

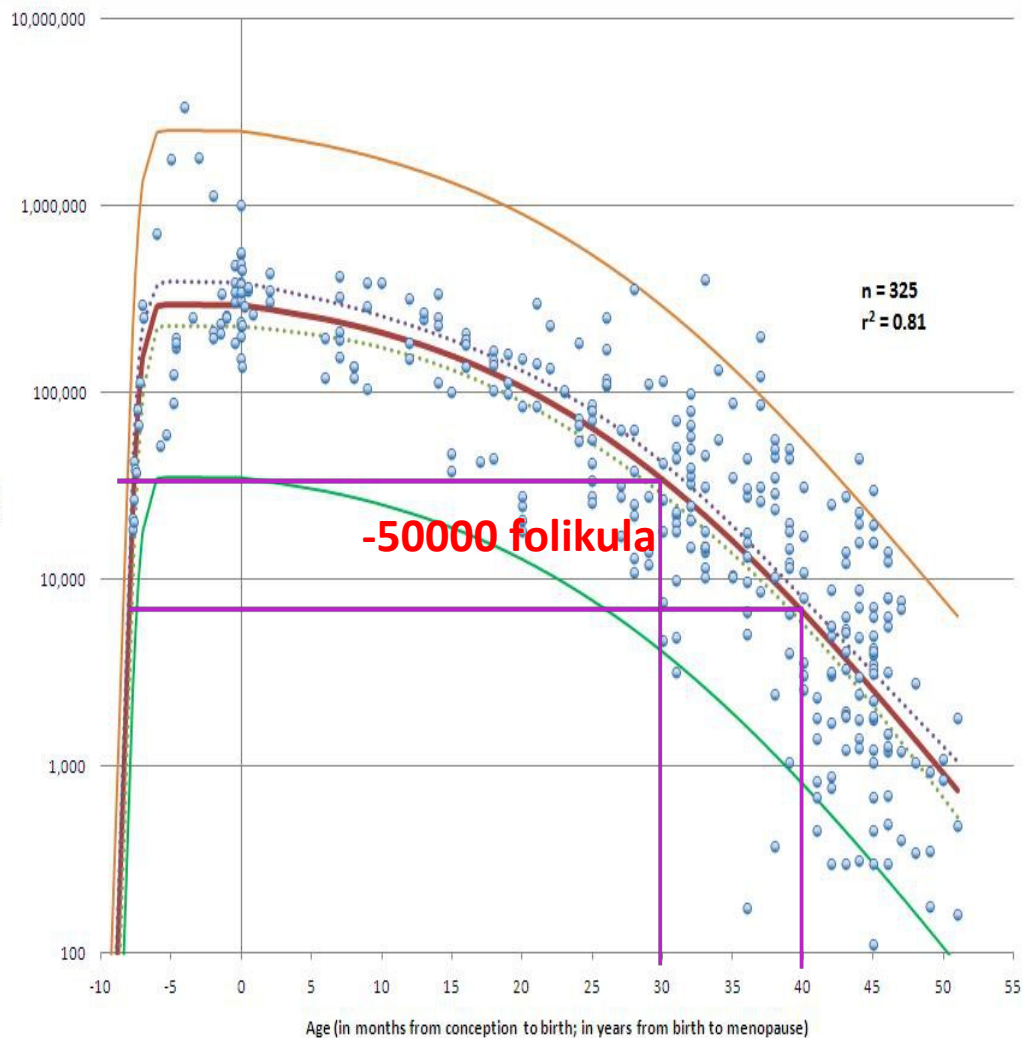
## **4. Hrvatski kongres o reprodukcijском zdravlju, planiranju obitelji, kontracepciji i IVF-u**

s međunarodnim sudjelovanjem

Prijevremena insuficijencija  
jajnika (dijagnoza, terapija,  
socijalno  
zamrzavanje) /  
Premature ovarian failure  
(diagnosis, therapy, social  
freezing)

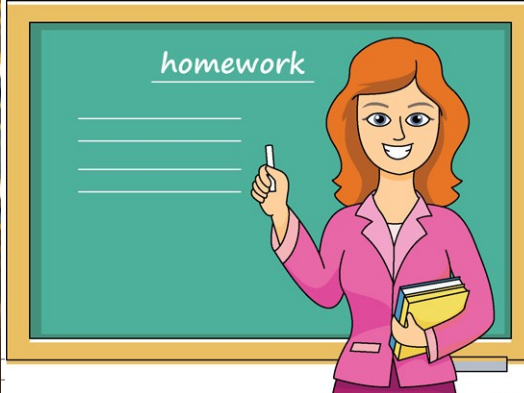
Miro Šimun Alebić



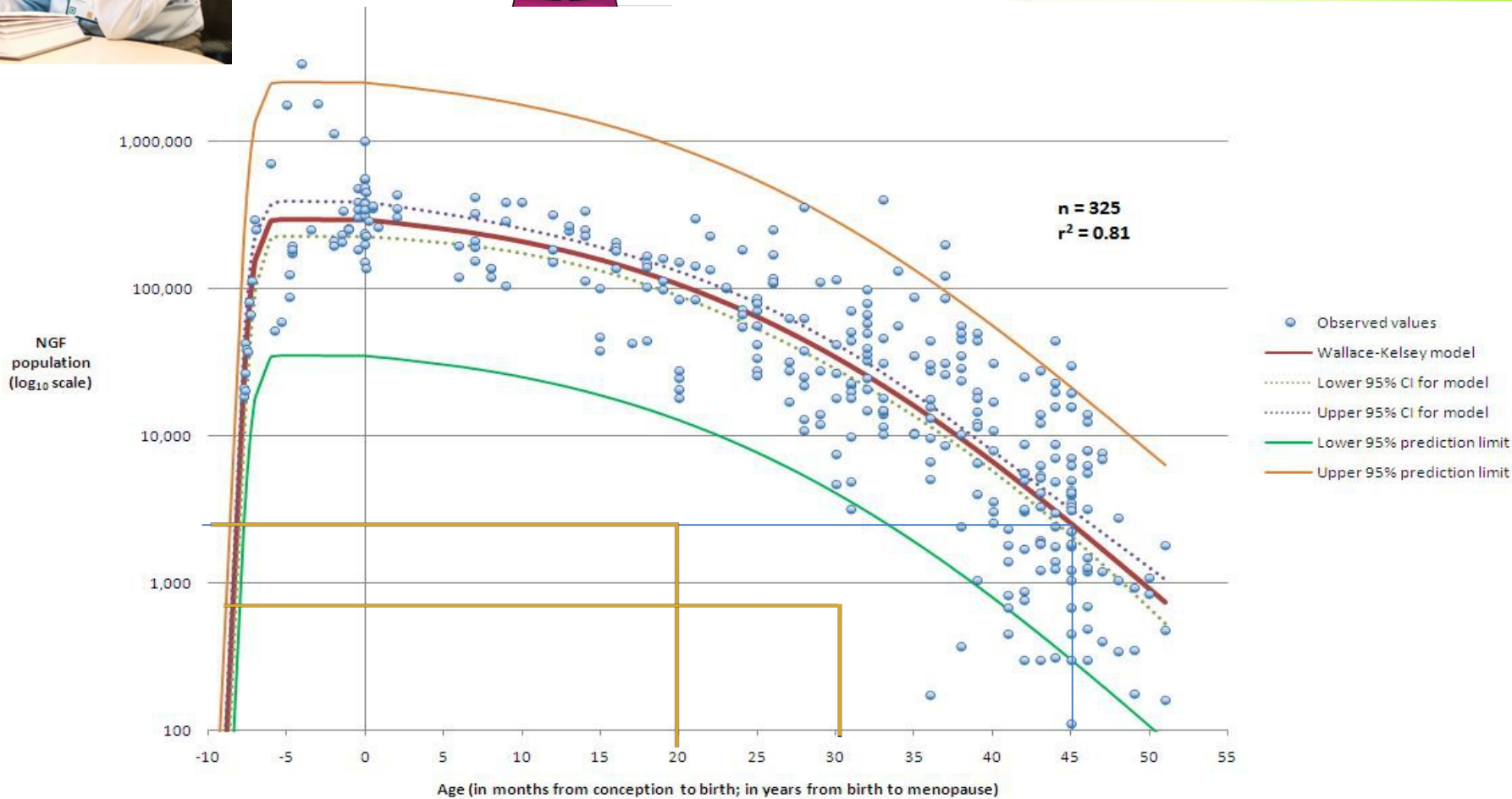


I choose the  
right moment

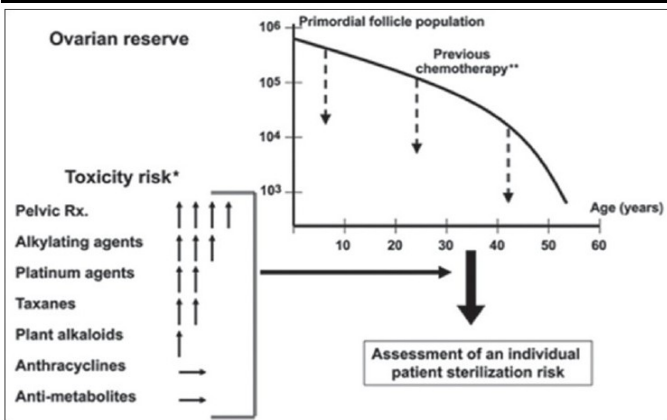
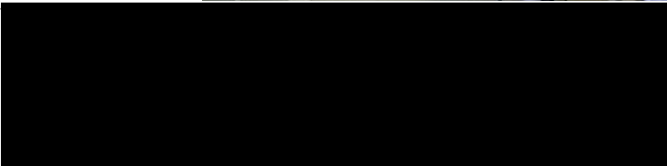
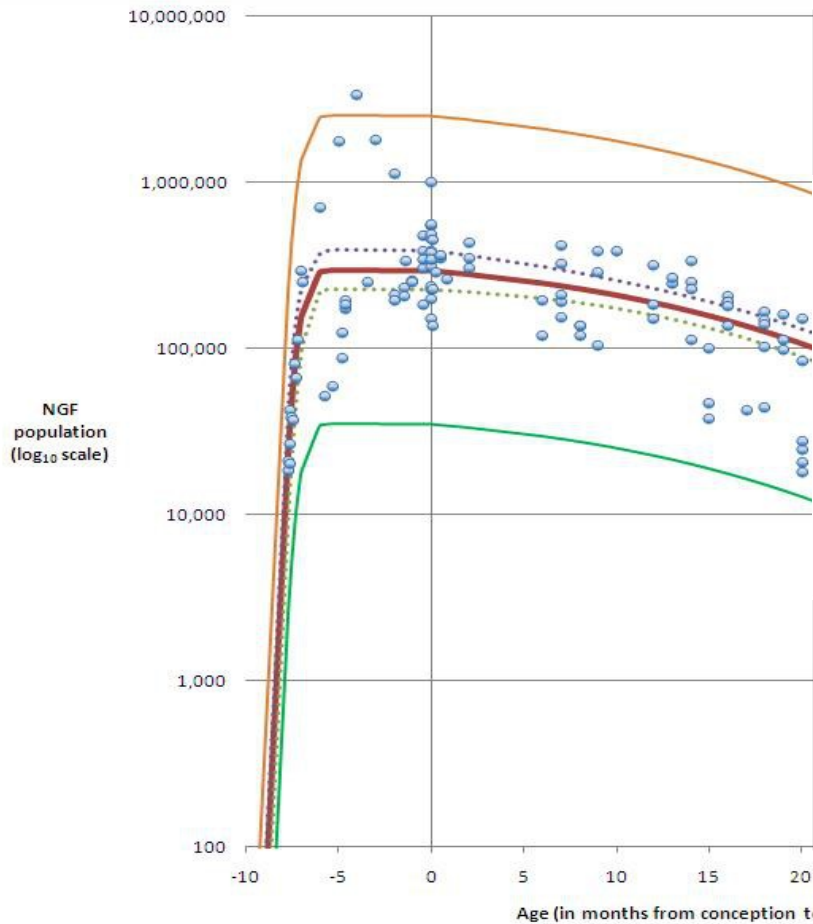
Find Mr. Right



I ♥ MY  
HUSBAND





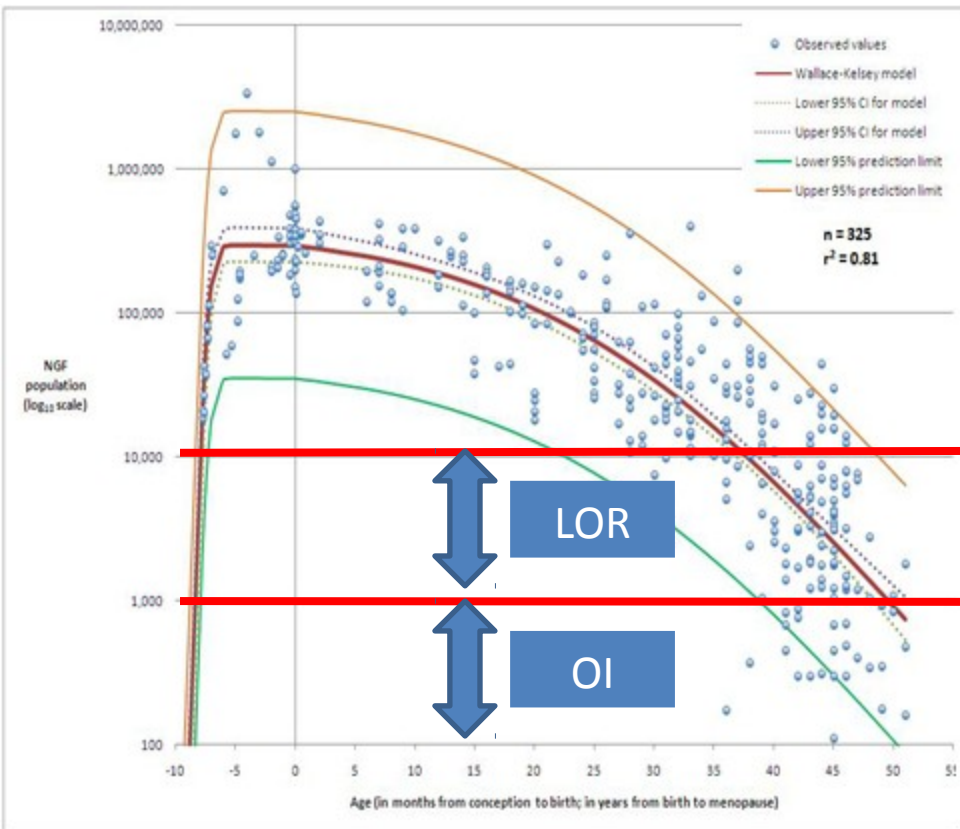


Mahajan N. Fertility preservation in female cancer patients: An overview. *Journal of Human Reproductive Sciences*. 2015;8(1):3-13. doi:10.4103/0974-1208.153119.



- Observed values
- Wallace-Kelsey model
- ..... Lower 95% CI for model
- ..... Upper 95% CI for model
- Lower 95% prediction limit
- Upper 95% prediction limit

# Ovarian reserve



- the pool of resting follicles at any given age

## Low or diminished ovarian reserve

- mostly age-associated but also caused by conditions affecting the ovaries
- irregular menses
- poor response to controlled ovarian stimulation
- diminished **reproductive** potential
- incidence: 9 to 24% (Keay, *et al.*, 1997).

Wallace and Kelsey.  
Human Ovarian Reserve from Conception to the Menopause. PLoS ONE 2011; 5: e8772



Management of women  
with premature ovarian  
insufficiency

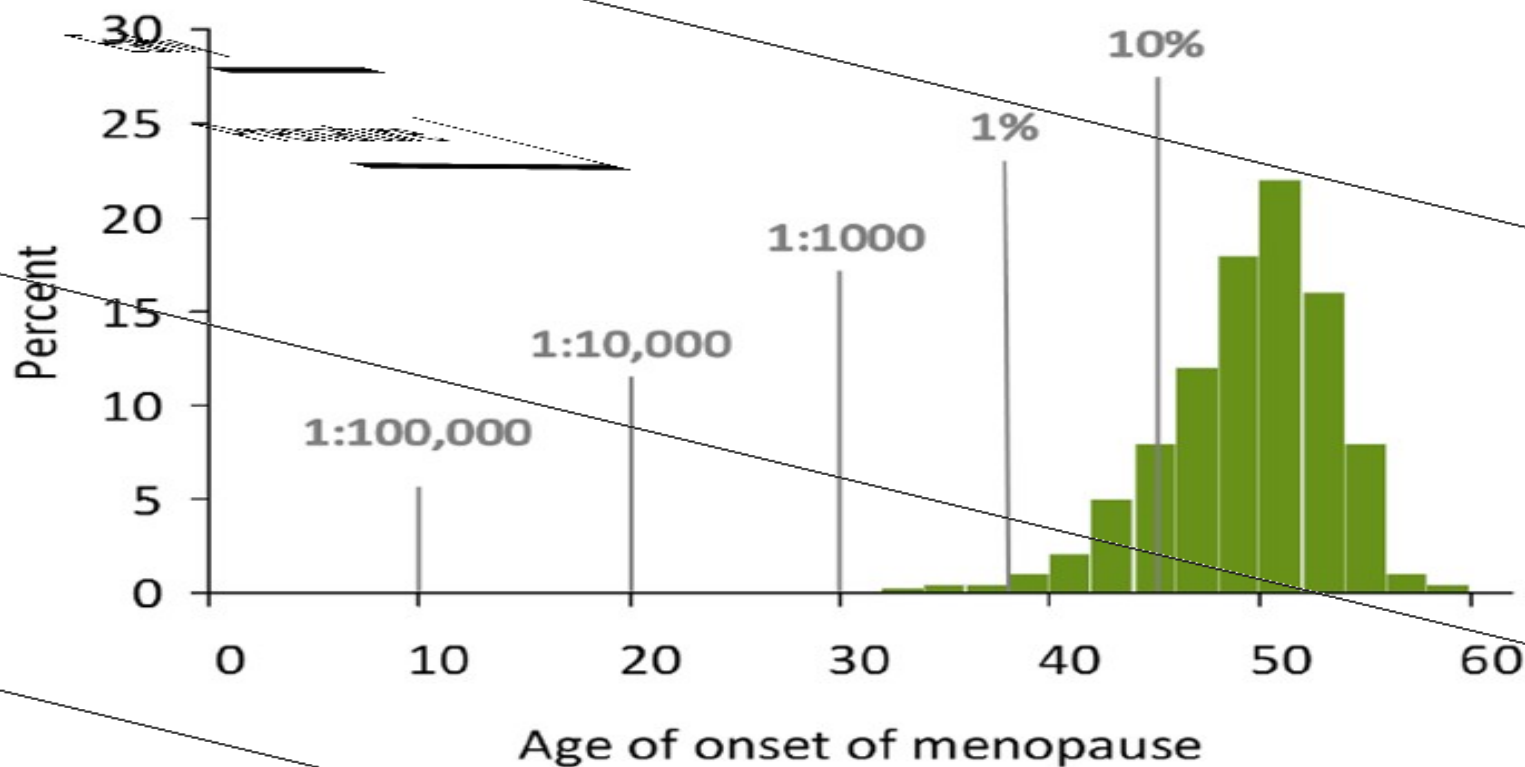
Guideline of the European Society of Human  
Reproduction and Embryology

POI Guideline Development Group  
December 2015

# Ovarian insufficiency

- loss of **ovarian activity**

*Distribution of age at menopause.*



# Terminology

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Primary Ovarian Insufficiency

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Premature Ovarian Failure

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Gonadal dysgenesis

---

Premature menopause

---

Early menopause

---

Hypergonadotropic hypogonadism

---

Premature Ovarian Insufficiency

---

Ovarian dysgenesis

---

Primary ovarian failure

---

Hypergonadotropic amenorrhea

---

Climacterium praecox

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Menopause praecox

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- “premature ovarian insufficiency” should be used to describe this condition in research and clinical practice.
- **loss of ovarian activity before age 40**



**Low or diminished ovarian reserve**



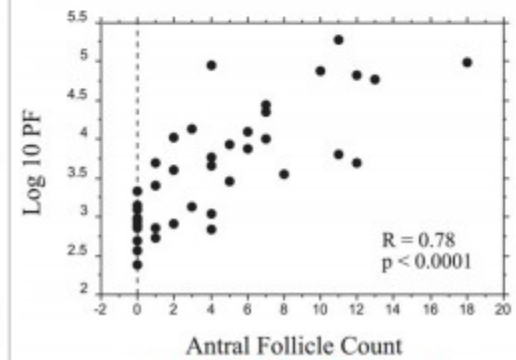
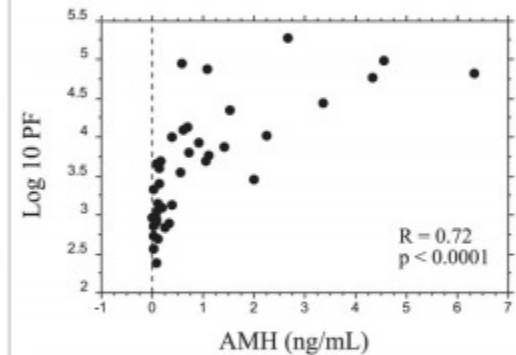
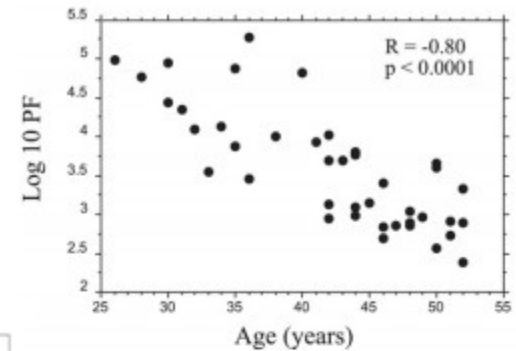
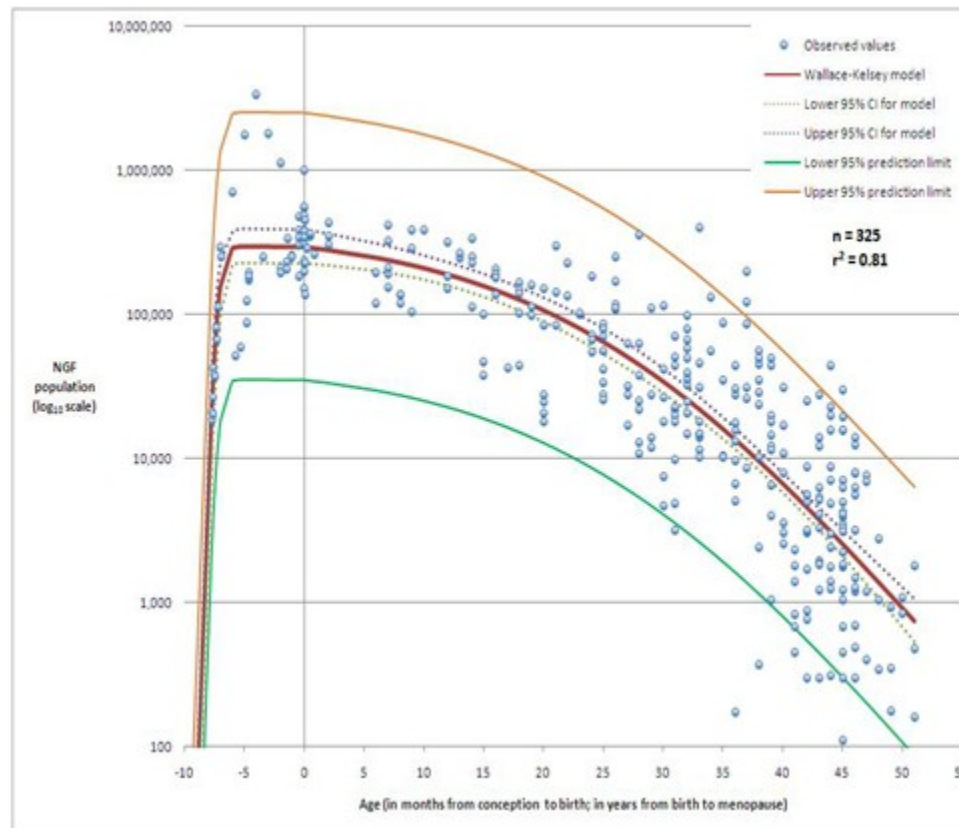
**Ovarian insufficiency**





# Ovarian reserve tests:

- AMH
- AFC

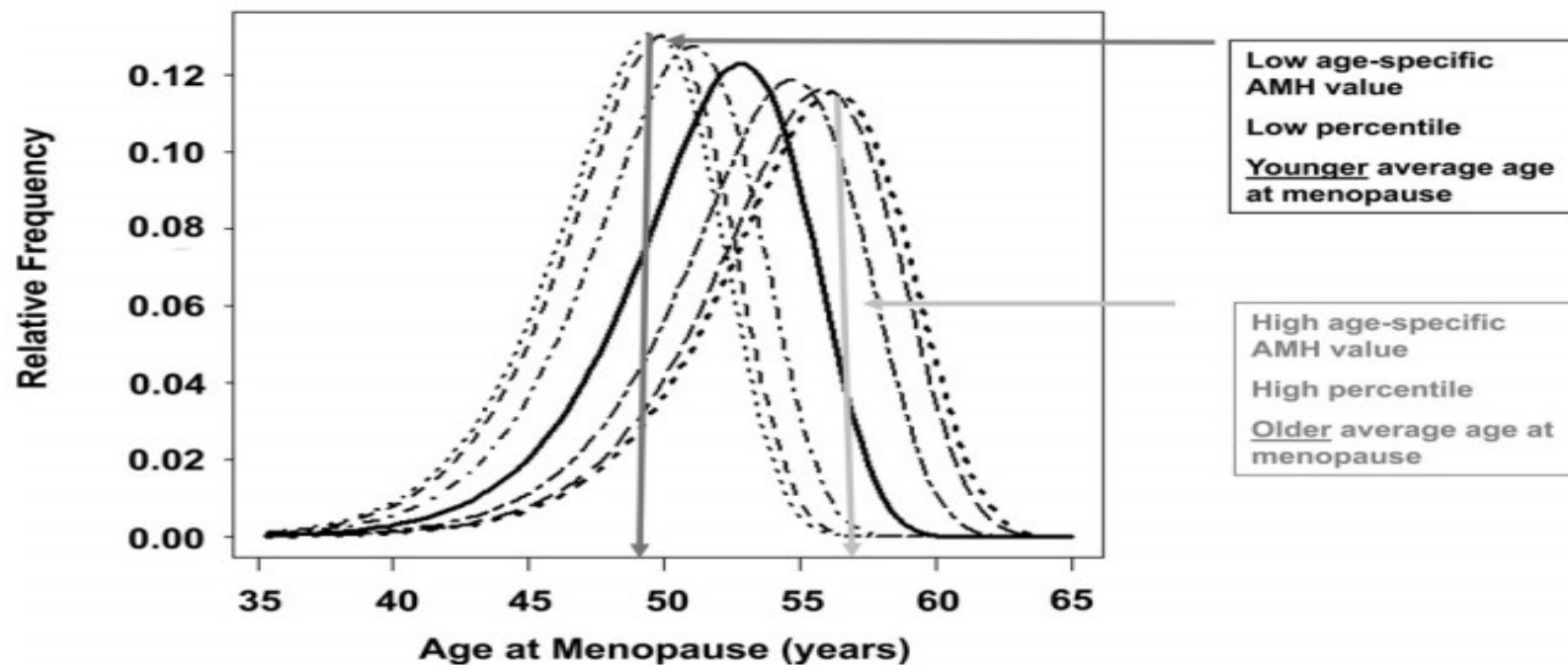
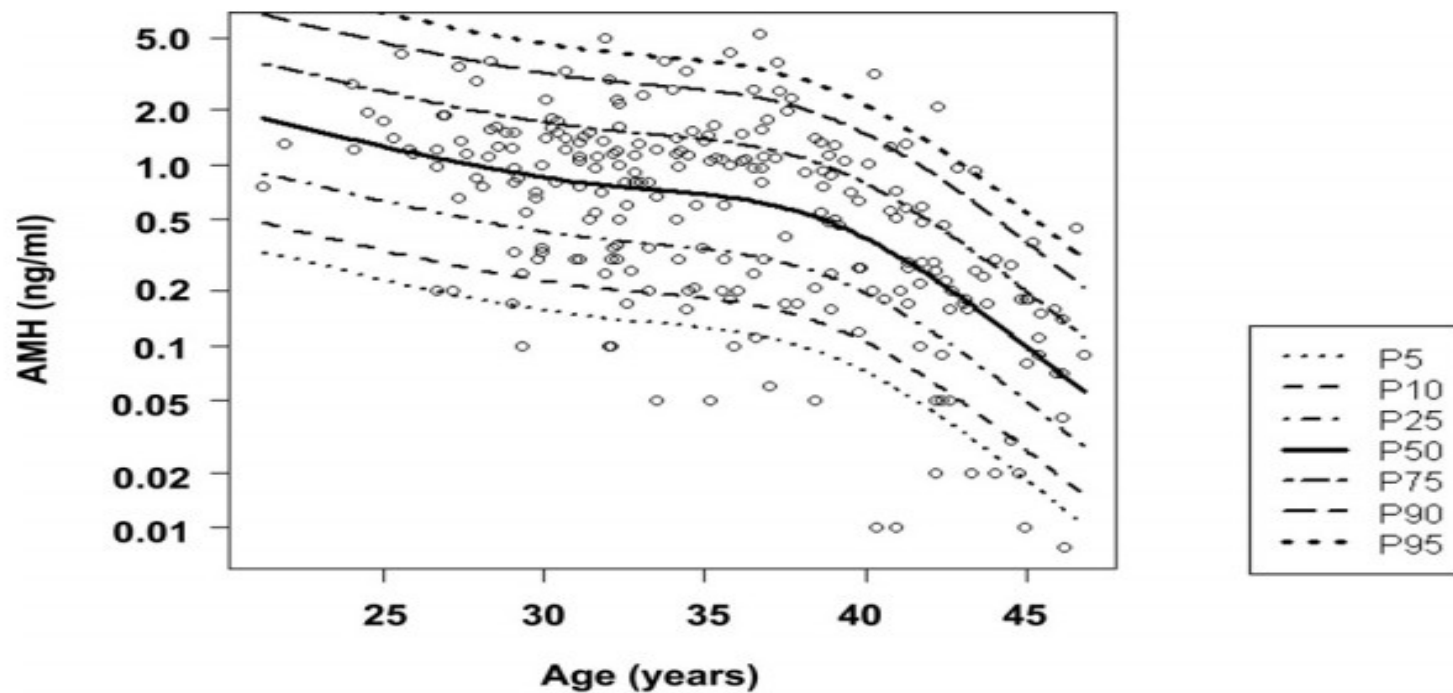


Hansen. Primordial follicle number and markers of ovarian function Fertil Steril 2011.

**Table 2.** Average Age at Menopause for Individual Women Aged 20 to 49 Years, When Different Serum Concentrations of AMH Are Assumed

| AMH,<br>ng/dL | Age, y       |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
|---------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
|               | 20           | 22           | 24           | 26           | 28           | 30           | 32           | 34           | 36           | 38           | 40           | 42           | 44           | 46           | 48           | 50           |
| 0.1           | 33 (27-36)   | 34 (28-38)   | 35 (29-39)   | 36 (30-40)   | 37 (31-41)   | 39 (32-43)   | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   |
| 0.3           | 34 (28-38)   | 35 (29-39)   | 36 (30-40)   | 37 (31-41)   | 39 (32-43)   | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   |
| 0.5           | 35 (29-39)   | 36 (30-40)   | 37 (31-41)   | 39 (32-43)   | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   |
| 0.7           | 36 (30-40)   | 37 (31-41)   | 39 (32-43)   | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   |
| 0.9           | 37 (31-41)   | 39 (32-43)   | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50-67)   |
| 1.1           | 39 (32-43)   | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50-67)   | 63 (51-69)   |
| 1.3           | 40 (33-44)   | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  |
| 1.5           | 41 (34-46)   | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |
| 1.7           | 43 (35-47)   | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |
| 1.9           | 44 (36-49)   | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |
| 2.1           | 45 (37-50)   | 47 (38-52)   | 48 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |
| 2.3           | 47 (38-52)   | 49 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |
| 2.5           | 49 (40-54)   | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |
| 2.7           | 50 (41-55)   | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |
| 2.9           | 52 (42-57)   | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |
| 3.1           | 53 (44-59)   | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |
| 3.3           | 55 (45-61)   | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |              |
| 3.5           | 57 (47-63)   | 59 (48-65)   | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |              |              |
| 3.7           | 59 (48-65)   | 61 (50->65)  | 63 (53->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |              |              |              |
| 3.9           | 61 (50->65)  | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |              |              |              |              |
| 4.1           | 63 (51->65)  | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |              |              |              |              |              |
| 4.3           | 65 (53->65)  | >65 (55->65) |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| 4.5           | >65 (55->65) |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |

Tehrani FR, Solaymani-Dodaran M, Tohidi M, Gohari MR, Azizi F. Modeling age at menopause using serum concentration of anti-mullerianhormone. J Clin Endocrinol Metab 2013;98:729-735.



Broer SL, Eijkema ns MJ, Scheffer GJ, et al. Anti-mullerian hormon e predicts menopa use: a long-term follow-up study in normoovulatory women. J Clin Endocrinol Metab 011;96: 2532-2539.

- AMH and mother's age of natural menopause
  - currently the most promising predictors of age at menopause
- models
  - lack the capacity to predict extreme
  - provide wide prediction intervals

**AMH is currently not applicable for predicting menopause or the end of natural fertility in the day-to-day clinical practice**

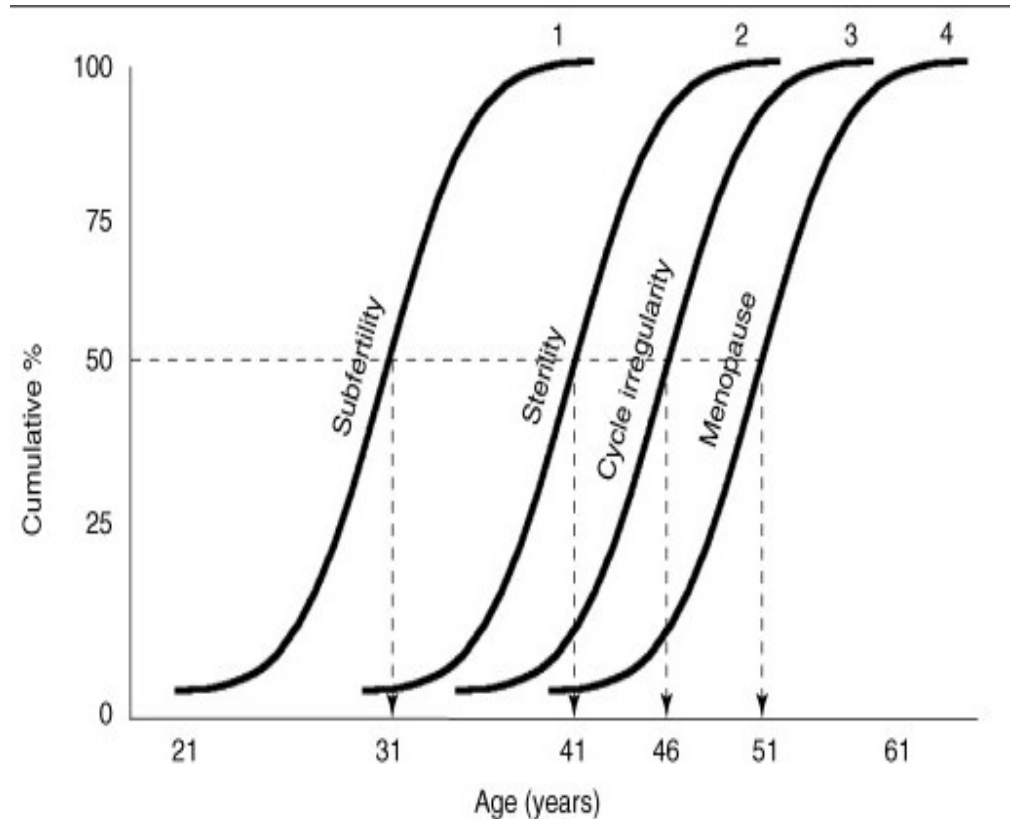


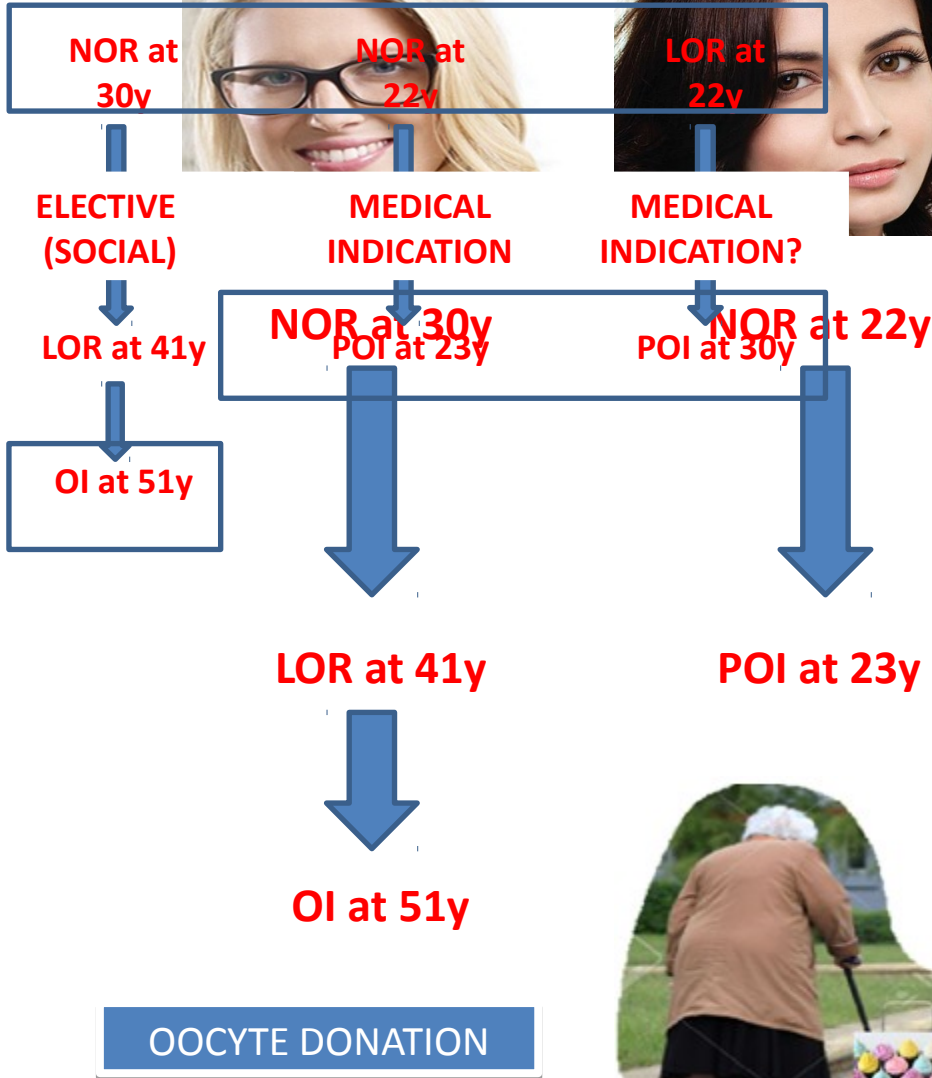
# Introduction

- age at menopause, the end of natural fertility and the start of subfertility - a fixed temporal relationship

te Velde and Pearson, 2002

Broekmans et al., 2009





# Oocyte freezing

12.8 frozen oocytes should be  
fertilized to achieve  
one delivery !!!

- 3043 oocytes
- 2115 live births,

ART results with frozen oocytes: data from the Italian ART registry (2005-2013). J Assist Reprod Genet. 2016 Jan;33(1):123-8

## Oocyte freezing

delay for a cancer treatment

negative effect on estrogen-sensitive tumors from high estradiol levels during stimulation

## Embryo freezing

reproductive autonomy is limited - partner's or donor sperm required

ethical, legal and religious implications regarding disposal of embryos in case patient dies

## Ovarian tissue cryopreservation (OTC)

does not delay the start of cancer therapy and avoids the risk of ovarian stimulation.

no need for partner or donor sperm

preserves a larger pool of follicles and allows for the resumption of ovarian function.

only technique available for preserving fertility in prepubertal girls.



# POI - diagnosis



- menstrual disturbance and biochemical confirmation
- diagnostic criteria:
  - oligo/amenorrhea for at least 4 months, and
  - an elevated FSH level  $> 25$  IU/l on two occasions  $> 4$  weeks apart
  - in women  $< 40$  years
- suspect if:
  - estrogen-deficiency symptoms
  - amenorrhea/oligomenorrhea
  - below the age of 40 years

- FERTILITY

- a small chance of spontaneous pregnancy
- no interventions that have been reliably shown to increase ovarian activity and natural conception rates
- use contraception to avoid pregnancy
- oocyte donation - established option for fertility
- if established - missed opportunity for fertility preservation



BONE HEALTH - ↓BMD ↑fracture risk

CARDIOVASCULAR HEALTH - ↑ CVD risks

SEXUAL AND GENITO-URINARY FUNCTION

NEUROLOGICAL HEALTH

- healthy lifestyle
  - weight-bearing exercise
  - avoidance of smoking
  - maintenance of normal body weight
- HRT

# Hormone replacement therapy (HRT)

- treatment of low estrogen symptoms
- potential role in :
  - primary prevention of CVD
  - bone protection

**not been found to increase the risk of  
breast cancer  
before the age of natural menopause**



# Hormone replacement therapy (HRT)

- progestogen in combination if uterus is intact
- $17\beta$ -estradiol rather than ethinylestradiol or conjugated equine
- oral cyclical combined treatment - the strongest evidence of endometrial protection
- consider patient preference for route and method of administration
- clinical review annually, attention to compliance
- no routine monitoring tests are required

# POI – causes and interventions

- iatrogenic
  - **discuss POI** as a potential consequence **prior a medical or surgical intervention**
- non-iatrogenic
  - chromosomal analysis
  - screening for 21OH-Ab and thyroid (TPO-Ab) antibodies
- unexplained or idiopathic
  - significant number



Primary Ovarian Insufficiency

Premature Ovarian Failure

Gonadal dysgenesis

Premature menopause

Early menopause

Hypergonadotropic hypogonadism

**Premature Ovarian Insufficiency**

Ovarian dysgenesis

Primary ovarian failure

Hypergonadotropic amenorrhea

Climacterium praecox

Menopause praecox

**TO TAKE HOME**

**PRIJEVREMENA  
INSUFICIJENCIJA  
JAJNIKA**

oligo/amenorrhea  $\geq 4$  months  
2x FSH  $> 25$  IU/l  $> 4$  weeks apart  
in women  $< 40$  years

- healthy lifestyle
  - weight-bearing exercise
  - avoidance of smoking
  - maintenance of normal body weight

- **HRT**





## Activation of dormant mature eggs

Jing Li<sup>a</sup>, Kazuhiro Kawamura<sup>b</sup>, Yuan Cheng<sup>a</sup>,

<sup>a</sup>Department of Obstetrics and Gynecology, Program of Reproductive and Stem Cell Biology, Stanford University School of Medicine, Stanford, CA 94305-5317; <sup>b</sup>Department of Obstetrics and Gynecology, Akita University School of Medicine, Akita 010-8543, Japan; and <sup>c</sup>State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, People's Republic of China



stimulation of

Li-hong Ho<sup>c</sup>,  
Hosoi<sup>1</sup>,

ation  
ification  
arian

of  
1 of

<sup>1</sup>, Yodo Sugishita<sup>1</sup>,  
orimoto<sup>2</sup>, and

Rajareddy,<sup>1\*</sup>

Early follicular development by the  
roles for an old timer

Shirna Jagarlamudi<sup>a</sup>, Karin Boman<sup>b</sup>,  
p Reddy<sup>a</sup>