PRE-CONGRESS COURSE 10

Fertility preservation in women: Facts and dilemmas

Middle East Fertility Society Exchange course
Munich - Germany, 29 June 2014

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Fertility preservation in women: Facts and dilemmas

Munich, Germany
29 June 2014

Organised by
Middle East Fertility Society (MEFS)

Contents

Course coordinators

Johnny Awwad (Lebanon) and Mohammad Aboulghar (Egypt)

Course description

Fertility preservation refers to the management approach aimed at preserving and restoring fertility in women undergoing treatment for cancer. It is a substantial quality of life issue in cancer survivors. It may also benefit other clinical conditions, such as incipient ovarian failure and ovarian ageing in women.

This course aims to provide an updated review on the medical and surgical means to reduce the devastating effects of cancer treatment on ovarian function; the current scientific and clinical development of fertility preservation strategies; and the ethical and legal challenges ahead.

To achieve these objectives, a panel of distinguished researchers and scholars has agreed to share with the audience their expertise and knowledge, laying grounds for an exceptional opportunity for exchange and networking.

Target audience

- Reproductive Endocrinologists and Fertility Specialists
- Biologists involved in assisted reproductive technologies
- Oncologists
- Oncology nurses
- Psychologists and Social workers

Educational needs and expected outcomes

At the completion of this pre-congress course, participants should be able to:

- Explain the effects of cancer treatment on ovarian function and reproduction
- Describe the most recent clinical collection techniques associated with oocyte cryopreservation
- Evaluate the current status of ovarian tissue cryopreservation and transplantation
- Assess the cost-effectiveness of social egg banking
- Recognize the psychological, ethical, and legal challenges related to fertility preservation
- Provide informed counseling to women with cancer about fertility preservation options

Course type

Advanced

Scientific programme

Chairmen: Johnny Awwad – Lebanon, Mohamed A. Aboulghar – Egypt and Michel Abou Abdallah - Lebanon

09:00 - 09:25	Fertility in female cancer survivors: Pathophysiology and impact on ovarian reserve ***Tommaso Falcone - U.S.A.***
09:25 - 09:50	Mechanisms of chemotherapy induced ovarian damage: implications for future treatments ***Kutluk H. Oktay - U.S.A.***
09:50 - 10:15	Ovarian tissue cryopreservation: Current achievements ***Jacques Donnez - Belgium***
10:15 - 10:30	Discussion
10:30 - 11:00	Coffee break
11:00 - 11:30	Practice guidelines for fertility preservation in cancer patients ***S. Samuel Kim - U.S.A.***
11:30 - 11:45	Discussion
11:45 - 12:15	Fertility preservation in young women with breast cancer ***Kutluk H. Oktay - U.S.A.***
12:15 - 12:30	Discussion
12:30 - 13:30	Lunch break
13:30 - 13:55	Age Specific Success of Oocyte Cryopreservation: How to counsel your patient ***Kutluk H. Oktay - U.S.A.***
13:55 - 14:20	Ethical and moral dilemmas in social egg banking ***Jacques Donnez - Belgium***
14:20 - 14:45	Minimally Invasive approaches to Fertility Preservation ***Tommaso Falcone - U.S.A.***
14:45 - 15:00	Discussion
15:00 - 15:30	Coffee break
15:30 - 16:00	Current dilemmas with heterotopic ovarian transplantation: fertility or futility ***S. Samuel Kim - U.S.A.***
16:00 - 16:15	Discussion
16:15 - 16:45	The current fertility preservation consultation model: Are we adequately informing cancer patients of their options? ***Johnny Awwad - Lebanon***
16:45 - 17:00	Discussion

Fertility in female cancer survivors: Pathophysiology & impact on ovarian reserve

Tommaso Falcone, M.D.,FRCSC,FACOG
| Professor and Chair Obstetrics, Gynecology and Women's Health Institute |

Learning objectives

At the conclusion of this presentation, participants should be able to:

- Assess the toxicity of cancer treatment on fertility.
- Discuss the impact of cancer treatment on the menstrual cycle
- Discuss the long term consequences of cancer treatment on ovarian reserve

Financial Disclosure

- I have no financial relationships with industry
- Receive honoraria
  - Editor-in-Chief Journal of Minimally Invasive Surgery
  - Section Editor- Up-To-Date

Chronic Health Conditions in Adult Survivors of Childhood Cancer
Oeffinger et al 2006 NEJM

- **Survivors (N = 10,397)-Siblings (N = 3034) Relative Risk (95% CI)**
- *Mean age 26 years at the time of the study*
- Major joint replacement 54.0 (7.6–386.3)
- Congestive heart failure 15.1 (4.8–47.9)
- Second malignant neoplasm 14.8 (7.2–30.4)
- Cognitive dysfunction, severe 10.5 (2.6–43.0)
- Coronary artery disease 10.4 (4.1–25.9)
- Cerebrovascular accident 9.3 (4.1–21.2)
- Renal failure or dialysis 8.9 (2.2–36.6)
- Hearing loss not corrected by aid 6.3 (3.3–11.8)
- Legally blind or loss of an eye 5.8 (3.5–9.5)
- Ovarian failure 3.5 (2.7–5.2)---

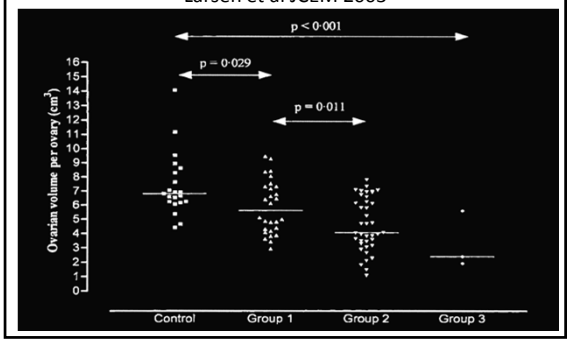
Fertility of female survivors of childhood cancers:
Green et al J Clin Oncol 2009

- N=6643- ages 15-44; sibling controls
- RR of a survivor being pregnant was .81 (95 % CI, 0.73 to 0.90)
- Pelvic Radiation exposure: RR of pregnancy
  - 5 to 10 Gy- 0.56 (95 % CI, 0.37 to 0.85)
  - greater than 10 Gy-0.18 (95% CI, 0.13 to 0.26)
- Hypothalamic-pituitary radiation dose of 30 GY- 0.61(95% CI , 0.44 to 0.83)
- **Chemotherapy:** RR of pregnancy
  - CCNU - .44; (95% CI: 0, 0.24-0.80)
  - Cyclophosphamide- 0.8 (95% CI:0.68-0.93)
    - Decreased with increasing dose and agent administered

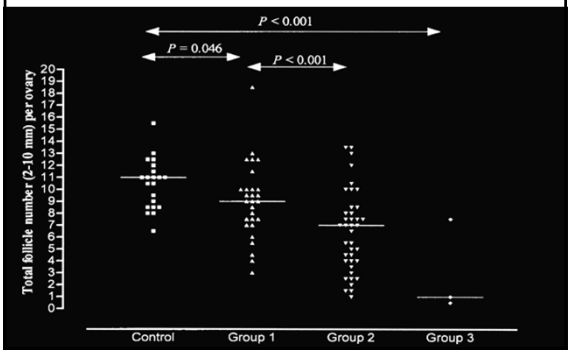
Ovarian function Long Term survivors of childhood cancers:
Larsen et al JCEM 2003

- Diagnosis 5.4 years- study 25 years of age
- **N=100**- N=17 had POF; 13 on OCs
- **Survivors that had spontaneous cycles- (N=70)** smaller ovarian volume per ovary than controls
- Lower number of antral follicles per ovary
- Lower inhibin B levels

Ovarian function Long Term survivors of childhood cancers:
Larsen et al JCEM 2003

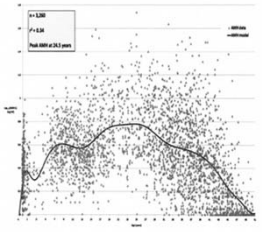


Ovarian function Long Term survivors of childhood cancers:
Larsen et al JCEM 2003



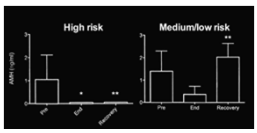
AMH model (Kelsey et al PloS ONE 2011)

- AMH peaks at 24.5 years
- Product of growing follicles but reflects the resting pool
- 34 % variation is due to age alone



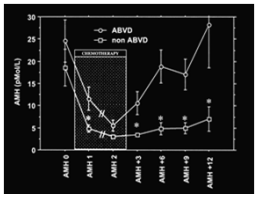
AMH as a marker of Gonadotoxicity
Brougham et al JCEM 2012

- Prospective longitudinal study
- N= 22 (17 pre-pubertal)
- AMH, inhibin B, FSH at diagnosis & then after each chemotherapy course
- AMH decreased with each chemotherapy course in pre-pubertal & pubertal girls
  - Undetectable in 50%
  - Recovery in the low/medium risk groups
  - High risk group AMH showed no recovery



Anti-Mullerian hormone follow up after chemotherapy for lymphoma
Decanter et al RBO 2009

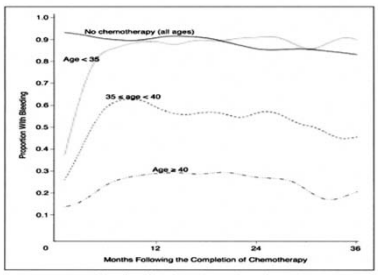
- N= 30; mean age 24 years
- ABVD vs. protocol with cyclophosphamide (non-ABVD)
- AMH fell in all patients
- Recovery seen in the ABVD group but not in the non-ABVD group



Prediction model for the individual patient

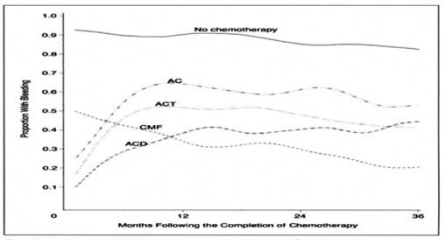
- Chemotherapy induced amenorrhea (CIA)
- Petrek et al J Clin Oncol 2006
- N=595- breast cancer patients age 20-45 (median 39 years)
- Prospective study
- Age & specific chemotherapy regimen determines return to regular cycles

Petrek et al J Clin Oncol 2006
Proportion of women with monthly bleeding after completion of chemotherapy



Bleeding after chemotherapy by patient age.

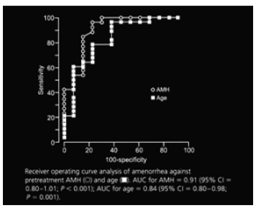
Petrek et al J Clin Oncol 2006
Proportion of women with monthly bleeding after completion of chemotherapy



Bleeding after chemotherapy by type of regimen. AC, doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, paclitaxel; CMF, cyclophosphamide, methotrexate, fluorouracil; ACD, doxorubicin, cyclophosphamide, docetaxel.

AMH & Breast Cancer treatment:
Anderson & Cameron JCEM 2011

- N=42- 5 year follow up of ovarian function (AFC & AMH)-Std. regimen included cyclophosphamide
- Age & Pre-treatment levels of AMH, FSH & AFC predicted CRA- **in multivariate analysis only pre-treatment AMH is significant**
  - Peak likelihood ratio of 7 at AMH 0.71 ng/ mL
    - Sensitivity 54% & specificity 92%



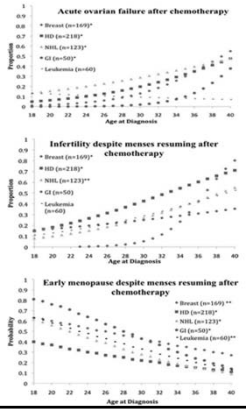
Receiver operating curve analysis of amenorrhea against pretreatment AMH (○) and age (■). AUC for AMH = 0.91 (95% CI = 0.80–1.01; $P < 0.001$); AUC for age = 0.84 (95% CI = 0.80–0.98; $P = 0.001$).

Reproductive Impairment in cycling women

- Letourneau et al Cancer 2012
- How impaired is fertility in normally cycling women s/p chemotherapy?
- Retrospective survey
- Age 18-40 years of age-
  - Diagnosed 1993-2007
  - 6709 identified
    - 4147 excluded because contact info inaccurate
    - 41 % response rate
    - Chemotherapy alone

Reproductive Impairment in cycling women

- Infertility in patients who resumed menses
- 49-65 % reported that they wanted children
- 30%-41% attempted-
- N=620
- Acute ovarian failure (AOF)
  - Leukemia-3%
  - Breast cancer & NHL- 9%-10%
- 18 year old woman with NHL
  - If they resume menstruation- 9 % chance of infertility
    - 60 % chance of early menopause

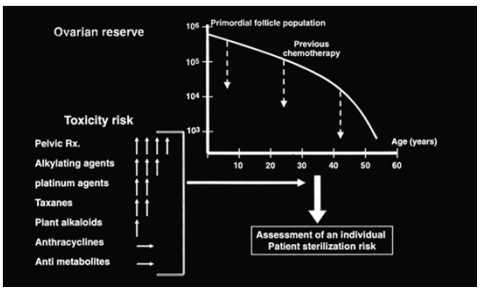


- Letourneau et al Cancer 2012

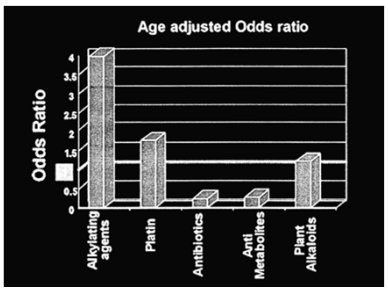
Fertility in cancer patients after cryopreservation of one ovary: Schmidt et al RBO 2013

- Questionnaire study of women that had ovarian cryopreservation- Danish central registry
  - Participation 78% (N= 143)
  - All scope oophorectomy
  - Post-chemotherapy in breast cancer patients (N=54) - 85 % had a normal menstrual cycle
    - Highest amenorrhea rate was in leukemia (85%)
  - 57 women tried to get pregnant- 41 succeeded (93 % spontaneous)

Meirow et al Clinical Ob Gyn 2010



Meirow et al Clinical Ob Gyn 2010



Radiation induced Ovarian damage

- Direction of beam & the scatter
- Direct radiation -97% ovarian failure
- LD_{50} is 2 Gy- ½ of the non-growing follicles are lost
- Lower dose required for an LD_{50} as age increases

Radiation induced Uterine damage

- Especially problematic in younger patients
- Ex. Whole body radiation
  - Uterine length is 4 cm compared with 7 cm in controls
  - Premature deliveries & miscarriages

Reproductive outcome

- Cancer treatment has mutagenic effects
  - Drug dependent
    - Alkylating & plant alkaloids - abortions & malformations
    - Cisplatin- high rate of embryonic mortality
- If conception occurs more than 1 year from cessation of treatment
  - No increase in abortions or congenital malformation
  - Concern if proceed to oocyte freezing after 1 cycle of chemotherapy

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Mechanism of Chemotherapy-Induced Ovarian Damage: Implications for Future Treatments

Kutluk Oktay, MD, FACOG

Professor of Obstetrics & Gynecology, Medicine, Cell Biology & Anatomy, and Pathology

Director, Division of Reproductive Medicine and Fertility Preservation

New York Medical College

Director, Innovation Institute for Fertility Preservation , Rye and Manhattan, NY

Innovative Care Fertility Preservation.org

New York Medical College

Disclosures

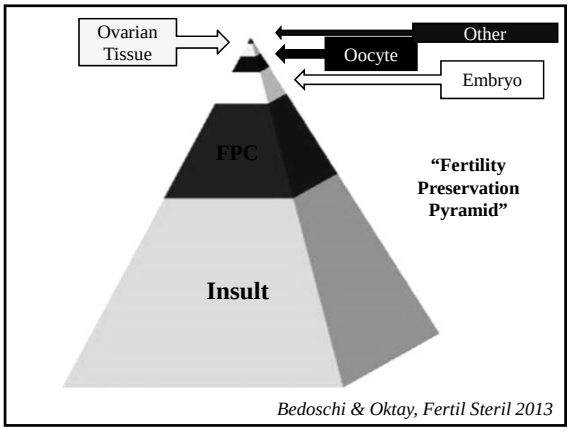
- **Medical Advisory Board Member, OvaScience**
- **Supported by National Institutes of Health:**
  - **R01 HD053112 from NICHD & NCI**
  - **R21 HD061259 from NICHD**

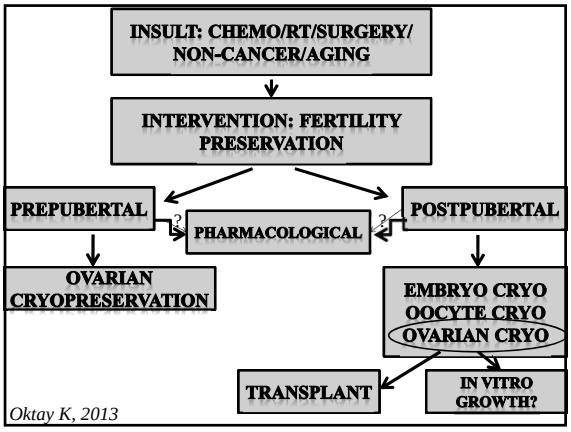
New York Medical College

Innovative Care Fertility Preservation.org

Learning Objectives

- **At the end of this presentation the participant is expected to comprehend:**
  - **Main classes of chemotherapy agents that damage ovarian reserve**
  - **Main mechanisms of this damage**
  - **Potential pharmacological approaches to preserve fertility by exploitation of these mechanisms of damage**





Background: We Know Little About the Insult

- **Information on chemo impact on fertility is still highly empirical**
- **Individual toxicity of chemotherapeutic agents is hard to determine**
- **Mechanism of damage unknown in humans**
- **Knowledge can improve counseling as well as resulting in the development of targeted treatments**

Ovarian toxicity of chemotherapeutic agents

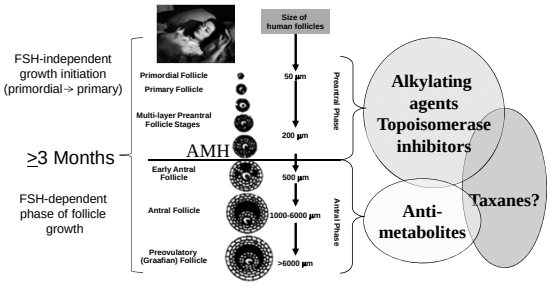
Drug	Class (action)
Definitely associated with ovarian damage	
Nitrogen mustard	Mechlorethamine (alkylating agent)
L-phenylalanine mustard	Mechlorethamine (alkylating agent)
Chlorambucil	Chloroethylamine (alkylating agent)
Cyclophosphamide	Chloroethylamine (alkylating agent)
Busulfan	Alkylalkane sulfonate (alkylating agent)
Procarbazine	Substituted hydrazine
Probably associated with ovarian damage	
Doxorubicin	Anthracycline
Vinblastine	Vinca alkaloid
Cytosine arabinoside (Ara-C)	Antimetabolite
Cis-platinum	Heavy metal
Carmustine	Nitrosourea (alkylating agent)
Lomustine	Nitrosourea (alkylating agent)
VP-16 (etoposide)	Podophyllotoxin
Unlikely to cause ovarian damage	
Methotrexate	Antimetabolite
Fluorouracil (5-FU)	Antimetabolite
6-mercaptopurine	Antimetabolite
Vincristine	Vinca alkaloid
Unknown	
VM-26	Podophyllotoxin
Daunorubicin	Anthracycline
Bleomycin	Peptide
Melphalan	Chloroethylamine
Decarbazine	Substituted hydrazine
Vindesine	Vinca alkaloid

Sonmezer & Oktay, Uptodate.com

Breast Cancer: Common During Reproductive Life

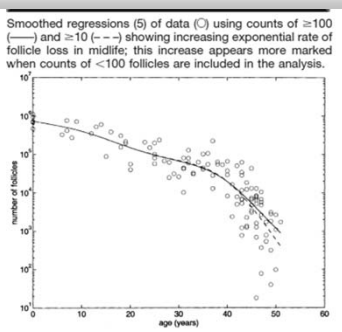
- **Breast cancer is the most common malignancy during reproductive ages**
- **Adjuvant/Neo-Adjuvant chemotherapy is associated with reproductive compromise**
- **Most common regimens: AC+T or AC, some CMF**

Impact of chemotherapy on different stages of follicular growth



Oktay & Rodriguez-Wallberg, 2011

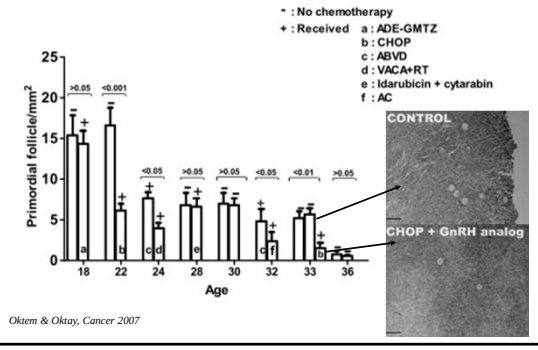
Primordial Follicle (Reserve) Decline Curve



Faddy, Gosden, Oktay & Nelson, Fertil Steril 1998

Clinical studies <u>cannot</u> quantify or <u>explain</u> the <u>mechanism</u> of ovarian damage and directly tell us the <u>toxicity</u> of individual drugs

Assessing the Impact of Chemotherapy on Ovarian Reserve by Histological Analysis



Oktem & Oktay, Cancer 2007

Chemotherapy Induced Decline in Follicle Reserve

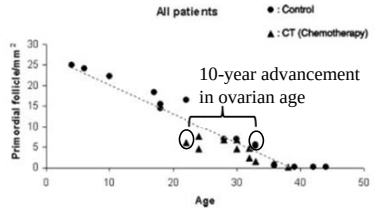
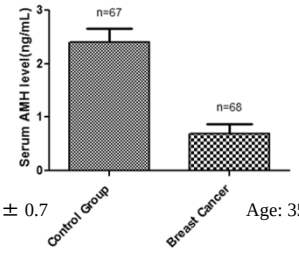


FIGURE 1. Correlation of age with baseline primordial follicle counts is depicted. Primordial follicle counts inversely correlated with age in both control (●) and chemotherapy (▲) groups.

Re-analyzed from Oktem & Oktay Cancer 2007

Impact of Breast Ca Chemotherapy on Serum AMH



Age: 34.6 ± 0.7

Age: 35.4 ± 0.7

Oktay Laboratory Nov 3, 2011

Reasoning for Fertility Preservation in Very Young Breast CA Patients

30-year-old Desiring 1 Child

↓

Chemotherapy

↓

Egg reserve reduced to 40 year old's

↓

5 year delay for tamoxifen treatment

↓

Egg reserve reduced to 45 year old's

↓

Pregnancy probability nearly 0%

Reasoning for Fertility Preservation in Young Breast CA Patients

25-year-old Desiring 1 Child

↓

Chemotherapy

↓

Egg reserve reduced to 35 year old's

↓

10 year delay for tamoxifen treatment

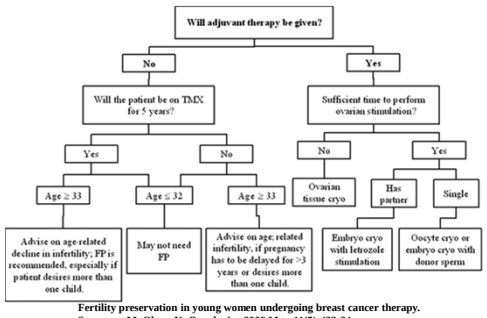
↓

Egg reserve reduced to 45 year old's

↓

Pregnancy probability nearly 0%

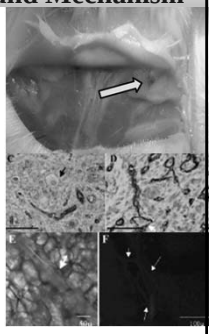
A Strategic Approach to Fertility Preservation in Breast Cancer



Fertility preservation in young women undergoing breast cancer therapy. Sonmezer M, Oktay K. Oncologist. 2006 May;11(5):422-34.

There are so many new drugs and how do we know how and if each drug causes damage?

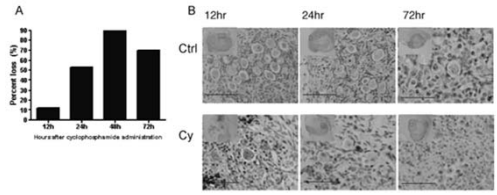
Human Ovarian Xenograft Model to Test Individual Gonadotoxicity and Mechanism



- **Ovarian cortex from females undergoing ovarian cryo or organ donor**
- **~ 1 mm^3 fragments grafted s.c. (2-4 grafts/mouse)**
- **NOD-SCID mice (n=8-12/group)**

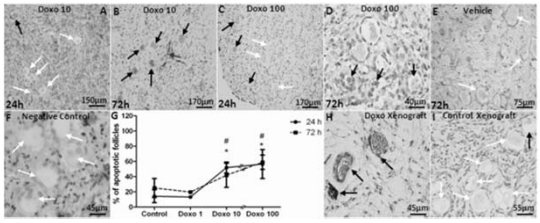
Oktay et al, Hum Reprod 1998
Oktem & Oktay, Cancer Research 2007

Cyclophosphamide Induces Massive Apoptotic Follicle Death in Human Ovary

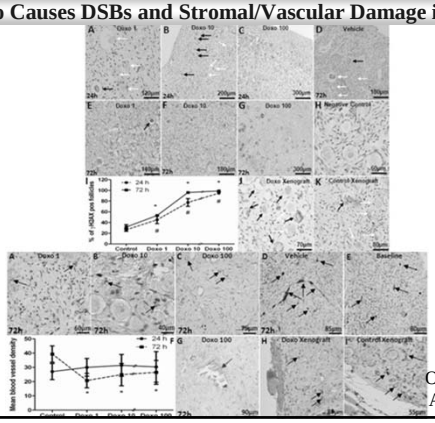


Oktem & Oktay, Cancer Research 2007

Doxorubicin Causes Apoptotic Death of Human Primordial Follicles

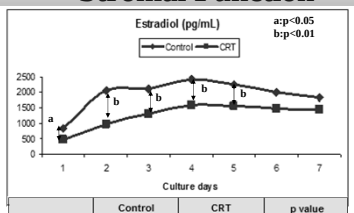


Doxo Causes DSBs and Stromal/Vascular Damage in Ovary



Oktay Lab, Aging 2011

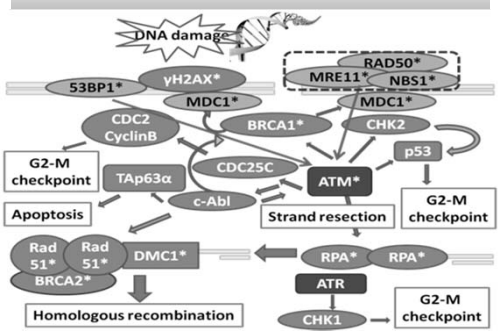
Impact of Chemotherapy on Stromal Function



	Control	CRT	p value
Mean age	27.7 ± 2.4	27.5 ± 2.7	>0.05
Follicle density PF/mm^2	9.31 ± 2.6	5.78 ± 1.5	<0.05
Mean Estradiol	1891.8 ± 192.6	1141.7 ± 116.6	<0.05

Oktem & Oktay Cancer. 2007 Nov 15;110(10):2222-9.

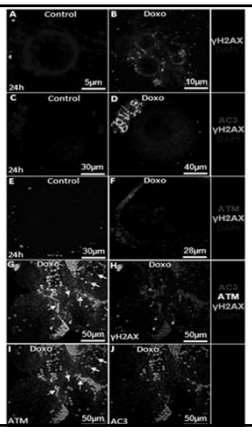
DNA DSB Repair Pathway



Titus…Oktay et al, 2013

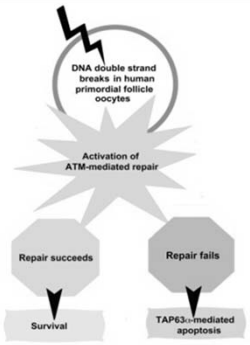
Doxorubicin induces double strand DNA breaks, activates ATM, and causes apoptosis in mouse oocytes

Some maybe repaired by the ATM Pathway



Soleimani..Oktay, Aging 2011

Mechanism of Chemotherapy-Induced Follicle Death



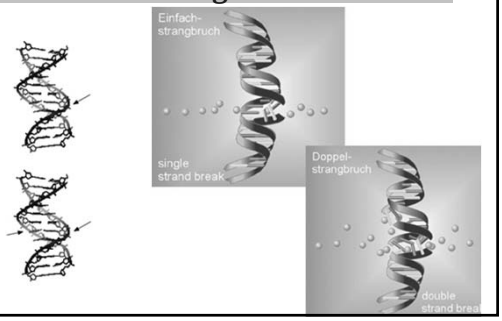
BRCA: Background

- **Double strand DNA break repair gene**
- **Mutations associated with breast/ovarian cancer risks**
- **1 in every 1000 women is BRCA mutation-positive**
- **2.5% in certain ethnic groups, such as people with Jewish-Ashkenazi origin**

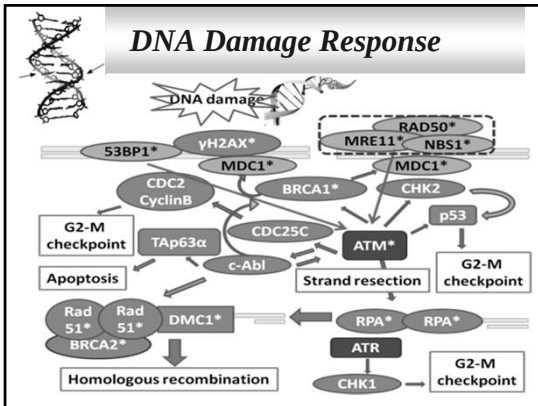
Age, FSH, and oocyte number comparisons among BRCA mutation-negative, -positive, and untested women.

	All BRCA mutation-positive [a]	BRCA mutation-negative [b]	BRCA untested [c]	BRCA1 mutation Positive [d]	BRCA mutation-negative and untested [e]	*P*
Age	33·1±2·8 (n=12)	32·8±2·9 (n=33)	33·0±2·9 (n=35)	33·9±2·7 (n=8)	32·9±2·9 (n=68)	NS
Day2 FSH (mIU/mL)	5·7±3·0	7·1±2·7	6·4±2·3	6·2±3·4	6·7±2·5	NS
N Oocytes (95% C.I.)*	7·9 (4·6-13·8)	11·3 (9·1-14·1)	13·5 (11·4-16·0)	7·4 (3·1-17·7)	12·4 (10·8-14·2)	a vs. b: 0·025 a vs. e: 0·003 d vs. e: 0·03

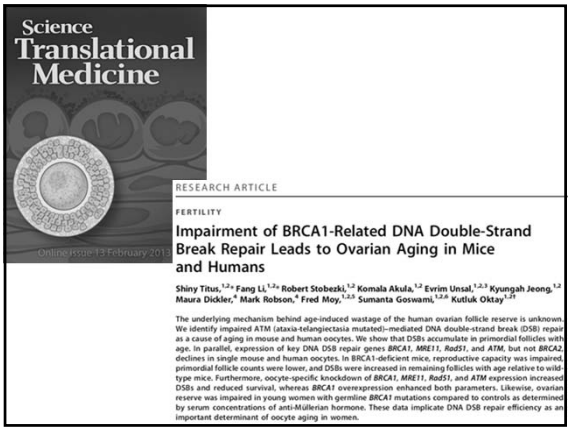
DNA Double Strand Breaks are the most lethal form of insult on human genome



DNA Damage Response



Oktay et al



Science Translational Medicine

Online Issue 13 February 2013

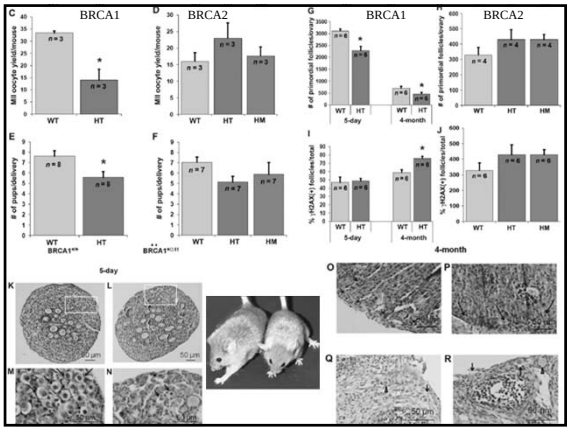
RESEARCH ARTICLE

FERTILITY

Impairment of BRCA1-Related DNA Double-Strand Break Repair Leads to Ovarian Aging in Mice and Humans

Shiny Titus,[1,2]* Fang Li,[1,2]* Robert Stobezki,[1,2] Komala Akula,[1,2] Evrim Unsal,[1,2,3] Kyungah Jeong,[1,2] Maura Dickler,[4] Mark Robson,[4] Fred Moy,[1,2,5] Sumanta Goswami,[1,2,6] Kutluk Oktay[1,2]†

The underlying mechanism behind age-induced wastage of the human ovarian follicle reserve is unknown. We identify impaired ATM (ataxia-telangiectasia mutated)–mediated DNA double-strand break (DSB) repair as a cause of aging in mouse and human oocytes. We show that DSBs accumulate in primordial follicles with age. In parallel, expression of key DNA DSB repair genes *BRCA1*, *MRE11*, *Rad51*, and *ATM*, but not *BRCA2*, declines in single mouse and human oocytes. In BRCA1-deficient mice, reproductive capacity was impaired, primordial follicle counts were lower, and DSBs were increased in remaining follicles with age relative to wild-type mice. Furthermore, oocyte-specific knockdown of *BRCA1*, *MRE11*, *Rad51*, and *ATM* expression increased DSBs and reduced survival, whereas *BRCA1* overexpression enhanced both parameters. Likewise, ovarian reserve was impaired in young women with germline *BRCA1* mutations compared to controls as determined by serum concentrations of anti-Müllerian hormone. These data implicate DNA DSB repair efficiency as an important determinant of oocyte aging in women.



Women with BRCA1 mutations have diminished ovarian reserve

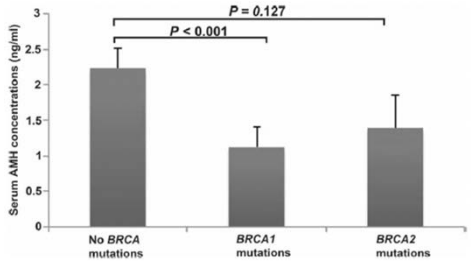
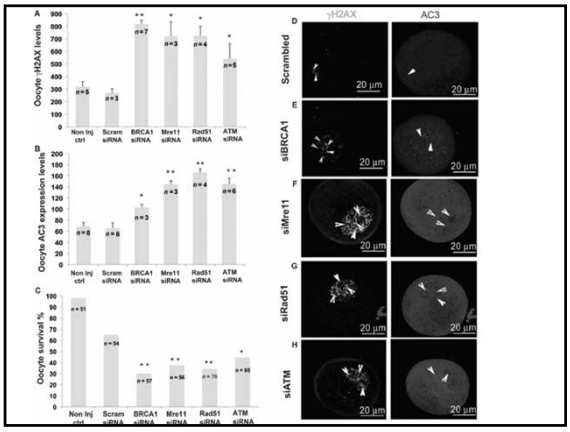
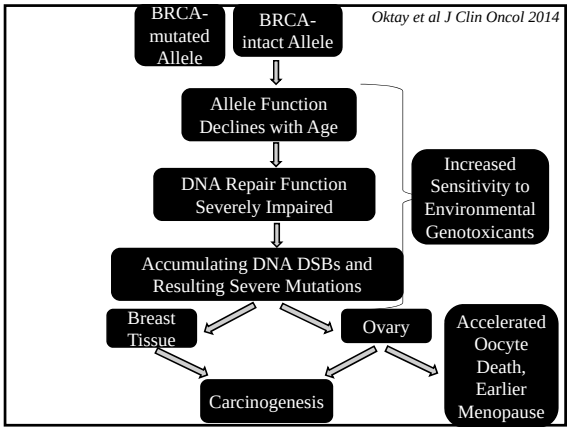
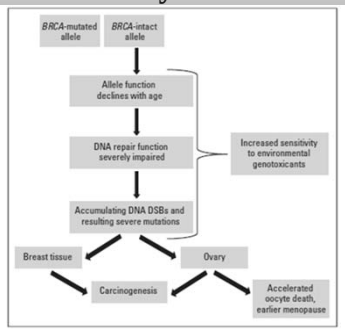


Fig. 6. Diminished ovarian reserve in *BRCA1*-deficient individuals. Women with significant *BRCA1* ($P < 0.0001$, ANOVA), but not *BRCA2* ($P = 0.127$, ANOVA), mutations had lower mean serum AMH concentrations compared to those with no *BRCA* mutations. All bar graphs show means ± SEM.





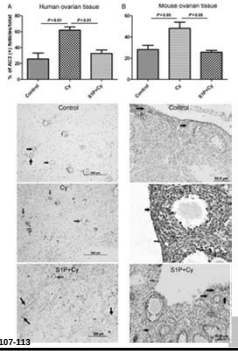
BRCA Mutations, Carcinogenesis, and Ovarian Sensitivity to Chemotherapy



Oktay et al J Clin Oncol 2014

Future Implications for Therapy

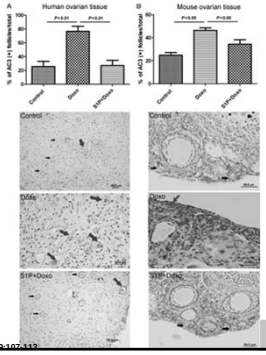
S1P Prevents Cyclophosphamide-Induced Apoptotic Follicle Death in Human



human reproduction

LI F...Oktay K. Hum. Reprod. 2014;29:107-113

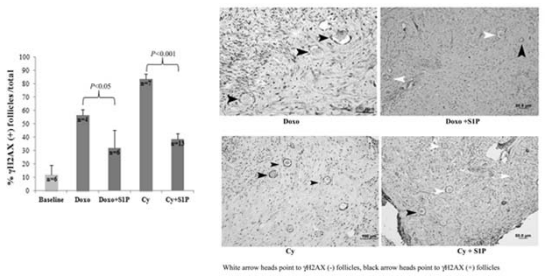
S1P Prevents Doxorubicine-Induced Apoptotic Follicle Death in Human



human reproduction

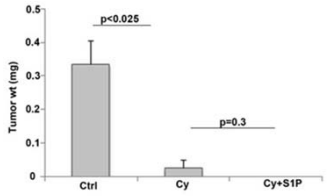
LI F...Oktay K. Hum. Reprod. 2014;29:107-113

S1P Reduces Chemo-Induced DNA DSBs?



White arrow heads point to γH2AX (-) follicles, black arrow heads point to γH2AX (+) follicles

S1P Does not Reduce Effectiveness of Chemotherapy



Does Chemo Cause Follicle "Burnout" in Humans?

- **It has been claimed Cyclophosphamide induces primordial follicle growth initiation and "burn out" in mice**
- **Via PIP3/akt/PTEN activation**
- **Can be blocked by AS101?**
- **Not supported with human data**

Conclusions

- **Main mechanism of chemotherapy-induced follicle loss in humans is DNA damage**
- **Stromal and microvascular damage may indicate chemo may cause dysfunction even in postmenopausal ovary**
- **Targeted fertility preservation approaches maybe developed exploiting this mechanistic knowledge**

- **Molecular Reproduction & Fertility Preservation Laboratory at NYMC:**
  - **Shiny Titus, PhD**
  - **Volkan Turan, MD**
  - **Fred Moy, PhD (Biostat)**
  - **Robert Stobezki, PhD cand.**
  - **Samir Babayev, MD**

Supported by R01 HD053112 and R21 HD061259

•**Collaborators:**
Sumanta Goswami, PhD, Yeshiva/AECOM
Maura Dickler, MD & Mark Robson, MD, Memorial Sloan Kettering Cancer Ctr
Evrim Unsal, PhD, & Volkan Baltaci, MD, PhD, Bilim University, Istanbul, Turkey

- **Innovation Institute for Fertility Preservation**
  - **Kutluk Oktay, MD**
  - **Giuliano Bedoschi, MD**
  - **Fernanda Pacheco, MD**
  - **Jhansi Reddy, MD**
  - **Allison Rosen, PhD**
  - **Kirsten Acosta, BS**
  - **Ashundia Jeffers, RN**
  - **Gina Triggs**
- **Past Fellows:**
  - **Samir Babayev, MD**
  - **Kyungah Jeong, MD**
  - **Fang Li, MD, PhD**
  - **Enis Ozkaya, MD**
  - **Erol Arslan, MD**
  - **Murat Sonmezer, MD**
  - **Aylin Cil, MD**
  - **Sanghoon Lee, MD**
  - **Ozgur Oktem, MD**
  - **Kenny Rodriguez, MD, PhD**
  - **Elke Heytens, PhD**
  - **IlginTurkcuoglu, MD**
  - **Margalida Sastri, MD**
  - **Sinan Ozkavukcu, MD, PhD**

fertilitypreservation.org i-fertility.net

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Ovarian tissue cryopreservation: Current achievements

J. DONNEZ
Prof emeritus (Catholic University of Louvain)
Director of SRI (Society for Research in Infertility)
Former head of GYNE Research Unit (Pr. Dolmans)

Conflict of interest disclosure

Jacques Donnez

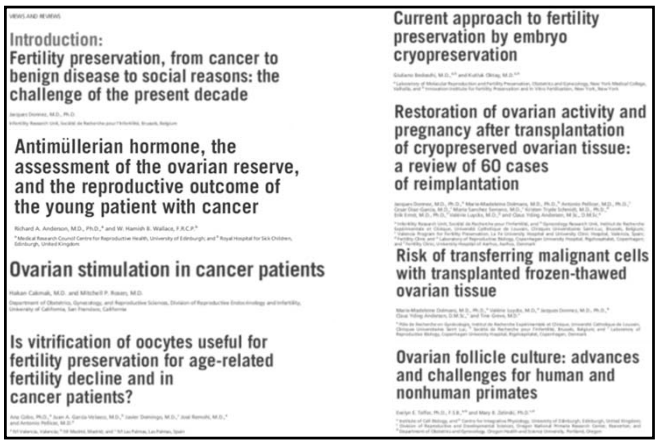
I do have a financial interest in commercial products or service

Companies with whom I have relationships are below*:*

Preglem SA, Gedeon Richter, Serono, MSD, Organon, Ferring and Storz

Learning objectives

- Analyse the different options for fertility preservation
- For each option, discuss the indications and contraindications
- Describe the techniques and results of ovarian tissue cryopreservation and grafting
- Discuss the aspects of future research



VIEWS AND REVIEWS

Introduction:
Fertility preservation, from cancer to benign disease to social reasons: the challenge of the present decade

Antimüllerian hormone, the assessment of the ovarian reserve, and the reproductive outcome of the young patient with cancer

Ovarian stimulation in cancer patients

Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients?

Current approach to fertility preservation by embryo cryopreservation

Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation

Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue

Ovarian follicle culture: advances and challenges for human and nonhuman primates

NATURE REVIEWS ENDOCRINOLOGY | REVIEW

Fertility preservation in women

Jacques Donnez & Marie-Madeleine Dolmans

Nature Reviews Endocrinology (2013) doi:10.1038/nrendo.2013.205
Published online 29 October 2013

Abstract

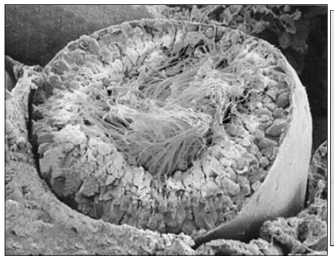
In women, ~10% of cancers occur in those <45 years old. Chemotherapy, radiotherapy and bone marrow transplantation can cure >90% of girls and young women with diseases that require such treatments. However, these treatments can result in premature ovarian failure, depending on the follicular reserve, the age of the patient and the type and dose of drugs used. This article discusses the different fertility preservation strategies: medical therapy before chemotherapy; ovarian transposition; embryo cryopreservation; oocyte vitrification; and ovarian tissue cryopreservation. The indications, results and risks of these options are discussed. Whether medical therapy should be used to protect the gonads during chemotherapy remains a source of debate. Fertility preservation needs to be completed before chemotherapy and/or irradiation is started and might take 2–3 weeks with established techniques such as embryo or oocyte cryopreservation. Further studies are needed in patients with cancer to confirm the excellent outcomes obtained in patients without cancer or in egg donation programmes. For prepubertal girls or cases where immediate therapy is required, cryopreservation of ovarian tissue is the only available option. Finally, possible future approaches are reviewed, including *in vitro* maturation of nonantral follicles, the artificial ovary, oogonial stem cells and drugs to prevent follicle loss.

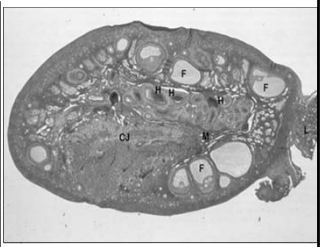
Fertility:preservation A New Discipline in Reproductive Medecine

- The primary function of ovary is R**EPRODUCTION**: « pass the genetic paternal on to the next generation »

- The primary function of ovary is R**EPRODUCTION**: « pass the genetic paternal on to the next generation »
- The second function is STEROID SECRETION

ANATOMY & PHYSIOLOGY

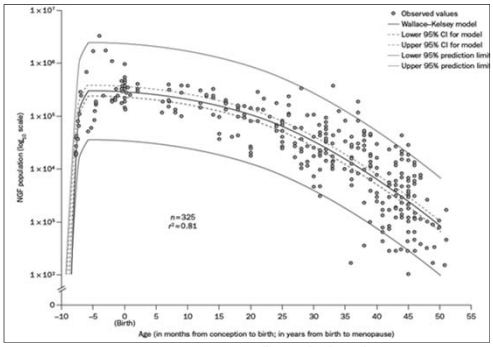




The Ovarian Reserve

- <u>In utero:</u>
  - In the fetus, some 100-2,000 primordial germ cells colonize the genital ridges and enter a massive proliferation process,resulting in 7 x 10^6 potential oocytes at mid-gestation
- <u>At birth:</u>
  - In human ovary, around 85% of these potential oocytes are lost before birth
  - Apoptosis-inhibiting gene BCL_2 and apoptosis-inducing BAX gene might act as rheostats to determine survival or death of germ cells

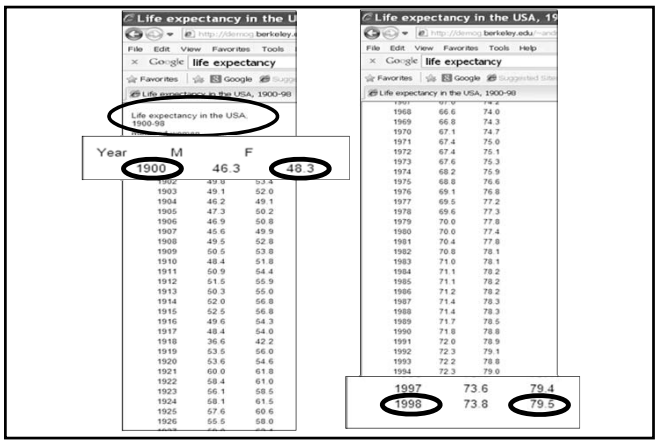
Who is candidate for fertility preservation?



Wallace and Kelsey, Plos One

The Ovarian Reserve

- Decline of ovarian reserve is characterized by the number of PFs (primordial follicles) also known as NGFs (non-growing follicles)
- Only ~ 450 ovulatory monthly cycles occur during reproductive life
- Remaining PFs → folliculogenesis and atresia
- At menopause, ~ 1,000 PFs remain

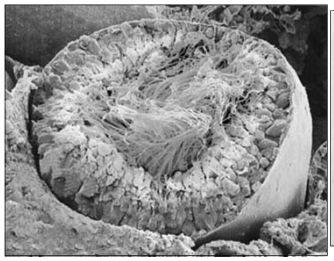


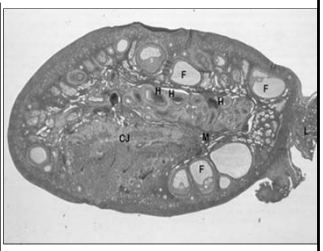
The Reality:

- The cost…the price to pay
- Indeed, treatments such as chemotherapy, radiotherapy, and/or surgery might induce premature ovarian failure (POF)

THE OVARIAN RESERVE

ANATOMY & PHYSIOLOGY





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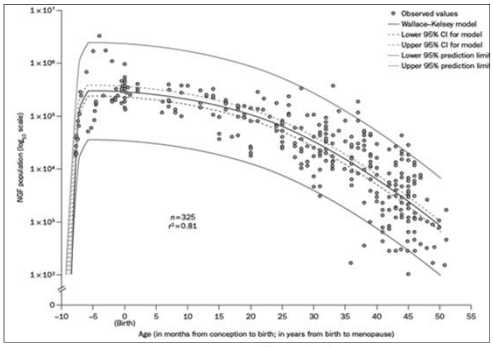
The question of ovarian reserve



Wallace and Kelsey, Plos One

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Gonadotoxicity factors

- **Patient's age: follicular reserve**
- **Chemotherapy**
  - **Type of agent (alkylating agents) (busulfan, cyclophosphamide, procarbazine)**
  - **Dose**
- **Radiotherapy**
  - **Irradiation area (total, abdominal, pelvic)**
  - **Total dose (LD50 oocytes < 2 Gy)**
- **Combination chemotherapy + radiotherapy : 100% of POF**

Gonadotoxicity factors

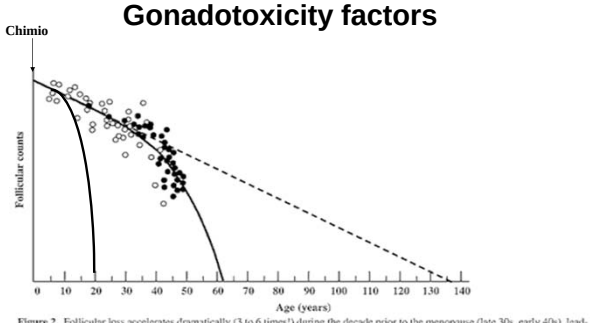


Figure 2. Follicular loss accelerates dramatically (3 to 6 times!) during the decade prior to the menopause (late 30s, early 40s), leading to complete depletion of the follicular endowment by the time most women are in their fifties. If the rate of follicular loss remained constant throughout the lifespan, the follicular reserve would not be exhausted until women were in their 100s! It is interesting how closely this coincides with the maximum human lifespan of 120 years. (Adapted and redrawn from Gougeon, et al, 1994).

Moreover…….

- Non-malignant diseases such as autoimmune and haematological conditions sometimes require chemotherapy and/or radiotherapy
- BMT (Bone Marrow Transplantion) may be also required

Non-malignant pathologies with risk of premature ovarian failure

Bone marrow transplantation
Sickle cell anemia
Thalassemia major
Aplastic anemia
Autoimmune diseases unresponsive to immunosuppressive therapy

Autoimmune diseases requiring chemotherapy
Systemic lupus erythematosus
Rheumatoid arthritis
Behçet's disease
Wegener's disease
Multiple sclerosis

Ovarian pathologies
Recurrent ovarian cysts
Ovarian torsion

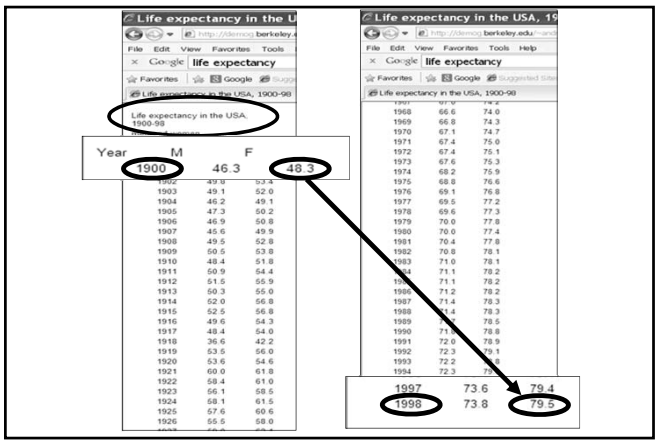
Endocrine or genetic diseases
Turner syndrome
Galactosemia
Family history of premature ovarian failure

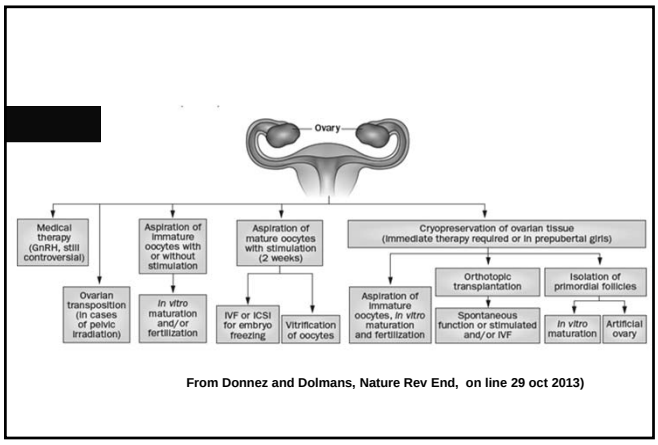
Jadoul et al, HRU, 2010

Donnez and Dolmans, Nature End Rev , 2013

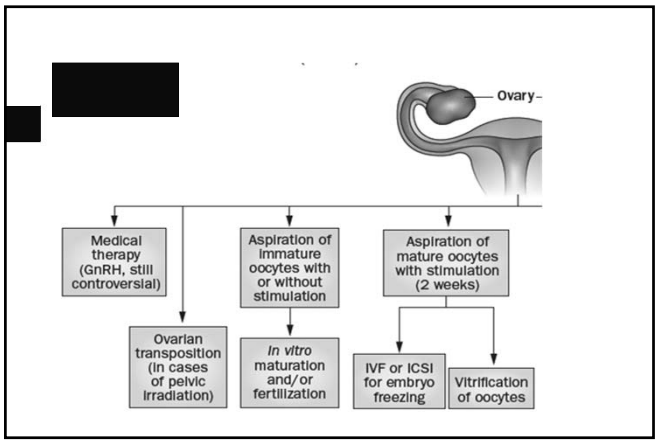
Moreover…….

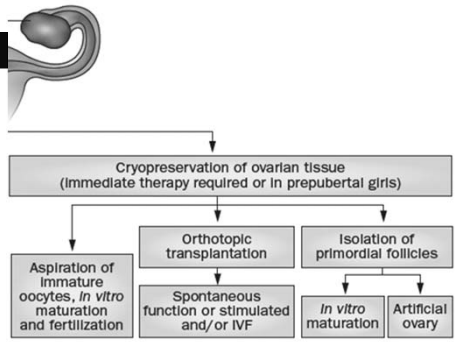
- Non-malignant diseases such as autoimmune and haematological conditions sometimes require chemotherapy and/or radiotherapy
- BMT (Bone Marrow Transplantion) may be also required
- Social reasons !!!!!!!!





From Donnez and Dolmans, Nature Rev End, on line 29 oct 2013)





Options for preserving fertility before starting treatment

Oncologist, pediatrician, gynecologist and patient

- **Options:**
  - **Cryopreservation of embryos**
  - **Cryopreservation of oocytes**
  - **Cryopreservation of ovarian tissue**

Fertility preservation options

A. Embryo

- **Need for partner/donor**
- **Post-Pubertal**
- **Delay in cancer treatment**

But it should be pointed out that cryopreserved embryos are the joint property of the women and her male partner

Embryo cryopreservation

- **Need for a stimulated cycle and IVF (partner)**
- **Harvest of viable embryos cannot be guaranteed**
- **Not recommended after chemotherapy is initiated**

Embryo cryopreservation

Efficacy of in vitro fertilization after chemotherapy. Dolmans et al, Fertil Steril 2005

TABLE 1

IVF outcome in cancer patients during (patients 1–4) or before (patients 5–11) chemotherapy.

Patient	Age (y)	Pathology	Chemotherapy before IVF	E_2 at hCG (pg/mL)	Ampules used	Oocytes	Cryopreserved embryos
1	32	NHL	1 regimen[a]	671	102	6	1
2	22	AML	2 regimens[b]	121	78	0	0
3	26	AML	2 regimens[b]	<10	82	0	0
4	24	ALL	3 regimens[c]	<10	74	0	0
5	31	MA	0	2430	32	10	6
6	24	HL	0	2500	24	13	10
7	28	HL	0	2610	27	25	11
8	33	NHL	0	1202	24	8	5
9	25	BOT	0	6750	104	12	5
10	26	HL	0	1576	34	11	4
11	26	OC II	0	1540	63	9	4

Note: ALL: acute lymphoblastic leukemia; AML: acute myoblastic leukemia; BOT: borderline ovarian tumor; HL: Hodgkin's lymphoma; MA: medullar aplasia; NHL: non-Hodgkin's lymphoma; OC II: ovarian carcinoma, stage II.

[a] One regimen of ACVBP (adriamycin, cyclophosphamide, vincristine, bleomycin, prednisone).

[b] Two regimens of cytarabine and idarubicin.

[c] One regimen of COP followed by two regimens of COPADM (cyclophosphamide, oncovin, prednisone, adriamycin, methotrexate).

Efficacy of in vitro fertilization after chemotherapy MMDolmans, D Demylle, B Martinez-Madrid, J Donnez.
Fertil Steril 2005, 83: 897-901

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IVF (N° patients)	N° Oocytes	N° Embryos
Between chemo (n=4)	6 in 1 pat. No in 3 pat	1
Before (n=7)	88 (8-25/patient)	45 (4-11 /patient)

Fertility preservation options

A. Embryo

B. Oocyte

- **Oocytes: mature (& immature)**
- **Post-Pubertal**
- **Delay in cancer treatment**

C. Ovarian tissue

Mature oocyte cryopreservation

- **Need for a stimulated cycle**
- **Specific COS protocols (AI for breast cancer women ….triggering ovulation with GnRH ag..)**
- **Should not delay chemotherapy**
- **Any complications or delay in IVF may delay the start of chemotherapy**
- **Harvest of good quality oocytes can not be guaranteed**
- **Not recommended after chemotherapy is initiated**

Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients?

Ana Cobo, Ph.D.,[a] Juan A. Garcia-Velasco, M.D.,[b] Javier Domingo, M.D.,[c] José Remohí, M.D.,[a] and Antonio Pellicer, M.D.[a]

[a] IVI Valencia, Valencia; [b] IVI Madrid, Madrid; and [c] IVI Las Palmas, Las Palmas, Spain

Mature oocyte vitrification

Comparison of concomitant outcome achieved with fresh and cryopreserved donor oocytes vitrified by the Cryotop method

Ana Cobo, Ph.D.,[a] Masashigue Kuwayama, Ph.D.,[b] Sonia Pérez, Ph.D.,[a] Amparo Ruiz, M.D.,[a] Antonio Pellicer, M.D.,[a] and José Remohí, M.D.[a]

[a] IVI Universidad de Valencia, Valencia, Spain; and [b] Kato Ladies Clinic, Nushishinjuku, Shinjuku, Tokyo, Japan

Fertility and Sterility® Vol. 89, No. 6, June 2008

Survival rate of vitrified oocytes: 96.9 %

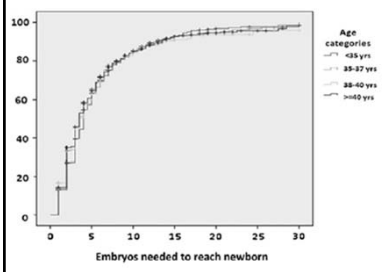
Mature oocyte vitrification

Cumulative newborn rates increase with the total number of transferred embryos according to an analysis of 15,792 ovum donation cycles

Nicolás Garrido, Ph.D., M.Sc.,[a] José Bellver, M.D.,[a] José Remohí, M.D.,[a] Pilar Alamá, M.D.,[a] and Antonio Pellicer, M.D.[a,b]

[a] Instituto Universitario IVI Valencia, University of Valencia; and [b] Hospital Universitario y Politécnico La Fe, Valencia, Spain

Mature oocyte vitrification



Newborn rate:

- **5 E: 64,8%**
- **15 E: 92,4%**
- **10 E: 85,2%**
-

Pregnancy rate after oocyte vitrification:

- **10 oocytes: 40%**
- **12 oocytes: 60%**
- **20 oocytes: 90%**

- **Major improvements in oocyte cryopreservation by vitrification (Cobo et Pellicer and Rienzi et al)**
- **Results from ovum donation program CAN NOT be extrapolated to cancer women**
- **Two life births after oocyte vitification in cancers women (Kim et al ,2012 ; Velasco et al 2013)**

Cryopreservation options for preserving fertility before starting treatment

A. Embryo

B. Mature oocyte:

C. Ovarian tissue

- **Prepubertal / pubertal**
- **No delay in cancer treatment**

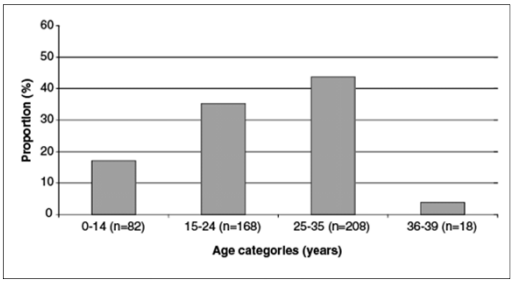
J Assist Reprod Genet
DOI 10.1007/s10815-013-9952-x

FERTILITY PRESERVATION

A review of 15 years of ovarian tissue bank activities

Marie-Madeleine Dolmans · Pascale Jadoul · Sébastien Gilliaux · Christiani A. Amorim · Valérie Luyckx · Jean Squifflet · Jacques Donnez · Anne Van Langendonckt

Received: 9 November 2012 / Accepted: 28 January 2013



% of patients undergoing OTC by age group:

96.2% of patients were < 35 years

52.5% of patients were <24 years

17.2% of patients were <14 years

Dolmans et al, JARG 2013

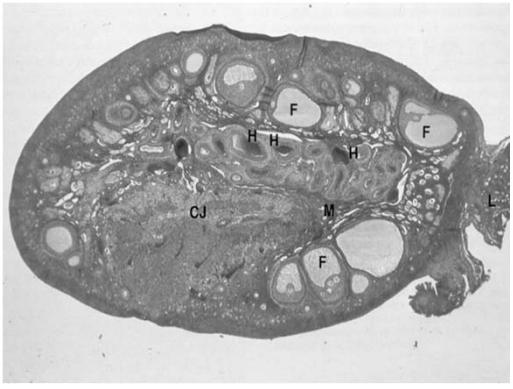
1) Epidemiology – indications

Human Reproduction Update, Vol.16, No.6 pp. 617–630, 2010
Advanced Access publication on May 12, 2010 doi:10.1093/humupd/dmq010

human reproduction update

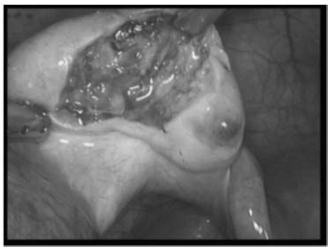
Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed?

Pascale Jadoul, Marie-Madeleine Dolmans, and Jacques Donnez*



The prepubertal ovarian tissue: Retrieval technique

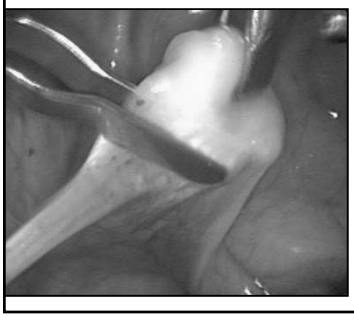
Laparoscopy : biopsies

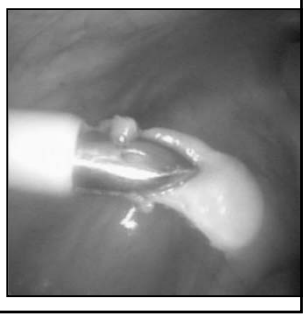


How much ovarian cortex to remove?
~ estimated risk of ovarian failure (related to the planned treatment)

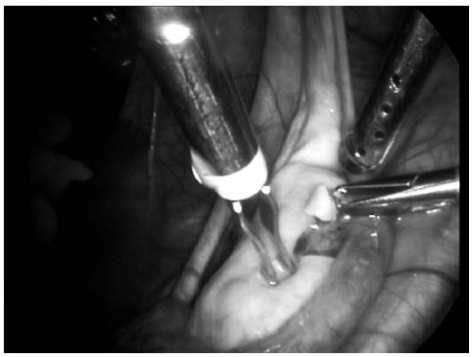
The prepubertal ovarian tissue: Retrieval technique

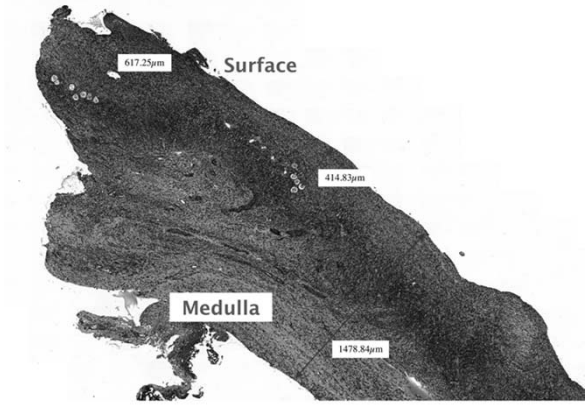
Laparoscopy : oophorectomy





Ovarian biopsy before chemotherapy

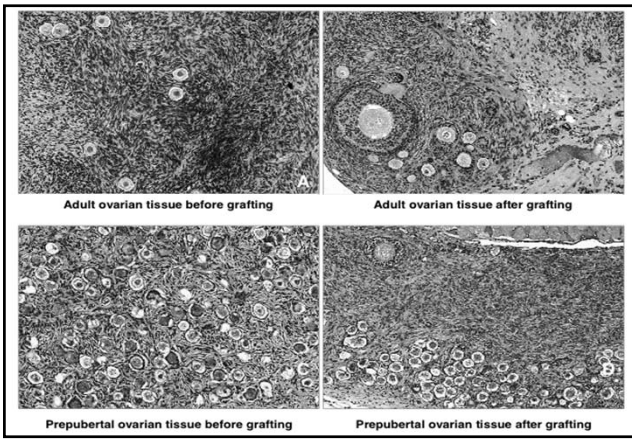


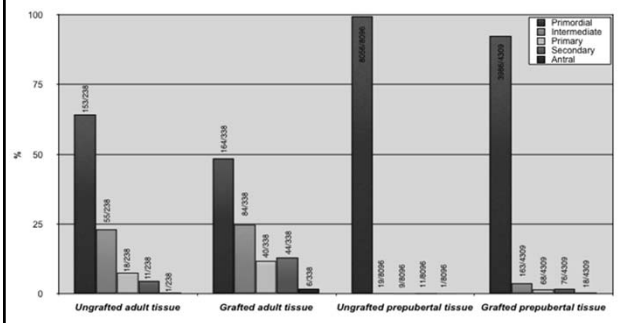


<u>Oophorectomy</u> should be performed

- in cases with high risk of POF:
pelvic irradiation,
TBI,
high doses of alkylating agents

- in very young girls owing to the small size of the ovaries





1. **Who is candidate for ovarian tissue transplantation?**
2. **Techniques, results and safety of ovarian tissue transplantation.**
3. **How to improve the results?**

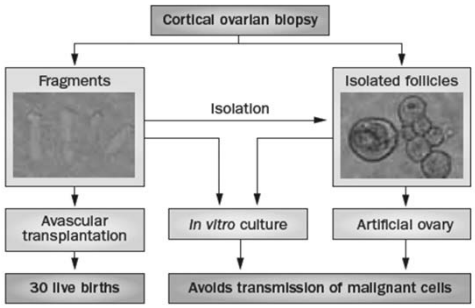
Candidates for ovarian tissue reimplantation

1) clinical symptoms of POF
- **.amenorrhea**
- **.severe oligospaniomenorrhea**

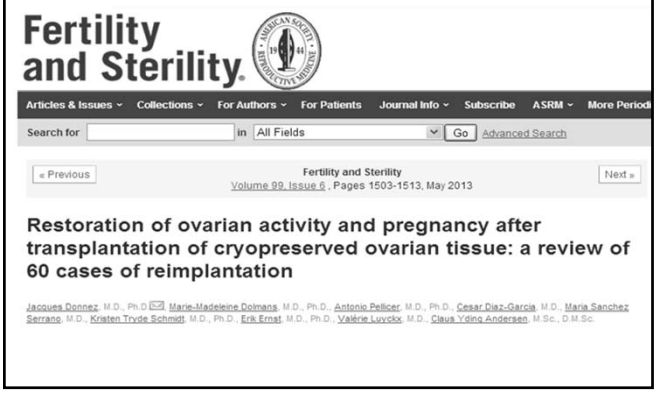
2) Biological signs of POF
- **.FSH > 50 mIU/ml**
- **.AMH very low (0 in the majority of cases)**
- **.Decreased ovarian volume**
- **.AFC nearly 0**

1. **Who is candidate for ovarian tissue transplantation?**
2. **Techniques, results and safety of ovarian tissue transplantation.**
3. **How to improve the results?**

Techniques and results of OT transplantation

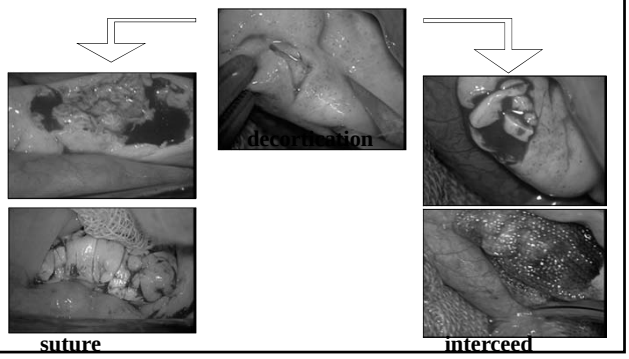


Donnez and Dolmans, Nature Rev Endocrinol, in press



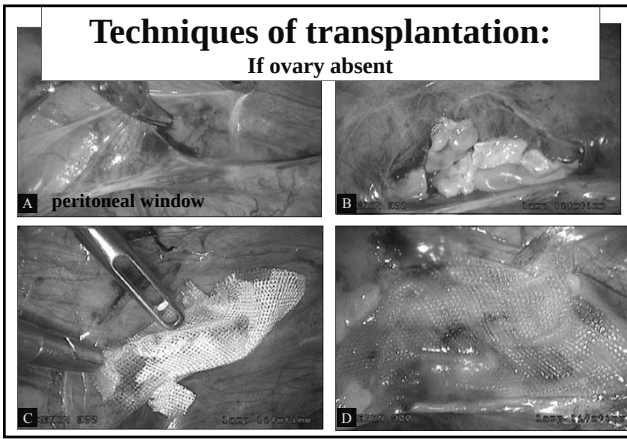
Techniques of transplantation:

If ovary present

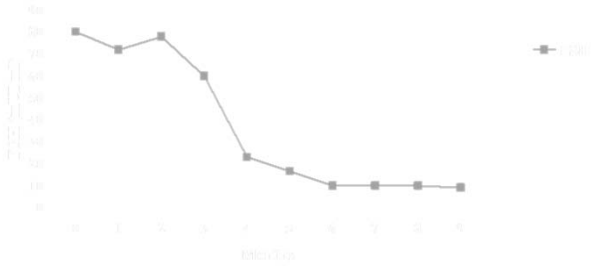


Techniques of transplantation:

If ovary absent



FSH values after reimplantation of frozen ovarian tissue (Annals of medecine, Donnez et al, 2011)



ORIGINAL ARTICLE

Endocrine Research

Limited Value of Ovarian Function Markers following Orthotopic Transplantation of Ovarian Tissue after Gonadotoxic Treatment

Femi Janse, Jacques Donnez, Ellen Anckaert, Frank H. de Jong, Bart C. J. M. Fauser, and Marie-Madeleine Dolmans

Department of Reproductive Medicine and Gynecology (F.J., B.C.J.M.F.), University Medical Center Utrecht, 3584 CX Utrecht, The Netherlands; Universite Catholique de Louvain (J.D., M.-M.D.), Institut de Recherche Experimentale et Clinique, Unite de Recherche GYNE, Department of Gynecology, Cliniques Universitaires St. Luc, B-1200 Brussels, Belgium; Laboratory of Clinical Chemistry and Radioimmunology (E.A.), Universitair Ziekenhuis Brussel, B-1090 Brussels, Belgium; and Department of Internal Medicine (F.H.d.J.), Erasmus Medical Center, 3000CA Rotterdam, The Netherlands

J Clin Endocrinol Metab, April 2011, 96(4):1136–1144

TABLE 2. Ovarian function and endocrinology after ovarian transplantation

Patient	First menses (months since transplantation)	Duration of graft function (months)[a]	Pregnancy	Hormone assays (months since transplantation)	Cycle day	FSH (IU/liter)	E_2 (pg/ml)	AMH (μg/liter)	Inhibin B (ng/liter)
1	5	>86	Yes[b]	3	6	31	25	<0.025	23
				6	24	21	58	<0.025	30
2	4	43	No	0[c]	c	c	c	<0.025	c
				7	NA	17	44	<0.025	15
3 (1)	5	30	No	31	32	47	89	0.0–0.01	55
				0[c]	c	c	c	<0.025	c
				5	NA	42	194	<0.025	27
				14	25	5.5	126	<0.025	12
3 (2)	5	>32	No	5	NA	27	128	<0.025	13
4	4.5	42	No	0[c]	c	c	c	<0.025	c
				4	NA	70	13	<0.025	6
				8	6	18	70	<0.025	8
5 (1)	6.5	24	No	1[c]	c	c	c	<0.025	c
				4	5	80	26	<0.025	19
				7	96	10	69	<0.025	63
5 (2)	6	18	No	0[c]	c	c	c	0.0-0.01	c
				5	16	6.8	186	<0.025	55
6	3.5	>9	Yes[d]	0[c]	c	c	c	<0.025	c
				5	43	11	83	<0.025	99
				8	8	6.8	62	<0.025	100
7		0	No	2[c]	c	c	c	<0.025	c
				5	NA	64	12	<0.025	10
8	7	28	No	0[c]	c	c	c	<0.025	c
				20	120	4	167		21
9	3.5	>19	No	1	NA	40	19	<0.025	28
				3	9	6.7	104	0.33	83
10	3.5	>17	No	1[c]	c	c	c	0.09	c
				5	8	14	196	0.09	97

(1), First transplantation; (2), second transplantation; NA, not appropriate, when the blood sample was taken before the first menstruation after grafting.

[a] Assessed by cessation of menses (often coinciding with elevated FSH).

[b] Pregnancy spontaneously achieved 11 months after transplantation.

[c] Only AMH concentrations are reported because samples were drawn at or shortly after transplantation during administartion of GnRH analogs or combined oral contraceptives.

[d] Pregnancy spontaneously achieved 9 months after transplantation.

30 live births

References	Cryopreser. procedure	graft site	Live birth	
			Spont.	IVF
Donnez et al., 2004,2010,2011, 2012	SF	peritoneal window (2 steps) ovarian medulla	+ +++	+ +
Meirow et al., 2005,2012	SF	beneath the ovarian cortex	+	+++
Demeestere et al., 2007	SF	ovarian and peritoneal windows (2 steps)	++	-
Andersen et al., 2008,2009,2013	SF	subcortical ovarian pocket ovarian medulla	++ +	+
Silber et al., 2008, 2010	SF	ovarian medulla	+ +	-
Piver et al., 2009 **Roux et al, 2010**	SF	ovarian and peritoneal windows (1 and 2 steps)	+ +	-
Sanchez et Pellicer., 2009,2013	SF	ovarian medulla	++	++ (twins)
Revel et al, 2011,2012	SF	peritoneal window	-	+ +
Dittrich et al, 2011	SF	ovarian medulla	-	+
Revelli et al, 2012	SF	ovarian medulla	+	

30 life births

- Slow freezing
- 16 girls 14 boys
- Spontaneous (n=17) vs IVF (n=13)
- Ovarian medulla and peritoneal window

(Donnez et al,,Fertil.Steril, 2012,2013
Donnez and Dolmans, Nature Rev End, 2013)

Fertil Steril. 2012 Sep;98(3):720-5. Epub 2012 Jun 13.

Live birth after transplantation of frozen-thawed ovarian tissue after bilateral oophorectomy for benign disease.

Donnez J, Jadoul P, Pirard C, Hutchings G, Demylle D, Squifflet J, Smitz J, Dolmans MM.
Department of Gynecology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, and Institut de Recherche Expérimentale et Clinique, Pôle de Gynécologie, Université Catholique de Louvain, Brussels, Belgium.

Abstract

OBJECTIVE: To report the restoration of ovarian function and pregnancy in a woman after bilateral oophorectomy for benign disease after autotransplantation of cryopreserved ovarian cortex.

DESIGN: Case report.

SETTING: Gynecology research unit in a university hospital.

PATIENT(S): A 28-year-old woman who underwent bilateral adnexectomy for ovarian abscesses at the age of 18 years.

INTERVENTION(S): We performed ovarian cortex autotransplantation to a peritoneal pocket in the broad ligament.

MAIN OUTCOME MEASURE(S): Restoration of ovarian activity and pregnancy.

RESULT(S): Restoration of ovarian function began at 20 weeks and was achieved 24 weeks after transplantation. After the fifth stimulation attempt, two mature oocytes were obtained and microinjected. One embryo (seven cells) was obtained and transferred, leading to a normal pregnancy. The patient delivered a healthy baby boy weighing 2,370 g at 38 weeks of gestation.

CONCLUSION(S): Ovarian cortex cryopreservation can be performed at the time of surgery for benign diseases when fertility is impaired. We report the first pregnancy to occur after ovarian tissue cryopreservation for benign ovarian pathology after bilateral oophorectomy.

The denominator?

Indeed , we don't know how many cases of reimplantation were carried out throughout the world

Fertility and Sterility

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« Previous Fertility and Sterility Next »
Volume 99, Issue 6 , Pages 1503-1513, May 2013

Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation

Jacques Donnez, M.D., Ph.D., Marie-Madeleine Dolmans, M.D., Ph.D., Antonio Pellicer, M.D., Ph.D., Cesar Diaz-Garcia, M.D., Maria Sanchez Serrano, M.D., Kristen Tryde Schmidt, M.D., Ph.D., Erik Ernst, M.D., Ph.D., Valérie Luyckx, M.D., Claus Yding Andersen, M.Sc., D.M.Sc.

The denominator?

In a series of 60 cases , the pregnancy (LB) rate is 23%

Advantages and disadvantages of heterotopic and orthotopic sites for ovarian tissue transplantation

	Heterotopic site (subcutaneous)	Orthotopic site
Advantages	•No limitation of the number of fragments transplanted •Easy transplantation procedure •Easy access for follicular monitoring and oocytes collection	•Possibility of natural conception •Restoration of fertility demontrated •Favourable environment for follicular development
Disadvantages	•Restoration of fertility not yet demonstrated •IVF procedure required •Effect of the local environment on the oocyte quality is unknown	•Number of fragments transplanted limited by the ovarian size •Invasive transplantation procedure

Human Reproduction, Vol.0, No.0 pp. 1–4, 2013
doi:10.1093/humrep/det360

human reproduction

CASE REPORT *Infertility*

First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy

C.J. Stern[1,*], D. Gook[1], L.G. Hale[1], F. Agresta[1], J. Oldham[2], G. Rozen[3], and T. Jobling[4]

[1]Reproductive Services, Melbourne IVF and Royal Women's Hospital, Parkville, VIC, Australia [2]Women's Ultrasound East Melbourne, East Melbourne, VIC, Australia [3]Reproductive Services, Royal Women's Hospital, Parkville, VIC, Australia [4]Gynaecological Oncology, Monash Health, Moorabbin, VIC, Australia

*Correspondence address. 3/320 Victoria Parade, East Melbourne 3002, Australia. Tel: +61394151838; Fax: +61394162581; E-mail: kate.stern@mvf.com.au

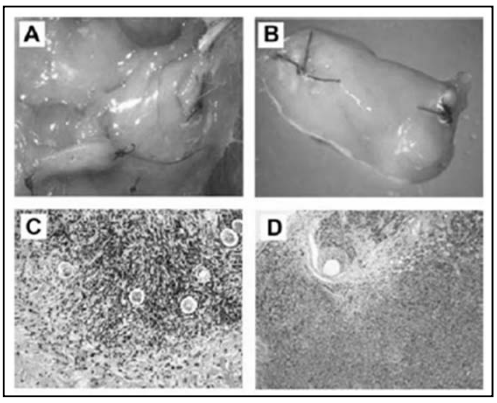
Submitted on July 10, 2013; resubmitted on August 11, 2013; accepted on August 16, 2013

blood

Prepublished online Jul 1, 2010;
doi:10.1182/blood-2010-01-265751

Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe

Marie-Madeleine Dolmans, Cristina Marinescu, Pascale Saussoy, Anne Van Langendonckt, Christiani Amorim and Jacques Donnez



Risk of reintroducing malignant cells with the ovarian graft is a reality for leukemic patients

There are not candidates for ovarian transplantation

See for review : Dolmans et al ,Fertil.Steril ,2013

Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue

Marie-Madeleine Dolmans, M.D., Ph.D.,[a] Valérie Luyckx, M.D.,[a] Jacques Donnez, M.D., Ph.D.,[b] Claus Yding Andersen, D.M.Sc.,[c] and Tine Greve, M.D.[c]

[a] Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Cliniques Universitaires Saint Luc; [b] Société de Recherche pour l'Infertilité, Brussels, Belgium; and [c] Laboratory of Reproductive Biology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Conclusion of the » present »

- Orthotopic reimplantation of cryopreserved ovarian tissue
  - Feasible
  - Resulted in 30 livebirths (38 if the » non published « LB are taken into account)
- Some prognostic factors are established
  - Ovarian reserve (age)
  - Previous chemotherapy
  - Experimental evidence of the primordial role of the revascularisation process

Practice Guidelines for Fertility Preservation in Cancer Patients

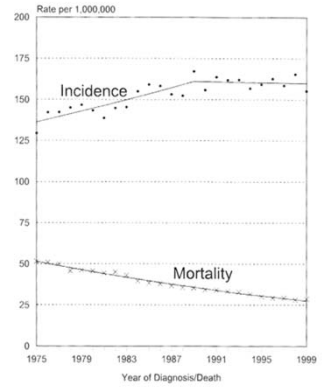
S. Samuel Kim, MD, FACOG, Professor
Division of Reproductive Endocrinology
University of Kansas School of Medicine

Disclosure: Nothing to Disclose

Learning objectives

1. To recognize the importance of fertility preservation (FP)
2. To understand current and future FP options
3. To comprehend the ISFP Practice Guidelines for FP

Why fertility preservation is an important issue for young cancer patients ?



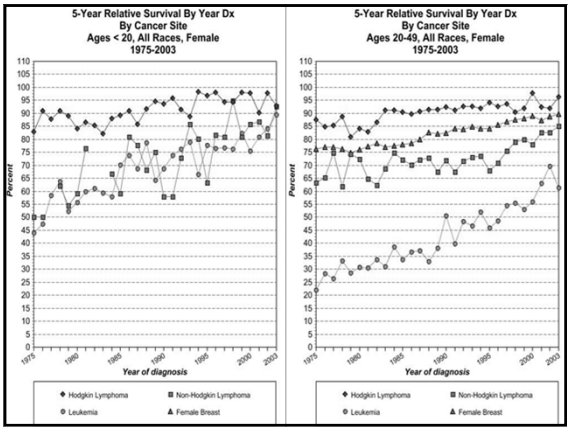
Advances in cancer therapy
↓
Decreased mortality
↓
Increased survivals

- To date, more than 13 million cancer survivors are living in the US.
- Approximately 450,000 cancer survivors are of reproductive age.
- For young cancer survivors, fertility is one of the most important quality of life issues.

• The 5-year relative survival rate for all cancers combined is over 83% in women with age 0-44.

• The 5-year relative survival rate for childhood cancers (age 0-14) is over 81%.

• The 5-year survival for breast cancer is approaching 90%. (in young patients under 35 years, the survival is lower ~70%)



Advanced cancer therapy resulted in the increased number of cancer survivors.

However, aggressive cancer treatment can lead to gonadal failure, since gonads are susceptible to cytotoxic treatment especially treatment with alkylating agents and radiation.

Radiation

- The estimate dose at which half of the follicles are lost in humans (LD50) : 4Gy
  (Wallace et al., 1989)
- Single dose of TBI (under 10 Gy) before puberty : Ovarian failure rate of 55-80%
- Fractionated TBI (over 15 Gy) : 100%
  (Thibaud et al., 1998)

Chemotherapy:
Factors affecting gonadal function after chemotherapy

- type of chemo regimens (procarbazine, melphalan, CTX).
- dosage and number of cycles of chemotherapy
- pubertal status
- age of the patient (female)
- ovarian reserve (pre-treatment 'intrinsic' patient factors)

Treatment regimen	Target disease	Age group	No. of patients	% attempting parenthood	% achieving pregnancy\ parenthood (median follow up)	% of gonadal dysfunction (median follow up)	Type of study	References
VACOP-B or MACOP-B	NHL	Adults	7			14% (28 months)	Retrospective	(Muller & Stahel, 1993)
CHOP	NHL	Adults	36	NA	50% (84 months)	5% (84 months)	Retrospective	(Elis et al, 2006)
Hyper-CVAD	NHL, ALL	Adults	7	NA	43% (27 months)	14% (27 months)	Retrospective	(Seshadri et al, 2006)
MOPP, pelvic radiation or both	HL	Children	86	NA	28% (9 years)	19% (9 years)	Retrospective	(Sy Ortin et al, 1990)
ABVD	HL	Adults	36	100%	70% (12 months)		Retrospective	(Hodgson et al, 2007)
Various chemotherapy regimens ± radiotherapy	HL	Adults	184	50%	75% (NA)		Retrospective	(Kiserud et al, 2007)
Cyclophosphamide-based conditioning for HSCT	SAA, ALL, AML, CML, lymphoma	Adults	708	NA	4·5% (NA)		Retrospective	(Sanders et al, 1996)
Autologous HSCT	NHL, HL, AML, ALL, SAA, CML	Adults	122	NA	3% of those attempting (11·2 years)		Retrospective	(Carter et al, 2006)
Allogeneic HSCT		Adults	170	NA	2% of those attempting (10·2 years)		Retrospective	(Carter et al, 2006)

Risk of infertility in female after cancer treatment
(Leader et al, 2011, BJH)

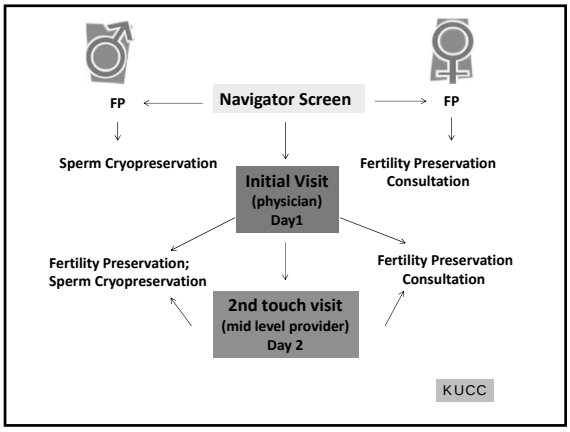
- Most young women with cancer are concerned about their fertility after cancer treatment.
- 75% of childless young adult patients and 80% of teen girls want future children.

Compromised fertility can result in significant psychosocial stress and reduced quality of life, even long after the disease has been successfully treated.

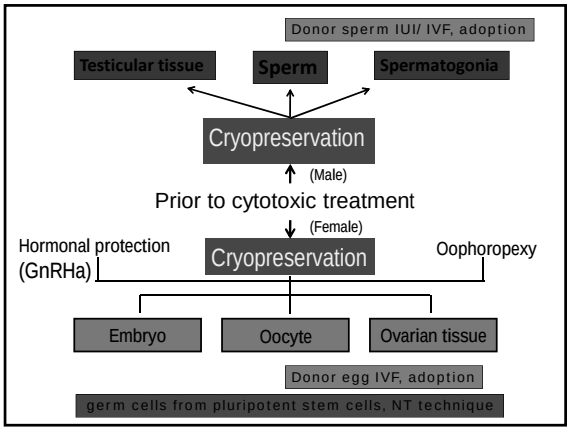
Although the use of fertility preservation services may help alleviate this burden, access to these services is often inadequate, because of logistical barriers and a lack of appropriate patient referral by healthcare providers.

Murk et al., Curr Opin Obstet Gynecol. 2011 Jun;23(3):143-50

- Less than half of oncologists refer women routinely for fertility preservation.
  Quinn et al., J Clin Oncol 2009
  Forman et al., Fertil Steril 2010
  Goodman et al., Hum Reprod 2012
- 46% of pediatric oncologists refer teens for sperm banking more than 50% of the time, and 12% refer females for fertility preservation >50% of the time.
  Köhler et al., J Assist Reprod Genet 2011



Current and Future FP Options



Current status

- Sperm cryopreservation: established
- Spermatogonia cryopreservation: experimental
- Testicular tissue cryopreservation: experimental

- Embryo cryopreservation: established
- Oocyte cryopreservation: established
- Ovarian tissue cryopreservation: experimental

- GnRHa: efficacy still unknown

Randomized Trials with GnRHa to preserve ovarian function

Trial	Number of patients	Results
ZIPP (Sverrisdottir et al.)	123	P< .01
PROMISE-GIM6 (Del Mastro et al.)	281	P< .001
Egyptian study (Badawy et al.)	80	P< .05
ZORO (Gerber et al)	60	NS
CCOP (Munster et al.)	49	NS
OPTION trial (Leonard et al.)	140	NS

Cryopreservation of embryos, Cryopreservation of oocytes

- Clinically well established techniques.
- May not be applicable to patients who cannot delay cancer treatment.
- May not be safe for women with ER+ tumor, as it requires controlled ovarian stimulation.


PN stage (day 1)


Cleavage stage (day 3)


Blastocyst stage (day 5)


MII stage oocyte

GV stage oocyte

ASRM PAGES

Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population. Evidence indicates that oocyte vitrification and warming should no longer be considered experimental. This document replaces the document last published in 2008 titled, "Ovarian Tissue and Oocyte Cryopreservation," Fertil Steril 2008;90:S241-6. (Fertil Steril® 2013;99:37–43. ©2013 by American Society for Reproductive Medicine.)

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Outcomes of human oocyte vitrification

	Egg- bank	Fresh	P value
Number of subjects	295	289	
MII oocytes retrieved	3286 (11.1 ±3.2)	3185 (11.0 ±2.8)	0.634
Survival rate	3039 (92.5)	-	-
Oocytes inseminated	3039 (10.3±2.9)	3185 (11.2 ±3.4)	0.091
Fertilization rate (2PN)	2256 (74.2)	2334 (73.3)	0.393
Top quality day-3 embryos/inseminated oocyte	1098 (36.1)	1201 (37.7)	0.198

Cobo et al Hum Reprod. 2010

Table III Clinical outcome according to the type of oocytes received

	Egg-bank	Fresh
Number of embryos transferred	267 (90.5)	259 (89.6)
Mean number of embryos replaced	513 (1.74 ± 0.7)	498 (1.72 ± 0.7)
Number of cycles with embryo 're-vitrification'/cryopreservation	196 (66.7)	216 (74.7)*
Mean number of re-vitrified or cryopreserved embryos	592 (2.0 ± 2.1)	743 (2.5 ± 2.3)*
Implantation rate	205 (39.9)	204 (40.9)
Positive hCG test/cycle	165 (55.9)	159 (55.0)
Clinical pregnancy rate/cycle	148 (50.2)	144 (49.8)
Positive hCG test/transfer	165 (61.8)	159 (61.4)
Clinical pregnancy rate/transfer	148 (55.4)	144 (55.6)
Twin pregnancy rate	48 (32.4)	54 (37.5)

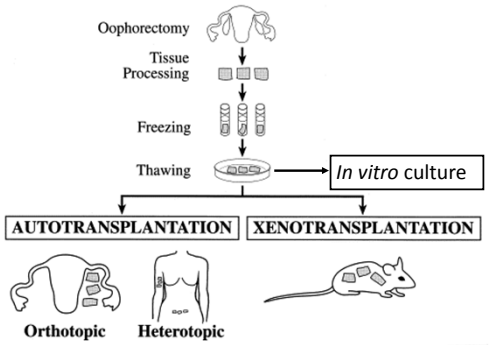
Unless otherwise indicated values are mean ± SD or *n* (%).
*$P < 0.05$.

Cobo et al., Hum Reprod, 2010

Cryopreservation of Ovarian Tissue

- Option for women with rapidly growing tumor who need treatment without delay or unwilling to undergo ovarian stimulation.
- The only option for pre-pubertal girls

How to develop follicles in stored ovarian tissue?



Kim SS, Fertil Steril 2001

ISFP Practice Guidelines: lymphoma, leukemia, breast cancer

The Practice Committee of ISFP

J Assist Reprod Genet. 2012; 29(6):465-8

Incidence & survival

Lymphoma/ leukemia (female)	Total number of women newly diagnosed with cancer in 2011	Number and percentage of women under age 34 with newly diagnosed cancer in 2011		5 year relative survival
HL	4000	1760	(44%)	90-95%
NHL	30300	1650	(5.5%)	80-85%
ALL	2410	1750	(70.6%)	64%
CLL	600	20	(0.3%)	78%
AML	6120	810	(12.7%)	23%
CML	2150	220	(10.3%)	57%

http://seer.cancer.gov

LYMPHOMA

- Hodgkin Lymphoma (HL)
- Non Hodgkin Lymphoma (NHL)

Risks of ovarian failure after treatment in women with HL

- *ABVD* (adriamycin, bleomycin, vinblastine, dacarbazine): POI <10% (3% if age <32 y) in the reproductive age.
- *BEACOPP* (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, predisone), *MOPP* (chlormethamine, oncovine, procarbazine, p-d): POI 20- 50% in women younger than 30 *(German Hodgkin Lymphoma Study Group).*
- *HSCT*: POI 70-100%, post-treatment parenthood rates as low as 3-8% *(Carter et al, 2006)*

Risks of ovarian failure after treatment in women with NHL

- *CHOP* (cyclophosphamide, doxorubicin, vincristine, p-d): POI 5-10% *(Elis et al., 2006)*
- *Hyper-CVAD* (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, MTX): POI 14-50% *(Sheshadri et al., 2006)*
- *HSCT*: POI 70-100%, post-treatment parenthood rates as low as 3-8% *(Carter et al., 2006)*

Recommendations for Fertility Preservation in Lymphoma Patients

- Post-pubertal female (i):

  Cryopreservation of embryos or oocytes if cancer treatment can be delayed.

  Otherwise, cryopreservation of ovarian tissue should be considered.

  Alternatively, immature oocyte retrieval followed by IVM and cryopreservation of oocytes or embryos can be considered.

Recommendations for Fertility Preservation in Lymphoma Patients

- Post-pubertal femalec (ii):
  The protective effect of GnRHa is questionable and still undetermined. However, GnRHa co-treatment can be considered for female patients undergoing chemotherapy (not for HSCT) if there is no other option.
- Pre-pubertal female:
  Ovarian tissue cryopreservation, if the risk of ovarian failure after cancer treatment is high enough to justify the procedure.

Recommendations for Fertility Preservation in Lymphoma Patients

- Post-pubertal male:

  Cryopreservation of spermatozoa.
  GnRHa co-treatment is not recommended in male.

- Pre-pubertal male:

  No good option. Cryopreservation of testicular tissue may be available in some centers as a strictly experimental procedure.

LEUKEMIA

- Acute lymphocytic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)
- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)

Infertility after Leukemia treatment

- The risk of infertility in patients with ALL or AML (unless treated with HSCT) is low as contemporary treatment protocols entail lower doses of alkylating agents or are devoid of alkylating agents.
- CML can be treated with tyrosin kinase inhibitors such as imatinib or rituximab. Although tyrosin kinase inhibitors may not impair fertility in humans, there is insufficient data on these medications on reproductive potential.

Leader et al., 2011, BJH

Recommendations for Fertility Preservation in Leukemia Patients

- Post-pubertal female:

  No ideal option to date.

  However, cryopreservation of ovarian tissue should be considered before HSCT.

  Any harvested tissue from leukemia patients should not be used for auto-transplantation because of high risk of cancer cell reintroduction.

Recommendations for Fertility Preservation in Leukemia Patients

- Pre-pubertal female:

  May not need for fertility preservation except HSCT. If treatment with HSCT is required, ovarian tissue cryopreservation should be considered before HSCT.

Recommendations for Fertility Preservation in Leukemia Patients

- Post-pubertal male:

  cryopreservation of spermatozoa

- Pre-pubertal male:

  no currently available option

Breast Cancer

Effects of breast cancer treatment on ovarian function

The primary factors affecting chemotherapy induced gonadotoxicity are the age of the patient, and dose and number of cycles of the alkylating agent received.

Kim et al., 2011, Fertil Steril

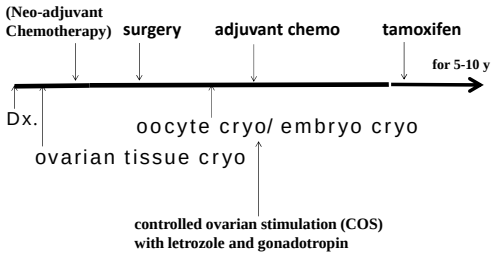
Recommendations for Fertility Preservation in Breast Cancer Patients

- Fertility preservation consultation should be arranged at the time of initial diagnosis.
- The best time for fertility preservation is after surgery and before adjuvant therapy.

Recommendations for Fertility Preservation in Breast Cancer Patients

- Cryopreservation of oocytes or embryos is recommended as a fertility preservation option before chemotherapy.
- *The risk of increased peak estradiol levels with COS in breast cancer patients (especially with ER+ tumor) should be discussed before the procedure.*
- For women who require urgent cancer treatment such as neo-adjuvant chemotherapy, cryopreservation of ovarian tissue should be considered.

Breast Cancer



Conclusions

ISFP Committee Opinions

ISFP Committee Opinions

- Fertility issue should be addressed to all patients in reproductive age before cancer treatment.
- Fertility preservation before cancer treatment is strongly recommended if the chance of losing fertility is over 20-30% with cancer therapy.
- In pediatric patients, the risk of gonadal failure with chemotherapy is low in the absence of HSCT.
- Recommendations should be individualized and should not violate the ethical principles.

ISFP Committee Opinions

- In men, cryopreservation of sperm should be offered to all cancer patients in reproductive age regardless of the risk of gonadal failure.
- In women, the recommendation of fertility preservation should be individualized based on the multiple factors such as the urgency of treatment, the age of the patient, the marital status, the regimen and dosage of cancer treatment.

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Fertility Preservation in Young Women with Breast Cancer

Kutluk Oktay, MD, FACOG

Professor of Obstetrics & Gynecology, Medicine, Cell Biology & Anatomy, and Pathology

Director, Division of Reproductive Medicine and Fertility Preservation

New York Medical College

Director, Innovation Institute for Fertility Preservation , Rye and Manhattan, NY

Innovative Care Fertility Preservation.org

New York Medical College

Disclosures

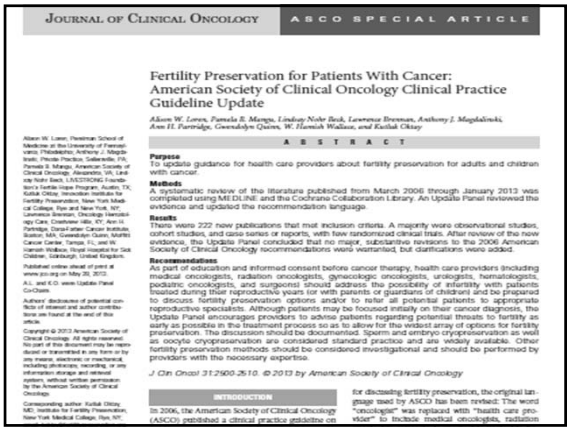
- **Medical Advisory Board Member, OvaScience**
- **Supported by National Institutes of Health:**
  - **R01 HD053112 from NICHD & NCI**
  - **R21 HD061259 from NICHD**
- **Will discuss non-approved use of aromatase inhibitors**

New York Medical College

Innovative Care Fertility Preservation.org

Learning Objectives

- **At the end of this presentation the participant is expected to comprehend in women with breast cancer:**
  - **Overall approach to fertility preservation**
  - **Specific issues and approaches for ovarian stimulation**
  - **Concerns specific to BRCA mutation carriers**



JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Alison W. Loren, Pamela B. Mangu, Lindsay Nohr Beck, Lawrence Brennan, Anthony J. Magdalinski, Ann H. Partridge, Gwendolyn Quinn, W. Hamish Wallace, and Kutluk Oktay

ABSTRACT

Purpose
To update guidance for health care providers about fertility preservation for adults and children with cancer.

Methods
A systematic review of the literature published from March 2006 through January 2013 was completed using MEDLINE and the Cochrane Collaboration Library. An Update Panel reviewed the evidence and updated the recommendation language.

Results
There were 227 new publications that met inclusion criteria. A majority were observational studies, cohort studies, and case series or reports, with few randomized clinical trials. After review of the new evidence, the Update Panel concluded that no major, substantive revisions to the 2006 American Society of Clinical Oncology recommendations were warranted, but clarifications were added.

Recommendations
As part of education and informed consent before cancer therapy, health care providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation. This discussion should be documented. Sperm and embryo cryopreservation as well as oocyte cryopreservation are considered standard practice and are widely available. Other fertility preservation methods should be considered investigational and should be performed by providers with the necessary expertise.

J Clin Oncol 31:2500-2510. © 2013 by American Society of Clinical Oncology

INTRODUCTION

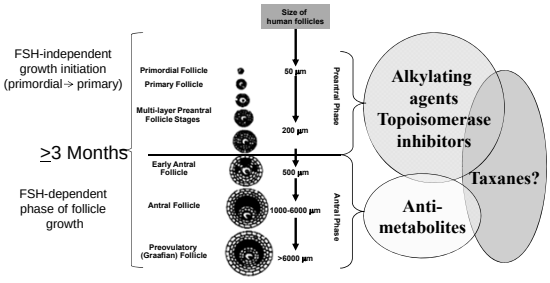
In 2006, the American Society of Clinical Oncology (ASCO) published a clinical practice guideline on

for discussing fertility preservation, the original language used by ASCO has been revised: The word "oncologist" was replaced with "health care provider" to include medical oncologists, radiation

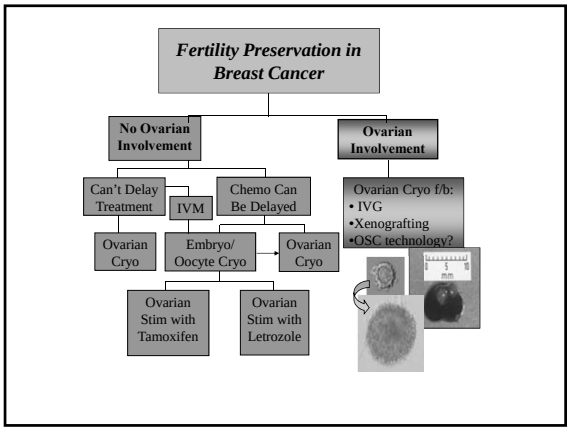
Breast Cancer is the Most Common Indication for Fertility Preservation

- **Breast Ca**
- **Hematologic malignancies**
- **Solid tumors: Gyn Ca, GI, Osteosarcoma etc.**
- **Childhood cancers**
- **Recurrence, relapses etc**
- **Cancer prophylaxis: e.g. BRCA**

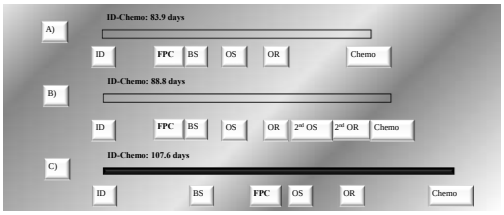
Impact of breast cancer chemotherapy on different stages of follicular growth



Oktay & Rodriguez-Wallberg, 2011



Value of Early Referral



Referral prior to breast surgery (hollow line) results in the initiation of chemotherapy on average 3 weeks earlier in single FP cycles (A), as well as when the data from double cycles are included (B), compared to those referred post breast surgery (C). This additional time enables multiple cycles of FP (B), if desired, in a shorter time period before chemotherapy than those referred after breast surgery (C).

ID: Initial diagnosis with cancer, FPC: First fertility preservation consultation, BS: Breast surgery, OS: Initiation of ovarian stimulation, OR: Oocyte retrieval, Chemo: Initiation of chemotherapy

Lee et al, JCO 2010

Early Referral Enables Multiple FP Cycles/Increases Yield

	PreS	PostS	P-value
Ratio of patients who underwent a second FP cycle	9/35 (25.7%)	1/58 (1.7%)	<0.001
Ratio of oocytes retrieved in 2nd cycle out of total	93/584 (15.9%)	5/800 (0.6%)	<0.0001
Ratio of embryos frozen in 2nd cycle out of total	40/187 (21.4%)	2/355 (0.6%)	0.0001

•Patients who initiated the first oocyte retrieval within 5 weeks of the surgery were able to complete a second cycle within 9 weeks of the surgery

Lee et al, JCO 2010

PreS: Patients referred prior to breast surgery
PostS: Patients referred post breast surgery

Referral Prior to Breast Surgery Enables Earlier Initiation of Chemotherapy

	PreS (n=35) (mean±SD)	PostS (n=58) (mean±SD)	P -value
ID to OS	42.6±27.7	71.9±30.7	<0.001
ID to BS	28.6±20.6	33.4±24.3	NS
FPC to OS	25.1±26.0	15.2±13.0	0.088
OS to OR	11.5±1.5	11.5±1.6	NS
ID to Chemo (single cycle only)	83.9±24.3	107.8±42.9	0.045
ID to Chemo (including double cycles)	88.8±45.7	107.4±42.3	0.058

PreS: Patients referred prior to breast surgery, PostS: Patients referred post breast surgery, ID: Initial diagnosis with cancer, OS: Ovarian stimulation, BS: Breast surgery, FPC: First fertility preservation consultation, OR: Oocyte retrieval, Chemo: Chemotherapy NS: Not significant

Lee et al, JCO 2010

Points to Consider when Stimulating Cancer Patients

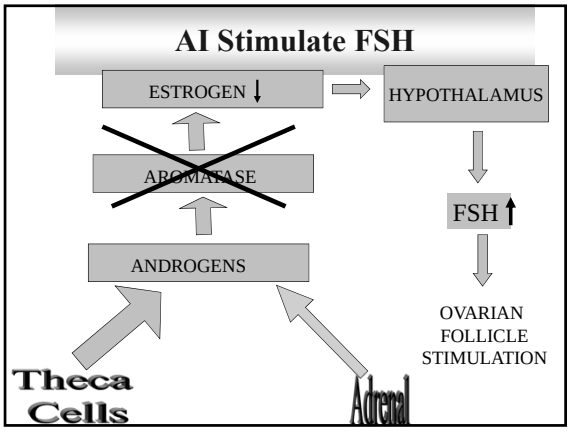
- **Most <u>aggressive</u> <u>not</u> necessarily the best**
- **<u>Can't take a chance</u> with cancellation of cycle or delay of chemo due to OHSS**
- **<u>Tendency to infection</u>, blood clots etc. should be considered**
- **<u>High risk pregnancy</u> due to past chemo side effects: e.g. cardiomyopathy, pulmonary fibrosis, breast reconstruction**

Letrozole for Ovulation Induction

- **Third generation aromatase inhibitor**
- **Half life 48 hours**
- **Alternative to tamoxifen in breast cancer[1]**
- **Suppresses estradiol production**
- **Used for ovulation induction [2]**

[1] *Goss et al. NEJM 2003;349:1793-802*
[2] *Marinko M et al· Fertil. Steril. (2002) **78**(Supplement 1):S55*

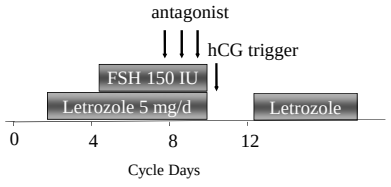
AI Stimulate FSH



AI Study in Breast Cancer Patients

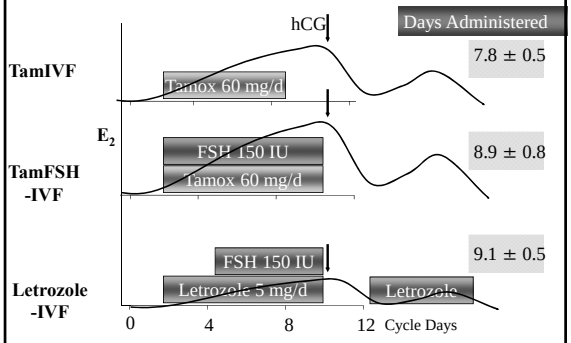
- **Prospective-controlled**
- **2003-2010**
- **N=313**
- **Stage I-III**
- **Desires Fertility Preservation**

Letrozole-FSH Protocol for Oocyte/Embryo Cryopreservation in Breast Cancer



Oktay et al, J Clin Oncol 2005 Jul 1;23(19):4347-53.

Prospective Comparison of Tamox vs. Letrozole in Breast Ca Patients Undergoing IVF



Oktay et al. J Clin Oncol 2005 Jul 1;23(19):4347-53.

COST-LESS is Superior to Tamoxifen

Variable	Tam-IVF	TamFSH-IVF	LetrozoleFSH-IVF	P value
Age	**36.6 ± 1.6**	**38.3 ± 1.9**	**36.2 ± 0.8**	**NS**
Baseline FSH (mIU/ml)	**9.4 ± 1.5**	**9.4 ± 1.5**	**7.2 ± 0.8**	**NS**
PeakE_2* (pg/mL)	**419 ± 39[a,b]**	**1182 ± 271[a]**	**405 ± 45[a,b]**	**a < 0.01 b > 0.05**
Total Follicle	**2 ± 0.3[a]**	**6 ± 1 [a,b]**	**8.3 ± 0.6[a,b]**	**a < 0.001 b > 0.05**
Follicle ≥17mm	**1.2 ± 0.1[a]**	**2.6 ± 0.4[a,b]**	**3.6 ± 0.3[a,b]**	**a < 0.05 b > 0.05**
Total Oocyte	**1.7 ± 0.3[a]**	**6.9 ± 1.1[a,b]**	**11.0 ± 1.2[a,b]**	**a < 0.001 b > 0.05**
Mature Oocyte	**1.5 ± 0.3[a,c]**	**5.1 ± 1.1[a,b,c]**	**8.0 ± 0.9[a,b]**	**a < 0.001 b,c < 0.05**
Total 2-PN Embryo	**1.3 ± 0.2[a]**	**3.8 ± 0.8[a,b]**	**5.3 ± 0.6[a,b]**	**a < 0.001 b > 0.05**

Oktay et al. J Clin Oncol 2005 Jul 1;23(19):4347-53.

Letrozole Reduces E2 Exposure in Agonist Cycles

- Ben-Haroush A et al, Isr Med Assoc J 2011 Dec;13(12):753-6.
- Similar outcomes long vs. short protocol.
- Long protocol may not be as suitable because of timing issues.

Is Letrozole-IVF as Efficient as the "Standard" IVF?

Table-2. Comparison of various characteristics between letrozole+FSH and control groups.

	Letrozole+FSH[a] mean ± standard error	Control[b] mean ± standard error	P-value[c]
Age at IVF	36.1 ± 0.5	36.9 ± 0.5	0.69
Baseline FSH	7.6 ± 0.5	4.3 ± 0.2	<0.001
Estradiol at hCG	459.1 ± 42	1453.3 ± 80.7	<0.001
Endometrial thickness	8.7 ± 0.4	10.8 ± 0.3	<0.001
Follicle N>17	4.0±0.2	2.6±0.2	<0.001
Peak follicle size (mm)	21.4 ± 0.4	18.8±0.2	<0.001
Total oocyte N	11.8±1	10.7±0.7	0.31
Mature oocyte N	8.4±0.7	9.2± 0.6	0.47
Mature oocyte (%)	74.3±3.4	84.3±1.9	< 0.01
N of 2 pn embryos	6.3±0.6	6.6±0.5	0.65
Fertilization rate (%)	76.3.1±3.4	72.7±3.0	0.71
N of days stimulated	11.8 ±0.3	12.1±0.2	0.66
Total FSH dose (I)	1461.11±100	2355.0± 135.5	<0.001

[a] 47 patients, 53 initiated IVF cycles resulting in 46 retrievals
[b] 56 patients with male factor infertility, 64 initiated IVF cycles resulting in 63 retrievals
[c] computed from the ANOVA test.

Oktay et al, JCEM 2006

The effects of letrozole on ovarian stimulation for fertility preservation in cancer-affected women

Miguel A Checa Vizcaino [a,b,*], Anna Robles Corchado [a], Margalida E Sastre I Cuadri [a], Mireia Gonzalez Comadran [a], Mario Brassesco [b], Ramón Carreras [a]

[a] Department of Obstetrics and Gynaecology, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain;
[b] Centro de Infertilidad y Reproducción Humana, Barcelona, Spain

Abstract Survival rates for fertile women with cancer have increased significantly, lending importance to considering the possibility of motherhood after cancer. This study was a retrospective analysis of a prospective database comparing two groups of patients who underwent fertility preservation after being diagnosed with either breast cancer or a non-hormone-dependent cancer between 2009 and 2011. Nineteen oncology patients were included in the study. The objective was to assess the efficacy of ovarian stimulation with aromatase inhibitors versus a standard antagonist protocol. This study sought to quantify oestradiol concentrations in patients receiving letrozole and to determine the length of time between diagnosis of malignancy and onset of fertility preservation. Number of mature oocytes retrieved in the non-hormone-dependent cancer group was comparable to that in the breast cancer group (15.4 ± 8.19 versus 16.3 ± 7.31). Oestradiol concentrations were higher for patients with non-hormone-dependent cancer (1666.4 ± 739.42 pg/ml versus 829 ± 551.11 pg/ml, $P = 0.006$). There were no differences between the groups in the length of time between diagnosis and fertility preservation (17.4 ± 4.93 versus 16.4 ± 1.74 days). Oestradiol concentrations of breast cancer patients on the letrozole protocol remained much lower than those of patients on the antagonist protocol.

KEYWORDS: breast cancer; fertility preservation; letrozole; non-hormone-dependent cancer

Table 2 Outcomes for ovarian stimulation and vitrification.

Outcome	Non-hormonal-dependent cancer (n = 10)	Breast cancer (n = 9)	P-value
Stimulation days	11.11 ± 1.79	11.22 ± 0.66	NS
Total FSH dose (IU/ml)	2055 ± 565.9	2275 ± 484.60	NS
Oestradiol on GnRH day (pg/ml)	1666.40 ± 739.42	829 ± 551.11	0.006
Total oocytes retrieved	15.40 ± 8.19	16.3 ± 7.31	NS
Total oocytes vitrified	11.50 ± 6.65	14.0 ± 5.59	NS
Immaturity rate (%)	11.8	10.7	NS
Oestradiol per oocyte (pg/ml)	127.61 ± 57.47	55.5 ± 38.95	0.002

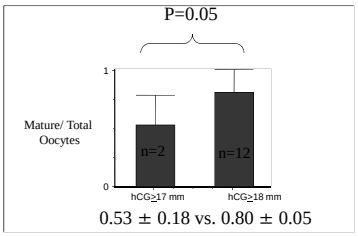
Values are mean ± standard deviation unless otherwise stated. GnRH = gonadotrophin-releasing hormone; NS = not statistically significant.

Please cite this article in press as: Checa Vizcaino, MA, et al. The effects of letrozole on ovarian stimulation for fertility preservation in cancer-affected women. Reproductive BioMedicine Online (2012), doi:10.1016/j.rbmo.2012.02.020

Is Letrozole-FSH Superior to Gonadotropin-only Protocol in Cancer Patients?

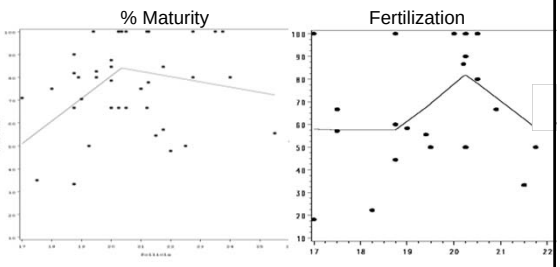
	Letrozole-FSH (127)	FSH-Only (20)	P
Age(years)	39.6±5.2	32.2±6.4	<0.005
Parity	0.2±0.6	0.1±0.3	NS
BMI	22.8±3.7	22.8±2.8	NS
SERUM AMH	2.9±2.4	2.5±3	NS
Starting FSH Dose	241.2±69.8	245±70.5	NS
Total FSH Dose	1888.1±1078	2124.6±1029	NS
# of follicles>17 mm	5.3±2.1	4.4±2.3	NS
Trigger-day FSH	22.3±8.1	20.6±8.3	NS
E2 on trigger day	609.1±416.1	1528.7±642.9	<0.005
Total oocyte number	16.5±8.5	12.2±9.6	NS
Mature oocyte #	10.8±5.1	7.2±4.6	<0.005
Maturity rate	71.6±19.2	64.4±33.4	NS
2-PN embryo #	8.5±6.4	5.8±4.4	NS
Day 2 embryo #	7.6±5.6	5.6±4.2	NS
Day 3 embryo #	8.4±4.8	4±2.8	<0.005

Delaying hCG injection Improves Mature Oocyte Yield in Let-FSH Stimulation



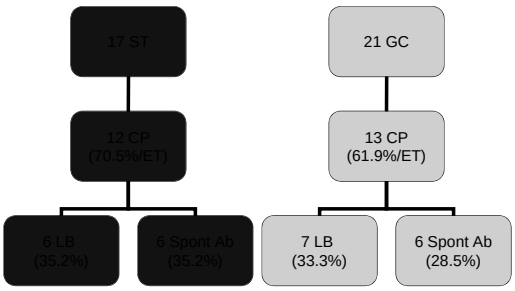
0.53 ± 0.18 vs. 0.80 ± 0.05

Peak Maturity & Fertilization when hCG is Given at 20mm



Oktay et al, JCEM 2006

Pregnancy Outcomes Based on Transfer Type



HOW ARE THE LETROZOLE BABIES DOING?

19 Born!

No Increase in Congenital Malformations after Letrozole Treatment

- **911 infants from letrozole or clomiphene**
- **Similar rates of malformation:**
  - **2.4% vs. 3.0% in CC**
  - **Cardiac anomalies <u>less</u> frequent in letrozole:**
    - **0.2 vs. 1.8% (p=0.02)**

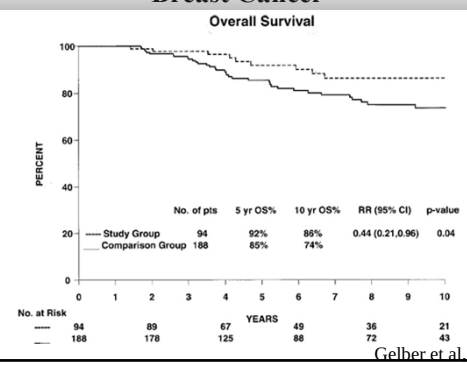
Tulandi---Casper. Fertil Steril, June 2006

Recurrence Rates are Lower with Letrozole-IVF?

	Letrozole-IVF (n=129)	Control* Group (n=141)	P -value
Mean Follow up	2.4±1.6 (8m-5.6y)	2.9±1.7 (4m-6.8y)	NS
Recurrence Rate	2.0%	25.0%	HR = 0.08, 95%C.I. (0.06, 0.48), p=0.01

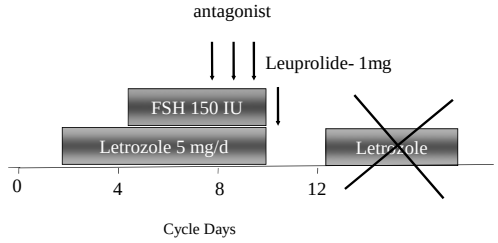
*** Control group:** women with breast cancer (mean age 35.7±4.7, similar projected 10-year relapse rate by Adjuvant-online! at the outset, p=0.91)

Safety of Pregnancy After Breast Cancer



Gelber et al. 2001

Improved Letrozole-FSH Protocol for Oocyte/Embryo Cryopreservation in Breast Cancer



GnRHa Trigger Reduces Estrogen Exposure and Improves Outcomes

	GnRHa (n=27)	hCG (n=47)	p
Peak E_2, pg/mL	695.5 ± 539.0	472.6 ± 345.5	0.044
Endometrial thickness, mm	8.4 ± 2.3	8.8 ± 1.8	0.504
Total oocytes	16.4 ± 10.3	12.8 ± 7.7	0.083
Mature oocytes	11.9 ± 6.6	7.4 ± 4.9	<0.001
Oocyte maturation rate, %	77.3 ± 21.1	68.5 ± 23.3	0.049
2-PN Embryo*	9.3 ± 5.7	6.3 ± 4.6	0.008
Fertilization rate, %	84.1 ± 11.1	74.0 ± 24.9	0.027
Drop in E2 from day 0 to 4, %	89.5 ± 6.3	79.0 ± 13.4	0.013
Mild or moderate OHSS, n (%)	1 (3.7)	10 (21.3)	0.047

Oktay et al, RBM Online 2010

GnRHa Trigger May Have Advantages Over hCG?

	GnRHa (n=37)	hCG (n=78)	P value
Age	34.1 ± 4.5	34.8 ± 4.4	NS
AFC	13.5 ± 7.5	13.7 ± 10.6	NS
AMH	2.8 ± 2.5 (n=31)	1.9 ± 1.2 (n=5)	NS
Starting FSH	275.7 ± 42.7	223.2 ± 68.5	<0.001
Total FSH	2127.0 ± 574.9	1758.0 ± 841.2	0.01
Total Letrozole	49.1 ± 7.4	48.0 ± 12.3	NS
Stimulation days	11.4 ± 1.6	12.1 ± 2.0	NS
Peak E_2, pg/mL	626.0 ±472.2	481.9 ± 293.3	NS
FSH on trigger day	26.6 ± 8.3	21.7 ± 9.9	0.01
Total oocytes	16.5 ±10.0	13.6 ±9.3	NS
Mature oocytes	**10.9 ±6.6**	**8.4 ±6.0**	**0.02***
Oocyte maturation rate, %	67.8 ± 23.2	66.8 ±26.0	NS
2-PN Embryo*	**8.3 ±4.9**	**6.2 ±5.0**	**NS***
Fertilization rate, %	81.6 ± 13.6	75.0 ± 23.6	NS*

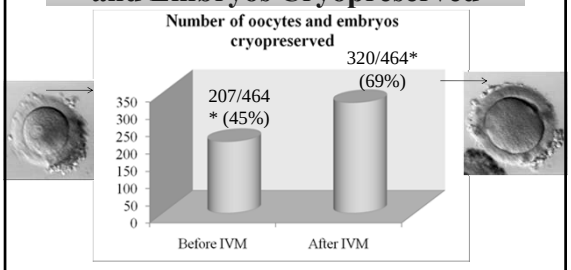
** Adjusted for Age, AFC, FSH on trigger day* *Extended from Oktay et al, RBM Online 2010*

Pregnancy Outcomes After Low vs. High Dose Letrozole-FSH

	FSH ≤ 150 IU (n=14)	FSH > 150 IU (n=11)	P value
Live birth rate	8/14	2/12	0.017
Abortion rate	3/14	4/12	NS

Use of In Vitro Maturation and Luteal/Random Start Strategies in Breast Cancer

IVM Improves Number of Oocytes and Embryos Cryopreserved

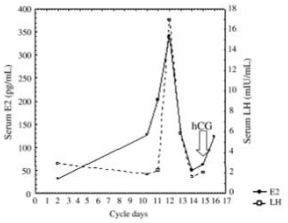


*464: total number of oocytes retrieved
P<0.0001, 95% CI: 1.4-2.4

Oktay et al RBM Online 2010

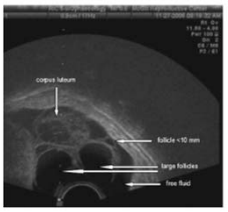
IVM with Ooocytes Retrieved After Premature LH Surge

Estradiol, LH, and P levels during the ovarian stimulation cycle.



Oktay. IVM in luteal phase. Fertil Steril 2007.

Appearance of large follicles alongside of multiple corpora lutea at the time of oocyte retrieval.



Oktay. IVM in luteal phase. Fertil Steril 2007.

•2/4 IVM'ed and frozen at 4-cell stage on day-2

Luteal Phase Ooocyte Retrieval and IVM for Urgent Fertility Preservation

ABLE 2

Treatment outcome.

	Luteal phase IVM, n = 5	Follicular phase IVM, n = 13	*P* value
No. of oocytes aspirated	12.8 ± 8.4	17.3 ± 13.5	NS
Range	3-26	4-44	NS
MII oocytes after 24 h	4.0 ± 5.7	4.5 ± 3.8	NS
Total MII oocytes[a]	7.0 ± 7.6	9.5 ± 7.73	NS
Maturation rate, %	48.6 ± 18.3	57.8 ± 29.2	NS
Fertilization rate, %[b]	69.2 ± 47.4	63.2 ± 27.3	NS
Mean total oocytes and embryos cryopreservation	6.4 ± 6.6	7.8 ± 7.5	NS

Note: Data are mean ± SD unless otherwise specified.
[a] Total MII in 48 hours.
[b] From injected oocytes only.

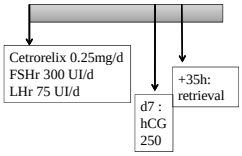
Mamsen. IVM for fertility preservation. Fertil Steril 2010.

- **Luteal phase-IVM can be offered as an optional treatment for urgent fertility preservation when there is insufficient time.**

Luteal Phase Initiation of COS for Urgent Fertility Preservation

Case 1:

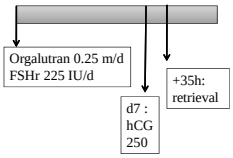
- **Breast Ca**
- **Stim start at CD-17**



- **7 high quality embryos**

Case 2:

- **Hodgkin Lymphoma**
- **Stim start at CD-22**



- **12 mature oocytes**

Bedoschi GM J Assist Reprod Genet. 2010 May 9

Random Start Controlled Ovarian Stimulation

TABLE 1

Baseline characteristics and COH outcome of the patients with breast cancer undergoing emergency fertility preservation.

Characteristic	Case 1	Case 2	Case 3
Age (y)	29	26	26
Stage	I	II	II
Histology	Invasive ductal	Mixed invasive ductal + lobular	Invasive ductal
COH start day	14	11	17
FSH (mIU/mL)	6.2	2.8	4.6
LH (mIU/mL)	5.8	2.8	1.2
E_2 (ng/mL)	62	269	50
P (pg/mL)	1.2	0.4	2.5
Endometrial thickness (mm)	7	6.5	9
Antral follicle count (n)	11	20[a]	20[b]
GnRH antagonist start day	5	1	5
Peak E_2 (pg/mL)	499	988	478
Duration of COH (d)	9	12	9
Oocytes retrieved (n)	9	17	16
Metaphase II, no. (%)	7 (77.7)	10 (58.8)	11 (68.75)
Metaphase I + germinal vesicle, no. (%)	2 (22.3)	7 (41.2)	5 (31.25)
Fertilization rate, no. (%)	7/8 (87.5)	10/12 (83.3)	9/13 (69.2)
Cleavage rate (%)	7/7 (100)	NA	NA
Embryos frozen (n)	7	10	9

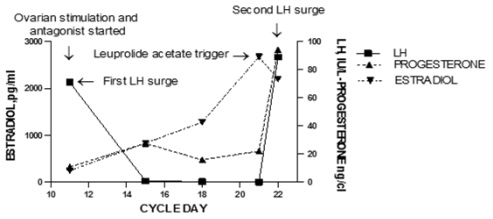
Note: GnRH antagonist start day was defined as the day of COH start. Fertilization rate was calculated as the ratio of number of two-pronuclei embryos divided by the sum of number of metaphase II plus IVM metaphase I oocytes. NA = not applicable.

[a] One dominant follicle measuring 20 mm in diameter was observed.

[b] A corpus luteum was observed.

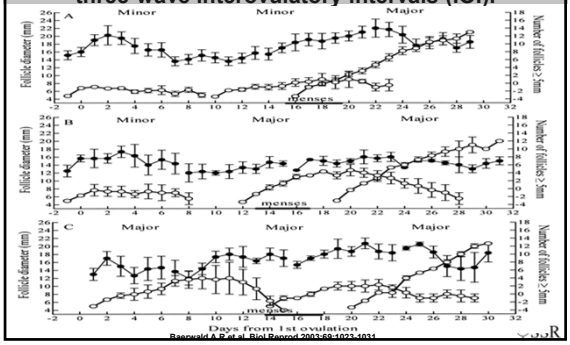
Stoneyer. Random-start ovarian hyperstimulation. Fertil Steril 2011.

GnRHa Trigger in Random Start



Ozkaya et al, JARG 2012

Diameter of the largest follicle of each wave (○) and the number of follicles ≥5 mm (•) in women with three-wave interovulatory intervals (IOI).



Baerwald A R et al. Biol Reprod 2003;69:1023-1031

BRCA: Background

- Double strand DNA break repair gene
- Mutations associated with breast/ovarian cancer risks
- 1 in every 1000 women is BRCA mutation-positive
- 2.5% in certain ethnic groups, such as people with Jewish-Ashkenazi origin

Age, FSH, and oocyte number comparisons among BRCA mutation-negative, -positive, and untested women.

	All BRCA mutation-positive [a]	BRCA mutation-negative [b]	BRCA untested [c]	BRCA1 mutation Positive [d]	BRCA mutation-negative and untested [e]	*P*
Age	33·1±2·8 (n=12)	32·8±2·9 (n=33)	33·0±2·9 (n=35)	33·9±2·7 (n=8)	32·9±2·9 (n=68)	NS
Day2 FSH (mIU/mL)	5·7±3·0	7·1±2·7	6·4±2·3	6·2±3·4	6·7±2·5	NS
N Oocytes (95% C.I.)*	7·9 (4·6-13·8)	11·3 (9·1-14·1)	13·5 (11·4-16·0)	7·4 (3·1-17·7)	12·4 (10·8-14·2)	a vs. b: 0·025 a vs. e: 0·003 d vs. e: 0·03

BRCA Mutations Are Associated with Low Ovarian Response*

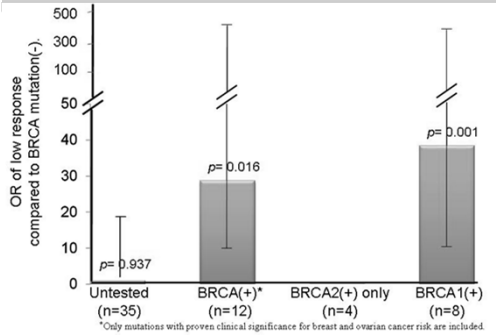
	BRCA mutation-positive [a]	BRCA mutation-negative [b]	BRCA untested [c]	*P*
Low Response Rate	**4/12 (33.3%)**	**1/33 (3.3%)**	**1/35 (2.9%)**	***a vs. b:*** **0.0014** ***a vs. c:*** **0.012**

*Retrieval of ≤4 oocytes[1,2]

1Surrey et al, Fertil Steril 1998;69;419-24.
2 Ubaldi et al, Reprod Biomed Online 2005:10;235-46.

Oktay et al, J Clin Oncol 2010

Odds Ratios (OR) of Low Ovarian Response in Women with BRCA Mutations



Oktay K et al J Clin Oncol 2010

Age of Natural Menopause in BRCA Carriers

	BRCA1	BRCA2	All
#	44	55	99
Average	48.5	48.9	48.7
SD	3.16	3.89	3.57
95%CI	47.5~49.4	47.9~49.9	48.0~49.4
p-value	<0.001	<0.001	<0.001

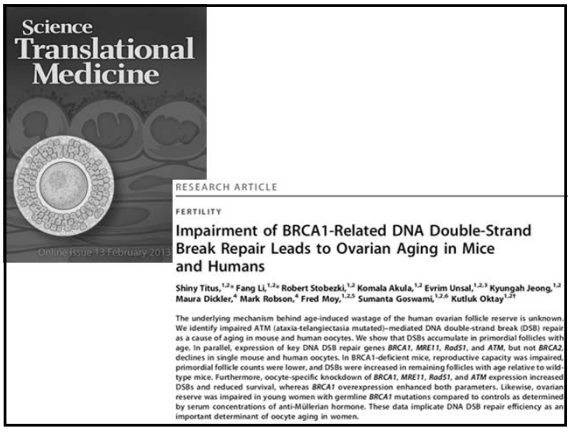
** compared to presumed population mean by SWAN study: 51.4 years old

Courtesy of Mitch Rosen, MD

Diminished Ovarian Reserve in Breast Ca Patients?

- 223 cancer patients undergoing OV
- 98 age-matched controls (male factor)
- Significantly lower number of oocytes and higher incidence of low response in E2-sensitive cancer
- BRCA status was not studied

Domingo J et al, Fertil Steril April 2012



Women with BRCA1 mutations have diminished ovarian reserve

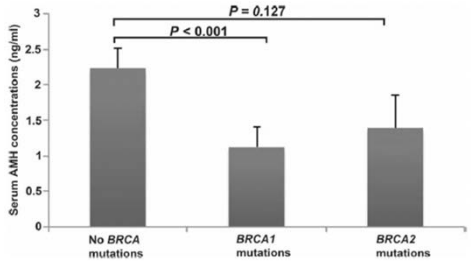
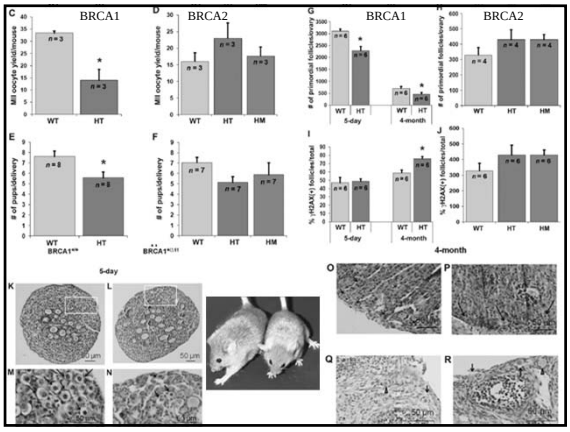


Fig. 6. Diminished ovarian reserve in *BRCA1*-deficient individuals. Women with significant *BRCA1* ($P < 0.0001$, ANOVA), but not *BRCA2* ($P = 0.127$, ANOVA), mutations had lower mean serum AMH concentrations compared to those with no *BRCA* mutations. All bar graphs show means ± SEM.



ROBOTx: Video

Robotically Assisted Ovarian Transplantation with Human Regenerative Matrix

(ROBOTx)

CONCLUSIONS

- **Early referral is essential**
- **Ovarian stimulation with letrozole appears to be <u>safe and successful</u>**
- **<u>GnRHa trigger</u> may have advantages over hCG**
- **Ovarian stimulation can be started at any time in the cycle**
- **BRCA disadvantage/ovarian aging**

- **Molecular Reproduction & Fertility Preservation Laboratory at NYMC:**
  - **Shiny Titus, PhD**
  - **Volkan Turan, MD**
  - **Fred Moy, PhD (Biostat)**
  - **Robert Stobezki, PhD cand.**
  - **Samir Babayev, MD**

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•**Collaborators:**
Sumanta Goswami, PhD, Yeshiva/AECOM
Maura Dickler, MD & Mark Robson, MD, Memorial Sloan Kettering Cancer Ctr
Evrim Unsal, PhD, & Volkan Baltaci, MD, PhD, Bilim University, Istanbul, Turkey

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- **Innovation Institute for Fertility Preservation**
  - **Kutluk Oktay, MD**
  - **Giuliano Bedoschi, MD**
  - **Fernanda Pacheco, MD**
  - **Jhansi Reddy, MD**
  - **Allison Rosen, PhD**
  - **Kirsten Acosta, BS**
  - **Ashundia Jeffers, RN**
  - **Gina Triggs**
- **Past Fellows:**
  - **Samir Babayev, MD**
  - **Kyungah Jeong, MD**
  - **Fang Li, MD, PhD**
  - **Enis Ozkaya, MD**
  - **Erol Arslan, MD**
  - **Murat Sonmezer, MD**
  - **Aylin Cil, MD**
  - **Sanghoon Lee, MD**
  - **Ozgur Oktem, MD**
  - **Kenny Rodriguez, MD, PhD**
  - **Elke Heytens, PhD**
  - **IlginTurkcuoglu, MD**
  - **Margalida Sastri, MD**
  - **Sinan Ozkavukcu, MD, PhD**

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Age Specific Success of Oocyte Cryopreservation: How to counsel your patient?

Kutluk Oktay, MD, FACOG

Professor of Obstetrics & Gynecology, Medicine, Cell Biology & Anatomy, and Pathology

Director, Division of Reproductive Medicine and Fertility Preservation

New York Medical College

Director, Innovation Institute for Fertility Preservation , Rye and Manhattan, NY

Innovative Care Fertility Preservation.org

New York Medical College

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New York Medical College

Innovative Care Fertility Preservation.org

Learning Objectives

At the conclusion of this presentation, participants should be able to:

- Outline current methods of oocyte freezing.
- Compare the current success rates with slow freezing and vitrification of oocytes.
- Determine the age-specific success of oocyte freezing compared.
- Equipped to counsel patients for oocyte cryopreservation.

Advantages of Oocyte Freezing

- No need for a partner
- Avoids issues with embryo storage
  - legal
  - ethical
- Simplifies oocyte donation

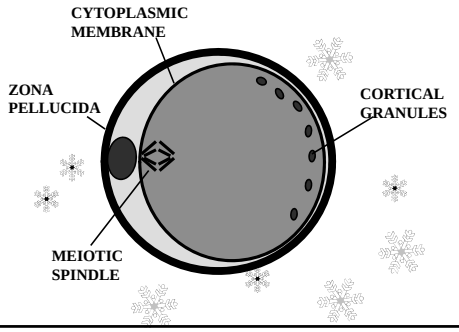
Indications for oocyte freezing

- Fertility preservation:
  - Patients undergoing sterilizing chemo and/or radiotherapy
  - Elective (Delayed childbearing)
- Oocyte donation (oocyte banking)
- Emergency measure (inability to obtain sperm)
- Ethical/legal barriers with embryo cryopreservation

Cryopreservation Methods

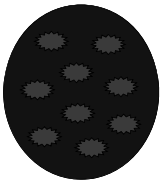
- "Slow" (Controlled rate/equilibrium freezing)
- "Fast" (Vitrification)

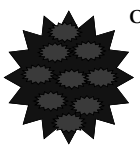
Trouble Spots For an Oocyte



Ice Crystals Damage the Oocyte Membrane

Intracellular Osmolarity Rapidly Increases During Freezing

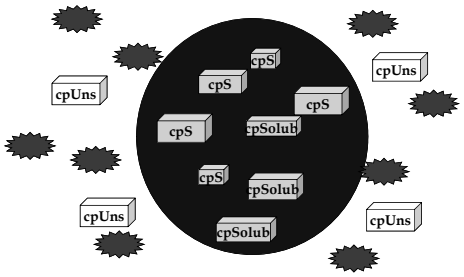




37 ℃

- 180 ℃

Cryoprotectants Prevent Intracellular Ice Crystal Formation and Control Osmolarity Changes



Controlled Rate (Slow) Freezing

- Relatively low cryoprotectant concentrations for dehydration (1.5M)
- Seeding to induce extracellular freezing
- Intracellular water vitrifies
- Similar to traditional approaches for embryo freezing

Slow Freezing: A Balancing Act

- To create a delicate balance between various factors causing damage including:
  - ice crystal formation
  - zonal fracture
  - toxic and osmotic damage
- Allows solution exchange between the extracellular and intracellular fluids without serious osmotic effects and deformation of the cells (equilibrium freezing)

Vitrification

- Freezing has to be rapid (at least 20,000 °C/min)
- No ice crystals form but rapid rise in osmolarity
- Higher concentrations of cryoprotectants needed depending on the volume

How to Increase the Speed of Vitrification?

- Direct contact with LN_2
- Lower temperature: Slush N_2
- As small volume as possible (<1 μL)
  - Cryoloop (<0.01 μL at 700,000 °C/min)
  - Cryotop (<0.1 μL, at 40,000 °C/min)
  - Cryotip
- Can lower cryoprotectant concentrations

Concerns with Vitrification

- Cross-contamination
  - *Kuleshova & Shaw 2000, Bielanski 2000, 2003*
- Toxic effects of cryoprotectants
- Not standardized/automated
- Fragile systems/risk of losing oocytes

Avoiding Risk of X-Contamination

- Separate freezing and storage phases
- Enclosed systems:
  - cryotip

What is the Clinical Efficiency of Oocyte Freezing? SF and VF Compared to Fresh Oocytes

First Pregnancies From Human Ooocyte Freezing

AUTHORS	YEAR	BIRTHS
Chen	1986	Twin (IVF)
	1987	Singleton (IVF)
van Uem	1987	Singleton (IVF)
Siebzehnruelb	1989	Singleton (IVF)
Porcu	1997	Singleton (ICSI)

Oocyte cryopreservation

- Numerous small reports
  - Slow freezing (SF)
  - Vitrification (VF)
- Relative efficiency?
  - Per oocyte success is not reported for IVF with fresh oocytes
  - Total number of pregnancies may not be accurately known

Efficiency of oocyte cryopreservation: a meta-analysis

Kutluk Oktay, M.D.,[a] Aylin Pelin Cil, M.D.,[a] and Heejung Bang, Ph.D.[b]

[a] Fertility Preservation Program at Center for Reproductive Medicine and Infertility and [b] Department of Public Health, Weill Medical College of Cornell University, New York, New York

New York, New York

Objective: To determine the efficiency of oocyte cryopreservation relative to IVF with unfrozen oocytes.
Design: Meta-analysis.
Setting: Academic assisted reproduction center.
Patient(s): Results of all reports from January 1997 to June 2005 with the patients undergoing IVF-intracytoplasmic sperm injection (ICSI) with cryopreserved cycles between 1996 and 2004 were compared with those of patients who underwent IVF-ICSI with unfrozen oocytes in 2002 and 2003 in our program.
Intervention(s): Mean age and number of ET cycles originating from unfrozen oocytes was matched with those for thaw cycles originating from oocytes cryopreserved with a slow-freezing (SF) protocol. Vitrification (VF) reports were not included in the comparative analysis because of a small number of pregnancies (10) before June 2005.
Main Outcome Measure(s): The comparison of fertilization rate, clinical pregnancy, and live-birth rates per injected oocyte, clinical pregnancy and live-birth rates per transfer, and implantation rate between IVF-ICSI cycles with frozen and unfrozen oocytes.
Result(s): Live-birth rates per oocyte thawed were 1.9% and 2.0% for SF and VF, respectively, before June 2005. Live-birth rates per injected oocyte and ET, respectively, were 3.4% and 21.6% for SF and were 6.6% and 60.4% for IVF with unfrozen oocytes. Compared to women who underwent IVF after SF, IVF with unfrozen oocytes resulted in significantly better rates of fertilization (odds ratio [95% confidence interval]; 2.22 (1.80, 2.74), of live birth per injected oocyte; 1.5 (1.26, 1.79), and of implantation; 4.66 (3.93, 5.52). These odds ratios were lower when oocyte cryopreservation success rates from 2002–2004 were compared with those for IVF with unfrozen oocytes. When the reports after June 2005 were considered, this trend did not appear to continue. With the consideration of VF reports after June 2005, however, higher pregnancy rates were achieved.
Conclusion(s): In vitro fertilization success rates with slow-frozen oocytes are significantly lower when compared with the case of IVF with unfrozen oocytes. Although oocyte cryopreservation with the SF method appears to be justified for preserving fertility when a medical indication exists, its value for elective applications remains to be determined. Pregnancy rates with VF appear to have improved, but further studies will be needed to determine the efficiency and safety of this technique. (Fertil Steril® 2006;86:70–80. ©2006 by American Society for Reproductive Medicine.)

Key Words: Oocyte cryopreservation, slow freeze, vitrification, IVF, ICSI, fertility preservation

Fertility and Sterility® Vol. 86, No. 1, July 2006

Update on SF and VF (Jan 1986-May 2008)

	SF	VF	OR(95%CI)
Mean age	34.5	32.2	
Fertilization Rate(%)	72.3(5745/7942)	80.4(2309/2870)	1.58(1.42-1.75)
Clinical preg/thawed	2.2(314/14215)	5.8(212/3672)	2.66(2.21-3.01)
Live birth/thawed	1.7(245/14215)	5.0(177/3672)	2.94(2.4-3.6)
CP/transfer	15(314/2095)	33.4(212/635)	2.86(2.32-3.57)
LB/transfer	11.7(245/2095)	28.7(177/635)	2.94(2.38-3.7)
Implantation rate	8.1(376/4642)	15.0(261/1741)	2.0(1.69-2.38)
Spontaneous Ab	21.7(68/314)	16.5(35/212)	0.76(0.55-1.1)

Oktay et al. Unpublished data.

Per Oocyte Success Rates with VF: Cryopreserved vs. Fresh (*Goldman et al, Fertil Steril 2013*)

	OC (n = 25)	Fresh IVF (n = 1,392)	P value
Age	33.6 Â± 0.7	34.1 ± 0.1	0.5
FSH on day 3	6.6 Â± 0.4	6.7 ± 0.1	0.79
E2 on day 3 (pg/mL)	38 Â± 2.6	36 ± 0.9	0.84
Gonadotropin dosage	2,124± 188	2,637± 31	0.03
Peak E2 (pg/mL)	2,362 ± 233	2,088 ± 29	0.21
No. ooocytes retrieved	21± 2.5	16 ± 0.2	0.001
No. MII retrieved	16 ± 2.2	12 ± 0.2	0.01
Oocyte survival %	82.5		
2PN fertilization %	81	78	0.18
No. of 2PN zygotes	10 ± 1.4	10 ± 0.16	0.74
BFR%	38.6	64	0.0001
No. of blastocysts	3.9 ± 0.9	6.3 ± 0.1	0.01
No. ET	2 ± 0.16	2 ± 0.01	0.07
LBR-ET %	45.8	51.9	0.68
LBR-MOR %	2.7	4.2	0.19

Study Weaknesses

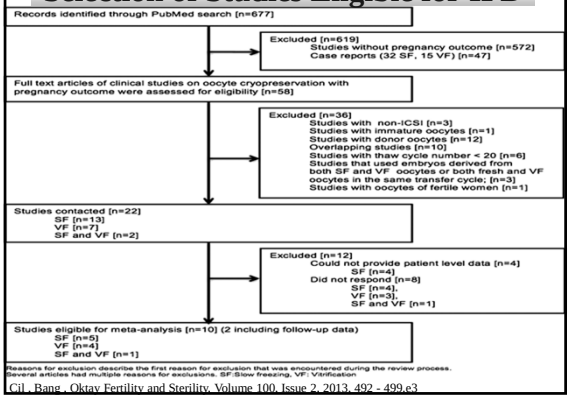
- **Indications for oocyte freezing and IVF were not specified**
- **Mixed donor and autologous oocytes**
- **Unclear if all oocytes were thawed**
- **Not all cryopreserved embryos were utilized from each patient to assess full potential**
- **Retrospective**

Table 1 Key publications relating to cryopreservation of human oocytes.

	Cryoprotectants	Survival rate (%)	Cryopreservation IR (%)		Fresh IR (%)
			Cleavage stage ET	Blastocyst ET	
Optimal slow cooling					
Cook and Edgar (2011)	1.5 M PROH, 0.2 M sucrose	75.8	30.0 (<38 years)		26.0 (<38 years)
Yang *et al.* (2002), donor	1.5 M PROH, 0.2 M sucrose	70.9	25.3		43.4
Bianchi *et al.* (2007)	1.5 M PROH, 0.2 M sucrose	75.1	16.7		17.3
Konc *et al.* (2008b)	1.5 M PROH, 0.3 M sucrose	76	15.4[a]		18
Ferraretti *et al.* (2010)	1.5 M PROH, 0.3 M sucrose	71.8	18.9 (≤35 years)		
Parmegiani *et al.* (2009)	1.5 M PROH, 0.3 M sucrose	71.6	15.1		
Optimal vitrification					
Antinori *et al.* (2007)	15% EG, 15% DMSO, 0.5 M sucrose	99.4	13.2		10.3
Renzi *et al.* (2010)	15% EG, 15% DMSO, 0.5 M sucrose	96.7–89.7	27.3 (≤34 years)		30.0 (≤34 years)
Ubaldi *et al.* (2010)					
Almodin *et al.* (2010)	15% EG, 15% DMSO, 0.5 M sucrose	84.9	14.9		21.3
Cobo *et al.* (2010a), donor	15% EG, 15% DMSO, 0.5 M sucrose	92.5	39.9		40.9
Trokoudes *et al.* (2011), donor	15% EG, 15% DMSO, 0.5 M sucrose	91.4	24.7		25.6
Cobo *et al.* (2008a), donor	15% EG, 15% DMSO, 0.5 M sucrose	96.9		40.8	
Nagy *et al.* (2009), donor	15% EG, 15% DMSO, 0.5 M sucrose	89		55.3	47.4
Garcia *et al.* (2011), donor	15% EG, 15% DMSO, 0.5 M sucrose	89.4		43.9	42.9
Comparison of slow cooled and vitrified (vit)					
Smith *et al.* (2010), slow	1.5 M PROH, 0.3 M sucrose	65	13[a,b]		
Smith *et al.* (2010), vit	15% EG, 15% DMSO, 0.5 M sucrose	75	38[a,b]		
Noyes *et al.* (2010), slow	1.5 M PROH, 0.3 M sucrose	85	NR (mixed transfers)		
Noyes *et al.* (2010), vit	15% EG, 15% DMSO, 0.5 M sucrose	88	NR (mixed transfers)		
Fadini *et al.* (2009), slow	1.5 M PROH, 0.3 M sucrose	57.9	4.3		
Fadini *et al.* (2009), vit	EG, PROH, sucrose (Medicult)	78.9	9.3		

PROH, propanediol; EG, ethylene glycol; DMSO, dimethyl sulphoxide; IR, implantation rate; NR, not reported; ET, embryo transfer; Donor, donor oocyte programme.
[a]Assisted hatching.
[b]Pregnancy rate.

Selection of Studies Eligible for IPD



Cil , Bang , Oktay Fertility and Sterility, Volume 100, Issue 2, 2013, 492 - 499.e3

IPD-MetaAnalysis

- **Studies from January 1986-July 2011**
- **Unpublished data (Drs J Boldt and E Lucena, thank you!!)**
- **Donor cycles excluded (studied separately)**
- **Associations between covariates & outcomes modeled and fitted via generalized estimating equations (GEE)**

IPD-MetaAnalysis Design

- **2,265 OC freeze/thaw cycles from 1,805 infertility patients**
- **1,962 (SF) and 303 (VF) cycles**
- **11,122 (SF) and 1,957 (VF) oocytes**
- **Retrieved 1997-2009**

Individual Patient Data (IPD) Meta-analysis from 2265 Oocyte Thaw Cycles in 1,805 women

- **SF: Pregnancies occurred until age 42**
- **VF: Pregnancies occured until age 44**
- **Overall success higher with VF vs. SF ($p<0.01$)**
- **Sharper age-related decline age>36**

Cil, Bang & Oktay, Fertil Steril 2013

IPDMA: SF vs. VF

Comparison of thaw cycle characteristics between SF and VF.

Characteristic	SF (n = 1,962)	VF (n = 303)	*P* value
Age (y)			.53
Mean ± SD	33.8 ± 4.0	34.1 ± 4.7	
Range	20–48	20–51	
Thawed oocytes			.003
Mean ± SD	5.7 ± 2.3	6.5 ± 4.5	
Range	2–18	2–32	
Survived			<.001
Mean ± SD	3.6 ± 1.6	5.2 ± 3.4	
Range	1–14	1–23	
Injected			<.001
Mean ± SD	3.0 ± 1.1	4.0 ± 2.3	
Range	1–11	1–18	
Fertilized			<.001
Mean ± SD	2.3 ± 1.0	3.2 ± 1.9	
Range	1–9	1–14	
Embryos transferred			<.001
Mean ± SD	2.2 ± 0.8	2.8 ± 1.3	
Range	1–6	1–8	
Cancellation rate (%)	12.9	7.3	.006

Note: Sample sizes are reduced for some rows owing to missing data. For some patients, multiple observations were included. Cancelled cycles were not included in calculations. *P* values are computed from GEE accounting for two-level clustering (i.e., within study and within patient).

Cil. Live birth probability with egg freezing. Fertil Steril 2013.

Lower Implantation and Higher Miscarriage Rates with SF vs. VF

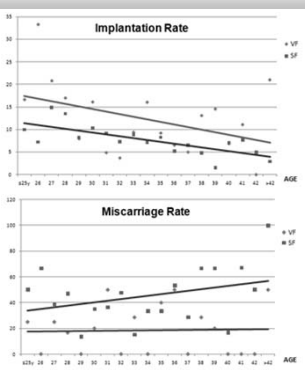
IPDMA: SF vs. VF

Representative probabilities (%) of live birth for ages 25–42 years, according to number of oocytes thawed, injected, or embryos transferred.

	SF									VF								
	Oocytes thawed			Oocytes injected			Embryos transferred			Oocytes thawed			Oocytes injected			Embryos transferred		
Age (y)	2	4	6	2	4	6	1	2	3	2	4	6	2	4	6	1	2	3
25	12.6	13.5	14.4	12.4	16.0	20.5	7.5	12.4	20.0	28.1	29.7	31.3	24.8	30.9	37.7	13.0	20.7	31.5
26	11.8	12.7	13.5	11.6	15.1	19.4	7.0	11.8	19.0	26.7	28.2	29.8	23.5	29.4	36.0	12.2	19.7	30.1
27	11.1	11.9	12.7	10.9	14.3	18.4	6.6	11.1	18.0	25.3	26.8	28.3	22.3	28.0	34.5	11.6	18.7	28.8
28	10.4	11.2	11.9	10.3	13.4	17.3	6.2	10.5	17.1	24.0	25.4	26.8	21.1	26.6	32.9	10.9	17.7	27.4
29	9.8	10.5	11.2	9.6	12.6	16.4	5.9	9.9	16.2	22.7	24.0	25.4	20.0	25.2	31.4	10.3	16.8	26.2
30	9.1	9.8	10.5	9.1	11.9	15.4	5.5	9.3	15.3	21.4	22.7	24.1	18.9	24.0	29.9	9.7	15.9	24.9
31	8.6	9.2	9.8	8.5	11.2	14.6	5.2	8.8	14.5	20.2	21.5	22.8	17.8	22.7	28.5	9.2	15.0	23.7
32	8.0	8.6	9.2	8.0	10.5	13.7	4.9	8.3	13.7	19.1	20.3	21.6	16.8	21.5	27.1	8.6	14.2	22.6
33	7.5	8.1	8.6	7.5	9.9	12.9	4.6	7.8	12.9	18.0	19.2	20.4	15.9	20.4	25.7	8.1	13.5	21.5
34	7.0	7.5	8.1	7.0	9.3	12.1	4.3	7.3	12.2	17.0	18.1	19.2	15.0	19.3	24.4	7.7	12.7	20.4
35	6.6	7.0	7.6	6.6	8.7	11.4	4.0	6.9	11.5	16.0	17.0	18.1	14.1	18.2	23.1	7.2	12.0	19.3
36	6.1	6.6	7.1	6.2	8.2	10.7	3.8	6.5	10.9	15.0	16.0	17.1	13.3	17.2	21.9	6.8	11.3	18.3
37	5.7	6.2	6.6	5.8	7.7	10.1	3.6	6.1	10.3	14.1	15.1	16.1	12.5	16.2	20.8	6.4	10.7	17.4
38	5.4	5.8	6.2	5.4	7.2	9.5	3.4	5.7	9.7	13.3	14.2	15.1	11.8	15.3	19.6	6.0	10.1	16.5
39	5.0	5.4	5.8	5.1	6.7	8.9	3.1	5.4	9.1	12.5	13.3	14.2	11.1	14.4	18.6	5.6	9.5	15.6
40	4.7	5.0	5.4	4.7	6.3	8.3	3.0	5.1	8.6	11.7	12.5	13.4	10.4	13.6	17.5	5.3	9.0	14.8
41	4.4	4.7	5.0	4.4	5.9	7.8	2.8	4.8	8.1	11.0	11.8	12.6	9.8	12.8	16.6	5.0	8.5	14.0
42	4.1	4.4	4.7	4.1	5.5	7.3	2.6	4.5	7.6	10.3	11.0	11.8	9.2	12.0	15.6	4.7	8.0	13.2

Cil. live birth probability with egg freezing. Fertil Steril 2013.

IPDMA: SF vs. VF



P=0.002

P=0.005

Studies that Met the Criteria for IPD Meta-analysis

TABLE 1

Characteristics and success rates of the studies from which IPD were available and used for meta-analysis.

Age (y)	Country	First author/year (reference)	Study type	Method	n	No. thawed oocytes	No. thaw cycles	SR (%)	FR (%)	IR (%)	CP/T (%)	LB/T (%)
31.7 ± 4.7	Taiwan	Chen/2005 (17)	Prospective	SF	21	159	21	76.1	66.1	10.7	33.3	33.3
31.7 ± 4.1	United States	Boldt/2006 (18)	Retrospective	SF	82	556	87	55.4	65.4	12.6	26.5	19.1
32.0 ± 3.6	United States	Boldt/2006[a]		VF	25	168	28	78.0	76.7	11.5	29.2	20.8
32.3 ± 3.6	Hungary	Konc/2008 (19)	Retrospective	SF	54	215	64	80.0	84.3	11.0	20.3	15.6
35.7 ± 5.7	Italy	Albani/2008 (20)	Retrospective	SF	949	7,584	1,280	58.1	70.2	6.9	12.8	8.4
34.1 ± 3.9	Italy	Parmegiani/2009 (21)	Retrospective	SF	424	2,608	510	70.7	82.6	8.2	16.3	8.8
34.5 ± 3.8	Korea	Yoon/2003 (22)	Prospective	VF	34	474	34	88.6	71.7	5.6	22.2	22.2
33.6 ± 4.3	Colombia	Lucena/2006 (23)[b]	Retrospective	VF	37	179	37	81.0	85.8	3.5	10.8	10.8
32.5 ± 5.8	Korea	Yoon/2007 (24)	Prospective	VF	28	364	30	83.0	77.1	14.2	43.3	36.7
35.7 ± 4.9	Italy	Fadini/2009 (25)	Retrospective	VF	46	285	59	78.9	72.8	9.3	19.2	11.5
31.9 ± 4.5	Italy	Ubaldi/F2010 (26)	Prospective	VF	105	487	115	89.7	85.4	16.2	31.5	26.1
		Total			1805	13,079	2,265					

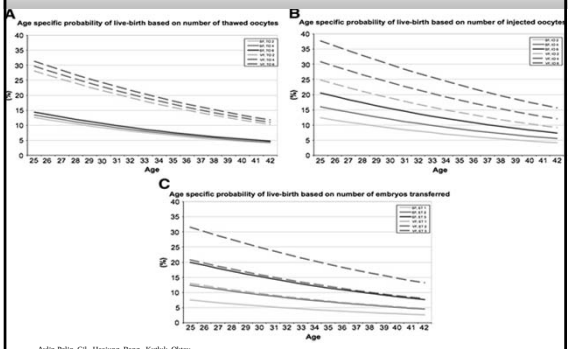
Note: For age, mean ± SD. The success rates of IPD available studies were recomputed from the data obtained. SR = survival rate; FR = fertilization rate; IR = implantation rate (scale/embryos transferred); CP/T = clinical pregnancy/transfer; LB/T = live birth/transfer.
[a] Follow-up data of reference 18, written in a different row because different cryopreservation method is used.
[b] Includes follow-up data.
[c] Includes RCT data from a previous study by the same group (27).
[d] Live birth probability with egg freezing. *Fertil Steril* 2013.

Cil , Bang , Oktay Fertility and Sterility, Volume 100, Issue 2, 2013, 492 - 499.e3

Study Aims

- **Primary Aim: To Develop three LB probabilities based on age, cryopreservation method, and**
  - **#oocytes thawed**
  - **#oocytes injected**
  - **#embryos transferred (1-3)**
- **Secondary Outcome: survival, fertilization, implantation rates**

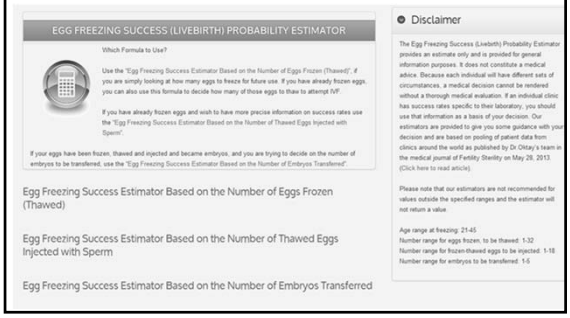
Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis



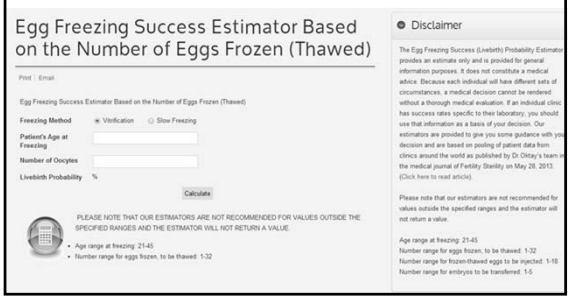
Aylin Pelin Cil , Heejung Bang , Kutluk Oktay
Fertility and Sterility, Volume 100, Issue 2, 2013, 492 - 499.e3

Age-Specific Success Probability of Egg Freezing: Online Estimator

http://fertilitypreservation.org/index.php/probability-calc



Age-Specific Success Probability of Egg Freezing: Online Estimator



Head to Head Comparison of SF vs. VF

	Controlled Rate	Vitrification
Time Consumption		✓
Cost		✓
Success		✓
Standardization	✓	
Safety	✓	
Experience	✓	✓

Outcome of Children Born From (Slow)Frozen Oocytes[1,2]

- 52 pregnancies, 32 live-born
  - Follow-up reported only in 30
  - 1 VSD, 1 triploidy, 28 "normal"
- 105 liveborn
  - 2 malformations, severe male factor[3]
- No karyotypic abnormalities[4]

[1]Porcu et al. Fertil Steril. 2000;74 (suppl1):S48. [2] Winslow KL et al. ASRM. 2001;28.
[3]Borini et al, ASRM 2007 abstract, [4] Tur-Kaspa et al, ASRM 2007 abstract

Is Pregnancy Outcome Data from Oocyte Cryopreservation Reassuring?

- **936 liveborns identified from published/unpublished data**
- **12 birth defects (1.3%): VSD(3), Club foot (3) Choanal (1) and Biliary (1) atresia, Runinstein-Taybi (1), Arnold-Chiari (1), Cleft palate (1)**
- **Only those that went to term, reported or voluntarily provided**

Noyes, Porcu, Borini. RBM Online 2009

Conclusions

- Ooocyte cryopreservation is a viable option for medical indications
- Vitrification appears to be superior but Slow Freezing may catch up
- Limited data on children
- Age specific success rate estimates are now available: http://www.fertilitypreservation.org/index.php/probability-calc

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3: Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril. 2006 Jul;86(1):70-80.

4: Goldman KN, Noyes NL, Knopman JM, McCaffrey C, Grifo JA. Oocyte efficiency: does live birth rate differ when analyzing cryopreserved and fresh oocytes on per-oocyte basis? Fertil Steril. 2013 Sep;100(3):712-7. doi:

5: Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online. 2009 Jun;18(6):769-76.

6: Cobo A, Remohí J, Chang CC, Nagy ZP. Oocyte cryopreservation for donor egg banking. Reprod Biomed Online. 2011 Sep;23(3):341-6.

- **Molecular Reproduction & Fertility Preservation Laboratory at NYMC:**
  - **Shiny Titus, PhD**
  - **Volkan Turan, MD**
  - **Fred Moy, PhD (Biostat)**
  - **Robert Stobezki, PhD cand.**
  - **Akula Komala, MS**

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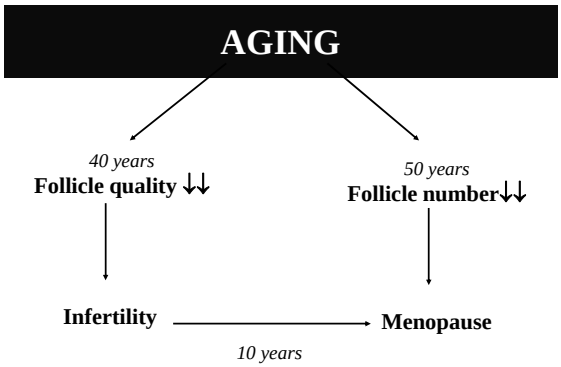
fertilitypreservation.org

i-fertility.net

- **Innovation Institute for Fertility Preservation**
  - **Kutluk Oktay, MD**
  - **Giuliano Bedoschi, MD**
  - **Fernanada Pacheco, MD**
  - **Jhansi Reddy, MD**
  - **Allison Rosen, PhD**
  - **Kirsten Acosta, BS**
  - **Ashundia Jeffers, RN**
  - **Gina Triggs**
- **Past Fellows:**
  - **Samir Babayev, MD**
  - **Kyungah Jeong, MD**
  - **Fang Li, MD, PhD**
  - **Enis Ozkaya, MD**
  - **Erol Arslan, MD**
  - **Murat Sonmezer, MD**
  - **Aylin Cil, MD**
  - **Sanghoon Lee, MD**
  - **Ozgur Oktem, MD**
  - **Kenny Rodriguez, MD, PhD**
  - **Elke Heytens, PhD**
  - **IlginTurkcuoglu, MD**
  - **Margalida Sastri, MD**
  - **Sinan Ozkavukcu, MD, PhD**

Ethical and moral dilemmas

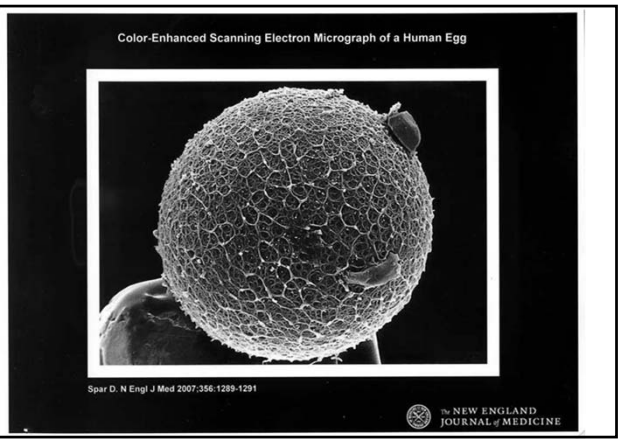
Pr. J. DONNEZ

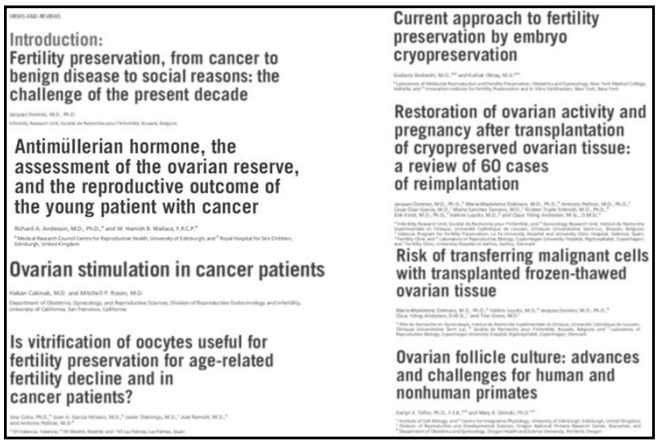


Female emancipation comes at a price

35 years: fertility ↓

Family size ↓ (mean < 2 children)





NATURE REVIEWS ENDOCRINOLOGY | REVIEW

Fertility preservation in women

Jacques Donnez & Marie-Madeleine Dolmans

Nature Reviews Endocrinology (2013) doi:10.1038/nrendo.2013.205
Published online 29 October 2013

Abstract

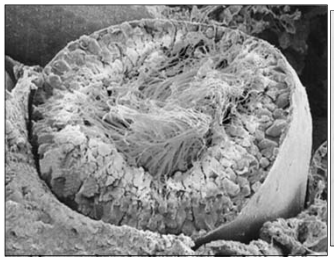
In women, ~10% of cancers occur in those <45 years old. Chemotherapy, radiotherapy and bone marrow transplantation can cure >90% of girls and young women with diseases that require such treatments. However, these treatments can result in premature ovarian failure, depending on the follicular reserve, the age of the patient and the type and dose of drugs used. This article discusses the different fertility preservation strategies: medical therapy before chemotherapy; ovarian transposition; embryo cryopreservation; oocyte vitrification; and ovarian tissue cryopreservation. The indications, results and risks of these options are discussed. Whether medical therapy should be used to protect the gonads during chemotherapy remains a source of debate. Fertility preservation needs to be completed before chemotherapy and/or irradiation is started and might take 2–3 weeks with established techniques such as embryo or oocyte cryopreservation. Further studies are needed in patients with cancer to confirm the excellent outcomes obtained in patients without cancer or in egg donation programmes. For prepubertal girls or cases where immediate therapy is required, cryopreservation of ovarian tissue is the only available option. Finally, possible future approaches are reviewed, including *in vitro* maturation of nonantral follicles, the artificial ovary, oogonial stem cells and drugs to prevent follicle loss.

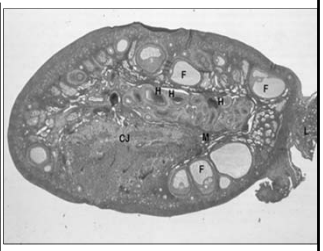
Fertility:preservation A New Discipline in Reproductive Medecine

- The primary function of ovary is R**EPRODUCTION**: « pass the genetic paternal on to the next generation »

- The primary function of ovary is R**EPRODUCTION**: « pass the genetic paternal on to the next generation »
- The second function is STEROID SECRETION

ANATOMY & PHYSIOLOGY





Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients?

Ana Cobo, Ph.D.,[a] Juan A. Garcia-Velasco, M.D.,[b] Javier Domingo, M.D.,[c] José Remohí, M.D.,[a] and Antonio Pellicer, M.D.[a]

[a] IVI Valencia, Valencia; [b] IVI Madrid, Madrid; and [c] IVI Las Palmas, Las Palmas, Spain

Mature oocyte vitrification

Comparison of concomitant outcome achieved with fresh and cryopreserved donor oocytes vitrified by the Cryotop method

Ana Cobo, Ph.D.,[a] Masashigue Kuwayama, Ph.D.,[b] Sonia Pérez, Ph.D.,[a] Amparo Ruiz, M.D.,[a] Antonio Pellicer, M.D.,[a] and José Remohí, M.D.[a]

[a] IVI Universidad de Valencia, Valencia, Spain; and [b] Kato Ladies Clinic, Nushishinjuku, Shinjuku, Tokyo, Japan

Fertility and Sterility® Vol. 89, No. 6, June 2008

Survival rate of vitrified oocytes: 96.9 %

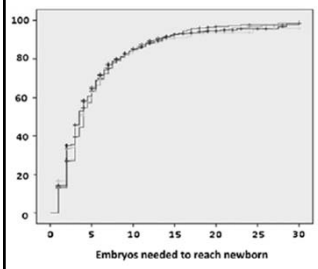
Mature oocyte vitrification

Cumulative newborn rates increase with the total number of transferred embryos according to an analysis of 15,792 ovum donation cycles

Nicolás Garrido, Ph.D., M.Sc.,[a] José Bellver, M.D.,[a] José Remohí, M.D.,[a] Pilar Alamá, M.D.,[a] and Antonio Pellicer, M.D.[a,b]

[a] Instituto Universitario IVI Valencia, University of Valencia; and [b] Hospital Universitario y Politécnico La Fe, Valencia, Spain

Mature oocyte vitrification

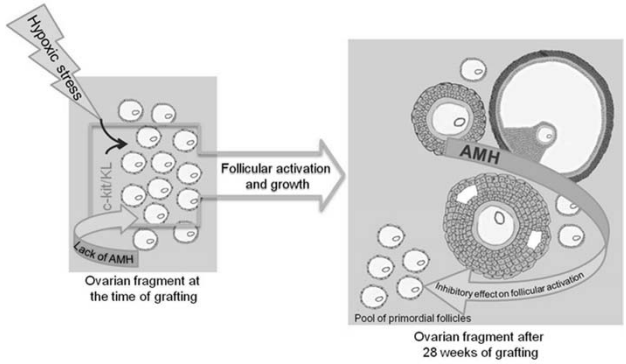


Newborn rate:

- 5 E: 64,8%
- 15 E: 92,4%
- 10 E: 85,2%

Pregnancy rate after oocyte vitrification:

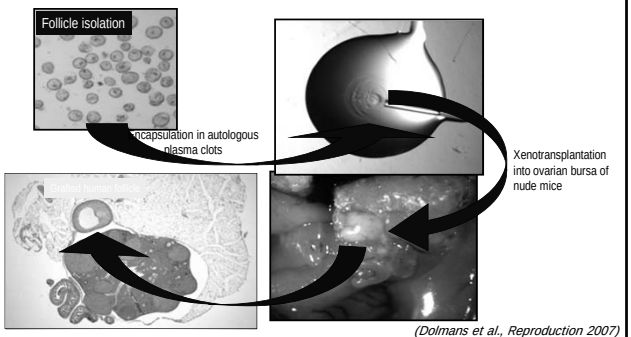
- 10 oocytes: 40%
- 12 oocytes: 60%
- 20 oocytes: 90%



David et al, Human Reproduction, 2012

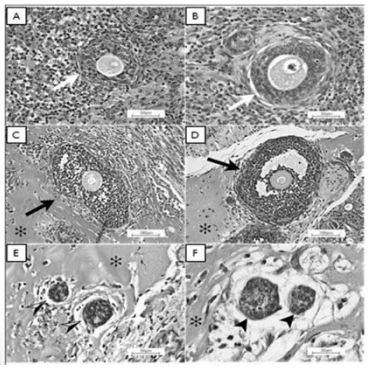
Isolated follicles: transplantation

Transplantation of isolated follicles in a <u>plasma clot</u>: pilot study



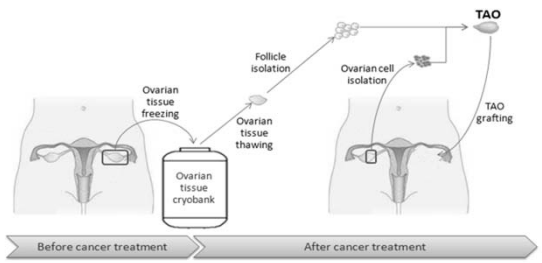
(Dolmans et al., Reproduction 2007)
(Dolmans et al., RBM Online 2008)

Fibrin



Autografting of murine ovarian follicles in a fibrin clot after one week. Some secondary follicles (white arrows) could be observed after 1 week of grafting in a (F25/T4) fibrin clot (A) and in a (F12.5/T1) fibrin clot (B). Antral follicles (black arrows) could be evidenced in both formulations: in F25/T4, an ovarian follicle at the beginning of antralisation (C), and in F12.5/T1 matrix, growing ovarian follicles up to the antral stage (D). Some follicular structures (bicolored arrow head) were found inside the fibrin matrix (E). Periodic acid Schiff staining was performed to evidence the basement membrane surrounding the follicles, colored in hard pink (black arrow head), and identify follicular structures when the oocyte was not present (F). In these different pictures, the residual fibrin after grafting, colored in pink, could be observed (*).

The artificial ovary



OSC (oogonia stem cells)

-Debate started in 2004

-Since,

1) White, Woods and Tilly were able to isolate mitotically active germ cells from adult mouse and human ovaries *(Nat Med 2012, Nat Prot 2013)*

2) Zou et al reported the production of offspring from a germline stem cell line derived from mouse neonatal ovaries *(Nat Cell Biol, 2009)*

OSC (oogonia stem cells)

BUT

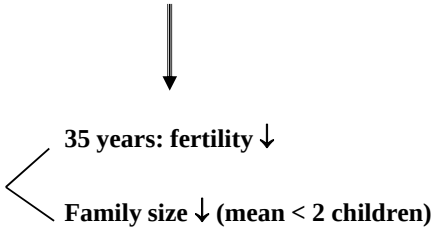
1) OSCs are extremely scarce (0.014% of all cells in mouse ovaries)

2) The potential of « early follicle-like » structures generated from OSCs remains unclear.

Fertility:preservation A New Discipline in Reproductive Medecine

WHY ?

Female emancipation comes at a price



Moral and ethical dilemmas

1. Convince the patients to be pregnant before their 30y
2. Is it ethically defendable? Notion of liberty?
3. Free to choose delayed childbearing
4. Cost-effectiveness
   1. Oocytes cryo > OTC
   2. Depends on the number of non-pregnant women who will come to use their oocytes or tissue
   3. Not possible for all women on a financial point of view

Moral and ethical dilemmas

5. Primum non nocere
   1. Risks are well known
   2. OHSS:
      - Trigger with GnRHa
      - Minimal risk as no pregnancy will occur during that cycle
   3. Minimally invasive surgery
6. High rate of pregnancies when oocytes vitrified at age of 25y are used
7. May be the future will be……

- At age of 25y, OC and OTC
- At age of 40y, if no natural conception use vitrified oocytes
- If no successfull use cryopreserved ovarian tissue

Minimally Invasive Approaches to fertility Preservation

Tommaso Falcone, M.D.,FRCSC,FACOG
| Professor and Chair Obstetrics, Gynecology and Women's Health Institute |

Learning objectives

At the conclusion of this presentation, participants should be able to:

- Assess which patients are candidates for for transposition of the ovaries.
- Discuss the potential minimally invasive approach to ovarian tissue transplantation
- Discuss the surgical approach to minimize ovarian tissue damage when removing an endometrioma

Financial Disclosure

- I have no financial relationships with industry
- Receive honoraria
  - Editor-in-Chief Journal of Minimally Invasive Surgery
  - Section Editor- Up-To-Date

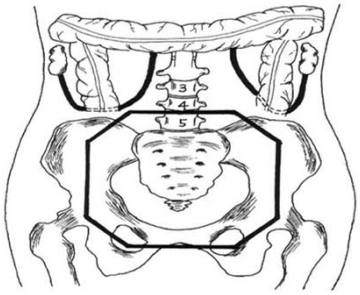
Conserving fertility:Transposition:

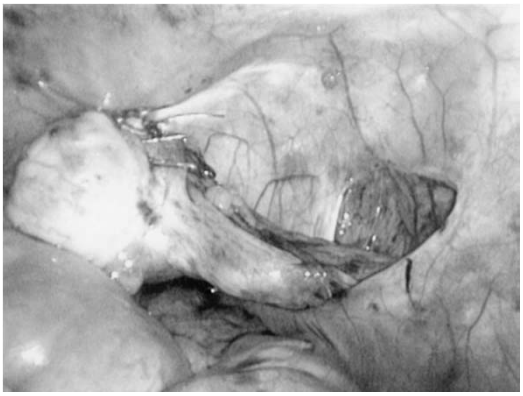
- Radical hysterectomy, radiotherapy, ovarian transposition
- Multiple studies
  - Ovarian function preservation in at least 50 %.
  - Outcome determined by cumulative dose
    - Work with radiotherapist to calculate scatter dose
  - Age of patient
  - Age menopause: decade earlier

Reasons for Failure

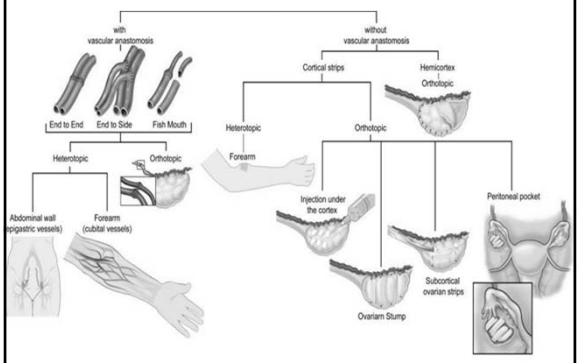
- Time from surgery to treatment
  - Laparotomy vs laparoscopy
  - Medial vs lateral transposition
  - Within the field, despite the transposition
  - Migration back to the field (technique)
  - Scatter radiation (keep more than 3 cm from the upper border of the field)
  - Concomitant chemotherapy

Location of Transplant related to the Radiation field





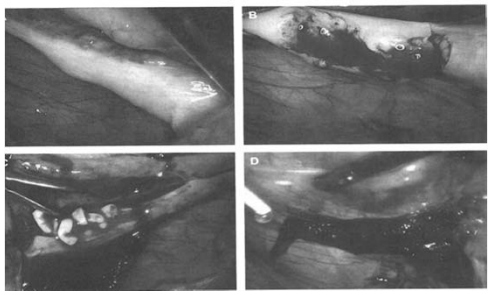
Ovarian Tissue transplantation



Technique: Avascular transplant

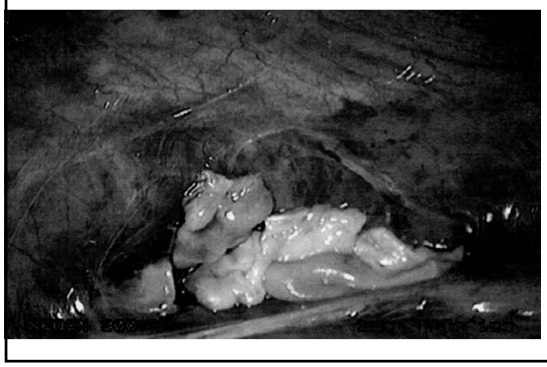
- Large strips 5-10mm x 10 mm (thickness of 1.5 mm)
  - Peritoneal window next to the ovarian hilus-
    - Interceed sutured with 6-0
  - ovarian remnant- decorticate to access the medulla
    - Pieces are sutured with 7-0 or 8-0 polypropylene (non absorbable) or polydioxanone (delayed reabsorbable suture)
- Small cubes 2 mm^3
  - Fragments are covered with Interceed & the Interceed is sutured

Courtesy of Dr. Donnez



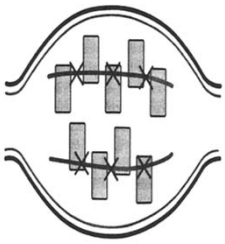
Courtesy Dr. Donnez

Peritoneal window

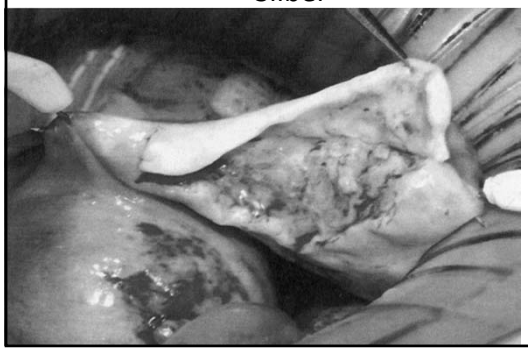


CY Andersen's Team-technique

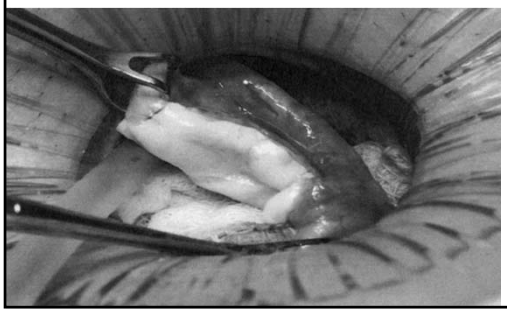
- Longitudinal incisions in the cortex creating 2 pockets
- Fragments are sutured with reaborsable 6-0 suture



Fresh tissue transplant: Courtesy Dr. Silber

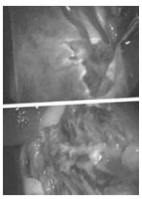


Courtesy Dr. Silber



Orthotopic Transplants: multiple procedure approach

- 3 scope procedure- first peritoneal window was created
- 7 days later - 1 large strip and 35 small cubes placed peritoneal window;
- third scope placed the rest of tissue
- pregnancy 11 months after transplantation-



Orthotopic Transplants: multiple procedure & multiple site approach

- (Demeestere) Hodgkins disease
  - 1 ovary removed; two scope procedure: first incised the peritoneum and the other the ovary; scope 2-transferred grafts into 3 sites- on the ovarian incision, in the peritoneal pocket & abdominal subcutaneus tissue- miscarriage occurred
  - A repeat transplant performed. Achieved 2 normal pregnancies

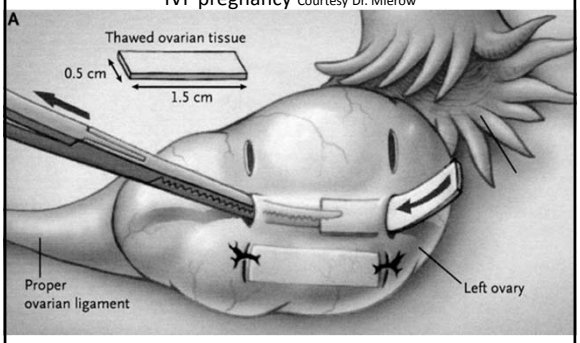
Outcome from 3 centers

- Donnez et al (F&S 2013) reviewed 60 women in about 10 years -3 centers- Belgium (N=13), Spain (N=22), Denmark (N=25) -11 women pregnant
  - Ovarian medulla & peritoneal window
    - Both were equally effective
  - 52/56 patients had restoration of ovarian function
    - Unevaluated follicle density pre-transplant
    - One was a 36 year old woman & another small quantity of tissue
  - 11 women had 18 pregnancies
    - 13 natural conception & 5 IVF
    - Donnez & Anderson's group each reported a woman that delivered 3 children

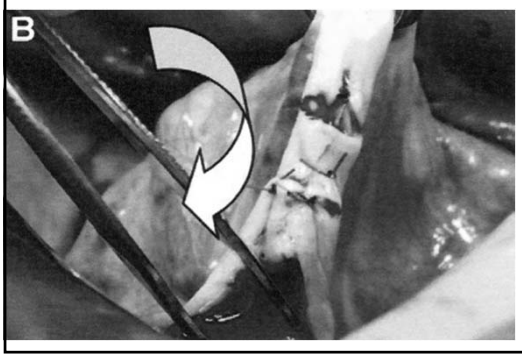
Orthotopic Fresh Transplants

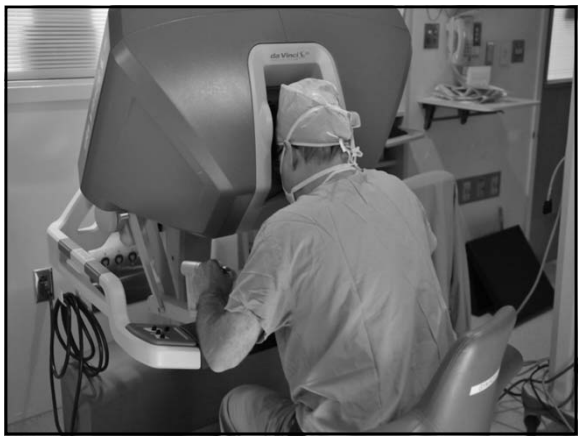
- Fresh transplants (Silber et al Mol Hum Reprod. 2012)
- All fresh ovary transplants were successful, resulting in 11 healthy babies in 7 of the 9 recipients
- Resumption of ovarian activity approximately 3 months in fresh and 4 months in the frozen

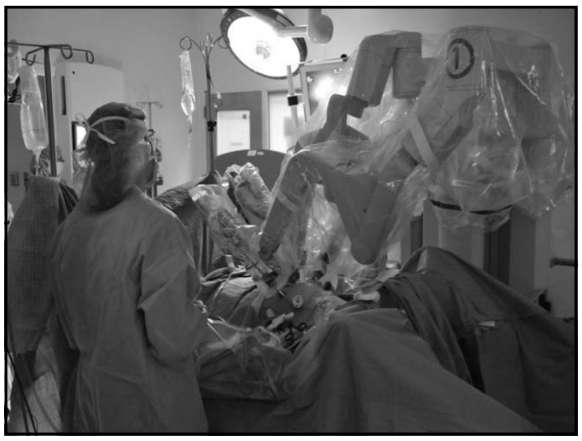
IVF pregnancy Courtesy Dr. Mierow



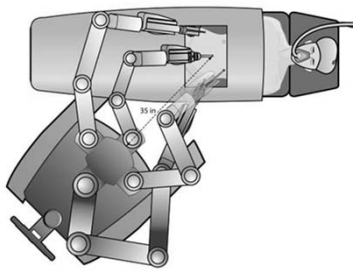
Courtesy Dr. Mierow







Side Docking – 4 arm



Orthotopic Transplants-IVF

- Meirow et al NEJM 2005
- NHL-1/3 to ½ removed after having received chemotherapy
- IVF performed- 3 cycles yielded no oocytes-4 cycle -1 oocyte obtained-1 embryo- achieved pregnancy
  - Patient also achieved a spontaneous pregnancy but miscarried; graft lasted about 2 years
- 8 pregnancies so far (3 spontaneous pregnancies)

Orthotopic Transplants: IVF pregnancy

- (Andersen's team)
  - Ewing's sarcoma of the ribs IVF- >=150 U FSH- 2 oocytes retrieved; 1 embryo transferred and pregnant & delivered; Second & third pregnancy were spontaneous
  - Hodgkins lymphoma-Ten fragments were sutured. 15 months later another 12 pieces wer e transplanted; surgery for adenomyosis of the uterus.IVF- 150 U 1 oocyte-1 embryo-1 baby
- (Piver)- Microscopic Polyangiitis- Pieces were placed peritoneal windows and ovarian medulla. IVF- 225 IU- cycle #1- 2 embryos- ectopic pregnancy cycle #2- 1 embryo- normal pregnancy

Common Themes

- 4-5 months before return of ovarian function
  - Large strips (8-10mm by 5 mm) or small cubes (2mm by 2mm)- equally effective
- Majority of pregnant women were under age 30
  - Ovarian medulla & peritoneal window
    - Both were equally effective
  - Slow freezing technique
- No relapse
- Denominator is from highly specialized centers
  - Can a failure get published?

Common themes

- Donnez et al F&S 2013 60 cases from 3 centers- 23 % pregnancy rate
- 30 live births in the world literature since 2004 report
  - Spontaneous 17; IVF 13
    - 24 cycles of IVF- rate of empty follicles is high
- During IVF- few oocytes are retrieved
  - Andersen, Dolmans, Meirow reported an empty follicle rate of 29% to 35% of IVF cycles
  - 37 % abnormal oocytes

Technique for Surgical Management of Endometriomas

- Cochrane database 2008 Hart R et al.
  - 2 RCTs:
  - Excision of cyst associated with a reduced rate of recurrence; reduced symptom recurrence and increased spontaneous pregnancy rates (OR 5.1) compared with ablative surgery.
- Clinicians can consider performing cystectomy rather than CO2 laser vaporization in women with ovarian endometrioma, because of a lower recurrence rate of the endometrioma (Carmona, et al., 2011).

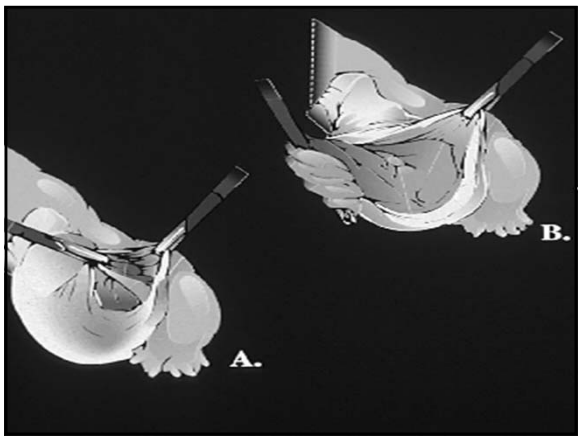
RCT = randomized controlled trial

Cystectomy: stripping technique

- Muzii et al. 2007 histological analysis
  - **Ovarian tissue removed with the cyst**.
  - Endometriosis of the inner cyst rarely penetrates more than 1.5 mm into the cyst capsule .

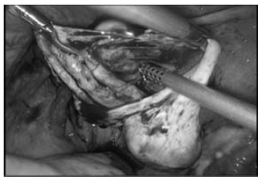
Impact of Excision on Ovarian Reserve

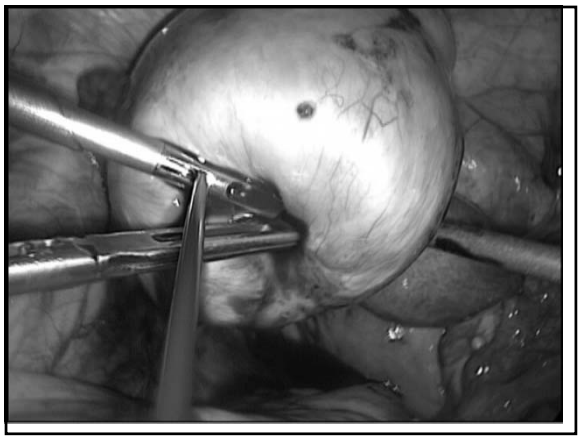
- The pool of oocytes available=ovarian reserve
  - Markers of ovarian reserve- Anti-Mullerian Hormone (AMH) & antral follicle counts (AFC)
- Raffi et al JCEM 2012
  - Meta-analysis using AMH & AFC
  - 8 studies
  - Cysts were more than 3-4 cm; mean 4-6 cm
  - Up to a 30 % fall in AMH in unilateral cystectomy & 44% fall in bilateral cystectomy
  - Gradient effect of increasing size of the endometrioma on the magnitude of the fall in AMH

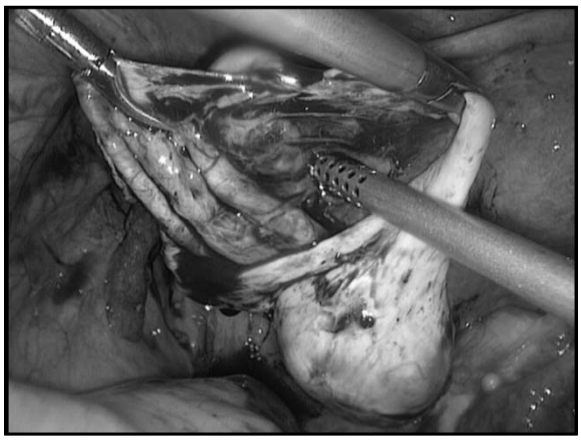


Factors associated with poorer outcomes

- Experience counts
  - Muzii et al 2011
  - Yu et al 2010
- Under many clinical conditions intervention is required
  - Technique is critical for best outcome
  - Excessive use of electrosurgery
  - Uncertain tissue planes

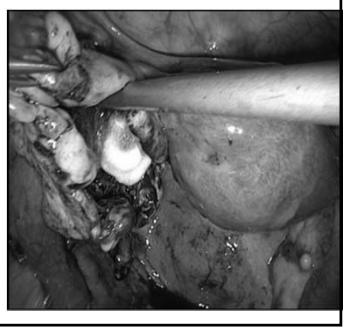






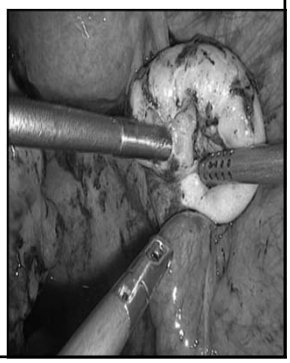
Technique to Minimize Damage

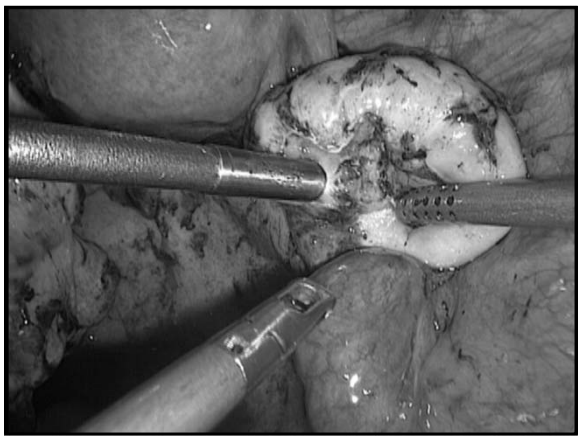
- Angioli R et al. JMIG 2009
  - Use of hemostatic agent

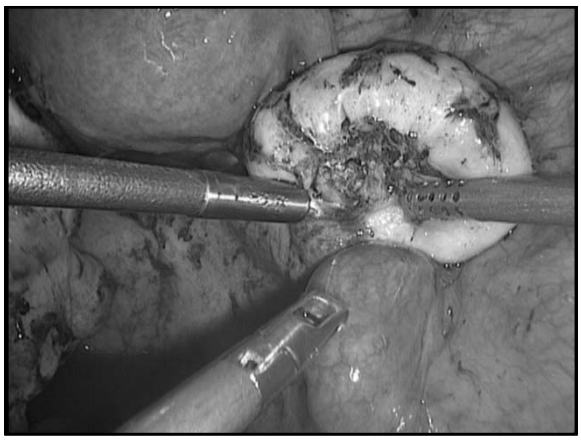


Ablative Therapy- alternative energy forms

- Donnez et al. Fertil Steril 2010
  - Cystectomy and laser vaporization in the hilar region
- Roman et al Fert Steril 2011-Plasma energy- recurrence 5-9 %







Factors associated with poorer outcomes

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  - Muzii et al 2011
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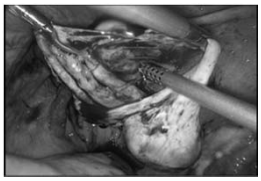
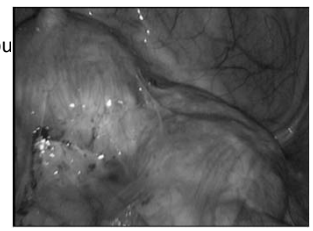


Technique to Minimize Damage

- Pellicano M et al. Fertil Steril 2008
  - Electrocoagulation vs. intra-ovarian suturing
  - Lower levels of day 3 FSH and fewer adhesions with suture

How do you decide on endometrioma Excision vs. ablation

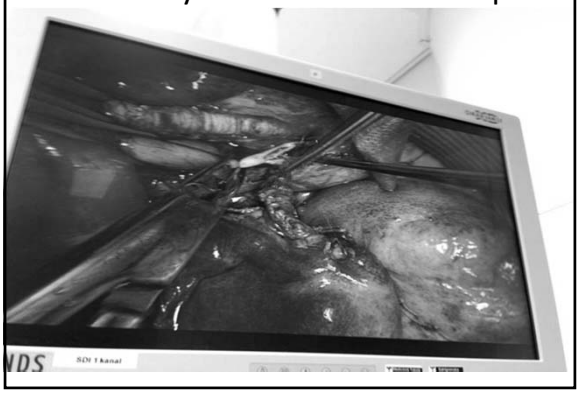
- Recurrence vs. desire for fertility
- Chance of spontaneou pregnancy vs. IVF



Uterus Transplant

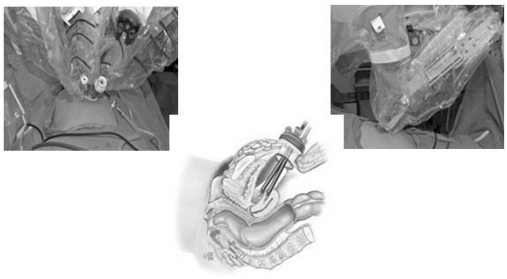
- A Swedish medical team has transplanted uteruses from nine women
  - mother-to-daughter transplants,
- Donor graft
  - Can it be done robotically?
  - Challenge with the pelvic veins

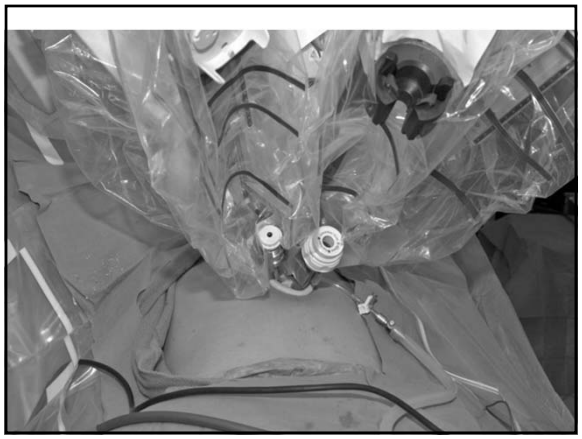
Courtesy of the Swedish Group



"Robotic Assisted Laparo-Endoscopic Single Site Surgery in Gynecology: Initial Report and Technique"

Escobar et al. J Minim Invasive Gynecol. 2009 Jul 7.





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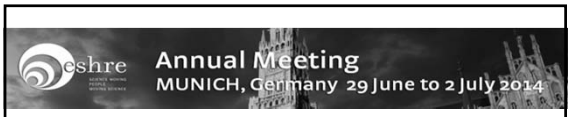


Current Dilemmas with Heterotopic Ovarian Transplantation: Fertility or Futility

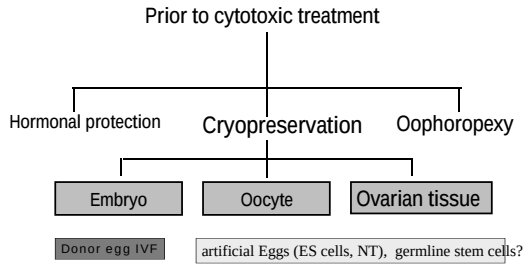
S. Samuel Kim, MD, FACOG, Professor
Center for Advanced Reproductive Medicine,
Reproductive Endocrinology & Infertility
University of Kansas School of Medicine

Disclosure: Nothing to Disclose

Learning objectives

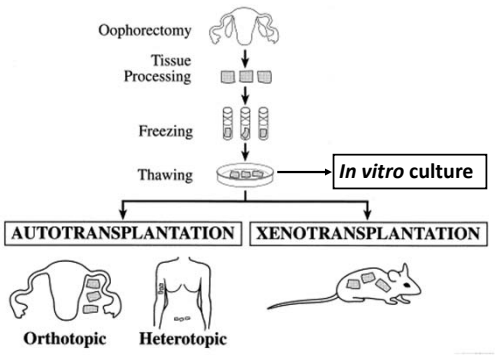
- To understand the current status and role of heterotopic ovarian transplantation
- To comprehend advantages and disadvantages of heterotopic ovarian transplantation
- To recognize the problems with heterotopic ovarian transplantation

Strategies for Fertility Preservation (FP)



Ovarian tissue cryopreservation has been successful for storing abundant follicles, mainly primordial and primary follicles (as most growing and mature follicles do not survive after freezing and thawing of ovarian tissue).

How to restore fertility with cryobanked ovarian tissue?



Kim SS, Fertil Steril 2001

•Orthotopic

Oktay K, 2000
Radford J, 2001

•Heterotopic

Kim SS, 2004, 2009, 2012
Oktay K, 2001, 2004, 2006
Rosendahl M, 2006
Stern CJ, 2013

Donnez J, 2004, 2010, 2011, 2012
Meirow D, 2005 , 2012
Anderson, 2007, 2008, 2009, 2011
Demeestere I, 2007
Silber S, 2008, 2010
Piver P, 2009
Roux, 2010
Sánchez-Serrano M , 2010
Revel A, 2011
Dittrich et al, 2011
Revelli et al, 2012
Garcia et al, 2012
Callejo et al., 2013

30+ live births (2004-2013)

Heterotopic Ovarian Transplantation: Past and Present

- 1895 ROBERT MORRIS: **12 ovarian transplantation in human (by 1901)**
- 1906 ALEXIS CARREL: whole ovary transplant


- 1987 M. Leporrier: Heterotopic ovarian transplant

A New Technique to Protect Ovarian Function Before Pelvic Irradiation

Heterotopic Ovarian Autotransplantation

MICHEL LEPORRIER, MD, PETER VON THEOBALD, MD, JEAN-LUC ROFFE, MD, AND GEORGES MULLER, MD

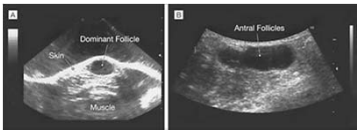
The authors describe a new technique for the subcutaneous heterotopic transplantation of the ovary before pelvic irradiation to treat Hodgkin's disease. Creation of a cavity to receive the transplant and the use of two surgical teams and the surgical microscope during the operation ensured its successful outcome. The transplanted ovary was followed up clinically and by ultrasound monitoring: ovarian cycles remained regular despite radiotherapy, and follicle growth occurred normally. In comparison to other types of oophoropexy described in the literature, the advantages of this technique included total protection of the ovary from irradiation, and conservation of ovarian function and fertility. One year after the procedure, puncture of the ovarian compartment produced a mature oocyte specimen.

Cancer 60:2201–2204, 1987.

Leporrier et al., Cancer, 1987

Heterotopic autotransplantation of ovarian cortical strips to the forearm

35 y female with Cx. CA fresh ovarian tissue transplantation before pelvic irradiation. Follicular growth 10 weeks after transplantation

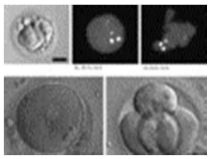


Oktay et al., JAMA. 2001;286

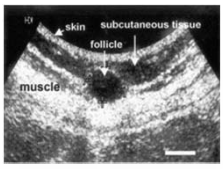
Embryo development after heterotopic transplantation of cryopreserved ovarian tissue

Case: 30 years old, stage II Breast Cancer

- Restoration of ovarian function: 85 days
- Eight consecutive percutaneous oocyte retrieval (six after ovarian stimulation)
- Of 20 oocytes retrieved, 8 were suitable for IVF (5 IVM)
- Two fertilized (one abnormal, one 4 cell stage embryo)



Oktay et al., Lancet, 2004

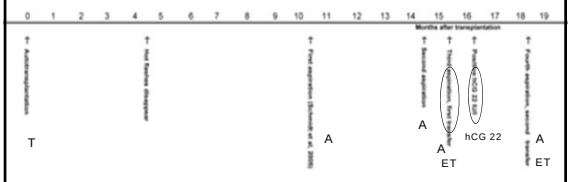


FERTILITY AND STERILITY®
VOL. 82, NO. 4, OCTOBER 2004

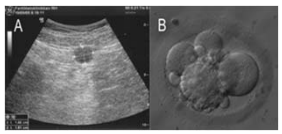
Heterotopic autotransplantation of cryobanked human ovarian tissue as a strategy to restore ovarian function

S. Samuel Kim, M.D., In-Tak Hwang, M.D., and Hoi-Chang Lee, M.Sc.

Kim et al., Fertil Steril, 2004



28 y female with HD stage IIB,
Follicle growth from
sub peritoneal transplant
under the abdominal wall
↓
follicle aspiration x4,
embryo transfer x2,
1 biochemical pregnancy



Rosendahl et al., Hum Reprod, 2006

Human Reproduction, Vol.28, No.11 pp. 2996–2999, 2013
Advanced Access publication on September 7, 2013 doi:10.1093/humrep/det360

human reproduction

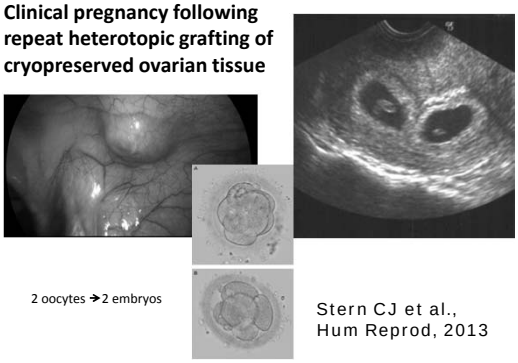
CASE REPORT *Infertility*

First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy

C.J. Stern[1,*], D. Gook[1], L.G. Hale[1], F. Agresta[1], J. Oldham[2], G. Rozen[3], and T. Jobling[4]

Hum Reprod, 2013

Clinical pregnancy following repeat heterotopic grafting of cryopreserved ovarian tissue



2 oocytes → 2 embryos

Stern CJ et al., Hum Reprod, 2013

Heterotopic Autotransplantation of Cryobanked Human Ovarian Tissue

Kim SS et al., 2009, F&S, 91

Kim SS, 2012, J Assist Reprod Genet, 29

Heterotopic Human Ovarian Transplantation

Pros	*Cons*
• Convenient and cost effective for repeated transplantations • less invasive procedure (site dependent) • Easily accessible for oocyte retrieval without anesthesia (site dependent) • Feasible for patients with severe pelvic adhesion	• IVF procedure required • Efficacy not proven (only one live birth) • Suboptimal (unknown) environmental effects on follicle growth and maturation (site dependent) • Possible poor quality oocytes

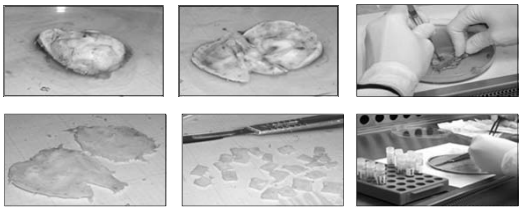
Kim SS, Reprod Biomed Online, 2014

Study patients (29-39 y at transplant):
cryopreservation (2000-2002) → heterotopic transplantation (2002-2011)

1. JH : 38 y, adenocarcinoma of cervix, stage IIb, radical hysterectomy plus irradiation (Ext+ICR) and chemotherapy (2002): deceased
2. AS : 37 y, squamous cell carcinoma of cervix, stage Ib, radical hysterectomy and lymph node dissection (2002 & 2003)
3. SH : 29 y, squamous cell carcinoma of cervix, stage IIb, external and intracavitary irradiation (2003 & 2004)
4. MS : 36 y, Breast cancer, Stage II, radical mastectomy & chemotherapy (2005 & 2006)
5. LM : 39 y, Hodgkin's lymphoma, Stage III, chemotherapy & radiation (2010 & 2011)

Cryopreservation

1.Preparation of ovarian tissue:



2. Slow freezing of ovarian tissue

Freezing solution (FS): 1.5 M DMSO + 1% human serum albumin + 0.1 M sucrose (in Leibovitz L-15 medium)

1) Start at 0°C and cool at 2°C/min to -7°C
2) Soak for 5 min before manual seeding
3) Seed at -7°C and hold for 5 min
4) Continue to cool at 0.3°C/min to -40°C
5) Cool at faster rate of 10°C/min to -120
6) Store at -196°C

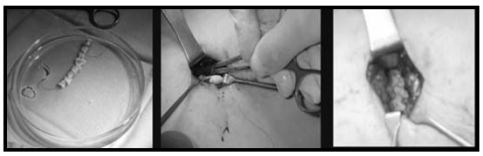
3. Thawing & Incubation:

- Warmed rapidly (~100°C/min) and washed in a stepwise manner (1.0M DMSO + 0.1M sucrose ▶ 0.5M DMSO + 0.1M sucrose ▶ 0.1M sucrose).
- Thawed cortical sections were incubated in α-MEM medium for 30 min at 37°C before transplantation.

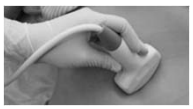
Transplantation

4. Heterotopic Transplantation:

- Thawed tissue was threaded onto 5-0 prolene sutures (8-12 pieces in each suture), and transplanted into the space between the rectus sheath and the rectus muscle.
- Gonadotropin (300 IU) was administered two days before and three days after transplantation to facilitate angiogenesis.



5. Monitoring:



Sequential blood sampling (FSH, LH, E2, progesterone, testosterone) and ultrasound examination.

6. IVF & embryo culture:

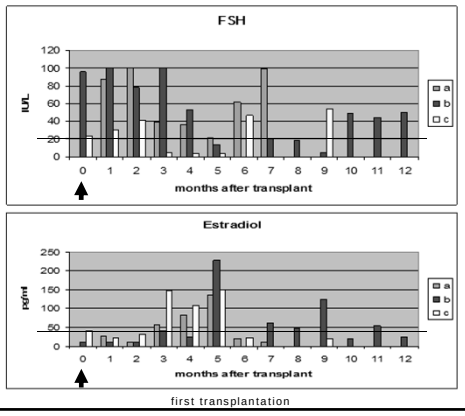
Endocrine Function

Restoration of Endocrine Function:

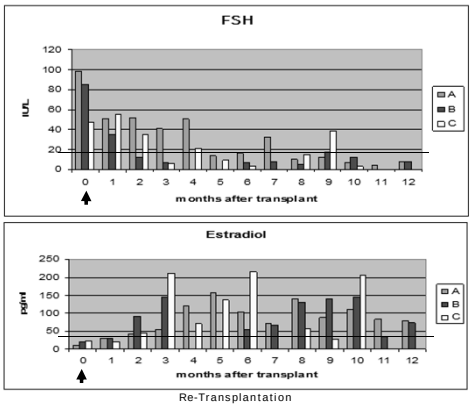
- The hormonal profiles of all 5 patients were consistent with the post menopausal levels before transplantation (FSH > 90 IU/L, E2 <10 pg/ml).
- 3-5 months after transplantation, the return of ovarian function was evidenced (FSH <20 IU/L, E2 >20 pg/ml), but lasted only for 4-6 months.

Restoration of Endocrine Function:

- One patient deceased because of cancer relapse and was eliminated from long-term follow up.
- Four patients underwent second transplantation. The return of ovarian function was faster (2-4 months) after second transplantation.
- Long term ovarian function lasting for 9-84 months has been established after second transplantation in all 4 patients

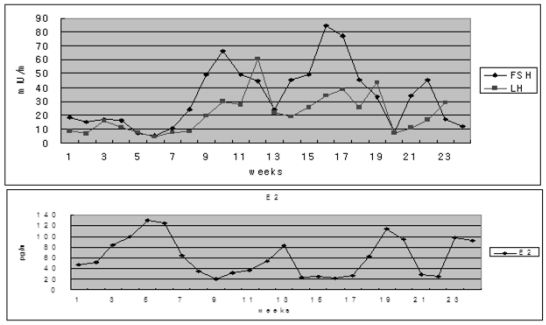


first transplantation



Re-Transplantation

cyclic hormonal production and spontaneous ovulation were evidenced



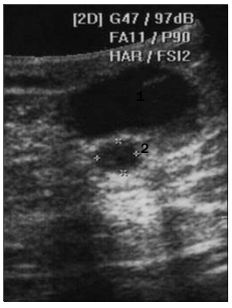
Weekly serum FSH/LH/E2 concentrations for 24 wk from May 2004 (8 months post-transplantation) through November 2004

Summary of characteristics and outcomes of heterotopic ovarian transplantation (frozen-thawed ovarian tissue)

	Age at cryo	Para	Dx	Storage Duration before grafting (year)	Number of cortical sections grafted 1st/2nd	Year of transplant 1st/2nd	Duration, endocrine function 1st/2nd (month)
A	37 y	G2P2	Cx CA	2	20/20	2002/2003	4/14
B	28 y	G0	Cx CA	2	9/8	2003/2004	6/84
C	29 y	G0	Breast CA	5	11/8	2005/2006	5/9
D	30 y	G0	HL	10	10/8	2010/2011	9/ongoing (30)

Kim SS, 2012, J Assist Reprod Genet

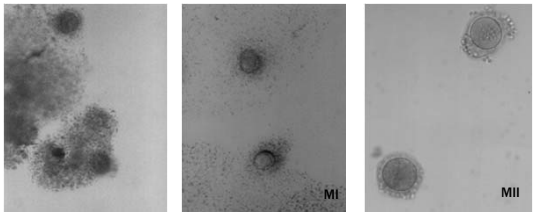
Fertility



Ovarian stimulation was initiated when growing follicles were identified by UTZ or palpation:
300 IU rFSH and ganirelix 0.25mg for 3 – 7 days.

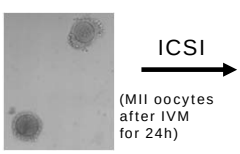
2 growing follicles in the ovarian graft (subcutaneous, pre-rectus)

Human oocytes retrieved from heterotopic grafts when the follicle size reached 14-20 mm.



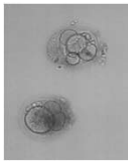
First oocyte retrieval: 9 months after transplantation (2 MI oocytes)

June 2005



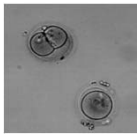
ICSI

(MII oocytes after IVM for 24h)



(6 cell & 3 cell embryos after 3 day culture)

Second oocyte retrieval: 14 months after transplantation (1 MII oocytes, 2 MI oocytes)



(2 cell & PN embryos after 2 day culture)

Is there any future for heterotopic transplantation of cryobanked ovarian tissue?

- **The study showed that it is possible to restore long-term endocrine function lasting for more than 7 years with heterotopic transplantation of cryobanked human ovarian tissue.**
- **When restoration of hormonal function is the main purpose, transplantation to heterotopic site can be advantageous.**
- **Re-establishment of long-term endocrine function after ovarian transplantation will benefit young cancer survivors with premature ovarian failure.**
- **Furthermore, the recent report of a live birth after heterotopic ovarian transplantation is encouraging for the future of this procedure.**

But there are still many issues which should be resolved to make this procedure clinically practicable.

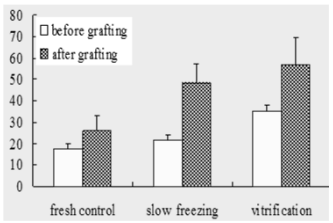
Issues with heterotopic ovarian transplantation

- Cryoinjury
- Ischemic injury
- Optimal heterotopic sites
- Environmental factors/ Follicle growth pattern
- Egg retrieval technique
- Efficacy

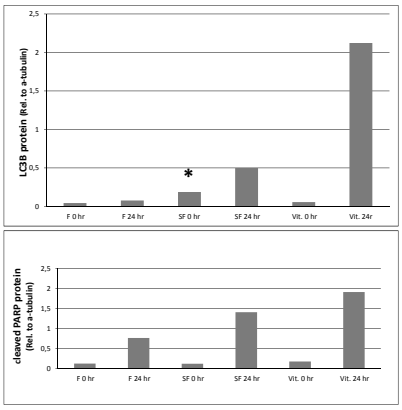
Issue 1: Cryoinjury

Cell damage (oocytes, granulosa cells, other somatic cells)

DNA damage

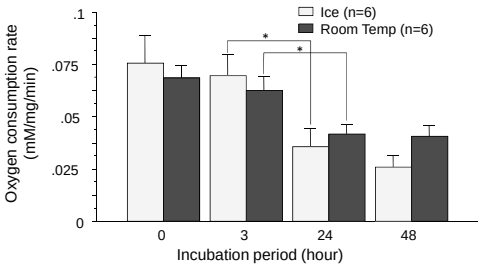


Apoptotic rates of primordial follicles
Kim et al. (2004) Fertil Steril 82:679-685

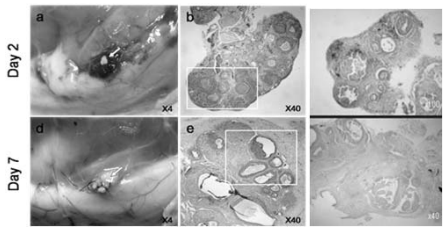


Optical Density

Issue 2: Ischemic Injury



Significant ischemic damage can be seen about 24 h after transplantation, but angiogenesis takes more than 48 h.



We need to develop new strategies that can protect ovarian tissue from ischemia or facilitate angiogenesis to make ovarian tissue transplantation clinically reliable and robust technology.

Issue 3: Optimal heterotopic site

- Rich in vasculature
- Ease of transplantation
- Easily accessible for egg retrieval
- Enough space to accommodate large ovarian graft and to support full follicular growth
- Surrounding environment mimicking the physiologic conditions (temperature, pressure, paracrine factors)

- **Tested sites: broad ligament, omentum, uterus, subcutaneous tissue (forearm, hip, abdominal wall), rectus muscle, breast tissue, superficial fascia of pectoralis muscle, subperitoneal tissue beneath the abdominal fascia, anterior abdominal wall just under the peritoneum.**

Issue 4: Environmental factors/ Oocytes quality

- Temperature
- Local pressure
- Paracrine factors
- Cytokines
- Blood supplies

Issue 5: Egg retrieval

- Ovarian stimulation protocol
- Aspiration needles (size, length)
- Aspiration pressure
- When to retrieve
- IVM

Issue 6: Efficacy

- Follicle development: <50%
- Egg retrieval: 3/5 (7/8) (17/29)
- Fertilization: 4/7 (2/20) (15/25)
- Embryo development: 3/4 (1/2) (15/15)
- Pregnancy rate: 0 (0) (1)

- Restoration of ovarian function: 100%
- Duration of ovarian function: 14 -90 months

Future Research

- Preventing cancer cell reintroduction with transplantation: development of robust screening methods, inventing technology to remove minimal residual disease, perfecting techniques for IVG, IVM of follicles.
- New technology to protect tissue from ischemic injury and DNA damage after transplantation: novel agents for angiogenesis, anti-apoptosis.
- Creating an optimal environment for follicle development after transplantation: application of biomaterials such as hydro-gel, bioengineering of paracrine factors etc.
- Studies on genetic and epigenetic integrities of developing oocytes in ovarian grafts.

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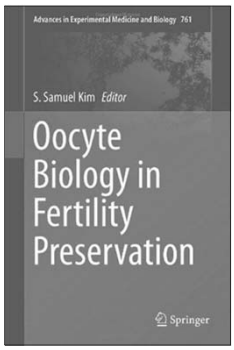
- WS Lee, MD
- MK Chung, PhD



Thank you !

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The current fertility preservation consultation model: Are we adequately informing cancer patients of their options?

Johnny Awwad, MD
Professor of OBGYN
American University of Beirut Medical Center

No Conflict of interest

NOTHING TO DISCLOSE

Learning Objectives

- Evaluate the attitudes of health professionals and cancer survivors towards fertility preservation
- Understand the barriers to proper counseling and access to fertility preservation services
- Discuss implications for improved referrals and effective counseling

Background

- Recent advances in cancer therapy have resulted in an increased number of long-term cancer survivors
- 5-year survival of childhood cancer lies between 75% and 80% [Wallace 2005]; and breast cancer of all stages at 89%
- Concerns about infertility after cancer therapy are extremely important to women, with up to 75 % interested in having children after cancer treatment, and up to 29 % refusing life-saving treatments because of fear of becoming infertile [Schover LR 2009; Patridge AH 2004]
- Currently it is estimated that a reproductive specialist sees only 2–5 % of women before they undergo treatment [Jenninga 2008; Letourneau 2011; Loprinzi 2008]
- While health professionals are getting better at counseling women on reproductive issues, many still need to be done

Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Intervention

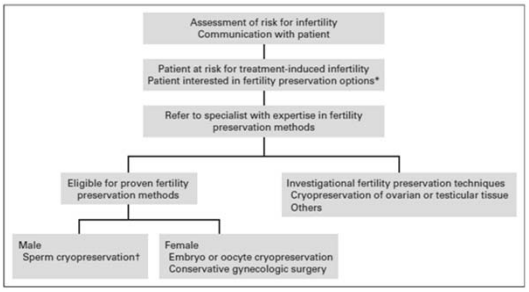
- Discuss the risk of infertility and fertility preservation options with patients with cancer anticipating treatment

Target Audience

- Medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons, as well as nurses, social workers, psychologists, and other nonphysician providers

Key Recommendations

- Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy
- Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists
- Address fertility preservation as early as possible, before treatment starts
- Document fertility preservation discussions in the medical record
- Answer basic questions about whether fertility preservation may have an impact on successful cancer treatment
- Refer patients to psychosocial providers if they experience distress about potential infertility
- Encourage patients to participate in registries and clinical studies



- "I wish that they had made it clear that my ability to have children would be significantly affected. I wish that they had grabbed me by the shoulders and said: "if you don't harvest eggs, you WILL NOT have the possibility of having a child!" When you are diagnosed with cancer, and dealing with facing treatment, it is all too much to deal with. And I had the hope that I would be one of the lucky ones the doctors told me about who had a beautiful healthy baby after chemo...."

Niemasik EE 2012

Patients Perceptions

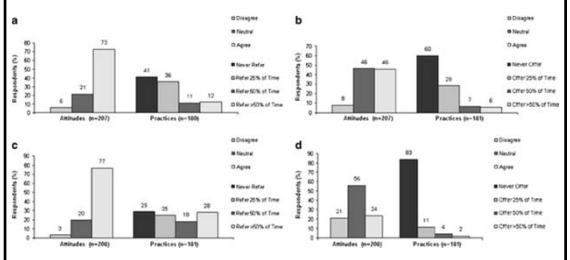
TABLE 2

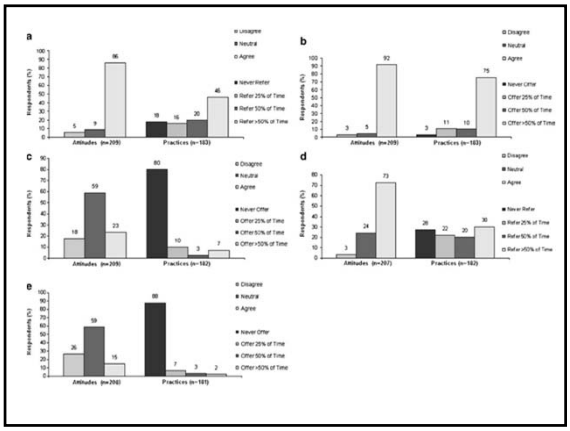
A description of the knowledge items and percent correct of the 41 subjects.

Knowledge question	Correct answer	% correct
All cancer treatment results in infertility.	False	63.4
A patient must be married or have a partner to receive fertility preservation treatment.	False	90.2
All fertility preservation treatments have a similar chance of achieving pregnancy.	False	48.8
Insurance never covers fertility preservation treatments.	False	34.2
My fertility preservation treatment options will be the same following my cancer treatment.	False	41.5
What is the percentage of women who freeze their embryos who will become pregnant in the future?	Depends on age at time of embryo freezing	9.8
Women who have fertility preservation treatment have an increased risk for recurrence of their cancer in the future.	False	17.1
Egg freezing has the same chances of future pregnancy as embryo freezing.	False	31.7
A woman who freezes her eggs will have them available in the future whenever she is ready to use them.	True	51.2
Frozen eggs are guaranteed to result in pregnancy in the future.	False	68.3
Frozen embryos are guaranteed to result in pregnancy in the future.	False	73.2
IVF with embryo freezing is an established treatment used in patients without a cancer diagnosis.	True	43.9
Chemotherapy increases the risk that my future children will have birth defects.	False	14.6

Balthazar. Previsit fertility preservation knowledge . Fertil Steril 2011.

Attitudes and Practices





Perceived Barriers in Counseling

- High financial costs
  - Lack of insurance coverage
- Complexity of integrating oncology care with a fertility specialist
- Perceived urgency to start treatment

Perceived Barriers in Counseling

- Insufficient time to discuss this issue with patients
- Lack of knowledge on fertility preservation techniques
- Oncologists believe that if patients did not raise the issue themselves they were not interested

Perceived Barriers in Counseling

- Omission of information by health professional and/or presentation of incorrect information on FP options
- Uncertain cancer prognosis
  - Patients with uncertain cancer prognosis or risk of cancer death are less likely to be counseled for FP options

Perceived Barriers in Counseling

- Risk of recurrence or vertical transmission
  - Patients with increased risk of recurrence from future pregnancy or increased risk of vertical transmission of a cancer gene to a future child are likely to receive less counseling
- Parity
  - Patients who already had children are less likely to be counseled about FP, with the unfounded assumption that they desire no more children

Perceived Barriers in Counseling

- Age at diagnosis
  - "Young" patients are more likely to be told their fertility would return to baseline
  - Too "young" to fully comprehend the reproductive threatening consequences
  - "Older" patients are often discouraged from childbearing due to their advanced maternal age
- Unsure desire
  - Patients unsure about future childbearing are less likely to be counseled about FP because they may have expressed uncertainty in fertility desire at time of diagnosis

Perceived Barriers in Counseling

- Gender
  - Male patients are more likely to be counseled because sperm cryopreservation is straight forwards
  - "Well I think that I find it very easy to talk to the men purely because there is something you can offer them and it is quite straightforward. …with the women it is not quite so easy'' [Puddie 2012]

Conclusions

- Patient education
  - Education at time of diagnosis about fertility preservation options could empower patients to make informed health care decisions and take control of their reproductive futures
- Communication
  - Between physicians and patients is extremely important to ensure proper patient's decision-making process

Conclusions

- The current single-consultation model deserves to be reevaluated
  - Baseline knowledge about fertility preservation treatment options in reproductive-age patients newly diagnosed with cancer remain poor despite counseling
  - Patients may not be capable to process information and make decisions on FP options during a single consultation

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UPCOMING ESHRE EVENTS

// ESHRE CAMPUS EVENTS

ESHRE's 30th Annual Meeting

www.eshre2014.eu

Munich, Germany
29 June - 2 July 2014

Epigenetics in reproduction

www.eshre.eu/lisbon

Lisbon, Portugal
26-27 September 2014

Endoscopy in reproductive medicine

www.eshre.eu/endoscopyoct

Leuven, Belgium
15-17 October 2014

Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering

www.eshre.eu/thessaloniki

Thessaloniki, Greece
31 October-1 November 2014

From gametes to blastocysts – a continuous dialogue

www.eshre.eu/dundee

Dundee, United Kingdom
7-8 November 2014

Controversies in endometriosis and adenomyosis

www.eshre.eu/liege

Liège, Belgium
4-6 December 2014

Bringing evidence based early pregnancy care to your clinic

www.eshre.eu/copenhagen

Copenhagen, Denmark
11-12 December 2014

An update on preimplantation genetic screening (PGS)

www.eshre.eu/rome

Rome, Italy
12-13 March 2014

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