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President's Medal best medical graduate of year 1970-75

Award from DMA on Dr. B.C Roy's birthday: outstanding contribution to medicine, 1999

Vikas Ratan Award by Nations economic development & growth society 2002

Chitsa Ratan Award by International Study Circle in 2007

Life time Medical excellence award Obs & Gyne Hippocrates foundation 2014

Abdul Kalam gold medal 2015 & **Rashtriya Gaurav Gold Medal award** 2017 by Global Economic Progress & Research Association.

Distinguished teacher of excellence award for PG medical education by ANBAI & NBE 2017 and **Inspiring Gynecologists of India** by Economic Times 2017. Highest Merck Serono honor award in 2018. Awarded at the Economic Times Health Care awards the "**ICON of IVF of North India**", her team as the '**Best integrated national team of IVF**', & the most coveted award as the '**IVF Champion of the year 2019**'.

Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE, since 2007, IFS since 2014, ISAR 2014 and by FOGSI for basic & advanced infertility training since 2008. Member of Editorial board of '**IVF Worldwide**', peer reviewer for '**Journal of Human Reproductive Sciences**', and member of advisory board for '**Journal of Fertility Science & Research**'.

Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection. and ART.



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Nuances of AMH in Reproductive medicine



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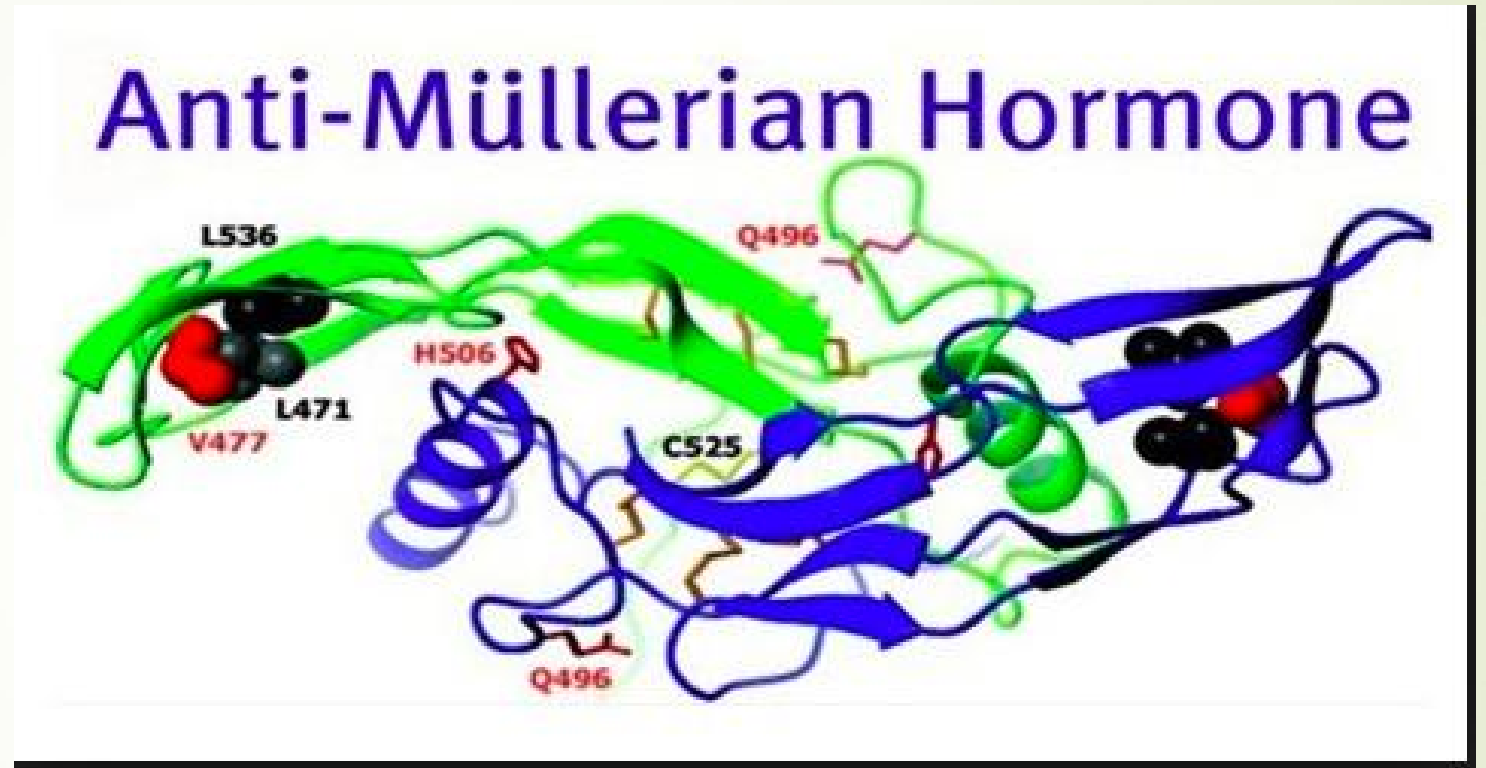
- What is AMH?
- Physiological functions of AMH
- AMH variability and its interpretation
- Clinical uses
 - Limitations and caution
 - What does evidence say

Topics covered

Anti-mullerian hormone

- Glycoprotein hormone
 - Dimeric
- Belongs to the TGF β superfamily.
 - Role in growth and differentiation
 - Others: inhibin and activin, BMP, PDGF

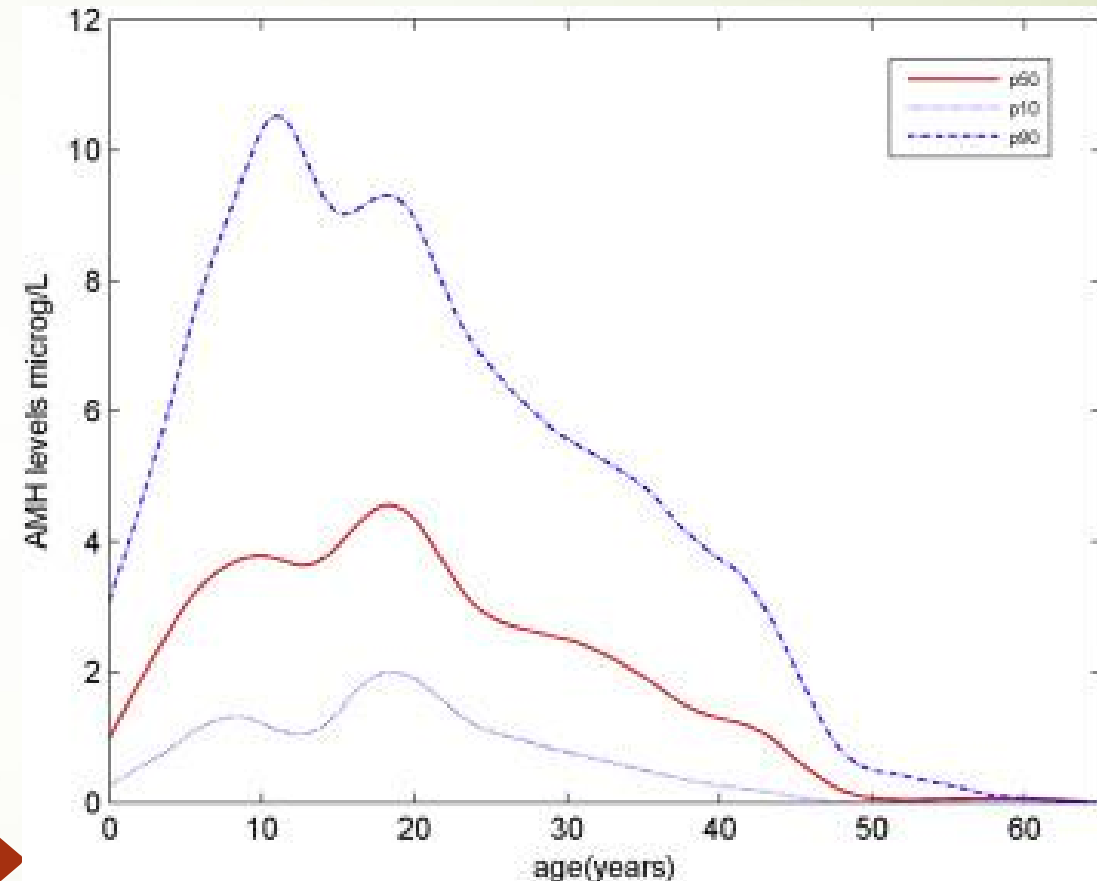
What is AMH?



Physiological functions

AMH secretion in women: From conception to menopause

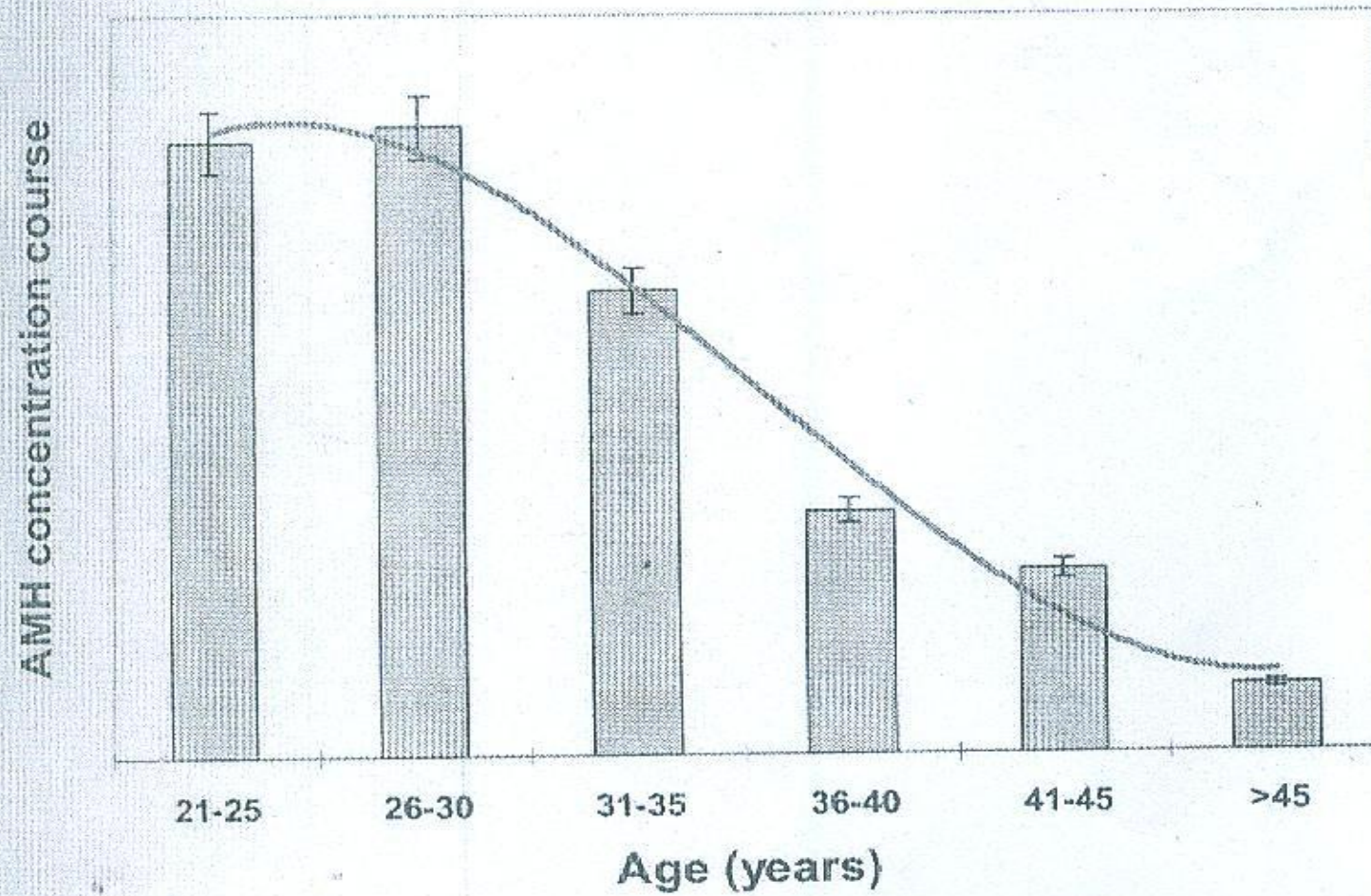
Mid gestation onwards



Fertility and Sterility

*Volume 105, Issue 2, February 2016 ,
Pages 481-485.e1*

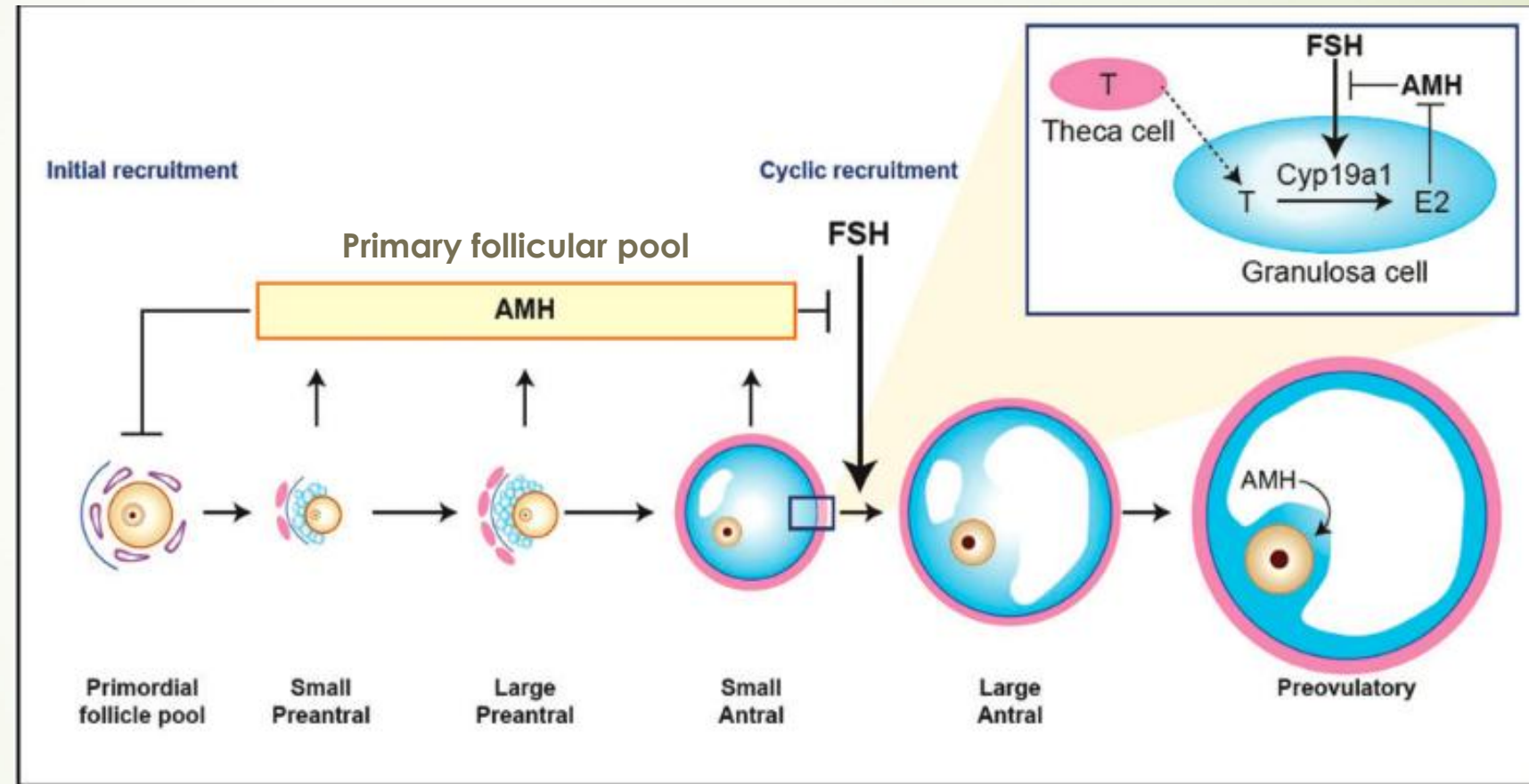
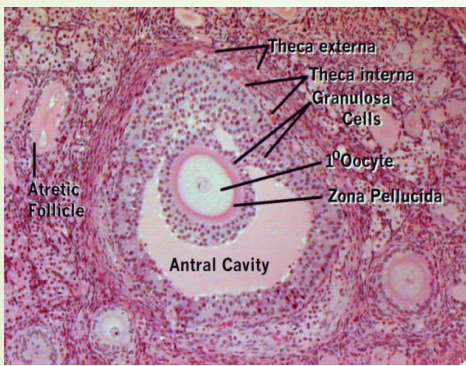
Fig.5: AMH levels in females throughout childbearing age



Physiological functions

Follicular gatekeeper

- Limits primordial to primary follicular conversion thus prevents follicular loss
- Limits FSH sensitivity of follicles



Granulosa cells of primary, preantral, small antral follicles (<4mm),

AMH and anovulatory PCOS

Anti-Müllerian hormone reduces follicle sensitivity to follicle-stimulating hormone in human granulosa cells

Laura Pellatt, Ph.D.,^a Suman Rice, Ph.D.,^a Nafi Dilaver, B.Sc.,^a Amira Heshri, B.Sc.,^a Raymond Galea, M.B., B.S.,^b Mark Brincat, Ph.D.,^b Kristy Brown, Ph.D.,^c Evan R. Simpson, Ph.D.,^c and Helen D. Mason, Ph.D.^a

^a Biomedical Sciences, St George's, University of London, London, United Kingdom; ^b Department of Obstetrics and Gynaecology, University of Malta Medical School, Mater Dei Hospital, Msida, Malta; ^c Prince Henry's Institute, Monash Medical Centre, Monash University, Melbourne, Victoria, Australia

Result(s): The AMH decreased gonadotropin-stimulated aromatase expression and decreased forskolin-stimulated aromatase in KGN cells and this effect was through a dose-dependent inhibition of promoter II. Surprisingly, AMH also reduced FSH receptor mRNA expression. High AMH doses had no effect on inhibin B, whereas a low dose stimulated production. There was no effect on inhibin A or vascular endothelial growth factor.

Conclusion(s): The AMH inhibits factors affecting FSH sensitivity. As AMH levels decrease with follicle growth, this inhibition would be removed. The AMH overproduction in anovulatory polycystic ovaries (PCO) may therefore restrict folliculogenesis by an inhibitory effect on FSH sensitivity, thereby contributing to anovulation. (Fertil Steril® 2011;96:1246–51. ©2011 by American Society for Reproductive Medicine.)



Variations in AMH levels

Role of

➤ Biology:

- Inter-individual
- Intra-individual
 - Inter-menstrual
 - Intra-menstrual

➤ Exposure:

- OCPs
- Vitamin D deficiency

➤ Laboratory



AMH variability: Biology

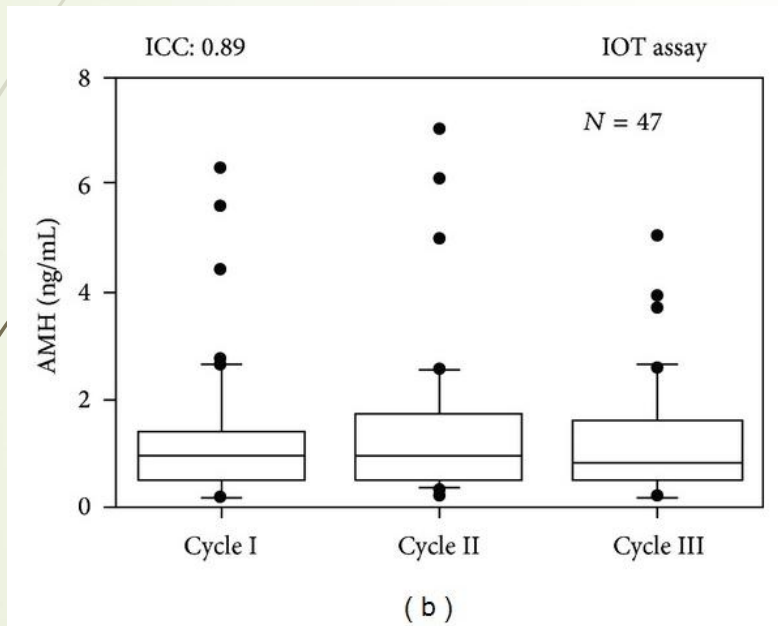
Inter individual variability

- High as at same age different reserves of follicular pool

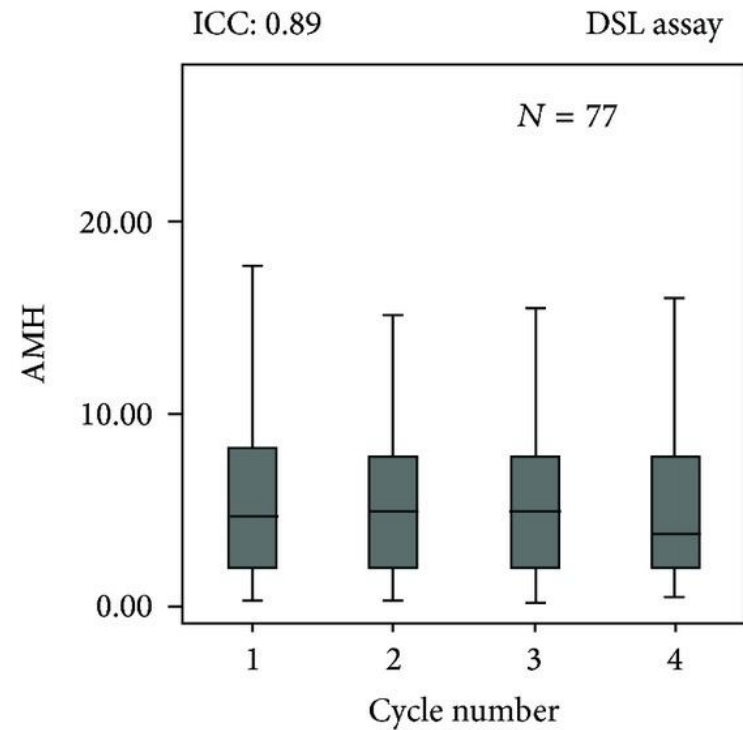
Intra-individual variability

- In different phases of a menstrual cycle
- Inter-menstrual (between 2 cycles) variability is low compared to other markers of ovarian reserve

Inter-cycle variability

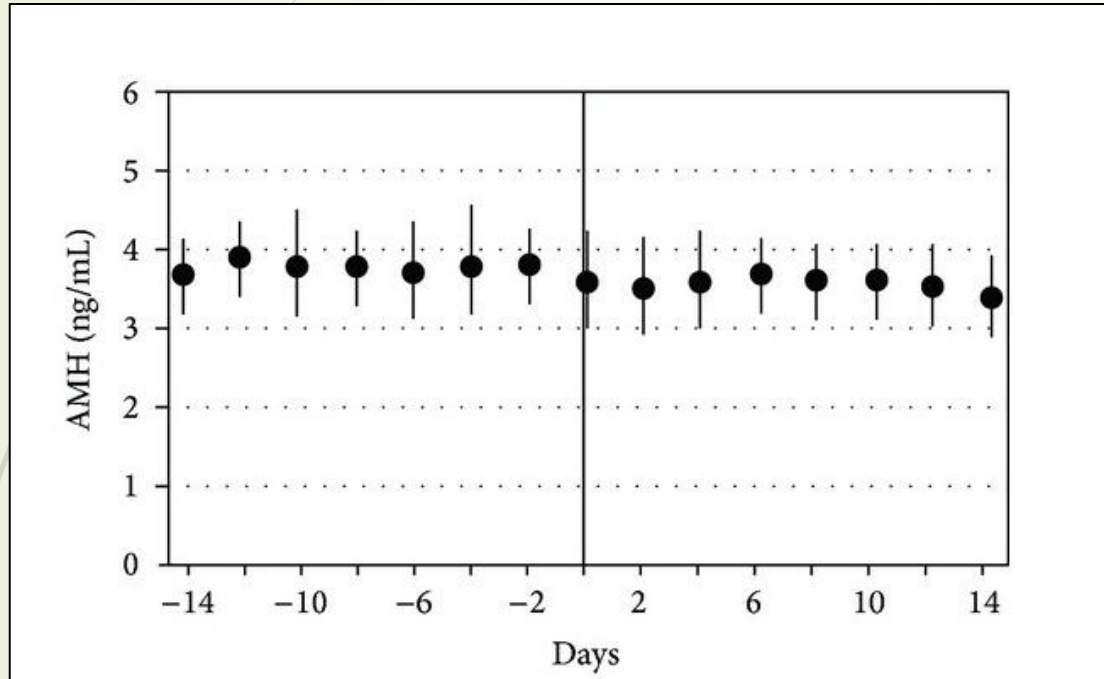


Fanchin R et al
Hum Reprod. 2005 Apr; 20(4):923-7



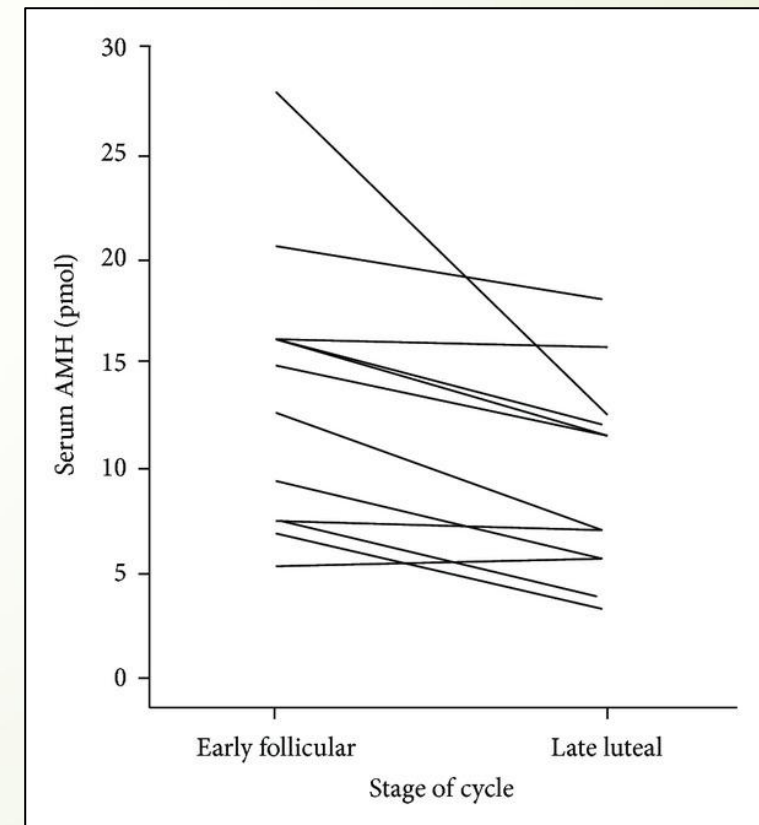
Sowers M et al.
Fertil Steril. 2010;94(4):1482-86.

Intra-cycle variability



Hadlow N et al. Variation in AMH concentration during the menstrual cycle may change the clinical classification of the ovarian response. *Fertility and Sterility*. 2013;99(6):1791–1797

12. La Marca A, Stabile G, Carducci Artensio A, Volpe A. Serum anti-Mullerian hormone throughout the human menstrual cycle. *Human Reproduction*. 2006;21(12):3103–3107. [[PubMed](#)]



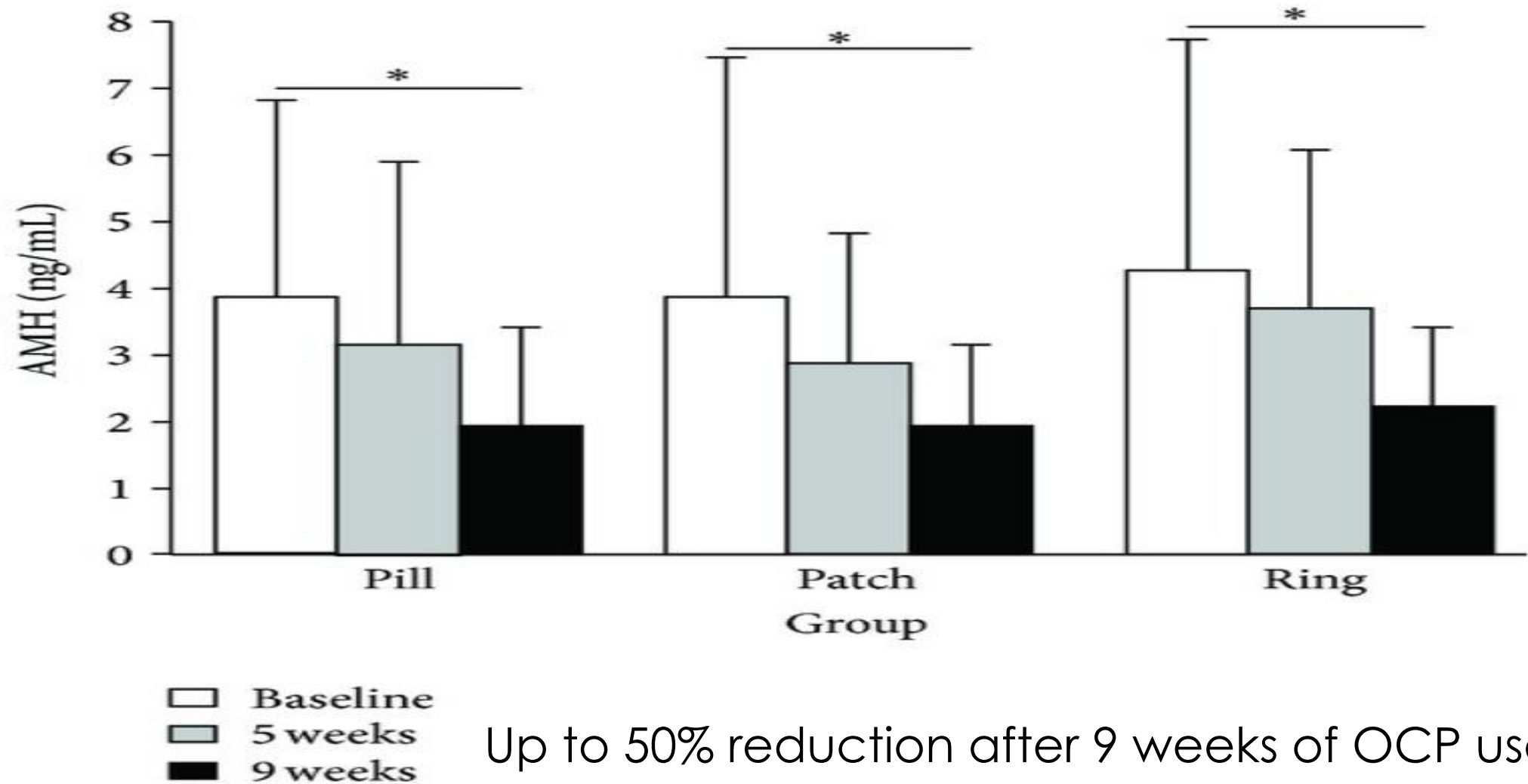


What importance does one place to these fluctuations.

- 25% showed no variation at all.
- Younger women had significantly larger fluctuations in AMH levels than older women.
- Random and noncyclic fluctuations in AMH

Measuring AMH on a fixed day of MC would not yield any advantage over random assessment

AMH variability: Exposure to OCP



Up to 50% reduction after 9 weeks of OCP use



Vitamin D deficiency and AMH

- Earlier studies have suggested a link suggesting supplementation in small studies improve AMH.
 - Naderi Z et al. Gynecol Endocrinol. 2017 Dec 6:1-4.
 - Dennis NA et al. Nutrients. 2017 Jul 8;9(7).
- Recent prospective large scale studies fail to find that link with AMH levels, oocyte recovery, pregnancy rates.
 - Drakopopuoulos et al. Hum Reprod. 2017 Jan;32(1):208-214.
 - Fabris A M et al. Reprod Biomed Online. 2017 Aug;35(2):139-144

AMH variability: Laboratory

- Storage of samples
 - 23% increase compared with fresh samples when stored at -20°C for 5 days
 - 58% increase when stored at room temperature
- AMH kits
 - Gen II ELISA AMH values ~ 20% lower than DSL assay (automated Beckman coulter)
- Technical error

Rustamov O, et al

Anti-Mullerian hormone: poor assay reproducibility in a large cohort of subjects suggests sample instability. Hum Reprod. 2012 Oct;27(10):3085-91.

A number of assays and protocols have been used since 1990 to measure serum AMH levels complicating the interpretation of the hormone

Older methods

DSL assay

(Diagnostic Systems Lab)

IOT or IBC assay

(immunotech)

Both are ELISA
(Enzyme Linked Immuno-assays)
and use different primary antibodies against AMH and different standards with **values much higher with IOT than DSL**

Modern methods

Consolidation of these 2 by Beckman coulter in 2011

GEN II assay

Uses DSL antibody & IOT calibrations (ELISA)

Fully automated assay
Elecsys Cobas by
Rosche

Analytical variability

Within person variability 21 to 32%

- GEN II 5.5 to 10.3 %
- Elecsys Cobas 2.8 to 3.3%


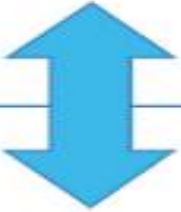
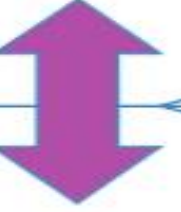

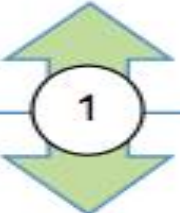

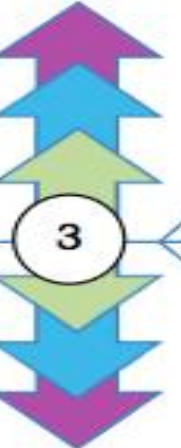

Optimal performance

- GEN II at high range only
- Elecsys Cobas throughout measuring range

Lowest values

- GEN II =3 pmol/l
- Elecsys Cobas 0.5pmol/l

Contribution of various sources

'True' AMH value (ng/ml)	<u>AMH variability by source</u>			Possible AMH results (ng/ml)
	Biology	Exposure	Laboratory	
1.5	One source of variability			
		or 	or 	
				2.0 1.5 1.0
1.5	3 sources of variability combined			
		or 	or 	
				2.5 1.5 0.5

Clinical uses of AMH

Diagnosis	Predictive marker	Assisting IVF
<ul style="list-style-type: none">➤ PCOS ?➤ POF & menopause?➤ Granulosa cell tumours	<ul style="list-style-type: none">➤ Ovarian reserve➤ Assessing ovarian tissue loss after surgery or therapy?➤ Fecundability?➤ AMH and time to pregnancy	<ul style="list-style-type: none">➤ Prediction of ovarian response to COS?➤ Development of Individualized COS regime?➤ Predicting live births?

Diagnosis

POF & menopause?

- ▶ women 45-49 years, undetectable AMH >60% probability of menopause in 5 years. **Kim C et al. Maturitas. 2017 Aug**
- ▶ Higher AMH=delayed menopause in PCOS women by 2 years. **Minooee S. et al Climacteric. 2018 Feb;21(1):29-34.**

granulosa cell tumours?.

- ▶ Mean AMH level can be upto 1124ng/ml
- ▶ As effective as inhibin B

PCOS?

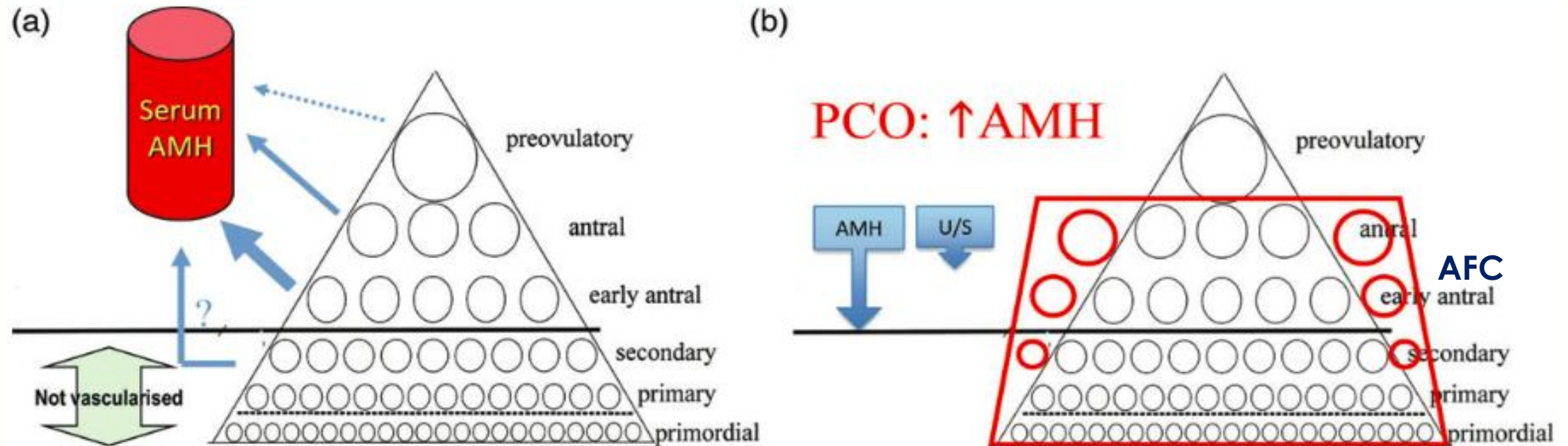
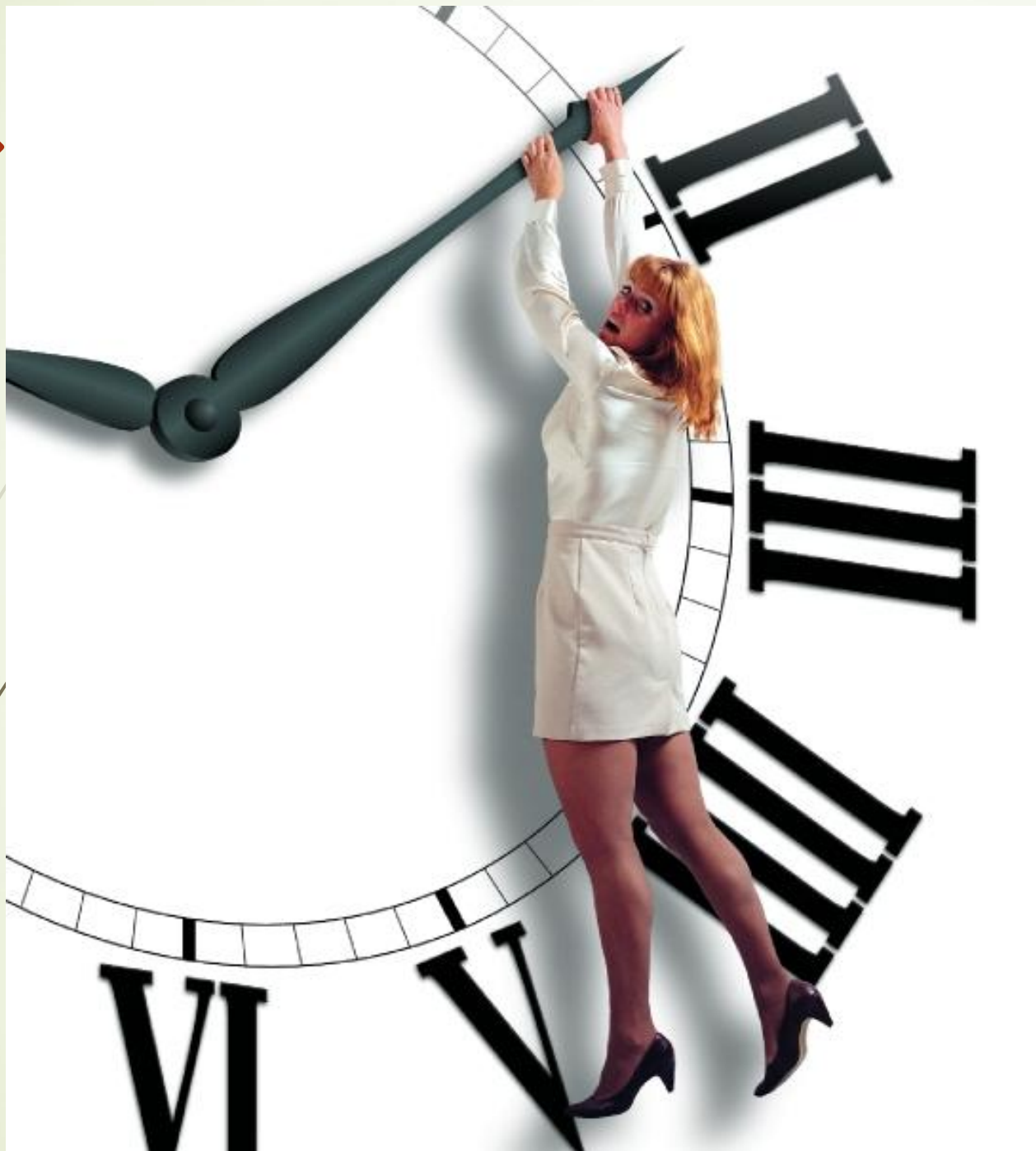
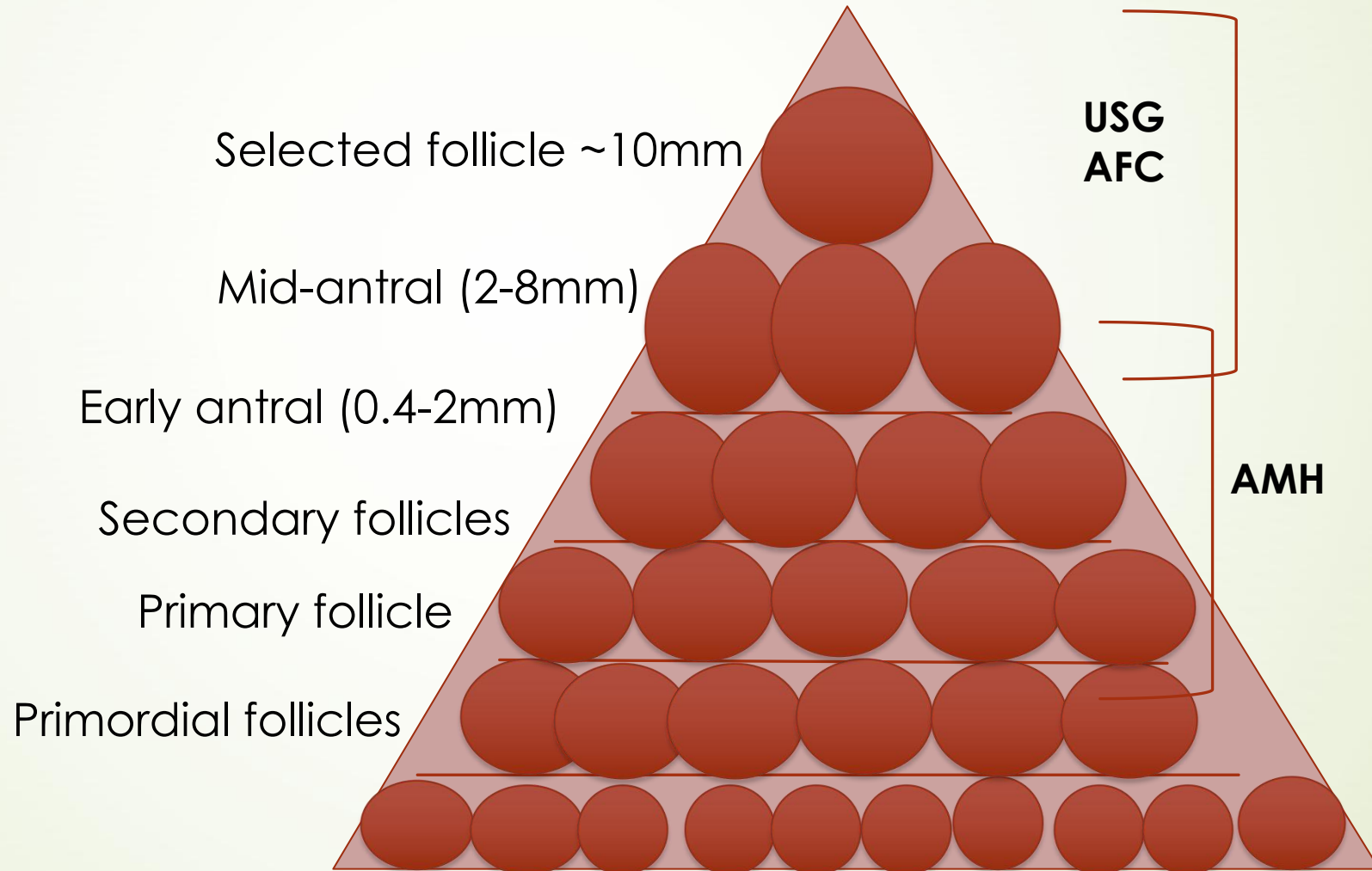


Figure 6 Rationale for the use of serum AMH assay as a probe for PCOM. **(a)** All growing follicles secrete AMH but serum AMH reflects only the secretion from bigger follicles that are in contact with the vascular bed. As the numbers of follicles in all growth stages are strongly related to each other, serum AMH is considered to reflect the sum of growing follicles but not the number of primordial follicles that do not secrete AMH. **(b)** In PCO, the numbers of all growing follicles is increased, resulting in a marked increase in serum AMH level. AMH may be considered as a deeper and more sensitive probe to define follicle excess than the follicle count by ultrasound (U/S) since it appraises more follicle classes (blue arrows).



The fertility clock

AMH: predictor of ovarian Reserve



AMH: Predictor of fecundability?

Low concentration of circulating antimüllerian hormone is not predictive of reduced fecundability in young healthy women: a prospective cohort study

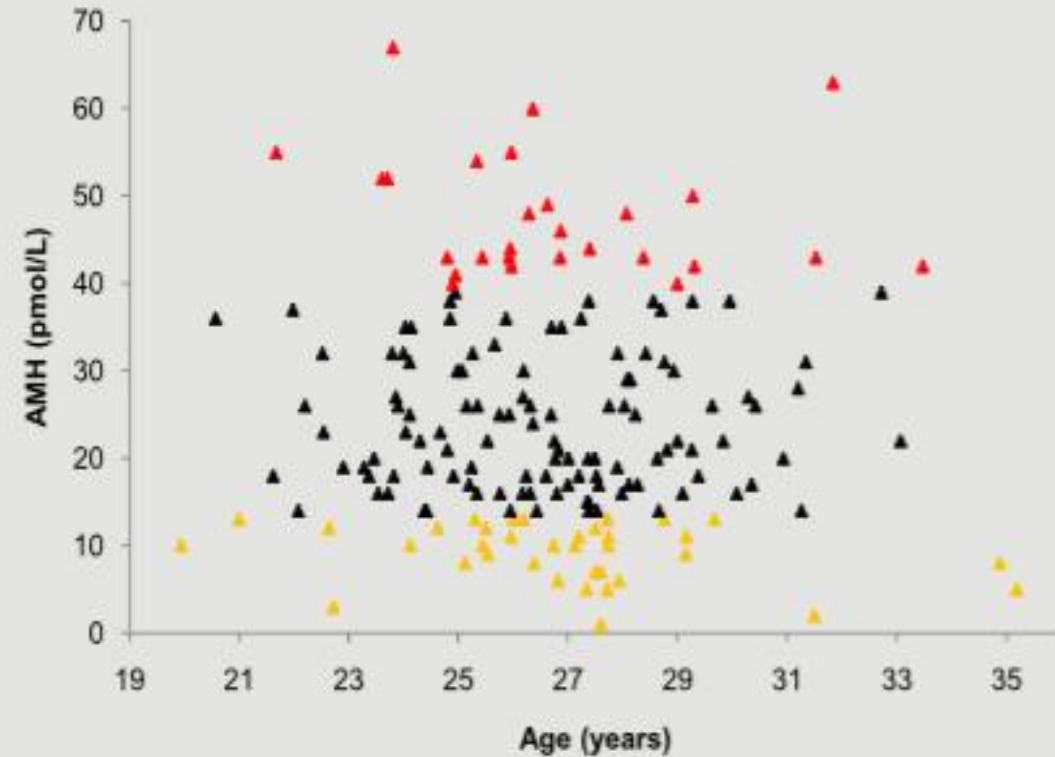
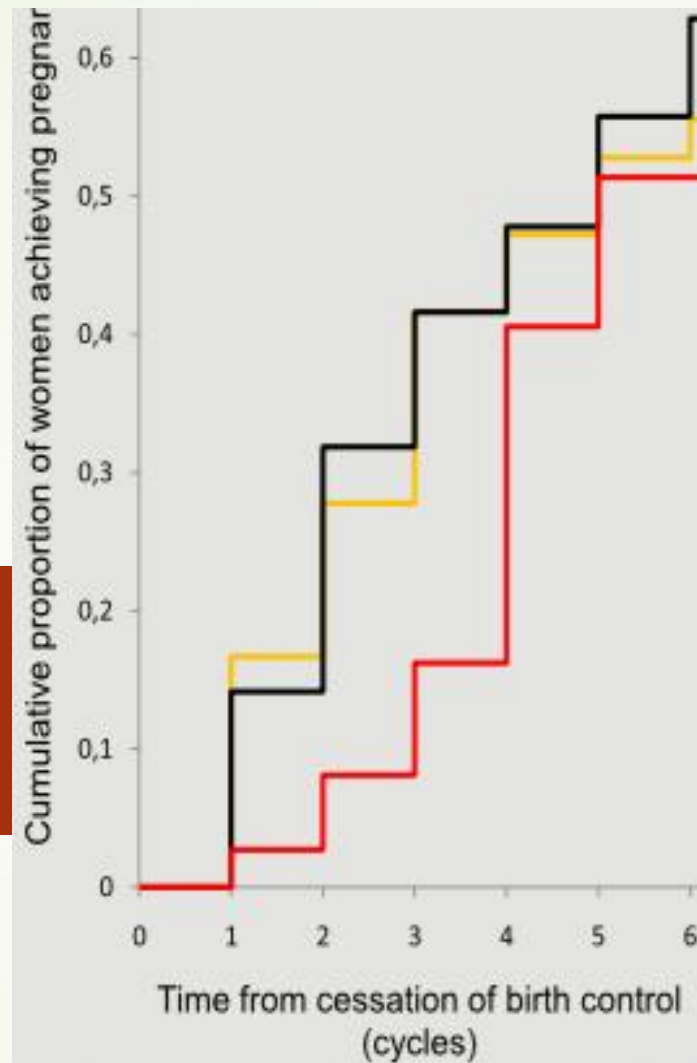
Casper P. Hagen, M.D.,^a Sonja Vestergaard, Ph.D.,^b Anders Juul, Dm.S.C.,^a Niels Erik Skakkebaek, Dm.S.C.,^a Anna-Maria Andersson, Ph.D.,^a Katharina M. Main, Ph.D.,^a Niels Henrik Hjöllund, Ph.D.,^{c,d} Erik Ernst, Ph.D.,^{d,e} Jens Peter Bonde, Dm.S.C.,^{d,f,g} Richard A. Anderson, Ph.D.,^h and Tina Kold Jensen, Ph.D.^{a,b}

Result(s): Fifty-nine percent of couples conceived during the study period. Compared to the reference group (AMH quintile 1), fecundability did not differ significantly in women with low AMH (AMH quintiles 2–4) (adjusted fecundability ratio [FR] 0.44–1.40). In contrast, women with high AMH (AMH quintile 5) had reduced fecundability (FR 0.48; 95% CI 0.27–0.85) after adjustment for covariates (woman's age, body mass index [BMI], smoking, diseases affecting regular menstrual cycles were more prevalent in women with high AMH compared with women with low AMH and they had higher levels of LH (geometric mean: 8.4 vs. 5.3 IU/L) and LH:FSH ratio (2.4 vs. 1.8). A

Conclusion(s): Low AMH in healthy women in their mid-20s did not predict reduced fecundability. Even after exclusion of women with irregular cycles, the probability of conceiving was reduced in women with high AMH. (Fertil Steril® 2012;98:1602–8. ©2012 by American Society for Reproductive Medicine.)

Key Words: AMH, MIS, time to pregnancy, fecundity, fecundability, PCOS

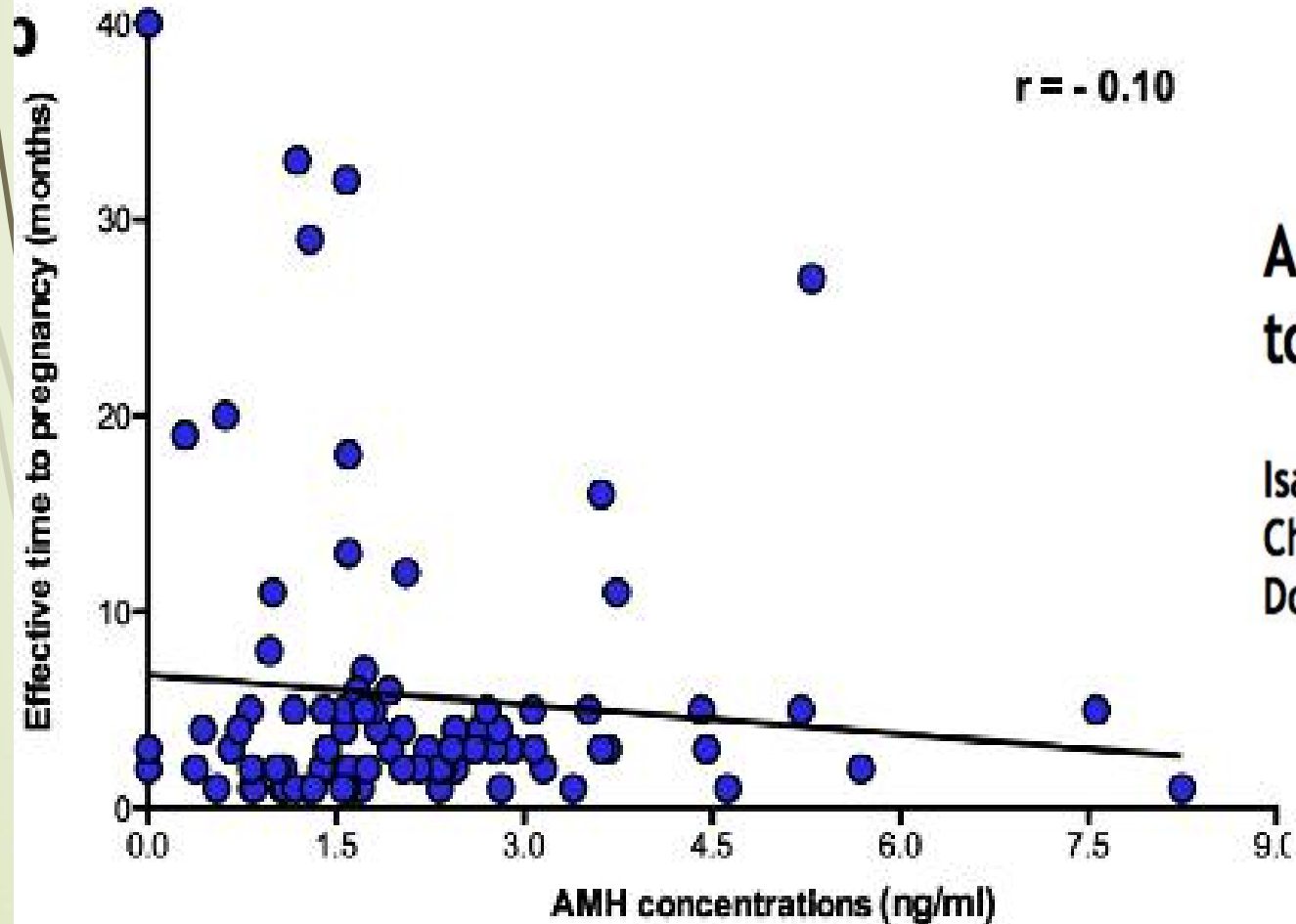
AMH and fecundability



(A) Kaplan-Meier curves showing cumulative proportion of pregnancy by serum level of antimüllerian hormone (AMH). Low AMH (quintile 1) orange line, medium AMH (quintiles 2–4) black line, high AMH (quintile 5) red line. P value describes difference between curves (log-rank test); $P=.289$. (B) Antimüllerian hormone level as a function of age in 186 participating women. Colors correspond to subgroups of AMH levels: low (orange), medium (black), and high (red).

Hagen. Low AMH predicts normal fecundability. *Fertil Steril* 2012.

AMH concentration and time to pregnancy



AMH concentration is not related to effective time to pregnancy in women who conceive naturally

Isabelle Streuli ^{a,*}, Jacques de Mouzon ^b, Céline Paccolat ^a,
Charles Chapron ^{a,c}, Patrick Petignat ^a, Olivier P Irion ^a,
Dominique de Ziegler ^b

AMH and IVF

- Predicting response to COS for IVF
- Tailoring treatment cycles (iCOS)
- Predicting live-birth rate?
- Excluding women who have low AMH from IVF/offering egg donation



J Hum Reprod Sci. 2012 May-Aug; 5(2): 206–212.

PMCID: PMC3493837

doi: [10.4103/0974-1208.101023](https://doi.org/10.4103/0974-1208.101023)

PMID: [23162361](https://pubmed.ncbi.nlm.nih.gov/23162361/)

Anti-mullerian hormone cut-off values for predicting poor ovarian response to exogenous ovarian stimulation in *in-vitro* fertilization

Ruma Satwik, Mohinder Kochhar, Shweta M Gupta, and Abha Majumdar¹

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Sensitivity specificity chart calculated from ROC of AMH

<i>Cut-off levels</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>Positive predictive value</i>	<i>Negative predictive value</i>
AMH of 2	12%	98%	64%	79%
AMH of 3	20%	92.8%	45%	80%
AMH of 4	33%	90.8%	51.7%	82.4%
AMH of 10	71%	69%	40%	89%
AMH of 20	91%	47%	33.6%	95%



Optimization of treatment strategies based on AMH levels

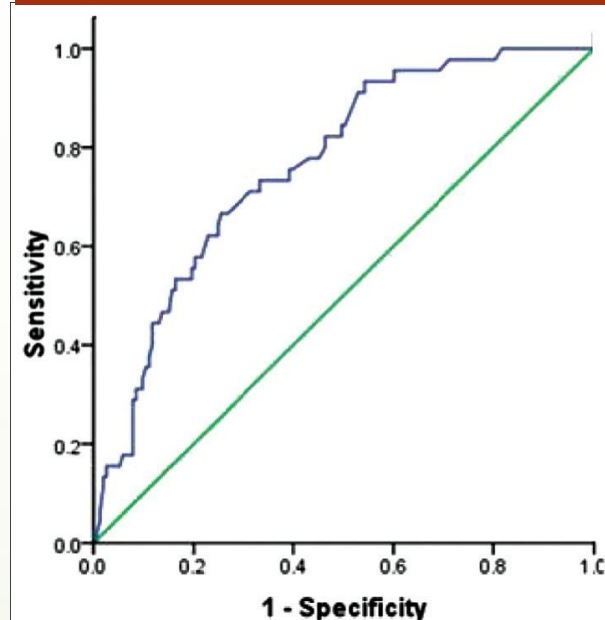
- In women with AMH levels of 2 pmol/L or less, cycle cancellation may be a good option.
- With AMH levels between 2 and 10pmol/L a high suspicion of poor response is raised. Higher starting dose of gonadotropins may be helpful, and appropriate counselling about the risks of poor oocyte recovery and poor reproductive outcome would be a god option.
- AMH levels above 25 pmol/L definitely call for caution while deciding on gonadotropin dosage in order to avoid risk of OHSS.

AMH as a predictor of ovarian response

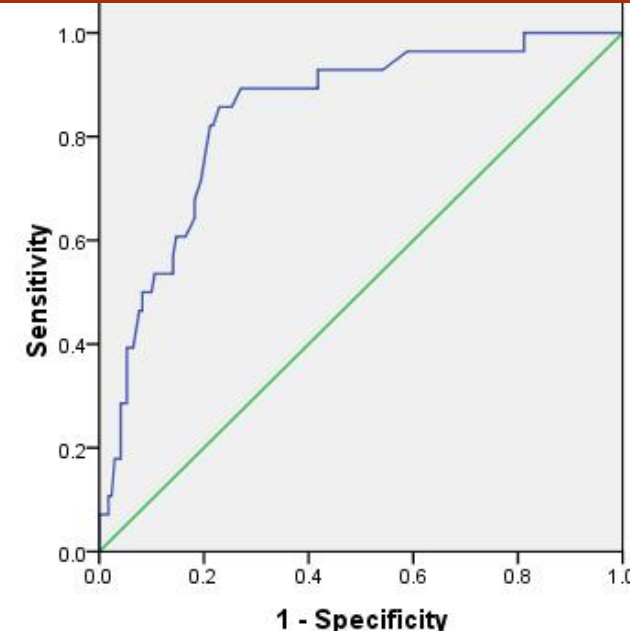
- Using specificity of 90%, detection rate for high and low response: cut-off 4.5ng/ml and 0.8ng/ml was 90% & 40% *Hamdine et al, Hum Reprod 2014*

High response cut-off: 3.5ng/ml (AUC 0.843) Low response: 0.3ng/ml (AUC: 0.768) *Satwik R, Majumdar A. Anti-mullerian hormone cut-off values for predicting poor ovarian response to exogenous ovarian stimulation in *in-vitro* fertilization. J Hum Reprod Sci 2012*

AMH for poor-response
AUC: 0.768, Sig: 0.000
Cut-off= 2pmol/L



AMH for hyper-response
AUC: 0.843, Sig: 0.000
Cut-off=25pmol/L



Tailor-making stimulation protocol

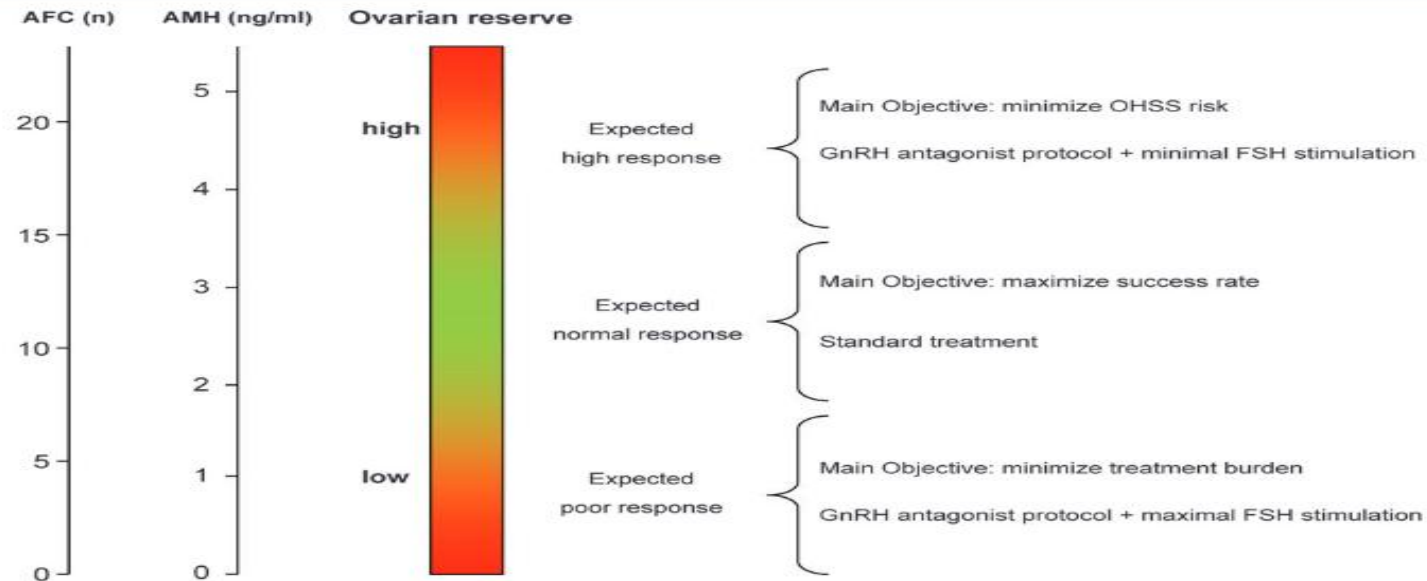
Human Reproduction Update, Vol.20, No.1 pp. 124–140, 2014

Advanced Access publication on September 29, 2013 doi:10.1093/humupd/dmt037

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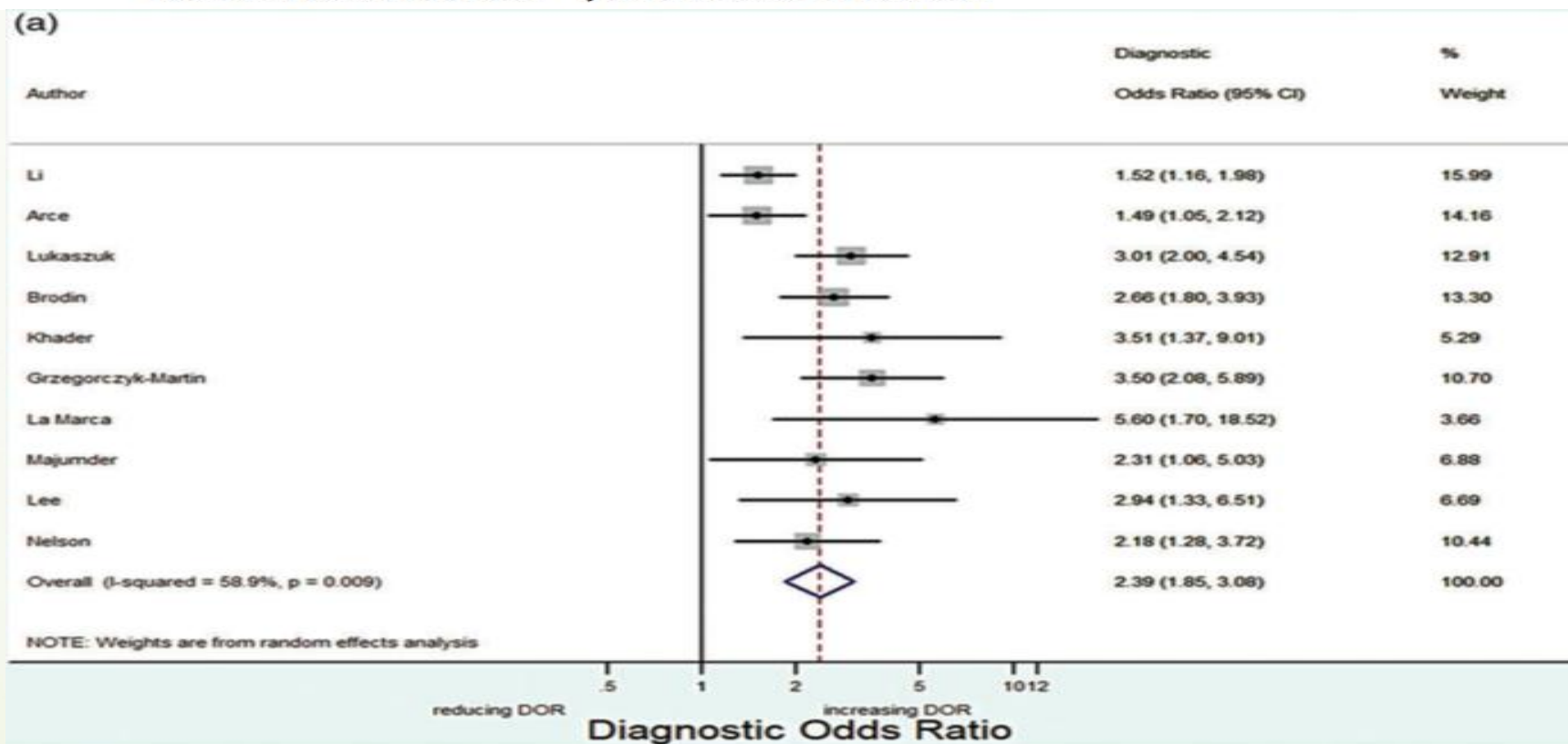
Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice

Antonio La Marca^{1,*} and Sesh Kamal Sunkara²



The predictive accuracy of anti-Müllerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature

Stamatina Iliodromiti^{1,*}, Thomas W. Kelsey², Olivia Wu³, Richard A. Anderson^{4,†}, and Scott M. Nelson^{1,†}



AMH and live births in IVF

Weak association with live births in IVF AUC: 0.631, 0.534)

Exclusion from autologous IVF or enrolment in donor IVF programs

Human Reproduction, Vol.26, No.7 pp. 1905–1909, 2011

Advanced Access publication on April 30, 2011 doi:10.1093/humrep/der134

human
reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

Live birth chances in women with extremely low-serum anti-Mullerian hormone levels

Andrea Weghofer^{1,2,*†}, Wolf Dietrich^{3,†}, David H. Barad^{2,4},
and Norbert Gleicher^{2,5}

BACKGROUND: To determine whether women with extremely low-serum anti-Mullerian hormone (AMH) levels (<0.1 – 0.4 ng/ml) still demonstrate live birth potential with assisted reproduction and whether such potential is age dependent.

METHODS: Between January 2006 and October 2009, 128 consecutive infertility patients with AMH ≤ 0.4 ng/ml were retrospectively evaluated for pregnancy chances and live birth rates after IVF.

CONCLUSIONS: With extremely low-serum AMH levels, moderate, but reasonable pregnancy and live birth rates are still possible. Extremely low AMH levels do not seem to represent an appropriate marker for withholding fertility treatment.

Key words: anti-Mullerian hormone / dehydroepiandrosterone / diminished ovarian reserve / IVF / pregnancy



‘At present, due to the low accuracy of ORTs in pregnancy prediction, exclusion of patients other than on the basis of female age is not to be supported.’

Low AMH or low AFC should not be a criteria to refuse IVF with self oocytes



Conclusion

- The variability in AMH stems more from the laboratory rather than from women's biology
- AMH appears the most reliable marker presently to diagnose PCOS, POF and granulosa cell tumors clinically as well as determine change in ovarian reserve post therapy
- It is possibly better in efficacy to AFC for ovarian reserve prediction
- Low AMH concentration is not predictive of lowered fecundability
- AMH levels are not related to effective time to pregnancy in natural pregnancies



Conclusion

- AMH has become one of the most important prognosticator of ovarian response to stimulation in IVF
- The use of AMH in ovarian reserve prediction has enabled us to develop individualized COS for IVF to optimize cycle outcome
- Low AMH has poor association with live birth rate in IVF
- Low AMH levels should not be used to refuse women from IVF with self oocytes, unless they are of high age

**"Education is not
the learning of
facts, but the
training of the mind
to think."
-Albert Einstein**

