eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Clinical management planning for fertility preservation in female cancer patients

Task Forces Basic Science and Fertility Preservation in Severe Diseases
in collaboration with the 'US OncoFertility Consortium'

11

3 July 2011
Stockholm, Sweden

Clinical management planning for fertility preservation in female cancer patients

Stockholm, Sweden
3 July 2011

Organised by
The Task Force Basic Science and Infertility and the Task Foce Fertility Preservation in Severe Disease in collaboration with the "US OncoFertility Consortium"

Contents

Background

The mission of the ESHRE and the US OncoFertility Consortium is to explore and expand the options for preserving the reproductive future of cancer survivors. This program must be a collaboration between oncologists, fertility specialists to better understand the demands and boundary conditions for each practice plan (medical oncology, surgical oncology, radiation oncology, pediatric oncology together with reproductive medicine).
Leaders fr

Learning objectives

1. To understand cancer and cancer treatments impact in fertility
2. To understand what current fertility management options exist
3. To understand what emerging fertility options are under development

Scientific programme

Chair: Carlos Plancha (Portugal)

09.00 - 09.30	Building national networks of oncofertility centers in the US: lessons learned and opportunities for global collaborations – **Teresa Woodruff (USA)**
09.30 - 09.45	Discussion
09.45 - 10.15	Perspectives for a European network for fertility preservation **- Michael von Wolff (Switzerland)**
10.15 - 10.30	Discussion
10.30 - 11.00	Coffee break
11.00 - 11.30	Management strategies for oncology consults and collaboration - **Jacqueline Jeruss (USA)**
11.30 - 11.45	Discussion
11.45 - 12.15	Management strategies for centralised cryobanks and the European directive **- Markus Montag (Germany)**
12.15 - 12.30	Discussion
12.30 - 13.30	Lunch
13.30 - 14.00	Clinical management: fertility risks by diagnosis - What cancer requires immediate intervention **- Dror Meirow (Israel)**
14.00 - 14.15	Discussion
14.15 - 14.45	Addressing the specific needs of young children with cancer - **Hamish Wallace (United Kingdom)**
14.45 - 15.00	Discussion
15.00 - 15.30	Coffee break
15.30 - 16.00	Where research becomes treatment: ethical issues - **Françoise Shenfield (United Kingdom)**
16.00 - 16.15	Discussion
16.15 - 16.45	The Oncofertility Scholar - A new subspecialty with important training opportunities **– Cristos Coutifaris (USA)**
16.45 - 17.00	Discussion

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

ESHRE – European Society of Human Reproduction and Embryology

What is ESHRE?

ESHRE was founded in 1985 and its **Mission Statement** is to:

- promote interest in, and understanding of, reproductive science
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform policy makers in Europe
- promote improvements in clinical practice through educational activities
- develop and maintain data registries
- implement methods to improve safety and quality assurance

Executive Committee 2009/2011

Chairman	• Luca Gianaroli	Italy
Chairman Elect	• Anna Veiga	Spain
Past Chairman	• Joep Geraedts	Netherlands
	• Jean François Guérin	France
	• Timur Gürgan	Turkey
	• Ursula Eichenlaub-Ritter	Germany
	• Antonis Makrigiannakis	Greece
	• Miodrag Stojkovic	Serbia
	• Anne-Maria Suikkari	Finland
	• Carlos Plancha	Portugal
	• Françoise Shenfield	United Kingdom
	• Etienne Van den Abbeel	Belgium
	• Jolieneke Schoonenberg-Pomper	Netherlands
	• Veljko Vlaisavljevic	Slovenia
	• Søren Ziebe	Denmark

ESHRE Organisation

- General Assembly of Members
  - Executive Committee
  - Committee of Nat. Representatives
  - Central Office
  - ESHRE Consortia
    - EIM Consortium
    - PGD Consortium
  - Sub-Committees
    - Finance Sub-Committee
    - Comm. Sub-Committee
    - Publ. Sub-Committee
      - Editorial Office
      - Publisher
      - Editors-in-Chief
    - Int'l Scientific Committee
    - SIG Sub-Committee
      - SIG Coordinators
  - Task Forces

ESHRE Journals

Human Reproduction with impact factor 3.859

Human Reproduction Update with impact factor 7.042

Molecular Human Reproduction with impact factor 3.005

Campus Activities and Data Collection

Campus / Workshops

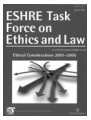
- Meetings are organised across Europe by Special Interest Groups and Task Forces
- Visit www.eshre.eu under CALENDAR

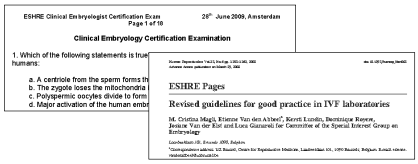
Data collection and monitoring

- European IVF Monitoring Group data collection
- PGD Consortium data collection

ESHRE Activities

- Embryology Certification
- Guidelines
- Position papers
- News magazine “Focus on Reproduction”




ESHRE Clinical Embryologist Certification Exam 20th June 2009, Amsterdam
Page 1 of 10

Clinical Embryology Certification Examination

1. Which of the following statements is true
humans:

a. A centriole from the sperm forms th
b. The zygote loses the mitochondria
c. Polyspermic oocytes divide to form
d. Major activation of the human embr

ESHRE Pages

Revised guidelines for good practice in IVF laboratories

M. Cristina Magli, Etienne Van den Abbeel, Kevrli Lundin, Berenice Revnes, Jessica Van der Elst and Luca Gianaroli for Committee of the Special Interest Group on Embryology

ESHRE COMMUNITY

RSS feeds for news in reproductive medicine

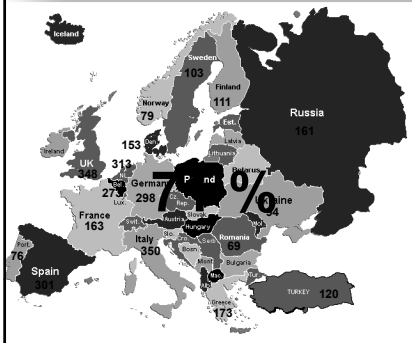
Since launch 12/2009: **1,360 Fans**

Since launch 12/2009: **190 followers** (journalists, scientific organisations, patient societies, governmental bodies)

Retweets to MHR

Find a member

ESHRE Membership (1/3)



4,017	Europe
476	Asia
372	North America
332	Middle East
221	Africa
142	Oceania
99	South America

TOTAL MEMBERSHIP*: 5 659 members

* as of July 2010

ESHRE Membership (2/3)

	1 yr	3 yrs
Ordinary Member	€ 60	€ 180
Paramedical Member*	€ 30	€ 90
Student Member**	€ 30	N.A.

*Paramedical membership applies to support personnel working in a routine environment such as nurses and lab technicians.
**Student membership applies to undergraduate, graduate and medical students, residents and post-doctoral research trainees.

ESHRE Membership – Benefits (3/3)

1) Reduced registration fees for all ESHRE activities:

Annual Meeting	Ordinary	€ 480	(€ 720)
	Students/Paramedicals	€ 240	(€ 360)
Workshops*	All members	€150	(€ 250)

2) Reduced subscription fees to all ESHRE journals – e.g. for Human Reproduction €191 (€ 573!)

3) ESHRE monthly e-newsletter

4) News Magazine "Focus on Reproduction" (3 issues p.a.)

5) Active participation in the Society's policy-making

*workshop fees may vary

Special Interest Groups (SIGs)

The SIGs reflect the scientific interests of the Society's membership and bring together members of the Society in sub-fields of common interest

- Andrology
- Early Pregnancy
- Embryology
- Endometriosis / Endometrium
- Ethics & Law
- Safety & Quality in ART
- Psychology & Counselling
- Reproductive Genetics
- Reproductive Surgery
- Stem Cells
- Reproductive Endocrinology

Task Forces

A task force is a unit established to work on a single defined task / activity

- Fertility Preservation in Severe Diseases
- Developing Countries and Infertility
- Cross Border Reproductive Care
- Reproduction and Society
- Basic Reproductive Science
- Fertility and Viral Diseases
- Management of Infertility Units
- PGS
- EU Tissues and Cells Directive

ESHRE – Annual Meeting

- One of the most important events in reproductive science
- Steady increase in terms of attendance and of scientific recognition

Track record:

ESHRE 2010 – Rome: 9,204 participants
ESHRE 2009 – Amsterdam: 8,055 participants
ESHRE 2008 – Barcelona: 7,559 participants

Future meetings:

ESHRE 2011 – Stockholm, 3-6 July 2011
ESHRE 2012 – Istanbul, 1-4 July 2012

ESHRE 2011, Stockholm, Sweden

When: **3 - 6 July 2011**
Where: **Stockholmsmässan, Mässvägen 1, Älvsjö, Sweden**
www.stockholmsmassan.se

Chair of conference: **Kersti Lundin**

Hotel and Travel:
MCI - Stockholm Office
Phone: +46 (0)8 54651500
E-mail: eshre@mci-group.com

For updates visit www.eshre.eu

ESHRE 2011, Stockholm

Keynote Lectures

Aneuploidy in humans: what we know and we wish we knew – Terry Hassold (USA)

Historical Lecture

A brave new world with a brave old humankind; quo vadimus – E. Diczfalusy (SE)

MHR Symposium – The paternal genome

Sperm chromatin packaging – B. Robaire (CDN)

The human sperm epigenome – B. Cairns (USA)

ESHRE 2011, Stockholm: Debates

This house believes that obese women should not receive treatment until they have lost weight

- **Yes: Mark Hamilton *(UK)***
- **No: Guido de Wert *(NL) - TBC***

Paramedical invited session: Should we pay donors?

- **Yes: Herman Tournaye (BE)**
- **No: Laura Witjens (UK)**

Annual Meeting – Pre-Congress Courses

- PCC 1: The challenges of embryo transfer (Paramedical Group)
- PCC 2: The blastocyst: perpetuating life (SIG Embryology and SIG Stem Cells)
- PCC 3: From genes to gestation
  (SIG Early Pregnancy and SIG Reproductive Genetics)
- PCC 4: Lifestyle and male reproduction (SIG Andrology)
- PCC 5: Ovarian ageing (SIG Reproductive Endocrinology)
- PCC 6: The impact of the reproductive tract environment on implantation success (SIG Endometriosis/Endometrium)
- PCC 7: Adhesion prevention in reproductive surgery
  (SIG Reproductive Surgery)

Annual Meeting – Pre-congress Courses

- PCC 8: Theory and practice update in third party reproduction
  (SIG Psychology and Counselling)
- PCC 9: Ethical aspects of non-invasive prenatal diagnosis
  (SIG Ethics & Law)
- PCC 10: Patient-centered fertility services
  (SIG SQUART)
- PCC 11: Clinical management planning for fertility preservation in female cancer patients
  (TF Basic Science and TF Preservation in Severe Disease in collaboration with the US OncoFertility Consortium)
- PCC 12: Opportunities for research in female germ cell biology
  (TF Basic Science)

Annual Meeting – Pre-congress courses

- PCC 13: Assisted reproduction in couples with HIV
  (TF Fertility and Viral Diseases)
- PCC 14: Prevention of infertility – from preconception to post-menopause
  (TF Reproduction and Society)
- PCC 15: Hot topics in male and female reproduction
  (ASRM exchange course)
- PCC 16: Academic Authorship programme
  (Associate Editors ESHRE journals)
- PCC 17: Science and the media, an introduction to effective communication with the media
  (Communications SubCommittee ESHRE)

Certificate of attendance

1/ Please fill out the evaluation form during the campus

2/ After the campus you can retrieve your certificate of attendance at www.eshre.eu

3/ You need to enter the results of the evaluation form online

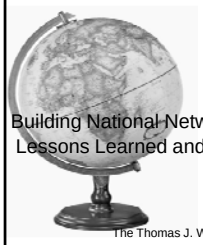
4/ Once the results are entered, you can print the certificate of attendance from the ESHRE website

5/ After the campus you will receive an email from ESHRE with the instructions

6/ You will have TWO WEEKS to print your certificate of attendance

Contact

ESHRE Central Office
Tel: +32 (0)2 269 09 69
info@eshre.eu / www.eshre.eu



Building National Networks of Oncofertility Centers in the U.S.: Lessons Learned and Opportunities for Global Collaborations

Teresa K. Woodruff, Ph.D.
The Thomas J. Watkins Professor of Obstetrics and Gynecology

Northwestern University
Feinberg School of Medicine
Chicago, IL

the Oncofertility® Consortium
AT NORTHWESTERN UNIVERSITY

Learning Objectives

1) To understand cancer and cancer treatments impact in fertility

2) To understand what current fertility management options exist

3) To understand what emerging fertility options are under development

the Oncofertility® Consortium

Preservation of Fertility After Cancer

- Life preserving treatments
  - Chemotherapy
  - Radiation
  - Surgery
- Can threaten fertility

...exploring and expanding options for the reproductive future of cancer survivors

the Oncofertility® Consortium

Who is at risk?

- More than 1.4 million people are diagnosed in the U.S. with cancer annually.
- 10 million new cases of cancer are diagnosed globally each year.
- 10% of these individuals are in their reproductive years (up to 45 years old).
- Approximately 11% of breast cancer patients are diagnosed before the age of 40 years old.

Jeruss and Woodruff, NEJM, 2009
West, et al. Pediatric Blood Cancer, 2009

...exploring and expanding options for the reproductive future of cancer survivors

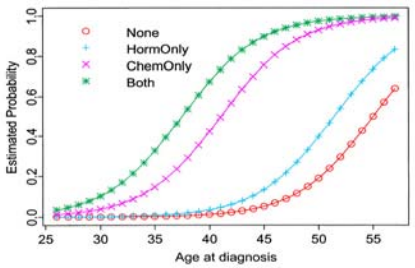
How big is the fertility problem?

- In 2006, estimated 1,700,000 female cancer survivors in US who were <40 at diagnosis.
- 20% reduction in achieving first pregnancy in pediatric survivors.
- 50% decrease in women diagnosed as young adults.
- Estimate that 748,000 currently have had their childbearing interrupted (plus another 38,500 per year).

Green D et al, J Clin Oncol, 2006
Shover, personal communication

...exploring and expanding options for the reproductive future of cancer survivors

Probability of Menopause



Goodwin PJ, et al. J Clin Oncol ,17:2365-2370, 1999

...exploring and expanding options for the reproductive future of cancer survivors

Fertility concerns beyond cancer treatment?

- Patients with rheumatologic diseases such as lupus, RA, and ulcerative cells
- MS patients receiving new generation treatments
- Patients undergoing bone marrow or stem cell transplants for an indication
- Individuals with genetic mutati
  and early menopause (e.g. Tuner
- Individuals who carry a mutatic
  individual to certain types of ca
  treatment-induced risk of infert

Hirshfield, Gracia and Woodruff, submitted

...exploring and expanding options for the reproductive future of cancer survivors

Fertility preservation for adolescents and children

- 12,500 children diagnosed with cancer each year
- 290,000 survivors of childhood cancer
- Survival rate for kids has risen to nearly 80%
- Late effects of treatment are taking on new urgency for survivors of this disease

Jeruss and Woodruff, NEJM, 2009
Nieman, CL et. al, J. Supportive Oncol, 2006
Nieman, CL, et al. Cancer Treatment Research, 2007

...exploring and expanding options for the reproductive future of cancer survivors

Attitudes about Fertility Preservation from Adult Survivors of Childhood Cancer

"…it was very upsetting when I was told at the onset of treatment that…my ability to conceive may or may not be affected, so even at 15 I was still very upset about that…"

"I didn't want to continue with treatment after they told me that I had ovarian failure. You know it was…it was very traumatic."

"…my first reaction was had this been offered when I was I was 14, I would have been like yes, yes, just do it. And I know my mother, my parents probably, would have been absolutely with let's do it."

"It's about options. It just gives you another option. And the more options you have in life the better off you are, you know?"

Nieman, CL et. al, J. Supportive Oncol, 2006
Nieman, CL, et al. Cancer Treatment Research, 2007

...exploring and expanding options for the reproductive future of cancer survivors

The Mission of the Oncofertility Consortium

To focus on the fertility threat poised by cancer treatment and serve as an authoritative voice for patients while creating corridors of discovery between research disciplines, clinical practice and training that can be created at the intersection of oncology, pediatrics, reproductive science, policy research, reproductive health law, bioethics, communication science, and cognitive and learning science.

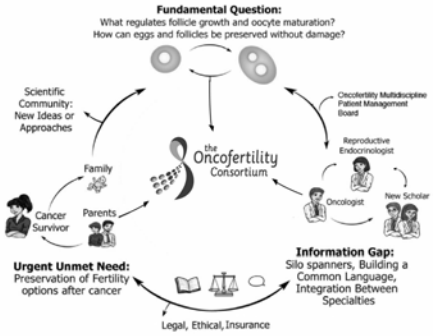
This work was supported by the Oncofertility Consortium NIH UL1DE019587

...exploring and expanding options for the reproductive future of cancer survivors

Building a Global Oncofertility Community

Shared Vision
Shared Technology
Shared Commitment to Patients and the Public
Shared Resources

An unparalleled opportunity to catalyze research and translate to patient care



Woodruff, TK Nature Review 2010

The Ribbon

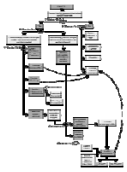
the Oncofertility® Consortium
AT NORTHWESTERN UNIVERSITY

http://oncofertility.northwestern.edu/branding-materials

New discoveries...societal

- Legal concerns
- Religious constraints
- Ethics discussion
- Historical context
- Patient-Provider communication and decisions



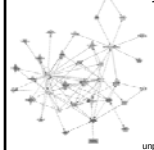
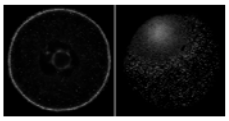



Dolin et al., SCLR. 2009
Zoloth L et al., AJB, 2008
Campo-Engelsten, L JCO, 2010
Gardino et al, JARG, 2010
Woodruff, Nature Review Clin. Oncol. 2010

...exploring and expanding options for the reproductive future of cancer survivors

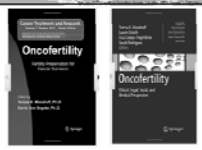
New discoveries...basic

- Egg quality (aging)
- Ovarian context (rigidity)
- Gene networks
- Mechanisms of ovulation and lutenization
- In vitro assay for new chemotherapeutics


unpublished, Barnhart, Barrett, Duncan, Galdones, Kim, Xu

The Oncofertility Consortium



Numerous review and peer-reviewed publications

...exploring and expanding options for the reproductive future of cancer survivors

The Oncofertility Common Language

Developed a robust data sharing and communication enterprise:

The Oncofertility Hub
http://oncofertility.northwestern.edu/

The Patient-focused Authoritative Voice of the Oncofertility Consortium
http://www.myoncofertility.org/

...exploring and expanding options for the reproductive future of cancer survivors

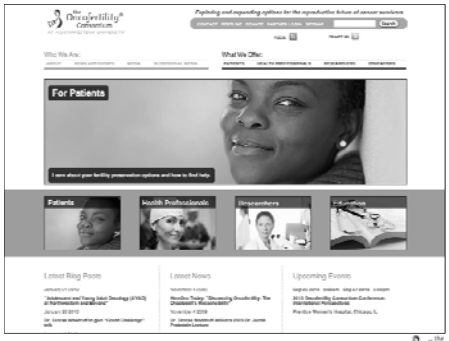
ASCO and ASRM practice guidelines

- ASCO
  - Discuss at the earliest possible moment potential fertility impairment
  - Prompt referral to qualified specialist if patient is interested
  - Promote clinical trials to advance state of knowledge
- ASRM/AAP

  "Parents may act to preserve fertility of cancer patients who are minors if the child assents and the intervention is likely to provide net benefits to the child"
- Oncologists - limited time to act
  - multidisciplinary approach (allied health professional)
  - survivorship is paramount
  - small window of opportunity

...exploring and expanding options for the reproductive future of cancer survivors

Oncofertility Consortium



...exploring and expanding options for the reproductive future of cancer survivors

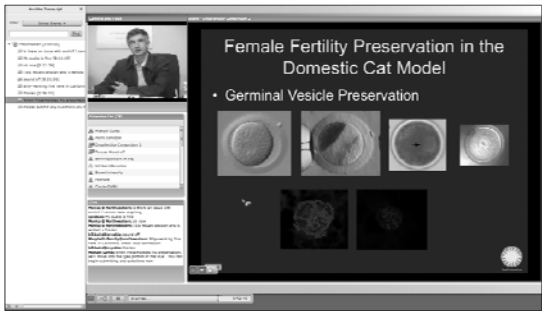
Mobile Compatiblity

...exploring and expanding options for the reproductive future of cancer survivors

Media Files

...exploring and expanding options for the reproductive future of cancer survivors

Virtual Grand Rounds -GLOBAL



...exploring and expanding options for the reproductive future of cancer survivors

Google Maps

...exploring and expanding options for the reproductive future of cancer survivors

What would a global Oncofertility Consortium look like?

- Virtual Lab meetings
  - Shared technology
  - Rapid research
  - Reduce duplication
- Virtual Grand Rounds
  - Better case management
  - Shared skills
  - Shared capacity to act
- Bench to Bedside to Practice
  - reduced hurdles
  - faster adoption of best practices
  - shared commitment to IRB consent, transparency and altruism
  - inclusion of ethics, economics and legal issues

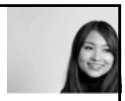
...exploring and expanding options for the reproductive future of cancer survivors

The Oncofertility Blog

...exploring and expanding options for the reproductive future of cancer survivors

Take home message

- Practice guidelines exist and recommend that the fertility threat associated with cancer treatment be discussed with all young cancer patients
- Options exist!
- The Oncofertility Consortium was funded to:
  - solve and intractable problem
  - engage basic biology and social science
  - create a global community of practice that is coordinated and sustainable



...exploring and expanding options for the reproductive future of cancer survivors

EXPECTATION OF EXCELLENCE

...exploring and expanding options for the reproductive future of cancer survivors

Our goal is to build the program as a global team and in so doing...

...expand options for the reproductive future of cancer survivors

This work was supported by the Oncofertility Consortium NIH UL1DE019587

Support

The work presented in this talk was supported by the SCCPIR Center for Reproductive Research, NICHD U54 HD041857; the Northwestern University Reproductive Science Training Grant T32; the Oncofertility Consortium NIH HD0058295; and the generosity of an anonymous donor.

Final thought...

When oncologists and fertility scientists and clinicians work together, patient needs are met and can
change a devastating diagnosis into life-affirming interventions.

This work was supported by the Oncofertility Consortium NIH UL1DE019587

Thank you!

References and Resources

- Fertile Hope. Cancer and Fertility: Fast Facts for Reproductive Professionals. 2008. www.fertilehope.org/uploads/pdf/FH_RP_FastFacts_08.pdf. Accessed February 11, 2011.
- Fertility preservation and reproduction in
- Jensen JS, Woodruff TK. Preservation of f
- Lee SJ, Schover LR, Partridge AH, et al. A 2006;24:2917-2931.
- Meirow D, Biederman H, Anderson RA, V
- Thewes B, Meiser B, Taylor A, et al. Ferti 2005;23:5155-5165.
- Tschudin S, Bitzer J. Psychological aspect 2009;15:587-597.
- Woodruff TK. The Oncofertility Consortiu
- SaveMyFertility.org
- Oncofertility Consortium: www.myoncofer
- Find-an-Endocrinologist: www.hormone.o
- Infertility and Women (bilingual fact shee
- Fertile Hope: www.fertilehope.org
- Sharing Hope Program: http://www.fertile
- American Society for Reproductive Medi
- American Society of Clinical Oncology
- Cancer Information: www.cancer.net
- RESOLVE: The National Infertility Asso

I hereby confirm that we do not have

any commercial and financial

relationships related to this presentation

and its contents

Perspectives for a European network for Fertility Preservation

INSELSPITAL

Michael von Wolff, MD

University Women`s Hospital
Department of Gynecological Endocrinology and Reproductive Medicine

IVF – Data collection in Europe

Human Reproduction, Vol.25, No.8 pp. 1851–1862, 2010
Advanced Access publication on June 22, 2010 doi:10.1093/humrep/deq124

human reproduction ESHRE PAGES

Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE†

J. de Mouzon*, V. Goossens, S. Bhattacharya, J.A. Castilla, A.P. Ferraretti, V. Korsak, M. Kupka, K.G. Nygren, A. Nyboe Andersen, and The European IVF-monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE)‡

ESHRE Central Office, Meerstraat 60, B-1852 Grimbergen, Belgium

*Correspondence address. Service de Gynécologie Obstétrique II et de Médecine de la reproduction, Groupe Hospitalier Cochin-Saint Vincent-de-Paul, 82 Avenue Denfert-Rochereau, 75014 Paris, France. Tel: +33-1-58-41-22-68 or +33-1-58-41-15-29; Fax: +33-1-58-41-18-70; E-mail: jacques.demouzon@inserm.fr

Submitted on April 7, 2010; resubmitted on April 7, 2010; accepted on April 16, 2010

20 countries, 359.000 cycles in a population of 422 million

Fertility preservation in Europe – Legal restrictions

For example:

	IVF covered	Embryo freezing	Embryo storage	Oocyte donation	Surrogacy
Denmark	no	yes	yes, 2y	no	no
Germany	no	no	no	no	no
Austria	yes	yes	yes	no	no
U.K.	Yes	Yes	Yes	Yes	Yes
Israel	Yes	Yes	Yes	partially	no

Fertility Preservation techniques and success rates

Estimated birth rates following fertility preservation

Cryopreservation of tissue	**max. 20% ???** (von Wolff et al., 2009; Donnez et al., 2011)
Cryopreservation of unfertilized oocytes	**≈ 50% lower than after cryo of fertilized oocytes** (Scaravelli et al., 2010)
Cryopreservation of fertilized oocytes	**25%- (36-40y) 40% (18-25y) ?** (Lawrenz et al., 2010)
GnRH-agonists	**Reduction of POF: x 3.5 ??** (Bedaiwy et al., 2010)
Transposition of the ovaries	**???**

Fertility Preservation techniques and risks

Estimated complications of fertility preservation techniques
(Lawrenz et al., 2011)

Cryopreservation of tissue	**1/500 cases: revision due to bleeding**
Cryopreservation of fertilized / unfertilized Oocytes	**6/221: Ø cryopreservation; Ø OHSS III°**
GnRH-agonists	**0 %**
Transposition of the ovaries	**???**

Fertility preservation in Europe

Who thinks, fertility preservation should be better organised nationally?

Who thinks, fertility preservation should be better organised in Europe?

The ESHRE Task Force „Fertility preservation in severe diseases“

Founded: 2007

2007 – July 2010: 1 coordinator, ≈ 20 members, representing several SIGs and different techniques

Activities:
2 campus workshops: Heidelberg, 2008; Bologna, 2010

Papers:
- **Psychology:** Tschudin & Bitzer, 2009
- **Ovarian tissue:** von Wolff, Donnez, Hovatta, Keros, Maltaris, Montag, Salle, Sonmezer, Andersen, 2009
- **GnRHa:** Blumenfeld et al., 2008

Since July 2010: Coordinated by Helen Picton, U.K.,

The situation in Europe (ESHRE)

28 countries

Some countries with:
- **Large and very active groups**
- **Large national networks**

and

Many countries, requiring
- **logistical**
- **technical**
- **(political?) support**

But: What is actually going on in ESHRE countries?

National programmes

To learn more about national activities, we (The Task Force and Bruno van den Eede from the ESHRE office) sent round a questionaire by e-mail to the National representatives in April 2011, followed by 2 reminders.

We evaluated, if national or local programmes and registries exist for men and women and if data are available concerning fertility preserving treatments.

Survey - results

28 countries were contacted, 23 replied:

Country	replied	Country	replied
Austria	yes	Italy	yes
Belgium	yes	Norway	yes
Bulgaria	yes	Poland	yes
Croatia	yes	Portugal	yes
Cyprus	no	Russia	yes
Czech Republik	yes	Serbia	yes
Denmark	yes	Slovenia	yes
Finland	yes	Spain	yes
France	yes	Sweden	yes
Germany	yes	Switzerland	yes
Greece	yes	The Netherland	yes
Hungary	no	Turkey	yes
Ireland	no	Ukraine	no
Israel	?	U.K.	yes

Survey – National / Large local programmes - women?

National programmes for women: 6/23 countries:

- Germany
- Denmark
- Bulgaria
- Finland (in preparation)
- France (in preparation)
- Sweden
- Switzerland (in preparation)
- Netherlands
- Norway

No national programme, but large local programmes:

- Czech Republic (in preparation)
- France
- Slovenia (in preparation)
- Turkey (in preparation)

Survey – National / Large local programmes - men?

National programmes for men: 3/23 countries:

- Germany (in preparation)
- Denmark
- Finland (in preparation)
- Czech Republik
- Netherlands
- Norway (in preparation)
- Poland (in preparation)
- Serbia (in preparation)

No national programme, but large local programmes:

- France
- Sweden
- Norway
- Turkey

Survey – National / Large local programmes - women?

„Established“ national programmes / Large local programmes:

	No. of centres	Registry		
		treatments	pregnancies	complications
Germany	70	yes	yes	yes
Denmark	1	yes	yes	yes
Bulgaria	?	?	?	?
Czech Republic	6	no	no	no
Sweden	?	no	no	no
Netherlands	13	yes	yes	yes
Norway	1	yes	no	no

Survey – National / Large local programmes - men?

„Established“ national programmes / Large local programmes:

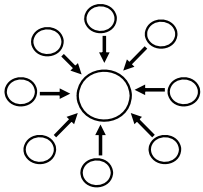
	No. of centres	Registry	
		treatments	pregnancies
➢Denmark	1	no	no
➢Czech Republic	6	?	?
➢Sweden	?	?	?
➢Netherlands	13	no	no
➢Norway	3	no	no
➢Poland	2	no	no
➢Slovenia	2	yes	no

Survey – National / Large local programmes - women?

„Established“ programmes with centralized registries (2010):

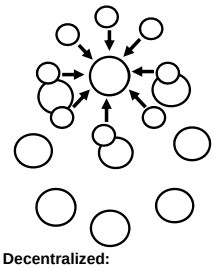
	Patients	Pregnancies	
		tissue cryo	oocytes/embryos cryo
➢Germany	619	1	1
➢Denmark	?	3	
➢Netherlands	?		
➢Norway	21		

National networks



Centralized:

Few specialised national medical centers, i.e. Denmark



Decentralized:

Many specialised medical centers with a central coordinating body, i.e. Germany

National networks

What can be offered centralized or decentralized:

- **Counselling**
- **Tissue cryopreservation**
- **Ovarian stimulation**
- **Cryopreservation of gametes (i.e. Vitrification)**
- **Information material (leaflets, websites etc.)**
- **Documentation / Registries**

National networks

What else can national networks offer ?

- **Networks can set up registers to evaluate efficacy and safety of fertility preserving techniques**
- **Networks can increase efficacy by integrating highly specialised centers**
- **Networks can integrate clinical work and research**
- **National networks can put pressure on the health system to integrate fertility protection in oncology treatments**

National networks

So, why not ?

Summary

- Some fertility preservation techniques are still experimental and need effective quality control systems
- Fertility preservation programmes have been started in many European countries
- Nevertheless, national programmes and networks have only been implemented in very few countries
- Data about these programmes are very limited.
- Should national representatives or ESHRE itself set up programmes and registers?

References

Bedaiwy MA, Abou-Setta AM, Desai N, Hurd W, Starks D, El-Nashar SA, Al-Inany HG, Falcone T. (2010) Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. Fertil Steril. 95:906-914.

Blumenfeld Z, von Wolff M. (2008) GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update 14:543-552.

Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, Pellicer A, Dolmans MM. (2011) Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births. Ann Med. Jan 13. [Epub ahead of print]

Lawrenz B, Jauckus J, Kupka M, Strowitzki T, von Wolff M. (2010) Efficacy and safety of ovarian stimulation before chemotherapy in 205 cases. Fertil Steril 2010;94: 2871-3

Lawrenz B, Jauckus J, Kupka M, Strowitzki T; von Wolff M. (2011) Fertility preservation in > 1000 patients – patients characteristics, spectrum, efficacy and risks of applied preservation techniques. Arch Gynecol Obstet, 283: 651-6.

Scaravelli G, Vigiliano V, Mayorga JM, Bolli S, De Luca R, D'Alojа P. (2010) Analysis of oocyte cryopreservation in assisted reproduction: the Italian National Register data from 2005 to 2007. Reprod Biomed Online. 21:496-500.

Tschudin S, Bitzer J. (2009) Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases. Hum Reprod Update. 15: 587-97.

von Wolff M, Donnez J, Hovatta O, Keros V, Maltaris T, Montag M, Salle B, Sonmezer M, Andersen CY. (2009) Cryopreservation and autotransplantation of human ovarian tissue prior to cytotoxic therapy--a technique in its infancy but already successful in fertility preservation. Eur J Cancer. 45:1547-53.

Management strategies for oncology consults and collaboration

Jacqueline S. Jeruss MD, PhD
Department of Surgery
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine

Young Breast Cancer Patients

- 180,000 women diagnosed each year, 16,000 younger than 45
- Diagnosis often traumatic for younger patients- isolation
- Initial consultation focused on establishing a plan of cancer care and reassurance
- Can be difficult to also discuss fertility preservation
- Patients present in all phases of life from single to committed relationships

The Initial Consultation

- Establish a rapport with patient
- Take history and review medical record
- Physical exam
- Review workup
- Discuss treatment options
- Establish plan of care
- Address fertility concerns and discuss options for fertility preservation

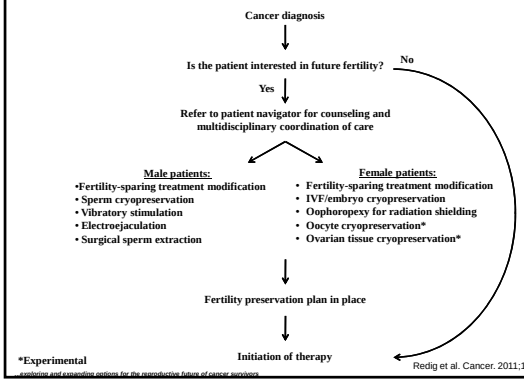
Critical Factors for Success

- Primary treating physician to support fertility preservation
- Patient navigator readily available to meet/call patient
- Reproductive specialist on call for fertility “emergencies”
- Entire multidisciplinary oncology team willing to modify plan to accommodate fertility preservation when possible

Making a Referral

- Timeliness is essential
- Ideally, hand-off to patient navigator should be as soon as possible
- Patients often anxious about moving ahead with cancer care
- Concern that fertility preservation may interfere with treatment plan
- Ideally, fertility preservation should be seamlessly integrated into care

Navigating the oncofertility treatment path



*Experimental

Redig et al. Cancer. 2011;117,4-10.

Impact of Breast Cancer Treatment on Fertility

- 16,150 women diagnosed younger than 45 in US
- Majority patients diagnosed early stage disease have excellent prognosis
- Risk of chemotherapy related amenorrhea and POF largely dependent on agent used, patient age
- Most regimens include alkylating agents which pose greatest risk for ovarian failure, OR 3.98 compared to unexposed patients
- 12M amenorrhea
  - AC (n=75) 44% ≤ 40; 81% >40
  - AC+T (n=116) 61% ≤ 40; 85% >40
- Amenorrhea permanent for AC and AC+T regimens
  - ≤ 40 60% (n= 52)
  - > 40 82% (n= 23)
- Effects of tamoxifen on the ovary thought to be reversible

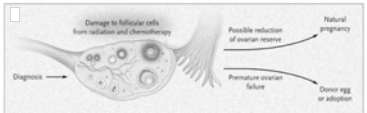
Tham et al. Am J Clinical Oncology, 30, 2007

Breast Cancer and Hormone Exposure

- Association between pregnancy after breast cancer and increased risk for recurrence not shown
- Yet ER/PR positive breast cancer hormonally driven- questions regarding safety of hormone stimulation yet to be answered
- Recent data also suggests indirect mitogenic effect in hormone receptor negative patients
- Stimulation with tamoxifen and aromatase inhibitors has been employed
- Gestational surrogacy may be considered

Early Stage Breast Cancer

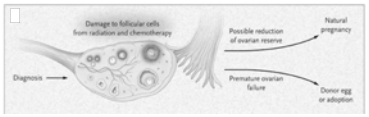
- Early stage patients with favorable biology: radiation therapy and antiestrogen therapy for 5 years
- Fertility measures should not be taken during radiation therapy
- Indirect evidence supports delay in antiestrogen treatment to allow for pregnancy



Jeruss and Woodruff, NEJM, 2009

Breast Cancer: Chemotherapy Indicated

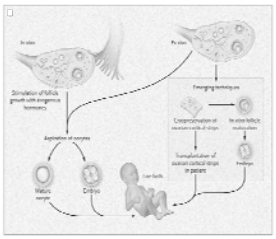
- Tumors larger than 1 cm, locally advanced disease, hormone receptor negative
- Cyclophosphamide, fluorouracil, doxorubicin, paclitaxel, docetaxel
- Alkylating agents: cyclophosphamide- effect primordial follicles represent ovarian reserve
- HER2+ herceptin for one year
- Treatment related effects, baseline ovarian reserve patient specific, pronounced decrease by age 40
- Determination ovarian reserve complex- basal levels of AMH, FSH, inhibin B, estrogen, antral follicle count



Hormonally Based Options

Hormonally Based

- Patient may elect to delay treatment to undergo one cycle of hormone stimulation, delay up to 1 month
- Cyropreservation embryo or mature oocyte
- Mature oocyte cyropreservation experimental > 500 lives births

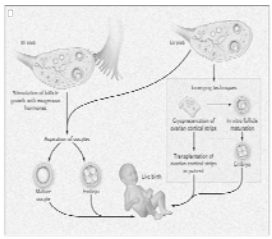


Jeruss and Woodruff, NEJM, 2009

Hormone Independent Options

Hormone Independent

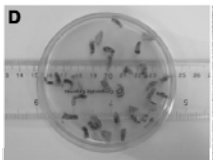
- Ovarian tissue retrieved at time of diagnosis
  - Cyropreserve cortical strips or aspirated oocytes
  - In vitro follicle maturation
  - Autologous transplantation of cortical strips
- Outcomes
  - Natural cycle IVF: success rate low
  - IVFM: live births in murine model, human studies progressing
  - Transplantation: 5 live births, risk for re-exposure of cancer cells, not for BRCA positive patients



- Donor egg, surrogacy
- Adoption

Ovarian Tissue Cryopreservation

- **Candidates**
- Patients with short time line to treatment
- Patients who are having oophorectomy, but not those with mass in same ovary
- Patients who will not take fertility drugs
- Prepubertal patients
- **Concerns**
- Will patient be able to make use of her tissue?
- Time line to treatment, health of patient
- Age of the patient
- Is patient a candidate for transplant?
- How soon will technology "Catch Up" to patient?
- Combination with more mature technologies: egg or embryo banking, conventional IVM

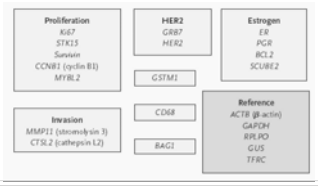


Anderson et al 2008; Demeestere, 2006; Donnez et al, 2004; Meirow, 2005; Silber 2006

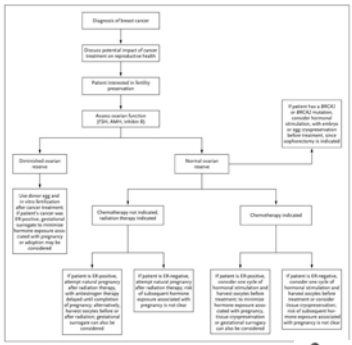
...exploring and expanding options for the reproductive future of cancer survivors

Genetic Assays and Fertility Preservation

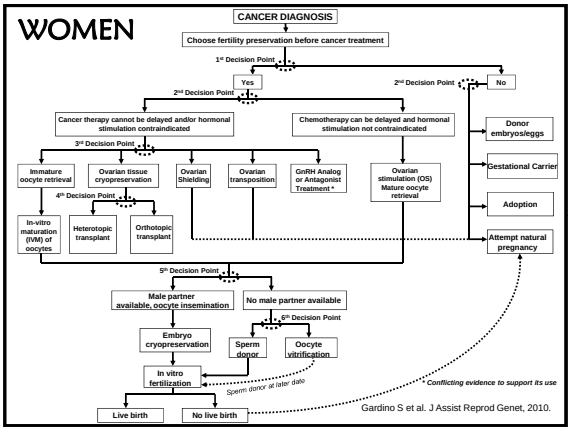
- Currently, subgroups of patients being overtreated
- Oncotype DX test being incorporated into clinical practice
- 21 gene assay generates a recurrence score
- May help guide patients/clinicians regarding usefulness of chemotherapy
- More refined selection of patients, spare fertility by minimizing unnecessary exposure to toxic chemotherapy

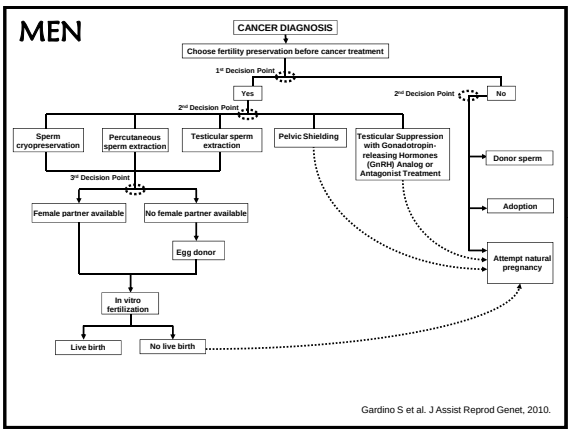


Algorithm of care for breast cancer patients



Jeruss and Woodruff, NEJM, 2009





Young Breast Cancer Patient

- 34-year-old women with 4 cm cancer, ER/PR/HER2 negative
- Patient opted for lumpectomy to be followed by chemotherapy and radiation
- Fertility preservation was discussed. Patient was single, no children wanted to pursue all fertility options possible
- After meeting with surgical oncologist, patient met with patient navigator
- Case then presented to multidisciplinary team: oncologists from all specialties, REI, psychologist, patient navigator
- After discussion with REI, patient started on OCPs and then underwent breast cancer surgery
- During 4 week recovery underwent ovarian stimulation/harvest. Cryopreserved oocytes and frozen embryos with anonymous sperm donor
- Underwent adjuvant therapy and intends to pursue pregnancy in future

exploring and expanding options for the reproductive future of cancer survivors

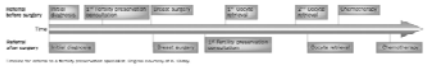
Young Patient Who Refuses Treatment

- 36 year old high level executive, elite athlete, married
- Diagnosed with invasive, ER/PR/HER2 positive disease, at surgery found to be node positive
- Fertility preservation discussed at initial consultation and post-operatively
- Patient refuses, focused on athletic goals
- 9 months into treatment patient and husband return for follow-up and state desire for children
- Patient amenorrheic, 6 months of herceptin therapy remaining
- At completion of herceptin therapy pt remains amenorrheic and states regret at not pursuing fertility preservation prior to therapy

Young Patient Who Desires Treatment

- 34 year old mother of 2 in supportive marriage
- Diagnosed with high grade stage IIIA breast cancer
- Fertility preservation discussed postoperatively, patient very interested
- Successfully pursues embryo cryopreservation
- Often states knowledge of fertility preservation helped her persevere through treatment
- Patient now pregnant in 2nd trimester
- Can we reconcile poor prognosis known prior to fertility preservation?

Timeline for Treatment



- Study of 93 patients: 35 referred for fertility preservation prior to surgery and 53 post surgery
- Mean age 35
- Higher percentage of patients who had referral prior to surgery underwent 2 retrieval cycles resulting in larger number of oocyte and embryos for these patients
- Controversial interval between surgery and chemotherapy (9 weeks)
- Northwestern breast cancer program: treatment time delay for one cycle

Lee S et al. JCO, 2010.

Practice Guidelines

- Cases illustrate means of fertility preservation integration into plan of care
- Success depends on early/open communication with patients, flexibility in scheduling appointments/procedures for cancer care and fertility preservation
- Presence of multidisciplinary team that can see patients and discuss cases on short notice
- Current ASRM/ASCO guidelines advocate for education regarding fertility preservation options, underscore importance of early intervention, state sperm and embryo cryopreservation are only established techniques for fertility preservation
- Why guidelines not followed: lack of knowledge, uncertainty about success of fertility measures, language/ cultural barriers

Effect of Infertility on Survivorship

- Infertility associated with diagnosis of depression 2X that of fertile population
- Adult survivors of childhood cancer report increased anxiety regarding finding a mate, not prepared for long-term side effects of treatment
- Overall, young men and women have equal concerns regarding fertility
- Young breast cancer survivors: 57% report substantial concern about fertility, 29% concerns influenced treatment decisions

Duffy C, Allen S, The Cancer Journal, 2009
Schover L, Medical and Pediatric Oncology, 1999
Syrjala K et al, JCO, 2007

Psychosocial Impact of Infertility on Female Cancer Survivors

- Study included patients with cervical cancer, breast cancer, Hodgkin's disease, and non-Hodgkin's lymphoma
- Patients interviewed 10 years post diagnosis
- Patients who desired a child at diagnosis but were not successful highest level of distress and intrusive thoughts
- Patients who had children through adoption or stepchildren had intermediate level of distress
- Patients with one biological child least distressed
- Underscores importance of fertility preservation consultation prior to treatment and mechanisms to address grief associated with cancer-related infertility

Canada A, Schover L. Psyco-Oncology, 2010.

Gender Disparities for Adolescent Fertility Preservation Referrals

- 1428 pediatric oncologist contacted
- 209 started survey, 180 completed (93% were physicians)
- Survey: 22 questions about attitudes/practice patterns regarding fertility
- Majority stated a major concern and agreed that pubertal patients should be offered consultation
- Yet on 46% referred male patients > 50% of time
- Only 12% referred female patients > 50% of time
- 44% familiar with ASCO guidelines, 39% used in > half of patients
- Study shows motivation to preserve fertility yet barriers to referral and gamete cryopreservation
- Female patients referred much less frequently then males

Kohler T et al. J Assist Reprod Genet. 2010

Fertility and Cancer Treatment Planning

- Modification of treatment plans for cancer care
  - Less aggressive resection for endometrial and ovarian cancer, ongoing studies for conical excision for cervical cancer
  - Pelvic radiation for GU/GYN/GI cancer: sperm/oocyte, embro cryopreservation, ovarian transpostion prior to treatment
  - Potential to opt for less gonadotoxic chemotherapy on case-by-case basis (avoidance of alkylating agents)
  - Incorporation of more refined diagnostics: Oncotype DX for breast cancer patients
  - Timing for treatment for breast cancer: chemotherapy delay 1 month for ovarian stimulation/oocyte retrieval, tamoxifen delay for pregnancy

Exploring and expanding options for the reproductive future of cancer survivors.

❖Established a national referral line for patients and providers

866-708-FERT (3378)

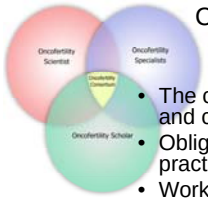
❖Two websites launched to enhance patient referral to local programs and serve as a resource for patients and providers

www.myoncofertility.org
(Patients)

www.oncofertility.northwestern.edu
(Researchers and Physicians)

❖Participation in multicenter research studies and access most up to date technologies and information

Conclusions



- The connections between fertility and cancer are complex
- Obligation to consider how our practices effect the whole patient
- Work together as multidisciplinary team
- Counsel patients about risk and how to process this risk
- Intersection between clinical recommendations and patient choice

Management strategies for centralised cryobanks and the European directive

Prof. Markus Montag, Ph.D.
Dept. Gynecol. Endocrinol. & Reprod. Medicine / Cryobank
University of Bonn, Bonn, Germany
markus.montag@ukb.uni-bonn.de

Disclosure

- Head of Cryobank at Bonn



Learning objectives

Following this lecture you should know:

- The main aspects related to managing a centralised cryobank
- How real is centralised cryobanking in Europe
- The legal frame and the impact of the European Tissue Directive
- Which questions still need to be solved in an international perspective

Content of lecture

- Centralised cryobanking
  - Examples from Europe
- Managing a centralised cryobank
  - Requirements
  - QC
  - Services
- Legal frames
  - European Tissue Directive
  - European Transplantation Directive
- Issues to be solved

Examples from Europe I

- 15 colleagues from different countries and known to be active in ESHRE for fertility preservation were contacted via e-mail
- Questions asked:
  - Does your country have a centralised cryobank for ovarian tissue freezing and how is the legal regulation
- 7 replied with detailed informations

Examples from Europe II

- Greece and Turkey:
  - No centralised cryobank for ovarian tissue
  - Few centers (mostly ART centers) do offer ovarian tissue banking
- Israel:
  - 4 major referral hospitals with own cryobanks
  - Ministry of Health included ovarian tissue cryopreservation equal to embryo freezing
  - Financially supported

Examples from Europe III

- Denmark:
  - One centralised cryobank for ovarian tissue
  - Licensed according to EU-Tissue Directive
- Italy:
  - One centralised cryobank just opened
  - Numerous private/public centers (mostly ART centers) do offer ovarian tissue banking

C.Y. Andersen; A. Borini

Examples from Europe IV

- Belgium:
  - No centralised cryobank for ovarian tissue
  - Numerous private/public centers (mostly ART centers) do offer ovarian tissue banking
  - No reimbursement
  - Controlled under EU Tissue Directive
- Scotland:
  - One centralised cryobank for ovarian tissue

J. Smitz; H. Wallace

Germany / Austria / Switzerland

- Network FertiPROTEKT
- Centers from German-speaking countries can join
- Aim of FertiPROTEKT:
  - to optimize patient counselling and treatment
  - to run a registry
  - to give recommendations
- To encourage cryopreservation of ovarian tissue in specialized cryobanks

Germany / Austria / Switzerland FertiPROTEKT members only

- Austria:
  - 3 surgical centers
  - 2 cryobanking facilities (1 serves 2 surg.cent.)
- Switzerland:
  - 3 surgical centers
  - 1 cryobanking facility
- Germany:
  - 66 surgical centers (30 are members of FP)
  - 12 cryobanking facilities
    - 10 work only locally
    - 1 serves 2 surgical centers
    - 1 serves 54 surgical centers (Cryobank Bonn)

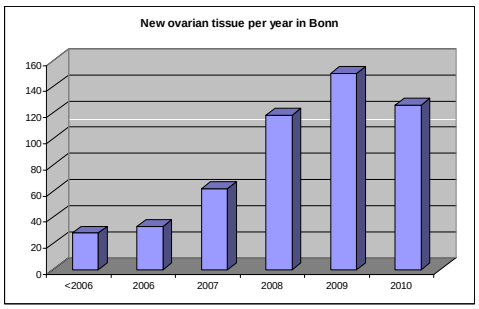
What does this show?

- There is no common strategy in Europe
- There are country-specific solutions
- The legal situation is partly unclear
- Costs have to be paid by the patient
- Long distance transportation and cryopreservation is available in only 2 cryobanks
  - Copenhagen, Denmark
  - Bonn, Germany

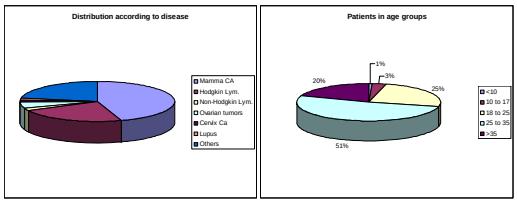
Content of lecture

- Centralised cryobanking
  - Examples from Europe
- Managing a centralised cryobank
  - Services
  - Requirements
  - QC
- Legal frames
  - European Tissue Directive
  - European Transplantation Directive
- Issues to be solved

Patients per year for centralised ovarian tissue freezing / Bonn



Patient characteristics - Cryobank Bonn -



What services should one expect from a centralised cryobank?

- Cryopreservation
  - Ovarian tissue / Testicular tissue / Sperm / Oocytes
- Transportation of tissue to / from cryobank
- Storage of frozen samples
- Administrative (paper) work
  - Contracts / Documentation / Patient files
- QC of all processes involved
- Information for patients / physicians
- Continuous (annual) contact with the patients
  - during storage period / after transplantation

Requirements of a centralised cryobank

- Transportation logistics for ovarian tissue
- Laboratory for tissue processing
- Proper equipment (freezers etc.)
- Room for cryo-storage
- Room for documentation
- Research lab for tissue QC
- Staff (Lab / documentation)
- QC / Safety issues / Monitoring
- Consistency over decades

Requirements: some examples

- Basic equipment: approx. 90.000 €
  - Freezing device (programmed freezer)
  - Nitrogen supply tanks
  - Storage freezer system
    - Incl. racks / boxes
  - O2-monitor system
  - Alarm notification system

Requirements: Transplantation

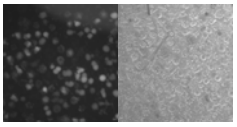
- First contact with the cryobank is established through patient / center
- Test-thawing at cryobank to determine viable follicle count
- Discussion about number of pieces
- Transport of samples is ordered by patient
- Organisation by cryobank:
  - Thawing by local biologist
  - Thawing by biologist from cryobank

Quality control in a centralised cryobank

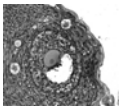
- Contract with surgical unit
- Responsability declarations
- SOPs for all steps involved
  - Transportation
  - Tissue processing
  - Freezing
  - Storage
  - Patient management (contract, consent,…)
  - Transplantation

QC: some examples

- Tissue viability testing
  - after transport
  - after freezing/thawing



- Tissue potential
  - SCID-mouse transplant



Integrated cryobanking concept

- Ovarian biopsy, tissue processing, cryopreservation, transplantation: is one aspect but not enough
- Psychological work-up
- Continuous contact with the patient
- Patient file with all relevant informations
- Patient-oriented research
- Investigating disease related parameters
- Follow-up

Content of lecture

- Centralised cryobanking
  - Examples from Europe
- Managing a centralised cryobank
  - Requirements
  - QC
  - Services
- Legal frames
  - European Tissue Directive
  - European Transplantation Directive
- Issues to be solved

Cryobanking: Legal aspects

- EU Tissue Directive
  - Copenhagen, DK has been inspected and received a licence for ovarian tissue
  - Most countries: no inspection reported
- Bonn, GER has been inspected
  - Inspectors decided that ovarian tissue should be covered by transplantation law
  - Transplantation law does not require licencing
  - Annual report to PEI, however, no feedback

EU Transplantation Directive

- DIRECTIVE 2010/45/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 7 July 2010
- On standards of quality and safety of human organs intended for transplantation
- Does in no way cover ovarian tissue

EU-Tissue Directive 2004/23/EG

- Legal frame for cryobanking of cells and tissues
  - Ovarian tissue / whole ovaries / isolated follicles are covered in most but not all countries, too
- Regulates in particular retrieval, transportation, cryopreservation, storage and future use of tissues and cells
  - Every center involved in one of these topics will be inspected on a regular base and must be registered
- Cryobank needs contracts with surgical units
- Testing for infectious diseases is mandatory
  - HIV, Hep B, Hep C
- Technical requirements for all related procedures
- Handling of serious adverse events

EU-Commission Directive 2006/86/EC

- Technical requirements for all related procedures
- Handling of serious adverse events

EU-Commission Directive 2006/17/EC

- Testing for infectious diseases is mandatory
  - HIV, Hep B, Hep C

Cryobanking: Legal aspects

- Having proper contracts is mandatory
  - With surgical units delivering tissue
  - With patients
- Contracts must be made by professionals
  - What if a patient cannot be traced any more?
  - What happens with the tissue if a patient dies?

Content of lecture

- Centralised cryobanking
  - Examples from Europe
- Managing a centralised cryobank
  - Requirements
  - QC
  - Services
- Legal frames
  - European Tissue Directive
  - European Transplantation Directive
- Issues to be solved

Compliance of patients

- Cryopreserved semen samples
  - Most of them will never be used
  - Men don´t care / simply forget about it
- Women having cryopreserved ovarian tissue
  - Are highly compliant
  - They do care
  - Are very concerned about storage etc.

Pending issues

- European network on fertility preservation
- Training courses in tissue processing / testing
- Assistance in setting up a cryobank facility
- Assistance in setting up transportation logistics
- Legal frame within Europe is not uniform
- New concepts:
  - Cryopreservation / Administration / QC center
    - Maybe even under a national health scheme

Pending issues

- The questionnaire regarding national attitudes was very preliminary
- Therefore ESHRE (Task Force Fertility Preservation) should circulate a questionnaire among the national representatives to get more detailed infromation about cryobanking for fertility preservation

Summary

Managing a centralised cryobank for ovarian tissue:

- involves much more than freezing
- is a task which requires multi-disciplinary interactions and coordination
- is a balance between patient needs, legal requirements and cost-effectiveness
- requires the ability to design innovative concepts
- is still a continuously growing project

Example of an integrated approach

- Patient with Morbus Hodgkin:
  - Ovarian biopsy in Dresden, 2005
  - Over-night transport to Bonn
  - Cryopreservation in Bonn until 2010
  - Frozen tissue transported from Bonn to Erlangen
  - Transplantation in Erlangen, 2010 (age: 32)
  - Pregnancy in Dresden, 2011

Selected References

- www.en.wikipedia.org/wiki/EU_Tissue_Directive
  - pdf of Directive and annexes
- www.fertiprotekt.de
  - Homepage of FertiPROTEKT network
  - Button for english version available on the front page

Clinical management:
fertility risks by diagnosis-
What cancer requires immediate intervention

Professor Dror Meirow M.D.

Fertility preservation Center,
Sheba Medical Center,
Sackler school of medicine, Tel Aviv University, Israel.

ESHRE 27th annual meeting 2011
Stockholm, Sweden

Learning objectives

- Know the risk of different cancer treatments on fertility and the role of age.
- Understand the effect of chemotherapy on growing follicles and its clinical application.
- Understand how to evaluate patients seeking to preserve fertility prior to chemotherapy.
- Compare different methods for fertility preservation in specific cancer situations. Case studies.

Chemotherapy induced gonadal damage
Clinical data- Lack of sufficient information

- **Menstrual history- most available data.**
- **Hormone profile- when to perform? Reliability?**
- **Ovarian reserve assessment- AMH, AFC**
- **Reports on pregnancies.**
- **IVF Results- Response to stimulation**

  Egg number, fertilization rate,

  Embryo quality, pregnancies

Chemotherapy induced gonadal damage
Basic research

***In-vivo* studies**

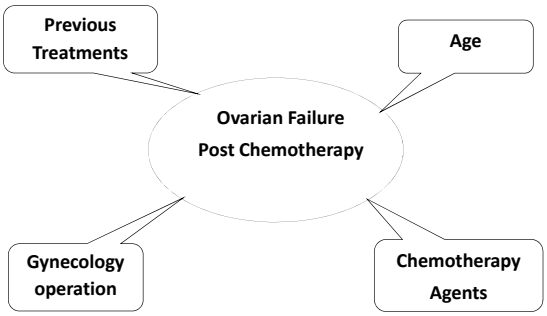
- **Animal studies – mating, pregnancies, abortions.**
- **Ovary - follicles: primordial, growing.**
- **Ovary- organ injury- stroma, blood vessels.**

***In-vitro* studies**

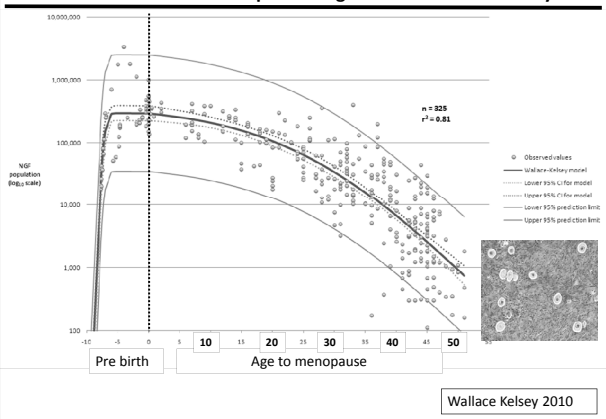
- **Mechanism of follicle injury: primordial, growing.**
- **Mechanism of ovarian stromal injury.**

Often no correlation between basic studies and clinical data

Assessment of sterilization risks



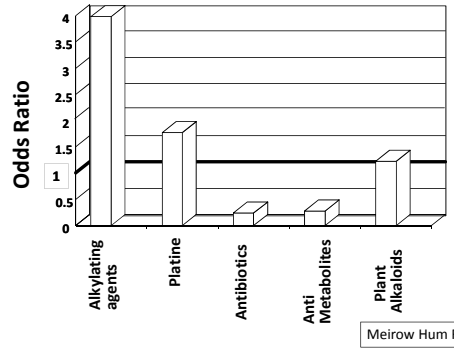
Human Follicle count representing the reserve of the ovary



Wallace Kelsey 2010

Ovarian Failure by Drug Families

Age adjusted Odds ratio exposed vs. unexposed



Meirow Hum Reprod 2001

American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

S. Lee *et. al.* 2006

Risks of Permanent Amenorrhea in Women Treated With Modern Chemotherapy and Radiotherapy

High risk (80%)	BMT with Cy/ TBI or Cy/busulfan radiation to a field that includes the ovaries CMF, CEF, CAF X 6 in women > 40
Intermediate risk	CMF, CEF, CAF X 6 in women age 30-39 AC 4 in women age > 40
Lower risk (20%)	ABVD, CHOP X 4-6 AML therapy (anthracycline/cytarabine) ALL therapy (multi-agent) CMF, CEF, CAF 6 cycles in women <30 AC X 4 in women < 40

Hodgkin's Disease

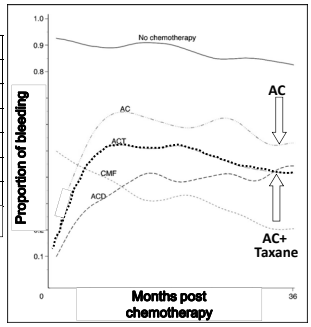
Ref.	Treatment	Ovarian failure
Howell & Shalet Review 98	Aggressive treatment	38% - 57%
Meirow 99	Relapse post 1st treatment	32%
Bokemeyer	Infradiaphragmatic Rx.	50%
Brusamolino 2000	Ovarian sparing protocol	<25y – 0% <45y – 30%

Wallace & Meirow 2010

Ovarian failure in breast cancer patients

Chemo	Age	Ovarian failure
AC	< 30	0 %
AC	30- 39	13 %
FAC	< 30	0 %
FAC	30- 39	10-25 %
CMF	< 30	19 %
CMF	30- 39	30-40 %
+ Taxane		

Wallace & Meirow 2010



Petrek, J. J Clin Oncol 2006

Breast cancer -ovarian failure post treatment

Reference	Age/ treatment		Ovarian failure
Lower E.E 1999	Pre menopause		45%
	<35 years		28%
Meirow D 1999	<44 years		50%
Goodwin P. 1999	CMF	43.7 +/- 5.2	65%
Burstein H. 2000	CMF	> 30	19%
		30-39	30-40%
	CAF	> 30	0%
		30-39	10-25%
	AC	> 30	-------
		30-39	13%
Jonat W. 2001	Pre menopause		60%
Petrek 2006	<35		15%
	35-39		39-55%
	>39		> 55%

Ablative Chemotherapy & Bone Marrow Transplantation

	No.	Age	% failure
Sanders 96	73	mean 38	99
Teinturier 98	21	2 - 17	72
Thibaud 98	31	3.2 - 17	80
Meirow 99	63	mean 29	79
Grigg 2000	19	mean 30	100

Ovarian failure risk - very high.

Meirow, Amderson, Wallace 2010

Premature ovarian Failure in Childhood Cancer Survivors

Disease	Odds ratio (patients)
Hodgkin's D.	3.8 (66 / 487)
Non- Hodgkin's Ly.	3.2 (19 / 168)
Sarcoma	2.6 (27 / 290)
Wilm's tumor	3.0 (35 / 329)
Leukemia	1.0 (43 / 1088)

W. Chemaitilly, C. Sklar et. Al. JCEM 2006

Ovarian reserve after chemotherapy for breast cancer Premenopausal survivors compared with controls.

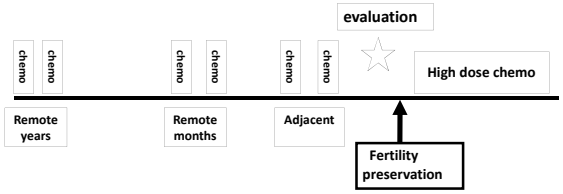
		Mean	Min-max	P value
AFC	Controls Survivors	11 5	1 - 34 0 - 12	**0.0042**
AMH	Controls Survivors	1.8 0.6	0.3 - 6.3 <0.1 - 2.4	**0.0004**
FSH	Controls Survivors	8.0 11.6	3.1 - 17.7 3.3 - 24.5	0.02
Inh B	Controls Survivors	46.6 24.3	10.0-152.1 10.0-91.8	0.02
E2	Controls Survivors	38.8 126	12.0-89.0 14.4-806.0	0.14

20 pt. in each group

A. Partridge Fertil Steril 2010

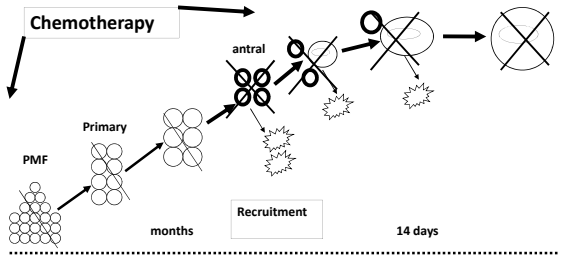
- **The effect of chemotherapy on growing follicles and its clinical application**

Fertility preservation post initiation of chemotherapy



IVF > 40% of patients with Hematological malignancies had previous chemotherapy.

OTCP > 50% of patients with Hematological malignancies had previous chemotherapy.



primordial follicles <<< Large follicles

Ovarian tissue cryo-preservation post recent Chemotherapy

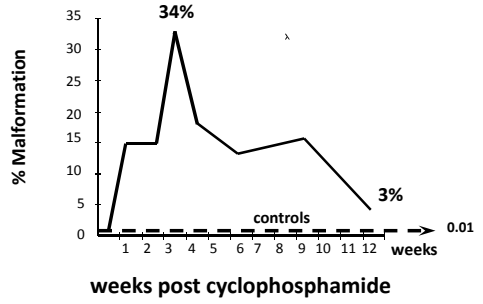
2-3 months post chemotherapy

Disease	Age	IVF Eggs	Biopsy PMF
Non-Hodgkin's D	21	0	+ +
Hodgkin's D	25	0	+ + +
Hodgkin's D	25	0	+ + +

13 patients with hematological malignancies cryopreserved ovarian tissue post recent chemotherapy.

Meirow et.al. Leukemia Lymphoma 2007

Malformation rate - time scale



weeks post cyclophosphamide

Meirow D. Gosden R. et. Al. Hum Reprod 2000

Clinical implications
Effects of chemotherapy on growing follicles

- **Large follicles - Immediate Apoptosis.**
- **Follicle loss - Large >> Primordial follicles.**
- **Very low response post chemotherapy exposure.**
- **High abortion & malformation rate (animal study).**

We do not collect mature or immature eggs for fertility preservation in patients recently exposed to chemotherapy (up to 6 months)

The effect of irradiation to the ovaries in young women.

Dose-related effect on the No. of surviving Primordial follicles. Gosden et.al 1997

LD_{50} - 4 Gy

Wallace et.al. 1989

Radiation to the ovaries
ovarian failure risk – young patients

Total abdominal irradiation 20-30 Gy

- **97% ovarian failure**
- **72% prepubertal**

TBI 10-15 Gy single exposure 90%

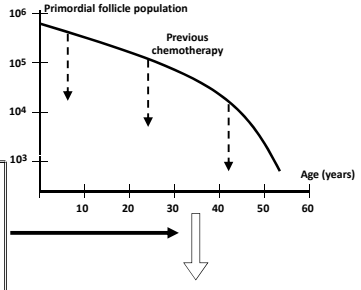
Wallace 2003

Ovarian radiation 10 Gy can induce ovarian failure in patients with additional risk factors (A.A, older age)

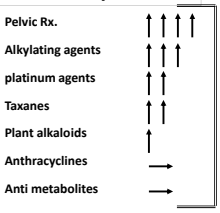
Chemaitilly Sklar *et al* 2006 JCEM

Consulting young female cancer patients-
Risk assessment

Ovarian reserve



Toxicity risk



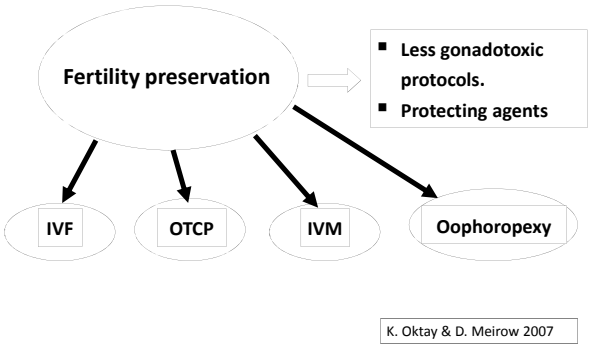
Assessment of an individual Patient sterilization risk

Meirow & Wallace 2010

Evaluation of patients before
Fertility preservation procedure

- Diagnosis, staging, Is complete evaluation indicated?
- Sterilization risk: disease, treatment protocol, age
- Ovarian reserve
- Previous exposure to chemotherapy.
- Time available – window for fertility preservation.
- Medical status - complications
  - Leukemia - anemia, thrombocytopenia
  - Lymphoma- mass, pressure, effusion
- Risk of ovarian involvement.
- Estrogen sensitive tumors.

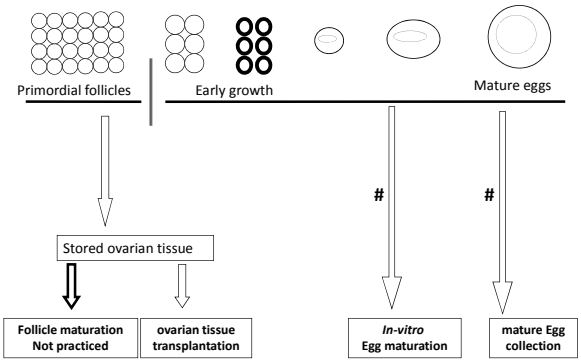
Planning for fertility preservation before cancer treatment



K. Oktay & D. Meirow 2007

Different approaches for fertility preservation

Currently used & experimental



IVF in cancer patients - Dilemmas

- Time needed for IVF before chemotherapy.
- Cancer within the ovary.
- Age –children, aged patients- ovarian reserve.
- Patient's health condition.
- No partner –Egg freezing or Donor sperm.
- Success rate in cancer patients.
- IVF post exposure to chemotherapy.
- Hormone sensitive tumors.

IVF for fertility preservation in cancer Patients

Reference	Eggs		2PN		P
	cancer	controls	cancer	controls	
Oktay 2005	12.3		5.3		
Knopman 2009	14 ± 9	12 ± 7			NS
Quintero 2010	13	11.5	7.4	6.8	NS
Robertson 2010	12 ± 8	14 ± 9	6 ± 5	7 ± 6	NS
Lawrenz 2011	11.6 ± 7.7		7		

Luteal Stimulation with GnRH ant

- Embryo cryopreservation with IVF 24 pt. 6 luteal patients underwent GnRH-ant concurrent with FSH simulation/
- Luteolysis within 4d (early luteal) or 2d (midluteal).

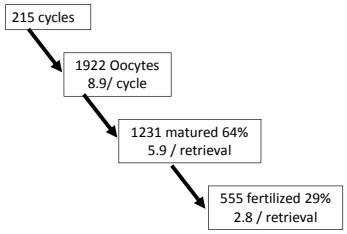
	follicular	Luteal
Gonadotropin used		More NS
Stimulation duration	10.6	11.4
Oocytes obtained	13	10
Fertilization rate	61	76

Von Wolff M et al Fertil Steril 2009

Minimal Stimulation/ IVM Protocol

	Shalom Paz 2010	Maman 2010 Luteal	Maman 2010 follicular	Strowitzki 2010
No. cycles	31	5	13	215
Oocytes /cycle	9.7 ± 6.4	12.8 ± 8.4	17.3 ± 13.5	8.9
Total MII in 48h		7.0 ± 7.6	9.5 ± 7.7	
Maturation rate		48%	58%	
Fertilization rate	77.8 %	69%	63%	
Embryo stored	4.5 ± 2.71			2.8

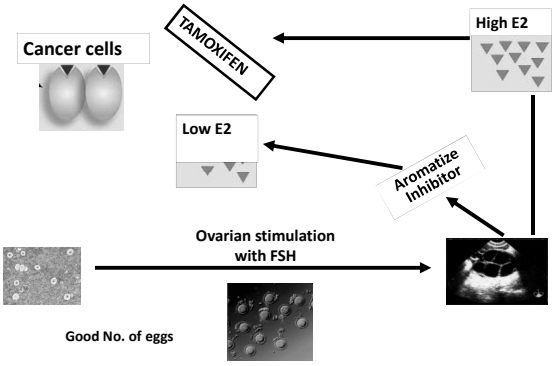
IVM results for fertility preservation



- Better results vitrifying mature rather than immature oocytes.
- Vitrification of in vivo mature + in vitro mature better results.

T. Strowitzki 2010

Breast cancer protocols



laparoscopic ovarian transposition in patients who need pelvic irradiation. Indications

- **Pt. not planned for surgery.**

  (Hodgkin's d. hematological malignancies, CNS tumors)
- **Prior laparotomy without transposition.**
- **Laparotomy + oophoropexy, but the ovaries migrated back prior to Rx.**

Complications

- Vascular injury, Fallopian tube infarction.
- Ovarian cysts.
- Risk of remigration of the ovaries.

(should be performed adjacent to radiation)

- Failure 50% (Scatter radiation; ovarian blood supply)
- IVF will often be required / spontaneous pregnancies.
- Oocyte retrieval more complicated.

Reposition

Abdominal egg collection (reduced efficiency)

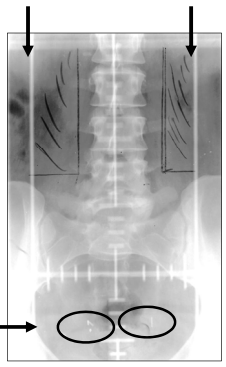
ASCO recommendation on fertility preservation JNCI 2006

Low medial transposition

21 y patient
pineal tumor

Irradiation field
CNS + spine 40 Gy
+ Chemotherapy

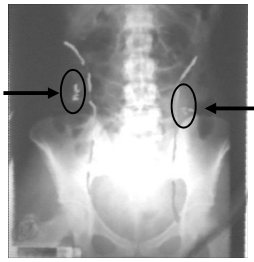
New position of the ovaries



Hodgkin's Disease groin

Rt. transposed ovary

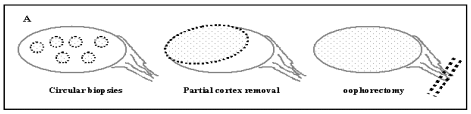
Lt. transposed ovary



Cryopreservation and transplantation of ovarian tissue.

A realistic technique for fertility preservation.

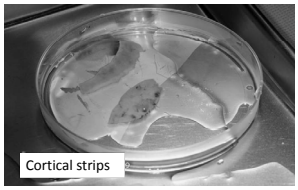
Operation – laparoscopy or Laparotomy

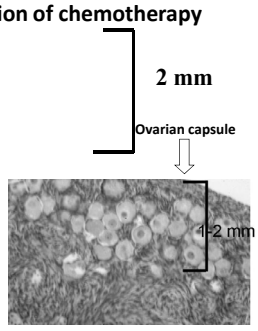


Follicles stored

Mostly non growing follicles are stored.

Can be practiced post initiation of chemotherapy

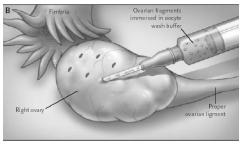




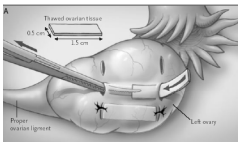
Transplantation of Ovarian Tissue

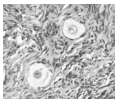
A patient with Non Hodgkin's lymphoma
Ovarian failure post bone marrow transplantation

Rt. ovary



Lt. ovary





Follicles from thawed ovarian tissue

The NEW ENGLAND JOURNAL of MEDICINE

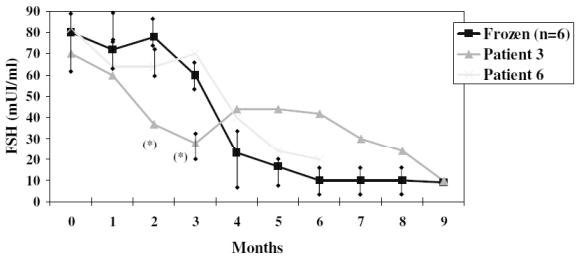
Meirow, Dor *et al*
2005

Children born after ovarian transplantation. A review of 13 live births.

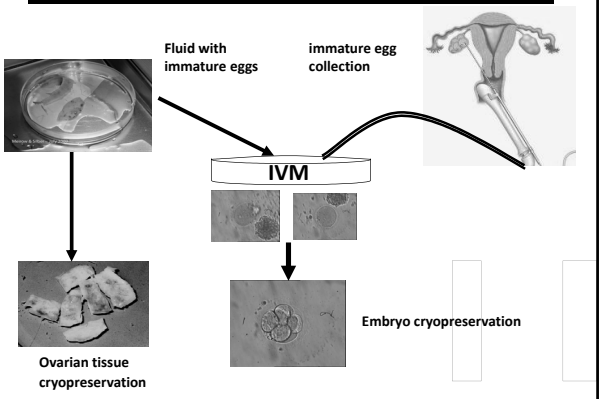
- Age at tissue collection 19-36
- Previous chemotherapy 40%.
- Endocrine results.
- IVF / Spontaneous pregnancy 50%.
- Pregnancy results- normal babies 100%.

Over all Success Rate?

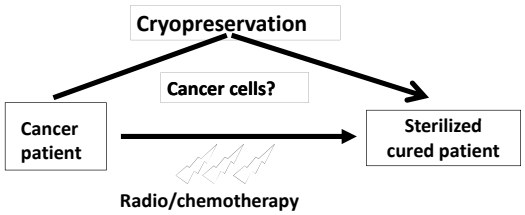
Recovery of Endocrine function



single procedure- IVM + ovarian tissue



Detection of Microscopic Metastases in Cryopreserved Ovaries.



- Use the most sensitive techniques for detection.

Pelvic and abdominal operations- Consider Fertility preservation actions

Gynecology cancer

- Cervical cancer
- Ovarian cancer
- Endometrial cancer

Abdominal cancers

- Rectal cancer.
- Colon cancer
- Urological cancer.
- Soft tissue and bone sarcomas.

Cesarean Section

Hematology- Cases for discussion

- 18 years old patient suffering from recurrence of Hodgkin's lymphoma prior to high dose chemotherapy and bone marrow transplantation.
- 24 years old patient, single, diagnosed with acute myeloid leukemia.

Breast cancer- Cases for discussion

- 36 years old patient, married mother of 3 years old child, diagnosed with intra ductal breast cancer, estrogen receptor positive.

Gynecology- Cases for discussion

- 32 years old patient diagnosed with bulky cervical cancer, prior to chemotherapy followed by trachelectomy or irradiation.
- 18 years old patient diagnosed with germ cell tumor.
- 36 years old patient diagnosed with ovarian cancer.

Reproduction & fertility preservation center

Addressing the specific needs of young children with cancer

Hamish Wallace

Contribution not submitted by speaker

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

When research becomes treatment: ethical issues

Françoise Shenfield, RMU, UCLH, London; Member of ESHRE Ethics and Law Taskforce; Co chair of FIGO 's ethics committee

Stockholm, July 2011, Clinical management planning for fertility preservation in female cancer patients

No conflict of interest (1) Objectives (2)

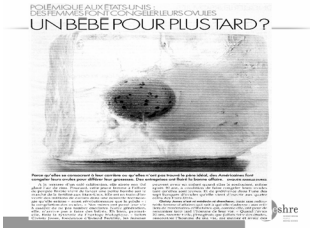
No conflict of interest

- Commercial relationship: **none**
- Activities that might be perceived as a potential conflict of interest : **none**

- **Objectives**
- To understand the ethical issues involved in the difficult **transition** from research **("emerging fertility options")** to practice **,** both for professional and patients involved, (women, adolescent and children), as well as future children

Hoping for genetically related offspring

- Female (or male) cancer patients wish for … .



What are the core questions ?

- **Innovative reproductive technologies: risks and responsibilities**

(**Wybo Dondorp,** Rome, 2010; now in press, with G De Wert)

facts: there is a global burden of infertility (here iatrogenic), but > 4M children born from IVF

Need for sound evaluation of efficacy, effectiveness, safety of technologies introduced in clinical practice

Safety: both for (mostly) the woman and her offspring (risks)

Responsible innovation = N steps of research : pre clinical investigations, clinical trials and follow up

The question of "when"?...

- **When research becomes treatment: ethical issues**
- **1.in general:** N steps of research : pre clinical investigations, clinical trials and follow up
- **2. in particular: cryopreservation =? treatment stricto sensu or "insurance" for the future**
- **Good practice, but "future" treatment:**
- **This enables a breathing space for applications and further safety studies**

Innovative treatment or research: pros and cons

- **? Just semantics**:
- Innovative treatment or "clinical innovation" is when clinicians " try something new" **not yet thoroughly tested"** in a research setting
- **+**: **allows earlier application** to patients in need, by- passes the "research route which (too often) stifles innovation"
- **-** : But … ? Harm (ex PGS) now re-evaluated in a different form with polar body biopsy in a proper research setting
- **In practice, the question**: benefits v possible harms (magnitude, "serious", frequency…)

Livebirth after orthotopic transplantation of cryopreserved ovarian tissue

J Donnez, MM Dolmans, D Demylle, P Jadoul, C Pirard, J Squifflet, B Martinez-Madrid, A Van Langendonckt

Lancet 2004; 364: 1405–10

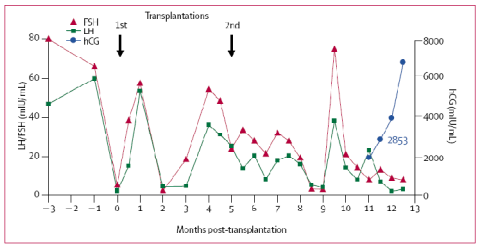


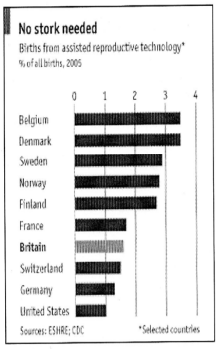
Figure 2: Sequential serum concentrations of FSH and LH
hCG=human chorionic gonadotrophin. 5 months after reimplantation, restoration of ovarian endocrine function was shown by assessment of hormone concentrations. 11 months after reimplantation, an ongoing intrauterine pregnancy was diagnosed.

An ethical calculus for clinical (? Innovative) practice

- Respect the **autonomy** of the patients: willing to take **risk** for **herself** after the first published case
- Other risks: risk for the **future child** : as ART clinicians , we are responsible for the **welfare of child(ren)** born as a result of our treatment
- **In practice, 2 (/3) principles**: respect of **autonomy** entails respect of consent (and refusal), **beneficence v non maleficence** (benefits v risks)
- **3rd principle**: **justice (equitable access to all with the same needs):** for now impossible for low and middle resources countries

Assisted reproduction | No IVF please, we're British | Economist.com Page 2 of 4

Home
This week's print edition
Daily news analysis
Opinion
All opinion
Leaders
Letters to the Editor
Blogs
Columns
KAL's cartoons
Correspondent's diary
Economist debates
World politics
All world politics
Politics this week
International
United States
The Americas



privately.

The consequences were in
July 12th at Bourn Hall, wh
"babies", one for each year
technology, gathered to cel
Brown's birthday. The clinic
Cambridgeshire—the world
dedicated to fertility treatm
up in 1980 by Dr Steptoe a
Edwards, after two years o
somewhere to continue the
funding for it. "The NHS, m
charities, everyone turned
explains Mike Macnamee, t
CEO. "Bourn Hall had to be
privately because the NHS
for it."

Research ethics, and transition to practice

- **Existing frames for research**: The **Nuremberg** code: participation must be **voluntary**; Declaration of **Helsinki**, submitted to ethics committee (IRB) approval

Consent based on **understanding** the information (reliable , evidence based) and appraisal of **clinical outlook**: cryo of tissues v ability of the uterus to carry a pregnancy to term depends on the modality of treatment (radiation induced damage)

- **Understanding** depends on **capacity** (not merely age, although legally this differs amongst states)
- Explain alternatives and current success rate

Information is the key to (proper) consent

- 1. **Consent to what**: Is it for **therapy** (best known, or best available) or for **research** (unknown, but scientifically valid hypothesis) explained in patient friendly terms; or for **both** (ca, therapy and cryopreservation/biopsy at the same time)
- 2. **Whose consent**: adults, adolescent (explained in terms suitable to their maturity and understanding) , or children patients (generally parental consent): differ in **capacity**
- 3. Consent for cryo -preservation (whether research or part of therapeutic options) is **consent for storage** …does not imply **use**
- ***Consent for use*** *will be* ***separate****, based on further scientific evidence, and will be given by a different person in the case of children, and a more mature person for adolescents*

Clinical research in general and ART in particular

- clinical infertility research **not** within the HFE Act in UK, unless embryos are created
- Regulated like all research (**consent** ; ethics committees)
- **ESHRE** annual meeting 2010 (Dondorp and de Wert): one may (and should) question the safety of some ART techniques on the born children
- A **question often asked**: will it be safe for my/ my child's offspring
- **Solution**: international registers and follow up of outcomes

ESHRE Ethics and law Taskforce 7

Cryo preservation of gametes and reproductive tissues for self use, Human Rep , 2004

- Adults and children have different decision making capacity (**competence**)
- Apply the **proportionality** principle , more good than harm (bene/maleficence)
- Specific considerations: length of cryopreervation, posthumous use

A simple case (in comparison)?

Parents create dead daughter's child

30.1.97

by Steve Connor and Cherry Norton

A 23-YEAR-OLD has become the world's first surrogate mother to carry the unborn child of a dead woman. She has become pregnant after the successful implantation of a frozen embryo from a woman who died of cancer almost a year ago.

The grandparents of the unborn child, who are both in their sixties, said that although they would like to duplicate their daughter, their main motive stemmed from her desire to be a mother from beyond the grave.

The ethical dilemma posed by the prospect of the first birth of a dead woman's child is the

A much more difficult equation

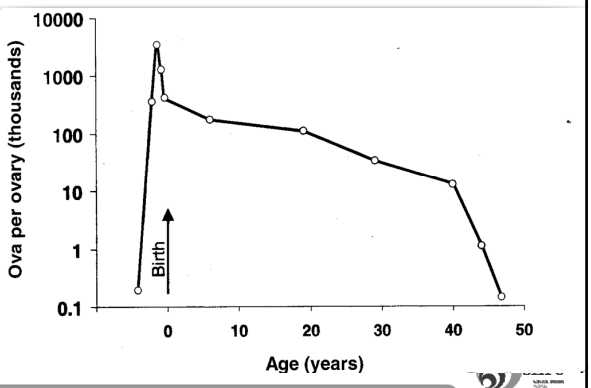
- **Timing of transition** form research to practice
- **Is it always possible/appropriate to conduct ideal trials?** (prospective randomised) :(Wallace and Barr) "**neither feasible nor ethical** to perform a randomised study in women of laparoscopic collection v dummy collection or non intervention"

What is the evidence today?: very rapid change in the last 2-3 years

- What are the **dangers** to the patient: **measurable** (surgery, iatrogenic menopause v **less easily measurable** (? Loss of chance for pregnancy with one's own genetic offspring)
- What are the other issues: the **"hope factor",** considering future fertility is life enhancing

Adult women

- **Fair amount of evidence** means : may decide with facts to cryo-preserve or not (depends on age, prognosis, previous fertility..)
- Must be informed about alternatives with "**third party reproduction**": oocyte donation, surrogacy, and may decide not to crypreserve
- Probably not research anymore ("in view of transition time during which research becomes therapy, the TF considerations will need revision when new evidence is available: statement 7 years ago)



Adolescents

- May **Gillick competence** (based on maturity and understanding), used in medical and healthcare practice, **apply to participation in research?**
- **No** (Hunter and Pierscionek): generally research seeks to answer specific questions, and benefits for the participants can be incidental rather than a primary aim
- **BUT "legitimate"** : (1) when the research is likely to generate **significant advantages for the participants** , while exposing them to **relatively minor risks**
- (2) when it is likely to generate **great societal benefit**, pose **minimal risks** for the participants

Consent: Adolescents, and children

- There is no need to fix a **specic age** at which an adolescent becomes competent to make these decisions. In fact, it is more appropriate to speak of **emerging autonomy** rather than of a specific age to consent (ESHRE Taskforce 7)
- The child: In the ideal situation parents and caring team concur in their appraisal….
- ….But for the parents **: imperative nature of offer** (anticipated decision regret); + may feel **parental responsibility** to take up "anything" in spite of risk

Research ethics, TF 13 (Welfare of the child)

- Assessment of risks of ART: technology and research must be **subordinate** to the welfare of the future offspring
- The **proportionality** principle demands that the possible harm to the people involved (included the future child) is outweighed by the possible benefits
- Usual steps: animal studies (several species), not always transferable to humans, thus additional human studies may be necessary
- **Embryo research** with creation of embryos (oocyte freezing), when necessary

Clinical trials

- Continuous evaluation with immediate feed back
- Ideally multi –centered to avoid bias due to centre specific factors
- **Follow up studies**: long term, so if started on a child, his/her consent should be sought when competent
- **Participation in follow up** "could be made a condition" for "treatment offered"

Ethics of mitochondrial gene replacement: from bench to bedside (BMJ)…an analogy

- Moving from animal and other preclinical studies to a first human application is always **uncertain** and **ethically contentious**.
- To what extent are we allowed to (or should we) use **embryos** to determine the safety of mitochondrial gene replacement
- Steps to be considered : assessing the risks and benefits
- First human use (**from "bench to bedside"): this appraisal involves "much intuition" and depends also "on a person's attitude towards risk"**
- **Solution: decision not by one person but by "expert community", with "transparent public debate"**

Professional responsibility

- The adoption of new techniques should be preceded by a thorough evaluation of their **safety, efficacy effectiveness and social and economic consequences**
- **Proportionality principle** demands that possible harm is outweighed by the possible benefits
- (eg: mitochondrial gene replacement, …should present a favourable balance of risks and benefits in comparison with the available alternatives)
- Bredenoord A and Braude P , 2011

Analogies

- ASRM "**experimental procedures**" until " there is **adequate** scientific evidence of safety and efficacy from appropriately designed peer reviews studies by different investigator groups"; oocyte vitrification as an exemple
- If there is little risk, is there "nothing to loose"?
- If the risk is minimal , what else may be done: the multi track approach (Dondorp and de Wert)

Common themes

- Good>harm or **proportionality**
- **Consent**: capacity, information, understanding
- Information re **unknown** as well as known benefits and risks: knowing and explaining any scientific uncertainty is an ethical imperative

Cryopreservation precedes use; this "separation principle" , different information, consent and risk benefit analysis enhances the ethical safeguards as it allows more time to gather evidence

The ethical calculus will be repeated/confirmed (infirmed?) at the time of **use**

Recommendations to be discussed

- Gather and pool data
- Organise international registers
- Follow up: patients and their children
- Permit creation of embryos for research when necessary
- Public debate
- **Safety valve**: cryopreservation and use of tissues (gametes) are separate issues, involving 2 separate processes , consent each time
- ……

References : transition from research …

Dondorp W and de Wert G (2011). **Innovative reproductive technologies: risks and responsibilities**, Hum Rep (in press)

Bredenoord A and Braude P (2011): **Ethics of mitochondrial gene replacement: from bench to bedside**, BMJ 342:87-89

Hunter D and Pierscionek BK (2006). **Children, Gillick competency and consent for involvement in research**, JME :659-662

- Stegman BJ (2010). **Unique ethical and legal implications of fertility preservation research in the paediatric population**, Fert and Ster, 93:1037-1039

Other refs

- Shenfield et al, ESHRE Ethics and Law Taskforce 7 (2004): **Cryopreservation of gametes and reproductive tissues for self use**. Hum Reprod, 19: 460-462
- Pennings et al, ESHRE Ethics and Law Taskforce 13 (2007) , **Welfare of the child in ART**. Hum Reprod, .22: 2585–2588
- Jadould P, Dolmans MM and Donnez J (2010): **Fertility preservation in gilrs during childhood: is it feasible, efficient and safe, and to whom should it be proposed** ? Human rep
- Wallace WHB and Barr RD (2010): **Fertility preservation for girls and young women with cancer: what are the remaining challenges?,** Hum Reprod Update, 16:614-616

Course 11
ESHRE Annual Meeting
Stockholm, Sweden
July 2, 2011

The Oncofertility Scholar: A new subspecialty with important training opportunities

Christos Coutifaris, MD, PhD
The Nancy and Richard Wolfson Professor and Chief,
Division of Reproductive Endocrinology and Infertility
University of Pennsylvania
Philadelphia, Pennsylvania
USA

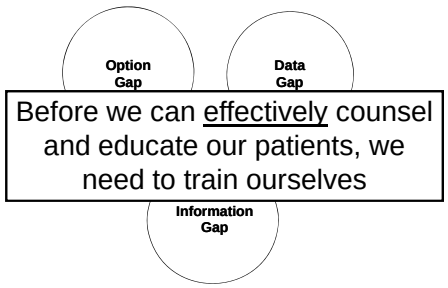
** There are no conflicts to disclose*

Learning Objectives

- Identify the gaps in knowledge and describe the need for an oncofertility subspecialty
- Describe the qualifications of the oncofertility specialist
- Describe an educational program for the development of an oncofertility specialist

Is there a need for an Oncofertility specialist ?

The Gaps



The Oncofertility Specialist

- Education and Laboratory Training
  - ✓Effects of XRT and Chemo
  - ✓Cancer Genetics and Pharmacology
  - ✓Bio-psychosocial impact of Ca Dx
  - ✓Repro Bioethics and Repro Health Policy
  - ✓In vitro Maturation of Follicles
  - ✓Cryopreservation of Reproductive Tissues
- Develop Research Program
  - ✓Basic or Clinical

The Oncofertility Specialist

- Reproductive Endocrinologists
  - 3-year fellowship program
  - Research intensive (1.5 - 2 years)
- Other specialists
  - Medical Oncologists
  - Pediatric Oncologists
  - Medical Endocrinologists
  - Bench Scientists

How do we achieve that?

- Additional year(s) of training -?-
  - Dedicated to education, laboratory work and research related to oncofertility
- Introduce “interdisciplinary” to academic departments
- Future leaders of Fertility Preservation Divisions

Commitment to the Global Community

- The World is Flat
- Socioeconomic disparities in fertility-related treatments
- Global disparities in fertility-related treatments
- International Trainees (R90)

The key is “inter / multidisciplinary” mentoring

Reproductive Endocrinologist
Oncologist
Material Scientist
Social Scientist
Bioethisist

A Success Template (?)

- NIH T32 Funded REI Training Program
  - Consortium of REI Fellowship programs with strong research infrastructure and track record
  - Currently 2 positions per year x 2 years
  - Full time research training with minimal clinical responsibilities
  - Started 2002 successfully re-competed 2006
    - Approved for 3 positions per year
    - One earmarked for clinical research training

The OncofertilityTraining Program I

- Northwestern University
- University of California, San Diego
- Oregon Primate Research Center
  - OHSU
- University of Pennsylvania

Other academic programs to partner with us in this training initiative?
The National Physicians Cooperative

The Oncofertility Training Program II

- One month at Northwestern
  - Ovarian Follicle Culture System
- Mentor at one of the Four Participating Institutions
  - Guide a focused research project

Oregon Primate Center:	Regulation of Primate Follicle Development and Culture; Cryobiology of Gonadal Tissues and Cells
Northwestern and UCSD:	Mouse and Human Follicular Development (*in vivo* and *in vitro*)
University of Pennsylvania:	Regulation of Epigenetic Modifications during Mouse and Human Follicular Maturation

The Oncofertility Training Program III

- Additional Mentor(s) outside the field of Reproduction
  - Guide the interdisciplinary aspects of professional development

The Oncofertility Training Program IV

- Course Work
  - Cancer genetics and biology
  - Cancer pharmacology
- Clinical exposure to adult and pediatric Ca patients at risk for compromise of their fertility potential
- Formal instruction in the responsible conduct of research
- Seminars and conferences
- Networking at national level (retreats)
- Complete on-line educational program (R25)

OPEN

- Oncofertility Professional Education Network
- R25 component of this U54
- Educational Materials
  - ✓Virtual Grand Rounds
  - ✓Archived versions of Grand Rounds
  - ✓Self-paced e-learning modules

The budding oncofertility specialists

Need for Role Models

- Clarisa Gracia, MD, MSCE **(PI, K01)**
- Jackie Jeruss, MD, PhD
- Beth Plunkett, MD

(Co-PI's Pilot Project)

- Laxmi Kondapalli, MD **(co-PI, R01C)**
- Monica Mainigi, MD **(T90)**
- Fanzen Hong, MD **(R90)**

Selection of Fellows

- Research Proposal
- Three letters of recommendation
- Description of academic enrichment program
  - ✓ Courses
  - ✓ Ethical conduct of research
- IRB or animal committee approval
- Program has plan for recruitment of
  - ✓ Women
  - ✓ URM
  - ✓ Diverse populations

Tracking and Program Evaluation

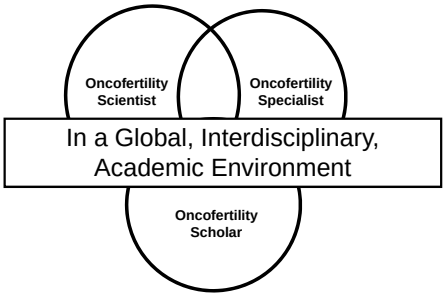
- Entrance into academic positions
- Institutional K's (RSDP, WRHR, BIRCWH)
- Individual K grants
- Applications and awards for R01 and R03 grants
- Applications and awards for subprojects in P01 and/or U54 grants
- Publication record
- Evidence of interdisciplinary and collaborative research
- Promotion record
- Attrition record from academic ranks

Building the Humanpower for an Interdisciplinary Field (Oncofertility)

- Training in Science
  - R01A – Cryobiology (Oregon)
  - R01B – Primate Follicle Culture (Oregon)
  - R01C and T90/R90 Mentors
    - Mouse and Human Follicle Culture
    - Clinical Research
  - P30A – Biomaterials
- Collaborative Work – (P30B – NPC)
- Social Sciences (R01D) - Mentors
- Education (OPEN - R25)

Need to coordinate internationally

The Ultimate Goal



Mark your calendar for the upcoming ESHRE campus workshops!

- Early pregnancy disorders: integrating clinical, immunological and epidemiological aspects
  23-26 August 2011 - Copenhagen, Denmark
- The management of infertility – training workshop for junior doctors, paramedicals and embryologists
  7-8 September 2011 - St. Petersburg, Russia
- Basic genetics for ART practitioners
  9 September 2011 - Bucharest, Romania
- The whole man
  22-23 September 2011 - Sevilla, Spain
- Accreditation of a Preimplantation Genetic Diagnosis Laboratory
  3-4 October 2011 - Athens, Greece
- Human reproductive tissues, gametes and embryos: Innovations by science-driven culture and preservation systems
  9 October 2011 - Cairns, Australia
- Comprehensive preimplantation screening: dynamics and ethics
  13-14 October 2011 - Maastricht, The Netherlands
- Endometriosis and IVF
  28-29 October 2011 - Rome, Italy
- Endoscopy in reproductive medicine
  23-25 November 2011 - Leuven, Belgium
- What you always wanted to know about polycystic ovary syndrome
  8-10 December 2011 - Sofia, Bulgaria

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES