Biomarkers to Redirect Response to Ovulation Induction

Pablo Diaz-Spindola, MD, FACOG

Medical Director IECH Fertility Center Monterrey

Professor of Endocrinology and Reproductive Medicine

Fellowship of UNAM

Monterrey, Mexico

gfa

Global Fertility Academy

Objectives
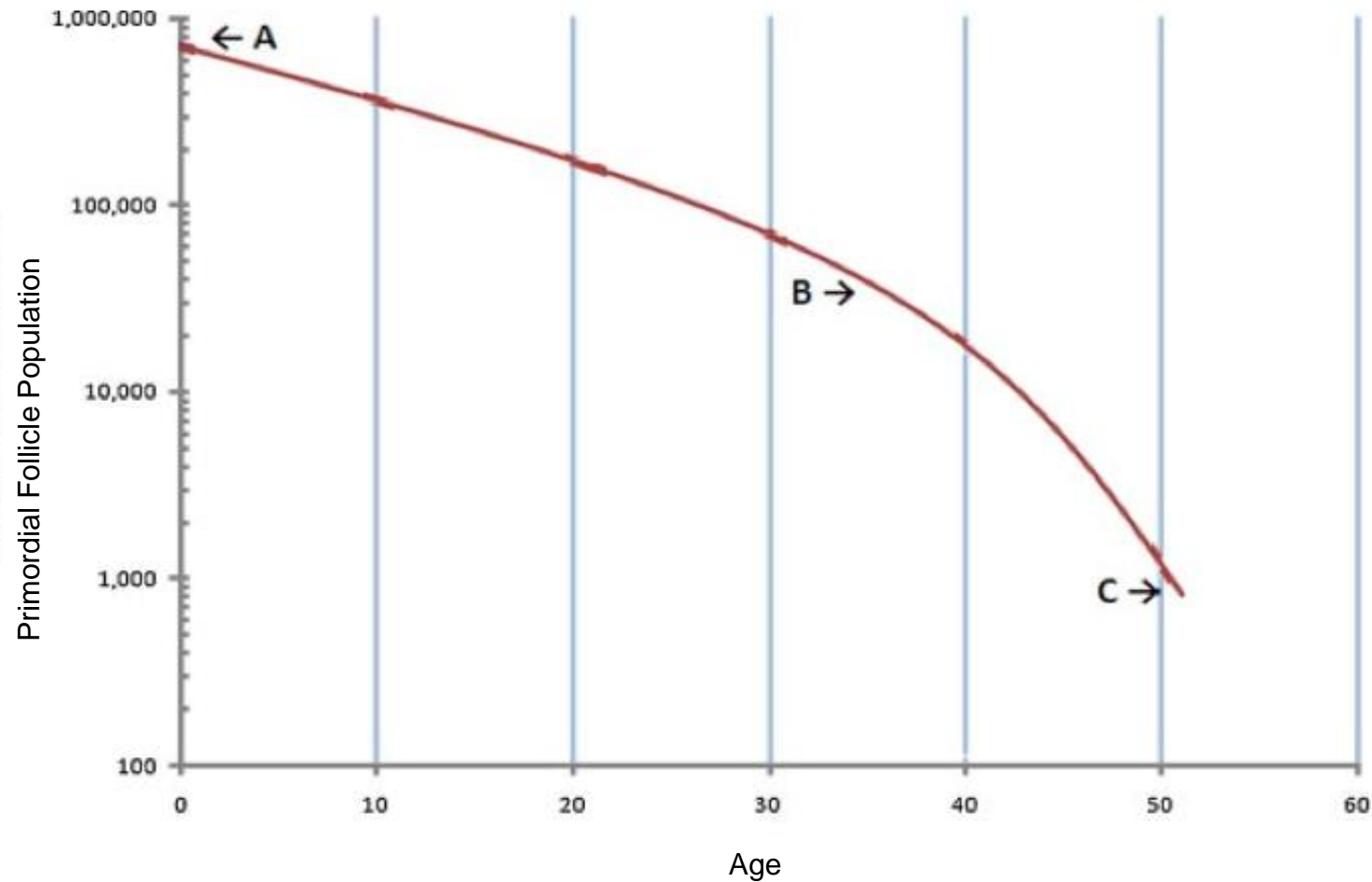
Background

What is AMH

iCOS Biomarkers

Protocols

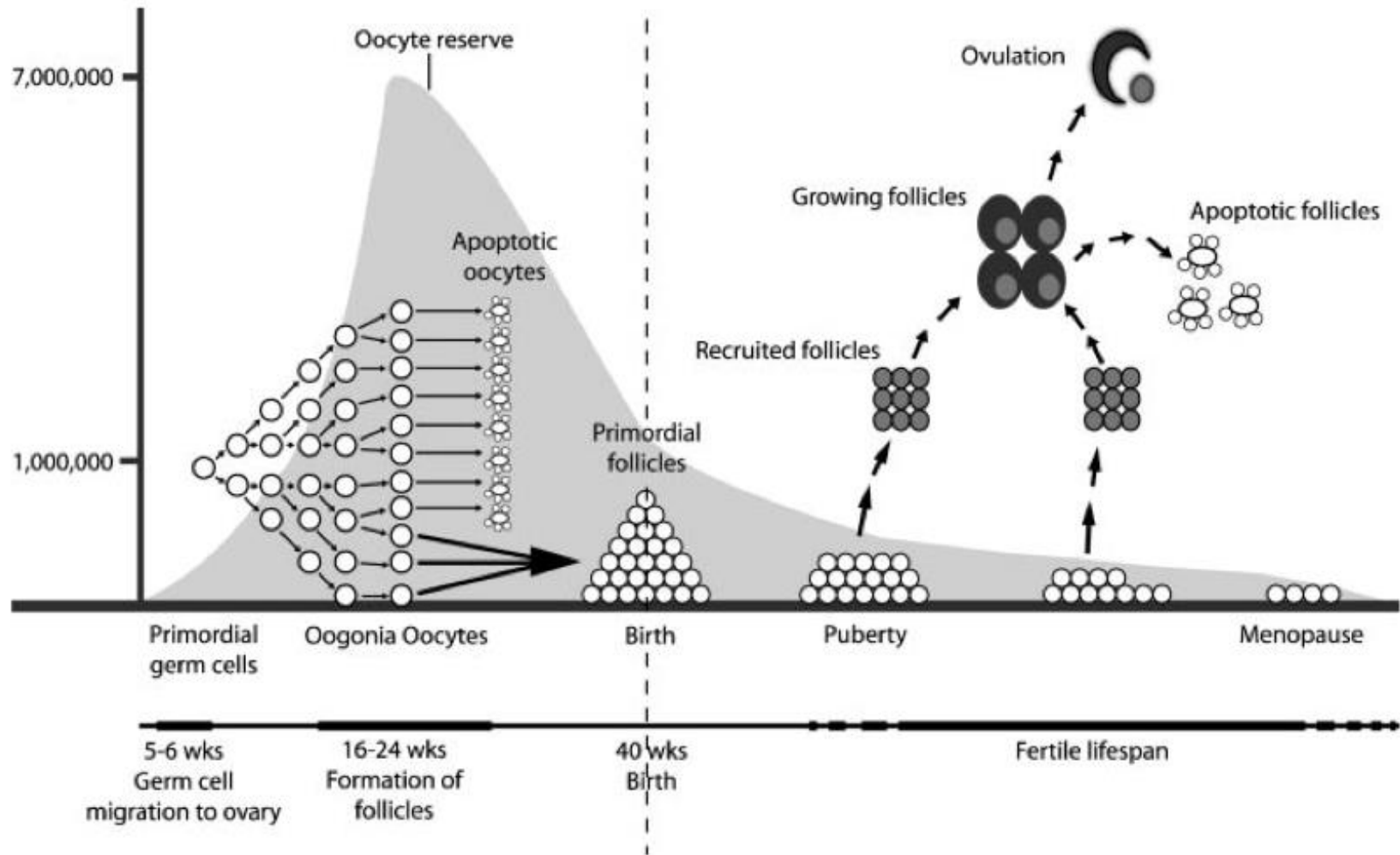Discussion of advantages

Conclusions

Decrease of the Female Fertility Based on Age

Johnson RJ., and Wallace WH., Normal ovarian function and assessment of ovarian reserve in the survivor of childhood cáncer. Pediatr blood cáncer 2009;53:296-302.

Decrease of the Female Fertility Based on Age

Johnson RJ., and Wallace WH., Normal ovarian function and assessment of ovarian reserve in the survivor of childhood cáncer. Pediatr blood cáncer 2009;53:296-302.

Risk Factors that Decrease the Ovarian Reserve

Reproductive older (over 35 years).
Family history of early menopause.
Genetic conditions (eg. Mosaic 45 X)

Permutation of the FMR1 (fragile X)
Conditions that can cause ovarian damage
(eg. Endometriosis, pelvic infection)
after ovarian surgery

Oophorectomy
Medical history of use of medicinal
gonadotoxics
smoking

Ovarian Reserve Testing. The American Colleage of obstetricians and Gynecologist. Committee Opinion. January 2015, Number 618.

Wait… What is all this about.

Redirect Response to Ovulation Induction

Global Fertility Academy

Biomarker: Definition

- NIH " A characteristic that is objetively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention"

Palmer SS et al. Biomarkers in reproductive medicine: The promise, and can it be fulfilled?. Fertil Steril 2013 March 15;99(4):954-962

Objective for Having an Ovarian Biomarker

- Avoid excesive responce and reduce ovarian responses.

- Identified poor responders to dimish cycles cancelation.

- Facilitate an optimal treatment strategy, potentially minimizing complications and the risk of treatment failure
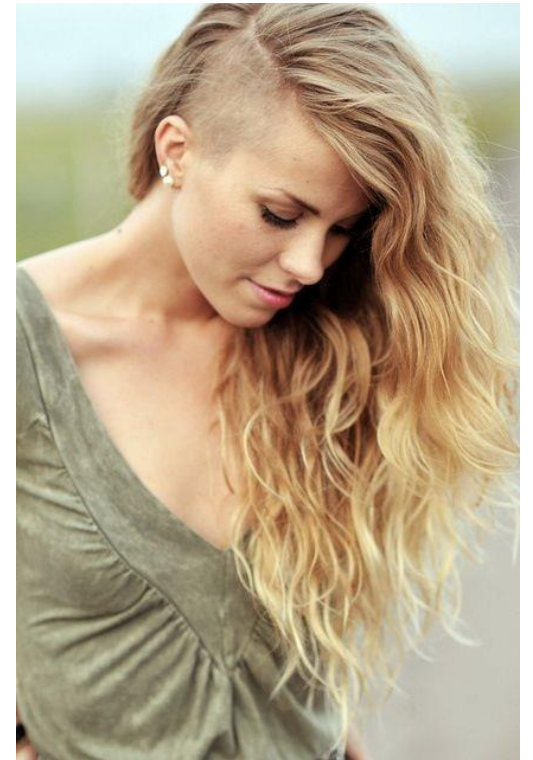
- Reduce the cost

Women Always Want to be a Little Different....

Poor Responder
AMH 0.2 ng/ml

Normal Responder
AMH 1.9 ng/ml

Hyper Responder
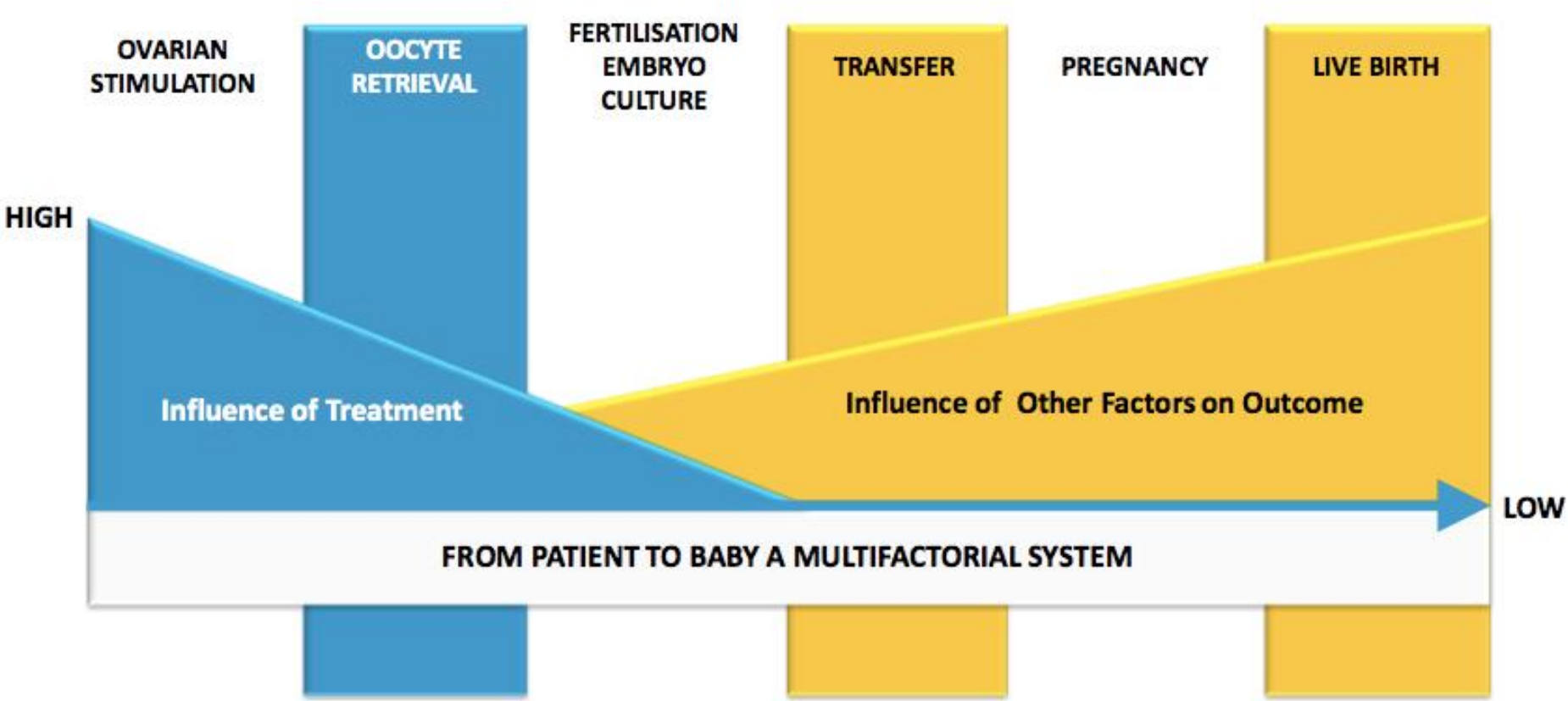AMH 3.6 ng/ml

So, we need to act differently.
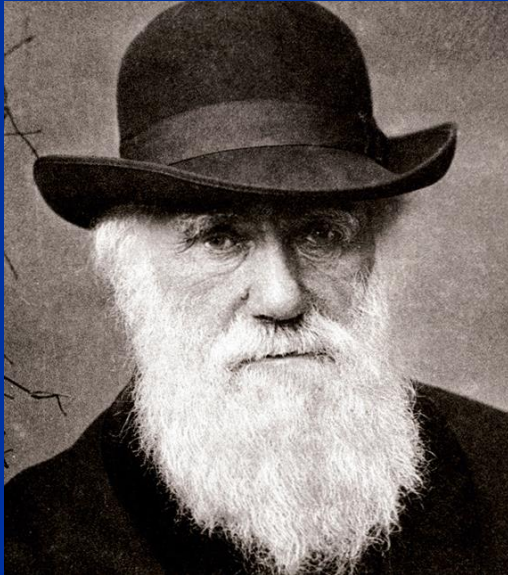
How Easy is the IVF Treatment?

The way we would like it. The way it really is.

Our Focus are Biomarkers, but There are so Many Factor…

Which one is the best Biomarker to define ovarian response?

Discovered 1940 by Alfred Jost

Müllerian inhibiting substance

Human Gen
- 20 years later it was isolates and his sequence was known.

Homodiméric Glycoprotein
- Molecular weight 140 kDa
- 4 times heavier than FSH and LH
- Gene on chromosome 19 p13.3

TGF-b
- It belongs to the super family of beta transforming growth factor

Müllerian Inhibiting Substance: An Instructive Developmental Hormone with Diagnostic and Possible Therapeutic Applications

JOSE TEIXEIRA, SHYAMALA MAHESWARAN, AND PATRICIA K. DONAHOE

Pediatric Surgical Research Laboratories, Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Physiology of AMH
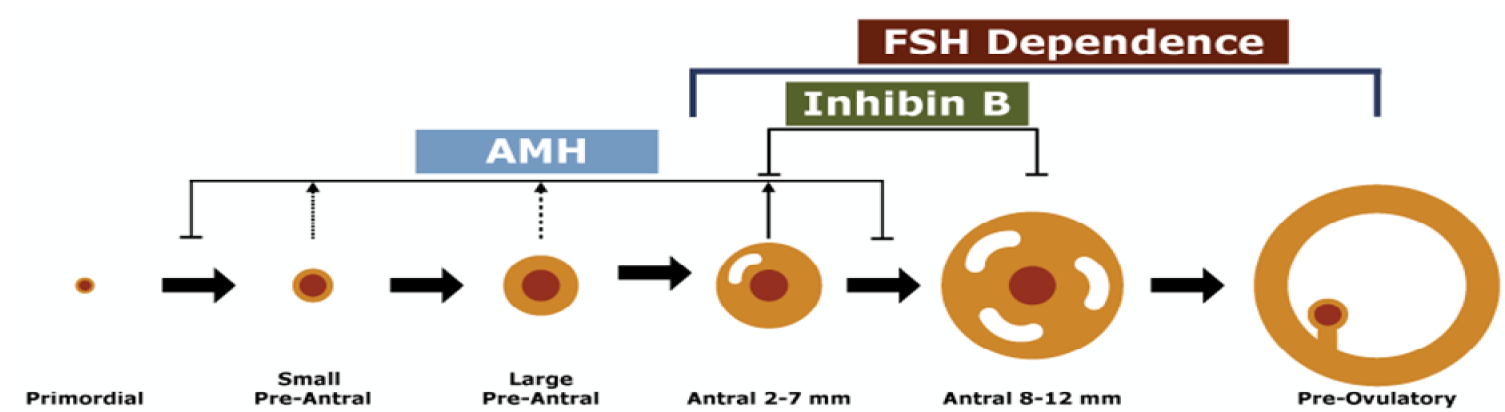
Secreted by the primordial and prenatal follicle granulosa cells.

- They lose this ability from antral follicles (6-8 mm), mediated by FSH.
- The number of follicles in growth are those that produce the AMH.
- Effect on the primordial follicles remaining, inhibiting their recruitment.

Visser JA, Themmen APN. Anti-Müllerian hormone and folliculogenesis. Mol Cell Endocrinol 2005;234:81-86.

Stability of the AMH

Factors that could influence on the serum concentration of AMH:

Reduce it:	Increase it:	Have no influence:
Age	PCOS	Menstrual cycle
BMI		GnRh agonists
Administration of chemotherapy and radiotherapy		oral contraceptives
Oophorectomy		pregnancy

Seifer D, MacLaughlin D. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. Fertil Steril 2007;88:539-46.

AMH Assays
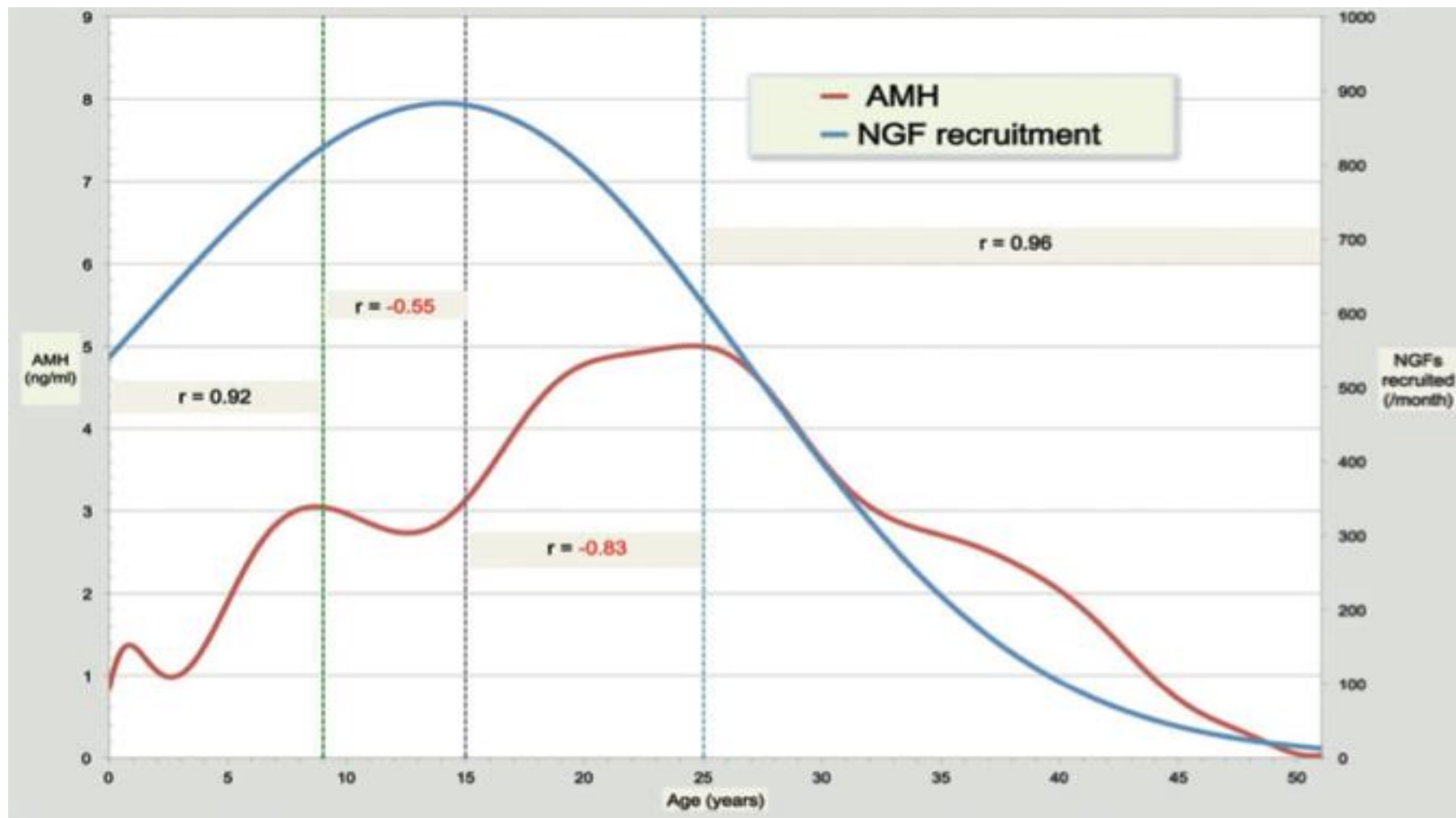
Broer S.L. Et cols. Anti-müllerian hormone: Ovarian reserve testing and its potential clinical implications. Human reproduction update 2014;20(5):688-701.

Characteristics of the Most Commonly Used Markers of Ovarian Reserve

Test	Details
FSH plus estradiol	• Serum level on cycle day 2–3 • Variation between cycles possible • High FSH value is associated with poor response to ovarian stimulation • Does not predict failure to conceive
AMH	• No specific timing for the test • Stable value within and between menstrual cycles • Low AMH value is associated with poor response to ovarian stimulation • Does not predict failure to conceive
AFC	• Number of visible follicles (2–10 mm) during transvaginal ultrasound • Performed on cycle days 2–5 • Number of antral follicles correlates with ovarian response to stimulation • Does not predict failure to conceive

Abbreviations: AFC, antral follicle count; AMH, antimüllerian hormone; FSH, follicle-stimulating hormone.

Ovarian Reserve Testing. The American Colleage of obstetricians and Gynecologist. Committee Opinion. January 2015, Number 618.

Markers of Ovarian Reserve and its Influence on Pregnancy

Assessment	Outcome	
	Favourable	Unfavourable
Prior COH cycle	Delivery	No pregnancy
Age (years)	<35	≥35
FSH (IU/l)[a]	<10	≥10
d3 E$_2$ (pg/ml)	<75	≥75
d10 P$_4$ [b]	<0.9	>1.1
AMH (pmol/l)[c]	15.7–48.5*	<15.7
d3 inhibin-B (pg/ml)[d]	>45	≤45
AFC[e]	≥5	<5
Ovarian vascularity	Lower PI	Higher PI
Ovarian volume (cm^3)[f]	≥3	<3
CCCT [FSH only (IU/ml)][g]	<12	≥12
GAST	Early E$_2$ flare	Persistent E$_2$↑ or no response

Sills ES., Alper MM., Walsh PH., Ovarian reserve screening in infertility: Practical applications and theorical directions for research. European journal of obstetrics and gynecology and reproductive biology 2009;146:30-36.

Comparative Table of More Common Characteristics of the Ovarian Reserve Markers

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	+++	++	−	++
Applicable to all patients	+++	++	+	+
Economic	+++	−	−	−

−, not appropriate; +, not very appropriate; +++, very appropriate. AFC, antral follicle count; AMH, anti-Mullerian Hormone.

La Marca A., Sunkara SK., Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Human reproduction update 2014;30(1):124-140.

Both Technologies are Improving and Increasing Accurate
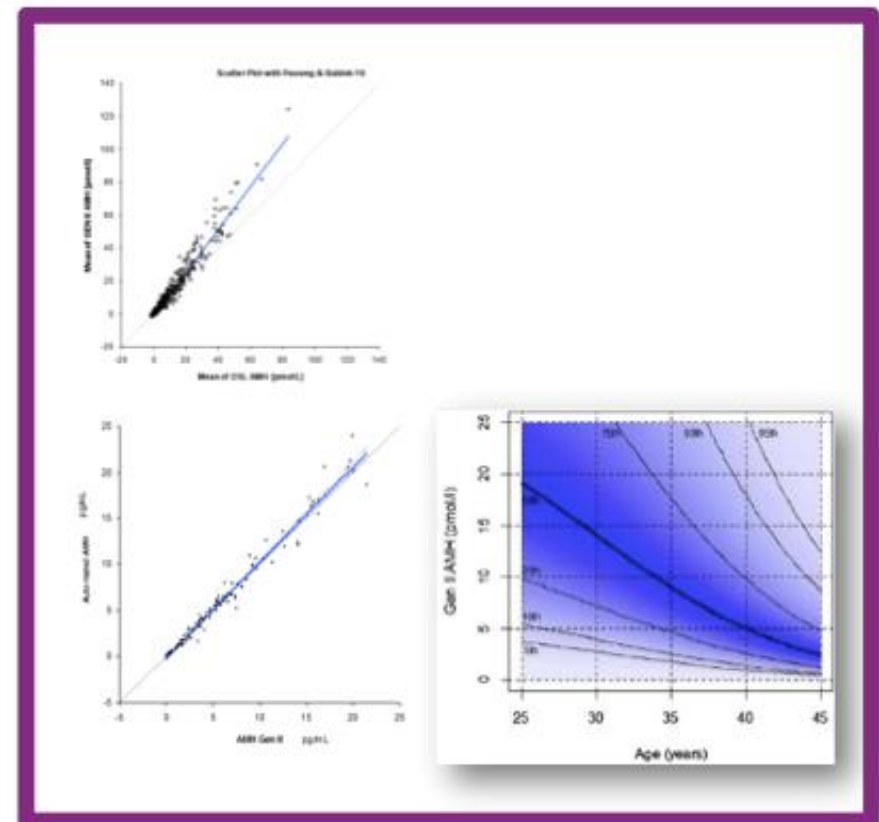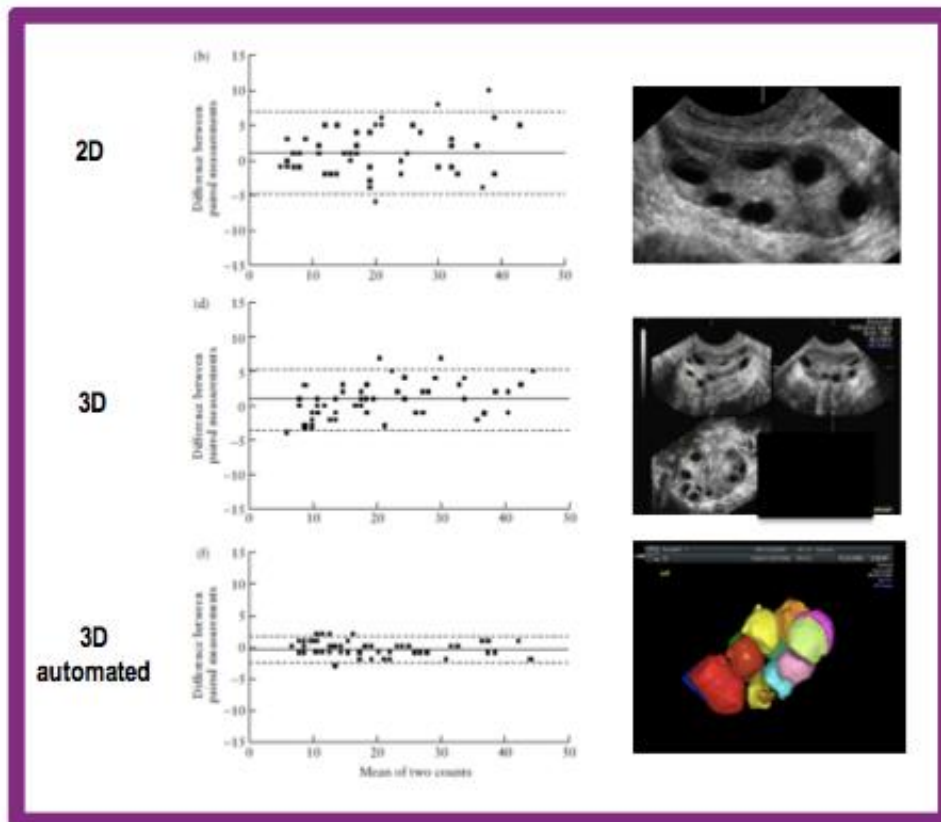
Deb S, et al. *Ultrasound Obstet Gynecol.* 2009; Van Disseldorp, et al. *Hum Repro* 2009; Wallace, et al. *Ann Clin Biochem. 2011;* Nelson, et al. *Fertil Steril.* 101:523-529, 2014.

Markers of Ovarian Reserve of Today

La Marca A., Sunkara SK., Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Human reproduction update 2014;30(1):124-140.

Normal Values Ovarian Reserve

Non-response: <1.1 pmol/l

Poor responder: 1 – 5 pmol/l or <0.5 ng/ml	Normal responder: 5 – 15 pmol/l or 1.0-3.5 ng/ml	Hight responder: >15 pmol/l or >3.5 ng/ml

Fleming R. Et cols. Can Anti-Mullerian hormone concentrations be used to determine gonadotrophins treatmemnt protocol for ovarian stimulation?Reproductive BioMedicine Online (2013) 26, 431. 439

Toner JP., et cols. Why we may abandon basal FSH testing: a sea change in determining ovarian reserve using AMH. Fert Stert 2013;99:1825-30.

AMH Conversion Factor

$$1 \text{ ng/ml} = 7.143 \text{ pmol/lt}$$

Somebody explain me, please.

Strategic Modelling of Controlled Ovarian Stimulation on the Basis of Ovarian Reserve Markers

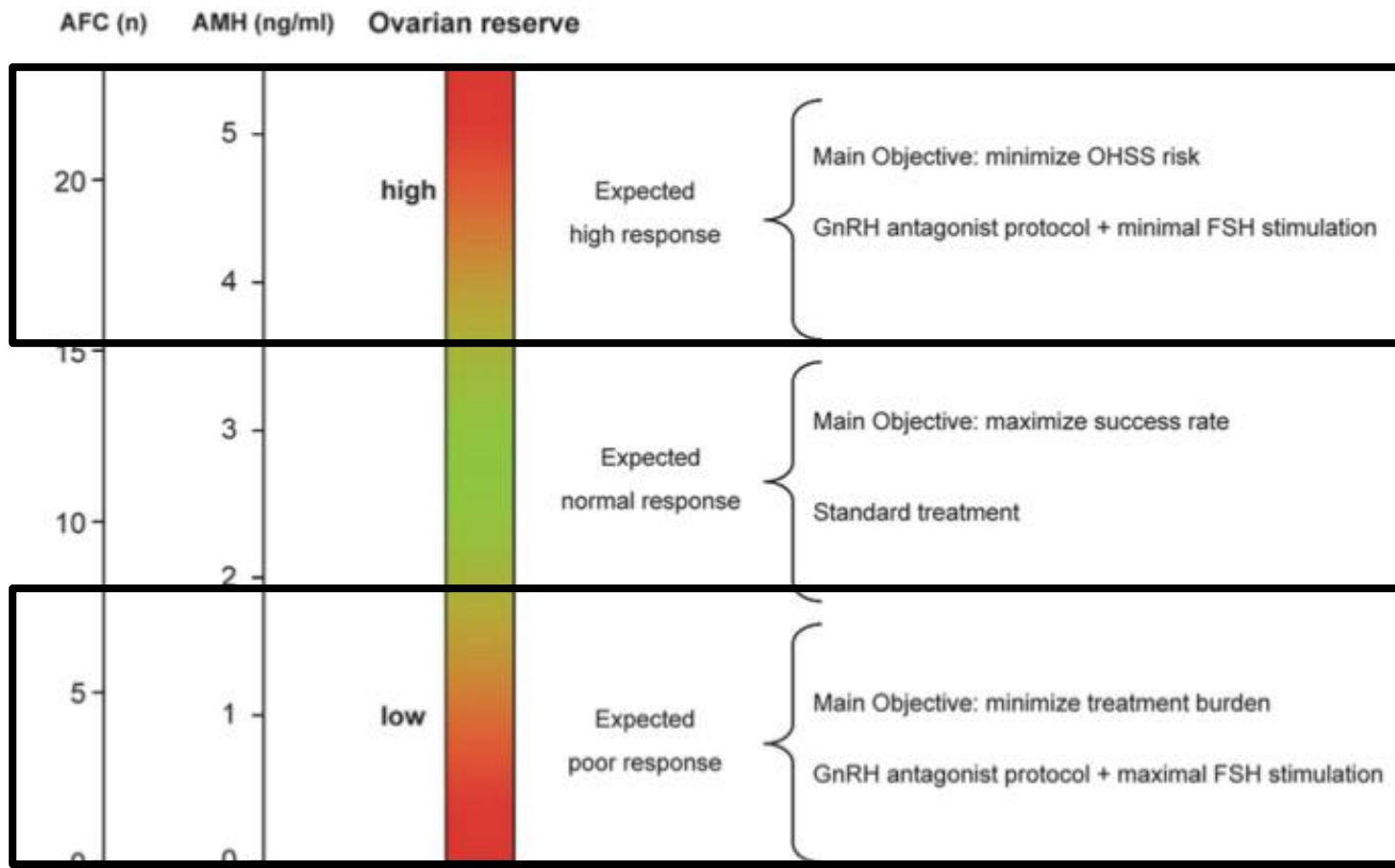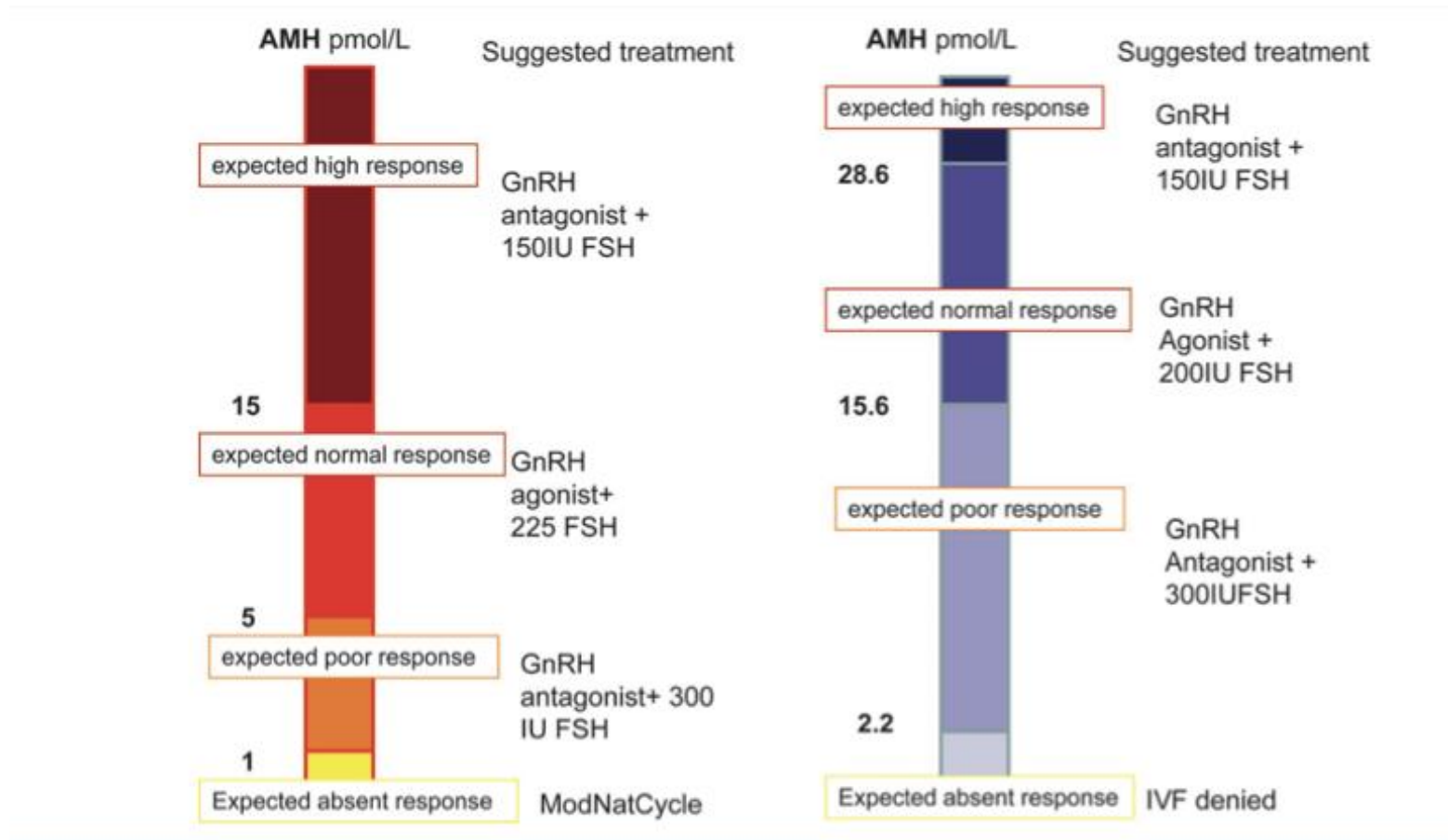Nelson et al. (2009)   Yates et al. (2011)

La Marca A., Sunkara SK., Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Human reproduction update 2014;30(1):124-140.

Is This Nomogram Useful?
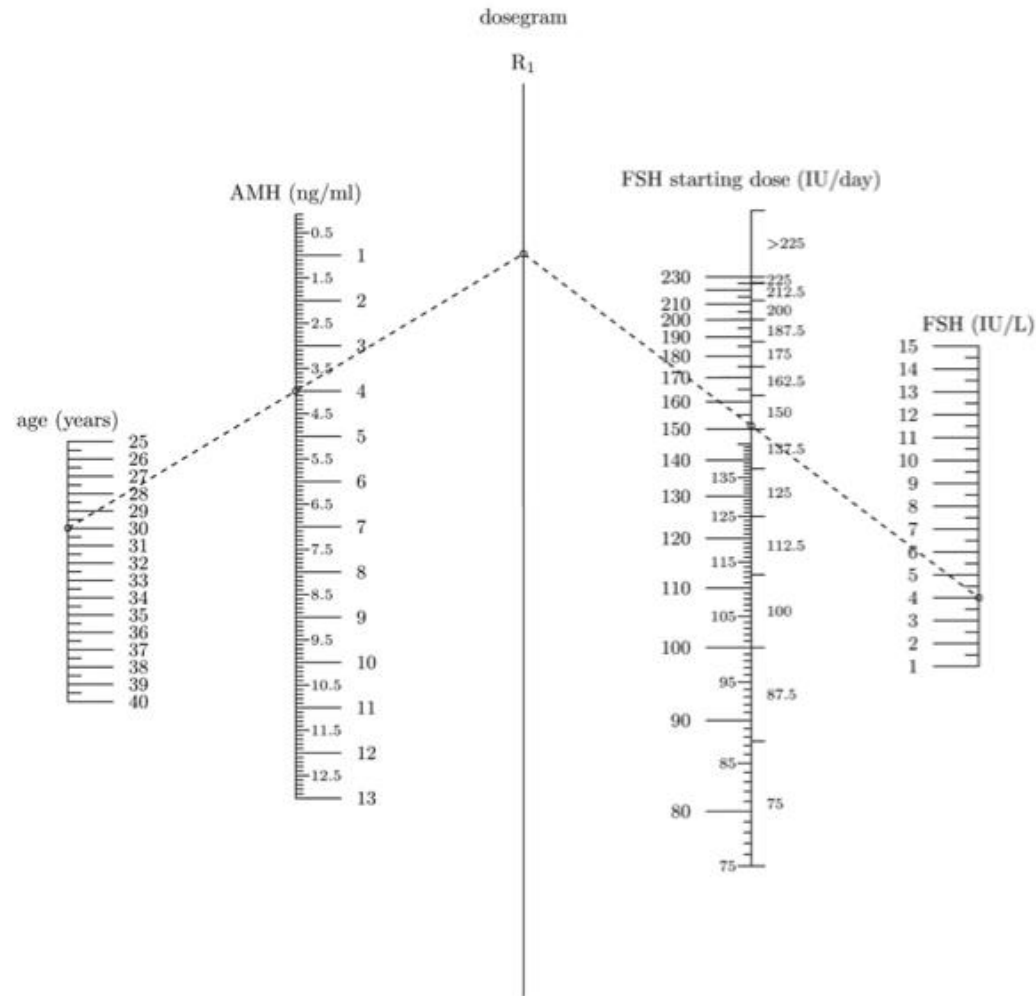
La Marca A., Sunkara SK., Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Human reproduction update 2014;30(1):124-140.

Can We Relate AMH to COS Protocols?

Nelson, et al. *Fertil Steril.* 99:963-969, 2013.
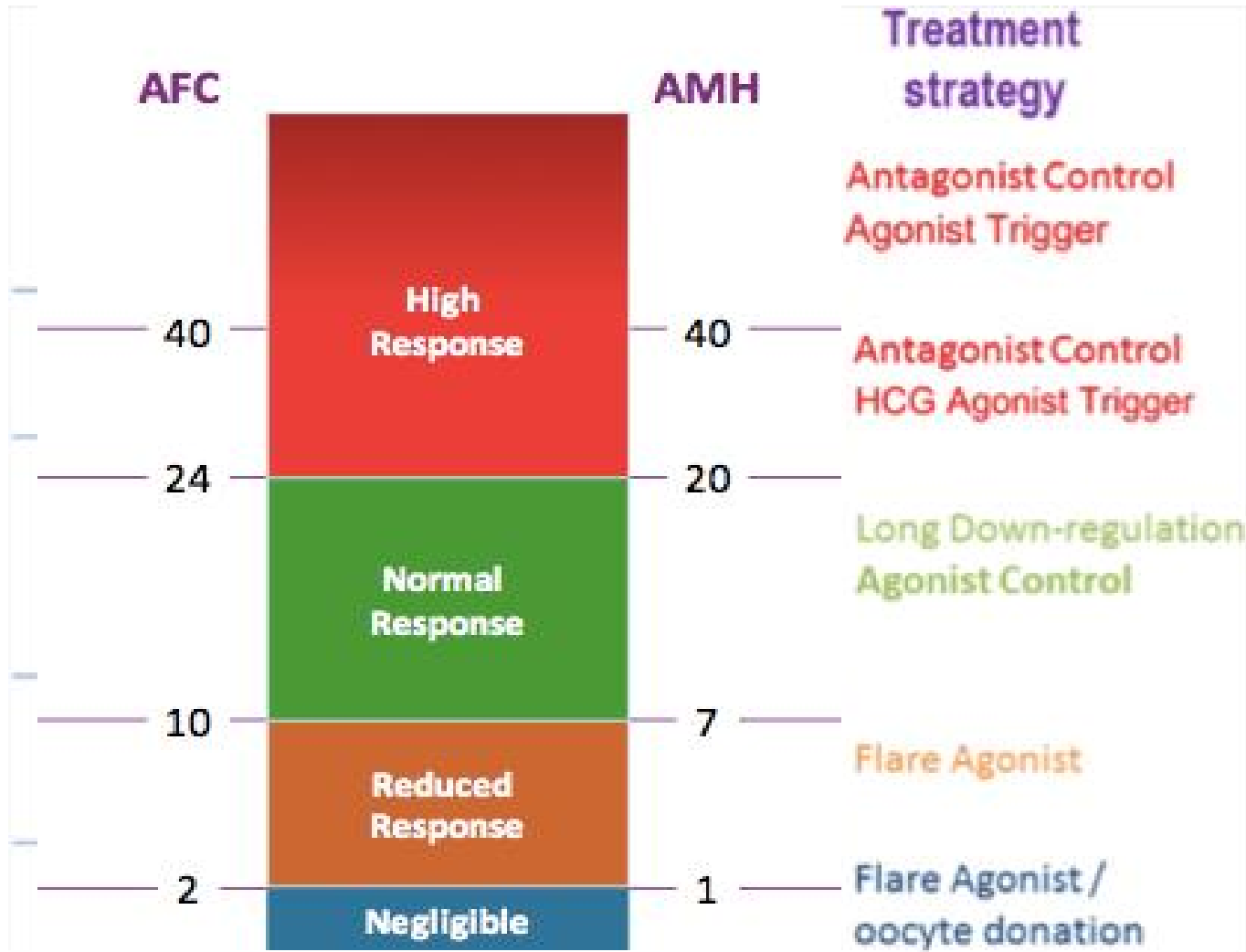
High Responder Patient
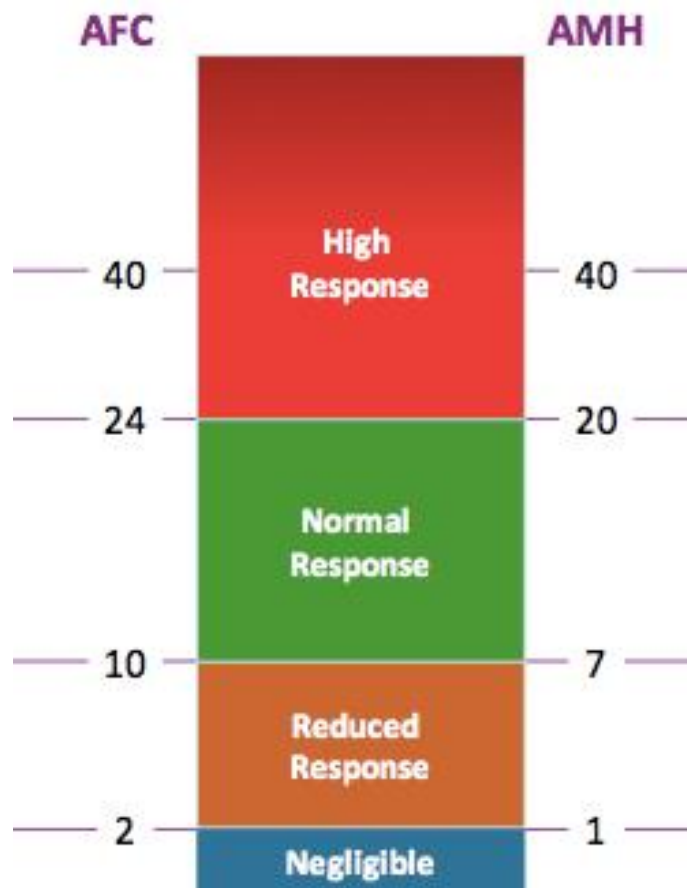
- Definition >15-20 oocytes
- AMH > 20 pmol/lt
- PCOS type
- History of OHSS
- Therapy suggested:
  - Antagonist protocol
  - rFHS alone
  - 100-125 IU/d
  - Eventually agonist triggering
  - Freeze all strategy

Fleming R. Et cols. Can Anti-Mullerian hormone concentrations be used to determine gonadotrophins treatmemnt protocol for ovarian stimulation?Reproductive BioMedicine Online (2013) 26, 431. 439

Normal Responder Patient

AFC / AMH response chart:
- High Response — AFC 40, AMH 40 to 24/20
- Normal Response — AFC 24–10, AMH 20–7
- Reduced Response — AFC 10–2, AMH 7–1
- Negligible — AFC 2, AMH 1
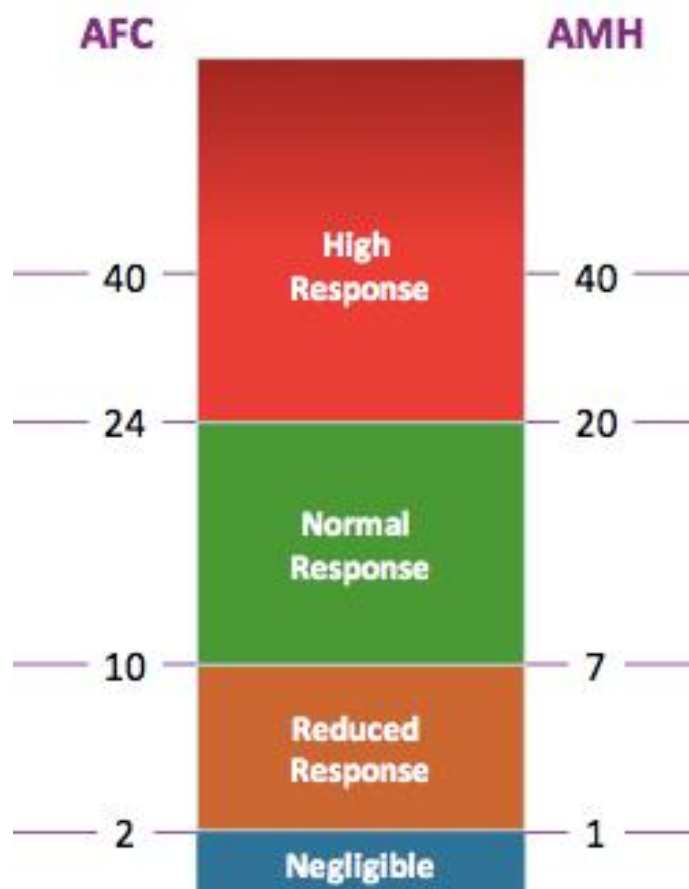
- Definition 8 -15 oocytes
- AMH 7-19.9 pmol/lt
- History of normal response
- Therapy suggested:
  - Antagonist protocol
  - rFHS alone
  - 150-225 IU/d
  - hCG triggering

Fleming R. Et cols. Can Anti-Mullerian hormone concentrations be used to determine gonadotrophins treatmemnt protocol for ovarian stimulation?Reproductive BioMedicine Online (2013) 26, 431. 439

Low Responder Patient

AFC / AMH response chart:
- High Response: AFC 40, AMH 40 down to AFC 24, AMH 20
- Normal Response: AFC 24, AMH 20 down to AFC 10, AMH 7
- Reduced Response: AFC 10, AMH 7 down to AFC 2, AMH 1
- Negligible: below AFC 2, AMH 1
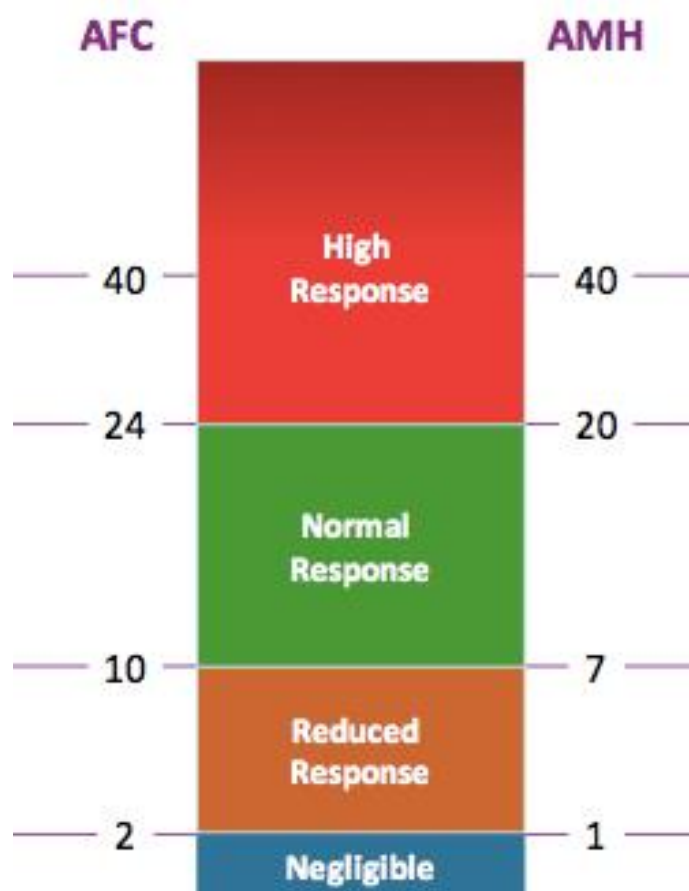
- Definition 5 -8 oocytes
- AMH 1.1-6.9 pmol/lt
- Women <40 years of age
- History of Low response
- Therapy suggested:
  - Antagonist protocol
  - rFHS and LH
  - 300 IU/d FSH + 75-150 IU/d
  - hCG triggering

Fleming R. Et cols. Can Anti-Mullerian hormone concentrations be used to determine gonadotrophins treatmemnt protocol for ovarian stimulation?Reproductive BioMedicine Online (2013) 26, 431. 439

Poor Responder Patient

AFC — AMH

High Response
40 — 40
24 — 20

Normal Response

10 — 7

Reduced Response

2 — 1
Negligible
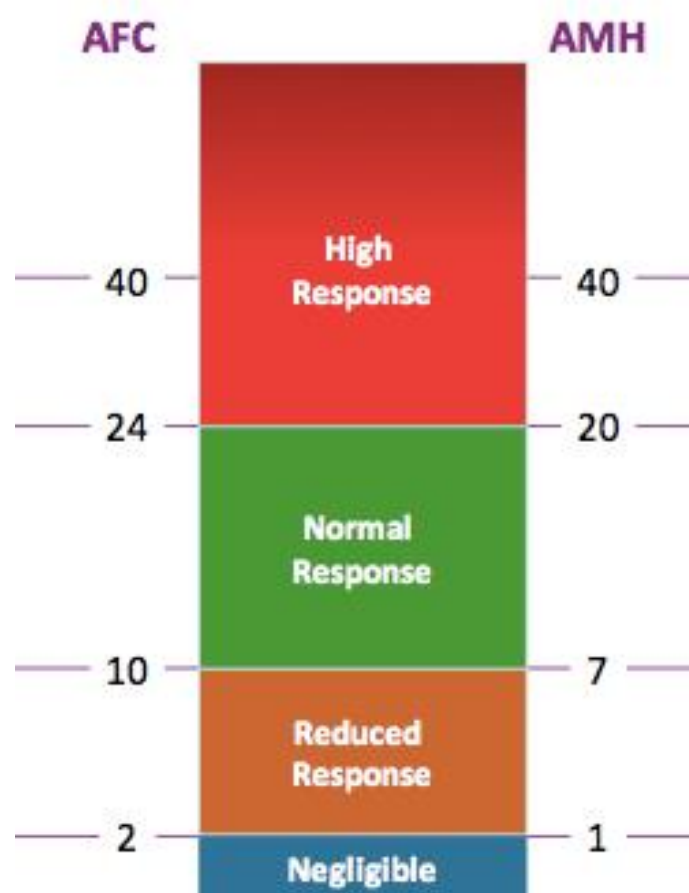
- Definition <5 oocytes
- AMH < 1.1 pmol/lt
- Negligible chance of response
- Therapy suggested:
  - Antagonist or flare-up agonist protocol
  - 300 IU/d FSH plus 150 LH
  - hCG triggering

Fleming R. Et cols. Can Anti-Mullerian hormone concentrations be used to determine gonadotrophins treatmemnt protocol for ovarian stimulation?Reproductive BioMedicine Online (2013) 26, 431. 439

Not all agree

Predictor of Response in ART

IECH
Centro de Fertilidad

Most useful tool when evaluating the ovarian reserve (fertile and infertile).

Detectionl imit 0.05 ng/ml

More specific prediction than FSH

Inter- and intra-ciclo variability and stability make handy tool. 6-8 months

AMH serum levels correlate more with CFA than other markers in day 3 of cycle (FSH, LH, estradiol and inhibin B).

Loh y Maheshwari. Anti-Müllerian hormone· is it a crystal ball for predicting ovarian ageing? Hum Reprod. (2011) 26 (11): 2925-2932.

Predictor of Response in ART

IECH
Centro de Fertilidad

Predictive markers response in ovarian stimulation:

Only the AHM was the determinant of the number of mature oocytes obtained

Low ovarian response cut-off point: 2.97ng/ml

- FSH, LH
- Estradiol
- Inhibin B
- AMH
- AFC

ESHRE: AMH 0.5-1.1 ng/ml

100% Sensitivity

90% Specificity

Kunt C, et al. Anti-Mullerian hormone is a better marker than inhibin B, follicule stimulating hormone, estradiol or antral follicle count in predicting the outcome of in vitro fertilization. Arch Gynecol Obstet. 2011;283:1415-21

Predictor of Pregnancy

It does not predict who will become pregnant

Ovarian reserve tests: do not evaluate the quality of the oocytes.

AMH is a good predictor of ovarian response

Age

Time of infertility

Cause of infertility

Factors involved in the prediction of pregnancy

Low AMH should not be the only factor for refusing the opportunity to ART.

Most obvious limitations when HAM 0.4 ng/dl.

Extremely low levels of HAM are associated to not pregnancy.

Scott M. Nelson, et al. Anti-Müllerian hormone: clairvoyance or crystal clear? Hum. Reprod. (2012) 27 (3): 631-636.

Predictor of Ovarian Response

IECH
Centro de Fertilidad

> HAM as ovarian predict response sensitivity 82% and specificity 76%

- AFC sensitivity 82% y Specificity 80%.

Low response <1.0 ng/ml

- 2-30% will be low responers.
- Lower pregnancy rates compared with normoresponders of the same age.

- Premature ovarian failure

(OHSS) ovarian hyperstimulation syndrome. >3.75 ng/ml

- Moderate: 15-20%
- Severe: 1-3%.
  - Poor quality eggs
  - Hiperestimulados cycles can cause multiple organ failure.
- AMH predicts OHSS
  - sensitivity of the 90.5%
  - specificity of the 81.3%

Nardo LG, et al. Circulatin basal anti-mullerian levels as predictor of ovarian response in women undergoin ovarian stimulation for invitro fertilization . Fertil Steril (2009) ;92 i586-93

HAM Values Used in Mexico as Predictors of Response

Cuadro 1. Características demográficas y bioquímicas de la población

	Normorrespon-dedora (6-15 OC, n=20)	Hiporres-pondedora (≤5 OC, n=10)	Hiperrespon-dedora (≥16 OC, n=9)	P
Edad	35 ± 6	37 ± 7	35 ± 5	0.667
AMH8ng/ml)	1.46 ± 1.43	0.355 ± 0.33	3.10 ± 1.86	0.015*
FSH (UI/L)	7.40 ± 3.53	10.37 ± 9.23	5.53 ± 1.62	0.146
AFC en FFT	7.8 ± 2.4	1.6 ± 1.1	16 ± 2.2	<0.01**

Media ± desviación estándar (DE).
*Normorrespondedoras *vs* hiperrespondedoras
** Normorrespondedoras e hiperrespondedoras *vs* Hiporrespondedoras

Godoy-Morales HS, et al. Hormona antimulleriana como marcador de respuesta ovárica en fertilización *in vitro.* Ginecol Obstet Mex 2012;80(1):1-7

AMH Values Used in the IECH as Predictors of Response
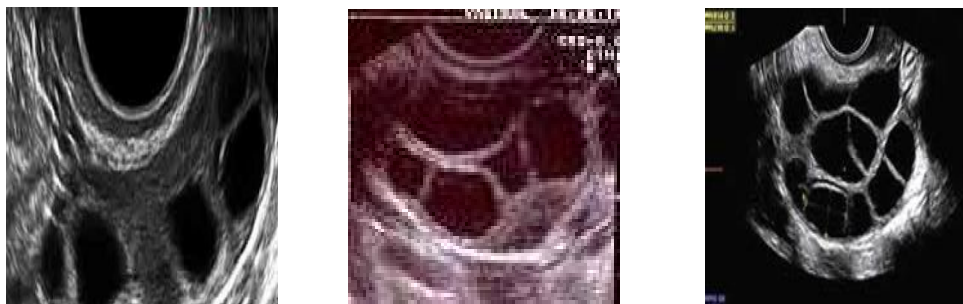
TABLA No. 1	0-5 OVOCITOS (n=10)	6-16 OVOCITOS (n=26)	17 O MÁS (n=12)	Valor P
Edad	38.8± 3.58	27.69±6.94	27.6±7.67	<0.000
IMC	22.53±4.33	24.64±4.31	23.47±2.95	0.344
FSH	8.78±3.43	5.22±1.65	4.55±1.70	<0.000
Estradiol día 10	555.10 ±489.64	2416.27±1428.44	3564.75±1678.39	<0.000
Folículo > 15 mm	2.30±1.89	9.54±3.89	11.58±2.31	<0.000
HAM	0.59±0.40	2.27±1.36	4.74±1.97	<0.000
Ovocitos Totales	2.50 ±2.17	11.73±1.19	20.08±2.64	<0.000
Ovocitos Maduros	2.30±2.11	9.15±3.45	15.17± 3.83	<0.000

Mojica-Martinez K., et al. Correlation between serum AMH, day 3 FSH and response to controlled ovarian hyperstimulation (COH) in a population of infertile Mexican patients. Fert Ster. 2011;96(3, Supl):S121.

Applications

Predict IVF response: Low response hyperesponse cancellation and ovarian hyperstimulation Syndrome

Future in reproductive medicine: Pregnancy predictor

Ovarian reserve: age of menopause after surgery or radiation therapy.

AMH

Impact of chemotherapy

Polycystic ovary Syndrome PCOS

Scott M. Nelson, et al. Anti-Müllerian hormone: clairvoyance or crystal clear? Hum. Reprod. (2012) 27 (3): 631-636.

Conclusions

- There are so many infomation about AMH as a biomarker for ovulation induction

- Today we can standardized level of AMH

- There are many protocols depends of AMH levels, and we need to avoid HOSS, and cancellation for poor responder patient.

- We would like to have always the "perfect patient with the perfect protocol" to help them to get pregnant.

Conclusions
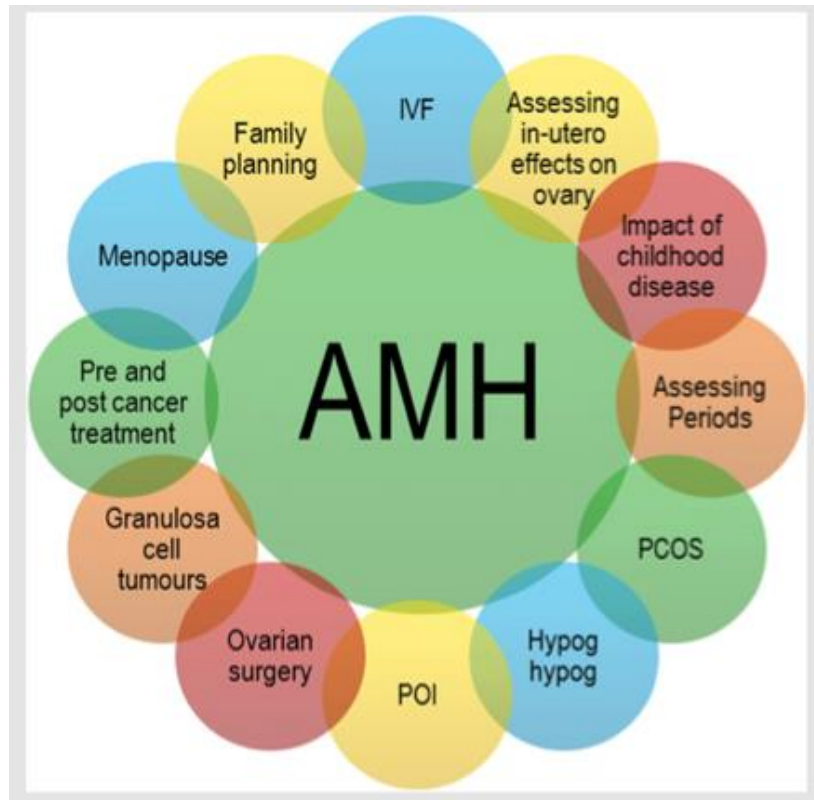
Anti-Müllerian Hormone is an excellent biomarker of follicular reserve, however cannot be considered as a predictor of pregnancy

Gynecologic Concerns in childrens and adolescents with cáncer. The American Colleage of obstetricians and Gynecologist. Committee Opinion. August 2014 Number 607.

Nelson SM., Biomarkers of ovarian response: current and future applications. Fertil Steril 2013;99:963-969

Biomarkers to Redirect Response to Ovulation Induction

Pablo Diaz-Spindola, MD, FACOG

Medical Director IECH Fertility Center Monterrey

Professor of Endocrinology and Reproductive Medicine

Fellowship of UNAM

Monterrey, Mexico

gfa Global Fertility Academy