Antral Follicle Count
and ovarian reserve
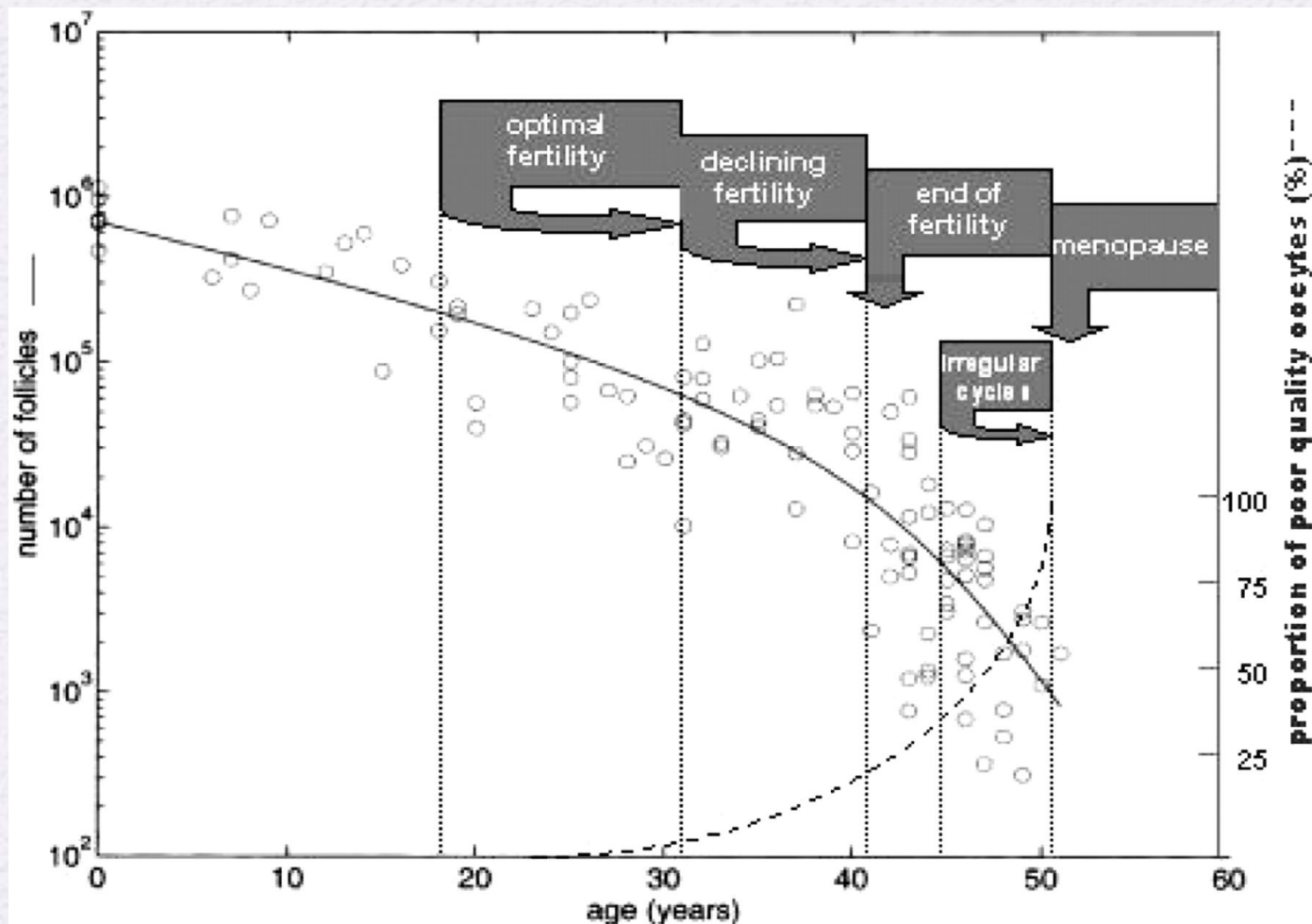
Candido Tomás, LT

AVA Klinikka, Tampere

Follicle development

adapt. **McGee & Hsueh Endocr Rev 2000**
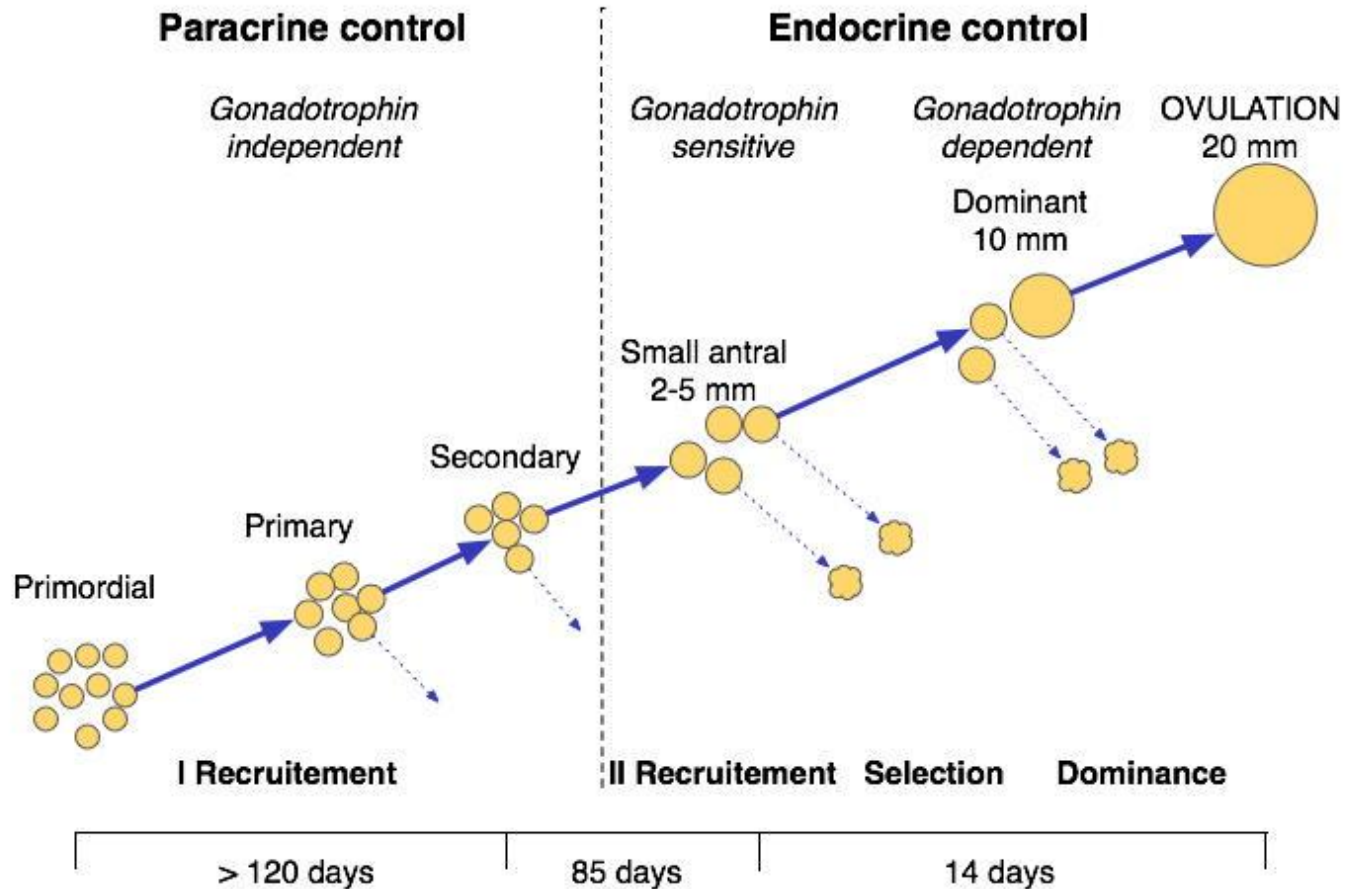
Decline of ovarian pool

de Bruin and te Velde (2004)

Ovarian Reserve

- Age-related decline in female reproductive function is due to:
  - Reduction of ovarian follicle pool
  - Quality of oocytes

- High variability!

- **Potential of ovarian reserve tests :**
  - Prediction of spontaneous pregnancy
  - Prediction of response to ovarian stimulation
  - Prediction of the outcome of IVF: live births
  - Prediction of time of menopause

Optimizing IVF treatment

- **The assessment of OR can be considered normal:**
  - after stimulation with gonadotrophins will result in 8–10 follicles
  - retrieval of a similar number of healthy oocytes
  - In this situation, the chances of producing a live birth through IVF are considered optimal

    Fasouliotis et al., 2000

  - Poor response: 2-30% (Hendriks et al. 2005)

Ovarian reserve tests

- **Biochemical markers**
  - Basal FSH
  - Inhibin B
  - AMH
  - Other tests (CC-challenge test, etc)
  - …

- **Ultrasound parameters**
  - Antral Follicle Count (AFC)
  - Ovarian volume
 - Ovarian blood flow

REPRODUCTIVE ENDOCRINOLOGY

Antimüllerian hormone serum levels: a putative marker for ovarian aging

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Anti-Müllerian Hormone

- Independent of menstrual cycle

- Reflects the ovarian reserve

- Correlated with other markers (AFC)

- Useful in various ovarian dysfunctions
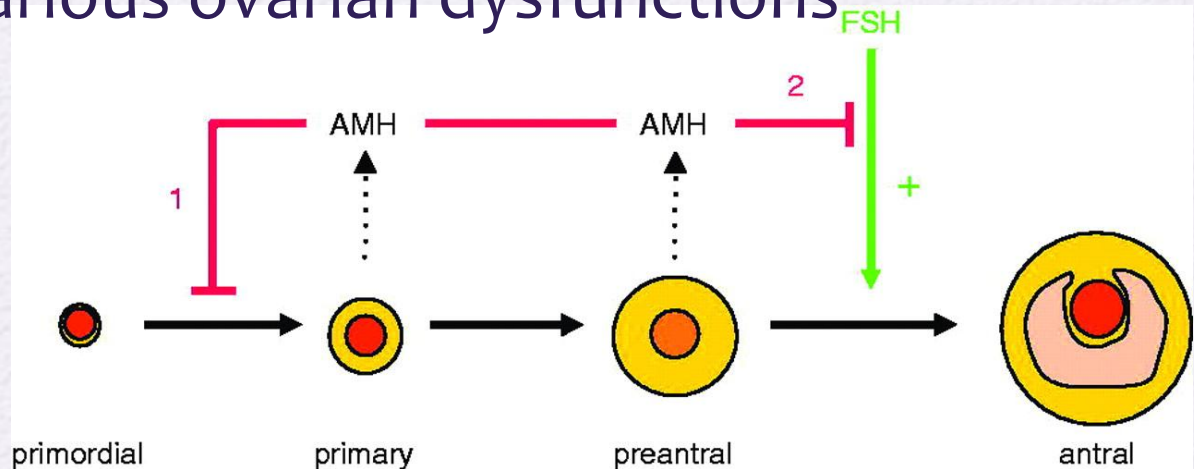
**Broekmans et al. Trends Endoc Metab 2008,
Visser et al. Reproduction 2006**

AMH

- Related to the response to ovarian stimulation

- Correlation with obtained oocytes

- Predicting menopause (Sowers et al., 2008; Van Disseldorp et al., 2008).

- In predicting pregnancy rates, not very good

FIGURE 1

Plot of the number of follicles obtained after stimulation against the basal AMH. The three lines represent the regression line, with the 95% CI of the mean appearing as well.
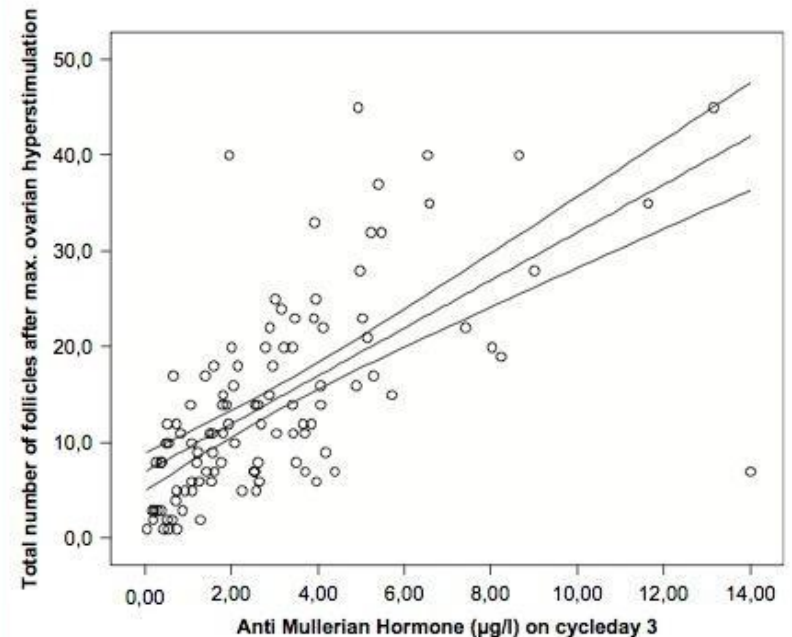
Kwee. AMH for the prediction of ovarian reserve. Fertil Steril 2008.

Kwee et al. Fertil Steril 2008

Markers of ov. response

Table I Studies on AMH as marker of ovarian response to controlled ovarian stimulation (COS)

Author	n	R with oocytes*	AMH better than						
			AFC	Ov. Vol	d3 FSH	d3 E2	d3 inhB	Age
Seifer et al. (2002)	107	0.48			√	√		
Van Rooij et al. (2002)	130	0.57	=		√	√	√	√
Fanchin et al. (2003a, b)	93	0.43						
Muttukrishna et al. (2004)	69	0.69			√		√	
Hazout et al. (2004)	109	0.38			√	√	√	√
Muttukrishna et al. (2005)	108	0.5	=		√			
Eldar-Geva (2005)	56	0.64	✕		√		√	
Silberstein et al. (2006)	257	0.33			√			
Fiçicioglu et al. (2006)	50	0.56	√		√	√		√
Lekamge et al. (2007)	126	0.34	=					
La Marca et al. (2007)	48	0.7						
Kwee et al. (2007)	110	0.63	✕	√	√			√
Nakhuda et al. (2007)	77	0.63			√			
McIlveen et al. (2007)	84	0.78	√	√	√		=	√
Nelson et al. (2007)	340	0.71			√			√
Elgindy et al. (2008)	33	0.88	=	√	√			
Lie Fong et al. (2008)	125	0.47						
Jee et al. (2008)	59	0.53					✕	
Jayaprakasan et al. (2008)	135	0.47	=	√	√	√		√
Wunder et al. (2008)	276	0.35			√		✕	

Comparison with other predictors.
*R with oocytes: correlation between serum AMH levels and the number of retrieved oocytes; √, better than; ✕, worse than; =, equal to.

La Marca et al. Hum Rep Update 2010

Markers of ov. response

Table V Comparison of characteristics of the most widely used markers of ovarian reserve

Characteristics for a good marker	Age	AMH	FSH	AFC
Prediction of poor response	+	+++	++	+++
Prediction of hyper response	+	+++	−	++
Low inter-cycle variability	+++	++	−	++
Low intra-cycle variability	+++	++	−	++
Blinded to the operator	+++	+++	+++	−
Applicable to all patients (a)	+++	+++	+	+
Cheapness	+++	−	−	−

(a) FSH and antral follicle count (AFC) are not informative in patients on hormonal contraception or GnRH agonist treatment. Moreover the count of antral follicles may be difficult in women with ovarian cysts or with previous pelvic surgery.

La Marca et al. Hum Rep Update 2010

Meta-analysis

- AMH and AFC: meta-analysis about the response to stimulation

- At present, AMH has the same level of accuracy and clinical value for the prediction of ovarian response as AFC

Broer et al. 2008

AMH, AFC and Age

- Hystological studies from 42 women shows a good correlation of AMH and AFC with primordial follicles

- Strongest correlation: between AMH and AFC

TABLE 2							

Correlation matrix[a] of endocrine parameters, ultrasound-determined AFC, and log 10 ovarian primordial follicle count.

	Age	AMH	Inhibin B	FSH	E_2	AFC	Log(PF)
Age		<0.0001	0.0288	0.0674	0.9865	<0.0001	<0.0001
AMH	−0.616		0.0046	0.1241	0.351	<0.0001	<0.0001
Inhibin B	−0.337	0.429		0.0542	0.5091	0.0034	0.01
FSH	0.285	−0.241	−0.299		0.0107	0.0285	0.0402
E_2	−0.020	−0.147	0.105	−0.390		0.8432	0.4575
AFC	−0.670	0.754	0.442	−0.338	−0.031		<0.0001
Log(PF)	−0.800	0.718	0.398	−0.322	0.119	0.782	

Note: AMH = anti-Müllerian hormone; AFC = antral follicle count; PF = primordial follicle.
[a] Pearson correlation coefficients. The lower left cells contain the correlation coefficients, the upper right cells the corresponding P values.

Hansen. Primordial follicle number and markers of ovarian function. Fertil Steril 2011.

Hansen et al. Fertil Steril 2011

AFC-
Antral Follicle Count
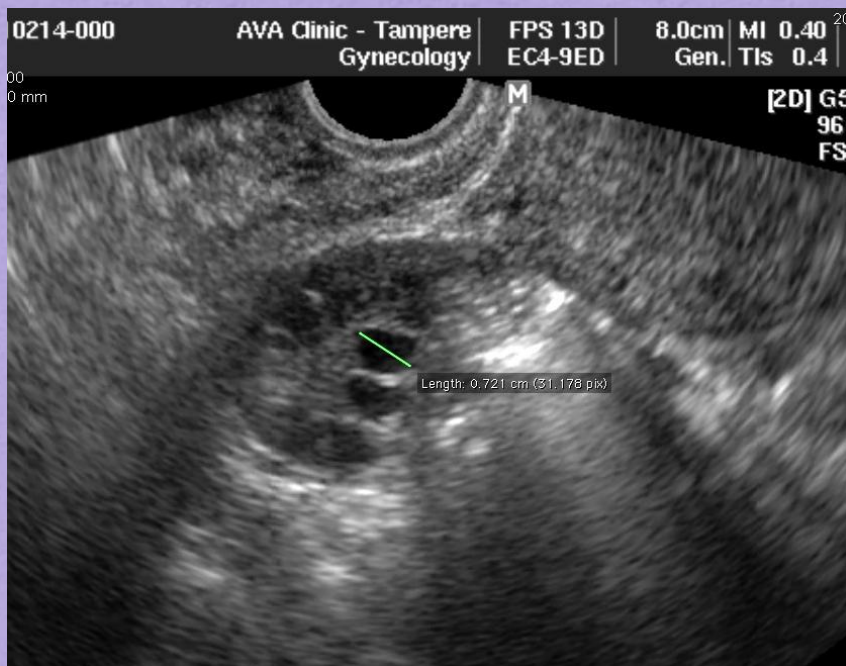
- No. of small follicles 2-10 mm by vaginal US, in both ovaries, in early follicular phase

- Better predictor of ovarian response than age or FSH (Gibreel et al 2009, Hendriks et al. 2007, Kwee et al. 2007, Maseelall et al. 2009)

AFC - Characteristics

- Easily performed

- Low intercycle variability

- Low or moderate inter-observer variability (Hansen et al. 2003, Bancsi et al. 2002)

1. AFC and age

- N=362 women with normal bleeding

- AFC was related to age in a linear form
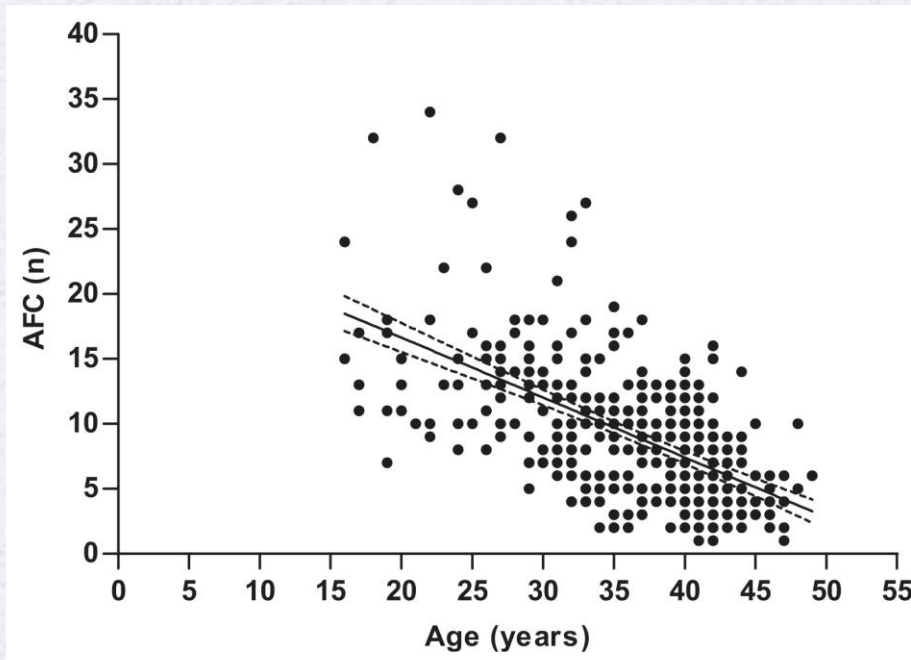
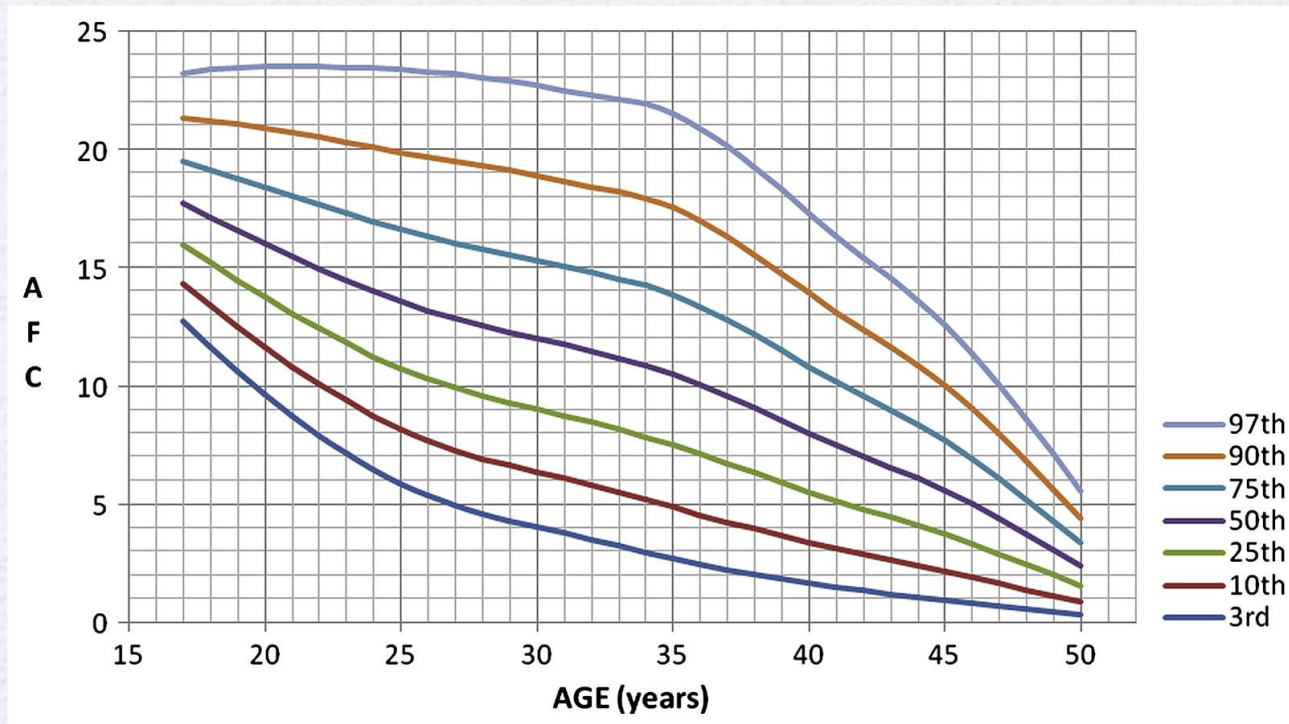- <37 yrs: AFC pool declines at a mean of 4.8% per year
- > 37 yrs: decrease of 11.7% per year

Scheffer et al. Fertil Steril 1999

La Marca et al. Fertil Steril 2011

1. AFC and age

- N=1866 infertile patients

- age-related normogram for AFC

Almog et al. Fertil Steril, 2011

2. AFC - prediction of ovarian response

TABLE 2

Univariate and multivariate analysis of baseline markers of ovarian reserve for the prediction of the number of oocytes retrieved at egg collection during assisted reproduction treatment.

Parameters	Regression coefficient (mean and 95% CI)	P value	R^2
Age	−0.148 (−0.341, 0.046)	.133	
Basal FSH	−0.062 (−0.442, 0.325)	.753	
Basal E_2	−0.008 (−0.019, 0.003)	.156	
Anti-Müllerian hormone	2.353 (1.041, 3.665)	<.001	0.470
Antral follicle count	0.481 (0.230, 0.733)	<.002	
Mean ovarian volume	0.028 (−0.375, 0.431)	.892	
Mean vascular index	0.161 (−0.701, 1.023)	.713	
Mean vascular flow index	−0.209 (−2.209, 1.791)	.156	

Note: Significant predictors on univariate analysis are included in the multiple linear regression analysis model. Body mass index, basal LH, inhibin-B, ovarian flow index, and ovarian echogenicity were not predictive on univariate analysis. CI = confidence interval.

Jayaprakasan. AMH and 3D US markers of ovarian reserve. Fertil Steril 2010.

Jayaprakasan et al. Fertil Steril 2010

2. AFC - prediction of ovarian response

- Reflects the ovarian reserve

- Can have a predictive value of success in spontaneous pregnancy

- Predictive value for IVF treatment

- For the couples doctors it is a sign of the potential outcome of a IVF cycle, helping to take certain decisions

3. Cancellation rates

- The Antral Follicle Count predicts cancellation rate: a fivefold increase in cancellation rate between the lowest and highest AFC groups as (Frattarelli 2000)

- When used in counseling, this cancelation can be reduced from 40% to 20% (Frattarelli et al. 2003, Hsu et al. 2011)

4. Prediction of pregnancy?

- Relation between oocyte quantity and quality is less clear

- AFC is a weak predictor of pregnancy, like AMH (Broer et al. 2009)

- The success of treatment depends on much more factors than the size or number of follicles

- Many poor responders, however, achieve pregnancy!

AFC in egg donors

- Egg donation program: 1074 donations

- Good predictor of ovarian response

- Good for helping choosing starting dose

- In donors with AFC <10
  - significantly higher cancellation rate
  - higher no-donation rate

- BUT: no correlation with the quality of the oocyte or embryos or IVF outcome

Melo et al., Fertil Steril, 2009

5. AFC-correlation with live birth?

- Retrospective study, 278 first IVF treatments
- AFC, age and max. gonadotrophin dose are independent variables for predicting live birth

TABLE 1

Comparison of clinical parameters and patient characteristics between women with antral follicle count number ≥11 or ≤10 (rank sum, chi-square).

Antral follicle count	AFC ≥11 Group 1	AFC ≤10 Group 2	P value
Basal FSH level	4.90 IU/L (4.00, 6.18)	5.70 IU/L (4.60, 7.00)	<.001
Total gonadotropin use	1800 IU (1350, 2719)	3150 IU (2025, 4181)	<.001
Maximum daily gonadotropin use	225 IU/day (150, 300)	375 IU/day (300, 450)	<.001
Peak estradiol levels	1595 pg/mL (1104, 1959)	1192 pg/mL (723, 1700)	<.001
Patient age, years	34 (31.0, 36.2)	37 (33.3, 40.0)	<.001
Number of oocytes retrieved	13 (9, 18)	10 (7, 13)	<.001
Number of embryos transferred	2 (2, 2)	2 (2, 3)	.047
Live birth	52/132 (39.4%)	36/146 (24.7%)	.01
Cancellation rates	7/132 (6.8%)	28/146 (22.5%)	<.001
Miscarriage rates	11/63 (17.5%)	10/46 (21.7%)	.037
Clinical pregnancy rate	63/132 (47.7%)	46/146 (31.5%)	.005

Note: Median (1st quartile, 3rd quartile).

Maseelall. Correspondence. Fertil Steril 2009.

Maseelall, Fertil Steril, 2009

In most studies AFC does not correlate with live birth

- Meta-analysis did not find relationship between AFC and pregnancy (Hendriks et al. 2005)

- A recent large study with 975 oocyte recipient cycles suggests that AFC cannot be used to predict the quality of oocyte or embryo or the IVF outcome (Melo et al. 2009).

3D US and Inversion mode

- Three-dimensional (3D) US
  - reduced observer and inter-observer variability
  - shorter time for US procedures
  - posterior image analysis

  - Inversion mode
    - SonoAVC: Automatic Volume Calculation, GE Medical Systems, Zipf, Austria
    - automatic identification and quantification of hypoechogenic areas of digital 3D datasets

Jayaprakasan et al. 2007, Raine-Fenning et al. 2007, Deb et al. 2009
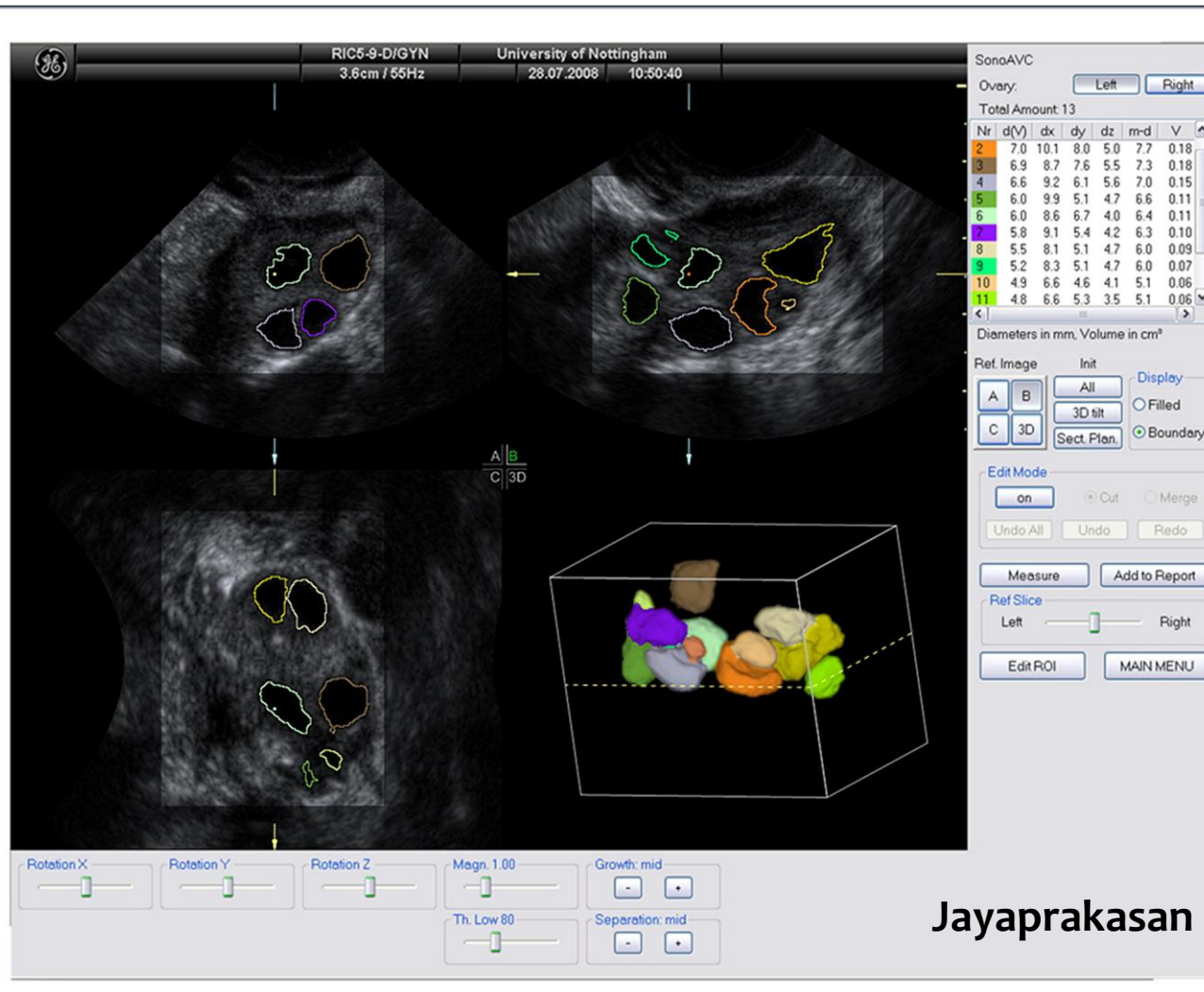
Follicles 2-6 mm
- correlation with AMH
- Best predictor of response than the bigger follicles

Jayaprakasan et al., Fertil Steril, 2010

The software individually color codes each identified follicle and provides an objective measurement of the number of antral follicles with its mean and absolute diameters and its volume.

Conclusion

- AMH is the best endocrinological marker for assessing ovarian reserve and aging

- Good in predicting low and high response

- AMH is a marker for primary ov insufficiency and ov dysfunctions

- Seems to be related with the age of menopause

- Not so good for prediction of pregnancy

Conclusion

- AFC is one of the most commonly used parameters to study the ovarian reserve and predict response

- Nomogram of AFC values is the first step to counsel patients on a scientific basis (La Marca 2011)

- AFC - minimal invasive, easily performed

- In practice: combination of AFC, AMH and age are useful for counseling, planning or to stop treatments

Engagements

- MD, PhD, infertility specialist

- **Main occupation**
  - Fertility Doctor in Tampere, AVA Klinikka
  - Clinical Director of AVA Clinic in Lisbon

- **Other engagements**
  - Member of Fertility Advisory Board (MSD Finland)

Thank You!