

ONKOFERTILITETNI POSTUPCI NAŠA ISKUSTVA

Vrtačnik Bokal Eda



KLINIČNI ODDELEK
ZA REPRODUKCIJO

GINEKOLOŠKA KLINIKA • UKC LJUBLJANA

IN RECENT DECADES

a trend toward delaying childbearing

proportion of first-time mother > 30 years in USA (1990 -2002, 4.1% to 21.2 %)

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



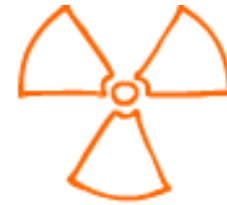
PATIENTS WITH MALIGNANT DISEASES

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.



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

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

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

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

3 birth after alkylating-agent chemotherapy



PREMATURE MENOPAUSE POI

total dose of chemotherapy or radiation

age of patients– increasing age at the time of treatment is directly correlated with rates of permanent amenorrhea

one-half – had not received high risk therapy-
outcomes were affected



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

*Himmelstein-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

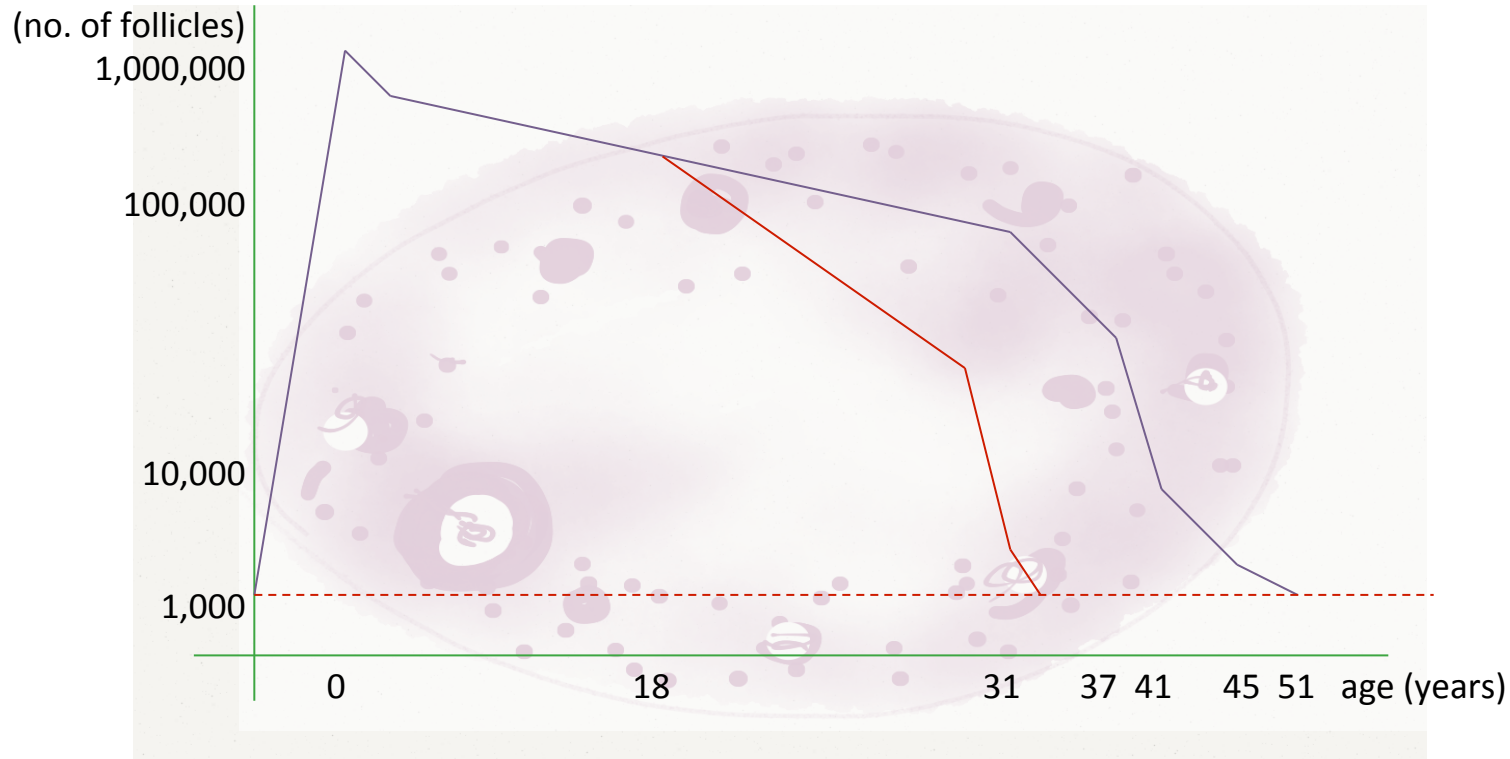
*Wallace WH, Thomson AB, Saran F and Kelsey TW (2005) Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 62,738–744

**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

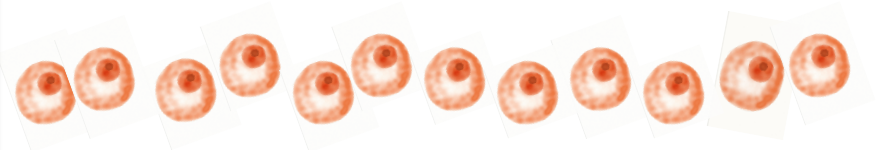
presentations of procedures, complications
and expectations



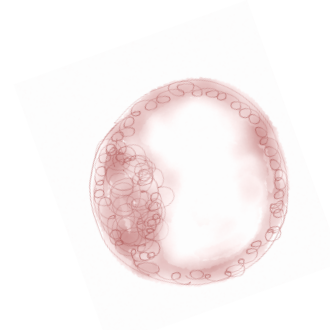
OOCYTES & EMBRYOS

**CHANCES FOR FUTURE
PREGNANCIES?**

OOCYTES



12-20 oocytes



PREGNANCY



FERTILITY PRESERVATION

to postpone oncological treatment for the duration of the ovarian stimulation, i.e. for 2 to 6 weeks

and at the same time should not worsen the prospects of the oncological treatment



FERTILITY PRESERVATION

we can preserve:

mature and immature oocytes

embryos and ovarian tissue

Disadvantages of embryos cryopreservation:

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)



OOCYTE PRESERVATION

Best results after vitrification of mature oocytes

Immature oocyte : HCG – largest follicle is 12 mm-
HCG+36 h OA (advantage of shorter time, even in
luteal phase)

Immature oocytes can be also matured and
fertilized



OVARIAN TISSUE CRYOPRESERVATION

By laparoscopy at maximum age limit of 37 years

Decision 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 medulla, 60 pregnancies)

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



CONTROLLED 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



PATIENTS WITH BREAST CANCER

7 % of women with BC are diagnosed < 40 years

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



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

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

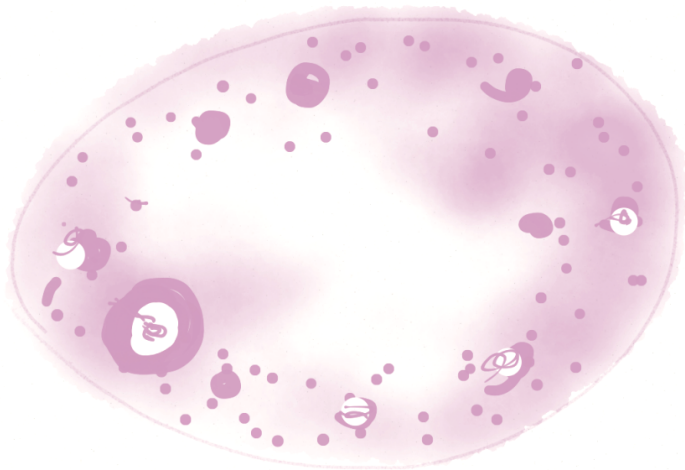
last dose **24 h before oocyte retrieval**

reinitiate 12 h after retrieval



FERTILITY PRESERVATION PROCEDURES

Ovarian suppression



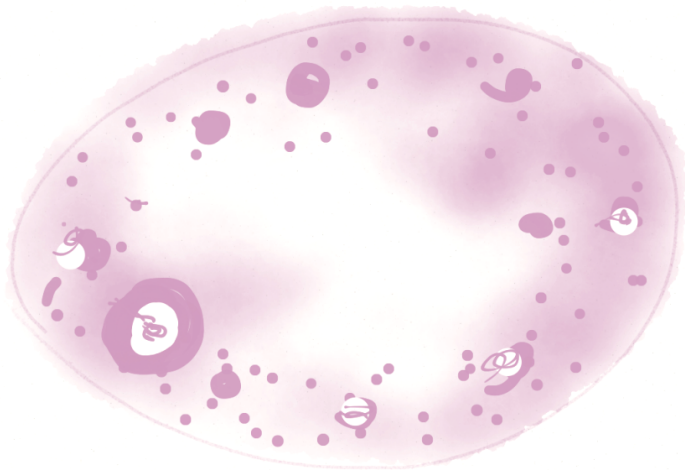
EARLY OVARIAN FAILURE

coadministration of GnRH α and adjuvant chemotherapy has an ovarian protective effect



FERTILITY PRESERVATION PROCEDURES

Ovarian suppression



OVARIAN PROPHYLAXIS

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

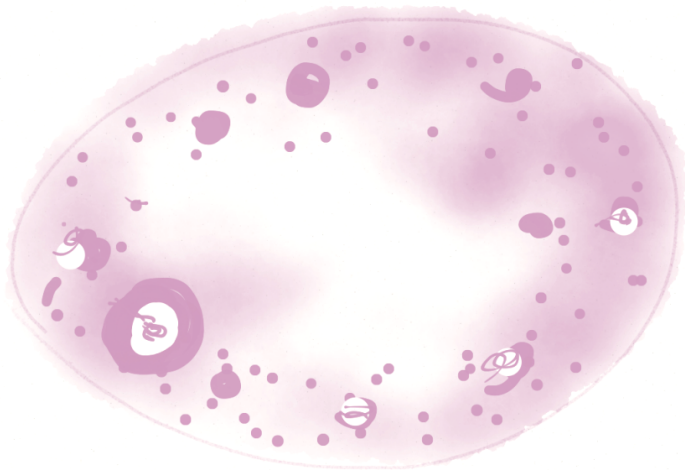
The American Society of Clinical Oncology:
there is **insufficient** evidence that ovarian
suppression protects fertility from
gonadotoxic therapies

*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



OVARIAN SUPPRESSION

CHEMOTHERAPY VS CHEMOTHERAPY+GnRHa

OVARIAN FAILURE
8% vs 22 % $p=0.04$

Disease free survival rate
 $p=0.03$

Overall survival rate
 $p=0.05$



PREGNANCY OUTCOME

Moore HCF. N Engl J Med 2015

outcome	Chemotherapy (n=113)	Chemotherapy plus GnRHa (n=105)	OR with GnRH	P value
Attempted 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 address 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) – little 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



NON-HODGKIN'S LYMPHOMA

5-years survival rate – 69%

Therapy: local radiation

chemotherapy: alkylating agents

immunotherapy

haematopoietic stem cell

transplantation (HSCT) – before TBI and/or
alkylating agents

Should be discussed with hematologists



ACUTE LYMPHOBLASTIC LEUKEMIA

The most common childhood cancer

5-years all survival rate 66 %

Contemporary 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 tyrosine 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



RESPIRATORY DYSFUNCTION

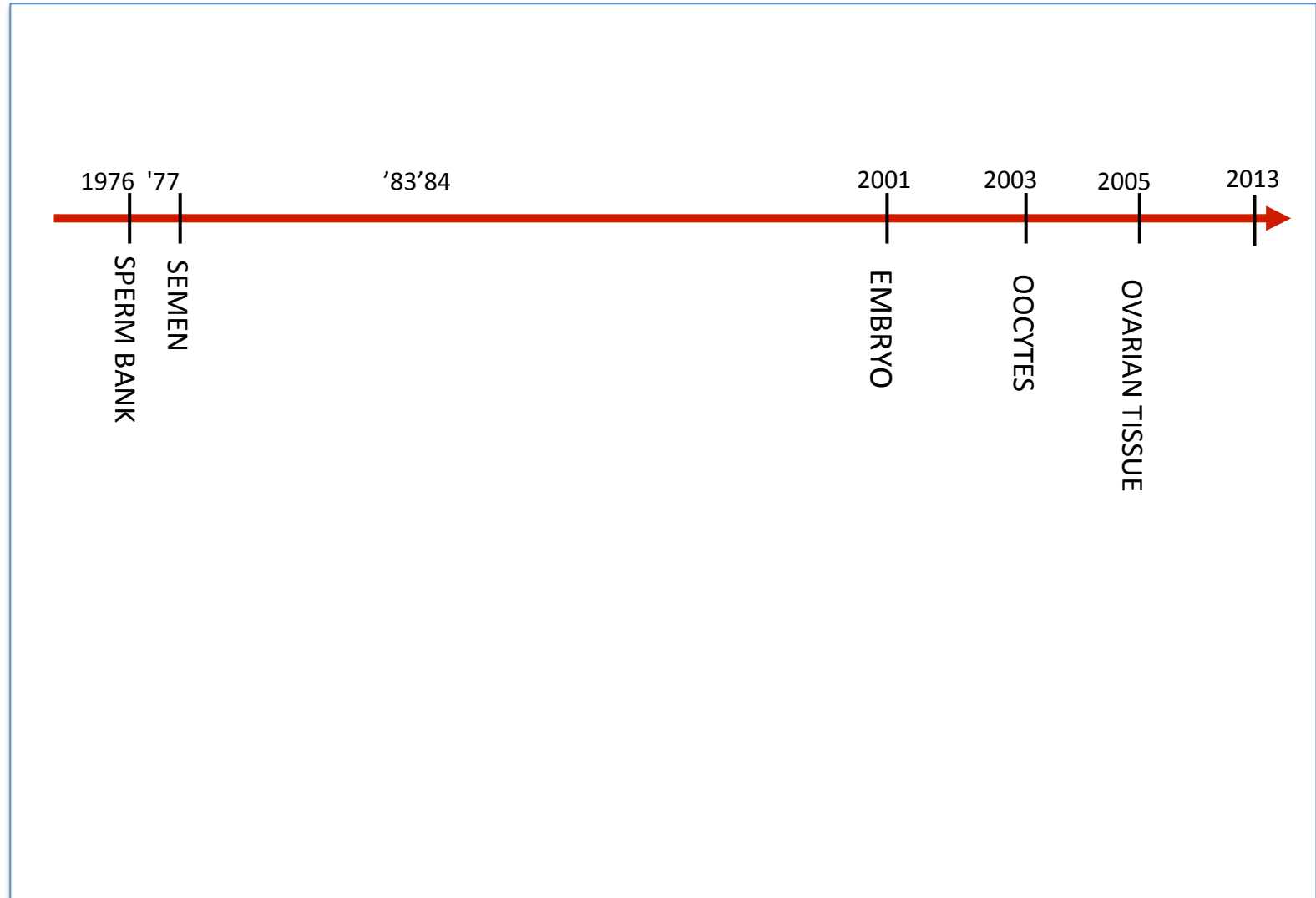
due to tracheal compression, mediastinal mass,
large pleural effusion.....

anesthesia consultation should be obtained in
advance

Cakman H, FS 2013



OUR EXPERIENCE



KONTAKTIRAJTE NAS

01 522 62 60 ali 01 522 62 61
vsak delovni dan med 8.00 - 14.00

info@reprodukcija.si

Po prejemu tel. klica ali elektronski pošti bomo v **24 urah** sklicali **Konzilij za hranjenje genetskega materiala**, na katerem bomo skupaj z lečečim onkologom opredelili indikacijo za postopek za vsako bolnico individualno.

Pri tem bomo upoštevali starost bolnice, vrsto malignoma, stadij, prognozo bolezni, morebiten vpliv nosečnosti na osnovno bolezen, morebiten vpliv osnovne bolezni na plod, načrtovani način zdravljenja. Bolničina maternica mora biti ohranjena in nepoškodovana.

Po končanem konziliju se bomo **pomenili z bolnico** (in njenim partnerjem) ali starši (če gre za mladoletno osebo)



HOW TO GET US



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01-522-62-61

01-522-62-60

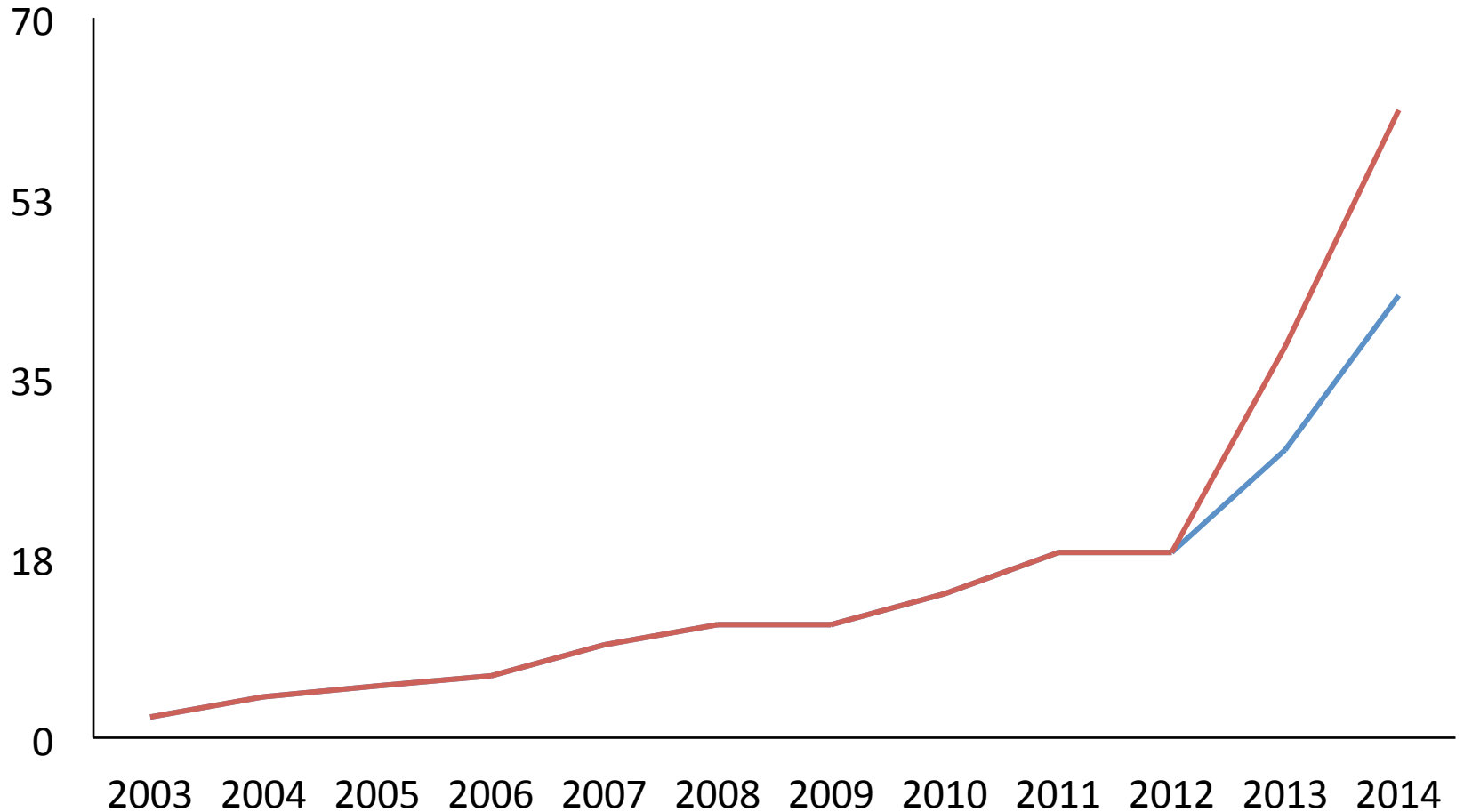
every day from 8.00 to 14.00

info@reprodukcija.si



OUR EXPERIENCE

Cryobanking in University Medical Centre Ljubljana from 2001 to dec 2014



— No. of pts in stimul. protocol
— No. of pts consulted



OUR EXPERIENCE 2013-2014

41 pts consulted

14 to 43 years old, average 30 years

25 stimulation protocols

165 frozen oocytes in 15 pts

11 oocytes/pts (1 min, 31 max)

23 embryos in 7 pts

3,3 embryos/pts

1 pts died



OUR EXPERIENCE

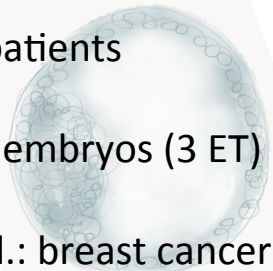
Cryobanking in University Medical Centre Ljubljana from 2001 to sep 2012

EMBRYOS

6 patients

13 embryos (3 ET)

Ind.: breast cancer
Mb. Hodgking's



OOCYTES

22 patients in 24 stimulations

21-38 years

143 oocytes (6,5 oocytes/patient)

Ind.:

breast cancer
Mb. Hodgking's
Turner's sy.
borderline ovarian cancer

2 died



Ovarian tissue

33 patients

13-38 years

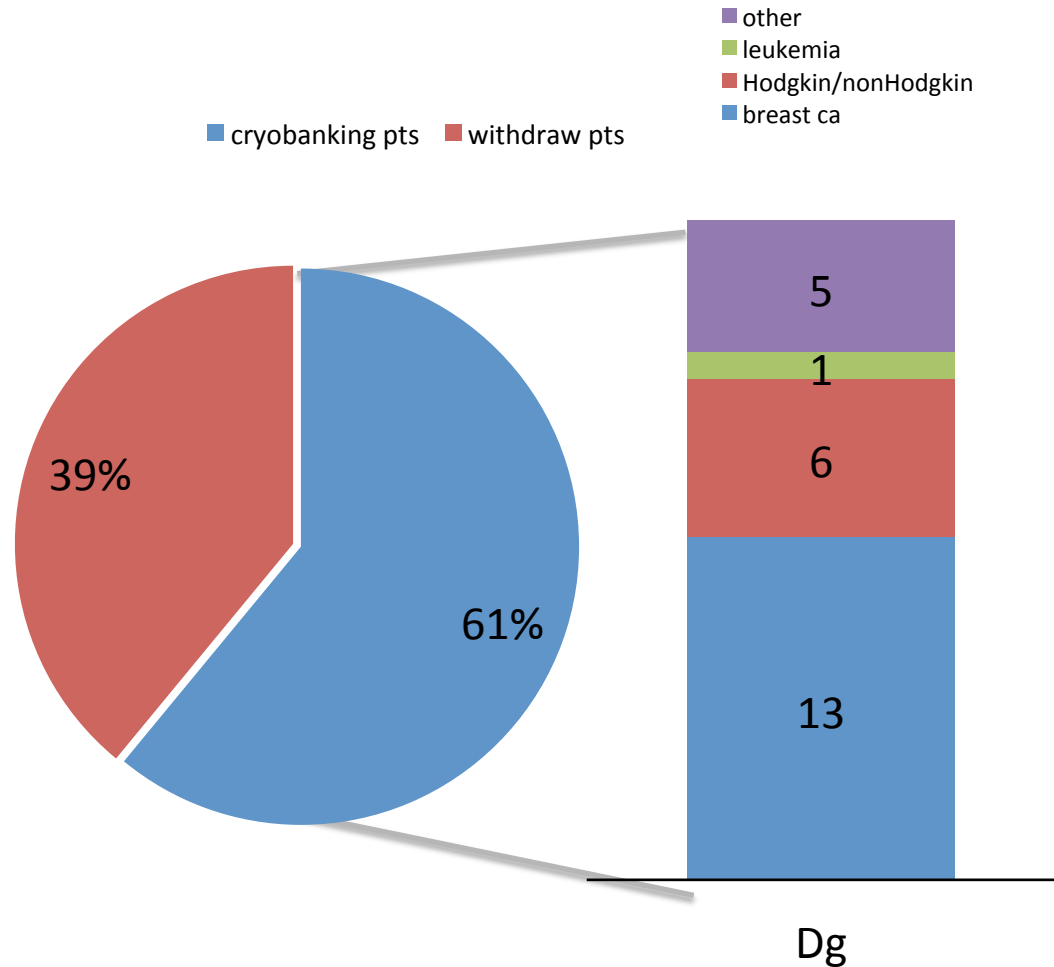
208 ovarian tissue (6,3/patient)

Ind.: borderline ovarian cancer
early cervical cancer
early uterus cancer
praecox menopaussis
2 patients: oocytes



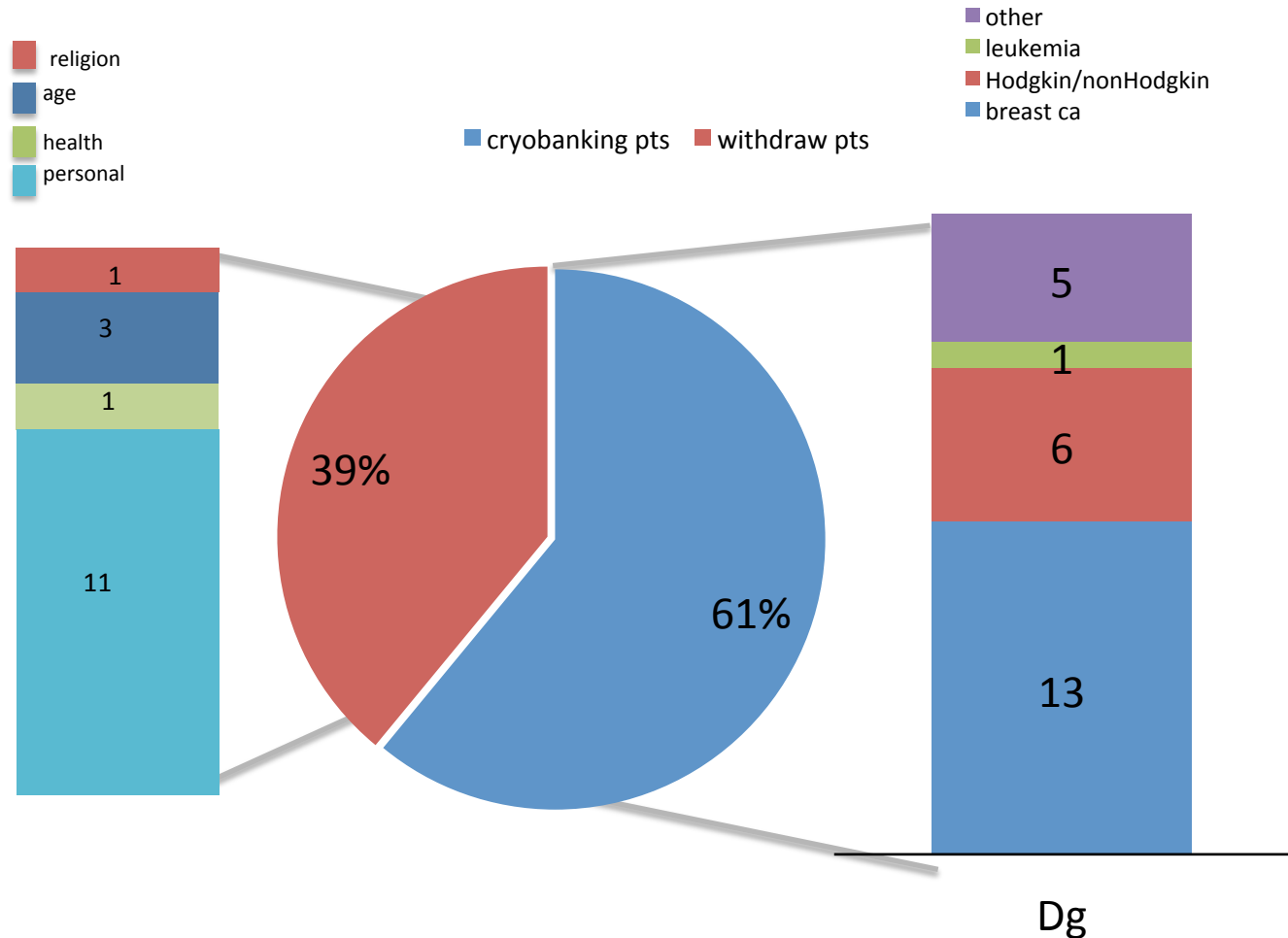
OUR EXPERIENCE

Cryobanking in University Medical Centre Ljubljana from 2013 to dec 2014



OUR EXPERIENCE

Cryobanking in University Medical Centre Ljubljana from 2013 to dec 2014



TAKE HOME MESSAGE

FERTILITY PRESERVATION OF POST PUBERTAL WOMEN

RADIATION OF THE PELVIS

ovarian transposition
and /or
cryopreservation of ovarian tissue
and /or
ovarian stimulation
and
cryopreservation of unfertilized or fertilized oocytes

CHEMOTHERAPY CAN BE POSTPONED BY 2 WEEKS

ovarian stimulation & cryopreservation of unfertilized or fertilized oocytes
aromatase inhibitors* (estrogen dependent tumor)
and /or
cryopreservation of ovarian tissue
and/or
GnRH-agonists*

CHEMOTHERAPY CAN BE POSTPONED BY <2 WEEKS

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

