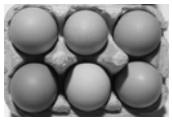
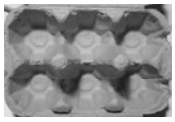
Erasmus MC
University Medical Center Rotterdam

ESHRE Campus workshop

Modena Italy 18 & 19 April 2008

Circulating Anti-Müllerian hormone levels from fetus to adulthood





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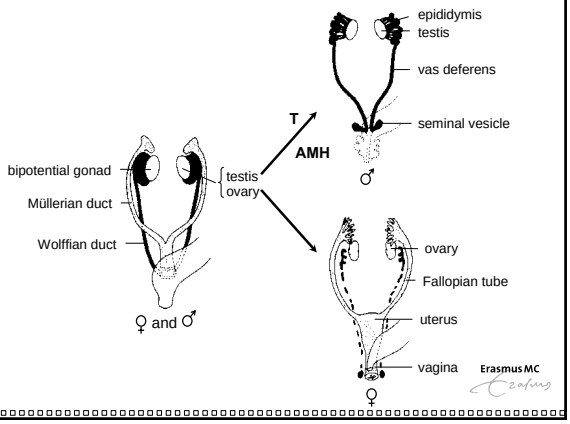
Marlies Kevenaar, Anke McLuskey, Piet Kramer, **Jenny A. Visser**, Bas Karels, Frank H. de Jong, Axel P.N. Themmen

Joop S.E. Laven, *Rotterdam, The Netherlands*
André G. Uitterlinden, *Rotterdam, The Netherlands*
Bart Fauser, *Utrecht, The Netherlands*
Manuela Simoni, *Münster, Germany*
Nigel Groome, *Oxford, UK*

AMH action during sex differentiation



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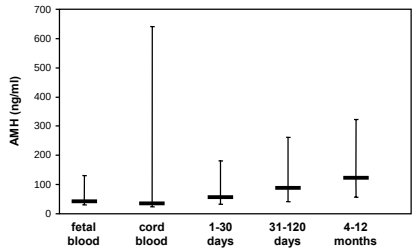
AMH levels in male fetuses and newborns



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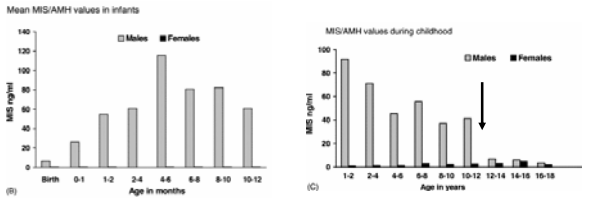
Data modified from Guibourdenche et al. (2003) Mol Cell Endo 211:55-63

AMH levels in infants and children



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Lee et al. (2003) Mol Cell Endo 211:01-08

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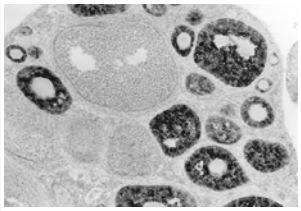
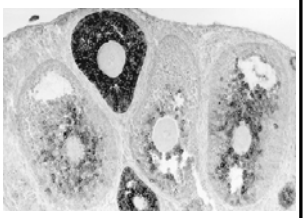
AMH expression in the ovary (mouse)





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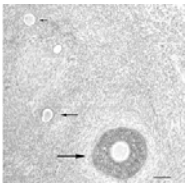
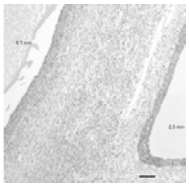
AMH expression in the ovary (human)



primordial, primary, secondary

small antral <1 mm



large antral follicles: 6.1 and 2.5 mm

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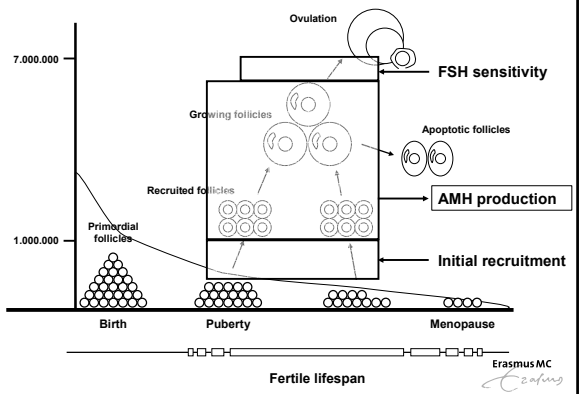
Weenen et al. (2004) Mol Hum Reprod 10:77-83

Ovarian follicle development



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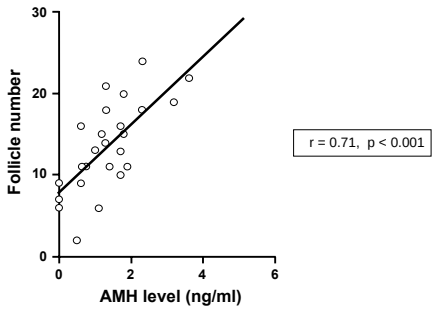
AMH levels correlate with AFC



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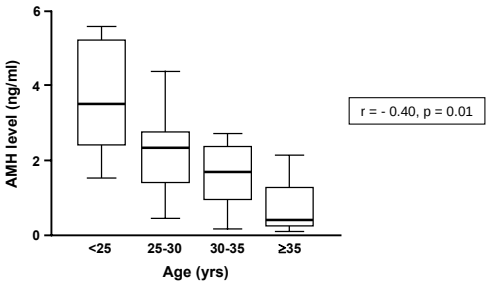
de Vet et al. (2002) Fertil Steril 77:357-362

AMH levels decline with aging



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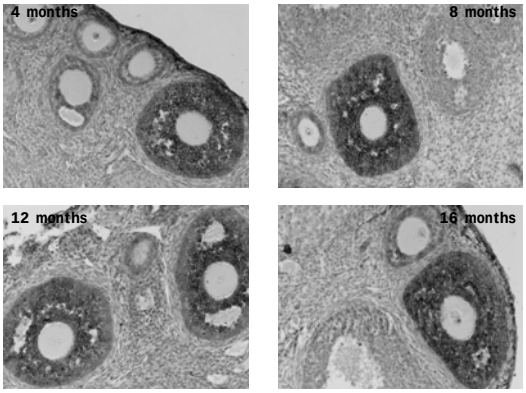
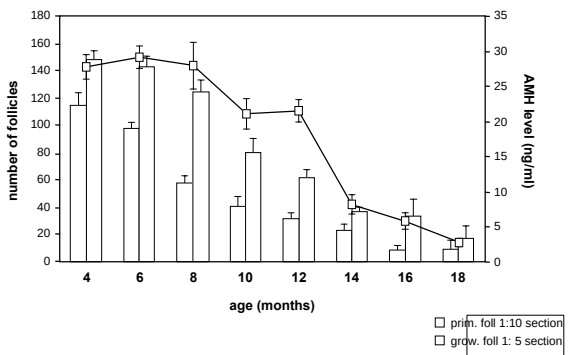
de Vet et al (2002) Fertil Steril 77:357-362

AMH expression in aging mice

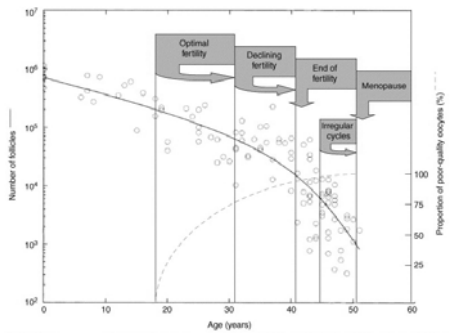


Follicle numbers decline in aging mice



Kevenaar et al (2006) Endocrinology 147: 3228-3234

Age related decline in fertility in women



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Broekmans et al (2007) Trends Endocrinol Metab. 18:58-65

Early decline in AMH levels with aging

	Visit 1	Visit 2	*P* value
AMH (ng/ml)	2.1 (0.1-7.4)	1.3 (0.0-5.0)	< 0.001
FSH (IU/L)	6.0 (1.4-13.5)	5.8 (2.4-13.4)	0.29
Inhibin B (pg/L)	112 (12-213)	110 (4-206)	0.92
E2 (pmol/L)	151 (64-404)	161 (70-620)	0.52
AFC	14 (6-28)	14 (2-24)	0.27

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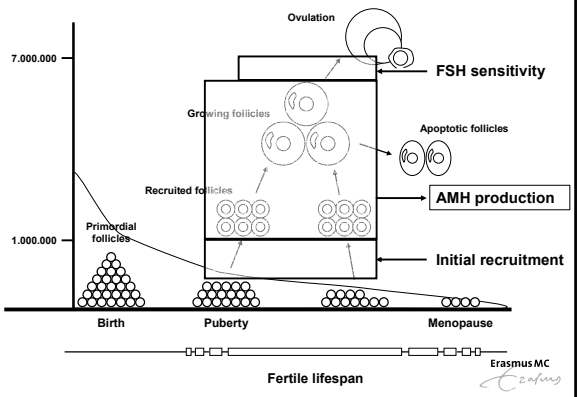
de Vet et al (2002) Fertil Steril 77:357-362

Ovarian follicle development



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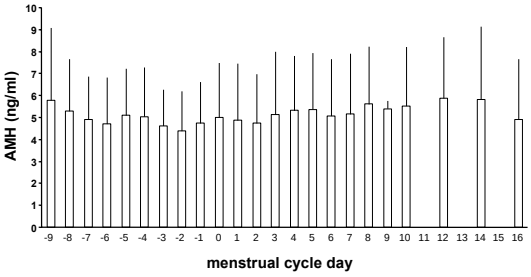
AMH levels during the menstrual cycle

21 women; median age 25.5 yr



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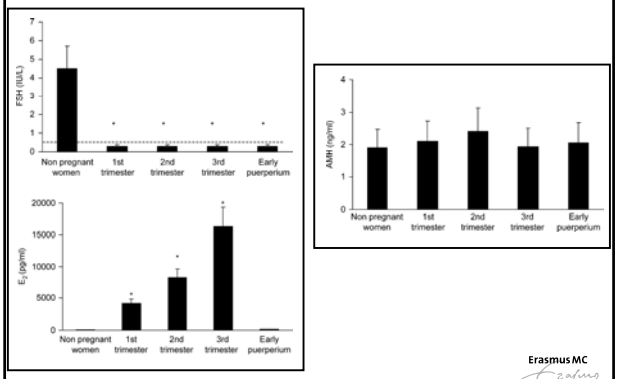
unpublished

AMH levels during pregnancy



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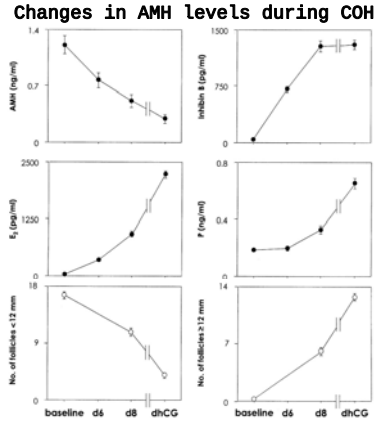
La Marca et al (2005) Hum Reprod 20: 1569-1572

Changes in AMH levels during COH



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Fanchin et al (2003) Hum Reprod 18:328-332

AMH as predictor of poor response in IVF treatment

119 IVF patients

- divided in normal (84) and poor (35) responders on basis of oocyte number after stimulation cycle (poor≤3<normal)
- normal responder group: more tubal pathology and male factor
- poor responder group: more unexplained
- no difference in age, duration of infertility

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Van Rooij et al (2002) Hum Reprod 17:3065-3071

Pretreatment hormone parameters on cycle day 3

	Total	Normal	Poor	p
AMH (µg/l)	0.9	1.4	0.2	<0.001
AFC (n)	8	11	4	<0.001
FSH (IU/l)	6.6	6.0	10.5	<0.001
Inhibin B (ng/l)	103	115	73	<0.001
Estradiol (pmol/l)	158	160	158	-

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Van Rooij et al (2002) Hum Reprod 17:3065-3071

AMH in women

➔ AMH levels correlate with primordial follicle pool
➔ AMH levels decline with age
➔ AMH levels are cycle independent

➔ **Cut off value?**

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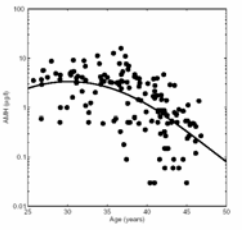
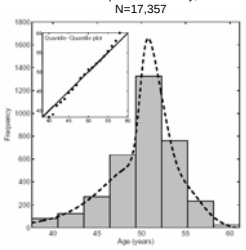
Distribution of AMH levels and age at menopause

Healthy, regularly cycling women
N=144



Prospect-EPIC study,
N=17,357



Maximum likelihood estimation of an AMH threshold to predict menopause: 0.086 µg/l

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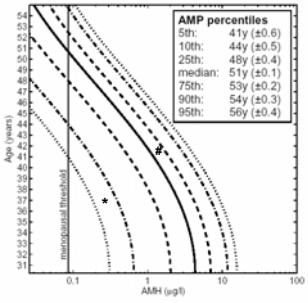
van Disseldorp et al (2008) J Clin Endocrinol Metab. Epub

Prediction of age at menopause



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van Disseldorp et al (2008) J Clin Endocrinol Metab. Epub

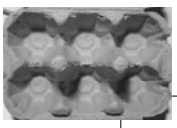
AMH in women

➔ **Serum levels in ovarian pathophysiology**

Premature Ovarian Failure

Idiopathic: POF

Induced: cancer patients



AMH as marker of ovarian reserve in childhood cancer survivors

32 women treated during for Hodgkin's Lymphoma

- Age at diagnosis: 14y; age at follow-up: 25.0 y;
- 11.6 y follow-up

- Chemotherapy: ABVD/EBVD -/+ MOPP
  - A(E)BVD: adriamycin (epirubicin), bleomycin, vinblastin, dacarbazine
  - MOPP: mechlorethamine, vincristine, prednisone, procarbazine

- Day 3-5 Hormones to determine ovarian status

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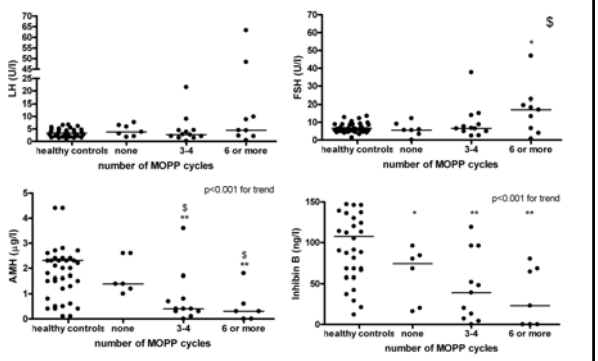
van Beek et al (2007) JCEM 92:3869-3874

Childhood cancer survivors – Hormone levels



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van Beek et al (2007) JCEM 92:3869-3874

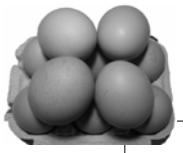
AMH in women

➔ **Serum levels in ovarian pathophysiology**

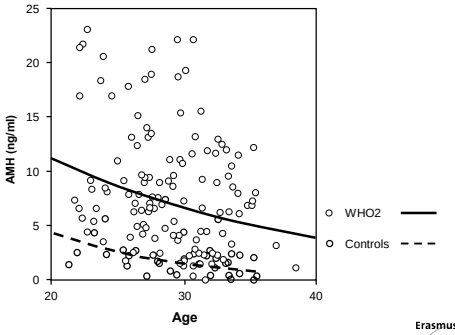
Polycystic Ovary Syndrome

Most common endocrine disorder in reproductive age women

Prevalence 5-10% in general population



Serum AMH levels in PCOS women



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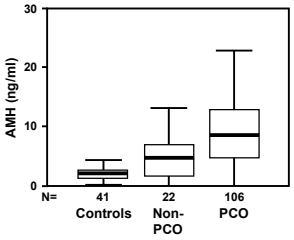
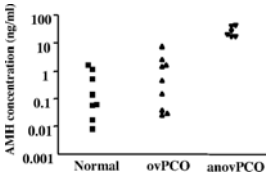
AMH serum levels are elevated in PCOS patients

Serum levels



Granulosa cell-conditioned medium



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Laven et al (2004) JCEM 89: 318-323 Pellatt et al (2007) JCEM 92: 240-245

Conclusion

Serum AMH levels in females

- undetectable in female fetuses
- relatively low compared to males
- increase until puberty
- decline with increasing age
- undetectable at menopause

Challenges

- assay and assay standards
- cut off values for:
  - Age at menopause
  - Reduced fertility/infertility
  - PCOS

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