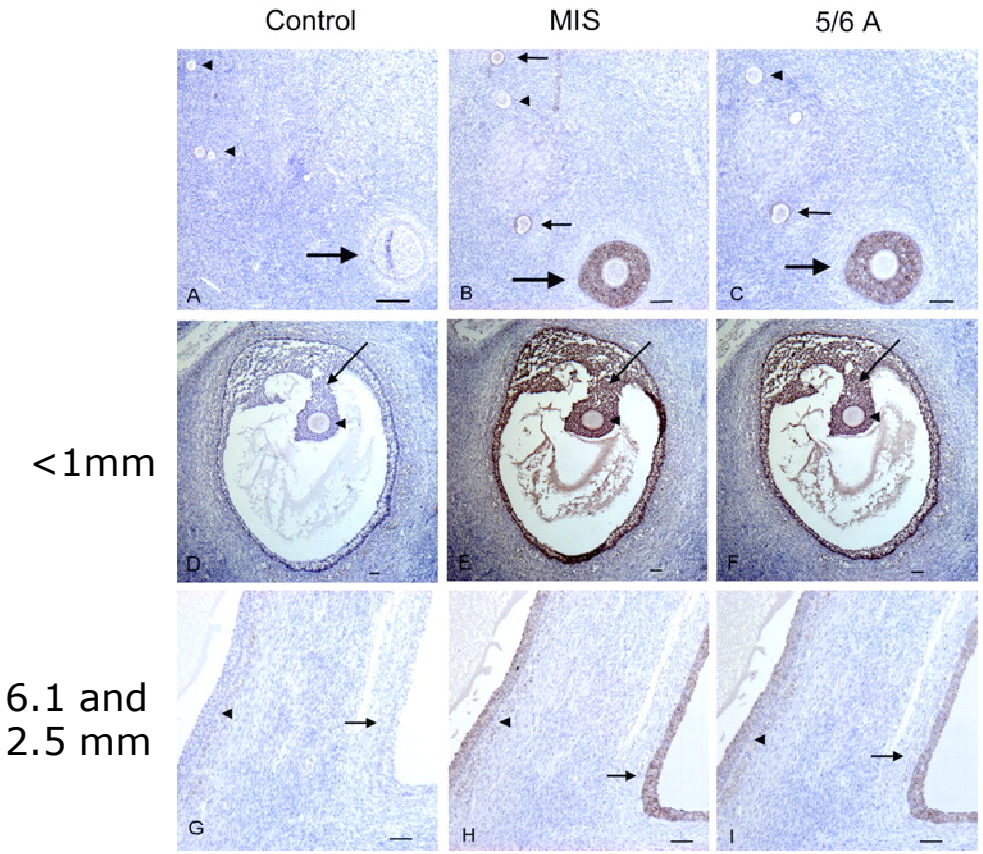
Yong PYK et al Human Reprod 2003, 18, 35

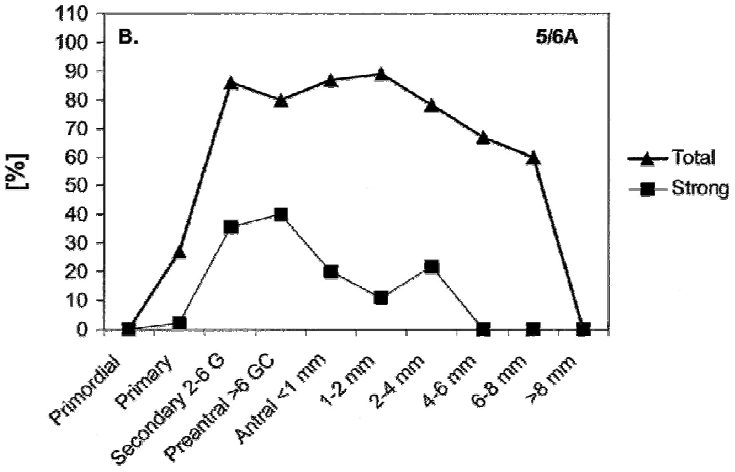
AMH is expressed in small but not larger follicles



Macaque ovary, courtesy of Prof Hamish Fraser

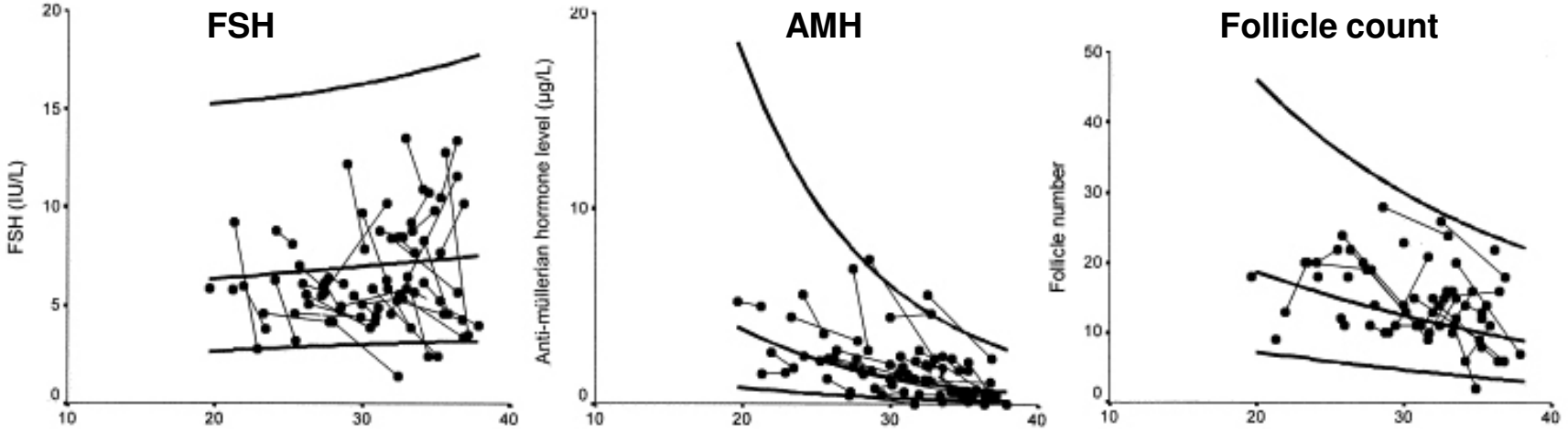
AMH expression in human ovary





Weenen C et al Mol. Hum. Reprod. 2004 10:77

Changes in markers of the ovarian reserve with age



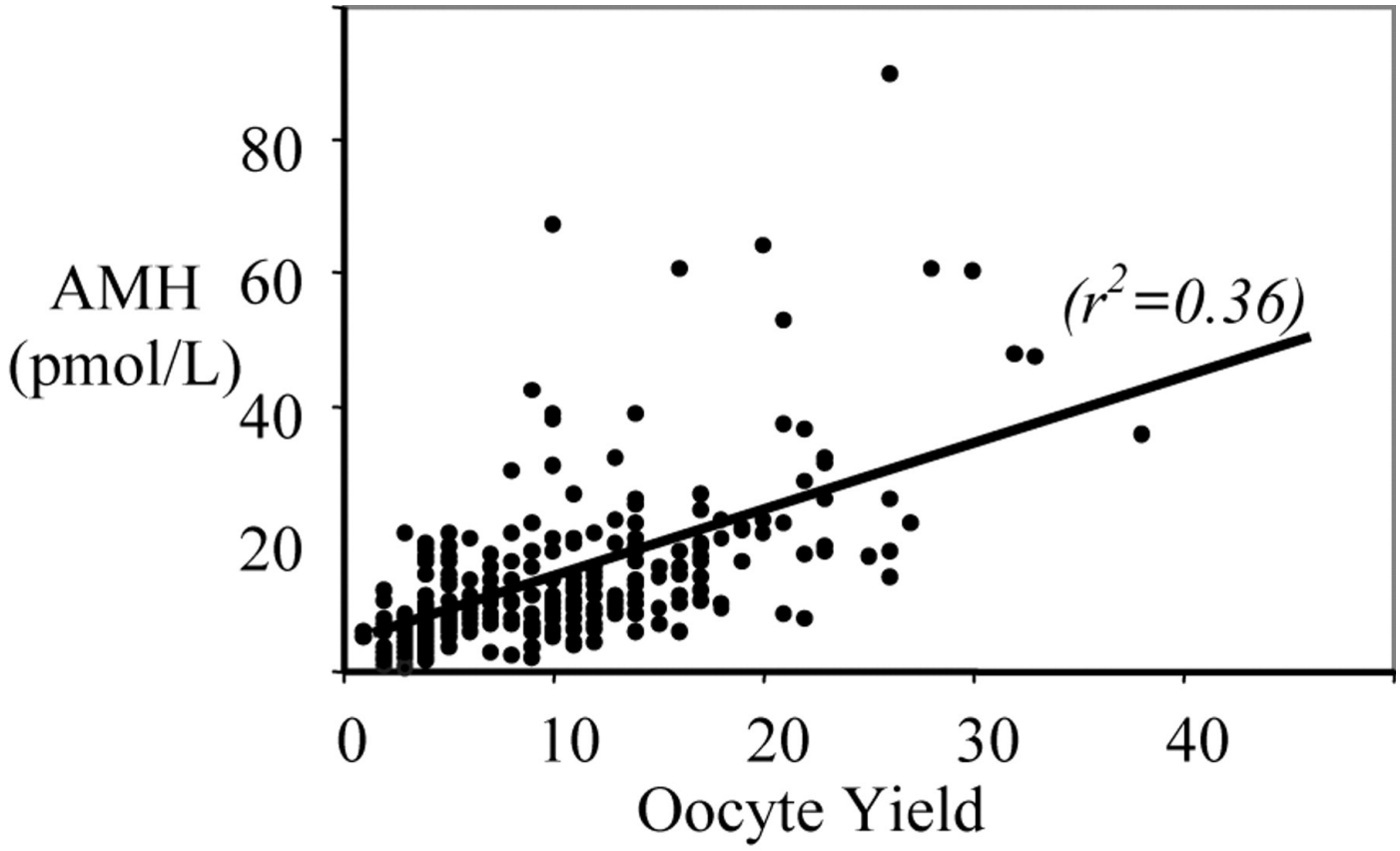
de Vet et al, 2002

In COS, AMH predicts no of oocytes (better than inhibin B)

Conveniently, AMH does not vary across the menstrual cycle

Seifer et al., 2002: Fanchin et al., 2003

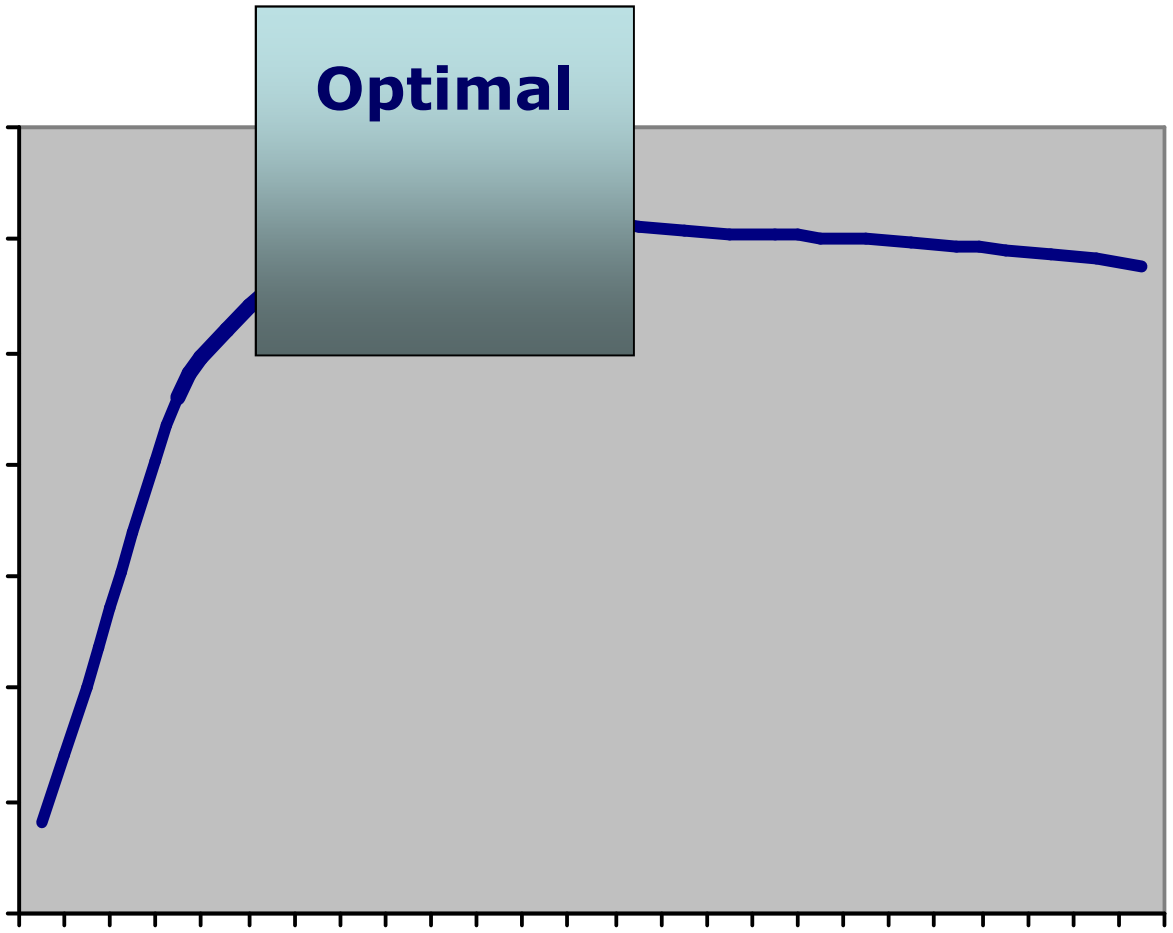
Anti-Mullerian hormone and prediction of oocyte yield



Any better than (stimulated) inhibin B? Probably not!

Fleming R et al. Hum. Reprod. 2006 21:1436

There is a relationship between oocyte number and pregnancy rate

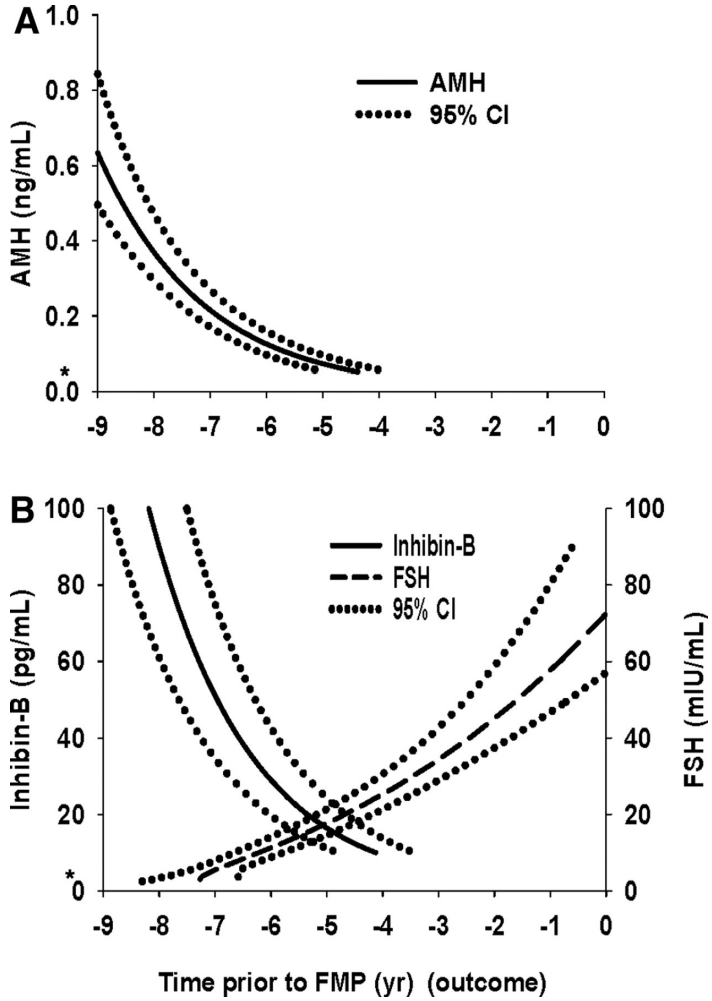


Van der Gaast et al, RBM Online, 2006

Prediction of menopause

50 women followed prospectively
(Michigan Bone Health and Metabolism Study)
6 annual assessments

Mean initial age 42 yr



Sowers, M. R. et al. J Clin Endocrinol Metab 2008;93:3478-3483

The association of age at FMP with AMH and inhibin B profiles

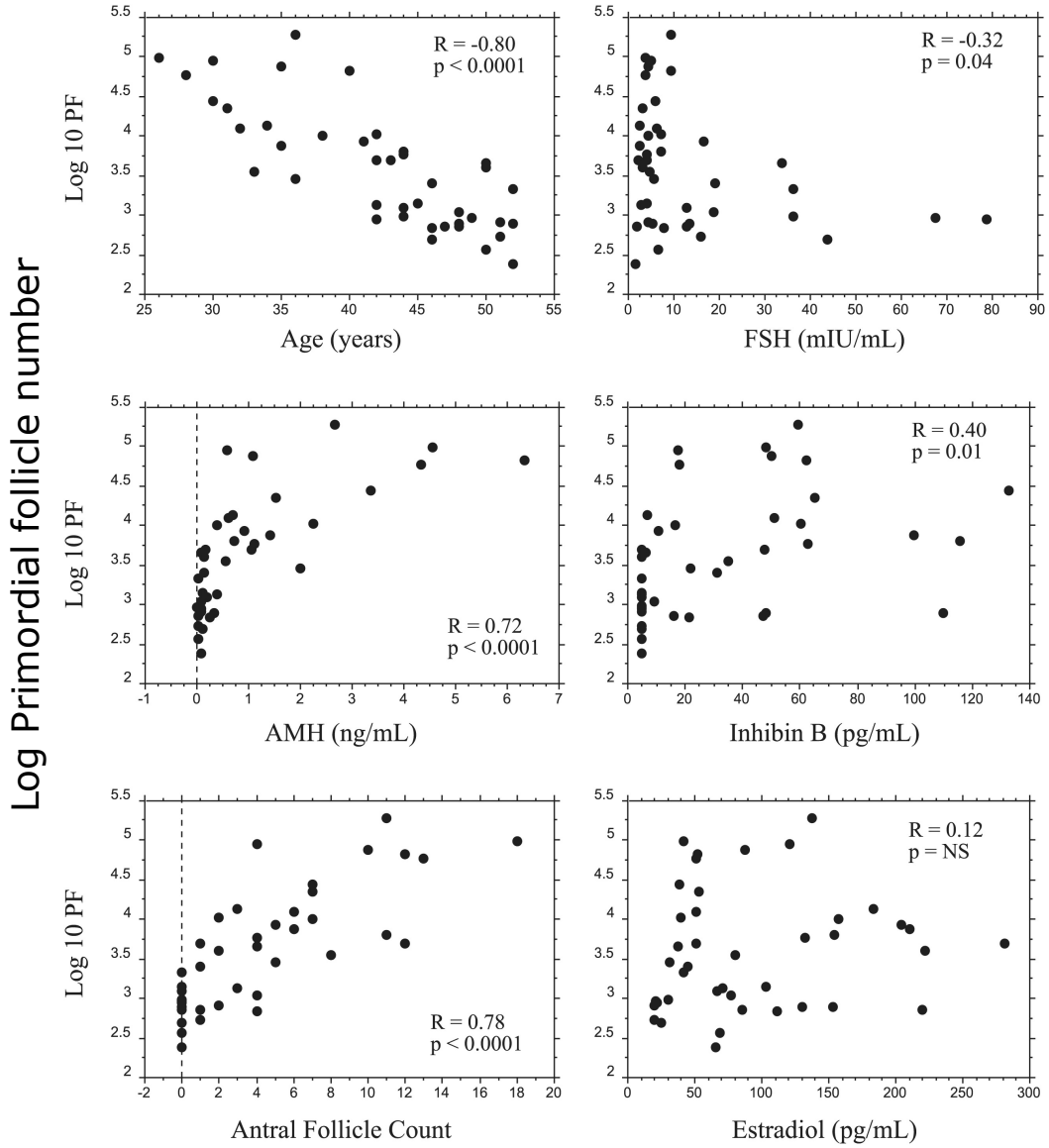
	β ± SE	P value
Log AMH intercept	0.83 ± 0.38	0.035
Log AMH slope	0.75 ± 3.52	0.83
Log Inhibin B intercept	1.83 ± 1.77	0.31
Log Inhibin B slope	–0.07 ± 3.52	0.98

Poor responders=earlier menopause

	IVF poor responders			IVF normal responders			OR or HR
	n	Median follow-up	% menopausal	n	Median follow-up	% menopausal	
Retrospective cohort	636	6 years	22	3675	5 years	7	3.1
Retrospective cohort	118	5 years	50	265	5 years	16	3.1
Case control	12	7 years	92	24	7 years	17	5.3

Data from De Boer et al 2002, 2003; Nikolaou et al 2002; Lawson et al., 2003

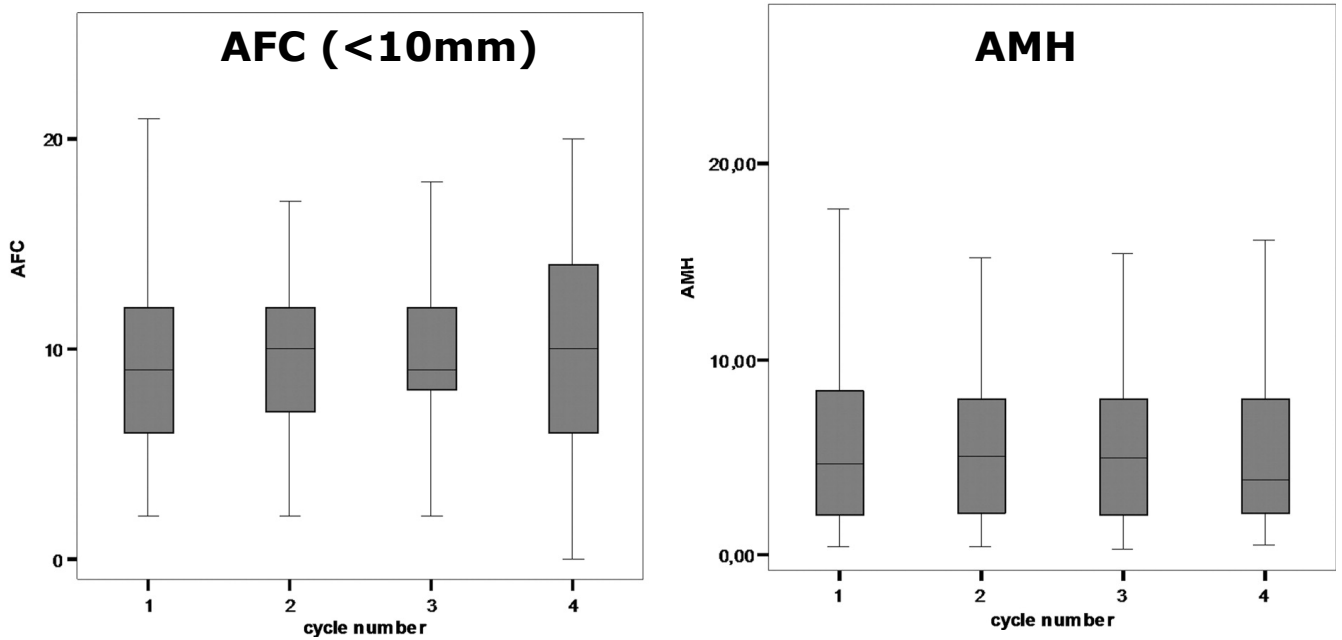
AMH and AFC reflect primordial follicle number



Stereological analysis following oophorectomy, n=42

Hansen et al 2010 Fertil Steril

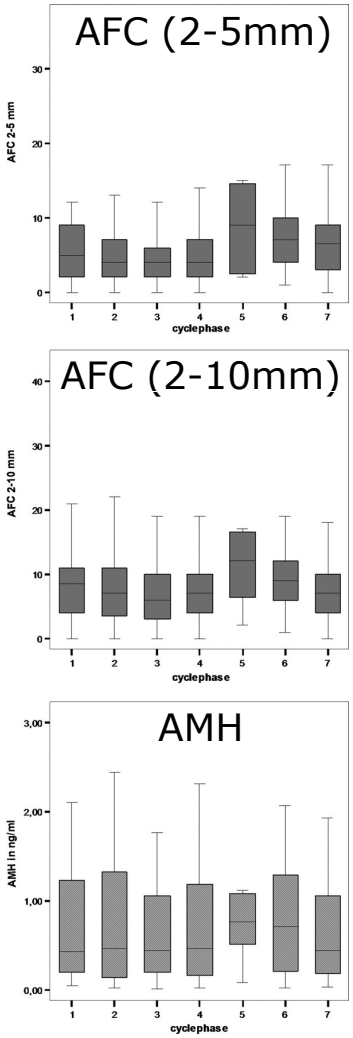
Intercycle variability in AFC and AMH



AMH: 89% of variation is between-subject, 11% is true individual cycle fluctuation.
AFC: 71% of variation is between-subject, 29% is individual cycle variation.

van Disseldorp, J. et al. Hum. Reprod. 2010 25:221-227

Intracycle variability

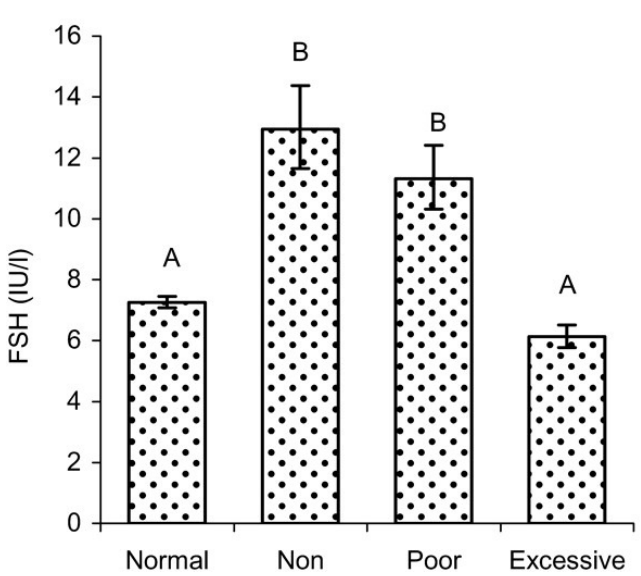


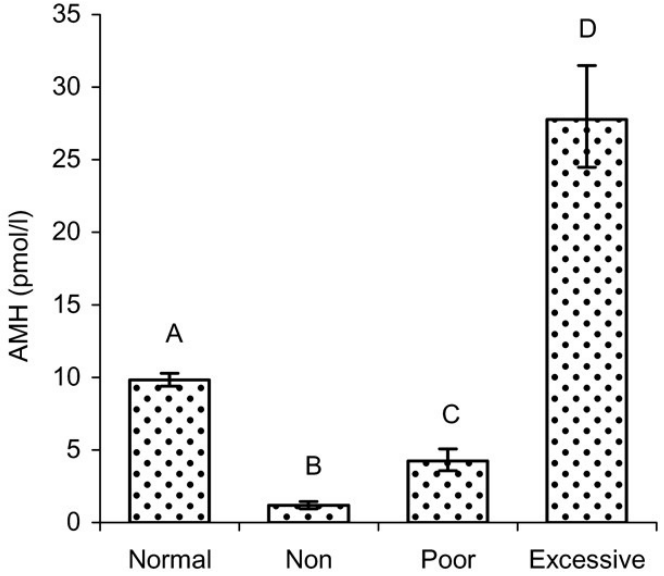
AFC
Same quintile: 41% and 45% (2–5 and 2–10 mm).
Different q: 21% and 16%.

AMH
Same quintile 72%
Different q: 1%

van Disseldorp, J. et al. Hum. Reprod. 2010 25:221-227

FSH vs AMH and ovarian response





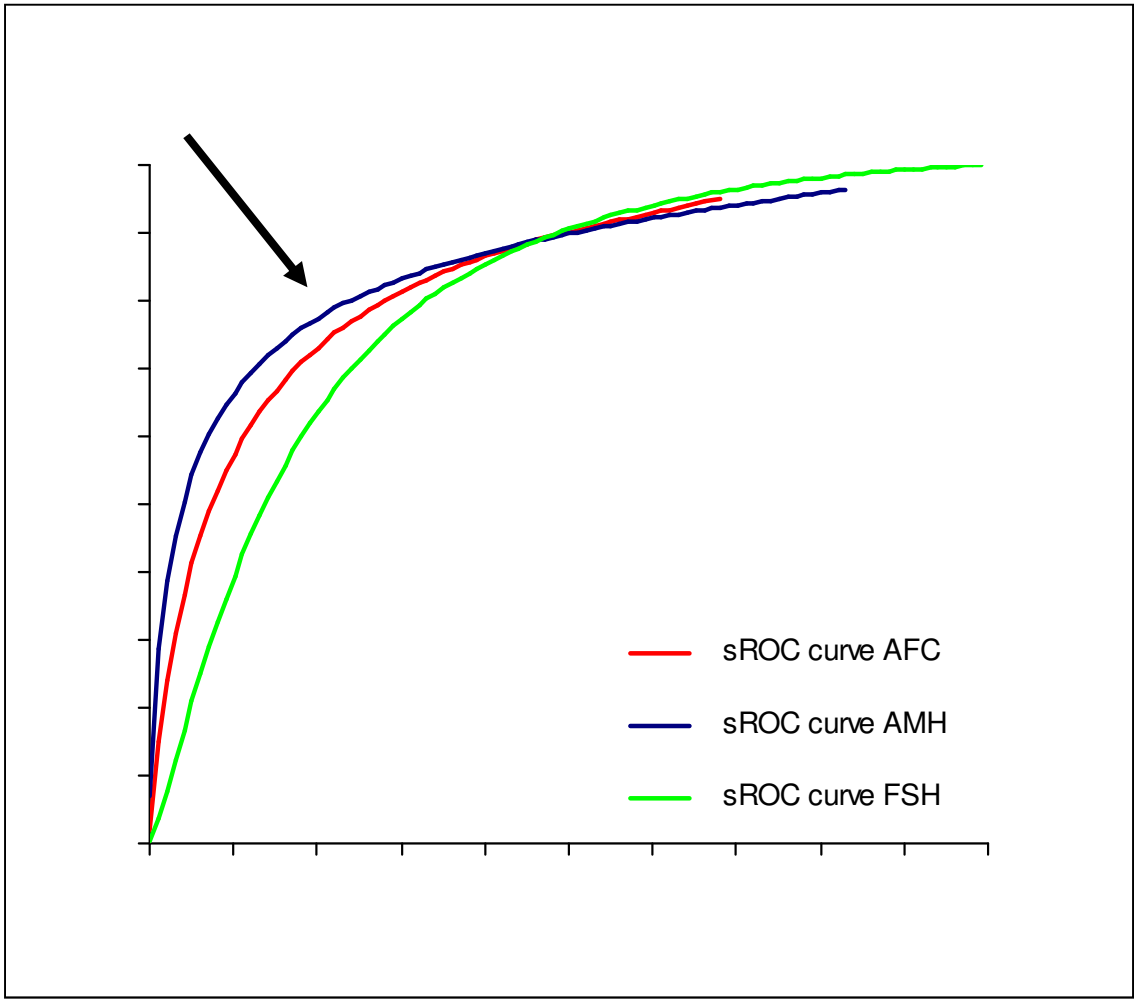
AMH discriminates between response groups better than FSH

Nelson SM et al. Hum. Reprod. 2007 22:2414

Accuracy of ORTs: response

At the best cut off:

Sensitivity 70%
False pos rate 10%

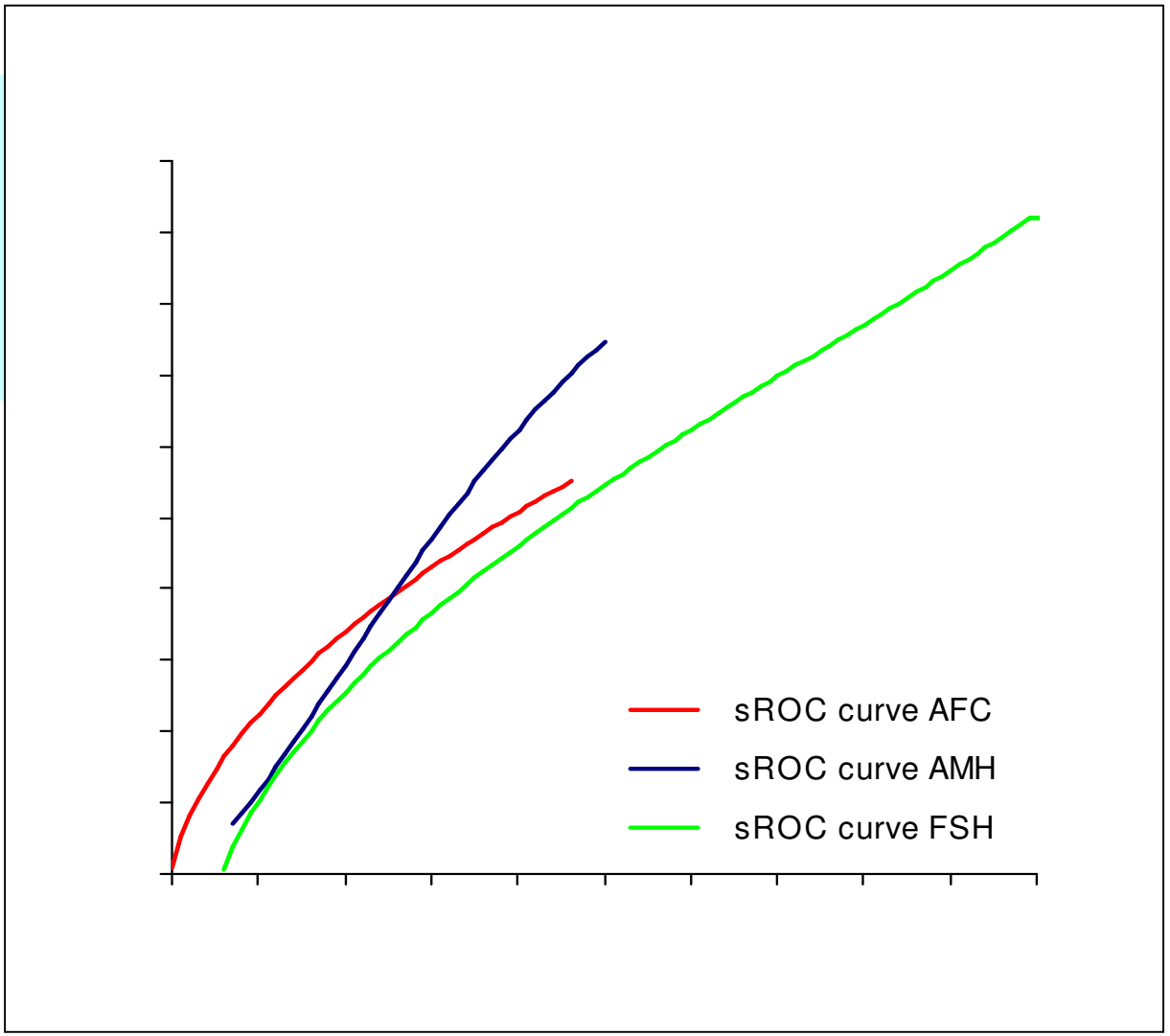


Hendriks DJ et al. Fertil Steril 2005; 83: 291-301
Broekmans FJ et al. Hum Reprod Update 2006; 12: 685–718
Broer SL et al. Fertil Steril 2009; 91: 705–714

Accuracy of ORTs: pregnancy

Accuracy is poor: only at extreme cut-off levels can a few zero prognosis cases be identified

n=558 meta-analysis

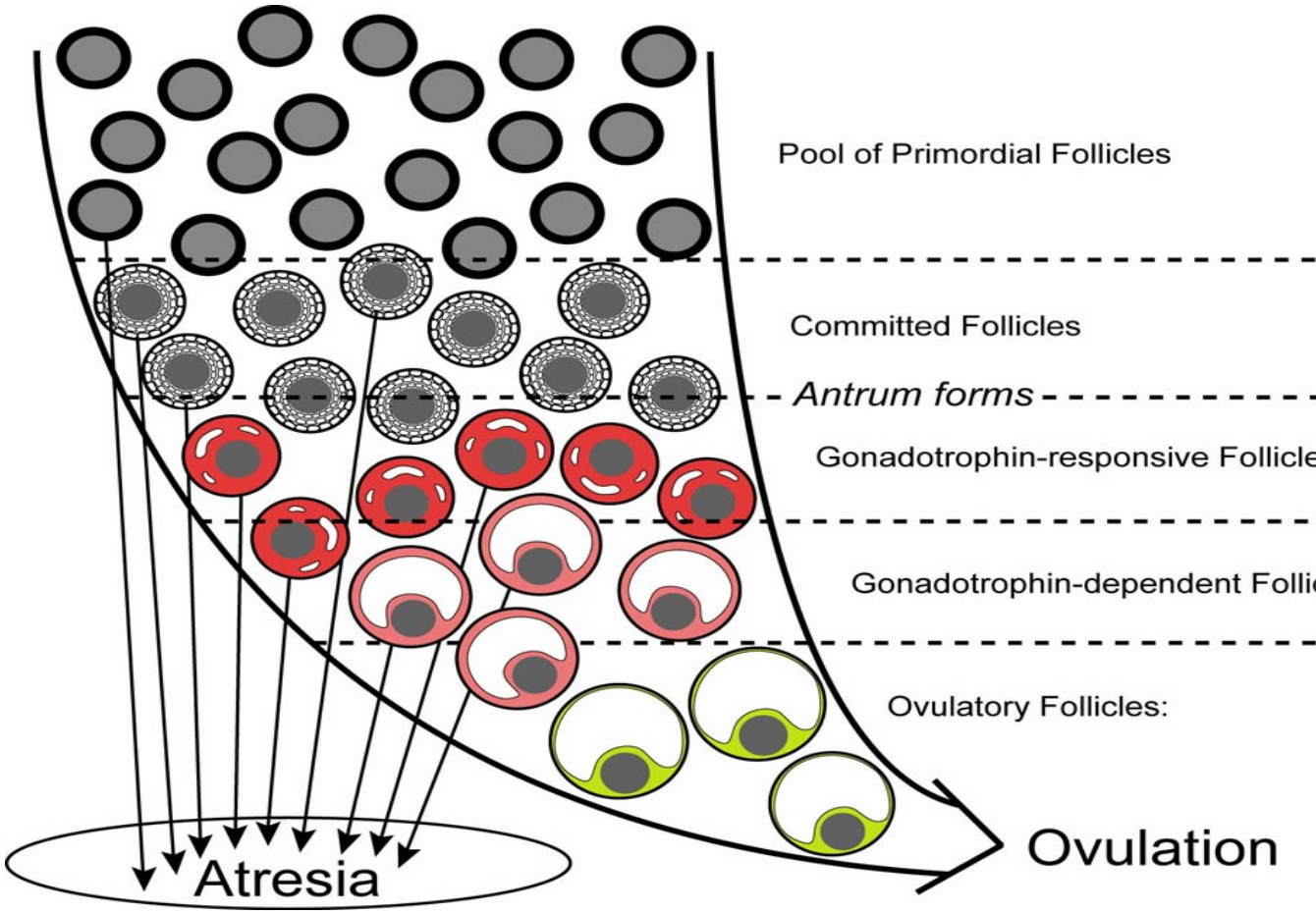


Hendriks DJ, et al. Fertil Steril 2005; 83(2): 291-301;
Broekmans FJ, et al. Hum Reprod Update 2006; 12(6): 685–718;
Broer SL, et al. Fertil Steril 2009; 91(3): 705–714

Conclusions

- Ovarian ageing: mostly genetic and unavoidable
- The various markers predict oocyte number
- Of course they do: by their nature they indicate the number of growing follicles
- How to improve prediction of oocyte quality?

What is the 'ovarian reserve'?



'True' ovarian reserve

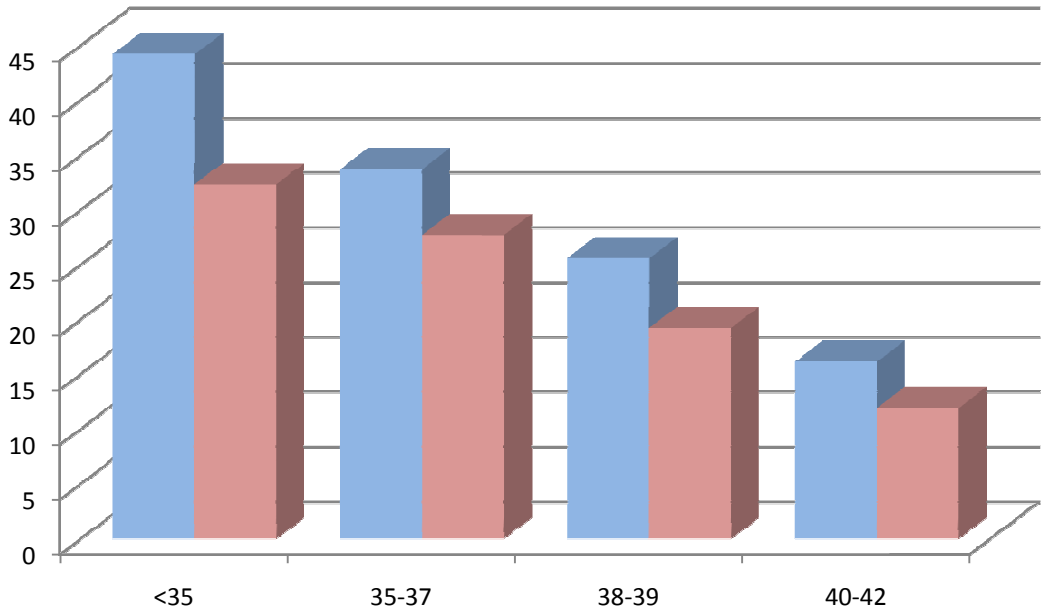
'IVF' ovarian reserve

Scaramuzzi R et al 1993 Reprod Fertil Develop 5: 459-478

Indirect evidence for AMH prediction of pregnancy

Age related decline

Good compared to UK standards



Clinical pregnancy rates for N=1217 cycles started
Versus national UK data

Data courtesy of Prof Scott Nelson, University of Glasgow

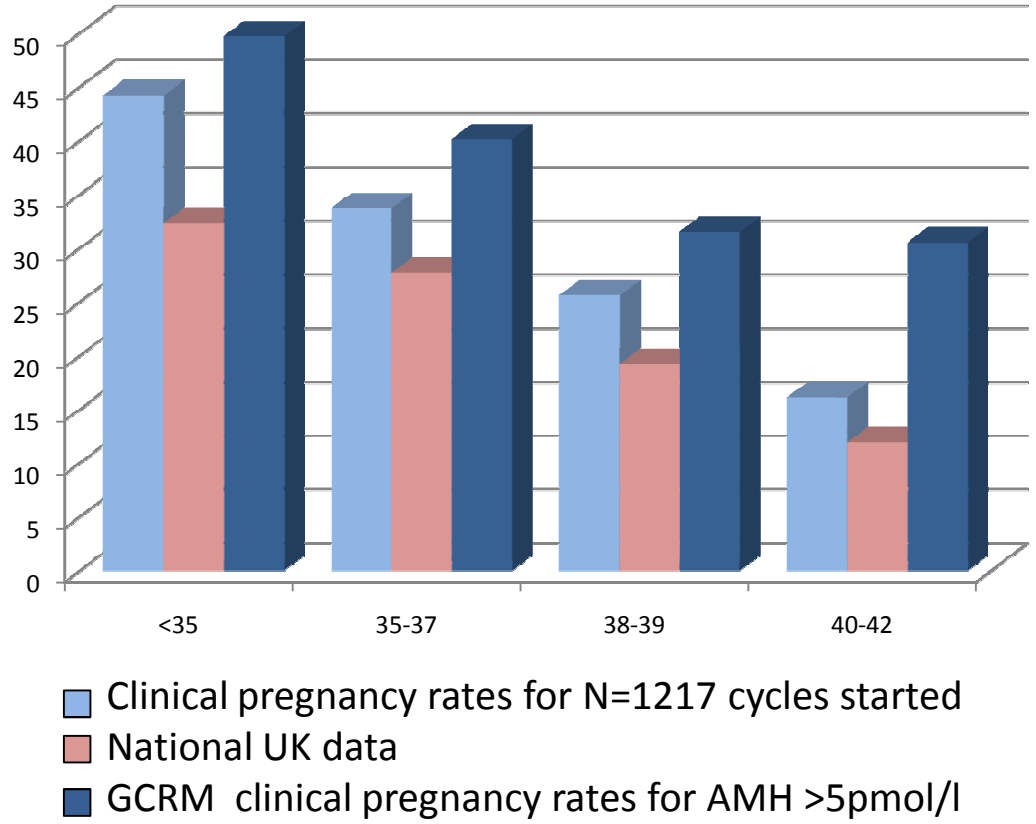
GCRM
Glasgow Centre for Reproductive Medicine

Indirect evidence for AMH prediction of pregnancy

Just treat AMH >5pmol/l
(50% centile at age 40)

Improvement in success rates for all ages

Consistent with independent prediction



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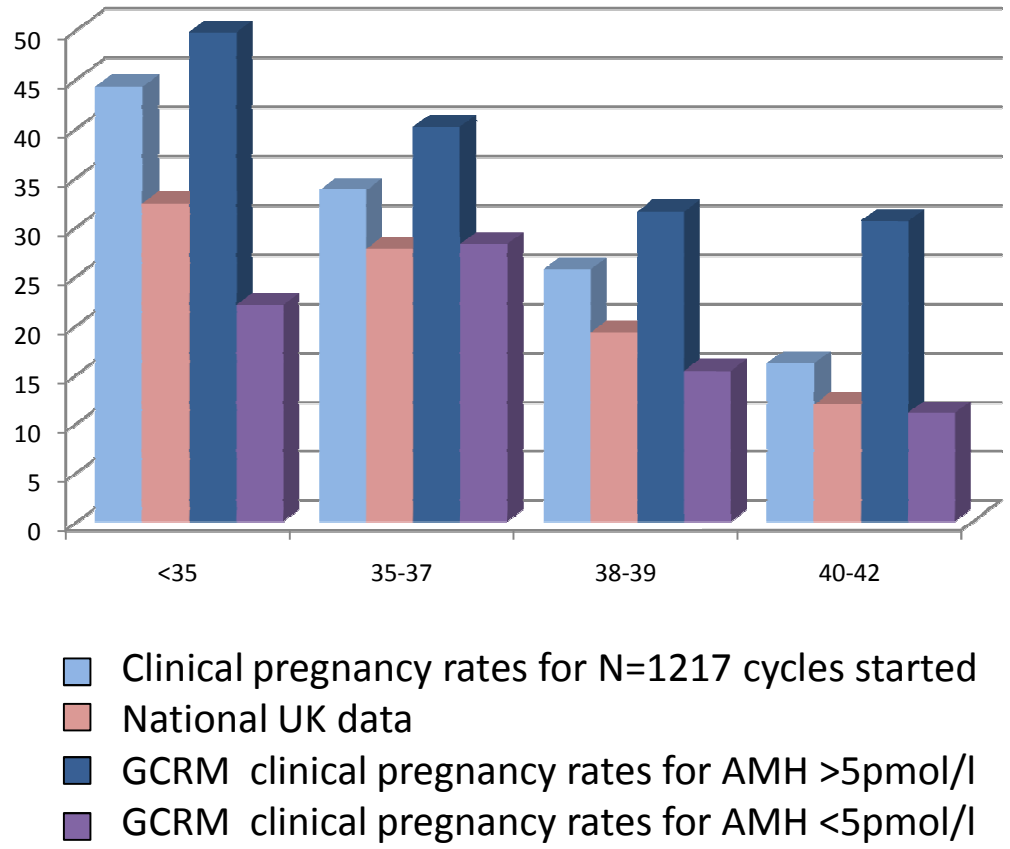
Indirect evidence for AMH prediction of pregnancy

If AMH <5pmol/l

Poor ovarian reserve at young ages very poor results



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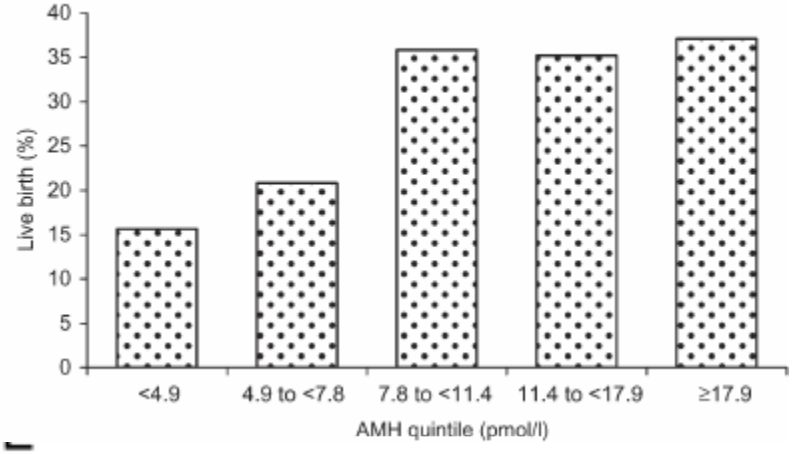
So can AMH predict live birth?

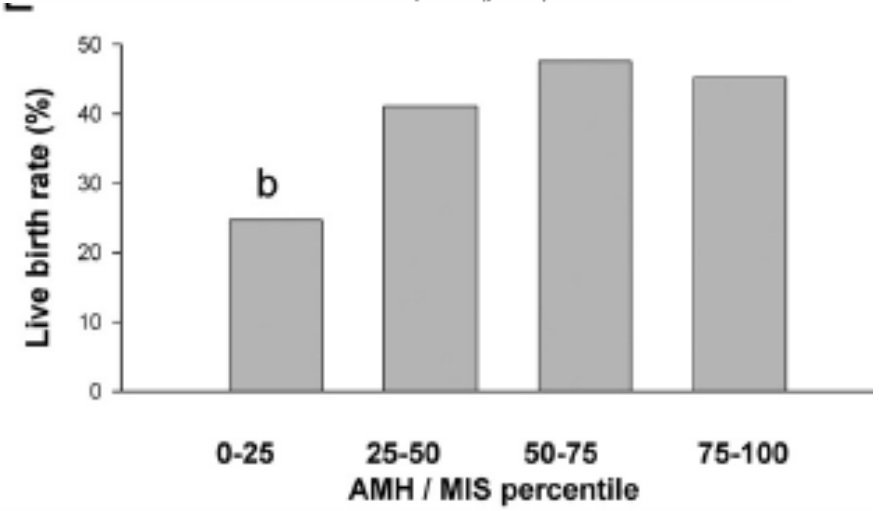
Paper 1:

- N = 340
- Increasing AMH associated with higher live birth
- Conversely higher FSH lower LB rate
- AMH AUC 0.62 95% CI 0.55 – 0.68



Paper 2:

- N = 336
- Increasing AMH but again threshold effect



Nelson et al Hum Repro (2007)
Lee et al Rep Biology and Endocrinology (2009)

Conclusions

- Prediction models to date have been limited in their applicability
- Multiple factors influence live birth success rates
- The decline in AMH parallels the reduction in follicles
- AMH can predict live birth
- Large cohorts to establish accurate measures of degree to which AMH can enhance the current best prediction models
- Still trying to equate egg quality with quantity: a real test of quality is elusive