Cryopréservation ovocytaire: quand et pour qui ?

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CONTENU

- Pour qui?

- Introduction

- Raisons médicales
  - Conditions oncologiques
  - Syndrome de Turner

- Raisons non-médicales

POUR QUI? RAISONS NON-MÉDICALES

Women with a low likelihood of trying for a baby before 40y

Women at risk of ovarian insufficiency

Women who will start a family late and want multiple children

ARTICLE

Oocyte vitrification for elective fertility preservation: a SWOT analysis

Elisa Gil-Arribas[1,*], Christophe Blockeel[2,3], Guido Pennings[4], Julie Nekkebroeck[2,5], Juan A. García Velasco[6,7], José Serna[1], Michel De Vos[2,8,9]

30-35 Y

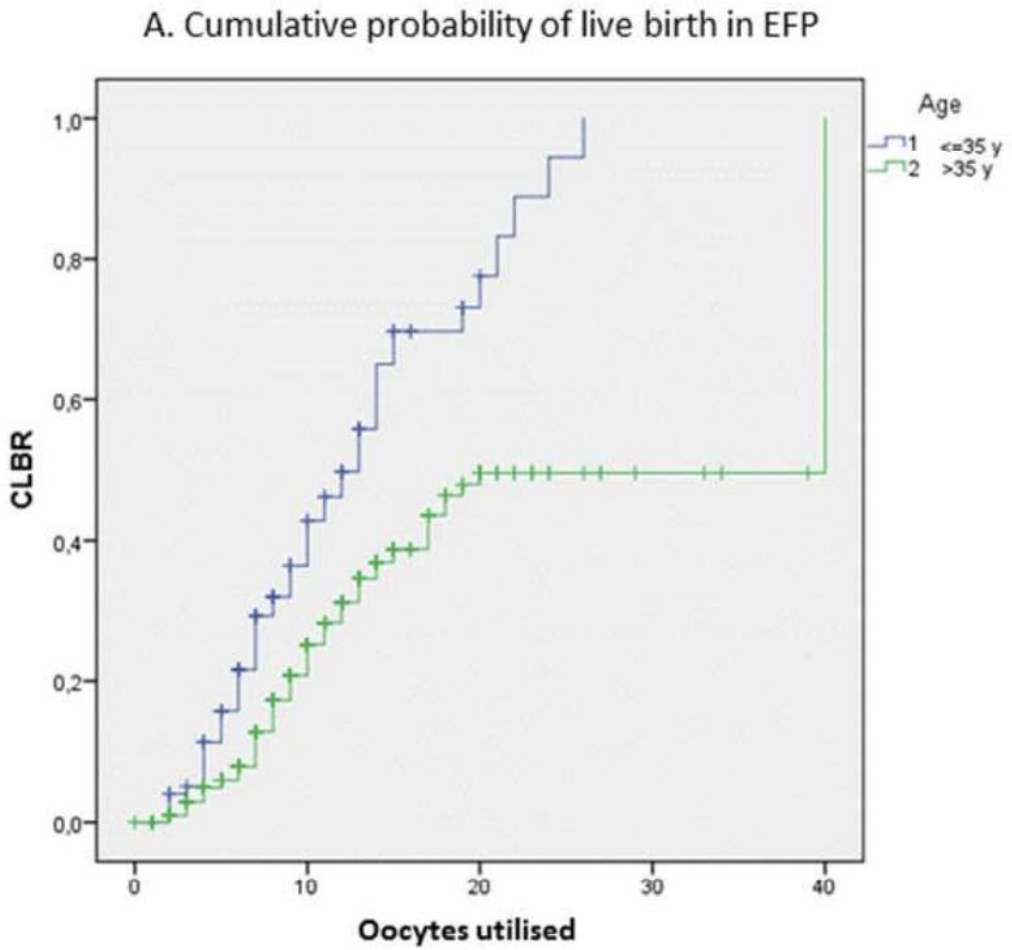
Single
Unsuitable partner
No desire for children yet
Career

No POC → ≥40y with infertility → IVF

POC → ≥40y with infertility → Oocyte warming → Better chance of having 1 LB (at lower $)
Higher probability of having 2 LB

Gil-Arribas et al., RBMO 2022; Bakkensen et al., F&S 2022

INTRODUCTION



Age ≤35. N = 123	
N°oocytes	CLBR(95%CI)
5	15.8 (8.4-23.1)
8	32.0 (22.1-41.9)
10	42.8 (31.7-53.90)
15	69.8 (57.4-82.2)
20	77.6 (64.4-90.9)
24	94.4 (84.3-100.4)

Age >35. N = 518	
N°oocytes	CLBR(95%CI)
5	5.9 (3.6-8.3)
8	17.3 (13.3-21.3)
10	25.2 (20.2-30.1)
15	38.8 (32.0-45.6
20	49.6 (40.7-58.4)

CI: confidence interval; CLBR: cumulative live birth rate
EFP: elective fertility preservation

INTRODUCTION

Blastocyst euploidy probability *per* mature (MII) oocyte

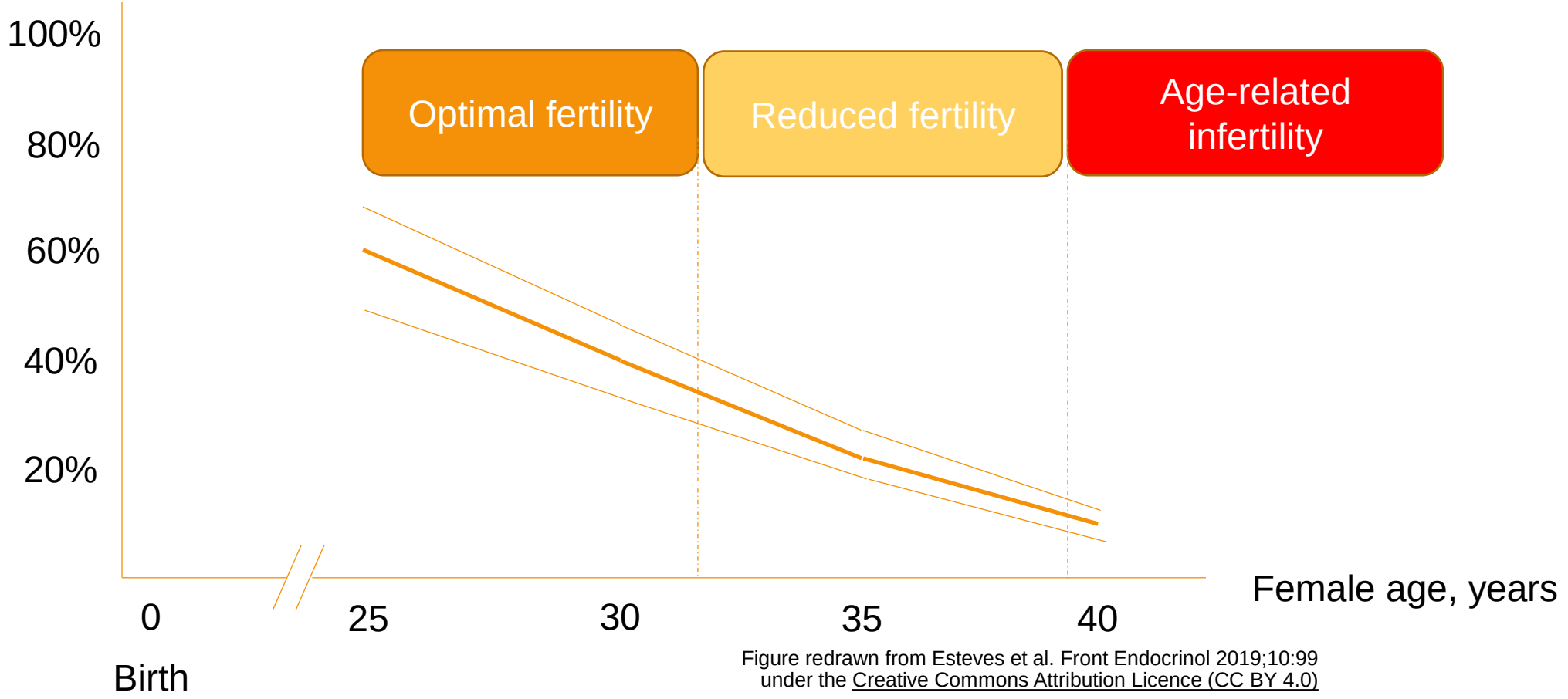
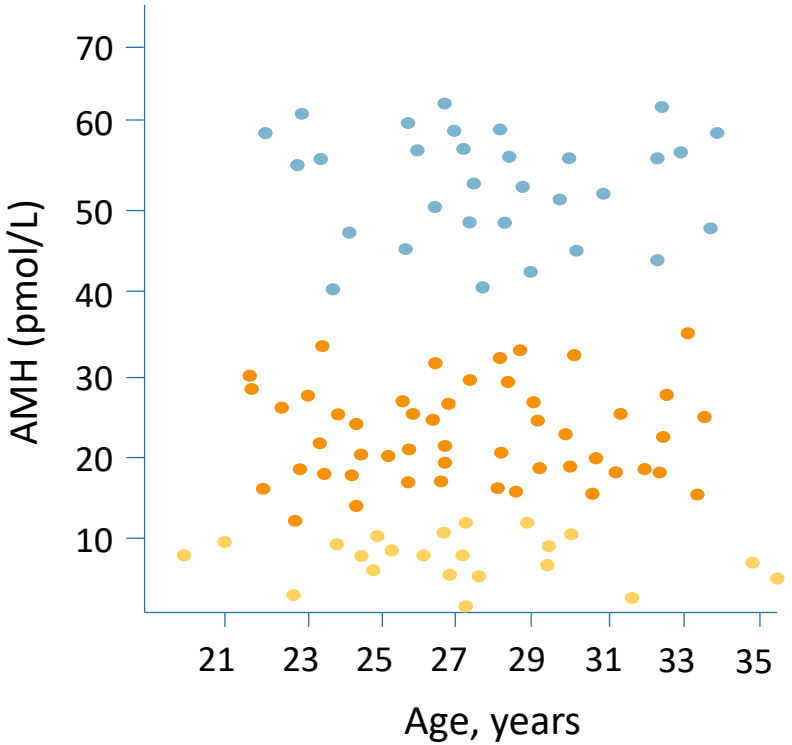


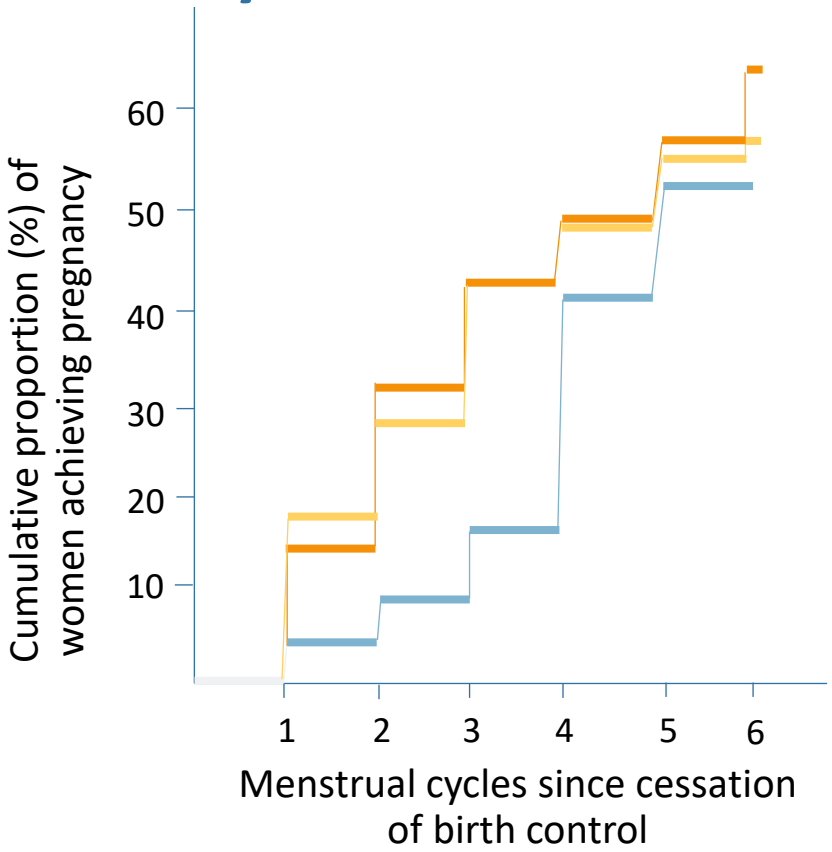
Figure redrawn from Esteves et al. Front Endocrinol 2019;10:99 under the Creative Commons Attribution Licence (CC BY 4.0)

MII: metaphase II

INTRODUCTION

AMH is a not marker of a woman's fecundity





Low AMH (quintile 1), n=30

Medium AMH (quintiles 2–4), n=113

High AMH (quintile 5), n=37

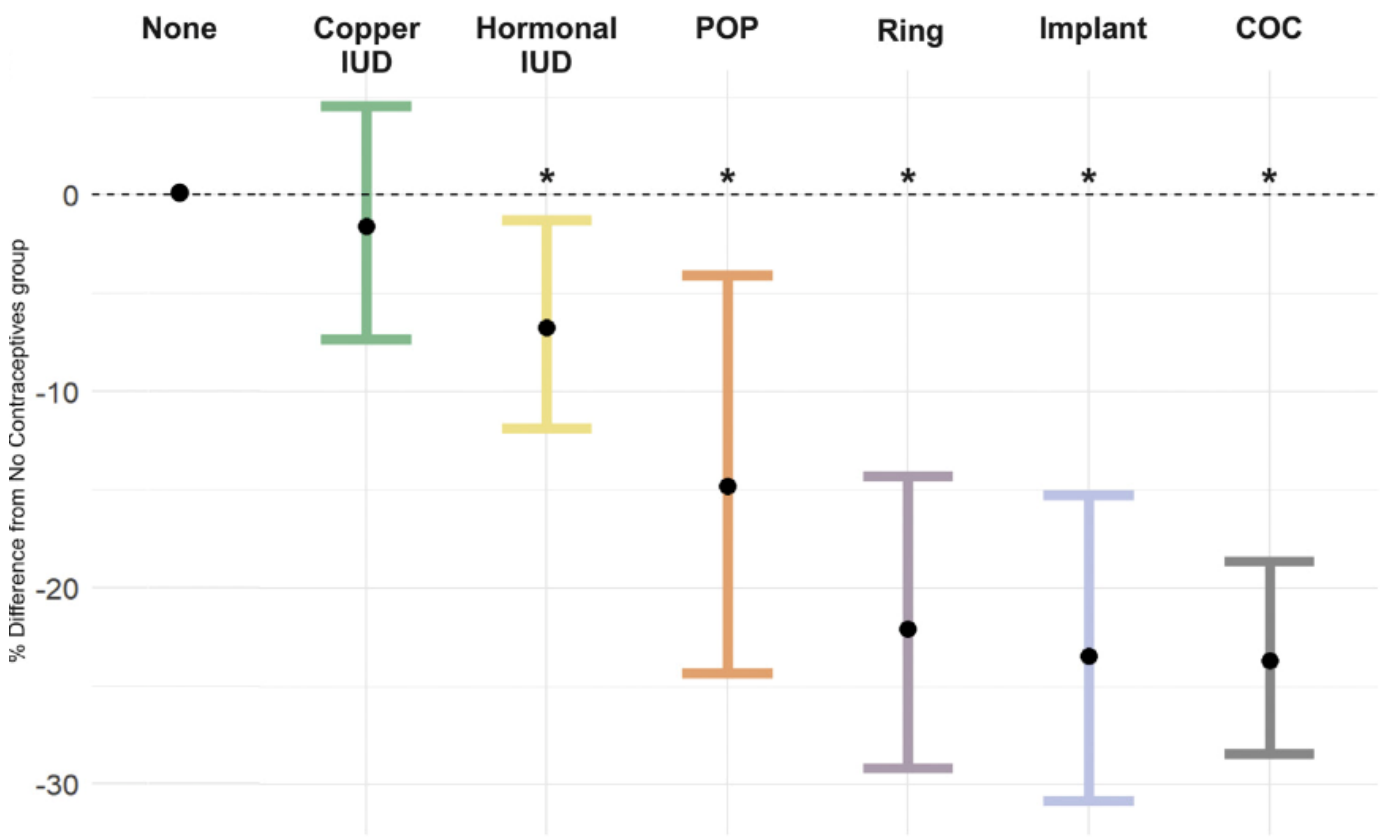
AMH: anti-Müllerian hormone

Figures redrawn from Hagen et al. Fertil Steril 2012

Case for combined hormonal contraception holiday in fertility preservation patients

Franasiak, F S Reports 2020

Estimations de la différence en pourcentage et intervalles de confiance à 95 % de l'AMH dans les groupes de contraceptifs par rapport aux femmes ne prenant pas de contraceptifs.



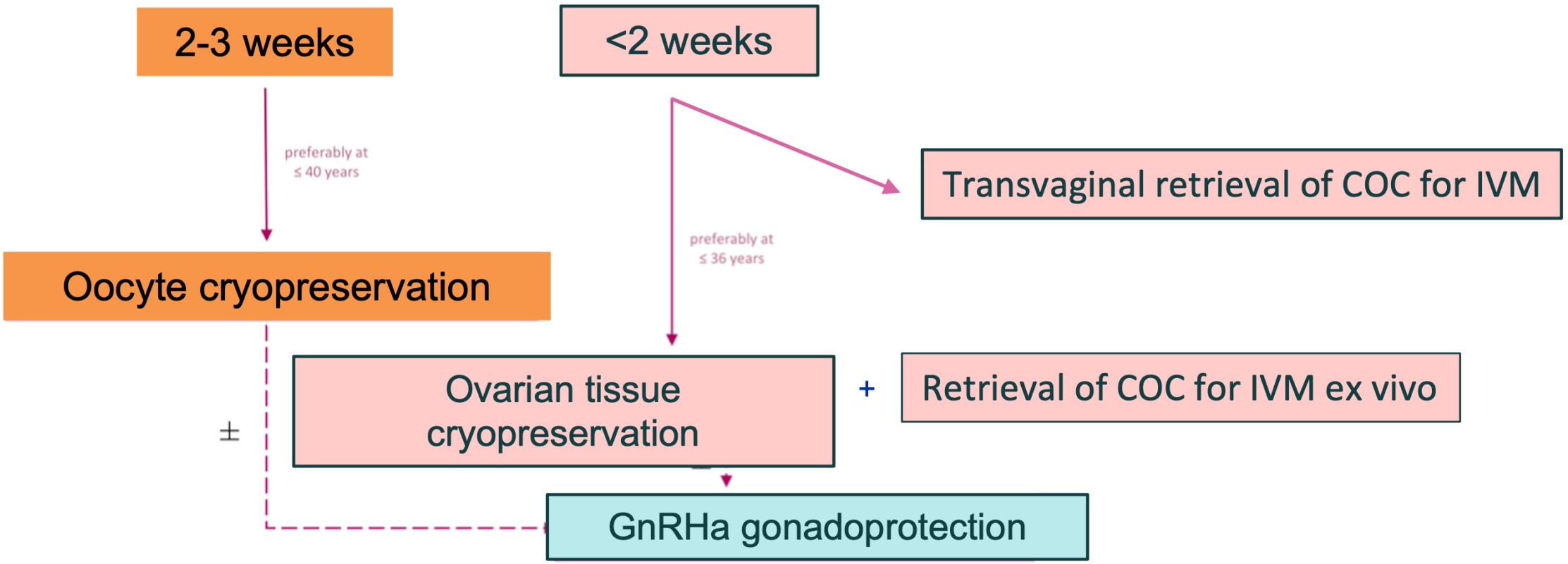
Hariton et al., Am J Obstet Gynecol 2021

POUR QUI?

Raisons médicales

Préservation de la fertilité chez les patientes atteintes d'un cancer après la ménarche

Algorithm based on available time

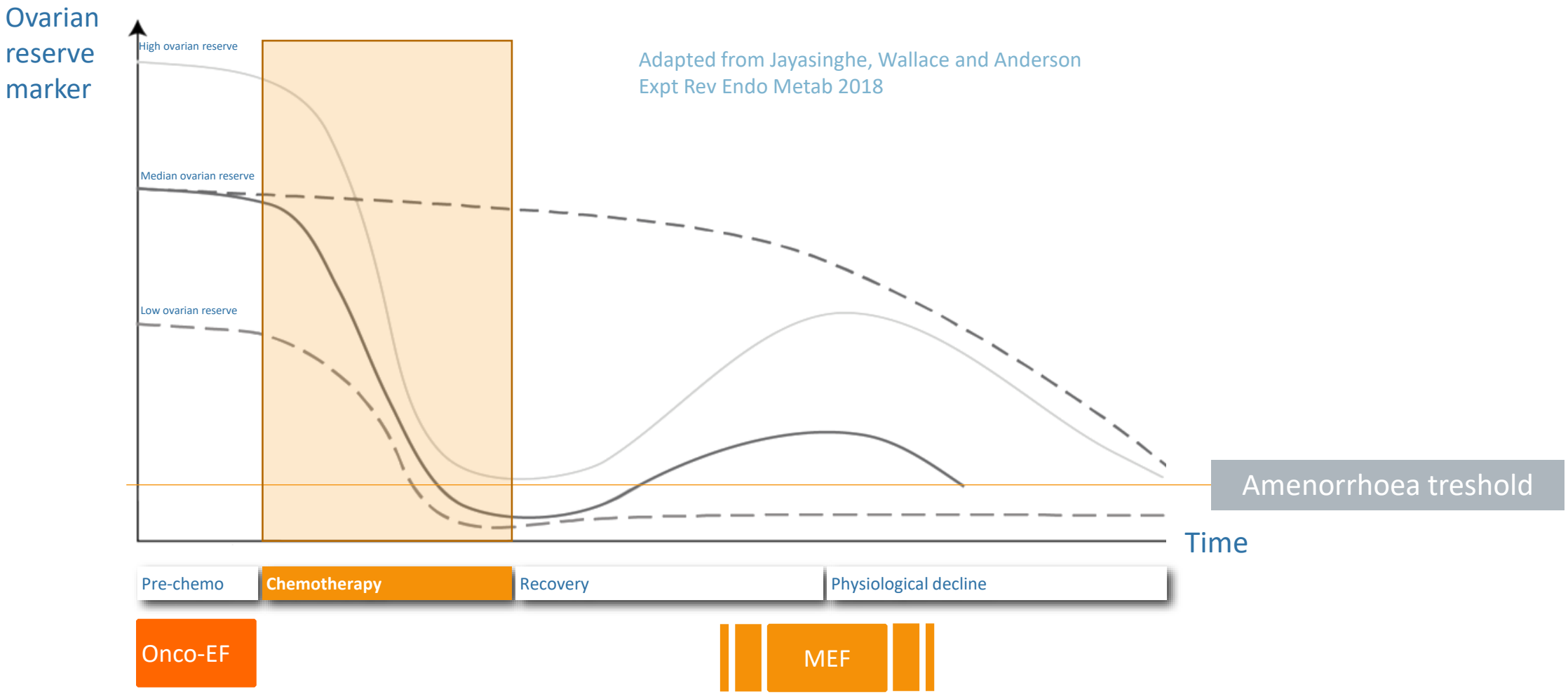


Cryopreservation d'ovocytes chez les patientes atteintes d'un cancer

- What is the purpose?
  - NOT: to guarantee future offspring
  - To mitigate the risk of infertility
  - To enhance future options of reproduction
  - “Frozen hope” [1]
- Onco-FP
  - In post-menarcheal young adults
  - Time-keeping: patient navigator – oncologist/haematologist – counselling/decision making
  - One cycle of ovarian stimulation before cancer treatment
  - Long-term follow-up of ovarian reserve markers after cancer treatment [2]
  - Oocyte cryopreservation after cancer treatment

1. Quinn et al., J Midwifery Wom Hlth 2010
2. Zhou et al., Fertil Steril 2022

Quand faut-il procéder à la cryopreservation des ovocytes ?



Onco-EF = onco- egg freezing; MEF = medical egg freezing

Tout dépend de l'âge et du nombre d'ovocytes

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

Reproductive potential of cryopreserved oocytes:

LOW

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

Tout dépend de l'âge et du nombre d'ovocytes

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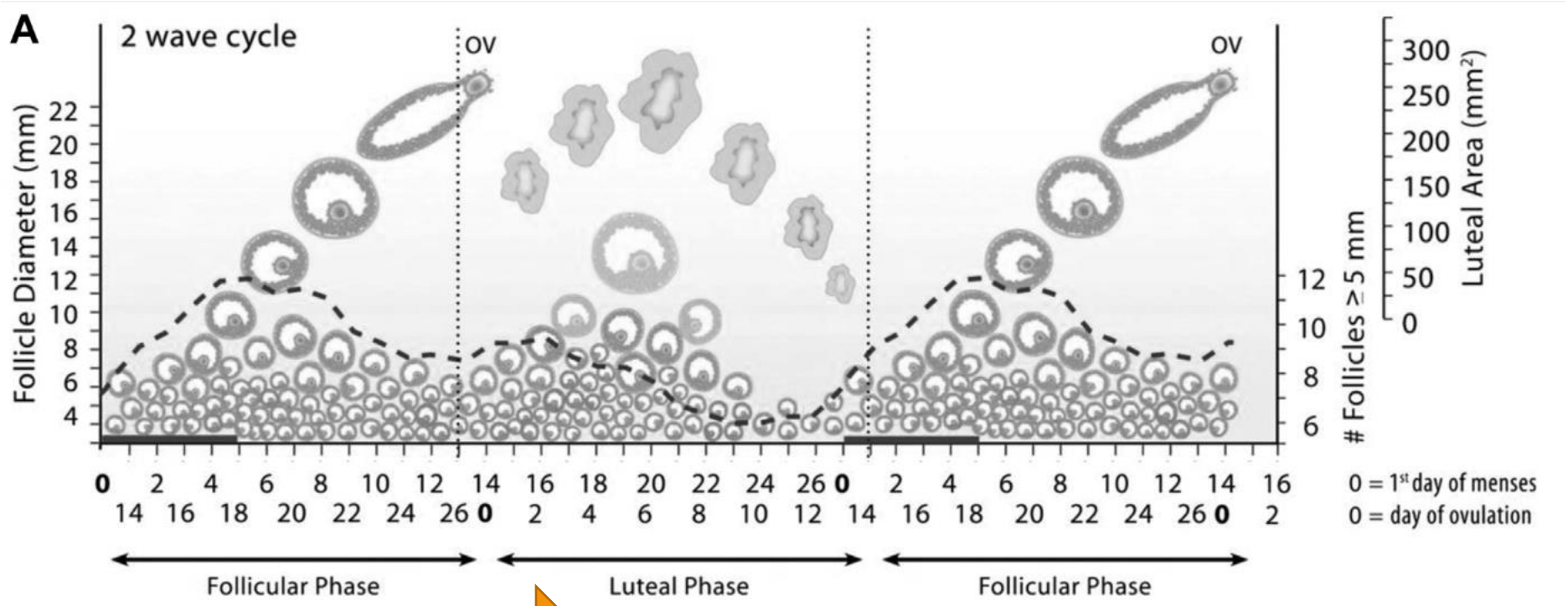
Unknown risk	Targeted agents, immunotherapy

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

Stimulation ovarienne:
Random start ovarian stim (RSOS)



Early foll phase start

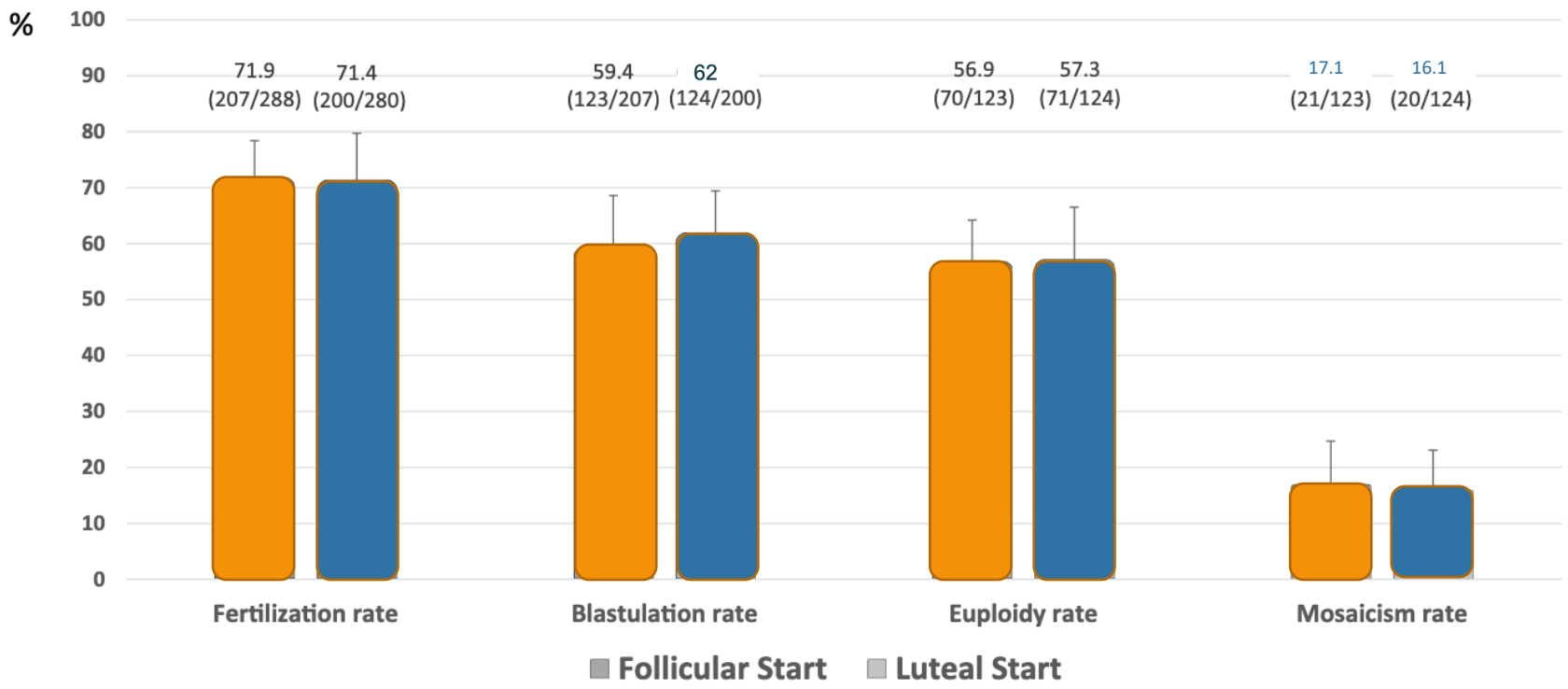
Late foll phase start

Luteal phase start

No LH suppression needed

Sécurité et efficacité de RSOS

RCT comparing number of euploid embryos after follicular phase vs. luteal phase stimulation in the same woman



Timing of ovarian stimulation has no impact on embryo ploidy

Modulation des œstrogènes pendant la stimulation ovarienne chez les patientes atteintes d'un cancer du sein

- 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

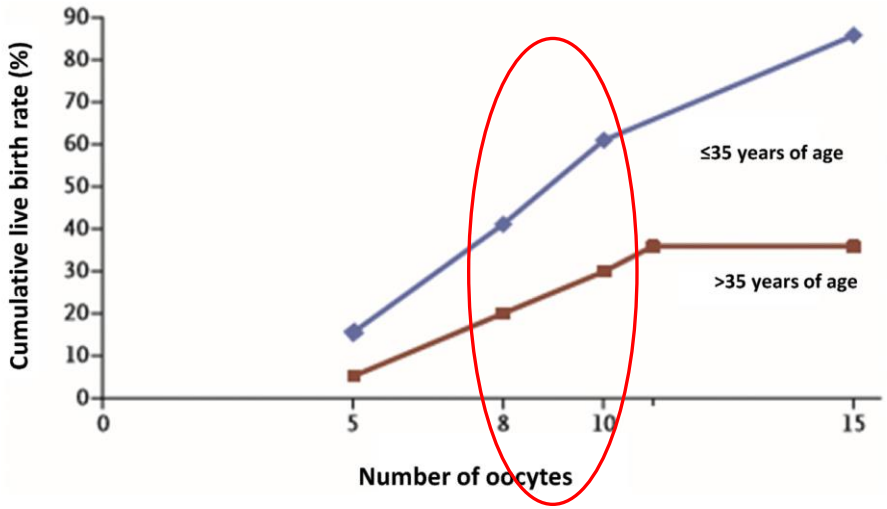
Oktay et al., JCEM 2006

In the absence of evidence that safety is improved by estrogen modulation, there is no real rationale for ovarian stimulation with estrogen modulation

ctDNA = circulating tumour DNA
AI = aromatase inhibitors

[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

Résultats cliniques de l'utilisation d'ovocytes vitrifiés chez les survivants du cancer



Adapted from Cobo et al., Fertil Steril 2016

- Limited number of oocytes (1 stim. cycle)
- Impact from disease on oocyte quality?
- ↑ Obstetric complications [1]

[1] Lambertini et al., JNCI 2018

	ONCO-fertility preservation	
Patients who had their eggs warmed	80/1073 (7.4%)	
Mean age at vitrification (Y)	34.8 +/- 2.1	
Mean age at warming (Y)	38.8 +/- 3.5	
Warmed oocytes/patient	7.5 +/- 2.8	
Age at vitrification	<36 Y	≥36 Y
Oocyte survival rate	81.2%	82.7%
CLBR/patient (%)	42.1 (EFP: 68.8%)	29.0 (EFP: 25.5%)

Cobo et al., Hum Reprod 2018

EFP = elective fertility preservation

COÛT-EFFICACITÉ

Does EOC make sense?

Van Loendersloot et al., Hum Reprod 2011
Hirshfeld-Cytron et al., Fertil Steril 2012
Mesen et al., Fertil Steril 2015
Devine et al., Fertil Steril 2015

EOC would be profitable if ~60% of women who had their eggs frozen before the age of 38 would use these eggs.

Fuchs Weizman et al., BJOG 2021

EOC resulted in an increased likelihood of achieving 1 or 2 LB and was cost-effective when pursued before age 39, compared to IVF/PGT-A at a more advanced age

Bakkensen et al., Fertil Steril 2022

Does EOC improve mental health/quality of life?

Stoop et al., Hum Reprod 2015
Hammarberg et al. Hum. Reprod 2017
Inhorn et al., JARG 2019
Wafi et al., RBMOnline 2020

CONCLUSIONS

- La stimulation ovarienne pour la cryoconservation des ovocytes chez les patientes atteintes d'un cancer après la ménarche donne de l'espoir et augmente les options reproductives futures
- Stimulation ovarienne urgente et aléatoire avec déclenchement de l'ovulation par agoniste de la GnRH pour plus de sécurité
- Le taux d'utilisation limité des ovocytes cryoconservés nécessite un examen plus approfondi.

EXEMPLE

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

Speaker's own data

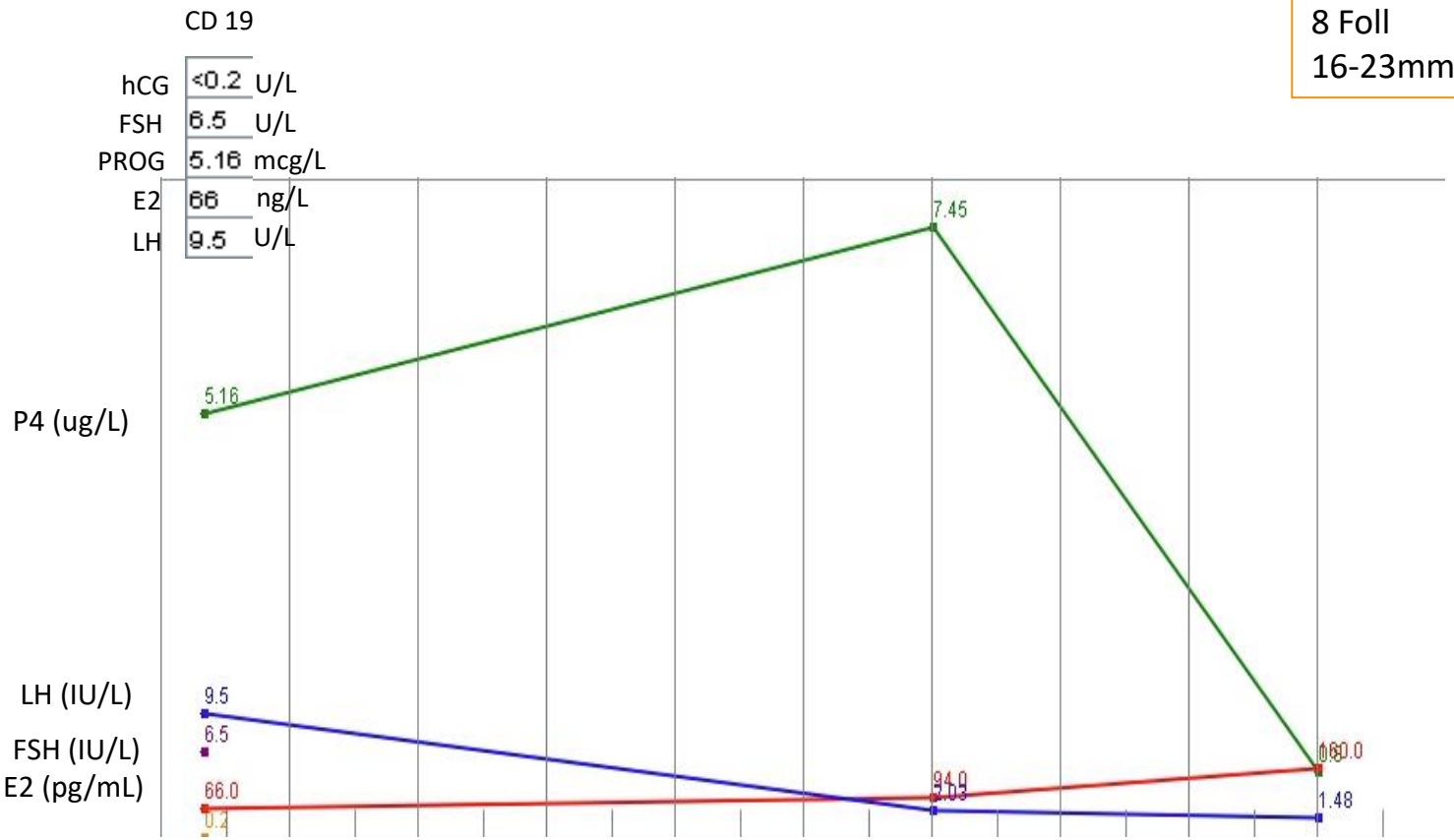
AI	2.5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	2.5mg	GnRH antag[1]	0.25mg	0.25mg	0.25mg	...	0.25mg
rFSH	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	225 IU	TRL SR 3.75 mg	OPU		+1	+2		+7

8 Foll
16-23mm

7 COC

7 MII

VIT



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

Speaker's own data

Brussels IVF

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

VRIJE UNIVERSITEIT BRUSSEL

Universitair Ziekenhuis Brussel

When there is no time for ovarian stimulation and OTC is not indicated

Referred by haematologist

28 years

Nulliparous, married

Long-term combined contraceptive pill use

Diagnosed with B-precursor acute lymphoblastic leukemia (B-ALL): GRAALL-2003 Chemotherapy planned

Ovarian parameters on day of intake

AMH (Elecsys automated assay): 2.31 ng/mL (16.5 pmol/l) (ref. 0.69-2.27 ng/mL)

AFC 10+11 small antral follicles

hCG <0.2 IU/L

FSH <0.3 IU/L

PROG 0.09 ug/L

E2 <5 ng/L

LH 0.3 IU/L

Which FP options are available here?

Ovarian stimulation? No time

Ovarian cortex cryo? Not yet

Oocyte retrieval for IVM

22/12/2021 00:00-23:5	23/12/2021 00:00-23:5	24/12/2021 00:00-23:5	25/12/2021 00:00-23:5	26/12/2021 00:00-23:5	27/12/2021 00:00-23:5	28/12/2021 00:00-23:5	29/12/2021 00:00-23:5
hCG	<0.2					<0.2	
FSH	<0.3					6.30	
PROG	0.09					<0.05	
E2	<5					<5	
LH	0.30					2.40	
							+OPU

OPU

29/12/2021 8:30 AM: 14 COC retrieved

29/12 9:00 insertion of portacath

29/12/2021 9:43: IVM started

30/12/2021: 10 MII oocytes vitrified

Intake at oncofertility clinic

No ovarian stimulation needed [1]

FP Intervention

OTC before conditioning chemotherapy[2]:

To be considered

Speaker's own data

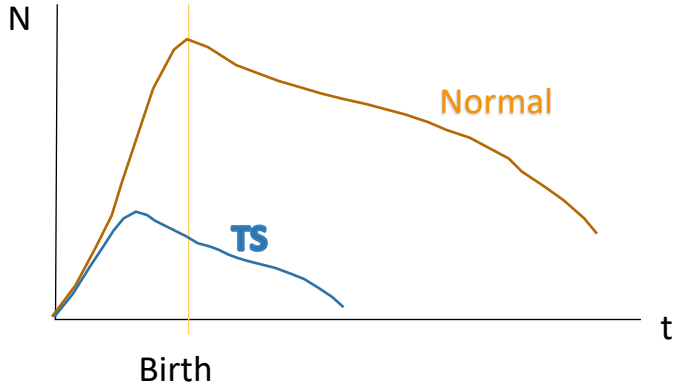
POUR QUI?

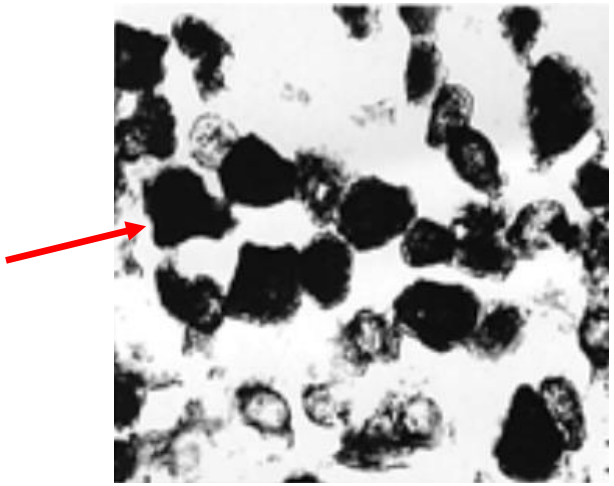
Raisons médicales

Troubles de la fertilité dans le syndrome de Turner

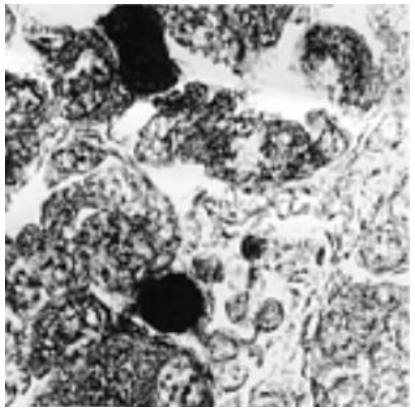
Premature follicular depletion and gonadal dysgenesis due to:

- Accelerated germ cell apoptosis
- Impaired folliculogenesis during fetal life





At 15 weeks nearly 50% of oocytes in fetal XO ovaries are TUNEL positive

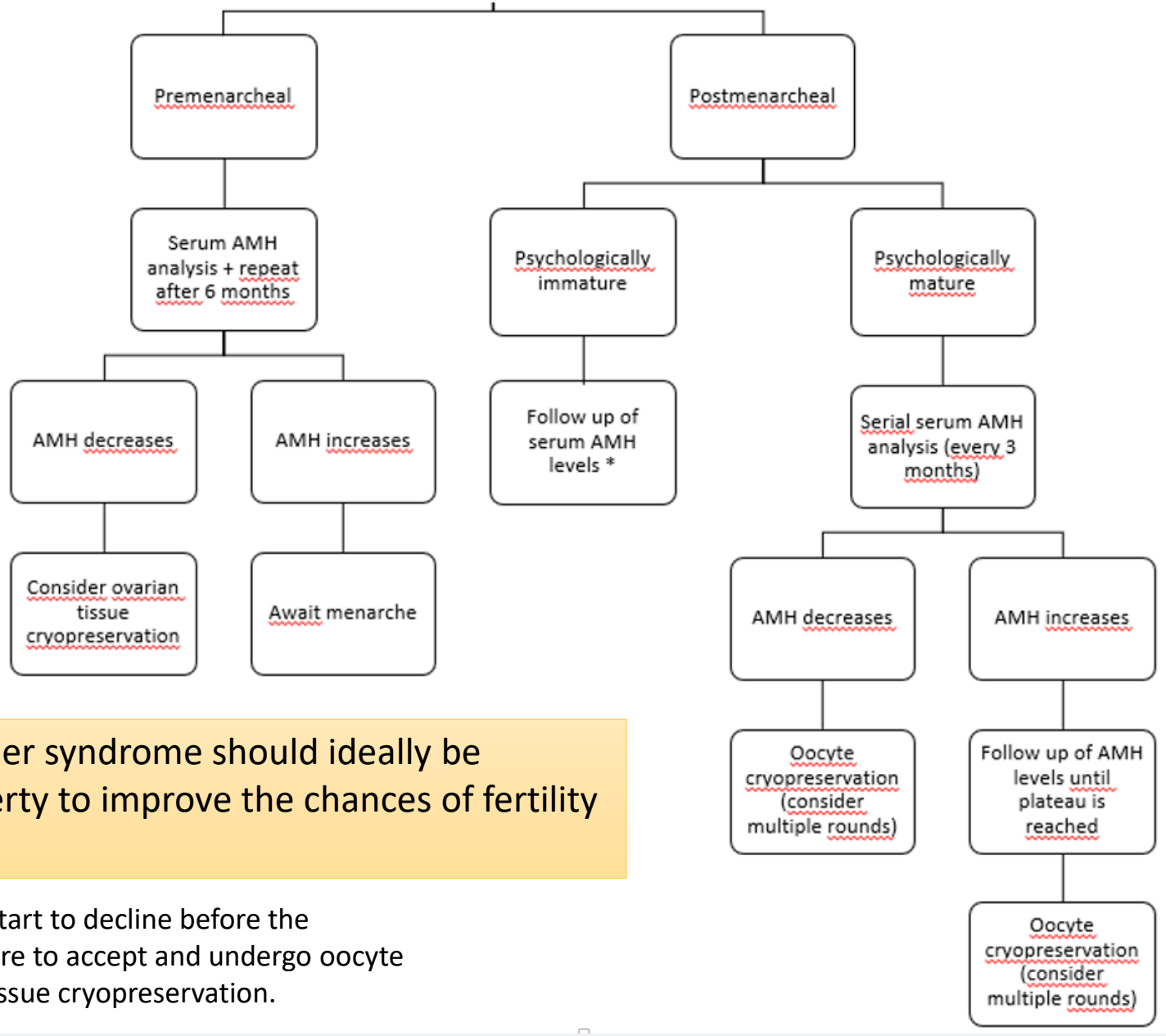


Only 3-5% of germ cells are apoptotic in age-matched normal XX ovaries

Modi et al., Mol Hum Reprod 2003

Reynaud et al., Fertil Steril 2004

Proposed algorithm for FP in individuals with mosaic TS



Fertility counselling for girls with Turner syndrome should ideally be offered at onset of spontaneous puberty to improve the chances of fertility preservation.

* If serum AMH levels reach a plateau or start to decline before the adolescent with TS is psychologically mature to accept and undergo oocyte cryopreservation, then consider ovarian tissue cryopreservation.

Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-022-02420-4

FERTILITY PRESERVATION

First live birth after fertility preservation using vitrification of oocytes in a woman with mosaic Turner syndrome

L. Strypstein[1] · E. Van Moer[1] · J. Nekkebroeck[1] · I. Segers[1] · H. Tournaye[1,2] · I. Demeestere[3,4] · M.-M. Dolmans[5,6] · W. Verpoest[1,7] · M. De Vos[1,2,8]

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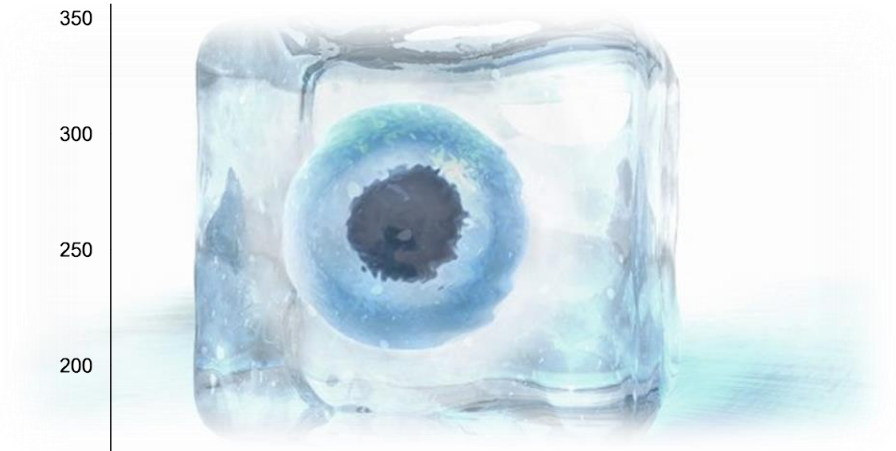
POUR QUI?

Raisons non-médicales

Non-medical oocyte cryopreservation



POURQUOI?

La cryopréservation élective ou planifiée d'ovocytes (CPO) est de plus en plus utilisée par les femmes qui :

- cherchent à obtenir un soulagement mental

- espèrent augmenter leur potentiel reproductif à un âge plus avancé.

POURQUOI les femmes se lancent-elles dans le projet de CPO ?

Absence d'un partenaire approprié (>80%)

- les femmes célibataires (qualifiées plus hautement que la moyenne)
- après un divorce ou une rupture
- partenaire "pas prêt" ou incertain

Brown, E., Patrick, M., 2018. Am. Sociol. Rev. 83, 959–982.
Carroll, K., Kroløkke, C., 2018. Cult. Health Sex. 20, 992–1005.
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Hammarberg, K., et al. 2017. Hum. Reprod. 32, 575–581.
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Inhorn MC, et al. J Assist Reprod Genet. 2018 Aug 3;35(11):2003–11.

COÛT-EFFICACITÉ

La CPO a-t-elle un sens ? Est-elle utile ?

Évaluation de sa valeur :

Études coût-efficacité

Van Loendersloot et al., Hum Reprod 2011
Hirshfeld-Cytron et al., Fertil Steril 2012
Mesen et al., Fertil Steril 2015
Devine et al., Fertil Steril 2015

La suspension de l'horloge biologique améliore-t-elle la santé mentale / la qualité de vie ?

Enquêtes de suivi

Stoop et al., Hum Reprod 2015
Hammarberg et al. Hum. Reprod 2017
Inhorn et al., JARG 2019
Wafi et al., RBMOnline 2020

AVANT la CPO : Importance du conseil

Discutez:

- Il ne s'agit pas d'une assurance
- Un faible pourcentage de femmes utilisent les ovocytes
- Projections basées sur les paramètres de la réserve ovarienne (AMH, CFA)
- Nombre d'ovocytes requis pour une reproduction réussie en fonction de l'âge (données bibliographiques)
- Nature, risques et limites de la procédure, les conditions de stockage, le délai d'utilisation, les coûts, les taux de survie du centre, l'utilisation et le sort des ovocytes restants.
- Alternatives
- La sécurité à long terme de la progéniture

A éviter:

- Donner de faux espoirs
- Présenter cette option comme une garantie de réussite de la reproduction future (Harwood, 2009)
- Recommander la cryoconservation d'ovocytes pour les femmes de plus de 38 ans.

Satisfaction à l'égard de la cryocongélation ovocytaire	Wafi et al. 2009-2016
Recommanderiez-vous à d'autres personnes de faire cryocongeler leurs ovocytes ?	N=131 OUI 128 (98%) NON 3 (2%)
Envisageriez-vous de faire à nouveau l'intervention ?	N=128 OUI 103 (80.5%) NON 25 (19.5%)
Regrettez-vous d'avoir fait une congélation d'ovules ?	N=128 OUI 17 (13%)

Wafi et al., RBMOnline 2020

39% des personnes interrogées ont regretté de ne pas avoir subi de cycles supplémentaires.
68% ont déclaré qu'elles auraient eu plus de cycles si le traitement avait été moins cher.

N=65	62 (95.4%)
N=201	98 (49%)

Stoop et al., Hum Reprod 2015

Greenwood et al., Fertil Steril 2018

La perception d'une moindre adéquation de l'information et du soutien émotionnel au cours du processus, ainsi qu'un faible nombre d'ovocytes prélevés, étaient associés au regret de la décision.

LES TAUX D'UTILISATION (≠ “RETURN RATES”)

Author	Mean age at freezing (SD)	Mean age at warming (SD)	Average time to utilisation	Proportion utilising the vitrified oocytes
Cobo 2018	37.2 (4.9)Y	39.9 (0.7)Y	25M	12.1% (641/5289)
Wennberg 2019	36.9Y	42.7Y	48M	15% (38/254)
Nekkebroeck 2020	37.0Y	40Y	36M	7.3% (49/668)
Baker 2020	37.3 (3.4)Y	39.9 (4.3)Y	31M	8.5% (80/942)
Blakemore 2021	38.2Y	43.9Y	59M	38.1% (88/231)

Cobo et al., Hum Reprod 2018
Wennberg et al., Acta Obst Gyn Scand 2019
Nekkebroeck et al., abstract ESHRE 2020
Baker et al., abstract ASRM 2020
Blakemore et al., 2021

CONCLUSION

- Objectif: l’obtention d’un soulagement mental
- L’importance de l'information et du soutien émotionnel au cours du processus
- Importance d’une interprétation correcte de l’AMH
- Une minorité de femmes utiliseront leurs ovocytes
- Selon notre expérience, le taux de grossesse évolutive cumulé par femme après décongélation d’ovocytes à un âge moyen de 41 ans se situe à environ 50%.


Merci!