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Egg freezing and the clinical application

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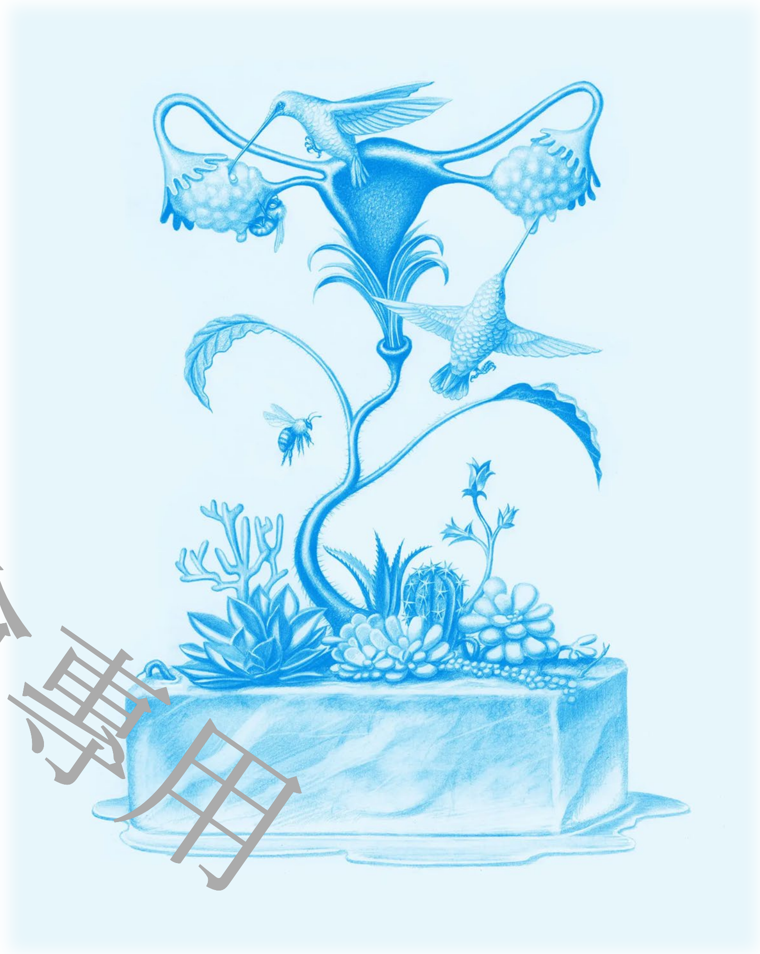
Outline

- Historical aspect
- Clinical aspect
  - Indications, challenges
  - Prediction model, real-world data
- Socio-economical aspect
  - Usage rate, cost-effectiveness analysis
- Unsolved problems



The New York Times Magazine, 2019/12/11, illustrations by Armando Veve

Historical aspect

History of oocyte cryopreservation

1940's
Development of cryopreservation technique

1953
First pregnancy after frozen sperm

1984
First pregnancy after frozen embryo

1986
First pregnancy after frozen oocytes[1] (slow freezing)

1997
Live birth after ICSI of cryopreserved oocytes[2]

1999
Live birth following vitrification of oocytes[3]

2012
The ASRM Practice Committee: removal of experimental label[4]

1. Chen, 1986
2. Porcu, et al., 1997
3. Kuleshova, et al., 1999
4. Practice Committees of the ASRM, 2013

Current guidelines on oocyte cryopreservation for age-related fertility loss

- ASRM (2018)[1]: The Committee concludes that planned oocyte cryopreservation may allow women who, in earlier times, would have faced infertility and childlessness to potentially have a child to whom they are genetically linked. Planned oocyte cryopreservation is an ethically permissible medical treatment that may enhance women's reproductive autonomy and promote social equality
- RCOG (2020)[2]: Elective egg freezing for non-medical reasons provides an opportunity for women to mitigate the decline in their fertility with age, but women undertaking oocyte cryopreservation should only do so with a full understanding of the likelihood of success, as well as costs and risks.
- ESHRE (2020)[3]: Oocyte cryopreservation should be offered as an established option for fertility preservation

1. Ethics Committee of the ASRM, 2018
2. Anderson, et al., 2020
3. ESHRE Guideline Group on Female Fertility Preservation, 2020

Available clinical data for research

- Healthy women undergoing oocyte cryopreservation for age-related fertility loss
- Oocytes used in donor cycles

- The number of women who have returned to use frozen oocytes after fertility preservation indicated for malignant or benign medical indications is low.

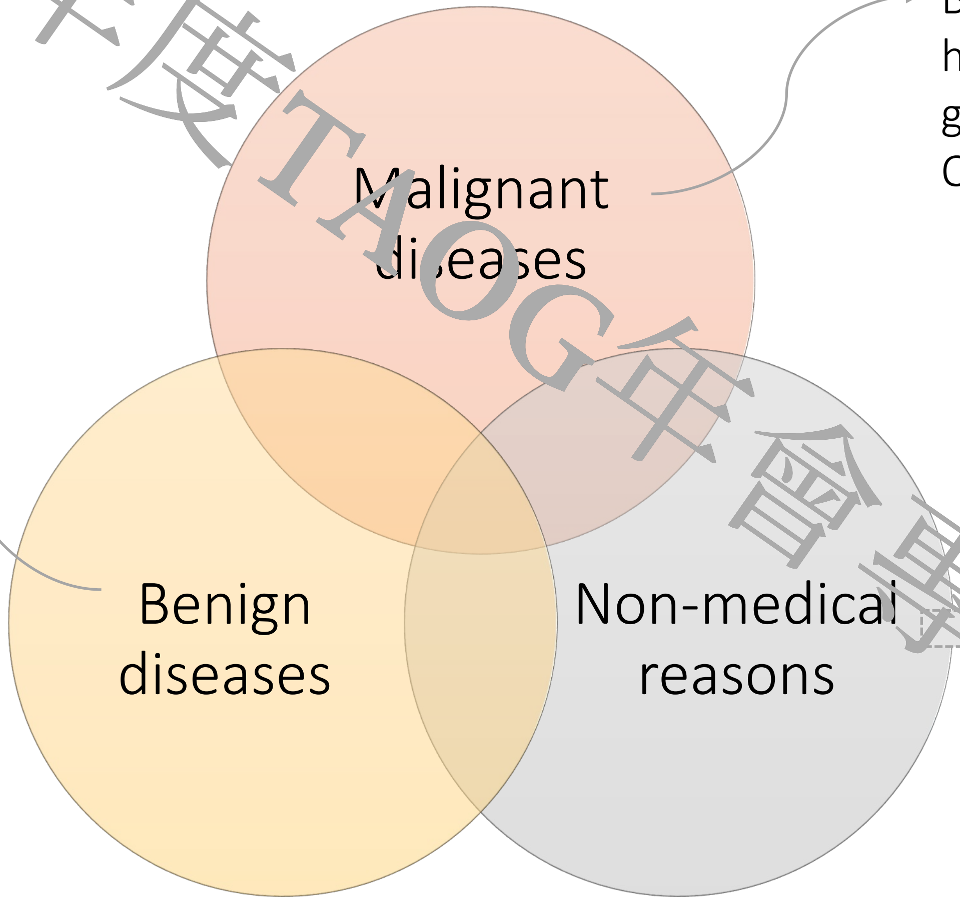
ESHRE Guideline Group on Female Fertility Preservation, 2020

Clinical aspect

Reasons for oocyte cryopreservation

Gynecological diseases:
endometriosis
ovarian cysts
borderline tumor.

Other benign diseases:
Autoimmune diseases
(systemic sclerosis, Wegener granulomatosis, systemic lupus erythematosus, ANCA-associated vasculitis);
Hematologic diseases
(thalassemia, sickle cell disease, aplastic anemia, Fanconi anemia, myeloproliferative syndromes).



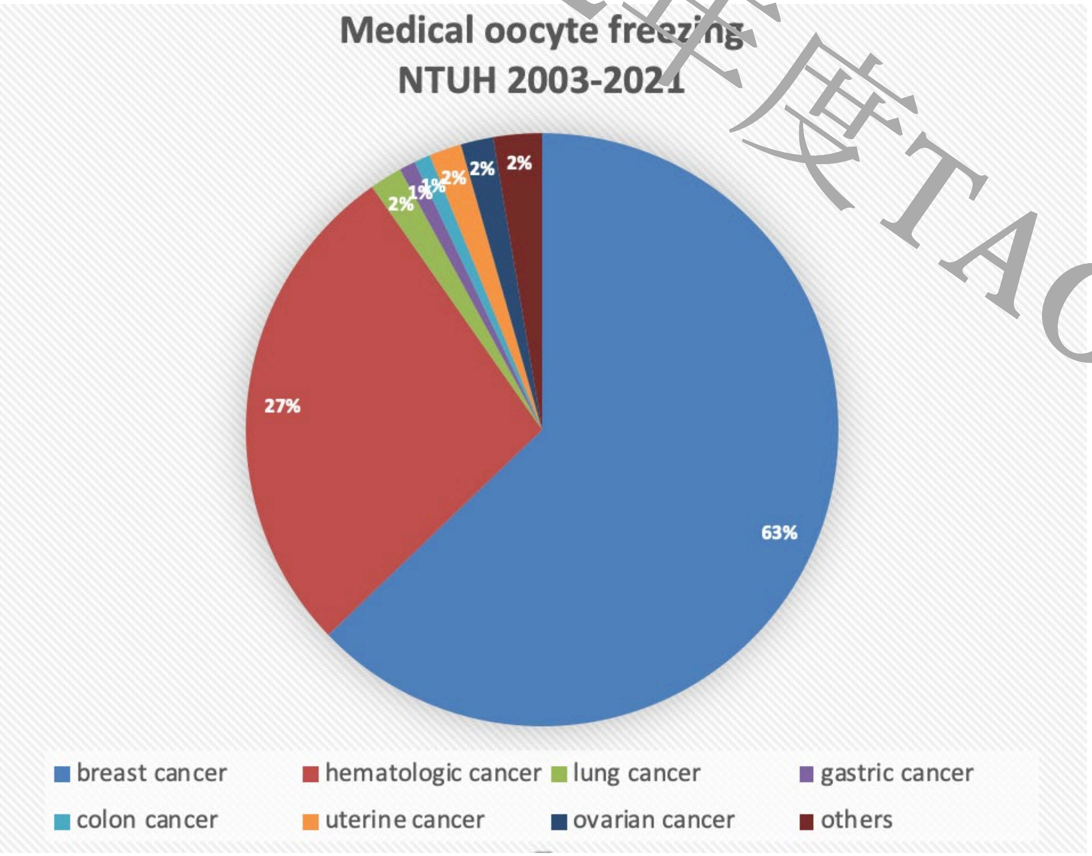
Breast cancer,
hematologic cancer,
gynecologic cancer,
Other cancers

Social/elective/planned,
age-related fertility loss

*Exclusions: male factors, religious reasons

ESHRE Guideline Group on Female Fertility Preservation, 2020

Challenges in patients of malignant diseases (1)



- Consultation for fertility preservation:
  - Expectations, costs, risks
  - Long-term risk of relapse
- Random start
- Letrozole or Tamoxifen for estrogen-sensitive cancer
- Prevention of ovarian hyperstimulation syndrome
  - Risk of severe OHSS may be increased when a long-acting GnRH agonist is used for ovarian suppression immediately following oocyte retrieval.[1]

1. Christ, et al., 2021

Case discussion

Severe OHSS

- 35 y/o woman
- Breast cancer
- Random start, OPU, 33 oocytes retrieved
- 10/31 OPU, s/p Dostinex 7 days
- 11/05 long-acting GnRH agonist
- 11/06 progressive bloated abdomen with oligouria => severe OHSS

Tx Cycle	M				10	10	10	10	10	10	10	10	10	10	10	10	10
	D				19	20	21	22	23	24	25	26	27	28	29	30	31
	#day				1	2	3	4	5	6	7	8	9	10	11	12	13
Rx	Orgalutran										1	1	1	1	1		OPU
	Lupro														1		
	Femara					1	1	1	1	1	1	2	2	2			
	Gonal-F					225	225	225	225	225	225	225	225	225			
	Ovidrel														0.5		
	Dostinex																1
Hor data	E2					69				263		1436		2481	2572		
	FSH					5.91											
	LH					10.4				3.79		7.21		3.57	1.24		
	P4									0.498		1.81		2.43	3.06		
	β-hCG																
U/S	R(mm)									10*3 -----x12		14*2 12*2 ....x20		20 16 15 14 13*3 12*4 11	20 17 15 14*2 13*6 12		
	L(mm)									11 10*2 8*2 ---x15		13*2 12*3 ....x15		15*3 14*3 13*4 11	19 18*2 17 16*3 15*2 14*2 13*2		
	E									5.3		6		5	7		

Challenges in patients of malignant diseases (2)

- Oocyte cryopreservation in critically-ill patients
  - Multidisciplinary approach
  - Anesthesiology evaluation
  - Pre-operative evaluation
  - Propofol use
  - Alternative "In hospital" procedure
  - Abnormal blood counts
  - Thromboembolic risk
  - Potential risk of cycle cancelation
  - Delayed cycle after chemotherapy

Table 1 Several unique steps for avoiding complications and maintaining patient safety

Ovarian stimulation in the acutely ill; essential steps for avoiding complications
• Regular and frequent communication between ALL members of the care team (oncologist, anesthesiologist, reproductive endocrinologist, internist)
• In person anesthesiology evaluation
• Conservative dosing of gonadotropins
• Required labs: CBC
• Labs to consider: BMP, AST/ALT, coagulation studies
• Imaging to consider: chest x-ray, ECHO
• Close monitoring by physicians of symptoms during stimulation
• Consideration of low dose hCG and FSH or Lupron for trigger
• Retrieval kit and setup for retrieval in main operating room if necessary
• Close monitoring by physicians of symptoms following stimulation, with low threshold for OHSS evaluation

Wald, et al., 2019

Table 8 Risk of treatment-induced gonadotoxicity in cancer patients associated with the main systemic gonadotoxic therapies

RISK CATEGORY	TYPE OF GONADOTOXIC TREATMENT
High risk **(> 80% risk of treatment-induced amenorrhoea)**	• Cyclophosphamide-based regimens (with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P, TC) in breast cancer patients aged ≥ 40 years • Conditioning regimens for HSC transplantation with cyclophosphamide and/or TBI in patients with haematological cancers • Abdominal and pelvic radiotherapy to a field that includes the ovaries
Intermediate risk **(40%-60% risk of treatment- induced amenorrhoea)**	• Cyclophosphamide-based regimens (with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P, TC) in breast cancer patients aged 30-39 years • Alkylating agent-based regimens (e.g. MOPP, RSQB, BEACOPP, CHOP, CHOPE) in lymphoma patients
Low risk **(< 20% risk of treatment-induced amenorrhoea)**	• Cyclophosphamide-based regimens (with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P, TC) in breast cancer patients aged ≤ 30 years • Non-alkylating agent-based regimens (e.g. ABVD or EBVP) in lymphoma patients aged ≥ 32 years • BEP / EP in patients with non-epithelial ovarian cancers • FOLFOX, XELOX or capecitabine in patients with colorectal cancers • Multi-agent chemotherapy (EMA-CO) and platinum-based combinations) for gestational trophoblastic tumours • Radioactive iodine (I-131) in patients with thyroid cancer
Very low or no risk	• Targeted agents (trastuzumab, lapatinib and rituximab) ? • Tamoxifen and GnRH analogue • Non-alkylating agent-based regimens (e.g. ABVD or EBVP) in lymphoma patients aged < 32 years • Single-agent methotrexate
Unknown risk	• Platinum- and taxane-based chemotherapy in patients with gynaecological and lung cancers • Majority of targeted therapies (monoclonal antibodies and small molecules like tyrosine kinase inhibitors) and immunotherapeutic agents

ESHRE Guideline Group on Female Fertility Preservation, 2020

Case discussion

Thrombocytopenia

- 22 y/o woman
- Myelodysplastic syndrome with excess blasts
- Random start, OPU, 17 oocytes retrieved, 14 MII frozen
- 2022/02/09 Hb 8.6 g/dL, PLT 26 K/uL
- 2022/02/20 Hb 8.1 g/dL, PLT 16 K/uL
- transfusion goal: PLT > 50 K/uL, Hb > 8 g/dL
- IVIG, PLT 24U since midnight, F/U CBC 6am
- 2023/02/20 FSH 93.07 mIU/ml, E2 <5 pg/ml

Tx Cycle	M				02	02	02	02	02	02	02	02	02	02	02	02	02	02	02	
	D				07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	
	#day				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Rx	Orgalutran													1(pm)	1	1			OPU	
	Lupro																1			
	Gonal-F						100	100	100	100	100	100	100	100	100	100				
	Menopur						75	75	75	75	75	75	75	75	75	75				
	Ovidrel																0.5			
Hor data	E2						<5					252		966		1151				
	FSH						2.22													
	LH						0.588					0.234		1.34		0.116				
	P4						<0.20					<0.2		0.529		0.587				
	β-hCG																			
U/S	R(mm)					small						12 11*3 10 9*2		14 12 11 10*3 9 8 7		17*2 16*2 15 14 13*2 ...x18				
	L(mm)					small						11*3 10 9 8*2 6*2		14*2 12*2 11 10*2 9 8		18*2 17 16 14*3 13 12 11 ...x18				
	E					0						3.8		7.2		8.1				

Case discussion

Elevated liver enzymes

- 22 y/o woman
- EBV-associated gamma-delta T-cell lymphoma
- Random start, OPU, 6 oocytes retrieved

	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)
05/03	51	24	134	97
05/17	1847	1209	490	232

- Consult anesthesiologist before OPU
- Post-operative admission
- Expired 3 months later due to disease pogression

Tx Cycle	M				05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
	D				03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18
	#day				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Rx	Orgalutran														1	1	1	1		OPU
	Gonal-F						150	150	150	150	200	200								
	Menopur												3	3	3	3	3			
	Ovidrel																	1		
Hor data	E2						51				114		256		467					
	FSH						5.14													
	LH						4.50				2.10		0.863		0.261					
	P4						1.09				<0.20		<0.20		<0.20					
	β-hCG																			
U/S	R(mm)				16x1[illegible]cyst						9 <8X3		11*2 10 9*2 8*2		15 14 13 12*4					
	L(mm)										<8X4		10 9 6		13*2 9*2					
	E				5.1						3.8		--		7					

Benign diseases

Table 9 Overview of benign medical diseases for which ovarian reserve testing has been performed

Disorder/Disease	Observations of ovarian reserve tests	Reference
Autoimmune diseases		
Autoimmune thyroid disease	Lower pre-treatment AMH levels than HC	(Magri, et al. 2015, Saglam, et al. 2015)
Rheumatoid arthritis	Lower pre-treatment AMH levels than HC	(Henes, et al. 2015)
Early rheumatoid arthritis	Same AMH levels than HC	(Brouwer, et al. 2013)
Juvenile Idiopathic arthritis	Lower AMH levels than HC, AMH levels not related to time to pregnancy	(Ferreira, et al. 2019)
Spondyloarthritis	Lower pre-treatment AMH levels than HC	(Henes, et al. 2015)
Behçet's disease	Lower pre-treatment AMH levels than HC	(Henes, et al. 2015)
	No difference in AMH, AFC, FSH or LH levels with HC	(sahln, et al. 2017)
Antiphospholipid syndrome	More patients with low AFC count and AMH levels	(Yamakami, et al. 2014)
	Antiphospholipid levels in blood were correlated to AMH levels in infertile women	(Vega, et al. 2016)
Takayasu arteritis	More patients with low AFC count and AMH levels	(Mont'Alverne, et al. 2015)
Crohn's disease	Lower AMH levels in >30 years old	(Freour, et al. 2012)
	Lower AMH levels if disease is restricted to colon	(Freour, et al. 2012)
	Lower AMH levels in patients. AMH levels inversely correlate to disease activity index.	(Senates, et al. 2013)
IBD patients treated with Thalidomide	Treatment with thalidomide decreases AMH levels and AFC	(Peng, et al. 2017)
Granulomatosis with polyangiitis	Treatment with CP decreases AMH levels	(Clowse, et al. 2011)
Wegener's syndrome	CP decreases AMH levels in patients	(Clowse, et al. 2011)
Multiple sclerosis	Lower AMH, AFC and ovarian volume in high disease activity index patients	(Sepulveda, et al. 2016)
	Lower AFC and OV, higher LH in MS treated with immunomodulatory drugs compared to HC	(Cil, et al. 2009)
Sjogren's syndrome	Lower AMH, AFC and higher LH in patients compared to HC	(Karakus, et al. 2017)
Fragile X and Turner Syndrome		
Fragile X syndrome	Lower AMH, AFC and OV in carriers versus non-carriers	(Tsafrir, et al. 2010)
	Lower AMH levels in longer sequence repeats than shorter sequence repeats	(Rohr, et al. 2008)
	Higher FSH in carriers	(Welt, et al. 2004)
	No correlation between FSH and the number of CGG repeats in fragile X premutation carriers,	(Welt, et al. 2004)
Turner Syndrome	AMH correlates to ovarian function	(Hagen, et al. 2010)
	AMH levels associate to spontaneous pubertal development	(Hamza, et al. 2018)
Other diseases		
Galactosemia	Lower AMH than HC	(Sanders, et al. 2009)
	AMH correlates to spontaneous menarche	(Frederick, et al. 2018)
Fanconi Anaemia	Lower AMH than HC	(Sklavos, et al. 2014)
Sickle cell disease	Lower AMH than HC	(Kopeika, et al. 2019)
Beta Thalassemia	Lower AMH and AFC in women with transfusion dependent beta thalassemia than HC	(Talaulikar, et al. 2019)
Diabetes I	Lower AMH and Inhibin B, than HC (Specially at later reproductive ages)	(Kim, et al. 2016, Wellons, et al. 2017)
Bone Marrow Syndrome	Lower AMH than HC	(Sklavos, et al. 2015)
Interventions		
Gender reassignment	AMH levels reduced after GnRH and testosterone treatment in gender reassignment	(Caanen, et al. 2015)

ESHRE Guideline Group on Female Fertility Preservation, 2020

Challenges in elective oocyte freezing

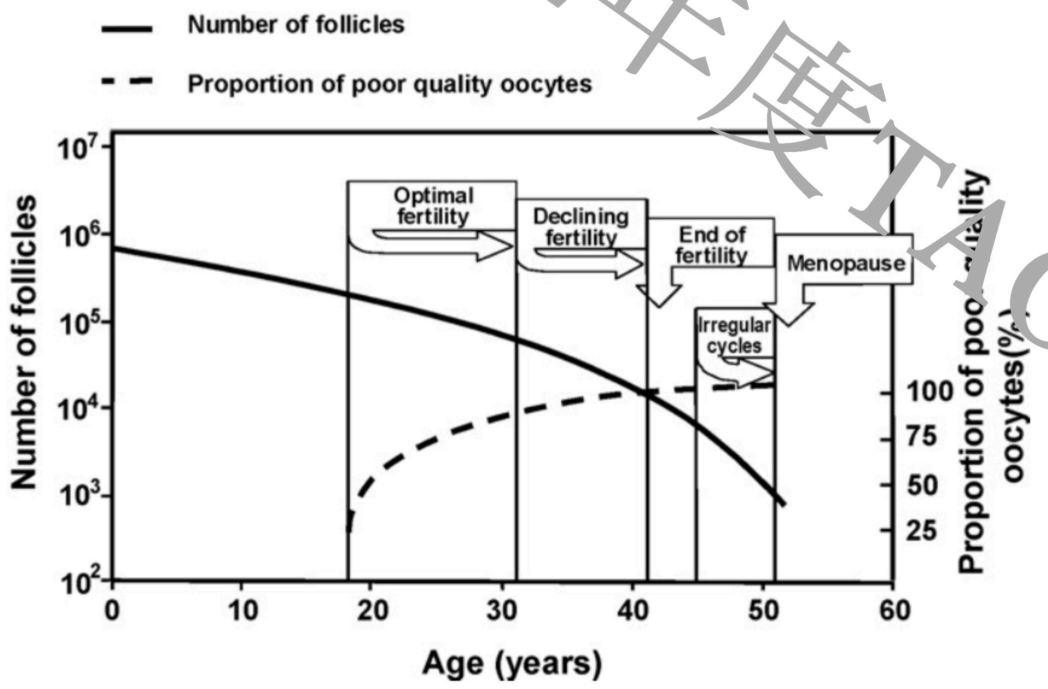
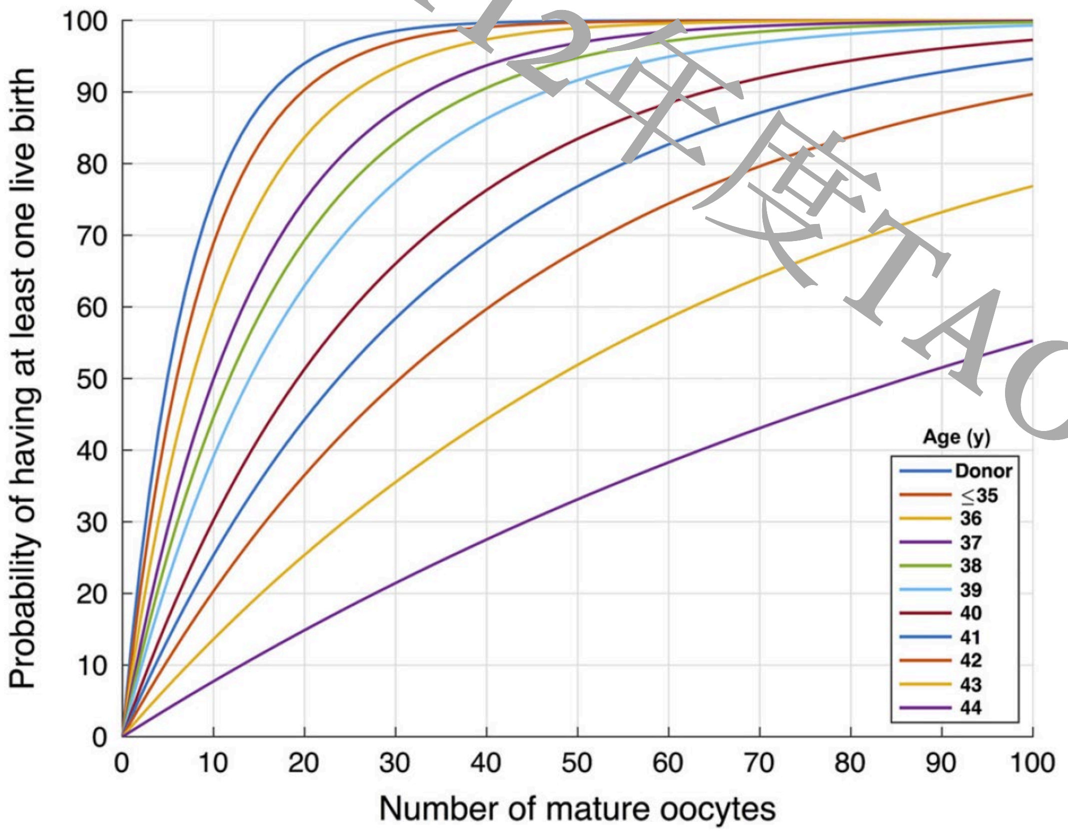


Fig. 1. The decline in follicle number and the increase in the proportion of poor quality oocytes in relation to reproductive events with increasing female age (redrawn after [18,19]).

- The provision of information of women with childbearing plans and delaying pregnancy for social reasons
- Decision aids to support patients' decision making; to decrease decisional conflict or decisional regret

Lambalk, et al., 2009

Prediction model



$$p(blast) = 0.95 * \exp(2.8043 - 0.1112 \times Age)$$

$$p(\text{livebirth}) = 1 - [1 - 0.6p(\text{euploid}) \times p(\text{blast})]^{\text{Number of mature oocytes}}$$

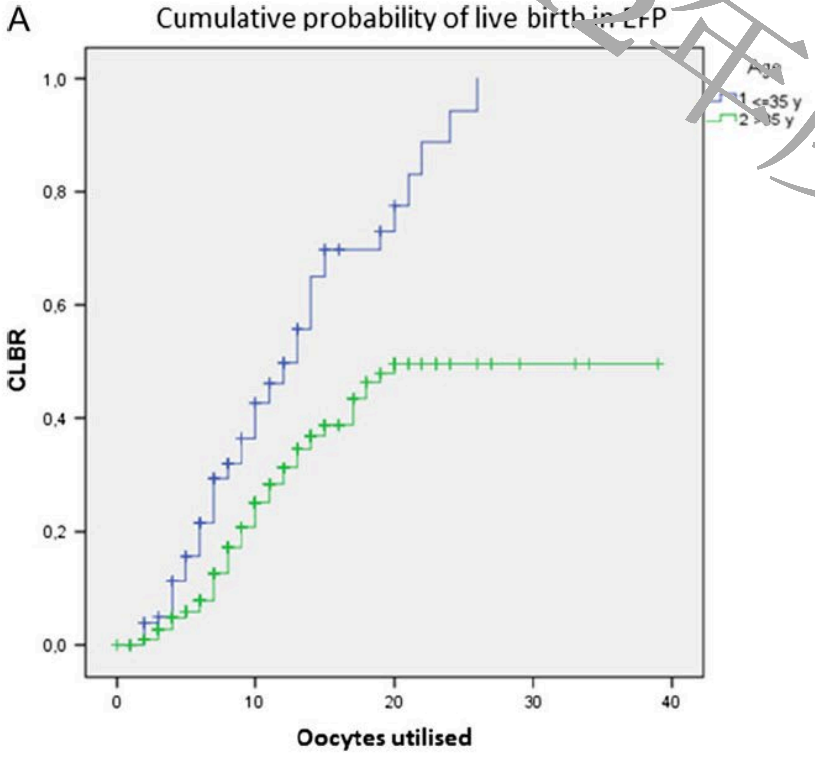
- Data extrapolated from oocyte donors and IVF patients with normal ovarian reserve (male or tubal factor).
- Exclusions: (1) hydrosalpinx (2) diminished ovarian reserve (3) PGD/PGS
- Assumptions
  - Oocyte survival rate 95% if <36 y/o; 85% if > or = 36 y/o (predict)
  - Fertilization rate 73% (cohort)

Goldman, et al., 2017

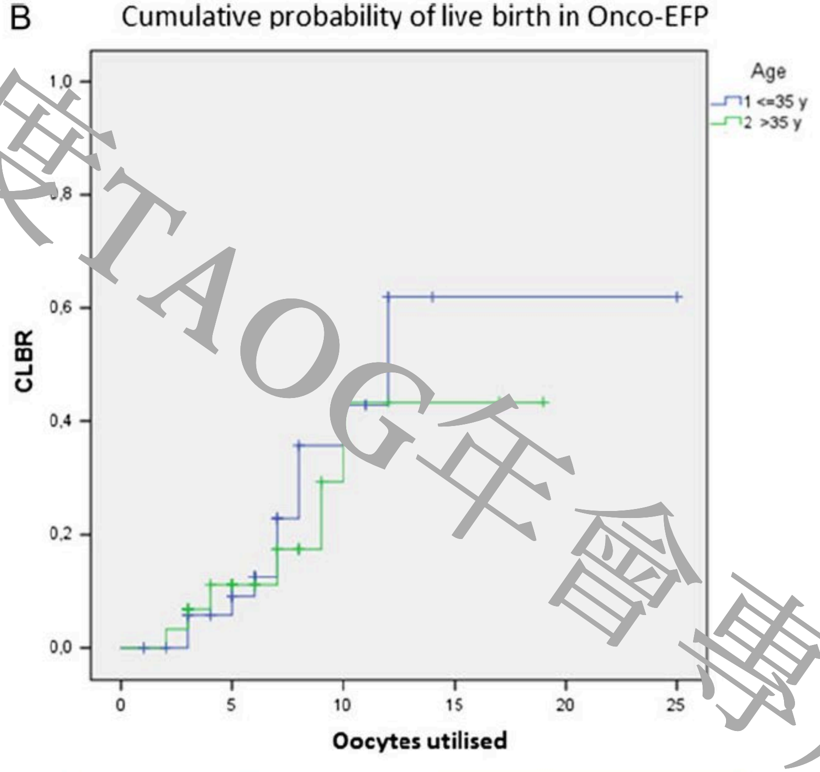
Real world data

Articles	Author / Hospital	Design	Facility	Study duration	Mean age of OC	Frozen oocytes	Thaw case	Oocyte survival rate	Fertilization rate	Live birth rate	OC method	
HR 2018	A. Cobo / IVI	Retrospective cohort	Multicenter	2007-2018	37.2 ± 4.9	9.8 ± 6.4	641	83.90%		CLBR 33.9%	Vitrification	
AOGS 2019	A Wennberg / Sweden	Retrospective cohort	Single center	2011-2017	36.9	7.6	38	78%	62%	CLBR 26.3%	Vitrification	
JARG 2019	ZB Gürtin / UK	Retrospective	Two center	2008-2017	37.7	14	46			17.4% per patient	Vitrification	
RBMO 2021	AQ Leung / Boston, USA	Retrospective cohort	Single center	2006-2020	38.1 ± 1.8		68	V=84.9%, S=57.1%	74%	CLBR 32.4% (22/68)	SF and vitrification	
JARG 2022	A Tsafrir / Israel	Retrospective cohort	Single center	2011-2018	37.9 ± 2.0	10.3±8.2	57	78%	65%	CLBR 27%	Vitrification	
FS 2022	SD Cascante / NY, USA	Retrospective	Single center	2004-2020	38.3	14 (MII 12)	543	79%	66%	CLBR 39%	SF and vitrification	
AGO 2022	LS Kasaven / London, UK	Retrospective cohort	Single center	2008-2018	38	8 (MII 6)	36	81%/76%/67.5%	53%/68%/58%	29.7% per ET	Vitrification	≤ 35, 36–39, ≥ 40
RB&E 2022	IJ Yang / NTUH, TW	Retrospective cohort	Single center	2002-2020	37.5±3.8	11 (MII 9)	54	73.7% MII 76.8%	66.3%	CLBR 38.9%	SF and vitrification	
JCM 2023	P Kakkar / London, UK	Retrospective cohort	Single center	2016-2022	37.1	9.5	27	74%	67%	35% per ET	Vitrification	

Success rates: elective vs oncologic patients



Age ≤35. N = 123		Age >35. N = 518	
Nºoocytes	CLBR(95%CI)	Nºoocytes	CLBR(95%CI)
5	15.8 (8.4-23.1)	5	5.9 (3.6-8.3)
8	32.0 (22.1-41.9)	8	17.3 (13.3-21.3)
10	42.8 (31.7-53.90)	10	25.2 (20.2-30.1)
15	69.8 (57.4-82.2)	15	38.8 (32.0-45.6
20	77.6 (64.4-90.9)	20	49.6 (40.7-58.4)
24	94.4 (84.3-100.4)		



Age ≤35. N = 42		Age >35. N = 38	
Nºoocytes	CLBR(95%CI)	Nºoocytes	CLBR(95%CI)
5	9.1 (-0.7-19)	4	11.1 (-0.8-23.1)
8	35.8 (14.3-57.2)	9	29.3 (3.7-54.8)
10	42.9 (19.7-66.1)	10	43.4 (11.3-75.3)
12	61.9 (35.4-88.5)		

small sample size of the patients who returned to attempt pregnancy

Cumulative live birth rate

	≤35 y/o	>35 y/o
EFP	68.8%	25.5%
Onco-FP	42.1%	20.0%

Cobo, et al., 2018

Socio-economical aspect

Return rate / Usage rate

Cost-effectiveness analysis

Return rate (Usage rate)

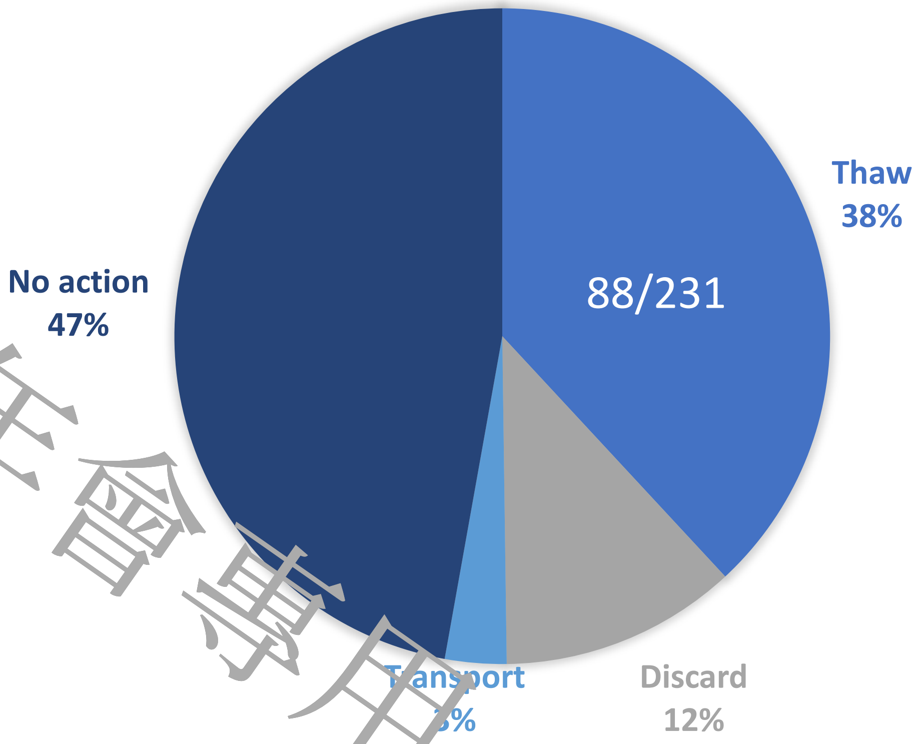
Articles	Author / Hospital	Design	Facility	Study duration	Mean age of OC	Freeze case	Thaw case	Return rate	Donor sperm
HR 2018	A. Cobo / IVI	Retrospective cohort	Multicenter	2007-2018	37.2 ± 4.9	5289	641	12.1%	41.7% (Cobo 2016)
AOGS 2019	A Wennberg / Sweden	Retrospective cohort	Single center	2011-2017	36.9	254	38	14.96%	available for lesbian or heterosexual couples with absolute male factor infertility
RBMO 2021	AQ Leung / Boston, USA	Retrospective cohort	Single center	2006-2020	38.1 ± 1.8	921	68	7.40%	35.30%
JARG 2022	A Tsafrir / Israel	Retrospective cohort	Single center	2011-2018	37.9 ± 2.0	4[illegible]6	57	13.00%	39%
AGO 2022	LS Kasaven / London, UK	Retrospective cohort	Single center	2008-2018	38	373	36	9.70%	36%
JOGC 2022	R Harjee / Canada	Retrospective cohort	Single center	2013-2022	36.5	556	50	8.99%	NA
RB&E 2022	IJ Yang / NTUH, TW	Retrospective cohort	Single center	2002-2020	37.5±3.8	645	54	8.40%	0
JCM 2023	P Kakkar / London, UK	Retrospective cohort	Single center	2016-2022	37.1	165	27	16%	

Long-term data (Blakemore et al. 2021 FS)

Planned oocyte cryopreservation—10–15-year follow-up: return rates and cycle outcomes

Jennifer K. Blakemore, M.D., M.Sc., James A. Grifo, M.D., Ph.D., Shannon M. DeVore, M.D., Brooke Hodes-Wertz, M.D., and Alan S. Berkeley, M.D.
New York University Langone Fertility Center, New York, New York

- Retrospective cohort study
- Patients underwent ≥ 1 cycle of planned oocyte cryopreservation between 2005-2009.
- This time frame was chosen specifically for its 10–15-year span since the first retrieval to represent the cohort of patients most likely to have a final disposition on their oocytes.
- 37.5% with donor sperm.
- Of these, 20 had nothing for ET (arrested/aneuploid), and of the 60 who had ≥ 1 ET, 27 had a total of 32 infants, with a live birth rate of 33.8% (27/80).



Elective vs oncofertility (Cobo et al. 2018 HR)

Elective and Onco-fertility preservation: factors related to IVF outcomes

A. Cobo[1,*], J. García-Velasco[2], J. Domingo[3], A. Pellicer[1], and J. Remohí[1]

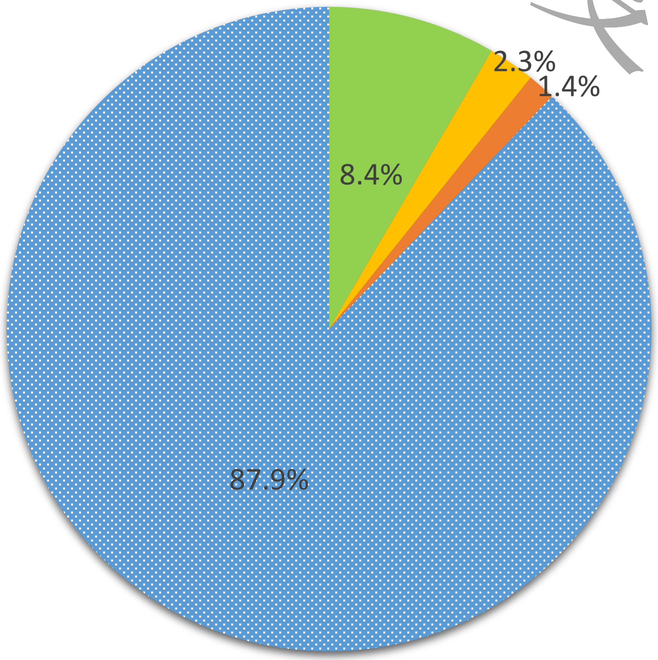
[1]IVIRMA-Valencia, Plaza de la Policía Local 3, 46004 Valencia, Spain [2]IVIRMA-Madrid, Av. del Talgo, 68, Palmas, Av. Juan Carlos I, 17, Edificio Corona, 35010 Las Palmas de Gran Canaria, Las Palmas, Spain

- Retrospective cohort study, multicenter, 2007-2018
- Elective 5289 women (EFP)
- Oncological 1073 women (Onco-FP)

	EFP	Onco-FP	P value
Mean age at FP	37.2 ± 4.9	32.3 ± 3.5	<0.0001
Return rate	641 /5289 (12.1)	80/1073 (7.4)	<0.0001
Mean age at vitrification	37.6 ± 3.5	34.8 ± 2.1	<0.0001
Mean storage time (years)	2.1 ± 1.6	4.1 ± 0.9	<0.0001
Cumulative Live births/Patient (%)	162/477 (33.9)	25/71 (35.2)	0.835

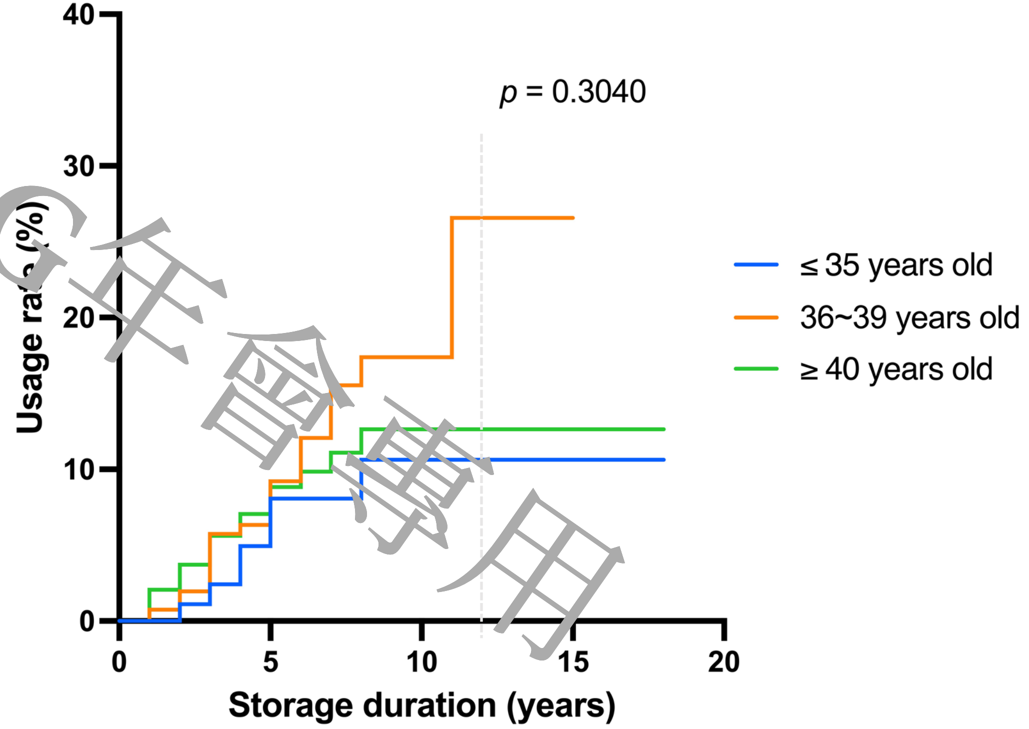
Data from NTUH (Yang et al. 2022)

Overall Usage Rate 8.4%



Median of storage duration: 3.0 (1.4-4.7) years.

Cumulative incidence among the different age groups at oocyte freezing



Cost-effectiveness analysis

Costs

Effectiveness

Cost-effectiveness analysis (1)
Loendersloot et al. 2011 HR. The Netherlands.

Expanding reproductive lifespan: a cost-effectiveness study on oocyte freezing

L.L. van Loendersloot*, F. van der Veen, and M.
Center for Reproductive Medicine, Department
1105 AZ Amsterdam, The Netherlands

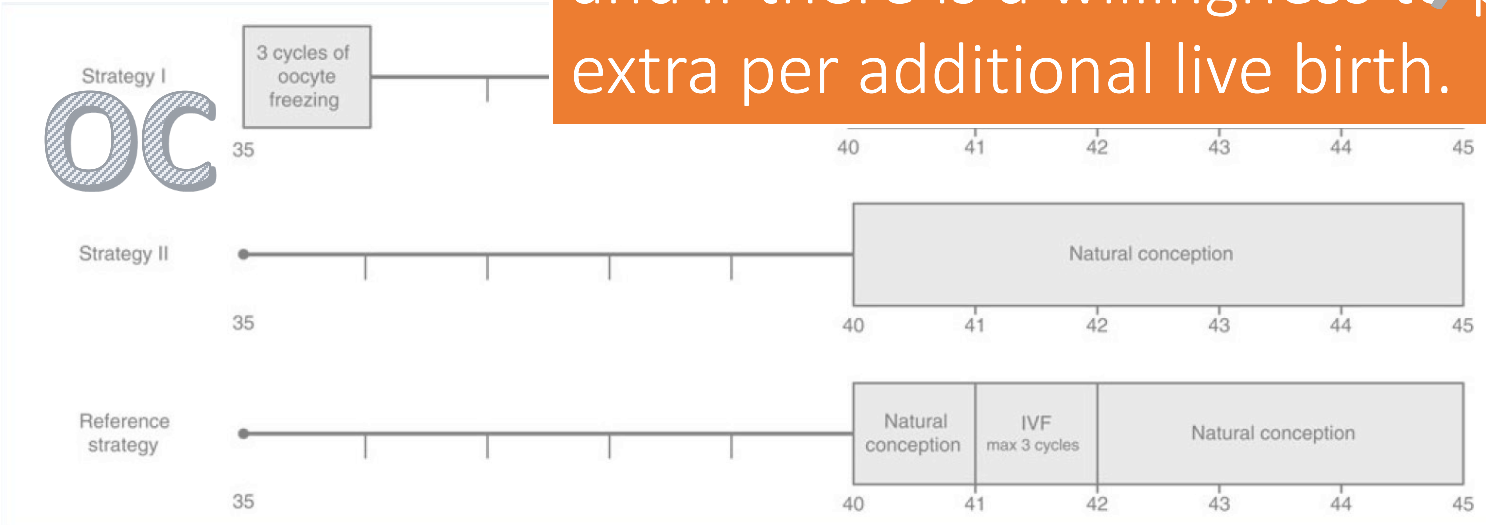
- Assumption: 35 y/o women want to postpone their child-bearing until they are 40.
- Reimbursement of 3 cycles of IVF in the Netherlands.

*ICER: the extra costs per additional live birth.

cost-effective the strategy.

		Costs per live birth	ICER*
		€12,326 43萬	€13,156 46萬
52.3%	€310	€593 2萬	€60,717 212萬
64.6% (31.4+33.2)	€7,798	€12,071 42萬	(ref)

Oocyte freezing is cost-effective, if at least 61% of the women return to collect their oocytes and if there is a willingness to pay €19,560 extra per additional live birth.



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Cost-effectiveness analysis (2)
Hirshfeld-Cytron et al. 2012 FS. Illinois, USA.

Fertility preservation for social indications: a cost-based decision analysis

Jennifer Hirshfeld-Cytron, M.D., M.S.C.I.,[a] William A. Grobman, M.D., M.B.A.,[b] and Magdy P. Milad, M.D., M.P.H.[a]

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- Assumption: 25 y/o women want to postpone their child-bearing until they are 40.
- All women at age 40 attempted natural conception for 6 months before using ART.

Cost and effectiveness outcomes.

Strategy	Cost	Marginal cost	Effectiveness (Live birth)	Marginal effectiveness	Marginal cost-effectiveness
No action taken at age 25	16,000		0.7183		
Oocyte cryopreservation	26,000	10,000	0.7922	0.0738	135,520
OTC	27,000	2,000	0.7320	–0.0601	Dominated

Hirshfeld-Cytron. Fertility preservation for social reasons. Fertil Steril 2012.

OC

Cost-effectiveness analysis (3)
Devine et al. 2015 FS. Texas, USA.

Baby budgeting: oocyte cryopreservation in women delaying reproduction can reduce cost per live birth

Kate Devine, M.D.,[a] Sunni L. Mumford, Ph.D.,[b] Kara N. Goldman, M.D.,[c] Brooke Hodes-Wertz, M.D., M.P.H.,[c]
Sarah Druckenmiller, B.S.,[c] Anthony M. Propst, M.D.,[d] and Nicole Noyes, M.D.[c]

- Assumption: 35 y/o women want to postpone their child-bearing until they are 40.
- All women at age 40 attempted natural conception for 6 months before using ART.

Strategy	Live birth ra
OC => TO	62%
OC => IVF => TO	74%
No OC => IVF	42%

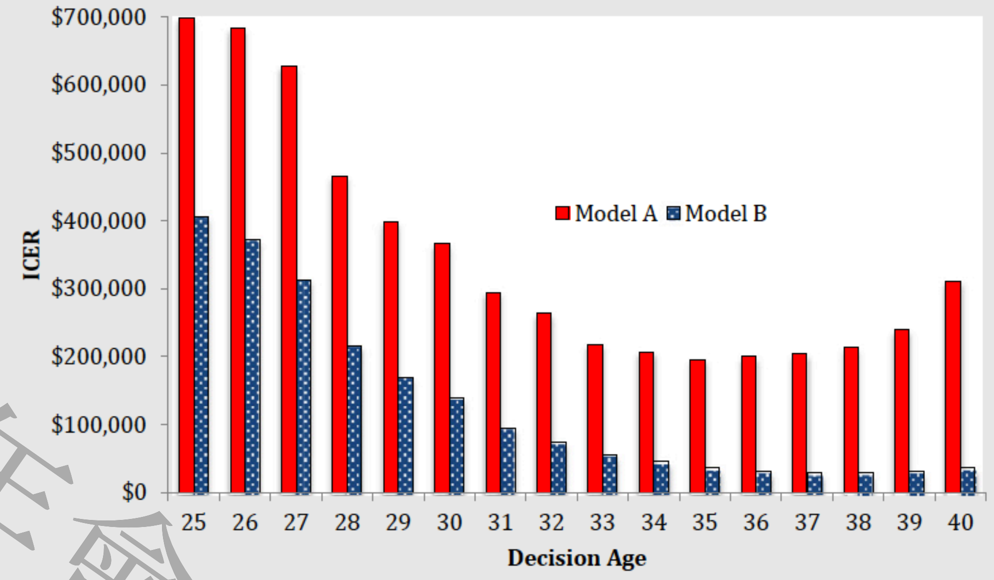
Oocyte cryopreservation was determined to be cost effective when more than 49% of those women, who did not achieve a live birth after 6 months of attempting spontaneous pregnancy at age 40 years, returned to thaw their oocytes for fertilization and ET.

Cost-effectiveness analysis (4)
Mesen et al. FS 2015. North Carolina, USA.

Optimal timing for elective egg freezing

Tolga B. Mesen, M.D.,[a] Jennifer E. Mersereau, M.D., M.S.C.I.,[a] Jennifer B. Kane, Ph.D.,[b] and Anne Z. Steiner, M.D., M.P.H.[a]

- The model was run at each decision age from 25 to 40 years, allowing for an age-based estimate of the LBR and of the cost per live birth.
- Model A: assumed that a woman will only attempt to conceive after marriage and included the probability of marriage by the horizon age in the decision tree.
- Model B: assumed that all women would attempt pregnancy at the horizon age regardless of marital status (with a spouse, partner, or donor sperm).



Cost per additional live birth at horizon age when electing to cryopreserve oocytes versus no action at decision age, which is presented on the x axis. Model A represents women requiring marriage before attempting pregnancy. Model B represents women who do not require marriage before attempting pregnancy (will attempt pregnancy with husband, donor sperm, or unmarried male partner).

Mesen. Timing of elective egg freezing. Fertil Steril 2015.

Cost-effectiveness analysis (4)
Mesen et al. FS 2015. North Carolina, USA.

1. What is your current age?

- select -

2. How long do you think you will wait before attempting to conceive?

- select -

3. If you do not have an intimate male partner in the time frame chosen above, would you use donor sperm to help you conceive without a partner?

- select -

Calculate

https://uncfertility.com/treatment-options/egg-calculator/

Cost-effectiveness analysis (5) Klüber et al. 2020 Arch G Obstet. Germany.

Cost-effectiveness of social oocyte freezing in Germany: estimates based on a Markov model

C. M. Klüber[1] · B. H. Greene[2] · U. Wagner[1] · V. Ziller[1]

- Assumption: postponing pregnancy until the age of 40 for various reasons.

	Cumulative live birth rate (%)	Cost per woman (€)	Cost per live birth (€)
Strategy 1: Freezing oocytes at different ages, IVF and ICSI with frozen oocytes at age 40			
Oocytes cryopreserved with 25	71.4	17,512	24,526
Oocytes cryopreserved with 28	69.9	16,632	23,794
Oocytes cryopreserved with 30	71.1	15,939	22,418
Oocytes cryopreserved with 35	70.9	18,086	25,520
Oocytes cryopreserved with 38	67.6	17,299	25,590
Strategy 2: Spontaneous conception	51.5	–	–
Strategy 3: Women of age 40, IVF/ IVF and ICSI with fresh oocytes after 1 year of subfertility	60.8	12,338	20,293

Although social freezing could lead to additional live births it is still far from what it seems to promise as far as cost-effectiveness is concerned.
The opportunity to freeze oocytes of higher quality for later use must not be mistaken as a guarantee of achieving a live birth.

Cost-effectiveness analysis (6)
Bakkensen et al. FS 2022. Illinois, USA.

A SART data cost-effectiveness analysis of planned oocyte cryopreservation versus in vitro fertilizatio[n with preimplantation] genetic te[sting] considerin[g]

Jennifer B. Bakkensen, M.D.,[a] K[…]
Anne P. Hutchinson, M.D.,[a,e] Ela[…]
Eve C. Feinberg, M.D.,[a] and Kar[…]

- In each strategy, a patient desires delayed childbearing and pursues no OC or 1 or 2 cycles OC at age 33.
- Patients desiring 1 LB attempt conception at age 43 for up to 6 months, whereas patients desiring 2 LB attempt conception at age 40.

Probability of live birth and cost-effectiveness by delayed reproduction treatment strategy

Treatment strategy	Probability of ≥ 1 LB	Probability of 2 LB	Average individual cost	Maximum individual cost	Cost per percentage point increase in success, 1 LB	Cost per percentage point increase in success, 2 LB
Desires 1 child						
No OC + IVF/PGT	50%	0%	$62,708	$84,536	*Ref*	
OC	73%	0%	$30,333	[illegible]	−$1,376	
Desires 2 children						
No OC + IVF/PGT without embryo banking	76%	19%	$79,057	$145,518	*Ref*	*Ref*
No OC + IVF/PGT with embryo banking	78%	48%	$79,728	$97,802	$278	$23
OC 1 cycle + IVF/PGT	93%	61%	$76,100	$122,528	−$176	−$71
OC 2 cycles	94%	77%	$52,479	$63,092	−$1,441	−$458

See Figure 1 and methods for a detailed description of each treatment strategy. Negative cost per percentage point increase in live birth reflects a net cost savings. OC, oocyte cryopreservation; IVF/PGT, in vitro fertilization with preimplantation genetic testing for aneuploidy; LB, live birth; *Ref*, referent strategy.

Bakkensen. Cost-effectiveness of planned OC. Fertil Steril 2022.

Cost-effectiveness analysis (7) oncofertility Schumacher et al. HR 2017. North Carolina.

Modeling of live-birth rates and cost-effectiveness of oocyte cryopreservation for cancer patients prior to high- and low-risk gonadotoxic chemotherapy

B. Lyttle Schumacher[1,*], N. Grover[2], T. Mesen[3], A. Steiner[1], and J. Mersereau[1]

[1]Obstetrics and Gynecology, Division of Reproductive Endocrinology, University of North Carolina, Chapel Hill, NC 27599, USA [2]Hematology, University of North Carolina, Chapel Hill, NC 27599, USA [3]Carolinas Fertility Institute, 2614 E 7th St. Suite C, Charlotte, NC 28205, USA

- When comparing FP–OC to no FP–OC, maximum improvement in LBR was achieved at age 37 for LRC and at age 27 for HRC.
- When patients who received LRC or HRC chose not to
- undergo FP–OC, their probability of LB after attempting natural conception and IVF-T was a maximum of 56 and 14% respectively

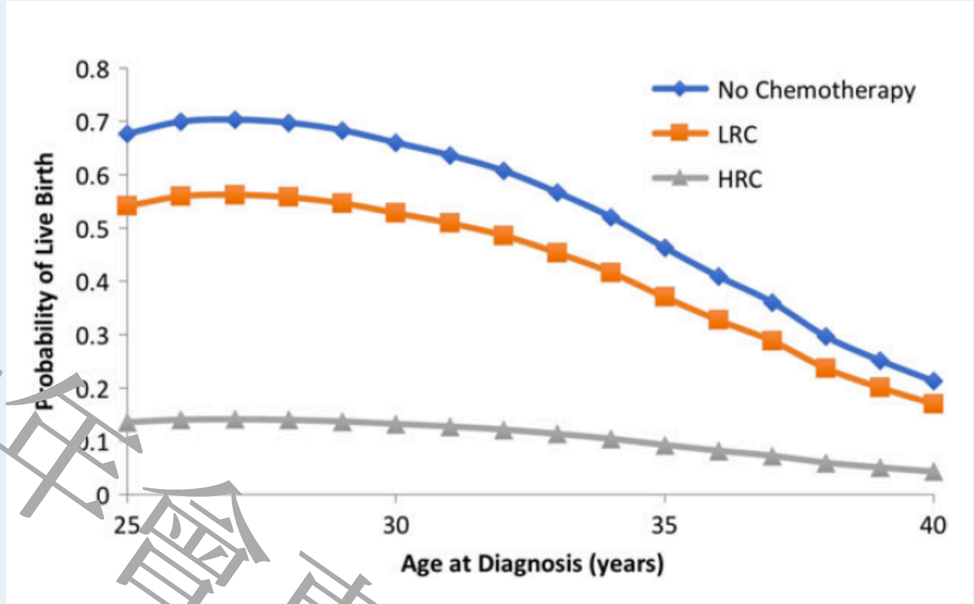


Figure 2 The y axis represents the probability of live birth after 6 months of attempted conception beginning 5 years from the time of diagnosis. Probabilities of live birth are shown after treatment with low-risk chemotherapy (LRC) or high-risk chemotherapy (HRC). Probability of live birth with no cancer diagnosis and therefore no treatment is shown for comparison. Age at diagnosis is presented on the x axis.

Cost-effectiveness analysis (7) oncofertility Schumacher et al. HR 2017. North Carolina.

Modeling of live-birth rates and cost-effectiveness of oocyte cryopreservation for cancer patients prior to high- and low-risk gonadotoxic chemotherapy

B. Lyttle Schumacher[1,*], N. Grover[2], T. Mesen[3], A. Steiner[1], and J. Mersereau[1]

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When undergoing FP–OC prior to LRC, women between ages 35 and 40 years had the lowest ICER suggesting cost effectiveness is maximized in this age group. In contrast, patients undergoing HRC received the greatest benefit for the lowest cost at younger ages (25–30 years).

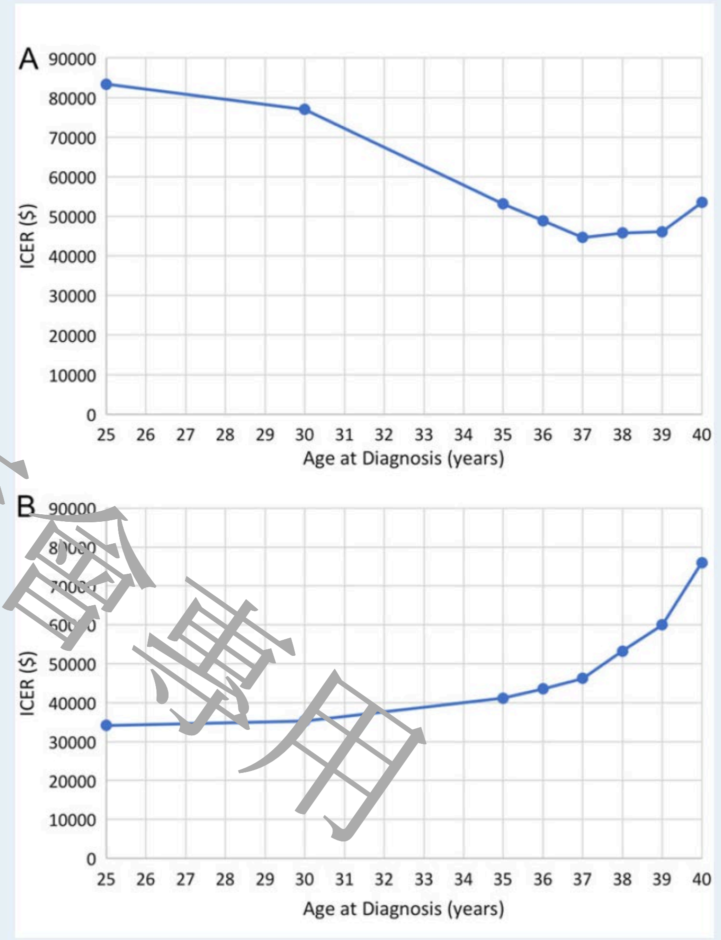


Figure 4 Cost per additional live birth after fertility preservation with oocytes (FP–OC) at 5 years from cancer diagnosis for both low-risk chemotherapy (LRC) (**A**) and high-risk chemotherapy (HRC) (**B**).

Data from NTUH (Yang et al. 2022)

Table 3 Cumulative costs and cost-effectiveness analysis

	Total		Age ≤ 35 years		Age 36–39 years		Age ≥ 40 years		P value
Freezing cases	645		189		263		193		
Thawing cases	54		11		26		17		
Embryo transfer cases	41		11		21		9		
Delivery cases	17		6		8		3		
Total live births	21		7		11		3		
Cumulative live birth/thawed case	21/54 (38.9)		7/11 (63.6)		11/26 (42.3)		3/17 (17.6)		0.045
Oocyte freezing cycles per case, mean ± SD	1.28 ± 0.25		1.09 ± 0.20		1.46 ± 0.51		1.11 ± 0.17		0.608
Storage duration, y	3.0 (1.4–4.7)		3.4 (2.6–4.3)		3.1 (2.2–5.2)		2.8 (1.2–4.3)		0.817
Cost for oocyte freezing/cycle, USD	$3131 ($2843-$3404)		$3264 ($3092-$3474)		$3213 ($2864-$3442)		$2903 ($2681-$3066)		0.187
Cost for oocyte freezing/case, USD	$3223 ($2903-$3474)		$3343 ($3217-$3490)		$3237 ($2970-$3580)		$2951 ($2806-$3346)		0.202
Cost for oocyte thawing/cycle, USD	$1873 ($1152-$2127)		$1894 ($1498-$2502)		$1987 ($1384-$2188)		$1855 ($743-$1890)		0.474
Cost for oocyte thawing/case, USD	$2101 ($1855-$3177)		$3044 ($1899-$3738)		$2125 ($1873-$[illegible])		$1856 ($1011-$1922)		0.015
Cumulative cost/case, USD	$6905 ($5916-$8471)		$7444 ($6603-$9062)		$7271 ($6021-$8500)		$6273 ($5089-$6965)		0.067
Cumulative costs for one live birth, USD	$17,750	49.7萬	$11,704	32.8萬	$17,189	48.1萬	$35,642	99.8萬	< 0.001
Usage rate	54/645 (8.4)		11/189 (5.8)		26/263 (9.9)		17/193 (8.8)		0.650

Unless otherwise indicated, data are presented as the median number (IQR) or as the number/total number (n/N) (percentage). A P value lower than 0.05 is defined as significantly different

SD Standard deviation, *IQR* Interquartile range, *USD* United Sta

380萬

Theoretical calculation (Ben-Rafael et al.)

TABLE 1 – THEORETICAL CALCULATION OF THE MAXIMAL 'USAGE PERCENTAGE' EXPECTED FOR EACH AGE GROUP USING THE RESULTS FROM MALCHOU *ET AL.* (*2017*)

Age (years)	Adjusted odds ratio[a] (%)	Infertile (%)	Pregnant spontaneously (%)	Pregnant with treatment (%)	Cumulative pregnant (%)	Overall infertile women pregnant (%)	Overall not pregnant (%)[b]
26–35	4	15	16	64	80	12	3
35–39	15	40	10	50	60	24	16
>40	33	60	11	16	27	16.2	45

[a] Adjusted odds ratio: annual decrease in adjusted odds ratio for live birth rate with age.

[b] Calculation of the maximal possible usage rate expected if entire age group freezes eggs and all opt to use the banked eggs after treatment failure.

TABLE 2 – COST PER BABY, ASSUMING COST PER EGG RETRIEVAL PLUS STORAGE OF $8000, AND ASSUMING ONLY ONE OR TWO CYCLES OF OOCYTE FREEZING PER PATIENT FOLLOWING EGG BANKING

Study	Cycle cost ($)	Years	Number of women freezing eggs	Mean age (years)	Women using frozen eggs n (%)	Pregnancies from frozen oocytes n (%)	Cost per baby ($)
Cobo et al., 2016	One cycle: 8000	2007–2015	1468	37.7	137 (9.3)	40 (2.7%)	293,600
	Two cycles: 16,000						587,200
Hammarberg, 2017	One cycle: 8000	1999–2014	193	37.1	6 (3.1)	3 (1.6%)	514,666
	Two cycles: 16,000						1,029,332

936萬

1641萬

Elective egg freezers' disposition decisions: a qualitative study

Lucy E. Caughey, B.Beh.Sc. (Honors Psychology),[a] Katherine M. White, Ph.D.,[b] Sarah Lensen, Ph.D.,[a] and Michelle Peate, Ph.D.[a]

Disposition decisions are dynamic.

Triggers for the final disposition decision.

Motherhood.

Conceptualization of oocytes.

Considering the impact of donations to others.

External factors that affect the final outcome.

Unsolved problems

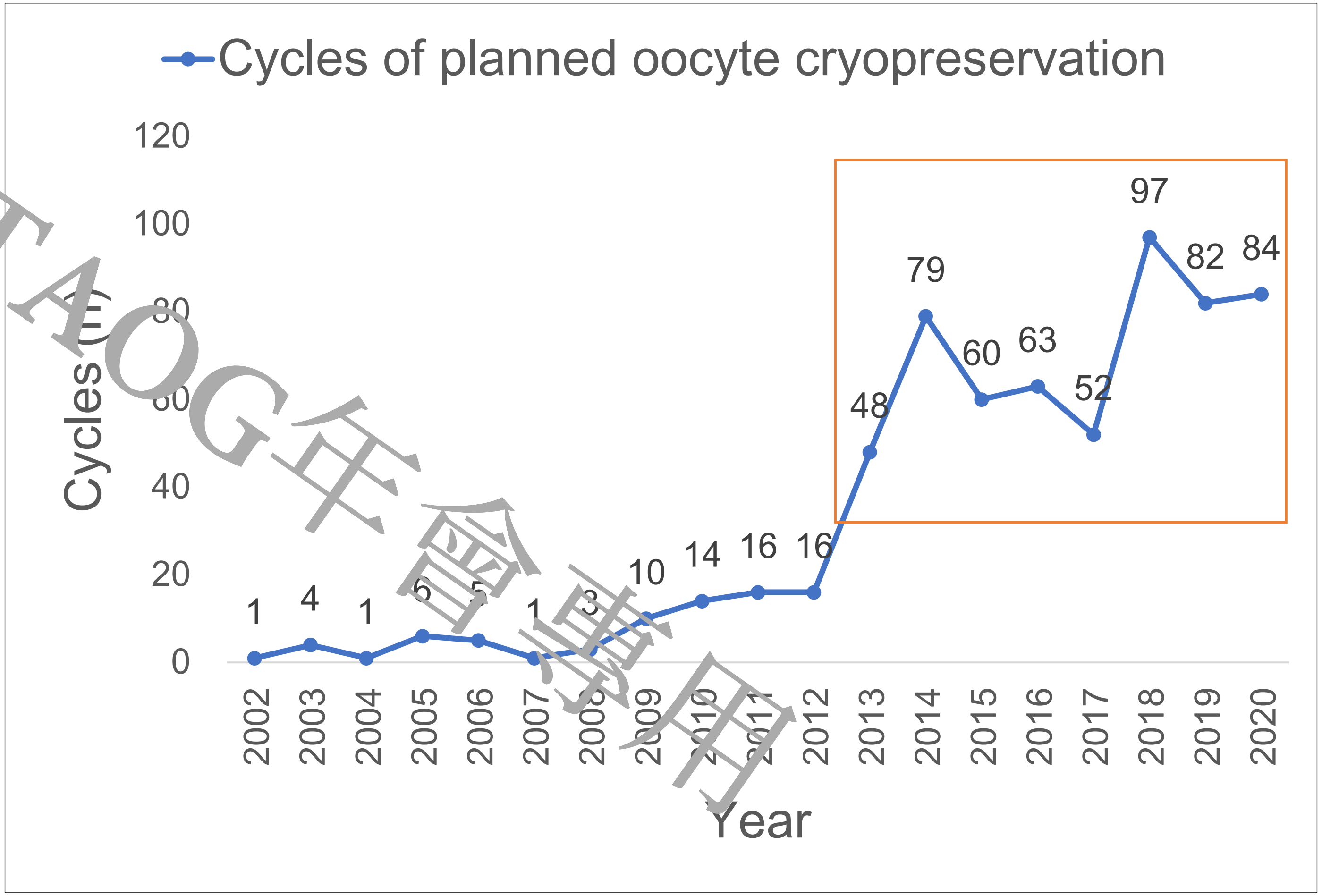
Debates

- Individual's reproductive autonomy
- Promote social justice
  - Gender inequality
  - Financial outlay
- Inappropriate high-pressure sales practices
- Age restriction, "extra" childbearing years

Unsolved problems

- 個案篩選、風險評估
- 社會/政府補助
- 冷凍卵子使用率（長期觀察）
- 成本效益分析
- 冷凍保存保險
- 未使用卵子的處置

- 國健署資料登計收集



Take home messages

- Challenges in patients of malignant diseases.
- The usage rate was low in all studies up to date.
- It is cost-effective for individual to utilize oocyte freezing for postponing child-bearing. However the societal cost for additional live birth is huge. The estimated usage rate is too low to make it cost-effective.
- Long-term data (over 10 or 15 years) is needed to obtain a final disposition for the cryopreserved oocytes.

Acknowledgement

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