



Fertility preservation regulations for oocytes, embryos and ovarian tissue: storage (and use)

And an ESHRE roposal to gather data on cryopreservation (including testicular tissue)

Françoise Shenfield, past coordinator ESHRE SIG
GSCAIF, joint coordinator of ESHRE registry project

Vienna, IFPS, November 2017

A need to know the rules: why?

- **Cryopreservation regulations and practice** are far from universal or standardised in Europe, or worldwide
- The **demand** is growing thanks to improved **cancer (and serious disease)** care and longevity of patients; *“non medical” requests as well*
- **Society** cares both in cases of **serious disease and (women)** for *non medical reasons*
- If **no law/regulations**, access may vary, be **impeded** (in + law countries) or slowed (little state financing in others), ...*or be better (+ more CBRC)*
- First step of **information giving** (to patients and all interested parties, regulators, funders...) is always gathering facts and data



What do we need to know? Who stores What ?

- 1. **Laws and regulations** re **cryopreservation** (**access, who consents, duration**)
- 2. Laws and regulations re **use** (*patient +- partner, +- alive*)
- 3. in all cases for OoC, OtC, Embryos *and TtC (sperm) where consent is for research*
- *Clinically: the incidence, eg **denominator** (how many start the process)*
- **End point:** *how to influence stakeholders on behalf of our patients taking **equity** into account*



The (first) OoC/OtC ESHRE study (HR open)

- EIM register 2011, number of freezing cycles **not recorded** (indications, number retrieved, ...) although It and Sp started
- **Knowledge gap:** stimulation, storage, and use
- **Aim of first study: obtain knowledge** Oocyte Cryopreservation (**OoC**) practice, frequency and indications in Europe, re-imbursment policies + **start use data** register; also **ovarian tissue (OtC)**

Human Reproduction Open, pp. 1–9, 2017, doi:10.1093/hropen/hox003, ESHREPAGES

Oocyte and ovarian tissue cryopreservation in European countries: statutory background, practice, storage and use. The ESHRE Working Group on Oocyte Cryopreservation in Europe, Shenfield F, deMouzon J, Scaravelli G, Kupka M, Ferraretti AP, Prados ,and Goossens V



ESHRE OoC Study: questionnaire part I

Country regulations and funding:

- **Is there specific national regulation for oocyte cryopreservation**
No; Yes; ? National register
- **Are there criteria for freezing?**
- **1. Medical indications** (Serious disease, adolescent, poor ovarian reserve / poor responders, OHSS risk, Egg donation)
- **2. Authorized for non medical indications?**
- **Funding available:** a) **medical reasons:** free/state; personal insurance; retrieval or storage b) **non medical reasons:** free/state; personal insurance; retrieval; storage



Laws

Table I Regulations, criteria, and funding (total 27 countries)

Country	Specific regulation	ART Register		Criteria for freezing			Funding	
		General	OoC	Age	Medical	Non-Medical	Medical	Non-Medical
Austria	Law	Yes	No	No	Yes	forbidden	No	No
Belarus	No	No	No	No	Yes	No	No	No
Belgium	No	Yes	Yes	<45	No	No	Yes	No
Bulgaria	No	No	No	No	Yes	Yes	No	No
Czech Republic	No	Yes	No	No	No	No	Yes	No
Denmark	Law	Yes	Yes	<46	Yes	No	Yes	No
Estonia	No	No	No	No	No	No	No	No
Finland	Law	Yes	No	No	No	Yes	Yes	---
France	Law / COP	Yes	Yes	18-42	Yes	forbidden	Yes	No
Germany	Law / COP	Yes	Yes	20-49	Yes	Yes	No	No
Greece	No	No	No	No	No	No	No	No
Hungary	Law	Yes	No	No	Yes	No	No	---
Italy	Law	Yes	Yes	No	Yes	Yes	Yes	No
Ireland	No	No	No	No	---	---	Yes	No
Lithuania	No	No	No	No	No	No	No	No
Malta	Law / COP	Yes	NO	25-42	Yes	forbidden	Yes	No
Netherlands	Law / COP	No	Yes	No	Yes	Yes	Yes*	No
Norway	Law	Yes	No	No	Yes	No	Yes	No
Romania	COP	Yes	No	No	No	No	No	No
Russia	No	No	No	No	Yes	No	No	No
Slovakia	No	No	No	No	No	No	No	No
Slovenia	Law	No	No	<45	Yes	No	Yes	No
Spain	Law	Yes	No	>18	No	No	Yes	No
Sweden	No	Yes	No	No	No	No	Yes	No
SZ	Law / COP	Yes	No	No	No	No	No	No
UK	Law / COP	Yes	No	No	No	No	Yes	No



Part 2: OoC cryopreservation data

- **General numbers** (2010-2014):
- Total number of aspirations in the country (IVF+ OD+ PGD)
- **Aspirations for** oocyte cryopreservation: Cycles, total number cryopreserved oocytes
- **Indications** (2010-14): *Cycles/oocytes*
- Serious disease*
- (Other) medical reasons* (describe at the bottom of the page)
- Non medical reasons (social freezing)



data on OoC practice in Europe, year 2013

Countries	Numbers			Indications oocyte cryopreservation				Cryopreserved oocytes use	
	Total ART aspirations	OoC aspirations	Oocytes number	OD cycles/oocytes	Serious disease cycles/oocytes	Other medical cycles/oocytes	Non-medical cycles/oocytes	Medical cycles/oocytes	Non-medical cycles/oocytes
Belarus	2000	3	7	0/0	0/0	3/7	0/0	3/7	0/0
Belgium	19590	386	3750	NA	NA	NA	366/2698	NA	NA
Czech Rep	18574	471	5799	169/2178	NA	302/451	NA	182/1455	NA
Estonia	1836	4	31	0/0	0/0	2/23	2/8	1/11	2/8
Finland	4861	23	NA	NA	NA	NA	NA	NA	NA
France	62235	798	NA	NA	324/NA	474/NA	0/0	258/NA	0/0
Germany	56075	235	1350	NA	NA	NA	NA	1/2	NA
Greece	NA	34	203	2/14	10/35	8/105	7/33	2/13	0
Hungary*	3535	5	36	0/0	NA	4/27	NA	1/2	NA
Italy	50174	477	3689	0/0	152/1456	296/1999	29/234	NA	NA
Malta	100	41	NA	0/0	0/0	41/NA	NA	NA	1/2
Romania	2156	NA	NA	45/240	NA	NA	NA	2/9	NA
Slovenia	3668	16	210	0/0	9/135	7/75	0/0	5/42	0/0
Spain ^b	54129	5620	NA	4853/NA	262/1970	8/60	497/3738		42/321
Switzerland	4964	NA	NA	NA	41/NA	NA	7/NA	41/NA	7/NA
UK	46421	810	7042	118/1099	165/1366	270/2462	257/2115	174/1417	9/91
Ukraine	12707	155	1538	136/1354	3/21	16/163	0/0	61/544	0/0
Total: 17	343025	9078	23655	5123/4885	966/4983	1431/5372	1165/8826	796/3823 ^b	19/101
Cycles: :n		2596	---	470	601	916	1158	516	12
Oocytes: :m (SD)			9.1	10.4 (2.3)	8.3 (1.3)	5.9 (3.3)	7.6 (0.4)	8.0	8.4



Worldwide: Where do we stand?

- *Global Reproductive Health 2016* Vol 1 • Issue 1, **IFFS SURVEILLANCE 2016** | 7th EDITION, chapter 20
- *Rashedi et al, Journal Global Oncology (American Soc Clin Onco), Survey of Fertility Preservation Options Available to Patients With Cancer Around the Globe, June 2017*, jgo.ascopubs.org
- *Shenfield et al, May 2017, HR open (for Europe)*
- **Prospective plans** : the new ESHRE register plan with EIM, and **international** contacts to gather data and regulation status
- (please contact FS, RA and AA)



A few examples: illustration complexities

- 1. embryos v gametes or tissues
- 2. tissues v gametes (UK HT Act)
- 3. duration of storage
- 4. Child's consent
- 5. Posthumous use
- 6. Trans sexuals



The (legal) concerns about embryo storage

- **Two people** need to **consent for preservation**; also at **use** major variation: the number E transferred (1 Austria since Feb 2015 v $\frac{3}{4}$ Bulgaria; mandated Be and Nth)
- The (contentious) status of the **embryo v** status of **gametes: 40 years + of debate**; may cases like the **Evans case** avoided?; also status of woman: single allowed (UK) v Portugal (forbidden)

[Evans v United Kingdom, 46 Eur. H.R. Rep. 34\(2008\)](#), Grand Chamber, European Court of Human Rights | 04 October 2007 (IVF, ca ovary, divorce); no infringement of article 8 (“respect of family and private life”), or article 2 (embryo no right to life) and no “discrimination” (article 14



France, free for medical indications

Tableau AMP6. Préservation de la fertilité : conservation de gamètes et de tissus germinaux en 2014

	2014
Spermatozoïdes	
Nombre de centres concernés	44
Nouvelles conservations (patients)	4374
Conservations au 31 décembre (patients)	47369
Ovocytes	
Nombre de centres concernés	33
Nouvelles conservations (patients)	514
Conservations au 31 décembre (patients)	992
Tissus testiculaires	
Nombre de centres concernés	12
Nouvelles conservations (patients)	87
Conservations au 31 décembre (patients)	319
Tissus ovariens	
Nombre de centres concernés	28
Nouvelles conservations (patients)	338
Conservations au 31 décembre (patients)	1985



A British (guidance) table for ovarian tissue

	Scenario 1 Ovarian or testicular tissue intended for fertility treatment (eg. in vitro induction of gametes)	Scenario 2 Ovarian or testicular tissue intended for autologous (own use) transplantation	Scenario 3 Ovarian or testicular tissue, intended future use not certain at time of storage	Scenario 4 Ovarian or testicular tissue from a donor or deceased person
Processing	The Grade C cell quality requirements for processing gametes apply (as required by HFEA standard licence condition T35)	The Grade A cell quality and other requirements of the Human Tissue Quality and Safety for Clinical Applications Regulations 2017 apply. Grade C concerns are set out in the Code of Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment.	Processing requirements outlined in Scenario 2 or Grade A cell quality should be applied from the outset if there is a possibility the tissue may be transplanted. Advice should be sought from the HTA, on a case-by-case basis, as to whether these processes in Grade C cell quality can be transplanted.	Contact your HFEA inspector before considering processing or storing tissue from a donor or deceased person. Where no effective written consent is obtained from the donor/deceased person, their tissue should not be processed (NB: this is not a licence condition, in violation of consent or otherwise).
Storage	Storage at an HFEA-licensed centre (HFEA licence not required).	Storage at an HTA-licensed centre (HFEA licence not required).	Storage at either an HFEA or HTA-licensed centre until the preferred site of the tissue is determined.	If transmittal technology develops, to make transplantation of donor tissue possible, microchips will need to be put in place to ensure appropriate regulation.
Use	Derivation and use of gametes must be carried out at an HFEA-licensed centre. The use of gametes obtained from the tissue and any related adverse events and reactions are reportable to the HFEA.	Tissue must be processed at an HTA-licensed facility before transplantation. The fate of the tissue, and any serious adverse events, and reactions are reportable to the HTA.	When the use of the tissue is determined it should be transferred to an appropriately licensed HFEA or HTA facility. Tissue cannot be received directly from an HFEA-licensed centre or a transplant site.	
Distribution	Tissue can be imported or exported if the requirements set out in HFEA General Directions (GD3) are followed or if Special Treatments are granted.	Tissue can be imported within the UK and EU under the terms of an HTA licence.	Tissue to be used for fertility treatment can be imported or exported if the requirements set out in HFEA General Directions (GD3) are fulfilled, or if Special Treatments are granted. Tissue to be used for transplant can be imported within the UK and EU under the terms of an HTA licence.	



From storage to use, via methods



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Use: ART law specific (HFE Act 1990 rev 2008)

- **Welfare of the (future) child:** minimal v max (high risk of serious harm) threshold *eg relevance of would be parental health* of cancer survivor (TF13,2007, Human Rep 22: 2585-88)
- **Other specific concerns:** duration of cryopreservation, research consent, **Posthumous use** (*forbidden* in many countries, *allowed* for a named recipient with prior consent in UK)
- OoC for **non medical reasons** only allowed 10 years (5+5), so young women are freezing embryos with donor sperm (consent may continue)

Alternative of gametes donation (and surrogacy): anonymity, compensation, ...



Consent: Children and adolescents

- Children, adolescents : **capacity** differs (variable autonomy and ability to consent): *more gradient than date of birth (varies in EU countries, US, ...)*
- **Child** : generally the (legal) test for treatment is “best interest”; definition varies (age, maturity)
- **Parents** are proxy to this decision,... And ...they may experience “**anticipated decision regret**”
- Parental **responsibility (not right in UK)**

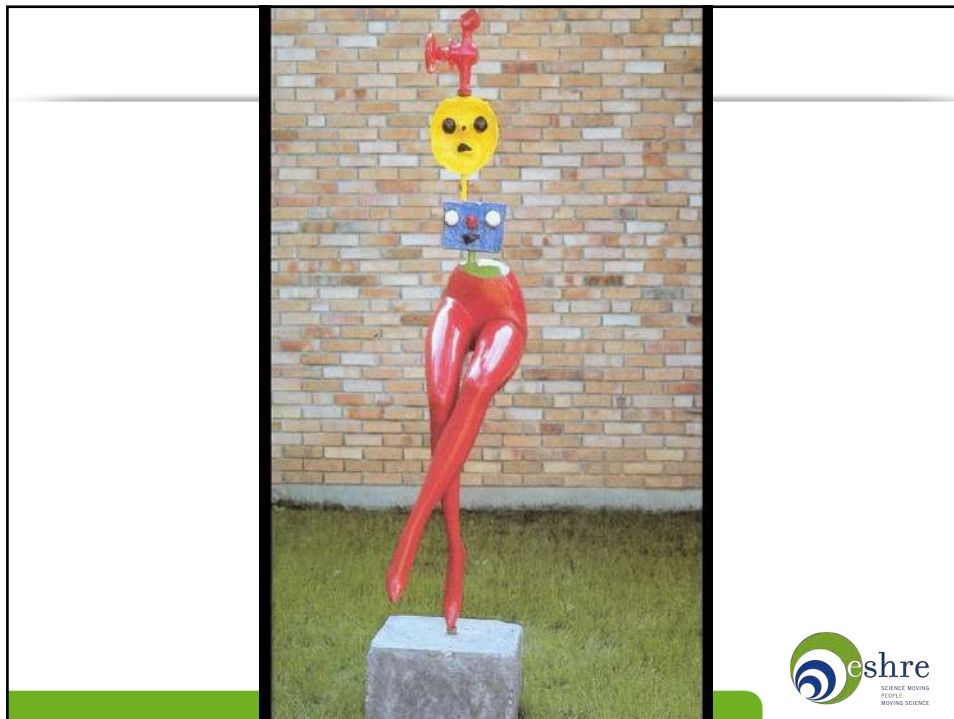
(Wynns et al, 2011, Management of fertility preservation in pre pubertal patients: 5 years' experience at the Catholic University of Louvain, Hum Reprod, Vol.26: No.4 pp. 737–747)



Research law and guidance in Europe

- the **Clinical Trials Directive of 2001**= requirements for clinical trials of medicinal products .. all member states are required to transpose into their national laws (eg: *generic or specific consent*)
- CTD leaves the definition of ‘minor’ to national governments to determine, ...the EU Paediatric Regulation ..defines the paediatric population as <18
- Many European countries (not UK) similarly interpret minors as being under 18





New ESHRE register: immediate and future

- 1. **Aim** : Current and **Prospective** knowledge OoC, OtC, TtC regulations, practice, frequency and indications in Europe and worldwide
- 2. **Objectives**: Obtain reliable information on **OoC, practice** (med and non med reasons, including egg donation); : countries where it is practiced, reimbursement policies, conditions for access and existing codes of practice if any, indications for freezing,
- 3. **Future** Obtain reliable information about **OoC, OtC and TtC (when approved) use** (scarce eg Stoop et al. (2015):50.8% of women who cryopreserved their oocytes anticipated using them at some point)

Conclusion: (legal) Justice: promotes equity?

- 1. **solidarity**: Cancer, severe disease patients cryo: free/ mandatory insurance
- Treatment (funded) post cure or remission (eg conditional?, WOC); with the progress of vitrification and storage for self use, **should there be age limits ? Law or Good Practice Code**
- 2. ?? **Posthumous treatment ?**
- 3. means to follow up offspring and analyse results: a **REGISTER (patients and children)**
- Cancer and fecundity issues mandate a **multidisciplinary approach**, (de Ziegler et al, Fert and Ster, 2015)

