AMH CUT-OFF VALUES FOR PREDICTING OVARIAN RESPONSE IN IVF

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INTRODUCTION

- Ovarian stimulation is an important process in IVF treatment, aiming at obtain a number of quality oocytes.
- To avoid OHSS and poor response.

- Reproductive endocrinologists check following biochemical tests to predict the efficiency of stimulation:
  - Woman's Age
  - FSH
  - E2 day 3
  - AFC

INTRODUCTION

- Recently, AMH has been researched to evaluate the relationship between number of obtained oocytes and the rest of process.

- However, studies have shown that value of AMH still varies for predicting ovarian response.

OBJECTIVES

1. *To determine AMH cut-off values for predicting ovarian response in IVF*

2. *To compare AMH values with FSH, AFC and E2 for predicting ovarian response.*

BACKGROUND

1. Ovarian stimulation in IVF treatment

- **Definition**: ovarian stimulation in IVF is a method of using hormones to stimulate number of follicles in order to obtain higher number of oocytes, getting higher pregnancy rate.
- **Antagonist protocol:** FSH used in the beginning of menstrual period. Then, Antagonist was used in day 6 or when diameter of follicles over 14 mm, to avoid peak of LH.

BACKGROUND

2. Ovarian responsiveness

- **Normal responder:** obtained oocytes ranged from 5-15.

- **High responder**: Obtained more than 15 oocytes, no different in pregnancy rate, over 18 oocytes increase the risk of OHSS

- **Poor responder:** obtained oocytes under 4, lower pregnancy rate, drop-out due to non-response, increase cost of treatment.

BACKGROUND

3. Ovarian reserve

- **Ovarian reserve** is a term that is used to determine the capacity of the **ovary** to provide **egg** cells that are capable of fertilization resulting in a healthy and successful pregnancy.
- reduce with female's age
- Reduce ovarian reserve leads to poor response

BACKGROUND

4. Factors that determine ovarian reserve

- Wife's age
- Level of FSH
- AFC
- LEvel of E2
- Level of AMH

AGE

Age	PR (%)
< 30 years	13.6
30 – 34 years	13.5
35 – 39 years	12.6
≥ 40 years	5.0

Embryo implantation rates as a function of female age (42).

Age	Implantation rate
25–29	18.2%
30–34	16.1%
35–39	15.3%
40–44	6.1%

Reprinted with permission (Fertil Steril 1996;65:783–790) (42).

- Age related significantly to low pregnancy rate

($P < 0.05$) in woman > 40 years old *(Wainer R et al, 2004)*

- *PR* 24.9% (66/265) (< 30 yrs) *VS*. 12.9% (11/85) (≥ 30 yrs) per cycle *(Zadehmodarres S et al, 2009)*

- Implantation rate decresed by age *(ASRM Practice Committee. Aging and Infertility in women. Fertil Steril 2006)*

Evidence Level
2b

Understanding Biomarkers

FSH is not very accurate to assess ovarian response or pregnancy risk in ART

FSH

What is known?

- Cut-off point of 11.4 IU/L*:
  - ➢ **High specificity** (83%-100%) to predict ≤4 retrieved oocytes → Low number of false positives
  - ➢ **Low sensitivity** (10%-30%) to predict DOR and failure to achieve pregnancy in ART → High number of false negatives → 'Normal' FSH values → DOR or failure to pregnancy
- Cannot Identify High Responders

*Standardized assays by WHO IRP 78/549

Esposito et al. *Hum Reprod* 2002;17:118; ASRM Practice Committee, *Fertil Steril* 2012;98:147.

Esteves, 10

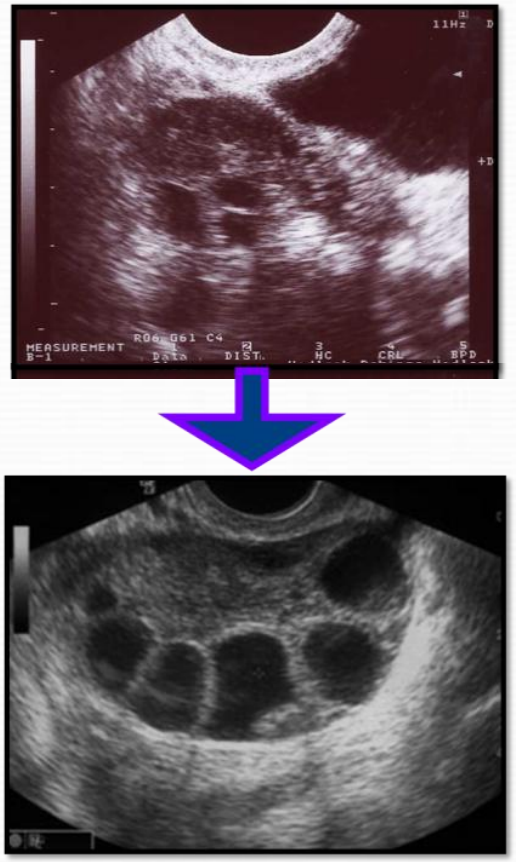
Understanding Biomarkers

What is known?

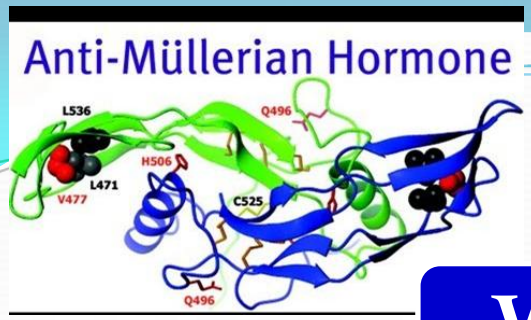
AFC

Direct Biomarker of Functional Ovarian Reserve:

- Sum of antral follicles in both ovaries on TVUS at early follicular phase (D2-D4):
  - 2-10 mm (mean diameter)
  - Greatest 2D-plane
- Decrease in the number of detectable (TVUS) antral follicles with aging
- Reflect the number of antral follicles in the ovaries at a given time that can be stimulated by exogenous gonadotropins



Broekmans et al. *Fertil Steril*, 2010; 94(3):1044-51; Scheffer et al. *Hum Reprod* 2003;18:700



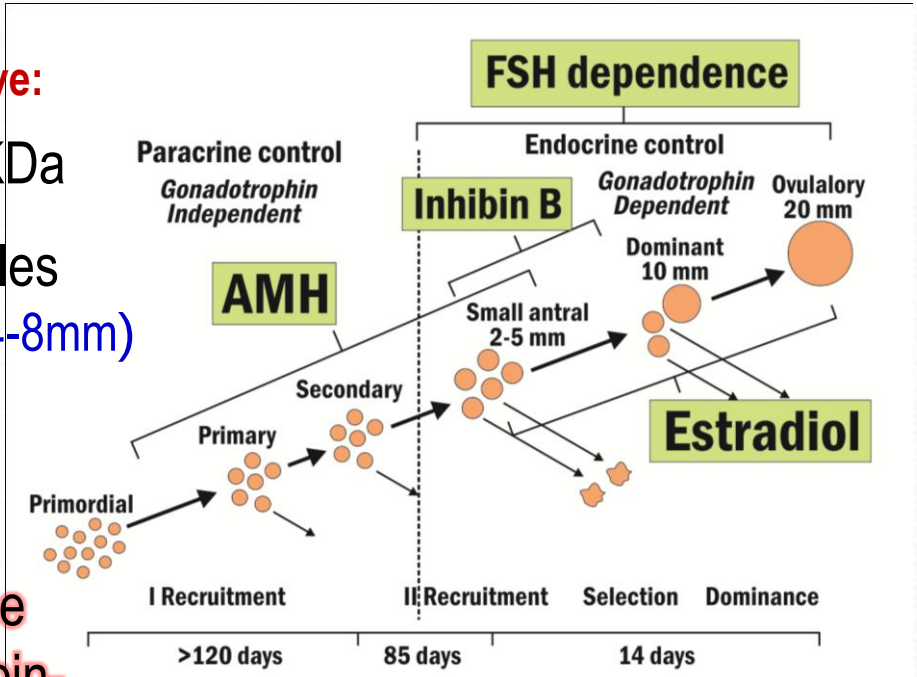
Understanding Biomarkers

What is known?

AMH

Direct Biomarker of Ovarian Reserve:

- Dimeric glycoprotein; ~140KDa
- Product of GCs of early follicles
  Pre-antral and small antral (≤ 4-8mm)



- Reflect both the number of small growing follicles and the primordial pool at gonadotropin-independent folliculogenesis

La Marca et, *Hum Reprod* 2009;24:2264; Fleming et al, *Fertil Steril* 2012;98:1097.

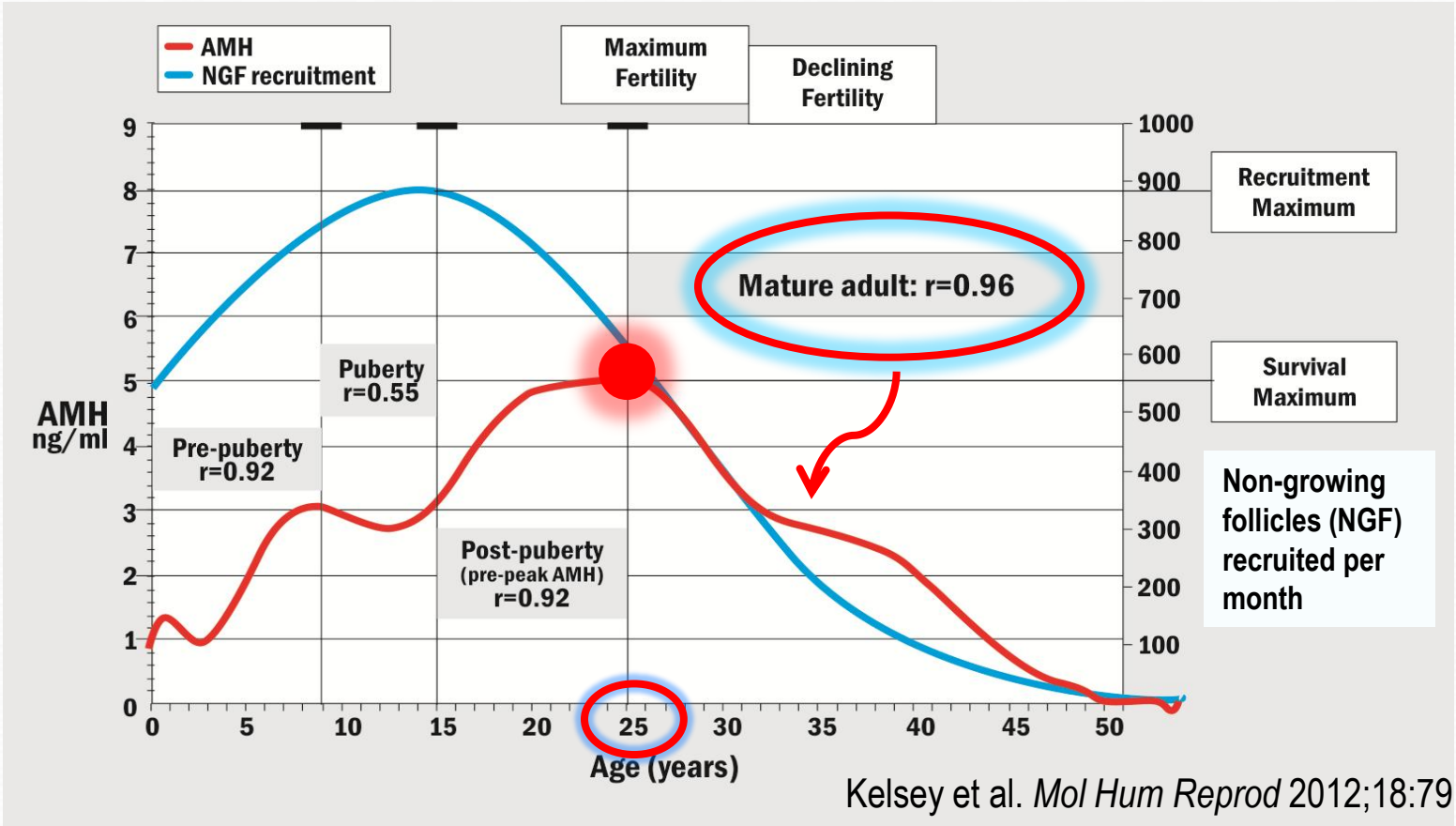
Understanding Biomarkers

Basic Concepts

AMH

AMH Serum Levels:

- Peak at age 25 and decrease with aging
- Early marker of diminished ovarian reserve



Kelsey et al. *Mol Hum Reprod* 2012;18:79

Esteves, 13

Evidence Level
2a

Understanding Biomarkers

AMH is accurate to assess ovarian response

AMH

What is known?

- Cut-off point of 3.5 ng/mL* (Nardo et al, *Fertil Steril* 2009;92:1586)
  - ➢ High sensitivity (88%), specificity (70%) and accuracy (0.81) to predict excessive response[1]
- Cut-off point of 1.4 ng/mL* (Kwee et al, *Fertil Steril* 2008;90:737)
  - ➢ High sensitivity (76%) and specificity (86%) to predict DOR[2]

Caution to apply AMH cut-off points!

Make sure the assay you rely on is the same used in the reference population

*DSL assay; [1]>20 oocytes retrieved; [2]≤5 oocytes retrieved;
Conversion: ng/mL to pmol/L = value in ng/mL X7.14

Esteves, 14

BACKGROUND

5. Factors affect AMH

- Age
- Race
- Alcohol users, smoking users
- Diabetes
- PCOS
- Using contraceptive methods
- Administration of chemotherapy or radiation
- Surgical removal of one or both ovaries

MATERIALS AND METHODOLOGY

1. Materials

- IVF Patients from October, 2014 to June, 2015 at National Center for ART.

➢ **Study design**

- Prospective study.

➢ ***Sample size***

$$TP + FN = Z^2 \frac{SN \times (1 - SN)}{W^2}$$

$$N = \frac{TP+FN}{P}$$

Sample size: 600 patients.

RESULTS AND DISCUSSION

1. Personal characteristics

Age

Age group	n	%
18-24	31	5,2
25-29	179	29,8
30-34	252	42,0
35-39	86	14,3
40-45	52	8,7
Mean (min – max)	31,7 ± 5,2 (18 – 45)	

RESULTS AND DISCUSSION

Types of infertility

	n	Tỷ lệ %
Primary	328	54,7
Secondary	272	45,3
TOtal	600	100,0

RESULTS AND DISCUSSION

Length of infertility

	n	%
< 5	313	52,2
5-10 years	254	42,3
> 10 years	33	5,5
Total	600	100,0
Mean	5,0 ± 3,2 (1,5 – 26,0)	

RESULTS AND DISCUSSION

Cause of infertility

	n	%
Female	232	38,6
Male	59	9,8
Both	44	7,4
Unknown	265	44,2
Total	600	100,0

RESULTS AND DISCUSSION

2. To determine AMH's predictive value for ovarian response

Mean of AMH

	n	%	Mean	Min – Max	p
Poor	28	4,7	1,04 ± 0,52	0,22 – 3,5	<0,001
Normal	374	62,3	3,52 ± 2,17	0,4 – 22,0	
High	198	33	7,02 ± 3,73	2,0 – 23,6	
Total	600	100%	4,57 ± 3,25	0,22– 23,6	

RESULTS AND DISCUSSION

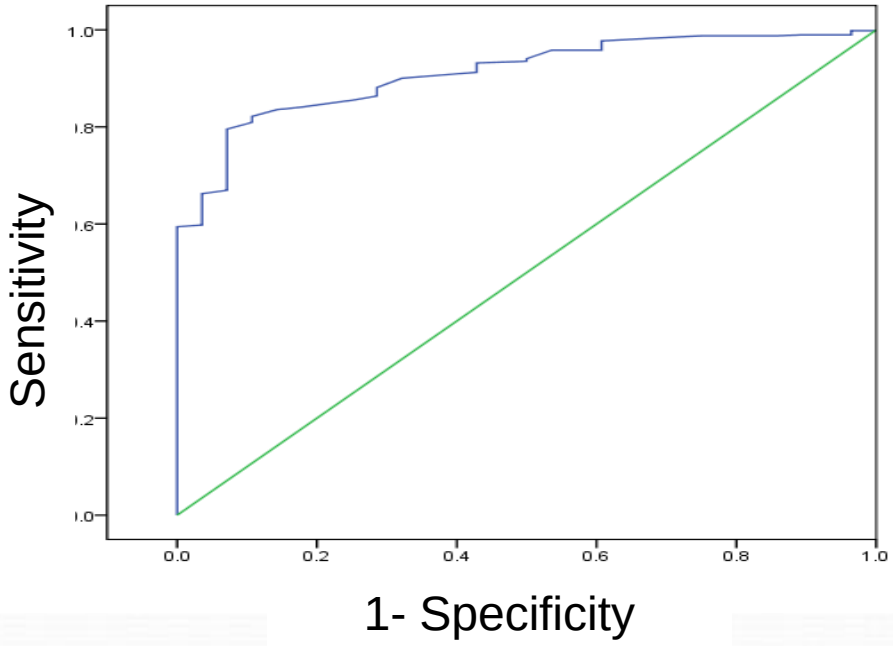
AMH's predictive value of ovarian response

	Predicted poor response (< 4 oocytes)		
	cutoff	Sen	Spec
AMH ng/ml	1,13	88%	71%
	1,25	85%	75%
	1,36	84%	85%
	1,47	81%	89%
	1,52	80%	93%
	1,58	79%	92%
	1,63	73%	92%
	1,69	74%	92%

Vương Thị Ngọc Lan, cutoff: 1,25 ng/ml, Sen 87%; Spec 85%
Ebner, Cutoff 1,66 ng/ml, Sen 69%; Spec 86%.

RESULTS AND DISCUSSION

ROC for poor response



AUC of AMH: 91%, p < 0,01.

Vương Thị Ngọc Lan, AUC: 92%, p < 0,01.

Relationship between level of AMH and number of oocytes

	r	equation	p
Poor response	0,512	Number of oocyte = 0,534xAMH+1,904	<0,01

RESULTS AND DISCUSSION

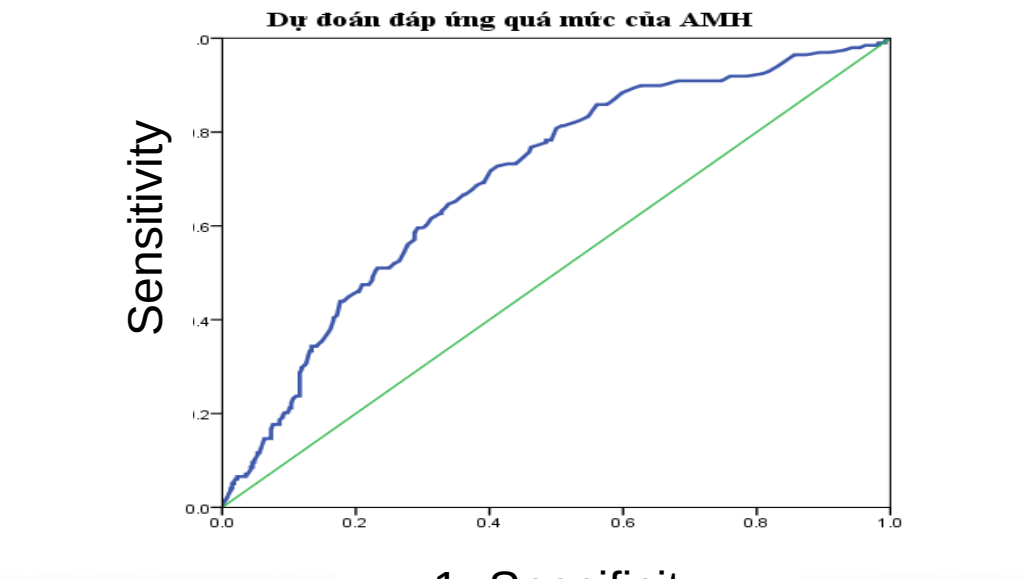
AMH's predictive value to high response

	Predicted high response (>15 oocytes)		
	Value	Sensitivity	Specificity
AMH ng/ml	3,62	78%	54%
	3,87	73%	58%
	3,95	73%	59%
	4,04	73%	61%
	4,12	72%	61%
	4,21	71%	61%
	4,25	69%	62%

Vương Thị Ngọc Lan, cutoff: 3,97 ng/ml, Sen 82%; Spec 81%.
Ebner, Cutoff: 4,52 ng/ml, Sen 67%; Spec 78%.

RESULTS AND DISCUSSION

ROC of AMH with high response



AUC of AMH in high response: 71%, p < 0,01.

Relationship between level of AMH and number of oocytes

	r	Equation	p
high response	0,338	number of oocyte = 0,382xAMH+17,336	<0,01

RESULTS AND DISCUSSION

3. Comparision of predictive value of AMH to AFC,FSH, E2

Mean of AFC in groups of response

response	n	Mean	Min – Max	p
Poor	28	5,29 ± 3,92	3– 7	< 0,001
Normal	374	11,91 ± 5,86	1 – 30	
High	198	14,25 ± 5,65	1 – 30	
Total	600	12,71 ± 6,23	1 – 30	

RESULTS AND DISCUSSION

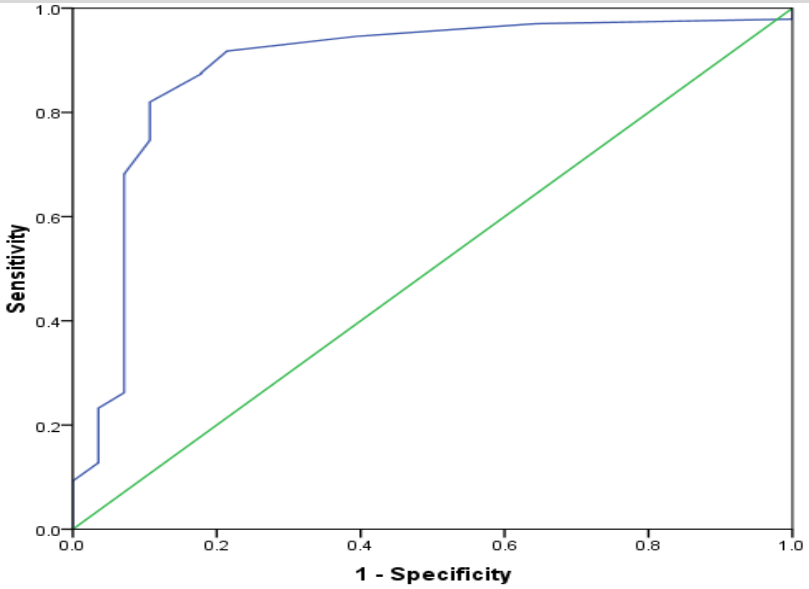
AFC's predictive value to poor response

	Predictive value for poor response (<4 oocytes)		
	cutoff	Sen	Spec
AFC	3,5	97%	35%
	4,5	94%	60%
	5,5	91%	78%
	6,5	87%	84%
	7,5	81%	89%
	8,5	74%	89%
	9,5	68%	92%
	10,5	60%	92%
	11,5	54%	92%

Vương Thị Ngọc Lan, cutoff: 5 oocytes, Sen 78,7%, Spec 85,9%.

RESULTS AND DISCUSSION

ROC of AFC to poor response



AUC of AFC in poor response: 88,5%, p < 0,01.
Vương Thị Ngọc Lan, AUC: 88%, p <0,01.

Relationship between AFC and number of oocytes

	r	equation	p
Poor response	0,492	No of oocytes = 0,90xAFC+1,701	<0,05

RESULTS AND DISCUSSION

Mean of FSH in response groups

Response	n	Mean	Min – Max	p
Poor	28	8,76 ± 3,39	3,00 – 15,00	<0,001
Normal	374	6,39 ± 1,96	0,30 – 15,00	
High	198	5,60 ± 1,66	0,09 – 14,55	
Total	600	6,21 ± 2,03	0,09 – 15,00	

RESULTS AND DISCUSSION

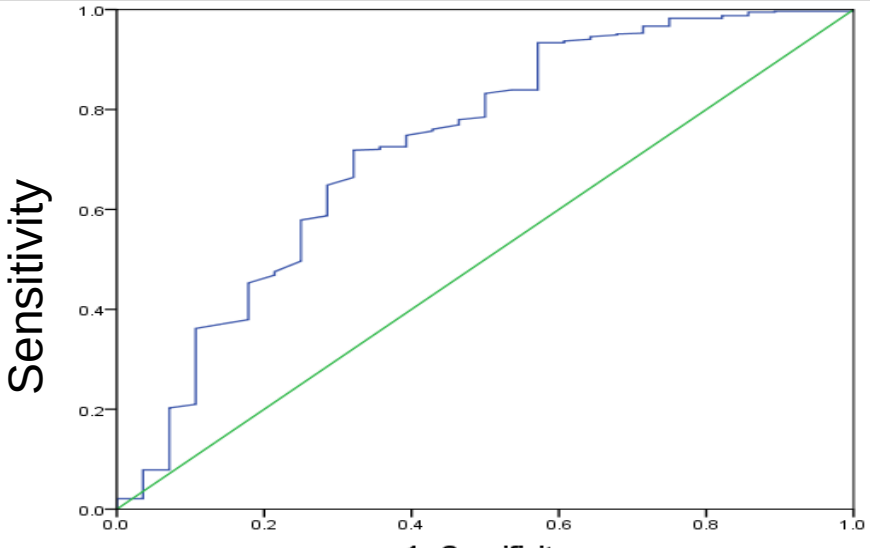
FSH's predictive value to poor response

	Predictive value to poor response (< 4 oocytes)		
	cutoff	Sen	Spec
FSH (IU/L)	6,79	67,8%	70,2%
	6,80	67,8%	71,3%
	6,81	67,8%	71,5%
	6,82	67,8%	71,6%
	6,83	67,8%	71,9%
	6,85	64,2%	72,0%
	6,87	64,2%	72,2%
	6,88	64,2%	72,5%
	6,89	60,7%	72,5%

Vương Thị Ngọc Lan, Cutoff: 8,94; Sen 57,5%, Spec 85,4%

RESULTS AND DISCUSSION

ROC of FSH in poor response



AUC of FSH = 72,6%, p < 0,01.

Vương Thị Ngọc Lan, AUC = 75%, p < 0,01.

Relationship between level of FSH and number of oocytes

	r	Equation	p
Poor response	-0,315	No. of oocyte = -0,033xFSH+2,519	< 0,05

RESULTS AND DISCUSSION

Mean of E2 in response groups

response	n	Mean	Min – Max	p
Poor	22	34,83 ± 12,35	19,28 – 69,00	P>0,05 (0,464)
Normal	374	35,59 ± 18,72	4,10 – 174,00	
High	198	37,57 ± 20,11	1,54 – 119,40	
Total	594	36,22 ± 19,00	1,54 – 174,00	

RESULTS AND DISCUSSION

Comparision of values of AMH, FSH, AFC to poor response

	Predict poor response (<4 oocytes)			
	Cutoff	Sen	Spec	AUC
AMH(ng/mL)	1,52	80%	93%	91%
AFC	6,5	87%	84%	88,5%
FSH(IU/L)	6,83	67,8%	71,9%	72,6%

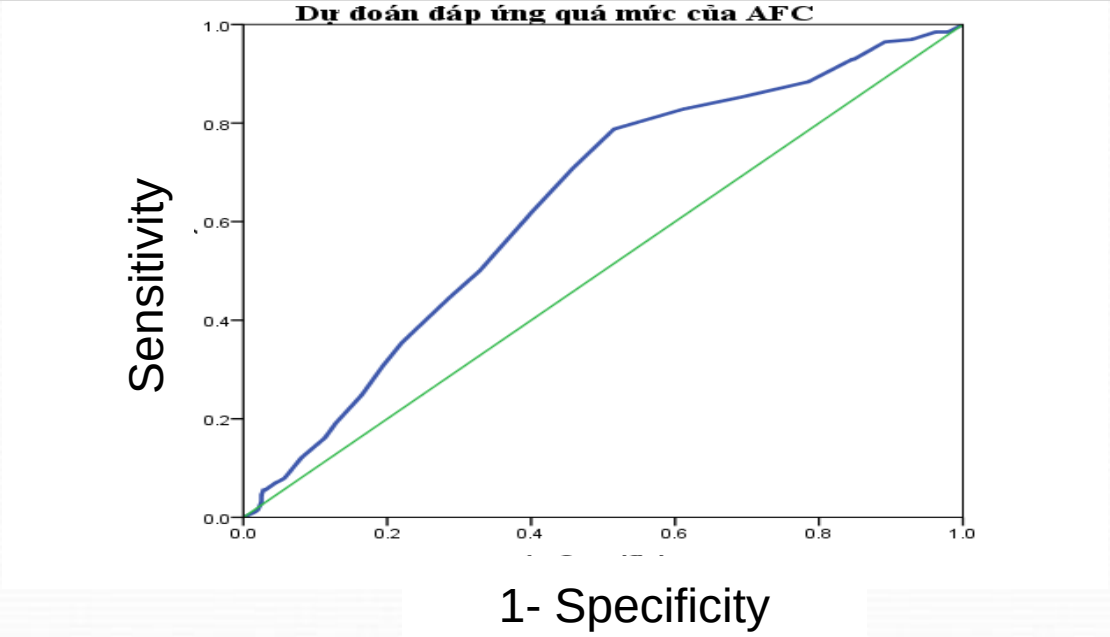
RESULTS AND DISCUSSION

❖ **Predictive value of AFC in high response**

	Predict high response (>15 oocytes)		
	Cutoff	Sen	Spec
AFC	7,5	88,3%	25%
	8,5	85,3%	34,1%
	9,5	82,8%	42,4%
	10,5	78,7%	52,0%
	11,5	70,7%	56,3%
	12,5	61,6%	61,6%
	13,5	50,0%	68,6%
	14,5	44,4%	72,9%

RESULTS AND DISCUSSION

ROC of AFC in high response



AUC of AFC in high response = 65%, p < 0,01.

Relationship between AFC and number of oocytes in high response

	r	Equation	p
high response	0,167	No. of oocytes = 0,108xAFC+19,281	<0,05

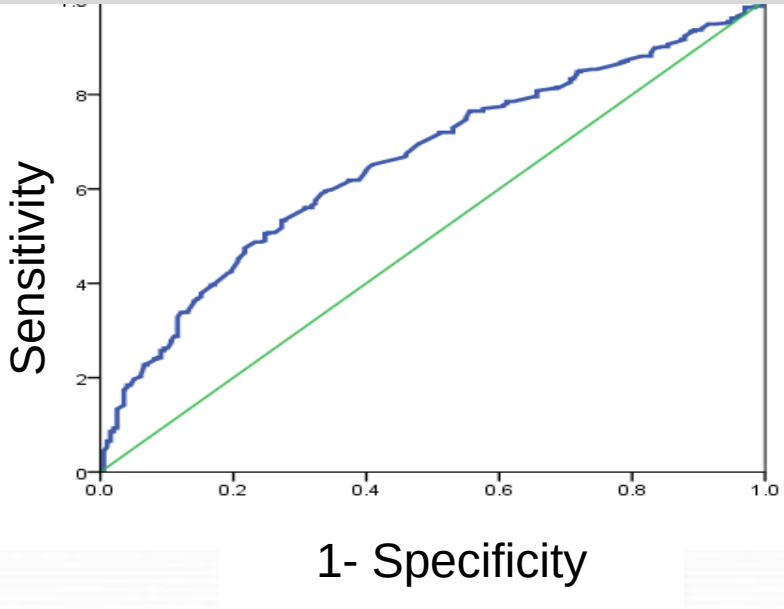
RESULTS AND DISCUSSION

Predictive value of FSH in high response

	High response (> 15 oocytes)		
	Cutoff	Sen	Spec
FSH (IU/L)	6,07	56,0%	69,1%
	6,09	55,8%	69,2%
	6,10	53,5%	72,2%
	6,12	53,2%	72,2%
	6,14	53,2%	72,7%
	6,15	53,0%	72,7%
	6,17	52,7%	72,7%
	6,18	52,0%	72,7%

RESULTS AND DISCUSSION

ROC of FSH in high response



AUC of FSH = 62,7%, p < 0,01.

Correlation of FSH and number of oocytes in high response

	r	equation	p
High response	-0,10	No. of oocyte = -0,271xFSH+22,344	> 0,05

RESULTS AND DISCUSSION

Comparision of values of AMH, FSH, AFC in high response

	high response (>15 oocytes)			
	Cutoff	Sen	Spec	AUC
AMH (ng/mL)	4,04	73%	61%	71%
AFC	10,5	78,7%	52,0%	65%
FSH (IU/L)	6,145	53,2%	72,7%	62,7%

Clinical Utility in Ovarian Stimulation

Biomarkers

		FSH	AMH	AFC
Excessive Ovarian Response	Avoid over-aggressive stimulation in 'true' high responders (↑Sensit.)	–	+++	+++
	Avoid over-conservative stimulation in 'false' high responders (↑Specif.)	–	+++	+++
Diminished Ovarian Reserve (DOR)	**Avoid over-conservative stimulation in 'true' DOR (↑Sensit.)**	+	+++	+++
	Avoid over-aggressive stimulation in 'false' DOR (↑Specif.)	+++	+++	+++

Esteves, 39

CONCLUSIONS

1. *To determine AMH's predictive value to ovary's response in ovarian stimulation*

- Cut-off of AMH in poor response:
  - 1,52 ng/ml; Sen 80%; Spec 93%.
  - ≤1,52 ng/ml: risk of poor response 7,4 times higher
- Cut-off of AMH in high response:
  - 4,04 ng/ml; Sen 73%; Spec 61%.
  - ≥ 4,04 ng/ml: risk of poor response 2,69 times higher

CONCLUSIONS

2. To compare AMH's predictive value to that of FSH, AFC and E2 in ovarian stimulation

2.1. In poor response:

- Predictive value: AMH (Sen: 80%, Spec: 93%) >> AFC (Sen: 87%, Spec: 84%) >> FSH (Sen: 67,8%, Spec: 71,9%).
- E2 day 3: no predictive value

2.2. In high response:

- Predictive value: AMH (Sen: 73%; Spec: 61%) >> AFC (Sen: 78,7%; Spec: 52,0%).
- FSH: no predictive value
- E2 day 3: no predictive value

Take home messages

1. AMH and AFC are currently the best biomarkers to predict ovarian response to COS.

2. Individualization of COS guided by such biomarkers is sound, and it is aimed to maximize the beneficial effects of treatment while minimizing complications and risks.


THANK YOU FOR YOUR ATTENTION!
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