

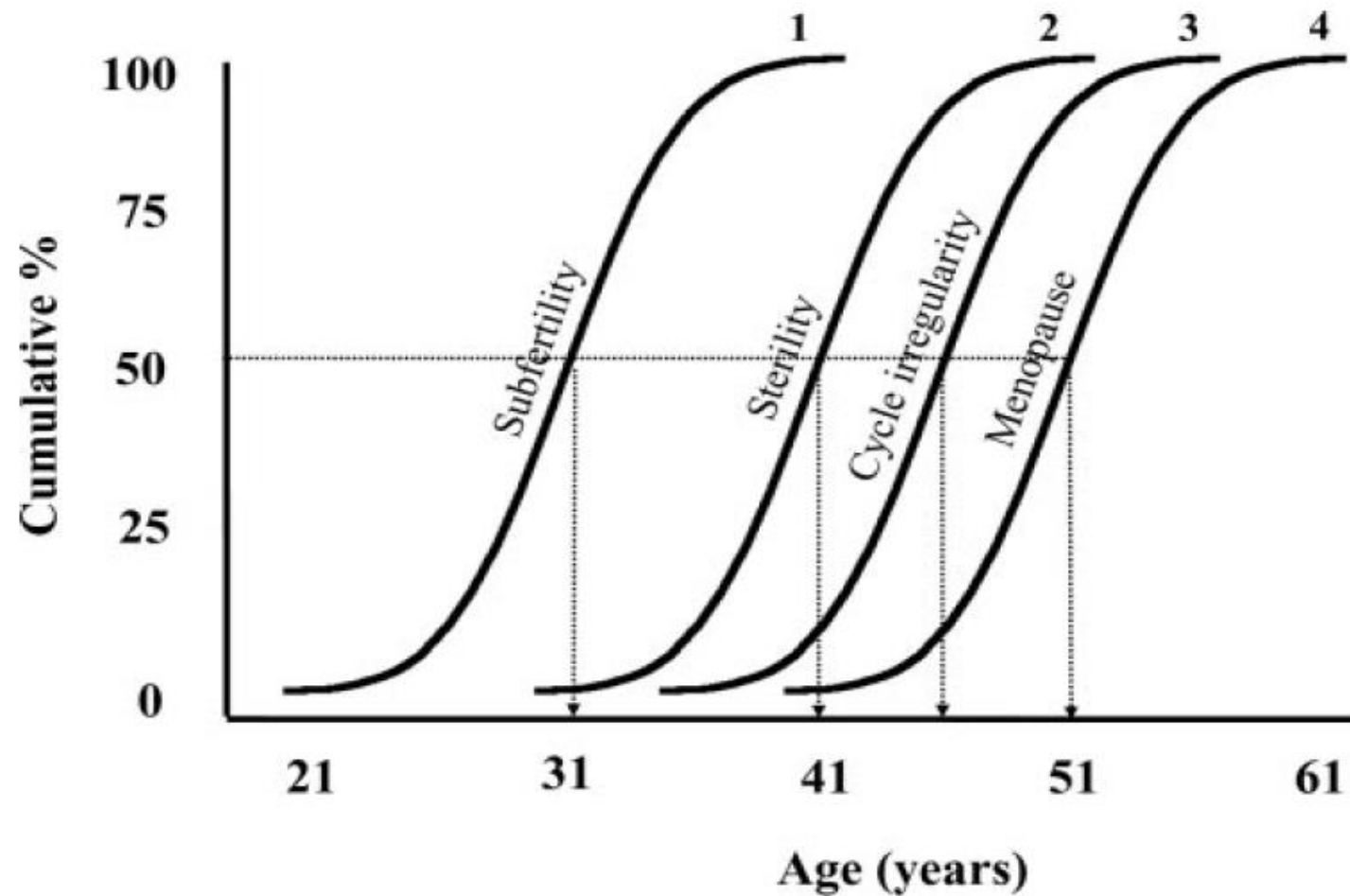


# Viljakuse hindamine ja säilitamine, onkofertiilsus

Dr. Aivar Ehrenberg

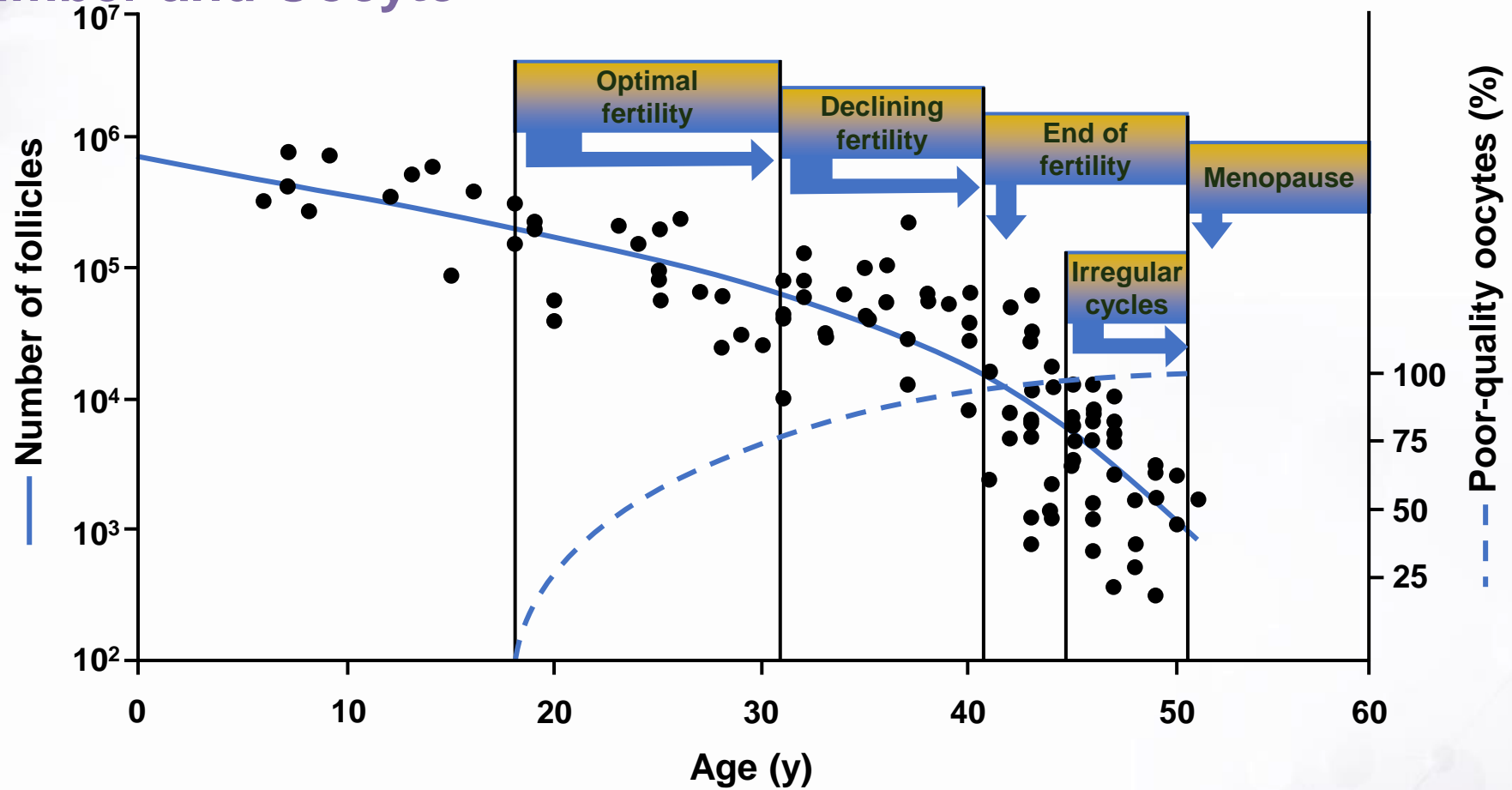
 Tartu Ülikooli Kliinikum



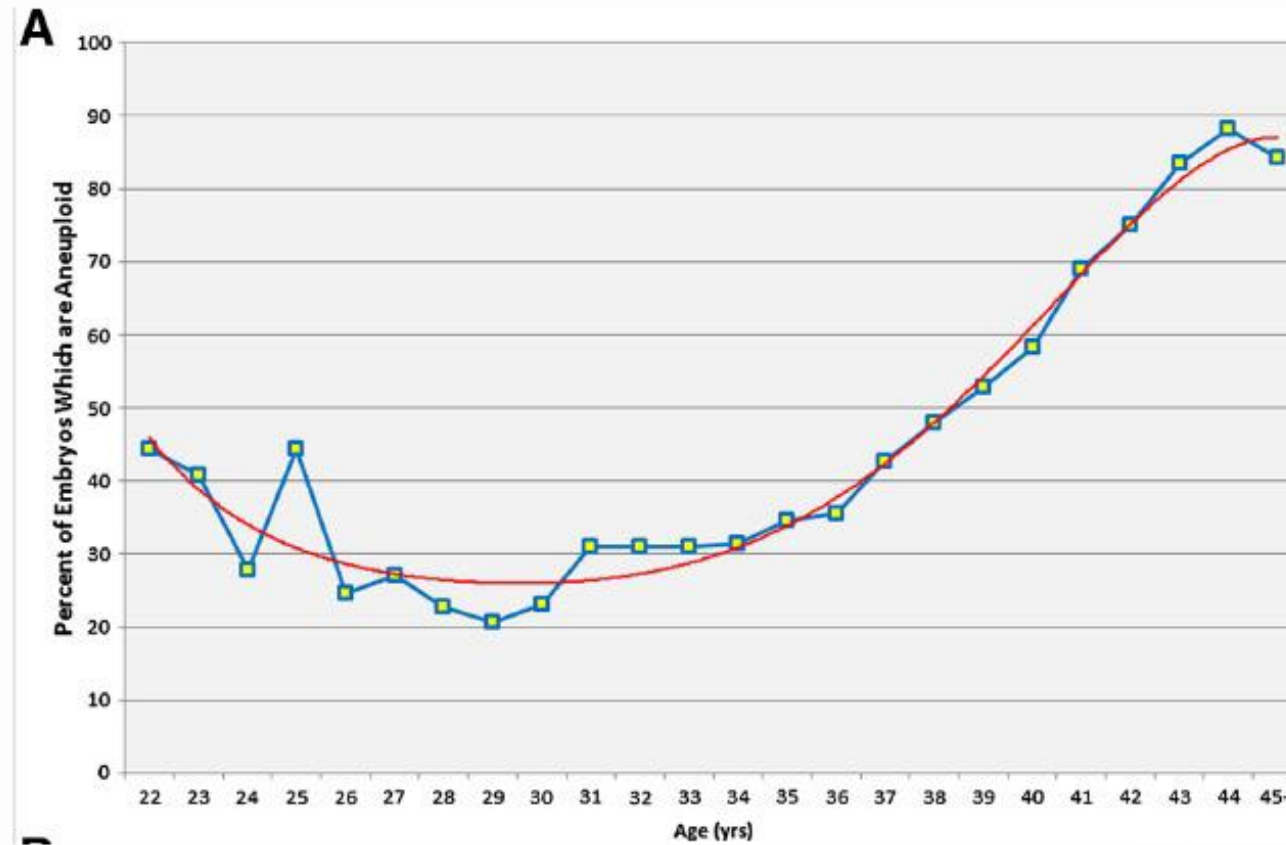


**Figure 2.** Variations in age at the occurrence of specific stages of ovarian ageing. For explanation of the background of data, see te Velde and Pearson (2002). Reprinted with permission from te Velde and Pearson (2002).

# Increasing Maternal Age Is Associated With Decline in Follicle Number and Oocyte Quality



## Aneuploidsete embrüote osamäär



*Franasiak et al, FS, 2014*

**TABLE 1**

Embryo implantation rates as a function of female age  
(42)

Age	Implantation rate
25–29	18.2%
30–34	16.1%
35–39	15.3%
40–44	6.1%

Reprinted with permission (Fertil Steril 1996;65:783–790) (42).

*Source:* Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, RESOLVE. 1999 Assisted Reproductive Technology Success Rates. Atlanta, GA. Centers for Disease Control and Prevention;2001.4

Human Reproduction Update, Vol.11, No.3 pp.261–276, 2005

Advance Access publication April 7, 2005

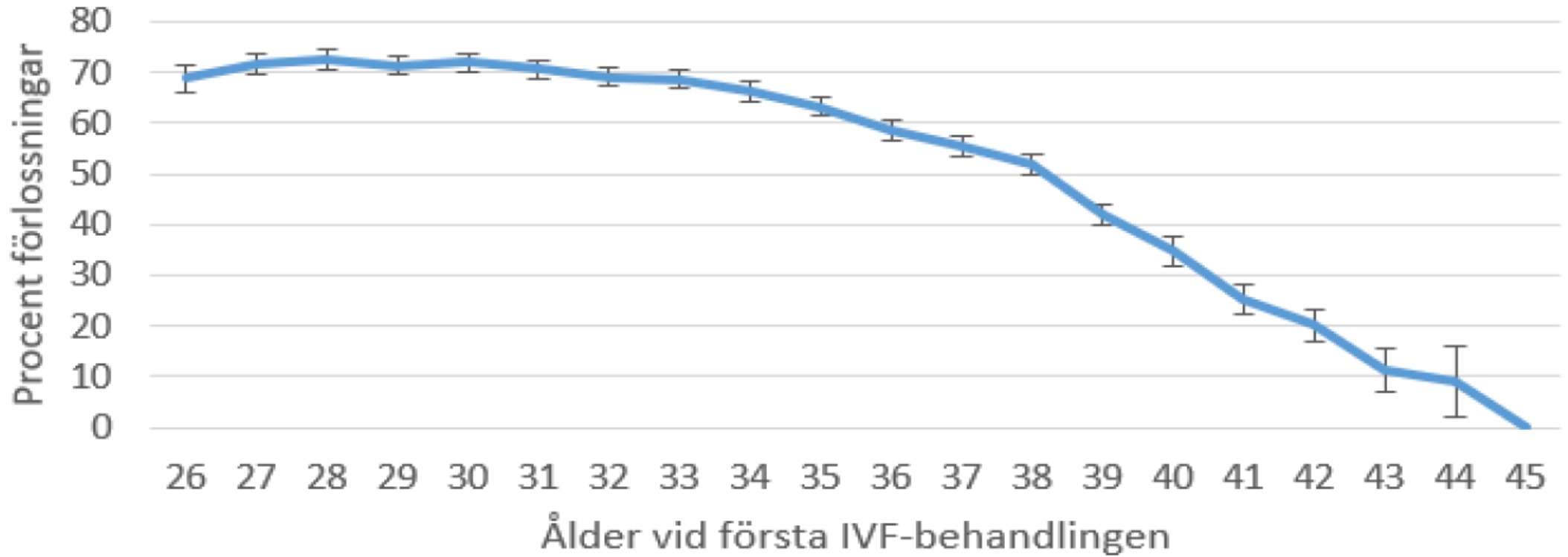
## Fertility and ageing

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ESHRE Capri Workshop Group\*

Naise vanus	Elussünniga lõppeva raseduse tõenäosus 1a jooksul (%)	Elussünniga lõppeva raseduse tõenäosus 4a jooksul (%)
30	75	91
35	66	84
40	44	64

**Figure 1.** Proportion of women achieving a delivery after treatment started within 18 months of the first IVF-treatment (own oocytes).



The graph above includes women who underwent their first oocyte retrieval from January 1, 2012 to June 30, 2019. The numbers 26 to 45 in the graph indicate a woman's age at the start of the first treatment.

## Munasarjade reservi hindamine

**Table I.** Potential predictors of ovarian function

---

Biochemical

- FSH
- Inhibin A
- Anti-Müllerian hormone
- E<sub>2</sub>
- Inhibin B

Imaging

- Antral follicle count
- Ovarian volume
- Uterine artery flow dynamics

Dynamic tests

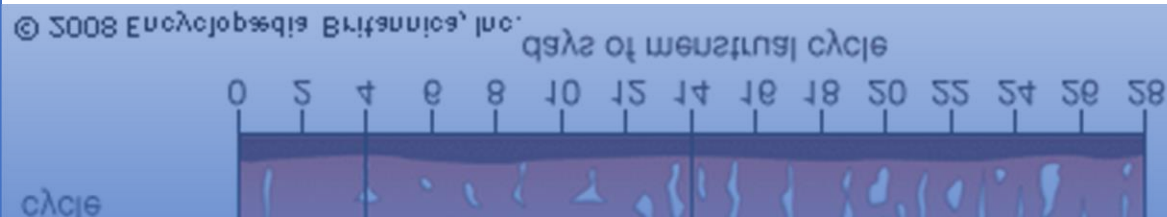
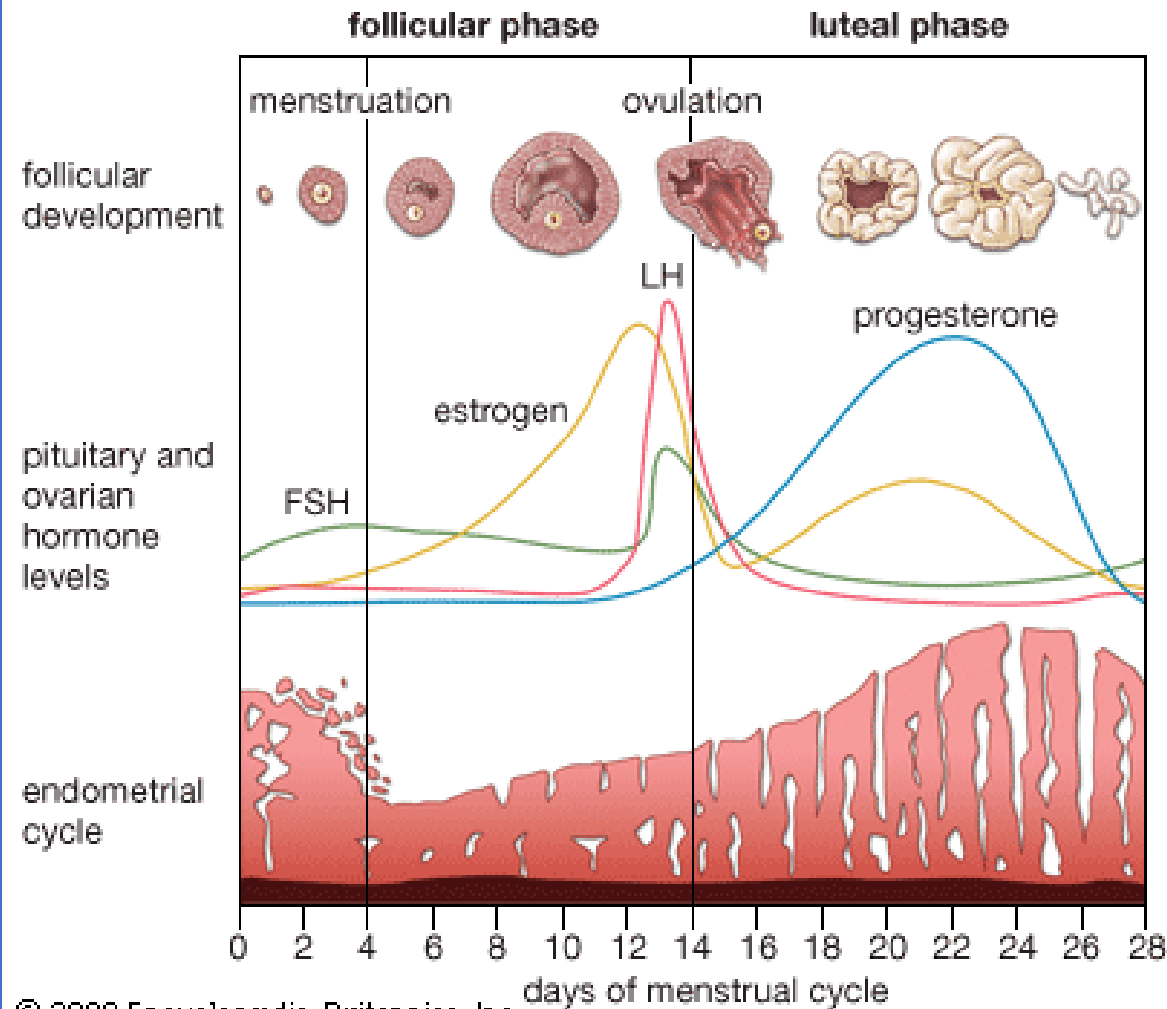
- CCCT: clomiphene citrate challenge test
  - EFORT: inhibin and E<sub>2</sub> response to FSH
  - GAST: inhibin and E<sub>2</sub> response to GnRH agonist
-



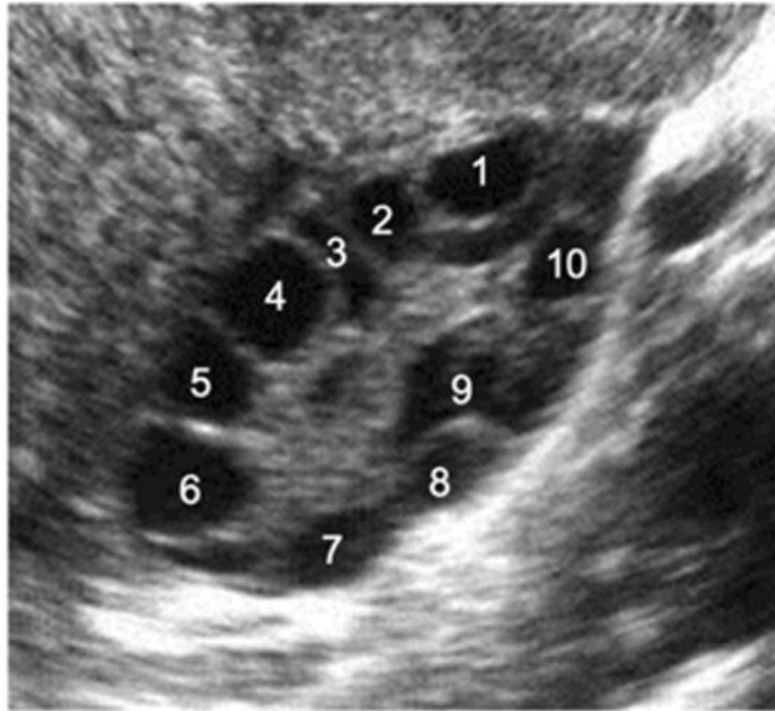
# Ovariaalse reservi hindamine

- vanus
- FSH
- AFC (*antral follicle count*)
- AMH

# The menstrual cycle



## 2. Antral Follicular Count (AFC)

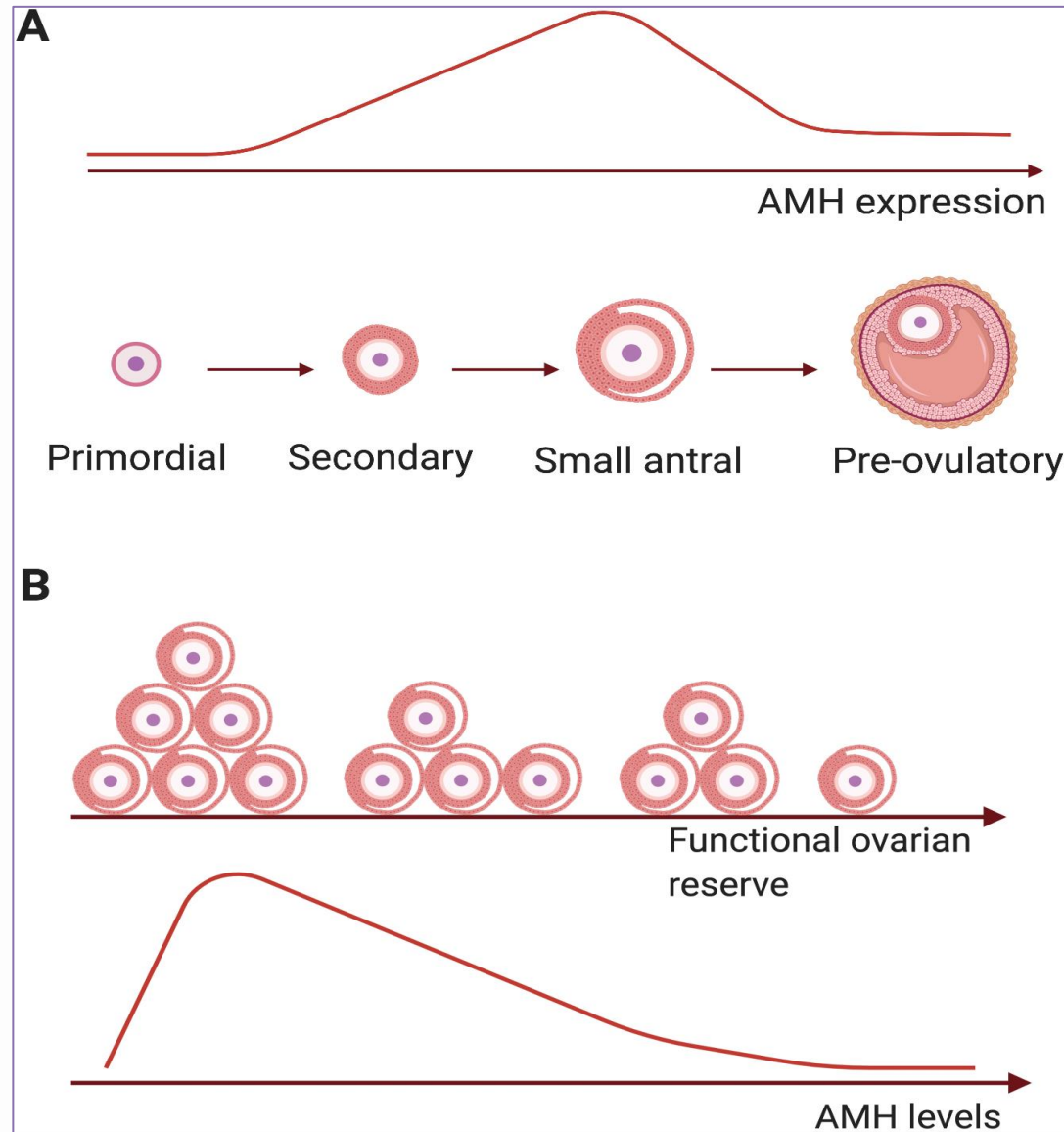


High AFC with 10 follicles



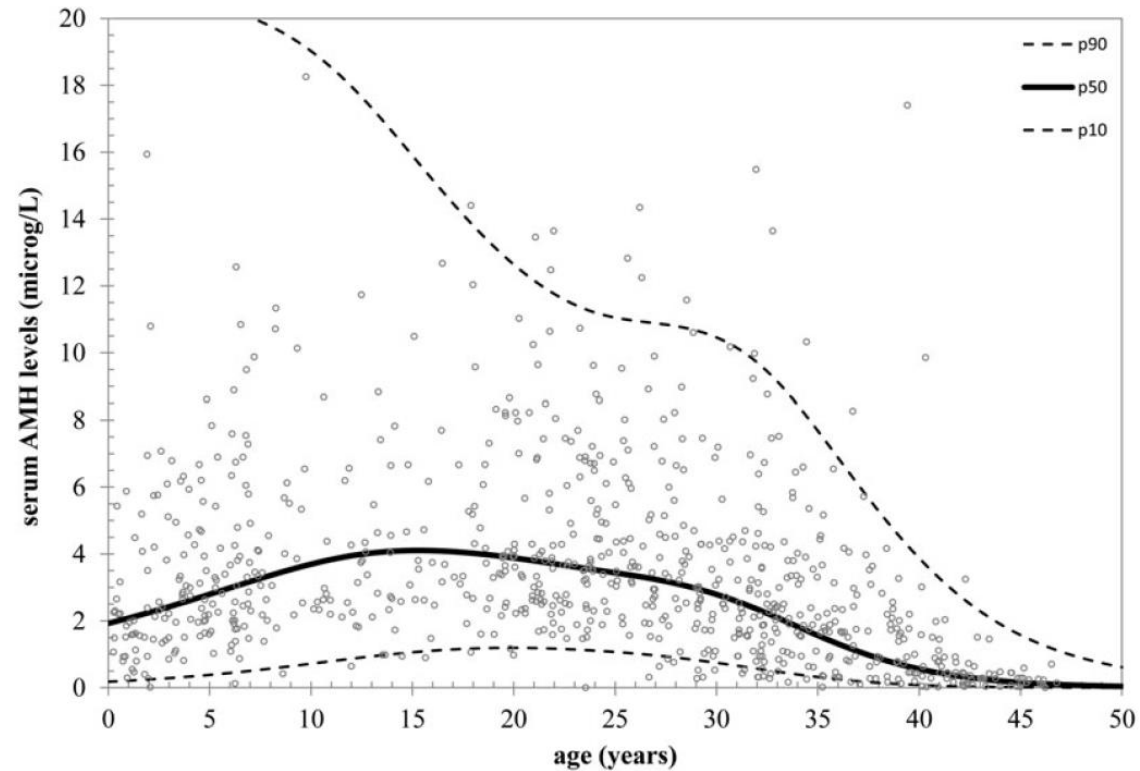
Low AFC with 2 follicles

# Anti-Mülleri Hormoon ja ovariaalne reserv



**Figure 1.** Anti-müllerian hormone expression and concentration in relation to folliculogenesis and ovarian reserve. **(A)** Anti-müllerian hormone (AMH) expression increases from the secondary stage onward until the small antral follicle stage. In preovulatory follicles, AMH is only expressed in cumulus granulosa cells surrounding the oocyte (dark pink layer). **(B)** With increasing age, the functional ovarian reserve decreases as a result of exhaustion of the primordial follicle pool. This leads to a decrease in the number of small antral follicles and consequently to a decrease in serum AMH levels, reaching undetectable levels at menopause. *Figure created with Biorender.*

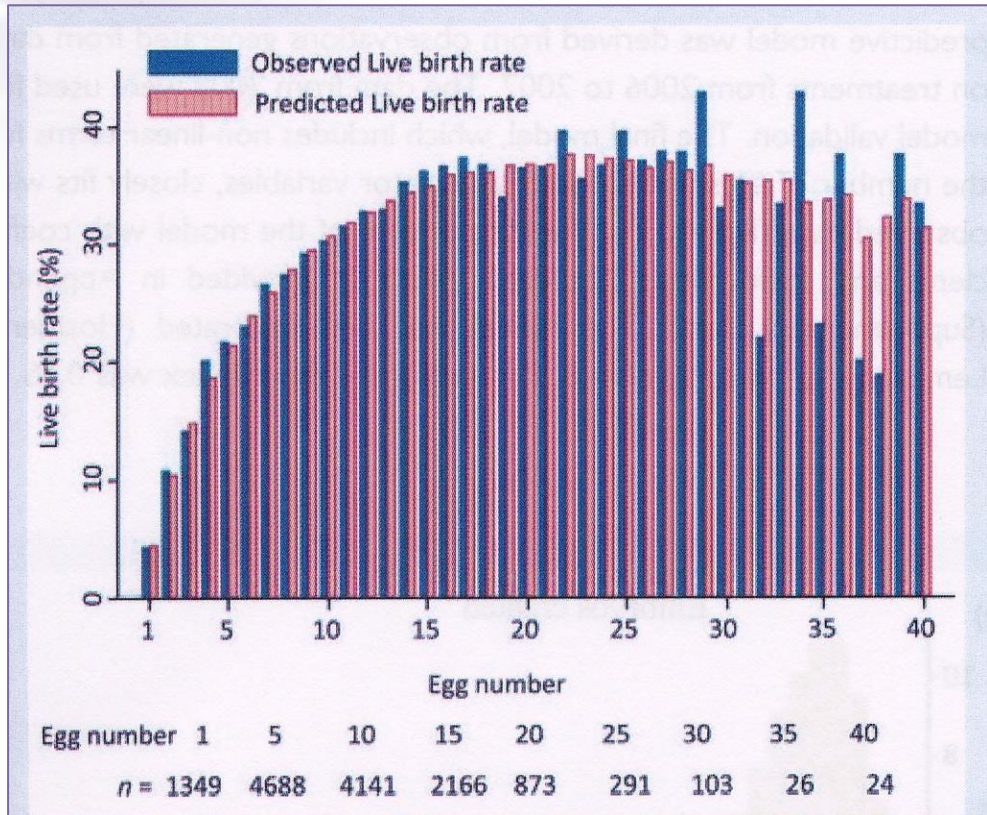
## AMH tase sünnist menopausini



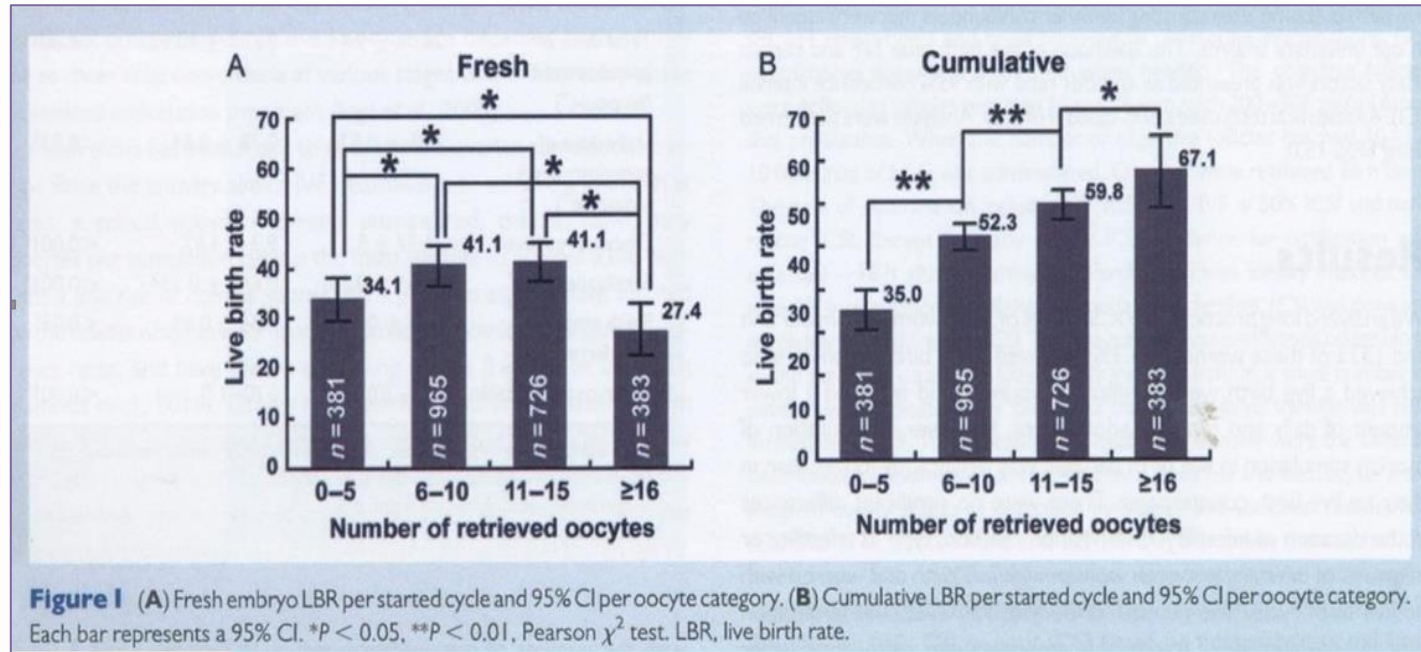
**Figure 4** AMH nomogram from birth to menopause in 804 healthy females from [Lie Fong et al. \(2012\)](#). Reference lines of serum AMH for the 10th, 50th and 90th percentiles of predicted AMH values versus age.



# Ovariaalreservi hindamise olulisus reproduktiivmeditsiinis



**Figure 4** Observed versus predicted live birth rate in data from 2006 to 2007.



# Ovarian reserve and the possibilities of its determination

Comparison	AMH	FSH, basal levels of LH	AFC* (USG)
Variability between cycles	Minimal	High	Moderate (different findings due to the individual experience of the doctor and the type of device)
An exact date of the examination is necessary	No	Yes	No
Correlation with the clinical condition	High	Lower	Moderate

\*AFC = Antral-Follicle-Count, ultrasound evaluation of the number of antral follicles;

Bancsi LF, et al. Fertil Steril 2002;77:328-36. 2. Muttukrishna S, et al. BJOG 2005;112:1384-90. 3. Hansen KR, et al. Fertil Steril 2011;95:170-5.

4. Tsepelidis S, et al. Hum Reprod 2007;22:1837-40. 5. van Disseldorp J, et al. Hum Reprod 2010;25:221-7. 6. Fanchin R,

et al. Hum Reprod. 2005;20(4):923- 7. Epub 2005 Jan 7. 7. Practice Committee of the American Society for Reproductive Medicine. Fertil Steril

2012;98:1407-15.8. Broekmans FJ, et al. Fertil Steril 2010;94:1044-51.

# Menopausi aja ennustamine

	Cross-sectional relation with age	Longitudinal relation with age	Predictive of age at menopause
Qualitative assessment of potential factors involved in long term prediction of age at menopause (10–30 years in advance)			
Chronological age	NA	NA	++
FSH	+/-	+/-	-
Anti-Müllerian hormone	+++	+++	+/-
Antral follicle count	+++	+++	+/-
Inhibin B	+/-	+/-	-
Genetic information			
Family history	NA	NA	++
Candidate SNPs/genes	NA	NA	+
Qualitative assessment of potential factors involved in short term prediction of age at menopause (2–10 years in advance)			
Cycle characteristics			
Cycle shortening	++	?	+
Cycle lengthening	++	?	+
Cycle irregularity	++	?	+
Vasomotor symptoms	++	?	++
FSH	++	++	+
Anti-Müllerian hormone	++	+	+
Antral follicle count	+	+/-	+
Inhibin B	++	+	+
Poor ovarian response to ART	++	++	+





## Ennetatavad viljatuse põhjused

Top 3:

1. KMI > 25.

2. Suitsetamine

3. Liigne alkoholi tarvitamine - enam kui 6 ühikut nädalas naistel, 12 ühikut nädalas meestel

<https://www.britishfertilitysociety.org.uk/fei/what-are-the-main-preventable-causes-of-infertility/>



# Smoking and infertility: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Approximately 21% of women of reproductive age and 22% of men of reproductive age in the United States smoke cigarettes. Substantial harmful effects of cigarette smoke on fecundity and reproduction have become apparent but are not generally appreciated. This committee opinion reviews the potential deleterious effects of smoking on reproductive parameters, gamete mutations, early pregnancy, and assisted reproductive techniques, and discusses strategies of smoking cessation. This document replaces the 2012 committee opinion (Fertil Steril® 2012;98:1400–6). (Fertil Steril® 2018;110:611–8. ©2018 by Ar

**TABLE 1**

## Public knowledge of the risks of smoking.

Smoking risk	Knowledge of risk (%)
Lung cancer	99
Respiratory disease	99
Heart disease	96
Miscarriage	39
Osteoporosis	30
Ectopic pregnancy	27
Infertility	22
Early menopause	17

ASRM. Smoking and infertility. Fertil Steril 2018.



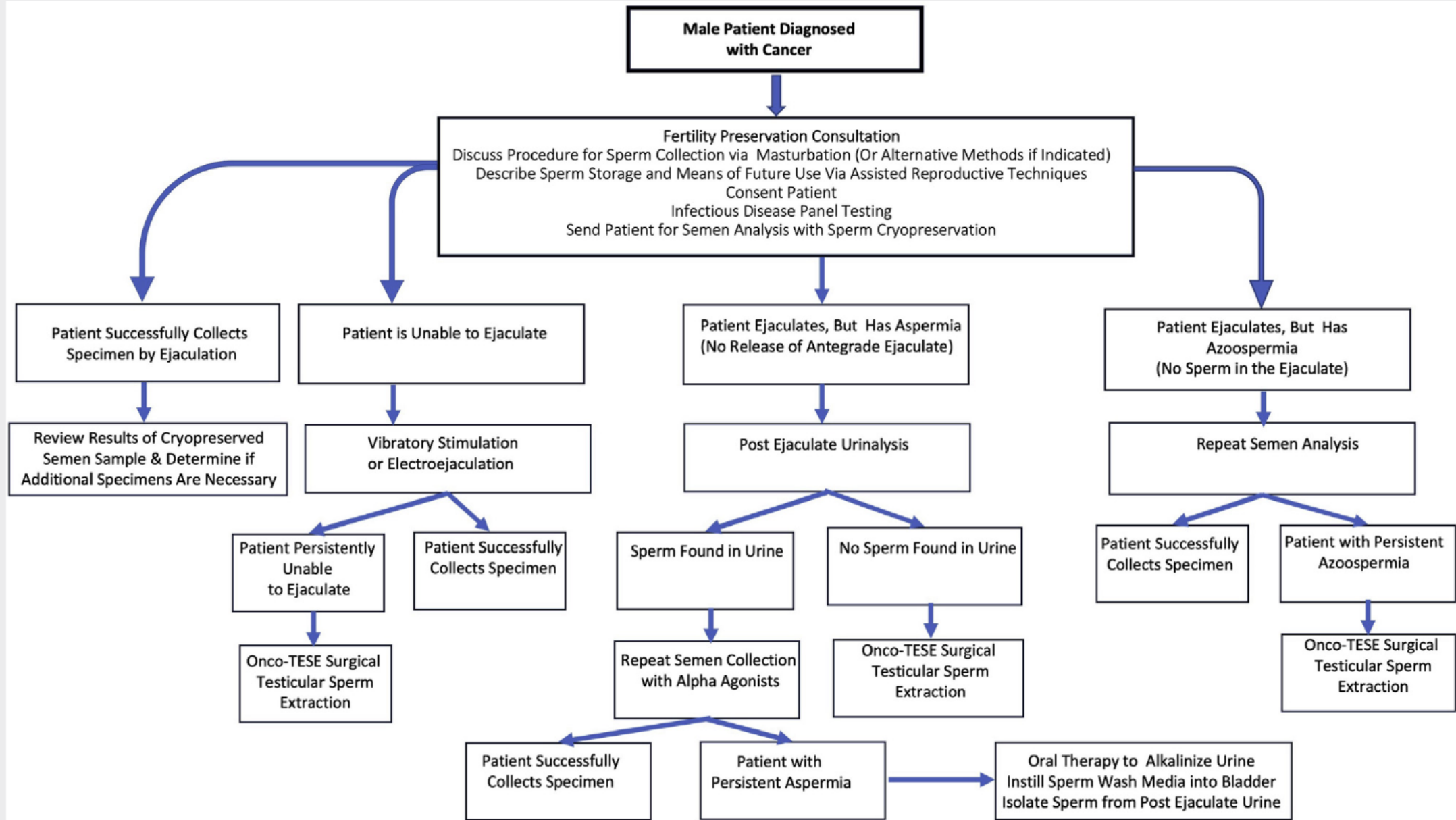
**Tabel 5-1.A.** Vastajate jaotus (%) suitsetamise, soo ja vanuse järgi

**Table 5-1.A.** Distribution (%) of respondents by smoking status, sex and age

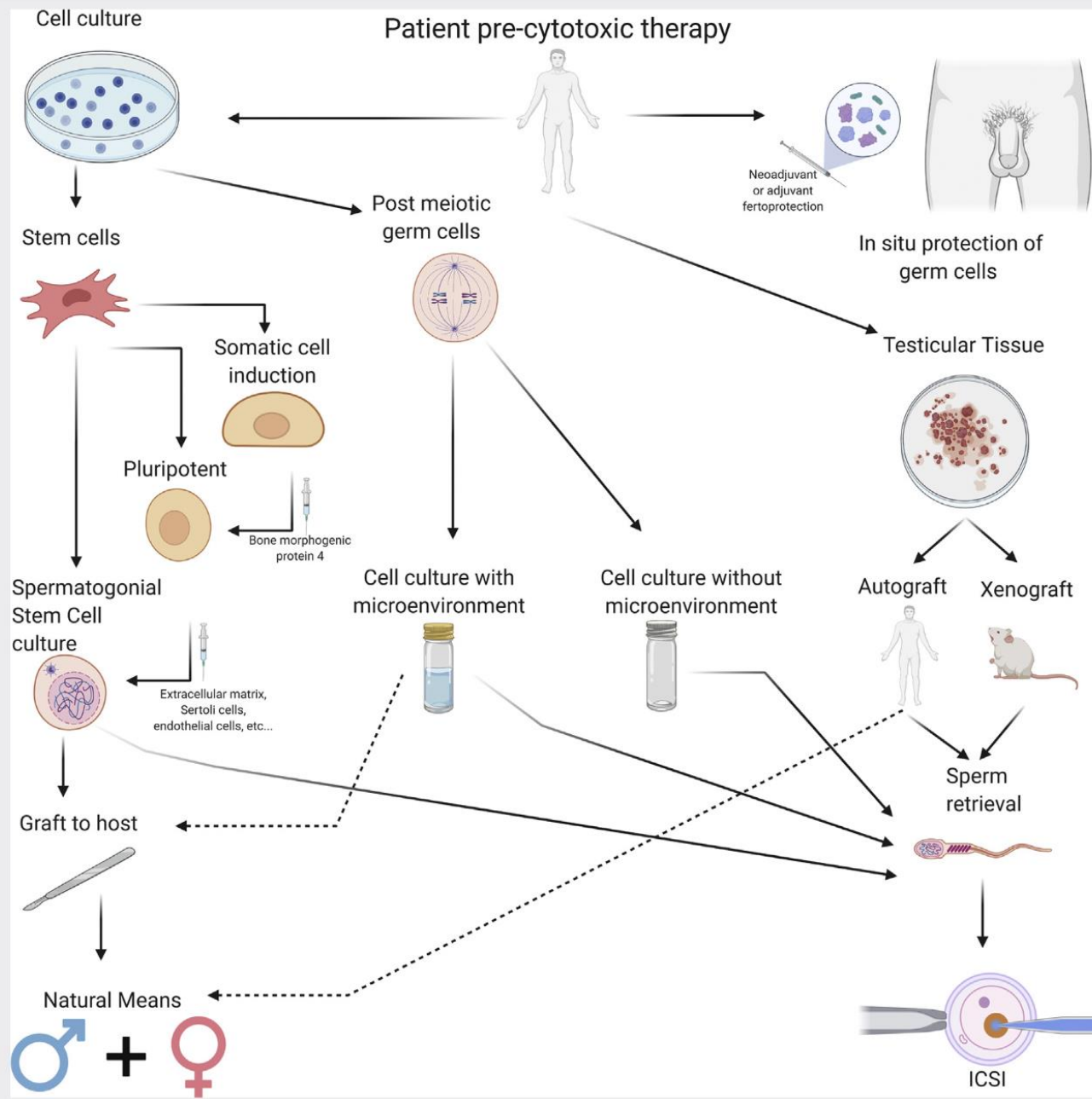
	Mehed/ Males					Kokku Total	Naised/ Females					Kokku Total	
	Vanuserühm/ Age group						Vanuserühm/ Age group						
	16–24	25–34	35–44	45–54	55–64		16–24	25–34	35–44	45–54	55–64		
Igapäevasuitsetaja/ Daily smoker	19,5	22,9	26,6	28,0	28,4	25,7	10,7	10,0	13,9	13,4	13,7	12,6	17,9
Juhusuitsetaja/ Occasional smoker	14,6	10,1	8,0	6,9	4,8	8,3	18,6	10,3	5,9	4,8	5,6	8,1	8,2
Endine suitsetaja/ Ex-smoker	18,7	26,8	32,7	38,5	42,8	33,3	15,8	35,6	23,3	26,8	22,7	25,4	28,6
Mittesuitsetaja/ Non-smoker	47,2	40,2	32,7	26,6	24,0	32,7	54,8	44,1	56,9	55,0	57,9	54,0	45,3
Kokku/ Total (%)	100	100	100	100	100	100	100	100	100	100	100	100	100
Kokku (arv)/ Total (No.)	123	179	199	218	208	927	177	261	288	313	321	1360	2287
Vastamata (arv)/ Missing (No.)	3	3	3	4	1	14	5	6	3	4	5	23	37

# Onkofertiilsus



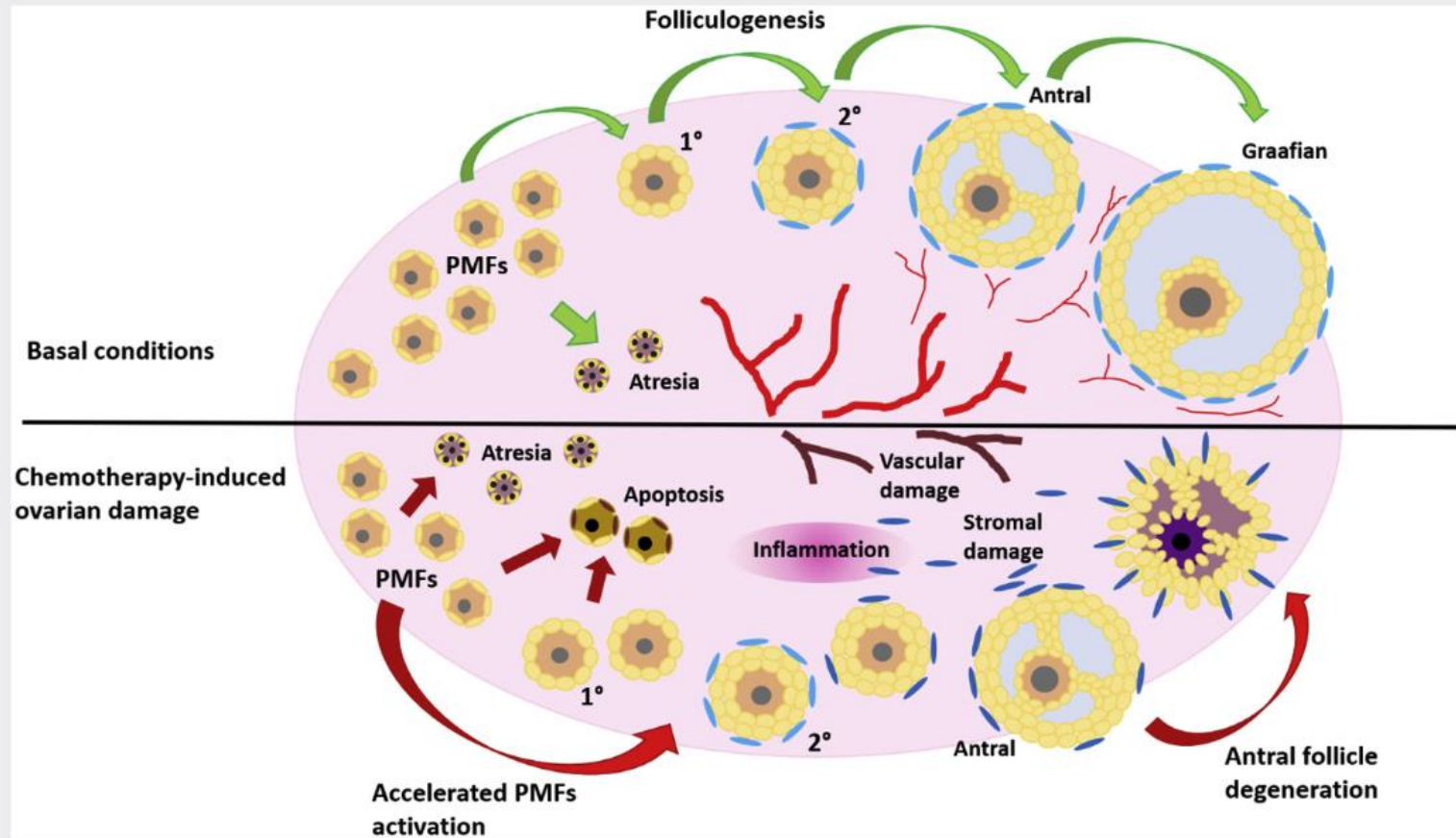


Contemporary paradigm for male fertility preservation. A contemporary, comprehensive approach to fertility preservation for male patients diagnosed with cancer is presented. This paradigm includes numerous methods to obtain sperm from individuals who are otherwise unable to provide a sufficient ejaculated semen specimen. onco-TESE = oncologic testicular sperm extraction.



Future directions: experimental and investigational approaches to fertility preservation. Numerous experimental and investigational methods are currently under study to facilitate fertility preservation in males. A wide array of techniques is considered, including fertoprotection, tissue grafting, cell culture, and stem cell techniques. ICSI = intracytoplasmic sperm injection.

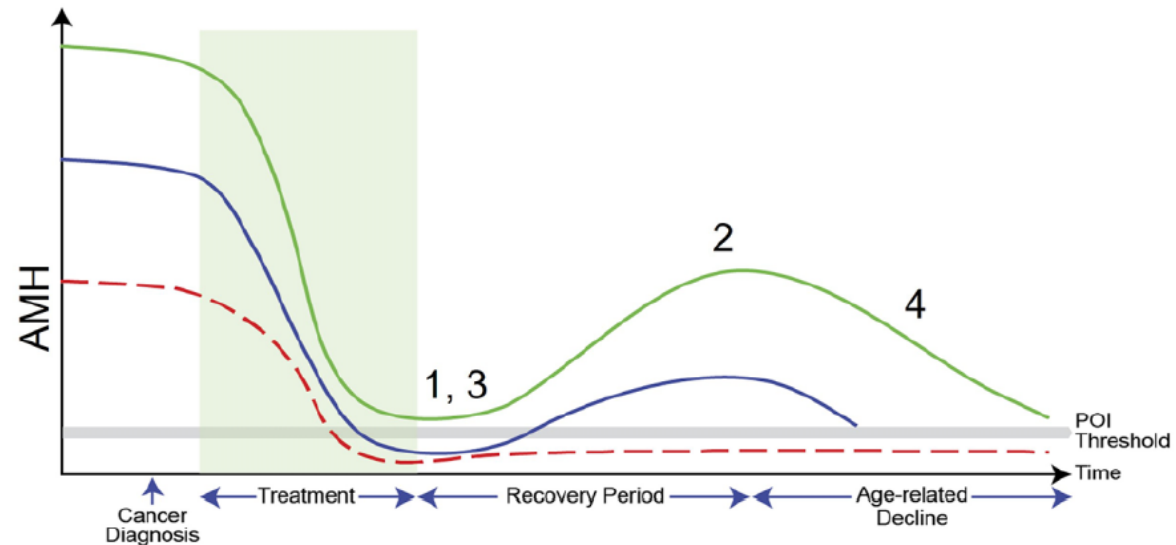




Chemotherapy exerts numerous damaging mechanisms on the ovary: loss of primordial follicles by apoptosis, accelerated activation of primordial follicles, enhanced follicular atresia, inflammation in the stroma, and damage to the intraovarian vascularization. PMFs = primordial follicles. Reproduced with permission from (52).

Dolmans. *Ovarian tissue transplantation outcomes. Fertil Steril* 2021.

# Anti-Müllerian hormone as a marker of ovarian reserve and premature ovarian insufficiency in children and women with cancer



**Figure 3. Summary of findings of systematic review represented graphically.** The three lines represent women with high (green), average (blue) and low (red) AMH levels before treatment, with treatment represented by the shaded area and a threshold indicating POI is also represented. (1) AMH concentrations are reduced by cancer treatments. (2) Recovery is variable, depending on patient age, treatment regimen and pre-treatment AMH levels. Recovery can be near complete or absent, with the latter resulting in permanent POI. The relationship of post-treatment AMH to POI needs to be explored further. (3) Prediction of permanent POI at the time of end of treatment may be possible in some situations, but further studies are required to determine the patient groups for which this may and may not be possible. (4) There are insufficient data to be able to predict the duration of post-recovery ovarian function using AMH levels before or after treatment, which will interact with the physiological decline in AMH with increasing age. Reproduced from [Jayasinghe et al. \(2018\)](#) with permission.

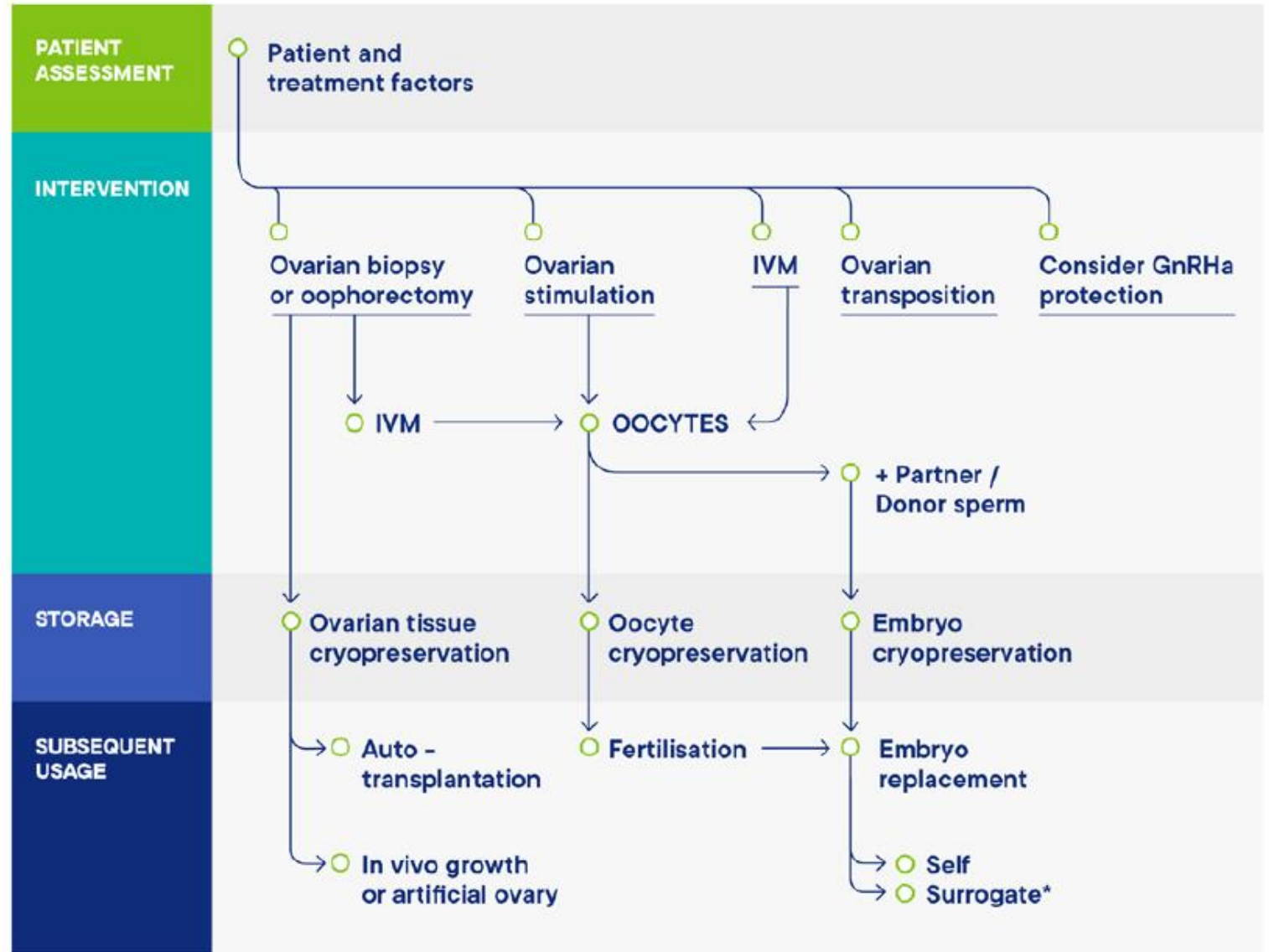


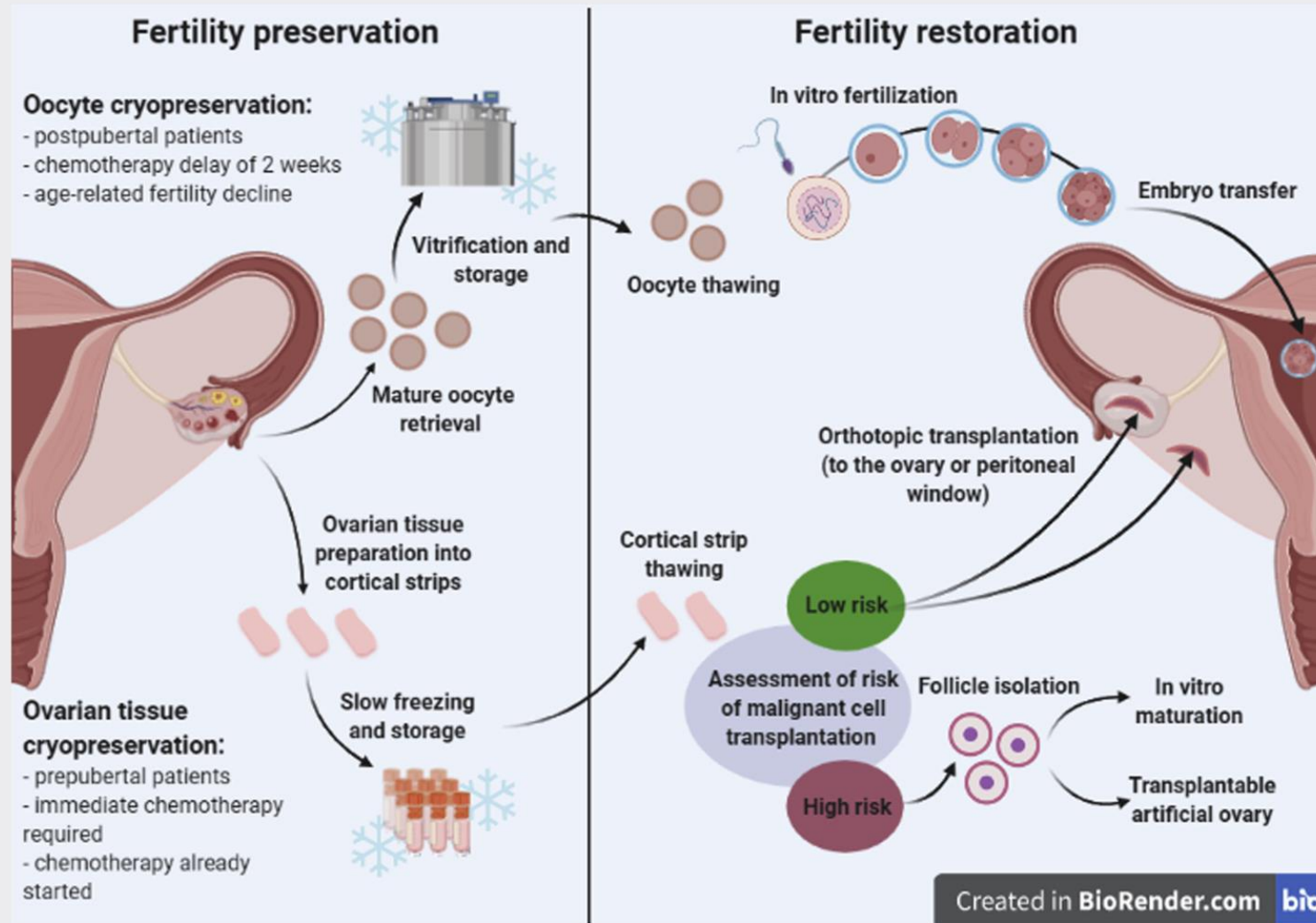
## Which options are available for fertility preservation in women – emergency and non-emergency?

# Female Fertility Preservation

Guideline of the European Society of Human Reproduction and Embryology

2020  
ESHRE Female Fertility Preservation Guideline Development Group





Patients of postpubertal age, patients in whom chemotherapy can be postponed for approximately 2 weeks, or those in a fertility preservation program for age-related fertility decline undergo mature oocyte retrieval after controlled ovarian stimulation. Oocytes are cryopreserved by vitrification. After thawing, they can be fertilized in vitro to obtain embryos for transfer to the uterine cavity. Patients of prepubertal age, patients requiring immediate chemotherapy, or those who have already started chemotherapy undergo ovarian tissue cryopreservation. Ovarian tissue is removed in the form of multiple biopsy specimens, cut into cortical strips, and cryopreserved by slow freezing. After thawing, if there is no risk of malignant cell transmission, the tissue can be grafted to the ovarian medulla (if at least 1 ovary still remains) or reimplanted inside a specially created peritoneal window. If there is a risk of malignant cell transmission, ovarian follicles can be isolated and either grown in vitro to obtain mature eggs or used to create a transplantable artificial ovary. Figure created in [BioRender.com](https://www.biorender.com).

# Oocyte vitrification for fertility preservation for both medical and nonmedical reasons

Ana Cobo, Ph.D.,<sup>a</sup> Juan Antonio García-Velasco, M.D.,<sup>b</sup> José Remohí, M.D.,<sup>a</sup> and Antonio Pellicer, M.D.<sup>a</sup>

<sup>a</sup> IVIRMA Valencia, Valencia, Spain, and <sup>b</sup> IVIRMA Madrid and Universidad Rey Juan Carlos, Madrid, Spain

Fertil Steril® 2021;115:1091–101.

**TABLE 1**

**Oocyte survival rates and clinical outcomes with the use of vitrified oocytes for fertility preservation in different populations.**

Author	Indication	No. of patients	No. of warming cycles	No. of warmed oocytes	Survival rate (%)	Clinical pregnancy rate (%)	Live birth rate (%)
Sanchez-Serrano et al., 2010 (32)*	Onco-FP	1	1	9	100	100	100
Kim et al., 2011 (33)	Onco-FP	1	1	7	71.4	100	100
García-Velasco et al., 2013 (34)*	Onco-FP	1	1	4		25	25
	EFP	26	26	191	84.8	42.3	19.2
Alvarez et al., 2014 (35)	Onco-FP	1	1	8	87.5	100	100
Da Motta et al., 2014 (36)	Onco-FP	1	2	19		50	50
Martinez et al., 2014 (37)	Onco-FP	11	11	65	92.3	54.5	
Perrin et al., 2016 (38)	Onco-FP	1	1	5	100	100	100
Cobo et al., 2016 (24)*	EFP	137	148	1,182	85.2	46.2	20.9
Doyle et al. 2016 (39)	EFP		128	1,283	86.1	57.1	38.6
Specchia et al., 2019 (40)	Onco-FP	11	14	73	86.3	30.8	15.4
Díaz-García et al., 2018 (16)*	Onco-FP	49			77.3	36.4	29.1
Cobo et al., 2018 (26)*	EFP	641	680	5,830	83.9	50.7	33.7
	Onco-FP	80	81	605	81.8	41.4	31
Wennberg et al., 2019 (41)	EFP	38	49	393	78		26.3
Cobo et al., 2020 (42)*	Endo-FP	485	529	4,531	83.2	45.9	46.4

Note: Totals have not been calculated because the studies marked with asterisks (\*) belong to the same investigators; therefore, the data may be overlapping. EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

Cobo. FP results—elective and medical reasons. Fertil Steril 2021.

<b>Tervishoiuteenuse nimetus</b>	<b>Kood</b>	<b>Piirhind eurodes</b>
Munarakkude külmutamine (ühe tsükli kohta)	7396	797,70
Seemnerakkude külmutamine (ühe annetuse kohta)	7398	477,31

(8) Tervisekassa võtab koodiga 7396 tähistatud tervishoiuteenuse eest tasu maksmise kohustuse üle **kuni 35-aastaselt patsiendilt** enne viljakust kahjustava ravi (sh onkoloogilise või autoimmuunse haiguse süstemaatiline ravi) alustamist või viljakust kahjustava seisundi esinemise korral juhul, kui otsuse teenuse rakendamiseks on teinud eksperdikomisjon, millesse kuuluvad vähemalt patsiendi raviarst ja günekoloog või IVF-spetsialist.


(9) Koodiga 7396 tähistatud tervishoiuteenuse piirhind sisaldab **munarakkude seitsme aasta säilitamise kulu**.

(10) Tervisekassa võtab koodiga 7398 tähistatud tervishoiuteenuse eest tasu maksmise kohustuse **üle kuni 40-aastaselt patsiendilt** enne viljakust kahjustava ravi (sealhulgas onkoloogilise või autoimmuunse haiguse süstemaatiline ravi) alustamist või viljakust kahjustava seisundi esinemise korral juhul, kui otsuse teenuse rakendamiseks on teinud eksperdikomisjon, millesse kuuluvad vähemalt kaks arsti, kellest üks on patsiendi raviarst või onkoloog ja teine IVF-spetsialist.

(11) Koodiga 7398 tähistatud tervishoiuteenuse piirhind sisaldab seemnerakkude hankimise kulu ja seemnerakkude **seitsme aasta säilitamise kulu**.



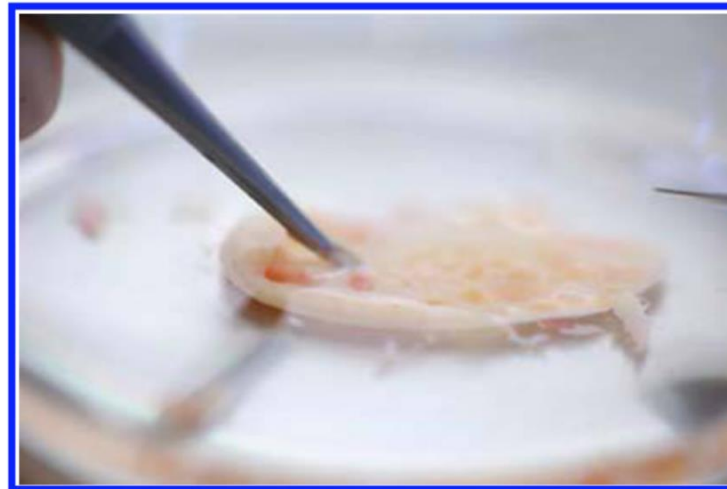
**Summarized recommendations of the Edinburgh Criteria for Ovarian Tissue Cryopreservation (2005, 2014):**

1. Age < 30 (in 2005), Age <35 (in 2014)
  2. Having no history of previous chemotherapy or radiotherapy (if the patients below 15 years old, previous mild and low-risk chemotherapy can be considered)
  3. A chance of long-term survival for 5 years
  4. High-risk estimation for premature ovarian failure (>50%)
  5. Informed consent from the patients or the parents (in children)
  6. Negative syphilis, HIV, and hepatitis serology
  7. No pregnant or existing children
- 





(A)



(B)



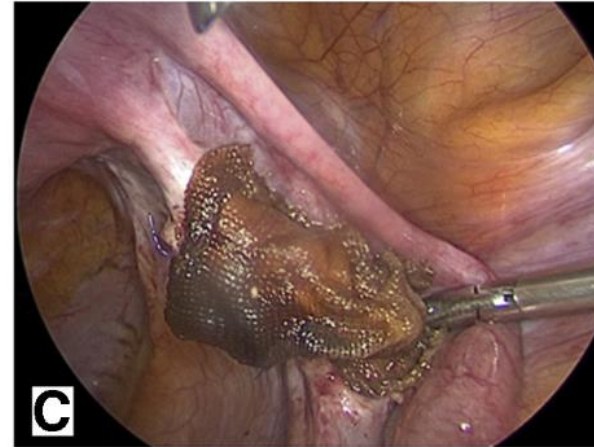
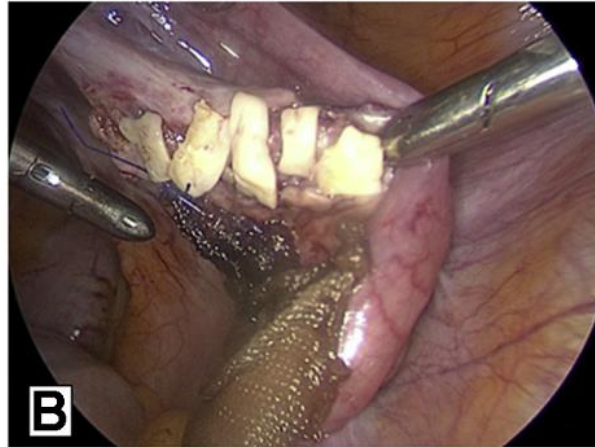
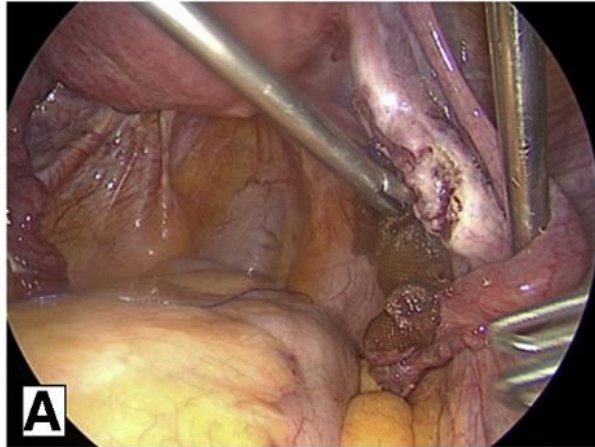
(C)



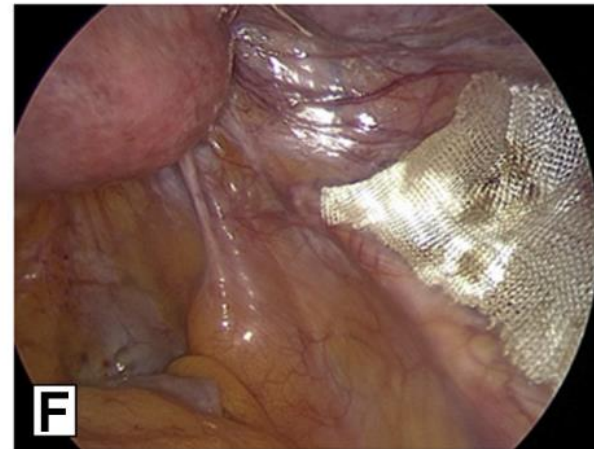
(D)

*Figure 58.2* Cryopreservation of human ovarian tissue for fertility preservation. (A) One ovary or part of an ovary is surgically removed. (B) The medulla is removed and the cortex is trimmed to a thickness of 1–2 mm. (C) The cortex is then cut into pieces of 5 × 5 mm. The pieces of cortex equilibrate in cold freezing solution for 25 minutes on ice. (D) The cortex pieces are transferred to individual cryotubes and slow-frozen in liquid nitrogen.

## Transplantation to the ovary

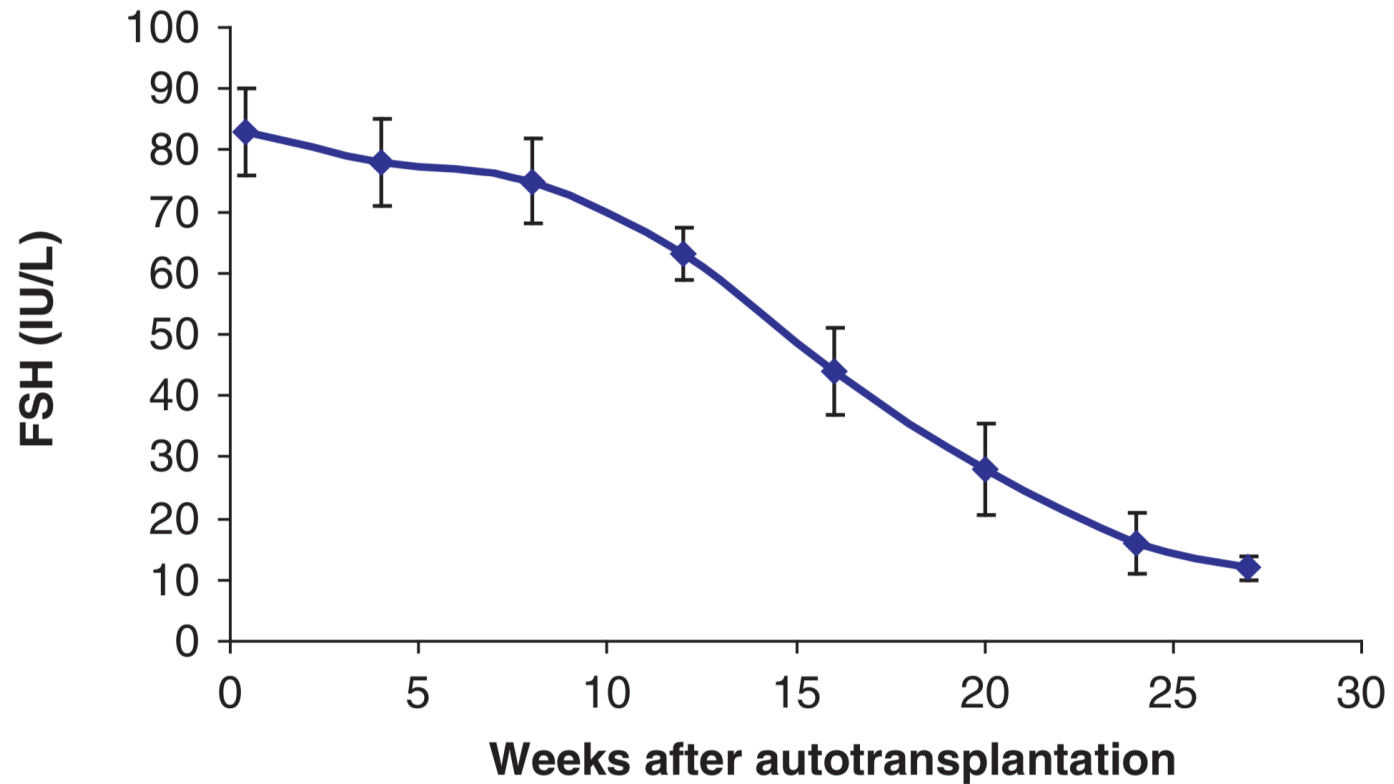


## Transplantation to a peritoneal pocket



Ovarian tissue transplantation to the ovary: (A) Image of a decorticated ovary showing the medulla and its vascular network. (B) Ovarian cortical pieces placed in the denuded ovary without stitches and (C) subsequently covered and fixed with Interceed or fibrin glue. Ovarian tissue transplantation to a peritoneal window: (D) Creation of a peritoneal window using scissors. (E) Ovarian cortical fragments positioned with the cortex surface facing the abdominal cavity and (F) covered and fixed with Interceed or fibrin glue.

*Dolmans. Ovarian tissue transplantation outcomes. Fertil Steril 2021.*



*Figure 58.8* Restoration of ovarian function serum levels of FSH (IU/L) in 12 Danish patients after autotransplantation of frozen-thawed ovarian tissue (mean  $\pm$  standard error of the mean). *Abbreviation:* FSH, follicle-stimulating hormone.





## Summary of the ISFP congress, Brussels, 10–12 November, 2022

Lara Houeis<sup>1</sup> · Marie-Madeleine Dolmans<sup>1,2</sup> 

Received: 10 January 2023 / Accepted: 10 January 2023 / Published online: 11 February 2023  
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### Munasarja koe siirdamine

esimene elussünd 2004

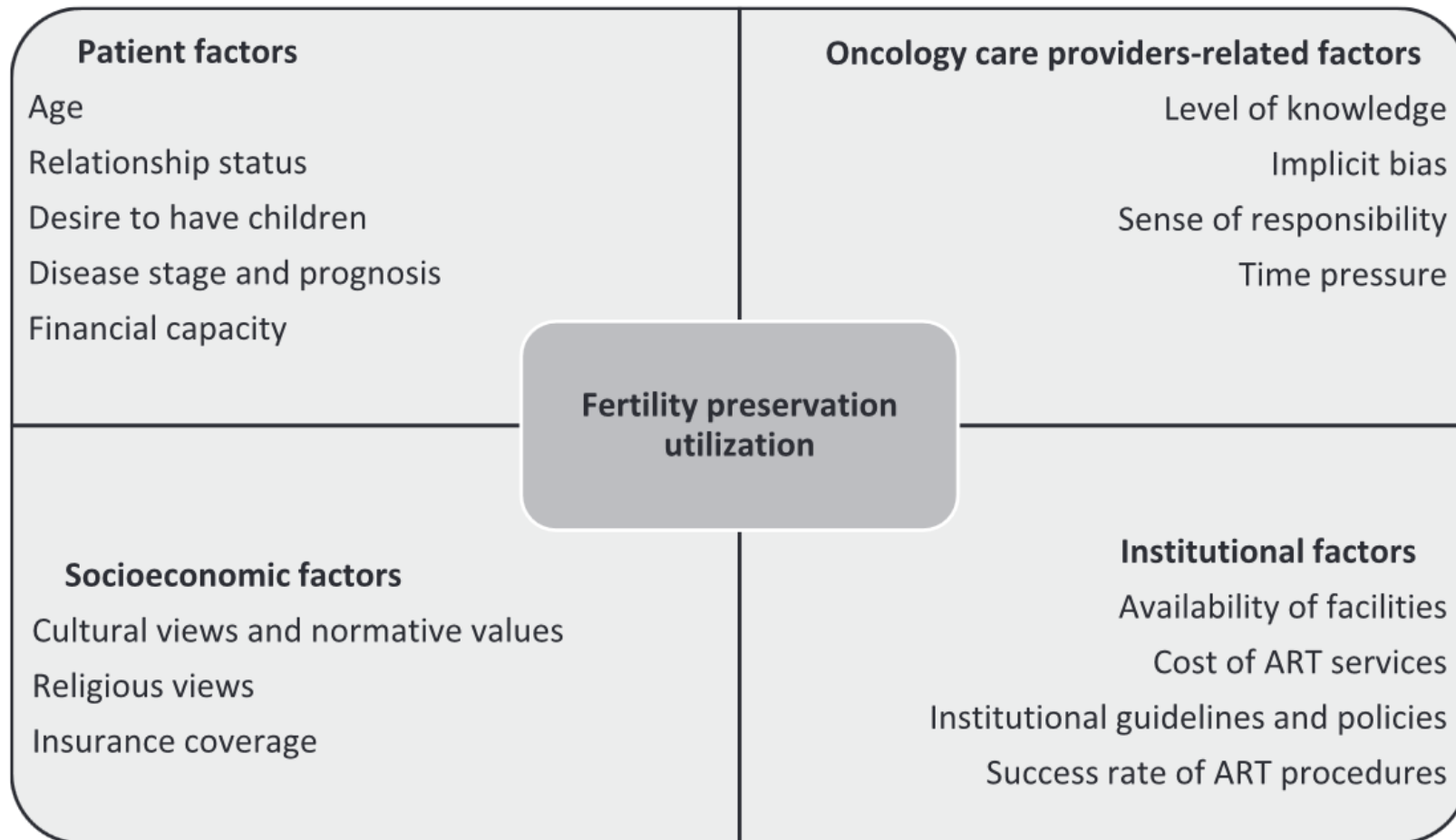
2022 lõpuks teatatud 300 sünnist

elussünni tõenäosus 30-40%



## Global uptake of fertility preservation by women undergoing cancer treatment: An unmet need in low to high-income countries

Ademola S. Ojo<sup>a,\*</sup>, Christina Lipscombe<sup>b</sup>, Mojisola O. Araoye<sup>c</sup>, Oluwasegun Akinyemi<sup>d</sup>

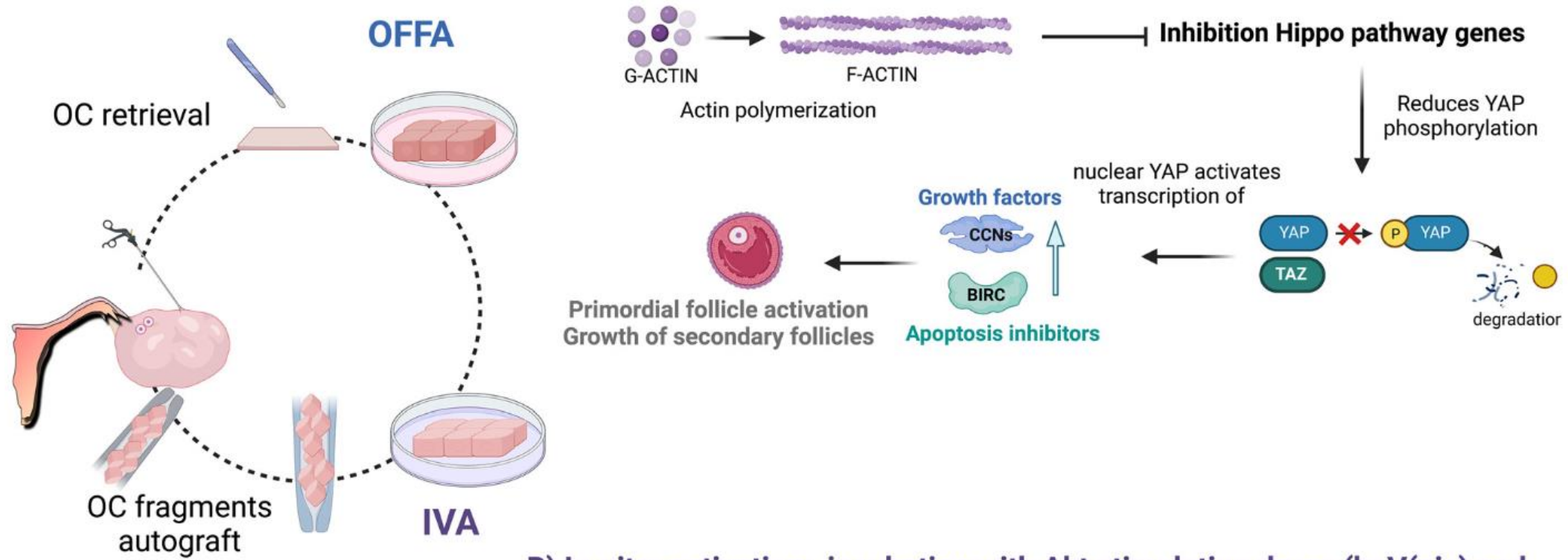


**Fig. 3.** Determinants of fertility preservation utilization.

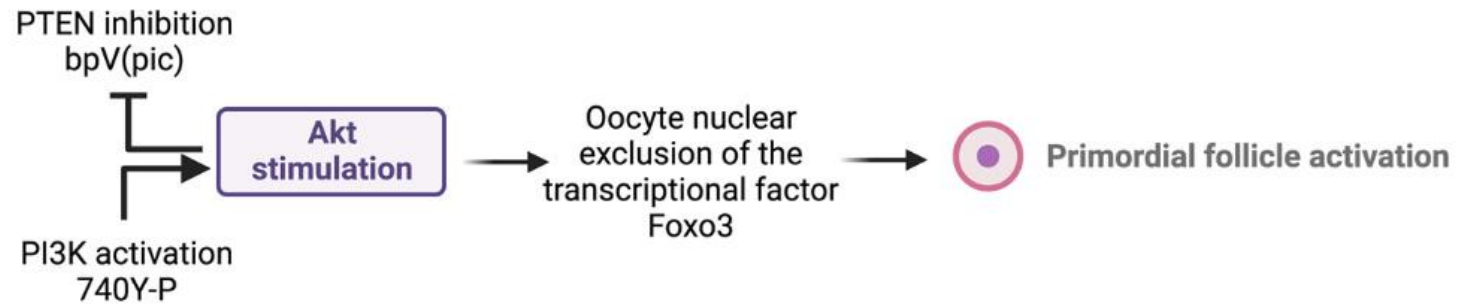
# Folliikulite aktiveerimine



## A) Mechanical OC fragmentation into 1mm<sup>2</sup> cubes induces



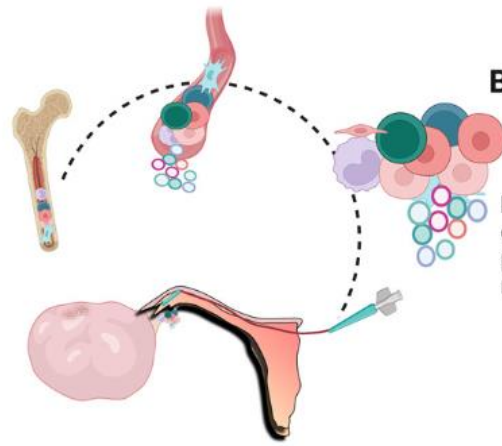
## B) In-vitro activation: incubation with Akt stimulating drugs (bpV(pic) and 740Y-P) for 48h



RBMO VOLUME 46 ISSUE 3 2023

**FIGURE 1** Mechanisms of ovarian fragmentation and in-vitro activation (IVA) of dormant follicles. (A) Ovarian fragmentation for follicle activation (OFFA). (B) IVA with Akt stimulators. bpV(pic), dipotassium bisperoxo (picolinato) oxovanadate (V); OC, ovarian cortex. Created with BioRender.com.

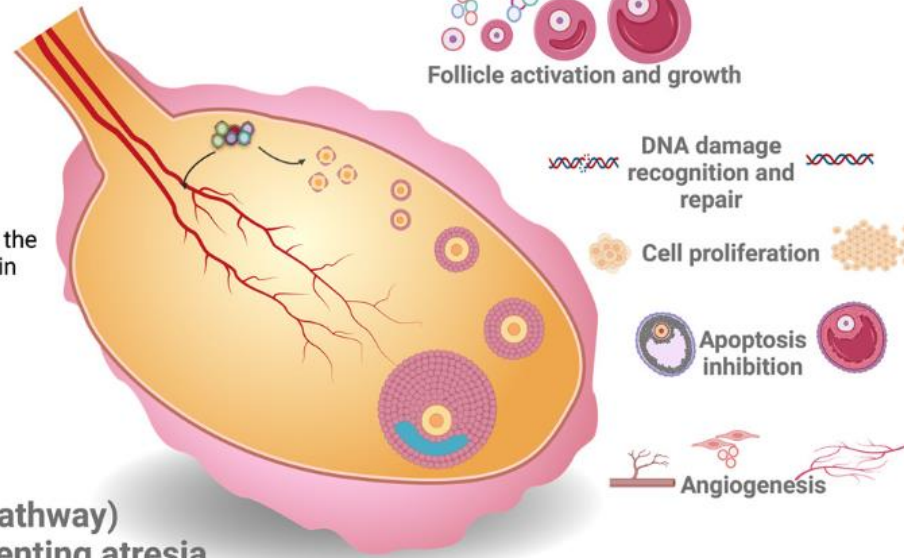
## A. ASCOT



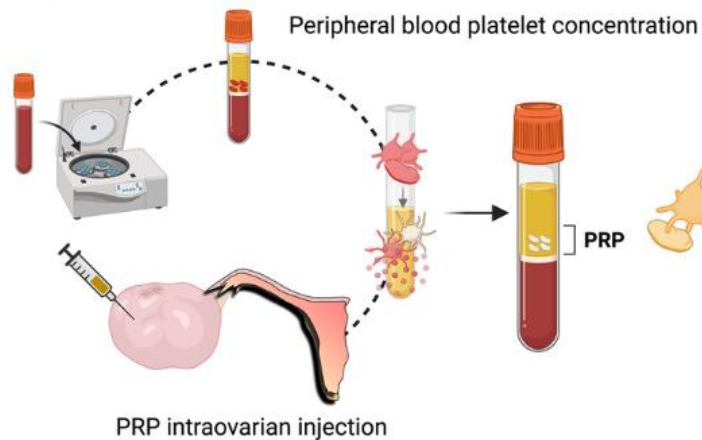
### BMDSC

**BMDSC soluble growth factors** involved in the cell cycle, gene expression, DNA repair and in pathways related to RhoGTPases, death receptors, HIPPO and PI3K-Akt pathway.

**Primordial follicle activation (Akt pathway)**  
**Rescue secondary follicles by preventing atresia**  
**Increased ovarian local vascularization**

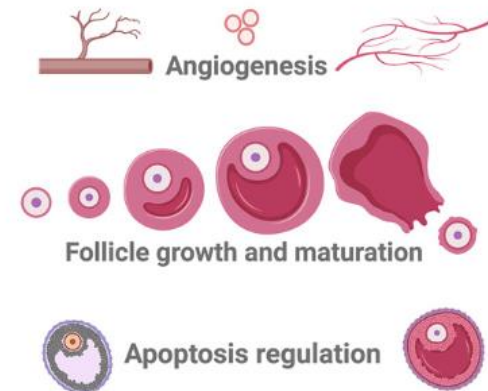


## B. PRP



### Platelet activation

**Platelet enclosed growth factors** with proangiogenic, proliferative, proinflammatory activity and regulation of apoptosis



**FIGURE 2** Mechanisms of ovarian reactivation techniques (ovarian fragmentation for follicle activation). (A) Autologous ovarian stem cell transplantation (ASCOT) of bone marrow-derived stem cells (BMDSC) and infusion of secreted soluble factors. (B) Ovarian injection of platelet-rich plasma (PRP). Created with BioRender.com.



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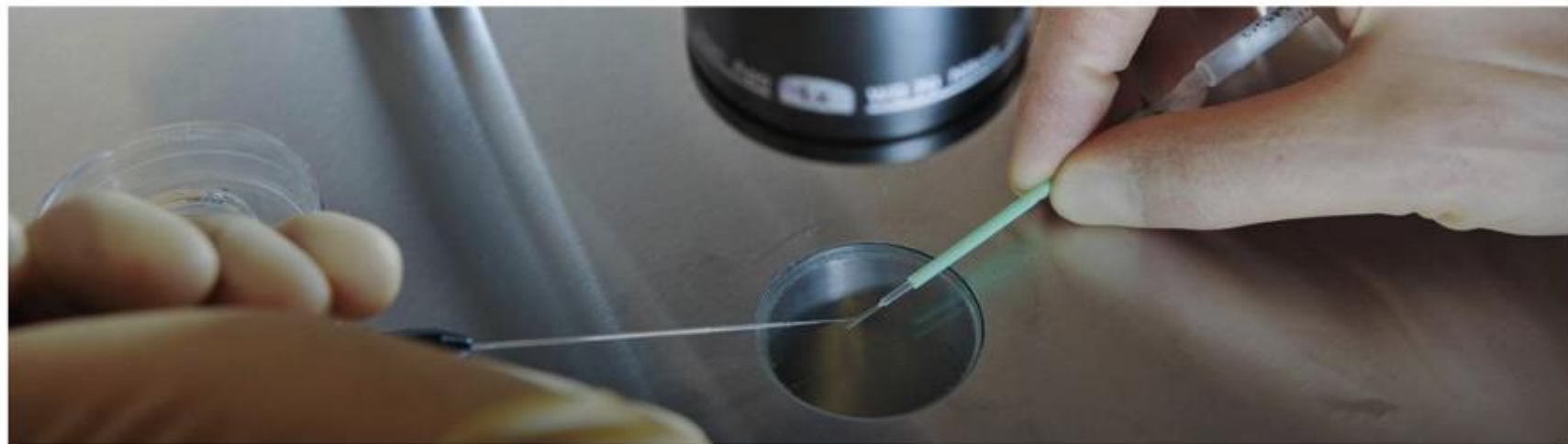
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# Perk Up: Facebook and Apple Now Pay for Women to Freeze Eggs

by DANIELLE FRIEDMAN

Embryos are placed onto a CryoLeaf ready for instant freezing. © Ben Birchall / PA Wire via AP file

# Sarah Silverman considering freezing her eggs

IANIS | Jan 8, 2016, 05.00 PM IST

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Sarah Silverman

Actress Sarah Silverman, 45, wants to have children and she is considering freezing her eggs to ensure the opportunity doesn't pass her by. 🐦  
"A few years ago, I casually said something in an interview about being afraid to have kids because I might pass depression onto them, but I don't know if I

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[Sarah Silverman | glamour magazine](#)

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Fertility and Sterility® Vol. 115, No. 6, June 2021





# Jutuks oli:

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