DIFFERENT APPROACHES TO FERTILITY PRESERVATION PROGRAM

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KLINIČNI ODDELEK ZA REPRODUKCIJO

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IN RECENT DECADES

a trend toward delaying childbearing

as a consequence, malignant diseases in young women often occurs before the completion of reproductive plans

PATIENTS WITH MALIGNANT DISEASES

a major health, psychological and social problem

modern approaches to cancer treatment have significantly **improved the survival** rates of cancer patients.

THERAPY

Aggressive **chemotherapy** (especially alkylating agents) and **radiation** cause infertility in young cancer survivors.

WOMEN WITH MALIGNANT DISEASE

damage by *itself*

may adversely influence the *quality* of oocytes

lower number of oocytes retrieved

cancelation rate due to *poor response*?

Friedler S, FS 2012

Friedler S, FS 2012

CANCER SURVIVORS

53 survivors, survived for > 5 years

breast cancer and hodgkin lymphoma comprised 58 % of the cancer diagnoses

half of them received treatment:

- alkylating-agent chemotherapy
- pelvic/abdominal radiotherapy
- total body irradiation

Barton SE, FS 2012

CANCER SURVIVORS

the risk for **premature menopause** was tenfold higher

COH: required higher doses of gonadotropins, lower E2

significantly **fewer oocytes** were retrieved and **embryos** available for transfer

5/39 live birth, no birth after pelvic or abdominal RT

3 birth after alkylating-agent chemotherapy

cycle canceled 5 times higher comparing all IVF, 10 times higher comparing male factor of infertility

Effects of cancer treatment on fertility

chemotherapy

*chemotherapy causes **depletion of the primordial follicle pool** in a drug- and dose-dependent manner

the prevalence of **ovarian failure following cancer treatment is high

**follicular depletion may occur despite maintenance of regular menstrual cycles

*Himelstein-Braw R, Peters H and Faber M (1978) Morphological study of the ovaries of leukaemic children. Br J Cancer 38,82–87.

**Bath LE, Wallace WHB, Fitzpatrick C, Shaw P and Anderson RA (2003) Depletion of the ovarian reserve in young women following treatment for cancer in childhood: detection by anti-Müllerian hormone, inhibin B and ovarian ultrasound. Hum Reprod 18,2368–2374.

Effects of cancer treatment on fertility

radiotherapy

*the dose of **5–20 Gy** administered to the ovary is sufficient to completely impair gonadal function, whatever the age of the patient

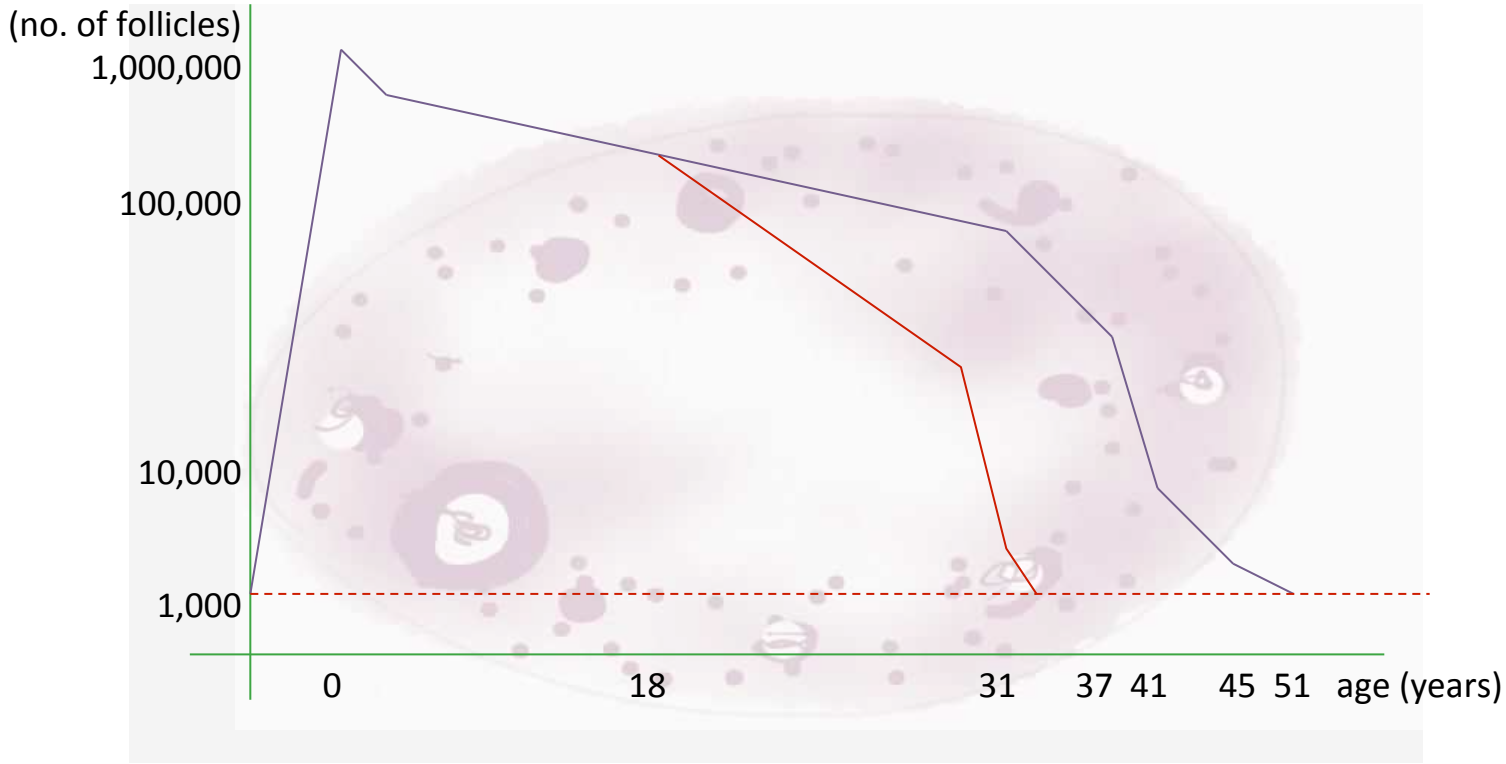
the dose of radiation required to destroy 50% of the oocyte reserve has been found to **be <2 Gy

*Wallace WH, Thomson AB, Saran F and Kelsey TW (2005) Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 62,738–744

**Wallace WH, Thomson AB and Kelsey TW (2003) The radiosensitivity of the human oocyte. Hum Reprod 18,117–121.

Effects of cancer treatment on fertility

chemotherapy



The impact of combination cytotoxic chemotherapy on gonadal function is dependent on the **nature and total dosage** of the drugs administered and is very strongly influenced by the **age of patient.**

COUNSELING & EXPERT GROUP

COUNSELING

American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Karen Hagerty, Lindsay N. Beck, Lawrence V. Brennan, and Kutluk Oktay

A B S T R A C T

Purpose
To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer.

Methods
An expert panel and a writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature from 1987 to 2005 was performed, and included a search of online databases and consultation with content experts.

Results
The literature review found many cohort studies, case series, and case reports, but relatively few randomized or definitive trials examining the success and impact of fertility preservation methods in people with cancer. Fertility preservation methods are used infrequently in people with cancer.

Recommendations
As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists. Clinician judgment should be employed in the timing of raising this issue, but discussion at the earliest possible opportunity is encouraged. Sperm and embryo cryopreservation are considered standard practice and are widely available; other available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise.

Conclusion
Fertility preservation is often possible in people undergoing treatment for cancer. To preserve the full range of options, fertility preservation approaches should be considered as early as possible during treatment planning.

Fertility preservation procedures

options in females depend on the patient's*:

CRYOPreservation

age

diagnosis

type of treatment

whether she has a partner

the time available

*Roberts JE, Oktay K: Fertility preservation: A comprehensive approach to the young woman with cancer. J Natl Cancer Inst Monogr 57-59, 2005

COUNSELING & EXPERT GROUP

APPOINTMENT	gynecologist, oncologist….
	patient (relatives, partner)
	in 24 hours after the call

CONSELING & EXPERT GROUP

APPOINTMENT

- impact of oncologic treatment on fertility
- presentations of procedures, complications and expectations
- impact of preservation procedures on oncologic treatment

OOCYTES& EMBRYOS

CHANCES FOR FUTURE PREGNANCIES?

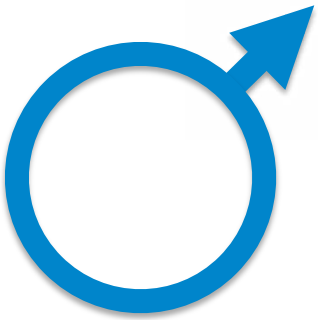
OOCYTES

12-20 oocytes

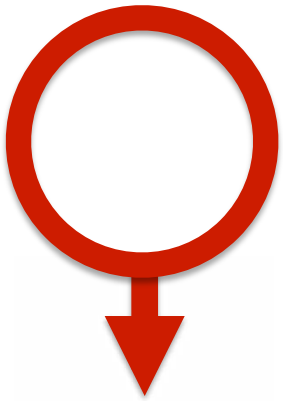
PREGNANCY

FERTILITY PRESERVATION

we do not need extra time or stimulation with medication to preserve genetic material of men, which makes preservation easy and almost always accessible



in case of preserving women's genetic material we need efficient procedures of ovarian stimulation in order to obtain the greatest possible number of oocytes



FERTILITY PRESERVATION

we can preserve:

mature and immature oocytes

embryos and ovarian tissue

the most effective is the preservation of embryos

disadvantages:

it is only available for women with a partner and cryopreserved embryos are the property of both partners

Is not recommended after 1-2 courses of chemotherapy (quality of embryos, risk of congenital anomalies)

OVARIAN TISSUE CRYOPRESERVATION

By laparoscopy at maximum age limit of 37 years

Decission should be individualized – AFC, AMH

Visible follicles should be aspirated

Histological evaluation should be done to exclude cancer cells and confirm the presence of follicles

Slow freezing

OVARIAN TISSUE REIMPLANTATION

- Oncologist's approval
- All pregnancies after orthotopic reimplantation (peritoneal window, ovarian medula)
- Strips 8-10 mm
- Restoration of ovarian function 3-6 month after
- Persistence up to 7 years
- 50 % conceived spontaneously
- In IVF – 30 % more empty follicles

CONTROLED OVARIAN HYPERSTIMULATION

CONVENTIONAL

RANDOM-START

CONVENTIONAL COH

we begin the ovarian stimulation in the early follicular stage of the menstrual cycle, usually **from 2nd to 5th day** after the onset of the menstrual bleeding

GnRH ant. – follicles > 14 mm

Ovarian stimulation protocol starting in the early follicular phase of the cycle

Day of the cycle	Procedure	Gonadotropin (Recombinant FSH or urinary gonadotropin in a specific dose)	GnRH antagonist (Cetrotide 0,25 mg)	GnRH agonist (Suprefact 0,6 ml)
Day 1- 7	CASE PRESENTATION			
2.	US	+		
3.		+		
4.		+		
5.		+		
6.	US	+		
7.		+		
8.	UZ – dominant follicle ≥ 14 mm	+	+	
9.		+	+	
10.	US	+	+	
11.		+	+	
12.	US	+	+	
13.		+	+	
14.	US- follicles ≥ 18 mm			+
15.				
16.	Oocytes aspiration			

RANDOM-START COH

no time to wait for the next menstrual period

urgency of the cancer treatment

repeat the COH

Random start COH starting in the luteal phase of the cycle (von Wolff M, FS 2009)

Day of the cycle	Procedure	GnRH antagonist (Cetrotide 0,25 mg)	Gonadotropin (Recombinant FSH in a specific dose)	GnRH agonist (Suprefact 0,6 ml)
14th or later	CASE PRESENTATION			
15	US	+	+	
16.		+	+	
17.		+	+	
18.		+	+	
19.	US	+	+	
20.		+	+	
21.	US	+	+	
22.		+	+	
23.	US	+	+	
24.		+	+	
25.	US	+	+	
26.		+	+	
27.	US- follicles ≥ 18 mm			+
28.				
29.	Oocytes aspiration			

Random-Start COH in the follicular phase of the cycle (Cakman H, FS 2012)

Day of the cycle	Procedure	Gonadotropin (Recombinant FSH or urinary gonadotropin in a specific dose)	GnRH antagonist (Cetrotide 0,25 mg)	GnRH agonist (Suprefact 0,6 ml)
7th or later	CASE PRESENTATION			
8.	US – follicles < 12 mm	+		
9.		+		
10.		+		
11.		+		
12.	spontaneous LH surge	+		
13.		+		
14.	US	+		
15.		+		
16.	US– dominant follicle ≥ 14 mm	+	+	
17.		+	+	
18.	US	+	+	
19.		+	+	
20.	US- follicles ≥ 18 mm			+
21.				
22.	Oocytes aspiration			

21.				
22.	Oocytes aspiration			

Random-Start COH in the late follicular phase of the cycle (Cakman H, FS 2012)

Day of the cycle	Procedure	Gonadotropin (Recombinant FSH or urinary gonadotropin in a specific dose)	GnRH antagonist (Cetrotide 0,25 mg)	GnRH agonist (Suprefact 0,6 ml)
12th or later	CASE PRESENTATION			
13.	US – dominant follicle ≥ 16 mm			+ or HCG
14.				
15.				
16.	US	+		
17.		+		
18.		+		
19.	US	+		
20.		+		
21.	US– dominant follicle ≥ 14 mm	+	+	
22.		+	+	
23.	US	+	+	
24.		+	+	
25.	US- follicles ≥ 18 mm			+
26.				
27.	Oocytes aspiration			

PATIENTS WITH BREAST CANCER

7 % of women with BC are diagnosed < 40 years

BC accounts for more than 40 % of all cancers < 40 years

GLOBOCAN: WHO 2012; Anders CK,Semin Oncol 2009

LETROZOL, GONADOTROPIN STIMULATION PROTOCOL

letrozol 5 mg/d on menstrual cycle 2 or 3

FSH (150-300 IU/d) is added two days later

all medication are discontinued on the day of HCG or GnRH a trigger

letrozol is reinitiated after oocyte retrieval and continued until E2 levels fell to < 50 pg/ml (Johnson LN, RBMO 2013)

MEDICAL CONSIDERATIONS IN CANCER PATIENTS

we have to prevent serious life-threatening complications with prophylaxis

cancer patients are at increased risk of **trombembolic events** because of hypercoagulable state induced by their malignancy and high E2

Cakman H, FS 2013

ANTICOAGULATION PROPHYLACTIC TH

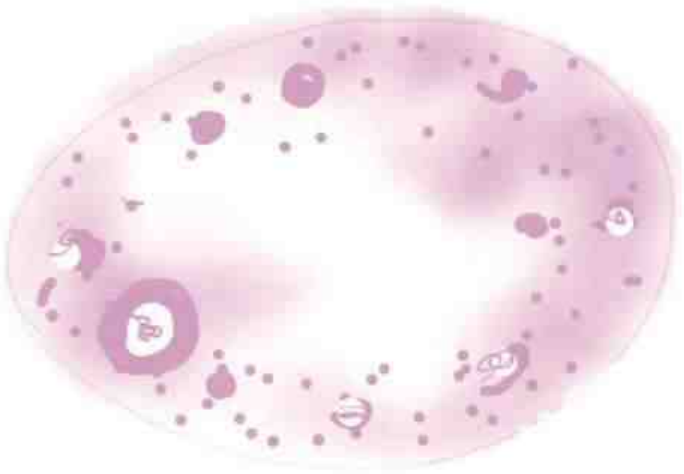
low-molecular-weight **heparin** with ovarian stimulation

last dose **24 h before oocyte retrieval**

reinitiate 12 h after retrieval

FERTILITY PRESERVATION PROCEDURES

Ovarian suppression



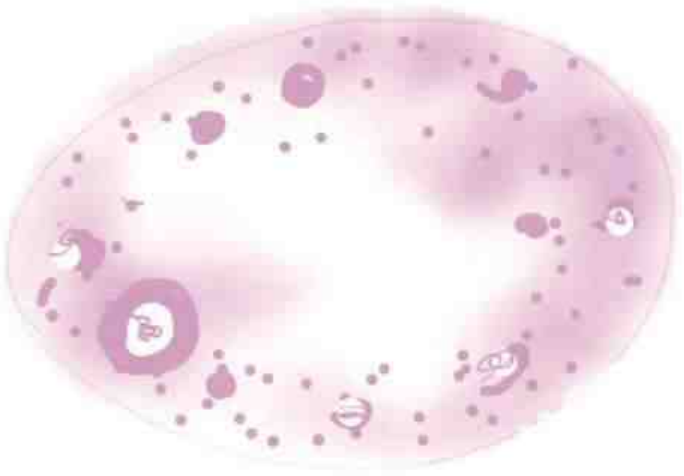
EARLY OVARIAN FAILURE

coadministration of GnRHa and adjuvant chemotherapy has an ovarian protective effect

Ruddy KJ,et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol 2014;32:1151-6
Moore HCF, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015;372:923-32

FERTILITY PRESERVATION PROCEDURES

Ovarian suppression



OVARIAN PROPHYlaxis

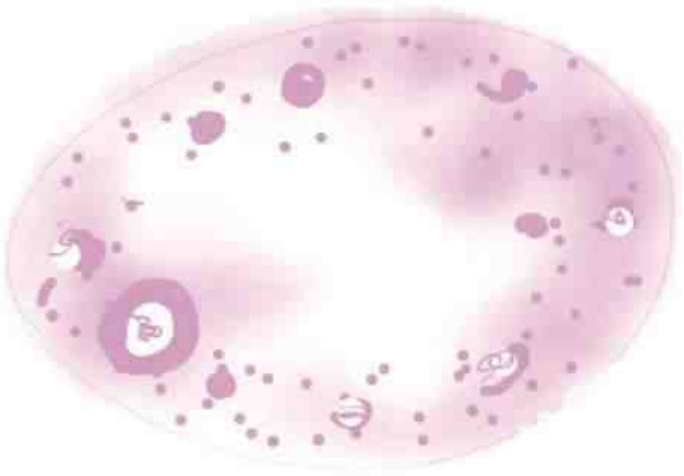
*clinical studies are **controversial**:
not/ shown benefit of ovarian suppression by GnRH-a

The American Society of Clinical Oncology: there is **insufficient** evidence that ovarian suppression protects fertility from gonadotoxic therapies

*Waxman JH, Ahmed R, Smith D et al. Failure to preserve fertility in patients with Hodgkin's disease. Cancer Chemother Pharmacol. 1987;19:159-162.
Blumenfeld Z, Avivi I, Linn S et al. Prevention of irreversible chemo-therapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy. Hum Reprod. 1996;11:1620-1626.

FERTILITY PRESERVATION PROCEDURES

Ovarian suppression



OVARIAN PROPHYlaxis

257 premenopausal women with operable hormone-receptor-negative breast cancer (18 to 49 years)

chemotherapy vs chemotherapy + GnRHa

Primary study end point: rate of ovarian failure at 2 years (absence of menses in the preceding 6 month, postmenopausal FSH level)

Secondary end point:

pregnancy outcome
disease - free survival rate
overall survival rate

Moore HCF. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015

OVARIAN SUPRESSION

CHEMOTHERAPY VS CHEMOTHERAPY+GnRHa

OVARIAN FAILURE
22 % vs 8 % p=0.04

Disease free survival rate
p=0.03

Overall survival rate
p=0.05

Moore HCF. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015

PREGNANCY OUTCOME

Moore HCF. N Engl J Med 2015

outcome	Chemotherapy (n=113)	Chemotherapy plus GnRHa (n=105)	OR with GnRH	P value
Attemped pregnancy-n (%)	18 (16)	25 (24)	1.78	0.12
Achieved pregnancy-n (%)	12 (11) **67%**	22 (21) **88 %**	2.45	0.03
Delivery and Ongoing pregnancy- n (%)	10 (9) **56 %**	19 (18) **76 %**	2.45	0.04

LIMITATION of GnRHa

- The safety of concurrent administration GnRHa with chemotherapy is confirmed only in ER-negative breast cancer

- It cannot adress the safety of GnRHa therapy with chemotherapy in ER + breast cancer patients

HODGKIN'S LYMPHOMA

5-year survival rate (87% to 96%)

ABVD (doxorubicin, bleomycin, vinblastine,decarbazine) – litle risk of POF

Alkylating agents (MOPP, CHOP, BEACOPP)-up to 70% risk of POF

Refractory disease and relapse cannot be predicted

Fertility issue and preservation methods should be discussed under the age of 37

ACUTE LYMPHOBLASTIC LEUKEMIA

The most common childhood cancer

5-years all survival rate 66 %

Conteporary treatment protocol : low doses, cyclophosphamide – no cause infertility

For patients undergoing HSCT – ovarian tissue preservation in children

In adult patients – oocytes, embryos

ACUTE MYELOID LEUKEMIA

5 –years all survival rate 24 %

Fertility preservation issues the same as in ALL

CHRONIC MYELOID LEUKEMIA

Is treated with inhibitors of thyrosine kinase (Gleevec) – no gonadotoxic effect

In case of HSCT – fertility preservation methods

Ovarian tissue may be infiltrated by the disease

BONE MARROW INFILTRATION

trombocytopenia

platelet dysfunction or

defective coagulation factor synthesis

platelet or plasma transfusion –before oocyte retrieval

PELVIC INFECTION

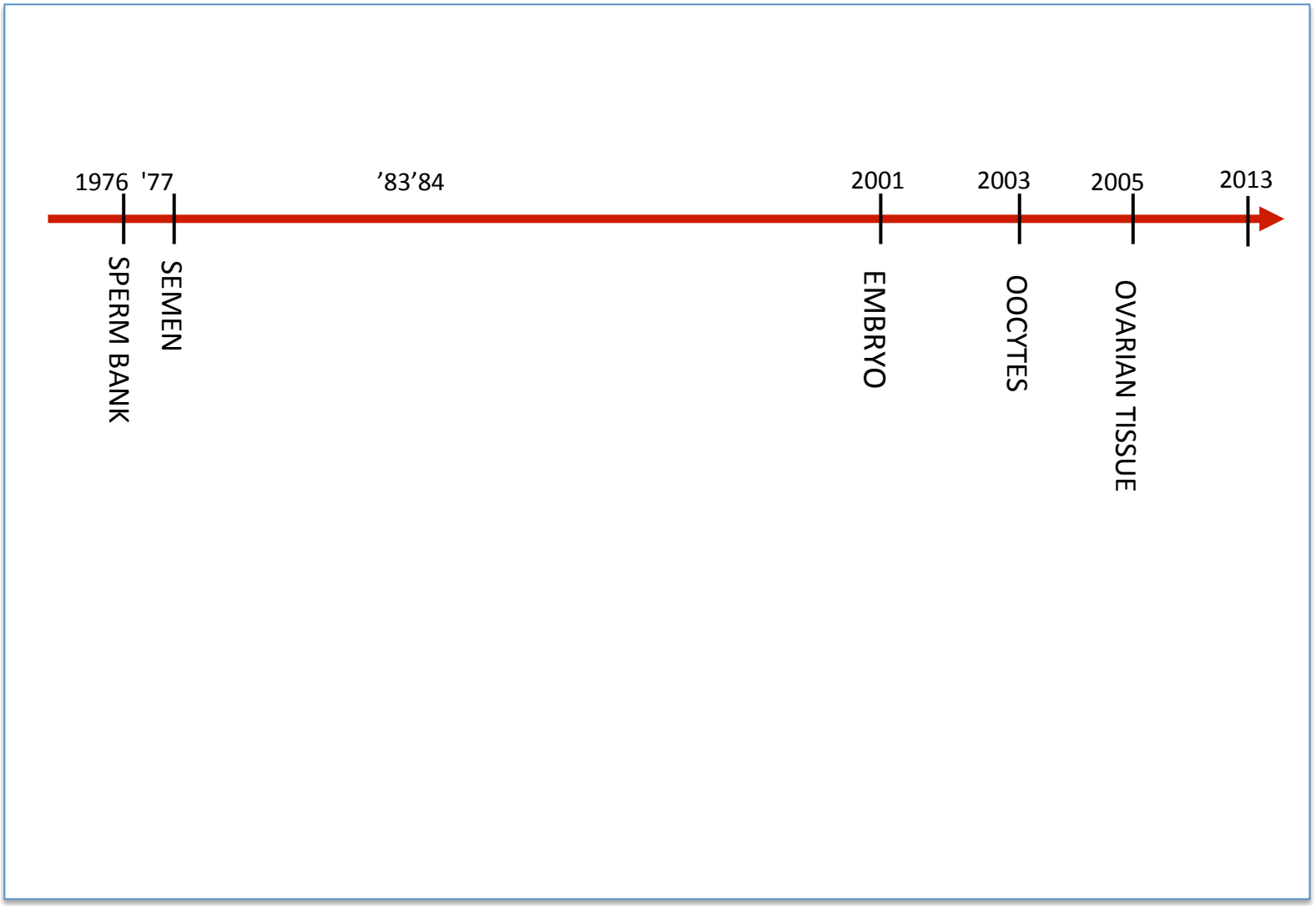
patients with neutropenia

granulocyte colony-stimulating factor

prophylactic antibiotics

Cakman H, FS 2013

OUR EXPERIENCE



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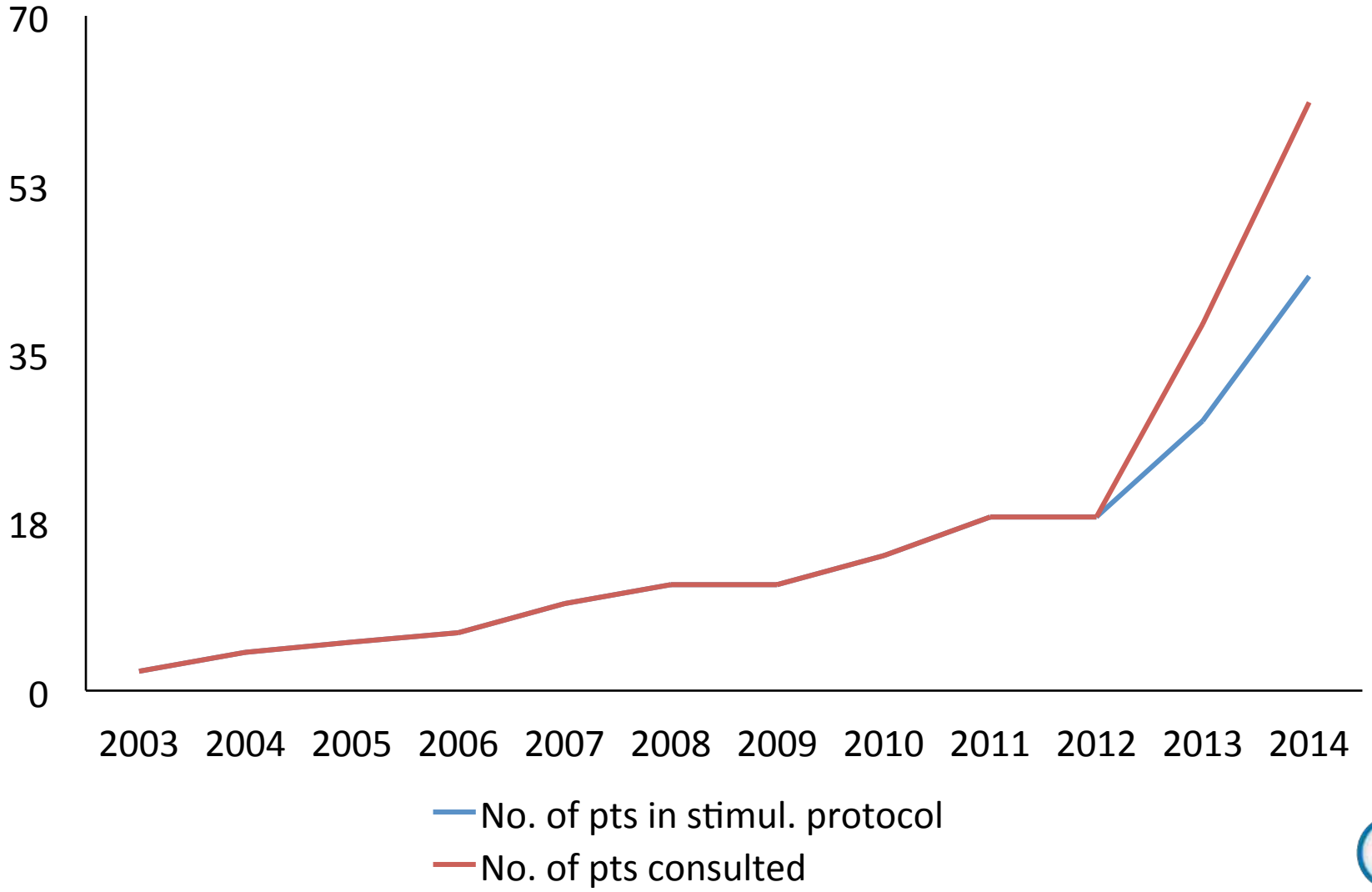
OUR EXPERIENCE

Cryobanking in University Medical Centre Ljubljana from 2001 to dec 2014



OUR EXPERIENCE 2013-2014

41 pts consulted
14 to 43 years old, average 30 years

25 stimulation protocols

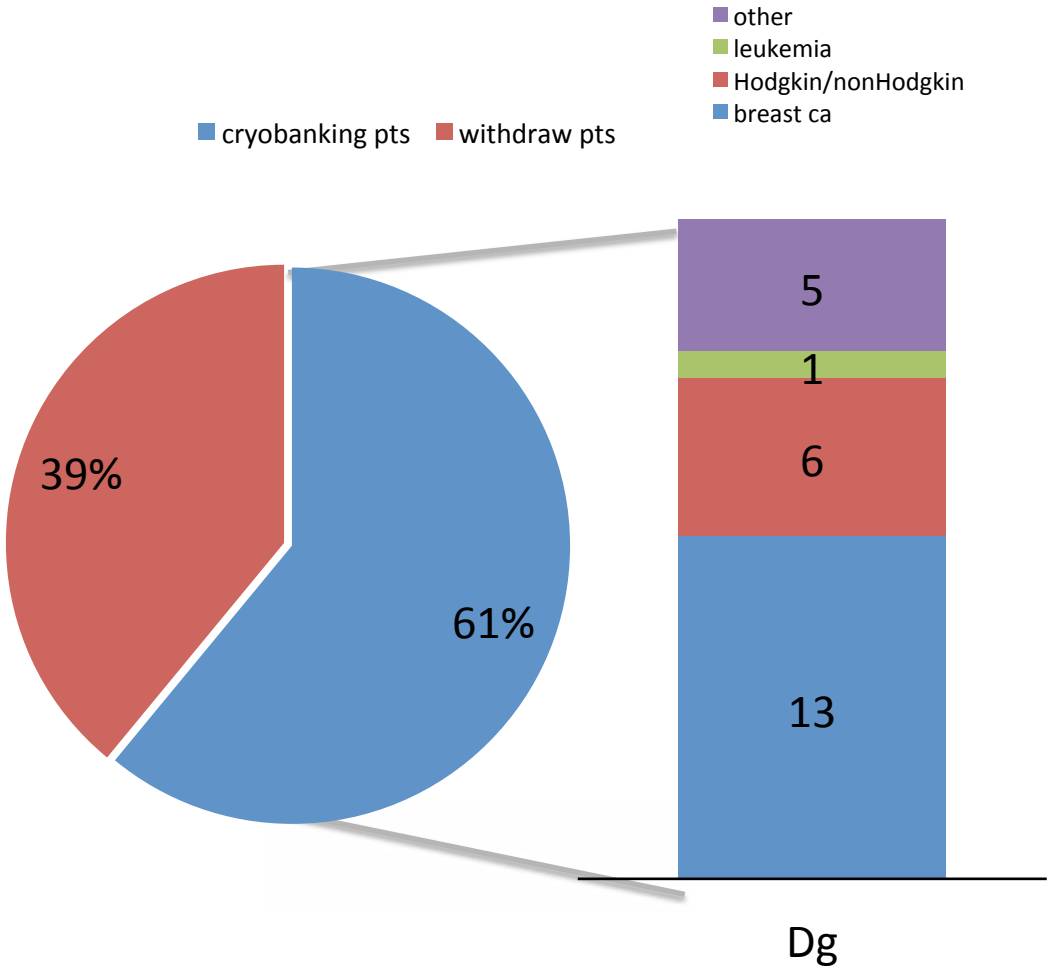
165 frosen oocytes in 15 pts
11oocytes/pts (1 min, 31 max)

23 embryos in 7 pts
3,3 embryos/pts

1 pts died, 1 mts

OUR EXPERIENCE

Cryobanking in University Medical Centre Ljubljana from 2013 to dec 2014



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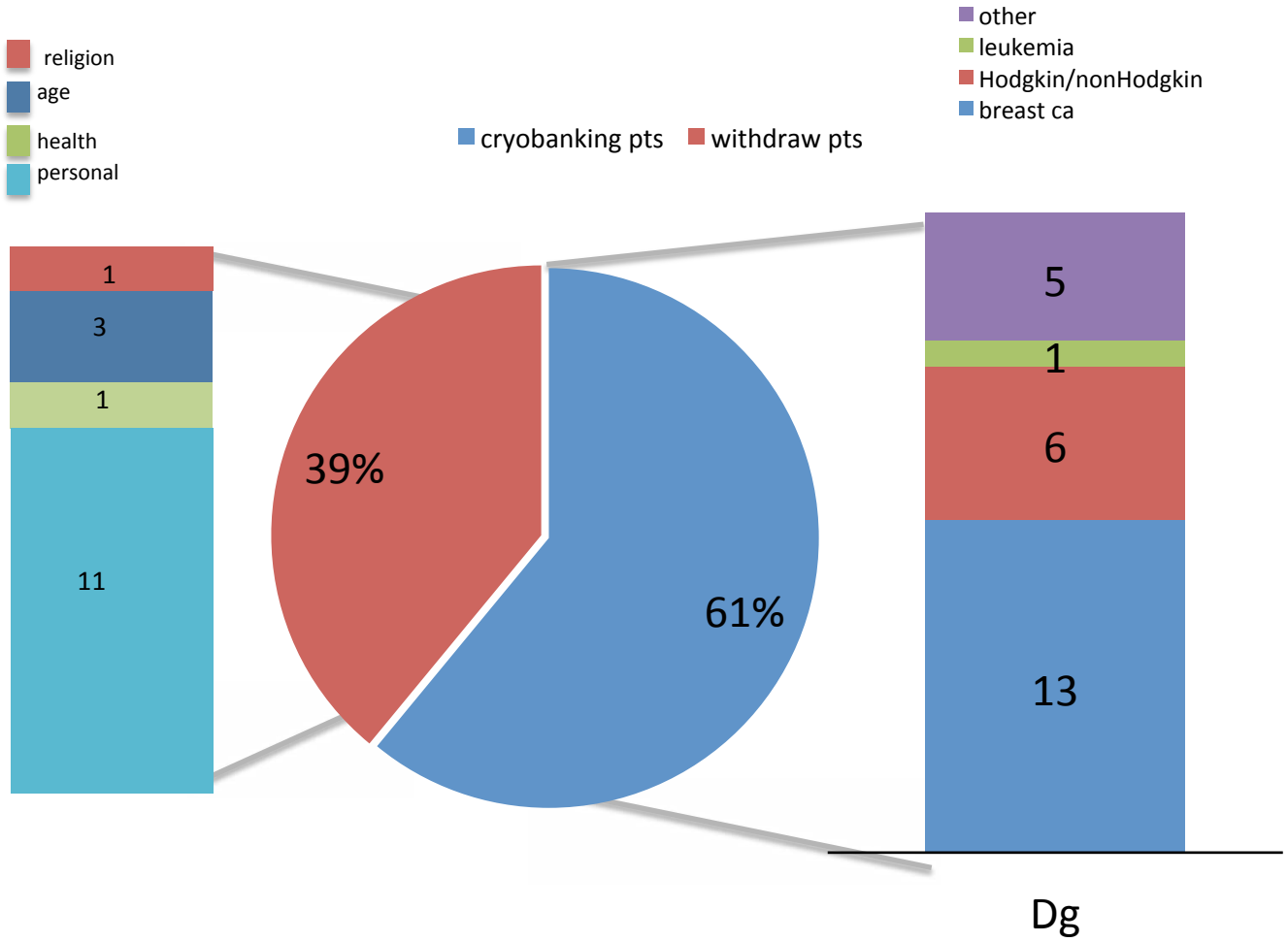

TAKE HOME MESSAGE

Fertility preservation of post pubertal women

Radiation of the Pelvis	Chemotherapy can be postponed By 2 weeks	Chemotherapy can Be postponed by <2 Weeks
ovarian transposition and /or cryopreservation of ovarian tissue and /or ovarian stimulation and cryopreservation of unfertilized or fertilized oocytes	ovarian stimulation & cryopreservation of unfertilized or fertilized oocytes aromatase inhibitors* (estrogen dependent tumor) and /or cryopreservation of ovarian tissue and/or GnRH-agonists*	cryopreservation of ovarian tissue and/or GnRH-agonists*

*Fertility preservation in women—a practical guide to preservation techniques and therapeutic strategies in breast cancer, Hodgkin's lymphoma and borderline ovarian tumours by the fertility preservation network FertiPROTEKT