AMH: clinical relevance in ART

A. La Marca, MD, PhD

Institute of Obstetrics and Gynecology
University of Modena and Reggio Emilia

Role of AMH measurement in ART

- **prediction of poor response / cancellation**
- **prediction of hyperresponse / OHSS**
- **prediction of pregnancy**

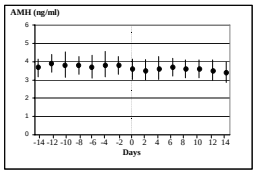
AMH as marker of ovarian reserve: comparison with other predictors

			AMH better than					
Author	n	R with oocytes	AFC	Ov. Vol	d3 FSH	d3 E_2	d3 inhB	age
Seifer (2002)	107	0.48			√	√		
Van Rooij (2002)	130	0.57	=		√	√	√	√
Fanchin (2003)	93	0.43						
Muttukrishna (2004)	69	0.69			√		√	
Hazout (2004)	109	0.38			√	√	√	√
Muttukrishna (2005)	108	0.5	=		√			
Elder Geva (2005)	56	0.64	X		√		√	
Ficicioglu (2006)	50	0.56	√		√	√		√
La Marca (2007)	48	0.7						
Kwee (2007)	110	0.63	X	√	√			√
Elgindy (2007)	33	0.88	=	√	√			
Nelson (2007)	340	0.71			√			√
Wunder (2008)	276	0.35			√		X	

AMH as marker of ovarian reserve: CUT-OFF values

Author	n	Study design	CUT-OFF value (ng/ml)	Sens (%)	Spec (%)
Van Rooij (2002)	119	Prosp	**0.3**	**60**	**89**
Muttukrishna (2004)	69	Prosp	**0.1**	**87.5**	**72.2**
Muttukrishna (2005)	108	Retro	**0.2**	**87**	**64**
Tremellen (2005)	75	Prosp	**1.1**	**80**	**85**
Panarrubia (2005)	80	Prosp	**0.69**	**53**	**96**
Ebner (2006)	141	Prosp	**1.66**	**69**	**86**
Ficicioglu (2006)	50	Prosp	**0.25**	**90.9**	**90.9**
La Marca (2007)	48	Prosp	**0.75**	**80**	**93**
Smeenk (2007)	80	Prosp	**1.4**	**62**	**73**
McIlveen (2007)	84	Prosp	**1.25**	**58**	**75**
Kwee (2007)	110	Prosp	**1.4**	**76**	**86**
Nelson (2007)	340	Prosp	**0.7**	**75** (correctly classified)	
Gnoth (2008)	132	Prosp	**1.26**	**97**	**41**

AMH on any day of the cycle predicts ovarian response



48 women attending the IVF/ICSI program

blood samples for AMH on the day in which it was decided to address the couple to IVF/ICSI procedure, independently of the last menstrual cycle.

the IVF/ICSI procedure was performed in the next one or two months after the sampling

A. La Marca, Hum Reprod 2006, Hum Reprod 2007

AMH on any day of the cycle predicts ovarian response

	AMH <25°	AMH 25°-50°	AMH 50°-75°	AMH >75°
AMH Range (ng/ml)	0-0.4	0.5-2.5	2.6-6.9	7-11
N	12	12	12	12
Age (years)	38±4*	37±3.8	37±1.3	34±3 *
Total FSH (IU)	4762±1018*	4041±1545	3145±829	2691±717 *
Retrieved Oocytes (n)	2.2±1.2*	4.3±2.7	6.8±2.6	18±5.4 *
Cancellation for no response (n)	4 *	0	0	0
Cancellation for risk of OHSS (n)	0	0	0	2 *

A. La Marca, Hum Reprod 2007

AMH on any day of the cycle predicts ovarian response

Performance of AMH serum levels in predicting poor ovarian response

AMH cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
0.5	85	82.3	81.2
0.75	80	93	87.5

A. La Marca, Hum Reprod 2007

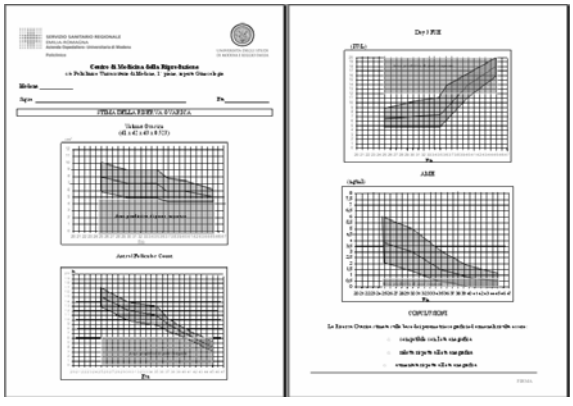
AMH on any day of the cycle predicts ovarian response

Correlations between markers and retrieved oocytes

Markers	R	p
d3 AMH	0.7	<0.01
AFC	0.69	<0.01
any day AMH	0.65	<0.01
Age	-0.3	<0.05
d3 FSH	-0.3	<0.05
d3 InhB	0.2	<0.05

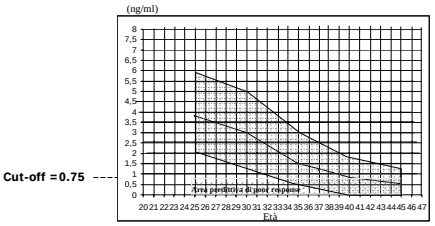
A. La Marca, unpublished

Ovarian Reserve Assessment



Ovarian Reserve Assessment

AMH



Values obtained using the Beckman assay

A. La Marca, unpublished

When to propose the Ovarian Reserve Assessment

Ovarian Reserve Test

Before 1st IVF

Previous ovarian surgery

Previous chemotherapy / radiotherapy

Already known high-day 3 FSH

Not "reassuring" ultrasound image

When to propose the Ovarian Reserve Assessment

Ovarian Reserve Test

After 1st IVF

Poor response

Poor ovarian reserve confirmed

Counselling

Avoid other ovarian stimulations

Poor ovarian reserve not confirmed

Increase the FSH starting dose

Change the protocol

Role of AMH measurement in ART

- **prediction of poor response / cancellation**
- **prediction of hyperresponse / OHSS**
- **prediction of pregnancy**

AMH as predictor of hyper-response / OHSS

Author	design	n	Mean AMH levels (ng/ml)		OHSS	Significativity
			Normal response	Excessive response (>20 oocytes)		
Tremellen (2005)	Prosp	75	2.1		2.95	yes
Eldar Geva (2005)	Prosp	56	2	5.3		yes
Nakhuda (2005)	Retro	30	0.63		3.6	yes

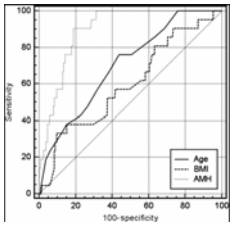
AMH as predictor of hyper-response / OHSS

CUT-OFF values

Author	n	Study design	CUT-OFF value (ng/ml)	Sens (%)	Spec (%)	Prediction of hyper-response	Prediction of OHSS
Kwee (2007)	110	Prosp	**5**	**53**	**91**	√	
Nelson (2007)	340	Prosp	**3.52**	**60**	**94.9**	√	
Lee (2008)	262	Prosp	**3.36**	**90.5**	**81.3**		√

AMH as predictor of hyper-response / OHSS

262 patients
⇩
21 OHSS (8%)



Variable	ROC
Age (years)	0.710
BMI (Kg/m^2)	0.612
Basal serum AMH level (ng/ml)	0.902
Serum E_2 level on day of hCG administration (pg/ml)	0.811
Number of follicles (≥10 mm) on day of hCG administration	0.846
Number of oocytes collected	0.853

Strenght
- High number of patients
- Optimal classification of OHSS
- Only moderate to severe OHSS considered

Limitations
- Limited to Chinese population
- Not clear definition of PCOS women included

TH Lee, Hum Reprod (2008)

Optimization of treatment strategies based on AMH levels

Low AMH (< 0.75 ng/ml) ⇨ **cycle cancellation or poor response**

a. **Inform the patient about the cycle cancellation or no transfer**
b. **low possibility of pregnancy**
c. **avoid a long suppression**
d. **maximal FSH administration - natural IVF cycle (?)**

Normal AMH (0.75-3.5 ??) ⇨ **normal response**

a. **Standard protocol**

High AMH (>3.5 ??) ⇨ **high response**

a. **Inform about the risk of OHSS**
b. **avoid depot GnRHa**
c. **low FSH dose**

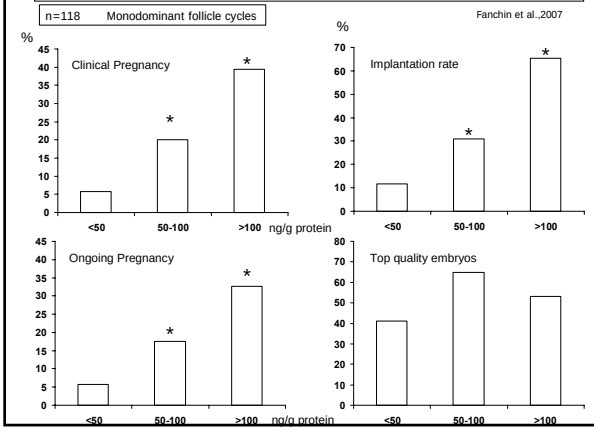
Role of AMH measurement in ART

- **prediction of poor response / cancellation**
- **prediction of hyperresponse / OHSS**
- **prediction of pregnancy**

Follicular fluid AMH and oocyte / embryo quality

n=118 Monodominant follicle cycles

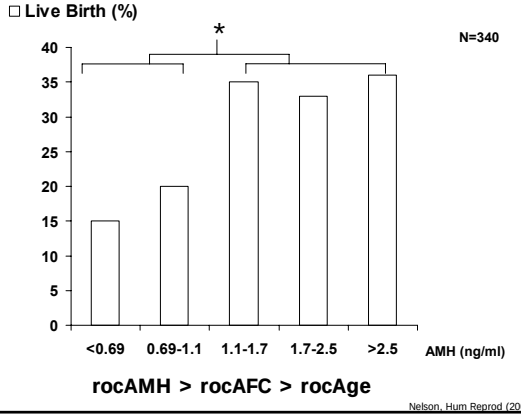
Fanchin et al.,2007



AMH as predictor of pregnancy

Author	n	Study design	CUT-OFF value (ng/ml)	Sens (%)	Spec (%)
Van Rooij (2002)	106	Prosp	Not useful		
Fanchin (2003)	93	Prosp	Not useful		
Hazout (2004)	109	Retro	**1.1**	**na**	**na**
Eldar Geva (2005)	56	Prosp	**2.5**	**67**	**69**
Panarrubia (2005)	80	Retro	Not useful		
Ebner (2006)	132	Prosp	Not useful		
Ficicioglu (2006)	50	Prosp	Not useful		
Silberstein (2006)	257	Prosp	Not useful		
Van Rooij (2006)	222	Prosp	Not useful		
Kwee (2007)	104	Prosp	**1.4**	**34**	**79**
Smeenk (2007)	112	Prosp	Not useful		
Fanchin (2007)	118	Prosp	Not useful		
Mc Ilveen (2007)	84	Prosp	Not useful		
Elgindy (2008)	33	Prosp	**2.7**	**83**	**82**
Gnoth (2008)	132	Prosp	Not useful		

AMH as predictor of pregnancy

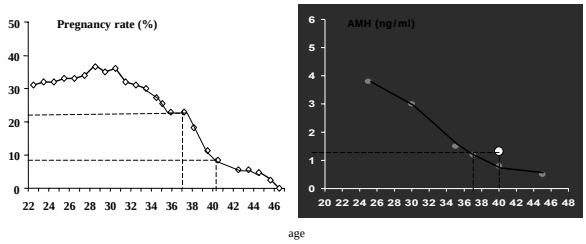


rocAMH > rocAFC > rocAge

Nelson, Hum Reprod (2007)

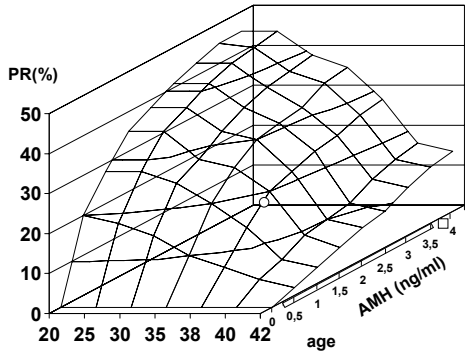
Prediction of pregnancy

Could AMH refine our counselling on the probability of pregnancy following IVF?



age

Prediction of pregnancy



A. La Marca, unpublished

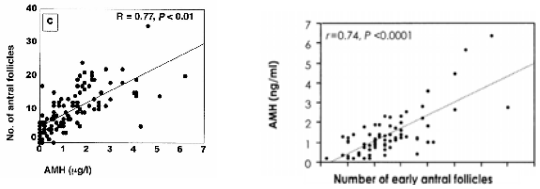
Advantages of AMH as marker of ovarian reserve

- **earliest marker to change with age**
- **the least intercycle variability**
- **the least intracycle variability**
- **randomly measured during the cycle**
- **no modifications during GnRHa**
- **no modification during hormonal contraception**
- **no modification in hypothalamic amenorreha**

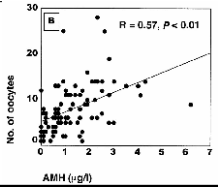
Prof. A. Volpe
Dr. S. Giulini
Dr. A. La Marca
Dr. A. Tirelli
Dr. F. Tortolani
Dr. D. Tagliasacchi
Dr. T. Marsella
Dr. S. Xella
Mrs P. Levratti

E-mail: medicina.riproduzione@unimore.it

AMH as marker of ovarian reserve



AMH = AFC > FSH, InhB, E2, Ov Volume, age



Van Rooij et al., Hum Reprod 2002
Fanchin et al., Hum Reprod 2003

Potential roles of AMH measurement

- **Assessing ovarian reserve**
  - **general population**
  - **infertile population**
  - **before and after cancer therapy**
- **Assessing the risk of OHSS**
- **Diagnosis and surveillance of PCOS therapy**
- **Diagnosis and surveillance of gonadal cancer**
- **Diagnosis of ambiguous genitalia**

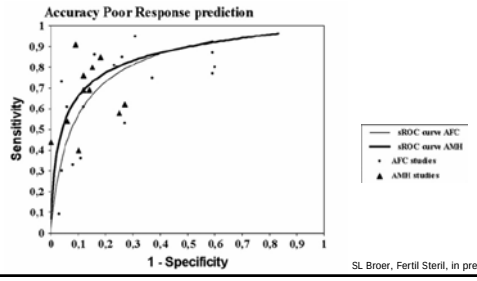
ARTICLE IN PRESS

CLINICAL ARTICLE

The role of antimullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count

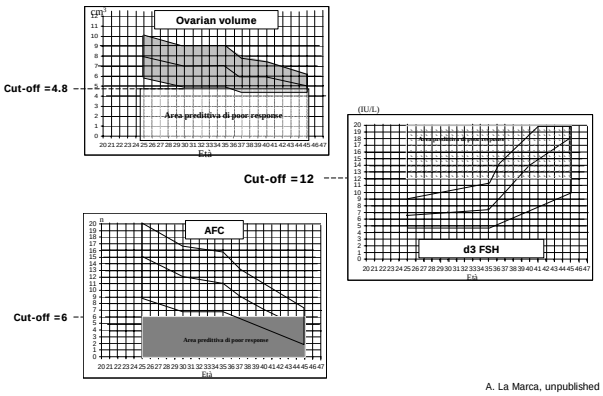
Simone L. Broer, B.Sc.,* Ben Willem J. Mol, M.D., Ph.D.,† Dave Hendriks, M.D., Ph.D.,* and Frank J. M. Broekmans, M.D., Ph.D.*

AMH = AFC > FSH, InhB, E2, Ov Volume, age



SL Broer, Fertil Steril, in press

Ovarian Reserve Assessment



A. La Marca, unpublished