Highlights in Ematologia
Treviso, 17-18 Novembre 2017

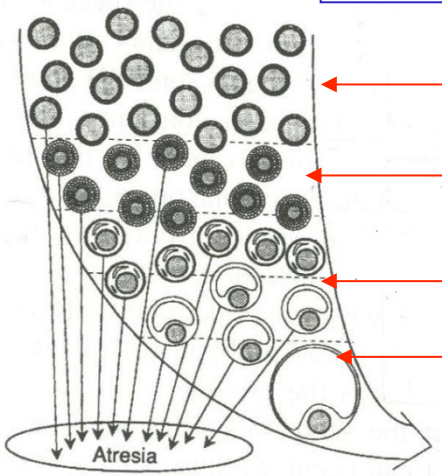
L'ESPERIENZA DEL CENTRO PER LA PRESERVAZIONE DELLA FERTILITA' FEMMINILE DEL POLICLINICO S.ORSOLA DI BOLOGNA

Dott.ssa Maria Macciocca
Azienda Ospedaliero-Universitaria Policlinico S.Orsola di Bologna

CHEMO/RADIOTHERAPY

SURVIVAL OF CHILDREN AND YOUNG WOMEN SUFFERING FROM MALIGNANT DISEASES

GONADOTOXIC ACTION



PRIMORDIAL FOLLICLES

SECONDARY FOLLICLES

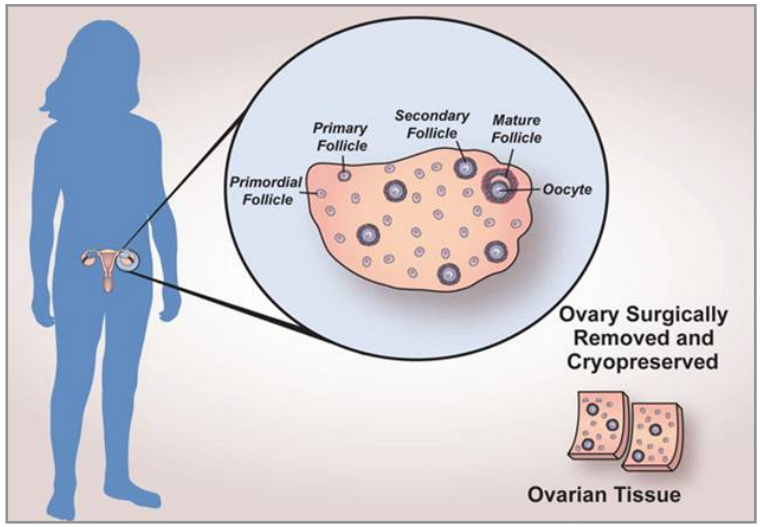
PREANTRAL FOLLICLES

ANTRAL FOLLICLES

OVARIAN FUNCTION ALTERATIONS

Reduction of follicle number – hormonal production - fertility
Risk of premature ovarian failure (POF)

OVARIAN TISSUE CRYOPRESERVATION



- IT ALLOWS TO PRESERVE STEROIDOGENIC AND REPRODUCTIVE FUNCTION
- IT ALLOWS TO RETRIEVE A HIGH NUMBER OF PRIMORDIAL FOLLICLES
- IT CAN BE PERFOMED AT ANY TIME OF MENSTRUAL CYCLE
- IT IS THE ONLY OPTION FOR PREPUBERTAL GIRLS

OVARIAN TISSUE CRYOPRESERVATION INDICATIONS

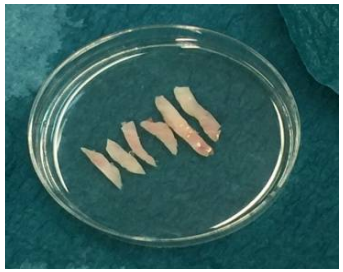
MALIGNANT DISEASES		
PELVIC	Non Gynecological	Gynecological
	Sarcoblastoma Rabdomyosarcoma Sacral Cancer Recto-Sygmoidal Cancer	Cervical Cancer Vaginal Cancer Vulvar Cancer
EXTRAPELVIC	Ewing /Osteo Sarcoma Breast Cancer Kidney,Thyroid Cancer Melanoma Neuroblastoma	
SYSTEMIC	Hodgkin/ non-Hodgkin Lymphoma Myeloma Myelodisplasia	

BENIGN DISEASES	
BONE MARROW TRANSPLANTATION	Drepanocytosis Thalassemia Aplastic Anemia
AUTOIMMUNE DISEASE	Lupus Erythematosus Rheumatoid arthritis Multiple sclerosis
RISK OF POF	Turner's Syndrome Family History
BI/UNILATERAL OOPHORECTOMY	Severe Endometriosis Recurrent Ovarian Cysts Ovarian Torsion

OVARIAN TISSUE CRYOPRESERVATION PROCEDURE

SLOW FREEZING

1. BIOPSY BY LAPAROSCOPY



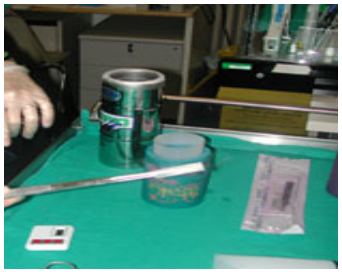
2. SMALL STRIPS

3. FREEZING SOLUTION

4. PROGRAMMABLE FREEZER

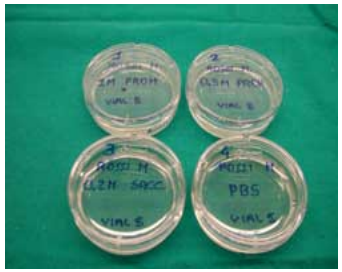
5. NH2 TANK STORING

RAPID THAWING



1.VIALS AIR-WARMED FOR 30 secs

2. IMMERSED IN A 37°C WATER BATH FOR 2 mins

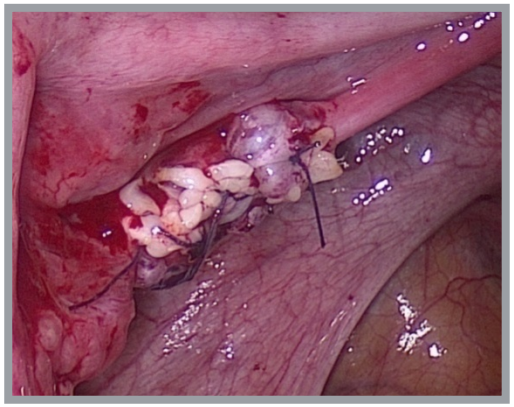


3. CRYOPROTECTANT REMOVAL BY STEPWISE DILUTIONS

R Fabbri et al. Reproductive BioMedicine Online (2010) 21, 819–828

OVARIAN TISSUE CRYOPRESERVATION APPLICATION

ORTHOTOPIC TRANSPLANTATION



↓

SPONTANEOUS CONCEPTION

HETEROTOPIC TRANSPLANTATION

↓

ASSISTED REPRODUCTIVE TECHNOLOGIES

Curr Opin Obstet Gynecol 2015, 27:222–230

Ovarian tissue freezing: current status

Jacques Donnez[a] and Marie-Madeleine Dolmans[b]

Results of 4 Centres (Denmark, Spain, Belgium, Germany)

Table 2. Results from four centers, allowing evaluation of pregnancy and live birth rates, as the number of transplants is known

Teams	Number of transplanted women	Women who conceived	Women who gave birth	Number of live births	Miscarriages
Donnez, Dolmans	13	3	3	6 (*)(**)	
Andersen, Macklon	25	6	4	6(*)(**)	2
Pellicer	22	4	3	4	1
Dittrich	20	7	4 (+2***)	4 (+2***)	1
	80	20 (25%)	14 (20%)	20	4 (20%)

*One woman delivered twice.
**One woman delivered three times.
***Two ongoing pregnancies.

First Pregnancies, Livebirth and In Vitro Fertilization Outcomes After Transplantation of Frozen-Banked Ovarian Tissue with a Human Extracellular Matrix Scaffold using Robot-Assisted Minimally Invasive Surgery

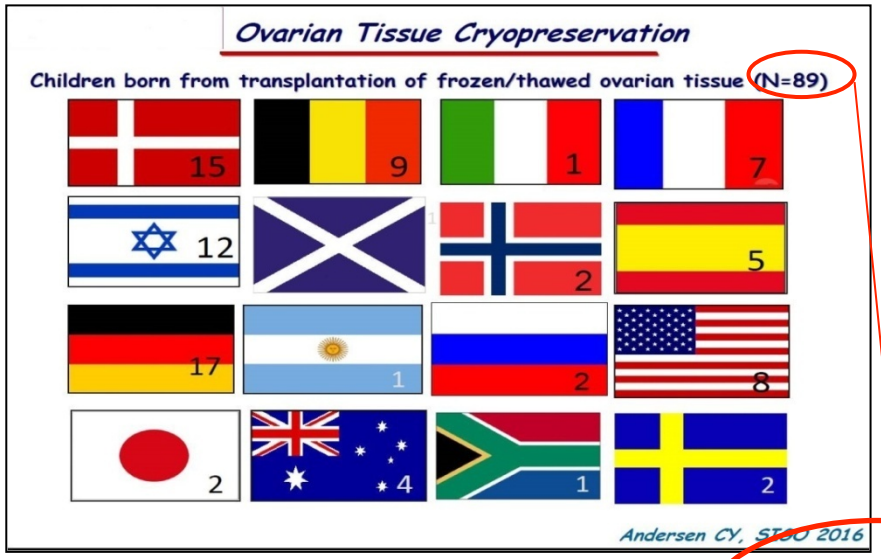
Kutluk Oktay, M.D, Ph.D.[a,b], Giuliano Bedoschi, M.D.[a,b,c], Fernanda Pacheco, M.D.[a,b,d], Volkan Turan, M.D.[a,b,e], and Volkan Emirdar, M.D.[a,b]

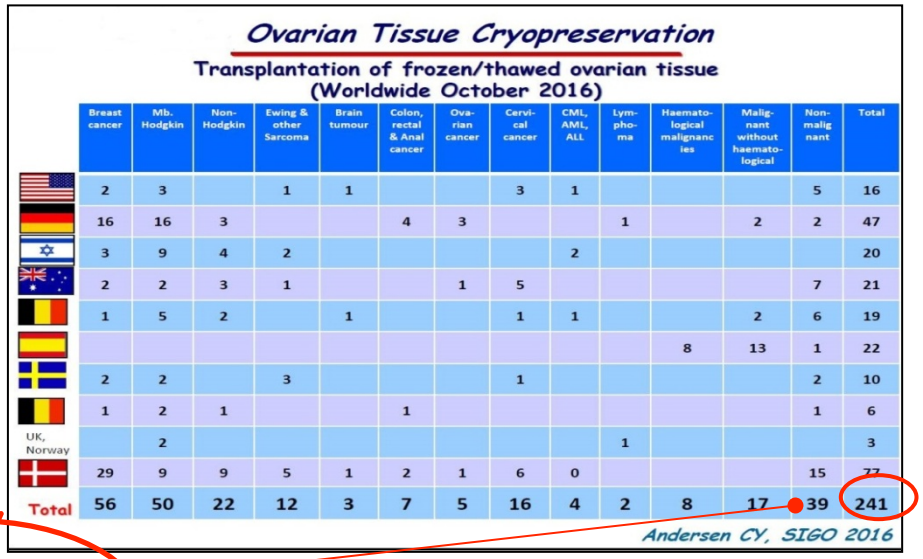
Am J Obstet Gynecol 2016;214:94.e1-9.

Current outcomes and success rates with transplantation of cryopreserved ovarian tissue

Age at Cryopreservation (range)	23.5 ± 4.7 years (17–36)
Age at Transplantation[a] (range)	30 ± 4.2 years (21–38)
Maternal Age at Delivery	35.6 ± 1.9 years (25–39)
Gestational Age at Delivery[b]	38.1 ± 1.6 weeks (33–41)
Clinical Pregnancy/Patient (%)	24/66[c] (36.3%)
Live + Ongoing Pregnancy/Patient (%)	18/66[c] (27.2%)
Endocrine Function/Patient	62/66[d], (93.9%)

OVARIAN TISSUE CRYOPRESERVATION TRANSPLANTATION





	Breast cancer	Mb. Hodgkin	Non-Hodgkin	Ewing & other Sarcoma	Brain tumour	Colon, rectal & Anal cancer	Ovarian cancer	Cervical cancer	CML, AML, ALL	Lymphoma	Haematological malignancies	Malignant without haemato-logical	Non-malignant	Total
	2	3		1	1			3	1				5	16
	16	16	3			4	3			1		2	2	47
	3	9	4	2					2					20
	2	2	3	1			1	5					7	21
	1	5	2		1			1	1			2	6	19
											8	13	1	22
	2	2		3				1					2	10
	1	2	1			1							1	6
UK, Norway		2								1				3
	29	9	9	5	1	2	1	6	0				15	77
Total	56	50	22	12	3	7	5	16	4	2	8	17	39	241

36.9%

CHILDREN BORN UP TO 2017 > 130

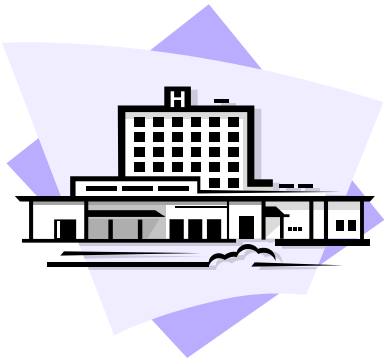
(Donnez J & Dolmans MM, N Engl J Med. 2017 Oct;377(17):1657-1665)

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Policlinico S. Orsola-Malpighi
Dipartimento Attività Integrate
Salute della Donna, del Bambino e dell'Adolescente
Unità Operativa Ginecologia
e Fisiopatologia della Riproduzione Umana - Prof. S. Venturoli

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

EXPERIENCE IN OVARIAN TISSUE CRYOPRESERVATION SINCE 1997



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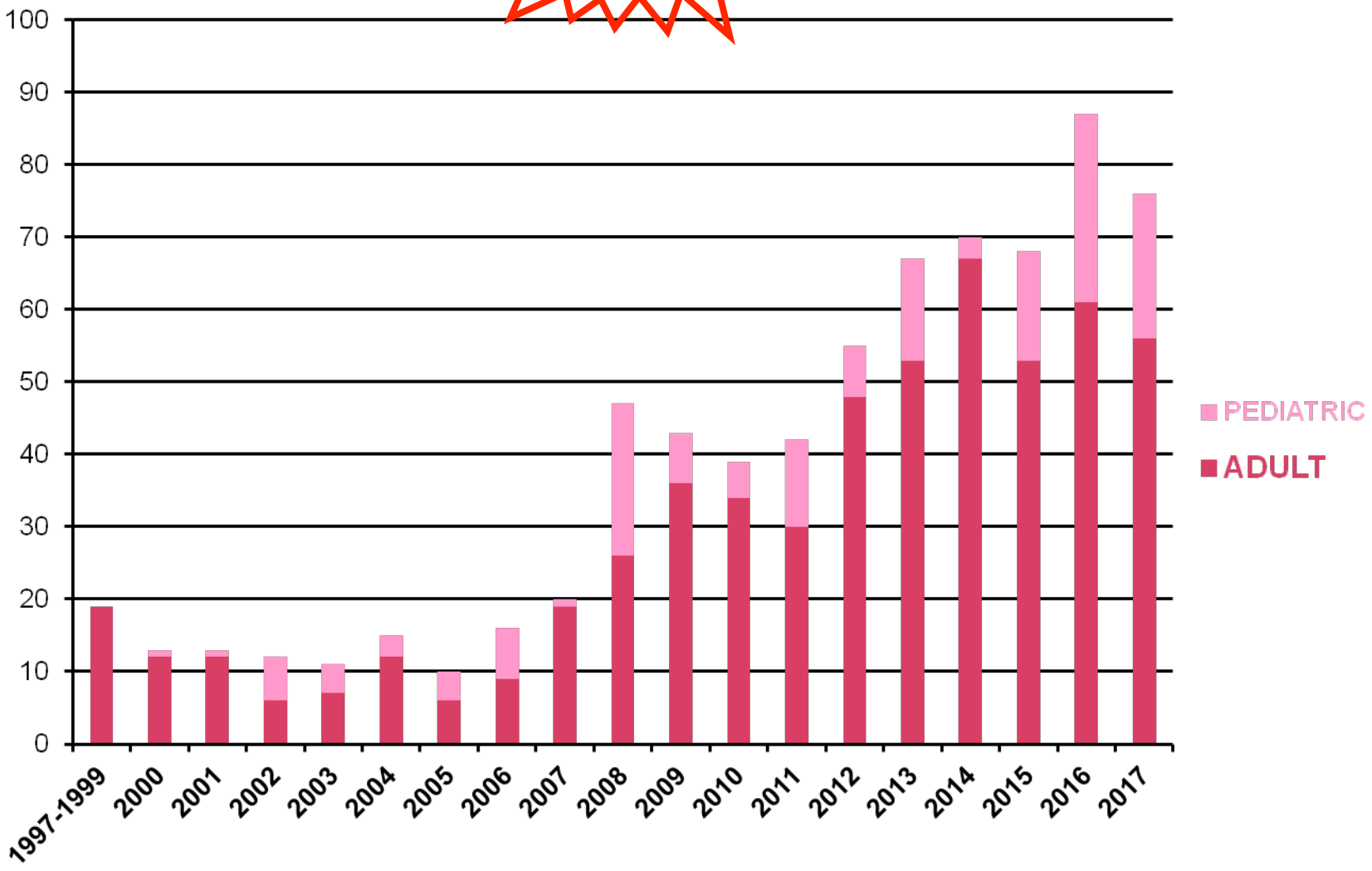
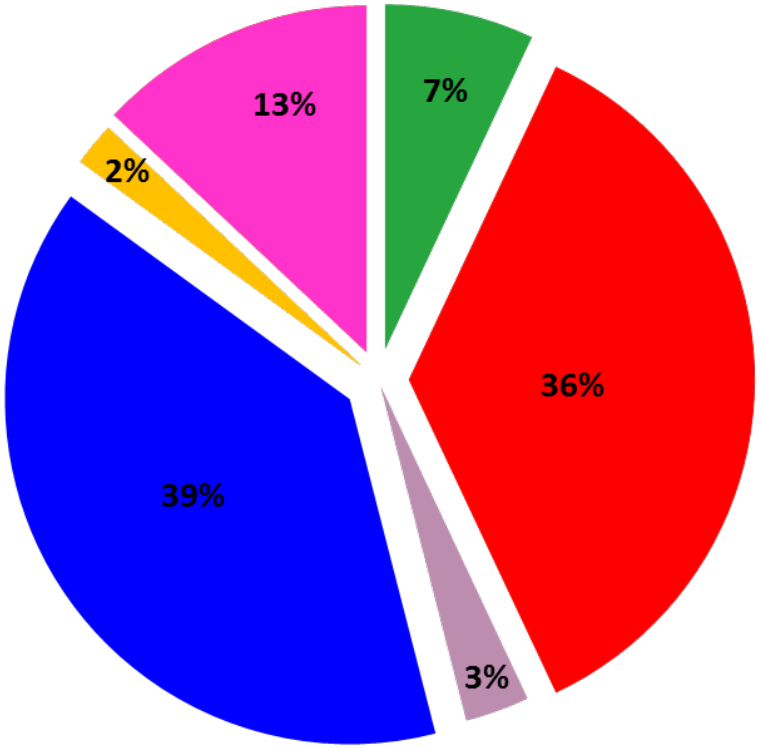

100
90
80
70
60
50
40
30
20
10
0
1997-1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
PEDIATRIC
ADULT

546 ADULTS (28.44 ± 5.76 years)



BREAST CANCER

LYMPHOMA

SARCOMA

LEUKAEMIA

OTHERS

GENETIC DISEASE

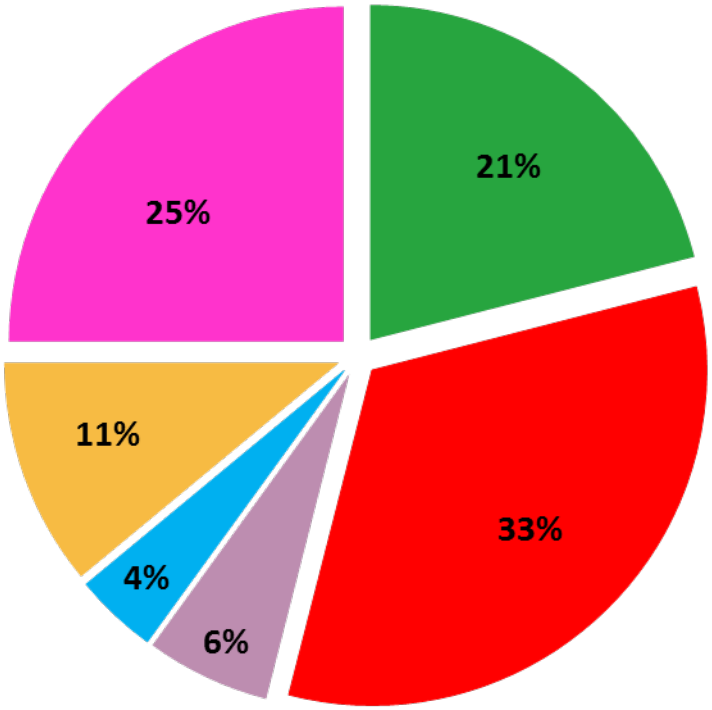
Gynecology and Pysiopathology of Human Reproduction Unit
S. Orsola-Malpighi Hospital, University of Bologna, Italy

153 PEDIATRICS (13.38 ± 3.96 years)

Cryopresevation of ovarian tissue in pediatric patients

Fabbri R, Vicenti R, Macciocca M, Pasquinelli G, Lima M, Parazza I, Magnani V, Venturoli S.

Obstet Gynecol Int 2012; Article ID 910698



Gynecology and Pysiopathology of Human Reproduction Unit
S. Orsola-Malpighi Hospital, University of Bologna, Italy

OVARIAN TISSUE CRYOPRESERVATION TRANSPLANTATION

PATHOLOGY	PATIENTS	GRAFT SITE
COLORECTAL CANCER	1	ORTHOTOPIC
BREAST CANCER	5	ORTHOTOPIC
MULTIPLE MYELOMA	1	ORTHOTOPIC
MEDULLOBLATOMA	1	ORTHOTOPIC
EWING SARCOMA	1	ORTHOTOPIC
NON-HODGKIN LYMPHOMA	1	2 ORTHOTOPIC
HODGKIN LYMOHOMA	2	1 ORTHOTOPIC – 2 HETEROTOPIC
STRUMA OVARII	1	1 ORTHOTOPIC – 1 HETEROTOPIC
TOTAL	**13**	**16**

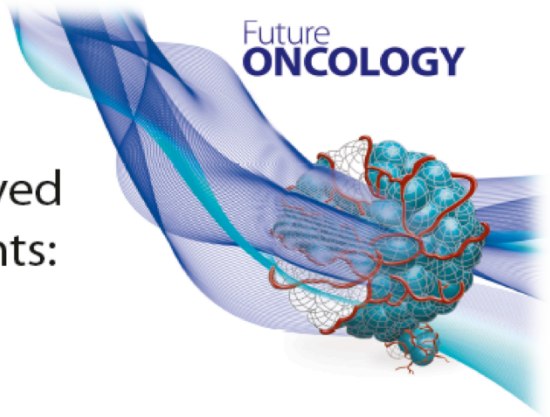
Gynecology and Pysiopathology of Human Reproduction Unit
S. Orsola-Malpighi Hospital, University of Bologna, Italy

OVARIAN TISSUE CRYOPRESERVATION TRANSPLANTATION

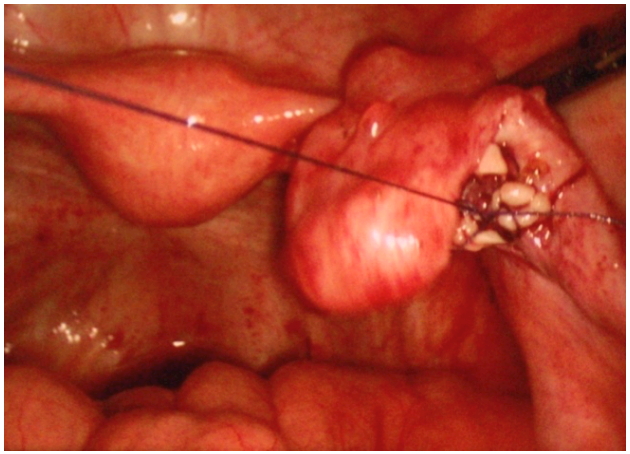
Future Oncol. (2014) 10(4), 549–561

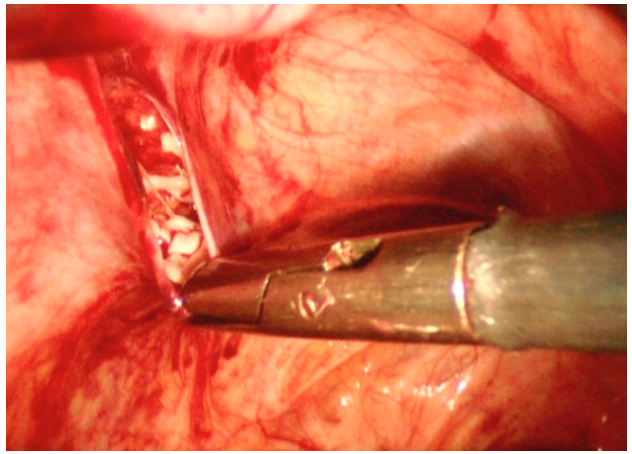
RESEARCH ARTICLE

Autotransplantation of cryopreserved ovarian tissue in oncological patients: recovery of ovarian function



Raffaella Fabbri*[1], Gianandrea Pasquinelli[2], Valentina Magnani[1], Maria Macciocca[1], Rossella Vicenti[1], Isabella Parazza[1], Roberto Paradisi[1], Cesare Battaglia[1], Stefania Rossi[1] & Stefano Venturoli[1]





PATIENT 1 (A. P.): COLORECTAL CANCER

- COLORECTAL CANCER (23 yrs)
- CHEMOTHERAPY (5 FU - 3 CYCLES)
- OVARIAN TISSUE CRYOPRESERVATION
- CHEMOTHERAPY (5FU – 9 CYCLES)
- PELVIC RADIOTHERAPY (4500 Gy) + BOOST (540 Gy)

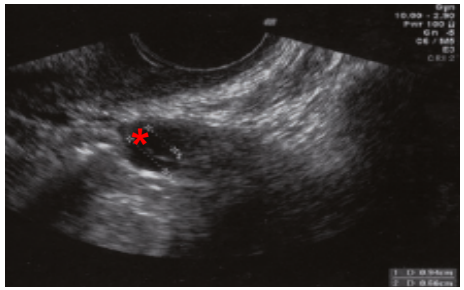
POF

PRE TRANSPLANTATION:

- FOLLICULAR DENSITY 8 FOLLICLES / mm^2
- IMMUNOHISTOCHEMISTRY → CAM 5.2 → NO MALIGNANT CELLS

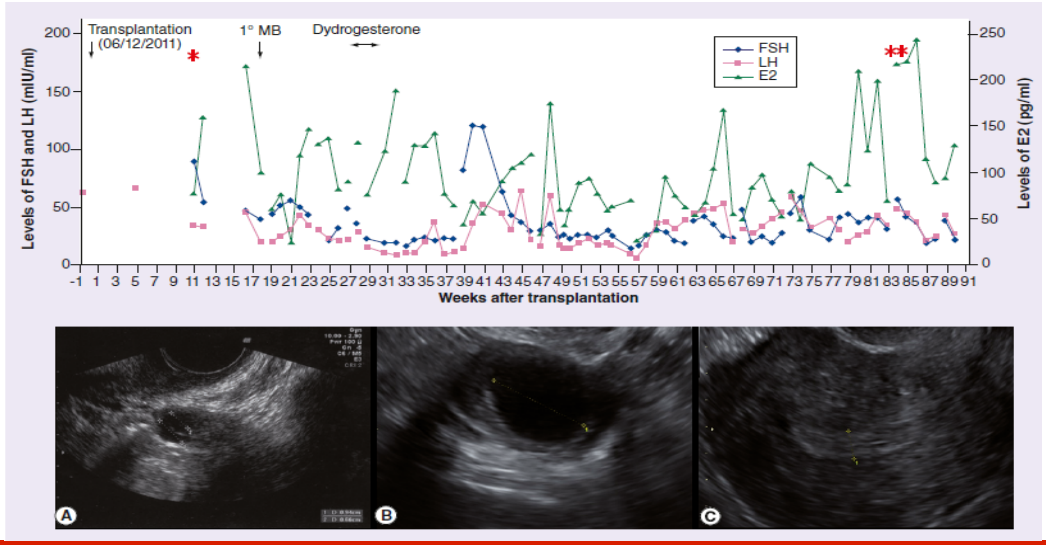
RESULTS

- **OVARIAN FUNCTION RECOVERY:** **2.5 MONTHS POST TRANSPLANTATION**



	TRANSPLANT	
HORMONE LEVELS	PRE	POST*
FSH mIU/mL	134.6	55.1
E2 pg/mL	<12	159

- **1° MENSTRUAL CYCLE:** **4 MONTHS POST TRANSPLANTATION**



OVARIAN FUNCTION LASTED 23 MONTHS

PATIENT 2 (A. R.): BREAST CANCER

- BREAST CANCER (34 yrs)
- OVARIAN TISSUE CRYOPRESERVATION
- CHEMOTHERAPY (AC – 5 CYCLES)
- RADIOTHERAPY BOOST (60 Gy)
- TAMOXIFEN AND LEUPRORELIN (for 2 yrs)
- IRREGULAR MENSTRUAL CYCLES

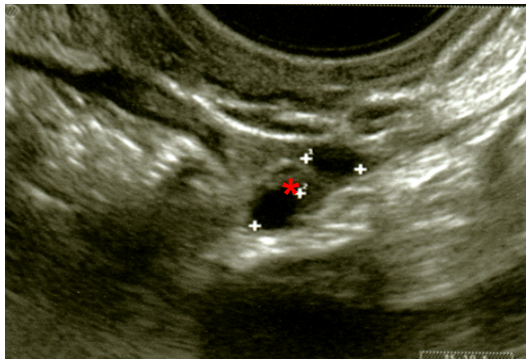
POF (40 yrs)

PRE TRANSPLANTATION:

- FOLLICULAR DENSITY: 1 FOLLICLE / mm^2
- IMMUNOHISTOCHEMISTRY → CAM 5.2; WT1 → NO MALIGNANT CELLS

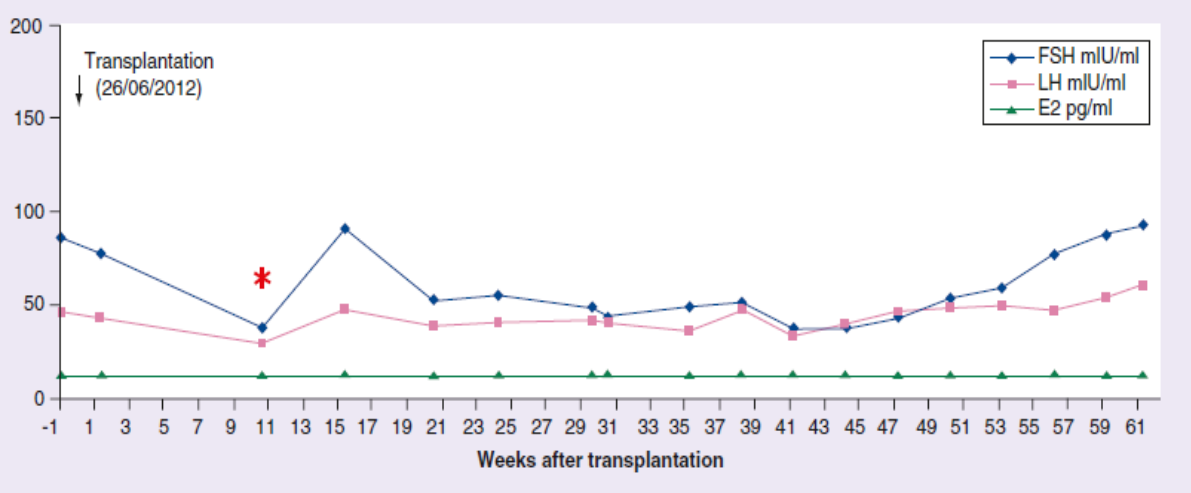
RESULTS

- **OVARIAN FUNCTION RECOVERY: 2 MONTHS POST TRANSPLANTATION**



	TRANSPLANT	
HORMONE LEVELS	PRE	POST*
FSH mIU/mL	86.1	37.1
E2 pg/mL	<12	<12

- **NO HOT FLUSHING**
- **NO MENSTRUAL CYCLES**



OVARIAN FUNCTION LASTED 7 MONTHS

PATIENT 3 (S. R.): HODGKIN LYMPHOMA

- HODGKIN LYMPHOMA (21 yrs)
- OVARIAN TISSUE CRYOPRESERVATION
- CHEMOTHERAPY (ABVD - 6 CYCLES; IGEV 2 CYCLES)
- HEMATOPOIETIC STEM CELL TRANSPLANTATION
- MEDIASTINAL RADIOTHERAPY (30Gy)
- IRREGULAR MENSTRUAL CYCLES AFTER THERAPIES

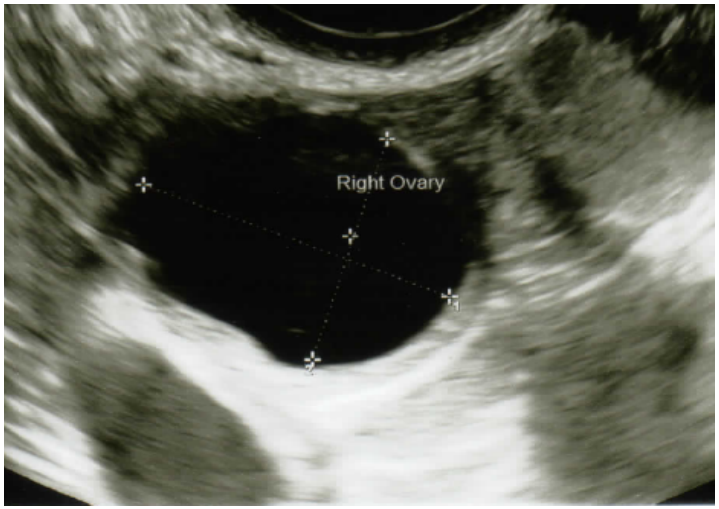
POF

PRE TRANSPLANTATION:

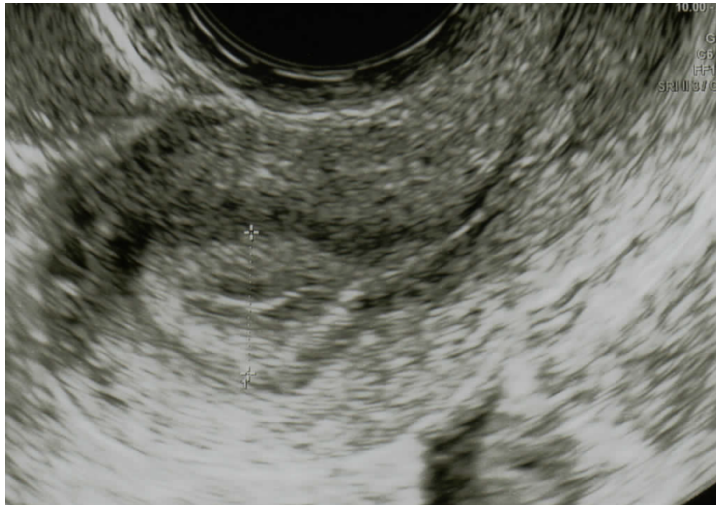
- FOLLICULAR DENSITY: 15 FOLLICLES / mm^2
- IMMUNOHISTOCHEMISTRY → CD30 → NO MALIGNANT CELLS

RESULTS

- **OVARIAN FUNCTION RECOVERY:** 4,5 MONTHS POST TRANSPLANTATION
- **1° MENSTRUAL CYCLE:** 5 MONTHS POST TRANSPLANTATION



OVULATORY FOLLICLE



TRILAMINAR ENDOMETRIUM

- MENSTRUAL CYCLES EVERY 26-33 DAYS

MONITORING IS ONGOING

PATIENT 4 (F. A.): HODGKIN LYMPHOMA

- HODGKIN LYMPHOMA (29 yrs)
- OVARIAN TISSUE CRYOPRESERVATION
- CHEMOTHERAPY (ABVD - 6 CYCLES)
- SUPRA- (92 Gy) and SUB-DIAPHRAGRAMATIC (67 Gy) RADIOTHERAPY
- IRREGULAR MENSTRUAL CYCLES
- 2 SPONTANEOUS PREGNANCIES

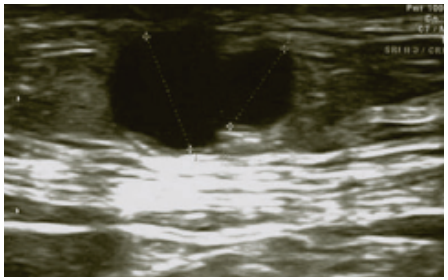
POF (38 yrs): HOT FLUSHING AND SEVERE OSTEOPOROSIS

PRE TRANSPLANTATION:

- FOLLICULAR DENSITY: 8 FOLLICLES / mm^2
- IMMUNOHISTOCHEMISTRY → CD30 → NO MALIGNANT CELLS

RESULTS

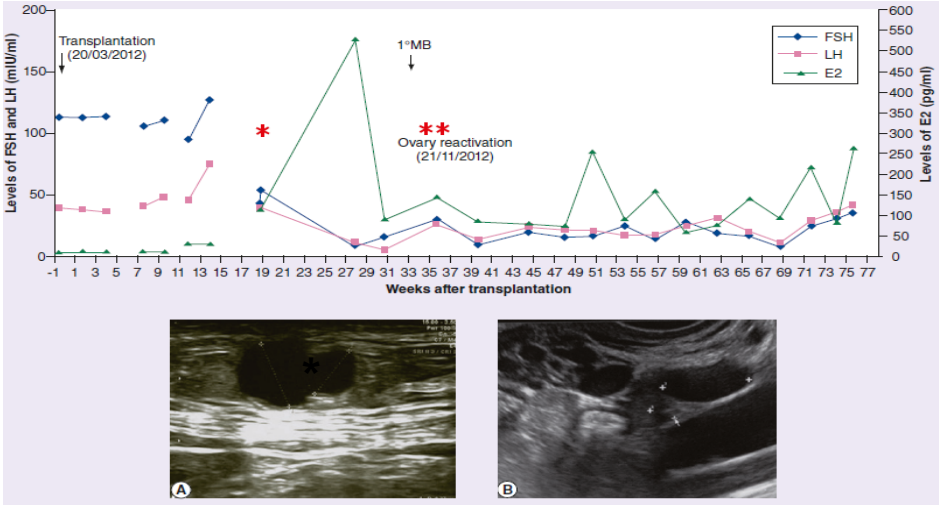
- **OVARIAN FUNCTION RECOVERY: 4 MONTHS POST TRANSPLANTATION**



	TRANSPLANT	
HORMONE LEVELS	PRE	POST*
FSH mIU/mL	113.1	43.2
E2 pg/mL	<12	112.8

NO HOT FLUSHING

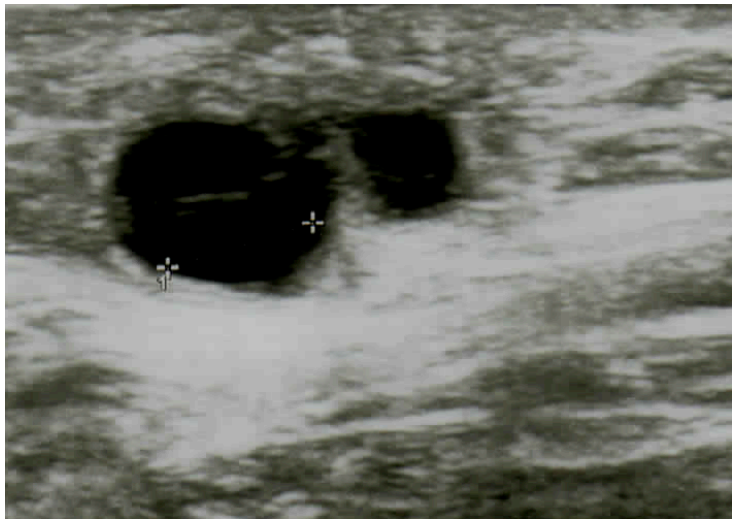
- **1° MENSTRUAL CYCLE: 7.5 MONTHS POST TRANSPLANTATION**
- **CYCLES EVERY 26 DAYS**



OVARIAN FUNCTION LASTED 36 MONTHS

RESULTS

- **OVARIAN FUNCTION RECOVERY:** 4 MONTHS POST TRANSPLANTATION



ULTRASOUND CONFIRMED THE PRESENCE OF GROWING FOLLICLES IN THE GRAFT SITE

- **1° MENSTRUAL CYCLE:** 4.5 MONTHS POST TRANSPLANTATION

MONITORING IS ONGOING

CONCLUSIONS

MORE THAN 130 LIVE BIRTHS - SUCCESS RATES 30-40% :

OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION

SHOULD NO LONGER BE CONSIDERED EXPERIMENTAL

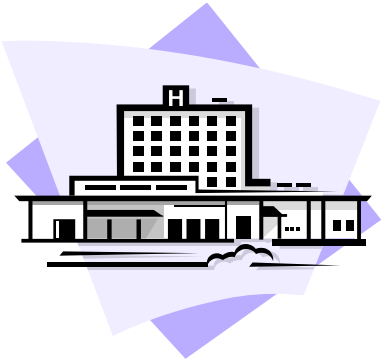
THESE FINDINGS ARE ALSO NOTEWORTHY FOR THE

SAFETY OF LONG-TERM BANKING

IN ONCOFERTILITY PROGRAMS

CONCLUSIONS

SPECIALISED CENTRE



- PATIENT COUNSELLING
- SURGICAL PROCEDURES
- CRYOPRESERVATION PROTOCOL
- QUALITY CONTROL
- FOLLOW-UP

↑ NETWORK
ONCOLOGISTS - PATIENTS

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Prof. Renato Seracchioli

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