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FULLY AUTOMATED AMH TESTING OF OVARIAN RESPONSE IN IVF

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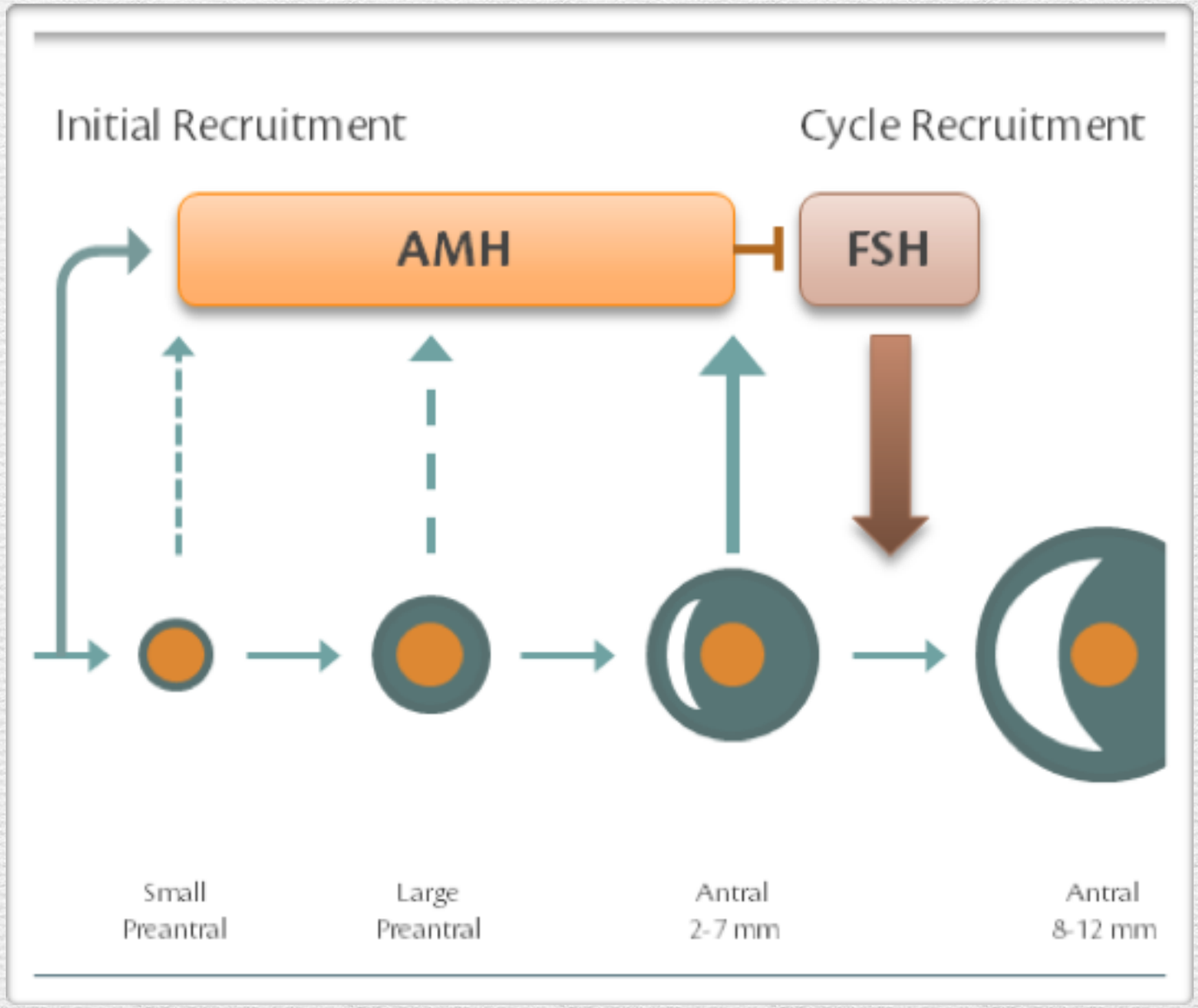
What is AMH?

- Substance produced by granulosa cells in ovarian follicles
- Production is highest in preantral and small antral stages
- The levels are fairly constant
- AMH test can be done on any day of the cycle



* La Marca et al. Hum Reprod Update 2010

AMH VS FSH

- AMH is stable and does not vary from cycle to cyle
- AMH can be measured independently of the day of the menstrual cycle
- AMH is independent to estradiol levels and history of using oral contraceptive pills

Standard AMH assay

- AMH testing was firstly introduced by Beckman Coulter
  - limit of detection is 0.88 ng/mL
- AMH testing then was upgraded to AMH Gen II
  - limit of detection is 0.08 ng/mL
- AMH Gen II became clinical standard assay

LIMITATIONS OF STANDARD AMH*

- Complement interference phenomenon
- Whole-blood samples are instability and variability compared to serum samples
- Sample storage issues

*Vương Thị Ngọc Lan. “Giá trị các xét nghiệm AMH, FSH và AFC dự đoán đáp ứng buồng trứng trong Thụ tinh ống nghiệm”. 2016

FULLY AUTOMATED AMH ASSAY

- Two new fully automated AMH assays: Access 2 IA AMH (Beckman Coulter) and Elecsys AMH (Roche)
- May overcome the limitations of standard AMH assay*

*Gassner và cs. “First fully automated immunoassay for anti-Mullerian hormone”. ClinChem Lab Med. 2014

Access AMH vs AMH Gen II

	Access AMH*	AMH Gen II**
Type	Fully automated assay	Standard assay
Imprecision	2.9% - 4.3%	< 8%
Sample type	serum, lithium heparin	serum, plasma
Time to first result	40 minutes	< 3 hours
Limit of Detection	≤ 0.02 ng/mL	0.08 ng/mL
Limit of quantitation	≤ 0.08 ng/mL	0.16 ng/mL
Measuring range	0.02 - 24 ng/mL	0.16 - 22.5 ng/mL

*Beckman Coulter. “Access AMH Instructions for Use”. 2014
**Beckman Coulter. “AMH Gen II ELISA package”. 2013

Fully automated AMH testing of ovarian response at IVF Tudu

- Retrospective analytical research
- 1870 patients included
- Data collected from women treated in IVF Tudu from 3/2015 to 3/2016

Inclusion criteria

- At the age 18 or beyond
- Using GnRH antagonist protocol

Exclusion criteria

- Ovarian cyst (including endometriosis)
- History of ovarian cyst surgery
- Primary or secondary amenorrhea
- Premature ovarian failure
- Hypothalamic-pituitary dysfunction
- Hyperprolactinemia
- Thyroid disorders

Characteristics of the study

- All AMH values were analysed by Access AMH assay at the Laboratory of Tudu hospital
- All AFCs were accessed at day 2 or 3 of the cycle by physicians of IVF Tudu
- Poor responder: ≤ 3 eggs retrieval*
- Hyper-responder: ≥ 16 eggs retrieval**
- Trigger by: recombinant hCG or GnRH agonist

*Broer và cs.”Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data aproach”.Hum Reprod Update. 2011

**Sunkara và cs.”Association between the number of eggs and live birth in IVF treatment: an analysis of 400,135 treatment cycles”. Hum Reprod. 2011

Characteristics of the samples

Age group	(n)	percentage (%)
18 - 25	61	3.2
26 - 30	374	20
31 -35	686	36.7
36 - 40	435	23.3
> 40	314	16.8

Type of infertility	(n)	percentage (%)
Primary	1,300	69.5
Secondary	570	30.5

Duration of infertility (month)	(n)	percentage(%)
≤ 24	396	21.2
25 - 48	531	28.4
49 - 72	395	21.2
≥ 73	548	29.2

Indications of treatment	(n)	percentage(%)
Male factors	904	48.3
Women of advanced age	118	6.3
Ovarian insufficiency	90	4.8
Fallopian tube disorders	232	12.4
Unknown cause	192	10.3
Other conditions	334	17.9

	Mean ± standard deviation
AMH (ng/mL)	5.28 ± 3.74
AFC	11.3 ± 6.65
Total days of stimulation	10 ± 1.28
Total dose of FSH (IU)	2347 ± 900
Number of eggs > 13mm on the day of trigger	12.39 ± 6.42
Endometrial thickness (mm) on the day of trigger	10.83 ± 3.57

Results

	Mean ± standard deviation
Total number of eggs retrieved	13.49 ± 7.79
Number of mature eggs retrieved	11.93 ± 6.85
Number of eggs fertilized	8.61 ± 5.52
Total number of embryos	8.3 ± 5.59
Number of good/fair embryos	3.74 ± 4.44
Number of embryos cryopreserved	5.66 ± 4.66

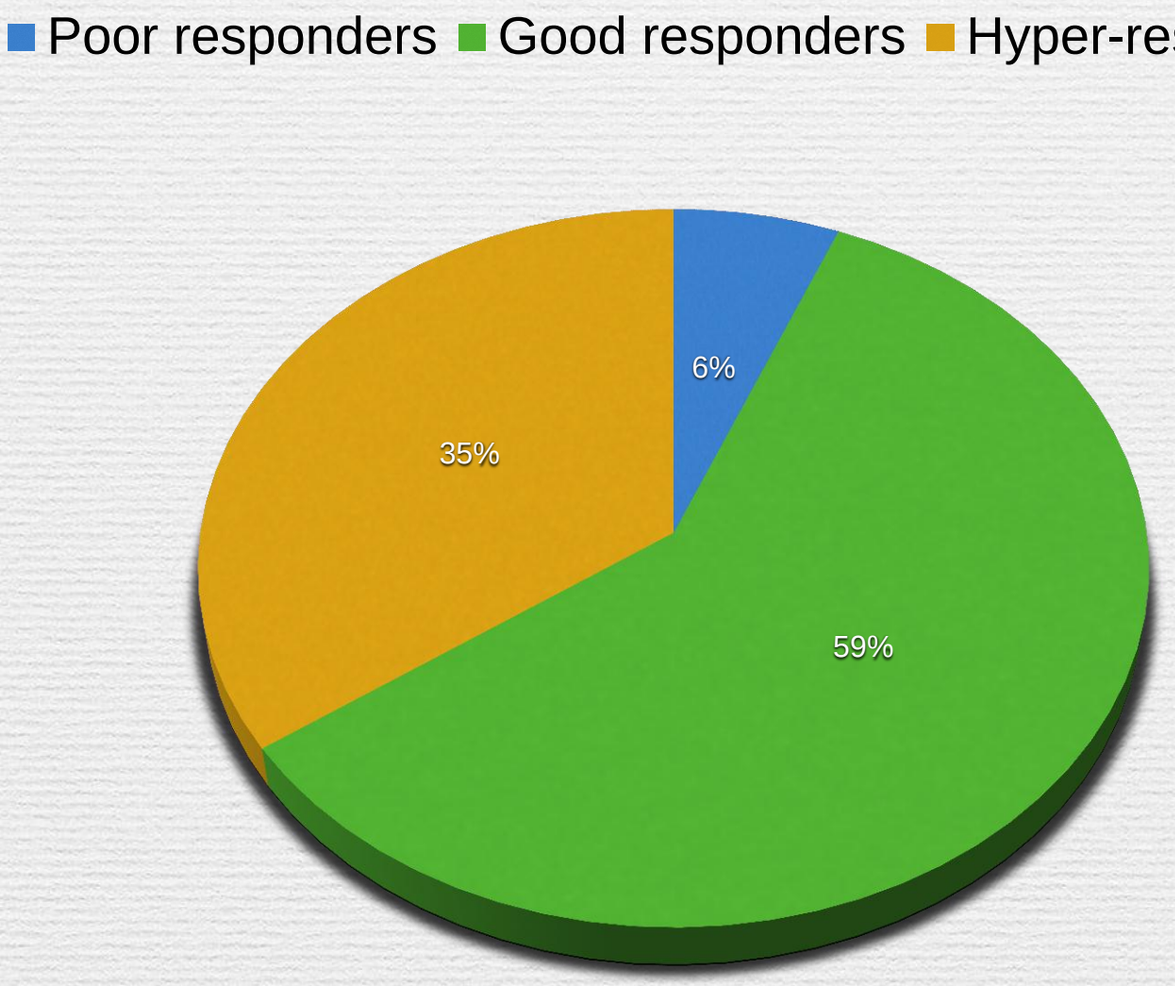
Pregnancy results

	frequency	percentage (%)
Pregnancy/fresh embryo transfer	163/541	31.7
Clinical pregnancy (FHB+)	125/541	23.1
Multiple pregnancy (≥ 2 embryos)	21/541	4
Ectopic pregnancy	3/541	0.5
Miscarriage	7/541	1.3

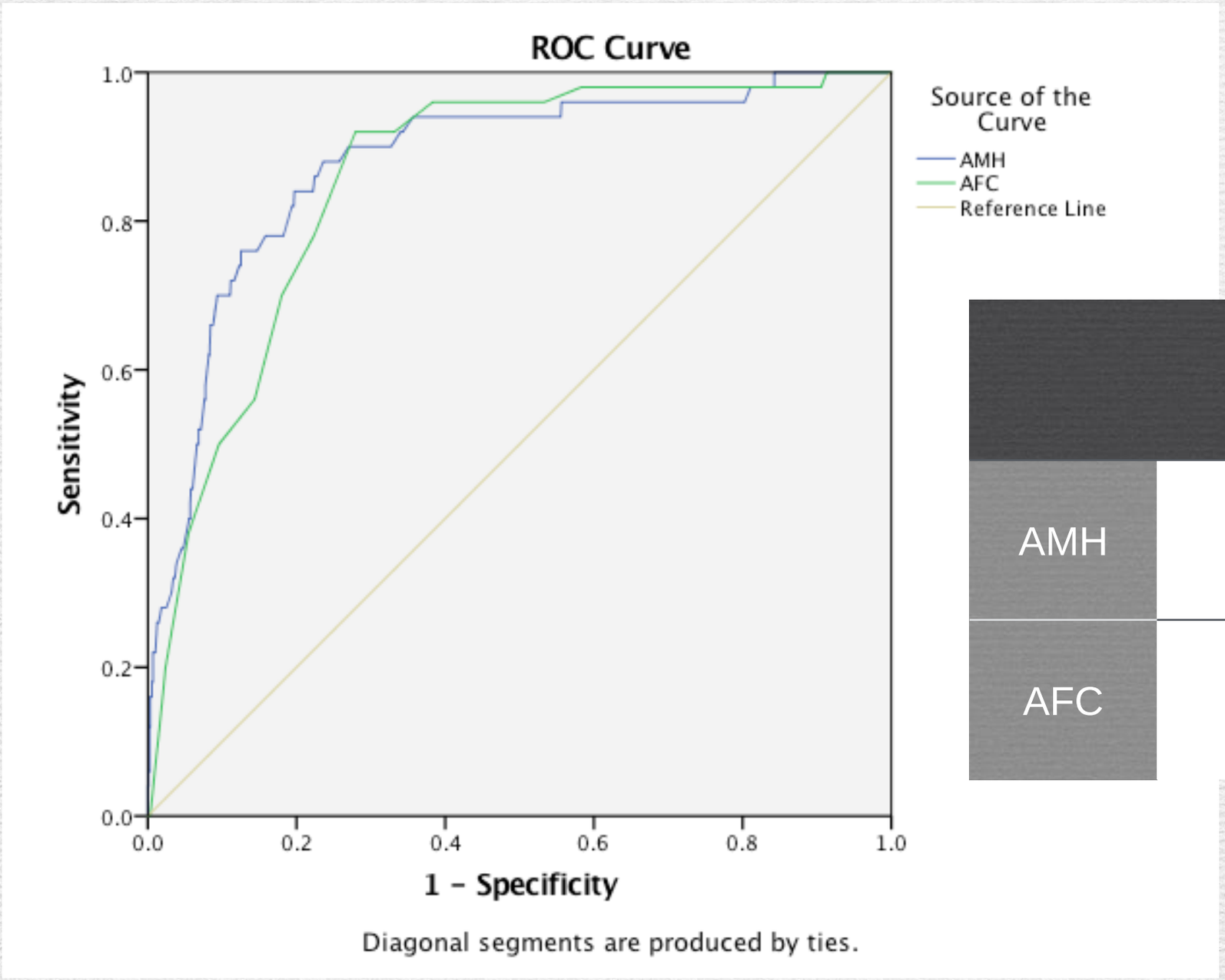
OHSS

	frequency	percentage (%)
Mild OHSS	39	2.08
Moderate - severe OHSS	1	0.05

Results of ovarian response



Poor response predicting



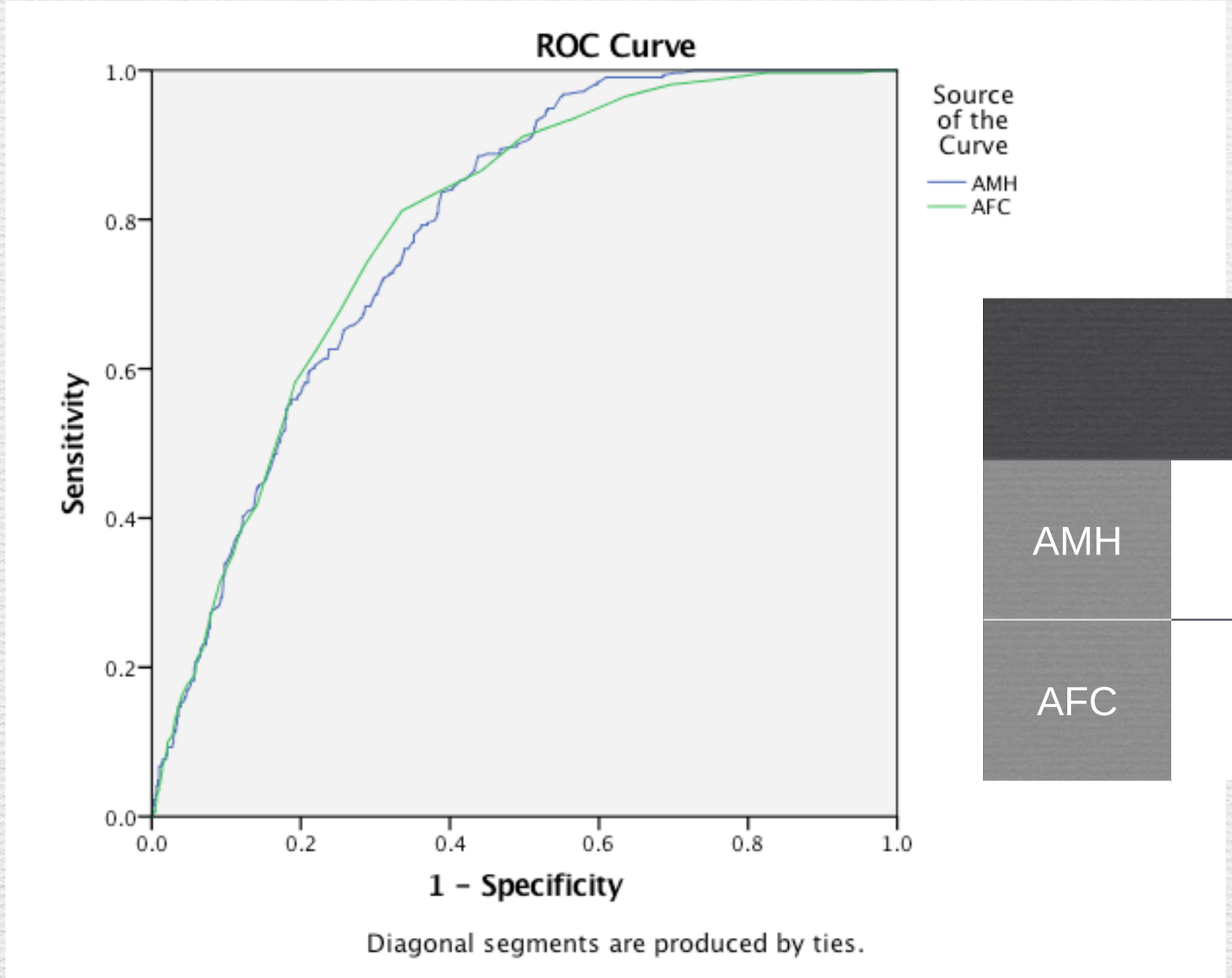
	AUC	Standard deviation	p
AMH	0.919	0.013	< 0.01
AFC	0.868	0.022	< 0.01

*Hanley & McNeil, 1982

AMH, AFC value to predict poor response

	Value	Sensitivity (%)	Specificity (%)	LR+	LR-	+PV	-PV
AMH (ng/mL)	**≤ 1.8**	80.2	90.7	8.6	0.2	35.3	98.8
AFC	**≤ 7**	75.5	90.4	7.9	0.65	22.2	97.5

Hyper-response pridicting



	AUC	Standard deviation	p
AMH	0.82	0.009	< 0.01
AFC	0.78	0.013	< 0.01

*Hanley & McNeil, 1982

AMH, AFC value to predict hyper- response

	Value	Sensitivity (%)	Specificity (%)	LR+	LR-	+PV	-PV
AMH (ng/mL)	**> 4.73**	78.2	71.7	2.8	0.3	69.1	80.2
AFC	**≥ 14**	81.2	65.6	2.4	0.3	65	81.5

Discussions

- Currently, AMH is the best predictor of ovarian response in IVF (AUC=0.92 and 0.82)
- AFC remains a good predictor of ovarian response (AUC=0.87 and 0.78)

Compare AUC of this study with others*

Study	Methods	AMH - AUC	AFC - AUC
Acre et al. (2013)	749, retrospective	0.9	0.74
Broer et al. (2013)	5705, meta-analysis	0.81	0.73
Polyzos et al.(2013)	210, retrospective	0.84	0.83
VTN Lan (2016)	820, prospective	0.93	0.89
This study (2016)	**1870, restrospective**	**0.92**	**0.87**

*Vương Thị Ngọc Lan. “Giá trị các xét nghiệm AMH, FSH và AFC dự đoán đáp ứng buồng trứng trong Thụ tinh ống nghiệm”. 2016

Compare AMH value to predict poor response of this study with others*

Study	Value (ng/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-
Polyzos et al. (2013)	≤ 1.37	74.1	77.5	3.29	0.33
Arce et al. (2013)	≤ 1.68	92	83	-	-
VTN Lan (2016)	≤ 1.25	86.7	84.8	5.7	0.8
This study (2016)	**≤ 1.8**	**90.2**	**80.7**	**8.6**	**0.2**

*Vương Thị Ngọc Lan. “Giá trị các xét nghiệm AMH, FSH và AFC dự đoán đáp ứng buồng trứng trong Thụ tinh ống nghiệm”. 2016

Compare AMH value to predict hyper- response of this study with others*

Study	Value (ng/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-
Hamdine et al. (2013)	> 2.75	82	72	2.96	-
Arce et al. (2013)	> 4.34	76	74	-	-
VTN Lan (2016)	> 3.57	83.7	79.8	4.1	0.2
This study (2016)	**> 4.7**	**78.2**	**71.7**	**2.8**	**0.3**

*Vương Thị Ngọc Lan. “Giá trị các xét nghiệm AMH, FSH và AFC dự đoán đáp ứng buồng trứng trong Thụ tinh ống nghiệm”. 2016

Conclusions

- AMH is a reliable test to predict ovarian response to stimulation in IVF
  - *Considering AMH to be a regular test for all IVF patients*
- AFC still an irreplaceable predictor of ovarian response
  - *Mainly depends on subjectivity and experience of the physician*
- Some noise factors not fully controlled in this study
- Require a prospective study of fully automated AMH assay to have a precise value of AMH to predict ovarian response

Thanks for your attention

~IVF Tudu 2016