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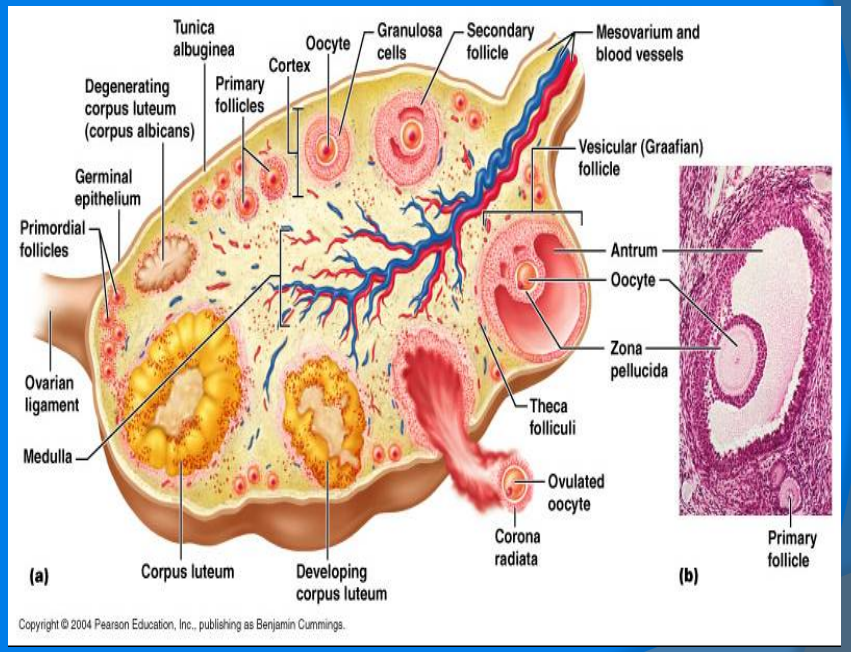
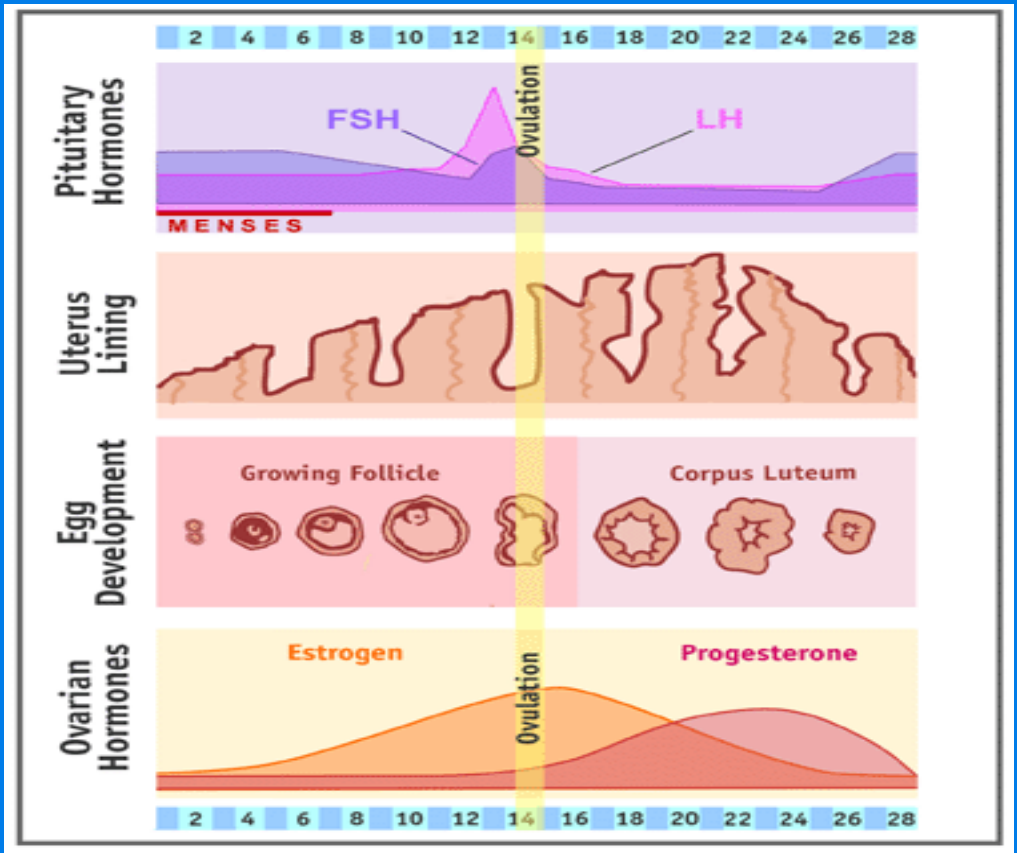
RELATIONSHIP BETWEEN AMH AND FOLLICLE NUMBER THROUGHOUT LIFE

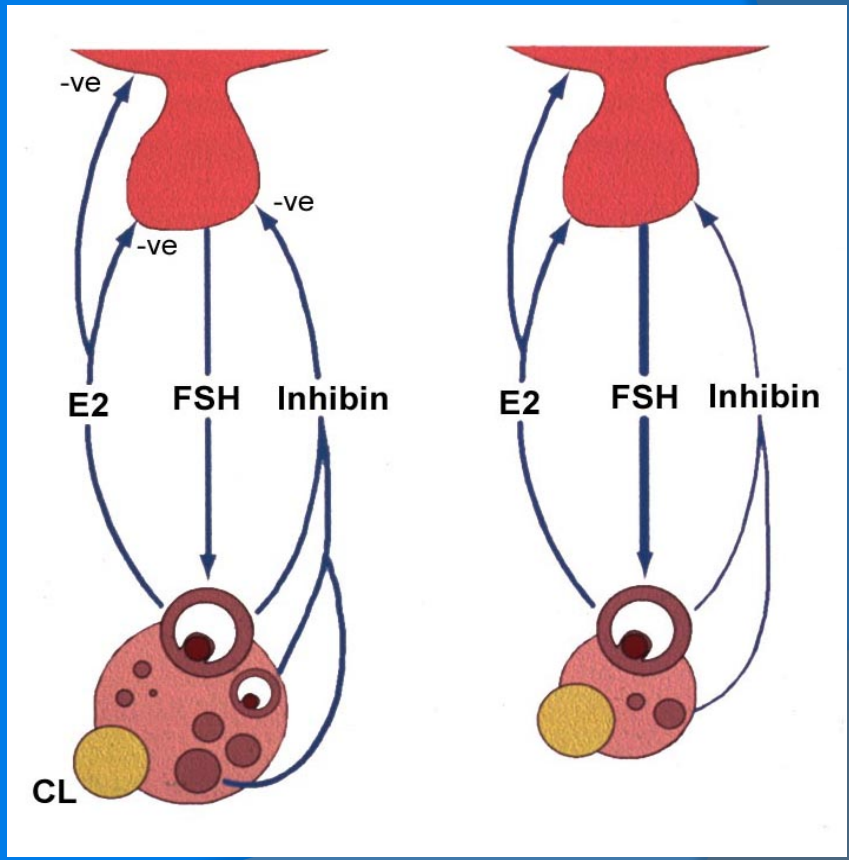
ESHRE, Lille, France.
10th May 2012

The Egg Store in Quito, Ecuador!



The Menstrual Cycle and role of The Anterior Pituitary





AMH (MIS)

In the 1940's Jost revealed the means of sexual differentiation.

Male characteristics must be **imposed** on the fetus by the testicular hormones - **testosterone** and **AMH**.

Testosterone virilizes the Wolffian ducts, urogenital sinus and external genitalia.

AMH induces **regression of Mullerian ducts**.

Without the actions of these hormones, the fetus becomes phenotypically female.

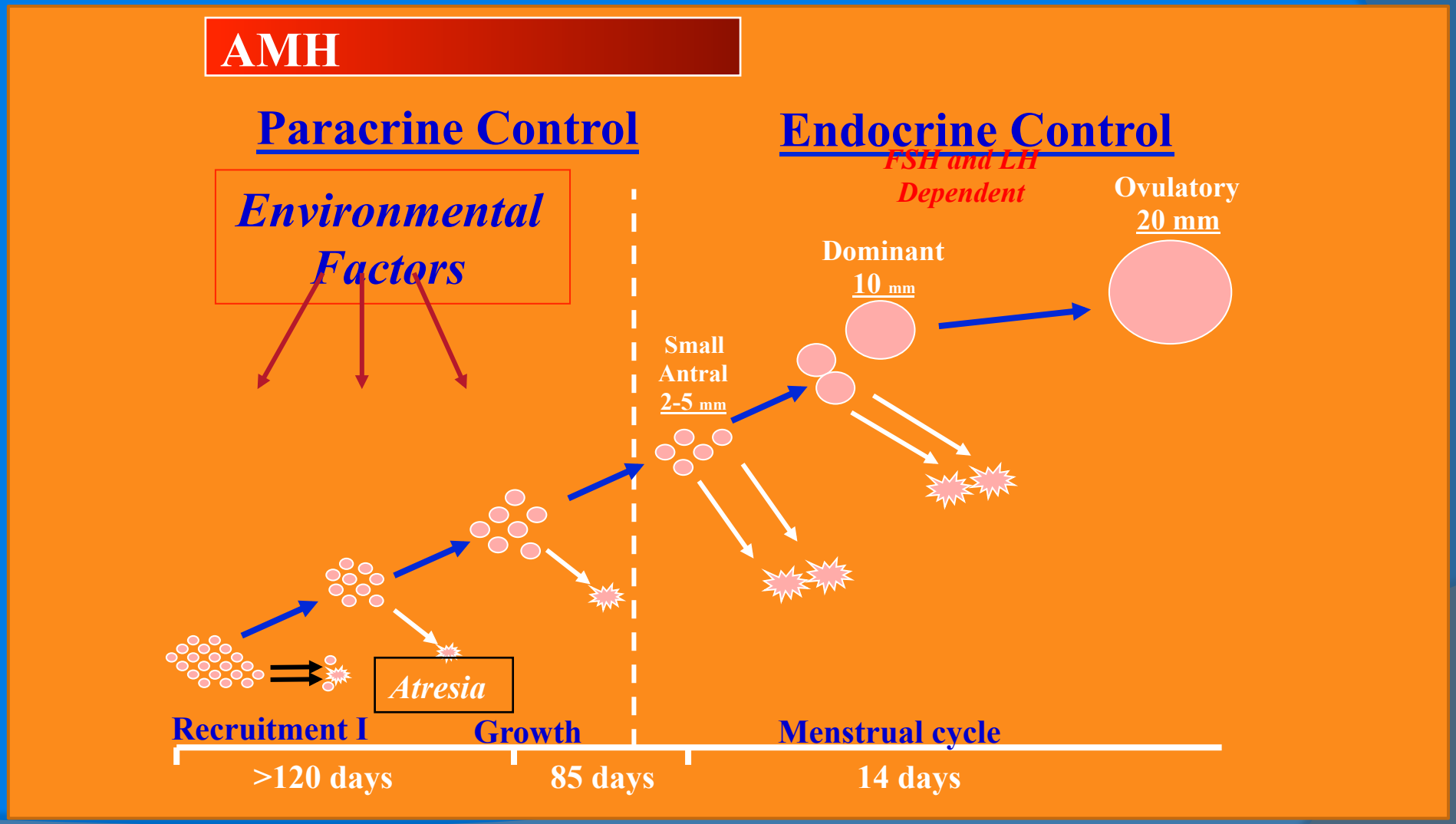
AMH is a 'hormone' in this regard.

It is also a growth factor – with autocrine and paracrine roles.

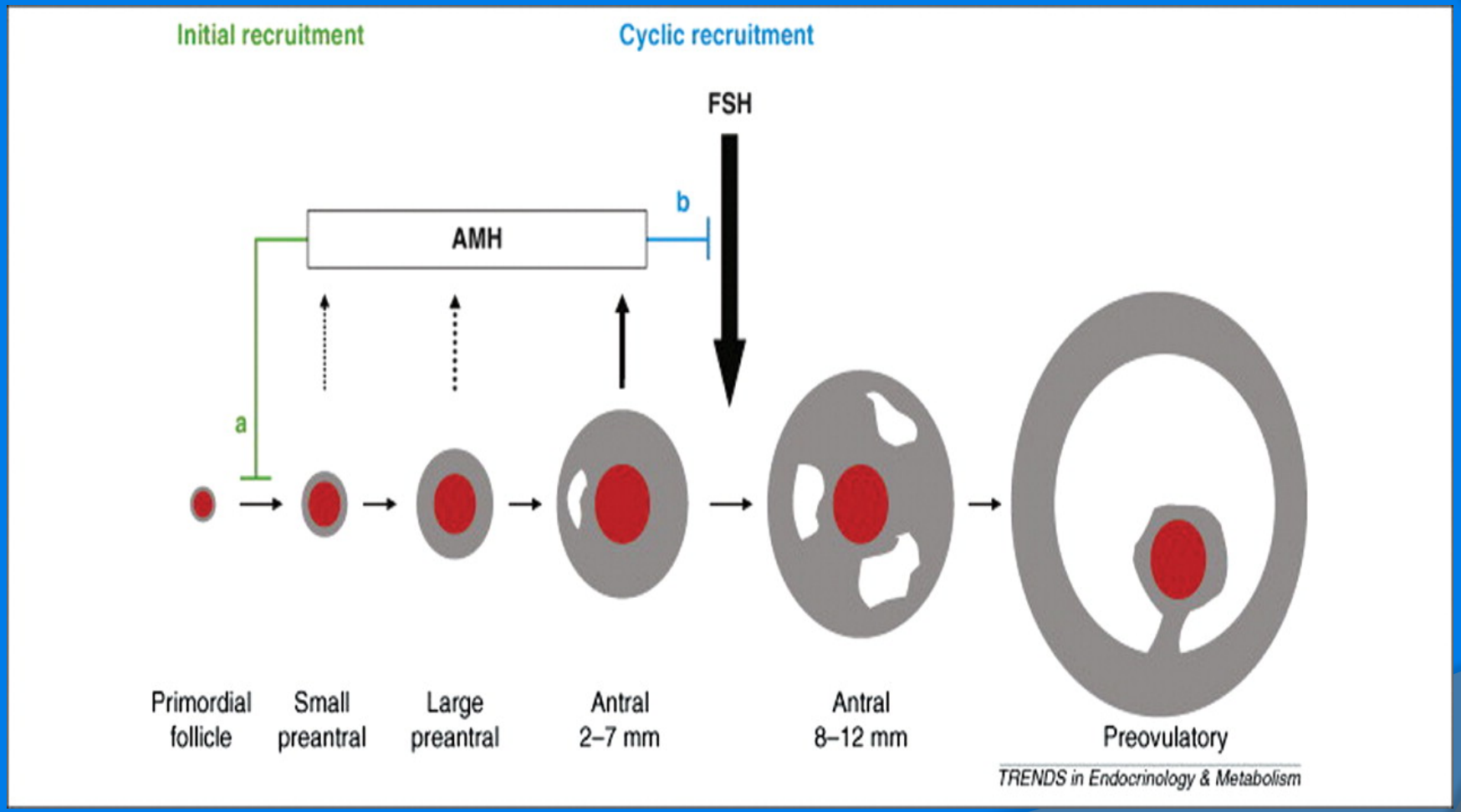
A member of the TGF β super-family of Growth Factors

- AMH is a product of the *immature* Sertoli cell in the male, and the **granulosa cells** of human ovarian follicles in the female.
- It operates through molecular pathways common to the TGF β family, with a specific **type II** receptor which dimerises and elicits internal messages through **SMADS 1,5,8** to effect control of nuclear gene transcription.

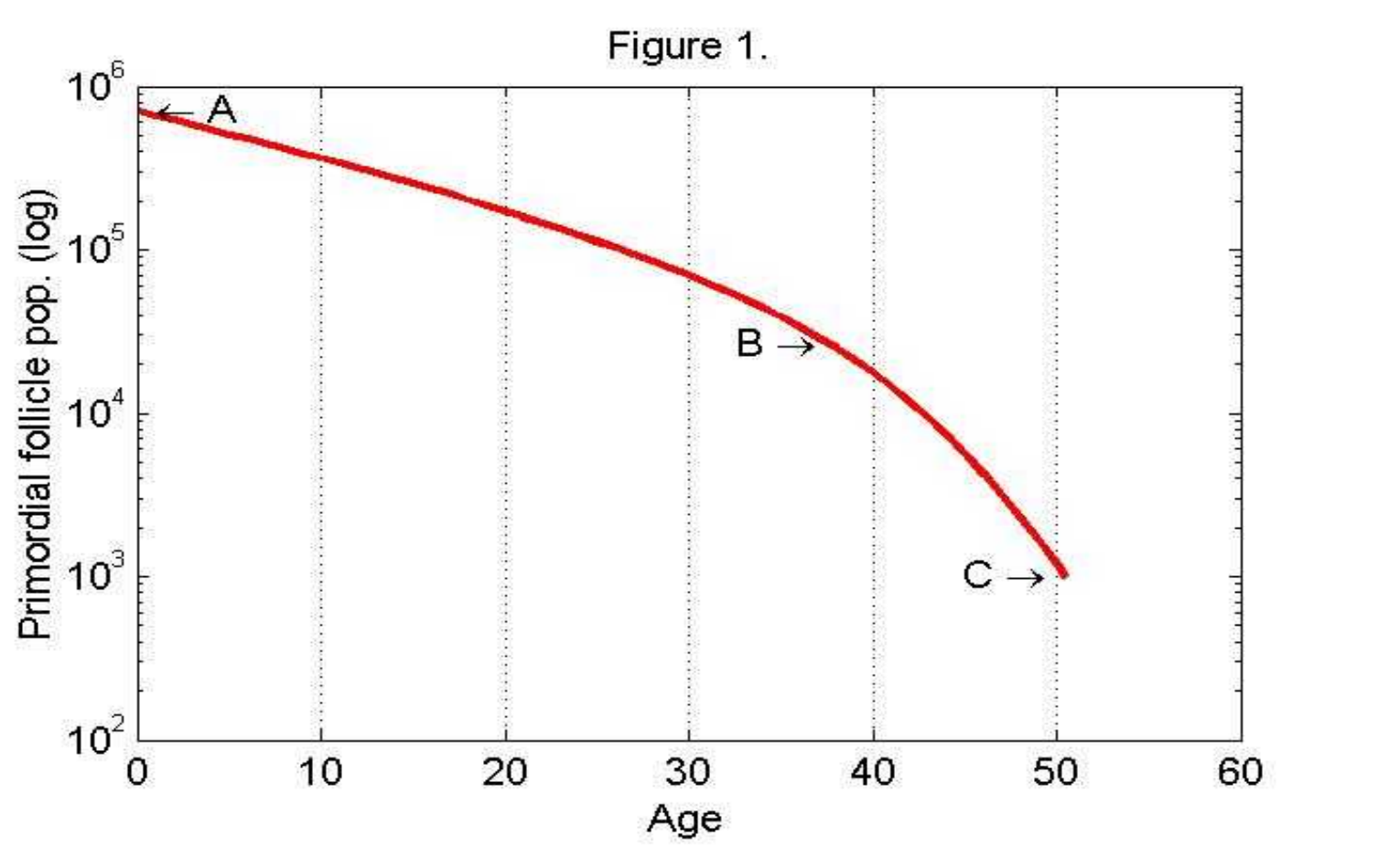
Follicular development in the adult



AMH and normal ovarian follicle development

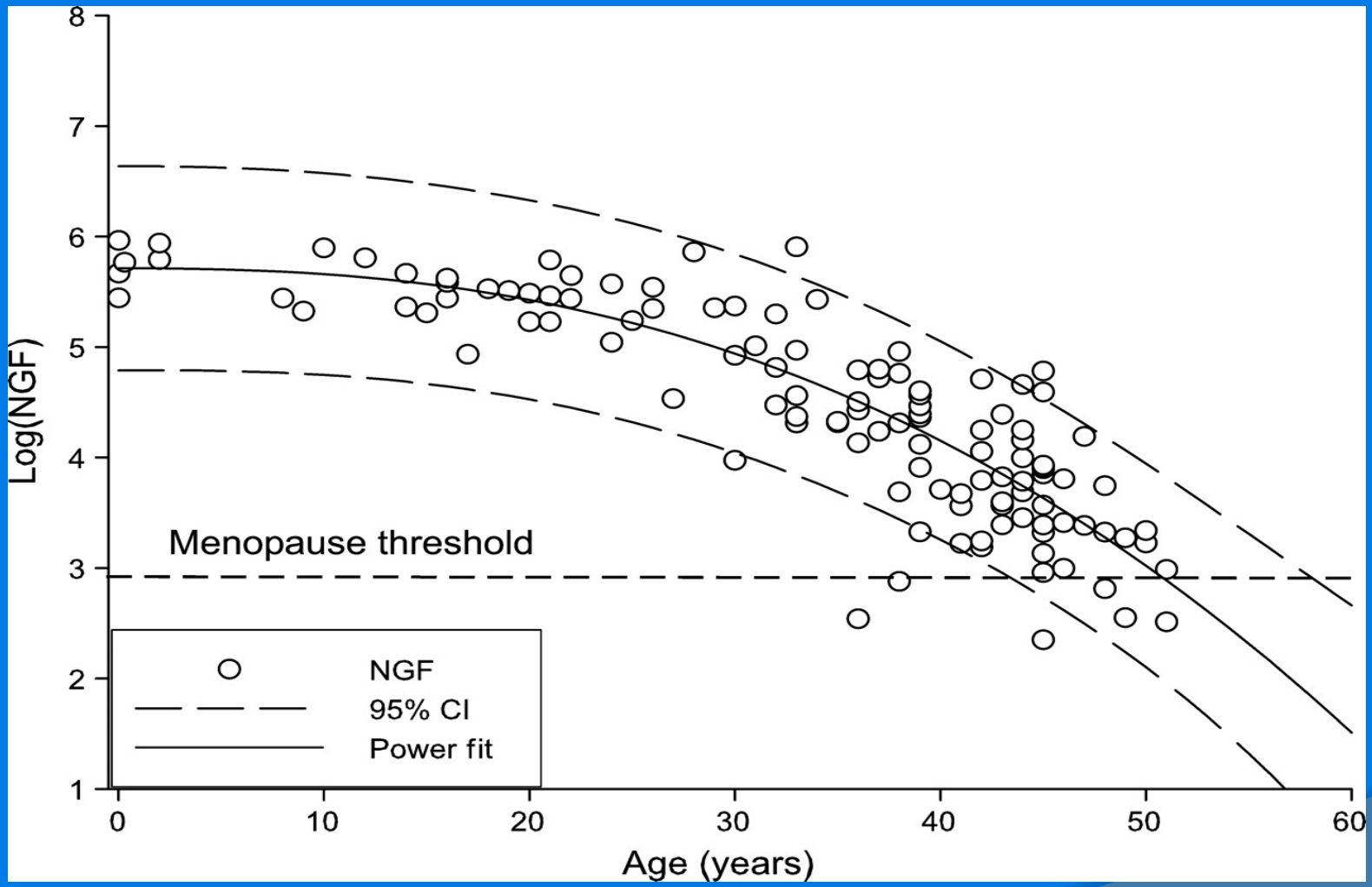


The Faddy-Gosden model of primordial follicle decline (birth-menopause)



Faddy MJ, Gosden RG (1996) A model conforming the decline in follicle numbers to the age of menopause in women. Human Reproduction 11: 1484–1486.

Power-model of human ovarian NGF decay



Hansen, K. R. et al. Hum. Reprod. 2008 23:699-708

Methodology

- Data aggregation
  - Systematic search for data sources from the literature
    - Tables, charts, descriptive statistics
  - Our own data – if available
- Data selection to create data set
  - Exclusion & Inclusion criteria (eg exclude infertile)
  - Homogeneous data set that approximates the healthy population for a wide range of ages.

Methodology

- Comparative analysis of biologically plausable models
  - goodness of fit (coefficient of determination: r^2)
  - minimise overfitting
    - too accurate to generalise to unseen data
    - too many peaks and troughs
  - minimise underfitting
    - not accurate enough
    - too few peaks and troughs

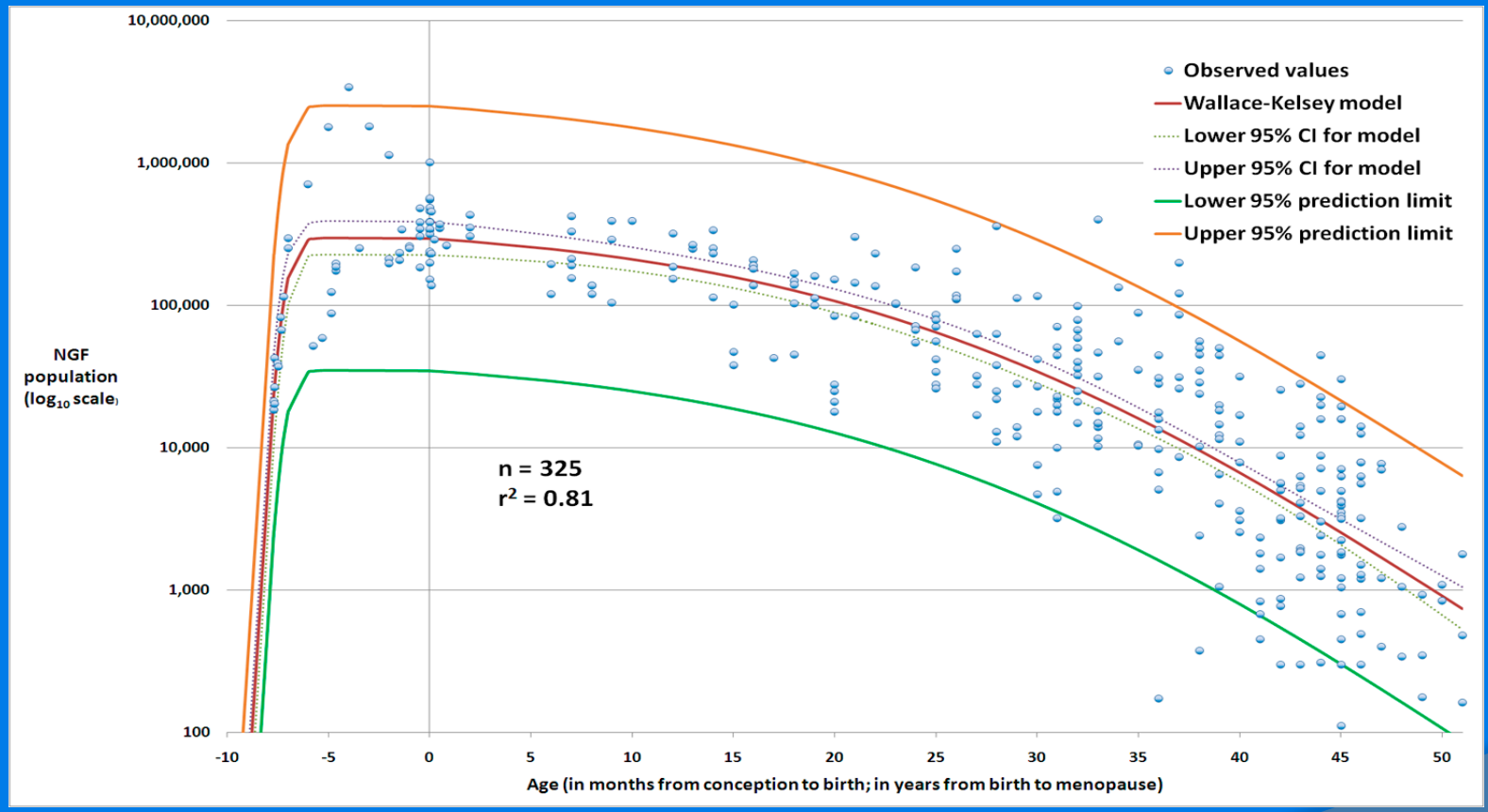
Methodology

- Model validation is important
  - the highest-ranked candidate could be a result of serendipity
  - small changes in the data could promote other candidates
- There are various techniques
  - k-fold: split the data into 10 equal subsets
  - train on 90%, test using 10%, for each choice of 10%
  - model validated if the prediction error is similar each time

Data set:
Eight quantitative histological studies

Study			Statistics			
Number	First author	Year	No. ovaries	Min. age	Max. age	Median age
1	Bendsen	2006	11	−0.6	−0.6	−0.6
2	Baker	1963	11	−0.6	7.0	−0.2
3	Forabosco	2007	15	−0.5	0.5	−0.3
4	Block	1953	19	−0.2	0.0	0.0
5	Hansen	2008	122	0.1	51.0	38.0
6	Block	1951	86	6.0	44.0	28.0
7	Gougeon	1987	52	25.0	46.0	39.5
8	Richardson	1987	9	45.0	51.0	46.0
Overall			325	−0.6	51.0	32.0

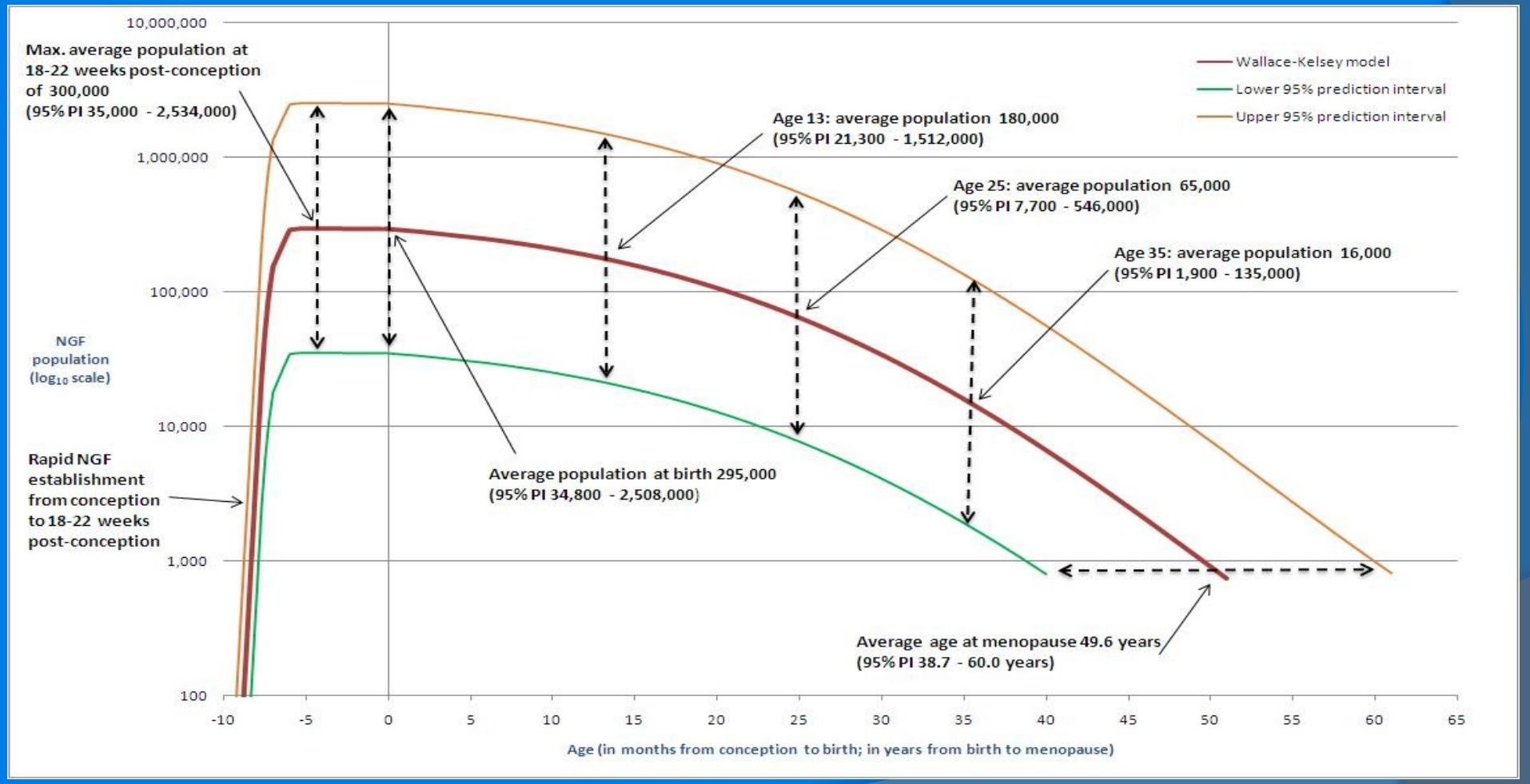
The Wallace-Kelsey Model
(Five parameter asymmetric double-Gaussian cumulative curve)



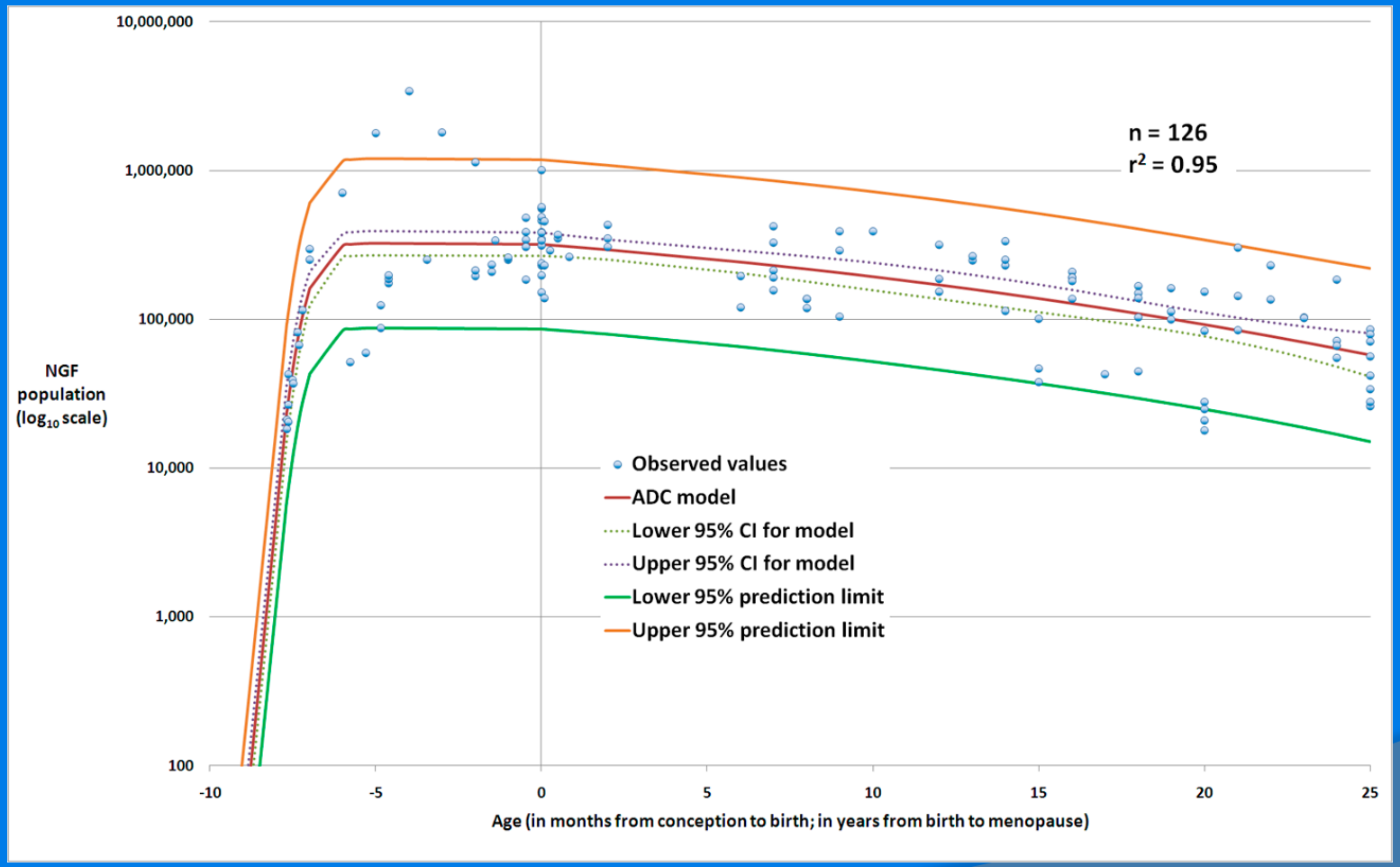
$$log_{10}(y) = \frac{a}{4}\left[1 + \mathrm{Erf}\left(\frac{x+b+\frac{c}{2}}{d\sqrt{2}}\right)\right]\left[1 - \mathrm{Erf}\left(\frac{x+b-\frac{c}{2}}{e\sqrt{2}}\right)\right]$$

Wallace &Kelsey (2010) PloS ONE

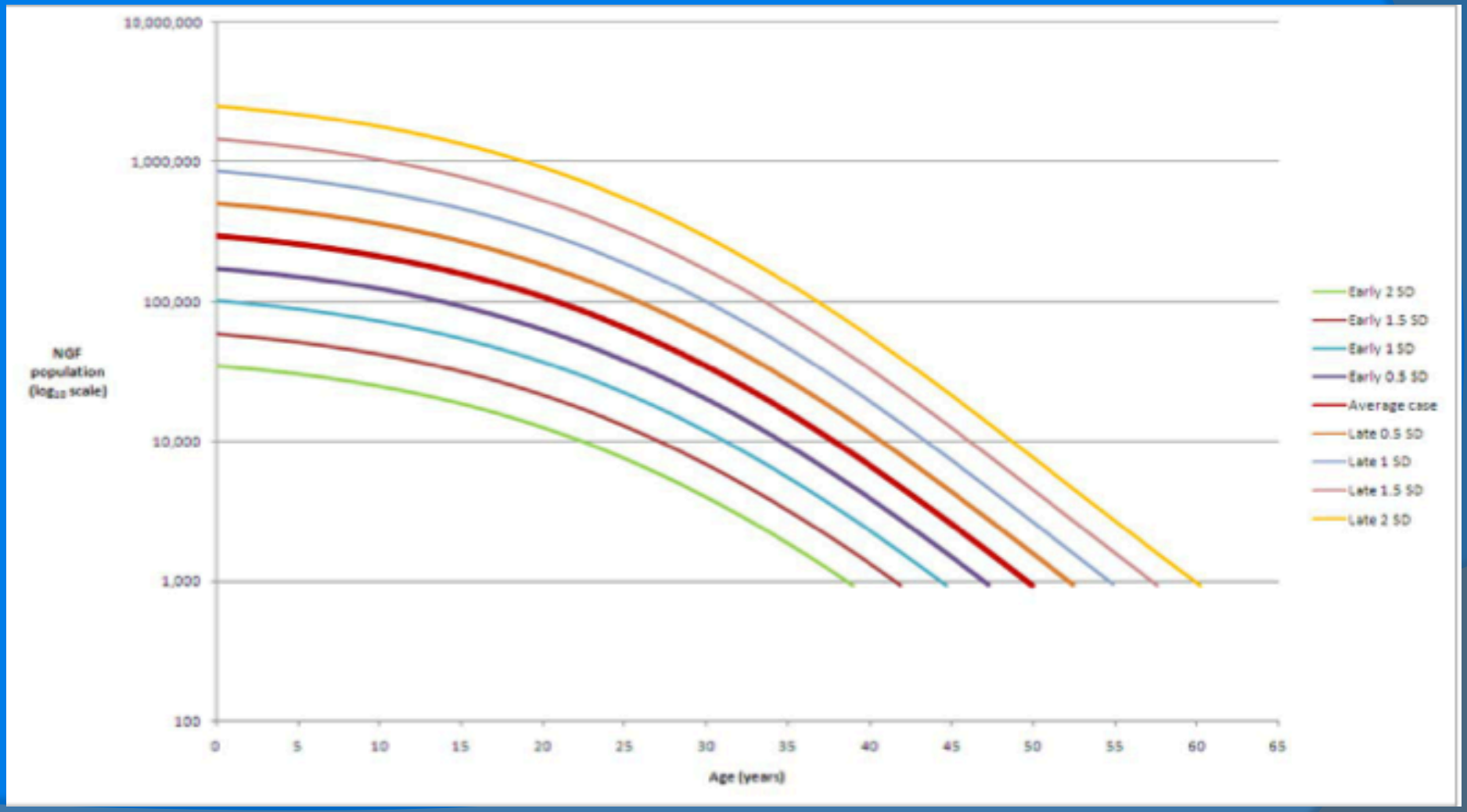
Ovarian reserve: Conception to Menopause (NGF population)



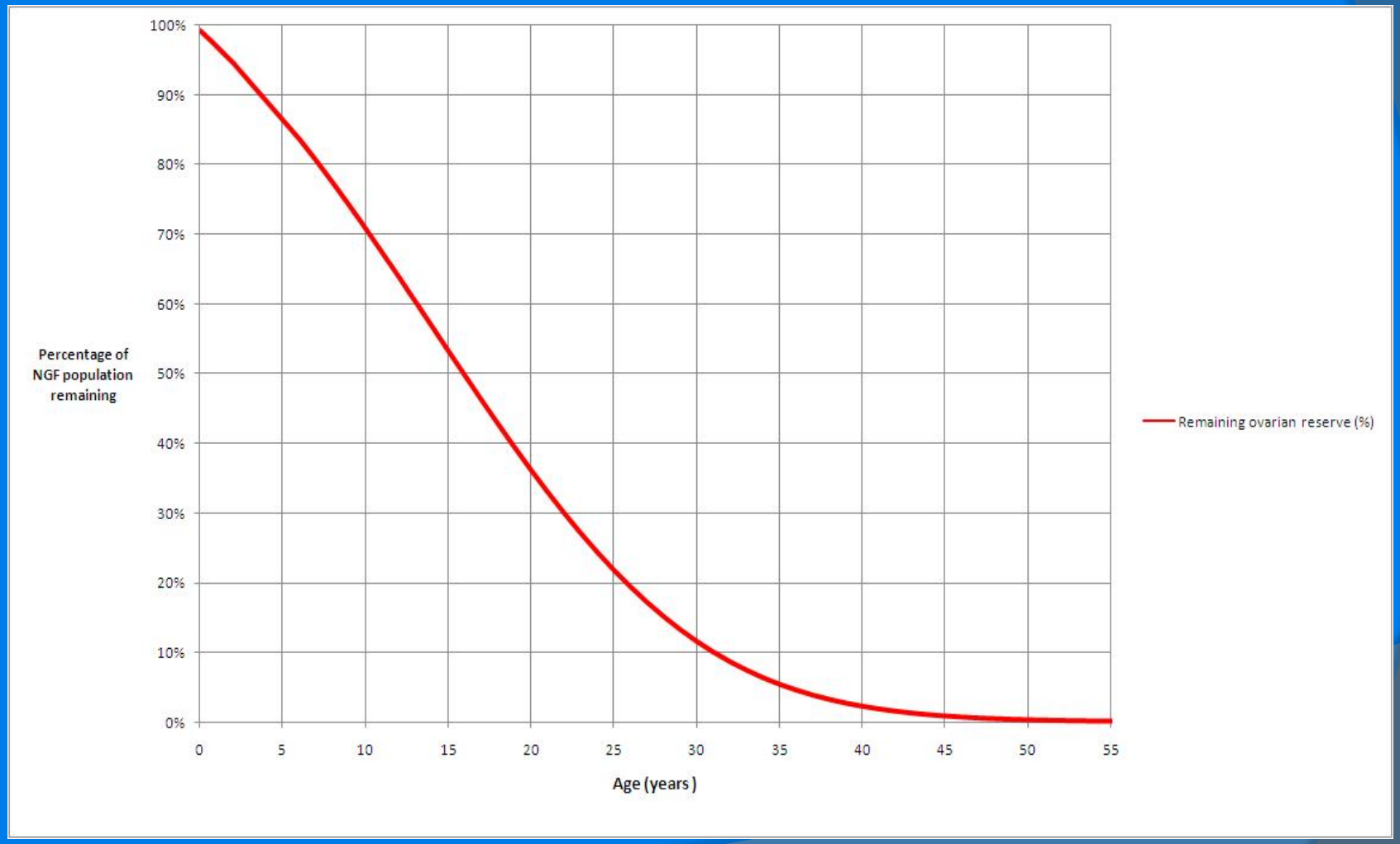
Wallace &Kelsey (2010) PloS ONE


10,000,000
1,000,000
100,000
10,000
1,000
100
NGF population (log_{10} scale)
n = 126
r^2 = 0.95
Observed values
ADC model
Lower 95% CI for model
Upper 95% CI for model
Lower 95% prediction limit
Upper 95% prediction limit
-10
-5
0
5
10
15
20
25
Age (in months from conception to birth; in years from birth to menopause)

A hypothetical link between ovarian reserve and age at menopause.

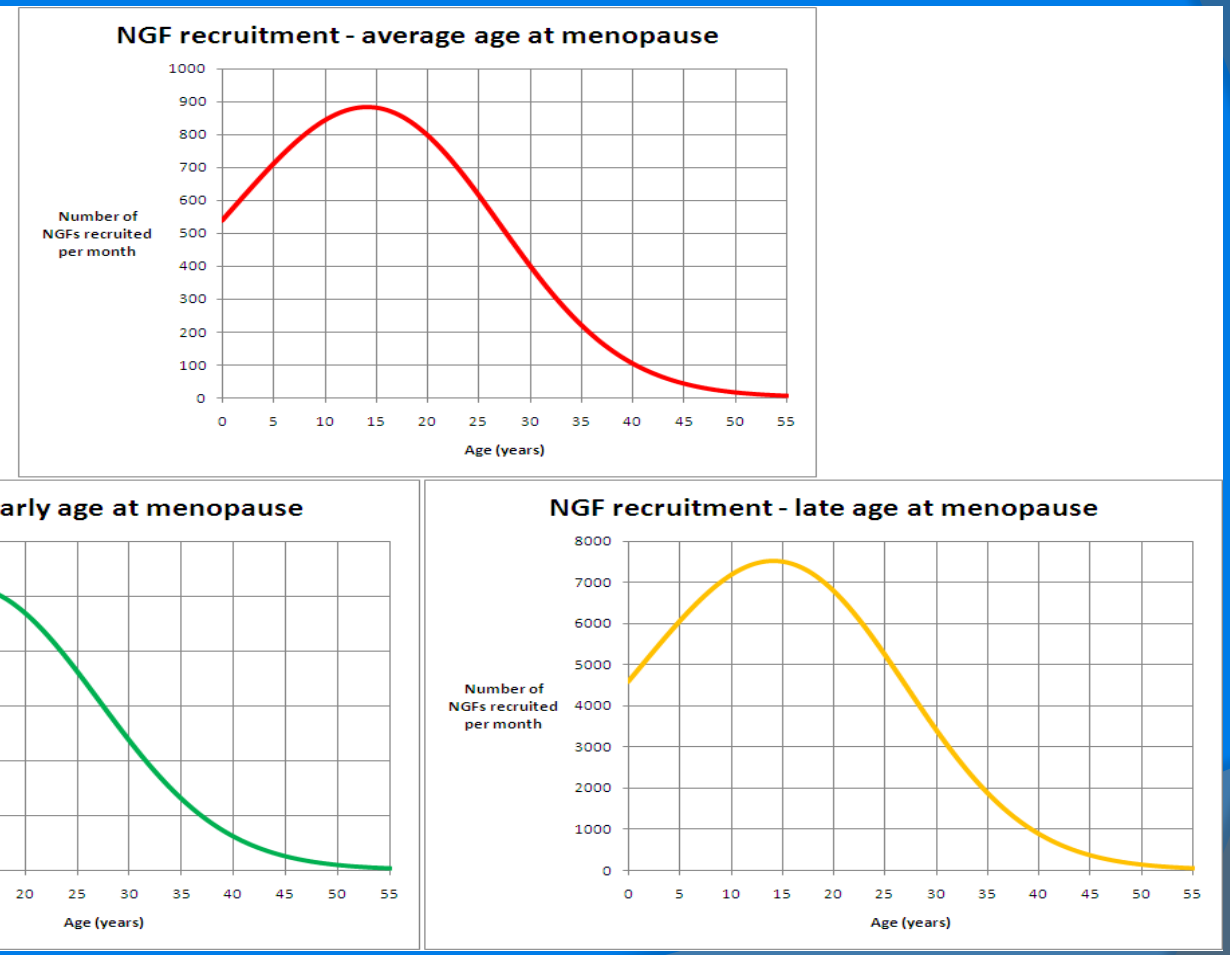


Percentage of NGF population remaining with increasing age



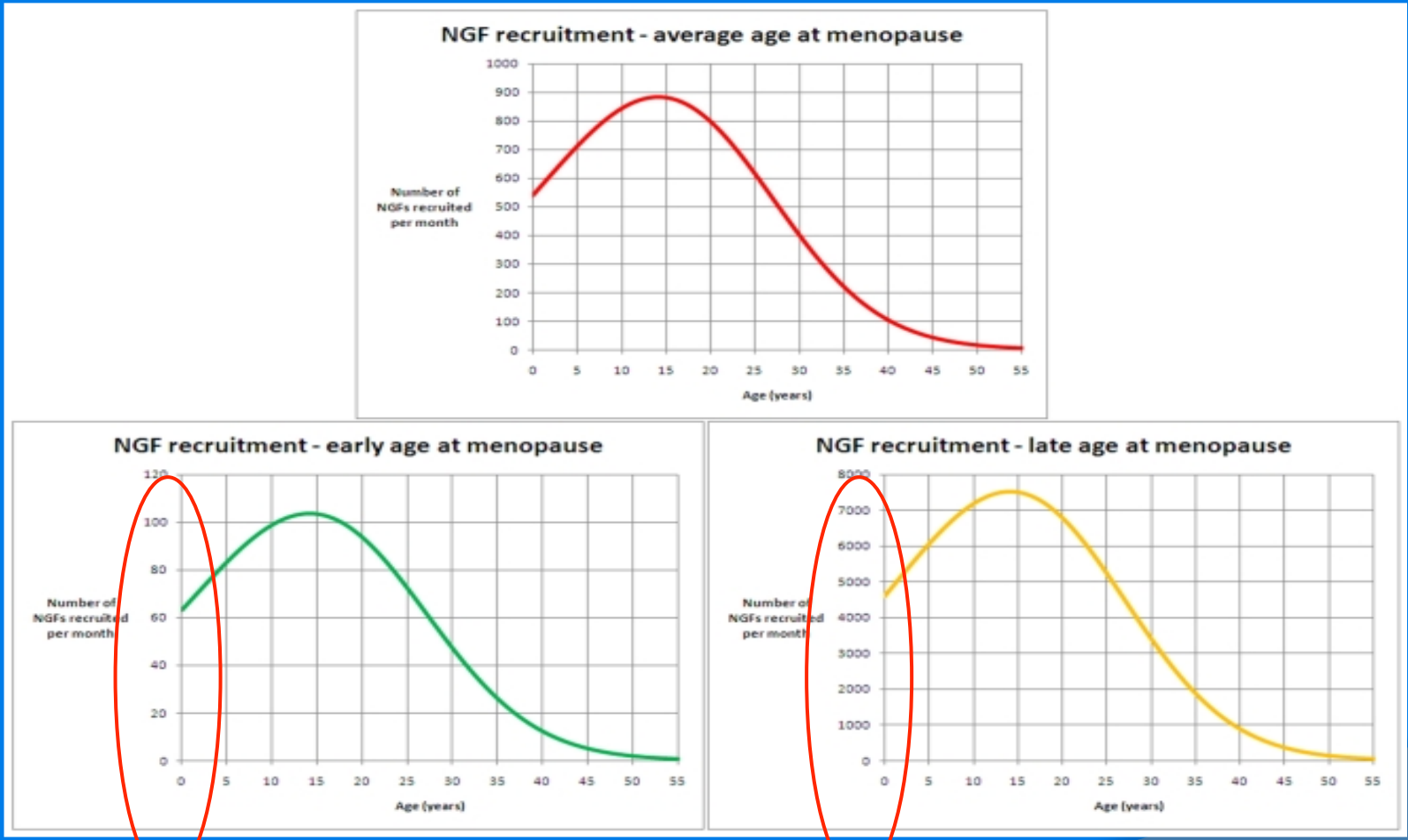
Wallace &Kelsey (2010) PloS ONE

Follicular Recruitment from the Pool according to age of menopause



Wallace & Kelsey, 2010

Follicular Recruitment from the Pool according to age of menopause



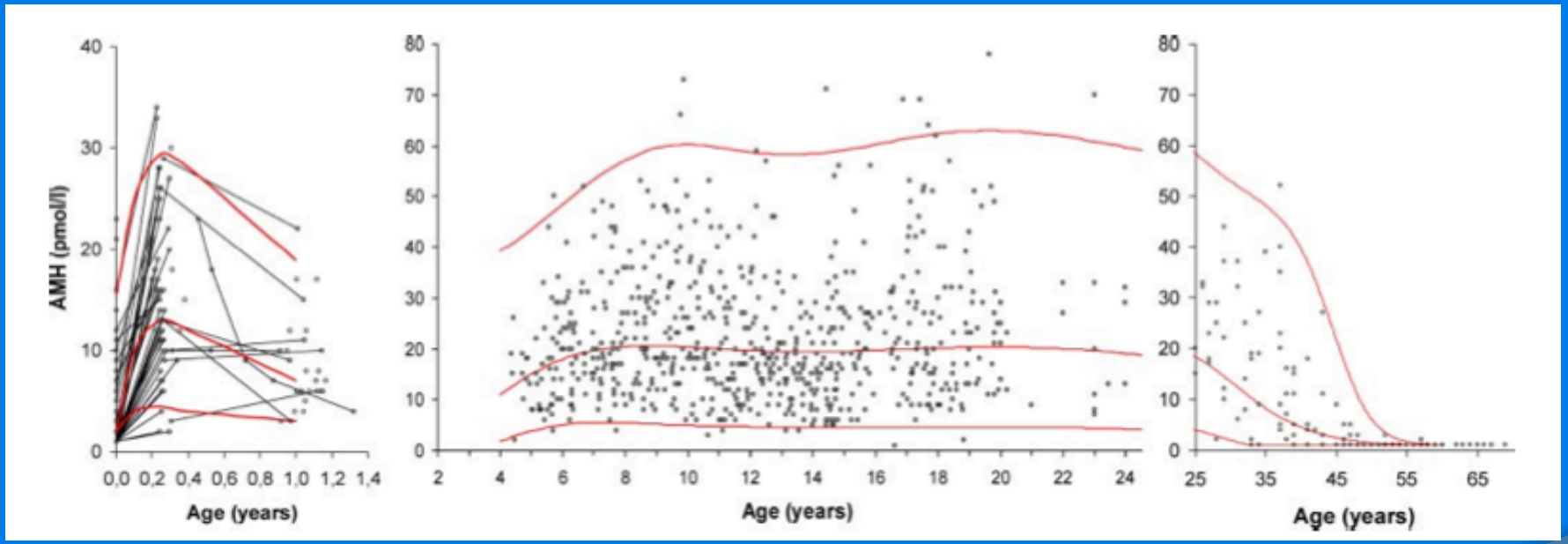
There is close to 100 fold difference in recruitment between the early and late menopause groups

Wallace & Kelsey, 2010

Prediction of ovarian reserve

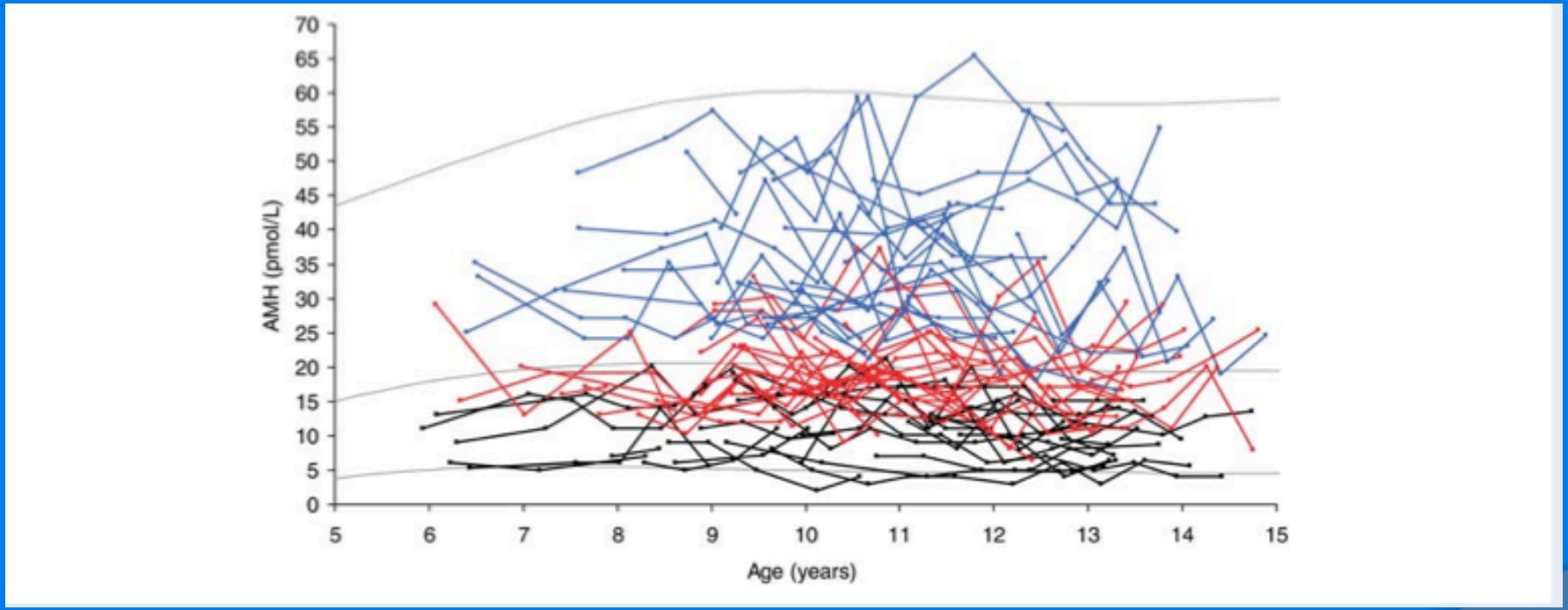
* Anti Mullerian Hormone (AMH) is an important product of the adult ovary, produced by the granulosa cells of small growing follicles
* AMH has little variation across and between menstrual cycles
* AMH is the best currently available marker of the number of small-growing follicles in the ovary

Serum AMH in 926 healthy infants, girls, adolescents, and adult women



Hagen C et al.
J Clin Endocrinol Metab, 2010

Longitudinal serum levels of AMH (pmol/l) in 85 healthy girls and adolescents (n=504)



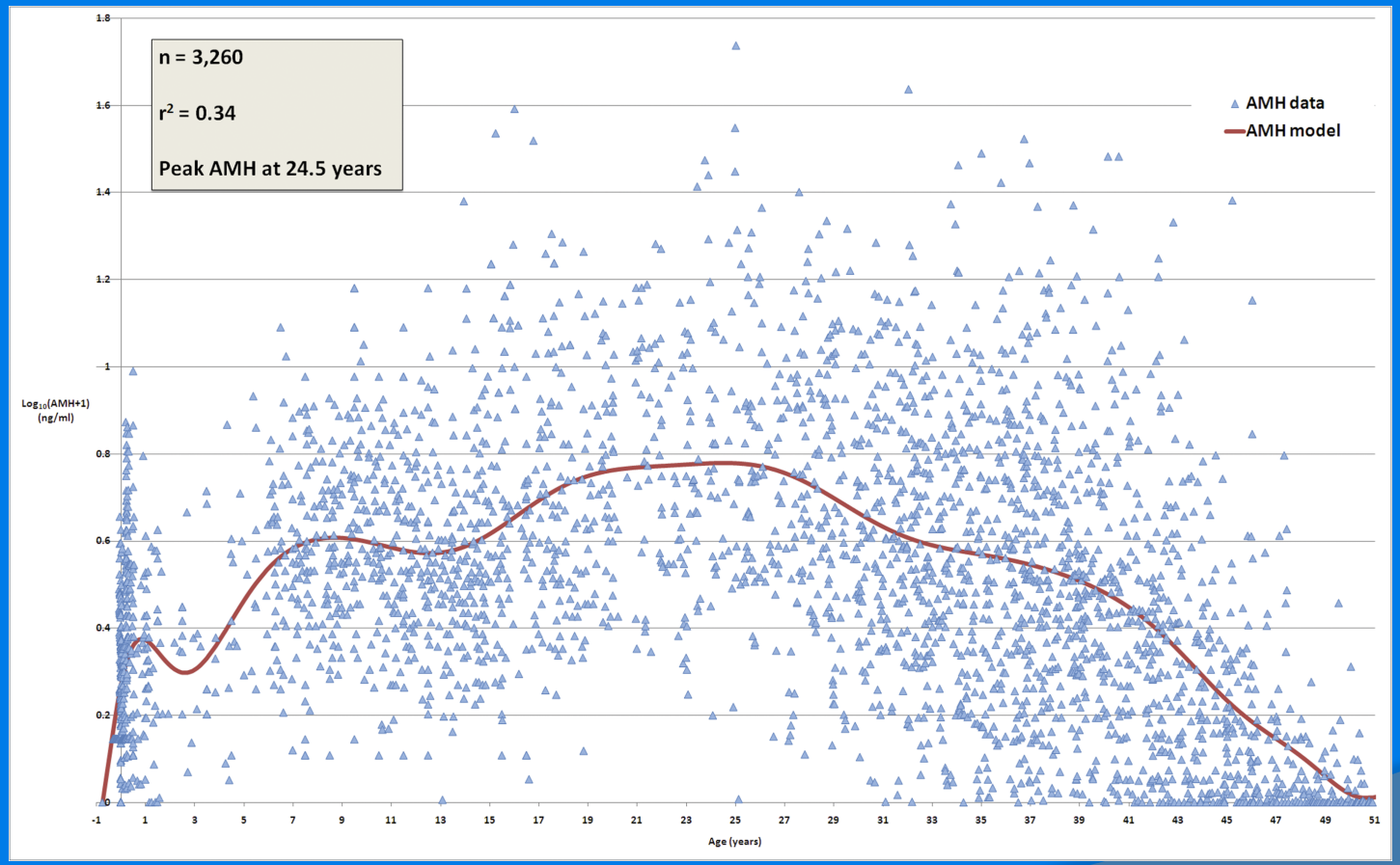
Hagen C et al. Human Reproduction, Vol.27, No.3 pp. 861–866, 2012

AMH Data set

Ref.	1st Author	Data	Assay	*n*	Average age	Age range	Det. lim.	Intra CV	Inter CV
[35]	Soto	Graph	IBC	58	30.3 (mean)	±8.7 SD	0.10	5.3	8.7
[38]	Guibourdenche	Graph	IBC	192	NS	−0.3–1.0	0.30	5.3	8.7
[39]	Hudecova	Graph	IBC	64	46.3 (mean)	±6.4 SD	0.70	12.3	12.3
[40]	Mulders	Graph	IBC	82	29.9	19.6–35.6	NS	5.0	8.0
[41]	Pastor	Graph	IBC	42	NS	18.0–50.0	0.10	5.3	7.8
[42]	Piltonen	Graph	IBC	44	31.6 (mean)	21.0–44.0	NS	5.1	6.6
[20]	van Rooij	Graph	IBC	162	NS	25.0–46.0	0.05	5.0	8.0
[43]	Laven	Graph	IBC	41	NS	20.0–36.0	0.05	5.0	8.0
[19]	de Vet	Graph	IBC	82	29.0	±4.0 SD	0.05	5.0	8.0
[44]	Knauf	Graph	IBC	83	34.2 (mean)	±3.4 SD	0.03	11.0	11.0
[45]	Lee	Graph	IBC	225	NS	0.0–51.0	0.50	9.0	15.0
[36]	La Marca	Graph	IBC	24	44.0 (mean)	±2.8 SD	0.24	5.0	8.0
[29]	Hagen	Graph	IBC	891	NS	0.0–68.0	0.03	7.8	11.6
[46]	van Beek	Graph	DSL	82	29.0	20.0–35.0	NS	5.0	15.0
[47]	Sanders	Graph	DSL	43	24.1 (mean)	0.1–51.0	0.01	NS	11.4
[34]	van Disseldorp	Graph	DSL	144	37.9 (mean)	25.0–46.0	0.03	11.0	11.0
[48]	Tehrani	Graph	DSL	267	27.1	16.0–44.0	0.01	5.2	9.1
[49]	Dorgan	Graph	DSL	204	44.7 (mean)	33.3–54.7	0.06	8.0	8.0
[30]	Ahmed	Raw	DSL	128	8.5	0.5–16.5	0.50	8.0	8.0
[25]	Nelson	Raw	DSL	441	36.1	21.9–47.8	0.03	3.4	8.6
	Total IBC			1,990	15.8	−0.3–68.0			
	Total DSL			1,309	35.4	0.2–54.7			
	Total *n*			3,299	34.0	−0.3–68.0			
	Censored total n			**3,260**	**28.3**	**−0.3–54.3**			

A validated model of serum anti-Mullerian hormone from conception to menopause

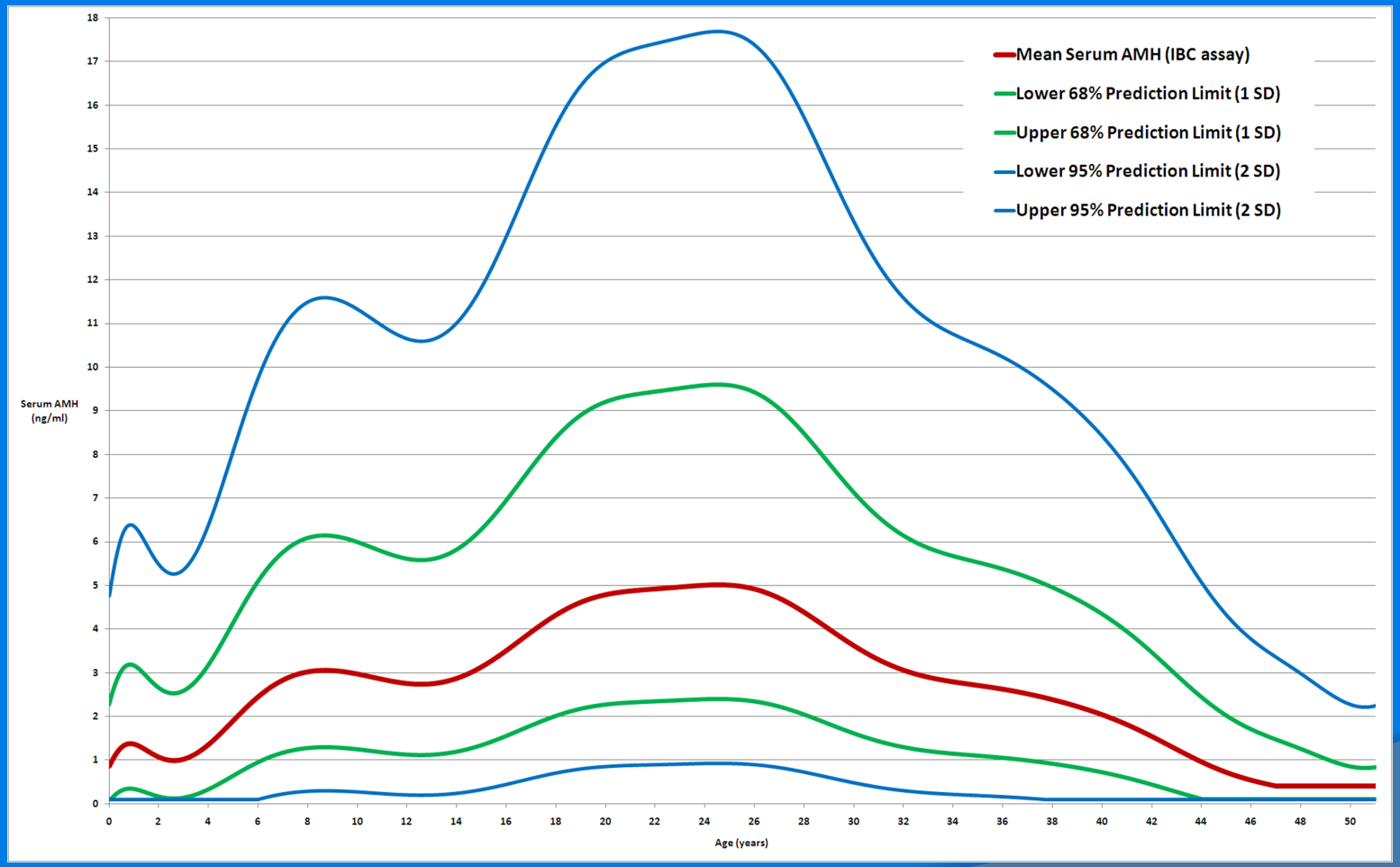
(a single data set of healthy females (n=3260) from twenty different sources)



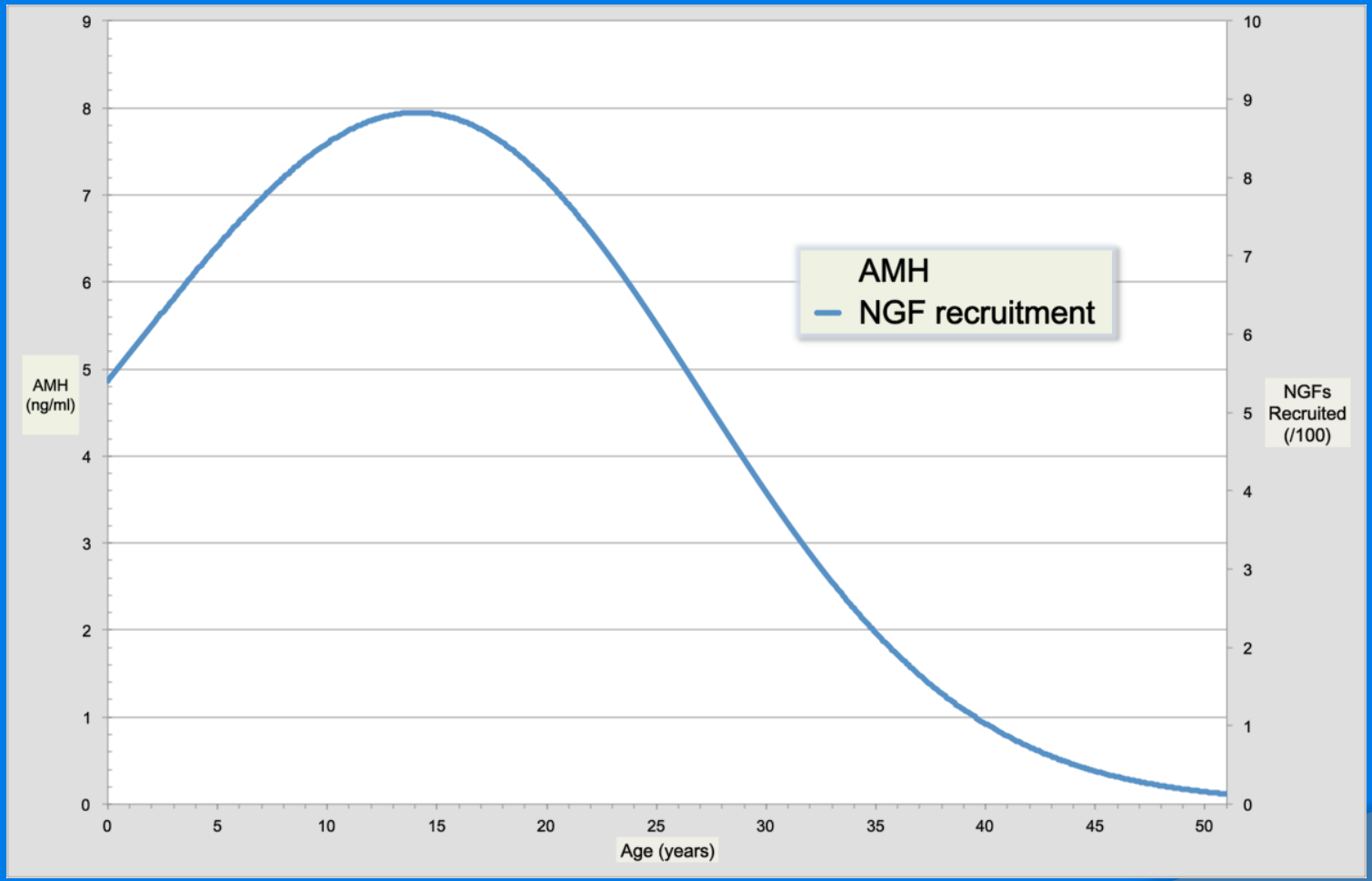
Kelsey et al. PLoS ONE 2011

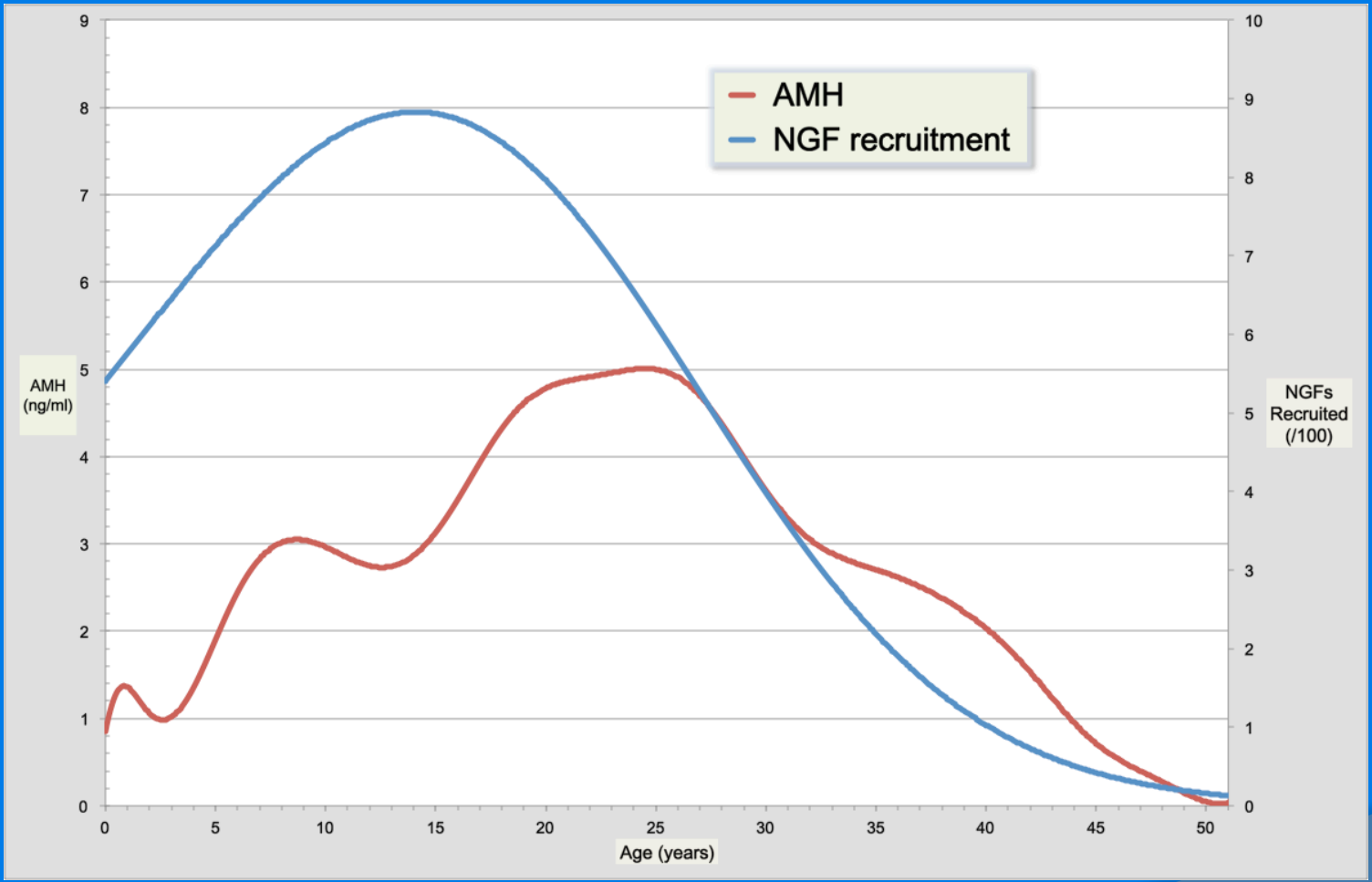
AMH: Normogram from birth to menopause

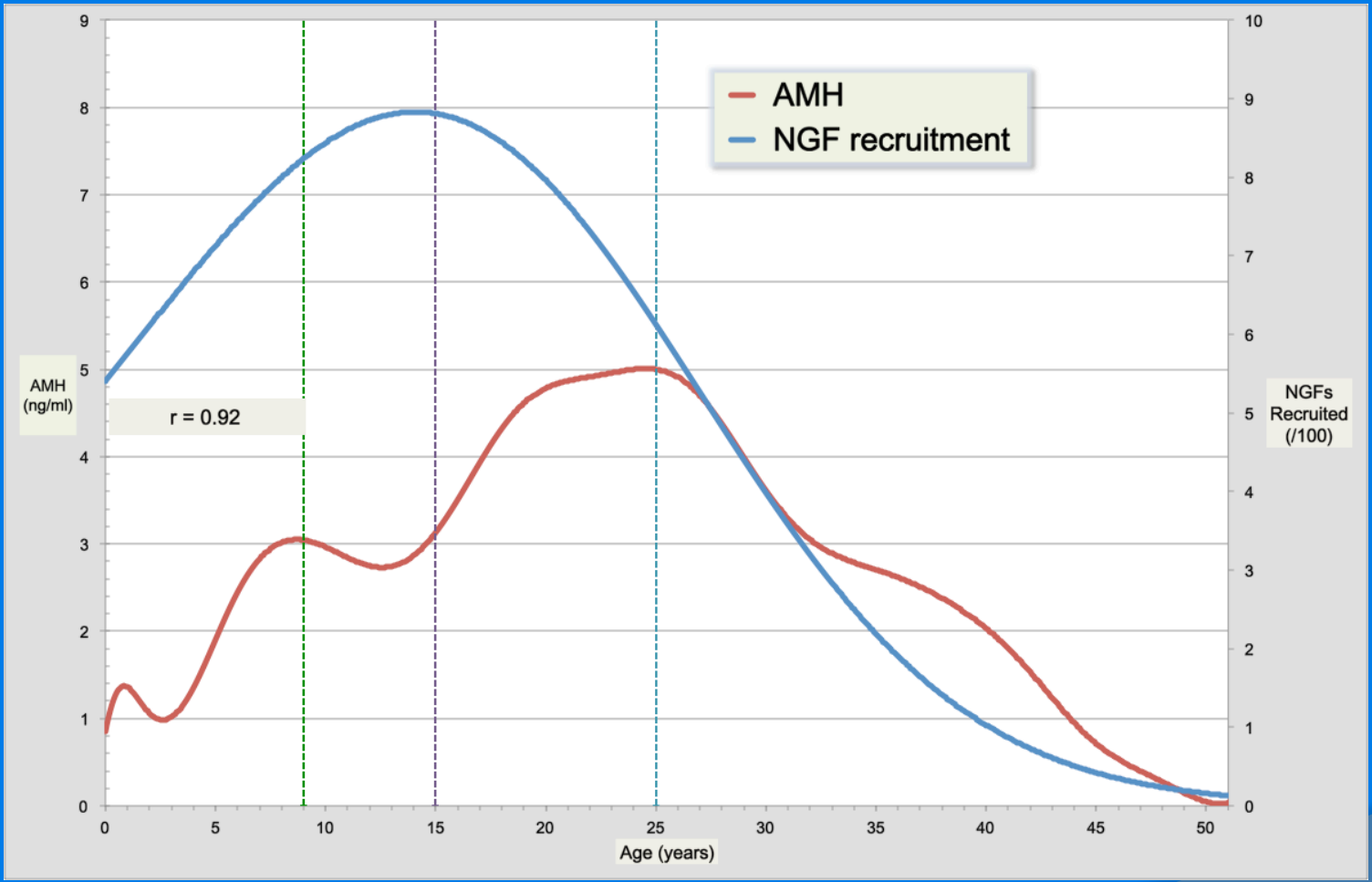
The green and blue lines are the 68% and 95% prediction limits for the model

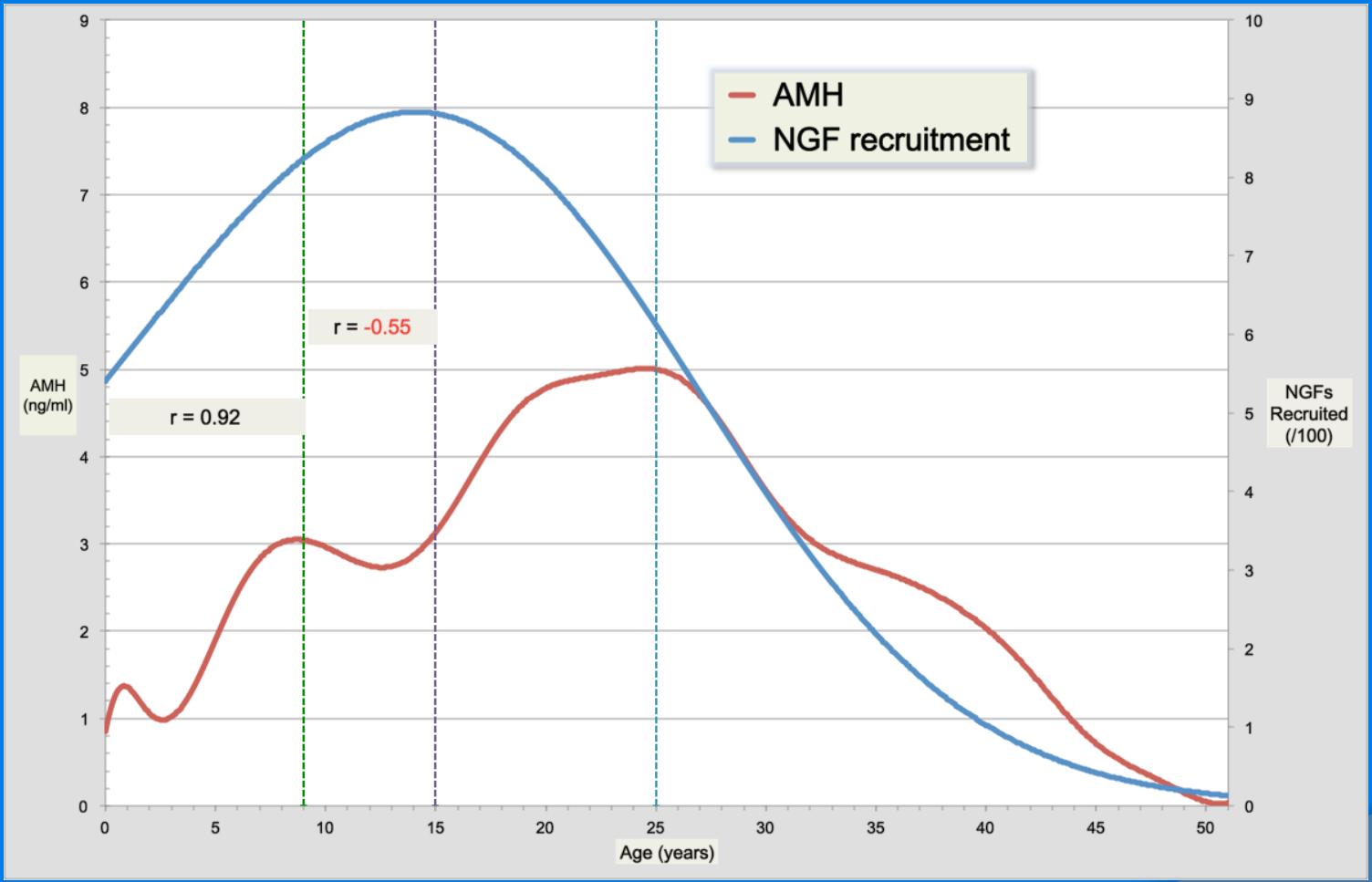


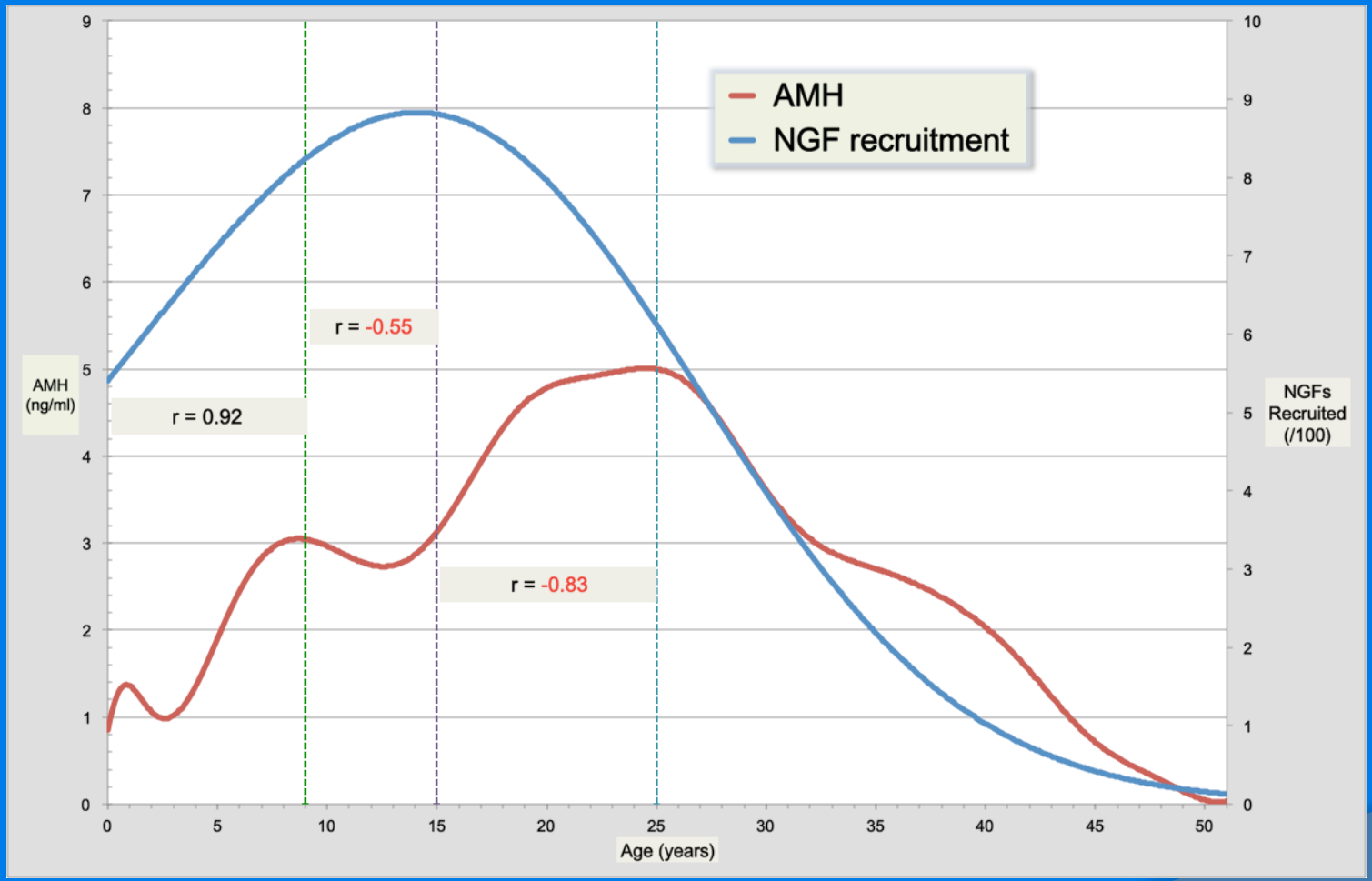
Kelsey et al. PLoS ONE 2011

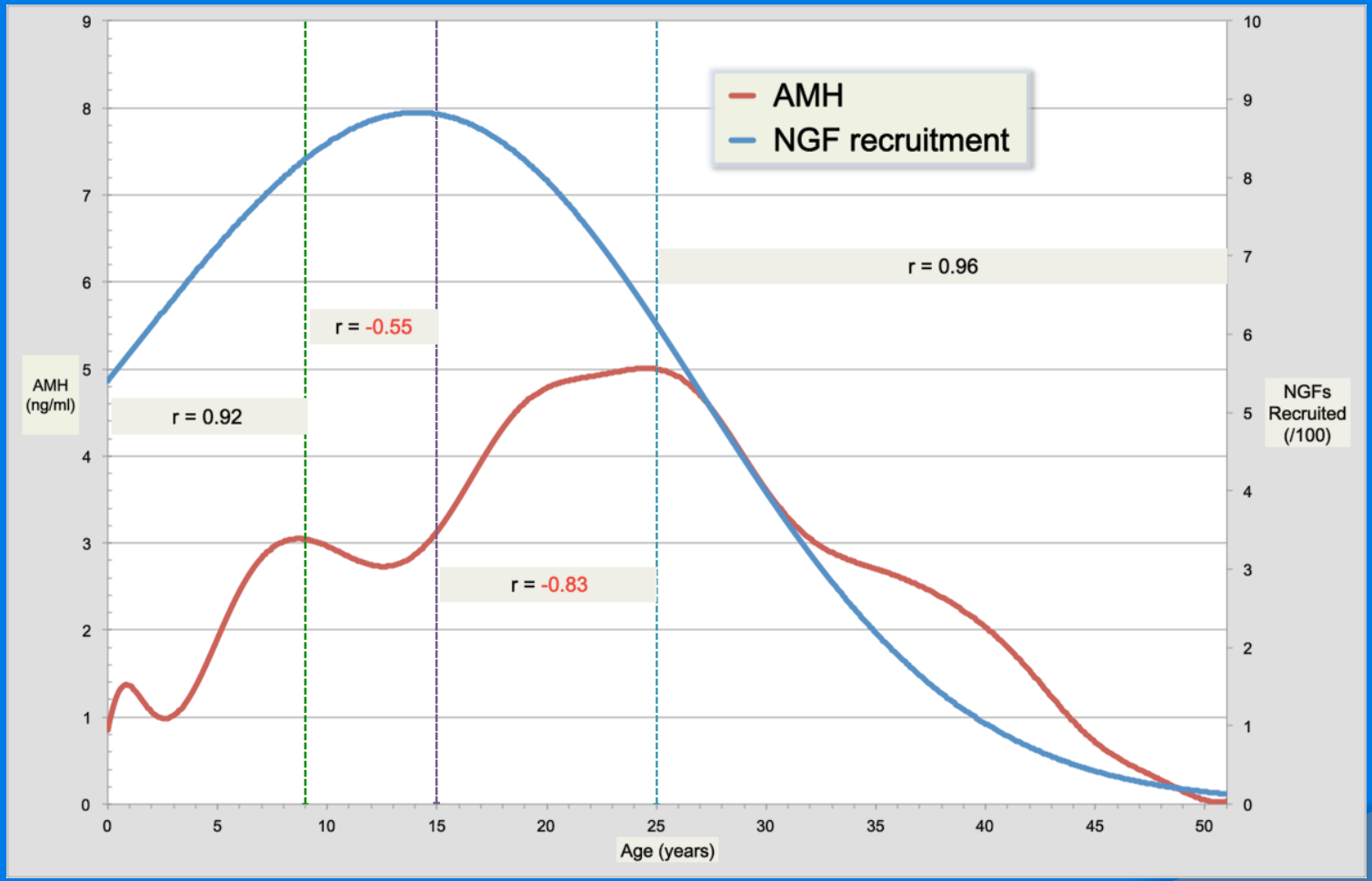

AMH
NGF recruitment
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50


AMH
NGF recruitment
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50


AMH
NGF recruitment
r = 0.92
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50

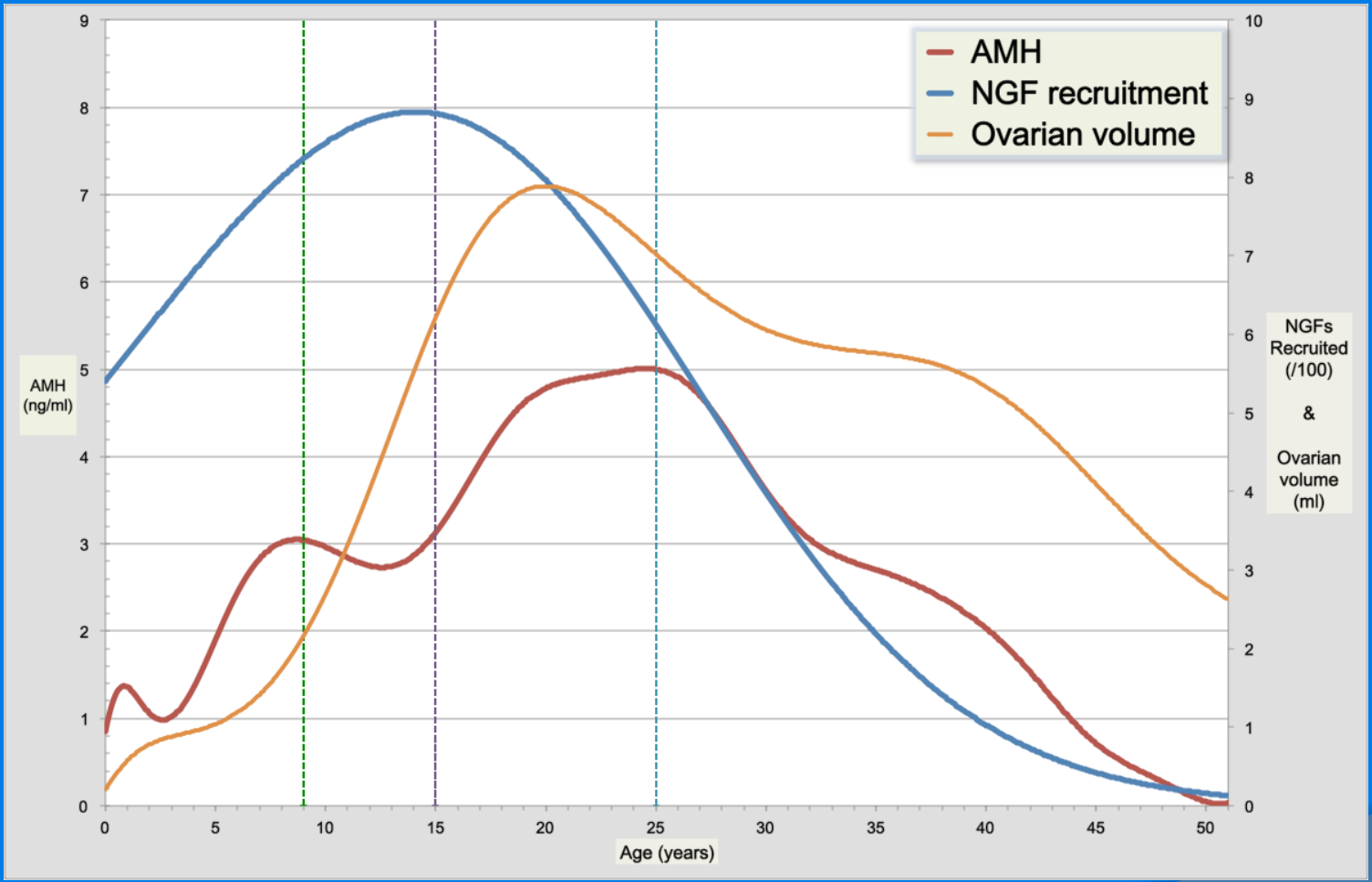

AMH
NGF recruitment
r = -0.55
r = 0.92
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7
8
9
10


AMH
NGF recruitment
r = -0.55
r = 0.92
r = -0.83
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
5
10
15
20
25
30
35
40
45
50
1
2
3
4
6
7
8
9


AMH
NGF recruitment
r = 0.92
r = -0.55
r = -0.83
r = 0.96
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
5
10
15
20
25
30
35
40
45
50
1
2
3
4
6
7
8
9

Relationship between AMH and Follicular recruitment

- Pre-puberty: Strong positive correlation (r = 0.92). AMH and follicular recruitment increasing
- Pubertal: Moderate negative correlation (r = -0.55). AMH falls as follicular recruitment continues to rise (Transition Phase)
- Post–pubertal (15 - 25): Strong negative correlation (r= -0.83). AMH rises as Follicular recruitment falls.
- Post Age 25 years: Very Strong positive correlation (r=0.96). AMH level is a good surrogate marker of declining ovarian reserve


AMH
NGF recruitment
Ovarian volume
AMH (ng/ml)
NGFs Recruited (/100) & Ovarian volume (ml)
Age (years)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7
8
9
10

Acknowledgements

- Tom Kelsey
- Richard Anderson
- Phoebe Wright
- Scott Nelson
- Richard Fleming

THANK YOU