Hope for tomorrow: clinical approaches to oncofertility

Michel De Vos, MD PhD

Disclosures

- No conflicts of interest with regard to this lecture.

- Member of the Female Oncofertility Scientific Committee of The Oncofertility Consortium (Michigan State University)
- Member of the International Advisory Board on Cancer, Infertility and Pregnancy (INCIP)
- Member of the Belgian Fertility Education Initiative (BFEI)
- Past Chair of the IVMSIG of ASRM

Overeenkomst oncofreezing – convention oncofreezing

Cancer patient with ovaries <38y

- Ovarian tissue cryopreservation
- Oocyte cryopreservation

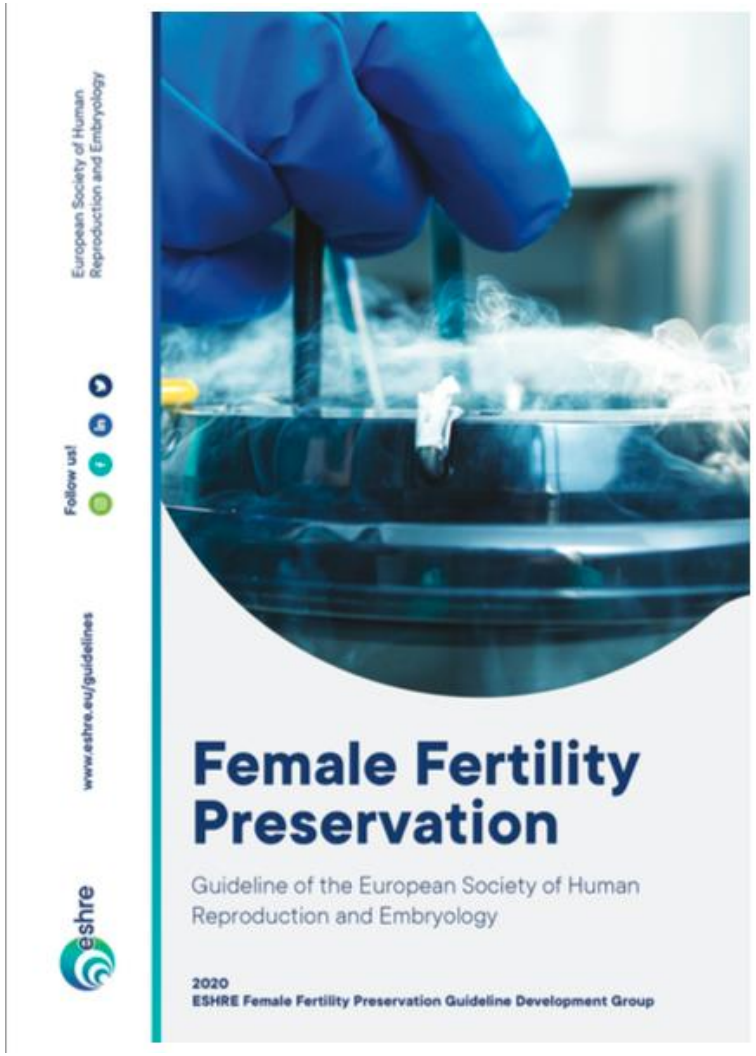
Cancer patient with testicles <45y

- Sperm cryopreservation
- Testicular tissue cryopreservation

- Cancer patients who will need treatment that is potentially gonadotoxic and who are diagnosed with:
  - Solid tumours
  - Haematological tumours (e.g. leukaemia, lymphoma)
  - BEFORE or AFTER cancer treatment
- Testicular cancer requiring orchidectomy
- Borderline ovarian tumour (BOT)
- Women with a breast cancer predisposing mutation who are eligible for prophylactic oophorectomy (BRCA, CHEK2, (PALB2?))
- Haematopoietic conditions requiring bone marrow transplantation

Fertility preservation in young cancer patients with ovaries

Fertility preservation (FP) approaches



Stand-alone approaches

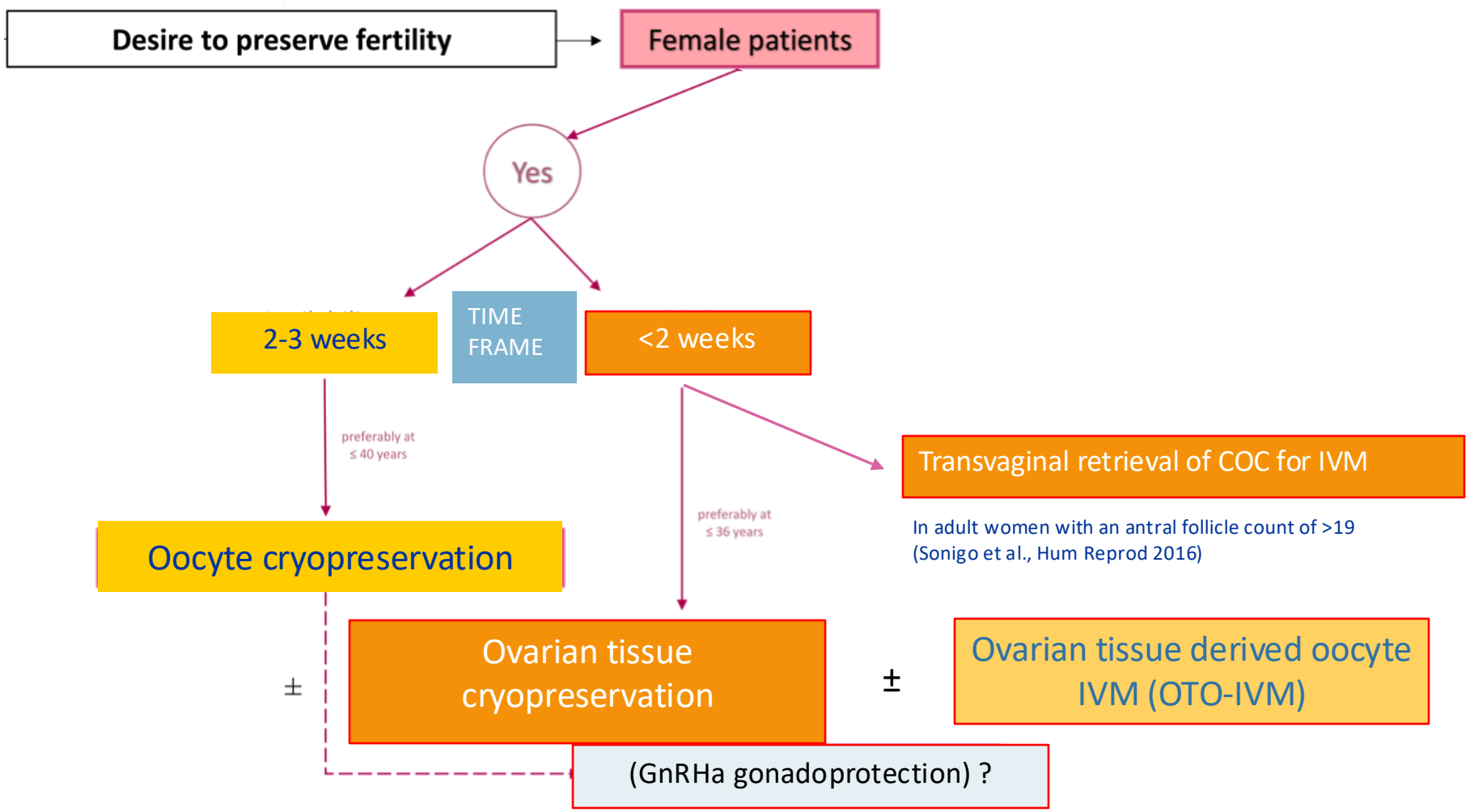
- **Oocyte cryopreservation** is an established FP option (2011)
- **Embryo cryopreservation** is an established FP option
- **Ovarian tissue cryopreservation** is no longer considered experimental and should be offered to patients who undergo moderate/high risk gonadotoxic treatment where oocyte/embryo cryopreservation is not feasible, or at patient preference (2019)
- **IVM-OPU** is an innovative option – not experimental (2020)

Supplementary approaches

- **OTO-IVM*** is an experimental option
- **Ovarian protection:** GnRH agonists or ovarian transposition
- **Uterine protection:** uterine transposition

The ESHRE Guideline Group on Female Fertility Preservation, Human Reproduction Open 2020;* OTO-IVM = ovarian tissue derived oocyte IVM

Fertility preservation algorithm based on the available time frame



Oocyte cryopreservation

The paradox of egg freezing: conflict between risk of infertility and the potential of oocyte cryopreservation

Amenorrhoea risk category	Type of gonadotoxic treatment
High risk	Cyclophosphamide-based in breast cancer patients aged ≥40 years
Intermediate risk	Cyclophosphamide-based regimens in breast cancer patients aged 30-39 years
Low risk	Cyclophosphamide-based regimens in breast cancer patients aged ≤30 years Non-alkylating agent-based regimens
Unknown risk	Targeted agents, immunotherapy

→ **LOW**

Reproductive potential of cryopreserved oocytes:

Wennberg et al., Acta Obstet Gynecol Scand 2019*
Blakemore et al., Fertil Steril 2021*
Kasaven et al., Arch Gynecol Obstet 2022*

* Based on data in women who had Planned Oocyte Cryopreservation

Lower oocyte yield and lower oocyte quality with increasing age

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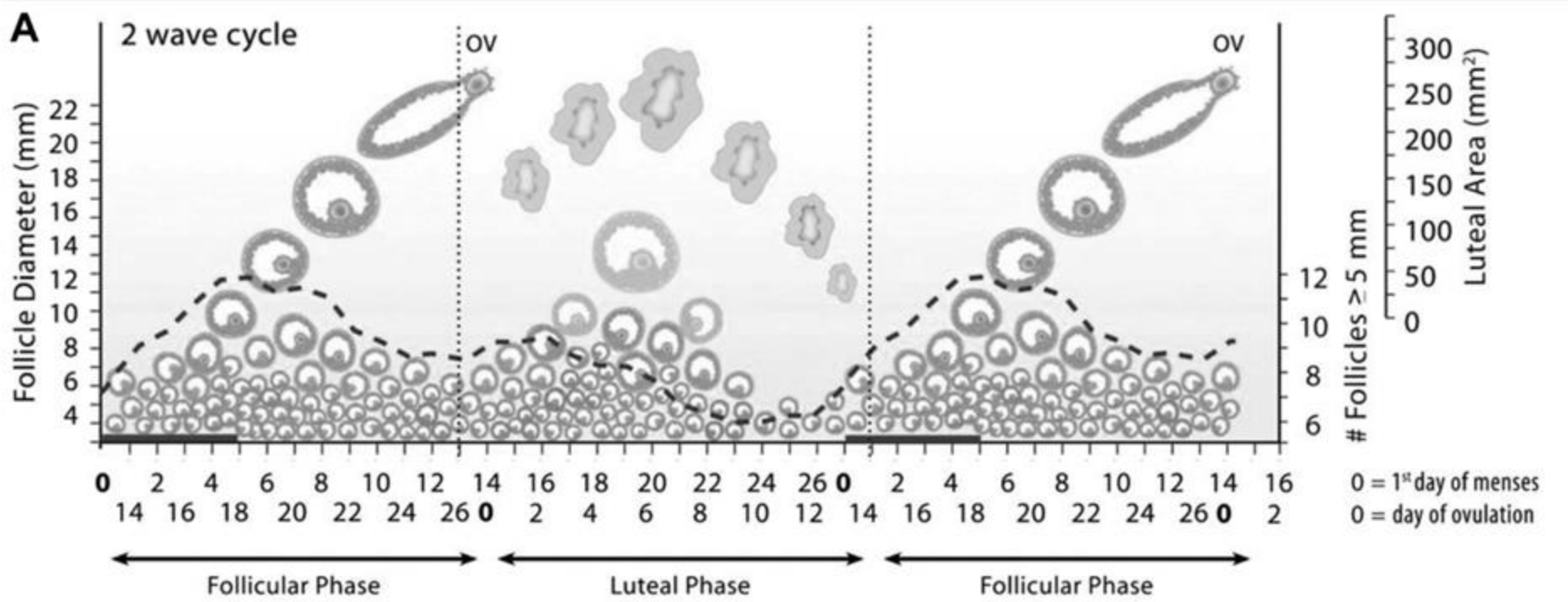
Unknown risk	Targeted agents, immunotherapy

Reproductive potential of cryopreserved oocytes:

HIGHEST in those women who may expect the LOWEST impact on fertility from cancer treatment

Walker et al., Reproductive Biology and Endocrinology 2022

Random start ovarian stim (RSOS)



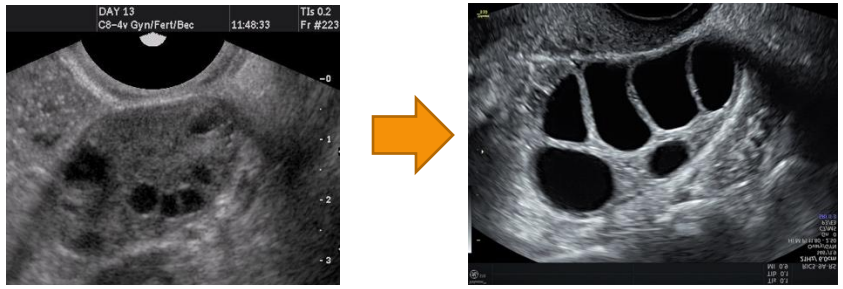
Early foll phase start

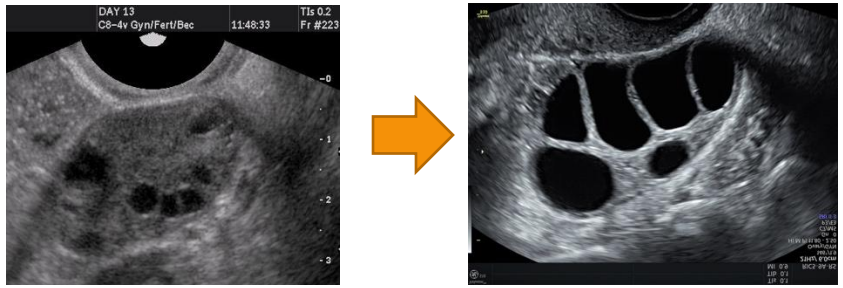
Late foll phase start

Luteal phase start

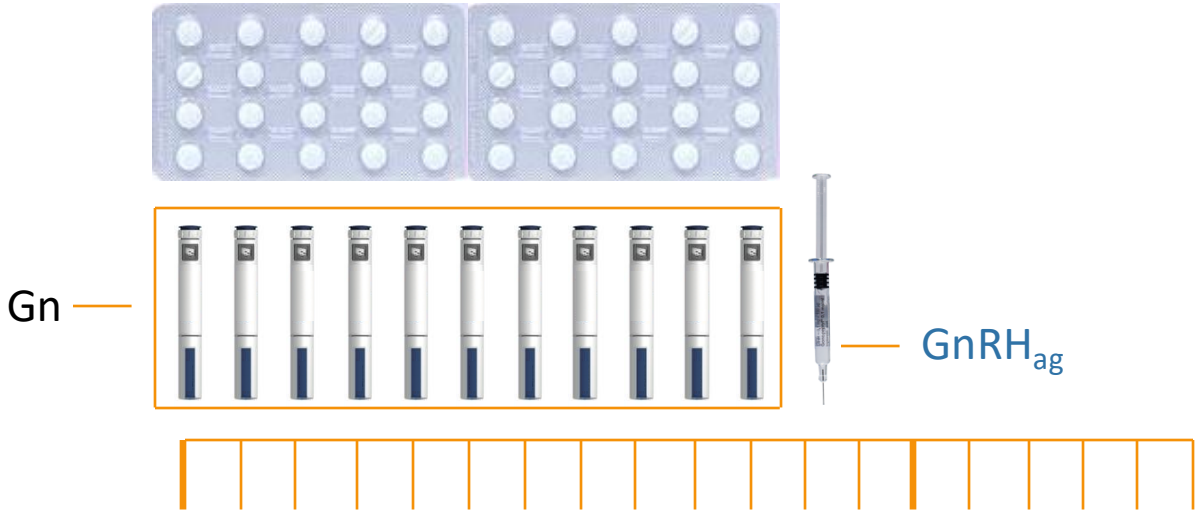
No LH suppression needed

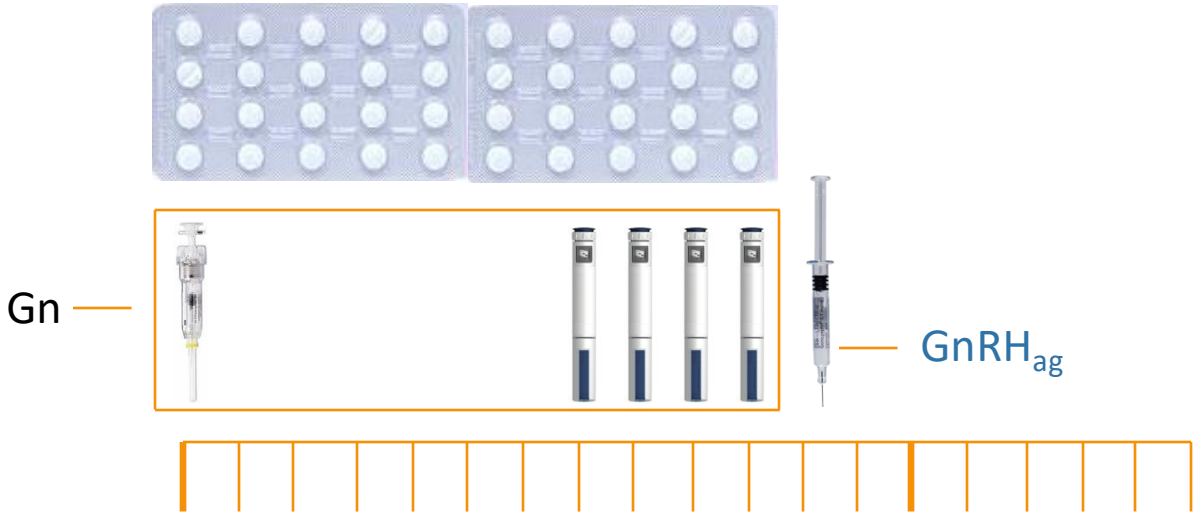
Cakmak et al., Fertil Steril 2013; adapted from Baerwald and Pierson, Fertil Steril 2020


DAY 13
C8-4v Gyn/Fert/Bec
11:48:33
TIs 0.2
Fr #223


DAY 13
C8-4v Gyn/Fert/Bec
11:48:33
TIs 0.2
Fr #223

progestins


Gn
GnRH$_{ag}$
Random start
OPU


Gn
GnRH$_{ag}$
Random start
OPU

An example

34 year old married woman, P1, IUCD

AMH 0.66ng/mL (ref. 0.69 - 2.27ng/mL)

ER pos PR pos breast tumour pT1c pN1a(sn) G2

Neo-adjuvant chemotherapy planned

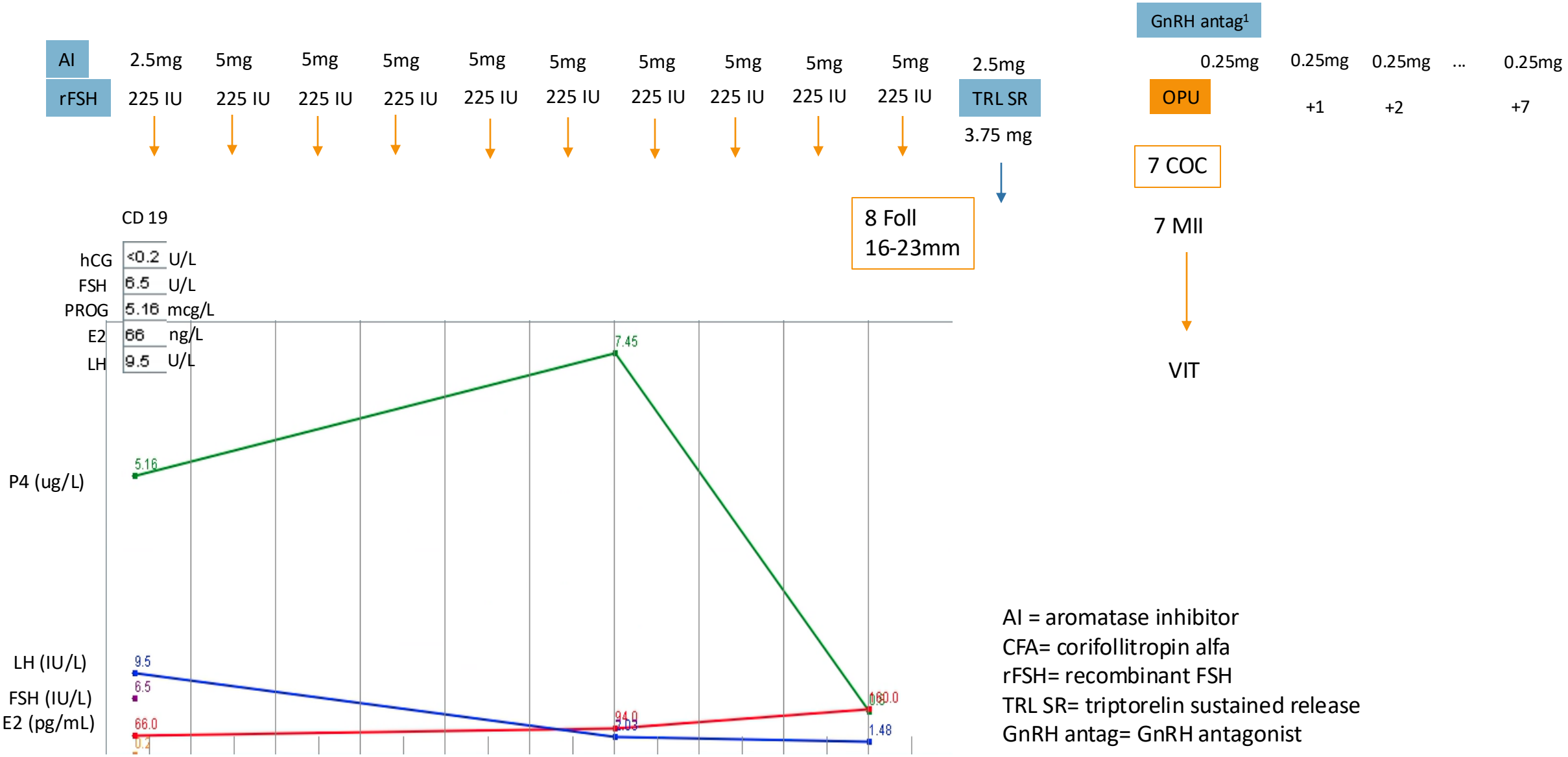
Ovarian stimulation for oocyte vitrification

Oncologist agrees

Cycle day 19

	CD 19	
hCG	<0.2	IU/L
FSH	6.5	IU/L
PROG	5.16	mcg/L
E2	66	ng/L
LH	9.5	IU/L

RSOS = random start ovarian stimulation
IUCD = intrauterine copper device
ER = estrogen receptor
PR = progesterone receptor



AI = aromatase inhibitor
CFA= corifollitropin alfa
rFSH= recombinant FSH
TRL SR= triptorelin sustained release
GnRH antag= GnRH antagonist

[1] Von Wolff et al., Fertil Steril 2011

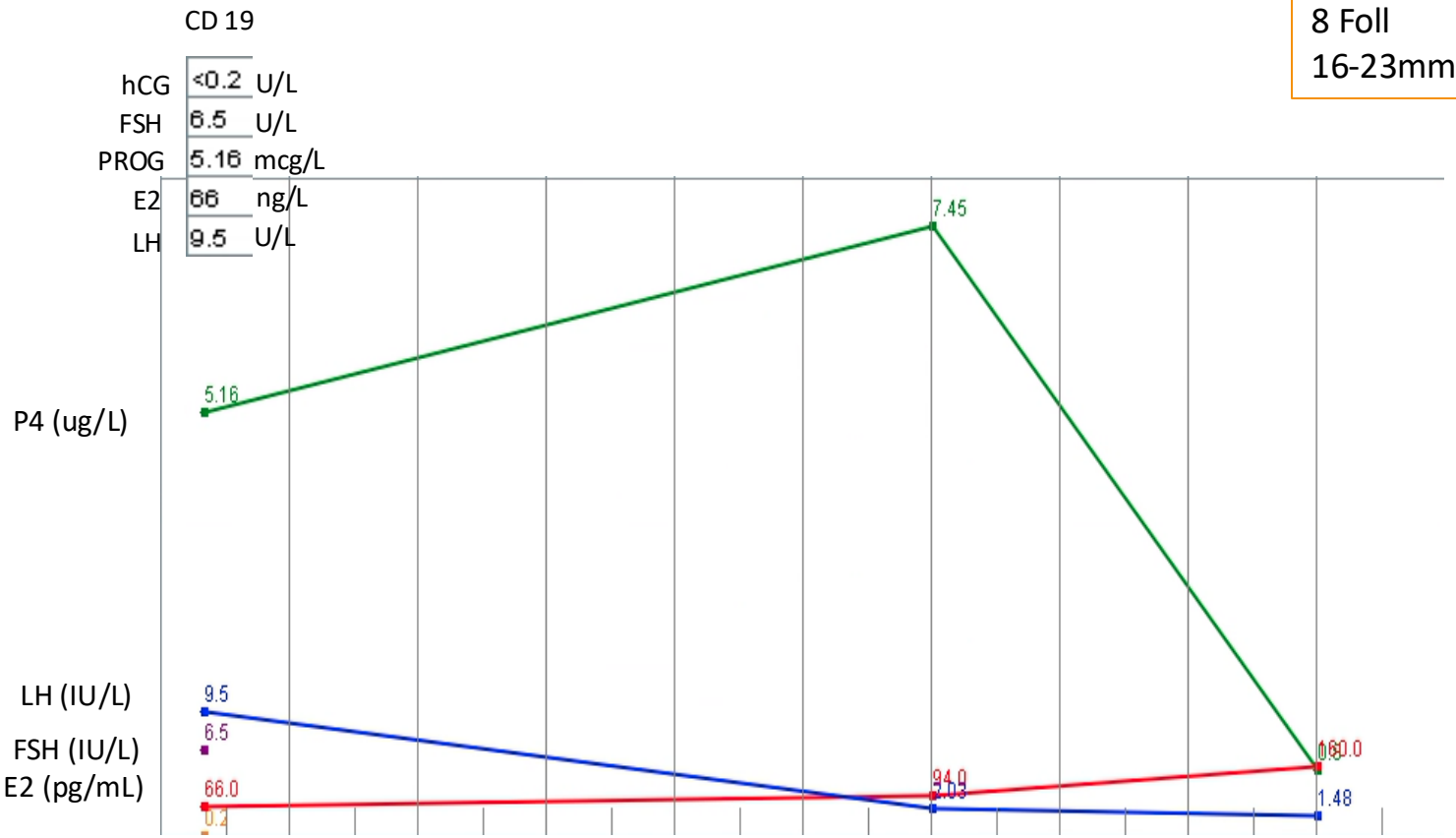
AI	2.5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	2.5mg
rFSH	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	TRL

0.2 mg

OPU

8 Foll
16-23mm

Vitrification of metaphase II stage oocytes



To rescue or not to rescue immature oocytes: prospects and challenges

Giovanni Coticchio, Ph.D.,[a] Danilo Cimadomo, Ph.D.,[b] Michel De Vos, M.D., Ph.D.,[c] Thomas Ebner, Ph.D.,[d] Marga Esbert, Ph.D.,[e] Maria Jose Escribá, Ph.D.,[f,g] Robert B. Gilchrist, D.Sc.,[h] and Laura Rienzi, Ph.D.[b,i]

Estrogen modulation during ovarian stimulation in breast cancer patients

- In breast cancer patients co-treated with an aromatase inhibitor, an equivalent number of MII oocytes are vitrified [1,2]
- Cotreatment with aromatase inhibitors is safe: ctDNA levels are not increased in >90% of patients receiving AI-cotreatment [3]
- No difference in survival rates in more than 400 breast cancer patients in Sweden who had FP with or without AI cotreatment [4]

Purpose:
To reduce estrogen exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy

Oktay et al., JCEM 2006

In the absence of evidence that safety is improved by estrogen modulation, is there a rationale for ovarian stimulation with estrogen modulation?

[1] Bonardi, et al., Front Oncol 2020
[2] Balkenende et al., Hum Reprod 2022
[3] Rothé et al., Front Oncol 2021
[4] Marklund et al., Hum Reprod 2020

ctDNA = circulating tumour DNA
AI = aromatase inhibitors

Case

28 year old woman, G0P0, on COAC since 2018

Diagnosed with AML, referred for FP by haematologist

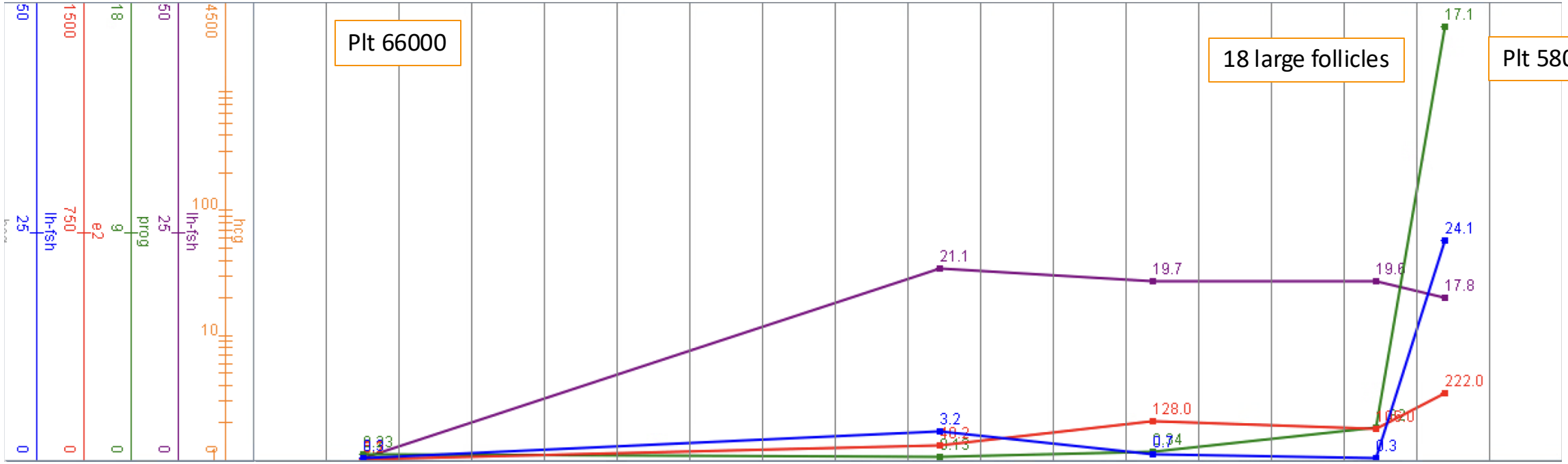
Haematologist asks for letrozole cotreatment, no clexane needed

Ovarian stimulation for oocyte vitrification

BMI 23 kg/m^2, AMH 2.0ng/mL

hCG	<0.2	IU/L
FSH	<0.3	IU/L
PROG	0.23	µg/L
E2	5.2	ng/L
LH	<0.3	IU/L

		05/10 zo	06/10 ma	07/10 di	08/10 wo	09/10 do	10/10 vr	11/10 za	12/10 zo	13/10 ma	14/10 di	15/10 wo	16/10 do	17/10 vr	18/10 za	19/10 zo	20/10 ma	21/10 di	22/10 wo
Gonapeptyl	IU																t0.2		
Letrozole	mg			2.5	5	5	5	5	5	5	5	5	5	5	5	5	5		
SPR Duphaston	mg			10	30	30	30	30	30	30	30	30	30	30	30	30	30		
STM Elonva	µg			1540	×	×	×	×	×	×									
STM Puregon	IU										200	200	200	200	200	200			
TRG Ovitrelle 250	µg																	0	



Plt 66000

18 large follicles

Plt 58000

OPU

11 oocytes vitrified

Laparoscopy for haemoperitoneum after OPU
+ Plt transfusion

CASE

- 28 year-old woman
- On combined oral contraceptives
- Philadelphia negative B-ALL with MLL translocation
- GRAALL2003 planned

Referred by haematologist

- AFC 21
- AMH 2.31ng/mL
- Plt 118.10^3/mm^3

Agrees with IVM-OPU

Ei-nr	Uur	Maturiteit	Uur	Maturiteit
1	15:41	PB		
2	15:41	PB		
3	15:41	PB		
4	15:41	PB		
5	15:41	PB		
6	15:41	PB		
7	15:41	PB		
8	15:41	PB		
9	15:41	PB		
10	15:41	M1	9:30	PB
11	15:41	GV		
12	15:41	GV		
13	15:41	GV		
14	15:41	DEG		

No stim given -> 10 vitrified oocytes

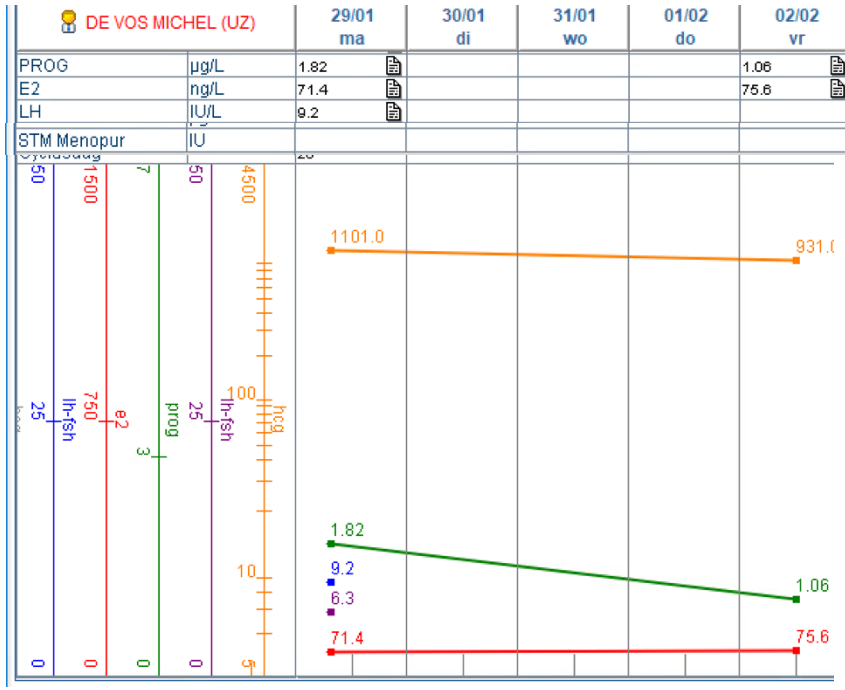
OTC between induction and consolidation chemotherapy

CASE

- 27 year-old woman
- Recent miscarriage
- Invasive breast cancer
- Oncologist agrees with ovarian stim for oocyte vitrification
- AMH 3.63ng/mL

hCG >1000 IU/L at FP intake

IVM-OPU



150IU HP-hMG 42 hours before OPU

Ei-nr	Uur	Maturiteit
1	16:00	PB
2	16:00	PB
3	16:00	PB
4	16:00	PB
5	16:00	PB
6	16:00	PB
7	16:00	PB
8	16:00	PB
9	16:00	PB
10	16:00	PB
11	16:00	PB
12	16:00	PB
13	16:00	PB
14	16:00	M1
15	16:00	M1
16	16:00	GV
17	16:00	GV

13 mature oocytes vitrified

Ovarian tissue cryopreservation

What do the professional societies say about ovarian tissue cryopreservation (OTC)?

- OTC should be considered an **established** medical procedure with limited effectiveness that should be offered to carefully selected patients (ASRM 2019).

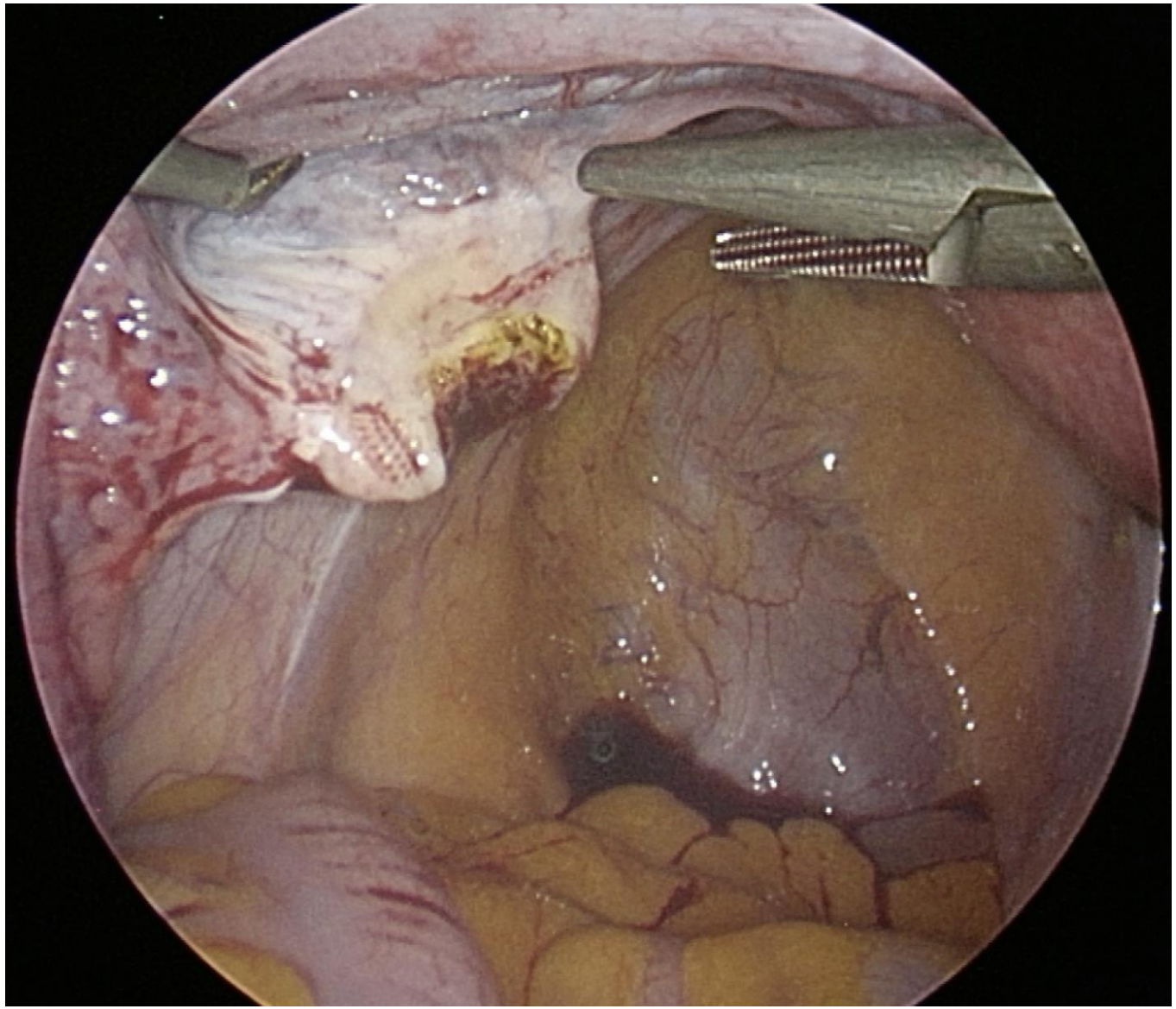
- OTC is no longer considered experimental and should be offered to patients who undergo **moderate/high risk gonadotoxic treatment** where oocyte/embryo cryopreservation is *not feasible*, or at *patient preference* (ESHRE 2020)

  - When there is insufficient time for ovarian stimulation
    Pre-pubertal patients
  - When ovarian stimulation is deemed risky

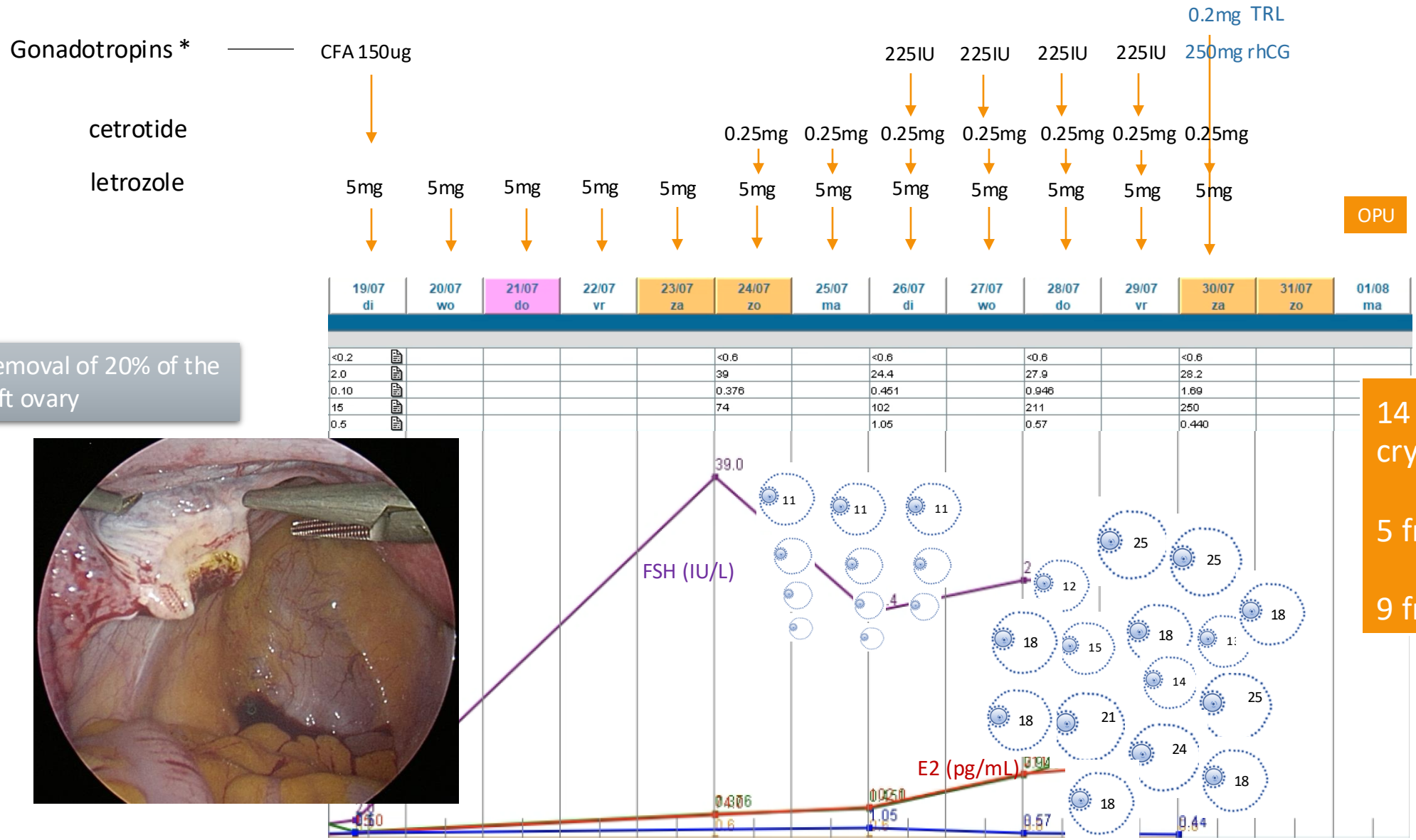
- OTC should probably **not** be offered:
  - to patients with low ovarian reserve or advanced age considering the unfavourable risk/benefit (ESHRE 2020).
  - to patients with a high risk of complications with general anaesthesia or abdominal surgery (CFAS 2024).
  - in case of a lack of resources or expertise using this technology (CFAS 2024).

Practice Committee of the American Society for Reproductive Medicine, Fertil Steril 2019; The ESHRE Guideline Group on Female Fertility Preservation, Human Reproduction Open 2020; Roberts et al., RBMO 2024.

Ovarian tissue cryopreservation (OTC)



Removal of 20% of the left ovary



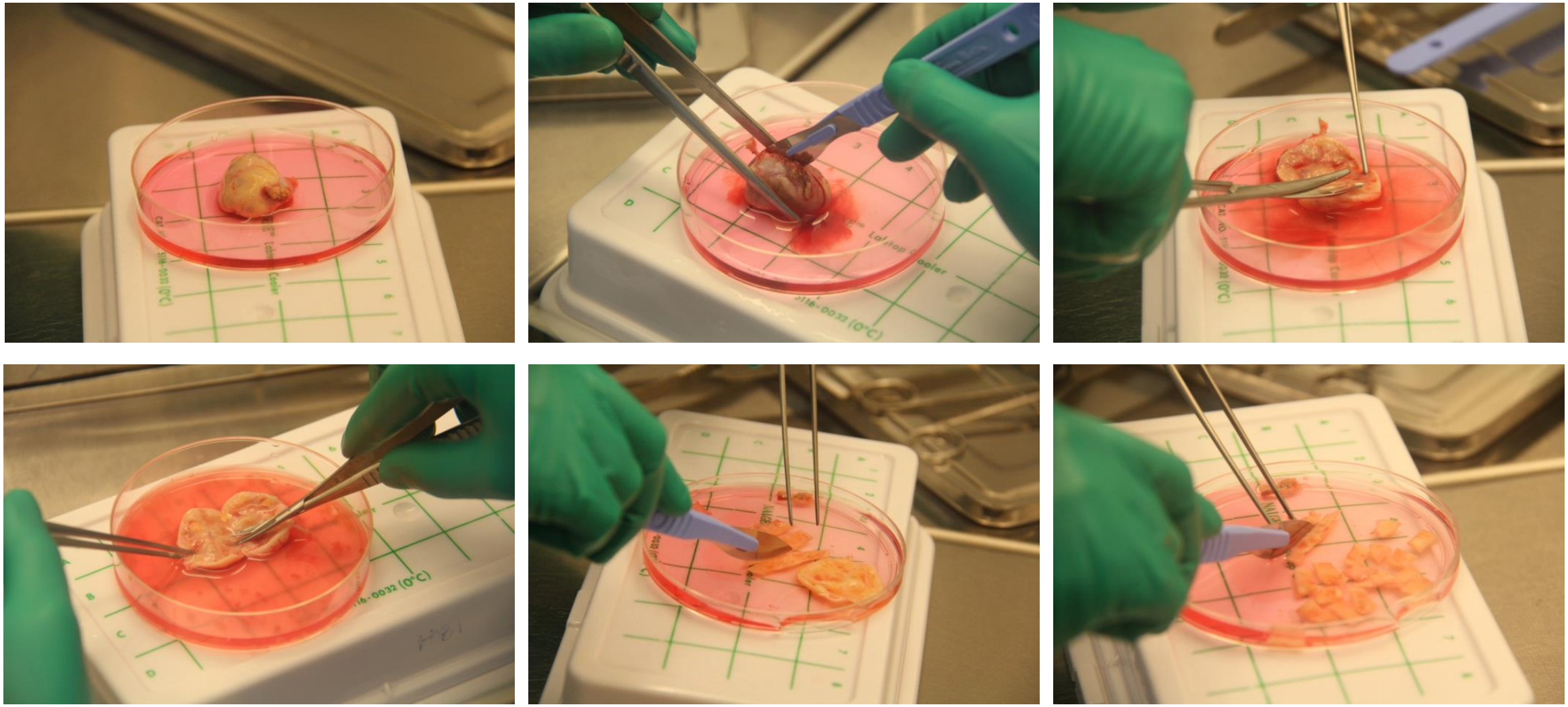
Removal of 20% of the left ovary

14 mature oocytes cryopreserved

5 from left ovary

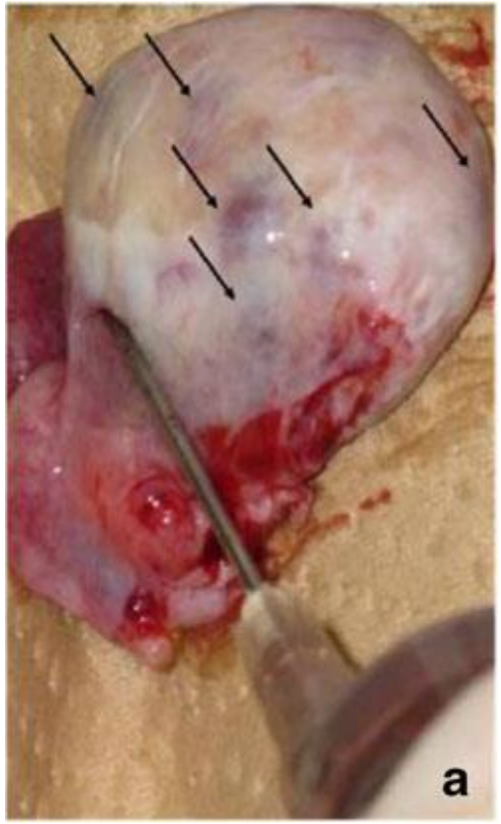
9 from right ovary

OTC + OTO-IVM

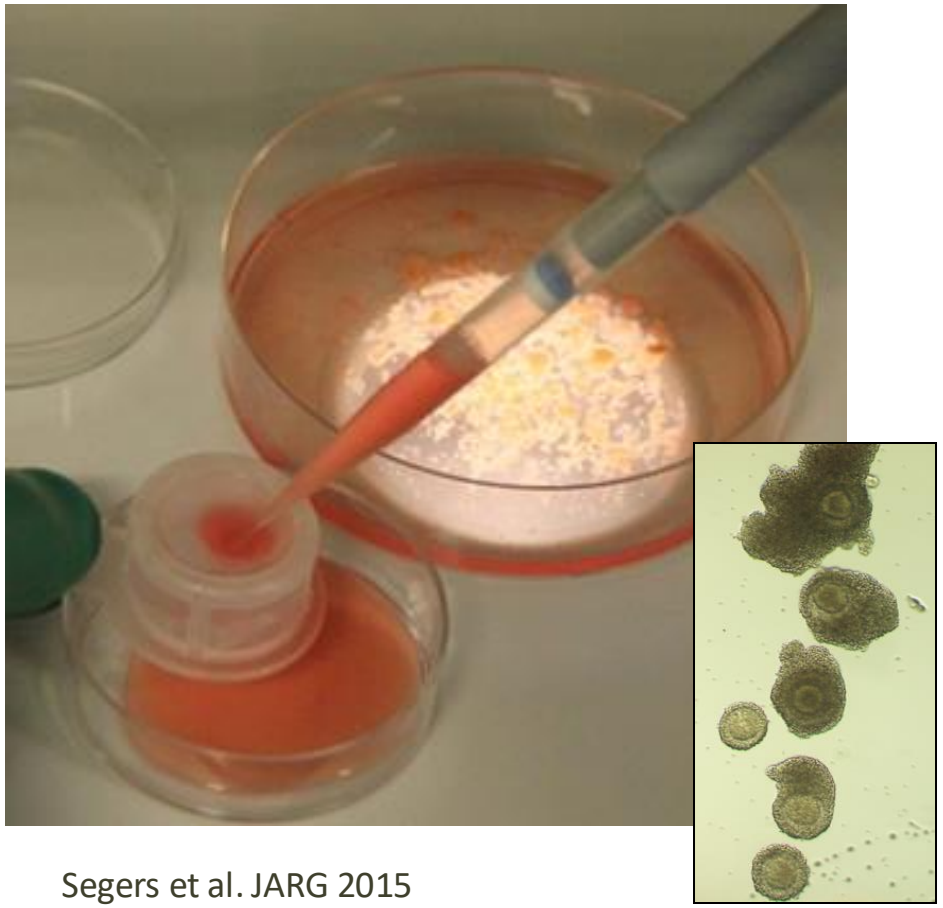


Segers, I., Mateizel, I., Wouters, K., Van Moer, E., Anckaert, E., De Munck, N., De Vos, M. Ovarian Tissue Oocyte-IVM for Fertility Preservation. J. Vis. Exp (2024).

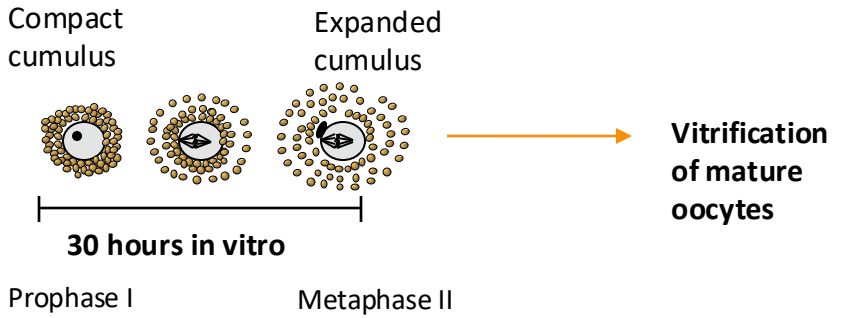
OTO-IVM



Shirasawa et al. JARG 2013



Segers et al. JARG 2015



IVM medium + HSA + HPhMG + uhCG

Experimental

Useful in patients with (potential) malignant involvement of the ovaries

Fertility preservation in female cancer patients - conclusion

- Increased awareness of the importance of fertility preservation counseling: focus on **quality of life after cancer**
- Fertility preservation (oocyte and/or ovarian tissue cryopreservation) may increase **hope** but does it increase birth rates?

You will find out in my next talk

Thank you

Brussels IVF

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Ziekenhuis
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