Predviđa li AMH dob menopauze?

Doc.dr.sc. Jelena Marušić
Ante Mršić, dr.med.
KBC Split
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Problematika

1. Predviđa li AMH menopauzu – prijevremenu menopauzu?

2. Što ako zaista predviđa?

Menopauza

Posljednja menstruacija

- **~51 god** (40-60 god)
- Posljednji znak da je reproduktivna sposobnost iscrpljena
- Postmenopauza: kardiovaskularne bolesti i moždani udar, osteoporoza, karcinom dojke, demencija i Alzheimer

De Vos. Primary ovarian insufficency.Lancet 2010.

Opadanje broja folikula

- **Konačan broj jajnih stanica** - 20. tjedan
- 1-2 mil oocita zaustavljenih u profazi prve mejotičke diobe
- 400 000 na početku puberteta/25 000 ubrzan pad
- **99,9% oocita propada atezijom - apoptozom**
- 1000 u vrijeme posljednje menstruacije

Lobo RA. Early ovarian ageing: a hypothesis. What is early ovarian ageing? Hum Reprod.2003.

Perez GI et al. Prolongation of ovarian lifespan into advanced chronological age by Bax-deficiency. Nat Genet. 1999.

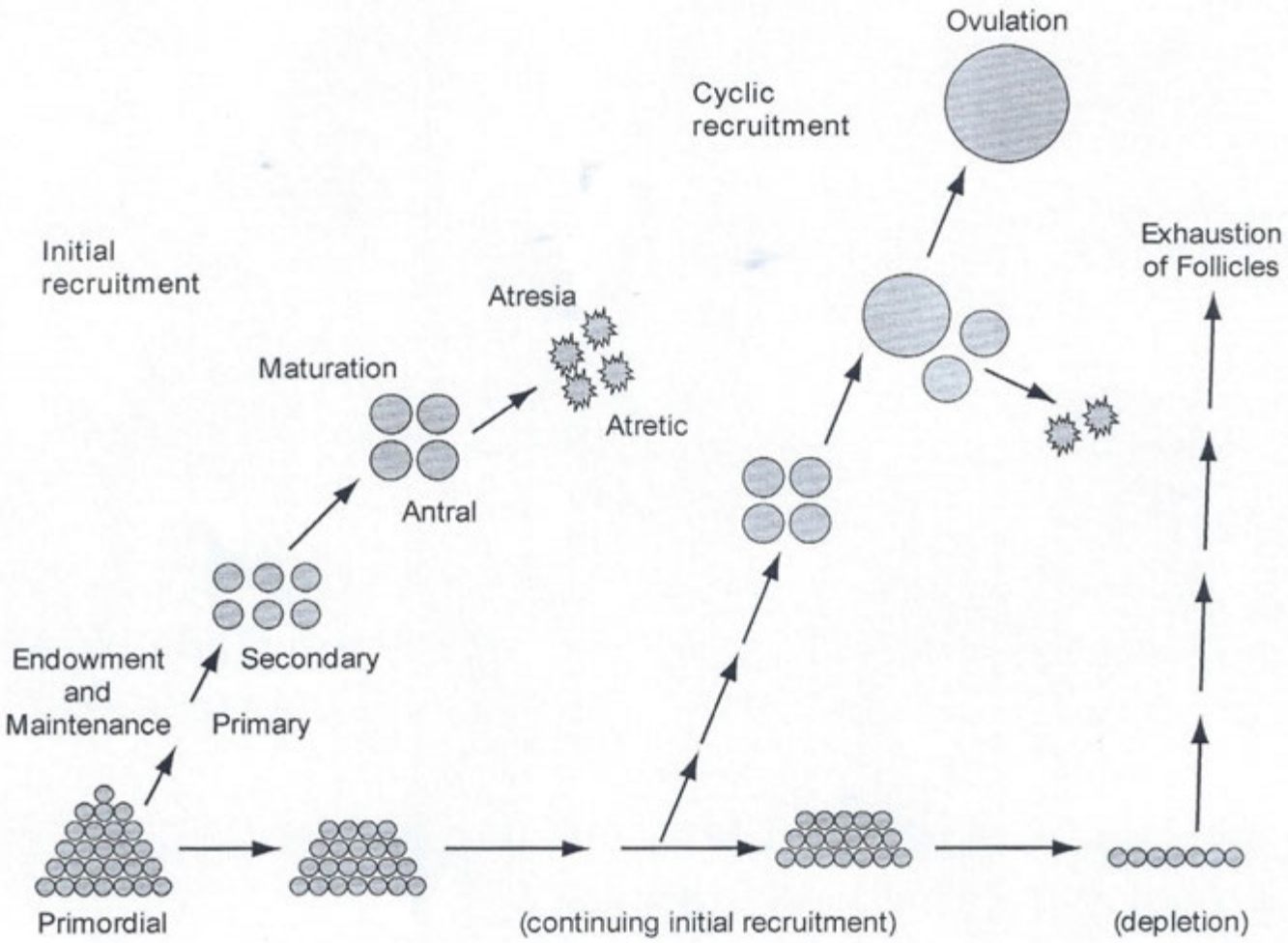


Figure 2
Life history of ovarian follicles endowment and maintenance, initial recruitment, maturation, atresia or cyclic recruitment, ovulation, and exhaustion. Reproduced with permission from McGee and Hsueh. Initial and cyclic recruitment of ovarian follicles. *Endocr Rev* 2000, **21**:200-214. © 2000. The Endocrine Society.

Starenje jajnika

- Starenje jajnika podrazumijeva redukciju broja i kvalitete jajnih stanica

Starenje jajnika je individualno!

- Menopauza nastupa u 1/10 žena prije 45 godine, 1/100 prije 40 godine

Biološka/kronološka dob

- Starenje jajnika ovisi o početnom **broju jajnih stanica stvorenih za vrijeme intrauterinog razvoja** i **brojnim čimbenicima tijekom života**

Akande VA et al. Biological versus chronological ageing of oocytes, distinguishable by raised FSH levels in relation to the success of IVF treatment. Hum Reprod.2002.

Starenje jajnika

- Brojni testovi procijene rezerve jajnika:

  FSH, E2, inhibin B, **AMH**, AFC, volumen jajnika...

- **AMH** u procijeni rezerve jajnika od 2002.

- AMH prvi puta nam je omogućen uvid u **intrinzičku, „acikličku" ovarijsku aktivnost**

van Rooij IA. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. Hum Reprod 2002.

AMH (anti-Müllerian hormone)

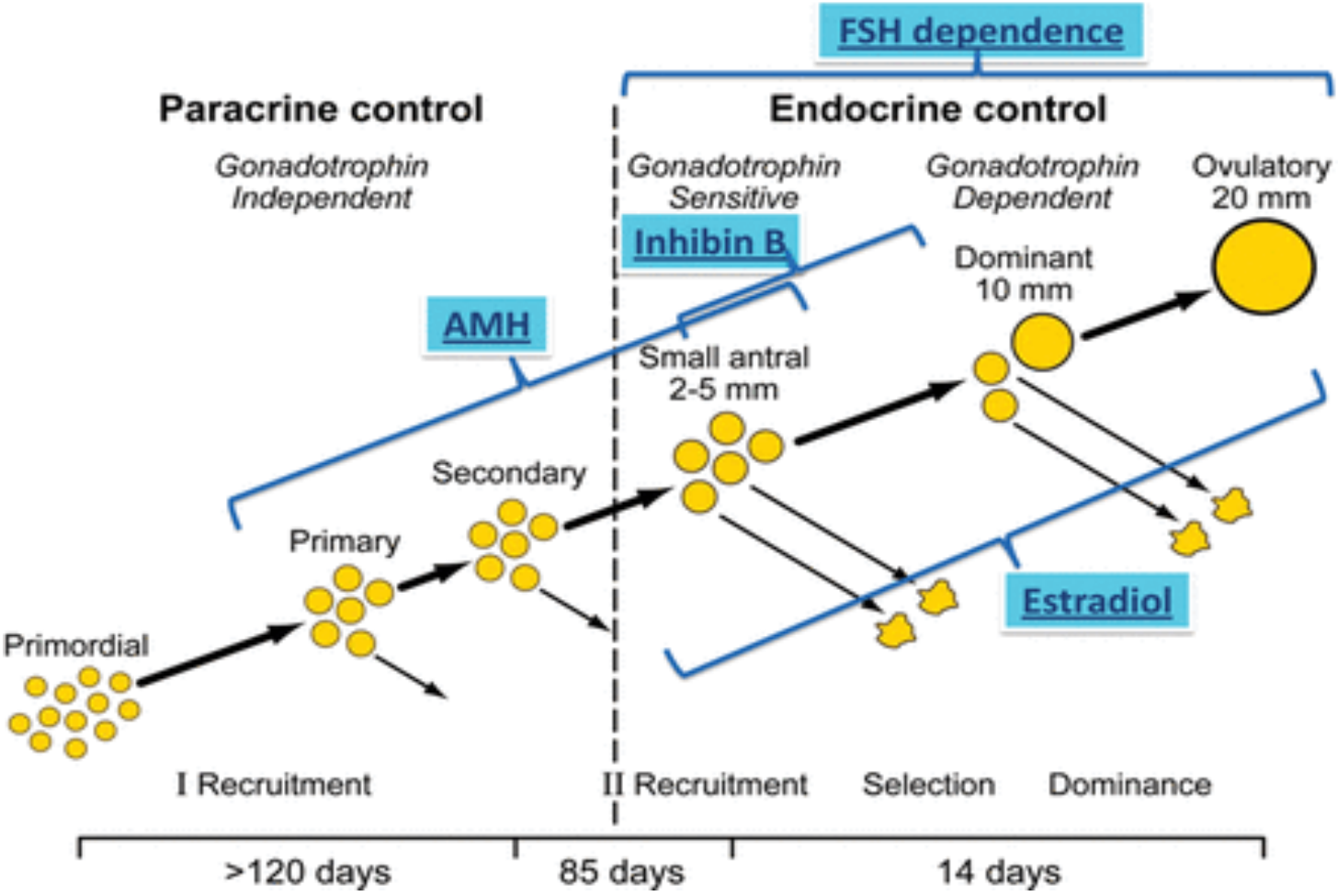
- MIS (Müllerian inhibiting substance)
- Glikoprotein, TGF-β obitelji
- Gen kratki krak 19 kromosoma
- Dva tipa receptora: AMHRI i AMHRII

Cate RL et al. Isolation of the bovine and human genes for MIS and expression of the human gene in animal cells. Cell 1986.
Cohen-Haguenauer O et al. Mapping the gene for anti-Müllerian hormone to the short arm of human chromosome 19. Cytogenet Cell Genet 1987.

AMH – fiziologija izlučivanja

- Granuloza stanice folikula
- Primarnih, sekundarnih, preantralnih i ranih antralnih folikula

Weenen C. Anti-Mullerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod 2004.



McGee EA, Hsueh AJ. *Initial and cyclic recruitment of ovarian follicles. Endocr Rev 2000.*

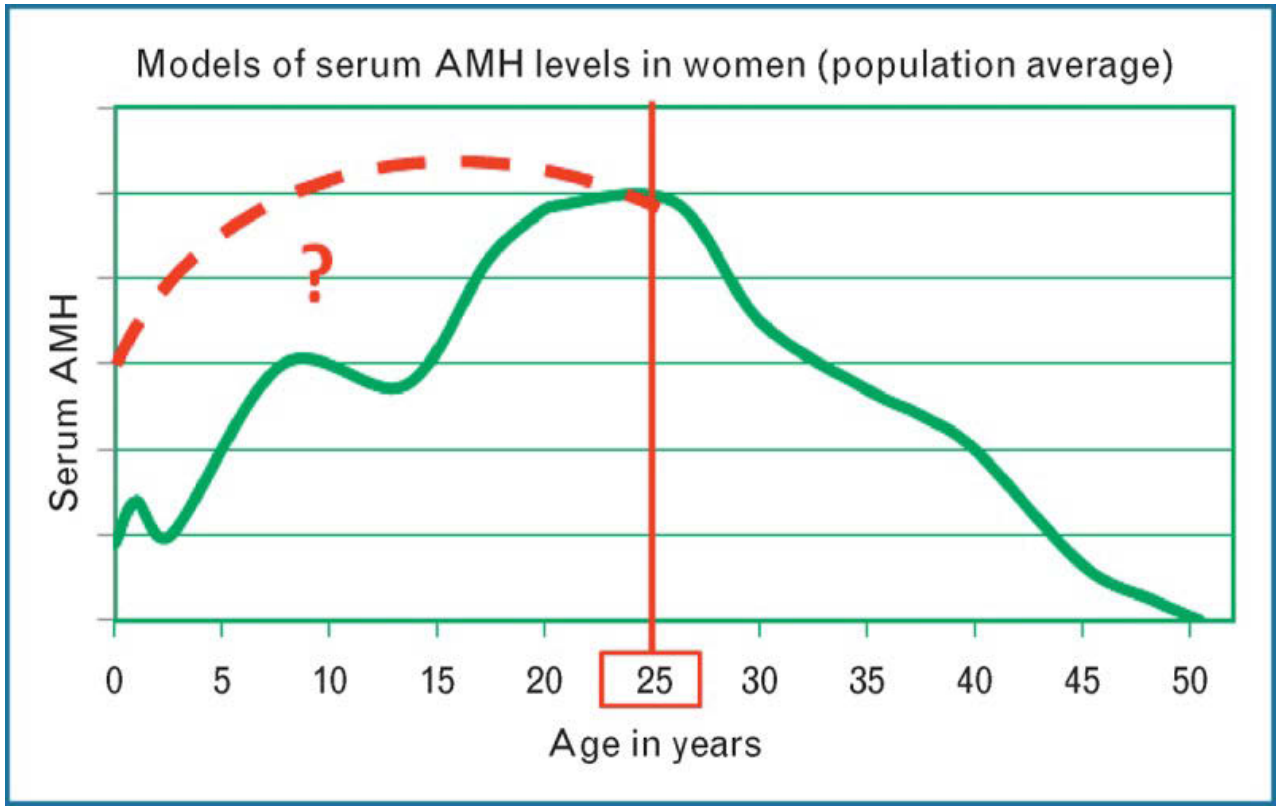
AMH – fiziologija izlučivanja

- 36. tjedan trudnoće kod ženskog ploda
- Skokovit porast do 25 godine
- **Postepen pad!?**

Rajpert-De Meyets. Expression of anti Mullerian hormone during normal and pathological gonadal deverlopment. J Clin Endocrinol Metab 1999.

Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. PloS ONE 2010.

AMH i dob



Wallace WH, Kelsey TW. *Human ovarian reserve from conception to the menopause. PloS ONE 2010.*

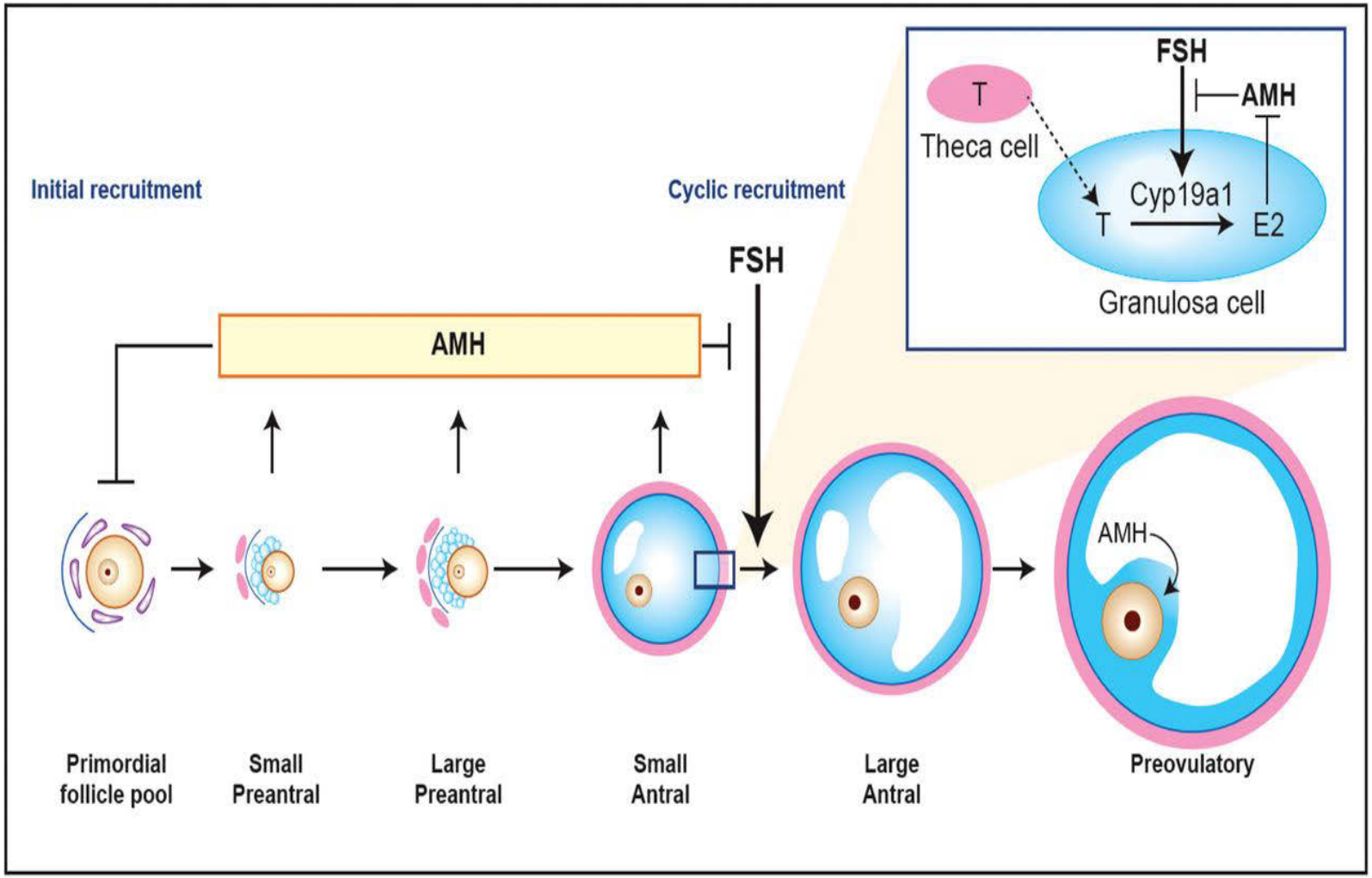
AMH – mehanizam djelovanja

Mehanizam djelovanja u jajniku nije do kraja rasvijetljen

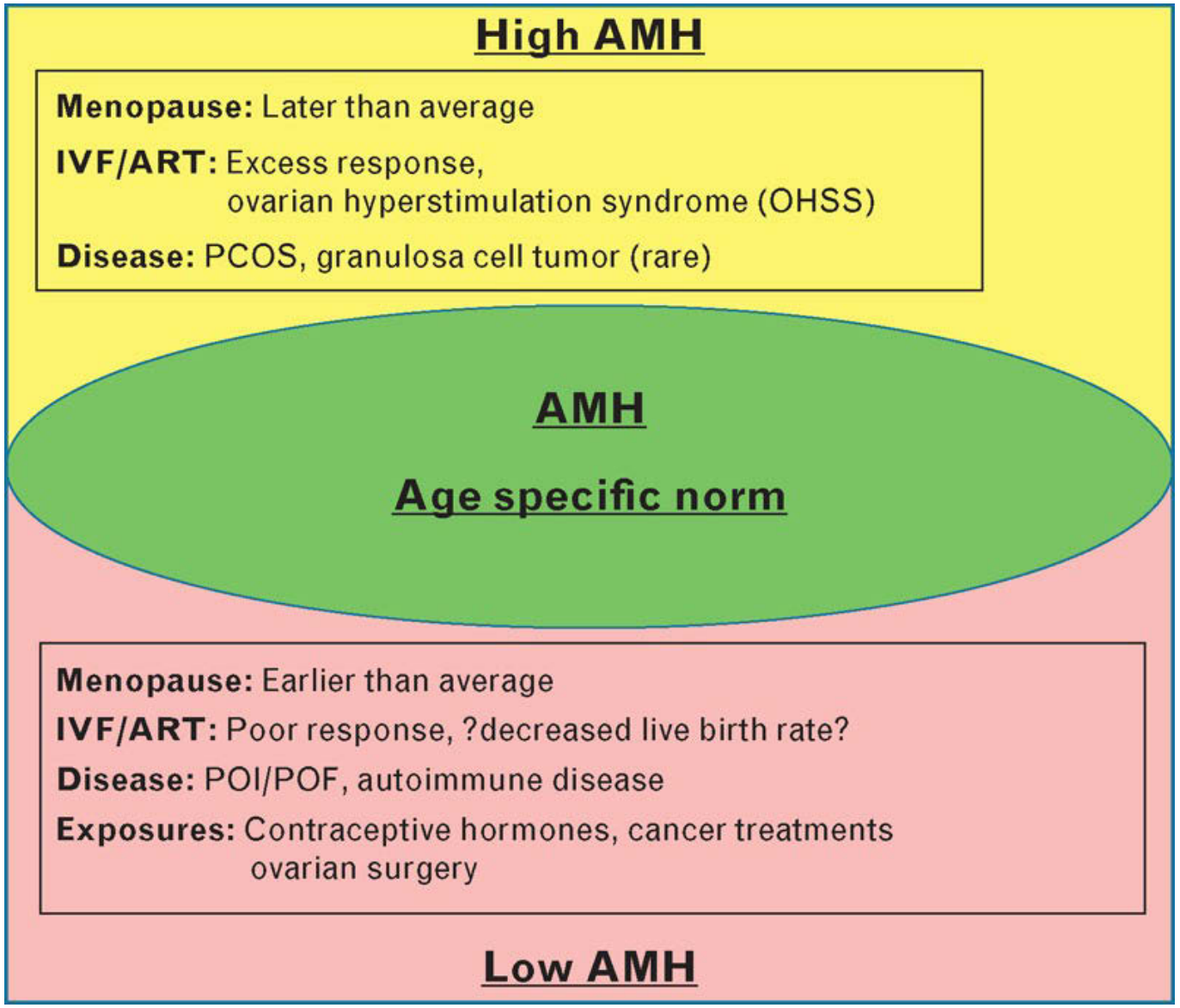
- Inhibira regrutaciju primordijalnih folikula i umanjuje odgovor odabranih folikula na FSH
- AMH preko aromataze umanjuje sintezu E2
- AMH je izražen i u stanicama cumulusa
- Hipofizni učinak? AMH receptori

Durlynger AL. Regulation of ovarian function: the role of anti-Mullerian hormone. Reproduction 2002.

Grynberg M. Differential regulation of ovarian AMH by estradiol through α- and β- estrogen . J Clin Endocrinol Metab 2012.

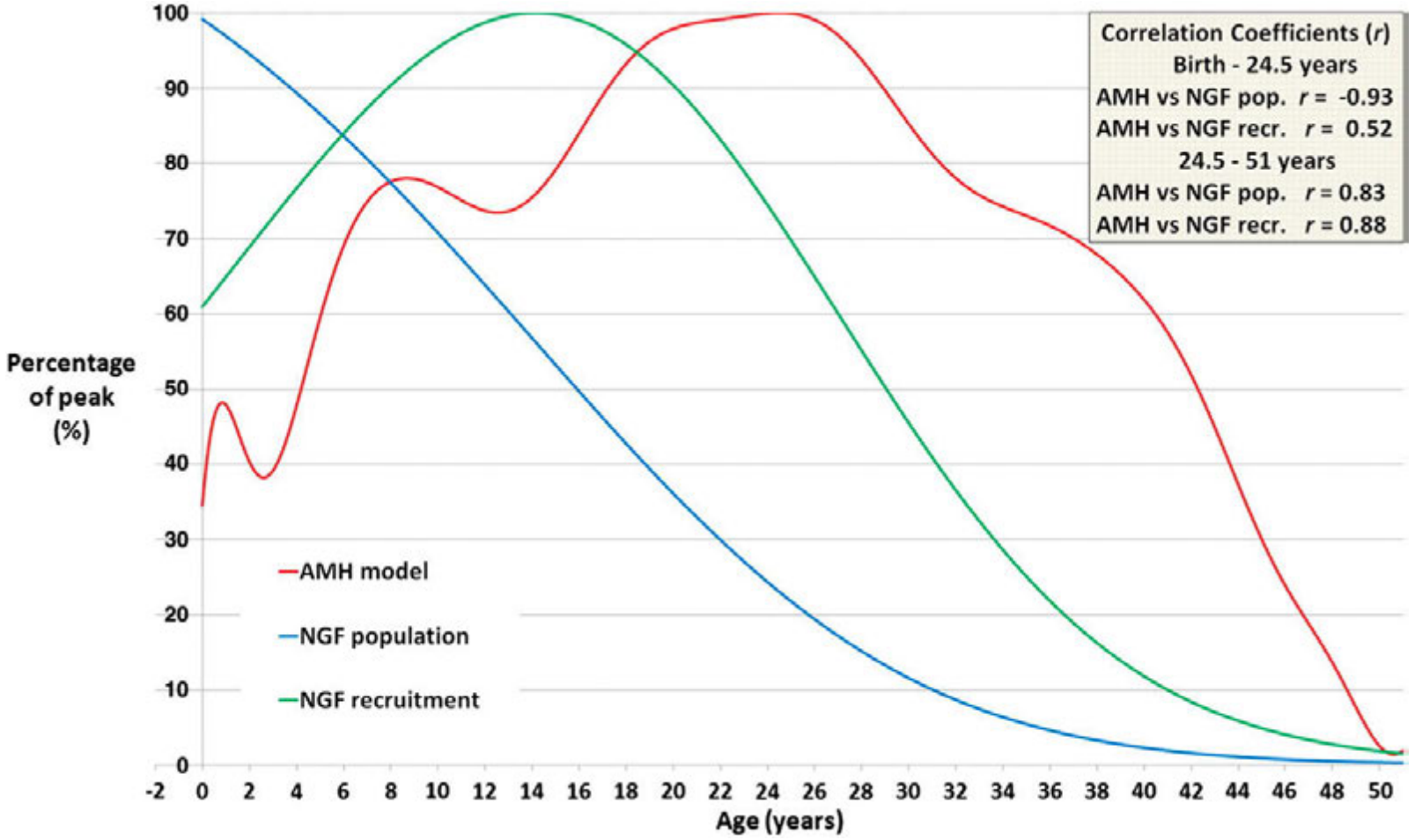


van Houten EL. Anti-Müllerian hormone (AMH): regulator and marker of ovarian function. Ann Endocrinol (Paris) 2010.



Leader B, Baker VL. Maximizing the clinical utility of AMH testing in women's health. Curr Opin Obstet Gynecol 2014.

AMH –marker starenja jajnika



Wallace WH, Kelsey TW. *Human ovarian reserve from conception to the menopause. PloS ONE 2010.*

AMH – čimbenici

Čimbenici koji smanjuju serumsku vrijednost AMH:

- BMI (↑)
- operacije
- kemo/radio
- OHK (za vrijeme uzimanja)
- trudnoća (2.i 3. trimestar)

Čimbenici koji povećavaju serumsku vrijednost AMH:

- PCOS

Karkanaki A. The clinical significance of anti-Müllerian hormone evaluation in gynecological endocrinology . Hormones 2011.

AMH i menopauza

- Menopauza je kompleksan događaj
- **Ne postoji jedinstveni test...do danas!**

AMH znatno pridonosi predviđanju nastanka menopauze

Dewailly D, et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update 2014.

AMH i FSH i inhibin B

- AMH predviđa menopauzu **puno bolje** nego **FSH, inhibin B ili iregularni ciklusi**
- Prvi konsenzus o AMH i menopauzi

Harlow SD et al. Executive summary of the stages of Reproductive Aging Workshop +10 addressing the unfinished agenda of staging reproductive aging. Fertil Steril 2012.

AMH i majčina dob

- AMH predviđa bolje nego **majčina dob**
- 46% poboljšanje ukoliko se u procjenu uključi AMH uz majčinu dob

Dolleman M et al. Anti-mullerian hormone is a more accurate predictor of individual time to menopause than mother's age at menopause.

Hum Reprod 2014.

AMH i čimbenici menopauze

Čimbenici zajedno s AMH mogu poboljšati predviđanje nastanka menopauze:

- Pušenje
- Debljina (BMI)
- OHK
- Vitamin D
- Rasna pripadnost

Dewailly D et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update 2014.

AMH i BMI i pušenje

Pušenje, nizak BMI uz niži AMH znače raniju menopauzu

Žene s AMH ispod 5 percentile:

43,4 godine za deblje i nepušačice u odnosu na mršave pušačice **37,6** godina

Žene s AMH iznad 95 percentile:

deblje nepušačice **55,4** vs. **52,4** mršave pušačice

La Marca A et al. Prediction of age at menopause from assessment of ovarian reserve may be improved by using body mass index and smoking status. *PLoS One* 2013.

AMH i rasa

Rasna pripadnost

- Crnkinje, latinoamerikanke niže vrijednosti AMH od bjelkinja
- Japan/USA usporedba

Seifer DB. Variation in mullerian inhibiting substance between white, black and Hispanic women. Fertil Steril 2009.

Tal R, Seifer DB. Potential mechanisms for racial and ethnic differences in antimullerian hormone and ovarian reserve. *Int J Endocrinol* 2013.

5 prospektivnih studija AMH i menopauza:

A single test of antimullerian hormone in late reproductive-aged women is a good predictor of menopause.

Tehrani FR, et al. Menopause. 2009

n-147
40-50 godina
regularni ciklusi
9 godina
3 mjerenja/9 godina

Anti-mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women.

Broer SL, et al. J Clin Endocrinol Metab. 2011

n-257
21-46 godina
regularni i iregularni ciklusi
11 godina
2 mjerenja

Contribution of the rate of change of antimüllerian hormone in estimating time to menopause for late reproductive-age women.

Freeman EW, et al. Fertil Steril. 2012

n-293
35-48 godina
14 godina
2 mjerenja

Modeling age at menopause using serum concentration of anti-mullerian hormone.

Tehrani FR, et al. J Clin Endocrinol Metab. 2013

n-1015
20-50 godina
regularni ciklusi
10 godina, 3x/10 godina
datum menopauze (277)

Anti-mullerian hormone (AMH) is associated with natural menopause in a population-based sample: The CARDIA Women's Study.

Nair S, et al. Maturitas. 2015

n-716
39-45 godina
regularni i poremećeni ciklusi
9 godina
barem 2 mjerenja

Zaključak svih 5 prospektivnih studija:

duže praćenje

veći uzorak

standardizirano mjerenje AMH

↓

Stvaranje percentilnih krivulja

ZAKLJUČAK:

DANAŠNJA INTERPRETACIJA JE KVALITATIVNA

Žene s većim/manjim AMH za dob će ući kasnije/ ranije u menopauzu

Smanjena ovarijska rezerva

- Žene rođene kao IUGR
- Diabetes tip 1
- Autoimune bolesti (SLE...)
- Operirane (jajnik)
- Embolizacija mioma
- BRCA1/2
- Visoke žene liječene estrogenima

Broer SL. Anti-Mullerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update 2014.

Budućnost:

Genetika!!!

- 17 genskih lokusa u predviđanju dobi menopauze

He C. Genome-wide association studies of age at menarche and age at natural menopause. menopauze Mol Cell Endocrinol 2014 .

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PLOS ONE

Interactions between Genetic Variants in *AMH* and *AMHR2* May Modify Age at Natural Menopause

Marieke G. M. Braem[1]*, Marlies Voorhuis[1,2], Yvonne T. van der Schouw[1], Petra H. M. Peeters[1], Leo J. Schouten[3], Marinus J. C. Eijkemans[4], Frank J. Broekmans[2], N. Charlotte Onland-Moret[1]

1 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, **2** Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands, **3** Department of Epidemiology, GROW–School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands, **4** Department of Biostatistics and Research Support, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Abstract

The onset of menopause has important implications on women's fertility and health. We previously identified genetic variants in genes involved in initial follicle recruitment as potential modifiers of age at natural menopause. The objective of this study was to extend our previous study, by searching for pairwise interactions between tagging single nucleotide polymorphisms (tSNPs) in the 5 genes previously selected (AMH, AMHR2, BMP15, FOXL2, GDF9). We performed a cross-sectional study among 3445 women with a natural menopause participating in the Prospect-EPIC study, a population-based prospective cohort study, initiated between 1993 and 1997. Based on the model-based multifactor dimensionality reduction (MB-MDR) test with a permutation-based maxT correction for multiple testing, we found a statistically significant interaction between rs10407022 in *AMH* and rs11170547 in *AMHR2* ($p = 0.019$) associated with age at natural menopause. Rs10407022 did not have a statistically significant main effect. However, rs10407022 is an eQTL SNP that has been shown to influence mRNA expression levels in lymphoblastoid cell lines. This study provides additional insights into the genetic background of age at natural menopause and suggests a role of the AMH signaling pathway in the onset of natural menopause. However, these results remain suggestive and replication by independent studies is necessary.

Human Reproduction, Vol.26, No.11 pp. 2925–2932, 2011
Advanced Access publication on August 16, 2011 doi:10.1093/humrep/der271

human reproduction

DEBATE *Reproductive endocrinology*

Anti-Müllerian hormone—is it a crystal ball for predicting ovarian ageing?

Justine Shuhui Loh [1] and Abha Maheshwari [2,*]

[1]Department of Obstetrics and Gynaecology, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen AB25 2ZL, UK [2]Department of Obstetrics and Gynaecology, Division of Applied Health Sciences, University of Aberdeen, Aberdeen AB25 2ZL, UK

Što sada???

- **Zamrzavanje oocita, zametaka**
- **Prevencija menopauzalnih posljedica**

Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology Mature oocyte cryopreservation: a guideline. Fertil Steril 2013.

Hvala