


Rigshospitalet
Fertility Clinic

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



REGION


Storing ovarian tissue for non-malignant conditions

Kirsten Tryde Macklon, M.D., Ph.D.

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 1

Rigshospitalet
Fertility Clinic

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



REGION


Disclosure

- Advisory Board for TEVA

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 2

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Non-malignant reasons for fertility preservation


- Conditions disposing to POI
- Diseases requiring treatment with chemotherapy or ovarian surgery
- Social freezing

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 3

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Conditions disposing to POI


- Genetic
 - Fragile-X, BPES, Turner
- Metabolic
 - Galactosemia
- Autoimmune
 - Autoimmune polyglandular syndrome *or* autoimmune polyendocrine syndrome

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 4

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Diseases requiring treatment with chemotherapy


- Hematological
 - Thalassemia, aplastic anemia and other anemias, MDS,
- Renal
 - Nephrotic syndrome and others
- Autoimmune
 - Lupus
- Neurological
 - Multiple Sclerosis

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 5

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



How big is the need?




REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 6

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Chronic diseases and ovarian function post-chemotherapy

- **Harward LE, *Lupus*, 2012:**
 - 43 women < 35 years with SLE, vasculitis, scleroderma
 - Conclusion: *more women with prior CYC had a higher frequency of amenorrhea, nulliparity and infertility*
- **Rüth EM, *J Pediatr*, 2005:**
 - 42 patients with SSNS since childhood
 - Conclusion: *patients with ≥ 2 courses of CYC had a significantly higher risk of not having children*

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 7

Permanent amenorrhea in 39 patients treated with i.v. cyclophosphamide for lupus nephritis depending on age and intensity

Age	All, N (%)	7 doses, N (%)	15 doses, N (%)
< 25	2/16 (12)	0/4 (0)	2/12 (17)
26-30	4/15 (27)	1/8 (12)	3/7 (43)
> 31	5/8 (62)	1/4 (25)	4/4 (100)
All ages	11/39 (28)	2/16 (12)	9/23 (39)

50% > 32 years developed amenorrhea at doses of 8g/m²
90% > 32 years developed amenorrhea at doses of 12g/m²

REGION

Mersereau og Dooley, 2010

Fertility after bone marrow transplantation

- European multicentre study
- 138 girls; 206 boys
- Median age 13 years [4-28]
- Median follow-up time 6 years [3-12]
- Loss of gonadal function ♀: 89%; ♂:69%
- Risk factors: treated ≥ 13 yo (OR 4,7; 95% CI 1,5-14,9) and treated with Busulfan (OR 47,4; 95% CI 5,4-418,1)

Borgmann-Staudt, 2012, *Bone Marrow Transpl*

REGION

Premature Ovarian Failure in Patients with Autoimmune Addison's Disease: Clinical, Genetic, and Immunological Evaluation

JCEM, 2011

G. Reato, L. Morlin, S. Chen, J. Furmaniak, B. Rees Smith, S. Masiero, M. P. Albergoni, S. Cervato, R. Zanchetta, and C. Betterle
 Endocrine Unit (G.R., L.M., S.M., S.Ce., R.Z., C.B.), Department of Medical and Surgical Sciences, University of Padova, I-35128 Padova, Italy; FRS Laboratories RSR Ltd. (S.Ch., J.F., B.R.S.), Cardiff CF14 4EDU, United Kingdom; and Blood Transfusion Service (M.P.A.), Azienda Ospedaliera-Universitaria di Padova, 35122 Padova, Italy

Patients
 In all, 258 women with a study, Neufeld's criteria (1,1)

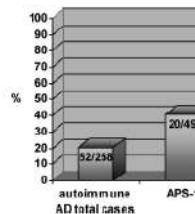


FIG. 1. Prevalence of POF

TABLE 1. Mean age at onset of AD and POF in the different patient groups

	Patients with AD and POF	
	Mean age of onset of AD (yr)	Mean age of onset of POF (yr)
Total cases of AD and POF (n = 52)	26.7 (range 3–62)	28.5 (range 16–40)
APS-1 and POF (n = 20)	17 (range 3–39)	24.1 (range 14–39)
APS-2 and POF (n = 26)	35.5 (range 17–62)	32.3 (range 18–40)
APS-4 and POF (n = 6)	23.2 (range 10–42)	25.8 (range 17–37)

REGION

ORIGINAL ARTICLE

Endocrine Care

Fertility Preservation in Girls with Turner Syndrome: Prognostic Signs of the Presence of Ovarian Follicles

Borgström Birgit, Hreinsson Julius, Rasmussen Carsten, Sheikh Maryam, Fried Gabriel, Kerös Victoria, Fridström Margareta,* Hovatta Outi*

Karolinska Institutet, Departments of Pediatrics (B.B.) and Clinical Science, Intervention, and Technology (C.S.M., F.G., K.V., F.N., H.O.), Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden; and Department of Women's and Children's Health (H.J.), Uppsala University Hospital, SE-751 85 Uppsala, Sweden

47/57 girls aged 8-19 years had OTC
15/57 (26%) showed follicles in the ovarian tissue upon histology
Those aged 12-16 years had the highest proportion of follicles in the ovary

The authors concluded: "Signs of spontaneous puberty, mosaicism, and normal hormone concentrations were positive and statistically significant but not exclusive prognostic factors as regards finding follicles"

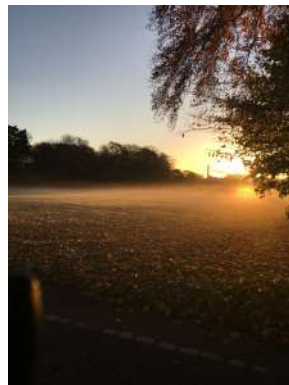
REGION

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Do we offer OTC to our patients with non-malignant diseases?



REGION

Titel/beskrivelse (Sidehovedfoto)

Rigshospitalet, University of Copenhagen

12

Rigshospitalet FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Yes!

- Demeestere, *Hum Reprod Update*, 2009
 - Autoimmune diseases, haematological disorders
- Dolmans, *JARG*, 2013
 - Benign ovarian cysts, endometriosis, POI, Turner, galactosaemia, SLE, systemic diseases, benign haematology
- Von Wolff, *RBMonline*, 2015
 - Autoimmune diseases, benign ovarian cysts, sclerosis, aplastic anaemia,
- Oktay, *J Ped Adolescent Gynecol*, 2016
 - Turner
- Borgström, *JCEM*, 2009
 - Turner

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 13

Rigshospitalet FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Patients with non-malignant diagnoses in our cohort, N=109

Thalassaemia	7	Galactosaemia	5
Aplastic anaemia	15	Aggressive fibromatosis	2
Other anaemias	11	PNH	6
MDS	13	Dermatomyositis	2
Tumer	10	Glomerulonephritis	4
BPES	1	Granulomatosis	4
XY girl	2	Sclerosis	4
POI	6	Sclerodermia	3
BRCA-1 pos	2	Minimal change disease	1
Benign ovarian cysts	5	Bechet's disease	1
Endometriosis	1	Osteopetrosis	1
SLE	11	Hemophagocytic lymphistiocytosis	3
Vasculitis	3	APS	3

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 14

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Our results

Human Reproduction, Vol.38, No.12 pp. 2838–2845, 2015
Advanced Access publication on October 6, 2015 doi:10.1093/humrep/dev130

human reproduction ORIGINAL ARTICLE *Infertility*

Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark

A.K. Jensen¹*, S.G. Kristensen¹, K.T. Macklon², J.V. Jeppesen¹, J. Fedder³, E. Ernst⁴, and C.Y. Andersen¹

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 15

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Auto transplantation to 41 women

2840 Jensen et al.

Table 1 Diagnosis and age of 41 women undergoing transplantation with frozen/thawed ovarian tissue in Denmark.

Diagnosis	No. of women	1st/2nd/3rd transplantation	Tissue transported on ice prior to freezing	Age (years) (mean; range)			
				Cryopreservation	1st transplant	2nd transplant	3rd transplant
Breast cancer	12/3	9		31.9 (26.0–38.7)	36.5 (28.7–43.2)	38.0 (36.7–39.4)	
Mb. Hodgkin	5/4	4		29.4 (25.6–34.1)	32.0 (28.0–37.3)	32.3 (29.4–36.7)	
Non-Hodgkin	5/3/1	1		31.1 (25.9–35.1)	33.8 (29.6–37.3)	37.6 (35.4–39.1)	39.8
Cervical cancer	3/1	3		25.8 (21.2–30.7)	29.1 (24.3–30.2)		
Aplastic anaemia	2	–		29.3 (24.2–32.3)	33.1 (31.3–35.0)		
Esoph. Atresia	2	2		18.3 (9.5–27.1)	21.3 (13.8–28.8)		
Atresia/ectopia vaginae	2	–		22.2 (19.0–25.4)	25.1 (21.7–28.5)		
Sarcoid	2	2		35.7 (32.5–37.8)	37.8 (35.9–39.4)		
Chromosomal aberrations	1	1		33.3	36.5		
Ovarian cancer	1	1		23.5	31.9		
Colon cancer	1	1		26.1	28.8		
Anal cancer	1	1		37.0	38.1		
Various others*	4	4		26.4 (23.1–30.0)	31.0 (27.9–33.0)		
Total	53 (41/11/1)	29		25.8 (9.5–38.7)	32.9 (13.8–43.2)	35.4 (29.4–39.4)	

*Autismisme, Småll-Testel, Myeloid Leukæ, Malignt Blandt, Choriocarcinoma, Wegener's Granulomatose.

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 16

Rigshospitalet FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Results of autotransplantation to 41 women

Table II The current reproductive outcome of women having frozen/thawed ovarian tissue transplanted in Denmark (January 2015; data represent women who had a pregnancy-wish at transplantation).

Diagnosis	Number of		Number of pregnancies				
	Women	Transplantations	NC	IVF	Pos hCG	Clinical	Children
Breast cancer	11	13	6	3	3	3	3
Mb. Hodgkin	4	8	–	4	4	2	2
Non-Hodgkin	5	9	1	4	5	2	1 ongoing singleton*
Acute leukemia	2	2	1	–	1	1	1
Lung sarcoma	1	1	2	1	3	3	3
Fatigonal rectal haemoglobinuria	2	2	1	–	1	1	1
Ovarian cancer	1	1	–	2	2	2	2
Colon cancer	1	1	–	1	1	1	1 miscarriage*
Anal cancer	1	1	–	–	–	–	–
Various others ^b	4	4	2	–	2	2	1
Total	22	42	12	15	29	24	12 (+1 ongoing)

NC, natural conceived; IVF, in vitro fertilization.
^aOngoing pregnancies.
^bVarious other diagnoses include: PPKOM, Autoimmune Small-Vessel Vasculitis, Morbus Behcet, Choroidarcoma, Wegener's Granulomatosis.

Rigshospitalet, University of Copenhagen 17

Rigshospitalet FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Results worldwide

J Assist Reprod Genet (2017) 34:325–336
DOI 10.1007/s10815-016-0843-9

FERTILITY PRESERVATION

86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children

Annette Kliver Jensen¹, Kirsten Tryde Macklon², Jens Fejler³, Erik Ernst⁴, Peter Humaldan⁴, Claus Yding Andersen¹

We searched the literature and in 40 of these deliveries information on the perinatal outcome was provided

Rigshospitalet, University of Copenhagen 18

Rigshospitalet FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Live births published in peer-reviewed papers from women with non-oncological conditions

Child	Diagnosis	group	Birth weight, g	GA
1	Sickle cell anemia	Roux	3700	38
2	Thalassaemia	Revel	3026	term
3	PID	Donnez	2370	38
4	POI	Kawamura	3254	37
5	Thalassaemia	Revelli	3970	39
6	Dermoid cysts	Callejo	3500	38
7	Microscopic polyangitis	Donnez	2030	37
8 + 9	PNH	Macklon	3351/4230	40/40
10	POI	Suzuki	2970	38
11	Sickle cell anaemia	Tanbo	3140	NS
12	Aplastic anaemia	Jensen	3195	37

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 19

Rigshospitalet FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Recommendations

Human Reproduction, Vol.31, No.9 pp. 1802–1811, 2017
Advanced Access publication on July 21, 2017 doi:10.1093/humrep/dex218

human reproduction **ESHRE PAGES**

Update on fertility preservation from the Barcelona International Society for Fertility Preservation–ESHRE–ASRM 2015 expert meeting: indications, results and future perspectives^{†‡}

Francisca Martinez[§], on behalf of the International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group[†]

Hospital Universitario Dexeus, Gran Via Carlos III, 71-75, 08028 Barcelona, Spain

[†]Correspondence address: Hospital Universitario Dexeus, Barcelona, Spain. E-mail: p.martinez@dexeus.com

Submitted on March 27, 2017; accepted on May 19, 2017

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 20

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

FP options should also be discussed with adult and younger women and men affected by several non-oncological medical conditions

Table 1 Non-oncological conditions requiring fertility preservation.

Indication	Disease
Autoimmune diseases (Dominko and Dolmans, 2013; Bedalov and Botros, 2014)	Systemic lupus erythematosus (SLE) Behçet's disease Churg-Strauss syndrome (eosinophilic granulomatosis) Steroid resistant glomerulonephritis Granulomatosis with polyangiitis (formerly Wegener's granulomatosis) Inflammatory bowel diseases Rheumatoid arthritis Pemphigus vulgaris
Hormatoplasia stem cell transplantation (Dominko and Dolmans, 2013, Joshi et al., 2014)	Autoimmune diseases unresponsive to immunosuppressive therapy Haematological diseases (sickle cell anaemia, thalassemia major, plectic anaemia)
Medical conditions causing POI (ESHRE POI Guideline Development Group, 2015)	Advanced hypohalamic-pituitary-gonadal axis (Demeaz and Kim, 2011, Harward et al., 2013) Ovarian oophoritis Benign ovarian tumours Pituitary tumour's syndrome Fragile X Mental Retardation 1 (Giles et al., 2015) Cockayne's (Fridovsky-Kell et al., 2011) Beta-thalassaemia (Razouk et al., 2013) Endometriosis (Soni glare et al., 2015) Klinefelter's syndrome (Bedalov and Botros, 2014)
Male genetic disorders Testicular damage (Ball et al., 2010) Gender reassignment procedures (Dorney, 2008) Severe body trauma requiring surgical intervention POI, premature ovarian insufficiency.	

REGION

Titel/beskrivelse (Sidehovedfod)

Rigshospitalet, University of Copenhagen 21

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Novel indications for OTC

- Female-to-male transsexuals
 - Ott, *Arch Gynecol Obstet*, 2010
- Social freezing or banking for anticipated gamete exhaustion
 - Stoop, *Lancet*, 2014; Andersen and Kristensen, *RBMonline*, 2015


REGION

Titel/beskrivelse (Sidehovedfod)

Rigshospitalet, University of Copenhagen 22

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Conclusion


OTC should be considered in cases of:

1. Genetic conditions
2. HSCT for hematological or autoimmune diseases unresponsive to standard treatment
3. Systemic diseases requiring treatment with cyclophosphamide
4. Ovarian surgery for benign cysts or endometriosis
5. Other diseases/disorders with a risk of POI

REGION

Titel/beskrivelse (Sidehovedfod) Rigshospitalet, University of Copenhagen 23

Thank you for your attention!



REGION