Ovarian Ageing and Tests of Ovarian Reserve

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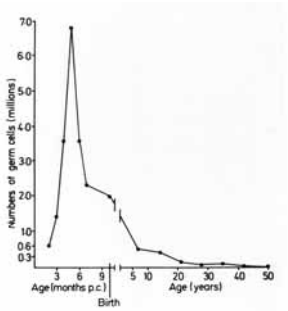
ESHRE Campus, Kiev, May 2010

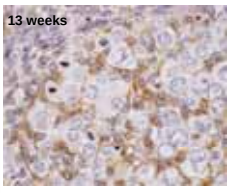
Age at menopause: health impact

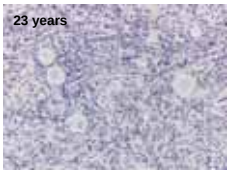
- Early
  - Osteoporosis
  - Cardiovascular risk
- Late
  - Breast cancer

The ovarian follicular complement

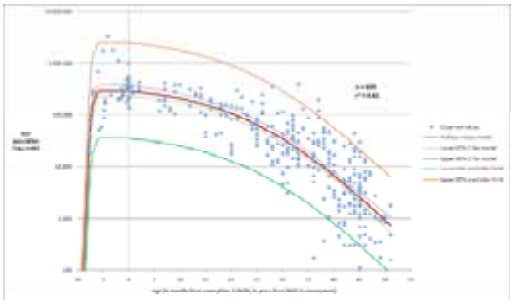


Data from Block 1952; Baker 1963



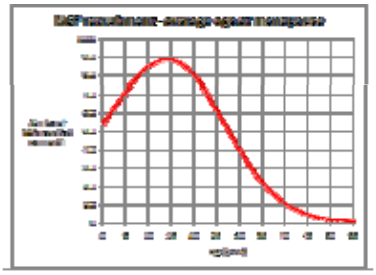


Current model of follicular depletion



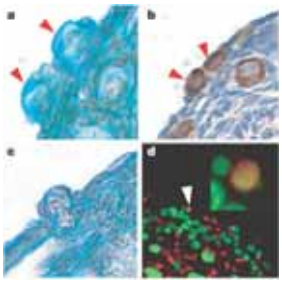
Wallace and Kelsey 2010 PLoS One 5; e8772

Follicle recruitment rate by age



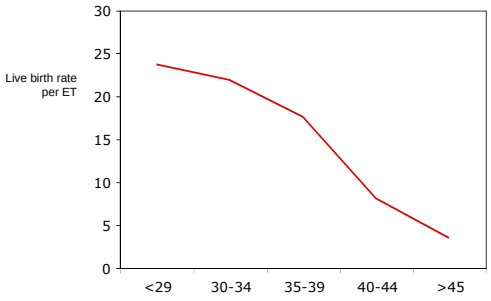
Wallace and Kelsey 2010 PLoS One 5; e8772

Germ stem cells in the mammalian ovary?



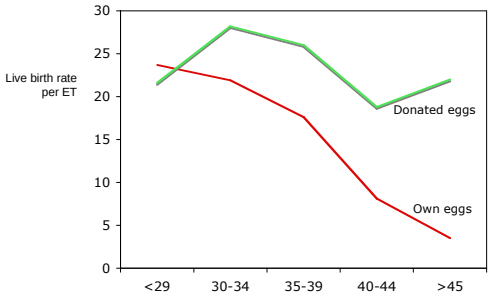
Johnson J, Canning J, Kaneko T, Pru JK and Tilly JL (2004) Nature 428, 145-150

Age and reproductive success



Templeton et al 1996 Lancet 384; 1402

Age and reproductive success



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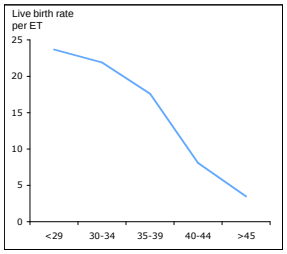
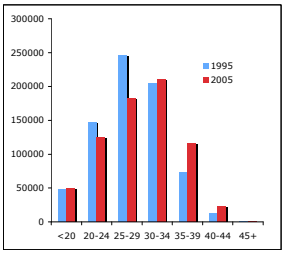
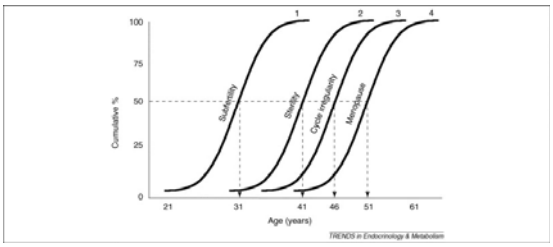


Templeton et al 1996 Lancet 384; 1402



OHE Compendium of Health Statistics

Progressive loss of reproductive function



From Broekmans et al 2007 TEM 18, 58

Environmental determinants of age at menopause

- Age at first childbirth
- Age at last childbirth
- Age at menarche
- Alcohol use
- Birth weight
- Body mass index
- Coffee consumption
- Cognition
- Depression
- Diet
- Educational level
- Ethnicity
- Employment
- Height
- Income
- Left-handedness
- Marital status
- Meat consumption
- Menstrual cycle irregularity
- Menstrual cycle length
- Miscarriages
- Oral contraceptive use
- Parity
- Physical acitivity
- Psychosocial stress
- Rank in birth order
- Religion
- Siblings
- Smoking
- Type 2 diabetes
- Unilateral Oophrectomy
- Year of birth
- Weight
- Weight gain
- Weight reduction diet

Total impact: 3%

From Kok et al 2005, Hum Reprod Update 11, 483

Heritability

30 to 85% (Snieder et al., 1998; Treloar et al., 1998; de Bruin et al., 2001; Kok et al., 2004)

Single/multiple gene defects as causes of POF
- FSH receptor, FoxL2, X chromosome deletions

Association studies
- Factor V Leiden (+smoking), APOE4 (Van Asselt et al., 2003, Koochmeshgi et al., 2004)

Genome quantitative trait loci (QTL) analysis
- Requires no hypothesis but will not detect common genes with a small impact

Genome-wide scanning

- 165 Dutch families
- 9q21.3 and Xp21.3

van Asselt et al. 2004 Am J Hum Genet 74, 444

Chromosome 9 locus: Bcl2

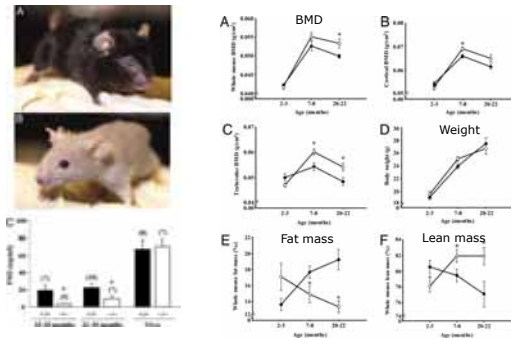
Human studies on genetics of the age at natural menopause: a systematic review

Marlies Voorhuis, N. Charlotte Onland-Moret, Yvonne T. van der Schouw, Bart C.J.M. Fauser and Frank J. Broekmans

Hum Reprod Update Jan 2010

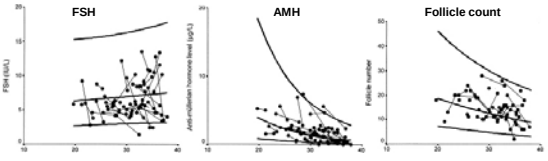
'…very few consistent associations were found'

Ovarian function in Bax-deficient mice



Perez et al. 2007 Proc. Natl. Acad. Sci. USA 104, 5229

Changes in markers of the ovarian reserve with age



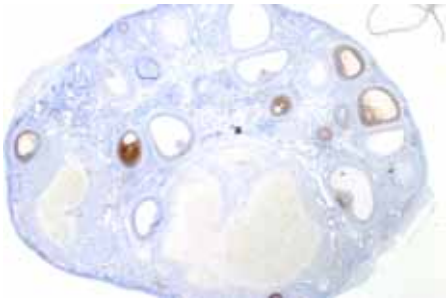
de Vet et al, 2002

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

Conveniently, AMH does not vary across the menstrual cycle

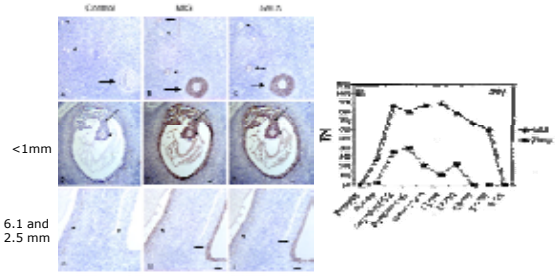
Seifer et al., 2002: Fanchin et al., 2003

AMH is expressed in small but not larger follicles



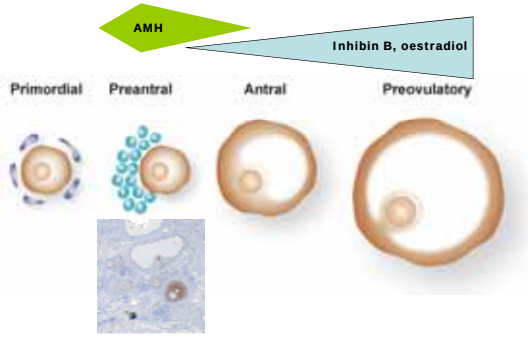
Macaque ovary, courtesy of Prof Hamish Fraser

AMH expression in human ovary

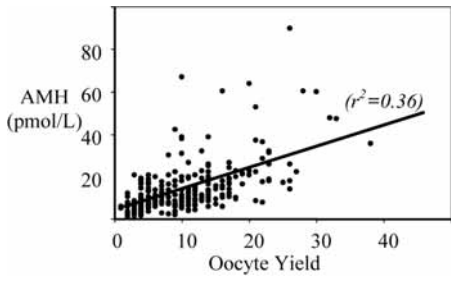


Weenen C et al Mol. Hum. Reprod. 2004 10:77

The growing follicle produces changing hormones

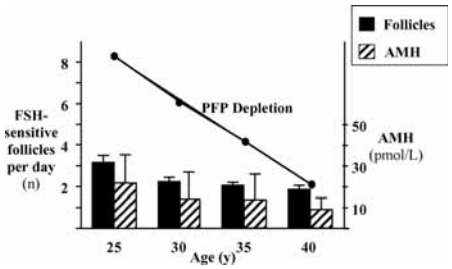


Anti-Mullerian hormone and oocyte yield



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

Primordial follicle pool depletion and FSH sensitivity according to age



Little change in FSH-recruitable follicles with age compared with PFP

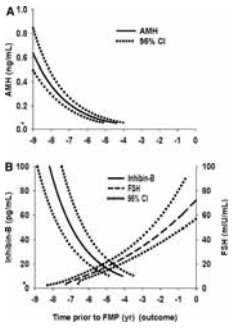
PFP depletion data from Faddy 2002

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

Prediction of menopause

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

Mean initial age 42 yr



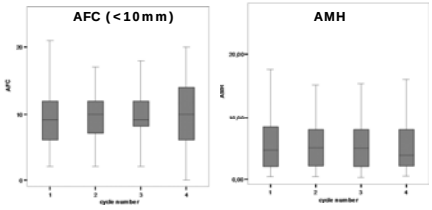
Sowers, M. R. et al. J Clin Endocrinol Metab 2008;93:3478-3483

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

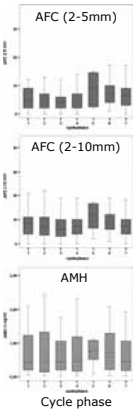
Sowers, M. R. et al. J Clin Endocrinol Metab 2008;93:3478-3483

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%

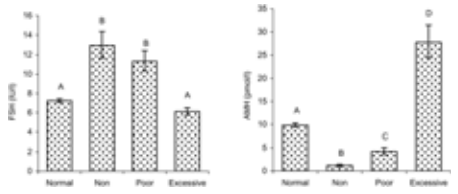
van Disseldorp, J. et al. Hum. Reprod. 2010 25:221-227

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

FSH vs AMH and ovarian response

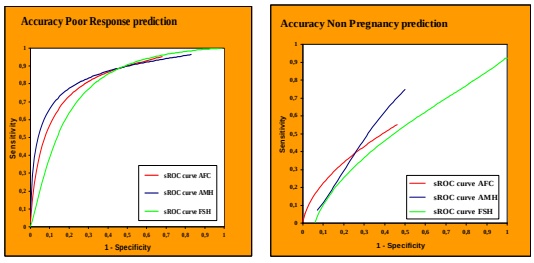


AMH is a better discriminatory of ovarian response than FSH

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

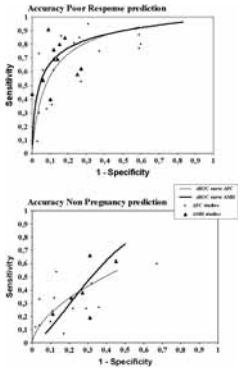
Predictive value of ovarian reserve tests

AFC, AMH and FSH



Broekmans, Kwee, Hendriks, Mol & Lambalk, Hum Reprod Update , 2006

Comparison of AMH and AFC in IVF



13 studies
No significant differences between AFC and AMH

Both good prediction of response

Both poor prediction of outcome

Broer SL et al 2009 Fertil Steril 91 705-714

Conclusion

- Despite increased debate, female reproduction is time-limited
- Follicle number is established in fetal life
  thus the intrauterine environment can influence it
- Strong genetic input, but largely unknown genes

- Markers of ovarian age include FSH, AMH and AFC
- AFC and AMH are both better than FSH
- AFC and AMH are of comparable value in prediction response in IVF
  but they predict quantity, not quality